COMPREHENSIVE ORGANIC SYNTHESIS

Selectivity, Strategy & Efficiency in Modern Organic Chemistry

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Volume 3

CARBON–CARBON σ-BOND FORMATION

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Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

Techniques

CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
CT	charge transfer
GLC	gas–liquid chromatography
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORD	optical rotatory dispersion
PE	photoelectron
SCF	self-consistent field
TLC	thin layer chromatography
UV	ultraviolet

Reagents, solvents, **etc.**

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BHT	2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene)
bipy	2,2′-bipyridyl
Bn	benzyl
t-BOC	*t*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl
CAN	ceric ammonium nitrate
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or –)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or –)
DMA	dimethylacetamide
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	*N*,*N*′-dimethylimidazolone
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
E^+	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EWG	electron-withdrawing group
HMPA	hexamethylphosphoric triamide
HOBT	hydroxybenzotriazole
$IpcBH_2$	isopinocampheylborane
Ipc_2BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri-*s*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LITMP	lithium tetramethylpiperidide
L-selectride	lithium tri-*s*-butylborohydride
LTA	lead tetraacetate
MCPBA	*m*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MEM-Cl	β-methoxyethoxymethyl chloride
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl
Ms	methanesulfonyl
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
Nu^-	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SEM	β-trimethylsilylethoxymethyl
Sia_2BH	disiamylborane
TAS	tris(diethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDMS-Cl	*t*-butyldimethylsilyl chloride
TBHP	*t*-butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBS-Cl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPS-Cl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMS-Cl	trimethylsilyl chloride
TMS-CN	trimethylsilyl cyanide
Tol	tolyl
TosMIC	tosylmethyl isocyanide
TPP	*meso*-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTFA	thallium trifluoroacetate
TTN	thallium(III) nitrate

1.1
Alkylations of Enols and Enolates

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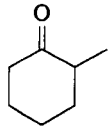
1.1.1 INTRODUCTION

The α-alkylation of carbonyl compounds by their conversion into nucleophilic enolates or enolate equivalents and subsequent reaction with electrophilic alkylating agents provides one of the main avenues for regio- and stereo-selective formation of carbon–carbon σ-bonds.[1–6] Classical approaches to α-alkylation typically involve the deprotonation of compounds containing doubly activated methylene or methine groups and having pK_a values of 13 or below by sodium or potassium alkoxides in protic solvents. Since these conditions lead to monoenolates derived from deprotonation only at the α-site of the substrate, the question of the regioselectivity of *C*-alkylation does not arise (however, there is competition between *C*- and *O*-alkylation in certain cases). In more recent years, dienolates of β-dicarbonyl compounds have been utilized in γ-alkylations with excellent success.

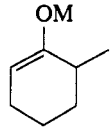
α-Alkylations of active methylene compounds followed by removal of one of the activating groups to produce monofunctional products is quite useful for large scale synthesis of relatively simple carbonyl compounds. Indeed, if one wishes to use conventional methods of enolate formation in alkylations of

simple unsymmetrical ketones, extraneous methylene blocking groups or activating groups, which are to be removed eventually, must be applied.[2,4] However, modern synthetic methodology has focused upon α-alkylation of monofunctional carbonyl systems *via* their metal enolates or enolate equivalents produced quantitatively by direct or indirect methods. Since monofunctional carbonyl compounds have pK_a values in the 20–27 range, strong bases in aprotic solvents are required for direct enolate formation by deprotonation. Many of these substrates (aldehydes, carboxylic acid derivatives and certain ketones) contain only one reactive α-site. In these cases, the question of regioselective enolate formation does not arise, although in most cases stereoisomeric (*E*)- or (*Z*)-enolates or mixtures of these species may be produced, depending upon the substrate and reaction conditions.[2] However, the challenging problems encountered in the total synthesis of steroids, terpenoids or other complex molecules have required the development of methods of regioselective alkylation of unsymmetrical ketones, which are capable of enolization in two directions.

Upon treatment with strong bases unsymmetrical ketones such as 2-methylcyclohexanone (**1**) can lose a proton to give the tri- or tetra-substituted enolates (**2**) or (**3**). Under kinetic control, where the ketone is added slowly to a soluble strong base in an aprotic medium, the enolate mixture composition is determined by the relative rates of proton removal from the alternative α-positions. Because the less-substituted α-position is less hindered, the less-substituted enolate, *e.g.* (**2**), is usually favored under kinetic conditions. However, when relatively basic Group I sodium or potassium enolates are employed, enolate equilibration, brought about by proton transfer reactions involving the initially formed alkylated ketones and unalkylated enolates, is normally faster than alkylation. As a result, products derived from alkylation of the more highly substituted enolate (**3**), which is normally the more thermodynamically stable isomer, usually predominate. Rapid proton transfer reactions also account for the formation of di- and even trialkylated products in alkylations involving potassium or sodium enolates.



(1)



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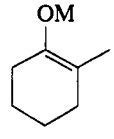
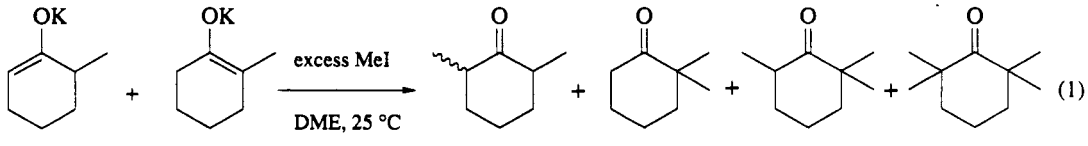
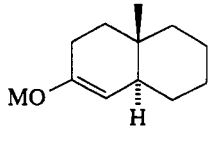


(3)

An illustration of this behavior is provided in equation (1). A 67:33 mixture of the less- and more-substituted potassium enolates was produced upon treatment of 2-methylcyclohexanone with tritylpotassium in DME. However, the major product of alkylation of this mixture with methyl iodide was 2,2-dimethylcyclohexanone and significant amounts of tri- and tetra-methylcyclohexanone were also obtained.[7]



The modern era of enolate alkylations began in 1961 when Stork *et al.*[8] showed that the less thermodynamically stable lithium 1-enolate (**4**) of *trans*-10-methyl-2-decalone, produced by lithium–ammonia reduction of the corresponding octalone, could be alkylated regiospecifically with reactive alkylating agents in liquid ammonia. Regiospecificity was not maintained if potassium or sodium was employed in the reduction, or if the enolate (**4**) was transferred to DMSO prior to alkylation. These conditions gave 3-alkyl-substituted products *via* the more thermodynamically stable 2-enolate, as did deprotonation of the parent decalone with strong bases.



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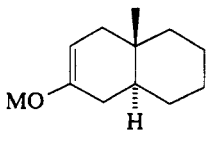


(5)

The above results led to an explosion of interest in the use of lithium enolates in α-alkylation reactions. It was quickly demonstrated that specific lithium enolates of a variety of unsymmetrical ketones could be trapped with the more reactive alkylating agents in liquid ammonia or aprotic solvents such as

DME or THF. Clearly, the ratio of the rate of alkylation to the rate of proton transfer is significantly larger for less basic lithium enolates than for their sodium and potassium counterparts.

In order to exploit the unique behavior of lithium enolates, a wide variety of highly hindered, non-nucleophilic bases such as LDA, LICA, LITMP, lithium hexamethyldisilylamide (LHDS) and lithium tetramethyldiphenyldisilylamide (LTDOS), which kinetically convert unsymmetrical ketones to their less-substituted enolates with high regioselectivity, have been developed.[2] Lithium *t*-octyl-*t*-butylamide (LOBA) has recently been shown to be a highly useful base for this purpose.[9] Likewise, a variety of indirect methods for formation of lithium enolates such as lithium–ammonia reduction of enones,[10] conjugate additions of organocuprate reagents to enones[11] and the cleavage of silyl enol ethers with organolithium reagents[12] have been developed or expanded. An excellent survey of methods of formation of lithium and other enolates derived from less electropositive metals is found in Volume 2, Chapter 1.4 of this series.[13]

The majority of α-alkylations currently being reported are accomplished *via* lithium enolates. However, these reactions have several drawbacks, *e.g.* loss of regioselectivity when sterically congested β,β-disubstituted enolates are involved or when less reactive alkylating agents are employed, polyalkylation, elimination rather than substitution of the alkylating agent, and poor π-facial diastereoselectivity in many cases. Fortunately, most of these limitations have been overcome by the methodology to be described below.

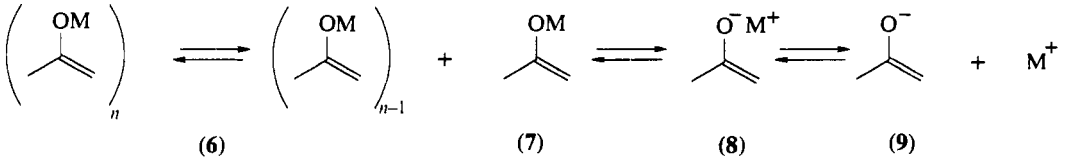
This chapter will provide coverage of the scope and limitations of alkylations of metal enolates of saturated and unsaturated ketones, aldehydes and carboxylic acid derivatives, together with a discussion of alkylations of various enols and enolate equivalents. Where applicable, the utility of these reactions for the diastereoselective and enantioselective synthesis of α-substituted carbonyl compounds will be described. Inevitably, the coverage of a vast research area such as this will be incomplete and in part will reflect the author's interests. However, it is hoped that most of the useful methods of carbon–carbon σ-bond formation by alkylations of enolates and enols will be included.

1.1.2 ALKYLATIONS OF METAL ENOLATES OF KETONES AND ALDEHYDES

1.1.2.1 Regiospecific Alkylations of Unsymmetrical Acyclic and Cyclic Ketones

There are numerous base–solvent combinations that are capable of quantitatively converting even weakly acidic simple ketones into their enolate anions.[1] However, in order to avoid aldol condensation and unwanted equilibration of enolates of unsymmetrical ketones during enolate formation, it is best to choose conditions under which the ketone, the base and the metal enolate are soluble. Likewise, solutions should be produced when indirect methods of enolate formation are employed. While certain metal cations such as Hg^{2+} form α-metallated ketones, most of the metal cations in Groups I, II and III exist as *O*-metallated tautomers.[13] For organotin derivatives both the *O*-metallated and *C*-metallated forms probably exist in equilibrium.[14]

Metal enolate solutions consist of molecular aggregates (**6**) such as dimers, trimers and tetramers in equilibrium with monomeric covalently bonded species (**7**), contact ion pairs (**8**) and solvent-separated ion pairs (**9**), as shown in Scheme 1.[15] The nature of the metal cation, the solvent and, to a degree, the structure of the enolate anion itself may significantly influence the extent of association between the anion and the metal cation.[1] In general, the factors that favor loose association, *e.g.* solvent-separated ion pairs, lead to an increase in the nucleophilicity of the enolate toward alkylating agents and also its ability to function as a base, *i.e.* to participate in proton transfer reactions.



(6) (7) (8) (9)

Scheme 1

Both physical measurements[15,16] and kinetic studies[17] show that association between metal cations and enolate anions is stronger, *i.e.* the oxygen–metal bond has more covalent character, when small metal cations and less electropositive metals are involved. The degree of aggregation and extent of association of

metal cations and enolate anions is reduced as one goes from monodentate *n*-donor solvents such as diethyl ether and THF to di- and poly-dentate *n*-donor solvents like DME, the higher glymes and crown ethers. These effects are particularly marked in dipolar aprotic solvents such as HMPA, DMSO and DMF, which strongly solvate metal cations by a π-donor mechanism.

The reactivity of metal enolates can be greatly enhanced by adding dipolar aprotic substances to their solutions in ethereal solvents such as THF, where HMPA has become the additive of choice for this purpose.

The geometry of the enolate anion and the degree of substitution on the carbon–carbon double bond may influence the degree of enolate aggregation. Less-substituted metal enolates, which are probably capable of forming larger aggregates, are somewhat less reactive than more-substituted enolates.[18] In the latter species, the increase in nucleophilicity resulting from the presence of an electron-releasing alkyl group is offset by the steric bulk of such groups, which retard alkylation rates. Substituents which are located at positions other than the α-position may influence the extent of enolate aggregation in a particular solvent, or sterically hinder the approach of an alkylating agent. These effects not only influence the rates but the stereochemistry of enolate alkylations (Section 1.1.2.2).

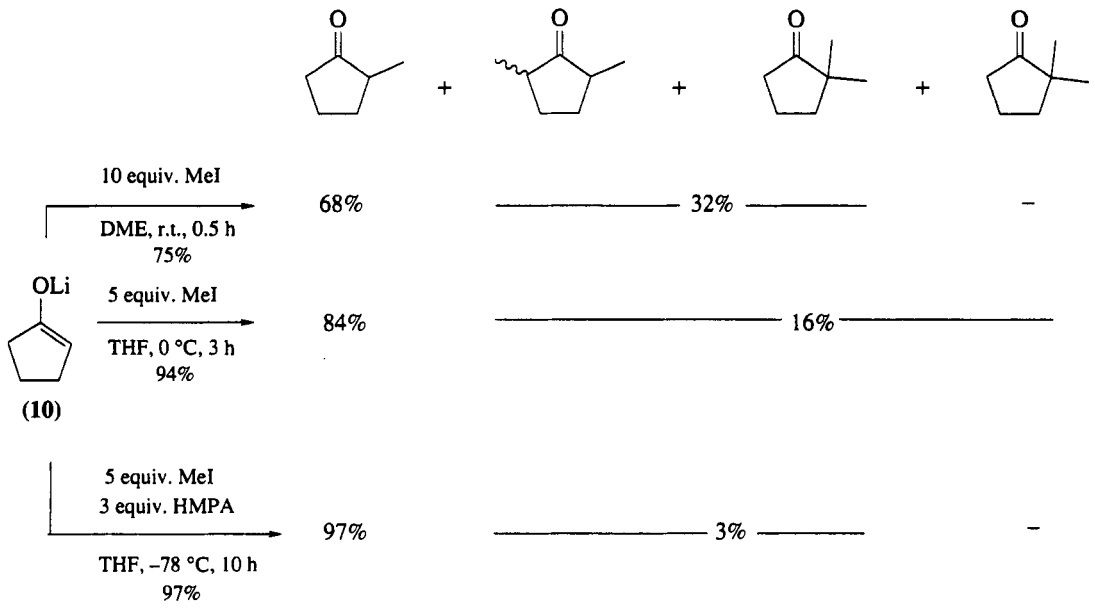
Activated allylic, benzylic and propargylic halides and α-halo esters, as well as methyl and primary halides, are useful reagents for *C*-alkylation of metal enolates. The order of reactivity of the various halogens is as expected for an S_N2 process, *i.e.* I > Br > Cl. The order of reactivity of a particular halide is usually benzyl > allyl > primary alkyl and branching at the β-carbon reduces reactivity. Branching at the α-carbon reduces reactivity significantly. Thus, secondary halides react with metal enolates slowly and yields of α-alkylation products are usually poor. Tertiary halides undergo elimination almost exclusively upon reaction with enolates. Elimination is also a serious problem when β-vinyl (homoallylic), β-alkynic and β-phenyl halides as well as β-halo ketones, esters or nitriles are employed in alkylations. Alkyl tosylates and benzenesulfonates are also useful reagents for α-alkylation of metal enolates. Their reactivities are similar to those of the corresponding iodides.

O-Alkylation is generally not a problem when lithium and less electropositive metal enolates are involved, unless highly reactive alkylating agents such as dialkyl sulfates, trialkyloxonium salts or α-chloro ethers are employed in solvents of relatively high polarity. As the degree of dissociation between the metal cation and the enolate anion is increased, the anion becomes more capable of exercising its ambident character. The competition between *C*- and *O*-alkylation has been traditionally explained in terms of the Pearson–Klopman principle, which states that hard electrophilic reagents should attack the hard oxygen atom of the enolate anion, while soft reagents should attack the soft α-carbon site.[19,20] However, recent *ab initio* calculations[21] and experimental gas-phase data[22] indicate that free enolate anions react on oxygen irrespective of the hardness or softness of the electrophilic reagent. Coordination of the metal cation with the oxygen must be responsible for reducing its reactivity to the point where *C*-alkylation is usually preferred in solution. Other data on the variations of *C*:*O*-alkylation ratios with the nature of the alkyl halide indicate that it is the ability of the halide to influence the structures of enolate aggregates rather than its 'hardness' or 'softness' which is the controlling factor.[23] This section will be devoted mainly to reactions in which little, if any, *O*-alkylation is observed.

Enolate equilibration and di- and poly-alkylation are the major side reactions, which lead to reduced yields of desired products in ketone alkylations. These processes occur as a result of equilibration of the starting enolate (or enolate mixture) with the neutral monoalkylation product(s) *via* proton transfer reactions. Polyalkylation may also occur when bases, in addition to the starting enolate, which are capable of deprotonating the monoalkylated ketone are present in the medium. With symmetrical ketones, *e.g.* cyclopentanone and cyclohexanone, the problem of regioselectivity does not arise. However, except under special conditions, polyalkylation occurs to a significant extent during enolate alkylations of more kinetically acidic ketones such as cyclobutanone, cyclopentanone and acyclic ketones, particularly methyl ketones.[24] Polyalkylation is also a troublesome side reaction with less acidic ketones such as cyclohexanone.

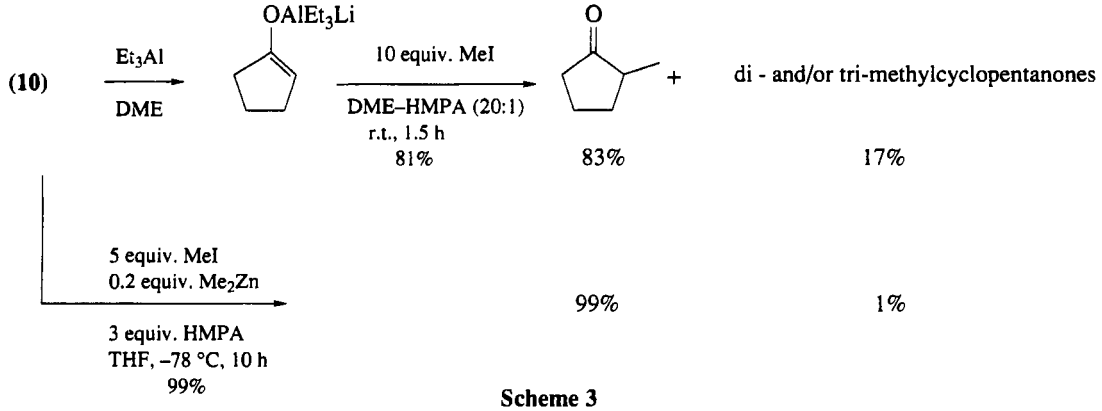
Scheme 2 shows the results of two studies on the methylation of the lithium enolate of cyclopentanone (**10**), which was prepared by deprotonation of the ketone with trityllithium in DME[25] or by cleavage of the 1-trimethylsiloxycyclopentene with methyllithium in THF.[26] A significant quantity of over-alkylation occurred when the enolate was treated with methyl iodide, particularly when DME was employed as the solvent at room temperature. Also, as indicated in Scheme 2, Noyori and coworkers[26] showed that by adding 3 equiv. of HMPA to the enolate (**10**) and reducing the temperature at which the reaction was conducted, the yield of 2-methylcyclopentanone was greatly improved.

As shown in Scheme 3 conversion of the lithium enolate (**10**) to its complex lithium triethylaluminum enolate prior to alkylation in DME–HMPA at room temperature also significantly reduced the amount of polyalkylation.[25] However, the most dramatic results were obtained by addition of dimethylzinc to the



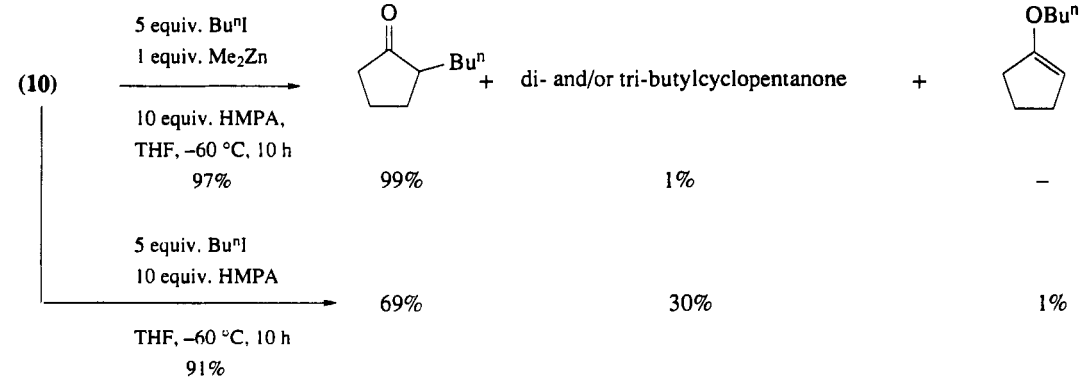
Scheme 2

solution of (**10**) in THF–HMPA; even when only 0.2 equiv. of the additive was used an insignificant amount of over-alkylation occurred.[26]



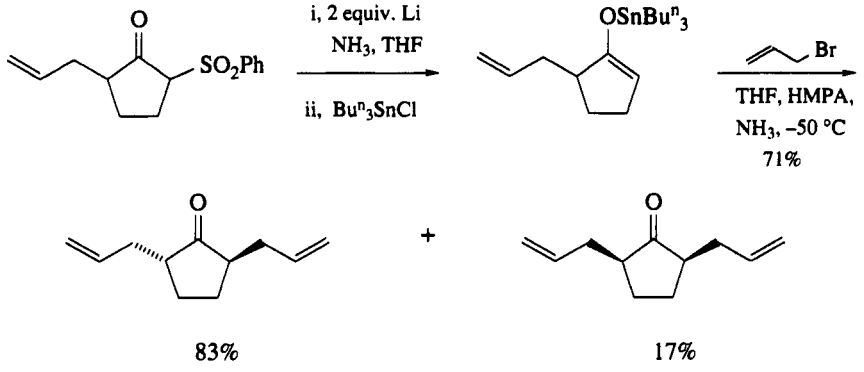
Scheme 3

A comparison of the results of *n*-butylation of the enolate (**10**) in THF–HMPA with and without the addition of 1 equiv. of dimethylzinc is shown in Scheme 4. Although *n*-butyl iodide is 50–100 times less reactive than methyl iodide, monobutylation occurred with high efficiency in the presence of the additive. It is not clear whether dimethylzinc reacts with (**10**) to produce a complex lithium dimethylzinc enolate, or whether it influences the reactivity of the enolate in some other way, possibly by changing its state of aggregation and/or the structures of the aggregates.

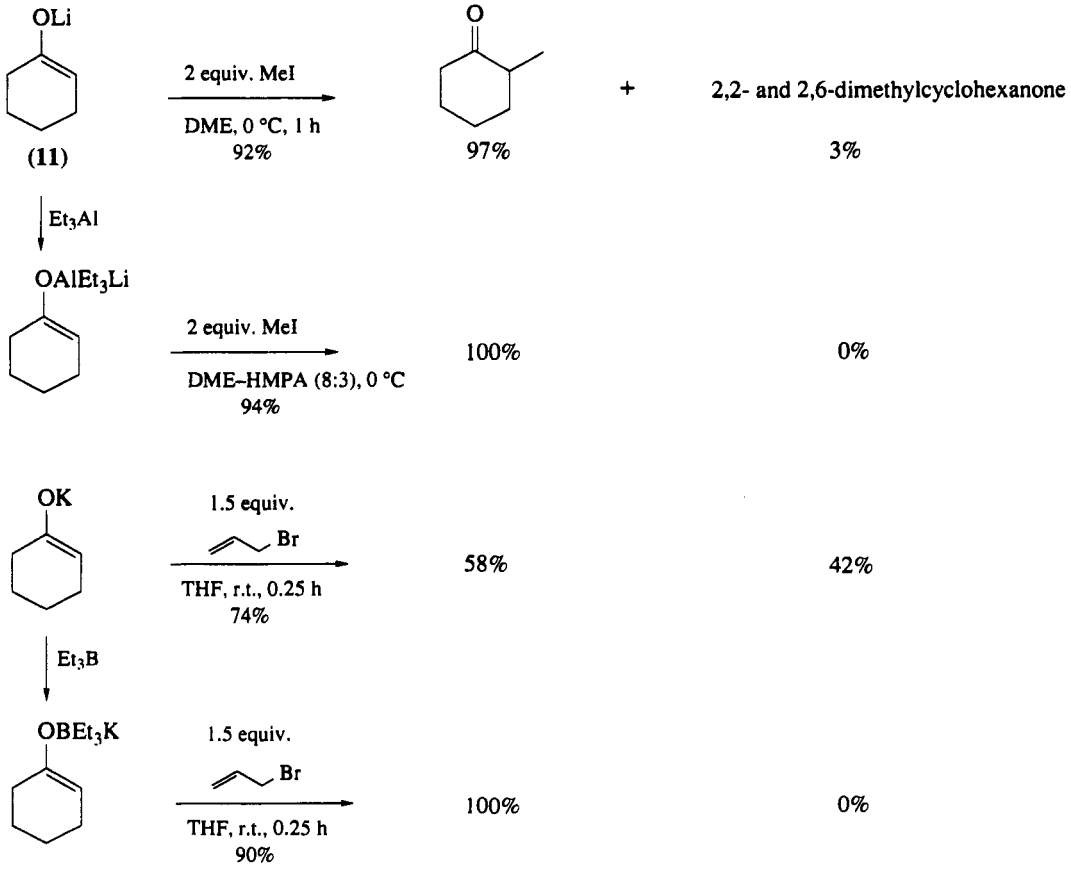


Scheme 4

The addition of copper(I) salts to THF–HMPA solutions of the lithium enolate (**10**) caused a dramatic reduction in the amount of polyalkylation.[27] The exact role played by the copper(I) cation is not clear. 2-Benzylcyclopentanone, free of the dibenzylation product, was prepared in 67% yield by alkylation of the 'naked' tetraalkylammonium cyclopentanone enolate generated *in situ* by reaction of trimethylsiloxycyclopentene with BTAF in the presence of benzyl bromide in THF;[28] 2-allylcyclopentanone contaminated with ≤3% diallylated ketone was obtained in a similar manner using trimethylsiloxycyclopentene, allyl bromide and TAS difluorotrimethylsiliconate in THF.[29] The less-substituted tri-*n*-butyltin enolate of 2-allylcyclopentanone, prepared by reductive desulfurization of the corresponding β-keto sulfone with lithium in liquid ammonia followed by addition of tri-*n*-butyltin chloride, was alkylated with allyl bromide to give the 2,5-diallyl ketone in good yield (Scheme 5).[30]



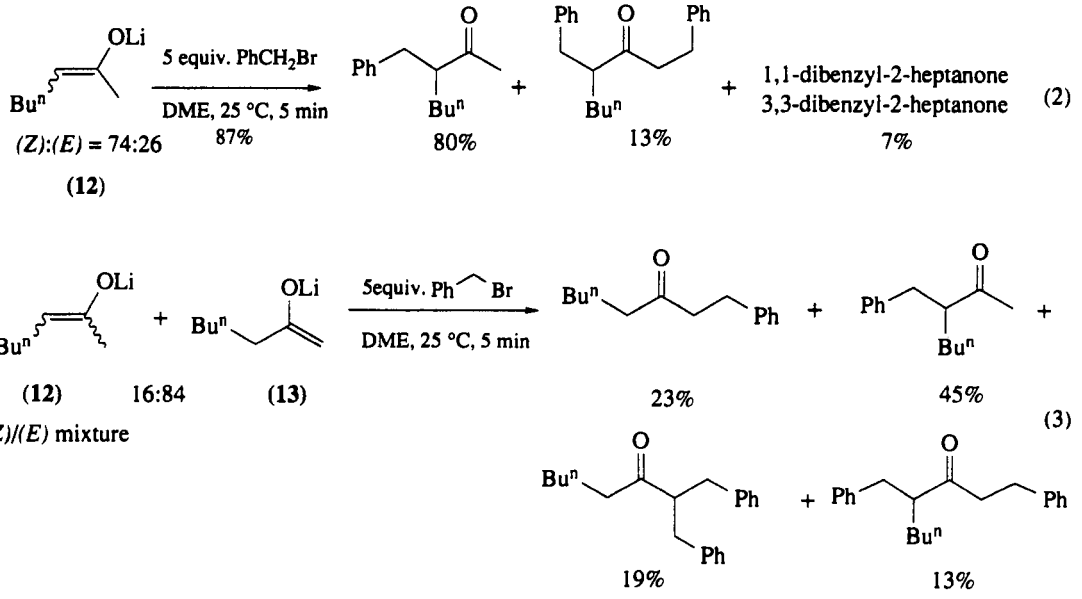
Scheme 5



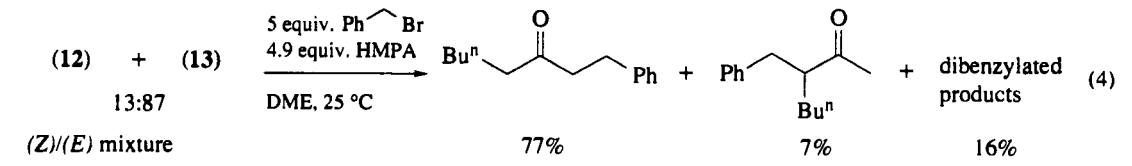
Scheme 6

Lithium,[25] lithium triethylaluminum,[25] sodium triethylboron,[31] sodium triethanolamine borate,[31] potassium triethylboron[32] and tri-*n*-butyltin[25,33] cyclohexanone enolates have been successfully monoalkylated. In Scheme 6 the behavior of the lithium enolate of cyclohexanone (**11**) and the lithium triethylaluminum enolate upon reaction with methyl iodide is compared. The latter enolate gives better results since no dimethylation products were detected, but clearly the cyclohexanone enolate (**11**) is much less prone to dialkylation than the cyclopentanone enolate (**10**). Scheme 6 also provides a comparison of the results of alkylation of the potassium enolate of cyclohexanone, where almost equal amounts of mono- and di-alkylation occurred, with the alkylation of the potassium triethylboron enolate where no polyalkylation occurred. The employment of more covalently bonded enolates offers an advantage in cyclohexanone monoalkylations but not nearly as much as in the cyclopentanone case.

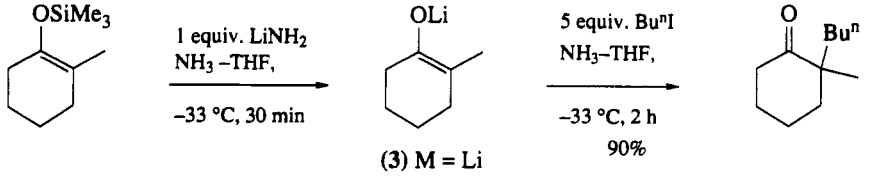
The same conditions which are useful for monoalkylation of enolates of symmetrical ketones also favor regioselective alkylation of specific enolates of unsymmetrical ketones. Since more highly substituted enolates of unsymmetrical ketones are usually the more thermodynamically stable and also undergo alkylation faster than the less-substituted enolates, it is generally possible to successfully alkylate these species.[18] For example, as shown in equation (2), when a (*Z*):(*E*) = 74:26 mixture of the lithium 2-enolates of 2-heptanone (**12**) was benzylated in DME, the 3-benzyl derivative was the only monoalkylation product obtained, although significant amounts of dibenzylated products were produced. However, as shown in equation (3), benzylation of an 84:16 mixture of the lithium 1-(**13**) and a (*Z*)/(*E*)-mixture of the lithium 2-enolates of 2-heptanone (**12**) gave primarily the internally benzylated product. The equilibrium composition of the structurally isomeric lithium enolates of 2-heptanone in DME at 25 °C is 65% (*Z*)-2-enolate, 22% (*E*)-2-enolate and 13% 1-enolate.[34] Thus, substantial enolate equilibrium occurred during the reaction.



Equation (4) shows the results of benzylation of an 87:13 mixture of the enolates (**13**) and (**12**) in the presence of the dipolar aprotic additive HMPA, where a substantial amount of benzylation occurred *via* the terminal enolate.[17] Other additives, such as DMF and benzo-14-crown-4, increased the amount of terminal alkylation in comparison with the use of DME alone. The influence of the additive is possibly to prevent the formation of aggregates of the enolate (**13**) and lithium bromide formed during the reaction. This could cause the terminal enolate to remain as a reactive dimer, which undergoes alkylation more rapidly than equilibration to the internal enolate.[17]

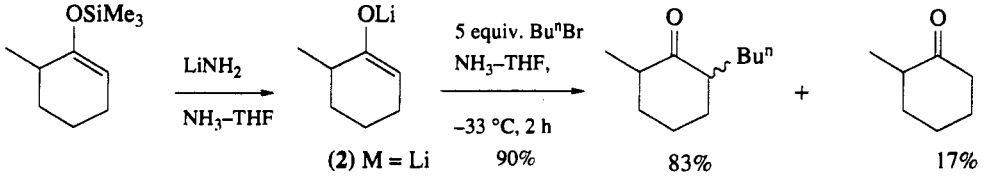


Deprotonations of unsymmetrical ketones with lithium bases under thermodynamic control usually give the more-substituted enolates with good regioselectivity. However, even better results are provided by various indirect methods of enolate formation, such as cleavage of more-substituted TMS enol ethers with organolithium reagents in ethereal solvents[12,18,35] or lithium amide in liquid ammonia[36] or lithium–ammonia reduction of appropriate α,β-unsaturated ketones. The former procedure provides a 'clean' enolate,[37] one free of extraneous bases, which can promote polyalkylation. Several highly regioselective methods of preparing thermodynamic TMS enol ethers of unsymmetrical ketones such as 2-methylcyclohexanone have been reported recently.[38–40] Alkylations with less reactive alkylating agents such as *n*-butyl iodide provide an important test of regiocontrol in enolate alkylations.[1] An excellent yield of 2-*n*-butyl-2-methylcyclohexanone was obtained when the more highly substituted TMS enol ether of 2-methylcyclohexanone was treated with lithium amide in liquid ammonia–THF and the resulting enolate (**3**; M = Li) reacted with *n*-butyl iodide (Scheme 7).[36]



Scheme 7

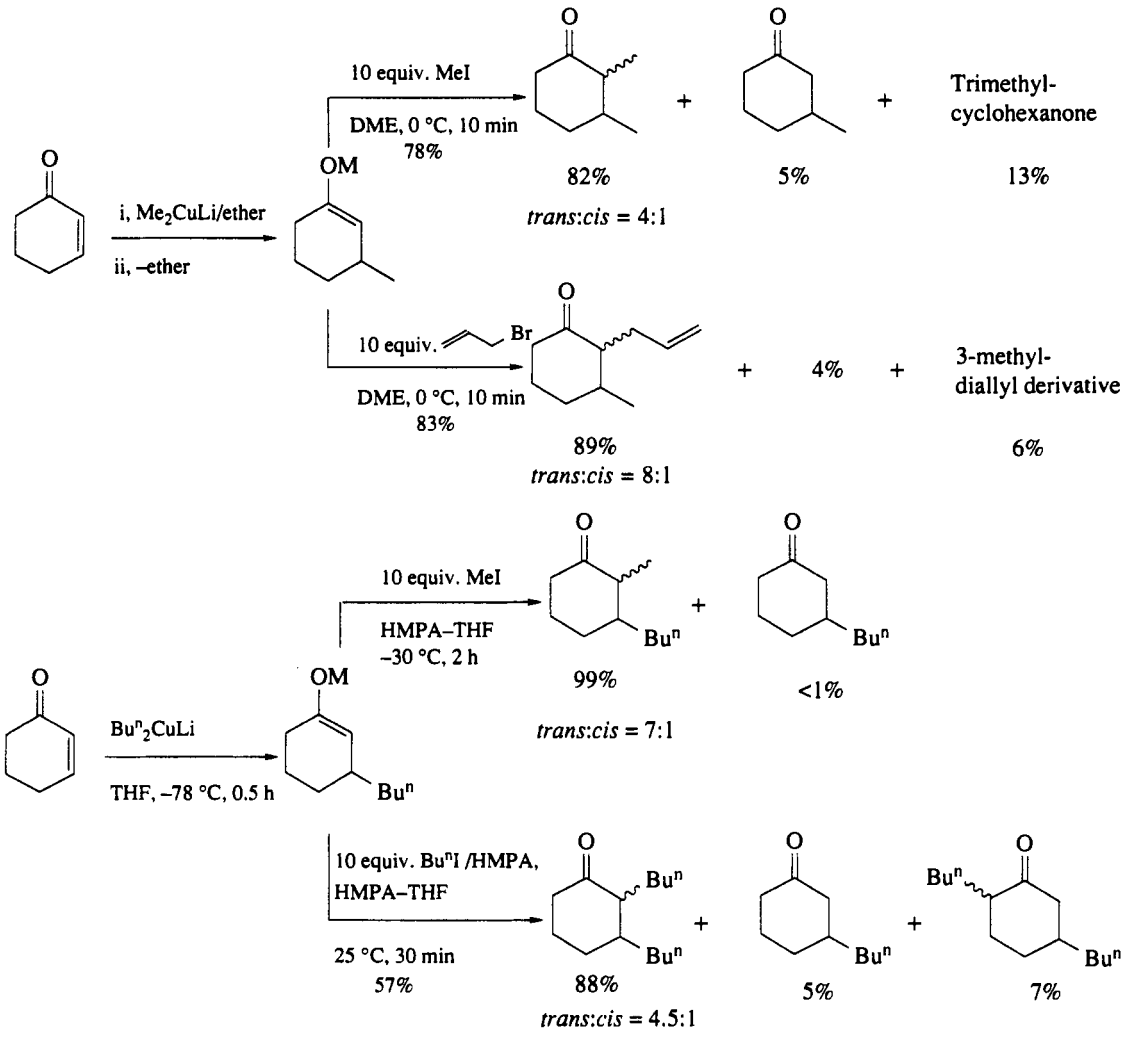
Regioselective alkylations at C-6 of 2-methylcyclohexanone have been accomplished *via* the alkylation of thermodynamically unstable trisubstituted lithium, lithium triethanolamine borate,[31] potassium triethylboron,[32] tri-*n*-butyltin[14] and benzyltrimethylammonium enolates (*cf.* **2**).[28] Alkylation is faster than equilibration for the more reactive alkylating agents. Although enolate equilibration has been shown to compete with butylation using *n*-butyl iodide under certain conditions,[41,42] butylation of the enolate (**2**; M = Li) in liquid ammonia–THF gave a mixture of *cis*- and *trans*-2-methyl-6-butylcyclohexanone along with 2-methylcyclohexanone in an 83:17 ratio in 90% yield; no 2,2-dialkylcyclohexanone was obtained in this reaction (Scheme 8).[36]



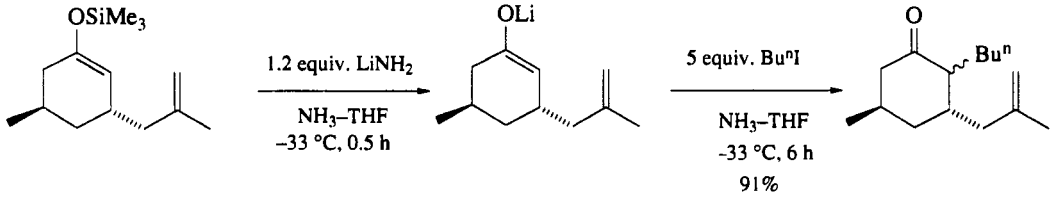
Scheme 8

α,β-Dialkylation of enones by conjugate addition–enolate alkylation has been widely used for the synthesis of α,β-dialkyl ketones, particularly cyclohexanones and cyclopentanones. This subject has been recently reviewed by Taylor, who has pointed out the problems associated with tandem, one-pot conjugate addition–enolate alkylation procedures.[11] The most frequently used reagents for conjugate additions are lithium dialkylcuprates, and the enolates produced in such reactions are likely to be largely lithium enolates.[43] However, copper(I) salts, which may influence lithium enolate reactivity even in low concentration, are undoubtedly present in solution.[41] Conjugate additions usually proceed best in ether, but enolate alkylations are unacceptably slow in this solvent. However, if the reactivity of the medium is adjusted by addition of appropriate cation-complexing agents such as TMEDA[41,44] or THF/HMPA,[45] or if the ether is exchanged for a more appropriate solvent for alkylation, *e.g.* DME,[44] regioselective alkylations can be effected with simple, reactive alkylating agents in many cases. Conjugate additions can also be performed in THF.[41] Examples of the use of one-pot conjugate addition–enolate alkylations for the synthesis of 2,3-dialkylcyclohexanones are shown in Scheme 9.[41,44]

A useful technique to accomplish overall vicinal dialkylation of enones is to trap the enolate initially formed in the conjugate addition with TMS-Cl, and then regenerate the enolate under suitable conditions for its alkylation. Lithium 1-enolates of 3,5-dialkylcyclohexanones generated from the reaction of the corresponding TMS enol ethers with lithium amide in liquid ammonia–THF can be alkylated efficiently in liquid ammonia–THF, even with an unreactive alkylating agent such as *n*-butyl iodide (Scheme 10).[36]



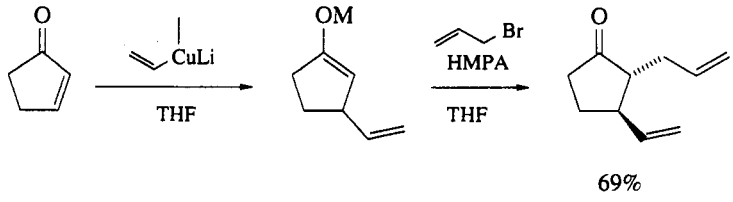
Scheme 9



Scheme 10

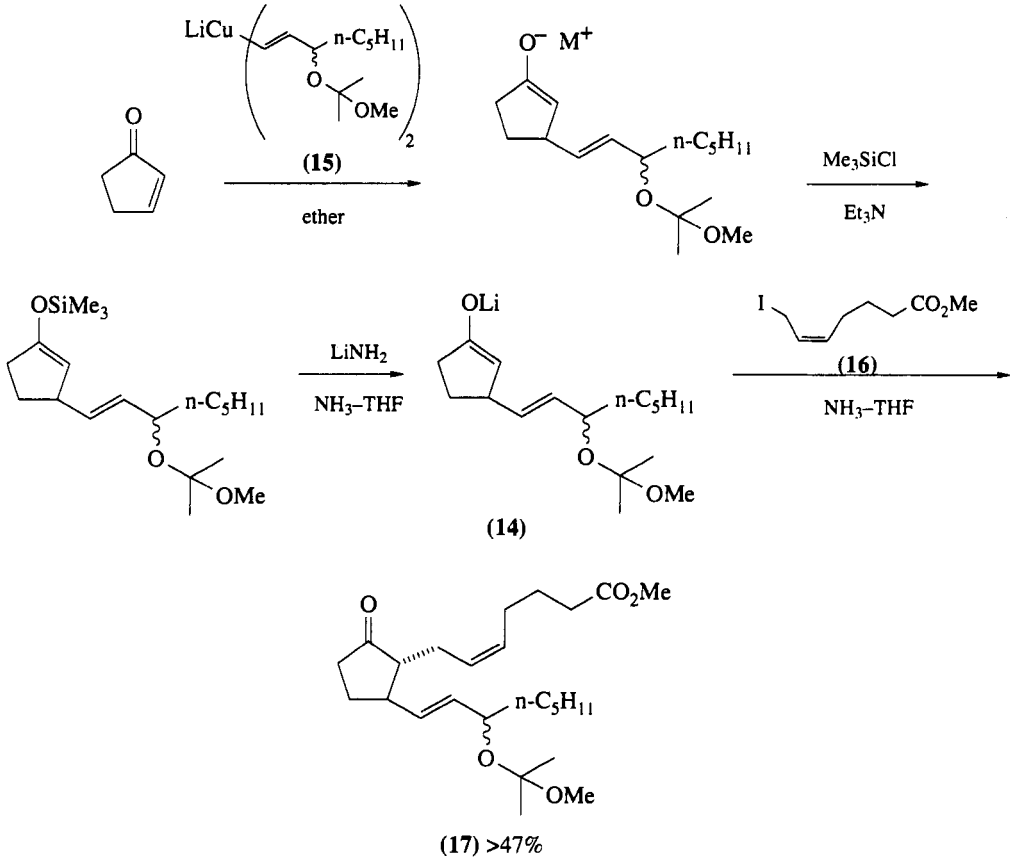
2,3-Dialkylcyclopentanones, *e.g.* the prostaglandins, are found widely in nature. An obvious route to the synthesis of these systems is a triply convergent approach involving tandem conjugate addition–enolate alkylation of an appropriate cyclopentenone.[41,46–48] However, the propensity of cyclopentanone enolates toward equilibration has presented difficulties, which until recently have prevented synthesis of the natural products themselves by this approach.[47,48] Using cyclopentenone as the substrate, Posner and coworkers found that tandem conjugate addition–enolate alkylations could be accomplished in reasonable yields with relatively small nucleophiles and electrophiles under carefully controlled conditions (Scheme 11).[41] However, the alkylation failed when bulkier nucleophiles and electrophiles bearing the functionality of prostaglandin side chains were employed.

Patterson and Fried found that the clean lithium enolate (**14**), generated by conjugate addition of the lithium divinylcuprate (**15**) to cyclopentenone with subsequent trapping of the initial enolate with TMS-Cl and cleavage of the TMS enol ether with lithium amide in liquid ammonia–THF, could be alkylated in a reasonable yield with the (*Z*)-allylic iodide (**16**) to give the 11-deoxyprostaglandin derivative (**17**;



Scheme 11

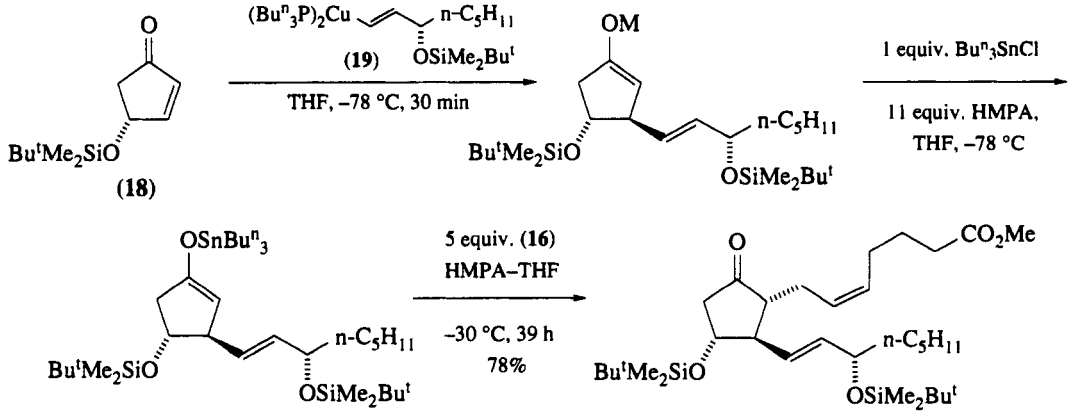
Scheme 12).[46] However, the sequence failed when applied to a protected 4-hydroxycyclopentenone because of equilibration of the initially formed 1-enolate to the 5-enolate followed by β-elimination of the protected hydroxy substituent.



Scheme 12

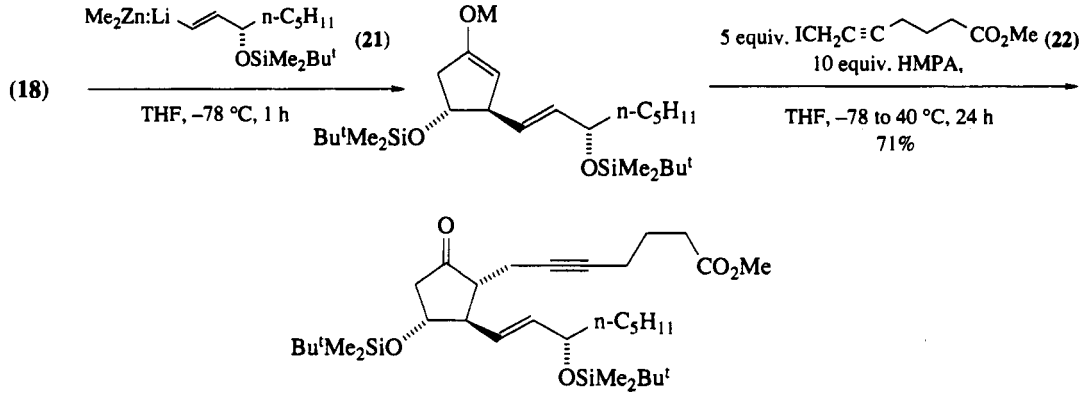
Noyori and coworkers[47] have provided an elegant solution to the problem of enolate equilibration by transmetallation of the enolate obtained from addition of the homochiral phosphine-complexed vinylcopper reagent (**19**) to the protected homochiral 4-hydroxycyclopentenone (**18**), with tri-*n*-butyltin chloride, followed by addition of the alkylating agent (**16**). This sequence gave the PGE_2-type product (**20**) in 78% yield along with 3% of the C-8 epimer (Scheme 13). Likewise, the propargylic iodide related to (**16**) provided a 5,6-didehydro-PGE_2 derivative in 82% yield, but use of methyl 7-iodoheptanoate as the alkylating agent provided only a 20% yield of the corresponding PGE derivative. It was found that halide ions must be present in the medium for alkylation to proceed; thus, penta- or hexa-valent tin species may be involved.

An interesting and simple variation on the three-component coupling protocol for prostaglandin synthesis has been recently reported by Noyori and coworkers.[26] This variation involved conjugate addition of a reagent formed from a 1:1 mixture of dimethylzinc and the (*E*)-vinyllithium reagent (**21**) to the enone (**18**), followed by alkylation of the enolate intermediate with the propargylic iodide (**22**) to give



Scheme 13

the prostaglandin derivative (**23**) in 71% overall yield (Scheme 14). The remarkable ability of dimethylzinc to suppress proton transfer reactions of lithium enolates is further illustrated by this experiment.



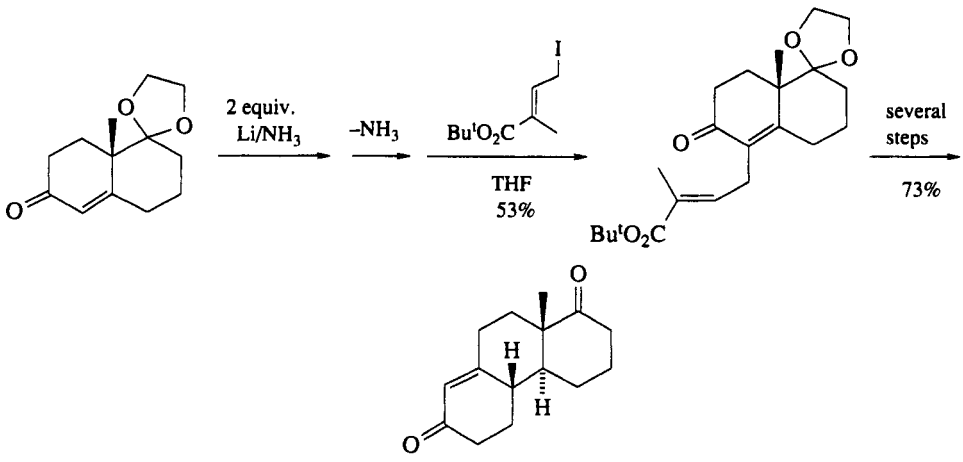
(**23**)

Scheme 14

In related work, Johnson and Penning showed that the vinylcopper reagent (**19**) added to a homochiral protected 4,5-dihydroxycyclopent-2-enone to give an enolate intermediate, which upon trapping with the (*Z*)-allylic iodide (**16**) in the presence of HMPA gave a 2,3-dialkylated precursor of (–)-PGE$_2$ methyl ester in good yield.[48] Apparently, the presence of the oxygen substituent at C-5 of the starting enone reduces the rate of enolate equilibration and allows alkylation to occur at the 2-position.

Regiospecific alkylations have been employed in the synthesis of a large number of alkylated decalones, hydrindanones and tricyclic and steroidal ketones.[1] Regiospecific annulations are often carried out by: (i) regiospecific α-alkylation of a specific enolate with an electrophilic reagent containing latent 2- or 3-ketoalkyl functionality; (ii) transformation of the side chain into a 1,4- or 1,5-diketone; and (iii) formation of a ring by an intramolecular aldol condensation.[49] (*E*)-3-Trimethylsilyl-2-butenyl iodide[50] and *t*-butyl γ-iodotiglate[51] are some of the more useful alkylating agents for this purpose. The requisite lithium enolates are often generated by lithium–ammonia reduction of α,β-unsaturated ketones or cleavage of TMS enol ethers with methyllithium. The use of kinetically generated 1-enolates of *trans*-2-decalones in sequences of this type provide important routes to phenanthrene derivatives, which are useful intermediates in steroid total synthesis (Scheme 15).

Base-promoted alkylations of bicyclic ketones such as 1-decalones and 1-hydrindanones give largely nonangular alkylated products. The application of blocking groups at the 2-position provided an early approach to angular alkylations of such systems.[1,52,53] However, angularly alkylated ketones can be prepared from appropriate lithium enolates generated by indirect methods.[8,18,54] These enolates exhibit a diastereofacial bias toward the formation of *cis*-fused products. A possible explanation for this is presented in Section 1.1.2.2.



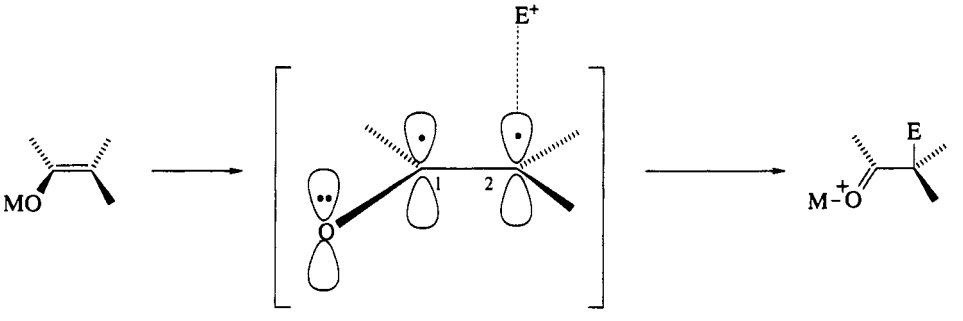
Scheme 15

The focus of this section has been upon uncatalyzed α-alkylations of metal enolates with alkylating agents bearing leaving groups at sp^3-hybridized carbon atoms. However, in certain cases where conventional alkylations give poor results, palladium(0)-catalyzed regioselective allylations of complex potassium[55,56] and lithium[57] triethylboron, zinc,[58] trialkyltin[59,60] and other enolates[58] have been accomplished with relatively inert reagents, *e.g.* allylic acetates. These reactions proceed *via* nucleophilic attack of the metal enolate on a π-allylpalladium complex formed by oxidative addition of the allylic reagent to palladium. The reactions of trialkyltin enolates may involve the intermediacy of 'ate' complexes.[60]

α-Arylations and α-vinylations of metal enolates also provide regioselective routes for carbon–carbon bond formation. The literature on this subject prior to 1978 has been reviewed.[61] More recent work in this area has involved palladium-catalyzed reactions of trialkyltin enolates with aryl[62,63] and vinyl bromides.[62]

1.1.2.2 Stereochemistry of Enolate Alkylations

Existing evidence indicates that *C*-alkylations of metal enolates with common electrophiles proceeds by an S_N2-type mechanism; that is, the highest occupied molecular orbital (HOMO) of the enolate attacks the lowest unoccupied molecular orbital (LUMO) of the alkylating agent. Scheme 16 illustrates the principle of stereoelectronic control,[64,65] which states that the electrophile should approach in a plane perpendicular to the enolate to allow maintenance of maximum orbital overlap in the transition state (**24**) between the developing C—C bond and the π-orbital of the carbonyl group.



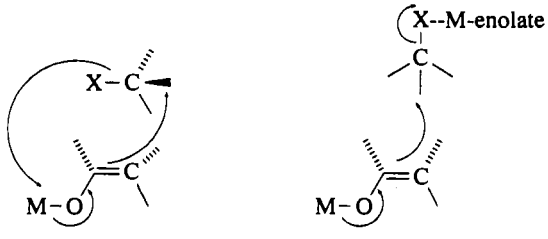
(24)

Scheme 16

Recent *ab initio* molecular orbital calculations indicate that the developing electrophile–C(1)–C(2) angle is actually larger than 90°.[21] However, they provide no evidence for the suggestion that the electro-

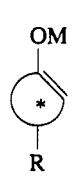
phile's trajectory is tilted away from perpendicularity to the enolate plane because of the repulsive interaction between the electrophile LUMO and the oxygen atom of the enolate HOMO.[66]

The suggestion that a cyclic six-membered ring transition state of the type (**25**), in which the metal cation assists the reaction by coordinating with the leaving group seems unlikely.[67] Such a transition state requires very unfavorable bond angles for an S_N2 displacement.[68] However, since enolate aggregates are likely to be present, the possibility exists that a transition state (**26**), related to (**24**), in which the cation of a second enolate ion-pair assists the reaction by coordinating with the leaving group, is involved.

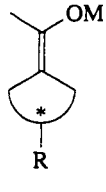


(**25**)

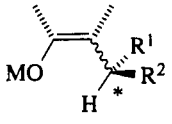
(**26**)



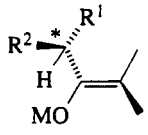
(**27**)



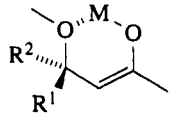
(**28**)



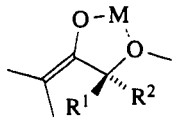
(**29**)



(**30**)



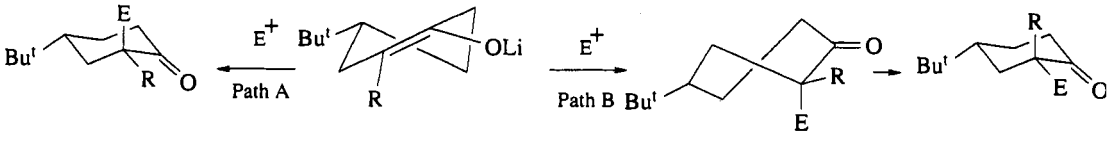
(**31**)



(**32**)

If the metal enolate contains a center of chirality, diastereoselection may be exhibited in the C—C bond formation process. Evans[2] has identified three classes of metal enolates in which chirality transfer may occur: (i) endo- and exo-cyclic enolates such as (**27**) or (**28**), which contain a chiral center (*) in a ring bonded to the enolate at two points; (ii) acyclic enolates such as (**29**) or (**30**), in which the moiety containing the chiral center (*) is bonded to the enolate at only one point; and (iii) chelated enolates such as (**31**) or (**32**), in which the chiral center is a part of the chelate ring. (*Z*)-Endocyclic enolates are also possible for large ring cyclic ketones.

The stereochemical outcome of alkylations can be ascribed to stereoelectronic and steric effects, including the influence of allylic strain[69] on metal enolate conformations. Metal enolate alkylations are strongly exothermic, and the results of many studies indicate that the transition states closely resemble the reactants.[1,2,4] Therefore, steric factors within the enolate play a dominant role in determining π-diastereofacial selectivity. This is illustrated in Scheme 17 for alkylation of the chiral lithium enolate of 4-*t*-butylcyclohexanone (**33a**), which can take place *via* path A, leading to a chair conformation (**34a**) of the product having the alkyl group axial to the ring and *trans* to the *t*-butyl group. Path B attack leads initially to a twist-boat conformation (**35a**), which may undergo conformational inversion to the chair conformation (**36a**) having the new group equatorial to the ring and *cis* to the *t*-butyl group. Paths A and B (Scheme 17) are normally referred to as axial and equatorial alkylation, respectively.



(**34**) (**33**) (**35**) (**36**)

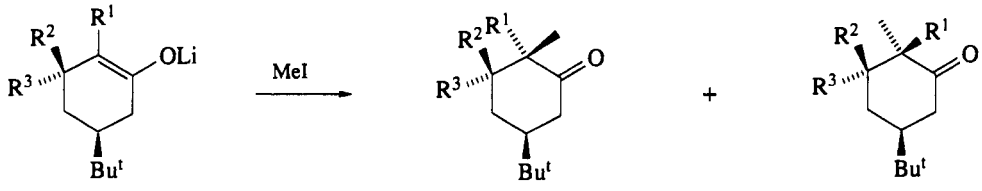
a: R = H
b: R = Me

Scheme 17

In the enolate (**33a**), the top and bottom π-faces of the molecule present about the same degree of steric hindrance to approach of the alkylating agent. However, if the transition state resembled the alkylation product, the thermodynamically more stable chair conformation (**34a**) would be expected to develop much faster than the less stable twist-boat conformation; thus, axial alkylation would be strongly

preferred. However, this is not the case. House *et al.*[70] reported that ethylation of (**33a**) with ethyl iodide in DME gave approximately equal amounts of axial and equatorial alkylation products. Similar results were obtained in the alkylation of (**33a**) with methyl iodide.[71] More recent studies on the stereochemistry of alkylation of (**33a**) under carefully controlled conditions and on the alkylation of the corresponding tetraalkylammonium enolate have indicated that there is a small, but apparently real, preference for axial alkylation. For example, axial:equatorial product ratios of 74:26[72] and 70:30[28] have been reported for the reaction of (**33a**) and the corrsponding 'naked' enolate with methyl iodide in THF. If equilibration of the product mixture occurred during alkylation, the axial:equatorial alkylation ratio would be reduced. Perhaps this accounts for the lower ratios obtained in the earlier studies. As expected, alkylations of the lithium enolate (**33a**) were less stereoselective when more reactive alkylating agents than methyl iodide were used.[70,72] Also, when the counterion was varied, the axial:equatorial ratio was shown to follow the order: Li > Na > K.[72] However, the cation effect was quite small.

Lithium enolates having α-methyl substituents, such as (**33b**) and the related species (**37b**), derived from 5-*t*-butylcyclohexanone, show a somewhat greater stereoselectivity of axial alkylation than the corresponding α-unsubstituted compounds.[73] For example, the enolate (**37a**) gave the products (**38a**) and (**39a**) in a 68:32 ratio upon treatment with methyl iodide in THF, while the 2-methyl-substituted derivative (**37b**) gave an 83:17 mixture of (**38b**) and (**39b**) upon reaction with trideuteriomethyl iodide in DME (Scheme 18).[73] Similarly, a greater stereoselectivity for axial alkylation has been observed for other α-substituted enolates compared with their counterparts lacking α-substituents.[71,74–78]

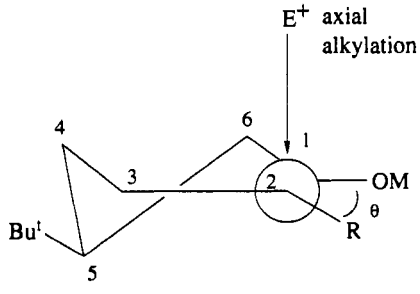


(**37**) (**38**) (**39**)

a: $R^1 = R^2 = R^3 = H$	68:32
b: $R^1 = Me$, $R^2 = R^3 = H$	83:17
c: $R^2 = Me$, $R^1 = R^3 = H$	25:75
d: $R^3 = Me$, $R^1 = R^2 = H$	96:4

Scheme 18

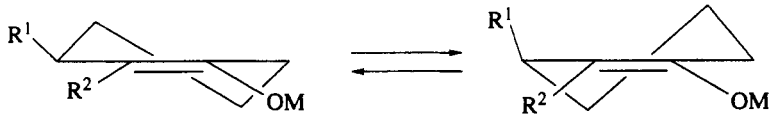
As depicted in (**40**), House and Umen have proposed that 2-substituted enolates undergo distortion in order to relieve interactions between the R group and the OM substituent and to avoid eclipsing ($A^{1,2}$-strain)[69] of the OM group by the 6-quasiequatorial group (hydrogen) and of the R group by the 3-quasiequatorial group (hydrogen). Thus, some rehybridization of the *p*-orbital at C-2 toward an sp^3-orbital should occur. In such a distorted species, the top π-face of the enolate should be more open to attack by an electrophile than the bottom π-face.[73]



(**40**)

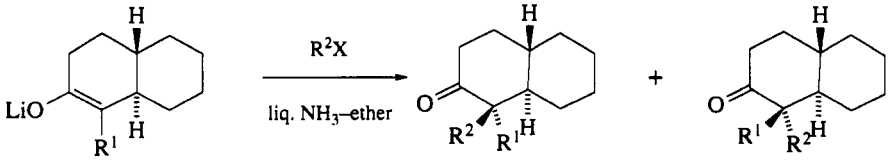
Quasiaxial and quasiequatorial substituents at C-6 in conformationally rigid lithium enolates such as (**33a**) have a very small effect on the stereoselectivity of the reaction.[71,72] In the case of the lithium 1-enolate of *cis*-3-methyl-5-*t*-butylcyclohexanone (**37c**), the steric effect of the quasiequatorial methyl group at C-3 and the stereoelectronic preference of axial alkylation oppose each other, and equatorial alkylation is preferred by 3 to 1. However, in the *trans* isomer (**37d**), where the C-3 methyl group is quasiaxial, these effects reinforce each other and axial alkylation is significantly favored by 24 to 1 (Scheme 18). Relatively rigid 1-enolates of 2-substituted cyclohexanone derivatives having quasiequatorial substituents at C-6[77] or C-3[74–76,78] show an enhanced tendency toward axial alkylation. In such systems, the dihedral angle θ in structure (**40**) should increase even more with the placement of bulky groups at C-6 and C-3.[73] The stereoselectivity of alkylations of sterically congested enolates such as those derived from 2,6-dimethyl-6-phenyl- and 2-methallyl-6-methyl-6-phenyl-cyclohexanone[77] is probably best accounted for by equatorial alkylation of a conformation of the 1-enolates having the 6-phenyl groups quasiaxial.[2]

The results of several studies (*cf.* Scheme 9) show that alkylations of conformationally mobile 1-enolates of 3-alkyl- and 2,3-dialkyl-cyclohexanones give products having the new groups at C-2 *trans* to the groups at C-3 with stereoselectivities in the 75 to 95% range.[41,44,45,79] Enolates of this type may exist as an equilibrium mixture of conformations (**41**) and (**42**). Conformation (**42**), having the 3-alkyl quasiaxial, is likely to be quite important, particularly when an alkyl group is present at C-2, because $A^{1,2}$-strain would destabilize conformation (**41**), which has a 3-alkyl group quasiequatorial. Steric interactions involving the 3-alkyl group and the approaching electrophilic reagent appear to be minimized in either of the two possible transition states which lead to the introduction of the new group *trans* to the C-3 substitutent. However, it is somewhat surprising that the stereoselectivity in favor of the *trans* product is apparently somewhat greater for the allylation of the C-2-unsubstituted enolate (**41a**) ↔ (**42a**) than for the 2-methyl enolate (**41b**) ↔ (**42b**).[45,79]



(**41**) a: R^1 = Me, R^2 = H (**42**)
b: R^1 = R^2 = Me

The results of methylations of lithium 1(2)-enolates of (**43a**)[75] and (**43b**)[76] of *trans*-2-decalones are shown in Scheme 19. An enolate such as (**43**) may be regarded as a special case of a conformationally rigid 3-alkylcyclohexanone derivative. As in the case of *t*-butylcyclohexanone derivatives such as (**37**), the presence of a substituent at the α-position of the enolate significantly increases the stereoselectivity in favor of axial alkylation. This may be attributed to a distortion of the enolate, which forces the methyl group at C-1 downward to relieve its interaction with the OLi group and the quasiequatorial 8-methylene group.[73] A tricyclic lithium enolate related to (**43a**) was found to undergo axial alkylation almost exclusively.[80]



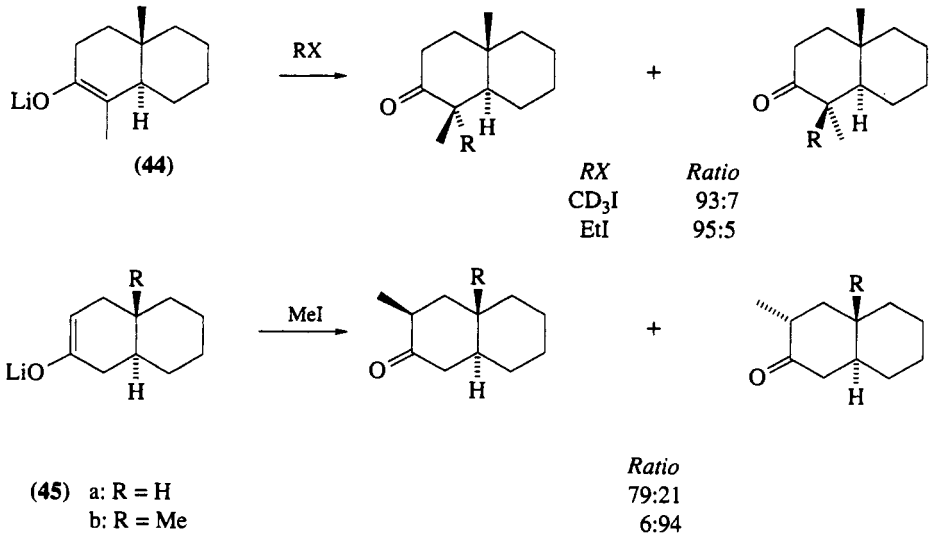
(**43**) a: R = Me
b: R = D

Compound	*R^2X*	*Ratio*
(**43a**)	CD_3I	83:17
(**43a**)	EtI	>95:<5
(**43b**)	MeI	40:60

Scheme 19

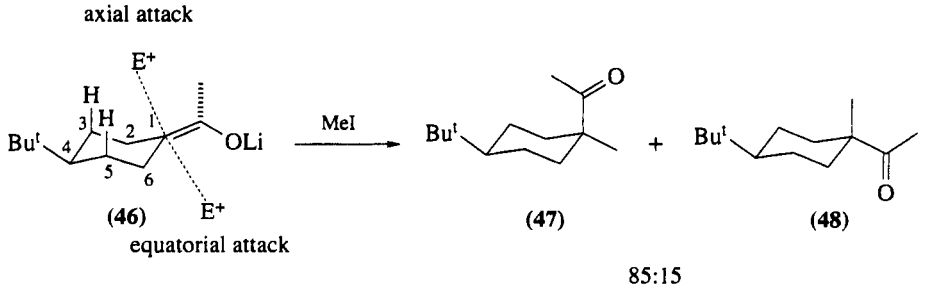
A comparison of the data for alkylation of the 10-methyl-2-decalone lithium enolate (**44**)[75] with those for enolate (**43a**) clearly shows that if axial alkylation involves development of a 1,3-interaction with an

axial methyl group, equatorial alkylation is the major pathway (Scheme 20). Likewise, alkylations of lithium 2-enolates of *trans*-2-decalones (**45a**) and (**45b**) gave largely axial and equatorial methylation products, respectively (*cf.* Scheme 20).[72]



Scheme 20

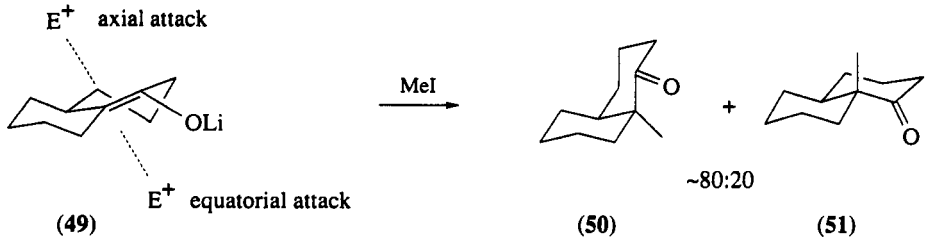
Methylation of the conformationally rigid exocyclic enolate (**46**) derived from 4-*t*-butylcyclohexyl methyl ketone has been shown to yield an 85:15 mixture of products (**47**) and (**48**) derived from equatorial and axial attack of the electrophile, respectively (Scheme 21).[81] In species such as (**46**) geometric factors associated with a stereoelectronically controlled approach to either π-face of the enolate are very similar. It has been suggested that the interaction of the filled *p*-orbital at C-1 with the vacant symmetrical antibonding orbital of the C(2)—C(3) and C(5)—C(6) bonds causes an increase in electron density on the equatorial π-face of the enolate and favors approach of the electrophile from that side.[82] However, the more generally accepted argument is that in a reactant-like transition state the axial hydrogen atoms at C-3 and C-5 hinder axial attack, while equatorial attack is relatively unencumbered.[81]



Scheme 21

Angular alkylations of the lithium 1(9)-enolate (**49**) of 1-decalone with methyl iodide in liquid ammonia–ether[8] or DME[54] have been shown to yield a mixture of products in which the *cis* isomer (**50**) is favored by 4:1 or 5:1 over the *trans* isomer (**51**; Scheme 22). The 10-methyl derivative of (**49**) also has been reported to give *cis*-9,10-dimethyl-1-decalone exclusively upon methylation.[45] In systems such as (**49**) the enolate double bond is exocyclic to the six-membered nonoxygenated ring. Thus, the same factors that control the stereochemistry of alkylation of simple exocyclic enolates such as (**46**) are likely to be involved. In the axial approach pathway, the electrophile would experience a 1,3-interaction with the axial hydrogen atoms at C-4, C-5 and C-7. Thus, the equatorial approach pathway, which is less sterically hindered, is preferred. The observation that alkylation of (**49**) with the highly reactive alkylation agent trimethyloxonium 2,4,6-trinitrobenzenesulfonate gave 95% of the *cis*-fused ketone (**50**), is in keep-

ing with this explanation.[54] Under these conditions, the transition state should resemble the reactant enolate to an even greater extent than when methyl iodide is employed as the alkylating agent.

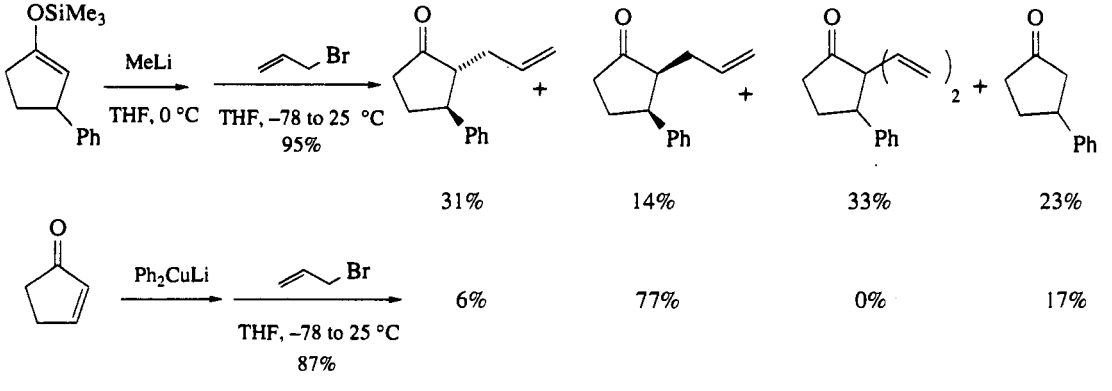


Scheme 22

Angular alkylations of 1-decalone enolates provide important models for angular alkylations of 18-nor-D-homo steroids. The manner in which structural modifications influence *cis*:*trans* product ratios in alkylations of various enolates of 1-decalones containing blocking groups at C-2 has been thoroughly investigated[52] and reviewed.[1]

Angular alkylations of lithium enolates of hydrindanones with carbonyl groups in the five-[83] or six-membered ring[84] yield *cis*-fused products with almost complete stereoselectivity. The lithium enolate of bicyclo [2.2.1]heptan-2-one undergoes *exo* alkylation with very high stereoselectivity.[72,85] The presence of a *syn* methyl group at C-7 reduces the preference for *exo* alkylation, but it is still preferred over *endo* alkylation by about 3:1 unless a 5,6-double bond is also present;[72] then, *endo* attack is preferred.[86,87] The expected steric effects control the stereochemistry of alkylation of other bridged bicyclic systems.[8,88]

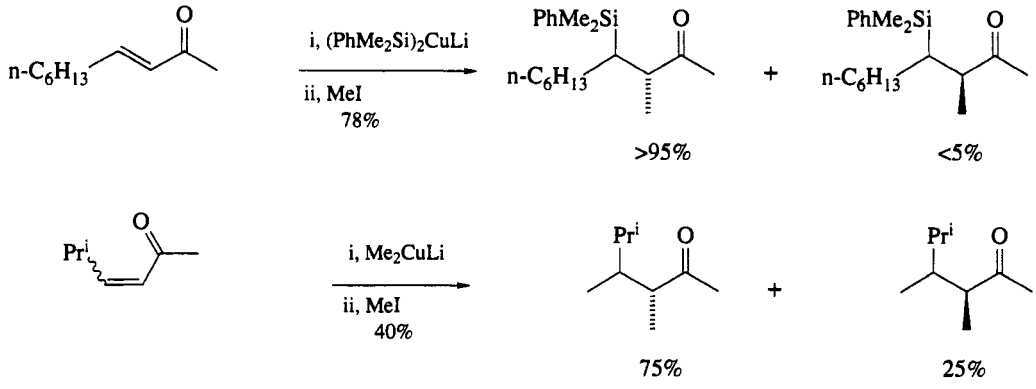
The results presented in Schemes 11 to 14, as well as numerous other studies,[89–91] show that alkylations of 1-enolates of 3-alkyl- and 3-alkenyl-cyclopentanones usually yield *trans*-2,3-disubstituted cyclopentanones with high stereoselectivity. As shown in Scheme 23, the stereoselectivity of alkylation of the 1-enolate of 3-phenylcyclopentanone is dramatically affected by the presence of copper(I) in the medium. Similar results have been obtained for the corresponding 3-methyl-3-phenylcyclopentanone enolates. On the basis of ^{1}H and ^{13}C NMR evidence and on the results of deprotonation of 3-phenylcyclopentanone with strong bases, Posner and Lentz[27] have proposed that lithium–arene coordination occurs in the enolates that would be present in the reactions shown in Scheme 23 as well as related cyclohexanone enolates. It was proposed that this complexation directs alkylation at C-2 to occur primarily *cis* to the phenyl ring at C-3 in both lithium and 'copper' enolates, but that the presence of copper(I) in the medium retards equilibration of the 2,3-*cis* product to the more stable 2,3-*trans* product. It should be noted that the extent of diallylation was greatly diminished in the presence of copper(I) species compared with the lithium enolate alone. Alkylation was found to occur *trans* to the phenyl group when a methyl substituent was present at C-2.



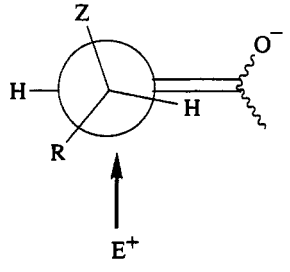
Scheme 23

Extraannular chirality transfer has been observed for alkylations of acyclic ketone enolates having chiral β-carbon atoms (Scheme 24).[92,95] In these reactions, methylation occurs *anti* to the β-dimethylphenylsilyl and β-isopropyl groups with good to excellent diastereoselectivity. Variation in the size of the

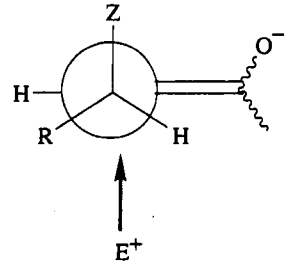
alkyl group at the β-carbon atom of β-silicon-substituted enolates has indicated that the preference for *anti* attack to silicon is probably electronic in origin. In the transition states for alkylation, *anti* attack of the electrophile may occur on a conformation of the enolate such as (**52**) with the hydrogen atom eclipsing the double bond and the larger groups staggered,[92–94] or a conformation such as (**53**) with the more electron-releasing β-substituent perpendicular to the plane of the enolate.[96] Recent studies by McGarvey and Williams on alkylations of chiral ester enolates indicate that the latter type of transition state is likely to be more favorable.[97] Further discussion of extraannular and chelate-enforced chirality transfer is provided in Sections 1.1.6.3 and 1.1.6.4.



Scheme 24



(**52**) a: Z = $SiMe_2Ph$, R = $n\text{-}C_6H_{13}$
b: Z = Pr^i, R = Me



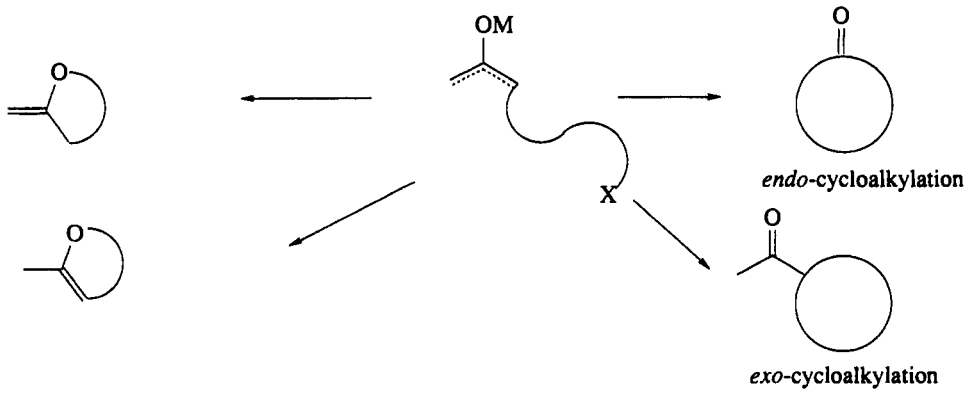
(**53**) a: Z = $SiMe_2Ph$, R = $n\text{-}C_6H_{13}$
b: Z = Pr^i, R = Me

1.1.2.3 Cycloalkylation Reactions of Saturated Ketones

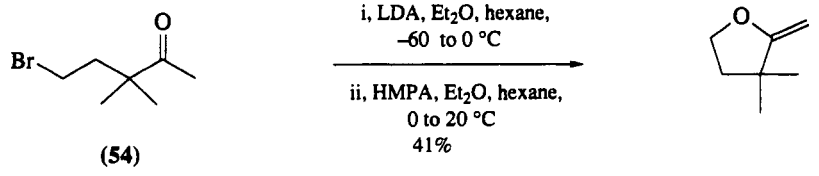
Cycloalkylation reactions have been utilized for the synthesis of a variety of cyclic compounds including monocyclic, fused-ring, spirocyclic and bridged systems. These reactions require the generation of an enolate in the presence of a suitably disposed leaving group (halide, tosylate, epoxide, *etc.*). Possible modes of cycloalkylation are represented in Scheme 25. If the transition state for *C*-alkylation is strained, *O*-alkylation becomes a competitive process. Traditionally, sodium or potassium enolates were employed for these reactions, but, more recently, lithium enolates, generated by treatment of the substrate with bulky, non-nucleophilic bases, have been generally utilized.

Ketone enolate cycloalkylations may be used to form small to medium and even larger rings under appropriate conditions. Space limitations permit only a few examples of these reactions to be covered here. The literature prior to 1978 has been reviewed.[1]

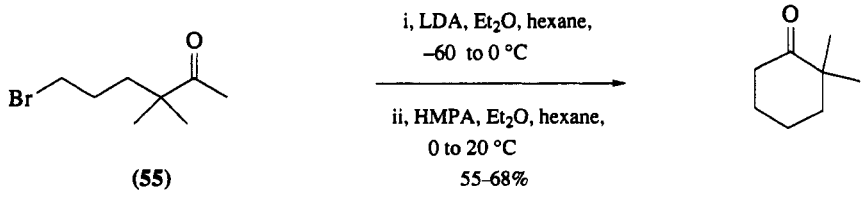
Detailed studies on the modes of cycloalkylation of the terminal lithium enolates of 5-bromo-3,3-dimethyl-2-pentanone (**54**) and 6-bromo-3,3-dimethyl-2-hexanone (**55**)[98,99] have shown that (**54**) undergoes exclusively *O*-cycloalkylation, while (**55**) undergoes only *C*-cycloalkylation (Scheme 26). The transition states for the two modes of alkylation are shown in formulas (**56**) and (**57**). In the *C*-alkylation, the electrophilic ω-carbon atom must approach the enolate α-carbon perpendicularly along a path colinear with the C—Br bond that undergoes cleavage. This pathway is highly strained when $n = 0$ or 1 and *O*-alkylation, which can take place *via* attack of the basic *syn* nonbonding electron pair lying in the plane of the enolate, is favored. When $n = 2$ or larger the *C*-alkylation transition state can be easily attained and this pathway becomes favored.



Scheme 25

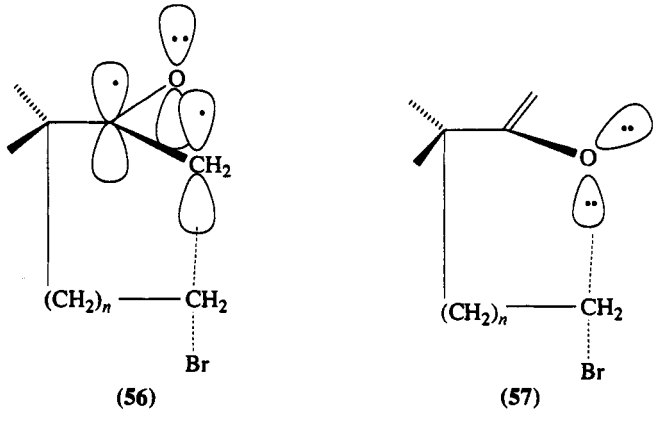


(54)



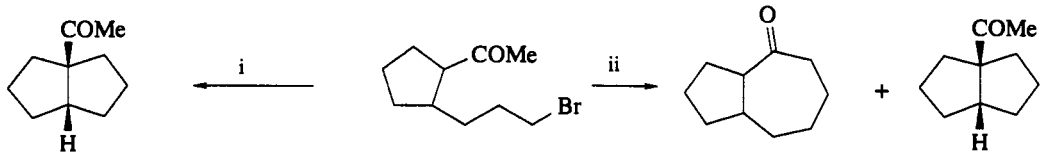
(55)

Scheme 26



(56) **(57)**

Scheme 27 illustrates how different conditions of enolate formation may affect the outcome of cycloalkylation reactions.[100] Deprotonation of the bromo ketone (**58**) under equilibrating conditions with potassium *t*-butoxide in *t*-butyl alcohol resulted in *exo* cycloalkylation *via* the more-substituted metal enolate to give the 5,5-fused bicyclic ketone (**59**) in good yield. On the other hand, when (**58**) was treated with LDA in THF under kinetic conditions, deprotonation occurred at the terminal position and *endo* cycloalkylation was faster than enolate equilibration and gave the 5,7-fused ketone (**60**), also in good yield. The conversions of 3(2-tosyloxyethyl)cyclohexanone to bicyclo[2.2.2]octan-2-one[101] and of 3(2-tosyloxyethyl)-[102] and 3(2-bromoethyl)-cyclopentanones[103] to the corresponding bicyclo[2.2.1]heptan-2-ones provide additional examples of cycloalkylations which lead to bridged ring systems.

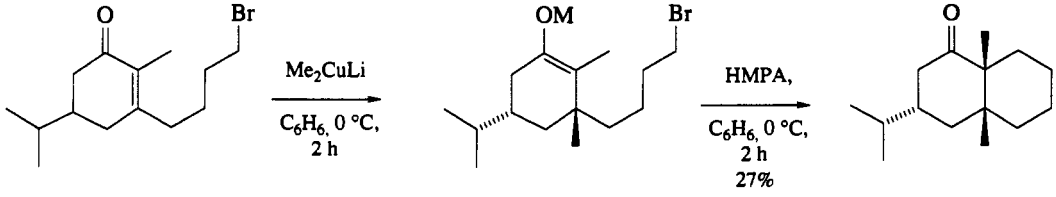


(59) 86–94% (58) (60) 77–84% (59) 2%

i, Bu^{t}OK, Bu^{t}OH, pentane, 25 °C, 30 min ; ii, LDA, THF, –72 to 65 °C, 2 h

Scheme 27

Exo cycloalkylations have been used to synthesize *cis*-1-decalones. For example, treatment of 2-methyl-3(4-tosyloxybutyl)cyclohexanone with sodium *t*-pentylate in benzene gave *cis*-9-methyl-1-decalone (**50**) in 60% yield.[104] Also, as shown in Scheme 28, conjugate addition–cycloalkylation was employed to synthesize a *cis*-fused decalone related to the sesquiterpene, (±)-valerane.[41] Apparently, in these cases, the enolate intermediate adopts a conformation having the 4-bromobutyl side chain quasi-axial, and C—C bond formation occurs *via* equatorial attack to give initially a twist-boat conformation of the product.



Scheme 28

In addition to (±)-valerane, a wide variety of other sesquiterpenes, including (±)-ishwarane,[105] (±)-ishwarone,[106] copaene,[107] ylangene,[107] (±)-seychellene[108,109] (±)-sativene,[110] (±)-longifoline,[111] (±)-copacamphene,[112] (±)-damsin,[113] (±)-$\Delta^{9(12)}$-capnellene,[114] (±)-pentalenene,[115] (–)-β-vetivone[116] and (±)-β-eudesmol[117] have been synthesized by pathways involving cycloalkylation of saturated ketone enolates.

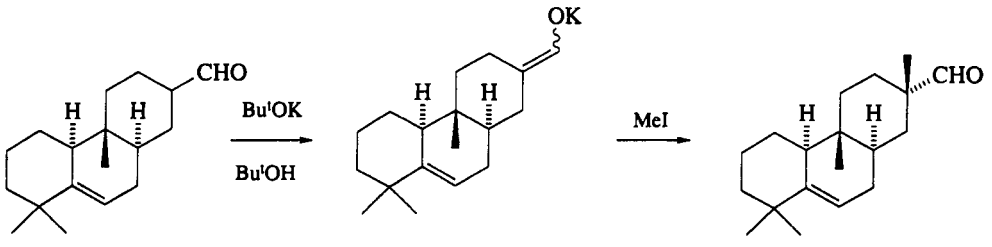
1.1.2.4 Alkylations of Metal Enolates of Saturated Aldehydes

Because of their tendency to undergo self (aldol) condensations, Cannizzaro and Tichshenko reactions, the direct alkylation of aldehydes *via* metal enolates has numerous drawbacks.[118] Indeed, poor results have been obtained, even with preformed lithium enolates.[118] However, much better yields have been achieved through the use of enolates derived from less or more electropositive metals than lithium. In early experiments in this area, Odic and Pereyre showed that tri-*n*-butyltin aldehyde enolates, prepared by reaction of aldehyde enol acetates with tri-*n*-butyltin methoxide, were *C*-alkylated in good yields with reactive alkylating agents in THF–HMPA.[119] Although these reactions were slower than those of alkali metal enolates and higher temperatures and longer reaction times were required, *O*-alkylation was not a problem. It was also shown by Jung and Blum that the tri-*n*-butyltin enolate of acetaldehyde could be alkylated by this method.[120] Later, van der Gen and coworkers[121] found that potassium enolates of α,α-disubstituted aldehydes, such as 2-methylpropanal and 2-ethylhexanal, prepared by reaction of the substrate with potassium hydride in THF, were rapidly *C*-alkylated in good yields with reactive alkylating agents at room temperature. When less reactive primary and secondary iodides were used, there was a significant amount of competition between *C*- and *O*-alkylation. When aldehydes containing two α-protons were employed, mixtures of mono- and di-alkylated products were produced because of rapid proton exchange between the alkylated products and the starting enolates. Aldol condensations probably occur in these reactions, but, because potassium is a relatively poor chelating cation, there is likely to be a mobile equilibrium between the potassium aldolate and the enolate so that the alkylation step can proceed to completion.

Aldehydes that contain only one α-hydrogen atom may be alkylated in reasonable yields with reactive alkylating agents such as methyl iodide, allyl chloride or benzyl chloride in an emulsion of benzene and 50% aqueous sodium hydroxide in the presence of a catalytic amount of a tetra-*n*-butylammonium

salt.[122] When less reactive alkylation agents were employed or when the aldehyde contained bulky α-substituents, aldol condensations and/or *O*-alkylations became significant problems.

Aldol condensations of more complex aldehydes are often sufficiently slow to allow successful alkylation reactions. There are numerous examples of aldehyde enolate methylations in the field of natural product synthesis.[123,124] As shown in Scheme 29, the methylation of a tricyclic aldehyde, which was employed in the synthesis of (±)-rimuene, provides an illustrative case.[123] As expected for an exocyclic enolate intermediate such as (**61**), the methyl group was introduced equatorial to the six-membered ring with a high degree of stereoselectivity. α-Alkylated aldehydes may be prepared efficiently by alkylations of enamines, Schiff base anions, hydrazone anions and other methods. A discussion of this methodology is provided in Section 1.1.5.

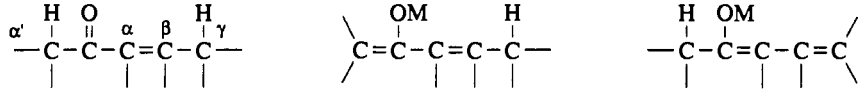


(**61**)

Scheme 29

1.1.3 ALKYLATIONS OF METAL DIENOLATES OF α,β-UNSATURATED KETONES

α,β-Unsaturated ketones of the general structure (**62**), which contain α′- and γ-protons undergo deprotonation with strong bases under kinetic control to yield cross-conjugated metal dienolates such as (**63**).[1] Under thermodynamic conditions, extended metal dienolates such as (**64**) are produced.[1]

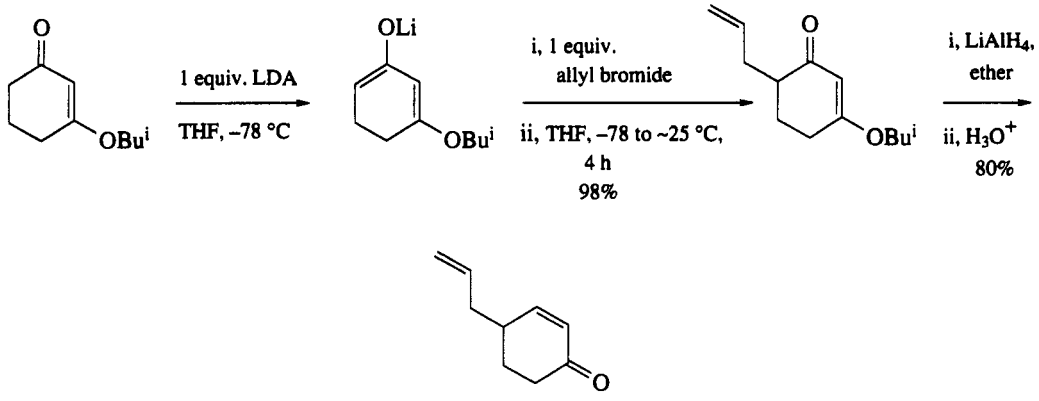


(**62**) (**63**) (**64**)

A variety of lithium dialkylamide bases can be used to produce cross-conjugated lithium dienolates, which may then be alkylated with even less reactive alkylating agents, *e.g.* propyl iodide, in good to excellent yields without equilibration to the corresponding extended dienolates.[125] α′-Alkylations of cyclohex-2-enones, certain cyclopent-2-enones, 1(9)-octalin-2-ones and steroidal 4-en-3-ones have been accomplished by this procedure.[1]

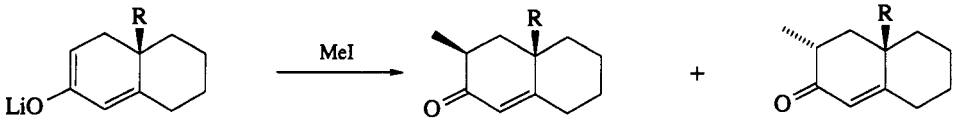
Stork and Danheiser have developed a highly useful procedure for the synthesis of 4-alkylcyclohex-2-enones, which involves α′-alkylations of cross-conjugated lithium dienolates of 3-alkoxycyclohex-2-enones, followed by metal hydride reduction of the carbonyl group and hydrolysis (Scheme 30).[126] Numerous applications of this procedure have been reported.[1,127,128] Two different alkyl groups may be introduced at the 6-position of a cyclohex-2-enone derivative without difficulty.[127] While dialkylation is generally not a problem in alkylations of cross-conjugated dienolates of cyclohex-2-enones, it was observed when relatively acidic 3-chlorocyclohex-2-enones were employed.[129]

A comparison of the data shown in Scheme 31 for methylations of cross-conjugated lithium dienolates of 1(9)-octalin-2-ones (**65a**) and (**65b**) with those shown in Scheme 20 for the corresponding decalone 2-enolates (**45**) reveals that the tendency for axial β-attack is significantly greater in the former systems.[66,130] Similar results have been obtained in alkylations of related steroidal cross-conjugated dienolates.[131] Two explanations for these results have been offered: (i) the cross-conjugated dienolate systems can easily adopt a relatively low energy quasi-*cis* conformation with the β-face exposed to electrophilic attack;[130,131] or (ii) the effect of the 1,9-double bond in species such as (**65**) could alter the trajectory of attack of the electrophile on the HOMO of the dienolate (*cf.* formula **24**).[66] However, Agami *et al.* showed that the cross-conjugated dienolate (**66**), isomeric with (**65b**), gave exclusively the product of equatorial methylation, *i.e.* α-attack at C-1.[130] The electronic factor would be expected to increase the degree of axial alkylation of (**66**) relative to the corresponding simple enolate (**44**). Since this was not



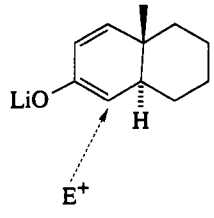
Scheme 30

found to be the case, the conformational factor seems to be the better explanation for the results of the alkylations of (**65a**) and (**65b**).[130]



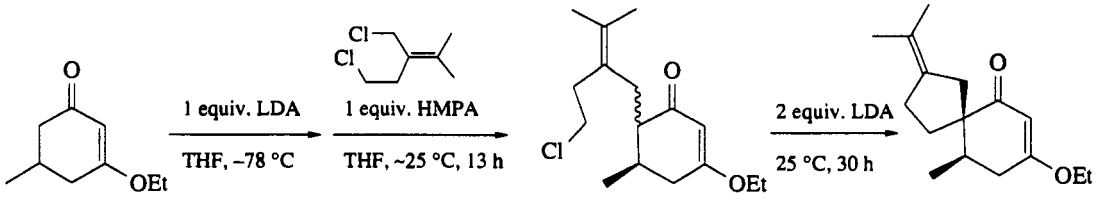
(**65**) **a**: R = H 93:7
(**65**) **b**: R = Me 50:50

Scheme 31



(**66**)

By the use of appropriate dialkylating agents, it is possible to spiroannulate cyclohex-2-enones at the 6-position *via* kinetic lithium dienolates. This method was used by Stork *et al.*[132] to prepare the enone (**67**), a key intermediate for the total synthesis of (±)-β-vetivone (Scheme 32). In the cycloalkylation step the cross-conjugated dienolate presumably adopts a conformation with the 5-methyl group quasiaxial to the ring to avoid $A^{1,2}$-strain and the new C—C bond is formed *trans* to this group.



(**67**)

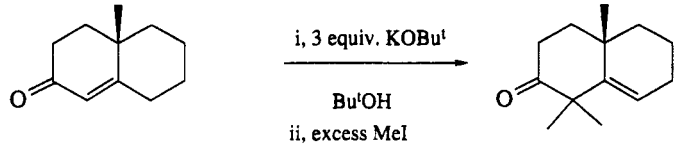
Scheme 32

Although the reaction failed with cyclopent-2-enone itself, methylations of kinetic lithium dienolates of 3-alkylcyclopent-2-enones have been carried out in acceptable yields.[133] Intramolecular α′-alkylations

of 5,6- and 6,6-fused ring bicyclic α,β-unsaturated ketones bearing 2-bromoethyl groups at the angular positions have been reported.[134] A total synthesis of (±)-clovene has been accomplished using an intramolecular α′-enolate cycloalkylation of 4-(3-chloropropyl)-4-methyl-6-(2-ethylallyl)cyclohex-2-enone to give 5-(2-ethylallyl)-1-methylbicyclo[3.3.1]non-2-en-4-one as a key step.[135]

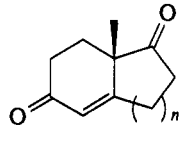
In general, the thermodynamically stable extended dienolates (**64**) have been prepared by deprotonation of enones (**62**) with sodium or potassium alkoxides in protic solvents or with sodium or potassium hydride in aprotic solvents.[1,2,4,49] Kinetically formed cross-conjugated lithium enolates may be converted into the corresponding extended systems in the presence of excess ketone but in certain cases equilibration is quite slow.[136] Presumably, because the π-electron density is higher at the α-carbon than the γ-carbon, extended dienolates normally react with alkylating agents to produce α-alkyl-β,γ-unsaturated ketones.[137]

If the α-position of an extended dienolate is unsubstituted, dialkylation may be an important reaction or, under certain conditions, the major reaction, particularly when reactive alkylating agents, *e.g.* methyl iodide, are employed.[138] Equation (5) provides an example of the synthetic utility of the dimethylation process.[139] Ringold and Malhotra have provided a detailed mechanism to account for the facile dialkylation of these systems.[138] Briefly, deprotonation by bases present in the medium converts the initially formed α-alkylated β,γ-unsaturated ketone to its dienolate, which then undergoes a second alkylation faster than the β,γ-double bond is isomerized to the α,β-position. When the alkylating agent is of low reactivity or its concentration is limited by dropwise addition, the rate at which the double bond moves into conjugation becomes faster than the second alkylation step. As is described in Section 1.1.5.1, extended lithiated dienamines are the nucleophilic reagents of choice for α-methylation of α,β-unsaturated ketones.[140]

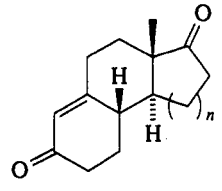


77% (5)

With less reactive alkylating agents monoalkylation of extended dienolates at the α-position is feasible. In connection with the total synthesis of steroids, dienolates of bicyclic enones such as (**68a**) and (**68b**), or various derivatives of the saturated carbonyl function of these compounds, have been alkylated with a variety of reagents containing latent 3-ketoalkyl functionality.[49] The products of these reactions may be converted into tricyclic enones such as (**69a**) and (**69b**). Even diannulating agents which allow elaboration of both the A and B rings of the steroid skeleton have been utilized.[49]



(**68**) a: $n = 1$
b: $n = 2$

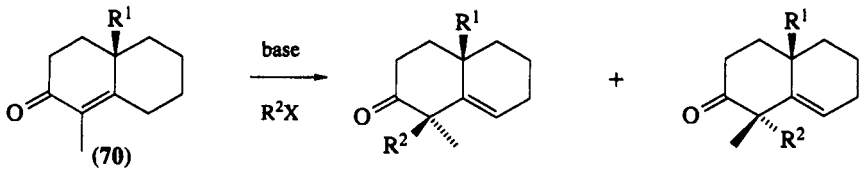


(**69**) a: $n = 1$
b: $n = 2$

Normally *C*-alkylation occurs predominantly in reactions of alkali metal extended dienolates with the usual alkylating agents in solvents of low to medium polarity. However, highly reactive benzyloxymethyl halides yield extensive amounts of *O*-alkylation products;[141] when highly polar solvents are used *O*-alkylation may occur even with unreactive alkylating agents.[142] As expected, the *C*-alkylation:*O*-alkylation ratio is influenced by: (i) the polarity of the solvent; (ii) the nature of the alkylating agent; and (iii) the nature of the metal cation.

The stereochemistry of alkylations of extended dienolates of enones such as (**70**) has been extensively investigated (Scheme 33).[141,143] In general, the results are similar to those found for the related decalone enolates (**43a**) and (**44**), *i.e.* steric factors within the anion play a dominant role. Thus, axial attack is preferred with (**70**; R^1 = H), but equatorial attack is strongly favored when an angular methyl group is present (**70**; R^1 = Me). There is a modest preference for axial alkylation when an angular ethoxycarbonyl

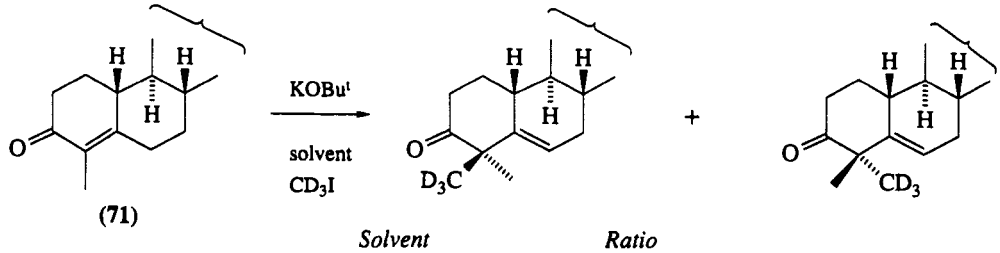
group is present, as in (**70**; $R^1 = CO_2Et$). This effect has been attributed to the polar nature of the angular ester group, but since an ethoxycarbonyl group is smaller in size than a methyl group, an explanation based upon steric effects alone possibly can apply.



R^1	*Base (solvent)*	R^2X	*Ratio*
H	$KOBu^t$, PhH	CD_3I	70:30
Me	$KOBu^t$, PhH	CD_3I	10:90
Me	NaH, dioxane	$PhCH_2OCH_2Cl$	16:84
CO_2Et	NaH, dioxane	$PhCH_2OCH_2Cl$	67:33

Scheme 33

As shown in Scheme 34, a rather profound solvent effect on dienolate alkylation diastereoselectivity has been noted for the steroidal enone (**71**).[143] Such large solvent effects have not been documented for other systems. Possible explanations based upon the position of the transition state along the reaction coordinate and/or 'specific' solvation of the dienolate have been advanced to account for preferential axial alkylation in benzene and equatorial alkylation in *t*-butyl alcohol.[143] However, in view of the fact that the degree of aggregation of the dienolate as well as the structure of the aggregates may be modified considerably in going from one solvent to the other, rationalization of the results is difficult.



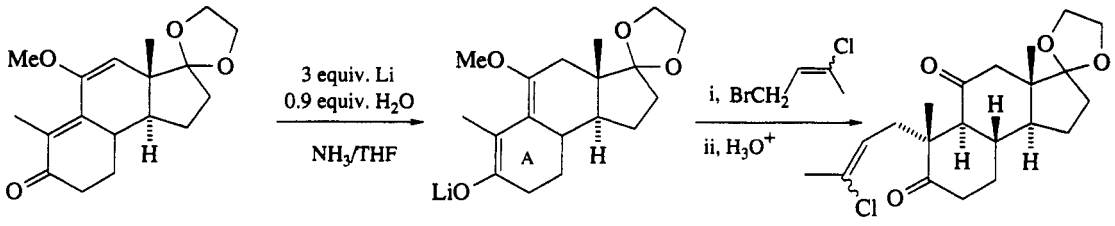
Solvent	*Ratio*
PhH	70:30
Bu^tOH	9:91

Scheme 34

Stork *et al.* have shown that heteroannular extended dienolates such as (**73**), which contain substituents at both the α- and γ-positions, undergo predominantly equatorial alkylation (Scheme 35).[144] The dienolate (**73**) was produced by lithium–ammonia reduction of the tricyclic dienone (**72**) and the product of its alkylation with 1-bromo-3-chloro-2-butene and hydrolysis of the resulting enol ether, *i.e.* (**74**), was a key intermediate in a short, highly stereoselective synthesis of (±)-adrenosterone. It was pointed out that equatorial alkylation is obtained with dienolates such as (**73**) and related compounds because a *peri* interaction (Me ↔ OMe) of the α- and γ-substituents forces the ring A to adopt a half-boat conformation in which the α-face of the π-system is accessible to attack.

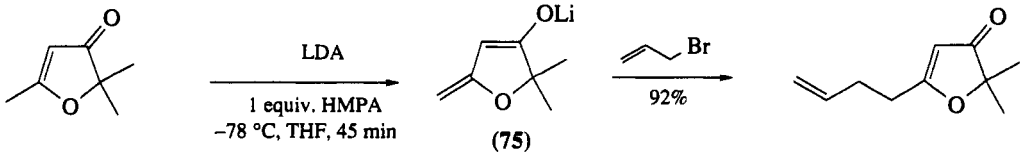
γ-Alkylations of extended dienolates of β-amino-α,β-cyclopentenones,[145] β-amino-α,β-cyclohexenones[136,146] and related acyclic systems[147] have been reported. Koreeda and coworkers[148] have found that deprotonation of β-alkoxy-α,β-cyclopentenones with LHDS in THF gave dienolates, which underwent regioselective γ-alkylations. However, attempted γ-alkylations of β-alkoxy- or β-thioalkoxy-α,β-cyclohexenones were unsuccessful.[146,149]

As shown in Scheme 36, 2,2-disubstituted-5-alkyl-3(2*H*)-furanones also undergo γ-alkylation *via* their extended dienolate intermediates (**75**).[149] Similarly, 4-isopropyl-6-methyl-(2*H*)-pyran-2-one, which may be regarded as a vinylogous 5-alkyl-3(2*H*)-furanone, was deprotonated and alkylated at the methyl group.[150]



(72) (73) (74)

Scheme 35



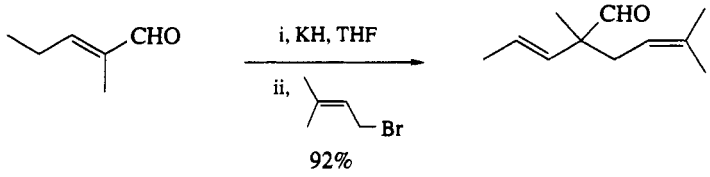
(75)

Scheme 36

The reason γ-alkylations occur in certain systems having heteroatom β-substituents is unclear. The electron density at the γ-carbon of the dienolate may be enhanced through conjugation with the unshared electron pair on the heteroatom. The presence of an exocyclic β,γ-double bond in systems such as (**75**) seems to be an important structural requirement for γ-alkylation.[149]

The reader is referred to two reviews for numerous examples of intramolecular γ-alkylations of ketone dienolates.[1,2] Lansbury *et al.* have achieved some success in synthesizing γ-alkylated α,β-unsaturated ketones *via* the use of dienolates of γ-benzenesulfonyl enones[151] and trilithiated derivatives of α′-benzenesulfonyl enones[152] as nucleophiles.

Potassium hydride in THF is the base–solvent combination of choice for preparing dienolates of α,β-unsaturated aldehydes. These enolates are more stable than the corresponding saturated aldehyde enolates.[121] Equation (6) shows that excellent yields of α,α-disubstituted β,γ-unsaturated aldehydes can be obtained by trapping α-substituted aldehyde potassium dienolates with allylic halides.



(6)

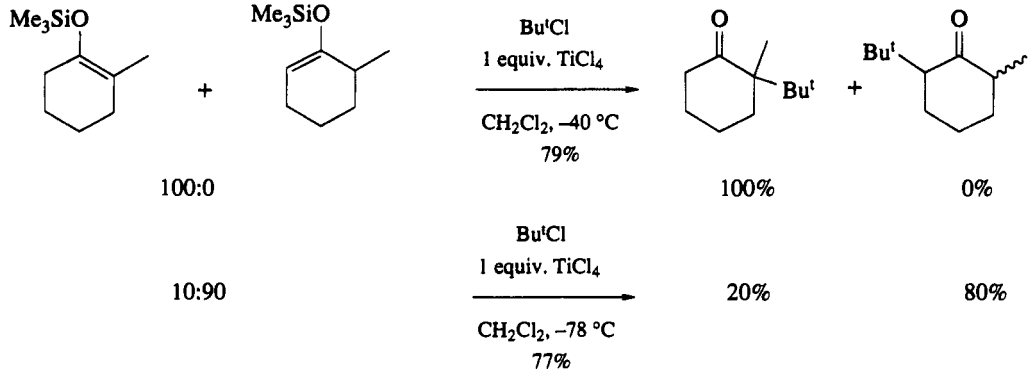
1.1.4 ALKYLATIONS *VIA* SILYL ENOL ETHERS AND OTHER ENOL DERIVATIVES

As discussed in Section 1.1.2, *C*-alkylations of metal enolates are restricted to the use of relatively S_N2-reactive alkylating agents. Loss of regioselectivity, failure of the reaction, or at least poor yields are observed with alkylating agents that undergo the S_N2 reactions slowly and/or are prone to elimination. A significant advance in *C*-alkylation chemistry was made when it was shown that silyl enol ethers, and also enol esters and alkyl enol ether derivatives of ketones and aldehydes, are effective nucleophiles for combination with S_N1-reactive alkylating agents in the presence of Lewis acids.[12,153–157] The most commonly used Lewis acid catalysts are titanium tetrachloride and zinc bromide. Methylene chloride is used as the solvent. Experimentally, best results are obtained by adding the Lewis acid catalyst to a mixture of the enol derivative and the alkylating agent.[156,158] TMS triflate is also an effective catalyst for this type of reaction.[159]

Tertiary halides, acetates and methyl ethers, aryl-activated secondary halides, prenyl halides and acetates, acetals, ketals, thioacetals, α-chloroalkyl ethers, and, particularly, α-chloroalkyl phenyl sulfides have been widely used as alkylating agents. Such reagents may contain a variety of functional groups including alkenes, esters, halides, ketones, nitro groups and silyl ethers.

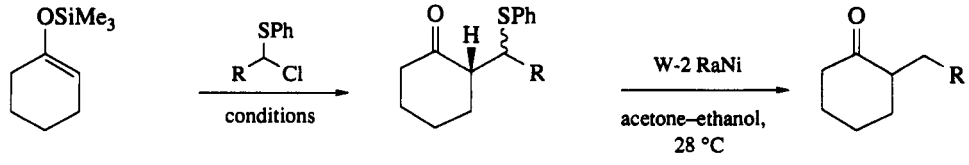
As illustrated in Scheme 37, using the data of Reetz *et al.*,[160] the more- and less-substituted TMS enol ethers of 2-methylcyclohexanone have been *t*-butylated with high regiospecificity and in good yields by this method. Paterson has also reported that titanium tetrachloride promoted phenylthioalkylations of the

more- and less-substituted trimethylsilyl enol ethers of a wide variety of unsymmetrical cyclic and acyclic ketones can be accomplished regiospecifically.[156] Loss of regioselectivity was not observed even for rather hindered systems.



Scheme 37

As shown in Scheme 38, several primary alkyl-substituted cyclohexanones have been prepared by Lewis acid catalyzed phenylthioalkylation of the TMS enol ether of cyclohexanone followed by reductive removal of a phenylsulfenyl group.[156] The two-step neopentylation sequence is particularly noteworthy. This methodology has been used to prepare numerous α-alkylated cyclic and acyclic ketones. α-Alkylated aldehydes can be produced in a like manner. α-Alkylidenation can also be accomplished by oxidative removal of sulfur.[156] Lee and coworkers have found that TMS triflate-catalyzed reactions of silyl enol ethers of cyclic ketones and aldehydes with saturated and unsaturated 1,1-dimethoxy-ω-trimethylstannanes, followed by addition of titanium tetrachloride, provide novel routes to fused and spirocyclic ring systems.[161] Phenylthiomethylstannylations of silyl enol ethers have also been reported.[162]



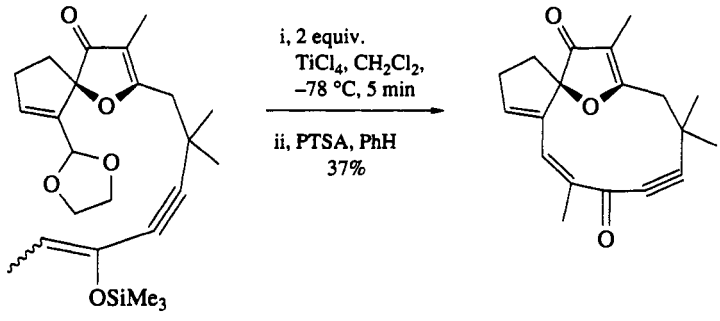
R	*Conditions*	*Yield* (%)	*Yield* (%)
Me	1.1 equiv. $TiCl_4$, CH_2Cl_2, –23 °C	78	95
Pr^n	1.1 equiv. $TiCl_4$, CH_2Cl_2, –23 °C	83	90
Pr^i	1.1 equiv. $TiCl_4$, CH_2Cl_2, –23 °C	66	91
Bu^t	0.02 equiv. $ZnBr_2$, CH_2Cl_2, 20 °C	78	93

Scheme 38

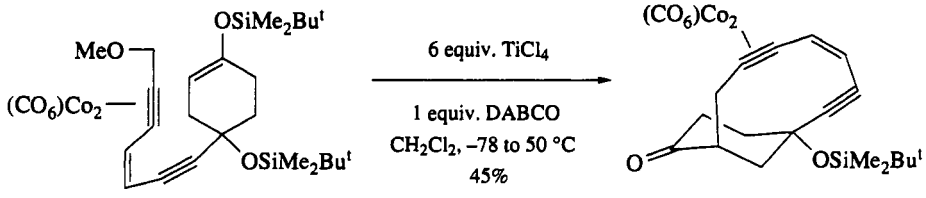
Studies pertaining to diastereoselectivity in Lewis acid catalyzed alkylations of enol derivatives have been limited. Reetz has reported that *t*-butylation of 1-trimethylsiloxy-4-*t*-butylcyclohex-1-ene gave an 85:15 mixture of *cis*- and *trans*-2,4-di-*t*-butylcyclohexanone, which could result from kinetic equatorial and axial alkylation, respectively. However, equilibration of the products, which would favor formation of the former isomer, was not ruled out. Titanium tetrachloride promoted phenylthiomethylation of the more-substituted TMS enol ether of 1-decalone gave a 4:1 mixture of *cis*- and *trans*-fused 1-decalones.[156] In this case, where equilibration of the product could not occur, the diastereoselectivity was similar to that of methylation of the corresponding lithium enolate (**49**).[8,54]

Lewis acid catalyzed intramolecular alkylations of silyl enol ethers containing S_N1-reactive functionality provide useful routes to a variety of carbocyclic systems.[163,164] Smith *et al.*[165] have employed an intramolecular Mukaiyama reaction of the enol derivative (**76**) to produce the tetracyclic system (**77**) (equation 7). This transformation was a key step in their elegant synthesis of jatrophone. The synthesis

demonstrated that the molecules involved in the reaction may contain some rather sensitive functionality and that intramolecular formation of large rings is possible. Cycloalkylation of a silyl enol ether has been reported by Magnus and Carter in connection with their research on the antitumor antibiotic esperamicin A (equation 8).[166] They found that upon treatment with titanium chloride the cobalt-complexed propargylic ether (**78**) gave the cyclization product (**79**) as a stable compound. Oxidative decomplexation of (**79**) produced an aromatized tricyclic ketone *via* a diynene intermediate. Lewis acid catalyzed intramolecular cyclizations of enol acetates, containing suitably disposed isopropenyl and isopropylidene groups capable of forming tertiary carbocations, have been employed in a creative manner in the synthesis of several complex natural products.[155]

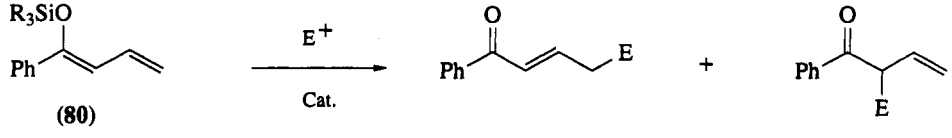


(76) (77) (7)



(78) (79) (8)

Unlike lithium dienolates, where α-alkylation is the rule in simple systems, Lewis acid catalyzed reactions of extended silyl dienol ethers with S_N1-reactive alkylating agents may give extensively or exclusively γ-alkylation products. Scheme 39 shows some selected data from the work of Fleming and coworkers who have thoroughly studied reactions of silyl enol ethers such as (**80**) derived from crotonophenone.[154] These results clearly show that the γ:α-alkylation ratio is increased by: (i) the use of alkylating agents, which give better-stabilized electrophilic species; and (ii) silyl dienol derivatives which contain electron-withdrawing groups on silicon.[154] The effect of a change in the Lewis acid was not very clear cut because overall product yields often changed dramatically. In other work, it was shown that when methyl groups are present at the γ-position of the dienol ether, the γ:α-ratio is reduced.[167]



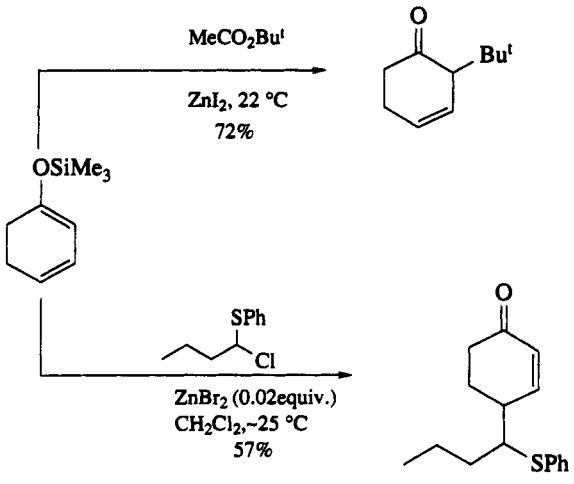
(80)

R	*E⁺/Cat.*	γ:α *Ratio*	*Yield* (%)
Me	$PhSCH_2Cl/ZnBr_2$	45:55	65
Ph	$PhSCH_2Cl/ZnBr_2$	86:14	93
Me	$(EtO)_2CMe_2$, $TiCl_4$	100:0	78

Scheme 39

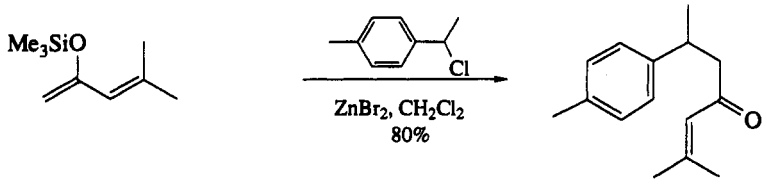
The position of alkylation of homoannular silyl dienol ethers is apparently dramatically influenced by the nature of the alkylating agent and catalyst. Reetz and coworkers[155] reported that 1-trimethylsiloxy-

1,3-cyclohexadiene is *t*-butylated exclusively at the α-position with *t*-butyl acetate/zinc iodide, while Fleming's research group[154] found that phenylthioalkylation of this compound occurred exclusively at the γ-position with 1-chloro-1-phenylthio-*n*-butane/zinc bromide (Scheme 40). The reasons for these contrasting results are unclear.



Scheme 40

Lewis acid catalyzed alkylations of cross-conjugated silyl dienol ethers provide routes to α′-alkylated ketones. A short synthesis of the sesquiterpene (±)-*ar*-turmerone has been accomplished using the cross-conjugated TMS dienol ether of mesityl oxide (equation 9).[168]



(9)

Palladium(0)-catalyzed α-allylations of TMS enol ethers can be carried out cleanly with allylic carbonates.[169] These reactions are highly regioselective, *e.g.* the more- and less-substituted TMS enol derivative of 2-methylcyclohexanone (*cf.* Scheme 37) gave 2-allyl-2-methylcyclohexanone and 2-methyl-6-allylcyclohexanone, respectively. Allylations of aldehyde silyl enol ethers occur similarly. Allylations of enol acetates occur with allyl carbonates in the presence of catalytic amounts of palladium(0) complexes and tri-*n*-butyltin methoxide.[169]

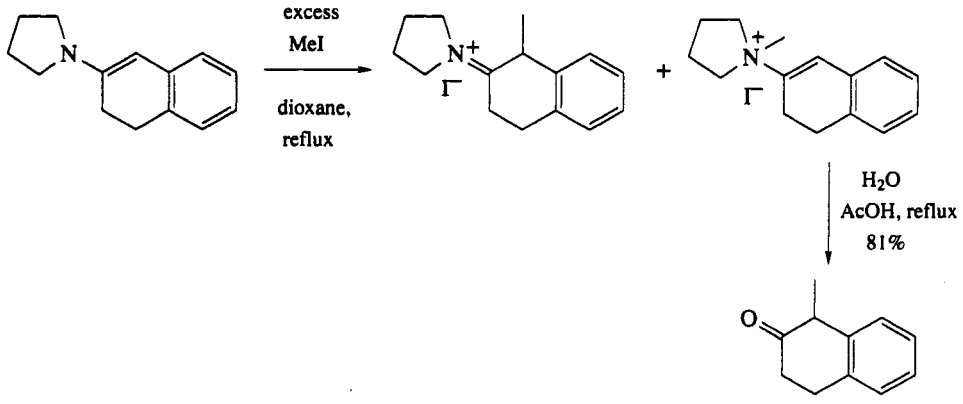
1.1.5 ALKYLATIONS OF CARBONYL COMPOUNDS *VIA* THEIR NITROGEN DERIVATIVES

1.1.5.1 Regiochemistry and Stereochemistry of Alkylations of Nitrogen Derivatives of Carbonyl Compounds

Prior to the discoveries that lithium and other less electropositive metal cations were valuable counterions for enolate alkylations, the Stork enamine reaction was introduced to overcome problems such as loss of regioselectivity and polyalkylation that plagued attempts to alkylate sodium or potassium enolates of ketones or aldehydes.[170–172] Methods of synthesis of enamines by reactions of ketones and aldehydes with secondary amines have been thoroughly reviewed.[171,172] Enamine alkylations are usually conducted in methanol, dioxane or acetonitrile. Enamines are ambident nucleophiles and *C*- and *N*-alkylations are usually competitive. Subsequent hydrolysis of the *C*-alkylated product (an iminium salt) yields an

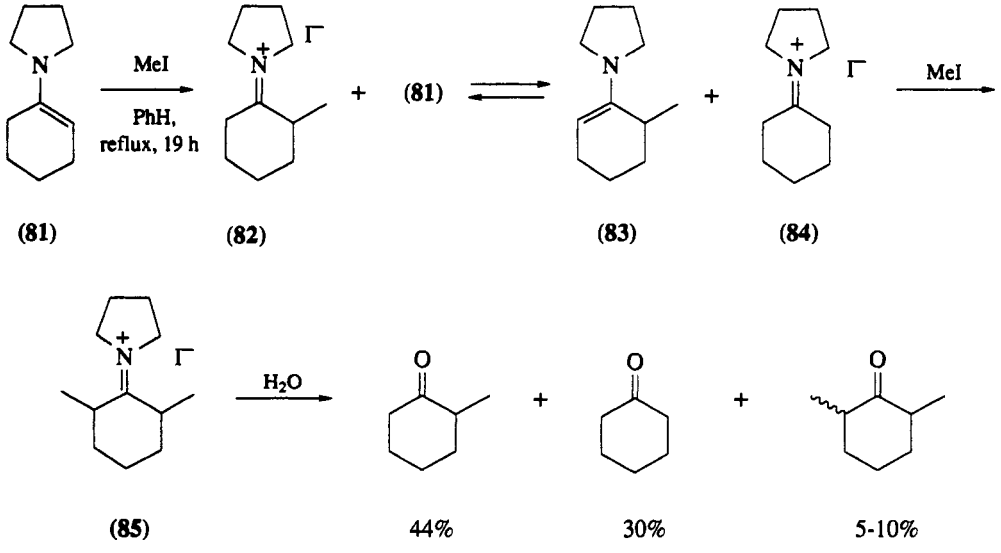
α-alkylated ketone, while the *N*-alkylated product (a quaternary ammonium salt) is usually water soluble and relatively inert to hydrolysis.

The monomethylation of the pyrrolidine enamine of β-tetralone shown in Scheme 41 provides a highly successful example of the reaction. Attempted alkylation of the ketone with 1 equiv. of methyl iodide in the presence of a strong base gave almost exclusively the recovered ketone and its dimethylated derivative.



Scheme 41

Although dialkylation was not a problem in the above case, it is frequently a significant side reaction. As illustrated in Scheme 42 for the pyrrolidine enamine of cyclohexanone (**81**), the initially formed *C*-alkylated iminium salt (**82**) can transfer a proton to the starting enamine to yield the enamine of the alkylated product, *e.g.* (**83**), which can be further alkylated to give the dialkylated iminium salt (**85**). As a result, the starting ketone (derived from the unalkylated iminium salt **84**), the monoalkylated product and the dialkylated product may be isolated after hydrolysis. Although dialkylation is not such a serious problem when higher molecular weight alkylating agents are used, because mono- and di-alkylated ketones can be separated by distillation, the yields in enamine alkylations are usually rather low.

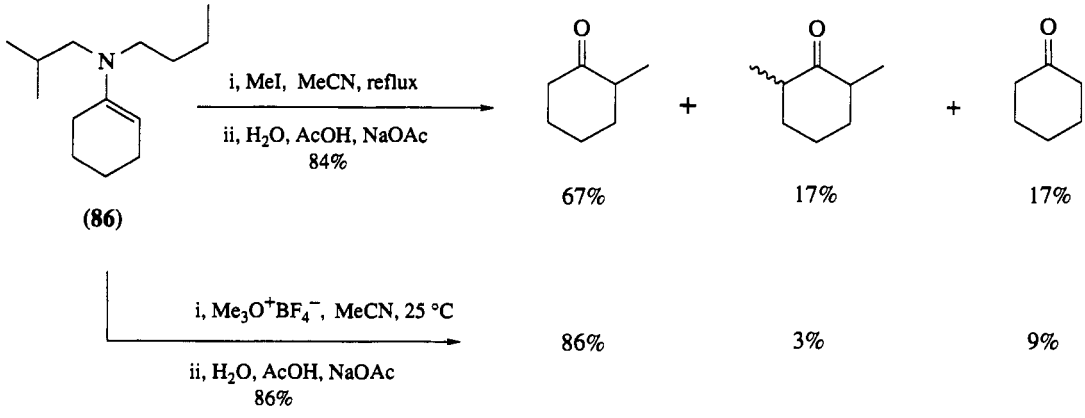


Scheme 42

When unreactive alkylating agents are reacted with enamines, both the *C*- and *N*-alkylation processes are essentially irreversible. However, strongly electrophilic reagents such as methyl iodide, allylic halides, benzylic halides, propargylic halides, α-halo ethers and α-halocarbonyl compounds and nitriles can undergo reversible *N*-alkylation. Thus, higher yields of *C*-alkylated products are obtained with these reagents. Allylic and propargylic groups are transferred from nitrogen to carbon by intramolecular 3,3-

sigmatropic rearrangements, but, in other cases, the process is intermolecular. In some cases, it has been found that the *C*- to *N*-alkylation product ratio may be increased by increasing the temperature.[173]

A comparison of the results of the methylation of the pyrrolidine enamine of cyclohexanone (**81**; Scheme 42) with those shown in Scheme 43 for the methylation of the *n*-butylisobutylamine derivative (**86**) shows that yields are improved with the latter compound.[174] Presumably, the more sterically hindered amine reduces the amount of *N*-alkylation and retards the rate of proton transfer between the *C*-alkylated iminium salt and the unreacted enamine.



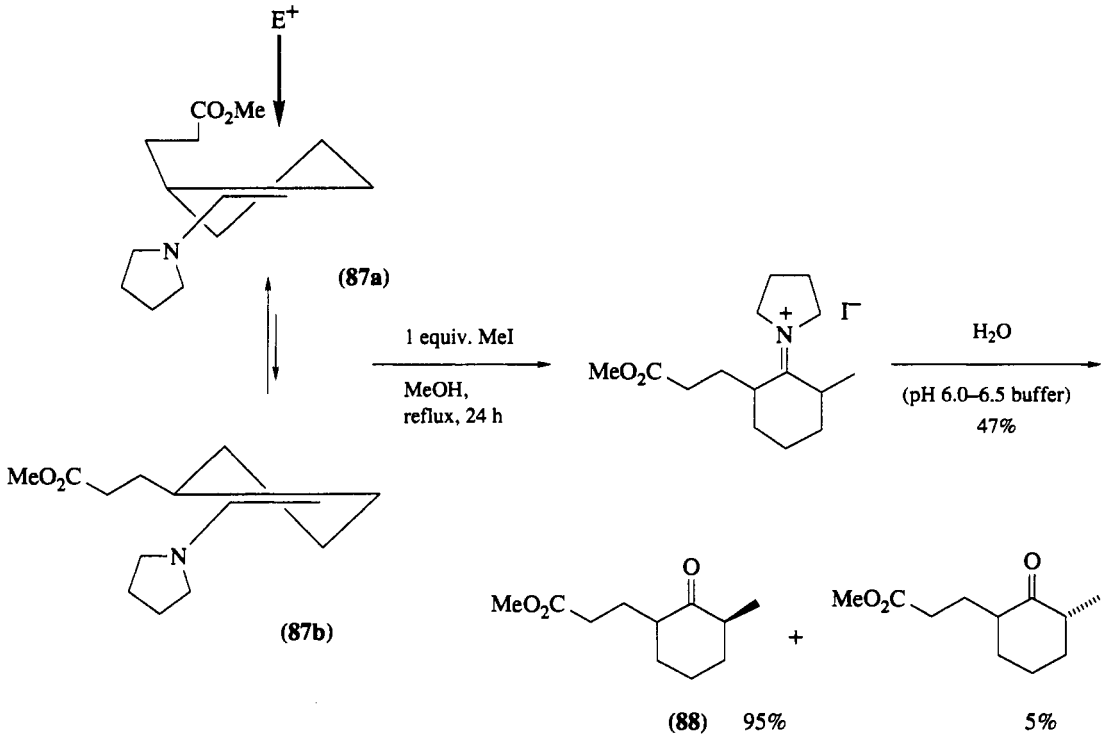
Scheme 43

In contrast to the results of base-catalyzed alkylations of sodium or potassium enolates under thermodynamic control, alkylations of enamines of unsymmetrical ketones occur largely or exclusively at the less-substituted α-position. More-substituted ketone enamines are destabilized relative to the less-substituted isomers by $A^{1,2}$-strain involving the substituents on the nitrogen atom and at the β-carbon atom. Although in most systems some of the more-substituted enamine is present in equilibrium with the less-substituted isomer, the former is less reactive toward *C*-alkylation because steric effects prevent effective overlap of the lone pair of electrons on nitrogen with the carbon–carbon π-bond.

Enamines are relatively unreactive nucleophiles and compared with metal enolates the transition states for their alkylations lie much closer to the products. Thus, the stereoelectronic effect is predominant and axial alkylation of cyclohexanone derivatives is observed.[175,176] There is such a high propensity for axial alkylation that it obtains even when a 1,3-interaction of the approaching electrophile and a quasiaxial substituent exists. Thus, methylation of the pyrrolidine enamine (**87**), which is expected to exist largely in the conformation (**87a**) having the C-6 side chain quasiaxial, gave largely the *cis*-2,6-disubstituted ketone (**88**) after hydrolysis under nonequilibrating conditions (Scheme 44).[176] It was considered unlikely that the *cis*-2,6-disubstituted product could have arisen by equatorial alkylation of the conformer (**87b**) of the starting enamine, which has the side chain quasiequatorial.

C-Alkylations of hindered aldehyde enamines can be effected with a variety of alkylating agents, but only allylic and benzylic reagents are useful for alkylations of unhindered systems.[177] Acyclic, homoannular and heteroannular dienamines undergo alkylation primarily at the α-positions.[170,178] As discussed above, reactions of enamines with electrophiles containing sp^3-hybridized carbon atoms have numerous limitations. On the other hand, enamine reactions with electrophilic alkenes are highly useful and have received wide coverage in the literature.[171]

In order to overcome some of the limitations of enamine alkylations and consequently those associated with metal enolate alkylations, Stork and Dowd introduced metallated imines as metal enolate equivalents in 1963.[179] These reagents, along with the closely related metallated hydrazones introduced by Stork and Benaim[140] and thoroughly investigated by Corey and Enders[180] and oxime dianions[172] provide the synthetic chemist with the potential of achieving an enormous amount of regiochemical and stereochemical control when synthesizing α-alkylated aldehydes and ketones.[171,172,181] Additionally, as described in Section 1.1.5.2, through the use of metallated imines and hydrazones derived from certain chiral, nonracemic imines and hydrazine derivatives, asymmetric syntheses of α-alkyl carbonyl compounds can be achieved with high enantioselectivity.



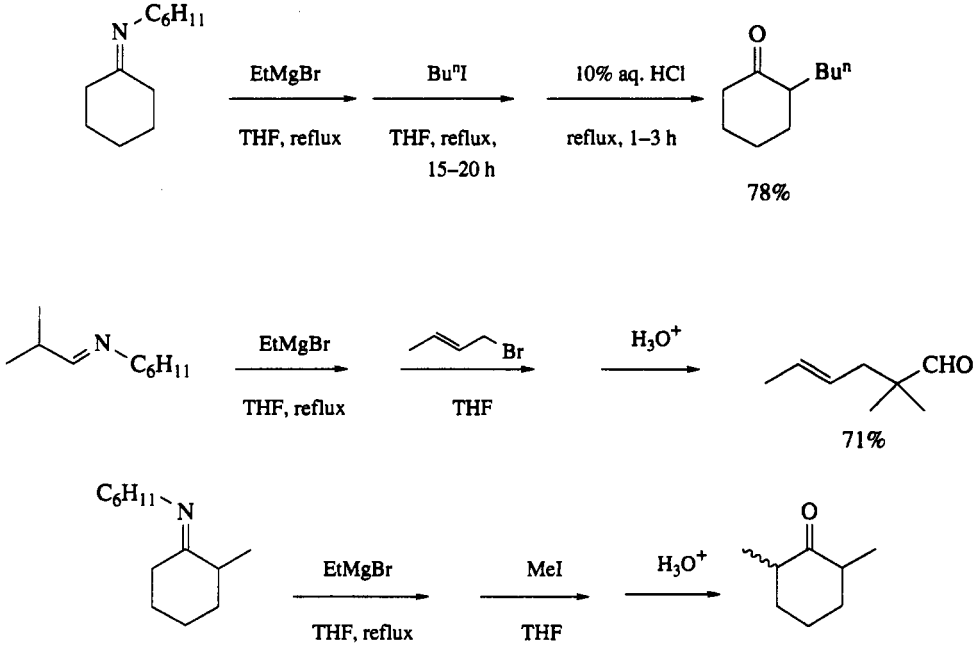
Scheme 44

Metallated imines can be formed from imines derived from enolizable carbonyl compounds by deprotonation with Grignard reagents or organolithium reagents, but more recent studies have generally involved the use of lithium dialkylamides, *e.g.* LDA, as the base. Alternative methods of producing metallated imines, *e.g.* addition of *t*-butyllithium to the imine double bond of 2-azadienes,[182] are known.

In their initial work, Stork and Dowd showed that halomagnesium imine alkylations offered the following advantages over enamine alkylations: (i) *C*-alkylations occurred in high yields with unreactive primary and secondary halides, even those prone to elimination; (ii) aldehyde derivatives were directly *C*-alkylated in high yields; (iii) alkylations usually occurred at the less-substituted α-position of unsymmetrical systems; and (iv) formation of the halomagnesium salt could be conducted in the presence of the alkylating agent, which allowed *in situ* generation and trapping of unstable species. Examples of these reactions are presented in Scheme 45. Lithiated imines often exhibit similar behavior to halomagnesium species, but the presence of the more electropositive metal cation, *i.e.* Li^+, allows alkylations to be conducted at much lower temperatures. The success of these reactions depends upon the fact that metallated imines undergo proton transfer reactions much more slowly than the corresponding metal enolates. Alkylations of metallated imines are usually conducted in THF or DME. Hydrolysis of the alkylated imine to the alkylated ketone can be effected with aqueous dilute mineral acids, aqueous acetic acid (recommended for aldimine hydrolysis),[118] or, if epimerizations of α-alkyl carbonyl compounds need to be avoided, slightly acidic aqueous buffered solutions.

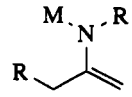
Whitesell and Whitesell[172] have tabulated some of the many types of electrophilic reagents that *C*-alkylate metallated imines. These are potent nucleophiles and undergo substitution reactions even with weakly electrophilic species such as epoxides and oxetanes. Lithiated ketimines and aldimines have been frequently used in reactions with alkylating agents containing latent 2-keto (or aldehydo) groups[183] or 3-keto (or aldehydo) groups.[184]

Recent research by Bergbreiter, Newcomb, Meyers and their respective coworkers[185] has shown that a variety of factors, such as the base, the temperature of deprotonation, and the size of the substituent on nitrogen, control the structure of the metallated imine and ultimately the regiochemistry of the alkylation reaction. In contrast to metal enolates, where the more-substituted species is usually the more thermodynamically stable, less-substituted *syn*-metallated ketimines, *e.g.* (**89**), are the most thermodynamically stable of the possible isomers of unsymmetrical systems. An explanation for the greater stability of *syn* imine anions compared with *anti* imine anions has been presented by Houk, Fraser and coworkers.[186]

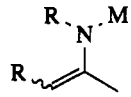


Scheme 45

They suggested that the latter species are destabilized by an electrostatic repulsion between the polar metal–nitrogen bond, which lies in the N—C=C plane and the imine β-carbon atom, which bears a substantial amount of negative charge. Because there is significant carbanion character at the β-carbon, the less-substituted *syn*-metallated ketimine (**89**) would be expected to be more stable than the more-substituted *syn* isomer (**90**).



(89)

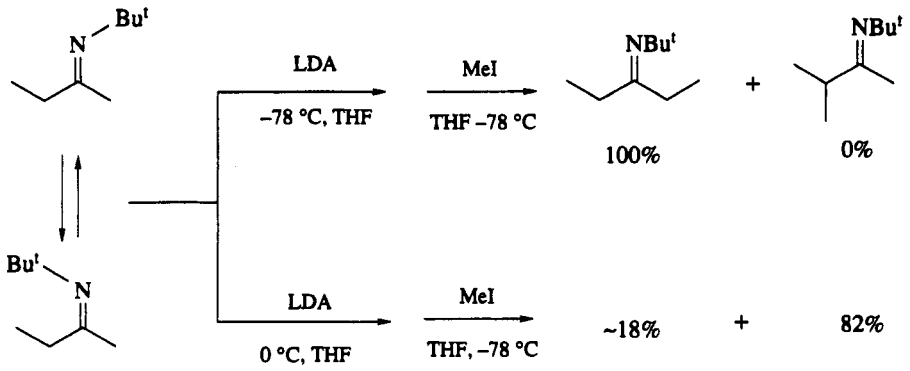


(90)

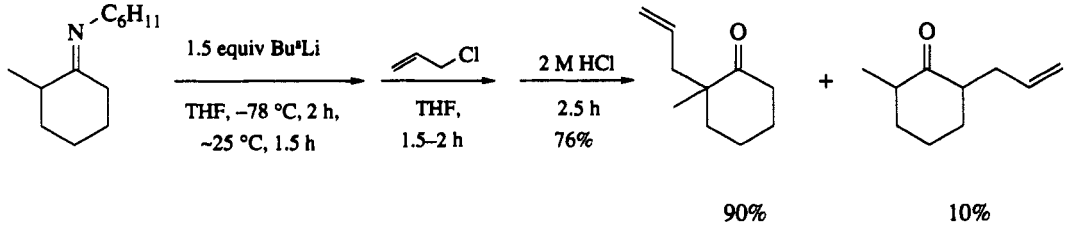
Ironically, species such as (**89**; M = Li) are also the major isomers obtained when unsymmetrical ketimines are deprotonated with LDA at –78 °C.[185] There is a kinetic preference for deprotonation *anti* to the substituent on nitrogen. At very low temperatures, deprotonations with LDA occur at the less-substituted carbon atom *via* the less stable (*Z*)-imine. Rearrangements then occur to the *syn*, less-substituted imine, which is in turn alkylated. On the other hand, deprotonations conducted at –23 to 0 °C with LDA are faster than imine isomerization and the imine anion mixture composition reflects the (*E*):(*Z*) ratio of the starting imine. *Anti–syn* imine anion isomerization occurs to give predominately the more-substituted *syn*-metallated imine (*cf.* **90**), which then undergoes alkylation. These results are summarized in Scheme 46 using the *t*-butylimine of 2-butanone as an example.

The first examples of alkylations at the more-substituted position of an unsymmetrical ketimine were actually reported by Hosomi *et al.*, who carried out deprotonations with alkyllithium reagents at lower temperatures (Scheme 47).[187]

Fraser *et al.* have shown that, unlike the corresponding lithium enolates, conformationally rigid lithiated imines such as (**91**) undergo axial alkylation almost exclusively (Scheme 48).[188] Reaction of (**91**) with methyl iodide at –78 °C gave 90% of the *syn* axial alkylation product (**92**). The small quantities of the *anti* axial (**93**) and *anti* equatorial products (**94**) obtained were considered to arise from isomerization of (**92**). Hydrolysis of the alkylated imine mixture gave largely *trans*-2-methyl-4-*t*-butylcyclohexanone. The preference for axial alkylation is so great that it even occurs when a quasiaxial methyl group is present at C-6 on the cyclohexane ring. Thus, further deprotonation and methylation of the mixture of (**92**)–(**94**) gave 94% of the 2,6-axial–axial dimethylation product and 6% of the 2,6-axial–equatorial isomer, which again probably arose *via* epimerization of the axial–axial product. Apparently, in these systems,

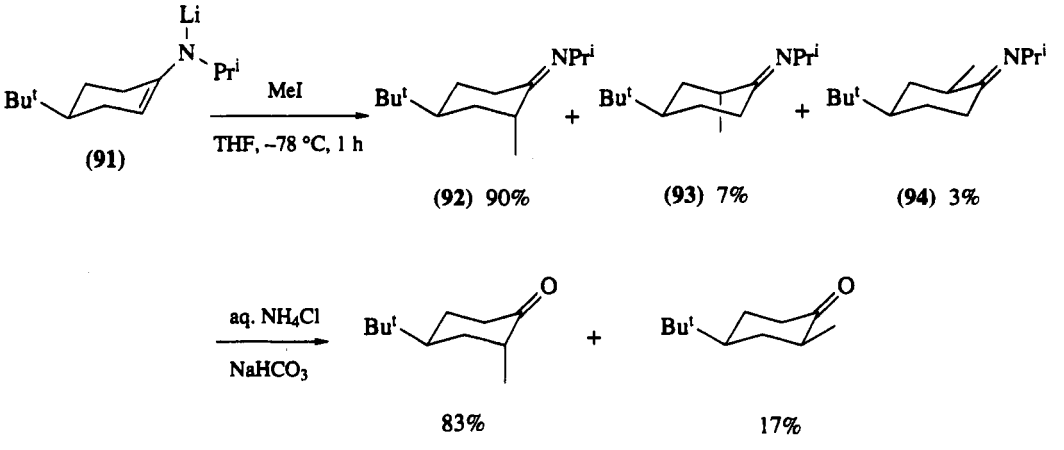


Scheme 46



Scheme 47

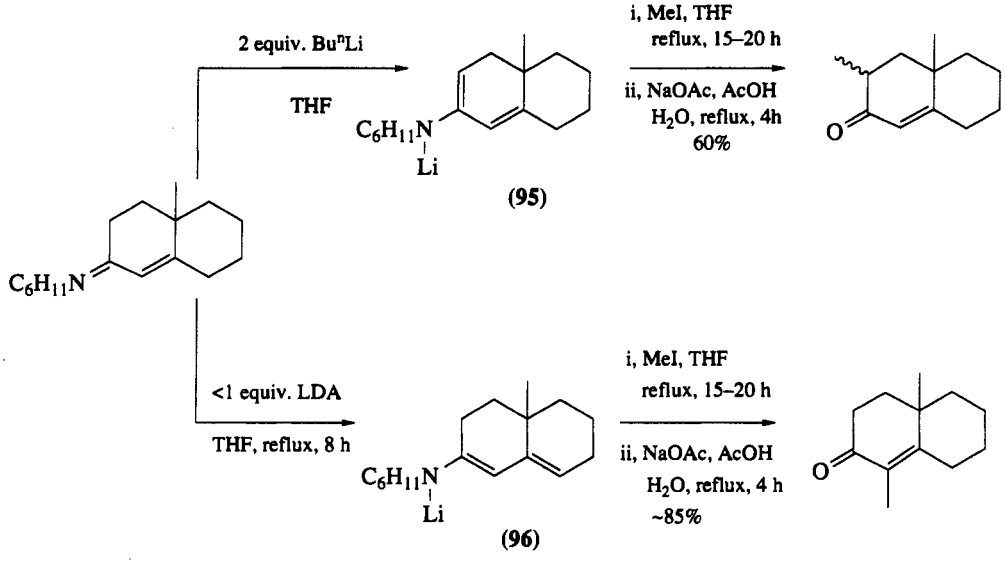
the stereoelectronic factor favoring axial alkylation is greatly reinforced by a steric effect of the *syn* substituent on nitrogen, which strongly retards equatorial approach of the electrophile. However, as has been pointed out recently, solvation and aggregation effects may play an important role in determining the stereochemistry of metallated imine alkylations.[189] The remarkably high stereoselectivity observed in alkylations of metallated imines greatly enhances their value as metal enolate equivalents.



Scheme 48

As shown in Scheme 49, the cyclohexylimine of 10-methyl-1(9)-octalin-2-one has been methylated at C-3 *via* the kinetically formed cross-conjugated dienamine anion (**95**) or monomethylated at C-1 *via* the thermodynamically more stable extended anion (**96**).[140] Steroidal and simpler enones have also been monoalkylated at the α-position *via* their corresponding hetero- or homo-annular extended dienamine anions. Likewise, α-alkylations are the rule for lithiated α,β-unsaturated aldimines.[190] The thermodynamically controlled procedure for the synthesis of α-methyl α,β-unsaturated ketones is a vast improvement over conventional methodology using extended metal dienolates where α,α-dimethylation is a severe

complication (Section 1.1.3). It is successful because the unsaturated lithiated dienimine intermediates undergo proton transfer processes too slowly to allow a significant amount of dimethylation to occur.[140]



Scheme 49

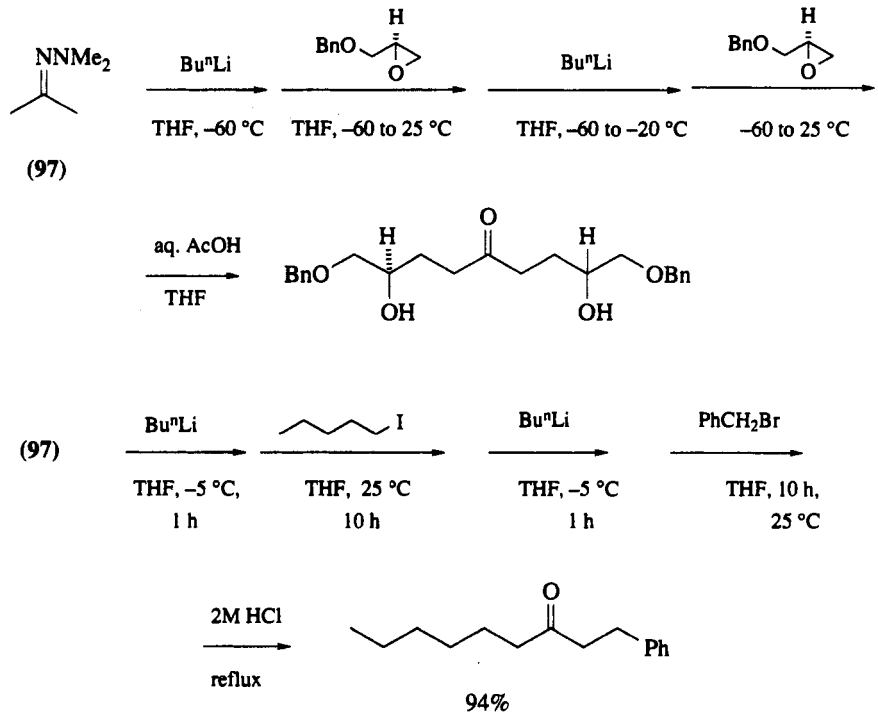
Metallated *N,N*-dialkylhydrazones exhibit similar regioselectivity and stereoselectivity to metallated imines in alkylation reactions, but the former reagents have higher reactivity, and afford higher yields, among other advantages.[180,191] The diastereoselective and enantioselective synthesis of α-alkylated carbonyl compounds requires mild methods of cleavage of α-alkylated hydrazones. Many of these have been developed by Enders and coworkers[191] and they have been recently reviewed by Bergbreiter and Momongan.[192]

Hydrazone deprotonations are normally carried out with lithium dialkylamides or alkyllithium reagents. *N,N*-Dimethylhydrazones differ from the corresponding imines, which undergo kinetically controlled *anti* deprotonation in that there is little preference for deprotonation *syn* or *anti* to the dimethylamino group on nitrogen in symmetrical systems.[193]

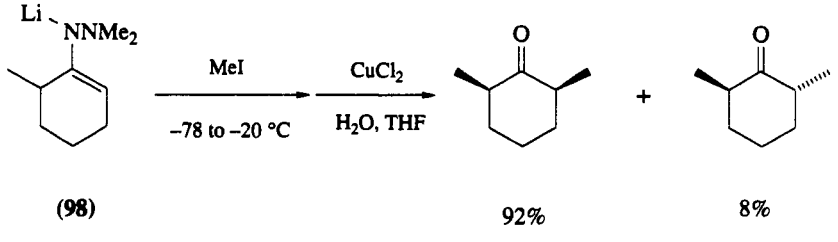
In general, deprotonations of unsymmetrical hydrazones occur with high regioselectivity at the less-substituted α-carbon atom. Since metallated hydrazones are highly resistant to proton transfer reactions with neutral ketone hydrazones, regiospecific, *C*-alkylation then occurs at the less-substituted carbon atom. Scheme 50 provides examples of how complex symmetrical[194] or unsymmetrical[195] α,α′-alkylated acetone derivatives may be prepared in one-pot sequences starting with the *N,N*-dimethylhydrazone of acetone (**97**). The conjugate addition of trimethylsilyllithium to α,β-unsaturated hydrazones, followed by trapping of the lithiated hydrazone intermediates has been reported recently.[196] Both hydrazones[180] and imines[197] may be deprotonated at the more-substituted α-carbon if an electron-withdrawing group is located there.

Conformationally rigid lithiated *N,N*-dimethylhydrazones exhibit axial alkylation preferences exceeding 98%. On the basis of the X-ray crystal structure of lithiated 2-methylcyclohexanone dimethylhydrazone,[198] kinetic studies[199] and other data, Collum, Clardy and coworkers have proposed that the electrophile attacks the anion from the face opposite to an η^4-coordinated disolvated lithium cation. If the η^4-complexed lithium cation occupies the 'equatorial' face of the anion, the stereoelectronic factor favoring chair–axial alkylation and the steric factor operate in concert to strongly direct axial alkylation. It was also shown that the lithiated cyclohexanone derivative (**98**) having a methyl group at C-6 yielded mainly *cis*-2,6-dimethylcyclohexanone upon methylation and hydrolysis (Scheme 51).[198] Thus, the stereoselectivity of alkylation of (**98**) was opposite to that originally reported.[180] It appears that, as expected, (**98**) undergoes axial alkylation mainly *via* a conformation with the 6-methyl group quasiaxial to give the *cis*-2,6-disubstituted product.

Cyclic α,β-unsaturated *N,N*-dimethylhydrazones may be monoalkylated cleanly at the α- or α′-position depending upon the conditions of formation of the metallated unsaturated hydrazone.[192] By using: (i) less reactive bases such as sodium hydride; (ii) additives such as HMPA; and/or (iii) allowing the metallated hydrazone to stand for a period of time before the alkylating agent is added, α-alkylations *via* the



Scheme 50



Scheme 51

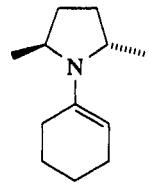
more thermodynamically stable homoannular or heteroannular linearly conjugated anions are favored.[140,200] On the other hand, deprotonations with LDA in THF followed immediately by addition of the alkylating agent have provided high yields of α′-monoalkylated products *via* the kinetically formed cross-conjugated anions.[180,201] α-Alkylations of α,β-unsaturated aldehyde hydrazones containing γ-hydrogen atoms are also known.[202]

Unsymmetrical ketoximes or ketoxime methyl ethers undergo rapid deprotonation to give *syn* dianions or monoanions, which react regioselectively with electrophilic reagents.[203,204] Axial alkylation is observed in conformationally rigid systems. Aldoximes can also be converted to their dianions and alkylated in high yields.[205]

1.1.5.2 Enantioselective Syntheses *via* Alkylations

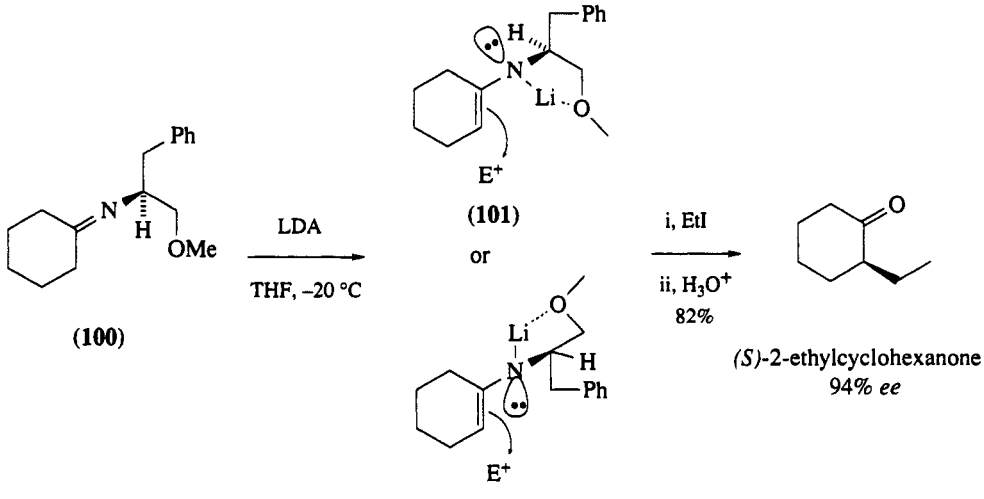
Enamines,[171] metallated imines[171,206,207] and metallated hydrazones[171,191,206,207] derived from chiral, nonracemic amines have proved to be excellent reagents for the enantioselective synthesis of α-alkylated ketones and aldehydes. Although other optically active systems had been studied,[171] the first efficient enantioselective synthesis using a chiral enamine was reported by Whitesell and Felman.[208] They found that the cyclohexanone enamine from (+)-*trans*-2,5-dimethylpyrrolidine (**99**) underwent alkylation and hydrolysis to give 2-substituted cyclohexanones with the (*R*)-configuration in good optical and chemical

yields. For the enamine (**99**) the same face of the cyclohexene ring is shielded from attack irrespective of the conformer which undergoes alkylation.



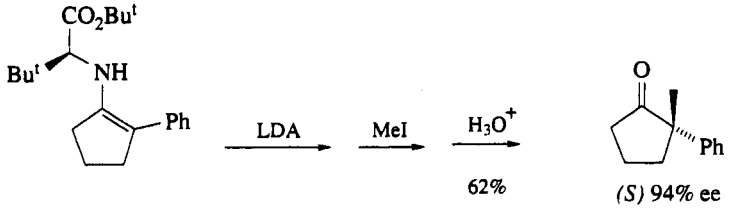
(**99**)

Attempted asymmetric alkylations of metallated chiral imines gave poor results unless, as discovered by Meyers *et al.*[209] and Whitesell and Whitesell,[210] a β-ether group was present in the optically active amine component. This allows formation of a five-membered chelate ring involving the metal cation, which imparts rigidity to the system and restricts the number of conformations available for alkylation. The synthesis of (*S*)-2-ethylcyclohexanone from the imine (**100**) provides an illustration of the method (Scheme 52). Meyers *et al.* have proposed that alkylation occurs on the top-face of the chelated structure (**101**).[209] However, based upon a proposal by Whitesell and Whitesell[210] for a related case and experimental data indicating that the lithiated imine exists largely in a *syn* configuration, a better explanation for the 1,4-asymmetric induction is provided by a structure such as (**102**), which has the chiral center closer to the reaction site and may undergo alkylation from the top-face of the π-system.



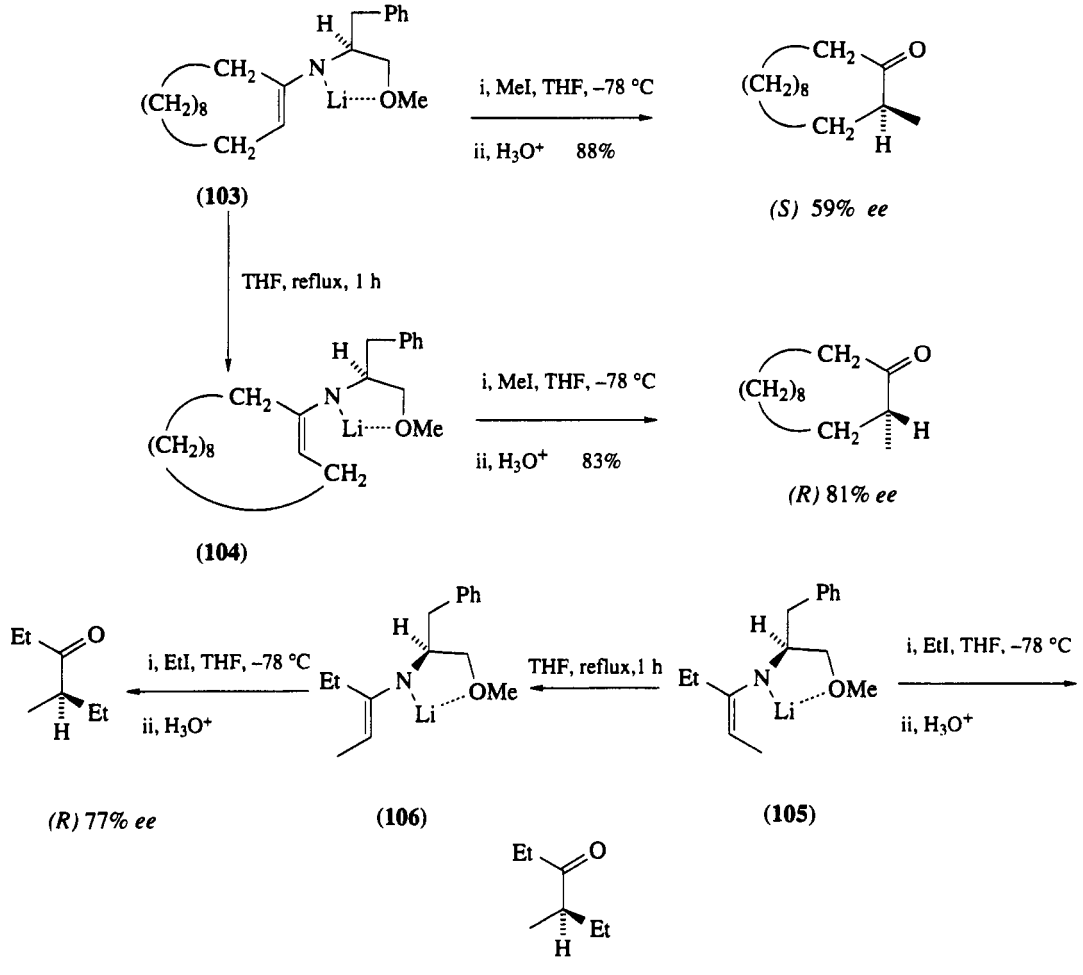
Scheme 52

(*S*)-2-Alkyl-2-phenylcycloalkanones have been synthesized in high optical yields using enamines derived from *t*-leucine *t*-butyl ester or valine *t*-butyl ester and 2-phenylcycloalkanones (Scheme 53).[211]



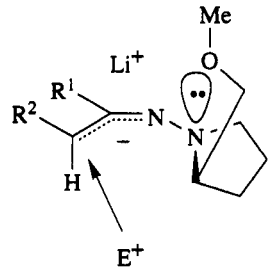
Scheme 53

Macrocyclic ketones and acyclic ketones are capable of yielding (*Z*)- or (*E*)-lithiated imines upon deprotonation. For example, Meyers *et al.*[212] found that methylation of the kinetically formed (*E*)-lithiated imine (**103**), derived from cyclododecanone and (*S*)-phenylalaninol methyl ether, gave (*S*)-2-methylcyclododecanone in low enantiomeric excess (*ee*), *i.e.* 59%, upon methylation and hydrolysis (Scheme 54). However, refluxing of (**103**) in THF effected its isomerization into the more thermodynamically stable (*Z*)-isomer (**104**), which upon methylation and hydrolysis gave (*R*)-2-methylcyclododecanone in 81% *ee* (Scheme 54). Likewise, ethylation and hydrolysis of the acyclic (*Z*)-lithiated imine (**105**) gave (*R*)-3-methylhexan-4-one in only 3% *ee*, but isomerizations to the more stable (*E*)-isomer (**106**), followed by ethylation and hydrolysis increased the optical yield of the (*R*)-ketone to 77% (Scheme 54). (Note: the (*Z*)/(*E*) transformation did not lead to a change in configuration of the acyclic ketone product.) Because of problems with (*Z*)/(*E*) isomerism and conformational flexibility, metallated aldimines are rather poor reagents for asymmetric syntheses of α-alkylated aldehydes.

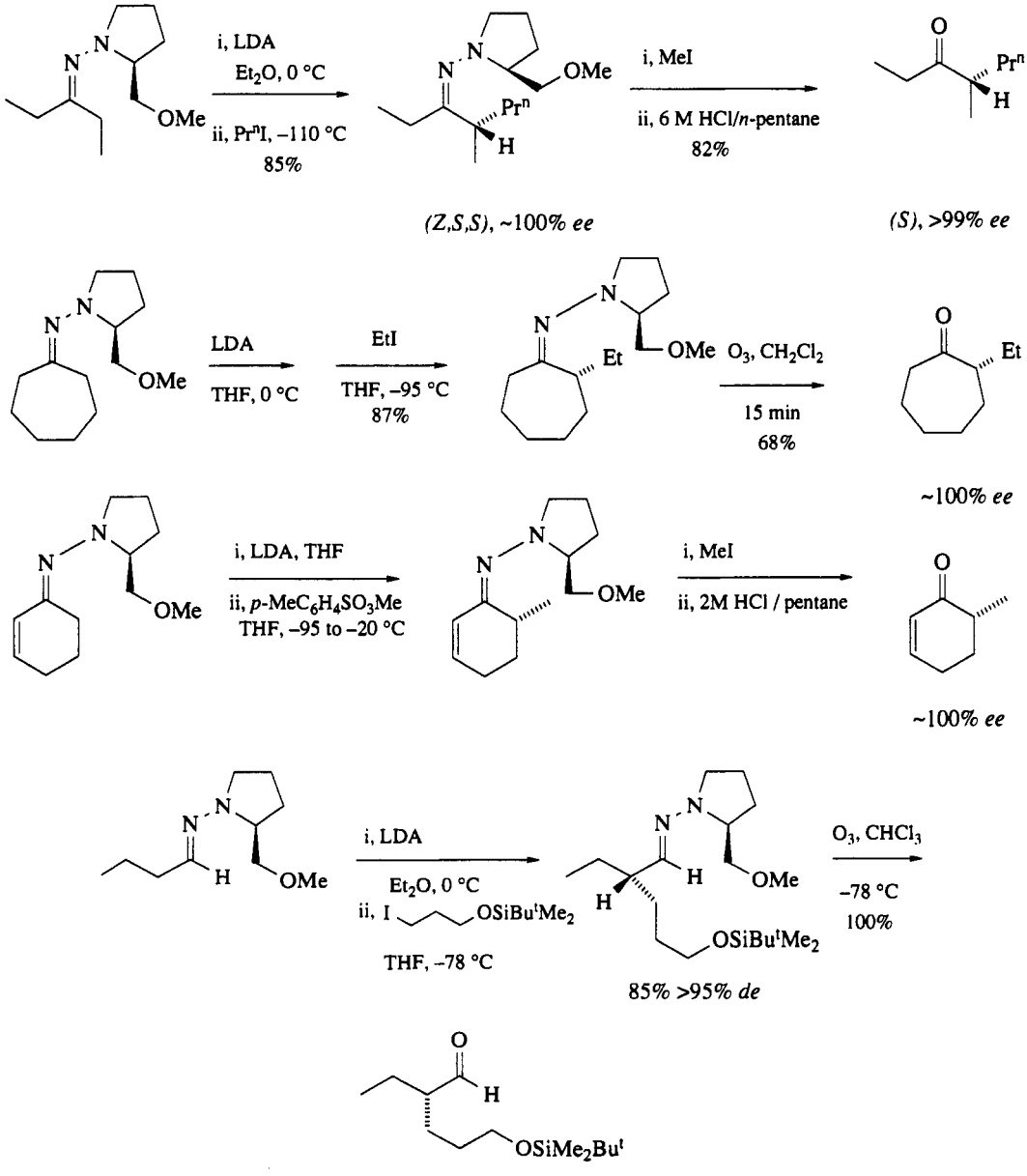


Scheme 54

Fortunately, the use of lithiated hydrazones derived from (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP) as nucleophiles for asymmetric alkylations have provided a solution to the problems described above with metallated acyclic ketimines and aldimines.[191] Lithiated SAMP or RAMP hydrazones of cyclic ketones are also alkylated in high yields. A major advantage of these chiral hydrazones is that their derivatives of aldehydes, acyclic and cyclic ketones all yield mainly $(E)_{CC}$-, $(Z)_{CN}$-lithiated species on deprotonation with LDA in ethereal solvents under kinetic control. The $(E)_{CC}$-configuration obtains as a result of the minimization of steric interactions in the usual closed transition



(107) R^1 = H or alkyl; R^2 = alkyl



Scheme 55

state for the deprotonation step.[171] These chelated lithiated hydrazones are quite conformationally rigid and they exhibit a high degree of diastereofacial differentiation. The high nucleophlicity of lithiated hydrazones allows alkylations to be performed with a variety of alkylating agents in relatively nonpolar solvents such as diethyl ether at very low temperatures, *e.g.* −110 °C. Such conditions coupled with appropriate hydrazone cleavage methodology[191,192] can yield α-alkylated aldehydes and acyclic ketones in optical yields usually exceeding 90%. In light of the recent model proposed by Collum, Clardy and coworkers[198,199] for the stereoselectivity of lithiated hydrazone alkylations, it appears likely that alkylations of $(E)_{CC}$-,$(Z)_{CN}$-SAMP hydrazones may occur *via* a species such as (**107**), in which the electrophilic reagent attacks from the opposite face of an η^4-coordinated lithium cation. Considerably lower alkylation enantioselectivities are observed for less rigid $(Z)_{CC}$-,$(E)_{CN}$-SAMP hydrazones, which may be obtained by deprotonation of hydrazones in the presence of HMPA. In this solvent, deprotonation probably proceeds *via* an open transition state.[171]

Asymmetric synthesis *via* chiral, nonracemic hydrazones have gained wide acceptance in the community of synthetic organic chemists. Some examples of asymmetric alkylations of acyclic,[213] saturated[214] and unsaturated cyclic ketones[201,215] and aldehydes,[216] which are applicable in the natural products field, are shown in Scheme 55. Various methods of cleavage of the alkylated hydrazones are also illustrated in Scheme 55.

1.1.6 ALKYLATIONS OF METAL ENOLATES OF CARBOXYLIC ACID DERIVATIVES

1.1.6.1 Introduction

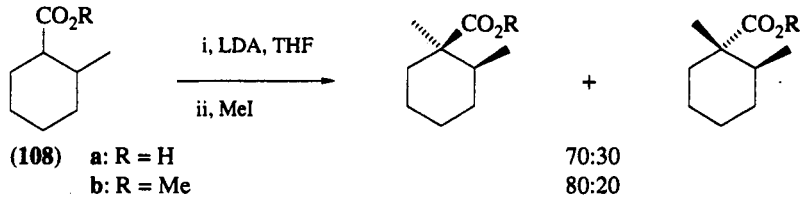
Although carboxylic acids and their derivatives are somewhat weaker carbon acids than aldehydes and ketones, it is generally possible to quantitatively convert them to the corresponding metal enolates with dialkylamide bases, the most popular of which is LDA.[4,217,218] Thus, monoanions of saturated esters, lactones, nitriles, *N,N*-dialkylamides and *N*-alkyllactams and dianions of carboxylic acids and *N*-unsubstituted amides and lactams are easily prepared in aprotic solvents such as THF and *C*-alkylated with a variety of simple and functionalized S_N2-reactive alkylating agents at room temperature or below. When more-hindered systems are involved, the basicity of the metal dialkylamide and the reactivity of the metal enolate can be enhanced by the addition of HMPA. Of course, many of the indirect methods used for the generation of aldehyde and ketone enolates are also applicable to the preparation of enolates of carboxylic acid derivatives (Section 1.1.2.1). *O*-Alkylations or dialkylations at carbon generally are of minimal importance with metal enolates of carboxylic acid derivatives.

In recent years, investigations of the diastereoselectivity and enantioselectivity of alkylations of metal enolates of carboxylic acid derivatives have become one of the most active areas of research in synthetic organic chemistry. Intraannular, extraannular and chelate-enforced intraannular chirality transfer may be involved in determining the stereochemistry of these alkylations.

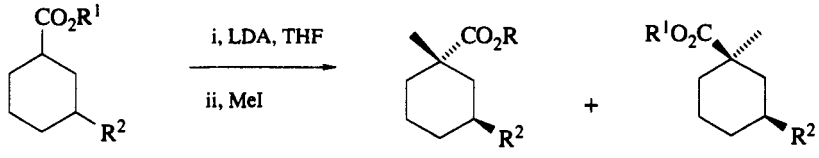
1.1.6.2 Diasteroselective Alkylations of Exocyclic and Endocyclic Enolates of Carboxylic Acid Derivatives

Intraannular chirality transfer may control alkylations of both exocyclic and endocyclic enolates. Scheme 56 provides examples of 1,2-, 1,3- and 1,4-asymmetric induction in substituted cyclohexylidine enolates.[219] For compounds such as (**108**) selective *anti* alkylation probably results from axial attack of the alkylating agent on the conformation of the enolate with the methyl substituent quasiaxial. Sterically preferred equatorial attack on a conformation with the ring substituent equatorial seems to provide a reasonable explanation for most of the results of alkylations of compounds (**109**) and (**110**). The proportion of equatorial and axial attack observed in the alkylations of ester (**110a**) is essentially identical to that of the related ketone enolate (**46**). In the case of the acid (**109d**), some sort of chelation phenomenon involving the carboxylate dianion and the methoxy group may cause the ring to prefer a conformation with the methoxy group axial. In such a conformation equatorial alkylation, which would be greatly favored sterically, would give the major product with the carboxylate and methoxy groups *cis* to each other.

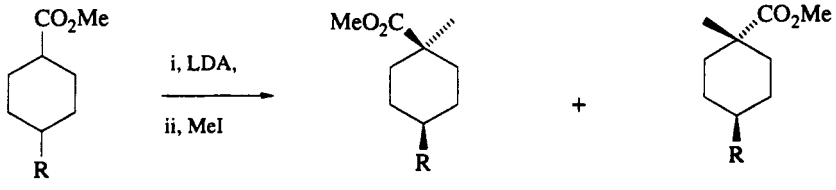
Although there are only a few examples of alkylations of carboxylate enolates which are exocyclic to five-membered carbocyclic rings, the usual steric factors seem to control the stereoselectivity of these reactions. Thus, the dienolate (**111**) underwent reaction with 4-bromo-1-butene *anti* to the methoxymethyl substituents with high diastereoselectivity[220] and enolates derived from norbornane-2-carboxylates (**112**)



(108) **a**: R = H 70:30
b: R = Me 80:20



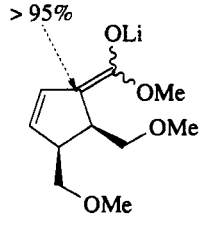
(109) **a**: R^1 = H, R^2 = Me 52:48
b: R^1 = R^2 = Me 90:10
c: R^1 = Me, R^2 = OMe 78:22
d: R^1 = H, R^2 = OMe 27:73



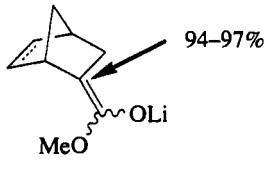
(110) **a**: R = Bu^t 84:16
b: R = OMe 84:16

Scheme 56

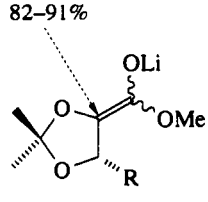
undergo largely *exo* alkylation.[219] An interesting reversal of the stereoselectivity of alkylations of exocyclic enolates of five-membered ring heterocyclic systems has been observed.[221,222] For example, the dioxalone-derived enolates (**113**)[222,223] and (**114**)[221] are alkylated primarily *syn* to the existing substituents, while for the dihydrooxazole- and oxazolidine-derived enolates (**115**)[221] and (**116**)[221] alkylation occurred *anti* to the substituents. The preference for *syn* attack on enolates of the type (**113**) and (**114**) has been attributed to folding of the hetereocyclic ring to avoid electronic repulsion between the enolate π-system and the nonbonding electron pairs on the heteroatoms.[221,223]



(**111**)

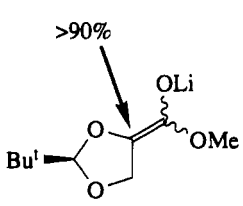


(**112**)

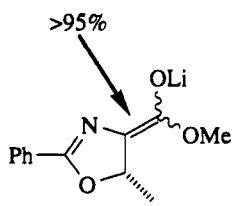


(**113**) **a**: R = CO_2Me
b: R = Et

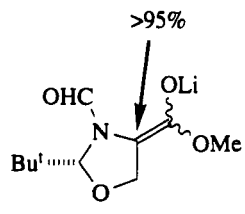
The ester precursors of the enolates (**114**) and (**116**) were prepared from reactions of glyceric acid or serine with pivaldehyde. After alkylation, the parent alkylated acids were recovered by hydrolysis. Seebach and coworkers, who have pioneered this type of procedure, have called it 'self-reproduction of chir-



(114)



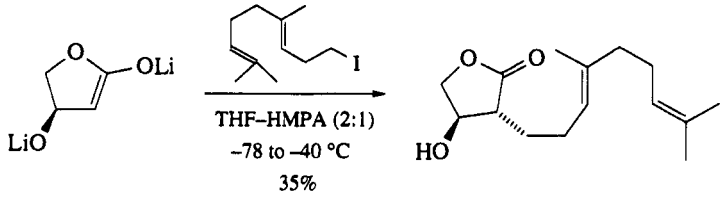
(115)



(116)

ality.'[223] As will be described below, self-reproduction of chirality can be accomplished through alkylations of endocyclic as well as exocyclic enolates. It generally entails: (i) production of a ring containing a temporary, auxiliary chiral center by derivatization of an optically active α-hydroxy or α-amino ester; (ii) formation of an enolate by deprotonation at the original asymmetric α-carbon atom; (iii) use of intramolecular chirality transfer to control the stereochemistry of alkylation of the enolate; and (iv) generation of the chiral α-alkylated ester by hydrolysis.

The stereochemistry of alkylations of endocyclic enolates derived from lactones has been reviewed recently[2] and will be discussed only briefly. β-Substituted β-lactone enolates undergo alkylation *anti* to the substituent with high stereoselectivity, particularly when the β-substituent is a bulky group. Alkylations of β- and γ-substituted γ-lactones are directed almost exclusively to the π-face of the enolate *anti* to the substituent by 1,2- and 1,3-asymmetric induction.[224] As shown in equation (10), the dilithium dianion (**117**) of (*R*)-β-hydroxy-γ-butyrolactone underwent alkylation *anti* to the alkoxy group, to give the *trans*-α,β-isomer (**118**) exclusively.[225] γ-Lactone enolates which are *cis*-fused at the β- and γ-positions to five- or six-membered rings undergo methylation mainly from the convex π-face of the molecule. If the enolate is *trans*-fused at the β- and γ-positions to a six- or seven-membered ring, alkylation occurs *anti* to the γ-ring residue.



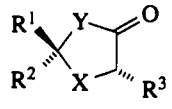
(10)

(117) (118)

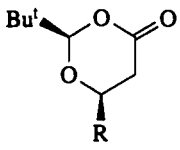
Alkylations of β-substituted δ-lactone enolates occur *anti* to the substituent with high diastereoselectivity unless bulky groups are present at the α-position.[224] Then, conformational effects may lead to a reversal of the diastereofacial differentiation. Other δ-lactone enolates are alkylated with poor diastereoselectivity unless they are *cis*-disubstituted at the γ- and δ-positions. Still and Galynker have shown that remote substituents may exert a considerable amount of asymmetric induction in medium-ring lactone enolate alkylations.[226] The remote substituent can determine which of the lower energy conformations of the enolate are available for alkylation.[226]

Within the past several years, Seebach and coworkers have made extensive use of five-membered ring *O,O*-, *S,O*-, *O,N*- and *N,N*-acetals of the general structure (**119**), derived from pivalaldehyde, as protecting groups to preserve both the functionality and the chirality of α-heterosubstituted carboxylic acid derivatives during their conversion to endocyclic enolates and alkylation.[223,227] Frater *et al.* also made an important original contribution in this field.[228] Alkylation of lithium enolates derived from systems such as (**119**) occur *anti* to the *t*-butyl group with high diastereoselectivity. Thus, by the choice of the proper diastereomer it is possible to accomplish enantioselective synthesis of α,α-dialkylated α-amino or α-hydroxy acids with overall inversion (from **119a**) or retention (from **119b**) of configuration. The use of chiral, nonracemic glycine derivatives such as (**119**; R^3 = H) obtained by resolution even allowed the enantioselective synthesis of unbranched α-amino acids.[229] More recently the Seebach research group has extended its studies to the alkylations of endocyclic enolates of six-membered ring *O,O*-acetals (**120**) derived from β-hydroxy acids.[230] Highly diastereoselective α-alkylations were accomplished. β-Unsubstituted compounds such as (**120a**) underwent alkylation predominantly *syn* to the *t*-butyl group, but in β-substituted systems such as (**120b**) alkylation occurred predominantly *anti* to the β-substituents. An

excellent review provides much more thorough coverage of alkylations of heterocyclic systems such as (**119**) and (**120**) for 'self-reproduction of chirality.'[223]

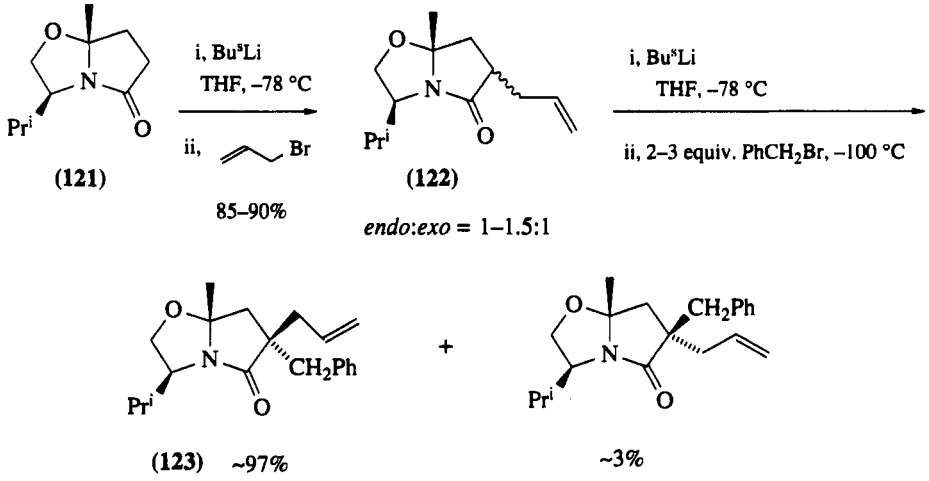


(**119**) **a**: $R^1 = Bu^t$, $R^2 = H$, R^3 = alkyl
b: $R^1 = H$, $R^2 = Bu^t$, R^3 = alkyl



(**120**) **a**: R = H
b: R = Me

By carrying out sequential alkylations of chiral, nonracemic bicyclic lactams, Meyers and coworkers have developed highly efficient syntheses of chiral compounds containing quarternary carbon atoms with high enantiomeric purity.[231,232] The sequence of steps is illustrated in Scheme 57 using the bicyclic lactam (**121**). The diasteroselectivity of the first alkylation step was low in this case, but the second step yielded the dialkylated lactam (**123**), which resulted from *endo* entry of the second alkyl group, with high diasteroselectivity.[232] In a related system where the angular substituent was a phenyl rather than a methyl group, the *endo*:*exo* ratios were 9:1 and 42:1 for methylation in the first step and benzylation in the second step.[231] Other explanations for the preference for *endo* alkylation of enolates such as that derived from (**122**) have been offered, but most recently Meyers and Wallace proposed that the lone pair electrons on the convex β-face of the molecule perturb the enolate π-system so as to favor *endo* attack by the electrophile.[233]



Scheme 57

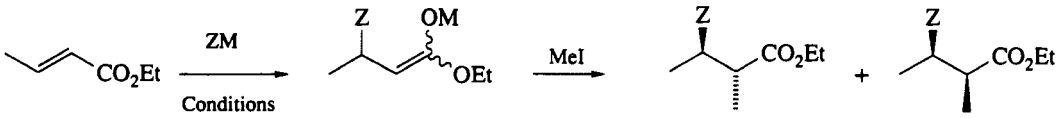
By Red-Al reduction, acid hydrolysis (to a keto aldehyde) and base-catalyzed intramolecular aldol cyclization, compounds such as (**123**) have been converted into 4,4-dialkylcyclopentenones in good chemical yields and 99% enantiomeric purity.[232] The Meyers research group has made extensive use of this exciting methodology for the synthesis of a variety of natural products.[234]

1.1.6.3 Diastereoselective Alkylations of Acyclic Enolates of Carboxylic Acid Derivatives

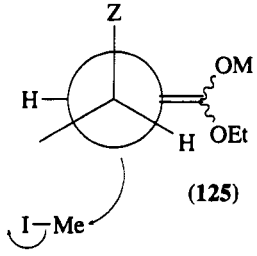
Extraannular and chelate-enforced intraannular chirality transfer in enolate alkylations of carboxylic acid derivatives may occur in cases where: (i) the chiral center, *e.g.* a β-carbon atom, is present and remains in the carboxylic portion of the molecule; or (ii) the substrate contains a chiral auxiliary, *e.g.* the alcohol portion of an ester or the amine portion of an amide, which is removed after the alkylation to generate a chiral carboxylic acid. Alkylations of the former type will be discussed in this section. Alkylations of systems containing chiral auxiliaries are described in Section 1.1.6.4.

Fleming and coworkers[94] and McGarvey and Williams[97] have shown that acyclic ester enolates, *e.g.* (**124**), containing relatively strong electron donor groups such as dimethylphenylsilyl and tri-*n*-butylstan-

nyl at the β-carbon atom, undergo α-alkylation *anti* to such groups with high diastereoselectivity (Scheme 58). These groups presumably do not participate in chelation with the metal cation and enolate oxygen atom. Therefore, a transition state such as (**125**), in which the β-substituent is aligned perpendicular to the plane of the enolate, seems to adequately account for the observed results.[97] The ester enolate alkylations reported by Koga and coworkers[235] and Yamamoto and Maruyana[236] are consistent with this explanation.



(**124**)

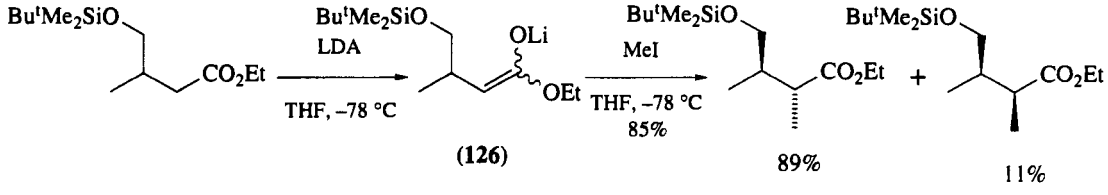


(**125**)

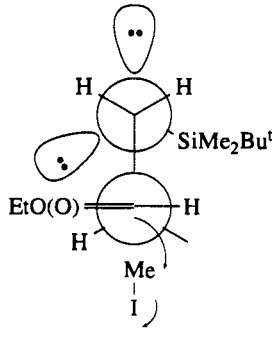
ZM/Conditions	*Ratio*	*Yield (%)*
$(PhMe_2Si)_2CuLi$, THF, –23 °C	99:1	82
Bu^n_3SnLi, THF, –78 °C	98:2	86

Scheme 58

The results of alkylations of ester enolates such as (**126**) with β-methyl and β-CH_2OR substituents (which have similar steric requirements) provide additional evidence that alkylation occurs *anti* to the more strongly electron-releasing β-substituent (Scheme 59).[97] Presumably in (**126**) a lone pair of electrons on oxygen facilitates electron release by the β-carbon–γ-carbon bond. Thus, an alkylation transition state such as (**127**) may obtain in such cases. Alkylations of dilithium dianions of 3-benzoylaminobutanoic acid esters have also been shown to give mainly the *anti* 2,3-disubstituted diastereomers.[237]



(**126**)

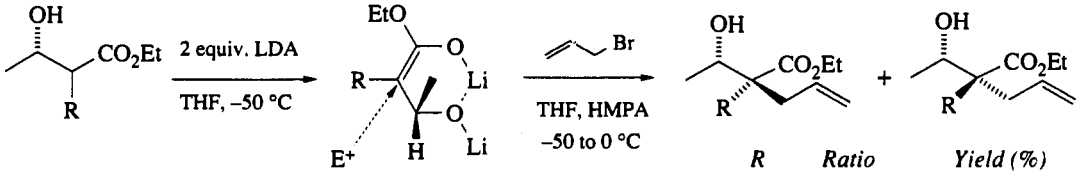


(**127**)

Scheme 59

β-Hydroxy esters may be alkylated *via* their dilithium dianions.[238] Deprotonation of the hydroxy group by the base prevents its elimination to form an α,β-unsaturated system. Two recent publications by Frater *et al.*[239] and by Seebach *et al.*[240] provide summaries of the results of the alkylations of nonracemic

β-hydroxy esters such as (*S*)-ethyl 3-hydroxybutanoates (**128**) and (*S*)-diethyl malate. A rational explanation for the data shown in Scheme 60 for the alkylation of (**128**) is that a chelated (*Z*)-enolate, *i.e.* (**129**), is formed kinetically and then *C*-alkylation occurs *anti* to the larger group at the β-position. The direct formation of the (*Z*)-enolate contrasts with the situation for simple esters whose kinetic deprotonations with LDA in THF give largely (*E*)-isomers.[2] Presumably, in β-hydroxy systems a chelated β-alkoxy ester is formed initially and its deprotonation at the α-carbon atom leads to the (*Z*)-enolate. The involvement of chelated species similar to (**129**), which undergo alkylation *anti* to the alkoxycarbonyl group, also explains the diastereoselectivity observed in malate ester alkylations.[240] Such diastereoselective alkylations have found extensive use in the synthesis of optically active natural products. Snieckus and coworkers have shown that alkylations of succinamide dienolates yield largely *threo* dialkylation products.[241] It is not clear whether extraannular chirality transfer or chelate-enforced chirality transfer account for these results.[2]

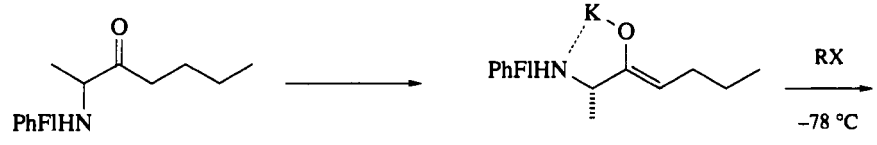


(**128**) (**129**)

R	*Ratio*	*Yield (%)*
H	96:4	75
Me	96:4	35

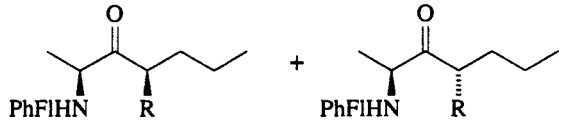
Scheme 60

α-Substituted *N*-(9-phenylfluoren-9-yl)amino ketones, *e.g.* (**130**), have been found to undergo deprotonation and alkylation at the α′-position to give *syn* α,α′-disubstituted products (**132**) with modest diastereoselectivity (Scheme 61). It has been proposed by Lubell and Rapoport that the major alkylation product arises *via* electrophilic attack on the less-hindered face of a chelated (*Z*)-enolate such as (**131**).[242]



(**130**) (**131**)

(PhFl = 9-phenylfluoren-9-yl)



(**132**)

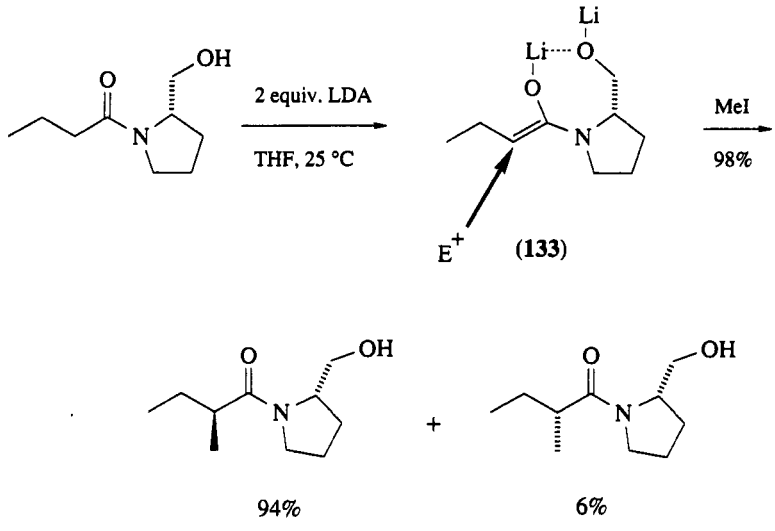
RX	*Ratio*	*Yield (%)*
MeI	69:31	94
$PhCH_2Br$	83:17	80
$CH_2{=}CHCH_2Br$	83:17	77

Scheme 61

1.1.6.4 Diastereoselective Alkylations of Acyclic Carboxylic Acid Derivatives Containing Chiral Auxiliary Groups

Alkylations of acyclic enolates containing a collection of chiral auxiliary groups have been used successfully for the asymmetric synthesis of carboxylic acids. The chiral, nonracemic substrates that have been used include amides, imides, esters, imine derivatives of glycinates and acyl derivatives of chiral transition metals. In these systems either extraannular or chelate-enforced intraannular chirality transfer may control the sense of the alkylation step.

In 1978, Larcheveque and coworkers reported modest yields and diastereoselectivities in alkylations of enolates of (–)-ephedrine amides.[243] However, two years later, Evans and Takacs[244] and Sonnet and Heath[245] reported simultaneously that amides derived from (*S*)-prolinol were much more suitable substrates for such reactions. Deprotonations of these amides with LDA in the THF gave (*Z*)-enolates (due to allylic strain that would be associated with (*E*)-enolate formation) and the stereochemical outcome of the alkylation step was rationalized by assuming that the reagent approached preferentially from the less-hindered *si*-face of a chelated species such as (**133**; Scheme 62).[246] When the hydroxy group of the starting prolinol amide was protected by conversion into various ether derivatives, alkylations of the corresponding lithium enolates were *re*-face selective. Apparently, in these cases steric factors rather than chelation effects controlled the stereoselectivity of the alkylation.[2,246] It is of interest to note that enolates such as (**133**) are attached primarily from the *si*-face by terminal epoxides.[247]

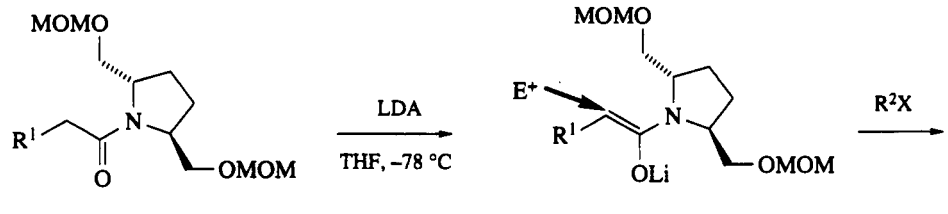


Scheme 62

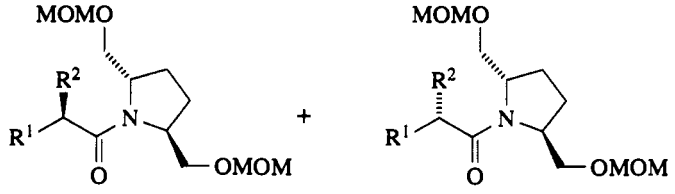
More recently Katsuki and coworkers have reported that (*Z*)-enolates of α-alkyl and α-heterosubstituted amides such as (**134**), derived from pyrrolidine derivatives having a C_2 axis of symmetry, undergo very diastereoselective alkylations with secondary alkyl and other alkylating agents in good to excellent chemical yields (Scheme 63).[248] As with prolinol ether amide enolates, it appears that the direction of approach of the alkylating agent to the enolate (**134**) is controlled mainly by steric factors within the chiral auxiliary, *i.e.* chelation effects seem to be of little importance.

In order to overcome the problems associated with acid hydrolysis of amides of prolinol, the Evans research group has investigated the diastereoselectivity of the alkylation of imides derived from chiral 2-oxazolidones.[2,246] Imide enolates are somewhat less nucleophilic than amide enolates, but they have the advantage that their diastereomeric alkylation products are easily separated and the imide linkage is cleaved with a variety of reagents under mild conditions. As shown in Scheme 64, alkylation of the chelated (*Z*)-enolate of the propionimide derived from (*S*)-valinol (**135**) with benzyl bromide occurred in high chemical yield and with high *si*-face diastereoselectivity.[249] In addition to oxazolidones, imidazolidiones have proved to be useful chiral auxiliaries for diastereoselective enolate alkylations.[250]

While deprotonations of *N,N*-dialkylamides with lithium dialkylamides in THF yield (*Z*)-enolates both in the presence and absence of HMPA, simple alkanoate esters give predominantly (*Z*)-enolates in the presence of HMPA and predominantly (*E*)-enolates in the absence of the dipolar, aprotic additive.[2] Presumably, deprotonations occur *via* an open transition when HMPA is present to complex with the lithium cation and *via* a closed transition state in THF alone. Helmchen and coworkers have reported that alkylations of esters such as (**136**)–(**138**), containing chiral auxiliaries derived from (+)-camphor, afford the opportunity for an exceptional amount of configurational control.[251] Alkylations of enolates derived from (**136**)–(**138**) occur from the face of the enolate anion opposite the benzenesulfonamide group. Since compound (**136**) is heterochiral with respect to compounds (**137**) and (**138**), as far as the ester and sulfonamide portions of the molecules are concerned, their enolates give alkylation products with opposite configurations under the same reaction conditions. Scheme 65 provides an example of how the configuration of the alkylation product was reversed when the configuration of the enolate was changed by the conditions of deprotonation, *i.e.* the (*E*)-enolate gave largely the (*R*)-alkylation product and the (*Z*)-enol-

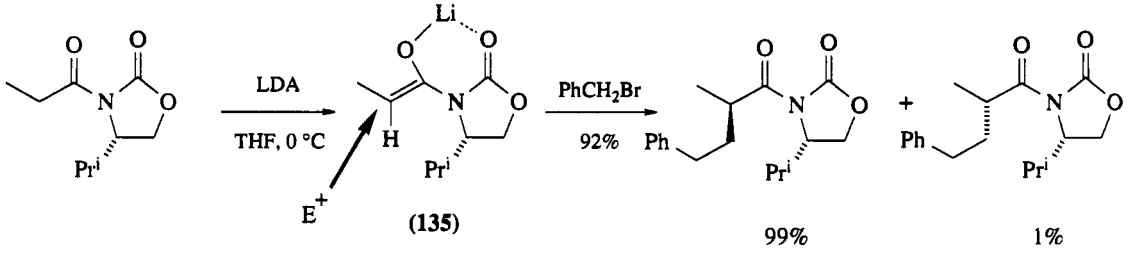


(134)



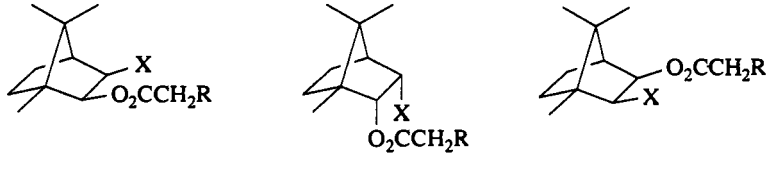
R^1	R^2X	*Ratio*	*Yield (%)*
Me	$PhCH_2Br$	98:2	80
$PhCH_2O$	Pr^iOTf	98.5:1.5	76
$Me_2C{=}N$	$HC{\equiv}CCH_2Br$	99:1	95

Scheme 63

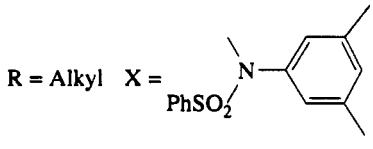


Scheme 64

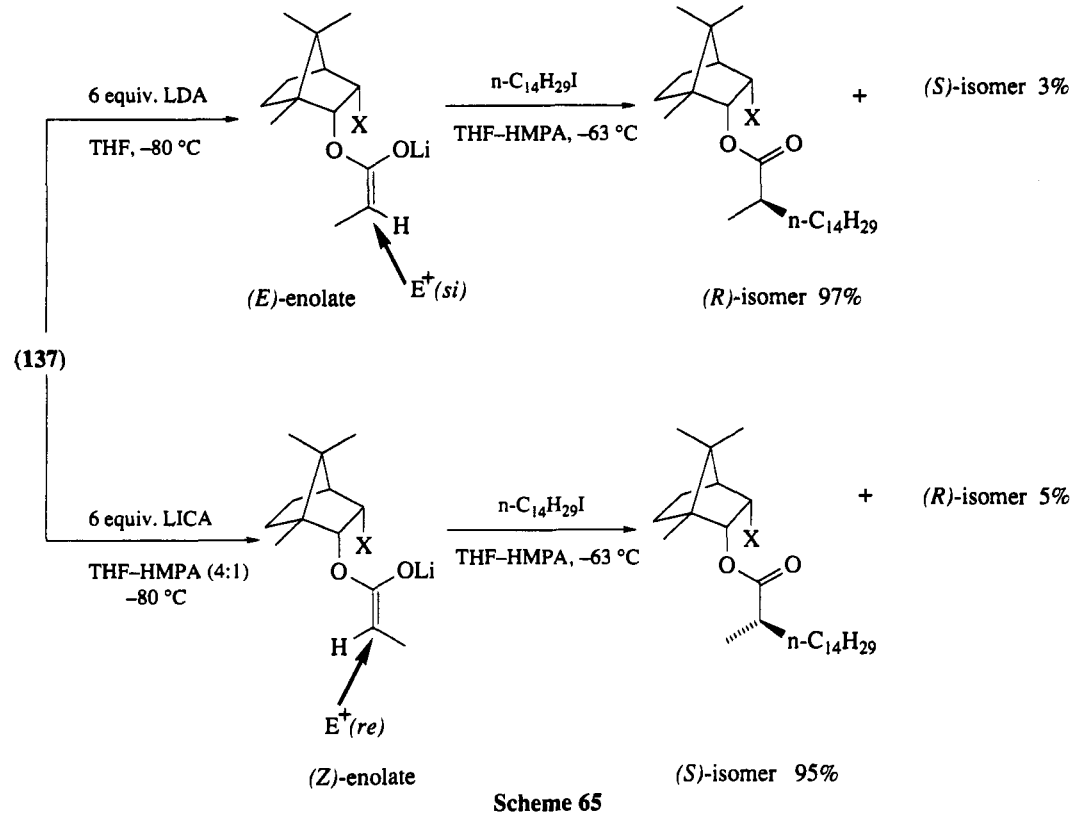
ate gave mainly the (*S*)-alkylated system. Esters of the type (**136**) and (**137**) derived from benzyl-protected glycolates were found to yield (*E*)-enolates both in the absence and presence of HMPA. The (*E*)-enolate of a chiral propionate ester derived from 10-sulfonamidocamphor was diastereoselectivity alkylated from the *si*-face.[252]



(**136**) (**137**) (**138**)

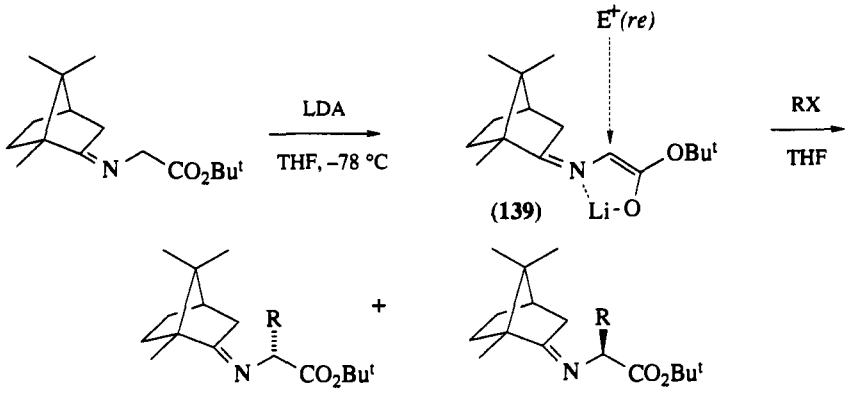


Chiral auxiliaries may be applied to α-amino acid esters by forming imine derivatives. Enolates from 2-hydroxy-3-pinanone glycinate esters have been alkylated to produce mono-[253] and di-substituted[254] α-amino acids in good optical yields after hydrolysis. Recently, McIntosh *et al.*[255] reported the results of alkylations of the enolate (**139**) derived from the (+)-camphor imine of *t*-butyl glycinate with a variety of



Scheme 65

alkylating agents. Selected examples of these reactions are shown in Scheme 66. An electrostatic interaction of the π–π or Li–π type between the lithium enolate and the alkylating agent was suggested as a possible explanation for the high preference for *re*-face selectivity, which was observed when alkylating agents containing electron rich π-systems, *e.g.* benzyl bromide, were employed.[255] Enantioselective alkylations of imines of glycinate esters have been carried out in low optical yields using allyl acetate and palladium(0) catalysts containing chiral phosphine ligands.[256] Diastereoselective alkylations of asymmetrically substituted transition metal acyl enolates is an active area of investigation,[257] but space does not permit coverage of this subject.

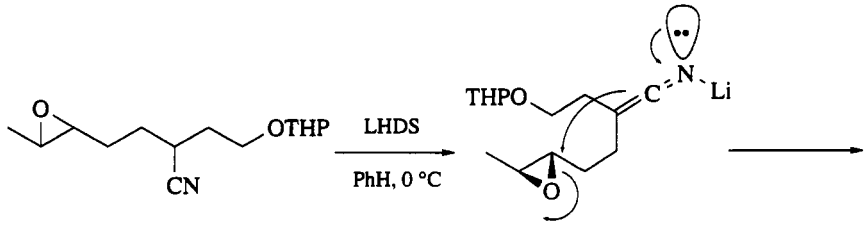


RX	*Ratio*	*Yield (%)*
EtI	67:34	38
CH_2=$CHCH_2Br$	82:12	85
$PhCH_2Br$	>99:<1	89

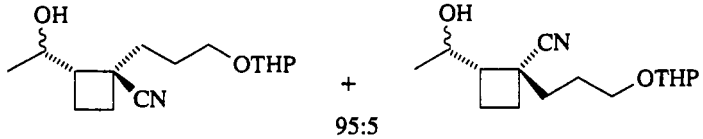
Scheme 66

1.1.6.5 Cycloalkylations of Enolates of Carboxylic Acid Derivatives

Like aldehyde and ketone enolates, enolates of carboxylic acid derivatives containing appropriately located leaving groups undergo cycloalkylations to yield monocyclic or more complex ring systems. Intramolecular alkylations of anions of simple nitriles and protected cyanohydrins have been thoroughly reviewed.[218,258] Stork *et al.* have uncovered some interesting aspects of the regiochemistry of intramolecular alkylations of nitriles containing *cis*-epoxides.[259] They showed that these reactions are subject to two important constraints, *i.e.* (i) the usual preference for nucleophilic attack to occur at the less-substituted carbon atom of the epoxide ring; and (ii) the need for a colinear arrangement of the nucleophile and the leaving group in the transition state for cyclization. In cases where both carbons of the epoxide ring were equally substituted, it was observed that the colinearity requirement always favored formation of the smaller ring. The transformation shown in Scheme 67 was a key step in the synthesis of (±)-grandisol, a boll weevil sex attractant.[259] As illustrated in structure (**140**) the preferred transition state for the reaction produces stereoselectively the cyclobutane derivative with the 1,2-alkyl substituents *cis* to each other; the lithium α-nitrile anion appears to have a larger effective size than the α-substituent. Cyclopentane derivatives, which would result from attack at the more remote carbon atom of the epoxide ring were not isolated.



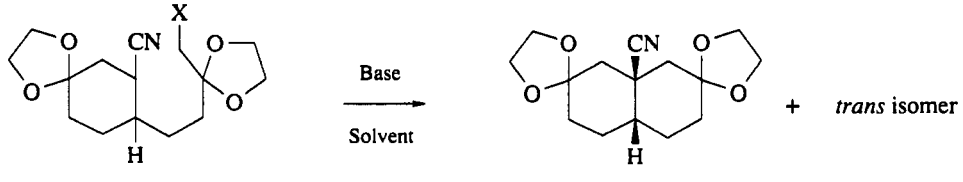
(**140**)



(**141**)

Scheme 67

The research group of Stork has also shown that decalin or hydrindane ring systems containing angular cyano groups can be prepared by base-promoted intramolecular cyclizations of cyanocyclohexane derivatives containing ketalized 3-keto-4-halo (or 4-tosyloxy) groups or 2-keto-3-halo groups at C-2.[260] *Cis*-fused hydrindanes were formed irrespective of whether the cation present was potassium or lithium. However, as shown in Scheme 68, the nature of the leaving group, the solvent and, especially, the metal cation profoundly affected the *cis*:*trans* ratio of the decalin products. It was proposed that conditions favoring the *trans* product involved cyclization through a transition state of the anion with the side chain equatorial to the ring. On the other hand, the *cis* product was expected to be obtained in situations where

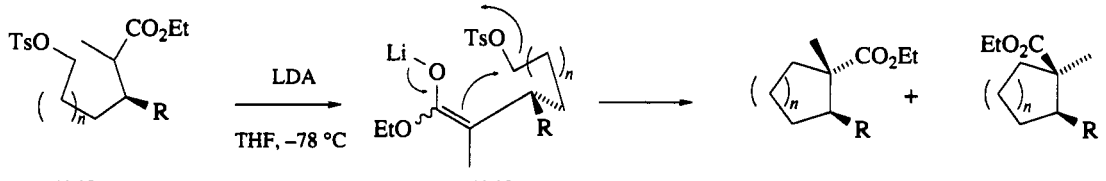


X	*Base*	*Solvent*	*Ratio*
Br	KHDS	PhH	95:5
Br	LHDS	PhH	5:95
OTs	LHDS	PhH	90:10
Cl	LHDS	PhH	30:70
Cl	LHDS	THF	80:20

Scheme 68

the preferred transition state required the side chain to be axial to the ring. Chelation involving the α-nitrile anion, the cation and an oxygen atom of the ketal ring on the side chain may play a role in determining the preferred conformation of the anion for cyclization.

As shown in Scheme 69, Kim and coworkers[261] have reported highly stereoselective routes to *cis*-1,2-dialkylcycloalkanecarboxylates by intramolecular alkylations of tosyloxy esters such as (**142**). The reaction appears to proceed *via* the 'eclipsed' conformations of the enolate (**143**), rather than the 'bisected' one that would result from a 180° rotation about the α,β-sigma bond.

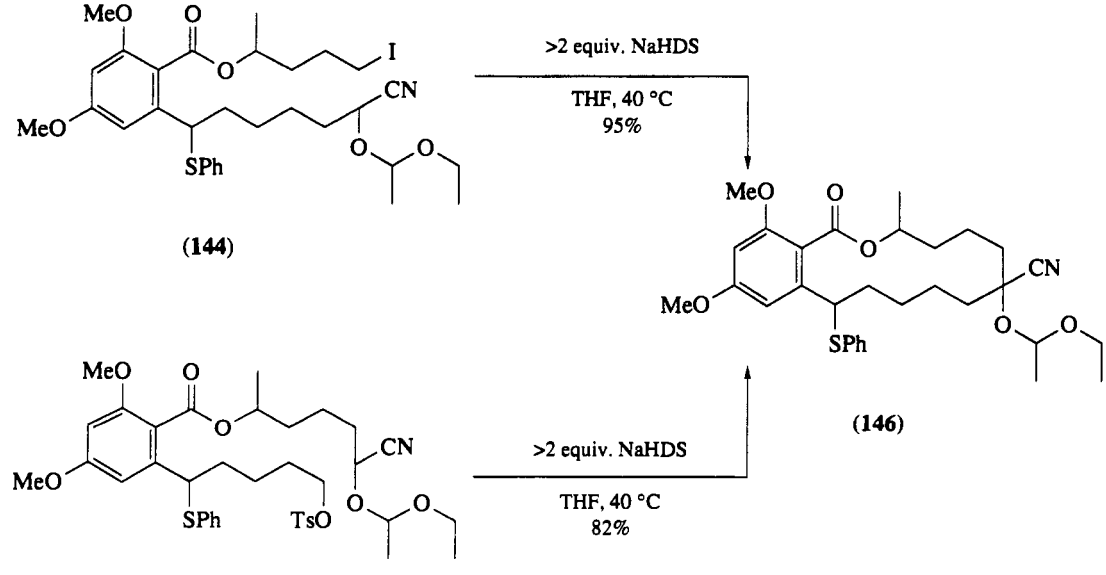


(**142**) (**143**)

n	*R*	*Ratio*	*Yield (%)*
0	isopropenyl	97:3	45
1	vinyl	92:8	45
2	Bu^n	98:2	–

Scheme 69

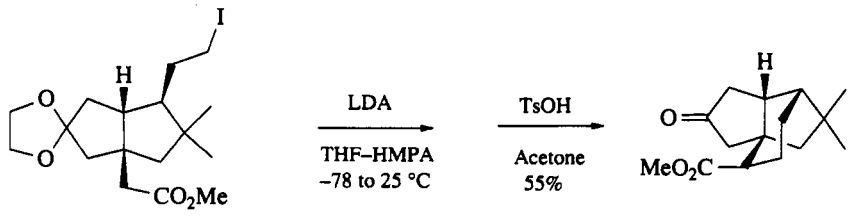
Intramolecular alkylations of nitrile-stabilized carbanions have been used to synthesize large rings such as those with 10[262] and 14 members.[263] Tsuji and coworkers carried out a synthesis of the macrocyclic antibiotic zearalenone by this route.[263] As shown in Scheme 70, conversion of either of the protected cyanohydrins (**144**) or (**145**) to the corresponding dianions, resulting from deprotonation at the benzylic positions and α to the nitrile groups, gave the same cyclization product (**146**) in excellent yields. Dianion formation: (i) provided control of the conformation of the side chain; (ii) protected the ester from nucleophilic attack; and (iii) appeared to increase the rate of the intramolecular cyclization.



(**144**) (**146**) (**145**)

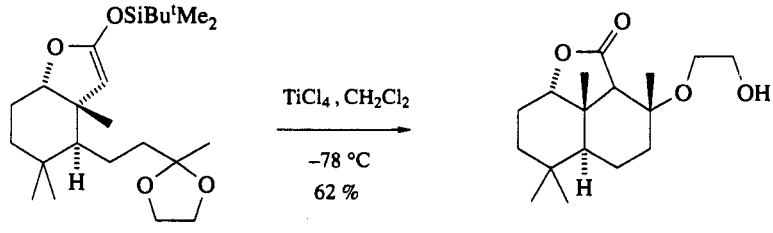
Scheme 70

There are many examples of intramolecular cyclizations of carboxylate enolates which lead to fused- and bridged-ring systems. The reaction shown in Scheme 71, which was used by Danishefsky *et al.* as a part of their synthesis of (±)-quadrone, is illustrative.[264]



Scheme 71

Lewis acid catalyzed reactions of silyl enol derivatives of esters (ketene acetals) with S_N1-reactive alkylation agents are well known, but space limitations have prevented coverage of this subject here. The reaction shown in equation (11), which was employed by Pattenden and coworkers[265] in their synthetic studies on forskolin, provides an example of an intramolecular Mukaiyama reaction of a silyl enol ester derivative.

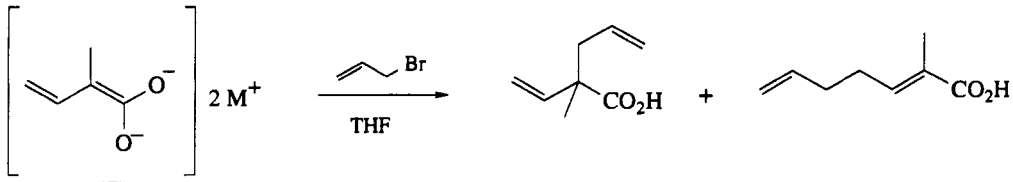


(11)

1.1.6.6 Alkylations of Dienolates of α,β-Unsaturated Carboxylic Acid Derivatives

Except in special cases where there is severe steric hindrance,[266] lithium dienolates of all classes of carboxylic acid derivatives undergo almost exclusive α-alkylation with various types of alkylating agents, *e.g.* allyl, benzyl, saturated, *etc.* However, Katzenellenbogen and coworkers,[267] and Snieckus and coworkers,[268] have shown that γ-alkylation may become the predominant mode of reaction when copper(I) dienolates are involved. This was found to be particularly true for dianionic species derived from α,β-unsaturated carboxylic acids and *N*-alkylamides where the negative charge density on the γ-site would be expected to be higher than for the corresponding monoanionic systems, *e.g.* esters or *N,N*-dialkylamides.

While γ-alkylations did not occur with saturated and benzylic halides, γ-selectivities in the 62–99% range were observed in reactions of dicopper(I) dianions of a variety of α,β-unsaturated acids with allylic halides.[267] γ-Unsubstituted allylic halides reacted by an S_N2' mechanism, γ-disubstituted compounds underwent direct S_N2 displacement and γ-monosubstituted systems reacted by both S_N2' and S_N2 pathways. Scheme 72 provides an example of the dramatic reversal in regioselectivity that was observed in the allylation of the dianion (**147**) of tiglic acid when the metal cation was changed from lithium to copper(I).[267] The γ-alkylation product from the latter species was exclusively the (*E*)-isomer.



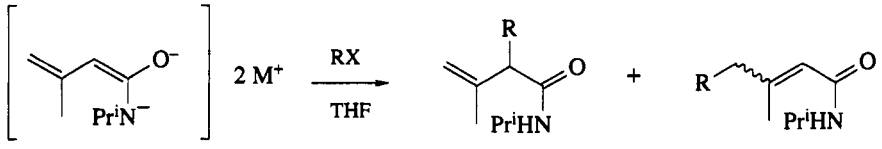
(**147**)

M	*Ratio*	*Yield (%)*
Li	100:0	80–90
Cu^I	4:96	95

Scheme 72

Scheme 73 shows the results of alkylations of dilithium and dicopper(I) dianions (**148**) of senecioic acid *N*-isopropylamide with alkylting agents of various classes.[268] A major difference in the behavior of (**148**; M = Cu^I) and the corresponding dicopper(I) dianion of senecioic acid itself was that a significant

amount of γ-alkylation occurred with methyl iodide and benzyl bromide. Also, the amide dianion was γ-alkylated with higher (*Z*)/(*E*)-stereoselectivity than the acid dianion. The role played by copper(I) in affecting the regiochemistry of alkylations of species such as (**147**) and (**148**) is unclear. Possibly *C*-metallated species are more likely to be involved when copper(I) rather than lithium is employed as the cation.



(**148**)

M	*RX*	*Ratio*	*(Z):(E) ratio*	*Yield (%)*
Li	MeI	98:2	–	98
Cu^I	MeI	59:41	91:9	80
Li	CH_2=$CHCH_2Br$	98:2	–	90
Cu^I	CH_2=$CHCH_2Br$	30:70	60:40	90
Li	$PhCH_2Br$	98:2	–	90
Cu^I	$PhCH_2Br$	75:25	80:20	80

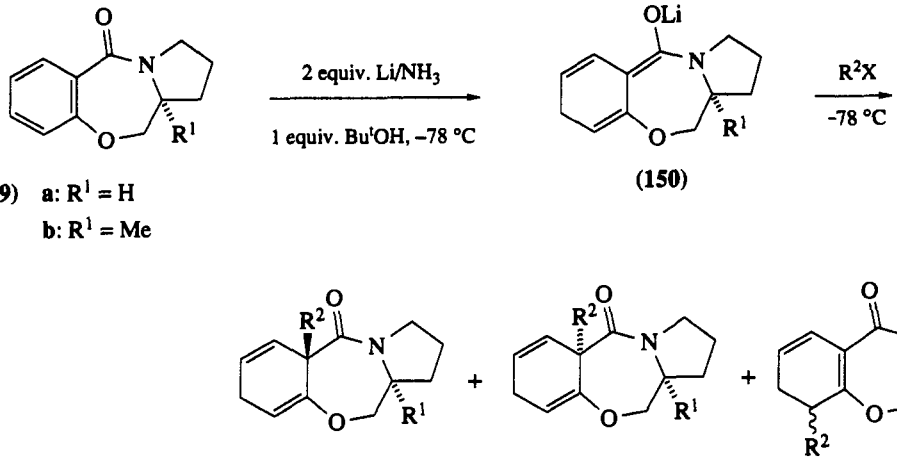
Scheme 73

Kende and Toder have reported that deconjugative alkylations of (*Z*)-2-alkenoates give the corresponding (*E*)-3-enoate derivatives, while (*E*)-2-alkenoates give (*Z*)-3-enoate isomers unless the 4-substituent is larger than methyl.[269] They suggested that the stereoselectivity of these reactions is probably determined by the conformation of the α,β-unsaturated ester that undergoes deprotonation at C-4.

Birch reductions of arylbenzoic acid derivatives provide a highly useful method of generating enolates of unsaturated carboxylic acid derivatives that can be trapped with a variety of electrophilic reagents. Especially interesting data have been obtained by Schultz *et al.* utilizing arylbenzoic acid derivatives containing chiral auxiliaries derived from L-prolinol.[270] The results of alkylations of the lithium amide enolates (**150**) obtained by reduction of benzoxazepinones (**149**) are shown in Scheme 74. Enolate (**150a**) was found to undergo highly diastereoselective β-face attack at the α-position with a variety of alkylating agents. However, γ-alkylation was the major pathway for reaction of enolate (**150b**). It was proposed that when a methyl group is present at the angular position, the enolate adopts a conformation in which the α-position is shielded from attack on both faces.

Schultz *et al.*[270] have also conducted studies on the methylation of the chiral lithium amide enolate (**152**), which was obtained by lithium–ammonia reduction of the 2-methoxybenzamide (**151**). This compound is an acyclic counterpart of the benzoxazepinone (**149a**). Enolate (**152**) was shown to have the (*Z*)-configuration by ^1H NMR analysis. As shown in Scheme 75, methylation of (**152**) in the presence of ammonia gave the amide (**153**), which resulted from attack of methyl iodide at the α-position and from the underside of the enolate almost exclusively. On the other hand, if the ammonia was removed or if the enolate (**152**) was protonated and reformed with *n*-butyllithium prior to alkylation, compound (**154**) resulting from topside attack at the α-position was formed almost exclusively. This dramatic change in diastereoselectivity in the absence of ammonia was attributed to a major change in enolate structure that could result from rotation about the C—N bond and inversion of configuration at nitrogen of the chiral auxiliary. The enolate was considered to exist as a dimer in the presence and absence of ammonia.

Takahashi and coworkers have employed intramolecular reactions of anions of unsaturated protected cyanohydrins to produce unsaturated carbocyclic systems containing 10-, 14- and 16-membered rings which are convertible into natural products.[271] These reactions occur regiospecifically at the α-position and usually do not involve (*E*) → (*Z*) isomerization of β,γ-double bonds. The preparation of 2-cyclopentadecenone (**155**), which is convertible into the macrocyclic perfumes muscone and exaltone, is illustrative of this methodology (Scheme 76).

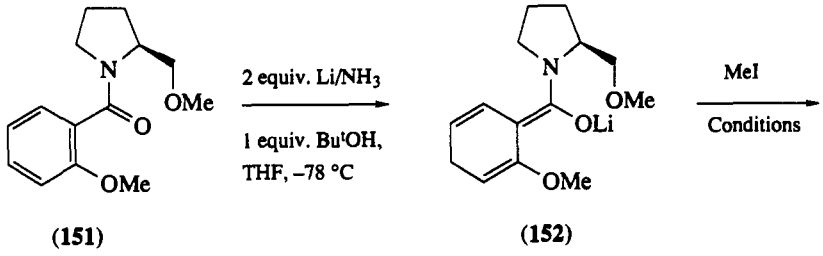


(149) **a**: $R^1 = H$
b: $R^1 = Me$

(150)

R^1	R^2X			*Yield (%)*	
H	MeI	57		10	3
H	EtI	81		1	0
H		~87		~2	0
Me	MeI	——	18	——	80 (80:20 mixture)

Scheme 74

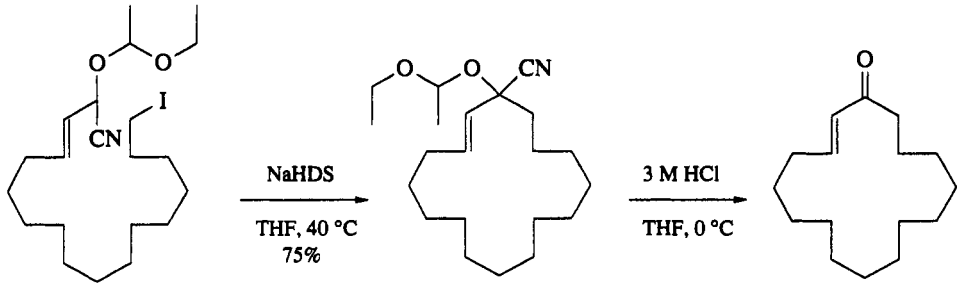


(151) **(152)**

(153) **(154)**

Conditions	*Ratio*	*Yield (%)*
NH_3–THF, –78 °C	99.6:0.4	85
i, warm to 25 °C with loss of NH_3		
ii, THF, –78 °C	1:99	80

Scheme 75



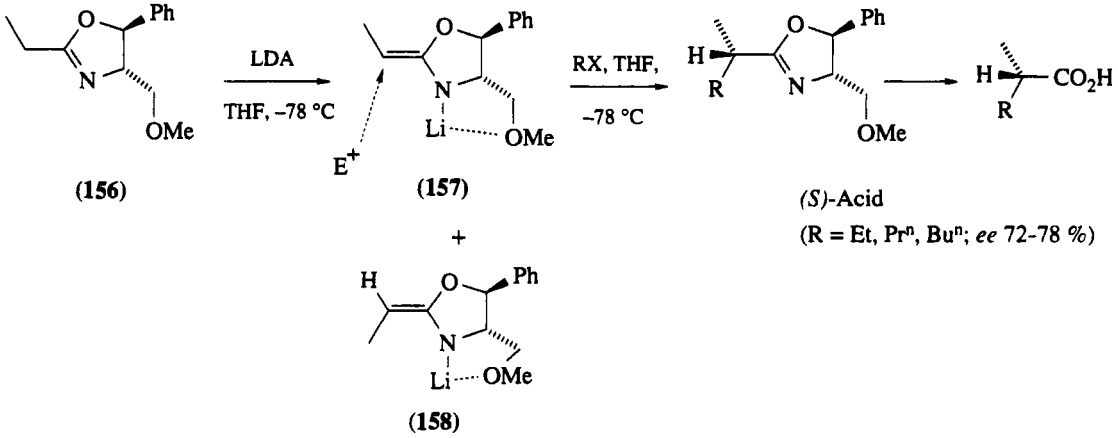
(155)

Scheme 76

1.1.6.7 Asymmetric Synthesis *via* Alkylations of Anions of Masked Carboxylic Acid Derivatives

Over the past 20 years, Meyers and coworkers have developed an elegant methodology for the synthesis of complex carbonyl compounds, which involves alkylations of anions of masked carboxylic acid derivatives. Their earlier work, which involved the use of heterocyclic analogs of imino esters such as 2-alkyldihydro-1,3-oxazines, 2-alkylthiazolines and 2-alkyloxazolines has been thoroughly reviewed.[5,6,272] Anions of 2-alkyloxazolines turned out to be the most useful reagents for the synthesis of alkylated carboxylic acids and esters, and, by using chiral, nonracemic oxazolines such as (**156**), derived from commercially available amino alcohols, the research group of Meyers extended this methodology to the asymmetric synthesis of α,α-dialkylcarboxylic acids.[273] It was found that both enantiomers of a carboxylic acid derivative could be produced by starting with selectively substituted oxazolines or reversing the order in which the alkyl groups were introduced.

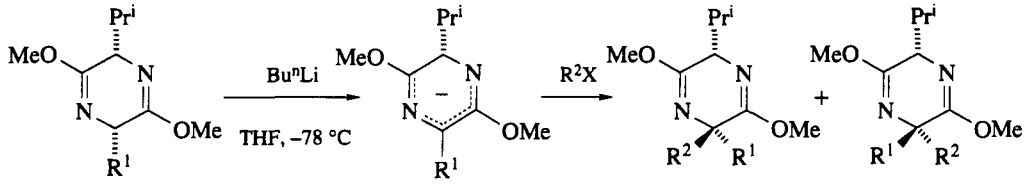
As shown in Scheme 77, deprotonation of compound (**156**) with LDA in THF at –78 °C gave a 95:5 (*E*)/(*Z*)-mixture of lithiated anions (**157**) and (**158**). Upon addition of an alkylating agent at –78 °C or below, the major anion (**157**) was attacked from the underside with high diastereoselectivity. The highly effective intramolecular chirality transfer was ascribed to the fact that (**157**) exists as a rigid chelated structure with the lithium cation located on the underside of the molecule and the phenyl group sterically shielding the topside of the molecule. The presence of both the methoxy group and the phenyl were essential for high diastereoselectivity to be observed. Alkylations of (**157**) with ethyl, propyl or *n*-butyl iodide followed by unmasking of the carboxylic acid by hydrolysis gave the corresponding (*S*)-2,2-dialkylacetic acids in 72–78% enantiomeric excess (*ee*) and good chemical yields. The optical purity of the product was reduced because the minor azaenolate (**158**) gave the corresponding (*R*)-acids.



Scheme 77

Schöllkopf and coworkers have pioneered the development of anions of another type of masked carboxylic acid derivative, *i.e.* bislactim ethers such as (**159**), derived from (*S*)-valine and glycine or alanine, for the asymmetric synthesis of amino acids.[274] As shown in Scheme 78, compounds such as

(**159**) are deprotonated exclusively at C-5 with *n*-butyllithium or LDA in THF to give endocyclic chiral enolate equivalents such as (**160**). Alkylations of (**160**) with saturated primary, allylic and benzylic halides occur *anti* to the 2-isopropyl substituent with high diastereoselectivity. It has been proposed that both coordination of the lithium cation and attack of the alkylating agent occurs on the π-face of the delocalized anion opposite the bulky substituent. When the C-2 substituent was smaller than isopropyl or when systems with C-2 disubstituted were employed, alkylation diastereoselectivities were reduced somewhat. A disadvantage of this method is that after acidic methanolysis of the new bislactim ethers, two amino acid esters which must be separated are produced.



(**159**) (**160**)

R^1	R^2X	*Ratio*	*Yield (%)*
H	$PhCH_2Br$	>95:5	81
Me	$PhCH_2Br$	>98:2	68
H	$PhCH{=}CHCH_2Br$	>95:5	90
Me	$PhCH{=}CHCH_2Br$	>98:2	89
H	$Me(CH_2)_5CH_2Br$	>87:13	62
Me	$Me(CH_2)_5CH_2Br$	>98:2	43

Scheme 78

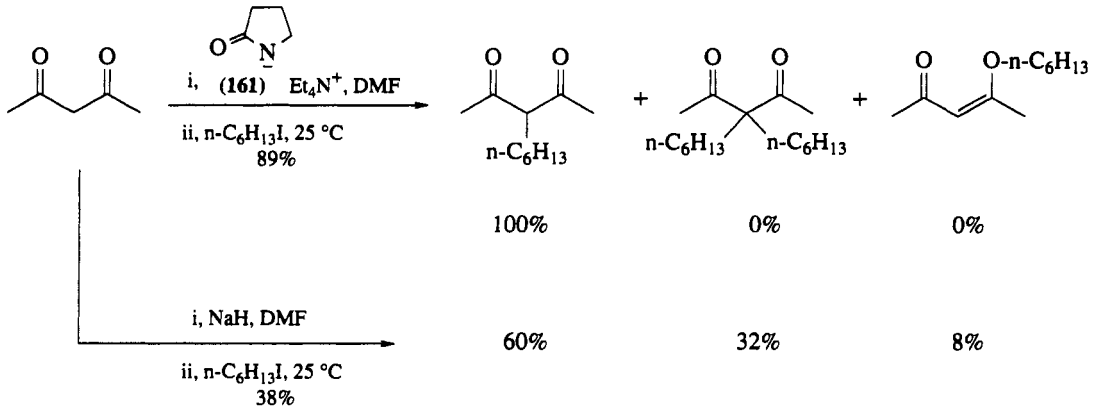
1.1.7 ALKYLATIONS OF STABILIZED METAL ENOLATES

1.1.7.1 Alkylations of Monoanions of β-Dicarbonyl and Related Compounds

Conventional methods of alkylation of stabilized metal enolates such as those derived from β-diesters, β-cyano esters, β-keto esters, β-keto aldehydes, β-diketones, β-keto sulfoxides and β-keto sulfones have been thoroughly discussed elsewhere.[4,5,6,15] *O*-Alkylation often competes strongly with *C*-alkylation in these systems. Factors which tend to favor *O*-alkylation generally include the use of: (i) substrates that are highly enolic, *e.g.* β-keto aldehydes and cyclic β-diketones; (ii) electropositive metals, *e.g.* potassium, as counterions; (iii) highly dipolar aprotic solvents, *e.g.* HMPA; and (iv) highly reactive alkylating agents, *e.g.* chloromethyl alkyl ethers or secondary alkyl halides. Factors that favor *C*-alkylation include the use of: (i) hetereogeneous conditions; (ii) less electropositive metal cations, *e.g.* lithium; (iii) nonpolar or protic solvents; and (iv) polarizable alkylating agents such as alkyl iodides and allylic, propargylic and benzylic halides. In addition to *O*-alkylation, side reactions such as dialkylation, Claisen condensation, β-keto cleavage and oxidative coupling may compete with *C*-alkylation.

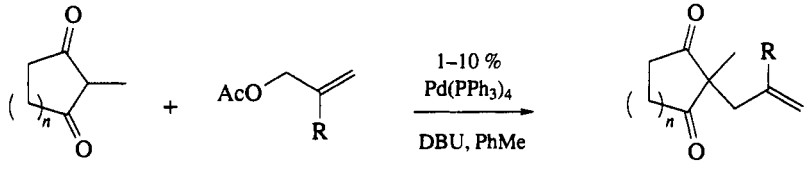
Two methods which reduce or avoid *O*-alkylation and employ heterogeneous reaction conditions include: (i) the heating of crystalline thallium(I) enolates of β-keto esters or β-diketones with primary or secondary alkyl iodides;[275] and (ii) the heating of stabilized sodium enolates with methyl- or ethyl-sulfonium salts.[276] However, the reproducibility and generality of the former method has been questioned.[277]

Excellent yields of *C*-alkylation products have been obtained by the reaction of β-dicarbonyl compounds with alkyl halides in the presence of tetraalkylammonium fluorides[278] or salts such as (**161**).[279] The latter method appears to have broad generality. Scheme 79 provides a comparison of the alkylation of acetylacetone with *n*-hexyl iodide in the presence of reagent (**161**) and *via* conventional methodology. Reagent (**161**) was assumed to generate quaternary ammonium enolate intermediates from β-dicarbonyl compounds. However, it seems possible that the alkylating agent actually attacks an enol intermediate which is hydrogen-bonded to the pyrrolidone anion. This type of pathway was proposed in cases where quaternary ammonium fluorides were utilized.



Scheme 79

Enolates of cyclic 1,3-diketones, such as 2-methyl-1,3-cyclopentanedione and 2-methyl-1,3-cyclohexanedione, are especially prone to *O*-alkylation because of their 'W' geometry and steric hindrance at carbon. However, *C*-alkylations of these species can be conducted reasonably successfully in protic solvents, *e.g.* water.[280] Trost and Curran[281] have reported high yields for the *C*-alkylation of cyclic 1,3-diketones with allylic acetates in the presence of palladium(0) catalysts and DBU (Scheme 80).

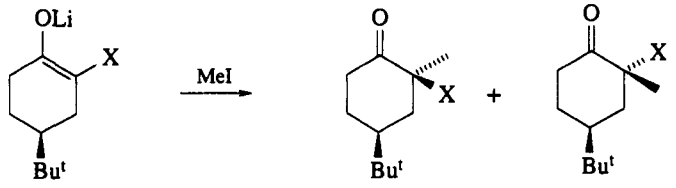


n	*R*	*Yield* (%)
1	OEt	76
1	H	94
2	OEt	81

Scheme 80

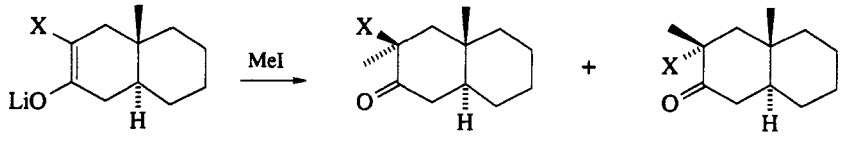
The stereochemical results of methylations of stabilized metal enolates such as (**162**), derived from 4-*t*-butylcyclohexanone, and (**163**) and (**164**), derived from *trans*-10-methyl-2-decalone, are shown in Scheme 81. Kuehne and Nelson[282] found that the unhindered α-cyano and α-methoxycarbonyl enolates (**162a**) and (**162b**) both underwent stereoelectronically controlled axial alkylation preferentially, although not with high diastereoselectivity. Also, the related pair of 3-substituted 2-decalone enolates (**163a**) and (**163b**) both underwent mainly equatorial alkylation, presumably because the 10-methyl group provides significant hindrance to axial attack of the electrophile.[282] These stereochemical results are entirely consistent with those obtained for the alkylations of related unstabilized enolates discussed in Section 1.1.2.2. However, the 1-substituted 2-decalone enolates (**164a**) and (**164b**) were found to undergo alkylation in the opposite sense, *i.e.* the α-cyano species underwent primarily equatorial methylation,[282] while the related α-methoxycarbonyl species underwent largely axial methylation[283] (similar results were obtained for alkylations of related pairs of enolates derived from tri- or tetra-cyclic β-keto esters[2]). Kuehne and Nelson have suggested several factors which may account for the difference in the behavior of (**164a**) and (**164b**).[282] A major reason may be that in (**164b**) a *peri* interaction between the methoxy group of the chelated enolate ring and the B-ring methylene group (C-8), which is not present in (**164a**), distorts the A-ring so as to open up the top π-face of the enolate to attack.

The formation of cyclic compounds by intramolecular alkylations of stabilized enolates has been widely used in organic synthesis. A recent study of the kinetics of the reaction of diethyl (ω-bromoalkyl)malonates in DMSO using tetramethylammonium hydroxide as the base has shown that relative rates of closure of rings of varying size follow the order: 3 > 5 > 6 > 4 > 7 > 12–21 > 8 > 9 > 11 > 10.[284] These results are consistent with earlier studies in which other base–solvent combinations were employed.[4] The high rates of closure of three-membered rings allow the formation of a variety of cyclopropane deriva-



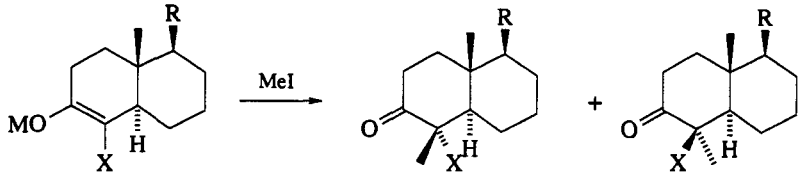
(162) **a**: X = CN
b: X = CO_2Me

Compound	*Ratio*	*Yield (%)*
(162a)	77:23	84
(162b)	83:17	97



(163) **a**: X = CN
b: X = CO_2Me

Compound	*Ratio*	*Yield (%)*
(163a)	>90:<10	46
(163b)	83:17	94



(164) **a**: M = Li, X = CN, R = H
b: M = Na, X = CO_2Me, R = OTHP

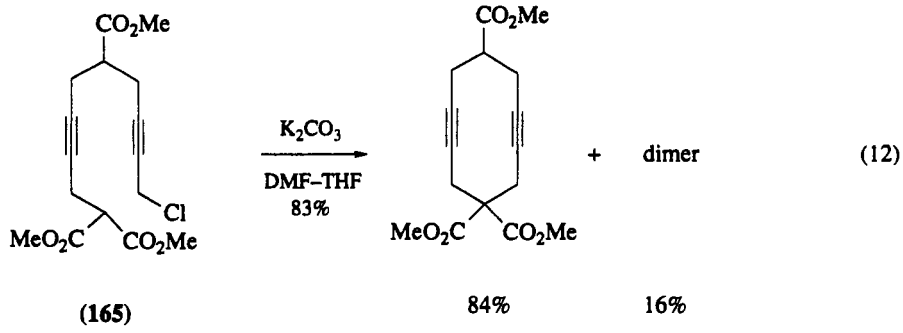
Compound	*Ratio*	*Yield (%)*
(164a)	<10:>90	58
(164b)	93:7	67

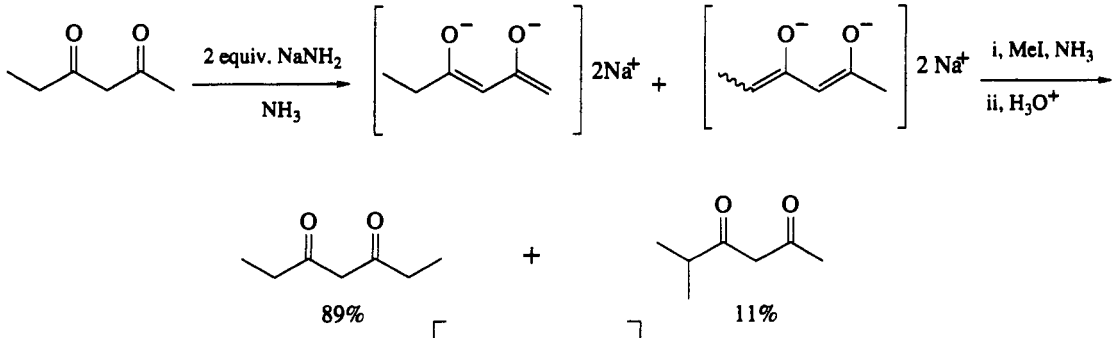
Scheme 81

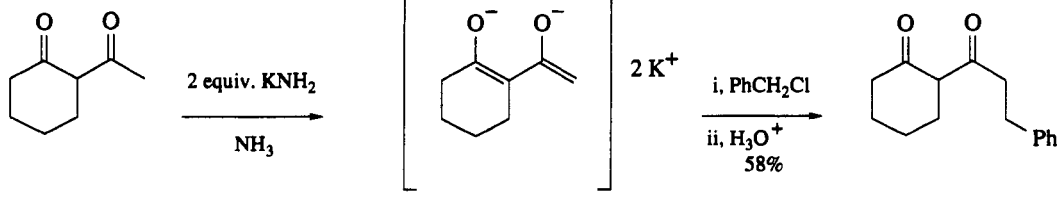
tives from active methylene compounds under mild conditions. Quinkert *et al.*[285] have shown that base-promoted reactions of chiral malonic esters, prepared from chiral, nonracemic alcohols such as (–)-8-phenylmenthol, with 1,4-dihalo-2-butenes lead to intermolecular alkylation followed by S_N2' closure of a three-membered ring to give chiral 2-alkenyl-1,1-cyclopropanedicarboxylates. These products have been shown to be useful building blocks for the synthesis of a variety of natural products.

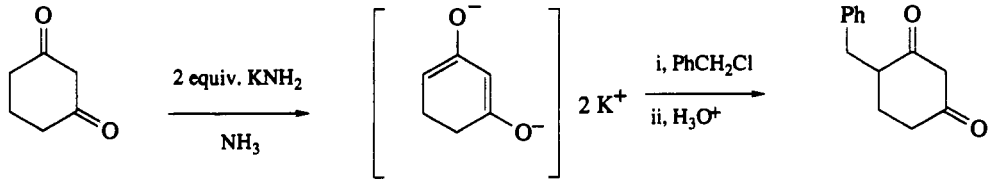
Ten-membered rings are formed slowly in cycloalkylations because the entropy factor is unfavorable and transannular interactions are severe in the transition state for ring closure. Deslongchamps *et al.*[286] have shown that the introduction of double and triple bonds into the carbon chain reduces the importance of these factors by restricting the degrees of freedom of the molecule and partially eliminating transannular interactions. As shown in equation (12), the cyclization of the malonic ester derivative (**165**) was carried out in good yield without the use of high dilution techniques.

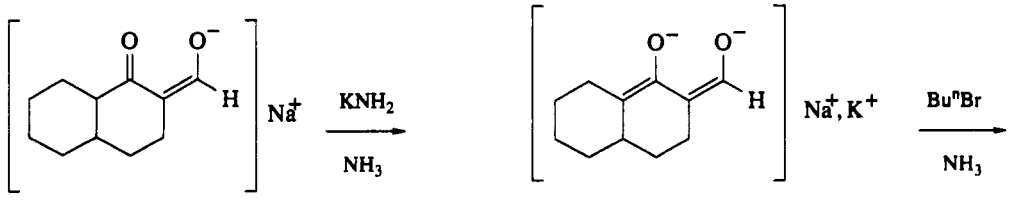
The research group of Trost has shown that stabilized enolates derived from β-diesters and α-phenylsulfonyl esters are excellent nucleophiles for palladium(0)-catalyzed reactions with allylic acetates.[287] Since these reactions involve π-allylpalladium intermediates, they proceed with net retention of configuration and, therefore, differ from traditional displacement reactions where inversion is the rule. Moreover, the transition metal imposes a template effect on intramolecular versions of these reactions and

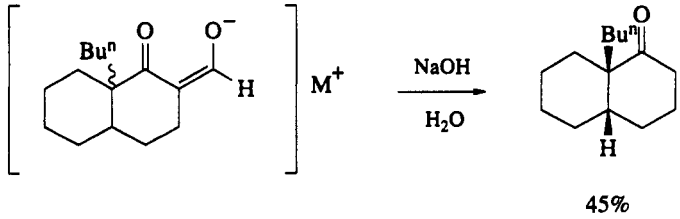

CO2Me
Cl
MeO2C
CO2Me
K2CO3
DMF–THF
83%
CO2Me
MeO2C
CO2Me
+ dimer
(12)
(165)
84%
16%


2 equiv. NaNH2
NH3
2Na+ +
2 Na+
i, MeI, NH3
ii, H3O+
89%
+
11%


2 equiv. KNH2
NH3
2 K+
i, PhCH2Cl
ii, H3O+
58%
Ph


2 equiv. KNH2
NH3
2 K+
i, PhCH2Cl
ii, H3O+
Ph


Na+
KNH2
NH3
Na+, K+
Bu^nBr
NH3


Bu^n
M+
NaOH
H2O
Bu^n
45%

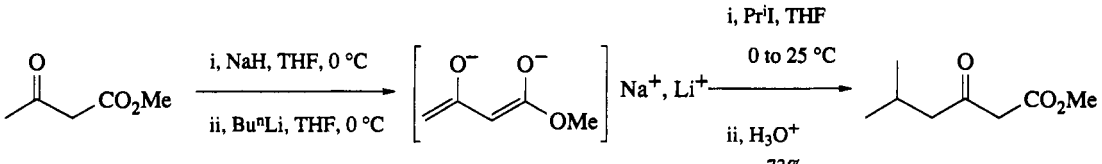
Scheme 82

medium and large rings which are difficult to obtain by traditional methods can be formed easily. The reader is referred to recent reviews for thorough coverage of this important methodology.[287]

1.1.7.2 γ-Alkylations of Dianions of β-Dicarbonyl Compounds

The synthetic flexibility of β-dicarbonyl compounds was greatly expanded when it was discovered by Hauser and Harris that many of these systems can be converted to their dianions by treatment with 2 equiv. of potassium or sodium amide in liquid ammonia.[288] These dianions could then be monoalkylated at the γ-position with high regioselectivity. Early research in this area was devoted to studies on β-diketones and β-keto aldehydes, and this is covered in an excellent review by Harris and Harris.[289] It was found that unless activating groups were present, the second proton was removed regioselectively from the less-substituted γ-position of unsymmetrical β-diketones. Of course, β-keto aldehydes are capable of yielding only a single dianion. Scheme 82 provides examples of these reactions. The last reaction in Scheme 82 is particularly interesting since it involves preparation of an angularly alkylated 1-decalone derivative.

Attempted γ-alkylations of β-keto esters by forming their dipotassium dianions with potassium amide and alkylating them in liquid ammonia gave poor results. However, Huckin and Weiler[290] found that treatment of methyl acetoacetate with 1 equiv. of sodium hydride, followed by 1 equiv. of *n*-butyllithium, or 2 equiv. of LDA in THF gave dimetal dienolates (**166**) which alkylated in good yields with several different alkylating agents including isopropyl iodide at 0–25 °C (Scheme 83).



(166)

Scheme 83

The method of Huckin and Weiler has enjoyed widespread use in synthesis. For example, recently reported syntheses of *trans*-bicyclo[4.3.1]decan-10-one[291] and a bicyclo[4.4.1]undecan-7-one derivative[292] have employed γ-alkylations of β-keto ester dianions as key steps. This methodology has also been extended to the formation and γ-alkylation of dianions of γ,δ-unsaturated β-keto esters.[293]

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1.2
Alkylations of Nitrogen-stabilized Carbanions

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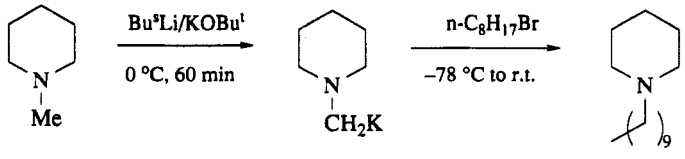
1.2.1 INTRODUCTION

The deprotonation of an sp^3-hydrogen α to nitrogen has been developed into a highly useful synthetic tool in recent years.[1,2] Although some authors have suggested that this type of reactivity is a reversal of the 'normal' reactivity adjacent to nitrogen,[2,3] we submit that this notion is inappropriate and should be discontinued. The α-deprotonation of dimethyldodecylamine[4] and triethylamine[5] was reported over 20 years ago. In 1984, Ahlbrecht reported that *s*-butylpotassium readily deprotonates *N*-methylpiperidine, *N*-methylpyrrolidine and triethylamine, and that the derived organometallics add readily to aldehydes, ketones and alkyl halides.[6] An example is shown in Scheme 1.

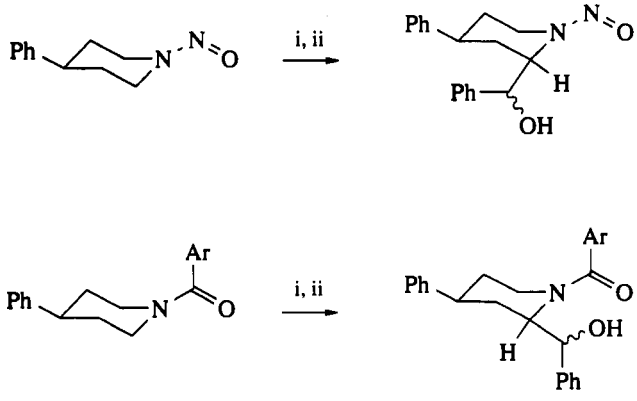


Scheme 1

The above examples notwithstanding, for an efficient and mild deprotonation the nitrogen is best derivatized. Two closely related amine derivatives activate the α-protons: nitrosamines[1,2,7,8] and amides.[2] The chemistry of nitrosamine and amide anions and related systems was thoroughly reviewed in 1984,[2] and so this chapter concentrates on recent developments. Most of these developments are in the area of dipole-stabilized species: amides, amidines and similar compounds. Synthetic applications of these systems have been investigated in two broad categories of substrates: achiral (or racemic) and chiral (nonracemic). In the latter case, the dipole-stabilized organometallic is chiral and nonracemic, affording interesting opportunities for asymmetric synthesis. Indeed, highly stereoselective methods for the prep-

aration of enantiomerically pure compounds have been developed that employ the stereoelectronic requirements of the organometallic to advantage. Thus, this chapter is divided along the following lines: synthetic applications of achiral and racemic systems, followed by synthetic applications of homochiral systems. Within each class, the examples are further categorized as either acyclic or heterocyclic according to the location of the carbanion/metal.

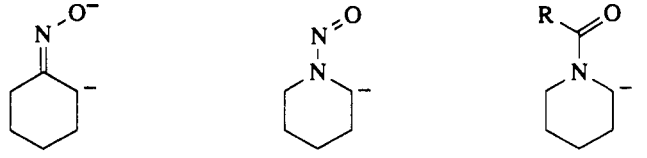
The geometries of amide and nitrosamine anions differ in a fundamental way, and this difference has important implications for synthesis. Although cyclic nitrosamines lose the axial proton *syn* to the nitrosamine oxygen[9] and alkylate by axial approach of the electrophile,[10] cyclic amides lose the equatorial proton and alkylate equatorially[11] to give the thermodynamically less stable product,[12] as illustrated in Scheme 2.



i, BuLi; ii, PhCHO

Scheme 2

Thus the nitrosamine anion is a resonance-stabilized species in which the carbanionic lone pair overlaps the π-system of the nitrosamine. By contrast, the amide anion is a dipole-stabilized species in which the lone pair remains in or near the nodal plane of the amide π-system. Given the similarity of the two systems, this difference in behavior is striking. Although the geometry observed in nitrosamine anion alkylations is similar to that of their isoelectronic counterparts, oxime dianions,[13,14] it is puzzling that amide anions differ, since they are also isoelectronic, as shown in Figure 1.



Alkylation: *syn*-axial *syn*-axial *syn*-equatorial

Figure 1 Isoelectronic anions

One explanation of the unique stereoelectronic requirements of amide anions ensues from *ab initio* studies conducted by Houk *et al.*,[12] Bach *et al.*,[15] and Bartolotti and Gawley.[16] To explain the equatorial alkylation, Bach argued, on the basis of calculations on a model system, that the rotation of the carbanion lone pair of $HCONHCH_2^-$ out of the amide nodal plane and into conjugation with the p-system results in a large increase in energy (16–18 kcal mol^{-1}; 1 cal = 4.18 J). The source of the increase is a destabilizing interaction between the HOMO of the amide and the carbanion lone pair. When mixed, Ψ_3 of the amide is raised 44.6 kcal mol^{-1}, while Ψ_2 is lowered only 27.4 kcal mol^{-1}, resulting in a net increase of 17 kcal mol^{-1} for the two frontier orbitals.[15] Even so, it is the *less* stable anion geometry (**1**; Figure 2) that is *syn* to the carbonyl.[15,16] It is not until the effect of the lithium cation is considered that

the *syn* geometry is seen to be the more stable (Li-**2**; Figure 2), by 28 kcal mol^{-1}.[16] It therefore seems most appropriate to call the reactive species 'dipole-stabilized organometallics'.

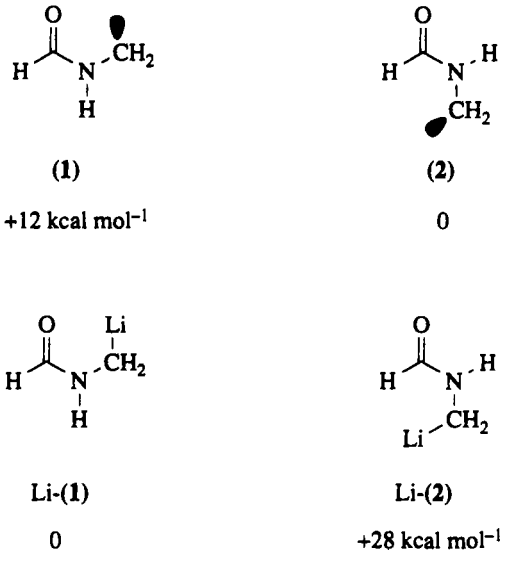
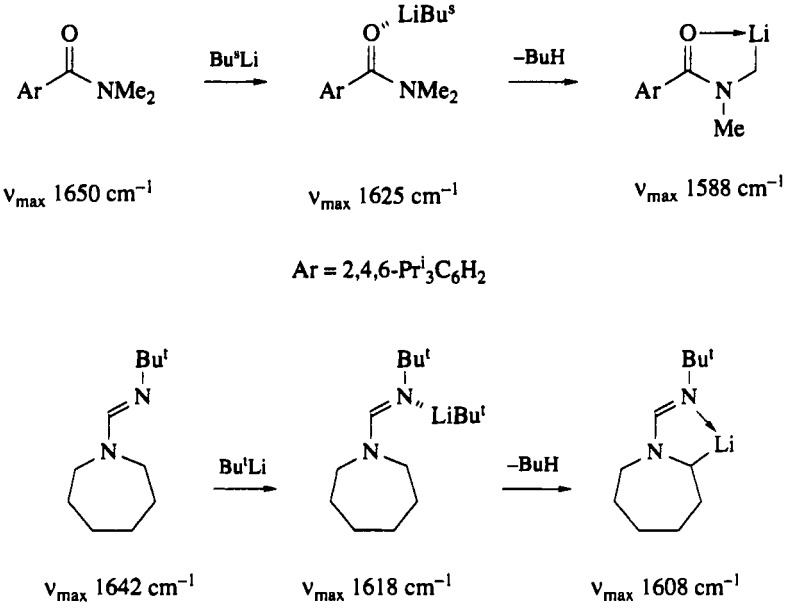


Figure 2 *Ab initio* structures and relative energies of N-methylformamide anion

The amide deprotonation step involves a prior coordination complex between the amide (or amidine) and the butyllithium base.[17,18,19] As shown in Scheme 3, formation of a coordination complex between an amide or amidine substrate and butyllithium is observed by IR shortly after mixing, but before the deprotonation. A recent mechanistic study has shown that this coordination complex is between the amide and the *s*-butyllithium aggregate, and that the effect of the coordination is to increase the reactivity of the complex.[20] In fact, the aggregate may be activated by adding TMEDA prior to the amide, with a similar increase in reactivity. However, because these studies were conducted in cyclohexane, extrapolation of these observations to ethereal solvents is somewhat problematic.[20]



Scheme 3

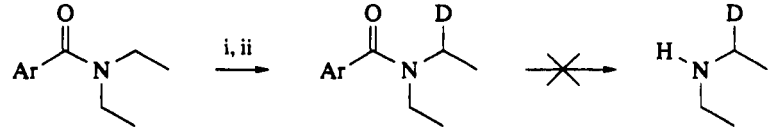
When the α-protons are allylic or benzylic, the selectivity of the deprotonation is attenuated by the competing stereoelectronic requirements of allylic activation and dipole stabilization. Stabilization of a

developing negative charge by resonance delocalization into a double bond and stabilization by an amide dipole which avoids resonance delocalization must be accommodated in the transition state and a balance of both effects must be achieved.[21] Moreover, the organolithium species must accommodate the amide dipole as well as the allyl system, since reaction with electrophiles at the γ′-position is common. These aspects of reactivity are discussed further in Section 1.2.3.1, in the context of deprotonation and alkylation of homochiral substrates.

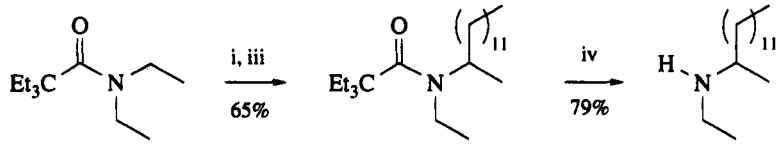
1.2.2 ACHIRAL AND RACEMIC PRECURSORS

1.2.2.1 Acyclic Systems

The alkylation of carbons α to nitrogen in acyclic systems has not developed much since the 1984 review.[2] Although amides may serve as excellent precursors of dipole-stabilized organolithiums, they are quite difficult to remove. For example, the two amide systems shown in Scheme 4 were designed to hinder approach of a nucleophile to the carbonyl carbon in order to preclude addition of the butyllithium base. Metalation on the carbon *syn* to the carbonyl oxygen is then the favored process, and alkylation occurs smoothly. The triisopropylbenzamides, however, could not be cleaved under a variety of acidic, basic, or reductive conditions. The diethylbutanamides behaved similarly in the alkylation step, and could be cleaved in good yield by acid hydrolysis.[22]



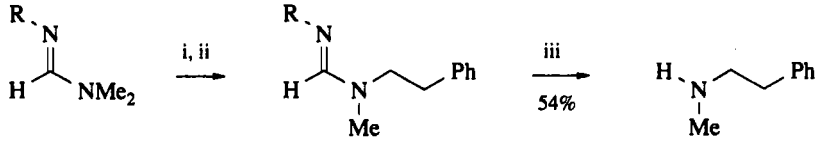
Ar = 2,4,6-$Pr^i_3C_6H_2$



i, Bu^sLi, TMEDA, Et_2O, –78 °C; ii, MeOD; iii, $Me(CH_2)_{11}I$; iv, HCl, H_2O, reflux 72 h

Scheme 4

Even though the diethylbutanamides are cleavable, the conditions required are quite harsh: aqueous hydrochloric acid at reflux for 3 d. A much better activating group was introduced in 1980 by Meyers: the formamidines shown in Scheme 5.[23] The decreased reactivity of the C═NR bond relative to the C═O bond toward nucleophilic attack obviates the need for a bulky group to shield the carbonyl carbon. In the initial report, both *N*-cyclohexyl-, *N*-*n*-butyl- and *N*-*t*-butyl-formamidines were employed, but subsequent reports have focussed on the latter.

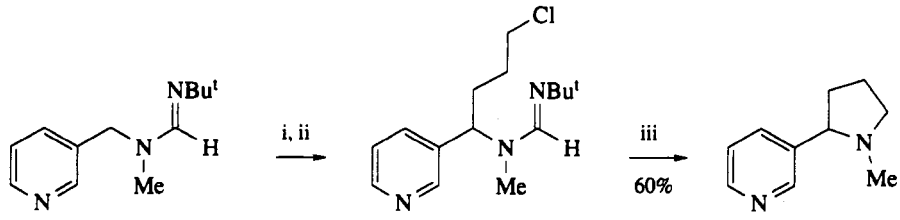


R = cyclohexyl, Bu^n, Bu^t

i, BuLi, THF, –78 °C; ii, BnBr, iii, HCl, H_2O, MeOH

Scheme 5

One aspect of the reactivity of unsymmetrical formamidines such as those shown in Scheme 6 is the selective deprotonation at a benzylic position. This selectivity was used in the illustrated synthesis of nicotine, which also demonstrates the mild conditions for removal of the formamidine activating group by hydrazinolysis.[24]

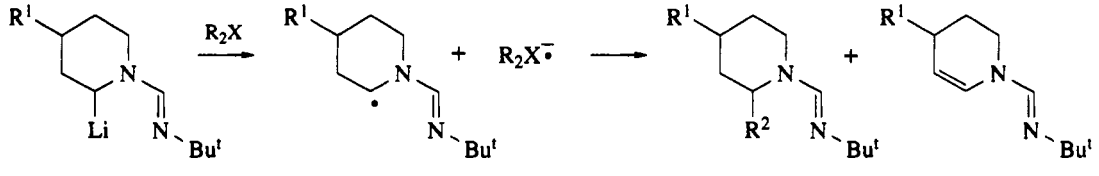


i, BuLi, THF, –78 °C; ii, $I(CH_2)_3Cl$; iii, N_2H_4, AcOH, EtOH, r.t.

Scheme 6

1.2.2.2 Heterocyclic Systems

Because of the difficulty of removing other activating groups, most of the work since the 1984 review[2] has been done with the formamidine auxiliary. In discussing this chemistry, an important point is that the acidity of the α-protons is considerably enhanced when they are also allylic or benzylic, and their chemistry is also somewhat different. The most important difference is the occurrence of single-electron transfer (SET) processes in the reaction of the lithiated amidines of five-, six- and seven-membered ring saturated heterocycles. For example, reaction of benzophenone with the lithiated piperidine (**3**), shown in Scheme 7, affords only benzophenone ketyl with no addition.[25] Reaction of (**3**) with alkyl halides results in low yields of alkylation products such as (**5**), with an oxidation product (**6**) being produced as well. That radical processes are involved is suggested by the reaction of (**3**) with hexenyl bromide,[26] affording a coupling product (**5**; R^2 = cyclopentylmethyl).[25] Conformationally locked systems such as (**3**; R = Bu^t) seem less likely to oxidize, and it was suggested that a conformationally mobile system might undergo ring inversion, thus placing the C—Li bond in an electronically unfavorable axial orientation, thereby encouraging SET.[25] Once oxidized, the radical (**4**) probably produces (**6**) by disproportionation.



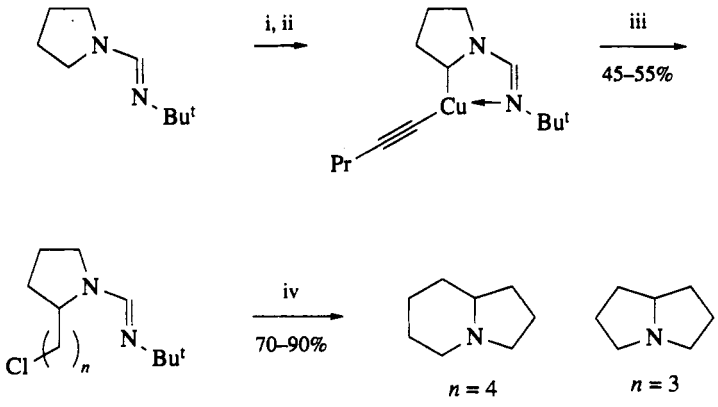
(**3**) (**4**) (**5**) (**6**)

Scheme 7

Two protocols circumvent, or at least minimize, the SET processes discussed above. One is addition of HMPA to the lithiated formamidines prior to addition of the alkyl halides, while the second is transmetalation to a cuprate.[25] Heterocycles having the C—Li bond in an allylic or benzylic position do not undergo SET at all.

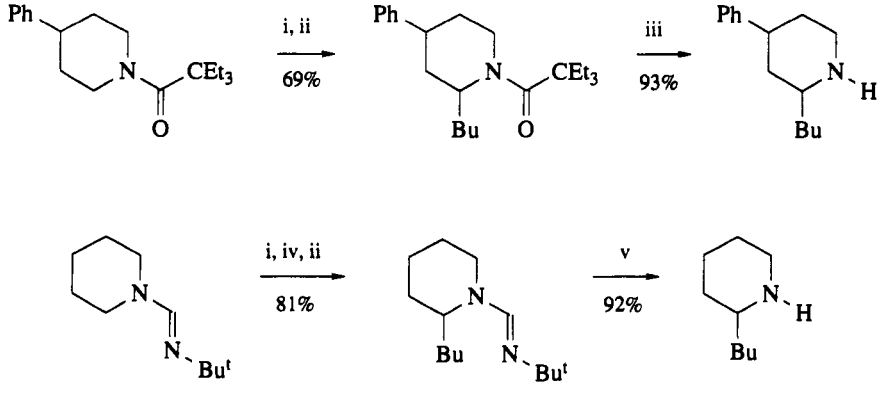
The following discussion is organized by the type of heterocycle being alkylated, beginning with pyrrolidines. Pyrrolidine formamidines, as their pentynyl cuprate derivatives, may be alkylated in good yield;[25] a process for the synthesis of 1-azabicyclic ring systems utilizing this methodology is illustrated in Scheme 8.[27] An analogous process was also reported for piperidine formamidines.

Metalated piperidine amides[22] and formamidines[25] may be converted to α-alkylated piperidines, as illustrated in Scheme 9. Again, the two examples illustrate the superiority of the formamidine moiety in both yield and ease of removal.



i, Bu^{t}Li, Et_2O–THF, –78 to –20 °C, 1 h; ii, PrC≡CCu; iii, I$(CH_2)_n$Cl; iv, KOH, MeOH, H_2O, 55 °C, 8–12 h

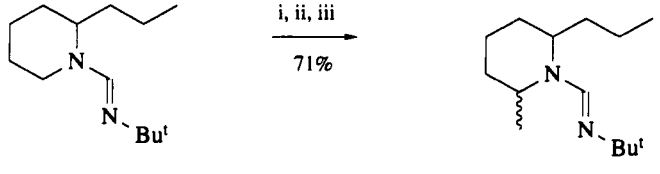
Scheme 8



i, Bu^{s}Li, –78 to –25 °C; ii, BuI; iii, HCl, H_2O, reflux, 3 d; iv, PrC≡CCu; v, KOH, MeOH, H_2O, 8–12 h

Scheme 9

An α-substituted piperidine formamidine may be metalated at the α′-position selectively, but the alkylation is not stereoselective, providing a 1:1 mixture of *cis* and *trans* stereoisomers, as illustrated in Scheme 10.[25]



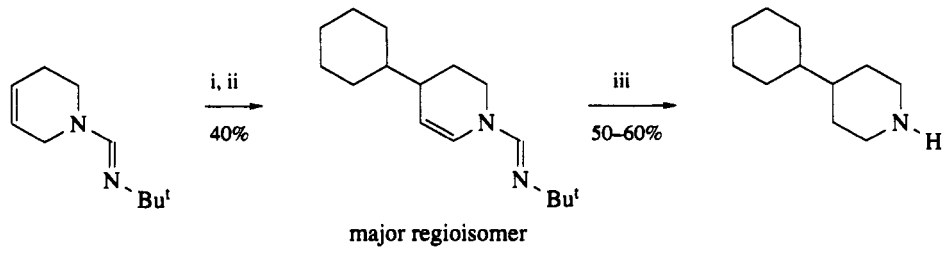
1:1 mixture of isomers

i, Bu^{s}Li, –78 to –25 °C; ii, PrC≡CCu; iii, MeI

Scheme 10

When the α-position is allylic, metalation is easier, and the resulting organolithium is not prone to oxidation; γ-substitution then predominates over α-substitution, as shown by the example in Scheme 11.[25]

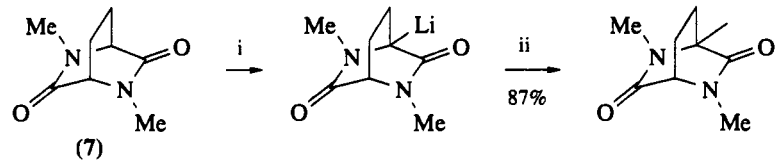
The stereoelectronic preference of dipole-stabilized organolithiums for the nodal plane of the amide or amidine π-system makes possible the directed metalation of bridgehead positions. Two examples are il-

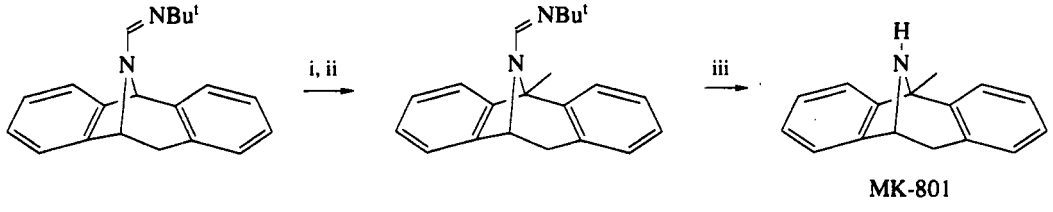


i, Bu^nLi, THF, –78 °C; ii, $C_6H_{11}I$; iii, $NaBH_4$, pH 6

Scheme 11

lustrated in Scheme 12. In the first, compound (**7**) is metalated selectively at the bridgehead methine, in preference to the methyl.[28] In the second, the bridgehead methine that is bisbenzylic is preferentially deprotonated.[29] The second example is the key step in the synthesis of the anticonvulsant agent MK-801; similar reactions afford access to a number of structural analogs.





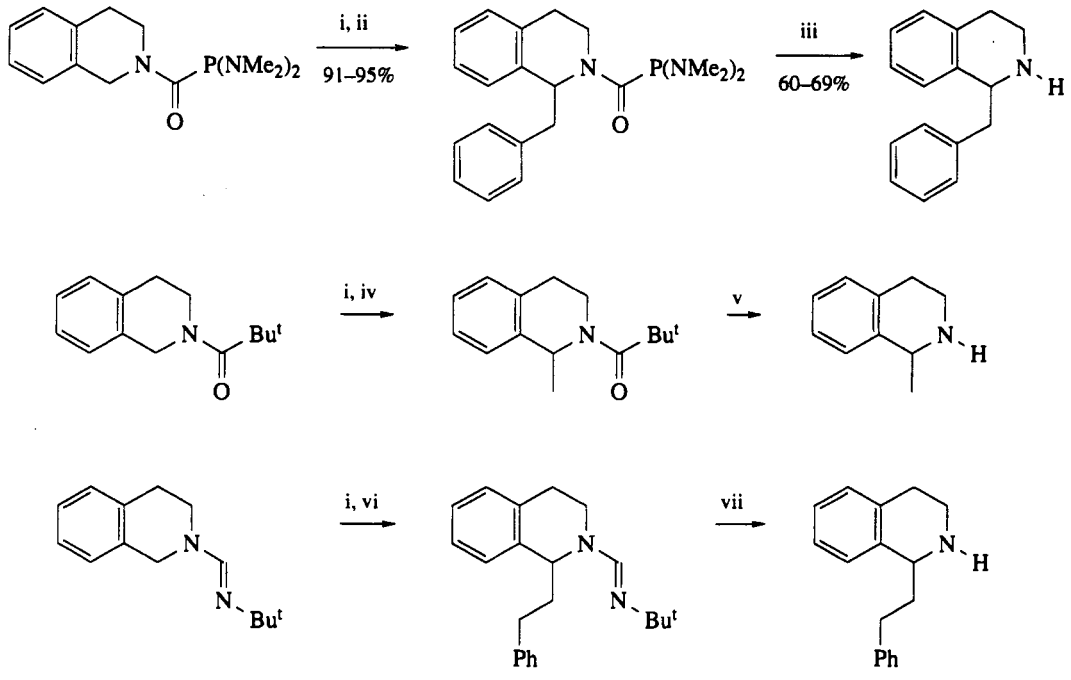
i, BuLi, THF, –78 °C; ii, MeI; iii, KOH, $HO(CH_2)_2OH$ or H_2SO_4, EtOH

Scheme 12

In 1981, several papers appeared detailing the alkylation of the 1-position of tetrahydroisoquinolines through the intermediacy of lithiated amides[30,31] phosphoramides,[32,33] and formamidines.[34] These systems are discussed thoroughly in Beak's 1984 review,[2] and so we will only provide one illustration of each in Scheme 13.

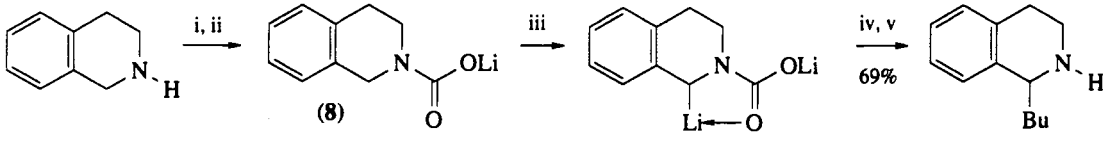
More recently, an ingenious 'one-pot' procedure for the activation, alkylation and deactivation sequence was reported by Katritzky.[35] Reaction of tetrahydroisoquinoline with *n*-butyllithium followed by carbon dioxide affords the lithium carbamate (**8**), which can be further metalated with *t*-butyllithium and alkylated, as shown in Scheme 14.

Both tetrahydroisoquinoline amides[31] and formamidines[34] may be successively alkylated at the 1-position. The second deprotonation is somewhat less facile, however, since it entails removal of a methine proton. In applying this methodology to the synthesis of naturally occurring tetrahydroisoquinoline alkaloids, a problem is encountered. The presence of oxygen substituents on the aromatic ring destabilizes the benzylic carbanion, and since this effect is felt in the transition state, the acidity of the benzylic protons is lowered. Thus, successive alkylation of *t*-butylformamidines of oxygenated tetrahydroisoquinolines is not possible. To circumvent the decreased acidity, a study of the relative acidity of various *N*-substituted formamidines was done[36] that resulted in a solution to the problem.[37] As shown in Scheme 15, successive alkylation of the methoxymethylphenylformamidine (**9**) is readily achieved.



i, BuLi, THF, –78 °C; ii, BnCl; iii, HCl, MeOH, H_2O, reflux; iv, MeI; v, Red-Al, C_6H_6; vi, $Ph(CH_2)_2Br$; vii, KOH, MeOH, H_2O, reflux

Scheme 13



i, Bu^nLi, THF; ii, CO_2; iii, Bu^tLi, –20 °C; iv, BuI; v, 2 M HCl

Scheme 14

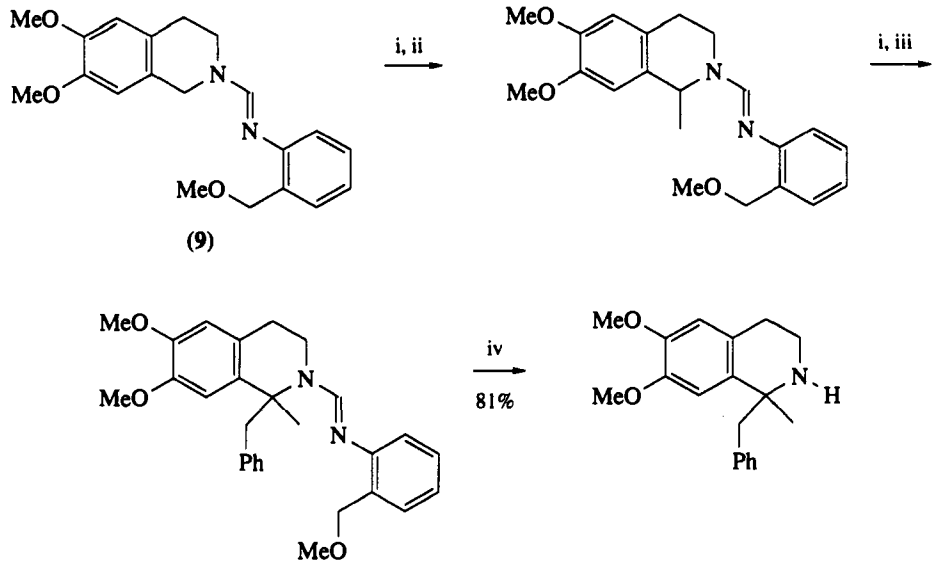
In 1982, Meyers extended the formamidine methodology to the elaboration of β-carbolines.[38] The indole nitrogen of the β-carboline is protected as either its MOM derivative[38] or its potassium salt.[39] The latter method was used in the short synthesis of (±)-yohimbone illustrated in Scheme 16.[40]

Finally, formamidines may be used to mediate the alkylation of perhydroazepines, as illustrated in Scheme 17.[25] As was the case with alkylation of the saturated heterocycles above, transmetalation to a cuprate or addition of HMPA was necessary to preclude SET reactions.

1.2.3 HOMOCHIRAL PRECURSORS

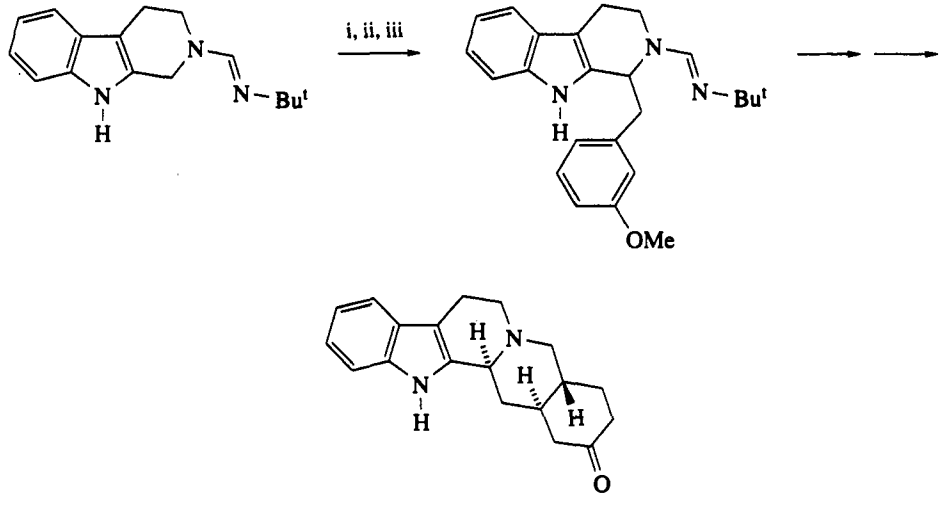
1.2.3.1 Mechanistic Aspects

The vast majority of stereoselective reactions in organic chemistry, especially in asymmetric synthesis, involve diastereofacial differentiation of a trigonal, sp^2-atom. The stereoelectronic considerations outlined in the introduction to this chapter afford a rare opportunity in stereoselective synthesis: the preparation of a chiral organometallic in which the carbon bearing the metal is stereogenic. As a result of the



i, Bu^{n}Li, THF, –78 °C; ii, MeI, –100 °C; iii, BnX; iv, N_2H_4, EtOH, H_2O, AcOH, reflux

Scheme 15



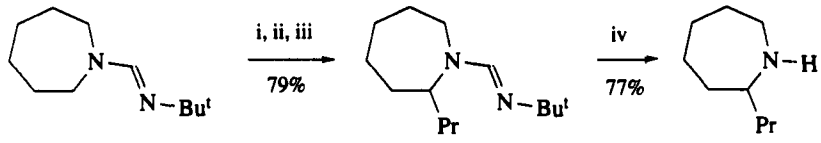
Yohimbone; 38% overall

i, KH, THF; ii, Bu^{t}Li, –78 °C; iii, $ArCH_2Cl$

Scheme 16

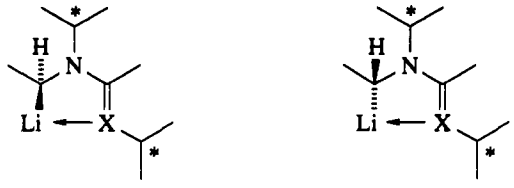
tendency of the carbon–metal bond of a dipole-stabilized organometallic to orient in the nodal plane of the amide (or amidine) π-system, the carbanion retains sp^3-geometry, as illustrated above in Figure 2.

When the precursor is achiral, two enantiomeric dipole-stabilized organolithiums may be formed. On the other hand, if the precursor is chiral, the two organolithiums are diastereomeric (Figure 3), and of unequal energy. The chirality center of the substrate may in principle be anywhere in the molecule, but the examples reported to date all have the stereocenter immediately adjacent to one end or the other of the amide group. Thus, the stereogenic carbon bearing the lithium may be influenced by an existing stereocenter either three or five atoms distant.



i, Bu^{t}Li, THF, –78 to –20 °C; ii, PrC≡CCu; iii, PrI; iv, KOH, MeOH, H_2O

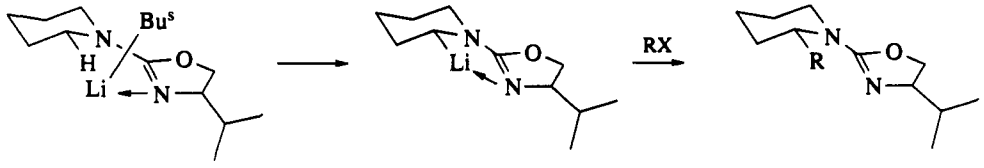
Scheme 17



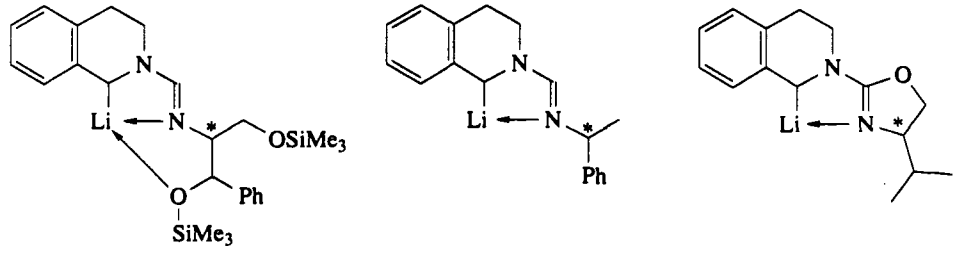
X = O, N; * = stereocenter

Figure 3 Diastereomeric dipole-stabilized organolithium compounds

There are two steps in the overall alkylation process: (i) deprotonation of diastereotopic protons; and (ii) electrophilic attack on the intermediate dipole-stabilized organolithium(s). Either of these processes might, in principle, be the source of the diastereoselectivity observed in the overall process. *Ab initio* studies suggest that the barrier to inversion for a free dipole-stabilized anion is 16–18 kcal mol^{-1},[15] and that the *syn* lithiated species is 28 kcal mol^{-1} more stable than the *anti* (Figure 2).[16] Thus, in the absence of other functionality, the two diastereomers shown in Figure 3 do not invert. Because the stereoelectronic effects of dipole stabilization are felt in the transition state for deprotonation of conformationally locked piperidines, the equatorial proton is removed selectively in both amides[11,12] and amidines,[25] as shown in Scheme 3 above. Note also that prior coordination of the alkyllithium base promotes selective removal of the equatorial proton *syn* to the amide oxygen or amidine nitrogen by a complex-induced proximity effect.[41] In a conformationally mobile piperidine having an oxazoline chiral auxiliary, the selective removal of the equatorial proton from one of two chair conformers has been postulated to explain the formation of a single diastereomer of alkylation product, as shown in Scheme 18.[42]



Scheme 18



	(a)	(b)	(c)
Selectivity at –78 °C	9:1	1.2:1	9:1

Figure 4 Chiral auxiliaries for isoquinoline alkylation

Virtually all of the synthetic applications of chiral dipole-stabilized organolithiums reported to date have the C—Li bond in an allylic or benzylic system. The most important consequence of this fact is that the two stereoisomers shown in Figure 3 *can interconvert* by pyramidal inversion. Therefore, the stereoselectivity of the deprotonation is irrelevant to the stereoselectivity as manifested in the product diastereomer ratio.[43] The source of the selectivity in the organolithium alkylation step has not been determined. The available data do not permit a distinction between at least three possibilities: thermodynamic control as determined by the equilibrating organolithium diastereomers,[43,44] kinetic control according to Curtin–Hammett kinetics,[45] or increased carbon–lithium covalency at low temperature.[46]

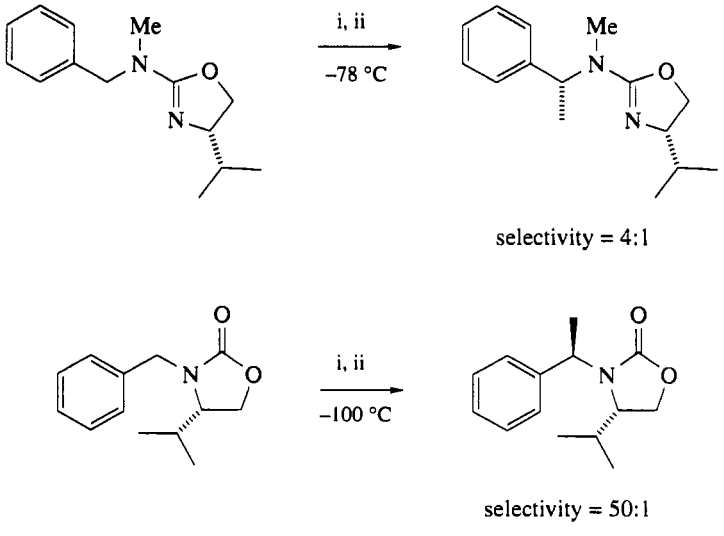
The seminal paper on the stereoselective alkylation of chiral dipole-stabilized organolithiums appeared in 1983. In the preliminary communication[47] and the full paper which followed,[48] Meyers made the important observation that formamidines lacking an oxygen atom in the auxiliary afford poor selectivity. The mechanistic rationale originally provided[47] for this observation was later revised.[49,50] The current picture can be explained by comparison of the structures illustrated in Figure 4. In (a), the dipole-stabilized organolithium is internally chelated by both the nitrogen and the oxygen of the formamidine, an effect which prevents rotation around the bond from the chelating formamidine nitrogen to the stereocenter (*).[47] In (b), this bidentate chelation is absent and free rotation diminishes the efficient transfer of stereochemical information and poor stereoselection ensues. In (c), free rotation is again precluded, this time by incorporation of the stereocenter into an oxazoline ring.[42,43,51]

There is another important feature of these systems to keep in mind: the effect of alkylation temperature on the diastereomer ratio. The selectivity observed in the alkylation of the tetrahydroisoquinoline formamidine illustrated in Figure 4(a) (with methyl iodide) increases from 9:1 to 99:1 when the temperature is lowered from –78 to –100 °C.[47,48] Similarly, the selectivity with the oxazoline illustrated in Figure 4(c) (with methyl iodide) increases from 9:1 at –78 °C to 19:1 at –100 °C.[43,51]

One last effect is seen in alkylations of chiral isoquinoline derivatives: the effect of oxygen substitution on the aromatic nucleus.[43] When electron-donating oxygen substituents are present in the 6- and/or 7-positions of the tetrahydroisoquinoline, the stereoselectivity of the alkylations is increased. This may be interpreted as a decreased tendency of the benzylic carbanion to be delocalized into the ring, and a consequential increase in the importance of dipole stabilization, with its strict stereoelectronic requirements.

1.2.3.2 Acyclic Systems

Whereas acyclic stereoselection in enolate alkylations is now a relatively mature field,[52] the stereoselective alkylation of acyclic dipole-stabilized systems is virtually undeveloped. The only report to date

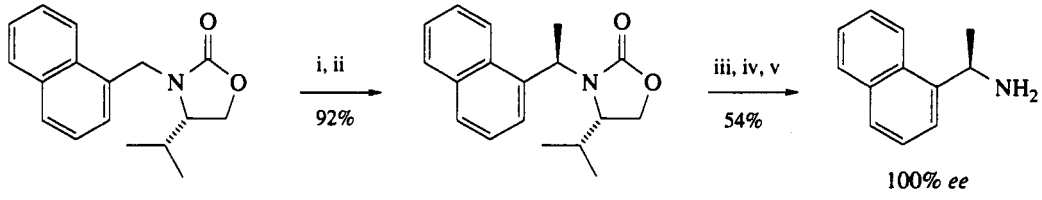


i, Bu^{n}Li, THF; ii, MeI

Scheme 19

originates from our own laboratories.[53] We made a comparison between two systems having the existing stereocenter on either end of the amide/amidine function (*cf.* Figure 3). The pertinent results are shown in Scheme 19. In the first instance, the stereocenter is in a chiral auxiliary appended to *N*-methylbenzylamine, and is a case of 1,5-asymmetric induction. Not surprisingly, the selectivity is poor (4:1), although the absolute configuration of the new stereocenter is the same as the well-studied[43] tetrahydroisoquinolyloxazolines (*vide infra*). The second example moves the stereocenter to the other end of the amide system (1,3-asymmetric induction, *cf.* Figure 3), and the selectivity is improved dramatically to 50:1.[53]

The second example has been used in a stereoselective synthesis of α-alkylbenzylamines, as shown by the example illustrated in Scheme 20.[53] Note that this sequence destroys the existing stereocenter. Because the original stereocenter is deliberately destroyed after the creation of a new one, the overall process constitutes a 'self-immolative chirality transfer'.[54]

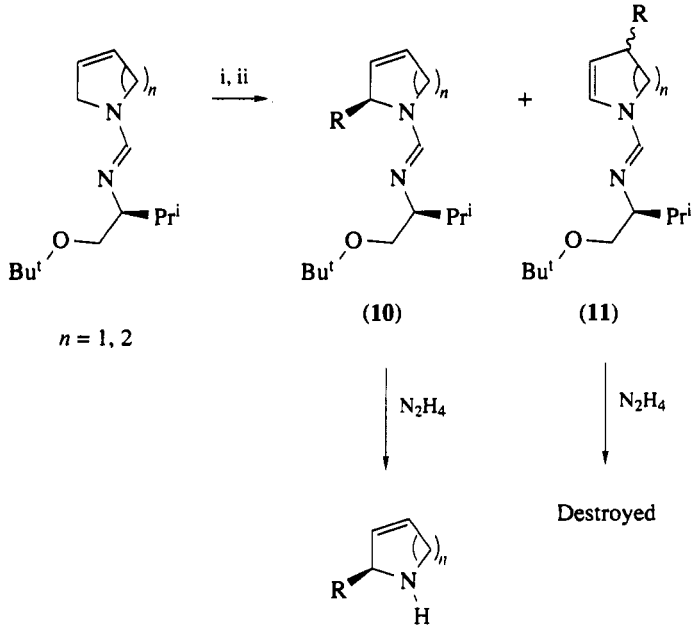


i, Bu^{n}Li, –78 °C; ii, MeI, –100 °C; iii, KOH, ether; iv, $Pb(OAc)_4$, CH_2Cl_2, MeOH; v, HCl, EtOH

Scheme 20

1.2.3.3 Heterocyclic Systems

The following discussion is organized according to the type of heterocycle being alkylated, as follows: dehydropyrrolines and isoindolines, followed by dehydropiperidines, tetrahydroisoquinolines and β-carbolines. As mentioned previously, the alkylation of saturated heterocycles (the acidic protons being neither allylic nor benzylic) is problematic. Either they fail to metalate when the nitrogen contains a



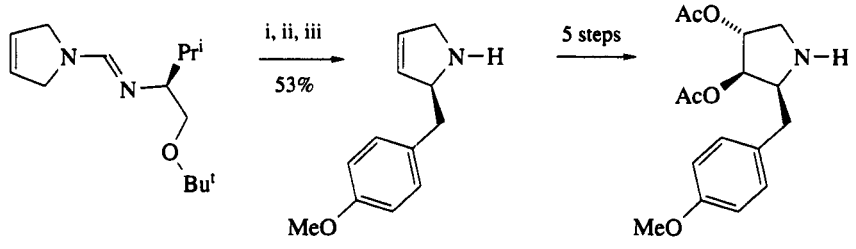
i, Bu^{n}Li, –78 °C; ii, RX, –100 °C

Scheme 21

chiral formamidine auxiliary,[55] or they fail to undergo cross-coupling after metalation when the nitrogen contains a chiral oxazoline auxiliary.[42] In the latter instance, SET processes predominate.

These shortcomings have been circumvented by using a heterocycle containing a double bond, as illustrated by the examples in Scheme 21. As was the case with the achiral systems (*cf.* Scheme 11), a mixture of regioisomers is obtained, but now the α-substitution product (**10**) predominates. The amount of γ-substitution product (**11**) produced depends on the ring size, and may be as high as 30% of the product mixture for the dehydropiperidines.[55] Nevertheless, the unwanted γ-isomer (**11**) is destroyed chemoselectively when the mixture is treated with hydrazine to remove the chiral auxiliary. Double bond reduction would then give the α-alkylated saturated heterocycle.

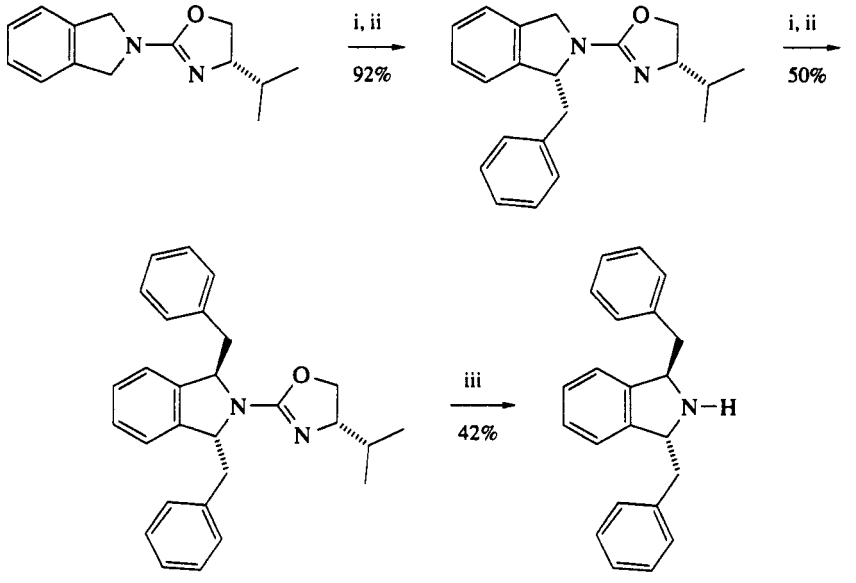
The asymmetric alkylation of Δ^2-pyrroline has been used in the synthesis of anisomycin in 90% *ee* using a formamidine chiral auxiliary, as shown in Scheme 22.[56]



i, Bu^{t}Li, THF, –78 °C; ii, $ArCH_2Cl$, –100 °C; iii, N_2H_4, AcOH, EtOH

Scheme 22

An oxazoline auxiliary has been used to alkylate stereoselectively and regioselectively isoindoline at the α- and α′-positions to produce the C_2-symmetric amine (**12**), as shown in Scheme 23.[57]



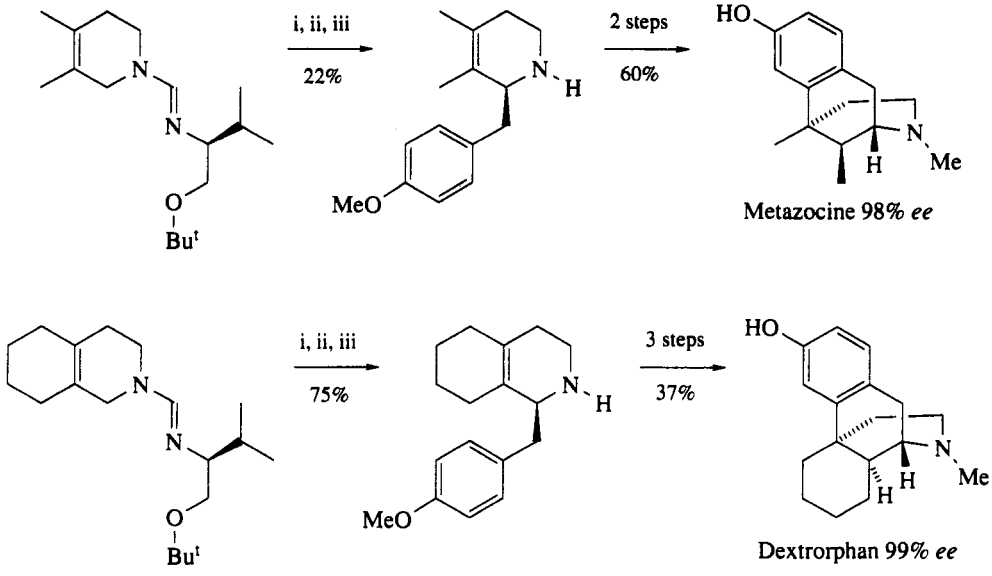
(**12**) 100% *ee*

i, Bu^{n}Li, –78 °C, THF; ii, BnCl; iii, N_2H_4, *p*-TsOH, EtOH, reflux

Scheme 23

Scheme 24 illustrates the use of a formamidine auxiliary for asymmetric alkylation of dehydropiperidine derivatives in the synthesis of metazocine[55] and dextrorphan[58] in 98% and 99% *ee*, respectively.

The enormous number of naturally occurring isoquinoline alkaloids, and their importance biologically,[59] has stimulated a great deal of effort in their synthesis. The asymmetric alkylation of the 1-position of the tetrahydroisoquinoline nucleus affords an extremely valuable method for the construction of



i, Bu^nLi, –78 °C; ii, $ArCH_2Cl$, –100 °C; iii, N_2H_4, AcOH

Scheme 24

both simple and complex isoquinoline alkaloids by the simple retrosynthesis illustrated in Figure 5. The following discussion presents selected examples of the synthesis of simple isoquinoline alkaloids, followed by a few examples of the use of this method for the synthesis of key intermediates in the preparation of more complex systems.

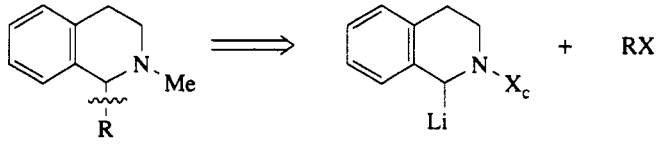
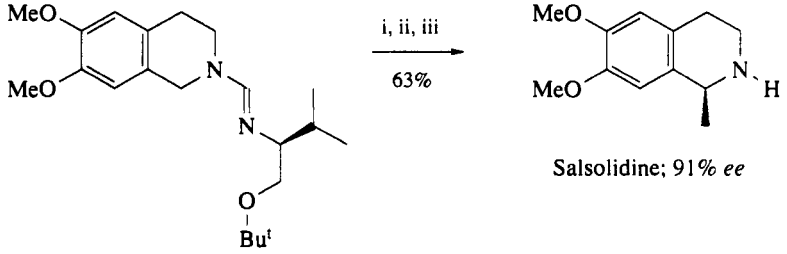


Figure 5 Retrosynthesis of simple isoquinoline alkaloids

Perhaps the simplest of the isoquinoline alkaloids is salsolidine. It has been synthesized by asymmetric alkylation of 6,7-dimethoxytetrahydroisoquinoline using either a formamidine[60,61] or oxazoline[51] chiral auxiliary. Scheme 25 illustrates the recently published *Organic Syntheses* preparation of salsolidine on a 5 g scale.[62] It is of interest to note that, in this and all subsequent examples of asymmetric alkylation of tetrahydroisoquinolines, formamidines derived from L-valine afford (1*S*)-tetrahydroisoquinolines, while oxazolines derived from L-valine afford the (1*R*)-enantiomer. The reason is simply the opposite orienta-

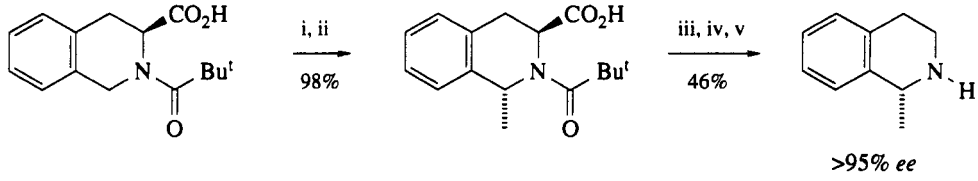


i, Bu^tLi, THF, –78 °C; ii, MeI, –100 °C; iii, N_2H_4, AcOH, EtOH

Scheme 25

tion of the isopropyl group in the two auxiliaries. In the lithiated formamidine, bidentate chelation by both heteroatoms places the isopropyl on the β-face, whereas it is on the α-face in the oxazolines.

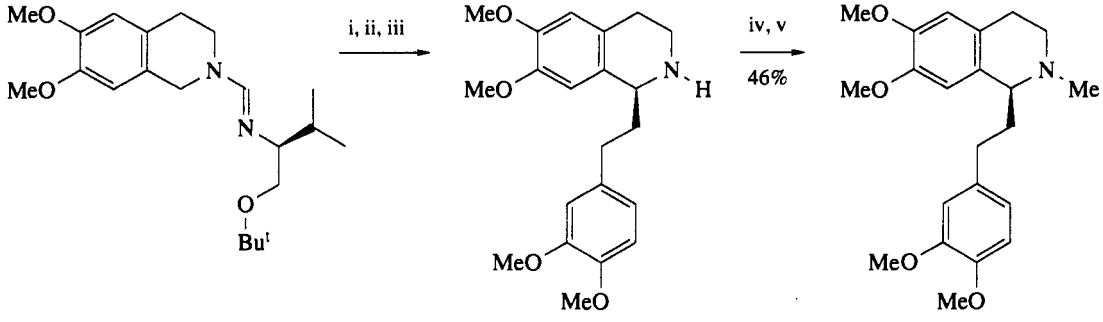
The stereoselective alkylation of tetrahydroisoquinoline pivalamides containing a stereocenter at the 3-position was reported in 1987 by Seebach.[63] The self-immolative chirality transfer process illustrated in Scheme 26 affords only one diastereomer. Oxidative decarboxylation and reduction afford the alkylation products in ≥95% *ee*.



i, 2 Bu^{t}Li, THF, –75 °C; ii, MeI; iii, anode, MeOH; iv, $NaCNBH_3$; v, $NaAlH_4$

Scheme 26

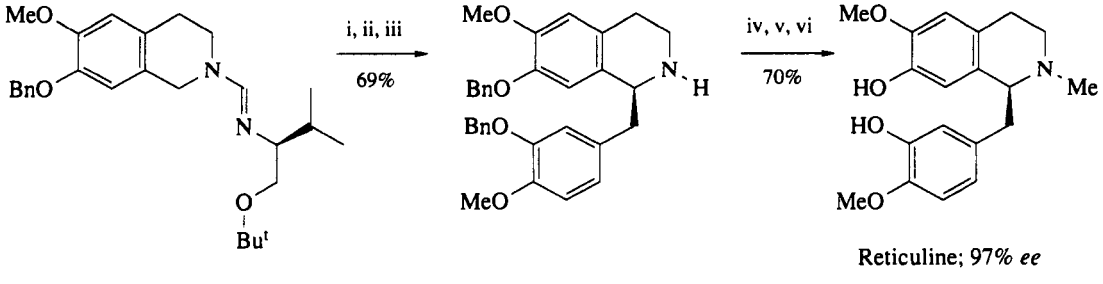
The alkylation of the tetrahydroisoquinoline nucleus, mediated by a formamidine auxiliary, with a dimethoxyphenethyl iodide has afforded (*S*)-homolaudanosine in 95–96% *ee*, as shown in Scheme 27.[60,61]



i, Bu^{t}Li, THF, –78 °C; ii, $Ar(CH_2)_2I$, –100 °C; iii, N_2H_4, AcOH; iv, HCO_2Et; v, $LiAlH_4$

Scheme 27

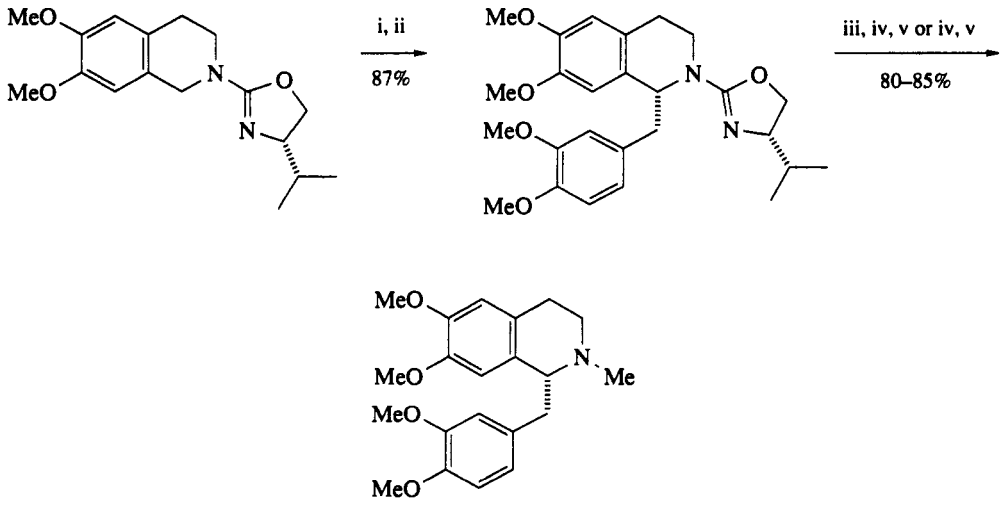
Reticuline, the biosynthetic precursor of all the morphine alkaloids, was synthesized by a similar approach (97% *ee*), as shown in Scheme 28.[64]



i, Bu^{t}Li, THF, –78 °C; ii, $ArCH_2Br$, –100 °C; iii, N_2H_4, AcOH, EtOH; iv, $ClCO_2Et$; v, $LiAlH_4$; vi, H_2, Pd/C

Scheme 28

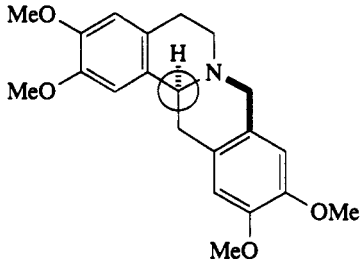
Another benzylisoquinoline alkaloid, laudanosine, is the synthetic precursor of morphinans. It has been synthesized in 95–96% *ee* by asymmetric alkylation of an isoquinolyloxazoline, as shown in Scheme 29.[43,65] An interesting point here is the discovery of a shortcut for removing the auxiliary and



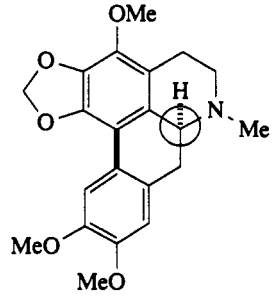
Laudanosine; 94–96% *ee*

i, Bu^tLi, THF, –78 °C; ii, $ArCH_2Cl$, –100 °C; iii, $N_2H_4 \cdot H_2O$, *p*-TsOH, EtOH; iv, HCO_2COMe; v, $LiAlH_4$

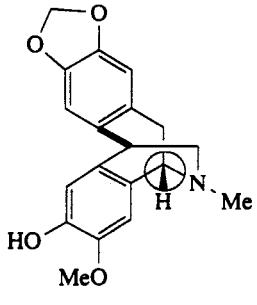
Scheme 29



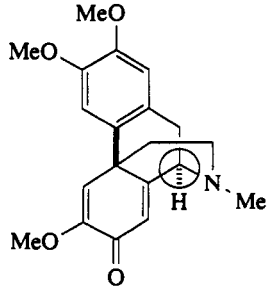
Norcoralydine; 99% *ee*



Octoeine; 93% *ee*



Reframoline; 98–99% *ee*



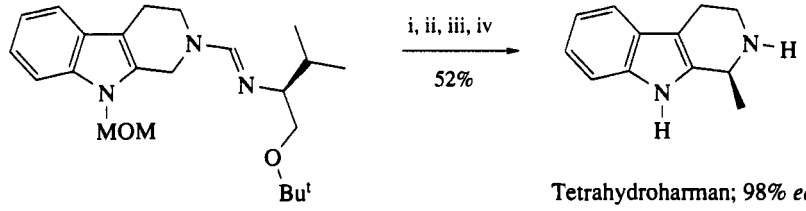
O-Methylflavinantine; 94–96% *ee*

Figure 6 Complex isoquinoline alkaloids synthesized by elaboration of simple benzylsoquinolines. The bond(s) formed after the asymmetric alkylation are bold; the stereocenter created in the asymmetric alkylation is circled

methylating the nitrogen. Treatment of the alkylated isoquinolyloxazoline with acetic formic anhydride removed the oxazoline and formylated the nitrogen in a single operation.[65]

Because benzylisoquinolines have been available synthetically (in racemic form) for decades, there is quite a bit of chemistry known regarding their use as key intermediates in the synthesis of a number of more complex isoquinoline alkaloids. The asymmetric synthesis of benzylisoquinolines has been used to complete total synthesis of representative members of several of these alkaloid classes. As shown in Figure 6, the protoberberine alkaloid norcoralydine,[60,61] the aporphine alkaloid ocoteine,[61,66] the isopavine alkaloid reframoline[61] and the morphinan *O*-methylflavinantine[65] have been made available in optically active form for the first time (except by isolation or resolution) using this approach.

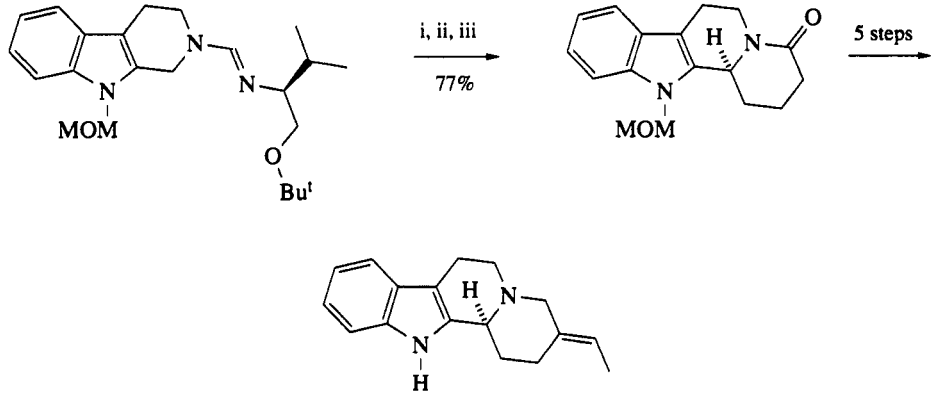
The asymmetric alkylation of the β-carboline ring system affords access to indole alkaloids. The simplest is tetrahydroharman, whose synthesis is mediated by asymmetric alkylation of a formamidine, as shown in Scheme 30.[67] In the racemic series (*cf.* Scheme 16), the indole nitrogen may be protected simply by deprotonation with potassium hydride. However, in the chiral series the presence of a potassium ion lowers the selectivity. Thus, the methoxymethyl protecting group was used.



i, Bu^{n}Li, THF, –78 °C; ii, MeI, –100 °C, iii, N_2H_4, AcOH; iv, H^+

Scheme 30

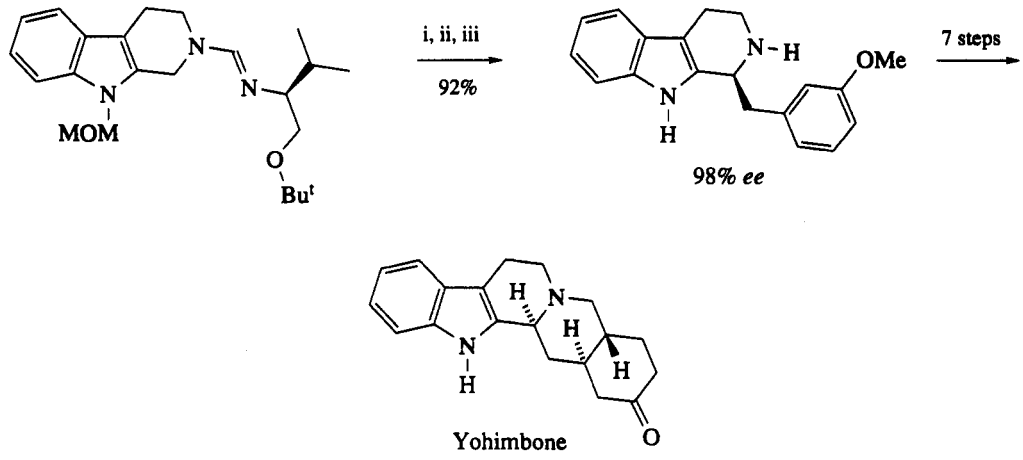
The asymmetric alkylation of the β-carboline formamidine was also used in the asymmetric synthesis of deplancheine in 96% *ee* (Scheme 31), a synthesis which served to correct the previously assigned absolute configuration of the natural product.[68]



i, Bu^{n}Li, THF, –78 °C; ii, $Br(CH_2)_3OBO$; iii, N_2H_4, H^+

Scheme 31

A similar approach was used for the asymmetric synthesis of yohimbone,[40] a process that uses the stereocenter created by asymmetric alkylation as the control element for the stereoselective formation of two more stereocenters, as shown in Scheme 32.



i, Bu^nLi, THF, –80 °C; ii, $ArCH_2Cl$, –80 °C; iii, N_2H_4, H^+

Scheme 32

1.2.4 REFERENCES

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1.3
Alkylations of Sulfur- and Selenium-containing Carbanions

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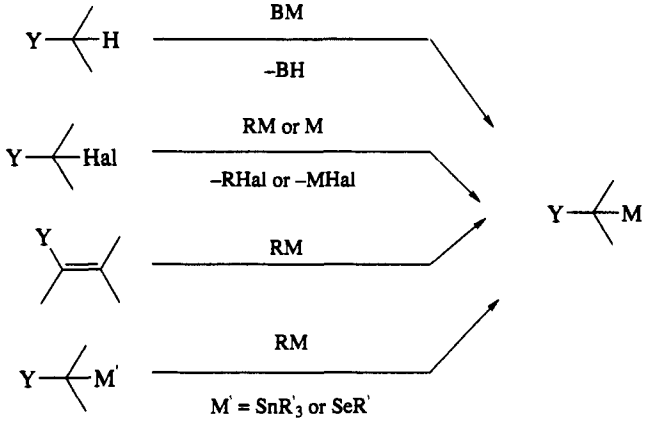
1.3.1 INTRODUCTION

α-Thio organometallics[1–44] and their seleno analogs[1,3-6,10,11,17,18,23,25,45-56] have proved to be extremely useful reagents and they have been used extensively in synthesis over the past 20 years. Upon reaction with compounds bearing an electrophilic carbon atom, they allow the efficient formation of a new carbon–carbon bond to which the heteroatomic moiety is directly linked. The large variety of reactions possible through use of organosulfur and organoselenium reagents with subsequent selective removal of the heteroatomic moiety permits the synthesis of a large variety of compounds.

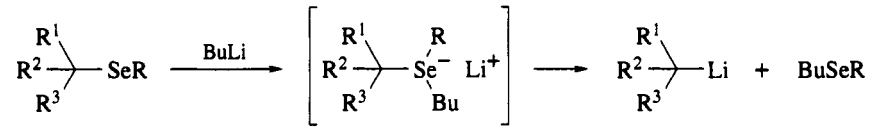
This chapter is devoted exclusively to the alkylation of the above mentioned organometallic reagents with alkyl halides, epoxides and oxetanes. It includes a large variety of organosulfur- and organoselenium-stabilized carbanions derived from saturated and unsaturated sulfides, selenides, sulfoxides, selenoxides and sulfones as well as those carbanions bearing another heteroatomic moiety. The chapter excludes, however, those organometallics which can be viewed as α-thio and α-seleno enolates.

Although α-thio and α-seleno organometallics can be prepared by a large array of reactions[4,23,57] which are listed in Scheme 1 and involve: (**i**) hydrogen–metal exchange, (**ii**) halogen–metal exchange, (**iii**) addition of organometallics on α-heterosubstituted carbon–carbon double bonds, and (**iv**) heteroatom (Sn,Se)–metal exchange, the first reaction has proved to be by far the most convenient due to the availability of the starting material and of a large array of bases.



Scheme 1

Butyllithiums in THF (often without an additive, and in some cases with the help of a complexing agent such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA),[58] diazabicyclooctane (DABCO),[59] hexamethylphosphoramide (HMPA),[60] and crown ethers) have been used successfully for the metallation of sulfides such as dimethyl sulfide,[58] methyl phenyl[59] and primary alkyl phenyl sulfides,[60,61] cyclopropyl phenyl sulfide,[17,25,61] as well as allyl,[14,16,24] benzyl[14,16] and vinyl sulfides,[20] thioacetals,[20,26,27,30] sulfoxides,[14,16,32,33] sulfones[36,37] and sulfoximides (sulfoximines).[62] However these bases are not able to metallate *s*-alkyl sulfides, due to their low acidity,[60] or sulfonium salts[41] (except Bu^{t}Li in some cases) or almost all selenium derivatives[23,25,52,54] due to their high propensity to react at the sulfur and selenium atoms respectively of these compounds. The last reaction which leads finally in the case of selenides to a butyl selenide and to a novel organometallic, the one possessing the most stabilized carbanionic center, (Scheme 2) is the method of choice[23,25,46,52,54] for the synthesis of a large variety of α-selenoorganolithium compounds.



Scheme 2

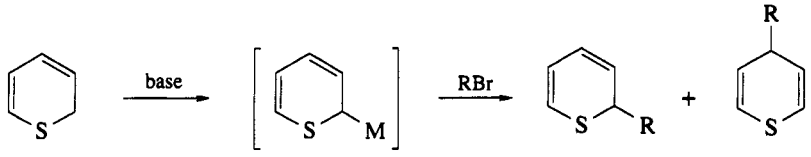
Thus, α-selenoalkyllithiums[23,25,45,47,54,63–75] (see Volume 1, Chapter 2.6), α,α-di(seleno)alkyllithiums[64,65,76–78] as well as related α-selenobenzyl-,[72,79,80] α-selenoallyl-[81] and α-selenovinyl-lithiums[82,83] belonging to the phenyl- and the methyl-seleno series have been successfully synthesized from the corresponding selenoacetals,[64,74,84–87] selenoorthoesters[64,65,76] and keteneselenoacetals[88–90] respectively using *n*-butyllithium in THF or *s*-butyllithium in ether. The Se/Li exchange method has also proved to be particularly efficient for the synthesis of α-thioalkyllithiums including those which possess dialkyl-substituted carbanionic centers from mixed S,Se acetals.[68,69,73,91–93]

α-Selenoallyl-,[81,94–101] α-selenopropargyl-,[102,103] α-selenoallenyl-[103] and α-selenobenzyl-metals,[74,80,104–106] 1,1-di(seleno)alkylmetals,[64,74,76,107,108] 1,1-di(seleno)benzylmetals,[80] and α-selenovinylmetals[107–111] have been produced by metallation of the corresponding carbon acid with metalloamides. Although lithium diethylamide, lithium diisobutyramide, lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LITMP) in THF or THF–HMPA have been used for that purpose, KDA[80,108] (a 1:1 mixture of LDA and potassium *t*-butoxide) has proved to be by far the most suitable base for this purpose. However the metallation reaction is strictly limited (except rare cases) to the arylseleno series and does not apply to their methylseleno analogs; hence the method employing the Se/Li exchange is preferred. The metallation reaction is the only reasonable route to α-metalloalkyl selenoxides,[112–115] α-metallovinyl selenoxides,[107] α-metalloalkyl sulfonium salts,[41] α-metalloalkyl selenonium salts[116,117] and α-metalloalkyl selenones.[117–119]

Successful alkylation or hydroxyalkylation of the above mentioned species requires that these organometallics, which are potential carbenoids: (i) do not decompose to carbene or to an isomeric organometallic under the conditions required for their reactions with electrophiles; and (ii) that they act as nucleophiles rather than as bases. This has effectively proved to be the case for most of them.

As will be discussed later in this chapter, although the alkylation reaction is in almost all cases reasonably successful with methyl iodide and primary alkyl halides, ethylene oxide and terminal epoxides, it is

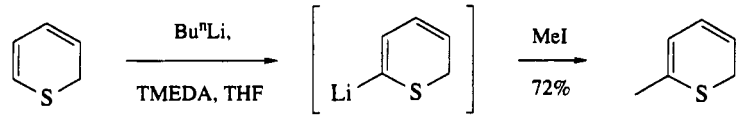
(a)



(ref. 120)

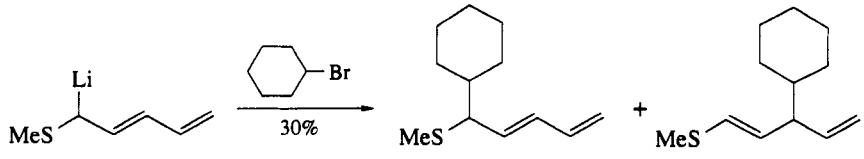
Base	*R*	*Yield (%)*	*Product ratio*
KNH_2/NH_3	c-C_6H_{11}	82	85:15
KNH_2/NH_3	Bu^t	54	100:0
LDA, THF–HMPA	Bu^t	31	100:0

(b)



(ref. 213)

(c)



(ref. 120)

product ratio not given

Scheme 3

less general with *s*-alkyl halides and α,β-disubstituted epoxides and is exceptional with tertiary alkyl halides[120] (Scheme 3, entries a and c) and almost unprecedented with tetraalkyl-substituted oxiranes.

The alkylation reaction has proved to be more efficient with the softer organometallics of the series and proceeds *via* an ionic pathway, and *via* radical species with the most substituted alkyl halides.[120,121] Although alkyl iodides are usually more reactive than the corresponding bromides and chlorides, the use of the former compounds does not seem to be crucial.

Allylation and benzylation reactions usually take place more efficiently than alkylation reactions due to the higher reactivity of the former derivatives. Allylation and benzylation is however difficult with the hardest organometallics of the series such as seleno- or thio-alkyllithiums. Finally, alkyl halides are usually less reactive towards α-thio- and α-seleno-alkyllithiums than aldehydes or ketones (see Scheme 11)[25,122] which seem to possess a reactivity closer to that of allyl halides (see Scheme 12).[123]

1.3.2 REACTIONS OF α-THIO- AND α-SELENO-ALKYLLITHIUMS BEARING HYDROGEN AND/OR HYDROCARBON SIDE CHAINS ON THEIR CARBANIONIC CENTER

1.3.2.1 Alkylation

1.3.2.1.1 Alkylation of α-thio- and α-seleno-alkyllithiums

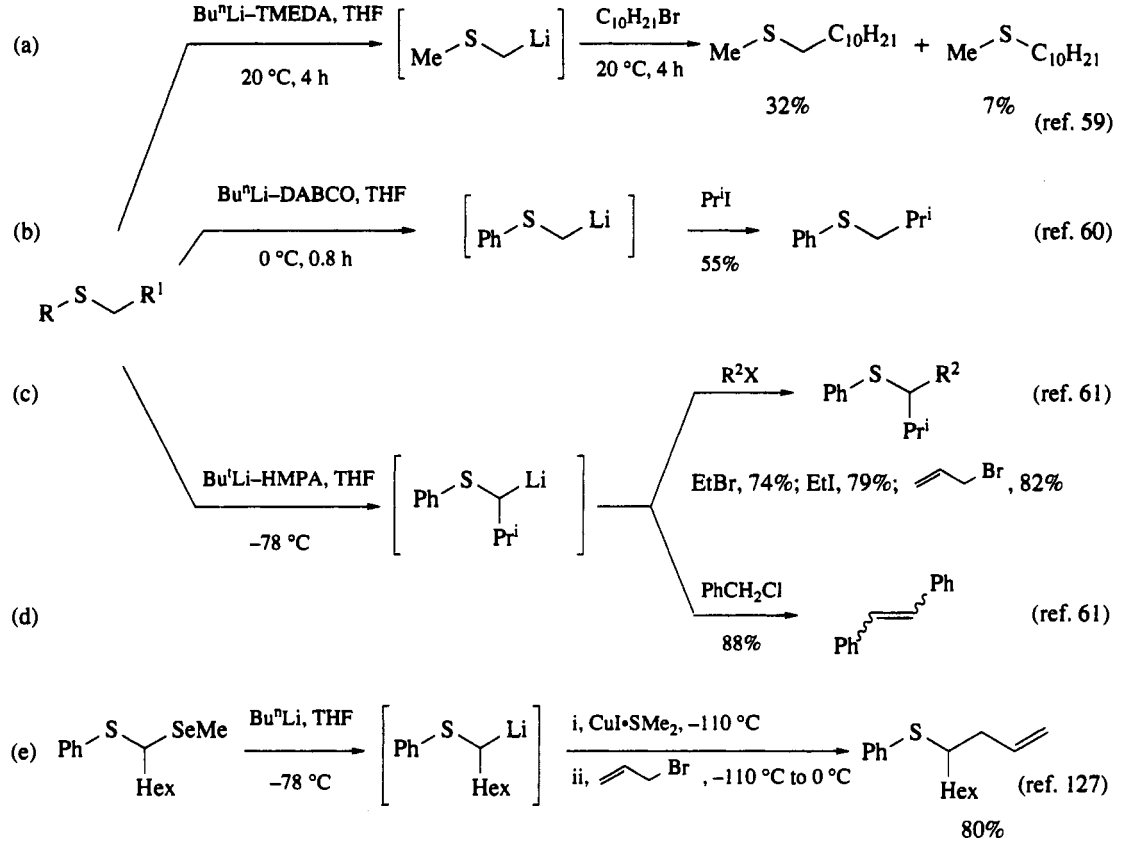
α-Thioalkyllithiums (even those derived from polymer-bound derivatives)[124] bearing hydrogen or alkyl groups on their carbanionic center have been alkylated efficiently in the presence of TMEDA,[58] DABCO[59,124–126] or HMPA[60] (usually required in the metallation step) by primary,[58,59,125] secondary[59] and allylic halides (Scheme 4, entries a–d; see Scheme 53, entry a). The alkylations are much less successful in the absence of HMPA[125,127] but addition of copper(I) iodide (CuI)[125] or CuI·SMe_2 complex (Scheme 4, entry e), which probably leads to the formation of a cuprate intermediate, restores the reactivity. Under these conditions phenylthiomethyl carbanion reacts[125] in a regioselective manner with geranyl bromide and produces homogeranyl phenyl sulfide with preservation of the (*E*)-stereochemistry of the carbon–carbon double bond (see Scheme 53, entry b).[125]

The latter conditions also proved to be much more successful than those involving lithium derivatives[128] for the methylation[129] and the allylation[127] of phenylthiocyclopropane (Scheme 5), but none of the above mentioned α-thio organometallics can be benzylated in reasonable yield since stilbene, rather than the expected benzylated sulfides, was produced quantitatively, probably *via* benzylidene formation (Scheme 4, entry e).[60]

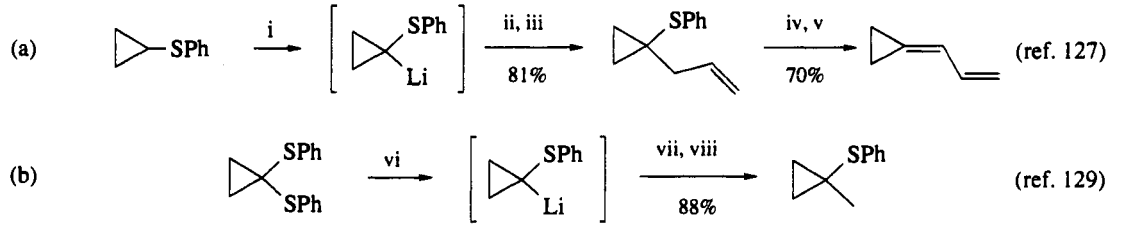
Use of α-thioalkylmetals whose carbanionic centers are dipole-stabilized, such as α′-lithioalkyl carbamates,[130,131] α′-lithioalkyl thioesters,[130,131] α-lithioalkyl thiothiazolines[132,133] and related species[134] offer interesting advantages over the classical α-alkylthio- and α-phenylthio-alkyllithiums (Scheme 6, entries a–d) since not only is there a large variety of such species, including those bearing two alkyl substituents on the carbanionic center, available by metallation of the corresponding carbon acid (this is not for example feasible for 2-phenylthio-2-propyllithium[60]) but also because they can be alkylated,[130–135] allylated[130–133] and even benzylated[131–134] in reasonably good yields (Scheme 6, entries a–d).

In fact all these organometallics can be viewed as chelated species which are softer than unchelated ones. In that respect the behavior of the methylthioamidines described in Scheme 6 (entries e and f) is interesting in that the anion derived from the seven-membered ring compound where negative charge can be stabilized by internal chelation is cleanly metallated and alkylated at the SMe group, whereas its lower homolog whose analogous carbanion is expected to be less prone to chelation leads instead to an alkylated enamine.[135]

Haloalkyl phenyl sulfides produce cycloalkyl phenyl sulfides on treatment with base. The synthesis of cyclopropyl phenyl sulfides has attracted particular interest since these compounds can be metallated[17,25,61] by Bu^nLi in THF and the resulting 1-phenylthiocyclopropyllithium has been used for spiroannelation of various cycloalkanones.[17,25] Thus, 3-chloro-1-phenylthiopropane leads[136,137] to phenylthiocyclopropane on reaction with potassium amide in liquid ammonia (Scheme 7, entry a), but attempts to prepare 2-methylcyclopropyl phenyl sulfide from 3-chloro-1-phenylthiobutane by an analogous route failed in the cyclization step.[61] Neither 3-mesyloxy- and 3-tosyloxy-1-phenylthiododecanes[138] nor 3-tosyloxy-1-phenylthiobutane produce cyclopropane derivatives either on reaction with LDA in THF[139] (Scheme 7, entry b). Failure in these ring closure reactions has been attributed to inadequate car-



Scheme 4



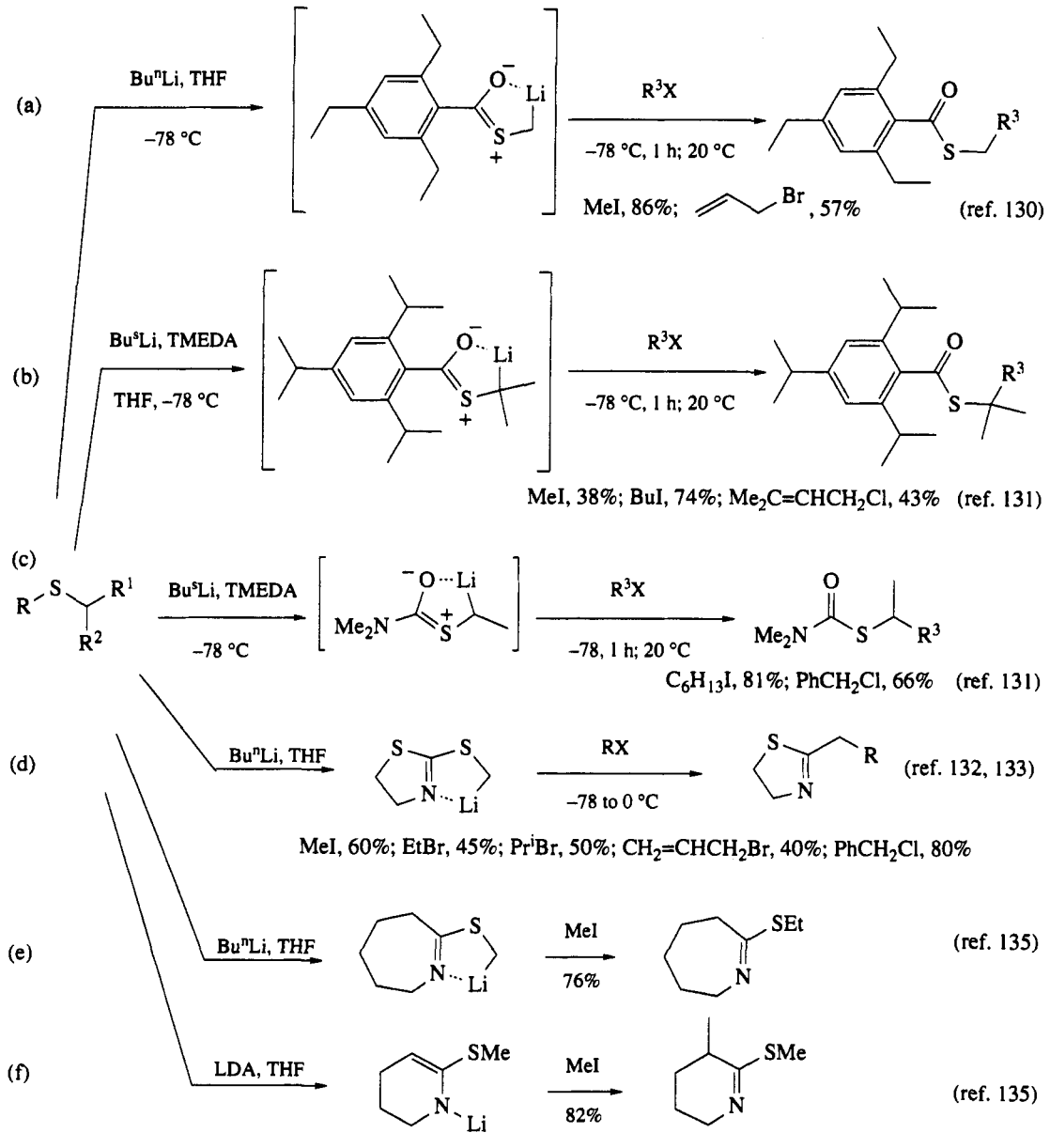
i, Bu^{n}Li; ii, CuI•SMe$_2$; iii, CH_2=$CHCH_2Br$, –78 to 0 °C; iv, $MeSO_3F$; v, KOH, DMSO; vi, LDMAN, THF, –45 °C; vii, CuI, –78 °C; viii, MeI

Scheme 5

banion stabilization by the phenylthio group since closure of the corresponding sulfones (see Section 1.3.6.1.2, Scheme 109) proceeds easily under the same conditions.[138,139] Addition of methyl iodide to the sulfide shown in Scheme 7 (entry b) gives the 4-ethylbenzenesulfonate, suggesting that a successful ring closure might be achieved if the benzenesulfonate was used instead of the tosylate. Indeed, with the corresponding benzenesulfonate (Scheme 7, entry c) a mixture of isomers (*Z*:*E* = 63:37) of 2-methylcyclopropyl phenyl sulfide is obtained in high yield. Interestingly, the isomer distribution obtained complements that resulting from an alternative route involving 3-chloro-2-methyl-1-phenylthiopropane and potassium amide (*Z*:*E* = 17:83; Scheme 7, entry d).[61]

The alkylations of α-selenoalkylmetals share some similarities with those of their thio analogs. Thus α-methylseleno- and α-phenylseleno-alkyllithiums, available by cleavage of the corresponding selenoacetals by *n*-butyllithium in THF or *s*-butyllithium in ether, usually react with methyl iodide and primary alkyl halides to produce the corresponding alkylated selenides.[23,25,52,68,70,71,110,122,127,140–145]

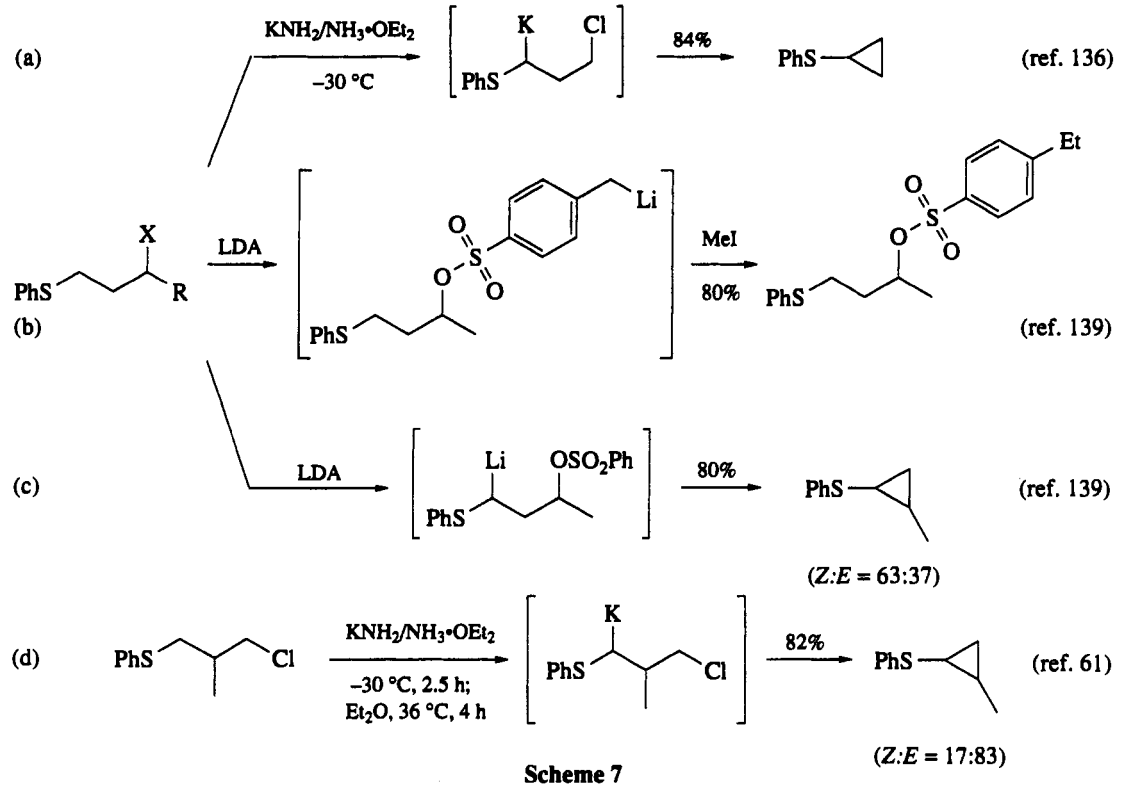
The alkylations of α-selenoalkyllithiums, bearing one or two alkyl substituents on the carbanionic center, with primary alkyl halides take place at low temperatures (–78 °C) in THF[68,143] but at much higher



Scheme 6

temperatures (20 °C for 1 h) when performed in ether. Best results are obtained by use of methylseleno derivatives and when the reaction is performed in THF at the lowest possible temperature (Scheme 8).

The parent compounds, methylselenomethyllithium and phenylselenomethyllithium, are less reactive towards alkylating agents than their higher homologs. They require higher temperatures (–20 °C instead of –78 °C) for a reasonable reaction rate irrespective of whether ether or THF is used.[141] Unfortunately they produce, along with the expected alkylated selenides, appreciable amounts of the selenide resulting from substitution of the alkyl halide by the selenolate ion (Scheme 8, entry a). Apparently, under these conditions, the selenoalkyllithiums are in equilibrium with methylene and lithium selenolates. This side reaction can be avoided if the reactions are performed in THF–HMPA,[140] under which conditions alkylation proceeds at temperatures as low as –78 °C (Scheme 8, compare entry b to a). In several cases HMPA aids the alkylation of α-selenoalkyllithiums. For example HMPA has been used[145] for the alkylation of 1-phenylseleno-1-hexyllithium, and also for 1-selenocyclopropyl-[25,70] and 1-selenocyclobutyllithiums[25,71] (Scheme 8, entries c and e).



Scheme 7

α-Selenoalkyllithiums cannot be alkylated with secondary alkyl halides[141] (Scheme 9); instead either an alkene resulting from an elimination reaction or a selenide, derived from substitution of the halide by the selenolate ions formed as mentioned earlier, is produced, depending upon the conditions employed (THF or THF–HMPA; Scheme 9).[141]

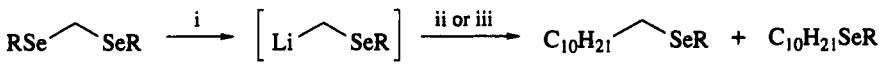
Allylation of α-selenoalkylmetals takes place[140] rather sluggishly and leads to homoallyl selenides in modest yields (Scheme 10, entry a). However the yields are greatly improved by using instead[123,127] the corresponding cuprate[146] (formed from the organolithium compound and copper iodide–dimethyl sulfide complex at –110 °C; Scheme 10, entries b and c). The reaction must be performed at low temperatures since the novel species decomposes around –30 °C, and instead produces an alkene resulting from coupling of the hydrocarbon framework of two units. When applied to neryl and geranyl halides the reaction occurs regioselectively at their primary carbon and does not affect the original stereochemistry of the carbon–carbon double bond.[147] Unfortunately benzylation of α-selenoalkyllithiums could not be achieved even by use of the corresponding cuprates.[147]

As far as chemoselectivity is concerned, α-selenoalkyllithiums react exclusively with the carbonyl carbon of aldehydes or ketones rather than with alkyl halides (Scheme 11).[25,122]

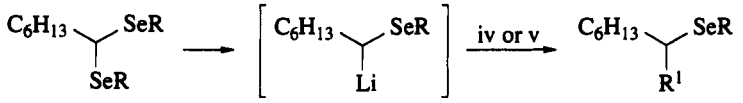
Allyl bromide and benzaldehyde appear to be equally reactive towards α-selenoalkyllithiums (Scheme 12, entries a and c), whereas α-selenoalkylcuprates exhibit a different behavior with allylation occurring almost exclusively, even when the reaction is performed in the presence of benzaldehyde (Scheme 12, entries b and d).[123]

The alkylation of a highly functionalized α-selenoalkyllithium has been reported once. In this study the di(methylseleno)acetal resulting from the conjugate addition of 1,1-di(methylseleno)-1-ethyllithium to cyclohexenone, followed by trapping the resulting enolate with trimethylsilyl chloride, led to the corresponding methylated selenide on cleavage of one of the C—Se bonds followed by reaction with methyl iodide (Scheme 8, entry f).[148]

α-Selenoalkyllithiums also react with terminal epoxides[71,141,149,150] and oxetanes[141,149] to provide γ- and δ-hydroxy selenides in good yields (Scheme 13). The reactions are usually carried out in *THF*, except in the case of selenomethyllithiums which require the use of HMPA as the cosolvent in order to prevent formation of a by-product resulting from opening of the heterocyclic ring by selenolate ions. Similar observations have already been made for the reaction of alkyl halides (see above).[23,52,141]

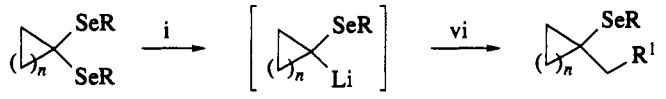


(a) ii: R = Ph, 100% (41:59); R = Me, 89% (54:46) (ref. 122)
(b) iii: R = Ph, 87% (97:3); R = Me, 92% (98:2) (ref. 23)



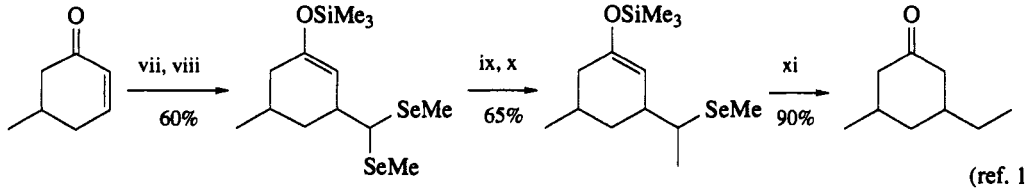
(c) iv: R = Ph, 40%; R = Me, 85% $R^1 = C_6H_{13}$ (ref. 140)
(d) v: R = Me, 17% $R^1 = C_7H_{15}$ (ref. 127)

(e)



R = Me, Ph; n = 1, 2, 4; 45–84% (ref. 70, 71, 122, 140, 143)

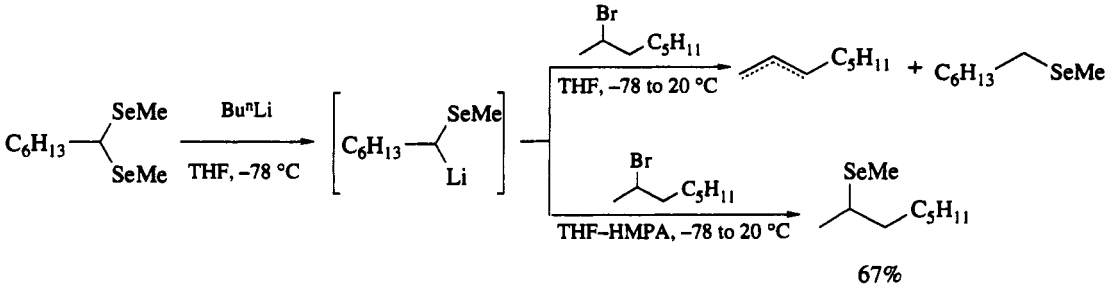
(f)



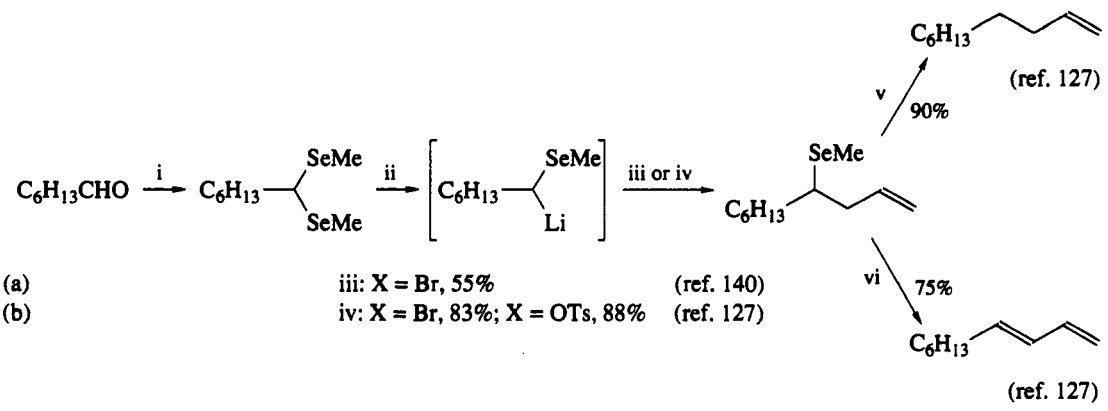
(ref. 148)

i, Bu^nLi, THF, –78 °C; ii, $C_{10}H_{21}Br$, THF, –78 °C; iii, $C_{10}H_{21}Br$, THF–HMPA, –78 to 0 °C; iv, $C_6H_{13}Br$, THF, –78 °C, 1 h, then MeOH, –78 °C; v, CuI, –78 °C, then $C_7H_{15}I$, –78 to 20 °C; vi, R^1CH_2X, THF or THF–HMPA; vii, $LiCH(SeMe)_2$, THF–HMPA; viii, Me_3SiCl, Et_3N; ix, 1 equiv. Bu^nLi; x, excess MeI; xi, Bu_3SnH, *p*-TsOH

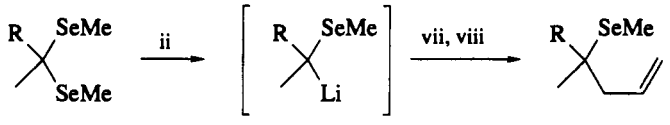
Scheme 8



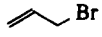
Scheme 9



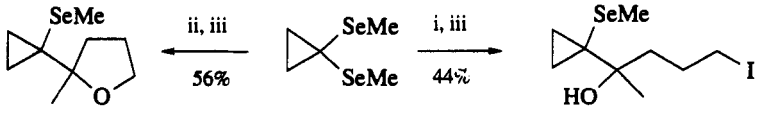
(a) iii: X = Br, 55% (ref. 140)
(b) iv: X = Br, 83%; X = OTs, 88% (ref. 127)



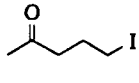
(c) R = C_6H_{13}, 77%; R = Bu^t, 71% (ref. 123, 127)

i, MeSeH, $ZnCl_2$; ii, Bu^nLi, THF, –78 °C; iii,  , THF, –78 to 20 °C;
iv, CuI, Me_2S, –110 °C, then  , THF, –78 to 20 °C; v, Bu_3SnH,
AIBN, 80 °C, 2 h; vi, Bu^tO_2H–Al_2O_3, 80 °C, 2 h; vii, CuI, Me_2S, –110 °C; viii, 

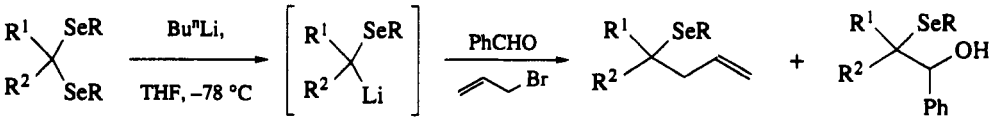
Scheme 10



(ref. 25, 122)

i, Bu^tLi, Et_2O; ii, Bu^nLi, THF; iii, 

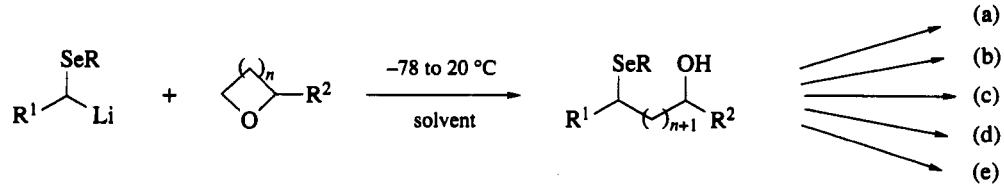
Scheme 11



	R^1	R^2	*Conditions*	*Yield (%)*	*Yield (%)*
(a)	H	C_6H_{13}	i	38	40
(b)	H	C_6H_{13}	ii	83	0
(c)	Me	Bu^t	i	21	15
(d)	Me	Bu^t	ii	52	trace

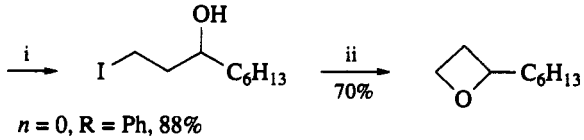
i, addition of electrophile to organolithium at –100 °C, then –100 to 20 °C; ii, addition of CuI•SMe_2 to organolithium at –78 °C, addition of electrophile, then –78 to –30 °C

Scheme 12

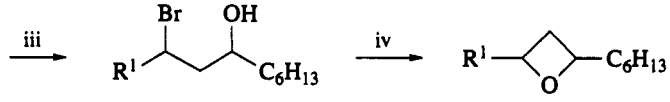


R = Ph; R^1 = H; *n* = 0; R^2 = C_6H_{13}; solvent = THF– HMPA; 82%

R = Ph, Me; R^1 = Me, Et, $PhCH_2$, C_6H_{13}; *n* = 0, 1; R^2 = H, C_6H_{13}; solvent = THF–hexane; 70–75%

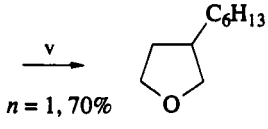
(a) 

n = 0, R = Ph, 88%

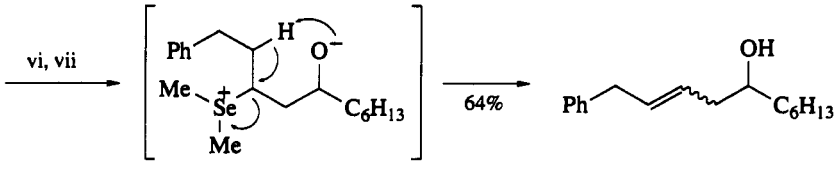
(b) 

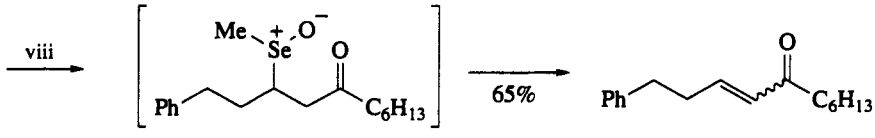
n = 0, R = Ph, R^1 = Me, 67% 60%

n = 0, R = Ph, R^1 = Et, 74% 16%

(c) 

n = 1, 70%

(d) 

(e) 

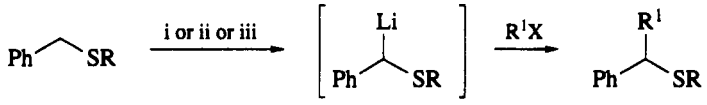
i, MeI, NaI, DMF, $CaCO_3$, 80 °C, 1 h; ii, Bu^{t}OK, DMSO, 20 °C; iii, Br_2, EtOH–H_2O, 20 °C; iv, MeMgBr, HMPT, 80 °C; v, Br_2, EtOH–H_2O, 20 °C, 3 h; vi, MeI; vii, Bu^{t}OK, DMSO, 20 °C; viii, CrO_3, H_2SO_4, acetone, 0 °C, 3 h, then 25 °C, 29 h

Scheme 13

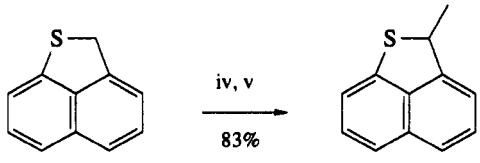
1.3.2.1.2 Alkylation of α-thio- and α-seleno-benzyl metals

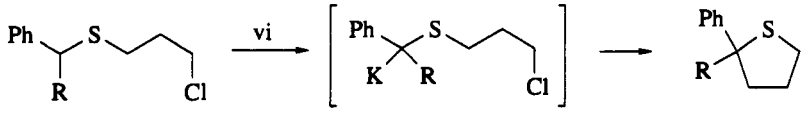
α-Thio-[14] and α-seleno-benzylmetals[17,18,23,25,45,52–56] are more accessible than their alkyl counterparts, probably due to the extra stabilization afforded by the aromatic ring. Also they are usually more nucleophilic towards organo halide derivatives presumably due to their relative softness. α-Thiobenzyllithiums are however prone to rearrange to benzylthiolates *via* a Wittig type rearrangement.[14,23]

A series of benzyllithiums bearing a phenylthio (Scheme 14, entries a and d, Scheme 15; see Scheme 43),[14,126,151–155] a thiothiazolino (Scheme 14, entry b)[132a,133] or a dithiocarbamato[156,157] group (Scheme 14, entry c; see Scheme 49 and Scheme 50) have been successfully alkylated with primary[151–156] and secondary alkyl halides,[126] benzylated[157] or allylated (see Scheme 43)[151,153,156,157] without special requirements. Intramolecular alkylation has allowed the synthesis of cyclic compounds, including aromatic lactones of medium and large ring size (14- and 15- but not 12-membered rings)[153] and cyclopropane derivatives.[137] Furthermore, benzyl 1-(3-chloropropyl) sulfide cyclizes[137] on reaction with KNH_2 to 2-phenyltetrahydrothiophene rather than to benzylthiocyclopropane (Scheme 14, entry e).



	R	*Conditions*	*R¹X*	*Yield (%)*	*Ref.*
(a)	Ph	i	MeI	98	151
	Ph	i		81	151
(b)		ii	MeI	60	132
(c)		ii	$PhCH_2Br$	45	133
		iii	MeI	99	156

(d)  (ref. 154)

(e)  (ref. 137)

R = H, 95%; R = Me, 76%

i, Bu^nLi–DABCO, THF, 0 °C, 0.5 h; ii, Bu^nLi, THF, –30 °C, 0.5 h; iii, LDA, THF, –78 °C, 0.1 h; iv, Bu^nLi, THF, –60 °C, 0.1 h; v, MeI; vi, KNH_2, NH_3–Et_2O

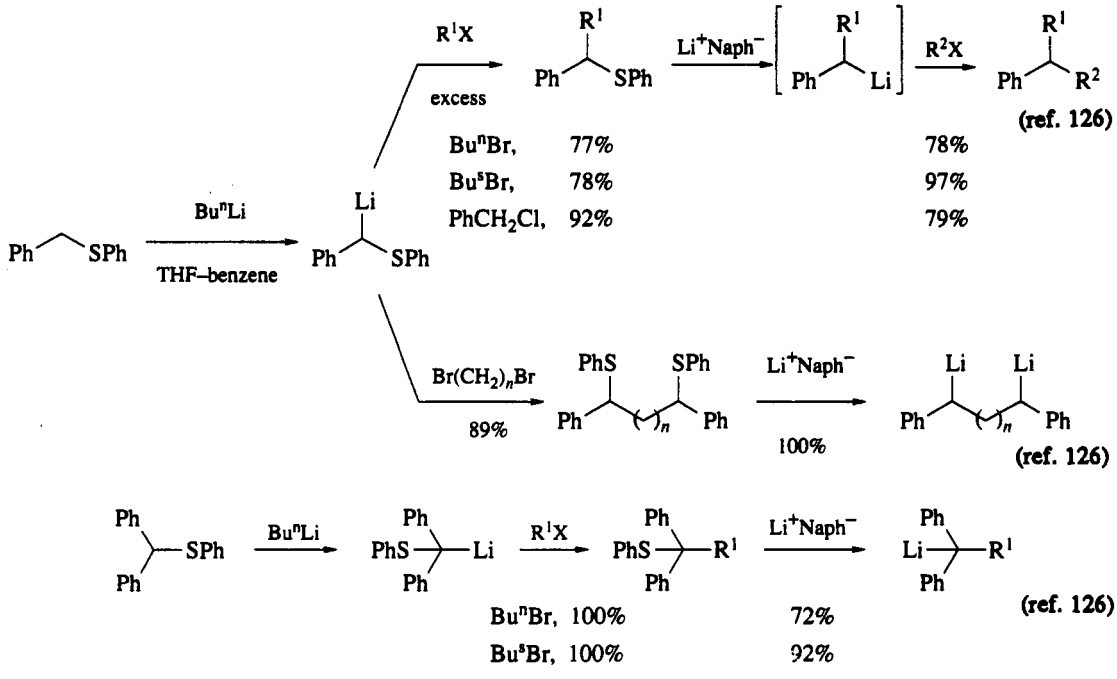
Scheme 14

The case of thiobenzaldehyde dianions, which are available from benzylthiol and two equivalents of *n*-butyllithium–TMEDA complex, merits further comment since alkylation or allylation of these species occurs selectively at the carbanionic site and then a second alkylation can be carried out on the thiolate group (Scheme 16, entry a).[158,178]

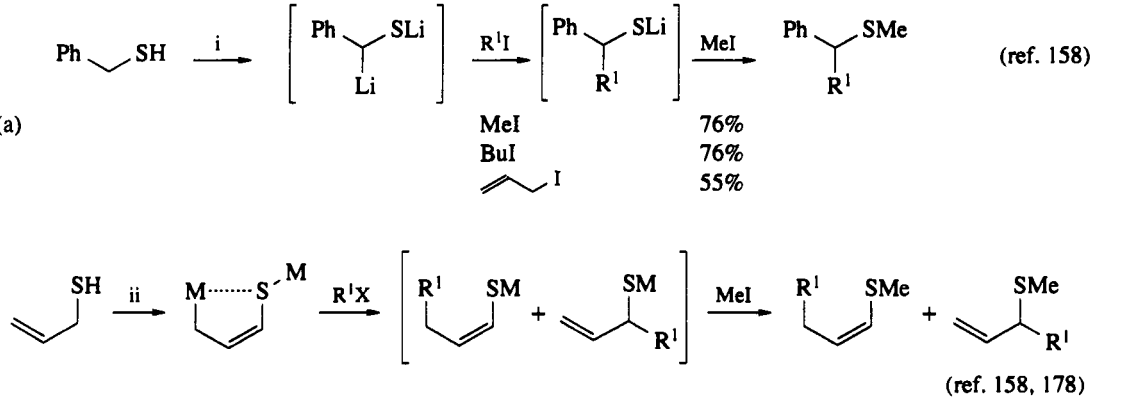
α-Selenobenzyllithiums, even those bearing a bulky alkyl group at their carbanionic center, react efficiently not only with primary and secondary alkyl halides[72,74,79,80,104–106] but also with allyl halides,[159] benzyl halides (Scheme 17)[105,159] and epoxides (Scheme 18)[106,160] without requiring an additive or the formation of a cuprate intermediate (see above).

1.3.2.1.3 Alkylation of α-thio- and α-seleno-allylmetals

α-Thio-[14,16,24] and α-seleno-allylmetals[17,18,23,46,52,54] display a reactivity profile similar to their benzylic analogs, but they also exhibit a tendency to act as ambident nucleophiles.[14] They can react at either the carbon directly linked to (α-carbon) or that which is two carbons away (γ-carbon) from the



Scheme 15



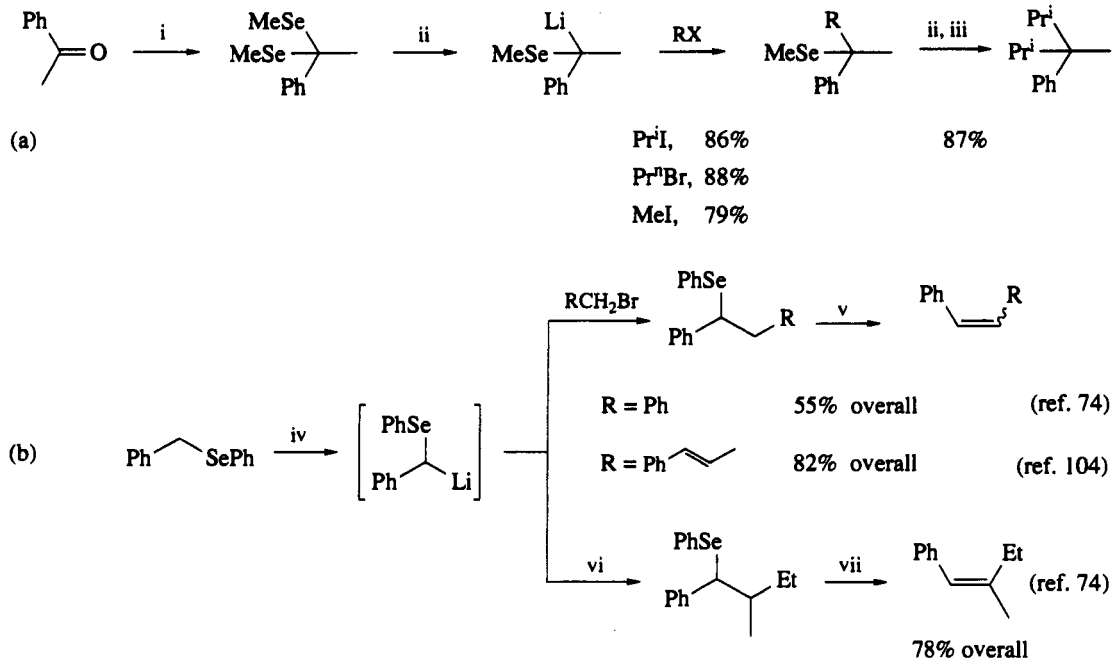
	R¹X	*Additive*	*Yield (%)*	*Product ratio*
(b)	n-C_8H_{17}Cl	none	81	73:27
	Pr^{i}Cl	none	85	59:41
(c)	Pr^{i}Cl	30% HMPA	82	22:78
(d)	C_8H_{17}Cl	Bu^{t}OK, 12% HMPA	80	88:12
	Pr^{i}Cl	Bu^{t}OK, 12% HMPA	50	35:65

i, 2 Bu^{n}Li, THF–TMEDA, –80 °C; ii, 2 Bu^{n}Li, THF, 2 TMEDA

Scheme 16

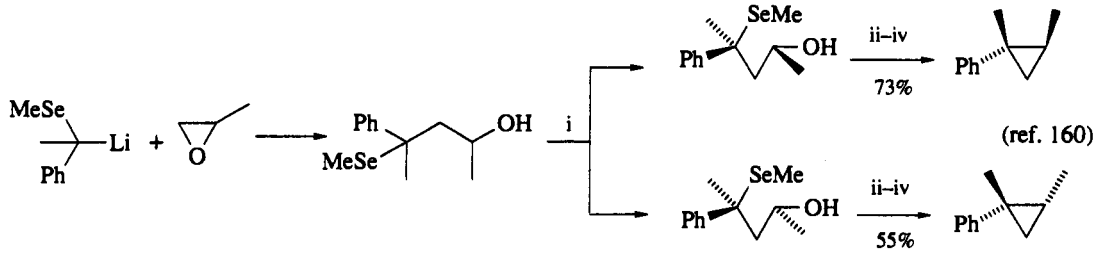
heteroatom itself. The regioselectivity is in general highly dependent upon the location of the metal on the system.

Alkyl,[151,161,162] aryl (Scheme 19; Scheme 20)[16,151,161,164,165] and vinyl thioallyllithiums (Scheme 21)[166,167] react selectively with organic halides at their α-site (α:γ ratio = 95:5 to 80:20) when the reaction is carried out in THF without any additive such as TMEDA, DABCO or HMPA. In contrast to the above mentioned cases, thioallyllithiums in which there is the possibility of lithium chelation at the α-site [such as 2-pyridylthio (Scheme 19; see Scheme 45),[15,16,168,169] thioimidazoyl (Scheme 19; see



i, MeSeH, $TiCl_4$; ii, Bu^nLi, THF, –78 °C; iii, Pr^iI, THF, –78 to 0 °C; iv, LDA, THF, –78 °C; v, H_2O_2, THF, 20 °C; vi, Bu^sBr; vii, O_3

Scheme 17



The stereochemistries of the products have not yet been established

i, separation of stereoisomers on silica; ii, Bu^nLi; iii, TosCl; iv, Bu^nLi, –78 °C

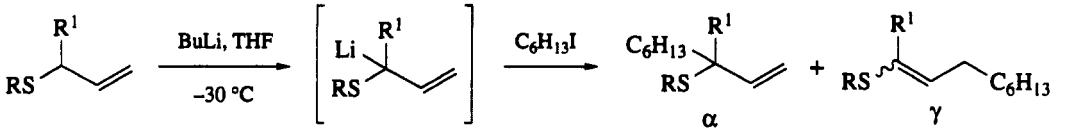
Scheme 18

Scheme 51)[16,170,171] and dithiocarbamato (see Scheme 50 and Scheme 51)[16,156,172–177] moieties] exhibit a dramatic selectivity for α-alkylation (Scheme 19).

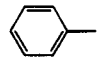
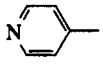
The *N*-methylthioimidazoyl moiety, among the various aromatic and heteroaromatic moieties used in the sulfur series, proved to be the one with the highest propensity to direct the alkylation of the corresponding organometallics (even those bearing an alkyl group in the α-position) to the α-carbon atom (Scheme 19, entry e).[16,170]

On the other hand, doubly metallated 2-propanethiol (thioacrolein dianion) reacts preferentially (γ:α ratio ≈ 70:30, Scheme 16, entries b and d) at its γ-position[158,178] with alkyl and benzyl chlorides and bromides and with epoxides. The *cis* stereochemistry found in the γ-adduct suggests that the organometallic is internally chelated as shown in Scheme 16. The nature of the metal (Li or K) does not affect the percentages of the alkylated vinyl sulfides,[158] whereas addition of HMPA to the dilithio derivative inverts the regioisomeric ratio obtained (Scheme 16, entry c, compare to entries b and d).[158]

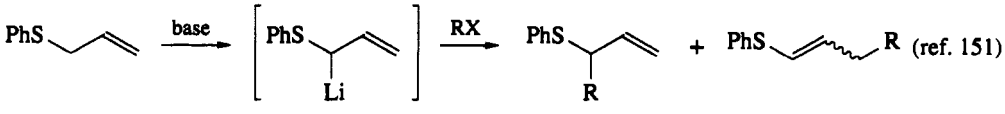
There is some evidence that factors other than chelating capability operate in altering the regioselectivity of alkylation. For example a higher α:γ ratio is observed[16] when phenylthio is replaced by a 4-pyridylthio moiety, neither of which can participate in intramolecular chelation. Consequently an explanation



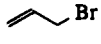
(ref. 16)

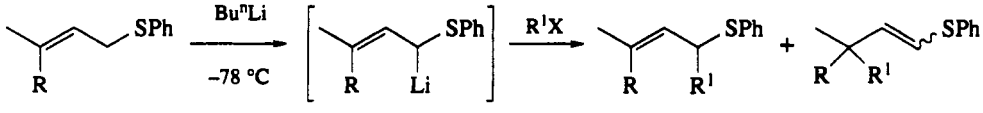
	R	*R*^{1}	*Yield* (%)	*THF* (α:γ)	*THF–HMPA* (α:γ)
(a)		H	93	75:25	68:32
		Me	84	75:25	70:30
(b)		H	78	–	88:12
(c)		H	90	99:1	>99:1
		Me	79	90:10	79:21
(d)		H	95	–	99:1
		Me	94	–	80:20
(e)		H	92	99:1	>99:1
		Me	86	92:8	84:16

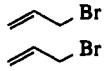
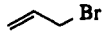
Scheme 19



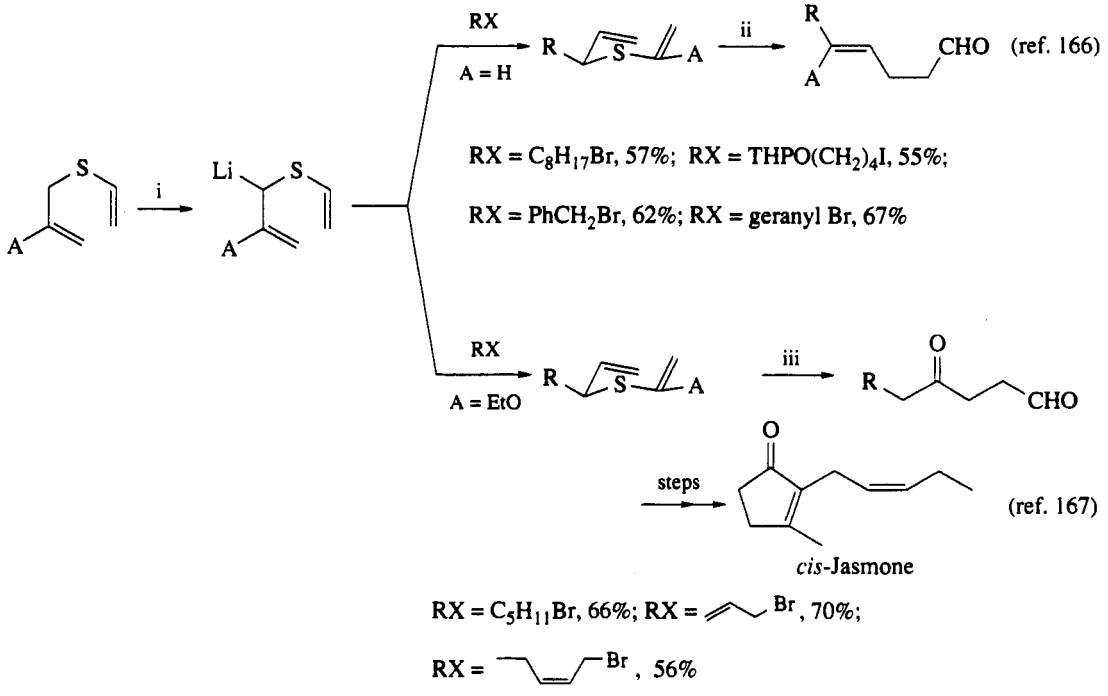
(ref. 151)

	Base	*RX*	*Yield* (%)	*Product ratio*
(a)	Bu^{s}Li, THF	MeI	–	71:29
(b)	Bu^{n}Li, DABCO	MeI	100	95:5
	Bu^{n}Li, DABCO		–	62:38



	R	*Additive*	*R*^{1}*X*	*Yield* (%)	*Product ratio*	
(c)	H	DABCO	MeI	92	98:2	(ref. 161)
(d)	Me	None	MeI	100	95:5	(ref. 164)
(e)	Me	DABCO	MeI	100	99:1	(ref. 164)
(f)	Me	HMPA	MeI	100	98:2	(ref. 164)
(g)	Me	[2.2.2] crown ether	MeI	80	60:40	(ref. 164)
(h)	Me	DABCO		100	87:12	(ref. 164)
(i)	Me	[2.2.2] crown ether		60	50:50	(ref. 164)

Scheme 20



i, Bu^sLi, THF, –78 °C; ii, DME/H_2O (3:1), $CaCO_3$, reflux 12 h; iii, DME/H_2O (3:1), reflux 12 h

Scheme 21

that attributes high alkylation regioselectivity exclusively to intramolecular chelation must be considered tenuous.[16] Furthermore benzyl allyl sulfide is predominantly metallated[179] at the allylic site with *n*-butyllithium–TMEDA complex and provides almost exclusively the α-methylated homolog (Scheme 22, entry a). Surprisingly however the α:γ ratio of alkylation of the related dilithio salt derived from allyl carboxymethyl sulfide, shown in Scheme 22 (entry b) depends upon the nature of the ester.[180]

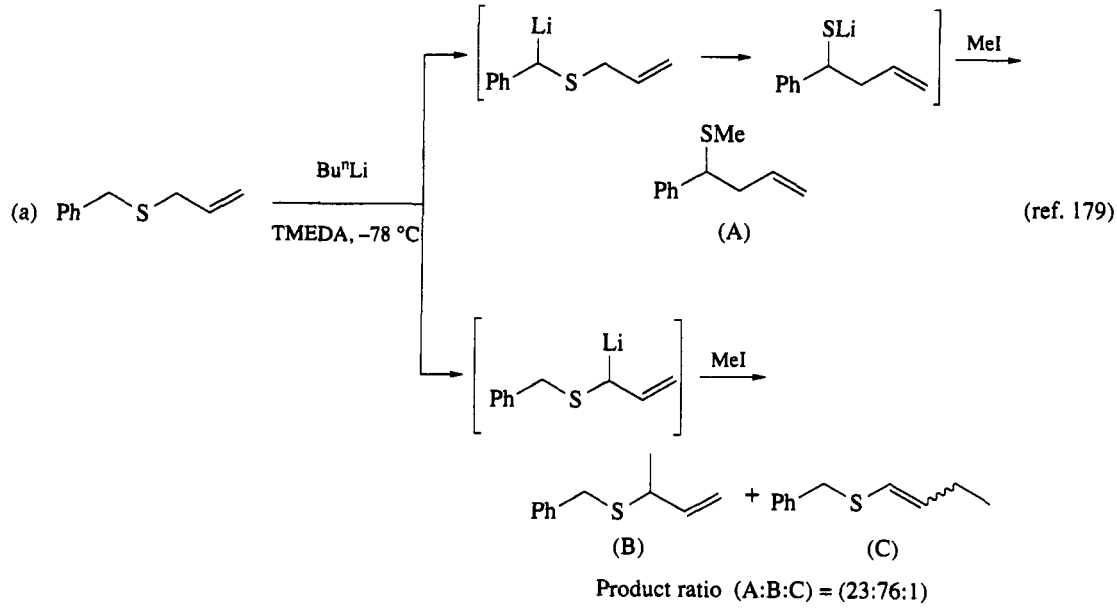
There are several examples where the α:γ ratio of alkylation depends to some extent on the nature of the halide and of the organic residue.[164,181] In that respect, the softer the electrophile, the higher the percentage of γ-attack observed. Typical examples are displayed in Scheme 23.

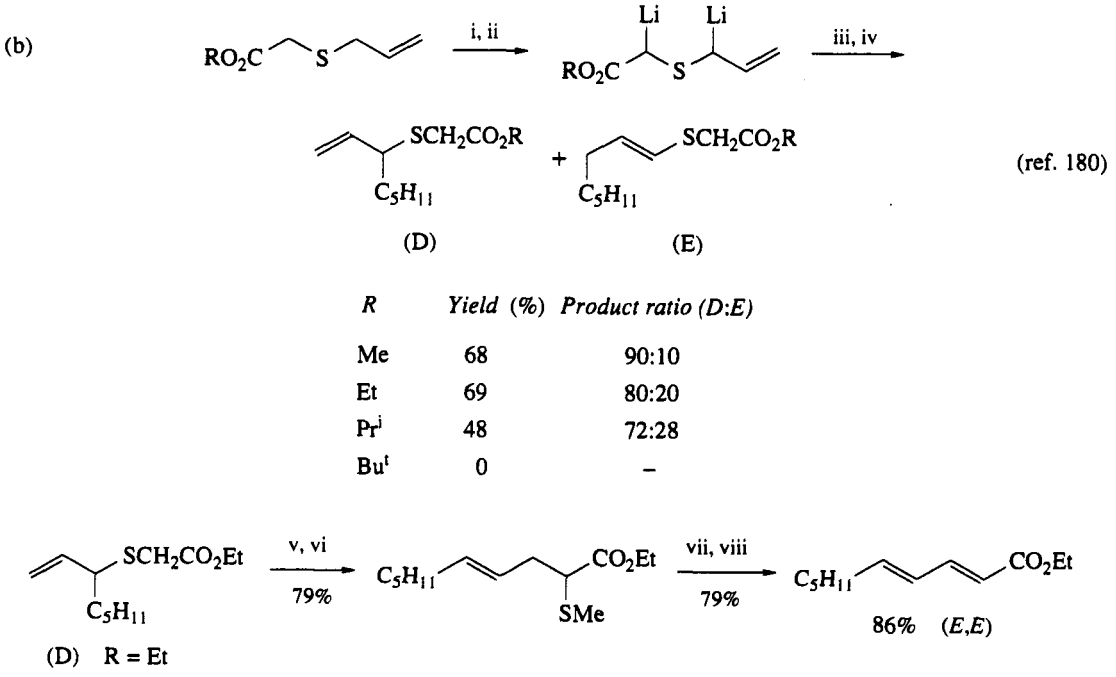
In several cases the conditions used are crucial for control of the regiochemistry. The highest percentage of α-attack has been achieved in THF, with *s*-butyllithium being used as the base (Scheme 19; Scheme 20, entry a).[16,166,181] The presence of an additive such as DABCO,[151] TMEDA, crown ethers or HMPA, required in some cases for successful metallation of the allyl sulfide has a detrimental effect on the regiochemical control (Scheme 16; Scheme 19; Scheme 20).[16,151,158,164,166,178] This result tends to support the theory that 'internal chelation' may play a role in defining regiochemistry. Such cation-coordinating cosolvents appear to partially negate the directive effect: (i) of the heterocyclic ligand (Scheme 24),[16] or (ii) of the internal chelation in dilithiothioacrolein (Scheme 16)[158,178] or (iii) to disrupt, in the case of phenylthioallyllithiums[151,164,166] the intimate and/or solvated ion pairs which are expected to react at the α-position to finally produce solvent-separated ion pairs or free ions more inclined to react unselectively at the α- and γ-sites (Scheme 19; Scheme 20).

Phenylthioallylpotassium and phenylthioprenylpotassium in petroleum ether exhibit a higher tendency for methylation at the γ-site compared to their lithium analogs, and addition of THF to the medium tends to increase the γ-selectivity (Scheme 24).[182]

Reactions between α-thioallyllithiums and allyl halides, which usually proceed predominantly *via* α–α′ (head-to-head) coupling, have proved to be valuable in synthesis.[132a,133,165,183–192] They have been used successfully for example in the synthesis of 1,5-dienes such as squalene,[132a,133,165] (*R*)-(+)-10,11-epoxyfarnesol,[184] (*R*)-(+)- and (*S*)-(–)-2,3-oxidosqualene[184] and mokupalide,[188] dendrolasin,[187] cembranolides,[189] methyl ceriferate[190] and *Cecropia* juvenile hormone (Scheme 25 and Scheme 26).[191,192]

However, allylation of alkylthioallylcopper compounds, generated in ether from alkylthioallyllithium and CuI at –78 °C (the synthesis of phenylthio analogs fails[162]), affords exclusively[98,162,163] γ–γ′ (tail-to-tail) coupled products (Scheme 27), whereas alkylthio allylic aluminum and boron 'ate' complexes, readily available from reaction of alkylthioallyllithium compounds with trialkylaluminum[98] and





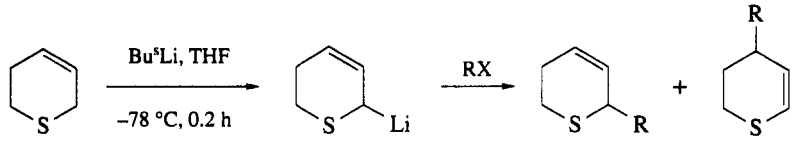
R	*Yield (%)*	*Product ratio (D:E)*
Me	68	90:10
Et	69	80:20
Pr^i	48	72:28
Bu^t	0	–

i, LDA; ii, Bu^sLi; iii, $C_5H_{11}Br$; iv, H_3O^+; v, LDA, −78 to 0 °C; vi, MeI, 0 °C; vii, MCPBA; viii, $CaCO_3$, benzene, Δ, 24 *h*

Scheme 22

trialkylboranes respectively, undergo regiocontrolled α–γ′ (head-to-tail) coupling with allylic halides[183] (Scheme 28). In general, both the regioselectivity and the yields are higher with Bu^n-9-BBN-ate complexes than with triethylaluminum[98] or tri-*n*-butylboronates;[98,183] and allylic bromides give better results[98,183] than the corresponding chlorides.

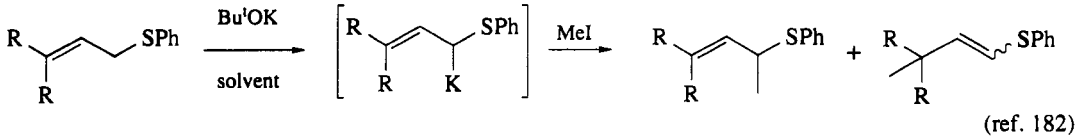
Reactions between α-thioallyllithiums and epoxides have been used in a large number of important syntheses.[14,193–202] In one example involving an epoxy alcohol,[202] the concomitant use of magnesium



(ref. 181)

RX	*Yield (%)*	*Product ratio*
Bu^{n}Cl	70	97:3
Bu^{n}Br	79	91:9
Bu^{n}I	100	70:30
$PhCH_2Cl$	96	73:27

Scheme 23

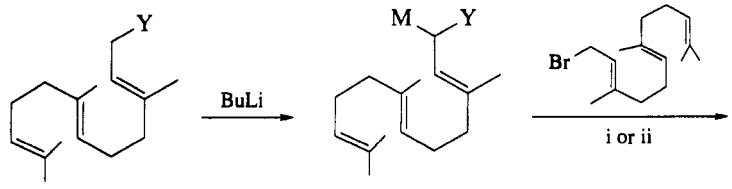


(ref. 182)

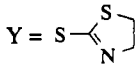
Solvent	*R*	*Product ratio*
Pet. ether 25 °C, 2 h	H	45:55
Pet. ether 25 °C, 2 h	Me	77:23
Pet. ether–THF	H	94:6
Pet. ether–THF	Me	98:2

Scheme 24

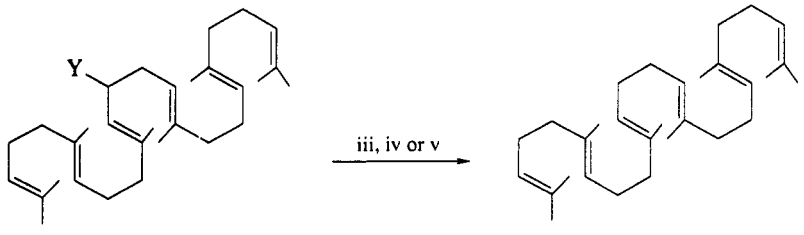
(a)



Y = SPh i, 82%

Y =  i, 44%

Y = *p*-$MePhSO_2$ ii, 86%

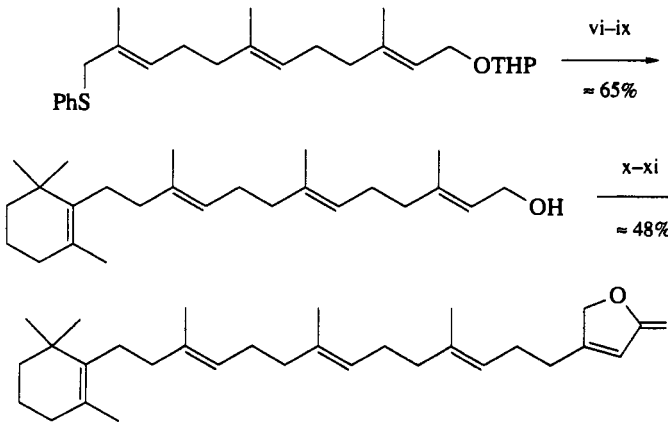


iii, 70% (ref. 165)
iv, 80% (ref. 132a, 133)
v, 80% (ref. 506)

i, Bu^{n}Li, THF, –78 °C; ii, Bu^{n}Li, THF, –20 °C, RBr, –78 to 0 °C; iii, Li, H_2NEt, –30 °C; iv, Raney Ni, EtOH–THF; v, Li, H_2NEt

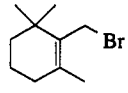
Scheme 25

(b)

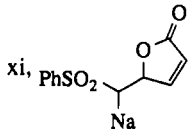


(ref. 188)

Mokupalide

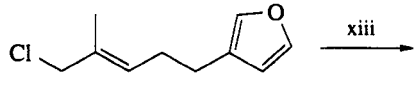
vi, Bu^nLi, DABCO, –23 °C; vii,  , THF, –23 to 0 °C; viii, NiB, EtOH, 25 °C;

ix, TsOH, MeOH, 25 °C; x, Bu^nLi, MsCl, LiBr, Et_2O, –78 to 25 °C;

xi, 

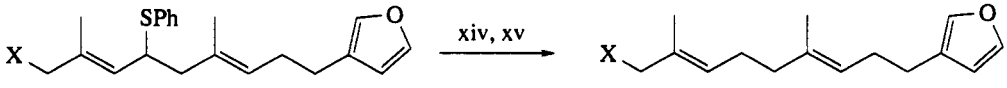
; xii, Na–Hg, MeOH, –10 °C

(c)

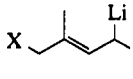


(ref. 187)

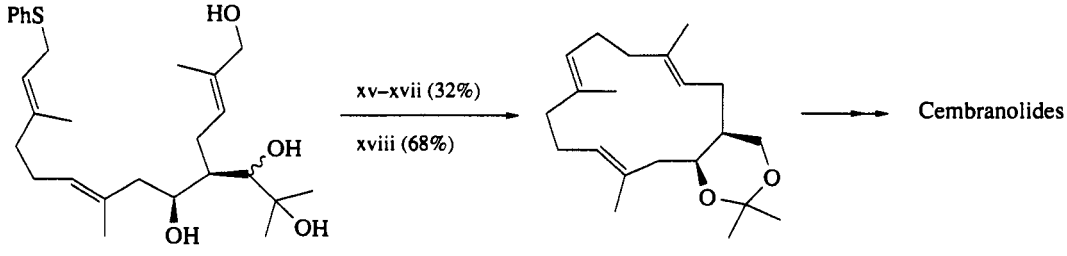
X = H, 84%
X = OLi, 83%



X = H, 83%, Dendrolasin
X = OH, 73%, Neotorreyol

xiii, 

, DABCO (X = H) or HMPA (X = OLi); xiv, Li, H_2NEt; xv, H_3O^+



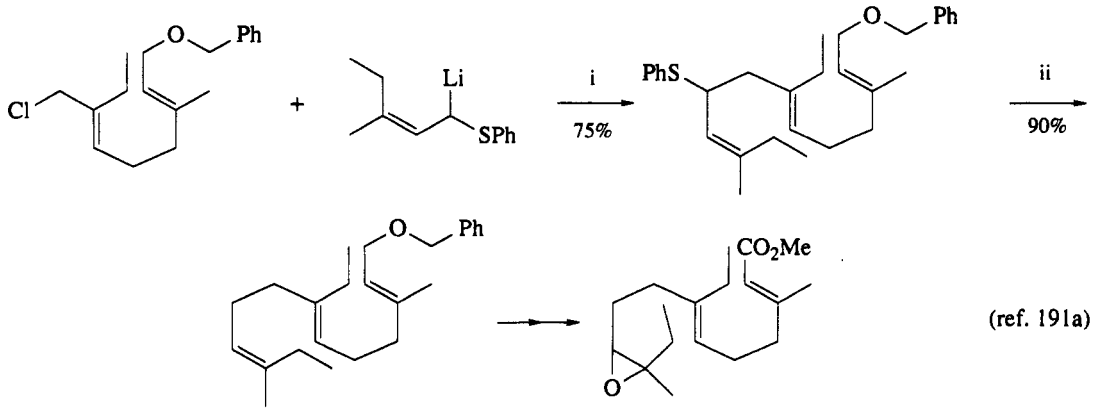
(d)

Base nucleus of crassim acetate

(ref. 189)

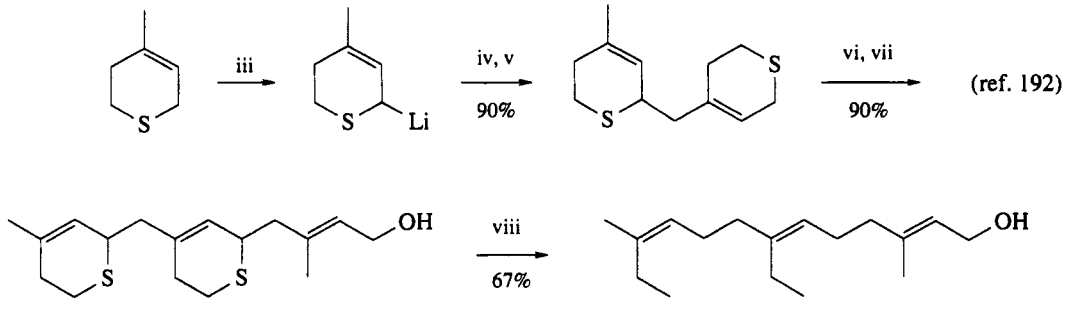
xv, TosCl, DMAP, 0 °C, 3 h; xvi, LDA, THF–hexane, –78 °C; xvii, MeOH, –78 °C; xviii, Li, Et_2NH

Scheme 25 *(continued)*



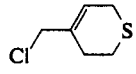
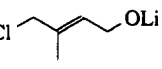
(ref. 191a)

C_{18} *Cecropia* Juvenile hormone



(ref. 192)

i, THF, –78 °C, 1 h; ii, Li, $EtNH_2$, –78 °C, 0.3 h; iii, Bu^sLi, TMEDA, THF, –50 °C;

iv,  ; v, $POCl_3$; vi, Bu^sLi, TMEDA; vii,  ; viii, Li, $EtNH_2$ (excess), –78 °C

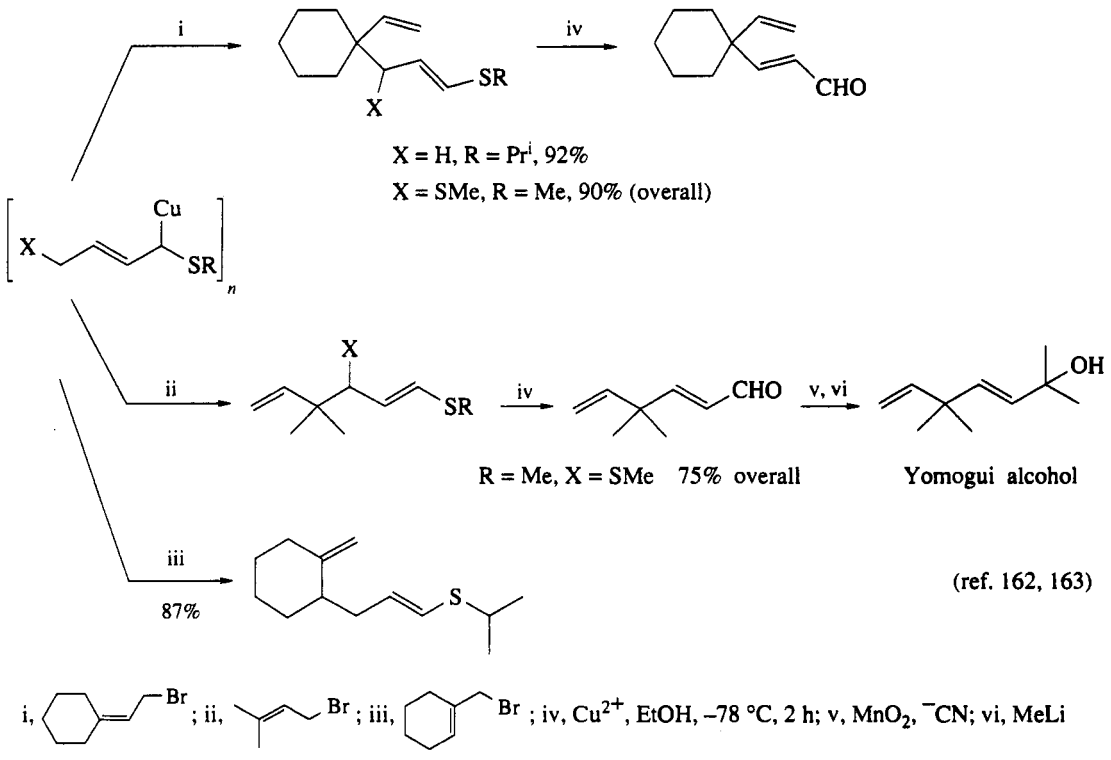
Scheme 26

alkoxide in HMPA increased both the rate of the reaction and its yield. Most of these reactions involve intramolecular reactions and allow the synthesis of macrocyclic terpenoids from trisubstituted epoxides.[193–195,198,200,201] Racemic 6,7-epoxygeranyl *t*-butyl sulfide on reaction with Bu^nLi–TMEDA produces two cyclobutyl carbinols possessing the fragranol and grandisol carbon skeletons and a single cyclopentanol of undefined stereochemistry.[198] The latter compound arises from the reaction of the α-lithio allyl sulfide at its γ-site, although it is fully substituted (Scheme 29). Higher homologs react from the less hindered site and provide 10-membered,[194,195,200] 12-membered[201] and 14-membered[193] ring terpenoids (Scheme 30).

Several functionalized α-metalloallyl sulfides have been successfully alkylated or hydroxyalkylated on reaction with organic halides or epoxides. Among them, 1-metallo-1,3-di(thio)propenes[203–205] which play the role of β-metallo-α,β-unsaturated aldehydes (—CH=C—CHO; Scheme 31) have proved[203,206,207] particularly useful for the synthesis of δ-alkoxy-α,β-unsaturated aldehydes; they have been used in[203,206] the neat synthesis of prostaglandin $F_{2\alpha}$ from a functionalized oxidocyclopentene derivative (Scheme 31, entry e).

Similar transformations can be achieved from γ-methylthioallyl thiocarbamates[176] or from allyl thiocarbamates[176] (Scheme 32, entries c and d). Both reaction sequences take advantage of the easy sigmatropic rearrangement of allyl thiocarbamates. Furthermore, β-methoxyallyl thiocarbamates have played the role of an acetone enolate (Scheme 32, entry a).[175]

As already mentioned, α-metalloallyl vinyl sulfides[166] and their 2-ethoxy analogs[167] have been selectively alkylated, benzylated and allylated at their α-site, then the resulting compounds have been thermally rearranged to γ,δ-unsaturated aldehydes or γ-oxo aldehydes on heating in aqueous DME (Scheme 21).



Scheme 27

Relatively few α-selenoallylmetals have been prepared[81,95,96,99,101,208,209] compared to their thio analogs (Scheme 33). These species have proved to be powerful nucleophiles which react efficiently with primary,[81,95,100,101,208,209] secondary[95,100] and benzylic bromides[95,208] and with *N*-(bromomethyl)phthalimide–$ZnCl_2$,[96] as well as with terminal and α,β-dialkyl-substituted epoxides[95,100] (Scheme 33). The reactions take place almost instantaneously (<0.2 h) at low temperature (–78 °C) with primary alkyl halides[95] but require higher temperatures and/or longer reaction times with secondary halides. As for the sulfur analogs α-alkylation prevails (α:γ ratio from 80:20 to 90:10) with allyl phenyl selenides but, in contrast to the 2-thiopyridyl derivative,[16,168,169] 2-pyridylselenoallyllithium[95] did not display efficient enhancement of alkylation from the α-site. This has been associated with the presence of diisopropylamine resulting from the metallation of the selenide with LDA (Bu^{n}Li cannot be used since it leads to allyllithium by Se/Li instead of H/Li exchange)[101] which might prevent[95] lithium chelation with the pyridine nitrogen. Alkylation takes place selectively at the α-position of ω-alkoxy-,[99] γ-chloro-,[95] γ-seleno-[100] and γ-seleno,γ-silyl-substituted α-selenoallyllithiums (Scheme 33).[100]

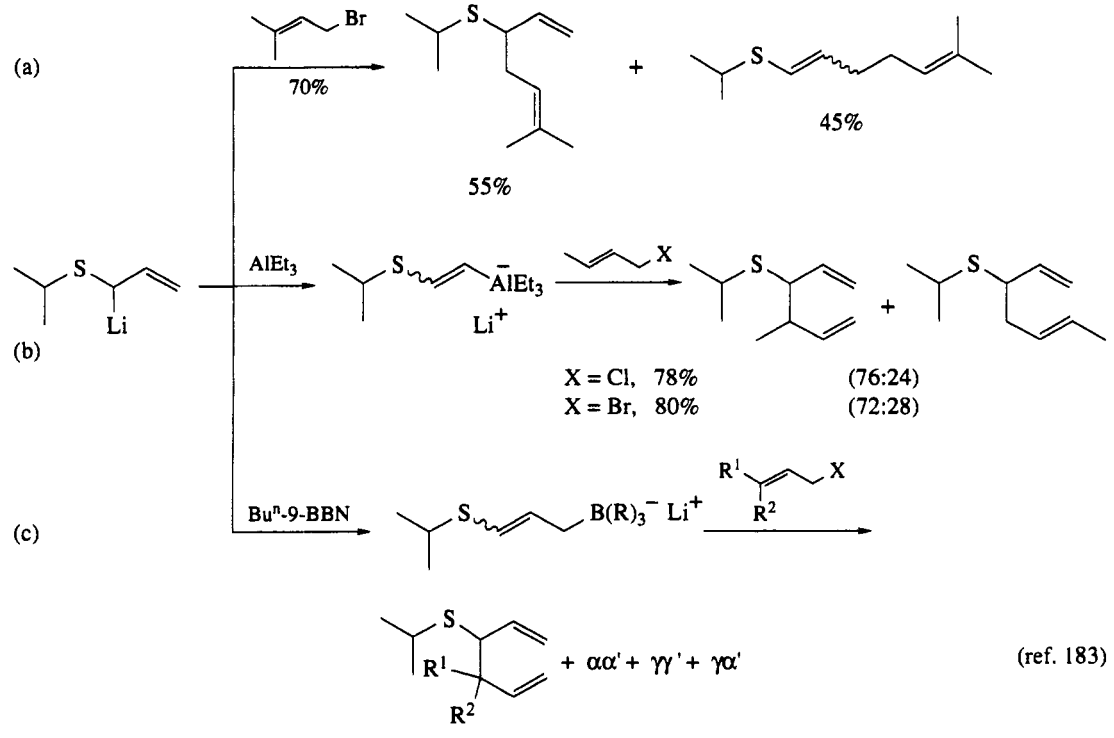
1.3.2.1.4 Alkylation of α-thio-[21,31] and α-seleno-propargylic metal derivatives

Propargylic sulfides[210,211] and selenides have been metallated[102,103] with *n*-butyllithium and lithium amide respectively, and allylated[211] or alkylated selectively at the propargylic position (Scheme 34) with primary and secondary alkyl halides.[102,103,210]

Phenyl propargyl sulfide[211] and selenide[102,103] are rapidly deprotonated by 2 equiv. of base. The resulting dilithio derivatives react at their allylic rather than at their alkynic carbon centers (Scheme 34, entries c and d). Reduction of the sulfides allows the synthesis of 1,5-enynes (Scheme 34, entry b), whereas oxidation of the selenides leads to α-phenylseleno-α,β-unsaturated carbonyl compounds (Scheme 34, entry d).[102,103]

1.3.2.1.5 Alkylation of α-metallovinyl sulfides and selenides

Vinyl sulfides[20] and selenides can be alkylated efficiently at the α-position in a two step–one pot reaction which involves their α-metallation and further reaction of the resulting anion with alkyl halides.



(ref. 183)

R^1	R^2	X	*Yield* (%)	αγ'	αα'	γγ'	γα'
Me	Me	Cl	68	97	3	–	–
Me	H	Br	77	99	1	–	–
H	H	Br	52	90	–	5	5

Scheme 28

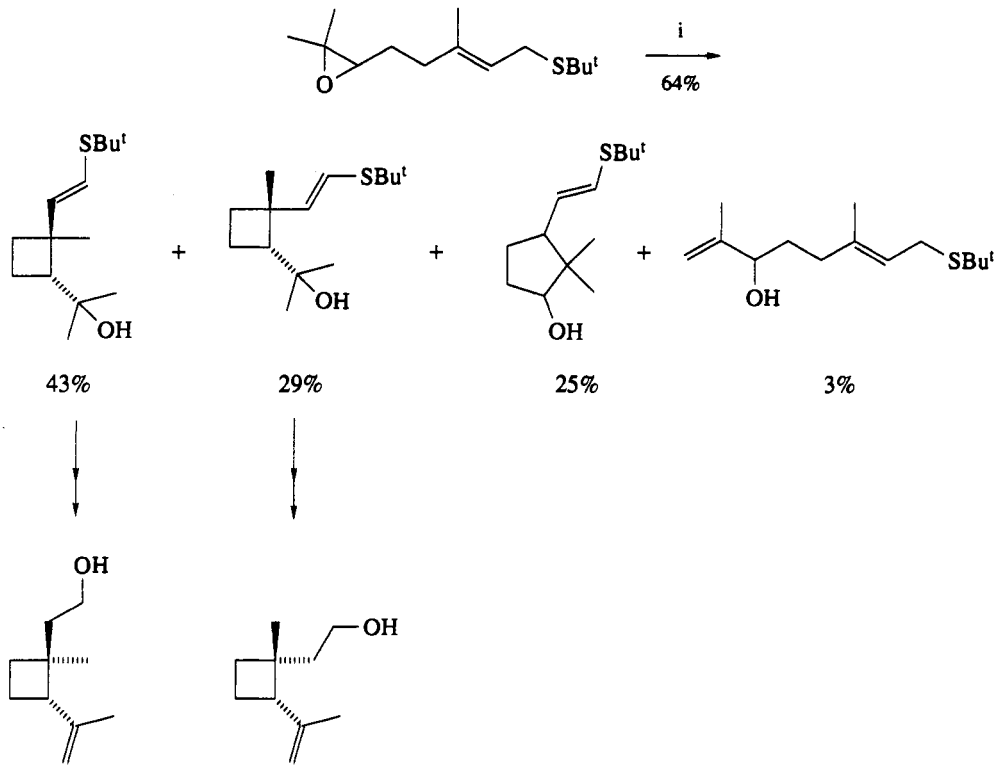
Side reactions which involve Michael type addition of the metallating agent at the terminus of the alkenic double bond[27,110,145,212–214] or cleavage of the C—Se bond[110,145] can be avoided by employing low temperatures and using nonnucleophilic metallating agents in the case of sulfides, and avoiding the use of alkyllithiums for vinyl selenides.

Thus, aryl[107,131,166,215] and alkyl[216] vinyl sulfides have been transformed to the corresponding 1-metallovinyl sulfides with LDA in THF alone,[107,215] or in THF–HMPA,[107] and also with Bu^{s}Li in THF[131] or in THF–HMPA[131,166,216] (Scheme 35, entries a–c), and have been subsequently alkylated with primary alkyl halides and α,ω-dihalides (Scheme 35). However it has not proved possible to extend the reaction to 1-(2-methylpropenyl) phenyl sulfide.

The corresponding 1-(lithiovinyl) sulfides and related derivatives can be produced in THF alone by reaction of ketene thioacetals with lithium naphthalenide (Scheme 36, entry b).[129,217] This reductive lithiation is however less preferable to deprotonation when alkylation of the anion is planned, since the thiophenoxide anion which is necessarily present, destroys one equivalent of the alkylating agent.[217] Alternatively 1-metallovinyl sulfides, which have been prepared by Sn/Li exchange[82] from 1-(stannyl)vinyl phenyl sulfide or by thiophilic addition[218] of phenyllithium on thioketones, have been methylated with methyl iodide (Scheme 35, entry d).[82,218]

The alkylations of 2-ethoxy-[219] and 2-(*Z*)-alkylthio-1-(alkyl or phenylthio)ethylenes[220] with primary alkyl halides and ethylene oxide have been reported (Scheme 37). The metallations are usually easy, but the alkylation of the former organometallic can be achieved only with primary alkyl halides and on condition that HMPA is used as a cosolvent. Unfortunately the reaction does not take place with benzyl bromide or isopropyl iodide.[219]

1,3-Dienyl sulfides,[213,221] which have been otherwise efficiently alkylated[120] at the allylic position using KNH_2 or LDA as the base (Scheme 3, entries a and c) or have added *n*-butyllithium at their δ-site (Scheme 38, entry a),[213] have been selectively alkylated at their α-vinylic site by use of a strong metallating base such as Bu^{n}Li–TMEDA (Scheme 3, entry b) or Bu^{n}Li–Bu^{t}OK (Scheme 38, entry b).[213]



i, Bu^{n}Li–TMEDA, THF–hexane, –75 °C, 3 h; 5 °C, 2 h

Scheme 29

Metallation of various 1-alkynyl sulfides,[222–224] followed by alkylation of the resulting anion leads exclusively to α-alkylated allenyl sulfides (Scheme 39).

The alkylation of aryl vinyl selenides has been carried out by the usual metallation/alkylation sequence.[107,108,110,111] Although the metallation of phenyl and *m*-$CF_3C_6H_4$ vinyl selenide can be achieved with LDA–HMPT,[110] or LDA alone,[107] best results have been obtained with KDA in THF in the case of phenyl vinyl selenide,[108] and with LDA for pyridyl vinyl selenide (Scheme 40).[111] The latter combinations proved valuable for the synthesis of higher homologs bearing one alkyl group in the β-position,[108,111] especially because metallation and alkylation both occur stereoselectively with retention of configuration. Unfortunately, however, alkylation of those aryl vinyl selenides bearing two alkyl groups in the β-positions has not yet been achieved.[107,108]

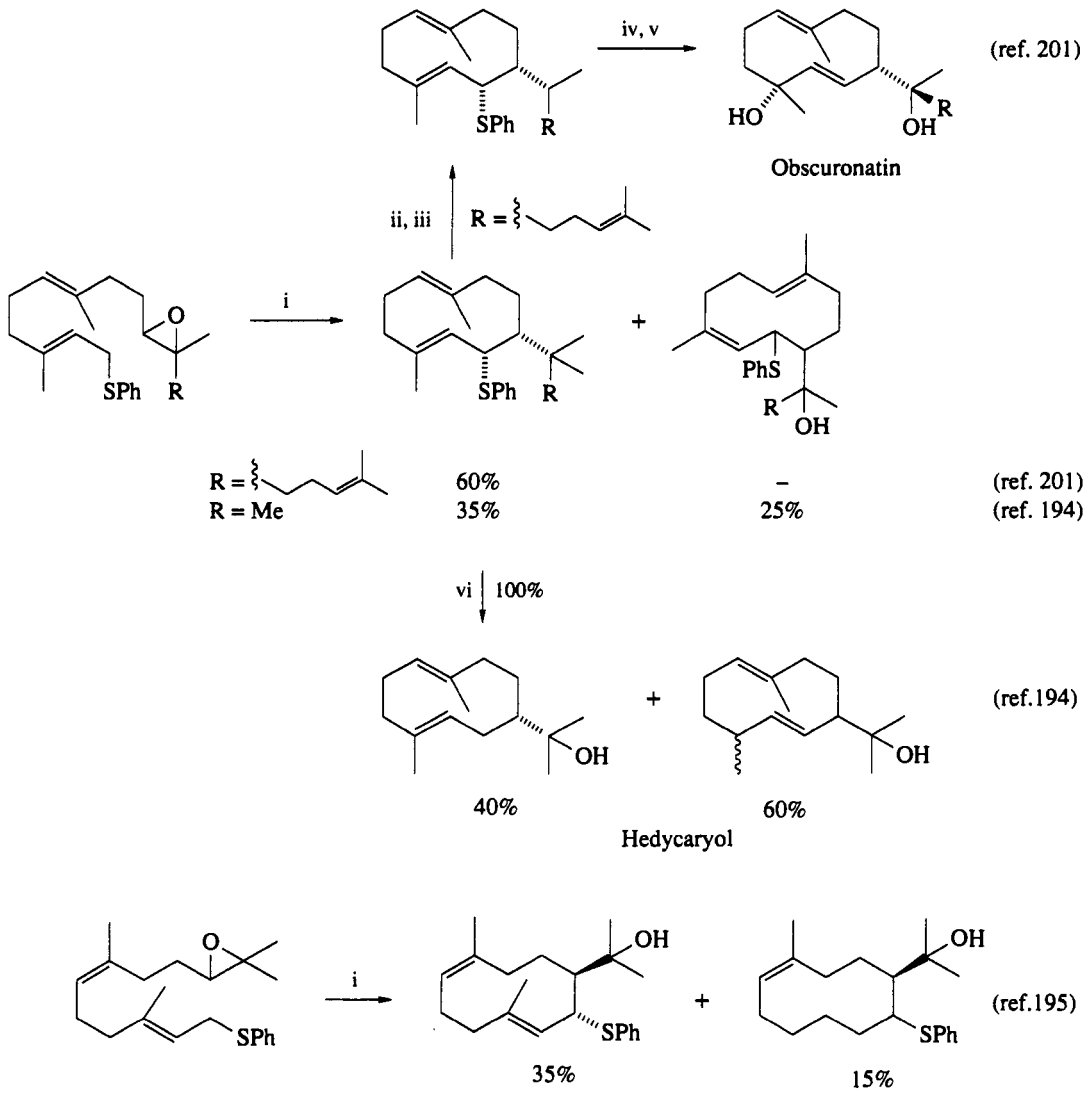
Alternatively, 1-lithio-1-alkenyl phenyl and methyl selenides have been obtained on reduction of the C—Se bond of 1,1-di(seleno)alkenes with alkyllithiums; this reaction is the only one which allows the synthesis of the methylseleno derivatives (Scheme 41).[83]

Furthermore, allenyl phenyl selenides have been prepared by alkylation of 1-lithioallenyl phenyl selenide, itself produced[103] on metallation of phenyl 1-propynyl selenide or of allenyl phenyl selenide[103] (Scheme 42). 1-Lithioallenyl phenyl selenide has poorer nucleophilic properties[103] than that of α-selenoallyllithiums, since the reaction of the former with 2-phenyl-1-bromoethane gives predominantly styrene, whereas the latter leads to products of substitution in good yield.[103]

1.3.2.2 Synthetically Useful Transformations of Alkylated Sulfides and Selenides

1.3.2.2.1 Synthetic transformations involving the reduction of sulfides and selenides

Alkyl, benzyl, allyl and propargyl sulfides and selenides arising from the alkylation of the corresponding heterosubstituted organometallics have been used in several interesting transformations. These transformations take advantage of the easy reduction of the C—S and of the C—Se bond which can be carried



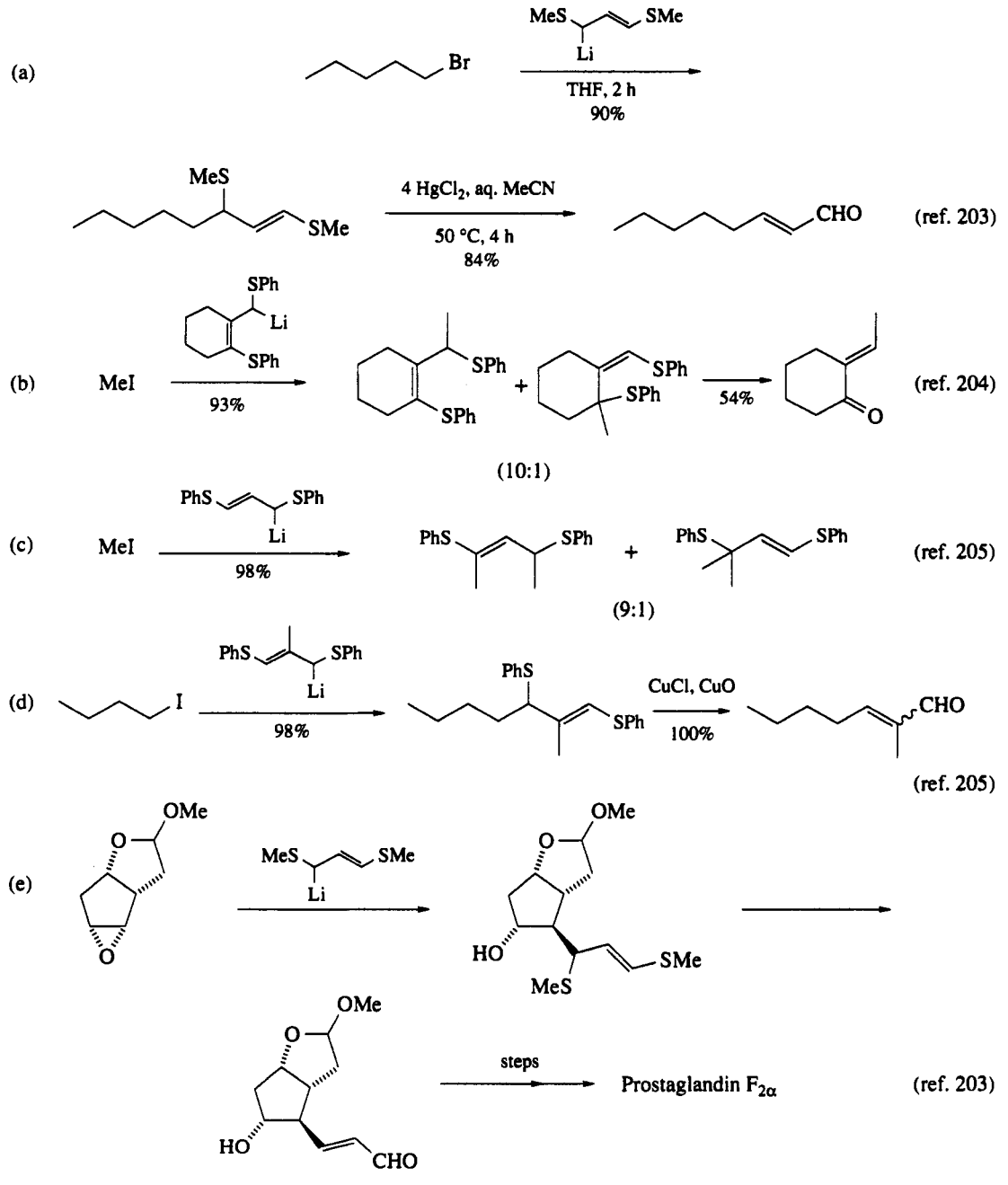
i, Bu^{n}Li, THF, –78 to 20 °C; ii, $POCl_3$, pyridine; iii, H_2, $Rh(PPh_3)_3Cl$; iv, $NaIO_4$; v, Et_2NH; vi, Li, Et_2NH, –78 °C

Scheme 30

out in both cases with Raney nickel (Scheme 25; Scheme 43; Scheme 44, entry a),[132a,133,140,153] lithium in ethylamine (Scheme 25, entries a, c and d; Scheme 26; Scheme 34, entry b; Scheme 43),[140,165,186,187,189,191,192,211] nickel boride (Scheme 25),[188] or lithium naphthalenide (Scheme 15).[126] Tributyl- or triphenyl-tin hydrides[144] for their part proved particularly efficient for the reduction of selenides (Scheme 44, entry b).[225,226] Care must be taken in performing such reactions however in the presence of C—C double bonds, to prevent the formation of a five- or a six-membered ring by cyclization of the radical intermediate formed.[227–229]

Selective reduction of allyl sulfides implies that no scrambling of the carbon–carbon double bond occurs during the process. Effectively this has proved to be the case especially when lithium in ethylamine is used, and the method has allowed the regio- and stereo-selective synthesis of a large variety of 1,5-dienes including squalene[165] (Scheme 25, entry a),[165] mukapolide (Scheme 25, entry b),[188] dendrolasin (Scheme 25, entry c), the basic nucleus of crassin acetate (Scheme 25, entry d)[189] from γ,γ-dialkylallyl sulfides and allyl halides, and also of 1,5-enynes[211] from propargyl sulfides and allyl halides (Scheme 34, entry b).

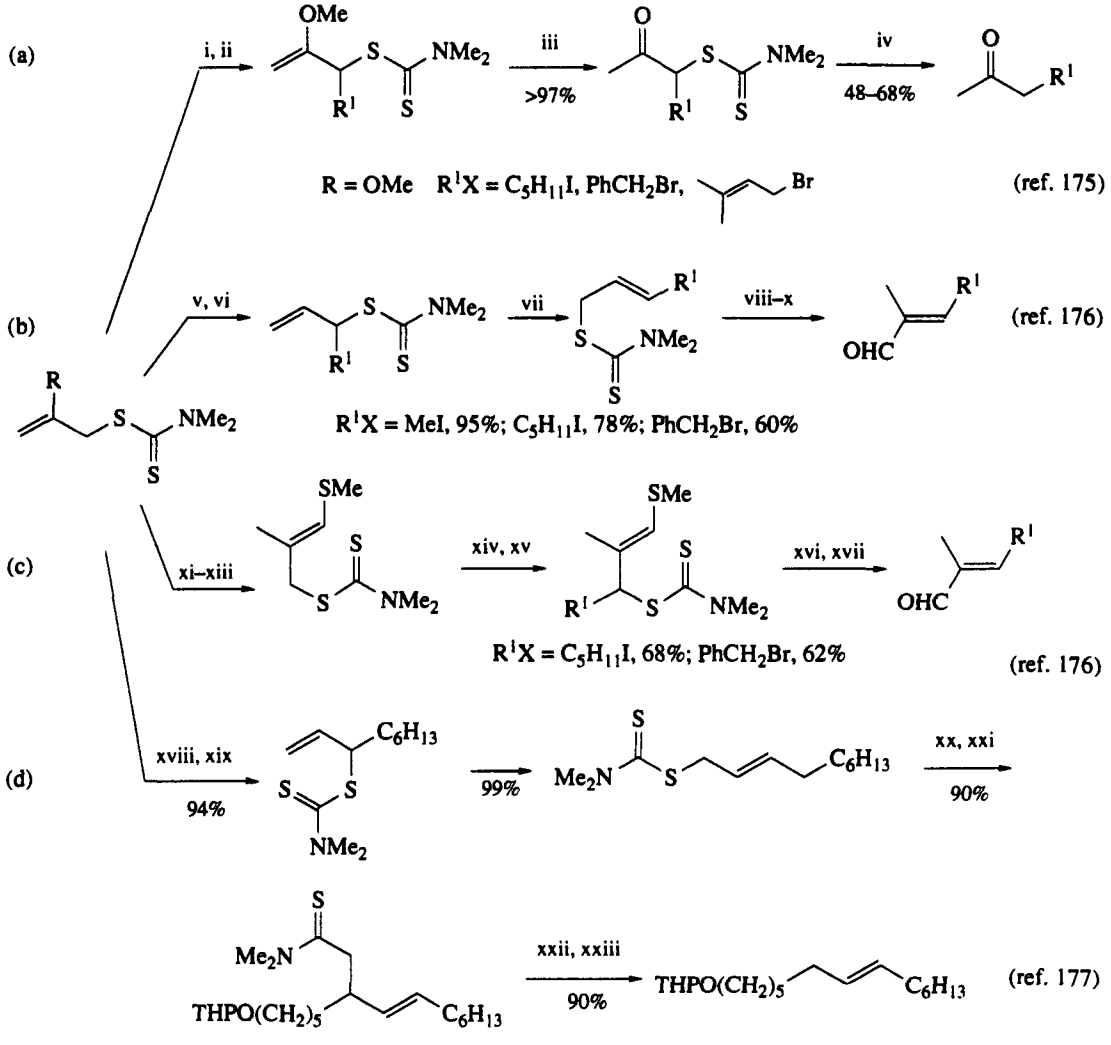
Two original syntheses of C_{18} *Cecropia* juvenile hormones are depicted in Scheme 26,[191,192] both of which use the strategy presented above. The second synthesis is particularly ingenious since the dihydro-



Scheme 31

thiopyran building block allows both the regioselective construction of the polyenic system and the control of the stereochemistry of the (*Z*)-trisubstituted carbon–carbon double bonds. Reduction of benzyl and allyl sulfides, including allyl 2-pyridyl sulfides has also been performed[168,169] with $CuCl_2$–$LiAlH_4$, in some cases in the presence of lithium methoxide.[169] Sequential alkylation of allyl 2-pyridyl sulfide and reduction with $CuCl_2$–$LiAlH_4$ proceeds regioselectively and leads[15,168] to terminal as well as trisubstituted alkenes (Scheme 45).[169] Under similar conditions γ,γ-dimethylallyl 2-pyridyl sulfide is alkylated or benzylated selectively in the α-position, but finally leads to a mixture of alkenes resulting from the partial scrambling of the carbon–carbon double bond. This set of reactions has been applied to the synthesis of *cis*-bergamotene (Scheme 45, entry b).[169]

Otherwise, reduction of allylic dithiocarbamates proved regio- and stereo-selective when carried out with lithium in ethylamine (Scheme 32),[177] but leads to a mixture of alkenic compounds when carried out with Raney nickel.[174]

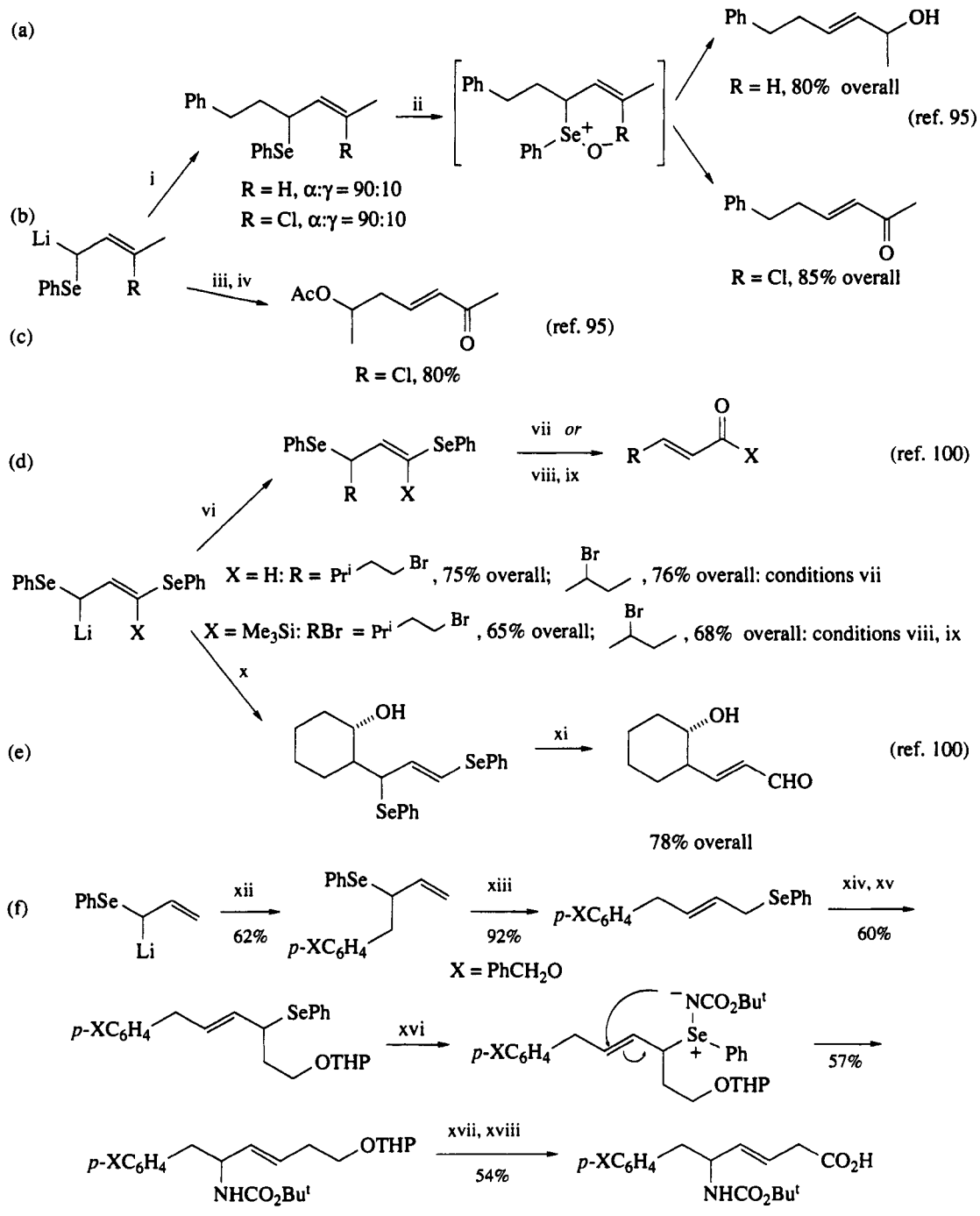


i, LDA; ii, R^1X; iii, H_3O^+, MeOH; iv, Raney Ni, acetone, reflux, 3 h; v, LDA; vi, R^1X; vii, Δ, 3 h; viii, LDA; ix, MeSSMe; x, Hg^+, aq. MeCN; xi, LDA; xii, MeSSMe; xiii, Δ; xiv, LDA; xv, R^1X; xvi, Δ; xvii, Hg^+, aq. MeCN; xviii, LDA; xix, $C_6H_{13}I$; xx, $Pr^i(C_6H_{13})NLi$; xxi, $THPO(CH_2)_5I$; xxii, Li, H_2NEt; xxiii, 3-hexyne

Scheme 32

Benzyl phenyl sulfides can be sequentially metallated and alkylated. The cleavage of the carbon–sulfur bond in the resulting product leads to a benzyllithium and lithium phenylthiolate.[126] Alkylation of the former organometallic then produces an alkylbenzene (Scheme 15), but competing alkylation on the thiolate is however observed.[126]

An efficient geminal 'reductive alkylation' of the carbonyl group of aliphatic aldehydes and ketones, including that of cyclic ketones, takes advantage of: (i) the great availability of α-selenoalkyllithiums (themselves readily prepared from the corresponding carbonyl compounds *via* the selenoacetals);[84] (ii) their alkylation with primary alkyl halides; and (iii) the reduction of the corresponding selenides.[140] A specific example of this process, presented in Scheme 44 (entry a), describes an efficient synthesis of vitamin D.[144] A related reaction involving the reductive allylation of heptanal is recorded in Scheme 10.[123,127,147,226] The case of aromatic aldehydes and ketones is even more interesting since (i) the related α-selenobenzyllithiums can be alkylated even with *s*-alkyl halides[74,79,80,105,106] as well as with benzyl bromide,[105] and (ii) because the resulting benzyl selenides on reaction with *n*-butyllithium can be cleaved to produce benzyllithiums. The benzyllithiums in turn can be alkylated even with secondary alkyl



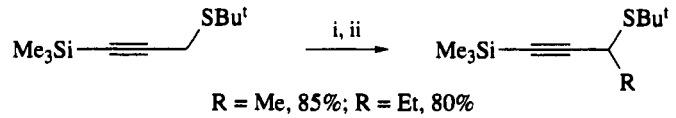
i, Ph Br, −78 to 20 °C; ii, H_2O_2; iii, O ; iv, Ac_2O; v, H_2O_2; vi, RBr;

vii, H_2O_2; viii, $MeCO_3H$; ix, Et_2NH; x, O ; xi, H_2O_2; xii, *p*-$XC_6H_4CH_2Br$, −78 °C, 2 h;

xiii, PTSA, H_2O, benzene, Δ; xiv, LDA, THF; xv, THPO Br ;

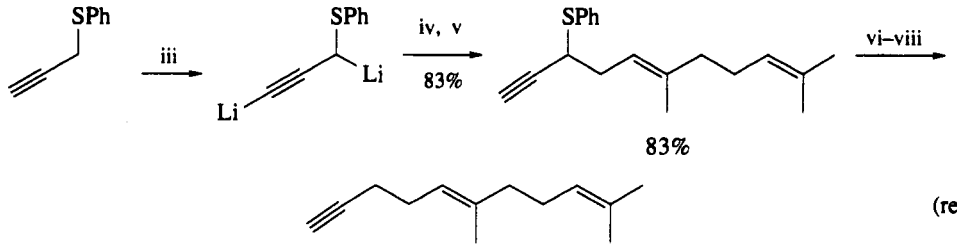
xvi, Bu^tOCONH_2, Et_3N, NCS, MeOH; xvii, HCl; xviii, CrO_3, acetone

Scheme 33

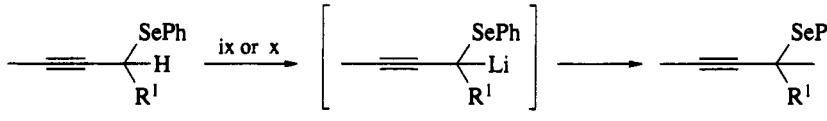
(a) 

(ref. 210)

R = Me, 85%; R = Et, 80%

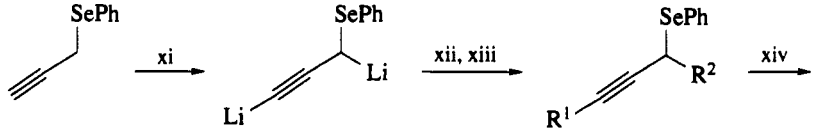
(b) 

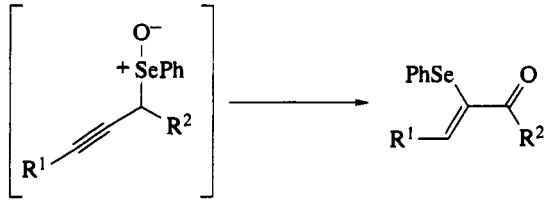
(ref. 211)

(c) 

(ref. 102, 103)

R^1 = H, Me exclusive, predominantly α-methylation

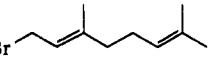
(d) 



(ref. 102, 103)

R^{1}X = Ph(CH$_2$)$_3$I, R^{2}X = MeI, 59%

R^{1}X = Pr^{i}I, R^{2}X = H$_2$O, 60%

i, Bu^{n}Li; ii, RX; iii, 2 BuLi; iv, 

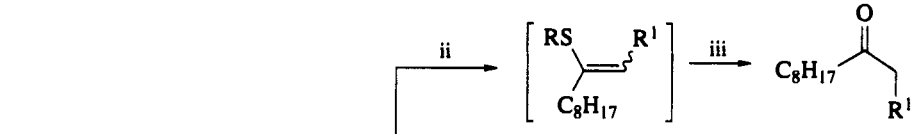
; v, H_2O; vi, $NaNH_2$;

vii, Li, NH_3; viii, H_3O^+; ix, LDA; x, $LiBu^i{}_2N$, –78 °C; xi, 2 LDA; xii, R^{1}X; xiii, R^{2}X; xiv, MCPBA

Scheme 34

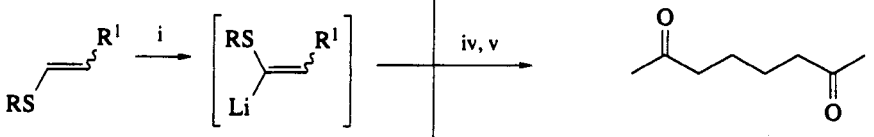
halides. This process therefore allows the geminal dialkylation of the carbonyl group of aromatic aldehydes and ketones, and permits the synthesis of particularly hindered alkylbenzenes (Scheme 17, entry a).[79,80,230] Selenoacetals derived from aromatic carbonyl compounds as well as benzyl selenides bearing carbon–carbon double bonds in a suitable position possess a high tendency to cyclize leading to aryl cycloalkanes on reaction with tin hydrides or on reaction with *n*-butyllithium, followed by hydrolysis of the resulting alkyllithium (Scheme 46).[228,231,232] The reaction of tin hydrides with the benzyl selenide shown in Scheme 46 (entry c) leads to a mixture of cyclopentane and cyclohexane derivatives (Scheme 46, entry d).[228] The reaction is much more selective when carried out with Bu^{n}Li since not only does it provide the five-membered cycle exclusively, but it also produces stereoselectively each of the two stereoisomers depending upon the solvent used.[228]

(a)



R = Et, R^1 = H, 90%; R = Me, R^1 = C_8H_{17}, 82%;
R = Me, R^1 = Ph, 65%

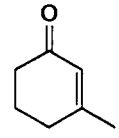
(b)



(ref. 216)

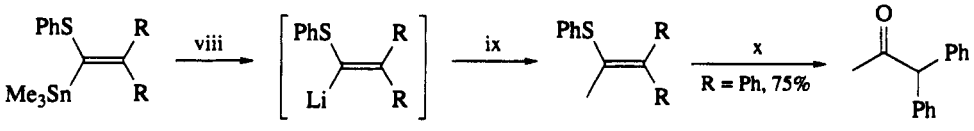
R = Et, R^1 = H, 50%

(c)



R = Et, R^1 = H, 52%

(d)



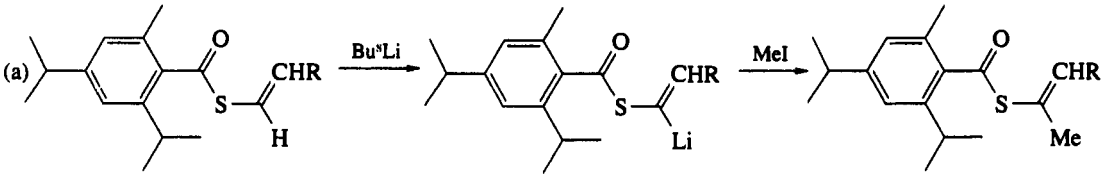
R = Ph, base = MeLi, 92%
R = H, base = Bu^nLi, 78%

(ref. 59, 82)

i, Bu^sLi, THF–HMPA, –78 °C; ii, $C_8H_{17}Br$; iii, $HgCl_2$, aq. MeCN; iv, $Br(CH_2)_4Br$; v, $HgCl_2$, aq. MeCN; vi, $Br(CH_2)_3Br$; vii, $HgCl_2$, aq. MeCN; viii, base; ix, MeI; x, $TiCl_4$, aq. $MeCO_2H$

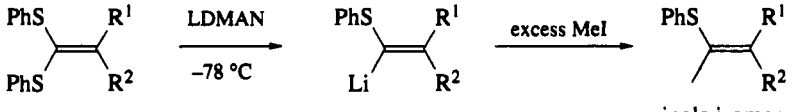
Scheme 35

(a)



R = H, Me; 86% overall (ref. 131)

(b)

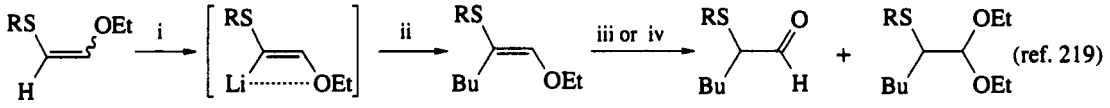


(ref. 129)

single isomer

R^1, R^2 = $-(CH_2)_5-$, 89%
R^1 = Pr^i, R^2 = H, 76%

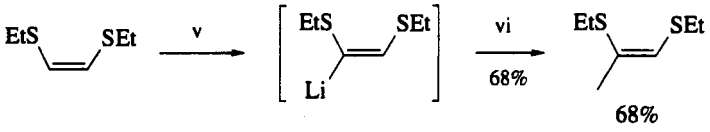
Scheme 36



(a) R = C_5H_{11}, X = Br, 42% iii, exclusively –

(a) R = C_5H_{11}, X = I, 60% iv, – exclusively

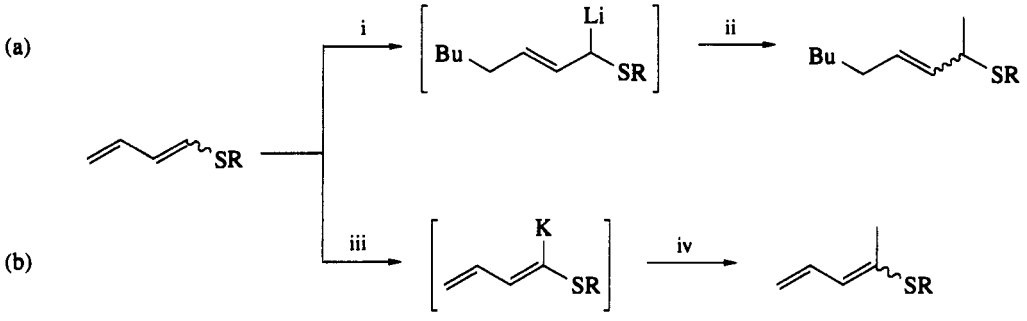
(b) R = Ph, X = I, 55%



(ref. 220)

i, Bu^{t}Li, THF, –70 °C, 1 h; ii, BuX, THF–HMPA; iii, AcOH, 50%; iv, *p*-TsOH, EtOH, 50 °C; v, LDA, THF, –78 °C, 1 h; vi, MeI

Scheme 37

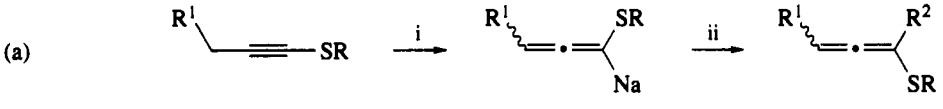


Starting material *(E)*: R = Me, 90% *(E)*; R = Bu^t, 85% *(E)*

Starting material *(Z)*: R = Me, 85% *(Z)*; R = Bu^t, 83% *(Z)*

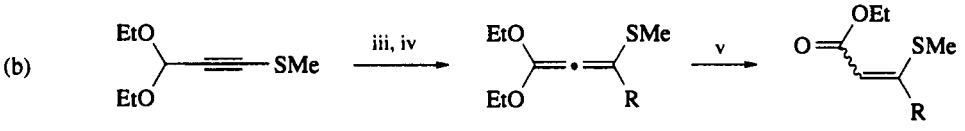
i, Bu^{n}Li; ii, MeI; iii, Bu^{n}Li–Bu^{t}OK, THF, –65 °C; iv, MeI

Scheme 38



R = Et; R^1 = H, Me; R^2 = Et, Pr^i; 70–75% (ref. 222)

R = Me; R^1 = OMe; R^2 = Et, 93%; R^2 = Pr^i, 56%; R^2 = Pr^i, 86% (using 1 equiv. HMPA) (ref. 224)

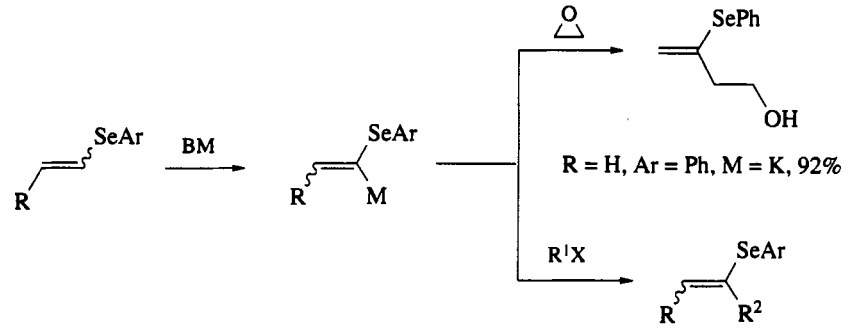


(ref. 223)

R = Me, 90%; R = Et, 89%; R = Bu^i, 80%

i, $NaNH_2$, liq. NH_3; ii, R^2Br, THF; iii, $LiNEt_2$; iv, RX; v, $HgCl_2$, MeOH

Scheme 39

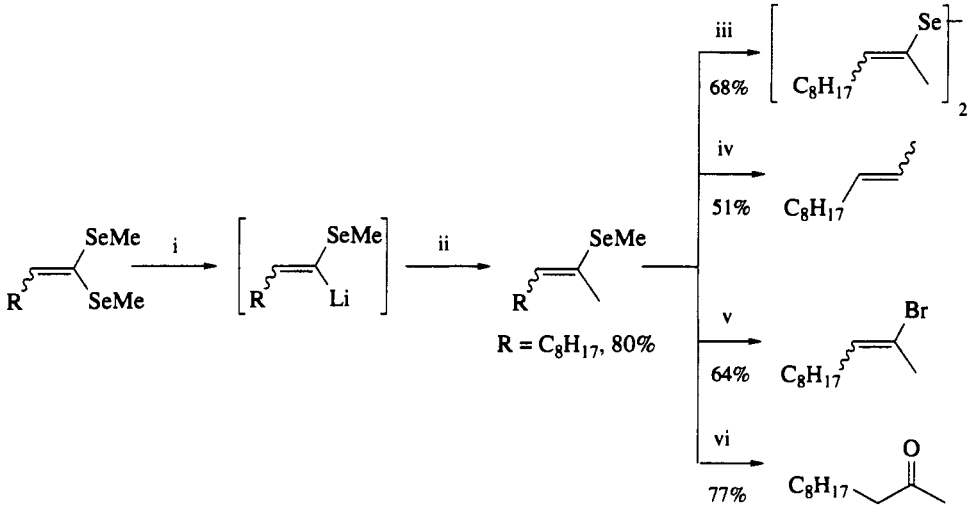


(ref. 108)

	Reactants	*Temperature* (°C)	*R*	*Ar*	*R¹X*	*Yield* (%)	*Ref.*
(a)	LDA, THF–HMPA	–78	H	Ph	$C_{10}H_{21}Br$	70	110
(b)	LDA, THF–HMPA	–78	H	*m*-$CF_3C_6H_4$	BuI	85	107
(c)	KDA, THF	–78	H	Ph	MeI	98	108
	KDA, THF	–78	H	Ph	$C_{10}H_{21}Br$	94	108
(d)	KDA, THF	–78	Bu	Ph	MeI	85[a]	108
(e)	LDA, THF	–78	C_6H_{13}	Pyr	MeI	94[a]	111

[a](*E*/*Z*) stereochemistry retained

Scheme 40

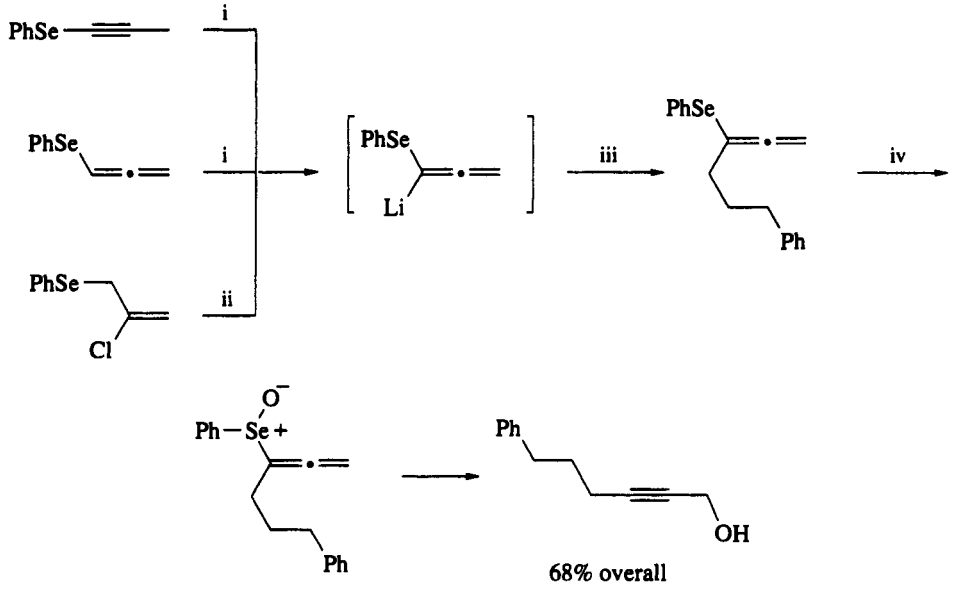


i, Bu^{n}Li, THF, –78 °C; ii, MeI; iii, Li, $EtNH_2$, –15 °C, 1 h; iv, Bu_3SnH, AIBN, 90 °C, 3 h; v, Br_2, benzene; vi, Br_2, EtOH, 90 °C, 6 h

Scheme 41

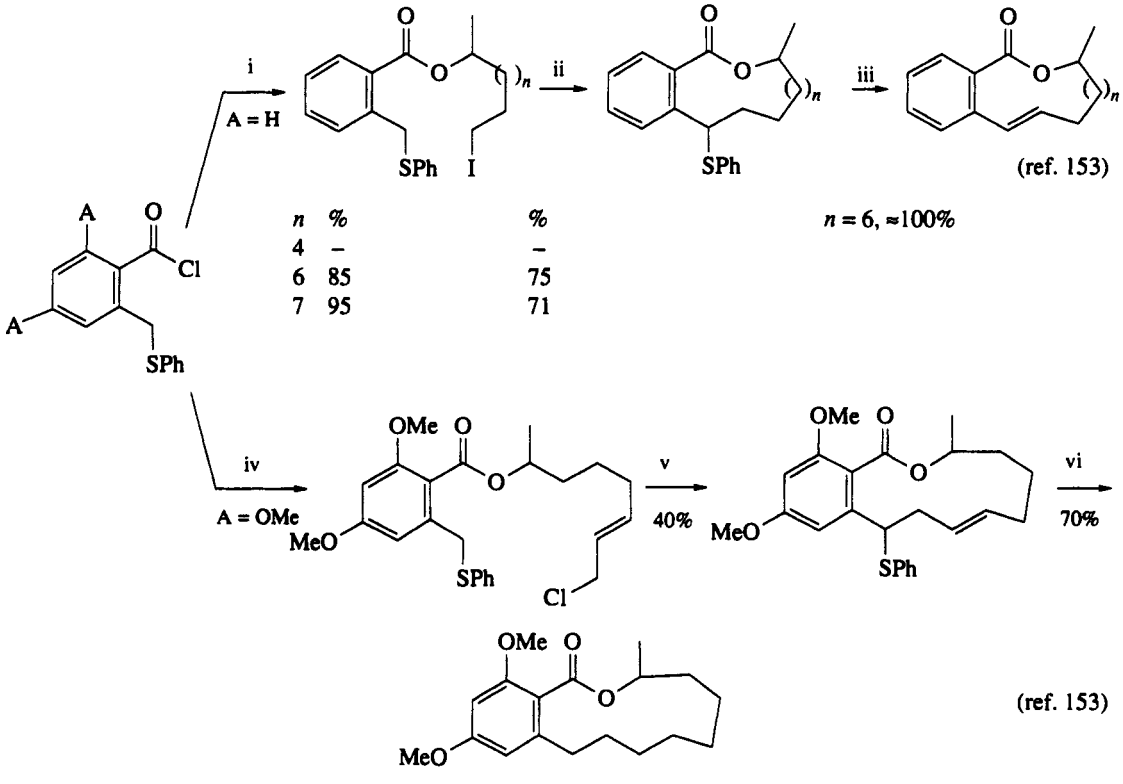
1.3.2.2.2 Transformations of sulfides and selenides to alkenes

Alkyl sulfides and selenides have proved to be valuable precursors of alkenes (Scheme 17, entry b; Scheme 47; Scheme 48; Scheme 49; Scheme 50).[74,104,157] These transformations can be achieved *via* the corresponding sulfoxides (Scheme 47)[153,233] and selenoxides (Scheme 17, entry b)[23,45,47,52,53,63,74,104,234] which collapse to alkenes and sulfenic or seleninic acid respectively on thermolysis. The elimination reaction takes place under particularly mild and neutral conditions with selenides (Bu^{t}O$_2$H, Al_2O_3, THF,

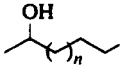
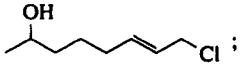


i, LDA, THF, –78 °C; ii, 2LDA, THF, –78 °C; iii, $Ph(CH_2)_3I$, 1 h; iv, 30% aq. H_2O_2, CH_2Cl_2, pyridine

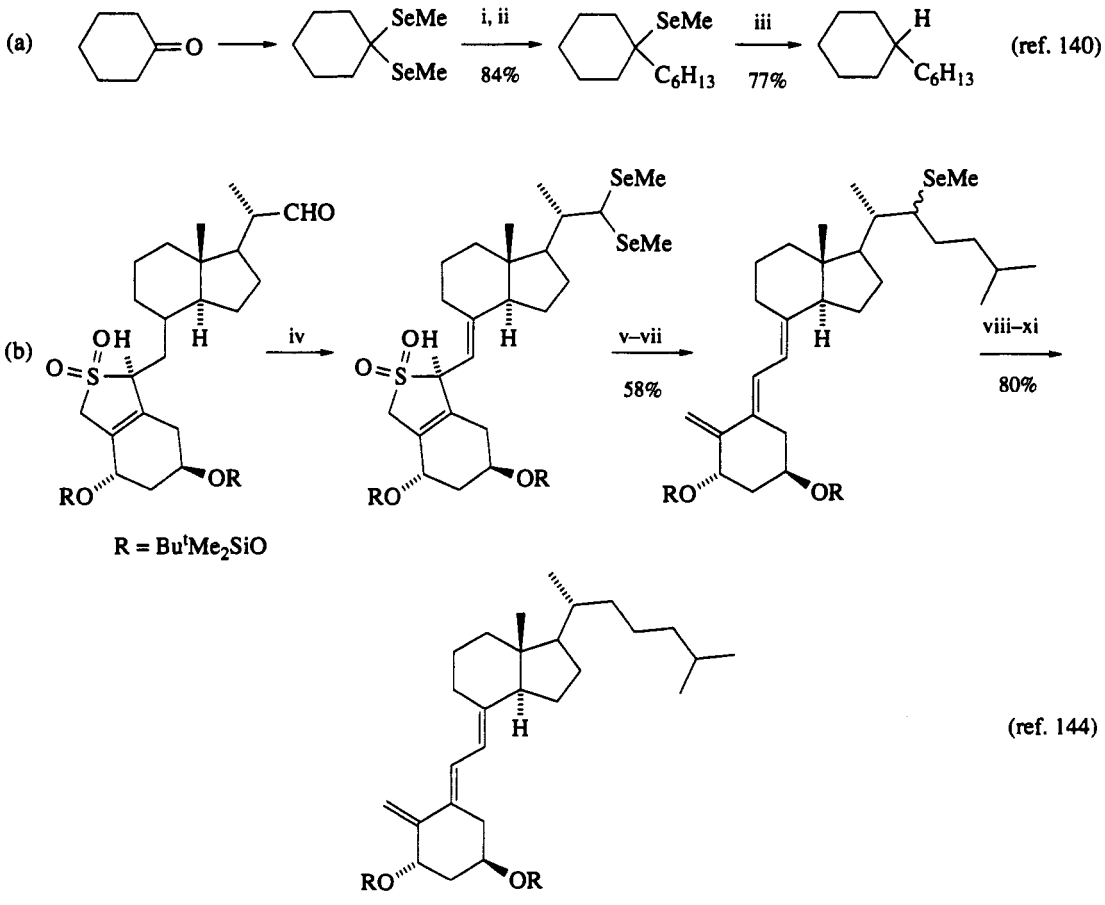
Scheme 42



O-Methyllasiodiplodin

i,  ; ii, $KN(SiMe_3)_2$, 40 °C, 2 h; iii, $NaIO_4$, toluene, 110 °C; iv,  ;
v, $KN(SiMe_3)_2$, 40 °C; vi, Raney Ni, EtOH, 80 °C

Scheme 43



i, Bu^nLi, ii, $C_6H_{13}I$; iii, Li/H_2NEt; iv, $B(SeMe)_3$, CF_3CO_2H, CH_2Cl_2, 5 °C; v, $NaHCO_3$, EtOH, 80 °C;

vi, 1 Bu^nLi, 0.2 h; vii, 1.5 Br⟨ ⟩; viii, Bu_3SnH, AIBN, toluene, 100 °C; ix, SO_2;

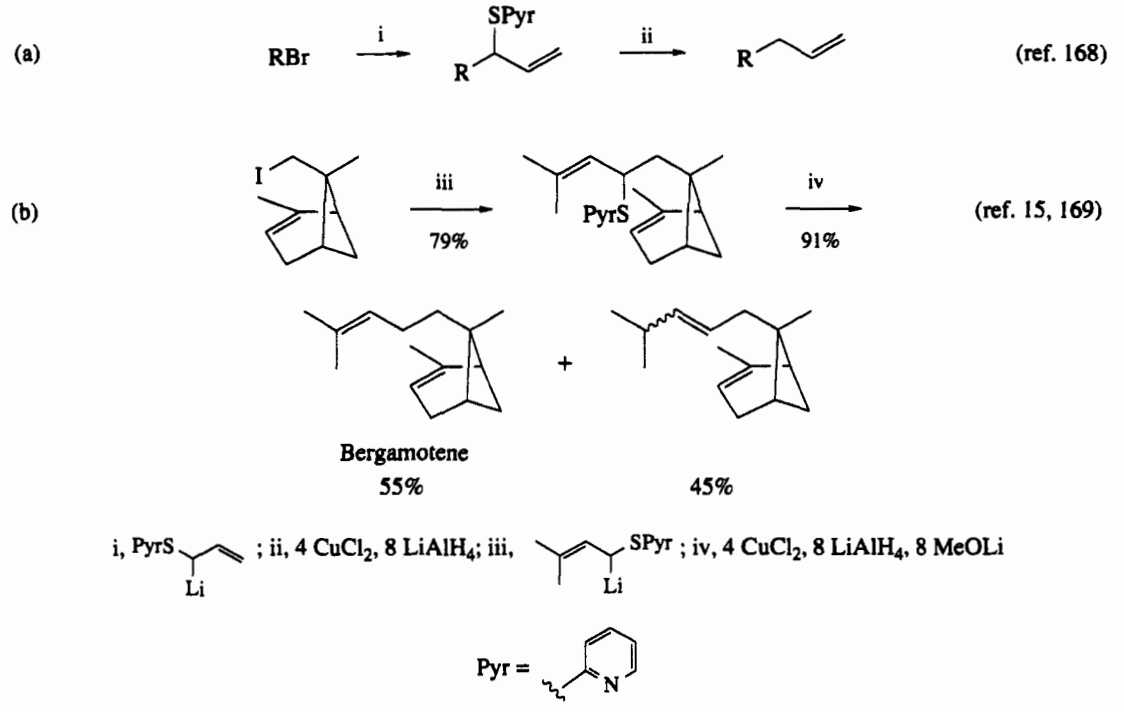
x, 2.2 Bu_3SnH, *hν*, toluene, 20 °C; xi, $NaHCO_3$, EtOH, 80 °C

Scheme 44

60 °C, 3 h or H_2O_2, THF, 20 °C),[142] but usually leads to a regioisomeric mixture of alkenes. It is however, particularly useful for the synthesis of 1-alkenes and 1-arylalkenes from the corresponding selenides, themselves available from alkyl halides and selenomethyllithiums or selenobenzyllithiums[74,104,105] respectively, since, in these examples, there is only one possible regiochemical outcome, and also for the synthesis of 1,3-dienes from allyl halides[74,127] and α-selenoalkyllithiums (Scheme 10; Scheme 17, entry b) because the presence of an allylic hydrogen in the β-position to the selenoxide directs the elimination towards the original double bond. The overall strategy is particularly useful for the synthesis of terminal alkenes, alkylidene-cyclopropanes and -cyclobutenes from primary alkyl halides and selenomethyllithium,[52,70] 1-selenocyclopropyllithiums[70] and 1-selenocyclobutyllithiums[71] respectively (Scheme 48), and for the synthesis of allylidene cyclopropanes from allyl halides and 1-seleno-[70] or 1-thio-cyclopropyllithiums (Scheme 5, entry a).[127]

The other set of reactions which allow the transformation of sulfides and selenides to alkenes require the intermediary formation of a sulfonium or selenonium salt, and their treatment with a base such as KOH or Bu^tOK.[52,70,71,127] Furthermore, conjugated dienes, trienes and polyenes have been produced[157,172,173] from allyl halides and benzyl and allyl dithiocarbamates respectively, using the set of reactions illustrated in Schemes 48, 49 and 50, and the transformation has been applied *inter alia* to the synthesis of β-parinaric acid (Scheme 50).[172]

The oxidation of allylic sulfides with equivalent amounts of, for example, peroxyacids or sodium periodide leads to allylic sulfoxides.[16] These sulfoxides do not usually eliminate sulfenic acid to provide



Scheme 45

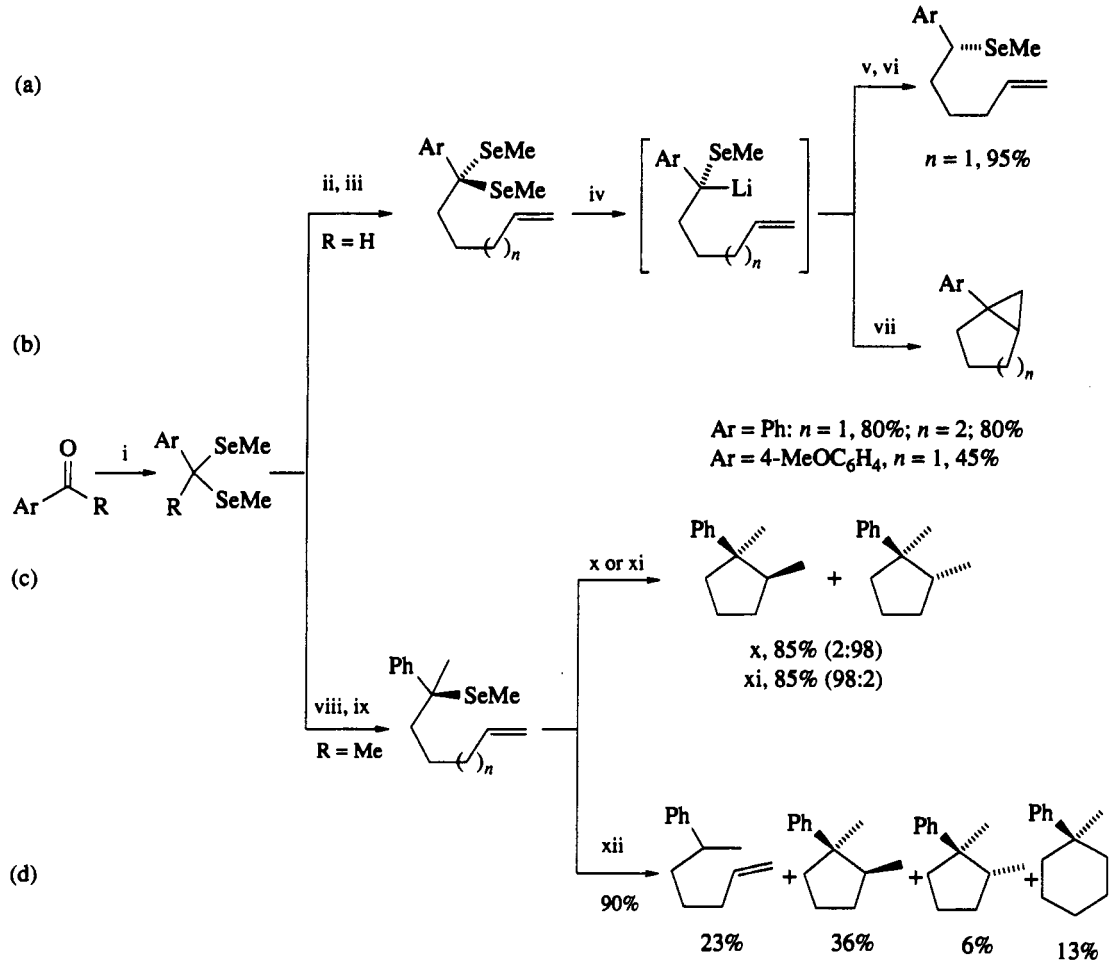
dienes, but instead produce[16,170] allyl alcohols *via* a [2,3] sigmatropic rearrangement when treated with a thiophilic agent such as a secondary amine or a phosphite (Scheme 51).[235,236]

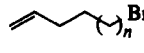
The rearrangement of allyl selenoxides is even easier; it takes place directly at room temperature when allyl selenides are oxidized with hydrogen peroxide (30% aq. solution in THF)[45,46,52–54,56,63] or peroxyacids. Allyl selenides produce allyl alcohols, whereas γ-chloro-,[95] γ-seleno-[100] and γ-seleno-γ-trimethylsilyl analogs[100] lead to α,β-unsaturated aldehydes, ketones and trimethylsilyl ketones respectively (Scheme 33, entries a–e). Therefore the corresponding α-lithium salts play the role of a masked β-lithioallyl alcohol (Li—C═C—COH) or a masked β-lithio-α,β-unsaturated carbonyl compound (Li—C═C—C(═O)X) respectively.

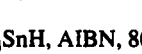
Oxidative rearrangements of allylic selenides in the presence of various amine nucleophiles provide synthetic access to a variety of allylic amine derivatives.[208,209] The stereochemical outcome of these reactions is consistent with a [2,3] sigmatropic rearrangement. The reaction has been applied to the synthesis of β,γ-unsaturated-α-amino acids[209] or to their *trans*-alkene isosteres (see for example Scheme 33, entry f). The [2,3] rearrangement of allylic selenoxides has been successfully extended to the propargylic[102,103] and allenyl[103] analogs, and provides α-seleno-α,β-unsaturated carbonyl compounds and propargylic alcohols respectively (Scheme 34, entry d; Scheme 42). This process does not occur with sulfur analogs as a consequence of the greater stability of the sulfoxide compared to the rearranged sulfenate.[102]

Finally, α-alkylated allylic dithiocarbamates bearing a terminal C—C bond rearrange smoothly to the allylic dithiocarbamates in which the heteroatomic moiety is terminal (Scheme 52, entry b).[174]

As shown earlier, alkenes and allylic alcohols can be prepared from alkyl and allyl sulfides or selenides by a series of reactions which involve alkylation of the corresponding organometallic, followed by oxidation of the resulting sulfides or selenides and further reaction of these species. One can think of the reverse order of reactions involving first the oxidation of the sulfide or selenide followed by alkylation of the resulting oxide. This procedure has in fact been performed in some cases as will be shown in the next section (Section 1.3.5). Of course the second approach offers the advantage of an easier metallation reaction. However, it possesses several disadvantages which have been observed from time to time. For example, alkyl selenoxides are prone to eliminate and are hygroscopic and therefore their metallation, although efficiently achieved, requires tedious manipulation in order to avoid these side reactions.[46,47,54] As mentioned above, allyl selenoxides are too unstable and have only been postulated in the oxidation of allyl selenides. Their metallation and alkylation have not yet been attempted. Furthermore it has been reported in many instances that selective alkylation at the α-site of allyl sulfides can be



i, 2 MeSeH, $ZnCl_2$ or $TiCl_4$; ii, KDA, THF, –78 °C; iii,  ; iv, Bu^nLi, THF, –78 °C;

v, –78 °C, 0.5 h; vi, MeOH; vii, 0 °C, 1 h; viii, Bu^nLi, THF; ix,  ;

x, Bu^nLi, THF, –78 °C, 0.1 h; xi, Bu^nLi, Et_2O, –30 °C, 0.1 h; xii, Bu_3SnH, AIBN, 80 °C

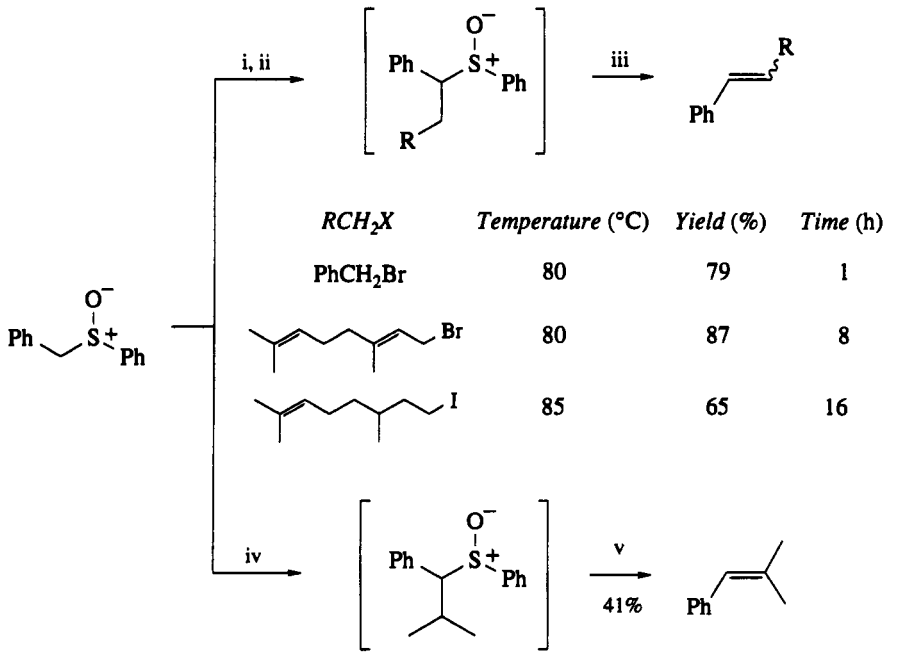
Scheme 46

achieved on condition that a substituent is chosen which is suitable for metal chelation. This is not possible with the corresponding sulfoxide.[16] Therefore, at least in these cases, the approaches reported in this section offer definite advantages over related ones.

1.3.2.2.3 Transformations of sulfides and selenides to organic halides: the haloalkylation and halopropenylation of alkyl and allyl halides

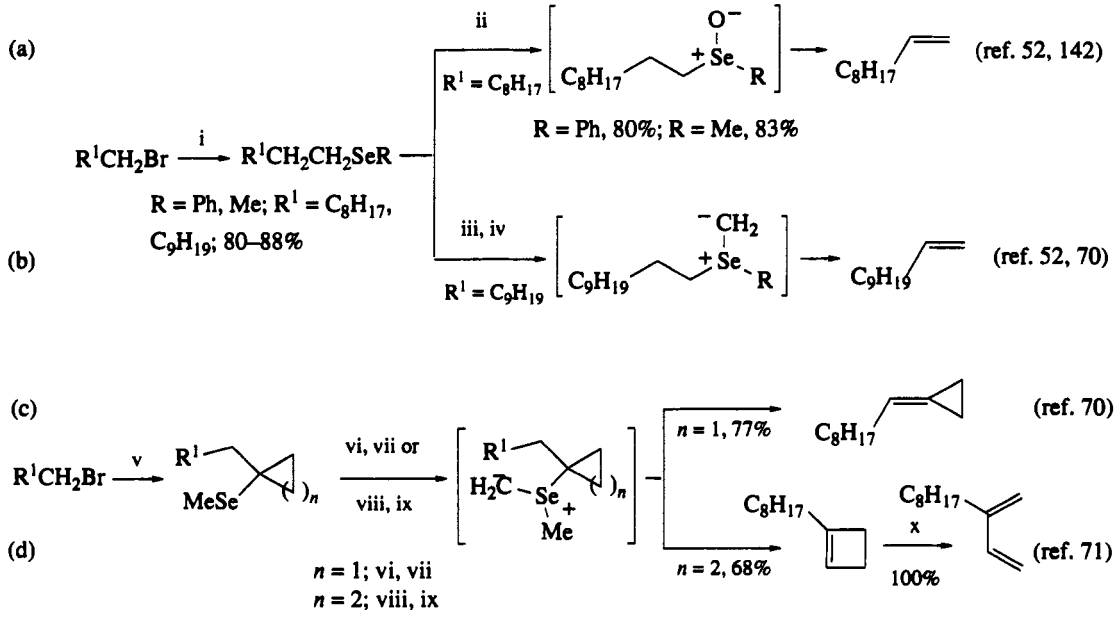
Alkyl and allyl sulfides and selenides can be transformed readily into the corresponding alkyl and alkenyl halides respectively. This reaction takes advantage of the easy formation of the corresponding sulfonium and selenonium salts on reaction with alkyl halides,[125,143] alkyl bromoacetates[141] or bromine[143,237] (Scheme 53). A related process involves the intermediary formation of a selenoxide and its further reaction with hydrochloric or hydrobromic acids.[238]

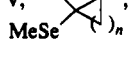
These reactions, coupled with the alkylations of sulfides and selenides, allow the homologation of primary alkyl halides[124,125,141,143,237,238] and the transformation of allyl halides to homoallyl halides.[125] A related process, employing 2-methylthio- and 2-allylthio-thiazoline, allows the iodomethylation (ICH_2—) and the iodopropenylation ($ICH_2CH{=}CH$—) of alkyl halides (Scheme 54).[131a,132,171]



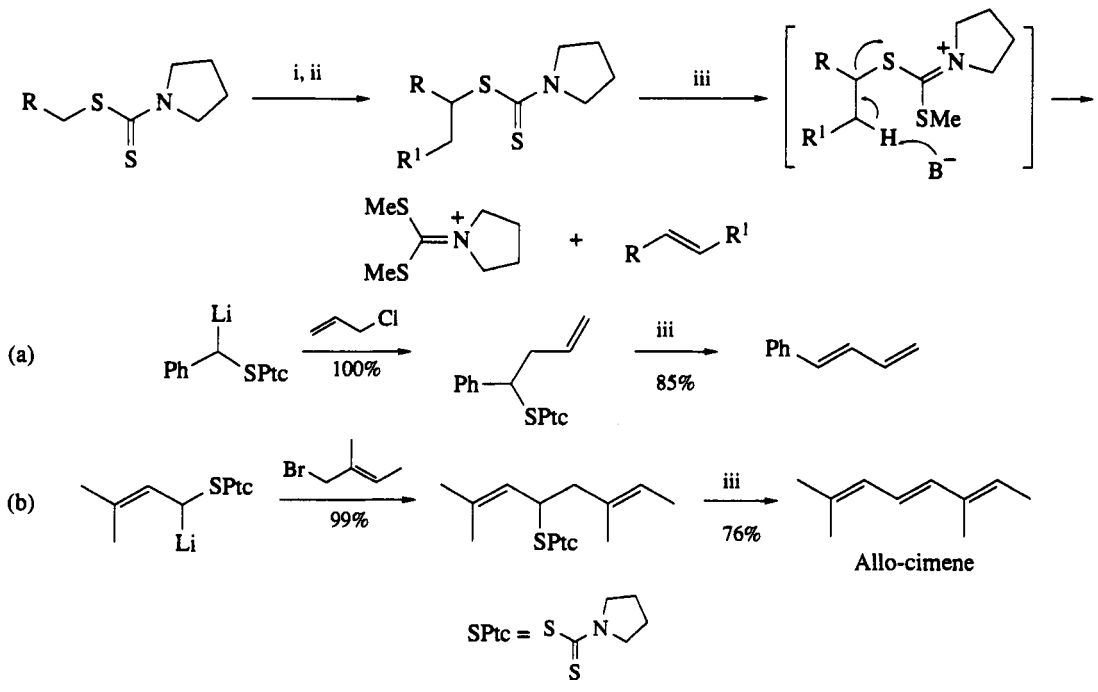
i, LICA, DME; ii, RCH_2X, 20 °C, 1 h; iii, DMF; iv, LICA, DME, PrⁱI, 20 °C, 0.3 h; v, heat, 180 °C, 0.2 h

Scheme 47



i, $RSeCH_2Li$, THF, HMPA, –78 °C to 20 °C; ii, Bu^tO_2H, THF, –60 °C, 3 h; iii, MeI, $AgBF_4$; iv, Bu^tOK, DMSO, 20 °C; v,  ; vi, $MeSO_3F$; vii, Bu^tOK, DMSO, 20 °C, viii, MeI, $AgBF_4$; ix, Bu^tOK, DMSO, 20 °C; x, 180 °C

Scheme 48



i, LDA; ii, R^1CH_2X; iii, MeI, HMPA, Li_2CO_3, LiF

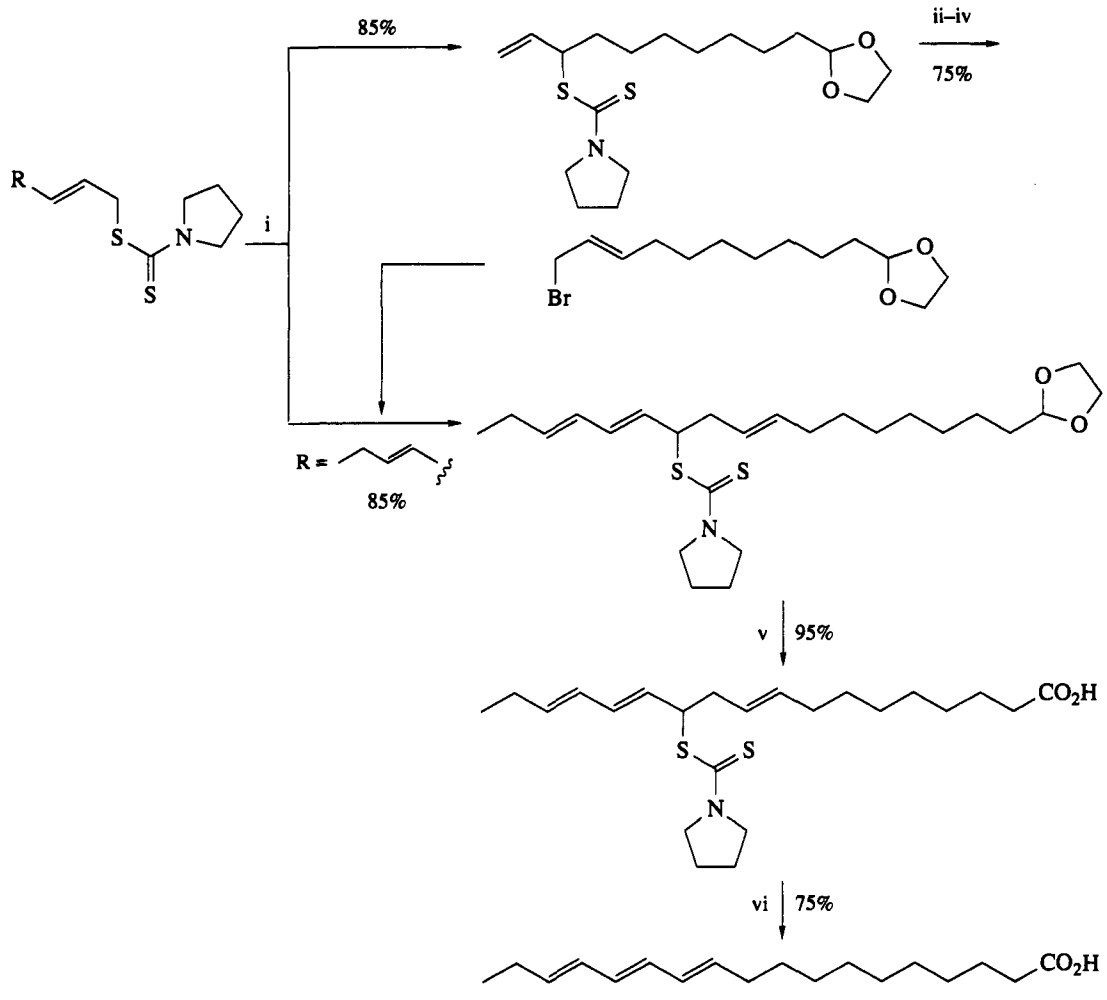
Scheme 49

γ- and δ-hydroxy selenides which result from the reactions of α-selenoalkyllithiums with epoxides have been transformed to various selenium-free compounds. Thus γ-hydroxyalkyl iodides and bromides have been produced in good yields from γ-hydroxyalkyl selenides and methyl iodide or bromine respectively (MeI, NaI, $CaCO_3$, DMF, 80 °C, 1 h; Br_2, EtOH–H_2O or Et_3N, CH_2Cl_2, 20 °C, 3 h). Under similar conditions δ-hydroxyalkyl selenides instead produce tetrahydrofurans directly.[149] The high propensity of the hydroxyalkyl selenonium salt intermediates to cyclize to a five-membered rather than to a four-membered heterocycle is responsible for these differences. Oxetanes however are available on treatment of the above mentioned γ-hydroxyalkyl halides with base (Bu^{t}OK, DMSO, 20 °C or MeMgBr–HMPA, 20 to 80 °C; Scheme 13, entries a and b). The reaction works well with those compounds in which the bromine is attached to a methine group, but increasing the substitution at this carbon dramatically lowers the yield of the heterocycle (Scheme 13, entry b) due to the concomitant formation of homoallyl alcohols.[149] The synthesis of the latter compounds is best achieved by first preparing the γ-hydroxyalkyl selenonium salts (MeI, neat, 20 °C for methylseleno derivatives) then treating them with a base (Bu^{t}OK, DMSO, 20 °C or 50% aq. KOH, CH_2Cl_2, phase-transfer catalyst).[150] The high regioselectivity observed for this process has been explained by the cyclic transition state depicted in Scheme 13 (entry d). Oxidation of γ-hydroxyalkyl selenides under Sharpless conditions (H_2O_2, THF, 20 °C) produces a mixture of allyl and homoallyl alcohols which suggests that the corresponding selenoxides lead to an indiscriminate elimination reaction.[150] Selective elimination leading to the α,β-unsaturated ketones can however be achieved using Jones' reagent (CrO_3–H_2SO_4, acetone; Scheme 13, entry e).[150]

γ-Hydroxyalkyl selenides derived from α-selenobenzyllithiums and epoxides have proved to be valuable precursors of arylcyclopropanes.[160] The reaction proceeds through the corresponding γ-tosyloxybenzyllithiums. Although the synthesis of the γ-hydroxyalkyl selenides is not stereoselective, the subsequent steps occur with high stereoselectivity, and have led to the conclusion that the benzyllithiums possess the opposite stereochemistry to that of the selenides and that this stereochemistry is retained in the next step (Scheme 18).[160]

1.3.2.2.4 Transformation of alkylated vinyl sulfides and selenides to carbonyl compounds

Vinyl sulfides[20,82,162,163,166,240] and selenides[82,83,90,239,241–244] available on alkylation of α-metallovinyl sulfides and selenides[107,108,110,239] (Scheme 35), themselves available from the corresponding vinyl



β-Parinaric acid

i, LDA, R^1X, –78 °C, 0.5 h; ii, Δ, $CHCl_3$, 4.5 h; iii, MeI; iv, NaBr, DMF, 50 °C, 24 h;
v, HCl, acetone, O_2, 5 °C, 1 week; vi, MeI, LiF, $LiCO_3$, DMF, 20 °C, 24 h

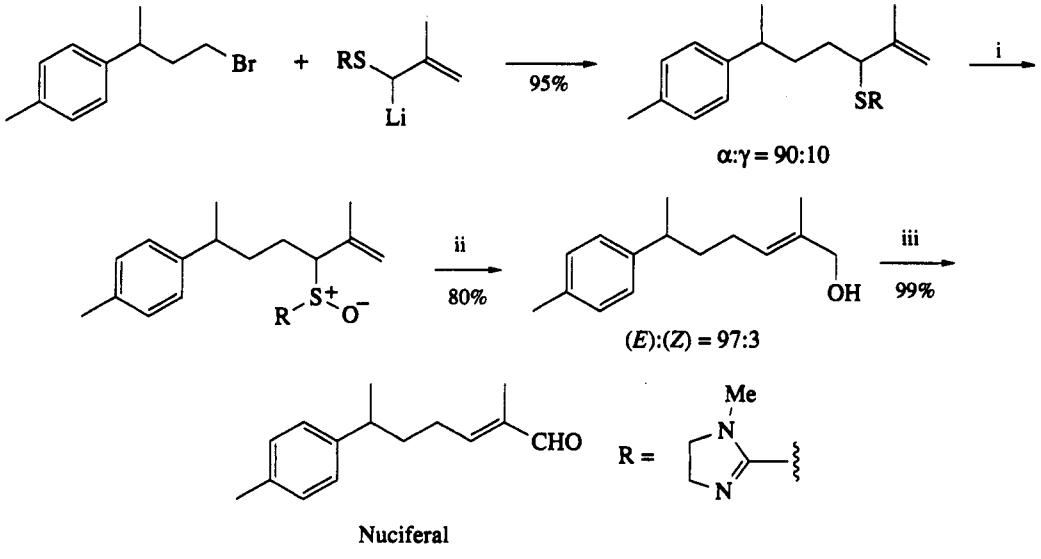
Scheme 50

sulfides and selenides or from 1,1-diselenoalkenes, (Scheme 41),[83] or on γ-alkylation of α-metalloallyl sulfides,[158,162,163] Scheme 27 and Scheme 52a) have been hydrolyzed to the corresponding carbonyl compounds *inter alia* with acids, mercury(II) or copper(II) salts. Therefore α-metallovinyl sulfides and selenides play the role of acyl anion equivalents in these transformations.

1.3.3 REACTIONS OF α-THIO- AND α-SELENO-ALKYLMETALS BEARING FURTHER HETEROATOMIC MOIETIES ON THEIR CARBANIONIC CENTER. APPLICATION TO THE FORMATION OF ACYL ANION EQUIVALENTS

1.3.3.1 Alkylations of 1-Metallo-1,1-dithioalkanes Bearing Hydrogen and/or Alkyl Groups on Their Carbanionic Center and Their Synthetic Applications

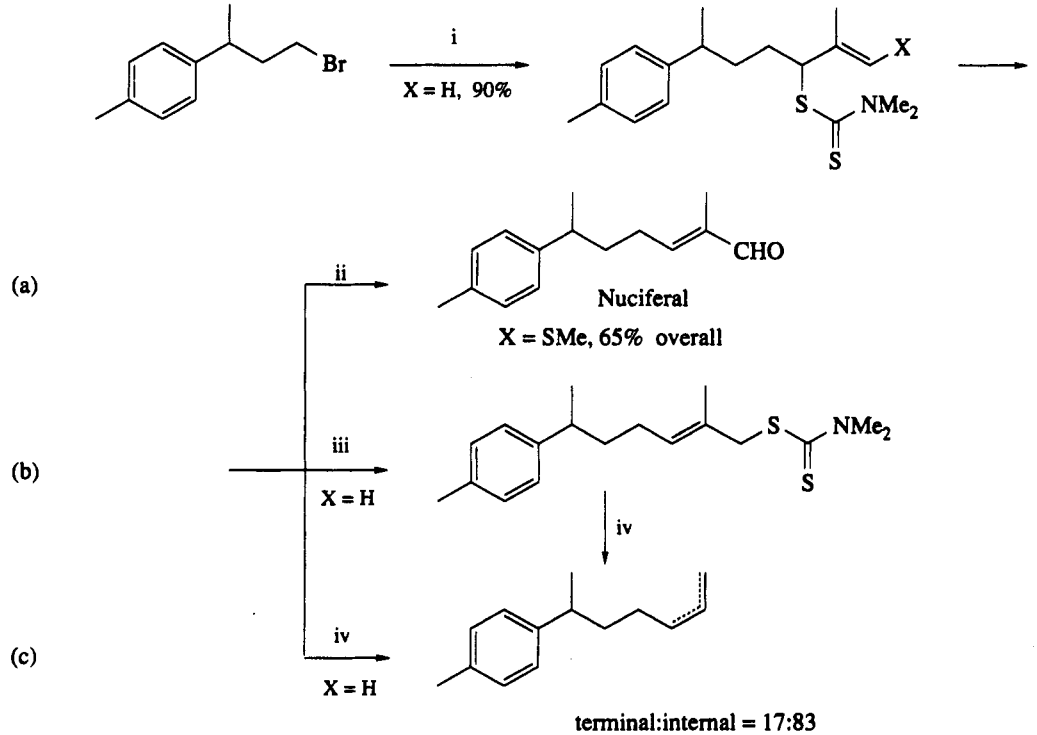
Organometallics bearing two heteroatomic moieties on their carbanionic center have found an important place in organic synthesis since the first report of Arens.[245] In particular, they have played a crucial role as formyl or acyl anion equivalents.[7,8,18–22,26–30]

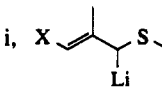


Nuciferal

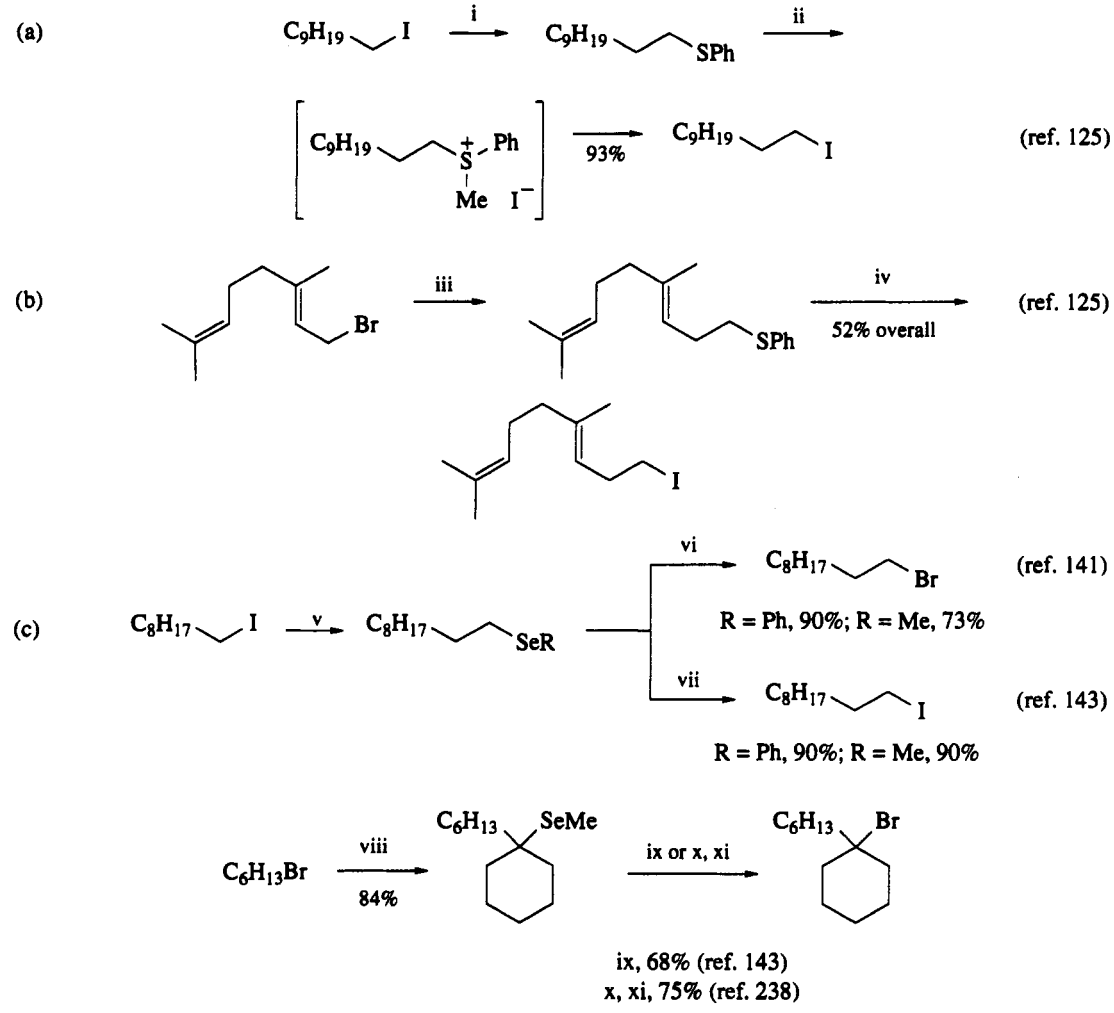
i, MCPBA, CH_2Cl_2, 20 °C; ii, Et_2NH, MeOH, 20 °C; iii, MnO_2

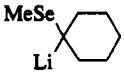
Scheme 51



i, 

Scheme 52



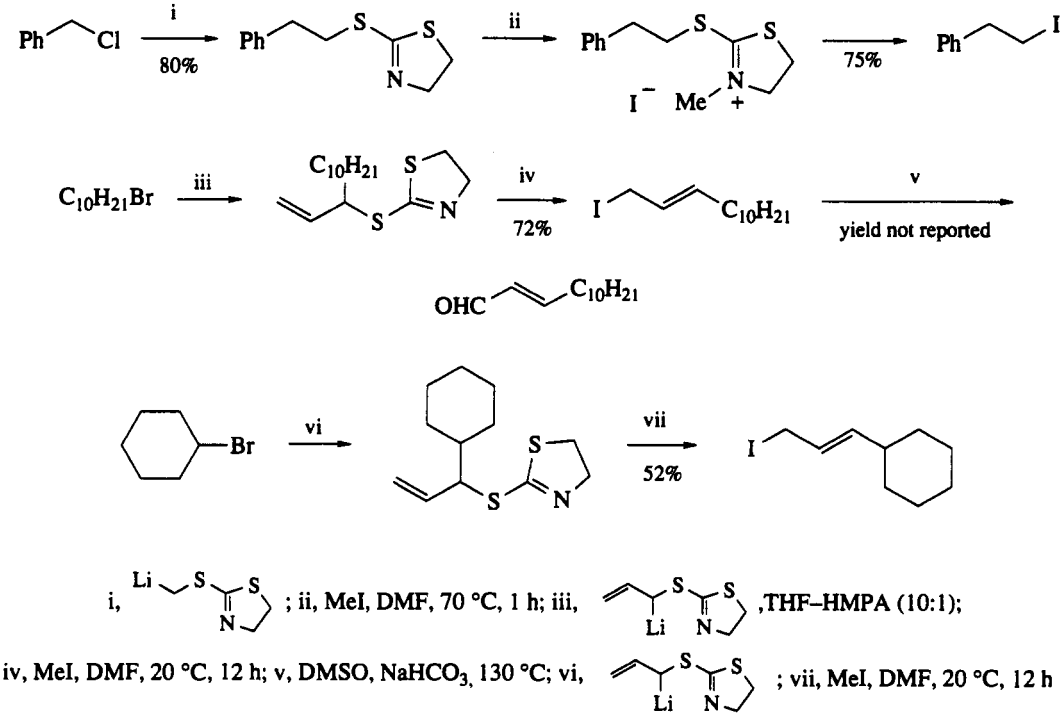
i, $PhSCH_2Li$, THF, –70 °C, 3 h, then 20 °C; ii, MeI, NaI, DMF, 75 °C, 18 h; iii, $PhSCH_2Li$, CuI, –50 °C, 2 h, then 20 °C; iv, MeI, NaI, DMF, 75 °C, 18 h; v, $RSeCH_2Li$, THF, HMPA; vi, $BrCH_2CO_2Et$, NaBr, DMF, 80 °C; vii, MeI, NaI, $CaCO_3$, DMF, 80 °C, 5 h; viii,  , THF, –78 to 20 °C; ix, Br_2, Et_3N, CH_2Cl_2, 20 °C, 3 h; x, O_3; xi, HBr, Et_3N, CH_2Cl_2, 20 °C

Scheme 53

1.3.3.1.1 Synthetic uses of 1-metallo-1,1-di(alkylthio)alkanes and -di(phenylthio)alkanes

1,1-Di(ethylthio)alkanes have been alkylated by sequential reaction with metalloamides in liquid ammonia[245,246] or in HMPA[247] followed by addition of alkyl halides. The reaction, which is usually conducted with 2 equiv. of the base is more efficient when carried out with sodium rather than lithium amides[246] and, although it works well with all primary alkyl halides, only the parent compound and the one bearing an aryl substituent on the carbanionic center are alkylated with *s*-alkyl halides (Scheme 55, entry a).

Di(phenylthio)methyllithium[59,126] and di(phenylthio)benzyllithium,[248,249] which are synthesized from the corresponding carbon acids and *n*-butyllithium in THF, have been monoalkylated with primary but not with secondary alkyl halides. Higher homologs have not found widespread use because of the difficulties encountered in their alkylation.[59,126,250–252] The successful alkylation of such compounds has been achieved[252] by carrying out the reactions in TMEDA (1 equiv.) in hydrocarbons (Scheme 55, entry c). Even the presence of THF with TMEDA almost completely suppresses the alkylation. However, double



Scheme 54

alkylation of di(phenylthio)methane is possible[250] in the presence of 2 equiv. of alkyl halides and an excess (4 equiv.) of sodium amide in THF. Interestingly the dianion derived from the conjugate addition of lithio tri(phenylthio)orthoformate on cyclohexenone followed by S/Li exchange involving *s*-butyllithium, has been methylated selectively at the carbanionic site (Scheme 56, entry a).[253]

A further interesting example is the use of 1,1-di(phenylthio)methyllithium to open an epoxide[254] followed by a Grob fragmentation process as shown in Scheme 56 (entry b). The reaction of 1,1-di(thio)methyllithium with epoxides has also been used[255,256] in the one-pot synthesis of 1,1-di(thio)cyclopropanes involving an intramolecular cyclization of the γ-tosyloxydi(phenylthio)alkyllithium. This intramolecular alkylation reaction proceeds even more efficiently than its intermolecular version, and allows the synthesis of a large variety of 1,1-di(thio)cyclopropanes from 3-chloro-[257] and 3-phenylthio-1,1-di(thio)alkanes[258] and *n*-butyllithium in THF (Scheme 57 and Scheme 58).

1,1-Di(methylthio)cyclopropanes have been converted[255,256] into ketones resulting from the fission of the C(2)—C(3) bond and elimination of dimethyl disulfide on reaction with aqueous trifluoroacetic acid (Scheme 58). Since the epoxides are usually synthesized by oxidation of an alkene, the sequence alkene → cyclopropanone → thioacetal → ketone allows the insertion of a carbonyl group in between the sp^2 carbons of the alkene (Scheme 58).[255] Furthermore, reaction of di(phenylthio)cyclopropanes sequentially with lithium dimethylaminonaphthalene, carbonyl compounds and acid allows the synthesis of cyclobutanones by ring expansion of the intermediary 1-(1-hydroxyalkyl)-1-phenylthiocyclopropanes.[17,25,61,128]

Related reactions involve the alkylation, allylation or benzylation of: (i) α,α-di(thio)alkylmagnesium halides, resulting from the thiophilic addition of Grignard reagents on dithioesters (Scheme 55, entry b);[259,260] (ii) 2-lithio-1,3-benzodithioles (Scheme 55, entry d);[261] (iii) 2-aryl-2-lithio-1,3-dithiolanes[262] and 2-lithio-1,3-dithianes derived from the 1,2-dimethyl-4,5-di(mercapto)methylbenzene (Scheme 55, entry e).[263,264]

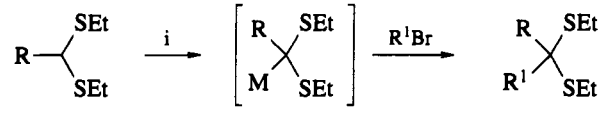
1.3.3.1.2 Synthetic uses of 2-metallo-1,3-dithianes and related derivatives

2-Lithio-1,3-dithianes, (the Corey–Seebach reagent) have proved by far the most widely used organometallic reagents of this series (Scheme 59).[27–29,265] This is due to: (i) the easy preparation of 1,3-dithianes from aldehydes and 1,3-propanedithiol; (ii) their metallation reaction which proceeds efficiently with Bu^nLi in THF, irrespective of whether the parent formyl derivative, higher homologs or 1-aryl-substituted derivatives are involved;[267–271] (iii) the high nucleophilicity of all these species towards various electrophiles,[27,28] including alkyl,[265,266,270,272–284] allyl,[266,268,269,285–289] and benzyl halides,[266] and arene-

sulfonates derived from primary alcohols[290] as well as with terminal,[255,266,279,289,291–300] α,β-disubstituted,[255,299,301] and α,β-unsaturated epoxides[255] and with oxiranes;[266] and (iv) selective removal of the dithianyl moiety which produces[27–29] a carbonyl group on reaction with metal ion, alkylative or oxidative hydrolysis[302,303] such as $HgCl_2$ alone[291] or with $CaCO_3$,[280,292] HgO,[268,272,275,283–285,304] HgO–BF_3OEt_2,[279,286,300,305,306] HgO–aq. HBF_4,[307] $CdCO_3$,[281,301] NClS,[275] NBS[275] alone or with $AgNO_3$;[275] with $CuCl_2$ and CuO,[308] an aroyl peroxide,[304] thallium(I) trinitrate[309] or bis(trifluoroacetoxy)iodobenzene.[302]

This reaction has been used for the synthesis of a large variety of aldehydes and ketones[20,27,28,278] including: (i) deuterio aldehydes;[313] (ii) optically active aldehydes and ketones;[283,284] (iii) alicyclic (Scheme 60, entry d)[282] and cyclic diketones (Scheme 60, entry c),[274,278,281] including those derived from metacyclophanes,[267,271] 1,9-dienes and macrocyclic acetylacetone ligands for metal cations;[281] (iv) silyl and germyl ketones;[314] and (v) the synthesis of many natural products or their model compounds, notably

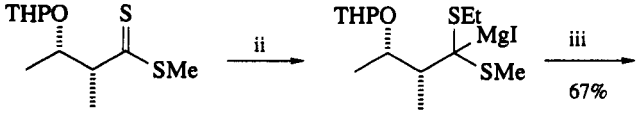
(a)

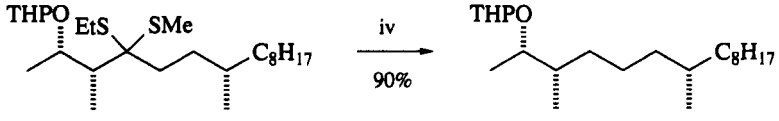


(ref. 246)

R	*R*^{1}	*M*	%	*R*	*R*^{1}	*M*	%
H	Et	Li	44	Me	Et	Na	44
H	Et	Na	87	Me	C_7H_{15}	Na	30
H	C_7H_{15}	Na	82	Me	Bu^s	Na	0
H	Bu^s	Li	18	Ph	Et	Na	87
H	Bu^s	Na	55	Ph	Bu^n	Na	85
				Ph	Bu^s	Na	84

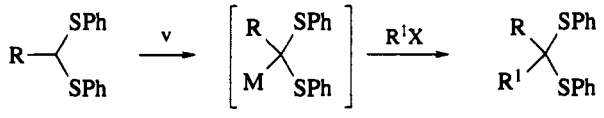
(b)



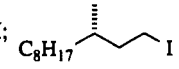


(ref. 259)

(c)

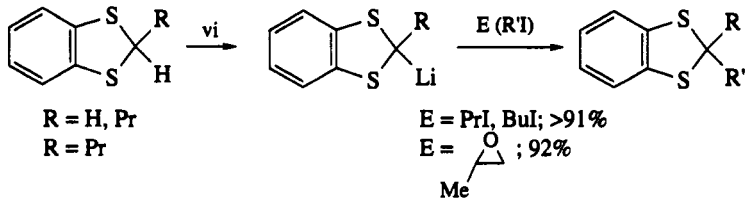


R	*Conditions* (v)	*R*^{1}*X*	%	*Ref.*
H	Bu^{n}Li, THF, 1 h	Bu^{n}Br	96	59, 126
		Bu^{s}Br	0	
H	4 $NaNH_2$, THF–HMPA	Bu^{n}Br (2 equiv.)	70	250
		(R = R^1 = Bu^n)		
C_5H_{11}	Bu^{n}Li, TMEDA, 0 °C	EtI	91	248
		PrI	89	
		$PhCh_2Br$	56	
Ph	Bu^{n}Li, TMEDA	EtI	87	248
		PrI	91	
		$PhCH_2Br$	44	

i, 2 MNH_2, liq. NH_3; 2 EtMgI;  , THF–HMPA; iv, Raney Ni

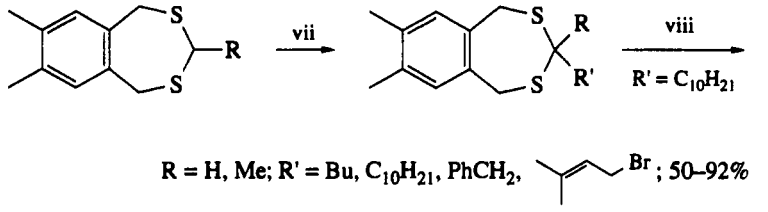
Scheme 55

(d)



(ref. 261)

(e)

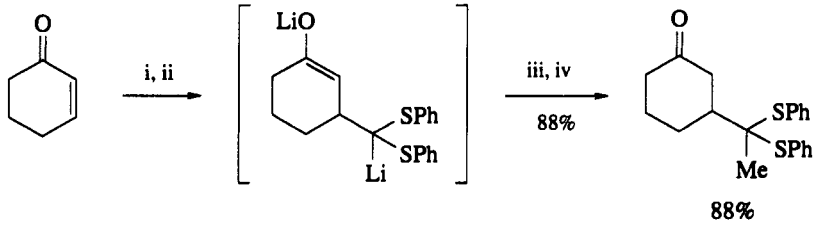


(ref. 263)

vi, Bu^nLi, THF, –30 °C; vii, Bu^nLi, R'Br; viii, $CuCl_2$, CuO

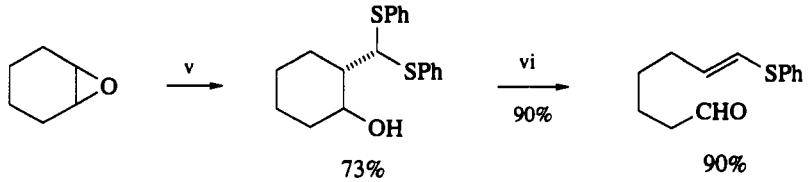
Scheme 55 *(continued)*

(a)



(ref. 253)

(b)



(ref. 254)

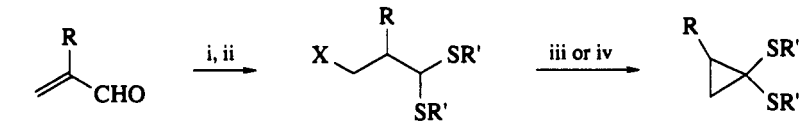
i, $(PhS)_3CLi$; ii, Bu^sLi; iii, MeI; iv, H_2O; v, $(PhS)_2CHLi$; vi, Bu^nLi, 4 CF_3CO_2Cu, 20 °C, 3 h

Scheme 56

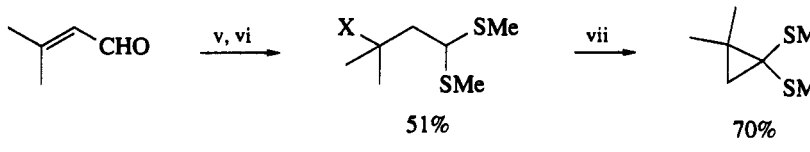
calcimycin,[280] norpyrenophorin, pyrenophorin and vermiculin antibiotics,[279] carbohydrates,[315–317] 2-methyllysergic acid,[311] terpenes and terpenoid derivatives[268,285,318] (including α-turmeron[268] (Scheme 61, entry a), *cis*-verbenol[318] and linaloyl oxide,[298]), alnusone,[20,319] rethrolones,[20,272] prostaglandins[276] and analogs,[301] debromoaplysiatoxin and aplysiatoxin (which are extracted from marine blue green algae),[294] (3*R*)- and (3*S*)-2,3-epoxysqualene,[20,304] 11α-hydroxyprogesterone,[320] modified steroids,[20,296] corticosteroids,[295] laurencin (a representative of naturally occurring halo compounds possessing a medium-sized cyclic ether skeleton as well as an enyne moiety),[306] and the northern part of maytansin.[291,292]

Reduction of the dithianyl moiety to a methylene group has been achieved[20] with Raney nickel,[267,293,305,310] or Na in NH_3 or in ether,[285,305,311] or with $LiAlH_4$ in the presence of $CuCl_2$ and $ZnCl_2$.[312]

The whole process, which involves the synthesis of the 1,3-dithiane and the reduction of the product resulting from its alkylation, has been used *inter alia* for the synthesis of metacyclophanes (Scheme 60,



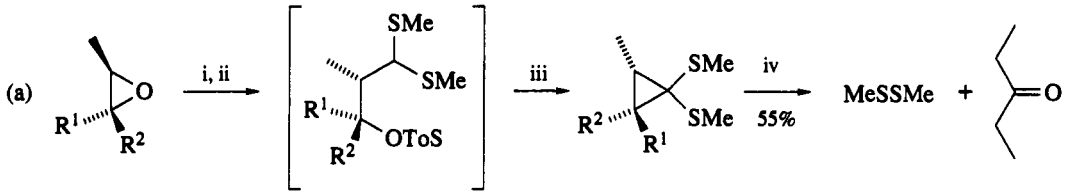
X	*R*	%	*Conditions*	%	*Ref.*
Cl	H	90	iii	71	257
Cl	Me	68	iii	68	257
PhS	H	98	iv	99	258
PhS	Me	–	iv	100	258



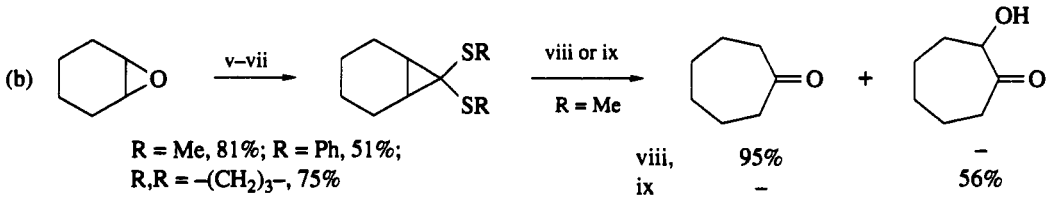
51% 70% (ref. 257)

i, HX; ii, EtSH; iii, Bu^{n}Li, THF; iv, MeLi, THF–TMEDA; v, HCl; vi, PhSH; vii, Bu^{n}Li, THF

Scheme 57



R^1 = Me, R^2 = H, 66%; R^1 = H, R^2 = Me, 67%



R = Me, 81%; R = Ph, 51%; R,R = –$(CH_2)_3$–, 75%

viii, 95%; ix, –; R = Me

56%

i, $(MeS)_2CHLi$, –78 °C, then 0 °C, 15 h ; ii, TosCl; iii, Bu^{n}Li, THF, –50 °C then 0 °C, 15 h; iv, CF_3CO_2H, H_2O, reflux, 30 h; v, $(RS)_2CHLi$, THF, –78 °C, then 0 °C, 15 h; vi, TosCl; vii, Bu^{n}Li, –50 to 0 °C; viii, CF_3CO_2H, H_2O, reflux, 7 h; ix, HCO_2H, H_2O, 100 °C, 20 h

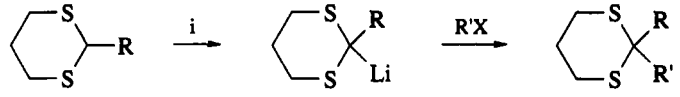
Scheme 58

entries a and b),[267,270,271] the cannabinoid side chain[305] and terpenes such as α- and β-curcumin (Scheme 61, entry b)[268] and (20*S*)-hydroxycholesterol (Scheme 62).[293]

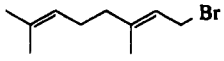
The key step in all these transformations is without doubt the reaction of 1-lithio-1,3-dithianes with organic halides and epoxides.[27–29] The alkylation usually proceeds extremely rapidly with primary alkyl iodides[265] (–78 °C, 0.2 h) and with allylic[265,286] and benzylic halides[265,267,271] (Scheme 59, entry a) but is much slower with secondary alkyl iodides and bromides. The reaction is best carried out at low temperature in order to obtain good yields by lowering the competitive elimination reaction; it has been found to proceed with inversion of the configuration at the asymmetric carbon when optically active alkyl halides are used.[283]

Tertiary and cyclic alkyl halides (cyclohexyl iodide), secondary alkyl chlorides and primary and secondary tosylates cannot be used in these intermolecular alkylations.[266] This is also the case with dibromoethane[28,274] and 2-bromo-2-nitropropane,[321] which both lead instead to α,β-dithianylalkanes resulting from the oxidative coupling of the carbanion.

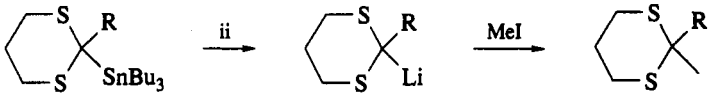
(a)



(ref. 265)

R	*R'X*	%	*R*	*R'X*	%
H	$BrCH_2CH_2CH(OEt)_2$	77	Bu^t	Pr^iI	45
Me	$ClCH_2CONEt_2$	50	C_5H_{11}		90
Me	Pr^iI	90			
Me	$PhCH_2Br$	84	Ph	Pr^iBr	77

(b)



(ref. 322)

i, Bu^nLi, THF, –78 °C; ii, Bu^nLi, THF, –78 °C, 0.2 h

Scheme 59

Dialkylation of bis-dithianes has proved to be an efficient route to diketones.[266,270,271,282] This might be carried out by successive monoalkylations, each requiring the metallation of the intermediate bisdithiane) followed by treatment with the alkylating agent (Scheme 63, entry a) or in an operationally simpler alternative by adding 2 equiv. of the base (Bu^nLi) followed by 2 equiv. of the alkylating agent (Scheme 63, entry b). The success of the latter approach depends either on the possibility of generating the dianion directly or more likely on the ability of the excess alkylating agent to survive attack by the second equivalent of base while the first alkylation step on the monoanion is in progress.

Stepwise alkylations have been carried out successfully with primary alkyl halides,[282] isopropyl iodide,[282] 1-chloro-3-iodopropane[278] and benzyl bromide[282] (Scheme 63, entry b). Other secondary halides and *t*-butyl halides fail to react.[282]

The proof given in support of dianion formation does not however seem to be sufficient.[282] Nevertheless the single step process is reasonably efficient when primary alkyl halides are used but none of the dialkylated compound is produced with isopropyl iodide and benzyl bromide. 2-(ω-Haloalkyl)-1,3-dithianes have proved to be valuable precursors of 1,3-dithianes derived from cyclic ketones.[278] Halogenated 1,3-dithianes have been in turn prepared from 2-lithio-1,3-dithiane and stoichiometric amounts of ω-chloro- or bromo-alkyl iodides or with an excess of the corresponding dichloride[278] (Scheme 64, entry c). Use of ω-bromoalkyldithianes is often impractical because of the ease with which these compounds are transformed into cyclic sulfonium salts.[278]

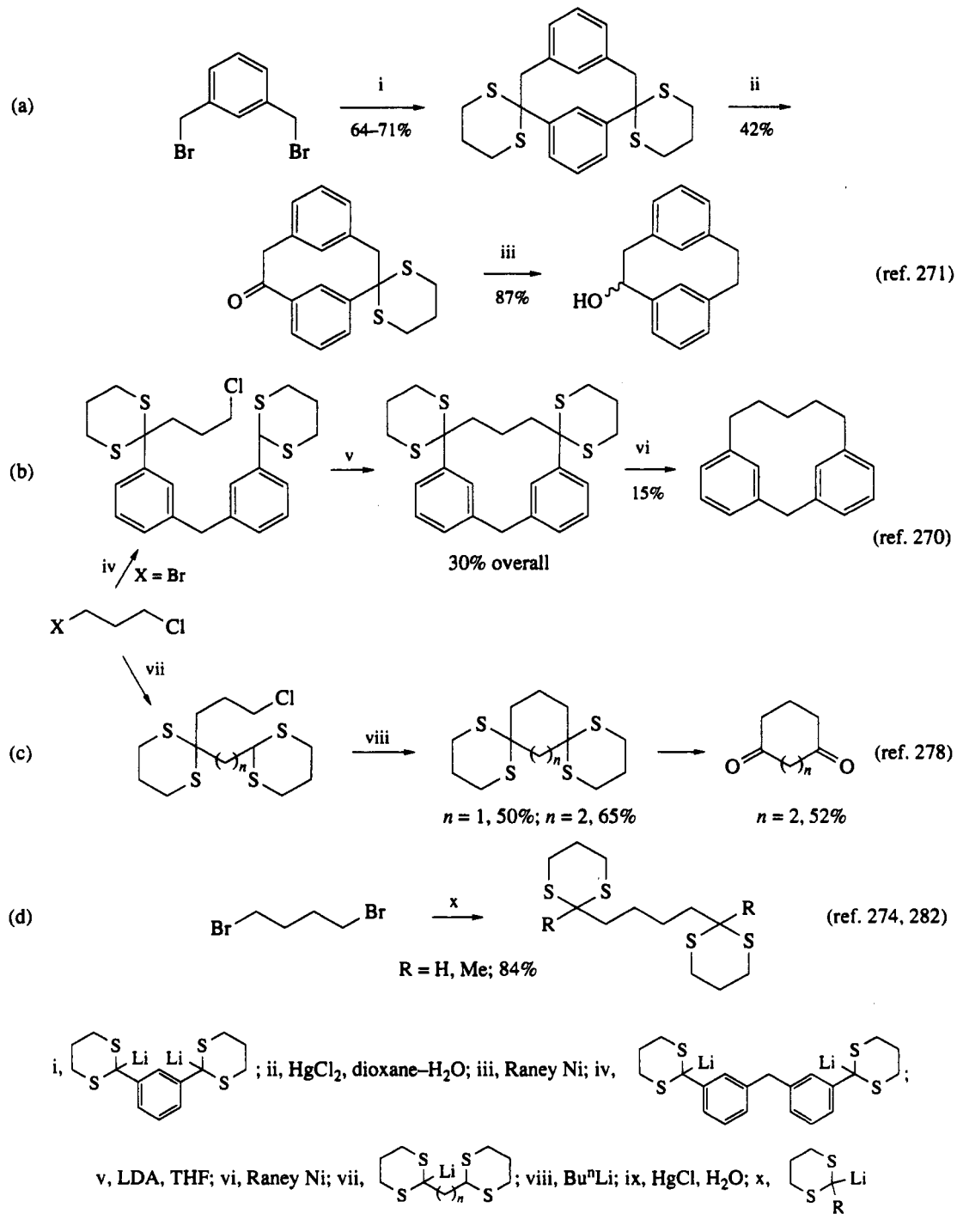
Another, but longer, synthesis of such ω-haloalkyldithianes has been achieved by reaction of 1-lithio-1,3-dithianes with epoxides (see below)[255,256,278,322] followed by tosylation of the corresponding alkoxides and displacement of the tosylate with chloride ion (LiCl, DMF, 30 °C, 6 d; Scheme 64, entries a and b; Scheme 58, entry b).[278]

Furthermore specifically 2-deuterated-4,6-dimethyl-1,3-dithiane[273,287,323] and 2-phenyl-4,6-dimethyl-1,3-dithiane[287,288] produce, on sequential reaction with *n*-butyllithium in THF or in THF—HMPA and with methyl iodide, the corresponding 2-*cis*-4,6-trimethyldithianes in which the 2-methyl group lies in the equatorial position (Scheme 65).

The results displayed in Scheme 65 (entry a) show that, although equatorial abstraction of hydrogen is favored kinetically,[287] the ratio of equatorial to axial proton abstraction is considerably less than the ratio of equatorial to axial methylation. Most probably the lithium derivative rapidly reorients itself in such a way as to have the lithium held in the equatorial position by the cooperative effect of the two sulfur atoms.[287,288,323]

Epoxide[255,266,278,300] and oxirane[266] ring opening by 2-lithio-1,3-dithianes requires the use of low temperatures (–20 to 0 °C), since these organometallics are not sufficiently stable in THF at higher temperatures. Under these conditions the reaction is often slow (1 or 2 h) and requires in some cases 1 or even 2 days to go to completion (Scheme 58, entry b; Scheme 62; Scheme 66; Scheme 67).[293,296,297]

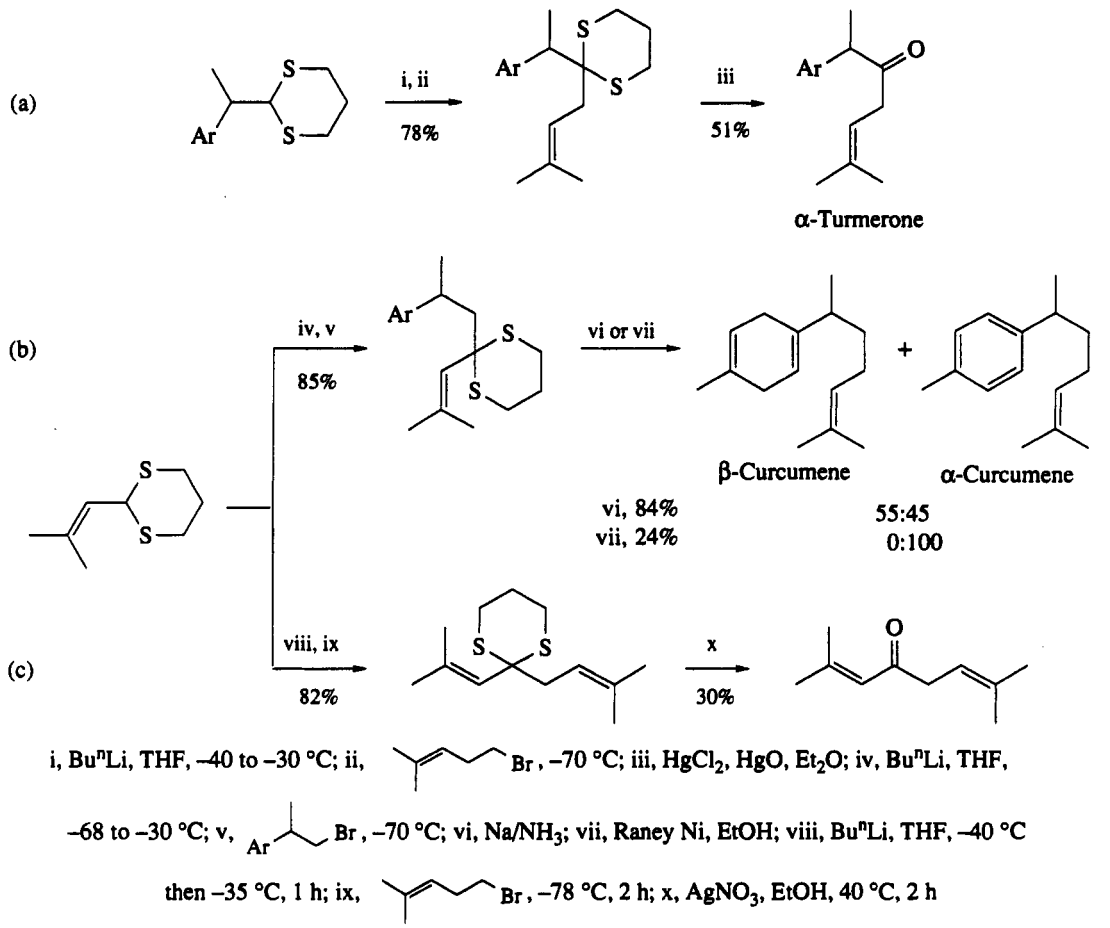
The reaction usually occurs at the less substituted carbon of the oxirane ring (Scheme 62 and Scheme 67).[293,297] However regioisomeric dithianyl alcohols are obtained[301] from 2-lithio-1,3-dithianes and the protected β,γ-epoxy alcohols shown in Scheme 66 (entry b). The observed regioselectivity is very different when methoxymethyl or benzyl protecting groups are used. This has been explained by the different



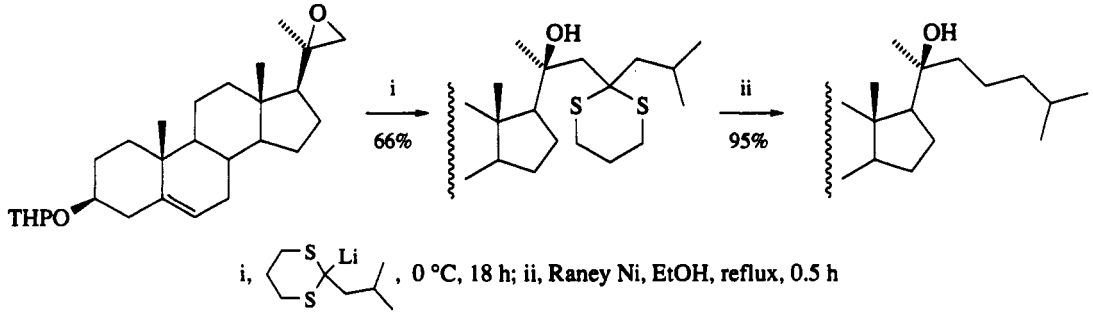
Scheme 60

capacities of these two protecting moieties to form initial coordination complexes with the lithiodithiane reagent.[301]

The reaction of 2-lithio-1,3-dithianes with epoxides has been used in a large number of valuable synthetic transformations including the synthesis of: (i) the corresponding thioacetals of cyclopropanones and of carbonyl compounds resulting from their acid-catalyzed ring opening (Scheme 58, entry b);[255] (ii) γ-hydroxy[297,301] or acetoxy[300] aldehydes resulting from the selective hydrolysis of the related thioacetals (Scheme 66); and (iii) α,β-unsaturated aldehydes, including functionalized ones as shown in Scheme 66.[300]



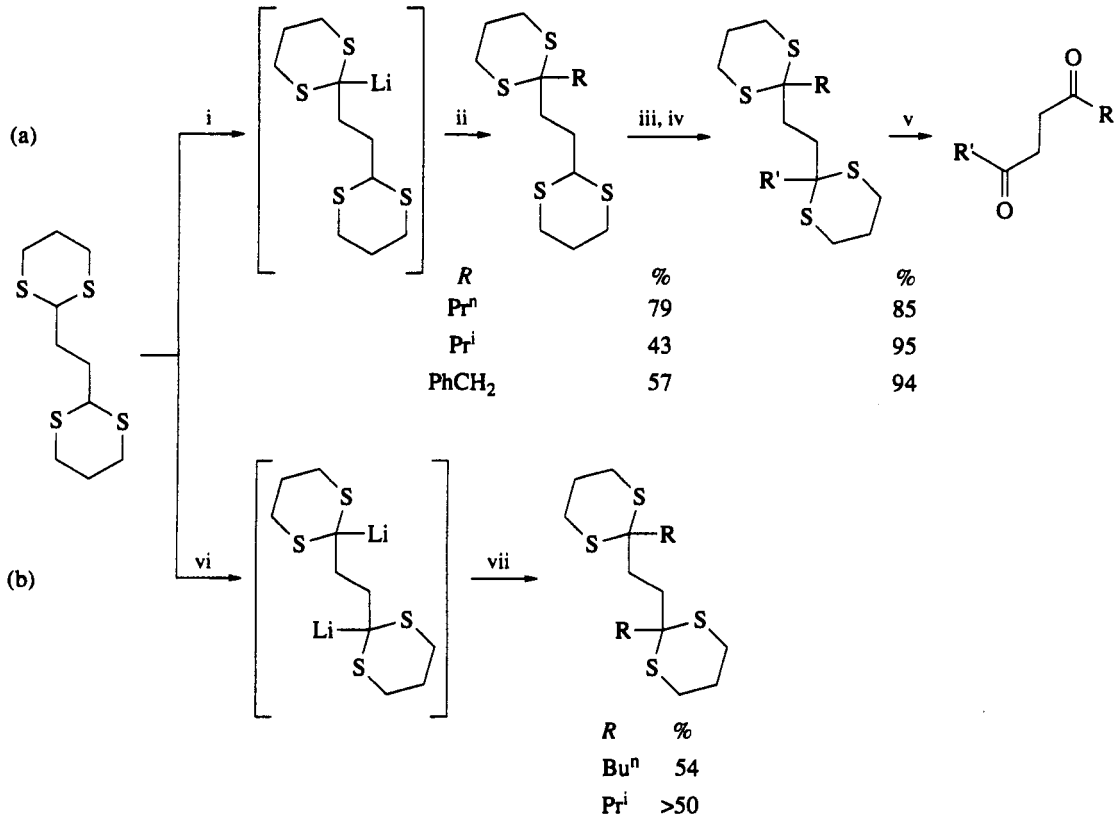
Scheme 61



Scheme 62

It has also been shown[322] that the Sn/Li exchange at the 2-position of 2-stannyldithiane takes place within minutes at –78 °C, whereas H/Li metallation does not occur at all at this temperature (Scheme 59, entry b). This reaction, when applied to 2-(ω-oxidoalkyl)-2-stannyl-1,3-dithiane, takes place within a few minutes and the intramolecular nucleophlic reaction, which immediately follows, is usually complete within 0.1 h at –78 °C. The total yield of cyclization products by the tin route has proved to be twice as high as that by direct metallation (Scheme 68).[322]

Finally, although 2-lithio-1,3-dithianes do not usually react with tetrahydrofurans, an intramolecular ring opening of such heterocycles has been once reported and has been applied to the synthesis of a dithiane derived from a functionalized cyclohexanone (Scheme 67).[297,298]



i, Bu^nLi, THF, –30 °C; ii, RX (X not cited); iii, Bu^nLi; iv, R'X; v, $HgCl_2$, HgO; vi, $2Bu^nLi$, THF, –78 °C; vii, 2 RX

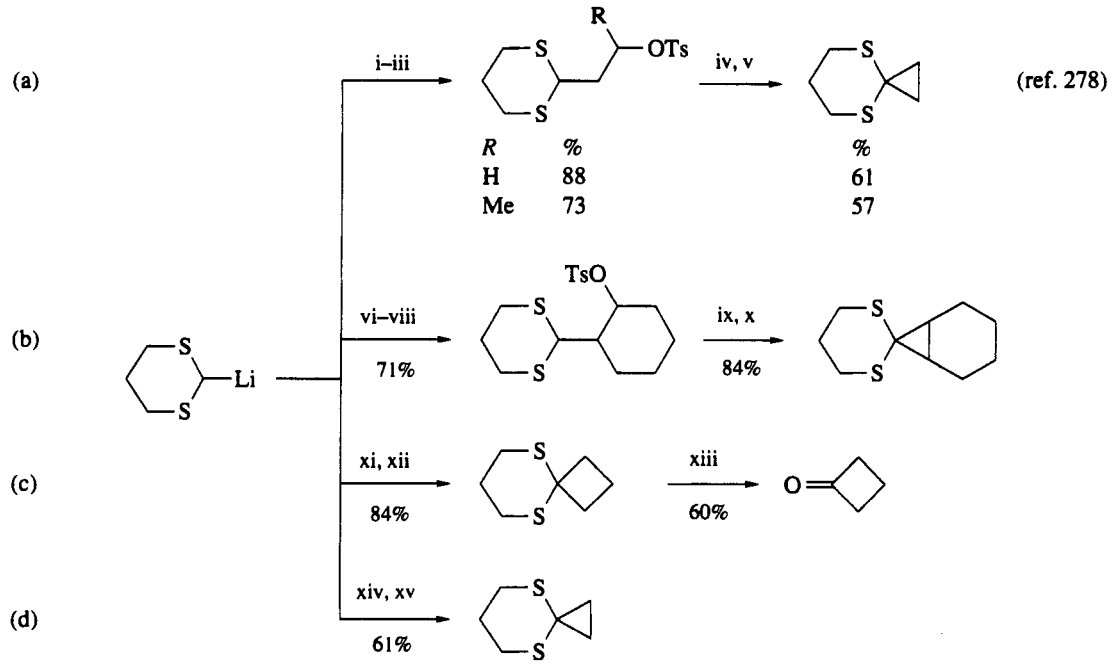
Scheme 63

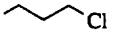
1.3.3.2 Alkylations of 1,1-(Dithio)allyl- and 1,1-(Dithio)propargyl-metals and their Synthetic Uses

1,1-(Dithio)allyllithiums, which are available on metallation of ketene thioacetals (Scheme 69, entry a; Scheme 70, entry c)[324–327] or 1,1-(dithio)alk-2-ene (Scheme 61, entries b and c)[268,328–330] and from the addition of alkyllithiums to unsaturated ketene thioacetals) a (Scheme 71, entry a),[331] possess a high propensity to be alkylated[324,326,331] or benzylated[324,326] at their α-site (Scheme 70, entries a–c; Scheme 71, entry a). The 1,3-dithianyl derivative bearing a phenyl group at the γ-position (the softer site) however exhibits a greater aptitude for reaction at this site (Scheme 70, entries d and e).[328,329] The α:γ ratio in this case increases by increasing the hardness of the electrophile at both the acid ($PhCH_2^+ < Me^+ < Et^+$) or the leaving group ($I^- , Br^- < Cl^- < {}^-OTs < {}^-SO_4Me$).[332] The latter effect was found to be greatest in the case of methylation (Scheme 70, entry d).[328,329]

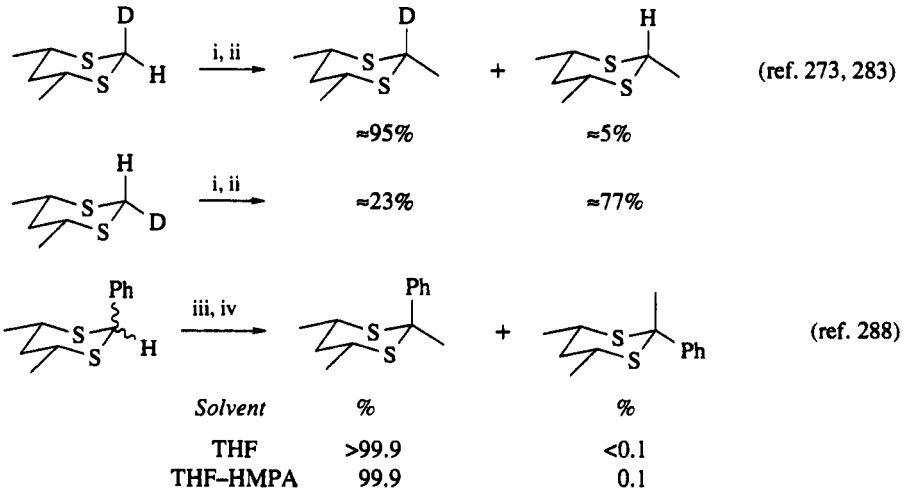
Allylation of all these species is apparently less selective (Scheme 69, entry a),[325] and among the various thioacetals tested 1,3-dithianes proved to be the ones which lead to the highest α:γ ratio.[325,326,327,330] The use of HMPA as a cosolvent was shown to have no effect on the regioselectivity of the allylation.[325] However, both exclusive γ-allylation and γ-methylation have been achieved by performing the reaction in the presence of copper(I) iodide–trimethyl phosphite complex (Scheme 69, entries a–e). The reaction is best achieved with allylic chlorides, bromides and phosphate esters and does not occur with acetates, although these compounds usually react with cuprates. In all cases where isomers could be formed with respect to the electrophile, the ratio of $S_N2':S_N2$ products was found to be greater than 0.67 (Scheme 69, entries b–e).[325] Related reactions have already been described with allylic sulfides (Scheme 27, see Section 1.3.2.2.4).[162,163]

On the one hand, thioacetals of α,β-unsaturated ketones resulting from the α-alkylation reaction reported above have been transformed efficiently into the corresponding unsaturated ketones on reaction with mercury(II) chloride and oxide in methanol (Scheme 71, entry a)[329,331] or on reaction[326,333] with methyl iodide or methyl fluorosulfonate followed by hydrolysis, with sulfonyl hydroxylamine.[324] On the



i,  ; ii, H_3O^+; iii, TsCl, pyridine; iv, LiCl, DMF; v, Bu^nLi, THF; vi,  ; vii, H_3O^+;
viii, TsCl, pyridine; ix, LiCl, DMF; x, Bu^nLi; xi,  ; xii, Bu^nLi, THF; xiii, $HgCl_2$, HgO, 80 °C, 3 h;
xiv,  , THF; xv, Bu^nLi, THF

Scheme 64

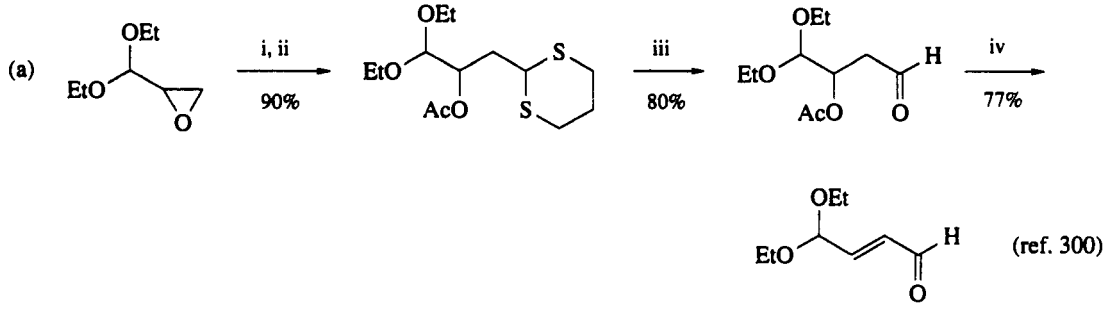


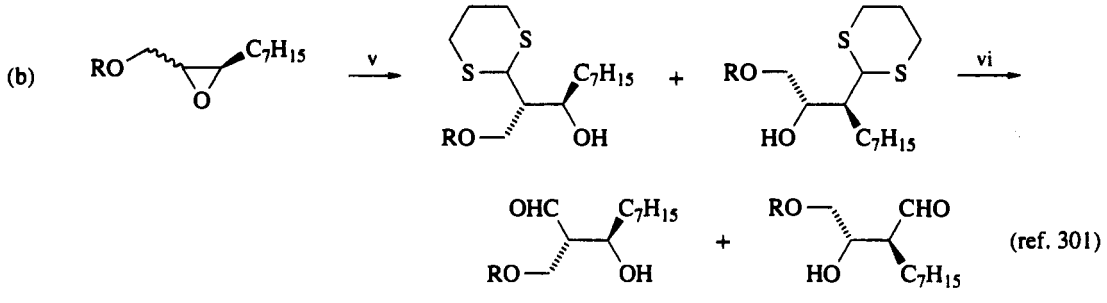
i, Bu^nLi, THF, –78 °C; ii, MeI; iii, Bu^nLi, solvent, –78 °C; iv, MeI

Scheme 65

other hand, ketene thioacetals resulting from a γ-alkylation reaction lead to carboxylic acids on reaction with mercuric chloride and oxide.[329] Thus the 2-metallo-2-vinyl-1,3-dithianes in the above mentioned transformations have played the role of α,β-unsaturated acyl anion or homoenolate equivalents respectively.

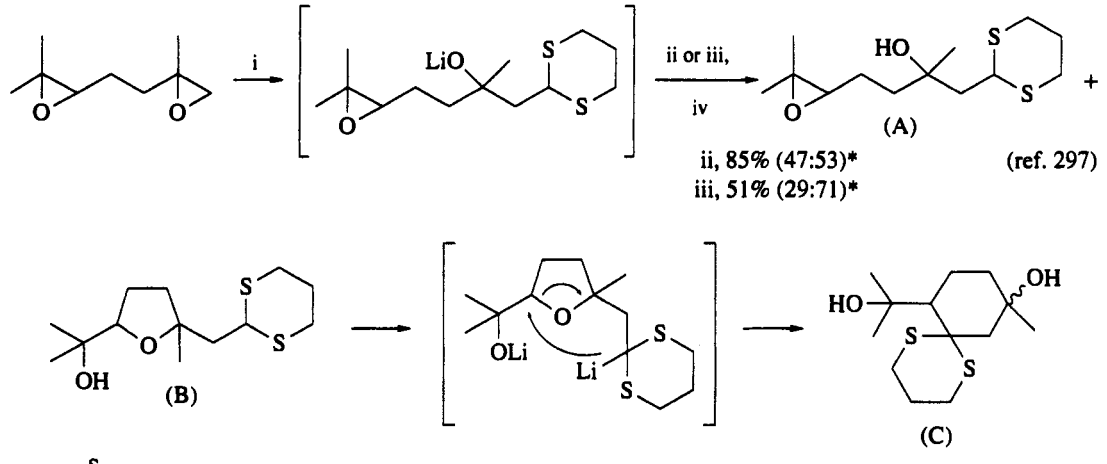
2-Ethynyl-1,3-dithiane when treated with 1.1 equiv. of *n*-butyllithium then with methyl iodide affords[334] only the γ-products as a 1:1 mixture of alkyne and allene, resulting from the direct methylation of the lithioalkyne and of the γ-methylation of 2-ethynyl-2-lithio-1,3-dithiane respectively (Scheme 72,





i, Li–(S,S)-dithiane, THF, –30 °C, 3 h; ii, Ac_2O, HgO–BF_3, THF, 0.3 h; iv, DBU, >30 °C, 0.3 h; v, Li–(S,S)-dithiane;
vi, $HgCl_2$, $CdCO_3$, reflux, 5 h

Scheme 66

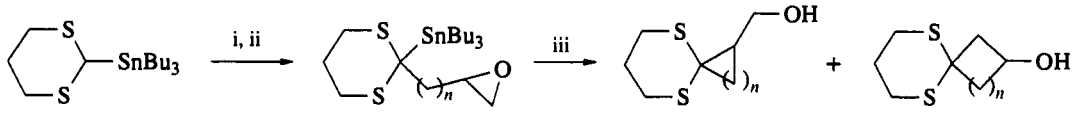


i, Li–(S,S)-dithiane; ii, 1.6 Bu^nLi + 1.25 BuLi–TMEDA, –20 °C, 3 d; iii, 2 Bu^nLi + 1.25 BuLi, 20 °C, 3 d; iv, H_3O^+

* Refers to A:(B + C) ratio

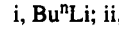
Scheme 67

entry a). Interestingly, the dilithio species produced on reaction with 2.5 equiv. of *n*-butyllithium (0.5 h at –70 °C) leads[334] exclusively to the ethynyl product by selective alkylation at the propargylic site, to the virtual exclusion of the allene (Scheme 72, entry b). 2-Lithio-2-(2′-silylethynyl)-1,3-dithiane has proved to be a valuable reagent which can be methylated[334] or allylated[335] exclusively at its 2-position (Scheme 72, entries c and d). The resulting products have been transformed into the corresponding functionalized ketones on successive treatment with thallium(III) nitrate trihydrate and hydrochloric acid (Scheme 72, entries c and d).[335]

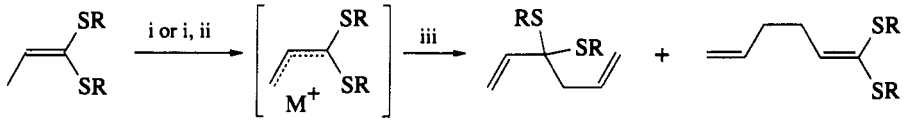


(ref. 322)

X = Cl; n = 1; 84% overall (100:0)
X = Br; n = 3; 63% overall (59:41)

i, Bu^nLi; ii,  ; iii, Bu^nLi

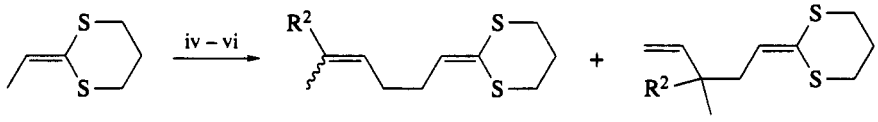
Scheme 68



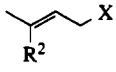
Conditions

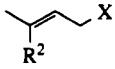
(a) i R,R = $-(CH_2)_3-$, 71% (88:12); R = Me, 82% (74:26); R = Pr^i, 89% (43:57)

(b) i, ii R,R = $-(CH_2)_3-$, 68% (0:100)



(c) R^1X =  ; R^2 = H; X = Br, 91% (46:54); X = $OPO(OEt)_2$, 96% (52:48)

(d) R^1X =  ; R^2 = H; X = Br, 91% (21:79); X = $OPO(OEt)_2$, 91% (5:95)

(e) R^1X =  ; R^2 = Me; X = Br, 84% (33:67); X = $OPO(OEt)_2$, 60% (15:85)

i, LDA, –25 °C; ii, CuI, $(MeO)_3P$, –78 °C; iii,  , –78 to 25 °C; iv, LDA, –25°C;

v, CuI, $(MeO)_3P$; vi, R^1X

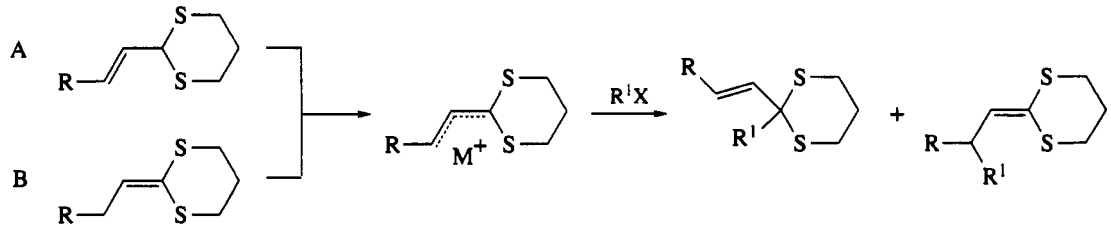
Scheme 69

1.3.3.3 Alkylations of Acyl Anion Equivalents Containing at Least One Sulfur or Selenium on their Carbanionic Center

1.3.3.3.1 Alkylations of sulfur-containing acyl anion equivalents

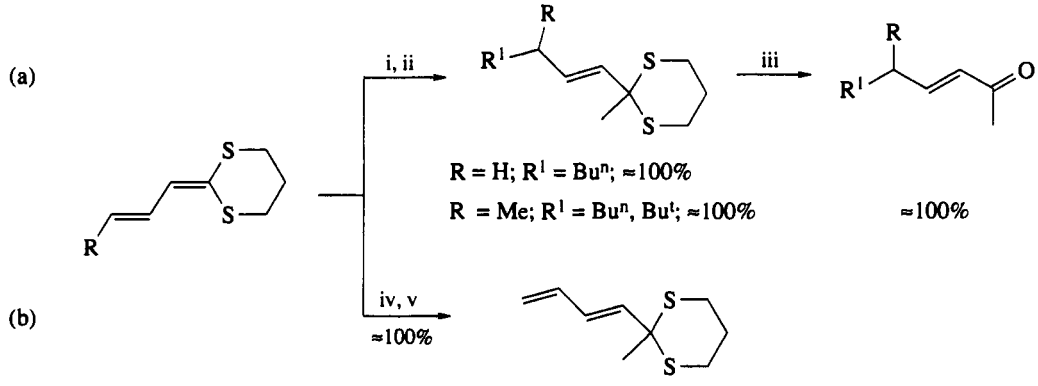
Although 2-lithio-1,3-dithianes are easily synthesized and have proved to be valuable nucleophiles towards, *inter alia*, alkyl halides, their use has been limited by the not infrequent difficulty of generating the carbonyl function.[302] Thus several functionalized α-thioalkylmetals have been proposed as their alternative.

The methylations of 1,3-dilithio-5,7-dimethyl-2,4,6,8-adamantane[336] and of 1,3,5,7-tetrathiacyclooctane tetraanion[337] are of theoretical value only. 1,3,5-Trithiane and both mono- and 2,4,6-trialkyl-substituted derivatives have been metallated[28,338,339] with *n*-butyllithium and alkylated[338,339] with reactive alkylating agents such as primary alkyl iodides or bromides and benzyl bromide (Scheme 73, entries a and b). The metallation of monoalkylated trithianes occurs at one of the two unsubstituted sites and leads eventually to the product having both substituents in the equatorial position.[273,323] Thus the high equatorial preference for lithium in 2-lithio-1,3-dithiane is also present in 2-lithio-2-methyl-1,3,5-trithiane. Mer-



Entry	*A or B*	*R*	*Conditions*	*R¹X*	*Yield (%)*	*Product ratio*	*Ref.*
(a)	B	Pr	LDA, THF–HMPA	MeI	88	100:0	326
(b)	B	Pr	Bu^nLi, THF–HMPA	MeI	90	100:0	324
(c)	A	H	Bu^nLi, THF	MeI	50	100:0	324
(d)	A	Ph	Bu^nLi, THF	MeI	60	56:44	328, 329
				MeOTs	80	82:18	
				Me_2SO_4	55	100:0	
(e)	A	Ph	Bu^nLi, THF	$PhCH_2Cl$	66	22:78	328, 329
				$PhCH_2Br$	75	14:86	
				$PhCH_2I$	60	10:90	

Scheme 70

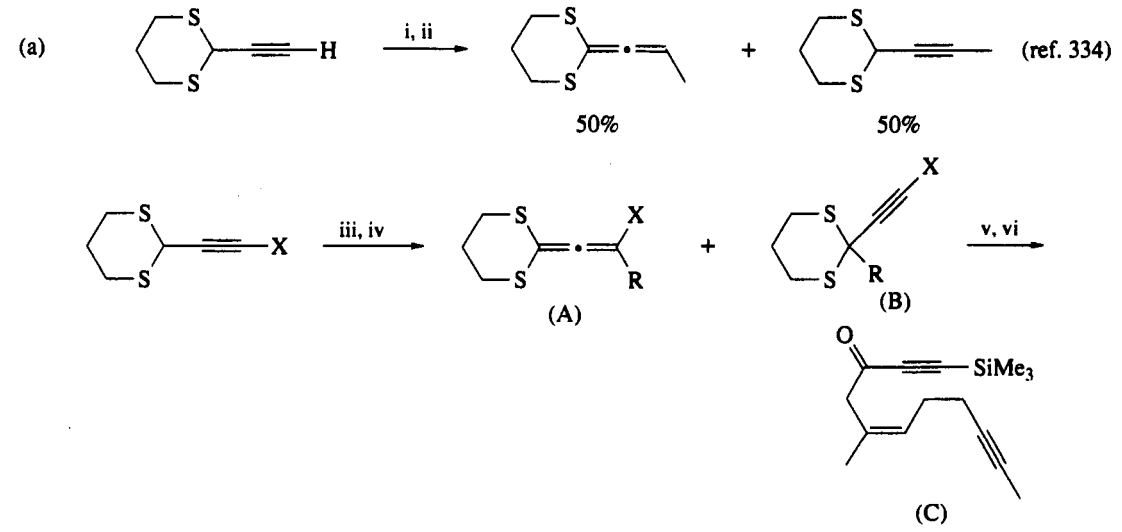


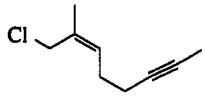
i, R^1Li, –80 to 20 °C; ii, MeI; iii, $HgCl_2$, HgO; iv, LDA; v, MeI

Scheme 71

cury(II)-assisted solvolysis of the alkyl trithianes then liberates the most highly substituted carbonyl compounds (Scheme 73, entry b).[338,339] Thus 1,3,5-trithiane after monoalkylation leads finally to aldehydes, whereas alkylation of lithio-2,4,6-trialkyl-substituted analogs would lead to the corresponding alkyl ketones (Scheme 73, entry b).

Several other acyl anions or potential acyl anion equivalents bearing at least one nonoxidized sulfur atom have since been proposed, and some of them have been alkylated successfully. This is effectively the case for the following metallated compounds: (i) *N*-methylthioformaldine (Scheme 73, entry c);[340] (ii) 1,3-oxathianes,[341,342] and α-trimethylsilylmethyl analogs;[343] (iii) α-methoxythioanisole (Scheme 74, entry a; Scheme 75, entry c);[344–347] the parent compound also allows[345] the synthesis of acetals (on acid-catalyzed methanolysis), of vinyl ethers (on oxidation to the sulfoxide and heating at 120 °C) and carboxylic acids (CrO_3, H_2SO_4, Jones reagent; Scheme 75, entry b) and its α-vinyl-substituted derivatives (Scheme 76);[347,348] (iv) α-trimethylsilylmethylthioanisole (Scheme 77, entries a–c; Scheme 78, entries e and f),[252,349–354] and its α-aryl derivative (Scheme 77, entry c);[355] (v) methylthiomethyl methyl sulfoxide (Scheme 74, entry b; Scheme 79; Scheme 80, entries b and c),[356–364] its α-alkyl homologs (Scheme 79; Scheme 80, entries b and c)[356,359–362] and related diethyl (Scheme 74, entries c and d; Scheme 80, entry a)[358,365,366] or di-*t*-butyl[365] derivatives as well as 1,3-dithiane-1-oxide[367,368] and its 2-alkyl- and 2-phenyl-



	X	Base	RX	Yield of A + B (%)	A:B ratio	Yield of C (%)	Ref.
(b)	H	2.5 Bu^nLi	excess MeI	–	0:100		334
(c)	$SiMe_3$	1 Bu^nLi or LDA	MeI	>90	0:100		334
(d)	$SiMe_3$	1 Bu^nLi, –20 °C 4 h		84	0:100	86	335

i, 1.1 Bu^nLi; ii, MeI; iii, base; iv, RX; v, $Tl(NO_3)_3$, MeOH; vi, 5% HCl

Scheme 72

substituted homologs;[368] (vi) methylthiomethyl *N,N*-dimethyl dithiocarbamate (Scheme 74, entry e);[369] (vii) methylthiomethyl *p*-tolyl sulfone and homologs (Scheme 74, entries f–h; Scheme 80, entry d);[370,371] (viii) bis(*N,N*-dimethyldithiocarbamato)methane;[372] and (ix) 4,4-dimethyloxathiolane 3,3-dioxide.[373]

1.3.3.3.2 Alkylations of selenium-containing acyl anion equivalents

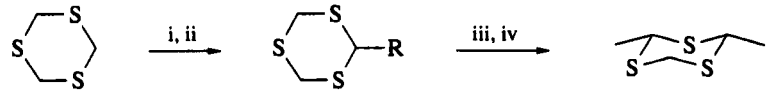
Related reactions involve 1-metallo-1,1-di(arylseleno)-[64,65,76,78,106,108,122] and 1-lithio-1,1-di(methylseleno)-alkanes (Scheme 81; Scheme 82),[76,78,122] 1-lithio-1-phenylseleno-1-phenyltelluromethane (Scheme 78, entry h)[374] as well as 1-trimethylsilyl-1-arylselenomethyllithiums (Scheme 78, entries a–f)[74,106,353,375] and their 1-aryl homolog[74,106] and 1-trimethylsilyl-1-methylselenoalkyllithiums (Scheme 78, entry g).[77] Intramolecular cyclizations of 3-halo-1,1-di(seleno)alkanes[78,122] and of 3-tosyloxy-1,1,1-tri(seleno)alkane[78] with LDA and *n*-butyllithium respectively lead to the corresponding 1,1-di(seleno)cyclopropanes (Scheme 82, entries b–g). These in turn have proved to be valuable precursors of 1-seleno-1-cyclopropyllithiums (Scheme 8, entry e; Section 1.3.2.1.1).

Interestingly, the synthesis of 1,1-di(phenylseleno)cyclopropane has been performed[78,122] from 3-chloro-1,1-di(phenylseleno)propane and Bu^tOK (Scheme 82, entry c) or, in a longer sequence, on reaction of 1-(3-chloropropyl)-1-phenylseleno-1-phenyl selenoxide[113] with LDA and further reduction of the resulting 1-phenylseleno-1-phenylselenoxycyclopropane (Scheme 82, entry a). Surprisingly the reaction of Bu^tOK with 3-chloro-1,1-di(methylseleno)propane takes another course and leads to 1,1-di(methylseleno)-1-propene rather than to 1,1-di(methylseleno)cyclopropane.[78]

Most of the organometallics reported above, with the exclusion of 1,1-di(methylseleno)- (Scheme 81, entry e)[76,78] and α-silyl-α-methylselenoalkyllithiums (Scheme 78, entry e)[77] have been prepared by metallation of the corresponding carbon acid. The Se/Li exchange method however proved to be the method of choice for the synthesis of almost all the α-selenoalkylmetals described in this section.[64,65,76,78,106,108,122]

As far as the further reaction of the above mentioned organometallics with electrophiles is concerned, most of these reagents work well with primary[341–344,347–352,356–360,362,363,365,366,368–373,375] and secondary[341–343,349,350,352,358,360,361] alkyl halides, benzyl bromides[341–344,348,350,352,357,369–373] and allylic bro-

(a)

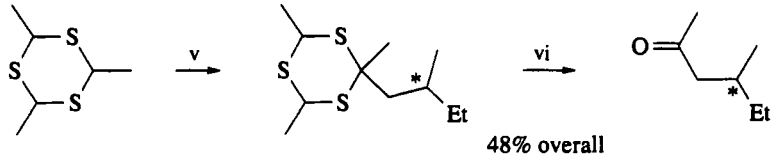


R	%
Me	92
$C_{14}H_{29}$	90
$PhCH_2$	90

R = Me, 32%

(ref. 338)

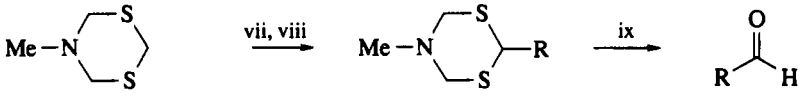
(b)



48% overall

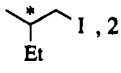
(ref. 338)

(c)



RX	%
$C_6H_{13}I$	100
$C_6H_{13}Br$	95
$C_6H_{13}Cl$	40
$C_6H_{13}Mes$	0
n-$C_{10}H_{21}I$	86 overall
$MeCHIC_8H_{17}$	80

(ref. 340)

i, Bu^nLi; ii, RX; iii, Bu^nLi, THF; iv, MeI; v, Bu^nLi, THF,  , 2 d, –30 °C;

vi, $HgCl_2$, HgO, Δ, 3 h; vii, Bu^nLi; viii, RX; ix, $HgCl_2$, HgO, 20 °C, 2 h

Scheme 73

mides[344,347,350,358,370,373] or chlorides.[347,360,361] Only a few have been reacted with epoxides[298,344,349,376] and even fewer with trialkyl-substituted halides (Scheme 77, entries f and g).[349]

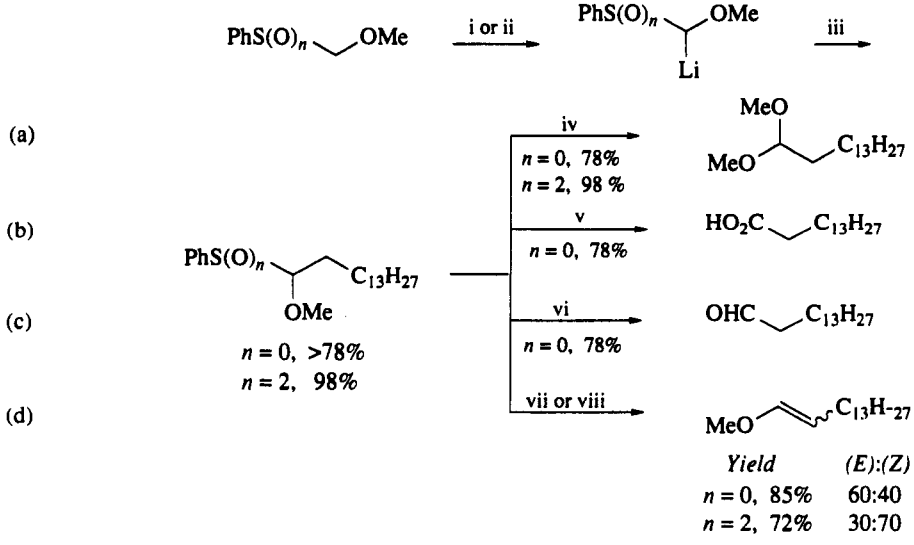
Some of the reactions reported above merit further comment. This is especially the case of methylthioformaldine (Scheme 73, entry c)[340] and trimethylsilylmethylthioanisole (Scheme 77)[349,355] which can be alkylated once, but not twice, because of the lack of basic reagents sufficiently reactive to metallate the monoalkylated compound. Alternative routes to trimethylsilyl(*s*-alkyl)thioanisoles however exist.[254,352] It must be pointed out that the synthesis of fully alkylated seleno analogs also cannot be achieved by metallation reaction,[77] but takes place by Se/Li exchange from 1-silyl-1,1-di(methylseleno)alkanes and butyllithium and further alkylation of the resulting organometallics (Scheme 78, entry e). Trimethylsilyl(phenylthio)methyllithium is a particularly nucleophilic reagent toward primary and secondary alkyl halides[349,352,353,355] and epoxides (Scheme 77; Scheme 78; entries c and d).[349] Its successful alkylation with trisubstituted epoxides[349] and cyclohexyl iodide[349] is exceptional (Scheme 77, entries d and e). Alkylation of α-heterosubstituted organometallics with cyclohexyl halides[350,352] is usually unsuccessful and poor yields result from reaction with *s*-alkyl halides.[353] Allyl halides,[350] but surprisingly not propargyl halides,[351] also react efficiently with this organometallic. Most of these reactions have been carried out in THF, even though it has been suggested that better results are obtained in TMEDA–hexane.[350]

2-Lithio-1,3-oxathiane[341,342] has proved to be much less reactive than phenylthiomethyllithium (Scheme 74, entry a).[344] Although the latter reacts well with alkyl or benzyl bromides and with alkyl iodides without distinction, 2-lithio-1,3-oxathiane works well only with alkyl iodides.[341]

Monoalkylation of the carbanion generated from methyl thiomethyl sulfoxide[357] and 1,3-dithiane 1-oxide[368,377] has been reported (Scheme 74, entry b) but reexamination of both reactions[358,359] proved unsatisfactory under conditions similar to those previously described or slightly modified. Neither the stepwise[359] nor the one-pot dialkylation[357] was successful at 20 °C, but the latter reaction was apparently achieved by Schill[359] by performing it at 50 °C with a slight excess (2.2 equiv.) of *n*-alkyl bromides in

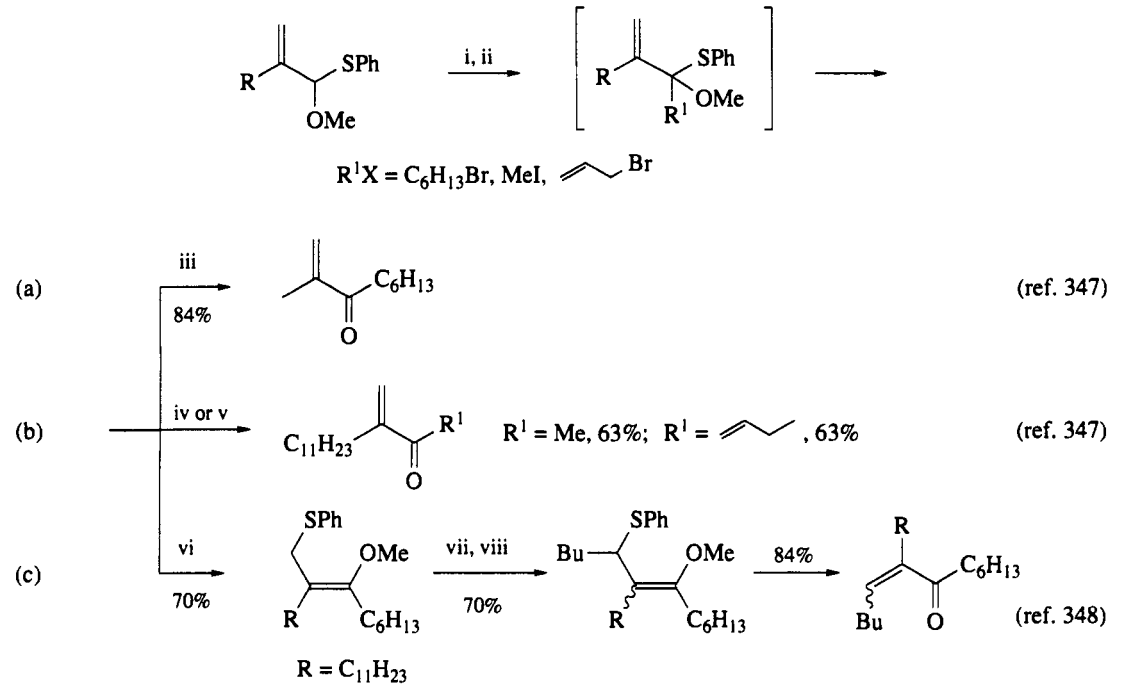
	R	*R*^{1}	*X*	*i*	*ii*	%	*iii*	%	*Ref.*
(a)	Ph	H	OMe	Bu^{t}Li, THF, –78 °C	MeI	94	–	–	344
					$C_6H_{13}I$	84			
					$PhCH_2Br$	88			
					$H_2C{=}CHCH_2Br$	76			
(b)	Me	H	S(O)Me	NaH, THF, 20 °C	MeI, 20 to 40 °C	92	HCl, H_2O	84	357
					BuI	72		91	
					$PhCH_2Br$	92		88	
(c)	Et	H, Et	S(O)Et	Bu^{n}Li or LDA, THF, 2 °C	EtI, 25 °C, 2 h	>95	$HgCl_2$, HCl,	>80	357
					Pr^{i}Br		THF, 0 °C, 1 h	>80	
					$H_2C{=}CHCH_2Br$			>80	
(d)	Me	H	$SC(S)NMe_2$	Bu^{n}Li, THF, –50 °C	$C_8H_{17}I$, –60 °C, 1 h, 20 °C		aq. HCl, 20 °C	66 overall	369
					$PhCH_2Br$			68 overall	
(e)	Me	H	SO_2Tol	50% aq. NaOH, toluene	$C_{12}H_{25}Br$, 20 °C, 4 h	84	Dioxane, H_2O, NaOH, *hν*	72	370
					$PhCH_2Br$, 50 °C, 3 h	88		–	371a
(f)	Me	H	SO_2Tol	2.5 equiv. NaH, DMF	2 $C_{12}H_{25}Br$, 20 °C, 48 h		H_2SO_4, MeOH, Δ, 3 h	90 overall	371a
					2 $PhCH_2Br$, Δ, 3 h			74 overall	371a

Scheme 74



i, Bu^{n}Li, THF, –78 °C (n = 0); ii, LDA, THF, –78 °C (n = 2); iii, RX; iv, cat. TosOH, MeOH, Δ, 2 h; v, CrO_3, H_2SO_4, 0 °C, 1 h, acetone; vi, MCPBA, –5 to 0 °C, toluene, then 40 °C; vii, MCPBA, toluene, 0 °C, then 120 °C (n = 0); viii, Bu^{t}OK, THF (n = 2)

Scheme 75



i, Bu^nLi, HMPA; ii, R^1X; iii, SiO_2–H_2O_2, 20 °C, 3 h; iv, $NaIO_4$, dioxane, 20 °C, 3 h; v, MCPBA, CH_2Cl_2, –30 °C, 1 h; vi, SiO_2, hexane; vii, Bu^nLi–TMEDA, THF, 0 °C, 0.5 h; viii, BuI

Scheme 76

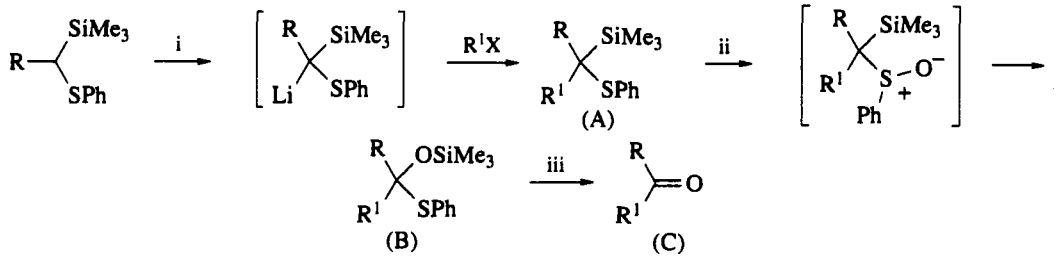
the presence of an excess of sodium hydride in THF. More recently, this reaction has been successfully used by Evans in a synthesis of the ionophore antibiotic A-23187 (Scheme 79, entry b).[363]

Slight variations of the structure of this acyl anion equivalent have led in fact to the discovery of particularly valuable alternative reagents. Among them, ethyl ethylthio sulfoxide can be both monoalkylated[358,365,366] or sequentially dialkylated[359] (Scheme 74, entries c and d). *t*-Butyl methylthio sulfoxide[359,365] and phenyl methylthio[378] analogs have also been monoalkylated but not dialkylated (Scheme 79, entry c; Scheme 80, entry a).

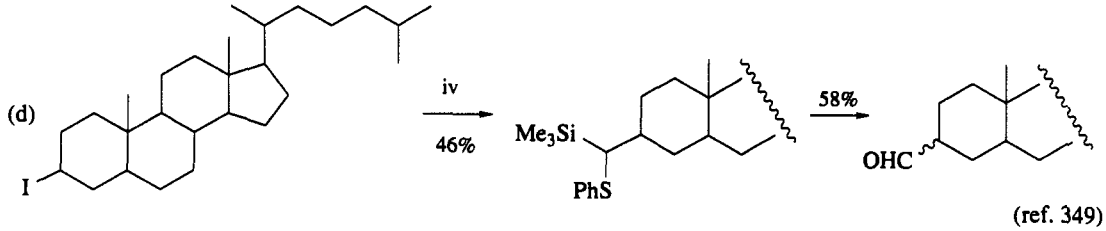
Reaction of methyl methylthio sulfoxide with 1,*n*-dihalo or 1,*n*-(tosyloxy)alkanes in the presence of 2 to 2.8 equiv. of Bu^nLi or KH as a base gave three- to six-membered not seven-membered 1-methylsulfinyl-1-methylthiocycloalkanes (Scheme 80, entries b and c). These cycloalkanes have been subsequently transformed to the corresponding ketones under mild conditions.[356,360–362,364] The tosyloxy route, which is often inefficient[340] with related organometallics has proved to be particularly attractive[360,364] for the construction of the cyclopropane ring which cannot be produced from 1,2-dibromoethane (Scheme 80, compare entries b and c). This cyclization reaction may involve[360,361] the formation of an intermediary sulfonium salt (see Scheme 80, entry b), which is metallated and then rearranges to the desired product, *via* a Stevens-type rearrangement. This process allows the high yielding synthesis of diversely substituted (even in the 2-position) cyclobutanones,[360] 3-cyclopentenone from (*Z*)-1,4-dichlorobut-2-ene (Scheme 83, entry a)[360] and of (*R*)- and (*S*)-4-hydroxycyclopentenones,[362] which are valuable precursors of prostaglandins (Scheme 83, entry c). Particularly impressive is the efficiency of the last mentioned synthesis, which uses tartaric acids and methyl methylthio sulfoxide as the two building blocks. An unusually facile cyclization employing a mesyloxycyclopentane, and leading finally to a bicyclo[3.3.0]octanone (Scheme 79 entry a), a valuable precursor of isocarbacyclin, has also been reported.[364]

As expected (*E*)-1,4-dichlorobut-2-ene reacts[360] differently from its (2*Z*)-isomer with methyl methylthiomethyl sulfoxide, and produces a vinylcyclopropane instead of the cyclopentene derivative (Scheme 83, entry b, compare to entry a).

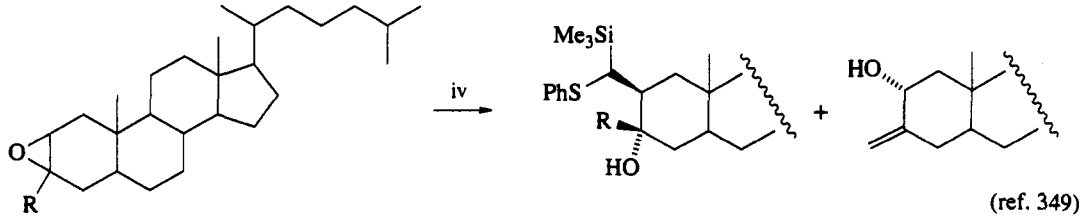
Methyl methylthiomethyl sulfone and methylthiomethyl *p*-tosyl sulfone have been monoalkylated, benzylated or alkylsilylated with 1.5 equiv. of the electrophile in the presence of aqueous sodium hydroxide and trioctylmethylammonium chloride (TOMAC).[370,371] Without doubt the organometallic is less reactive than the one derived from the corresponding sulfoxide since the reaction is rather slow with



Entry	*R*	*R'X*	*A* (%)	*B* (%)	*C* (%)	*Ref.*
(a)	H	MeI	99	80	–	352
	H	Bu^nBr	84	70	72	
	H	Bu^sBr	45	76	74	
(b)	H	$PhCH_2Br$	83	87	77	352
		$c\text{-}C_6H_{11}Br$	0	–	–	
(c)	H		90		62	349



(ref. 349)



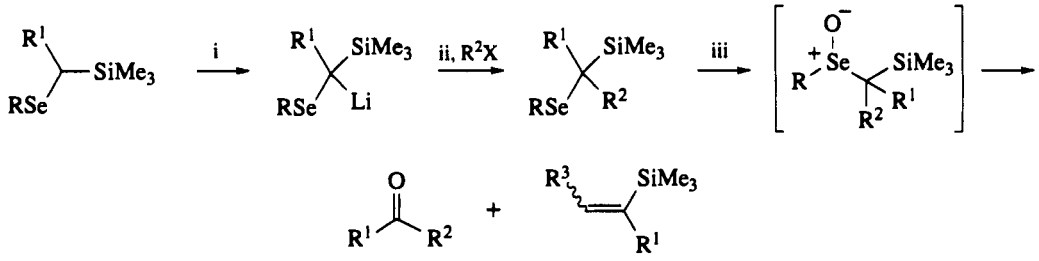
(ref. 349)

(e) R = Me 65% (40:60)
(f) R = H 91% (100:0)

i, Bu^nLi, TMEDA, 0 °C; ii, MCPBA, −15 °C; iii, H_2O; iv, $LiCH(SiMe_3)SPh$

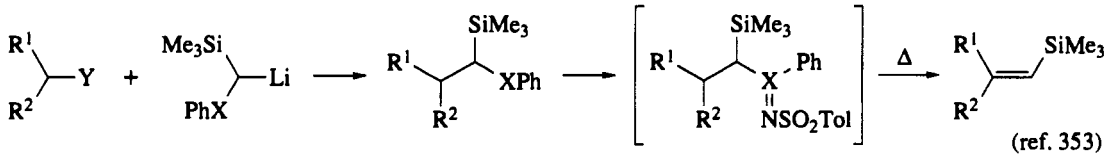
Scheme 77

allyl and benzyl halides (20 °C, 48 h) and requires heating to 60 °C to go to completion with primary alkyl bromides. The second alkylation, alkynylation and benzylation have been carried out[370] with NaH in DMF (1.3 equiv.) at 20 °C for long periods of time (19 to 48 h) or more rapidly with heating (3 h at 60 °C). Cyclo-butane, -pentane and -hexane[371] as well as cyclopentene derivatives[380] have been obtained from the corresponding dibromides. The synthesis of the cyclobutane derivative requires the use of an excess of NaH in DMF[371a] or Bu^nLi in THF.[371b] For the other cases, however, phase-transfer conditions can be used (Scheme 80, entry d). Unfortunately, as with methyl methylthio sulfoxide (Scheme 80, entry c), seven-membered rings cannot be synthesized[371b] (Scheme 80, entry d) by this method.



(a) R^1 = H; R = Ph; i, LDA, -30 °C, 0.5 h; ii, $C_{10}H_{21}Br$, 75%; iii, H_2O_2, THF (ref. 77, 375)

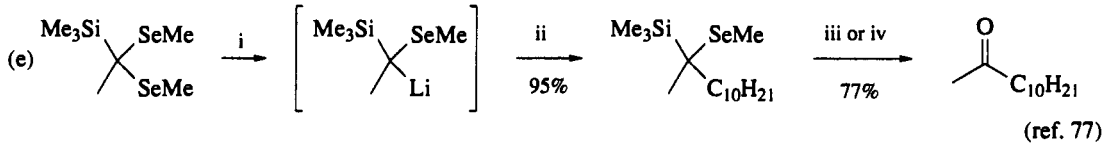
(b) R^1 = H; R = 4-$CF_3C_6H_4$; i, LDA, –78 °C, 0.5 h; ii, $PhCH_2Br$, 83%; iii, MCPBA, THF, Pr^i_3N, 71% (66:34) (ref. 74, 106)



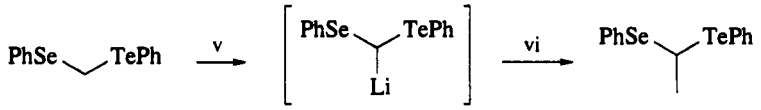
(ref. 353)

(c) R^1CHR^2 = n-C_9H_{19} X = S, 92% X = S, 69%, 100 °C
X = Se, 82% X = Se, 70%, 20 °C
X = Te, 64% X = Te, 72%, 40 °C

(d) R^1CHR^2 = $C_6H_{13}CHMe$ X = S, 30% X = S, 42%, 100 °C
X = Se, 34% X = Se, 48%, 20 °C



(ref. 77)



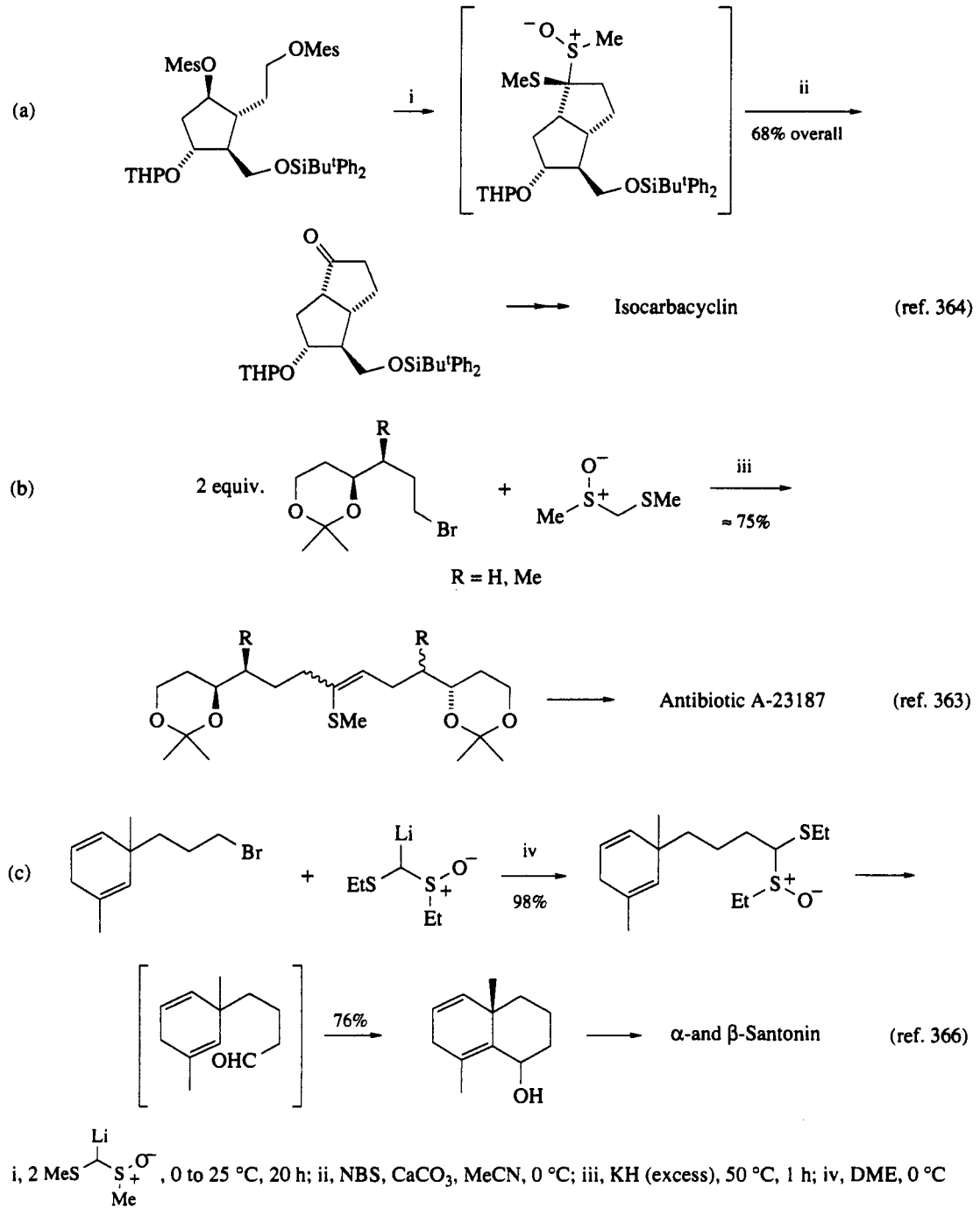
(ref. 374)

i, Bu^nLi, THF, –78 °C; ii, $C_{10}H_{21}Br$; iii, H_2O_2, THF; iv, $NaIO_4$, EtOH; v, LDA, THF, –78 °C, 0.5 h; vi, MeI

Scheme 78

1.3.3.3.3 Synthesis of aldehydes and ketones from α-heterosubstituted sulfides and selenides and related compounds

Most α-heterosubstituted alkyl sulfides discussed in this section have proved to be much easier to transform to aldehydes or ketones than the corresponding 1,3-dithianes. In particular this is the case of (i) formaldines[340] ($HgCl_2$, HgO, 20 °C, 2 h; Scheme 73, entry c), (ii) α-methoxyalkenyl phenyl sulfide[348] ($NaIO_4$, H_2O, dioxane, 20 °C; Scheme 77) and (iii) the α-silylalkyl phenyl sulfides[349–351,355] (MCPBA, –15 °C then H_2O; Scheme 77) and α-silylalkyl selenides[74,77,106,375] (H_2O_2, THF, $NaIO_4$, MCPBA, 20 °C; Scheme 78, entries a–e). The last mentioned reactions involve the transformation of the α-silyl sulfoxide or selenoxide first produced to the corresponding trimethylsilyl hemithio or hemiseleno acetal *via* a Sila–Pummerer rearrangement. This requires overnight reaction at 20 °C or 0.5 h at 60 °C in the case of sulfur, but proceeds almost instantaneously with the seleno analog. Interestingly, this rearrangement can be sup-

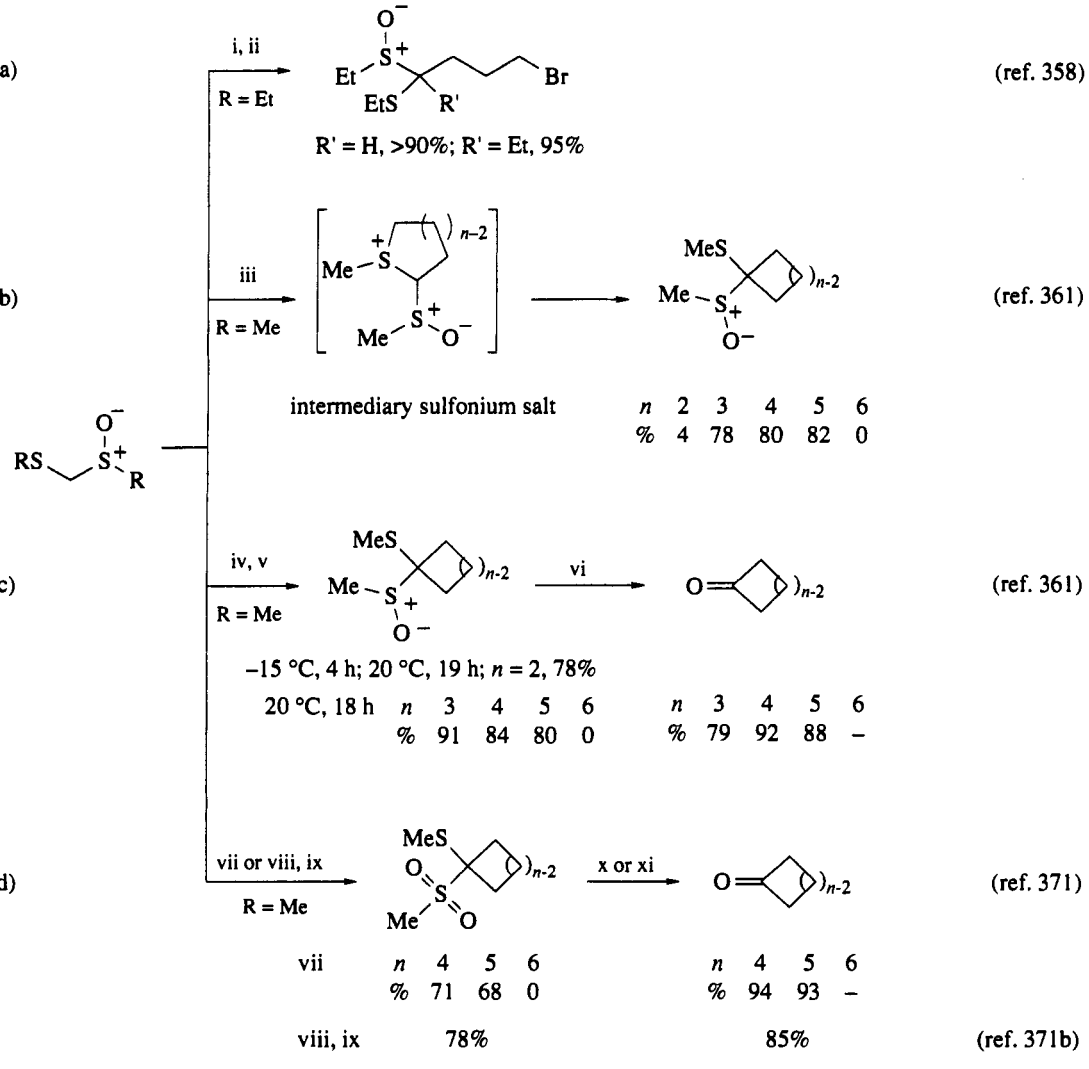


Scheme 79

pressed and the elimination reaction which leads to vinylsilane favored if the α-silyl sulfide, selenide or telluride is instead treated with chloramine T (Scheme 78, entries c and d).[353]

1,1-Di(seleno)alkanes have been easily transformed to carbonyl compounds on reaction with a large array of reagents including $HgCl_2$–$CaCO_3$, $CuCl_2 \cdot 2H_2O$–CuO,[86,243] hydrogen peroxide,[86] benzeneseleninic anhydride[86] or clay-supported metal nitrates[379] in ways similar to those used with thio analogs. In some cases, an elimination reaction produces vinyl selenides instead of the carbonyl compound. In such an event, the latter derivative can be obtained by further hydrolysis[243,244] of the vinyl selenide, for example with $HgCl_2$ in the absence of an added base (Scheme 81).

The transformations of thioacetal monosulfoxides to carbonyl compounds[357-361,365,366] have been

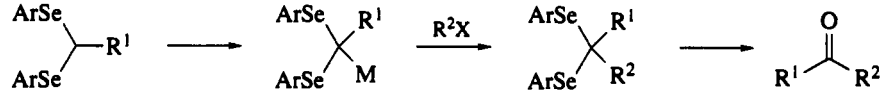


i, 1 LDA; ii, $Br(CH_2)_3Br$, 25 °C, 2–10 h; iii, $Br(CH_2)_nBr$, 2.8 KH, THF, 20 °C, 19–48 h; iv, Bu^sLi; v, 0.5 $Tos(CH_2)_nTos$; vi, 4.5 M H_2SO_4, 20 °C, 4–15 h (or 20 h, 45 °C if $n = 3$); vii, 50% aq. NaOH, toluene, TOMAC, 60 °C, 64–144 h, $Br(CH_2)_nBr$; viii, BuLi; ix, 0.5 $Br(CH_2)_3Br$, 20 °C, 22 h; x, conc. HCl, MeOH; xi, conc. HCl, dioxane, Δ, 3.5 h

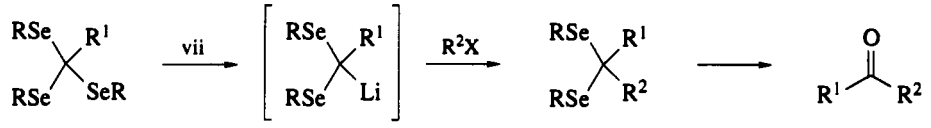
Scheme 80

carried out with hydrochloric, perchloric, or sulfuric acid in water, ether or THF (Scheme 80, entries c and d; Scheme 83, entries a and c) and often in the presence of mercury(II) salts in order to remove the disulfide concomitantly produced,[358] or with NBS in the presence of $CaCO_3$ (Scheme 74, entries b–d; Scheme 79, entries a and c).[364] These conditions are sufficiently mild to allow, for example, the almost exclusive formation[360] of 3-cyclopentenone from (*Z*)-1,4-dichlorobut-2-ene without substantial isomerization to the thermodynamically more stable 2-cyclopentenone (Scheme 83, entry a). The synthesis of the more strained cyclobutanone requires slightly more drastic conditions however to go to completion (4.5 M H_2SO_4, 20 °C, 18 h and 45 °C, 5 h).[371b]

Finally, ketone dimethylthioacetal *S,S*-dioxides[371] are more difficult to transform to ketones than their *S,S*-monoxides[357] (Scheme 74, entries f–h). Effective transformation usually requires heating at reflux in the presence of concentrated acid. Moreover, dimethyl thioacetal *S,S*-dioxides[371a] derived from aldehydes resist the above mentioned hydrolysis conditions and require, in order to be transformed to the aldehyde, preliminary photochemical cleavage of the C—SO_2 bond[371a] ($h\nu$ then aq. NaOH; Scheme 74,

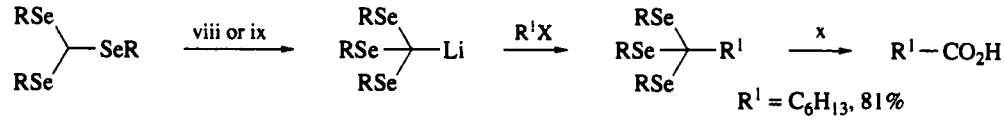


Entry	*Ar*	*Conditions*	R^1	R^2	%	*Conditions*	%	*Ref.*
(a)	Ph	i	H	C_6H_{13}	80			64, 65
(b)		ii	Me	C_6H_{13}	74			76
			C_6H_{13}	C_6H_{13}	44			
(c)		iii	Me	C_6H_{13}	82			
			C_6H_{13}	C_6H_{13}	86			
(d)		iv	Me	$C_{10}H_{21}$	95	v	64	86, 108
			Me	Pr^i	70			
			Pr^i	$PhCH_2$	71			
(e)	4-$CF_3C_6H_4$	vi	H	C_6H_{13}	85			106



(f) R = Ph — $R^1 = R^2 =$ Me; 72% — (ref. 64, 65, 76)

(g) R = Me — $R^1 = R^2 = C_6H_{13}$; 75%



(h) R = Ph — viii — R^1X = MeI, 93% — (ref. 64, 65)

(i) R = Me — ix — (ref. 76, 77)

R^1X	MeI	$C_{10}H_{21}Br$	$C_6H_{13}Br$
%	80	66	80

i, Bu^i_2NLi, THF, –78 °C, then –30 °C, 0.2 h; ii, LDA, THF–HMPA; iii, LiTMP, THF–HMPA, –30 °C, then 20 °C, 0.2 h; iv, KDA, THF, –78 °C, 0.2 h; v, $HgCl_2$, $CaCO_3$, 20 °C, 2 h; vi, LDA, THF, –78 °C, 0.1 h; vii, Bu^nLi, THF–hexane, –78 °C; viii, LIDBA, THF, –78 °C; ix, LDA, THF, –78 °C; x, H_2O_2, THF

Scheme 81

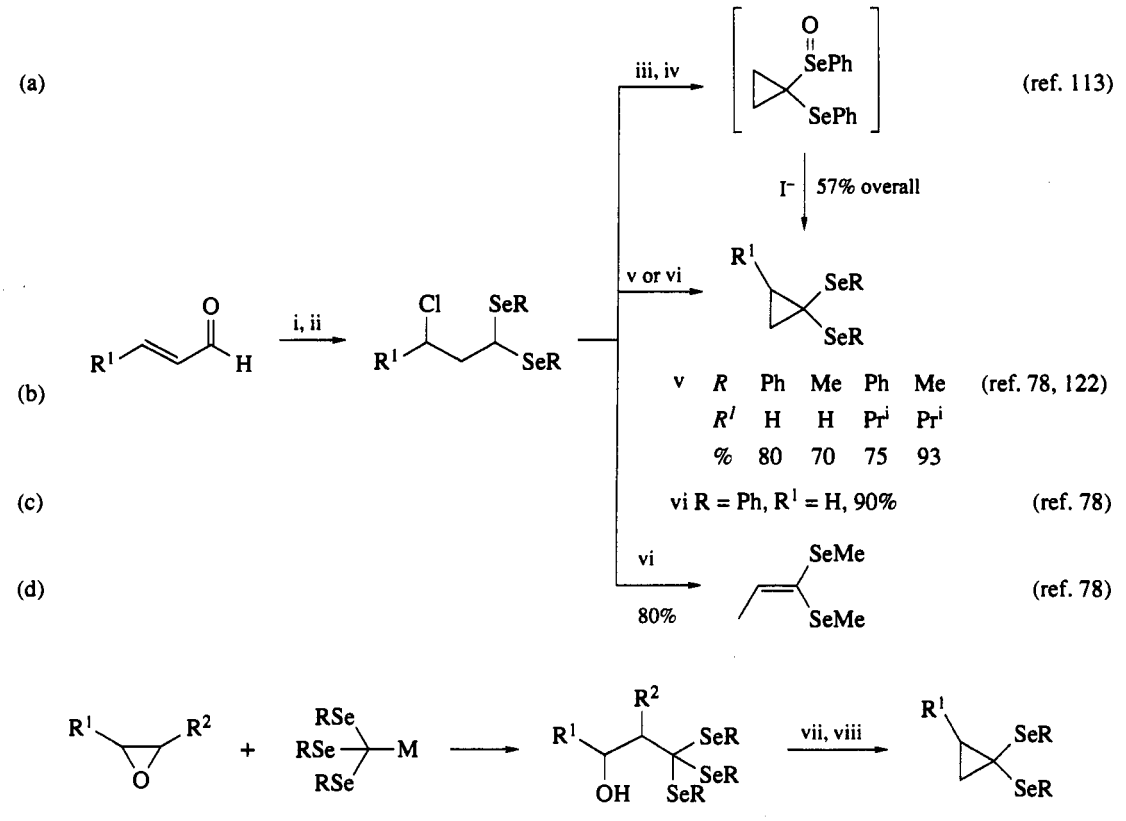
entry f). Similar conditions can be used for ketones but they are less efficient than acid-catalyzed hydrolysis.[371a]

In conclusion, the 1,3-dithiane unit still remains among the most valuable acyl anion equivalents, although that involving methyl methylthio sulfoxide or its diethyl analog offers the definite advantages of proceeding with metal hydride or even under phase-transfer catalysis conditions and of producing the carbonyl compound under reasonably mild conditions.

Otherwise α-methoxy allyl sulfides have played the role of an α-methylenated acyl anion[347] (Scheme 76, entry a) or a homoenolate dianion[348] (Scheme 76, entry b) equivalent.

1.3.4 α-METALLOORTHOTHIO- AND α-METALLOORTHOSELENO-FORMATES AS PRECURSORS OF ESTERS

Metallated orthothioformates and their seleno analogs (available by metallation of orthothio-[28,381–383] and orthoseleno-formate[64,65,76–78] with lithium amides or on S/Li or Se/Li exchange between orthothio-[381,382] and orthoseleno-carbonates[65] react efficiently with methyl iodide[64,65,381,382,384] as well as with reactive electrophiles such as benzyl chloride and *n*-butyl iodide (Scheme 84, entry a).[383]



(e) R = Ph, $R^1 = R^2 = H$, 82%

(f) R = Ph, R^1, $R^2 = -(CH_2)_4-$, 91%

(g)

R	R^1	R^2	%	%
Me	H	H	70	60
Me	Me	H	61	60
Me	C_6H_{13}	H	61	47

i, HCl, benzene; ii, RSeH, $ZnCl_2$; iii, MCPBA; iv, LDA; v, LDA, THF, 0 °C; vi, Bu^{t}OK, DMSO, 20 °C; vii, TosCl, pyridine, 20 °C; viii, Bu^{n}Li, THF, –78 to 20 °C

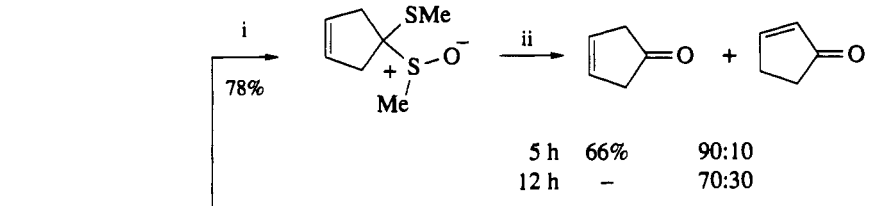
Scheme 82

Tri(phenylthio)methyllithium does not react properly with less reactive electrophiles such as *n*-butyl chloride,[382] 2-iodopropane (Scheme 84),[381,382] propylene oxide (Scheme 85)[381,382] and especially cyclohexene oxide (Scheme 85, entry b)[382] owing to its high propensity to decompose into $(PhS)_2C$ and PhSLi (see below).[381,382,384,385]

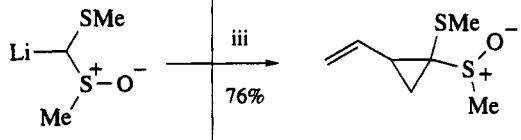
1-Lithio-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane, which is far more stable due to its favorable stereochemistry gives the highest alkylation yields.[381] Tri(phenylseleno)methyllithium[25,64,65,78] and especially its methylseleno[25,76–78] analog, although they share similar behavior, have proved to be more stable however than their thio analogs and have provided reasonable yields of alkylated (Scheme 81, entries f and g)[64,65,76,77] or hydroxyalkylated (Scheme 82, entries e–g)[25,78] compounds on reaction with alkyl halides and epoxides respectively.

The resulting orthothio- and orthoseleno-esters are valuable precursors of carboxylic esters and acids.[383,386] The former conversion requires quite drastic conditions ($HgCl_2$, HgO, MeOH–H_2O, 100 °C, 6 h; Scheme 84, entry b),[383] whereas the same transformation takes place under very mild conditions with the seleno derivatives (aq. H_2O_2, THF, 20 °C, 0.1 h; Scheme 81, entry g).[76]

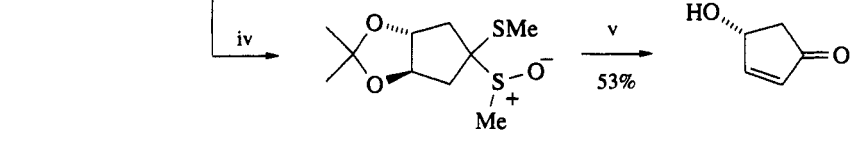
Tri(thio)- and tri(seleno)-alkyllithiums possess a high propensity to act as carbenoids, and they have been found to add to various nucleophilic alkenes, leading to 1,1-di(thio)-[382] and 1,1-di(seleno)-cyclopropanes (Scheme 85, entry c).[64,65]

(a) 

(ref. 360)

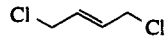
(b) 

(ref. 360)

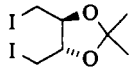
(c) 

(ref. 362)

i, 

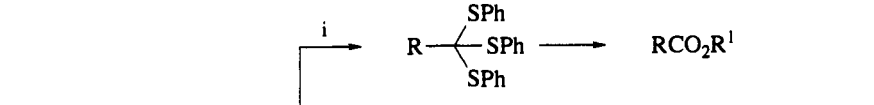
, THF, –78 to 20 °C; ii, 4.5 M H_2SO_4, acetone, H_2O, 20 °C; iii, 

,THF;

iv, 

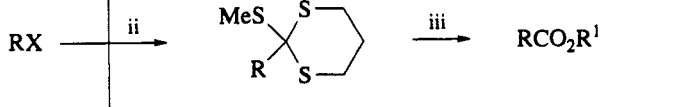
, THF, –70 °C, 1 h, then 20 °C, 2 d; v, 0.5 M H_2SO_4, 0 to 20 °C, 3 d

Scheme 83

(a) 

(ref. 361, 362)

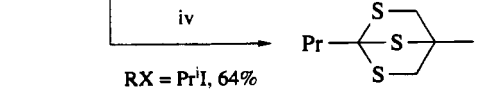
RX	MeI	BuCl	Pr^iI
%	95	35	30

(b) 

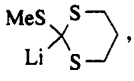
(ref. 363)

RX	Bu^nI	$PhCH_2Cl$
%	78	92

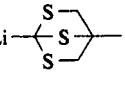
R^1 = Et, 97%; R^1 = Me, 87%

(c) 

(ref. 361)

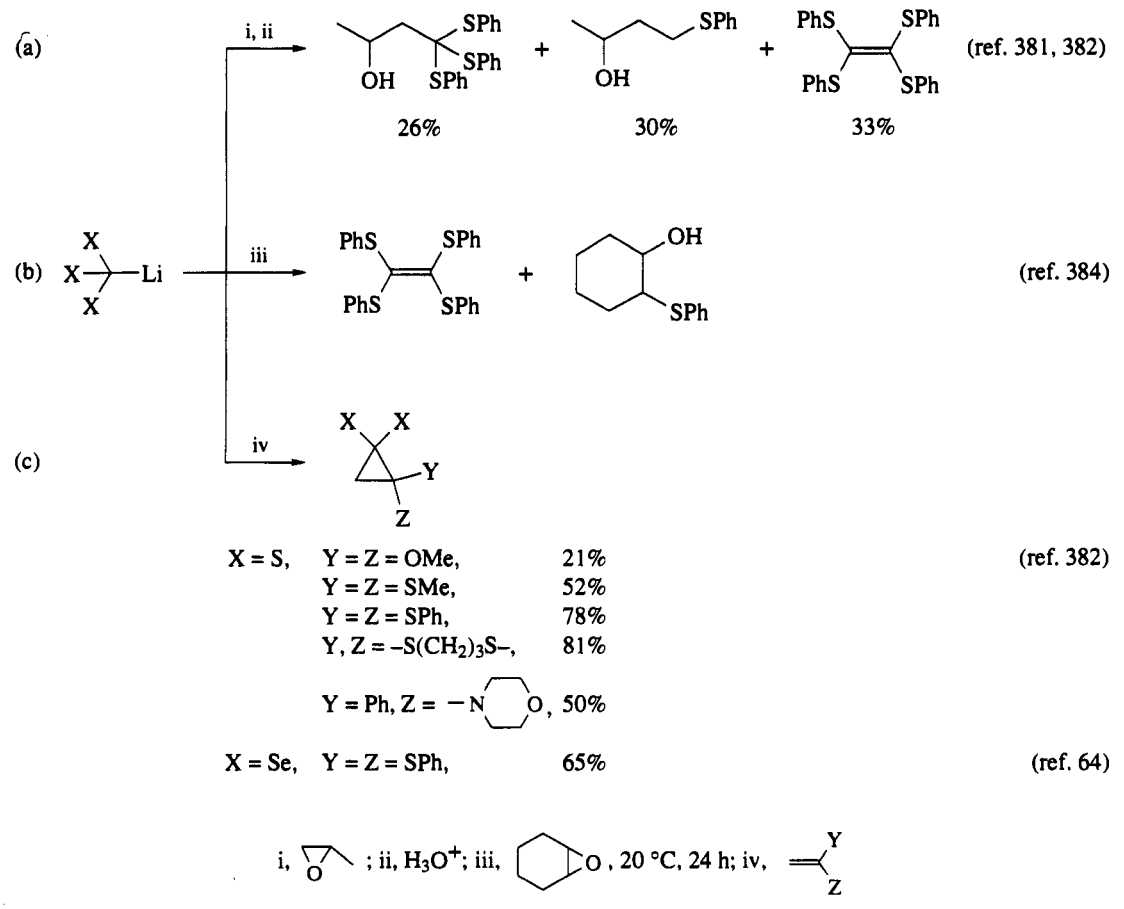
i, $LiC(SPh)_3$; ii, 

, –35 °C, 3 h, then 0 °C, 16 h; iii, $HgCl_2$, HgO, 100 °C, 6 h ;

iv, 

, –78 to 20 °C

Scheme 84



Scheme 85

1.3.5 REACTIONS INVOLVING α-METALLOALKYL SULFOXIDES AND SELENOXIDES

1.3.5.1 Reactions Involving Sulfoxides

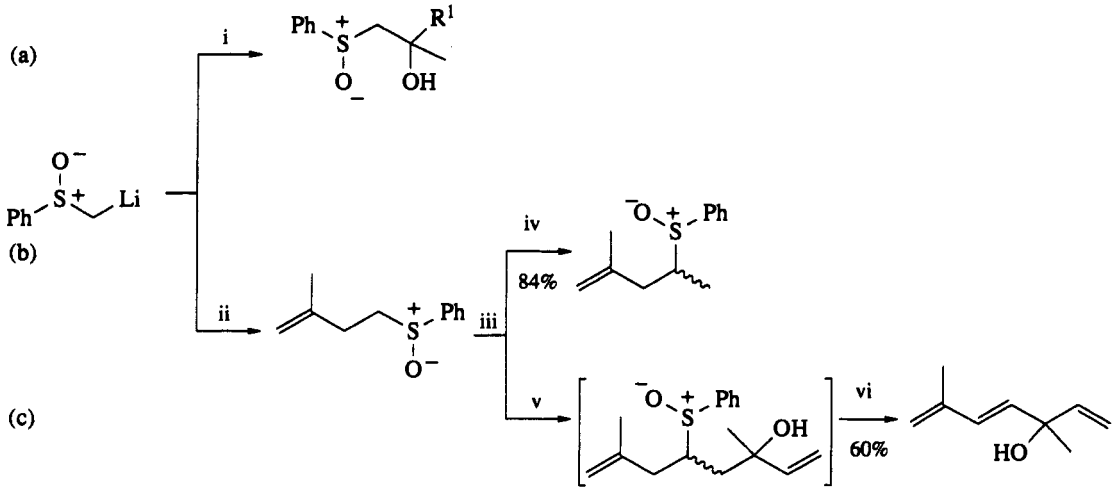
1.3.5.1.1 Reactions involving alkyl sulfoxides

(i) Alkylations of α-metalloalkyl sulfoxides and selenoxides

The reactions between α-metalloalkyl sulfoxides and electrophiles[8,31–34,387] have been extensively studied. Although alkylations of the sodium or potassium salts of dialkyl sulfoxides are not always very efficient since α,α′-dialkylated sulfoxides[388,389] are often produced (or stilbene in the case of methylsulfinyl carbanion and benzyl bromide[391]), those employing the lithioalkyl aryl sulfoxides work more efficiently with alkyl or allyl halides[32,34,390,392,393] and with epoxides.[394–396] Typical examples of these alkylations, allylations and hydroxyalkylations (from epoxides) are illustrated in Scheme 86.

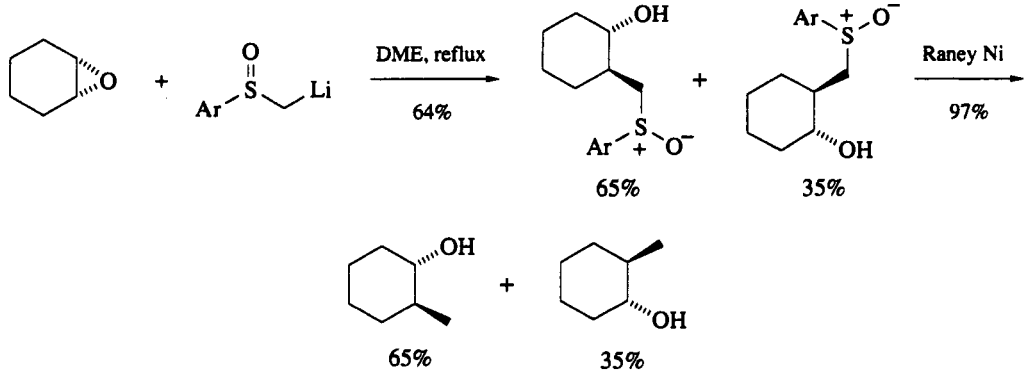
The chirality present at the sulfur atom of, for example, *p*-tolylsulfinyl carbanion leads to the formation of a diastereoisomeric mixture of γ-hydroxy sulfoxides on reaction with prochiral epoxides[394] (Scheme 87). This reaction, coupled with the efficient desulfurization of the resulting sulfoxide by Raney nickel, has been used ingeniously[394] for the enantioselective synthesis of *trans*-2-methylcyclohexanol from epoxycyclohexane and (+)-*p*-tolylsulfinylmethyllithium (Scheme 87).

Both the metallation of sulfoxides and the reaction of α-lithio sulfoxides in THF are known to be highly stereoselective.[32,34,390,397–399] It has been found that, on reaction with base, the diastereotopic methylene protons of benzyl methyl sulfoxide exchange at different rates, the relative ratio being

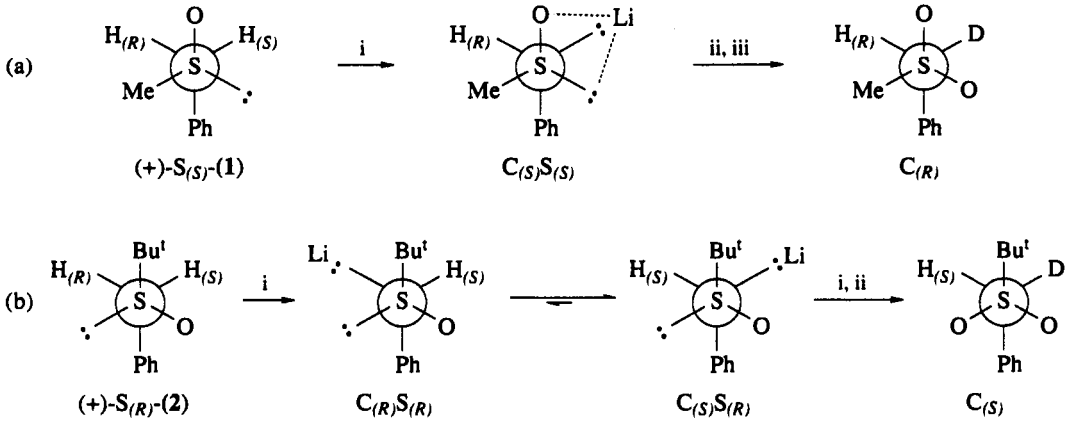


i, , –78 °C, 0.5 h, 20 °C, 4.5 h; ii, , –78 °C, then 20 °C, 3 h; iii, –78 °C, 0.8 h, then –30 °C, 24 h; iv, MeI, –78 °C, 1 h; v, , –78 °C, 0.5h, then 20 °C, 24 h; vi, toluene, 50 °C

Scheme 86



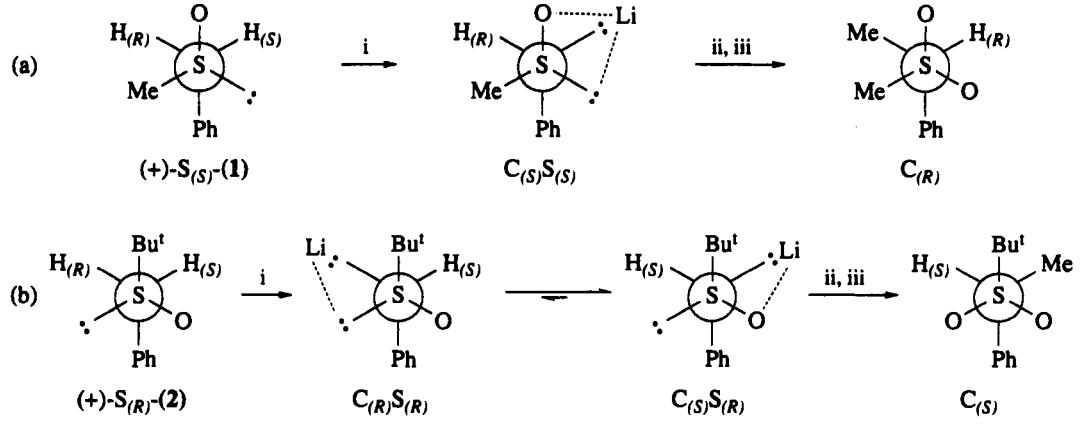
Scheme 87



i, BuLi, THF, –78 °C; ii, D_2O; iii, oxidation

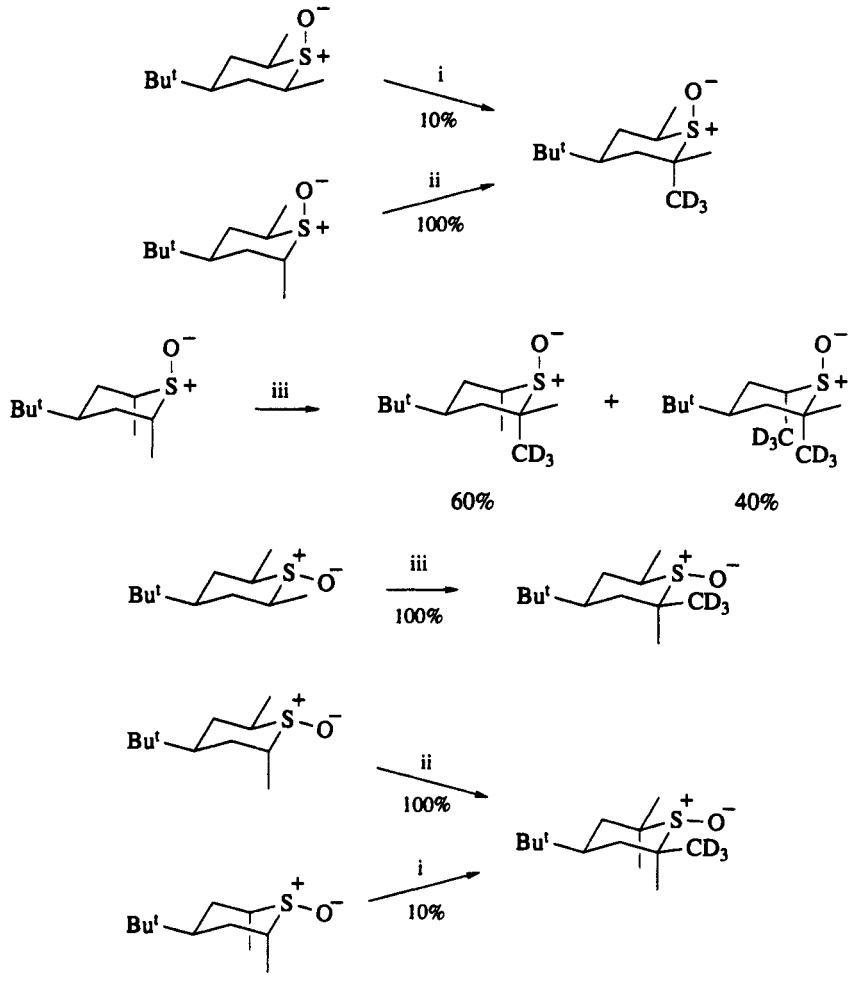
Scheme 88

15:1.[34,390,397,398] Since this discovery the stereochemistry of the H:D exchange, as well as the stereochemical course of deuteration (Scheme 88) and of alkylation (Scheme 88; Scheme 89; Scheme 90; Scheme 91; Scheme 92), a number of acyclic (Scheme 89)[392,397,400–406] and cyclic sulfoxides (Scheme 90; Scheme 91; Scheme 92)[390,398,407–413] have been intensively studied and have been the subject of intense controversy.[387]



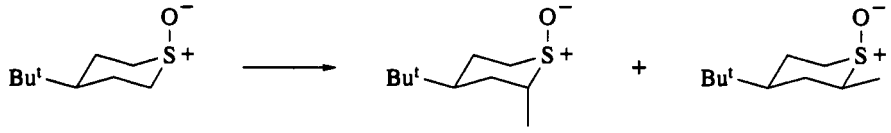
i, MeLi, THF, –78 °C; ii, MeI; iii, oxidation

Scheme 89

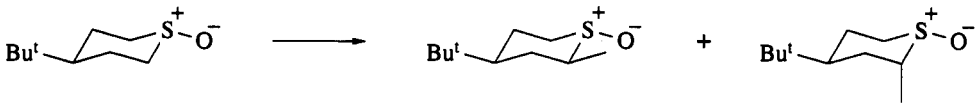


i, 4 BuLi, CD_3I; ii, 1.5 BuLi, CD_3I; iii, 3 BuLi, CD_3I

Scheme 90

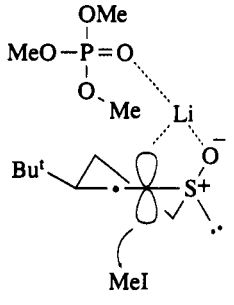


(a)	i, ii 75%	100%	0%	(ref. 407, 411)
(b)	i, iii	30%	70%	(ref. 407)
(c)	i, iv	92%	8%	(ref. 407)

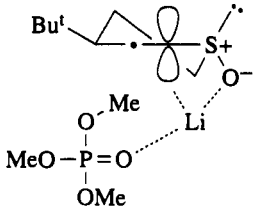


(d)	i, ii	90%	10%	(ref. 411)
(e)	i, v	80%	20%	(ref. 407)
(f)	i, iii	7%	93%	(ref. 407)
(g)	i, vi	60%	40%	(ref. 407)

(h)



(3)



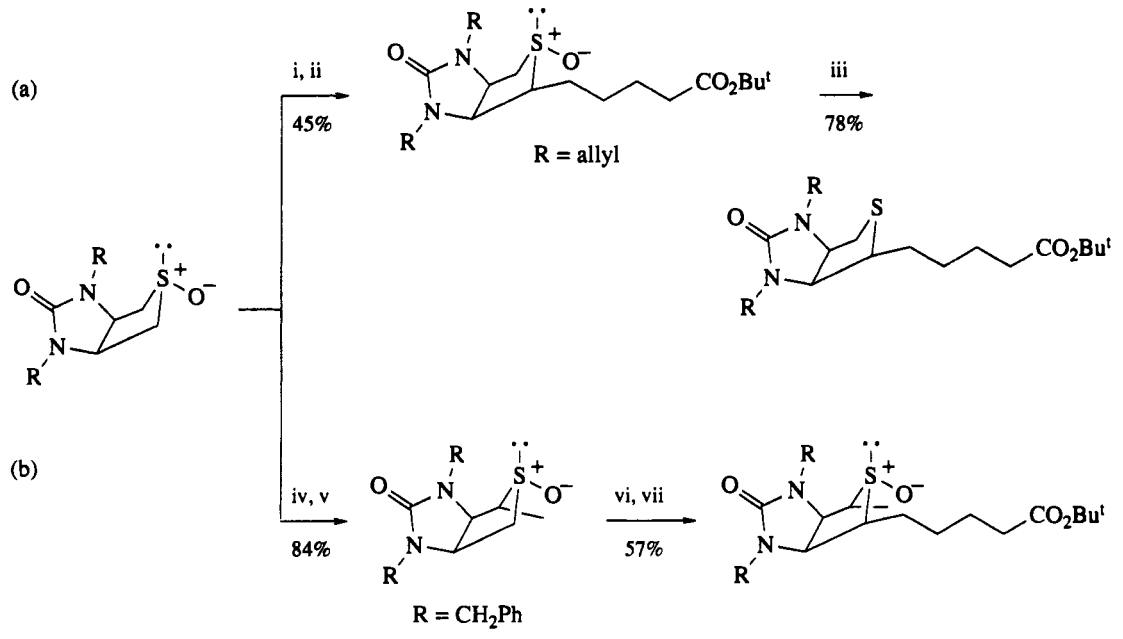
(4)

i, Bu^{n}Li, THF, –78 °C, 0.3 h; ii, MeI, –30 °C; iii, $(MeO)_3PO$, 20 °C; iv, $(MeO)_3PO$, 10 $LiClO_4$; v, MeI, 20 °C; vi, $(MeO)_3PO$, 10 $LiClO_4$, 20 °C

Scheme 91

It was found[34,397,402,403] (see ref. 34, and ref. 387 for a correction) that for α-deuterated benzyl methyl and benzyl *t*-butyl sulfoxides of known configurations, methyllithium in THF at –78 °C abstracts the *pro*-(*S*) hydrogen of (*S*)-benzyl methyl sulfoxide (**1**) with a selectivity of 15:1 (Scheme 88 and Scheme 89, entries a), whereas the same reaction performed on the (R)-benzyl *t*-butyl sulfoxide (**2**; Scheme 88 and Scheme 89, entries b) possessing the same chirality as (**1**) (it should be noted that the (*R*,*S*) notation appears different in methyl and *t*-butyl sulfoxides because of the definition) leads almost exclusively to the removal of the *pro*-(*R*) hydrogen (selectivity 117:1; note that an incorrect absolute configuration of the (+)-(**2**) sulfoxide was quoted in the original paper, ref. 397).[34,387] Finally the *pro*-(*S*) hydrogen atom of (*S*)-benzyl *t*-butyl sulfoxide is abstracted preferentially by a kinetic factor of 1.7:1. As far as alkylation is concerned, the reactions proceed with high stereoselectively, in all cases by inversion of configuration of the originally produced benzyllithiums (Scheme 89); deuteration (or protonation) on the other hand usually occurs with retention with benzyl phenyl sulfoxides and with inversion with benzyl *t*-butyl sulfoxides (Scheme 88).[34,410]

The stereochemistry of the reaction products is dependent on the nature of the α-sulfinyl carbanion. Thus: (i) its kinetic acidity, controls the stereochemistry of the organometallics initially formed; (ii) its thermodynamic acidity defines the stereochemistry or the conformation of the intermediate organometallic; and (iii) reactivity of the organometallic towards the electrophile controls the stereochemistry of the product. The alkylation reaction has proved to be far more selective than is the metallation. Therefore the contribution of kinetic acidity can be neglected because the carbanion in THF has sufficient time to reorganize into its most stable conformation before it reacts with an electrophile.[387] The α-sulfinyl benzyllithiums produced from $S_{(S)}$-(**1**) and $S_{(R)}$-(**2**) should adopt the more stable conformations shown in



i, MeLi, THF–HMPA; ii, 5 I$\sim\sim\sim$$CO_2Bu^t$, –30 °C; iii, $TiCl_3$, H^+, 4 h; iv, MeLi, DME; v, 5 MeI, –30 °C, 1 h; vi, MeLi, DME; vii, 5 I$\sim\sim\sim$$CO_2Bu^t$

Scheme 92

Schemes 88 and 89, in which the lithium cation is coordinated to the sulfinyl oxygen and, in the former, with the sulfur lone pair also. Methyl iodide, which is a nonpolar substrate, prefers to react at the more nucleophilic side which is *anti* to the sulfur lone pair. It has been suggested,[387] in other words, that the *si* and the *re* faces of the benzyllithium derived from $S_{(S)}$-(**1**) are hard and soft reaction centers respectively, whereas the same *si* face has both hard and soft reaction centers; therefore the soft methyl iodide is expected[387] to react at the *re* face in the first case and at the *si* face in the second one, which in fact explains the observed products. This type of rationalization also explains[387] the stereochemistry of the protonation (deuteration) of these organometallics (for a controversal discussion see ref. 34).

The metallations of rigid molecules such as 4-*t*-butylthiacyclohexane take place more efficiently with hydrogens *syn* to the S—O bond[390] (Scheme 90), and the alkylation with alkyl halides gives products of *anti* attack with respect to the S—O bond[390,397,407–411] (Scheme 90; Scheme 91). The last reaction has been purposely used by Marquet[408–410] in an original synthesis of ±-biotin and its analogs (Scheme 92).[409,410]

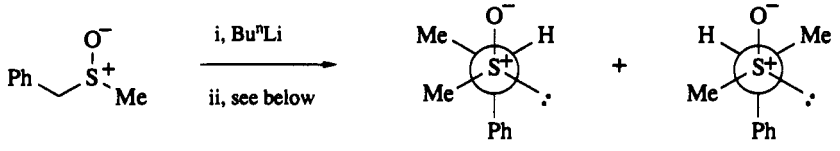
The overall process takes advantage also[409,410] of: (i) the selective oxidation of the sulfur in the corresponding sulfide, leading to the predominant formation of the isomer with the S—O bond *cis* to the junction hydrogens, which is the isomer required for the stereoselective alkylation; and (ii) of the easy reduction of the alkylated sulfoxide to the desired sulfide which has been *inter alia* achieved with Ti^{3+} (Scheme 92). The alkylation yield does not exceed 30% if the reaction is carried out with *n*-butyllithium in THF since both starting material and products resulting from β-elimination of the sulfoxide are isolated.[408–410] This elimination reaction can be suppressed if methyllithium is used instead[409,410] but the yield remains quite low, even when a large excess of the alkylating agent is added (Scheme 92, entry a).

Alkylation takes place predominantly on the less substituted site of dialkylsulfoxides,[388,407,409,410] and this feature has been used advantageously for the synthesis of biotin analogs bearing a methyl group in the α′-position on the thiophane ring (Scheme 92, entry b).[410]

Although reactions with epoxides[413] proceed with a similar stereochemical outcome to that of the alkylation reaction, the deuteration (D_2O),[397,402,403,406] and carbonation[405] reactions occur predominantly with opposite stereochemistry.

The finding that the stereochemistry of such reactions can be drastically affected as shown in Scheme 93, by: (i) a solvent change,[392,404] (ii) addition of macrocyclic polyethers[404] (especially if the reaction is carried out in TMEDA), or (iii) addition of lithium salts[392,406,407] has supported the idea that the stereochemistry may be largely governed by cation–carbanion interactions,[390,413] and more particularly by the ability of Li^+ to form a chelate structure involving the carbanionic carbon and the sulfoxide oxygen (Scheme 89; Scheme 91, entry h, structures **3** and **4**).[404,407]

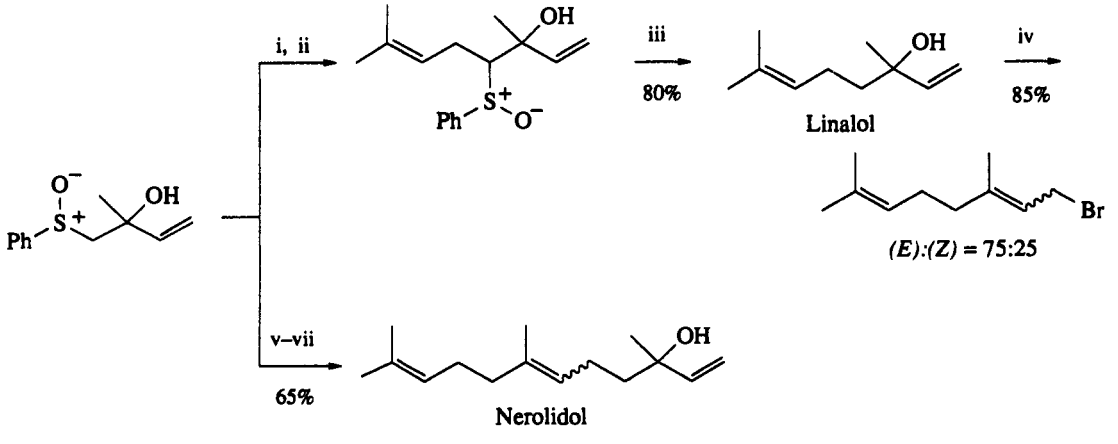
This chelate would undergo electrophilic displacement of Li^+ with predominantly retention of configuration when the electrophile-donating species can itself act as a chelating agent but with inversion in the absence of this chelating ability.[406,407] Strong support for these hypotheses has been provided by the experiments with chelating methylating agents such as trimethyl phosphate[406,407] as compared to nonchelating methyl iodide (Scheme 91, compare entries b to a and entry f to d and e; Scheme 93; similar differences between chelating D_2O and nonchelating proton donors Et_3ND^+ and D^+-sponge have been reported[406]).

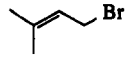


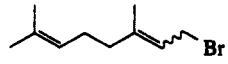
(a)	MeI, THF, 0.1 or 0.5 h; 100%	95%	5%	(ref. 404)
(b)	MeI, THF, excess HMPA; 100%	90%	10%	(ref. 404)
(c)	MeI, [2.2.2]macrobicyclic polyether, 2 h	83%	17%	(ref. 404)
(d)	MeI, TMEDA, [2.2.2], 1 h	80%	20%	(ref. 404)
(e)	$(MeO)_3PO$, 0 °C	40%	60%	(ref. 406)
(f)	$(MeO)_2SO_4$, 0 °C	95%	5%	(ref. 406)

Scheme 93

This interpretation satisfactorily explains all the results reported so far with the exception of those involving the methylations of α-lithiotiepane 1-oxide and thiocane 1-oxide (the seven- and eight-membered homologs of thiacyclohexane)[413] which provide mainly the compounds having *cis* stereochemistry between the methyl group and the S—O bond (*cis:trans* ratio of 93:7 and 83:17 respectively). The



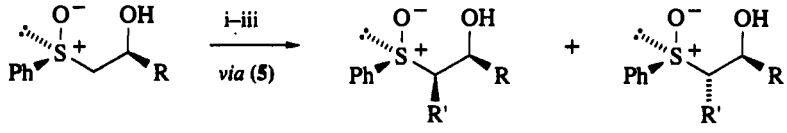
i, 2 Bu^{n}Li, THF, –78 °C, 0.3 h; ii,  , –60 °C, 0.5 h, then 0 °C; iii, Li, $EtNH_2$, –78 °C;

iv, PBr_3, pyridine, –70 °C, 1 h; v, 2 Bu^{n}Li, THF; vi,  ; vii, Li, $EtNH_2$, –78 °C

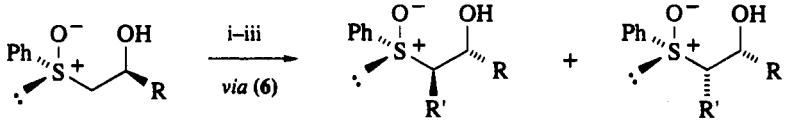
Scheme 94

reactions of oxiranes with these species are slower, but the stereochemical results are substantially the same as in alkylation with methyl iodide.[396,413]

Alkylations[414–416] of the dianions derived from β-hydroxyalkyl sulfoxides, shown in Scheme 94 and in Scheme 95, occur stereoselectively.[415,416]



Entry	*R*	*R'*	*Yield (%)*	*Product ratio*	*Ref.*
(a)	Me	Me	86	89:11	415
	C_9H_{19}	Me	70	95:5	
	$PhCH_2$	Me	84	97:3	
(b)	C_9H_{19}	C_6H_{13}	59	99:1	415
(c)	i-C_7H_{15}	$C_{10}H_{21}$	58	80:20	416



Entry	*R*	*R'*	*Yield (%)*	*Product ratio*	*Ref.*
(d)	Me	Me	86	72:22	415
	C_9H_{19}	Me	72	81:19	
	$PhCH_2$	Me	58	95:5	
(e)	C_9H_{19}	C_6H_{13}	42	98:2	415
(f)	i-C_7H_{15}	$C_{10}H_{21}$	75	95:5	416

(5) (6)

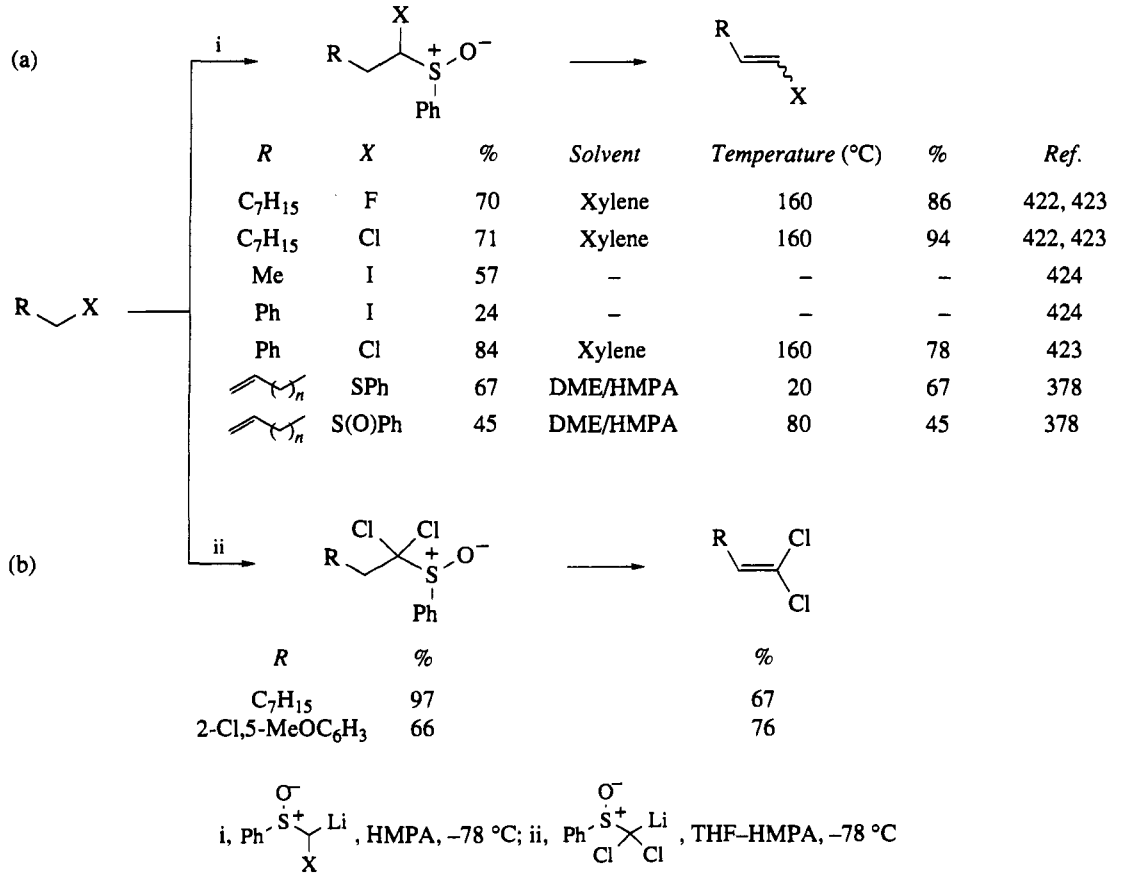
i, 2.2 Bu^nLi, THF, –78 °C; ii, R^1I, –78 °C; iii, H_3O^+

Scheme 95

The steroselectivity increases by increasing the bulkiness of the R and R^1 groups, and is not affected when the reactions are carried out in the presence of TMEDA or HMPA (2 equiv.).[415] The alkylation is therefore controlled by the stereochemistry of the carbon bearing the hydroxy group rather by that of the sulfinyl group.[416] The preference for *threo* stereochemistry has been explained by the six-membered chair transition states (**5** and **6**; Scheme 95) produced by the chelation of both oxygens of the hydroxy and sulfinyl groups to the lithium cation. The axial attack of the alkylating agent from the upper side, due to the steric interaction with the axial R group, leads to the selectivity shown in Scheme 95 (entries a–c), whereas equatorial attack on (**6**) leads to the thermodynamically more stable *threo* derivatives shown in Scheme 95 (entries d–f). In contrast to the reported reversal of the stereochemistry in the reaction of α-lithiobenzyl methyl sulfoxide with methyl iodide and trimethyl phosphate respectively,[406,407] the reaction of the dianion derived from β-hydroxyalkyl sulfoxide with trimethyl phosphate leads to the same *threo* stereoisomer produced with methyl iodide[416] supporting therefore the chelated structures shown in Scheme 95. This reaction when performed on optically active β-hydroxyalkyl selenides, shown in Scheme 95 (entries c and f), afforded *threo* β-hydroxyalkyl sulfoxides which are useful precursors of optically active *cis*-epoxides.[416] The utility of the above mentioned reactions has been demonstrated in the

asymmetric synthesis of (+)- and (–)-*cis*-7,8-epoxy-2-methyloctadecanes, the female-produced pheromone of the gypsy moth (Scheme 95, entry f).[416]

Sulfoxides are known to produce alkenes on heating, by elimination of sulfenic acids.[8,31,32,233,417–420] This reaction has been applied successfully to a large variety of alkyl sulfoxides and functionalized alkyl sulfoxides. Many of these sulfoxides have been synthesized from simpler sulfoxides by alkylation of the corresponding lithium salts. Thus, methylbenzyl[378] (Scheme 47), 3,4-dioxomethylenebenzyl,[378] phenylsulfinylmethyl,[378] phenylsulfonylmethyl,[380,421] fluoromethyl,[422] chloromethyl,[423] iodomethyl[424] and dichloromethyl[425] phenyl sulfoxides have been metallated with lithium amides[378,421–423,425,426] or butyllithium[378] in THF or in DME[378] then alkylated,[378,422–425] benzylated[378,421,422,424,425] and allylated (Scheme 96).[378,380]



R	*X*	%	*Solvent*	*Temperature* (°C)	%	*Ref.*
C_7H_{15}	F	70	Xylene	160	86	422, 423
C_7H_{15}	Cl	71	Xylene	160	94	422, 423
Me	I	57	–	–	–	424
Ph	I	24	–	–	–	424
Ph	Cl	84	Xylene	160	78	423
	SPh	67	DME/HMPA	20	67	378
	S(O)Ph	45	DME/HMPA	80	45	378

R	%	%
C_7H_{15}	97	67
2-Cl,5-$MeOC_6H_3$	66	76

Scheme 96

The reactions are usually carried out at 20 °C except with α-halomethyl sulfoxides whose lithium salts are particularly unstable and which have instead been reacted in THF at –78 °C in the presence of HMPA (Scheme 96).[422–425] α-Lithiobenzyl phenyl sulfoxide has proved to be the most nucleophilic species among the different functionalized sulfoxides used (Scheme 47).[378] Thus, it has been smoothly alkylated, allylated or benzylated in THF and is the only one which has been reported to undergo alkylation with secondary alkyl halides.[378] The sluggish alkylation of the organolithium compound derived from di(sulfinyl) methane with an unactivated alkylating agent dictated the use of HMPA and elevated temperatures, although no complications were encountered.[378]

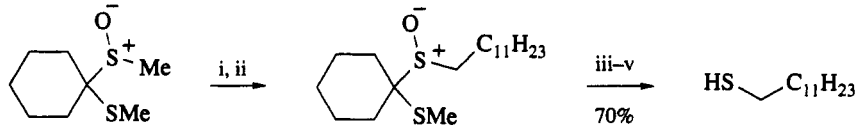
(ii) Synthetic uses of alkylated sulfoxides

(*a*) *Synthesis of alkenes and dienes* via *sulfoxide elimination reactions*. The pyrolysis of various sulfoxides takes place between 80 and 150 °C.[378,421,422,425,426] In some instances the elimination reaction has been carried out in the same pot and the same solvent in which the alkylation reaction has been achieved.[378] In other cases trimethyl phosphite, a scavenger of sulfenic acid, has been employed to avoid decomposition and to facilitate isolation of the product.[378] Aryl and phenylthio substituents α to the

sulfinyl moiety facilitate the elimination of sulfenic acid whereas a phenyl sulfinyl moiety decelerates elimination.[378] The ease of hydrogen abstraction decreases in the order allylic > benzylic > secondary > tertiary. Thus in the absence of conformational restraints there exists the possibility of regioselection. Finally, in several cases (*E*)-alkenic double bonds are produced selectively.[378]

The method employing the sequential alkylation and elimination of sulfoxides, reported above, has been successfully applied to the synthesis of dienes (Scheme 86, entry c),[395] aryl alkenes and dienes (Scheme 47),[378] vinyl sulfides,[378] α,β-unsaturated sulfoxides,[378] vinyl fluorides[422] and vinyl chlorides (Scheme 96, entry a),[423] and 1,1-dichloro-1-alkenes (Scheme 96, entry b).[425]

(*b*) *Reactions employing the reduction of alkyl sulfoxides.* Reduction of sulfoxides to sulfides have been successfully carried out with a large variety of reducing agents including $TiCl_3$,[408–410] Me_3SiI, $NaHSO_3$[396] and PI_3,[427] and they have been used advantageously, as already mentioned, for the synthesis of biotin (Scheme 92, entry a).[408–410] The PhSO/H exchange can be performed with Raney nickel[418] or with lithium in ethylamine;[414] the latter procedure has allowed the synthesis of linalol and nerolidol (along with 25% of its *Z*-isomer; Scheme 94).[414] A number of other interesting transformation of sulfoxides can be cited, including: (i) a synthesis of trisubstituted alkenes which takes advantage of the regio- and stereo-selective γ-substitution of allylic sulfoxides with lithium dimethylcuprate;[428] and (ii) the transformation of primary alkyl halides into alkanethiols which have a carbon chain longer by one methylene unit than the original halides (Scheme 97).[429] The key step in this reaction involves the alkylation of cyclohexanone dimethyl acetal *S*-oxide, followed by acid hydrolysis and reduction of the resulting compound with lithium aluminum hydride (Scheme 97).



i, Et_2NLi, THF, –15 °C; ii, $C_{11}H_{23}I$, –78 °C, then 20 °C, 2 h; iii, H_3O^+ ; iv, $LiAlH_4$; v, H_3O^+

Scheme 97

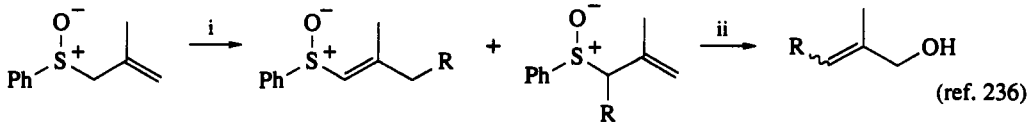
1.3.5.1.2 Reactions involving allylic sulfoxides

A range of diverse substituted allyl phenyl sulfoxides, which are available by addition of dimethyl cuprate to allenyl sulfoxides[430] or more generally by alkylation of simpler analogs,[16,235,236,414,431] have been converted into allylic alcohols possessing predominantly (*E*)-stereochemistry (*E*:*Z* ≥ 90:10) following simple admixture with trimethyl phosphite[235,236] or thiophenolate (MeOH, 60 °C, 7 h; Scheme 98; Scheme 99; for a lower selectivity see Scheme 98, entry a).[431]

Metallations of allyl sulfoxides have been achieved at –78 °C with *n*-butyllithium in THF[431] or more efficiently with LDA under similar conditions.[16,235,236] Alkylations with primary alkyl iodides[16,235,236,431] and allylations with allyl[235,430] or phenyl[236] bromides proceed in good yield, usually below –20 °C and in less than 6 h. The reaction takes place predominantly at the α-site but there is often competition from γ-alkylation leading to α-alkenyl sulfoxides (Scheme 98; Scheme 99). Changing the solvent, or introducing metal ion complexing agents, such as TMEDA were unsuccessful in changing the α:γ ratios observed in THF.

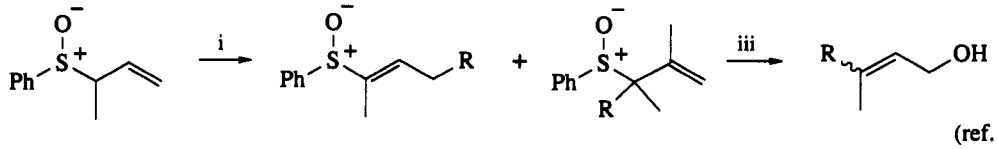
α-Alkylation occurs almost exclusively when the γ-carbon is dialkylated (Scheme 99, entry e) or with 1-phenylsulfinyl-2-cycloalkenes (Scheme 98, entries e and f). Apart from these cases the α:γ ratio ranges between 80:20 and 55:45. In general, allyl halides react less selectively than alkyl halides,[235,236] which in fact lead to the highest α:γ ratio. This competing reaction lowers the overall yield of allyl alcohols resulting from the reaction of allylic sulfoxides with thiophilic reagents. Therefore the route employing: (i) the alkylation of allyl sulfides, (ii) their transformation to the corresponding sulfoxide, and (iii) the rearrangement of the latter to allyl alcohols, which has been reported in Section 1.3.2.2.2, is preferred to that just described due to higher regiocontrol. The first reported set of reactions has been ingeniously applied to the synthesis of a series of cyclopentene-3,5-diols, which are potential precursors of the prostaglandins (Scheme 100).[166]

Alkylations of 1-alkenyl aryl sulfoxides have attracted little attention compared to other cases.[432,433] However it has been found that α-metallation occurs on reaction with LDA and that alkylation, allylation and benzylation occur there as a result (Scheme 101). Interestingly, γ-alkylation resulting from a competitive γ-metallation reaction has not been observed. The last mentioned reaction, coupled with treatment

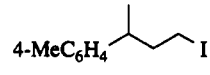


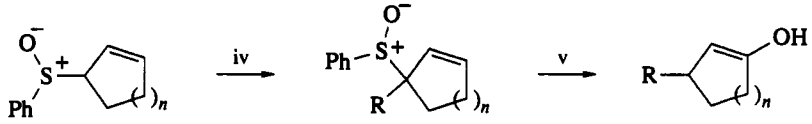
(ref. 236)

Entry	*RX*	*Product ratio*	*Yield (%)*	*(E):(Z)*
(a)	MeI	27:73	59	
	EtI	26:74	48	73:27
	$Me_2C{=}CHCH_2Br$	45:55	35	93:7
(b)	$Me_2C{=}CH(CH_2)_2I$	30:70	55	90:10



(ref. 236)

Entry	*RX*	*Product ratio*	*Yield (%)*	*(E):(Z)*
(c)	MeI	9:91	75	>96:4
	$C_6H_{13}I$	28:72	42	>96:4
	$Me_2C{=}CHCH_2Br$	33:67	46	>96:4
(d)	4-MeC_6H_4 	33:67	43	95:5

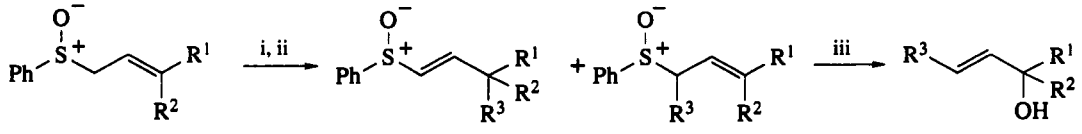


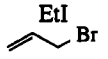
(ref. 235)

(e)	$n = 1$	MeI	>96%	99%
(f)	$n = 2$	MeI	>96%	100%
		EtI	>96%	45%
		$Me_2C{=}CHCH_2Br$	>96%	32%

i, LDA, THF, –78 °C, RX, –60 or –8 °C, 1 or 0.2 h; ii, $(MeO)_3P$, MeOH, 20 °C, 12 h; iii, $(MeO)_3P$, MeOH, 20 °C, 1 h; iv, LDA, THF, –78 °C, –50 or –40 °C, 0.5 or 2 h; v, $(MeO)_3P$, MeOH, 1 h

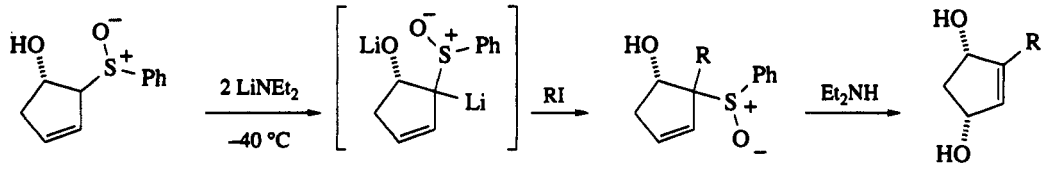
Scheme 98



Entry	R^1	R^2	R^3X	*Product ratio*	*Overall yield (%)*
(a)	H	H	MeI	15:85	74
	H	H	EtI	25:75	60
	H	H		45:55	45
(b)	Me	H	MeI	9:91	85
			EtI	12:88	50
(c)	Me	Me	$C_6H_{13}I$	9:91	70

i, LDA, THF, –60 °C; ii, R^3X, –50 or –30 °C, 0.5 to 4 h; iii, $(MeO)_3P$, MeOH, 12 h, 20 °C

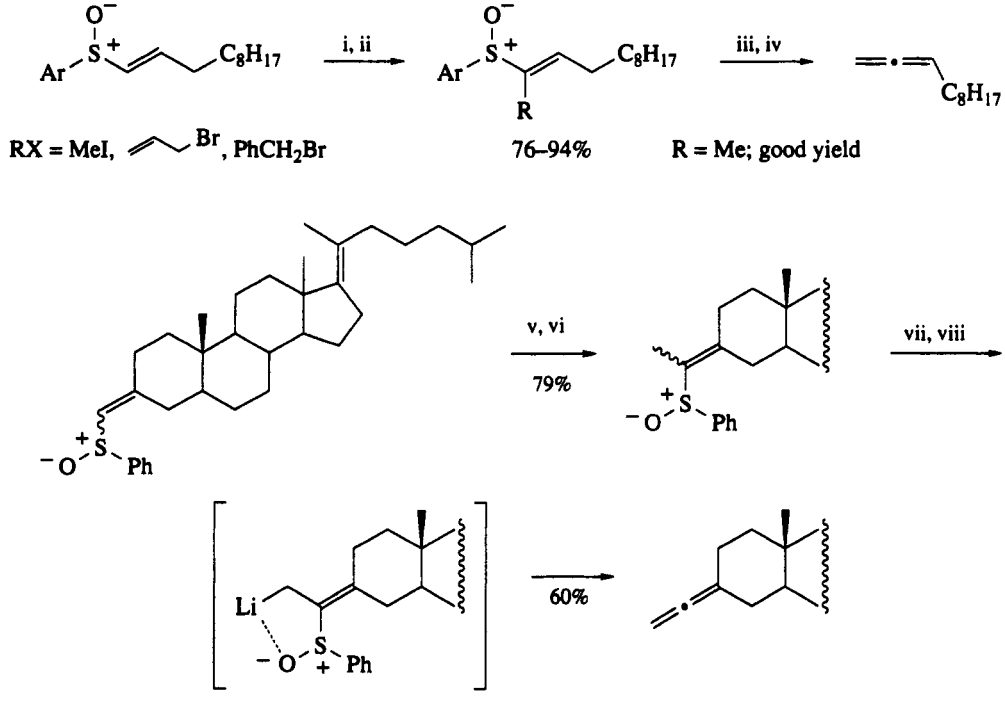
Scheme 99



R	C_6H_{13}	$PhCH_2$	$(CH)_6CO_2Bu^t$
%	65	40	45

Scheme 100

of the α-methylated vinyl sulfoxides with lithium tetramethylpiperidide, provides an original synthesis of allenes (Scheme 101).[433]

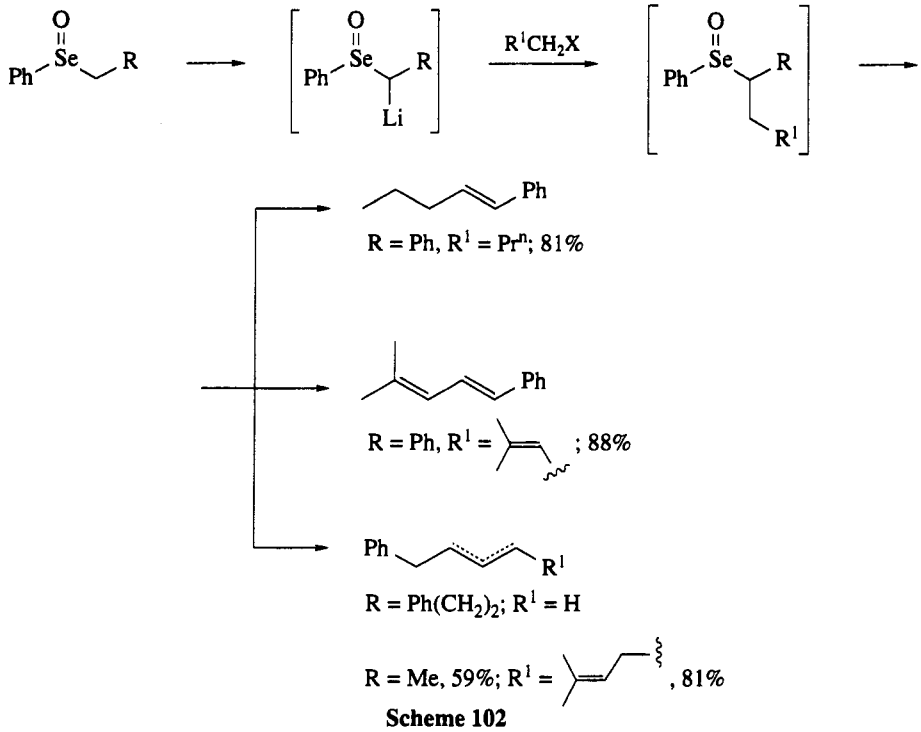


i, LDA, –78 °C, 0.3 h; ii, RX; iii, LITMP, THF, –100 °C, 0.8 h; iv, NH_4Cl; v, LDA, –78 °C; vi, MeI; vii, LITMP, THF, –100 °C, 0.8 h; viii, NH_4Cl

Scheme 101

1.3.5.2 Alkylations of α-Metallo-alkyl and -vinyl Selenoxides

α-Lithioalkyl selenoxides, which are available from *in situ* oxidation–metallation of the corresponding alkyl aryl selenides, have been alkylated at –78 °C with methyl iodide and allyl bromides (Scheme 102).[98,112,113] Unfortunately the utility of this process is limited,[113] as in the case of the corresponding sulfoxides, by the lack of regioselectivity of the subsequent *syn* elimination (Scheme 102, compare entries a and b to entry c) since two alkenes are formed, unless structural features dictate the formation of only a single isomer (Scheme 102). The α-deprotonation of vinyl phenyl selenoxide with LDA has been studied[107] at –78 °C for different time spans. A maximum of 50% of the expected methylation product, α-phenylseleno-2-propene, was isolated after reduction of the intermediate selenoxide with NaI in acetic acid. Deprotonation, even in the presence of methyl iodide, gave poor results.[107]



Scheme 102

1.3.6 REACTIONS INVOLVING SULFONES

1.3.6.1 Reactions Involving α-Metalloalkyl Sulfones

1.3.6.1.1 Alkylations of α-metalloalkyl sulfones

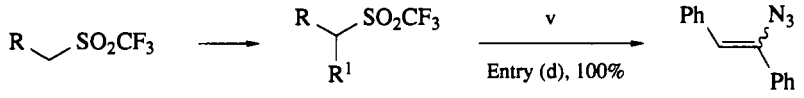
Although the sulfone functional group has been an integral part of organic chemistry for more than a century, it has been only within the last few decades that a more diverse range of chemistry involving this group has been discovered and used, particularly in the total synthesis of various natural products. Various aspects of sulfone chemistry have been reviewed earlier by Magnus[36] and by Durst[37,38] Typically, sulfones exhibit a high degree of chemical and thermal stability. They are stable to oxidizing agents and to acids, but can be reduced to sulfides.[36–38] The sulfonyl group can be replaced[36,37] by hydrogen using Raney nickel, lithium in ethylamine or under less severe experimental conditions (6% Na/Hg). On reaction with a base they are usually readily metallated, and when the hydrogen attached to the carbon β to the one bearing the sulfonyl group is sufficiently acidic (*e.g.* α to a carbonyl group or to a C=C double bond) elimination of sulfinic acid occurs leading to a new C=C double bond. Furthermore, the sulfone oxygen atoms show only relatively weak bonding with electrophiles as compared to sulfoxides and selenoxides. These possibilities and this chemistry, as well as the aptitude of some specific sulfones to take part in the Ramberg–Bäcklund reaction[434] and extrude SO_2 thermally or photochemically, have led to an increasing use of sulfones in synthesis.[434,435]

The alkylation of sulfones has played an important role in this development. Most of this work has been performed with aryl sulfones, and in only rare cases have triflones (RSO_2CF_3)[436] or dialkyl sulfones been employed.[437–440]

Sulfones, including dimethyl sulfones, have been routinely converted into their monoanions by a variety of basic reagents which *inter alia* include: (i) Grignard reagents,[439–441] (ii) organolithiums,[36–38,440,442] (iii) potassium *t*-butoxide,[442] (iv) sodium hydride,[391,436] (v) metallo amides,[438,443,444] and (vi) in rare cases, with phenylsodium or phenylpotassium.[442]

The presence of another group such as an aryl,[436,445–447] an allyl,[448] or an isocyanide,[449] capable of further stabilization of the carbanionic center allows the use of less strong bases such as 50% sodium

hydroxide solution under phase-transfer catalysis,[445,446,448] sodium hydroxide in DMF (Scheme 103, entries a and b)[447] or even potassium carbonate in acetonitrile (Scheme 103, entry d).



Entry	*R*	*R*^{1}*X*	*Conditions*	*Yield* (%)	(ref. 436)
(a)	H	$Ph(CH_2)_2Br$	i	73	
		$PhCH_2Br$	i	18	(48% dialkylation)
(b)	H	Pr^iI	ii	60	
(c)	Me	MeI	iii	60	
(d)	Ph	$PhCH_2Br$	iv	70	

i, R^1X, NaH, DMF, 25 °C, 10–18 h; ii, R^1X, NaH, glyme, HMPA, reflux, 8 h; iii, R^1X, NaH, glyme, 25 °C, 2.5 h; iv, K_2CO_3, MeCN, 84 °C, 36 h; v, 2 NaH, *p*-$TolSO_2N_3$, 0 °C, 0.5 h

Scheme 103

α-Sulfonyl Grignard reagents are not usually alkylated efficiently; for example phenylsulfonylmethylmagnesium bromide does not undergo alkylation[441] with *n*-hexyl iodide or *t*-butyl chloride. However it reacts with benzyl chloride, but leads to the corresponding product in only very modest yield (34%).[441] Similarly α-(*p*-tolylsulfonyl)isopropylmagnesium bromide is alkylated only to the extent of 38% when treated with 3-chloropropyl *p*-toluenesulfonate, but steric hindrance may intervene in this instance (for an intramolecular version of this reaction see Scheme 109).[441]

The alkylations of related organolithium derivatives bearing hydrogen or alkyl groups on their carbanionic centers proceed with much better yields, but often involve primary alkyl (Scheme 103; Scheme 104, entries a, b, and d; Scheme 105, entries a and b; Scheme 106, entries a–d; Scheme 107; Scheme 108, entries a and b; Scheme 109),[13,24,138,436,443,450,451–461] benzyl[138,436,437,451,454,456,459] or allyl[138,445,452,454,455,459,460,462] halides or sulfonates as well as 2,3-dihalogeno- and 1,3-dihalogeno-1-propenes[463] and related dihalides (Scheme 110).[463]

In one case considerable difficulty was encountered in the alkylation of the anion of methyl phenyl sulfone with *o*-chlorobenzyl bromide since, under a variety of conditions, mixtures containing starting sulfone, mono- and di-alkylated products were obtained.[37] Allylation of α-lithio sulfones with allylvinyl dihalides[463] has been reported to produce a large amount of the monoallylated compound in addition to some diallylated derivative. The formation of the latter compound can be avoided however if the reaction is carried out in the presence of copper(I) iodide (Scheme 110, entry a).[463]

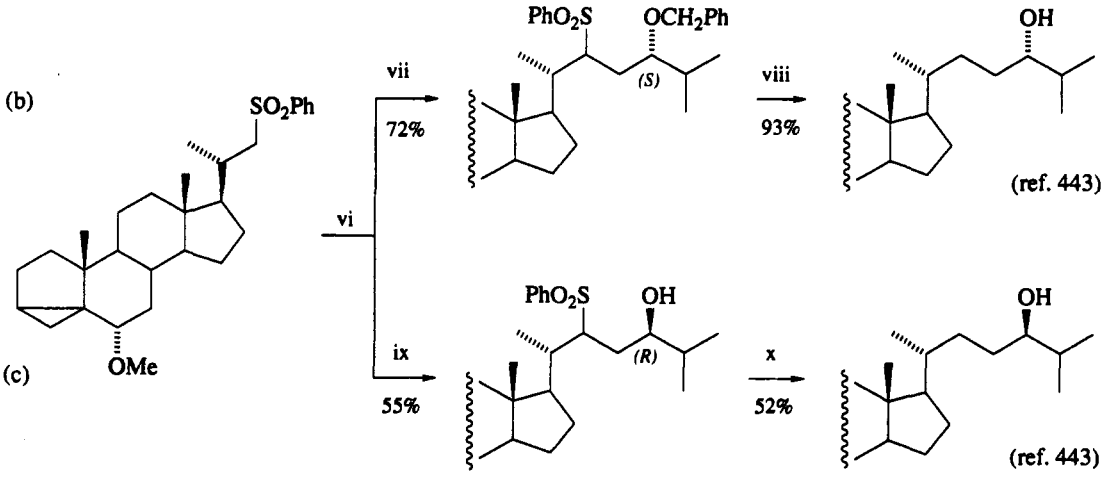
Although alkylations of α-metallo sulfones with sodium iodoacetate proceed efficiently (Scheme 105, entry b),[455] 1:1 mixtures of products are formed on reaction with ethyl iodoacetate in THF (Scheme 110, entry b).[461] The mixtures arise from the expected alkylation reaction and from competitive addition to the carbonyl group of the ester. The product resulting from the alkylation reaction is almost exclusively produced however if the above mentioned reaction is performed in the presence of HMPA (10%) and a trace amount of potassium iodide (Scheme 110, entry c). The resulting β-sulfonyl ester has been further transformed to an α,β-unsaturated ester, taking advantage of the facile elimination of sodium phenyl sulfinate (Scheme 110, entry c).

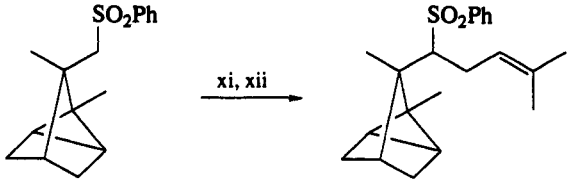
Alkylations of sulfones with secondary alkyl halides have been described only rarely.[456,458] They usually proceed with modest yields and require both long reaction times and the presence of HMPA (Scheme 106, entry b). The presence of an aryl group on the carbanionic center softens this site however, and usually favors the alkylation reaction.[445,461,463]

Mono- or di-alkylation of dimetalloalkyl sulfones has been reported from time to time. Apparently the geminally dilithiated alkyl aryl sulfones are more reactive towards alkyl halides than the monolithiated species. Therefore they can be monoalkylated (Scheme 111, entries a and b)[443,464] or dialkylated (Scheme 111, entries c and d),[438,464,466,467] depending upon the conditions employed (*i.e.* excess of alkylating agent and more severe conditions for dialkylation) but success also depends upon the structures of the sulfones and the nature of the alkylating agents. Thus, ferrocenylmethyl phenyl sulfone is efficiently dimethylated or transformed to the corresponding cyclopropane derivative on sequential treatment with 2

(a) $C_{10}H_{21}$–SO_2p-Tol —i, ii→ $C_{10}H_{21}$–CR(SO_2p-Tol) —iii, iv→ $C_{10}H_{21}$–C(R)(SMe)(SO_2p-Tol) —v→ $C_{10}H_{21}$–C(=O)–R (ref. 451)

RX = $Ph(CH_2)_2Br$, 58% overall; RX = $PhCH_2Br$, 62% overall
RX = $C_5H_{11}C{\equiv}C(CH_2)_3I$, 72% overall, moth pheromone

(b) 

(d) 

(ref. 471)

i, Bu^nLi, THF, –20 °C; ii, RX; iii, Bu^nLi; iv, $(MeS)_2$; v, 2 $CuCl_2$, SiO_2; vi, LDA, –50 °C; vii, $PhCH_2O$, Pr^i, I, 50 °C, 3 h; viii, Li, $EtNH_2$, 0 °C, 2 h; ix, O, Pr^i, –50 °C, 3 h; x, Li, $EtNH_2$, 0 °C, 2 h; xi, Bu^nLi; xii, Br

Scheme 104

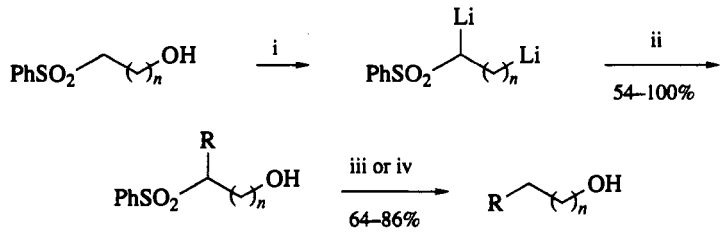
equiv. of *n*-butyllithium and 2 equiv. of methyl iodide or 1 equiv. of 1,2-dichloroethane respectively, but it is monoalkylated with *n*-butyl or benzyl bromide under similar conditions (Scheme 111, entry b).[465]

Reactions of dimethyl,[438] and dibenzyl[437] sulfones (Scheme 112) and of tetrahydrothiophene 1,1-dioxide (Scheme 107, entry a)[453] with 2 equiv. of base, followed by 2 equiv. or more of alkyl halides, take another course since α,α′-dialkylated rather than α,α-dialkylated derivatives are produced.

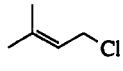
1.3.6.1.2 Synthetic applications of alkyl sulfones

Alkylation or allylation reactions of α-metalloalkyl sulfones followed by oxidation of the carbon center bearing the sulfonyl group (Bu^nLi and dimethyl disulfide,[451] or a three-fold excess of molybdenum peroxide[468] or a slight excess of bis(trimethylsilyl) peroxide, BTSP[469]) have led to novel routes to

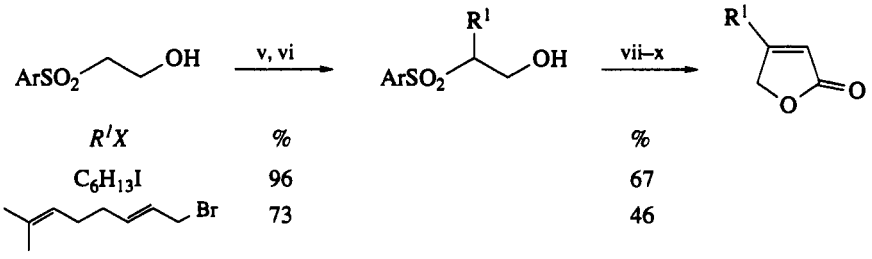
(a)



(ref. 454)

n = 1, 2, 5; RX = BuBr, $C_6H_{13}Br$,  , $PhCH_2Cl$

(b)



(ref. 455)

R^1X	%	%
$C_6H_{13}I$	96	67
	73	46

i, 2 Bu^{n}Li, –78 °C; ii, RX, –78 °C, 0.5 h, then 25 °C, 2–3 h; iii, Raney Ni; iv, Hg/Na; v, 2.2 Bu^{n}Li, THF–TMEDA; vi, R^1X; vii, 2.2 Bu^{n}Li, THF–TMEDA; viii, 1.2 ICH_2CO_2Na; ix, *p*-TsOH, benzene, Δ; x, 2.5 equiv. Et_3N, benzene, 20 °C

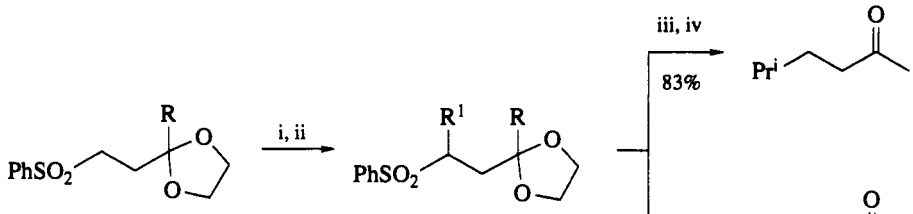
Scheme 105

ketones.[451] The first reagent has been used,[451] *inter alia*, in a synthesis of the sex pheromone of Douglas fir tussock moth (Scheme 104, entry a). Furthermore by taking advantage of the fact that one oxygen of BTSP becomes the carbonyl oxygen of the product, it is possible to label specifically this oxygen by using the readily available $(TMS^{18}O)_2$.[469] Reduction of the sulfonyl group, subsequent to alkylation, has been used for the synthesis of 24-hydroxycholesterols (Li/H_2NEt; Scheme 104, entry c),[443] (+)-dihydrocompactin (NaHg; Scheme 111, entry a)[464], sesquifenchene (Li/$EtNH_2$)[462], α-santalene (Na/Hg, HMPA),[470] cyclopropane (Scheme 108, entry a)[444] or phenylcyclopropane (Scheme 109),[138] benzocyclobutane (Na/Hg; Scheme 107, entries c and d)[460] as well as for the coupling of: (i) an alkyl side chain with a functionalized alkyl or alkenyl halide (see for example Scheme 108, entry a);[463] and (ii) a functionalized side chain with an alkyl, alkenyl or benzylic halide (Scheme 105, entry a; Scheme 106, entry a; Scheme 107, entries c and d).[454,456,458,460] In the above mentioned transformations the sulfone has therefore played the role of an alkyl- or functionalized alkyl-metal.

Thus β-, γ- and ω-hydroxy,[454] β-dioxy- and ω-carboxy-alkyl sulfones have proved to be valuable precursors of alcohols (Scheme 105, entry a),[454] acetals, aldehydes or ketones (Scheme 106, entries a–d)[456,458] and carboxylic acids,[471] respectively, whereas 1-(ω-alkenyl) halides have been synthesized[463] from 1,3-dichloropropene and α-metalloalkenyl sulfones (Scheme 110, entry a). 1-(ω-Alkenyl)-1-sulfonylbenzocyclobutanes are good precursors of quinodimethanes, which are themselves particularly useful reactive intermediates.[460] Although an internal Diels–Alder reaction leading to the tricyclic compound shown in Scheme 107 (entry c), takes place efficiently on thermolysis of the compound missing the sulfonyl group, the reaction takes another course with the highly electron-deficient diene bearing the sulfonyl moiety which instead leads to the aryl vinyl sulfone shown in Scheme 107 (entry d).

Furthermore, several syntheses of α,β-unsaturated carbonyl compounds have involved the alkylation of suitably functionalized sulfones, followed by the base-promoted elimination of the sulfenate moiety on related alkyl sulfones bearing an oxygen atom at the γ-position (Scheme 106, entries b–d; Scheme 110, entry c; Scheme 105, entry b).[455,456,458,461] Particularly interesting is the synthesis of nuciferal (Scheme 106, entry d)[458] which involves sequential alkylation of γ,γ-dioxy sulfones, deblocking of the acetal moiety and sulfenate elimination. In this and related reactions γ,γ-dioxy-α-metalloalkyl sulfone has played the role of a masked β-metallo-α,β-unsaturated carbonyl compound (MC=C—C—C=O), which is not a directly available synthon.

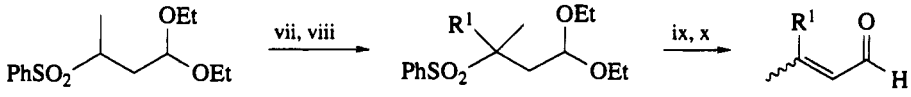
(a)



(ref. 456)

(b) R = H, Me; $R^1X = C_8H_{17}Br$, Pr^iBr, $PhCH_2Br$; 52–90% (ref. 458)

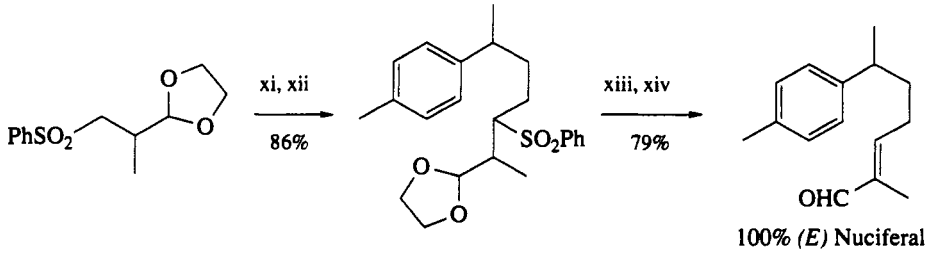
(c)



(ref. 456)

$R^1 = C_6H_{13}$, 65%; R = Pr^i, 32% R = C_6H_{13}, 90%; R = Pr^i, 100%

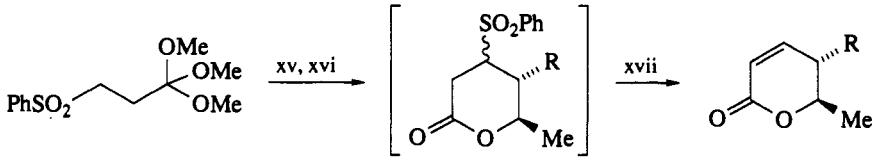
(d)



(ref. 458)

100% *(E)* Nuciferal

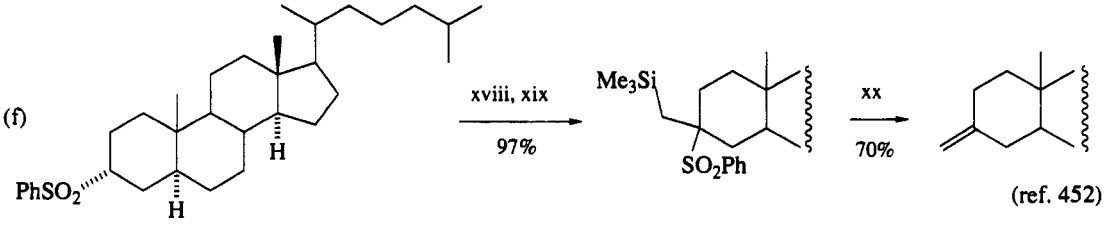
(e)



(ref. 487)

R = H, 82%; R = Me, 35%

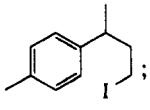
(f)



(ref. 452)

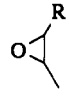
i, Bu^nLi, THF, –30 °C; ii, R^1X, 20 °C, 6–8 h; iii, Na/Hg, MeOH, 0 to 20 °C; iv, H_3O^+; v, H_3O^+;

vi, Et_3N, THF, H_2O; vii, Bu^nLi, THF; viii, R^1Br; ix, H^+; x, base; xi, Bu^nLi, THF; xii,



;

xiii, H^+; xiv, base; xv, Bu^nLi, THF; xvi,

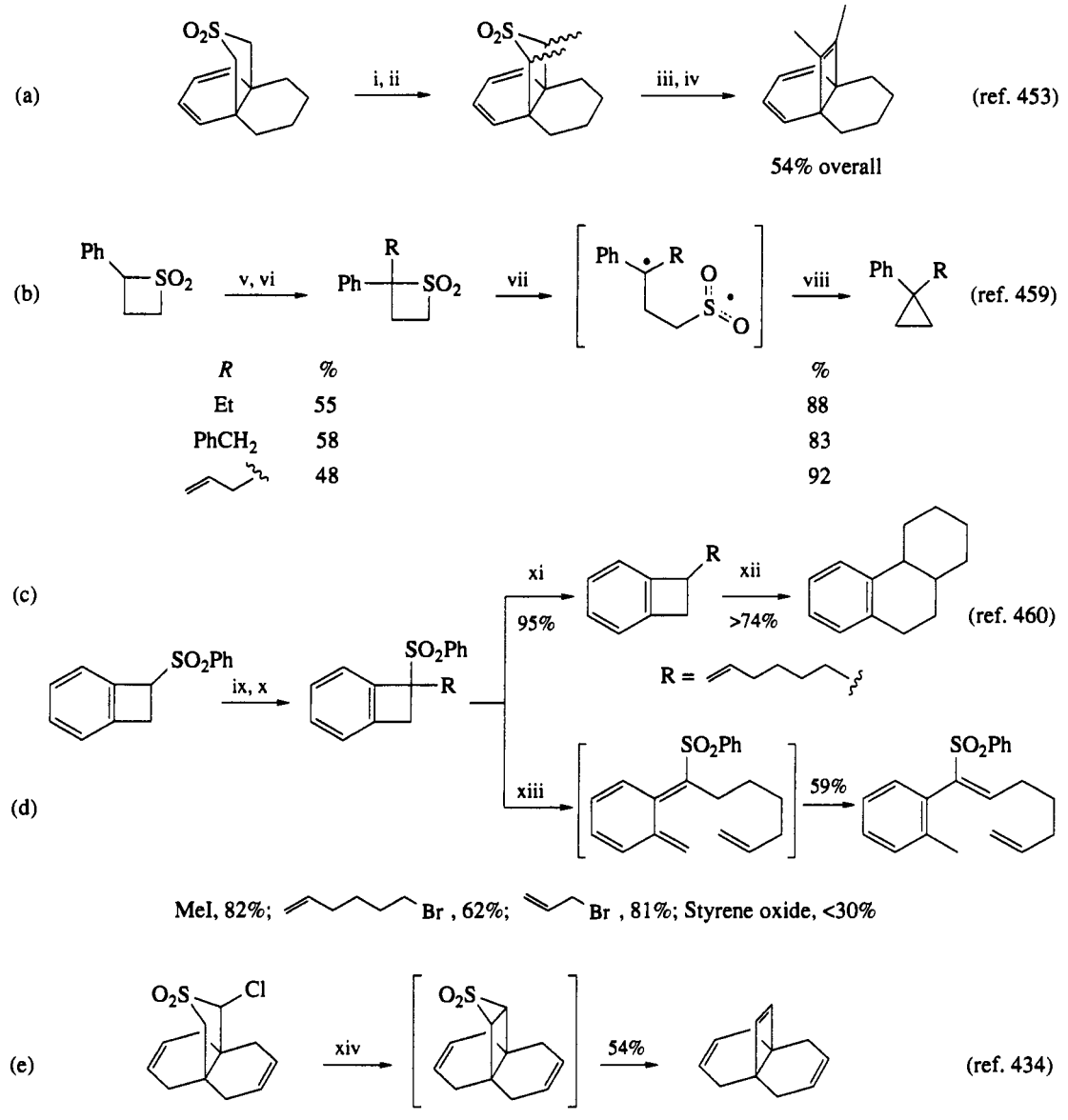


; xvii, Et_3N or DBU; xviii, Bu^nLi, THF, 0 °C; xix, Me_3SiCH_2I;

xx, $Bu^n{}_4NF$, THF, reflux

Scheme 106

Nonfunctionalized alkenes such as terminal alkenes are not available on similar treatment of, for example, 2-sulfonylalkanes with bases. However, these have been obtained on alkylation of α-metallo sulfones with trimethylsilylmethyl iodide[452] and subsequent reaction of the resulting β-silyl sulfone with



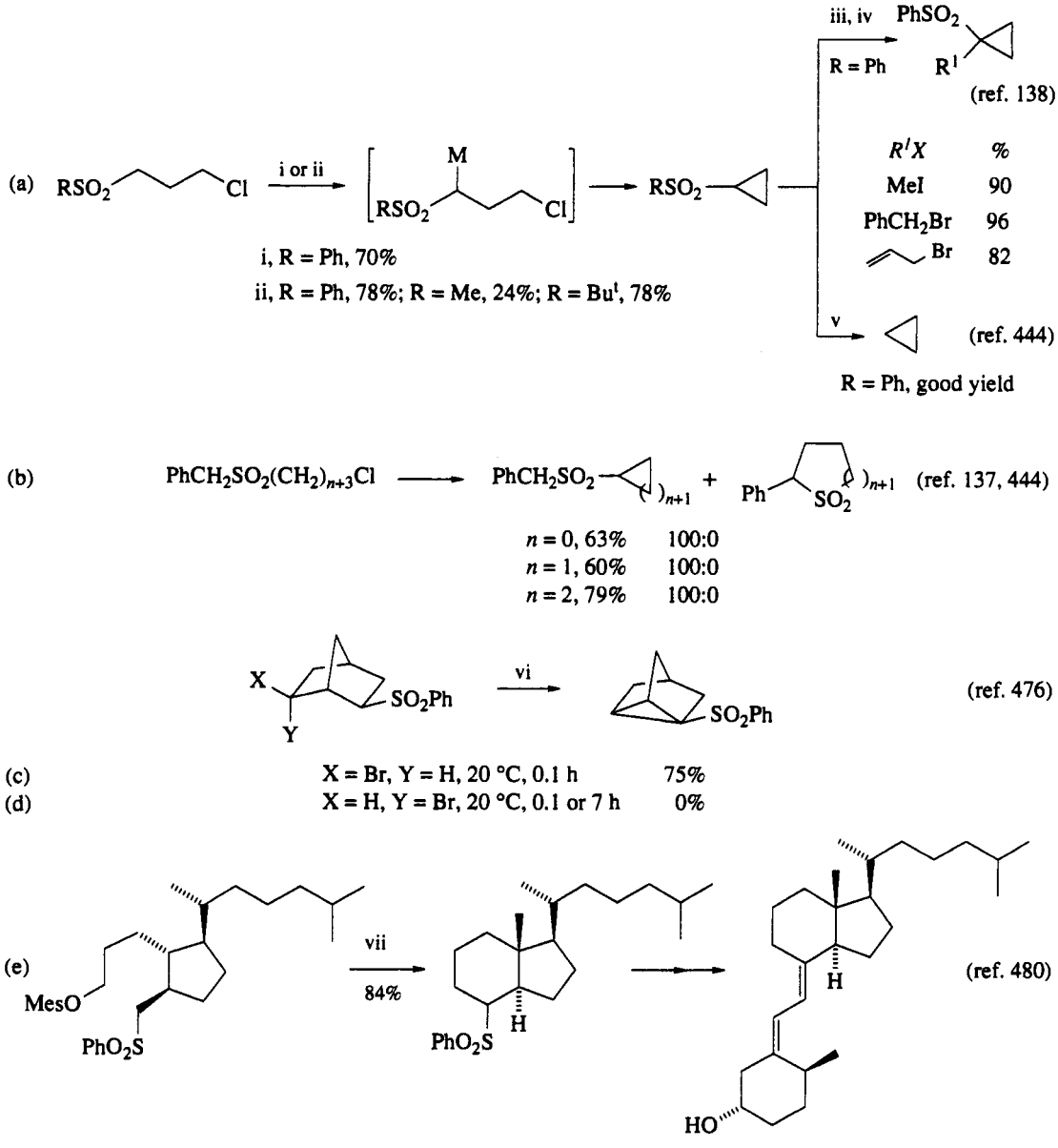
i, 2 Bu^{n}Li, THF, –80 °C; ii, excess MeI; iii, Bu^{n}Li; iv, $LiAlH_4$, dioxane, Δ; v, Bu^{n}Li, Et_2O, –78 °C, 1 h; vi, RBr, –78 °C, then 20 °C, 2 h; vii, *hν* (254 nm), CH_2Cl_2; viii, $-SO_2$; ix, MeLi, THF, –78 °C; x, RX, –78 to 20 °C, <1 h; xi, Na/Hg, MeOH, $NaHPO_4$; xii, 250 °C, 24 h; xiii, 250 °C, c-C_6H_{12}, 20 h; xiv, Bu^{t}OK, THF, 0 °C, 5 h

Scheme 107

fluoride ion (Scheme 106, entry f). A related procedure involving the alkylation,[452] the allylation,[452] and the reaction of α-metallo-β-(trimethylsilyl)alkyl phenyl sulfones with epoxides[471] allows the synthesis of 1-alkenes,[452] 1,4-dienes[452] and cyclopropyl sulfones[471] respectively.

Extrusion of sulfur dioxide from the products resulting from the alkylation of tetrahydrothiophene 1,1-dioxides[453,472] and the 2-phenylthietane 1,1-dioxides,[459] using *n*-butyllithium and lithium aluminum hydride[453] or photochemically[459] leads to the synthesis of the corresponding cyclobutenes[453] and cyclopropanes,[459] respectively (Scheme 107, entries a and b).

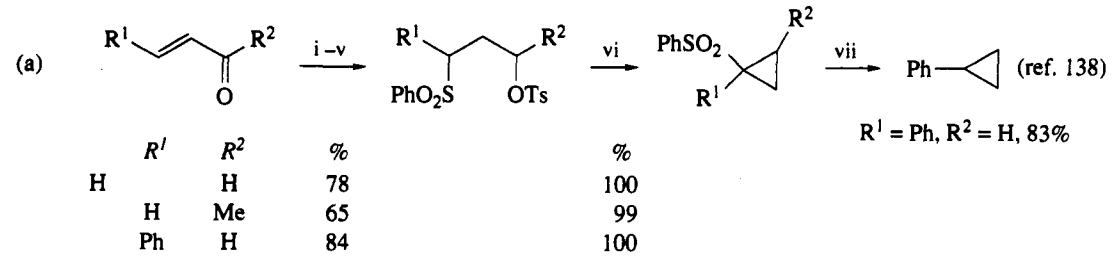
Internal alkylation takes place on reaction of α-haloalkyl alkyl sulfones with bases and produces episulfones as intermediaries. These intermediates are usually unstable and provide alkenes by thermal extrusion of sulfur dioxide. This reaction, known as the Ramberg–Bäcklund rearrangement, has been widely used in synthesis and has been thoroughly reviewed (Scheme 107, entry e).[36,38,434,473]

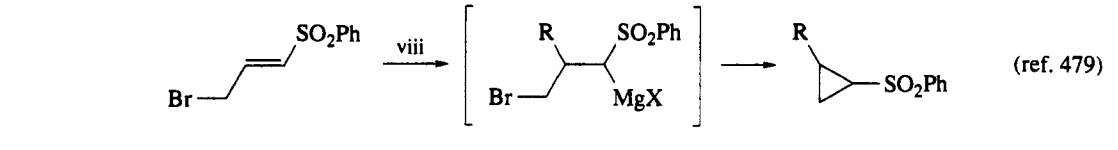


i, Bu^tOK, Bu^tOH, Δ, 6 h; ii, $NaNH_2$, DME, 60 °C, 2 h; iii, Bu^nLi, THF; iv, R^1X, 0 °C; v, Raney Ni, EtOH; vi, Bu^tOK, DMSO; vii, LDA, THF, –78 to 20 °C

Scheme 108

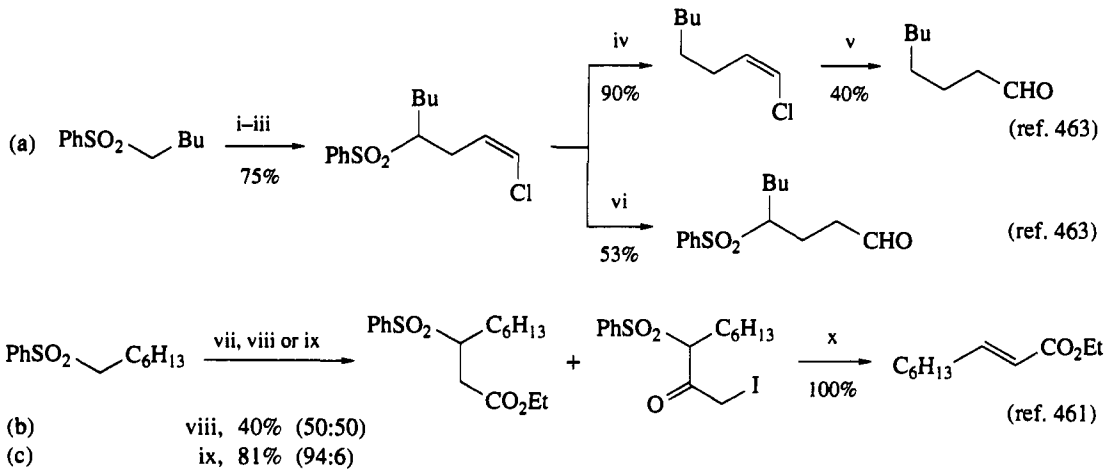
Treatment of γ-halo[444,474,475] or γ-tosyloxy sulfones[138] with base results in their conversion to cyclopropyl sulfones in good yields (Scheme 108; Scheme 109).[35,37,138,450,475] The base/solvent systems that have been used in this reaction include Bu^tOK/Bu^tOH,[442,475] $NaNH_2$/glyme (but not $NaNH_2$ in ether),[444] LDA/THF[138] and Bu^nLi/THF (Scheme 108, entry a; Scheme 109, entry a).[474] Treatment of the *exo* bromide shown in Scheme 108 (entry c) with base results in the rapid formation of the sulfonyl quadricyclane,[476] while the *endo* bromide, whose carbanion cannot assume the suitable semi-ω conformation in the transition state,[477] does not cyclize under similar or even forcing conditions (Scheme 108, compare entry d to c). Alkylation, benzylation or allylation of the resulting cyclopropyl sulfone has in turn been performed successfully[138] (Scheme 108, entry a). Its reduction to cyclopropane was achieved[138] with Raney nickel (Scheme 108, entry a). Cyclopropyl and cyclopentyl phenyl sulfones have been obtained directly[478] from (phenylsulfonyl)methylenedilithium and 1,2-dichloroethane and 1,4-diiodopentane, and from related ferrocenyl species and dichloroethane (Scheme 111, entry b).[465] *trans*-2-Substituted-cyclopropyl sulfones have been produced in up to 80% yield by addition of allylic, propargylic, aryl and

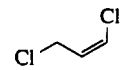




i, PhSNa; ii, $NaBH_4$; iii, H_2O_2, HOAc; iv, K_2CO_3, MeOH; v, TosCl, pyridine; vi, LDA, THF; vii, Na/Hg; viii, RMgX

Scheme 109

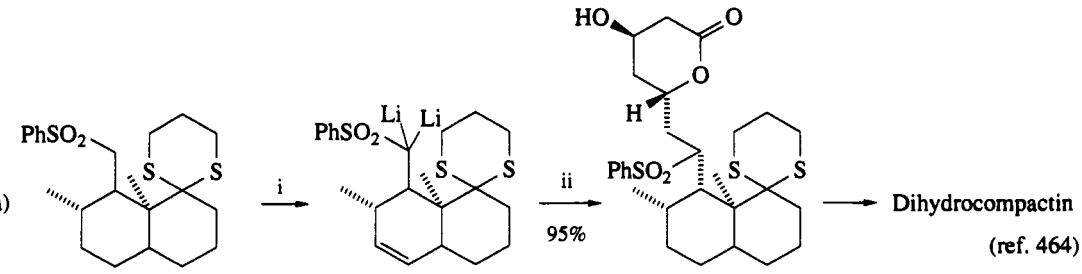


i,Bu^nLi, THF, –78 °C; ii, CuI, –25 °C, 1 h; iii,  , THF, 24 h; iv, Na/Hg, MeOH, 0 °C; v, HgOAc, 65 °C, 60 h; vi, HgOAc, 60 °C, 60 h; vii, Bu^n Li, THF; viii, ICH_2CO_2Et, THF; ix, ICH_2CO_2Et, THF–HMPA (10%), KI; x, Na_2CO_3, EtOH, reflux, 5 h

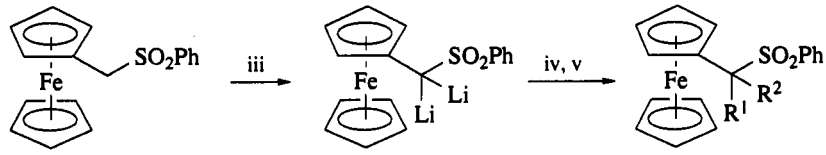
Scheme 110

benzyl Grignard reagents to 3-bromo-1-(phenylsulfonyl)-1-propene (Scheme 109, entry b).[479] Unfortunately however, alkyl Grignard reagents do not lead to the corresponding cyclopropyl sulfones (Scheme 109, entry c).[479]

Cyclobutyl,[137] cyclopentyl[137] and cyclohexyl[137,480] aryl sulfones can also be prepared by the analogous cyclization involving the corresponding halo[137] or sulfonyloxyalkyl sulfones (Scheme 108, entries b and e).[480] This reaction has been used as a key step in the stereoselective synthesis of de-A,B-cholestanes

(a) 

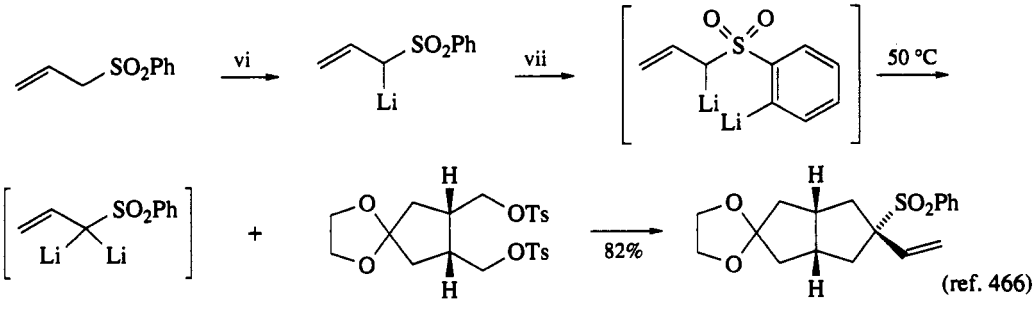
(ref. 464)

(b) 

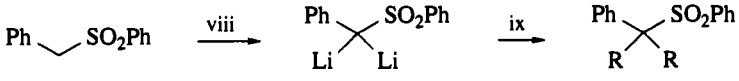
(ref. 465)

RX = MeI; $R^1 = R^2$ = Me; 74%

RX = Cl⌒Cl ; R^1,R^2 = $-CH_2CH_2-$; 89%

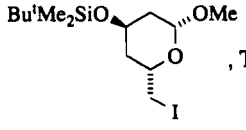
(c) 

(ref. 466)

(d) 

(ref. 467)

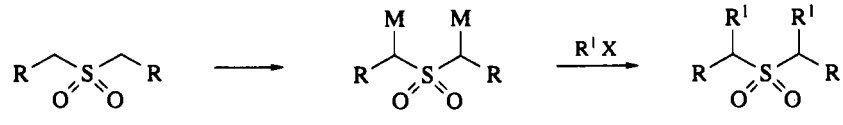
BuI, 72%; $PhCH_2Cl$, 83%

i, 2 BuLi, THF, 20% HMPA, 0 °C, 0.5 h ; ii, 

, THF, –78 °C to 20 °C, 4 h;

iii, 2 BuLi, THF, 20 °C, 0.5 h; iv, 2 RX, reflux, 0.5 h; v, H_3O^+; vi, Bu^nLi, THF; vii, Bu^nLi, low temp.; viii, 2 Bu^nLi, THF, 1 h; ix, 2 RX, THF, reflux, 24 h

Scheme 111



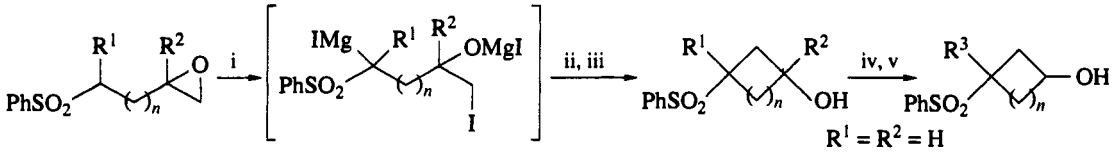
(a) R = H; $NaNH_2$, NH_3 or Bu^nLi, THF — 2 BuBr; 44% (ref. 438)

(b) R = Ph; KNH_2, NH_3 — 2 $PhCH_2Cl$; good yield (ref. 437)

Scheme 112

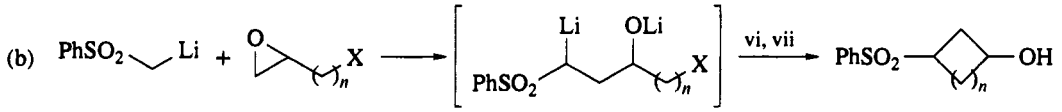
(Scheme 108, entry e). When the possibility of forming rings of different size exists, the product of cyclization is controlled by ring size and not by the acidity of the potential carbanion sites as in sulfides (compare scheme 108, entry b to Scheme 14, entry e).[137,444]

α-Metallo-alkyl or -benzyl sulfones[294,443,460,470,478,481–484] and also triflones[483] have been reacted with a large variety of terminal epoxides (Scheme 104, entry c)[294,443,458,460,478,483,484] and with α,β-di[470,483] and tri-substituted epoxides[483] (Scheme 106, entry e) including allylic epoxides[481] and those which are part of the alkyl side chain of the sulfone (Scheme 113).[482,485,486] The reactions often require heating (45 to 65 °C) for a prolonged period[483] but take place under milder conditions when dilithio derivatives are

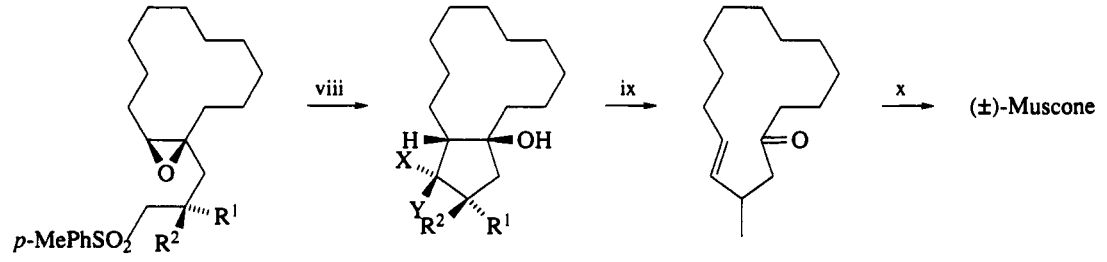


(a)

n	R^1	R^2	%	*n*	R^3	%
1	H	H	96	1	Bu	68
1	H	Me	51	1	Pr^i	71
1	Ph	H	98	1	Bu	88
2	H	H	75	2	Ph	76



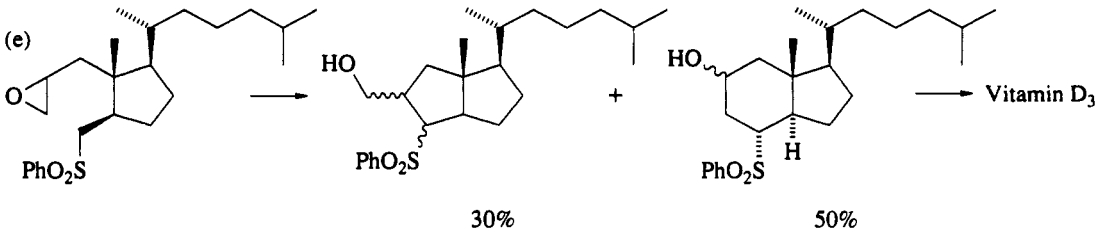
X	Cl	Br	Br
n	1	2	3
%	80	84	64



(c) R^1 = Me, R^2 = H, X = H, Y = SO_2Ph, 83% 73% *(E):(Z)* = 100:0

(d) R^1 = H, R^2 = Me, X = H, Y = SO_2Ph, 64% 62% *(E):(Z)* = 50:50

X = SO_2Ph, Y = H, 21% 55% *(E):(Z)* = 50:50



i, MeMgI, THF, –70 °C, then 20 °C; ii, cyclization; iii, H_3O^+; iv, 2 MeLi, THF; v, R^3Br; vi, cyclization; vii, H_3O^+; viii, $NaNH_2$, toluene, reflux, 5–10 h; ix, Bu^tOK, HMPA, toluene, 12 °C, 6 h; x, H_2 (catalyzed)

Scheme 113

used instead.[294,380] The sequence has been used[481] in conjunction with reduction of the sulfonyl group on the resulting γ-hydroxysulfone *inter alia* for the synthesis of diastereoisomers of (±)-labda-7,14-dien-13-ol[484] isolated from *Aster spathulifolins* Maxim, debromoplysiatoxin[294] and aplysiatoxin[294] from α-sulfonyl dianions and of 24-hydroxycholestane derivatives (Scheme 104, entry c).[443]

Using 3-(phenylsulfonyl)orthopropionate and epoxides, Ghosez *et al.*[487] have described a practical synthesis of 6-alkyl, 6,6-dialkyl and 5,6-dialkyl α,β-unsaturated-δ-lactones, and this reaction has been used in a synthesis of argentilactone (Scheme 106, entry e).[487]

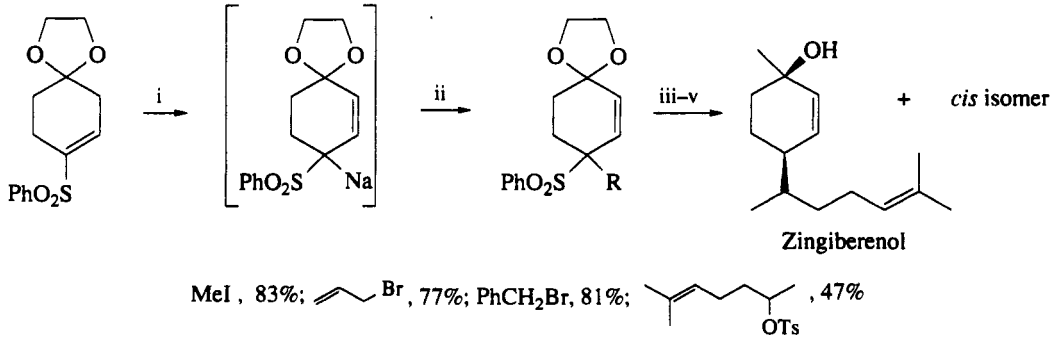
3,4-Epoxybutyl and 4,5-epoxypentyl sulfones react with about 2 equiv. of methylmagnesium iodide in THF to give 3-phenylsulfonyl-cyclobutanols and -cyclopentanols in good to excellent yields (Scheme 113, entry a).[486]

The cyclization reaction does not apparently take place on the epoxide ring, but instead occurs on the β-oxido alkoxide resulting from the epoxide ring opening.[486] The synthesis of both γ-sulfonyl-cyclobutanols and -cyclopentanols could also be achieved in 'one pot' sequentially from α-lithioalkyl phenyl sulfones, ω-bromo-1-oxidoalkenes and butyllithium,[486] or even more expediently and in higher yield from the 1,1-dilithioalkyl sulfones and the same electrophile.[478] The last reaction, which was found to take place chemoselectively on the epoxide ring has been successfully extended to the synthesis of 3-phenylsulfonylcyclohexanol (Scheme 113, entry b).

Application of the above mentioned epoxy sulfone cyclization reaction has been ingeniously used in a synthesis of muscone (Scheme 113, entries c and d)[485] and also of vitamin D_3 (Scheme 113, entry e).[482] In the latter case surprisingly the terminal epoxide, when subjected to the intramolecular cyclization gave a mixture of sulfonylcyclopentane and sulfonylcyclohexane derivatives arising respectively from the epoxide ring opening at the most (30%) and the least (50%) substituted carbons.[482]

1.3.6.2 Reactions Involving α-Metalloallyl Sulfones

α-Metalloallyl sulfones, which are readily available on metallation of allyl[202,448,481,488–504,506–508] or in a few cases, of 1-alkenyl[505] sulfones (Scheme 114), have proved to be the most valuable organometallics of this series. In almost all cases the alkylation,[488,489,499,505,506] the benzylation[488,495,505] and the allylation[490,491,493,494,497–502,504,505,507,508] as well as the reaction with epoxides[202,481] take place selectively at the α-position (Scheme 114; Scheme 115; Scheme 116) even if this site is already substituted by an alkyl group (Scheme 114; Scheme 115, entry c; Scheme 116; for one exception see ref. 496).[489,503,505]



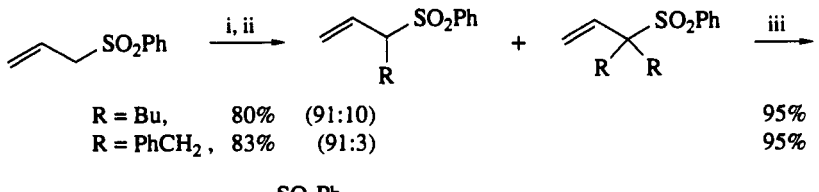
i, NaH, DMF; ii, RX; iii, desulfonation; iv, PPTS, acetone, NaOMe, MeOH; v, MeLi

Scheme 114

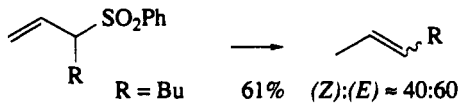
These results are particularly significant since mixtures of regioisomers are usually observed when related sulfoxides or sulfides are used instead (Sections 1.3.2.1.3 and 1.3.5.1.2). In the latter case, as already mentioned in Section 1.3.2.1.3, the presence of a heteroaryl group capable of chelation with the lithium salt is required in order to observe any α-selectivity comparable to that obtained with allyl sulfones.[16]

The methylation of the cyclohexenyl sulfone shown in Scheme 116 (entry a) proved most interesting in that equatorial attack predominates.[489] Such a result is quite surprising since a twist boat conformation leading to (**7**; Scheme 116, entry a) would be required as an initial product in order to maintain orbital overlap.[489] The stereochemistry resulting from the methylation of the bicyclic sulfones (**9**) and (**10**) is also most unusual (Scheme 116, entries b and c). Not only is the stereochemistry of the alkylation inde-

(a)



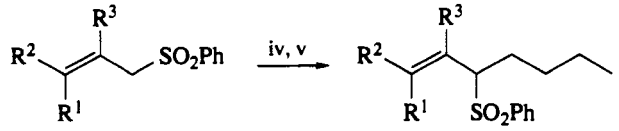
R = Bu, 80% (91:10) 95%
R = $PhCH_2$, 83% (91:3) 95%



R = Bu 61% *(Z):(E)* ≈ 40:60
R = $PhCH_2$ 26% *(Z):(E)* ≈ 40:60

(ref. 488)

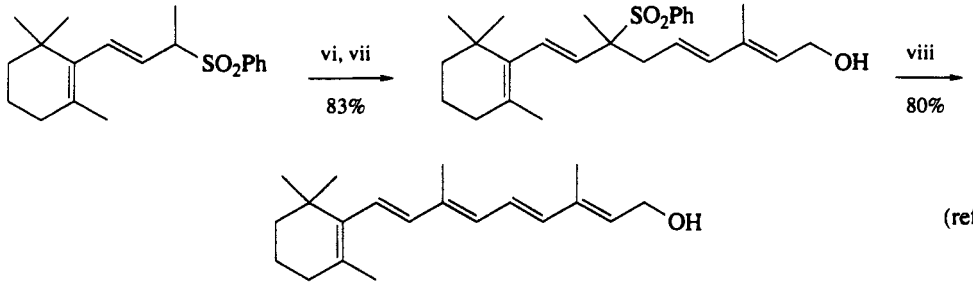
(b)



R^1	R^2	R^3	%
H	H	Ph	97
H	H	Me	88
Me	Me	H	73

(ref. 489)

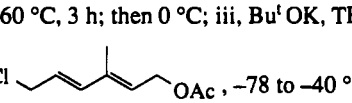
(c)



(ref. 503)

(E):(Z) = 38:52

i, Bu^nLi, THF, TMEDA, –60 °C; ii, RX, –60 °C, 3 h; then 0 °C; iii, Bu^tOK, THF, 20 °C, 3 h; iv, Bu^nLi, THF;

v, Bu^nI; vi, Bu^tOK, DMF, THF; vii, 

, –78 to –40 °C; viii, KOH, MeOH, reflux

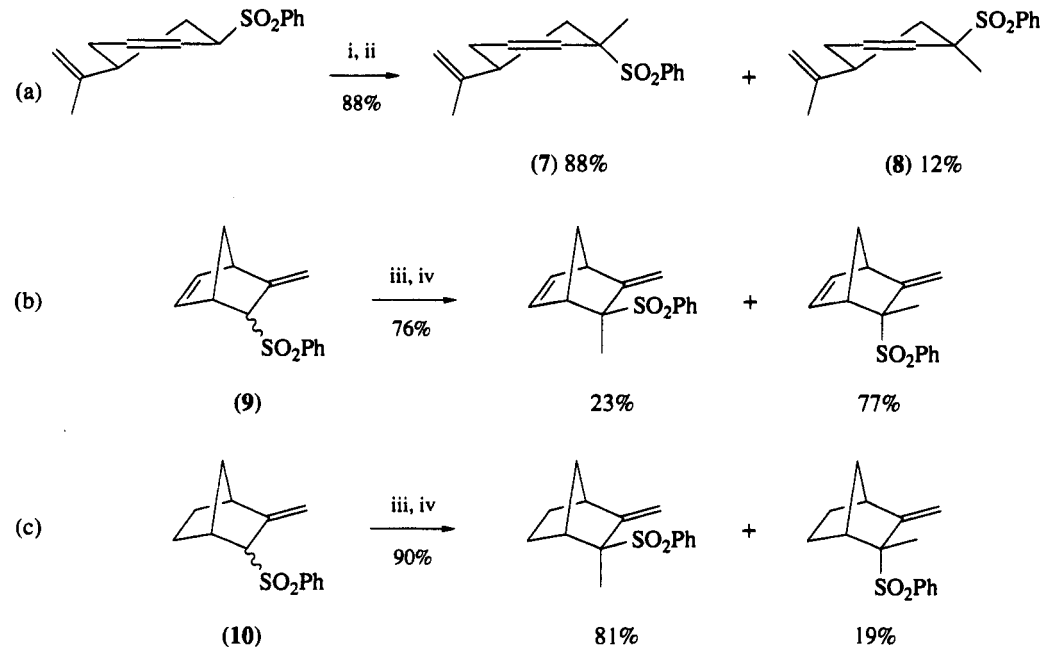
Scheme 115

pendent of the stereochemistry of the sulfone (**9**), but while the norbornenyl sulfone is mainly alkylated, as expected, from the least hindered *exo* face, the norbornyl system gives[489] predominantly *endo* attack in a contrasteric approach (Scheme 116, entry b).

Allyl sulfones have been used in a large number of valuable syntheses, but notably in the synthesis of alkenes, dienes and polyenes. Thus α-alkylallyl tolyl sulfones afford terminal alkenes regioselectively when treated sequentially with 2 equiv. of tin hydride and concentrated hydrochloric acid (Scheme 117, entry b).[509] Allyltin derivatives, which are intermediates in this transformation, can be isolated if the acidic treatment is omitted (Scheme 117, entry a).

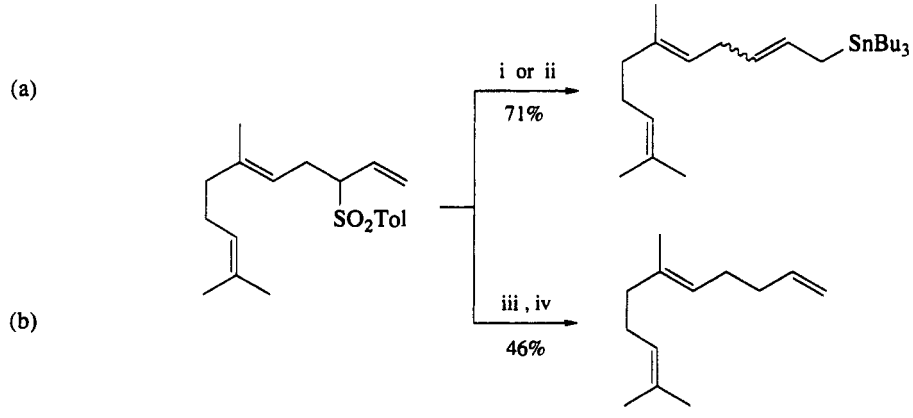
Allyl sulfones produce 1,3-dienes directly on sequential reaction with *n*-butyllithium and tri(*n*-butyl)stannylmethyl iodide.[492] Interestingly, the reaction is completely stereoselective as the (*E*)- or (*Z*)-1,3-dienes are obtained selectively from (*E*)- or (*Z*)-sulfones.[492] The procedure has been applied[492] to the synthesis of the major sex pheromone of the red bollworm moth. Ferruginol, which is a precursor of taxodione, a tumor inhibitory diterpene, has been prepared[495] by coupling of C_{10} units between 2-(phenylsulfonylmethyl)-1,3,3-trimethylcyclohexane and 3-isopropyl-4-methoxybenzyl bromide followed by desulfonation and acid-catalyzed cyclization. The same α-metallo sulfone also proved to be a valuable precursor of other alicyclic terpenoids, such as deoxytrisporone[499] and the methyl ester of vitamin A acid.[500] Allylation of related metalloalkyl sulfones followed by base-assisted desulfonation of the resulting sulfones has been used in several different syntheses of vitamin A[491,493,503,507] (selected syntheses of vitamin A using allylic sulfones are gathered in Scheme 118 and Scheme 115, entry c) as well as in syntheses of retinoic acid methyl ester,[508] of the 11-*cis*-locked cyclopentatrienylidene retinals,[490] and of carotenoids[498,502] including β-carotene.[502]

The allylation of α-metalloallyl sulfones followed by reduction of the carbon–sulfur bond, usually with lithium in ethylamine,[36,494,501,504,510] or with Na/Hg[501,506] (the first cited method being the most se-



i, LDA, THF; ii, MeI; iii, Bu^nLi, –78 °C, 0.7 h; iv, MeI, –78 to 20 °C

Scheme 116



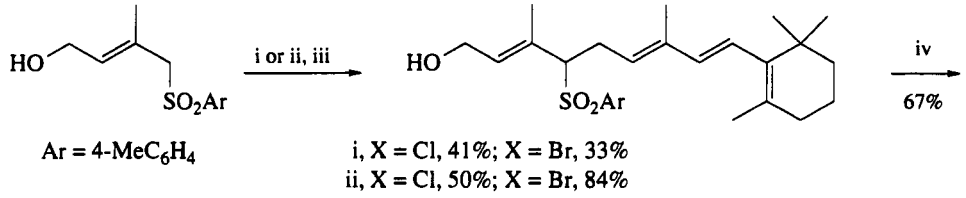
i, Bu_3SnH, AIBN, benzene, Δ, 2 h; ii, *hν*, 20 °C, 10 h; iii, Bu_3SnH, AIBN, Δ, 2 h; iv, conc. HCl, 20 °C, several hours

Scheme 117

lective one), has been used in stereoselective syntheses of squalene (Scheme 25, entry a),[506] bisgeranyl[506] and several polyprenols, including (*Z,Z*)-farnesol (*Z,Z,Z*)-nerylnerol,[504] solanesol[497,501] and a series of betulaprenols.[494] Related reactions involving allyl sulfones and α,β-unsaturated epoxides have also allowed the syntheses of linalol, (*Z*)-nerolidol and vitamin A (Scheme 119, entry a).[481]

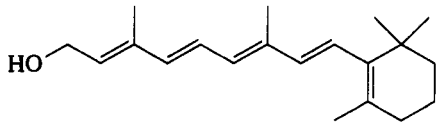
The α-lithioallylic sulfone (**11a**; Scheme 119, entry b) obtained upon deprotonation with *n*-butyllithium in THF–HMPA of the corresponding carbon acid undergoes smooth coupling with the epoxymagnesio alkoxide (**12a**) at –78 °C to give the β,γ-dihydroxy sulfone diol (**13**) in high yield. A facile coupling is also observed when the same epoxide (**12a**) is reacted with the related lithiated sulfide (**11b**). In contrast, the epoxy lithium alkoxide (**12b**) is only slowly attacked by the lithiated sulfide (**11b**), but not at all by the lithiated sulfone (**11a**).[202]

Stereoselective syntheses of (*E,Z*)- and (*E,E*)-conjugated dienes have also been performed, with alkylation of 3-sufolenes as the key step (Scheme 120; Scheme 121).

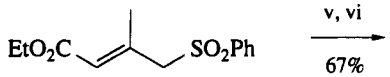


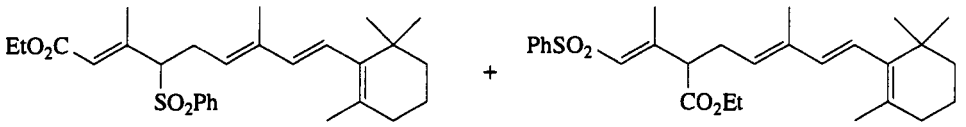
Ar = 4-MeC_6H_4

i, X = Cl, 41%; X = Br, 33%
ii, X = Cl, 50%; X = Br, 84%

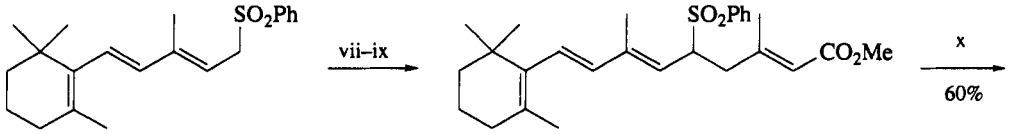


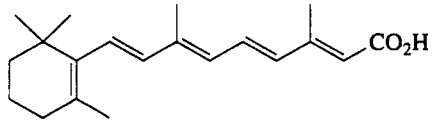
Vitamin A (ref. 493)



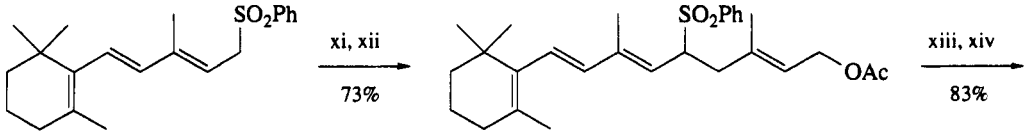


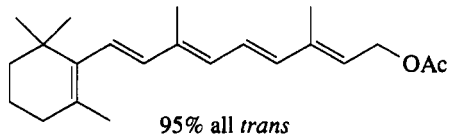
not isolated (ref. 507)



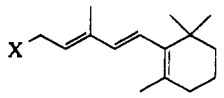


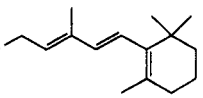
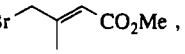
~60% (ref. 507)

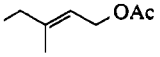




95% all *trans* (ref. 491)

i, 2Bu^{n}Li, –75 °C; ii, 2LDA, –75 °C; iii,  ; iv, $NaNH_2$, Bu^{t}OK, NH_3; v, Bu^{t}OK, THF;

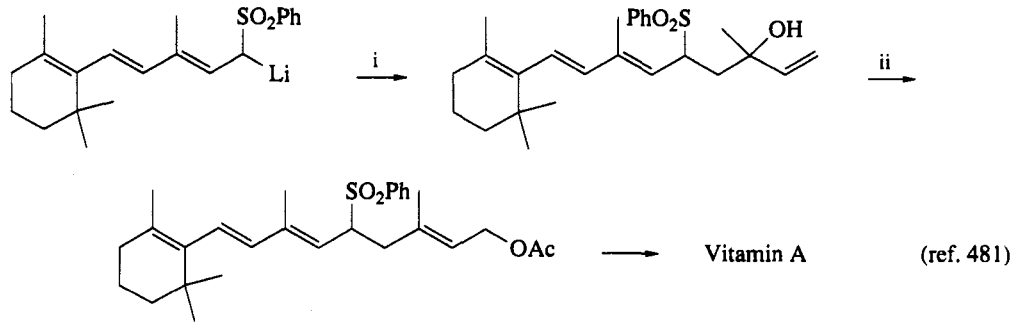
vi,  ; vii, 2Bu^{t}OK, THF, –65 °C; viii,  , –65 °C; ix, –65 to 20 °C;

x, KOH, MeOH; xi, NaH, DMF, –5 °C; xii,  , –10 °C, 0.3 h, then 10 °C, 0.2 h;

xiii, EtONa, EtOH; xiv, Ac_2O, Et_3N

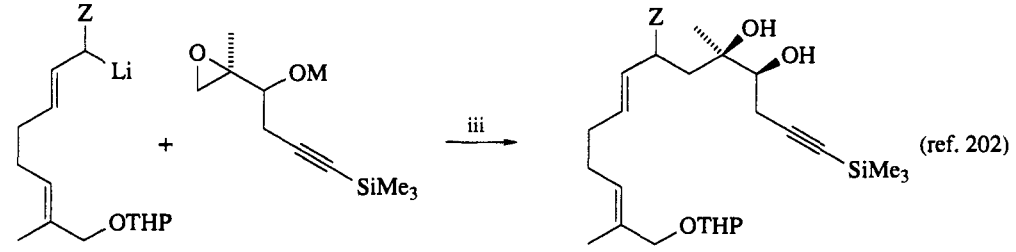
Scheme 118

(a)



(ref. 481)

(b)



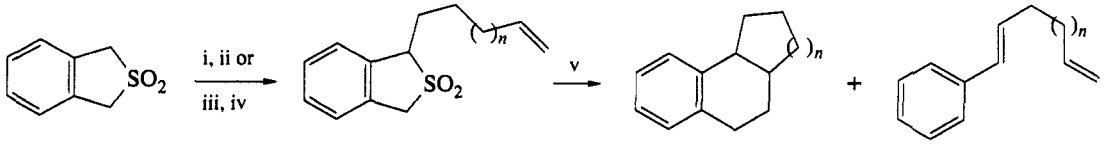
(ref. 202)

(11a) Z = SO_2Ph **(12a)** M = MgBr **(13)**
(11b) Z = SPh **(12b)** M = Li

(11a)	+ **(12a)**,	6 h,	70%
(11b)	+ **(12a)**,	0.5 h,	77%
(11a)	+ **(12b)**,	6 h,	9%
(11b)	+ **(12b)**,	0.5 h,	–

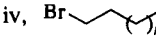
i,  , THF, –78 to 20 °C, 4 h; ii, AcOH, Ac_2O, TosOH, 0 °C, 3 h; iii, THF–HMPA, –78 °C

Scheme 119



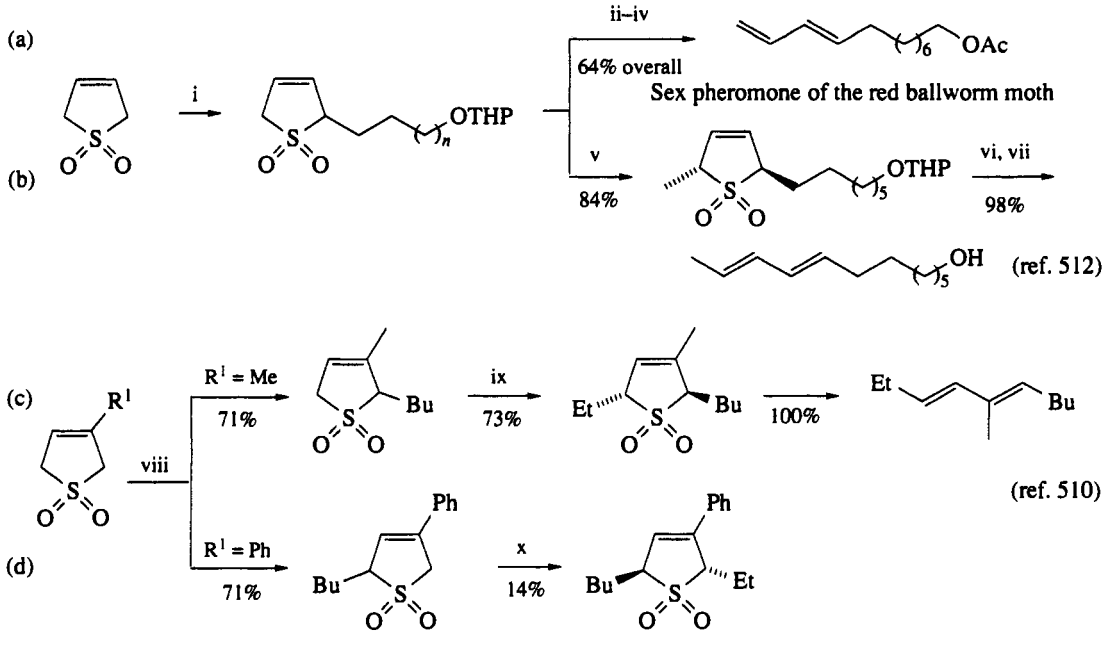
i, ii: n = 1, 76%; n = 2, 61%
iii, iv: n = 3, 52%

n = 1, 95% (90:10); n = 2, 87% (92:8)

i, LITMP, –78 °C, HMPA; ii,  , –78 to 0 °C; iii, BuLi, –78 °C;
iv,  , –78 to –10 °C; v, Δ

Scheme 120

Although the 3-sulfolene α-carbanion is labile it is possible to synthesize the mono- and the di-alkylated derivatives by performing the metallation in the presence of an alkylating agent.[511–513] The most successful conditions have used lithium hexamethyldisilazide in THF as the base in the presence of HMPA as the cosolvent.[511] The reactions proceed in reasonable yield with primary alkyl iodides, including functionalized ones, and also with benzyl iodides and lead to α-monoalkylated derivatives (Scheme 121, entry a). It is much less efficient with the corresponding bromides and does not occur with *s*-alkyl halides.[511,512] A remarkable directing effect of the substituent on the double bond of 3-sulfolene has been found in reactions with alkyl iodides[510,514] or allylic bromides.[513] Electron-donating groups effect selective substitution at the 2-position while electron-withdrawing groups effect exclusive substitution at the 5-position (Scheme 121, entries c and d).[510,514] Vitamin D–sulfur dioxide adducts can be alkylated regioselectively at either the 6-position when the adduct is treated with sodium hydride in the presence of an alkyl iodide,[515] or at the 19-position when the adduct is treated under similar conditions but with a stronger and more bulky base such as lithium tetramethylpiperidide.[515,516]



i, I$(CH_2)_n$OTHP, $(Me_3Si)_2NLi$, HMPA; ii, PPTS, MeOH, CH_2Cl_2 ; iii, Ac_2O, pyridine; iv, $NaHCO_3$, aq. EtOH, 125 °C; v, MeI, $(Me_3Si)_2NLi$, HMPA; vi, PPTS, MeOH; vii, K_2CO_3, aq. EtOH, 125 °C; viii, 0.5BuI, 0.5$(Me_3Si)_2NLi$, HMPA; ix, EtI, THF, HMPA; x, EtI, THF, HMPA, 7 °C

Scheme 121

The alkylation of 2-alkyl-substituted sulfolenes takes place with complete regio- and high stereo-selectivity to yield approximately 60% of *trans*-2,5-disubstituted 3-sulfolenes. When 1,4-diiodobutane[517] and 1,3-diiodopropane[517] are used instead, one-pot dialkylation occurs at the 2-position in the first case and leads to a spiro sulfolene, whereas 2,3-dialkylation proceeds in the second case leading to a fused bicyclic product. Interestingly 2,5-dialkylation has been achieved, from 3-bromo(bromomethylpropene), thus allowing the synthesis of bicyclo[3.2.1]sulfones.[517]

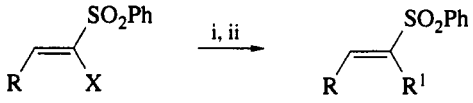
Sulfolenes are valuable precursors of 1,3-dienes. Thermolytic desulfonylations of 2,5-disubstituted derivatives lead exclusively to (*E,Z*)-dienes in agreement with the symmetry rules.[435] The stereoselectivity of the reaction is dramatically changed however by carrying out the reaction in a protic solvent and in the presence of a base (which probably isomerizes the *trans* sulfolene to the *cis* isomer), since (*E,E*)-dienes are now obtained exclusively and contrary to the symmetry rules.[435] α-Metallo sulfolenes may be viewed therefore as masked 1,3-dienyl anion equivalents ($^-$C=C—C=C—R). The above mentioned set of reactions has been used for the regioselective syntheses of 6- and 16-alkyl-substituted vitamin D_3 analogs,[515,516] as well as *trans*-β-ocimene[513] and α-farnesene.[513]

Related reactions have been reported by Oppolzer[457] from the benzosulfolene derivative shown in Scheme 120 which has proved to be a valuable precursor of *o*-quinodimethane, and by Bloch[518] from the corresponding cyclopentadiene–sulfolene adduct.

1.3.6.3 Reactions Involving α-Metallovinyl Sulfones

The alkylation of α-lithiovinyl sulfones, which are available by metallation[519,520] of vinyl sulfones or by bromine–lithium exchange[519] on α-bromovinyl sulfones, takes place efficiently when the β-carbon carries an aryl, a methyl or a methoxy group (Scheme 122, entries a, b and d). Surprisingly however the alkylation does not proceed with the β-alkoxymethyl-substituted derivatives (Scheme 122, entry c).[479]

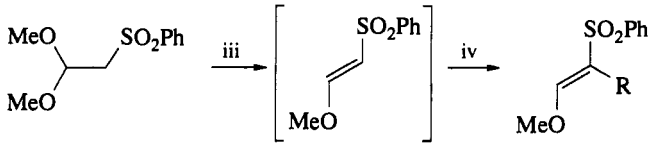
The chemistry of sulfoximides (sulfoximines)[62] is somewhat related to that of sulfones.[8,35–38] Although several methods are available for the preparation of free sulfoximines from di- and tri-valent sulfur compounds, the methods are of limited applicability when the desired sulfoximines contain labile functional groups. An alternative approach involving alkylating the readily available anion derived from *N*-substituted methylsulfoximides has been described[521] but preparation of the free sulfoximides has proved



(a) X = H; R = Ph, Me; R^1 = Me, Bu; 75–90%

(b) X = Br; R = Ph, Me; R^1 = Me; 75–90%

(c) X = H; R = CH_2OLi; R^1 = alkyl; 0%

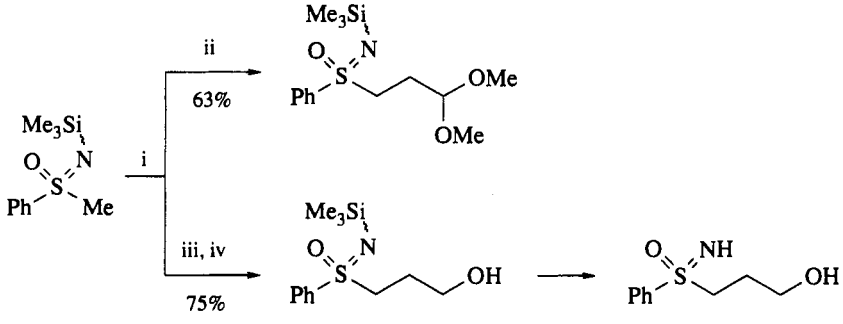


RX = MeI, 88%; RX = $PhCH_2Br$, 77%

i, MeLi, THF, –95 °C; ii, R^1I; iii, Bu^nLi; iv, Bu^nLi, RX

Scheme 122

difficult.[522] These compounds have in fact been synthesized on reaction of *S*-lithiomethyl-*N*-trimethylsilyl-*S*-phenylsulfoximide with alkyl halides or epoxides, followed by ready desilylation with bis(trimethylsilyl)acetamide (BSA) or (trimethylsilyl)diethylamine (Scheme 123).[522]



i, BuLi, THF, –78 °C; ii, $BrCH_2CH(OMe)_2$, HMPA, –78 to 20 °C, 16 h; iii, , –78 to 0 °C, 1 h; iv, H_3O^+

Scheme 123

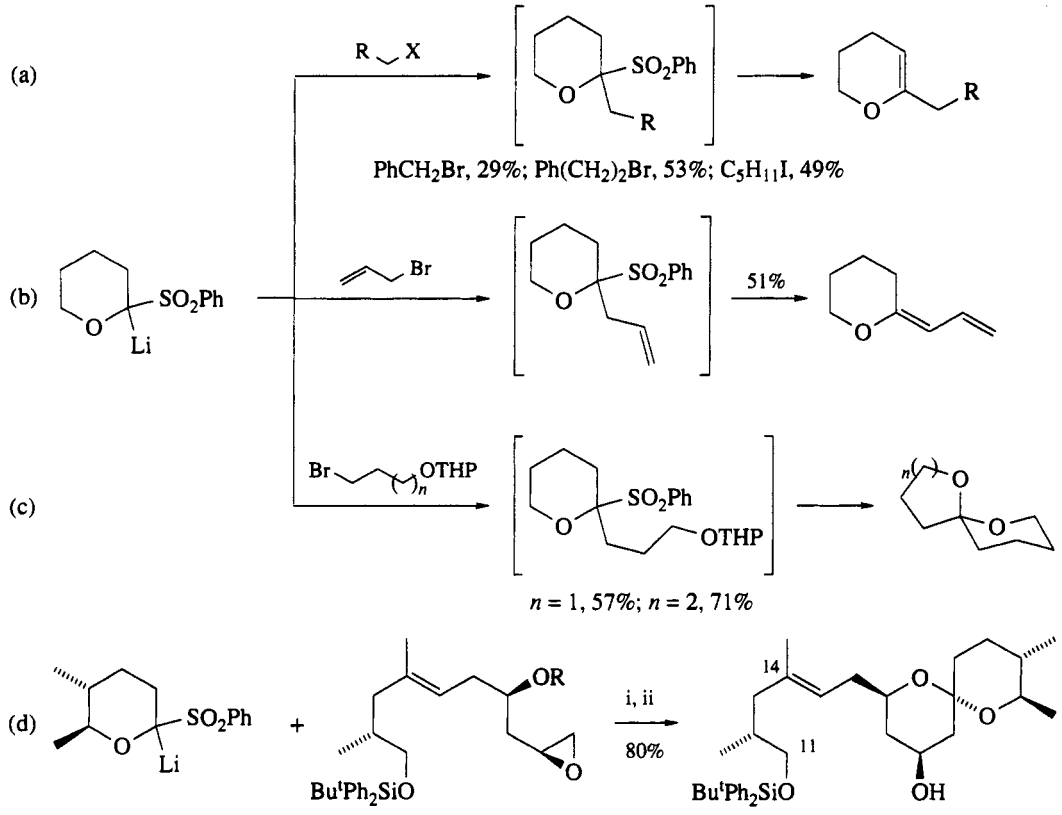
1.3.6.4 Reactions Involving α-Metallo-α-heterosubstituted Alkyl Sulfones

Alkylation reactions of α-metallo sulfones bearing another heteroatomic moiety at their α-site have been widely used in synthesis. These reactions include the alkylations of α-isocyanoalkyl sulfones[449,523,524] α-alkoxyalkyl sulfones[36,345,525–527] (including 2-benzenesulfonyltetrahydropyrans[527]) α-haloalkyl[528] or α-haloallyl[529] sulfones, α-silylalkyl sulfones,[530] α-sulfonylalkyl[380,531–535] and α-sulfonylalkenyl[536,537] or α-triflylalkyl[538,539] sulfones. Among these compounds alkoxyalkyl phenyl sulfones (Scheme 75, entries a and d)[36,345,526] and tosylmethyl isocyanide (TosMIC)[449,523,524] have been used as precursors of acyl anion equivalents, the latter being the most popular due to the ease with which it can be metallated.

1.3.6.4.1 Reactions involving 2-lithio-2-benzenesulfonyltetrahydropyrans

2-Lithio-2-benzenesulfonyltetrahydropyrans which are readily available on metallation (Bu^nLi, THF, 78 °C) of 2-benzenesulfonyltetrahydropyrans, have been alkylated[527a,b] with a large variety of organic halides including allyl (Scheme 124, entry a), alkyl and benzyl halides (Scheme 124, entry b) as well as with 3- or 4-(3-tetrahydro-2*H*-pyran-2-yl)oxy- or (*t*-butyldimethylsilyl)oxy-1-haloalkanes (Scheme 124, entry c). Benzenesulfinic acid is usually eliminated spontaneously from the intermediate alkylated products as the reaction warms to room temperature, presumably due to the slightly basic medium and the inherent leaving ability of the benzenesulfonyl group. The *endo* hydrogen is usually removed (Scheme

124, entry a), except with the allylated product, (Scheme 124, entry b) in which case the *exo* hydrogen is taken off selectively. Many of the resulting enol ethers undergo acid-catalyzed cyclization to spiroketals, which are found in many natural products (Scheme 124, entry c). This sequence of reactions has been used for the synthesis of several insect pheromones such as those derived from the olive fly *Dacus oleae* (Scheme 124, entry c)[527a,b] and the common wasp *Paravespula vulgaris*.[527a]

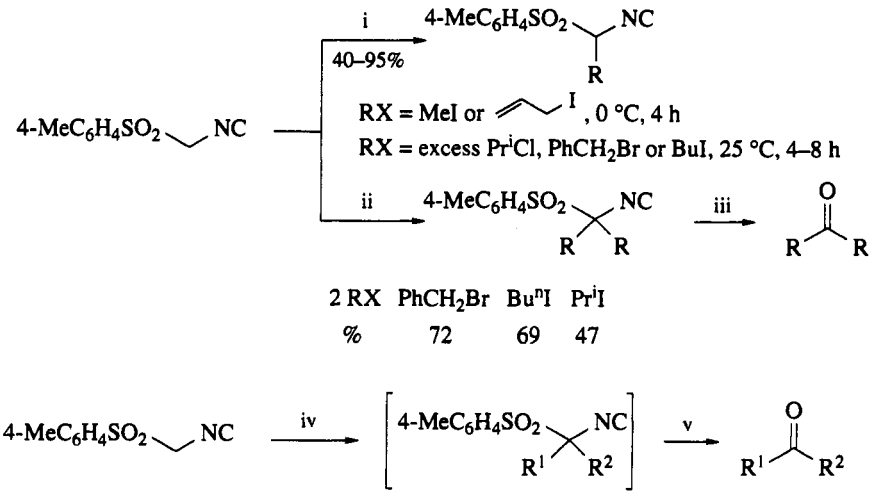


Scheme 124

2-Lithio-2-benzenesulfonyltetrahydropyrans also add[527c] to epoxides which contain additional oxygen functionality to permit, after acid hydrolysis, spiroketal formation. The whole process, which is an extremely rapid and efficient entry to hydroxy substituted spiroketals, has allowed the synthesis of a minor component of the insect pheromone derived from the olive fly *Dacus oleae*[527c] as well as of the C-11 to C-25 fragment of the milbemycins which are potent antiparasitic agents (Scheme 124, entry d). In the latter case the epoxide ring opening was carried out in the presence of titanium isopropoxide. In all of these reactions the lithio sulfones behave as the equivalents of 2-lithiodihydropyrans, but with the added advantage that the initial sulfones are stable, crystalline and easily handled materials.

1.3.6.4.2 Reactions involving α-isocyanoalkyl sulfones

TosMIC can be efficiently alkylated with primary alkyl halides, isopropyl iodide and benzyl bromide both to the corresponding mono-[523] or di-alkyl[449] derivatives using NaH in DMSO or 40% aq. NaOH in CH_2Cl_2[449,523] and in the presence of Bu^n_4NI (Scheme 125). The resulting compounds have then been transformed to aldehydes and ketones, including cycloalkanones,[449] and the method has been successfully applied to the synthesis of optically active 2-methylcyclobutanone from the chiral sulfonylmethyl isocyanide and 1,3-dibromobutane.[524]



i, aq. NaOH, CH_2Cl_2, Bu^n_4NI, RX; ii, aq. NaOH, CH_2Cl_2, Bu^n_4NI, 2RX; iii, 38% HCl; iv, aq. NaOH, CH_2Cl_2, Bu^n_4NI, R^1I, 0.5 h, then R^2I; v, 38% HCl

Scheme 125

1.3.6.4.3 Reactions involving α-sulfinyl sulfones

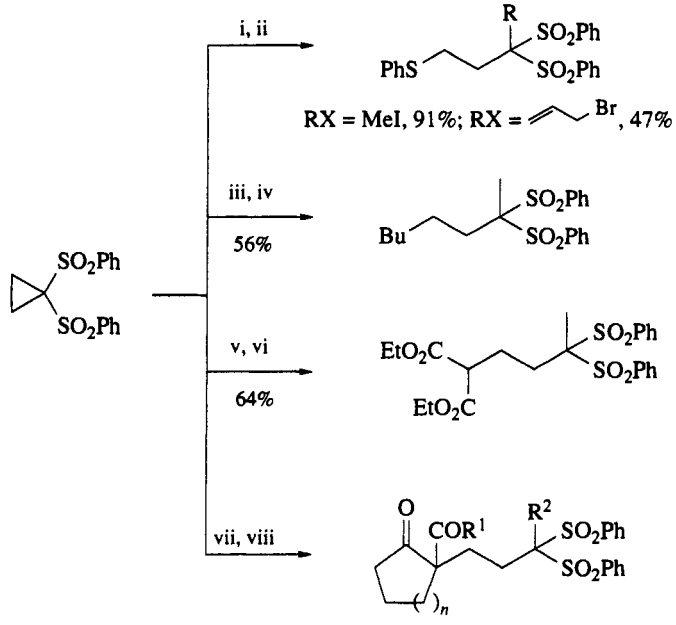
1,1-Disulfones have been increasingly used in synthesis over the last decade. Their alkylation takes place smoothly and has allowed a large variety of synthetically useful reactions (Scheme 127; Scheme 128; Scheme 129).[380,531,532,535–537] Although most of the alkylations have been carried out *via* metallation of the corresponding carbon acid (see below), some of the alkylations have been performed[540] on the sodium, potassium or copper salts derived from the ring opening of 1,1-di(benzenesulfonyl)cyclopropane, performed with a variety of nucleophilic reagents (Scheme 126).

These nucleophilic reagents include thiolates, alkoxides, metallo amides, Grignard reagents in the presence of copper salts, and enolates.[540] The reductive cleavage of the sulfonyl moiety in protic media, which can be readily achieved by lithium phenanthrenide, offers the opportunity to pursue further carbanionic chemistry. Therefore this new conjunctive reagent[540] can serve as the equivalent of species such as $^+CH_2CH_2CH_2^-$ and $^+CH_2CH_2CH^{2-}$ as well as $^+CH_2CH_2C^{3-}$. Furthermore, homoallyl and allyl disulfones have proved valuable precursors of 1,3-dienes[537] and (*E*)-alkenes,[536] respectively (Scheme 127, entries a and b). The former derivatives have been produced stereoselectively by allylation of 1,1-di(sulfonyl)methane with (*Z*)- or (*E*)-allyl halides and they can be transformed to the corresponding (*Z*,*E*)- or (*Z*,*Z*)-1,3-dienes respectively by a sequence of reactions which involves the reduction of one of the two sulfonyl groups, followed by the elimination of the remaining one (Scheme 127, entry a).[537]

This route to 1,3-dienes is more efficient than the more direct one employing homoallyl sulfones.[537] 1,1-(2-Alkenyl) disulfones display[536] only (*E*)-geometry, whereas corresponding monosulfones are difficult to isolate at the same level of stereochemical purity (*i.e. ca.* 20% of the (*Z*)-isomer at equilibrium). Alkylation, which can be readily achieved in the presence of NaH in DMF, takes place predominantly at the α-position, but less selectively than with the corresponding monosulfone (α:γ ratio 90:10 instead of 100:0) probably due to the steric hindrance of the two bulky sulfonyl groups (Scheme 127, entry b). The product resulting from the α-alkylation leads quantitatively to the (*E*)-allylic sulfone on reduction with aluminum amalgam (Scheme 127, entry b)[536] or to (*E*)-alkene upon total reduction by lithium in ethylamine.[536]

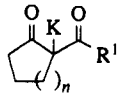
1,1-Disulfonyl-cycloalkanes[534,535] and -cycloalkenes[380,531] have been synthesized by treatment of ω-halo-alkyl- or -alkenyl 1,1-disulfones with sodium ethoxide in ethanol or from 1,1-di(sulfonyl)methylmetals and 1,4-dihalo-(2*Z*)-alkenes, respectively (Scheme 127, entry c; Scheme 128, entry a).

The rate of cyclization of the 1,1-di(phenylsulfonyl) carbanion bearing distal leaving groups has been determined[534,535] and proved to be very sensitive to the ring size. For iodides in ethanol the ratios for ring size 3:4:5:6:7 are $1:1.1 \times 10^{-5}:1.0 \times 10^{-2}:1.6 \times 10^{-6}:1.6 \times 10^{-6}:7.3 \times 10^{-10}$. The contribution of strain in the product to the enthalpy of activation is slight, whereas the entropy of activation for cyclopropane formation is so favorable as to make this by far the most rapid process observed.[534,535] 1,1-Di(sulfonyl)cy-



R^1	OMe	OMe	OMe	OMe	OMe	Me
R^2	Me	Me	Me	Me	X	Me
n	1	2	4	8	2	2
%	86	86	70	74	86	70

i, PhSNa, DMF; ii, RX; iii, Bu^nMgBr, $CuBr{\cdot}SMe_2$, THF, 0–10 °C; iv, MeI, HMPA; v, $KCH(CO_2Et)_2$; vi, MeI;

vii,  , DMF, 90 °C, viii, R^2X

Scheme 126

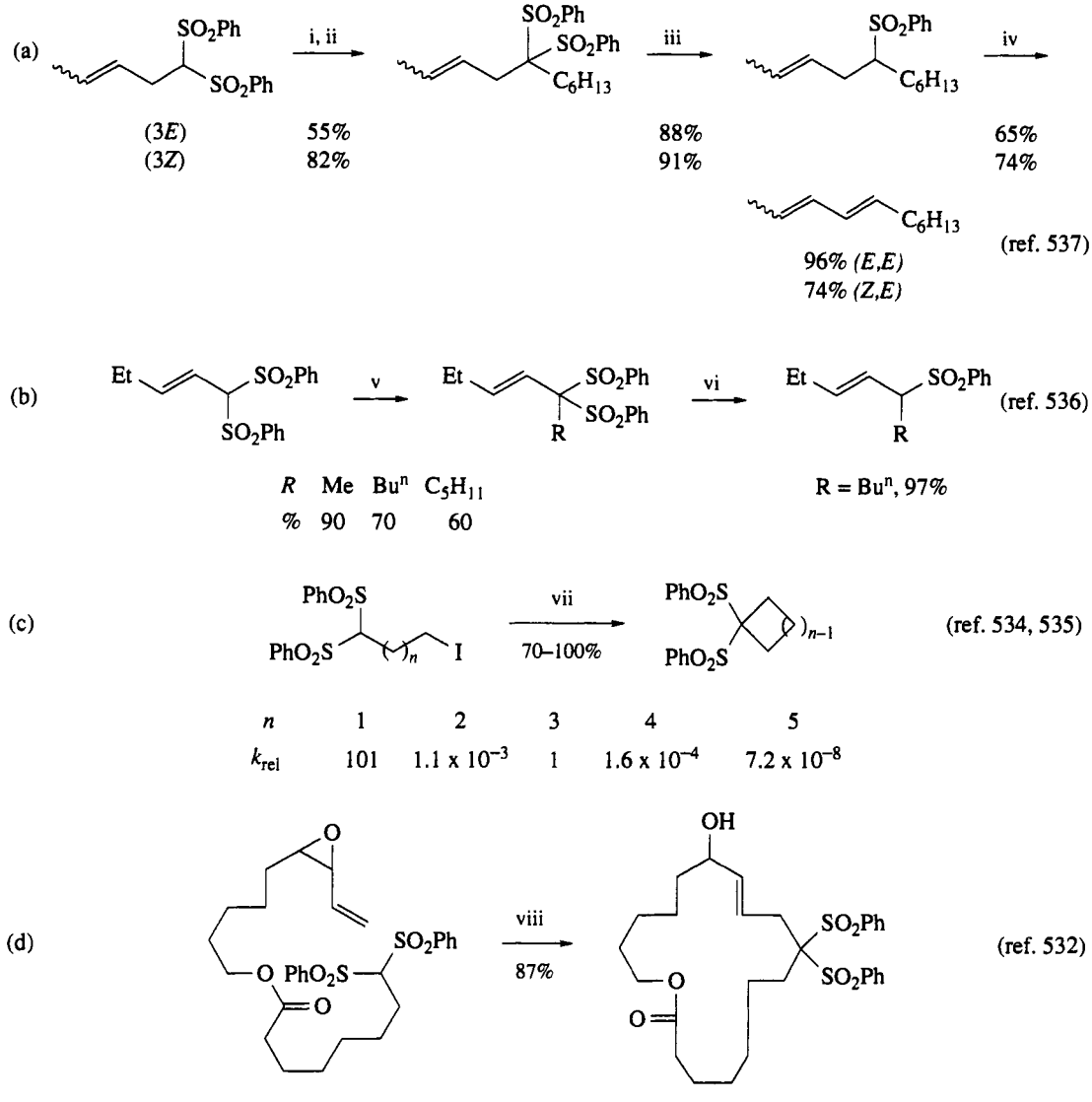
clopent-3-ene, produced from the allylation of di(sulfonyl)methane with 1,4-dihalo-2-alkenes, has been transformed selectively to cyclopentene and to 3-cyclopentenone derivatives by di-reduction (Na/Hg) or by sequential mono-reduction and oxidation α to the sulfonyl moiety (Scheme 128, entry a). Therefore 1,1-di(sulfonyl)methane plays the role of masked dimetallomethane and formyl dianion equivalents.[531]

1,1-Di(sulfonyl)alkanes have been reacted with allylic epoxides in the presence of polymerically bound transition metal catalysts.[532] This reaction has allowed the synthesis of macrolides in a sequence of reactions in which neither the nucleophilic nor the electrophilic centres are unmasked until the substrate encounters an active site on the polymer (Scheme 127, entry d). The sequence is completely regioselective since it occurs at only one (the terminal alkene) of the three potential active sites, and provides, in around 70% yield, a single 17- or 27-membered ring macrolide from the corresponding substrates.[39,532]

The alkoxydi(sulfonyl)methane shown in Scheme 128 (entry b) has been used as a useful carbonyl 1,1-dipole synthon (±C=O). Its alkylation with alkyl halides is best achieved using Cs_2CO_3 in DMF at 50 °C, and its palladium-catalyzed allylation requires the use of phase-transfer conditions (Scheme 128, entry b).[533] The unmasking of the carbonyl group was then achieved by reacting the resulting disulfone with boron trichloride (–78 °C, CH_2Cl_2) followed by the addition of alcohols or amines to provide esters or amides respectively (Scheme 128, entry b).[533]

Finally, α-triflyldimethyl sulfone ($CF_3SO_2CH_2SO_2Me$) is a reagent which allows successive polyalkylations of the CH_2 and CH_3 carbon centers with regiocontrol (Scheme 129). The polyalkylated triflylsulfones then undergo Ramberg–Bäcklund reactions with loss of triflinate anion and extrusion of sulfur dioxide to form alkenes (Scheme 129, entry e).[538,539]

In synthetic terms the net structural change is equivalent to regiospecific alkylation of tetrametalloethylene ($M_2C{=}CM_2$). The monoalkylated derivative is available on alkylation of the α,α-dilithio-



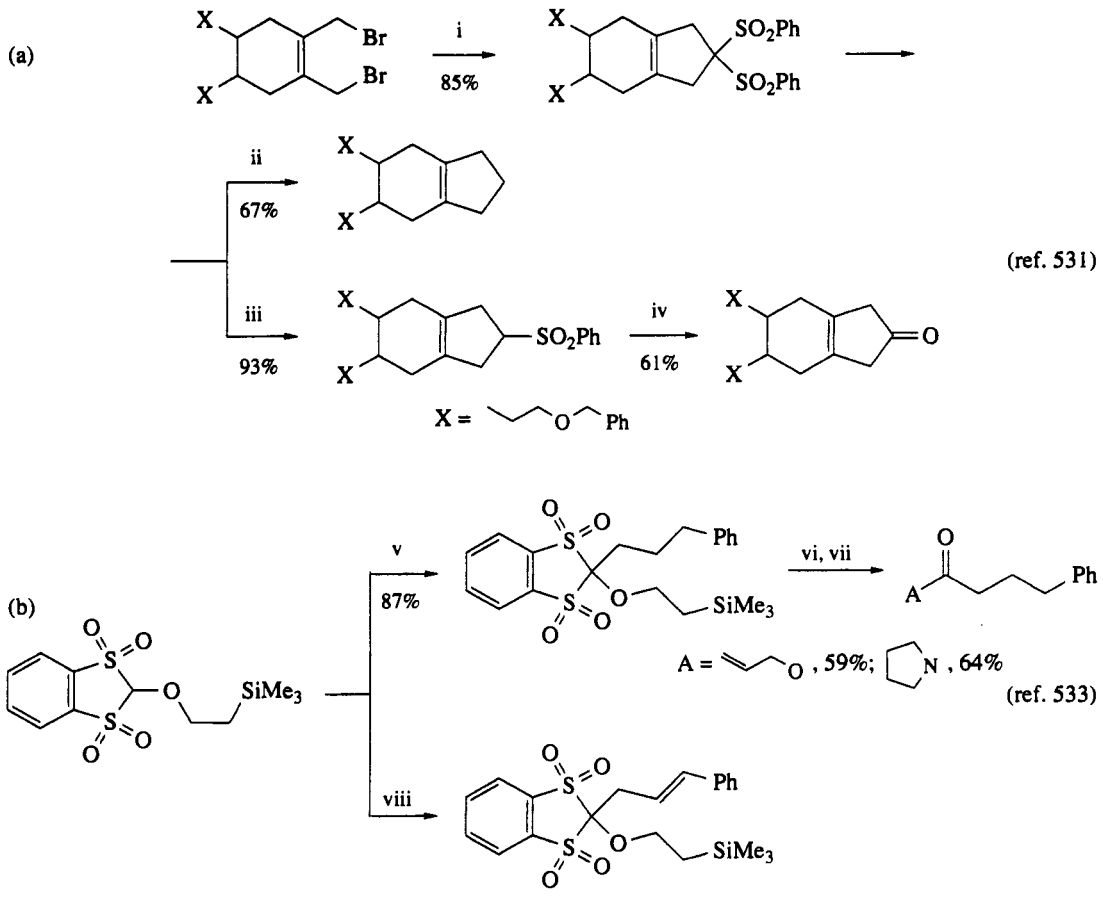
i, NaH, DMF, 80 °C, 5 to 15 h; ii, $C_6H_{13}I$; iii, Al/Hg, THF, H_2O, 20 °C, 1 h; iv, Bu^tOK, THF; v, NaH, DMF, 70 °C, RI; vi, Al/Hg, THF, 0 °C, 3 d; vii, 0.5 M EtONa, EtOH; viii, polymerically bound Pd, THF, 20 °C, 0.3 h

Scheme 127

methane derivative (Scheme 129, entry a), whereas the α,α′-dialkylated compounds can be selectively synthesized from the corresponding α,α,α′-trilithio compound (Scheme 129, entry b). Further alkylations of the above mentioned derivatives, as well as one example of alkene formation, are displayed in Scheme 129 (entries c, d and e).

1.3.7 ALKYLATION OF SULFUR YLIDES

Several examples of the alkylation of sulfur ylides are known.[41,541–544] This reaction is particularly useful for the synthesis of *s*-alkyl diphenylsulfonium salts which cannot otherwise be prepared from diphenyl sulfide, *s*-alkyl iodides and silver tetrafluoroborate, since the latter reaction usually leads to a mixture of regioisomeric sulfonium salts.[41] Diphenylsulfonium methanide on reaction with [^{14}C]methyl iodide allows the synthesis of [^{14}C]isopropyl diphenyl sulfonium salt which has been used for the synthesis of [^{14}C]-2,3-epoxysqualene[545] (Scheme 130, entry a). This reaction unfortunately is not general

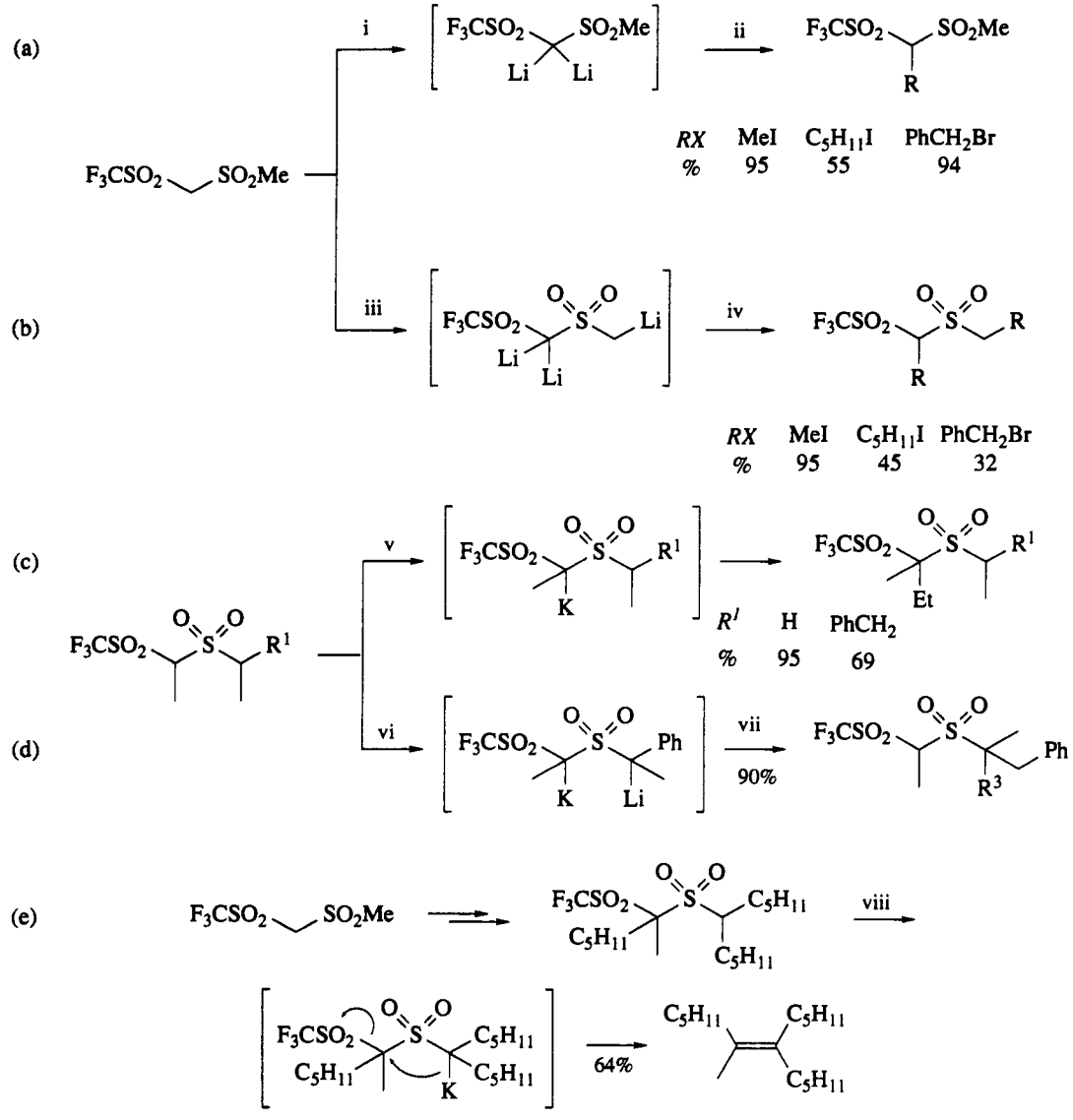


i, $(PhO_2S)_2CH_2$, NaH, DMF, 20 °C; ii, 6% Na/Hg, $NaHPO_4$, MeOH, MeCN; iii, 6% Na/Hg, MeOH, MeCN; iv, $KN(SiMe_3)_2$, THF, MoOPH; v, Cs_2CO_3, $Ph(CH_2)_3I$, DMF, 50 °C, 12 h; vi, BCl_3, –78 °C; vii, OH or N-H; viii, Ph OAc, $(Ph_3P)_4Pd$, Bu_4NOH, CH_2Cl_2, H_2O, 20 °C

Scheme 128

and, for example, attempted methylation of diphenyl sulfonium allylide, a more stable ylide, has led only to recovered starting material.[546]

Intramolecular alkylations of ylides appear facile.[41,543] For example, the cyclizations of diphenyl-3-halo-1-propylsulfonium fluoroborate and 3-halo-1-butylsulfonium fluoroborate proceed[543] on reaction with suitable bases at 25 °C *via* the intermediate ylides (Scheme 130, entry b). The chloro derivatives have proved more efficient than the corresponding iodides.[543] Low temperature methylations of five- and six-membered sulfur ylides have been performed,[542,547] and all three methylations shown in Scheme 130 (entry c) occur with a high degree of stereoselectivity on the thianium salts since a *trans* arrangement of the entering methyl and the *S*-phenyl groups is always obtained. The behavior closely matches that observed with the corresponding thiane-1-oxides (see Section 1.3.5.1.1.i). Thiolanium ylides however appear to react without any significant stereoselectivity (Scheme 130, entry d).[547] Dimethylsulfoxonium methanide reacts with diazomethane, iodoethane and dimethyl sulfate to form complex mixtures of products.[43] This is not the case of aryl(dimethylamino)oxosulfonium ethanide, whose sequential metallation and methylation produces aryl(dimethylamino)oxosulfonium isopropanide.[548] The intramolecular version of this reaction has been used for the synthesis of the corresponding cyclopropyl derivative (Scheme 130, entry e).[136]



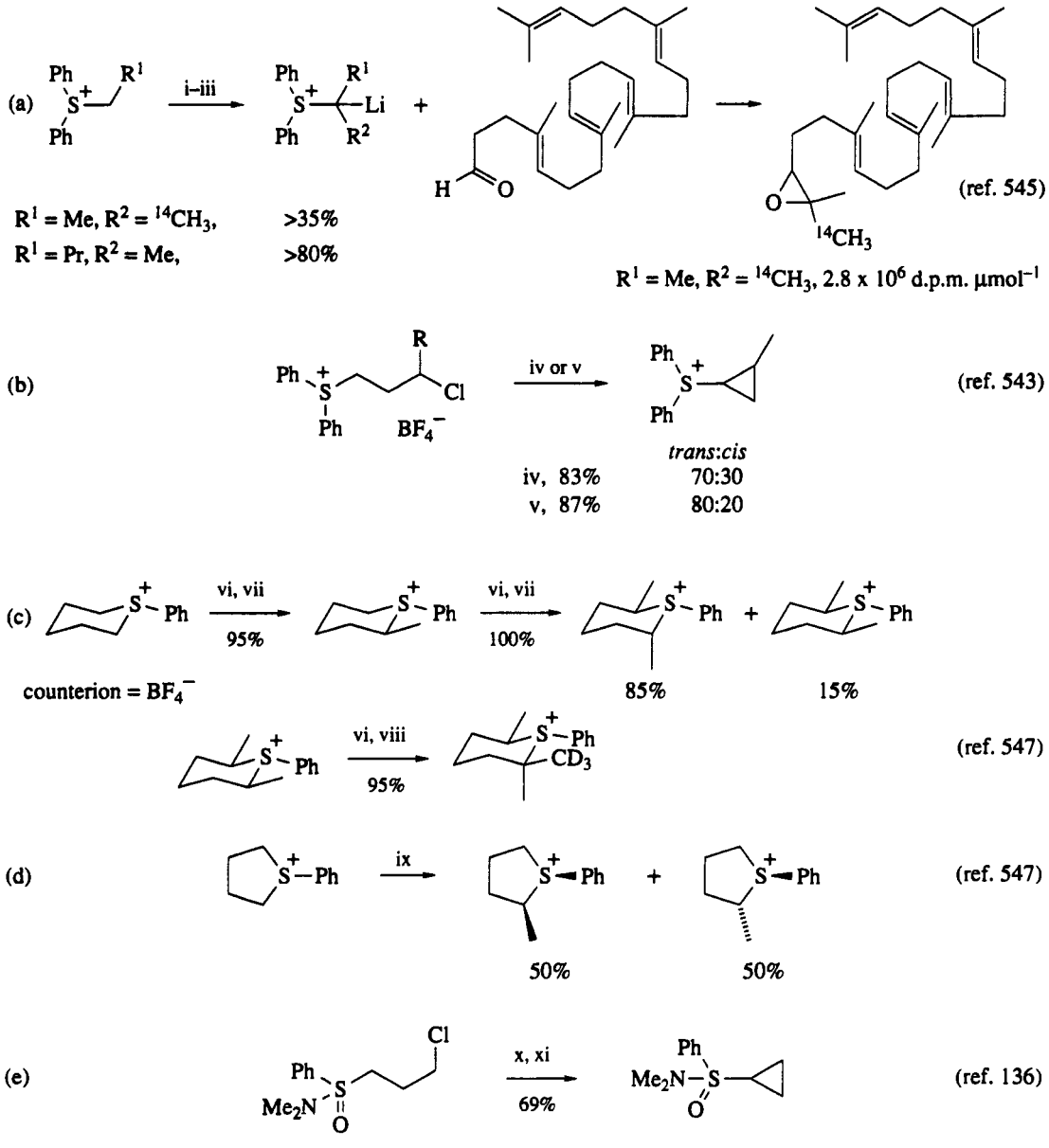
i, 2 Bu^{n}Li, THF, –78 to –55 °C, 0.5 h; ii, RX, –78 to 20 °C; iii, 3.2 Bu^{n}Li, THF, –78 to –50 °C, 1.5 h; iv, 2.4 RX, –78 to 20 °C; v, K_2CO_3, DMF, EtOTf, 70 °C, 24 h; vi, 2 Bu^{n}Li, THF, –78 °C; vii, R^3X, –78 to 20 °C; viii, 1.2 Bu^{t}OK, THF, 0 °C, 1 h

Scheme 129

1.3.8 ALKYLATION OF ALKYL SULFONATES, SULTONES AND SULFONAMIDES

Metallation of alkyl α-toluenesulfonates and alkyl alkanesulfonates and subsequent alkylations of the corresponding anions allow the facile synthesis of a range of substituted sulfonates (Scheme 131, entries a and b).[549] This method offers a useful route to esters of tertiary sulfonic acids which are otherwise difficult to obtain. Similar reactions, performed at low temperature (–78 °C) in order to avoid competing ring opening, permit the alkylations of 1,3-propanesultone with highly reactive alkylating agents such as methyl iodide and benzyl bromide (Scheme 131, entry b).[550] Less reactive electrophiles such as ethyl bromide or isopropyl iodide react[550] sluggishly however. The intramolecular version of this reaction permits the synthesis of *t*-butyl cyclopropanesulfonate (Scheme 131, entry d).[474]

Mono-*N*-substituted alkanesulfonamides react with 2 equiv. of *n*-butyllithium or LDA generating the corresponding dilithium salts which can then be alkylated chemoselectively on the carbon atom.[551]

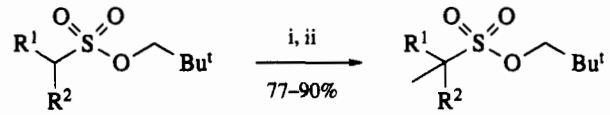


i, LDA, DME, –78 °C; ii, RI; iii, $LiCHCl_2$; iv, NaH, THF, 25 °C, 12 h; v, Bu^{t}OK, DMSO–THF, 20 °C, 0.1 h; vi, $LiCHCl_2$, DME, 1 h; vii, MeI; viii, CD_3I; ix, LDA, DME, –78 °C, 0.1 h,; x, NaH, DMSO, 25 °C, 1 h; xi, HBF_4

Scheme 130

Treatment of *N*-methanesulfonyl-1,4-dihydropyridine with *n*-butyllithium, followed by benzyl bromide, leads to the corresponding *N*-1-(2-phenylethyl)sulfonyl-1,4-dihydropyridine in low yield.[552] The sulfonamide shown in Scheme 131 (entry c) has proved a valuable *cis*-isoprenoid synthon which allows the two-step C_5-homologation of allyl halides.[553] This synthon was used for the remarkable two-step stereoselective synthesis of nerol from 3-methyl-2-butenyl chloride (Scheme 131, entry c).[553] Finally, the α-chloro dicarbanion of 4-(α-chloromethanesulfonyl)morpholine is readily available[554] on reaction with 2 equiv. of *n*-butyllithium in THF, and it leads to the corresponding dimethyl derivative with no detectable monoalkylated product or starting sulfonamide on methylation.[554] Intramolecular versions of these reactions allow the low yield synthesis of neopentyl cyclopropanesulfonate (scheme 131, entry d)[474] and the efficient preparation of cyclopropanesulfomorpholine (scheme 131, entry e).[474]

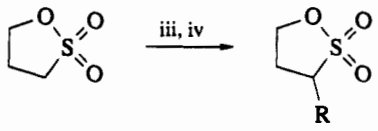
(a)



R^1	H	H	Me	Ph
R^2	H	Me	Me	Me

(ref. 549)

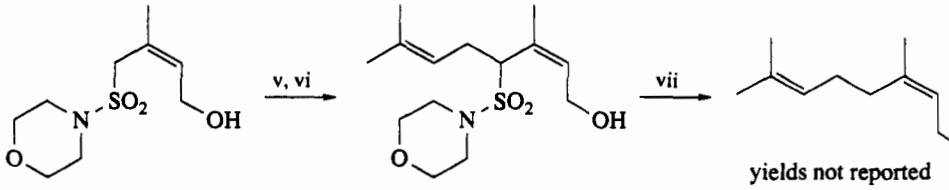
(b)



RX	$PhCH_2Br$	MeI	EtBr	Pr^iI
%	49	62	<25	<25

(ref. 550)

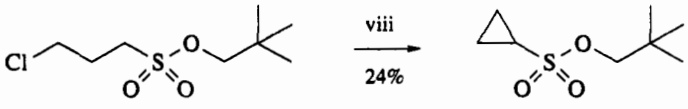
(c)



yields not reported

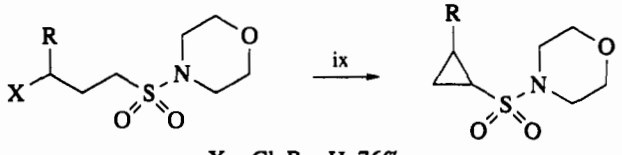
(ref. 533)

(d)



(ref. 474)

(e)



X = Cl, R = H, 76%
X = Br, R = Ph, 75%

(ref. 474)

i, 1.1Bu^nLi, THF, –78 °C, 0.3 h; ii, MeI, –78 °C, 2–12 h, then H_2O; iii, Bu^nLi, THF, –78 °C, 0.1 h; iv, RX, –78 °C, 0.1 h, then –20 °C, 2 h; v, 2Bu^nLi, THF, –70 °C; vi, , –70 to 20 °C; vii, 2 equiv. metal/amine or $2e^-$; viii, KH, THF, 20 °C, 5 d; ix, Bu^nLi, THF, 50 °C, then 20 °C, 3 h

Scheme 131

1.3.9 REFERENCES

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1.4
Alkylations of Other Heteroatom-stabilized Carbanions

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1.4.1 INTRODUCTION

The use of heteroatom-substituted carbanions has allowed the chemist to access a broad range of relatively stable and selective reagents capable of a wide range of synthetic transformations.[1–3]

This chapter deals with the formation of new C—C bonds by alkylation of sp^3-hybridized carbanions stabilized by a range of heteroatoms, including oxygen, boron, silicon, phosphorus and the halogens. The properties of the same carbanions with additional stabilization provided by an adjacent C=C double bond are also discussed.

1.4.2 CARBANIONS STABILIZED BY OXYGEN

Considering the prevalence of oxygen-containing groups in naturally occurring substances, synthetic methods based upon the reaction of α-alkoxy carbanions would be of considerable value. Such methods have been realized only recently despite theoretical evidence that these carbanions should be relatively stable. The stabilizing effect of the more electronegative first row elements is inductive in nature, whilst

the second row elements stabilize negative charges much more effectively, in part due to their greater polarizability. The first row elements may coordinate to the base, causing an increase in kinetic acidity.[2] Recently Schleyer *et al.*[4] have determined theoretically that a major factor contributing to the stabilization of first row heterosubstituted organolithiums is the possibility of bridging between lithium and the heteroatom.

1.4.2.1 Preparation by Hydrogen–Metal Exchange

Early attempts by Ziegler and Gellert[5] to deprotonate dimethyl ether with *n*-butyllithium gave products apparently derived from the decomposition of methoxymethyllithium. A number of attempts to deprotonate tetrahydrofuran also failed, as the desired metallated species underwent a facile cleavage reaction to give ethylene and the lithium enolate of acetaldehyde.[6] The successful preparation of the potassium salts of tetrahydrofuran, *t*-butyl methyl ether and dimethyl ether using lithium salt free *t*-butylpotassium was reported by Lehmann and Schlosser.[7] Corey and Eckrich[8] have described a method for the preparation of *t*-butoxymethyllithium (**1**), a synthetic equivalent of the hydroxymethyl anion (Scheme 1). Treatment of the *t*-butyl ethers with anhydrous iron(III) chloride in acetic anhydride affords the acetates.

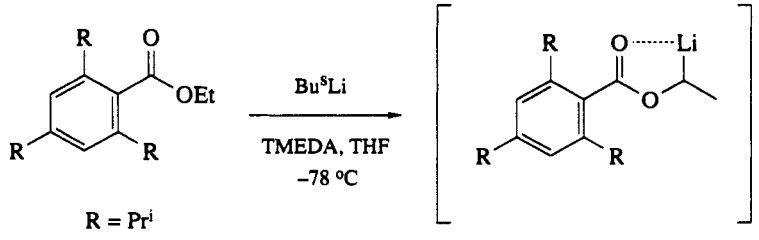
$$Bu^tOCH_3 \xrightarrow{i,\ ii} [Bu^tOCH_2Li] \xrightarrow[83\%]{iii} Bu^tOCH_2CH_2Ph$$

(1)

i, Bu^sLi, Bu^tOK, –78 °C; ii, LiBr, 2 equiv., THF; iii, $PhCH_2Br$

Scheme 1

The research groups of Seebach[9] and Beak[10] independently developed the use of hindered aryl esters for the preparation of heteroatom-stabilized carbanions. The success achieved in creating anions adjacent to nitrogen *via* the *N,N*-dialkylarylamides, and to sulfur *via* the analogous aryl thioesters led to the preparation of alkyl 2,4,6-triisopropylbenzoates, which have been successfully metallated with a strong base. For example, the lithium reagent (**2**), prepared as shown in equation (1), can be reacted with a wide range of electrophiles. It is suggested that the stabilization of these anionic carbanions is due to the dipole of the ester.[11] The bulky aromatic substituents force the plane of the aromatic ring to be orthogonal to that of the carbonyl, protecting it from the organolithium reagent.

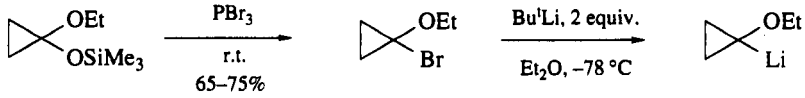


(2) (1)

A recent report describes the use of magnesium (2-ethoxy)ethoxide as an additive in reactions to prepare organolithium reagents.[12] The additive moderates the basicity of the prepared anion and prevents unwanted side reactions, for example with the solvent.

1.4.2.2 Preparation by Halogen–Metal Exchange

Schollkopf *et al.*[13] successfully prepared methoxymethyllithium by the reaction of lithium metal with chloromethyl methyl ether. The Grignard reagents of a variety of α-chlorodialkyl ethers have been prepared.[14] Although thermally unstable, they react with carbonyl compounds. A more recent example is the preparation of 1-ethoxy-1-lithiocyclopropane (**3**) from 1-bromo-1-ethoxycyclopropane using *t*-butyllithium as the metallating agent (Scheme 2).[15] The adducts between (**3**) and aldehydes or ketones can be rearranged to form cyclobutanes in good yields.



(3)

Scheme 2

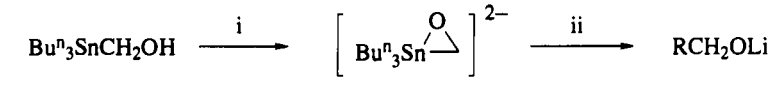
1.4.2.3 Preparation by Tin–Lithium Exchange

The use of organostannanes has considerably expanded the chemistry of α-alkoxy organolithiums.[16] As seen in Section 1.4.2.1, the conditions necessary for the generation of these species by hydrogen–lithium exchange are harsh and can result in their destruction. Halogen–metal exchange allows generation of α-alkoxylithiums, but the anions can be contaminated with reactive alkyl halides. These problems can be avoided by the use of tin–lithium transmetallation, producing as the side product the relatively inert tetraorganostannanes. The process is an equilibrium, the position of which is determined by the relative stability (basicity) of the organolithium species. Schollkopf[17] first described the preparation of a number of α-lithio ethers by reaction of *n*-butyllithium with the tetraalkoxystannanes as shown in equation (2).

$$(ROCH_2)_4Sn + 4Bu^nLi \xrightarrow[-60\ °C]{Et_2O\ or\ THF} 4LiCH_2OR + Bu^n_4Sn \qquad (2)$$

R = Me (60%), Et (70%), Pr^i (70%), $PhCH_2$ (65%)

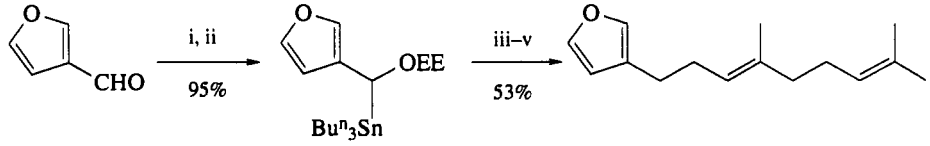
Meyer and Seebach[18] have described the preparation of the 'ate' complex (**4**) as a nucleophilic hydroxymethylating reagent (Scheme 3). Still[19] improved the potential of the method, approaching the preparation of the required organostannanes by reacting tributylstannyllithium with the appropriate carbonyl compound. The labile nature of the addition products necessitated their protection as the stable ethoxyethyl ethers. The α-lithio ethers were then smoothly generated by treatment of the organostannanes with *n*-butyllithium in THF at –78 °C. Still has demonstrated the use of the overall procedure by synthesizing dendrolasin from furan-3-carbaldehyde and geranyl chloride (Scheme 4).



(4)

i, Bu^nLi, 2 equiv., petroleum ether, –20 °C; ii, RX = n-$C_8H_{17}Br$ (45%), $PhCH_2Br$ (45%)

Scheme 3



EEO = ethoxyethyl ether

i, Bu^n_3SnH, LDA, THF, –78 °C; ii, α-chloroethyl ethyl ether, $PhNMe_2$, CH_2Cl_2, 0 °C;
iii, Bu^nLi, THF:glyme, –78 °C; iv, geranyl chloride, –78 °C; v, Li, NH_3, THF, –33 °C

Scheme 4

An exciting new dimension to the chemistry of α-alkoxy organolithium reagents was reported by Still and Sreekumar in 1980.[20] Thus, the aldehyde 2-methyl-3-phenylpropanal was treated with tributylstannyllithium and the diastereomeric carbinols were then protected as their methoxymethyl ethers. Each diastereomeric adduct was next treated separately with *n*-butyllithium. The products resulting from trapping with acetone and TMS-Cl were isomerically pure, showing that the anions were configurationally stable under the reaction conditions. Retention of configuration was implied by the recovery of starting material when the anions were quenched with tributylstannyl chloride. Thus α-alkoxy organolithiums

represented 'a new class of configurationally stable carbanions'. Still reported the preparation of optically active (*R*)-2-butanol (>95% *ee*) by chromatographic separation of the diastereomeric Moshers ester derivatives of the addition product between propanal and tributylstannyllithium. Transmetallation of the protected homochiral α-alkoxystannane with *n*-butyllithium (THF, –78 °C) gave the configurationally stable carbanion, which was alkylated with dimethyl sulfate.

A recent report by Chan and Chong[21] describes the enantioselective reduction of acylstannanes to the α-alkoxy organostannanes by the chiral 2,2′-dihydroxy-1,1′-binaphthyl modified lithium aluminum hydrides. Matteson has also described a possible route to such chiral organostannanes utilizing the chiral α-chloroboronic esters.[22]

Gadwood *et al.*[15] have prepared the 1-bromo-1-tributylstannylcyclopropane. The transmetallation proceeds easily in THF at –78 °C. The lower basicity of cyclopropyl carbanions compared with their acyclic analogs explains this ease of metallation. The group of Macdonald and McGarvey[23] has made a thorough investigation of α-alkoxy organolithiums, and estimate that each alkyl substituent destabilized the anion by 3–4 kcal mol^{-1} (1 cal = 4.18 J). A number of examples demonstrated the utility of tertiary α-alkoxy carbanions for the synthesis of highly substituted carbon centers.

Duchene and Quintard[24] have described the preparation of a number of *O*-ethyl organostannanes, for example by the reaction of ethoxy-α-chloromethyltributylstannane with Grignard reagents. (Diethoxymethyl)tributylstannane has been transmetallated to provide the formyl anion synthetic equivalent $(EtO)_2CHLi$.[25] Another report concerning tin–lithium transmetallation describes the preparation of the configurationally stable α- and β-glycosyllithiums from the α- and β-D-tributylstannylglucopyranosides.[26] In addition, α-alkoxy organocopper reagents derived from α-alkoxy organostannanes have been studied.[27]

1.4.2.4 Preparation from α-Sulfides

Cohen and coworkers[28] have described the preparation of α-lithio ethers from α-sulfides by a mechanistically novel route in the presence of lithium (dimethylamino)naphthalenide. The reaction is postulated to proceed through the radical anion produced by single electron transfer (SET) and subsequent homolytic cleavage (loss of thiophenoxide anion) to give a radical. Further reduction of the radical then leads to the α-alkoxy carbanion.

1.4.3 α-OXYGEN CARBANIONS WITH ADDITIONAL STABILIZATION

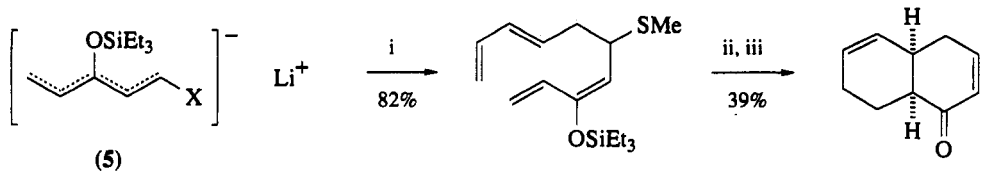
The introduction of an additional stabilizing influence on the α-alkoxy anion may serve two purposes. Firstly the anions are easier to prepare, generally by hydrogen–lithium exchange. Secondly the effective oxidation state of the α-carbon atom is increased.

1.4.3.1 Allylic and Benzylic α-Alkoxy Carbanions

A number of reviews exist describing the preparation and reactions of allylic heteroatom-stabilized organometallic species.[29] Reactions of the ambident anions can occur at either the α- or γ-carbon atoms (with respect to the heteroatom). There is no general rule for predicting the regioselectivity of the reaction, but experimental evidence indicates that alkylation generally occurs at the γ-carbon atom with alkyl or trialkylsilyl allylic ethers.[30] Attempts have been made to influence the regioselectivity of the reaction. Thus, Yamamoto *et al.*[31] have described the use of allylic 'ate' complexes to direct the reaction toward the α-position. The 'ate' complex is formed by reaction of triethylaluminum or trialkylboranes at the least-substituted γ-position, effectively blocking it to further attack by electrophiles.

An example of an oxaallylic carbanion has been described by Oppolzer *et al.*[32] In the alkylation of 3-triethylsilyloxypentadienyllithium (**5**; X = H) the γ-alkylated product predominated. With the anion (**5**; X = SMe) alkylation occurs exclusively at the γ-carbon atom. The synthetic potential of the anions (**5**) was demonstrated by the synthesis of bicyclic compounds *via* intramolecular Diels–Alder reactions of the alkylation products (Scheme 5).

Hoppe[29] has investigated the regioselectivity of the reaction of oxaallylic anions generated from the *N,N*-diisopropyl carbamates of a variety of allylic alcohols. With carbonyl compounds reaction was found to take place predominantly at the γ-carbon. The directing influence of the carbamoyloxy group was unfortunately diminished in alkylation reactions.



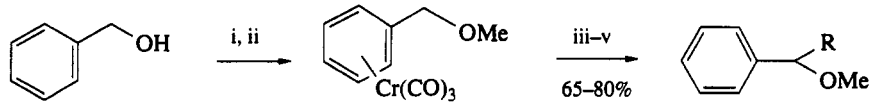
(5)

i, 1-bromo-2,4-pentadiene, THF; ii, KF, MeOH, –10 °C; iii, $NaIO_4$, aqueous MeOH, then refluxing CCl_4

Scheme 5

The rearrangement of 1-(trimethylsilyl)allylic alcohols to 3-(trimethylsilyloxy)allyllithiums in the presence of base is a convenient source of lithium homoenolates.[33] These can be alkylated to yield the corresponding silyl enol ethers.

α-Alkoxy carbanions generated from benzyl ethers are unstable and undergo the Wittig rearrangement in preference to reaction with electrophiles.[34] Yeh has reported, however, that deprotonation of benzyl methyl ether by *n*-butyllithium in the presence of TMEDA leads to the stable benzylic anion, which could then be alkylated.[35] Katriztky *et al.*[36] have described the successful lithiation of lithium benzyl carbonate generated by the reaction of the lithium benzylalkoxide with carbon dioxide. The chromium tricarbonyl complex of benzylic ethers also allows metallation to occur without rearrangement. A variety of bases can be employed for benzylic deprotonation. Davies *et al.*[37] have described the preparation of chromium tricarbonyl complexes of benzyl ethers and their subsequent alkylation chemistry (Scheme 6).

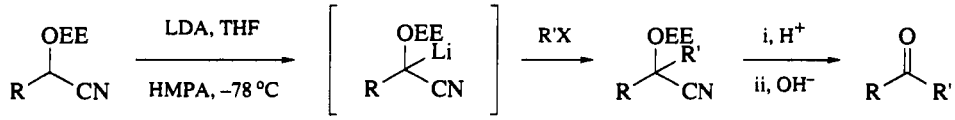


i, $Cr(CO)_6$, heat; ii, MeOH, HBF_4; iii, Bu^nLi, THF, –40 °C; iv, RX = MeI, EtBr, Pr^iBr, $PhCH_2Br$; v, sunlight or air, Et_2O

Scheme 6

1.4.3.2 α-Alkoxy Carbanions from Protected Cyanohydrins

Protected cyanohydrins, when deprotonated by a suitable base, are synthetic equivalents of the acyl anion.[38] They display 'umpolung' reactivity as the normally electrophilic carbonyl carbon is transformed into a nucleophile. Stork and Maldonado[39] first described the use of such anions for the synthesis of ketones. They found that the cyanohydrins, protected as their ethoxyethyl ethers can be deprotonated with LDA (Scheme 7). After reaction with the alkylating reagent the carbonyl function is restored by treatment with dilute acid and then base. A number of alkylating reagents were investigated, and no problems from competing elimination reactions were noted. The same authors also found similar reactivity in the more stable anions derived from aromatic aldehydes. Deprotonation of the cyanohydrin derivatives of α,β-unsaturated aldehydes gives rise to the ambident allyl anion. Interestingly, Stork found that alkylation occurred at the α-position allowing the synthesis of α,β-unsaturated ketones.

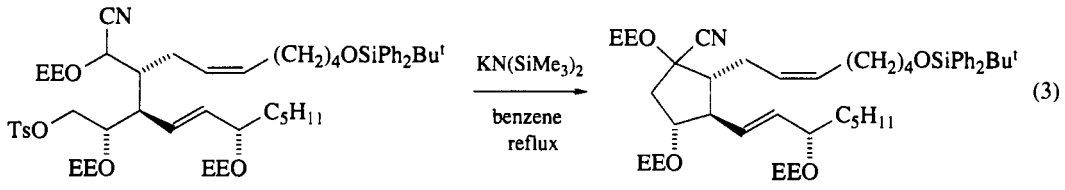


EEO = ethoxyethyl ether

Scheme 7

The alkylation chemistry of a considerable number of *O*-trimethylsilyl cyanohydrins derived from aryl and heteroaryl aldehydes has been reported by Hunig and coworkers.[40] The protected cyanohydrins are easily prepared by heating the aldehydes with trimethylsilyl cyanide in the presence of a Lewis acid. The use of dialkyl sulfates and tosylates as alkylating agents was also reported. Hata *et al.*[41] failed to alkylate the anion of the adduct of trimethylsilyl cyanide and acetaldehyde, suggesting that the trimethylsilyl group is incompatible with the more basic anions derived from aliphatic aldehydes. Ficini *et al.*[42]

demonstrated the utility of cyanohydrins in their synthesis of (±)-juvabione; a more recent example is the synthesis of (±)-trichostatin A.[43] Stork and his coworkers have applied the alkylation procedure to the synthesis of small rings,[44] for example in prostaglandins PGE_1[45] and $PGF_{2\alpha}$[46] as shown in equation (3). The cyanohydrin served as an effective equivalent of the sensitive carbonyl function.



(3)

Takahashi, Tsuji and coworkers have demonstrated that the intramolecular alkylation of carbanions derived from protected cyanohydrins can be applied to the synthesis of both large and medium-sized rings. Their first report described the synthesis of cyclohexadecanone.[47] Slow addition of a THF solution of the protected cyanohydrin of 16-iodohexadecanal to a THF solution of sodium hexamethyldisilazane gave the cyclized product. Treatment with acid and then base gave cyclohexadecanone in 60% overall yield. An advantage of the procedure is that high dilution conditions are not necessary. The method was later extended to the synthesis of several naturally occurring macrocyclic lactones.[38] Another development was to employ the cyclization reaction for the synthesis of (*E,E*)-2,6-cyclodecadienones and hence the synthesis of various sesquiterpenes.[48] The synthesis of germacrone, which contains the thermally labile (*E,E*)-1,5-cyclodecadiene system, serves to illustrate the strategy (Scheme 8). Deprotonation of (**6**) and cyclization yielded, after restoration of the carbonyl group, germacrone (**7**) in 66% yield.

(**6**) (**7**)

i, $NaN(SiMe_3)_2$, THF; ii, PTSA, MeOH, 0 °C; iii, aqueous 2% NaOH, Et_2O

Scheme 8

Garcia *et al.*[49] have described the synthesis of α-hydroxy-γ-lactones by the alkylation of protected cyanohydrin anions with epoxides.

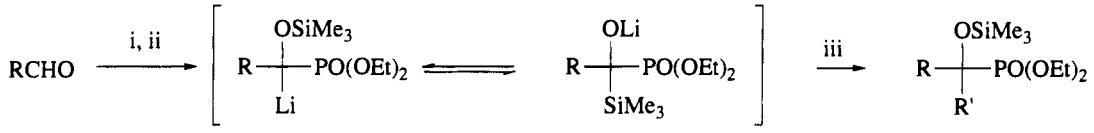
1.4.3.3 α-Alkoxy Carbanions Stabilized by Silicon

Eisch and Galle[50] have described the alkylation with methyl iodide of the configurationally stable anions derived by deprotonation of α,β-epoxyalkylsilanes. The alkylation chemistry is presently restricted to methylation, which is unfortunate as the α,β-epoxyalkylsilanes are easy to prepare and undergo a range of synthetically useful reactions.[51] Unsubstituted α-lithio epoxides derived by tin–lithium transmetallation decompose at –85 °C.

Recently Yoshida *et al.*[52] have employed silyl-stabilized α-alkoxy organolithium reagents for the synthesis of a variety of carbonyl compounds. Methoxy(trimethylsilyl)methane and methoxybis(trimethylsilyl)methane, when deprotonated with Bu^sLi and Bu^nLi respectively, give anions which can be alkylated with a variety of electrophiles. Electrolysis of a solution of the alkylated product in methanol yields, by virtue of the reduced oxidation potential of ethers α-substituted with silicon, either the dimethyl acetal or in the latter case the orthoester. The mildness of the electrolytic process recommends the method for the preparation of a variety of carbonyl compounds.

1.4.3.4 α-Alkoxy Carbanions Stabilized by Phosphorus

Hata and coworkers[41] have reported the preparation of unsymmetrical ketones employing the adducts of aldehydes with diethyl trimethylsilylphosphite (**8**). The adducts are easily deprotonated and then alkylated; treatment of the alkylated products with base provides the ketone (Scheme 9).



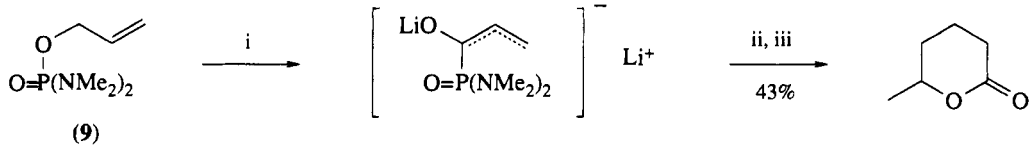
R = H, Me, Et, Pr^i, n-C_7H_{15}, *etc.*; R'X = MeI, EtI, $PhCH_2Br/I$, *etc.*

i, $Me_3SiOP(OEt)_2$, (**8**), benzene; ii, LDA, THF, –78 °C ; iii, R'X

Scheme 9

The anions generated from the adducts of α,β-unsaturated aldehydes and (**8**) are alkylated exclusively at the γ-position. Evans *et al.*[53] have also reported the alkylation of similar oxaallylic anions and the alkylation chemistry of diethyl (2-trimethylsilyl)ethoxymethylphosphonate has been reported.[54]

Sturtz *et al.*[55] have described the deprotonation of the allyl bis(dimethylamido)phosphonate (**9**). Treatment of (**9**) with two equivalents of base, followed by reaction with an epoxide and hydrolysis, yields the γ-lactone (Scheme 10). Alkylation with alkyl and alkenyl halides occurs at the γ-carbon and hydrolysis yields the saturated and unsaturated carboxylic acids respectively.



i, Bu^{n}Li, 2 equiv., THF, –50 °C; ii, propylene oxide; iii, H^+, H_2O

Scheme 10

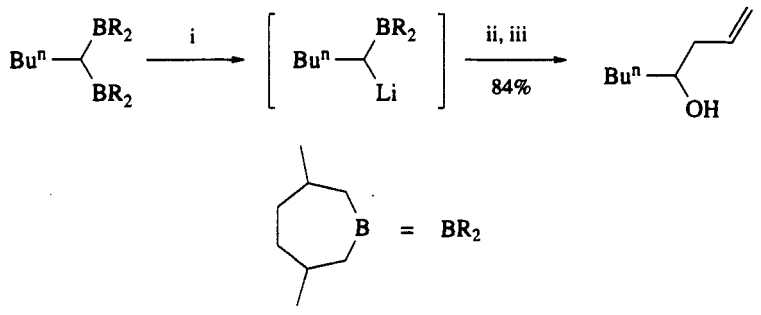
1.4.4 CARBANIONS STABILIZED BY BORON

The stabilization of a negative charge adjacent to boron has been known for some time.[56] Zweifel and Arzoumanian[57] demonstrated the facile base-induced cleavage of a geminal diboroalkane to give the boron-stabilized anion, which was then alkylated. A later approach employed 3,6-dimethylborepane (**10**) as the hydroborating agent.[58] After dihydroboration, addition of one equivalent of methyllithium forms the boron-stabilized anion, which upon alkylation and oxidation gives the secondary alcohol (Scheme 11). Matteson[59] has described the alkylation of the anion derived from the base cleavage of tris(dimethoxyboryl)methane.

Rathke and Kow[60] first reported the preparation of a boron-stabilized carbanion by direct deprotonation of the carbon acid. They made the important observation that the deprotonation needed a sterically demanding base to prevent its complexation with boron. Thus the anion of *B*-methyl-9-borabicyclo[3.3.1]nonane, prepared by deprotonation with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in benzene, can be alkylated successfully.

Matteson and coworkers have described the deprotonation and alkylation of bis(1,3,2-dioxaborin-2-yl)methane (**11**).[61] Deprotonation with LiTMP yields the stabilized anion, which can be alkylated with a variety of primary alkyl halides. Oxidation under basic conditions then unmasks the carbonyl group. Matteson has also described the deprotonation of some substituted boronic esters (**12**; X = SPh, $SiMe_3$).[62,63] The alkylated products derived from (**12**; X = SPh) can be treated with *N*-chlorosuccinimide under mild basic conditions to yield either the monothioacetals or the acetals.[64] Boron-stabilized carbanions can also be generated by transmetallation of the organostannanes.[65]

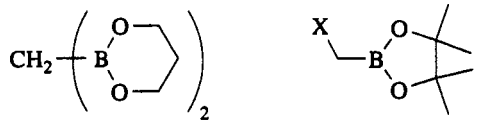
Pelter and Wilson[66] have described the deprotonation of the air stable dimesitylboranes. The use of two mesityl groups represents a compromise between steric shielding of the boron against the possible complex formation with the base, and easy oxidation of the product. Alkylation of the anion generated



(10)

i, MeLi, 1 equiv., 0 °C; ii, allyl bromide; iii, 3 N aqueous NaOH, 30% H_2O_2

Scheme 11



(11) **(12)**

by deprotonation of dimesitylmethylborane can be effected with a range of primary alkyl halides. The secondary anions derived from ethyl- and propyl-dimesitylborane can also be alkylated, but oxidation is more difficult. Allyldimesitylborane was also deprotonated using mesityllithium. Alkylation with primary halides occurs at the γ-position and the resulting *trans*-vinylboranes can be oxidized to give aldehydes.

1.4.5 CARBANIONS STABILIZED BY SILICON

The preparation and use of silicon-stabilized carbanions is well documented;[67] the vast majority of reports are concerned with the reaction of these reagents with carbonyl compounds to form alkenes.

Tamao *et al.*[68] have described the use of (diisopropoxymethyl)silylmethylmagnesium chloride as a reagent for effecting hydroxymethylation of reactive alkyl halides. The alkylation of tris(trimethylsilyl)methyllithium has also been reported.[69]

There are a number of examples where additional stabilization for the α-silicon anion is derived from the presence of one or more halogen atoms. For example, Larson and Rosario[70] have described the alkylation of a number of trialkylsilyldichloromethyllithiums; dehydrochlorination yields the *trans*-1-chloroalkenylsilanes.

Chan and coworkers[71] have investigated the regioselectivity in the alkylation of α-silicon allyllithiums. The alkylation of α-trimethylsilylallyllithium usually occurs at both the α- and γ-carbons, but if the reagent is prepared using Schlosser's base (Bu^{t}OK/Bu^{n}Li in hexane), γ-alkylation predominates, affording the *trans*-alkenylsilanes. Chan[72] has also recently described the successful use of metal-chelating substituents on the silyl group to direct the reaction toward the α-position.

1.4.6 CARBANIONS STABILIZED BY PHOSPHORUS

The Wittig reaction of phosphorus ylides derived from phosphonium salts with carbonyl compounds to form alkenes is widely used in synthetic chemistry. The alkylation of phosphorus ylides offers a route to a variety of phosphonium salts which can be further manipulated. Bestman and coworkers[73] have been responsible for a large number of reports based upon this and other aspects of phosphorus chemistry. Their work includes many examples of the intramolecular alkylation of ylides derived from phosphonium salts to form cyclic compounds. The salts can be prepared from dihalides either with triphenylphos-

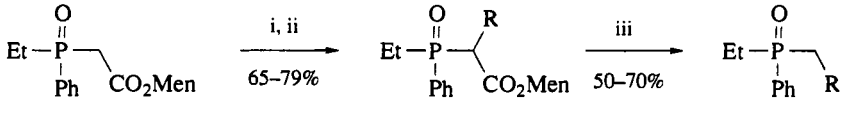
phine or triphenylphosphine methylide. The cyclic phosphonium salt formed can then be eliminated to form an alkene, or reduced or deprotonated to give a new ylide.

Axelrod *et al.*[74] have described the synthesis of 1,5-dienes by alkylation of an allylic phosphonium ylide with an allylic bromide. The method was used to synthesize pure all-(*E*)-squalene from (*E,E*)-farnesyl bromide and its tributylphosphonium salt. No isomerization occurred during the reaction and reduction of the resulting phosphonium salt with lithium in ethylamine gave squalene in 65% yield.

Alkylation chemistry has also been reported for alkylphosphine oxides and dialkyl phosphonates. The phosphonate carbanions are often preferred as they offer many advantages over the phosphonium ylides.[75] In particular, the phosphonate group is highly acidifying and the resulting organolithium can be smoothly alkylated.

Warren and coworkers[76] have described the alkylation of (diphenylphosphinoyl)alkyllithiums with epoxides as an effective means of synthesizing β-(diphenylphosphinoyl) ketones, homoenolate anion equivalents. The treatment of the adducts of lithiated phosphine oxides and epoxides with base to form cyclopropanes was reported by Toscano *et al.*[77]

Pietrusiewicz and coworkers[78] have developed methods for the synthesis of homochiral phosphine oxides. They play an important role in asymmetric synthesis as chiral ligands for catalysts. The readily prepared (S_p)-ethyl[(menthoxycarbonyl)methyl]phenylphosphine oxide (**13**) can be deprotonated, alkylated and then decarboxylated to afford the homochiral (R_p)-alkylethylphenylphosphine oxides (Scheme 12). Pietrusiewicz and Zablocka have also described the synthesis of chirally pure α,β-unsaturated phosphine oxides.[79]



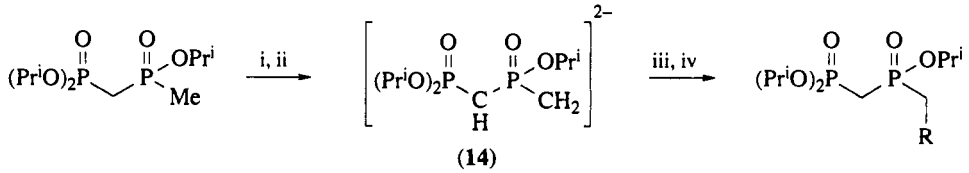
(**13**)

Men = L-menthyl

i, NaH, THF, 0 °C; ii, RX = CD_3I, EtI, $H_2C{=}CHCH_2Br$, $PhCH_2Br$; iii, LiCl, wet DMSO, 180 °C

Scheme 12

Recently there has been interest in the synthesis of analogs of the naturally occurring mono- and diphosphate group. Corey and Volante[80] have reported the alkylation of (dimethylphosphoryl)methyllithium with, for example, geranyl, farnesyl and 3-methyl-2-butenyl bromides. The products were assessed for their ability to inhibit the biosynthesis of squalene. McClard and coworkers[81] described the alkylation of the phosphonylphosphinyl anion (**14**) to yield the 'P—C—P—C' compounds, proven enzyme inhibitors (Scheme 13). The free acid derivatives were obtained by treatment of the alkylated products with bromotrimethylsilane.



(**14**)

RX = EtI, PriI, $Me_2C{=}CHCH_2Br$, geranyl bromide, $PhCH_2Br$, *etc.*

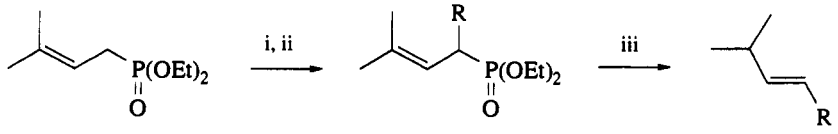
i, NaH, THF, 20 °C; ii, Bu^nLi, –78 °C; iii, RX, –78 °C; iv, H^+, H_2O

Scheme 13

Alkylation of (diethoxyphosphoryl)methylcopper(I)[82] and (dialkoxyphosphoryl)trimethylsilylalkyllithiums[83] with a variety of alkyl iodides and bromides has been reported by Savignac and coworkers. Tsuge *et al.*[84] have demonstrated the regioselective dipolar addition of (diethoxyphosphoryl)acetonitrile oxide with monosubstituted alkenes to yield the 3-[(diethoxyphosphoryl)methyl]-2-isoxazolines. The phosphonates can be deprotonated and alkylated in good yields.

The incorporation of fluorine into biologically active compounds can greatly enhance their potency; fluoroalkyl phosphonates are isosteres of the natural phosphonate monoesters. The alkylation chemistry of α-fluoro- and α,α-difluoro-alkyl phosphonates has been reported.[85] Burton and Sprague[86] have described the alkylation of (diethoxyphosphoryl)difluoromethylzinc bromide with allylic halides; the reaction is catalyzed by copper(I) bromide. The alkylation of (diethoxyphosphoryl)dichloromethyllithium was reported by Normant and coworkers.[87] The products can be transmetallated and further alkylated.

A method for the preparation of alkenes has been described by Tunemoto and coworkers,[88] whereby regioselective α-alkylation of γ-substituted allyl phosphonates, followed by reduction with LAH, gives the (*E*)-alkenes (Scheme 14).



i, Bu^nLi, THF, –60 °C; ii, X = Cl, Br, 25 °C; iii, $LiAlH_4$, Et_2O, 0 °C

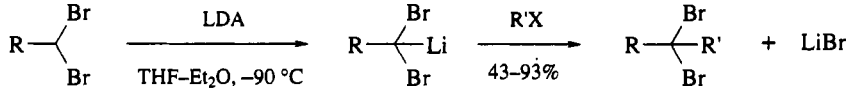
Scheme 14

A range of heteroaryl methyl phosphonates have been alkylated with alkyl halides; the anions were generated with sodium amide in liquid ammonia.[89]

1.4.7 CARBANIONS STABILIZED BY THE HALOGENS

Organolithiums bearing a halogen on the α-carbon are termed carbenoids.[90] Bromine and chlorine are sufficiently acidifying to allow preparation of the halocarbenoids, but fluorine requires additional stabilization, for example by phosphorus (*vide supra*). Lithium halocarbenoids are thermally unstable species whose chemistry must be performed at low temperatures and this feature has hindered their use in preparative synthetic organic chemistry.

Villieras and coworkers[91] have contributed a considerable number of synthetic methods employing lithium halocarbenoids. An early example was the alkylation of dibromomethyllithium and higher homologs (Scheme 15). The anion (**15**) is easily generated from 1,1-dibromoalkanes by deprotonation with LDA in THF at low temperature. Alkenes can then be generated simply by treating the products with Bu^nLi in Et_2O. Alkylation of dichloromethyllithium with primary alkyl halides followed by reaction of the dichloroalkanes with Bu^nLi represents a method for the preparation of 1-alkynes.[92]



(**15**)

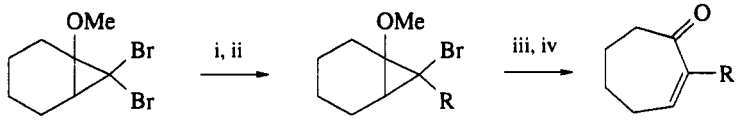
R = H, Bu^n, Me_3Si; R'X = $H_2C{=}CHCH_2Br$, Bu^nI, $n\text{-}C_5H_{11}I$, *etc.*

Scheme 15

Geminal substituted dibromoalkenes can be prepared by the alkylation of dibromomethyllithium with α-chloroalkyl methyl ethers.[93] Deprotonation of the alkylation products results in the elimination of methanol and the formation of the corresponding 1,1-dibromoalkenes. Despite the lower acidity of 1-bromo-1-chloroalkyllithiums relative to the dibromo analogs they exhibit similar nucleophilic properties.[94] Alkyl dichloroacetates can also be deprotonated with lithium diethylamide and alkylated with a range of alkyl halides.[95]

Cyclopropylidenelithium halocarbenoids are easily prepared by halogen–lithium exchange of the dibromocyclopropanes, and they undergo a variety of synthetically useful reactions including alkylation.[96] A recent report by Hiyama *et al.*[97] for example, describes the synthesis of alkyl-substituted 2-cycloheptenones (Scheme 16).

Seyferth and coworkers have prepared 1,1-dichloroallyllithium[98] and 1,1-difluoroallyllithium.[99] The former can be alkylated, the reaction occurring at the 'CCl_2' terminus, *i.e.* with α-regioselectivity. The latter reagent, however, is rather unstable and its alkylation chemistry has not yet been explored.



RX = $Me_2C{=}CHCH_2Br$ (46%) or n-$C_5H_{11}I$ (40%)

i, Bu^nLi, THF, HMPA, –95 °C; ii, RX; iii, MeOH, K_2CO_3; iv, H^+, H_2O

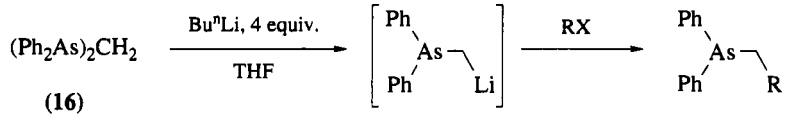
Scheme 16

1.4.8 CARBANIONS STABILIZED BY ARSENIC, GERMANIUM, TIN, ANTIMONY, LEAD AND BISMUTH

The chemistry of carbanions stabilized by the heavy main group elements has been extensively investigated by Kauffmann, and a thorough description of his work can be found in a recent review.[100] There are many similarities between the elements. The anions stabilized by the heavy main group elements listed above can generally be alkylated, and in some cases their reaction with carbonyl compounds is a useful alternative to the Wittig reaction. All the stabilized metallomethyl lithium anions (except bismuth) exhibit marked thermal stability.

Among the heavy main group elements arsenic has received the most attention. Arsonium ylides react with carbonyl compounds to yield either the alkenes or epoxides, depending upon the structure of the ylide and the reaction conditions.[101] Despite their toxicity, arsenic compounds can be handled safely.

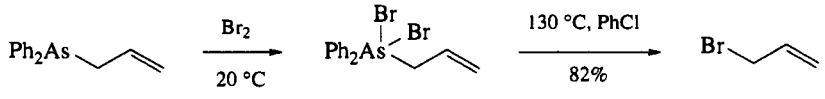
Diphenylarsinomethyllithium (**16**) can be prepared by transmetallation of bis(diphenylarsino)methane (Scheme 17), or by halogen–lithium exchange of diphenylarsinomethyl iodide. The anion derived by the former method can be alkylated.



RX = Pr^nI (93%), Bu^nBr (85%), n-$C_8H_{17}Br$ (57%)

Scheme 17

Alkylarsino compounds undergo halogenolysis of the metal–carbon bond as do the bismuth and antimony analogs (Scheme 18). Diphenylarsinomethyllithium can also be alkylated with epoxides.



Scheme 18

The major drawback to the use of diphenylarsinomethyllithium is the necessity to use a fourfold excess of *n*-butyllithium in order to prepare it. The arsane oxides offer a good alternative, as the diphenylarsinoyl group is strongly acidifying. Diphenylarsinoylmethane is easily deprotonated with LDA in THF and can be alkylated with alkyl halides and epoxides.

Addition of organolithium reagents to diphenylarsenoethene provides another route to α-arseno anions. This reaction is general to the second and third row elements (Si, P, S, Ge, As and Se) but does not occur with elements from the fourth and fifth rows (Sn, Sb, Te, Pb and Bi). Unlike their phosphorus analogs, triphenylarsonium salts cannot be prepared by reaction of triphenylarsine with an alkyl halide. Their preparation can be achieved by reaction of triphenylarsine with the more electrophilic alkyl triflates. It is also possible to alkylate arsonium ylides.[101,102]

The organometallic species Ph_nMCH_2Li (**17**; M = Sn, Pb, n = 3; M = Sb, Bi, n = 2) can be prepared by transmetallation of $(Ph_nM)_2CH_2$ with phenyllithium. In the case of germanium, the anion (**17**; M = Ge, n = 3) is prepared from the lead-, selenium- or tin-substituted triphenylgermanylmethane. The synthesis of (**17**) is sometimes possible *via* halogen–metal exchange of the appropriate iodide. Alkylation of the an-

ions, except (**17**; M = Bi, $n = 2$), is possible with alkyl halides and with epoxides in preparatively useful yields. With (**17**; M = Sb) transmetallation with copper is necessary for efficient alkylation.

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1.5
Alkylations of Nonstabilized Carbanions

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1.5.1 INTRODUCTION

The formation of carbon–carbon bonds is truly one of the cornerstones of organic synthesis. While the early organic chemists had the ability to modify the molecules of nature and to degrade them into simpler components, the possibility that complex molecules could be constructed from simpler precursors appeared inconceivable. The development of methodology for the construction of C—C bonds revolutionized that way of thinking, and the field of organic synthesis was born.

Conceptually, perhaps the simplest method of forming a σ-bond between two carbon fragments is the reaction of a carbanion with an electrophilic carbon center. Nature relies heavily upon reactions of carb-

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anions stabilized by adjacent electron-withdrawing substituents, which can be generated under equilibrium conditions at physiological pH. Similarly stabilized carbanions form the basis of much commonly used synthetic methodology as well, as discussed in Chapters 1.1–1.4 of this volume and also in a number of chapters in Volumes 1, 2 and 4 of the series. However, by a variety of techniques, the chemist is also able to introduce a metal atom at a carbon center that lacks heteroatom stabilization.

The properties and reactivity of the organometallic compounds so produced vary greatly, depending upon the metal counterion.[1] The bonds of carbon to the most electropositive metals, such as sodium and potassium, are predominantly ionic in character. Carbanions of this type are strongly basic, highly reactive and poorly able to discriminate between electrophiles. Also highly reactive are the alkyl and aryl compounds of lithium, magnesium and aluminum, in which the M—C (M = metal) bond is strongly polarized, albeit essentially covalent in nature. By contrast, less electropositive metals form covalent, only slightly polar bonds with carbon, producing organometallic reagents that are less prone to undergo undesired side reactions with functional groups present in the substrate, but that are also correspondingly less reactive. An additional metal catalyst is often necessary in order to achieve suitable reactivity with these reagents.

In this chapter, the substitution reactions of organometallic reagents with organic halides and related electrophiles are reviewed.[2,3] The major portion of the chapter is devoted to a discussion of organocopper compounds, which first transformed the alkylation of nonstabilized carbanions into a reaction of general synthetic utility. More recently, transition metals other than copper have also found widespread application in such coupling reactions, and developments in this area are outlined in Section 1.5.3.

1.5.2 ORGANOCOPPER REAGENTS

Although organoalkali metal reagents derived from stabilized carbanions can usually be alkylated smoothly in high yields, those derived from weak hydrocarbon acids are prone to undergo numerous competing side reactions (*e.g.* metal–halogen exchange, α-metalation, α- and β-elimination, and homocoupling to form symmetrical dimers). Neither type of reagent is effective in direct substitution reactions of vinyl or aryl halides. Other organometallics, such as organo-aluminum, -zinc, -cadmium and -magnesium reagents, although often useful for specific reactions, are also susceptible to undesirable side reactions or are unreactive toward important classes of noncarbonyl electrophiles.

That the chemical behavior of traditional organolithium and Grignard reagents can be significantly altered in the presence of copper salts has been known for many years, prominent examples being the Cu^{I}-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated compounds[4] and the transition metal catalyzed coupling of aryl Grignard reagents with vinyl halides,[5] both reported by Kharasch in the 1940s. Stoichiometric organocopper compounds also are not new, the oldest members of the class, copper acetylides,[6] having been reported as early as 1859. Phenylcopper[7] was prepared by Reich in 1923, and Gilman and coworkers reported preparations of methylcopper[8] and lithium dimethylcuprate[9] in 1936 and 1952, respectively. However, it was not until the mid-1960s that the widespread synthetic utility of organocopper reagents was finally appreciated. Their use in coupling reactions with organic electrophiles has been reviewed previously.[10]

The past 20 years have witnessed a virtual explosion in research involving organocopper reagents, as reactions employing them have become established in the organic chemist's growing arsenal of consistently reliable methodology. However, the term 'organocopper reagent' itself encompasses a vast array of reagents, possessed of widely divergent chemical behavior. The formulae by which these compounds are represented are indicative of stoichiometry only and are not true reflections of structure, about which information has traditionally been scarce. In addition, factors such as solvent, method of reagent preparation and the nature and purity of the copper source have proven to be critically important in determining the stability and reactivity of the reagents. Not surprisingly, many chemists have tended to view organocopper chemistry as an art as much as a science. Fortunately, during the past decade a rapidly increasing volume of structural and mechanistic data have become available,[11] promising eventually to dispel the mystery surrounding reactions of both stoichiometric and catalytic organocopper reagents.

1.5.2.1 Preparation of the Reagents

Commonly employed organocopper reagents can be divided into five general classes:

(1) catalytic organocopper compounds [RM + CuX(cat)]

(2) monoorganocopper compounds (RCu)

(3) homocuprates (R_2CuM, $RR'CuM$)
(4) heterocuprates [$RCu(Z)M$]
(5) higher-order cuprates [$R_2Cu(Z)Li_2$, $R_{m+n}Cu_mLi_n$ ($m + n > 2$)].

In each case, an additional ligand (usually an amine, phosphine, phosphite or sulfide) or other additive (usually a Lewis acid, especially BF_3) may be present, altering the physical and chemical properties of the reagent.

Typically, organocopper reagents are prepared according to one of the general methods outlined in equations (1)–(3) (with or without additional ligands). The choice of the copper salt employed in these reactions is often critical to the outcome. For example, in early investigations, Cu(SCN) and CuI were often used interchangeably, it being assumed that each gave rise to the same organocuprate, according to equation (1). It has since been established, however, that both Cu(SCN) and CuCN, when combined with 2 equiv. of an organolithium reagent RLi, produce, not the expected homocuprate R_2CuLi, but rather the higher-order mixed organocuprates $R_2Cu(Z)Li_2$ (Z = CN, SCN; equation 3). Even among the copper(I) halides differences are often observed, and debate continues as to whether the use of CuI or CuBr is to be preferred.[12] While copper(I) iodide continues to be most commonly employed for the preparation of dialkylcuprates, copper(I) bromide must be used for the preparation of diarylcuprates.

$$n\text{RM} + \text{CuX} \longrightarrow \text{R}_n\text{CuM}_{n-1} + \text{MX} \quad (1)$$

$$n\text{RM} + m\text{RCu} \longrightarrow \text{R}_{(m+n)}\text{Cu}_m\text{M}_n \quad (2)$$

$$n\text{RM} + \text{CuZ} \longrightarrow \text{R}_n\text{Cu(Z)M}_n \quad (3)$$

Since the presence of trace impurities (*e.g.* Cu^{II} salts) may have a profound effect on the course of reactions employing organocopper reagents, the purity of the copper source is of critical importance. Copper(I) iodide is usually purified by soxhlet extraction or recrystallization,[13] followed by *in vacuo* drying, while copper(I) bromide is recrystallized as its dimethyl sulfide complex.[14] If $CuBr{\cdot}SMe_2$ is to be used, it is important that the reagent not be dried *in vacuo*, since such handling may significantly alter its composition.[15] Tedious and repetitive recrystallizations of $CuBr{\cdot}SMe_2$ can be avoided by simply treating the reaction solution containing $CuBr{\cdot}SMe_2$ with copper wire, which serves to reduce any Cu^{II} that might be present.[16] Copper(I) cyanide offers the advantages that it is neither hygroscopic nor light sensitive, it is less easily oxidized than copper(I) halides, and it is less expensive than CuI.

A number of metals (M) have been employed in reactions (1)–(3), including lead, zinc, mercury, boron, aluminum, thallium, zirconium, lithium and magnesium, the latter two being the most commonly used. Catalytic organocopper compounds are best prepared from Grignard reagents, while organolithiums usually provide the most effective stoichiometric organocopper compounds. This requirement for organo-lithium or -magnesium precursors represents a significant synthetic limitation, prohibiting the formation of many reagents that bear functional groups with which the organocopper compound itself, once formed, would be compatible. In an effort to circumvent this difficulty, Behling[17] has prepared higher-order vinyl cuprate reagents by *in situ* transmetalation between $Me_2CuCNLi_2$ and the corresponding vinylstannane. Similarly, Knochel has reported[18] the successful preparation of functionalized benzylic cuprates by transmetalation of the organozinc bromides.

Particularly exciting within this context is recent research in the Reike group,[19] which has demonstrated that organocopper compounds can be prepared directly from organic halides upon treatment with the highly reactive zerovalent copper obtained by lithium naphthalenide reduction of copper(I) halides. Oxidative addition of the reactive copper to alkyl bromides occurs at temperatures as low as –78 °C, while aryl halides react at room temperature or below. Importantly, ester, nitrile, chloride, nitro, epoxide and ketone functionalities are all compatible with this procedure to varying degrees. The method works best in the presence of phosphine ligands, which render the reduced copper more reactive toward oxidative addition, and which also serve to produce a more nucleophilic organocopper species. Moderate to good yields have been obtained in cross-coupling reactions with acid chlorides and alkyl halides.

Several other methods of limited generality have been used to prepare specific types of organocopper compounds. Copper(I) acetylides are routinely prepared from the corresponding alkyne and a copper(I) halide in ammoniacal solution or in HMPA.[20] Metalation of compounds with acidic hydrogens has also been accomplished with $Cu(OBu^t)$. Alkenylcopper reagents have been prepared by stereospecific *syn* addition of organocopper reagents to alkynes.[21] Finally, it should be noted that the Ullmann biaryl synthesis,[22] thought to proceed *via in situ* generated arylcopper intermediates, may be considered to be an early predecessor to the Rieke method for the preparation of organocopper reagents.

1.5.2.2 Nature of the Reagents

1.5.2.2.1 Catalytic copper compounds [RM + CuX(cat)]

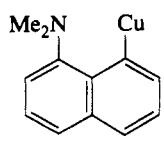
Copper(I)-catalyzed reactions of organolithiums and Grignard reagents have been reviewed.[10] The term catalytic here refers to the use of copper salts in amounts not exceeding 20 mol %; commonly employed quantities range from 1 to 20%, with 5 and 10% being most typical. While CuCl was an often-used catalyst in the years following Kharasch and Tawney's orginal report,[4] its virtual insolubility in ether has led to the more frequent use of CuI, CuBr or Kochi's catalyst, Li_2CuCl_4.[23] Although copper-catalyzed reactions of organometallics are generally believed to proceed by way of *in situ* generated organocopper compounds, little is known about the exact nature of the reactive species involved.

1.5.2.2.2 Monoorganocopper compounds (RCu)

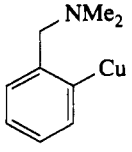
Alkylcopper reagents decompose readily at temperatures above –15 °C, with β-hydrogens and branching at the α-position contributing to decreased stability. By contrast, phenylcopper is stable in an inert atmosphere up to 100 °C, while copper(I) acetylides are even resistant toward hydrolysis. In general, the stability of RCu increases in the order alkyl < aryl ≈ alkenyl < alkynyl. Steric hindrance near the copper–carbon bond has a stabilizing influence on aryl- and alkenyl-copper compounds.[11] Organocopper reagents are more stable in THF than in ether, and thermal stability is further enhanced in the presence of donor ligands such as sulfides, phosphines and amines. The use of dimethyl sulfide as the solvent in reactions of alkylcopper compounds has recently been recommended.[24] Since solvent molecules occupy all available coordination sites on copper, hydride transfer cannot occur and decomposition by β-elimination is effectively minimized. In addition, organocopper reagents form more readily at lower temperatures in dimethyl sulfide than in ethereal solvents, solubility may be increased, and enhanced reactivity has also been observed.

Polynuclear structures have been suggested for most organocopper compounds, which tend to be insoluble in conventional organic solvents. In dimethyl sulfide solution, phenylcopper apparently exists as an equilibrium mixture of trimeric and tetrameric aggregates, while methylcopper is a yellow precipitate, presumably of polymeric composition.[24] A recurrent feature of known organocopper crystal structures[11a] is a central metal atom core, in which copper typically adopts a digonal or trigonal coordination geometry. The formation of 1:1 ArCu·CuBr adducts is not uncommon,[25] and the exact synthetic protocol often plays a critical role in determining the nature of the cuprate species isolated.

Particularly interesting bonding patterns have been observed for arylcopper derivatives with nitrogen-containing *ortho* substituents (**1–3**).[26] Tetrameric in the solid state, with the four copper atoms positioned in a butterfly arrangement, these compounds adopt one of the configurations schematically depicted in Scheme 1. As indicated by X-ray crystallography, diastereomer (**6**) is the ground-state structure for compound (**1**), while for (**2**) it may represent an intermediate in the interconversion of enantiomeric configurations (**4**) and (**5**), a process that is rapid on the NMR time-scale. The situation is more complex for



(1)



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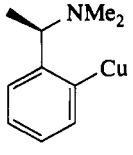
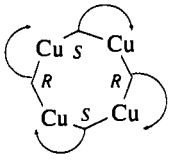
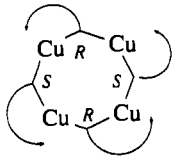


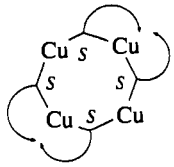
(3)



(4)



(5)



(6)

Scheme 1

compound (3), which possesses a chiral *ortho* substituent. The ways in which this ligand chirality influences the structures of the derived arylcopper and arylcuprate compounds may have relevance to the design of chiral cuprate reagents for asymmetric synthesis.

1.5.2.2.3 Heterocuprates [RCu(Z)Li]

The enhanced thermal stability of organocopper reagents imparted by the presence of donor molecules, as well as the high value of some R groups, prompted the development of heterocuprates, in which the donor ligand is incorporated into the reagent itself. Prepared according to the general equation (3), the same reagent is obtained regardless of the order of addition. Thus, the lithium anion of the donor ligand can be added to a solution of the alkylcopper compound, or an alkyllithium reagent can be added to a preformed heterocopper compound. Dicyclohexylamido-, dicyclohexylphosphido- and diphenylphosphido-cuprates have been particularly recommended, based on the enhanced thermal stability and reactivity of these reagents relative to other heterocuprates.[27] More recently, it has been reported[28] that di-*t*-butylphosphidocuprates exhibit significantly improved stability, while maintaining reactivity comparable to that of other phosphidocuprates. In contrast to diphenylphosphidocuprates, for which dimeric structures have been suggested, X-ray analysis indicates that $RCuP(Bu^t)_2Li$ is a monomer, presumably a result of the steric hindrance of the *t*-butyl substituents. In the crystal structure, both phosphorus and lithium exhibit tetrahedral geometries, with solvent molecules occupying three of the coordination sites on lithium (Figure 1).

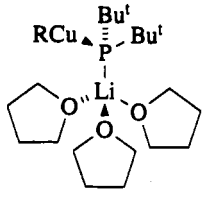


Figure 1

1.5.2.2.4 Homocuprates (R_2CuLi)

Diorganohomocuprates continue to be the most widely used organocopper reagents. These compounds are both more stable and more nucleophilic than their monoorganic counterparts.[29] They are, however, considerably less basic and less nucleophilic than the corresponding alkyllithiums. Like other organocopper compounds, diorganocuprates are very sensitive to heat and oxidants; oxidative decomposition to give the symmetrical organic dimer R—R occurs readily in the presence of oxygen, even at –78 °C. Of the dialkylcuprates, Me_2CuLi is the most stable, showing little decomposition at 0 °C, while secondary and tertiary organocuprates are best prepared at low temperature (–78 °C) in the presence of a stabilizing ligand. Very recently, the immobilization of cuprate reagents on solid supports has been described.[30] The dry polymer-bound cuprates are stable for up to two to three weeks at room temperature when stored under an argon atmosphere.

The dimeric structure (7) has long been suggested for Me_2CuLi, based on ^1H NMR, solution X-ray and vapor pressure depression data.[31] The proposed Cu_2Li_2 metal core with bridging organic substituents is, in fact, evidenced in the crystal structure of $Cu_2Li_2(o\text{-}C_6H_4CH_2NMe_2)_4$ (Figure 2a),[32] the only neutral cuprate for which X-ray crystallographic data are available. On the basis of spectroscopic information, a similar structure (Figure 2b) has also been proposed for $Cu_2Li_2(p\text{-tolyl})_4 \cdot 2Et_2O$, in which two solvent molecules are required to fill the lithium coordination sites occupied by the *o*-amino substituents in Figure 2(a). Evidence suggests that, in all of these compounds, the organic moiety is bonded more strongly to copper than to lithium, creating 'nucleophilic' and 'electrophilic' sites within the metal cluster.[33]

In the most pivotal structural investigation of organocuprates in recent years, Lipshutz reported[34a] the startling discovery that the classical Gilman reagent, Me_2CuLi, exists in halide-free THF solution, not as a discrete species, but rather as an equilibrium mixture containing significant amounts of free methyllithium. Attesting to the often crucial role played by lithium salts, the addition of a stoichiometric amount of LiI suppresses the equilibrium, and no methyllithium is detected. Interestingly, no equilibrium is observed when Me_2CuLi is prepared in ether, even if THF is then added to the mixture. However, the

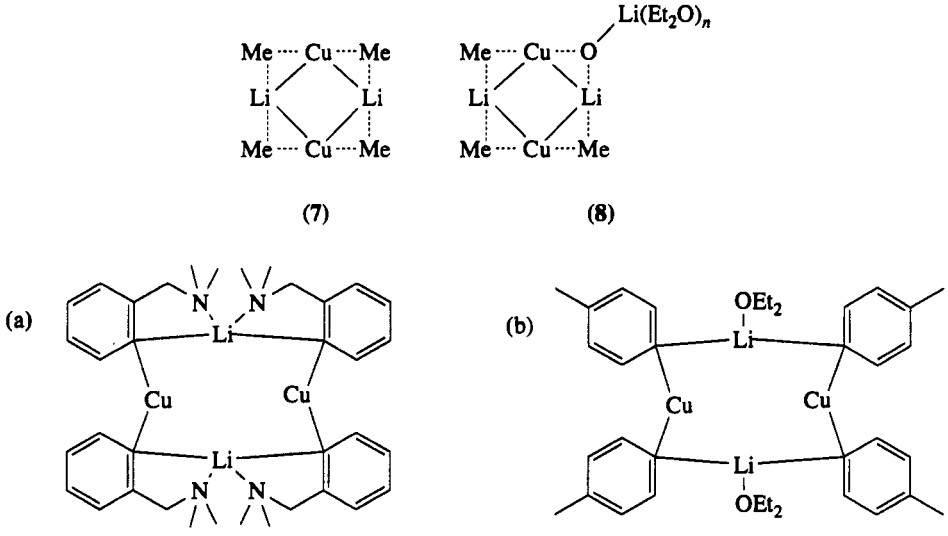


Figure 2

reagent is spectroscopically different from that prepared in THF or THF–ether.[35] Clearly, much remains to be learned about organocuprate reagents, but these findings do carry important synthetic implications.

The addition of $BF_3{\cdot}OEt_2$ to a solution of an organocopper compound often results in a reagent of enhanced reactivity and/or selectivity.[36] That organocopper compounds are compatible with $BF_3{\cdot}OEt_2$ at low temperature (*i.e.* transmetalation does not occur) has long been established, and the observed experimental results have been attributed primarily to substrate activation by complexation with the Lewis acid. However, recent spectroscopic and chemical evidence[34b,c] suggests that, when used in combination with an organocuprate, $BF_3{\cdot}OEt_2$ serves not only to activate the substrate, but also to modify the cuprate reagent itself. In particular, one equivalent of alkyllithium is irreversibly sequestered from the $R_4Cu_2Li_2$ reagent in the form of $RLi{\cdot}BF_3$, leaving R_3Cu_2Li as the species predominantly responsible for chemical reactivity. Excess $BF_3{\cdot}OEt_2$ must then function in its second, substrate-activating capacity, since R_3Cu_2Li is comparatively unreactive in its absence.

Corey has reported[37] the preparation of yet another type of modified cuprate reagent by mixing lithio dimethylcuprate and water in a 3:1 ratio. Of proposed structure (**8**), this new reagent exhibits enhanced reactivity and stereoselectivity in reactions with enones, effects that are proposed to be due to an increased ability of lithium to coordinate to the substrate. The Corey group has also prepared a rationally designed chiral heterocuprate reagent,[38] which undergoes highly enantioselective conjugate addition reactions with cycloalkenones.

1.5.2.2.5 Mixed homocuprates (RR'CuLi)CuLiCuLi

An obvious disadvantage of homocuprates is the fact that one potentially valuable organic ligand is necessarily wasted. Therefore, over the years considerable effort has been devoted to the search for suitable nontransferable (or 'dummy') ligands. A number of heteroatom substituents have been used for this purpose (see Section 1.5.2.2.3), and it should be noted that RCu(SPh)Li allows the successful transfer of secondary and tertiary alkyl groups, a feat not readily accomplished by homocuprates.[39] However, heterocuprates, including cyanocuprates, are generally less reactive than homocuprates. Alkynyl ligands have often been successfully employed as 'dummy' ligands; $MeOC(Me)_2C{\equiv}CH$ offers the advantage that the corresponding monoorganocopper compound is soluble in organic solvents. Most recently, the use of DMSO as a nontransferable ligand has been proposed.[40] Since product isolation is often complicated by the presence of added ligands, the fact that DMSO can be simply washed away represents a significant advantage.

1.5.2.2.6 Higher-order cuprates [$R_2Cu(Z)Li_2$, $R_{m+n}Cu_mLi_n$ $(m+n>2)$]

In contrast to earlier reports,[41] recent spectroscopic evidence[34a] indicates that cuprate reagents in which the stoichiometric ratio of RLi:RCu is >1:1 are not discrete species in ether or THF solution, but rather mixtures of the Gilman reagent, R_2CuLi, and free alkyllithium. The excess alkyllithium present in these mixtures may serve a beneficial role in some cases (*e.g.* converting the by-product RCu back into reactive R_2CuLi), accounting for the improved experimental results that have reportedly been obtained with 'R_3CuLi_2'.[42] By contrast, the higher-order cuprate Ph_3CuLi_2 is apparently observable in dimethyl sulfide solution.[43] Cuprate reagents in which the RLi:RCu ratio is <1:1 have also been described. R_3Cu_2Li is a discrete species in THF, while $R_5Cu_3Li_2$ is the first soluble cuprate formed upon addition of RLi to RCu in ether.[42b] The $R_5Cu_3Li_2$ reagent has proven to be particularly useful for effecting 1,4-conjugate addition to enals,[44] and it also exhibits better regio- and stereo-selectivity than does the Gilman reagent in S_N2' reactions with allylic carbamates.[45]

Better established are the higher-order cyanocuprates ($R_2CuCNLi_2$) extensively investigated by Lipshutz and coworkers.[46] These reagents represent a compromise between lower-order cyanocuprates and homocuprates, offering the increased stability of the former, while maintaining reactivity nearly comparable to that of the latter. The mixed gegenion compounds $R_2CuCNLiNa$ and $R_2CuCNMgX$ have also been examined; both are less reactive than the corresponding dilithio cyanocuprates.

Ashby[41] has reported that, like Me_2CuLi, Me_3Cu_2Li is dimeric in THF solution, but that $Me_5Cu_3Li_2$, which is formed only in ether, is monomeric. Lipshutz[46c] has presented spectroscopic evidence suggesting that higher-order cyanocuprates ($R_2CuCNLi_2$) are also dimeric in THF. However, for these reagents, the poorer Lewis basicity of ether apparently promotes higher states of aggregation in that solvent. The spectroscopic investigations conducted by the Lipshutz group have also provided fascinating insight into the dynamic behavior of organocuprates in solution, which stands in sharp contrast to the common perception of the essentially static nature of the reagents.

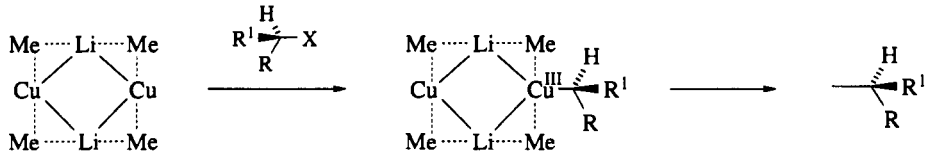
Like their lower-order homocuprate analogs, higher-order cyanocuprates suffer the disadvantage that only one organic ligand is transferred. Ligand transfer ability decreases in the order Bu > Ph > Me > vinyl, rendering selective vinyl transfer especially difficult. The 2-thienyl (2-Th) group has proven to be a particularly useful 'dummy' ligand for these reagents, allowing even vinyl substituents to be transferred with high selectivity.[47] The preparation of the mixed cyanocuprate $R(2\text{-Th})CuCNLi_2$ is most conveniently accomplished by simply adding an alkyllithium reagent to preformed 2-thienylcyanocuprate [(2-Th)CuCNLi], which is stable in THF solution for three weeks or more at room temperature and two months or more at –20 °C.[48]

1.5.2.3 Mechanism of the Reaction

Although much is now known about the coupling of organocopper reagents with organic electrophiles, many details of the reaction mechanism remain incompletely understood. In fact, recent findings indicate that more than one mechanism may be operative, depending upon the nature of the substrate involved (*vide infra*). Several general features of the reaction are clear: (i) the rate law is usually first order in both substrate and organocuprate; (ii) substrate reactivity follows the pattern typical for S_N2 reactions: primary > secondary >> tertiary; (iii) reactions of secondary bromides and tosylates proceed predominantly with inversion of configuration; (iv) alkenyl halides and alkenylcuprates both couple predominantly with retention of configuration; and (v) the reactivity of the transferred group decreases in the order primary > secondary > tertiary. These facts all argue against a process involving free radical intermediates, in agreement with the finding that free radical traps generally have little effect on the course of the reaction.

On the basis of this information, the reaction is now believed to proceed by way of an oxidative addition–reductive elimination pathway, in which the rate-determining oxidative addition step occurs with inversion of substrate configuration by a bimolecular nucleophilic substitution mechanism (Scheme 2). The retention of sp^2-configuration is also consistent with an oxidative addition process,[3b,49] and a stereoelectronic rationale for this stereochemical outcome has been proposed.[50] The intermediate (**9**) has been the focus of much debate, however, since a Cu^{III} species of this type is expected to be very unstable.[51,52] In a modification of this mechanism, it has been suggested[31] that the dimeric structure of the organocuprate reagent plays a critical role in the reaction, allowing the formal $2e^-$ oxidation to take place by way of cooperative single-electron oxidations of both copper atoms in the metal cluster, thereby eliminating the need to generate a high energy Cu^{III} transient intermediate (equation 4).

Inconsistent with both of the above mechanistic proposals is the recent finding that secondary iodides, unlike bromides and sulfonates, undergo nearly complete racemization in coupling reactions with organocuprates.[54] In addition, bicyclic compounds are produced in reactions of 6-iodocyclooctene with

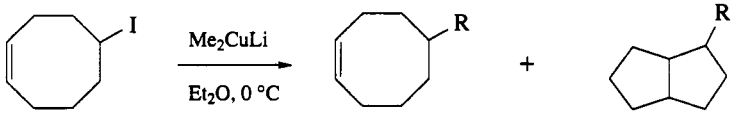


(7) (9)

Scheme 2

$$[Cu^{I}_{2}Li_{2}Me_{4}] + RI \longrightarrow [Cu^{II}_{2}Li_{2}Me_{4}R]I \longrightarrow MeR \qquad (4)$$

lithium cuprate reagents (equation 5),[55] strongly supportive evidence for the intermediacy of free radicals in these reactions. In fact, bicyclic products are also found in reaction mixtures of the alkenic bromide substrate. By contrast, elimination is the only competing pathway observed in reactions of the corresponding *p*-toluenesulfonate.



R = H; 17%
R = Me; 13%

R = H; 23%
R = Me; 4%

(5)

An explanation for these results may be found in a comparison of the electrochemical reduction potentials for the various substrates.[56] Secondary alkyl iodides give two waves at potentials considerably more positive than the single wave exhibited by alkyl bromides, while reductive cleavage of alkyl sulfonates occurs at the S—O bond rather than the C—O bond. Two competitive pathways therefore appear to be operative for reactions of organocuprates: (i) the S_N2-like mechanism depicted in Scheme 2; and (ii) an alternative mechanism involving single-electron transfer (SET). The observed difference in reactivity order between primary substrates (OTs ≥ I > Br > Cl) and secondary substrates (I >> OTs > Br > Cl) is a reflection of this mechanistic duality. Thus, while an energetically favorable electron transfer pathway is available for secondary alkyl iodides, secondary tosylates are constrained to react by the much slower S_N2-like mechanism. For primary alkyl substrates, on the other hand, the S_N2-like process is considerably more competitive, reactivity follows the standard order of leaving group ability, and the occurrence of free radical side reactions (*e.g.* cyclization, alkylative cyclization, reduction) is diminished. Even primary iodides give significant amounts of the dehalogenated by-product in reactions with $R_2CuCNLi_2$, however.[57]

More extensive investigations[55] have revealed additional complexities in the SET mechanism. Thus, evidence supportive of both free radical and radical anion ($S_{RN}1$) chain processes has been observed in reactions of alkyl iodides, both pathways presumably being initiated by electron transfer between cuprate and substrate. Although incapable of sustaining free radical chain processes, alkyl bromides do apparently react, at least in part, by an $S_{RN}1$ mechanism. While the intervention of free radical processes in reactions of alkyl bromides would appear to be inconsistent with the predominant stereochemical inversion exhibited by these substrates, Ashby has demonstrated[58] that electron transfer processes can occur with inversion of configuration.

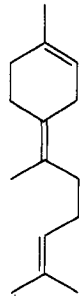
In summary, while alkyl sulfonates react exclusively by the S_N2-like mechanism of Scheme 2 (or equation 4), evidence for alternative SET processes in reactions of both alkyl iodides and alkyl bromides has recently accumulated. The relative contributions of S_N2 and SET mechanisms in reactions of alkyl halides is difficult to quantify, however, since the 'normal' substitution product can arguably arise *via* either pathway.

1.5.2.4 Reactions With Organic Substrates

1.5.2.4.1 Alkyl halides and sulfonates

Primary alkyl halides and sulfonates react readily with organocopper reagents, the order of reactivity being that typical of nucleophilic substitution reactions (OTs > I > Br >> Cl). Since alkene, ester, amide, ketone and nitrile functionalities are all tolerated, the method is of widespread generality, and innumerable synthetic applications have been reported in the literature. The spectacular success enjoyed by organocopper reagents in reactions with unactivated alkyl halides is to be contrasted with the general failure of other transition metal catalyzed cross-coupling reactions of these substrates (see Section 1.5.3), in which β-elimination is usually a predominating side reaction.

Monoorganocopper compounds are generally less reactive than organocuprates and are therefore less often used in reactions with unactivated alkyl halides. Interestingly, however, in one recently reported[59] reaction, an alkylcopper species derived from the Grignard reagent and one equivalent of CuI coupled satisfactorily at a neopentyl center, while all other reagents failed. Vinylcopper compounds, although not especially reactive, can be alkylated smoothly in the presence of HMPA and a trialkyl phosphite.[21a] In an application of this procedure, tetrasubstituted alkenes have been prepared in a stereodefined fashion from (2-stannylalkenyl)boranes by sequential transmetalation and alkylation of the borane and stannane moieties.[60] A similar strategy was utilized in recently reported syntheses of (*E*)- and (*Z*)-γ-bisabolene (**10**).[61] Alkynyl copper reagents are not effective coupling partners with alkyl halide substrates.



(10)

The coupling of organocopper reagents with primary alkyl substrates is often accomplished as effectively under catalytic conditions as it is with stoichiometric organocopper reagents. Whereas a large excess of the stoichiometric reagent is often necessary, the use of copper in catalytic amounts appears to ameliorate this requirement. Alkyl sulfonates are reported to be particularly successful substrates in copper-catalyzed coupling reactions.[62] Grignard reagents are by far the most frequently employed organometallics in these reactions, but copper-catalyzed alkylations of alkyllithium reagents are not uncommon.[10c,63] The copper-catalyzed alkylation of a vinyl aluminate has also been reported.[64] Copper catalysis is known to alter the regioselectivity of reactions of allylic Grignard reagents. Thus, although allylic Grignard reagents ordinarily exhibit a strong preference for reaction at the γ-position, even when that position is the more sterically hindered, under copper catalysis, prenylmagnesium chloride is alkylated at the primary α-position with >99% regioselectivity.[65]

As a rule, stoichiometric cuprate reagents have provided the most consistently successful results in reactions with primary alkyl electrophiles. Diethyl ether is the solvent of choice for reactions of alkyl sulfonates, while reactions of alkyl halides appear to be facilitated by THF. The enhanced basicity of the cuprate reagent in THF may be problematic, however, when racemization of an adjacent chiral center or elimination is a competing side reaction. For example, reactions of serine-derived β-halo esters must be performed in ether, since elimination by-products are the only products isolated when THF is employed as the solvent;[66] elimination is more problematic with sulfonate than with halide leaving groups.

A number of mixed homocuprates and heterocuprates have been successfully employed in coupling reactions with alkyl halides (see Sections 1.5.2.2.5 and 1.5.2.2.3). The phosphido heterocuprates $RCuP(Bu^t)_2Li$[28] and $RCuPCy_2Li$[27b] react readily with primary bromides and iodides, providing coupled products in yields comparable to those obtained with homocuprates. Heterocuprates, of course, offer the advantage that only one equivalent of the organic ligand is required. In a recently reported[67] synthesis of

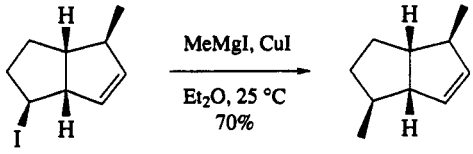
12-HETE, a new higher-order heterocuprate of the type $RCu(CN)_2NBu_4Li$ was the only reagent to provide satisfactory yields in the coupling of a 1,4-dienylcuprate with an alkyl iodide.

Higher-order cyanocuprates ($R_2CuCNLi_2$)[46] have proven to be the most reactive of all organocopper reagents in reactions with alkyl halides.[68,69] In fact, the reagents are too reactive with primary iodides for the reaction to be of general synthetic utility, since reduction is usually a serious side reaction even at low temperature. Coupling with primary bromides, on the other hand, is facile at –50 °C, and less than 2 equiv. of the cuprate reagent are required. Even primary chlorides, typically very poor substrates, react well with $R_2CuCNLi_2$, although chemospecific displacement of bromide in the presence of chloride is easily accomplished.

Higher-order cyanocuprates are particularly useful for reactions of secondary alkyl substrates. Although substitution of secondary halides can be successfully effected with lower-order cuprate reagents, results are variable due to competing elimination and reduction side reactions. By contrast, the $R_2CuCNLi_2$ reagents generally provide reproducibly high yields of coupled products in reactions with secondary iodides and bromides. Exceptions are transfers of phenyl and *s*-alkyl, for which the corresponding Gilman reagents are more effective. Secondary chlorides are not reactive with any of the reagents. Interestingly, higher-order cyanocuprates do not react with secondary mesylates and react only sluggishly with secondary tosylates. By contrast, sulfonates are more reactive than halides in reactions with lower-order homocuprates.

Double substitution of geminal dibromides is best accomplished by treatment with an organocuprate, followed by the addition of an alkyl iodide to the crude reaction mixture.[70] The reaction has found especial application for the synthesis of dimethylcyclopropanes, ubiquitous in natural product chemistry. Excellent yields are often obtained with Me_2CuLi,[71] but with less reactive substrates higher order cyano- and thiocyano-cuprates sometimes provide better results.[72] Spiro dialkylation of geminal dibromides has also been accomplished.[73] Vicinal dibromides, on the other hand, afford alkenes upon treatment with dialkyl cuprates.[74]

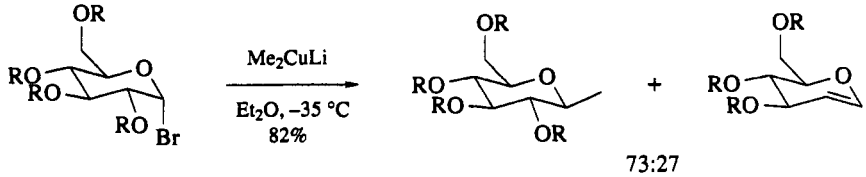
The issue of stereochemistry in reactions of organocopper reagents with secondary electrophiles was addressed briefly in Section 1.5.2.3. In general, bromides and sulfonates react predominantly with inversion of configuration, while iodides undergo extensive racemization by a free radical pathway. Iodide (**11**), with a strong bias for substitution from the *exo* face, was reported[75] to react with complete retention of configuration (equation 6). The corresponding tosylate, for which an electron transfer pathway is not available, was unreactive. Net retention of configuration has also been observed in reactions of secondary sulfonates, although not in this case by an SET mechanism. In one example, intramolecular carbamate participation was invoked to explain the observed stereochemical results.[76] Poor stereospecificity in reactions of alkyl sulfonates may also result from a competing double inversion process when I^- is present in the reaction mixture.[77]



(6)

(**11**)

C-Glycosides have been prepared by the reaction of α-glycosyl halides with dialkylhomocuprates (equation 7).[78] The reaction proceeded with complete inversion of configuration, despite the fact that α-halo ethers are expected to be especially susceptible to electron transfer processes. Reductive elimination was a serious side reaction, however. With these substrates, higher-order cyanocuprate reagents were surprisingly unreactive, while Grignard reagents gave mixtures containing both α- and β-glycosides, as well as elimination and reduction by-products.



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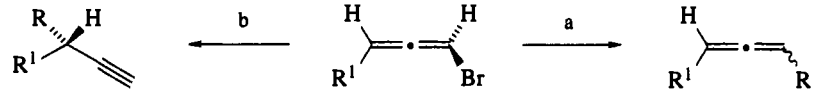
(7)

1.5.2.4.2 Alkenyl halides and related electrophiles

Cross-coupling of alkylcopper compounds with alkenyl halides is not generally successful, because the reagents are unstable at the temperatures usually required to effect reaction. Vinyl halides do undergo facile substitution by lithium dialkylcuprate reagents, however. As mentioned in Section 1.5.2.3, alkenic geometry is predominantly retained, but stereochemical scrambling may be observed when an alternative conjugate addition–elimination pathway is available.[2] In combination with hydrometalation and halometalation methodology, the procedure allows the regio- and stereo-specific preparation of trisubstituted alkenes from alkynic precursors. Methyl substitution is an especially common synthetic operation, due to its application to the synthesis of terpenoid natural products. Substitution reactions of vinyliodonium salts, themselves derived from vinylsilanes, have also been reported.[79]

Cuprate reactions of allenyl halides have been the focus of considerable investigation. The ratio of product resulting by a direct substitution pathway (Scheme 3, path a) to that produced by an S_N2' mechanism (path b) is dependent upon both the nature and structure of the reagent and the substitution pattern of the substrate.[80] In general, the Gilman reagents, R_2CuLi, afford allenic products exclusively, while RCuCNLi and (RCuBr)MgX·LiBr exhibit highly selective S_N2' reactivity, except when this pathway would be strongly disfavored due to steric hindrance (R = secondary or tertiary alkyl). Unpredictably, phenylcyanocuprate affords the product of direct substitution with high regioselectivity, while (PhCuBr)MgBr·LiBr provides the alkynic S_N2' product with equally high selectivity.



Scheme 3

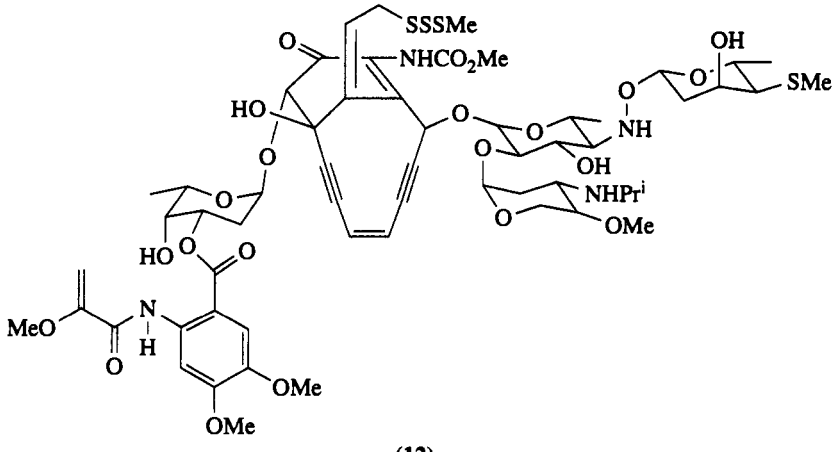
The stereochemistry of the direct substitution reaction has been the subject of some debate.[81] Most recently, it has been reported[80b] that reactions of alkylheterocuprates proceed with high *syn* selectivity, while inversion of allenyl configuration, or *anti* selectivity, is observed in reactions of phenylcopper reagents. The degree of selectivity is variable and may be a reflection of product isomerization under the reaction conditions.[82] Predominant *anti* stereoselectivity (*anti:syn* ratios range from 91:9 to >99:1) is observed also in S_N2' reactions of allenyl halides (see Scheme 3),[80b,83] a finding that is consistent with the known preference for *anti* substitution of allylic substrates (see Section 1.5.2.4.5). This method for alkyne preparation has found application in the leukotriene area,[84] and also for the synthesis of alkoxy alkynes.[85]

Vinylcopper reagents, in contrast to their alkyl analogs, have proven to be extremely unreactive toward vinyl halide substrates. However, the desired cross-coupling reaction can be effected in the presence of a palladium catalyst, providing access to stereodefined 1,3-dienes, valuable synthetic intermediates. The procedure has been extensively investigated by Normant and Alexakis,[21] who have additionally discovered that zinc halide cocatalysts allow the transfer of both vinyl ligands of cuprates derived from Grignard reagents. Likewise, although lithium cuprates transfer only one organic ligand in these zinc–palladium catalyzed reactions, both groups can be successfully transferred if a magnesium halide is also added to the reaction mixture. These reactions are all highly stereospecific, proceeding with virtually exclusive retention of configuration in both components.

In a recent application of similar methodology, α-vinyl acrylates were prepared by palladium-catalyzed cross-coupling of lithium (α-carbalkoxyvinyl)cuprates with vinyl halides.[86] Use of the dicyclohexylamido group as the nontransferable ligand in this reaction was necessary, since alkyne ligands transferred preferentially over the α-carbalkoxy moiety. It should be noted that (α-carbalkoxyvinyl) cuprates are, in general, extremely unreactive reagents, reacting in the absence of catalysts only with activated halides (allylic, propargylic, acyl, α-halo ethers).[87] α-Cupriopyrone, a special member of the class, is, in fact, the least nucleophilic organocopper reagent known.[88]

Palladium catalysis is also involved in an exceptionally mild procedure for the stereospecific preparation of enynes.[89] A catalytic version of the Stephens–Castro coupling,[90] the reaction presumably involves *in situ* generated copper(I) acetylide intermediates and proceeds with retention of alkenyl configuration. Several experimental modifications have been reported.[91] Notable synthetic applications include ynenol lactone inhibitors of human leukocyte elastase,[92] an irreversible inhibitor of soybean lipoxygenase,[93] and a number of eicosanoid metabolites of arachidonic acid.[94] Most recently, the reaction has been utilized extensively in synthetic approaches[95] to the bicyclic enediyne core common to the esperamicin, *e.g.* (**12**), and calichemicin antitumor agents, compounds that are of considerable biological interest. The reaction sequence depicted in Scheme 4[95a] is representative of the general approach and is illustrative of the effi-

ciency of the coupling procedure. The coupling of alkynes with allenyl bromides has also been reported.[96] Palladium-catalyzed coupling reactions of organometallics other than organocopper reagents are discussed in Section 1.5.3.2.



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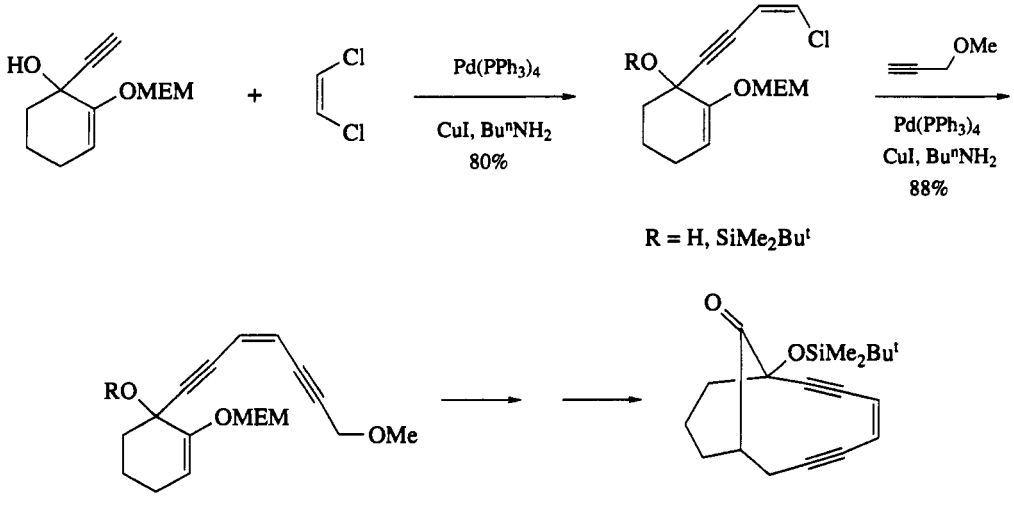
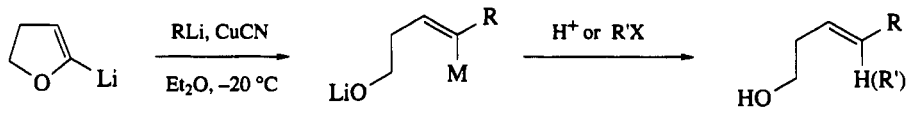


Scheme 4

The coupling of organocopper reagents with nonhalide vinyl electrophiles has also been accomplished. Displacement of enol phosphates can be effected in good yields with very reactive dialkylcuprates.[97] However, less reactive cuprates (*e.g.* Me_2CuLi) give low yields of the coupled product, and hindered enol phosphates are unreactive. Diphenyl phosphates derived from chlorodifluoromethyl aryl ketones do not undergo direct substitution of the enol phosphate moiety, but are rather metalated to give a fluorinated vinylcopper intermediate, which can then be alkylated with allylic halides.[98] Like enol phosphates, vinyl triflates can be regioselectively prepared from the corresponding ketones, and they have proven to be more reactive than enol phosphates in reactions with cuprates.[99] Again, retention of alkenyl configuration is the rule, but some isomerization may occur.

Dihydrofuran and dihydropyran substrates react with organocopper reagents to provide homoallylic and bishomoallylic alcohols of (*E*)-configuration (equation 8).[100b] This reaction works best with ratios of RLi:CuX well exceeding 2:1; in fact, only 2 mol % of CuCN is required.[100] The stereochemical outcome of the reaction is attributed to the formation of a mixed dihydrofuranylalkylcuprate, followed by migratory insertion with inversion of configuration, a process that is well precedented in organoboron chemistry.

Organometallic substitution of iron-complexed dioxolenes has been reported.[101] The reaction proceeds with net inversion of configuration, the result of a two-step addition–elimination pathway. Dialkylcuprates, higher order cyanocuprates and Grignard reagents have all been employed, and sequential dis-



(8)

placements of both vinyl ether substituents can be accomplished. A single diastereomeric product is produced in reactions of enantiomerically pure dioxolene substrates.[102]

1.5.2.4.3 Alkynyl halides

Like the Stephens–Castro reaction, Cadiot–Chodkiewicz coupling of terminal alkynes with alkynyl halides is presumed to proceed by way of copper(I) acetylide intermediates. The use of preformed copper acetylide reagents is also successful and, in fact, circumvents the problem of homocoupling sometimes encountered in the classical procedure. The reaction is convenient and high yielding, and is compatible with numerous functionalities, including free hydroxy and carboxy groups.[103] Arylcopper compounds react analogously with alkynyl halides,[104] providing a route to arylalkynes that is complementary to the Stephens–Castro coupling (see Section 1.5.2.4.4).

Metal–halogen exchange is a competing side reaction in the coupling of vinylcopper reagents with alkynyl halides. With monovinylcopper compounds, this problem can be overcome by performing the reaction in a mixture of THF–TMEDA, but lithium divinylcuprates undergo nearly exclusive metal–halogen exchange regardless of the reaction conditions.[21a] They can, however, be converted to the corresponding vinylcopper compounds by treatment with another equivalent of copper(I) halide prior to the addition of the alkynyl halide substrate, an advantageous procedure in light of the ready availability of divinylcuprates by carbocupration of alkynes.[21b] High yields of stereoisomerically pure 1,3-enynes can be obtained in this fashion. More recently, Stang and Kitamura have reported the stereospecific preparation of conjugated enynes by direct coupling of vinylcopper compounds with alkynylphenyliodonium tosylates.[105]

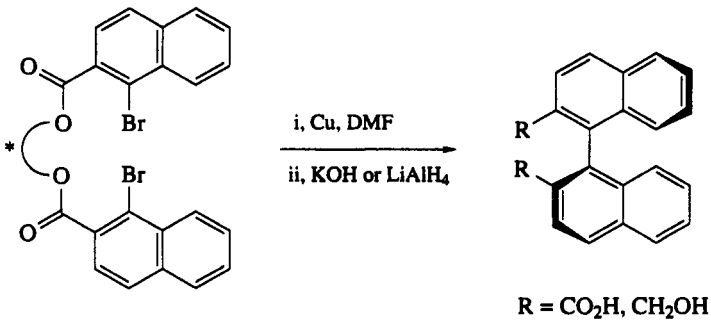
1.5.2.4.4 Aryl halides

Because aryl ligands are better able than alkyl ligands to adopt the bridging, two-electron three-center bonding pattern characteristic of organocopper reagents (see Section 1.5.2.2),[11a] metal–halogen exchange predominates in reactions of aryl halides with alkylcopper reagents, especially dialkylcuprates. Therefore, alkyl–aryl coupling is often better accomplished by the alternative reaction of an arylcopper reagent with an alkyl halide. If aryl halide substitution must be effected, RCu·Lig reagents are more successful than R_2CuLi. Alkyl substitution of halopyridines has been accomplished with magnesium dialkylcuprates;[106] copper-free Grignard reagents, lithium dialkylcuprates, and nickel- or palladium-catalyzed coupling procedures were all ineffective for this transformation.

Aryl triflates undergo successful cross-coupling with higher-order cyanocuprates.[99] Heterocyclic triflates are also reactive, but the yield may be strongly dependent upon the structure of the reagent.[107] Lower-order Gilman reagents, although effective in coupling reactions with vinyl triflates, cause only S—O bond cleavage in reactions with aryl triflates.

The majority of reported reactions of aryl and heteroaryl substrates with organocopper reagents are examples of Stephens–Castro coupling[90] or the more recent catalytic version of that reaction.[89] The reaction has found recent application in syntheses of C-(6)-substituted pterins and pteridines,[108] substituted pyridines,[109] and the antitumor antibiotic fredericamycin A,[110] to name a few. Aryl iodide can be chemospecifically displaced in the presence of bromide,[110] and 2,5-dibromopyridine is regioselectively substituted at the 2-position.[109] Substitution of halobenzenes by propargyl alcohol, followed by oxidative cleavage, provides a convenient route to terminal arylalkynes.[111] Fused heterocycles are formed in reactions of aryl halides bearing nucleophilic *ortho* substituents.[90,112]

The classical Ullmann reaction has also attracted renewed interest in recent years. Miyano has prepared optically enriched binaphthyl derivatives by intramolecular biaryl coupling, as shown in equation (9).[113] Diastereoselectivities of up to 70% have been obtained with a binaphthol chiral auxiliary in the linking chain. Intermolecular cross-coupling is best accomplished with preformed arylcopper compounds.[114]

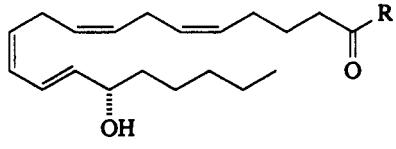


(9)

1.5.2.4.5 Allylic, benzylic and propargylic electrophiles

Allylic, benzylic and propargylic electrophiles are more reactive than the corresponding saturated compounds toward nucleophilic attack, and organocopper reagents of virtually every description, both catalytic and stoichiometric, have been employed successfully in reactions with these activated substrates. In addition to the typical halide and sulfonate leaving groups, ordinarily unreactive ether, ester, sulfone,[115] phosphonate,[116] carbonate[117] and carbamate[118] moieties can all be displaced from an allylic or propargylic position. Apart from their obvious synthetic potential, reactions of allylic and propargylic electrophiles are also of considerable mechanistic interest, because of the intriguing regio- and stereochemical questions posed by these substrates. It is primarily these issues that will be addressed in the following section.

Primary allylic halides exhibit a preference for direct substitution (α-attack) in reactions with a variety of organocopper reagents, including lithium cuprates, copper(I) acetylides and catalytic organocopper compounds. Regioselectivity is often quite high, especially with γ,γ-disubstituted substrates, and alkenic stereochemistry is usually retained. For example, in a recently reported synthesis of (15*S*)-HETE (**13**) sequential substitution at both primary positions of (*Z*)-1,4-dichlorobutene was accomplished without loss of the (*Z*)-alkenic geometry.[119] Palladium-catalyzed Stephens–Castro coupling (see Section 1.5.2.4.2) was another key step in the synthesis.

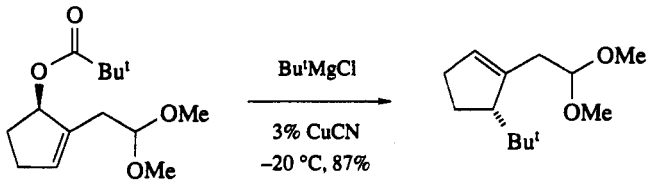


(**13**)

Secondary allylic halides, on the other hand, exhibit regioselective S_N2' reactivity (γ-attack), particularly when the γ-position is unsubstituted. Thus, although sometimes highly regioselective, reactions with these reagents are not regiospecific.[120] Regioselectivity is also dependent upon the substitution pattern of the substrate in reactions of allylic esters with lithium cuprates and catalytic organocopper compounds. Again, a preference for nucleophilic attack at the less hindered position is evidenced, and regioisomeric substrates give rise to the same product mixtures.[121] Reactions of acyclic substrates that proceed with allylic rearrangement (γ-attack) often display moderate to good (*E*)-selectivity in formation of the new double bond.

Regioselectivity is less predictable when both termini of the allylic system are comparably substituted. Results can be dependent on the leaving group; oxygen leaving groups appear to favor α-attack more than halides, and chloride is more S_N2 selective than bromide.[122] Very high S_N2' selectivity has been reported for reactions of some cyclic allylic esters with lithium cuprate reagents,[123] but exclusive α-substitution has been observed when γ-attack was disfavored by steric crowding at the δ-position.[124] Regioselective (*ca.* 9:1) α-attack has also been reported for reactions of (*Z*)-4-hexenolide with both lithium and magnesium cuprates.[125] As part of research efforts directed toward the total synthesis of ginkgolide B, Corey and Gavai[126] discovered that highly selective (≥98:2) S_N2' displacement of cyclopentenyl pivalate (**14**) could be effected with a Grignard reagent and 3 mol % of CuCN (equation 10). By contrast, the stoichiometric higher-order lithium cyanocuprate was much less regioselective and favored direct substitution.

A number of organocopper reagents reportedly exhibit S_N2' selectivity even when steric factors would appear to favor α-attack. Magnesium cuprates, in general, show greater propensity to undergo reaction

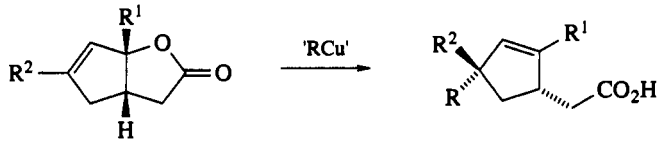


(10)

(14)

$S_N2':S_N2$ = >98:2

with allylic rearrangement than do their lithium counterparts.[127] The complex organocopper species RCu·MgBrX·LiBr displayed high (≥98:2) S_N2' selectivity in reactions with 1,4-diacetoxy-2-butene,[128] but only with R = alkyl; reactions of the phenyl reagent were low yielding and S_N2 selective. Curran has reported[129] almost exclusive S_N2' stereospecificity, regardless of substitution pattern, in reactions of the bicyclic lactones (**15**) with MeMgBr–CuBr·Me_2S (1:1) (equation 11). One full equivalent of CuBr·SMe_2 was required for high regiospecificity, and CuBr·SMe_2 produced a more selective reagent than did CuI or CuCN. Reactions of the same substrates with lithium cuprates, on the other hand, were controlled by the substrate substitution pattern, but were highly regioselective in favorable cases. This procedure has found recent application in syntheses of the triquinane sesquiterpenes, (±)-hypnophilin (**16**) and (±)-coriolin (**17**).[130]



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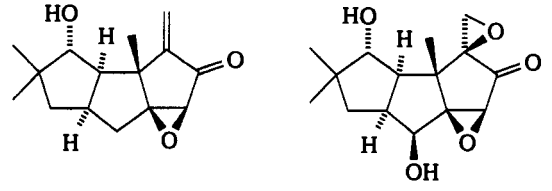
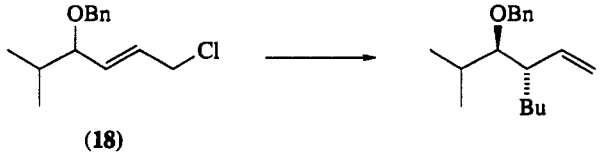


(16) (17)

Copper-catalyzed reactions of organozinc reagents exhibit high S_N2' regiospecificity in reactions with allylic halides, even when steric and/or electronic factors would appear to favor S_N2 attack.[131] The regiospecificity of these copper-catalyzed reactions stands in contrast to nickel- or palladium-catalyzed reactions of organozinc reagents, in which attack occurs regioselectivity at the least hindered position. Very recently, Nakamura[132] has reported virtually complete diastereofacial selectivity in S_N2' reactions of organocopper reagents with 4-alkoxyallylic chlorides (equation 12). Whereas lithium dialkylcuprates reacted with (**18**) predominantly by an S_N2 pathway, $Bu_2CuZnCl$,[133] $Bu_2CuTi(OPr^i)_3$, BuCu·BF_3, and Bu_2Zn/cat. CuBr·SMe_2 all provided the γ-substituted products with regioselectivities of ≥98:2 and *anti*-diastereoselectivities of ≥99:1. Reactions of other substrates and reagents were also highly *anti*-S_N2' selective. This procedure promises to find widespread application for the stereoselective construction of acyclic quaternary centers.



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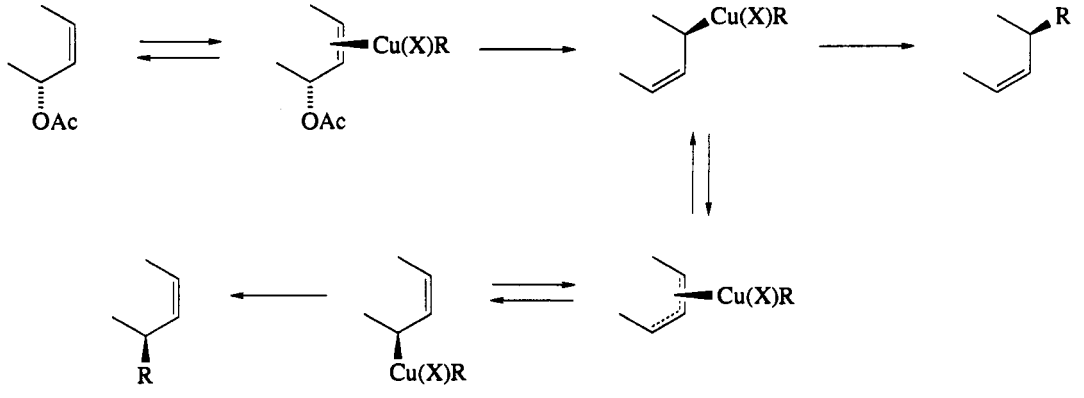
(18)

Suzuki reported[134] that copper borates ($R_3MeB^-Cu^+$) exhibit predominant S_N2' reactivity toward allylic halides. A similar 'ate' complex ($RF_3B^-Cu^+$) is also proposed to be the reactive intermediate in the RCu·BF_3 system developed about the same time by Yamamoto and coworkers.[36] This latter reagent exhibits remarkable S_N2' regiospecificity in reactions with a variety of allylic substrates, including halides,

esters and alcohols. Lithium cuprates[135] and higher-order cyanocuprates[136] have also been used in conjunction with $BF_3{\cdot}OEt_2$, again with S_N2' regiospecificity. The $R_2CuCNLi_2{\cdot}BF_3$ reagent has proven especially useful for S_N2' reactions of γ-oxygenated α,β-unsaturated esters, substrates which are highly susceptible to reduction side reactions. It should be noted, however, that a seemingly similar reagent, $RCu{-}(AlCl)_n$, effects highly selective S_N2 substitution (α:γ = 97:3) of γ-acetoxy-α,β-unsaturated esters.[137]

A mechanistic proposal that accommodates these diverse experimental results is presented in Scheme 5. The result of extensive research efforts in Goering's laboratory,[121c,138] it postulates that coordination of the organocopper reagent to the alkenic π-system is followed by formation of a σ-complex with attachment of copper at the γ-position. Immediate reductive elimination then directly affords the S_N2' product, whereas prior isomerization to a π-complex results in the loss of regiochemical information and leads to the possible formation of both α- and γ-substituted products. Investigations with isotopically labeled, symmetrical substrates confirm that, as required by the proposed mechanism, *all* organocopper reagents exhibit some degree of S_N2' regiospecificity in completely unbiased systems. In agreement with the experimental observations discussed earlier, this S_N2' specificity is barely detectable in reactions of lithium dialkylcuprates, a result attributable to rapid σ–π isomerization. By contrast, isomerization is minimized in reactions of lower-order cyanocuprates RCuCNLi or $RCu{\cdot}BF_3$, and virtually exclusive S_N2' substitution obtains. Bäckvall[139] has invoked a similar mechanistic rationale to explain his finding that regioselectivity in copper-catalyzed reactions of allylic acetates with alkyl Grignard reagents is strongly dependent upon the rate of addition of the organometallic reagent to the reaction mixture.



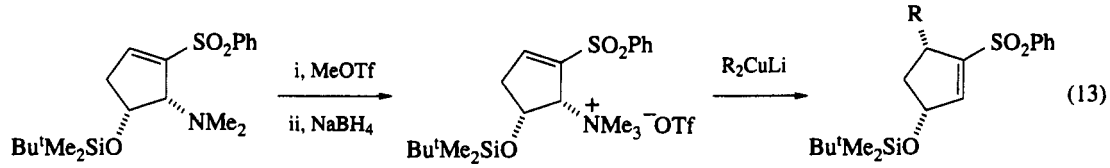
Scheme 5

The stereochemical outcome of the substitution of allylic substrates by organocopper reagents can also be explained by the mechanism depicted in Scheme 5.[138b] Initial coordination of the organocopper reagent is expected to occur on the less hindered face of the allylic system. In most substrates, this will be the face opposite the leaving group, thus accounting for the predominant *anti* substitution observed in all of the reactions (both S_N2 and S_N2') discussed thus far. It should be noted, however, that *syn* substitution may prevail when *anti* attack is strongly disfavored by steric factors.[138b,140]

By contrast, reactions of allylic *N*-phenylcarbamates with lithium cuprates proceed with very high *syn*-S_N2' selectivity, regardless of steric considerations.[118,141] Goering proposes that the reversal in stereoselectivity and the enhanced regiospecificity observed in reactions of carbamate substrates are both consequences of a modified reaction mechanism, in which initial complexation of the copper reagent to nitrogen is followed by intramolecular, *syn*-facial delivery of copper to the γ-position of the allylic system.[142] A similar mechanism is presumably operative in the substitution of allylic alcohols by $RCu{\cdot}BF_3$, a reaction that also proceeds with *syn*-S_N2' specificity. On the other hand, selective *anti*-S_N2' substitution of allylic alcohols can be effected by means of the procedure developed by Murahashi,[143,144] which apparently involves addition of an *in situ* generated heterocuprate to a phosphonium ion intermediate.

Calo has reported[145] very high S_N2' regiospecificity in reactions of benzothiazolyl ethers with RMgX–CuBr. Again, the enhanced regiospecificity is attributed to coordination of the reagent to the ether moiety, and the isolation of coordination complexes lends credence to the proposal. Regioselectivity is completely reversed if the substrate is pretreated with copper(I) bromide prior to addition of the Grignard reagent, however. In that case, the Grignard reagent apparently attacks regioselectively at the least hindered position of a presumed copper(I) halide–substrate complex. The stereospecificity of the reaction has not been investigated. Ammonium salts are apparently also capable of intramolecular participation,

as indicated by the *syn*-S_N2' reaction of (**19**) with lithium cuprates (equation 13).[16] However, reaction of the regioisomeric substrate occurs in an *anti*-S_N2 fashion, since in that case the *syn*-S_N2' pathway is disfavored by steric hindrance of the adjacent silyloxy moiety.



(13)

(**19**)

Much of the foregoing discussion regarding allylic substrates applies also to propargylic electrophiles, which exhibit an even greater propensity to undergo reaction with organocopper reagents by an S_N2' mechanism. The preparation of allenes from propargylic substrates by this method has been reviewed elsewhere,[146] and will be discussed only briefly here. Among numerous synthetic applications, the reaction plays a central role in Okamura's synthetic approach to vitamin D[147] and vitamin A[148] analogs, and it has also been utilized for the synthesis of oxabetweenallenes.[149] Propargyl esters and sulfonates are the most commonly employed substrates, but halogen, amide, carbonate, phosphonate, ether and epoxide leaving groups have also been used. Direct conversion of propargyl alcohols to the corresponding allenes can be accomplished by means of the Murahashi procedure.[150] α-Allenyl phosphates and imides also undergo S_N2' substitution by organocopper reagents, in this case providing dienyl products.[183]

Regioselectivity is subject to steric control[152] when dialkylcuprates are employed as the nucleophilic reagents, but the complex organocopper species RCu·MgBrX·LiBr affords the allenic product exclusively, regardless of substrate structure.[153] In addition, monoorganocopper compounds are less susceptible than cuprate reagents to reduction side reactions. Higher-order cyanocuprates appear to be more effective than Gilman reagents for transfer of phenyl or of secondary or tertiary alkyl groups, although the reverse is true for *n*-alkyl reagents. *Anti* stereospecificity is observed in all of these reactions,[154] allowing the preparation of enantiomerically enriched allenes from optically active propargylic substrates. In the presence of donor ligands, racemization of the product allene by the cuprate reagent is minimized, and the stereospecificity of the reaction is increased.

In contrast to reactions of all other organocopper reagents, reactions of copper(I) acetylides with propargylic substrates result in regiospecific α-substitution. This procedure for the preparation of 1,4-diynes has proven useful in pheromone synthesis.[155]

1.5.2.4.6 Epoxides

Long valued by organic chemists as versatile synthetic intermediates, epoxides have experienced a resurgence in popularity over the past decade as a result of newly developed and highly efficient procedures for their preparation in homochiral form.[156] Owing to the polarity and strain of the three-membered ring, epoxides undergo reaction with a wide variety of reagents, the reactions proceeding in a stereospecific and often highly regioselective fashion.[157] Ring opening by carbon nucleophiles is arguably among the most synthetically useful of epoxide transformations, and organocopper reagents have proven to be especially well suited for this purpose. Not only are they more reactive toward epoxides than are organolithium or organomagnesium compounds, but the side reactions (*e.g.* rearrangement, elimination) that are promoted by the basicity or Lewis acidity of these other organometallics are not usually observed in reactions of organocopper reagents.

The reaction between epoxides and Gilman reagents was first reported in 1970,[158] and in the 20 years since, both lithium and magnesium homocuprates have been widely employed to effect ring opening of reactive mono- and di-substituted epoxide substrates. In reactions of monosubstituted epoxides, comparable results are also obtained with the heterocuprates, RCuCNLi,[159] but yields drop dramatically with less reactive di- and tri-substituted epoxides. In light of their enhanced reactivity toward alkyl halides (see Section 1.5.2.4.1), it is perhaps not surprising that the higher-order cyanocuprates, $R_2CuCNLi_2$, are also significantly more reactive than lower-order cuprates toward epoxide substrates.[46,160] Less than 1.5 equiv. of the cuprate reagent are usually sufficient, in contrast to the 2–5 equiv. commonly required in reactions of lithium homocuprates, and even poorly reactive cyclic and trisubstituted epoxides are successfully substituted under mild conditions. Tetrasubstituted epoxides afford only elimination by-products, however.

Epoxide opening has also been effectively accomplished with catalytic organocopper compounds.[161,162] Owing to the easy accessibility of many Grignard reagents, this is often the most convenient procedure by which to effect the desired transformation. In some cases, results are superior to those obtained with stoichiometric reagents.[163] However, epoxide opening by the halide ion of the Grignard reagent or of the copper halide catalyst is a common side reaction, and at times the halohydrin may become the sole product of the reaction.[163a,164] In fact, treatment with Li_2CuCl_4 constitutes a preparatively useful procedure for the synthesis of chlorohydrins from the corresponding epoxides.[165] It should be noted that the lithium halide salts present in most preparations of monoorganocopper compounds and homocuprate reagents may also participate in the epoxide opening reaction to produce halohydrin by-products.[166] This side reaction is virtually eliminated with higher-order cyanocuprate reagents, which are both more reactive and can easily be prepared in halide-free form.

Unreactive epoxides[166,167] and/or reagents[168] undergo successful reaction in the presence of $BF_3{\cdot}OEt_2$, which has proven to be uniquely effective among the Lewis acids examined in activating epoxides toward nucleophilic attack by organocuprate reagents. Lithium and magnesium homocuprates and higher-order cyanocuprates have all been used in combination with $BF_3{\cdot}OEt_2$ to good effect. The closely related reaction of aziridines with organocopper reagents is also facilitated by $BF_3{\cdot}OEt_2$.[169]

In general, the rate of epoxide opening by organocuprate reagents is more rapid in diethyl ether than in the more highly coordinating solvent, THF, which interferes with the coordination of the epoxide to Lewis acidic components in the reaction mixture. Also, elimination to form an allylic alcohol is a more problematic side reaction in THF than in ether.[170] On the other hand, organocopper compounds are often only poorly soluble in ether, and mixed solvent systems have proven advantageous in some cases.[171]

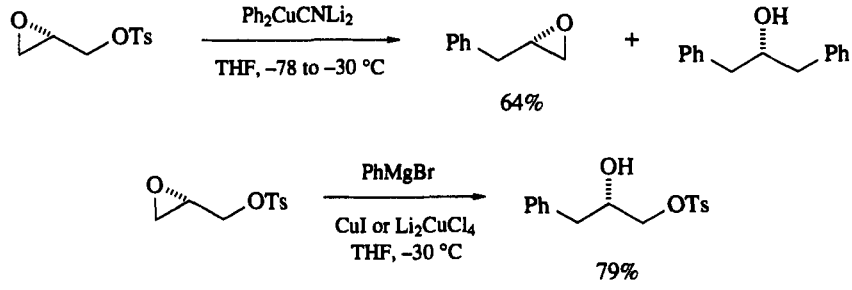
Chemoselectivity in reactions of functionalized epoxides is an issue of growing importance in light of the increasingly widespread use of epoxy alcohols and related derivatives as synthetic building blocks. Epoxy halides undergo reaction with organocopper reagents primarily by way of epoxide opening when both groups are comparably substituted.[172] In contrast, 'hard' nucleophiles, such as organolithium compounds, react with these substrates exclusively at the halo-substituted position.[172b,173] Steric factors have an overriding influence on chemoselectivity, however, and reactions of unsymmetrically substituted epoxy halides with organocopper reagents occur predominantly at the least hindered position. Thus, a primary iodide can be displaced in the presence of an internal, disubstituted epoxide. Although no substitution at the epoxide center is detected, reaction conditions must be carefully controlled in order to prevent reductive cleavage of the iodide, with concomitant epoxide opening and formation of an allylic alcohol.[174] The regio- and chemo-selective displacement of a primary allylic chloride in the presence of a trisubstituted epoxide has also been reported.[175]

Chemoselective reaction of epoxy sulfonates represents a more significant challenge, since the two electrophilic moieties are reported to be of nearly equivalent reactivity toward organocuprate reagents.[176] As expected on the basis of the epoxy halide results just discussed, the displacement of a primary tosylate can be smoothly accomplished in the presence of an adjacent disubstituted epoxide,[174c,177] and this reaction has been utilized in syntheses of disparlure and of other insect pheromones.[177] On the other hand, a recently reported[178] reaction of a cyclic glucopyranose-derived epoxide with either Me_2CuLi or MeMgCl–CuBr afforded in high yield the desired ring-opened product, leaving intact an exocyclic primary mesylate.

Symmetrically substituted vicinal epoxy mesylates undergo chemoselective epoxide opening by $R_2CuCNLi_2$–$BF_3{\cdot}OEt_2$ to provide the corresponding hydroxy sulfonates in good yield.[179] In the absence of $BF_3{\cdot}OEt_2$, ring closure occurs *in situ*, and doubly substituted compounds are produced. Similarly, the reaction of homochiral glycidyl tosylate with $Ph_2CuCNLi_2$ proceeds *via* a hydroxy sulfonate intermediate to afford the substituted epoxide, along with varying amounts of the product of double addition (Scheme 6).[180] In reactions of the same substrate with RMgBr–CuI, ring closure does not occur, and the hydroxy tosylates can be isolated in moderate to good yield. The very high chemoselectivity exhibited by this sterically unbiased epoxy tosylate substrate may be attributable in part to a deactivating effect of the adjacent epoxide moiety on the reactivity of the sulfonate toward S_N2 attack.

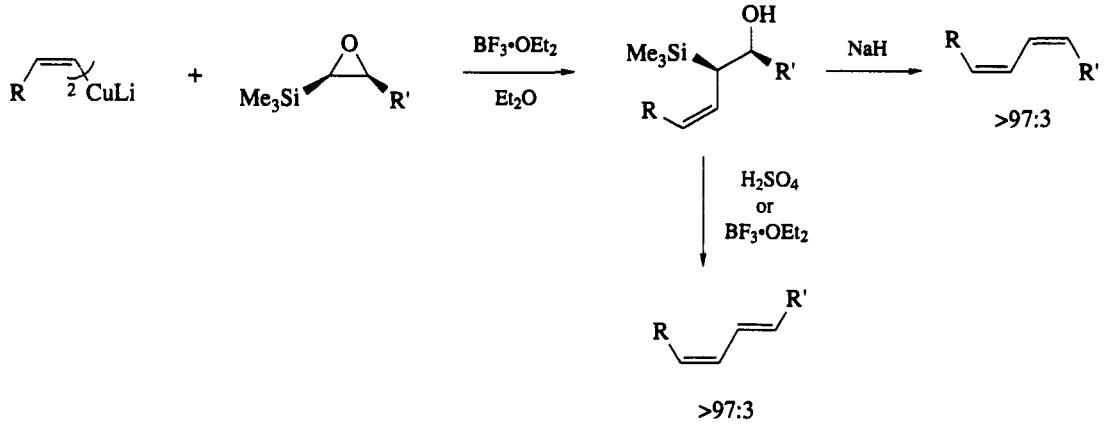
Like chemoselectivity, regioselectivity is also governed largely by steric factors, with attack occurring preferentially at the least hindered epoxide center. This generalization holds true even for reactions performed in the presence of $BF_3{\cdot}OEt_2$. However, stereoelectronic factors predominate in reactions of cyclic epoxides, which generally proceed predictably in a *trans*-diaxial fashion.

Epoxide substitutents that are capable of stabilizing a positive charge may direct nucleophilic attack to the α-position. For example, styrene oxide exhibits a greater proclivity than other terminal epoxides for substitution at the internal position;[166,181] regioselectivity is dependent upon the nature of the organocopper reagent. Ring opening of epoxysilanes occurs regiospecifically at the α-position, and this reaction forms the basis for the Hudrlik version of the Peterson alkene synthesis.[182] The use of vinylcuprate



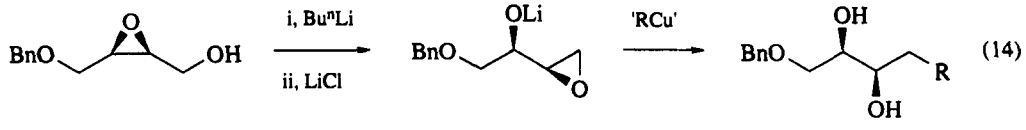
Scheme 6

reagents allows the stereospecific synthesis of conjugated dienes (Scheme 7),[167b] and homochiral allylic alcohols have been prepared by combining kinetic resolution of a silyl-substituted secondary allylic alcohol with Hudrlik–Peterson reaction of the resulting epoxysilane.[183] It should be noted, however, that epoxysilanes in which silicon bears at least one isopropoxy substituent undergo deoxygenation rather than substitution upon treatment with Pr^{i}MgBr–CuCN.[184]



Scheme 7

2,3-Epoxy alcohols that are branched at C-4 (γ-position) undergo exclusive substitution at C-2,[185] but in the absence of steric constraints reactions are usually nonregioselective. Significant regioselectivity has been observed in reactions of some sterically unbiased γ-oxygenated epoxy alcohols, however. In one case, it was reported that RMgBr–CuI provided a higher ratio of the C(2)-substituted product than did R_2CuLi.[171] Recently, Chong has reported[186] that C-2 selectivity is improved when reactions of unbranched epoxy alcohols are conducted in coordinating solvents, while the addition of BF_3·OEt_2 results in enhanced C-3 selectivity. Epoxy ethers exhibit a slight preference for reaction at C-3,[187] but, again, regioselectivity is subject to numerous contributing factors and is not easily predictable. Substitution at C-1 of a 2,3-epoxy alcohol can be accomplished under Payne rearrangement conditions (equation 14).[188] Lithium dialkylcuprates exhibit poor regioselectivity, but less reactive reagents (*e.g.* RCu, RCuCNLi) attack at C-1 with very high selectivity.



(14)

Although unsubstituted glycidic esters undergo reaction with organocuprate reagents exclusively at the terminal (C-3) position,[189] predominant C-2 attack is observed in reactions of substituted glycidic esters.[164,190] Moderate to high C-2 selectivity is also observed in reactions of (*E*)-glycidic acids, but sterically unbiased (*Z*)-glycidic acids react with unexpectedly high C-3 selectivity.[191]

Vinyl epoxides, like allylic halides and carboxylates, have available both S_N2 and S_N2' reaction pathways. For the most part, regio- and stereo-selectivity follow patterns similar to those discussed in Section

1.5.2.4.5. Although first reported in 1970,[192] the S_N2' addition of organocopper reagents to vinyl epoxides was not further investigated until nearly a decade later. In the past 10 years, research efforts have concentrated primarily on rigid cyclic systems, which exhibit a pronounced preference for *anti*-S_N2' reactivity. The stereospecificity of the reaction has been exploited to introduce steroidal side chains with the proper exocyclic stereochemistry.[193]

Reactions of cycloalkadiene monoepoxides have received considerable attention. In general, cyanocuprates have provided better S_N2' selectivity than lithium homocuprates, and the alternative S_N2 reaction is more competitive with vinyl- or phenyl-cuprates than with alkylcuprate reagents.[194] Reactions of cyclopentadiene monoepoxides with cyanocuprates have found application in prostaglandin synthesis.[194a] Effective electrophilic α′-alkylation of cyclic enones can be accomplished by S_N2' cuprate addition to the corresponding epoxy enolate,[195] enol phosphate[196] or silyl enol ether.[194]

Macrocyclic α-methylenecycloalkylidene epoxides undergo exclusive S_N2' reaction with RMgBr–CuI.[197] By contrast, the corresponding allylic halides and phosphonates provide mixtures of S_N2 and S_N2' products. With ring sizes of 10–14, these substrates exhibit a strong preference for *syn*-S_N2' reaction from an *exo–trans* conformation. Smaller ring substrates are, of course, constrained to a *cis* conformation. α-Alkenylcyclohexylidene epoxides exhibit a preference for *anti*-S_N2' reaction with lithium homocuprates, but regio- and stereo-selectivity are both subject to steric control.[198]

Recently, reactions of acyclic vinyl epoxides have attracted increased attention. In many cases, regioselectivity is strongly dependent upon substrate structure, with (*E*)- and (*Z*)-isomers providing different results.[199] Similarly, stereoselectivity is the result of a complex interplay of steric and conformational effects, but *anti* addition to an *s-trans* conformation appears to be preferred. The regio- and stereo-selective α-alkylation of γ,δ-epoxy-α,β-enoates has been reported recently.[200] Again, S_N2' selectivity was greater with cyanocuprates than with the 'harder' homocuprates, but in no case was conjugate addition detected.

1.5.2.4.7 Acyl halides

The reactivity of organic electrophiles toward organocopper reagents follows the general order RCOCl ≈ RCHO > tosylate, epoxide > RI > ketone > ester > nitrile. Therefore, the addition of organocuprates to acyl halides occurs cleanly and rapidly at temperatures low enough that the product ketone is essentially inert. Because most other functional groups are also stable to the reaction conditions, halo-, cyano- and carbonyl-substituted ketones can all be prepared from the corresponding acyl chlorides.[201] Acyl bromides and fluorides are also suitable substrates. Phenylthiocuprates have proven to be more effective than homocuprates in these reactions; fewer equivalents of the reagent are required, and secondary and tertiary alkyl groups can be successfully transferred.[39a,d] More recently, Rieke has achieved the preparation of functionalized ketones by the coupling of acyl halides with functionalized organocopper reagents.[202]

The preparation of α,β-unsaturated ketones by direct acylation of vinylcopper reagents has proven more problematic, since lithium cuprates do add to the product enones.[203] Better results are obtained with the less reactive monovinyl copper compounds in the presence of a palladium catalyst. Alkynic ketones have been prepared by a variation of the Stephens–Castro coupling.[204]

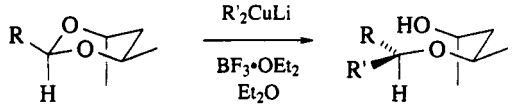
1.5.2.4.8 Acetals

Widely employed as protecting groups for carbonyl functionalities, acetals do not ordinarily react with organometallic reagents such as organo-lithium, -magnesium or -copper compounds, or lithium cuprates. However, in the presence of a Lewis acid, the carbon–oxygen bond is activated toward nucleophilic attack, and the cleavage of one C—O bond can be achieved. For example, Grignard reagents react with acetals in the presence of $TiCl_4$ to provide the monosubstituted ethers in high yields.[205] The reaction of allylic acetals with alkyl Grignards occurs regiospecifically at the α-position, and diastereomeric ratios of up to 96:4 have been observed in reactions of chiral acetals.[206] Cuprate reagents are not stable to $TiCl_4$, however, and provide only poor yields of the substitution products.

As mentioned in earlier sections (1.5.2.4.5 and 1.5.2.4.6), $BF_3{\cdot}OEt_2$ has proven to be uniquely well-suited for use in combination with organocopper reagents.[36] In fact, in the presence of $BF_3{\cdot}OEt_2$, acetals react smoothly in ether solution with either RCu or R_2CuLi, the latter being more reactive.[207] No reaction occurs in THF, which competes with the substrate for Lewis acid complexation. Mixtures of cyclic and ring-opened substitution products are obtained upon treatment of tetrahydropyranyl ethers with RCu–

$BF_3{\cdot}OEt_2$, but R_2CuLi–$BF_3{\cdot}OEt_2$ affords only the ring-opened products. Similarly, exclusive ring cleavage is also observed in reactions of THP ethers or glycopyranosides with Me_2BBr and R_2CuLi.[208]

Research efforts have focused primarily on reactions of chiral, nonracemic acetals,[205] compounds that have found increasingly widespread application in asymmetric synthesis. Acetals derived from C_2-symmetrical diols provide the best stereocontrol, and the major product is in every case that produced by *anti* nucleophilic displacement of the oxygen adjacent to the axial ring substituent (equation 15). This result has been rationalized on the basis of both steric and electronic considerations, arguments that are supported by the finding that the *meso* (diequatorial) compounds are much less reactive. Diastereomeric ratios are generally highest for six-membered cyclic acetals, which are possessed of greater conformational rigidity than the corresponding five- or seven-membered rings. Reactions of propargylic acetals proceed in a net *anti*-S_N2' fashion, again with cleavage of the C—O bond adjacent to the axial ring substituent. Allylic acetals also undergo regiospecific S_N2' substitution by aryl- and vinyl-copper compounds, but alkylcopper reagents afford mixtures of S_N2 and S_N2' products.



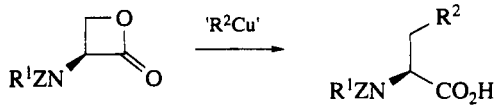
(15)

Recently, it was reported that acetals derived from homochiral β-hydroxybutyric acid react with R_3Cu_2Li in the absence of $BF_3{\cdot}OEt_2$.[209] These reactions proceed with highly diastereoselective *anti* displacement of the carboxylate, and treatment of the product with base liberates a secondary alcohol of high enantiomeric purity.

1.5.2.4.9 β-Lactones

While most organolithium and Grignard reagents attack the carbonyl group of lactone substrates, regiospecific carboxylate displacement can be effected with both stoichiometric and catalytic organocopper reagents.[210] The reaction provides a convenient method for three-carbon homologation that has proven useful in natural product synthesis.[211] The regiospecific S_N2' reaction of β-ethynyl-β-propiolactone has also been accomplished.[212] In general, these reactions are best performed in THF, and magnesium cuprates often provide better results than their lithium counterparts. Phenyl, vinyl and allyl transfers are more difficult to achieve than alkyl transfer, and stoichiometric magnesium cuprates have been most successful for these transformations.

Very recently, Vederas has reported[213] the extension of this methodology to serine β-lactone substrates (equation 16), providing an important addition to the growing number of procedures for amino acid synthesis. These substrates raise the specter of potentially worrying elimination and racemization side reactions in addition to the possibility of competitive 1,2-addition. In fact, substantial racemization was observed when diprotected amino-β-lactones were employed, but the use of monoprotected substrates (which exist in deprotonated form under the reaction conditions) minimized abstraction of the α-hydrogen. By the same token, racemization following substitution is disfavored by the adjacent carboxylate anion (*cf.* reactions of β-haloserine esters, Section 1.5.2.4.1). Although lithium homocuprates and higher order cyanocuprates provided reasonable yields of the desired products, catalytic magnesium cuprate reagents proved most successful.



(16)

1.5.3 NICKEL AND PALLADIUM CATALYSTS

The modification of organo-lithium and -magnesium reagents by the addition of catalytic amounts of copper salts was discussed in Section 1.5.2. Other transition metals also have been found to promote the cross-coupling reactions of organometallic reagents with carbon electrophiles, and dramatic advances in this technology over the past decade have served to extend significantly the synthetic utility of cross-coupling reactions for the selective construction of carbon skeletons. Of the transition metals examined,

nickel and palladium have produced the most successful results and have been the most widely used; the following section is limited to a discussion of reactions catalyzed by these two metals.

Given that the catalytic cycles proposed to be operative for reactions employing nickel and palladium catalysts are essentially identical, it is not surprising that the two may be used interchangeably for many reactions. Significant differences in reactivity and selectivity do exist, however, and an effort will be made to point out those differences in the discussion that follows. While meant to cover the important contributions in this area, this account is not intended to be exhaustive. The reader is referred to several excellent reviews[214] and to other chapters in this volume for additional information on the subject.

1.5.3.1 Organonickel Catalysis

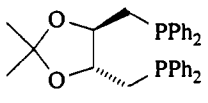
More than 15 years ago, Corriu[215] and Kumada[216] independently discovered that organonickel complexes greatly facilitated the reactions of Grignard reagents with alkenyl and aryl halides. Since that time, the reaction has been intensively investigated[217] and has proven to be quite general for the coupling of C(sp^2) halides with virtually any Grignard reagent. The proposed mechanism[53] of the reaction involves initial reaction of a Ni^{II} complex with the Grignard reagent, oxidative addition of the substrate to the resulting Ni^0 species, and transmetalation of the Grignard reagent. Reductive elimination then liberates the coupled product and regenerates the active catalyst. Reactions of alkenyl halides exhibit predominant retention of alkene geometry, while reactions of alkenyl Grignard reagents are complicated by competing (*Z*) to (*E*) isomerization.

In general, nickel complexes bearing phosphine ligands have been the most successful catalysts for these reactions, with bidentate phosphine ligands providing the greatest catalytic activity. The preferred catalyst for a particular reaction is dependent upon the nature of the Grignard reagent and of the halide substrate, with $NiCl_2$(dppp) (dppp = 1,3-bis(diphenylphosphino)propane) being most effective for simple alkyl and aryl Grignard reagents, $NiCl_2$(dmpe) (dmpe = 1,2-bis(diphenylphosphino)ethane) for vinylic and allylic Grignard reagents, and $NiCl_2(PPh_3)_2$ for sterically hindered aryl Grignard reagents and halides. In many cases, the corresponding palladium complexes are also suitable catalysts.

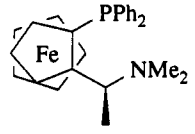
The choice of catalyst is particularly important for reactions of secondary alkyl Grignard reagents. Although primary Grignard reagents couple without rearrangement of the alkyl group, in reactions of secondary Grignard reagents that bear β-hydrogens, β-elimination competes with reductive elimination, resulting in the formation of both reduced and isomerized by-products.[218] β-Elimination is especially troublesome in reactions with hindered alkenyl halides, since the rate of product-forming reductive elimination is retarded. The catalysts $NiCl_2$(dppf)[219] and $PdCl_2$(dppf)[220] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) minimize these side reactions by accelerating the rate of desired reductive elimination relative to undesired β-elimination. By contrast, alkyl halides that possess β-hydrogens are not usually suitable substrates, regardless of catalyst, because the transmetalation step is slow in comparison to β-elimination.

Stereochemistry is an additional factor involved in reactions of secondary Grignard reagents in which the metal is attached to a chiral carbon atom, and this has proven to be a particularly fertile area of research for Hayashi, Kumada and their coworkers.[221] The first examples of asymmetric induction in reactions of secondary Grignard reagents employing a homochiral nickel catalyst were reported[222] shortly after the discovery of the original reaction. These early results were obtained using $NiCl_2$(DIOP) (*cf.* **20**) as the chiral catalyst, and the observed enantioselectivities were quite low (≤17%). In the years following these initial reports, numerous ligands have been examined, with ferrocenylphosphines (*e.g.* **21, 22**) and β-(dimethylamino)alkylphosphines derived from amino acids (**23**) being the most extensively investigated.

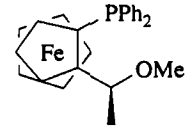
Of the ferrocenylphosphine ligands, (*R,S*)-PPFA (**21**) proved to be the most successful, with $NiCl_2$(PPFA) and $PdCl_2$(PPFA) producing comparable results. Organozinc reagents were somewhat more selective than the corresponding Grignard reagents in reactions employing $PdCl_2$(PPFA), but they



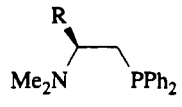
(**20**) (–)-DIOP



(**21**) (*R,S*)-PPFA



(**22**) (*S,R*)-PPFOMe



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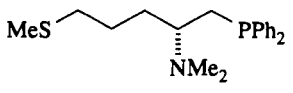
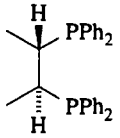


(24) Homomethphos

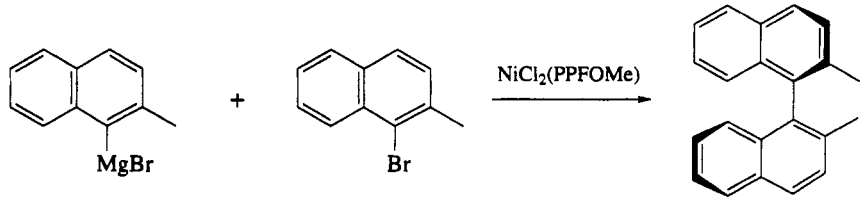


(25) *(S,S)*-Chiraphos

did not react with nickel catalysts. Higher enantioselectivities (up to 94%) were achieved when some of the amino acid derived ligands were used, although with these ligands palladium was less efficient than nickel. Ligands derived from (*S*)-amino acids generally give rise to the (*S*)-product, but it has been reported[223] that this trend is reversed in the presence of ZnX_2 (X = Br, I).

The use of alternative classes of ligands for these reactions has been explored, but with only moderate success.[224] In the most promising example of this work,[224a,b] a sulfide-containing side chain was appended to the familiar dimethylaminophosphine ligand. The sulfide moiety offers a third site for coordination to the metal, and it was hoped that such intramolecular participation would accelerate the rate of reductive elimination, minimizing the loss of enantiomeric purity resulting from competitive β-elimination. In fact, the enantioselectivity of the homomethphos ligand (**24**) is comparable to that of *t*-leuphos (**23**; R = Bu^t).

The asymmetric Grignard cross-coupling reaction has been utilized in syntheses of (*R*)-(–)-curcumene[225] and of optically active antiinflammatory agents.[226] A particularly successful application of the methodology has been for the preparation of optically active allylsilanes,[227] in which enantioselectivities of up to 95% have been achieved. Interestingly, $PdCl_2$(PPFA) was the most effective catalyst for silyl-substituted Grignard reagents, with nickel catalysts providing lower yields and selectivities. Most recently, substituted binaphthyls[228] and ternaphthyls[229] have been prepared in high enantiomeric purity by asymmetric biaryl cross-coupling with $NiCl_2$(PPFOMe) as the catalyst (*e.g.* equation 17). As in the original work with secondary alkyl Grignards, nickel catalysts were more successful than palladium catalysts, but, in this case, complexes containing bidentate ligands (*e.g.* diphosphines and aminophosphines) were unreactive due to steric hindrance.

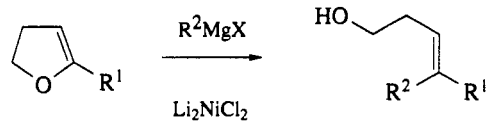


(17)

Asymmetric induction is also observed in nickel-catalyzed reactions of Grignard reagents with allylic alcohols and ethers.[230] Examples of high enantioselectivity have been reported;[230a] however, the enantioselectivity of the reaction is strongly and unpredictably dependent upon the allylic substrate, the Grignard reagent and the catalyst. In most cases, the best results have been obtained with $NiCl_2$(chiraphos) (*cf.* **25**) as the homochiral catalyst. Palladium complexes are not suitable catalysts for this reaction. In contrast to transition metal catalyzed reactions of allylic ethers and esters with 'soft', stabilized carbanions, in which the stereochemistry of the starting material is retained in the product, reactions with Grignard reagents proceed with net inversion of configuration.[231] There is a slight tendency favoring reaction at the more highly substituted allylic position of unsymmetrical electrophiles, but mixtures of regioisomers are usually obtained.

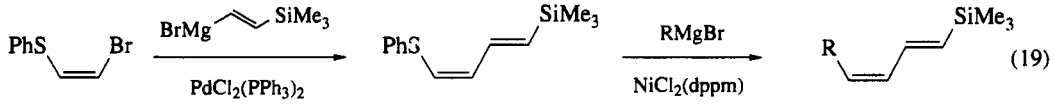
Vinyl and aryl ethers also react with Grignard reagents under nickel catalysis. Substitution reactions of aryl tetrazolyl ethers are reported[232] to be particularly facile, an effect that may be attributable to the ability of the tetrazolyl moiety to coordinate to magnesium. Reactions of dihydrofuran and dihydropyran substrates with Grignard reagents afford homoallylic and bishomoallylic alcohols, respectively (equation 18).[233] Retention of alkene geometry is predominantly observed, and by carefully controlling the work-up conditions, stereoselectivities of ≥98:2 can be achieved.[234] By contrast, reactions of the same substrates with cuprate reagents proceed with inversion of configuration (see Section 1.5.2.4.2, equation 8). As mentioned earlier, β-elimination with resulting substrate reduction is a competing process when Grignard reagents with β-hydrogens are employed. In reactions with dihydrofuran substrates, $NiCl_2$(dppe) provided the highest ratios of coupled products.

The nickel-catalyzed substitution of vinyl sulfides by Grignard reagents forms the basis of a procedure for the stereoselective synthesis of alkenes by sequential cross-coupling reactions developed by Naso and



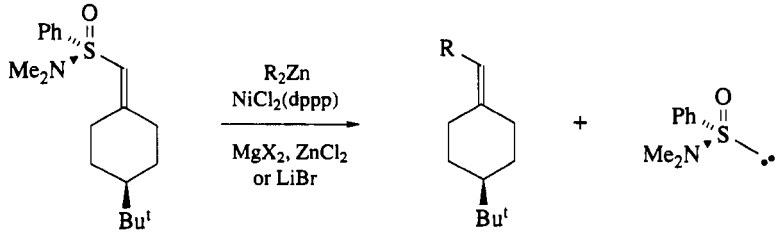
(18)

coworkers (equation 19).[235] The first step of the sequence is chemospecific, with only the bromide being displaced. Better stereoselectivity is obtained in the initial reaction of (*Z*)-1-bromo-2-phenylthioethylene when $PdCl_2(PPh_3)_2$ is employed as the catalyst. Nickel catalysts must be used for the second step, and the particular choice of catalyst can be critical to the stereochemical outcome. In a variation of the method,[236] a dienyl sulfide is stereospecifically prepared by addition of a vinyl cuprate reagent to phenylthioacetylene. Nickel-catalyzed Grignard cross-coupling then affords the desired dienyl product.



(19)

Optically active alkenylsulfoximines undergo nickel-catalyzed cross-coupling with organozinc reagents in the presence of an additional magnesium, lithium or zinc salt (equation 20).[237] No reaction occurs in the absence of the cocatalyst, and palladium catalysts are unreactive. The reaction proceeds with 99% retention of alkene geometry, and sulfoximine of ≥98% enantiomeric purity is liberated. Interestingly, reaction of (**26**) with Grignard reagents at –20 °C failed to afford the coupled product, but instead resulted in α-metalation.[238] At 0 °C, coupling with a second equivalent of Grignard reagent occurred to provide an α-functionalized alkenyl metal, but as a 1:1 mixture of (*E*)- and (*Z*)-isomers.



(**26**) 99:1

(20)

1.5.3.2 Organopalladium Catalysis

1.5.3.2.1 Aluminum, zinc and zirconium reagents

While ease of preparation and commercial availability contribute to the popularity of simple Grignard reagents for use in cross-coupling reactions, the scope of the reaction is seriously limited by the poor chemoselectivity of these reagents. In addition, alkenyl Grignard reagents are often isomerized under the reaction conditions, rendering them unsuitable for stereospecific diene synthesis. It is particularly this latter consideration that provided the impetus for an intensive investigation into the use of other organometallics in transition metal catalyzed cross-coupling reactions conducted by Negishi and coworkers.[239] Aluminum and zirconium reagents have received particular attention, since the corresponding alkenyl metals can be prepared in a regio- and stereo-defined fashion utilizing hydrometalation and carbometalation procedures.

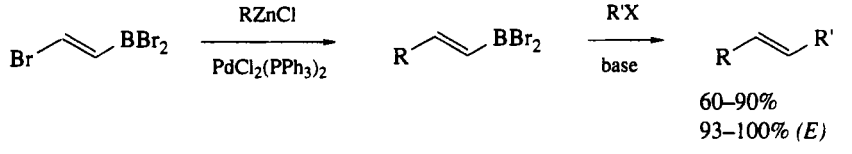
(*E*)-Alkenylalanes and (*E*)-alkenylzirconium derivatives readily undergo nickel-catalyzed cross-coupling with aryl halides to provide the arylalkenes in high yield and with ≥98% retention of alkene geometry. Ester, nitrile, ether and halide functional groups are compatible with the reaction. Alkenyl–alkenyl cross-coupling also proceeds in moderate to good yield, but homocoupling is a competing side reaction and the stereoisomeric purity of the product is only 95% for (*E*,*E*)-dienes and 90% for (*Z*,*E*)-dienes. Better results are obtained with palladium catalysts ($Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$), which provide both products in ≥98% stereoisomeric purity with only trace amounts of homocoupled byproducts.

In contrast to β-monosubstituted alkenyl metals, more highly substituted alkenyl metals containing aluminum or zirconium are only poorly reactive. This limitation is overcome by the addition of a catalytic amount of a zinc halide. In general, zinc reagents are far more reactive than the corresponding aluminum or zirconium reagents,[240] and their use is particularly advantageous in coupling reactions of aryl, alkynyl and heteroaryl metals. It is additionally noteworthy that, despite the potential problem of β-elimination, cross-coupling of homoallylic and homopropargylic organozinc compounds with alkenyl halides may be successfully accomplished, enabling the selective synthesis of 1,5-dienes and 1,5-enynes.[241] Palladium-catalyzed coupling reactions of β-, γ-, δ-, ε- and ζ-zinc ketones have also been reported.[242] Recently, Negishi has reported[243] the application of palladium-catalyzed cross-coupling reactions of organozinc compounds to the regio- and stereo-specific α-alkenylation and α-arylation of ketones.

1.5.3.2.2 Boron reagents

Like hydroalumination and hydrozirconation, hydroboration of alkynes also provides a convenient and stereospecific route to alkenyl metal reagents. However, initial attempts to achieve palladium-catalyzed cross-coupling of alkenylboranes with alkenyl halides were unsuccessful, due to the poor carbanionic character of these reagents. Later, Suzuki[244] discovered that the desired transformation could be effected in the presence of an alkoxide or hydroxide base; weaker bases, such as sodium acetate or triethylamine, were not generally effective. The reaction is suitable for the preparation of (*E,E*)-, (*E,Z*)- and (*Z,Z*)-dienes. Since reactions of alkenylboronates are higher yielding than those of alkenylboranes, the recent availability of (*Z*)-1-alkenylboronates[245] substantially improves the Suzuki method for the preparation of (*Z*)-alkenes.[246] An extension of the methodology to the synthesis of trisubstituted alkenes has also been reported.[247]

In an approach similar to the Naso alkene synthesis described earlier, Suzuki has reported[248] the stereospecific synthesis of alkenes from (*E*)-(2-bromo-1-alkenyl)dibromoborane by sequential cross-coupling reactions (equation 21). The reaction sequence can be carried out in one pot, without isolation of the intermediate. Transmetalation from boron to palladium occurs only after base has been added.



(21)

In addition to alkenyl halides, alkynyl, aryl, allylic and benzylic halides and β-haloenones[249] all couple efficiently with alkenylboron reagents in the presence of a palladium catalyst and 2 equiv. of base. The cross-coupling of aryl halides with arylboronic acids, regioselectively prepared by directed *ortho* lithiation methodology, has been investigated by Snieckus and coworkers. Applications to the synthesis of phenanthrols[250] and phenanthridines[251] have been reported most recently. Very recently, Suzuki reported[252] the extension of this methodology to include the coupling of alkylboron reagents with vinyl and aryl halides.

It was originally believed that addition of a base to reactions of organoboranes would facilitate the transmetalation step by increasing the carbanionic character of the boron reagent *via* formation of an 'ate' complex. However, the failure of alkenylborates to undergo efficient cross-coupling indicates that the base is not functioning in this manner, and suggests instead the involvement of an alkoxypalladium(II) intermediate, the formation of which is apparently rate limiting. It should be noted, however, that lithium tetraalkylborates do couple successfully.[252] Recently, Kishi and coworkers[253] reported that the use of thallium hydroxide had a dramatic rate-enhancing effect on these coupling reactions, allowing application of the methodology to palytoxin synthesis. The high molecular weight substrates involved in that study proved unreactive under the standard reaction conditions.

1.5.3.2.3 Tin reagents

Organotin reagents have proven to be particularly versatile partners in palladium-catalyzed coupling reactions. As impressively demonstrated by Stille and coworkers over the past decade,[254] organostannanes of many structural types undergo efficient cross-coupling with an assortment of organic electrophiles, including halides, triflates, acid chlorides and epoxides. Reaction conditions are mild, and a wide

variety of functional groups may be present in either component, allowing application of the methodology to the synthesis of sensitive and complex target molecules. Unlike most other organometallics, organotin reagents are easily prepared by a number of different routes, and they are not especially oxygen or moisture sensitive.

Of the electrophiles examined, vinyl triflates have received particular attention.[255] These compounds are conveniently prepared from the corresponding ketones, utilizing well-established methodology for regioselective enolate formation.[256] Coupling with organostannanes proceeds smoothly in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(Pd_3P)_4$] and a stoichiometric amount of LiCl. No reaction occurs in the absence of LiCl, which apparently allows formation of the catalytically active alkenylchlorobis(triphenylphosphine)palladium(II) complex. Aryl triflates, easily prepared from the corresponding alcohols, are also suitable electrophiles under similar reaction conditions.[257] Although successful in THF and other ethereal solvents, the reaction is faster in solvents such as DMF, which can both solubilize LiCl and act as good ligands.[258]

In reactions of unsymmetrically substituted organotins, unsaturated substituents transfer preferentially over saturated alkyl groups. For synthetic convenience, methyl and butyl groups are usually employed as the nontransferable ligands. In some cases,[259] the trimethyltin derivative provides better results due to a decrease in steric crowding, and trimethylorganostannanes offer the additional advantage that the by-products are water soluble. On the other hand, lower toxicity and greater stability are factors favoring the use of tributyltin derivatives.

Few limitations are imposed on the choice of the transferring group. Alkyl, vinyl, allyl and alkynyl compounds all couple effectively with aryl and vinyl triflates. Phenyl and benzyl reagents are unreactive toward vinyl triflates,[260] but biaryl coupling is successful. Because reductive elimination occurs more rapidly than β-elimination, organostannanes with β-hydrogens are acceptable coupling partners. However, β-hydrogens attached to an sp^3-carbon are not usually tolerated in the electrophile, since β-elimination is faster than the rate-determining transmetalation step.[261] Recent applications of the methodology include syntheses of vitamin D,[262] amphimedine[263] and cephalosporin analogs.[264]

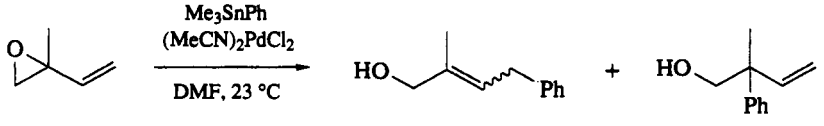
Like the other coupling reactions discussed thus far, palladium-catalyzed coupling reactions of organotin reagents proceed stereospecifically, with the alkene geometries of both vinyltin reagents and vinyl electrophiles being retained in the product. However, the utility of cross-coupling between vinyltins and vinyl triflates for 1,3-diene synthesis is seriously limited by the fact that no method currently exists for the preparation of acyclic vinyl triflates in a stereodefined manner. As mentioned in previous sections, stereospecific 1,3-diene synthesis has been accomplished by palladium-catalyzed coupling of organometallics with stereoisomerically pure vinyl halides, for which synthetic methodology is available. However, initial attempts to achieve the coupling of vinylstannanes with vinyl halides in the presence of $Pd(PPh_3)_4$ resulted in only modest yields of the desired products.[239a]

Recently, improved experimental procedures for the cross-coupling of organotin reagents with vinyl iodides have been reported,[265] which allow the preparation of (*E,E*)-, (*E,Z*)- and (*Z,Z*)-dienes in high yields and isomeric purities.[266] Bis(triphenylphosphine)dichloropalladium [$PdCl_2(PPh_3)_2$] and di(acetonitrile)dichloropalladium [$PdCl_2(MeCN)_2$] proved to be much more reactive than $Pd(PPh_3)_4$ in these reactions, with $PdCl_2(MeCN)_2$ in DMF providing the most reactive catalyst. The lower temperatures and shorter reaction times allowed by this system minimized alkene isomerization, which was a problem when less reactive catalysts were used. The coupling of alkynylstannanes with vinyl iodides under the same conditions provided stereoisomerically pure enynes, from which (*E,Z*)- and (*Z,Z*)-dienes could be prepared by stereospecific alkyne reduction.[259b] One limitation of this methodology is the fact that substantial amounts of homocoupled by-products are produced in reactions of silyl-substituted vinyltin reagents, limiting yields of the synthetically useful silyldienes.

While not useful for reactions of vinyl halides, $Pd(PPh_3)_4$ is a suitable catalyst for coupling reactions of organotins with aromatic bromides and iodides; a number of applications to the synthesis of coupled heterocycles have been reported recently.[267] Reactions of substituted bromobenzenes with vinyltributylstannane afford the corresponding styrene derivatives in high yield.[268] Exclusive displacement of halogen in the presence of a triflate substituent is simply accomplished by performing the reaction in the absence of LiCl, as evidenced in a recently reported synthesis of indole derivatives.[269] In the presence of LiCl, the order of electrophilic reactivity is I > Br > OTf when $Pd(PPh_3)_4$ is employed as the catalyst, but $PdCl_2(PPh_3)_2$ causes a reversal in this selectivity to I > OTf > Br.[257] In general, aromatic chlorides are insufficiently reactive to be suitable substrates for this reaction; however, chloroarylchromiumtricarbonyl complexes do undergo successful palladium-catalyzed cross-coupling with organotin reagents.[270]

Allylic halides couple effectively with vinyltin reagents to provide the corresponding 1,4-dienes in high yields.[271] Like nickel- and palladium-catalyzed Grignard reactions with allylic ethers, this reaction also proceeds with net inversion of configuration at the allylic center. Similarly, vinyl epoxides react

stereoselectively with aryl- and vinyl-stannanes to give the *anti*-substituted allylic alcohols.[272] In both cases, reaction occurs regioselectively at the least hindered allylic position of unsymmetrically substituted substrates. In the absence of steric bias, predominant 1,4-addition is observed in reactions of vinyl epoxides, while allylic chlorides apparently afford the products of α- and γ-attack in a 1:1 ratio. Interestingly, regioselectivity is improved when reactions of vinyl epoxides are performed in the presence of 10 equiv. of water (equation 22).



(22)

no additive: 70%; 96:4; *(E)*:*(Z)* = 52:48
10 equiv. H_2O: 85%; 98.5:1.5; *(E)*:*(Z)* = 69:31

1.5.3.2.4 Silicon reagents

Although low reagent nucleophilicity has proven advantageous in cross-coupling reactions of organostannanes, the extremely low polarity of the carbon–silicon bond has prohibited use of the analogous organosilanes in these reactions. Recently, however, it has been discovered that tris(diethylamino) sulfonium difluorotrimethylsilicate (TASF) renders the compounds more anionic, facilitating the transmetalation step and allowing successful palladium-catalyzed coupling with organic halides.[273] Allylpalladium chloride dimer is the catalyst of choice for these reactions, and the presence of triethyl phosphite as a cocatalyst markedly accelerates the rate of reaction with alkenyl iodides. More recently, it has been reported[274] that dimethylfluorosilanes are considerably more reactive than the corresponding trimethylsilanes; advantage may be taken of this fact in order to prepare 1-silyl-1,3-dienes. Although tetrabutylammonium fluoride (TBAF) was not effectual in reactions of trialkylsilanes, it was used successfully with the more reactive dimethylfluorosilane substrates.

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1.6
Alkylations of Vinyl Carbanions

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1.6.1 INTRODUCTION

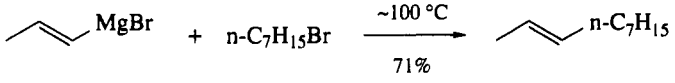
The scope of this chapter is limited to carbon–carbon bond forming reactions between sp^2-centered carbanions and alkyl halides, alkanesulfonates, epoxides and related carbon centered electrophiles. It does not include reactions between vinylic carbanions and electrophiles such as silyl chlorides, disulfides or other heteroaromatic electrophiles. Some members of this last group of electrophiles are often used to determine the extent to which a particular vinyl carbanion intermediate is formed; having shown that formation has occurred to a large or complete extent, many authors do not then proceed to examine the alkylation reactivity of a particular carbanionic species beyond using methyl iodide. Methyl iodide is such a special electrophile, however, that successful alkylations with it cannot usually be used as an indication that alkylations with higher homologs or with more reactive alkylating agents such as allylic or benzylic halides, will necessarily be so rewarding. Therefore, many potentially useful sp^2-carbanionic species are not mentioned in this review, specifically because their behavior with such alkylating reagents has not been reported. In general, the nucleophilicity of vinyl carbanions lies in between similar *sp*- and sp^3-centered species, and as such they usually react very well with aldehydes and ketones, and with the simple heteroaromatic electrophiles of the type mentioned above, whereas alkylation reactions give variable yields, depending upon the particular species involved. The high yields normally obtained with reactive electrophiles such as Me_3SiCl and MeI are often not extended to couplings with allylic or benzylic halides, despite the fact that satisfactory results may be obtained using saturated alkyl halides as electrophiles. Presumably in many cases, the carbanion acts as a base rather than a nucleophile and simply abstracts a proton from these more reactive electrophiles.

This review is organized primarily on the basis of the electrophiles used, with a view to allowing easy access to the information. However, within each section, a variety of routes to the same target type are included, as for example in alkylations using simple alkyl halides where both lithium- or magnesium-based carbanions can be used equally well. Both subsections should therefore be consulted.

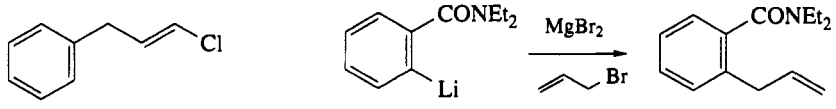
1.6.2 ALKYLATIONS USING ALKYL HALIDES AND SULFONATES

1.6.2.1 Alkylations of Vinyl and Aryl Grignard Reagents

The most direct method for effecting alkylation of a vinylmagnesium halide is simply to heat the organometallic species with a primary alkyl bromide at 90–100 °C (Scheme 1).[1] The Grignard reagent (a slight excess) is usually generated in tetrahydrofuran (THF) solution, the bromoalkane added and the THF removed by distillation until the required temperature is reached. However, the more reactive allyl halides can be used to alkylate Grignard reagents under milder conditions. Indeed the ease with which allylic halides undergo such couplings can lead to low yields during the attempted preparations of allylic or benzylic magnesium halides. In a nonpolar solvent such as toluene, temperatures of around 100 °C are still required to give good yields of alkylated products such as the phenylpropene (**1**) (from PhMgBr and 1,3-dichloropropene).[2] However, similar alkylations of arylmagnesium halides using allylic chlorides or bromides occur at much lower temperatures (15–30 °C) in ether[3] or THF,[4] and also lead to good to excellent yields of allylbenzene derivatives. Despite their generally greater popularity as carbanionic intermediates in alkylation reactions, many sp^2-centered carbanions having lithium as the countercation do not react efficiently with allylic halides (*vide infra*); in such cases, transmetallation to the corresponding magnesio species can sometimes obviate this limitation. One such example is the *ortho*-lithiated benzamide (**2**), which reacts cleanly with allyl bromide after treatment with magnesium bromide to give the *o*-allyl homolog (**3**) in good yield.[5]

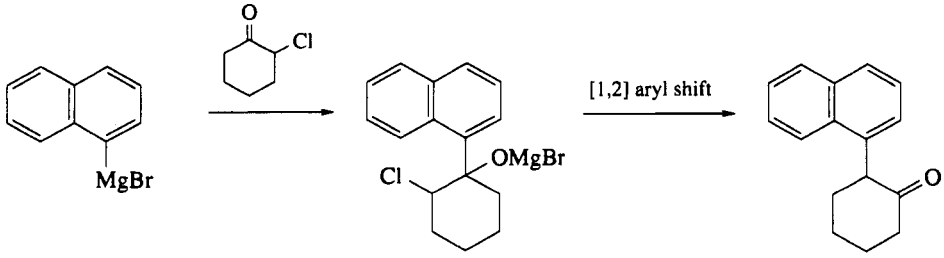


Scheme 1

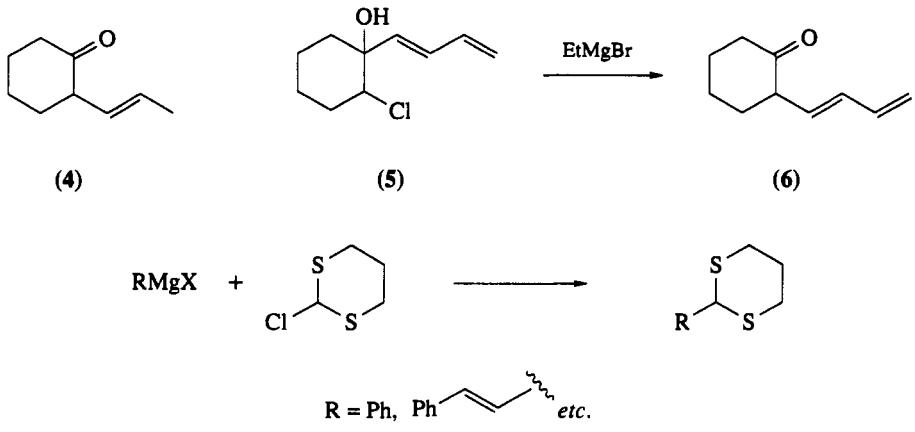


(1) **(2)** **(3)**

Another series of highly active electrophiles which react smoothly with vinyl and aryl Grignard reagents to give, overall, the products of direct alkylation, are the α-halo ketones; however, this type of reaction is a two-step process which proceeds *via* an intermediate halohydrin arising from initial attack on the ketone group (Scheme 2).[6] Similarly, vinylmagnesium halides can be transformed in a single flask reaction to α-ethenyl ketones, *e.g.* (**4**),[7] whereas vinyllithium species lead to isolable halohydrins, *e.g.* (**5**), which only rearrange to the α-ethenyl ketone upon reionization using a simple Grignard reagent as base.[8] The relative dearth of good vinyl cation equivalents lends particular significance to the latter methodology. α-Halo ethers and related species also couple in moderate to good yields with Grignard reagents,[9] an example being the reactions between 2-chloro-1,3-dithiane and RMgX (Scheme 3) in which the typical umpolung reactivity of the dithiane functionality is returned to normality.[10] The special reactivity of α-halo ethers means that good yields can be obtained by this method, despite the fact that secondary halides generally react poorly as alkylating electrophiles with organomagnesium and organolithium intermediates.

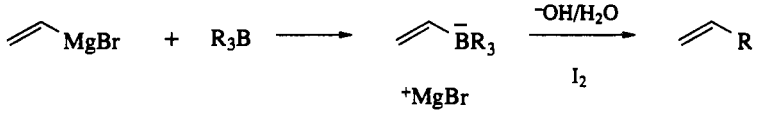


Scheme 2



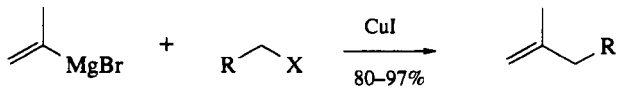
Scheme 3

An indirect way to effect alkylation at an sp^2-carbanionic center is by reaction with a trialkylborane (Scheme 4).[11] Decomposition of the intermediate borate results in overall alkylation of the original Grignard species by B → C alkyl migration; one drawback is that two of the alkyl groups are wasted and hence applications would probably be somewhat limited.



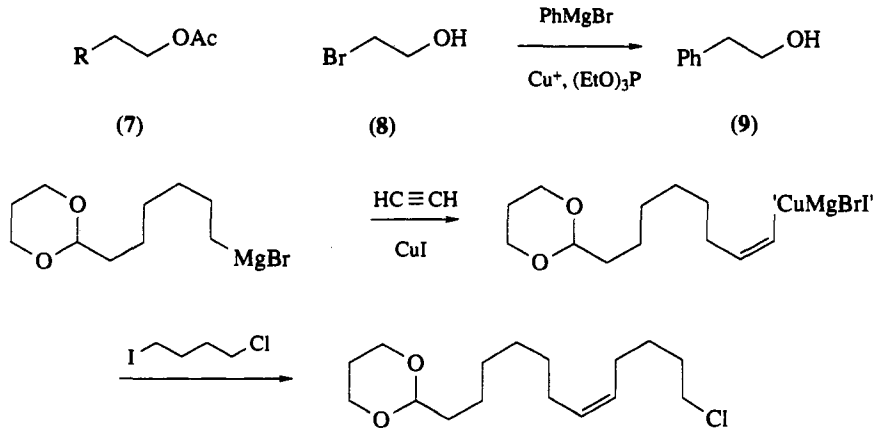
Scheme 4

In general, however, alkylations of both organomagnesium and organolithium intermediates (*vide infra*) more often rely on the presence of a copper salt, either in catalytic or stoichiometric quantities, or another transition metal species.[12] A general method is the alkylation of vinylmagnesium bromides by primary iodides or tosylates (Scheme 5)[13] in the presence of copper(I) iodide, which proceeds under much milder conditions than those required for the direct alkylation of vinyl Grignards by unactivated alkyl halides.[1] Less reactive alkyl bromides give much poorer yields (*ca.* 20%) and it is crucial that the copper catalyst is of a high quality. An alternative copper catalyst, Li_2CuCl_4 (*vide infra*) can also be used, but excess Grignard reagent is required if good yields are to be realized. The addition of copper salts to Grignard reagents gives rise to some useful modulations in the reactivity of the latter. For example, direct coupling between RMgX and 2-bromoethyl acetate is possible, leading to homologs (**7**),[14] and even bromoethanol (**8**) can be used to give phenethyl alcohols (**9**)[14] in this modification of an original Grignard method.[15] A useful source of vinyl magnesiocuprates is by the addition of alkylmagnesium halides to terminal alkynes, in the presence of stoichiometric amounts of a copper(I) salt; the usefulness of these reagents is indicated in Scheme 6 in which is shown an early stage in a synthesis of the insect pheromone trogodermal.[16] However, other authors[17] have indicated that closely related species derived from a monosubstituted alkyne can only be alkylated efficiently by allylic halides or epoxides (see Section 1.6.6). Much the same pattern of reactivity has been found with related lithium divinylcuprates similarly derived from alkynes (*vide infra*). An alternative catalyst system, CuX–TMEDA, has been shown to be useful for the alkylation of arylmagnesium halides, ArMgX, by primary iodides or benzylic chlorides.[18] Yields are usually around 80% but, as with most of these alkylations, the method fails with a secondary iodide.



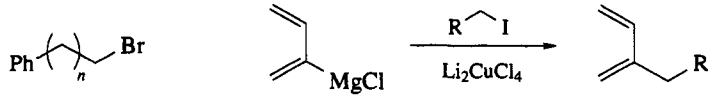
R = Et, n-C_7H_{15}; X = I or OTs

Scheme 5



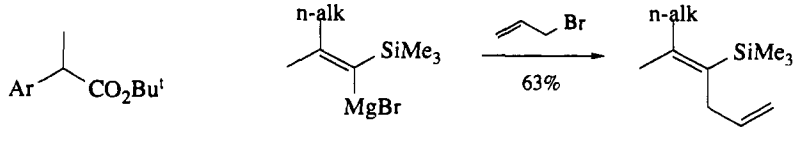
Scheme 6

Dilithium tetrachlorocuprate, Li_2CuCl_4, sometimes referred to as the Tamura–Kochi complex, has also found many applications in the alkylation of Grignard reagents in general.[19] Although originally reported to work best with primary alkyl iodides,[19] subsequent research indicated that primary tosylates are the best electrophiles.[20] The use of Li_2CuCl_4 allows alkylations of Grignard reagents by α,ω-dibromides leading to monobromides, *e.g.* (**10**) from PhMgBr, to be effected in moderate to good yields.[21] Similar couplings of aryllithiums require the presence of TMEDA (*cf.* ref. 18). Li_2CuCl_4 has also been found to be the catalyst of choice for conversions of the dienylmagnesium chloride (**11**) into the butadiene homologs (**12**).[22]

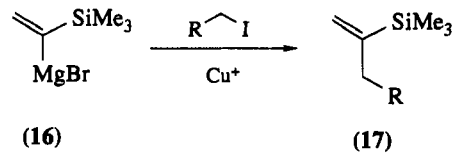


(**10**) $n = 2$–5, 9 (**11**) (**12**)

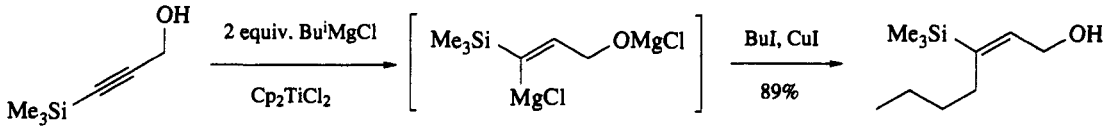
Palladium and nickel catalysts also occupy an important position in this type of chemistry. The readily prepared palladium complex $[(Ph)Pd^{I}(PPh_3)_2]$ effectively catalyzes the cross-coupling of arylmagnesium halides and alkyl halides, even when the former is sterically hindered, and is reported to be superior to many related nickel-based catalysts.[23] A ferrocene–palladium complex can also be used.[24] A combination of a nickel catalyst $[Ni(dppp)Cl_2]$ and *t*-butyl 2-bromopropionate (rather than the methyl ester)[23] allows direct coupling of the latter with ArMgX to provide respectable yields of 2-arylpropionates (**13**).[25] α-Silylvinylmagnesium bromides (**14**), prepared in general by Ni-catalyzed addition of an alkyl Grignard to a silylalkyne, undergo *in situ*, presumably nickel-catalyzed, alkylations by methyl iodide (50%) and allyl bromide, the latter leading to the potentially useful 'skipped' dienes (**15**).[26] The simpler α-silyl species (**16**) couples efficiently with primary alkyl iodides (but not primary bromides or tosylates) in the presence of a copper(I) salt to give good yields of homologs (**17**); both α- (**16**) and β-silylvinyl Grignards can also be alkylated using a palladium catalyst.[27] As expected,[3,4] alkylations using allylic halides do not require the addition of a catalyst. Alkoxide residues are tolerated in such reactions; thus hydromagnesiation of the silylpropargyl alcohol (**18**), followed by treatment with iodobutane–CuI leads to the allylic alcohol (**19**) with 95% retention of stereochemistry.[28] Such vinyl Grignard reagents can also be obtained by intramolecular cyclizations; again, homologation using an allylic halide proceeds without recourse to a catalyst (Scheme 7).[29]



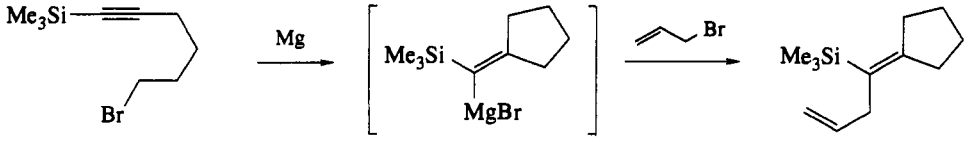
(**13**) (**14**) (**15**)



(16) (17)

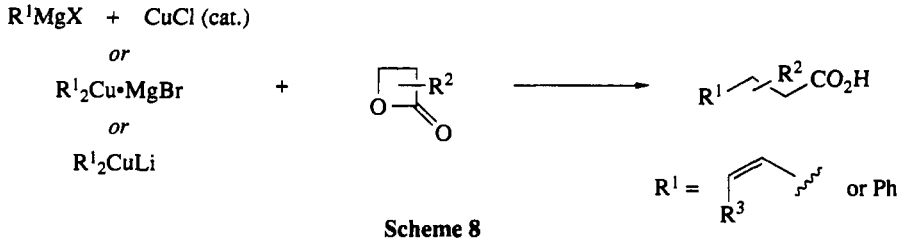


(18) (19)

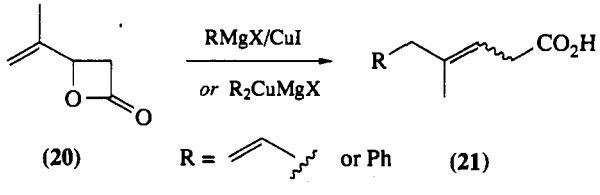


Scheme 7

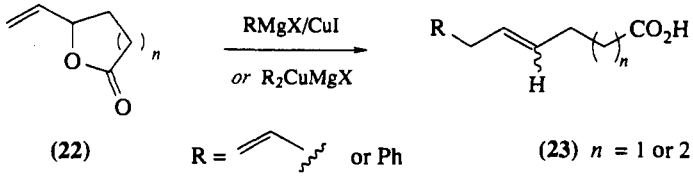
Copper-modified Grignard reagents can also be alkylated using β-lactones, resulting in a useful three-carbon homologation procedure in which attack occurs regioselectively with displacement of carboxylate (Scheme 8).[30] In general, reagents prepared using a stoichiometric quantity of copper give higher yields, based on the lactone. The propensity for undergoing conjugate or S_N2' additions imparted upon Grignard reagents by the presence of copper allows this methodology to be extended to ω-ethenyl lactones; thus, reactions between a variety of such species and β-lactone (**20**) afford good to excellent yields of the dienoic acids (**21**; R = CH_2CH, 49%; R = Ph, 84%).[31] This approach can also be extended to include 5-ethenylbutyrolactone and the corresponding valerolactone (**22**). Once again, good to excellent yields of dienoates (**23**) can be obtained, especially with the former substrate (*i.e.* $n = 1$).[32]



Scheme 8

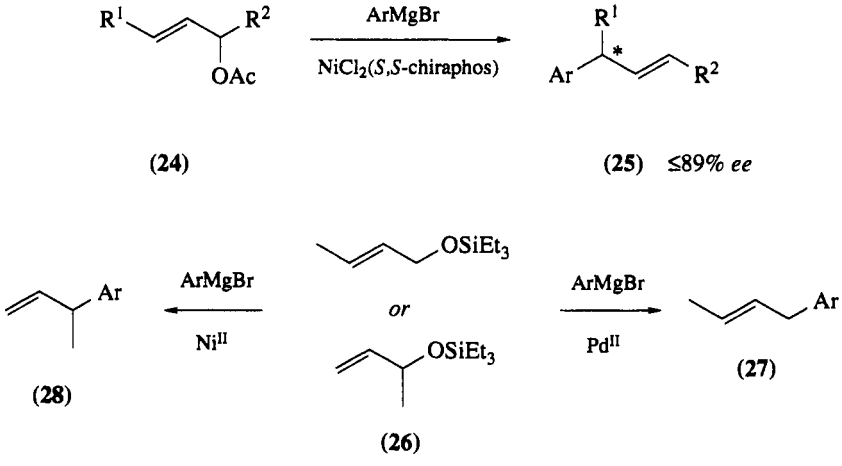


(20) (21)



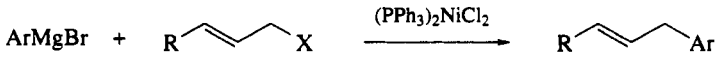
(22) (23) n = 1 or 2

These unsaturated lactones are special cases of a much more general theme whereby Grignard reagents can be alkylated by a wide variety of allylic systems, usually in the presence of a nickel- or copper-based catalyst. Arylmagnesium bromides react in an S_N2' fashion with allylic acetates and a nickel catalyst; when the latter is chiral, allylaryls of up to 89% enantiomeric enrichment can be obtained (**24** → **25**).[33] Copper catalysts, such as Li_2CuCl_4, can also be employed in such displacements, but usually *via* a direct S_N2 mechanism.[34] Similarly, primary allylic phosphates react with Grignard reagents under copper(I) catalysis exclusively *via* S_N2 displacement; usually no products from allylic rearrangement are observed.[35] Chiral allylaryl compounds (**25**) can also be prepared by alkylations of ArMgX using an allyl phenyl ether and a chiral Ni–phosphine catalyst. Optical yields are fair to good but a more serious problem is poor regioselectivity.[36] Much more regioselective are the related reactions with allyl silyl ethers (**26**); with a ferrocenepalladium(II) catalyst, either isomer of the ether gives very largely the internal alkenes (**27**) when treated with ArMgX, whereas nickel(II) catalysts lead mainly to the isomeric terminal alkenes (**28**; Scheme 9).[37]



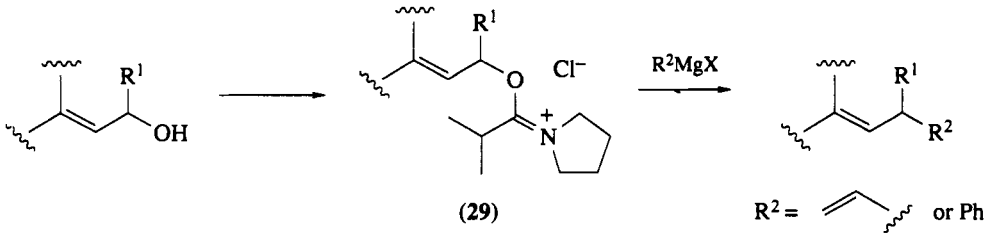
Scheme 9

In contrast, a whole range of allylic systems, including allylic alcohols, undergo nickel-catalyzed coupling reactions with arylmagnesium bromide to give, usually exclusively, primary allylaryl compounds uncontaminated by the corresponding conjugated isomers (Scheme 10).[38] The reactions proceed *via* an ω-allylnickel complex and require an excess, typically 4 equiv., of the Grignard reagent in examples of electrophiles with a labile proton (*e.g.* allyl alcohol). Allylic alcohols can be activated for this type of coupling by conversion to the iminium salts (**29**); subsequent coupling with Grignard reagents then occurs directly *via* S_N2 displacement (Scheme 11).[39] If, however, the Grignard reagent is treated with copper(I) iodide and HMPA prior to the coupling step, the alternative, S_N2', products are usually formed. In a related sequence, exclusively S_N2' products (**31**) are formed when 2-allyloxybenzothiazoles (**30**) are reacted with Grignard reagents in the presence of copper(I) bromide.[40] Finally, the modified aryl Grignard species, $PhCu{\cdot}MgBr_2{\cdot}LiBr$, react in an S_N2' fashion with allenic bromides (*e.g.* **32**) to give very largely alkynes (*e.g.* **33**) contaminated with very little of the corresponding allene.[41] Some less conventional electrophiles have also been used in efficient alkylations of Grignard reagents. For example, benzylamines (*e.g.* **34**) are available from alkylations of PhMgBr using either alkoxymethyl- or phenylthiomethyl-amines [$RXCH_2NR_2$];[42] similar products are obtainable from reactions between Grignard reagents or organolithium species and Eschenmoser's salt.[43] Finally, Grignard reagents can be efficiently allylated using allyltrialkylammonium salts in the presence of Li_2CuCl_4.[44]



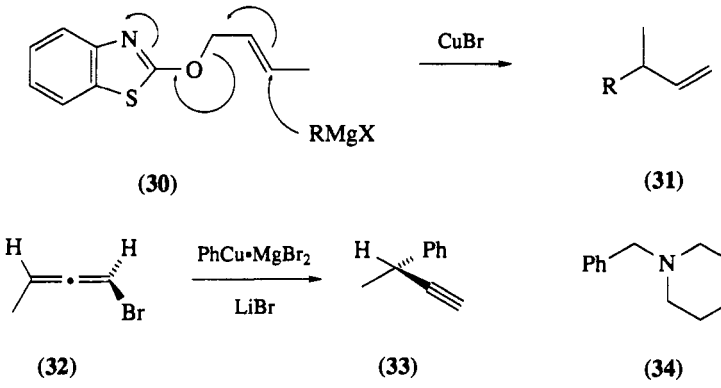
X = OH, OMe, OEt, SH or SMe

Scheme 10



(29)

Scheme 11

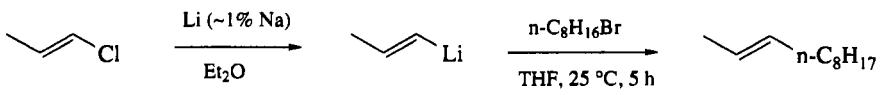


(30) (31)

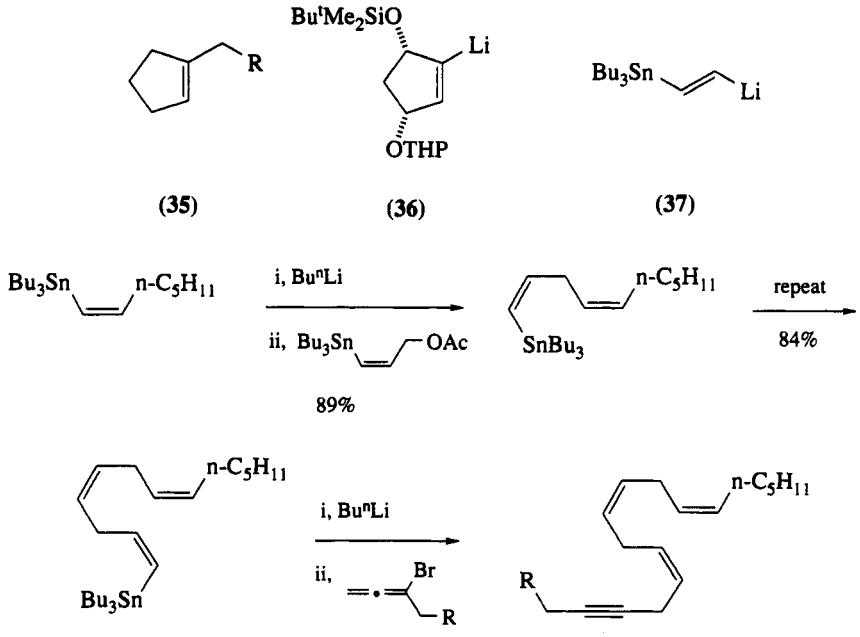
(32) (33) (34)

1.6.2.2 Alkylations of Vinyl- and Aryl-lithium Species

The simplest possible reaction in this section, that between a vinyllithium and a primary alkyl halide in general works extremely well (Scheme 12).[45] The corresponding alkyl iodide can equally well be used, but the reaction fails with secondary halides or primary tosylates and is much less satisfactory with alkyl chlorides or when performed in other ethereal solvents. ω-Bromoalkenes can even be obtained from 1,ω-dibromoalkanes in good yields;[18,21,46] virtually no alkene isomerization is observed and therefore both *trans*- and *cis*-alkenes are available using this method. 1-Alkylcycloalkenes (*e.g.* **35**) as well as acyclic trisubstituted alkenes can also be prepared in this way;[46] an alternative strategy is to treat the vinyl bromide with an alkyllithium at –70 °C thus generating the vinyllithium and alkyl bromide by halogen–metal exchange. Upon warming to room temperature, alkylation proceeds smoothly.[46] However, this latter method is limited by the availability of alkyllithiums. A way around this is to treat the vinyl halide with 2 equiv. of Bu^{t}Li, the extra equivalent of base serving to trap the *t*-butyl halide produced.[47] An excellent alternative is to employ tin–lithium exchange reactions between a vinyltrialkylstannane and an alkyllithium, usually MeLi or Bu^{n}Li, which results in the formation of an essentially inert tetraalkyltin by-product. This method has been used, for example, to generate the useful cyclopentenyllithium (**36**) which, although it couples efficiently with reactive electrophiles such as allyl bromide and benzyl chloromethyl ether, is reported to react poorly (*ca.* 30% yields) with primary alkyl iodides.[48] An extremely useful reagent in this respect is *trans*-1,2-bis(tri-*n*-butylstannyl) ethylene, which, upon treatment with Bu^{n}Li (THF, –78 °C), affords the vinyllithium (**37**), alkylation of which with a range of alkyl halides is reported to be very efficient.[49] The initial products, being vinylstannanes, can clearly be further homologated by the same methodology. An example of this type of strategy is to be found in the approach to 5,6-dehydroarachidonic acid outlined in Scheme 13.[50] Additional features of note in this scheme are the efficient alkylations of the intermediate vinyllithiums by allylic acetates and the S_N2'-like reaction[41] with an allenic bromide.

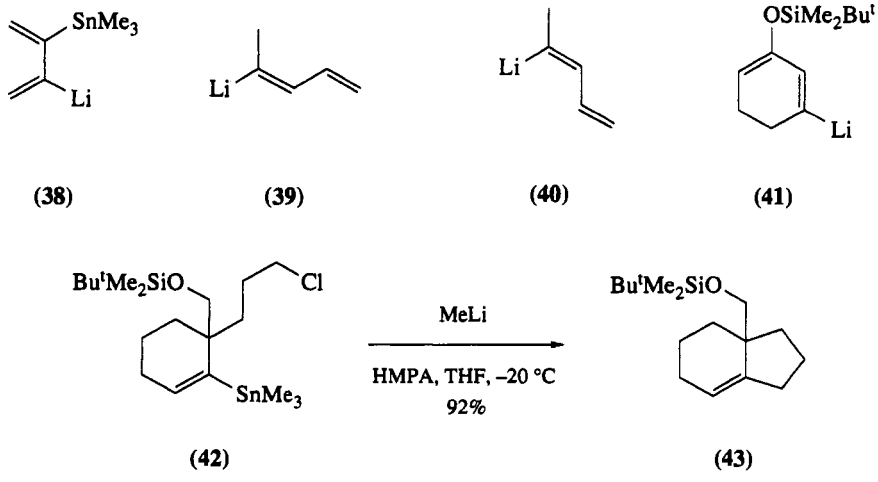


Scheme 12



Scheme 13

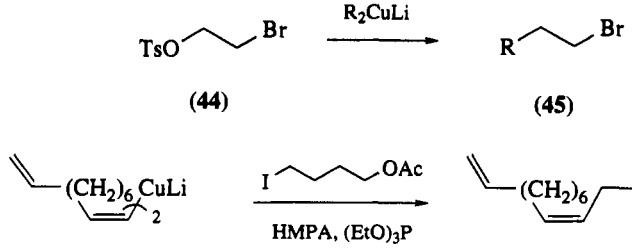
Further examples of useful vinyllithium intermediates which have been generated using tin–lithium exchange include the substituted butadiene precursors (**38**),[51] (**39**)[52] and (**40**),[52] and the cyclohexadiene (**41**);[53] all four intermediates react efficiently (60–86% yields) and directly with a range of primary alkyl bromides or iodides. Such alkylations can also be performed intramolecularly, as for example in a preparation of the hydrindane (**43**) from the vinylstannane (**42**).[54]



A very popular and often complementary alternative to the foregoing vinyllithium chemistry is the use of lithium divinyl- or diaryl-cuprate species, R_2CuLi, which also can be alkylated using primary alkyl bromides or iodides but often only in the presence of various additives, typically a stabilizing phosphine ligand and the correct solvent. For example, lithium divinylcuprate is alkylated by *n*-octyl iodide, after treatment with tri-*n*-butyl phosphine, to give 1-decene in 91% yield.[55] In contrast to the simple aryllithium species, Ph_2CuLi reacts smoothly with a secondary alkyl bromide to give an alkylbenzene with 84–92% inversion of stereochemistry, as expected of an S_N2 process.[55] Alkylations of this type generally result in almost complete retention of the original alkene geometry.[56]

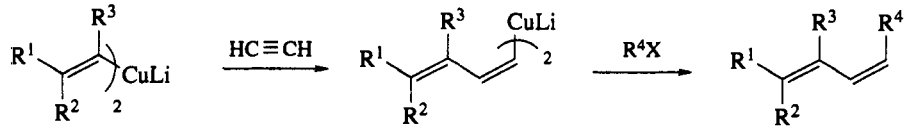
Two key differences in reactivity between vinyl- or aryl-lithiums and the corresponding R_2CuLi species are firstly that the cuprates couple efficiently (and more rapidly than with alkyl halides) with both primary and secondary tosylates,[55,57] which the lithiums do not,[45] and secondly the general lack of

reactivity between the cuprates and carbonyl functions such as those present in ketones, esters and acetates.[14,57] Thus, for example, cuprate species react with bromoethyl tosylate (**44**) to give excellent yields of the bromides (**45**),[14] and the cuprate (**46**) reacts smoothly with an acetoxy iodide leading to the acetoxydiene (**47**).[58]



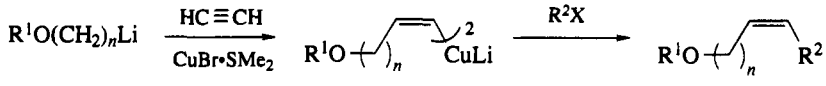
A major drawback in the use of homocuprates, R_2CuLi, is that one of the alkenyl or aryl groups can often be wasted; clearly, however, this is not a serious problem if the cuprate is derived from a simple organolithium. With reactive electrophiles such as allylic halides or α-halo ethers, both organic ligands are alkylated in the presence of 1 equiv. of HMPA, but with less reactive alkyl halides, at least 3 equiv. of $(EtO)_3P$ are required to stabilize the intermediate cuprate species during the much slower transfer of the second alkenyl ligand.[59]

Further extensions of this general methodology include a useful (*E,Z*)-diene synthesis (Scheme 14)[60] and an approach to (*Z*)-alkenols (Scheme 15).[61] Unfortunately such sequences are ineffective when applied to monosubstituted alkynes, a limitation which also applies to the corresponding alkenylmagnesiocuprates.[17] These intermediates also react smoothly with allylic halides to provide 1,4-dienes, especially when dimethyl sulfide is present as an extra ligand,[62] which is fortunate as some of the most convenient sources of copper(I) salts having the high purity requirements for this type of chemistry are the sulfide complexes $CuX{\cdot}SMe_2$ (X = Br or I).[63] One such allylation reaction forms a key step in an approach to α-*trans*- and β-*trans*-bergamotene (Scheme 16);[64] an additional noteworthy feature is that the cuprate species does not suffer from β-elimination of the amino function prior to alkylation.

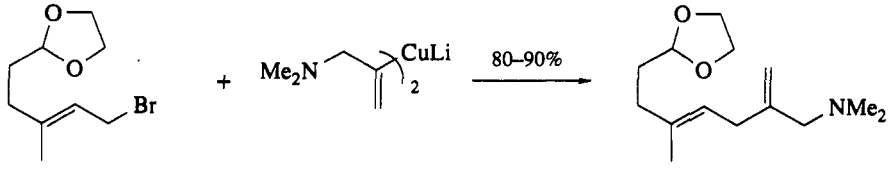


R = Me, Bu^n or CH_2NEt_2 (50–80%)

Scheme 14



Scheme 15

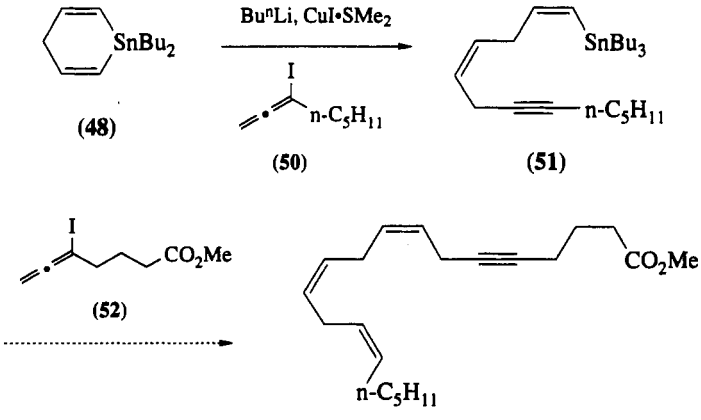


Scheme 16

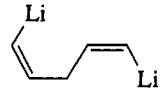
Alternative methods for obtaining these types of cuprates, R_2CuX (where R = alkenyl or aryl), include treatment of RBr with lithium metal and copper(I) iodide under ultrasonication,[65] reaction between a dialkylvinylborane and $CuBr{\cdot}Me_2S$[66] or between a chlorodivinylborane and methylcopper.[67] The latter

two intermediates react efficiently with allyl bromide to provide 1,4-dienes, but alkylations by simple alkyl halides require the addition of an extra ligand such as a phosphine or phosphonite, usually in considerable excess. A significant side reaction can be dimerization of the intermediate cuprates. Trialkylborons can also be used to alkylate vinyllithiums and related species.[68]

A neat combination of some of the foregoing chemistry is use of the cyclic stannane (**48**) as an equivalent of the 1,4-pentadienyl dianion (**49**).[69] Thus, treatment of the stannane (**48**) with Bu^nLi, copper(I) iodide–dimethyl sulfide complex and the iodoallene (**50**) smoothly leads to the dienyne (**51**) and thence, by a repetition of this sequence but using electrophile (**52**), to 3-dehydroarachidonic acid methyl ester (**53**).

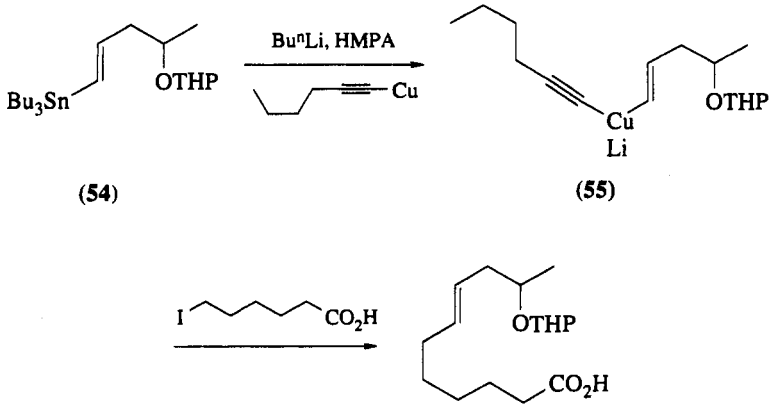


(48) (50) (51) (52) (53)



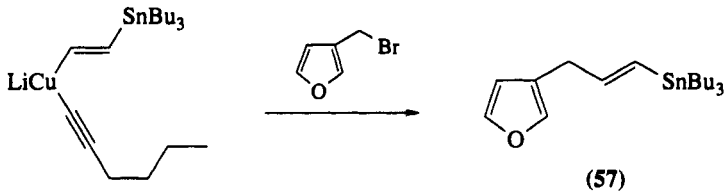
(49)

A valuable method whereby the wastage of one organic ligand in R_2CuLi species can be avoided is to employ mixed cuprates R^1R^2CuLi, where R^2 is a nontransferable ligand, such as an acetylide, cyanide or benzenethiolate. For example, conversion of the vinylstannane (**54**) into the corresponding vinyllithium followed by the addition of 1-pentynylcopper gives a mixed cuprate intermediate (**55**), which is then alkylated by transfer of only the vinyl ligand (Scheme 17).[70] Similarly, the mixed cuprate (**56**; *cf.* ref. 49) can be alkylated using 3-bromomethylfuran to provide the stannane (**57**), ready for further homologation.[71] A further important development in this area has been the introduction of 'higher order' cuprates in which various stoichiometries of the vinyl- or aryl-lithium are mixed with copper salts.[12,72] Particularly of note is the ability of the higher order cuprate (**58**) to couple efficiently with an *s*-alkyl iodide (Scheme 18);[73] in contrast, the corresponding lithium divinylcuprate gives only a 23% yield. The analo-



(54) (55)

Scheme 17

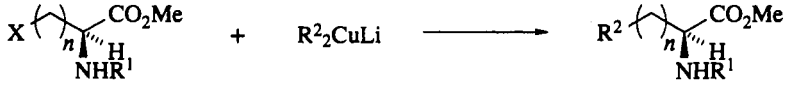


(56) (57)

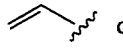
(58)

Scheme 18

gous aryl species, $Ph_2Cu(CN)Li_2$, is not alkylated efficiently by secondary iodides but does react extremely efficiently with primary chlorides and especially bromides or tosylates[74] (the simpler species, Ph_2CuLi, also couples efficiently with both primary and secondary bromides and tosylates).[55–57] An excellent illustration of the power of vinyl- and aryl-cuprates in synthesis is the finding that such intermediates couple smoothly with the halides (**59**; X = Br or I) to provide a racemization-free approach to chiral non-natural α-amino acids (Scheme 19).[75] As well as the regioselectivity of attack, it is especially noteworthy that no elimination to give dehydroalanine occurs with the lower homologs (**59**; $n = 1$). An excellent and convenient reagent for the preparation of mixed higher-order cuprates ($R^1R^2Cu(CN)Li_2$) is the shelf-stable, commercially available complex (2-thienyl)Cu(CN)Li; the cuprates formed from this species and R′Li react smoothly with primary alkyl iodides with transfer of only R′, the 2-thienyl ligand being essentially inert.[76]

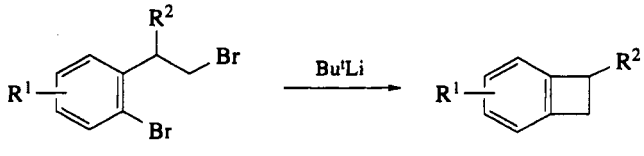


(59)

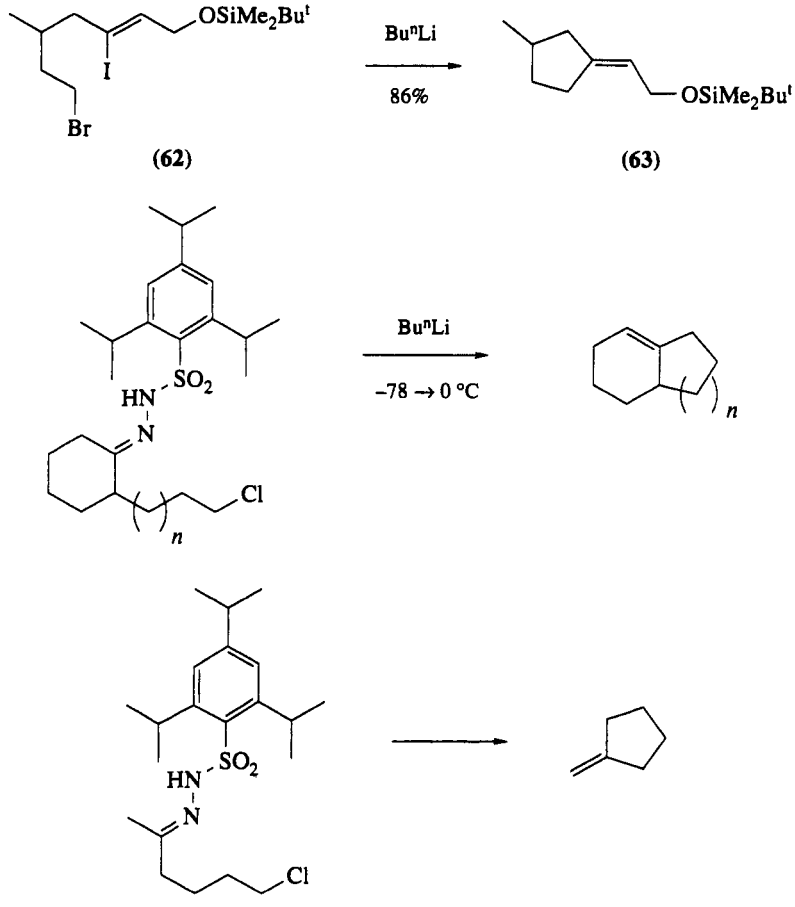
n = 1 or 2; R^1 = Boc, Z, Bz or Ts; R^2 =  or Ph

Scheme 19

Alkylations of vinyl carbanions can also be carried out intramolecularly to provide three-, four-, five- and six-membered rings (see also refs. 99 and 100). For example, treatment of the dibromides (**60**) with Bu^tLi at low temperature results in selective bromine–lithium exchange at the sp^2-center; on warming 'Parham-type' cyclization occurs, thus providing a useful route to substituted benzocyclobutanes (**61**).[77] Similarly, the vinyl iodide (**62**), upon treatment with Bu^nLi (–78 °C → +20 °C) smoothly cyclizes to give an 86% yield of the ylidenecyclopentane (**63**), with no scrambling of the alkene stereochemistry.[78] Similar approaches to related cyclohexane systems also work well.[78] Another useful method for generating vinyllithium species is the Shapiro reaction (such intermediates can be alkylated reasonably efficiently by primary alkyl bromides);[79] this methodology can also be applied intramolecularly (Scheme 20).[80] Presumably, in some cases, the intermolecular version could be improved by the addition of various ligands such as HMPA or $(EtO)_3P$ (*vide supra*).



(60) (61)

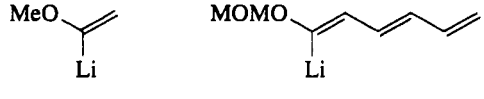


Scheme 20

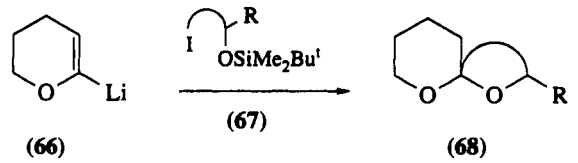
1.6.2.3 Alkylations of Heteroatom-substituted Vinyl Carbanions

The presence of a heteroatom either α or β to an sp^2-carbanion opens up many additional synthetic possibilities. Furthermore, their presence can often modify the reactivity of the intermediate and allow its generation by direct hydrogen–lithium exchange rather than halogen–lithium exchange, thus contributing an extra degree of simplicity to the reaction sequences. An excellent illustration of these features is the generation of vinyllithium (**64**) by treatment of methyl vinyl ether with Bu^{t}Li.[81] Formally an acyl anion equivalent, this intermediate can be alkylated efficiently by primary alkyl iodides or primary allylic bromides, although not by benzylic bromides, which instead react *via* halogen–lithium exchange. The corresponding cuprate, however, does couple smoothly with benzylic bromides as well as with secondary allylic bromides.[81,82] The vinyllithium (**64**) can also be generated using Sn–Li exchange and Bu^{n}Li,[83] while the higher homolog (**65**) can be generated directly only in the presence of the MOM function using Bu^{n}Li–TMEDA.[84] Cyclic analogs of the vinyllithium (**64**) have also proven useful in a variety of synthetic schemes, and can often be alkylated in high yield; for example metallation of 2,3-dihydropyran affords the vinyllithium species (**66**), which, upon alkylation using a protected ω-iodo alcohol (**67**), followed by acidification affords good yields of the spiro-acetals (**68**).[85]

As expected, related sulfur species can also be generated and used to good effect, an example being the vinyl sulfide (**69**), which can be alkylated with good efficiency (*e.g.* Bu^{n}I, 68% yield).[86] Similarly the β-lithio species (**70**) reacts satisfactorily with, at least, methyl iodide (99%) and allyl bromide (68%). It

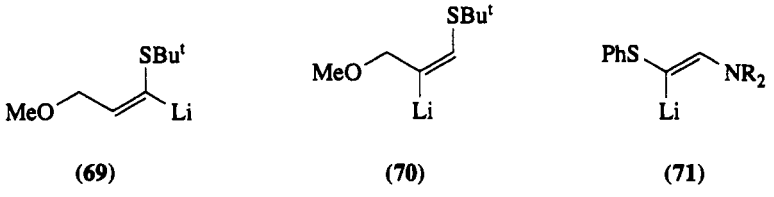


(**64**) (**65**)

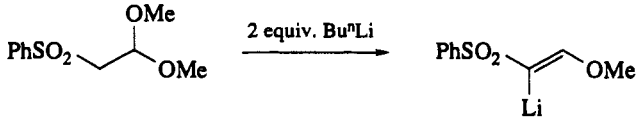


(66) (67) (68)

should be noted in this context that methyl iodide is a very special electrophile, often more suited to assaying the extent of anion generation rather than to synthetic utility. A much better indicator, and by no means a trivial change, is to examine the reactions of a new carbanion with ethyl or *n*-butyl iodides; good yields from these electrophiles bode well for the general utility of the intermediate. For instance, the α-thio enamine (**71**) is reported to give quantitative yields with both methyl and ethyl iodide;[87] the latter result is of much more significance. The related sulfones also show some promise as intermediates. Generated from either the acetal (**72**) by sequential E_2 elimination and deprotonation[88] or by direct deprotonation of either the (*E*)- or (*Z*)-vinyl sulfone,[89] the intermediates (**73**) can be alkylated using Bu^nI (76%), or benzyl bromide (60–77%), thus indicating at least a reasonably wide utility. The homologous acetal (**74**) has also been reported, although it has only been alkylated with MeI (96%) and with allyl bromide (81%).[90] Similarly, the vinyl selenide (**75**) can be obtained and reacts with *n*-octyl bromide to give the expected homolog in 69% yield,[91] indicating a good range of reactivity. These examples are relatively typical in that full ranges of electrophiles are often not examined (or at least not reported), and it is therefore sometimes difficult to judge the likely overall importance of a particular intermediate.



(69) (70) (71)

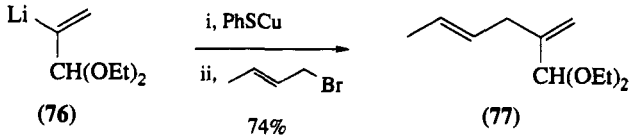


(72) (73)

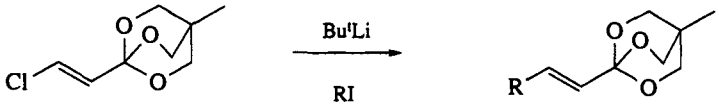
(74) (75)

Despite the presence of a potential β-leaving group, the α-lithio acrolein derivative (**76**)[92] can be obtained at low temperatures but only condenses efficiently with primary allylic halides after conversion to the corresponding mixed cuprate using PhSCu; direct, rather than S_N2', attack occurs at least with (*E*)-1-bromo-2-butene to give the functionalized 'skipped' diene (**77**). With many other intermediates, the problem of S_N2 *vs.* S_N2' attack is often only resolved by experimentation using the desired electrophile. The vinyl ortho ester (**78**) can be lithiated by halogen–lithium exchange and subsequently alkylated to provide the homologs (**79**) *via* a synthetic equivalent of β-lithio acrylate.[93] This example is reasonably typical of many such alkylations of lithiovinyl carbanions which work well with methyl iodide (and other reactive and simple electrophiles such as R_3SiCl, PhSSPh or CO_2), but are not so useful with homologous primary iodides. Vinyl carbanions can be generated α to an unprotected ester group in certain cases by Sn–Li exchange. For example, treatment of α,β-unsaturated esters (**80**) sequentially with Bu^nLi and RX leads to the homologs (**81**); once again, a typical pattern emerges in that methyl iodide and primary allylic halides afford high yields, whereas 3-chloro-1-iodopropane gives only a 42% yield of the homolog (**81**; $R^1 = (CH_2)_3Cl$).[94] Similarly, the β-stannyl analog (**82**) can be obtained; this intermediate exhibits essentially the same characteristics.[95] Subsequent conversion of the initial products arising from alkylations of the ester (**82**) into the allylic alcohol (**83**) (effectively the β-lithio analog) followed by alkyl-

ation results in a stereospecific approach to tetrasubstituted alkenes. The latter alkylations are somewhat more efficient, as primary alkyl iodides afford 65–72% isolated yields.

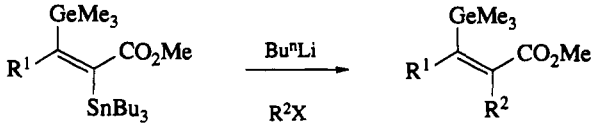


(76) (77)



(78) (79)

R = Me; 72%
R = Bu^n; 54%

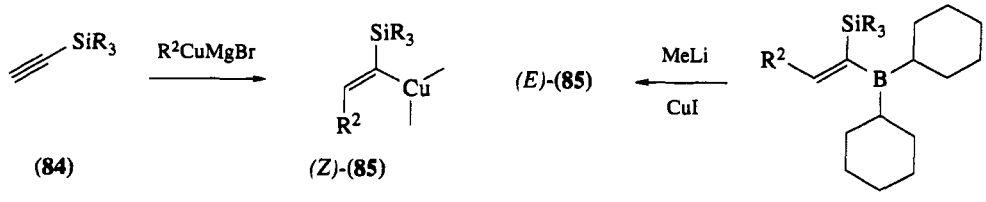


(80) (81)

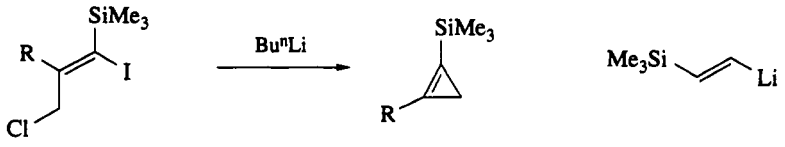
(82) (83)

Vinyl carbanions positioned α to a silicon substituent have also proven to be valuable synthetic intermediates, which in general undergo highly efficient alkylations by primary alkyl iodides or tosylates as well as by allylic halides, especially when a vinylcuprate species is used. Such intermediates (**85**) can be generated either by the addition of a copper-modified Grignard reagent to silyl alkyne (**84**)[96] or by a stereochemically complementary boron–lithium exchange procedure involving vinylboranes (**86**) derived from the corresponding silylalkyne.[97] The related vinyllithium species, obtained by halogen–lithium exchange, are also reported to react efficiently with, at least, primary alkyl iodides.[98] Such alkylations can also be carried out intramolecularly,[77–80] a rather spectacular example being the elaboration of silylcyclopropenes (**88**) upon treatment of allylic chloride (**87**) with Bu^{n}Li;[99] the methodology has been extended to the corresponding unsaturated four-, five- and six-membered rings.[100] The isomeric β-lithio silane (**89**), generated by Sn–Li exchange, shows little tendency to undergo elimination and can be alkylated using Bu^{n}Br (81%), indicating a reasonably wide utility for this species.[101]

In general, *ortho*-substituted aryllithiums give variable results in alkylation reactions, and in some cases only after conversion to a cuprate species. For example, the cuprate (**90**) can be allylated efficiently and then electrolyzed to provide the protected benzoquinone (**91**) in excellent overall yield.[102] Coupling

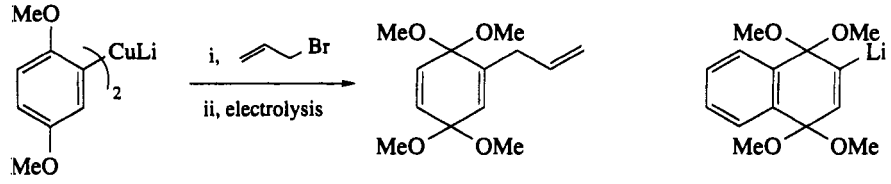


(84) (*Z*)-(85) (86)



(87) (88) (89)

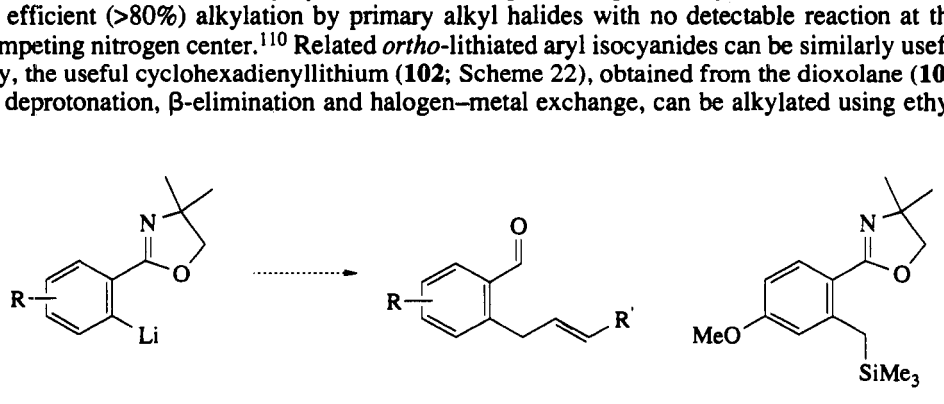
reactions with benzyl bromide are also viable when it appears that, unusually, more than 1 equiv. of the organic ligand in the cuprate (**90**) is alkylated, and direct allylations of the related naphthoquinone-derived species (**92**) are also successful, but again only after conversion to the corresponding cuprate.



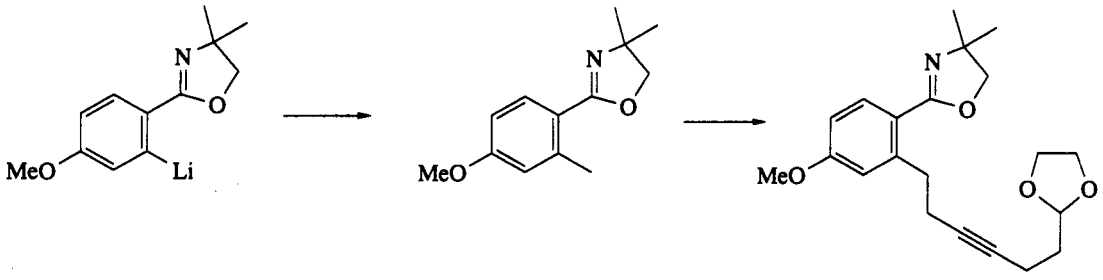
(90) (91) (92)

The oxazoline function is one of the most powerful directing groups in metallation chemistry, and allows the direct generation of the *ortho* lithio species (**93**).[103] These have been used with varying success in alkylation reactions; a particularly useful aspect is as precursors to *o*-allylbenzaldehydes (**94**) following allylation and reduction–hydrolysis of the oxazoline function.[104] Alkylations with iodomethyltrimethylsilane also work well, leading to quinodimethane precursors (*e.g.* **95**).[105] However, in common with many nucleophiles, alkylations using homoallylic or propargylic halides fail due to competing deprotonation and overall elimination of HX from the electrophile. A solution to this limitation, which can often be applied in the aromatic and heteroaromatic areas, is first to alkylate the sp^2-center with methyl iodide (usually a very efficient step), then remetallate to generate a (usually) more reactive sp^3-carbanion and finally alkylate with an allylic or propargylic halide. This technique is illustrated in Scheme 21, which forms the early stages of the preparation of enediynes suitable for Vollhardt-type cobalt-catalyzed cyclizations.[106] The closely related imidazolidine (**96**), however, requires an excess of alkylating agent, and even then only reacts well with methyl iodide (95%); with *n*-butyl bromide only a 45% yield is realized, while alkylation with benzyl bromide gives a 30% yield of the dialkylated product (**97**), a not uncommon feature with this type of reactive halide.[107] In contrast, the dianionic species (**98**) derived (BunLi–TMEDA) from benzyl alcohol reacts best with *n*-butyl chloride (55%) and gives only traces of product with primary alkyl iodides; presumably in these cases deprotonation of the iodides by the highly basic dianion takes precedence.[108] A related dianionic species (**99**) derived from benzaldehyde by sequential hemi-aminal formation using *N*-lithio-*N'*-methylpiperazine and deprotonation (BunLi) does react reasonably well with BunBr (47%), but only after the addition of copper(I) iodide.[109] The dianion (**100**), derived from the tosylhydrazone of benzophenone, provides yet another contrast as it does undergo efficient (>80%) alkylation by primary alkyl halides with no detectable reaction at the potentially competing nitrogen center.[110] Related *ortho*-lithiated aryl isocyanides can be similarly useful.[111]

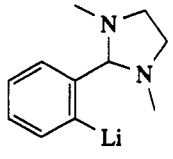
Finally, the useful cyclohexadienyllithium (**102**; Scheme 22), obtained from the dioxolane (**101**) by sequential deprotonation, β-elimination and halogen–metal exchange, can be alkylated using ethyl iodide,



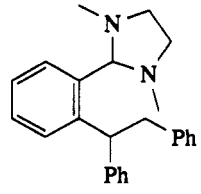
(93) (94) (95)



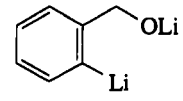
Scheme 21



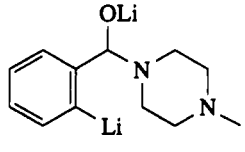
(96)



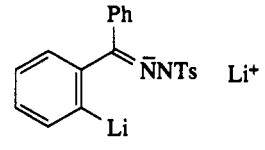
(97)



(98)

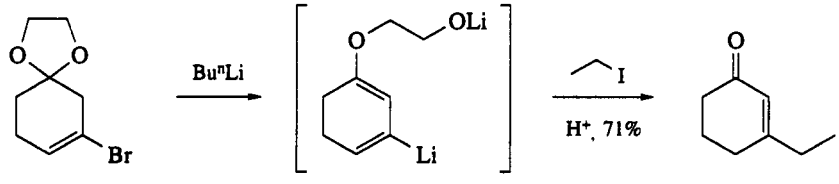


(99)



(100)

and hence probably by higher, primary homologous iodides, to provide a useful route to 3-substituted cyclohexenones.[112]



(101) **(102)**

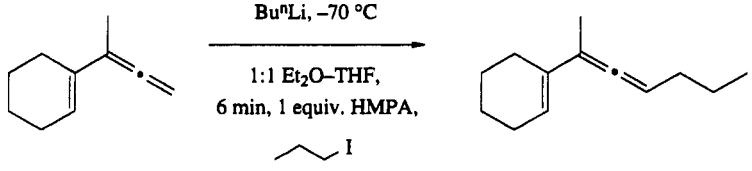
Scheme 22

It is hoped that the foregoing examples provide an indication of the variety of outcomes, both good and bad, which can result from alkylations of this type of sp^2-carbanion, together with some useful methods for obtaining good yields. Many anionic species are not included in the discussion simply because their alkylation chemistry has not been reported, except sometimes with methyl iodide which, as discussed above, is not always a typical or representative electrophile in this type of chemistry.

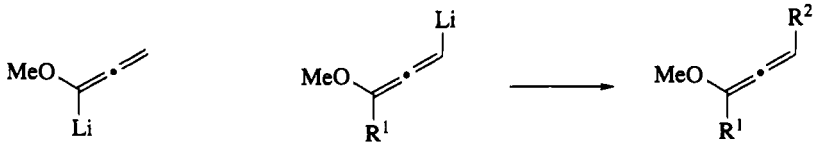
1.6.2.4 Alkylations of Allene Carbanions

Allenes can be directly deprotonated using alkyllithiums, and the intermediate lithio allenes can then be alkylated efficiently by primary alkyl bromides or iodides.[113] For example, good yields of homologated allenes can be realized under the conditions specified in Scheme 23 (the brief reaction time appears

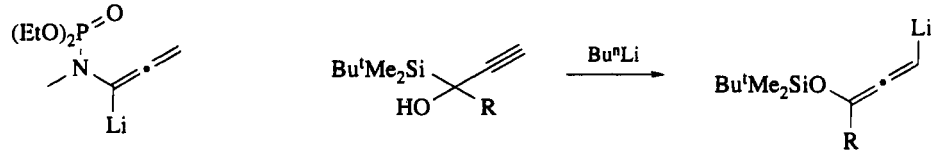
to be crucial) when very little of the alkynic isomer is formed. Similarly, the corresponding lithium diallenylcuprates, obtained either by hydrogen– or halogen–lithium exchange can also be alkylated.[114] In common with methyl vinyl ether,[81,82] methoxyallene can be directly deprotonated, although the resulting intermediate (**103**) gives only moderate to good yields of alkylated products upon treatment with a variety of primary alkyl or allylic halides.[115] Once the intermediate (**103**) has been alkylated, the products can be again deprotonated to provide the new lithio allene (**104**), and thence the dialkylated products (**105**), following treatment with a primary alkyl iodide (the addition of a copper(I) species is not necessary); these final educts are useful as precursors to α,β-unsaturated ketones, to which they are converted simply by acidic hydrolysis.[116] Much the same double alkylation sequence can be carried out using the phosphoramide (**106**), although the range of suitable alkylating reagents appears to be more limited.[117] The related silyloxy species (**108**), generated by rearrangement of the propargylsilane (**107**), can also be alkylated using a range of primary alkyl halides (71–87%) to give the expected homologs, again useful precursors to α,β-unsaturated ketones.[118]



Scheme 23



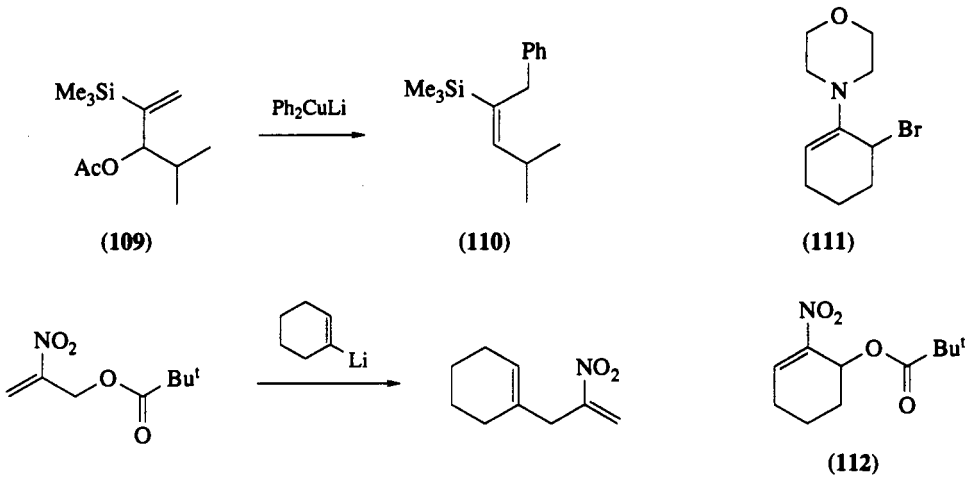
(103) **(104)** **(105)**



(106) **(107)** **(108)**

1.6.2.5 Alkylations by an S_N2' Process

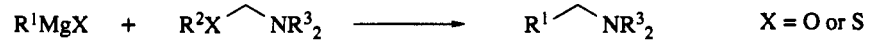
Many of the foregoing alkylations with allylic halides have only been carried out with symmetrical examples of the latter, and therefore it is not clear whether alkylation occurs *via* an S_N2 or S_N2' process. However, in common with Michael addition chemistry, vinyl and aryl carbanions generally add in a conjugate S_N2' fashion in the presence of a copper(I) salt, and in the absence of excessive steric demands.[33,39–41] Thus, in a typical example, lithium diphenylcuprate adds to the allylic acetate (**109**), derived from the corresponding α-lithio vinylsilane,[98] to provide a 61% yield of only the (*E*)-vinylsilane (**110**);[119] with other examples, the regioselectivity can be poorer.[120] Often such cuprates react with α-bromo ketones to give only poor yields of α-aryl ketones, a common side or even major pathway being halogen–metal exchange. This problem can be overcome by employing the corresponding enamine (*e.g.* **111**), which reacts smoothly with Ph_2CuLi, presumably *via* an S_N2' displacement, to give, in 87% yield, 2-phenylcyclohexanone after hydrolysis[121] (see also refs. 6–8). However, in cases of extreme steric and/or electronic demands, vinyllithium species will react in an S_N2' fashion as illustrated in Scheme 24.[122] The cyclohexene derivative (**112**) reacts similarly; these are perhaps not typical examples, despite the overall S_N2' process, since the first step is a Michael-type addition.



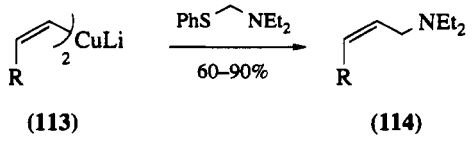
Scheme 24

1.6.3 ALKYLATIONS WITH LESS CONVENTIONAL ELECTROPHILES

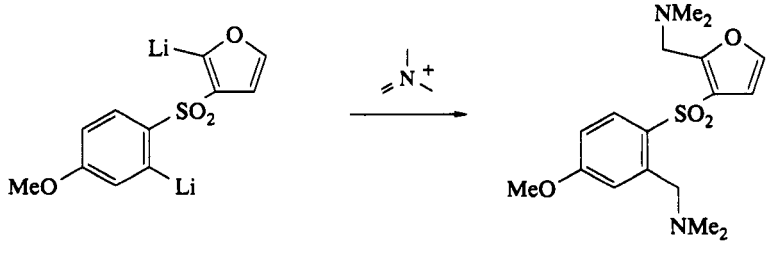
Some examples of less conventional electrophiles which react well with sp^2-carbanionic centers are grouped together here mainly for reasons of emphasis and because a variety of organometallic species are involved. Aminomethylations of Grignard reagents, for example, can be effected either using an aminomethyl ether[42,123] or an amino sulfide (Scheme 25).[124] The latter electrophiles also react well with (*Z*)-divinylcuprates (**113**), derived from alkylcuprate additions to acetylene, to provide a useful route to (*Z*)-allylamines (**114**).[125] Methyleneammonium salts (*e.g.* Eschenmoser's salt)[43] can also be applied in this way; for example, the dilithiated aromatic intermediate (**115**) reacts to form the diamino derivative (**116**).[126] Two useful extensions of this are that treatment of the precursor of the dianion (**115**) with 1 equiv. of base results in regioselective metallation of the furan and hence leads to the aminomethylfuran derivative; not unreasonably therefore, treatment of the dianion (**115**) with 1 equiv. of the electrophile gives the aminomethylphenyl isomer. Although aminoethylation can be achieved by condensations between (usually *N*-tosyl) aziridines and cuprates (**113**), much better yields are often obtained using mixed higher-order cuprates, $R_2Cu(CN)Li_2$.[127] With less reactive cuprates, the addition of BF_3 can be beneficial.



Scheme 25

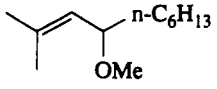


(113) **(114)**

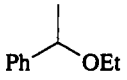


(115) **(116)**

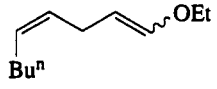
A variety of Grignard reagents also react with ortho esters and acetals leading to acetals and ethers respectively.[128] A particularly useful extension of this methodology is in its application to alkylations of divinylcuprates (**113**).[129] Thus, the ether (**117**) can be obtained from heptanal dimethylacetal, the appropriate cuprate and BF_3 in 93% yield; similarly acetaldehyde diethylacetal reacts with $PhCu{\cdot}BF_3$ to give an equally good yield of the ether (**118**). With unsaturated acetals, mainly and sometimes exclusively S_N2' addition takes place; thus acrolein diethylacetal and cuprate (**113**; R = Bu^n) modified using BF_3 react to give vinyl ether (**119**) in 66% yield. At the higher oxidation level, reactions with ortho esters provide a useful method for homologation to the (protected) aldehyde level as, for example, in the coupling of $PhCu{\cdot}BF_3$ and triethyl orthoformate to give benzaldehyde diethylacetal (92%).



(**117**)

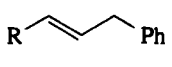


(**118**)

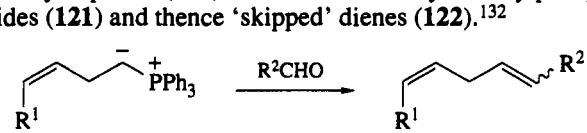


(**119**)

A somewhat unusual reaction is the coupling of phenyllithium–copper(I) iodide mixtures directly with allylic alcohols, in the presence of the salt $Ph_3PNMePh^+I^-$, allowing a usually stereoselective preparation of hydrocarbons (**120**).[130] Similar phenyllithium species can be directly alkylated using diazoacetates to give phenylacetates in moderate (*ca.* 50%) yields,[131] the latter usually being inferior to those produced by related boron-based methodology.[6] Divinylcuprates (**113**) also add efficiently to vinylphosphonium salts (*e.g.* Schweizer's reagent) to give ylides (**121**) and thence 'skipped' dienes (**122**).[132]



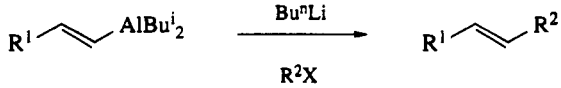
(**120**)



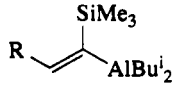
(**121**) (**122**)

1.6.4 ALKYLATIONS OF VINYL AND ARYL CARBANIONS, RM, WHERE M ≠ Li, Mg or Cu

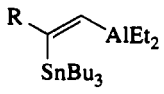
Some of the most important members in this group are the alkenylalanes (**123**), which are readily prepared by the addition of DIBAL-H to a terminal alkyne; however, in general, these can only be alkylated in respectable yields following formation of the corresponding 'ate' complexes, often using *n*-butyllithium.[133] Unfortunately, even these more reactive intermediates tend to give really good yields only with allylic bromides, although the very reactive chloromethyl methyl ether alkylates the alanes (**123**) directly, without the need to form an 'ate' complex, to give the expected ethers in 72–80% yield.[134] 'Ate' complex formation is also necessary in alkylations of the related alanes derived by the zirconium-catalyzed addition of trimethylaluminum to 1-alkynes.[133] Much the same is true of more highly substituted derivatives such as the α-silylalane (**125**)[135] or the β-stannyl homolog (**126**),[136] both of which react well (68–84%) with allylic halides after conversion to an 'ate' complex, whereas reactions with iodo-ethane or -butane are much less efficient. In contrast, the alkenylaluminum (**127**), the first example of such a species to contain a free carbonyl group, does alkylate directly with a variety of primary and secondary alkenyl bromides,[137] although S_N2 *vs.* S_N2' attack is a problem with appropriate electrophiles such as crotyl bromide. In a rather different reaction type, the allylic acetate (**129**) couples smoothly with the alane (**128**) under the influence of a Pd^0 catalyst to provide only the product (**130**) of overall S_N2 attack.[138]



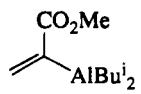
(**123**) (**124**)



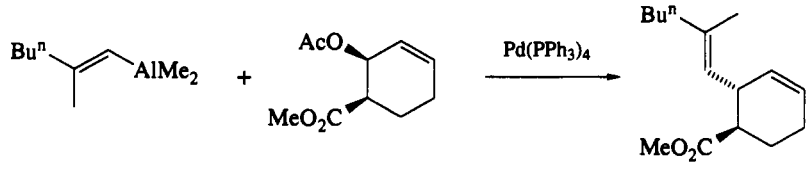
(**125**)



(**126**)

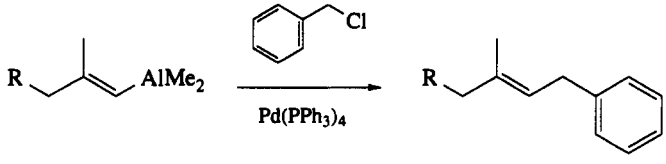


(**127**)

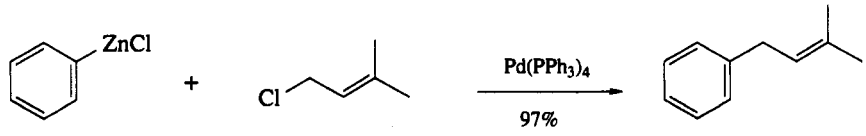


(128) **(129)** **(130)**

A related set of conditions (Scheme 26) provides an alternative to 'ate' complex formation, at least in alkylations using benzylic or allylic chlorides.[139,140] The reverse sense of coupling between benzylzinc species and alkenyl halides is also a viable option. In a similar fashion, arylzincs can be coupled readily with allylic halides (Scheme 27).[140] Both alkenylalanes and zinc species can be similarly coupled with allylic acetates, aluminum alkoxides, phosphates or silyl ethers. Again, problems can arise when the electrophiles can readily undergo both S_N2 and S_N2' displacements. In such examples, the ratio of products obtained is more dependent on the nature of the aryl metal and the solvent than on the position or nature of the allylic leaving group. Arylzinc intermediates can also be alkylated by bromoacetates to give phenylacetates, provided a nickel catalyst and phosphine ligand are present;[141] the corresponding aryl (and heteroaryl) acetonitriles can be similarly obtained using bromoacetonitrile as electrophile.[142] Phenylboranes can also be alkylated using haloacetonitriles.[143]



Scheme 26



Scheme 27

The rather unreactive arylcadmium reagents, ArCdCl, do react satisfactorily with both primary and secondary α-bromo esters and with secondary allylic bromides, but curiously they react much more poorly with allyl and benzyl bromide, and α-chloro ethers (*ca.* 40% yields); no coupling occurs using primary alkyl bromides.[144] Finally, the old Wurtz–Fittig methodology, whereby an aryl bromide and an alkyl iodide are coupled in the presence of elemental sodium, can sometimes lead to acceptable yields (40–60%); no rearrangement products are formed, and it is likely that free radicals are not involved.[145]

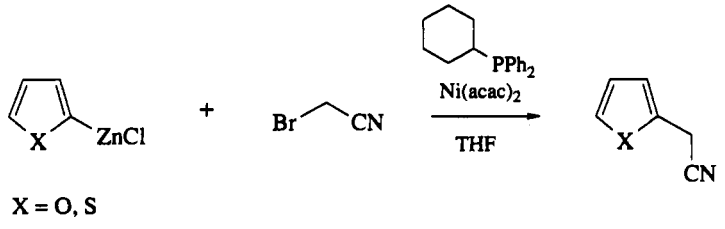
1.6.5 ALKYLATIONS OF HETEROAROMATIC CARBANIONS

Despite the plethora of metallated heteroaromatic intermediates which are available, there is often a dearth of information regarding their alkylation chemistry. Many such intermediates are claimed to be generally useful when the evidence provided only mentions very reactive electrophiles such as CO_2, MeSSMe, Me_3SiCl or MeI. As mentioned above, MeI however is not a typical alkylating agent and is often more suitable as an assay reagent to determine the extent of metallation. In general, alkylations of heteroaromatics give a wide variety of yields in coupling reactions with primary alkyl bromides or iodides (secondary halides usually give only poor yields); if an electrophile such as ethyl iodide affords a good yield, it is likely that other higher homologs will be similarly effective. Results from more reactive allylic and benzylic halides and α-halo ethers tend to be even more variable, and certainly not always an improvement upon alkylations using saturated analogs as is often the case with enolates. Two serious side reactions can account for this; firstly deprotonation of the allylic or benzylic species by the reactive intermediate, and secondly double alkylation. Typically, but by no means exclusively, such alkylations

are best performed in THF rather than ether, sometimes using HMPA as a cosolvent. Excellent yields are usually obtained with methyl iodide (and also especially aldehydes and ketones), moderate to good yields with higher primary homologs and variable, often poor yields with allylic halides and relatives.[146]

Both 2-lithiofuran and 2-lithiothiophene often afford respectable yields with a variety of alkylating reagents. The former furan species can be alkylated by *n*-butyl bromide (77%),[147] by the less reactive diethyl acetal of bromoacetaldehyde (70%)[148] and by allylic bromides generally but not always[148] in high yield.[146,149] The latter thiophene intermediate tends to give somewhat lower yields (*e.g.* Bu^nBr, 47%; $BrCH_2CH(OEt)_2$, 40%; $PhCH_2Br$, 62%),[150] while 2-lithiopyrroles can be even less satisfactory intermediates.[151] Much the same is true of the benzo analogs of these simple heterocyclic systems.[146]

Conversion of these species to various mixed or higher-order cuprate species (*vide supra*) does not usually improve this situation as the heteroaromatic ligands usually transfer sluggishly from copper; indeed the mixed cuprates R(2-thienyl)Cu(CN)Li_2 alluded to above[76] are valuable precisely because the thiophene ligand is *not* transferred to an attacking electrophile. However, some other transition metal reagents have proven useful in this area, such as 2-lithiofuran alkylation using allylic or benzylic halides in the presence of $Pd(PPh_3)_4$,[152] and the alkylation of heteroarylzinc chlorides by bromoacetonitrile using a combination of $Ni(acac)_2$ and a phosphine ligand (Scheme 28).[142]

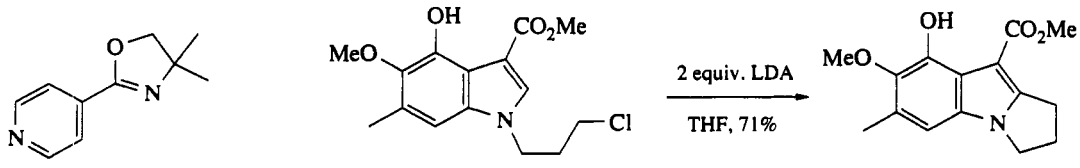


Scheme 28

The concept that doubly ionized species could be 'more reactive' and hence lead to enhanced yields is often not true, an example being the dianion (**131**), which follows a typical pattern, reacting exceptionally well with aldehydes and ketones (>90%), poorly with primary alkyl halides (30–40%) except methyl iodide (>95%), and not at all, in the sense of giving alkylated products, with allylic or benzylic halides.[153] By contrast however the dianion (**132**) does react well with allyl bromide to give the corresponding dialkylated product in 72% yield.[154]

(**131**) X = O, S (**132**)

In general, six-membered nitrogen heteroaromatics are not easily converted into carbanionic species,[146] and even if this is achieved, alkylation reactions are often poor.[146,155] An exception to this is the oxazoline derivative (**133**), which is metallated smoothly at the 3-position using methyllithium (Bu^nLi or LDA are not suitable); the resulting 3-lithio derivative can then be alkylated in reasonably good yields (*ca.* 55%) by primary alkyl iodides and allylic bromides.[103,156] The corresponding 3-oxazolinyl isomer reacts much less effectively. The yields in these types of reactions can often be increased by conducting the reactions intra- rather than inter-molecularly; this is the case in a synthesis of 7-methoxymitosene (**135**) in which the ring system is established by cyclization of an intermediate *N*-chloropropylindolecarboxylate (**134**) following treatment with LDA (Bu^nLi can be used in related examples).[157]

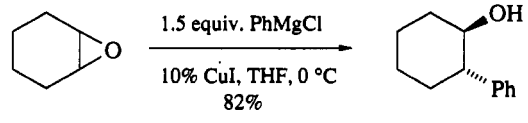


(**133**) (**134**) (**135**)

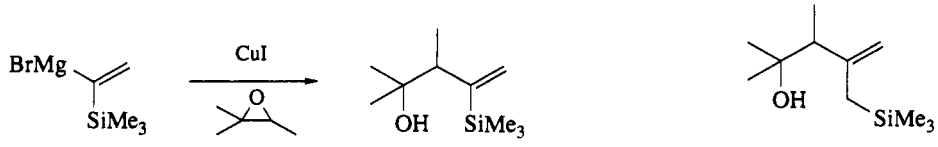
An alternative to this type of chemistry is to react the intermediate lithiated heteroaromatics with trialkylboranes and then induce B → C alkyl migration using iodine or *N*-chlorosuccinimide in the intermediate lithium boronates.[158] With simple trialkylboranes, two of the alkyl groups are wasted, although this can be avoided by using 9-BBN derivatives. A particularly notable feature of this methodology is that it is often more successful with secondary or tertiary alkyl groups, thus circumventing a currently universal limitation on direct sp^2-alkylation, that of the use of tertiary halides.

1.6.6 ALKYLATIONS AT sp^2-CENTERS USING EPOXIDES

Often, though not always, successful alkylations of vinyl carbanions using epoxides rely on the presence of copper, either in catalytic (*e.g.* CuI) or stoichiometric (*e.g.* R_2CuLi) amounts.[12] In the older literature, a common method was to form, say, an aryl Grignard species in ether then replace the solvent with higher boiling benzene or toluene prior to addition of the epoxide.[159] A later, systematic study revealed however that THF was also an eminently suitable solvent for this type of reaction,[160] although conversely for similar reactions of R_2CuLi, ether is a superior solvent (*vide infra*). Problems inherent with this method are usually associated with the inevitable presence of MgX_2 which, being a Lewis acid, can induce either epoxide opening and subsequent rearrangements or halohydrin formation, thus giving rise to sometimes poor yields of the expected products (*i.e.* those formed by attack at the less substituted carbon of the epoxide) possibly contaminated with difficult to separate regioisomers. The more sterically hindered the epoxide, often the more essential is the presence of copper. For example, the conversion (**136**) to (**137**) proceeds in only 3% yield in the absence of a copper salt; vinylmagnesium halides behave similarly.[161] The related process using Ph_2CuLi is significantly more wasteful as 1 equiv. of the organic ligand is lost,[162] hence the attraction of some of the mixed cuprates described below. This procedure is commonly employed in a wide range of Grignard additions to epoxides, two specific examples being extension of the vinylsilane (**138**) to give the butyrolactone precursors (**139**)[163] and elaboration of the allylsilanes (**140**) from the homologous Grignard reagent.[164] Copper(I) cyanide can be equally as effective as a copper(I) halide.[165] Similarly, while some aryllithiums are alkylated efficiently by simple epoxides,[166] the addition of a catalytic copper salt is usually necessary if good yields are to be realized.[167]

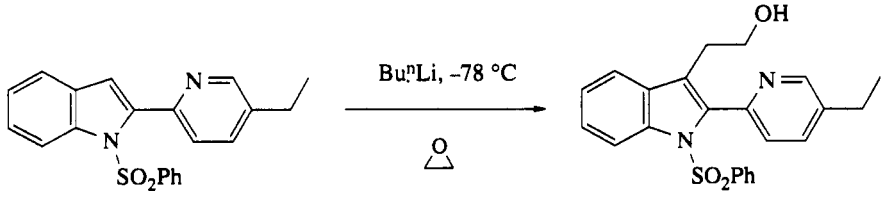


(**136**) (**137**)

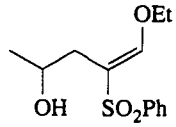


(**138**) (**139**) (**140**)

A more recent method for the activation of epoxides, especially in reactions with alkylcoppers and related species, is to add boron trifluoride etherate to the system.[168] Such additions will also facilitate alkyllithium additions to epoxides,[169] two specific examples being homologation of the pyridylindole (**141**) into the hydroxyethyl derivative (**142**)[170] and alkylation of the sulfone (**73**) using propylene oxide, which requires the presence of BF_3 if a good yield, in this example 80%, of the desired product (**143**) is to be obtained.[89]

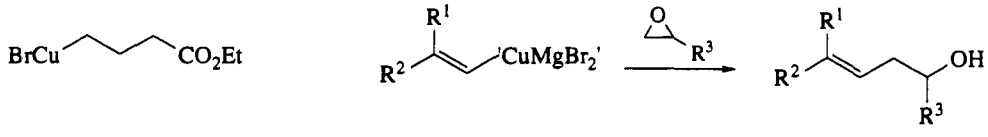


(**141**) (**142**)



(143)

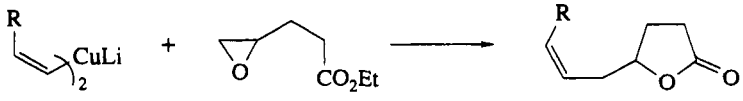
The bulk of methodology in this area has however been centered on the use of stoichiometric amounts of a copper reagent. A recently developed procedure for the preparation of 'active' elemental copper, by lithium naphthalide reduction of the CuI–PBu_3 complex, is capable of directly producing alkylcuprate species and could be of particular interest in the formation of the cuprate (**144**) and related intermediates which cannot be obtained *via* the corresponding organolithium or Grignard species[171] (in general, cuprates do not react with esters).[14,57] Both intermediates (**144**) and cuprates derived from aryl iodides and this active copper react well with epoxides without the need for further catalysis. Similarly, magnesiocuprates (**145**), obtained by copper-mediated additions of Grignard reagents to 1-alkynes, react well with ethylene oxide or monosubstituted epoxides but in general yields of the homologs (**146**) are improved by prior formation of an 'ate' complex using a lithium acetylide.[17,172] 1,2-Disubstituted epoxides, however tend to react poorly.



(144) **(145)** **(146)**

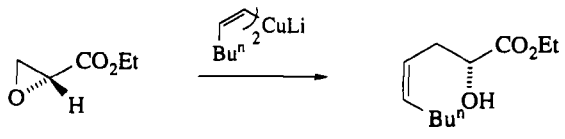
The related (*Z*)-lithium dialkenylcuprates (**147**) derived from acetylene itself also react well with epoxides to provide a useful route to (*Z*)-homoallylic alcohols; the lack of reactivity with esters allows an easy access to lactones (**148**) by condensations between epoxy esters and this type of cuprate (Scheme 29).[173] Likewise, the lower homologs (**149**) and (**151**), both of which are relatively easy to prepare in optically active forms, can be readily converted into homoallylic and bishomoallylic alcohols (**150**)[174] and (**152**)[175] respectively. An ester unit can also be incorporated into the cuprate functions; thus, addition of a mixed lithium cuprate, 'RCuYLi', to ethyl propiolate gives the cuprates (**153**), which add to epoxides to give unexpectedly the (*Z*)-crotonates (**154**).[176] Such isomerization is not uncommon with vinyl carbanions in general, and is obviously a limitation when isomeric mixtures are produced.

The origins of much of this methodology lie in the classical studies of Gilman, which were followed by an extensive investigation into the reaction between lithium diphenylcuprate and epoxides.[177] Whereas cyclohexane epoxide (**136**) is essentially inert to phenyllithium, Ph_2CuLi reacts well allowing the transformation (**136**) to (**137**) to be effected in high yield but using ether rather than THF[160–162] as the solvent and using 2 equiv. of the cuprate. Ph_2CuLi also does not usually attack esters. From the yields re-

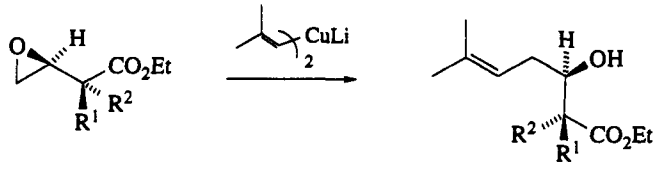


(147) **(148)**

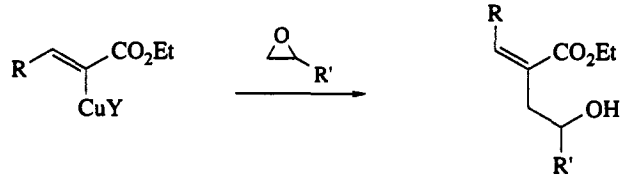
Scheme 29



(149) **(150)**

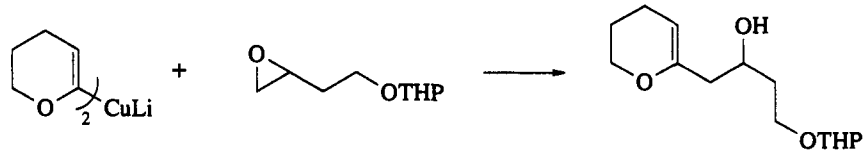


(151) (152)

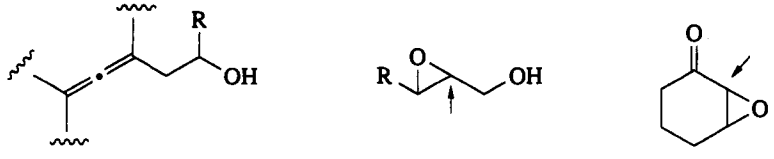


(153) (154)

ported, there is often little to choose between Ph_2CuLi and a combination of PhMgBr and CuI (see also ref. 186). A wide variety of substituted vinyllithium species also react well with epoxides, after conversion to the corresponding lithium divinylcuprate. For example the dihydropyran derivative (**155**) couples efficiently with the the epoxy ether (**156**) to give a good yield of the spiro-acetal precursor (**157**).[178] Allenyllithiums provide something of a contrast to this general pattern in that they condense efficiently and directly with monosubstituted epoxides,[179] especially in the presence of HMPA,[180] to provide a good route to alcohols (**158**). In all of these reactions, regioselectivity problems can clearly arise with 1,2-disubstituted epoxides; however, some useful regioselectivities have been discovered[181] including 1,2-diol formation from β,γ-epoxy alcohols (**159**)[182] and β-hydroxy ketone formation from α,β-epoxy ketones (**160**).[183]



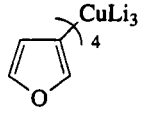
(155) (156) (157)



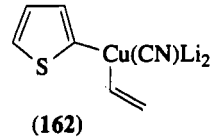
(158) (159) (160)

In common with lithioallenes, many lithiated heteroaromatic species react well with unhindered epoxides directly to give respectable yields of the expected homologous alcohols. For example, 2-furyllithium in THF reacts almost quantitatively with propylene oxide[146,148] but yields are rather lower in ether.[184] Returns are also generally poorer in examples of lithiated heteroaromatics which contain two heteroatoms.[146] In the cases of indoles and pyrroles, the corresponding Grignard reagents formed from the *N*-unsubstituted heterocycles can also be used, although yields are usually only good in the former group, when 3-hydroxyethylindoles are obtained.[159] Limited use has been made of the corresponding lithium diarylcuprates because in general the heteroaryl ligands, when 2-substituted, are very unreactive[76] (*vide infra*). However, such derivatives of 3-lithiofuran do add efficiently to monosubstituted epoxides, the best stoichiometry found being that indicated in formula (**161**).[185] Indeed, one of the best reagents for the transfer of a vinyl ligand to an epoxide is the mixed cuprate (**162**) in which the 2-thienyl ligand is essentially inert;[76,186] the simpler species $R_2Cu(CN)Li_2$ are also particularly useful in this respect, giving exceptionally high yields even with disubstituted epoxides.[72]

When vinyl epoxides are substrates for this type of reaction, Grignard reagents usually give mixtures of 1,2 (both possibilities) and 1,4 addition products; synthetically useful yields can nevertheless be ob-

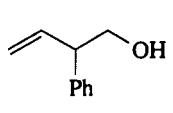


(161)



(162)

tained in some cases. For example, phenylmagnesium bromide in ether reacts with vinyloxirane to give largely (84%) the perhaps least expected product (**163**), whereas the corresponding 2-naphthyl reagent gives the alcohol (**164**) as the only isolated product in 58% yield, and 2-thienylmagnesium bromide the 1,4 addition product (**165**) but only in 26% isolated yield.[187] In contast, and in line with their excellence as Michael nucleophiles, lithium diorganocuprates usually react almost exclusively by the 1,4-pathway, a typical example being Ph_2CuLi in ether–benzene, which with vinyloxirane gives an 85% yield of the conjugate addition product (**166**), accompanied by only 15% of the alternative product (**163**).[72,187] In just the same way, (*Z*)-lithium divinylcuprates (**167**) can be used in a stereospecific synthesis of the 'skipped' dienes (**168**).[188] Similarly, cyclic allylic epoxides can participate in this useful type of reaction which is generally favored in ether rather than THF.[189] Thus, the epoxy enolate (**169**) undergoes a highly regio- and stereo-selective conversion into the cyclohexenol (**170**), formally by an umpolung process in which a nucleophile is added α to a ketone function.[190] Likewise, the simpler epoxycyclopentene (**171**) undergoes predominantly 1,4-attack to give mainly cyclopentenol (**172**).[191]



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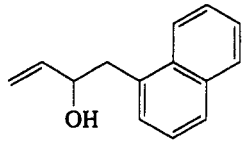
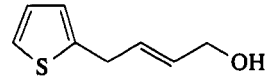
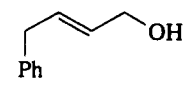


(164)



(165)



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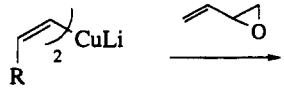
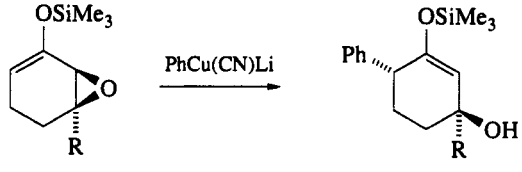
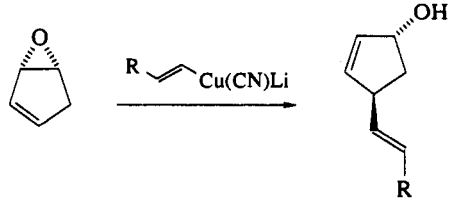


(167) (168)



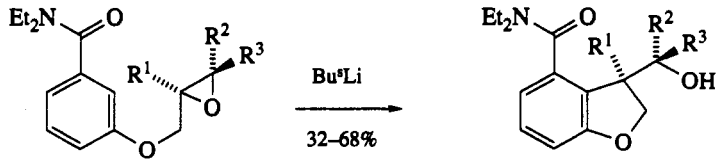
(169) (170)



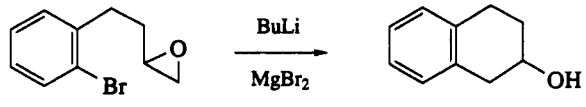
(171) (172)

Intramolecular alkylations of epoxides at sp^2-centers are also possible; thus treatment of the epoxyamide (**173**) with *s*-butyllithium affords moderate to good yields of the dihydrobenzofurans (**174**).[192] However, the homologous system (**175**) is converted into the tetralin framework (**176**) rather than to an indan derivative, with the magnesium bromide presumably serving to activate the epoxide.[193] Under similar conditions, the styrene oxide (**177**) is converted into the benzocyclobutanol (**178**) presumably by

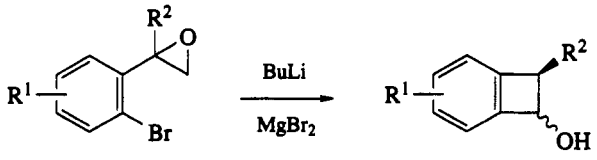
Lewis acid-induced rearrangement of the epoxide function to the corresponding aldehyde *via* a benzylic carbonium ion.[194]



(173) (174)

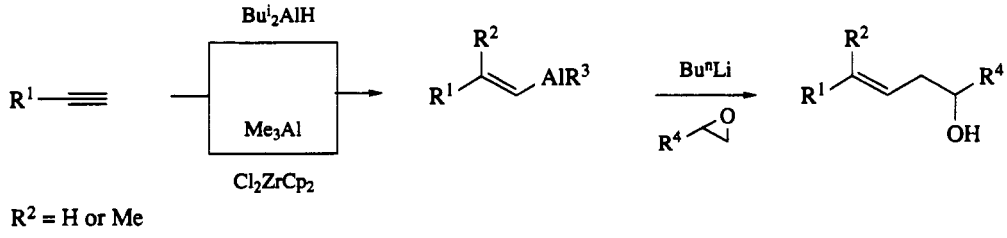


(175) (176)



(177) (178)

A final group of sp^2-carbanions which have been found to react well with at least monosubstituted epoxides are the vinylalanes formed either by direct hydroalumination[195] or by zirconium-catalyzed carboalumination[196] of a terminal alkyne. Both species are insufficiently reactive to couple with epoxides and must first be converted into their corresponding 'ate' complexes, usually by treatment with *n*-butyllithium (Scheme 30).



R^2 = H or Me

Scheme 30

1.6.7 REFERENCES

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1.7
Alkylations of Alkynyl Carbanions

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1.7.1 INTRODUCTION

The alkylation of *sp*-carbon can, in principle, involve the alkyne (acetylene) either as the nucleophile or the electrophile. In practice by far the most important process involves the alkyne as nucleophile since the acidity of the alkyne proton ($pK_a \approx 25$) allows the ready formation of alkynide ions. These are excellent nucleophiles and they readily undergo acylation and alkylation with appropriate electrophiles. The recent introduction of palladium-catalyzed reactions, usually involving copper(I) salts but also other cations, has greatly increased the use made of arylation and vinylation reactions.[1] In this chapter only the alkylation of the alkynide ion will be discussed; acylation, vinylation and arylation reactions are discussed elsewhere. The alkylation of alkynide anions is a reaction of considerable synthetic use and has been extensively reviewed.[2]

1.7.2 METALLATIONS OF ALKYNES

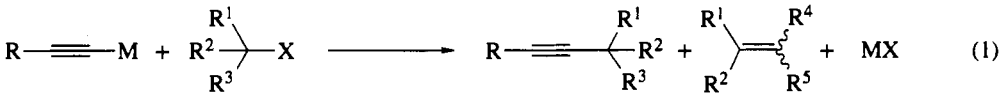
Monometallation of acetylene itself is possible under special conditions, and solutions of LiC≡CH and NaC≡CH in liquid ammonia, for example, can be prepared by simply adding pieces of metal to boiling ammonia while introducing acetylene. When acetylene is introduced into a solution of BuLi in ether (or THF) at 0 °C a fine suspension of LiC≡CLi is formed immediately. Ammonia (or other amines) stabilizes the monolithium species. Thus acetylene with BuLi–TMEDA at low temperatures gives a clear solution of LiC≡CH. The preparation of BrMgC≡CH is not easy, but can be achieved by adding a solution of EtMgBr to a solution of acetylene in THF kept below 30 °C. Solutions of BrMgC≡CMgBr and LiC≡CLi are produced by simply introducing acetylene into a solution of EtMgBr in THF (>40 °C) and BuLi in Et_2O (>0 °C) respectively.

The low acidity of 1-alkynes means that strong bases must be used to form the alkynide ions and that water is not a suitable solvent; aqueous solutions have a very low concentration of alkynide ions.[2] Some transition metal alkynides can be prepared by precipitation from aqueous solution because their solubilities are very low.[2] Suitable solvents for the preparation of alkynide ions must be less acidic than the alkyne, and preferably allow the alkyne and the alkynide ion to remain in solution. Liquid ammonia, tetrahydrofuran, ether and hydrocarbons have all been used, particularly the first, the alkynide anion being readily formed by metal amides. Alkynides of many types have been prepared from various metals. Besides Groups I and III, copper(I), silver, gold(I), zinc, mercury and, more recently, aluminum alkynides have been synthesized. The alkynides of Groups I and II have been principally used as nucleophiles in alkylation reactions, but there are now many examples of other metal alkynides in this role. Palladium-catalyzed reactions, as remarked above, have become increasingly important for the reactions of alkynides of metals other than Groups I and II, but these have not usually involved alkylation.

1.7.3 ALKYLATIONS OF ALKYNIDE IONS

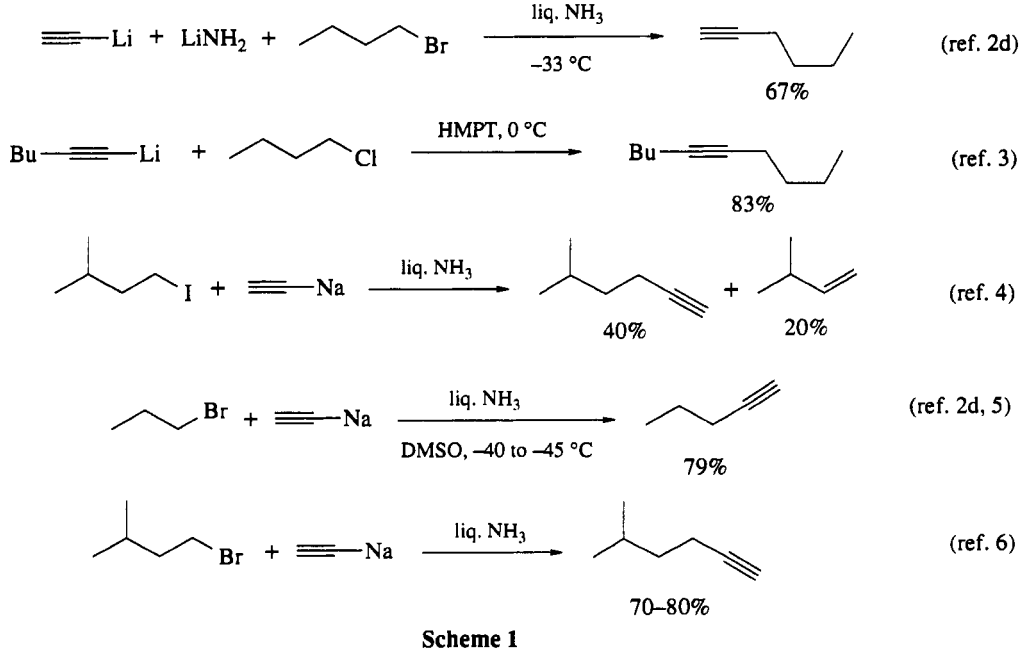
1.7.3.1 Alkylations with Alkyl Halides and Sulfates

The alkynide ion can undergo alkylation with a variety of alkylating reagents, such as haloalkanes and alkyl sulfates, with the formation of a carbon–carbon bond. The alkynide ion is also strongly basic so that elimination reactions may accompany or subvert the substitution reaction. Group I metal alkynides in liquid ammonia give mainly substitution products with primary haloalkanes but secondary and tertiary haloalkanes give mainly elimination products, as do 2-substituted primary haloalkanes (equation 1).

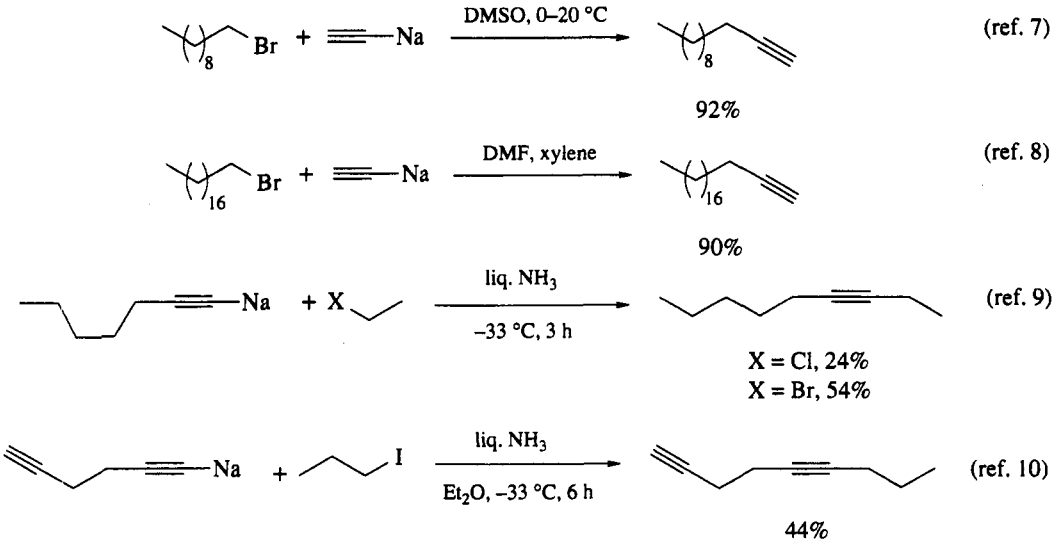


(1)

Lithium alkynides in tetrahydrofuran or dioxane often give substitution products with secondary haloalkanes, while alkynide Grignard reagents do not usually react with haloalkanes except in the presence of other metals such as cobalt and copper. Substitution of iodine or bromine for chlorine in the haloalkane often leads to an increased yield of the alkylation product and alkanesulfonates may give greater yields than haloalkanes. Scheme 1 illustrates examples of alkylation of haloalkanes and alkyl sulfates with alkynides of Group I metals.

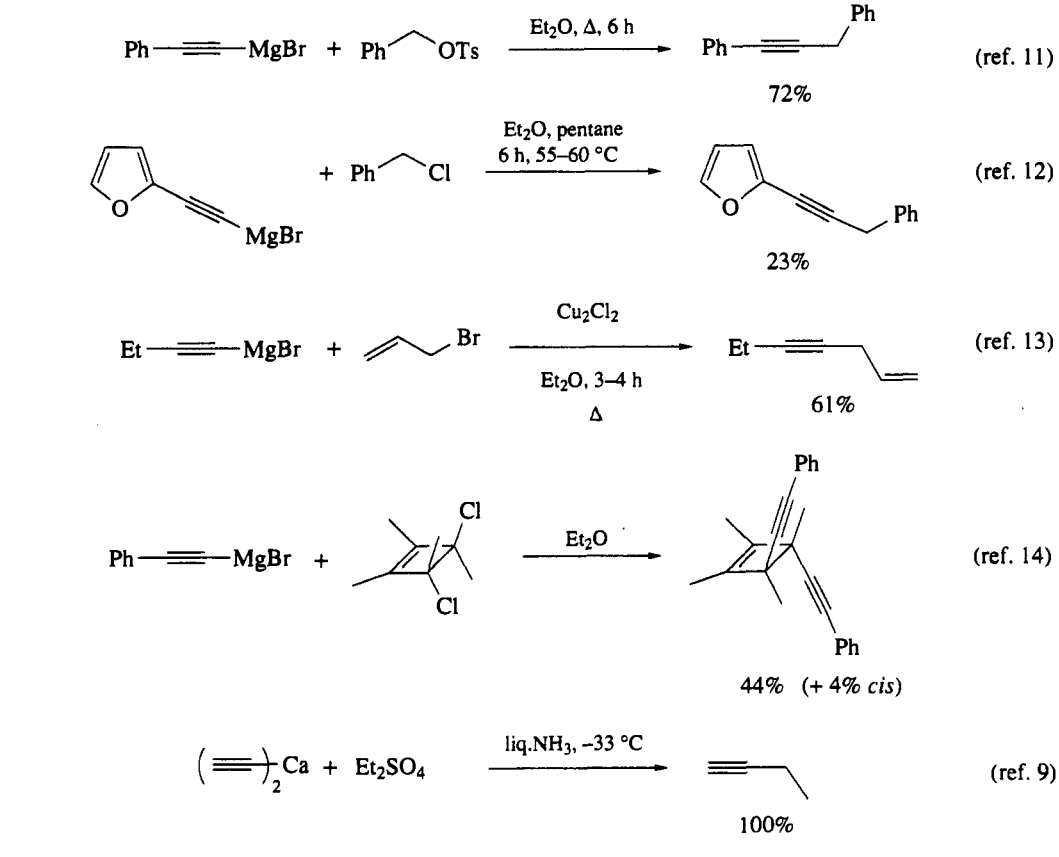


Scheme 1

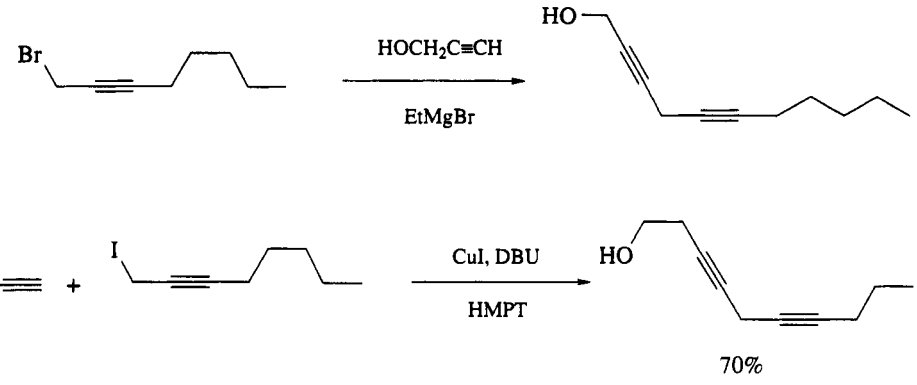


Scheme 1 *(continued)*

Alkylations of Grignard reagents usually require the presence of copper or other transition metal salts. Scheme 2 illustrates typical reactions involving Group II metals. Reaction between 1-bromo-2-octyne and the Grignard prepared from propargyl alcohol leads to undeca-2,5-diyn-1-ol in good yield (Scheme 3).[15] Similarly, treatment of 1-iodo-2-octyne with 3-butyn-1-ol in the presence of copper(I) iodide and DBU gave dodeca-3,5-diyn-1-ol in 70% yield (Scheme 3).[16]

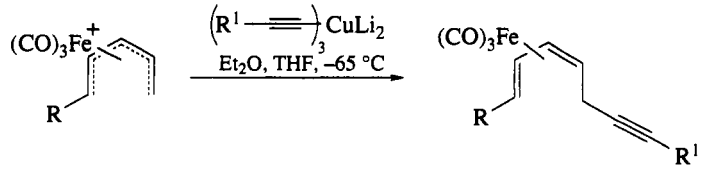


Scheme 2

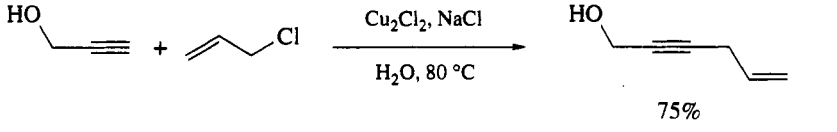


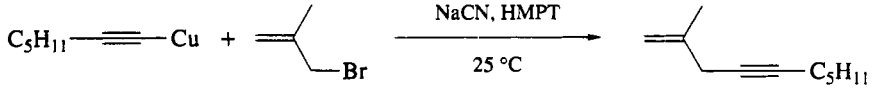
Scheme 3

Lithium alkynylcuprates react with haloallenes to give similar 'skipped' diacetylenes (see below). The related 'skipped' enynes can be prepared by treatment of (pentadienyl)iron(tricarbonyl) halide complexes with dilithium trialkynylcuprates, the compounds being isolated as the iron(tricarbonyl)(diene) complexes (Scheme 4).[17] Further examples of alkylation reactions of copper alkynides are illustrated in Scheme 5. Reaction between a lithium cyanoalkynecuprate and an iodoallene leads to a 'skipped' diacetylene. This useful reaction has been used by Corey in his synthesis of hybridalactone (Scheme 6).[20]



Scheme 4

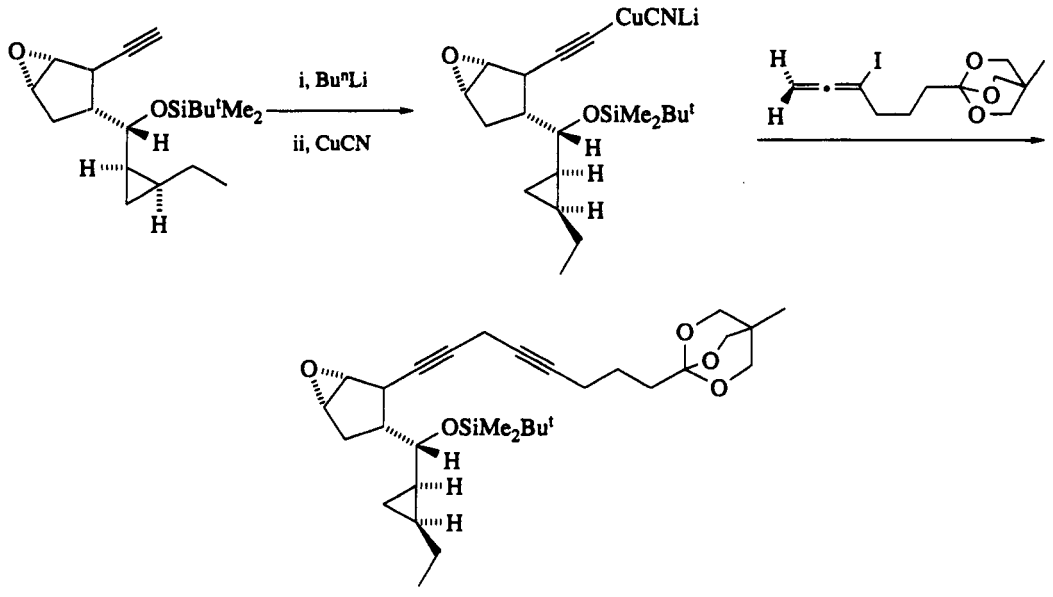




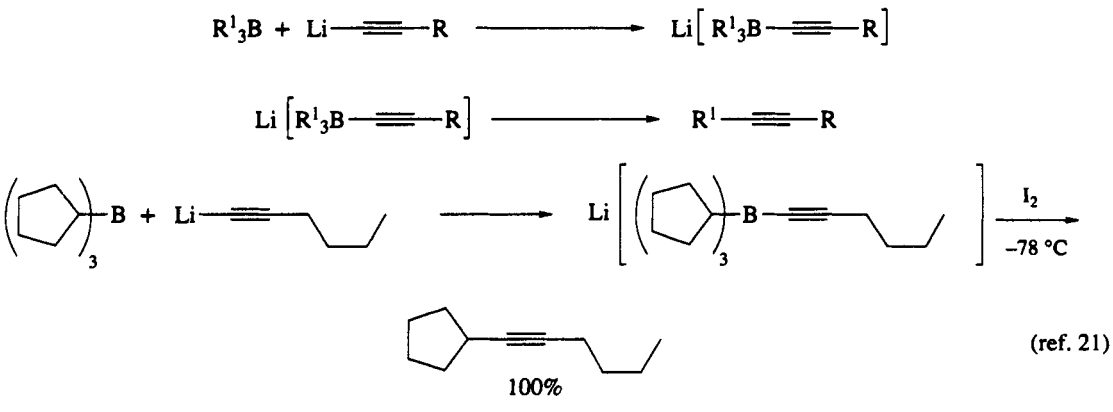
Scheme 5

Both boron and aluminum alkynides undergo alkylation. Thus, treatment of trialkylboron with lithium acetylide leads to a lithium trialkylethynylboride which, on treatment with iodine[21] or methanesulfonyl chloride,[22] gives the alkyl-substituted acetylene (Scheme 7). The lithium tris(alkylethynyl)boride intermediate can be trapped with an alkylating agent leading to the disubstituted acetylene or the adduct can be oxidized with basic hydrogen peroxide to give the corresponding ketone (Scheme 8).[23]

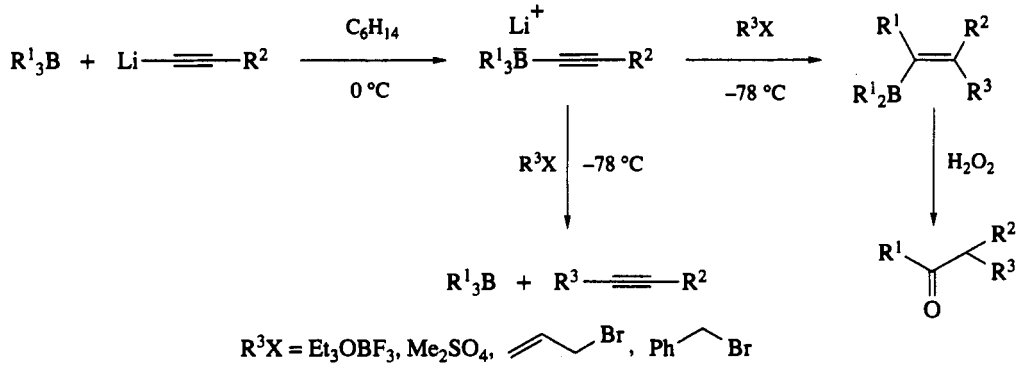
Treatment of lithium alkynides with aluminum trichloride leads to tri(ethynyl)aluminum intermediates, which on treatment with haloalkanes give the corresponding disubstituted acetylenes.[24] The reaction is successful with tertiary haloalkanes and a variety of alkynes have been prepared (Scheme 9). An interesting variation of this method has been reported by Trost and Ghadri who reacted a diethylethynylaluminum with an allyl sulfone in the the presence of the Lewis acid aluminum trichloride.[25] When the allyl sulfone was part of a six-membered ring, then the alkyne was introduced exclusively in a pseudo axial orientation (Scheme 10).



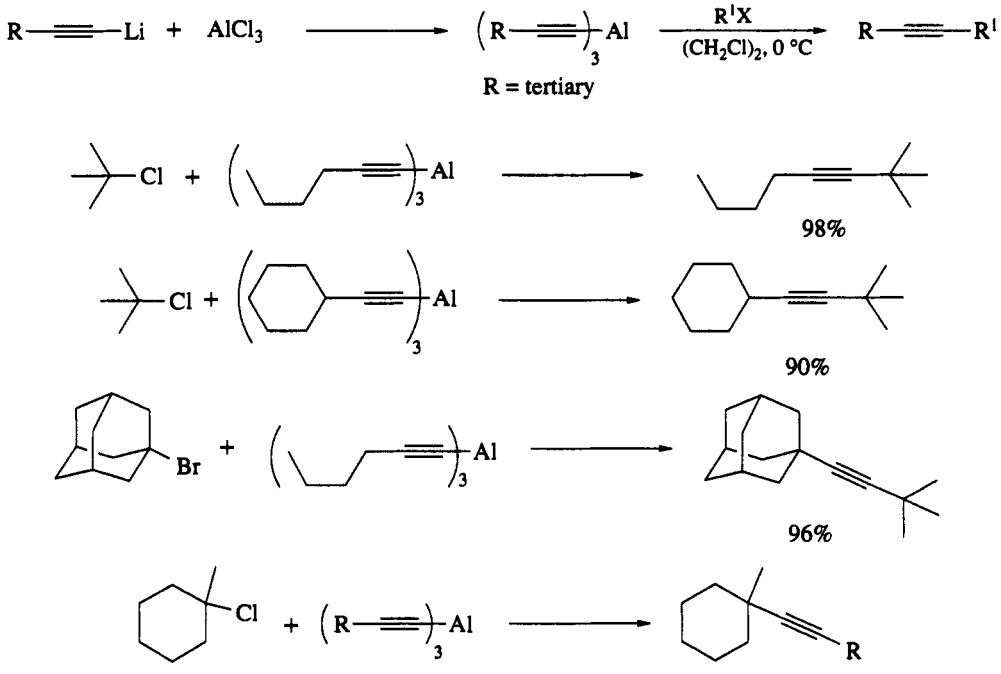
Scheme 6



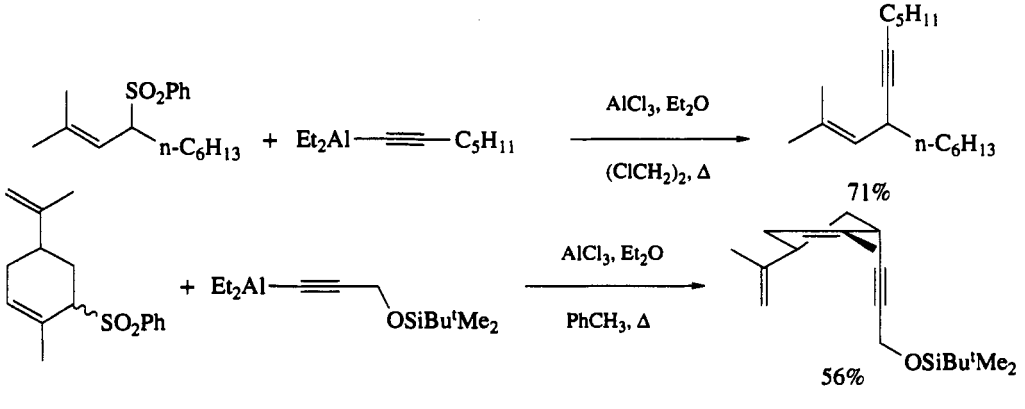
Scheme 7



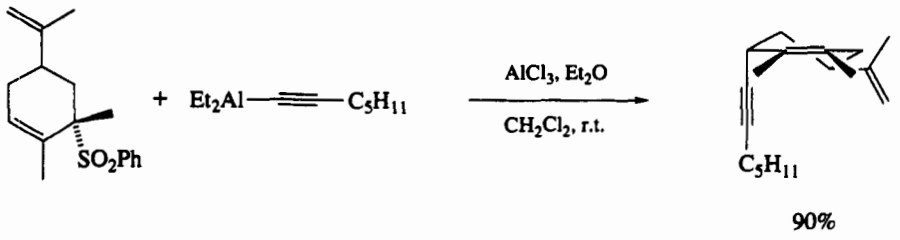
Scheme 8



Scheme 9

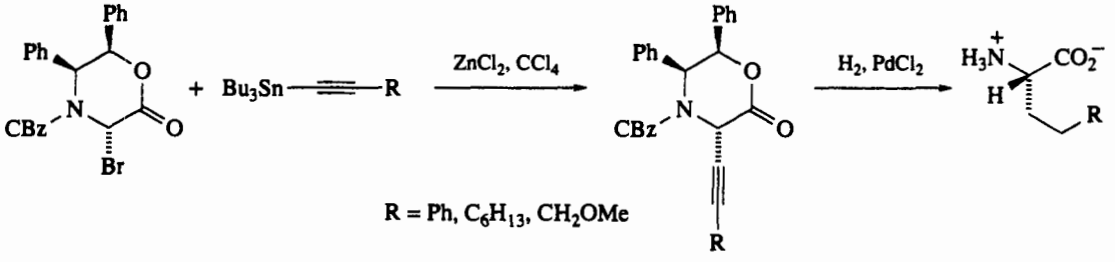


Scheme 10



Scheme 10 *(continued)*

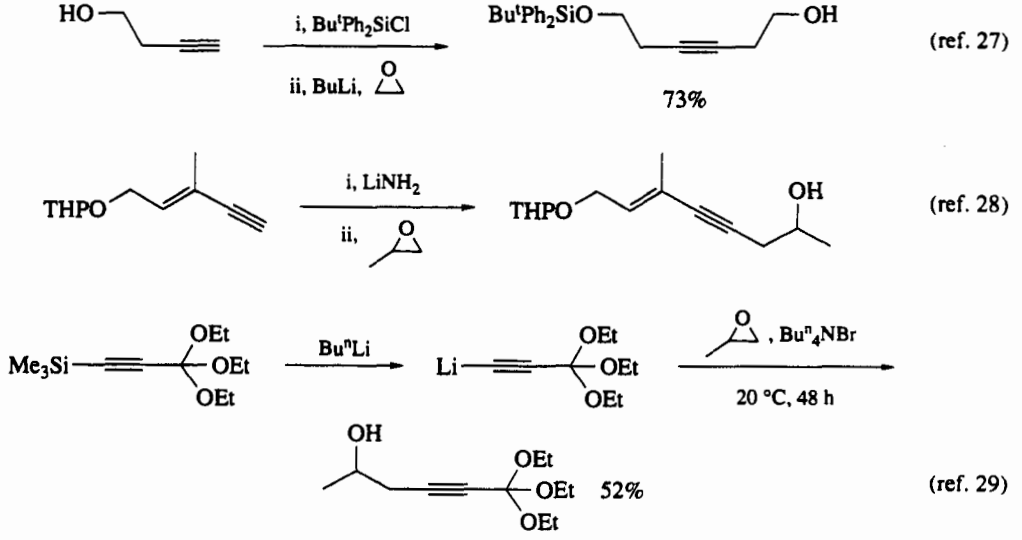
Examples of nucleophilic substitution with tin alkynides are also known. Thus, treatment of a masked α-bromo amino acid with tin alkynides in the presence of zinc chloride has been shown to lead to the corresponding ethynyl derivative (Scheme 11).[26]



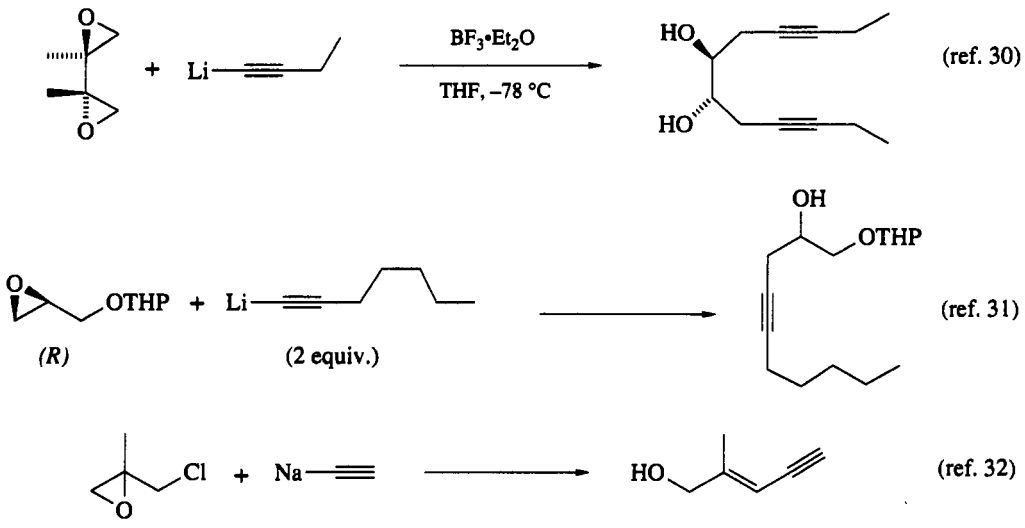
Scheme 11

1.7.3.2 Alkylations with Epoxides

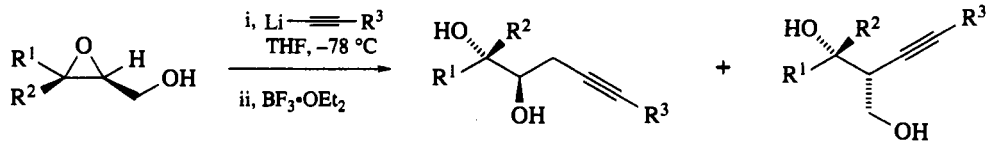
The reactions between alkynide ions and oxiranes (epoxides) are of considerable synthetic value, and generally provide two functional groups with known relative stereochemistry. Alkynide anions associated with many of the metal cations discussed above have been used, but the lithium alkynides have been by far the most popular, mainly because of their ease of synthesis from alkyllithiums. Examples are shown in Scheme 12; the last example in the scheme may involve rearrangement of the oxirane ring. This is certainly the case in the reactions of a number of hydroxymethyloxirane derivatives with lithium alkynides described by Yamaguchi and Hirao.[33] The reaction gives mixtures of rearranged and unrearranged products with the rearranged material predominating in a number of cases (Scheme 13).



Scheme 12



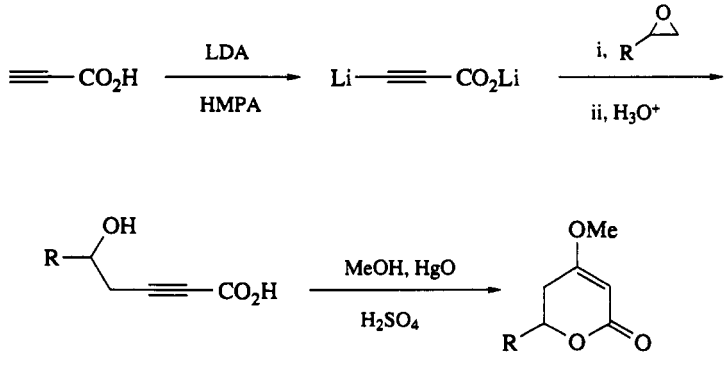
Scheme 12 *(continued)*



R^1	R^2	R^3	*Ratio (2):(3)*	*Yield (%)*
$(CH_2)_2CH{=}CMe_2$	Me	Ph	55:45	94
$(CH_2)_2CH{=}CMe_2$	Me	n-C_5H_{11}	80:20	87
Pr^n	H	Ph	72:28	77
Pr^n	H	n-C_5H_{11}	81:19	81
Me	$(CH_2)_2CH{=}CMe_2$	n-C_5H_{11}	50:50	100
H	Pr^n	Ph	42:58	81

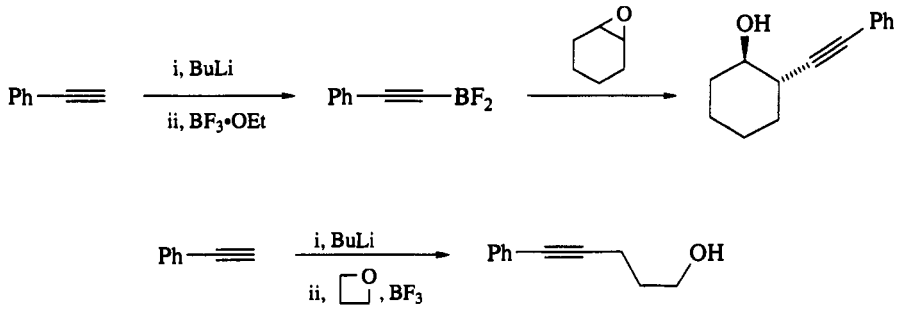
Scheme 13

Carlson and Olger have reacted the dilithium salt of propargylic acid with oxiranes and shown that the resulting δ-hydroxycarboxylic acids could be cyclized with solvation to 5,6-dihydro-2-pyrones (Scheme 14).[34] The method was subsequently used in a neat synthesis of pestalotin (R = Bu^nCHMe).



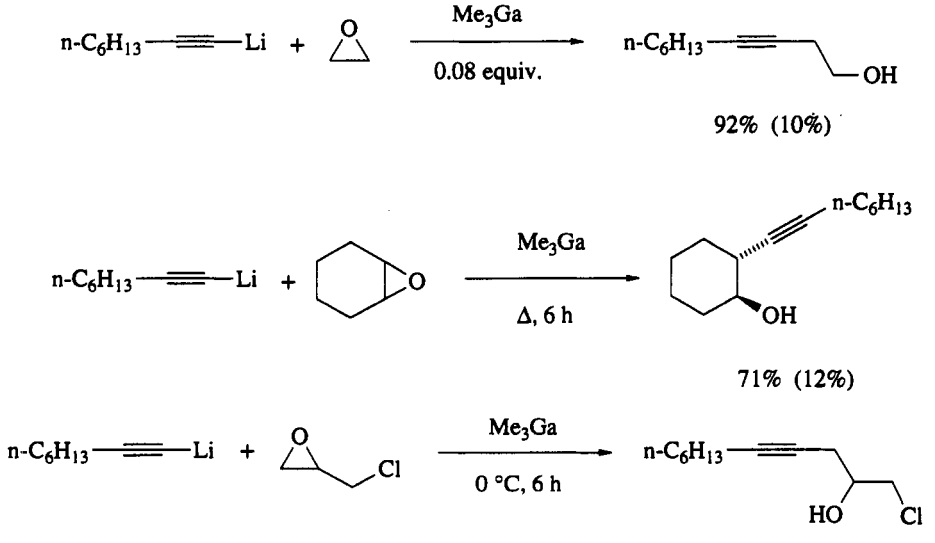
Scheme 14

Yamaguchi and Hirao found that alkyneboron difluorides, which are prepared from the alkynide ion and boron trifluoride etherate, react with oxiranes to give the 2-alkynols (Scheme 15).[35] The same research group also found that ring opening of oxetane could be accomplished,[36] but in this case boron trifluoride had to be added as a Lewis acid (Scheme 15).



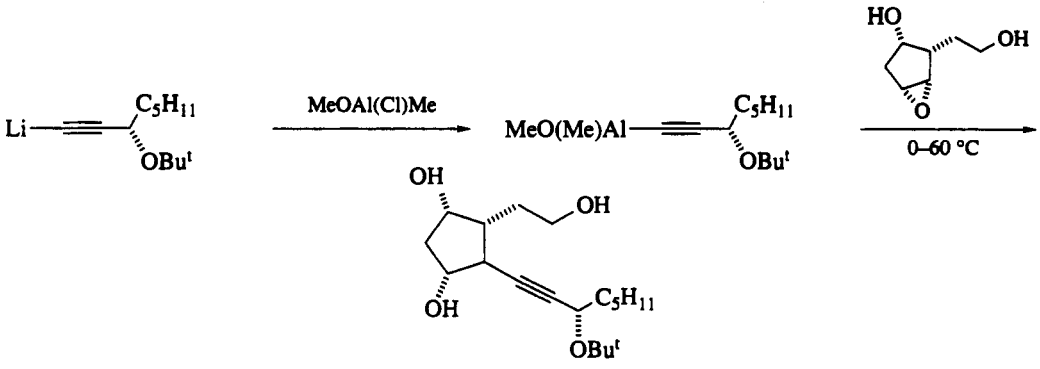
Scheme 15

In some instances only a low yield of product has been obtained during nucelophilic ring opening of oxiranes with lithium alkynides and it has been shown that in a number of these cases the yields can be greatly improved by the addition of a catalytic amount of trimethylgallium.[37] This is illustrated in Scheme 16, where the yields shown in brackets are those without the addition of the trimethylgallium. The improvement in yields by the addition of trimethylgallium may not be surprising in view of the fact that aluminum alkynides have been particularly successful as nucelophiles in additions to oxiranes. Fried and Sih, for example, in the course of a prostaglandin synthesis, prepared a methoxymethylaluminum alkynide which opened an oxirane in a regiospecific manner (Scheme 17).[38] The replacement of methyl for methoxy greatly reduced the regiospecificity.

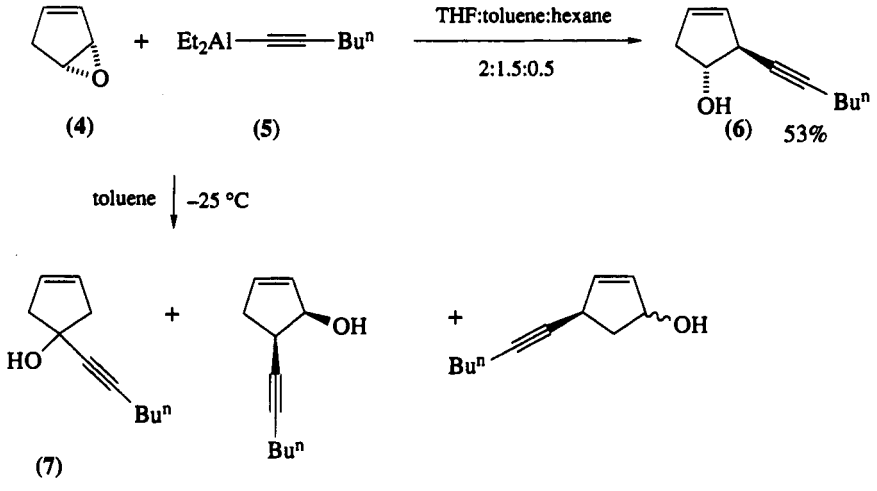


Scheme 16

3,4-Epoxycyclopentene (**4**) undergoes nucelophilic addition with the ethylaluminium alkynide (**5**) in a mixture of THF, toluene and hexane to give predominantly the isomer (**6**) in which the alkyne has been introduced at carbon 3, adjacent to the double bond (Scheme 18).[39] When the reaction was run in toluene at low temperature, the unexpected 4-hydroxy-4-(1-hexynyl)cyclopentene (**7**) was obtained, which the authors suggest may arise from an 'aluminum'-catalyzed rearrangement of the epoxide to cyclopent-3-enone, which then undergoes nucleophilic addition.

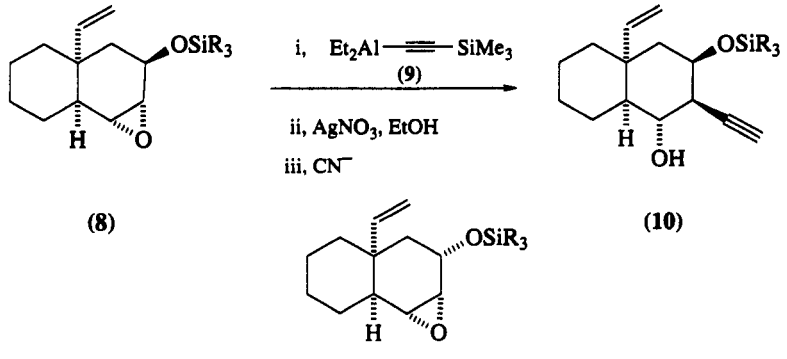


Scheme 17



Scheme 18

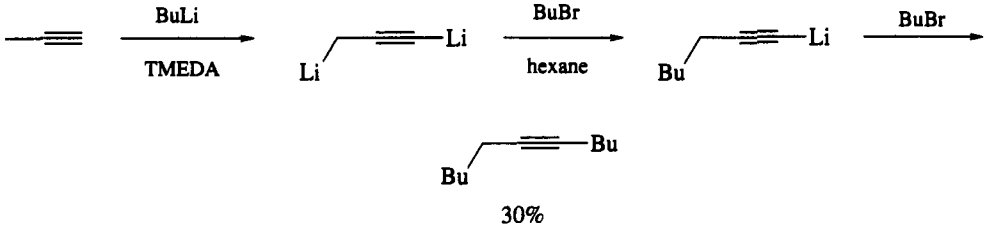
Heathcock and coworkers[40] in the course of their synthesis of vernolepin reacted the oxirane (**8**) with the diethylaluminum alkynide (**9**), when regiospecific ring opening of the oxirane occurred, leading to (**10**; Scheme 19). Interestingly, the stereoisomer (**11**) did not react under the same conditions.



Scheme 19

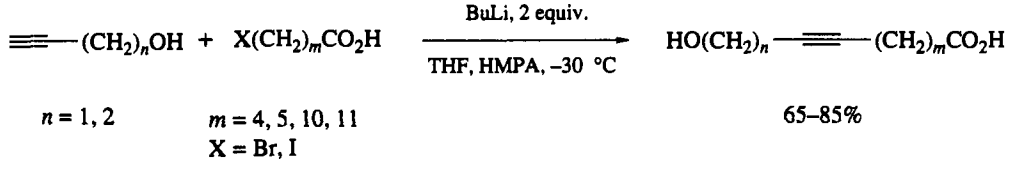
1.7.3.3 Other Alkylation Reactions

Bhanu and Scheinmann[41] have shown that the dilithium salt of propyne alkylates firstly on the methyl group and then on the alkyne. The process occurs sequentially and two different electrophiles can be used. The reaction gave superior yields when the second electrophile underwent nucleophilic addition rather than substitution (Scheme 20).

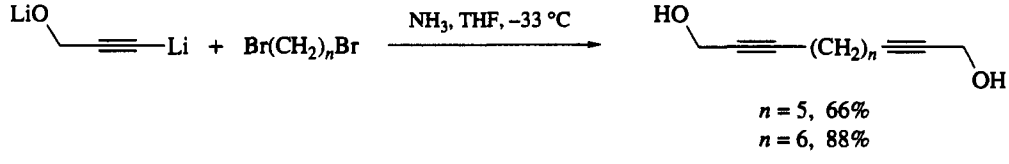


Scheme 20

Reactions between ω-hydroxyalkynes and ω-bromo- or ω-iodo-carboxylic acids in the presence of two equivalents of butyllithium give rise to ω-hydroxyynoic acids (Scheme 21).[42] Likewise, dilithiated propargyl alcohol has been found to react with α,ω-dibromoalkanes in liquid ammonia, leading to the corresponding diynediols (Scheme 22).[43]

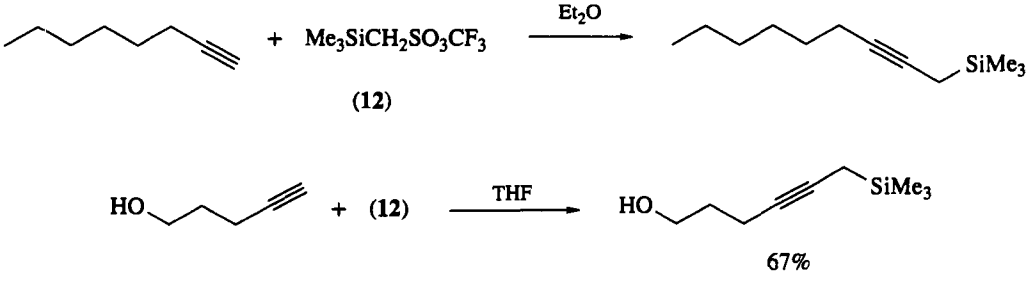


Scheme 21

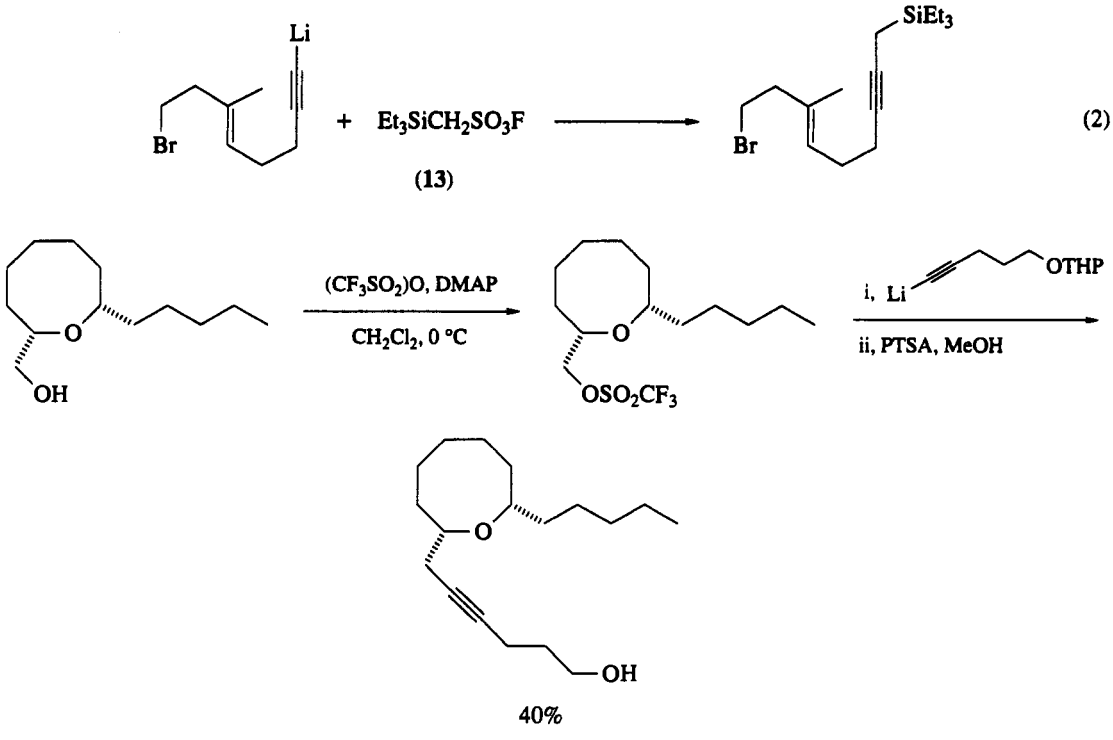


Scheme 22

A variety of other leaving groups have been used in alkylation reactions of alkynides. Thus, Chiu and Peterson[44] have treated lithium alkynides with the methyl triflate (**12**) to give the trimethylsilylmethylalkynes (Scheme 23). The reaction also worked with the corresponding chloride. Johnson and coworkers[45] had previously used the fluorosulfonate (**13**) in a similar reaction. In addition, Carling and Holmes[46] have used triflate as a leaving group in an alkylation step in their synthesis of gloeosporone, a germination self-inhibitor (Scheme 24).

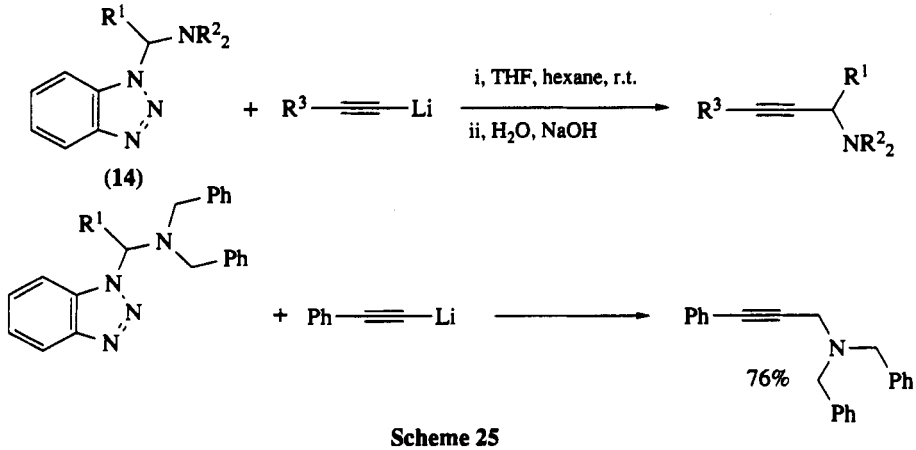


Scheme 23

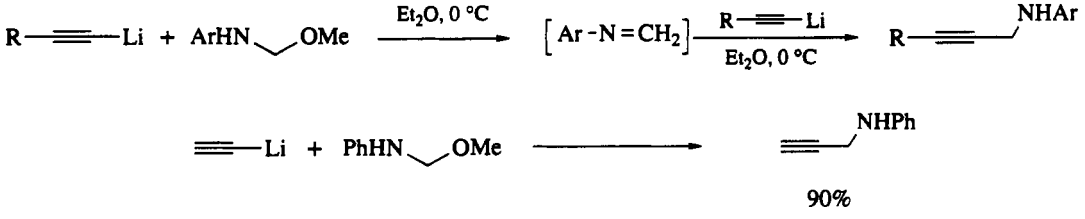


Scheme 24

Nitrogen derivatives have been used as leaving groups in reactions with alkynides. Thus, Katritzky and coworkers,[47] for example, have reacted *N*-substituted benzotriazolines (**14**) with lithium alkynides, which, after a basic work up, give the alkylated alkyne. This reaction was used to prepare α-amino-alkynes (Scheme 25). Reactions of α-arylamino ethers with lithium alkynides also gave α-amino-alkynes.[48] Mechanistically, this reaction may be considered to be an acylation since it probably proceeds through the corresponding methaldimine (Scheme 26).

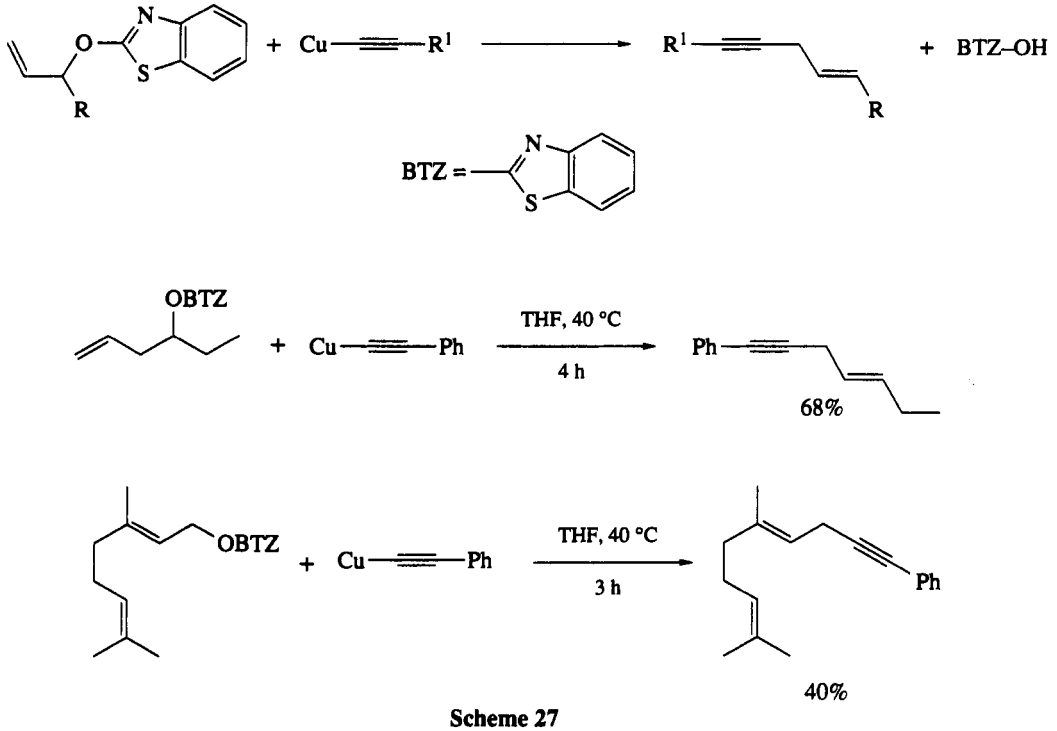


Scheme 25



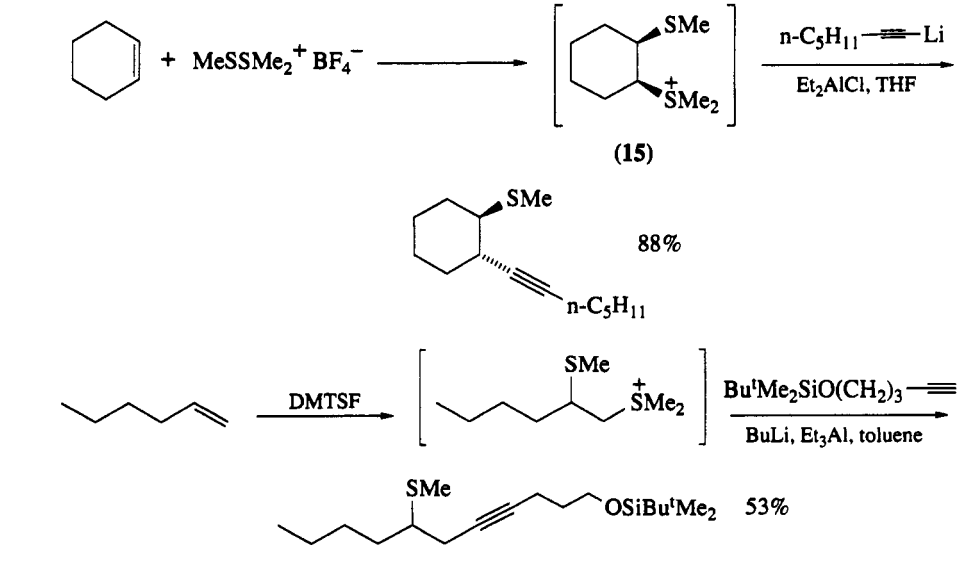
Scheme 26

2-Hydroxybenzothiazole has also been used as a leaving group in allylic displacement reactions with copper alkynides.[49] Furthermore, the copper alkynides can be used in wet solvents, THF normally being used (Scheme 27).



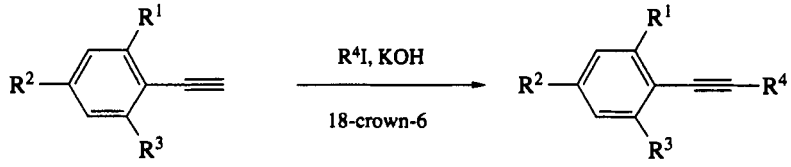
Scheme 27

Trost and Martin[50] have used the dimethylsulfoxonium ion to provide a leaving group. Thus, a *cis* addition of DMTSF to alkenes first led to adducts of the type (**15**), which then reacted with lithium alkynides in the presence of diethylaluminum chloride to give the *trans* adduct (Scheme 28). The reaction is presumed to involve the episulfonium ion, which then ensures the observed stereospecificity. The reaction is also regiospecific, the anti-Markovnikov addition being illustrated by the second example in Scheme 28. The adducts can be converted to alkanes with Raney nickel and to alkenes by sulfoxide formation and elimination.



Scheme 28

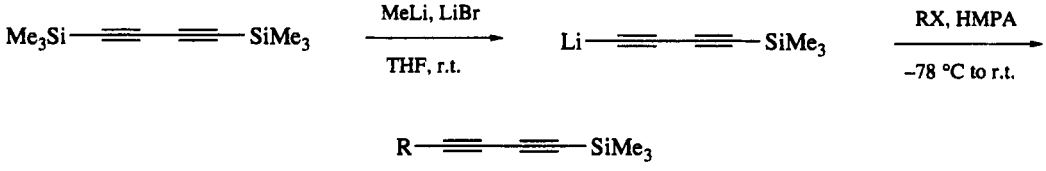
As was previously remarked, water and its associated base are, respectively, too acidic and insufficiently basic to act as solvent and base for the preparation of alkynide ions. Lissel has shown,[51] however, that with the addition of the crown ether 18-crown-6, alkylation of phenylacetylenes can occur with KOH and an iodoalkane (Scheme 29).



$R^1 = R^2 = R^3 = H, R^4 = Me$	74%
$R^1 = R^2 = R^3 = R^4 = Me$	69%
$R^1 = R^2 = R^3 = H, R^4 = Et$	70%
$R^1 = R^2 = R^3 = H, R^4 = n\text{-}C_8H_{17}$	63%

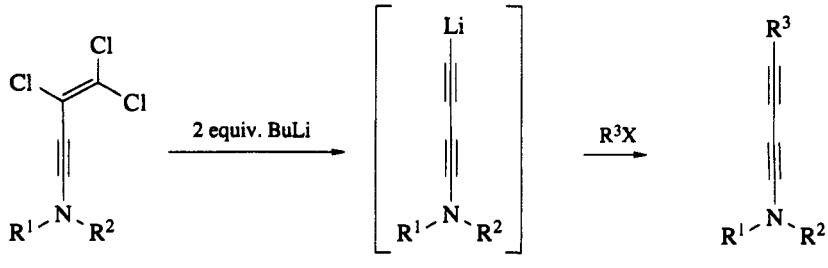
Scheme 29

1,3-Butadiyne has also been alkylated through the lithium alkynide. Thus, Holmes and Jones[52] treated bis(trimethylsilyl)buta-1,3-diyne with MeLi in the presence of lithium bromide and obtained the monolithium alkynide, which was then alkylated in HMPA (Scheme 30). If the lithium alkynide was complexed with ethylenediamine then DMSO could be used as solvent. In addition, Himbert and Feustel[53] prepared the lithium derivative of 1-*N*,*N*-dialkylbuta-1,3-diyne by treatment of 4-*N*-dialkyl-1,1,2-trichlorobut-1-en-3-yne with butyllithium. The lithium salt was not isolated but was alkylated to the 1-alkyl-4-*N*-dialkylbuta-1,3-diyne (Scheme 31).



RX = EtI, 65%; BuI, 64%; EtBr, 50%; $C_6H_{11}CH_2Br$, 57%

Scheme 30

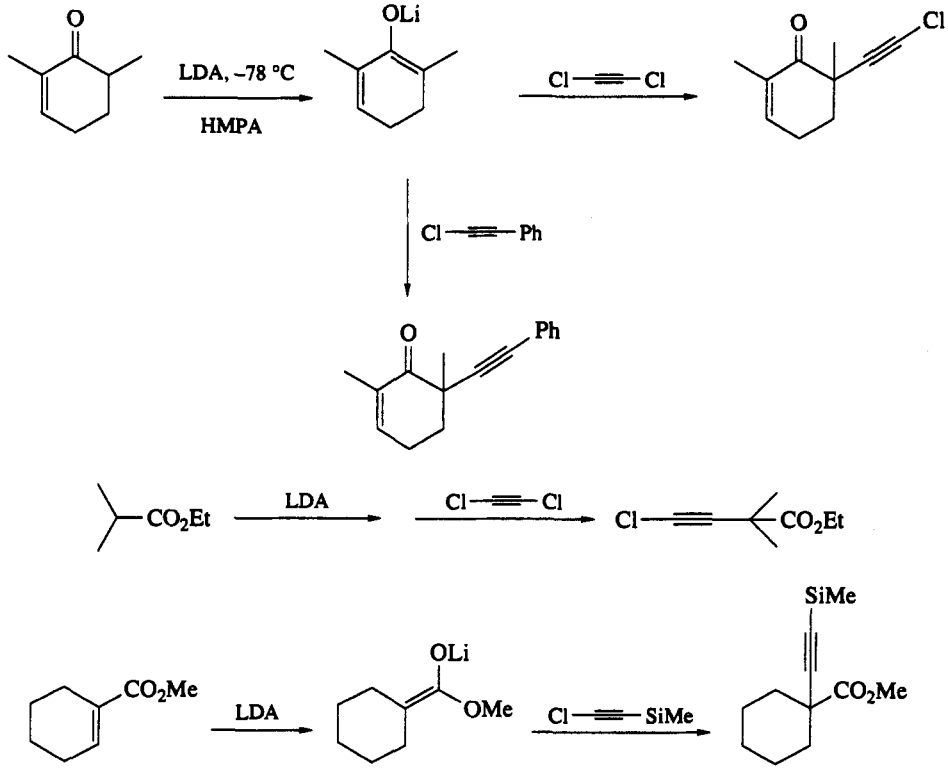


Scheme 31

1.7.4 ELECTROPHILIC SUBSTITUTION OF HALOALKYNES

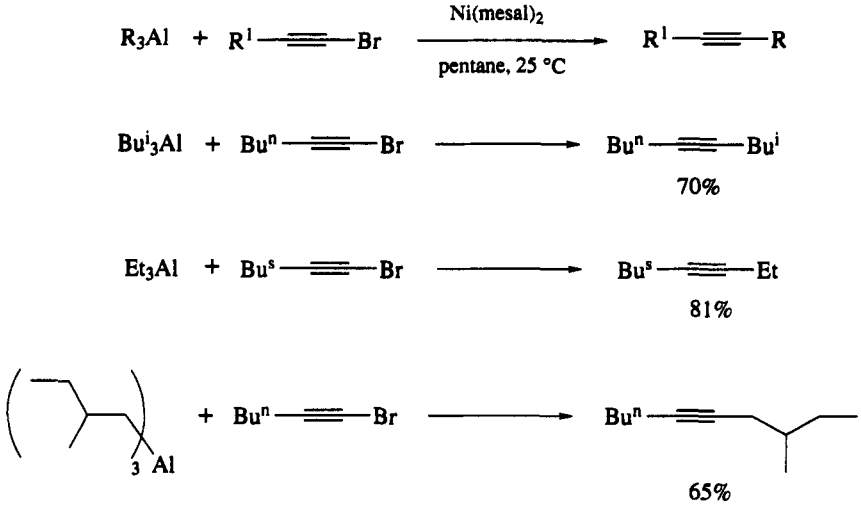
This process is much less common than nucleophilic substitution by alkynide anions and the actual mechanisms of the reactions in which electrophilic substitution of an *sp*-carbon appears to occur probably do not involve simple substitution. Kende and coworkers,[54] for example, have reacted tertiary enolate anions with chloroalkynes and obtained the corresponding alkylated products (Scheme 32). These

reactions appear to be addition–elimination reactions, and they only occur with chloroalkynes in which the other alkyne substituent is halo, aryl or a similar substituent capable of stabilizing a negative charge. Primary and secondary enolates gave rise to unidentifiable products except for the anion of dimethyl malonate, which adds twice to dichloroacetylene.



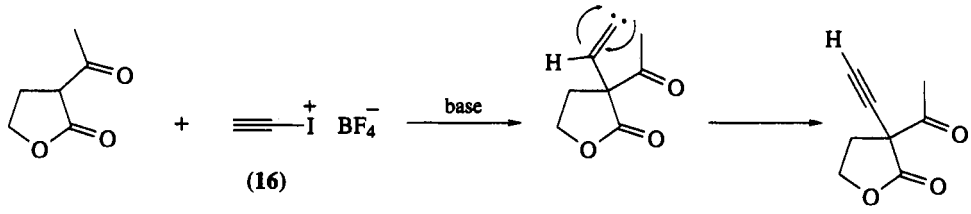
Scheme 32

Giacomelli and Lardicci[55] have treated bromoalkynes with trialkylaluminum in the presence of bis(*N*-methylsalicylaldimine)nickel and obtained an alkyl-substituted alkyne (Scheme 33). This reaction probably involves: (i) insertion of the nickel into the alkyne–bromine bond; (ii) exchange of alkyl for bromine; and (iii) formation of the alkyne–alkyl bond. Thus, although the process appears to be an electrophilic substitution, it is actually nucleophilic in character.



Scheme 33

Treatment of enolate anions derived from β-dicarbonyl compounds with either ethynyl(phenyl)iodonium tetrafluoroborate (**16**)[56a] or with ethynyl–lead tetraacetate[56b] provides a neat and direct synthesis of α-ethynyl-1,3-dicarbonyl compounds. The former reaction probably proceeds *via* 1,2-hydrogen migration of an alkylidenecarbene intermediate (see Scheme 34).

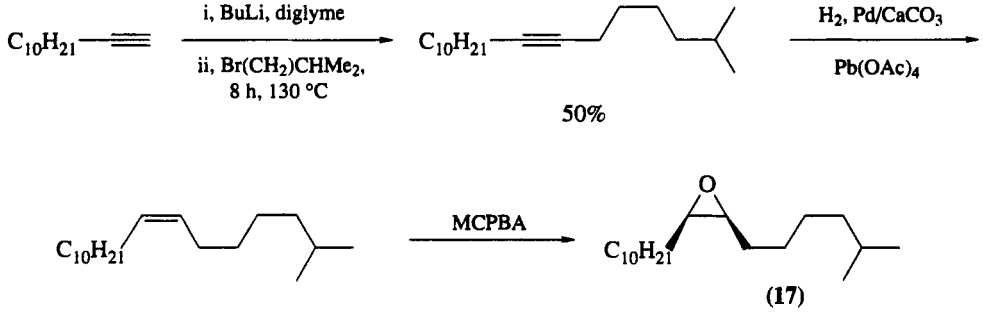


(16)

Scheme 34

1.7.5 SYNTHETIC APPLICATIONS

The ethynyl group is an extremely versatile two-carbon synthon and can be transformed to a variety of functions. The process is illustrated by a simple synthesis of the sex attractant disparlure (**17**) shown in Scheme 35.[57] Here the ethynyl group is first converted to the (*Z*)-alkene, which is then oxidized with *m*-chloroperbenzoic acid to give the oxirane.



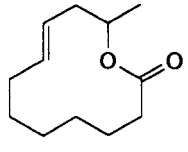
(17)

Scheme 35

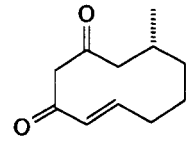
A large variety of natural products and biological materials have been prepared with reaction sequences involving alkylation of *sp*-carbon at some stage. Representative examples of the use of this synthetic manipulation in different classes of compounds are given below, but the examples are in no sense exhaustive.

1.7.5.1 Macrolides

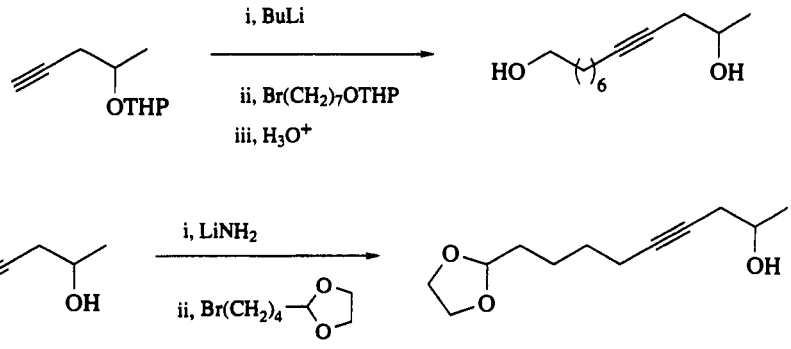
Both the Mukaiyama[58] and Bestmann[59] syntheses of the macrocyclic lactone recifeiolide (**18**), isolated from *Cephalosporium recifei*, involve *sp*-carbon alkylation steps (Scheme 36), and Shenvi and Gerlach[60] have synthesized diplodialides A (**19**) *via* a route that involved the *sp*-carbon alkylation step shown in Scheme 37.



(18)



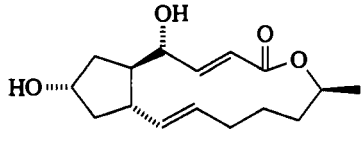
(19)



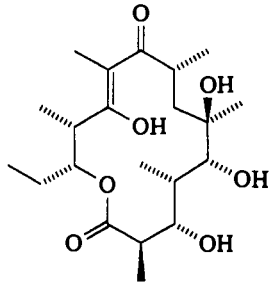
Scheme 36

Scheme 37

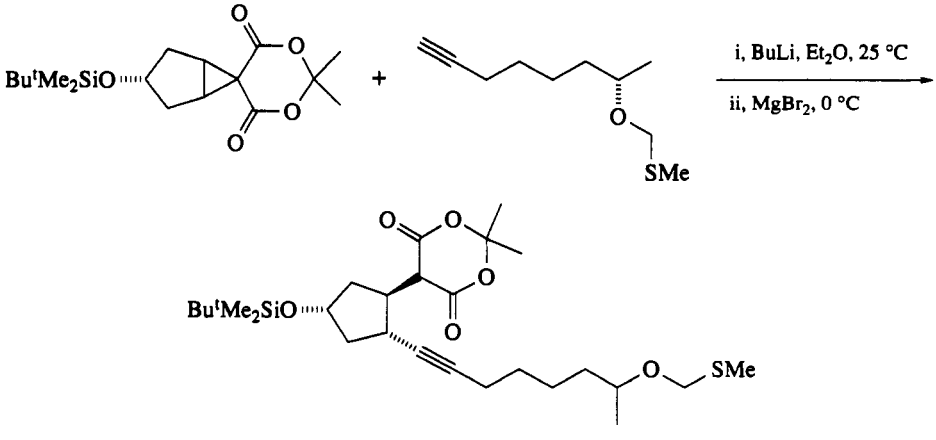
Brefeldin (**20**) is a 13-membered lactone isolated from a number of sources and has a wide spectrum of biological activity. Many of the syntheses of this lactone use alkynes as intermediates. Thus, Livinghouse and Stevens[61] used an elegant ring opening of a bicyclo[3.1.0]hexane to give the desired *trans* stereochemistry (Scheme 38), whereas in the synthesis of Kitahara and coworkers,[62] a more conventional alkynide alkylation was involved (Scheme 39).



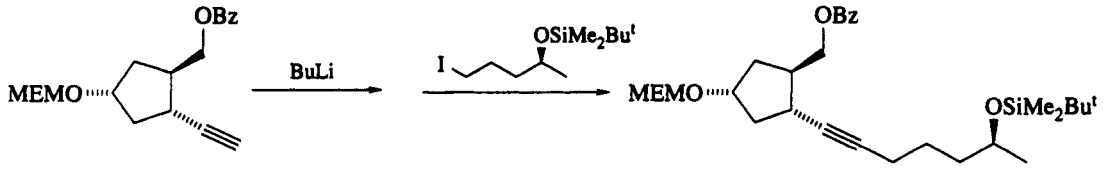
(**20**)



(**21**)

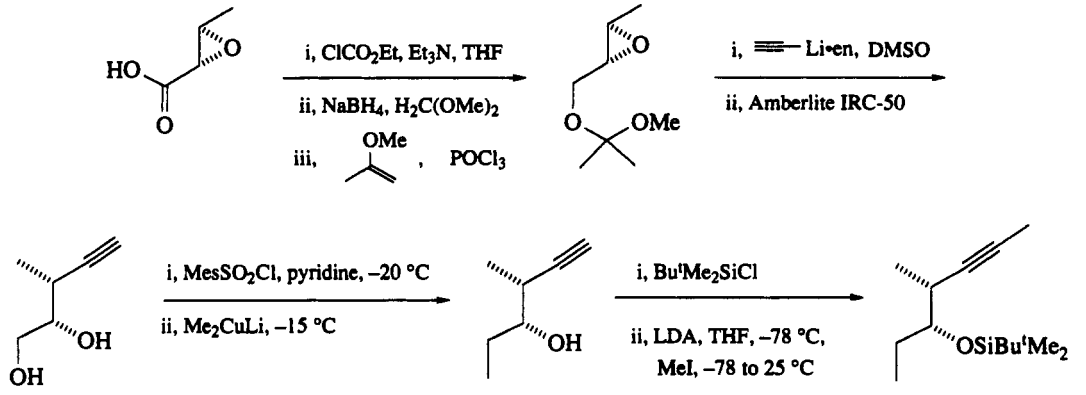


Scheme 38



Scheme 39

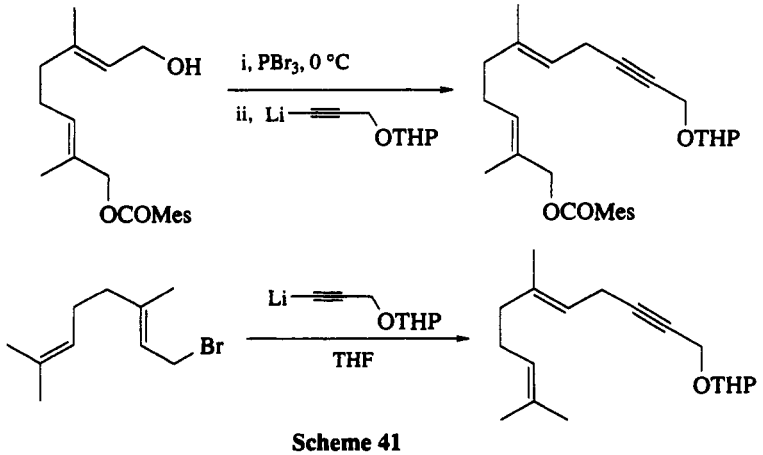
In their synthesis of erythronolide B (**21**), Corey and coworkers[63] used two alkylations of an alkynide ion in the preparation of one half of the molecule. One alkylation involved regiospecific ring opening of a resolved oxirane to provide the desired compound with the correct absolute stereochemistry, while the second used a simple methylation (Scheme 40).



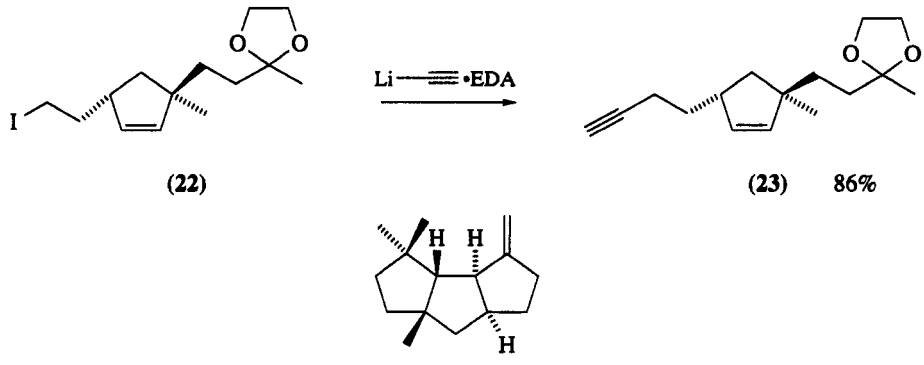
Scheme 40

1.7.5.2 Sesquiterpenes

Corey *et al.*[64] treated an allylic bromide with the THP-protected lithium propynol in their synthesis of (±)-sirenin, a sperm attractant of the water mold *Allomyces*, and the same reaction was also used in a synthesis of (±)-sesquicarene (Scheme 41). In addition, Meyers and Bienz[65] used an alkyne alkylation (**22**) → (**23**) to prepare the final intermediate for radical cyclization in their synthesis of the unnatural (+) isomer of the sesquiterpene, $\Delta^{9(12)}$-capnellene (**24**; Scheme 42).



Scheme 41



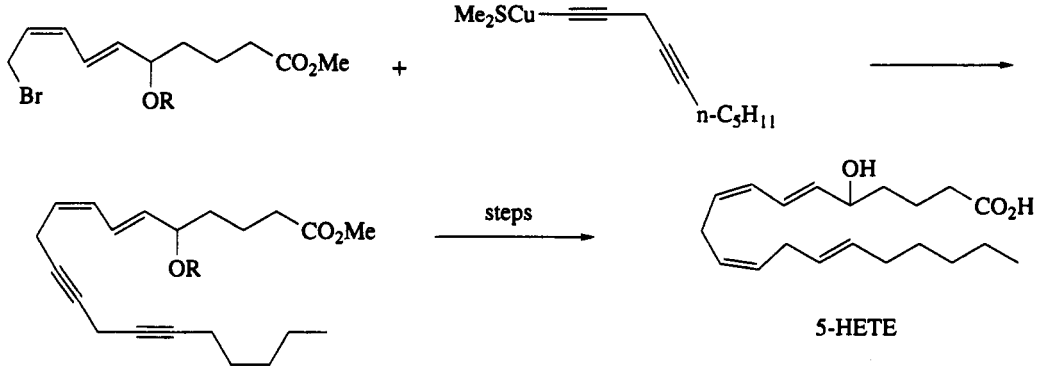
(22) (23) 86%

(24)

Scheme 42

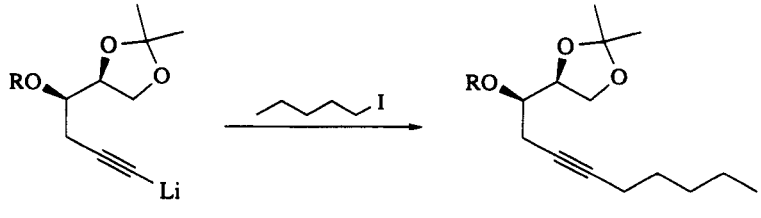
1.7.5.3 Leukotrienes and Prostaglandins

Some of the first syntheses of the leukotrienes involved alkynes as intermediates, since these are excellent synthons for the stereospecific formation of alkenes. The alkylation with the allyl bromide occurred quite late in the Merck–Frosst synthesis of 5-HETE (Scheme 43).[66]



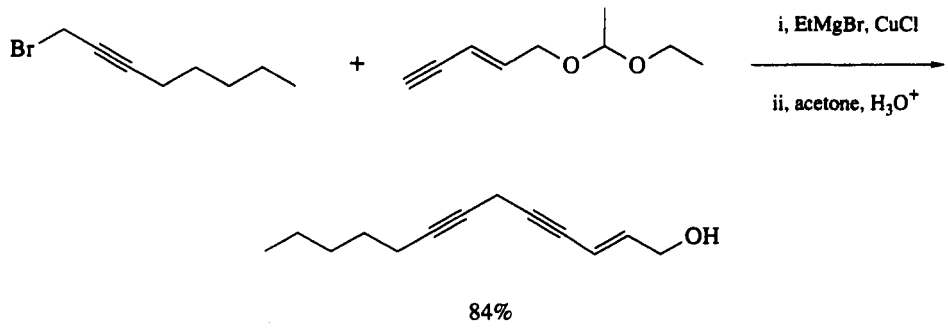
Scheme 43

The bromolithium cuprate analogue of the copper dimethyl sulfide shown in Scheme 42 was also alkylated by the *O*-protected allyl bromide to give a 65% yield of the same product. The Merck-Frosst group[67] also used a simple alkyne alkylation step in the synthesis of 14,15-dehydro-LTB_4 (Scheme 44).



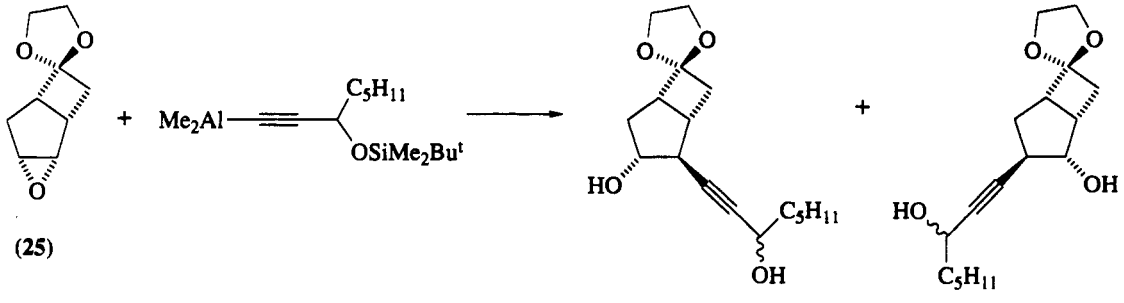
Scheme 44

In the course of their synthesis of LTB_4, Nicolaou and coworkers ring opened the THP-protected hydroxymethyloxirane (Scheme 12, ref. 31) in a regiospecific manner and they used a similar reaction in a later synthesis of (12*R*)-HETE.[68] A group at Hoffmann-La Roche[69] alkylated with a substituted propargyl bromide in a synthesis of (±)-LTA_4 (Scheme 45).



Scheme 45

A Glaxo research group has used an oxirane ring opening with a dimethylaluminum alkynide, *i.e.* (**25**) → (**26**), in one of their syntheses of prostaglandin $F_{2\alpha}$ (Scheme 46).[70] (The alkylation step in the Corey synthesis of hybridalactone was illustrated in Scheme 6.)



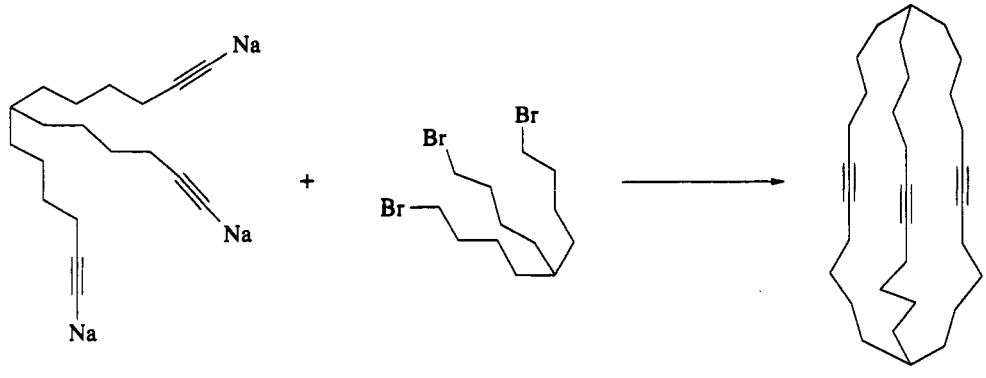
(**25**)

(**26**)

Scheme 46

1.7.5.4 Non-natural Products

As an example of the use of alkynes in the synthesis of non-natural products, Hubert and Hubert[71] have synthesized the novel bicyclic macrocycle (**29**) by high dilution treatment of the tris alkynide (**27**) with the tribromide (**28**).



(**27**) (**28**) (**29**)

Scheme 47

1.7.6 REFERENCES

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1.8
Friedel–Crafts Alkylations

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1.8.1 INTRODUCTION

In May 1877, Charles Friedel and James Mason Crafts made two communications to the Chemical Society of France of what were to become known as Friedel–Crafts reactions. Realizing the practical importance of their discovery, they lost no time in patenting their findings in France and Great Britain. Friedel and Crafts extended their studies of the catalytic effect of $AlCl_3$ in processes such asG: (i) reactions of organic halides and unsaturated compounds with aromatic and aliphatic hydrocarbons; (ii) reactions of anhydrides of organic acids with aromatic hydrocarbons; (iii) reactions of oxygen, sulfur, sulfur dioxide, carbon dioxide and phosgene with aromatic hydrocarbons; (iv) cracking of aliphatic and aromatic hydrocarbons; and (v) polymerization of unsaturated hydrocarbons.

Aluminum chloride and related catalysts bring about reactions between aromatic and aliphatic compounds, and inorganic and organic compounds; they also serve in the degradation of aromatic and aliphatic compounds, in substitution and addition reactions and various other reactions, such as polymerizations. Generally, any organic reaction effected by the catalytic action of $AlCl_3$, or related catalysts, is regarded as a Friedel–Crafts reaction. Many important industrial processes such as the manufacture of high-octane gasoline, ethylbenzene, synthetic rubber, plastics and detergent alkylates are based on Friedel–Crafts chemistry. The scope of Friedel–Crafts reactions is extremely wide, and forms a large part of the more general field of electrophilic reactions. A very large volume of literature has been published and the reader is referred to monographs,[1,2] comprehensive reviews[3,4] and an excellent treatise on Friedel–Crafts alkylation chemistry[5] for more detailed information.

For some time the main emphasis of Friedel–Crafts reactions was chiefly on aromatic compounds. The development of aliphatic Friedel–Crafts chemistry was of minor importance until World War 2, when isomerization of alkanes and cycloalkanes, preparation of high-octane aviation gasoline and synthetic rubber, and polymerization of alkenes achieved considerable importance; these contributed to the growth of aliphatic Friedel–Crafts chemistry.

Despite their seemingly wide variety, Friedel–Crafts reactions can be divided into two general categories: alkylations and acylations. Within these two broad areas, there is considerable diversity. Friedel–Crafts alkylations allow C—C bond formation in both aromatic and aliphatic systems, and are of substantial synthetic and industrial significance.

1.8.2 NATURE OF ALKYLATING AGENTS AND CATALYSTS

1.8.2.1 Alkylating Agents

Some of the earliest-known examples of Friedel–Crafts reactions were alkylations of arenes using alkyl halides. Since then, however, a wide variety of alkylating agents has been used (Table 1); they include alkenes, alkynes, alcohols and various other reagents.

Table 1 Most Frequently Used Alkylating Agents in Aromatic Alkylations

Alkyl halides	Ethers
Alkenes	Aldehydes and ketones
Alkynes	Alkanes and cycloalkanes
Alcohols	Mercaptans
Esters (of carboxylic and inorganic acids)	Thiocyanates

Alkyl fluorides are the most reactive alkyl halides in aromatic alkylation reactions. The high reactivity of the C—F bond over C—Cl, C—Br and C—I bonds enables the preferential reaction of alkyl fluorides to occur in a system containing mixed halides. However, due to their availability and low cost, alkyl chlorides and bromides are most frequently used as alkylating agents. The reactions that employ alkyl iodides as the alkylating agents are generally accompanied by side reactions and decomposition. The relative ease of alkylation with alkyl halides follows the order: tertiary, benzyl > secondary > primary. In the series of primary alkyl halides, methyl halides are the least reactive. A similar sequence of activity is also observed in alkylations with alcohols, ethers and esters. In alkylation reactions with alkyl halides and alkenes the catalyst is required only in very small quantities. However, with alcohols and related alkylating agents (esters, ethers, *etc.*) considerably larger quantities of catalyst are necessary because of the complexity of the reaction and interaction of the catalyst with the alkylating agents.

A number of important commercial applications of the Friedel–Crafts reaction are based on the alkylation of aromatic compounds with alkenes, as in the synthesis of styrene from benzene and ethylene, and cumene from benzene and propene. When di- and poly-functional alkylating agents are employed, a wide variety of products such as diarylalkanes, polycyclic arenes, indans, tetralins and alicyclic arenes are formed. In the case of an unsaturated alkyl halide, the reaction with an arene may occur either involving the halide and/or the double bond, depending on the type of catalyst and the reaction conditions. Protic acid catalysts generally favor reaction at the double bond, and metal halides favor reaction of the halide. Rearrangements of alkylating agents catalyzed by metal halides and strong acids have been extensively studied in order to understand the results of alkylations utilizing these reagents.[5] Particularly, much effort has been expended in determining whether or not these rearrangements occur simultaneous

with or consecutive to the alkylation reactions. Reactions involving primary alcohols, ethers and esters give different results depending on whether the Friedel–Crafts catalyst is a strong or a weak acid.

1.8.2.2 Catalysts

Friedel and Crafts themselves observed that aluminum chloride is by no means the only specific catalyst in the Friedel–Crafts reaction. A number of other acidic metal halides could also be employed; however, these were less reactive. The 'strength' or 'coordinating power' of different Lewis acids can vary widely against different Lewis bases. Hence it is extremely difficult to establish a scale of strength of Lewis acids in a manner analogous to that used for Brønsted acids. Despite the difficulties, a number of qualitative orders of reactivity have been proposed.[6] A comparative study of the activity of various Friedel–Crafts catalysts was performed by Olah and coworkers.[7] Thus the activity index[8] (the lowest temperature at which reaction occurs) of a large number of Lewis acid halides was measured using the benzylation reaction as the probe.

1.8.2.2.1 Acidic halides (Lewis acids)

Acidic metal halides, of which $AlCl_3$ and $AlBr_3$ are the most frequently used, comprise a large number of Lewis acid catalysts for Friedel–Crafts reactions. Other, frequently used active metal halide catalysts include: $BeCl_2$, $CdCl_2$, $ZnCl_2$, BF_3, BCl_3, BBr_3, $GaCl_3$, $GaBr_3$, $TiCl_4$, $TiBr_4$, $ZrCl_4$, $SnCl_4$, $SnBr_4$, $SbCl_5$, $SbCl_3$, $BiCl_3$, $FeCl_3$ and UCl_4. Such Lewis acids possess an electron-deficient central atom, capable of accepting electrons from basic substances. $AlCl_3$ and BF_3 (*vide infra*) are very important Friedel–Crafts catalysts and their applications cover a wide area of Friedel–Crafts-type reactions, including alkylations (both aromatic and aliphatic), different types of cyclizations, isomerizations, polymerizations and many other reactions.[2] One of the chief advantages in the use of BF_3 as a Friedel–Crafts catalyst is the fact that, being a low-boiling gas (b.p. −101 °C), it is easy to handle and to remove (or recover) from the reaction mixtures. Another advantage is that tarry and undesirable by-products are usually not obtained. Aluminum chloride has been particularly attractive in the industrial area due to its low cost and availability. Olah *et al.*[9] have prepared a new class of Friedel–Crafts catalysts which are triflate derivatives of boron, aluminum and gallium [$M(SO_3CF_3)_3$; M = B, Al, Ga]. These catalysts have been studied in detail for their effectiveness in catalyzing reactions such as alkylation with alkyl halides and isomerization processes. Due to the extreme moisture sensitivity of Lewis acids such as $AlCl_3$, it is rather difficult to carry out a Friedel–Crafts reaction under strictly anhydrous conditions. Trace amounts of acids (generated by hydrolysis of the metal halides), oxygen and organic halides invariably tend to be present in the reaction medium. However, such impurities, the so-called cocatalysts, have been found to accelerate rather than retard the reaction.[10]

Two main groups of cocatalysts can be identified in Friedel–Crafts systems: (i) proton-releasing substances, which consists of all hydroxy compounds (water, alcohol) and proton acids (HCl, H_2SO_4, H_3PO_4 and other organic and inorganic acids); and (ii) cation-forming substances (cations other than protons), which includes alkyl and acyl halides and a variety of other donor substances (O, S, N, halogen, *etc.* donors). Alkyl and acyl halides form carbocations as the activators. Other positively charged species, such as oxonium, sulfonium and halonium complexes, can also act as cocatalysts in different Friedel–Crafts reactions.

Anhydrous Lewis acids themselves are suitable catalysts for Friedel–Crafts reactions of compounds containing *n*-donor groups. However, they are generally insufficient as acceptors in reactions of alkenes or alkynes or isomerization of hydrocarbons. These reactions generally require a cocatalyst, such as a hydrogen halide or other cationic species.

Generally, Friedel–Crafts catalysts cannot be reused after aqueous work-up of the reaction mixture, although in some cases they can be recovered by special treatment. Fujiwara and coworkers,[11] however, found that lanthanide trihalide compounds ($ScCl_3$, YCl_3, $LaCl_3$, $CeCl_3$, $PrCl_3$, $NdCl_3$, $SmCl_3$, $EuCl_3$, $GdCl_3$, $TbCl_3$, $LuCl_3$, $DyCl_3$, $HoCl_3$, $ErCl_3$, $TmCl_3$ and $YbCl_3$) catalyzed the alkylation of aromatics, and the catalyst could be reused with no apparent loss of catalytic activity.

A Lewis acid catalyst can interact with the reagent containing a functional group having a donor atom with nonbonded pairs of electrons. This gives rise to a positively polarized complex or a carbocationic species, which then reacts with the π-donor substrate (aromatic, alkenic or alkynic hydrocarbons). Though this process can occur under strictly anhydrous conditions, this generally is not the case as impurity, moisture, or other cocatalysts are usually present. In the case of reactions of alkenes and alkynes

it is essential to have a cocatalyst to form a strong conjugate acid or carbocation, which then initiates the reaction. Neat Lewis acids by themselves generally do not initiate Friedel–Crafts alkylation with alkenes. Impurities, physical state and the method of preparation of the catalyst affect both yield and the course of a reaction. For example, although traces of moisture in $AlCl_3$ may accelerate the effect, other impurities, such as $FeCl_3$, can decrease the yield.

1.8.2.2.2 Metal alkyls and alkoxides

Alkyl derivatives of metals such as aluminum, boron and zinc are fairly active Friedel–Crafts catalysts. However, hyperconjugative effects result in a lowering of the electron deficiency. In the case of metal alkoxides this effect is even stronger, and, as a result, they are fairly weak Lewis acids. Metal alkyls, such as alkylaluminums, alkylaluminum halides and sesquihalides are also vital components of Ziegler–Natta catalyst systems which sometimes are utilized for Friedel–Crafts-type reactions. For example, alkylations of aromatics with alkenes in the presence of a Ziegler–Natta catalyst such as $AlR_3 + TiCl_4$ results in lower-chain alkylates. Even alkylaluminum halides and sesquihalides serve as Friedel–Crafts catalysts.

Among metal alkoxides, aluminum phenoxide is one of the most important Friedel–Crafts catalysts in the alkylation of phenol.[12]

1.8.2.2.3 Acidic oxides and sulfides (acidic chalcogenides), modified zeolites

A large variety of solid oxides and sulfides, both natural and synthetic, such as alumina, silica and mixtures of alumina and silica (either natural or synthetic), in which other oxides such as chromia, magnesia, molybdena, thoria, tungstic oxide and zirconia may also be present, as well as certain sulfides of molybdenum, come under this category of catalyst. Many synthetic chalcogenides other than silica–alumina systems are known; these include BeO, Cr_2O_3, P_2O_5, TiO_2, $Al_2(SO_4)_3$, $Al_2O_3{\cdot}xCr_2O_3$, Al_2O_3, Fe_2O_3, $Al_2O_3{\cdot}MnO$, $Al_2O_3{\cdot}CoO$, $Al_2O_3{\cdot}Mo_2O_3$, $Al_2O_3{\cdot}V_2O_3$, $Cr_2O_3{\cdot}Fe_2O_3$, MoS_2 and MoS_3. In the case of silica–alumina systems, which are the most extensively studied, the acidity could reside either at Lewis acid or Brønsted acid sites. It has been estimated that silica–alumina is quantitatively at least as acidic as 90% sulfuric acid.[13] Both natural and synthetic zeolites are very important catalysts for many commercial processes. They have good thermal and hydrothermal stabilities, and have the ability to absorb and concentrate hydrocarbons. The well-defined crystal structure enables these zeolites to have pores with one or more discrete diameters approaching molecular dimensions (<1 nm). This property is responsible for their molecular-sieving action and their ability to effect selective transformations. Shape-selective zeolite catalysis is a very powerful means of effecting selective processes. Factors that determine shape selectivity include pore shape (circular, elliptical), intersections of the channels within the zeolite, sizes and shapes of cavities, side pockets and crystal symmetry. Three types of shape selectivities are possible: (i) *reactant selectivity* — one part of the reacting molecules can pass through the catalyst pores; (ii) *product selectivity* — only products with proper dimensions can diffuse out from the pores; and (iii) *restricted transition state selectivity* — only those reactions occur where the transition state 'fits' the internal cavity.

One of the most active areas of zeolite chemistry involves efforts to improve the selectivity of zeolite catalysts. It includes selective deactivation of external acid sites with substances such as amines; replacement of the cationic sites by ion exchange with transition metal ions; and modification of the silica/alumina ratio to achieve optimum hydrophilicity (which increases with decreasing aluminum concentration), acid strength and good thermal, hydrothermal and acid stability. The literature, particularly the patent literature, abounds with numerous examples of these areas and others.[14] Various types of clays are being studied for their ability to catalyze shape-selective reactions. For example, pillared clays can provide discrete pore sizes between 6 and 40 Å. However, they suffer from the disadvantages of catalyst deactivation and thermal instability. Stabilized pillared clay catalysts have been prepared by pillaring the layers with suitable moieties. For example, boron trihalides react with the hydroxy groups on clay and form stable pillars. The resulting catalysts are especially useful for transalkylation reactions.[15]

1.8.2.2.4 Acidic cation-exchange resins

Solid acids are widely used to catalyze electrophilic reactions. Sulfonated styrene–divinylbenzene cross-linked polymers are efficient solid acids. These resins, such as Dowex 50, Amberlite IR-112 and

Permutit Q are effective catalysts for the alkylation of phenols with alkenes such as propene, isobutene and 2,5-dimethyl-2-hexene, and alkyl halides and alcohols.[16]

Modifications of these resins are also known. For example, aluminum phenoxide bonded to an acidic Dowex resin has been used as a heterogeneous catalyst for alkylation and transalkylation of phenols and polysubstituted phenols, respectively.[17]

1.8.2.2.5 Proton acids (Brønsted acids)

Reactions that are catalyzed by metal halide catalysts are also catalyzed by proton acids. The most commonly used Brønsted acids are H_2SO_4, H_3PO_4 and HF.

1.8.2.2.6 Superacids

Acids which are stronger than 100% sulfuric acid are called superacids.[18] Fluorosulfuric acid (HSO_3F) is one of the strongest Brønsted acids known, with H_0 (Hammett's acidity function) = −15.1. Its acidity is comparable to that of highly concentrated oleum, $H_2SO_4 \cdot SO_3$; however, because of its stability, ease of purification, wide liquid range (m.p. = −89 °C, b.p. = 162 °C) and relatively low viscosity (1.56 cP at 28 °C), and lesser oxidizing ability, it is more convenient to use.

Perfluoroalkanesulfonic acids also show high acidity. The parent trifluoromethanesulfonic acid (triflic acid), CF_3SO_3H, is prepared commercially by electrochemical fluorination of methanesulfonic acid.[19] It has an H_0 value of −14.1. Because it is not a sulfonating agent, its use as an acid catalyst is advantageous. The higher homologs show somewhat decreasing acidities. Perchloric acid and chlorosulfuric acid are also examples of Brønsted superacids.

1.8.2.2.7 Lewis superacids

Any Lewis acid that is stronger than anhydrous $AlCl_3$ has been arbitrarily defined as a Lewis superacid.[20] Examples of such Lewis superacids include SbF_5, NbF_5, BF_3, AsF_5, TaF_5 and BiF_3.

1.8.2.2.8 Brønsted–Lewis superacids

When a suitable Lewis acid halide and proton acid are combined, conjugate Friedel–Crafts acids are formed, which are, indeed, superacids with a wide range of acidity. Anhydrous HF–BF_3 and HCl–$AlCl_3$ (stable as conjugate pair only under pressure) are widely used examples of such acids. They effectively catalyze hydrocarbon transformations.[20] In the early 1960s, much stronger acid systems were prepared[21] comprising a pentafluoride of a Group V element, particularly SbF_5, and a strong Brønsted acid such as HF, FSO_3H, CF_3SO_3H, *etc.* Magic acid (HSO_3F–SbF_5) and fluoroantimonic acid (HF–SbF_5) are two of the best-known examples. The acidity of HF or HSO_3F is increased sharply by adding SbF_5.[22,23] For example, a composition of 4 mol % SbF_5 in HF has an H_0 value of −19, and with higher SbF_5 concentrations acidities can increase to −22. These very highly acidic systems are utilized for petrochemical transformations such as isomerization of straight chain alkanes, alkane–alkene alkylations, and the like.[24] Ternary systems, such as HSO_3F–HF–SbF_5 are also highly efficient superacid catalysts.[21] Vol'pin and coworkers[25] have reported novel, highly active systems derived from aluminum trihalide complexes of acyl and aryl halides, *viz.* $RCOX \cdot 2AlX_3$ (R = alkyl, aryl; X = Br, Cl). These effective electrophilic systems are termed aprotic organic superacids. They were found to catalyze efficiently the transformations of alkanes and cycloalkanes under mild conditions.

1.8.2.2.9 Solid superacids

Solid or supported catalysts are preferred in petrochemical and chemical industrial processes. Hence, solid superacid catalysts are of substantial interest. Acidic oxides, discussed earlier, are used extensively; however, their relatively low acidity necessitates higher operating temperatures. Even at higher temperatures, they are inefficient in promoting such reactions as the transethylation of benzene with di- and polyethylbenzenes. Consequently, new solid acid systems have been developed with considerably higher

acidities than those of acidic oxides. These include acidic zeolites, such as ZSM-5, which combine shape selectivity with high acidity. Graphite-intercalated $AlCl_3$ is an effective solid Friedel–Crafts catalyst but loses catalytic activity because of ready hydrolysis and leaching of the Lewis acid halide from the graphite.[20] Aluminum chloride can also be complexed to sulfonated polystyrene resins, but again the stability of the catalyst is limited. Anhydrous $GaCl_3$ coated on polystyrene–divinylbenzene copolymer beads forms a stable complex which shows good catalytic activity in a number of organic synthetic reactions. Most notably, the catalyst can be reused several times without losing its activity and it is easily separated from the reaction mixtures.[26] Similarly, $TiCl_4$ supported on polystyrene–divinylbenzene copolymer has been used as a reusable catalyst for many organic reactions including Friedel–Crafts alkylation.[27]

More stable catalysts are obtained by using fluorinated graphite or fluorinated alumina as backbones and Lewis acid halides, such as SbF_5, TaF_5 and NbF_5, which have a relatively low vapor pressure. These Lewis acids are attached to the fluorinated solid supports through fluorine bridging. They show high reactivity in Friedel–Crafts reactions including the isomerization of straight chain alkanes such as *n*-hexane.

Another type of solid superacid is based on perfluorinated resin sulfonic acids, such as the acid form of DuPont's Nafion resin, a copolymer of a perfluorinated epoxide and vinylsulfonic acid, or higher perfluoroalkanesulfonic acids such as perfluorodecanesulfonic acid, $CF_3(CF_2)_9SO_3H$. Such solid catalysts were found to be very efficient in alkylation of aromatic hydrocarbons and other Friedel–Crafts reactions. A comprehensive review is available on the application of Nafion-H in organic catalysis.[28]

1.8.2.2.10 Metathetic cation-forming agents[2]

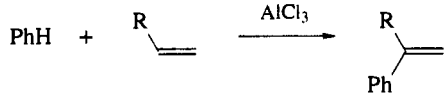
A number of metathetic agents are capable of forming carbocations from halide precursors. These materials react stoichiometrically with the carbocation precursor, and therefore cannot be considered strictly as catalysts, but initiate Friedel–Crafts-type reactions. Anhydrous silver salts, such as $AgClO_4$, $AgBF_4$, $AgSbF_6$, $AgPF_6$, $AgAsF_6$, Ag_3PO_4, *etc.* are representatives of this class of compounds.

1.8.3 ALKYLATION OF ARENES

In the alkylation of aromatic hydrocarbons generally, a hydrogen atom of the aromatic nucleus is replaced by an alkyl group through the interaction of an alkylating agent in the presence of a Friedel–Crafts catalyst. As pointed out earlier, a variety of alkylating agents can be used for this reaction. The reactions in equations (1) to (3) are characteristic of the most commonly employed alkylations of aromatic hydrocarbons.

$$PhH + RX \xrightarrow{AlCl_3} PhR + HX \quad (1)$$

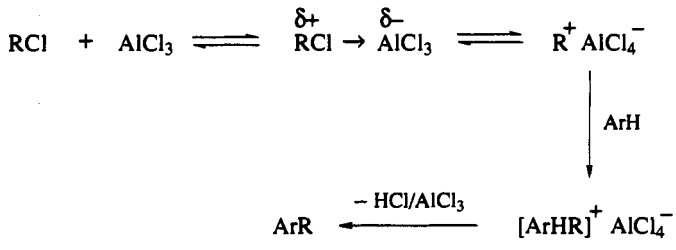
$$PhH + ROH \xrightarrow{AlCl_3} PhR + H_2O \quad (2)$$



(3)

The mechanism of alkylation of arenes can be best understood as a carbocationic electrophilic aromatic substitution — a review on this aspect is available.[29] The alkylating agent and the catalyst first form an alkyl cation or related polarized complex, which then reacts with the aromatic ring *via* a Wheland intermediate (arenium ion; Scheme 1).

Because of the exhaustive literature on the alkylation of aromatics with a variety of alkylating agents, it is most convenient to discuss the reaction according to various alkylating agents.

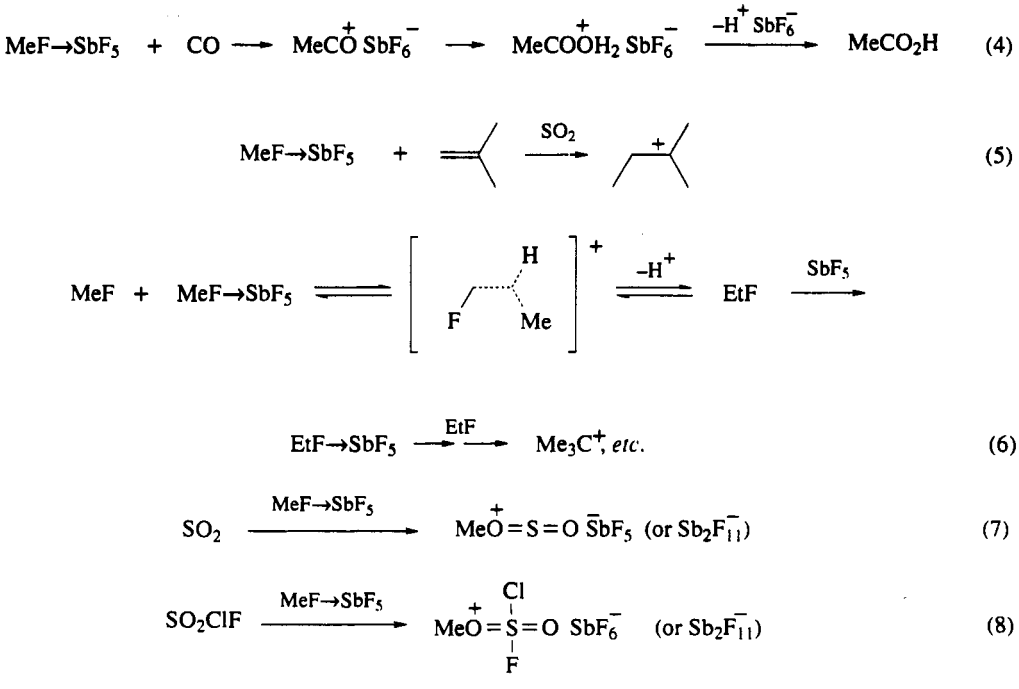


Scheme 1

1.8.3.1 Alkylation with Alkyl Halides

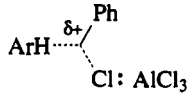
Methyl and benzyl halides were the earliest alkylating agents for the Friedel–Crafts alkylation of arenes. In fact Friedel and Crafts themselves reported the alkylation of benzene with methyl and benzyl chloride catalyzed by $AlCl_3$.[30] An earlier review by Price[31] covers the field until 1946, but more extensive treatment of this subject was presented by Olah in 1964 and 1973.[32] Further developments up to 1984 have been dealt with by Roberts and Khalaf in their book.[5] No repetition of the detailed and exhaustive discussion of the topic is, therefore, necessary. Instead, we point out briefly some of the significant work carried out to highlight the most important aspects of the reaction.

Central to the understanding of the Friedel–Crafts alkylation is the nature of the intermediate complexes formed between the catalysts and reactants. Earlier studies[33] on the exchange reactions of alkyl halides with Lewis acids such as $AlCl_3$ and $GaCl_3$ led to the postulation of dialkylchloronium ions as the intermediates formed when excess alkyl halide interacts with the Lewis acid. Olah *et al.* in their extensive studies indeed succeeded in preparing and studying dialkylhalonium ions, and the topic was covered in a monograph.[34a] Olah *et al.*[34b] also studied alkyl fluoride–antimony fluoride mixtures in solvents such as SO_2 and SO_2ClF, and suggested that they were tight donor–acceptor complexes (*e.g.* $MeF{\rightarrow}SbF_5$ and $EtF{\rightarrow}SbF_5$), which underwent rapid intramolecular fluorine exchange. They also observed that the $MeF{\rightarrow}SbF_5$–SO_2 solution was an extremely powerful methylating agent, capable of reacting with *n*-, π- and σ-donor bases as shown in equations (4) to (8). Even the solvents SO_2 and SO_2ClF are *O*-methylated by this system. These reactions showed that $MeF{\rightarrow}SbF_5$ and $EtF{\rightarrow}SbF_5$ can behave like methyl and ethyl hexafluoroantimonates, respectively.



The first kinetic study of the Friedel–Crafts alkylation reaction was reported by Brown and Grayson in 1953.[35] This involved the reactions of some substituted benzyl halides with aromatic compounds in the presence of $AlCl_3$–$PhNO_2$ catalyst. The transition state for the rate-determining step (attack of the aromatic component on a polar alkyl halide–$AlCl_3$ addition compound) was depicted as a σ-complex.

Further studies by Brown and coworkers[36] lent additional support to this mechanism and the absence of a free alkyl cation. Olah and coworkers[37] have applied the concept of competitive alkylation to the case of naphthalene in order to study both positional and substrate selectivities, and to clarify the nature of kinetically *versus* thermodynamically controlled product composition. They explained the observed results by suggesting that a π-complex, such as (**1**), was the intermediate involved when highly electrophilic catalysts or strongly basic aromatics were employed, and a σ-complex (as proposed earlier by Brown) was involved in reactions with weakly electrophilic catalysts or less basic aromatics.



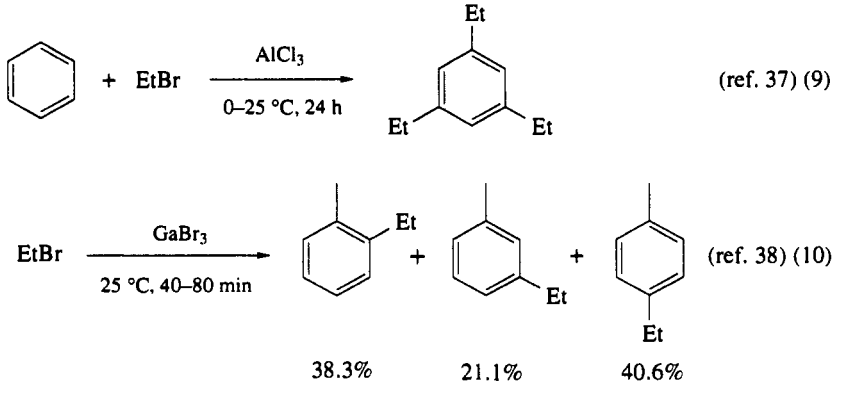
(**1**)

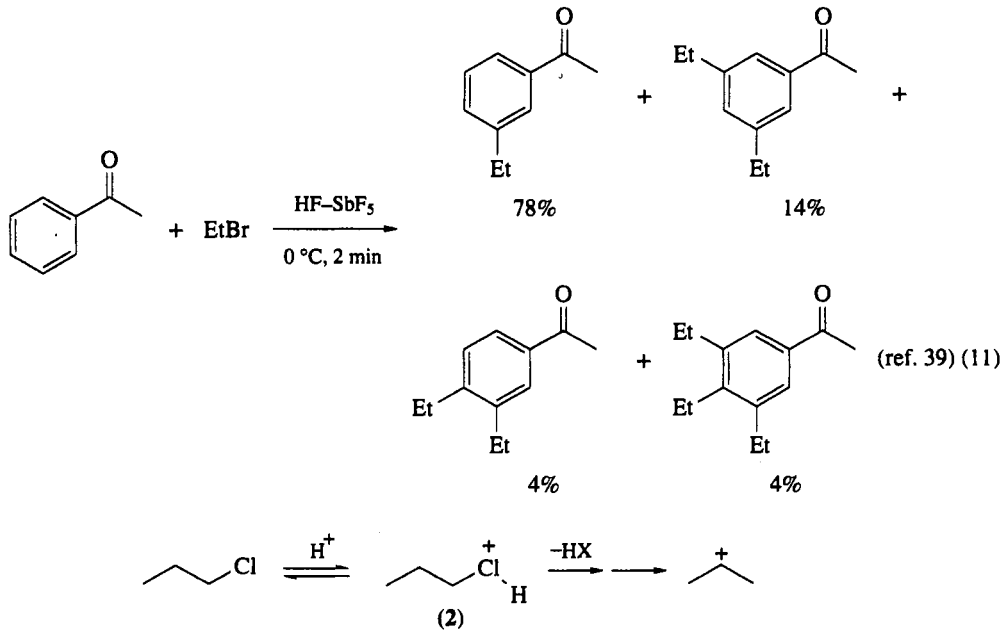
Similar explanations were put forth later by Nakane and coworkers[38] to explain their observed results. Olah's group[39] investigated the Friedel–Crafts alkylation of anisole and the analogous reaction with toluene.[31] A significantly lower degree of *meta* substitution was observed with anisole. The experimental data suggested that in the alkylation of anisole, in contrast to that of toluene, electrophilic attack by the alkylating agent at the *ortho* and *para* positions is less readily or not at all followed by thermodynamically controlled alkyl and hydrogen shifts, which could lead to increased *meta* substitution. Speranza and coworkers[40] have recently investigated the gas-phase benzylation of 2,6-dimethylanisole. Besides Friedel–Crafts catalysts, many other catalysts have also been utilized for studies on the benzylation reaction. Notable examples are arene tricarbonylmolybdenum, *i.e.* $[ArMo(CO)_3]$,[41] metal oxides[42] and calcined sulfate salts of Fe, Zn, Co, Mn and Cu.[31,43] Recently, Laszlo and Mathy[44] have studied the utility of K10 montmorillonite as a Friedel–Crafts catalyst by exchange of the interstitial cations with various transition metal ions such as Zn^{II}, Cu^{II} and Zr^{IV}. For example, in the benzylation of benzene using benzyl chloride, excellent conversion of benzyl chloride and good isolated yields (up to 66%) of the monobenzylated product were obtained. The effect of the nature of the metal ion on the reactivity and selectivity of alkylation reactions has also been dealt with.[5]

Alkylations of arenes by ethyl halides under Friedel–Crafts conditions have been carried out by numerous workers. Excellent accounts of the developments made in this area are available from a review,[31] as well as a recent book.[5] Equations (9) to (11) illustrate some ethylation reactions.[37–39]

In 1979, Olah and Meidar[45] found that alkylation of toluene offered solely a mixture of isopropyltoluenes. No *n*-propyltoluenes were detected. This was explained as proceeding by the initial formation of the Cl-protonated *n*-propyl chloride (**2**; Scheme 2), which rapidly rearranges to the isopropyl cation, followed by reaction with the aromatic ring.

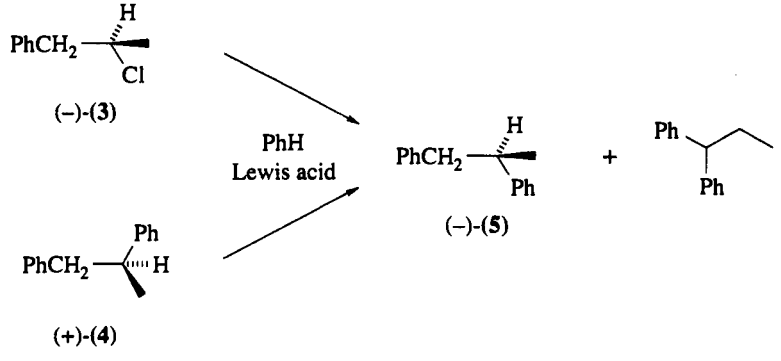
Masuda and coworkers[46] have found that both of the alkylating agents (–)-2-chloro-1-phenylpropane [(–)-**3**] and (+)-1-chloro-2-phenylpropane [(+)-**4**] react with benzene in the presence of $AlCl_3$ to give the same product, (–)-1,2-diphenylpropane [(–)-**5**] in 45–100% *ee*, which was not racemized under the



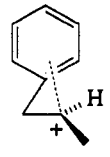


Scheme 2

reaction conditions (Scheme 3). A phenyl π-assisted cation (**6**) with an unsymmetrical bridging group has been proposed to account for the observed asymmetric induction.



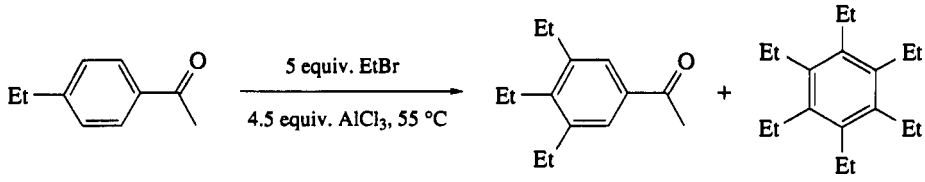
Scheme 3



(**6**)

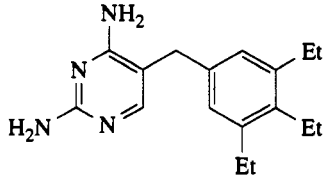
Kebarle and coworkers[47] have addressed the question of stability of the *t*-butylbenzenium ion obtained by gas-phase reaction of benzene with *t*-butyl cation.

Besides its application in mechanistic studies, the Friedel–Crafts alkylation has also been used to prepare synthetically useful compounds. Roth and Aig[48] attempted the Friedel–Crafts ethylation of *p*-ethylacetophenone (equation 12) under carefully optimized conditions to obtain the 3,4,5-triethyl derivatives (**7**) in reasonable yield. They also noted that when less ethyl bromide was employed, the product, surprisingly, was hexaethylbenzene. Compound (**7**) is a key intermediate in the synthesis of 2,4-diamino-5-(3,4,5-triethylbenzyl)pyrimidine (**8**), an antibacterial agent.



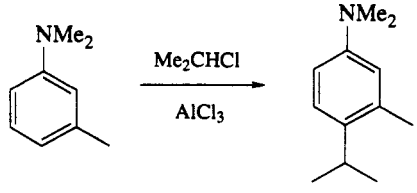
(12)

(7)



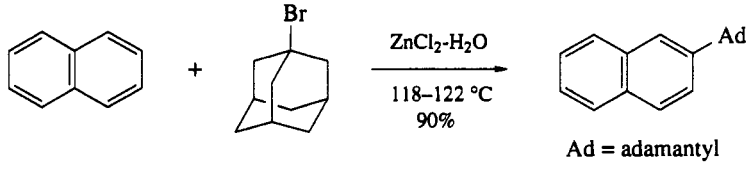
(8)

Highly selective (87%) isopropylation of an aniline at the *para* position has been achieved[49] by employing a particular mole ratio of the catalyst (aluminum halide) and the aniline (equation 13). Conversion of the substrate in the reaction was 87%.

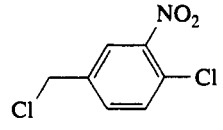


(13)

Zhukov and coworkers[50] alkylated naphthalene with 1-bromoadamantane in the presence of $ZnCl_2$–H_2O to afford 2-(1-adamantyl)naphthalene in 90% yield (equation 14).



(14)

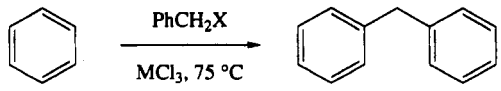


(9)

The Friedel–Crafts benzylation reaction has been employed to prepare polymer-bonded 2-mercaptopyridine and 2-mercaptonitrobenzene derivatives as new reagents for peptide synthesis.[51] Crosslinked polystyrene was subjected to benzylation using the benzyl chloride (9) as the alkylating agent, followed by further manipulation of the polyalkylated polymers. These polymeric reagents were used for the thiolytic cleavage of the 2-$(O_2N)C_6H_4S$ group in peptide synthesis.

Fujiwara and coworkers[11] have discovered that anhydrous lanthanoid trichloride salts[52] are reusable Friedel–Crafts catalysts for the benzylation of benzene. All of the lanthanoid trichlorides offer fairly good yields of benzylated product (equation 15). The yields do not drop if the recovered catalyst is used for a second time, or in some cases even a third time, for the benzylation of benzene.

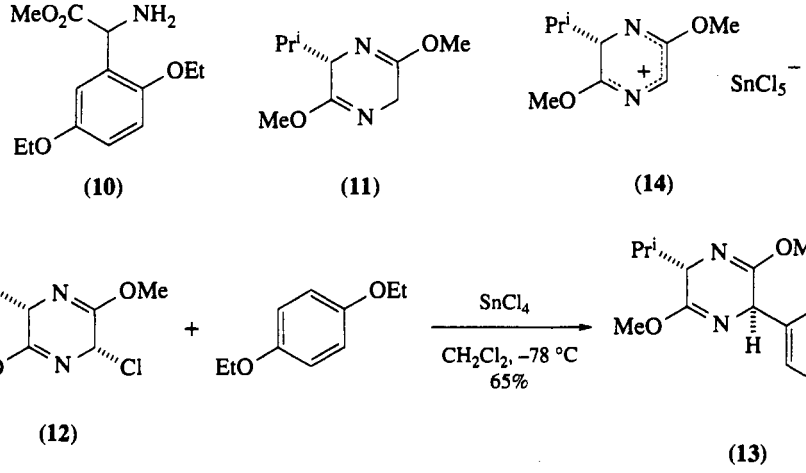
Asymmetric Friedel–Crafts alkylations, besides affording interesting mechanistic problems, also offer valuable synthetic utility. For example, reaction of benzene with optically active 2-chloro-1-phenylpropane or 1-chloro-2-phenylpropane in the presence of $AlCl_3$ affords good yield (60%) of alkylated product with up to quantitative optical yields (see Scheme 3).[46]



(15)

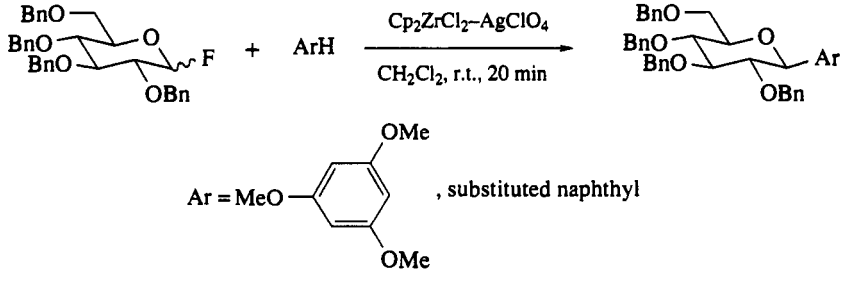
M = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

Optically active 2-arylglycine esters, such as (**10**), have been prepared[53] by Friedel–Crafts alkylation of alkoxybenzenes and naphthalenes with the chiral cation of the bislactim ether of cyclo-(L-Val-Gly). For example, when the chloride (**12**), prepared from the bislactim ether (**11**), was allowed to react with 1,4-diethoxybenzene in the presence of tin tetrachloride as the Lewis acid (equation 16), the adduct (**13**) was obtained in 65% yield. Acid hydrolysis of (**13**) furnished the previously unknown (*R*)-α-arylglycine methyl ester (**10**). The active species in the alkylation step has been proposed to be the ion pair (**14**). Unactivated arenes were found not to react under these conditions. 2-Arylglycines such as (**10**) are of pharmacological interest due to their potential biological activity and as components of drugs such as semisynthetic penicillins, ampicillins and amoxycillins.



(16)

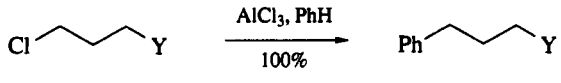
A practical application[54] of the benzylation reaction is the $AlCl_3$-catalyzed Friedel–Crafts alkylation of a styrene–ethylene–butene–styrene block copolymer with benzyl chloride to afford modified thermoplastic alkene elastomers. Another application[55] of Friedel–Crafts-type regiospecific alkylation of arenes with cycloalkyl fluorides derived from sugars (equation 17) constitutes a facile methodology to prepare *C*-arylglycosides, some of which are potent antitumor agents. The glycosyl fluorides are activated by the novel Lewis acid system, Cp_2ZrCl_2–$AgClO_4$.[56]



(17)

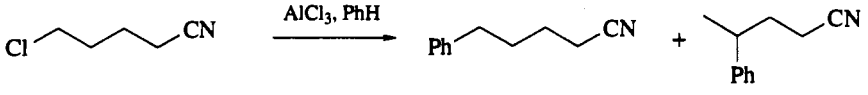
Alkylation of benzene by ω-chloroalkanoic acids $Cl(CH_2)_nCO_2H$ and their methyl esters and nitriles has also been studied.[57] It was found that introduction of electron-acceptor substituents such as —CO_2H, —CO_2Me and —CN into *n*-alkyl chlorides decreased the extent of isomerization of the alkyl chain below that of the corresponding 1-chloroalkanes, as seen from the examples in equations (18) and (19).

Besides these more recent examples, many instances of the use of benzylation reactions to prepare a variety of substituted aromatic compounds are known.[5] Some examples are shown in equations (20)[58] and (21).[58b]



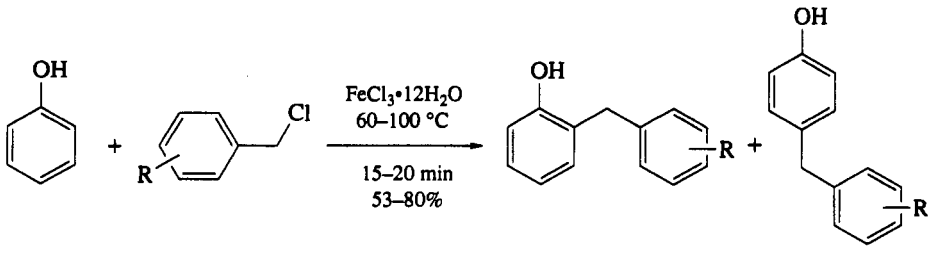
(18)

$Y = CO_2Me$, CN



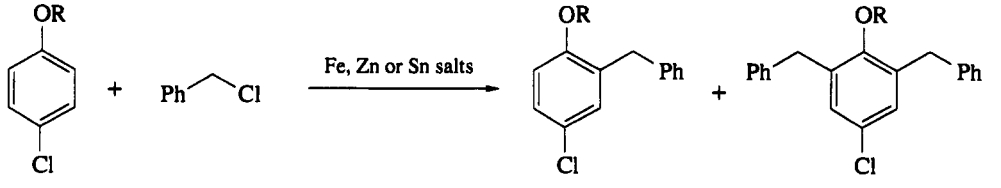
(19)

98% 2%



(20)

R = *o*-Me	54%	46%
R = *m*-Me	60%	40%
R = *p*-Me	58%	42%



(21)

major minor

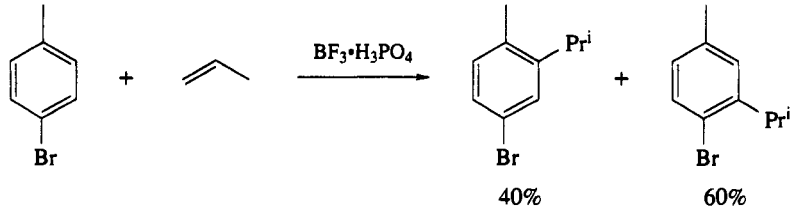
1.8.3.2 Alkylation with Alkenes

The alkylation of arenes with alkenes such as ethylene and propene are of great commercial interest. Ethylbenzene and isopropylbenzene (cumene), products of the Friedel–Crafts alkylation of benzene with ethylene and propene, respectively, are two of the most important petrochemical raw materials.[59] Roberts and Khalaf[5] have followed the developments made in this vast field up to the early part of this decade. This is evident from the large number of references quoted, most of which describe efforts to evaluate conditions for optimal production in the presence of various catalyst systems.

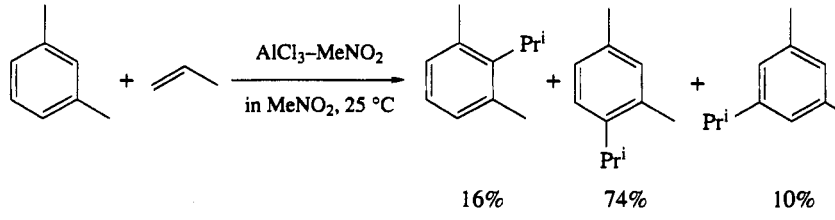
Reports of kinetic studies of positional and substrate selectivities for Friedel–Crafts ethylation and propylation reactions are available in the literature. Thus ethylene was used to alkylate aromatics such as toluene,[60] naphthalene[61] and biphenyl[62] using a variety of catalysts. Ethylation and propylation of aromatics such as naphthalene and biphenyl can give rise to varying mixtures of isomeric alkylated products depending on the nature of the catalyst and the severity of the reaction conditions. For example, in the isopropylation of naphthalene nonisomerizing catalysts such as BF_3–H_3PO_4, HF, BF_3·Et_2O or P_2O_5 gave higher 1-isomer:2-isomer ratios than the isomerizing catalysts.[63] Mechanistic studies on the alkylation of arenes with alkenes, particularly with propene, have been carried out using many techniques, such as standard kinetic methods and ^{14}C- and ^{2}H-labeling methods. These aspects are well documented.[5] More recent kinetic and mechanistic studies include: kinetic modeling of the liquid-phase alkylation of toluene with *n*-butenes;[64] thermodynamic analysis of the alkylation of phenols with branched alkenes;[65] kinetics of benzene alkylation with 1-decene in the presence of soluble quantities of $AlCl_3$ catalyst complex;[66] isomer distribution studies on the Friedel–Crafts alkylation of toluene with cycloalkenes;[67] a mathematical model for the homogeneous alkylation of benzene by ethylene in the presence of an aluminum chloride catalyst;[68] and kinetics of cycloalkylation of phenol and cresols by cyclohexene and cyclopentene using H_2SO_4 as catalyst.[69]

Friedel–Crafts alkylation of aromatics with a wide variety of alkenes has led to many useful applications in organic synthesis. Particularly, much effort has been devoted to choosing appropriate catalysts

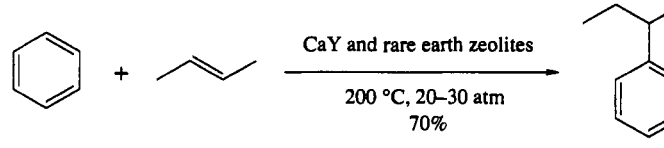
and reaction conditions to produce predominantly or selectively one product isomer. This is especially true of alkylations with both linear and branched C_4, C_5 and higher alkenes as the alkylating agents. Other factors such as steric and electronic interactions could also lead to regioselective formation of products as seen in equations (22) to (26).[70–74]



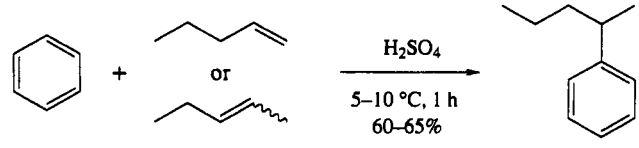
(ref. 70) (22)



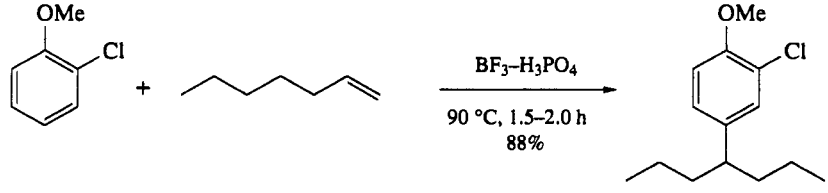
(ref. 71) (23)



(ref. 72) (24)



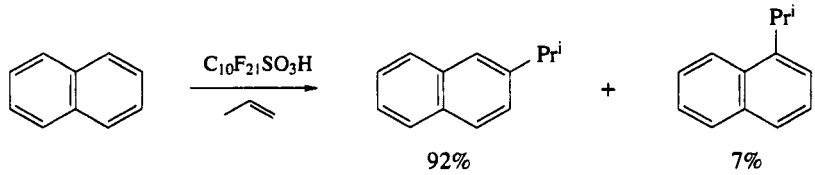
(ref. 73) (25)



(ref. 74) (26)

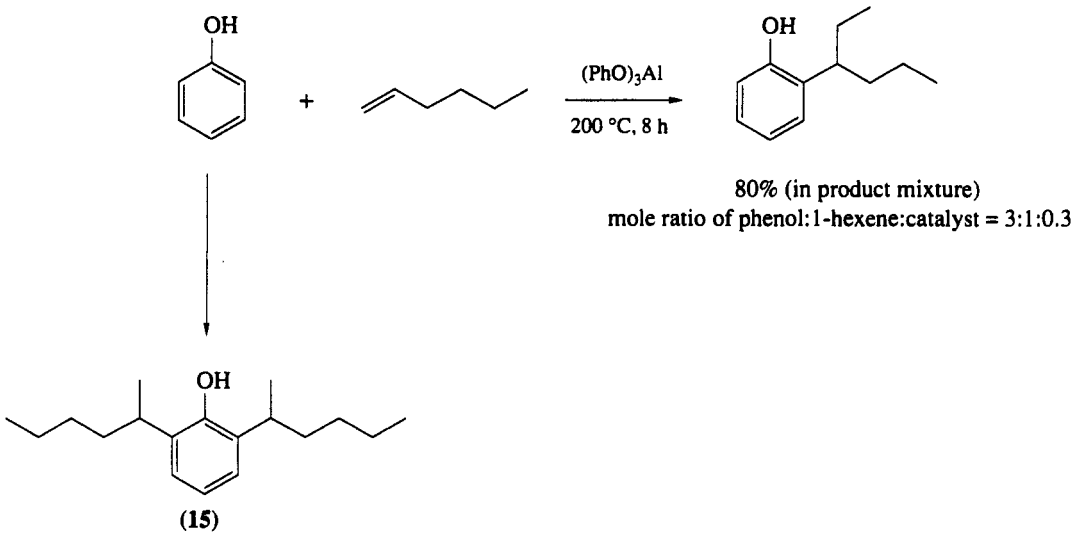
The effect of the acidity of polyfunctional zeolite catalysts on their activity in benzene alkylation by propene has been examined.[75a] Crystalline zeolites exist with a variety of characteristic pore and channel sizes. In the case of ZSM-5 zeolite, the interconnected channels formed by 10-membered rings of oxygen atoms allows certain benzene derivatives to fit rather closely, diffuse into the pores, and, after undergoing a reaction, diffuse out. This is the origin of the high *para* selectivity in reactions such as alkylation of toluene by methanol catalyzed by zeolites like ZSM-5 and related modifications.[75b,c]

Olah[76] has found perfluoroalkanesulfonic acids, such as perfluorodecanesulfonic acid (PDSA, $C_{10}F_{21}SO_3H$), to be very effective catalysts for regioselective isopropylation of naphthalene (equation 27).



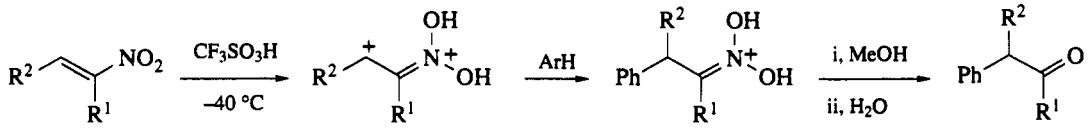
(27)

Controlled *ortho* alkylation of phenol by 1-hexene to produce the mono- or di-alkylated product has been achieved by using aluminum phenolate as the catalyst under carefully optimized reaction conditions.[77] Sterically hindered phenols such as (**15**) are of particular interest as antioxidants (Scheme 4).



Scheme 4

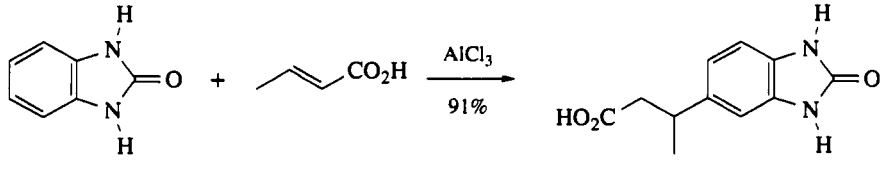
Shudo and coworkers[78] have reported that *O,O*-diprotonated nitroalkenes (**16**) behave as novel electrophilic species which can efficiently alkylate aromatics such as benzene, anisole, chlorobenzene, naphthalene, *etc.* under extremely mild conditions (equation 28). The reaction enables the synthesis of α-arylated ketones (**17**) which are difficult to synthesize by conventional Friedel–Crafts reactions.



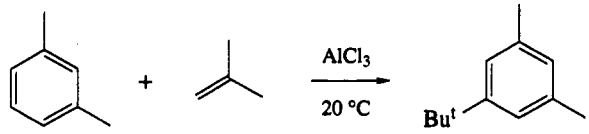
(**16**) (**17**) (28)

Crotonic acid has been used as a carboxyalkylating agent in its reaction with benzimidazolin-2-ones (equation 29).[79] It must be emphasized, however, that when long chain linear alkenes are used as alkylating agents, one frequently encounters a mixture of products containing rearranged forms of the alkyl group. With isobutene as the alkylating agent, the products are found to be exclusively *t*-butylated derivatives. A number of isomerically pure *t*-butylated aromatics have been thus prepared. The regioselectivity is also appreciably enhanced because of the greater steric factors operative. Alkylations with branched C_5 and higher alkenes, in general, are accompanied by side reactions,[80] such as reorientation, disproportionation, fragmentation, polymerization, hydride transfer and skeletal rearrangement of the alkylating group. However, use of moderated reaction conditions, including a milder catalyst, can afford one product selectively. Examples illustrating the synthetic utility of alkylations with isobutene and higher branched alkenes are shown in equations (30) to (34).[81–85]

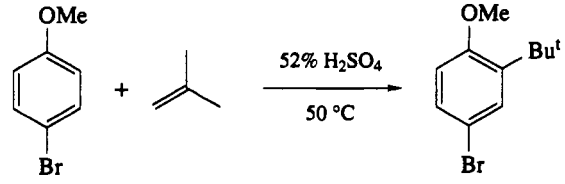
Alkylation of phenols with isobutene has also been accomplished[86] using a heterogeneous catalyst system comprising an aluminum phenoxide bonded to a solid polymeric resin having acidic functional



(29)



(ref. 81) (30)



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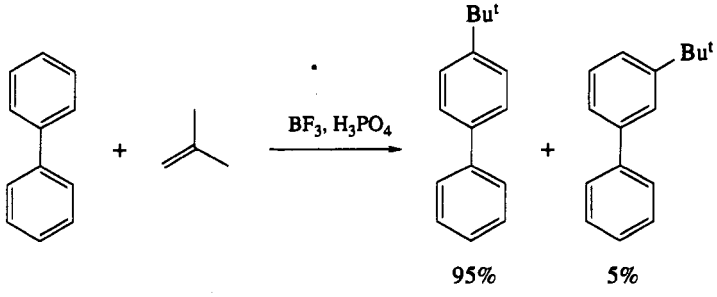

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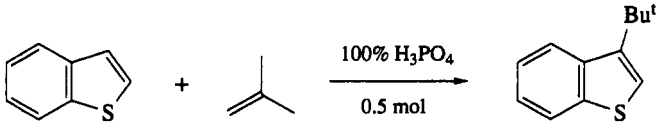

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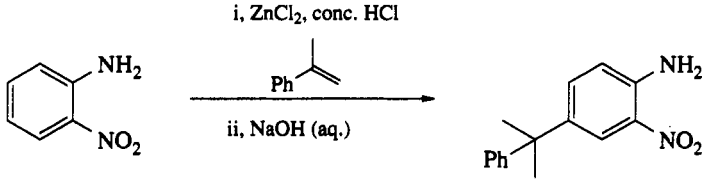
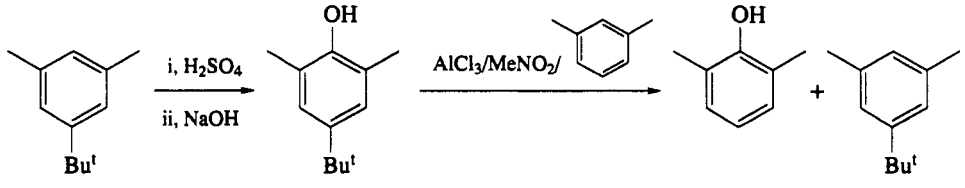


(ref. 85) (34)

groups. A strongly acidic ion-exchanger has been employed[87] as the catalyst for the Friedel–Crafts alkylation of phenols with diisobutene to afford *p*-*t*-octylphenol. Such alkylations in heterogeneous media are of great importance due to the ease of separation of the product from the catalyst.

The *t*-butyl group has been extensively utilized as a positional protective group in both separation and synthesis problems. This is due to the ease with which *t*-butyl groups can be introduced (by alkylation) and removed (by dealkylation). Tashiro's review[88] covers this topic very well. Examples to illustrate the utility of the *t*-butyl group for the selective preparations of phenolic compounds (equations 35 and 36),



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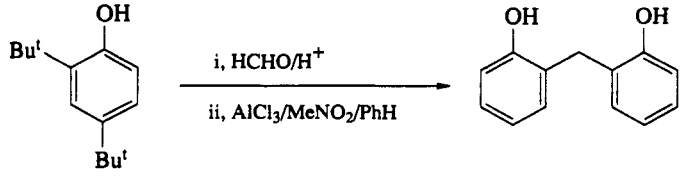

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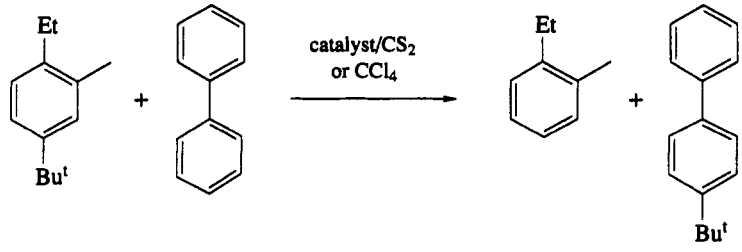

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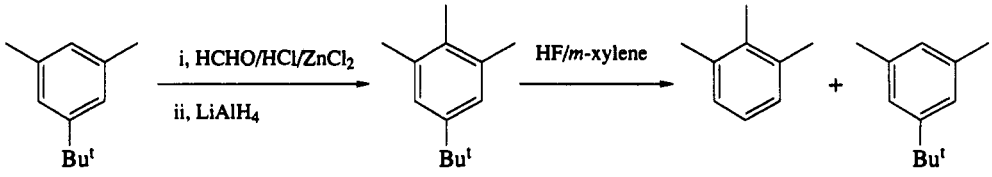

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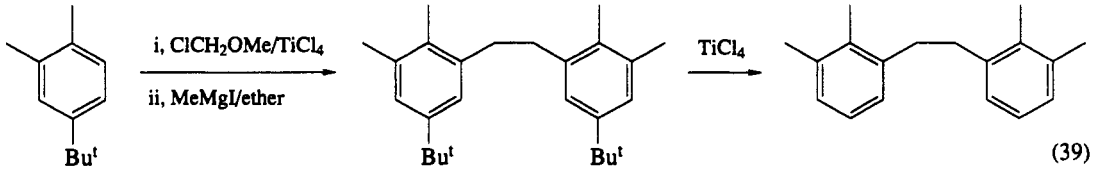

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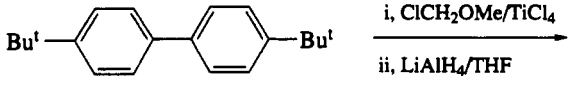

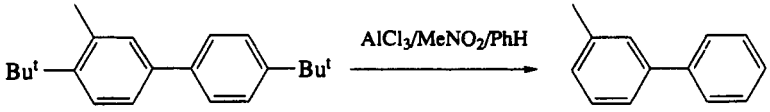

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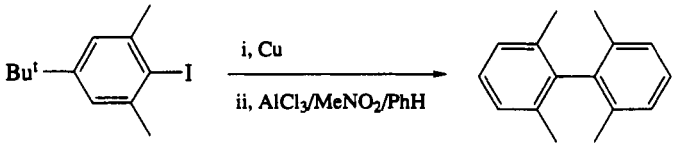

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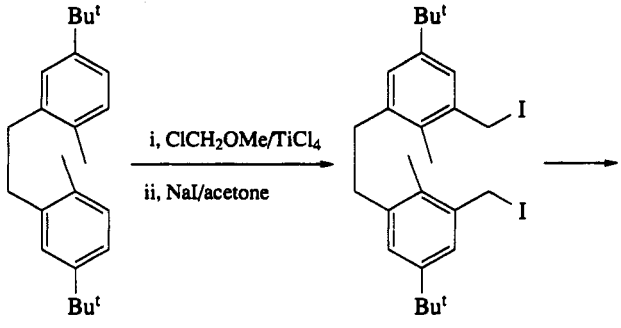

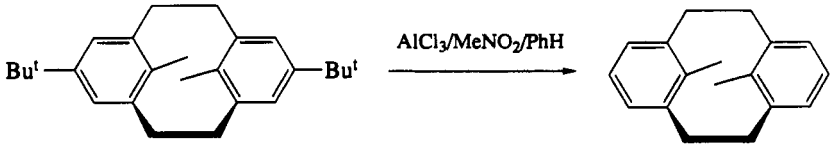

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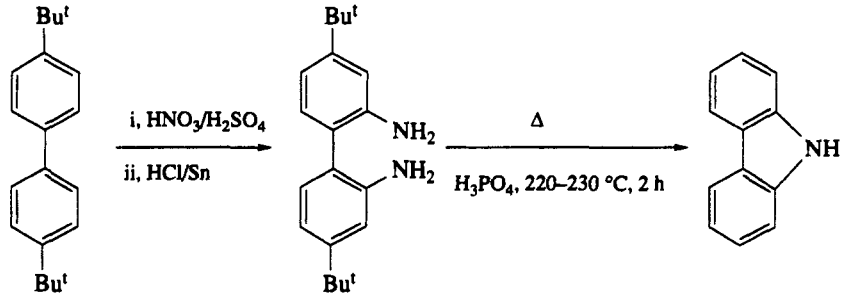
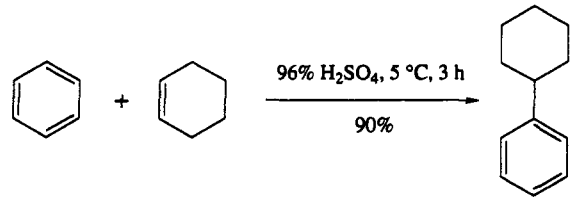


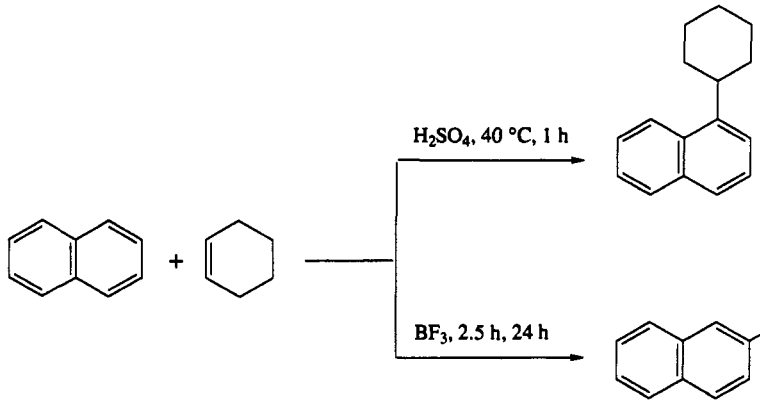
(43)

1,2-di- and 1,2,3-tri-substituted benzenes (equations 37 and 38), diarylalkanes (equation 39), 2-mono- and 2,2′-di-substituted biphenyls (equations 40 and 41), [2,2]metacyclophanes (equation 42) and carbazoles (equation 43) are shown.

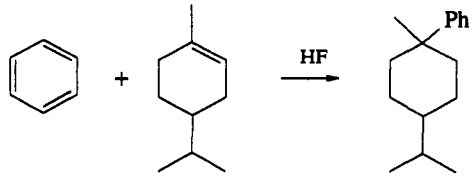
Alkylation of arenes with cycloalkenes (cycloalkylation) is also well documented in the literature. A variety of Lewis and Brønsted acids have been used as catalysts for these reactions. These reactions share many similarities with the alkylation reactions of arenes with other alkylating agents such as alkenes. The selectivity of the cycloalkylation reaction depends upon the conditions and catalyst. A few examples of cycloalkylation reactions are presented in equations (44) to (46).[89–91]



(ref. 89) (44)



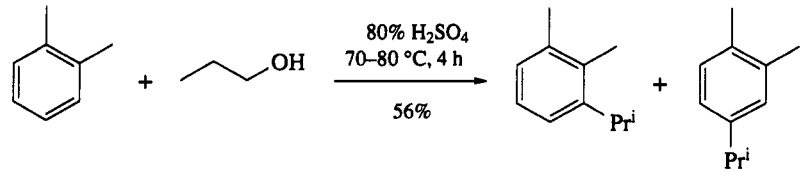
(ref. 90) (45)



(ref. 91) (46)

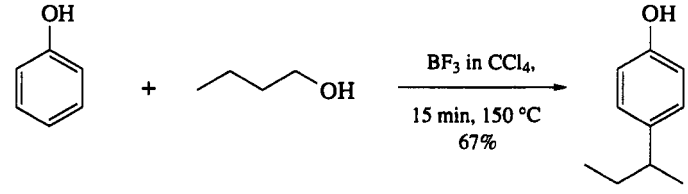
1.8.3.3 Alkylation with Alcohols, Ethers, Esters, Epoxides and Lactones

The alkylations of arenes by alcohols, ethers and esters, as well as with epoxides and lactones, are of considerable interest, and constitute a significant part of the field of Friedel–Crafts alkylations. Some of the earliest examples are the alkylations of arenes with primary alcohols,[92a] esters[92b] and ethers.[92c] Subsequent work over the years has revealed that these alkylations are often accompanied by various side

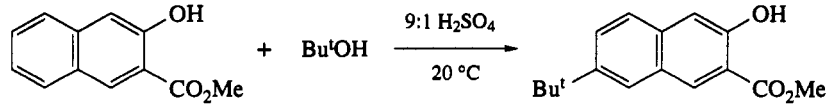


13% 87%

(ref. 93) (47)

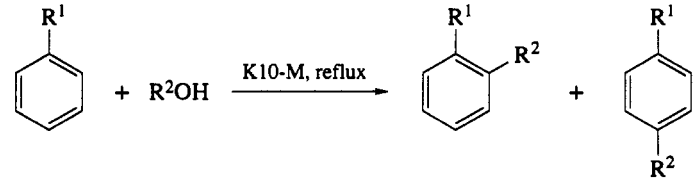


(ref. 94) (48)



(18)

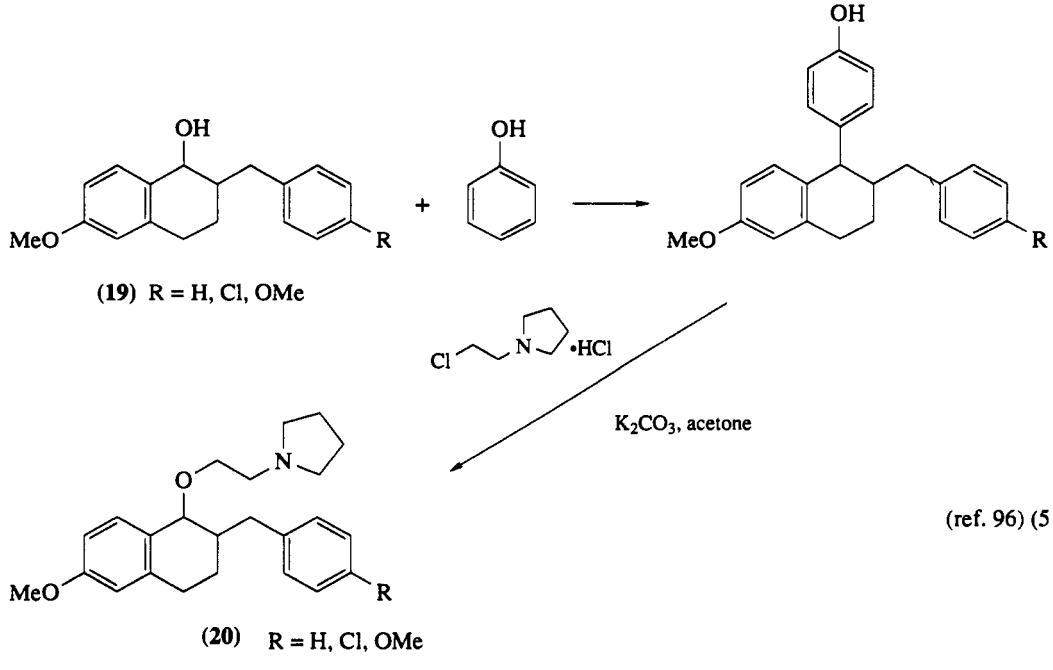
(ref. 95) (49)



(ref. 44) (50)

R^1 = H, Me; R^2 = $PhCH_2$, c-C_6H_{11}, 2-pentyl, 3-pentyl

M = Al^{III}, Ti^{V}, Fe^{III}, Co^{II}, Cu^{II}, Zn^{II}, Zr^{IV}, Nb^{V}, Ta^{V}



(19) R = H, Cl, OMe

(20) R = H, Cl, OMe

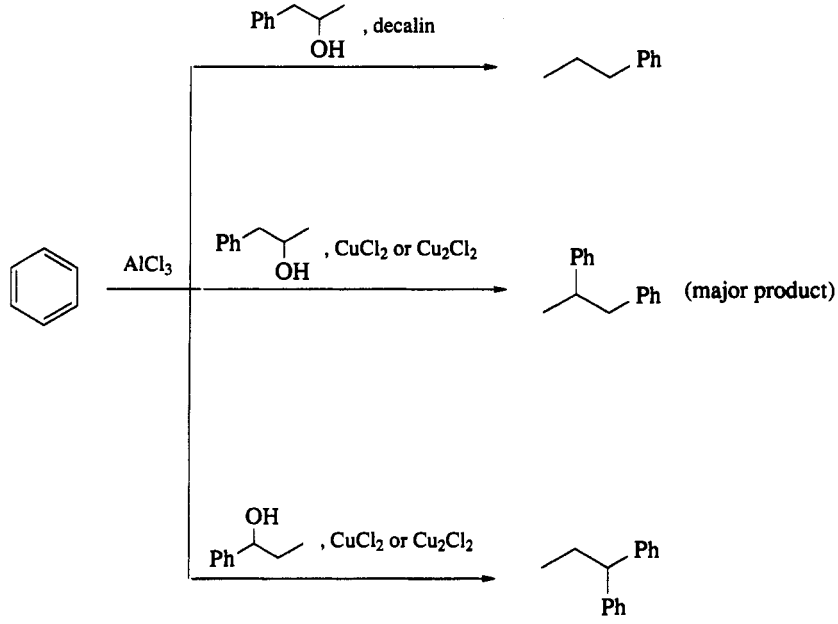
(ref. 96) (51)

reactions, such as isomerization, fragmentation and dealkylation, together with side-chain and positional rearrangements.

Early studies have shown that, compared to alkylations with alkyl halides or secondary alcohols, alkylations with primary alcohols require larger amounts of the Lewis acid catalyst (*ca.* 2 mol for 1 mol of alcohol) and longer heating at higher temperatures. The relative ease of alkylation with alcohols follows the order: benzyl, allyl, tertiary > secondary > primary > methyl. Besides using catalysts such as BF_3 and $AlCl_3$, many milder catalysts have been used for the alkylation of aromatics with alcohols, ethers and esters. These include weakly acidic metal halides, such as $AlCl_3$–$MeNO_2$, $FeCl_3$, $TiCl_4$, $SnCl_4$ and $ZnCl_2$; protic acids such as H_3PO_4, HF, H_2SO_4 and polyphosphoric acid; solid superacids such as Nafion-H; and inorganic acidic oxides such as P_2O_5, alumina, natural and synthetic aluminosilicates and zeolites. These milder catalysts afford solely or mostly the rearranged secondary alkylates.

A careful choice of catalyst and reaction conditions is necessary to obtain selective Friedel–Crafts alkylation. The following examples illustrate reactions with alcohols as the alkylating agent (equations 47 to 51).[44,93–96]

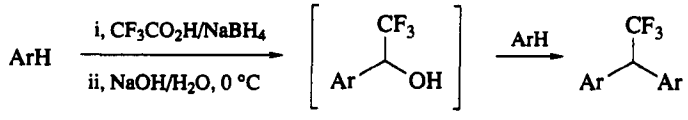
The *t*-butylated naphthalene derivative (**18**; equation 49) is of interest as an intermediate[95] for the synthesis of fungicides. Tetrahydronaphthalene derivatives, such as (**20**), have been evaluated[96] as antifertility agents. Sugita *et al.*[97] have studied the $AlCl_3$-catalyzed Friedel–Crafts alkylation of benzene with 1-phenyl-2-propanol and 2-phenyl-1-propanol in the presence of additives, such as $CuCl_2$, Cu_2Cl_2 and decalin. Highly regioselective formation of 1,1-diphenylpropane was observed with Cu^I or Cu^{II} chloride as the additive. Some pertinent results of synthetic value are shown in Scheme 5. The addition of decalin diminished the alkylation reaction to give the reduction product 1-phenylpropane.



Scheme 5

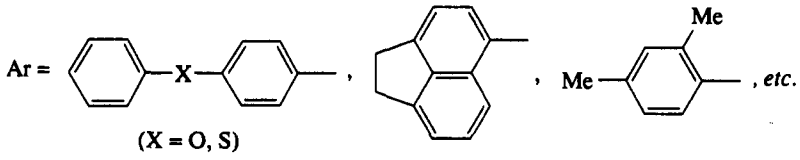
Nutaitis and Gribble[98] have found that arenes react with $NaBH_4$ in CF_3CO_2H to afford 1,1,1-trifluoro-2,2-diarylethanes, which were otherwise difficult to prepare. They proposed a Friedel–Crafts-type (Baeyer) condensation to give an intermediate carbinol (**21**; equation 52), which further alkylates benzene to give the observed products. The reaction with sterically congested arenes such as mesitylene and durene stops at the carbinol stage (equation 53).

Isopropylation of toluene by isopropyl halo- and alkyl-sulfonates (equation 54) has been performed by Olah *et al.*[99] A variety of catalysts, such as $AlCl_3$, $AlCl_3$–$MeNO_2$ and Nafion-H were employed, and the isomer distribution (*o*, *m*, *p*) in the product was determined. Sartori *et al.*[100] have recently reported an unusual Friedel–Crafts alkylation of lithium phenolates with ethyl pyruvate in the presence of $AlCl_3$ to afford α-(2-hydroxyphenyl)ethyl lactates (**22**), which are the precursors of 3-methyl-2,3-dihydrobenzofuran-3-ols (**23**; Scheme 6).

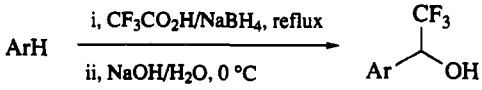


(52)

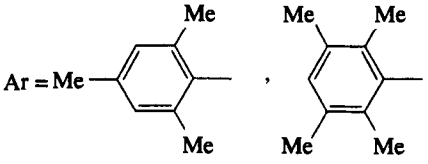
(21)

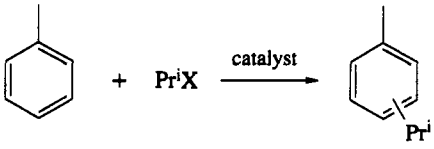


(X = O, S)



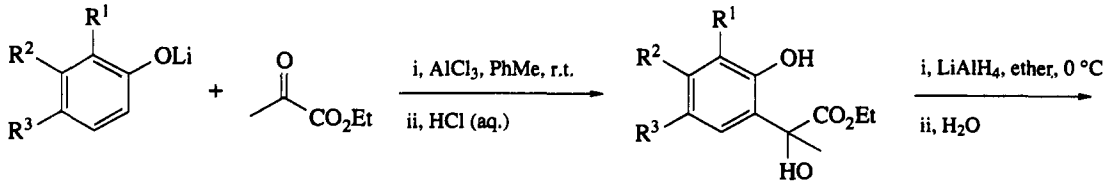
(53)





(54)

X = OSO_2Cl, OSO_2F, SO_2Ph, SO_2Cl, OSO_2-*p*-Tol, OCOCl



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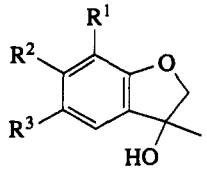
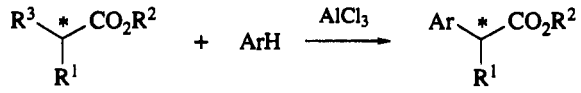


(23)

Scheme 6

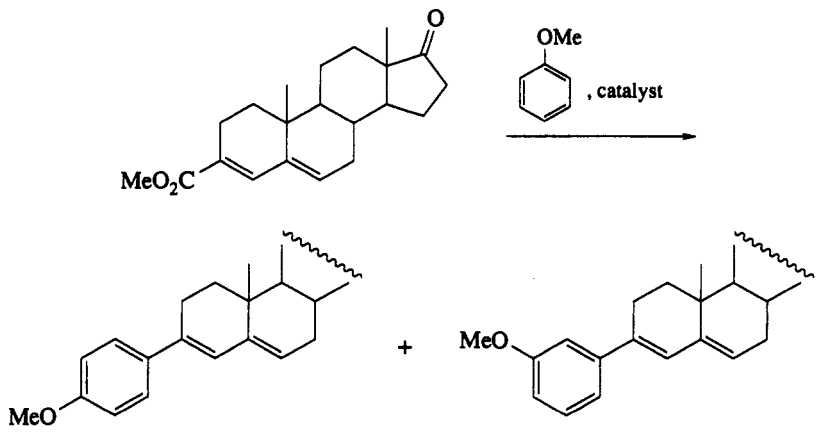
Optically active 2-arylalkanoic acid esters (**24**) have been prepared (equation 55)[101] by the Friedel–Crafts alkylation of arenes with optically active esters in the presence of $AlCl_3$. Piccolo and coworkers[102] have also found that alkylation of benzene with optically pure (*S*)-methyl 2-(chlorosulfonyloxy)- or 2-(mesyloxy)-propionate, in the presence of $AlCl_3$, gave (*S*)-methyl 2-phenylpropionate in good chemical (50–80%) and excellent optical yield (>97% *ee*, as determined by rotation), with inversion of configuration at the attacking carbon atom. In view of the ready availability of optically pure lactic acid derivatives, this reaction offers an attractive general method of preparing optically active compounds by further elaboration of the phenyl and ester groups in the alkylated product (**25**; $R^1C^*H(Ar)Y$, R^1 = Me; Y = CO_2Me, CO_2Et).



(55)

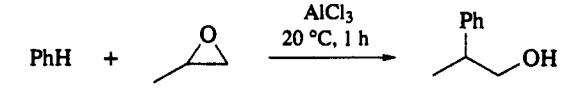
R^1, R^2 = alkyl; R^3 = Cl, Br, $ClSO_3$ — R^1, R^2 = alkyl (**24**)

Steroidal alkenol esters have been employed as alkylating agents to introduce aryl groups (equation 56).[103]

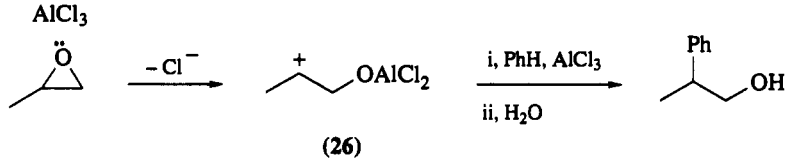


(56)

Examples of Friedel–Crafts alkylations of arenes with acyclic ethers are rare in the literature. With cyclic ethers (epoxides, oxetanes, *etc.*), however, a number of interesting alkylation reactions are known. With epoxides alkylation proceeds with ring opening to give β-hydroxyarylalkanes, which, depending on catalyst type and reaction temperatures, can react further with aromatics to produce 1,2-diarylalkanes. Milstein[104] found that benzene, for example, was alkylated by 1,2-epoxypropane in the presence of $AlCl_3$ to give a 64% yield of 2-phenyl-1-propanol (equation 57); the isomeric 1-phenyl-2-propanol was observed only in trace amounts. This was rationalized by suggesting that the $AlCl_3$–coordinated epoxide complex initially undergoes ring opening to give the most stable ion pair (**26**) before attacking the benzene (equation 58).



(57)

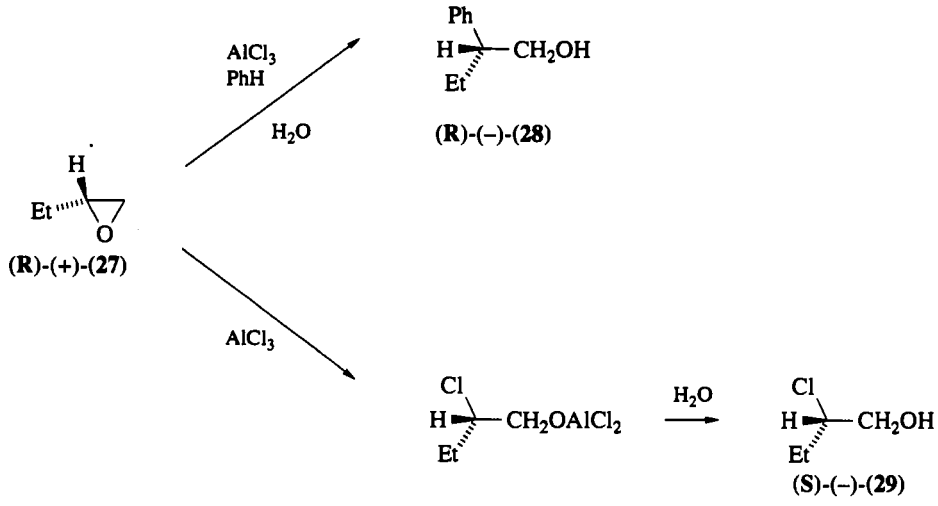


(58)

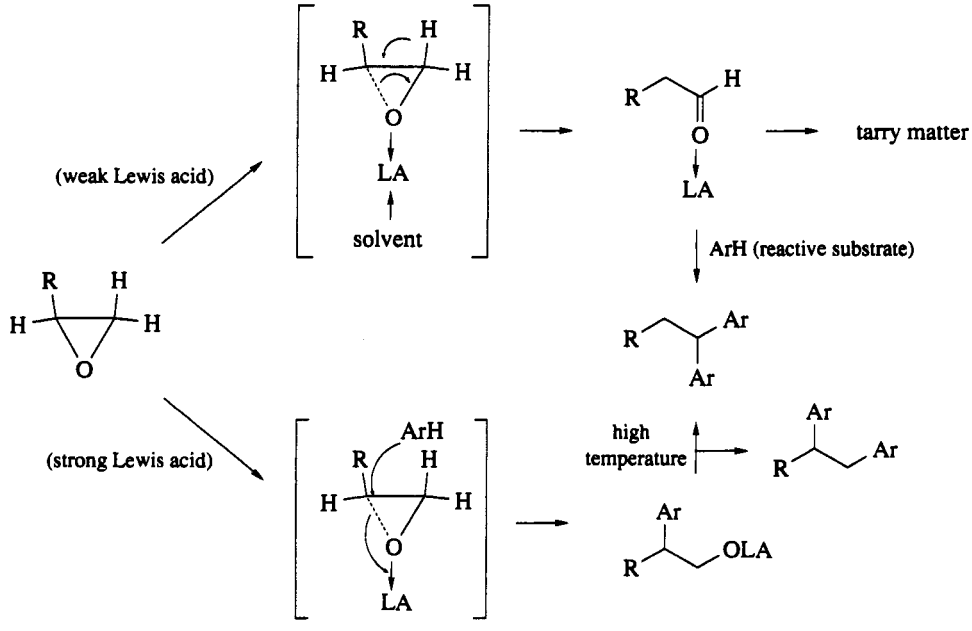
(**26**)

Suga *et al.*[105] studied the $SnCl_4$- or $AlCl_3$-catalyzed Friedel–Crafts alkylation of benzene with (*R*)-(+)-1,2-epoxybutane (**27**) to investigate the stereochemistry of the ring-opening process. The primary products were (*R*)-(–)-(**28**), with almost 100% optical purity, and (*S*)-(–)-(**29**), with 55–56% optical purity (Scheme 7).

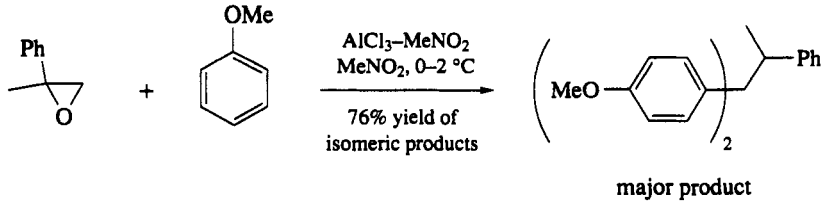
Under the influence of mild acid catalysts, such as $MgBr_2$, $ZnCl_2$ and $BF_3{\cdot}Et_2O$, epoxides are initially isomerized to an aldehyde which then alkylates the arene to afford 1,1-diarylated products (Scheme 8). With strong Lewis acids, however, an S_N2-type ring opening of the activated epoxide by the reactive aromatic component occurs to give the normal Friedel–Crafts alkylation product. Thus, in those cases where ring opening of the epoxide gives a more stable secondary or tertiary carbocation, good yields of diarylated products are obtained. Some examples using anisole as the arene are shown in equations (59) and (60).[106]



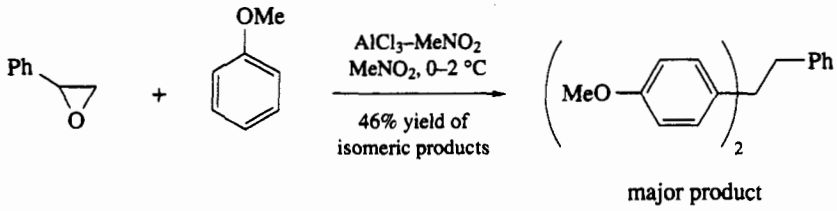
Scheme 7



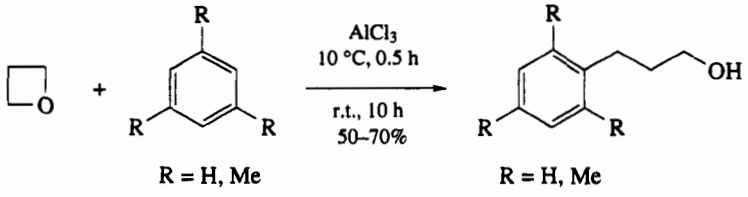
Scheme 8



The alkylation of arenes by an oxetane affords the carbinol *via* a ring-opening reaction as seen in equation (61).[107] Suga and coworkers[108] have examined the stereochemistry of the ring-opening process by carrying out the alkylations of benzene with (+)-2-methyloxetane in the presence of $AlCl_3$, $SnCl_4$ or $TiCl_4$.

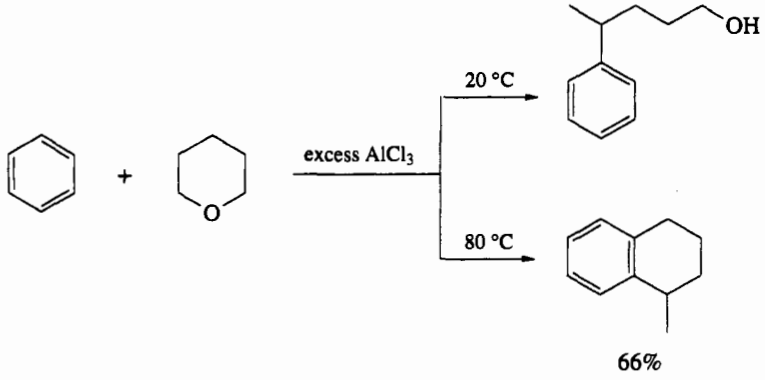


(60)



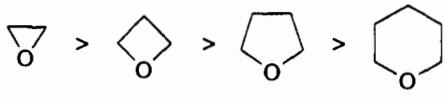
(61)

Friedel–Crafts alkylations of arenes with higher cyclic ethers such as tetrahydrofurans and pyrans are often accompanied by many side reactions such as intramolecular alkylation, condensation and further transformations of the initial alkylated product. However, it is possible to obtain one product selectively by choosing the proper reaction conditions. An example is shown in equation (62).[109]

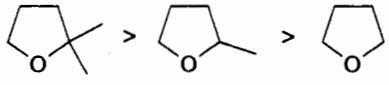


(62)

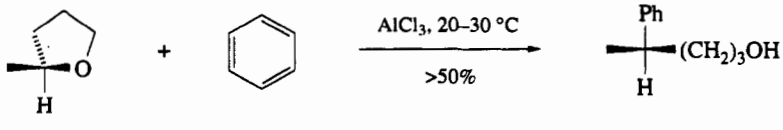
The ease with which cyclic ethers alkylate arenes is in the order[110]



It also decreases with the degree of branching,[111] as in

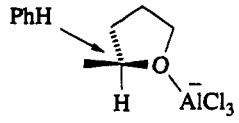


Brauman *et al.*[112] have alkylated benzene with (*S*)-(+)-2-methyltetrahydrofuran to give (*R*)-(–)-4-phenyl-1-pentanol. The reaction occurred with at least 35% inversion of configuration (equation 63). This result has been explained by an S_N2-type attack of benzene on a cyclic ion pair such as in (**30**). Studies on stereospecific Friedel–Crafts reactions by Sugita and coworkers[113] have also lent support to the suggestion that stereospecifity might be general for Friedel–Crafts reactions of cyclic compounds.



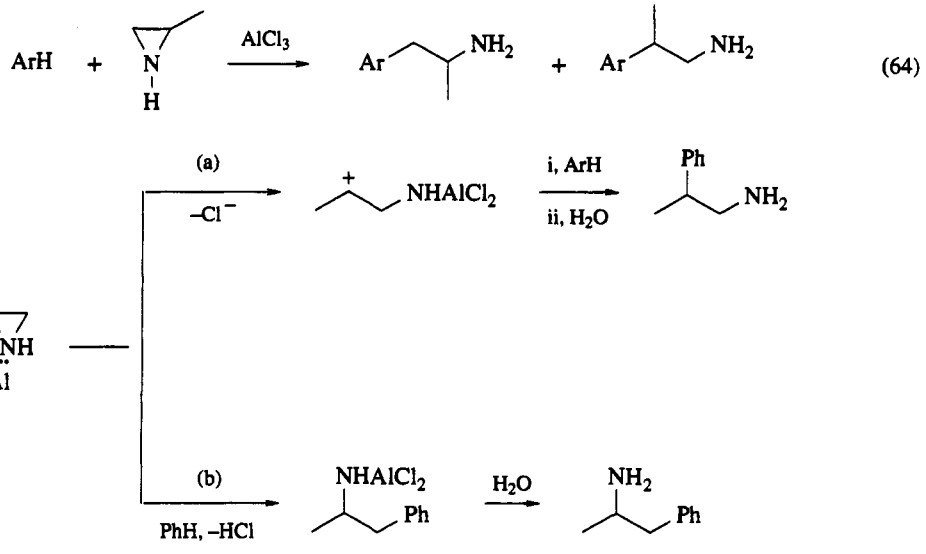
(63)

(S)-(+) *(R)*-(–)



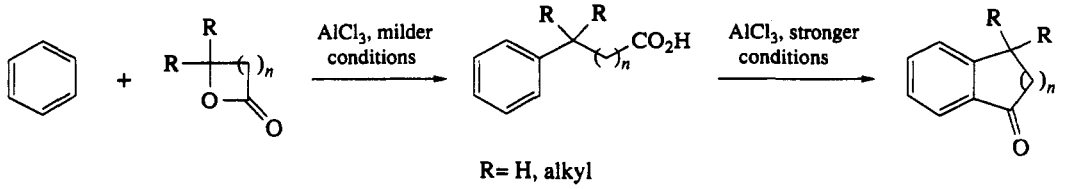
(30)

Aziridines also are capable of alkylating arenes to form β-arylethylamines. Milstein's work[114] on the alkylation of arenes with 2-methylaziridine revealed the formation of two isomeric products (equation 64). This was explained by the occurrence of two competing pathways, (a) and (b), as shown in Scheme 9.



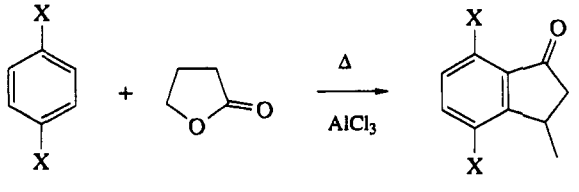
Scheme 9

The Friedel–Crafts alkylation of arenes with lactones provides a convenient method for the synthesis of arylalkanoic acids. However, depending on the nature of the arene, catalyst, temperature and reaction time, the resulting arylalkanoic acids can undergo partial or complete cyclization to the corresponding cyclic ketones (Scheme 10). Equations (65) to (68) show examples of Friedel–Crafts alkylations using lactones as the alkylating agents.[115–118]



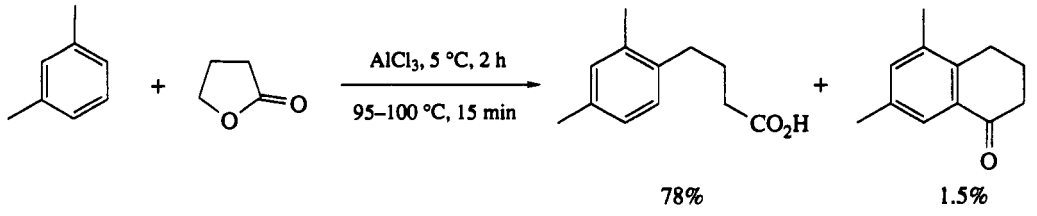
R= H, alkyl

Scheme 10

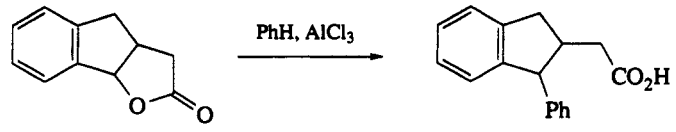


(ref. 115) (65)

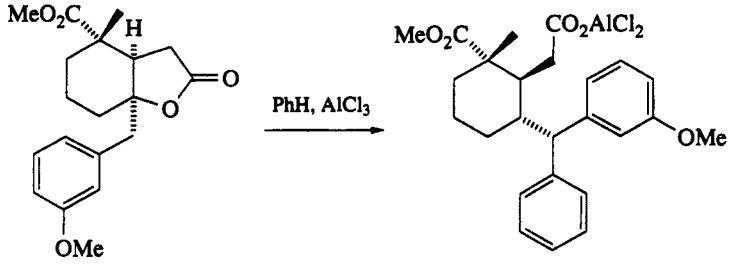
X = F, Cl



(ref. 116) (66)

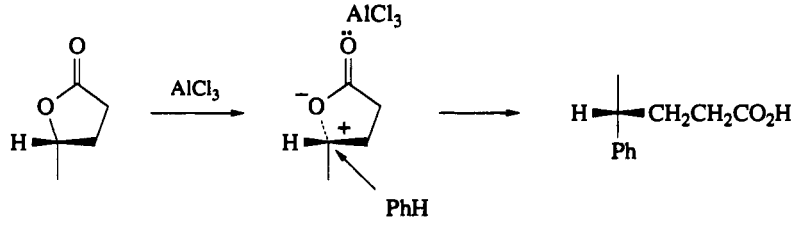


(ref. 117) (67)



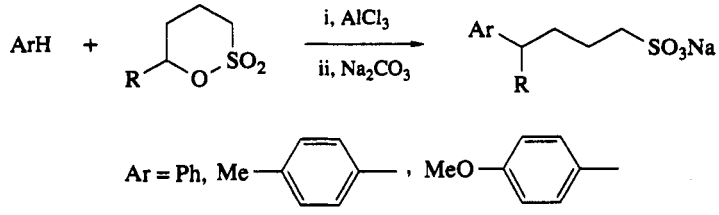
(ref. 118) (68)

Brauman *et al.*[119] have examined the mechanism of the alkylation of lactones by reacting optically active γ-valerolactone with benzene in the presence of $AlCl_3$. They found the reaction to proceed with nearly 50% net inversion of configuration (equation 69). The mechanism put forth to account for this result is similar to that proposed for the observed stereochemistry of the Friedel–Crafts alkylation of (*S*)-(+)-2-methyltetrahydrofuran[112] (*vide supra*).



(69)

Sultones have been shown to alkylate arenes in the presence of $AlCl_3$ (equation 70)[120] to give arylalkenesulfonates.

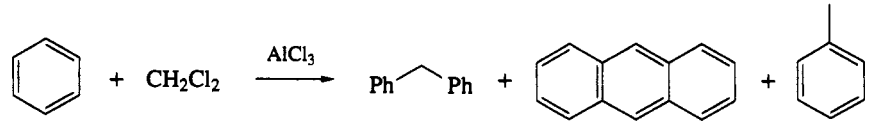


(70)

1.8.3.4 Alkylation with Di- and Poly-functional Alkylating Agents

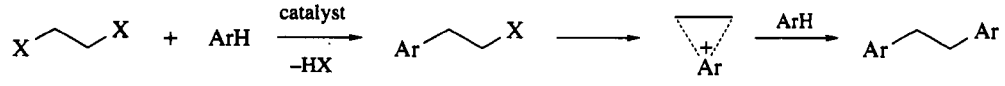
In 1884, Friedel and Crafts reported that the alkylation of benzene or toluene with dichloromethane in the presence of $AlCl_3$ afforded the corresponding diarylmethanes, besides other products derived from further alkylation and other transformations.[121] The products from the reaction with benzene are shown

in equation (71). Subsequent work on the alkylation reactions with toluene, other substituted arenes and naphthalene describes the efforts to understand the formation of a number of alkylated products derived from competing processes, such as isomerization and dealkylation.



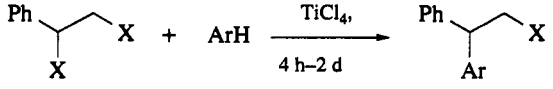
(71)

1,2-Dihaloethanes alkylate arenes under Friedel–Crafts catalysis by Lewis acids to afford 1,2-diarylated ethanes. Dolgov and Larin[122] suggested that the reaction proceeds *via* the intermediate monoarylated haloethane (Scheme 11) which affords the final product *via* a phenonium-type intermediate.



Scheme 11

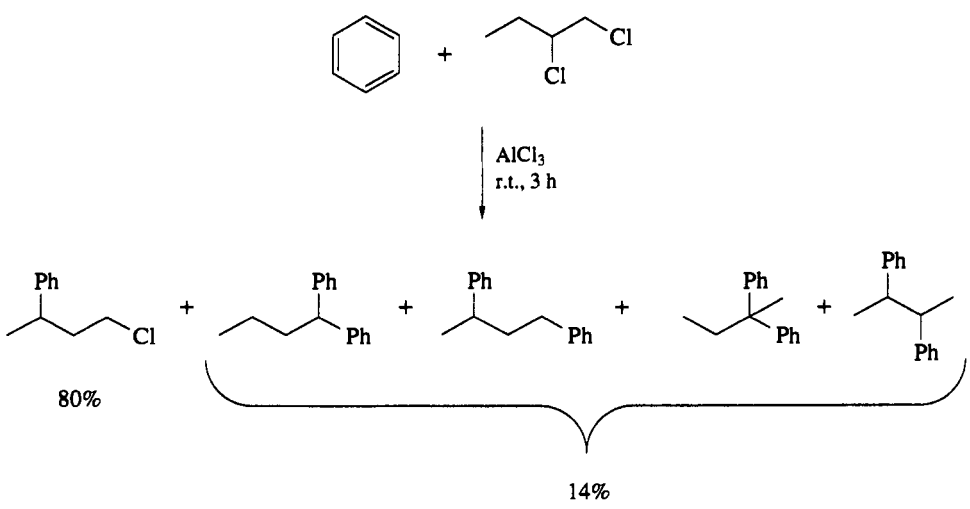
The reaction of 1,2-dihalo-2-phenylethane with arenes in the presence of $TiCl_4$ afforded a number of 1,1-diaryl-2-haloethanes in 40–73% yield (equation 72).[123]



(72)

X = Cl, Br; Ar = Ph, *p*-MeC_6H_4, *p*-$PhOC_6H_4$, *etc.*

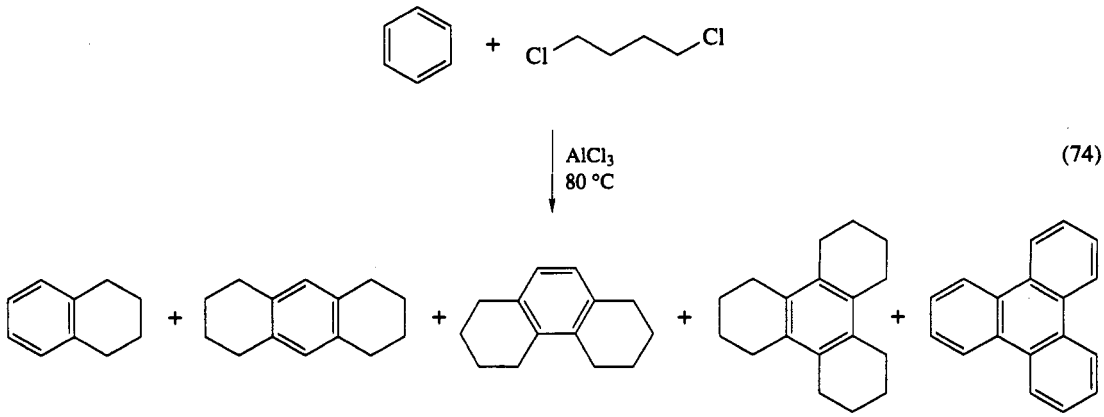
Friedel–Crafts alkylations with higher dihaloalkanes generally give a mixture of products derived from processes such as isomerization, multiple addition and dehydrogenation (caused by $AlCl_3$), as seen from the examples shown in equations (73)[124] and (74).[125]



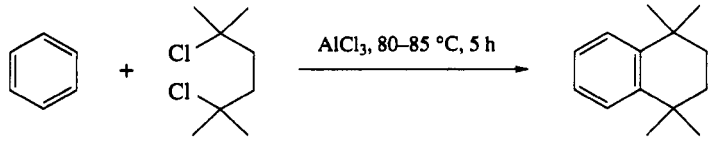
(73)

Ransley[126] has examined in detail the $AlCl_3$-catalyzed alkylation of benzene with a series of α,ω-dichloroalkanes, and suggested possible mechanisms for the formation of the various phenylated products. With 2,4-dihalohexanes as the alkylating agents for benzene, Gelin *et al.*[127] found that about 90% of the products consisted of 1,4-dimethyltetralin and compounds derived from it. The alkylation of 1,3-dimethylbenzene by 2,5-dichloro-2,5-dimethylhexane in the presence of $AlCl_3$ has been reported[128] to give a moderate yield of the tetrahydronaphthalene derivatives, as in equation (75).

Stereospecific (ranging from 15 to 60%) alkylation of benzene with optically active 1,2-, 1,3-, 1,4- and 1,5-dihaloalkanes in the presence of $AlCl_3$ has also been reported.[129] In the case of 1,3- and 1,5-dihaloal-



(74)

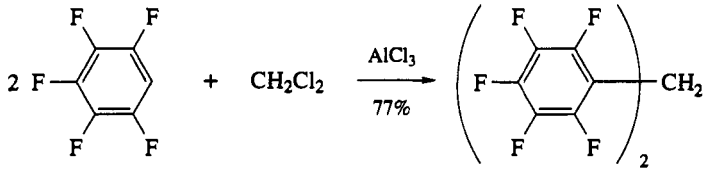


(75)

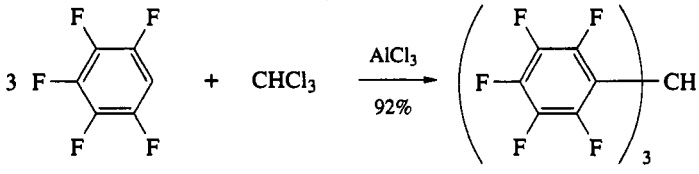
kanes, alkylation with inversion of configuration at the secondary halogen positions occurred predominantly.

Branched dihaloalkanes in general give a mixture of products resulting from processes such as isomerization and cycloalkylation. These processes in turn depend on the structure of the dihaloalkanes, the strength of the catalyst and the severity of the reaction conditions.

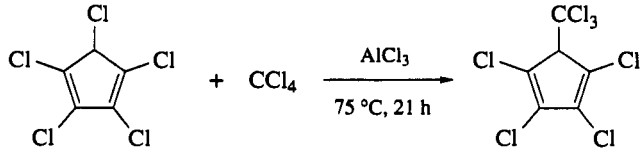
Other polyhaloalkanes, such as dichloromethane, chloroform and carbon tetrachloride, have also been used as alkylating agents. The examples in equations (76) to (79) serve to illustrate this aspect.[130–132]



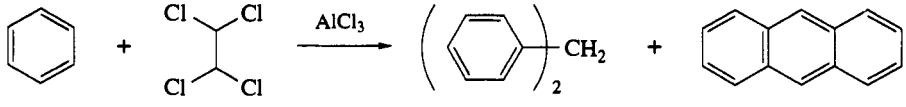
(ref. 130) (76)



(ref. 130) (77)



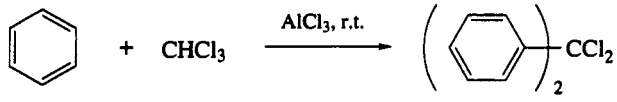
(ref. 131) (78)



(ref. 132) (79)

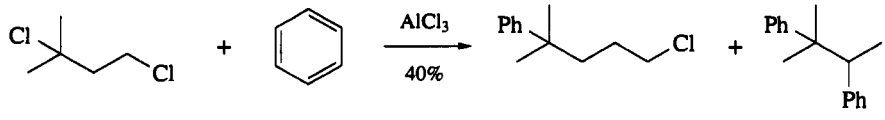
1.8.3.5 Haloalkylation

Haloalkylation of arenes by unsymmetrical or mixed halides occurs when one of the halogen atoms has a greater reactivity towards the Lewis acid catalyst. It is then possible to isolate the comparatively less reactive haloalkylated products. An example is the reaction of chloroform with benzene in the presence of $AlCl_3$. The major product (90%) is dichlorodiphenylmethane (equation 80).[133]



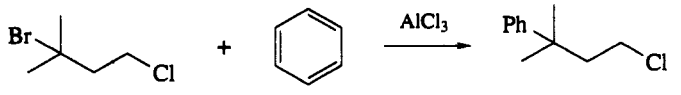
major product (80)

Haloalkylations have also been carried out with branched, unsymmetrical simple di- and poly-halides, straight-chain, unsymmetrical simple di- and poly-halides, and mixed di- and poly-halides. Schmerling *et al.*[133] have studied the Friedel–Crafts reactions of benzene with 1,3-dichloro-3-methylbutane in the presence of $AlCl_3$ and obtained a 28–29% yield of 1-chloro-3-methyl-3-phenylbutane (equation 81).

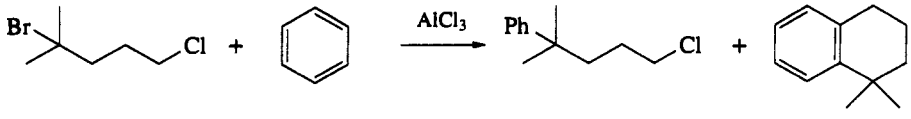


(81)

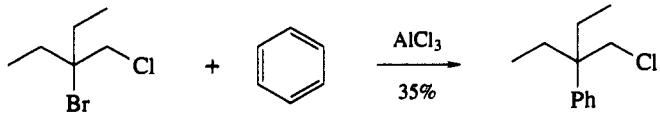
In the case of dihalides containing two different halogens, alkylation with an arene is influenced by factors such as reactivity and steric accessibility of the halogens with respect to the Lewis acid catalyst. Bugrova and Tsukervanik[134] have demonstrated this by carrying out the four reactions in equations (82) to (85). Higher reactivity of Br over Cl is seen in equations (82) and (83), and steric effects are demonstrated in equations (84) and (85).



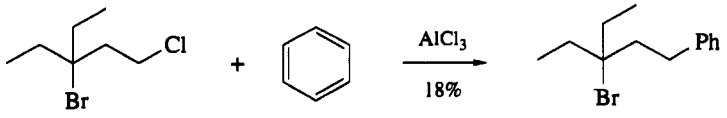
(82)



(83)



(84)



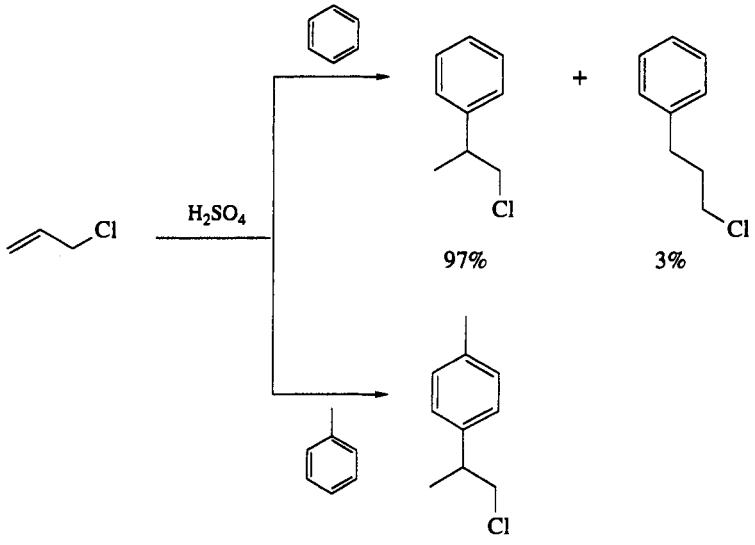
(85)

Olah and Kuhn[135] found that fluorochloro-, fluorobromo- and fluoroiodo-alkanes are effective chloro-, bromo- and iodo-alkylating agents, respectively, in Friedel–Crafts alkylations of arenes in the presence of boron halide catalysts (equation 86). Boron trihalides catalyze reactions of only the C—F bonds, but not of the C—Cl, C—Br or C—I bonds. The order of reactivity of the catalysts was found to be $BI_3 > BBr_3 > BCl_3 > BF_3$, and that of the carbon–halogen bonds C—F > C—Cl > C—Br > C—I.

$$ArH + F(CH_2)_nX \xrightarrow{BX_3} Ar(CH_2)_nX \qquad (86)$$

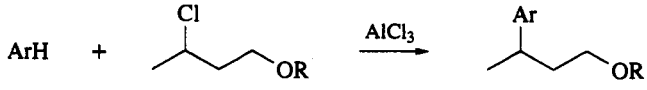
$n > 1$; X = Cl, Br, I

Allyl halides have been used to effect selective haloalkylations catalyzed by proton acids. For example, 3-chloropropylene reacts with benzene and toluene in the presence of H_2SO_4 to give haloalkylated products almost exclusively (equation 87).[136] The same result is obtained when $ZnCl_2$ is used as the catalyst.[137]



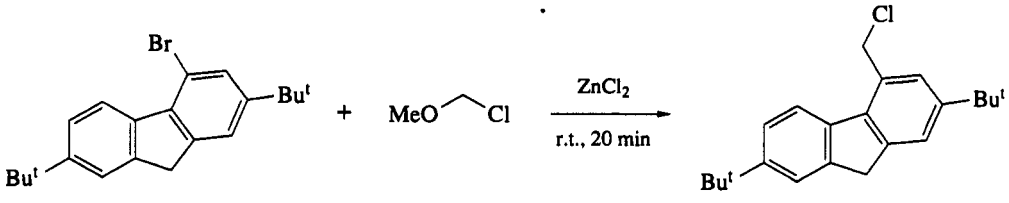
(87)

Selective haloalkylation of aromatic compounds has also been achieved by employing alkyl haloalkyl ethers as the haloalkylating agents, as seen from equations (88)[138] and (89).[139] However, the use of chloromethyl ethers in chloromethylation (equation 89) is discouraged due to the carcinogenic nature of the ether substrate. As an alternative, chloromethylation reactions can also be carried out using paraformaldehyde–HCl in the presence of $ZnCl_2$ or $SnCl_4$ as catalyst.[2]



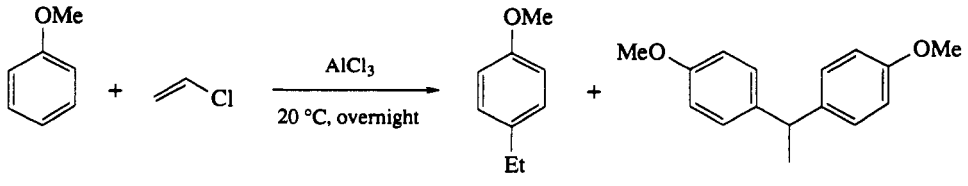
(88)

Ar = phenyl or alkylated phenyl; R = alkyl



(89)

Unsaturated alkyl halides, alcohols and ethers can also act as alkylating agents to give products derived by alkylation at one or more reactive sites. Tsukervanik and Yuldashev[140] examined the reaction of vinyl chloride with toluene and anisole in the presence of $AlCl_3$ by varying the ratio of reactants. For example, with anisole (equation 90) two products were formed. The diarylated product resulted from reaction of anisole with both reactive centers in vinyl chloride.

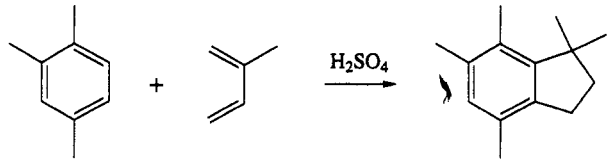


(90)

The nature of the catalyst also influences the course of the reaction. α-Substituted vinyl halides react more selectively with arenes to give diarylated products.

Allyl alcohols and ethers also react with arenes in the presence of Lewis and Brønsted acid catalysts to give alkylated products. The nature of the product depends upon the nature of the Lewis acid. However, in most cases the products are mixtures of regioisomeric allylated arenes.

Dienes also can alkylate arenes to give products which are generally cyclic. For example, isoprene reacts with 1,2,4-trimethylbenzene in the presence of H_2SO_4 to give an indane derivative (equation 91).[141] A large number of phenols have been used for alkylations with dienes. The products are either allylated phenols, or products derived by further ring closure of the phenolic oxygen with the side chain derived from the diene.

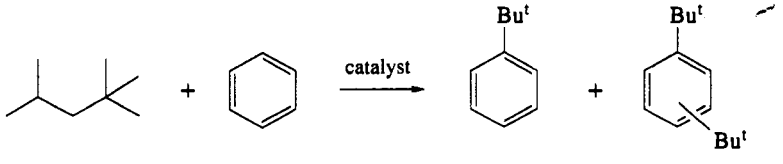


(91)

1.8.3.6 Alkylation with Alkanes

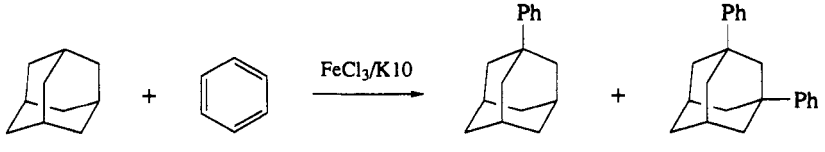
Friedel–Crafts alkylation of arenes with alkanes was studied extensively by Olah and coworkers[142a] as part of the general investigation of electrophilic reactions at single bonds. Benzene was alkylated with C_1–C_5 alkanes, alkane–alkene, and alkane–alkylbenzene mixtures in the presence of anhydrous HF–SbF_5 ($HSbF_6$). Products arising from alkylation by the alkanes as well as side reactions, such as isomerization and disproportionation, were observed. In the presence of added alkene, greater amounts of both alkane and alkene alkylation products resulted. When a *t*-alkylbenzene was present, products deriving from both transalkylation and alkylation by the alkanes were obtained. Kröger and coworkers[142b] studied the alkylation of benzene with cyclohexane in the presence of catalysts such as HBr–$AlBr_3$, HCl–$AlCl_3$ and HF–SbF_5, with isobutane as the promoter, under varying temperatures and reaction times. Four representative groups of hydrocarbons were found including cycloalkylbenzenes, substituted indanes or tetralins, C_1–C_6 alkylbenzenes and isomeric dicycloalkyls. Their formation was explained by a competition between alkylation (with or without isomerization), ring fission with cycloalkylation or fragmentation, and self-alkylation. Phenylcycloalkyl cations and phenylalkyl cations were proposed as intermediates. Mechanisms for the formation of complex product mixtures were also discussed.

Miethchen *et al.*[143] have carried out ultrasound-induced alkylation of benzene with 2,2,4-trimethylpentane in the presence of various highly acidic catalysts such as CF_3SO_3H–SbF_5, $H[B(SO_3CF_3)_4]$, $AlBr_3$, HF–TaF_5, HF–NbF_5 and HF–TiF_4 (equation 92). The effect of temperature and duration of the reaction on the yield and composition of *t*-butylbenzene and di-*t*-butylbenzenes was also determined.



(92)

Laszlo and coworkers[144] achieved the direct arylation of adamantane by employing $FeCl_3$-doped K10 montmorillonite (equation 93). Depending upon the amounts of adamantane, $FeCl_3$, the catalyst and the reaction time, varying proportions of mono- and di-arylated adamantanes were obtained. The results were taken to support the intermediacy of a 1-adamantyl cation.

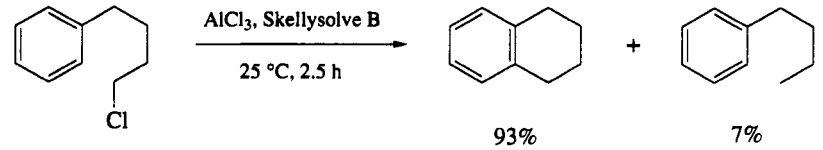


(93)

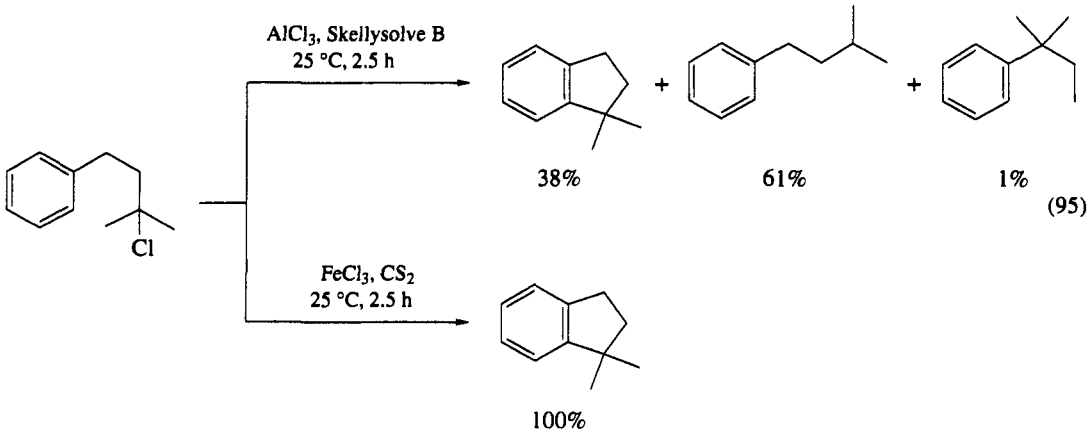
1.8.3.7 Cycloalkylation

A Friedel–Crafts cycloalkylation reaction occurs intramolecularly when an aryl-substituted monofunctional compound cyclizes to attach a new ring to the aromatic nucleus. In many instances, this process occurs during the course of the reaction between a difunctional alkylating agent and an aromatic compound — the intermediate arylated monofunctional compound subsequently undergoes cycloalkylation. However, only those cycloalkylation reactions involving intramolecular ring closures will be discussed at length here.

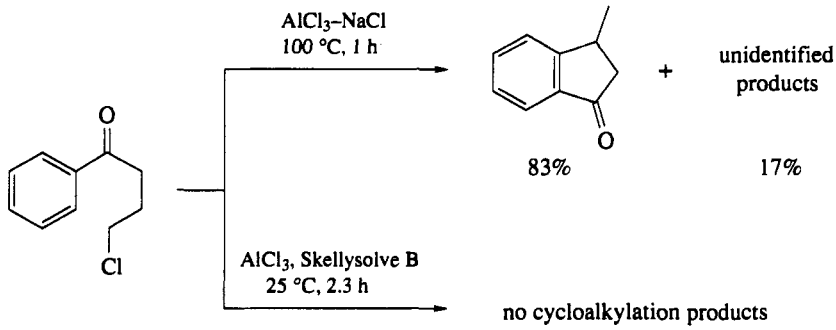
Arylalkyl halides undergo cycloalkylation reactions in the presence of a variety of Lewis acids. Depending upon the nature of the Lewis acid, varying amounts of cycloalkylated and other products can be obtained. Equations (94) to (96) show some cycloalkylation reactions of arylhaloalkanes.[145]



(94)

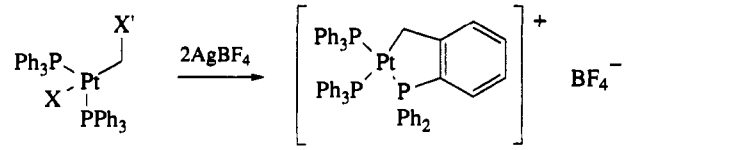


(95)



(96)

Yang and Young[146] have observed a novel Friedel–Crafts metallocyclization of halomethyl(arylphosphine)platinum(II) complexes (**30**) in the presence of $AgBF_4$ and a triarylphosphine to afford cationic metallacyclic species (**32**; equation 97).



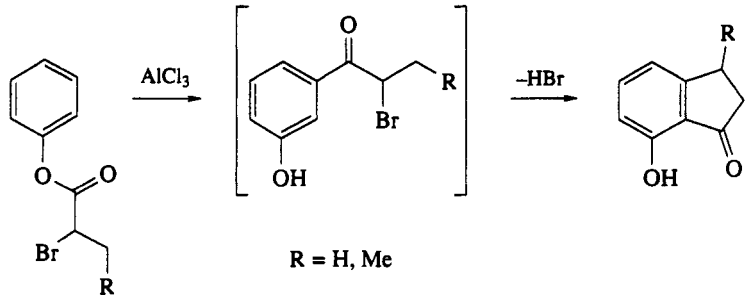
(97)

X = X' = I
X = I or Br; X' = Cl

(**32**)

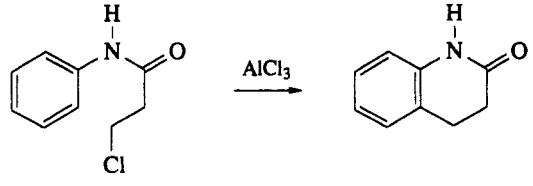
Cycloalkylations with primary and secondary phenylalkyl chlorides are often accompanied by rearrangements. The ease of formation of a six-membered ring (tetralin derivative) is much greater than that of a five-membered ring (indane derivative), based on entropy and strain factors. Khalaf and Roberts[147] have performed stereochemical studies on cycloalkylation reactions to determine the effect of stereochemistry and steric factors in the formation of six-membered rings.

Aryl esters such as those of α-halopropionic and α-halobutyric acids undergo cycloalkylation reactions, probably *via* preliminary Fries rearrangement to β-halohydroxy ketones, giving the corresponding substituted indanones (equation 98).[148]

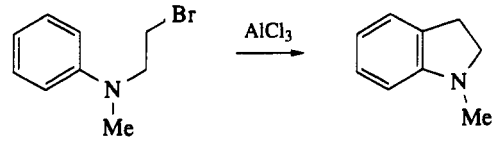


(98)

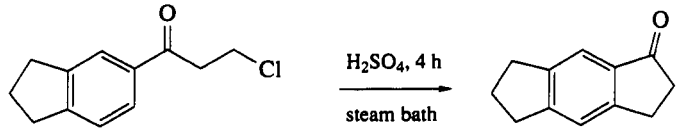
Similarly, arylalkylamides, haloalkylarylamines, haloalkylaryl ketones and haloalkyl ethers undergo Friedel–Crafts cycloalkylation to give six- or five-membered ring closure products. Representative examples of these reactions are shown in equations (99) to (103).[150–154] An excellent review by Bradsher[149] on the cycloalkylation of arylcarbonyl compounds is available.



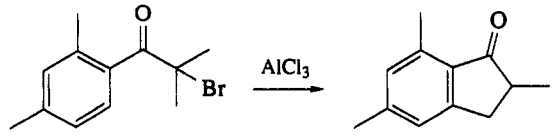
(ref. 150) (99)



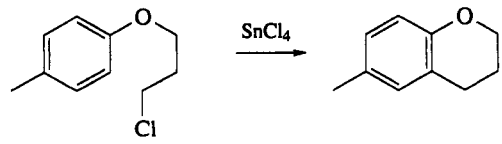
(ref. 151) (100)



(ref. 152) (101)

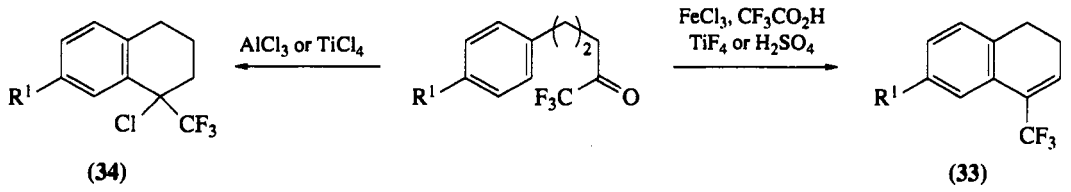


(ref. 153) (102)



(ref. 154) (103)

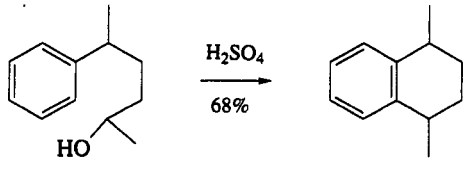
Charpentier-Morize and coworkers[155] have developed conditions for the cycloalkylation of γ-aryl-α-trifluoromethyl ketones selectively to either the cycloalkene (**33**) or the cycloalkyl chloride (**34**; Scheme 12) by varying the catalyst.



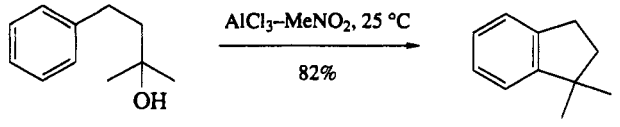
(34) (33)

Scheme 12

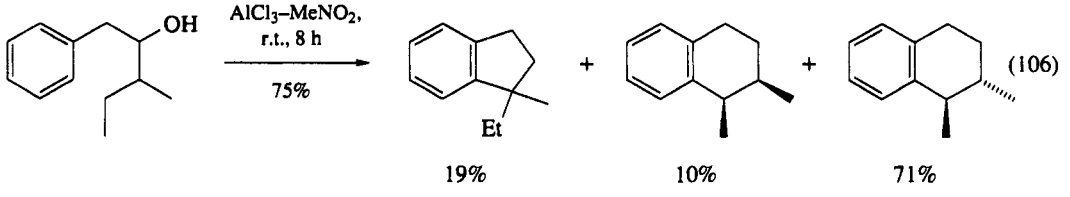
Cycloalkylations of arylalkanols and related systems are very well known in the literature. Many of the earlier examples were fraught with ambiguities in terms of product identification. However, Khalaf and Roberts[156] have carefully investigated an extensive series of variously substituted arylalkanols to help clear the ambiguities and provide more insight into the mechanism. Some examples from their study are shown in equations (104) to (106).



(104)



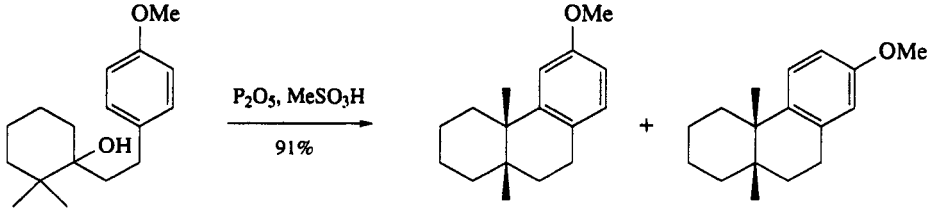
(105)



(106)

19% 10% 71%

The cycloalkylation reactions of suitable arylalkyl carbinols leading to tricyclic diterpenoids have been examined for their synthetic and mechanistic significance,[157] and the syntheses of some octahydrophenanthrenes, such as in equation (107), have been reported.

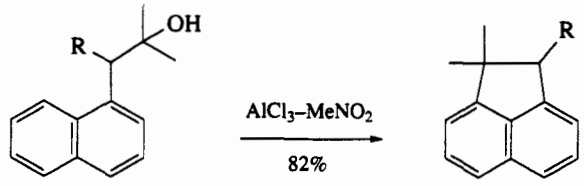


(107)

Khalaf and coworkers[158] have described a facile synthesis of substituted acenaphthenes (equation 108), and Sharma *et al.*[159] have reported a synthesis of the precursor for 8-methylbenzo[*j*]fluoranthene using the cycloalkylation of an arylalkylcarbinol precursor (equation 109).

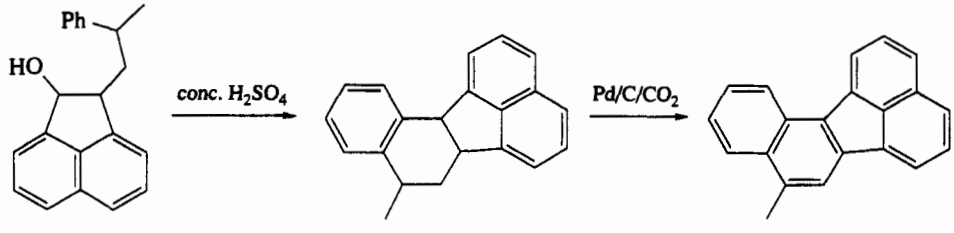
Khalaf and coworkers[160] recently reported an interesting case of carbonyl retardation of cycloalkylation of the enone (**35**) in the presence of $AlCl_3$. The isomeric enone (**36**), however, reacted to give the perinaphthenones (**37**) and (**38**) (Scheme 13). Numerous other examples of cycloalkylation reactions of aryl-substituted enones exist in the literature.

The cycloalkylations of arylalkyl epoxides were studied in detail by Taylor and coworkers,[161] in view of their applications[162] in natural product synthesis. Equation (110)[161a] shows an example of this reaction.

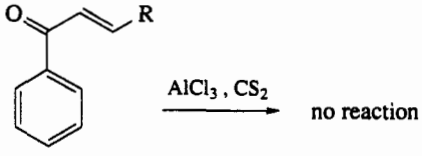


(108)

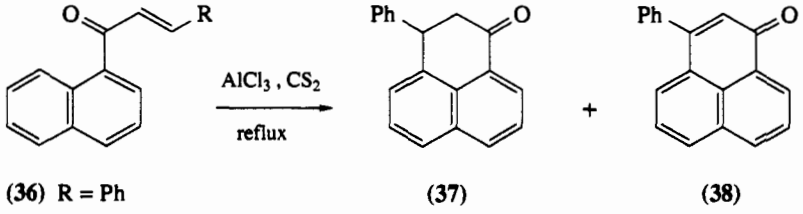
R = H, Me



(109)

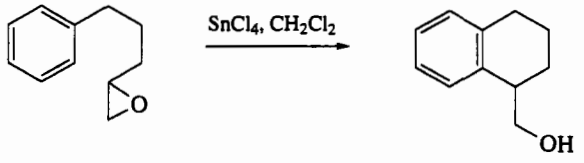


(35) R = Ph, 1-naphthyl



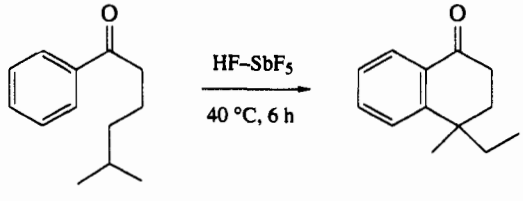
(36) R = Ph **(37)** **(38)**

Scheme 13



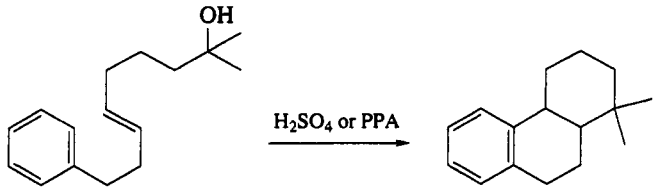
(110)

Superacids such as $HF–SbF_5$ have been used to cyclize alkyl phenyl ketones to the corresponding tetralone derivatives in good yield, as shown by the example in equation (111).[163]

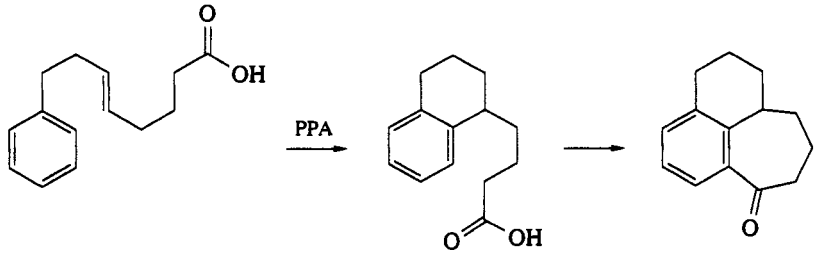


(111)

Multiple intramolecular ring closures of aryl-substituted unsaturated long chain alcohols, acids, acid chlorides and ethers in the presence of Friedel–Crafts catalysts have been extensively employed to synthesize polynuclear hydroaromatic hydrocarbons and polycyclic ketones. This is illustrated by two examples shown in equations (112)[164] and (113).[165] The application of stereospecific cycloalkylations in approaching the synthesis of complex organic molecules has been reviewed by Barclay.[166]

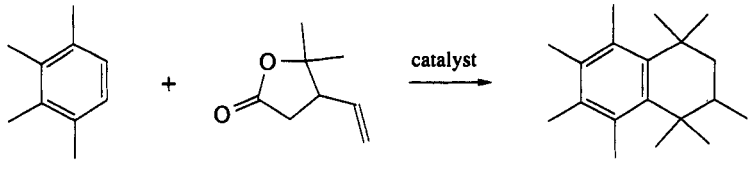


(112)



(113)

As pointed out earlier, cycloalkylation reactions can also result from the reaction of arenes with bifunctional alkylating agents or in cases where bifunctional intermediates are involved. An example of the former is shown in equation (114),[167] where a chiral, lactone-substituted alkene cyclizes with the arene to produce a chiral tetrahydronaphthalene derivative.



(S) *(R)*

(114)

1.8.3.8 Transalkylation, Isomerization, Disproportionation and Dealkylation

The general process of transfer of alkyl groups between aromatic rings is called transalkylation. When an alkylbenzene is converted into a mixture of benzene and dialkylbenzene which may further afford a trialkylbenzene, the process is termed disproportionation. Dealkylation of an alkylbenzene is a process where an alkyl group is removed to form the corresponding alkane. The isomerization of di- or polyalkylbenzenes refers to the process where the alkyl groups on the ring change their relative orientations. Such a process can occur either in an inter- or an intra-molecular fashion depending on the nature of the alkyl groups on the ring.

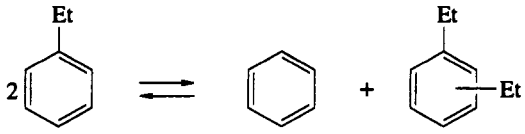
Transalkylation of alkylbenzenes, polyalkylbenzenes and other arenes can be brought about by a variety of catalysts including Lewis acids, Brønsted acids and various zeolites and silicates with or without being doped with various transition metals or their oxides. There has been a particularly explosive growth in the volume of literature pertaining to the use of various natural and modified zeolites. Recent developments include the study and applications of shape-selective catalysis by zeolites. Much of the work is patented, and largely applies to industrial processes.

Friedel–Crafts alkylation reactions are, in general, accompanied by isomerization processes. Olah *et al.*[168] reported the results of the water-promoted, $AlCl_3$-catalyzed isomerization of *o*-, *m*- and *p*-di-*t*-butylbenzene. No *ortho* isomer was present in the equilibrium mixture. The isomerization of *o*-di-*t*-butylbenzene was very rapid largely due to relief of steric strain. In these and other related sterically hindered arenes, intramolecular isomerization and not dealkylation was observed. Isomerization of di- and mono-methylnaphthalenes, catalyzed by HF–BF_3, was also reported.[169] Isomerization of *n*-alkyltoluenes and -xylenes, catalyzed by $AlCl_3$ at room temperature, afforded chiefly *m*-*n*-alkyltoluenes and *m*-*n*-alkylxylenes, respectively.[170] The process leading to the *meta* isomer has a lower energy than the other processes.

Due to the greater industrial importance of benzene and xylenes than toluene, a large number of studies have concentrated on the transalkylation and disproportionation of these two arenes.

Camacho *et al.*[171] have found that during the alkylation of benzene with ethylene in the presence of $AlCl_3$ as the catalyst, both alkylation and transalkylation (of the produced ethylbenzene) occur simulta-

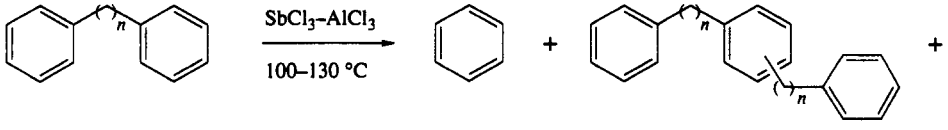
neously. They also found that the ethylene absorption rate was almost constant when the concentrations of polyalkylates higher than diethylbenzene (formed as in equation 115) were negligible.

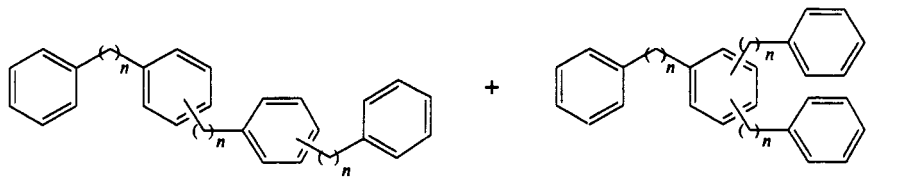


(115)

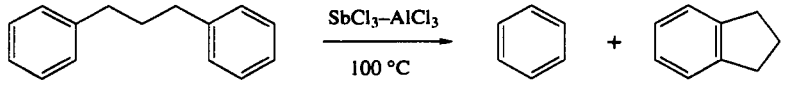
Among alkylarenes, methylarenes are unique in that they may undergo intramolecular isomerizations without any observable transalkylations. The other alkylarenes such as ethyl-, *n*-propyl- and *n*-butyl-benzenes, however, undergo isomerization and disproportionation reactions without rearrangements in the alkyl side chains. The mobilities of the alkyl groups in alkylbenzenes were measured using ^{14}C-labeling techniques,[172] and showed the ethyl group to have higher mobility than other *n*-alkyl groups. However, recent studies[173] on the transalkylations of *p*-ethylalkylbenzenes with ^{14}C-labeled benzene, using $AlBr_3$ as catalyst, revealed no marked difference in the mobilities of the ethyl and the other alkyl groups. Reactivity–selectivity relationships in the transalkylation of monoalkylbenzenes revealed an inverse sense for electrophilic reagents.[174] The mechanism and product distribution during the transalkylations of toluene[175] and alkyl and dialkylarenes[176] catalyzed by ZSM-5 zeolites have been discussed. The significance of shape-selective catalysis occurring in these processes was also pointed out. Again, it must be emphasized that ZSM-5 exhibits high *para* selectivity, and this property has been utilized for the production of aromatics such as *p*-xylene and *p*-ethyltoluene.

Buchanan *et al.*[177] conducted model studies on the hydrocracking of coal by studying in detail the action of $SbCl_3$ melts with (and in some cases without) $AlCl_3$ on α,ω-diphenylalkanes. They observed selective sp^2–sp^3 bond cleavage for the four classes of diphenylalkanes studied, as shown in equations (116) to (118). Notably, 1,3-diphenylpropane and 1,4-diphenylbutane gave only the indan and tetralin derivatives, respectively.

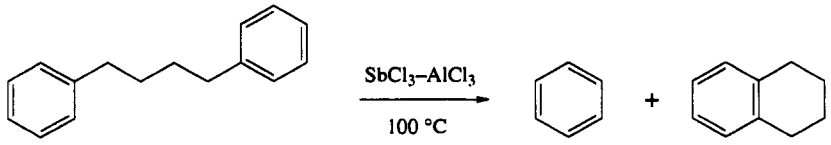




(116)



(117)



(118)

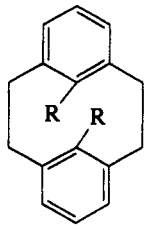
Besides the transarylalkylation reactions described above (equation 116), debenzhydrylation and transbenzhydrylation reactions are also well known, and these have been extensively reviewed.[178] Applications of the benzhydryl group as a protective group have also been discussed.

Transalkylation reactions of simple aromatics such as benzene and toluene with various coals have proved to be a valuable means of investigating the composition and structural features of coal.[179]

Wu and Leu,[180] and Bursian *et al.*[181] have carried out disproportionation and transalkylation of toluene with pseudocumene, using various modifications of mordenite zeolite catalysts. The disproportionation

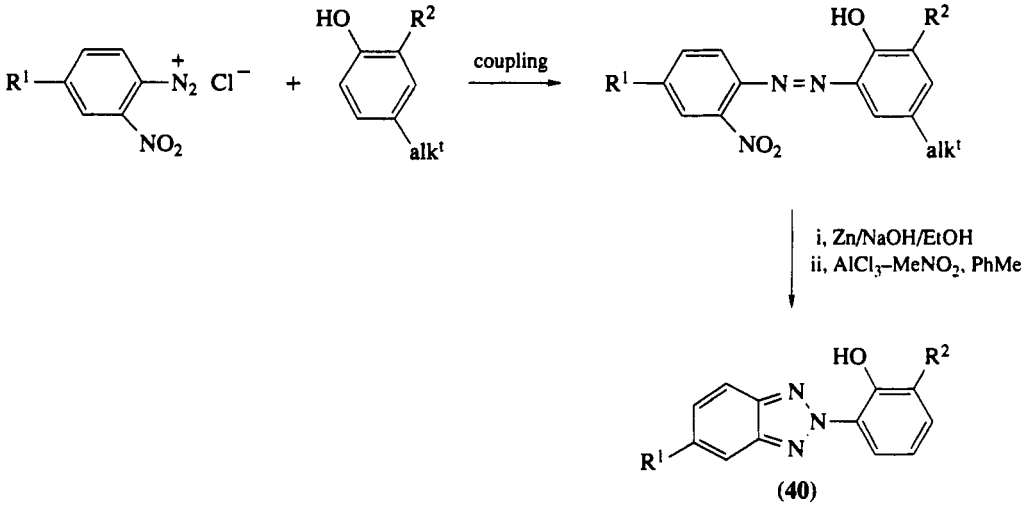
of *o*- and *p*-cresol, and the transmethylation between isomeric xylenols and phenol have been examined using a chromia–alumina catalyst.[182] It was found that *p*-cresol underwent disproportionation more readily than *o*-cresol, whereas *m*-cresol did not undergo this reaction. Also 2,6-, 2,4- and 3,4-xylenols underwent transalkylation reactions with phenol, whereas 3,5-xylenol did not. Mechanistic interpretations for these observations were also given. Transalkylation of phenol with ethyl- and isopropyl-benzene and ethyltoluene has also been reported.[183]

Trans-*t*-butylation and de-*t*-butylation reactions are facile processes, and form the basis of many applications of the *t*-butyl group as a positional protective group. This aspect was well reviewed by Tashiro,[88] and is also discussed in Section 1.8.3.2. Tashiro and coworkers[184] have more recently applied the trans-*t*-butylation and de-*t*-butylation reactions to prepare metacyclophanes (**39**) and related compounds.



(**39**) R = Me, OH, F

Olah *et al.*[185] showed Nafion-H to be a very efficient de-*t*-butylation agent for aromatic compounds, and Rosevear and Wilshire[186] have applied the trans-*t*-butylation reaction to the synthesis of a variety of ultraviolet absorbers of the general structure (**40**), as shown in Scheme 14.



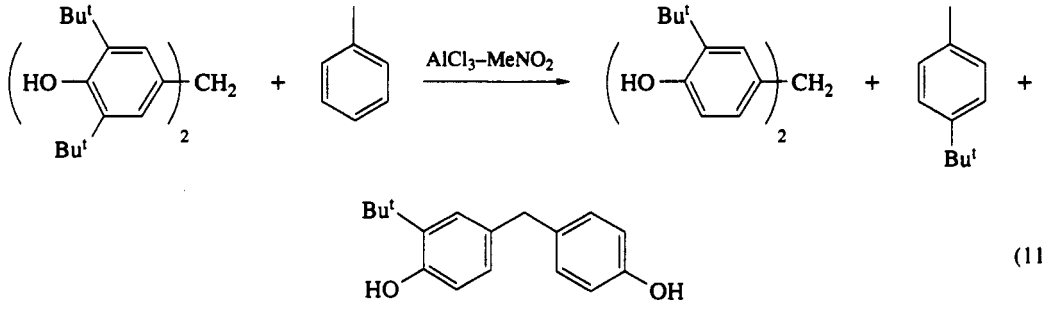
(**40**)

Scheme 14

Transbenzylation reactions are also used on occasion for deprotection as seen from the reaction shown in equation (119).[187]

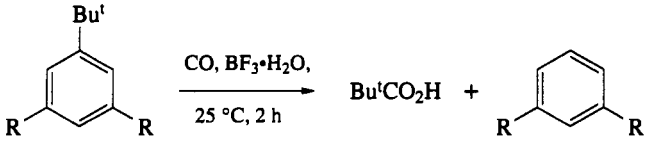
In 1937, Ipatieff and Pines[188] found that the ease of dealkylation of alkylbenzenes in the presence of $AlCl_3$ at 65–80 °C to give the corresponding alkane decreased in the order of the side chains: *t*-butyl > *s*-butyl > isopropyl. Ethyl and methyl groups were not cleaved.

From their studies on dealkylation of alkylbenzenes with $AlCl_3$ at 100 °C, Roberts *et al.*[189] found that, in general, the catalyst and experimental conditions required to produce dealkylation are forceful enough to effect several other reactions, such as disproportionation, isomerization, rearrangement of the side chain and fragmentation. The latter refers to a process in which the alkylbenzene affords alkanes and alkylbenzenes with fewer carbons than those in the original alkyl side chain. Formation of alkanes in the dealkylation process can take place even in the absence of an added hydride donor agent. In this case, a second molecule of the alkylbenzene acts as the hydride donor.



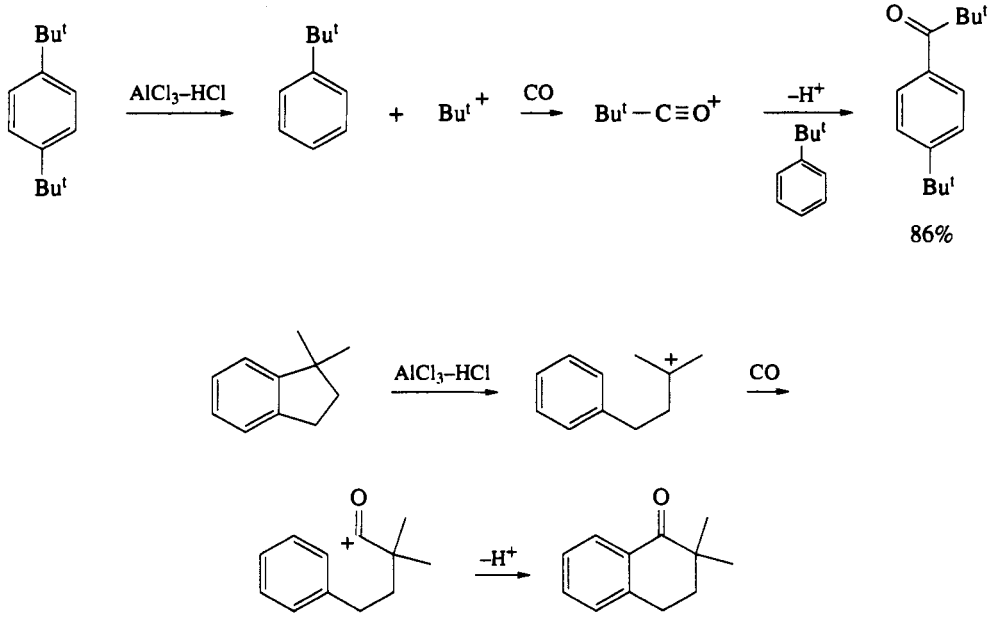
(119)

Due to the ease of dealkylation of *t*-alkylbenzenes, such as *t*-butylbenzene, some interesting applications of this process in both the synthetic and mechanistic areas have resulted. The intermediacy of the *t*-butyl cation was hinted to account for the observed products. Thus, Knight *et al.*[190] obtained excellent yields of pivalic acid by dealkylating *t*-butylbenzene and 1,3-dimethyl-5-*t*-butylbenzene in the presence of carbon monoxide and $BF_3{\cdot}H_2O$ as the catalyst (equation 120). They also found that H_3PO_4, H_2SO_4 and $MeSO_3H$ were ineffective for the dealkylation–carbonylation of *t*-butylbenzene.



(120)

Brouwer[191] and Olah *et al.*[192] obtained direct evidence for the *t*-butyl cation intermediate by ^1H NMR studies of *t*-butylbenzene in superacid solutions at low temperature. Fărcasiu and Schlosberg[193] demonstrated that, in the presence of carbon monoxide, the *t*-alkyl cation generated *in situ* from the dealkylation of a tertiary alkyl arene resulted in acylation of the dealkylated arene, as shown in Scheme 15.

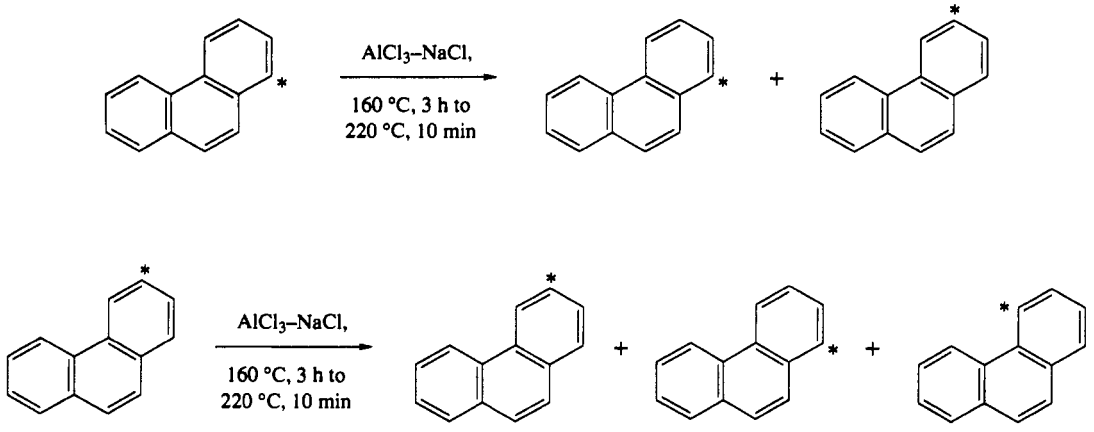


Scheme 15

Olson and Haag[194] observed a high selectivity for xylene isomerization *versus* disproportionation in the presence of ZSM-5 zeolite, and ascribed it to a transition state selective process rather than shape-selective diffusion. They were also able to produce *p*-xylene in high selectivity (up to 80%) from toluene disproportionation by using suitable modifications of the ZSM-5 catalyst. This selectivity was said to

arise from shape-selective diffusion due to the unique pore size of the catalyst. Ratnasamy *et al.*[195] reported that shape-selective zeolites isomerized *m*-xylene to *p*- and *o*-xylene with higher selectivities.

Balaban *et al.*[196] have reported the catalytic automerization of [1-^{13}C]- or [3-^{13}C]-phenanthrene in the presence of a 1:1 mixture of $AlCl_3$–NaCl. They found that [1-^{13}C]phenanthrene transferred part of the label to C-3, but [3-^{13}C]phenanthrene transferred the label to two positions, *i.e.* mainly C-1 and to a lesser extent C-4, as shown in Scheme 16. Possible reaction mechanisms to account for these observations were also proposed.



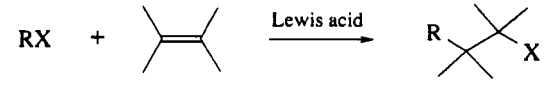
Scheme 16

1.8.4 ALKYLATION OF ALKENES

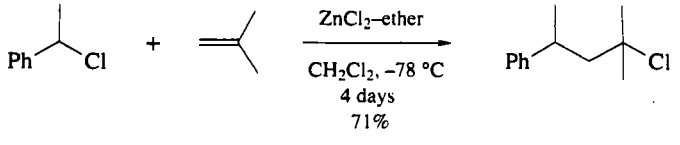
Ipatieff and coworkers[197] carried out the first alkylation with alkenes and branched and normal chain alkanes (except methane and ethane) in the presence of $AlCl_3$ as the catalyst. The sulfuric acid catalyzed alkylation reaction of arenes and isoalkanes, developed in 1938, is a still widely used industrial process[198] to produce alkylates with high octane numbers. For synthetic applications, however, Friedel–Crafts-type alkylations of alkenes and alkanes have limited value since they tend to give mixtures of products, including oligomers of alkenes.[199]

Oligomerization of aliphatic alkenes such as ethylene and propene, and aromatic alkenes, such as styrene, indene and their derivatives, catalyzed by a variety of Lewis acids, such as $AlCl_3$, BF_3, $AlBr_3$, and Brønsted acids, such as H_3PO_4, is a well-studied subject.[199] These reactions are important, particularly in the industrial arena.

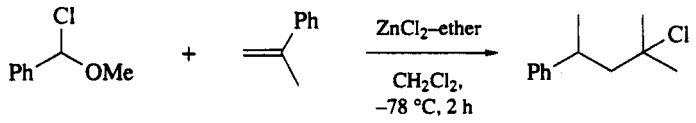
Olah and coworkers,[200a] and Mayr and Striepe[200b] discussed the scope and limitations of aliphatic Friedel–Crafts alkylations. In particular, they considered factors that would favor reactions of the type shown in equation (121), where an alkene is alkylated by an alkyl halide.[201] They reasoned that formation of the 1:1 addition products (**42**) can be expected, if (**41**) reacts faster with the alkene than (**42**), otherwise higher addition products will be formed. Mayr[202] suggested that the relative dissociation rates of (**41**) and (**42**) induced by the Lewis acid should reflect their relative rates of addition to a common alkene. Furthermore, it was assumed that the solvolysis rates in 80% ethanol were proportional to the Lewis acid induced dissociation constants. A few examples where good yields of alkylated (addition) products were obtained are shown in equations (122) and (123).



(41) (42) (121)



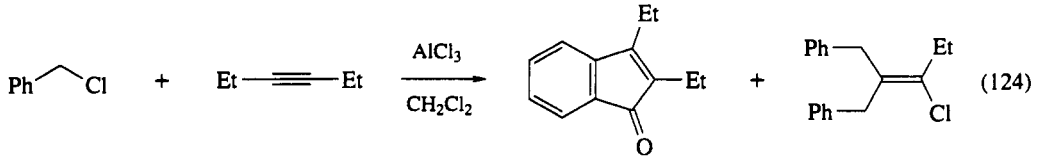
(122)



(123)

1.8.5 ALKYLATION OF ALKYNES

The benzylation reaction of 3-hexyne with benzyl chloride was reported to give a mixture of *cis* and *trans* addition compounds and 2,3-diethylindenone (equation 124).[203] It was found that in high polarity solvents the yield of the *trans* addition compound and of the indenone increased. An ionic mechanism was suggested to account for the *trans* addition compound, and a more covalent complex or ion pair to account for the *cis* isomer.

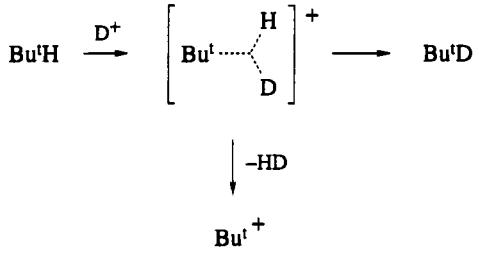


(124)

1.8.6 ALKYLATION OF ALKANES

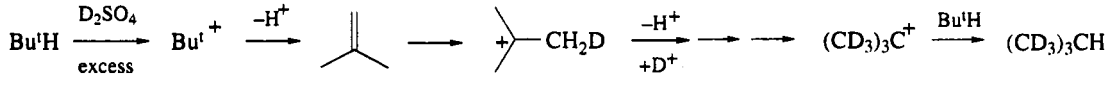
The electrophilic alkylation of alkanes using superacidic catalysts, allowing elimination or minimization of any equilibrium with related alkenes, has been successfully studied.[204,205] These alkylations demonstrate the difference between conventional acid-catalyzed alkylations, where alkenes always play a key role in the reactions, and superacidic chemistry which allows carbocationic reactions with the alkanes themselves.

The nonexistence of alkane–alkene equilibrium in superacid medium has been elegantly demonstrated by the behavior of isobutane in deuterated superacid medium (DSO_3F–SbF_5 or DF–SbF_5).[206] Isobutane at low temperature undergoes hydrogen–deuterium exchange only at the methine position through the involvement of a three-center bound pentacoordinate carbonium ion (Scheme 17).



Scheme 17

On the other hand, Otvos *et al.*[207] showed that acid treatment (D_2SO_4) of isobutane effects hydrogen–deuterium exchange at the methyl groups, involving isobutene as an intermediate. They suggested that under the reaction conditions a small amount of *t*-butyl cation is formed in an oxidative step which deprotonates to isobutene. The reversible protonation (deuteration) of isobutene is responsible for the H–D exchange on the methyl hydrogens, whereas tertiary hydrogen is involved in intermolecular hydride transfer from unlabeled isobutane (at the CH position, see Scheme 18).



Scheme 18

Olah and coworkers[34,208] have observed that alkyl fluoride–SbF_5 complexes, such as $MeF{\cdot}SbF_5$ and $EtF{\cdot}SbF_5$, or stable prepared alkylcarbenium hexafluoroantimonate salts directly alkylate alkanes (equations 125 and 126).

$$Bu^tH + EtF{\rightarrow}SbF_5 \longrightarrow Bu^t \qquad (125)$$

$$Bu^tH + Pr^iH^+\ SbF_6^- \longrightarrow Bu^t \qquad + HSbF_6 \qquad (126)$$

The pathway of these alkylations was clearly demonstrated by Olah *et al.*[209] from their extensive work on the alkylation of the lower alkanes by stable carbocations under superacidic, stable ion conditions. They found that the order of reactivity of C—C and C—H bonds reflected their σ-donor abilities and was in the order: tertiary C—H > C—C > secondary C—H >> primary C—H, although various specific factors, such as steric hindrance, can influence the relative rates.

Olah and his group[210] also investigated the direct ethylation of methane with ethylene using ^{13}C-labeled methane over solid superacid catalysts, such as TaF_5–AlF_3, TaF_5 and SbF_5–graphite. A high selectivity (up to 96% of label content of C_3 fraction) for monolabeled propane ($^{13}CC_2H_8$) was observed. This clearly indicated a direct electrophilic attack of the ethyl cation on methane *via* a pentacoordinated carbonium ion, as in Scheme 19.

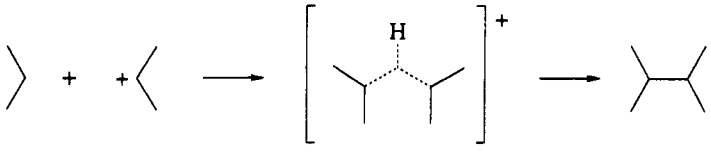
$$H_2C{=}CH_2 \xrightarrow{H^+} CH_3\overset{+}{C}H_2 \xrightarrow{^{13}CH_4} \left[\begin{array}{c} H \\ CH_3CH_2 \cdots \overset{\cdot}{C} \cdots CH_3 \end{array}\right]^+ \xrightarrow{-H^+} CH_3CH_2{}^{13}CH_3$$

Scheme 19

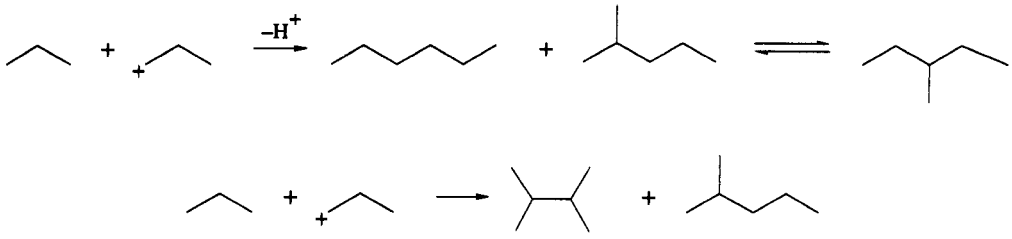
Similarly, Siskin[211a] found that when ethylene was allowed to react with ethane in a flow system, only *n*-butane was obtained. This was explained by the direct alkylation of ethane by ethyl cation through a pentacoordinated carbonium ion (equation 127). The absence of a reaction between ethyl cation and ethylene was explained by the fact that no rearranged alkylated product (isobutane) was observed.

$$H_2C{=}CH_2 \xrightarrow{H^+} Et^+ \xrightarrow{C_2H_6} \left[\begin{array}{c} H \\ Et \cdots \overset{\cdot}{C} \cdots Et \end{array}\right]^+ \qquad (127)$$

Alkylations of alkanes, such as propane, isobutane and *n*-butane, by *t*-butyl or *s*-butyl carbenium ions are always accompanied by competing hydride transfer and rearrangement processes. In general, once an incipient carbocation is produced, further alkylations and carbocation rearrangements can continue until the cation is quenched. This process constitutes a potentially powerful method of converting lower alkanes into higher alkylates in the gasoline range.[211b] Typically, these reactions are performed by first preparing the alkylcarbenium hexafluoroantimonates from the corresponding alkyl halides and SbF_5 in sulfuryl chloride fluoride as the solvent, and treating them in the same solvent with alkanes. For example, propylation of propane by the isopropyl cation gave a significant amount (26% of the C_6 fraction) of the primary alkylation product (equation 128). The C_6 isomer distribution, 2-methylpentane (28%), 3-methylpentane (14%) and *n*-hexane (32%), was very far from the thermodynamic equilibrium. This suggests that not only the isopropyl, but also the *n*-propyl cation was involved as intermediate (as shown by $^{13}C(2)$–$^{13}C(1)$ scrambling in the stable ion[212]) as illustrated in Scheme 20.



(128)

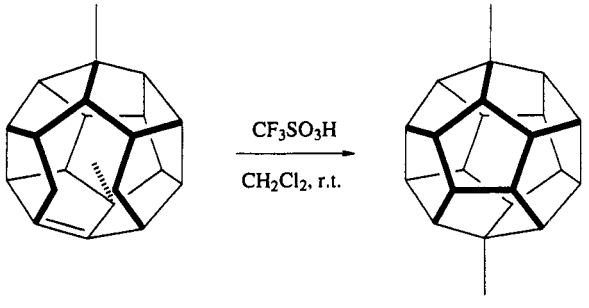


Scheme 20

Lower alkanes such as methane and ethane have been polycondensed in superacid solutions at 50 °C to yield higher alkanes.[213] Subsequently Roberts and Calihan[214] were able to prepare oligomeric and polymeric alkanes with molecular weights of up to 700 by direct condensation of C_1 to C_4 alkanes over the superacid FSO_3H–SbF_5 at room temperature. Alkylation of adamantane with lower alkenes (ethylene, propene and butenes) catalyzed by CF_3SO_3H or CF_3SO_3H–$B(O_3SCF_3)_3$ was studied recently by Olah *et al.*[215] A number of potential processes[216] were developed to use natural gas instead of pure methane in the alkylation of methane by alkenes. When natural gas is dehydrogenated, the C_2–C_4 alkanes it contains are converted into alkenes. The resulting methane–alkene mixture can then, without separation, be passed through a superacid catalyst resulting in exothermic alkylation condensation.

Isomerizations of alkanes catalyzed by superacidic media are very important reactions, particularly in the industrial arena. Conversion of linear C_5–C_8 alkanes to their branched counterparts substantially improves their combustion properties. The isomerization of *n*-butane to isobutane is of great importance because isobutane reacts under mildly acidic conditions with alkenes to give highly branched hydrocarbons in the gasoline range.[217] Various difficulties are encountered in handling liquid superacids and in separating the product from the catalyst. Solid superacids, such as SbF_5–intercalated graphite, SbF_5–SiO_2–TiO_2 and TiO_2–ZrO_2–SbF_5 have proved to be very efficient catalysts for the isomerization of alkanes and resulted in easy product separation.

The isomerization of a large number of isomeric tricyclic C_{10} hydrocarbons under Lewis acid catalysis gives the unusually stable isomer adamantane.[218] This unusual reaction was originally developed by Schleyer.[219] The method since has been adopted in the synthesis of diamantane and triamantane from the appropriate C_{14} and C_{18} precursors.[220] Olah *et al.*[221] extended this reaction by isomerizing a series of $C_{4n+6}H_{4n+12}$ (n = 1–3) polycyclic precursors to diamondoid hydrocarbons using superacidic catalysts[221a] as well as the $NaBH_4$–CF_3SO_3H reagent, which is used as a reagent for mild reductive isomerizations.[221b] Paquette's synthesis[222] of 1,16-dimethyldodecahedrane (**44**) from the alkene (**43**) involved a superacid-catalyzed isomerization (equation 129).

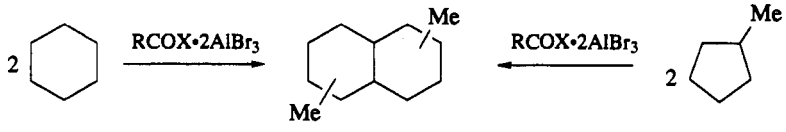


(129)

(**43**) (**44**)

Vol'pin *et al.*[25] found that complexes of the type $RCOX{\cdot}2AlX_3$ (termed aprotic organic superacids)[25] are extremely reactive towards alkanes, and catalyze a variety of hydrocarbon transformations. These complexes were prepared simply by mixing 1 mol of distilled acyl halide (MeCOX, Pr^nCOX, PhCOX, *etc.*; X = Br, Cl) with 2 mol of sublimed AlX_3 (X = Br, Cl) at room temperature. The liquid $RCOX{\cdot}2AlBr_3$ and solid $RCOX{\cdot}2AlCl_3$ complexes were stable at room temperature under anhydrous conditions. The superacidic systems appear attractive in terms of their availability, nontoxicity and ease of use. Facile coupling of C_5–C_6 cycloalkanes was observed in the presence of these catalysts. For example, high yields of isomeric mixtures of dimethyldecalins were formed when cyclohexane or methylcyclopentane were employed in excess (12:1) relative to $RCOX{\cdot}2AlBr_3$ (Scheme 21). With a

lower cycloalkane:complex ratio, acylation of the cycloalkane was observed. Mechanisms for such alkylation reactions, as well as applications of these complexes to catalyze efficiently other processes such as cracking, isomerization and ionic bromination of linear and cyclic alkanes, have been discussed.



Scheme 21

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1.9
Polyene Cyclizations

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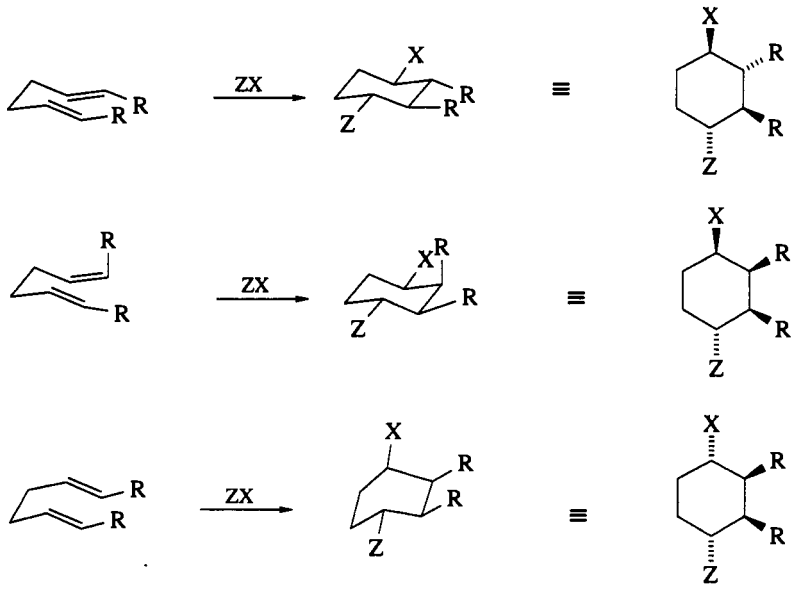
1.9.1 INTRODUCTION

Much of the early work on polyalkene cyclizations derives from the classical structural investigations on terpenes[1] and this, together with speculation concerning their biosynthesis and stereochemistry, culminated in the Stork–Eschenmoser hypothesis of 1955.[2] This postulated that polyalkenes could react in defined conformations which, in combination with antiperiplanar addition to the double bonds, allowed prediction of the relative stereochemistry of the cyclization products (Scheme 1). The attractiveness of these ideas as the basis of a general synthetic method is clear, not least because it suggests methods for forming C—C bonds between highly substituted atoms where organometallic methods are often subject to severe steric hindrance. To establish the method required the development of (a) suitable initiators for cyclization, (b) methods for the stereoselective synthesis of alkenes (Volume 1, Chapters 3.1 and 3.2) and (c) termination of cyclization by a single mechanism. Johnson's group has made major contributions to the development of polyalkene cyclization as a viable synthetic method; their earlier work has been reviewed[3] as has that of other groups.[4] There is also an excellent general review by Bartlett.[5]

In this chapter emphasis will be placed on preparatively useful procedures, the general 'rules' which pertain in polyene cyclization, and the circumstances under which the Stork–Eschenmoser hypothesis is valid. The success, or otherwise, of polyalkene cyclization depends on a complex interplay between the



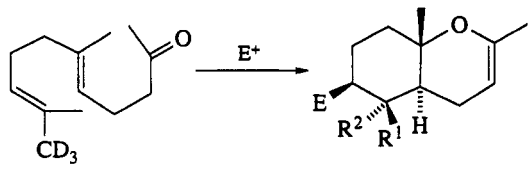
Scheme 1

method of initiation, the nucleophilicity of the double bonds involved, and the mechanism of termination. Because of this, it is rather artificial to consider these separately but still useful in a pedagogic sense. Since the mechanism of polyalkene cyclization is by no means firmly established (indeed, there is unlikely to be a unique mechanism) the process will be represented as involving 'simple' carbocations; this does not exclude concerted and part-concerted mechanisms or those involving bridged cations or π-complexes. Formulae representing racemates are drawn showing only one enantiomer. Where a single enantiomer is represented, it is described as chiral.

1.9.2 INITIATION OF CYCLIZATION

Cyclization is initiated by formation of a putative cation either by electrophilic addition to a double bond or by ionization, usually from an sp^3-hybridized carbon. Protonic and Lewis acids have been the most frequently used electrophiles but successful monocyclizations have been reported using HOBr,[6] $MeCOBF_4$,[7] $MeOCH_2BF_4$,[8] Br_2–$AgBF_4$,[9] $PhSBF_4$,[10] $PhSeBF_4$,[11] $Tl(ClO_4)_3$,[12] $Hg(OAc)_2$,[13] $Hg(OCOCF_3)_2$[14] and $HgTf_2$ (with and without $PhNMe_2$). The $Hg(OCOCF_3)_2$ reagents have been used successfully for the bicyclization of farnesol derivatives to drimnanes (Section 1.9.6.2). The Semenovskii group has shown[14] that, of the electrophiles tested, $Hg(OCOCF_3)_2$ is the only reagent which effects antiperiplanar addition to the initiating double bond; whether this is due to the bridged mercuricinium ion maintaining stereochemical integrity or a concerted cyclization is not known. Cyclization with H_2SO_4 gave a 1:1 mixture of equatorial and axial CD_3, establishing that it is a nonconcerted reaction (Scheme 2). This contrasts with the cyclization of 2,6-octadiene[15] (where a less-stable secondary cation would be the equivalent intermediate) having the characteristics of concerted protonation–ring formation (Scheme 3). PhSOMe–BF_3 and *N*-phenylselenylsuccinimide–BF_3 have also been established as initiators of bicyclizations (Section 1.9.6.2). Understandably, the electrophile-induced cyclizations are most efficient when the initial reaction occurs at the most nucleophilic double bond. However, these initiators have not been tested with a sufficient range of substrates to allow generalizations about their individual effectiveness.

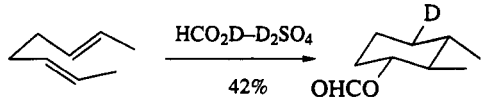
Ionization methods for production of the initiating cation have been more generally tested and shown to be ineffective at inducing cyclization at primary and secondary centers where the ion does not have additional stabilization. Acid-catalyzed cyclization of tertiary derivatives has been more successful. From a preparative viewpoint, biomimetic epoxide cleavage as a means of cyclization has been disappointing, though much useful mechanistic and structural information has been gleaned from this work, in particular that of the van Tamelen group.[4a] Certain methylcyclohexene epoxides give acceptable yields in monocyclizations[4d] but are not useful for bi- and tri-cyclizations. The most efficient general initiators of cyclization are cations which are stabilized by a heteroatom, a double bond or both. The allylic cations (**1**), (**2**), (**3**) and (**4**) introduced by the Johnson group and the acyclimonium ion (**5**) used by Speckamp

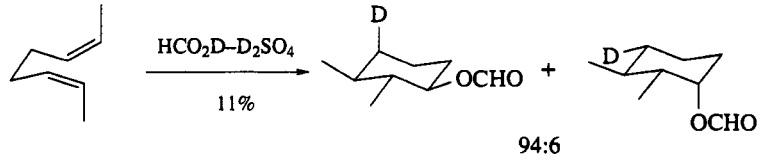


$E = HgOCOCF_3$ $R^1 = Me, R^2 = CD_3$

$E = H$ 1:1 mixture

Scheme 2

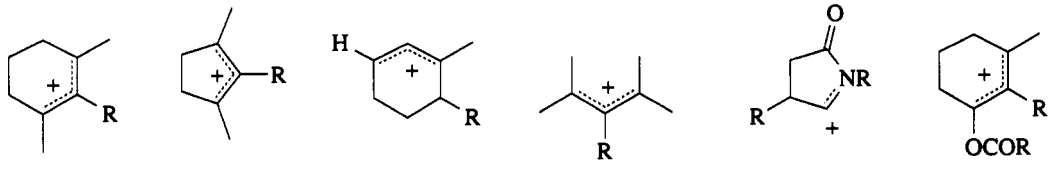




94:6

Scheme 3

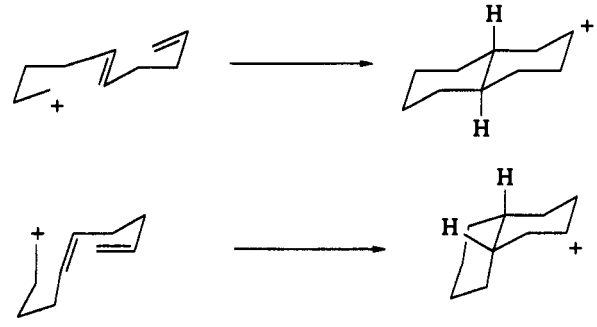
(Volume 2, Chapter 4.5) have been tested with a wide variety of substrates and shown to be efficient at inducing mono- and poly-cyclizations. The Johnson group has also used oxonium ions (derived from acetal cleavage) as initiators, in particular for preparing chiral cyclized products. Imonium[16] and acycloxallyl cations (**6**) are also useful initiators;[17] with the latter, carbon bond formation does not occur at the O-terminus. It is worth noting that the cyclopentenyl and cyclohexenyl cations with two hydrogens at the terminus are not particularly good initiators and that the trialkylated ions are preferentially attacked at the least-alkylated terminus when the choice is open. To summarize, monocyclizations can be achieved using a variety of electrophilic reagents or ionization methods, carbabi- or carbatri-cyclizations are achievable in good yield when preparing drimnane terpene derivatives; otherwise initiation of cyclization by stabilized cations is the preferred strategy.



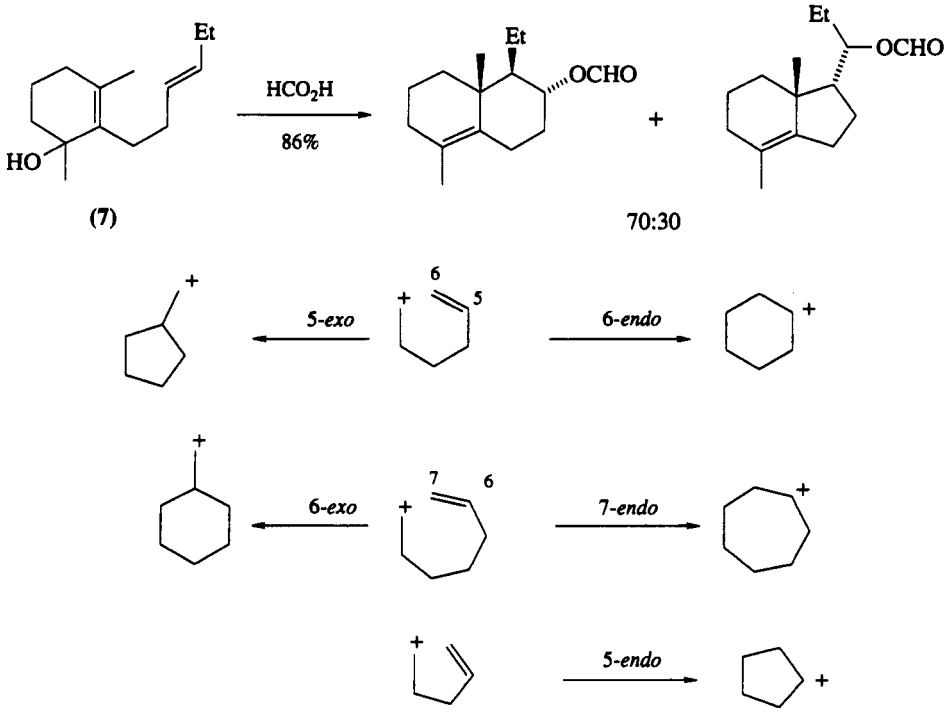
1.9.3 PROPAGATION OF CYCLIZATION

There are a host of examples of carbamonocyclizations, many bicyclizations, a substantial number of tricyclizations and a few tetracyclizations. Where cyclohexane rings are being formed, the overwhelming number of cases can be interpreted as forming *via* a chair-like transition state. Where ring junctions are formed in bi- and tri-cyclizations (Scheme 4) most examples are of (*E*)-alkenes cyclizing to form *trans*-fused rings giving the thermodynamically stable product. The corollary of the Stork–Eschenmoser hypothesis that a *cis* ring junction would form from the (*Z*)-alkene has been tested infrequently (Section 1.9.6.2). Where the comparison has been carried out, it is clear that the extent to which the hypothesis is upheld is dependent on the initiator and the nucleophilicity of the double bonds participating. Where a double bond is 5,6 to the initiating center and electronically unbiased or substituted at C-5, then 6-*endo* cyclization is almost invariably favored over the 5-*exo* mode (Scheme 5); the cyclization of (**7**) is a rare exception to this rule.[18] When there is additional substitution at C-6 polarizing the double bond, then 5-

exo cyclization is preferred; the products of cyclization can be complicated by the cyclopentylmethyl cation undergoing rearrangement following cyclization. A double bond 6,7 to the initiating center leads to 6-*exo* cyclization unless this contravenes the Markovnikov rule, in which case 7-*endo* cyclization ensues (Scheme 5). With 4,5 double bonds, 5-*endo* cyclization is seldom observed, in accord with Baldwin's rules.



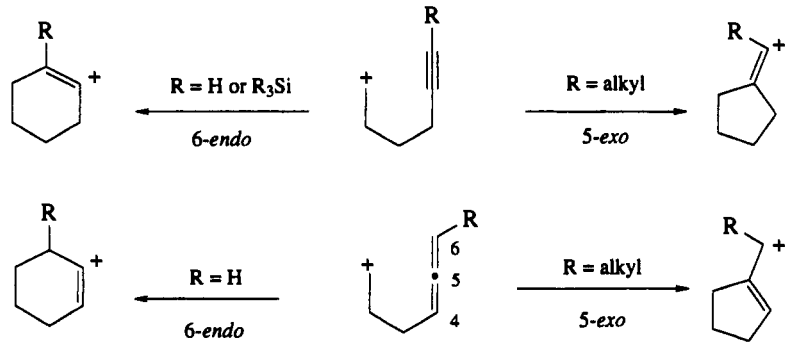
Scheme 4



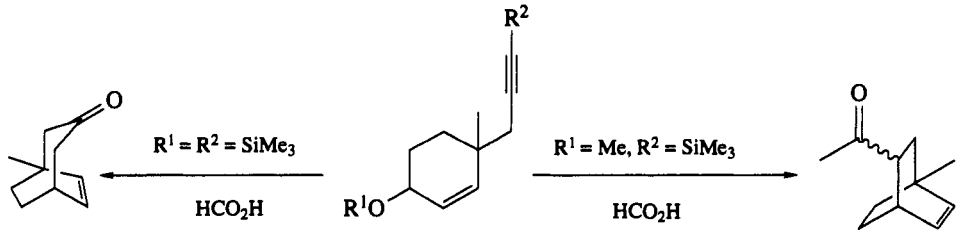
Scheme 5

Allenyl and alkynyl functions can also participate in cyclization, usually in the formation of the terminal ring. Alkynyl groups 5,6 to the cationic center cyclize 6-*endo* when the terminal group is hydrogen or silyl (Scheme 6) but dialkylalkynes have a kinetic preference for 5-*exo* cyclization though under certain conditions the 5-*exo* cations can rearrange to the thermodynamically more stable 6-*endo* ion. The homologous 6,7-alkynes behave in a parallel manner, *i.e.* terminal alkynes give seven-membered rings while dialkylalkynes cyclize 6-*exo* to cyclohexenes. An allenyl group 4,5,6 relative to the initiating center with at least one terminal alkyl group induces five-membered ring formation, whereas with a CH_2 terminus both five- and six-membered ring formation has been noted (Scheme 6). The reluctance of 4,5-alkynes to cyclize in either 4-*exo* or 5-*endo* modes is illustrated by the cyclizations to the bridged bicyclics (Scheme 7).[19]

When substituents are bonded to the sp^3-hybridized carbons between reacting double bonds then, for six-membered ring formation, the model with the substituent adopting an equatorial disposition in a



Scheme 6



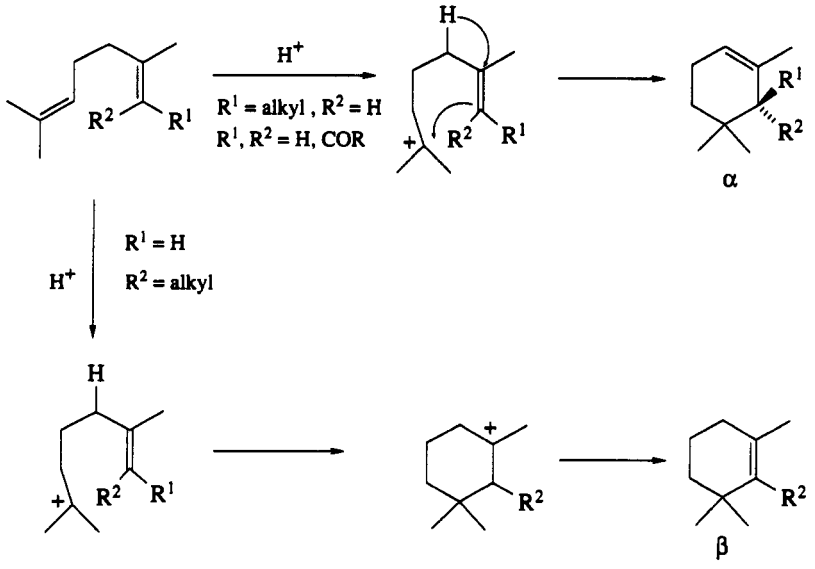
Scheme 7

chair-like transition state has strong predictive value; however, there are occasions when an axial disposition is adopted for understandable reasons.

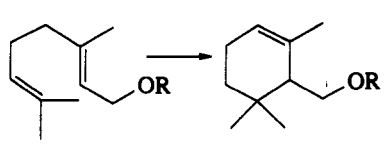
1.9.4 TERMINATION OF CYCLIZATION

The ideal for a synthetically useful polyalkene cyclization would be termination by one mechanism giving a single product. Termination can be achieved by elimination and/or attack by an internal or external nucleophile. Proton elimination can be regioselective or random. The cyclization of geraniol and its derivatives has been extensively investigated, in particular by the groups of Schinz[20] and Semenovskii.[21] Both (*Z*)- and (*E*)-isomers cyclize initially to the α-isomers when an electron-withdrawing group is conjugated to the second double bond (Scheme 8). It is suggested that the reduced nucleophilicity of the double bond leads to a concerted cyclization–elimination being favored over the two-step process. Where the nucleophilicity of the double bond is not reduced then (*E*)-isomers give the α-series and (*Z*)-isomers the β-compounds, consistent with elimination of an axial proton to give the most stable alkene attainable. This rule does not apply when there is oxygen functionality in the vicinity of the second double bond. Geraniol and its derivatives (**8**) cyclize initially to α-isomers. Utilization of the oxygen function as an internal base for proton removal has been invoked; this would require conformational inversion placing CH_2OR axial. The contrary behavior of lavandulol (**9**) illustrates that some subtle features are involved. Together with the allogeraniol (**10**) cyclization, the one common feature appears to be that elimination remote from the *gem*-dimethyl group is preferred. Another rule which seems to have some predictive value is that bicyclo[4.4.0]decenes (both *cis* and *trans*) formed from the C-2 cation favor the $\Delta^{2,3}$- rather than $\Delta^{1,2}$-double bond. However, in many cases, eliminations are not regioselective and the device of R_3Si elimination introduced by Fleming[22] is becoming increasingly popular as a method for preparing compounds of defined regiochemistry. Other terminating groups which remove any ambiguity concerning the structure of the product are alkynes, allenes, enols and enol derivatives. Aryl and heteroaryl rings, particularly if they are electron rich, are good terminators, but when appropriately substituted can give mixtures of positional isomers.

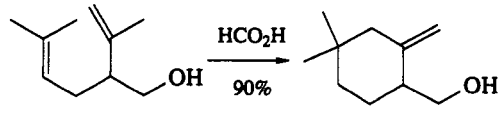
Proton elimination is the most common termination mode for tertiary cations and also for secondary cations when the cyclizing reagent is a Lewis acid. With protonic acids, nucleophilic attack is often observed and is usually stereoselective; in many cases, due to the electron deficiency of the double bonds involved, nucleophilic attack may be concerted with ring formation. Cyclization of the acids (**11**) is in



Scheme 8



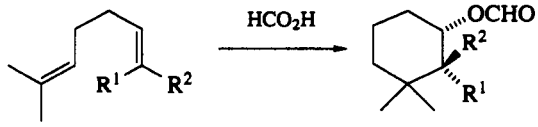
(8) R = H, Me, OAc



(9)

(10)

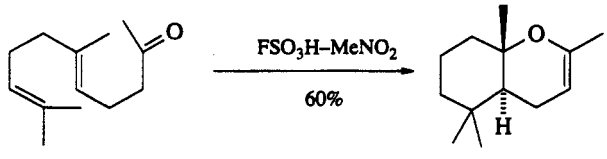
accord with this view.[23] In the few cases where a tertiary center undergoes intermolecular nucleophilic attack, epimeric mixtures have been obtained. However, intramolecular nucleophilic attack by heteroatoms can be stereospecific and efficient, as in the cyclization of geranylacetone (**12**).[24] The lack of predictability when alkenes terminate cyclizations has led to the development of terminators where the products can be more precisely anticipated.



(11)

$R^1 = CO_2H$, $R^2 = H$

$R^1 = H$, $R^2 = CO_2H$

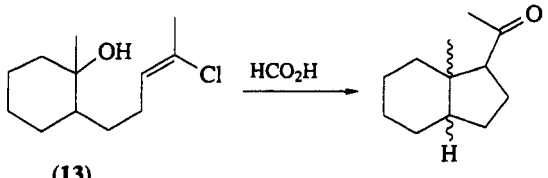


(12)

1.9.5 MONOCYCLIZATIONS

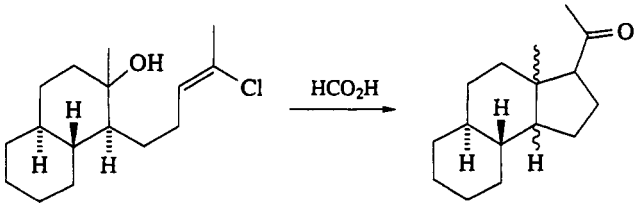
1.9.5.1 Five-membered Ring Formation

Examples of acyclic compounds being cyclized to cyclopentanes are sparse, but there are significantly more where an annulation is involved. 5-*Exo* cyclization of alkenes electronically biased to achieve this mode was used successfully, in particular by the Landsbury group.[25] Use of the chlorovinyl functionality gave acetylcyclopentanes with a preference for the *cis* ring junction with conformationally mobile substrates (**13**). When a conformationally rigid precursor (**14**) was used then predominant formation of a *trans* ring junction resulted; similar results were reported for the propargyl terminating group. Stereochemically constrained dienes,[26] *e.g.* (**15**), can be cyclized under mild conditions with high efficiency. Limitation of the degrees of rotational freedom of a diene is likely to increase the rate of cyclization provided that the double bonds are suitably aligned.



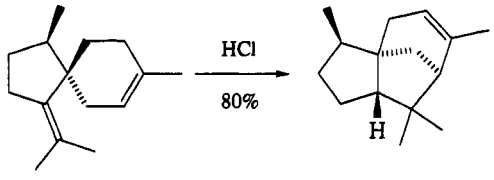
(**13**)

cis:*trans* = 3:1



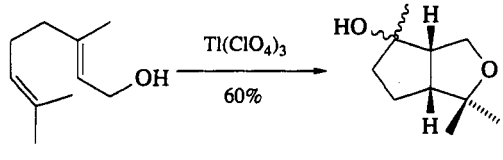
(**14**)

cis:*trans* = 1:2

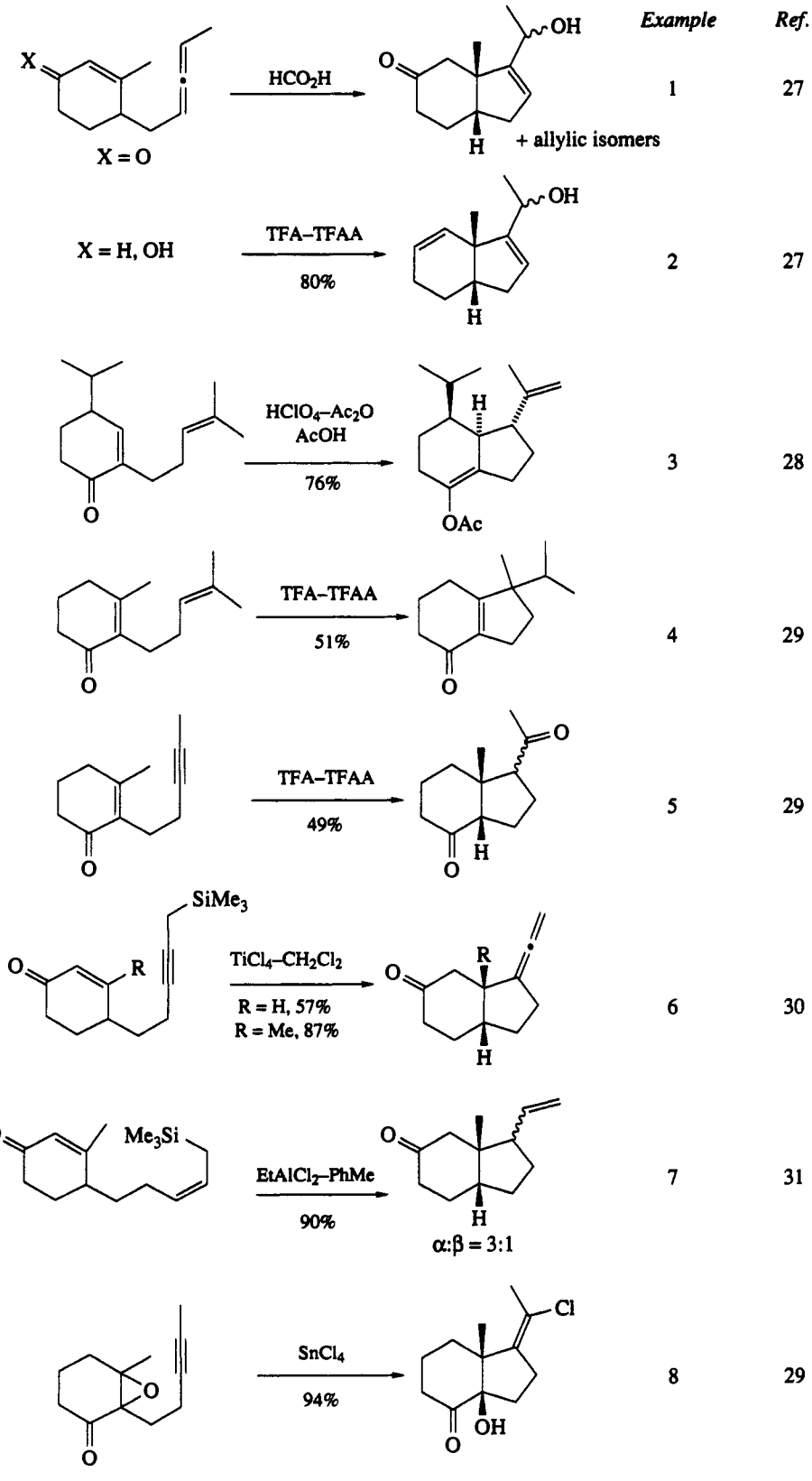


(**15**)

Anti-Markovnikov 5-*exo* cyclizations of geraniol derivatives (**16**) have been reported with $Tl(ClO_4)_3$;[12] however, a more normal 6-*endo* cyclization followed by ring contraction could account for the products. The most reliable prescription for cyclopentane annulations is to use allylic ion initiators with appropriate terminators. In Scheme 9 the *cis* stereochemistry of the ring junctions arises in two ways; for the 4-substituted cyclohexenone derivatives, the axial attack of the nucleophilic side chain on the allylic ion requires this stereochemistry. In the 2-substituted cyclohexenones the immediate product of cyclization is an enol ester which is hydrolyzed, giving the thermodynamically more stable *cis* ring junction. Other points to note are that stereochemical control in example 3 (Scheme 9) is consistent with the Pr^i group being equatorial and the isopropylidene being oriented '*endo*'. The subsidiary rearrangement seen in example 4 (Scheme 9) does not occur with the unmethylated compound. In example 6 (Scheme 9) there is a substantial difference in yield between the methyl and nor series. There are few examples of 5-*endo*

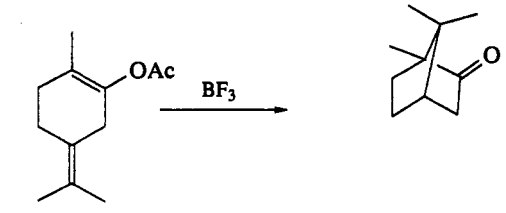


(**16**)

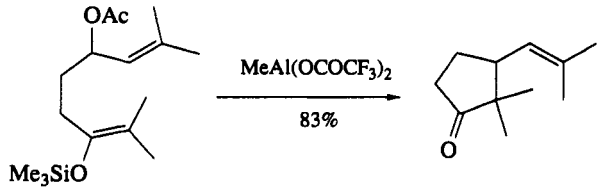

X
X = O
HCO2H
OH
O
H
+ allylic isomers
Example
Ref.
1
27
X = H, OH
TFA–TFAA
80%
OH
H
2
27
HClO4–Ac2O
AcOH
76%
H
OAc
3
28
TFA–TFAA
51%
O
4
29
TFA–TFAA
49%
O
H
5
29
SiMe3
R
TiCl4–CH2Cl2
R = H, 57%
R = Me, 87%
R
H
6
30
Me3Si
EtAlCl2–PhMe
90%
α:β = 3:1
7
31
SnCl4
94%
Cl
OH
8
29

Scheme 9

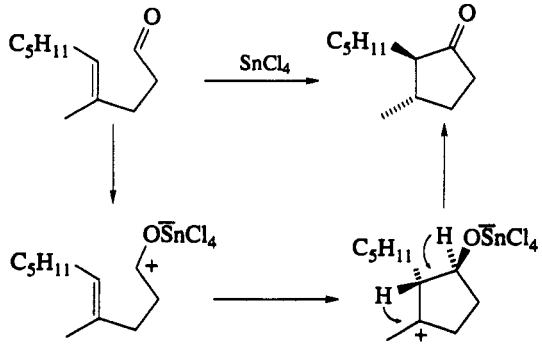
cyclizations; the conversion of the menthadiene (**17**)[32] to the camphor derivative is both 5-*endo* and 5-*exo*. The silylenol ether (**18**) cyclizes to cyclopentanone only when the allyl terminus is dimethylated;[33] with monomethyl derivatives the major mode of cyclization is 7-*endo* (Section 1.9.5.3). The Cookson group has shown (Scheme 10) that 4-en-1-als can be cyclized to cyclopentanones;[34] labeling and other evidence support the mechanism shown.



(**17**)



(**18**)

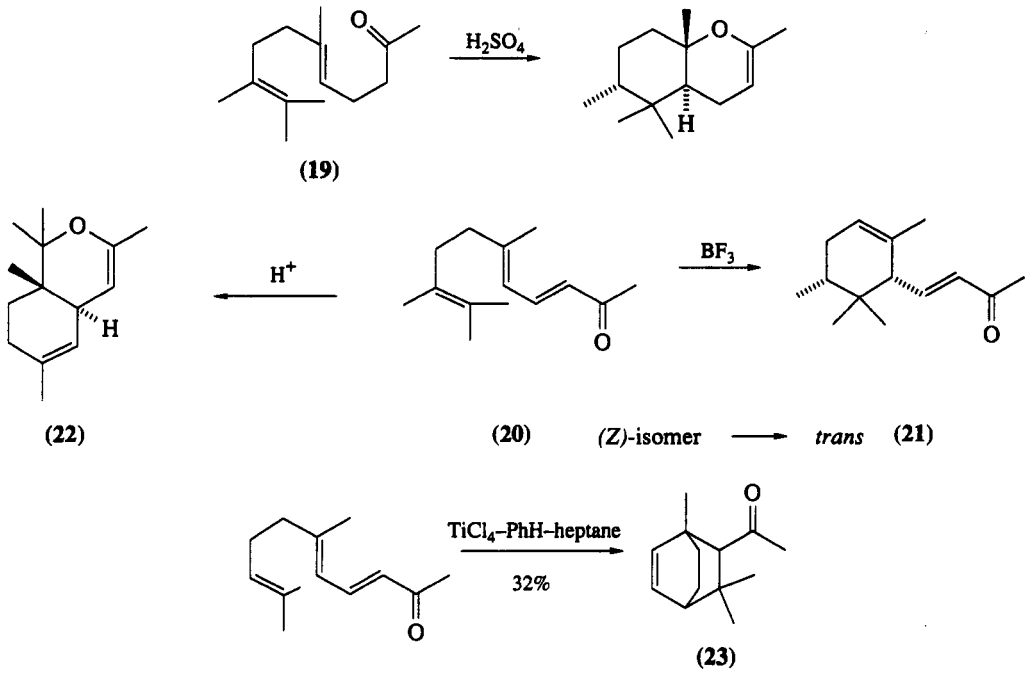


Scheme 10

1.9.5.2 Six-membered Ring Formation

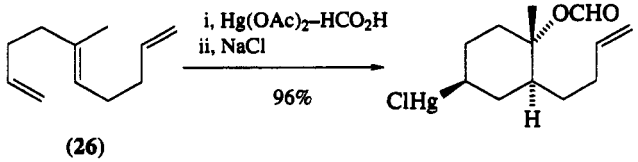
This is by far the most common mode of monocyclization. Some aspects of the cyclization of monoterpenes have been described (Sections 1.9.6.3 and 1.9.6.4). Proton-induced cyclizations are successful when an initial tertiary cation is formed, then participation of electron-deficient and other double bonds occurs provided the Markovnikov rule is not violated. The rare examples of cyclization induced by protonation to form a notional secondary cation probably do not involve such a species, but rather ring formation is concerted with cyclization. Such cyclizations do not occur when the ring-forming double bond is electron deficient. When the initiating double bond is tetraalkylated then intriguing differences from the trialkyl system appear (Scheme 11). It is known that in the proton-induced cyclization of geranylacetone the stereochemical distinction between the two methyls of the isopropylidene group is lost. However, the homolog (**19**) cyclizes stereoselectively,[35] implying either a concerted protonation cyclization or, less likely, that the axial orientation of the methyl group is favored in a two-step cyclization. Lewis acid induced cyclization of ψ-irone (**20**) takes a different stereochemical course, giving (**21**), while the (*Z*)-trisubstituted double bond isomer gives the product with the pendant groups *trans*.[36] The proton-induced cyclization of (**20**) follows a different path,[40] giving (**22**); applying similar conditions of cyclization to ψ-ionone gives α-ionone. The divergent stereochemical behavior of (**19**) and (**20**) requires

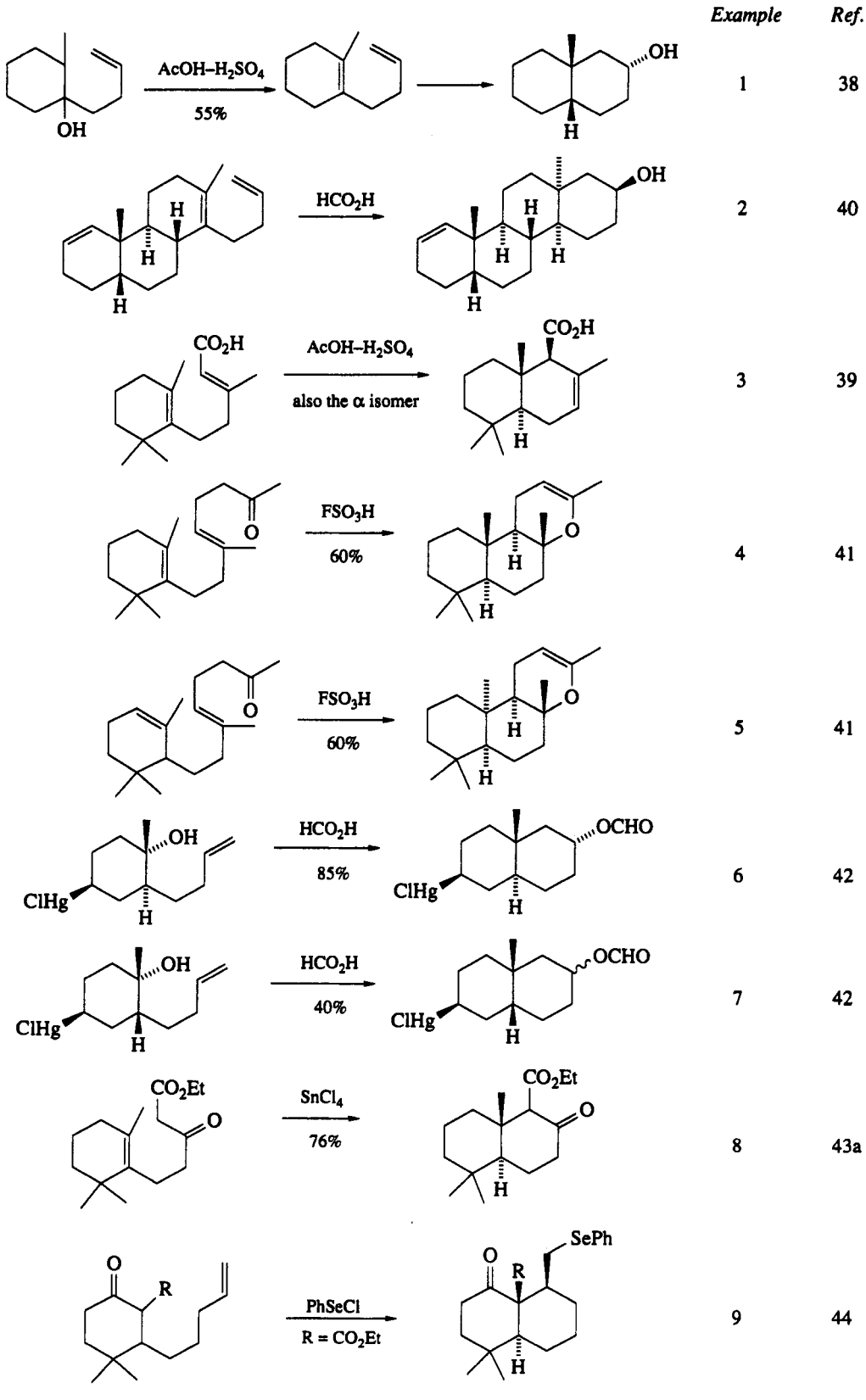
both reactions to be concerted and the Lewis acid–carbon bond of the cyclization product leading to (**21**) to be protonated with inversion of configuration. Alternatively, the cyclization of (**20**) can be stepwise, due to the electron-deficiency of the ring-forming double bond, and the transition state with methyl equatorial and BF_3 axial favored. With $TiCl_4$ ψ-ionone cyclizes in yet another fashion to give (**23**).[37]



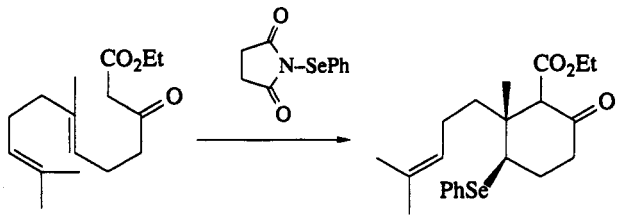
Scheme 11

In Scheme 12 some annulations leading to decalins are shown. The formation of *cis* isomers (examples 1 and 2, Scheme 12) accords with a fully-concerted mechanism, while the cyclization of both the α- and β-isomers of the acids (example 3, Scheme 12) to the *trans* compound supports stepwise formation of the cyclohexyl cation followed by concerted cyclization–elimination due to the electron-deficient double bond. The cyclization of the acetonyl β-isomer (example 4, Scheme 12) to the *trans* isomer implies a stepwise mechanism, which is perhaps surprising in the light of the first two results, since the ring-forming double bond is not electron deficient. There appears to be an unfavorable steric interaction between the angular methyl and two axial hydrogens in ring B (**24**). This may make the concerted reaction energetically unfavorable compared to the stepwise process. Cyclization of the isomer (example 5, Scheme 12) takes a different course and must involve some type of concerted process to give the unexpected stereochemistry found. A chair–chair transition state is disfavored due to the similarity with (**24**). A twist-boat ring B conformation suffers from similar interactions with the angular methyl. Diequatorial addition to the double bond in a chair–chair conformation has little precedent. However, a more plausible model




Example
Ref.
AcOH–H2SO4
55%
OH
H
1
38
HCO2H
2
40
CO2H
AcOH–H2SO4
also the α isomer
3
39
FSO3H
60%
O
4
41
5
41
ClHg
HCO2H
85%
OCHO
6
42
40%
7
42
CO2Et
SnCl4
76%
8
43a
R
PhSeCl
R = CO2Et
SePh
9
44

Scheme 12



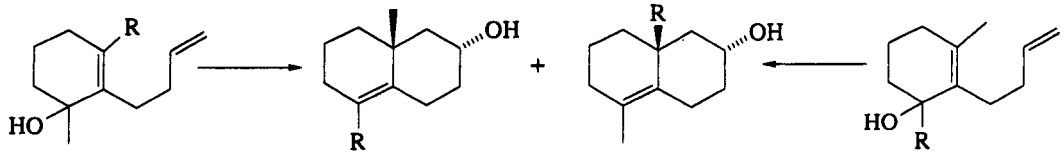
(27)

which effectively leads to diequatorial attack has ring A as a twist-boat (**25**) which minimizes interactions with the angular methyl and improves orbital overlap at the reacting centers. If this model is correct, it would imply that concerted cyclization of a 1,6-diene is energetically more favorable than the 1,5-diene concerted reaction. It should be noted that the *cis*-decalin conformations involved in the annulations are inverted compared to those obtaining in bicyclizations. The Julia group has observed remarkable stereochemical control on annulation stereochemistry by the chloromercuri substituent (examples 6 and 7, Scheme 12); similar control is found in the cyclization to hydrindanes. The dienes (from dehydration) do not exhibit this effect. The β-keto ester terminator has been successfully used in annulations (example 8, Scheme 12) as has the alkynyl group to form the cyclohexanone ring (example 1, Scheme 17).

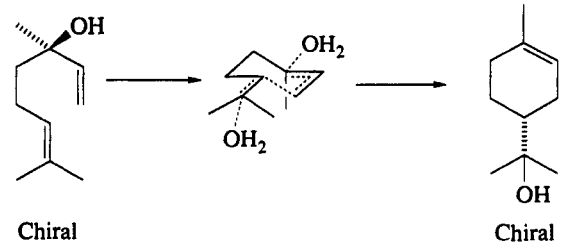
Other electrophiles have been applied mainly to geraniol derivatives (Section 1.9.2). Product stereochemistry is as anticipated except for initial addition to the double bond where, of the reagents examined, mercury salts appear to be unique in maintaining the stereochemical integrity of the double bond. $Hg(OAc)_2$ has the useful property of initiating cyclization at a vinyl group in the presence of a trisubstituted double bond (**26**);[42] this accords with the relative rates of reaction established for differently substituted alkenes.[43b] The reversible formation of the mercuricinium ion may also play its part. Phenylselenation provides a rare example[44] of initial attack at an 'internal' double bond to give (**27**).

The initiation of cyclization by ionization is best achieved using stabilized ions. The prototypical cyclization of allyl derivatives is the conversion of linalool to terpineol (Scheme 13), which the Arigoni group[45] has shown, in an elegant investigation, cyclizes with inversion of configuration. The Johnson group has examined a number of allylic alcohols which can be used as initiators (Scheme 14). Where ring junction stereochemistry is discernible in annulations (examples 1 and 5, Scheme 14) then *cis* stereochemistry, consistent with axial attack of the double bond, is observed. Terminal allenyl and alkynyl groups undergo *endo* cyclization, ultimately forming a cyclohexanone ring (example 4, Scheme 14).

Table 1 Isomer Ratios Formed from Regioisomeric Allylic Alcohols

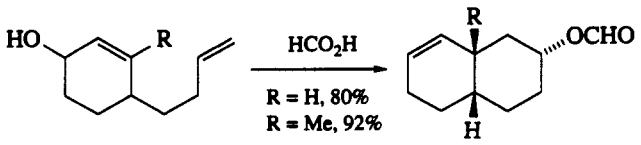


R			*R*
Et	48	52	—
—	60	40	Et
Pr^n	70	30	—
—	85	15	Pr^n
Bu^n	70	30	—
—	88	12	Bu^n

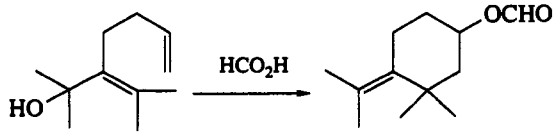


Chiral Chiral

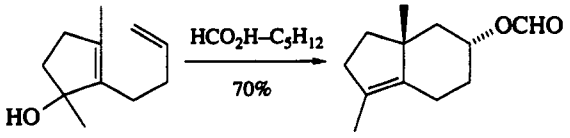
Scheme 13



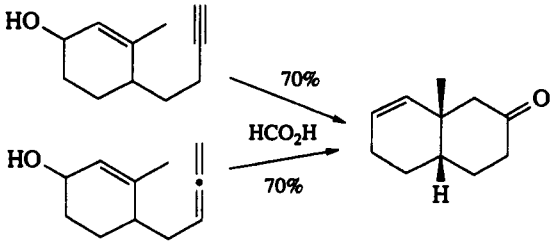
Example 1 *Ref.* 46



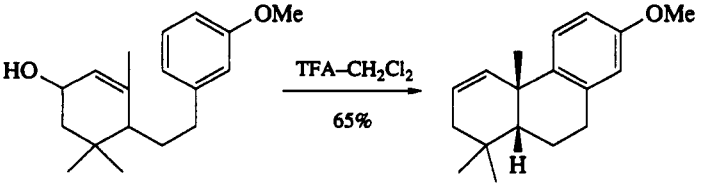
Example 2 Ref. 3



Example 3 Ref. 47

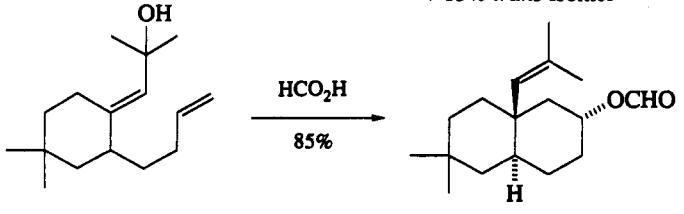


Example 4 Ref. 48

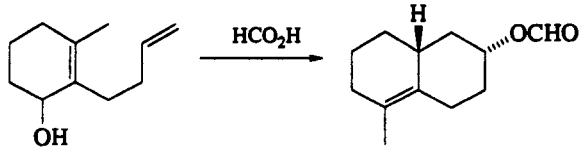


Example 5 Ref. 49

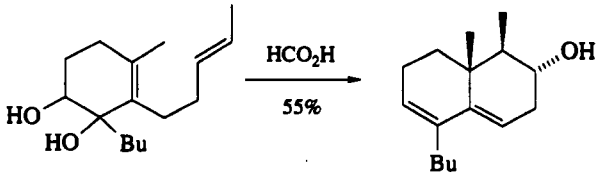
+ 15% *trans* isomer



Example 6 Ref. 50

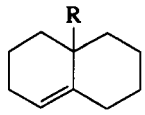


Example 7 Ref. 51



Example 8 Ref. 52

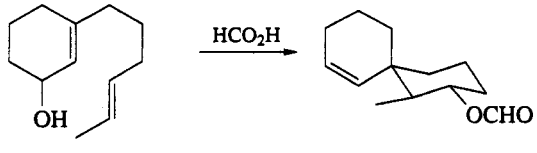
Scheme 14



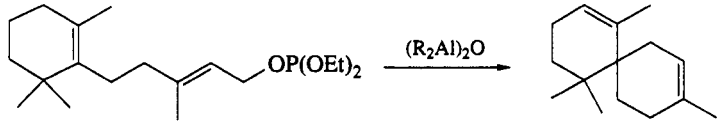
(28)

The anisyl ring is an efficient terminator (example 5, Scheme 14) and reacts mainly *para* to the methoxy, but *ca.* 15% of *ortho* reaction is also found. The exocyclic allylic alcohol cyclizes predominantly to a *trans*-decalin (example 6, Scheme 14); this parallels the stereochemical behavior of cyclohexyl cations. Where the putative allylic cation is unsymmetrical and cyclization to a six-membered ring can occur at either terminus, then reaction at the least-alkylated position is preferred (example 7, Scheme 14). Table 1 clearly establishes that a common allylic cation is not formed from the structurally isomeric alcohols, and reveals a tendency for bond formation at the least-hindered center.[50] Additionally there is a preference for bonding remote from the leaving group; however, unlike the linalool cyclization, chirality at the tertiary alcohol center does not lead to the formation of chiral products.[51] Little is known of the stereochemical fate of substituents on the cyclohexenyl ring; the diol (example 8, Scheme 14) cyclizes but under the reaction conditions dehydrates to a diene product. Prediction is complicated by the inability of octalins (**28**) to adopt a half-chair–chair conformation other than with the bridgehead substituent axial; with the substituent equatorial one of the rings must adopt a twist-boat conformation. Thus, to achieve efficient overlap at the reacting centers, it is likely that the cyclohexene ring is in a twist-boat conformation.

In spirocyclizations using the allylic initiators, the stereochemical question arises as to whether the initiator double bond shows a preference for the equatorial or axial position relative to the ring being formed. The Harding group has shown that the equatorial disposition is favored, especially when a 1,2-disubstituted alkene is cyclized, *e.g.* (**29**).[4c] As expected, when there is a choice between seven-membered ring formation or spirocyclization to a six-membered ring, the latter is observed (**30**).[60]

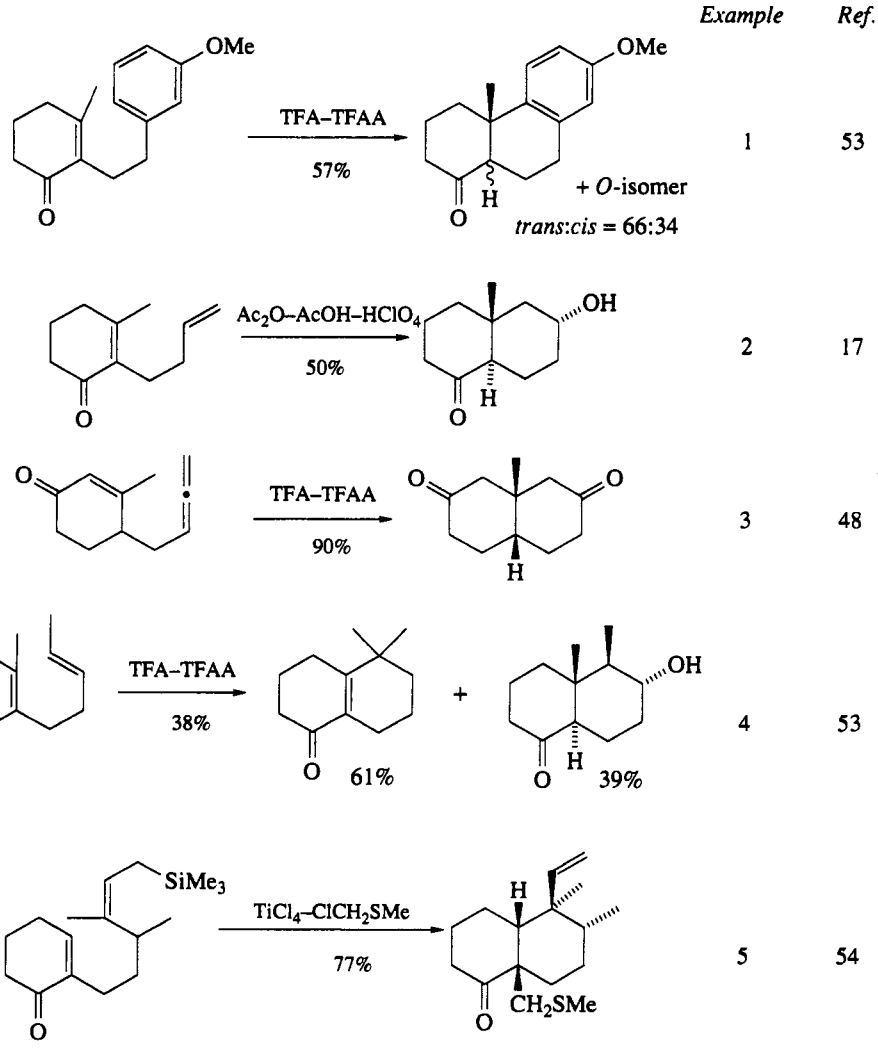


(29)

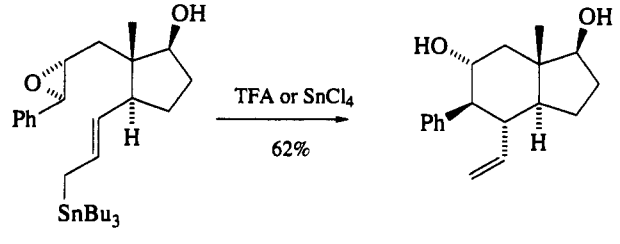


(30)

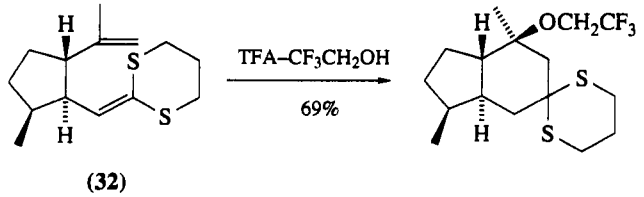
Enones are precursors of oxyallyl cations, either by enol ester formation and protonation as developed by the Harding group, or by coordination with Lewis acids. In Scheme 15 some typical cyclizations are illustrated. Under certain circumstances (example 4, Scheme 15) secondary rearrangement can occur by hydride migration. The vinyl compound (example 2, Scheme 15) does not give a rearrangement product, suggesting that the hydride migrations are not concerted. It is notable that cyclization of this enone in the absence of acetic anhydride leads to termination predominantly by elimination. In example 5 (Scheme 15) stereochemical control is exerted at four centers; in the cyclization a chair transition state with the pendant methyl group equatorial and the double bond oriented *exo* accounts for the relative stereochemistry at three centers. The fourth center is established by stereoselective alkylation of the immediate cyclization product, presumably a titanium enolate. Scheme 16 shows how oxonium ions derived from aldehydes or their acetals can induce cyclization. In certain cases (examples 1 and 4, Scheme 16) the stereochemistry found is consistent with a catalyzed 'ene' reaction. The oxidative cyclizations reported by the Corey group (example 5, Scheme 16) may involve oxonium ion intermediates. The successful cyclization[61] of the epoxide (**31**) suggests that benzylic ions could be useful initiators. Another ion which has not been widely examined is that derived from the ketene dithioacetal group (**32**).[62]



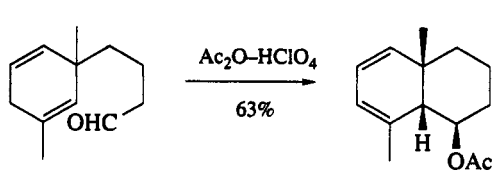
Scheme 15



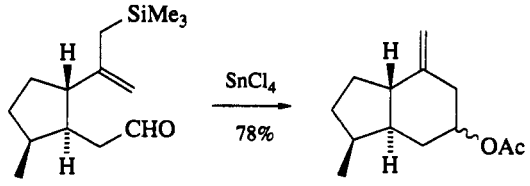
(31)



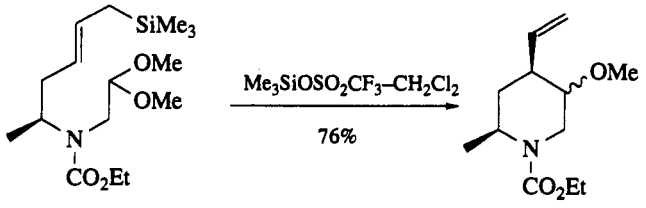
(32)



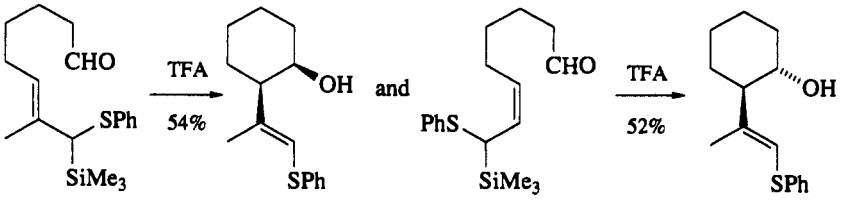
Example 1 *Ref.* 55



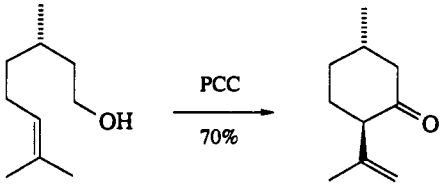
Example 2 Ref. 56



Example 3 Ref. 57



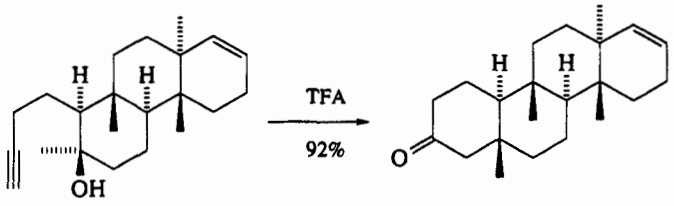
Example 4 Ref. 58



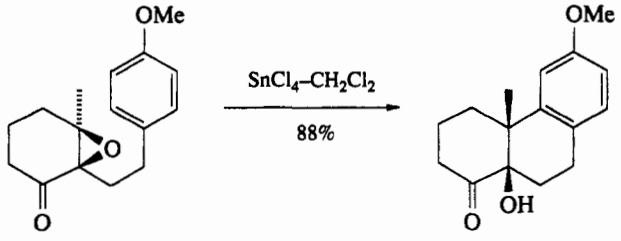
Example 5 Ref. 59

Scheme 16

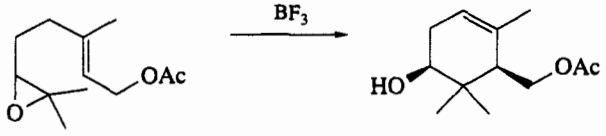
Ionization methods leading to unstabilized cations can give preparatively useful yields when the center is tertiary. In Scheme 17 a variety of examples is shown. Cyclohexene epoxides (example 2, Scheme 17) are generally useful initiators for monocyclizations. The cyclopropyl ketone is effective with aryl termination (example 4, Scheme 17), but in example 5 (Scheme 17) the ion obtained on cyclization is quenched by intramolecular attack of the enol.



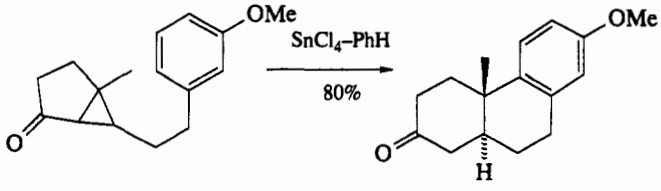
Example	*Ref.*
1	63



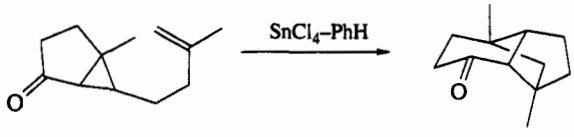
2	53



3	4a



4	64

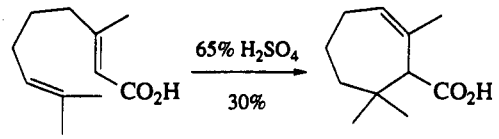


5	64

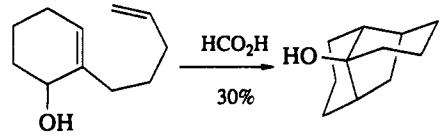
Scheme 17

1.9.5.3 Seven-membered Ring Formation

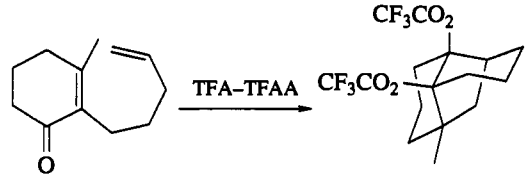
The 7-*endo* cyclization has been little investigated and can be complicated by secondary reactions. Some examples are shown in Scheme 18. The more stringent conditions required and the lower yield obtained in example 1 (Scheme 18) compared with the lower homolog (**11**) illustrate the difficulties associated with seven-membered ring formation. A common complicating factor (examples 2 and 3, Scheme 18) is further 5-*endo* cyclization of the ion (**33**) from monocyclization. This does not occur with the alkynyl compound (example 4, Scheme 18) nor when the double bond is endocyclic to the newly formed ring (examples 6 and 7, Scheme 18). Cyclization in the 7-*exo* mode (example 5, Scheme 18) is also accompanied by bicyclization and the Johnson group has made use of this in an elegant synthesis of longifolene. The use of recently developed terminators might prevent the second cyclizations occurring.



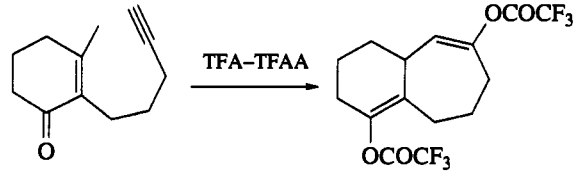
Example	*Ref.*
1	65



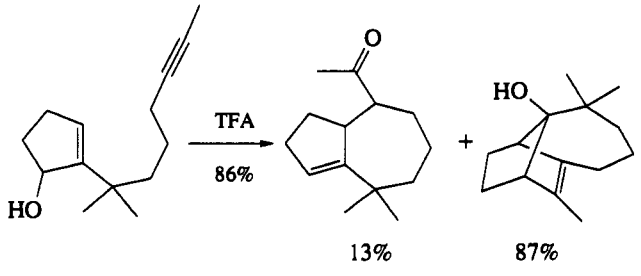
2	66



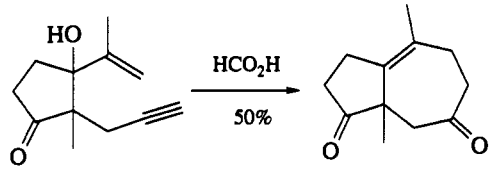
3	68



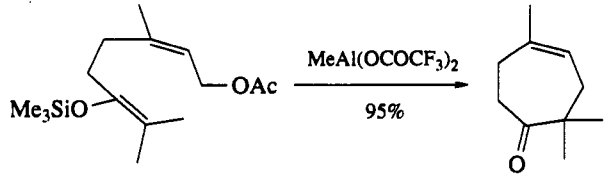
4	68



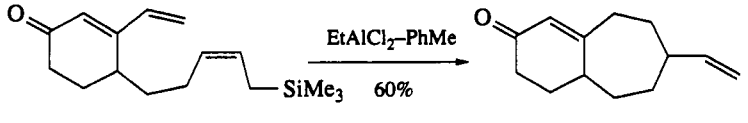
5	67



6	69

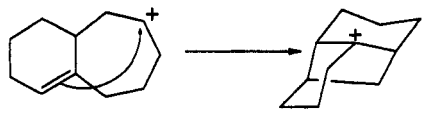


7	33



8	31

Scheme 18

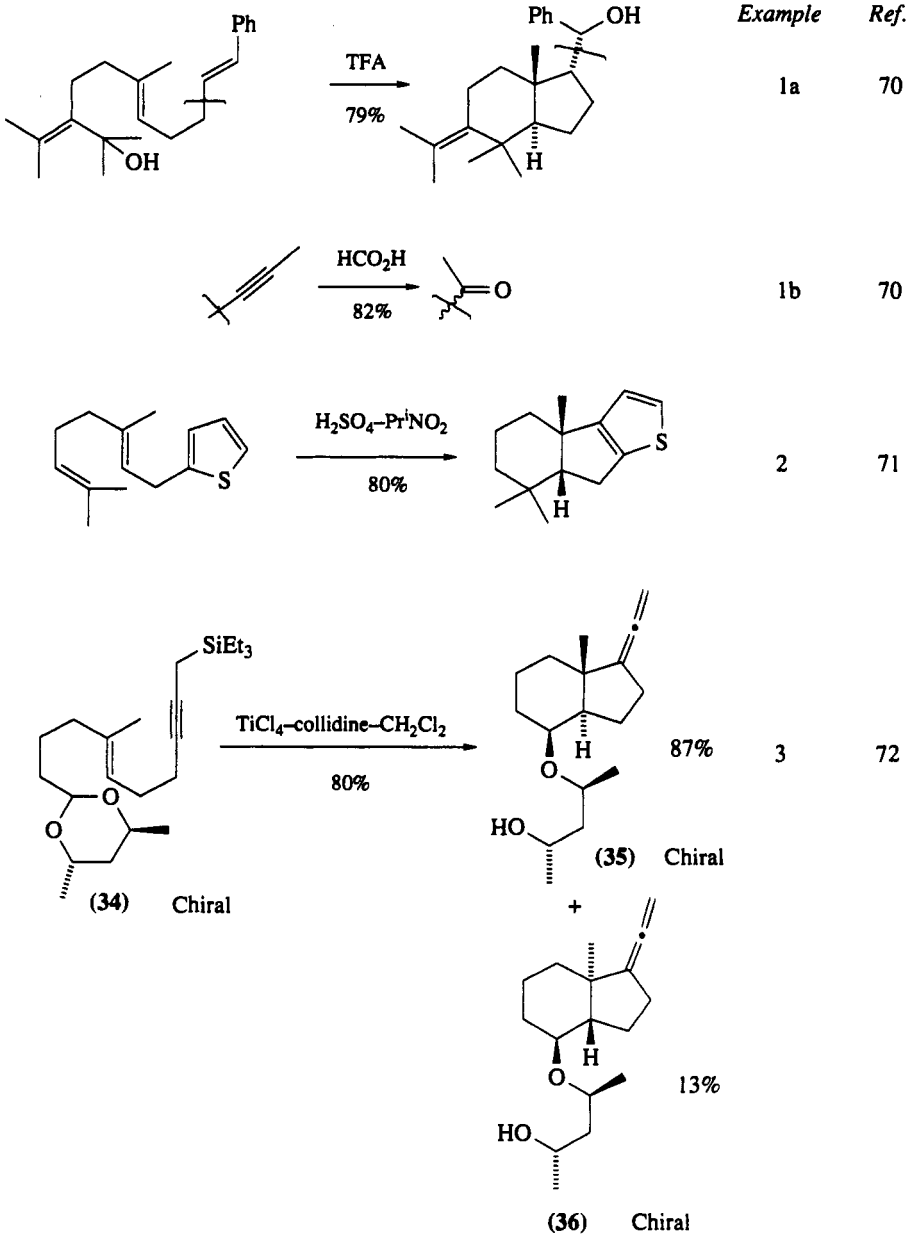


(33)

1.9.6 BICYCLIZATIONS

1.9.6.1 Bicyclo[4.3.0] Ring Formation

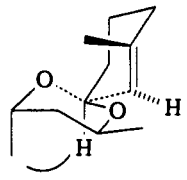
The Johnson group has used the tetramethylallyl cation as initiator for the synthesis of *trans*-hydrindanes (Scheme 19) using a variety of different terminating groups. The chiral acetal (**34**) has been



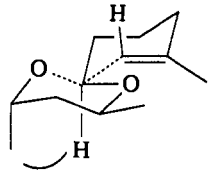
Example	*Ref.*
1a	70
1b	70
2	71
3	72

Scheme 19

cyclized[72] in an enantioselective manner to the *trans*-hydrindanes (**35**) and (**36**). This accords with the stereochemical model in which the C—O bond next to the axial methyl in the acetal ring breaks and the double bond attacks from the opposite face; the driving force for this selection is postulated to be relief of the axial methyl–hydrogen interaction in the acetal ring. There are two chair–chair conformations (**37** → **35**) and (**38** → **36**) which have this feature, and it is not immediately obvious why (**37**) is favored over (**38**).



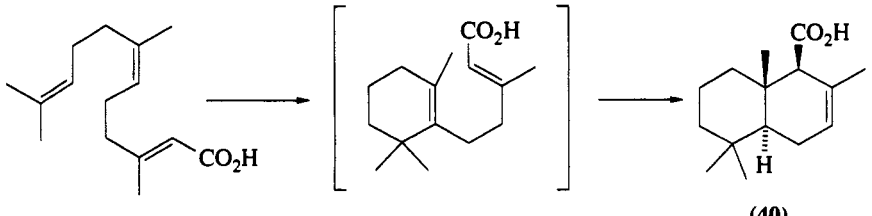
(37)



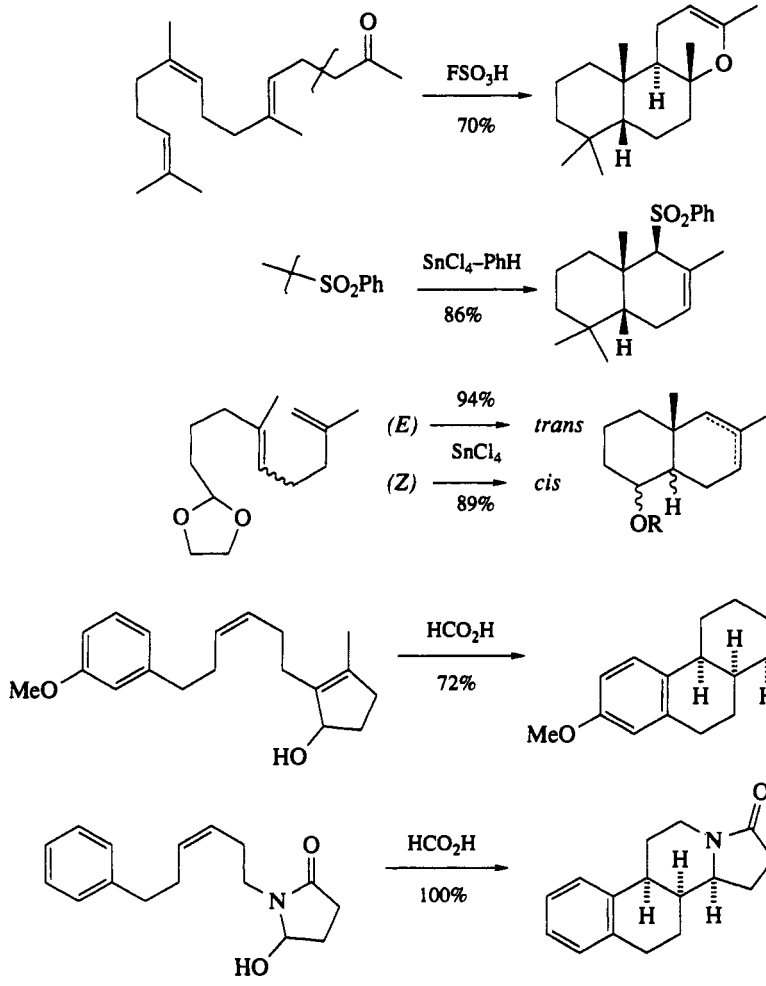
(38)

1.9.6.2 Bicyclo[4.4.0] Ring Formation

The majority of bicyclizations described lead to *trans*-decalin derivatives and the most extensive results relate to the cyclization of farnesol derivatives and the synthesis of estrone-related compounds (see Section 1.9.8.1). Early work was concerned with testing the validity of the Stork–Eschenmoser hypothesis in accounting for ring junction stereochemistry, and showed that both (*Z*)- and (*E*)-isomers gave *trans*-decalins when the terminating double bond was electron deficient due to conjugation with carboxylic acid or ester functions, *e.g.* (**39** → **40**).[2] The cyclization was shown to be a stepwise process *via* a common intermediate formed from (*Z*)- or (*E*)-alkenes. Subsequently, the Semenovskii group has shown that alkenes with internal (*Z*)-double bonds can be cyclized to *cis*-decalins in acceptable yields (Scheme 20). Other cases where good yields have been reported for *cis*-decalins are from the acetal (example 3, Scheme 20), the acylimonium ion initiated cyclization (example 5, Scheme 20) and with the estrone precursor (example 4, Scheme 20). However, there are a significant number of cases where varying proportions of *trans*-decalins are formed. As a route to *cis*-decalins this approach must be treated with some caution, and careful planning in terms of initiator, nucleophilicity of participating double bonds and termination is required to ensure success. The annulation approach (see Scheme 14) to *cis*-decalins is more predictable. There is no such reservation in applying the bicyclization route to the synthesis of *trans*-decalins. Scheme 21 shows a variety of farnesyl derivatives which have been cyclized to give useful synthetic intermediates. Where the stereochemical integrity of the initiating double bonds needs to be reflected in the product then, as for monocyclization, $Hg(OCOCF_3)_2$ is the reagent of choice (example 2, Scheme 21). Phenyl-selenyl and -sulfenyl cations offer promise in inducing bicyclizations (examples 4 and 5, Scheme 21), whereas epoxide ring opening and bromonium ion formations have given disappointing results in terms of yield. Undoubtedly the substituted allylic cations and oxonium ions are the most generally effective initiators of bicyclizations. In Scheme 22 some results obtained in these cyclizations are listed. In example 2 (Scheme 22) and example 5 (Scheme 22) bicyclization around a tetraalkylalkene is shown to be possible. The sulfur-stabilized cation, derived from the ketene dithioacetal (example 6, Scheme 22) shows promise as an initiator, as does the acylium ion (example 4, Scheme 22). In the latter case, the vinylsilane terminator is used and the chair–chair transition state geometry is adopted where the bulkier group is equatorial. Use of a chiral acetal allows enantioselective cyclization (example 3, Scheme 21). The preference for one series is in accord with the explanation developed for enantioselection in (**34**).

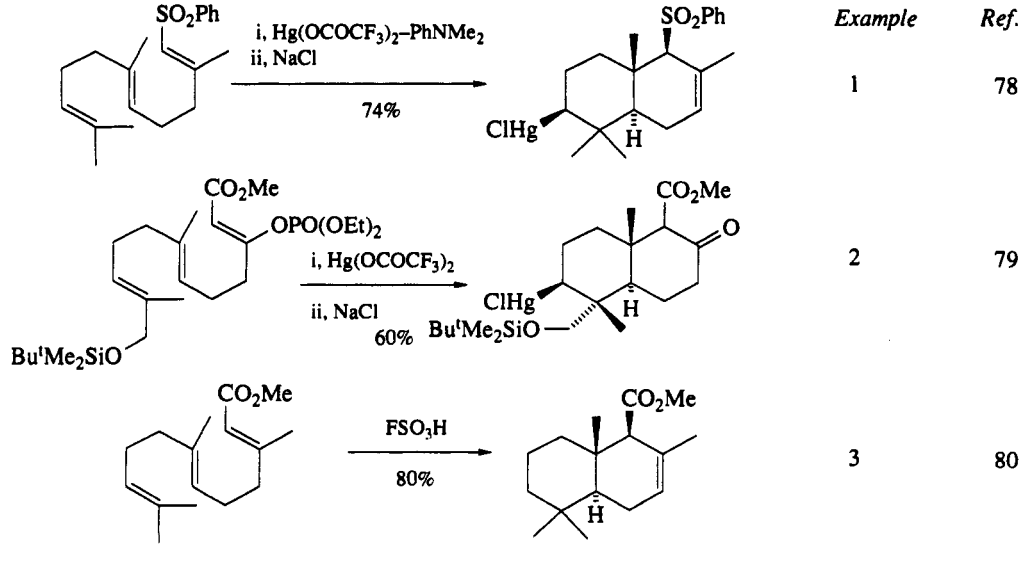


(39) (40)



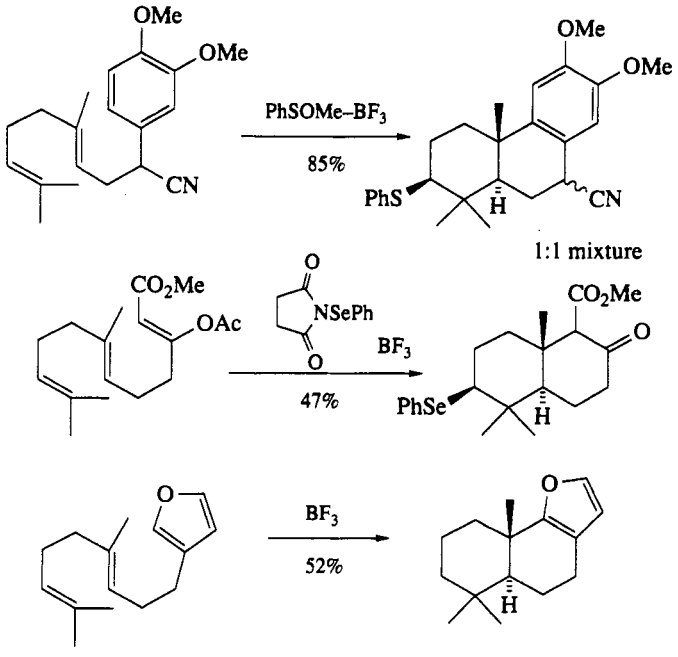
Example	*Ref.*
1	73
2	74
3	75
4	76
5	77

Scheme 20



Example	*Ref.*
1	78
2	79
3	80

Scheme 21

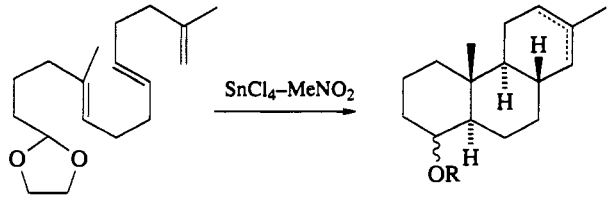


Example	*Ref.*
4	81
5	81
6	82

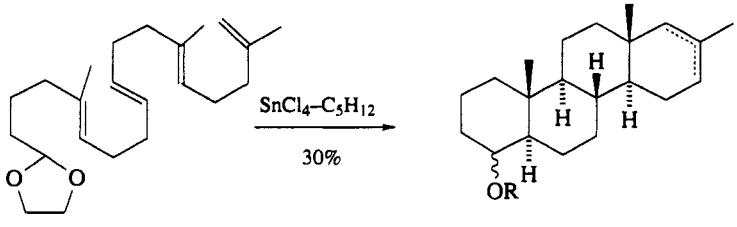
Scheme 21 ***(continued)***

1.9.7 TRI- AND TETRA-CYCLIZATIONS

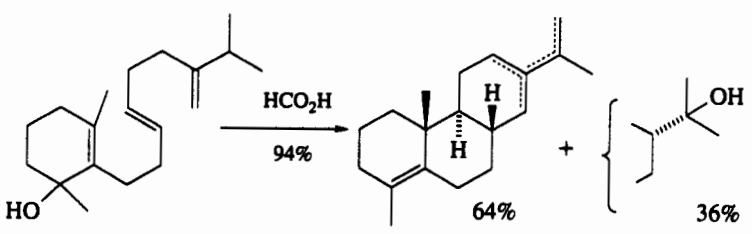
Most cyclizations in this category were designed to form steroids and related compounds and are discussed in Section 1.9.8. Early attempts to cyclize geranylgeraniol derivatives were not promising and it was not until the late 1960s that the Johnson group demonstrated that substantial yields of tri- and tetracyclic compounds could be prepared by Lewis acid induced cyclization of acetals, *e.g.* (**41**) → (**42**)[89] and (**43**) → (**44**);[90] mixtures of isomers were obtained due to initiation and termination not being specific, but the carbon skeletons were shown to be *trans–anti–trans–*(*anti*). Later the same group showed that the



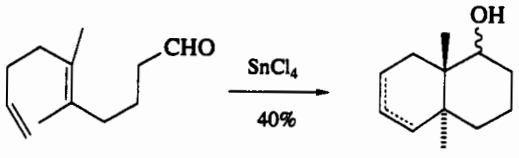
(**41**) (**42**)



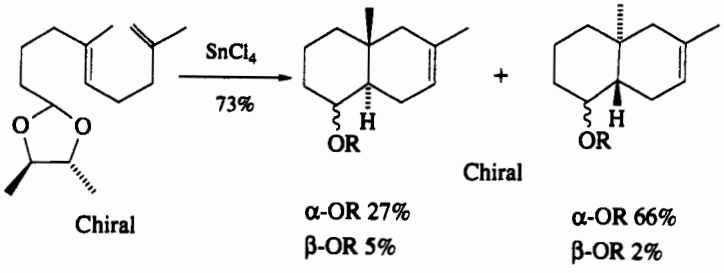
(**43**) (**44**)



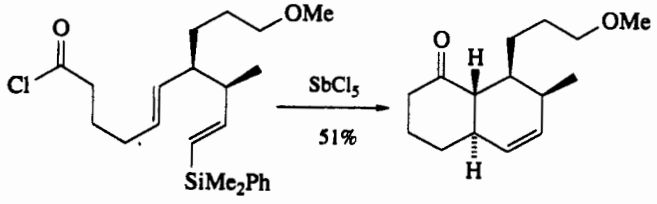
Example 1 *Ref.* 83



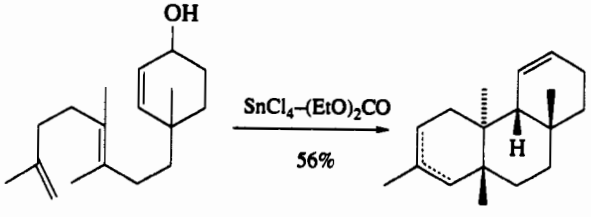
2 84



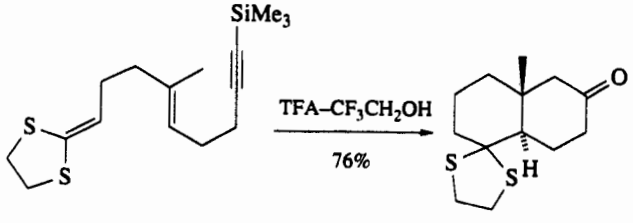
3 85



4 86



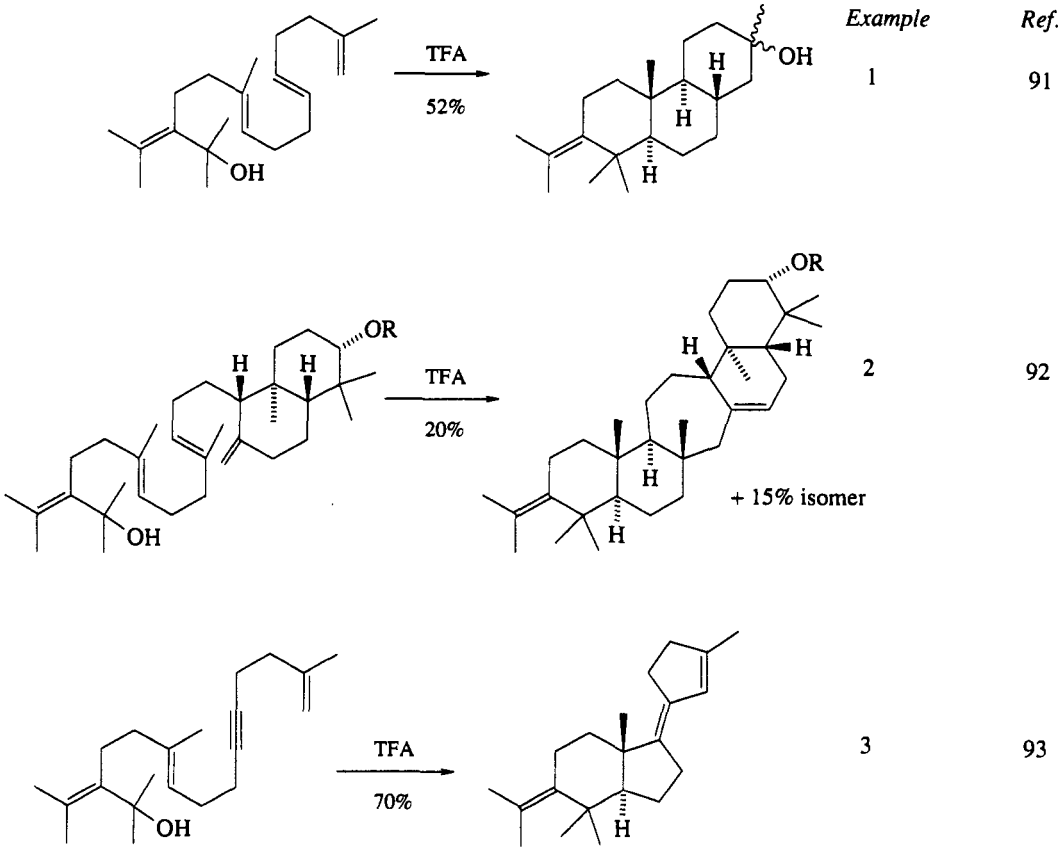
5 87



6 88

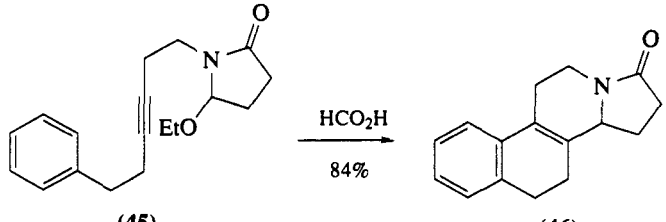
Scheme 22

tetramethylallyl initiating group was also effective (Scheme 23) in forming 6,6,6 and 6,6,7 ring systems. It is not surprising that two diastereoisomers are formed in example 2 (Scheme 23) since the initiating group is remote from the chiral terminating function and unable to induce enantioselections in the formation of the first two rings. The alkyne (example 3, Scheme 23) cyclized as anticipated with five-membered ring formation being favored. However, the acylimonium ion induced cyclization[77] of (**45**) generates the azasteroid skeleton (**46**), perhaps due to rearrangement of an intermediate cyclopentylidene cation. Polyalkene cyclizations to form triterpenes have also been examined (Scheme 24). The van Tamelen group has investigated epoxyalkene cyclizations (examples 1 and 2, Scheme 24) extensively, with yields varying from moderate to poor; however, true assessment of the method is difficult since the cyclization precursors were, in a number of cases, mixtures of diastereoisomers. The Ireland group assessed a number of initiating groups (examples 3, 4 and 5, Scheme 24) again with yields varying from moderate to poor. In all of the Scheme 24 examples substantial amounts of bicyclization products were

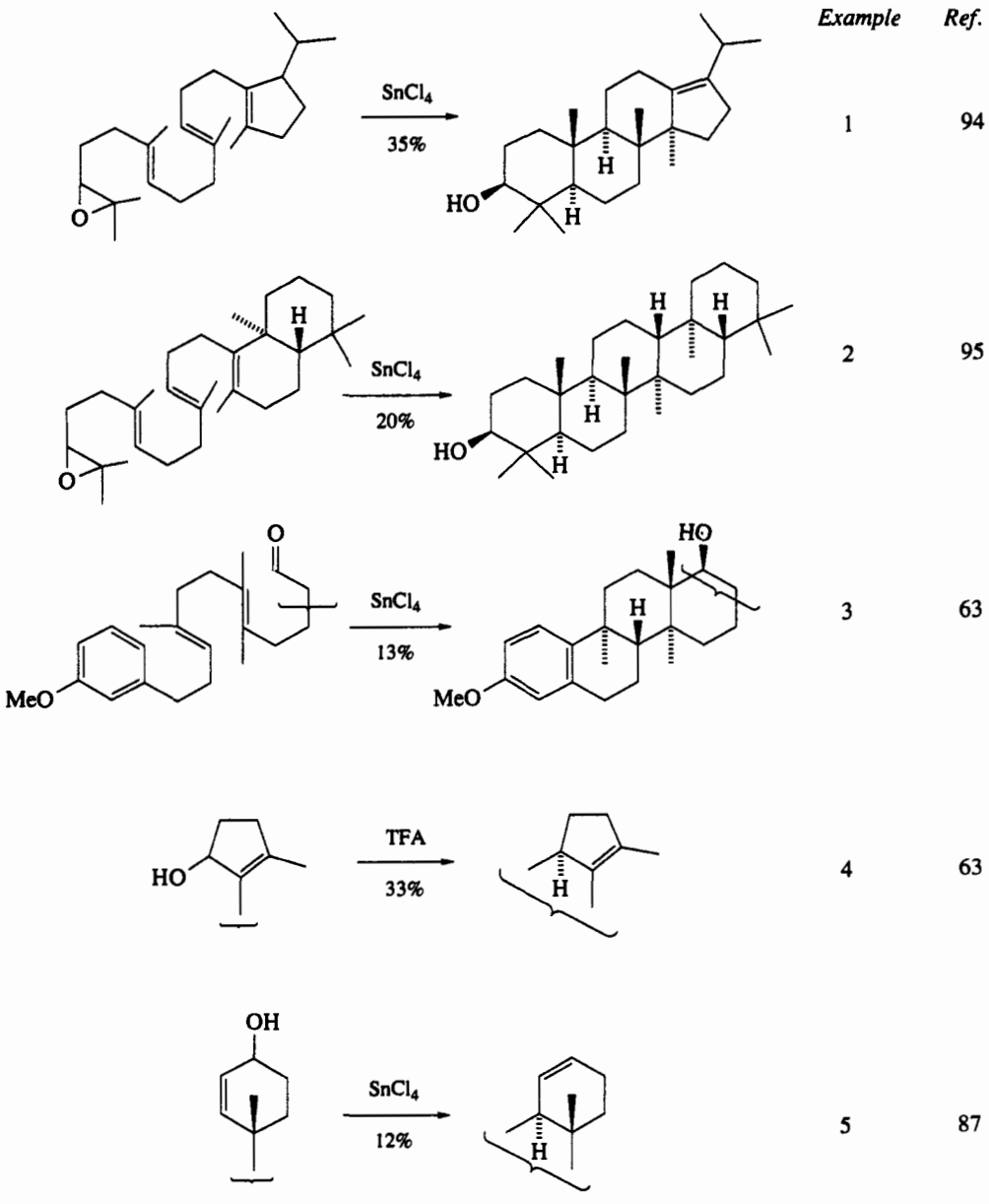


Example	*Ref.*
1	91
2	92
3	93

Scheme 23

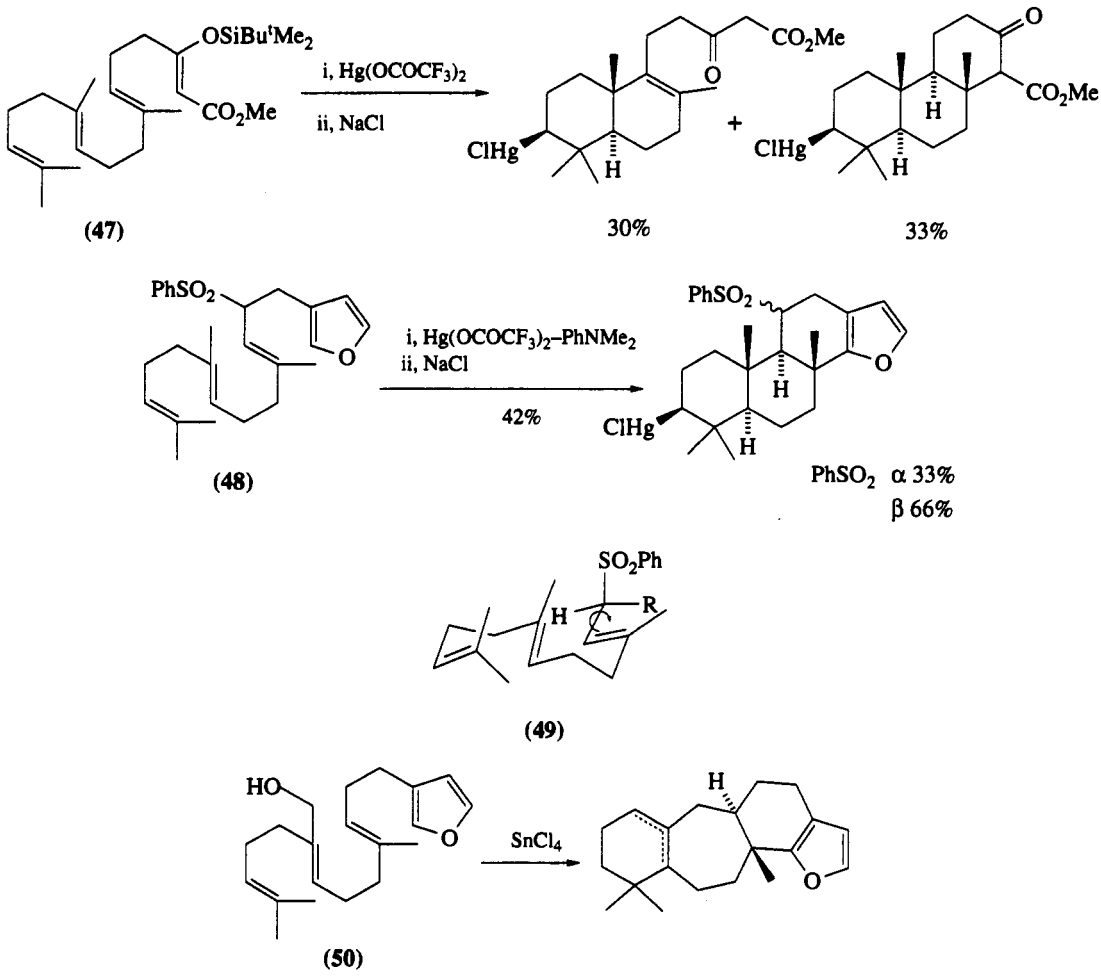


(**45**) (**46**)



Scheme 24

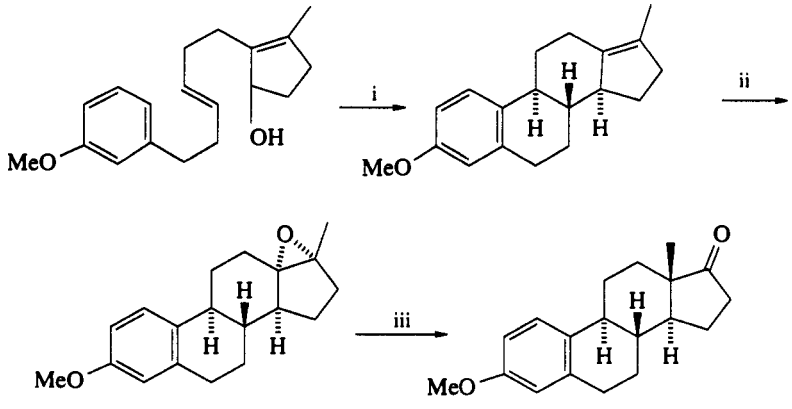
obtained. This was also observed by the Corey group[96] in the cyclization of the ester (**47**). The cyclization of the furan (**48**)[97] shows diastereoselection in favor of the isomer with the sulfonyl group axial. This can be rationalized using Bartlett's suggestion[5] that only bicyclizations are concerted (Section 1.9.10). The diastereoselection is then not determined by a chair-like conformation for the incipient ring C; instead it is dependent on the relative rates at which conformers form the enantiomeric bicyclic ring systems (**49**). In particular, the rates of cyclization of the rotamers about the bond indicated will influence diastereoselection. A similar explanation accounts for the formation of two diastereoisomers from cyclization of the alcohol (example 2, Scheme 23); the chiral unit is too distant to have any significant influence in determining the absolute configuration adopted by rings A and B. The tricyclization of the furan (**50**) must involve independent monocyclization and bicyclization and suggests that this might be a strategy worth exploring further.[98]



1.9.8 SYNTHESIS OF STEROIDS AND RELATED COMPOUNDS

1.9.8.1 Aromatic Steroids

The Johnson group's approach to estrone (Scheme 25)[99] has been much developed since variants of the basic cyclization have been used to elicit further stereochemical and mechanistic information. Groen

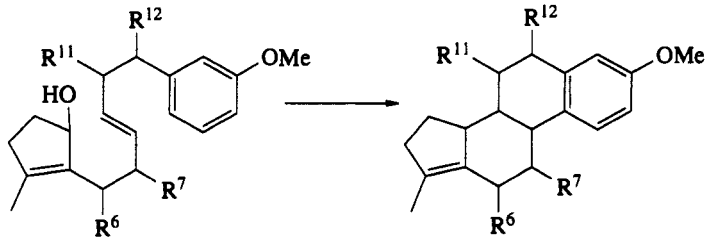


i,HCO$_2$H; ii, HOBr, KOH; iii, BF$_3$

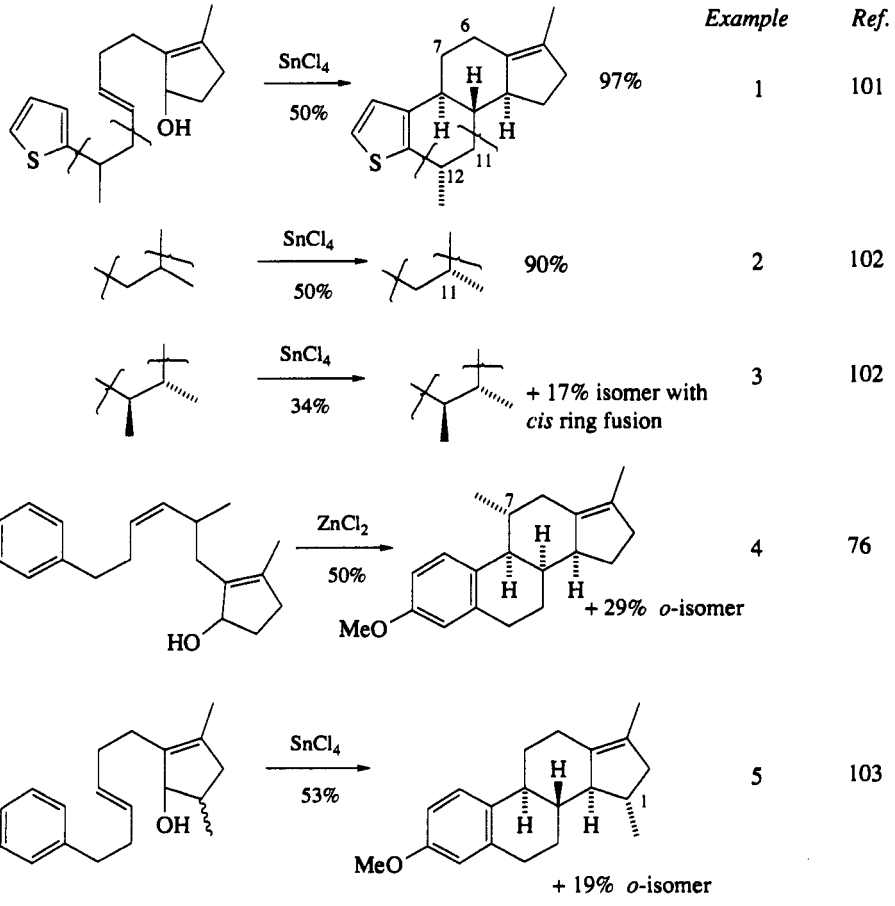
Scheme 25

and Zeelen[100] examined the diastereoselection obtained when a methyl group was introduced at varying positions on the methylenes of the carbon chain (Table 2). The results agree with a product-like chair–chair transition state where methyls at C-7 or C-12 favor the equatorial orientation. The methyl at C-6 is found only in the axial orientation, presumably to relieve an unfavorable equatorial methyl interaction with the vinylic methyl group. Axial disposition of the methyl at C-11 is also preferred, presumably to avoid the steric repulsion which would ensue with C-1 if the methyl were equatorial. Cyclization of the thiophene analogs (examples 1 and 2, Scheme 26) gives analogous results. With the dimethyl compound

Table 2 Stereochemistry of Cyclization of Monomethyl Derivatives



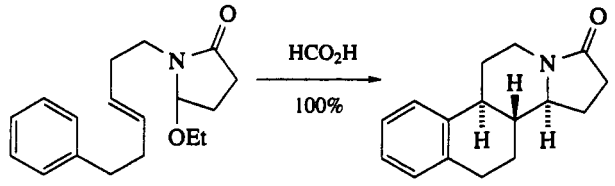
Me position	*Yield (%)*	*Axial:equatorial*
R^{12}	64	10:90
R^{11}	42	86:14
R^{7}	60	12:88
R^{6}	65	100:0



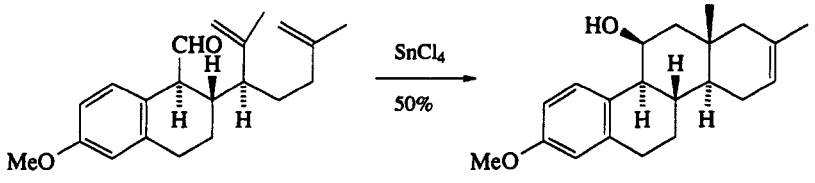
Example	*Ref.*
1	101
2	102
3	102
4	76
5	103

Scheme 26

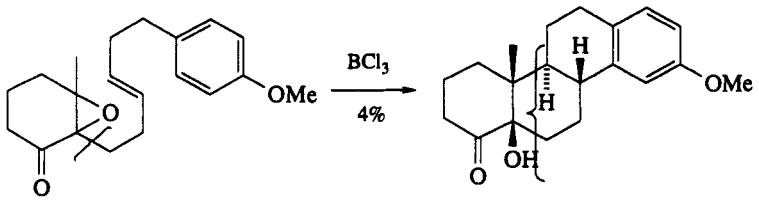
(example 3, Scheme 26), the diaxial dimethyl compound is the major product but appreciable amounts of the product with *cis* ring fusion are formed by a stepwise mechanism. A *cis* product is also formed from the (*Z*)-alkene (example 4, Scheme 26) with the methyl adopting an equatorial orientation. Diastereoselection is also found when a methyl is introduced at C-1 (example 5, Scheme 26), leading to preferred attack on the least-hindered face of the allyl cation. An azasteroid has been prepared by the Speckamp group[104] in excellent yield by cyclization of the amide (**51**), while the Ziegler group[105] has described the novel cyclization of the aldehyde (**52**). A comparison of different initiators by the Sutherland group (Scheme 27) showed that the epoxide (example 1, Scheme 27) was unsatisfactory, giving mainly monocyclization, but that both the enone (example 2, Scheme 27) and the derived methylcyclohexenol (example 3, Scheme 27) could be cyclized in acceptable yields.



(**51**)

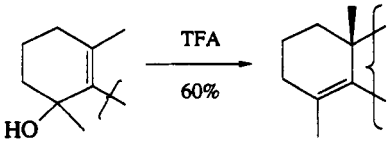


(**52**)



Example	*Ref.*
1	106

2	106

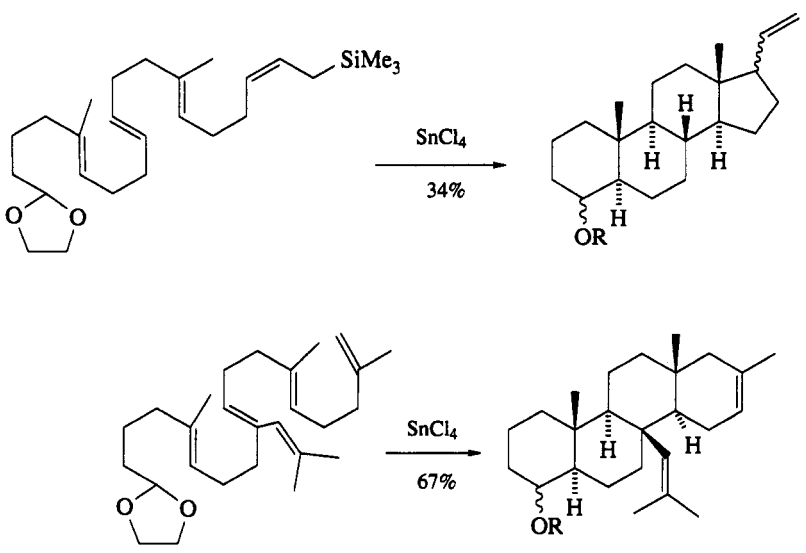


3	106

Scheme 27

1.9.8.2 Nonaromatic Steroids and Related Compounds

In the first successful production of tetracycles by polyalkene cyclization the Johnson group used oxonium ion initiation to convert an acetal to a D-homosteroid (**43**). The yield was moderate but *trans–anti–trans–anti* stereochemistry was demonstrated. Subsequently the steroid skeleton was prepared using the allylsilane terminator (example 1, Scheme 28) and, more recently, the yield has been almost doubled by stabilization of the ion notionally produced by bicyclization (example 2, Scheme 28); perhaps two consecutive concerted bicyclizations are involved. The methylcyclohexenyl cation was also an effective trigger for cyclization to D-homosteroids (Scheme 29) when the terminating group was methylene (example 1, Scheme 29) or trimethylsilylalkynyl (example 3, Scheme 29). With the isopropylidene terminator (example 2, Scheme 29) the steroid skeleton was formed, but the cation then underwent hydride and methyl migration. These migrations could be suppressed by stabilization of the terminal cation with aryl groups (example 4, Scheme 29) of which α-naphthyl was the most effective. The *p*-methoxystyryl group was ineffective, probably due to the independent formation of the highly stabilized *p*-methoxybenzyl cation by protonation of the *p*-methoxystyryl group. Clearly if the terminating cation is formed more readily or competitively with the initiating cation, successful cyclizations are unlikely. Cyclization of the alkyne (example 5, Scheme 29) forms the steroid skeleton without rearrangement. Trapping of the vinylic cation with ethylene carbonate prevents ring expansion to the D-homosteroid. When the terminal group was vinyl[40] then control over the C–D ring junction stereochemistry was lost; *cis* isomer was formed by a proton elimination–monocyclization sequence. The intervention of this mechanism can be detected by use of *O*-deuterated acids, since it leads to deuterium incorporation (Scheme 30).



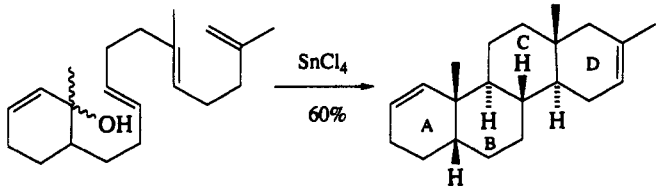
Example	*Ref.*
1	107
2	108

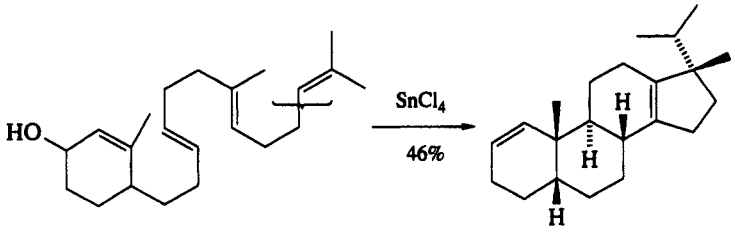
Scheme 28

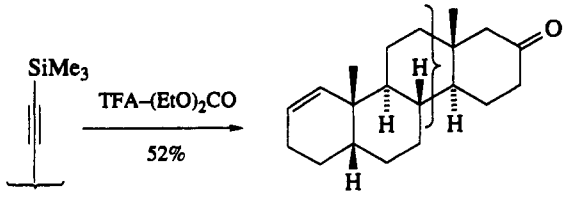
The dimethylcyclohexenyl cation has been used to prepare D-homosteroid (example 1, Scheme 31) and steroid skeletons (example 2, Scheme 31). One solution to the problem of preparing steroids without an alkyl substituent at C-4 is the use of a phenyldimethylsilyl substituent at one terminus of the allyl cation. Carbon bond formation occurs remote from the silyl substituent, which is then eliminated by protodesilylation *in situ* (Scheme 32). Reduction of the number of alkyl substituents on the allylic cation has a dramatic effect on yield (example 4, Scheme 31), suggesting that useful yields are obtained only when the allylic cations have three or four carbon substituents.

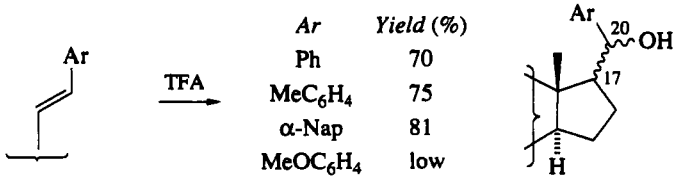
The initiator which has been studied most extensively (Scheme 33)[117–125] is the dimethylcyclopentenyl cation, which is generated from the corresponding alcohol by reaction with protonic or Lewis acids. An

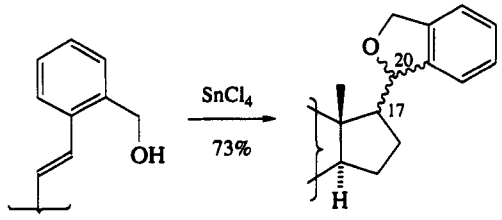
Example	*Ref.*
1	109
2	111
3	110
4	112
5	113

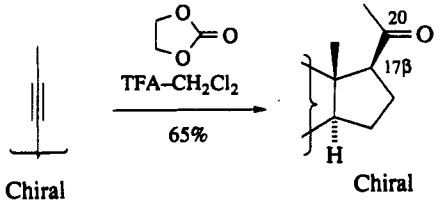




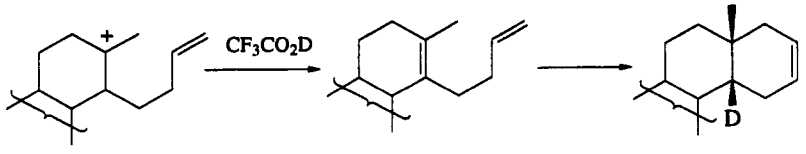




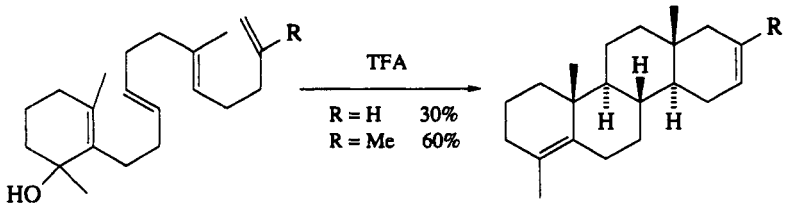




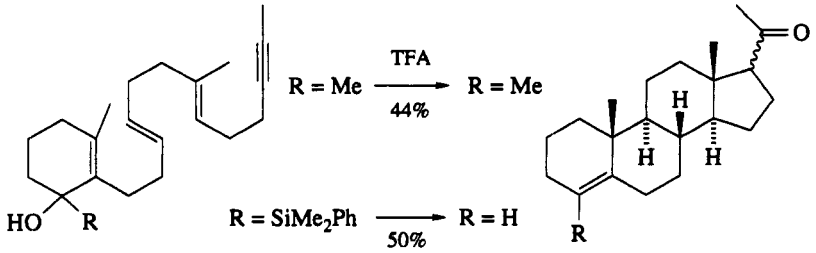
Scheme 29



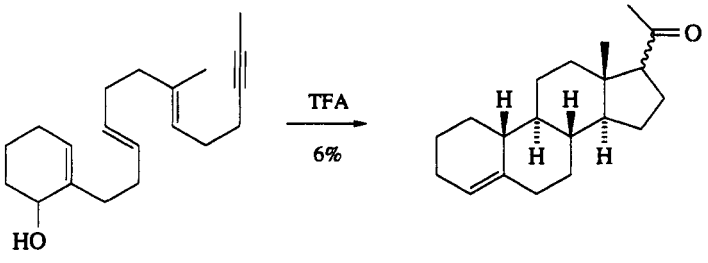
Scheme 30



Example	*Ref.*
1	114

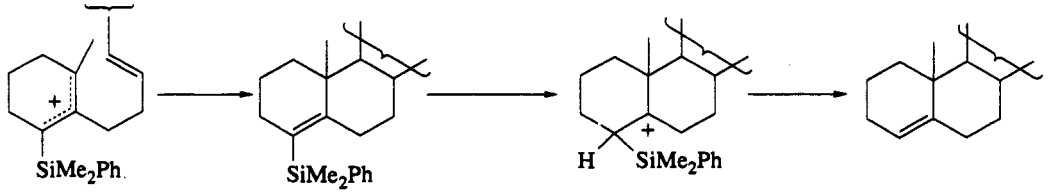


2	115
3	115



4	116

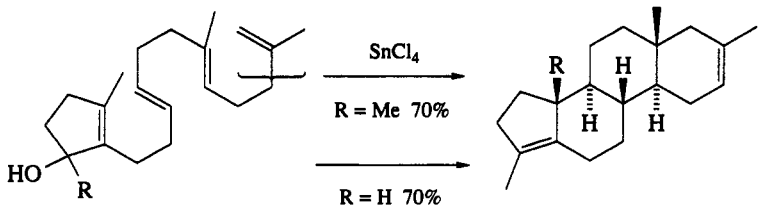
Scheme 31



Scheme 32

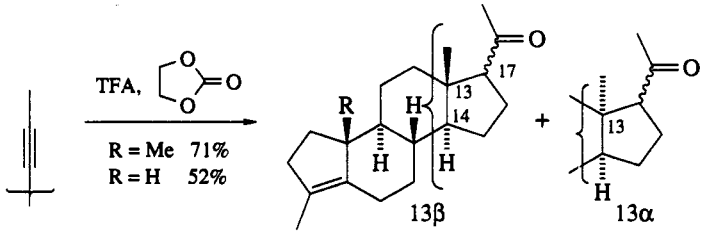
early testosterone synthesis was based on the cyclization (example 1, Scheme 33); ozonolysis and aldol cyclization of the product formed the steroid skeleton. 19-Norsteroids could also be prepared by this route (example 2, Scheme 33). Much time and ingenuity have been spent in deriving direct methods for forming the *trans*-C,D ring fusion of steroids. Besides the stereochemistry of the ring junction, the question of the orientation of pendant group on the cyclopentane also arises. The alkynyl group in various forms is an efficient terminator but up to 20% of the *cis*-C,D isomer (13α) is formed. The styryl (example 6, Scheme 33), fluorovinyl (example 7, Scheme 33), and allylsilyl (examples 8 and 9, Scheme 33) lead to significantly lesser amounts of 13α-isomer but roughly equivalent quantities of 17α- and 17β-isomers. This is not a major drawback as 20-ketones can be isomerized to mixtures rich in the 17β natural isomers at later stages. This lack of selectivity is to be contrasted with mono- and bi-cyclizations using these terminating groups where there is a distinct preference for the α-isomers.

As in the estrone cyclization (Scheme 25) substituents introduced on to the methylene chains can induce diastereoselection. The Johnson group cyclized a precursor with a methyl group at pro-C-11 to give only the 11α-isomer (example 1, Scheme 34). The origin of the diastereoselection is likely to lie with the unfavorable interaction between the vinylic methyl and the axially oriented 11β-methyl (**53**) excluding cyclization in this conformation; cyclization of the compound lacking the vinylic methyl exhibits no diastereoselection. When the methyl group was replaced by hydroxyl (example 2, Scheme 34), the yield and rate of reaction were both reduced, presumably due to the inductive effect of the hydroxyl reducing the double bond nucleophilicity; however, complete diastereoselection was observed and using chiral alcohol an enantiospecific synthesis of 11-hydroxyprogesterone was achieved. This must be regarded as the

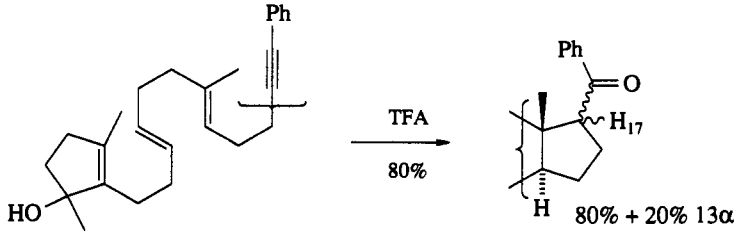


Example 1 — *Ref.* 117

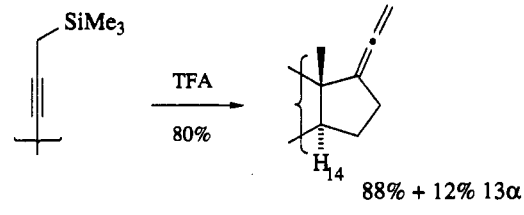
Example 2 — *Ref.* 117



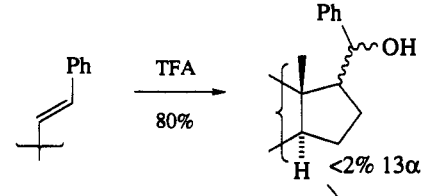
Example 3 — *Ref.* 118, 119



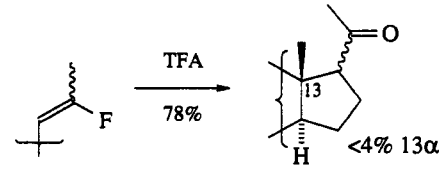
Example 4 — *Ref.* 122



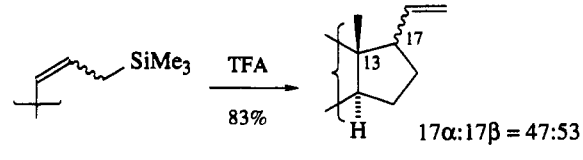
Example 5 — *Ref.* 122



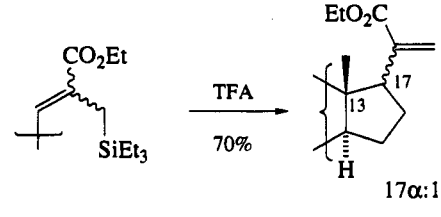
Example 6 — *Ref.* 120



Example 7 — *Ref.* 121



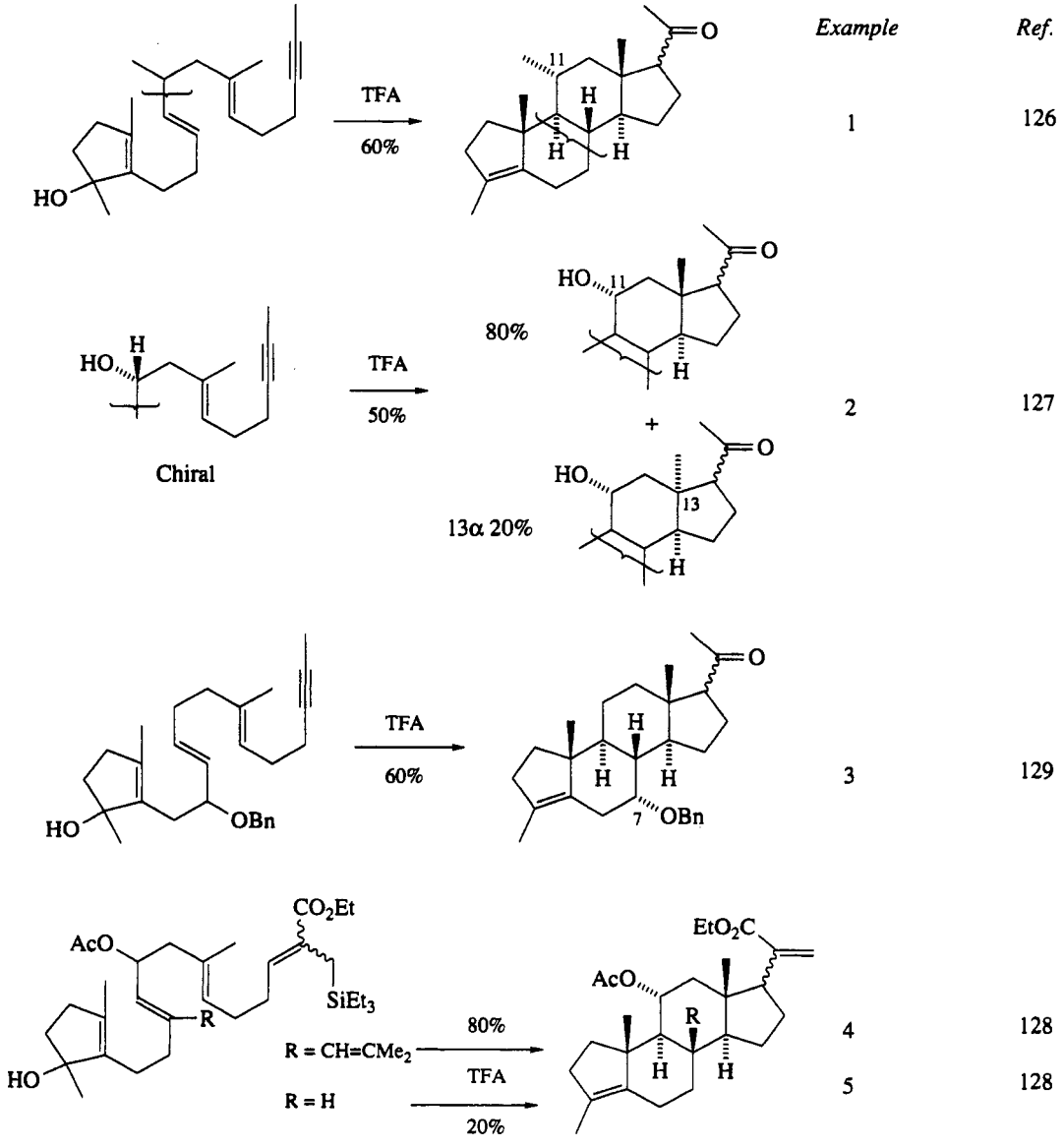
Example 8 — *Ref.* 124



Example 9 — *Ref.* 125

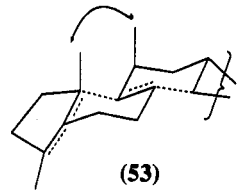
Scheme 33

major achievement of polyalkene cyclization up to the present. With a benzyloxy at pro-C-7 diastereoselection in favor of the axial 7α-ether was found (example 3, Scheme 34). This diastereoselection was improved in the cyclization of the normethyl secondary alcohol in contrast to the pro-C-11-substituted series. These results also contrast with the diastereoselections found in the closely related estrone cyclizations (Scheme 26) where the pro-C-11 methyl favors axial orientation; the absence of the 1,3 methyl–methyl interaction in the estrone precursor may offer a rationalization. The differing selectivities for the pro-C-7 compounds are more difficult to understand. Recently the Johnson group has used the device of two possible consecutive bicyclizations (example 4, Scheme 34) and achieved impressive yields and diastereoselectivity; the effectiveness of this approach is apparent when compared with the relatively poor yields obtained when the ion from bicyclization is not stabilized (example 5, Scheme 34). The Brunke steroid synthesis[130] has as its basis the cyclization of the tetraene (**54**) to the tetracycle (**55**). Presumably the first cyclization forms the allylic cation (**56**), which undergoes equatorial attack to form the tetracyclic ion. Equatorial attack is preferred over the more usual axial addition to allylic ions since the latter would require ring c to adopt a twist-boat conformation. This form of 'remote' stereochemical control might be capable of further exploitation. Van Tamelen and Hwu[131] have described a progesterone synthesis based on cyclization of a cyclohexene epoxide (**57**).

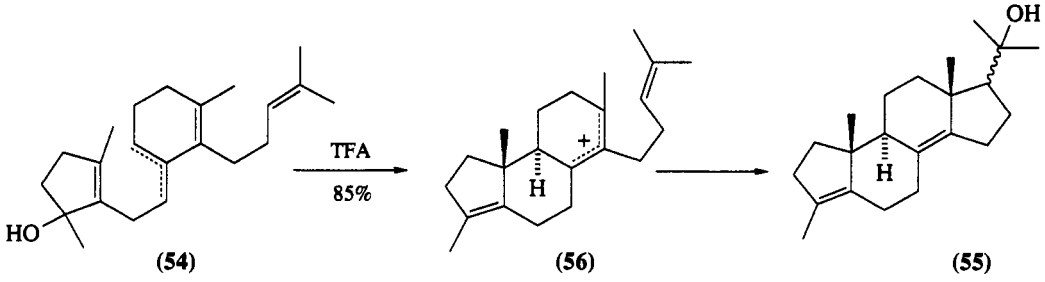


Example	*Ref.*
1	126
2	127
3	129
4	128
5	128

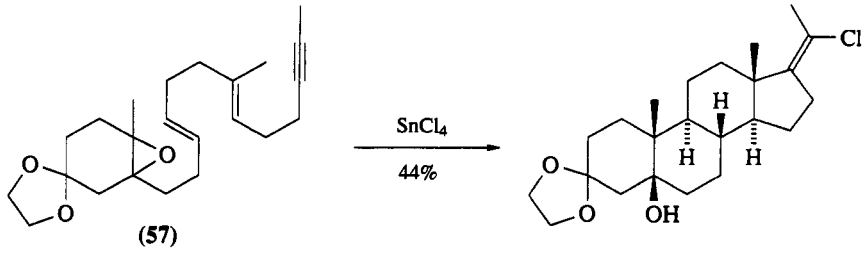
Scheme 34



(53)



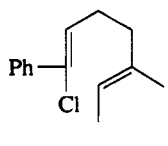
(54) (56) (55)



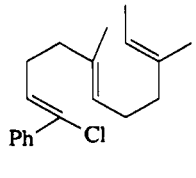
(57)

1.9.9 MECHANISM

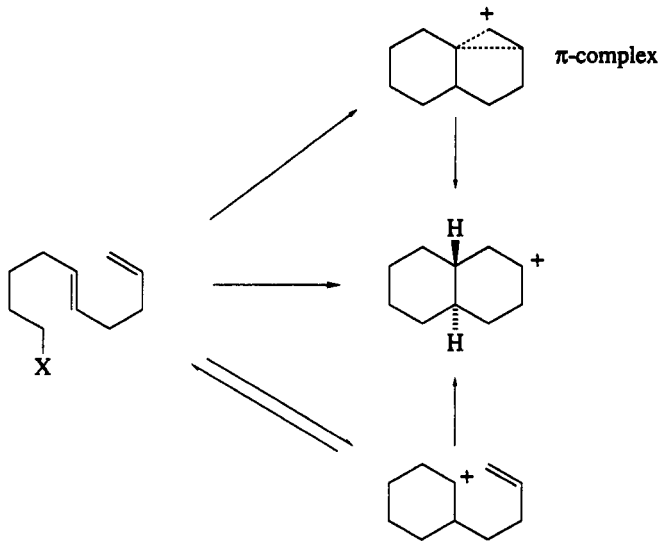
In 1983 Bartlett wrote an excellent and well-balanced account discussing possible mechanisms for polyalkene cyclizations. In it is summarized the powerful evidence that structural and electronic features in the incipient second ring can influence both the rate and the stereochemical outcome of a reaction. In one case Borčić *et al.*[132] found that the diene (**58**) solvolyzed nine times faster than the alkene (**59**), and that there were dramatic differences in the enthalpies ($\Delta H^{\ddagger}$) and entropies ($-\Delta S^{\ddagger}$) of activation. In his article[5] Bartlett asks 'is there concertedness beyond the second ring?', and argues persuasively that the likely answer is 'no', due to the entropic debt which would result in 'freezing' additional bonds. To account for the various effects in bicyclizations there are three distinct options — a concerted reaction, a concerted cyclization to a π-complex, or a stepwise process in which the cyclizations are reversible (Scheme 35). The geometric restrictions on the first two options are similar and distinction between them is difficult; thermodynamic arguments militate against the retrocyclization mechanism. Another mechanistic question arises from the strong tendency of cyclohexyl cations to undergo equatorial attack, particularly when produced by the cyclization route. This raises the possibility of two types of cyclohexyl cation separated by a small energy barrier, one arising from C—C hyperconjugation, the other from C—H hyperconjugation, with the empty *p*-orbital; the former would lead to equatorial attack. Recent work suggests that there could be two methylcyclohexyl cations.[133]



(58)



(59)



Scheme 35

1.9.10 SUMMARY

Polyalkene cyclization is a powerful synthetic method for the preparation of alicyclic compounds containing certain combinations of five-, six- and seven-membered rings. The Stork–Eschenmoser hypothesis can be adopted as a guiding principle in synthetic planning but it is not universally applicable. However, using stabilized cations as initiators and participating double bonds of appropriate nucleophilicity then the notion of concerted bicyclization *via* chair–chair transition states has good predictive value. It is the synthesis of *cis*-fused rings from (Z)-alkenes that requires the most careful planning. For tri- and tetra-cyclizations the formations of the third and fourth rings are governed by the rules for the cyclization of cycloalkyl cations. In future synthetic planning it may be advantageous to plan a tricyclization as a bicyclization followed by a monocyclization, and a tetracyclization as two consecutive bicyclizations, *i.e.* the initial bicyclization produces a cation which is itself a good initiator of cyclization. This will require a delicate 'tuning' of reactivity since initiation at the second center would be unproductive; indeed the approach of generating the second cyclization initiator from the terminator of the first cyclization in a separate chemical step may be more productive.

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1.10
Transannular Electrophilic Cyclizations

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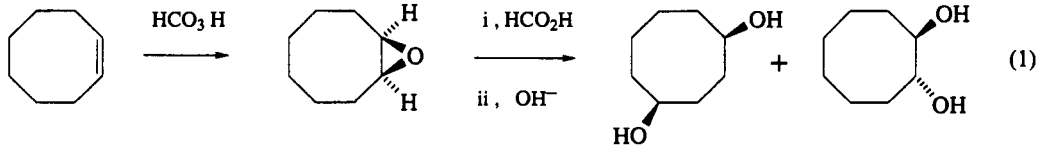
1.10.1 INTRODUCTION

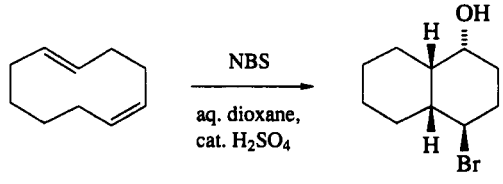
It is now almost 40 years since Cope and Prelog first described the phenomenon of 'transannulation' reactions during their independent studies of electrophilic additions to medium ring cycloalkenes.[1,2] Since that time transannular reactions have been encountered in an enormous variety of carbo- and hetero-cyclic medium ring compounds having a wide array of differing functionalities. Indeed, the chemistry of these fascinating processes has now become part of the day-to-day armoury of the modern synthetic chemist.[3]

Transannular reactions are defined as those reactions which lead to the formation of a covalent bond between atoms on opposite sides of a ring compound. They occur frequently in medium, *i.e.* 8-, 9-, 10- and 11-membered, rings where favored conformations allow opposite sides of the rings to come close to each other for bond formation. Probably the most commonly encountered transannulation processes are

those involving H-transfer reactions,[4] from, for example, ring epoxides, *i.e.* (**1**) → (**2**; equation 1),[5] and those involving ring closure reactions, *i.e.* (**3**) → (**4**; equation 2)[6] from cyclic polyenes in the presence of electrophilic reagents, *i.e.* conditions which favor carbonium ion formation. Transannular ring closure reactions *via* intermediate carbanions,[7] carbenes[8] and radicals,[9] and *via* pericyclic processes,[10] are also known. So too are several reactions involving nitrogen,[11] sulfur,[12] and oxygen[13] heterocyclic ring formation.



(1)



(2)

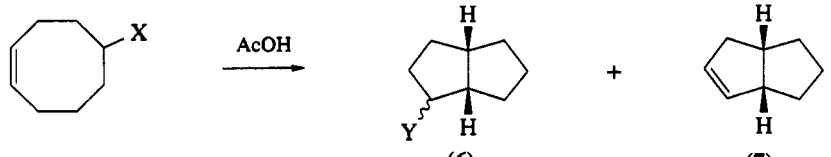
The chemistry of transannular cyclizations involving 1,5-diene units in medium ring carbocycles has been studied with particular vigor in recent years because of the relevance of this chemistry to the biogenetic origins of cyclic terpenes.[14] Indeed, these fundamental studies have now led to a number of novel 'biogenetically inspired' syntheses of a large range of complex ring-fused natural products of both biosynthetic significance and biological importance.[15]

This chapter summarizes those transannular reactions in medium ring carbocycles which result in carbon–carbon bond formation *via* alkylation of carbon, in the presence of electrophilic reagents. It is therefore a logical extension of two other chapters in this volume, covering Friedel-Crafts Alkylations (Chapter 1.8), and Polyene Cyclizations (Chapter 1.9). The discussion of these processes is organized according to the size of the cycloalkene from which transannular cyclization is effected.

1.10.2 CYCLOOCTENES

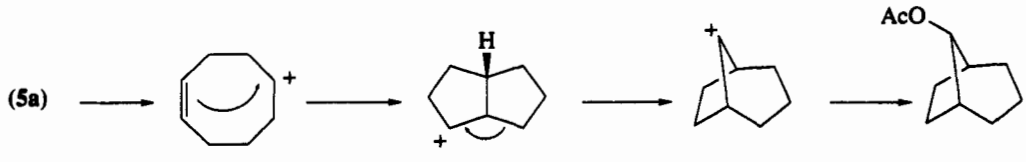
1.10.2.1 Bicyclo[3.3.0]octane and Bicyclo[3.2.1]octane Ring Formation

Following on from earlier work on transannular H-transfer reactions in cyclooctenes (*i.e.* equation 1), Cope and collaborators[1,5] carried out extensive studies of the solvolyses of a wide range of substituted cyclooctenes in a search for further unusual transannular processes. Thus, both the tosylate (**5a**) and the brosylate (**5b**) of cyclooct-4-en-1-ol were shown to produce the bicyclo[3.3.0]octanes (**6**) and the bicyclo[3.3.0]octene (**7**) on solvolysis and acetolysis respectively (equation 3).[16] The bicyclic molecules (**6**) and (**7**) are formed from (**5**) by transannular interaction in the cyclooctenyl carbonium ion (**8**), followed by quenching of the resulting carbonium ion (**9**) with a nucleophilic counterion (to form **6**), or deprotonation (to form **7**). In the case of acetolysis of (**5a**), a small amount of the bicyclo[3.2.1]octane (**10**) was produced concurrently *via* the rearranged carbonium ion (**11**; Scheme 1). Interestingly, the corresponding isomeric cyclooct-3-en-1-ol brosylate (**12**; equation 4) and the homologous brosylate (**14**; equation 5)



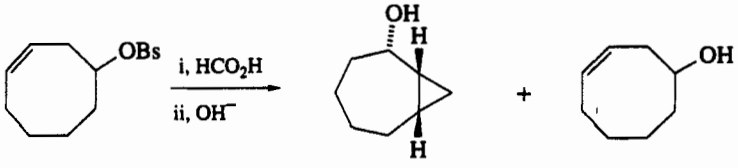
(3)

under the same conditions undergo transannulation to the bicyclic products (**13**) and (**15**), respectively.[16a,17–19]



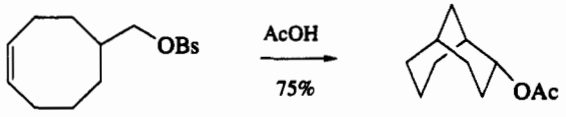
(**8**) (**9**) (**11**) (**10**)

Scheme 1



(4)

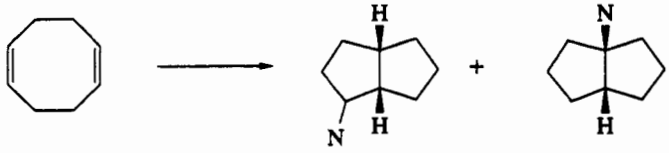
(**12**) (**13**) 52%; α:β = 3:1 25%



(5)

(**14**) (**15**)

Transannular cyclization in cycloocta-1,5-diene (**16**; equations 6 and 7) can be brought about by a wide variety of electrophilic reagents.[18–32] These reactions lead to a range of functionalized bicyclo[3.3.0]octanes (Tables 1 and 2), many of which have found widespread use in general synthesis.[33] Although the use of mineral acids favors the formation of bicyclo[3.3.0]octanes, other electrophilic agents

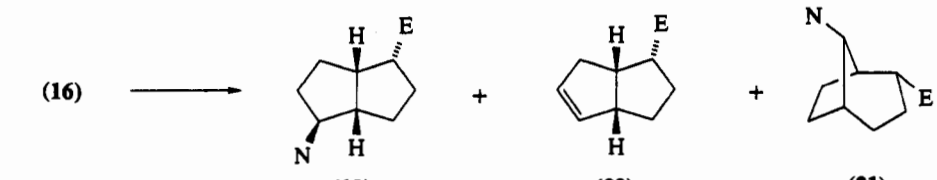


(6)

(**16**) (**17**) (**18**)

Table 1 Transannular Cyclization of (**16**; Equation 6)

Reagents	*N*	*Yield (%)* (*17*)	(*18*)	*Ref.*
$HF/H_2O/CO$	CO_2H	17	—	20
$CuCO_3/CO$	CO_2H	—	15	21
HCO_2H/H_2SO_4	CO_2H	—	33	22



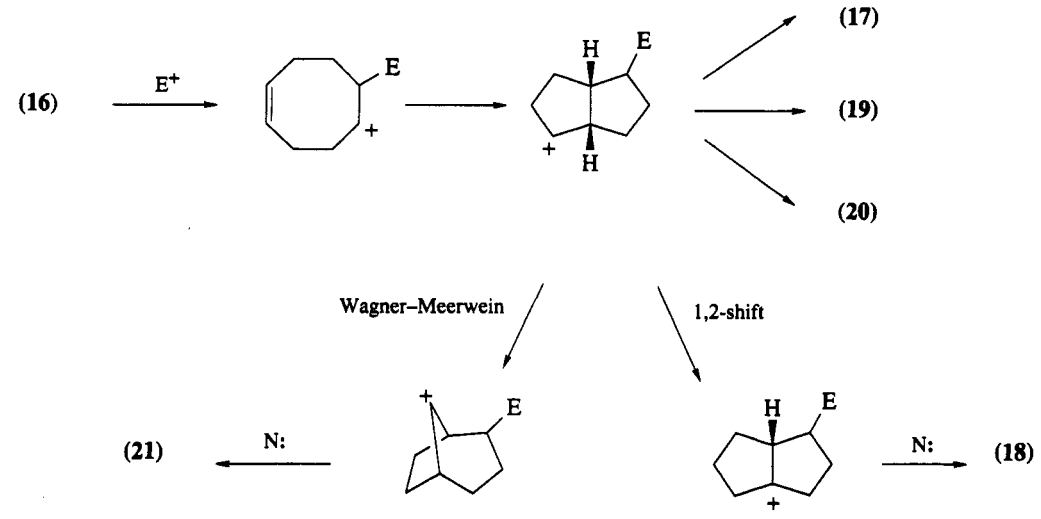
(7)

(**19**) (**20**) (**21**)

instead lead to bicyclo[3.2.1]octanes, *i.e.* (**21**), or to products resulting from hydride shifts, *i.e.* (**18**), and/or Wagner–Meerwein rearrangements, *i.e.* (**21**; see Scheme 2).

Table 2 Transannular Cyclization of (**16**; Equation 7)

Reagents	*E*	*N*	*Yield (%)*			*Ref.*
			(19)	*(20)*	*(21)*	
H_3PO_4/silica	H	—	—	72	—	23
$MeOCH_2OAc/BF_3$	CH_2OMe	OAc	24	26	11	24
$Hg(OAc)_2/HClO_4$	OAc	OAc	13	38	—	25
I_2/CCl_4	I	I	77	—	—	26
$(PhSe)_2/I_2/MeCN$	SePh	NHAc	63	—	—	27
NBS/HF/pyridine	Br	F	66	—	—	28
$SbCl_5/CCl_4$	Cl	Cl	—	—	70	29
$Tl(OCOCF_3)_2$	$OCOCF_3$	H	—	31	—	30
$Ni^{II}/EtAlCl_2$	H	—	—	96	—	31



Scheme 2

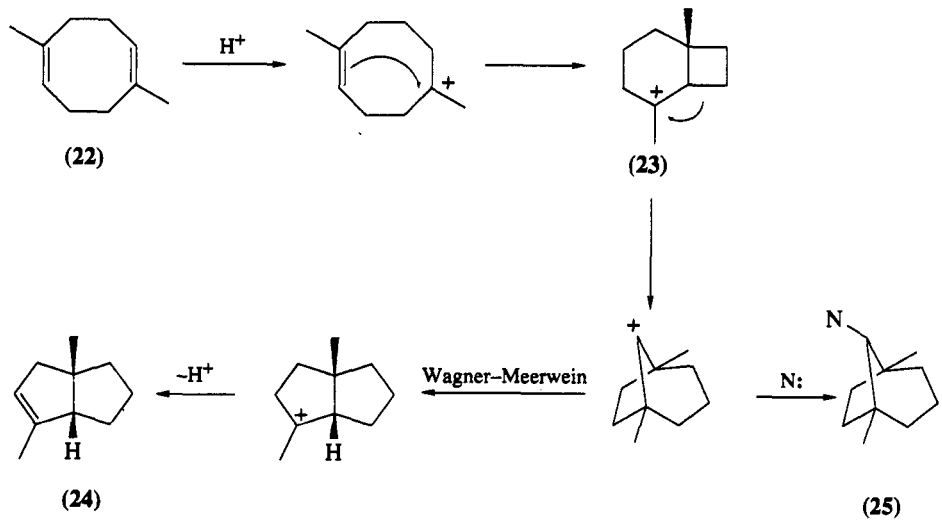
The high degree of selectivity observed in the aforementioned transannulation process can be rationalized in terms of Baldwin's rules,[34] and the possible low energy conformation available to the ring.[35,36] This situation becomes complicated however in the case of 1,5-dimethylcycloocta-1,5-diene (**22**), since transannulation first leads to the more stable bicyclo[4.2.0]octane carbonium ion (**23**), which then undergoes a series of Wagner–Meerwein rearrangements (Scheme 3) before producing either the bicyclo[3.3.0]octane (**24**) or the bicyclo[3.2.1]octane (**25**), as shown in Table 3.[37–39] Surprisingly the monoepoxide derived from 1,5-cyclooctadiene affords only a small yield of bicyclo[3.3.0]octane-2,6-diol on transannular cyclization.[3b,40]

Table 3 Transannular Cyclization and Rearrangement of (**22**; Scheme 3)

Reagents	*N*	*Yield (%)*		*Ref.*
		(24)	*(25)*	
$BF_3{\cdot}OEt_2$	H	60	—	37
TsOH	OTs	—	70	37
$HCO_2H/HClO_4$	OCHO	16	62	38
$AcOH/HClO_4$	OAc	32	38	38

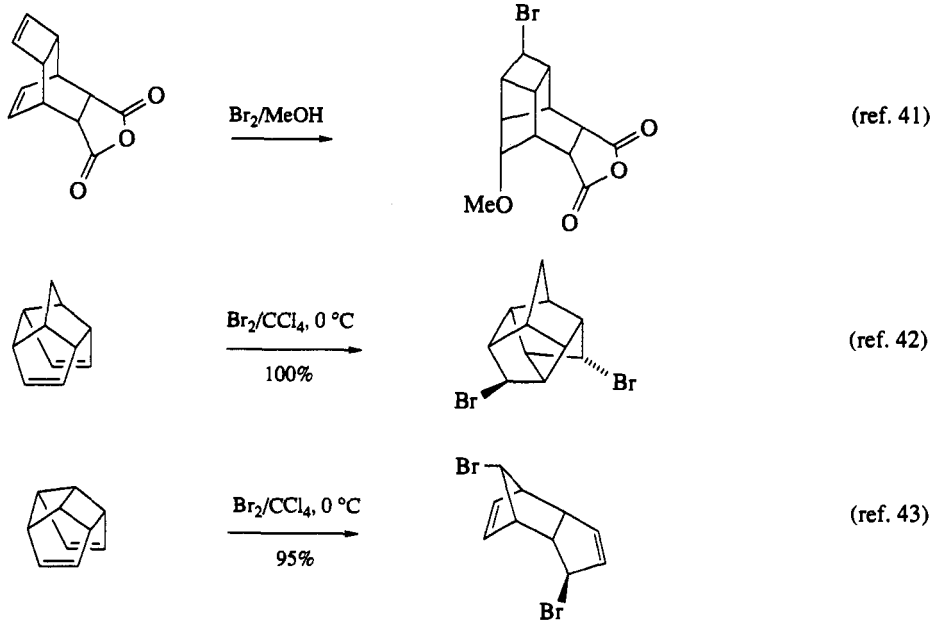
1.10.2.2 Caged Compounds

Numerous examples of transannulation reactions amongst caged compounds, which can be considered as conformationally restricted medium rings, have been studied, and some representative examples are



Scheme 3

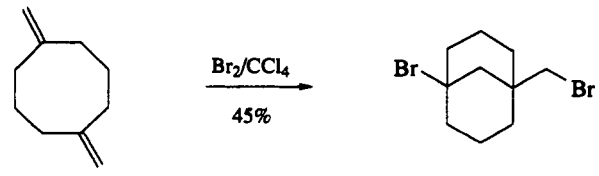
collected in Scheme 4.[41–44] Generally, such reactions lead to the products of 'crossed' rather than 'parallel' cyclization, *i.e.* fused 5,5-ring products predominate over fused 6,4-rings.[45]



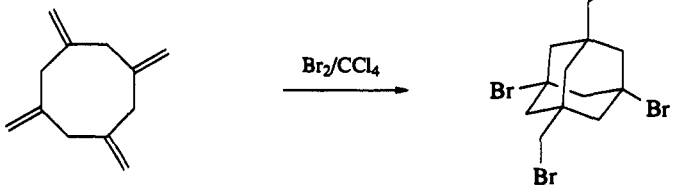
Scheme 4

1.10.2.3 Endocyclic 1,3- and 1,4-Cyclooctadienes

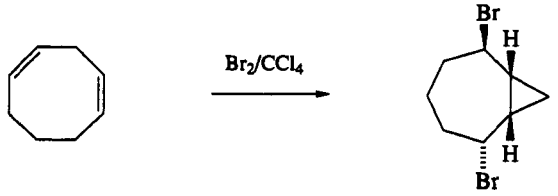
Transannulation reactions involving cyclooctenes are not restricted to endocyclic alkenes or to those systems which require a 1,5-relationship of the reacting centers. Thus, the exocyclic polyenes (**26**; equation 8) and (**27**; equation 9) take part in some novel transannulation processes when treated with bromonium ion,[46,47] and both cycloocta-1,3-diene and cycloocta-1,4-diene undergo transannulation reactions under favorable conditions producing the bicycles (**28**; equation 10) and (**29**; equation 11), respectively, in very acceptable yields.[48,49] Perhaps even more novel is the transannular cyclization of 5-methylenecyclooctanecarbaldehyde (**30**) in water, leading to the unstable bicyclo[3.3.0]octanecarbaldehyde (**32**); this reaction is best formulated as proceeding *via* the corresponding enol (**31**) under acid catalysis (equation 12).[50]



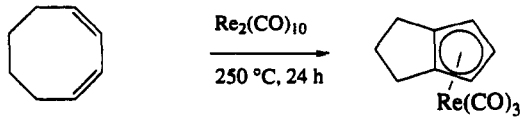
(26) (ref. 46) (8)



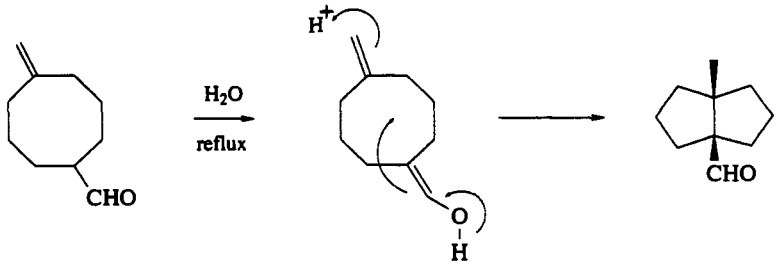
(27) (ref. 47) (9)



(28) (ref. 48) (10)



(29) (ref. 49) (11)

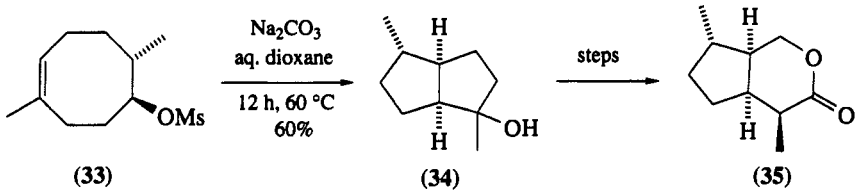


(30) (31) (32) (12)

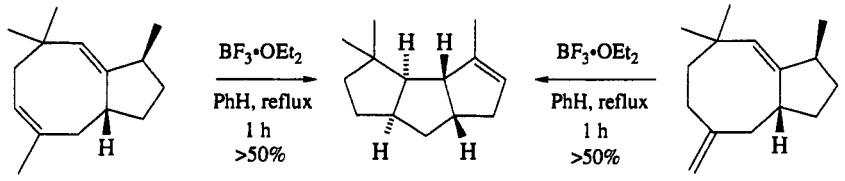
1.10.2.4 Synthesis of Natural Products

Transannulation of the mesylate (**33**), derived from 4,8-dimethylcycloocta-4-en-1-ol, using sodium carbonate in aqueous dioxane has provided the bicyclo[3.3.0]octanol (**34**), a central precursor to the monoterpene iridomyrmecin (**35**; equation 13).[51] In studies of the biomimetic synthesis of the natural triquinanes capnellene (**37**; equation 14) and pentalenene (**40**; equation 15) Pattenden *et al.* have shown that both molecules can be produced from appropriate cycloocta-1,5-diene precursors, *i.e.* (**36**) and (**39**) [or indeed their corresponding positional isomers (**38**) and (**41**), respectively] by treatment with boron trifluoride.[52,53] Mehta *et al.* have described an alternative transannulation approach to the triquinane unit found in pentalenene,[54] *i.e.* (**42**) → (**43**; equation 16), and also to the ring system (**44**; equation 17) found

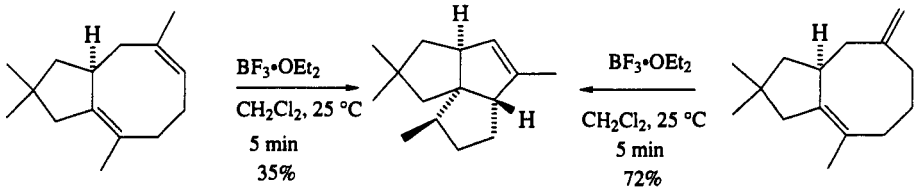
in the diterpene laurenene (**45**).[55] The key feature of Chatterjee's approach to the sesquiterpene isocomene (**47**) is the transannular cyclization of the alkene epoxide (**46**) in the presence of TFA in CH_2Cl_2 at –78 °C (equation 18); however, doubt has been cast on these results.[56]



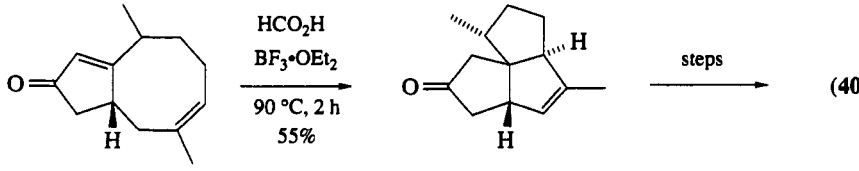
(33) (34) (35) (13)



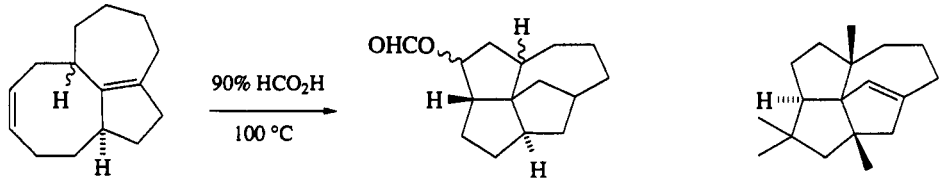
(36) (37) (38) (14)



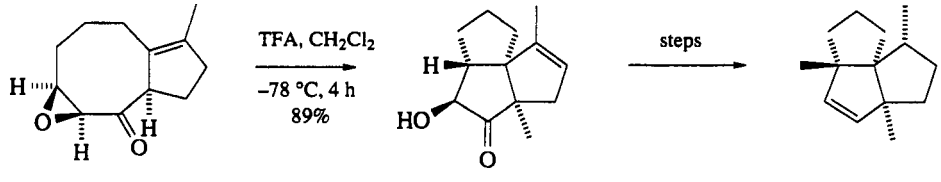
(39) (40) (41) (15)



(42) (43) (40) (16)



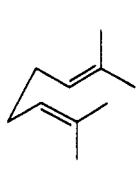
(44) (45) (17)



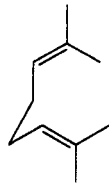
(46) (47) (18)

1.10.3 CONFORMATIONAL ARRANGEMENTS OF 1,5-DIENES IN MEDIUM RINGS

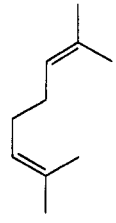
Three distinct conformational arrangements for a 1,5-diene set within a medium ring have been identified, and these are shown in formulae (**48**)–(**50**).[3c] Conformation (**48**) is referred to as 'crossed', abbreviated to C, whereas the conformation (**49**) is 'parallel', abbreviated to T. Formula (**50**) indicates an extended conformation. Models show that the C-conformation (**48**) can be adopted by (*E*,*E*)- and (*Z*,*E*)-1,5-dienes in medium rings, whereas the T-conformation (**49**) is possible for (*E*,*E*)-, (*Z*,*E*)- and (*Z*,*Z*)-isomers. The extended conformation (**50**) is available only to (*Z*,*Z*)-1,5-dienes. The conformations adopted by an isomeric 1,5-diene in a medium ring are crucial in determining the stereochemical outcome of any transannular cyclization product. These principles have been amply demonstrated during studies of the stereospecificities in the cyclizations of 9-, 10- and 11-membered cyclic 1,5-dienes, summarized below.[57]



(**48**)



(**49**)

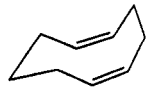


(**50**)

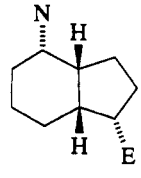
1.10.4 CYCLONONA-1,5-DIENES

Transannular cyclization of the (*Z*,*Z*)-isomer (**51**) of cyclonona-1,5-diene in the presence of a variety of electrophilic reagents provides a useful synthesis of a range of substituted *cis*-hydrindane derivatives (**53**; Table 4).[58–61] In each of these cases the 1,5-diene unit in (**51**) is reacting in the T-conformation shown in (**52**).

(**51**)



(**52**)



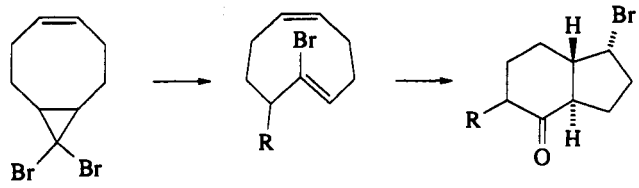
(**53**)

Table 4 Synthesis of *cis*-Hydrindane Derivatives (**53**) from 1,5-Diene (**51**)

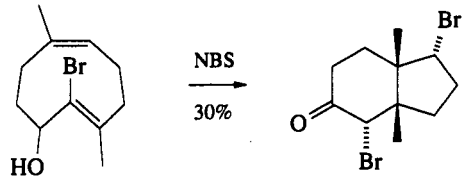
Reagents	*E*	*N*	*Yield* (%)	*Ref.*
Br_2/AcOH	Br	OAc	71	58, 59
$Hg(OAc)_2/NaBH_4$	H	OH	68	58, 60
Br_2/CCl_4	Br	Br		58
PhSeCl/AcOH	SePh	OAc	68	60
NBS/H_2O	Br	OH	44	59
NBS/MeOH	Br	OMe	90	59

Several (*Z*,*E*)-cyclonona-1,5-dienes of the type (**55**; equation 19) have been prepared *via* rearrangement of dibromobicyclo[6.1.0]nonenes (**54**) in the presence of silver salts.[62] On treatment with aqueous NBS these molecules undergo transannular cyclization, following initial attack on the (*Z*)-disubstituted double bonds, producing the corresponding *trans*-hydrindanes (**56**).[63] In related studies, Sutherland and his coworkers have also shown that similar treatment of (**57**; equation 20) leads to the bromo ketone (**58**),[64] and that when the epoxide (**59**; equation 21) is simply crystallized, it undergoes a unique transannular cyclization, producing a mixture of (**60**) and (**61**).[3c,65]

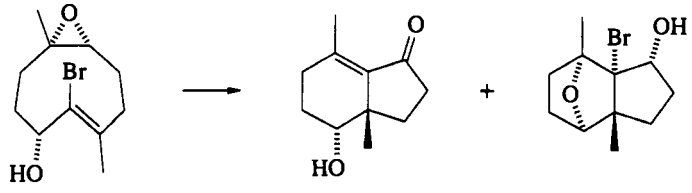
Some of the most remarkable transannular cyclizations have been uncovered during the treatment of natural caryophyllene (**63**) with mineral acids.[66–68] Thus, treatment of (**63**) with concentrated sulfuric acid has been shown to lead to a mixture of clovene (**62**), caryolan-1-ol (**64**) and neoclovene (**65**;



(54) (55a) R = OAc (55b) R = Br (55c) R = OH (56) (19)

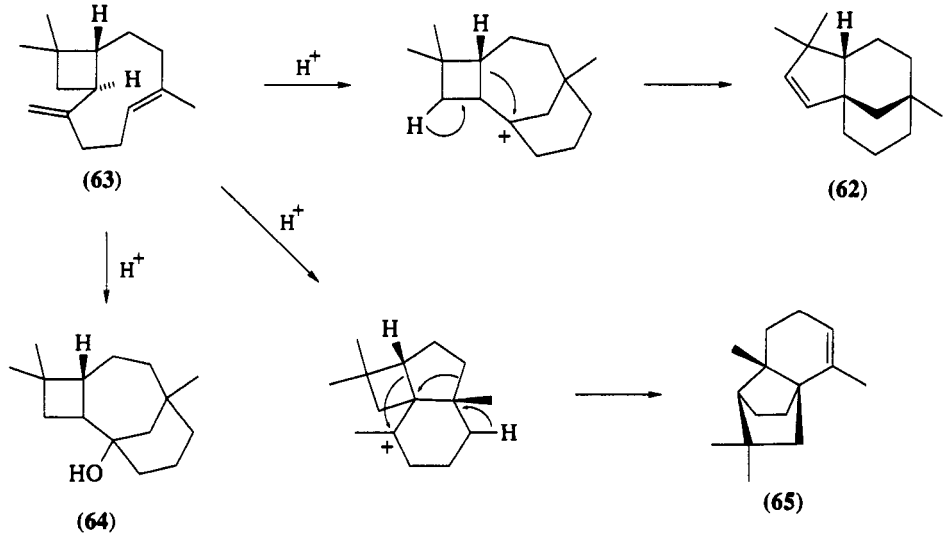


(57) (58) (20)

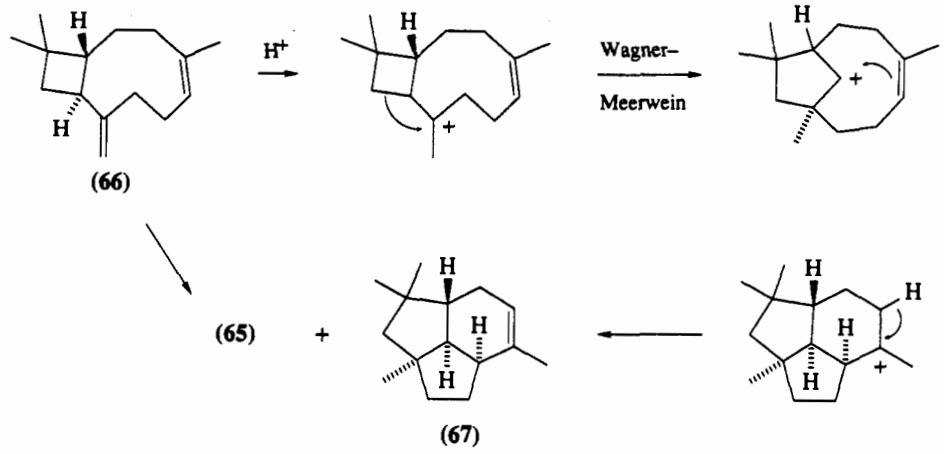


(59) (60) (61) (21)

Scheme 5). Similarly, isocaryophyllene (**66**) undergoes transannular cyclization in mineral acid to (**65**) and to the tricyclic alkene (**67**; Scheme 6) in high yield.



Scheme 5

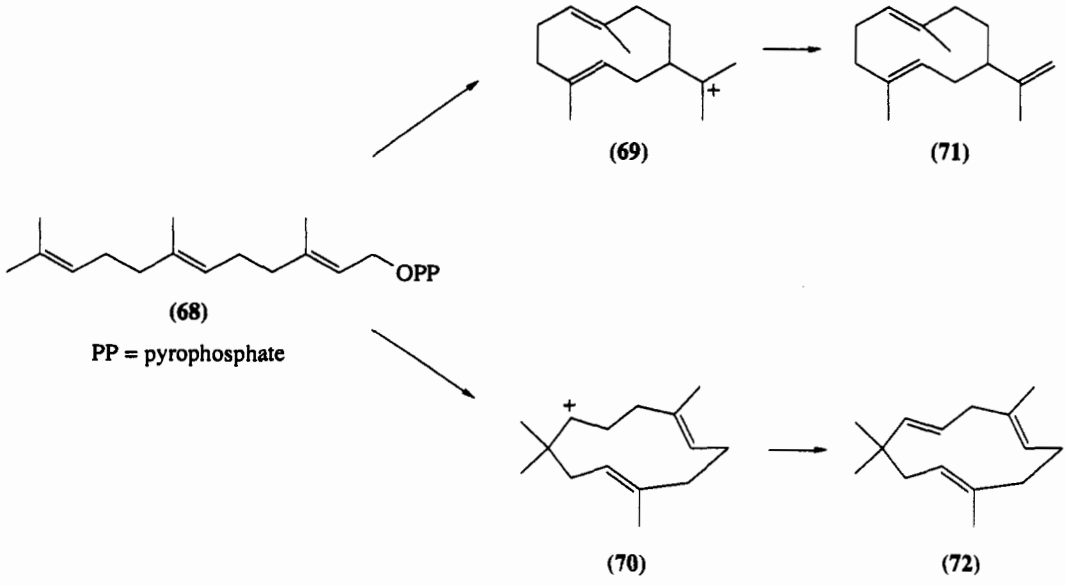


Scheme 6

1.10.5 CYCLODECENES

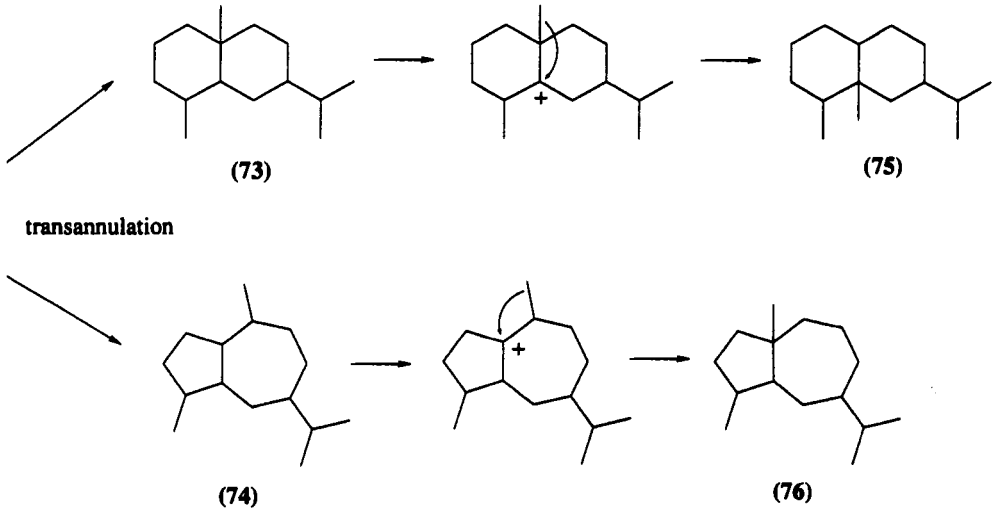
1.10.5.1 Relevance to the Biosynthesis of Polycyclic Sesquiterpenes

Transannular cyclizations involving carbonium ions generated from cyclodeca- and cycloundeca-polyenes have been the subject of extensive research, largely as a consequence of their relevance to our understanding of the biosynthesis of a wide range of polycyclic sesquiterpenes.[14] Thus, macrocyclization of farnesyl pyrophosphate (**68**) first produces both the 10-ring (**69**) and the 11-ring (**70**) carbonium ion intermediate precursors to germacrene (**71**) and humulene (**72**), respectively (Scheme 7). According to biogenetic speculation, transannulation involving the cyclodeca-1,5-diene system in germacrene (**71**) then produces the eudesmane (**73**) and guaiane (**74**) groups of natural sesquiterpenes.[14] It is generally accepted that the eremophilane (**75**) and the pseudoguianane (**76**) carbon skeletons are derived in nature by rearrangement of eudesmane and guaiane derivatives, respectively (see Scheme 8). In like manner, and using a series of regio- and stereo-selective transannulation reactions, sometimes in tandem with carbo-

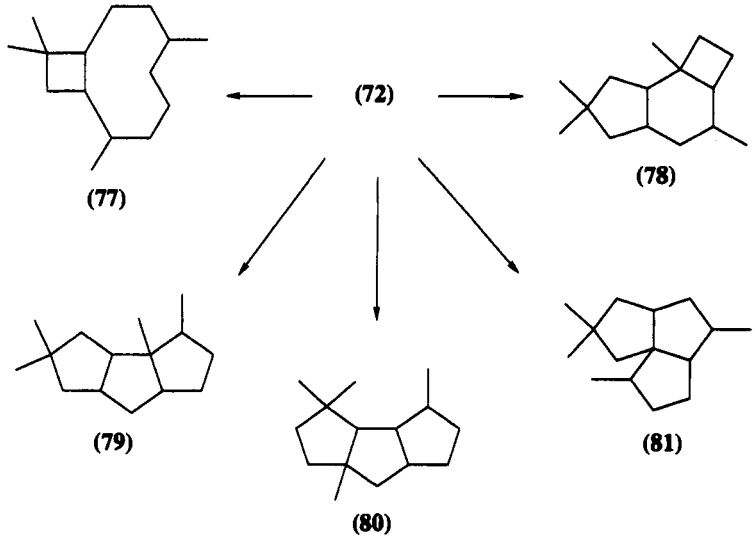


Scheme 7

nium ion rearrangements, the 11-ring humulene (**72**) gives rise to the caryophyllane (**77**), protoilludane (**78**), hirsutane (**79**), capnellane (**80**), pentalenane (**81**) and other families of sesquiterpenes (Scheme 9).[14]



Scheme 8



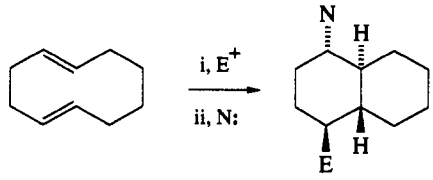
Scheme 9

1.10.5.2 Cyclodecadienes

1.10.5.2.1 Cyclodeca-1,5-dienes

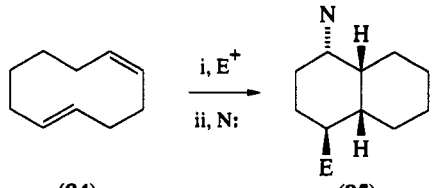
Although some detailed and fundamental studies of transannulation reactions involving cyclodeca-1,5-diene itself have been made, the main body of published work in this area has been associated with transannular reactions of germacrenes (**71**). These reactions generally proceed in both regio- and stereo-selective fashion leading to bicyclo[4.4.0]decanes of defined stereochemistry. This stereochemistry is determined largely by the geometrical configurations of the double bonds in the cyclodecadienes. Thus, the (*E,E*)-isomer (**82**; equation 22) of a cyclodeca-1,5-diene undergoes electrophilic cyclization

producing the *trans*-decalin (**83**), whereas the corresponding (*E,Z*)-isomer (**84**; equation 23) leads to the *cis*-decalin (**85**).



(22)

(**82**) (**83**)

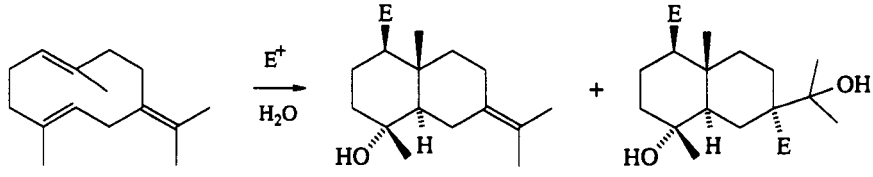


(23)

(**84**) (**85**)

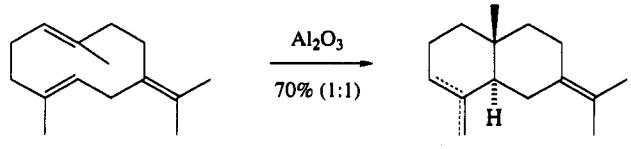
In a detailed study of transannular cyclizations of all the possible isomers of naturally occurring hedycaryol (**86**) in the presence of formic or tosic acid, Itô *et al.* have been able to rationalize the reaction pathways on the basis of the preferred conformations, *i.e.* crossed conformation (CC, CT) or parallel conformations (TT, TC), of the reacting dienes (Scheme 10).[69,70]

A selection of examples (equations 24–31) demonstrate the considerable scope for transannular reactions of cyclodeca-1,5-dienes in the synthesis, including biomimetic synthesis, of a wide range of isomerically pure, substituted bicyclo[4.4.0]decanes.[71–86]

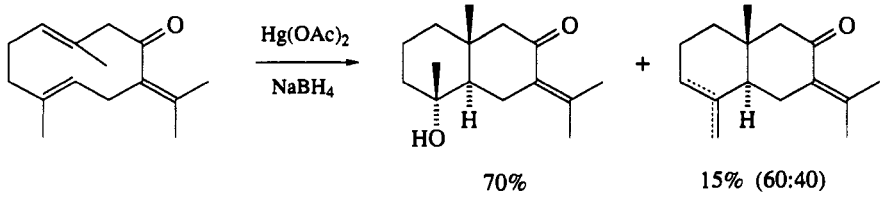


(24)

Reagents	*E*			*Ref.*
NBS, aq. acetone	Br	31%	–	71, 72
$Hg(OAc)_2/NaBH_4$	H	24%	10%	72
H_2SO_4, aq. acetone	H	–	95%	72



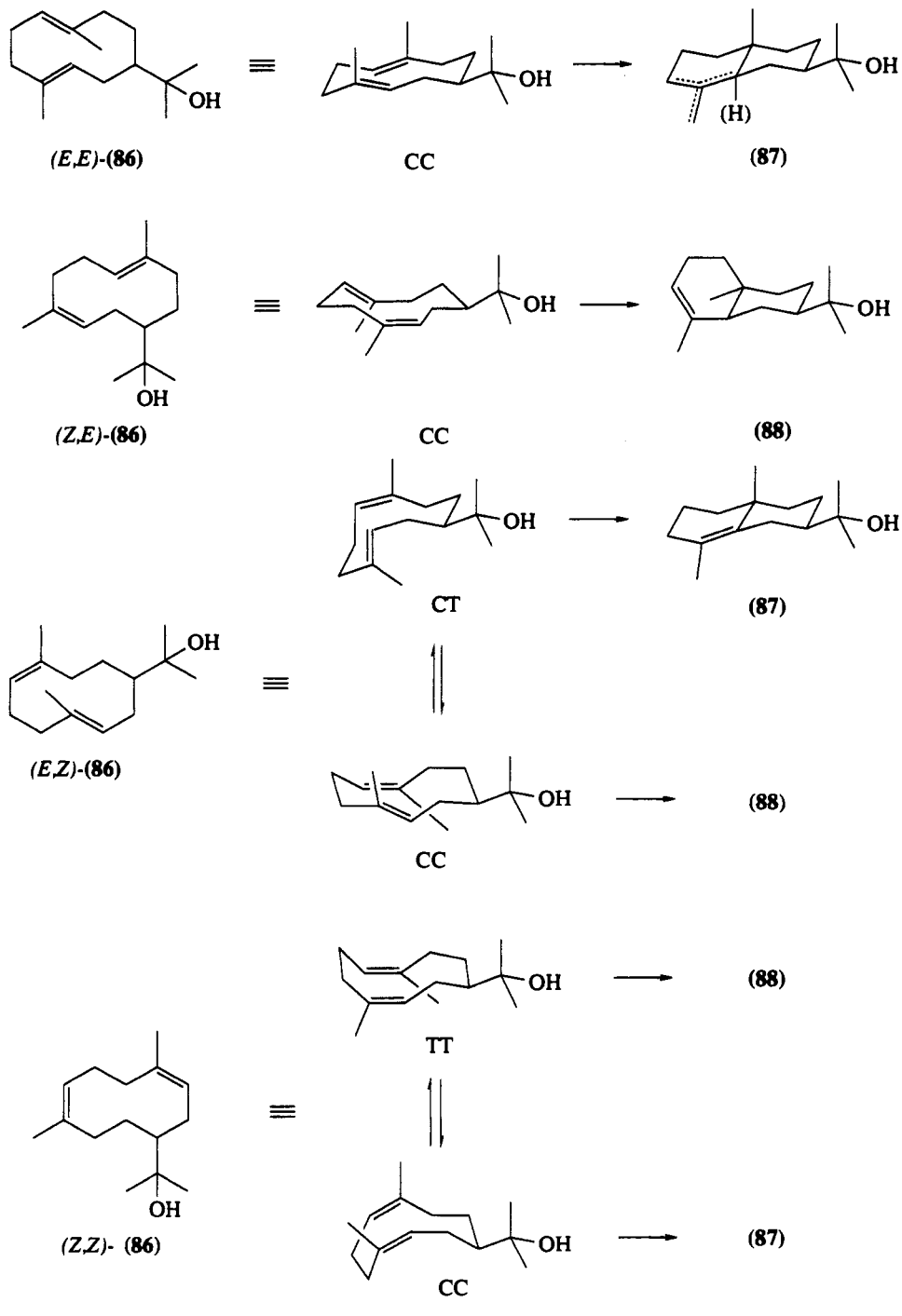
(ref. 72) (25)



(ref. 73) (26)

1.10.5.2.2 Other cyclodecadiene systems

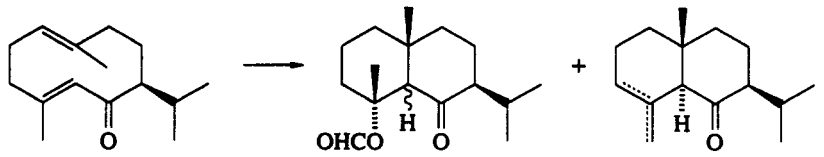
Treatment of the bicyclogermacrene (**89**; equation 32), containing a cyclopropane ring, with dilute sulfuric acid leads to the aromadendrene (**90**; *cf.* guaiane **74**), together with the bicyclo[4.4.0]decadiene



Scheme 10

(**91**).[87] Interestingly, when the 1,5-vinylcyclopropane (**92**; equation 33) is treated with acetic acid under reflux for six days it produces largely the tricyclic acetate (**93**; 58%).[88]

Geometrical isomers of cyclodeca-1,6-dienes show a similar reactivity profile to the corresponding 1,5-dienes in their transannular cyclizations to bicyclo[4.4.0]decanes, *i.e.* (*Z,Z*)-isomers lead to *cis*-decalins, whereas (*E,E*)-isomers produce *trans*-decalin products.[89–91] Some pertinent examples are shown in equations (34–37).

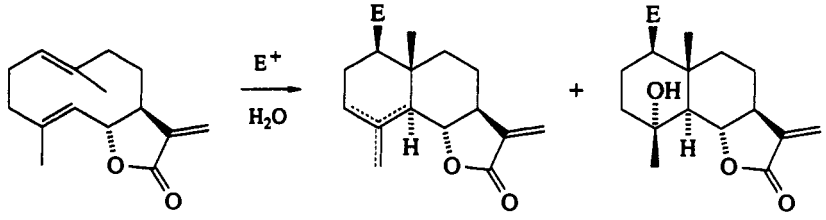


(ref. 74) (27)

80% HCO_2H
$AlCl_3$, Et_2O

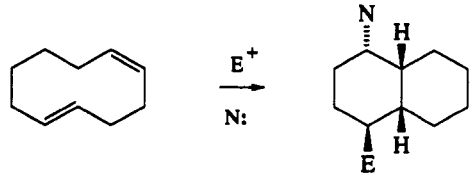
34% (1:1)
–

–
78% (55:23)



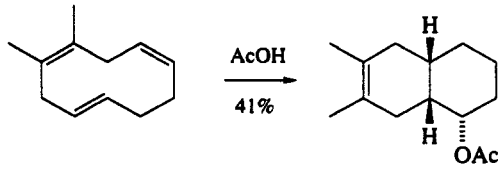
(28)

Reagents	*E*			*Ref.*
BF_3•OEt_2	H	65%	1.5%	75
Amberlite IR-120	H	67%	–	76
$SOCl_2$	H	96%	–	77
aq. NBS	Br	41%	50%	78

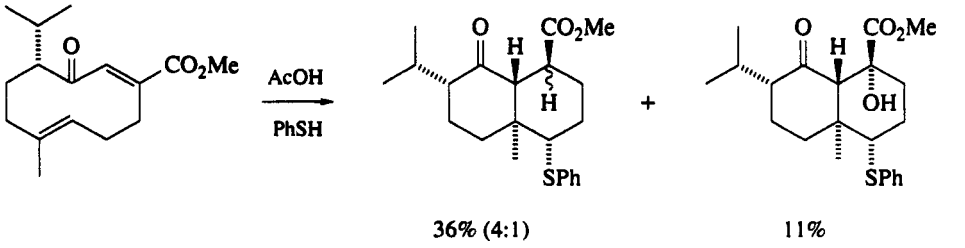


(29)

Reagents	*E*	*N*		*Ref.*
HCl, aq. dioxane	H	OH	40%	80
$Hg(OAc)_2/NaBH_4$	H	OH	80%	81
$Pb(OAc)_4$, AcOH	OAc	OAc	60%	81
I_2, CCl_4	I	I	90%	82



(ref. 84) (30)

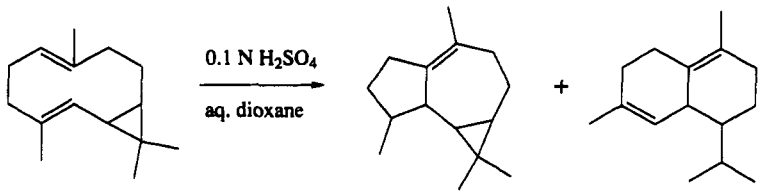


(ref. 85) (31)

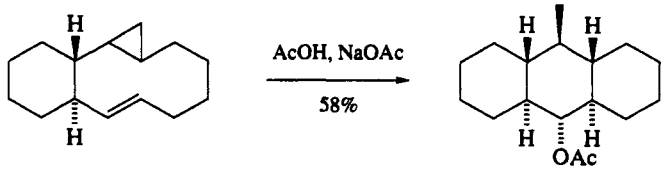
36% (4:1)

11%

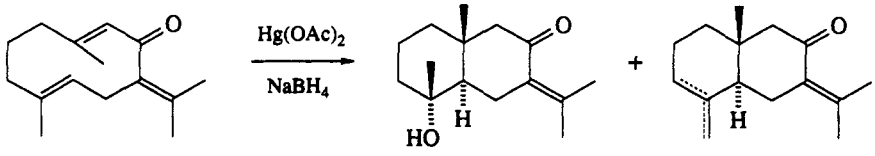
The cyclodecatetraene (**94**), incorporating an allene unit, undergoes transannulation accompanied by rearrangement in the presence of $HgSO_4$, producing a mixture of the bicyclo[4.4.0]decenol (**95**) and the vinylcyclopropane (**96**; Scheme 11).[92]



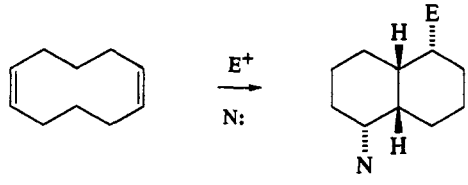
(89) (90) (91) (32)



(92) (93) (33)

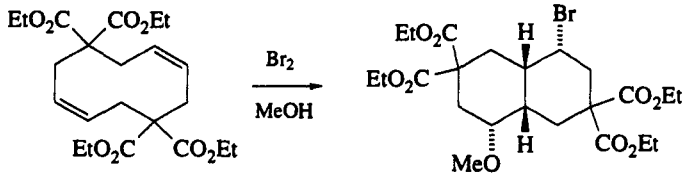


33% 10% (ref. 37) (34)

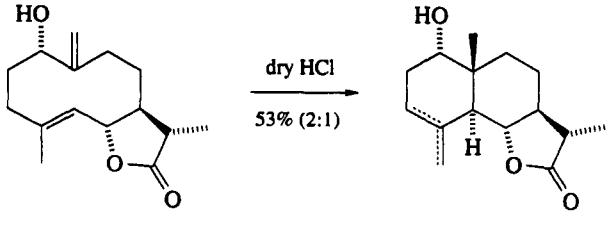


(ref. 61) (35)

AcOH: E = H, N = OAc; Br_2: E = Br, N = Br (ref. 3d)



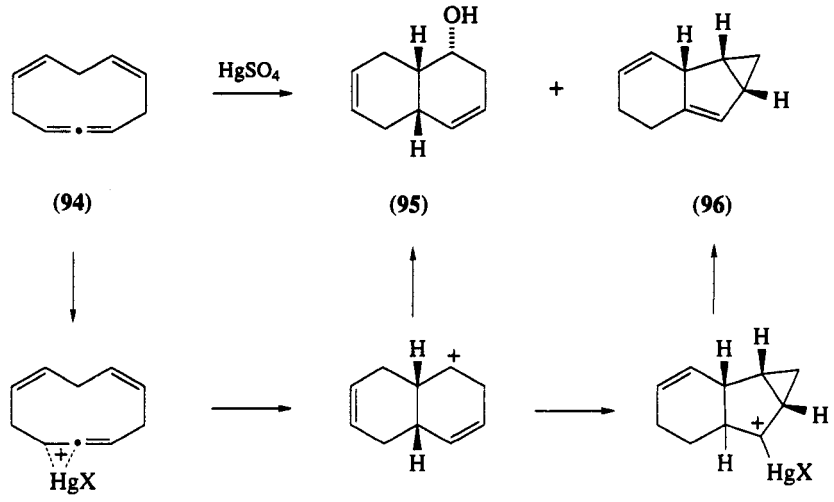
(ref. 89) (36)



(ref. 90) (37)

1.10.5.3 Cyclodecenols

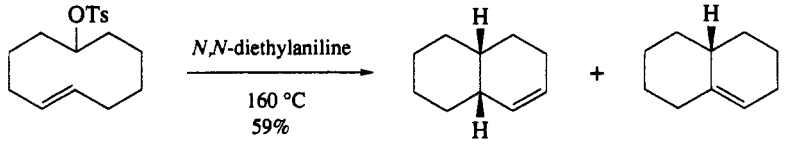
Very early on in the development of the principles of transannulation, Cope and coworkers showed that the tosylates (**97**; equation 38) and (**100**; equation 39), derived from (*Z*)- and (*E*)-cyclodec-5-enol, underwent smooth transannulation in the presence of acetic acid, leading to mixtures of the isomeric bicyclo[4.4.0]decenes (**98**), (**99**) and (**101**) together with the cyclodecenol (**102**).[93] Later work by Goering *et al.* demonstrated that the rate of solvolysis of the *p*-nitrobenzoate derivative of (*E*)-cyclodec-5-enol was such that chiral starting materials led to chiral products, (*e.g.* **103** → **104**; equation 40).[94] Similar to



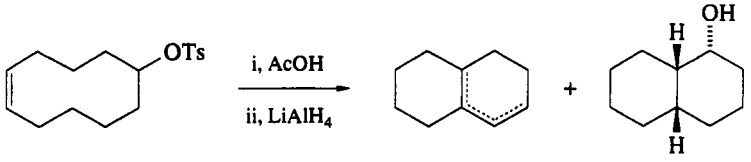
(94) (95) (96)

Scheme 11

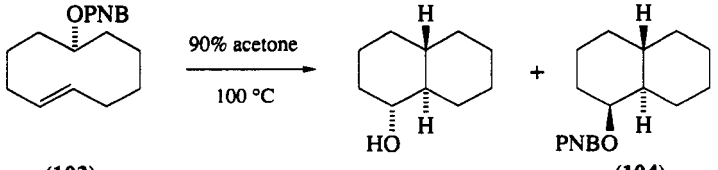
the observation made with geometrically defined cyclodeca-1,5-dienes, described earlier, the (*Z*)-cyclodecene (**105**; equation 41), corresponding to (**97**), produced the *cis*-decanol (**106**) on solvolysis in acetone at 100 °C.[95]



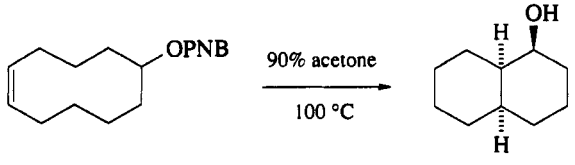
(97) (98) (99) (38)



(100) (101) (102) (39)



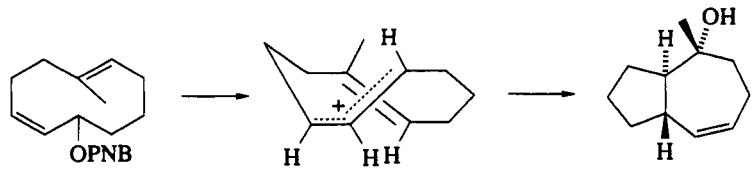
(103) (104) (40)



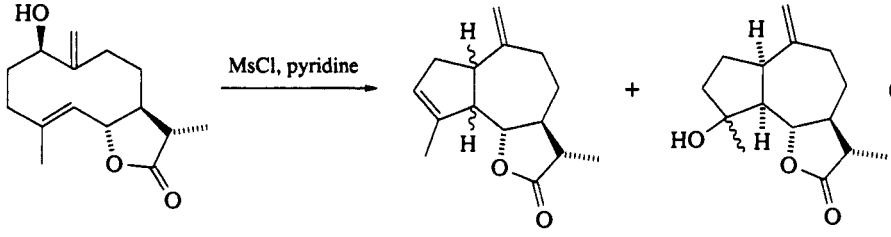
(105) (106) (41)

Marshall and Huffman have employed a neat combination of the aforementioned principles to access the hydroazulene system (**109**) by solvolysis of (**107**) in the presence of aqueous dioxane; the reaction (**107**) → (**109**; equation 42) proceeds *via* the incipient allylic carbonium ion intermediate (**108**).[96] Indeed, subsequent to this work, a wide range of cyclodecenols (many naturally occurring) have been used to

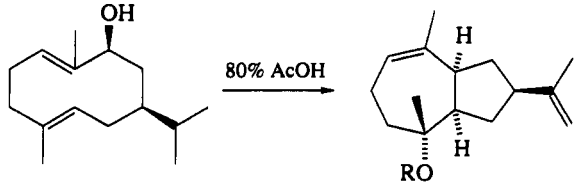
synthesize both hydroazulene (guaiane) and bicyclo[4.4.0]decane ring systems, and a selection is given in equations (43–48).[97–102]



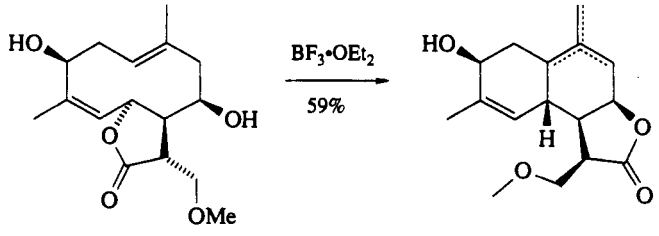
(107) (108) (109) (42)



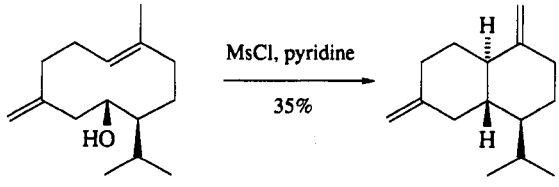
30% 19% (ref. 97) (43)



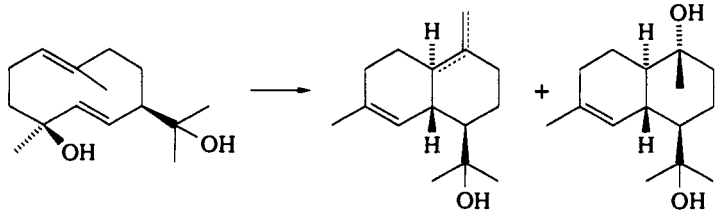
R = H, 59%
R = Ac, 29%
(ref. 98) (44)



(ref. 99) (45)

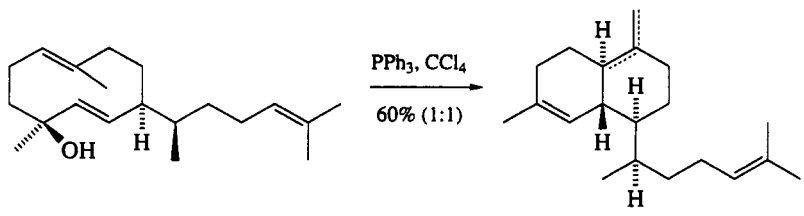


(ref. 100) (46)



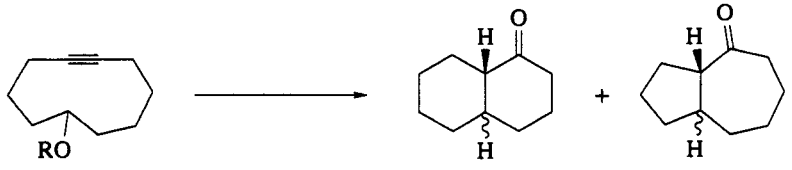
3 N H_2SO_4, aq. acetone	15% (1:1)	81%
p-TsOH, Et_2O	86% (1:1)	13%

(ref. 101) (47)



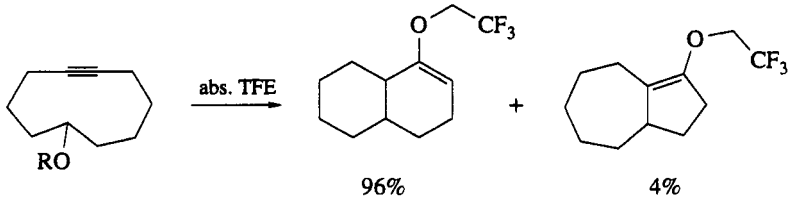
(ref. 102) (48)

Transannulations involving cyclodec-5-ynols have also been described, and they lead largely to bicyclo[4.4.0]decanones (equations 49–53).[103,104]

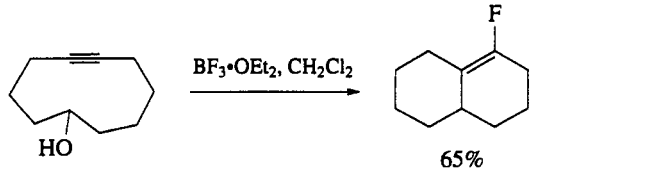


(49)

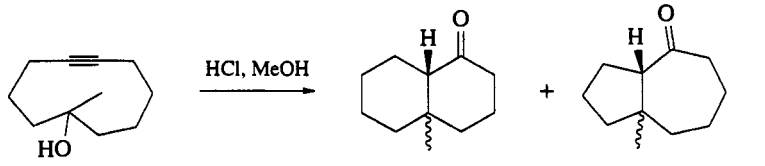
R = H	HCl, MeOH		75%	(ref. 103)
R = Ts	80% EtOH, 2,6-lutidine, 110 °C	93%	7%	(ref. 104)
R = PNB	50% EtOH, 2,6-lutidine, 110 °C	92%	8%	(ref. 104)



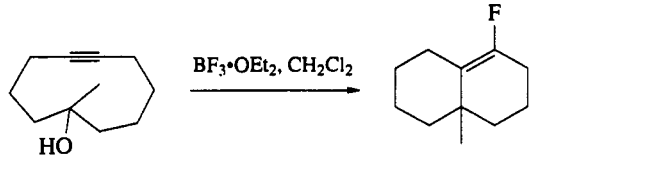
(ref. 104) (50)



(ref. 103) (51)



(ref. 103) (52)

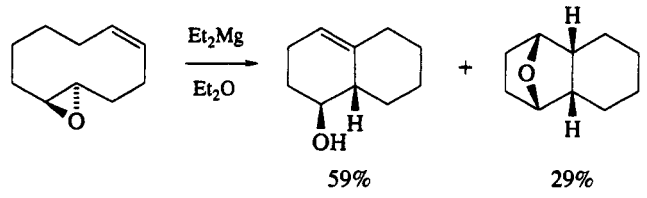


(ref. 103) (53)

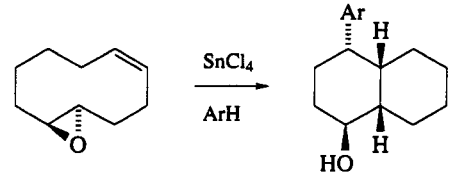
1.10.5.4 Cyclodecadiene Monoepoxides

Transannular cyclizations of cyclodecadiene monoepoxides have been studied in exhaustive detail, particularly amongst natural germacranolides, because of their relevance to biogenetic models for the synthesis of eudesmane- and guaiane-type sesquiterpenes.[105–115] A full discussion of this topic is beyond the scope of this chapter, but the examples collected in equations (54–64) provide the reader with an in-

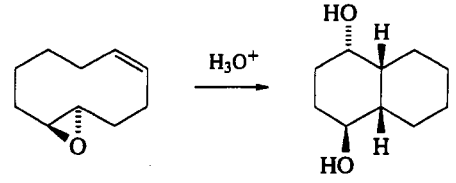
dication of the scope for this transannulation strategy in synthesis. The specificity of cyclization to either the [3,5]- or [4,4]-bicyclodecane systems can be predicted largely on the basis of the stability of the carbonium ion resulting from initial epoxide ring opening. In some instances rearrangement of the product resulting from transannulation of certain cyclodecene epoxides has been found to be a significant problem, *e.g.* (**110**) → (**111**; Scheme 12).[116]



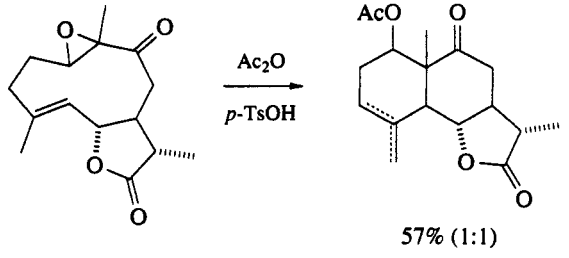
(ref. 105) (54)



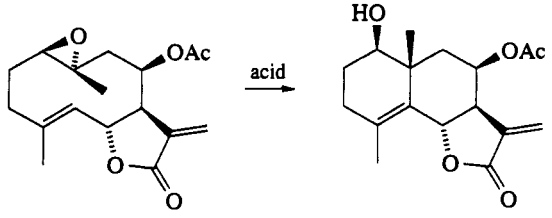
(ref. 106) (55)



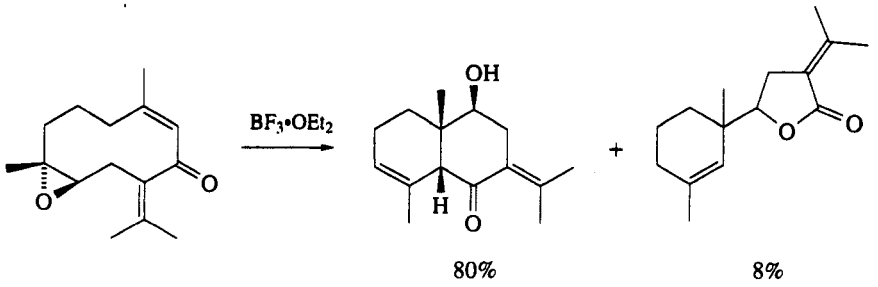
(ref. 107) (56)



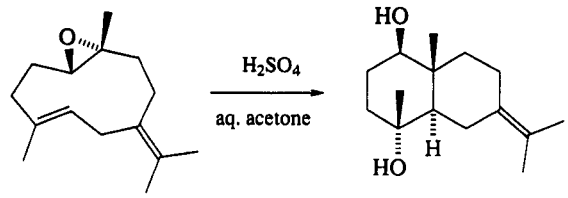
(ref. 108) (57)



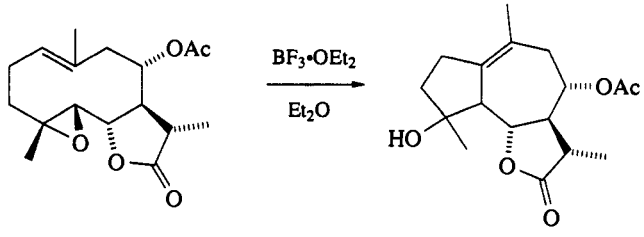
(ref. 109) (58)



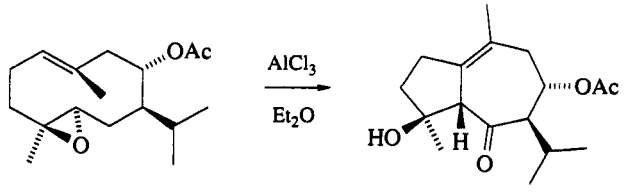
(ref. 110) (59)



(ref. 111) (60)

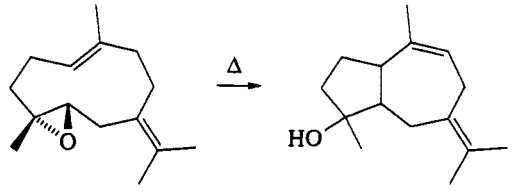


(ref. 112) (61)



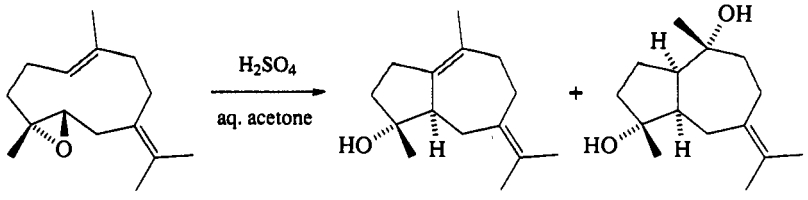
40%

(ref. 113) (62)



30%

(refs. 111, 114) (63)

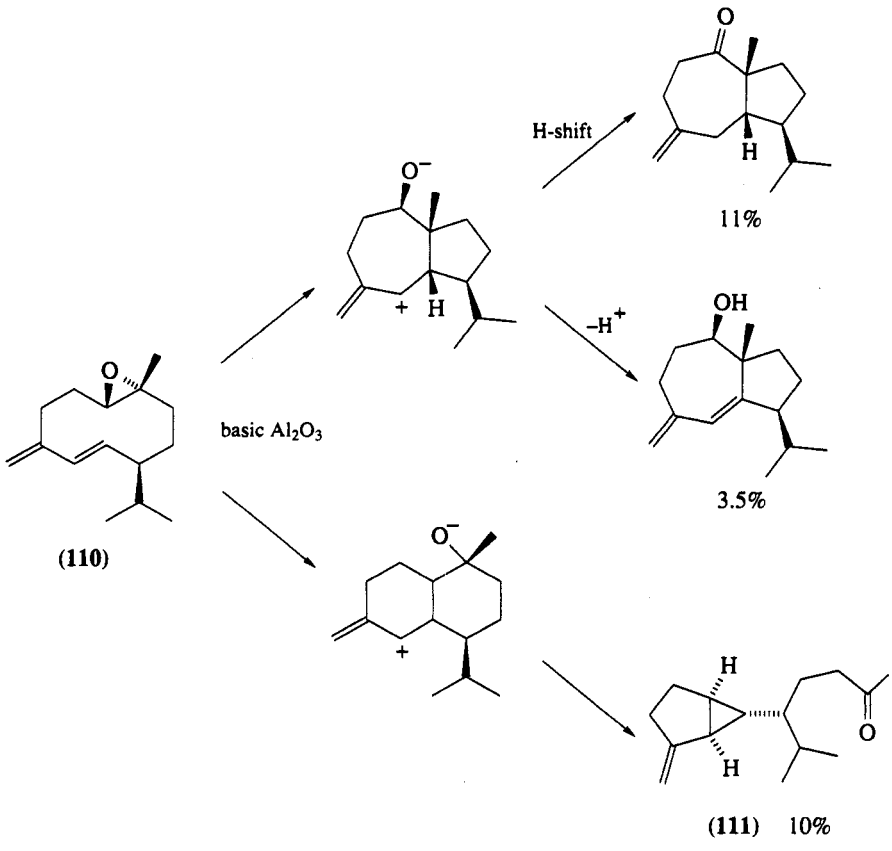


22% 42%

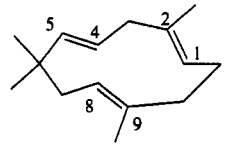
(ref. 111) (64)

1.10.6 CYCLOUNDECENES

As summarized in the above discussion (Section 1.10.5.1) and in Scheme 9, the 11-ring triene humulene (**72**) is a central intermediate in the biosynthesis of a very wide range of polycyclic sesquiterpenes. Consequently, studies of the chemistry, the stereochemistry and the conformation of humulene, together with its use in biomimetic synthesis have been the subjects of considerable research. Indeed, studies of transannulation reactions amongst cyclononadecenes have been dominated by humulene, and this is reflected in this discussion. The humulene ring system is numbered here according to the IUPAC recommendations, and this numbering is shown on formula (**112**). It should be noted that some authors, *e.g.* Shirahama *et al.*, use an alternative numbering scheme in their publications.



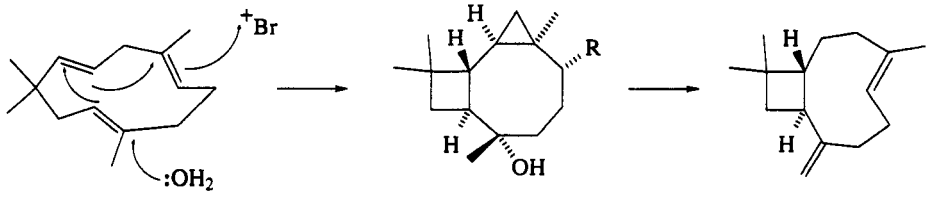
Scheme 12



(112)

1.10.6.1 Humulene

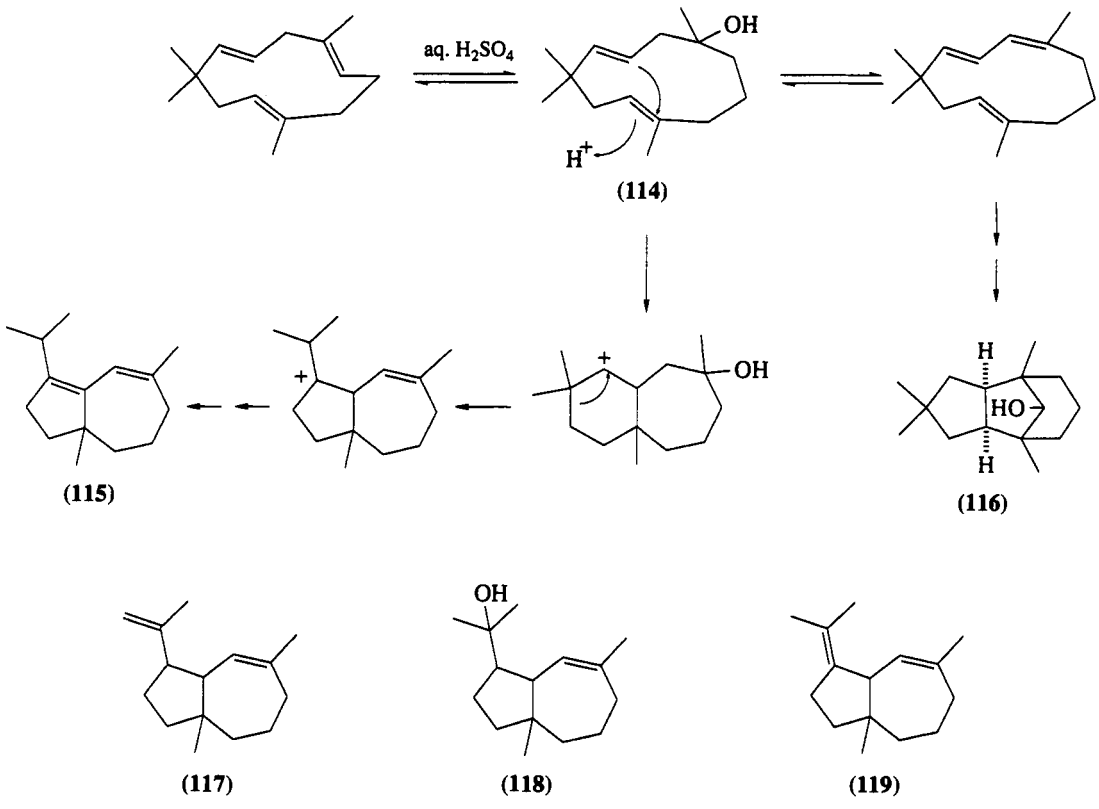
More than 20 years ago Sutherland *et al.*[117] first showed that when humulene (**72**) was treated with *N*-bromosuccinimide in aqueous acetone it underwent a remarkable transannulation, leading to the tricyclic bromohydrin (**113**) in 25% yield. Hydrolysis of (**113a**) then led to tricyclohumuladiol (**113b**), which was later found as a constituent of hop oil, and two synthetic steps converted (**113b**) into the cyclononadiene caryophyllene (**63**; equation 65).



(72) (113a) R = Br (113b) R = OH (63) (65)

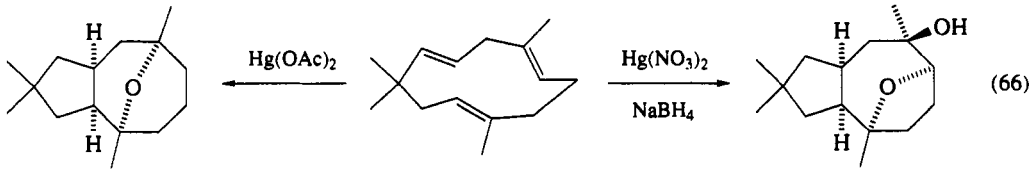
Later work by Parker *et al.*[118] demonstrated that extended treatment of humulene with aqueous sulfuric acid in acetone led largely to the bicyclo[5.3.0]deca-2,10-diene (**115**), *via* initial formation of humulol

(**114**). Other products which were isolated from this study were the related fused 5,7-ring molecules (**117**)–(**119**), together with α-caryophyllene alcohol (**116**; Scheme 13).

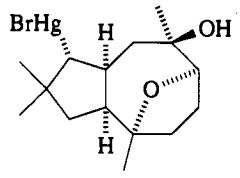


Scheme 13

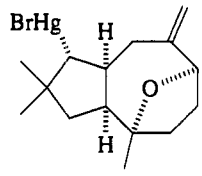
In extensive studies of oxymercuration reactions of humulene, Matsumoto and Shirahama have shown that, whereas oxymercuration with $Hg(OAc)_2$ in THF–H_2O followed by demercuration leads largely to the tricyclic ether (**120**; equation 66),[119] use of $Hg(NO_3)_2$ in AcOH–H_2O instead produces mainly the isomeric ether (**121**).[120] Interestingly, when humulene was treated with $Hg(NO_3)_2$ followed by aqueous HBr, chromatography led to the two bromomercury compounds (**122**) and (**123**) in a combined yield of 52%.[121] The mercury compounds were then elaborated, in several steps, to the novel cyclooctenol (**124**) which was beautifully set-up for a further transannulation reaction leading to the hydroxypentalenene (**125**); several synthetic steps then led to pentalenic acid (**126**; equation 67).[122] In further extensive studies Matsumoto and Shirahama and their collaborators have also shown how the 10α-alcohol (**127**), derived from (**123**), can be used to elaborate pentalenolactones G and H, (**128**) and (**129**) respectively (Scheme 14),[123] and how the ether (**121**) can be converted into pentalenene, pentalenolactone E (**130**) and pentalenolactone F (**131**; Scheme 15.[124] These studies are therefore based on the biogentic speculation alluded to earlier whereby the 11-ring humulene is converted into the angular fused pentalenane 5,5,5-ring system in sequence, *via* the intermediate fused 5,8-ring system (**132**; Scheme 16). In related work Pattenden and Teague[53] have also described a total synthesis of pentalenene (**40**), based on the transannulation reaction shown earlier, *i.e.* (**39**) or (**41**) → (**40**; Scheme 15). Other extensive studies of the transannulation chemistry of the tricyclic ether (**134**) by the same Japanese group, led by Matsumoto



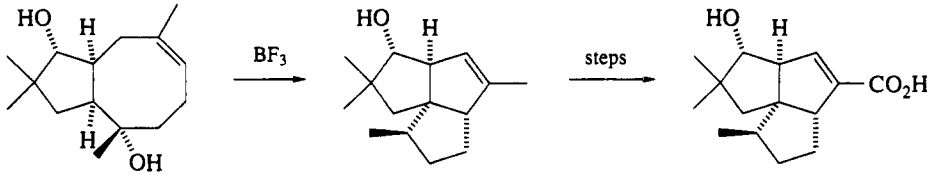
(66)



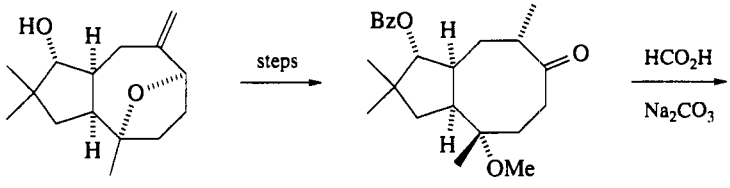
(122)



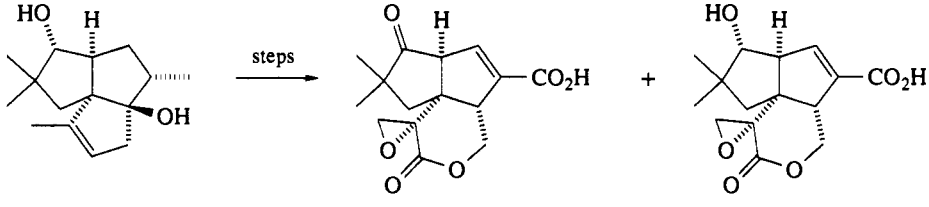
(123)



(124) (125) (126) (67)

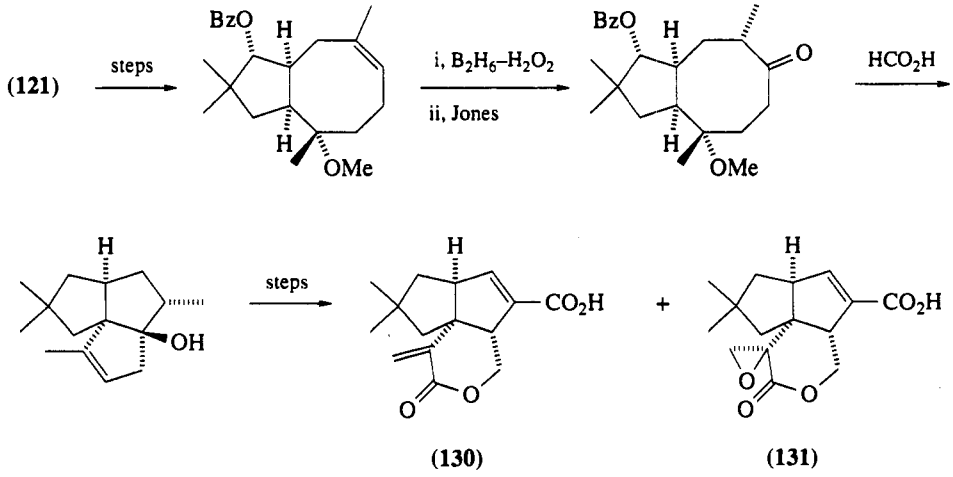


(127)



(128) (129)

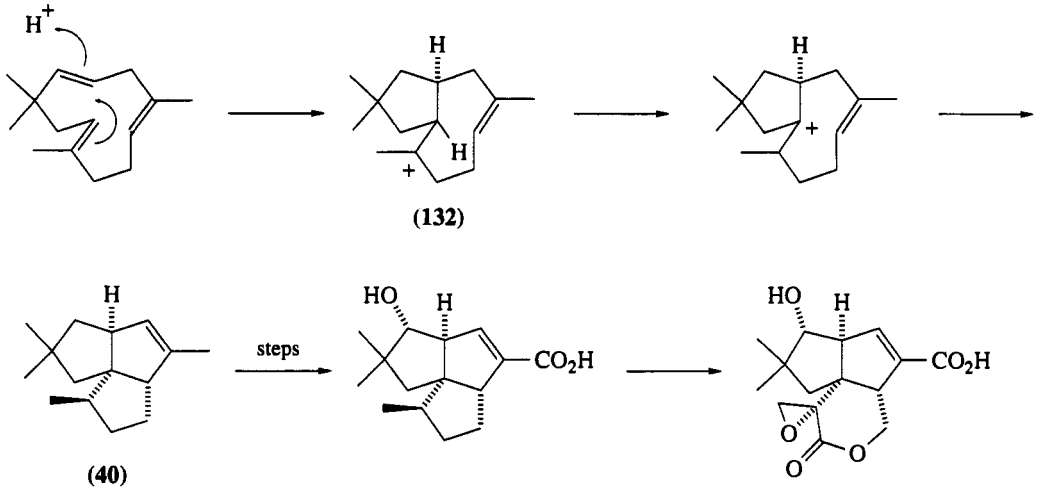
Scheme 14



(130) (131)

Scheme 15

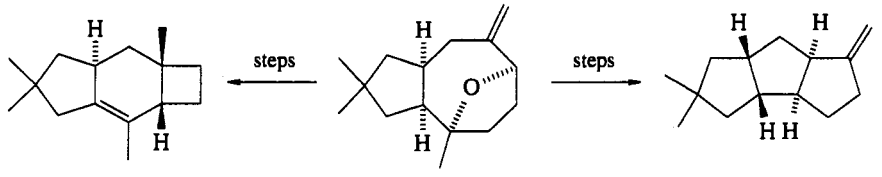
and Shirahama, have led to the synthesis of natural sterpurene (**133**)[125] and of hirsutene (**135**; equation 68).[126]



(132)

(40)

Scheme 16



(133) (134) (135) (68)

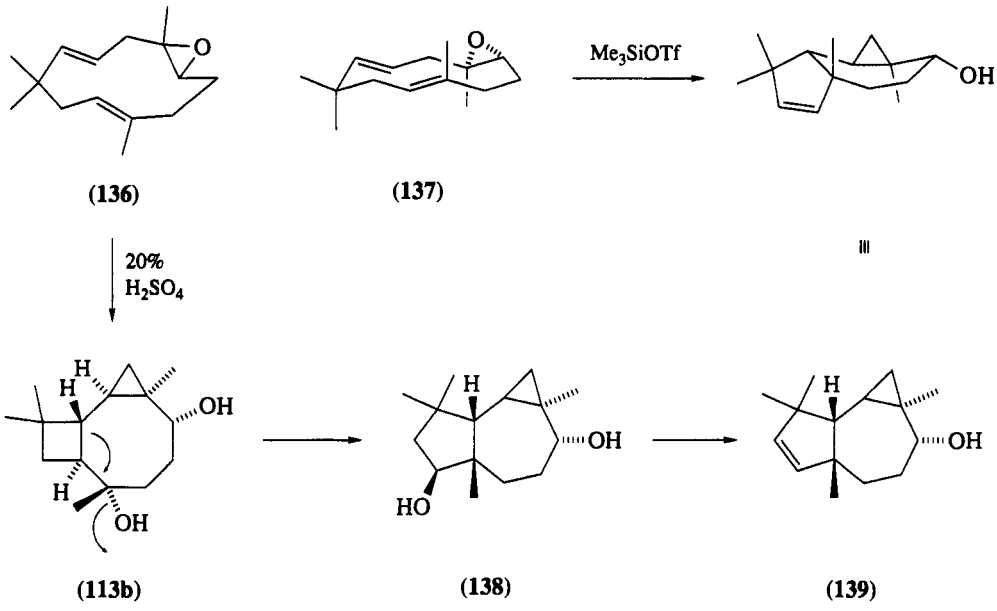
1.10.6.2 Humulene Epoxides

The three monoepoxides of humulene, *i.e.* (**136**), (**150**) and (**162**), occur in nature,[127] and there is every reason to assume that each epoxide is involved separately in transannulation processes leading to various fused-ring systems found amongst the sesquiterpenes. All three humulene monoepoxides have been synthesized and their individual chemistry with Lewis acids has been examined in an effort to effect their biogenetic conversions to natural terpenes.

1.10.6.2.1 Humulene-1,2-epoxide

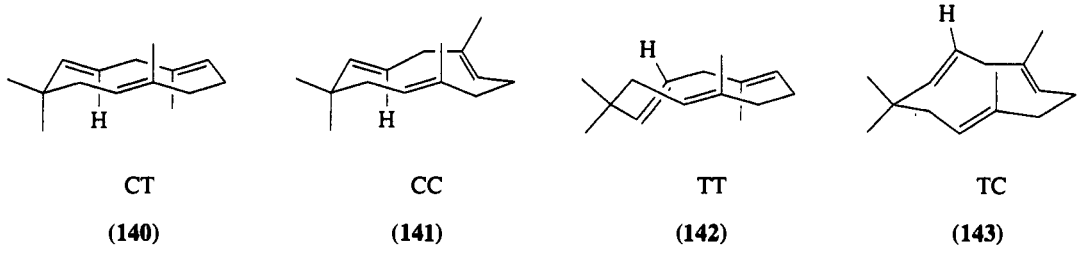
The $\Delta^{1,2}$-double bond in humulene (**72**) has been found to be the most reactive towards electrophiles, and hence the chemistry of the corresponding 1,2-epoxide (**136**) was the first to be studied. Thus, early work of McKervey and Wright[128] demonstrated that when (**136**) was treated with 20% H_2SO_4 in acetone, it produced the tricyclohumuladiol (**113b**), described earlier by Sutherland *et al.*[117] Subsequently Takahashi and his coworkers[129] showed that the diol (**113b**) could be produced in 95% yield from humulene-1,2-epoxide when the latter is treated with aqueous H_2SO_4 in acetone at 0 °C instead of at room temperature. Continuation of this reaction at room temperature for 7 h, however, gave rise to the new [6.3.0.$0^{2,4}$]undec-9-enol (**138**) in *ca.* 25% yield. Even later work by Shirahama *et al.*[130] showed that when (**136**) was treated with trimethylsilyl triflate (TMSOTf) at –75 °C the alkene (**139**) corresponding to (**138**) could be produced cleanly, in one step in 80% yield (Scheme 17).

Contemporaneous studies of the conformational behavior of humulene (**72**) by Shirahama *et al.*[131] using empirical force calculations have suggested that, although the molecule can assume any of the four stable conformations (**140**), (**141**), (**142**) and (**143**), abbreviated to CT, CC, TT and TC respectively, (see Section 1.10.3), only the CT- and the CC-conformers (**140**) and (**141**) are involved in biosynthetic transannulation reactions. Thus, Shirahama *et al.* have suggested that the transannulation reaction leading from (**136**) to (**139**) in the presence of TMSOTf proceeds *via* the CT-conformer (**137**) of humulene-1,2-epoxide. Interestingly, when (**139**) was converted into the epoxide (**144**), treatment with TMSOTf trig-

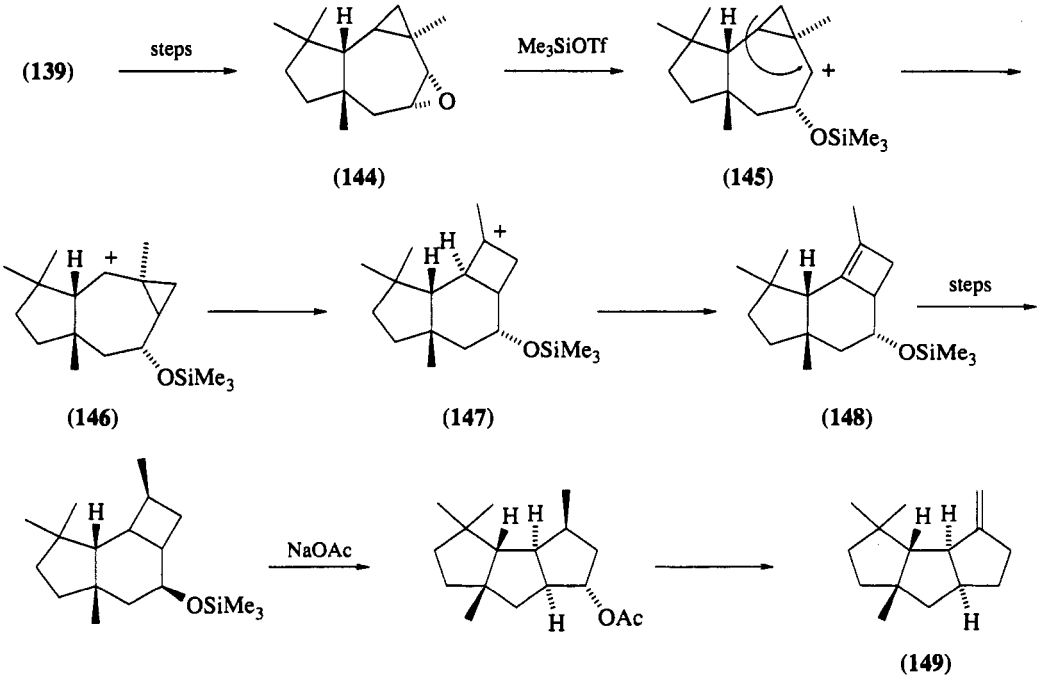


(136) (137) (113b) (138) (139)

Scheme 17



CT (140) CC (141) TT (142) TC (143)



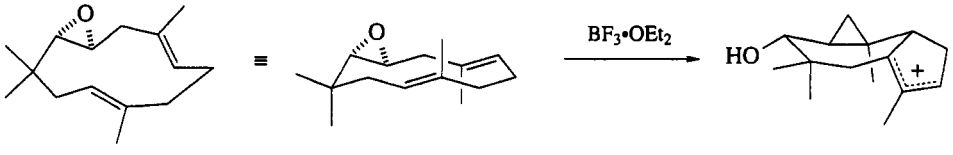
(144) (145) (146) (147) (148) (149)

Scheme 18

gered a series of carbonium ion rearrangements, *i.e.* (**145**) → (**146**) → (**147**) leading to the intermediate (**148**), which could be transformed into naturally occurring capnellene (**149**; Scheme 18).[132]

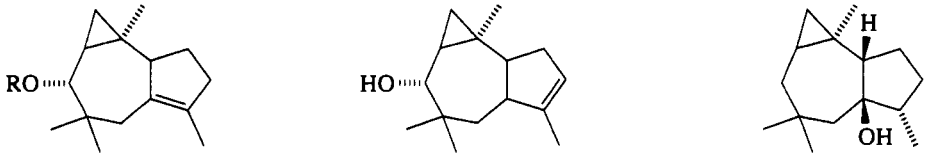
1.10.6.2.2 Humulene-4,5-epoxide

The biosynthesis of the hirsutane, protoilludane, marasmane, illudane and africane families of sesquiterpenes are all thought to occur *via* initial protonation of the $\Delta^{4,5}$-double bond in humulene (*cf.* Scheme 9). Attempts to mimic these reactions in the laboratory were frustrated for many years due to the inaccessibility of the 4,5-epoxide (**150**) of humulene. An indirect synthesis of humulene-4,5-epoxide permitted Roberts and coworkers[133] to study the cyclization of (**150**) in the presence of $BF_3{\cdot}OEt_2$ (equation 69). This study led to the formation of the two alcohols (**152a**) and (**153**), which had the same tricyclic carbon framework to that found in naturally occurring africanol (**154**) and the related ester (**152b**).[134]



(69)

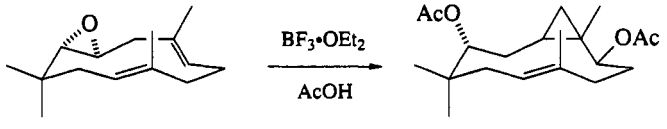
(**150**) (**151**)
CT-conformation



(**152a**) R = H
(**152b**) R = angelate

(**153**) (**154**)

Sometime later, Matsumoto and Shirahama[135] demonstrated that when humulene-4,5-epoxide (**150**) was treated with $BF_3{\cdot}OEt_2$ in HOAc at –50 °C, the only product isolated was the bicyclohumulenediol (**156**), in 70% yield. The formation of (**156**) was rationalized as occurring *via* the CC-conformation (**155**; equation 70) of the epoxide, whereas the production of the africanol system (**152**) occurs *via* the corresponding CT-conformation (**151**) of (**150**).

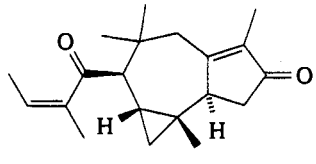


(70)

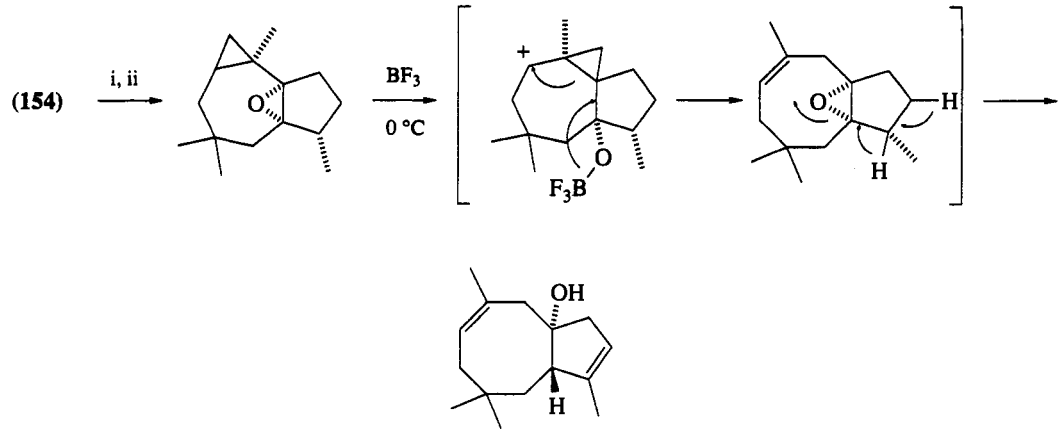
(**155**)
CC-conformer

(**156**)

Appropriate manipulations of the tricycle (**152a**) resulting from transannulation of humulene-4,5-epoxide permitted Roberts and Shirahama and their respective collaborators to access africanol (**154**) and 8-oxysenoxyn-4-en-3-one (**157**).[136] Shirahama *et al.*[137] have also described the *in vitro* conversion of africanol (**154**) to dactylol (**158**), found in the sea hare *Aplysia dactyloma, via* the novel and unusual cyclopropane-sliding reaction, summarized in Scheme 19.



(**157**)

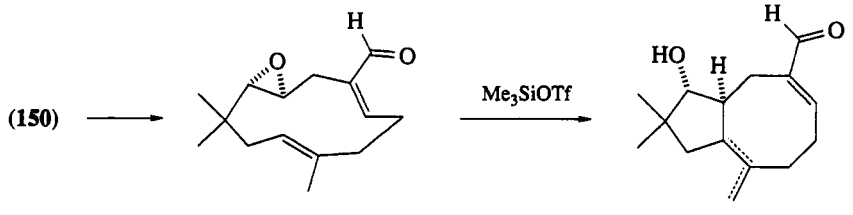


(158)

i, $POCl_3$/pyridine; ii, MCPBA + chromatography

Scheme 19

Finally, transannular cyclization involving the $\Delta^{8,9}$- rather than the $\Delta^{1,2}$-double bond in humulene-4,5-epoxide (**150**) can be achieved by first converting (**150**) to the corresponding aldehyde (**159**). Treatment of (**159**) with TMSOTf is then shown to lead to the fused 5,7-ring system (**160**) in good yield (equation 71).[138]

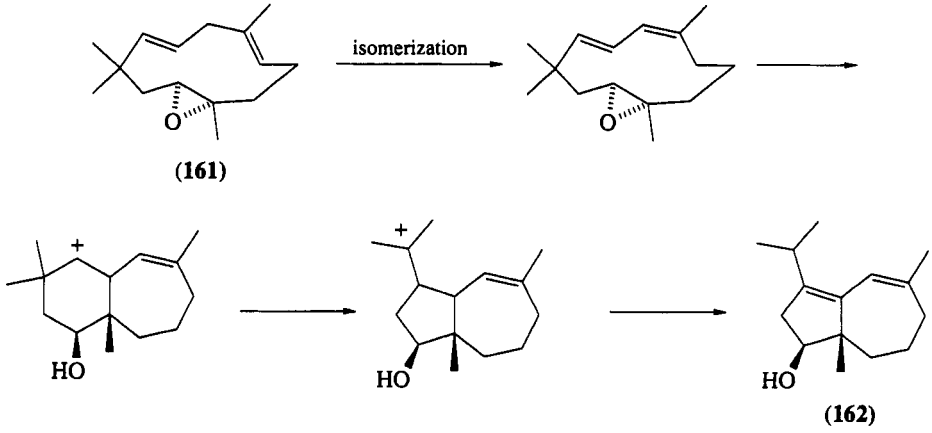


(71)

(159) **(160)**

1.10.6.2.3 Humulene-8,9-epoxide

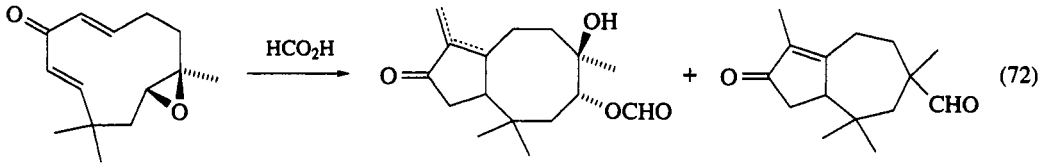
In contrast to the fascinating transannulation reactions associated with humulene-1,2- and humulene-4,5-epoxides, humulene-8,9-epoxide (**161**) undergoes transannulation and rearrangement in the presence of $SnCl_4$ leading only to the bicyclic alcohol (**162**), related to the rearrangement product (**115**) of humulene itself (Scheme 20).[139]



(161) **(162)**

Scheme 20

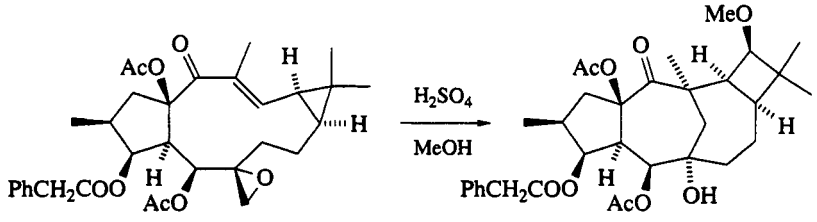
Formic acid catalyzed transannulation of the 8,9-epoxide (**163**), derived from natural zerumbone, has been shown to lead to a mixture of the bicyclo[6.3.0]undecane (**164**) and the hydroazulene (**165**; equation 72).[140]



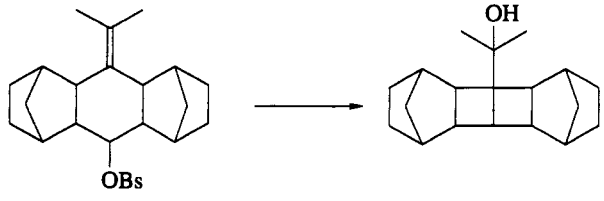
(**163**) (**164**) (**165**)

1.10.7 OTHER CYCLOALKENES

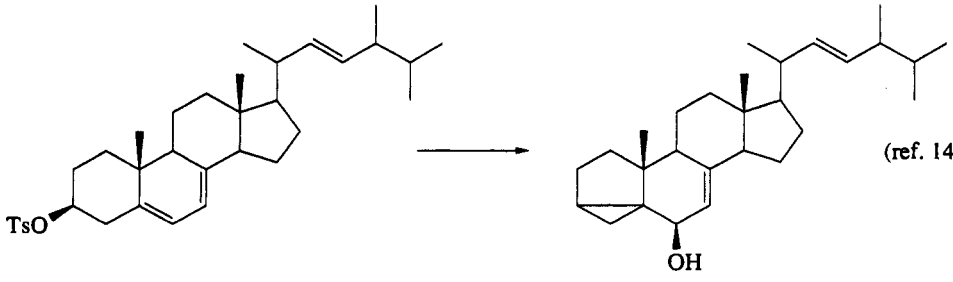
The transannular cyclizations described in Sections 1.10.1–1.10.6 are unique to medium-sized ring systems. Although transannular electrophilic processes are known with smaller rings, *i.e.* 3- to 7-rings, many of these processes can best be reviewed in terms of nonclassical carbonium ion phenomena. Some selected examples are collected in equations (73–77).[141–145]



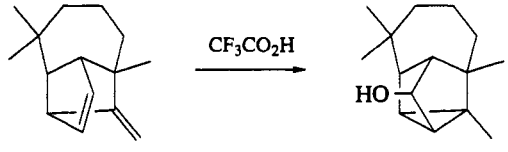
(ref. 141) (73)



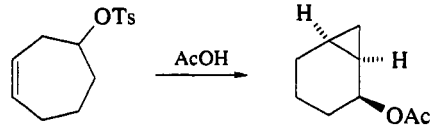
(ref. 142) (74)



(ref. 143) (75)

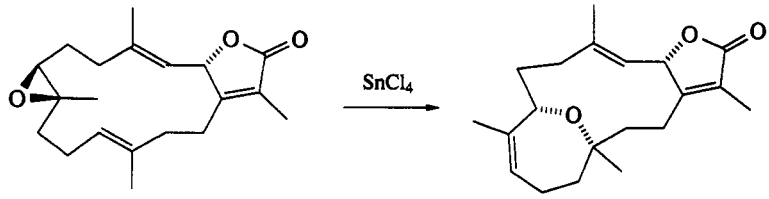


(ref. 144) (76)



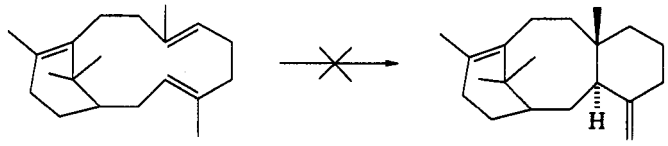
(ref. 145) (77)

Although transannular electrophilic cyclizations involving large rings have not been studied in any great detail, the available information suggests that these reactions occur only with difficulty. Thus, the cembranoid diterpene sarcophine (**166**) produces only the oxepine derivative (**167**; equation 78) on transannulation in acid,[146] and all attempts to synthesize the taxane ring system (**169**) *via* transannular cyclization of the 12-ring precursor (**168**; equation 79) have so far failed.[147] Interestingly however, when the 14-membered diterpene ovatodiolide (**170**) is treated with hot methanolic hydrochloric acid[148] or with *p*-toluenesulfonic acid (PTSA)[149] it produces the product (**171**; equation 80). In addition, the tobacco constituent (**172**) is reported to produce the tetracyclic ether (**173**; equation 81) upon heating with PTSA in benzene.[150]



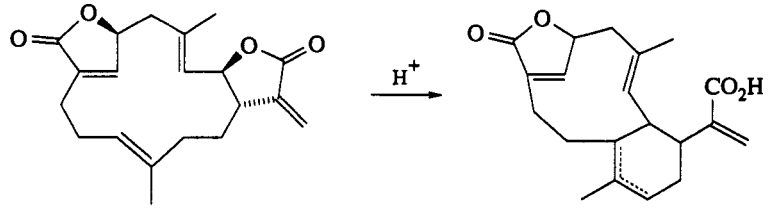
(78)

(166) (167)



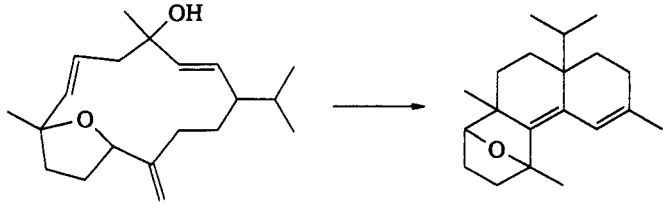
(79)

(168) (169)



(80)

(170) (171)



(81)

(172) (173)

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2.1
Coupling Reactions Between sp^3 Carbon Centers

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2.1.1 INTRODUCTION AND SCOPE

The classical method of coupling two sp^3-carbon centers is the Wurtz reaction (equation 1; M = Na). This chapter covers the generalized transformation shown in equation (1), where R and R^1 may be the same (dimerization) or different (cross-coupling) and where R and R^1 may represent a single molecule (intramolecular cyclization). In synthetic terms the most valuable type of coupling is the cross-coupling reaction. This reaction also presents the most problems, as the possibility of halogen–metal exchange and disproportionation of the reagents may lead to homo-coupled products (R—R and R^1—R^1 in equation 1), in addition to the desired cross-coupled product. As dimerization reactions are in general of less synthetic value, this treatment of the Wurtz-type coupling concentrates on cross-coupling reactions for each reagent considered, with less emphasis on dimerization reactions. The uses of coupling reactions for the synthesis of cyclic systems are treated separately in Section 2.1.2.5.

$$R{-}X + R^1{-}X \xrightarrow{M} R{-}R + R^1{-}R^1 + R{-}R^1 \quad (1)$$

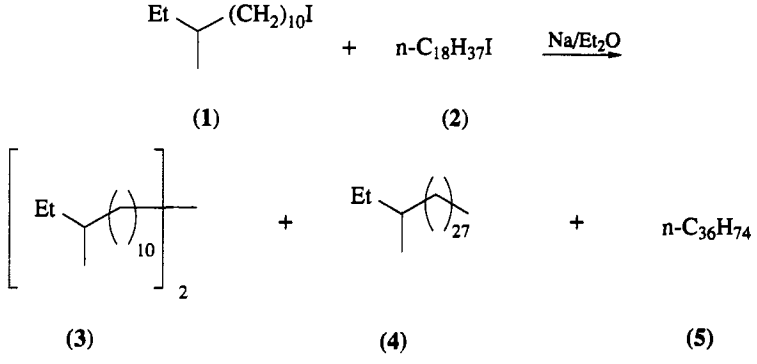
R = sp^3 center, X = halogen, M = metal

Severe limitations on the usefulness of the classical Wurtz reaction in the production of cross-coupled products have led to the development of many more generally useful variants. In particular, the use of copper catalysis and of stoichiometric organocuprate species have proved very valuable. The reactions of π-allylnickel halides with sp^3 halides is also represented by equation (1), and the uses of these reagents are treated separately. In order to provide a balanced view of the value of π-allylnickel halides, some additional reactions with centers other than sp^3 are described.

2.1.2 THE WURTZ REACTION AND VARIANTS

2.1.2.1 The Classical Wurtz Reaction

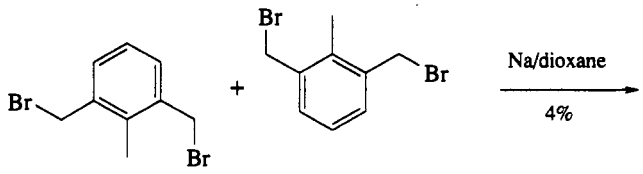
The Wurtz reaction involves the coupling of alkyl halides using sodium metal according to equation (1). The reaction is severely limited in scope as demonstrated by the following observations. (i) In the synthesis of noncyclic systems (dimerization or cross-coupling) reasonable yields require the use of primary alkyl halides, with iodides giving the best results. Secondary halides give very poor results. (ii) Cross-coupling reactions give approximately statistical ratios of cross-coupled:dimeric products, due to the high reactivity of the organosodium intermediates involved. Thus, in the synthesis of 3-methyluntriacontane (**4**; equation 2)[1] coupling of the iodide (**1**) with 1-iodooctadecane (**2**) under standard Wurtz conditions gave a mixture of (**3**) from dimerization of (**1**), (**4**) from the desired cross-coupling, and (**5**) from dimerization of (**2**), in the ratio 21:50:29. The classical reaction is however of value in the preparation of cyclic systems, notably [2.2]phanes and bicyclobutanes and in the preparation of symmetric dimers.

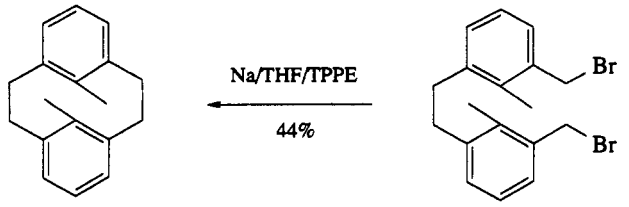


ratio of products (**3**):(**4**):(**5**) = 21:50:29

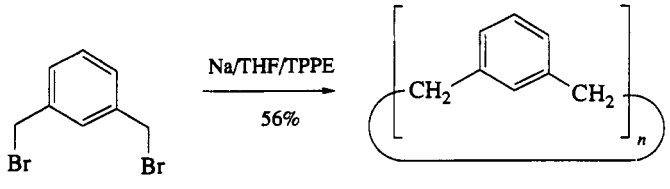
The synthesis of [2.2]phanes has been reviewed.[2,3] The Wurtz reaction provides one of the most successful approaches to this class of compounds, by ring-closure reactions. The reaction may proceed either intra- or inter-molecularly (as shown in equation 3), with intramolecular couplings giving better yields. The most efficient procedure[4] involves the reaction of the halo compounds with sodium metal in THF at –78 °C in the presence of catalytic quantities of tetraphenylethylene (TPE). Under these conditions the sodium metal dissolves as the disodium species, allowing a homogeneous reaction to take place, leading to better yields of coupled products. The modest yields of these products are due to competing oligomerization/cyclization reactions. This is demonstrated by the product distribution obtained on treatment of the dibromide (**6**) with sodium/TPE in THF at –80 °C (equation 4).[2] A homologous series of products is obtained under these conditions, the approximate yields of the metacyclophanes being 61%, 15%, 3.5%, 9%, 7%, 1%, 1%, 1%, 0.5%, for n = 2, 3, 4, 5, 6, 7, 8, 9, 10, respectively. Organolithium species also give acceptable yields of [2.2]phanes, from the treatment of suitable dibromides with phenyllithium.

The classical Wurtz reaction is also of value in the preparation of small cyclic systems such as bicyclo[1.1.0]butane and other cyclopropane derivatives. Treatment of the 1,3-dihalide (**7**) with sodium metal in refluxing dioxane,[5] for example, gives a high yield (78–90%) of bicyclobutane (**8**; equation 5). Although sodium may be used for the synthesis of other small rings, *e.g.* cyclobutane from dibromobutane, in general other metals (particularly zinc and potassium) give higher yields (equation 6).



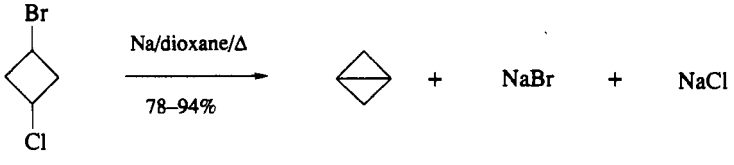


(3)



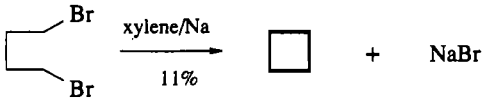
(4)

(6)



(5)

(7) (8)

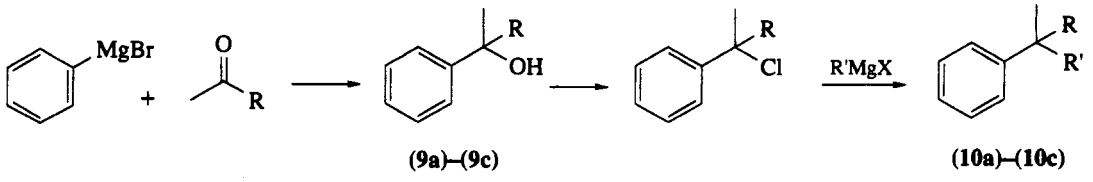


(6)

2.1.2.2 Organomagnesium-derived Reagents

Direct coupling of alkyl halides *via* conversion of one reactant to the Grignard reagent has limited synthetic utility. Simple Grignard reagents couple in rather low yields with tertiary alkyl halides,[6] improved yields being obtained by running the coupling reaction in a nonpolar solvent such as hexane or heptane. This method gives reasonable results for the preparation of highly branched hydrocarbons such as neopentane and hexamethylethane.[7] Examples of the use of this reaction are given in Scheme 1.[8] Grignard reagents derived from activated halides such as benzyl or related halides couple readily to give alkylbenzenes. *n*-Pentylbenzene and *n*-propylbenzene for example, may both be prepared in high yield by this procedure.[9] Intramolecular uncatalyzed Grignard coupling reactions are of value in the preparation of small ring cyclic systems (see Section 2.1.2.5).

In general, the cross-coupling of Grignard reagents with alkyl halides becomes much more synthetically useful in the presence of catalytic quantities of other metals, particularly copper species. Treatment of Grignard reagents with simple copper salts such as CuBr or CuI, or more complex species such as Li_2CuCl_4, leads to coupling with alkyl halides *via* transient organocopper species (equation 7). A very generalized order of reactivity of electrophiles toward organocopper species is as follows: acid chlorides > aldehydes > tosylates/epoxides > iodides > bromides > chlorides > ketones > esters > nitriles >> alkenes. In terms of coupling of sp^3 carbon centers, the approximate order of reactivity of alkyl halides is: allylic/benzylic > primary > secondary >> tertiary. In general, primary alkyl halides have been most widely used as sources of the Grignard reagent. Following the pioneering studies of Tamura and Kochi,[10]



(9a)–(9c) **(10a)–(10c)**

a: R = C_5H_{11}, R' = $C_{10}H_{21}$; 30%
b: R = C_6H_{11}, R' = C_8H_{17}; 32%
c: R = C_5H_{11}, R' = Bu; 17%

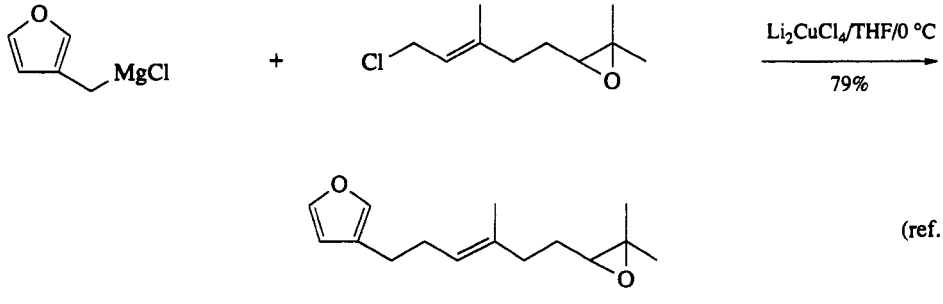
Scheme 1

widespread use has been made of the THF-soluble dilithium tetrachlorocuprate as a catalyst for the coupling of alkyl halides *via* their Grignard reagents.

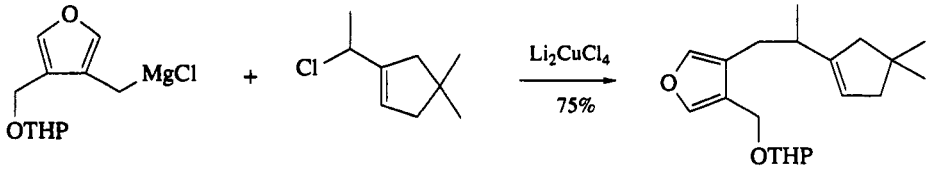
$$R^1{-}X \xrightarrow{Mg} R^1{-}MgX + R^2{-}X \xrightarrow{Cu^I} R^1{-}R^2 \qquad (7)$$

X = halogen; Cu^I = *e.g.* CuI or Li_2CuCl_4; R^1 and R^2 = alkyl sp^3 carbon

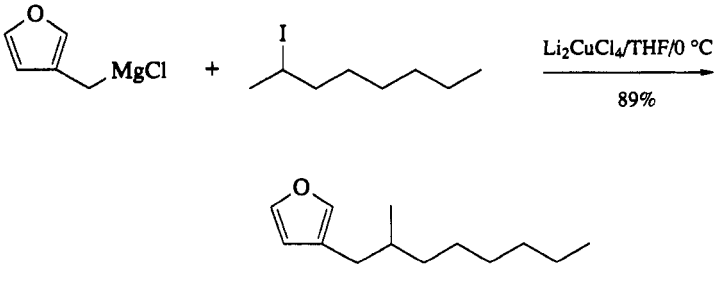
Under suitable conditions, the yields of homodimeric products (R^1—R^1 and R^2—R^2) are negligibly small and high yields of cross-coupled products are obtained (equation 7). These reactions are normally performed in THF, at low temperatures (–20 to 0 °C) and require only catalytic quantities of the readily prepared copper species. The reaction characteristics may be summarized by the following general observations.[11–22] (i) Coupling proceeds very readily with primary halides; iodides and bromides giving good yields and chlorides giving lower yields. (ii) Secondary iodides also give good yields; secondary bromides and chlorides do not react. (iii) Activated halides, such as allylic or benzylic bromides or chlorides, give good yields for both primary and secondary substrates. (iv) Tertiary halides generally give very poor results, with disproportionation of the reagents predominating. (v) The degree of substitution of the Grignard reagent is not very important in determining reactivity. From the examples in equations (8)–(18) it can be seen that high yields of the desired cross-coupled products are normally obtained



(ref. 11) (8)



(ref. 12) (9)



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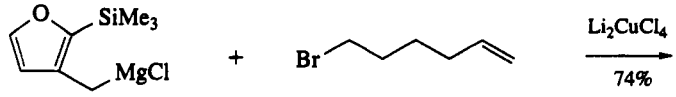

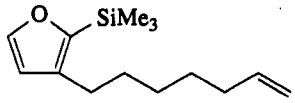

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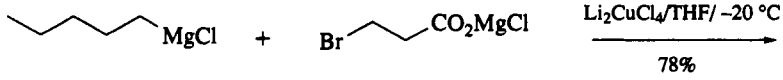

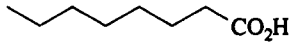

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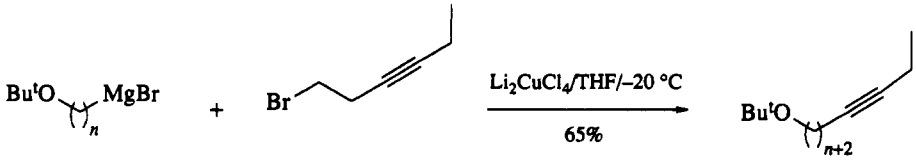

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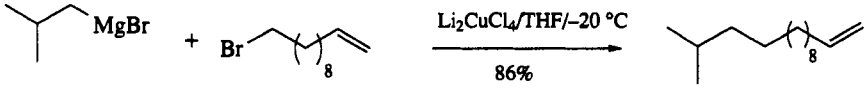

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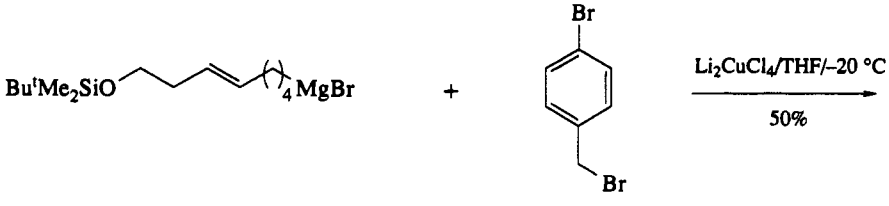
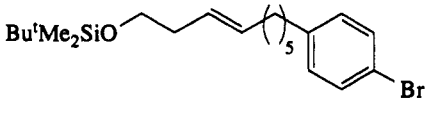
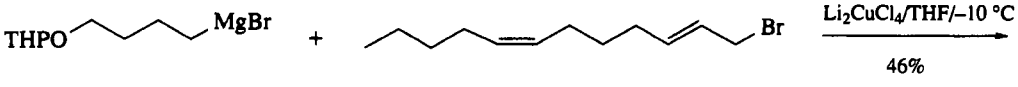
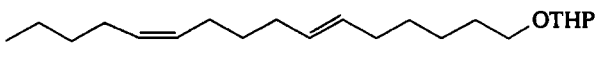




(ref. 17) (15)





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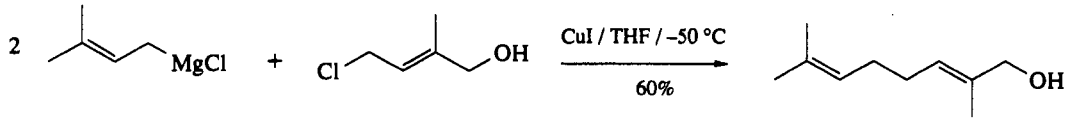
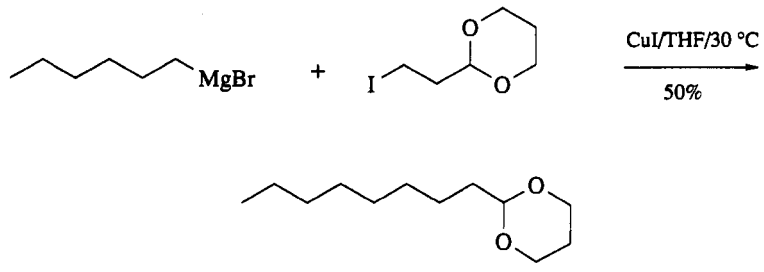


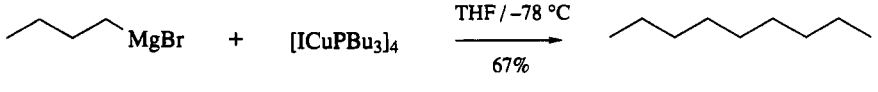
(ref. 20) (17)

and that a number of functional groups are inert in the reaction. Functionality that is tolerated includes alkynes, ethers, alcohols protected as THP or TBDMS ethers, epoxides, furans and unprotected alcohols and carboxylic acids, as their chloromagnesium salts. These observations have allowed the use of this catalyzed Grignard coupling in the preparation of a range of natural products, intermediates towards some of which are shown in equations (8)–(18). Other copper species used for the catalysis of Grignard couplings include copper(I) chloride, bromide and iodide[23] and some recent examples are given in equations (17) and (18).



(ref. 23) (18)

The dimerization of sp^3 centers *via* conversion of the alkyl halide to a Grignard reagent, followed by homo-coupling is promoted by a number of metals. Treatment of a Grignard reagent with a copper(I) species such as tetrakis[iodo(tri-*n*-butylphosphine)copper(I)],[24] followed by oxidation of the resulting ate complex with either oxygen or copper(II) salts, lead to dimerization (equation 19). 'Soluble silver' in THF may be prepared from silver nitrate and ethylmagnesium bromide in THF. The silver reagent is stable at greater than molar concentrations in THF for prolonged periods at 0 °C. Grignard reagents undergo efficient homo-coupling at room temperature in the presence of this silver catalyst.[10] Cross-couplings give approximately equimolar quantities of the two possible homo-coupled products together with the desired cross-coupled product (*cf.* equation 1). Disproportionation of the reagent becomes a major pathway for secondary and tertiary halides.[10,25,26] The special case of intramolecular homo-coupling *via* this method is treated in Section 2.1.2.5.



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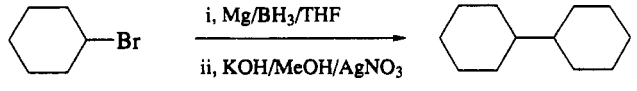
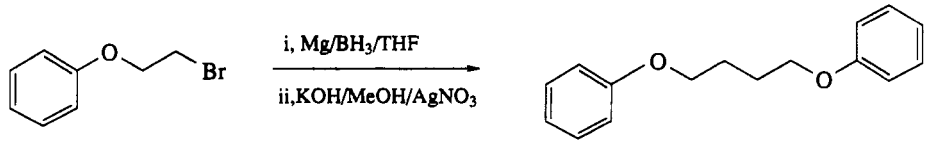


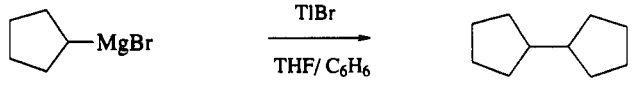
71%

(ref. 27) (20)



83%

(ref. 27) (21)



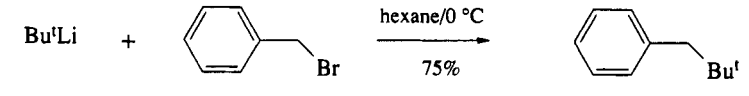
56%

(ref. 28) (22)

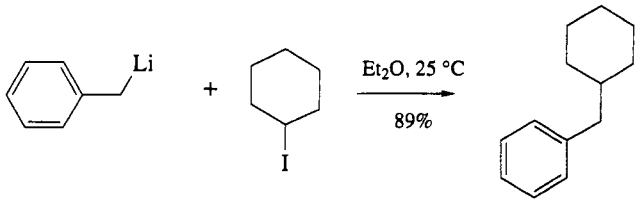
The *in situ* synthesis of organoboranes *via* reaction of alkyl halides with magnesium in the presence of diborane can also be used to prepare coupled products (equations 20 and 21).[27] Oxidation of the reaction mixture with alkaline silver nitrate leads to good yields of dimeric products. The reaction is successful for primary and secondary halides. A related reaction is the coupling of secondary alkyl halides in the presence of catalytic quantities of thallium salts.[28] This procedure fails for primary alkyl halides and gives modest yields for secondary alkyl halides (equation 22).

2.1.2.3 Organolithium-derived Reagents

The noncatalyzed coupling between organolithium reagents and organic halides leads to mixtures of hydrocarbons similar to the classical Wurtz reaction. The strongly basic and weakly nucleophilic nature of simple organolithium species leads to products derived from halogen–metal exchange, α-metalation and β-elimination, in addition to the desired coupling reactions. These factors mean that, in general, simple organolithium reagents are not useful intermediates for Wurtz-type couplings. Exceptions to this generalization include: the reaction of dihalides with *t*-butyllithium, to give cyclic systems (see Section 2.1.2.5);[29,30] the coupling of *t*-butyllithium with benzylic halides, giving highly branched systems (equation 23);[31] and the coupling of charge-delocalized alkyllithiums (*e.g.* benzyl- or allyl-lithiums) with organic halides (equation 24).[32,33] Several reviews concerning halogen–metal exchange reactions and the coupling behavior of organolithiums are available.[34–36]



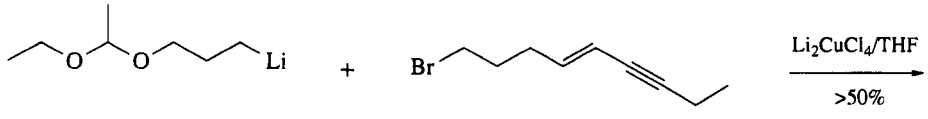
(ref. 31) (23)

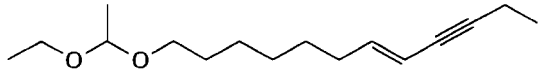


(refs. 32, 33) (24)

Reaction of an organolithium species with a copper(I) species at low temperature generates an organocopper reagent, which may have one of several different constitutions depending on the stoichiometry, exact reaction conditions, additives present, *etc.* Many types of organocopper reagent have proven very valuable in organic synthesis, and the use of these reagents is described in detail elsewhere in this work. In terms of the coupling of sp^3 carbon centers, the following general observations may be made about lithium organocopper species. (i) For catalytic reactions involving copper(I) intermediates, in general, Grignard reagents are preferred over organolithium species due to ease of preparation, and higher yields obtained in coupling reactions (see Section 2.1.2.2). (ii) For stoichiometric copper reagents, R_2CuLi reagents are more reactive, and give better results in coupling reactions than simple RCu species. (iii) A generalized order of reactivity towards lithium diorganocopper reagents is acid chlorides > aldehydes > tosylates/epoxides > iodides > bromides > chlorides > ketones > esters > nitriles >> alkenes. (iv) The relative reactivity of alkyl halides towards lithium diorganocopper reagents is allylic/benzylic > primary > secondary >> tertiary. (v) The kinetics of coupling are roughly first order in both cuprate reagent and alkyl halide. (vi) The cuprate reagent may be derived from a primary, secondary or tertiary halide.

Many reviews dealing with the chemistry of organocopper species have appeared,[37–42] and a comprehensive listing of organocopper substitution reactions reported prior to 1975 together with a detailed discussion of the factors influencing the reactions is available.[38] Many natural product syntheses have used cuprate couplings to prepare key intermediates and some representative examples of both stoichiometric and catalytic reactions are given in equations (25)–(29).[43–47] For a general introduction to the field of organocopper chemistry the reader is recommended to consult the excellent book by Posner.[42] Most organocopper reagents are extremely sensitive to heat and to oxidants, decomposing to the dimeric products of homo-coupling. Many organocopper species have been dimerized by heating or simple oxidation with oxygen.[38] Little use has been made synthetically of this method of coupling sp^3 carbon centers.





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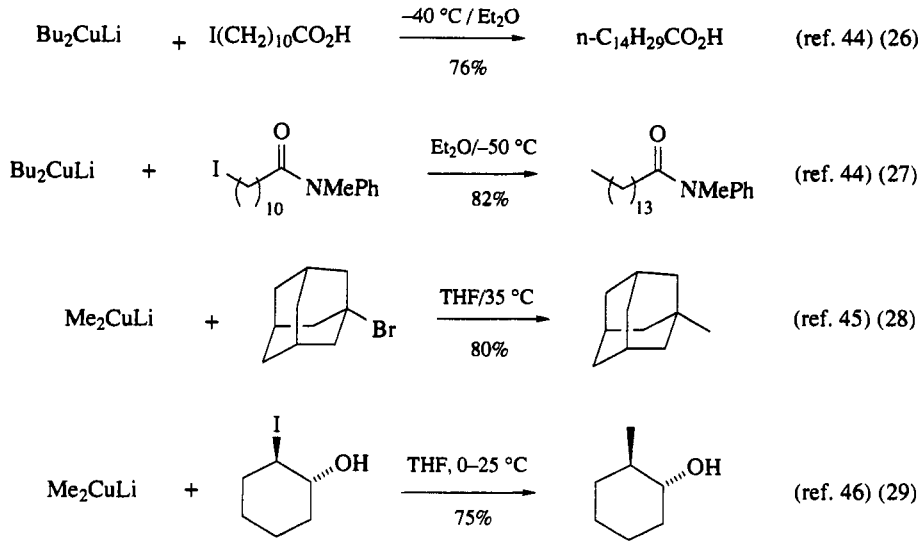
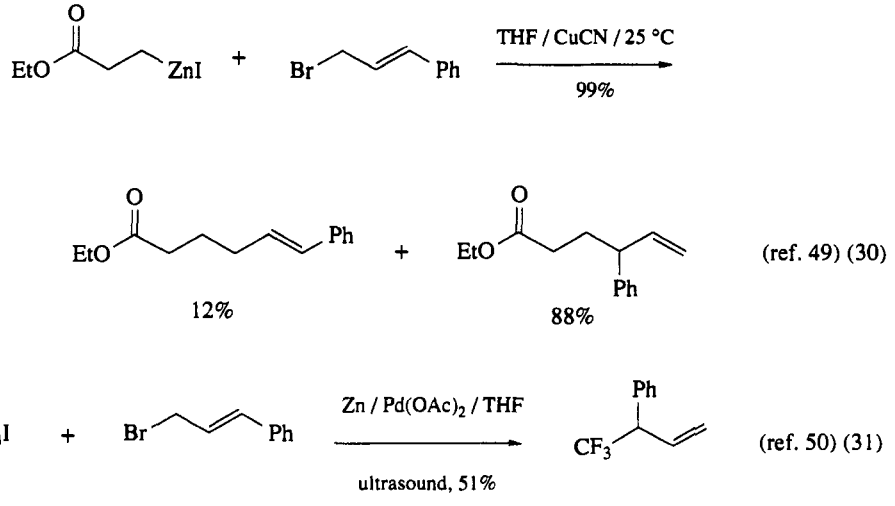


2.1.2.4 Other Organometallic Reagents

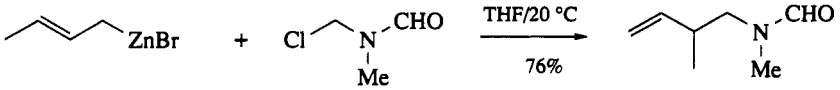
Many other metals, in addition to magnesium, lithium and copper, promote Wurtz-type couplings. In most cases cross-couplings are not possible and the methods are only of value in producing homo-coupled dimers. Reagents which do permit cross-coupling reactions are normally very limited in either the type of halide used for preparation of the metal derivative, or the halide to be cross-coupled, or both.

Organozinc species show some valuable facets for cross-coupling reactions. Primary iodo esters may be converted into organozinc species by direct treatment with a zinc–copper couple.[48] In the presence of catalytic copper cyanide these organozinc reagents couple efficiently with allylic halides and tosylates, unfortunately with low regioselectivity (equation 30).[49] Perfluoroalkyl-magnesium and -lithium halide species decompose readily into perfluoroalkenes and metal halides and are of little value for the introduction of perfluoroalkene substituents. In contrast, perfluoroalkylzinc species are much more stable and in the presence of ultrasound and a palladium catalyst, couple with allylic halides showing high δ-regioselectivity (equation 31).[50]

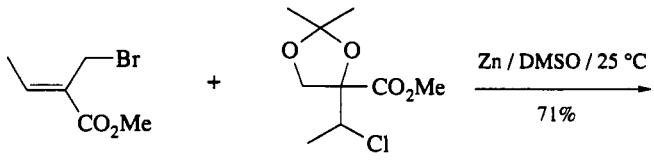


Organozinc reagents prepared from allylic bromides couple regioselectively in a δ-selective manner with *N*-chloromethyl-*N*-methylformamide, to give unsaturated tertiary formamides (equation 32).[51] Treatment of these formamides with butyllithium followed by hydrolysis removes the formyl group, giving secondary amines. In a total synthesis of retronecic acid, coupling of the allylic bromo ester (**11**) with the secondary chloride (**12**) was the only convenient way of obtaining the desired cross-coupled product

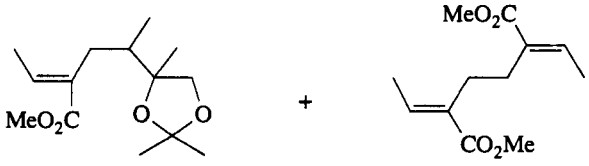
(**13**), albeit in low yield (equation 33).[52] Cross-coupling of allylic with benzylic halides may be achieved by oxidation of a mixture of the halides and triethylborane in THF with oxygen.[53]



(ref. 51) (32)



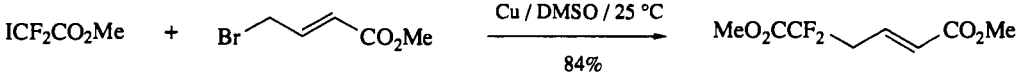
(**11**) (**12**)



(ref. 52) (33)

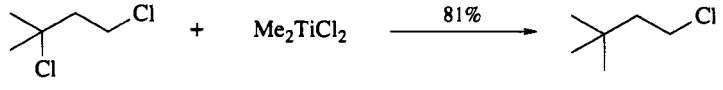
(**13**) 75% 25%

Iodofluoroacetate copper reagents can be prepared directly from the halide using copper powder in DMSO and the reagents couple with a range of electrophilic centers, including primary iodides and allylic bromides (equation 34).[54] Benzylic halides couple with bromoacetonitrile in the presence of metallic nickel in refluxing glyme (85 °C).[55] Organometallic species derived from methyllithium and manganese, cobalt or iron are all less suitable for cross-coupling reactions than the analogous species (R_2CuLi) derived from methyllithium and copper salts.[56]

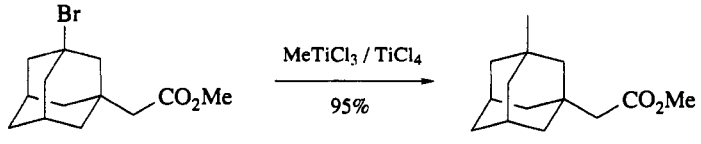


(ref. 54) (34)

Methyltitanium(IV) chlorides have been used for the methylation of tertiary alkyl halides, with good results. The reagents are prepared by treatment of dimethylzinc species (available from methyl iodide and zinc metal) with $TiCl_4$ and similar results are obtained by using dimethylzinc in the presence of catalytic quantities of $TiCl_4$.[57,58] The methylations are chemoselective, with esters and alkenes remaining unaffected and coupling only occurs at tertiary centers, primary and secondary alkyl halides being inert (equations 35 and 36). The method also works well in systems prone to skeletal rearrangements.

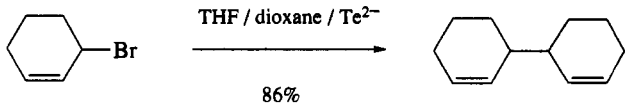


(ref. 57) (35)



(ref. 57) (36)

Benzylic and allylic halides dimerize (homo-couple) readily in the presence of a number of metal species. Synthetically useful yields of homo-coupled products have been obtained using chlorotris(triphenylphosphine)cobalt(I),[59] nickel(0) complexes generated *in situ*,[60] Te^{2-} species,[61] VCl_3/LAH,[62] $CrCl_3$/LAH[63] and $TiCl_3$ or $TiCl_4$/LAH.[64] Representative examples are given in equations (37) and (38). Treatment of δ-bromocrotonates with zinc(0) in DMSO leads to dimerization.[65]



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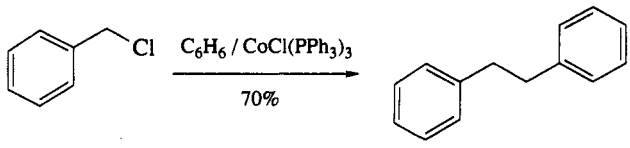
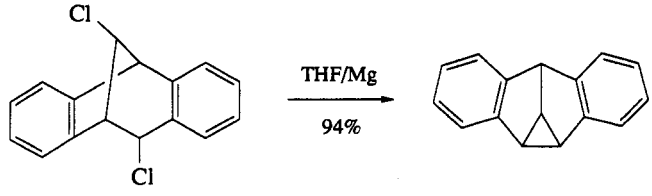


(ref. 59) (38)

2.1.2.5 Formation of Cyclic Systems

The classical Wurtz-type coupling leads to cyclic systems when applied to suitable dihalides. This intramolecular version of the Wurtz reaction is more efficient when metals other than sodium, and in particular zinc or Li/Hg amalgam, are used. A comprehensive review of the older literature on this intramolecular reaction is available.[66] The Wurtz coupling has proved particularly valuable for the synthesis of strained small ring systems. Bicyclobutane (**8**), for example, can be obtained in 80–90% yield by treatment of 1-bromo-3-chlorocyclobutane (**7**) with sodium at high temperatures (equation 5).[5] Other examples of the synthesis of strained cyclopropane-containing systems are given in equations (39) and (40).[67,68] The synthesis of cyclopropanes by reductive coupling reactions has also been reviewed.[69]

Cyclobutanes may also be prepared by this type of Wurtz reaction, but the approach is not successful for carbocyclic ring sizes greater than four. Studies of the reagents able to generate cyclobutane from 1,4-dihalo substrates have indicated that the use of Li/Hg amalgam in dioxane at high temperature gives the best yield.[70]



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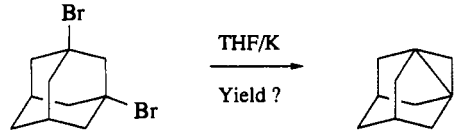
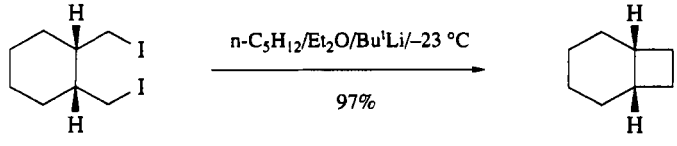


(ref. 68) (40)

Treatment of primary α,ω-haloalkanes with *t*-butyllithium at low temperature leads to efficient production of cycloalkanes, provided at least one of the halides is an iodide.[29,30] This method provides very good yields of three-, four- and five-membered rings, but produces only minor amounts of cyclic products for 1,6-dihalides. Examples of this approach are given in equations (41) and (42).



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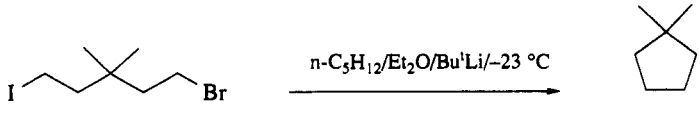
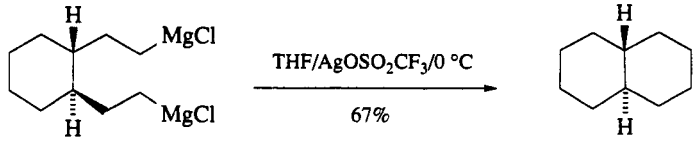


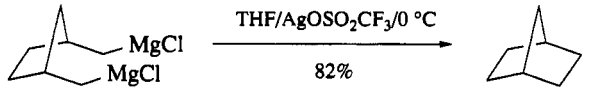
(ref. 30) (42)

A valuable modification to the coupling of alkylmagnesium halides involves the treatment of di-Grignard reagents with soluble silver salts, leading to cyclization. This method gives high yields of four-, five- and six-membered rings, but fails for larger ring sizes.[71] Examples of this synthesis are given in

equations (43) and (44). An interesting application of organocopper-type Wurtz coupling uses the novel 'cyclocuprate' (**14**),[72] which reacts with *gem*-dihalides to give spiro-annulation products (equation 45).



(ref. 71) (43)



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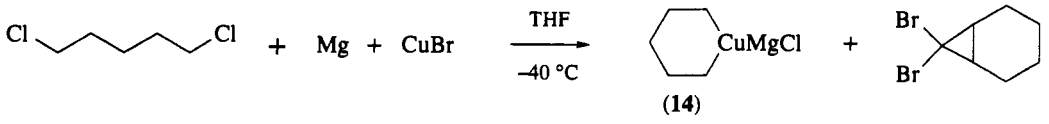
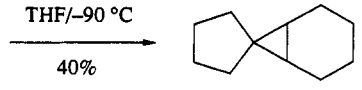




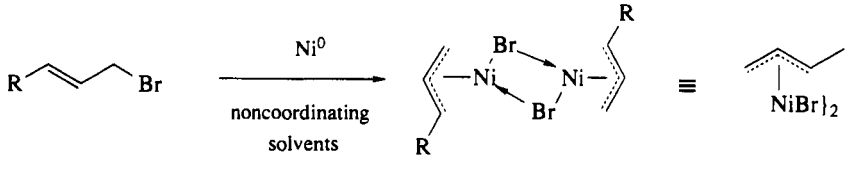
(ref. 72) (45)

2.1.3 π-ALLYLNICKEL HALIDES

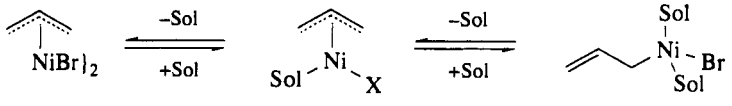
In recent years transition metal π-allyl complexes have emerged as efficient reagents for the introduction of allyl units into organic substrates.[73–78] The main advantage of the transition metal π-allyl complexes over normal allyl-magnesium, -lithium, -zinc, *etc.* systems is their much higher chemoselectivity. Two classes of reagents have proved particularly valuable, the π-allyl complexes of palladium[75,78] and π-allylnickel halides.[73,74,76,77] These complexes are complementary, since π-allylpalladium complexes react with electron-rich centers (*e.g.* stabilized anions) and π-allylnickel halides react with electron-poor centers, (*e.g.* alkyl halides and carbonyl groups). The high reactivity of π-allylnickel halides towards alkyl halides, coupled with their chemoselectivity and the use of heteroatom-substituted complexes make these reagents valuable alternatives to the normal Wurtz-type reagents.

2.1.3.1 Preparation, Structure and Experimental Techniques

The dimeric π-allylnickel halide complexes are most conveniently prepared from allylic halides and nickel(0) species, such as $Ni(COD)_2$ and $Ni(CO)_4$.[73] Although other allylic systems have been used,[79] the most common procedure involves treatment of an allylic bromide with $Ni(CO)_4$ at 50–70 °C.[80] This gives rise to the moderately air-sensitive dimeric π-allyl species (equation 46). In polar coordinating solvents, (DMF, HMPA, *N*-methylpyrrolidone, *etc.*) these dimeric species are converted into highly reactive monomeric species (equation 47).[81]



(46)



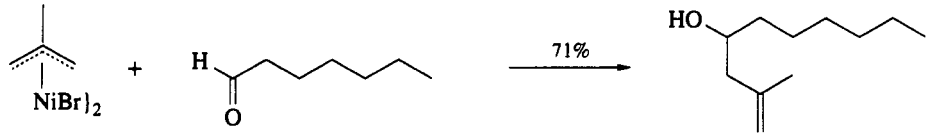
(47)

The following general protocol describes the preparation and use of the complexes. Treatment of an allylic halide with $Ni(CO)_4$ in benzene at 50 °C, or $Ni(COD)_2$ at *ca.* 0 °C generates the dimeric complex. Solvent removal, followed by addition of a polar coordinating solvent and the substrate leads to cross-coupling of the reactive monomeric allylnickel species with the substrate. Excellent practical details are available for these reactions and their synthetic uses have been reviewed,[73] together with the structure and bonding of the complexes.

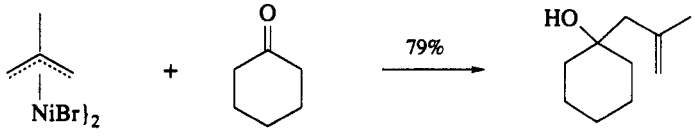
2.1.3.2 Reactivity Patterns

2.1.3.2.1 Chemoselectivity

The π-allylnickel halides show quite different reactivity profiles to the more normal organo-lithium, -sodium or -copper species used in Wurtz-type couplings. In particular, many functional groups which react rapidly with the conventional organometallic reagents are inert to π-allylnickel halides. Functional groups which are either inert to the complexes or react very slowly under forcing conditions include acid chlorides, esters, ethers, nitriles, alkynic protons, alkenes, alcohols, aryl, vinyl and alkyl chlorides, allylic ethers and acetals. Functional groups which react under forcing conditions (*i.e.* above 55 °C leading to extensive thermal decomposition of the complexes) include simple ketones and α,β-unsaturated ketones, with only 1,2-addition being observed (even in the presence of CuI). The complexes react slowly, with temperatures of 40–50 °C required for synthetic utility, with aldehydes, cyclic (and some acyclic) ketones, allylic chlorides and, in one report, epoxides. Examples of these reactions are given in equations (48)–(51).



(48)



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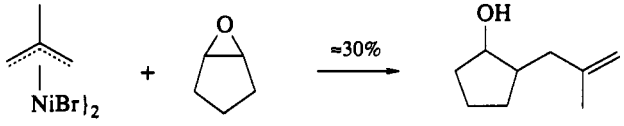
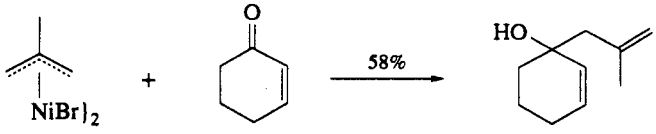
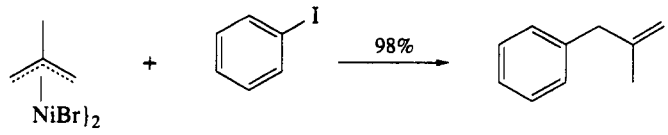


(50)



(51)

In contrast to this low reactivity towards many electron-poor centers, the complexes react at or below room temperature with primary and secondary alkyl iodides, bromides and allyl, vinyl and aryl bromides and iodides, giving cross-coupled products. Phenyl ketones react to give homoallylic alcohols, whereas quinones give allyl-substituted quinones or hydroquinones. 1,2-Diketones give α-ketohomoallylic alcohols (even in the presence of excess complex, reaction occurs at only one carbonyl group) and 2-pyridyl carboxylates give β,γ-unsaturated ketones as the major products. Examples illustrating this reactivity profile are given in equations (52)–(59).[73] This chemoselectivity allows the reaction of the complexes with substrates containing more than one functional group, *e.g.* secondary iodide and secondary alcohol or iodide and chloride in the same molecule (equations 59–61). It is also possible to prepare a range of complexes containing functional groups; thus the coupling reaction both forms a C—C bond and intro-



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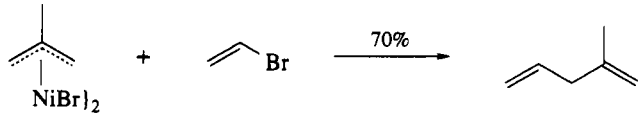

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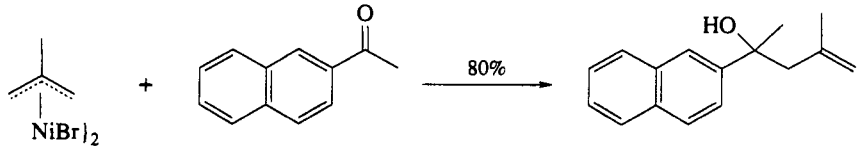

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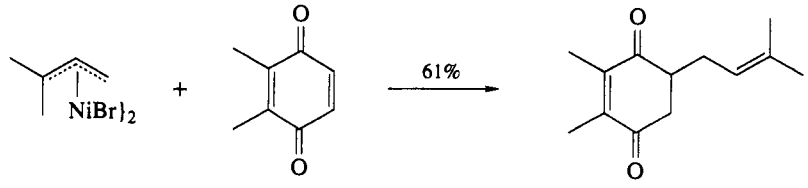

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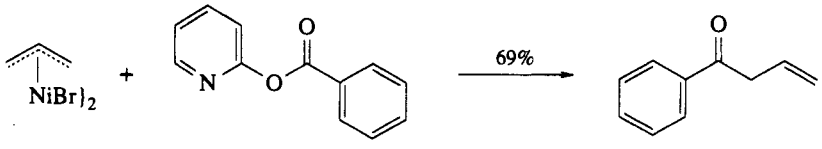
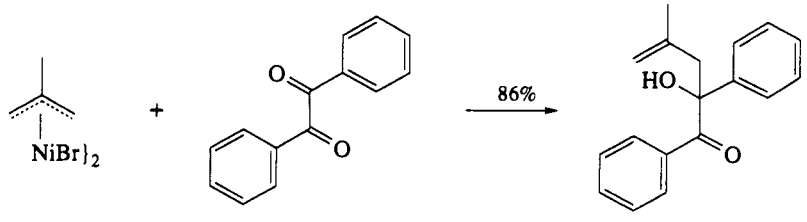


(56)



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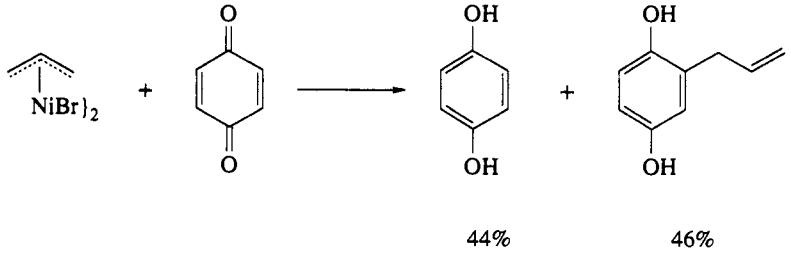

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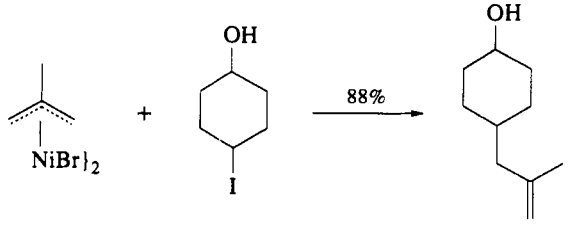

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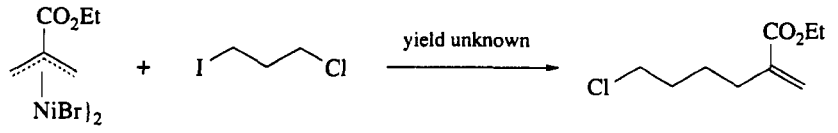

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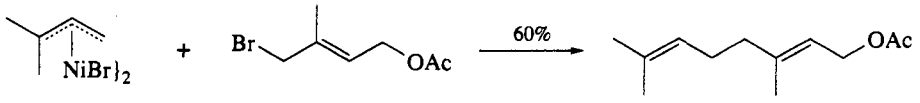
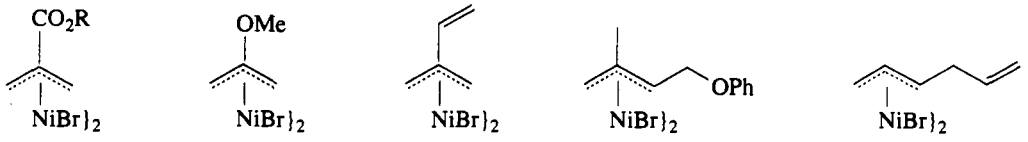


(61)



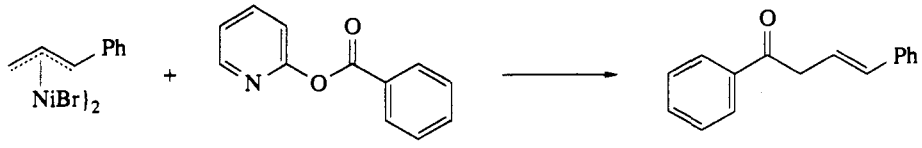
(15) (16) (17) (18) (19)

duces a functional group, possibly in a masked form, into the product. Examples of substituted complexes which have been prepared successfully and used in synthesis include structures (**15**)–(**19**).[73]

2.1.3.2.2 Regioselectivity

Substituted π-allylnickel complexes which could give products derived from reaction either at a primary or a secondary/tertiary terminus almost invariably react only at the primary center (equations 62 and 63).[82]

(62)



(63)

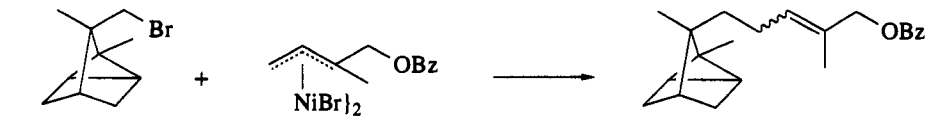
2.1.3.2.3 Stereoselectivity

Coupling of a π-allylnickel halide with an alkyl halide regenerates the double bond originally present in the allyl halide, in addition to forming a new carbon–carbon bond. For trisubstituted double bonds, the products are normally mixtures of (*E*)- and (*Z*)-alkenes, either in a close to 1:1 ratio or with the (*E*)-isomer in excess. In certain favorable cases[83,84] (*E*):(*Z*) ratios of up to 98:2 have been achieved, albeit at the expense of rather low yields of coupled products (see Scheme 2). In general, highly coordinating solvents (HMPA, DMF) give high yields but rather low stereoselection, whereas solvents of lower coordinating power give better stereoselection, coupled with lower overall yields.[83,84] Optically active halides couple with the reagents to give racemic products.[74]

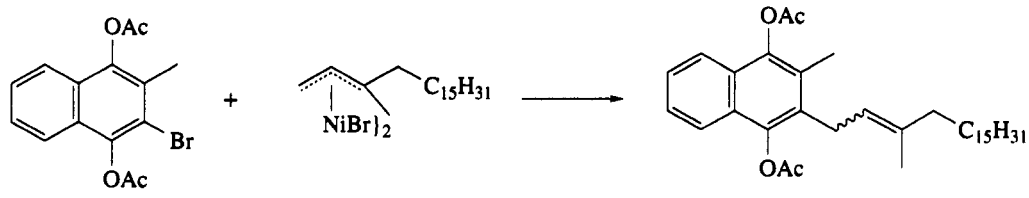
2.1.3.3 Coupling with sp^3 Carbon Centers

2.1.3.3.1 Alkyl halides

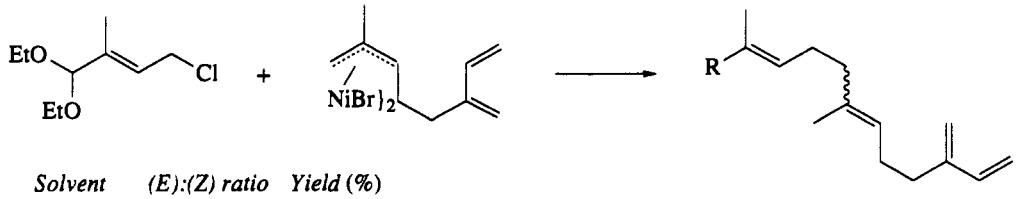
In natural product synthesis, the 1,1-dimethylallyl complex (**20**) has been used to introduce a 5-carbon unit into a number of complex carbon skeletons. Examples of the use of this complex include the prep-



(E):(Z) = 6:4



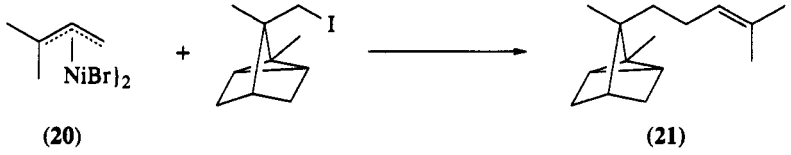
Solvent	*(E):(Z) ratio*	*Yield (%)*
HMPA	51:49	85
DMA	72:28	79
NMP	80:20	75



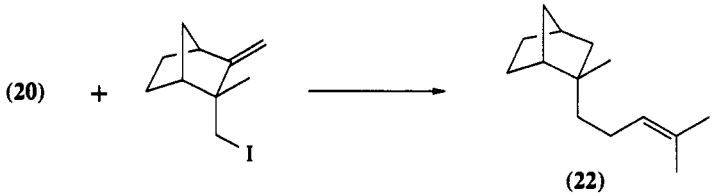
Solvent	*(E):(Z) ratio*	*Yield (%)*
DMF	93:7	50
THF	98:2	23

Scheme 2

aration of α-santalene (**21**) and epi-β-santalene (**22**),[85] campherenone (**23**) and epi-campherenone (**24**),[86] and desmosterol (**25**)[87] (equations 64–68). It is interesting that more traditional approaches to α-santalene *via* coupling with Grignard reagents give only very low yields, compared to the excellent yield obtained with the nickel complex.[88]

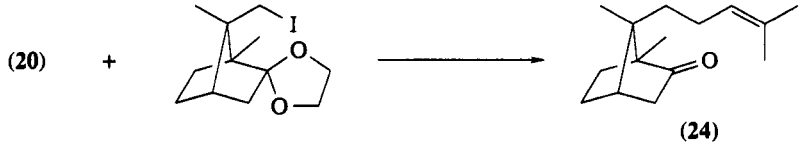


(**20**) (**21**) (64)

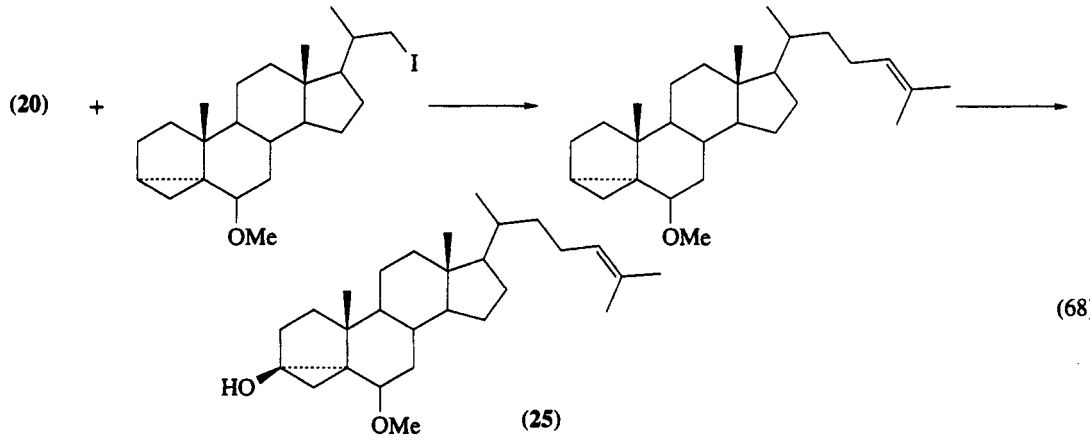


(65)

(66)

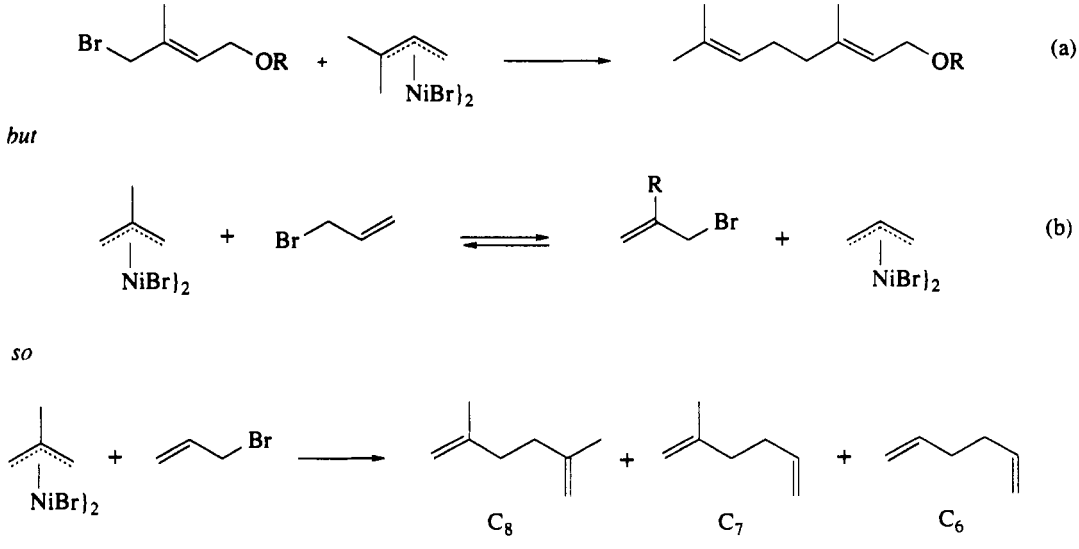


(67)

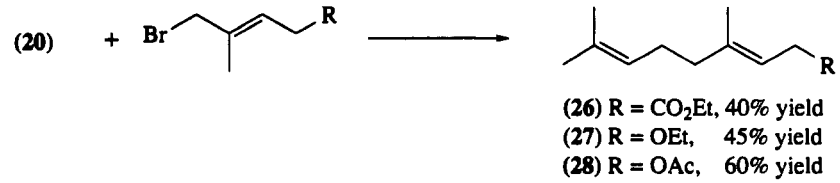


2.1.3.3.2 Allyl halides

Allylic halides may be coupled in the presence of $Ni(CO)_4$ to give 1,5-dienes (Scheme 3).[89] This approach is very attractive for the synthesis of terpenes by sequential addition of isoprene units. Reaction of 1,1-dimethylallylnickel bromide (**20**), for example, with the allylic halide shown in Scheme 3a gives the geranyl carbon skeleton.[90] Unfortunately this approach is complicated by the fact that the π-allylnickel halide complex can undergo ligand exchange with the substrate allyl halide,[91] giving a new complex (Scheme 3b); thus homo-coupling products derived from both of the allyl units result (Scheme 3b). The relative proportions of the homo- and cross-coupled products depend on the relative rates of ligand exchange and the rates of reaction of each complex with the allylic halides present. These reactions normally generate all possible 1,5-diene products in the expected statistical distribution; for example in Scheme 3b the ratio of the three 1,5-diene products is C_6:C_7:C_8 = 25:52:25. For simple complexes, the ratio of these products is not altered significantly by changes in solvent, addition of competing ligands or changes in the leaving group in the allylic substrate.[73] This approach has found application for certain complexes which undergo ligand exchange reactions only slowly. The 1,1-dimethylallyl complex (**20**) for example, reacts with a range of allylic bromo ethers and esters giving the geranyl derivatives (**26**), (**27**) and (**28**), cross-coupled products, in reasonable yields.[90] Only small quantities of homo-coupled products were observed in these reactions (equation 69). In contrast, the reaction of the bromo ester (**29**) with the complex (**20**) gave 70% of (**30**), the product of homo-coupling (*i.e.* dimerization of the substrate) as shown in equation (70).

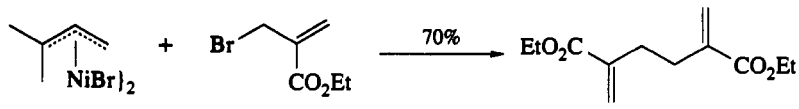


Scheme 3



(69)

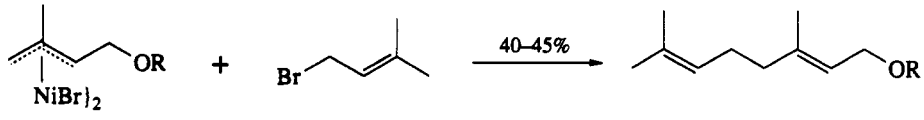
(26) R = CO_2Et, 40% yield
(27) R = OEt, 45% yield
(28) R = OAc, 60% yield



(70)

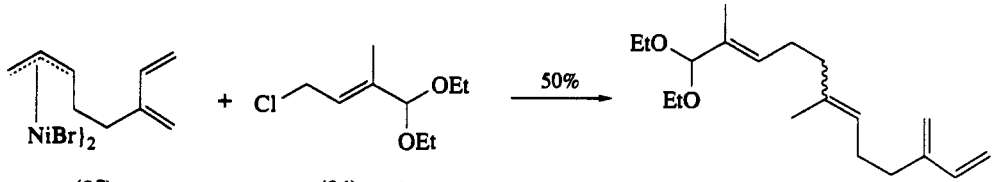
(20) **(29)** **(30)**

The substituted π-allylnickel bromide complexes (**31**) and (**32**) have been reacted with prenyl bromide to give geranyl ethers and with geranyl bromide to give farnesyl ethers (equation 71)[91]; (*E*):(*Z*) ratios of up to 93:7 were observed in these cross-couplings. The substituted complex (**33**) has been used to introduce the isoprene unit into a range of terpenoid skeletons;[82] thus reaction with prenyl bromide leads to myrcene and with geranyl bromide β-farnesene is formed, both reactions giving (*E*):(*Z*) mixtures. β-Sinensal has been prepared from the allylic chloride (**34**), by coupling with the π-allylnickel bromide complex (**35**; equation 72). The desired cross-coupled material (50% yield) was accompanied by lesser quantities (20% and 26%) of the homo-coupled products. The (*E*):(*Z*) ratio of the desired product was 93:7 in DMF and this ratio could be improved to 98:2 in THF, although the chemical yield fell to 23% under these conditions.



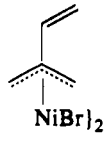
(71)

(31) R = Ph
(32) R = CH_2Ph



(72)

(35) **(34)**



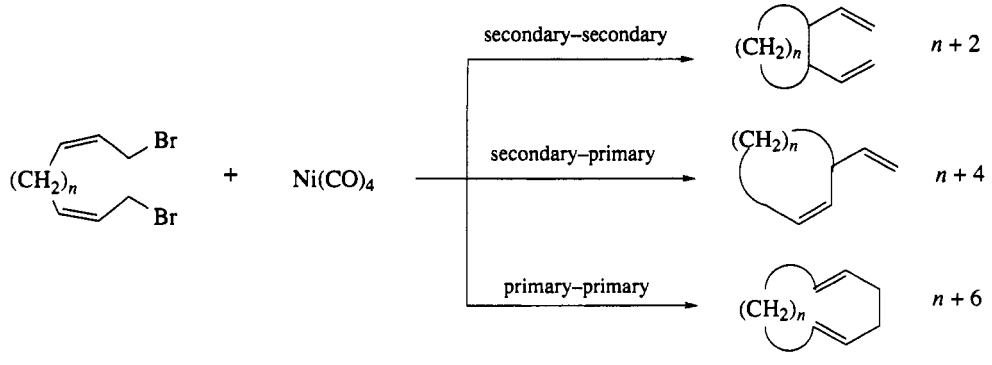
(33)

2.1.3.3.3 Formation of cyclic systems

Two allylic halides in the same molecule may, under high dilution conditions, be coupled using $Ni(CO)_4$ to give a cyclic 1,5-diene. As each allyl group can react to one of two positions, three possible cyclic products may result. In Table 1 this corresponds to ring sizes of $n + 2$, $n + 4$ and $n + 6$. In the generalized example shown, this corresponds to secondary–secondary, primary–secondary, and primary–primary coupling respectively. The relative proportion of each product for a given value of n is deter-

mined by the normal rules governing ring closure effects, together with the preference for primary–primary coupling shown by the π-allylnickel halide intermediates. The accepted normal rates of ring closure reactions are 3 < 4 < 5 > 6 > 7 > 8 < 9 <10 < 11 < 12, *etc.* up to 18, with the relative rate differences becoming smaller as the ring size increases. From the results in Table 1[92] it can be seen that for $n = 6$, 8 and 12, the ring size obtained is governed by the primary–primary bias of the coupling reaction as the largest available ring size predominates, rather than formation of a mixture of ring sizes due to roughly similar rates of closure, as would be predicted. For $n = 2$ and $n = 4$, however, the normal preference for formation of six-membered rings overcomes this bias and six-membered rings are formed by primary–secondary and secondary–secondary closures, respectively. The observed high yields for ring sizes > 12, coupled with the fact that regardless of starting geometry of the allyl halides the products are >95% (*E*),(*E*)-isomers, has led to the use of this method for the synthesis of macrocyclic natural products. Somewhat different results are obtained for exocyclic alkenes[93] and these are summarized in Table 2. It can be seen that this method is of no value for 12-membered rings. A cyclization with one endocyclic and one exocyclic alkenic bond gives intermediate results (equation 73). Related to these results is the interesting trimerization of (**36**) giving (**37**; Scheme 4). Corey *et al.* showed that (**36**), (**38**) and (**39**) added to (**36**) all give (**37**) on treatment with $Ni(CO)_4$.[94] This behavior is very interesting, as it requires (**39**) to undergo intermolecular reaction with (**36**), followed by ring closure to the nine-membered ring (**37**),

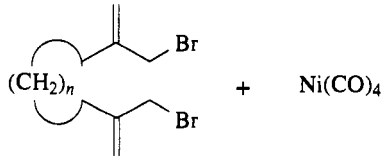
Table 1 Ring Closures with $Ni(CO)_4$ in DMF



Value of n	*Possible ring size of product*	*Observed ring size of product*	*Yield (%)*
2	4/6/8	6	42
4	6/8/10	6	a
6	8/10/12	12	59
8	10/12/14	14	74
12	14/16/18	18	84

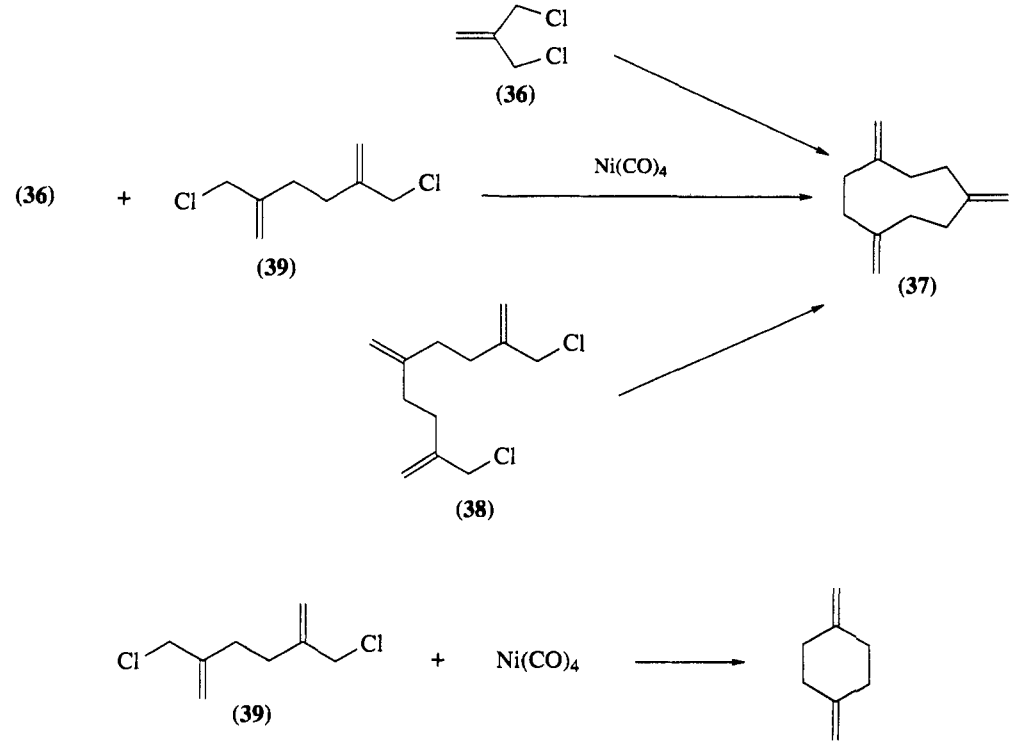
[a]Yield unknown.

Table 2

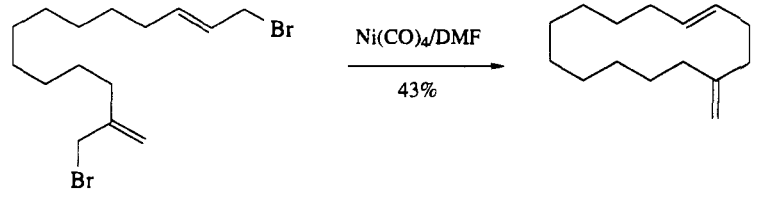


Value of n	*Possible ring size*	*Observed ring size*	*Yield (%)*
6	8/10/12		—
8	10/12/14	14	37
10	12/14/16	16	81
14	16/18/20	20	40

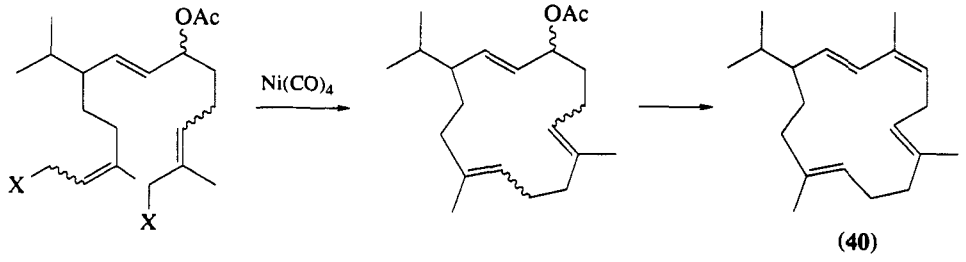
rather than intramolecular coupling to give a six-membered ring system. Indeed, treatment of (**39**) with excess $Ni(CO)_4$ gives only 10% of the six-membered ring derived from intramolecular coupling. Two 14-membered macrocyclic natural products have been prepared using this methodology, *i.e.* cembrene (**40**; equation 74)[95,96] and casbene (**41**; equation 75)[97,98] and the 11-membered macrocycle humulene (**43**; equation 76) has been prepared *via* its geometric isomer (**42**) obtained from a bisallylic bromide precursor.[99,100] In none of these cases were the reactions as clean or as high yielding as the simple model cyclizations would predict. The preference for formation of six-membered rings in this intramolecular coupling has been exploited in a synthesis of elemol (**44**; Scheme 5).[101] The stability of esters to the π-allylnickel reagents has allowed the extension of this method to the synthesis of macrocyclic lactones.[102]



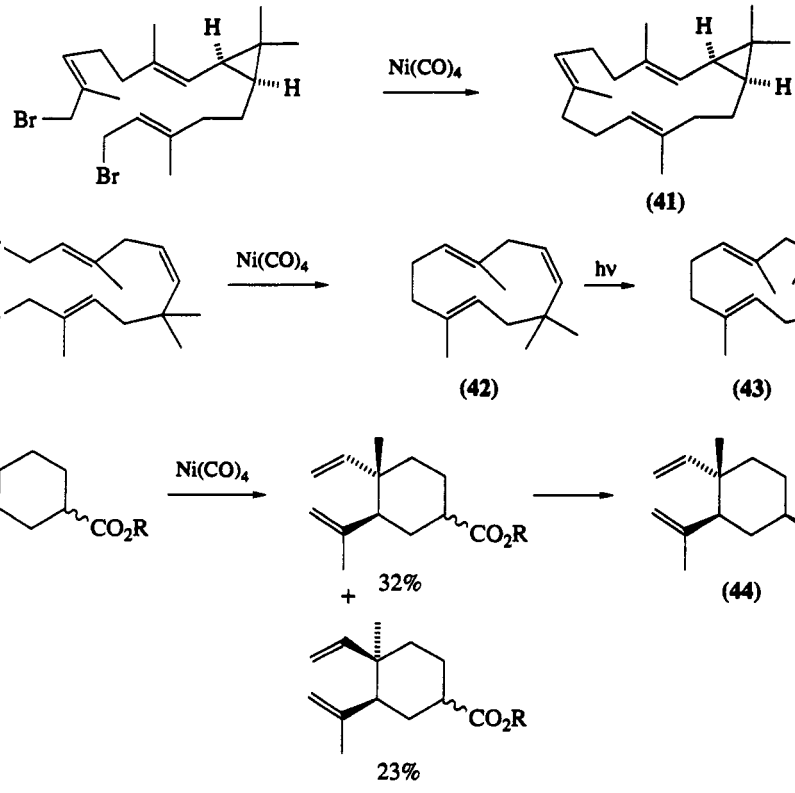
Scheme 4



(73)



(74)



Scheme 5

2.1.4 REFERENCES

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2.2
Coupling Reactions Between sp^3 and sp^2 Carbon Centers

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2.2.1 INTRODUCTION

Selective cross-coupling reactions between C(sp^3) and C(sp^2) centers had been one of the most difficult tasks in carbon–carbon bond synthesis until the early 1970s, when it was first reported that iron,[1,2] nickel,[3,4] palladium[5] and copper[2,6] catalysts are extremely effective for cross-coupling of Grignard reagents with organic halides. Now, nearly 20 years later, transition metal catalyzed cross-coupling has become the reaction of first choice for this purpose.

This section describes the cross-coupling reactions between organometallic reagents and organic halides and related reactions catalyzed by transition metal complexes or salts (<10 mol %). The following two types of reaction (equations 1 and 2) are treated, where R = primary, secondary or tertiary alkyl, alicyclic, allyl or functionalized alkyl groups; R′ = alkenyl, aryl or heteroaryl groups; M = Li, Mg, Cu, Zn, B, Al, Si, Sn, Cd, Hg, Ti or Zr; X = F, Cl, Br, I, OH, OR, OCOR, OTs, OTf, $OP(O)(OR)_2$, SH, SR, SO_2R, SR_2^+, SeR or NR_3^+; and catalyst = Mn, Fe, Ru, Co, Ni, Pd or Cu complex or salt. Among the catalysts listed above, Fe, Ni and Pd catalysts seem to be most effective for the coupling R(sp^3)—M + R′(sp^2)—X, while the coupling R(sp^3)—X + R′(sp^2)—M is catalyzed best by Cu complexes and the allylic R(sp^3)—X + R′(sp^2)—M by Cu, Ni or Pd complexes. Whilst coupling reactions are achieved efficiently with primary alkyl organometallics in the reaction shown by equation (1) and with primary alkyl halides in the reaction shown by equation (2), irrespective of the presence or absence of β-hydrogens, there are some limitations on the secondary and tertiary alkyl organometallics and halides. Thus, coupling reactions of β-H-bearing secondary and tertiary alkyl metallic reagents with C(sp^2) halides are frequently accompanied by reduction of halides or by alkyl group isomerization owing to β-H elimination in alkyl–transition metal intermediates, especially in Ni- or Pd-catalyzed reactions; these problems, however, may be suppressed by the appropriate choice of ligand or metallic reagent. The reaction occurring in equation (2) may also be complicated with β-H-bearing secondary alkyl halides owing to the competing β-H elimination. Not yet achieved are the coupling reactions between tertiary alkyl organometallics and aromatic halides and between tertiary alkyl halides and C(sp^2)-organometallics.

$$R(sp^3)\text{—}M + R'(sp^2)\text{—}X \xrightarrow{\text{catalyst}} R(sp^3)\text{—}R'(sp^2) + M\text{—}X \quad (1)$$

$$R(sp^3)\text{—}X + R'(sp^2)\text{—}M \xrightarrow{\text{catalyst}} R(sp^3)\text{—}R'(sp^2) + M\text{—}X \quad (2)$$

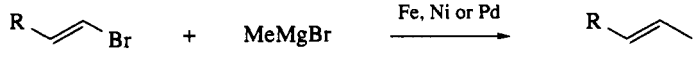
The literature has been surveyed up to 1988. Some recent reviews relevant to this section are as follows: Ni-,[7–12] Pd-,[7,11–17] and Cu-catalyzed[7,18] coupling reactions. Catalytic asymmetric cross-coupling reactions are not treated in this section, since the subject has recently been well reviewed.[19]

2.2.2 COUPLING BETWEEN C(sp^3)-ORGANOMETALLICS AND ALKENYL HALIDES

2.2.2.1 Primary Alkyllithium and Alkylmagnesium Reagents

2.2.2.1.1 Fundamental aspects of alkene stereochemistry

The coupling reactions between C(sp^3)-organometallics and alkenyl halides provide synthetically useful methods for the stereoselective synthesis of di-, tri- and tetra-substituted alkenes, since the reactions proceed with retention of alkene geometry of the stereodefined alkenyl halides in most cases. The most fundamental stereochemical aspects are summarized first. Thus, (*E*)- and (*Z*)-bromopropenes or bromostyrenes couple with the methyl Grignard reagent to form the methylated products in higher than 90% yields and with almost complete retention of configuration in the presence of $Fe(DBM)_3$ (DBM = dibenzoylmethanato),[20] $NiCl_2(DPPP)$[21] or $Pd(PPh_3)_4$[5] (equations 3 and 4). Similar stereospecific coupling



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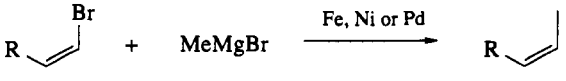
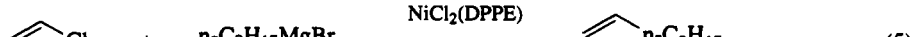


(4)

occurs with methyllithium in the presence of $Pd(PPh_3)_4$[22,23] or $RuCl(PPh_3)_3$[22] in refluxing benzene. Silver-catalyzed coupling of (*Z*)-bromopropene with MeMgBr proceeds with loss of stereochemistry.[24] The most useful catalysts seem to be Ni, Pd, or Fe complexes.

2.2.2.1.2 Alkenyl chlorides

Couplings between alkenyl chlorides and alkyl Grignard reagents are catalyzed best by nickel complexes,[25,26] as exemplified by the synthesis of terminal alkenes,[25] disubstituted alkenes,[27] cyclic alkenes[25] and a silylmethyldiene (equations 5–8),[28] while $Pd(PPh_3)_4$ has also been claimed to be useful for a few cases.[26]



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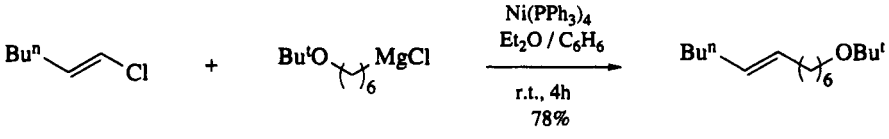
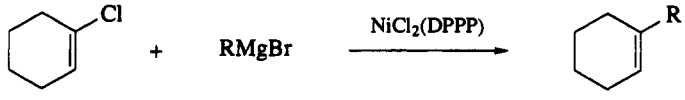
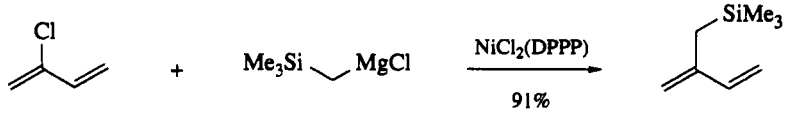


(6)



(7)

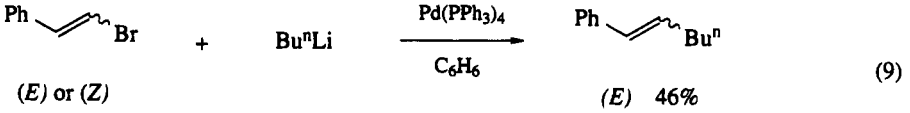


(8)

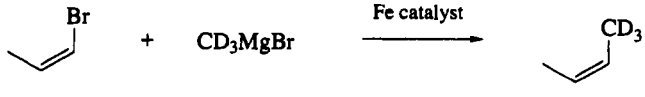
2.2.2.1.3 Alkenyl bromides

In addition to Ni catalysts, Fe and Pd complexes are also effective for couplings involving alkenyl bromides. Although organolithium reagents are not generally useful for transition metal catalyzed coupling reactions, moderate yields are achieved in the coupling of *n*-butyllithium with (*E*)- and (*Z*)-bromostyrene in the presence of $Pd(PPh_3)_4$ in benzene, the solvent being chosen to minimize side reactions such as metalation (equation 9).[22]

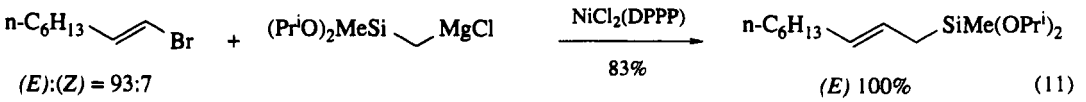
Coupling reactions of alkyl Grignard reagents lacking β-H substitution are exemplified by the stereoselective synthesis of a trideuteriomethylated alkene (equation 10)[29] and of allylsilanes (equations 11 and 12).[30,31] Cyclic bromoalkenes also undergo coupling smoothly (equation 13).[31]



(9)



(10)



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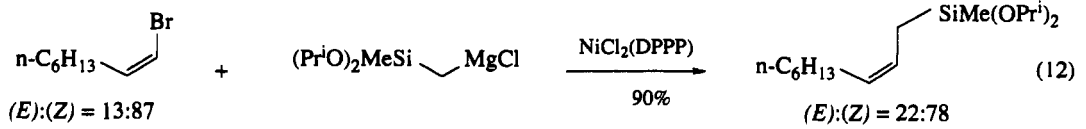
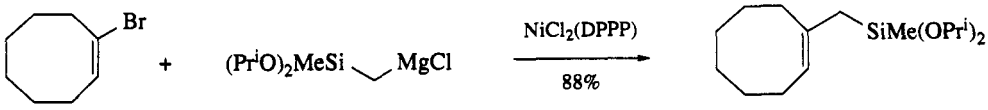


(12)

Coupling reactions of β-H-bearing alkyl Grignard reagents with parent vinyl bromide, (*Z*)- and (*E*)-alkenyl bromides are catalyzed by Fe,[2,20] Ni[32] and Pd[33] respectively (equations 14–16). Similar Pd-catalyzed alkylations can be applied to 1- and 2-bromoethenylsilanes (equations 17 and 18).[34] β-Branched primary alkyl Grignard reagents also undergo Fe-[35] or Pd- catalyzed[36] coupling smoothly (equations 19 and 20).



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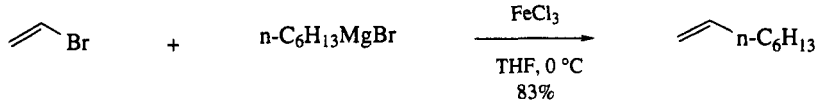

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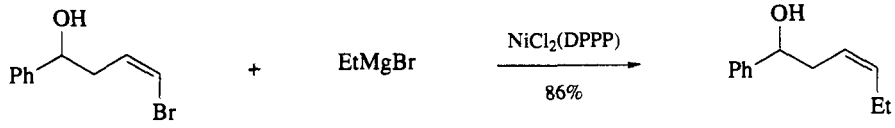

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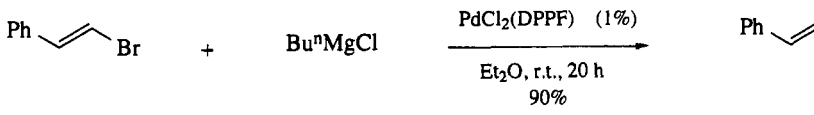

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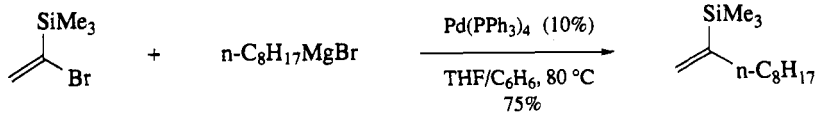

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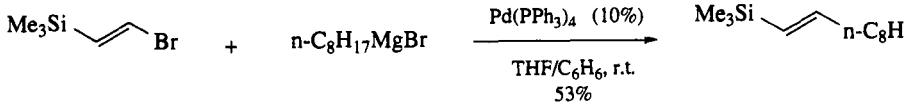

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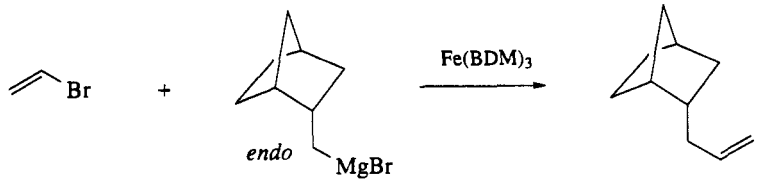

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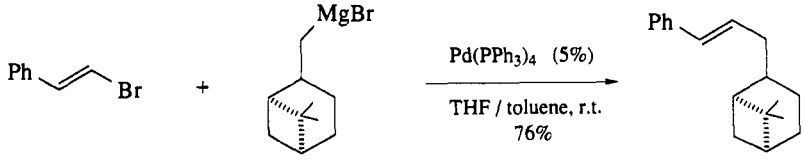
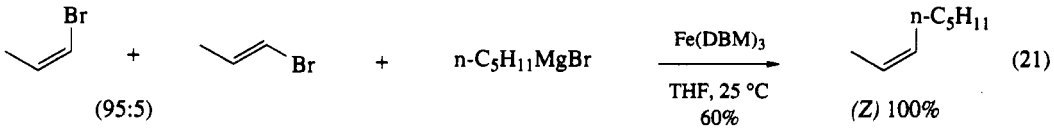


(20)

Interestingly, there seems to be a striking difference in reactivity between (*E*)- and (*Z*)-isomers of 1-bromoalkenes. (*E*)-Isomers are more reactive than the (*Z*)-isomers in the Pd-catalyzed reaction.[37] The reverse order is found in the Fe-catalyzed coupling reaction with β-H-bearing primary alkyl Grignard reagents,[20] but with the methyl and *s*-and *t*-alkyl Grignard reagents (*E*)-isomers seem to be more reactive. Therefore, coupling reactions of a geometrically isomeric mixture with molarly deficient alkyl Grignard

reagent can afford isomerically pure disubstituted alkenes, *i.e.* (*E*)-alkenes with Pd catalyst and (*Z*)-alkenes with Fe catalyst (equations 21 and 22).



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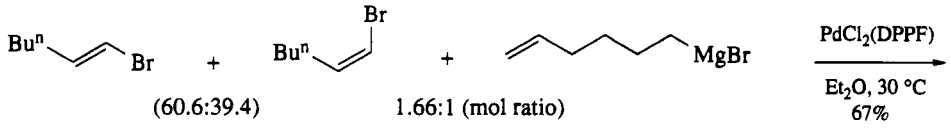
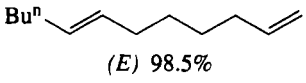
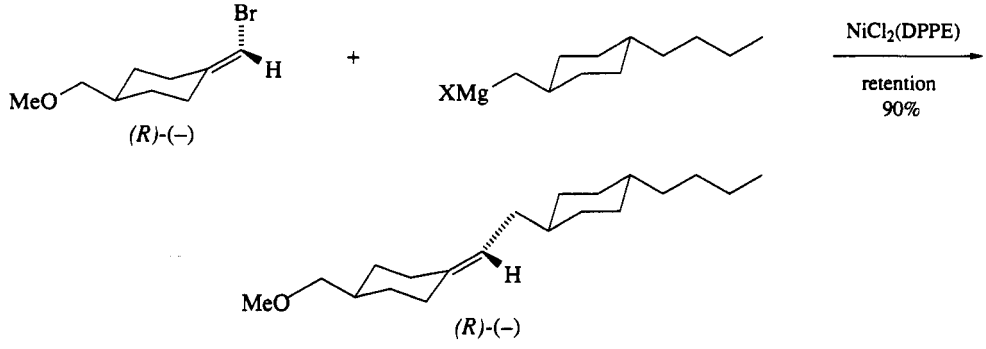




(22)

Axially chiral, optically active alkenyl bromides couple with methyllithium[38] or with alkyl Grignard reagents[39] with retention of configuration (96% retention) in the presence of $NiCl_2$(DPPE) or $Fe(DBM)_3$; the reaction may be useful for the synthesis of optically active liquid crystals (equation 23). Allenyl bromides also undergo coupling with alkyl Grignard reagents under the catalysis by $Ni(mesal)_2$ (mesal = *N*-methylsalicylaldiminato); coupling of optically active allenyl bromides proceeds with retention, but with substantial loss of stereochemistry (equation 24).[40,41]



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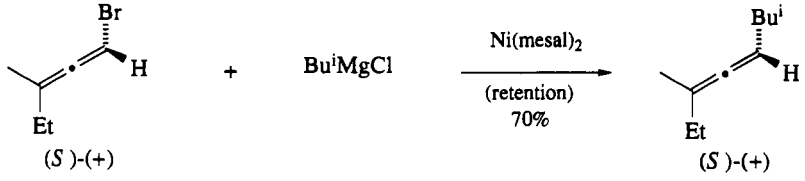
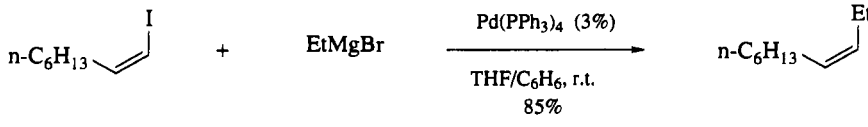


(24)

2.2.2.1.4 Alkenyl iodides

In addition to Ni and Pd catalysts, Li_2CuCl_4 is also an effective catalyst for the coupling of alkenyl iodides with Grignard reagents.[42] Since the stereochemistry of alkenyl iodides is also retained, the coupling reactions are useful for the stereoselective synthesis of disubstituted alkenes,[36,43] trisubstituted alkenes,[42] allylsilanes,[44] allyl alcohols[45] and tetrasubstituted alkenes (equations 25–29).[46]



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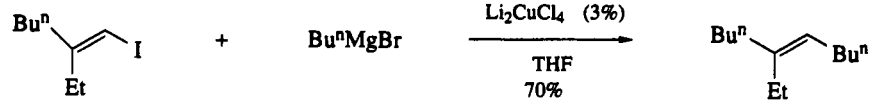
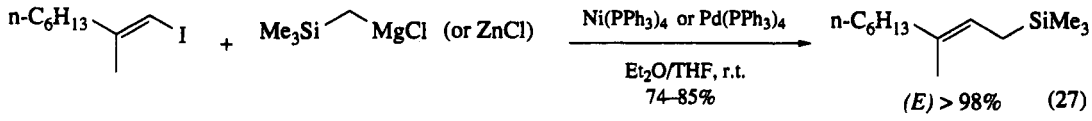


(26)



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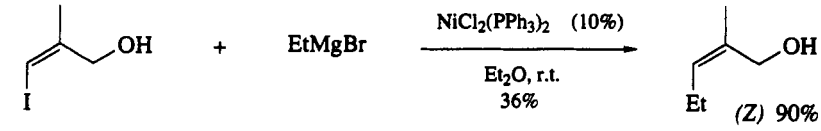

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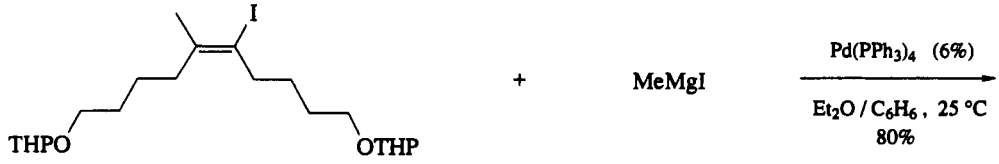
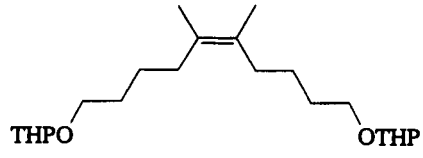


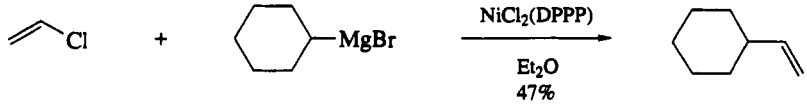


(29)

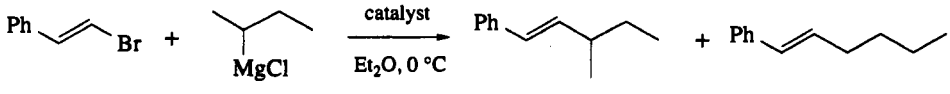
2.2.2.2 Secondary Alkyl Grignard Reagents

The cyclohexyl Grignard reagent couples smoothly with vinyl chloride in the presence of $NiCl_2$(DPPP) (equation 30).[25] Alkyl group isomerization from secondary to primary is frequently observed in the coupling of secondary alkyl Grignard reagents with alkenyl halides catalyzed by Ni or Pd complexes; the extent of the isomerization is strongly dependent upon the nature of ligand and metal in the catalyst as well as the organic halides (see also Section 2.2.5.2). Thus, in the coupling of (*E*)-bromostyrene with the *s*-butyl Grignard reagent (equation 31), while $NiCl_2$(DPPP) or $PdCl_2$(DPPP) as catalysts induce the isomerization to some extent, no isomerization is observed with $PdCl_2$(DPPF) at all, only the *s*-butylated product being formed in almost quantitative yields and with retention of the alkene stereochemistry.[47] The catalyst $PdCl_2$(DPPF) is also effective for similar coupling of less reactive alkenyl bromides, such as 2-bromopropene, without alkyl isomerization (equation 32).[47]

Cross-coupling reactions between the isopropyl Grignard reagent and alkenyl bromides or iodides are also catalyzed by Fe[20] or Cu[42] complexes, no alkyl group isomerization being observed (equations 33

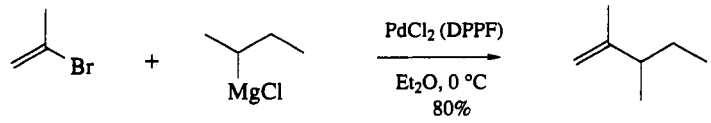


(30)



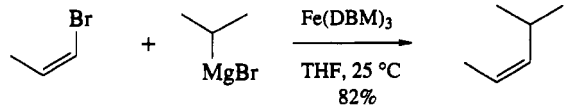
(31)

$PdCl_2$(DPPF)	97%	100:0
$NiCl_2$(DPPP)	89%	99:1
$PdCl_2$(DPPP)	81%	86:14
$Pd(PPh_3)_4$	69%	48:52



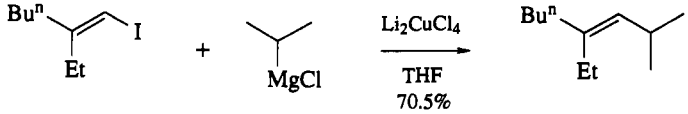
(32)

and 34). Here again, (*Z*)-1-bromoalkenes seem to be more reactive than the (*E*)-isomers in the Fe-catalyzed reactions.[20] In the cross-coupling reaction of (*E*)- and (*Z*)-1-bromo-2-phenylthioethylenes with secondary alkyl Grignard reagents, however, the extent of isomerization is less with $NiCl_2$(DPPE) than with $PdCl_2$(DPPF), no isomerization being observed with $Fe(DPM)_3$ (DPM = dipivaloylmethanato); stereoselectivities are higher than 97% in all cases (equation 35; see also Section 2.2.4).[48,49]

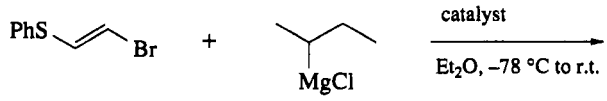


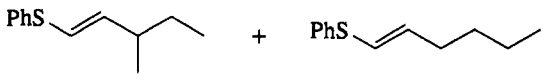
(33)

(*Z*):(*E*) = 95:5 (*Z*) 100%



(34)



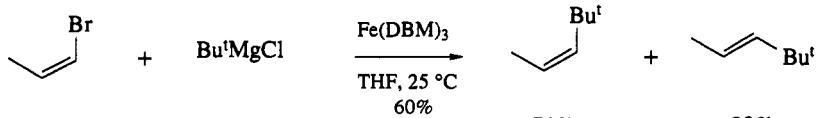


(35)

$Fe(DPM)_3$	80%	100:0
$NiCl_2$(DPPE)	86%	100:0
$PdCl_2$(DPPF)	74%	94:6

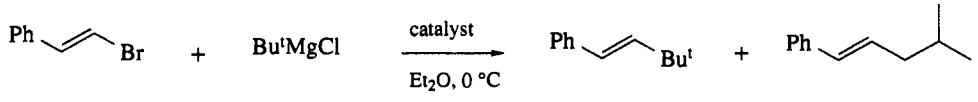
2.2.2.3 Tertiary Alkyl Grignard Reagents

There have been only three reports on cross-coupling of *t*-butylmagnesium chloride with alkenyl halides. An Fe-catalyzed reaction with (*Z*)-1-bromopropene affords a mixture of (*Z*)- and (*E*)-isomers of *t*-butylated product with some loss of stereochemistry (equation 36).[20] In the presence of $NiCl_2$(DPPF), (*E*)-bromostyrene couples with Bu^tMgCl without alkyl group isomerization and stereochemical scrambling, while alkyl group isomerization is induced by $NiCl_2$(DPPP) as catalyst (equation 37); the $NiCl_2$(DPPF)-catalyzed *t*-butylation, however, seems to be restricted only to a reactive alkenyl halide such as (*E*)-bromostyrene.[50] Trisubstituted alkenyl iodides undergo coupling with Bu^tMgCl in the presence of Li_2CuCl_4 with retention of configuration (equation 38).[42]



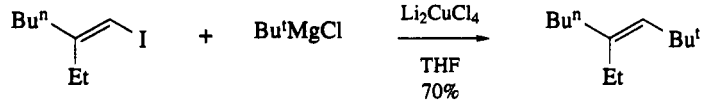
(36)

(*Z*):(*E*) = 95:5 71% 29%



(37)

$NiCl_2$(DPPF)	67%	100:0
$NiCl_2$(DPPP)	59%	78:22



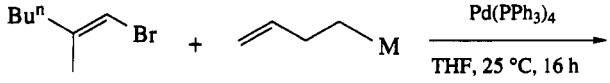
(38)

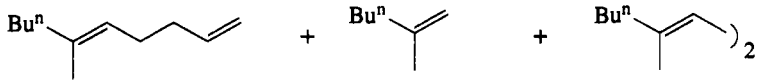
2.2.2.4 Organozinc and Organotin Reagents

Coupling reactions of alkylzinc and alkyltin reagents with alkenyl halides are catalyzed efficiently by Pd and, in some cases, by Ni complexes.

2.2.2.4.1 Primary and secondary alkylzinc reagents

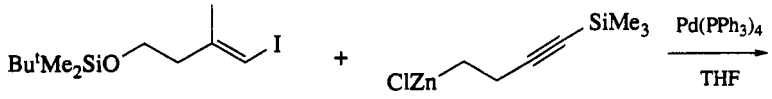
The advantages of zinc reagents over Grignard reagents are that yields of coupled products are generally higher and a wider degree of functionality can be tolerated. It should be noted that coupling of β-H-bearing alkylzinc reagents, as well as β-H-lacking alkylzinc reagents, with alkenyl bromides or iodides are catalyzed even by unidentate phosphine-ligated Pd complexes such as $Pd(PPh_3)_4$, as illustrated in equation (39).[51] *n*-Butyl–,[51] benzyl–,[52] 2-phenylethyl–,[53] homoallyl–[51,54] and homopropargyl–zinc[51,55] reagents all have been shown to couple with trisubstituted alkenyl iodides and β-bromo-α,β-unsaturated carboxylates with retention of the alkene stereochemistry, as exemplified by the stereoselective synthesis of terpenoid skeletons (equations 40 and 41).

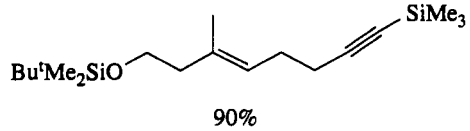




(39)

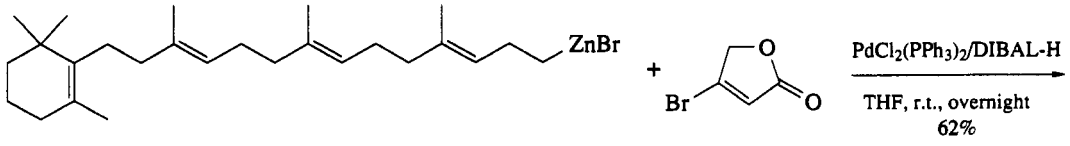
M = ZnCl 89% 91:trace: 9
M = MgBr 69% 30:54:16

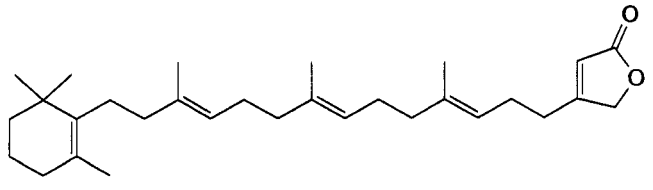




90%

(40)

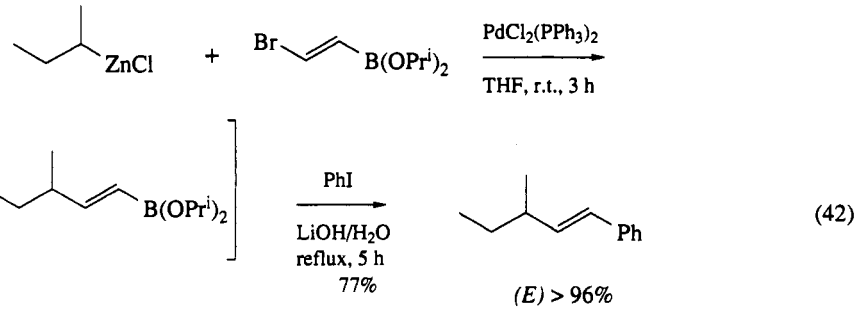




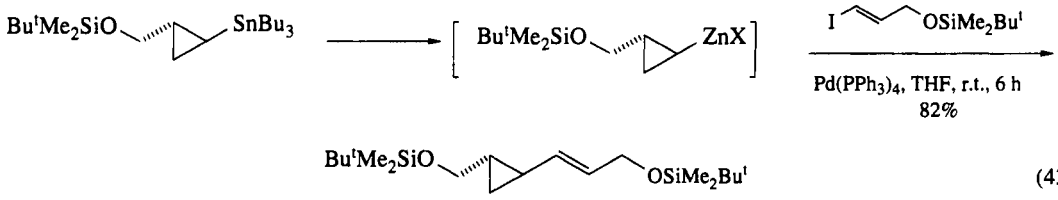
(41)

Mokupalide 62%

Secondary alkylzinc reagents also couple with a trisubstituted alkenyl iodide under similar conditions, but the coupling is accompanied by alkyl group isomerization from secondary to primary (sec:prim = 60:40);[51] no alkyl group isomerization has been observed in the Pd-catalyzed coupling of a *s*-butylzinc reagent with an (*E*)-bromovinylboron derivative (equation 42).[56] A cyclopropylzinc reagent undergoes a facile coupling with (*E*)-iodoalkenes catalyzed by $Pd(PPh_3)_4$ (equation 43).[57]



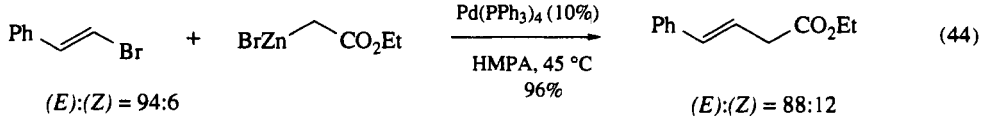
(42)



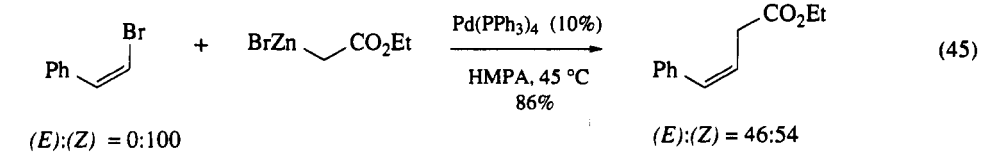
(43)

2.2.2.4.2 Reformatsky and related reagents

Cross-coupling reactions of the Reformatsky reagent with vinyl, 2-propenyl and styryl bromides are catalyzed by $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$ (10 mol %) in HMPA as an essential solvent to form β,γ-unsaturated esters in moderate yields.[58] While the (*E*)-stereochemistry of alkenyl bromides is almost retained, stereochemical scrambling is often observed with (*Z*)-isomers (equations 44 and 45). It may be mentioned here that similar, but stoichiometric, Ni-promoted couplings of lithium ester enolates with alkenyl bromides are also known.[59,60] Zinc reagents derivable *in situ* from ω-iodoalkyl ketones with Zn/Cu also undergo Pd-catalyzed coupling with iodoalkenes (equation 46).[61]



(44)



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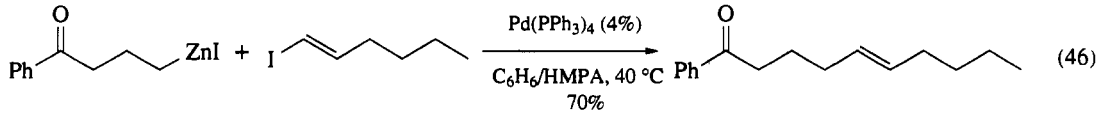
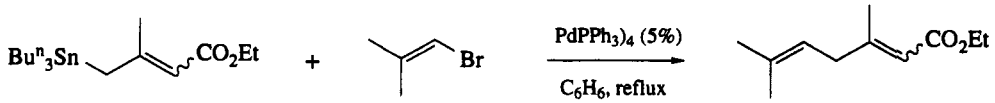


(46)

γ-Stannyl-α,β-unsaturated esters have been shown to couple with an alkenyl bromide at the γ-position selectively, but in low yield (equation 47).[62] α-Sulfonylalkylstannanes also undergo the Pd-catalyzed coupling with alkenyl iodides (equation 48).[63]



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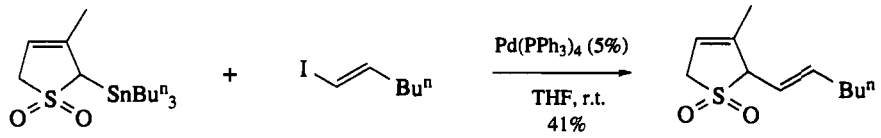
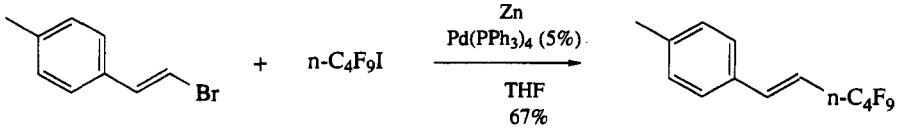


(48)

2.2.2.4.3 *Perfluoroalkylzinc reagents*

Perfluoroalkylzinc iodides, generated *in situ* from the iodides and zinc powder under ultrasound irradiation, couple smoothly with alkenyl bromides in the presence of $Pd(PPh_3)_4$ as catalyst, linear and branched perfluoroalkyl groups being coupled with retention of the (*E*)-alkene stereochemistry (equation 49).[64]



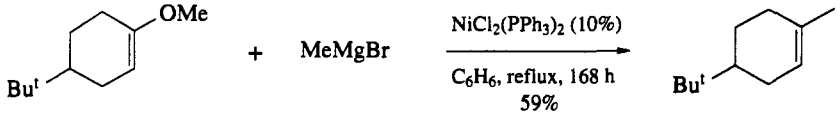
(49)

2.2.3 COUPLING OF C(sp^3)-ORGANOMETALLICS WITH ALKENYL O, S, Se AND Te COMPOUNDS

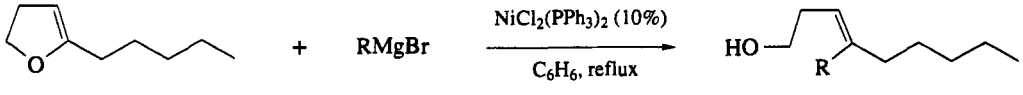
Only primary alkyl–metal reagents have been used in these cases, except in the instance of the Fe-catalyzed coupling of alkenyl sulfones.

2.2.3.1 Enol Ethers, Enol Carboxylates, Enol Phosphates and Enol Sulfonates

Enol ethers (equation 50),[65] dihydrofurans (equation 51),[66,67] dihydropyrans (equation 52)[65,68] and benzofuran (equation 53)[65] react with alkyl Grignard reagents in the presence of Ni catalysts to form the cross-coupling products through cleavage of C(sp^2)–oxygen bonds. Benzene is used as a suitable solvent for the coupling of enol ethers. $NiCl_2(PPh_3)_2$ is used mostly for alkyl Grignard reagents lacking β-H substitution, while $NiCl_2$(DPPP) is suitable for β-H-bearing alkyl Grignard reagents. Only primary alkyl Grignard reagents can be used in all cases. The stereochemistry present in the cyclic ethers is highly retained, especially in those cases where the oxygen-bearing carbon contains an exocyclic substituent (equations 51 and 52), thus providing stereoselective synthesis of trisubstituted alkenes with a hydroxy group on the side chain.



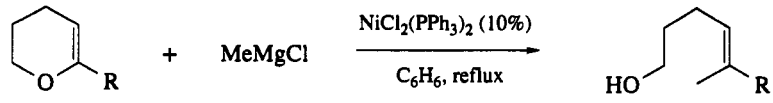
(50)



(51)

R = Me	87%
R = PhCH$_2$	79%
R = Me$_3$SiCH$_2$	77%
R = Bu^n	82%

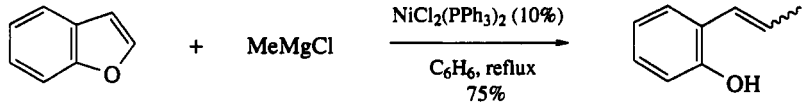
(*E*) > 95%



(52)

R = H 74% (*Z*):(*E*) = 76:24

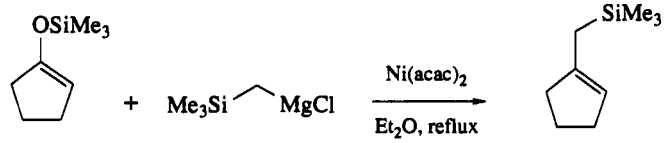
R = Bu^n 85% (*E*) > 97%



(53)

(*Z*):(*E*) = 80:20

Cross-coupling of enol silyl ethers with primary alkyl Grignard reagents is also catalyzed by Ni complexes, as exemplified by the conversion of an enol silyl ether into an allylsilane (equation 54)[69] and by stereoselective alkylation (equation 55).[70]



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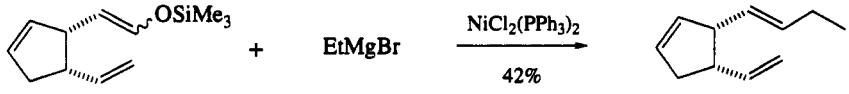
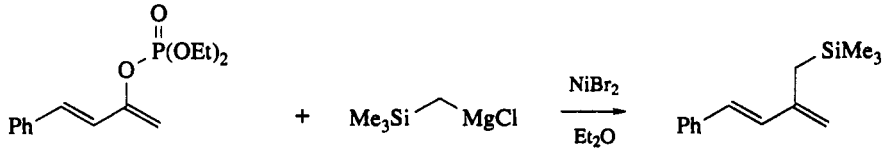


(55)

Enol phosphates couple with primary alkyl Grignard reagents in the presence of Ni complexes. While $NiBr_2$ is a suitable catalyst for trimethylsilylmethylation (equation 56),[71] $NiCl_2$(DPPP) should be used for β-H-bearing alkyl Grignard reagents (equation 57)[71,72] Enol phosphates also undergo $Pd(PPh_3)_4$-catalyzed coupling reactions with trimethyl- or triethyl-aluminum with retention of the enol stereochemistry (equation 58)[73] and with trialkylmanganates, R_3MnLi.[74]



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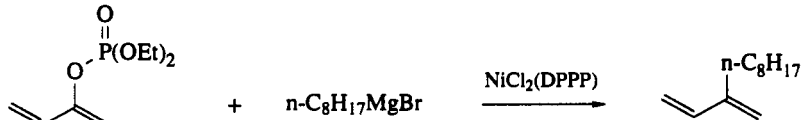
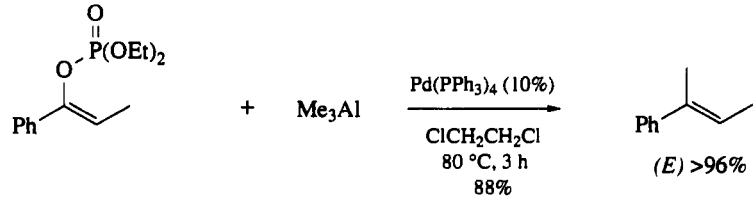


(57)

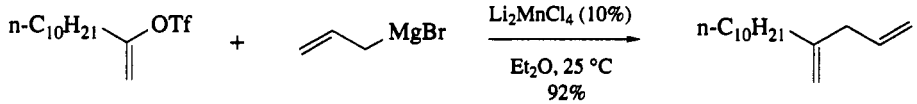


(58)

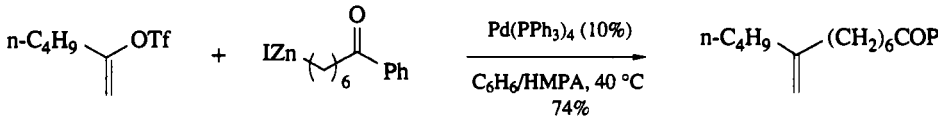
(*E*) >96%

Enol triflates couple with the allyl or benzyl Grignard reagent in the presence of Li_2MnCl_4 as a catalyst to give coupling products in high yields (equation 59).[74] Enol triflates can be alkylated with alkylzinc[61]

and alkyltin reagents[75] under catalysis by $Pd(PPh_3)_4$ with β-H-bearing alkyl groups being introduced; in the latter case LiCl is required as an essential additive (equations 60 and 61).



(59)



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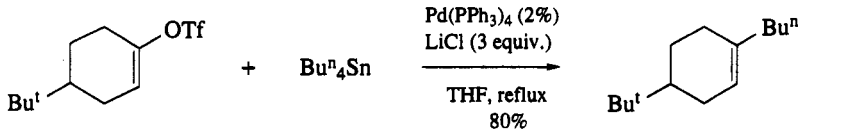
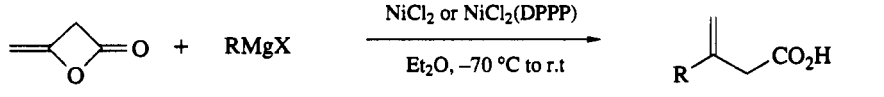


(61)

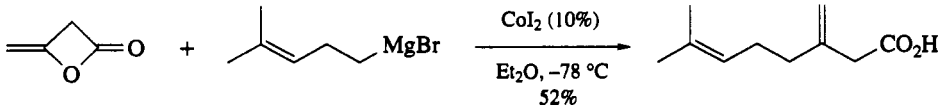
Diketene, a cyclic enol carboxylate, reacts with Grignard reagents in the presence of Ni[76,77] or Co[78] salts or complexes to form 3-methylenealkanoic acids; in addition to methyl, trimethylsilylmethyl (equation 62)[76] or benzyl groups and β-H-bearing primary alkyl groups can be introduced if $NiCl_2(DPPP)$[77] or CoI_2 (equation 63)[78] are used as a catalyst at low temperatures.



(62)

$R = Me_3SiCH_2$ 95%

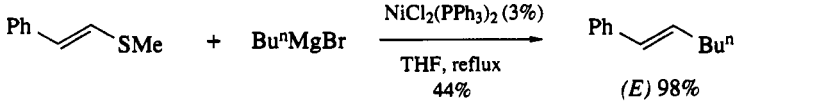
$R = Bu^n$ 51%



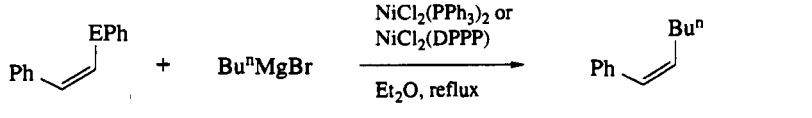
(63)

2.2.3.2 Alkenyl Sulfides, Sulfones, Selenides and Tellurides

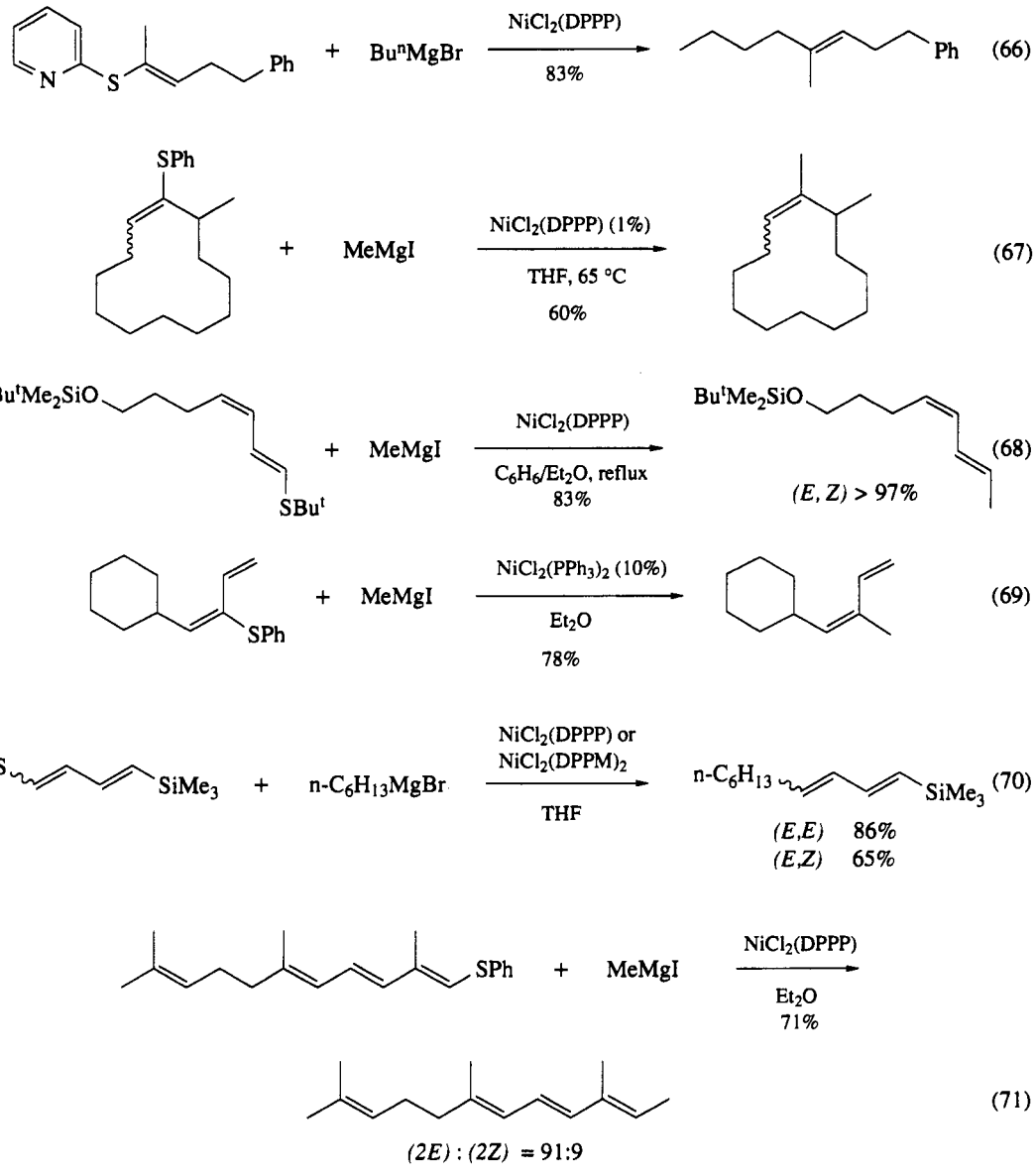
Nickel complexes, mostly $NiCl_2(PPh_3)_2$ and $NiCl_2(DPPP)$, are effective catalysts for cross-coupling reactions between alkyl Grignard reagents and alkenyl–S and alkenyl–Se compounds. Although the sulfide leaving groups may be alkylthio or arylthio groups, aryl–S bonds (see Section 2.2.6) are also cleaved competitively in coupling of alkenyl phenyl sulfides, thus requiring excess amounts of Grignard reagents. The coupling reaction proceeds with retention (>94%) of alkene geometry (equations 64 and 65).[79,80] The coupling reaction of alkenyl sulfides has been applied to the stereoselective synthesis of di-[81] and tri-substituted alkenes (equation 66),[82,83] cyclic alkenes (equation 67),[84] 1,3-dienes (equations 68–70)[85–88] and 1,3,5-trienes (equation 71);[89] in the case of (Z)-silyldienyl sulfides, $NiCl_2(DPPM)_2$ (DPPM = $Ph_2PCH_2PPh_2$) seems to be the most suitable catalyst.[87]



(64)

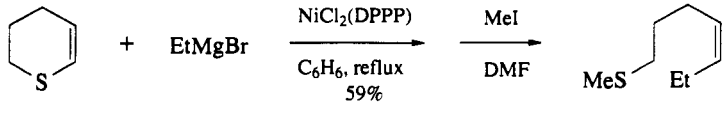


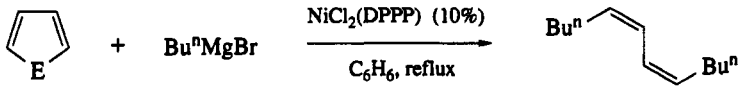
(65)



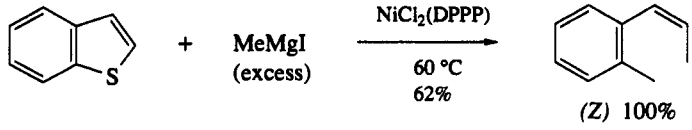
2,3-Dihydrothiopyran undergoes a ring-opening coupling with primary alkyl Grignard reagents catalyzed by $NiCl_2$(DPPP) in benzene to form, after *S*-methylation, a methylthio-containing (*Z*)-alkene stereoselectively (equation 72).[90] Thiophene, selenophene and tellurophene also undergo similar coupling reactions to form symmetrical (*Z,Z*)-1,3-diene derivatives (equation 73),[91,92] furan being almost inert under similar conditions. 1-Benzothiophene reacts with 1 equiv. of the methyl Grignard reagent in the presence of $NiCl_2$(DPPP) as a catalyst (50 mol %) to form an *o*-[(*Z*)-1-propenyl]phenyl sulfide derivative stereoselectively. The sequence occurs *via* preferential cleavage of the S–alkenyl bond rather than the S–aryl bond, the latter also being cleaved with excess amounts of the Grignard reagent to form a double methylation product (equation 74, see also Section 2.2.6).[90]

Alkenyl sulfones are methylated with MeMgX in the presence of $Ni(acac)_2$, the stereoselectivity being dependent upon the magnesium salt in the order MgCl > MgBr > MgI (equation 75).[93] Coupling of (*E*)- and (*Z*)-alkenyl sulfones with primary alkyl (except methyl) Grignard reagent occurs stereospecifically



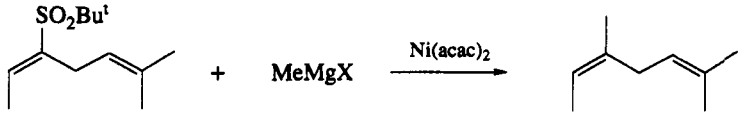


(73)



(74)

in the presence of $Fe(acac)_3$ as a catalyst to afford trisubstituted alkenes (equation 76).[94] Fe catalysts, rather than Ni, afford better results in the coupling of secondary alkyl Grignard reagents with alkenyl sulfones; the coupling is, however, accompanied by reduction and alkyl group isomerization (equation 77).[95]



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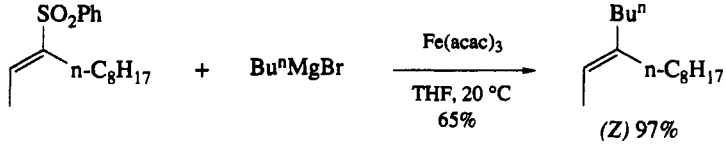

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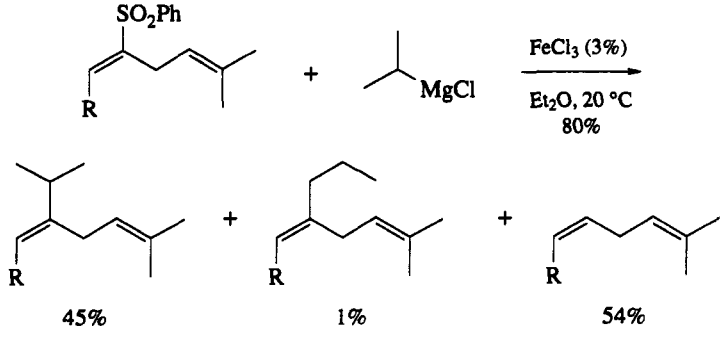
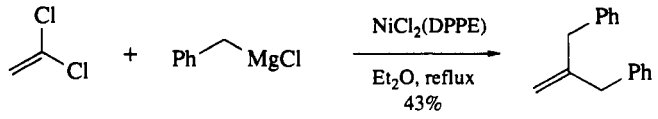


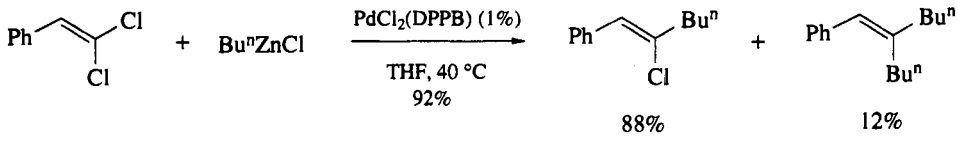
(77)

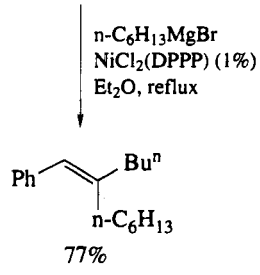
2.2.4 COUPLING BETWEEN C(sp^3)-ORGANOMETALLICS AND DIFUNCTIONAL ALKENES

1,1-Dichloroethylene undergoes a Ni-catalyzed double coupling reaction with the benzyl Grignard reagent (equation 78), but a complex mixture of products may result with β-H-bearing alkyl Grignard reagents.[25] Stereoselective, stepwise coupling of 1,1-dichloroalkenes can be achieved with a β-H-bearing primary alkylzinc reagent in the presence of $PdCl_2$(DPPB), followed by reaction with an alkyl Grignard reagent catalyzed by $NiCl_2$(DPPP) (equation 79); the higher reactivity of the chlorine atom *trans* to the 2-substituent may be noted (*cf.* Section 2.2.2.1.1).[96] 1,1-Disulfide analogs (ketene dithioacetals) also undergo stereoselective, stepwise coupling with primary alkyl Grignard reagents in the presence of Ni complex (equation 80).[97] These two reactions may be useful for the stereoselective synthesis of trisubstituted alkenes.

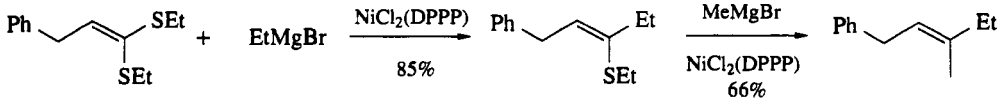


(78)



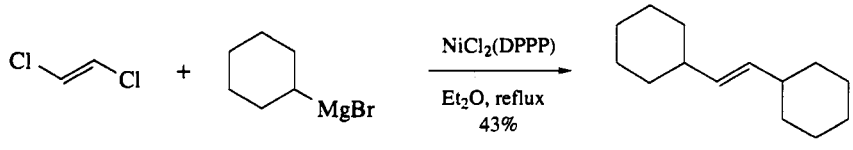


(79)

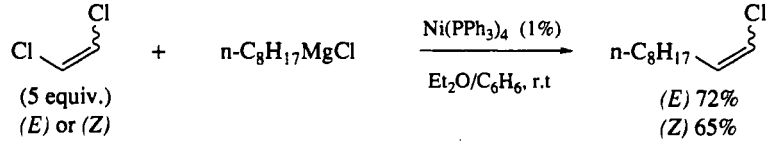


(80)

The predictabilities of Ni-catalyzed Grignard reactions involving 1,2-dichloroethylenes are not simple. Thus, whilst with the benzyl Grignard reagent bibenzyl is formed predominantly, double coupling products are obtained in moderate yields with β-H-bearing primary alkyl or cyclohexyl Grignard reagents, together with homocoupling of the Grignard reagent; only (*E*)-dicyclohexylethylene is formed both from (*E*)- and (*Z*)-dichloroethylenes (equation 81).[25] On the other hand, in the presence of excess amounts of (*E*)- or (*Z*)-dichloroethylene, selective monoalkylation by alkyl Grignard reagents may be realized in the presence of $Ni(PPh_3)_4$ as a catalyst to afford (*E*)- or (*Z*)-1-chloro-1-alkenes stereoselectively (equation 82).[98]

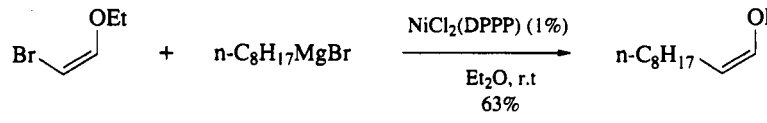


(81)

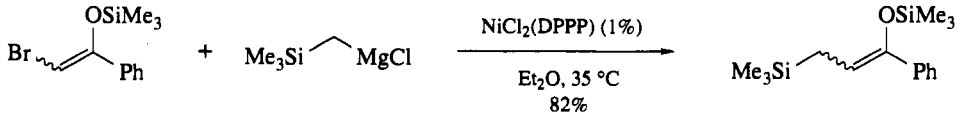


(82)

A chemoselective monoalkylation of two unlike leaving groups on alkenes can more easily be attained based on the general reactivity order Br > Cl > SR > OR in Ni-catalyzed reactions. Grignard coupling reactions of α-bromoenol ethers catalyzed by $NiCl_2(DPPP)$ generally stop cleanly at the monoalkylation stage to provide new routes to various enol ethers, primary alkyl, including β-H-bearing alkyl, Grignard reagents being employed (equations 83 and 84).[99,100] (*E*)- and (*Z*)-1-Bromo-2-phenylthioethylenes can be transformed into disubstituted alkenes stereoselectively [(*E*) > 99%, (*Z*) > 98%] by stepwise alkyl Grignard coupling in a one-pot manner; whilst the first step with the (*Z*)-isomer may be catalyzed best by $PdCl_2(PPh_3)_2$, the first step with the (*E*)-isomer and the second step with both isomers are catalyzed most efficiently by $NiCl_2(DPPE)$ (equation 85).[101] In the first step, secondary alkyl Grignard reagents may be used without alkyl group isomerization (*cf.* Section 2.2.2.2; equation 86).[48] In Pd-catalyzed reactions of trimethylaluminum, the reactivity is in the order alkenyl–$OP(O)(OPh)_2$ > –SPh (equation 87).[73]



(83)



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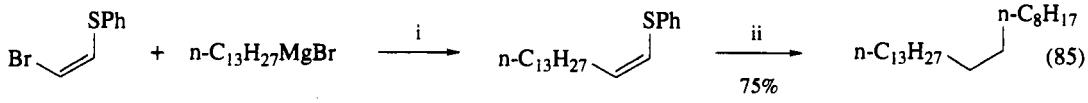
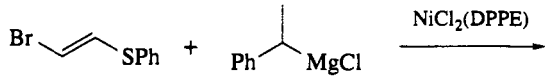
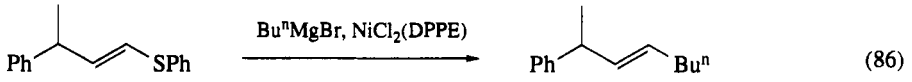


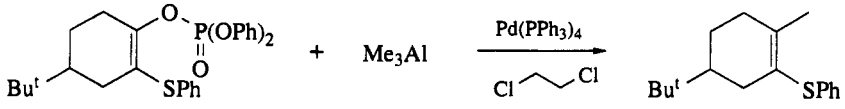
(85)

i, $PdCl_2(PPh_3)_2$ (3%), Et_2O, r.t., ii, n-$C_8H_{17}MgBr$, $NiCl_2$(DPPE) (6%), Et_2O, r.t.





(86)



(87)

2.2.5 COUPLING BETWEEN C(sp^3)-ORGANOMETALLICS AND AROMATIC HALIDES

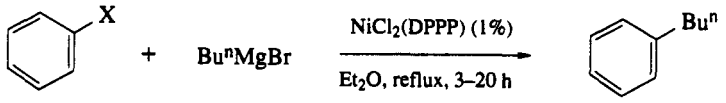
Cross-coupling reactions of alkyl–metal reagents with aromatic halides are catalyzed efficiently by Ni or Pd complexes.

2.2.5.1 Coupling of Primary Alkyl Grignard Reagents with Aromatic Halides

Primary alkyl Grignard reagents, regardless of the presence or the absence of β-hydrogens, couple with aromatic halides most efficiently in the presence of $NiCl_2L_2$ as catalyst, $NiCl_2$(DPPP) being most active and of general use.[25,26] The catalytic activity of the Ni complexes, however, depends strongly upon not only the nature of the ligands (L), but also on the combination of Grignard reagent and organic halide, as will be mentioned at appropriate positions. While Pd catalysts are usually used for coupling of β-H-lacking alkyl (Me or $PhCH_2$) Grignard reagents with aromatic bromides and iodides,[102,103] $PdCl_2$(DPPF) is also effective for coupling of β-H-bearing alkyl Grignard reagents with aryl bromides.[33]

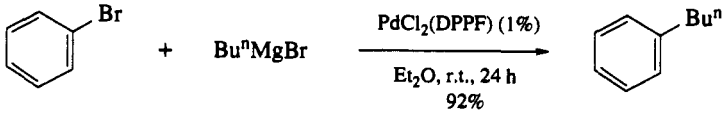
The reactivity order of halides is generally ArI > ArBr > ArCl >> ArF for Ni-catalyzed reactions and ArI > ArBr >> ArCl, ArF for Pd-catalyzed reactions. In the Ni-catalyzed reactions, chlorides usually give the most satisfactory results, since they exhibit a reasonable reactivity and give little side product; notably even fluorobenzene undergoes coupling (equation 88).[25] For couplings with bromobenzene, $PdCl_2$(DPPF) seems to be more effective (equation 89).[33] Generally, an electron-withdrawing substituent on the aromatic ring accelerates the coupling and an alkyl substituent deactivates the halide; methoxy group, however, seems to be an activating substituent (equation 90).[25] Dichlorobenzenes[25] and trichlorobenzenes[104] undergo dialkylation smoothly in the presence of $NiCl_2$(DPPP); even *o*-dialkylation is possible (equation 91, see Section 2.2.7 for monocoupling of polyfunctional compounds).[25,26] Coupling reactions of alkyl Grignard reagents, lacking β-H substitution, with sterically hindered aromatic halides are also catalyzed by Ni complexes,[25,105] but $NiCl_2(PEt_3)_2$ is better than $NiCl_2$(DPPP) in some cases (equations 92 and 93).[25] It should be noted that a reaction of sterically hindered mesityl bromide with

Bu^nMgBr catalyzed by $NiCl_2(DPPP)$ results in the formation of reduction product instead of coupling.[25] Coupling of the allyl Grignard reagent with bromobenzene is catalyzed by the complexes $NiCl_2(DMPE)$ (DMPE = $Me_2PCH_2CH_2PMe_2$) or $NiCl_2(PEt_3)_2$ that contains more electron-donating ligands than $NiCl_2(DPPP)$.[25]

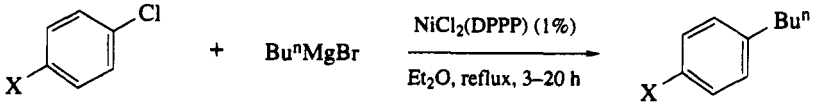


(88)

X	F	Cl	Br	I
%	31	95	54	80

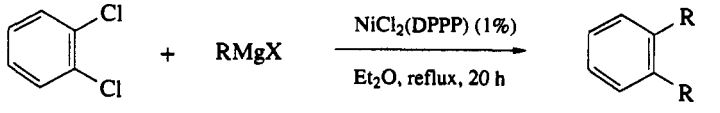


(89)



(90)

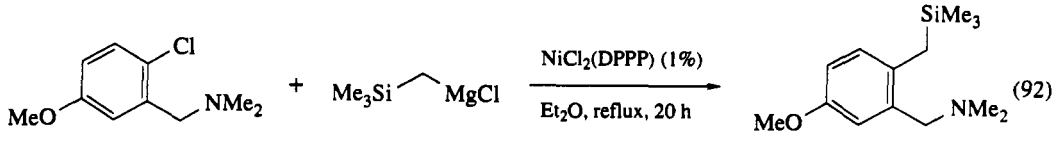
X	Me	OMe	CF_3
%	58	90	56



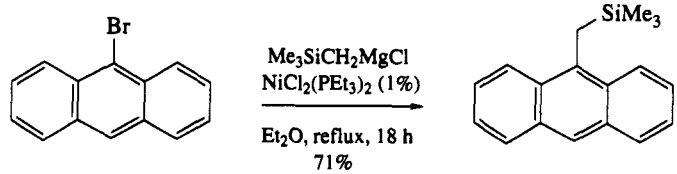
(91)

R = Bu^n 83%

R = Me_3SiCH_2 75%

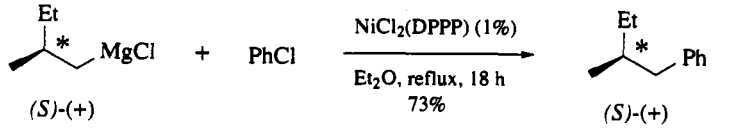


(92)



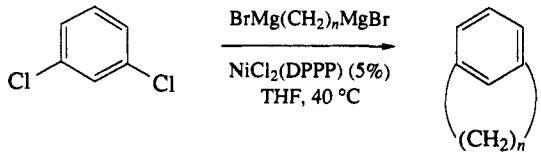
(93)

A β-branched, optically active primary alkyl Grignard reagent has been shown to undergo coupling with chlorobenzene without loss of optical activity in the presence of $NiCl_2(DPPP)$, while about 10% racemization is induced when $NiCl_2(PPh_3)_2$ or $NiCl_2(DMPE)$ are used as catalysts, possibly due to β-H elimination–addition sequences (equation 94).[106]



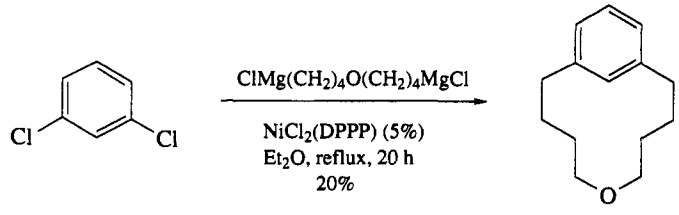
(94)

Di-Grignard reagents couple with *m*-dichlorobenzene to form *m*-cyclophanes in one step but in up to 20% yields depending on the chain lengths; oxamethylene bridges can also be introduced (equations 95 and 96).[107]



(95)

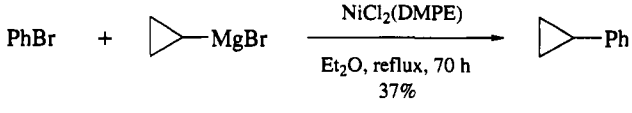
n	9	10	12
%	9	19	22



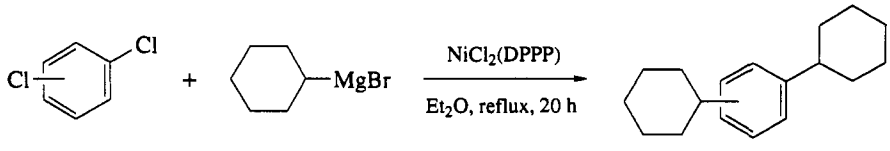
(96)

2.2.5.2 Coupling of Secondary and Tertiary Alkyl Grignard Reagents with Aromatic Halides

The cyclopropyl Grignard reagent undergoes coupling with bromobenzene in the presence of $NiCl_2$(DMPE) rather than $NiCl_2$(DPPP), but in only moderate yields (equation 97).[25] Coupling reactions of the cyclohexyl Grignard reagent are catalyzed by $NiCl_2$(DPPP) (equation 98)[25] or less effectively by a Pd complex.[108]



(97)



(98)

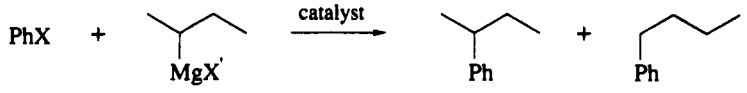
ortho 31%; *meta* 73%; *para* 63%

Alkyl group isomerization from secondary to primary occurs frequently in the Ni- or Pd-catalyzed coupling reactions of secondary alkyl Grignard reagents with aromatic halides, as described in the coupling reactions with alkenyl halides (Section 2.2.2.2). The isomerization is strongly dependent upon the nature of the phosphine ligands[33,106,109,110] and of the substituents on the aromatic ring;[111] while $NiCl_2$(DMPE) induces the isomerization most readily,[106] with $PdCl_2$(DPPF) the isomerization is completely suppressed (equation 99).[33] The 1-phenylethyl Grignard reagent undergoes $NiCl_2$(DPPP)-catalyzed coupling with chlorobenzene without isomerization.[109]

The reaction of the *t*-butyl Grignard reagent with chlorobenzene in the presence of $NiCl_2$(DMPE) results in the formation of isobutylbenzene in low yields through tertiary to primary group isomerization; no reaction whatsoever is observed with $NiCl_2$(DPPP) (equation 100).

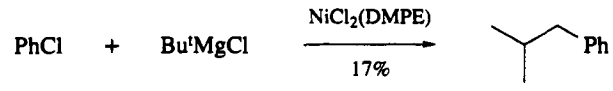
2.2.5.3 Organozinc and Organotin Reagents

Couplings of alkylzinc and alkyltin reagents with aromatic halides, mostly bromides, are catalyzed by Pd or Ni complexes; toleration of functional groups such as CN, COR, CO_2R, NO_2, Cl and F is the most outstanding feature.



(99)

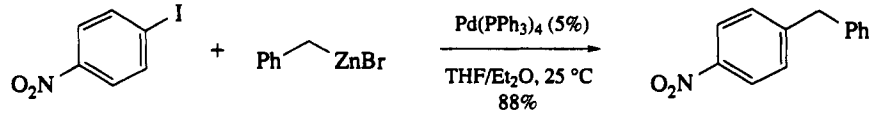
X = Cl	$NiCl_2$(DPPP)	90%	93:7
X = Cl	$NiCl_2$(DMPE)	67%	5:95
X = Br	$NiCl_2$(DPPF)	95%	100:0
X = Br	$NiCl_2$(DPPB)	76%	67:33
X = Br	$NiCl_2$(DPPP)	62%	69:31



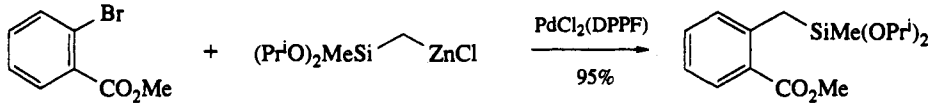
(100)

2.2.5.3.1 Primary alkylzinc and alkyltin reagents

Benzyl-, phenylethyl-, homoallyl-, homopropargyl- and silylmethyl-zinc reagents undergo coupling with aryl halides in the presence of Ni or Pd complexes (equations 101–103).[31,53,103] Methyl-,[112] hydroxymethyl-,[113] methoxymethyl-[113] and allyltin[114,115] compounds also couple with aryl bromides under the catalysis of Pd—PPh_3 complexes: the first two reagents require HMPA as solvent and in the last allylation the unusual reactivity order ArI < ArBr > ArCl has been noted (equations 104–106). With an α-ethoxyallyltin compound, the coupling occurs selectively at the γ-position, together with a low stereoselectivity at the resulting vinyl ether group (equation 107).[115]



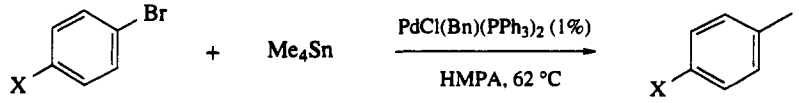
(101)



(102)

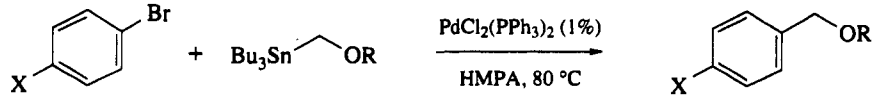
(103)

$Ni(PPh_3)_4$ (5%) 82%
$Pd(PPh_3)_4$ (5%) 78%



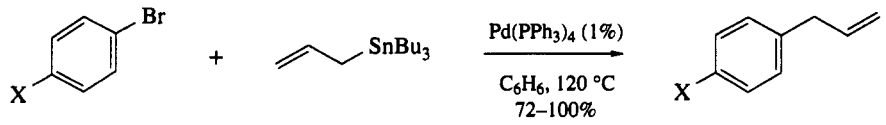
(104)

X = F, Me, OMe, COMe
84–95%



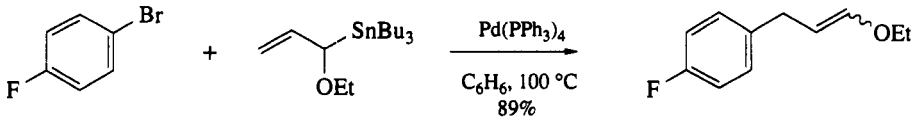
(105)

R = H;	X = H	60%
R = Me;	X = OMe, CN, NO_2	57–80%



(106)

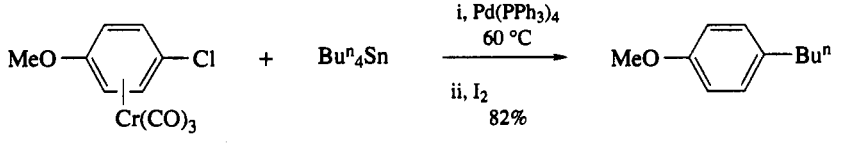
X = Cl, OMe, COMe, NO_2



(107)

(*E*):(*Z*) = 40:60

Chloroarene chromium tricarbonyl complexes undergo Pd-catalyzed coupling with tetrabutyltin, the butylated arenes being freed from chromium by oxidation with iodine; activation of the otherwise inert C—Cl bond by the electron-withdrawing $Cr(CO)_3$ group may be noted (equation 108).[116]

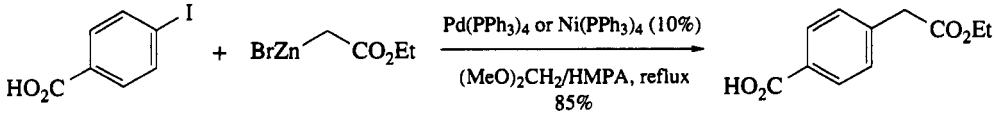


(108)

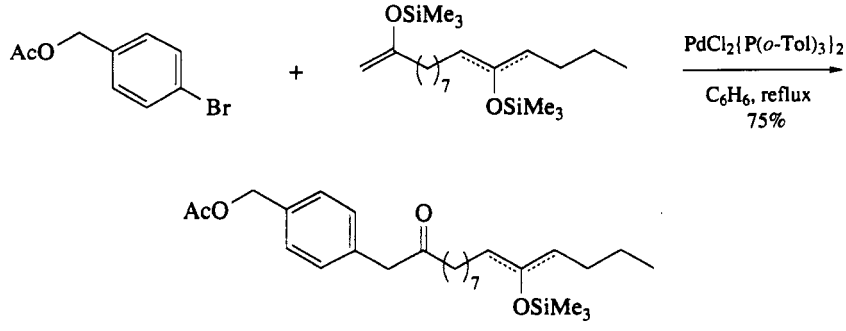
2.2.5.3.2 Reformatsky and related reagents

Couplings between Reformatsky reagents and aromatic halides are catalyzed by $Ni(PPh_3)_4$[117] or $Pd(PPh_3)_4$,[117,118] with DMF, NMP or HMPA being used as the essential cosolvents. While the Ni-catalyzed reaction can be applied to aromatic chlorides, bromides and iodides, the Pd-catalyzed reaction is useful only for iodides. Compatibility of the free carboxylic acid may especially be noted (equation 109).

Enol silyl ethers undergo Pd-catalyzed coupling with aromatic bromides in the presence of tributyltin fluoride, which converts the enol silyl ethers into the stannyl ethers or α-stannyl ketones regarded as real active species; chemoselective α-arylation of terminal ketones is possible (equation 110).[119]

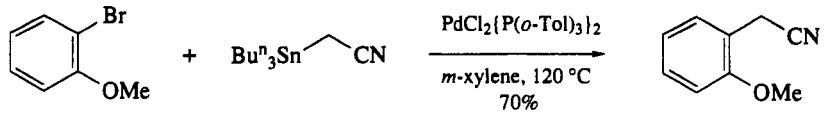


(109)

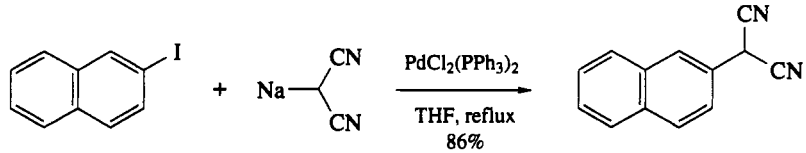


(110)

Cyanomethyltributyltin is a reagent for Pd-catalyzed cyanomethylation of aryl bromides with the Me, MeO or Cl substituent, but not with the MeCO, CN or NO_2 substituent (equation 111).[120] Dicyanomethylation of aryl iodides can be achieved with a sodium salt of malononitrile in the presence of Pd complexes (equation 112).[121]



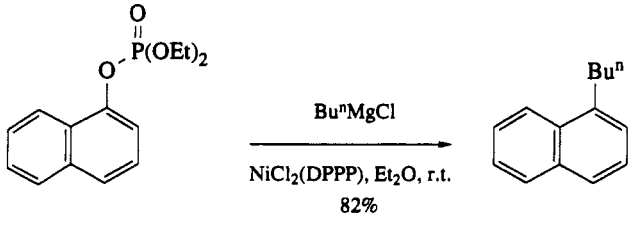
(111)



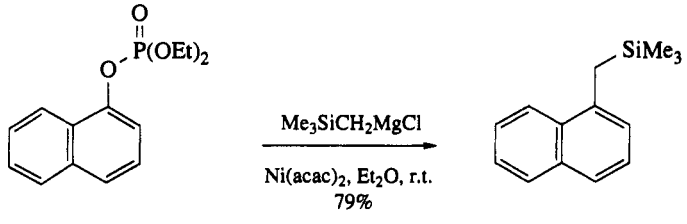
(112)

2.2.6 COUPLING OF C(sp^3)-ORGANOMETALLICS WITH ARYL O, S AND Se COMPOUNDS

Aryl phosphates undergo Ni-catalyzed coupling with primary alkyl Grignard reagents and triethylaluminum (equations 113–115).[122] Arene triflates[123,124] or homologous perfluoroalkanesulfonates[124] couple with primary alkyltin,[123] benzylzinc[124] and ester-containing alkylzinc (ester homoenolate) reagents[124] in the presence of Pd complexes as catalysts and LiCl as an essential additive (equations 116 and 117); compatibility of the free OH group in the coupling of alkyltin compounds is worthy of note. Allylation with allyltin compounds is accompanied substantially by 1-propenylation *via* alkene isomerization.[123] Siloxycyclopropanes serve as aldehyde, ketone and ester homoenolate equivalents in Pd-catalyzed coupling reactions with aryl triflates to form β-aryl carbonyl compounds (equations 118–120).[125]



(113)



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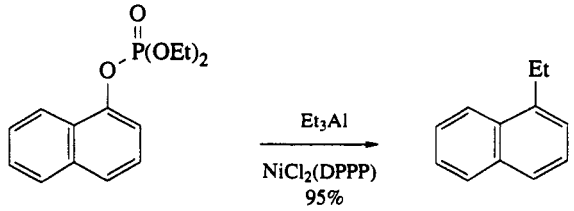

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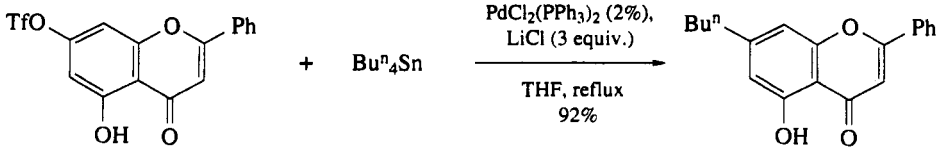

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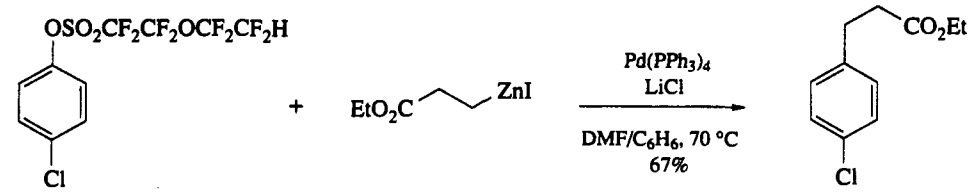
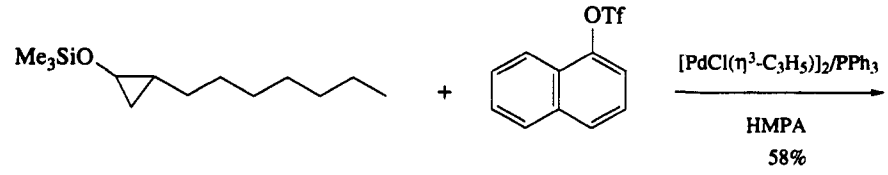
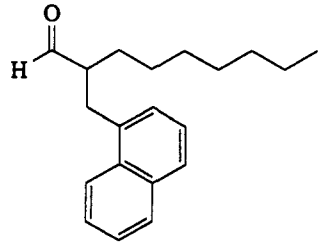
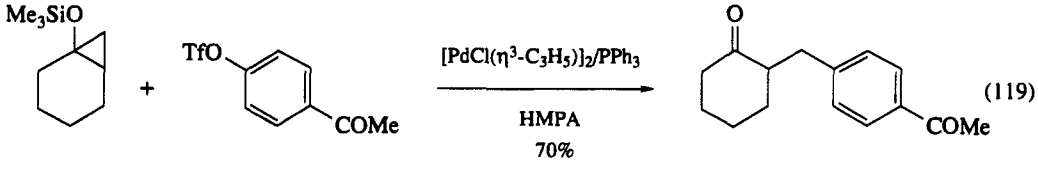


(117)

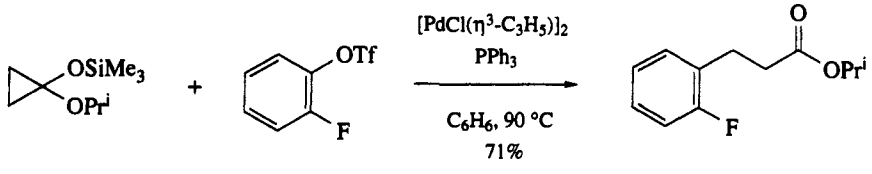




(118)



(119)



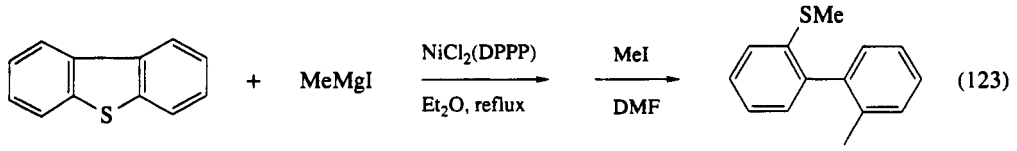
(120)

Nickel-catalyzed Grignard coupling reactions can be applied to arenethiols,[126] sulfides,[79,90,126] sulfoxides,[126] sulfones[126] and selenides.[80] Whilst the methyl Grignard reagent couples efficiently with all of them, β-H-bearing alkyl Grignard reagents give rather low yields of coupling products even in the presence of active $NiCl_2$(DPPP); the reactivity order is PhSeMe >> PhCl > PhSMe (equations 121 and 122).[80] Similarly, while benzothiophene may be converted into *o*-(*Z*)-1-propenyltoluene (see Section 2.2.3.2) and thioanthrene into *o*-xylene by the Ni-catalyzed methylation, dibenzothiophene gives a monomethylation product mainly, even in the presence of 2 equiv. of MeMgI (equation 123).[90]

$$PhX + MeMgBr \xrightarrow{NiCl_2(PPh_3)_2} PhMe \qquad (121)$$

X = SH, 64%; SMe, 97%; SOPh, 77%; SO_2Me, 97%

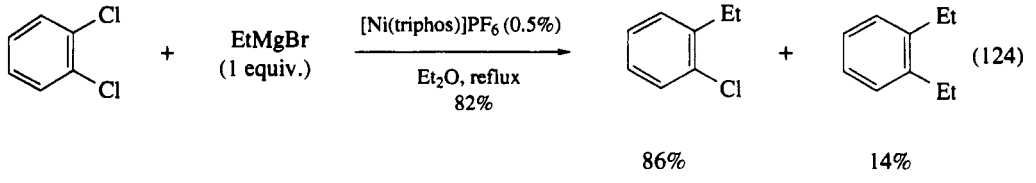
$$PhSeMe + Bu^nMgBr \xrightarrow[Et_2O,\ reflux\ 95\%]{NiCl_2(DPPP)} PhBu^n \qquad (122)$$



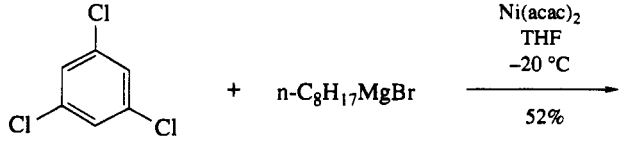
(123)

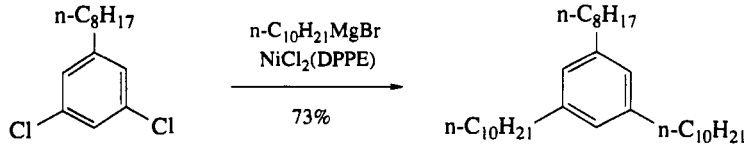
2.2.7 COUPLING OF C(sp^3)-ORGANOMETALLICS WITH POLYFUNCTIONAL AROMATICS

Chemoselective couplings of polyfunctional aromatic compounds may be achieved by Ni- or Pd-catalyzed coupling with alkyl Grignard reagents. Whereas Grignard coupling reactions of aromatic polyhalides catalyzed by active $NiCl_2(DPPP)$ or $NiCl_2(DPPE)$ tend to result in the complete alkylation of all the halogen atoms present (see Section 2.2.5.1), a highly selective monoalkylation of dichlorobenzenes and trichlorobenzenes can be achieved with 1 equiv. of primary alkyl Grignard reagents in the presence of $[Ni(triphos)Cl]PF_6$[127] (triphos = $PhP(CH_2CH_2PPh_2)_2$) or $Ni(acac)_2$[128] as catalyst (equations 124 and 125). Dibromobenzenes and 1,3,5-tribromobenzene can also be monoalkylated with primary alkyl Grignard reagents or with benzylzinc halides in the presence of $PdCl_2(DPPF)$ or $PdCl_2(DPPB)$ as catalyst (equation 126).[129,130]

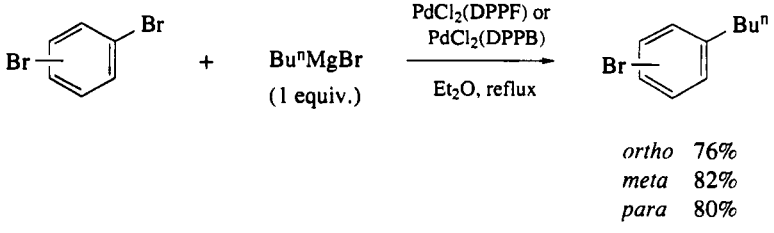


(124)



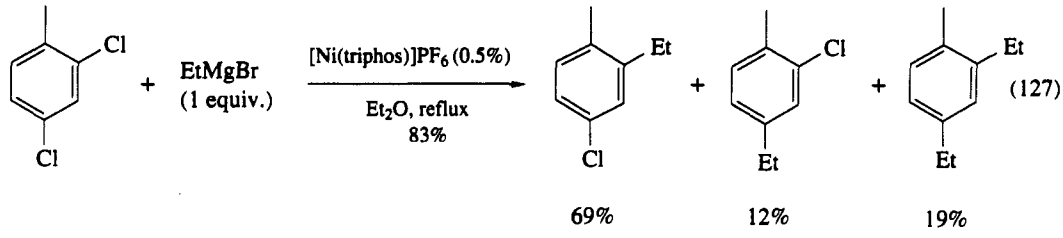


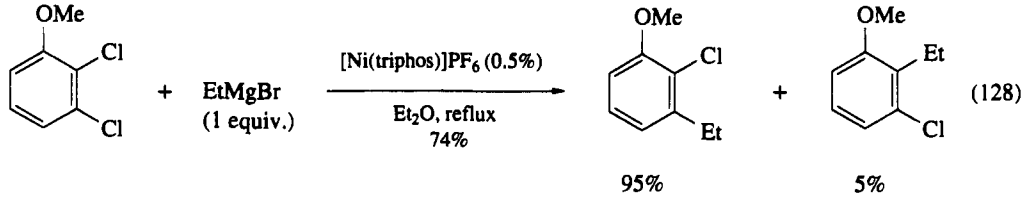
(125)

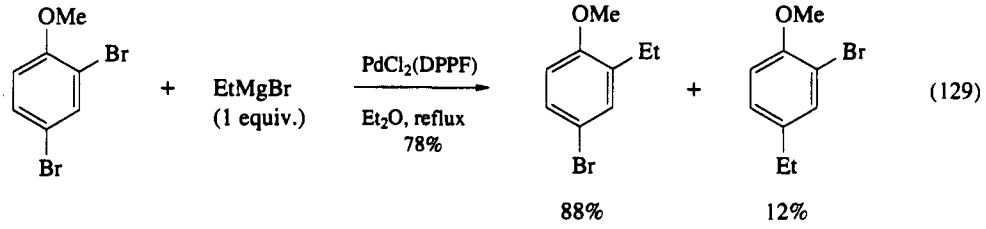


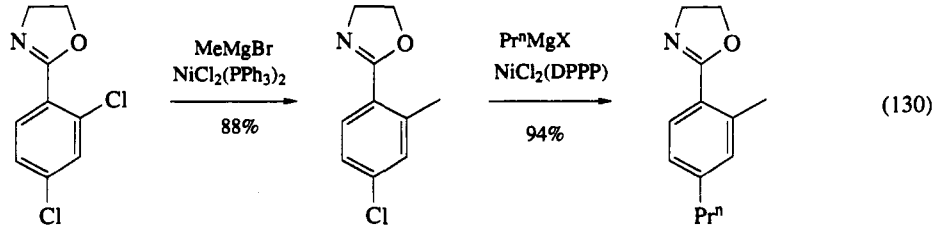
(126)

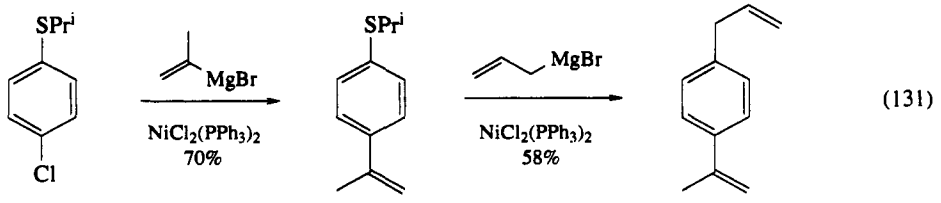
Certain substituents can activate one halogen atom specifically in polyhalogen compounds, as exemplified by monoalkylation directed by methyl,[127] methoxy,[127,131] and oxazolinyl groups (equations 127–130).[132] A stepwise Grignard coupling of two unlike leaving groups is also possible based on the reactivity order Cl > SR (equation 131).[133]



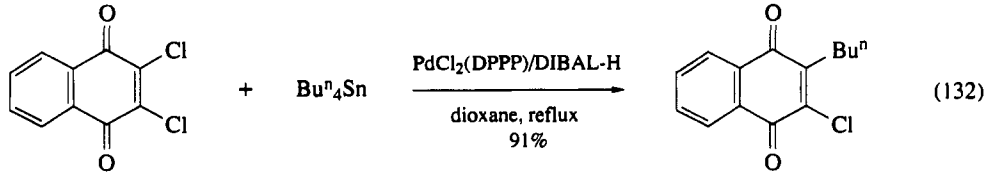








Monoalkylation of 2,3-dichloro-1,4-naphthoquinone is achieved by Pd-catalyzed reaction with tetraalkyltins or, less efficiently, with alkylzirconium complexes (equation 132).[134]

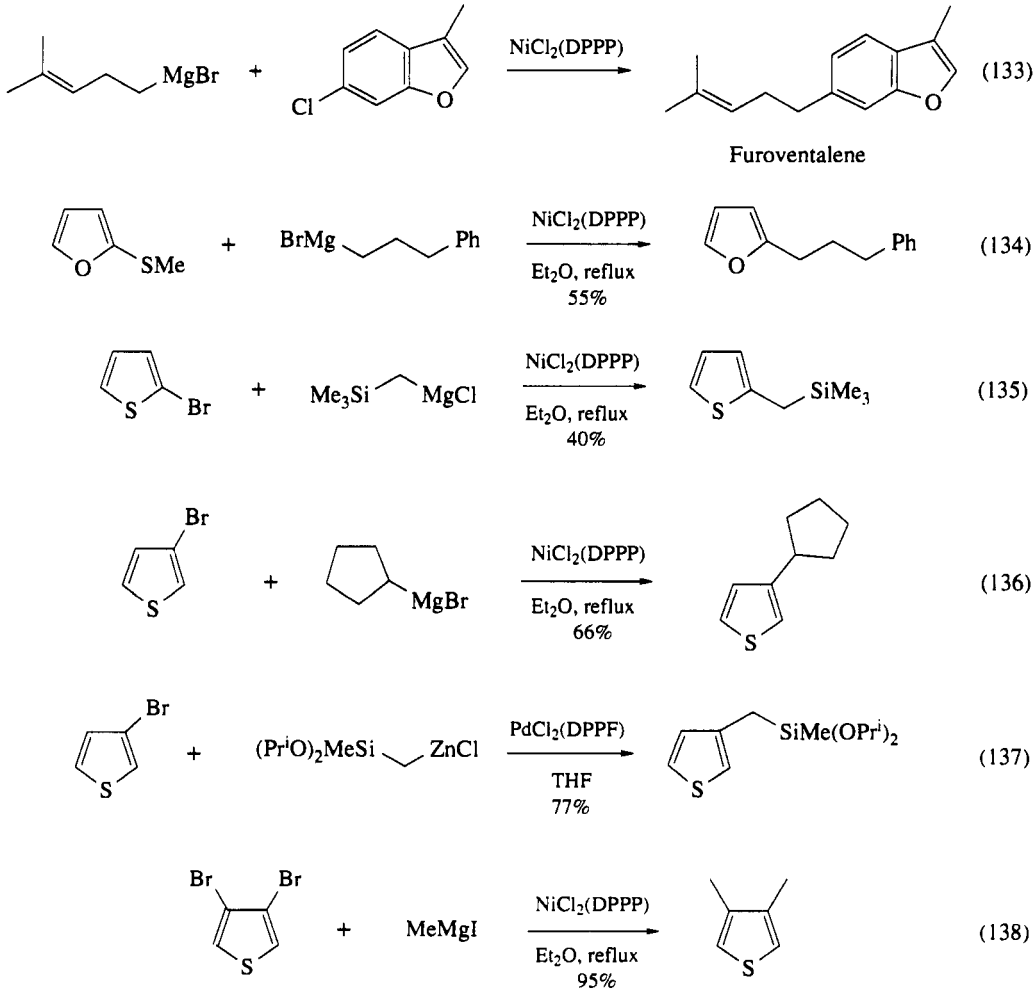


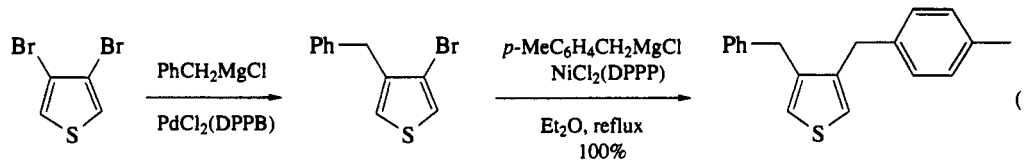
2.2.8 COUPLING OF C(sp^3)-ORGANOMETALLICS WITH HETEROAROMATIC HALIDES AND SULFIDES

Nickel- or palladium-catalyzed coupling reactions of alkyl Grignard or zinc reagents can be applied to heteroaromatic halides and sulfides. The characteristic features are, therefore, based on those described in the preceding sections and hence details are not repeated in this section. Aspects are summarized by the types of heteroaromatic compounds; $NiCl_2$(DPPP) is used as catalyst, unless stated otherwise hereafter.

2.2.8.1 Furans and Thiophenes

A chlorobenzofuran[135] and a 2-furyl sulfide[136] have been shown to couple with primary alkyl Grignard reagents (equations 133 and 134). 2-Bromothiophene undergoes a halogen–metal exchange reaction mainly with a basic primary alkyl Grignard reagent such as Bu^nMgBr to give only trace amounts of coupling products, but it couples smoothly with less basic Grignards such as $(TMS)CH_2MgCl$ (equation 135).[137] 3-Bromothiophene shows no such problem and undergoes the Ni-catalyzed coupling with primary and secondary alkyl (Me, Bu^n, $PhCH_2$, $(TMS)CH_2$, cyclopentyl) Grignard reagents (equation 136);[137,138] the Pd-catalyzed coupling with a silylmethylzinc reagent is also possible (equation 137).[31] One-step double coupling[137] and stepwise coupling[139] reactions of 3,4-dibromothiophene are possible under the catalysis by $NiCl_2$(DPPP) and $PdCl_2$(DPPF), respectively (equations 138 and 139).

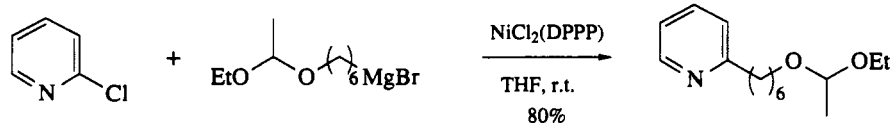




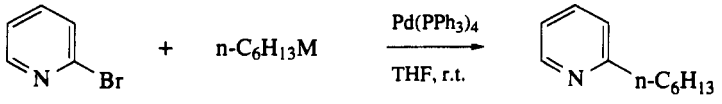
(139)

2.2.8.2 Pyridines and Quinolines

2-Chloro- and 2-bromo-pyridines undergo Ni-catalyzed coupling reactions with primary alkyl Grignard reagents (equation 140);[137,140,141] 3-halopyridines are less reactive and an '*ortho*' methyl substituent retards the coupling substantially.[140] Couplings of bromo- and iodo-pyridines with alkylzinc reagents seem to be catalyzed by Pd-complexes (equations 141 and 142).[142,143] 2-Pyridyl sulfides[136] and triflate[125] also undergo Ni-catalyzed Grignard coupling and Pd-catalyzed coupling with siloxycyclopropanes, respectively (equations 143 and 144).

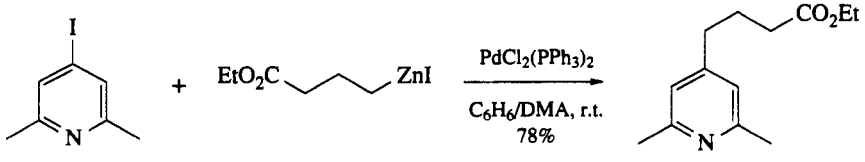


(140)

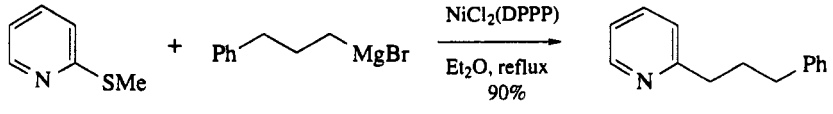


(141)

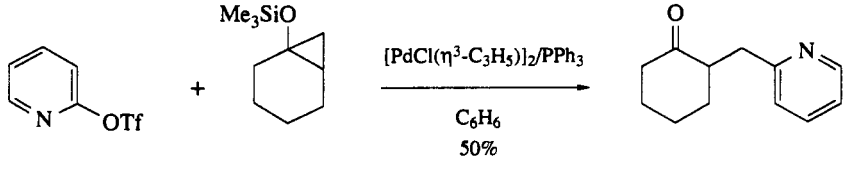
M = ZnCl 100%
M = MgBr <2%



(142)

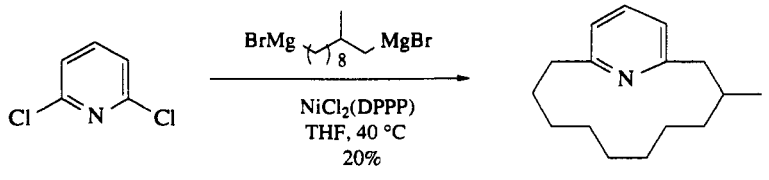


(143)

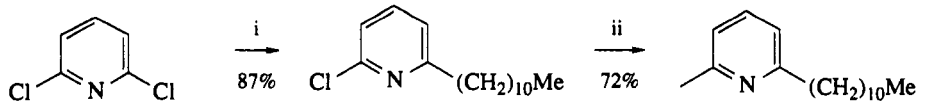


(144)

2,6-Dichloropyridine undergoes Ni-catalyzed double coupling reactions readily with primary alkyl Grignard reagents[137] and with di-Grignard reagents[107] as exemplified by the one-step synthesis of muscopyridine (equation 145). Pd-catalyzed monocoupling reactions occur selectively at the 2-position in 2,3-, 2,5- and 2,6-dichloropyridines and hence unsymmetrical dialkylpyridines are readily available (equation 146).[130]



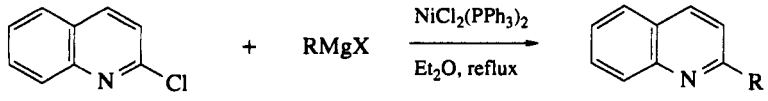
(145)



(146)

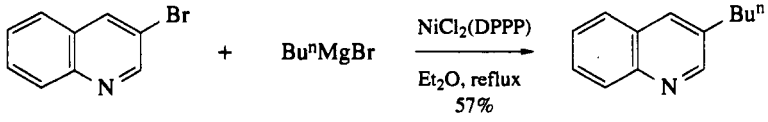
i, $Me(CH_2)_{10}MgBr$, $PdCl_2(DPPB)$, Et_2O, reflux; ii, MeMgI, $NiCl_2(DPPP)$, Et_2O, reflux

2-Chloro- and 3-bromo-quinolines and 2- and 4-chloroisoquinolines undergo Ni-catalyzed coupling with primary alkyl, allyl and cyclohexyl Grignard reagents; selective monoalkylation in 4,5-dichloroisoquinoline may be noted (equations 147–150).[137,144]

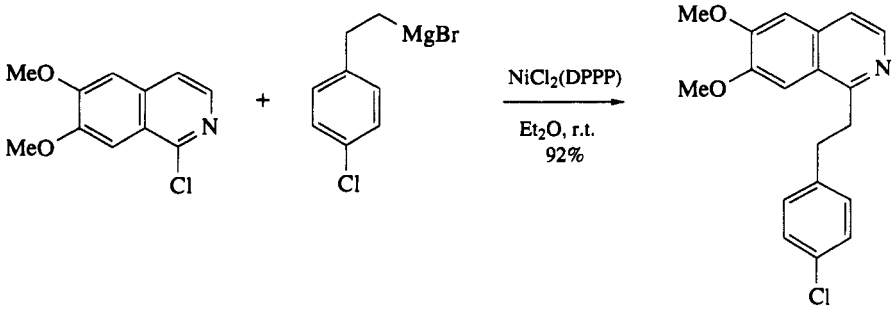


(147)

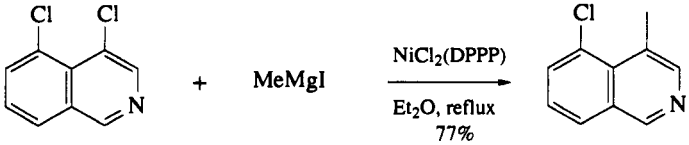
$R = CH_2{=}CHCH_2$ 54%
$R = c\text{-}C_6H_{11}$ 90%



(148)



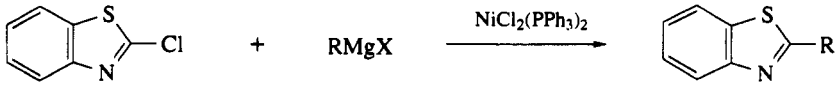
(149)



(150)

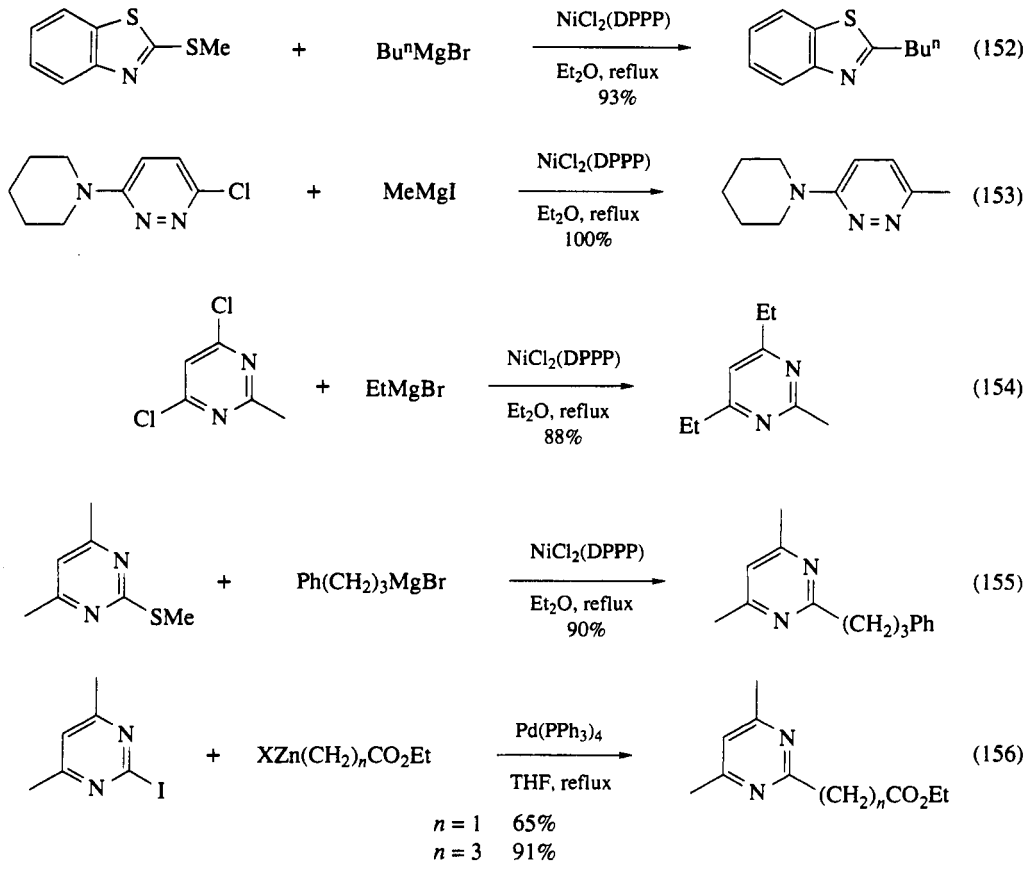
2.2.8.3 Heteroaromatic Compounds containing more than Two Heteroatoms

2-Chloro-[145] and 2-methylthio-benzothiazoles[136] undergo Ni-catalyzed coupling with alkyl Grignard reagents and the isopropyl group may also be introduced with ease (equations 151 and 152). 2-Methylthiobenzoimidazole is inert under similar conditions.[136] 2-Chloropyridazines,[146] 2-chloro-, 4-chloro-, 2,4-dichloro-, 4,6-dichloro- and 2,4,6-trichloro-pyrimidines[147] and 2-methylthiopyrimidines[136] are readily alkylated by primary alkyl Grignard reagents (equations 153–155). The Reformatsky reagent and homologs couple with 2- and 4-halopyrimidines in the presence of Pd complexes (equation 156).[143,148] Lower reactivities of halogens β to nitrogen are noted in all of these cases.

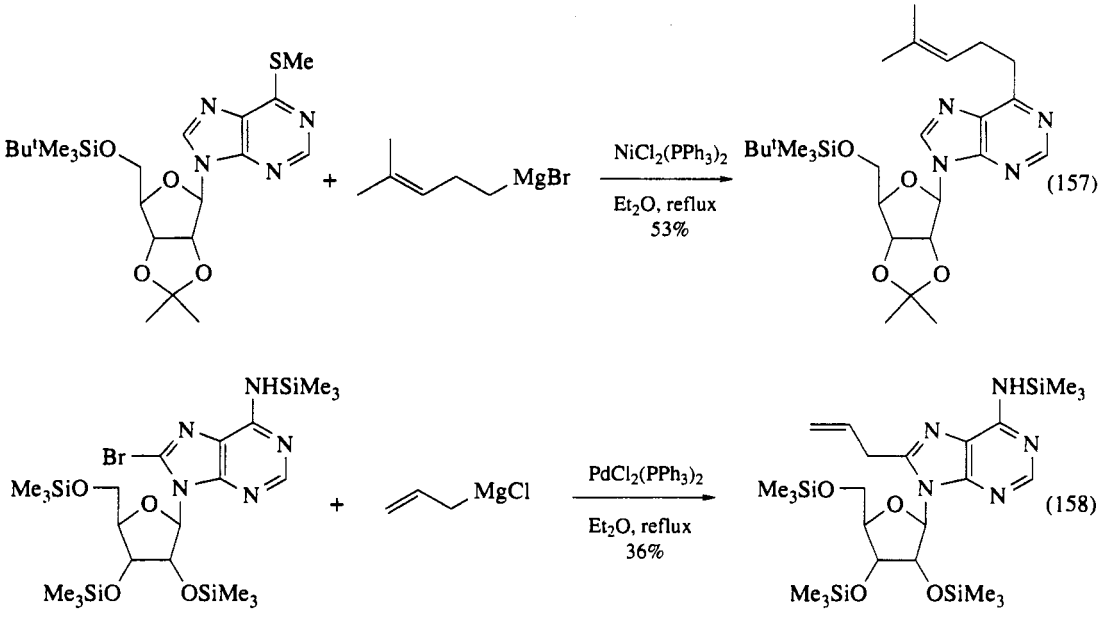


(151)

R = Me, Et, Pr^i, Bu^n; 50–95%

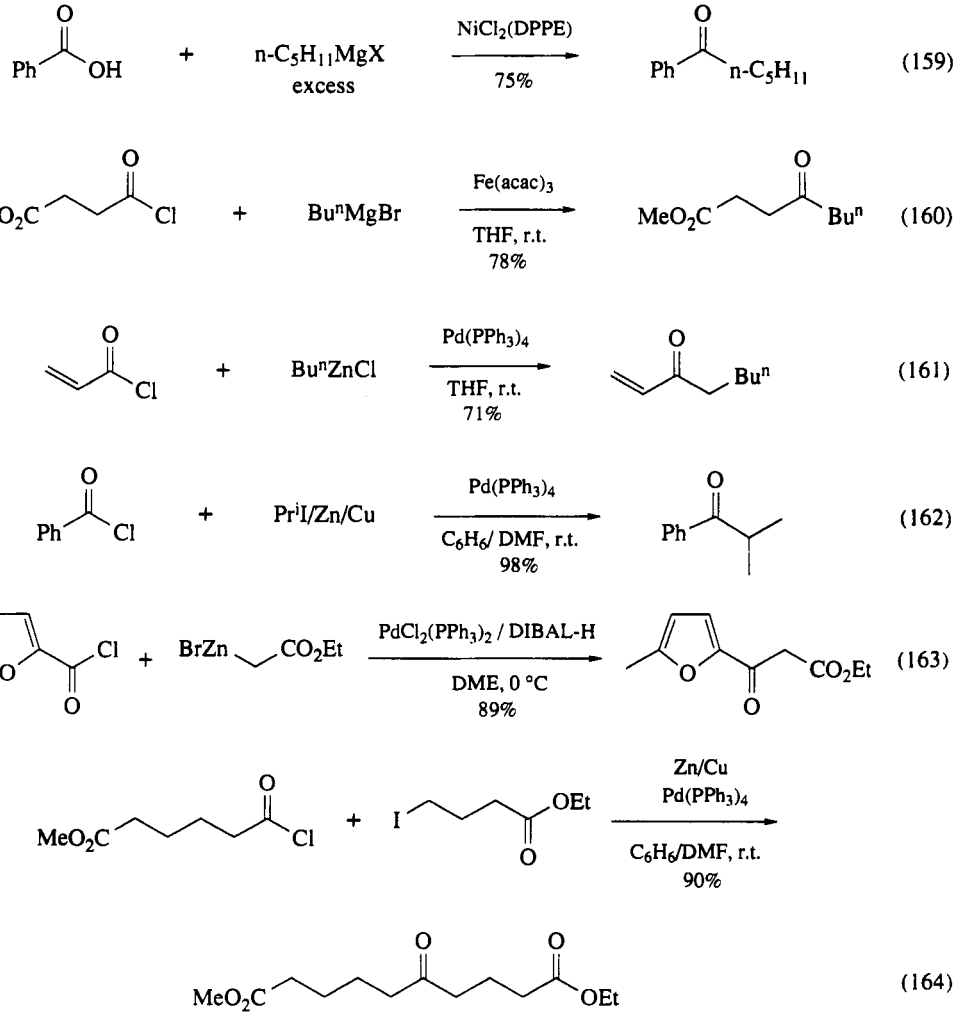


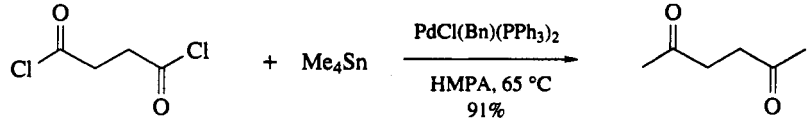
6-Chloro-[149] and 6-methylthio-purine[150] derivatives undergo Ni-catalyzed coupling reactions with primary alkyl Grignard reagents; the reactions have been applied to the synthesis of 6-alkylpurine nucleosides (equation 157). Similarly, 8-alkyl- and 8-allyl-adenosine derivatives are obtained by Pd-catalyzed Grignard coupling reactions of 8-bromoadenosines (equation 158).[151,152]



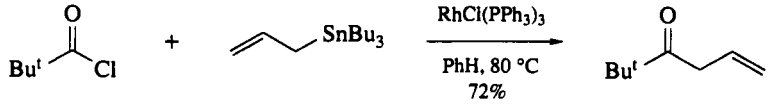
2.2.9 COUPLING OF C(sp^3)-ORGANOMETALLICS WITH ACYL CHLORIDES AND RELATED COMPOUNDS

This section describes ketone synthesis by transition metal catalyzed cross-coupling of alkyl metal reagents with acyl chlorides and related compounds. Carboxylic acids react with excess amounts of alkyl Grignard reagents in the presence of a Ni catalyst to form unsymmetrical ketones (equation 159).[153] Acyl chlorides readily couple with primary alkyl Grignard reagents in the presence of $Fe(acac)_3$ as catalyst even in the presence of functional groups, such as ester and cyano groups, susceptible to Grignard reagents (equation 160).[154,155] Acyl chlorides also undergo Pd-catalyzed coupling with primary and secondary alkylzinc reagents (equations 161 and 162),[156,157] with the Reformatsky reagents (equation 163)[158] and homologs (equation 164),[157,159] with alkyltins (equation 165)[160–162] and with dialkylmercurials;[163] coupling of allyl- and benzyl-tins with acyl chloride is also catalyzed by a Rh complex (equation 166).[164] Acyl chlorides and acid anhydrides also couple with tetraalkylaluminates in the presence of CuCl (equation 167).[165] While chloroformates undergo Pd-catalyzed coupling with alkylzinc reagents to form esters,[156] a chlorothioformate (carbonochloridothioate) is transformed into unsymmetrical ketones by a stepwise Grignard coupling; the first step is catalyzed by Ni and the second step by Fe complexes, secondary alkyl Grignard reagents being applicable in the second step (equation 168).[166] Finally, an imidoyl chloride couples with primary alkyl Grignard reagents in the presence of $PdCl_2$(DPPF) (equation 169).[167]

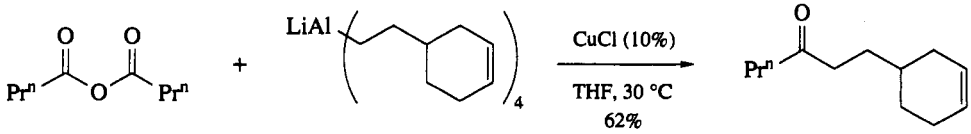




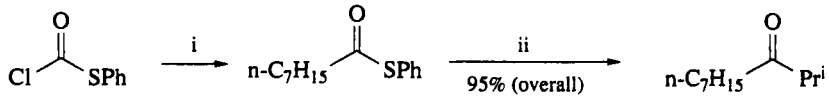
(165)



(166)

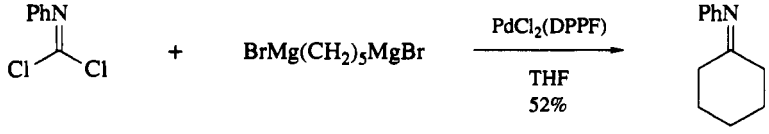


(167)



(168)

i, n-C_7H_{15}MgBr, $NiCl_2$(DPPE), THF, r.t.; ii, Pr^iMgCl, Fe(acac)$_3$, THF, 0 °C



(169)

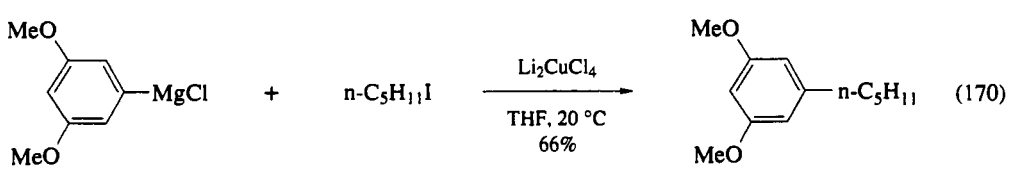
2.2.10 COUPLING OF C(sp^2)-ORGANOMETALLICS WITH C(sp^3) HALIDES AND RELATED COMPOUNDS

Coupling reactions between C(sp^2)-organometallics, mostly Grignard reagents, and C(sp^3) halides and related compounds are usually achieved with Cu catalysts. Primary alkyl halides react smoothly, secondary alkyls are applicable in only a few cases, and no successful coupling has been reported for tertiary alkyl halides. Allylic halides and related compounds are treated separately, since there are important regiochemical problems.

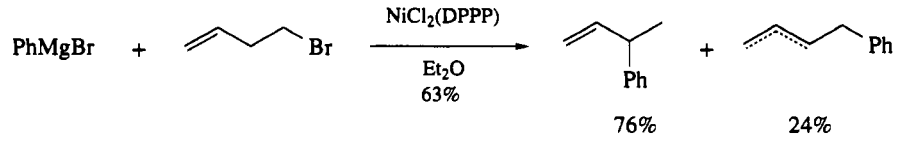
2.2.10.1 Coupling between C(sp^2)-Organometallics and Primary Alkyl Halides

Primary alkyl bromides and iodides and benzyl chlorides smoothly couple with aryl Grignard reagents in the presence of Li_2CuCl_4[168] or CuCl together with TMEDA (equation 170).[169] Cross-coupling of aryl Grignard reagents with primary alkyl iodides are also reported to be catalyzed by $PdCl_2$(DPPF).[170] In the presence of $NiCl_2$(DPPP), 3-butenyl bromide couples with the phenyl Grignard reagent to form mainly 3-phenyl-1-butene *via* primary to secondary isomerization (equation 171).[171] Bromohydrin undergoes Cu-catalyzed coupling with aryl Grignard reagents to give arylethanols (equation 172).[172] α,ω-Dibromoalkanes afford monoarylation products selectively with aryl Grignard reagents in the presence of Li_2CuCl_4 (equation 173),[173] while double coupling is also possible.[174,175]

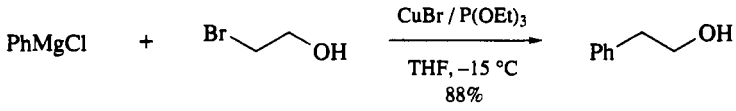
Vinyl, 1-alkenyl and 2-alkenyl Grignard reagents couple with alkyl bromides or iodides in the presence of CuI[34,176,177] or $AgNO_3$;[24] the configuration of the alkenyl Grignard reagent is essentially



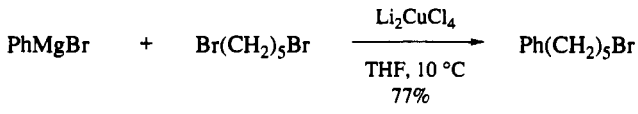
(170)



(171)

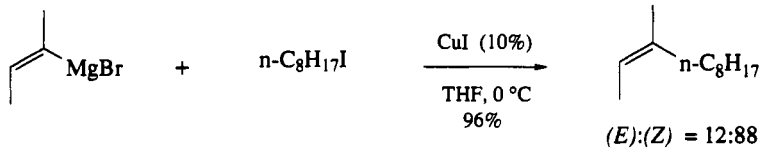


(172)

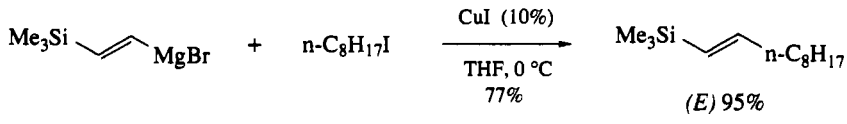


(173)

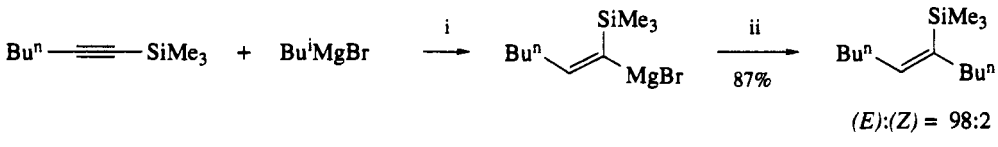
retained (equations 174–177). Alkenylboranes couple with benzyl bromides in the presence of $Pd(PPh_3)_4$ and NaOH also with retention of configuration (equation 178).[178] The 2-butadienyl Grignard reagent undergoes Cu-catalyzed couplings with alkyl bromides and iodides even in the presence of functional groups such as ester and cyano groups (equation 179); it may be noted that aromatic iodides are inert under these conditions (equation 180).[179]



(174)

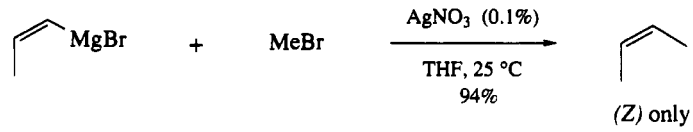


(175)

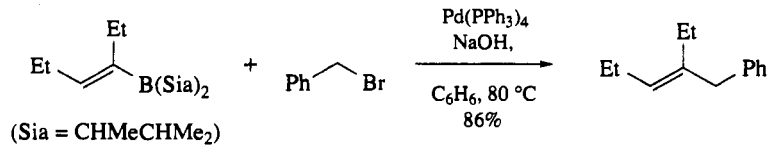


(176)

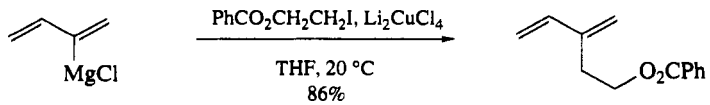
i, Cp_2TiCl_2; ii, Bu^nI, CuI (10%), THF, 0 °C



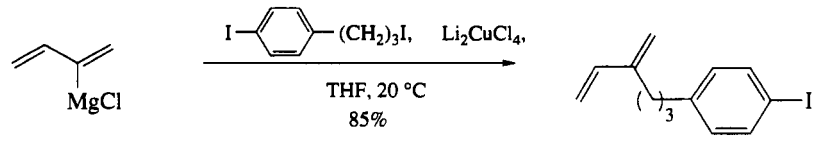
(177)



(178)

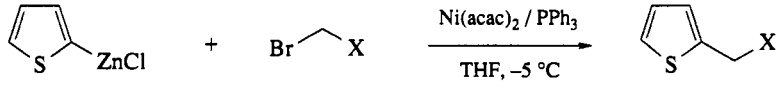


(179)



(180)

Arylzinc reagents couple with ethyl bromoacetate[180] and with bromoacetonitrile[181] in the presence of Ni complexes (equation 181).

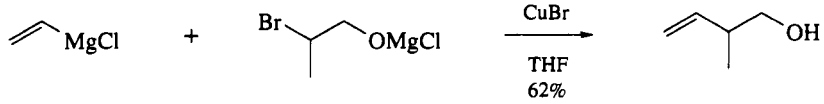


(181)

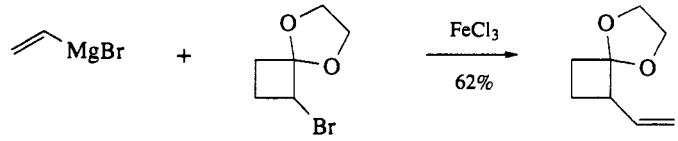
X = CO_2Et 60%
X = CN 46%

2.2.10.2 Coupling between C(sp^2)-Organometallics and Secondary Alkyl Halides

Coupling reactions between vinyl Grignard reagents and 2-oxy secondary alkyl bromides are reported to be catalyzed by Cu[182] or Fe salt (equations 182 and 183).[183]



(182)

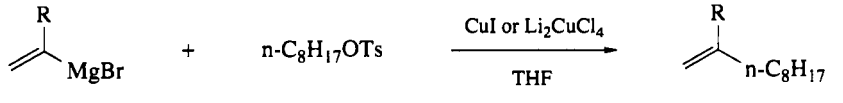


(183)

2.2.10.3 Coupling between C(sp^2)-Organometallics and C(sp^3)-Oxygen Compounds

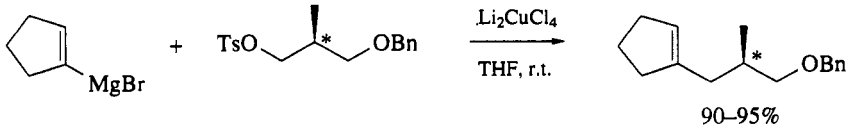
Primary alkyl tosylates are more reactive than halides in the Cu-catalyzed coupling with Grignard reagents.[184] Aryl,[184] alkenyl,[176] silylalkenyl[34] and 2-butadienyl[185] Grignard reagents have been used successfully for the coupling in the presence of CuI or Li_2CuCl_4; the coupling of optically active tosylates[186] and ditosylates[187] having chiral center(s) at the 2-position may also be noted (equations 184–186).

Ring opening of epoxides with Grignard reagents is greatly promoted by Cu catalysts;[188] terminal epoxides and epoxycyclohexane are readily cleaved by aryl,[188,189] and alkenyl[188,190,191] Grignard reagents (equations 187–189) Oxetane also undergoes similar Cu-catalyzed coupling with phenyllithium[192] and phenyl Grignard reagent (equation 190).[188] β-Propiolactone reacts with the phenyl Grignard reagent in the presence of CuBr to form β-phenylpropionic acid *via* cleavage of the C(sp^3)—O bond (equation 191).[193]



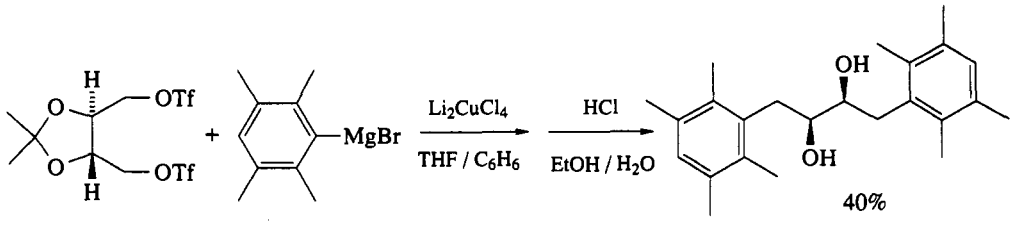
(184)

R = Me 80%
R = $SiMe_3$ 83%
R = CH_2=CH 55%

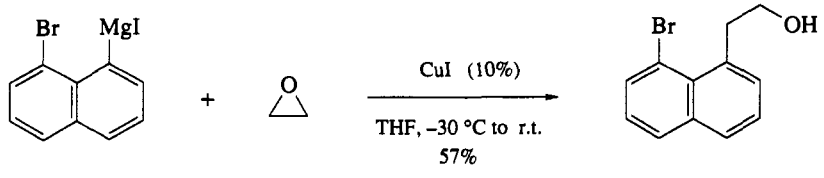


(185)

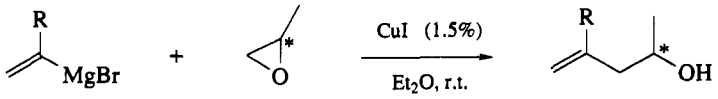
90–95%



(186)

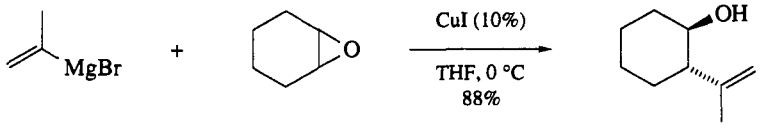


(187)

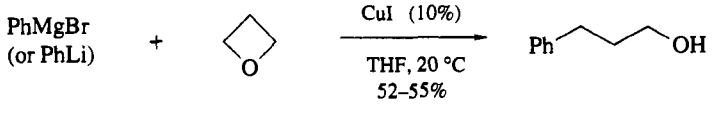


(188)

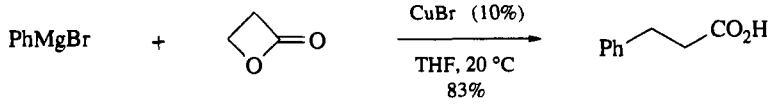
$R = SiMe_3$ 37%
$R = CH_2SiMe_3$ 85%



(189)



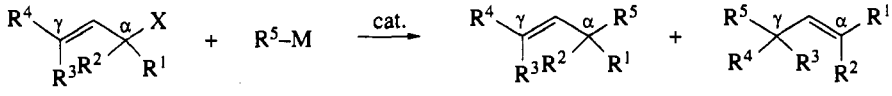
(190)



(191)

2.2.10.4 Coupling of C(sp^2)-Organometallics with Allylic Halides and Related Compounds

The most fundamental and important problem in coupling of allylic compounds with organometallic reagents is the regio- and stereo-control, as shown by the following general scheme (equation 192).[194]



(192)

Allylic halides, alcohols, ethers, acetates, lactones, phosphates, epoxides, sulfides, sulfonium salts, selenides and ammonium salts undergo transition metal catalyzed coupling reactions with C(sp^2)—Li, —Mg, —B, —Al, —Sn, —Zr, —Cd and —Hg reagents. Table 1 summarizes the allylic leaving groups, alkenyl and aryl metallic reagents, catalytically active metals and references and Table 2 the regio- and stereo-chemical aspects.

Table 1 Coupling of C(sp^2)-Organometallics with Allylic Halides and Related Compounds

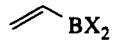
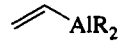
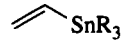
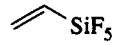
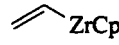
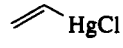
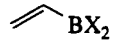
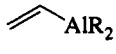
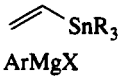
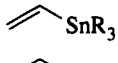
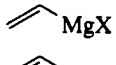
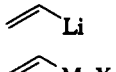
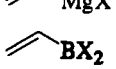
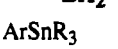
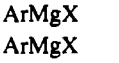
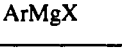
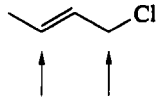
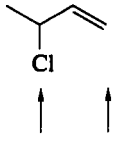
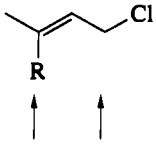
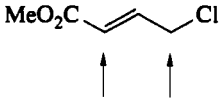
Allylic leaving group	*C(sp^2)-metallics*[a]	*Catalyst metal*	*Ref.*
Cl, Br		Pd Cu	178, 195, 205 196, 197
Cl, Br		Pd	198–200
Cl, Br		Pd	201
Cl, Br		Pd	203
Cl, Br		Pd	202
Cl, Br		Pd	204
Cl, Br	ArMgX	Ni, Pd	219
Cl, Br	$ArSnR_3$	Pd	201, 208
Cl, Br	ArHgCl	Pd	218, 220
Cl, Br	$RCOSnR_3$	Pd	216
OH	ArMgX	Ni	80, 221
OR		Pd	206
OR	ArMgX	Ni	80, 221
$OSiR_3$	ArMgX	Ni, Pd	219
OCOR		Cu	212, 213
OCOR		Pd	199, 210
OCOR		Pd	211, 215
OCOR	ArMgX	Cu	209, 212, 213
OCOR	ArZnX	Pd	199, 210
OCOR	ArCdX	Pd	199
OCOR	$ArAlR_2$	Pd	199
OCOR	$ArSnR_3$	Pd	215
OCO_2Me		Pd	199
$OP(O)(OR)_2$		Cu	223
$OP(O)(OR)_2$		Pd	215
$OP(O)(OR)_2$	ArMgX	Cu	223
$OP(O)(OR)_2$	$ArSnR_3$	Pd	215
Epoxide		Cu	214
Epoxide		Cu	214
Epoxide		Pd	207
Epoxide	$ArSnR_3$	Pd	211
SH	ArMgX	Ni	80
SR	ArMgX	Ni	224
$SR_2^+ X^-$		Cu	225
$SR_2^+ X^-$	ArMgX	Cu	225
SeR	ArMgX	Ni	79
$NR_3^+ X^-$		Cu	226
$NR_3^+ X^-$	ArMgX	Cu	226

Table 2 Regioselectivity in Coupling of C(sp^2)-metallics with Allylic Halides and Related Compounds

Allyl–X	*C(sp^2)–M*	*Catalyst*	*Ref.*
Alkenylmetallics			
			
25 75	Sn	$Pd(DBA)_2/PPh_3$	216
90 10	Zr	$[PdCl(C_3H_5)]_2/PPh_3$	202
8 92	Zr	$[PdCl(C_3H_5)]_2/MA$[a]	202
			
0 100	Si	$Pd(OAc)_2$	203
25 75	Sn	$Pd(DBA)_2/PPh_3$	216
			
0 100	Al	$Pd(PPh_3)_4$	198–200
0 100	Sn	$PdCl_2(MeCN)_2/PPh_3$	201
			
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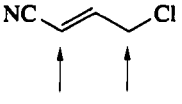
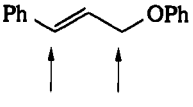
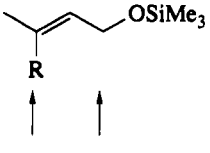
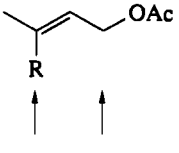
			
0 100	Sn	$PdCl_2(MeCN)_2/PPh_3$	201
			
0 100	[B]	$Pd(PPh_3)_4$	206
			
0 100	[Al]	$Pd(PPh_3)_4$	199
			
0 100	[Al]	$Pd(PPh_3)_4$	199

Table 2 *(continued)*

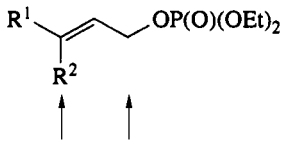
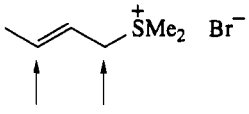
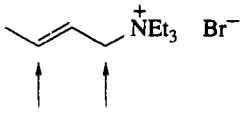
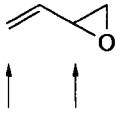
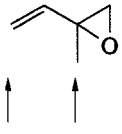
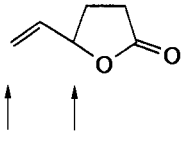
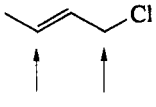
Allyl–X	*C(sp^2)–M*	*Catalyst*	*Ref.*
			
0 100	[Mg]	CuBr	223
0 100	[Al]	$Pd(PPh_3)_4$	199
			
35 65	[Mg]	CuBr	225
			
0 100	[Mg]	CuBr	226
			
26 74	B	$Pd(DBA)_2$	207
			
100 0	Li	CuBr	214
100 0	Mg	CuBr	214
100 0	Sn	$PdCl_2(MeCN)_2$	211
			
100 0	Mg	CuI	213
Arylmetallics			
			
75 25	Mg	$NiCl_2(DPPF)$	219
18 82	Mg	$PdCl_2(DPPF)$	219

Table 2 *(continued)*

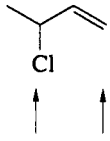
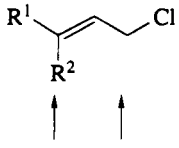
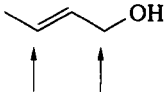
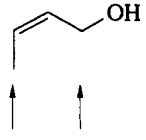
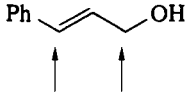
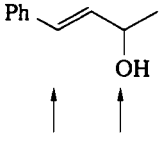
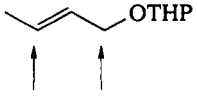
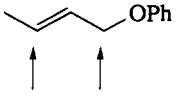
Allyl–X	*C(sp^2)–M*	*Catalyst*	*Ref.*
			
0 100	Sn	$Pd(DBA)_2/PPh_3$	201
0 100	Hg	$LiPdCl_3$	220
			
0 100	Sn	$Pd(DBA)_2/PPh_3$	201, 208
			
34 66 *(E)* > 99%	Mg	$NiCl_2(PPh_3)_2$	221
			
41 59 *(E)* = 84%	Mg	$NiCl_2(PPh_3)_2$	221
			
0 100	Mg	$NiCl_2(PPh_3)_2$	80
			
0 100	Mg	$NiCl_2(PPh_3)_2$	221
			
81 19	Mg	$NiCl_2$(DPPF)	219
11 89	Mg	$PdCl_2$(DPPF)	219
			
86 14	Mg	$NiCl_2$(DPPF)	219
10 90	Mg	$PdCl_2$(DPPF)	219

Table 2 *(continued)*

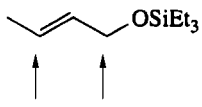
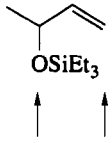
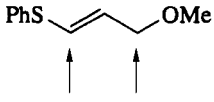
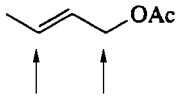
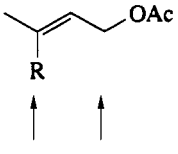
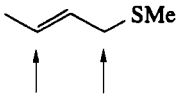
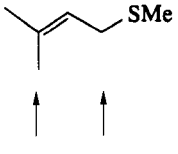
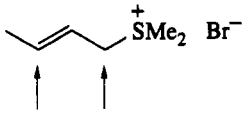
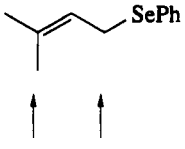
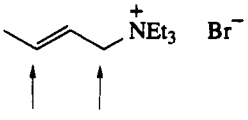
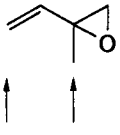
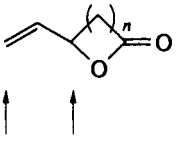
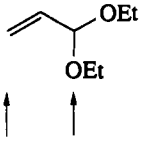
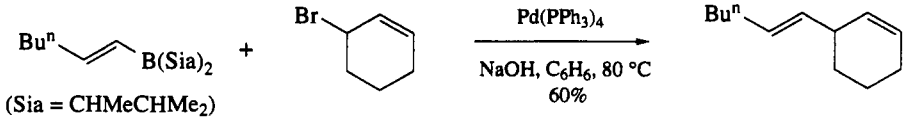
Allyl–X	*C(sp^2)–M*	*Catalyst*	*Ref.*
			
88 12	Mg	$NiCl_2$(DPPF)	219
33 67	Mg	$NiCl_2(PPh_3)_2$	219
4 96	Mg	$PdCl_2$(DPPF)	219
10 90	Mg	$Pd(PPh_3)_4$	219
			
81 19	Mg	$NiCl_2$(DPPF)	219
9 91	Mg	$PdCl_2$(DPPF)	219
			
0 100	Mg	$NiCl_2(PPh_3)_2$	222
			
52 48	[Mg]	$Pd(PPh_3)_4$	199
23 77	[Zn]	$Pd(PPh_3)_4$	199
23 77	[Cd]	$Pd(PPh_3)_4$	199
38 62	[Al]	$Pd(PPh_3)_4$	199
54 46	[Zr]	$Pd(PPh_3)_4$	199
			
0 100	[Mg]	Li_2CuCl_4	209
			
32 68	[Mg]	$NiCl_2(PPh_3)_2$	224
			
36 64	[Mg]	$NiCl_2(PPh_3)_2$	224

Table 2 *(continued)*

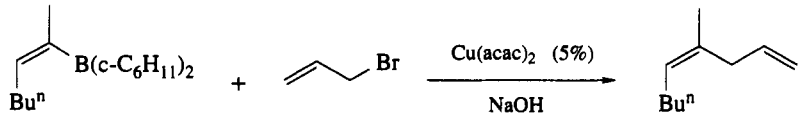
Allyl–X	*C(sp²)–M*	*Catalyst*	*Ref.*
 5 95	[Mg]	CuBr	225
 39 61	[Mg]	$NiCl_2(PPh_3)_2$	79
 11 89	[Mg]	CuBr	226
 98 2	[Sn]	$PdCl_2(MeCN)_2$	211
 (n = 1, 2 or 3) 100 0	[Mg]	CuI	214, 215
 100 0 (*E*/*Z* = 42/58)	[Mg]	CuBr	217

[a] MA = maleic anhydride.

Some other characteristic features, in focus on the stereochemical aspects, are described hereafter. Allylic chlorides and bromides couple with alkenyl–BR_2,[178,195–197] –AlR_2,[198–200] –SnR_3,[201] –$ZrCp_2Cl$,[202] –SiF_5^{2-},[203] and –$HgCl$[204] compounds in the presence of Pd or Cu catalysts to form 1,4-dienes with retention of stereochemistry of alkenylmetals (equations 193–200); in the Si and Hg cases, only allylic chlorides having a terminal alkene react with the complete allylic transposition. An intramolecular coupling of alkenylborane has been applied to the synthesis of humulene (equation 201).[205] In the Pd-catalyzed coupling of alkenyl–Al reagents the reactivity of allylic substrates depends on the leaving group in the order Cl, OAc > $OAlMe_2$ > $OP(O)(OEt)_2$ >> $OSiR_3$.[199] In contrast, the reverse order OPh >> OAc, Cl is found in the Pd-catalyzed coupling of alkenyl–B reagents, the alkene geometry being retained (equation 202); the reaction condition may be compared with that in the reaction occurring in equation (193), where the hydroxide ion is needed as the essential additive.[206] The stereochemistry of alkenyl–B reagents is retained also in the Pd-catalyzed coupling with epoxides.[207]



(193)



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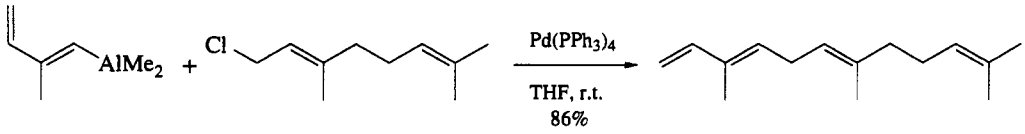

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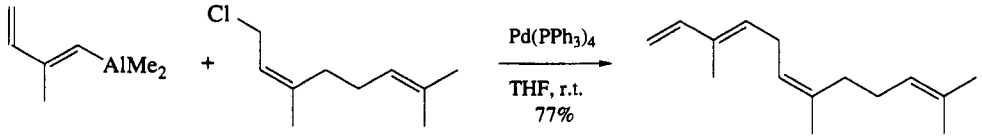

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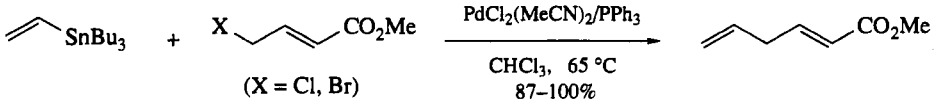

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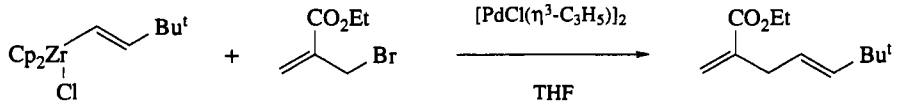

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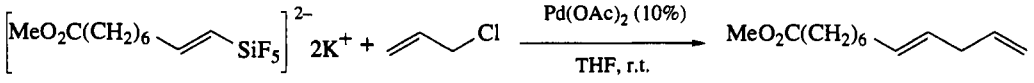

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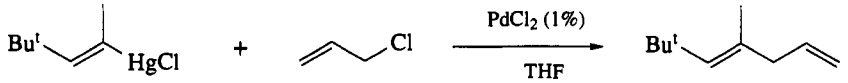

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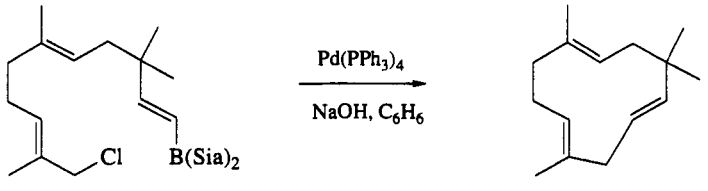
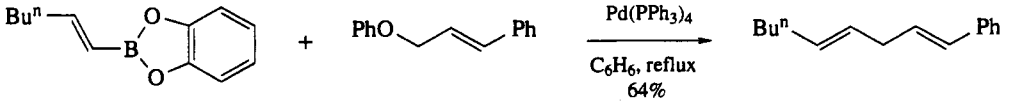


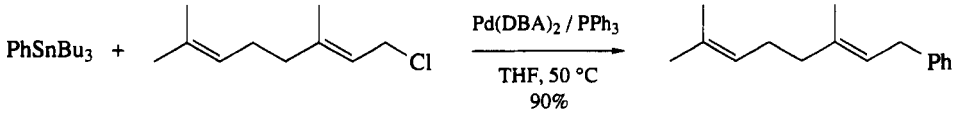
(201)



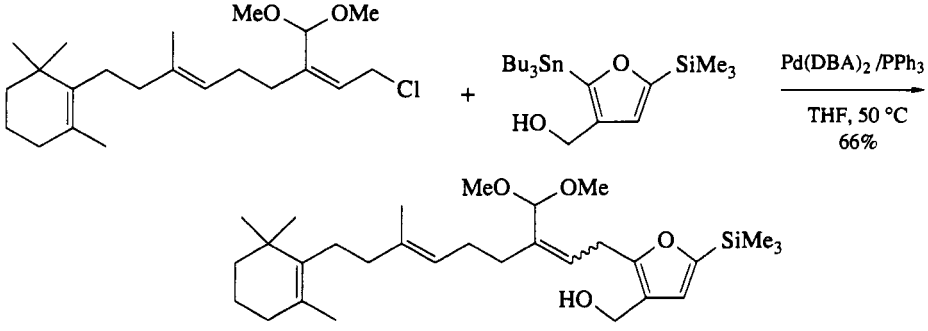
(202)

Remarkably, alkene stereochemistry in allylic chlorides is completely retained in the Pd-catalyzed coupling with alkenyl–Al (equations 195 and 196)[200] and aryl–Sn reagents (equation 203),[201] whereas stereochemical scrambling is also encountered in some cases (equation 204).[208] Retention of alkene stereochemistry is also observed in the Cu-catalyzed Grignard coupling of allylic acetates (equation 205).[209]

The Pd-catalyzed coupling reactions of cyclic allyl chlorides,[201] carboxylates[210] and epoxides[211] with alkenyl–Al, alkenyl–Sn and aryl–Sn reagents proceed with inversion of configuration of the allylic sp^3 carbon centers (equations 206–208).

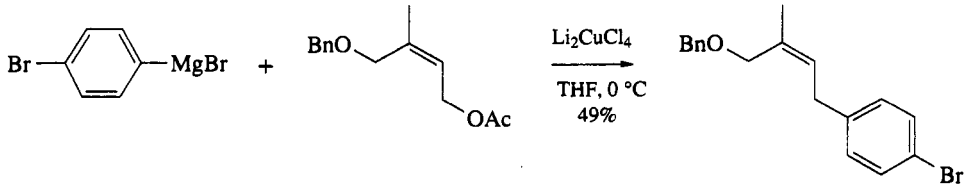


(203)

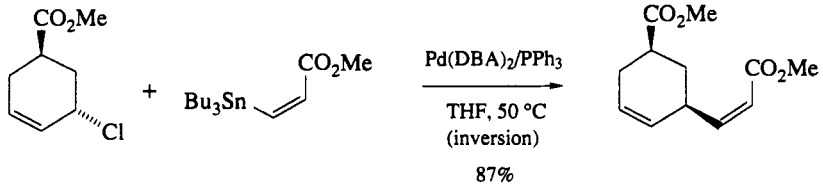


(204)

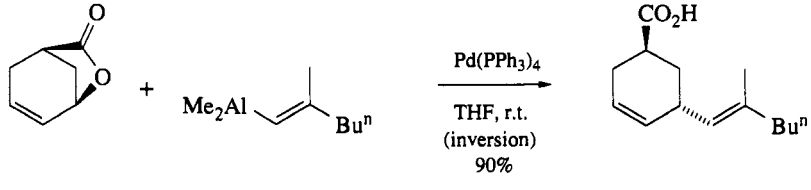
(E):*(Z)* = 1:1



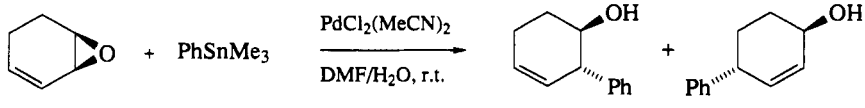
(205)



(206)

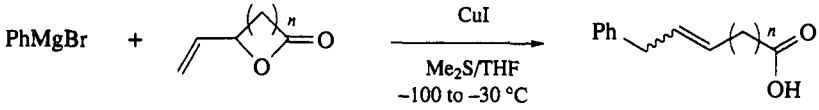


(207)



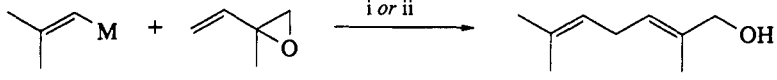
(208)

Some other synthetically interesting reactions are listed below. Thus, vinyl lactones undergo ring-opening and coupling with Grignard reagents in the presence of CuI to form β,γ-, γ,δ- or δ,ε-unsaturated carboxylic acids (equation 209),[212,213] and isoprene monoepoxide couples with alkenyl–Grignard reagents[214] or alkenyl–Sn reagents[211] to form terpenoid allylic alcohols (equation 210). Pd-catalyzed coupling of 1-ethoxyvinyl–[215] and acyl–Sn[216] reagents with allylic acetates, carbonates, phosphates or chlorides forms unsaturated vinyl ethers and ketones, respectively (equations 211 and 212). The formation of alkenyl ethers is also attained by Cu-catalyzed Grignard coupling with an allylic acetal (equation 213).[217] Finally, allyluridines can be obtained by Pd-catalyzed allylation of the corresponding mercury intermediates (equation 214).[218]



(209)

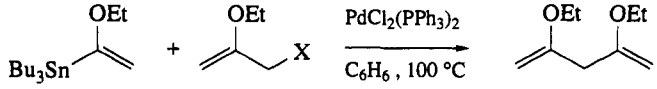
$n = 1$ 91% $(E):(Z) = 83:17$
$n = 2$ 75% $(E):(Z) = 62:38$
$n = 3$ 56% $(E):(Z) = 67:33$



(210)

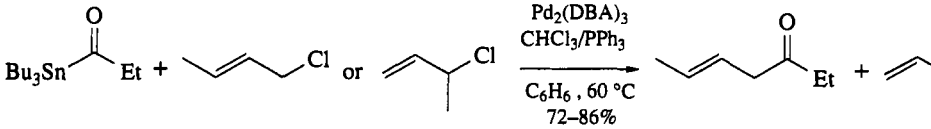
i, M = Li 94% $(E):(Z) = 88:12$
i, M = MgBr 77% $(E):(Z) = 96:4$
ii, M = $SnMe_3$ 72%

i, CuBr, Et_2O, −15 °C; ii, $PdCl_2(MeCN)_2$, DMF, H_2O, r.t.



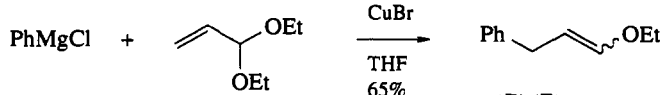
(211)

X = OAc 72%
X = OP(O)(OEt)$_2$ 99%
X = OCO_2Me 63%



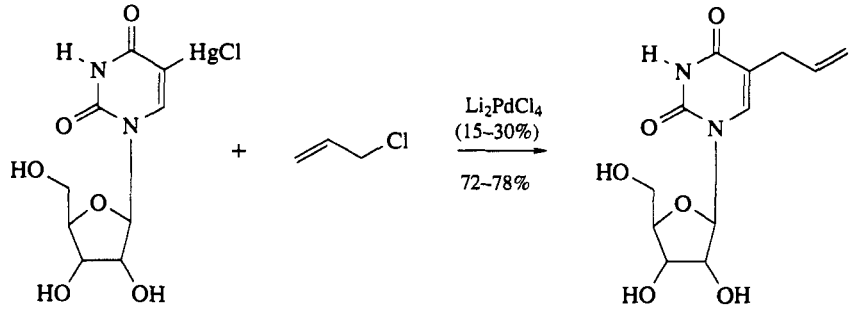
(212)

75% 25%



(213)

$(E):(Z) = 58:42$



(214)

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2.3
Coupling Reactions Between sp^2 Carbon Centers

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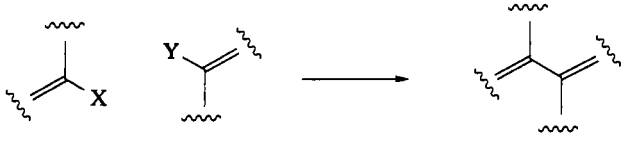
2.3.1 INTRODUCTION

The scope of this chapter is largely confined to the direct coupling reactions of sp^2-carbons as outlined in equation (1), where both X and Y are groups or atoms other than hydrogen. In retrosynthetic terms, such processes are usually best regarded as 'illogical' and indeed prior to the early 1970s, with the exception of the classical Ullmann biphenyl synthesis, few examples of such reactions were in general use. During the past 15 years, however, enormous progress has been made in this area, particularly since the introduction of zerovalent palladium and nickel catalysts for carrying out the coupling reactions.

Two important groups of reactions of the type outlined in equation (1) are not included in this chapter, as they are reviewed elsewhere in Comprehensive Organic Synthesis. Firstly, Heck-type processes (Y = H; equation 1) are discussed in Volume 4, Chapter 4.3. A second way to effect the overall process indi-



(1)

X, Y ≠ H

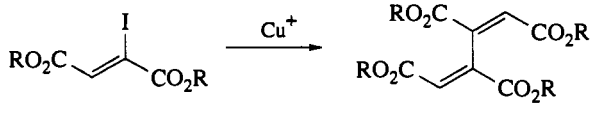
cated in equation (1) is by a tandem Michael addition–elimination sequence, such as the addition of a vinylcuprate species to methyl β-bromoacrylate; such methods are also covered in Volume 4.

The chapter has been organized so as to give rapid access to information regarding a particular structural type. This inevitably requires the inclusion of extensive cross-referencing as, not surprisingly, many of the coupling methods can and have been applied to targets belonging to more than one of these groups.

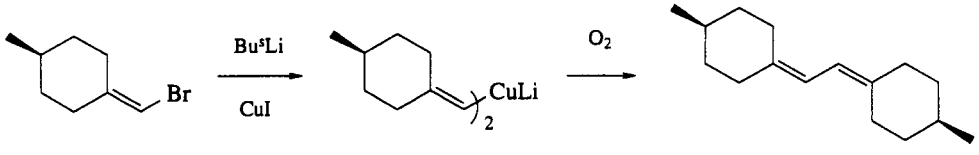
2.3.2 COUPLING REACTIONS INVOLVING ALKENES

2.3.2.1 Alkene–Alkene Dimerization

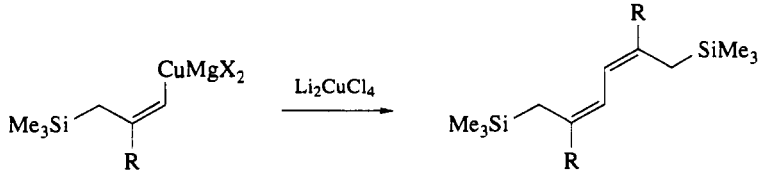
In common with the well-established Ullmann biphenyl synthesis, many methods for alkene dimerization feature the use of a copper species, either formed *in situ* using a copper salt (and often of an undefined nature) or by using a preformed vinylcuprate and a coupling reagent. For example, iodofumarates (**1**) can be converted into tetraesters (**2**) simply by using activated copper powder,[1] although later work has revealed that copper(I) triflate and saturated aqueous ammonia in acetone is a more effective reagent mixture.[2] The couplings are highly stereoselective and work almost equally well with iodomaleates. A general method for coupling vinyl halides consists of conversion to the corresponding lithium divinylcuprate followed by treatment with molecular oxygen (Scheme 1).[3] The method is general and usually high yielding and is also effective in coupling mixed vinylmagnesiocuprate species. The latter type of intermediate (*e.g.* **3**) also undergoes efficient dimerization when treated with dilithium tetrachlorocuprate (Li_2CuCl_4 from $CuCl_2$ + 2LiCl) resulting, in this particular example, in an expedient and stereospecific approach to bis(allylsilanes) (**4**).[4] The conversion (**3**) → (**4**) represents a general type of oxidative coupling which is also applicable to a wide range of vinyllithium and vinyl Grignard species, and which can be effected using CuCl or $CuCl_2$ in addition to Li_2CuCl_4, as well as by a variety of cobalt, manganese and chromium salts.[5] Symmetrical 1,3-butadienes can also be obtained from vinylcopper species and the corresponding vinylsilver(I) salts by a simple thermal decomposition process; in general both the yields and stereochemical retentions are high, even in the preparations of (*Z*,*Z*)-1,3-butadienes.[6] Silver salts can also be used to carry out dimerizations of vinyl Grignard reagents, in conjunction with a nitrogen-containing oxidizing agent such as $LiNO_3$, $MeNO_3$ or NO_2.[7] A wide range of simple transition metal halides have also been examined for their suitability as mediators of such coupling reactions. One of the best turned out to be palladium(II) chloride, which at the time it was described was certainly a signal for many of the later spectacular advances in sp^2–sp^2-coupling reactions. Two



(1) (2)



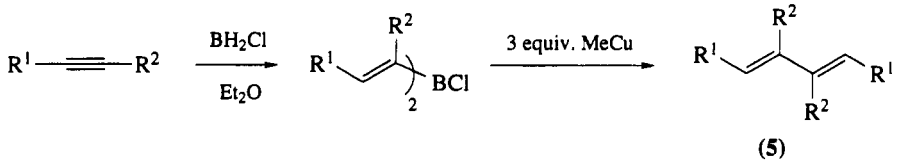
Scheme 1



(3) (4)

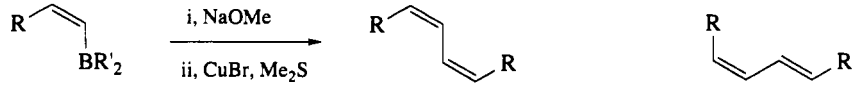
other reagents that have been used in this type of Grignard dimerization are $K_4[Ni_2(CN)_6]$[8] and, rather unexpectedly, thionyl chloride.[9]

Alkenylboranes have also been found to be valuable precursors of 1,3-butadienes and, once again, copper reagents play a crucial role in these procedures. For example, hydroboration of an alkyne using monochloroborane (Scheme 2) leads to a divinylborane, and thence to an (*E,E*)-1,3-butadiene (**5**) following treatment with 3 equiv. of methylcopper.[10] Monoalkenyldibromoborane species can be coupled in a similar fashion and both sequences are stereospecific; two limitations, however, are the potential lack of regioselectivity in the first step with unsymmetrical alkynes and the possibility of side reactions between the hydroborating reagent and other functional groups contained in the substituents R^1 and R^2. Both (*E*)- and (*Z*)-vinylboranes (**6**) can be coupled by sequential treatment with sodium methoxide and copper(I) bromide–dimethyl sulfide complex, thus providing a useful alternative approach to (*E,E*)-dienes (**5**; R^2 = H) as well as to (*Z,Z*)-butadienes (**7**).[11] Both procedures are reported to be stereospecific. A rather older procedure can be used to prepare (*E,Z*)-butadienes (**8**); thus, hydroboration of a terminal alkyne using thexylborane first affords an (*E*)-alkenyldithexylborane, which upon treatment with iodine and sodium hydroxide is then converted selectively into the (*E,Z*)-isomer (**8**).[12] Similarly, the (*E,Z*)-isomers of tetrasubstituted butadienes (**5**; $R^1 = R^2$) can be prepared from symmetrical internal alkynes.



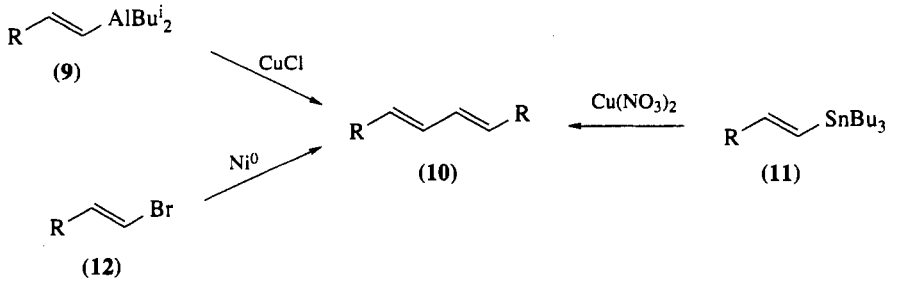
(5)

Scheme 2



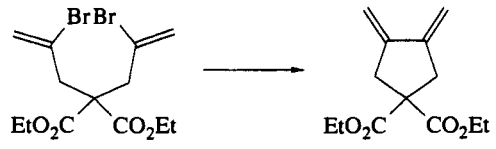
(6) (7) (8)

A closely related sequence which has been used for the specific preparation of (*E,E*)-butadienes (**10**) from terminal alkynes involves hydroalumination, usually using DIBAL-H, followed by coupling of the intermediate vinylalane (**9**) using copper(I) chloride (*vide supra*).[13] In much the same manner, hydrozirconation of a terminal alkyne and transmetallation using copper(I) iodide also leads smoothly to butadienes (**10**).[14] A rather different source of copper, hydrated copper(II) nitrate, is very effective for the rapid and efficient coupling of vinylstannanes (**11**), leading to butadienes (**10**).[15] (*Z,Z*)-Butadienes (**7**) can also be produced from (*Z*)-vinylstannanes by this method, which will also tolerate a substituent α to the tin functionality. A final example of the use of both copper(I) and silver(I) salts is as reagents for the coupling of (*E*)-alkenyl pentafluorosilicates to give symmetrical (*E,E*)-butadienes (**5**) in moderate to good yields; in contrast, reactions with copper(II) salts give only monomeric products by protonolysis of the C—Si bond.[16]



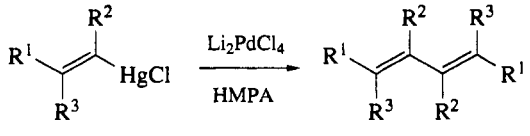
The direct dimerization of an alkenyl halide offers a potentially attractive alternative to many of the above two-step procedures. Such a transformation, (**12** → **10**), can be achieved using bis(1,5-cyclooctadiene)nickel(0) in the presence of triphenylphosphine.[17] This mild method tolerates the presence of sensitive functional groups such as acrylic esters[1,2] and has been improved since the original report by the introduction of more convenient catalyst systems such as triphenyl-[18] and trialkyl-phosphine–nickel(0)[19]

species and an Ni^0 reagent prepared by reduction of nickel(II) chloride using zinc in the presence of potassium iodide and/or thiourea.[20] An even simpler method for effecting such dimerizations is to employ 5 mol % $Pd(OAc)_2$ as catalyst in the presence of triphenylphosphine and potassium carbonate.[21] This methodology looks particularly attractive for various intramolecular dimerizations, such as in the conversion of the bis(vinyl bromide) (**13**) into the cyclopentane (**14**) in 95% yield. Simple vinylic chlorides have also been coupled using a catalyst system composed of platinum chloride and cesium fluoride in the presence of Et_4NSnCl_3 in aqueous DMF.[22]

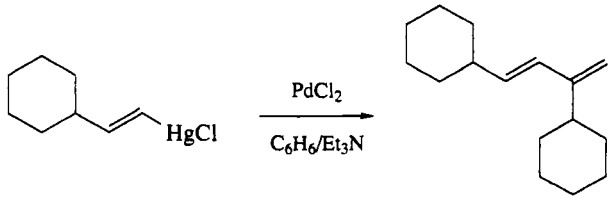


(13) (14)

Vinylmercury species (**15**) are very efficiently dimerized to dienes (**16**) upon treatment with palladium chloride and lithium chloride $[Li_2PdCl_4]$.[23] In addition to the high yields, a further attraction is the wide range of functionality which can be tolerated (this type of coupling does not appear to be too seriously affected by steric hindrance); this includes both α- and β-alkenyl and -alkynyl groups as well as aryl and β-acetoxy functions. An important disadvantage, however, along with the requirement for HMPA, is the need to use stoichiometric quantities of expensive $PdCl_2$; this can be overcome in many examples by using a rhodium species, $[Rh_2(CO)_4Cl_2]$·LiCl, which is only required in catalytic quantities.[24] A most unusual turnaround occurs with these couplings when they are carried out in nonpolar benzene using 0.5 equiv. of $PdCl_2$, in that the 'head to tail' product is obtained instead (*e.g.* **17** → **18**), thereby adding a useful facet to such vinylmercury chemistry.[25]



(15) (16)

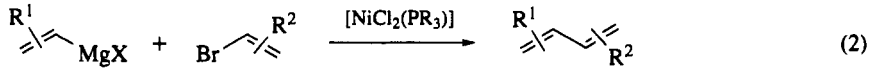


(17) (18)

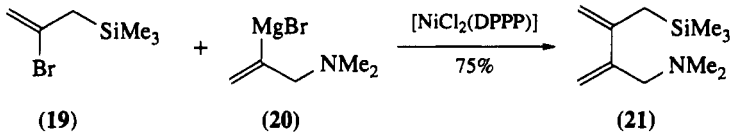
2.3.2.2 Crossed Alkene–Alkene Coupling

This type of coupling reaction has only become a really viable option in synthesis during the past 15 years or so, with the advent of a number of nickel and palladium complexes, especially zerovalent species. The direct coupling of alkenyl and aryl Grignard reagents with alkenyl and aryl halides, catalyzed by various nickel complexes, has been extensively studied by Kumada and his coworkers in particular, with the result that some of the most suitable catalysts discovered, such as $[NiCl_2(PPh_3)_2]$ and $[NiCl_2(DPPP)]$, are sometimes referred to as Kumada- or Tamao–Kumada-type catalysts, as is the zerovalent species $[Ni(PPh_3)_4]$. These catalysts are particularly effective in conjugated diene synthesis of the type indicated in equation (2).[26] In general, the reactions proceed efficiently and under mild conditions, although with a lack of stereospecificity in some cases, even though vinyl Grignard reagents tend to be relatively less reactive in such reactions than the corresponding aryl species. Given protection against the Grignard reagent, a wide range of functional groups can be tolerated and in sterically hindered examples it is usually best to utilize the more hindered Grignard reagent, rather than to couple a relatively unhindered vinyl Grignard with a crowded alkenyl halide. In those examples with similar steric demands, the

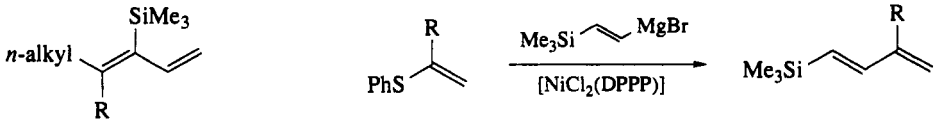
ordering can still be important. For example, coupling between the allylsilane (**19**) and Grignard reagent (**20**) produces a 75% yield of the useful butadiene (**21**); coupling in the opposite sense leads to a lower (56%) yield.[27] Vinyl Grignard reagents obtained by Ni(acac)-catalyzed additions of RMgX to silylalkynes can also be coupled directly to vinyl bromides to provide silylbutadienes (*e.g.* **22**, from vinyl bromide) in moderate yields; the second step is presumably also nickel catalyzed.[28] Isomeric silanes, as well as a variety of other butadienes, can be obtained by nickel-catalyzed displacements of thiol groups using vinyl Grignards (*e.g.* **23** → **24**).[29] Such reactions are quite general and have been successfully applied, for example, in styrene syntheses (Section 2.3.2.4).



(2)



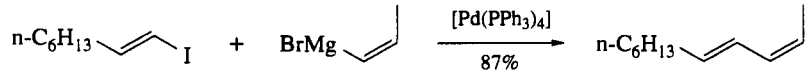
(**19**) (**20**) (**21**)



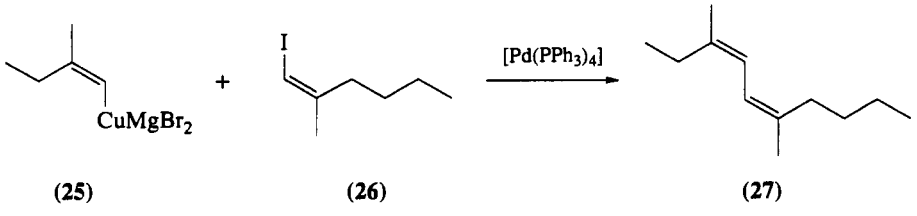
(**22**) (**23**) (**24**)

A major advance in this area came with the discovery that vinyl Grignard species could be smoothly coupled with vinyl halides using tetrakis(triphenylphosphine)palladium(0) as catalyst (Scheme 3).[30] Typical yields for such coupling reactions are 75–87% and stereochemical retention is normally excellent in both components, facts which often render this method more useful than a number of alternatives, such as couplings between various vinylcuprates and vinyl iodides (*vide infra*). As will be seen from the subsequent discussion, Pd^0 catalysts, especially $[Pd(PPh_3)_4]$, are undoubtedly the most important in this whole area of sp^2–sp^2-coupling reactions. As an example, the reaction shown in Scheme 3 can also be carried out using Cu^I catalysts, but yields are generally around 50% and the method cannot be applied to vinylmagnesium bromide itself, due to polymer formation.[31] However, preformed vinylmagnesiocuprates can be coupled to vinyl halides using 5 mol % of $[Pd(PPh_3)_4]$ or $[Pd(PO_3)_4]^4$ as catalyst in good yields (50–70%) and with high stereochemical retention.[32] A specific example is the formation of the (*Z*,*Z*)-diene (**27**) from the magnesiocuprate (**25**) and the iodide (**26**); two notable features of this particular transformation are the highly selective production of the (*Z*,*Z*)-isomer and the high degree of substitution present in both components.[33] A further important discovery[33,34] is that these and related reactions also benefit from the addition of a zinc salt, typically zinc chloride, an observation first reported by Negishi and coworkers (*vide infra*) during their studies on vinylaluminum coupling reactions. Not surprisingly perhaps, lithium divinylcuprates (*e.g.* **28**) can also be coupled with vinyl iodides (**29**) using $[Pd(PPh_3)_4]$ and $ZnCl_2$ as catalysts.[34] This route to (*E*,*Z*)-butadienes (**30**) also displays a further useful feature, *i.e.* couplings with the diiodide (**31**) proceed as expected in the usual ethereal solvents to give, for example, the dienyl iodide (**32**), whereas when HMPA is added alkylation of the vinyl carbanion occurs to give the alternative product, the homologated vinyl iodide (**33**). While this methodology can also be used to prepare (*Z*,*Z*)-butadienes, one major disadvantage is that one of the vinyl groups in the cuprate (**28**) is wasted, clearly a serious problem in cases when this function is valuable. This problem can be overcome by treating a divinyl species (**34**) with $ZnCl_2$; transmetallation then ensues to give two intermediates, (**35**) and (**36**), which both couple with a vinyl halide under the influence of a Pd^0 catalyst.[35] Such palladium(0) catalysts, especially $[Pd(PPh_3)_4]$, are also very useful for effecting couplings between organolithiums and vinyl halides, although this type of reaction has been used mostly with examples of aryl- and heteroaryl-lithium species, as well as alkyllithiums, and is discussed more fully in the relevant sections which follow.[36] In general, such couplings involving alkenyllithiums cannot be carried out directly using Pd^0 or related nickel catalysts. However, the discovery of the value of zinc chloride in Pd^0-catalyzed sp^2–sp^2-couplings has subsequently led to the development of what is perhaps the method of choice for coupling alkenyllithiums with alkenyl halides, which proceeds *via* transmetallation with zinc chloride followed by $[Pd(PPh_3)_4]$-[37] or $[Pd(DBA)_2]\cdot 2PPh_3$-catalyzed[38] coupling with an (*E*)- or (*Z*)-alkenyl halide. Yields and preservation of stereochemical integrity are generally very good and the method

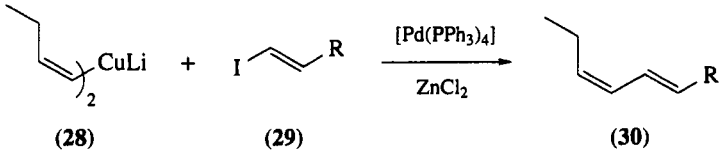
(Scheme 4) is also applicable to aryl halides and to allenyllithium reagents (*vide infra*). One drawback is that an excess of the vinylzinc species is usually required if good yields are to be obtained. The method is not limited to hetero substituted alkenyllithiums and, for example, has subsequently been used to prepare homologs, (**38**) and (**39**), from the alkenylzinc bromide (**37**) and the corresponding vinyl iodides, in 50–70% yields.[39] One of the first generally useful methods in this area of crossed couplings was between alkenylaluminum reagents and vinyl halides, catalyzed by either nickel or palladium salts and $ZnCl_2$. The couplings are essentially stereospecific, except in examples of nickel-catalyzed reactions of (*Z*)-vinyl iodides, where this usually falls to *ca.* 90% and they sometimes fail when the aluminum species carries bulky substituents.[40] A specific example (Scheme 5) has been described in detail[41] and, overall, the procedure complements many of the approaches developed by Normant and his coworkers[31–35] involving (*Z*)-alkenyl organometallics generated by stereospecific additions to terminal alkynes. In this present Negishi procedure, (*E*)-alkenylaluminum reagents are obtained by stereospecific hydroalumination of 1-alkynes, usually using DIBAL-H. As a stoichiometric amount of $ZnCl_2$ is employed, this method is clearly closely related to the foregoing examples (Scheme 4).[37–39] Zirconium species, which are prepared by hydrozirconation of terminal alkynes using Schwartz's reagent [$Cp_2Zr(H)Cl$], react in a similar fashion to that shown in Scheme 5 and are sometimes preferable to the corresponding alkenylaluminum species.[42] A number of functional groups can be tolerated in the vinyl halide partner, including acetals (OTHP), ethers, ketones and esters.[43] As would be expected from the foregoing results, mixed aluminum–zirconium species (**41**), obtained from 1-alkynes (**40**), also undergo smooth Pd^0- or Ni^0-catalyzed cross-coupling reactions with alkenyl bromides, but only following the addition of $ZnCl_2$ (or $CdCl_2$).[44] In examples where the alkenylaluminum intermediate is highly hindered, it can sometimes be advantageous to convert it to the corresponding vinyl iodide (using I_2) and then couple this with a (less-hindered) organometallic.



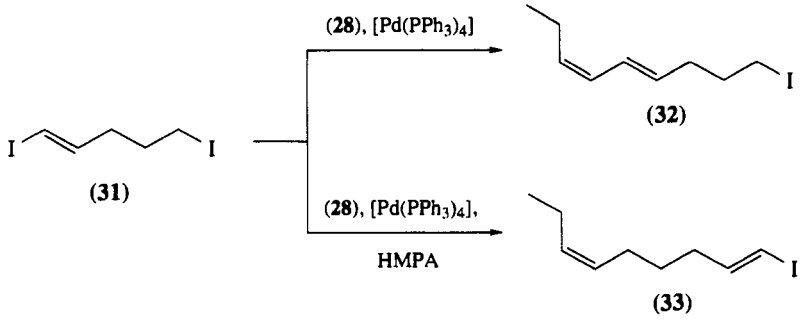
Scheme 3



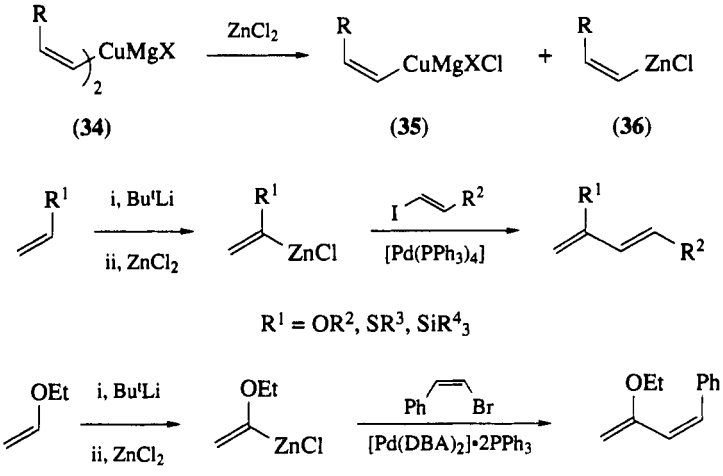
(**25**) (**26**) (**27**)



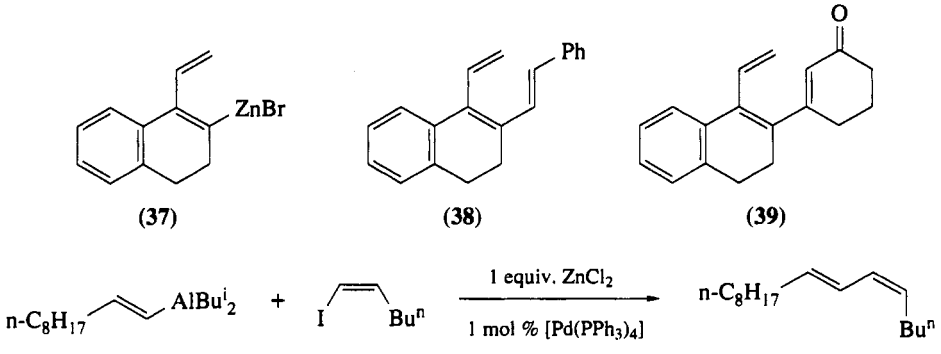
(**28**) (**29**) (**30**)



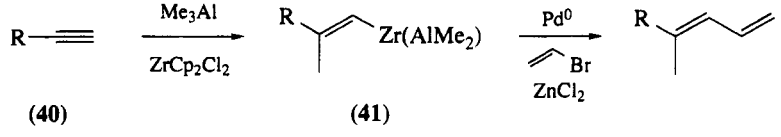
(**31**) (**32**) (**33**)



Scheme 4



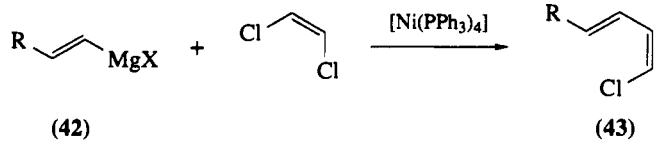
Scheme 5



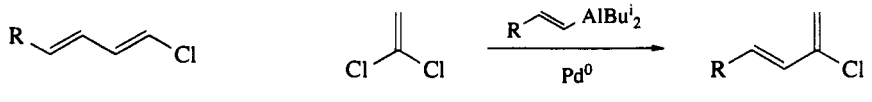
A useful series of coupling reactions with polychloroethylenes has been developed, based upon the foregoing type of chemistry. For example, 1 equiv. only of the vinyl Grignard reagents (**42**) can be added to (*Z*)-1,2-dichloroethylene to provide the (*E*,*Z*)-chlorobutadienes (**43**) in good yield.[45] The method also works for (*E*)-1,2-dichloroethylene, which can be coupled similarly to (*E*)-alkenylaluminums,[46] both routes leading to (*E*,*E*)-1-chlorobutadienes (**44**). The latter aluminum species can also be coupled with 1,1-dichlorethylene (**45**), using a Pd^0 catalyst at ambient temperature, leading to the useful 2-chlorobutadienes (**46**) in good yields.[47]

A further significant advance in the general area of sp^2–sp^2-coupling has been the finding that enol triflates can be coupled directly with lithium divinylcuprates (in addition to many related species) to provide butadienes in high yields and with good stereoselectivity (*ca.* 90% in the example shown in Scheme 6).[48] Enol triflates are readily prepared from the corresponding ketones, and are usually stable and easy to handle, and so the subsequent discovery that such intermediates could be smoothly coupled with vinylstannanes, under the catalytic influence of the ubiquitous $[Pd(PPh_3)_4]$, has enhanced their utility even further.[49] This latter protocol is of considerable merit, being highly efficient (80–100% yields) and stereoselective, as well as applicable to a wide range of substrates, both of which can be heavily substituted. The specific example shown in Scheme 7 represents a simple and efficient synthesis of the furanoses-quiterpene pleraplysillin 1. Many further examples have been described in full,[50] including a simple approach to 1-silylbutadienes (Scheme 8), and the elaboration of an advanced model precursor of anthramycin (Scheme 9).[51] In this latter example, the isolated yield was 78%, in contrast to a direct

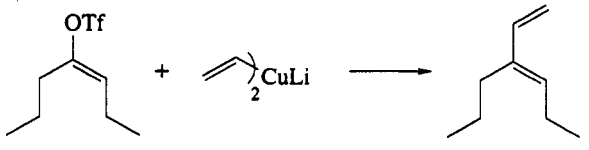
Heck-type coupling using ethyl acrylate, which afforded a lower 40% return. Such couplings can also be carried out intramolecularly, thus providing a novel disconnection in the retrosynthetic analysis of a wide range of targets, which is especially attractive because the required precursors are often highly accessible. Some generalized examples are the conversions shown in Scheme 10[52,53] for the formation of five- and six-membered rings; an application in the natural products area is in a neat synthesis of a dolastane diterpene in which the key cyclization (*cf.* Scheme 10) was effected in 81% yield by *in situ* formation of the vinyl triflate from the corresponding ketone (LDA, THF, HMPA, $PhN(SO_2CF_3)_2$) followed by the addition of $[Pd(PPh_3)_4]$ (catalytic) and work-up after only 5 min at 30 °C.[53] In general, such cyclizations are faster when carried out in acetonitrile rather than in THF. In a similar fashion, vinylstannanes can be coupled with vinyl iodides, both inter- and intra-molecularly. For example, a recently reported approach to the natural fatty acid 13-HODE (the hydroxy acid corresponding to ester **49**) had as a key step a palladium-catalyzed reaction between the vinyl iodide (**47**) and the stannane (**48**).[54] A notable feature with this and many related processes is the tolerance of function groups such as carboxylic esters, the presence of which would be precluded in much of the more well-established carbanion chemistry. The



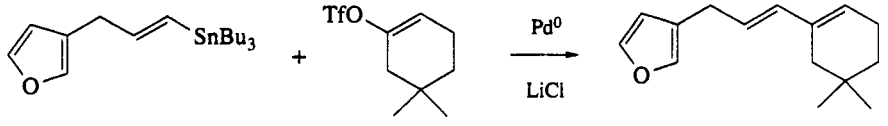
(42) (43)



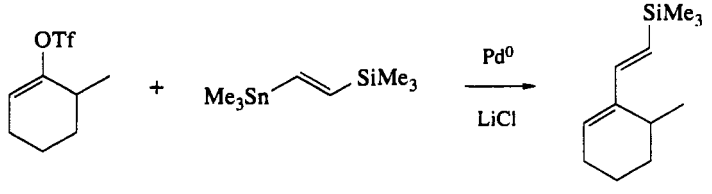
(44) (45) (46)



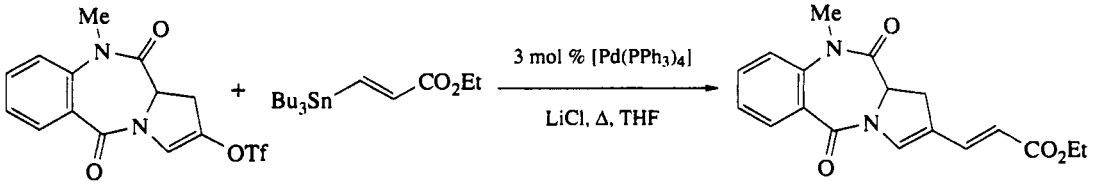
Scheme 6



Scheme 7

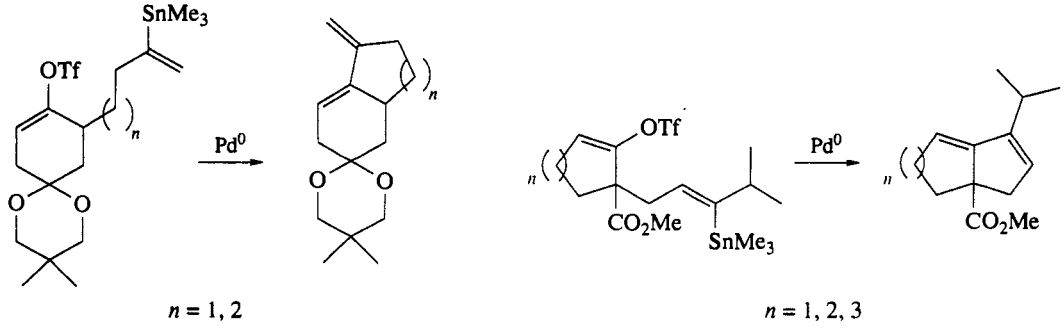


Scheme 8

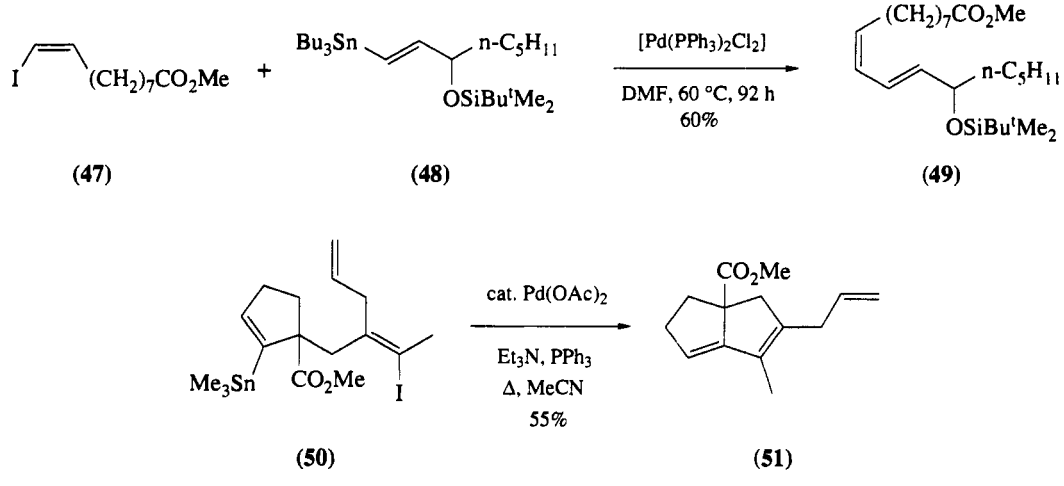


Scheme 9

intramolecular version of this reaction type, *e.g.* (**50**) → (**51**), is also catalyzed by a palladium(II) species, and is notable in this example for producing a 55% yield of a rather strained bicyclo[3.3.0]octadiene (**51**).[55]



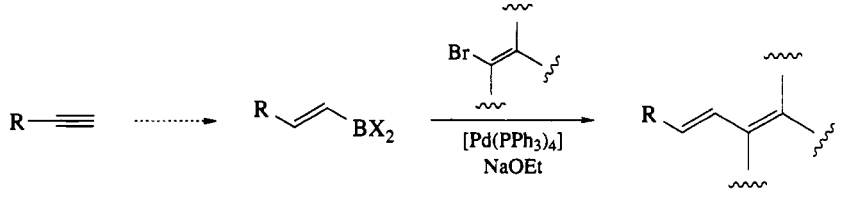
Scheme 10



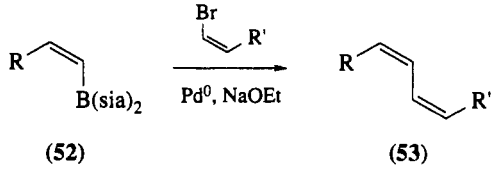
In a similar manner to vinyl triflates (Scheme 6),[48] vinylmercury chlorides also undergo direct coupling with vinylcuprates leading to butadienes in *ca.* 60–66% yield, but only when a higher order cuprate, R_3CuLi_2, is used.[56]

A final class of intermediates which are valuable in the synthesis of conjugated dienes are alkenylboranes and alkenylboronates; indeed such species were employed in some of the first reasonably satisfactory diene syntheses.[57] As with many of the foregoing reaction types, the advent of [$Pd(PPh_3)_4$] as a coupling catalyst has considerably transformed this area of chemistry. Much of the progress has been due to contributions made by Suzuki and coworkers, to the extent that such reactions involving alkenylboron species are often referred to as Suzuki couplings. In essence, the reactions consist of bond formation between an alkenylborane and an alkenyl halide in the presence of both [$Pd(PPh_3)_4$] and a base such as a sodium alkoxide (Scheme 11).[58] (*E,E*)-Butadienes can generally be obtained stereochemically pure by this method, but similar couplings involving (*Z*)-alkenyl halides often lead to isomeric mixtures, although in some cases even (*Z,Z*)-butadienes (**53**) have been obtained from (*Z*)-alkenylboranes (**52**), but in relatively low yields.[59,63,64] With more weakly basic conditions, head to tail coupling tends to occur. Under similar conditions, (*E*)-alkenylboronic acids couple smoothly and stereospecifically with alkenyl iodides (Scheme 12).[60] As the alkenylboronic acids are readily obtained by hydroboration of terminal alkynes, this method is especially suitable for the synthesis of (*E,E*)- or (*E,Z*)-dienes. A third class of intermediates are the alkenylboronates. All three species have been compared for their suitability in the synthesis of the diene-containing insect pheromone bombykol and its three geometric isomers.[61] The choice of method can often be important; for example, coupling the boronic acid (**54**) and the bromide (**55**) provides an 82% yield of the target (**56**), whereas an alternative using the vinyl iodide (**57**) and the borane (**58**) produces only a 50% yield. However, the latter type of coupling has been used successfully in a scaled-up preparation of leukotriene B_4 (Scheme 13).[62] Despite these successful applications,[63] most of the methods are still not satisfactory for the elaboration of (*Z,Z*)-conjugated dienes as, in general,

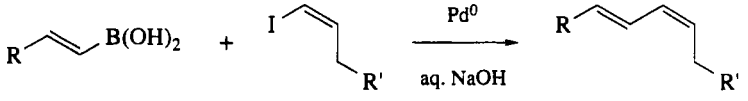
yields are rather poor in such preparations. Perhaps the best way to gain access to this class of compound is by coupling alkenylboronates with alkenyl bromides, using the usual Suzuki-type conditions (Scheme 14).[64] This methodology is now viable as the required (*Z*)-alkenylboronates can be readily obtained from 1-alkynes *via* the corresponding 1-bromo-1-alkenylboronate. The method can also be used to prepare (*E,Z*)-dienes from (*E*)-alkenyl bromides and has also been extended to the stereospecific elaboration of more highly substituted dienes, *e.g.* (**59**) and (**60**), by using 1,2-disubstituted alkenylboronates.[65] Related (*Z,Z*)-1-bromo-1,3-butadienes can be obtained using a haloboration–hydroboration sequence involving two alkynes; further elaboration of these initial products by, for example, halogen–lithium exchange and homologation provides yet another route to (*Z,Z*)-butadienes.[66]



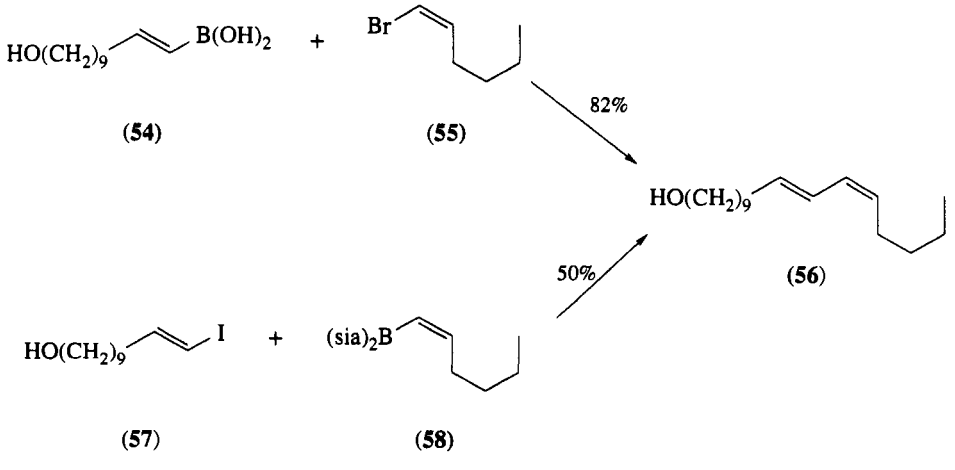
Scheme 11



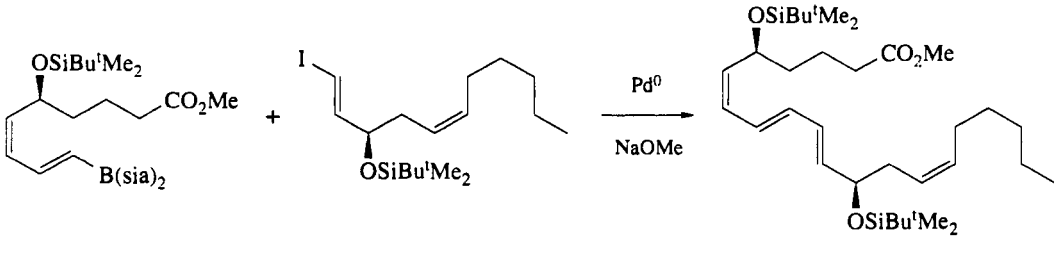
(**52**) (**53**)



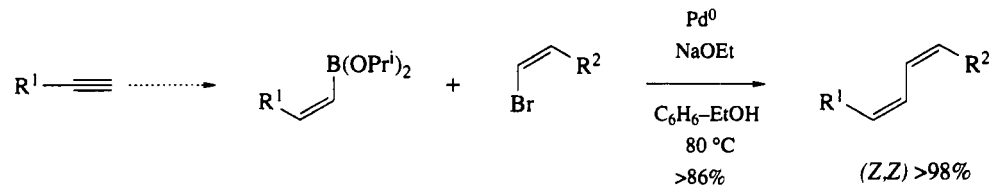
Scheme 12



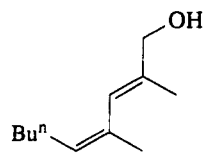
(**54**) (**55**) (**56**) (**57**) (**58**)



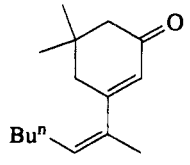
Scheme 13



Scheme 14



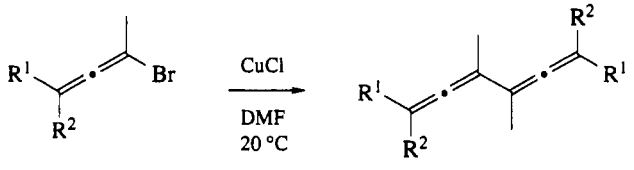
(59)



(60)

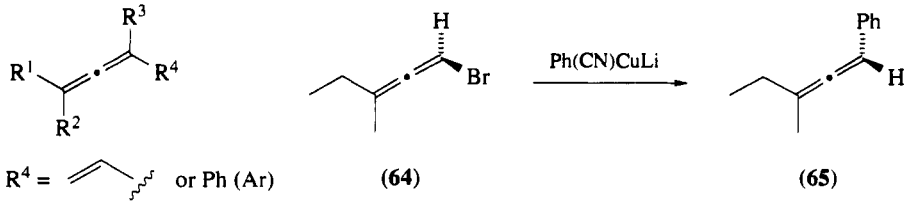
2.3.2.3 Allene Synthesis by sp^2–sp^2 Coupling

Not surprisingly, many of the methods which can be used in the synthesis of conjugated dienes can also be applied to dimerization of allenes. Thus, the bromoallenes (**61**) can be smoothly dimerized, for example, by treatment with 2 equiv. of copper(I) chloride in DMF at ambient temperature to give good yields of the diallenes (**62**).[1,2,67]



(61) **(62)**

The aforementioned method for coupling alkenylzinc halides with vinyl halides[37–39] is also applicable to the bromoallenes (**61**) (the corresponding bromoalkyne can also be used), which react smoothly with both 1-alkenylzinc chlorides and phenylzinc chloride in the presence of $[Pd(PPh_3)_4]$ to give the homologs (**63**) in good yields.[68] By studying such reactions with chiral haloallenes, a duality of mechanism has been found.[69] Iodoallenes react with ArZnCl–Pd^0 with retention of configuration suggesting that oxidative insertion by palladium into the C—I bond is the key step, whereas the corresponding chloro- and bromo-allenes react with moderate levels of inversion implying the participation of an *anti*-S_N2 like reaction followed by a [1,3] Pd shift with inversion. A direct S_N2-type inversion is observed when chiral bromoallenes, *e.g.* (**64**), are treated with the Lipshutz higher order cyanocuprates resulting in the generation of essentially enantiomerically pure homologs, *e.g.* (**65**), in 70–80% yields.[70] Other reagents such as '$PhCuMgBr_2$' give poorer optical yields and large amounts of the corresponding alkynic product.



(63) R^4 = or Ph (Ar) **(64)** **(65)**

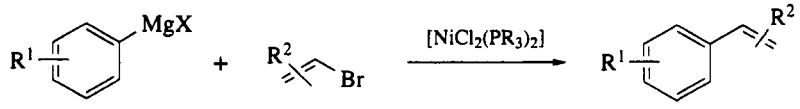
Aryl Grignard reagents also coupled satisfactorily with bromoallenes, using $[Pd(PPh_3)_4]$ as catalyst,[30] to give good yields of arylallenes (**63**; R^4 = Ar),[71] whereas couplings in the opposite sense between allenyllithiums derived from allenyl ethers or allenylsilanes and aryl iodides can also be achieved,[72] again using Pd^0 catalysts. This is in contrast to similar reactions with vinyllithiums,[36–39] which usually require

prior transmetallation to the corresponding alkenylzinc species before successful couplings can be achieved (for an example using an allenylzinc intermediate, see ref. 38).

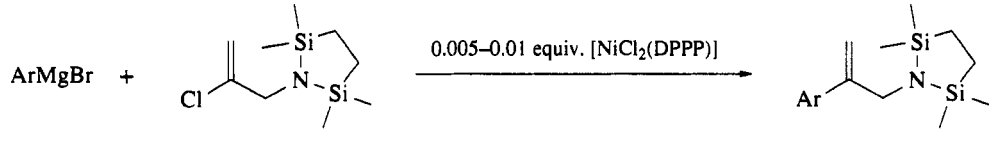
2.3.2.4 Alkene–Aryl Coupling

Many of the methods outlined in Section 2.3.2.2 (alkene–alkene coupling) are equally suited to alkene–aryl coupling reactions simply by either substituting an aryl halide for the alkenyl halide or conversely using an aryl organometallic in place of the corresponding alkenyl species. For example, arylmagnesium halides can be coupled to alkenyl halides using a variety of nickel(II) species as catalysts (Scheme 15).[26] In general, due to the relatively lower reactivity of vinylmagnesium halides, it is preferable to carry out these coupling reactions as shown, rather than the converse of reacting a vinylmagnesium species with an aryl halide. An exception to this could be with examples where the alkenyl function is highly substituted as, in general, it is better to use the Grignard reagent derived from the more sterically crowded partner in this type of coupling. A recent specific example of the utility of this general method is the elaboration of 2-arylallylamines (**68**) from arylmagnesium bromides (**66**; Ar = *m*- and *p*-$MeOC_6H_4$, -FC_6H_4 and -ClC_6H_4) and the vinyl chloride (**67**).[73] An additional key feature in the success of this method is the use of the Magnus stabase function ($Me_2Si(CH_2)_2SiMe_2$) to protect the amino group. Using these conditions, aryl Grignard reagents also couple in a regiospecific manner with β-halovinyl ethers (*e.g.* Scheme 16; silyl enol ethers[76] can also be used).[74] It should be noted that a variety of vinylic ether and sulfide groups can also be directly displaced by aryl Grignard and other organometallic species using nickel catalysts. For example, enol ethers (*e.g.* **69**) and phenylmagnesium bromide (**70**) react together in the presence of the usual type of nickel catalyst to give substituted styrenes (*e.g.* **71**) in >70% yields.[75] However, such coupling reactions are limited to relatively simple substrates as the reactions are rather sensitive to steric effects; enolates and enamines fail to react in a similar fashion. However, silyloxy groups in simple *O*-silyl enolates, *e.g.* (**72**), can be displaced by phenyl groups in the same way (PhMgBr, $[NiCl_2(PPh_3)_2]$) to give styrenes, *e.g.* (**73**), with a high degree (92%) of stereochemical retention,[76] while a method related to this and previously applied to butadiene synthesis (*vide supra*) consists of coupling lithium diarylcuprates with enol triflates (**74** → **75**).[48] In much the same way, enol phosphate groups can also be displaced (*e.g.* **76** → **77**) using an aryl Grignard reagent and $[NiCl_2(DPPE)]$ as catalyst.[77] This type of coupling can also be carried out in the reverse sense by reacting aryl phosphates (**78**), which are readily available from the corresponding phenol, with alkenylaluminums and using $[Ni(acac)_2]$ as catalyst.[78,94]

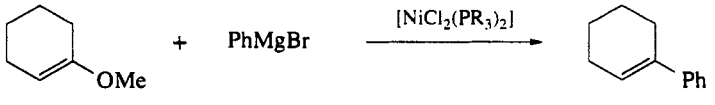
The sulfur function in vinyl sulfides can be displaced in the same manner, using Ni or Pd catalysts, and the methodology has been extended to tandem couplings using 1-bromo-2-phenylthioethene (Scheme 17).[79] The regioselectivity of the first step is exactly as that observed with the corresponding β-bromovinyl ether (Scheme 16).[74] In just the same way the 1,1-disubstituted alkene (**79**) can be converted into



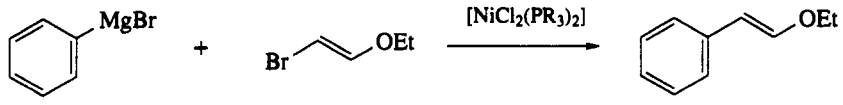
Scheme 15



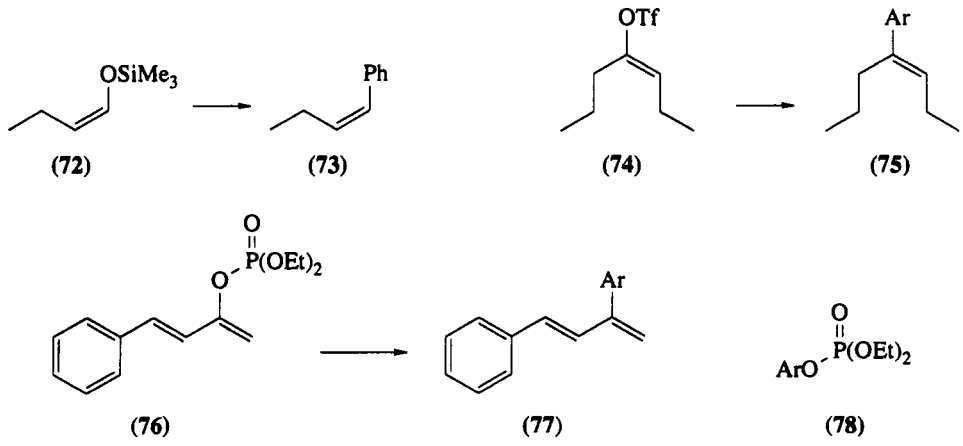
(66) **(67)** **(68)**



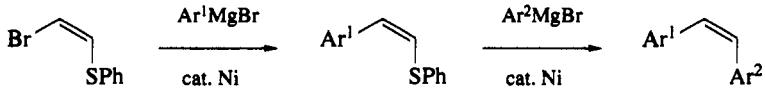
(69) **(70)** **(71)**



Scheme 16

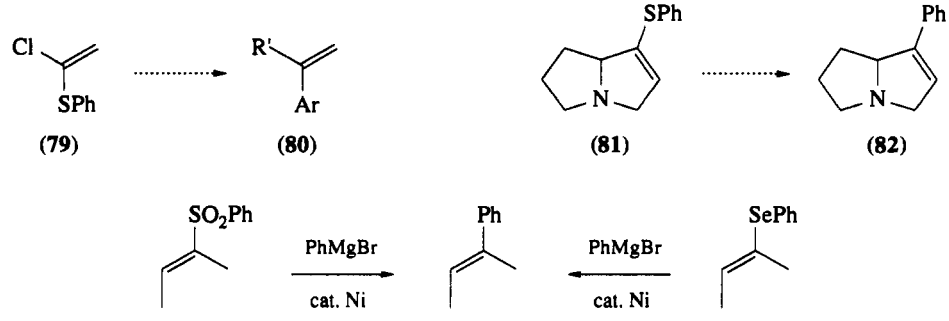


the derivatives (**80**);[29] although the whole sequence can be carried out in one pot, overall yields are higher if the intermediate vinyl sulfide is isolated. A recent application of this methodology has been in the homologation of the pyrrolizidine sulfide (**81**) to the phenyl-substituted alkaloid (**82**) using PhMgBr–$[NiCl_2(PPh_3)_2]$, usually the catalyst of choice for this type of displacement.[80] Vinyl sulfones[81] and vinyl selenides[82] also undergo such displacement reactions with aryl Grignard reagents; with the former substrates, the reactions proceed with complete retention of stereochemistry using either nickel or iron catalysts, while the latter reactions require the use of excess (*e.g.* 2.5 equiv.) aryl Grignard reagent and use Ni^{II}–phosphine complexes as catalysts. Both sequences afford good to excellent yields, at least for the relatively simple examples studied (Scheme 18).



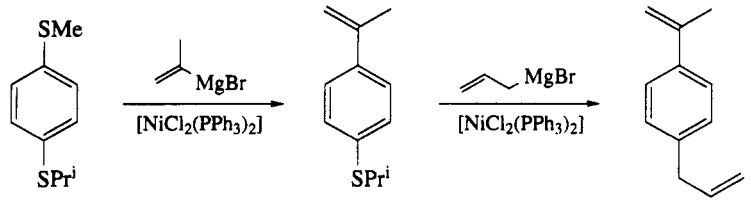
Ar^1, Ar^2 = Ph, naphthyl

Scheme 17



Scheme 18

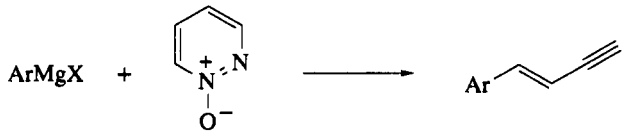
The sulfide displacement method has also been carried out successfully in the opposite sense (*cf.* Scheme 17), wherein aryl sulfides are reacted with vinylmagnesium halides, as well as with a variety of other Grignard reagents, using a nickel catalyst.[83] In examples with bis-sulfides, a high degree of regioselectivity is observed if the sulfur groups are differentially substituted, the less-hindered reacting much faster (Scheme 19).



Scheme 19

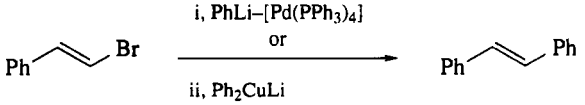
Despite the great preponderance of nickel(II) catalysts used in the foregoing methods, aryl Grignard reagents and alkenyl halides have been successfully coupled using other catalysts, most notably examples of iron(III) complexes, including $FeCl_3$,[84] $Fe(acac)_3$[84] and $Fe(DBM)_3$ [tris(dibenzoylmethido) iron(III)].[85] Yields are often not as good as with the nickel catalysts, but the relative cheapness of these reagents could be an advantage.

An entirely different method for effecting, overall, an sp^2–sp^2-coupling of aryl Grignard reagents is by reaction of the latter with pyridazine *N*-oxide (Scheme 20).[86] In the simple cases studied, yields of enynes were 52–77%. The possibility of applying this approach to more highly substituted substrates does not appear to have been examined.

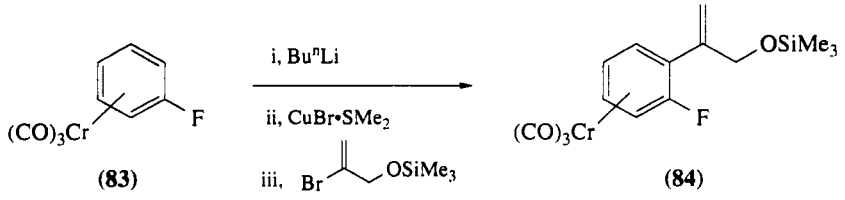


Scheme 20

Aryllithium species can also be efficiently coupled with alkenyl halides (Scheme 21) but using a palladium(0) catalyst (usually $[Pd(PPh_3)_4]$) or a related rhodium species; in general, nickel catalysts are not suitable for couplings involving organolithiums.[36] The reactions have a broad scope, within the limitation of providing protection for groups sensitive to organolithium species, and are generally very efficient and essentially stereospecific (*cf.* Scheme 15).[26] A way in which the requirement for an expensive catalyst can be avoided is to couple an alkenyl halide with a lithium diarylcuprate directly (Scheme 21).[87] The addition of various ligands, such as LiBr or Bu^n_3P, and the correct choice of solvent are all necessary considerations if high yields are to be obtained using this method. In view of its greater simplicity, the ArLi–Pd^0 combination is probably the method of choice. However, the latter method has been put to good use in the homologation of arylchromium complexes (**83**) to substituted styrene complexes (**84**), which are useful as benzofuran precursors.[88]



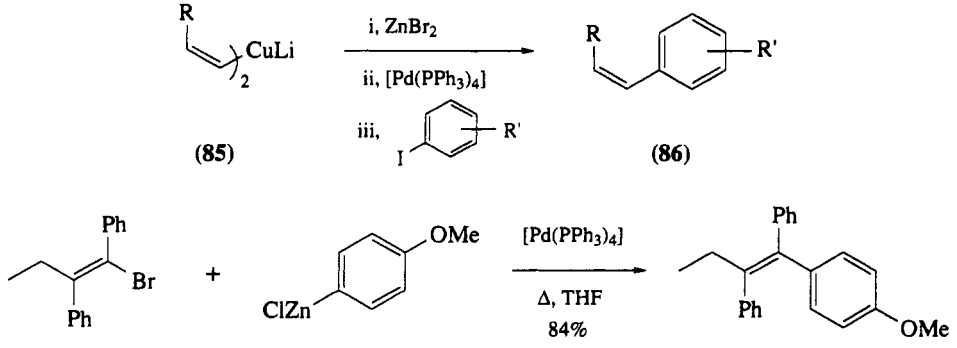
Scheme 21



(83) **(84)**

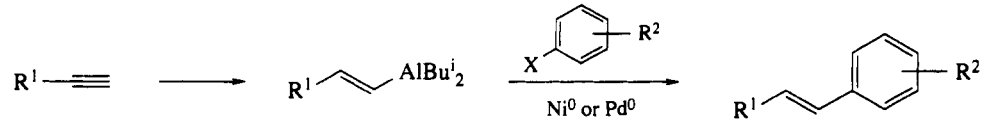
A combination of the foregoing methods has been used to obtain (*Z*)-styrenes (**86**) by the alternative approach of employing an alkenyl organometallic, initially a divinylcuprate (**85**) derived by addition of R_2CuLi to acetylene.[89] In contrast to the foregoing methods involving aryl organometallics, the aryl ring in the product (**86**) can be substituted by a wider variety of functional groups, including Br, OMe, NO_2 and CO_2Me. This procedure is also useful for the synthesis of conjugated dienes[34,35] and is notable for its

stereospecificity and efficiency, in that both alkenyl groups in the precursor (**85**) are utilized. However, there can sometimes be problems in forming this latter species cleanly and avoiding further addition of acetylene to give a bis(dienyl)cuprate species. Not surprisingly in view of the foregoing, alkenylzinc species,[37–39] directly generated by H/Li exchange and transmetallation ($ZnCl_2$), undergo smooth coupling with aryl iodides using [$Pd(PPh_3)_4$] as catalyst. Conversely, arylzinc chlorides can also be linked to alkenyl bromides (Scheme 22), again using a Pd^0 catalyst.[49,90] A notable feature of this example is the highly substituted nature of the alkenyl bromide. Usually, it is better to convert the more crowded partner into the initial organometallic species,[26] although in this case the success of the scheme probably reflects the higher reactivity of arylzinc species.[40]



Scheme 22

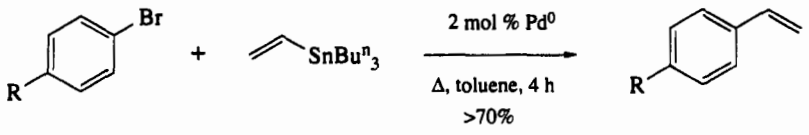
Both Ni^0 and Pd^0 catalysts induce the coupling of alkenylaluminum reagents to aryl halides (Scheme 23),[40,91] an approach which has been employed in an alternative synthesis, in a converse manner, of tetrasubstituted alkenes of the type shown in Scheme 22.[92] One limitation with this approach is the lack of flexibility in the available stereochemistries of the alkenylaluminum species; usually only the (*E*)-isomer is readily available. In just the same way, alkenylzirconium species, obtained either by hydrozirconation or the addition of R_3Al–Cl_2ZrCp_2 to a terminal or symmetrical internal alkyne, can also be coupled with aryl iodides using either Ni^0 or Pd^0 catalysts,[43,44] to give styrene derivatives in generally excellent yields. With hindered examples, the addition of zinc chloride is essential if good yields are to be obtained and in extreme cases, it has been recommended[44] that the best tactic may be to convert a hindered alkenylaluminum species into the corresponding alkenyl iodide (I_2) and then couple this with an organometallic species.



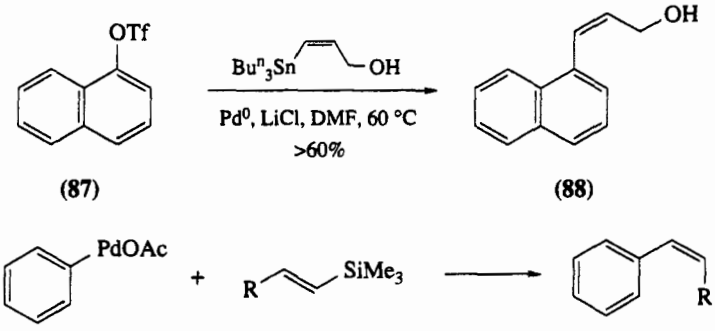
Scheme 23

Palladium(0)-catalyzed coupling of alkenyl halides with vinylstannanes[54,55] also constitutes a useful approach to styrenes (Scheme 24);[93a] a particularly attractive feature of this method is the toleration of a wide variety of substituents on the aromatic ring which include methoxy, nitro and bromide as well as unprotected carbonyls, acetate and 1,3-dione functions. One small limitation is that the reaction fails when free amino groups are present. β-Silylvinylstannanes can also be used, leading to β-silylstyrenes.[93b] A valuable extension to this method is the finding that aryl triflates, *e.g.* (**87**), can also be coupled to vinylstannanes to give generally excellent yields of arylalkenes (*e.g.* **88**).[94] Closely related to similar couplings of vinyl triflates[48–53] and of arylphosphates,[78] such reactions are mild (dioxane or DMF, <100 °C) and widely applicable, although the stereochemical integrity of the vinylstannane is not always preserved. An alternative approach to less readily available (*Z*)-arylalkenes is by palladium-catalyzed coupling reactions between aryl bromides and (*E*)-vinylsilanes,[95] which proceed with overall inversion (Scheme 25).[96]

In the same manner that various alkenylboron species can be coupled with alkenyl halides,[57–65] so too can aryl halides be homologated to styrenes (Scheme 26).[60,97] In general, such reactions require a Pd^0 catalyst and the presence of a base, such as sodium ethoxide, in order to achieve this type of head to head coupling.[59] In sharp contrast, mainly head to tail products are formed when a weak base, such as triethyl-

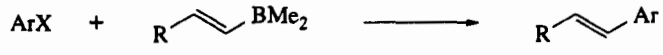


Scheme 24

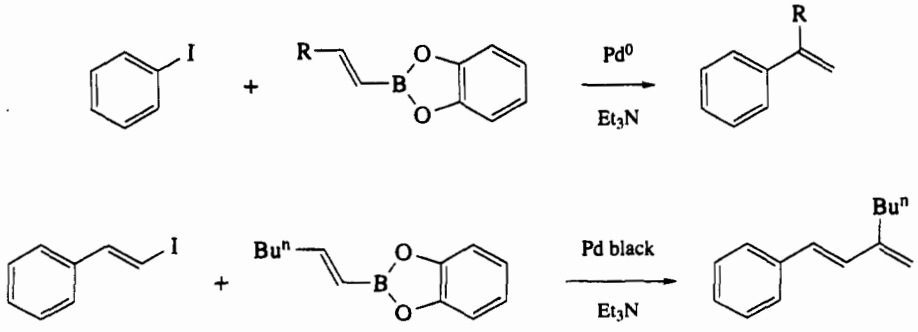


Scheme 25

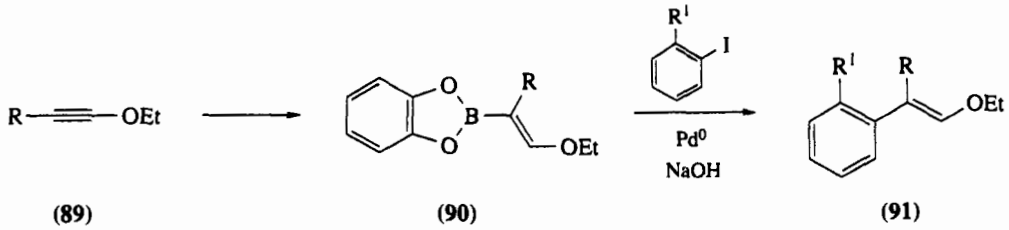
amine, is used in place of ethoxide in such reactions with alkenylboronates (Scheme 27).[98] A particularly attractive route to (*Z*)-styrenes, as well as to arylbutadienes, is by reaction between an aryl halide and a (*Z*)-alkenylboronate (*cf.* Scheme 14);[64,65] similar reactions using (*Z*)-alkenylboranes are generally much less satisfactory. Using standard Suzuki-type conditions ([Pd(PPh$_3$)$_4$], NaOH), the β-ethoxyboronates (**90**) derived from the corresponding ethoxyalkyne (**89**) and catecholborane, also couple smoothly with aryl iodides to give excellent yields of substituted styrenes (**91**).[99]



Scheme 26



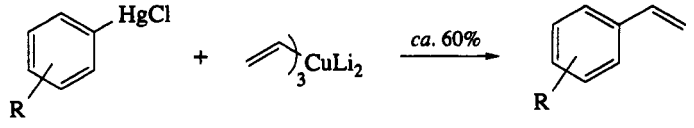
Scheme 27



(89) **(90)** **(91)**

R = *n*-alkyl; R^1 = OR^2, NR$^2_2$, X

As in some examples of the synthesis of conjugated dienes,[56] arylmercuric chlorides (**92**) react directly with vinylcuprates (**93**) (other stoichiometries are less satisfactory) to give substituted styrenes (**94**).[23] A number of relatively sensitive functions, such as CO_2Me, can be present on the aryl ring. An alternative method for the direct coupling of alkenyl iodides to mercurals (**92**) is to heat the two together in HMPA containing lithium chloride and Wilkinson's catalyst [$RhCl(PPh_3)_3$]; unfortunately, (*Z*)-1-alkenyl iodides give largely (*e.g.* 3:1) the (*E*)-substituted styrene.[23,100]



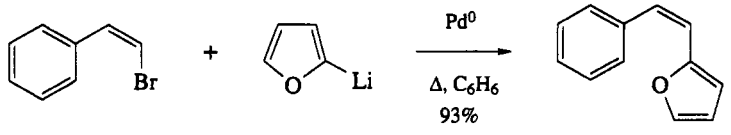
(**92**) (**93**) (**94**)

Another useful approach to styrenes *via* sp^2–sp^2-coupling reactions, which is beyond the scope of this section, is Meerwein-type arylations in which aryldiazonium salts undergo usually copper(I)- or palladium-catalyzed couplings with electron deficient alkenes, indicating a radical-based mechanism.[101] The method is also useful for the synthesis of stilbenes from unsubstituted styrenes[102] or β-silylstyrenes.[103]

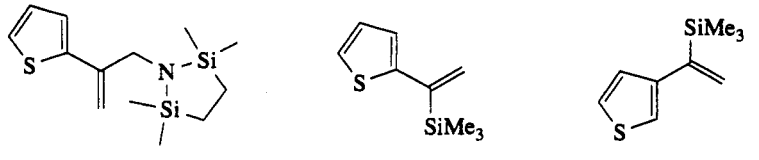
2.3.2.5 Alkene–Heteroaryl Coupling

Not surprisingly, much of the methodology suitable for alkene–aryl coupling is also applicable to the elaboration of conjugated alkenyl heteroaromatic systems. In many cases, both types of reaction, either between an alkenyl organometallic and an aryl halide or *vice versa*, are possible, with the optimum pathway often dependent on the relative substrate availability. Although many of the examples involve only the simplest of heteroaromatic compounds, such as 2-furyl- or 2-thienyl-lithium or the corresponding bromides, the mildness of the procedures and their generality in other areas strongly suggests that they should be applicable to the synthesis of many, more complex, targets.

2-Furyl- and 2-thienyl-lithium reagents undergo smooth Pd^0-catalyzed coupling with alkenyl bromides (Scheme 28); yields are generally excellent, as is the degree of stereochemical retention.[36] The method would certainly not be applicable to the corresponding 3-lithio species which undergo ring opening at well below the reaction temperature. 2-Thienyllithium can also be coupled to the vinyl chloride (**67**) using a nickel catalyst, [$NiCl_2$(DPPP)], to give the vinylthiophene (**95**) (*cf.* **67** → **68**).[73] In related work, access to the 2- and 3-vinylthiophenes, (**96**) and (**97**), has been shown to be possible by coupling a Grignard species with the appropriate bromide or, in the latter 3-substituted case, specifically by reaction between 3-bromothiophene and the alkenylmagnesium bromide in the presence of the palladium catalyst [$PdCl_2$(DPPB)].[104]



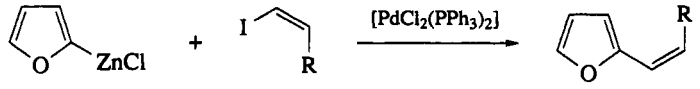
Scheme 28



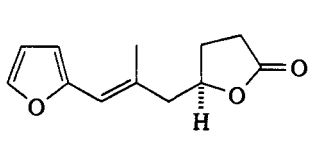
(**95**) (**96**) (**97**)

As mentioned in the foregoing sections, some of the most suitable intermediates for sp^2–sp^2-coupling reactions are alkenyl- or aryl-zinc species. In general, these species tend to be relatively the most reactive in such Pd- or Ni-catalyzed reactions and often lead to the highest yields.[40] For example, 2-furylzinc chloride reacts smoothly and efficiently with a range of alkenyl iodides (Scheme 29)[105] and this method has been used to prepare the Lophotoxin intermediate (**98**) in 70% yield.[106] Such coupling reactions can also be catalyzed by [$Pd(PPh_3)_4$] and can be carried out in either sense; thus the thienyldihydronaphthalene (**99**) has been obtained both from 2-thienylzinc bromide or from the corresponding alkenylzinc

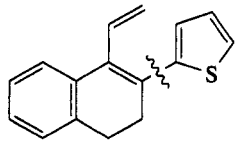
bromide and 2-iodothiophene.[39] Similarly, a variety of fluorinated vinylzinc chlorides can be reacted with a range of iodinated heteroaromatics to give the expected vinyl derivatives (*e.g.* **100**, from 2-iodopyridine and $CF_2CHZnCl$).[107] Vinylpyridines, *e.g.* (**101**), can also be obtained from alkenylalanes (prepared from terminal alkynes using Me_3Al–Cl_2ZrCp_2)[40] and bromopyridines using a Pd^0 catalyst.[40]



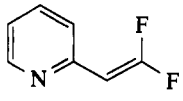
Scheme 29



(98)



(99)



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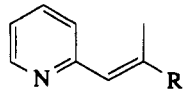
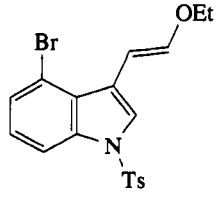
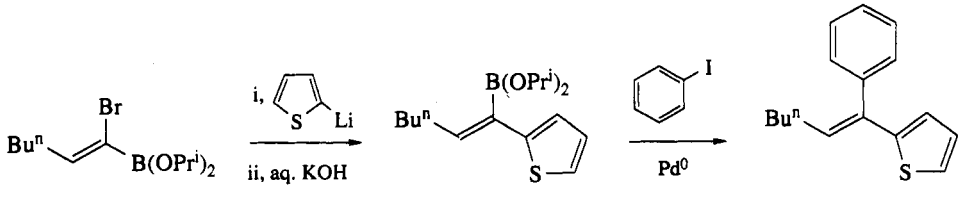


(101)

A variety of methods have been examined for the preparation of the vinyl ether homolog (**102**) of the corresponding 4-bromo-3-iodoindole.[108] Clearly, relatively unreactive species were required which would not displace the 4-bromo atom. The best approach was found to be a Negishi-type Ni^0-catalyzed coupling with an alkenylzirconium species obtained by hydrozirconation of ethoxyacetylene using Schwartz's reagent.[42] Other procedures such as Pd-catalyzed coupling reactions with alkenylboranes[99] or Heck-type reactions were less successful. However, related organoboronates have been found to be very suited as intermediates for the elaboration of trisubstituted alkenes *via* sp^2–sp^2-coupling reactions.[65] For example, formation of an 'ate' complex using 2-thienyllithium and the boronate (**103**), derived from 1-bromo-1-hexyne, followed by base-induced migration leads to the vinylboronate (**104**), and, thence to the alkene (**105**) following Pd^0-catalyzed coupling[59,64,98,99] with iodobenzene (Scheme 30). The overall yield in this particular case was 94% of material with >97% isomeric purity. Related isomers can be obtained by using an iodothiophene in the last step. Coupling reactions in the reverse sense, between pyridylboranes and vinyl bromides, also catalyzed by zerovalent palladium species, have been used to obtain a series of vinylpyridines.[109] Heteroaromatic mercurals can also be coupled directly to alkenyl halides, but using Wilkinson's catalyst.[100]



(102)



(103) **(104)** **(105)**

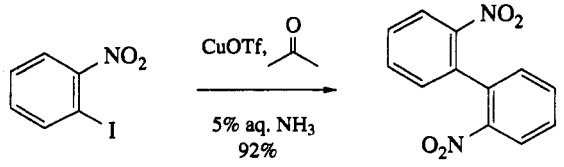
Scheme 30

2.3.3 ARYL–ARYL COUPLING REACTIONS

2.3.3.1 Aryl–Aryl Dimerization

Within the confines of equation (1), the most extensively studied and exploited methodology for the elaboration of symmetrical biaryls is the classical Ullmann reaction,[110] which is usually defined as the copper-mediated coupling of aryl halides (equation 3). The types of copper used in the older literature are copper powder itself, copper bronze[111] or copper(I) oxide, although this latter reagent is often more suited[112] to the Ullmann biaryl ether synthesis from phenols and aryl halides. The most common solvents employed are pyridine, quinoline, DMF and tetramethylurea (for reactions requiring higher temperatures than DMF[113]); temperatures of up to 260 °C have been used with success in examples involving robust substrates and such couplings can also be effected without the use of a solvent in sealed tubes. Rather more recent methods for obtaining activated copper reagents include pretreatment of the copper powder by EDTA[114] and generation of copper powder by zinc reduction of copper(II) sulfate[115] or by reduction of copper(I) iodide using potassium naphthalenide.[116] These methods, especially the latter, produce highly activated material which can allow Ullmann couplings to be conducted at lower temperatures. One of the mildest reagents discovered is copper(I) triflate in association with 5% aqueous ammonia in acetone or acetone–acetonitrile mixtures.[2,117,118] For example, 2-iodonitrobenzene (**106**) is converted into biphenyl (**107**) at 20 °C in just 5 mins. Unfortunately, other substrates often take an alternative pathway consisting of replacement of the halide by NH_2 or OH; thus methyl 2-iodobenzoate is transformed largely into methyl salicylate.

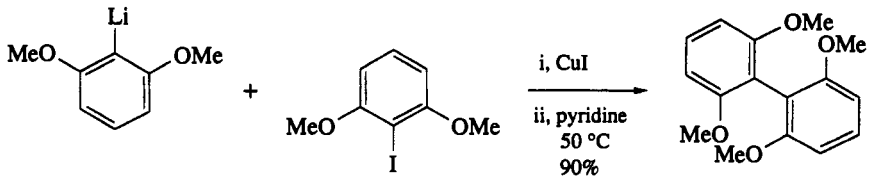
$$Ar{-}X \xrightarrow{\text{'Cu'}} Ar{-}Ar \qquad (3)$$



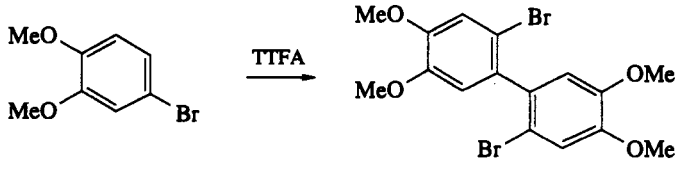
(106) **(107)**

The mechanism of Ullmann couplings most likely proceeds *via* discrete arylcopper species[1,110] and it is therefore not surprising that preformed arylcopper species can be used in such reactions, for which DMF rather than pyridine or quinoline is often the preferred solvent.[119] Arylcopper reagents can be generated by direct lithiation followed by Li/Cu exchange as exemplified by the facile synthesis of a tetramethoxybiphenyl (Scheme 31).[120,140] This type of approach is especially useful for sterically crowded cases, where the classical Ullmann approach (equation 3) fails,[121] and also for the elaboration of fluorinated biphenyls using pentafluorophenylcopper.[122] Such couplings are not limited to Li–Cu systems; oxidative couplings of both aryllithiums and arylmagnesium halides can be achieved using a variety of copper, cobalt, chromium, iron and manganese salts.[5,7,128] Silver salts, in the presence of a nitrogen-containing oxidizer, such as $LiNO_3$ or $MeNO_3$, are particularly effective in dimerizations of aryl Grignards,[7] which can also be carried out using thallium(I) bromide.[123] This latter method is relatively mild and high yielding although some drawbacks, beyond the need to protect Grignard-sensitive groups, include failure in attempted couplings of *ortho*-substituted Grignards and reagent toxicity, as excess of the thallium salt is usually required. Direct dimerizations of electron rich arenes, such as examples containing alkoxy groups, can be smoothly carried out using thallium tris(trifluoroacetate) (TTFA) in carbon tetrachloride or acetonitrile containing boron trifluoride etherate.[124] In general, classical Ullmann-type dimerizations are less satisfactory with electron rich substrates; a further bonus of the TTFA method is that halogen atoms are preserved (*e.g.* Scheme 32), allowing further manipulation of the initial biphenyl. Palladium(II) acetate can also be used as a catalyst in this type of coupling,[125] which is also especially suitable for the synthesis of binaphthyls and in intramolecular coupling reactions (Section 2.3.3.3).[140]

Many substituents are tolerated during classical Ullmann couplings. Nitro (*e.g.* **106** → **107**) and alkoxycarbonyl functions strongly activate the reactions when these groups are positioned *ortho* to the reaction site, but not when they are *meta* or *para*. Alkyl and alkoxy groups can activate from all positions, although with polysubstituted examples, excessive electron donation can be deleterious.[124] Ullmann couplings are not especially sensitive to steric effects, but are usually inhibited by the presence in either reactant of free OH, CO_2H or NH_2 groups. Fortunately, these can all be readily masked (and sub-



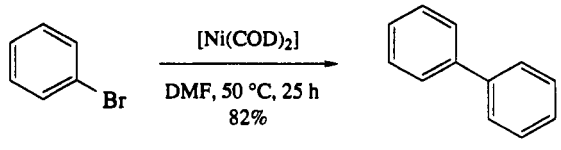
Scheme 31



Scheme 32

sequently easily deprotected) by trimethylsilylation[126] or, in the case of phenolic functions, by mesylation.[127]

A major advance on the traditional Ullmann method (equation 3) was made in the early 1970s, when Semmelhack and his coworkers discovered that Ni^0 species could be used in place of elemental copper.[128] The original complex used was bis(1,5-cyclooctadiene)nickel(0) which, as an indication of the much greater mildness of this and related procedures, affords an 82% yield of biphenyl from bromobenzene at 50 °C in DMF (Scheme 33). The limitations associated with nickel-based approaches are similar to the Ullmann reaction in that free hydroxy groups (OH, CO_2H) prevent coupling, although the former method does sometimes suffer more from the steric effects of *ortho* substituents, two of which usually prevent reaction entirely. The toleration of methoxy, methoxymethyl, ester and especially formyl groups renders this general approach more attractive than ones based on aryllithium or Grignard intermediates (*vide supra*). Subsequent developments have essentially been aimed at discovering alternative nickel catalysts to $[Ni(COD)_2]$ which do not require dry box techniques, *etc.* Successful examples include triphenylphosphine–Ni^0 complexes generated by zinc reduction of the corresponding nickel(II) chloride,[18] a process which can be catalytic in nickel[129] and which is promoted by the addition of various salts (*e.g.* KI,[129] NaI[130]) and of 2,2′-bipyridine[130] to such an extent that aryl chlorides can be coupled without excessive heating (65–80 °C), and aryl iodides coupled at room temperature.[129] Similar species derived by reduction of bis(trialkylphosphine)nickel(II) dichlorides[19] or from the related system ($NiBr_2$–Zn–HMPT–KI)[131] also lead to high yields of symmetrical biaryls under mild conditions. A full report from Semmelhack's research group indicates that $[Ni(PPh_3)_4]$ is a good reagent both for this type of coupling and especially for intramolecular versions.[132] Aryl triflates can also be dimerized using a nickel(0) catalyst similar to some of the foregoing examples generated *in situ* from nickel(II) chloride and zinc powder, in the presence of triphenylphosphine and sodium iodide.[133] A relatively large excess of the latter reagents is required and rates are considerably enhanced by sonication. Yields are generally above 80% with *ca.* 10% of the deoxygenated arene being formed as a by-product.



Scheme 33

In just the same way that vinylstannanes can be dimerized, (**11**) → (**10**), aryltri-*n*-butylstannanes react rapidly (10–30 min) with hydrated copper(II) nitrate in THF at 20 °C to afford high yields of biaryls,[15] although once again, *ortho* and especially bis-*ortho* substituents inhibit the coupling.

Biaryls can also be derived (70–90%) from mercury salts, ArHgX, using methodology very similar to a normal Ullmann coupling (copper powder, pyridine, reflux), except that a catalytic amount of $PdCl_2$ is also required.[23,134] Less basic solvents do not lead to such good yields, but otherwise the reaction charac-

teristics are very similar to the Ullmann method except that free amino groups can be present. Related procedures can also be used to extrude elemental mercury from diarylmercurals, Ar_2Hg, to give biaryls.[23,110] Excellent yields of biaryls can also be obtained from dimerizations of arylmercuric salts using a rhodium catalyst, $[Rh(CO)_2Cl]_2LiCl$, or stoichiometric amounts of Li_2PdCl_4.[24]

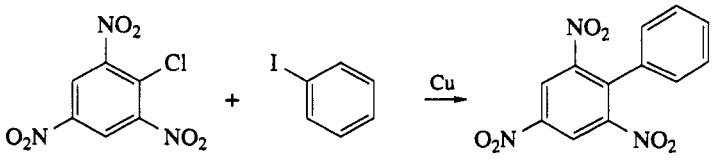
Palladium, in the form of palladium(II) acetate, has also been used to catalyze biaryl formation directly from aryl iodides (R_3N; 100 °C), especially *p*-NO_2 and *p*-Cl derivatives. As usual, *ortho* substituents severely hinder this type of coupling.[135] Related reductive couplings of aryl halides have been achieved using hydrazine and a Pd–Hg catalyst,[136] electrochemically generated Pd^0 catalysts,[137] or a palladium on carbon catalyst in the presence of aqueous sodium formate, sodium hydroxide and, crucially, a catalytic amount of a surfactant.[138] The first two procedures look to be particularly selective and efficient, while the latter, rather different, method is not so efficient but does look amenable to large scale work.

Symmetrical biaryls can of course also be prepared using methods designed for the elaboration of unsymmetrical biaryls, by a judicious choice of substrate.

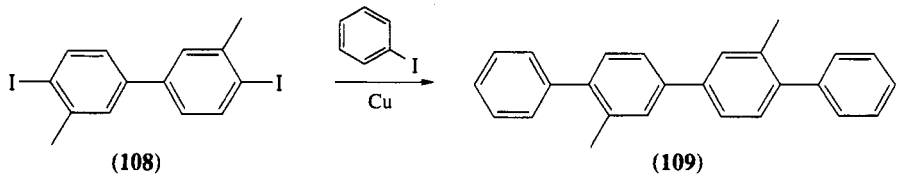
2.3.3.2 Crossed Aryl–Aryl Coupling

The standard Ullmann methodology can be applied to examples where sufficient differences exist between the two reactants that the desired crossed product is formed most rapidly. Usually, electronic factors are the most useful in this respect as in the example shown (Scheme 34), wherein one component is extremely electron deficient at the site of coupling.[110] Two such coupling reactions can also be viable as shown by a preparation of the tetraphenyl (**109**) from the biphenyl (**108**); despite a lowish yield (43%), this is still a rapid and efficient route to such compounds.[110] Quite complex biphenyls can be made in this way, given a sufficient electronic and reactivity (I > Br > Cl) difference. Thus, a good combination is the iodide of the more electron rich component, which will presumably form an arylcopper species more rapidly, and the bromide of the more electron deficient partner (Scheme 35).[127] This and the following example further exemplify the relative insensitivity of such couplings to steric crowding. An additional tactic for such reactions is to use a large excess of unactivated copper powder and a reaction temperature which is lower than that required for self-coupling of the less reactive component. The excess copper results in much shorter reaction times (Scheme 36),[139] even with such crowded substrates. Despite these successes, an obvious drawback with such reactions is the often very high temperature required. This can be circumvented by using the method of Ziegler and coworkers in which a preformed arylcopper, having the copper atom ligated both by triethyl phosphite and the lone pair of a substitutent atom, couples at below ambient temperature with an *o*-iodobenzaldehyde imine; an example (Scheme 37) is an approach to steganone.[140] In addition to the low temperature, once again steric hindrance is not a problem, which is certainly not the case with many of the related transition metal catalyzed processes using Ni^0 or Pd^0 catalysts, for example. The method is also very useful for the dimerization of *o*-bromobenzaldehydes, and in general appears to be the method of choice for obtaining this type of highly substituted biphenyl, given that a suitable ligand is present in the *ortho* position.

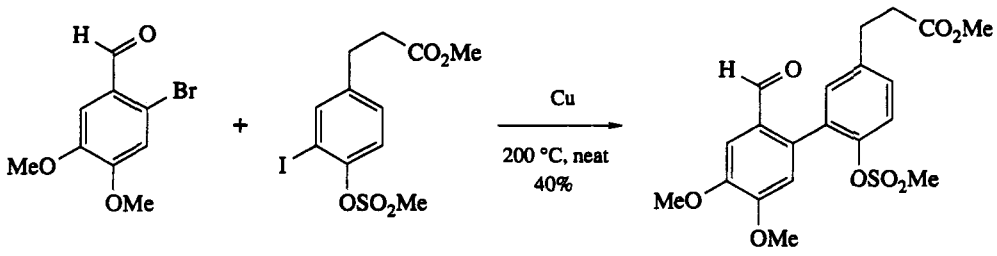
A less general but related method for obtaining 2,6-dinitrobiphenyls consists of metallation of 2,6-dinitrobenzene using copper(I) *t*-butoxide in a mixture of pyridine and DME followed by coupling with an



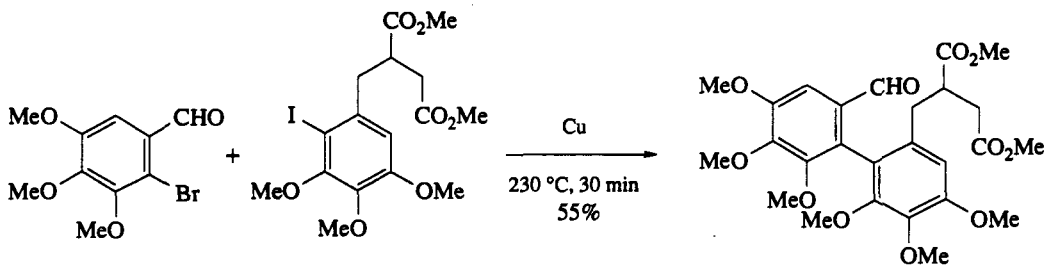
Scheme 34



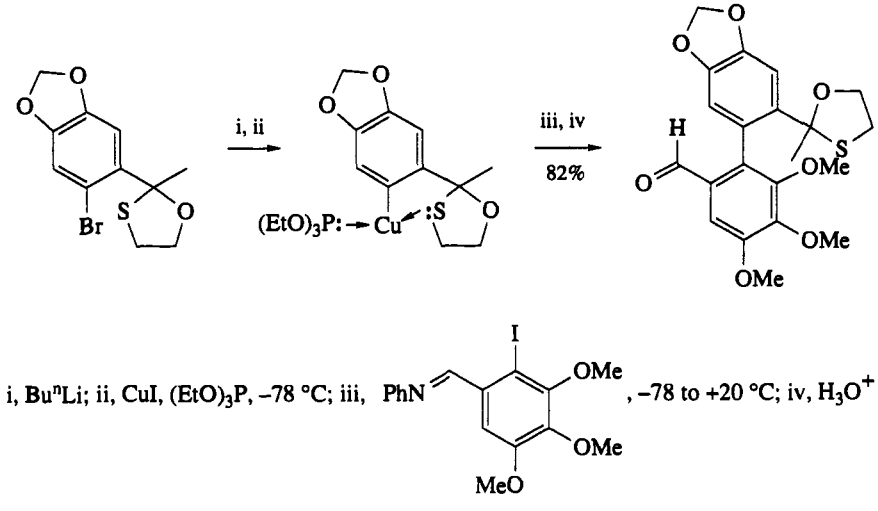
(**108**) (**109**)



Scheme 35

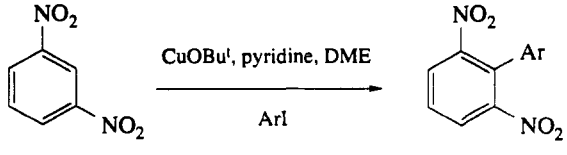


Scheme 36



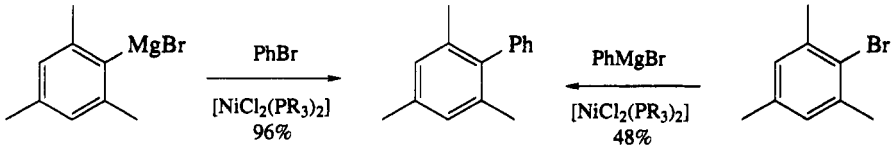
Scheme 37

iodoarene (Scheme 38).[141] Yields are generally in the range 50–95%. As would be expected from the foregoing discussion[140] (*cf.* Scheme 21), lithium diarylcuprates in general couple with iodoarenes to give good yields, at least in sterically unencumbered examples of unsymmetrical biaryls, given an appropriate additive (*e.g.* LiBr or Bu^n_3P) and solvent.[87]

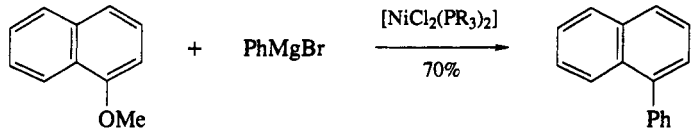


Scheme 38

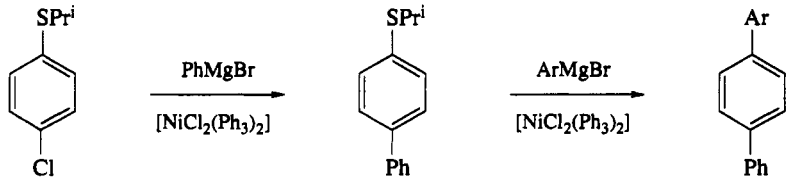
The by now well-established nickel-catalyzed procedure for coupling Grignard reagents with alkenyl and aryl halides (equation 2 and Scheme 15) is also highly suitable for biaryl synthesis, except in examples where both of the substrates have *ortho* substituents. In cases where one component does carry *ortho* substituents, it is preferable to generate the Grignard from this component, rather than the converse (Scheme 39).[26] In addition to the Tamao–Kumada catalysts, $[NiCl_2(PR_3)_2]$, a wide range of other nickel catalysts can also be used[142,143] and sequential replacement of two halogens in a dihaloarene is also possible.[143] Unsymmetrical 1,1′-binaphthyls can be prepared similarly in a procedure which is greatly facilitated by the application of ultrasound.[144] Full details of a related coupling (not sp^2–sp^2) using the Tamao–Kumada method have been given which will be of use to those wishing to use these procedures.[145] The same type of catalyst can also be used to induce the displacement of aryl methoxy groups (*cf.* **69** → **71**) by Grignard reagents.[75] As expected, this type of coupling (Scheme 40) can suffer from steric effects. Sulfide groups can be displaced similarly[29,79] by arylmagnesium bromides; a particularly attractive feature of this chemistry is its application to terphenyl synthesis by sequential introduction of two different aryl groups to a chlorophenyl alkyl sulfide (Scheme 41).[146] Presumably a wide variety of combinations of both alkenyl[29,79] and aryl groups could be introduced by this methodology, which is also applicable to both *o*- and *m*-chlorophenyl sulfides.



Scheme 39



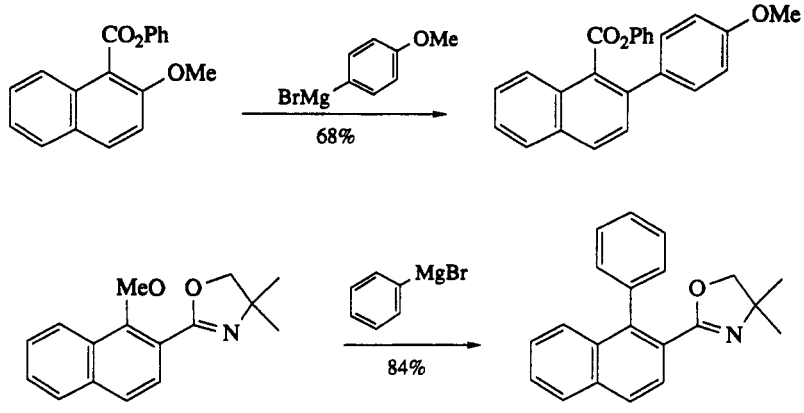
Scheme 40



Scheme 41

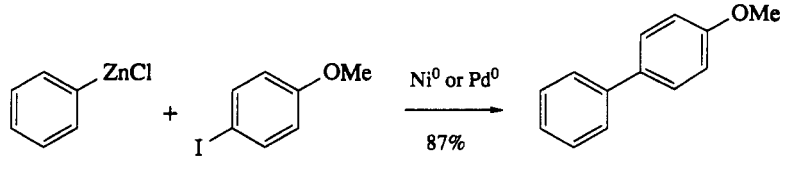
Often, reactions catalyzed by nickel species can also be effected using closely related palladium compounds; this is certainly the case with cross-coupling reactions between aryl Grignard reagents and aryl halides, which can be effected using a variety of palladium catalysts.[147] These reactions often show greater selectivity than the related nickel catalysts in, for example, couplings between ArMgX and 4-bromo-1-chlorobenzene, where the more reactive bromo substituent is displaced. A more recent study has shown that this approach is particularly suitable for the elaboration of polyoxygenated biphenyls.[148] An important feature of the chemistry of aryl Grignard reagents, which should be noted when contemplating the use of this type of coupling, is that such species are capable of directly displacing methoxy groups adjacent to electron-withdrawing functions; indeed such reactions constitute a rapid and simple entry into a variety of substituted biphenyls and binaphthyls (Scheme 42).[149] In general, poorer yields are obtained using the corresponding aryllithium species.

The Negishi method for coupling alkenyl- or aryl-zinc halides to sp^2-centers[37–40,90] can equally well be used to obtain biphenyls (Scheme 43).[150] This excellent method, in which the arylzinc species is usually generated by transmetallation of the corresponding aryllithium, has been described in graphic detail.[151] Related coupling reactions can also be achieved by using an arylstannane in place of an arylzinc species.[152] A special case of this type of reaction is useful for the elaboration of phenylaryls by transfer



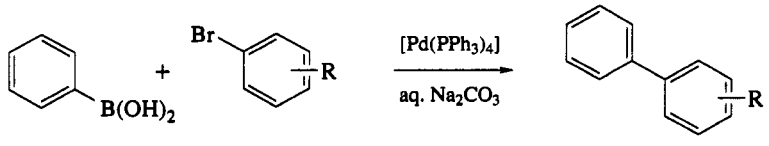
Scheme 42

of one (only) phenyl ligand from tetraphenyltin to an aryl halide using a palladium(II) catalyst.[153] Of potentially more general use is the finding that, under the influence of a Pd^0 catalyst, an aryl group can be transferred selectively from an aryltrialkylstannane to an aryl triflate; yields of biaryls are generally high, at least in the relatively simple cases so far studied.[94]

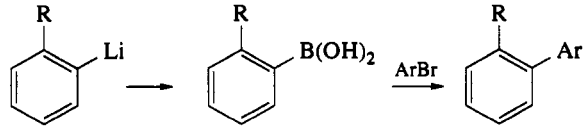


Scheme 43

The Suzuki method, using alkenylboronic acids as intermediates,[60–63,97] can also also be applied with great effect to the synthesis of biaryls (Scheme 44).[154] Yields are generally excellent and either aryl bromides or iodides (but not chlorides) can be used. Methoxy, methoxycarbonyl and nitro functions at least do not interfere and the method seems to be relatively insensitive to steric factors; furthermore catalyst levels as low as 3 mol % are adequate. A useful combination for the elaboration of substituted biaryls and higher homologs is the *o*-lithiation methodology, due mainly to Snieckus and coworkers, followed by Suzuki-type coupling (Scheme 45).[155] A good method for formation of the intermediate boronic acid species proceeds *via* sequential *o*-silylation (TMS-Cl) and *ipso*-boro-desilylation using boron tribromide. A simple hydrolytic work-up using 5% aqueous HCl then delivers the boronic acid.



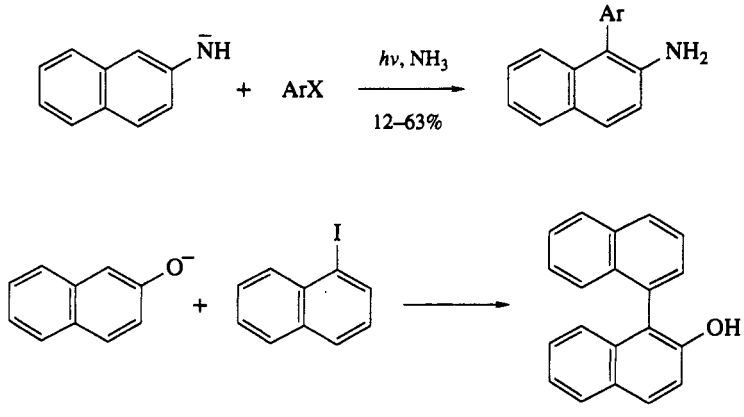
Scheme 44



R = $OCONEt_2$; $CONPr^i_2$; OMOM; $NHCO_2Bu^t$

Scheme 45

Although not strictly belonging to the class of reactions indicated in equation (1), a number of other approaches to biaryls are worth noting as these can be very useful in some circumstances. For example, reactions proceeding *via* $S_{RN}1$ mechanisms can be especially useful for the introduction of aryl groups at positions adjacent to either amino[156] or hydroxy[157] functions (Scheme 46). The latter type of transformation can also be effected using triphenylbismuth carbonate[158] or other pentavalent bismuth species.[159] Aryllead triacetates [$ArPb(OAc)_3$] are also useful for aromatic arylation reactions, especially with electron rich substrates.[160] A classical method for biaryl synthesis, again somewhat outside the scope of this chapter, consists of basification of an aryldiazonium salt in the presence of a second aryl component, often benzene itself. Variously referred to as the Gomberg, Gomberg–Bachmann or Gomberg–Bachmann–Hey process,[161] this and related free radical type methods[162] give only moderate yields of biaryls, but at least they are generally simple reactions to carry out. Also closely related is the Meerwein arylation procedure,[101] wherein aryldiazonium species are coupled with aryls usually using copper(II) salts as catalysts. In general, the reactions work well only with electron poor substrates. A more recent development with the Gomberg reaction is the possibility of using phase transfer conditions resulting in considerable increases in yields relative to the classical methods.[163] The method is, however, still largely limited to the elaboration of relatively simple 2- and 4-monosubstituted biaryls. Related alternatives include the photolysis of aryl iodides in an aromatic solvent[164] or similarly of arylthallium trifluoroacetates; this latter method often delivers yields in excess of 80%, although it is rather limited to relatively simple products.[165] Many of the above methods are perhaps more suited to intramolecular biaryl formation.

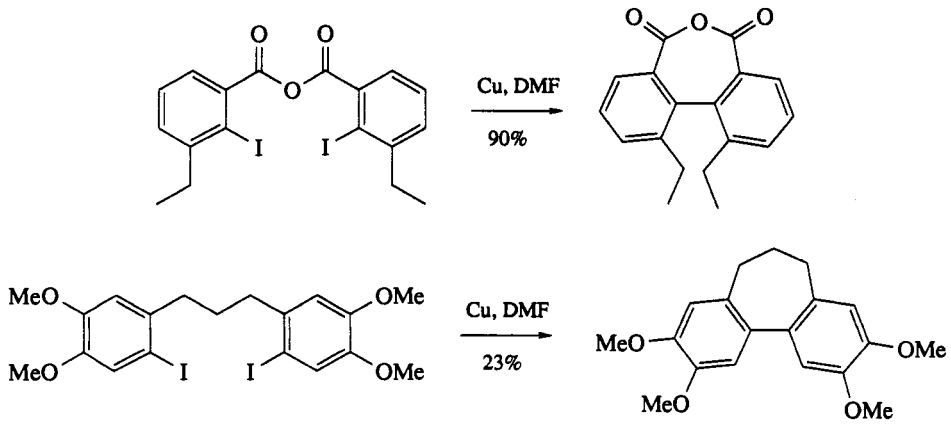


Scheme 46

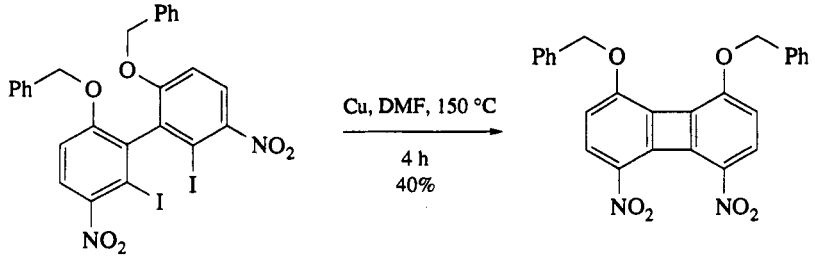
2.3.3.3 Intramolecular Aryl–Aryl Coupling

The classical Ullmann procedure[110] has often been applied to ring closure reactions by formation of an aryl–aryl bond. In general, yields are much higher when electron-withdrawing groups are positioned *ortho* to the halogen atoms, which should be iodine rather than bromine (Scheme 47). Similar conditions (Cu bronze, reflux in DMF) can also be used to close a four-membered ring in respectable yield (Scheme 48). As with the intermolecular version, it is often preferable to use one of the usual copper reagents rather than copper(I) oxide.[166] At the other end of the scale, both 12- and 24-membered rings have been formed from substituted 1,1′-binaphthyls using this methodology, although in rather poor yields (*ca.* 10%).[167] Identical types of substrates can be cyclized under somewhat milder conditions by using conditions developed by Semmelhack and his coworkers, in which $[Ni(PPh_3)_4]$ is used in place of copper powder.[132] This methodology has been elegantly illustrated in the natural product area by syntheses of the alnusone precursor (**110**) and the erythrina alkaloid skeleton (**111**; Scheme 49), although it is not suitable for syntheses in the steganone area (*vide infra*), possibly indicating a sensitivity to excessive steric crowding. Copper-mediated intramolecular coupling reactions of Grignard reagents[5] have also found occasional use in this area, as illustrated by a preparation of the 14π-aromatic system (**112**; Scheme 50).[168] The much lower temperatures required in this case are a particularly attractive feature. Similarly, aryllithium species can be coupled intramolecularly using copper salts; the particular example shown (Scheme 51) affords a 53% yield of the dimeric product, accompanied by only 3% of the monomeric dibenzocyclobutane.[5] More recently, palladium(II) catalysis has been found to be particularly effective for the ring closure of a monobromo precursor (Scheme 52).[169] The product (**113**), an advanced precursor of the un-

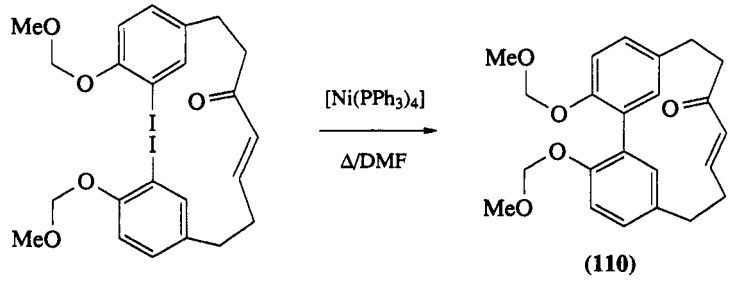
usual isoquinoline alkaloid ancistrocladine, is formed with reasonable stereoselectivity being accompanied by *ca.* 25% of the alternative diastereoisomer.



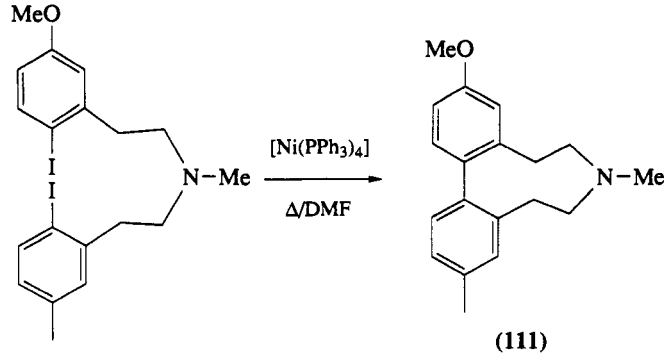
Scheme 47



Scheme 48

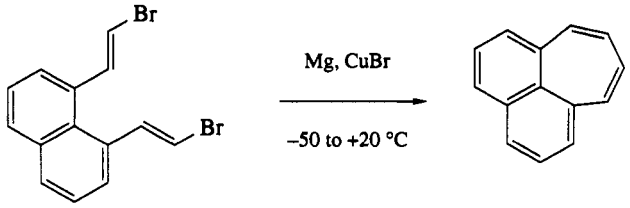


(110)



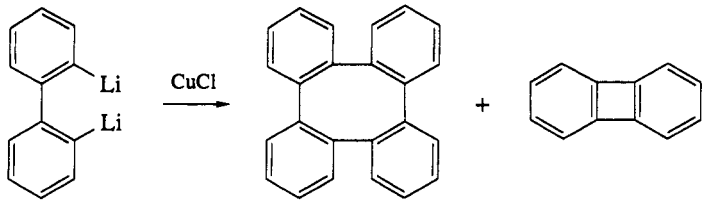
(111)

Scheme 49

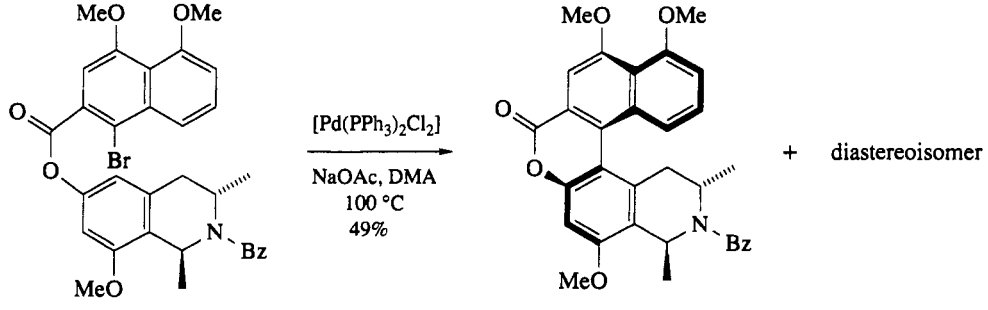


(112)

Scheme 50



Scheme 51

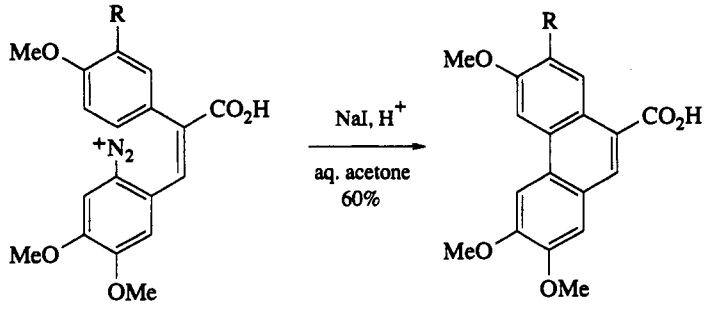


(113)

Scheme 52

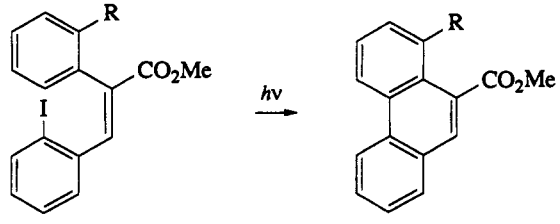
In spite of the foregoing methods however, many of the most useful ring closure reactions of this type tend to involve either radical or aryl cationic intermediates. Although beyond the formal scope of this review, a brief survey is included here for the sake of completeness. A classical method is the Pschorr ring closure (Scheme 53), essentially an intramolecular version of the Gomberg–Bachmann–Hey process,[161,162] which can be triggered using the usual Gomberg conditions (*i.e.* basification) or by Meerwein-type arylation procedures by treatment with Cu^I salts.[170] The poor yields which usually result from Pschorr closures have meant that the method does not enjoy a particularly prominent position in synthesis. However, one area where the reaction is particularly useful is in phenanthrene synthesis, especially when carried out under modified conditions. For example, when sodium iodide rather than a copper reagent is used, respectable yields can be realized (Scheme 54),[171] while a further improvement is to position a phenylsulfonyloxy function *para* to the site of attack (Scheme 54; R = OSO_2Ph).[172] A related photochemical cyclization of aryl iodides, the intramolecular version of methodology discussed above,[164] is also effective both for phenanthrene synthesis (Scheme 55)[173] and also for the elaboration of some alkaloid ring systems (Scheme 56).[174] Closely related to this is the overall oxidative ring closure between two unsubstituted positions by photolysis in the presence of iodine; the particular example shown (Scheme 57)[175] constitutes a key step in a synthesis of the natural alkaloid cryptopleurine. Indeed, some of the most useful methods in this area, especially for the elaboration of polymethoxylated natural products having at least one oxygen function *para* to the site of coupling (*cf.* Scheme 57), involve direct cyclization of substrates having no substituents at the two carbon sites to be coupled. In this respect, a combination of thallium(III) trifluoroacetate (TTFA) and boron trifluoride etherate is especially useful and has been used, for example, to prepare the biphenyl (**114**) from the unsubstituted precursor, in 81% yield, and aporphine (**115**), in 46% yield.[124] Similar nonphenolic oxidative couplings using vanadium(V)

Scheme 53

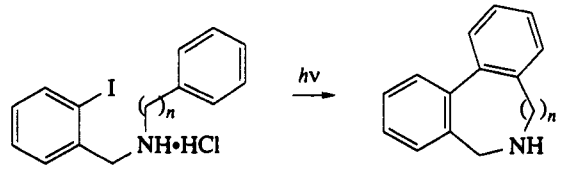


R = H

Scheme 54

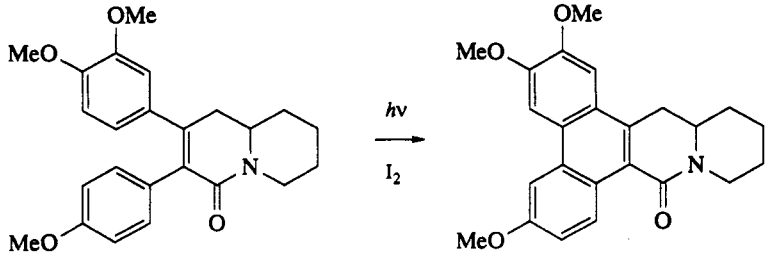


Scheme 55



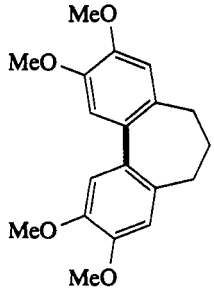
n = 1, 57%; *n* = 2, 25%

Scheme 56

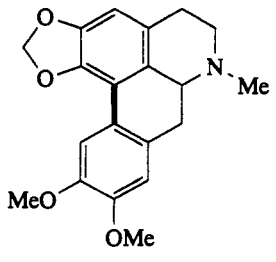


Scheme 57

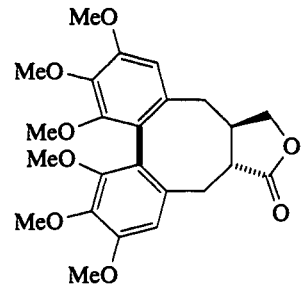
oxyfluoride generally produce lower yields than TTFA.[176] Subsequently, ruthenium(IV) tetrakis(trifluoroacetate) (RUTFA) has been found to be especially useful for carrying out such couplings in the steganane area.[177] The reagent is prepared from ruthenium dioxide, TFA–TFAA and boron trifluoride etherate and is said to be generally superior to TTFA; a particularly impressive example is a preparation of the highly crowded steganane (**116**) in 90–95% isolated yield using RUTFA at ambient temperature. The reagent is also useful for aporphine synthesis (*cf.* **115**).



(114)



(115)

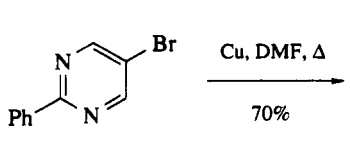


(116)

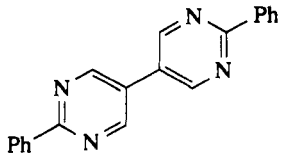
2.3.4 COUPLING REACTIONS INVOLVING HETEROARYLS

2.3.4.1 Heteroaryl–Heteroaryl Coupling

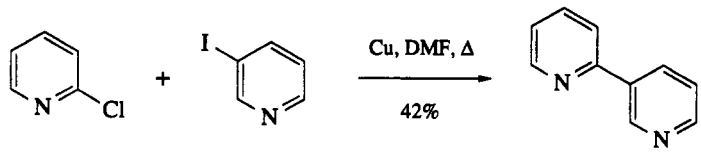
Not surprisingly, many of the methods described above are equally well-suited to the coupling of heteroaromatic intermediates. The Ullmann method[110] can be applied successfully to the dimerization of haloheteroaromatics (*e.g.* **117** → **118**) and to some cross-coupling reactions, where the reactivity differences[139] are sufficiently large (*e.g.* **119** → **120**). In general, this method is, however, less satisfactory when applied to five-membered heteroaromatics, although the intramolecular version has been used to prepare derivatives of this group (*e.g.* Scheme 58). Intermolecular dimerizations of furans and thiophenes are more efficiently carried out *via* the corresponding chloromercury derivatives, when the addition of catalytic amounts of palladium(II) chloride to a typical Ullmann system is particularly beneficial (Scheme 59).[23,134] The corresponding heteroaryllithium species can also be dimerized by treatment with a variety of transition metal salts.[5] The intermediacy of carbanions and the rather harsh Ullmann conditions can be avoided by direct coupling of heteroaryl halides using a variety of nickel(0) species. Although the earlier Semmelhack reagent, $[Ni(COD)_2]$, does not appear to be particularly suitable,[128] bis(trialkylphosphine)nickel(0) species can give rise to excellent yields (*e.g.* Scheme 60).[19] In this particular case, an anionic intermediate would normally be precluded due to facile ring opening. This approach is also successful with similar coupling reactions of halothiophenes but fails with halopyridines. However, both of the latter substrate types can be dimerized using catalytic nickel salts in the presence of triphenylphosphine and a reducing metal such as zinc or magnesium.[130] An arylnickel(I) complex may well be involved. Such a system has been found to be superior to Ullmann-type methods in a synthesis of the mushroom toxin orellanine (Scheme 61).[178] An excellent alternative is the system NaH–Bu^{t}ONa–$Ni(OAc)_2$–PPh_3 which gives high yields of homocoupled products from chloro- or bromo-pyridines and -quinolines under mild conditions (DME, 30–60 °C, 1.5–3.5 h).[179] It has been established for some time that the parent of this class, 2,2′-bipyridyl, can be prepared directly from pyridine by oxidative coupling using Raney nickel;[180] much better yields are obtained by heating 2-bromopyridine or simple alkyl derivatives with stoichiometric quantities of Raney nickel in toluene.[181,196] Electrochemically generated palladium(0) species can also be used for the very efficient homocouplings of bromopyridines.[137]



(117)

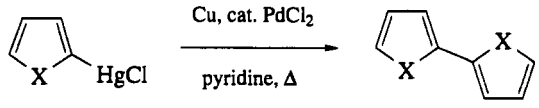


(118)



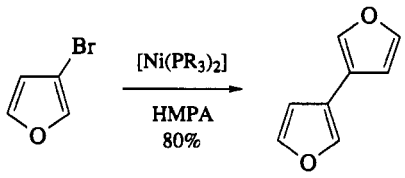
(119) **(120)**

Scheme 58

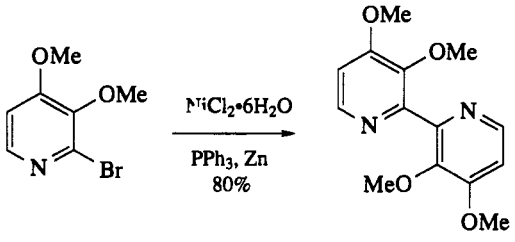


X = O, 86%; X = S, 95%

Scheme 59



Scheme 60

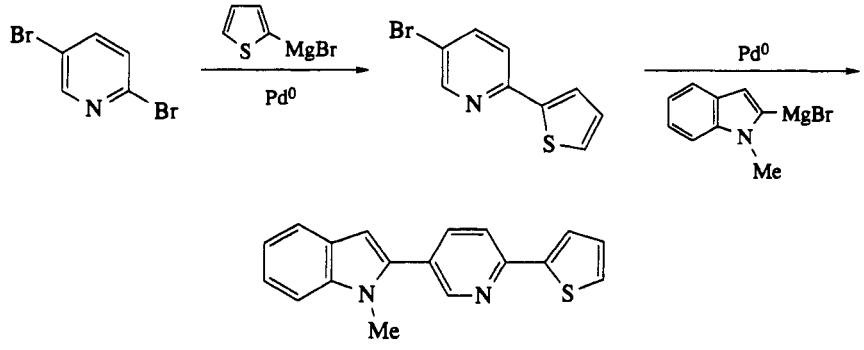


Scheme 61

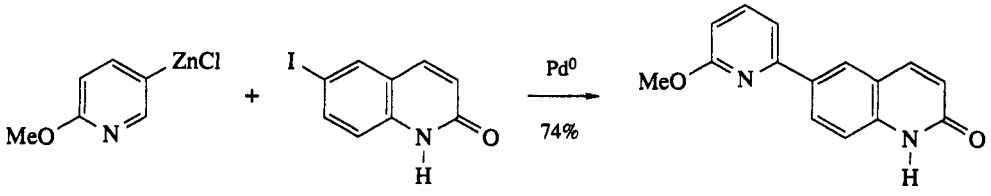
Unsymmetrical bipyridyls can be readily obtained, although in variable yields (14–75%), by direct coupling reactions between pyridyl Grignard reagents and pyridyl sulfoxides.[182] A more versatile type of reaction of heterocyclic Grignard reagents is their palladium(0)-catalyzed coupling reaction with heteroaryl halides.[183,206] As well as being useful for the elaboration of a wide variety of unsymmetrical dimers, a whole range of oligomers can also be prepared using this methodology by, for example, sequential coupling with a heterocyclic dihalide, in which the two halogens have different reactivities (Scheme 62). A particularly good alternative to this procedure is the closely related Negishi method, wherein arylzinc species (derived from the corresponding aryllithium or aryl Grignard) undergo Pd^0-catalyzed coupling reactions with aryl halides (Scheme 63).[184] The method is applicable to both 2- and 3-pyridylzinc chlorides. Even more general, given the availability of the starting materials, is the corresponding coupling reactions between pyridylstannanes and bromopyridines (Scheme 64).[185] Also applicable to quinolines and presumably many related systems, the method has one significant drawback, that of the requirement for lengthy heating (*ca.* 12 h) in xylene. Chloropyridines are inert, which should allow some useful regioselective couplings to be carried out; furthermore two groups can be added at once, as in the conversion of the distannylpyridine (**121**) into the tripyridylnicotelline (**122**). It is prob-

able that this type of coupling between a bromoaryl and an aryltin derivative will be very widely applicable and perhaps the method of choice in very many cases. For example, the 2-stannyloxazole (**123**) has been coupled with a wide variety of heteroaromatic bromides (2- and 3-thienyl, -furyl, -pyridyl and -quinonyl, 2-bromothiazole) to give excellent yields of the expected derivatives (**124**),[186] while a whole range of symmetrical and unsymmetrical thiazoles have been similarly prepared (Scheme 65).[187] However, another excellent route to unsymmetrical heterobiaryls, which also relies on a palladium(0) catalyst, is the Suzuki method,[58–66,97–99,154,155] wherein a heteroarylboronic acid is coupled with a heteroaryl halide.[188,212] Sequential additions of two aryl ligands to trialkoxyboranes can be used to obtain boronate species, which then collapse to give biaryls upon treatment with bromine or NBS; the methodology affords a variety of yields and is generally most suited to heteroaryl–heteroaryl coupling.[189]

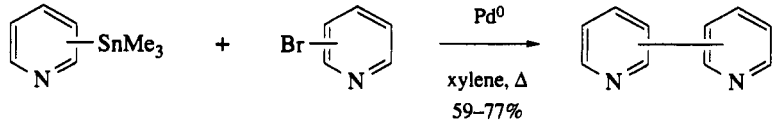
Although beyond the scope of this section, some related approaches to these compounds are worth mentioning. 2-Substituted pyridines and quinolines can be obtained in two steps from the parent compounds following nucleophilic attack by an aryllithium (*e.g.* 2-thienyllithium) and then oxidation.[190] Intramolecular oxidative coupling reactions between the 2-positions of two indole nuclei can be achieved using DDQ, in the presence of a trace of tosic acid.[191] A very efficient route to a variety of unsymmetri-



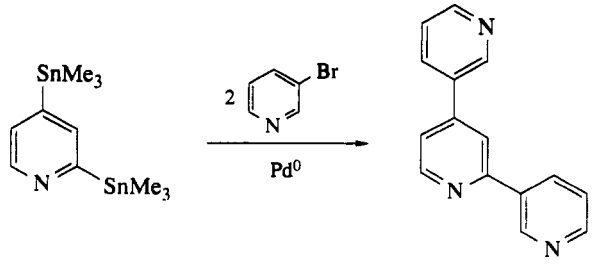
Scheme 62



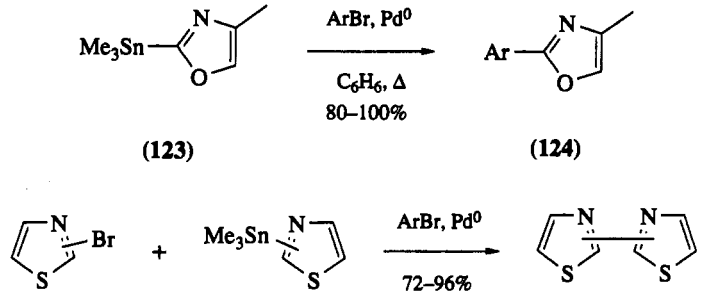
Scheme 63



Scheme 64



(121) **(122)**



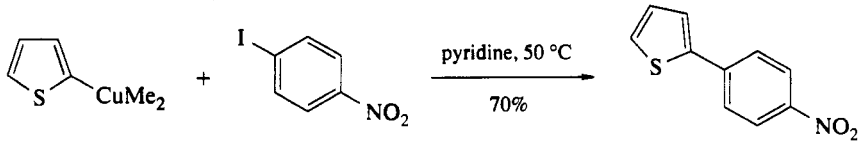
Scheme 65

cally substituted bithiophenes is by photolysis[164] of an iodothiophene in the presence of an excess of an α-unsubstituted thiophene.[192,213] Finally, a wide variety of Gomberg–Bachmann–Hey processes have been used to prepare biheterocyclic systems.[162]

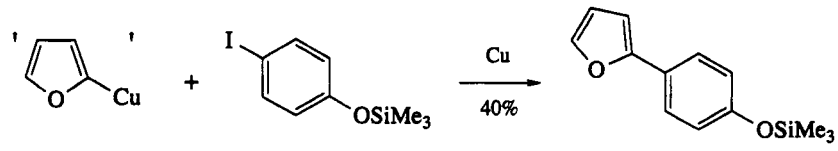
2.3.4.2 Aryl–Heteroaryl Coupling

Almost all of the foregoing methods which can be used to prepare unsymmetrical biaryls or biheteroaryls have been, or probably could be, applied to the elaboration of targets belonging to this section. Given sufficient reactivity differences[139] between the two components, Ullmann-type coupling[110] can be one of the simplest and most efficient methods in this area. 2-Substituted thiophenes are particularly suitable adducts (Scheme 66),[193] whereas 2-furylcoppers are not such good substrates,[194] although the convenience could sometimes outweigh the relative inefficiency (Scheme 67).[126] Good yields (50–80%) of 2-arylpyridines (**125**) can also be obtained by the Ullmann approach from 2-pyridylcopper species and aryl halides, but using rather different conditions consisting of heating the reactants together with triphenylphosphine in toluene, rather than the more usual basic solvent.[195] In general, 2-arylpyridines (**125**) are among the most accessible of this group as they can be obtained by direct nucleophilic attack by aryllithiums or Grignard reagents at the 2-position of a pyridine nucleus, followed by a facile oxidation back to the aromatic level. For example, reaction between phenyllithium and 2,2′-bipyridyl in ether affords a 54% yield of the 2-phenyl derivative (**126**) after oxidation.[196] Similarly, reaction with 2-lithiopyridine leads to the expected terpyridine.[197] More highly substituted pyridines can be obtained from similar reactions with stannylated pyridinium salts (Scheme 68).[198] The bulk of the tin substituent directs the incoming nucleophile and hence the tricyclohexylstannyl derivative is preferred. The intermediate stannyldihydropyridine can be easily acylated using an acyl chloride and a palladium catalyst and finally oxidation, using *o*-chloranil, regenerates the pyridine nucleus. Similarly, pyridine *N*-oxides can be converted to 2-arylpyridines (**125**) by reaction with arylmagnesium bromides followed by acetylation (Ac_2O) and spontaneous elimination of acetic acid.[199] Alkoxysulfonyl groups in the 2-position of a pyridine nucleus can be displaced by aryllithiums, leading directly to 2-arylpyridines (**125**) in good to excellent yields;[200] halopyridines can undergo similar couplings.[201] A related approach to 4-arylpyridines relies on activation of the 4-position by an adjacent oxazoline function;[149] attack by phenylmagnesium bromide, or better phenyllithium, leads to a dihydropyridine and thence to the corresponding pyridine (**127**), following oxidation.[202] Presumably, other aryl- and heteroaryl-lithiums could also be used. Activation of the usually nucleophilic 3-position of an indole to nucleophilic substitution can be achieved by formation of the iodonium species (**128**) which upon reaction with phenyllithium, in the presence of boron trifluoride etherate, leads to 3-phenylindole (**129**) in 62% yield.[203]

In common with much of the foregoing chemistry, some of the most flexible and versatile methods in this area are based on nickel- or palladium-catalyzed coupling reactions between organometallic species

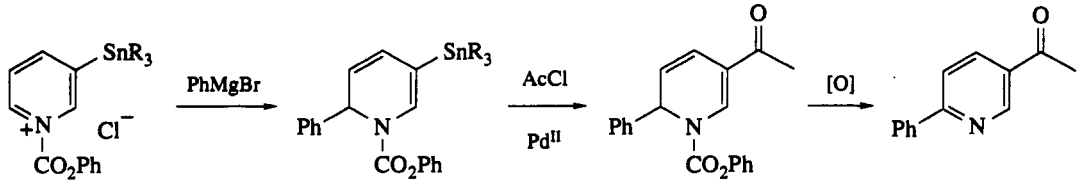


Scheme 66

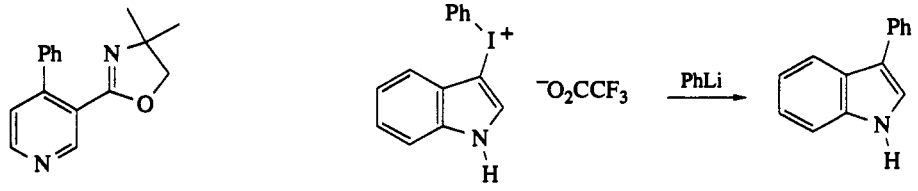


Scheme 67

(125) **(126)**



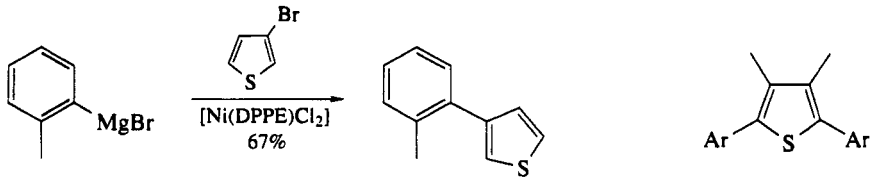
Scheme 68



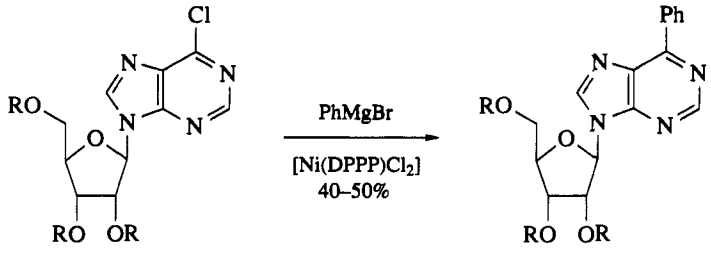
(127) **(128)** **(129)**

and aryl halides. Particularly useful in this respect are nickel(II)-catalyzed couplings involving arylmagnesium halides;[26] for example, Grignard reagent (**130**) can be coupled to 3-bromothiophene to give the arylthiophene (**131**) in 67% yield.[204] Double couplings can similarly be carried out, as in the case of a preparation of the diarylthiophene (**132**) from the corresponding 2,5-dibromothiophene and 2 equiv. of an arylmagnesium bromide, which requires only 1 mol % of the catalyst [Ni(DPPP)Cl_2].[205] It is even possible to prepare unsymmetrical derivatives of thiophenes (**132**) by sequential coupling reactions with different Grignard reagents, but using a palladium catalyst in the first step. In addition to bromothiophenes, the methodology can also be extended to chloropyridines and various homologs, such as chloroquinolines,[206] and to the elaboration of nucleoside analogs (**133** and **134**).[207] The nickel-catalyzed displacement of alkylthio groups from sp^2-centers using Grignard reagents[29,79,83,146] has also been used to prepare purine analogs under closely similar conditions, (**135** → **136**);[208] the method can also be applied to highly efficient preparations of 4-phenylpyridines (**137**) and 2-phenylindole (**138**) from the respective 4- and 2-methylthio derivatives.

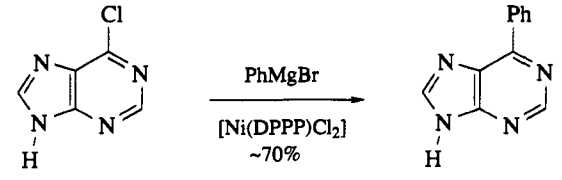
Equally useful palladium-catalyzed coupling reactions between aryl halides and aryl organometallics have been developed, in which the latter component is usually either a trialkylstannane derivative or the corresponding arylzinc chloride species. In contrast to the foregoing nickel-mediated couplings with



(130) **(131)** **(132)**



(133) (134)

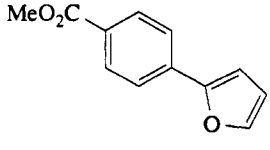


(135) (136)

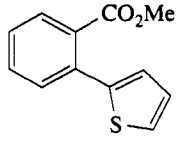
(137) (138)

arylmagnesium halides, the palladium-catalyzed processes often work best when the organometallic component is derived from the heteroaromatic substrate which is then reacted with an aryl halide, usually the bromide or iodide. A study in which compounds (**139**)–(**144**) were prepared in generally excellent yields from the corresponding heteroaryltrimethylstannane and iodobenzene serves to exemplify the potential of this methodology.[209] In all these examples, $[PdCl_2(PPh_3)_2]$ was used as the catalyst; in a related study, coupling between a rather unstable 2-trimethylstannylbenzofuran and a protected iodoresorcinol has been achieved using $[Pd(PPh_3)_4]$, leading to the arylbenzofuran (**145**).[210] In this example, coupling reactions with the tin derivative of the benzofuran were found to be more suitable than either use of the corresponding zinc bromide (*vide infra*) or coupling in the reverse sense, between the 2-bromobenzofuran and an arylzinc bromide. Particularly notable in this type of coupling is the tolerance of a wide range of functional groups, especially esters, acetates, nitriles and chlorines. Further examples of this approach are provided by coupling reactions between the 2-stannyloxazole (**123**) and a range of substituted bromobenzenes, including the 4-F, 4-Me, 4-SPh and 2-CN derivatives.[186] Also, using $[Pd(PPh_3)_4]$ as catalyst, the process is relatively mild (reflux, C_6H_6, 12–24 h) and usually very efficient (80–100% yields), even when a 2-substituent is present. The related procedure wherein arylstananes are coupled with aryl triflates[94] has been applied to an arylheteroaryl example, the alkaloid dubamine (**146**), which was obtained in 79% yield from the corresponding 2-quinolyltriflate and 5-(trimethylstannyl)-1,3-benzodioxole ($[Pd(PPh_3)_4]$, LiCl, dioxane, 98 °C, 68 h); it seems highly probable that this approach will find wide application in the elaboration of substituted heteroaromatics.

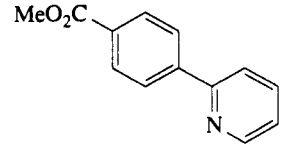
Despite some of the foregoing observations,[210] Negishi-type coupling reactions between furylzinc chlorides and bromobenzenes catalyzed by $[Pd(PPh_3)_4]$ have been found to be valuable for the preparation of arylfurans (Scheme 69).[211] Also applicable to the corresponding thiophenes, a particularly interesting aspect of this chemistry is the coupling of the bis(zinc chloride) (**147**) with 1,4-dibromobenzene,



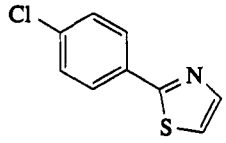
(139)



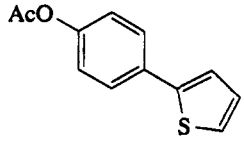
(140)



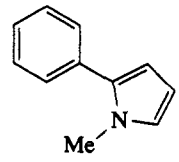
(141)



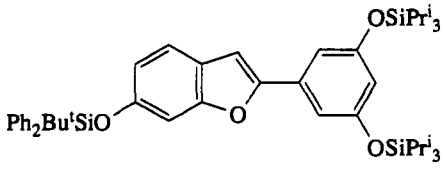
(142)



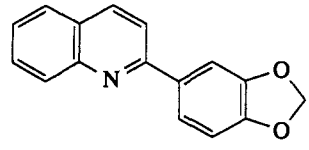
(143)



(144)

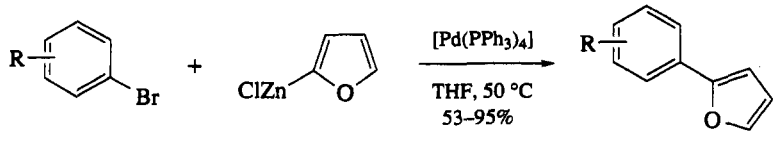


(145)

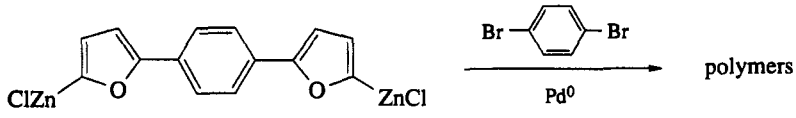


(146)

which gives rise to a series of potentially useful polymers. One or both of the zinc groups in the dianion (**147**) can be replaced by monobromobenzene simply by using 1 or 2 equiv. of the latter.

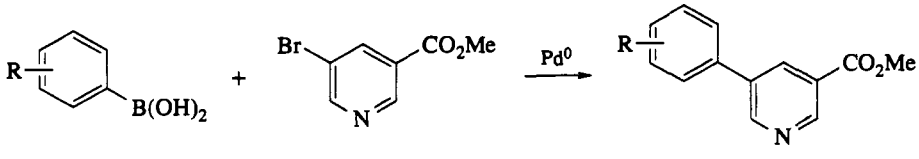


Scheme 69



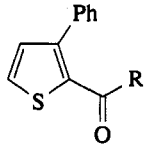
(147)

The Suzuki boronic acid method[58–66,97–99,154,155,188] is also likely to enjoy many applications in this area; one example is a brief and efficient synthesis of 5-arylnicotinates (Scheme 70).[212] One limitation of this approach, however, is its sensitivity to substituents *ortho* to the site of coupling.



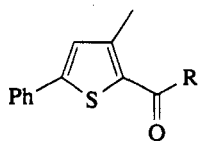
Scheme 70

A simple route to the phenylthienyl ketones and aldehydes (**148**) and (**149**) consists of photolysis of the corresponding bromothienylcarbonyl compounds in benzene,[213] in a similar fashion to the preparation of phenylbenzenes from iodobenzenes[164] and of bithiophenes from iodothiophenes.[192]



(148)

R = H or alkyl



(149)

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2.4
Coupling Reactions Between sp^2 and *sp* Carbon Centers

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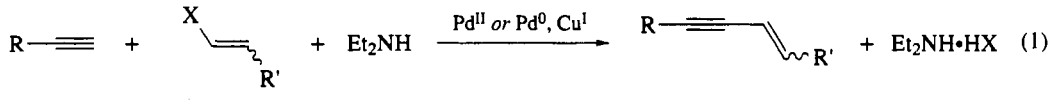
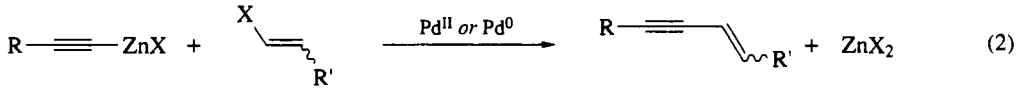
2.4.1 INTRODUCTION

A σ-bond between sp^2- and *sp*-carbon centers can be formed either by vinylation of a 1-alkyne or an organometallic alkynyl, or by alkynylation of a vinyl organometallic reagent.[1–3] Several copper(I) alkynides undergo successful coupling reactions with halogen compounds in which the halogen is linked to an sp^2-carbon center (vinylic, allenic, aromatic and heteroaromatic carbon). In all cases, however, a stoichiometric amount of a copper(I) salt appears to be necessary, which makes the synthesis less attractive for performance on a large scale.[4–6]

During the past 15 years, enormous advances have been made in the area of transition metal mediated reactions in organic synthesis. Two important transition metal mediated reactions are available for the coupling of alkynes with the halogen-bearing sp^2-carbon compounds mentioned above. These are: (i) reaction of the free alkyne with the halide in the presence of a catalytic amount of Pd^0 or Pd^{II} complexes, copper(I) iodide and an excess of an amine; here the amine is not only used as the solvent but also as a scavenger for the hydrogen halides generated during the reaction (equation 1);[7] and (ii) reaction of metallated alkynes, preferably alkynylzinc halides, with the halogen compound in the presence of catalytic amounts of Pd^{II} or Pd^0 compounds (equation 2).[8,9] As usual, the reactivity order with respect to the

halogen bound to the sp^2-carbon is I > Br > Cl[2] and with respect to the sp^2-center is vinylic > allenic > heteroaromatic > aromatic.





2.4.2 CROSS-COUPLING REACTIONS BETWEEN ORGANOMETALLIC REAGENTS AND VINYL, ARYL AND ALKYNYL HALIDES AND RELATED COMPOUNDS

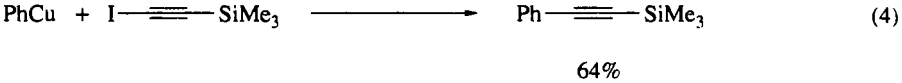
2.4.2.1 Organocopper Reagents

Organocopper and organolithium alkylcuprate reagents are finding ever-increasing usage in organic synthesis. Normally, these reagents are produced from the reaction between an organolithium or Grignard reagent and an appropriate copper(I) salt. Accordingly, the types of functional groups that can be tolerated are rather limited.[4–6] Rieke and his coworkers[10] have reported the preparation of a highly reactive zerovalent copper slurry, which readily undergoes oxidative addition to aryl, vinyl, alkynyl and alkyl halides under mild conditions. The corresponding organocopper reagents are stable and they undergo the usual types of homo- and cross-coupling reactions. Moreover, these reagents can be prepared in the presence of a variety of functional groups such as nitro, nitrile, ester and ketone.

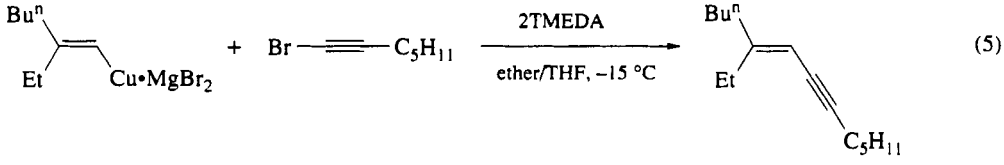
The reaction of aryl halides with copper(I) alkynides is known as the Castro reaction (equation 3).[4] The reaction has proved to be particularly important in the synthesis of a wide range of tolan and heteroaromatic alkynes. Vinyl and allenic halides[11–13] can also be used and several reviews of the reaction have been published.[5,6,14–16]

Aryl and alkenyl copper compounds also couple reasonably well with haloalkynes, leading to conjugated enynes (equations 4 and 5).[17,18] Normant *et al.* have reported that TMEDA is essential to promote the clean coupling of alkenylcopper reagents with 1-halo-1-alkynes (equation 5).[18,19] Alkenylcopper(I) derivatives undergo substitution with retention of configuration about the C—C double bond, leading to conjugated and functionalized enynes. However, Brown and his coworkers have pointed out that the TMEDA is not necessary and is, in fact, detrimental to the desired process.[20] Thus, alkenylcopper intermediates, which are readily generated from alkenylboron derivatives of 9-BBN, undergo coupling with 1-haloalkynes to provide stereodefined conjugated enynes of high isomeric purity and in 90–98% yields (Scheme 1). The same coupling reaction can be catalyzed using bis (acetylacetonate)copper.[21]

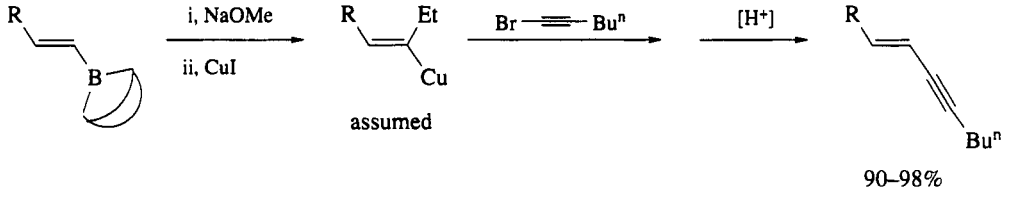
More recently, the stereoselective formation of 1,3-enynes has been reported, *via* a new carbon–carbon bond-forming reaction, involving the direct coupling of alkenyliodinium tosylates (**1**) with alkenylcopper(I) reagents.[22] A wide variety of alkynylcopper reagents (**2**) are easily made by addition of alkylcop-



64%

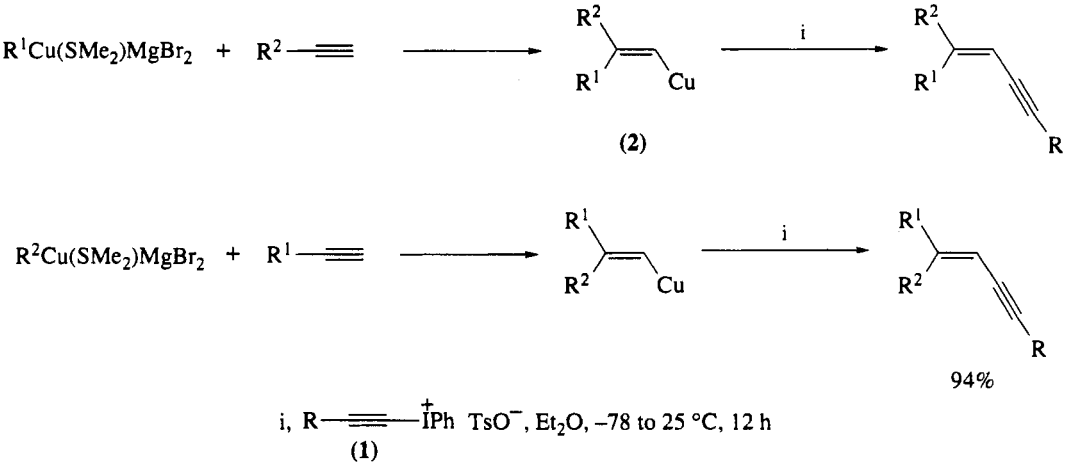


78%



Scheme 1

per reagents to terminal alkynes. The reaction is highly selective and occurs with complete retention of the alkenyl geometry. Furthermore, this stereospecific high-yielding route to conjugated enynes has been utilized in the synthesis of insect pheromones and other interesting natural products. What makes the method particularly attractive, as demonstrated by Scheme 2, is that by simple choice of the order of addition of the alkenylcopper reagent to the alkyne, either geometric isomer around the C—C double bond in the 1,3-enyne product may be obtained in pure form. This simple process, complementing the Pd–Cu-catalyzed sp^2–sp carbon couplings, will be of considerable synthetic utility (see Section 2.4.3.5).



Scheme 2

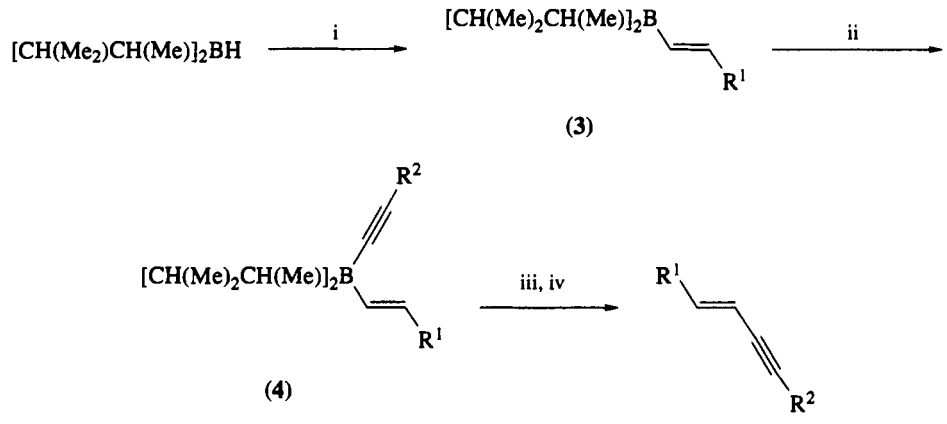
2.4.2.2 Alkynylboranes

The reactions of alkenyl- and alkynyl-boranes can provide efficient and selective methods for the coupling between two unlike boron-bound groups. General, highly stereoselective (>99%) syntheses of conjugated *trans*-enynes can be obtained by treatment of alkenylalkynylboranes (**4**), derived from the alkenylborane (**3**) and alkynyllithiums, with iodine (Scheme 3).[23] In addition, the alkynyl-9-BBN·THF complexes (**5**) undergo a facile reaction with enol alkyl ethers of β-keto aldehydes in hexane at room temperature to provide conjugated enynones (**6**) in excellent yields (Scheme 4).[24]

The (*Z*)-alkynylhaloalkenes (**7**) can be synthesized in relatively good yields from 1-alkynes in a regio- and stereo-selective manner, following haloboration with Br-9-BBN and subsequent treatment with lithium alkynides and iodine (Scheme 5).[25,26]

2.4.3 PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING REACTIONS

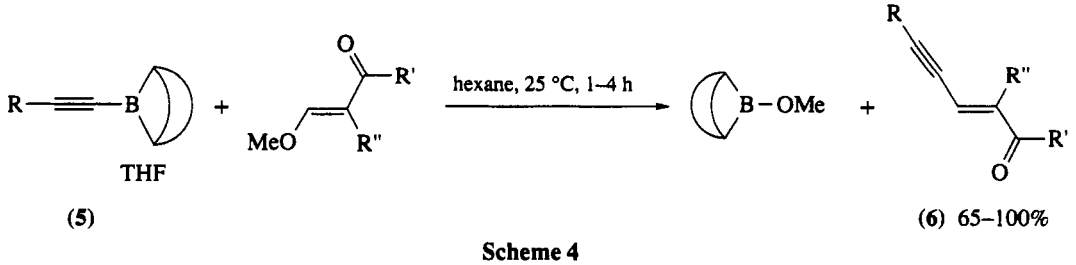
Transmetallations from main group metals to organometallic species produced by oxidative addition processes are becoming increasingly important in sp^2–sp carbon-coupling reactions (Scheme 6). In contrast to sp^2–sp^2 or sp^3–sp^2 coupling reactions, the product yields in Ni-catalyzed sp^2–sp coupling processes such as aryl–alkynyl and alkenyl–akynyl have been substantially lower than those realized with Pd catalysts, presumably because the alkynyl starting compound and/or product tends to react with the Ni catalyst to afford polymers and cyclic oligomers.



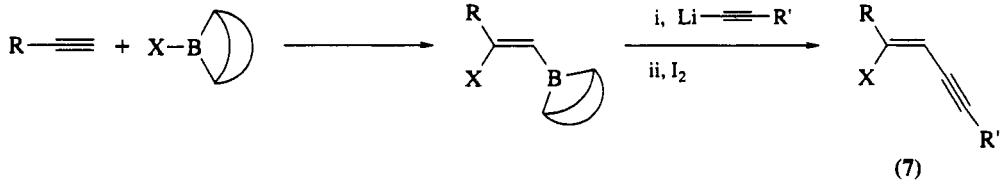
i, H—≡—R^1, THF, 0 °C, 1 h; ii, Li—≡—R^2, THF/hexane, –50 °C, 1 h;

iii, I_2, THF, –78 to 25 °C; iv, 3 N NaOH, 25 °C

Scheme 3



Scheme 4



R = R' = alkyl, cycloalkyl; X = Br, I

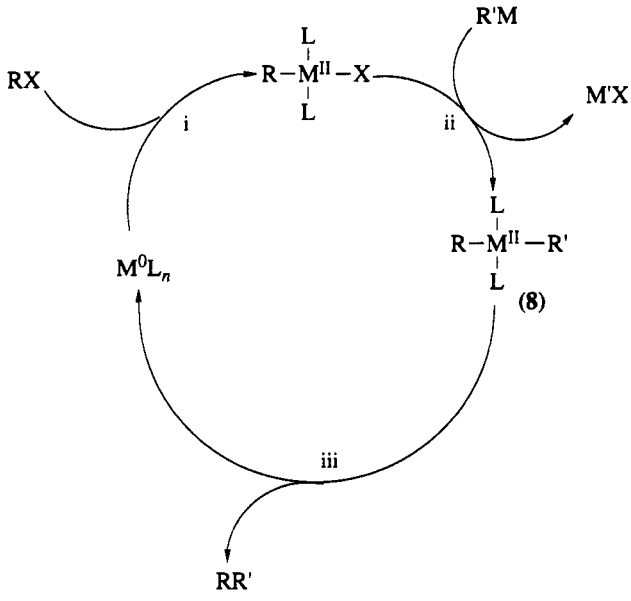
Scheme 5

A species such as (**8**), formed *via* transmetallation, often undergoes reductive elimination to complete a very useful coupling reaction. Thus, magnesium,[27] boron, zinc and tin are effective. The major asset of this method is the complete retention of the configuration in the alkene, resulting in products of exceptional isomeric purity. The halides involved include aromatic, alkenyl and allenyl. Several reviews of this method have been published.[8,9,28–34]

2.4.3.1 Alkynylzinc Chlorides

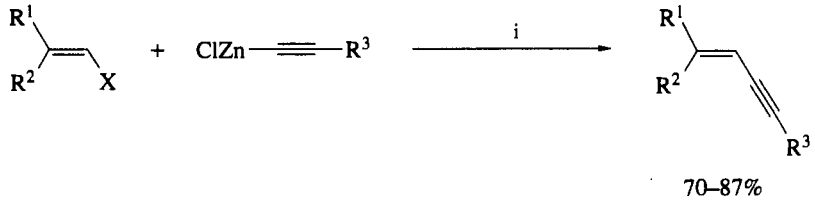
The Pd-catalyzed reactions of alkynylzinc chlorides, which are readily obtainable from zinc chloride, with alkenyl iodides or bromides provide the corresponding terminal or internal enynes in high yield and with high (>97%) stereospecificity (Scheme 7).[35] Aryl bromides or iodides can also be used to produce arylalkynes (equation 6).[36,37]

The interesting stereospecific Pd-catalyzed cross-coupling reactions of 1-alkynylzinc chlorides (**9**) with a diastereoisomeric mixture of alkenyl halides (**10**) have been described. The (*E*)-bromoalkene reacts preferentially in these reactions to afford good yields of (*E*)-enynes (**11**), (**12**) and (**13**) having very



i, oxidative addition; ii, transmetallation; iii, reductive elimination

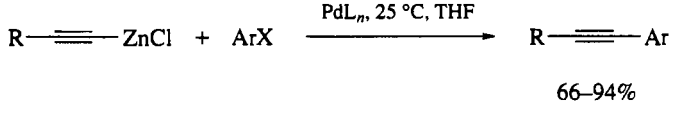
Scheme 6



R^1 = H, Bu^n, CO_2Me; R^2 = H, Me, Et, Bu^n; R^3 = H, Bu^n, n-C_5H_{11}; X = Br, I

i, Catalyst PdL_n (L = PPh_3), 0–25 °C, THF

Scheme 7



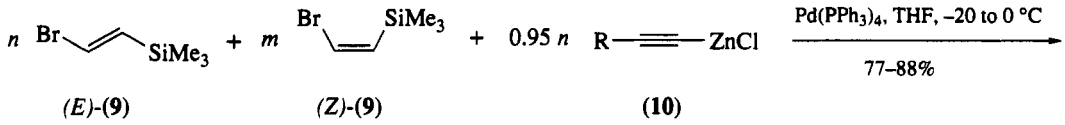
(6)

R = H, alkyl, aryl; X = I or Br

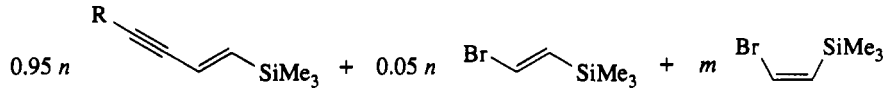
high stereoisomeric purities (equations 7, 8 and 9).[38–40] The enynes can easily be selectively transformed into the corresponding dienes, which may be used to prepare stereodefined polyunsaturated natural products.

Several fluorinated enynes (**14**) have been prepared by the reaction of alkynylzinc chlorides with fluoroalkenyl iodides (equation 10),[41] and the Pd-catalyzed cross-coupling reactions of aryl fluoroalkanesulfonates with organozinc reagents have been reported (equation 11).[42]

A general and convenient route to conjugated diynes, especially terminal diynes from the corresponding chloroenynes, has been developed.[43] Thus, readily available (*E*)-iodochloroethylene is first reacted with alkynylzinc derivatives in the presence of a Pd–phosphine complex catalyst to produce (*E*)-chloroenynes (**15**) in high yield. The chloroenynes (**15**) can then be readily converted into the corresponding

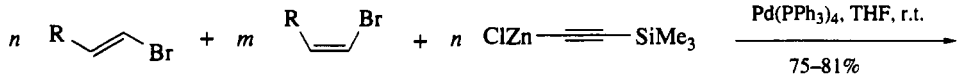


(E)-(**9**) *(Z)*-(**9**) (**10**)

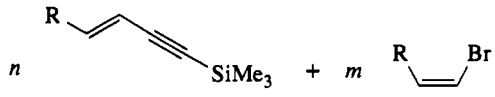


(E)-(**11**) (7)

stereoisomeric purity ≈ 99.5%; R = n-C_5H_{11}, Ph, Me_3Si

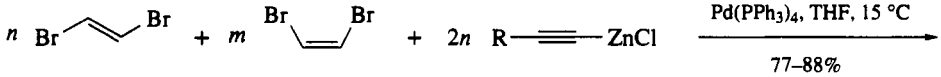


(E)-(**9'**) *(Z)*-(**9'**) (**10**)

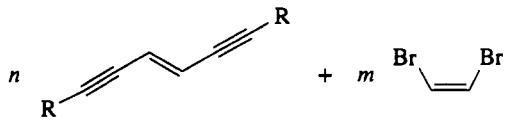


(E)-(**12**) (8)

stereoisomeric purity ≈ 95.5–98.4%; R = Pr^n, Bu^n, n-C_5H_{11}

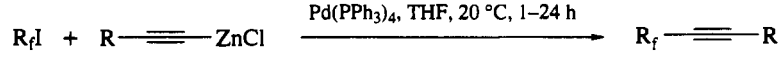


(E)-(**9''**) *(Z)*-(**9''**) (**10**)



(E)-(**13**) (9)

stereoisomeric purity ≈ 99.5%; R = Bu^n, n-C_5H_{11}, Ph, Me_3Si



(**14**) (10)

R_f = CF_2=CF, CF_2=CH, Bu^sCF=CF *(Z)*, C_7H_{15}CF=CF *(E)*; R = Bu^n, n-C_6H_{13}

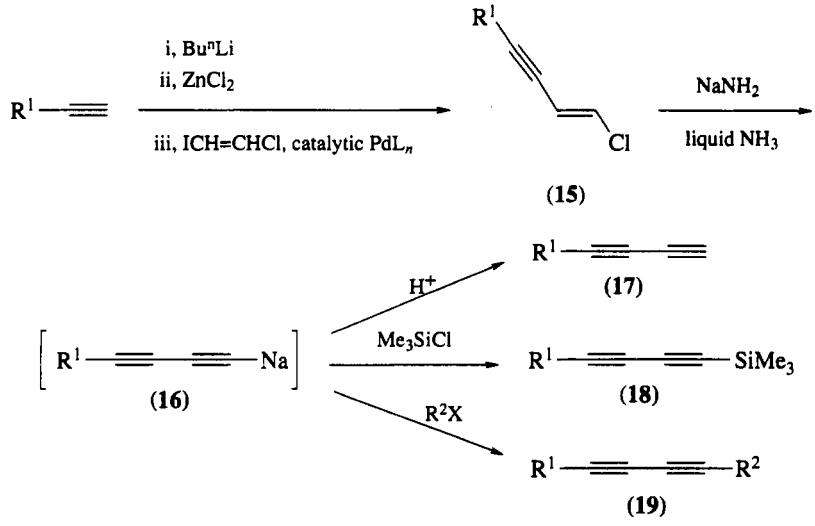
sodiodiynes (**16**), which can be transformed into terminal diynes (**17**), silylated diynes (**18**) and internal diynes (**19**; Scheme 8).

$$ArOSO_2R_f + R{\equiv}ZnCl \xrightarrow{Pd(PPh_3)_4,\ LiCl,\ DMF/THF,\ 70\text{–}80\ ^\circ C} Ar{\equiv}R \quad (11)$$

67–87%

R = Bu^n, $MeOCH_2$, Ph; Ar = Ph, *p*-ClC_6H_4, *o*-ClC_6H_4, *m*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$

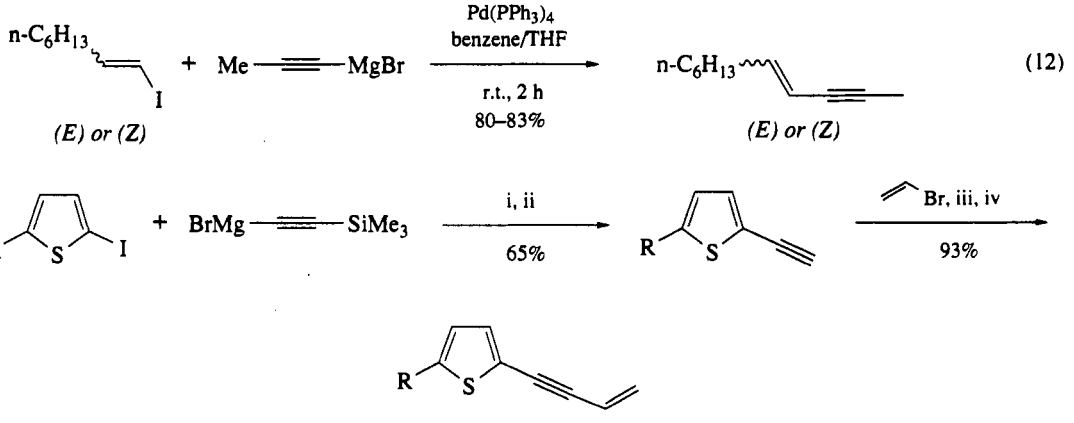
$R_f = CF_3$, $H(CF_2CF_2)_nOCF_2CF_2$ (n = 1, 2)



Scheme 8

2.4.3.2 Alkynylmagnesium Halides

The palladium-catalyzed cross-coupling reactions of vinyl iodides with alkynylmagnesium halides have been found to occur with retention of configuration (>97%; equation 12).[44] Using this procedure, the dithienylenyne (**20**), which is a natural antifungal and nematicidal agent, can be prepared by a combination of Pd-catalyzed cross-couplings (Scheme 9).[45]

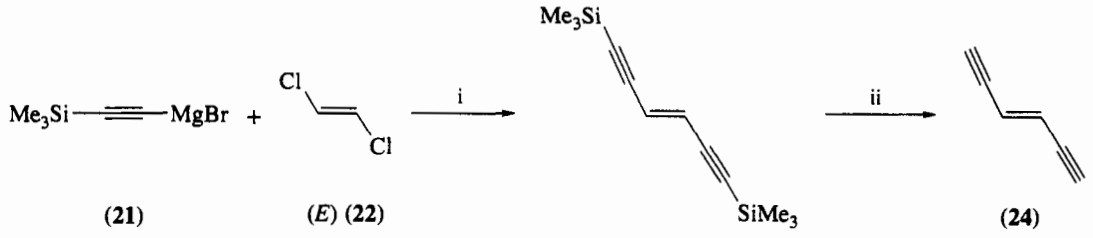


R = 2-thienyl, phenyl

i, $Pd(PPh_3)_4$, THF, benzene; ii, KOH, MeOH; iii, EtMgBr, THF; iv, CH_2=CHBr, $Pd(PPh_3)_4$, benzene

Scheme 9

The Ni-catalyzed cross-coupling reaction of alkynyl Grignard reagents (**21**) with *trans*-dichloroethylene (**22**) has been applied to a simple procedure for the preparation of the protected form (**23**) of an extremely unstable synthon, hexadiynene (**24**). Separation of the diastereomers (**23a** from **23b**) is facile since the former is an oil and the latter is a solid (Scheme 10).[46]



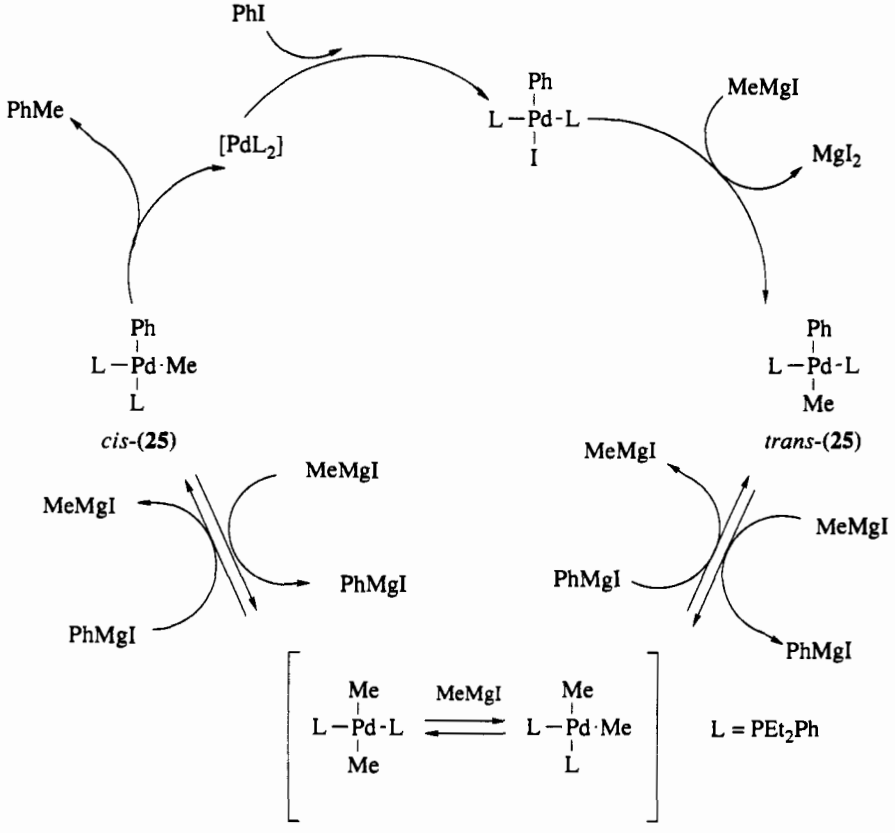
(**21**) (*E*) (**22**) (**24**)

(**23a**) *(E)*-isomer
(**23b**) *(Z)*-isomer

i, $Ni(dppp)Cl_2$, dppp = $Ph_2P(CH_2)_3PPh_2$; ii, NaH–catalyst, MeOH/dry THF

Scheme 10

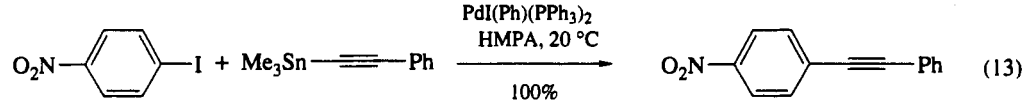
Recently, a mechanism for the cross-coupling reaction between phenyl iodide and methylmagnesium iodide, catalyzed by *cis*- and *trans*-[$(PEt_2Ph)_2Pd(Ph)(I)$], was proposed (Scheme 11).[47] The toluene produced from *cis*-(**25**) is thought to result *via* an intramolecular reductive elimination process without predissociation of the phosphine ligand.



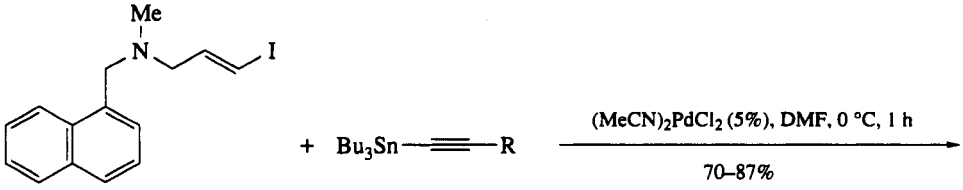
Scheme 11

2.4.3.3 Alkynyltin Reagents

The reactivity of tin–carbon bonds allows the creation of new sp–sp^2 carbon to carbon bonds through substitution reactions. General reviews of the organotin route for carbon–carbon bond formation are available.[28–31] With Pd catalysis, alkynyl groups are more readily transferred than alkyl groups to the aryl or vinyl iodides to afford sp–sp^2 carbon bonds (equations 13 and 14).[48,49]



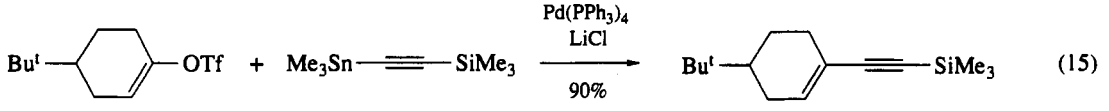
(13)



(14)

R = Bu^t, Bu^n, SiMe$_3$

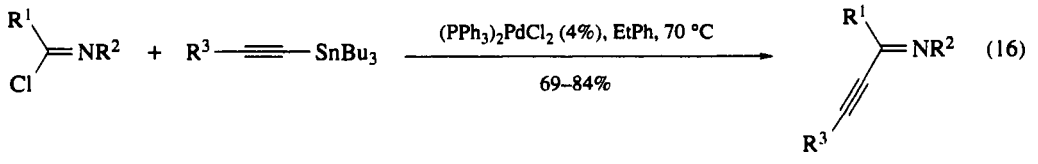
Extensions to sp^2–sp cross-coupling reactions with vinyl triflates can be successfully achieved, as exemplified by the synthesis of the enyne (**26**). It is noteworthy that this reaction is compatible with the presence of alkynylsilanes, emphasizing the different behavior of organosilicon and organotin derivatives (equation 15).[50]



(15)

(**26**)

Finally, imidoyl chloride can be transformed into the corresponding ketimines *via* palladium complex catalyzed cross-coupling reactions with alkynyltins (equation 16).[51,52]



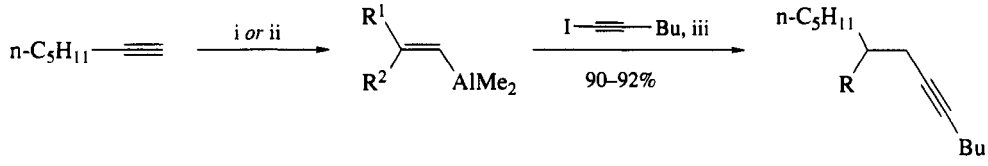
(16)

R^1 = Ph, 2-thienyl, Et, Cl; R^2 = *p*-tolyl, Bu^n, *p*-$C_6H_4CO_2Et$; R^3 = Bu^n, SiMe$_3$, EtC≡C

2.4.3.4 Reactions of 1-Alkenyl Metals with 1-Alkynyl Halides

Using (*E*)-methylalkenylalanes, obtained by highly stereo- and regio-selective Zr-catalyzed carboalumination of alkynes, the stereochemically defined enynes (**27**) can be synthesized by Pd-catalyzed cross-coupling reactions with 1-haloalkynes (Scheme 12).[53] Although the mechanism of the Zr-catalyzed

carboalumination is not very clear, certain aspects have been clarified,[54] and general reviews have been published.[9,55,56]

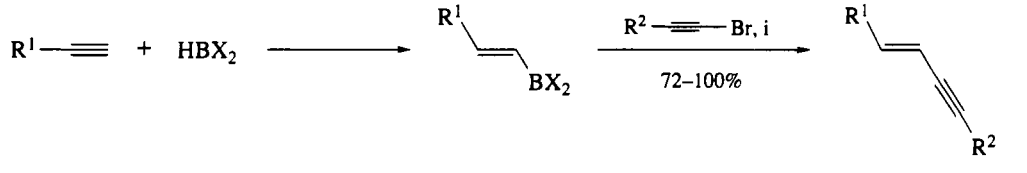


(27a) R = H
(27b) R = Me

i, Me_3Al–Cl_2ZrCp_2, 50 °C, 6 h; ii, H_2O for the case of R = Me; Bu^i_2AlH for the case of R = H;
iii, $ZnCl_2$, $Pd(PPh_3)_4$ (5 mol %), 20–25 °C

Scheme 12

Cross-coupling reactions between 1-alkynyl halides and 1-alkenylboranes, which are readily available *via* hydroboration of alkynes, can also be catalyzed by the Pd–phosphine complex (Scheme 13).[57,58]



isomeric purity > 96%

$X_2 = Sia_2$; R^1 = Bu, Ph, Me; $R^2 = C_6H_{13}$, Ph

i, $Pd(PPh_3)_4$, benzene, NaOMe/MeOH, 80 °C, 2 h

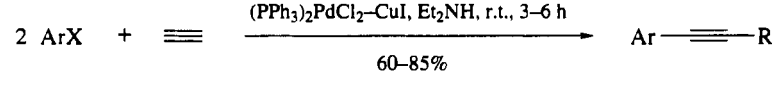
Scheme 13

2.4.3.5 Reactions of Terminal Alkynes with sp^2-Carbon Halides

2.4.3.5.1 General aspects

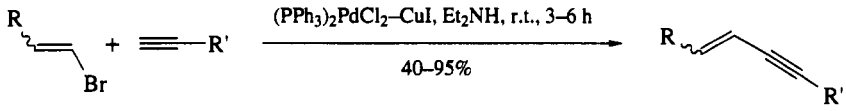
Terminal alkynes can be coupled directly to aryl and to vinyl halides in the presence of a palladium catalyst and a base. The mechanism of this reaction appears to involve oxidative addition of the sp^2 halide to palladium(0), followed by alkynylation of the intermediate organopalladium halide and reductive elimination of the disubstituted alkyne (equations 17 and 18).[7,59,60]

Different conditions have been employed for this reaction, depending on the reactivity of the halide, the alkynes and the base used. Copper(I) iodide is a particularly effective cocatalyst, allowing the reactions to occur at room temperature.[7] Additional examples of this type of coupling reaction are given in Table 1.[61–83]



(17)

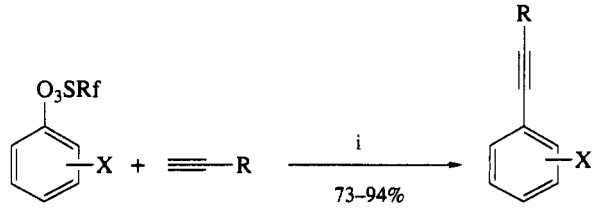
Ar = Ph, 2-pyridyl



(18)

R = H, Ph; R' = Ph, CH_2OH

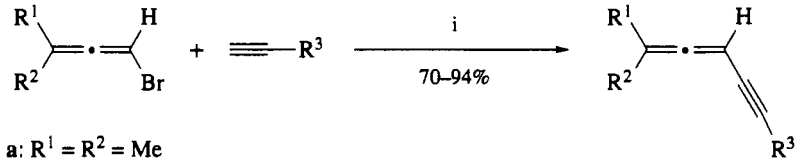
Aryl triflates, like aryl halides, can undergo Pd-catalyzed coupling reactions with terminal alkynes (Scheme 14),[67] and bromoallenes react with terminal alkynes[84,85] or acetylene[86] under similar conditions to form allenynes (Schemes 15 and 16).



R = Ph, Me_3Si; $R_f = CF_3$, $H(CF_2)_2O(CF_2)_2$

i, $(PPh_3)_2PdCl_2$, Et_3N/DMF, 90 °C, 3–17 h

Scheme 14

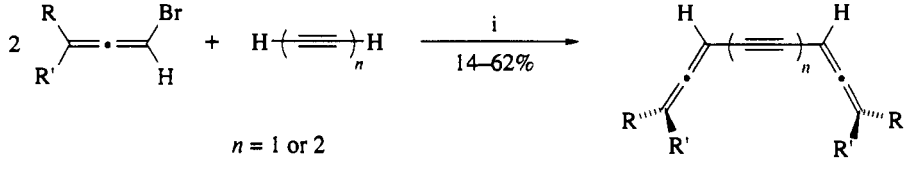


a: $R^1 = R^2 = Me$
b: $R^1 = Pr^n$; $R^2 = H$

R^3 = Ph, n-C_6H_{13}, CH_2OH, $CH(OH)Pr^n$, Pr^iNEt_2, $SiMe_3$, $(CH_2)_8OAc$

i, $Pd(PPh_3)_4$–CuI, Et_2NH, r.t., 2–3 h

Scheme 15



n = 1 or 2

i, $Pd(PPh_3)_4$–CuI cat., Et_2NH, 20 °C, 1 h

a: R = R' = Me
b: R = R' = Et
c: R = Me; R' = Et

Scheme 16

2.4.3.5.2 Synthesis of terminal alkynes

The sp^2–*sp* coupling reaction can be extended to the synthesis of terminal alkynes by use of protected alkynes such as trimethylsilylacetylene (**28**; TMSA) or 2-methyl-3-butyn-2-ol (**29**), followed by subsequent removal of the protecting group (Schemes 17, 18 and 20).[61,87,88] Thus, commercially available TMSA (**28**) reacts with aryl bromides or iodides in the presence of a palladium complex and copper(I) iodide, followed by treatment with dilute aqueous potassium hydroxide in methanol or a F^- source, such

Table 1 Formation of Disubstituted Alkynes by the Reaction of sp^2 Halides or Their Related Compounds with Terminal Alkynes

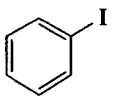
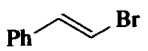
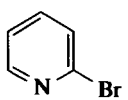
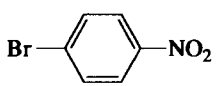
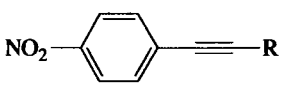
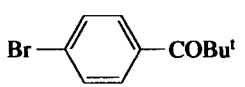
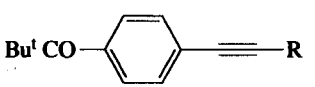
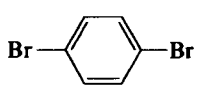
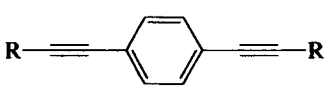
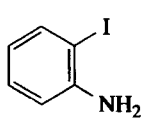
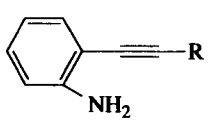
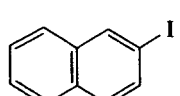
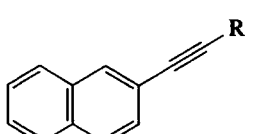
Alkyne RC≡CH	*Halide*	*Catalyst*[b]	*Conditions*	*Product*	*Yield (%)*	*Ref.*
R = H		A	r.t., 6 h		85	7
		A	r.t., 6 h		95	7
		A	r.t., 6 h		60	7
R = $SiMe_3$		A'	r.t., 4 h		92	61
		A	r.t.		—	62
		A'	50 °C		77	61
		A	30 °C		68	63
		A'	r.t.		85	61

Table 1 *(continued)*

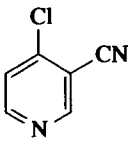
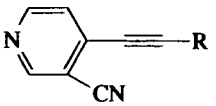
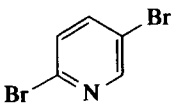
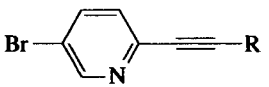
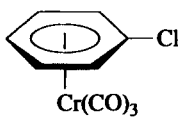
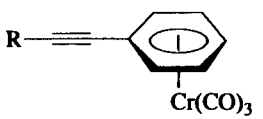
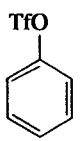
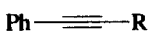
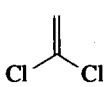
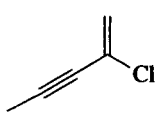
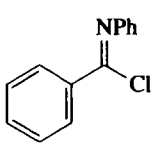
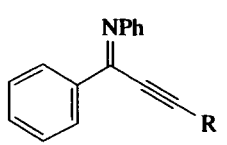
Alkyne RC≡CH	*Halide*	*Catalyst*[b]	*Conditions*	*Product*	*Yield (%)*	*Ref.*
$R = SiMe_3$		A'	100 °C,[a] 20 h		76	64
		A'	5 °C, 1 h, r.t., 1 h		74	65
		A'	20 °C, 18 h		85	66
		A'/DMF			87	67
		D	r.t., 5 h		82	68
		B	80 °C, 2 h		78	69

Table 1 *(continued)*

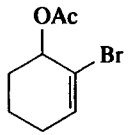
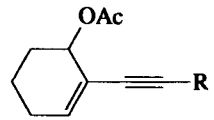
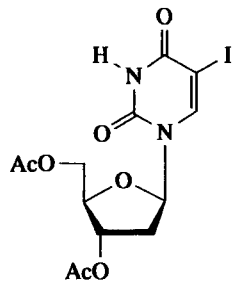
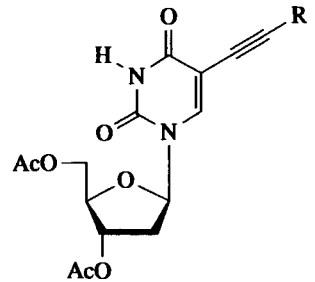
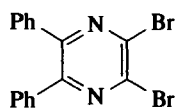
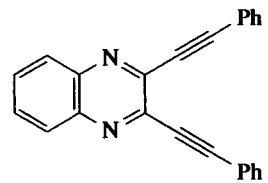
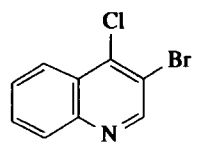
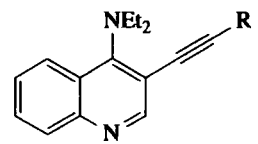
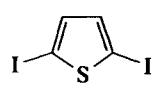
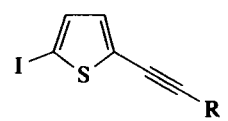
Alkyne RC≡CH	*Halide*	*Catalyst*[b]	*Conditions*	*Product*	*Yield (%)*	*Ref.*
R = $SiMe_3$			80 °C,[a] 3 h		47	70, 71
		A	50 °C, 2 h		80	72
PhC≡CCu	*p*-$MeOC_6H_4Br$	G	>20	*p*-$MeOC_6H_4C{\equiv}CR$	98	73
Ph—≡		A'/DMSO	r.t., 6 h		74	74
Ph—≡		A	r.t., 4 h		37	75
R = $CH_2CH_2OCOCH_2Pr^i$		F	80 °C, 6 h		50	76

Table 1 *(continued)*

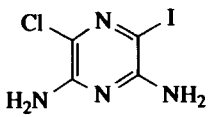
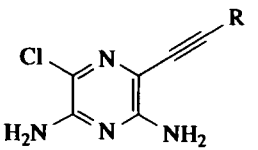
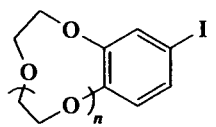
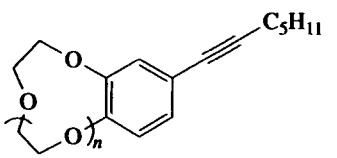
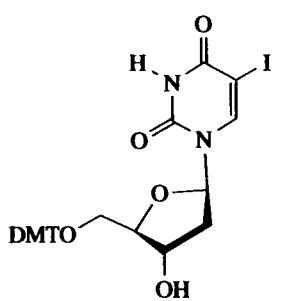
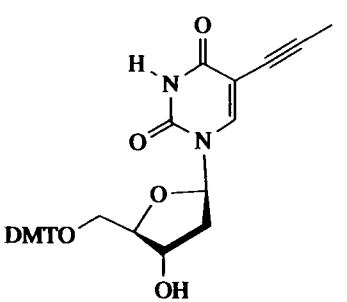
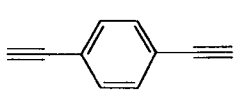
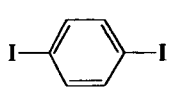
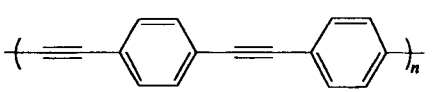
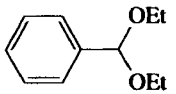
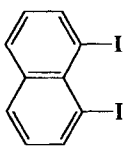
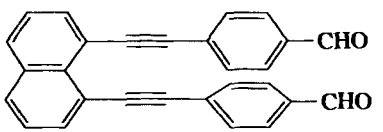
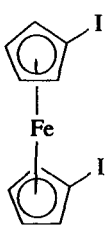
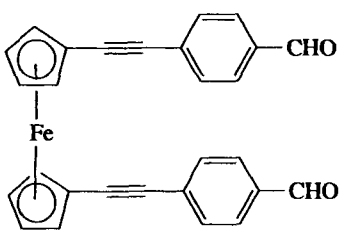
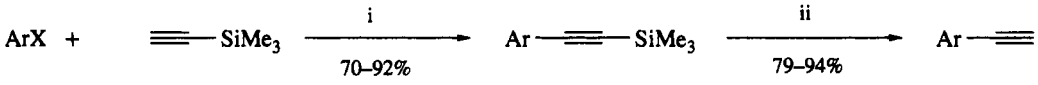
Alkyne RC≡CH	*Halide*	*Catalyst*[b]	*Conditions*	*Product*	*Yield (%)*	*Ref.*
R = $Me(CH_2)_4$		A	r.t., 24 h		63	77
	 $n = 3, 4$	A	Reflux, 24 h		84	78
R = $CF_3CONHCH_2$		A/EtOAc	r.t., 40 h		53	79
		A'	89 °C, 0.05 h		100	80

Table 1 *(continued)*

Alkyne RC≡CH	*Halide*	*Catalyst*[b]	*Conditions*	*Product*	*Yield (%)*	*Ref.*
R = 		A	80 °C, 10 h		35	81, 82
		A			27	83

[a] In sealed tube. [b] A = $(PPh_3)_2PdCl_2$, CuI/Et_2NH; A' = $(PPh_3)_2PdCl_2$, CuI/Et_3N; B = $Pd(OAc)_2$, PPh_3, CuI/Et_3N; C = $(PPh_3)PdCl_2$, CuI/Me_2NH; D = $Pd(PPh_3)_4$, CuI/Bu^nNH_2; E = $Pd(PPh_3)_4$/Et_3N; F = $Pd(PPh_3)_4$, CuI/Et_3N; G = $PhPd(PPh_3)_2I$, $Bu_4N^+I^-$/HMPA; Tf = CF_3SO_2; TMT = dimethoxytrityl.

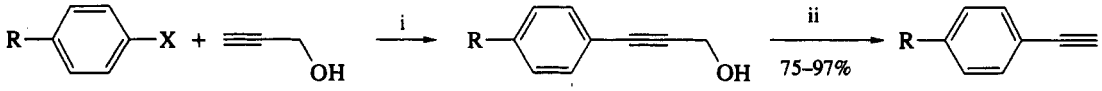
as KF–crown ether in DME or tris(dimethylamino)sulfonium trimethyldifluorosilicate (TASF), to give arylalkynes.[61,69,89,90]



(28)

i, $(PPh_3)_2PdCl_2$–CuI cat., Et_3N or pyridine, r.t. to 60 °C; ii, 1N aq. KOH/MeOH, r.t., 1 h

Scheme 17



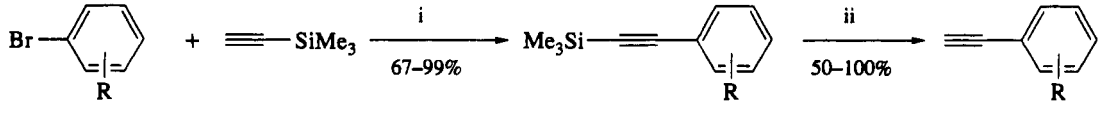
R = NO_2, CN, COMe, CO_2Me, OPr^n; X = Cl, Br, I

i, $PhPdI(PPh_3)_2$, CuI/NEt_3/C_6H_6, r.t. to 80 °C, 10 min to 2 h; ii, 10 equiv. MnO_2/5 equiv. KOH/C_6H_6, r.t., 10 min

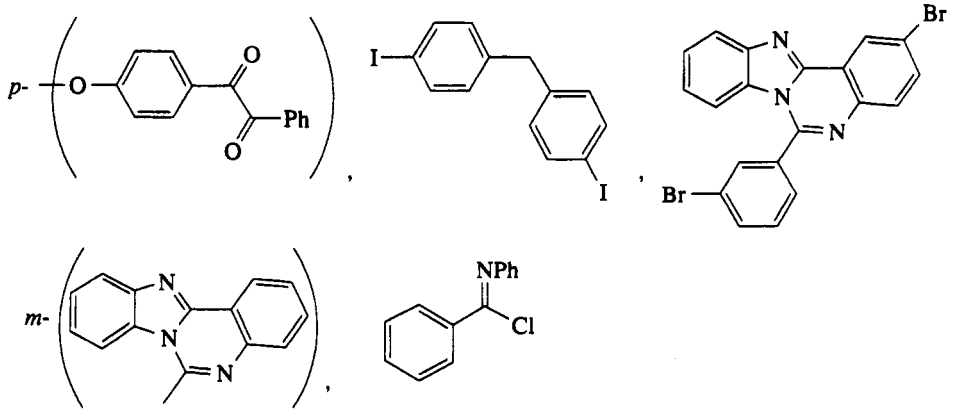
Scheme 18

Terminal arylalkynes can be prepared by oxidation–decarbonylation of 3-arylpropargyl alcohols using manganese dioxide in the presence of alkali. The corresponding arylpropargyl alcohols are available by palladium-catalysed cross-coupling of aryl halides with commercial propargyl alcohol. The yield of the second step can be improved by the addition of a phase-transfer catalyst (18-crown-6; Scheme 18).[88]

The coupling reaction between an aromatic halide and TMSA (**28**) in the presence of a Pd^0 catalyst generated *in situ*, followed by treatment with potassium carbonate in methanol, provides a simple approach to various ethynylated aromatic derivatives (Scheme 19).[69] By this method even hindered, electron-rich arylalkynes, such as (**30**), can be prepared from the corresponding aryl iodide by refluxing for 2 d in triethylamine.[89]



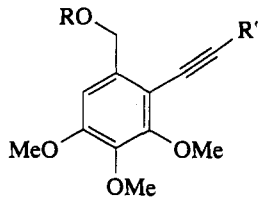
R = *o*-, *m*- or *p*-CHO, *m*- or *p*-CO_2Me, *m*-CF_3, 2-F-5-NO_2, 2-F-5-NH_2,



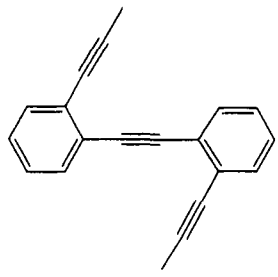
i, $(PPh_3)_2Pd(OAc)_2$, Et_3N, reflux for 2–20 h; ii, K_2CO_3, MeOH, 25 °C

Scheme 19

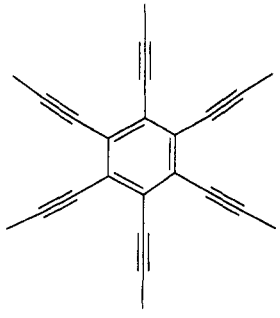
Using the above procedure, a wide variety of aromatic and heteroaromatic polyethynyl derivatives have been prepared, *e.g.* (**31**),[92] (**32**)[90] and (**33**).[91,93]



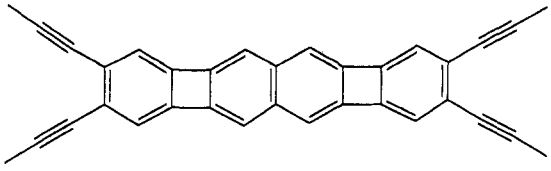
(**30**)



(**31**)

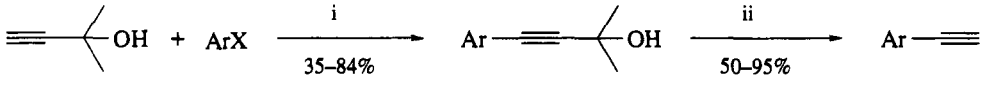


(**32**)

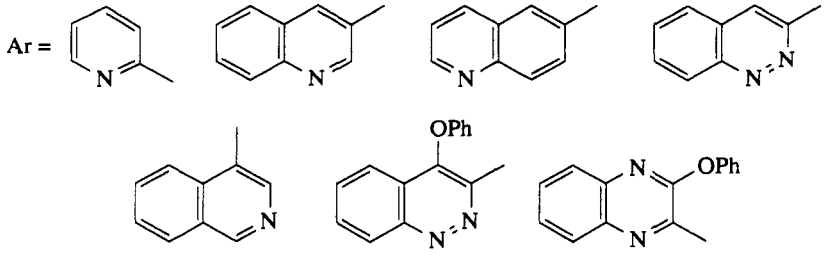


(**33**)

The more easily available starting material (**29**), as a protected alkyne, can condense with aryl halides, followed by treatment with sodium hydroxide and toluene also to provide terminal alkynes (Scheme 20).[87,94]



(**29**)



i, $(PPh_3)_2PdCl_2$–CuI, Et_2NH; ii, NaOH/toluene, reflux 2 h

Scheme 20

In the presence of TASF as a reagent for cleavage of the Si—C bond and allylpalladium dimer as a coupling catalyst, alkynylsilanes react with aryl and vinyl halides to give the corresponding coupled products in high yield and in a stereospecific manner (Scheme 21).[95] In a special case, piperidine and formic

acid can also cleave the Si—C bond (Scheme 22).[96] This technique has been extended to a one-pot synthesis of conjugated dienynes or arylalkynes by a palladium-mediated three-component cross-coupling reaction, as shown in Scheme 23.[97] Thus, the Pd-catalyzed reaction of the silylstannylacetylene, first with an alkenyl iodide (**34**) and secondly with another sp^2 iodide in the presence of newly added TASF, affords the conjugated dienyne (**35**) or arylenyne (**36**) with high stereospecificity.

2.4.3.5.3 Stereospecific synthesis

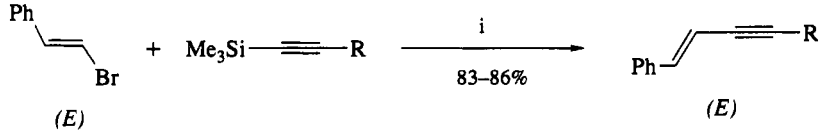
The coupling reaction between sp^2- and *sp*-carbon centers is stereospecific with (*Z*)- and (*E*)-vinylic bromides. For example, (*Z*)-methyl-3-bromoacrylate reacts with 1-hexyne in the presence of a Pd catalyst to form the (*Z*)-enzyne as the only product (Scheme 24).[98] This technique has also been applied in the stereoselective synthesis of 1-chloroenynes from (*Z*)-dichloroethylene (Scheme 25).[99]

Trimethylsilylacetylene affords the 2:1 coupled endiyne product (**37**) in a stereospecific manner on coupling with geometrical isomers of 1,2-dichloroethylene (Scheme 26). In the absence of copper(I) iodide, no reaction occurs.[100]

2.4.3.5.4 Phase-transfer catalysis

The technique of phase-transfer catalysis is useful for a variety of interesting metal-catalyzed reactions.[101,102] For the synthesis of 1,3-enynes, the procedure based on the Pd-catalyzed reaction of alkenyl halides with 1-alkynes under phase-transfer conditions offers distinct advantages, in terms of single procedure and cost, over methods involving the use of organometallic compounds or of amines as solvents. Moreover, this procedure can tolerate the presence of functional groups such as hydroxy groups. Better yields are obtained when the coupling reactions are carried out under phase-transfer conditions, at room temperature, employing benzyltriethylammonium chloride (1 mol %) as the phase-transfer agent, a large excess of 2.5 N aqueous sodium hydroxide as the base, and a mixture of tetrakis (triphenylphosphine)palladium (1 mol %) and copper(I) iodide (0.5–2 mol %) as catalyst. Using these conditions, a variety of alkenyl halides (**38**) react with aliphatic 1-alkynes (**39**; Scheme 27).[103,104]

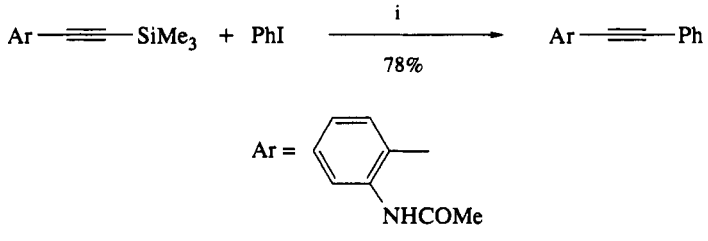
The Pd-catalyzed coupling reactions of alkenyl bromides with heterocyclic alkynes (**40**) under the above phase-transfer conditions have been employed to prepare a large number of heterocyclic alkyne derivatives, including some naturally occurring compounds (Scheme 28).[45] The experimental conditions



R = Ph, n-C_5H_{11}, CH_2OH

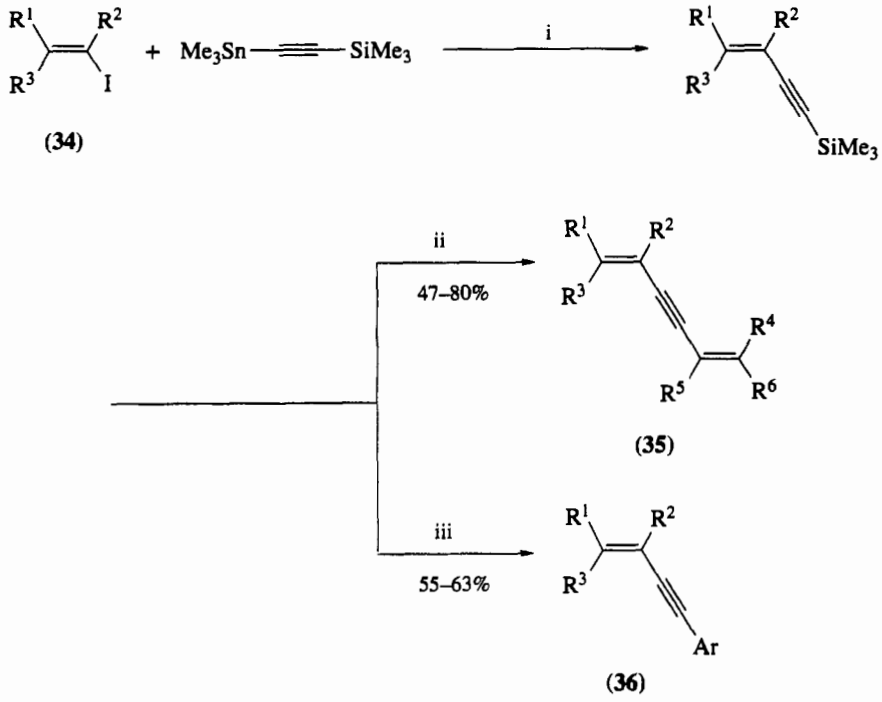
i, TASF, 2.5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, THF, r.t.

Scheme 21



i, $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H/DMF, 60 °C, 8 h

Scheme 22



(34)

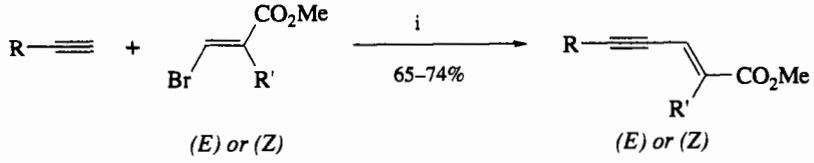
(35)

(36)

R^1 = H, $(CH_2)_4$ (cyclo), $AcOCH_2$, Ph, Pr^n, n-C_6H_{13}; R^2 = H, Bu^n, $(CH_2)_4$ (cyclo); R^3 = H, n-C_6H_{13}, n-C_8H_{17}; R^4 = H, n-C_6H_{13}, n-C_8H_{17}; R^5 = H, Bu^n; R^6 = H, Pr^n, n-C_6H_{13}; Ar = 1-naphthyl, 2-thienyl

i, 1 mol % of $Pd(PPh_3)_4$, 2.4 mol of TASF, THF, 50 °C; ii, $I(R^5)C{=}CR^4R^6$, TASF; iii, ArI, TASF

Scheme 23

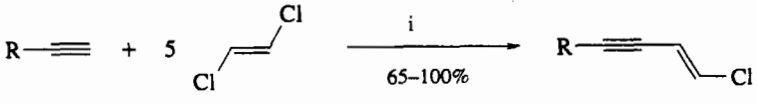


(E) or (Z) *(E) or (Z)*

R = cyclohexyl, Ph, Bu^n; R' = H, Me

i, $Pd(OAc)_2$ + $2PPh_3$, NEt_3, r.t., 40 h

Scheme 24



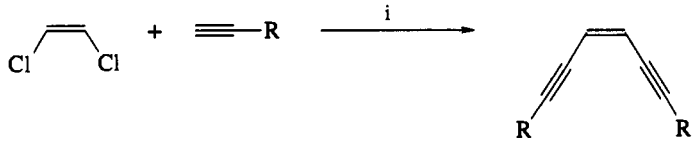
(E) or (Z) *(E) or (Z)*

>99% isomeric purity

R = n-C_5H_{11}, CH_2OTHP, CH_2OAc, CH_2SMe

i, $Pd(PPh_3)_4$–CuI cat., *n*-butylamine, r.t., 5 h

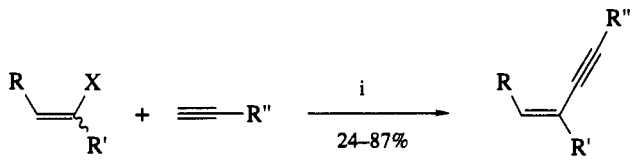
Scheme 25



R = Ph, Me_3Si **(37)**

i, $Pd(PPh_3)_4$–CuI cat., n-butylamine, benzene, r.t., 1 h

Scheme 26

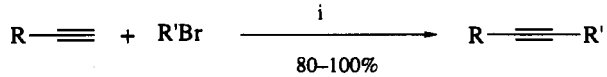


(38) **(39)**

R = H, Bu^n, $n\text{-}C_8H_{17}$; R' = H, Me; R" = $n\text{-}C_5H_{11}$, CH_2OH, $n\text{-}C_6H_{13}$, $(CH_2)_2OH$, $(CH_2)_8OH$

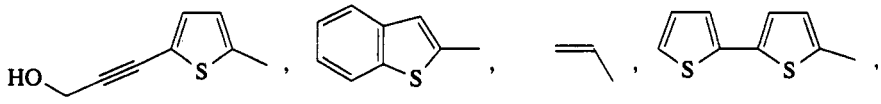
i, $Pd(PPh_3)_4$–CuI cat., 10% aq. NaOH, benzene, $BzEt_3\overset{+}{N}\ Cl^-$

Scheme 27



(40)

X = I, Br;

R = 

2-furyl, 2-pyridyl;

R' = 2-thienyl, $HO(CH_2)_2$, $HOCH_2$, 2-furyl, 2-pyridyl, Ph, $(EtO)_2CH$

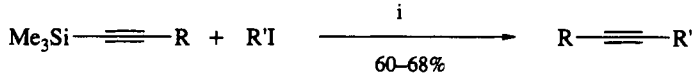
i, $Pd(PPh_3)_4$, CuI, C_6H_6, $BzEt_3\overset{+}{N}\ Cl^-$, aq. 2.5 N NaOH

Scheme 28

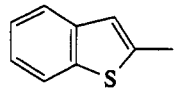
of the procedure allow the direct preparation of alkynic derivatives starting from 1-alkynyltrimethylsilanes (**41**) and heteroaryl halides (Scheme 29).[45] An efficient one-pot synthesis of arylalkynes can be achieved by application of the phase-transfer reaction using commercially available 2-methyl-3-butyn-2-ol (**42**) as the protected alkyne starting material (Scheme 30).[105] Using a similar method, oligo(thienylalkyne)s (**43**) have been synthesized in a stepwise manner.[105,106]

2.4.3.5.5 Syntheses of aromatic and heterorings via sp^2–sp *coupling reactions*

Alkynic intermediates derived from sp^2–*sp* coupling reactions can be applied to the syntheses of a variety of aromatic and heterocyclic molecules.[107–116] For example, a one-step synthesis of the aminoindolizines (**44a–e**) and the 5-aza analog (**44f**) from α-haloaza aromatics has been reported as outlined in Scheme 31.[107] The mechanism of this reaction appears to involve the initial formation of pyridylacetylene (**45**), followed by ring closure *via* the intermediate (**46**; Scheme 32).[107]

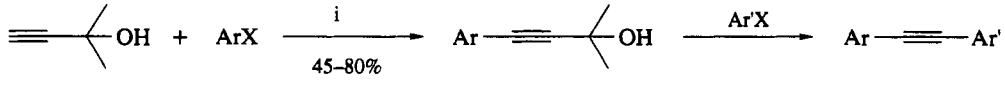


(41)

R = 2-thienyl,  ; R' = 2-thienyl, CH_2=$CMeCH_2$

i, $Pd(PPh_3)_4$–CuI cat., C_6H_6, 40 °C, $BzEt_3N^+Cl^-$, aq. 2.5 N NaOH

Scheme 29

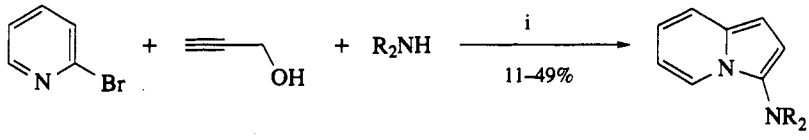


(42)

R = 2-thienyl, 2-pyridyl, nitrophenyl; R' = phenyl, 2-thienyl, 5-(2,3-benzothienyl)

i, $(PPh_3)_4Pd$–CuI cat., $BzEt_3N^+Cl^-$, 5.5 N NaOH/benzene, r.t.

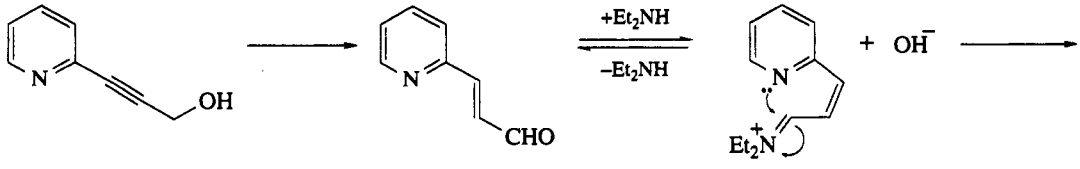
Scheme 30



(44) **a**: $NR_2 = N(CH_2)_5$
b: NR_2 = N, O
c: $NR_2 = NEt_2$

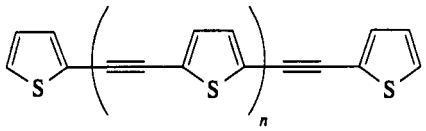
i, $(PPh_3)_2PdCl_2$–CuI cat., 70–80 °C, 3–16 h

Scheme 31



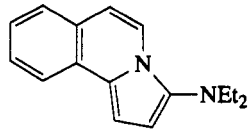
(45) **(46)**

Scheme 32

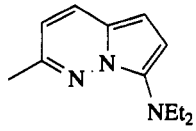


(**43**) $n = 0, 1, 2, 3$

(**44d**)

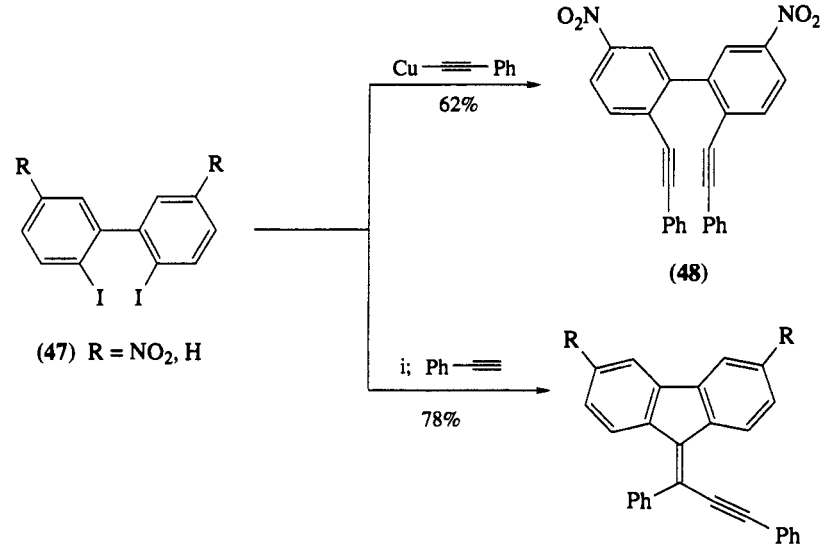


(**44e**)



(**44f**)

Although the stoichiometric ethynylation of (**47**) with copper(I) phenylacetylide gives the product (**48**) of a normal double ethynylation, the Pd-catalyzed coupling reaction affords the fluorene derivative (**49**) instead. The reaction leading to (**49**) can be rationalized as proceeding *via* the σ-fluorenyl–Pd complex (**50**; Scheme 33).[116]

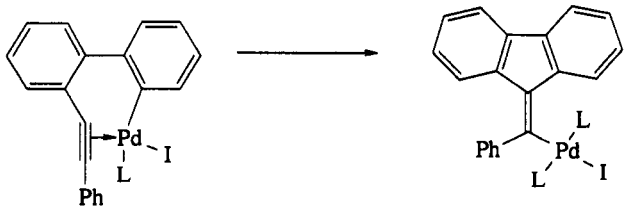


(**47**) R = NO_2, H

(**48**)

(**49**) R = NO_2, H

i, $(PPh_3)_2PdCl_2$–CuI, Et_3N, 80–85 °C, 3 h; ii, pyridine, 110 °C, 24 h

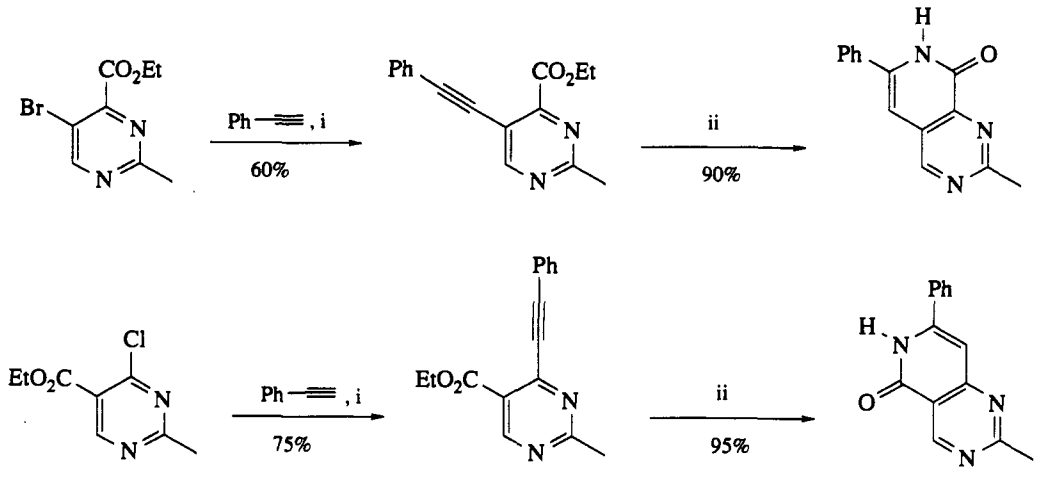


(**50**)

Scheme 33

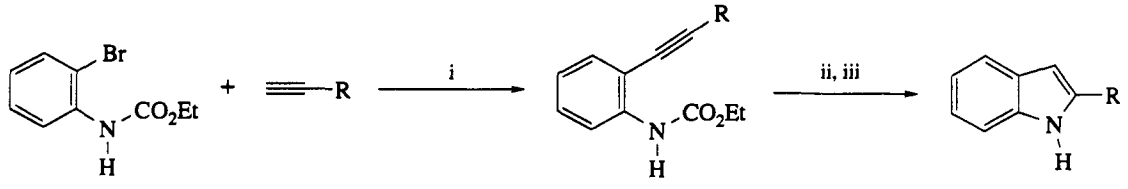
Pyridopyrimidines and pyrimidines fused with five- or six-membered heterocycles can be prepared *via* the ring closure of intermediate ethynylpyrimidines, which are themselves obtained by the Pd-catalyzed cross-coupling of halopyrimidines with alkynic compounds (Scheme 34).[108–110]

o-Alkynylanilines such as (**51**), which are made by Pd-catalyzed coupling reactions of alkynes with *o*-haloaniline precursors, are easily cyclized to the indoles in the presence of base (Scheme 35).[111,112] Similar methods can be employed in the synthesis of isocoumarins,[113] thienopyridines,[117] furopyridines[117] and the marine alkaloid asptamine.[118]



i, $(PPh_3)_2PdCl_2$–CuI cat., Et_3N, reflux 24 h; ii, Et_3N, EtOH, 120 °C, in a sealed tube, 12 h

Scheme 34



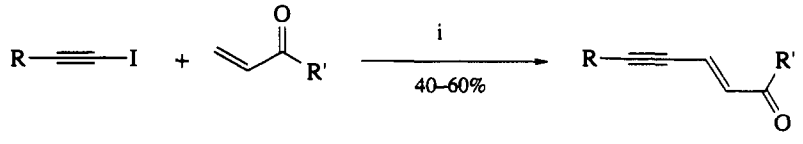
(51) R = H, Bu, Ph; 65–93%

i, $(PPh_3)_2PdCl_2$ cat., Et_3N, 100 °C; ii, NaOEt; iii, H_2O

Scheme 35

2.4.3.6 Palladium-catalyzed Vinylation of Alkynic Iodides

Heck-type vinylations of alkynic halides proceed only under solid–liquid phase-transfer conditions. These mild conditions allow the reaction to be performed with thermally unstable substrates. Thus, methyl (*E*)-enynoates can be obtained from the reaction of 1-iodoalkynes with methyl 2-propenoate in DMF at room temperature in the presence of potassium carbonate, tetrabutylammonium chloride and a catalytic amount of palladium acetate (Scheme 36).[119]



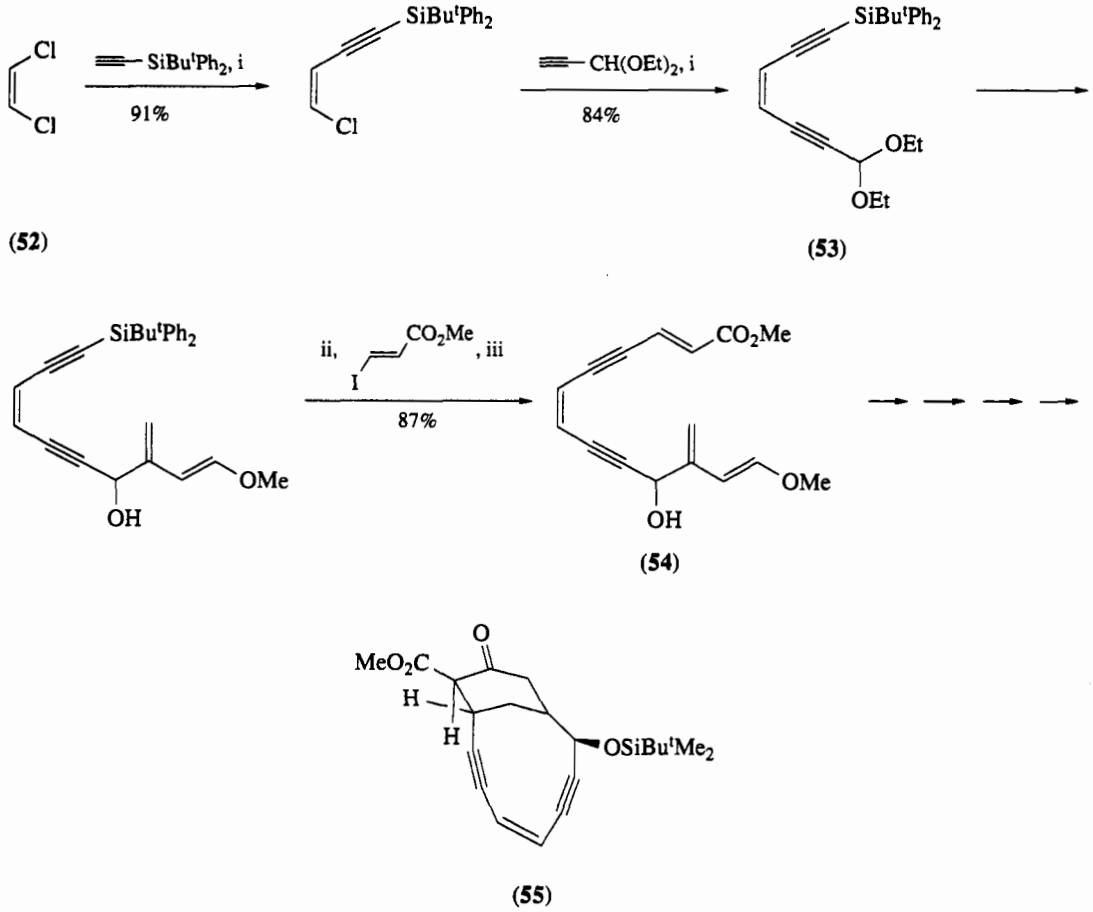
R = n-C_6H_{13}, Bu^n, $SiMe_3$, Ph, n-C_5H_{11}; R'= OMe, Me

i, $Pd(OAc)_2$ cat., K_2CO_3 or Na_2CO_3, $Bu^n{}_4NCl$/DMF, r.t.

Scheme 36

2.4.4 APPLICATIONS TO THE SYNTHESIS OF NATURAL PRODUCTS

As described already, Pd-catalyzed sp^2–sp coupling reactions are extremely useful in the synthesis of natural products. For example, the novel antitumor esperamycins have strong DNA binding/damaging properties which are related to the strained enediyne bridge present in their structures. A plausible biosynthetic pathway to the bicyclic core of the esperamycins could involve intramolecular [4 + 2] cycloaddition of a conjugated polyenyne (**54**).[120] This polyenyne precursor (**54**) has been assembled by palladium-catalyzed stepwise coupling reactions of two different alkyne units to *cis*-dichloroethylene (**52**),[99] leading to (**54**), which was then further elaborated to (**55**), which showed a striking similarity to the esperamycin bicyclic core (Scheme 37).



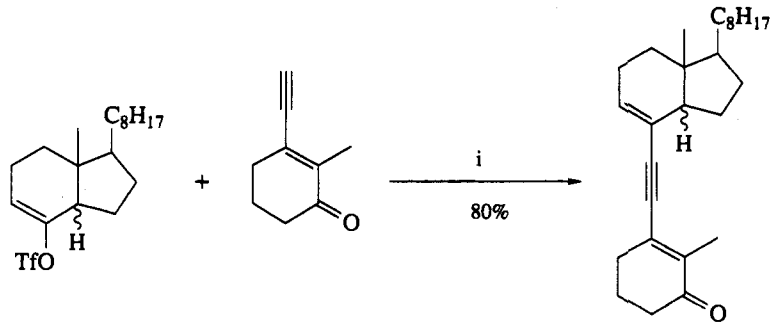
i, $Pd(PPh_3)_4$ (5 mol %), CuI (20 mol %), propylamine; ii, $Bu^n{}_4NF$ (98%); iii, $Pd(PPh_3)_4$ (5 mol %), CuI (20 mol %), methylamine

Scheme 37

Enynes of the structural type (**57**) have been used as key intermediates in the total synthesis of vitamin D. The enyne (**57**) can be obtained by a simple synthesis based on Pd-catalyzed coupling of the keto–enol triflate (**56**) and an alkynic compound containing the vitamin D A-ring fragment (Scheme 38).[121]

The insecticidally active natural isobutylamides, such as dehydropipercide (**60**), and their synthons have been synthesized by Pd-catalyzed coupling reactions. For example, the aryl iodide (**58**) can couple in the dark with the alkynic amide (**59**) in the presence of a Pd–CuI catalyst in triethylamine to give dehydropipercide (**60**).

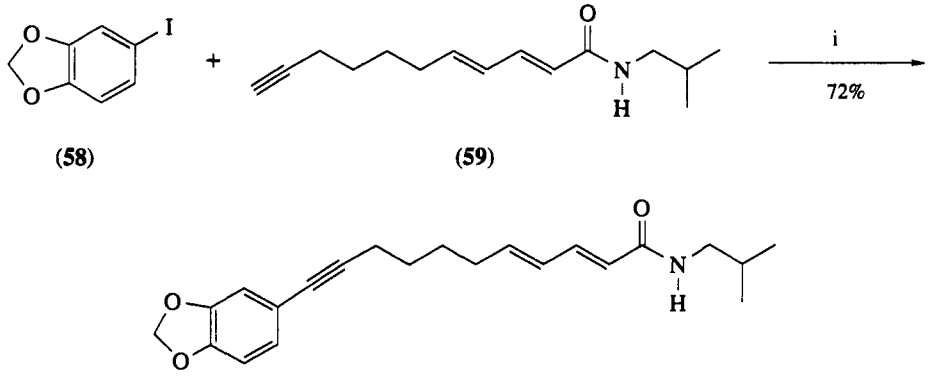
Enynes of the type (**62**), which are similar to those occurring in *Achillea tomentosa*, are made by a similar coupling reaction between vinyl bromide (**61**) and the alkyne (**59**). The stereoisomers of (**62**) can be separated by HPLC to give pure (*E*)- and (*Z*)-isomers in 24% and 19% yields, respectively (Scheme 39).[122]



(56) (57)

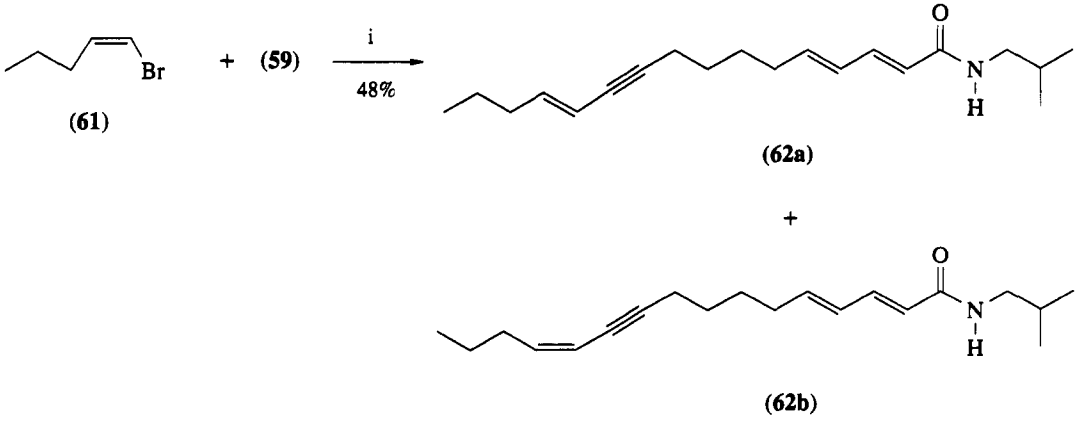
i, $(PPh_3)_2PdCl_2$ (2 mol %), Et_3N (3.4 equiv.) in DMF, 75 °C, 4 h

Scheme 38



(58) (59)

(60)

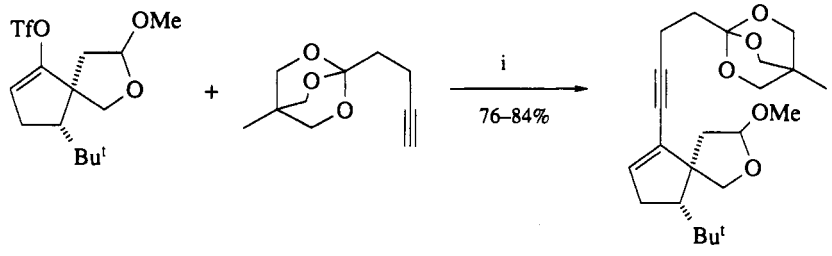


(61) (62a) (62b)

i, $(PPh_3)_2PdCl_2$–CuI cat., Et_3N

Scheme 39

Palladium-catalyzed coupling reactions have been utilized in the total synthesis of ginkgolide B, which has been extracted from the ginkgo tree and is a most active anti-PAF (platelet-activating factor) agent. The important intermediate (**65**) is obtained from the reaction between the enol triflate (**63**) and the alkynic OBO ester (**64**; Scheme 40).[123]

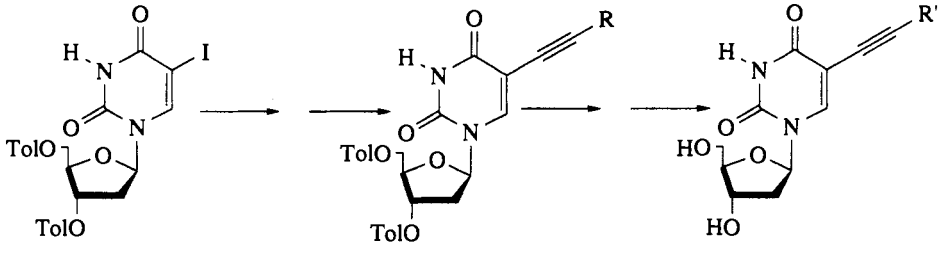


(63) **(64)** **(65)**

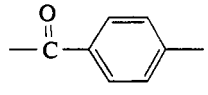
i, $Pd(PPh_3)_4$ (5.7 mol %), CuI (0.5 equiv.), n-propylamine (2.3 equiv.), in benzene, 16 °C, 4 h

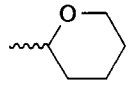
Scheme 40

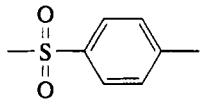
Despite the multitude of functional groups present and the insolubility of the nucleosides in inert solvents, palladium-catalyzed coupling reactions have been used in their synthesis. Thus, the coupling of terminal alkynes with iodinated uracyl nucleosides proceeds in high yield in the presence of a Pd^0–Cu^I catalyst in warm triethylamine, and several of the products obtained by this route have shown useful antiviral activity (Scheme 41).[124]



(66) **(67)** **(68)**

Tol = 

THP = 

Ts = 

	R		*R'*
a	Et	**a**	Et
b	Pr^n	**b**	Pr^n
c	Bu^n	**c**	Bu^n
d	n-C_5H_{11}	**d**	n-C_5H_{11}
e	Bu^t	**e**	Bu^t
f	Ph	**f**	Ph
g	$SiMe_3$		
h	H	**h**	H
i	CH_2OTHP		
j	CH_2OH	**j**	CH_2OH
k	CH_2CH_2OTHP		
l	CH_2CH_2OTol		
m	CH_2CH_2OH	**m**	CH_2CH_2OH
n	CH_2CH_2OTs	**n**	CH_2CH_2OTs
		o	$CH{=}CH_2$
p	$CH_2CH_2CH_2OTol$		
		q	$CH_2CH_2CH_2OH$

Scheme 41

2.4.5 REFERENCES

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2.5
Coupling Reactions Between *sp* Carbon Centers

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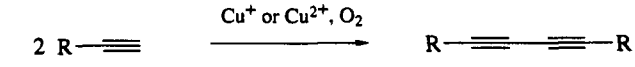
2.5.1 INTRODUCTION

Some of the most useful synthetic transformations of terminal alkynes involve intermolecular and intramolecular homo- and cross-coupling reactions between their *sp*-carbon centers, leading to butadiyne or polyyne derivatives. The two most widely used and practical systems are: (i) oxidative homocoupling reactions, *i.e.* Glaser and Eglington reactions; and (ii) heterocoupling reactions, *i.e.* Chodkiewicz–Cadiot coupling of a terminal alkyne with a haloalkyne.

Other methods for the synthesis of butadiynes and polyalkynes using organometallic alkynide derivatives are less widely used. Reviews describing the above two coupling methods have been published.[1–6] Oxidative couplings of terminal alkynes by a copper(I) catalyst or a copper(II) reagent (Glaser or Eglington reaction) are the best methods of preparing symmetrically substituted butadiyne or polyyne derivatives (equation 1). Unsymmetrically substituted butadiyne derivatives can be prepared by Chodkiewicz–Cadiot type couplings (equations 2 and 3).

These methods have been applied to the syntheses of a wide variety of alkynic compounds.[3] Recently there have been a number of reports describing the syntheses of natural products by oxidative coupling



(1)

$$R{-}{\equiv} + Br{-}{\equiv}{-}R' \xrightarrow{Cu^+,\ NH_2OH{\cdot}HCl} R{-}{\equiv}{-}{\equiv}{-}R' \quad (2)$$

$$R{-}{\equiv}{-}M + Br{-}{\equiv}{-}R' \longrightarrow R{-}{\equiv}{-}{\equiv}{-}R' \quad (3)$$

reactions of terminal alkynes, followed by stereo- or regio-selective addition of hydrogen or organometallic reagents (see Section 2.5.6.4 and Chapter 2.4).

2.5.2 OXIDATIVE HOMOCOUPLING REACTIONS OF TERMINAL ALKYNES

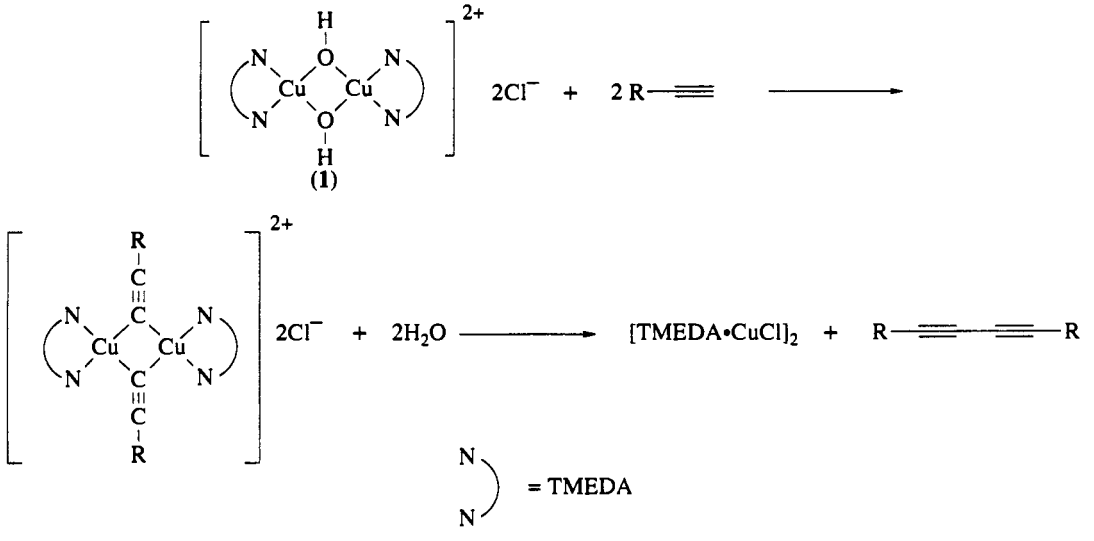
The oxidative coupling of terminal alkynes by copper salts, discovered in 1869 by Glaser, has evolved to the modified method reported in 1962 by Hay.[7] In the Hay procedure, oxygen is passed through a solution of the alkyne and a catalytic amount of a copper(I) salt in a complex-forming solvent, such as pyridine and TMEDA. Although the oxidative coupling by Cu^I salt catalysts in suitable amines has wide scope,[2–6] it is less successful for less acidic terminal alkynes, such as alkyl- or silyl-alkynes.

An essential step in the above process is the reversible formation of the alkynic anion, R—C≡C⁻, which is less acidic and less reactive than that of active alkynes such as phenylacetylene or conjugated polyynes. It has been found that the coupling rate can be accelerated[6] when a small amount of DBU is added to the solution in pyridine (equation 4). The addition of the stronger base facilitates the proton removal from the alkyne. If the product or reactants are oxygen sensitive, it may be necessary to shorten the reaction time.[6] Coupling in a nitrogen atmosphere by using a large excess of the Hay reagent has also been recommended.[8]

$$2\ Et{-}{\equiv} + O_2 \xrightarrow[30\text{–}35\ ^\circ C,\ \sim 90\%]{CuCl,\ DBU,\ pyridine} Et{-}{\equiv}{-}{\equiv}{-}Et + H_2O \quad (4)$$

Another modification of the coupling conditions for alkylalkynes has been reported by Knol *et al.*[9] Thus, the oxidative polymerization of 1,8-nonadiyne was carried out using a catalyst complex prepared by reacting a solution of TMEDA and CuCl in *o*-dichlorobenzene with oxygen gas at 1 atm. It proved to be necessary to dry the reagents as well as the monomer before use, and to add some molecular sieve to the reaction mixture in order to remove the water generated during the reaction.

A study of the kinetics of coupling has established that the reaction rate decreases with increasing water content and that it is enhanced by increasing the concentration and the basicity of the ligand.[10] The formation of water may occur in reversible reaction steps from alkynic end groups and a dimeric copper(II) complex (**1**), followed by intramolecular oxidative coupling of two complexed alkynic groups (Scheme 1). Reviews summarizing the mechanism of the oxidative couplings have been published.[3,5]

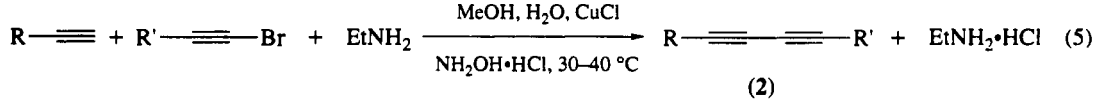


Scheme 1

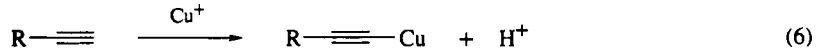
Coupling by copper(II) acetate in pyridine is also a useful procedure for active alkynes such as phenylacetylene and conjugated polyynes. This method is also a useful procedure for making cyclic alkynes.

2.5.3 CHODKIEWICZ–CADIOT REACTION

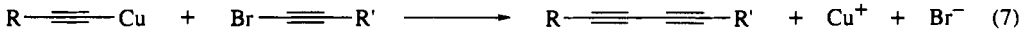
The heterocoupling of a terminal alkyne with a 1-bromoalkyne in the presence of an aliphatic amine and a catalytic amount of a copper(I) salt affords unsymmetrically substituted diynes (**2**; equation 5). This useful reaction, discovered by Chodkiewicz and Cadiot,[11] can be employed advantageously for the synthesis of several polyunsaturated systems.



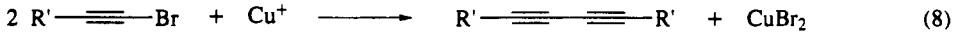
(5)



(6)



(7)



(8)

(3) (4)

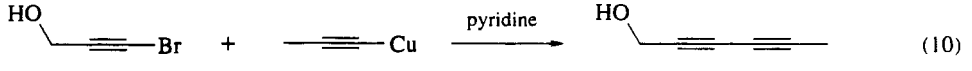
Generally the bromoalkyne RC≡CBr is introduced dropwise to a mixture of the alkyne RC≡CH, ethylamine, methanol or ethanol, in the presence of a catalytic amount of copper(I) chloride, and a small amount of $NH_2OH{\cdot}HCl$. The reaction is usually exothermic and efficient cooling is required during the introduction of the bromoalkyne. The copper(I) alkynyl (equation 6) is assumed to be the reactive intermediate, and the copper(I) ion generated in equation (7) can be employed in equation (6).

The formation of the symmetrical diyne (**4**), generated as in equation (8), can be suppressed by maintaining the concentration of the bromoalkyne (**3**). This side reaction is particularly serious in the case of less acidic alkynes such as alkylalkynes. The reducing agent, $NH_2OH{\cdot}HCl$, is used to reduce the copper(II) ion.

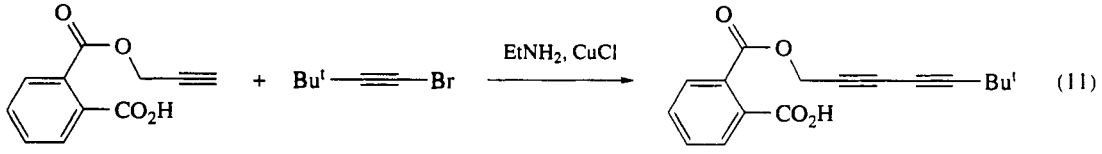
2.5.4 COUPLING OF ORGANOMETALLIC ALKYNIDES WITH 1-HALOALKYNES

The coupling reaction between alkyne Grignard derivatives and 1-haloalkynes has been investigated in some detail. Copper(I) and cobalt(I) salts are used as catalysts (equation 9; M = MgBr)[12,13] and the most effective alkynides appear to be organocopper reagents. Such reagents can be used in the presence of a range of functional groups (*e.g.* OH, equation 10;[14] CO_2H, equation 11[15]).

(9)



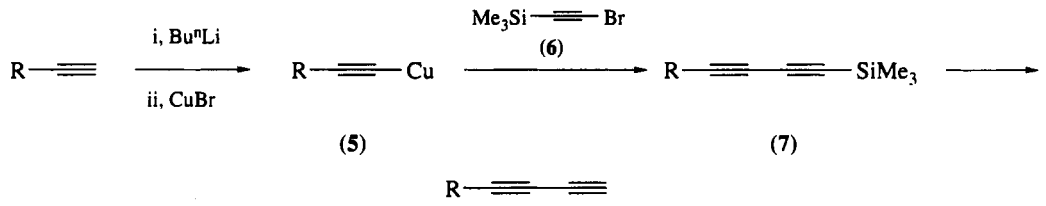
(10)



(11)

A useful and convenient synthesis of 1-trimethylsilyl-1,3-diynes (**7**) by the reaction of copper(I) alkynides (**5**) with bromoalkynes (**6**) has been reported by Zweifel and coworkers (Scheme 2).[16]

A highly reactive copper slurry, prepared by the reduction of $CuI{\cdot}PEt_3$ with 1 equiv. of lithium naphthalide, undergoes rapid oxidative addition to alkynyl halides under mild conditions, and induces their homocoupling when oxygen is bubbled through the mixture.[17]

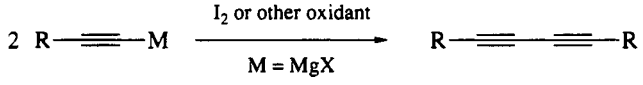


R = *n*-hexyl, cyclohexyl, 1-cyclohexenyl, *t*-butyl, THP-O$(CH_2)_9$

Scheme 2

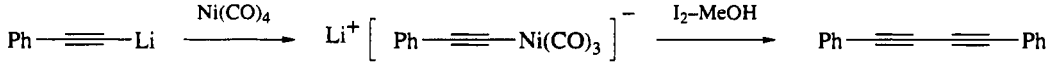
2.5.5 OXIDATIVE COUPLING REACTIONS OF ORGANOMETALLIC ALKYNIDES

Conjugated diynes may be prepared by the reaction of organometallic alkynides with iodine or other oxidants (equation 12).[18,19]



(12)

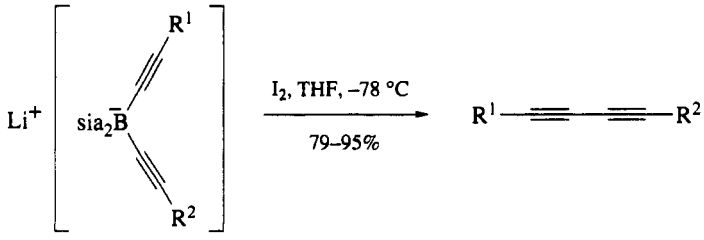
Alkynyllithium reagents add readily to metal carbonyls, leading to thermally unstable anionic alkynic metal carbonylates (**8**), which give mainly the 1,3-diyne, by treatment with iodine–methanol in THF (Scheme 3).[20,21]



(8)

Scheme 3

The reactions of alkynylborates can provide an efficient and selective method of coupling two unlike boron-bound groups. Both symmetrical and unsymmetrical conjugated diynes can be synthesized *via* iodination of the borates prepared by utilizing two cyclohexyl or siamyl groups as blocking groups (equation 13).[22–24] These intramolecular coupling reactions of organoborons provide viable alternatives to the more conventional cross-coupling procedures.



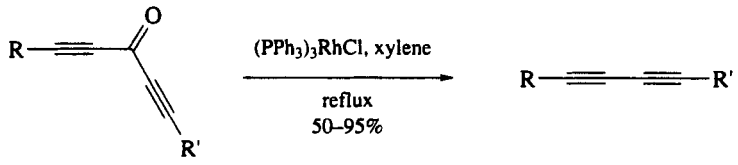
(13)

R^1 = *n*-hexyl; R^2 = Et, Bu^t, Ph

Conjugated diynes can also be prepared by decarbonylation of the corresponding diethynyl ketones using $(PPh_3)_3RhCl$ in boiling xylene (equation 14).[25] High temperatures may be needed to produce the intermediate dialkynyl–rhodium complex.

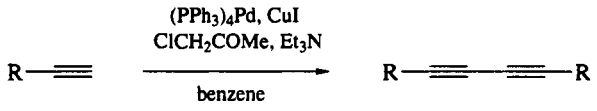
Alkynylpalladium reagents can be useful intermediates in the synthesis of diynes by catalytic coupling reactions since the dialkynyl–palladium complex $(PPh_3)_2Pd(C{\equiv}CR)_2$ (**9**) has been shown to easily produce the corresponding diyne on reductive elimination.[26]

Reactions of benzene solutions of arylalkynes with 1 equiv. of chloroacetone and 2 equiv. of Et_3N, using a mixture of $(PPh_3)_4Pd$ and CuI as a catalyst, afford 1,4-diarylbutadiynes in very good yields. Under similar reaction conditions aliphatic 1-alkynes yield a mixture of symmetrically disubstituted 1,4-dialkynyl-1,3-butadiynes and 3-alkyl-4(1-alkynyl)-hexa-1,5-diyn-3-enes (**10**; equations 15 and 16).[27] This method may represent a good alternative, in nonpolar organic solution, to the Glaser reaction.



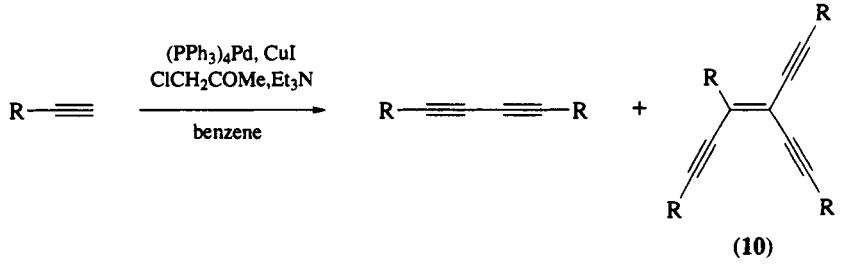
(14)

R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$



(15)

R = Ph, 2-thienyl

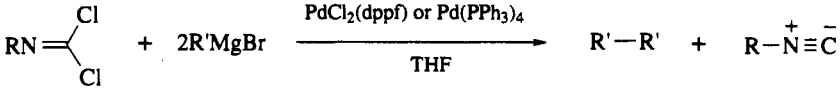


(16)

(10)

R = Bu^n, *n*-hexyl, Pr^n

Ito and his coworkers have reported that palladium-catalyzed oxidative coupling reactions of Grignard reagents in the presence of *N*-substituted isocyanide dichloride afford diynes (equation 17). Isocyanide dichloride may serve as a reoxidant of the palladium catalyst in this sequence *via* a catalytic cycle.[28] In addition Kiji and his coworkers have described the oxidative coupling of phenylacetylene by a Pd–Cu catalyst in the presence of 4-iodo-(3*H*)-phenothiazin-3-one.[29]



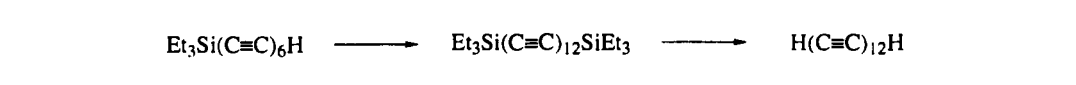
(17)

R = Ph, cyclohexyl; R^1 = PhC≡C, $Me_2(MeO)CC{\equiv}C$; dppf = 1,1-bis(diphenylphosphino)ferrocene

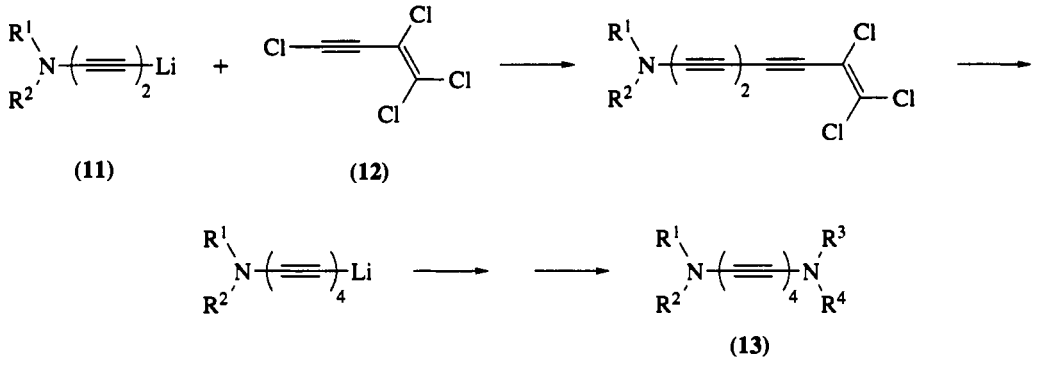
2.5.6 APPLICATIONS

2.5.6.1 Linear Polyalkynes

Many stabilized higher polyynes terminated with bulky groups such as *t*-butyl or trialkylsilyl can be derived from alkyne coupling reactions. Thus polyyne chain extensions using $Et_3Si(C{\equiv}C)_mH$ (m = 1, 2, 3, 6) in mixed oxidative couplings using the modified Hay method,[30] have been reported by Walton and coworkers (Scheme 4).[31] Another polyyne chain extension has been used in the synthesis of the unsymmetrically substituted octatetraynediamines (**13**) *via* the reaction of the lithium alkynide (**11**) with perchlorobutenyne (**12**) (Scheme 5).[32]



Scheme 4

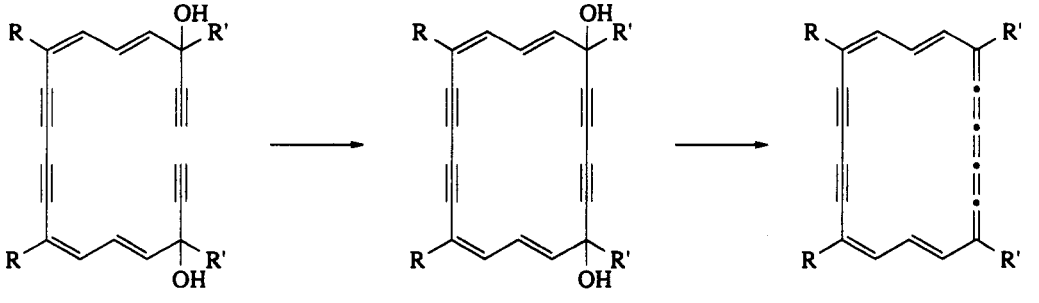


(11) (12) (13)

Scheme 5

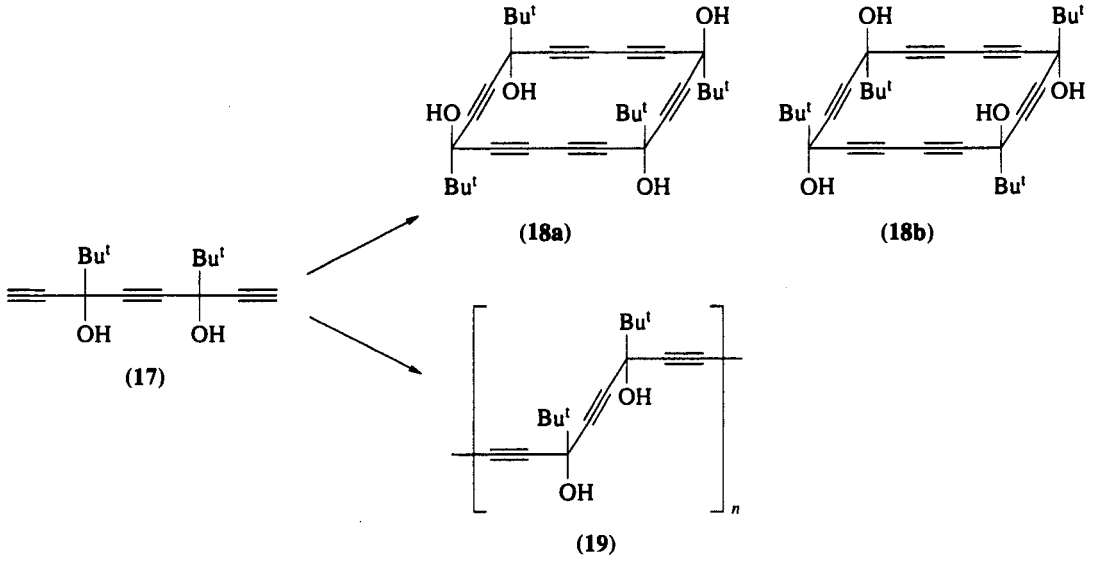
2.5.6.2 Cyclic Alkynes

The oxidative coupling of α,ω-diethynyl derivatives by the Eglington method, which can be performed under homogeneous high dilution conditions, is suitable to obtain cyclic diynes. A general review of cyclic alkynes is available.[33–35] A wide variety of dehydroannulenes have been synthesized by oxidative coupling reactions, *e.g.* the oxidative coupling reaction of the α,ω-diethynyl compound (**14**) to give the cyclic polyyne (**15**) (which could be separated into *meso* and racemic diastereomers), followed by base-induced prototropic rearrangement to provide the novel cyclic polyenepolyyne (**16**; Scheme 6).[36]



(14) (15) (16)

Scheme 6

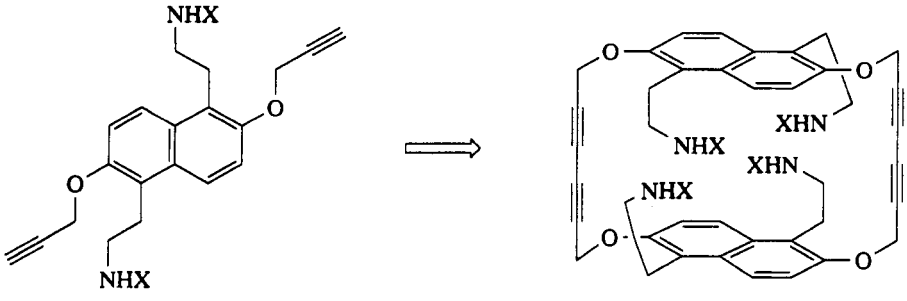


(17) (18a) (18b) (19)

Scheme 7

Toda and coworkers have found drastic differences in the reaction behavior of racemic and optically active 3,6-di-*t*-butylocta-1,4,7-triyne-3,6-diol (**17**) upon oxidative coupling by the Eglington method.[37,38] Thus, the noncentrosymmetric cyclic dimers, (**18a**) and (**18b**), can be obtained from the racemic monomer, but the corresponding optically active monomer does not lead to any of the cyclic dimer. In the latter case the optically active polymer (**19**) is obtained as the sole isolable product (Scheme 7).

Recently oxidative coupling reactions of α,ω-diethynyl compounds have been applied in the synthesis of cyclophanes, which are interesting functional host molecules.[39–42] Whitlock and coworkers,[43] for example, have reported the synthesis of the water-soluble cyclophane (**21**), designed as an esterase mimic by the Eglington reaction of (**20**; Scheme 8).

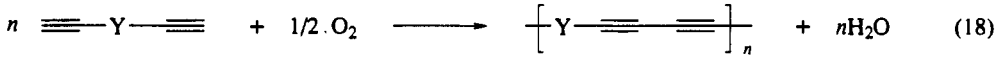


(**20**) (**21**)

Scheme 8

2.5.6.3 Polymer Synthesis

Since the yield in the oxidative coupling is practically quantitative, the oxidative polymerization of α,ω-diethynyl monomers would be expected to yield high molecular weight, linear polymers, as shown in equation (18). Hay has reported that almost any diethynyl monomer, even organometallic monomers, can be polymerized to high molecular weight polymers in the presence of a soluble amine complex catalyst of a copper(I) salt (Hay modification).[44,45]



(18)

2.5.6.3.1 Synthesis of organic polymers

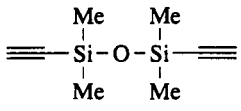
m-Diethynylbenzene gives a pale yellow polymer in quantitative yields when treated by the Hay procedure. The polymer is soluble in solvents such as chlorobenzene and nitrobenzene above 100 °C.[45,46] Recent commercial developments of organic solids from alkynic precursors date from the discovery of the above soluble butadiynylenephenylene polymer. The molecular weight and solubility of the polymer can be controlled by using a mixture of *m*-diethynylbenzene and phenylacetylene in the polymerization. The oligomers produced can then be further processed at high temperatures to form carbon films and fibers.[46]

In order to obtain high molecular weight polymers by the oxidative coupling of α,ω-diethynylalkanes as described in Section 2.5.2, higher temperatures (to increase the polymer solubility), optimized concentrations of the reagents, and addition of molecular sieves (to remove the water generated during the polymerization) have all been shown to lead to best results.[9]

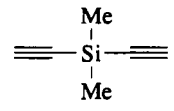
2.5.6.3.2 Synthesis of organometallic polymers

The Hay modification can be applied to organometallic diethynyl compounds such as Group IV alkynes.[45] Parnell and coworkers,[47] for example, have successfully used the procedure to carry out the oxidative coupling of 1,3-bis(dimethylethynyl)disiloxane (**22**). However, diethynyldimethylsilane (**23**) did not give the polymer, as cleavage of the silicon–ethynyl bond occurred instead.

An interesting class of polymers, *e.g.* (**25**) and (**27**), containing conjugated alkynic groups and σ-bonded transition metal atoms in the main chain has been reported.[48,49] Oxidative coupling reactions of



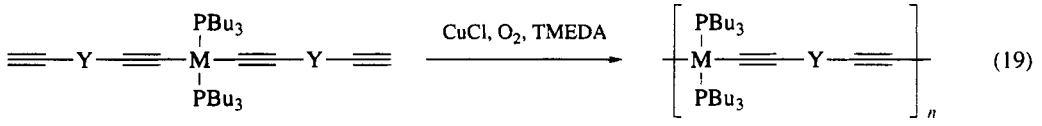
(22)



(23)

dialkynyl complexes are used as one of three methods for preparing the polymers. Polymerization using the Hay modification affords a high molecular weight product, *e.g.* $M = 1.5 \times 10^5$ (**25b**). However, there is a severe restriction on this method since it cannot be applied to monomer complexes such as alkynyl–nickel complexes which are unstable to the oxidant.

A platinum–polyyne polymer, containing diethynylsilane groups in the main chain, can be synthesized by the Hay reaction conditions after appropriate modification to protect the cleavage of Si—C bonds. The characteristics of the synthesis are as follows: (a) since the Si—C≡C bond may be cleaved by uncomplexed copper(II) chloride, a large excess of TMEDA, which is added to catch free copper(II) ion, may retard the formation of the oxygen complex; (b) a homogeneous catalyst solution is prepared by oxygen-bubbling for many hours to complete the formation of the oxygen complex in methylene chloride in the presence of molecular sieves; (c) polymerization is carried out in methylene chloride over the molecular sieves using 3.5 equiv. of the above reagent; (d) to optimize the molecular weight of the polymer the coupling is monitored by GPC, and it requires 7 h. Under the above conditions a white polymer film (**28**; $M = 77\,000$) can be obtained.[50]



(19)

(**24**) **a**: M = Pt; Y = —
b: M = Pt; Y = 1,4-C_6H_4

(**25**) **a**: M = Pt; Y = —
b: M = Pt; Y = 1,4-C_6H_4

(**26**) **a**: M = Pd; Y = —
b: M = Pd; Y = 1,4-C_6H_4

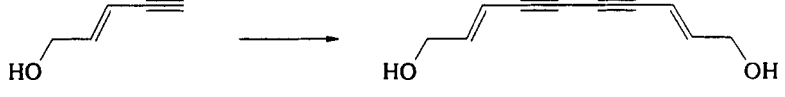
(**27**) **a**: M = Pd; Y = —
b: M = Pd; Y = 1,4-C_6H_4

(20)

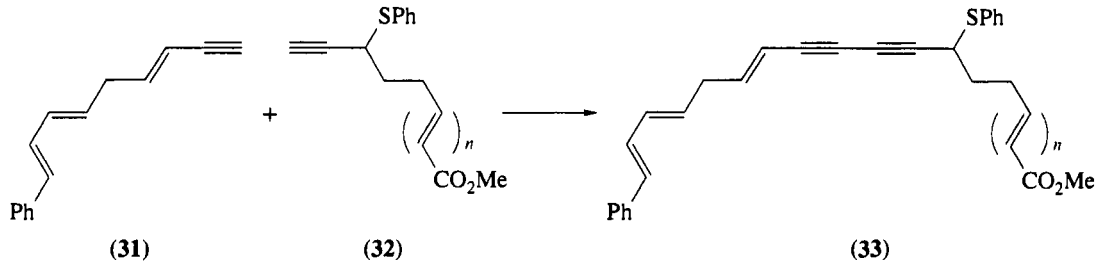
(**28**)

2.5.6.4 Natural Product Synthesis

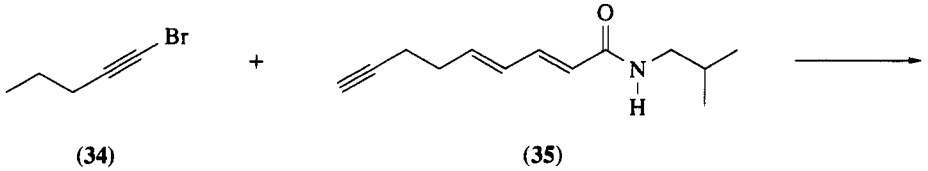
There is a very wide variety of natural products which, with their biological precursors, have structures based on straight-chain fatty acids, containing conjugated alkenic and/or alkynic linkages. Many of these natural polyalkynes have been prepared from alkynic precursors using oxidative couplings. For example, Nicolaou and his coworkers have reported the stepwise, stereocontrolled total synthesis of endiandric acids, utilizing the alkadiynic diol (**30**) as a key intermediate, which was readily available from *trans*-pent-2-en-4-yn-1-ol (**29**) by Glaser coupling.[51] Similarly the biomimetic precursor (**33**) of endiandric acids A–G was prepared by coupling (**31**) (1 equiv.) with the more plentiful (**32**) (5 equiv.) in pyridine–methanol (1:1), containing $Cu(OAc)_2$ (2 equiv.; Eglington method).[52] A further example is the coupling of the ω-alkynic synthon (**35**) with the bromoalkyne (**34**), by the Chodkiewicz–Cadiot method, to give anacyclin (**36**), an insecticide found in *Anacyclus pyrethrum*.[53]



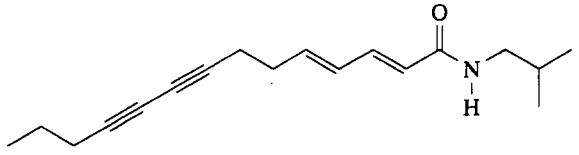
(**29**) (**30**)



(31) (32) (33)



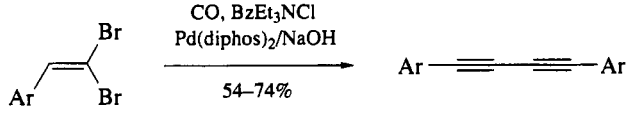
(34) (35)



(36)

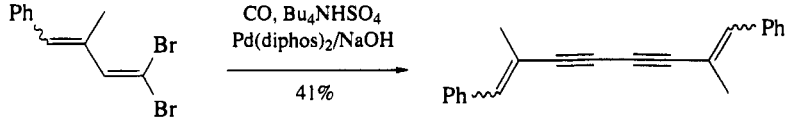
2.5.6.5 Phase-transfer Catalysts

Phase-transfer catalysis is a useful procedure for a variety of interesting metal-catalyzed reactions.[54,55] However, only one example of this approach has been reported for the synthesis of diynes by the *sp–sp* carbon coupling reaction. Thus vinylic dibromides derived from aromatic aldehydes have been shown to react with carbon monoxide, in the presence of zerovalent palladium compounds as the metal catalyst, and under phase-transfer conditions in a two-phase system (benzene, 5 M NaOH), to give the corresponding diynes in reasonable yields (equations 21 and 22).[56]



(21)

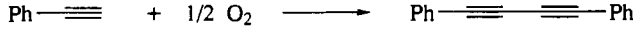
Ar = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$



(22)

2.5.6.6 Copper–Polymer Complexes as Catalysts for Oxidative Coupling Reactions

The oxidative coupling reaction of terminal alkynes is critically dependent on the water concentration in the reaction mixture (see Section 2.5.2). Since water is produced during the reaction, careful elimination of it may be required. Challa and Meinders[57] have demonstrated that the polymer catalyst derived from copper(II) chloride and either *N,N*-dimethylbenzylamine or *N,N*-dimethylaminomethylated atactic polystyrene (**37**) provides an extra protection of the catalytic copper complexes against water in the coupling reaction of phenylacetylene (equation 23), resulting in a higher reaction rate than the low molecular weight catalyst.



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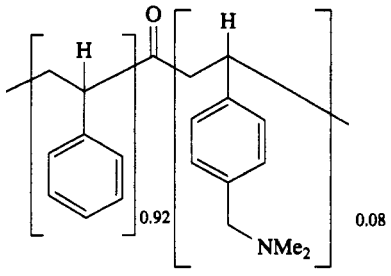

(37)

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2.6
Pinacol Coupling Reactions

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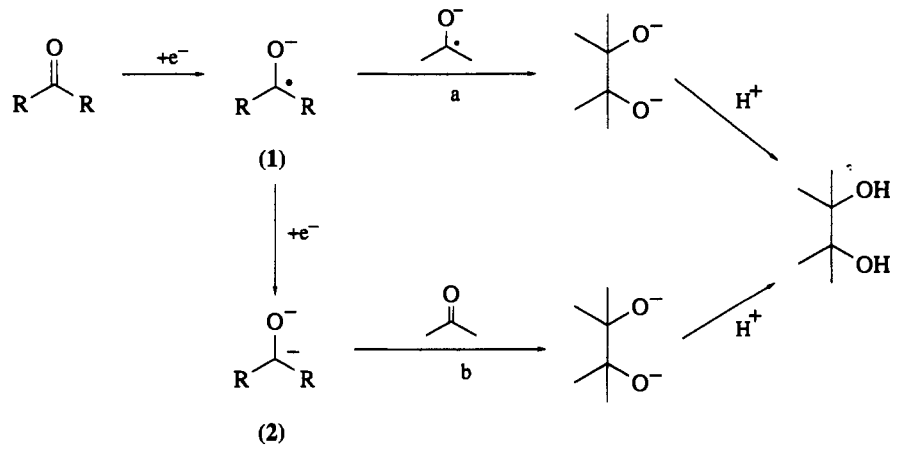
2.6.1 INTRODUCTION

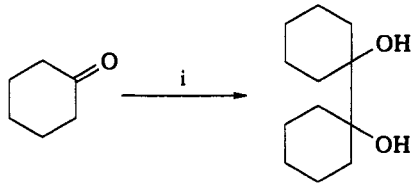
The reductive coupling of carbonyl compounds, especially ketones, to give pinacols is an important method for the formation of vicinally functionalized C—C bonds.[1] In addition, the related coupling of carbonyls to give alkenes, the McMurry reaction, provides a complementary route for C=C bond elaboration.[117]

The intermolecular pinacolic coupling of carbonyl compounds was first described in 1859[2] and, although the classical reagents lacked selectivity, it has since been refined into a mild and selective method for the synthesis of 1,2-diols. Coupling can be initiated photochemically, electrochemically, or with a range of metal reducing agents. A number of mechanisms have been proposed[3] and these can be generalized into two basic types, as shown in Scheme 1. Coupling is propagated by single-electron reduction of the carbonyl group to form a ketyl radical anion (**1**), which either undergoes radical–radical coupling (route a), or is further reduced to the corresponding dianion (**2**) and then nucleophilically attacks a second carbonyl group (route b), so leading to pinacol formation.



Scheme 1

By far the majority of pinacolic couplings occur *via* radical–radical coupling and generally afford a mixture of (±) (*like*) and *meso (unlike)* diols.[4] An alternative and often competing reaction to pinacolization is reduction to the corresponding alcohol.[5] Indeed, selective pinacol formation is critically dependent on many factors, including the reductant used, the solvent[6] and the reaction pH.[30,31,79] The traditionally used reducing agents such as alkali metals[7] or metal amalgams[8] suffered from lack of selectivity and/or sluggish reaction with only low to modest yields. Moreover electrochemical[9,10] and photochemical[11] methods were largely limited to aryl (activated) systems, as was the extensively used Gomberg–Bachman procedure, using Mg/MgI_2.[12] The first major improvement in reaction methodology was the use of aluminum amalgam in dichloromethane or THF (equation 1).[13] The use of these solvents greatly facilitates product isolation, thus improving yields to 40–60%.



(1)

i, Al(Hg), CH_2Cl_2 (or THF), reflux, 40–60%

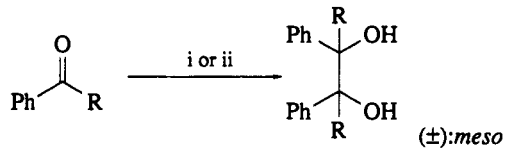
More recently the introduction of low-valent transition metal and lanthanoid based reducing systems, especially those based on titanium, has provided dramatic advances in efficiency and selectivity. It is now possible to select appropriate conditions for efficient coupling of all types of carbonyl compounds, often with high chemo-, regio- and stereo-selectivity. Moreover, imino- and thio-carbonyl derivatives are also coupled *via* pinacolic methodology. The coupling of imines to 1,2-diamines is particularly effective, with excellent control of vicinal stereochemistry.

2.6.2 INTERMOLECULAR COUPLINGS

2.6.2.1 Aromatic Carbonyl Compounds

The relative ease of pinacolization is primarily determined by the reduction potential of the carbonyl group involved. Many reductants are therefore selective for aromatic and other electronically activated systems. Moreover, as a result of this ready reduction, pinacolization of such carbonyls can be effected by either anionic or radical routes. For example, treatment of aromatic aldehydes or ketones with Mg/TMSCl in HMPA promotes pinacolization *via* formation of an α-silyloxy carbanion[14,15] and nucleophilic attack on a second carbonyl group (equation 2). Furthermore, with benzaldehyde the reaction is stereodirecting with a preference for *lk*-coupling.[4] Whilst an alternate coupling method using the milder

conditions of Zn/TMSCl in THF proceeds *via* radical–radical coupling,[16] interestingly ultrasonication of this reaction increases yields by up to 50%. In a similar manner reaction of aromatic aldehydes with hexamethyldisilane and a fluoride catalyst also gives 1,2-diarylethanediols in moderate to good yields, after hydrolytic work-up (equation 3).[17]

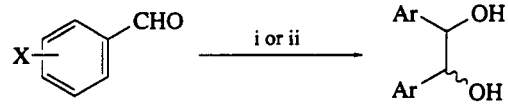


(±):*meso*

R = H, 90% 3:1
R = Me, 88% 1:1

(2)

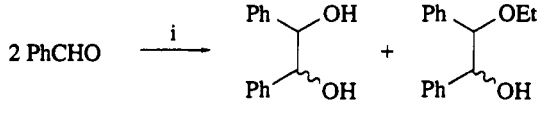
i, Mg, Me_3SiCl, HMPA, 95 °C; ii, Zn, Me_3SiCl, THF, 0–81% (stirring), 56–85% (ultrasonication)



(3)

i, $(Me_3Si)_2$, Bu_4NF, HMPA, 61–95%; ii, $(Me_3Si)_2$, CsF, HMPA, 26–100%

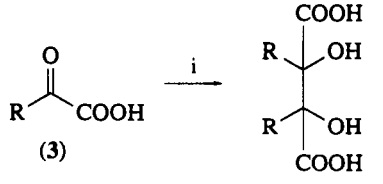
One-electron reductants promoting radical-mediated pinacolic coupling are more common however. Early examples were the use of organometallic species derived from vanadium(II)[18] or chromium(II) salts (equation 4)[18,19] which convert aromatic aldehydes to mixtures of pinacols and the corresponding monoalkyl ethers. Vanadium salts also effect the coupling of capto-datively activated carbonyls such as (**3**) to provide a convenient route to tartaric acid derivatives in good yields (70–80%; equation 5).[20] In contrast, chromium and europium salts give only reduction to the corresponding alcohols.



69% 11%

(4)

i, $Cr(ClO_4)_2$, HCl, EtOH, r.t.



(**3**)

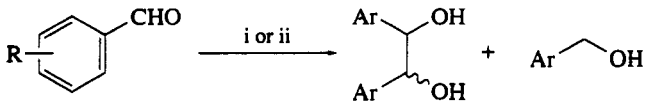
R = Me, 80%
R = Ph, 70%
R = Bn, 80%

(5)

i, $V(ClO_4)_2$, 1 M $HClO_4$, r.t., 10 h

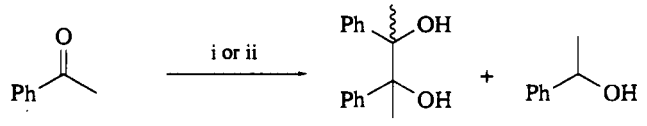
Treatment of aromatic aldehydes with $Fe(CO)_5$ or $Fe_3(CO)_{12}$ in pyridine (equation 6) gives the corresponding pinacols in good yield, together with some reduction.[21] Alternative iron-based reducing systems such as BuLi/$FeCl_3$ or BuLi/$Fe_4S_4(SPh)_4$ also reductively couple aromatic aldehydes and ketones to 1,2-diols (equation 7).[22] The former reagent, however, also produces significant amounts of the corresponding alcohol.

Of more general application are the titanium-based reagents first introduced by Mukaiyama[23] and by Trylik (equation 8).[24] Mukaiyama demonstrated that $TiCl_4$/Zn selectively coupled both aromatic or aliphatic aldehydes and ketones to either pinacols or alkenes by judicious choice of the appropriate reaction



(6)

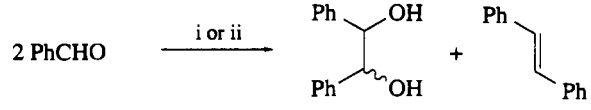
i, $Fe(CO)_5$, pyridine, 80 °C, 74–95%, 6–16%
ii, $Fe_3(CO)_{12}$, pyridine, 80 °C, 72–96%, 6–19%



(7)

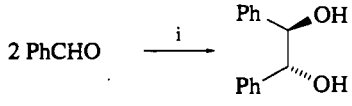
i, BuLi, $[Fe_4S_4(SPh)_4][Bu_4N]_2$, Et_2O, hexane, –93 °C 57% 3%
ii, BuLi/$FeCl_3$, Et_2O, hexane, –93 °C 43% 30%

conditions.[25] In contrast, the Trylik reagent, $TiCl_3$/Mg, gave alkenes with aromatic systems, but coupled aliphatic carbonyls to pinacols in moderate yields. Stable soluble Ti^{II} species can be prepared from $TiCl_4$ and Bu^i_2Te in an inert solvent.[26] In DME this reagent promotes selective *lk*-coupling of benzaldehyde to the corresponding (±)-pinacol (equation 9). More recently Seebach reported that the $TiCl_4$/BuLi system also promotes selective *lk*-coupling of aromatic aldehydes (equation 10).[27] The stereoselectivity is, however, dependent on the nature of the aryl substituent. Thus when R = H, 4-Me, 4-Cl or 2-Me the *l*-pinacol is formed selectively, but when R = 2-Me both *l*- and *u*-isomers are formed.[4] Reduction of Cp_2TiCl_2 with Bu^sMgCl also produces a titanium species exhibiting high *l-(threo)*-selectivity (equation 11).[28] In addition, this reagent is also capable of coupling both aromatic and α,β-unsaturated aldehydes.[28,29] Although most titanium-mediated pinacolic couplings employ Ti^0 or Ti^{II} as the reductant, Ti^{III} has also been used. The reducing power of Ti^{III} redox systems is strongly pH dependent. Thus whilst highly activated carbonyl compounds such as 2- or 4-acetylpyridines are coupled to their respective pinacols by treatment with aqueous acidic $TiCl_3$ (equation 12),[30] less reactive species like 3-acetylpyridine or benzaldehyde require the more strongly reducing basic $TiCl_3$ (equation 13).[31] A similar effect is observed in the electro-[32] and photo-pinacolization[33] of pyridinyl ketones, where the 3-isomers react more slowly.



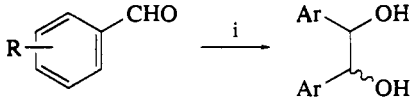
(8)

i, $TiCl_4$ / Zn, THF, 0 °C 98% 1%
ii, $TiCl_4$ / Zn, dioxane, reflux – 98%



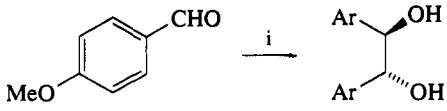
(9)

i, $TiCl_4$, Bu^i_2Te, DME, r.t., 99%



(10)

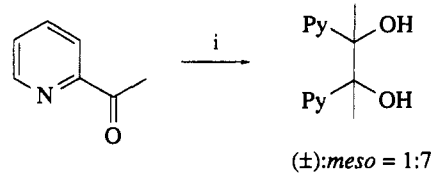
i, BuLi, $TiCl_4$, Et_2O, 50-92%



(11)

ds = 100:1

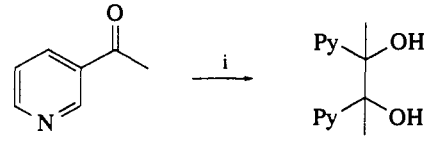
i, Cp_2TiCl_2, Bu^sMgCl, THF, -78 °C to r.t., 96%



(12)

(±):*meso* = 1:7

i, AcOH, aq. $TiCl_3$, r.t., 72%

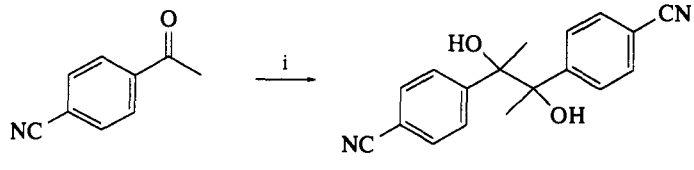


(13)

i, 30% NaOH, aq. $TiCl_3$, MeOH, pH 10–12, r.t., 73%

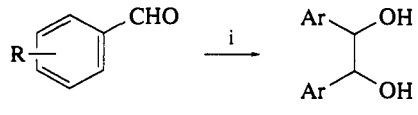
Chemoselective pinacolization has recently been established with the advent of lanthanoid metal based coupling reagents. Imamoto *et al.* employed low-valent cerium as a mild selective reagent (equation 14) suitable for both aromatic and aliphatic compounds.[34] Under these conditions carboxyl, cyano and vinyl halide groups are unaffected. This is in sharp contrast to the relatively low chemoselectivity shown by most titanium-based reagents. Similarly Kagan and coworkers have used samarium diiodide as an alternative chemoselective reductant for the coupling of either aromatic or aliphatic carbonyls (equation 15). With aromatic aldehydes this reagent exhibits complete selectivity for the carbonyl group in the presence of either carboxyl, cyano or nitro moieties.[35] Recently Fujiwara demonstrated that aromatic aldehydes and ketones can be coupled to pinacols using 0.5 equiv. of ytterbium metal (equation 16).[36] The reaction proceeds *via* the formation of an intermediate ytterbium species (**4**) which acts as a nucleophile toward a second carbonyl group.[190]

Photo-[11] and especially electro-chemical[9] pinacolizations of aromatic systems are well established routes to 1,2-diols. Furthermore, stereoselective pinacol formation is possible *via* both routes through control of the reaction media. For example, photopinacolization requires the use of an external hydrogen donor, usually a secondary alcohol or an amine,[37] and stereoselection can be influenced through changes in these hydrogen donors. Thus under neutral conditions approximately 1:1 (±):*meso* mixtures are



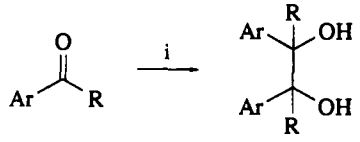
(14)

i, CeI_2, THF, 0 °C to r.t., 91%



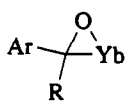
(15)

i, 2 SmI_2, THF, 66–95%

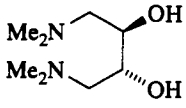


(16)

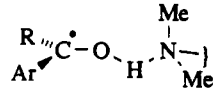
i, Yb (0.5 equiv.), THF, HMPA, 58–99%



(4)

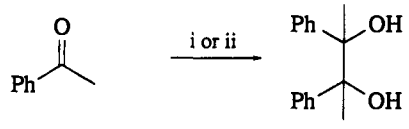


(5)



(6)

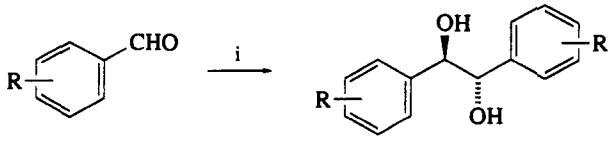
formed (equation 17), but under basic conditions *lk*-coupling, to give the (±)-pinacol, is favored due to increased charge interactions.[38] Amines are more efficient hydrogen donors than alcohols and therefore favor *meso* pinacol formation *via ul*-coupling of neutral ketyl radicals.[39] Recently homochiral amines have been studied as a method for chiral induction.[40] Optical yields of up to 23% have been obtained using the amine (**5**) *via* formation of complexes of the type (**6**).



(17)

	(±):*meso*
i, *h*v,Pr^{i}OH	1.08:1
ii, *h*v, Pr^{i}OH, 0.01 M NaOPr^i	2.98:1

Electropinacolization can be a highly stereoselective and in some cases a stereospecific reaction. The degree of selectivity has been ascribed to both solution and cathode surface effects. For example, the electropinacolization of hydroxybenzaldehyde in an aqueous basic medium gives the *meso* hydrobenzoin (**7**) stereospecifically (equation 18).[41] The related coupling of benzoin (**8**; X = OH) is also stereospecific, giving only one of six possible diastereomeric products, the *threo* isomer (**9**) in 50% yield *via* an *lk*-coupling.[42] However when X = Me, that is in the absence of an additional hydrogen-bonding site, two diastereomers are formed. In agreement with photopinacolic couplings, Stocker and Jenevein demonstrated[43] that at basic pH *lk*-coupling to give (±)-products is again favored (equation 20). A major drawback of electropinacolizations carried out in aqueous media is competing reduction to the corresponding alcohol. Selectivity for pinacol formation is much improved in aprotic media. Under these conditions coupling occurs between neutral radicals, and by the use of conditions that minimize protonation and hydrogen-bonding, (±):*meso* ratios of up to 19:1 can be obtained (equation 21).[44,45] Tetraalkylammonium salts have proven particularly useful in promoting high yielding selective pinacolizations under aprotic conditions, giving almost quantitative yields of pinacols (equation 22).[46] These salts not only lower the reaction potential, a feature that permits the electropinacolic coupling of aliphatic ketones,[57] but also facilitate very high (±):*meso* ratios of up to 50:1.[47] Increased yields have also been obtained using added bivalent transition metal cations, such as Cr^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+} or Zn^{2+}. Product distribution is dependent on the Lewis acidity and complexing power of the cation used.[48] The logical extension of using homochiral coelectrolytes to promote asymmetric couplings has also been investigated but with

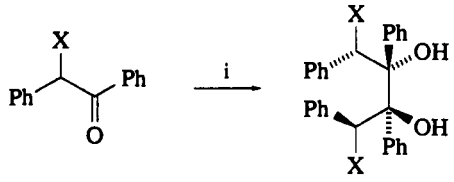


(18)

(7)

i, Hg, 2 M NaOH, or Hg, 4 M NaOH, EtOH, −1.6 to −2.0 V

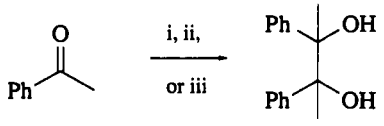
only limited sucess. Thus Seebach[49] has obtained optical yields of *ca.* 6% using the amine (**5**; equation 23), whilst van Tilborg[50] has obtained optical yields of up to 21% with the β-hydroxyamine salt (**10**).



(19)

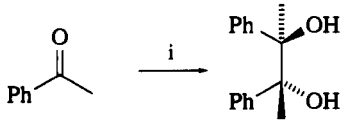
(**8**) X = OH, NH_2 (**9**)

i, Hg/Cu, basic aq. EtOH, 50%



(20)

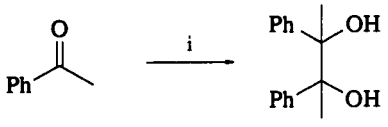
			(±):*meso*
i,	acidic	Hg, aq. AcOH, LiCl, 60%	1.2:1
ii,	neutral	Hg, aq. NH_4OH, aq. NH_4OAc, 46%	1.1:1
iii,	basic	Hg, 2M KOAc, 61%	2.8:1



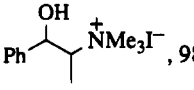
(21)

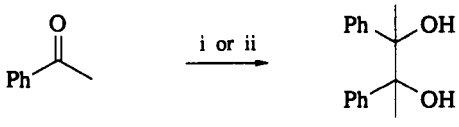
(±):*meso*
19:1

i, Hg, DMF, Bu_4NClO_4, aq. $LiClO_4$

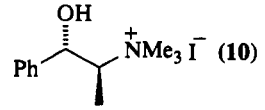


(22)

i, Hg, MeCN, −1.8 V,  , 98%

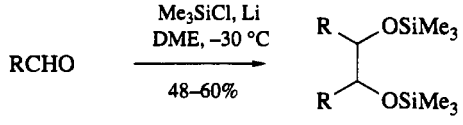


(23)

	optical yield %
i, Hg, DDB (**5**), MeOH, LiBr, 95%	6.4
ii, Hg, MeCN,  (**10**)	20.6

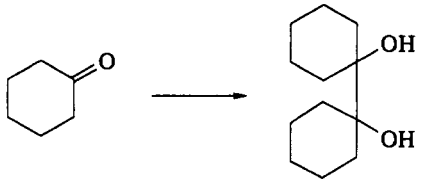
2.6.2.2 Aliphatic Carbonyl Compounds

The synthesis of pinacols from aliphatic carbonyl compounds requires the use of more efficient redox systems than does the corresponding reductive coupling of aromatic systems. Until the early 1970s there were few general efficient methods available. The classical alkali or alkaline metal amalgam reagents are not very selective and are of little use with complex substrates. The first general method for the intermolecular coupling of aliphatic aldehydes was reported in 1975[51] and employs TMSCl/Li as the reductant (equation 24). The use of TMSCl is essential for the *in situ* trapping of the intermediate alkoxides. Titanium(II)-based pinacolic coupling reagents are of more general use, but unfortunately both Mukaiyama's reagent, $TiCl_4/Zn$,[23] and Trylik's reagent, $TiCl_3/Mg$,[24] offer only limited scope. A systematic analysis of titanium-based reagents by Corey and his coworkers[52–54] led to the development of three generally applicable reagents. Thus $TiCl_4/Mg(Hg)$ efficiently promotes intermolecular couplings, whilst $CpTiCl_3/LiAlH_4$ or the hexamethylbenzene complex of $(Cl_2AlCl_2)Ti$ are more suitable for intramolecular examples.[53] The nature and yield of product are highly dependent on the type of titanium(II) species used. The relative efficacy of a selection of these reagents for the coupling of cyclohexanone is shown in Table 1.



(24)

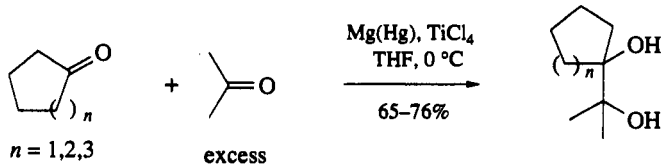
Table 1 Relative Efficacy of Ti^{II} Reagents at the Pinacolic Coupling of Cyclohexanone



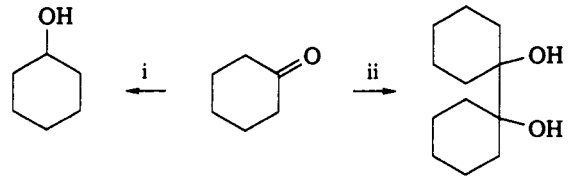
Ti^{II} system	*Yield (%)*
$Mg(Hg)/TiCl_4$	93
$Mg/TiCl_3$	45
$Zn/TiCl_4$	24
$LiAlH_4/TiCl_3$	(Alkene)

Both aldehydes and ketones are efficiently coupled (80–95%) by $TiCl_4/Mg(Hg)$, which is also suitable for unsymmetrical couplings (equation 25). For low molecular weight aldehydes $CpTiCl_3/LiAlH_4$ is the reagent of choice. Recently Wiedmann has introduced graphite-suspended magnesium, C_8Mg, and titanium, C_8Ti, as simple to use, universally applicable reagents.[55] These reagents couple both aromatic and aliphatic aldehydes or ketones efficiently in good yields (48–93%) with a high tolerance for other reducible substituents. Unlike many other reducing agents these reagents are also effective at both inter- and intra-molecular coupling. In addition C_8Ti also promotes McMurry-type coupling of carbonyls to alkenes[129] and the related cyclization of keto esters. Other highly chemoselective reagents based on low-valent lanthanoid metals[1h] have also been applied to aromatic and aliphatic couplings.[34,35] Thus, low-valent cerium (CeI_2) couples cycloalkanones in good yields (64–95%), although competing reduction can be a problem.[34] Organocerium reagents (RCeI) have also been used;[56] however these reagents also give Grignard-type products and reduction in addition to pinacols. Samarium diiodide, an efficient reagent for stereoselective intramolecular couplings, also promotes intermolecular couplings in high yields (80–95%).[35] Recently Kariv-Miller and Mahachi reported a potentially useful method for the electropinacolization of aliphatic carboyl compounds through the use of dimethylpyrrolidinium tetrafluoroborate ($DMPBF_4$) as an electrode potential reducing catalyst (equation 26).[57] In the absence of $DMPBF_4$ only reduction is observed, but using $DMPBF_4$ selective pinacolization occurs.

Although a range of chemoselective pinacolic coupling methods is becoming available the problem of stereoselective coupling of aliphatic carbonyls is less well defined. This is in contrast to couplings of aromatic systems, where both pinacolic coupling to 1,2-diols and reductive (McMurry-type) pinacolic couplings to alkenes can be highly selective. Controlling the stereochemistry of the diol formed from aliphatic carbonyls remains a problem. For example, Mundy *et al.* have shown that the coupling of homochiral



(25)

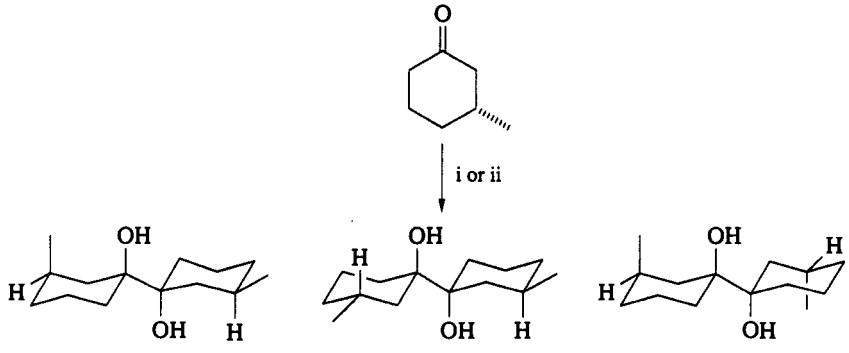


(26)

i, Hg, DMF, aq. diglyme, –2.9 V, 76%; ii, Hg, DMF, aq. diglyme, –2.7 V, $DMPBF_4$, 95%

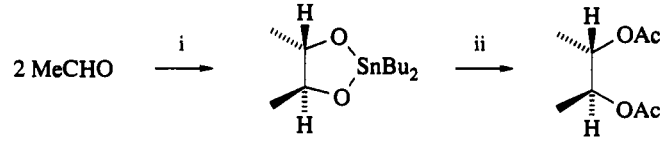
methyl cyclohexanones gives a mixture of stereoisomeric products whose distribution differs when using Al(Hg) or the strongly coordinating $TiCl_4$/Mg(Hg) reagent (Scheme 2).[58] Stereoselective *lk*-coupling of aliphatic aldehydes to (±)-pinacols with up to 100% selectivity (typically 70–96%) has however been achieved *via* photoinduced formation of 2-stanna-1,3-dioxolanes.[59] Formation of the cyclic organometallic intermediate (**11**) controls the stereochemical outcome of the reaction (equation 27). Unfortunately this method is not suitable for ketones since the transition state becomes too sterically hindered. A convenient method for stereoselective coupling of ketones is to link them *via* a chain containing a removeable heteroatom. Such intramolecular cyclizations are then equivalent to stereoselective intermolecular couplings (*e.g.* equation 40).[74,75] Highly *lk*-selective hydrodimerization of α,β-unsaturated aldehydes is possible using the Cp_2TiCl_2/Bu^sMgCl reagent (equation 28).[28] Again metal templating accounts for the observed stereoselection, with the complex (**12**) postulated as the stereocontrolling intermediate.

In some instances the carbonyls in pinacolic coupling reactions exhibit chirality (enantiomer) recognition, that is the ability of an enantiomer to recognize a molecule of like chirality and react exclusively



Reaction conditions	*% Yield*		
	(1*R*,1'*R**)	(1*R*,1'*S**)	(1*S*,1'*R**)
i, Al(Hg), C_6H_6, reflux	53	16	31
ii, $TiCl_4$, Mg(Hg), THF, –10 °C	17	83	–

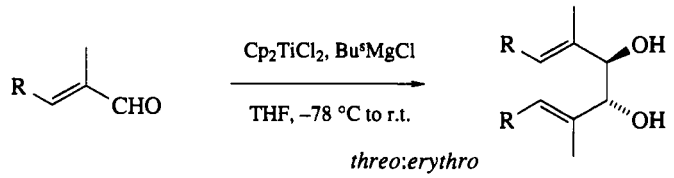
Scheme 2



(27)

(**11**) (±) only

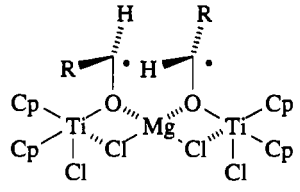
i, Bu_8Sn_3, *hv*, C_6H_6; ii, AcCl, 70%



(28)

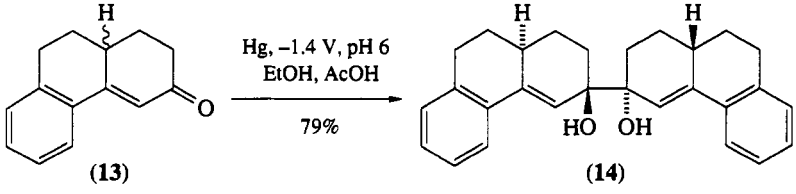
threo:erythro

R = H, 98% 100:1
R = Me, 87% 60:1



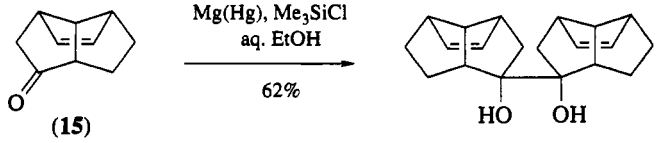
(12)

with it or its mirror image. For pinacolic couplings a reaction between two like ketones, (*R*) + (*R*) or (*S*) + (*S*), giving a homodiol is energetically preferred over reaction between opposite enantiomers to give heterodiols. Thus Tuoboul and Dana have shown that electropinacolization of racemic (**13**) yields exclusively the *trans-threo-trans* diol (**14**) in an enantioselective manner *via* an *lk*-type coupling (equation 29).[60,61] As part of a program directed towards the synthesis of dodecahedrane, Paquette and coworkers investigated the hydrodimerization of both homochiral and racemic ketone (**15**) promoted by mercury amalgam (equation 30).[62] In each case pinacolic coupling occurred only between molecules of the same absolute configuration to give homodiols. Chirality recognition has also been observed with (–)-carvone using the $TiCl_4$/Mg reagent[63] and with homochiral and racemic camphor using lithium in THF or liquid ammonia.[64]



(13) (14)

(29)



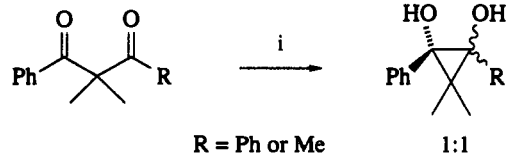
(15)

(30)

2.6.3 INTRAMOLECULAR COUPLINGS

Intramolecular pinacolic coupling reactions are a powerful and selective method for ring construction, enabling the synthesis of a variety of structures ranging from small-ring 1,2-diols to macrocyclic systems.[65] The success of these reactions over such a large range of ring sizes is largely due to the templating effect offered by coordination with the low-valent metal reductants employed, especially titanium. Such templating overcomes the angle strain invoked in synthesis of small rings and the entropic factors associated with macrocycle formation. The reaction can even be applied to the synthesis of cyclopropanediols (equation 31),[66] despite their high sensitivity towards acid or base. The classical methods for pinacolic coupling are generally not very effective in the intramolecular domain;[53] *e.g.* compare the efficacy of the Mg/MgI_2 reagent[67] with that of Corey's $TiCl_4$/Mg(Hg) reagent[53] in the formation of cyclobutane-1,2-diols (equation 32).[68]

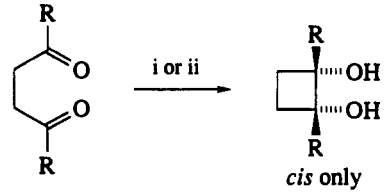
Corey and coworkers have developed a number of reagents (equations 33 and 34) for intramolecular pinacolic couplings during their studies on the synthesis of gibberellic acid (**17**)[52,69] *via* cyclization of the keto aldehyde (**16**). These reagents include Mg(Hg)/Me_2SiCl_2,[52] $TiCl_4$/Mg(Hg), and



(31)

R = Ph or Me 1:1

i, Hg, aq. MeOH, pH 3.7, −1.25 V (*vs.* SCE), 80%

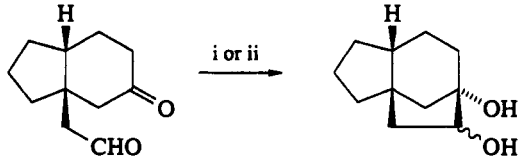


(32)

cis only

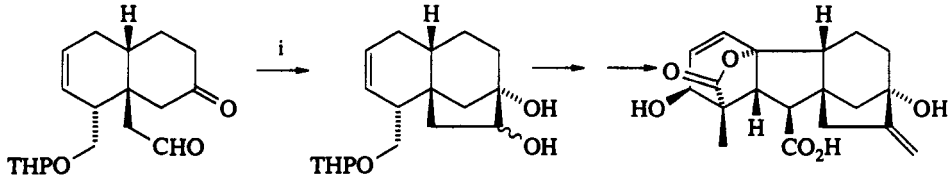
i, R = Ph Mg, MgI_2, 30%
ii, R = Me $TiCl_4$, Mg(Hg), THF, 90%

$CpTiCl_3/LiAlH_4$.[53,69] Titanium-based reagents have also been employed in a new approach to propellane systems, including the quadrone ring skeleton (equation 35).[70] More recently Takeshita *et al.* demonstrated the chemoselectivity of such reagents in a formal synthesis of cuparene (**18**; equation 36).[71] Similar chemoselectivity is observed in pinacolic cyclizations promoted by TMSCl/Zn (equation 37).[72]



(33)

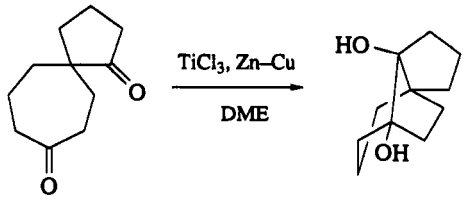
i, Mg(Hg), Me_2SiCl_2, THF, 75%; ii, $TiCl_4$, Mg(Hg), THF, 90%



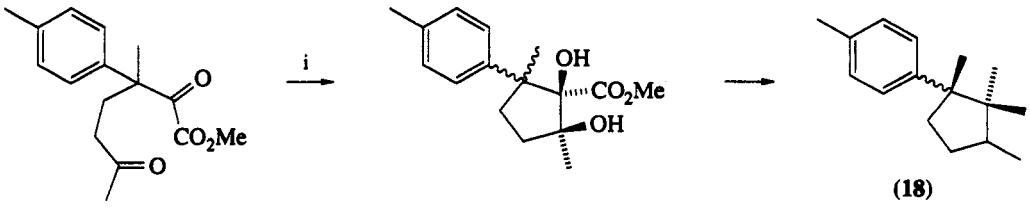
(34)

(16) **(17)**

i, $TiCl_3$, K, THF, 55% or $TiCl_3$, $LiAlH_4$, THF, 40–45%



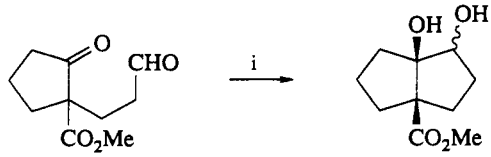
(35)



(36)

(18)

i, $TiCl_3$, Zn, pyridine, THF, reflux, 69%



(37)

α:β = 1:3

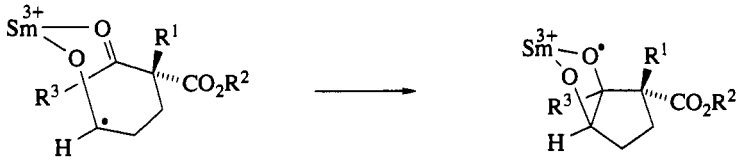
i, Me_3SiCl, Zn, 2,6-lutidine, THF, reflux, 75%

A more versatile reducing agent is samarium diiodide, which promotes chemoselective cyclizations of functionalized keto aldehydes in a stereodefined manner to form 2,3-dihydrocyclopentane carboxylate derivatives in good yields and with diastereoselectivities of up to 200:1 (equation 38).[73] The reaction proceeds *via* selective one-electron reduction of the aldehyde component and subsequent nucleophilic attack on the ketone moiety. Stereochemical control is established by chelation of the developing diol (**19**) with Sm^{3+} which thereby selectively furnishes *cis* diols (equation 39). The stereoselective *ul*-cyclization of 1,5-diketones to *cis* cyclopentane-1,2-diols using $TiCl_4$/Zn has been used to prepare stereodefined sterically hindered acyclic 1,2-diols when a removable heteroatom, such as sulfur[74] or selenium,[75] is included in the linking chain (equation 40).

(38)

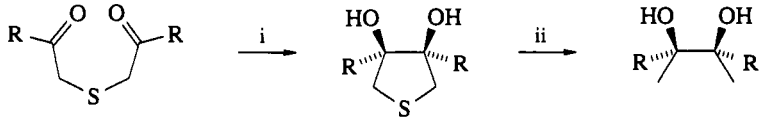
ds = 200:1

i, 2 SmI_2, MeOH, THF, –78 °C, 44%



(39)

(19)

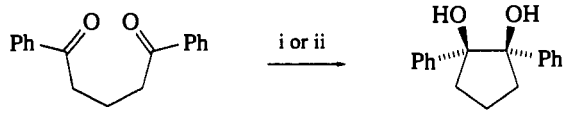


(40)

i, $TiCl_4$, Zn, THF, 0 °C; ii, Raney nickel, EtOH, reflux, 51–81%

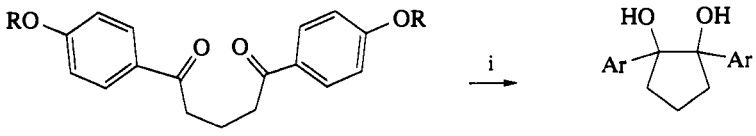
Cyclopentane-1,2-diols have also been prepared by cyclization of aromatic diketones *via* electrochemical pinacolization (equation 41).[76] In contrast to chemically induced reactions, electropinacolizations involve an anionic addition process and not a ketyl radical coupling.[77] Substituents on the aromatic ring can have a profound effect on the stereoselectivity of the reaction (equation 42),[78] as can the pH of the reaction medium.[79] In strongly acidic media *cis* 1,2-diols are formed preferentially *via* coupling of neutral radicals. In basic media a radical anion or anionic attack mechanism is operative and *trans* diols are favored due to charge interactions. In the medium pH range the two mechanisms are in competition and mixtures of *cis* and *trans* diols are formed. As would be expected, increasing steric hindrance decreases the efficacy of electropinacolization.[80]

Larger ring size carbocyclic 1,2-diols can be synthesized *via* extension of the methods used for cyclopentane formation (equations 43–45). Thus, cyclizations of 1,6-dicarbonyls give the corresponding *cis*



(41)

i, Mg cathode, NaI, pyridine, 20%; ii, Al(Hg), EtOH, 50%

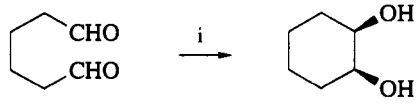


(42)

i, Hg, –2.0 V, 2M aq. (or ethanolic) KOH, r.t.

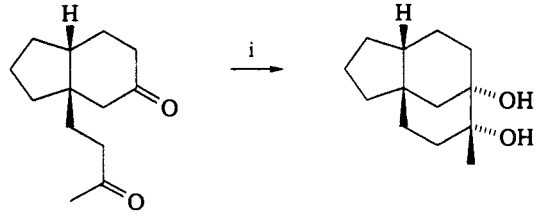
	Yield (%)		
R	*cis*	*trans*	*ratio*
H	42	47	0.9
Me	79	3	26.3

cyclohexane-1,2-diols *via ul*-selective pinacolizations.[53,73] Intramolecular pinacolic coupling is a particularly efficient method for the construction of cyclooctanes *via* cyclization of 1,8-dialdehydes. Takeshita and coworkers for example have used this route in their syntheses of the fusicoccin (**20**; equation 46)[81] and the ophiobolins (**21**) and (**22**; equation 47).[82] Pinacolic cyclizations are not restricted to the formation of small- and medium-sized rings. Through the use of high dilution techniques macrocycle synthesis, *via* C—C bond formation, is highly effective. Thus, nickel-promoted coupling of the diketone (**23**) gives the *meso* diol (**24**; equation 48) stereoselectively,[83] whilst the (+)-antipode (**26**) of the macrocyclic antibiotic (*S,S*)-(–)-grahamimycin A was recently synthesized using the chemoselective pinacolization of the homochiral dialdehyde (**25**; equation 49).[84]



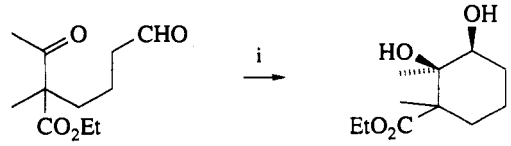
(43)

i, $TiCl_4$, Mg(Hg), THF, 32%



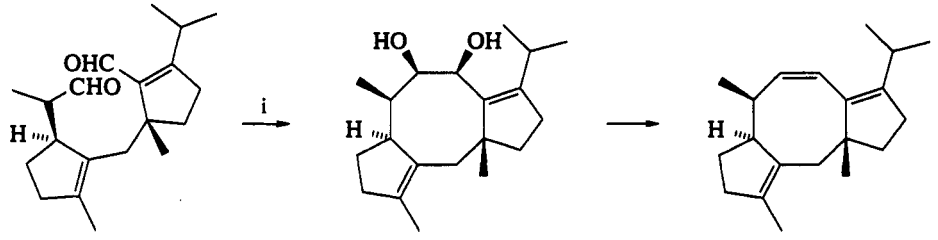
(44)

i, $TiCl_4$, Mg(Hg), THF, 43%



(45)

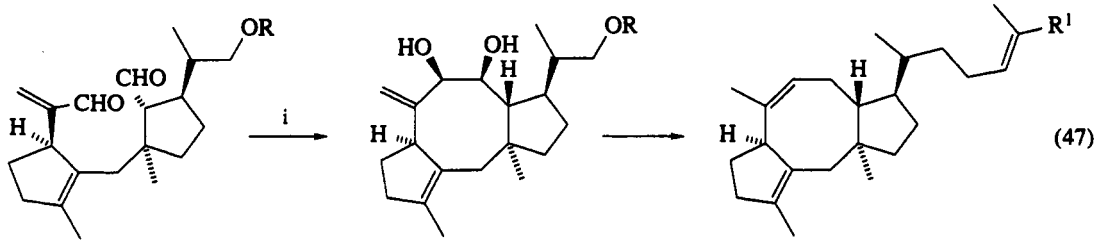
i, 2 SmI_2, THF, 47%



(46)

β:α = 8:1 **(20)**

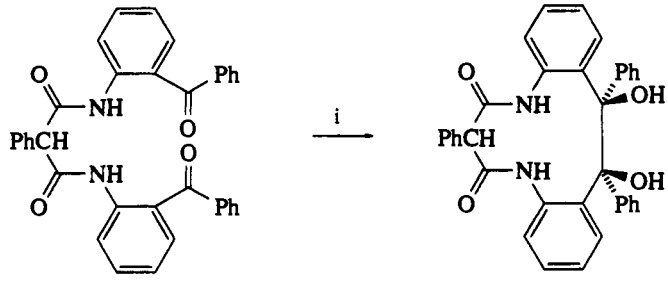
i, $TiCl_4$, Zn, pyridine, THF, 0 °C, 84%



(47)

(21) $R^1 = CO_2H$
(22) $R^1 = CH_2OH$

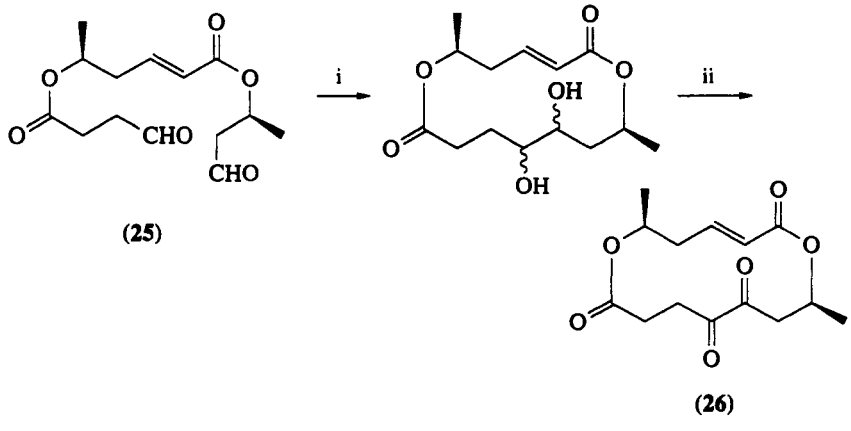
i, $TiCl_4$, Zn, THF, reflux, 96%



(48)

(23) **(24)**

i, $Ni(OAc)_2$, pyridine, DMF, H_2O, 1,2-diaminobenzene, 120 °C, 43%



(49)

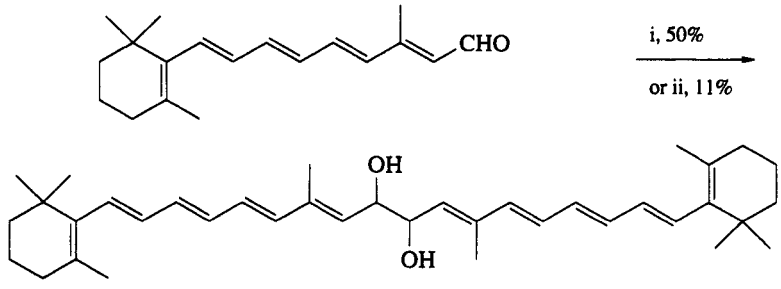
(25) **(26)**

i, $TiCl_4$, Zn/Cu, THF, reflux, 35%; ii, PDC, DMF, 4 °C, 20%

2.6.4 α,β-UNSATURATED CARBONYL COMPOUNDS

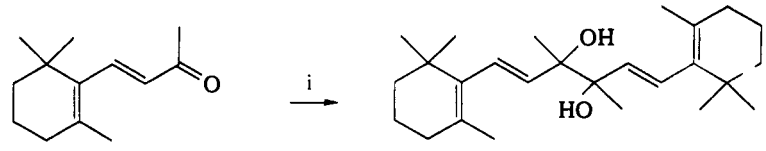
The reductive coupling of α,β-unsaturated carbonyl compounds can lead to three types of dimerization products; pinacols (1,2-coupling), 1,6-diones (1,4-coupling), and γ-hydroxycarbonyl compounds (mixed coupling). These couplings are further complicated by the ability of the initially formed dimerization products to undergo further reactions and complex product mixtures can sometimes result.[85,86]

In electrochemically initiated reactions coupling at the β-carbon to give 1,6-diones is preferred; even 2,2,6,6-tetramethyl-4-hepten-3-one couples selectively *via* this mode.[87] Pinacol formation is favored when β-coupling is sterically hindered. Thus polyenones, such as retinal, are hydrodimerized to the corresponding pinacol in the presence of efficient hydrogen donors (equation 50).[88] In the absence of added hydrogen donors the yield of retinal pinacol is much reduced, even though α- and β-ionone are efficiently coupled under these conditions (equation 51).[89]



(50)

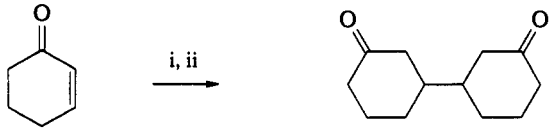
i, Hg, MeCN, Bu_4NClO_4, $CH_2(CO_2Et)_2$; ii, Hg, MeCN, Bu_4NOAc, 1 M AcOH



(51)

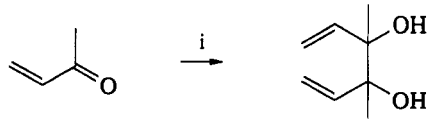
i, Hg, MeCN, Bu_4NOAc, 1M AcOH, 46%

Product distribution in couplings promoted by low-valent metals is dependent on the Lewis acidity/complexing power of the metal employed, and either 1,2- or 1,4-coupling is possible. Thus, cyclohexenone is selectively coupled at the β-position using a TMSCl, $TiCl_4$, Mg, HMPA reagent system (equation 52),[90] whilst methyl vinyl ketone couples *via* the 1,2-mode to give the corresponding pinacol with the less coordinating $TiCl_4$, Mg, Bu^tOH reagent system (equation 53).[91] Unsaturated carbonyls are



(52)

i, Me_3SiCl, Mg, $TiCl_4$, HMPA, 80 °C; ii, HCl, aq. EtOH, 65%

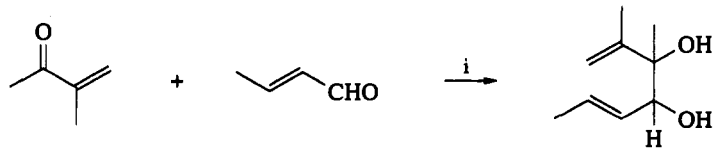


(53)

meso:(±) = 3:7

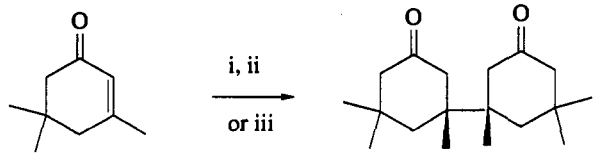
i, Mg, $TiCl_4$, Bu^tOH, 25%

also coupled to pinacols under acidic conditions using low-valent zinc as the radical initiator (equation 54).[16,92] Indeed efficient cross-coupling is possible with this reagent. Organomanganese reagents are normally associated with oxidative radical coupling processes. Organomanganese(II) compounds however can effect β-dimerization of enones (equation 55), although generally a mixture of conjugate addition and hydrodimerization results.[93]



(54)

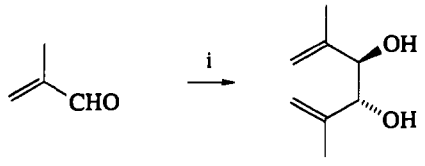
i, Zn, AcOH, Et_2O, –10 °C, 80%



(55)

i, Pr^iMn, THF, –30 °C to r.t., 89%; ii, $Pr^iMnMgCl$, THF, –30 °C to r.t., 80%;
iii, BuMgCl, 5% $MnCl_2$, THF, r.t., 77%

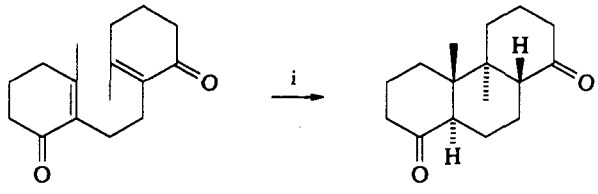
Generally the 1,2-coupling of α,β-unsaturated carbonyls is not highly stereoselective and generates a mixture of stereoisomeric products. A recently developed low-valent titanium species derived from Cp_2TiCl_2/Bu^sMgI overcomes this problem and is very effective at promoting such pinacolizations with high *lk-threo*-selectivity (equation 56).[28] Intramolecular coupling of enones is also possible and by using



(56)

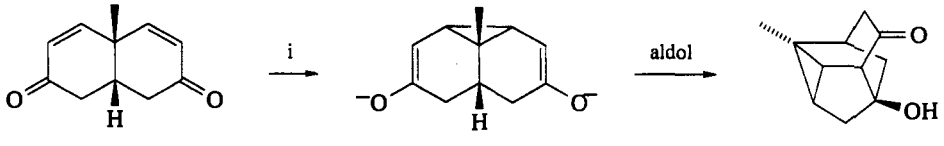
lk:ul = 100:1

i, Cp_2TiCl_2, Bu^sMgCl, THF, 98%



(57)

i, Hg, Et_4NCl, aq. MeCN, –1.80 V, 81%



(58)

(27) (28) (29)

i, Hg/Pt, Bu_4NBF_4, DMF, –2.35 V

linked cyclohexenones provides a stereoselective method for perhydrophenanthraene synthesis, suitable for application to steroidal systems (equation 57).[94] In a related manner, selective 1,6-coupling of the *cis* decalin dione (**27**) gives the tricycle (**28**), which then undergoes aldol cyclization to give the tetracycle (**29**; equation 58).[95]

2.6.5 IMINE COUPLINGS

2.6.5.1 Intermolecular Couplings

The reductive couplings of imines show some significant differences from those of their carbonyl counterparts.[96] Thus in the coupling of *N*-acylimines promoted by low-valent metals the product 1,2-diamines are frequently formed with higher (±)-selectivity than are similar 1,2-diols (equation 59).[97] Smith and coworkers have shown that this phenomenon results from equilibration of dimeric dianions (**31**) and the precursor monomeric radical anions (**30**), to give the thermodynamically preferred (±)-isomer, rather than from selective *lk*-coupling (equation 60).[98] Coupling of *N*-benzylimines also shows some selectivity for the (±)-amine.[99]

(59)

(±):*meso* = 15:1

i, Na, THF, 45–50 °C, 99%

(60)

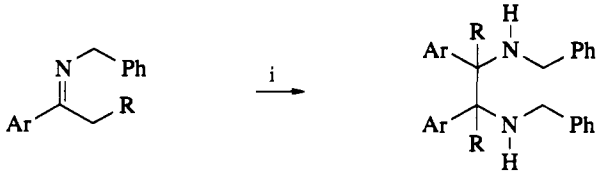
(**30**) (**31**)

In general, *N*-alkylimines show little reactivity with McMurry-type titanium reagents.[125] Mangeney however has demonstrated that symmetrical vicinal (±)-diamines can be prepared using low-valent titanium species generated from $TiCl_4$/Mg(Hg) (equation 61).[100] Furthermore with this reagent coupling is not restricted to aryl (activated) imines. *N*-Alkylimines derived from aldehydes or ketones are efficiently coupled using a Pb/Al bimetal redox system (equation 62);[101] while unsubstituted 1,2-diamines can be prepared from either *N*-(trimethylsilyl)imines or nitriles using the niobium reagent $NbCl_4(THF)_2$ (equation 63).[102] Coupling proceeds with excellent *lk*-diastereoselectivity with (±):*meso* ratios typically 16:1

(61)

(±):*meso* = 9:1 to 7:3

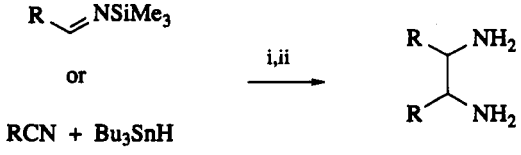
i, $HgCl_2$, Mg, THF, 0 °C to r.t., 40–75%



(62)

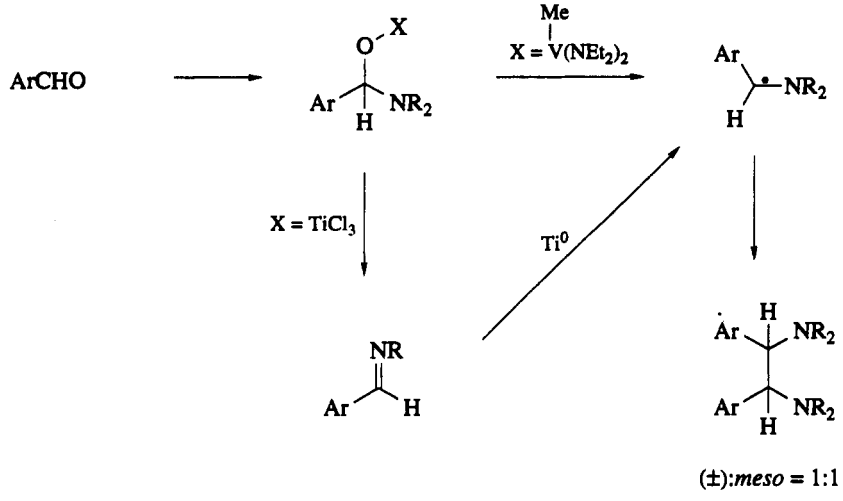
i, $PbBr_2$, Al, TFA, THF, r.t., 62–84% (aldimines)
i, $PbBr_2$, Al, $AlBr_3$, THF, r.t., 63–90% (ketimines)

to 24:1. Aldimines can also be coupled *via* an aminative reduction of aldehydes using either VCl_3[103] or McMurry-type conditions[104] to give 1,2-diarylethylenediamines (Scheme 3). Electroreductive dimerizations of *N*-benzylimines generally give (±):*meso* ratios of *ca.* 1:1.[105] Modest chiral induction has been observed using chiral coelectrolytes (equation 64).[106] In contrast to metal-promoted dimerizations, photopinacolic reactions of *N*-arylimines show a high preference for the *meso* product *via ul*-coupling of neutral ketyl-type radicals (equation 65).[107] For *N*-alkylimines, however, the ratio is dependent on the nature of the alkyl substituent (equation 66).[108]



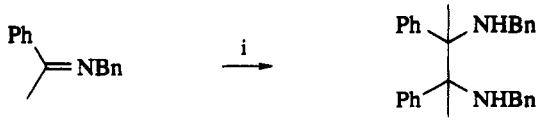
(63)

i, $NbCl_4(THF)_2$; ii, KOH or KF, 40–73%



VCl_3, $LiNR_2$, 14–54%
$TiCl_4$, $LiNR_2$, 23–81%

Scheme 3



(64)

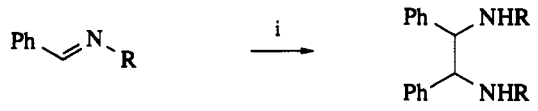
de 5.3% (+)-(*S*)

i, Hg, Ph $\overset{+}{N}Me_3\ I^-$, EtOH aq., MeOAc, 70%

(–)-(*R*)

(65)

i, *hv*, EtOH, 65–95%



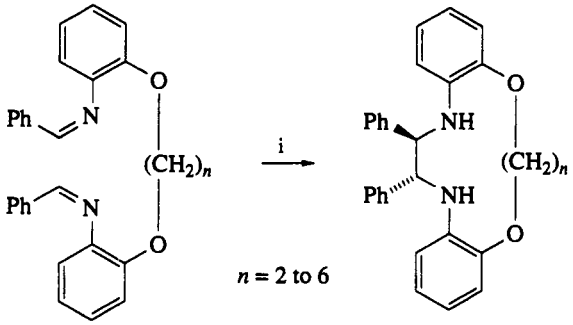
(66)

(±):*meso* = 0:1 to 1:1

i, *hν*, EtOH, 50–70%

2.6.5.2 Intramolecular Couplings

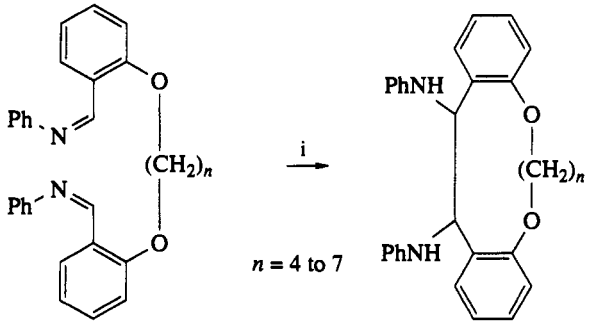
Diastereoselective reaction of diimines with sodium in ether leads to the formation of macrocyclic ethers of the type (**32**; equation 67) and (**33**; equation 68) in modest yields.[109] However, there are no reports of examples using the templating effect of low-valent transition metals, as used to good effect for intramolecular carbonyl couplings. Electrochemical reduction of imines has been used to produce a variety of bicyclic structures *via* cyclization–aromatization (equation 69) or transannular cyclization (equation 70).[110]



(67)

(**32**)

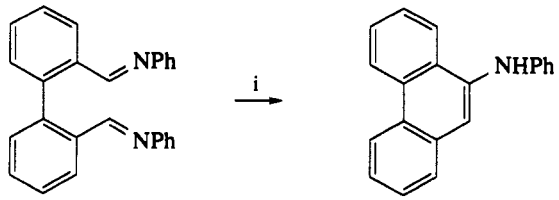
i, Na, Et_2O, reflux, 6–16%



(68)

(**33**)

i, Na, toluene, reflux, 6–15%



(69)

i, Hg, –2.70 V, Bu_4NNO_3, DMF, 60%

(70)

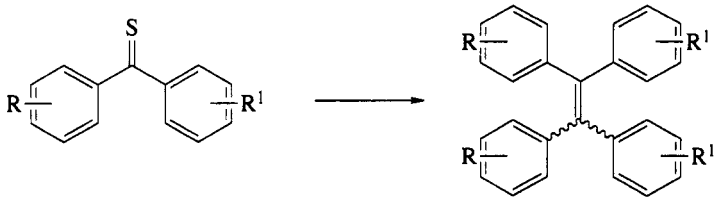
i, Hg, –2.6 to –2.7 V, Bu_4NClO_4, glyme, 94%

2.6.6 THIOCARBONYL COUPLINGS

The reductive coupling of thiocarbonyl compounds to give alkenes can be performed under a range of conditions.[111] This process, the Gatterman reaction,[112] in general requires the presence of conjugated electron-withdrawing groups to facilitate reaction. The traditionally used metal initiators such as copper or iron powder or zinc dust were initially replaced by more efficient initiators such as antimony, bismuth, dehydrogenated Raney nickel or silver.[111,113] Thus, for example, thioacetophenone can be coupled to give the *trans*-stilbene (**34**) by Raney nickel (18% yield)[113] or bismuth (35% yield),[114] but not by copper (equation 71). These initiators have in turn been superseded by even more efficient reductants, including copper powder in DMSO,[115] $FeCl_3/NaBHEt_3$,[116] $TiCl_3/K$,[125] and MgC_8 (Scheme 4).[55]

(71)

(**34**)

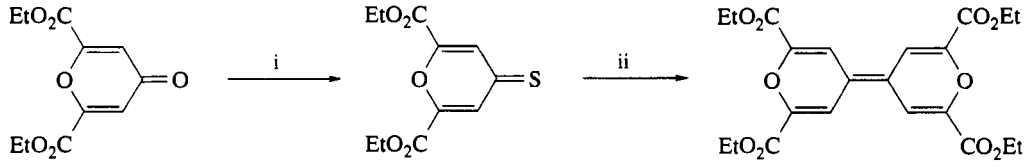


(E):*(Z)* = 1:1

Reagent	*Yield (%)*
Cu, DMSO	98
$FeCl_3$, $NaHBEt_3$	34
$TiCl_3$, K	90
C_8Mg	86

Scheme 4

Interestingly, there are no examples of the synthesis of thiopinacols by the coupling of thioketyl radicals. Moreover the longer C—S bond allows for the possibility of alternate reaction pathways and both episulfides and 1,2-dithietanes have been postulated as reaction intermediates.[111] Finally, certain thiocarbonyls can also undergo thermally induced alkene formation (equation 72).[117]



(72)

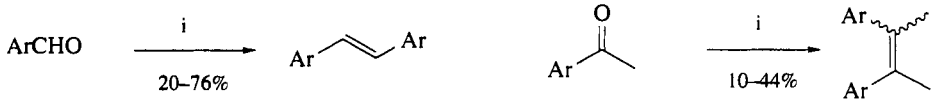
i, P_2S_5, C_6H_6, reflux; ii, 100 °C, 2 h, 50–70%

2.6.7 McMURRY-TYPE COUPLINGS

Although the reduction of carbonyls to alcohols or hydrocarbons is well documented, no general method was available for the reductive coupling of carbonyl compounds directly to alkenes prior to the use of low-valent transition metals. The reductive coupling of carbonyl compounds by low-valent transition metals is now an important method for C=C bond formation, and has been widely reviewed.[118]

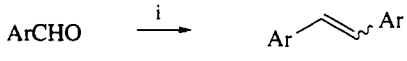
2.6.7.1 Intermolecular Couplings

The reductive pinacolic coupling reaction was introduced by Sharpless, who demonstrated that alkenes could be synthesized from aldehydes or ketones by treatment with tungsten-based reagents derived from WCl_6/BuLi (Scheme 5).[119] Aryl aldehydes are more efficiently coupled using the $WCl_6/LiAlH_4$ system developed by Fujiwara (equation 73).[120] Electrochemically generated tungsten species have also been used (equation 74).[121] Active metal slurries prepared from $MoCl_5/LiAlH_4$, $ZrCl_4/LiAlH_4$, and $VCl_3/LiAlH_4$ also promote coupling but with only modest to poor yields (8–33%).[122] Low-valent niobium generated from $NbCl_5/NaAlH_4$ or $NbCl_5/LiAlH_4$ is more effective and reductively couples both aromatic aldehydes and ketones stereoselectively (equation 75).[123] Interestingly the reaction selectively gives (*E*)-alkenes from aldehydes but (*Z*)-alkenes from ketones.



i, WCl_6, BuLi, THF, r.t.

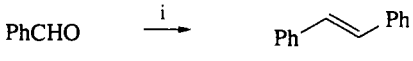
Scheme 5



(73)

(E):*(Z)* =13:1 to 31:1

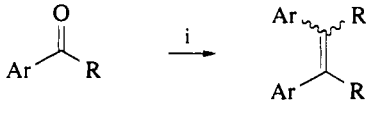
i, WCl_6, $LiAlH_4$, THF, r.t., 60–80%



(74)

(E):*(Z)*=10:1

i, WCl_6, Pt, −1.9 V, THF, 96%



(75)

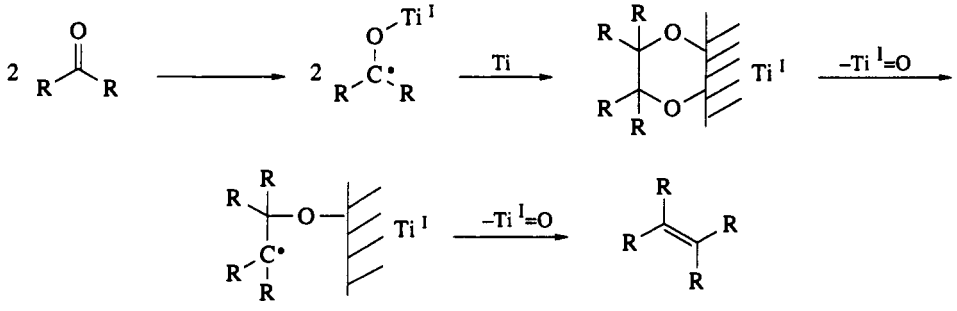
i, $NbCl_5$, $NaAlH_4$, C_6H_6, THF, reflux

R = H 56–95% *(E)*-selective
R = Me 73–75% *(Z)*-selective

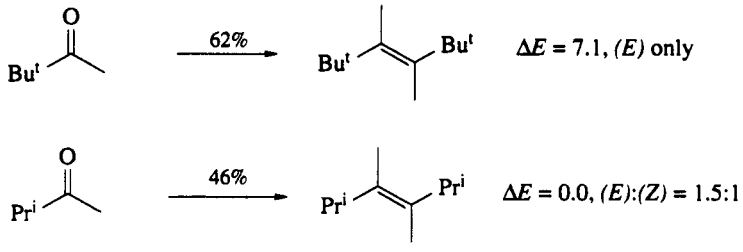
The most widely used systems are those employing low-valent titanium species. The reductive coupling of carbonyl compounds by titanium reagents was independently discovered in 1973 by Trylik[24] and Mukaiyama,[23] and has since been extensively developed by McMurry and his coworkers.[118d,124–126] The McMurry reaction, as it has become known, has proved to be a valuable synthetic tool for the construction of C=C bonds.

There are in fact 10 titanium-based reagents commonly used for the reductive coupling of carbonyls to alkenes; these are $TiCl_3/Mg$,[24] $TiCl_4/Zn$,[23] $TiCl_3/LiAlH_4$,[124] $TiCl_3$/K or /Li,[125,127] $TiCl_2/Zn$,[128] $TiCl_3/Zn/Cu$,[125] $TiCl_4/Al/AlCl_3$,[53] $TiCl_4/Mg(Hg)$,[53] $CpTiCl_3/LiAlH_4$[53] and $TiCl_3/C_8K$.[55,129] By far the most widely used reagent is the McMurry reagent, $TiCl_3/LiAlH_4$. However more reliable and consistent results are obtained using potassium or lithium metal for generation of the titanium(0) species,[125,127]

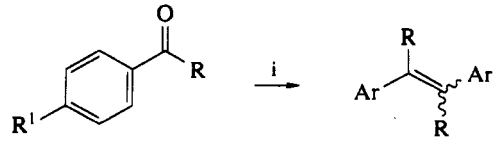
whilst $TiCl_3/Zn/Cu$ is the reagent of choice for intramolecular variants.[125] The nature of the titanium species formed is dependent on the method employed. Thus the $TiCl_3/LiAlH_4$ system can produce Ti^0 or Ti^I depending on the molar ratio of $TiCl_3$ to $LiAlH_4$, whilst the reactive species generated from either the $TiCl_3$/alkali metal or Zn/Cu systems is Ti^0.[125] The mechanism outlined in Scheme 6 has been proposed,[130] and proceeds through an intermediate titanium pinacolate. Indeed pinacols can be isolated from these reductive couplings after short reaction times. It has also been shown that 1,2-diols are deoxygenated to alkenes by Ti^0 reagents.[125] The stereochemistry of the alkene formed from aliphatic carbonyls is controlled by the rate-determining deoxygenation step. When the energy difference between the (*E*)- and (*Z*)-alkene exceeds 4–5 kcal mol^{-1} (1 kcal = 4.18 kJ) the (*E*)-isomer is formed selectively (Scheme 7).[131] Alkyl aryl ketones however can couple reductively to give predominately the (*Z*)-isomer (equation 76).[132] This phenomenon has been rationalized as arising from π-complex formation (**35**) between the phenyl rings and Ti^0.[132] Increased steric hindrance favors the (*E*)-isomer whilst *para* electron-withdrawing groups promote pinacol formation.



Scheme 6



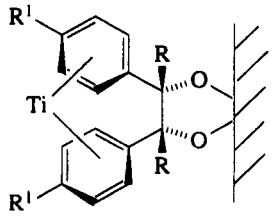
Scheme 7



(76)

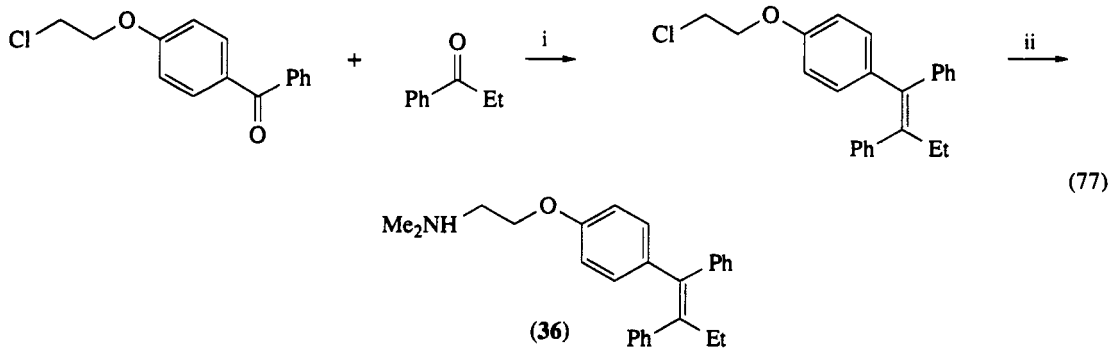
(E):*(Z)* = 1:3 to 1:9

i, $TiCl_4$, Zn, pyridine, THF, reflux, 44–81%



(35)

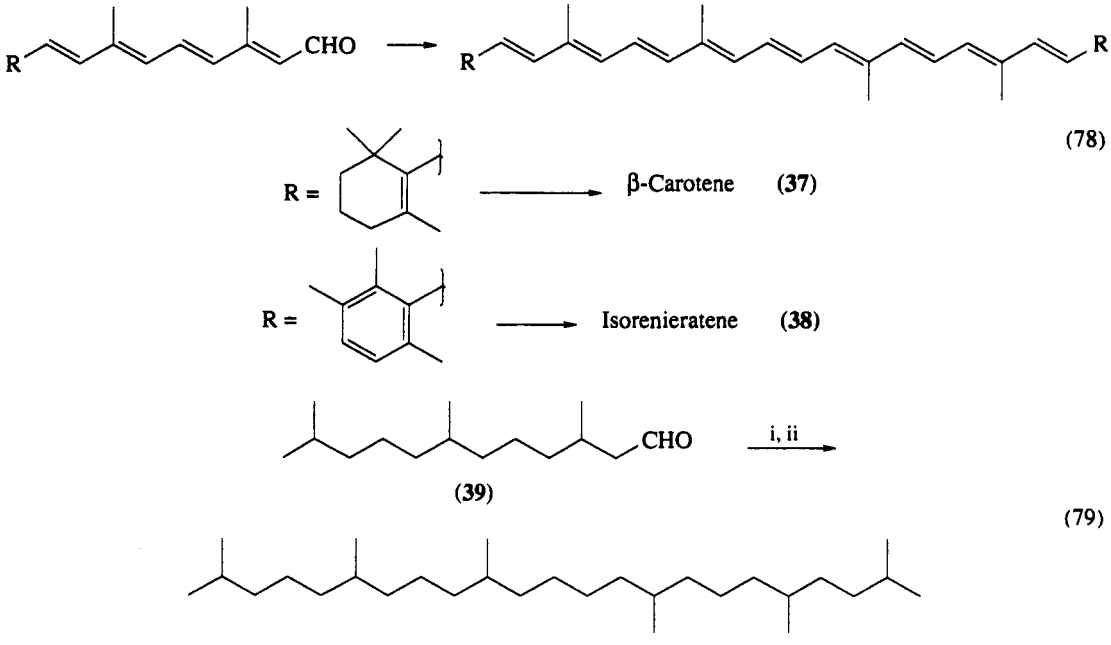
In general the McMurry reaction has been limited to substrates lacking other reducible functional groups.[125] More recently, and contrary to earlier results, various ester[133] and haloaryl groups[134] have proven to be compatible with the reaction conditions. Indeed such selectivity was observed in a new synthesis of the antitumor agent tamoxifen (**36**) using modified McMurry conditions (equation 77).[135]



(77)

i, $TiCl_4$, Zn, THF, reflux, 54%; ii, Me_2NH, EtOH, 75 °C, 83%

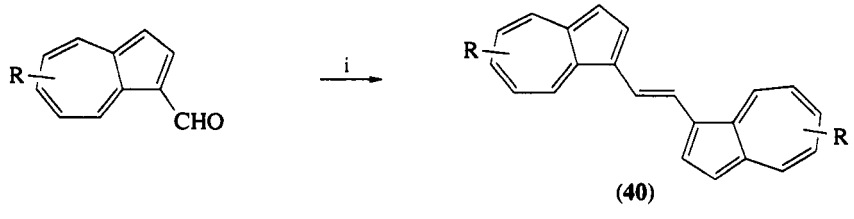
The intermolecular McMurry reaction has proven a particularly valuable route to alkenic hydrocarbons. This is especially true for polyenes and sterically hindered alkenes. For example, β-carotene (**37**; equation 78) can be prepared in 85% yield by reductive dimerization of retinal.[124,136] Isorenieratene (**38**; equation 78) is similarly synthesized in 96% yield,[137] and the aldehyde (**39**; equation 79) has been ela-



(78)

(79)

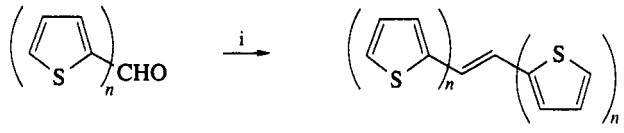
i, Mg(Hg), $TiCl_4$, THF, r.t.; ii, Pd/C, H_2, EtOH, 63%



(80)

i, $TiCl_3$, Li, DME, reflux, 40–70%

borated into perhydrosqualene *via* coupling followed by hydrogenation.[138] Highly conjugated alicyclic systems such as ω,ω′-diazulenylpolyenes (**40**; equation 80)[139] and di-2-thienylpolyenes (**41**; equation 81)[140] have also been prepared.

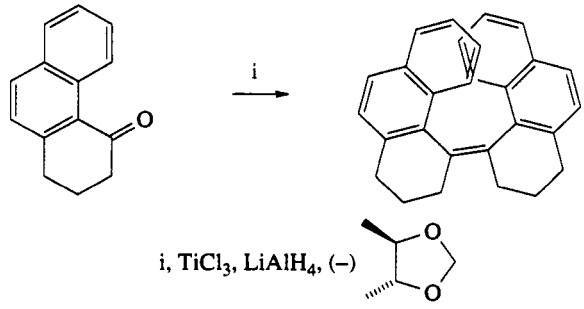


(81)

n = 1, 2, or 3 **(41)**

i, $TiCl_3$, Zn, THF, reflux, 63–71%

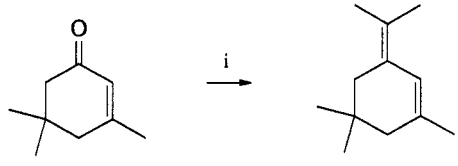
Strained and sterically hindered alkenes are of special interest in physical organic chemistry. By their very nature these structures are difficult to synthesize and the McMurry reaction represents the only viable route to many such compounds (see Table 2). Torsionally distorted alkenes, capable of exhibiting optical activity without a chiral center, have also been prepared.[151] If the reaction is carried out in a chiral solvent the (±) isomer is formed selectively (equation 82).



(82)

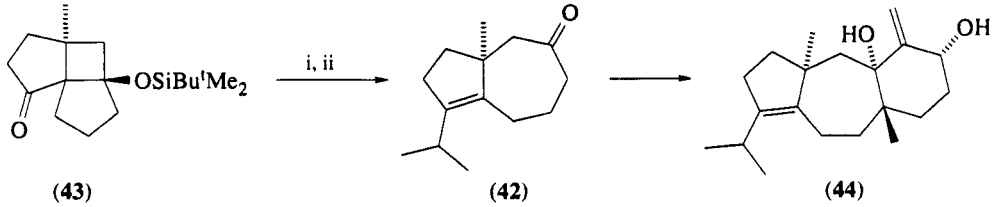
i, $TiCl_3$, $LiAlH_4$, (–)

Unsymmetrical alkenes can be prepared by mixed intermolecular reactions if one of the components, commonly acetone, is used in excess (equation 83).[152] As the isopropyl group is a common subunit of many terpenes this method provides a valuable route for its introduction. Pattenden and Robertson used such a reaction followed by a Grob-type fragmentation in their preparation of the daucenone (**42**) from the readily enolized ketone (**43**).[153] The bicycle (**42**) was used as an intermediate for the synthesis of the diterpene (±)-isoamijiol (**44**; equation 84). Mixed couplings are not restricted to acetone, and almost any carbonyl may be used. For example, Paquette *et al.* employed the aldehyde (**45**)[154] in a synthesis of (±)-α-vetispirene (**46**; equation 85).[155] More complex mixed couplings are also possible. For example, the aldehydes (**47**) and (**48**) are coupled efficiently to the stilbene (**49**), which in turn is converted to phenanthrene alkaloids such as atherosperminine and thalictuberine (equation 86).[156]



(83)

i, $TiCl_3$, $LiAlH_4$, acetone (4 equiv.), reflux, 63%

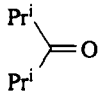
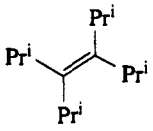
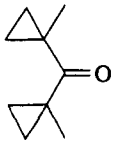
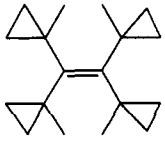
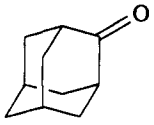
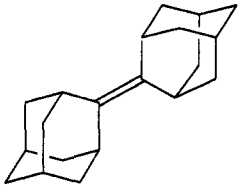
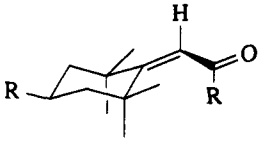
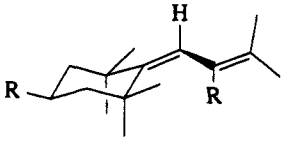
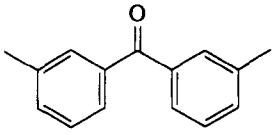
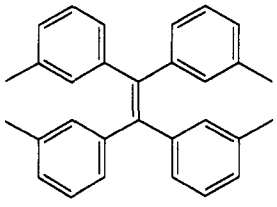
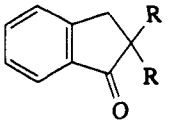
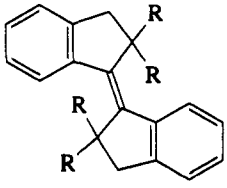


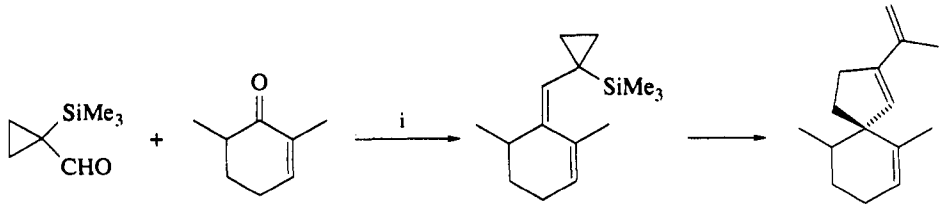
(84)

(43) **(42)** **(44)**

i, $TiCl_3$, Li, acetone, DME, reflux, 76%; ii, HF, THF, reflux, 62%

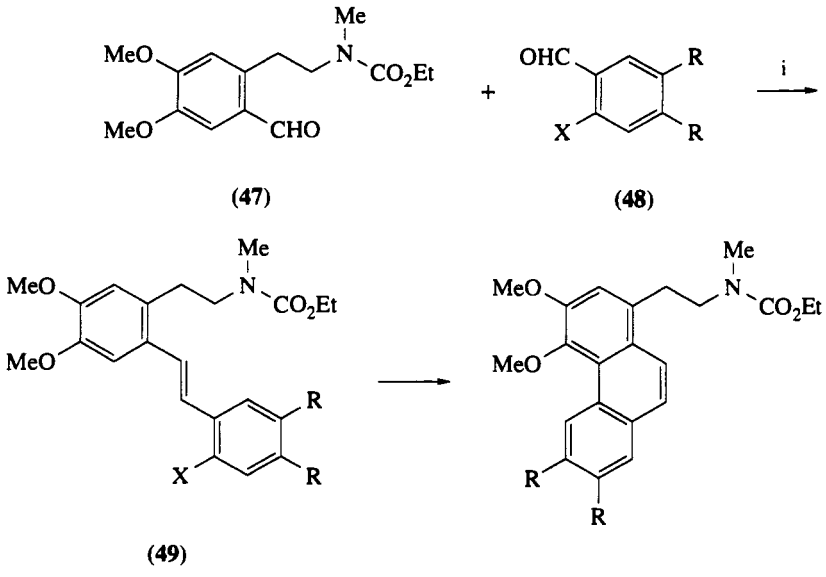
Table 2 Preparation of Sterically Hindered Alkenes by the McMurry Coupling Reaction

Substrate	*Product*	*Yield (%)*	*Ref.*
		6–12	141, 142
		13	143
		85–87	124, 144, 145
		28–85	146
		55–77	147, 148
		53–95	149, 150



(45) (46) (85)

i, $TiCl_3$, Li, DME, reflux, 50–60%

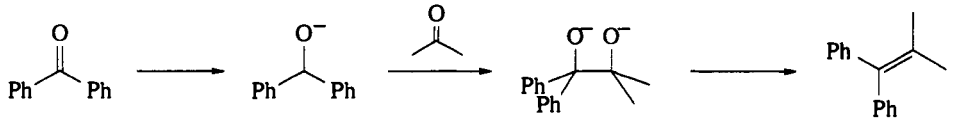


(47) (48) (49)

(86)

i, $TiCl_3$, Li, DME, reflux, 55–67%

When one of the reactants in a mixed coupling is a diaryl ketone an excess of the second component is not always necessary (Scheme 8),[125,152] since diaryl ketones are readily reduced to dianions, which then react selectively with unreduced aliphatic carbonyls.

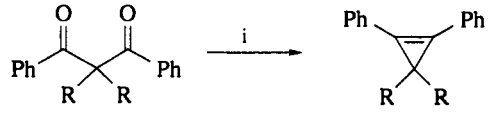


Scheme 8

2.6.7.2 Intramolecular Couplings

The intramolecular McMurry reaction has been used to prepare cycloalkenes of ring size 3 through 16 and up to 22, in good yields (46–95%).[157,159] The method is quite general and is applicable to the intramolecular coupling of dialdehydes, keto aldehydes or diketones. Through utilization of the templating effect conferred by deoxygenation on a titanium surface the reaction is highly efficient and is not affected by ring size effects in contrast to the related acyloin and Thorpe–Zeigler cyclizations. The versatility of the intramolecular McMurry reaction is demonstrated by the variety of ring types that have been synthesized. These range from highly strained cyclopropenes (equation 87)[157] and cyclobutenes[158] through medium-sized rings,[157,159] and on up to macrocycles such as (**50**; equation 88).[159] Although a number of titanium reagents have been employed for intramolecular couplings, the $TiCl_3$/Zn/Cu system[125] generally gives the best yields and represents the reagent of choice for the synthesis of medium ring and macrocyclic alkenes.

A variety of natural products have been synthesized *via* application of reductive pinacolic couplings. An early example is the cyclization of the keto aldehyde (**51**) to the alkene (**52**; equation 89); a precursor to the terpene, cuparene (**18**).[127a] A modified McMurry procedure provides a novel route to steroids such as estrone methyl ether, *via* chemoselective cyclization of the keto aldehyde (**53**; equation 90).[160] The



(87)

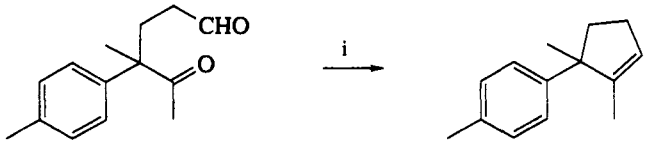
i, $TiCl_3$, $LiAlH_4$, THF, reflux R = Me, 46%; R = Et, 40%

(88)

(50)

i, $TiCl_3$, Zn/Cu, DME, reflux, 83%

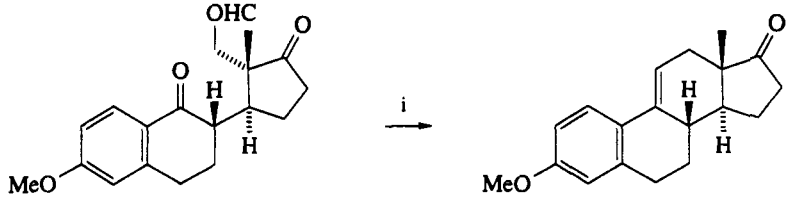
critical importance of the type of titanium reagent used is emphasized in Clive's recent synthesis of (+)-compactin and (+)-mevinolin (equations 91 and 92). Model studies[161] demonstrated that coupling of the keto aldehyde (**54**) was efficiently promoted by McMurry's $TiCl_3$/Zn/Cu reagent (equation 91). For the total syntheses however cyclization of the key keto aldehyde (**55**; equation 92) required the use of the Weidmann reagent $TiCl_3/C_8K$ in a specific molar ratio with respect to (**55**).[162] The use of any other low-



(89)

(51) (52)

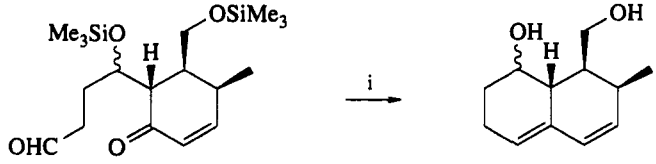
i, $TiCl_3$, K, THF, reflux, 55%



(90)

(53)

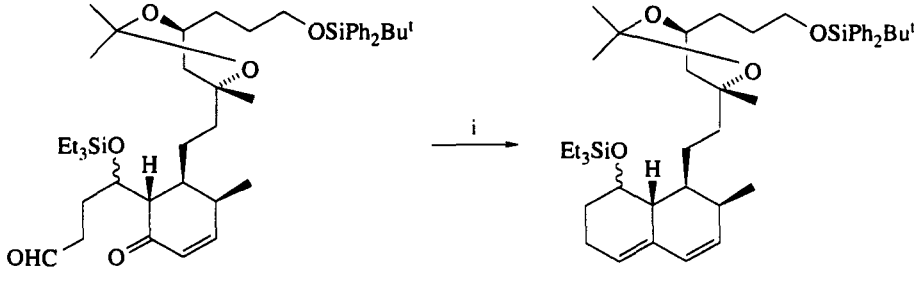
i, $TiCl_3$, Zn/Ag, DME, reflux, 56%



(91)

(54)

i, $TiCl_3$, Zn/Cu, DME, reflux, 72%

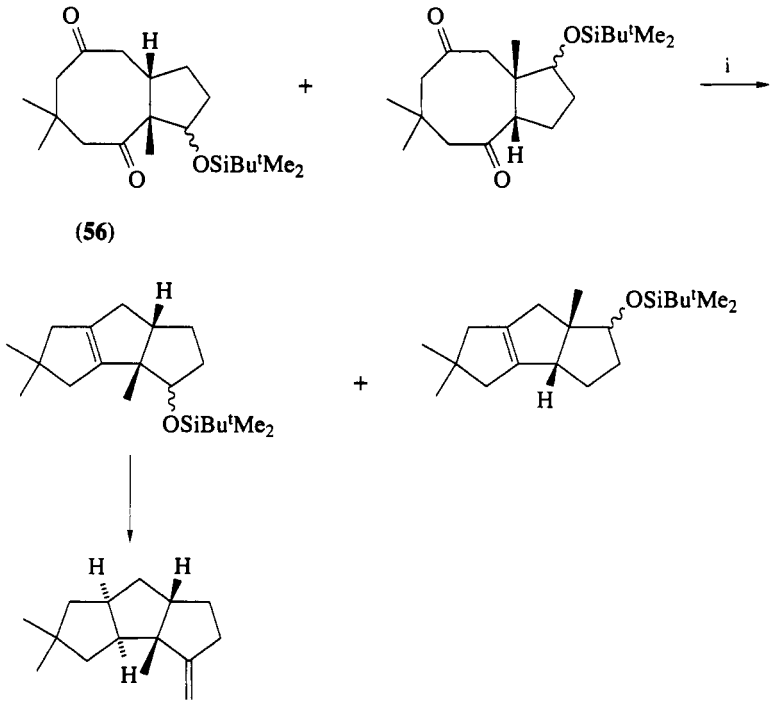


(92)

(55)

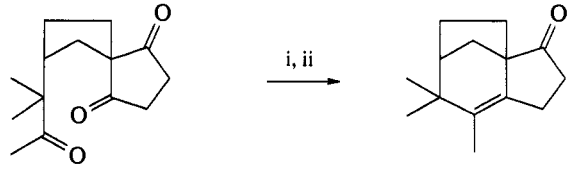
i, $TiCl_3$, C_8K, DME, r.t. to reflux, 85%

valent titanium reagent or departure from the ratio keto aldehyde:$TiCl_3$:C_8K of 1:17:34 gave much reduced yields. Transannular coupling of the diketone (**56**) is a key step in a short photochemical route to (±)-hirsutene (equation 93),[163] whilst regioselective coupling of the triketone (**57**) provides a new route to zizaene sesquiterpenes such as (±)-isokhusimone (**58**; equation 94).[164]



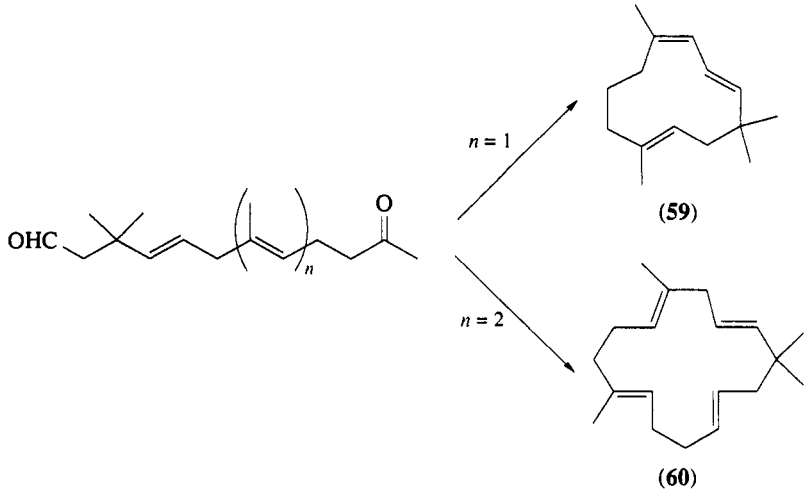
(**56**) (93)

i, $TiCl_3$, K, THF, reflux, 55%



(**57**) (**58**) (94)

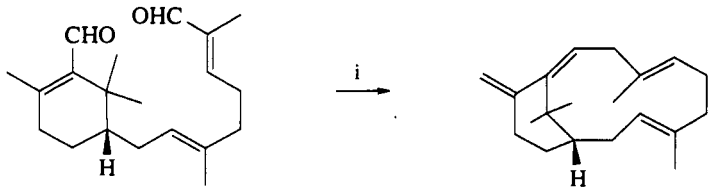
i, $TiCl_3$, Zn/Cu, DME, reflux; ii, PCC, 78%



(**59**)

(**60**) (95)

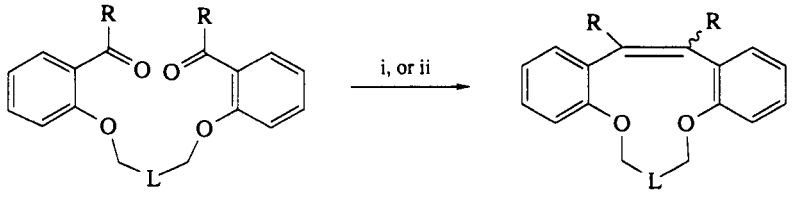
McMurry and coworkers have synthesized a range of medium and macrocyclic terpenes using the $TiCl_3/Zn/Cu$ system.[165–168] Of particular note are the syntheses of (±)-humulene (**59**) and (±)-flexibilene (**60**) which provide a show-case for transition metal based methodology (equation 95).[165] In a related fashion Jackson and Pattenden synthesized verticillene (**62**), a putative biogenetic precursor to the taxane alkaloids, by selective 1,2-coupling of the 1,12-dialdehyde (**61**; equation 96)[169] Several macrocyclic crown ethers of the type (**63**; equation 97) which act as enzyme catalytic models, have been prepared using titanium(0) or titanium(I) reagents.[170] Reductive coupling of the related dialdehyde (**64**) provides cyclophanes of the type (**65**; equation 98), which can be further elaborated to phenanthrenes, of which cannithrene II (**66**) is representative.[171]



(96)

(**61**) (**62**)

i, $TiCl_3$, Zn/Cu, DME, reflux, 25%

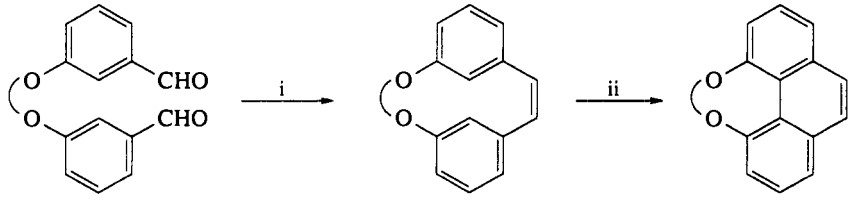


(97)

(**63**)

i, $TiCl_4$, Zn, dioxane, reflux, 83%
ii, $TiCl_3$, Zn, dioxane, reflux, 91%

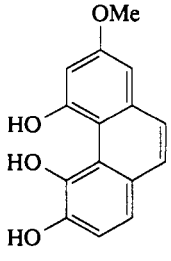
R = H; L = CH_2OCH_2
R = Me; L = $(CH_2)_3$



(98)

(**64**) (**65**)

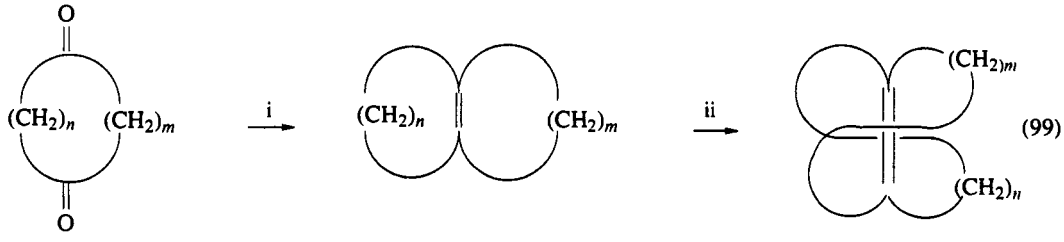
i, $TiCl_3$, Zn/Cu, THF, reflux, 57–78%; ii, Cu^{II} decanoate, I_2, Et_2O, *hν*, 450 W, 51–78%



(**66**)

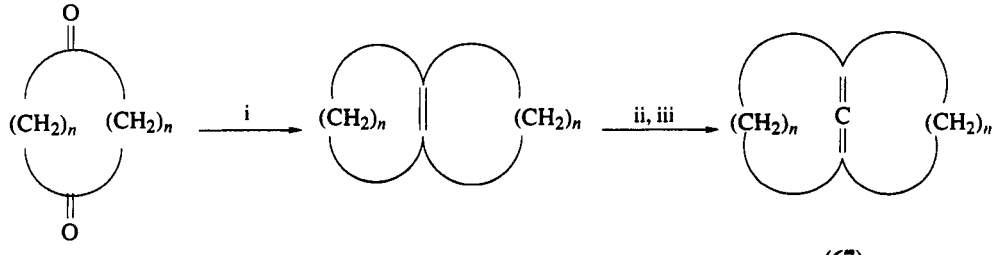
A wide range of alkenic compounds exhibiting interesting properties associated with their π-systems have been elaborated *via* the reductive coupling carbonyls. For example, Marshall and coworkers have studied the intramolecular McMurry reaction as a route to betweenanenes, a class of conformationally

flexible bicyclic alkenes (equation 99).[172] Nakazaki *et al.* have used a similar approach to optically active doubly bridged allenes of the type (**67**; equation 100).[173] A class of compounds with interesting intracyclic electronic properties are compounds such as (**68**) and (**69**) (equation 101). McMurry and coworkers have prepared these alkenes *via* cyclization of the appropriate diketones (**70**)[174] and (**71**)[175] respectively. It is worth noting that these cyclizations overcome considerable strain associated with distortion of the cyclohexane rings to boat topographies during coupling.[175] The alkene (**68**) exhibits an intracyclic π-sys-



(99)

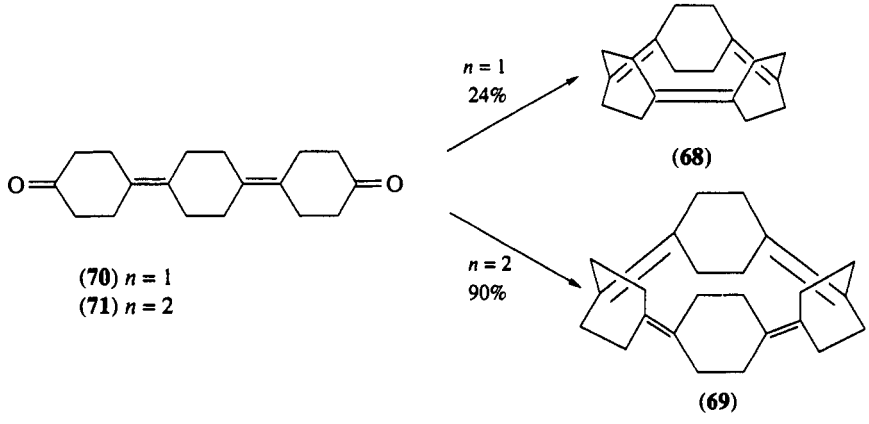
i, $TiCl_3$, Li, DME, reflux, 34–73%; ii, hv, 450 W, xylene



(100)

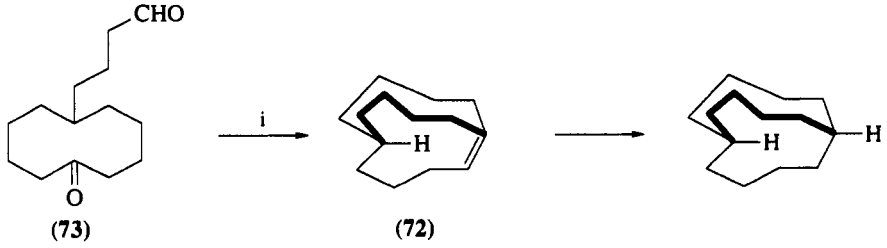
(**67**)

i, $TiCl_3$, Zn/Cu, DME, reflux, $n = 5$, 91%; $n = 6$, 72%;
ii, $KOBu^t$, $CHBr_3$, pentane, 55–81%; iii, MeLi, Et_2O, pentane, –78 °C, 71–89%



(**70**) $n = 1$
(**71**) $n = 2$

(101)



(**73**) (**72**)

(102)

i, $TiCl_3$, Zn/Cu, DME, reflux, 30%

Table 3 Preparation of Cyclic Polyenes by the McMurry Coupling Reaction

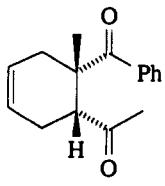
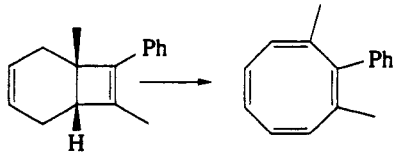
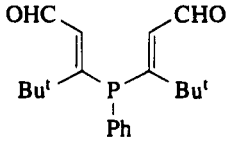
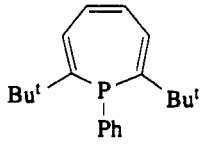
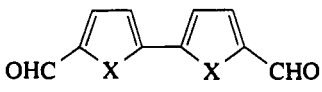
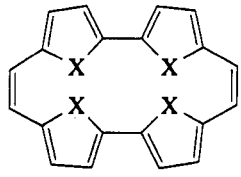
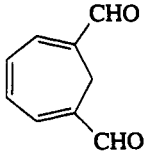
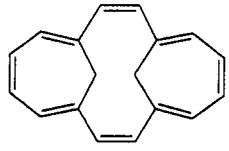
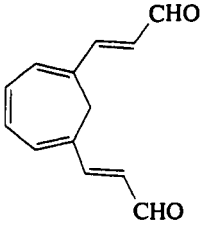
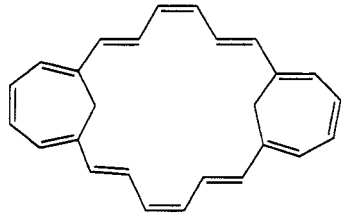
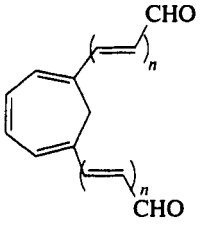
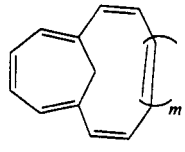
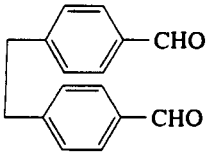
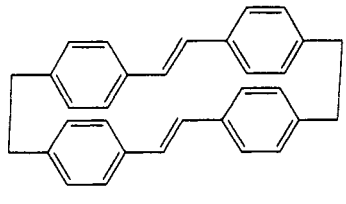
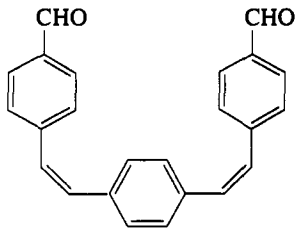
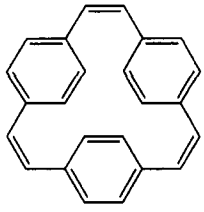
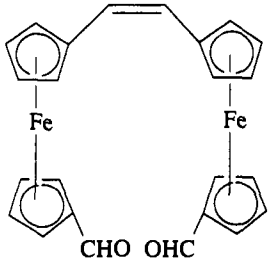
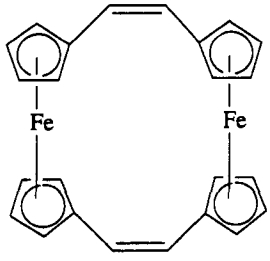
Substrate	*Product*	*Yield (%)*	*Ref.*
		97	177
		8–10	178
		X = NH, O 2–3	179
		2–5	180
		5	181
		4–12	182
		23	183

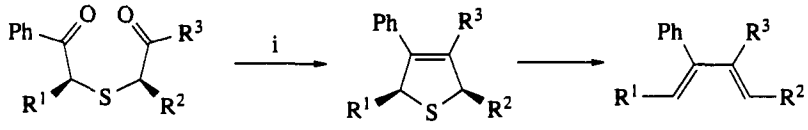
Table 3 *(continued)*

Substrate	*Product*	*Yield (%)*	*Ref.*
		50	184
		43	185

tem capable of forming a stable square planar d^{10}-complex with silver.[174] The in–out bicycloalkane (**72**) was recently synthesized by McMurry and Hodge *via* the coupling of the keto aldehyde (**73**) followed by hydrogenation. Protonation of (**72**) gives a stable μ-hydrido-bridged carbocation (equation 102).[176]

A wide range of cyclic polyenes, such as annulenes, porphycenes, cyclophanes and ferrocenophanes, have been prepared using McMurry methodology, and these are summarized in Table 3.

Cyclization of 1,5-diketones linked by a methylthiomethyl chain gives dihydrothiophenes (**74**), which upon oxidation and elimination provide stereodefined 1,3-dienes (equation 103).[186] Thus, *meso* diketones give *cis,cis* 1,4-disubstituted dienes whilst (±)-diketones give the *trans,cis* isomers.

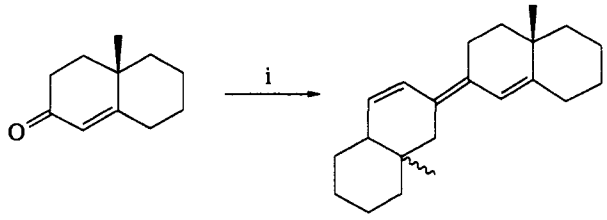


(103)

(**74**)

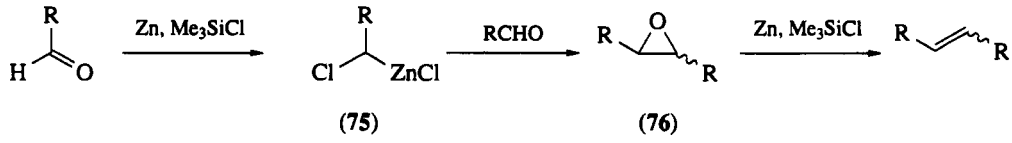
i, $TiCl_4$, Zn, THF, 66–86%

Finally an interesting system for the synthesis of alkenes from carbonyls based on TMSCl/Zn has been developed by Motherwell *et al.*,[187] and is compatible with esters and halogen groups (equation 104). The reaction does not however proceed *via* a ketyl radical coupling but rather *via* an organozinc carbeniod (**75**) which is trapped by a second carbonyl molecule to give an intermediate epoxide (**76**). The intermediate epoxide is then deoxygenated to the product alkene (Scheme 9).



(104)

i, Me_3SiCl, Zn, THF, –50 °C, 85%

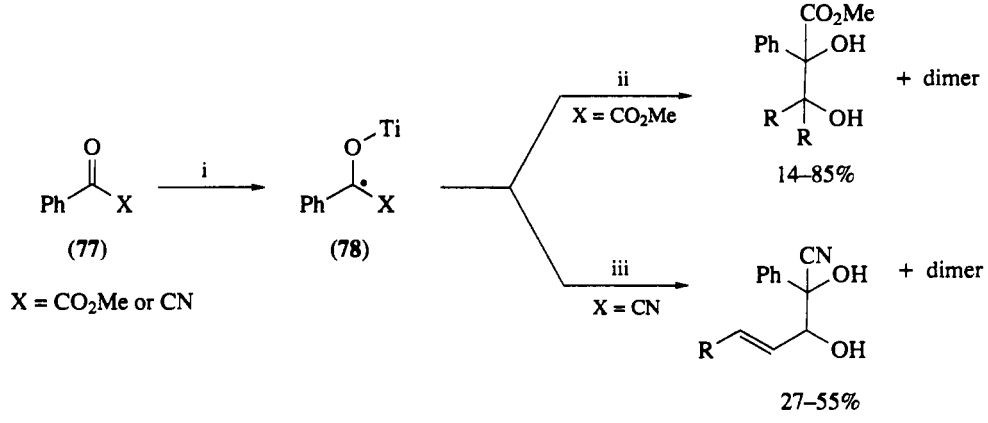


(75) (76)

Scheme 9

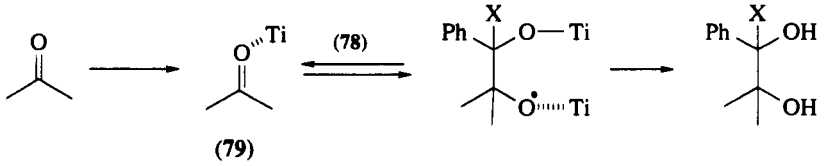
2.6.8 MIXED COUPLINGS

This section will deal with pinacolic couplings of fundamentally different C=X (X = O or NHR) groups, that is those with different reduction potentials. Examples involving similar C=X groups, such as aldehyde–ketone couplings have already been discussed under the relevant sections and will only be mentioned briefly.[188] A number of efficient methods have been devised for the cross-coupling of carbonyl compounds to mixed pinacols. This type of reaction is especially facile for the cross-coupling of aromatic and aliphatic ketones. Aromatic carbonyls especially diaryl ketones are much more readily reduced than their aliphatic counterparts. Indeed chemoselective reduction of aromatic systems in the presence of aliphatic carbonyls allows for efficient cross-coupling *via* nucleophilic attack of the aryl anion/radical.[125,190] Clerici and coworkers have extensively studied such reactions of aryl ketones (**77**) with saturated and α,β-unsaturated carbonyl compounds, promoted by aqueous $TiCl_3$ (Scheme 10).[189] Under these conditions chemoselective formation of capto-datively stabilized radicals such as (**78**) is followed by subsequent trapping by the aliphatic carbonyl group. The use of an excess of the aliphatic carbonyl compound increases the ratio of mixed pinacol to dimer up to a maximum of 6:1. These reactions provide the first examples of radical addition to saturated carbonyls such as acetone and proceed *via* activation of the saturated carbonyl by coordination with titanium to give the electrophilic intermediate (**79**) followed by combination with the ketyl radical (**78**; equation 105). Fujiwara has published a potentially important method for the coupling of diaryl ketones with electrophiles, including ketones, nitriles, epoxides and CO_2, mediated by ytterbium metal (equation 106).[190]



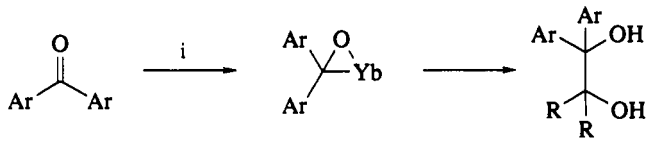
i, AcOH, 15% aq. $TiCl_3$, r.t.; ii, excess RCOR; iii, excess RCH=CHCHO

Scheme 10



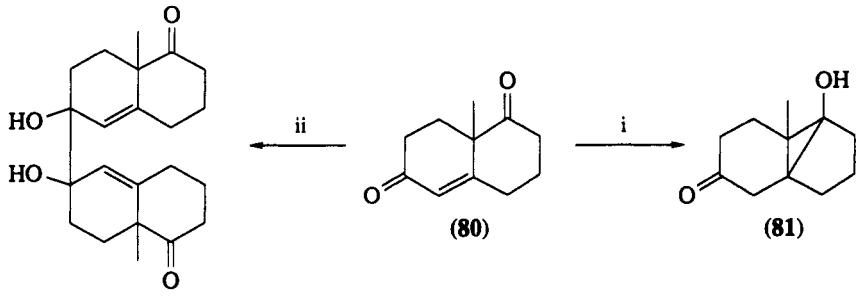
(79) (105)

Mixed coupling of ketones and α,β-unsaturated ketones can be profoundly affected by the pH of the solution. Thus the Wieland–Miesher ketone (**80**) undergoes intramolecular coupling to give the cyclopropanol (**81**) under basic conditions;[191] whilst in neutral media 1,2-hydrodimerization occurs leading to the pinacol (**82**; equation 107).[192]



(106)

i, Yb, HMPA, THF, RCOR, r.t., 63–90%

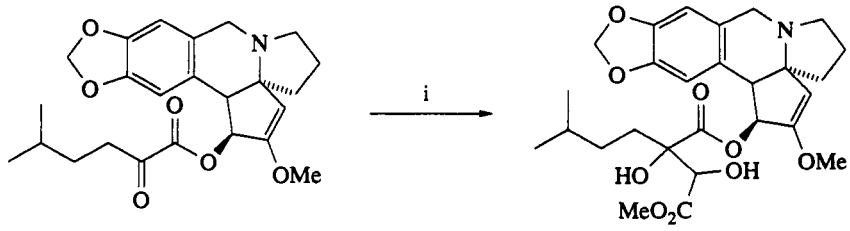


(107)

(82)

i, Li, NH_3, THF, –78 °C, 87%; ii, Hg, MeOH, 0.1M KCl (1:1), –1.7 V, 71%

The mixed coupling of aliphatic compounds is also well established. Through the use of an excess (usually 10-fold) of one of the reactants cross-coupling of aliphatic carbonyls is highly effective.[193] This protocol was first developed by Corey[53] and then applied to reductive pinacolic couplings by McMurry.[125] Li *et al.* applied this method to the synthesis of the alkaloid isoharringtonine (**83**; equation 108).[194]

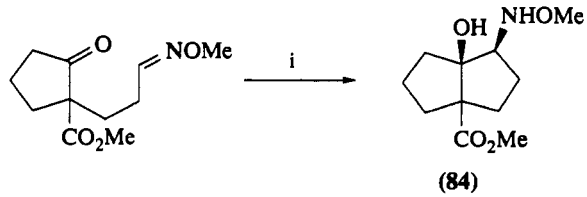


(108)

(83)

i, $CpTiCl_3$, $LiAlH_4$, THF, MeO_2CCHO

Early work on the electropinacolic coupling of aldehydes with imines was not promising since, as the reaction is reversible, complex product mixtures are formed.[195] However, recent developments in mixed coupling reactions have established some highly efficient and selective methods for the coupling of aldehydes or ketones with oximes or imines.[72,196] Thus stereoselective nonreversible coupling of ketones with oximes using TMSCl/Zn proceeds in excellent yield to give compounds of the type (**84**; equation 109),[72] and a highly versatile and selective method for the intermolecular coupling of imines with aldehydes or ketones uses a niobium(III) reagent providing a diastereoselective route to α-aminoalcohols

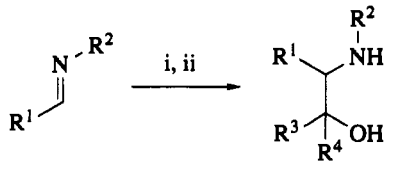


(109)

(84)

i, Me_3SiCl, Zn, 2,6-lutidine, THF, reflux, 84%

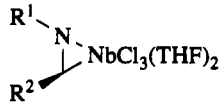
(equation 110).[196] Chemoselective formation of the metallaaziridine (**85**) in the latter reaction is followed by a highly efficient reaction with the carbonyl compound, even with only a 1.5 molar excess of the imine; no doubt this excellent method will be well exploited in the near future.



(110)

ds = 3:1 to 83:1

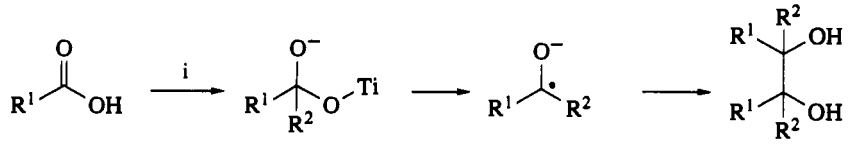
i, $NbCl_3$ (DME), THF; ii, R^3COR^4, THF, 33–97%



(**85**)

2.6.9 MISCELLANEOUS COUPLINGS

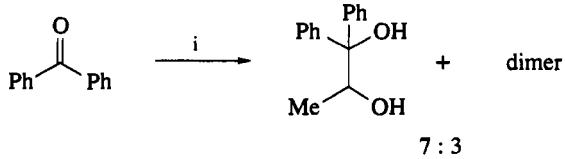
There are a number of alternative methods for the synthesis of 1,2-diols and their derivatives that do not proceed *via* the coupling of two carbonyl groups. Ketyl radicals can be generated by the alkylative deoxygenation of carboxylic acids, and in the presence of $TiCl_3$ coupled to give 1,2-diols (equation 111).[197] However, yields are limited (22–33%) and complex product mixtures are often formed.



(111)

i, $TiCl_3$, R^2Li, DME, –78 °C to r.t., 22–33%

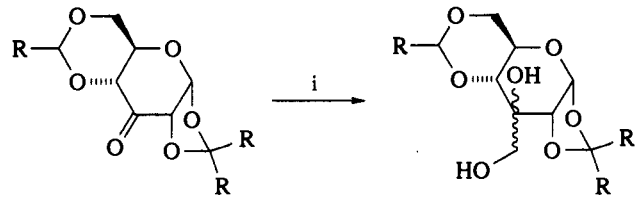
The formation of pinacols *via* the dimerization of alcohols is not feasible because of disproportionation or oxidation of the intermediate radical. Alcohols do however couple with ketyl radicals in photochemically initiated cross-pinacolization reactions (equation 112).[198] Product distribution is highly dependent on the light intensity. Photochemical cross-pinacolization has been used for a one-step conversion of osulose compounds to the corresponding hydroxymethyl branched derivatives (equation 113).[199] Alcohols protected as silyl ethers are efficiently coupled under free-radical conditions using di-*t*-butyl peroxide, to give, after hydrolysis, the corresponding pinacols in moderate to good yields (26–89%; equation 114).[200] Electroreductive cross-coupling of diaryl ketones with aldehyde-derived enol acetates yields unsymmetrical pinacols (equation 115) *via* nucleophilic attack onto the enol double bond.[201]



(112)

7 : 3

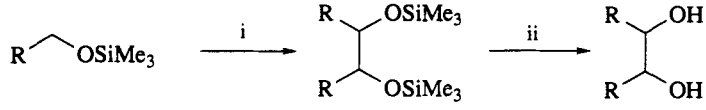
i, *hν*, MeOH



(113)

i, MeOH, *hν*, 450 W

	Yield (%)	
	α-OH	β-OH
$R^1 = R^2 = R^3 = Me$	20	22
$R^1 = H, R^2 = Et, R^3 = Ph$	30	25



(114)

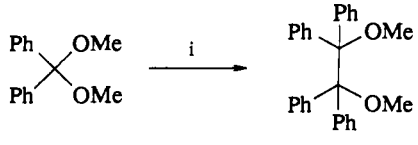
(±):*meso* = 1:1

i, $(Bu^tO)_2$, 145 °C, N_2 pressure; ii, ROH, 26–89%

(115)

i, C-electrode, RCH=CHOAc, Et_4NTs, DMF, H_2O, 200 mA, 45–76%

The reduction of dialkyl acetals of aromatic aldehydes or ketones with a titanium(II) reagent gives pinacol ethers or the corresponding alkene in high yield (46–100%; equation 116).[202] Acetals derived from aliphatic aldehydes or ketones are reduced to the corresponding ethers.



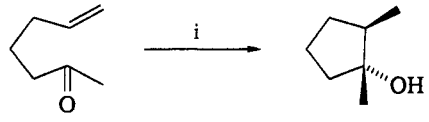
(116)

i, $TiCl_4$, $LiAlH_4$, THF, r.t., 100%

2.6.10 CARBONYL–ALKENE CYCLIZATIONS

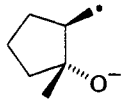
In addition to coupling with heteroalkenes (C=O, C=N and C=S) carbonyls also undergo intramolecular reaction with nonconjugated C=C bonds. Together with the related reactions with alkynes and allenes these cyclizations provide regio- and often stereo-selective routes to five- and six-membered rings *via* C—C bond formation with net retention of functionality.[9c,203] Although there are no intermolecular examples, the intramolecular variant is a powerful method for the synthesis of polycyclic systems. Thus, electroreductive cyclization of ω-unsaturated alkenic ketones gives cyclic tertiary alcohols of the type

(**86**) regio- and stereo-selectively (equation 117).[204,205,222] Cyclization occurs through formation of the ketyl radical anion and *exo* radical addition to the alkene to form the intermediate (**87**). The developing charge interactions formed between the alkyl radical and the oxyanion in (**87**), within the electrode double layer, control the stereochemical integrity of the reaction. The reaction is completely regio- and stereo-specific in contrast to similar chemically induced cyclizations with either $TiCl_4/Mg$,[204] or Na/Bu^{t}OH/*N*-ethylpyrrolidine,[206] both of which are stereorandom. A related cyclization of the ketoalkene (**88**) with TMSCl/Zn shows a 5:1 preference for the *trans* isomer (**89**; equation 118).[72]

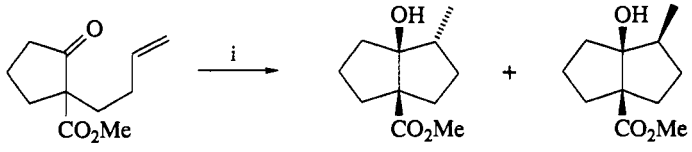


(117)

i, C-electrode, MeOH, dioxane, Et_4NTs, –2.70 V (*vs.* SCE), 32–98%
or Hg, $DMPBF_4$, DMF, –3.10 V (*vs.* SCE), 98%



(**87**)



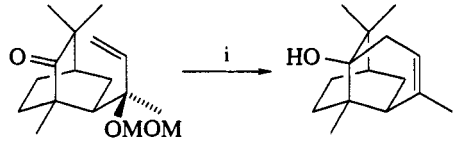
(**88**) (**89**) 5:1

(118)

i, Me_3SiCl, Zn, 2,6-lutidine, THF, reflux, 75%

The cyclizations of ketyl radicals onto double bonds occurs in an antiperiplanar fashion as demonstrated by the respective cyclizations of the epimers (**90**) and (**91**).[207] In ketone (**90**) the ether moiety is suitably disposed to act as a leaving group allowing *endo* cyclization to the alkene (**92**), whilst the epimeric ether (**91**) gives the cyclopentane (**93**) *via* the *exo* mode (equations 119 and 120). Stereochemical control can also be imparted by use of a chelating auxiliary as in the samarium-mediated cyclization of the ketone (**94**) to the spirolactone (**95**; equation 121).[73,208] The lactone moiety of (**94**) functions as a Lewis base enabling chelation of the Sm^{3+} ion and thus stereoselective cyclization (equation 122). Photochemical radical generation can also be stereoselective, thus the ketones (**96**) and (**97**) give their respective bicyclic tertiary alcohols in good yields (equation 123).[209] A short synthesis of the monoterpenoid (±)-actinidine (**98**) has been accomplished using a photoreductive cyclization of the ketone (**99**; equation 124).[210]

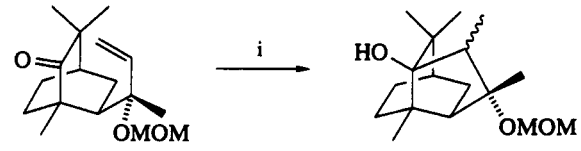
The radical cyclization of aldehydes onto alkenes was first demonstrated by Hutchinson and coworkers using a TMSCl/Mg reducing agent (equation 125).[211] The cyclization of the aldehyde (**100**) to loganin tetraacetate (**101**) serves as a model reaction for studying the mechanism of the biological conversion of loganin to secologanin. In a related fashion cyclization of the (stannyloxy)alkyl radical gener-



(**90**) (**92**)

(119)

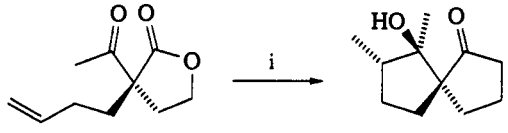
i, Na, THF, 64%



(120)

(91) (93)

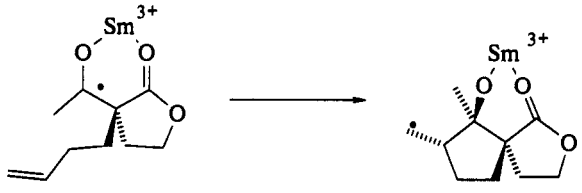
i, Na, THF, 70%



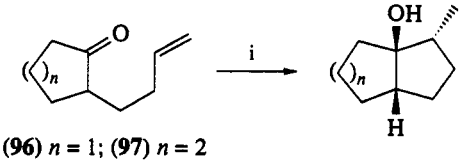
(121)

(94) (95)

i, 2 SmI_2, Bu^tOH, THF, –78 °C to r.t., 87%



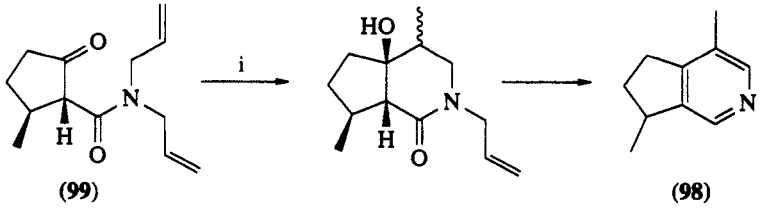
(122)



(123)

(96) n = 1; (97) n = 2

i, *hν*, HMPA, n = 1, 81%; n = 2, 76%



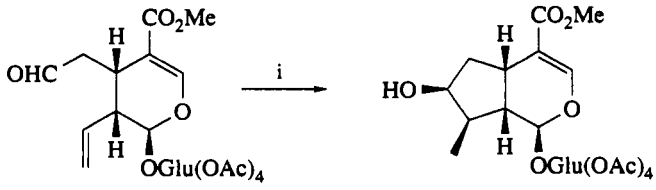
(124)

(99) (98)

i, *hν*, Et_3N, MeCN, 50%

ated from aldehyde (**102**) gives the alcohol (**103**; equation 126).[212] Further exploitation of the cyclization of aldehyde-derived radicals should provide a general route to polycyclic secondary alcohols.

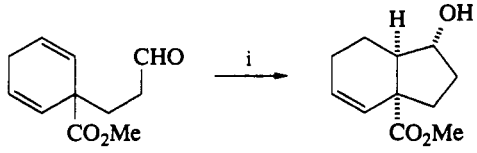
Transannular cyclization of ketoalkenes was first reported in 1965. Treatment of the conformationally restricted ketone (**104**) with sodium in moist ether gave the alcohol (**105**; equation 127).[213] Similarly the ketoalkene (**106**) transannulated in 73% yield by exposure to sodium in refluxing propanol (equation 128).[214] Conformational restriction is not a prerequisite for transannular reaction; thus the caryophyllene (**107**) undergoes cyclization to the alcohol (**108**) with lithium in liquid ammonia (equation 129).[215] Transannulation across a nine-membered ring has also been observed upon treatment of ketone (**109**; equation 130) with samarium diiodide, *via* cyclization of the ketoalkene (**110**).[216] Of more practical importance, the electrochemical transannulation of the cyclooct-4-en-1-one gives the bicyclo[3.3.0]octanol (**111**; equation 131).[217]



(125)

(100) **(101)**

i, Mg, Me_3SiCl, THF, r.t., 55%



(126)

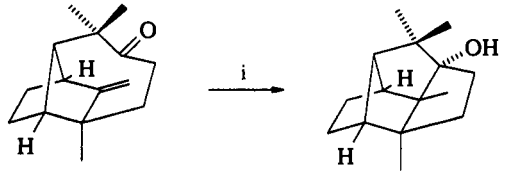
(102) **(103)**

i, Bu_3SnH, AIBN, C_6H_6, reflux, 90%

(127)

(104) **(105)**

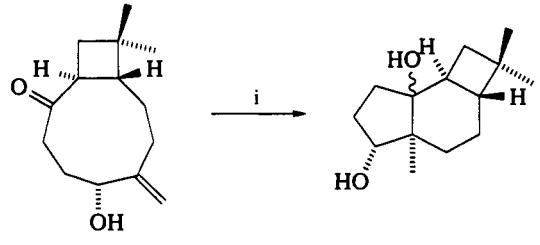
i, Na, moist ether



(128)

(106)

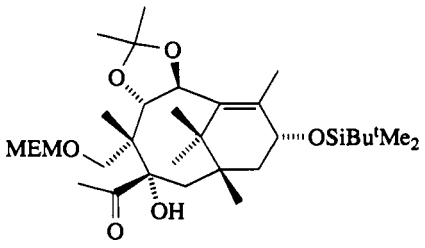
i, Na, Pr^nOH, reflux, 73%



(129)

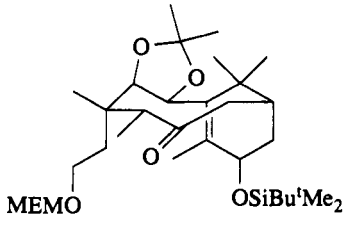
(107) **(108)**

i, Li, NH_3, 30%

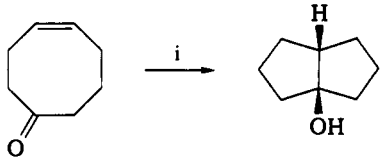


(130)

(109) i, 2 SmI_2,THF, 25 °C, 92%



(110)



(131)

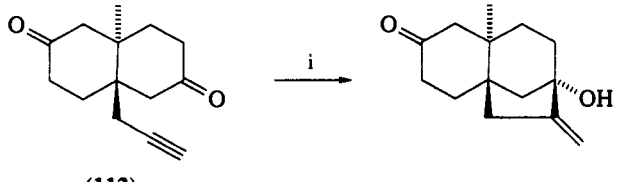
(111)

i, C-electrode, MeOH, dioxane, Et_4NTs, –2.70 V (*vs.* SCE), 69%

2.6.11 CARBONYL–ALKYNE CYCLIZATIONS

Cyclizations of ketoalkynes constitute an important method for the synthesis of ring junction allylic alcohols such as those in the polycyclic systems of gibberellins, capnellenols, and amijiols. Thus reductive cyclization of ketones (**112**; equation 132) and (**113**; equation 133) form the C/D rings of the gibberellic acid[218–220] and provide a one-step alternative to the corresponding pinacolic coupling/alkenation of the keto aldehyde (**16**).[69] Ketoalkynes have also been cyclized *via* electroreduction,[221,222] photoreduction,[223] and using the sodium naphthalene radical anion[224,225] or TMSCl/Zn (equations 134–139).[72] It should be noted that the enone (**114**) is cyclized by sodium naphthalene radical anion, but is 1,4-reduced under protic conditions using Na/NH_3 (equation 138).[224,225] Treatment of the homochiral ketone (**115**) with Na/NH_3 furnishes the hydrindane (**116**), a potential synthon for optically active steroids and terpenes (equation 140).[226]

The capnellene and hirsutene marine sesquiterpenes are ideal candidates for radical cyclizations and both have been elaborated *via* carbonyl–alkyne cyclizations (equations 141–143). Thus treatment of the ketone (**117**) with the sodium naphthalene radical anion gives the triquinane (**118**). Subsequent allylic

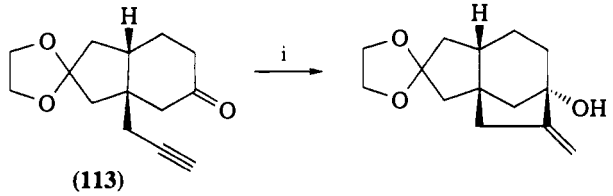


(132)

(112)

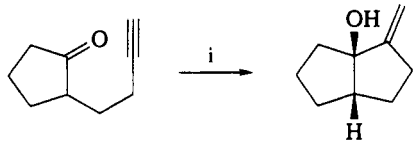
i, Li, NH_3, Et_2O, NH_4SO_4, ~50%

oxidation and inversion gives (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**119**).[227] Similar photoreduction of the ketone (**120**) gives the tertiary alcohol (**121**) from the α-epimer, whilst the β-isomer of (**120**) is reduced to the alcohol (**122**).[228] Conversion of the tertiary alcohol in (**121**) to a methyl group completes the synthesis of hirsutene. A particularly elegent tandem radical cyclization of the aldehyde (**123**) with SmI_2 provides the alcohol (**124**), a key intermediate in the synthesis of corriolin and hypnophilin stereoselectively (equation 143).[229] A synthesis of the dolastane diterpene, (±)-isoamijiol (**44**; equation 144), utilizing only seven C—C bond-forming reactions, of which four involve radical intermediates, is completed by stereospecific reductive cyclization of the ketoalkyne (**125**) to the alcohol (**126**) followed by allylic



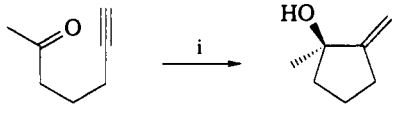
(**113**) (133)

i, Li, NH_3, NH_4SO_4, 50% or K, NH_3, THF, NH_4SO_4, 60–70%



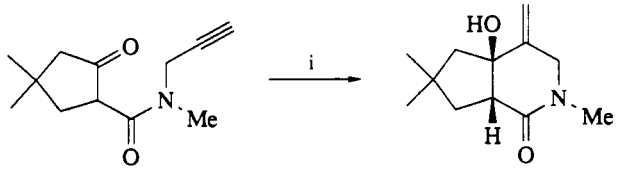
(134)

i, C-electrode, Et_4NTs, DMF, 75%



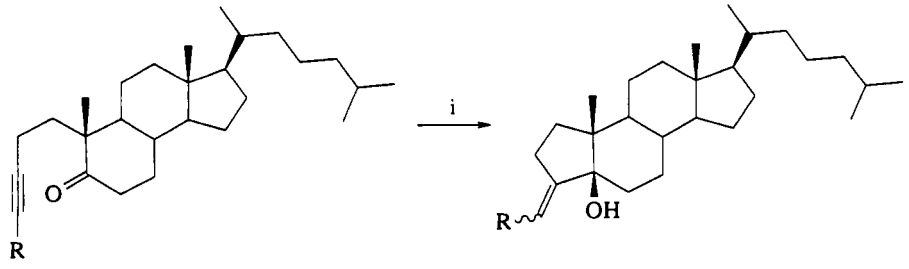
(135)

i, Hg, $DMPBF_4$, DMF, –2.70 V (*vs.* SCE), 85%



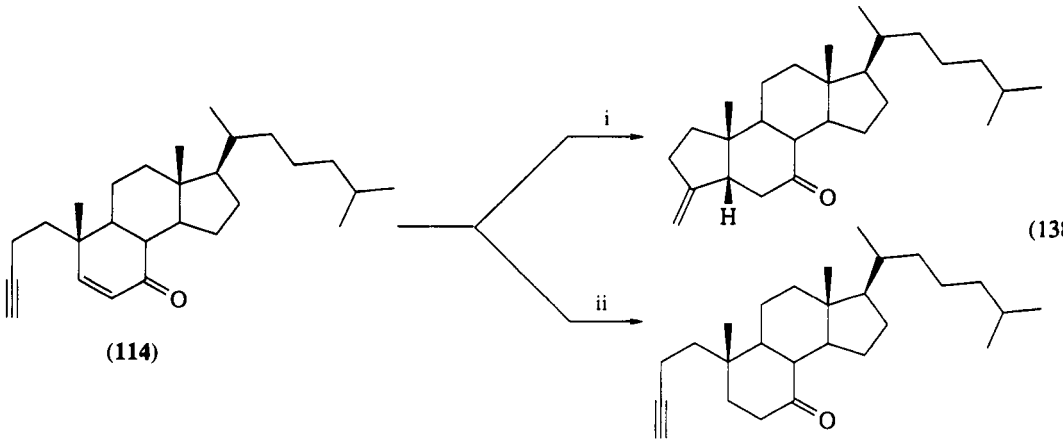
(136)

i, *h*ν, Et_3N, MeCN, 58%



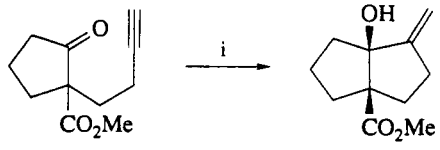
(137)

i, Na, $C_{10}H_8$, THF, 69–72%



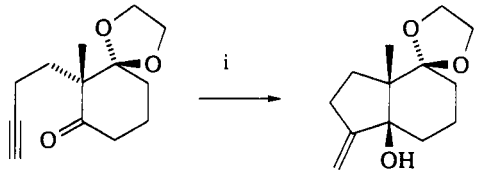
(114) (138)

i, Na, $C_{10}H_8$, THF, 20–25%; ii, Na, NH_3, THF, 94%



(139)

i, Me_3SiCl, Zn, 2,6-lutidine, THF, reflux, 77%

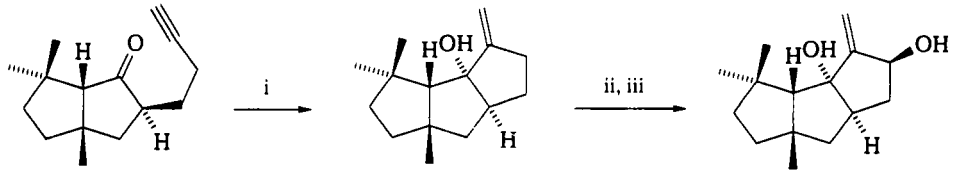


(140)

(115) (116)

i, Na, NH_3, $(NH_4)_2SO_4$, ~90%

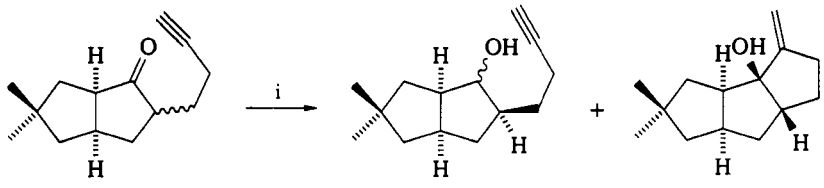
oxidation.[153] The stereochemical integrity of the unusual *trans* ring junction is controlled by steric interactions of the alkynic side chain and the azulenone nucleus. This cyclization has also been effected using homochiral (**125**) to furnish (+)-isoamijiol.[230]



(141)

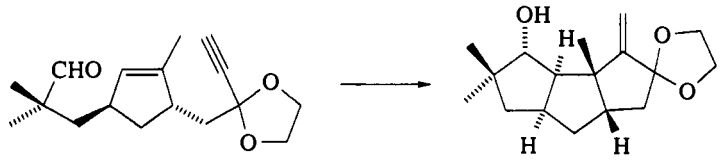
(117) (118) (119)

i, Na, $C_{10}H_8$, THF, 30%; ii, SeO_2, Bu^tO_2H, CH_2Cl_2, 40%; iii, MsCl, Et_3N, CH_2Cl_2; KO_2, DMSO, DMF, −5 °C to r.t., 40%



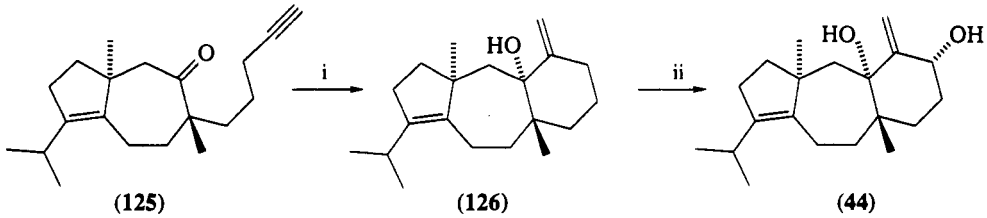
(120) (121) 58% (122) 20% (142)

i, *hv*, 254 nm, Et_3N, MeCN



(123) (124) (143)

i, 2 SmI_2, THF, HMPA

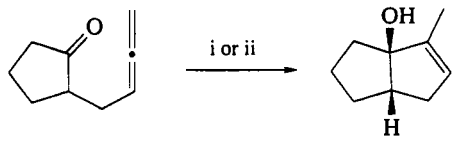


(125) (126) (44) (144)

i, Na, $C_{10}H_8$, THF, 41%; ii, SeO_2, Bu^tO_2H

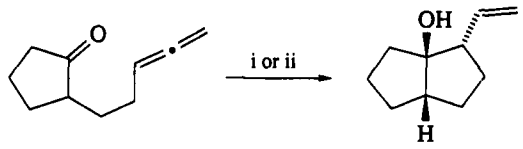
2.6.12 CARBONYL–ALLENE CYCLIZATIONS

Reductive cyclization of ketoallenes (**127**) and (**128**) either electrochemically, or by brief exposure to the sodium naphthalene radical anion, gives the tertiary alcohols (**129**) and (**130**) respectively, *via* regio- and stereo-specific reactions in an *exo* mode (equations 145 and 146)[231] The stereochemistry at the ring junction in (**130**) is *cis* with a *trans* relationship between the pendant vinyl group and the tertiary alcohol, in a similar fashion to ketoalkene cyclizations. Best yields are obtained electrochemically under nonenolizing conditions. In contrast, prolonged exposure to excess sodium naphthalene radical anion is not regioselective; thus ketone (**131**) gives a mixture of *exo* and *endo* double bond isomers (equation 147).[232]



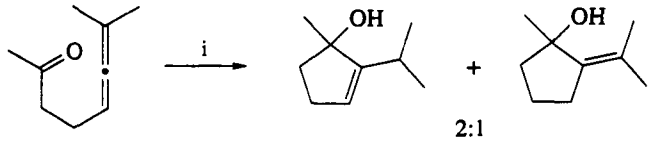
(127) (129) (145)

i, Hg, –2.43 V (*vs.* Ag/AgI_2), Et_4NTs, DMF, 41%; ii, Na, $C_{10}H_8$, THF, 28%



(128) (130) (146)

i, Hg, –2.43 V (*vs.* Ag/AgI_2), ET_4NTs, DMF, 37%; ii, Na, $C_{10}H_8$, THF, 28%



(131) (147)

i, Na, $C_{10}H_8$, THF, r.t., 5 h, 46%

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2.7
Acyloin Coupling Reactions

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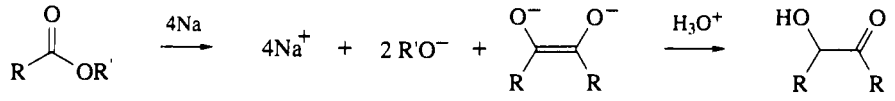
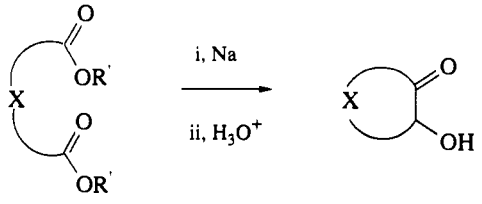
2.7.1 THE REDUCTION OF CARBOXYLIC ESTERS BY ALKALI METALS

Under certain circumstances the reduction of a carboxylic ester by an alkali metal leads to an enediolate. Protonation then gives an acyloin, an α-hydroxy ketone, in which two atoms which were originally the carbon atoms of the ester carbonyl groups are joined by a new single carbon–carbon bond. This coupling reaction, in both its intermolecular mode (Scheme 1) and, particularly, in its intramolecular mode (Scheme 2), is a useful synthetic operation.[1] It is, however, only one of a number of processes which can occur as a result of the reduction of a carboxylic ester by an alkali metal. For example, whereas the use of molten sodium dispersed in refluxing toluene converts a simple ester into the acyloin, the use of an excess of sodium in ethanol converts a simple methyl or ethyl ester into the corresponding primary alcohol (*i.e.* the Bouveault–Blanc reduction). A different reduction occurs when, for example, hindered esters are reduced by lithium in ethylamine[2] or sodium in HMPA in the presence of 2-methylpropan-2-ol.[3] Acyloin formation does not occur, and instead the alkoxy portion of the ester is deoxygenated (equation 1).

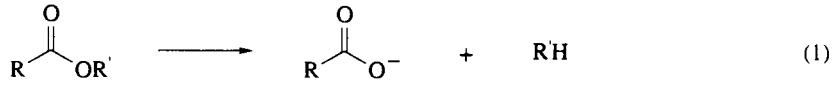
If the ester group is conjugated with a π-electron system, alternative reduction processes can occur. Benzoate esters are reduced to the 1,4-dihydrobenzoates by sodium in the system $NH_3/THF/H_2O$.[4] For



Scheme 1



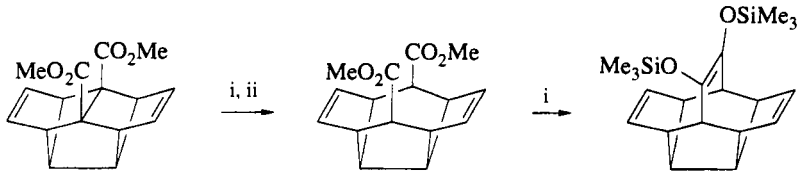
Scheme 2



(1)

α,β-alkenic esters both simple reduction at the carbon–carbon double bond and hydrodimerization at the β-position have been observed,[1] as a result of the action of alkali metals under particular conditions.

A further reductive process is often observed in the case of hindered vicinal diesters, where fragmentation occurs;[5] the cleaved products, still diesters, have sometimes then, in a separate step, been submitted to the acyloin coupling reaction. A typical sequence from the diester (**1**) is shown in Scheme 3.[6]



(**1**)

i, Na, toluene, Me_3SiCl, reflux; ii, MeOH

Scheme 3

In addition, many nonreductive side reactions occur. The choice of suitable reagents and conditions for an acyloin coupling reaction is still based on analogy and empiricism.

2.7.2 NECESSARY REACTION CONDITIONS FOR THE ACYLOIN COUPLING REACTIONS OF ESTERS

Two sets of conditions have commonly been employed in order to effect the acyloin coupling of esters. In each case it is important that both the condensation and the work-up should be performed in the absence of moisture and of oxygen.

2.7.2.1 Heterogeneous Conditions

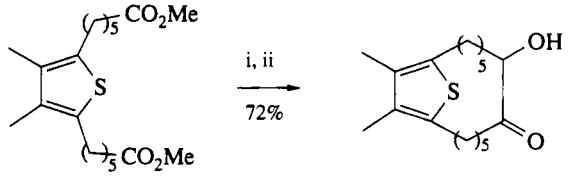
The solvent is usually refluxing toluene or xylene, though occasionally benzene or ether has been used. The substitution of DME, THF or dioxane offers no advantages. At the higher temperatures obtaining in refluxing toluene (b.p. 111 °C) or xylene, the alkali metal is molten. The reaction is a surface reaction and it is essential that the metal is finely dispersed, for example by efficient stirring. A slight excess of the metal is normally used.

2.7.2.2 Homogeneous Conditions

The solvent is liquid ammonia, at its boiling point –33 °C. The exact amount of the metal is used. In particular cases one or other set of conditions may give the better yield. In investigating a new acyloin coupling reaction the first choice would be heterogeneous conditions.

2.7.2.3 Reaction Variables

The initial interaction between an alkali metal and an ester leads, by single electron transfer, to the alkali metal derivative of a radical anion. Radical anions from nonphenolic esters normally fragment, to give the carbonylate anion and a radical derived from the alkyl group. It has been pointed out[2] that this makes the acyloin coupling a curiosity and difficult to rationalize. The alkali metal is usually sodium. The choice has an effect on the course of the reaction, partly due to the potential at which the initial single electron transfer step occurs, and partly due to differences in the nature and stability of the alkali metal derivative of the radical anion under the prevailing conditions. No systematic study of this aspect of the reaction has ever been undertaken. At the higher temperatures of the heterogeneous conditions, the reaction of the radical anion must be a surface reaction. At the lower temperatures used in the homogeneous conditions the free radical anion is formed, but only undergoes the competing fragmentation slowly, so that the acyloin coupling is favored. The use of a sodium–potassium alloy (with its lower melting point relative to the pure metals) allows the heterogeneous conditions to be used at lower temperatures. This type of procedure has been found to be particularly successful for thiophene-containing systems (Scheme 4).[7]



i, Na/K, xylene, 55–60 °C; ii, H_3O^+

Scheme 4

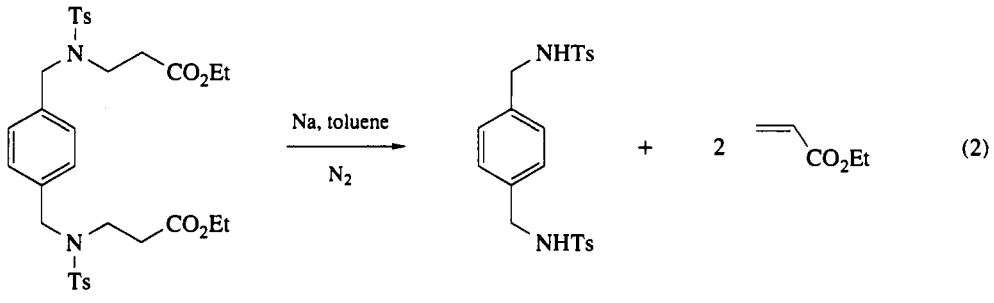
The products of an acyloin coupling reaction are an enediolate dianion and alkoxide ions. In the presence of the alkoxide the enediolate may be oxidized to the corresponding diketone by molecular oxygen.[8] It is therefore important that, even when the coupling is complete, all reaction mixtures should be worked up in an oxygen-free atmosphere so long as the mixture remains alkaline. For reactions performed in liquid ammonia, all the ammonia should be allowed to evaporate before the reaction is worked up.

2.7.3 COMPETING BASE-CATALYZED REACTIONS AND THEIR SUPPRESSION. TRAPPING WITH TRIMETHYLSILYL CHLORIDE

2.7.3.1 Side Reactions

Low yields in acyloin coupling reactions in the past were often the consequence of competing base-catalyzed processes, although the exact nature of the by-products, especially those of high molecular mass, has often not been established. The conditions which lead to Claisen or Dieckmann condensations are quite similar to those used in the acyloin coupling reaction and sometimes such processes predominate. For example, an attempt to prepare the cyclic acyloin from either the (±)- or *meso*-form of diethyl 3,4-diphenylhexanedioate, using sodium in benzene, gave only the Dieckmann product, 2-ethoxycarbonyl-3,4-diphenylcyclopentan-1-one,[9] and other similar cases have been collected.[10] Other base-catalyzed reactions have intervened. An attempt to prepare 2-hydroxycyclopentan-1-one, from dimethyl pentane-1,5-dioate, gave, instead, a C_{10} product derived by an aldol condensation,[1] and an attempt to effect the acyloin coupling reaction with the diester (**2**) led only to the products of base-catalyzed elimina-

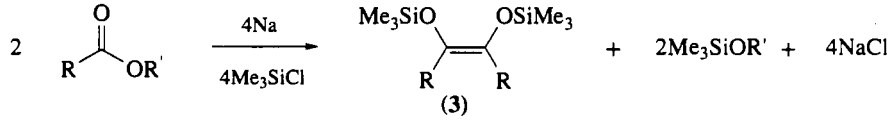
tion (equation 2).[1] Problems like these can now be overcome by carrying out the coupling reaction in the presence of the trapping agent TMS-Cl or by adding it before the work-up.[11]



(2)

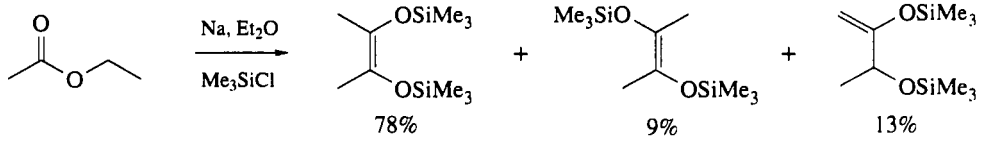
2.7.3.2 Trapping with Trimethylsilyl Chloride

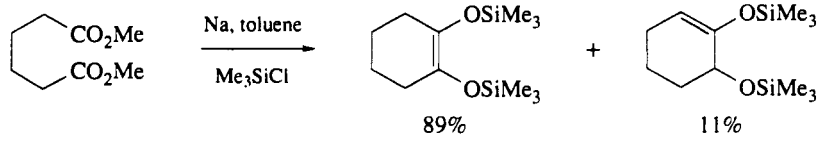
In the presence of TMS-Cl the enediolate dianion and, importantly, the alkoxide ions, are trapped as their neutral silyl ethers (Scheme 5). This leads to much improved yields of the coupled product; the acyloin is isolated in the form of its silyl enediol ether (**3**). Work-up is much easier. It is only necessary to filter the solution, evaporate the solvent, and isolate the product by distillation or chromatography. The TMS-Cl should be purified by distillation from calcium hydride, under a nitrogen or argon atmosphere, before use. A convenient procedure when using an organic solvent is to add the ester and the TMS-Cl together, dropwise, to the alkali metal finely dispersed in the solvent, at a rate sufficient to maintain the reaction. An explosion has been reported where this procedure was not followed.[1] For a reaction conducted in liquid ammonia[1] the TMS-Cl is added at the end of the reaction and after all the ammonia has been allowed to evaporate. Particularly in cases where sodium–potassium alloy has been used, a pyrophoric residue may have formed, so that the filtration must be carried out under an inert atmosphere.



Scheme 5

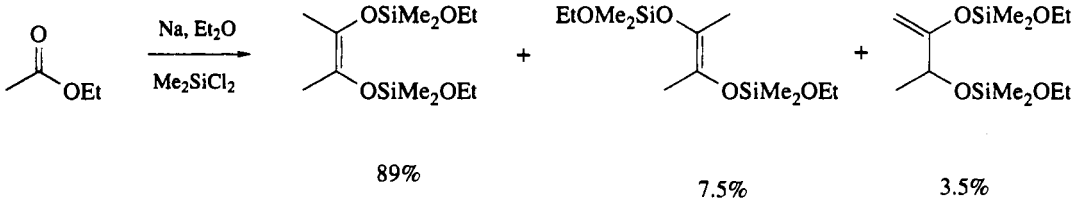
The kinetic product of an acyloin coupling is the enediolate, which may be formed in (*Z*)- and (*E*)-forms, and is accompanied by some of the thermodynamic product, the corresponding α-hydroxy enolate. Each of these dianions is trapped by the TMS-Cl. The products, and the proportions in which they are formed, for the reactions of ethyl ethanoate[12] and diethyl hexane-1,6-dioate[13] are shown in Scheme 6. Use of dichlorodimethylsilane in conjunction with the reduction of ethyl ethanoate[12] gave the *acyclic*





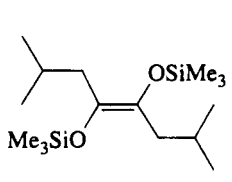
Scheme 6

products shown in Scheme 7. All the silylated products can be converted into the corresponding acyloin by hydrolysis with dilute aqueous acid, but better yields are obtained by treatment with methanol which has been completely deoxygenated by the passage of a stream of nitrogen.[5a,14] It is normally advantageous to prepare the acyloin as it is required, since most acyloins give dimers, through hemiacetal formation, on standing. Moreover several reactions, for example the oxidation to the α-diketone, can be performed on the silyl enediol ether without prior isolation of the acyloin.

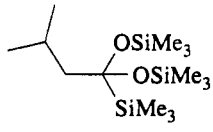


Scheme 7

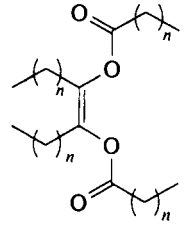
Although ethyl 3-methylbutanoate on reduction with sodium in the presence of TMS-Cl in benzene or ether gives the expected silyl enediol ether (**4**), in DME or THF the product is the noncoupled product (**5**).[15]



(**4**)



(**5**)



(**6**) n = 10, 12, 14 and 16

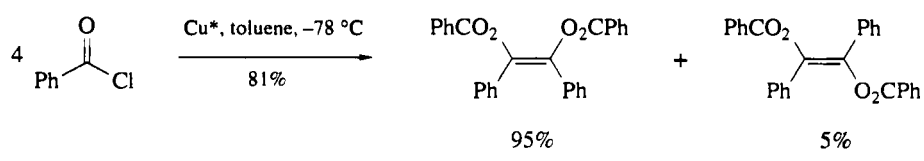
2.7.3.3 Preferred Reaction Conditions for an Attempted Acyloin Coupling Reaction

The preferred procedure at the present time would thus be to react an ester (or diester) in a heterogeneous system consisting of a highly dispersed alkali metal, probably sodium, in an organic solvent such as toluene, in the presence of trimethylsilyl chloride and under an inert atmosphere, and to decompose the isolated silylated products to the required acyloin by treatment with oxygen-free methanol.

2.7.4 ACYLOIN COUPLING REACTIONS WITH ACYL CHLORIDES AND ACID ANHYDRIDES

In principle the acyloin coupling of acyl chlorides, in which the enediolate dianion is trapped by unreacted acyl chloride, might be an effective alternative to trapping with TMS-Cl, but the method has rarely been used. Good yields of the enediol diesters (**6**) were obtained with several fatty acid chlorides using sodium in ether, and the enediol diesters could easily be hydrolyzed to give the acyloins.[16]

The coupling of aroyl chlorides to give 1,2-diaroyloxy-1,2-diarylethylenes has been known since 1865. The best reagent, from many which have been tried, is activated copper powder (Scheme 8).[17] It does not couple aliphatic acyl chlorides. The acyloin coupling of terephthaloyl chloride under either heterogeneous or homogeneous conditions, using sodium, has been shown to give a *para*-linked copolymer containing benzoin and benzil residues.[18]

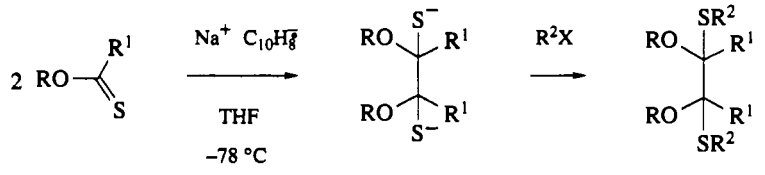


Scheme 8

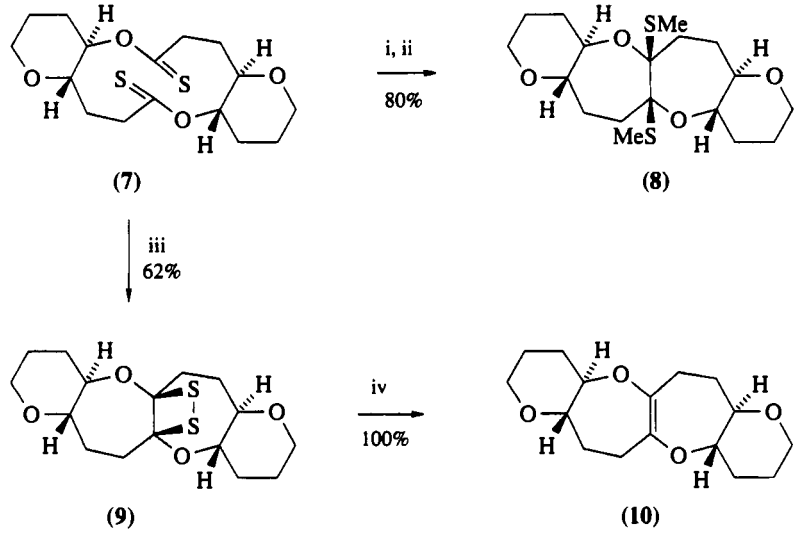
For the modern TMS-Cl trapping technique it has been shown that esters give considerably better yields than the corresponding acyl chlorides or acid anhydrides.[11,19]

2.7.5 REDUCTIVE COUPLING OF THIOESTERS

Nicolaou has recently shown that reductive coupling of thioesters can be accomplished using sodium naphthalenide; the resulting dianion can then be trapped, for example with an alkyl halide (Scheme 9). One of the six examples cited by Nicolaou[20] is shown in Scheme 10, where the tricyclic bisthiolactone (**7**) is reduced to the tetracyclic compound (**8**). A related coupling can be achieved photochemically. Ultraviolet irradiation of (**7**) for a short period, gives the stable 1,2-dithietane, dithiatropazine (**9**), together with a little of the tetracyclic alkene (**10**). Longer irradiation of (**7**) or the thermal decomposition of (**9**) also leads to (**10**).[21]



Scheme 9



i, Na^+, $C_{10}H_8^{\bullet-}$, THF, −78 °C; ii, excess MeI, −78 to 0 °C;
iii, UV light, toluene, room temperature, 15 min; iv, heat alone, or in xylene

Scheme 10

2.7.6 APPLICATIONS TO SPECIFIC SYSTEMS

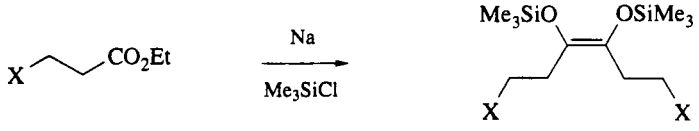
2.7.6.1 Acyclic Systems

2.7.6.1.1 Symmetrical condensations

Early applications of the acyloin coupling reaction to the esters of aliphatic monocarbocyclic acids, before the introduction of the TMS-Cl trapping technique, gave variable yields and the separation of the

pure acyloins from by-products was often troublesome. Nevertheless a satisfactory preparation of 5-hydroxyoctan-4-one in 65–70% yield, by the use of sodium dispersed in xylene, is described in *Organic Syntheses*.[22] Yields in the 50–75% range were recorded[22] for other acyloins prepared in the same way, including 4-hydroxy-2,2,5,5-tetramethylhexan-3-one (pivaloin). Even higher yields were recorded for the esters of fatty acids.[1] It was shown that a nonconjugated double bond and a nonconjugated, nonterminal triple bond in an aliphatic ester were unaffected by these simple coupling conditions.[1] Other successful acyloin coupling reactions[1] using the earlier procedures were those on methyl phenylacetate and ethyl 3-thienylpropionate, containing aromatic residues, and alicyclic esters such as methyl cyclohexanecarboxylate and ethyl adamantane-1-carboxylate.

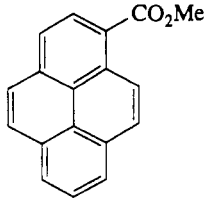
The introduction of the trimethylsilyl chloride trapping technique[11] led to improved yields in the case of simple aliphatic esters. The initial silylated products are easily isolated and can be converted into the acyloins simply and in high yield. For simple aliphatic esters the yields are in the range 56–92%. Use of trimethylsilyl esters, rather than simple alkyl esters, leads to faster reactions, but lower yields.[11,15] Substituted esters which have been successfully used in the newer procedure include ethyl 2-ethylhexanoate (83%),[23] ethyl trimethylsilylacetate (90%),[11] ethyl 3-trimethylsilylpropionate (65%),[11] ethyl phenylacetate (48%),[11] ethyl 3-phenylpropionate (79%)[11] and 2-(2-methoxycarbonylethyl)-2-methyl-1,3-dioxolane derived from levulinic acid (65%).[11] In the case of ethyl adamantane-1-carboxylate the yield using the newer procedure is reported to be inferior to that using the earlier procedure.



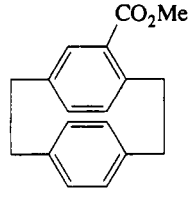
X = OEt (47%); SEt (69%); NEt_2 (62%)

Scheme 11

Because TMS-Cl scavenges basic products, the coupling reaction in its presence can be successfully conducted on esters containing a potential leaving group in the β-position, without any elimination occurring (Scheme 11).[11] However the reaction fails for β-halogen-substituted esters, due to reactions consequent on an initial reductive dehalogenation.[11] Reduction of either ethyl or trimethylsilyl benzoate with sodium only gives <15% of benzoin;[1] the trimethylsilyl enediol ether is formed in ~40% yield if trapping with TMS-Cl is employed.[11] However, an 86% yield is reported for the corresponding trimethylsilyl enediol ether when trimethylsilyl, but not ethyl, 4-methylbenzoate is used.[11] Reduction of ethyl benzoate with sodium in liquid ammonia gives a 50% yield of benzoin;[1] if water is added before the sodium, reduction of the benzene ring occurs (see Section 2.7.1).[4] Reduction of ethyl benzoate with sodium naphthalenide in THF gives benzoin in 86% yield,[24] but much lower yields of the acyloins are produced by the reduction of the esters (**11**) and (**12**) with lithium naphthalenide in THF.[25]



(**11**)



(**12**)

Reaction of methyl or ethyl benzoate with the potassium–graphite intercalation compound C_8K, in DME or THF under argon at 25 °C, followed by quenching with water and air oxidation, gives a 30% yield of phenanthraquinone (equation 3).[26] The conversion of benzoin into phenanthraquinone by C_8K at the layer edge of the intercalate, with loss of molecular hydrogen, had been described earlier.[27] The overall process (equation 3) has been described by its discoverers as the hyperacyloin condensation. The conversion of methyl 4-alkylbenzoates into 3,6-dialkylphenanthraquinone has also been reported.[26]

(3)

2.7.6.1.2 Mixed condensations

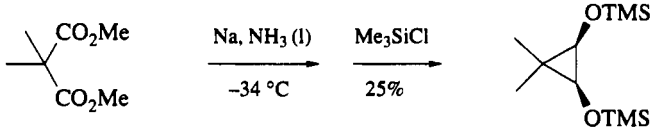
Very few intermolecular mixed acyloin coupling reactions using two different monocarboxylic esters have been attempted.[1] Inevitably, mixtures result, and the yields are low, especially when one component is a benzoate. No attempts to use the TMS-Cl trapping technique seem to have been made.

2.7.6.2 Cyclic Acyloins

2.7.6.2.1 Carbocyclic systems

(i) Small rings

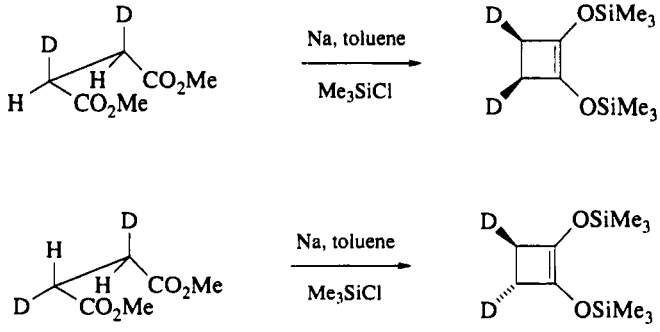
A single example of the formation of a cyclopropane on reduction of a malonate has been reported (equation 4);[1] most of the products of the reduction were acyclic, and the cyclopropane (**13**) is not a derivative of an acyloin.



(4)

(13)

The intramolecular acyloin coupling reaction, on the other hand, is a useful method for constructing cyclobutane rings, although by no means all vicinal esters can be used successfully in this way. Diethyl succinate is not converted into 2-hydroxycyclobutanone (succinoin) by sodium and refluxing toluene alone, but using trapping with trimethylsilyl chloride a 78% yield of the corresponding trimethylsilyl enediol ether can be obtained.[1,11] The procedure is described in detail in *Organic Syntheses*.[14] Although dimethyl tetramethylsuccinate is not reduced by sodium in refluxing toluene or sodium in liquid ammonia, treatment with sodium–potassium alloy in xylene gives the acyloin in 35% yield. It is better, however, to carry out the reduction with sodium in toluene in the presence of TMS-Cl, and then hydrolyze the trapped product with aqueous acid, when the overall yield rises to 60%. Other simple substituted succinates have been reduced by this preferred procedure.[1] Dimethyl (+)-(*R*)-2-methylsuccinate and dimethyl (–)-(*S*)-2-methylsuccinate both give the corresponding chiral trimethylsilyl cyclobutenediol ethers,[28] and the (±)- and *meso*-forms of dimethyl dideuteriosuccinate give deuterium-labeled products of known stereochemistry (Scheme 12).[29] Diethyl (±)-2,3-di-*t*-butylsuccinate is reduced by sodium in toluene, in



Scheme 12

the absence of TMS-Cl, to give the *trans*-di-*t*-butylsuccinoin in 90% yield,[1] but the corresponding *meso* form does not react,[1] presumably because of the severe steric interaction between the two adjacent *t*-butyl groups which would be involved during the coupling step. The successful acyloin coupling of simple succinates using sodium in THF in the presence of TMS-Cl has also been reported.[15]

Other vicinal diesters which have been used successfully in the acyloin coupling reaction, using TMS-Cl trapping, are shown in Figure 1.[1,30,31]

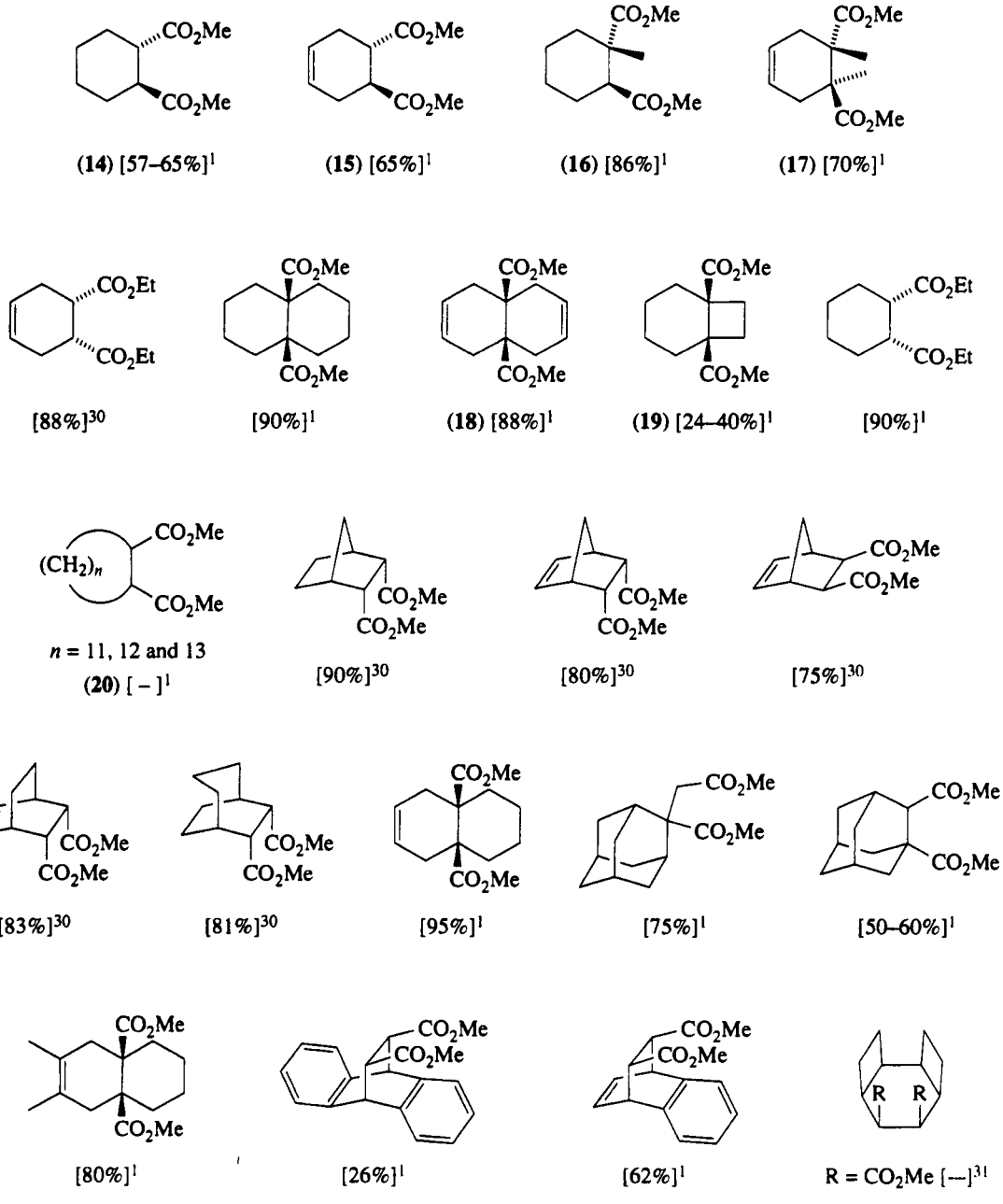
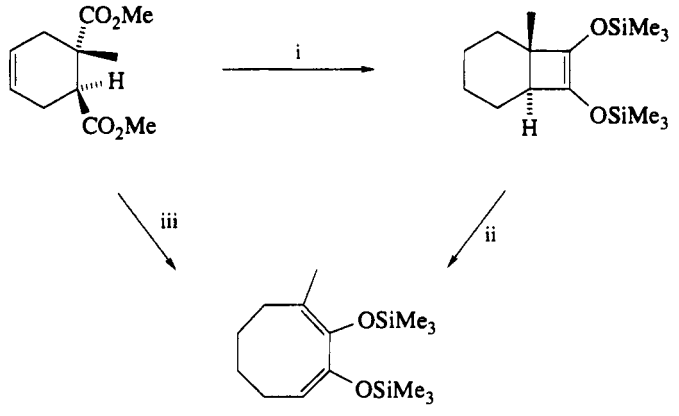


Figure 1 Vicinal diesters (in addition to those discussed in the text) which undergo the acyloin coupling reaction. Yields (in brackets), where quoted, and literature citations are given

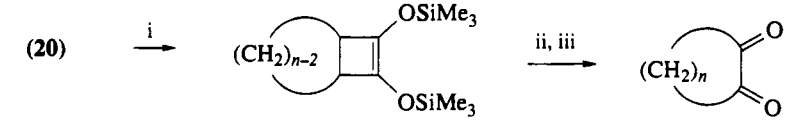
The derivatives of dimethyl *trans*-cyclohexane-1,2-dicarboxylate (**14–17**) give trimethylsilyl enediol ethers which are thermally labile and undergo an electrocyclic ring opening to give a derivative of *cis-cis*-octa-1,3-diene.[1] The acyloin coupling can be accomplished using sodium–potassium alloy at room temperature; in refluxing toluene the monocyclic product is formed (Scheme 13).[1] The corresponding products from dimethyl *cis*-cyclohexanedicarboxylate are thermally stable at the boiling point of tol-

uene.[1] With the medium-sized ring systems (**20**; $n = 11$, 12 or 13) a mixture of the *cis*- and *trans*-diesters was used. Owing to the larger ring size both the *cis*- and *trans*-trimethylsilyl cyclobutadienol ethers underwent thermal ring opening, at 140 °C, and hydrolysis then gave the medium ring α-diketones (Scheme 14).[1]



i, Na/K, Me_3SiCl, inert solvent, 20 °C; ii, Δ; iii, Na, Me_3SiCl, toluene, reflux

Scheme 13

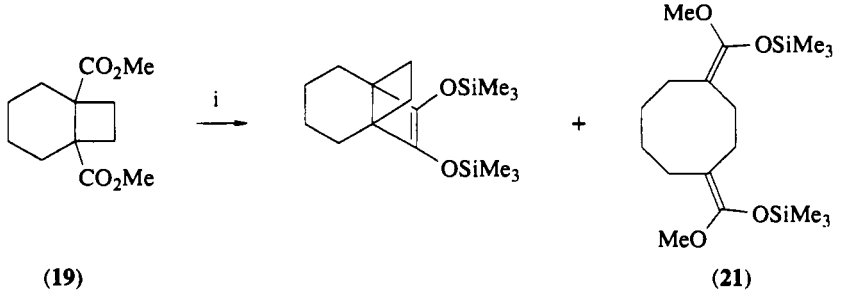


i, Na, xylene, Me_3SiCl; ii, 140 °C; iii, H_3O^+

Scheme 14

The diester (**18**) gives the trimethylsilyl enediol ether, a propellane, in 88% yield, using the preferred TMS-Cl trapping procedure,[1] although sodium–potassium alloy in benzene gives a 76% yield of the acyloin directly.[1]

The diester (**19**) with sodium and TMS-Cl in an inert solvent gives the trimethylsilyl enediol ether, another propellane, in only 24–40%, together with 58–40% of the silylated compound (**21**), formed by reductive cleavage of the central bond (**19**; Scheme 15).[1]

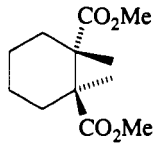


(**19**) (**21**)

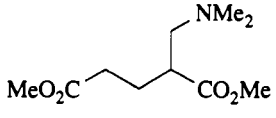
i, Na, Me_3SiCl, inert solvent

Scheme 15

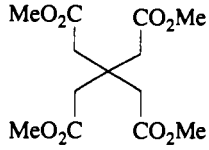
A combination of the alternative pathways illustrated in Schemes 13 and 15 explains why the derivative of dimethyl *trans*-cyclohexane-1,2-dicarboxylate (**22**) fails to give any of the silylated coupled enediol; even at 25 °C, using sodium–potassium alloy in benzene, thermal rearrangement to an octa-1,3-diene occurs, whereas use of sodium in liquid ammonia, at –78 °C, cleaves the bond joining the two functionalized carbon atoms, leading to dimethyl 2,7-dimethyloctane-1,8-dioate.[1]



(22)



(23)



(24)

The vicinal diester (**1**) is one of a number of complex vicinal diesters investigated by Paquette and his coworkers,[6,32] which does not undergo the acyloin coupling reaction but rather undergoes bond cleavage as shown in Scheme 3. Other vicinal diesters which have been reported *not* to undergo the acyloin coupling reaction are shown in Figure 2.[1,33–35]

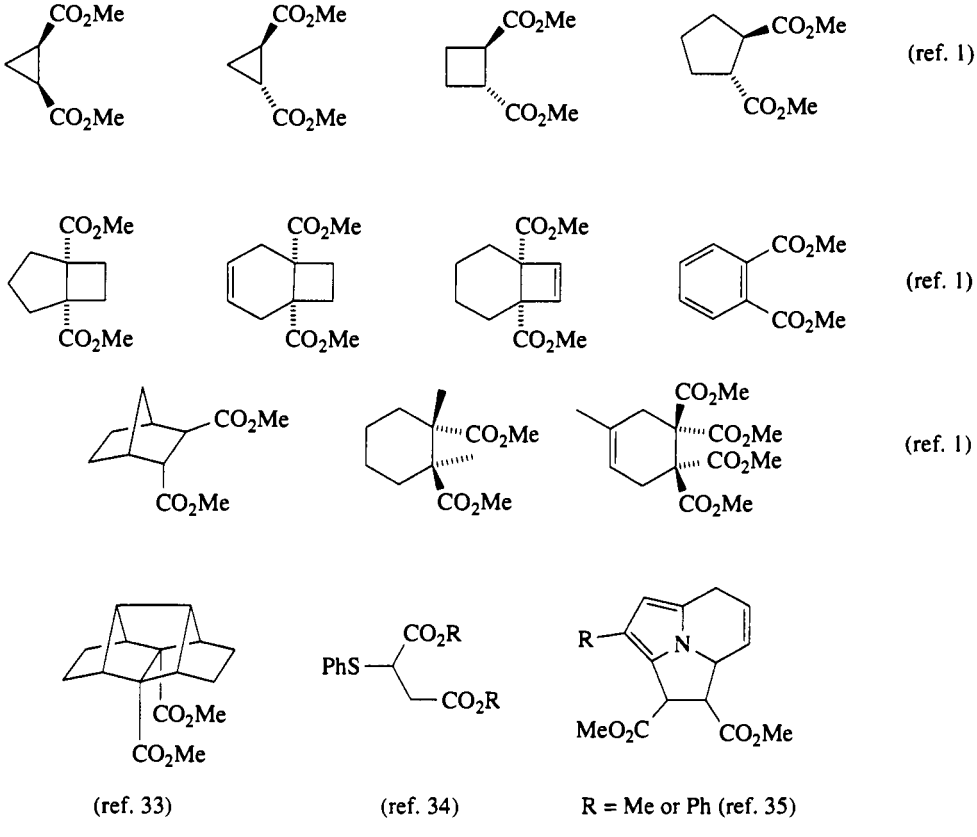
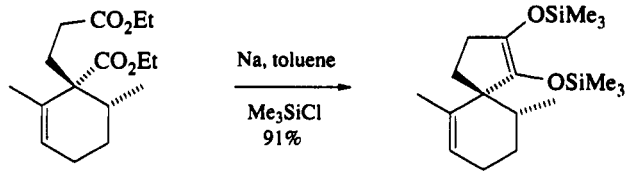
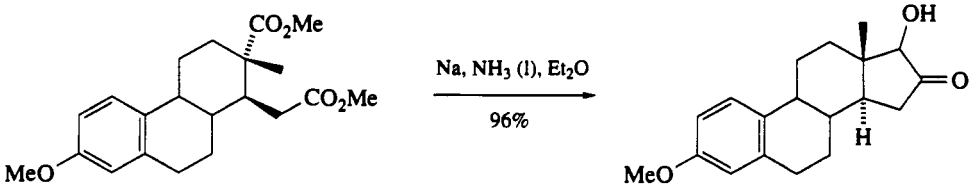


Figure 2 Vicinal diesters (in addition to those discussed in the text) which fail to undergo the acyloin coupling reaction. References are given in brackets

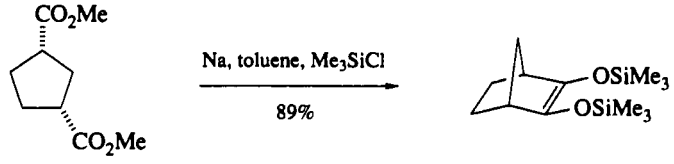
The acyloin condensation has also been used to construct five-membered rings. Very high yields are obtained using trapping with TMS-Cl after carbon–carbon bond formation following reduction with sodium in toluene. The reaction is also reported to succeed using THF as the solvent.[15] Diethyl glutarate, labeled with ^{13}C at the 2- and 4-positions, gives the cyclic trimethylsilyl enediol ether in 94% yield.[36] Similarly 2-substituted glutarates, *e.g.* (**23**),[37] and 3,3-disubstituted glutarates[1,38] give excellent yields of the corresponding cyclic enediol silyl ethers, including spiro ring systems formed from 1,1-bis(methoxycarbonylmethyl)cycloalkenes[1,11] and the tetraester (**24**).[1,11] A further spiroannelation[39] is illustrated in equation (5). Acyloin coupling has also been applied to the elaboration of fused systems incorporating a



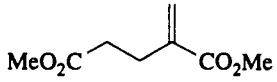
(5)



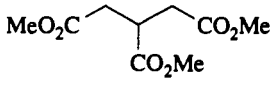
(6)



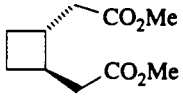
(7)



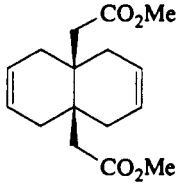
(25)



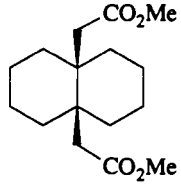
(26)



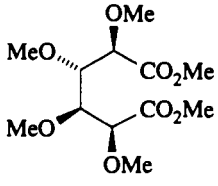
(27) [22%][1]



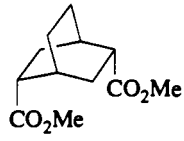
(28) [89–92%][1]



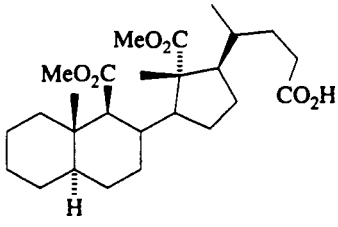
(29) [88–90%][1]



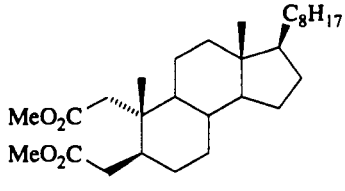
[51%][1]



[–][1]



[75–80%][1]



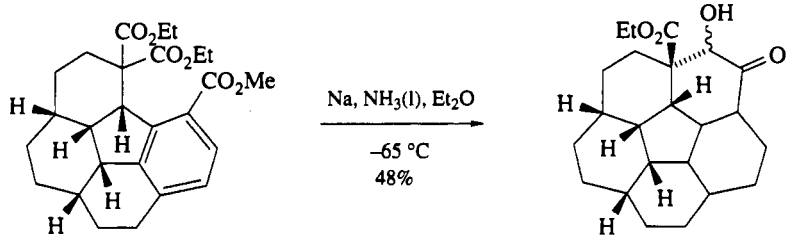
[82%][1]

Figure 3 Diesters (in addition to those discussed in the text) which give six-membered carbocyclic acyloins on reduction. Yields (in brackets), where quoted, and literature citations are given

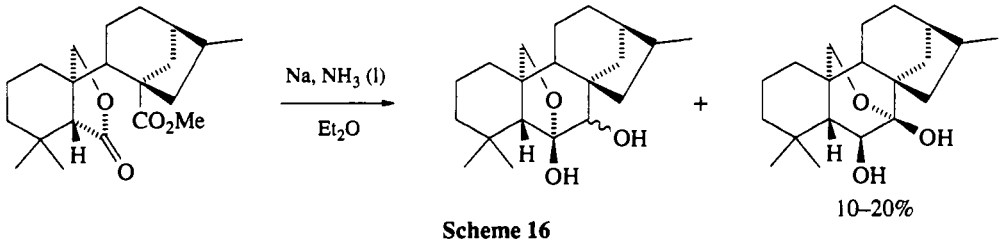
five-membered ring. Earlier work, not using TMS-Cl trapping, has been summarized[1] and includes several examples using seco-steroidal diesters. A high-yielding example is shown in equation (6). A few examples using the more modern procedures have also been reported,[1,11] including the one shown in equation (7).

Two 1,3-diesters which are reported *not* to undergo acyloin coupling are the unsaturated ester (**25**)[37] and the triester (**26**).[1]

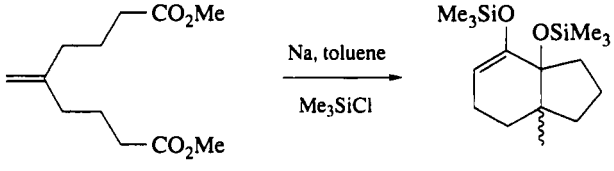
Six-membered rings can be made by the acyloin coupling reaction. Dimethyl 2,2,5,5-tetramethylhexane-1,6-dioate gives the corresponding acyloin in 91% yield on reduction with sodium and xylene,[1] but for dimethyl hexane-1,6-dioate itself a comparable yield is only achieved using a TMS-Cl trapping technique.[1] Some other diesters which give six-membered acyloins are shown in Figure 3. In the case of the diesters (**27**), (**28**) and (**29**), TMS-Cl trapping was used and the yields refer to the trimethylsilyl enediol ethers. A key step in the synthesis of corannulene was the acyloin coupling reaction shown in equation (8).[1] It was necessary to avoid any excess of sodium and to operate at the temperature of an acetone/solid carbon dioxide bath, to prevent reduction of the ester function in the product. Some work has been reported on the reduction by alkali metals of ester lactones in the diterpene field. Complex mixtures of products result. In the example illustrated in Scheme 16 products which are the cyclic hemiacetals of six-membered ring acyloins were isolated.[1] Two six-membered ring trimethylsilyl enediol ethers are produced in the acyloin coupling reaction of dimethyl 5-methylenenonane-1,9-dioate (**30**), as shown in equation (9). Their genesis must involve transannular bond formation after the initial coupling to give a nine-membered ring intermediate.[40]



(8)



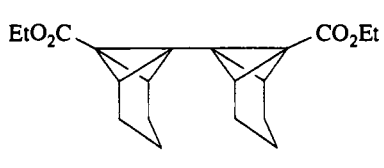
Scheme 16



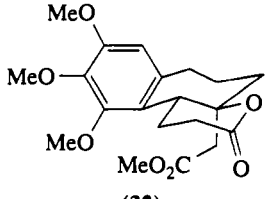
(**30**) *cis:trans* 1:2.3

(9)

Attempts to bring about the acyloin coupling reaction with the diester (**31**) were unsuccessful.[41] The failure can be attributed to the severe nonbonded interactions between the two ester groups in the cisoid conformation required for coupling to occur.



(**31**)



(**32**)

Examples of the formation of seven-membered rings by the acyloin coupling reaction are collected in Figure 4. The reduction of the ester lactone (32) to give an acyloin hemiacetal (*cf.* Scheme 16) in very low yield was reported as part of a synthetic route to colchicine.[1] In both these reductions of ester lactones, TMS-Cl trapping was not employed, and base-catalyzed β-elimination of the lactone oxygen would have been a competing process.

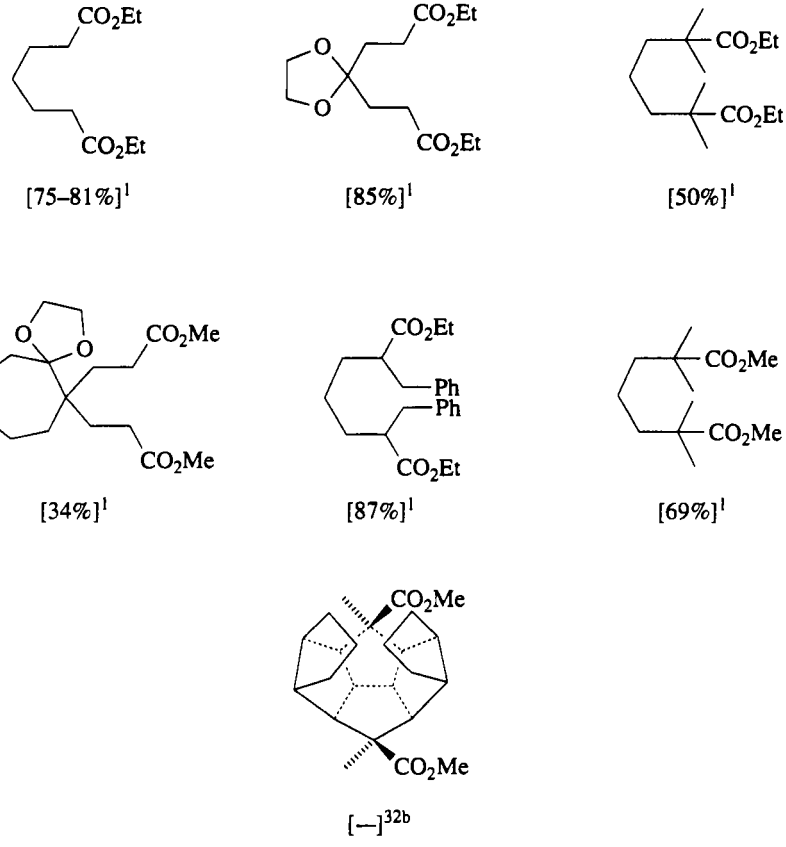
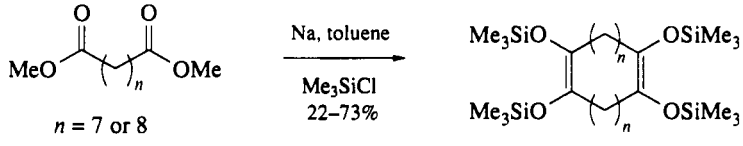


Figure 4 Diesters which give seven-membered carbocyclic acyloins on reduction. Yields (in brackets), where quoted, and literature citations are given

(ii) Medium rings

The yields in the Dieckmann and Thorpe–Ziegler cyclizations drop to almost zero for the production of nine- to twelve-membered rings. Fortunately the yields in the acyloin coupling reactions leading to the same ring sizes are quite good, making this procedure uniquely effective for the synthesis of medium-sized carbocyclic rings.



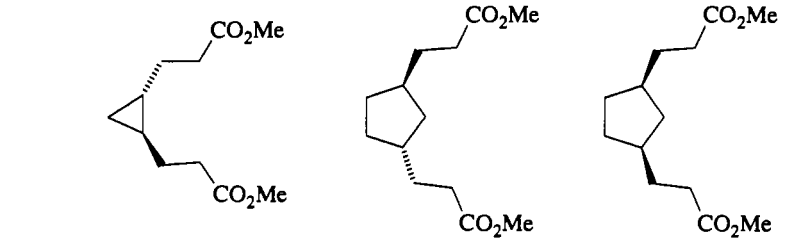
Scheme 17

The yields obtained in the preparation of medium-sized ring trimethylsilyl enediol ethers using TMS-Cl trapping and a high dilution strategy are shown in Table 1.[42] With rapid addition of the diester considerable dimer formation occurs (Scheme 17). The acyloin coupling reaction was earlier used without TMS-Cl trapping to prepare many eight-, nine-, ten- and eleven-membered cyclic acyloins directly, with yields in the range 24–97%.[1] For example (+)-dimethyl 2-methylnonanoate was converted into the (–)-form of the corresponding acyloin in 33% yield. Dimethyl decane-1,10-dioate behaves like a simple monocarboxylic ester in not undergoing the acyloin coupling reaction with sodium and TMS-Cl when

the solvent is THF.[15] Medium-sized ring acyloins in which the ring is fused to a smaller ring have been prepared by applying the acyloin coupling reaction to the diesters (**33**) and (**34**). The product from (**33**) was obtained in 75% yield using sodium in xylene,[1] but the product from (**34**) was only obtained in a reasonable yield, of 36%, by using sodium in dioxane.[1] No coupling product could be obtained from the diastereomeric ester (**35**) under a variety of conditions.[1] In more complex systems a coupling reaction leading to an eight-membered ring[6] is shown in Scheme 3, and the reduction of the diester (**36**) provides a further example.[6] On the other hand the diester (**37**) failed to take part in the acyloin coupling reaction;[43] the failure was attributed to the severe nonbonded interactions which would arise as the two carbon atoms, which would have to be linked together, align themselves for the reaction. A polycyclic system incorporating eight- and nine-membered trimethylsilyl enediol ether rings is formed by the reaction shown in equation (10).[1] As part of a program leading to the synthesis of betweenanenes and triannulenes, Marshall has used the acyloin coupling reaction to prepare trimethylsilyl enediol ethers possessing two fused medium-sized rings with a *trans* double bond common to both rings (Scheme 18).[44]

Table 1 Yields of Trimethylsilyl Enediol Ethers in the Acyloin Coupling Reactions of α,ω-Diesters Using High Dilution

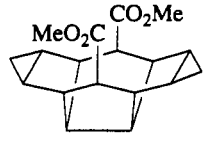
Substance	*Yield (%)*	*Substance*	*Yield (%)*
$MeO_2C(CH_2)_6CO_2Me$	72–85	$MeO_2C(CH_2)_9CO_2Me$	48
$MeO_2C(CH_2)_7CO_2Me$	68	$MeO_2C(CH_2)_{10}CO_2Me$	68
$MeO_2C(CH_2)_8CO_2Me$	58–69		



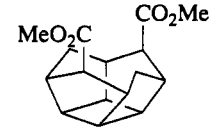
(33)

(34)

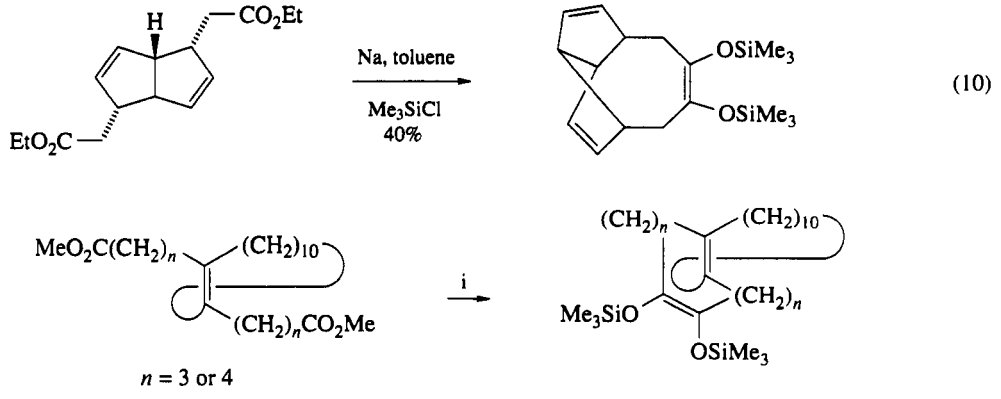
(35)



(36)



(37)



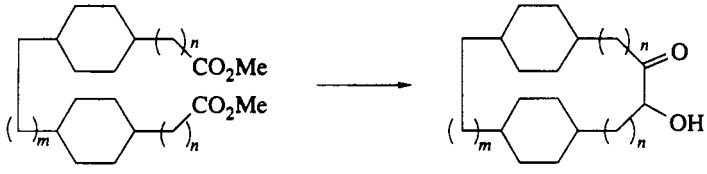
(10)

i, Na/K, xylene, Me_3SiCl, reflux

Scheme 18

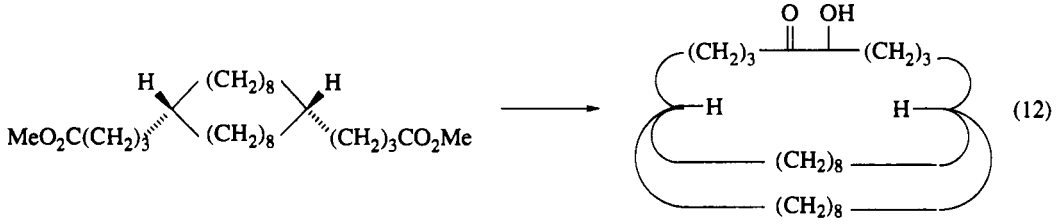
(iii) Large Rings

Even without the use of TMS-Cl trapping the acyloin coupling reaction was reported to give cyclic acyloins from dimethyl or diethyl esters of unsubstituted α,ω-diacids containing from 12 to 20 carbon atoms in yields of 64–96%.[1] Using TMS-Cl trapping, the cyclic trimethylsilyl enediol ethers are formed in similar yields;[1] for example, the cyclic trimethylsilyl enediol ethers containing 22 and 42 atoms in the ring are formed in *ca.* 90% yield, using sodium and toluene in the presence of TMS-Cl under argon.[45] An early route to paracyclophanes[1] completed the large ring by an acyloin coupling reaction using diesters containing two separated cyclohexane rings (equation 11); several of the yields were low, but moderate yields were obtained in other cases.[1] The presence of a (*Z*)-alkenic or an alkyne linkage near the center of a long chain α,ω-diester allows cyclic acyloins containing double or triple bonds to be constructed in good yield.[1] Similarly, a centrally placed ketone function, protected as a cyclic ethylene ketal, allows the synthesis of a large ring ketoacyloin.[1] The acyloin coupling reaction has also been performed with long chain α,ω-diesters with one or more alkyl branches.[1] An example of the synthesis of a 14-membered acyloin ring fused to a thiophene ring is illustrated in Scheme 4.



(11)

The acyloin coupling reaction, at high dilution, of the *cis* and *trans* forms of 1,9-bis(3-methoxycarbonylpropyl)cyclooctadecane was the key step in the synthesis of homeomorphic isomers of bicyclo[8.8.8]hexacosane.[1] The reaction of the *cis* isomer to give an acyloin, which was converted into the *in, in*-isomer of the hydrocarbon, is shown in equation (12).



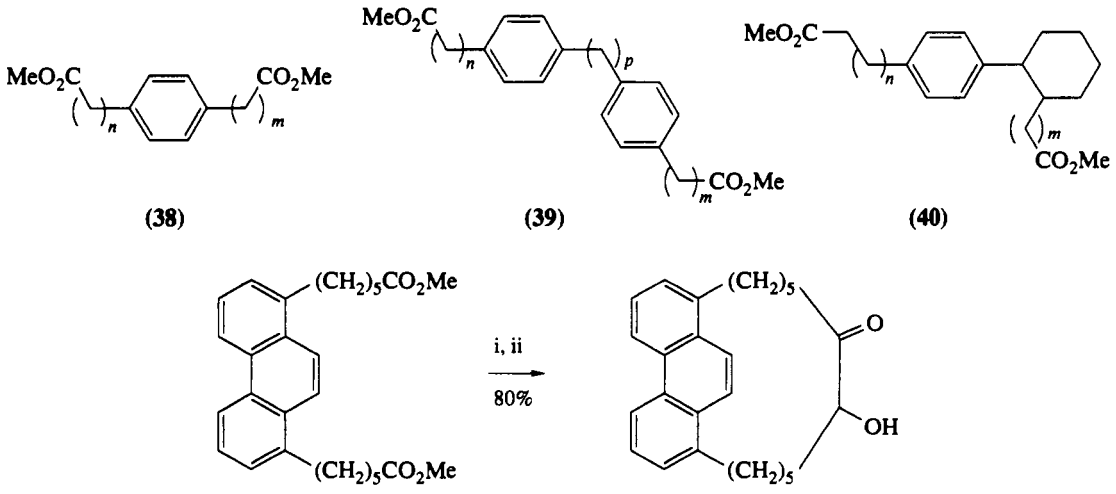
(12)

The first claim to have prepared a catenane was based on the use of the acyloin coupling reaction to prepare both the interlocking rings.[46] A pentadeuteriotetratriacontane was first prepared by chemical modification of the large ring acyloin obtained from diethyl tetratriacontane-1,34-dioate. A second acyloin coupling reaction in the presence of the deuterated hydrocarbon using diethyl tetratriacontane-1,34-dioate for the second time was then undertaken in the hope that some of the newly formed ring would interlock with the first ring.[46]

Other large ring acyloins have been prepared in connection with the preparation of rotaxanes, the acyloins forming the 'wheel' on the 'axle'. Using a slow addition technique dimethyl octacosane-1,28-dioate gave the acyloin in 78% yield.[47] Lower yields were earlier reported for the cyclization of diethyl pentacosane-1,25-dioate and diethyl hexacosane-1,26-dioate in the presence of molecules which might have led to rotaxanes, although no rotaxanes were detected.[1] The preparations of 30- and 32-membered cyclic acyloins, and of a mixture containing *every* cyclic acyloin with 14–42 carbon atoms in the ring, have also been reported.[1]

(iv) Paracyclophanes

Early work on the use of the acyloin coupling reaction in the synthesis of paracyclophanes has been summarized by Smith.[48] The intramolecular coupling of diesters of the type (**38**),[1] (**39**)[1] and (**40**),[49] using sodium and xylene under conditions of high dilution, is generally successful, but some failures, *e.g.* with (**38**) and (**39**); *n* and/or *m* = 1, have been reported, largely attributable, in the absence of TMS-Cl trapping, to base-catalyzed side reactions. The only example of the use of TMS-Cl trapping seems to be the one shown in Scheme 19.[50]



(38) **(39)** **(40)**

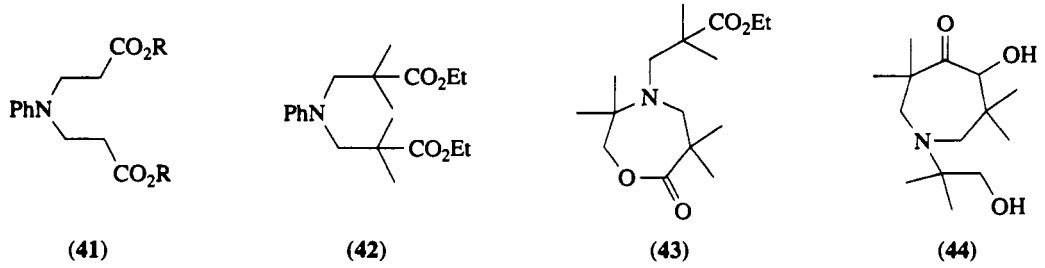
i, Na, toluene, Me_3SiCl; ii, H_3O^+

Scheme 19

2.7.6.2.2 Heterocyclic systems

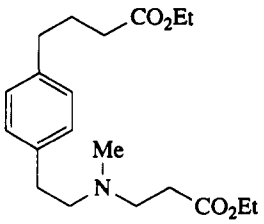
The acyloin coupling reaction has been used to prepare cyclic acyloins with ring sizes from six to 23, in which one of the ring atoms is a nitrogen atom bearing an alkyl, cycloalkyl, or aryl substituent, as shown in equation (13). The use of TMS-Cl trapping may be advisable for the synthesis of azacycloheptane derivatives,[1,51] but in most cases good yields have been reported without the use of TMS-Cl, particularly with diesters possessing no hydrogen atoms α to the ester groups. The yield of the acyloin from the diester (**41**; R = Et) was only 10%, but its tetramethyl derivative (**42**) gave the acyloin in 83% yield. However, using TMS-Cl, trapping the diester (**41**; R = Me) gave the trimethylsilyl enediol ether in 74% yield. Similarly the lactone ester (**43**) gave yields of the acyloin (**44**) of 35–62%, but with TMS-Cl trapping, followed by hydrolysis, the yield was improved to 68%.[52] The diester (**45**) underwent the acyloin coupling reaction in the presence of highly dispersed sodium in xylene in 56% yield, and the product was converted into a 3-aza[10]paracyclophane.[53] The related diesters (**46**) and (**47**; n = 1 or 2) all failed to give an acyloin, even in the presence of TMS-Cl.[54]

(13)

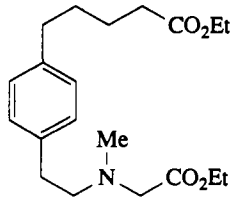


(41) **(42)** **(43)** **(44)**

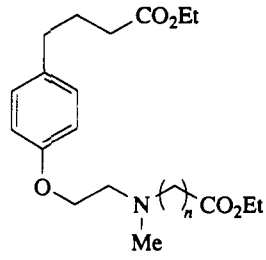
The acyloin coupling reaction has also been used to prepare cyclic acyloins in which one of the ring atoms is an oxygen, sulfur or silicon atom.[1] For seven- or eight-membered rings the use of TMS-Cl trapping may give improved yields.[1] An example is shown in Scheme 20.[1]



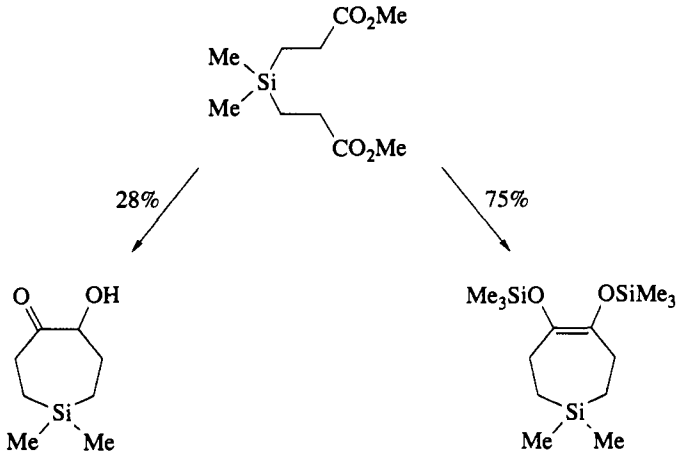
(45)



(46)

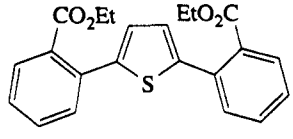


(47)



Scheme 20

Various acyloins which are 2,5-bridged thiophenophane derivatives have been prepared by the intramolecular coupling of the appropriate diesters; a typical example is given in Scheme 4. Attempts to effect the intramolecular acyloin coupling reaction with the benzoate-type diester (**48**) were unsuccessful under several standard conditions.[55]

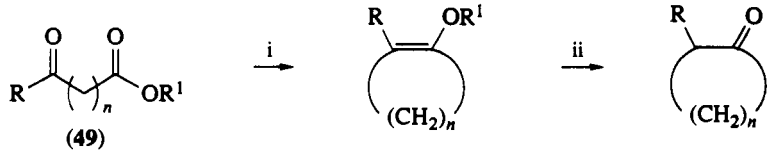


(48)

2.7.7 COUPLING REACTIONS BETWEEN ESTERS AND KETONES

Under conditions which have been used for the acyloin coupling reaction without TMS-Cl trapping, certain δ-keto esters, instead of undergoing intramolecular ester coupling to give diketoacyloins, give products derived by intramolecular coupling of the two carbonyl carbon atoms, and a five-membered carbocyclic ring is formed. In the few cases studied a mixture containing a range of functional groups was formed on reduction with sodium in ether–liquid ammonia or sodium naphthalenide in THF, and the method was not an attractive one.[1]

More recently a much superior and more generally applicable method for the intramolecular coupling of keto esters has been reported by McMurry.[56] The procedure leads to an enol ether, which can be isolated, but is normally hydrolyzed to a ketone (Scheme 21). McMurray used a heterogeneous coupling reagent formed by the action of lithium aluminum hydride on titanium(III) chloride in the presence of triethylamine in DME under argon. Recently titanium on graphite, produced by the action of the potassium–graphite intercalate on titanium(III) chloride, has been shown to give a higher yield in at least one case; no tertiary amine is necessary with this reagent, which was used in THF under argon employing a high dilution technique.[57] Table 2 lists the known examples of these coupling procedures; ring sizes of from four to 14 atoms have been prepared in this way. In the case of the keto ester (**51**), containing an



(49)

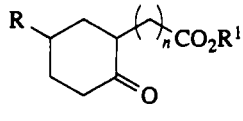
i, $TiCl_3$, $LiAlH_4$, Et_3N; ii, H_3O^+

Scheme 21

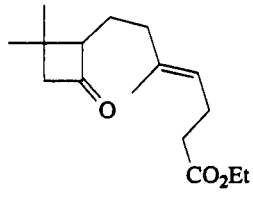
(*E*)-double bond, the product is the cyclic ketone (**52**) containing a (*Z*)-double bond.[58] The isomerization of the double bond is thought to be connected uniquely with the highly strained fused system which is being constructed, and the phenomenon is unlikely to be a general one.

Table 2 Yields of Ketones from the Intramolecular Coupling of Keto Esters by the McMurry Method

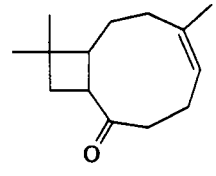
Compound	*R*	R^1	*n*	*Ring size formed*	*Isolated yield (%)*	*Ref.*
(**50**)	Bu^t	Et	1	4	57	56
(**50**)	H	Et	2	5	75	56
(**50**)	H	Me	3	6	91	57
(**50**)	H	Et	3	6	80	56
(**49**)	Me	Et	4	6	77	57
(**50**)	H	Et	4	7	82	56
(**50**)	H	Et	5	8	52	56
(**50**)	H	Et	6	9	50	56
(**51**)				9	38	58
(**49**)	Me	Me	8	10	56	56
(**49**)	Et	Me	9	11	45	56
(**49**)	Et	Me	10	12	63	56
(**49**)	Me	Me	11	13	60	56
(**50**)	H	Et	11	14	54	56



(**50**)



(**51**)



(**52**)

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2.8
Kolbe Reactions

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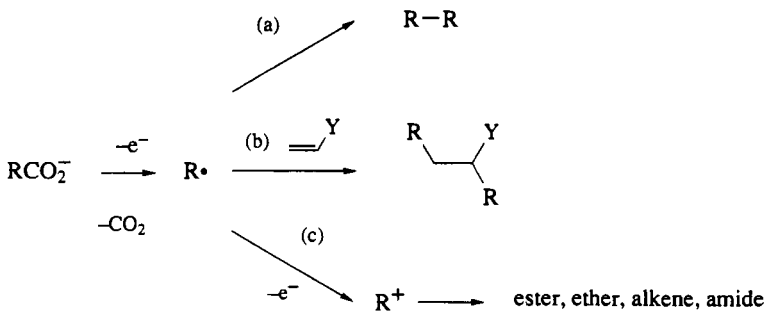
2.8.1 INTRODUCTION AND HISTORICAL BACKGROUND

By anodic decarboxylation carboxylic acids can be converted simply and in large variety into radicals. The combination of these radicals to form symmetrical dimers or unsymmetrical coupling products is termed Kolbe electrolysis (Scheme 1, path a). The radicals can also be added to double bonds to afford additive monomers or dimers, and in an intramolecular version can lead to five-membered heterocycles and carbocycles (Scheme 1, path b). The intermediate radical can be further oxidized to a carbenium ion (Scheme 1, path c). This oxidation is favored by electron-donating substituents at the α-carbon of the carboxylic acid, a basic electrolyte, graphite as anode material and salt additives, *e.g.* sodium perchlorate. The carbocations lead to products that are formed by solvolysis, elimination, fragmentation or rearrangement. This pathway of anodic decarboxylation is frequently called nonKolbe electrolysis.

Faraday probably experienced in 1834 the first example of a radical dimerization by anodic decarboxylation, when he noticed an inflammable gas whilst studying the conductivity of acetate.[1] However, it took another 15 years until Kolbe in 1849 recognized the nature and dimensions of this conversion.[2] This way the name of the reaction was coined. In 1855 Wurtz obtained unsymmetrical coupling products, when he coelectrolyzed two different carboxylates.[3] Crum-Brown and Walker later opened a simple entry to α,ω-dicarboxylic esters, useful products for the synthesis of 1,*n*-difunctionalized alkanes or medium- and large-sized rings, when they electrolyzed half esters of 1,*n*-diacids.[4] In the 1950s and 1960s Weedon *et al.* extensively applied the Kolbe electrolysis to the synthesis of rare fatty acids and to acyclic natural products.[5]



Scheme 1

Major contributions to the mechanism of the Kolbe electrolysis have been made by Conway *et al.*,[6] who mainly used electroanalytical techniques, and by Eberson[7] and Utley,[8] who drew their conclusions from the dependence of product structures on reaction conditions.

A large number of reactions have been published in the last 140 years on the Kolbe and nonKolbe electrolysis. Many of them have been compiled in reviews[5,6,9–15] and books.[8,16–23]

2.8.2 REACTION CONDITIONS FOR THE KOLBE ELECTROLYSIS

The pathway leading to radical products (Kolbe electrolysis) and/or cationic intermediates (nonKolbe electrolysis) is determined mainly by the substituents in the α-position of the carboxylic acid and some experimental factors.

The electrolysis products of different carboxylates have been compared with the ionization potentials of the intermediate radicals.[7c] From this it appeared that alkyl radicals with gas-phase ionization potentials smaller than 8 eV mainly lead to carbenium ions. Accordingly, α-substituents such as carboxy, cyano or hydrogen support the radical pathway, whilst alkyl, cycloalkyl, chloro, bromo, amino, alkoxy, hydroxy, acyloxy or aryl more or less favor the route to carbenium ions. Besides electronic effects, the oxidation seems also to be influenced by steric factors.[24] Bulky substituents diminish the extent of coupling. The main experimental factors that affect the yield in the Kolbe electrolysis are the current density, the pH of the electrolyte, ionic additives, the solvent and the anode material.

High current densities, together with high carboxylate concentrations favor the formation of dimers. This results from a high radical concentration at the electrode surface that supports the dimerization. Furthermore, at higher current densities a critical potential of 2.4 V (*versus* the normal hydrogen electrode) is reached,[25a] which seems to be a prerequisite for the Kolbe electrolyis, because at and above this potential the oxygen evolution and solvent oxidation is effectively suppressed.[6,26,27]

A weakly acidic medium favors the Kolbe electrolysis. Therefore the carboxylic acid is in most cases neutralized to an extent of only 2 to 5%. In an undivided cell the concentration of the carboxylate remains constant until near the end of the electrolysis, because when the carboxylate is converted at the anode it is continously regenerated from the carboxylic acid by the base formed at the cathode. The endpoint of the electrolysis is recognizable by a steep rise of the pH in the electrolyte. This procedure is called the salt-deficit method. The degree of neutralization can be as low as 0.5%. Low cell voltages, in spite of low conductivity, are obtained in these cases by using cells with a very small electrode distance (0.1 to 2 mm),[25b–28] as shown in the flow-through cell in Figure 1. Sometimes the carboxylic acid must be converted totally into the carboxylate to increase its solubility in aqueous solution or to achieve a uniform discharge in mixed Kolbe electrolysis, when the acidities of the two acids are too different. A mercury cathode is then applied, and the electrolyte stays neutral, because the alkali metal cations are discharged as amalgams.[29] In such cases a divided cell with a permselective ion-exchange membrane may also be suitable.

Temperature has only a minor effect on the Kolbe electrolysis. In the Kolbe coupling, temperatures higher than 50 °C should be avoided because they favor unwanted side reactions such as disproportionation or the esterification of the carboxylic acid.[30]

Ionic additives to the electrolyte can influence the Kolbe electrolysis in a negative way. Anions other than the carboxylate should be excluded, because they hinder the formation of a carboxylate layer at the anode, that seems to be a prerequisite for the decarboxylation. In the electrolysis of phenyl acetate the coupling to dibenzyl is totally suppressed when sodium perchlorate is present in concentrations of 5×10^{-3} mol l^{-1}; benzyl methyl ether, the nonKolbe product, is formed instead.[24] This shift from the radical

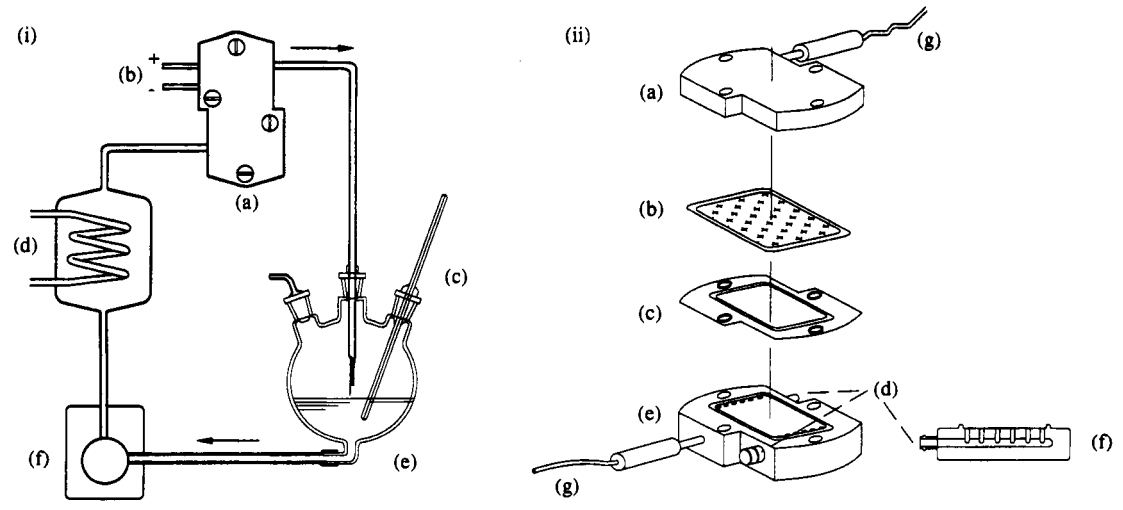


Figure 1 (i) Flow-through cell and accessories: (a) cell; (b) electrical connection to regulated d.c. power supply; (c) thermometer; (d) heat exchanger; (e) vessel for gas outlet, sample withdrawal and temperature control; (f) circulation pump. (ii) Exploded view of the flow-through cell: (a) brass lid (10 mm); (b) platinum anode (0.01 × 30 × 60 mm); (c) silicon seal (0.5 mm); (d) electrolyte in/out; (e) V4A-steel base (cathode); (f) V4-A steel base (side view); (g,h) electrical connections

to the carbenium ion pathway can be rationalized by a partial obstruction of the anode surface by co-adsorption of perchlorate. That way the radical concentration at the electrode is lowered, which disfavors the bimolecular dimerization and supports an electron transfer from the radical to the electrode to form a carbenium ion.

Whilst cations such as Fe^{2+}, Co^{2+}, Mn^{2+} and Pb^{2+} lower the yield in the Kolbe electrolysis,[11] alkali and alkylammonium ions have no effect[31] and are therefore preferably used as counterions for the carboxylate.

Methanol is the solvent of choice for the Kolbe electrolysis.[5,32] The following electrolytes with methanol as solvent have been used: methanol/sodium carboxylate, methanol/sodium methoxide/carboxylic acid,[33,34] methanol/water/sodium hydroxide/carboxylic acid,[35] methanol/triethylamine/pyridine/carboxylic acid.[36] An increasing amount of water often decreases the yield of dimer.

Dimethylformamide is also a useful solvent;[37] its relatively low oxidation potential,[38] however, prevents its frequent application. The ternary system water/methanol/dimethylformamide has been systematically studied, when the electrolyses of ω-acetoxy- or ω-acetamido-carboxylic acids were optimized.[25b] Wet acetonitrile has also been used as solvent.[39] The influence of various solvents on the ratio of Kolbe

Table 1 Anodic Decarboxylation[a] of Cyclohexanecarboxylic Acid in Different Solvents

Solvent	*Bicyclohexyl:carbenium ion product*[b]
H_2O/MeOH (30% v/v)[c]	0.97:1
MeOH[c]	1.76:1
MeCN[d]	2.26:1
$HCONMe_2$[d]	4.32:1

[a]Acid (0.78 M), neutralized to 25%; platinum anode, 0.25 A cm^{-2}. [b]Alcohol, ester, ether and acetamide according to solvent. [c]Sodium salt. [d]Tetrabutylammonium salt.

to nonKolbe products is shown in Table 1.[40]

Other electrolytes that have been applied, are dimethyl sulfoxide/sodium hydride,[41] glycol methyl ether/water/potassium carbonate[42] or acetic acid/potassium carboxylate.[11]

As anode material, smooth platinum, as foil or net, is most widely used.[25b,26] In nonaqueous solvents, additionally, platinized titanium, gold, hard graphite[43] and ruthenium dioxide on titanium[44] have been employed. To keep the amount of the costly platinum low, the foils have been glued to a graphite support.[27] With vitreous or baked carbon in protic solvents (methanol, ethanol, water) dimer yields nearly comparable to those at platinum have been obtained.[36]

The nature of the cathode material is uncritical in the Kolbe electrolysis. The discharge of protons from the carboxylic acid is in most cases the only cathode reaction, which allows the convenient electrolysis in an undivided cell. For the electrolysis of unsaturated carboxylic acids, however, platinum as cathode material should be avoided, since cathodic hydrogenation can occur; in this case a steel cathode should be used instead.

In summary, good yields and selectivities in the Kolbe electrolysis are favored by the following experimental conditions: an undivided beaker-type cell is sufficient for most cases, it should be equipped with a smooth platinum anode of small size (area of 1 to 10 cm^2) to assure a high current density (0.25 A cm^{-2} and higher) and a platinum, steel or nickel cathode in close distance; the current is provided by a regulated d.c. power supply (Figure 2); methanol is preferred as solvent, and the concentration of the carboxylic acid should be as high as possible. It is neutralized to an extent of 2 to 10% with sodium methoxide. A double-walled cell should be used to maintain temperatures between 10 to 45 °C by external cooling.

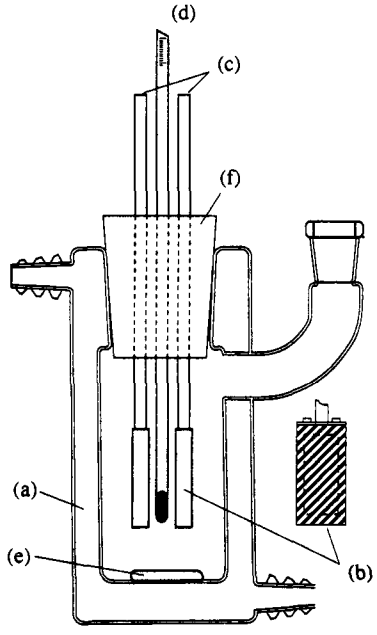
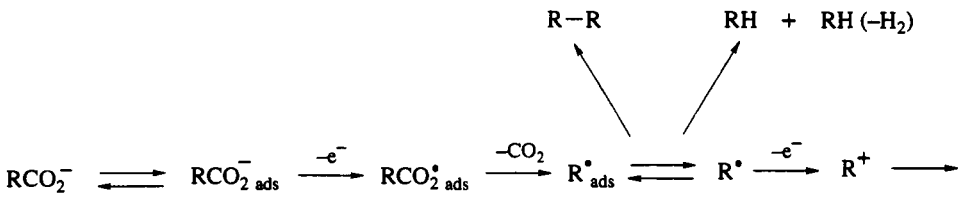


Figure 2 Beaker-type cell: (a) double-walled cell; (b) platinum sheet or grid on teflon support; (c) electrode leads (steel rods) to d.c. power supply; (d) thermometer; (e) magnetic stirring bar; (f) teflon stopper

2.8.3 MECHANISM OF THE KOLBE ELECTROLYSIS

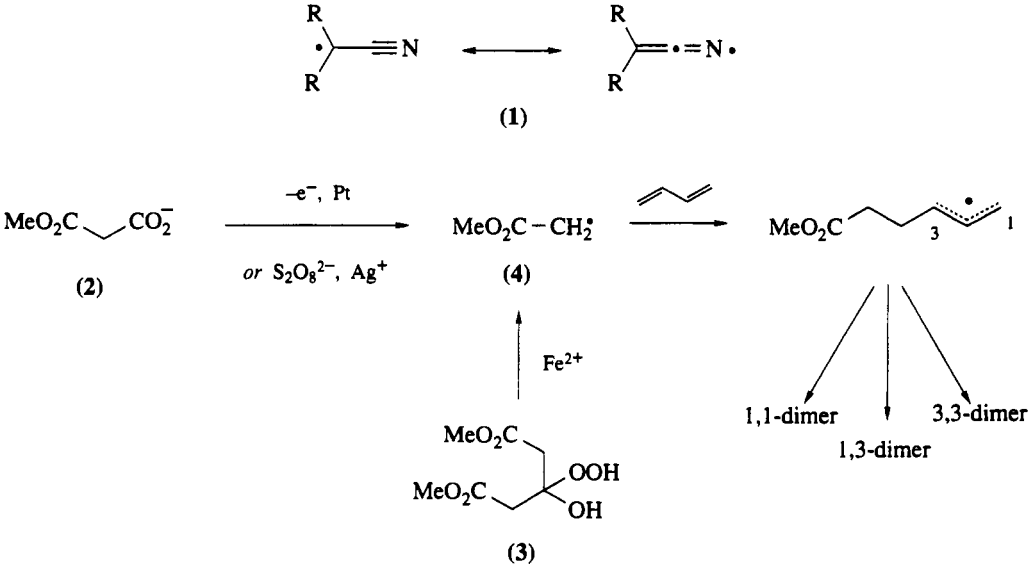
In the past, widely differing mechanisms have been proposed for the Kolbe electrolysis. The free-radical theory, which assumed acyloxy radicals as intermediates, was suggested by Crum-Brown and Walker.[45] According to Glasstone and Hickling[46] in aqueous solution hydroxyl radicals and hydrogen peroxide were formed, which converted the carboxylic acids into dimers and alcohols or esters, the so-called Hofer–Moest products.[47] Schall[48] and Fichter[16] proposed that the carboxylates are oxidatively coupled to diacyl peroxides, that subsequently decomposed. These mechanistic proposals have been reviewed.[49,50] The presently accepted mechanistic schemes have been reviewed,[6–8,51–54] and the general scheme summarized in Scheme 2 is assumed.

Current potential curves exhibit a critical potential at 2.1 to 2.4 V *versus* the normal hydrogen electrode. At this critical potential the coverage of the electrode with carboxylate increases sharply.[55] From electroanalytical data[55,56] it is deduced that at the critical potential, and higher, a rigid layer of adsorbed acyloxy or alkyl radicals is formed on top of the metal[7c,56,57] or metal oxide,[50] which inhibits oxygen evo-lution or solvent oxidation and promotes the Kolbe electrolysis.[6,7a,b,58] The oxide formation and the adsorption of intermediates during the Kolbe electrolysis have also been followed by modulated specular reflectance spectroscopy.[59] Examination of the electrode surface by polaromicrotribometry has indicated that at the critical potential a hydrophobic film is formed that seems to inhibit the oxygen discharge.[60] The rate-determining step for the Kolbe reaction is most probably an irreversible single electron transfer



Scheme 2

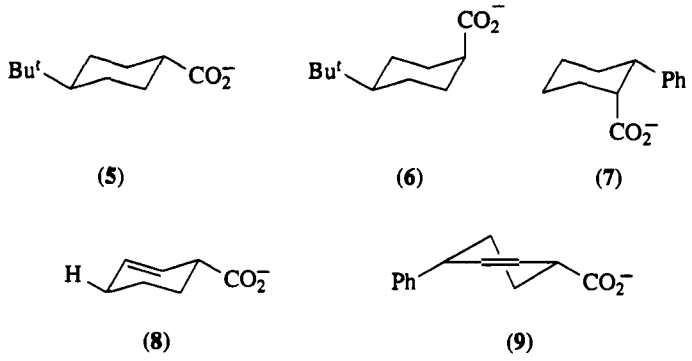
from the carboxylate with simultaneous bond-breaking, leading to the alkyl radical and carbon dioxide.[7] The electroanalytical data have been interpreted in favor of a mechanism where adsorbed radicals couple.[6,61] On the other hand, the stereochemistry of the products and the regioselectivity of the coupling reaction indicates that adsorption of alkyl radicals plays a minor role. This is indicated by the dimers of cyanoalkyl radicals (**1**),[7] which can combine at carbon and/or nitrogen. Here the same ratios of carbon to carbon and carbon to nitrogen coupling products are obtained, irrespective of whether (**1**) is generated by photolytic or thermal decomposition of the corresponding azonitrile, by persulfate oxidation or electrolysis of α-cyanoacetic acid in different solvents. However, when azonitrile is adsorbed on silica the decomposition yields only the carbon to carbon coupling product. The radical (**4**; Scheme 3) can add to butadiene to yield 1,1-, 1,3- and 3,3-additive dimers. The reaction gives a further indication that adsorption is not involved. The same product ratio is found, independent of the formation of (**4**) either by anodic or persulfate oxidation of methyl malonate (**2**) or reductive cleavage of the hydroperoxide (**3**).[62]



Scheme 3

Carboxylic acids, that bear an asymmetric center at C-2, lose all their optical activity in the Kolbe electrolysis.[63,64] This racemization can be interpreted as the result of a free radical or a fast equilibrium during desorption and adsorption at the electrode. A more detailed picture has been obtained by looking at the diastereoselectivity of the coupling of the cyclohexane- and cyclohexene-carboxylic acids (**5**)–(**9**).[65,66] The saturated acids (**5**) and (**6**) couple randomly, which indicated that the intermediate radicals in these cases are not significantly adsorbed. With the unsaturated acids (**7**)–(**9**) the ratio of dimers was not totally statistical, reflecting somewhat the different stabilities of the products. This result can be interpreted to be due to a more product-like transition state that indicates some adsorption of the unsaturated radical.

The intermediate radical can be further oxidized to form a carbenium ion, that undergoes solvolysis, rearrangement and elimination. This conversion is strongly influenced by the structure of the carboxylic acid, the electrolyte, the presence of foreign anions and the anode material (see Section 2.8.2). Besides



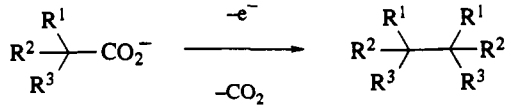
(5) (6) (7)

(8) (9)

the dimerization or addition to double bonds (Sections 2.8.4–2.8.6) disproportionation products of the radicals are also found. The ratio of disproportionation to coupling seems to be higher in the electrolysis than in the homogeneous reaction.[67]

2.8.4 SYMMETRICAL COUPLING REACTIONS OF CARBOXYLIC ACIDS

The alkyl groups of two identical carboxylic acids can be coupled to symmetrical dimers in the presence of a fair number of functional groups (equation 1). Since free radicals are the reactive intermediates, polar substituents need not be protected. This saves the steps for protection and deprotection that are necessary in such cases when electrophilic or nucleophilic C—C bond-forming reactions are involved. Furthermore, carboxylic acids are available in a wide variety from natural or petrochemical sources, or can be readily prepared from a large variety of precursors. Compared to chemical methods for the construction of symmetrical compounds, such as nucleophilic substitution or addition, decomposition of azo compounds or of diacyl peroxides, these advantages make the Kolbe electrolysis the method of choice for the synthesis of symmetrical target molecules. No other chemical method is available that allows the decarboxylative dimerization of carboxylic acids.



(1)

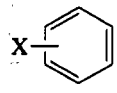
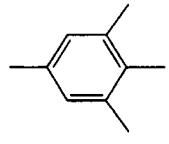
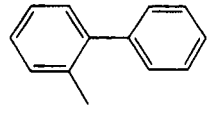
R^1, R^2, R^3 = H, alkyl, arylalkyl

R^1, R^2 = H; R^3 = CO_2Me, $(CH_2)_nX$ (X = COR, CO_2R, $n \geq 1$; X = OAc, NHAc, Hal, $n \geq 4$)

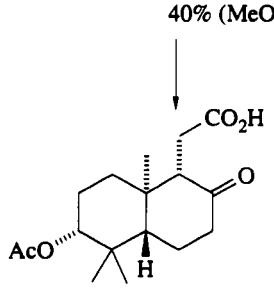
A large number of different Kolbe dimerizations has been compiled.[8,10,19,20] Without attempting a complete coverage of the published reactions, the scope and limitations of the Kolbe electrolysis to afford symmetrical compounds are indicated in Table 2. In general, only the substituents at C-2 are critical for the yield of dimer. Electron-attracting groups (cyano, alkoxycarbonyl, carbonyl substituents) or hydrogen favor the radical coupling. Electron-donating substituents (two or three alkyl groups at C-2, phenyl, vinyl, halo, hydroxy or amino groups) on the other hand, more or less shift the reaction towards nonKolbe products. The experimental conditions that favor the radical coupling, namely high current density, slightly acidic electrolyte, platinum as anode material and no anions other than the carboxylate, have been treated in Section 2.8.2. The dimerization of two identical carboxylic acids has been used for the efficient synthesis of symmetrical natural products. Thus, the Kolbe electrolysis of (**10**) is the key step in a (+)-α-onocerin synthesis,[89] and by dimerization of (**11**) a pentacyclosqualene has been prepared.[90] An alkane with two quaternary carbon atoms has been obtained from (**12**),[91] and 2,6,10,15,19,23-hexamethyltetracontane was accessible from (**13**).[92]

For the preparation of long chain alkanes from fatty acids it is useful to extract the electrolyte continously with a high-boiling nonpolar solvent,[93] *e.g.* 2-methylheptane. Cyclopropanecarboxylic acids in some cases have been dimerized, *e.g.* (**14**)[94] or (**15**);[34] in other cases the radical is further oxidized to a carbocation which then undergoes ring opening and solvolysis to allylic compounds. Specifically substituted 1,2-diphenylethanes have been prepared from phenylacetic acids (Table 2, entries 22 and 23). A variety of 2,3-disubstituted succinic acids and their derivatives have become accessible from malonic

Table 2 Symmetrical Coupling Reactions of Selected Carboxylic Acids

Entry	*Substituents in $R^1R^2R^3CCO_2^-$* R^1	R^2	R^3	*Yield[a] of coupling product (%)*	*Ref.*
1	H	H	H	93	5, 8
2	Alkyl (C_1–C_{17})	H	H	30–90	5, 8
3	Alkyl	Alkyl	H	0–26	8
4	$RO_2C(CH_2)n$ n = 3–15, R = Me, Et	H	H	40–95	5
5	Alkyl	EtO_2C	H	20–85	68, 69
6	Alkyl	Alkyl	EtO_2C	15–35	68, 70
7	Alkyl	CN	H, Alkyl	30–60	71
8	Alkyl	$CONH_2$	H, Alkyl	5–55	72
9	AlkylCO	Alkyl, H	Alkyl, H	32–40	73
10	$MeCO(CH_2)n$	H	H		
	n = 1			70	74
	n = 5			63	75
11	F, Br, Cl, I, OH, NH_2	H	H	0	5, 8, 76
12a	F	F	F	93	56b, 77
12b	F	F	Cl	43	78
13	$X(CH_2)n$	H	H		
	X = F, n > 3			45–70	79
	X = Cl, n = 1, 3, 4, 5, 7, 8, 9, 11			40–80	79, 80, 81
	X = Br, n = 4–11, 14			54–71	30a, 79
14	$RO_2C(CF_2)n$ n = 0–3, R = Me, Et	F	F	High yield	82
15	$H(CF_2)n$ n = 3, 5	F	F	40–86	83
16	$CF_3(C_2F_5)_2C$	H	H	75	84
17	$MeCO_2(CH_2)n$ n = 2–5	H	H	70–83	25b
18	$MeCONH(CH_2)_4$	H	H	24–39	25b, 85
19	Phthaloyl-$NCH(CO_2H)CH_2$	H	H	32	86
20		H	H		
	X = *p*-OMe to X = F_5			<1–74	24
21	Ph	Ph	H	25	87
22		H	H	45	87
23		H	H	39	88

[a]Electrolyses are normally performed at a platinum anode in water, methanol, ethanol or ethanol/water.



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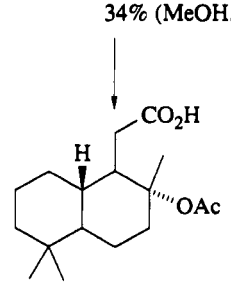

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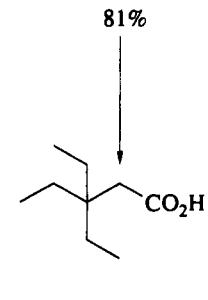

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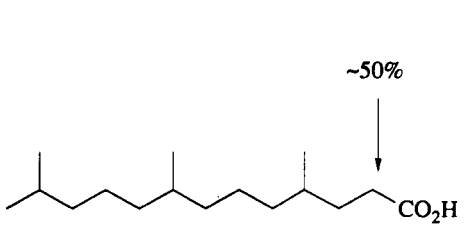

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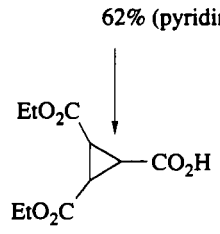

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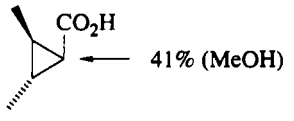

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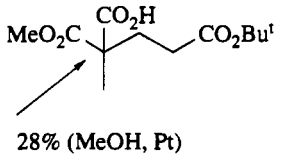

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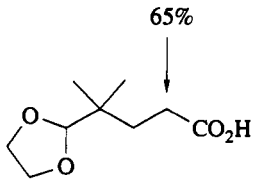

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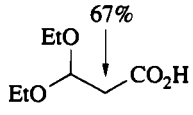


(18)

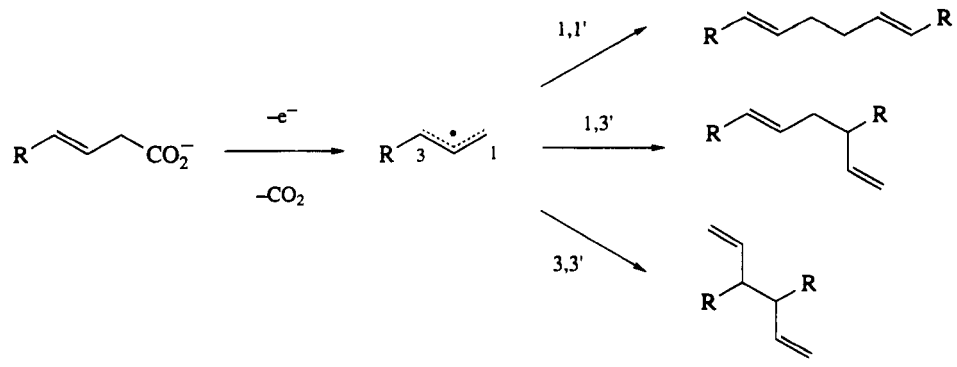
half esters, nitriles or amides (Table 2, entries 5–8). The anodic coupling of (**16**) has been used as part of a semibullvalene synthesis.[95]

The dimerization of half esters to 1,*n*-diesters is also called Brown–Walker electrolysis. Thereby valuable intermediates for the synthesis of medium-sized rings or 1,*n*-difunctionalized compounds can be prepared (Table 2, entry 4). This reaction is also of industrial interest since in this way sebacic acid can be prepared from adipic acid half ester.[96] This process has been scaled-up in Germany,[97] the USSR[98] and Japan,[99] and yields as high as 93% have been reported.[100] Reaction conditions and yields for the coupling of other half esters have also been studied in detail.[98] 1,*n*-Polyethylene- or polydifluoromethylene-dicarboxylic acids are reported to be formed by electrolysis of azelaic acid[101] or perfluoroglutaric acid.[102] Ketocarboxylic acids can be coupled to 1,4-, 1,6- or 1,14-diketones (Table 2, entries 9 and 10). Aldehydes must be dimerized in the form of their acetals to obtain good yields, as has been shown for (**17**)[103] and (**18**).[104] The arrow on (**10**)–(**18**) indicates the location of dimerization, along with the yield and reaction conditions.

Carboxylic acids that carry a halide, hydroxy or amino group at C-2 generally cannot be dimerized (Table 2, entry 11). In the case of trifluoroacetic acid, however, high yields of hexafluoroethane are reported (Table 2, entry 12). When the halide substituent is more distant from the carboxyl group the dimer yields are in general good (Table 2, entry 13). The coupling of fluorocarboxylic acids has been investigated intensively (Table 2, entries 14–16) because of the interesting properties of the fluorohydrocarbons produced.

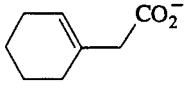
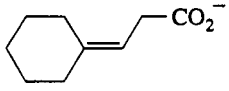
Hydroxy- and amino acids can be dimerized in good to moderate yields, provided the substituents are not at C-2 or C-3 and are additionally protected against oxidation by acylation (Table 2, entries 17–19). 2-Alkenoic acids cannot be dimerized, but lead to a severe passivation of the anode due to the formation of polymer films.[105] 3- and 4-alkenoic acids can be dimerized in moderate yields, when they are neutralized with tributyl- or triethyl-amine.[105] 3-Alkenoic acids, obtained from Stobbe condensations, can be dimerized in 14–30% yield; major side products arise from further oxidation of the allyl radical to its cation and subsequent solvolysis.[106] The 3-alkenoic acids dimerize to three isomeric 1,5-dienes (Scheme 4), that arise by 1,1′-, 1,3′- and 3,3′-coupling of the intermediate allyl radical.[107] By steric shielding of the 3-position the proportion of 3-coupling decreases. Depending on the bulkiness of the 3-substituent, the relative yield of the 1,1′-dimer can vary from 52 to 73% (Table 3). The configuration of the double bond is retained to a high degree.[107a]

In the case of 6-alkenoic acids the intermediate 5-hexenyl radical cyclizes to a cyclopentylmethyl radical in a 5-*exo-trig* cyclization (Scheme 5; see also Section 2.8.6)[107a,108,109] In some cases double bond migration has been observed. This can be avoided, however, when the electrolyte is prevented from becoming basic by using a mercury cathode. (*Z*)-4-Enoic acids isomerize partially to the corresponding (*E*)-isomers. The products from methyl- and deuterium-labeled carboxylic acids indicate that this isomerization occurs *via* a reversible ring closure to cyclopropylcarbinyl radicals. (*Z*)-Enoic acids where the double bond is more distant from the carboxylic acid group retain totally their configuration.[109] A key step in a perhydrophenanthrene synthesis involves the dimerization of (**19**) by Kolbe electrolysis.[110]

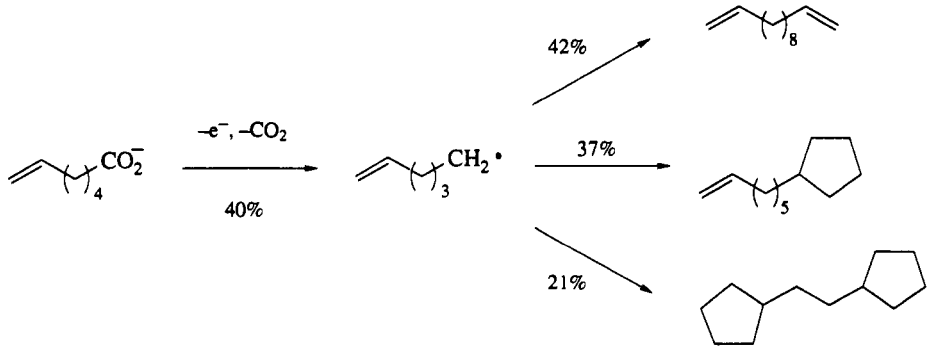


Scheme 4

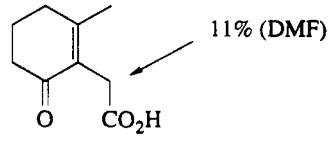
Table 3 Yields in the Kolbe Dimerization of 3-Alkenoic Acids[107b]

Carboxylic acid[a]	*Product distribution (%)* *1,1'*	*1,3'*	*3,3'*	*Yield (%)*
$Me(CH_2)_7CH{=}CHCH_2CO_2^-$	52	39	9	67
$Me_2CHCH{=}CHCH_2CO_2^-$	59	41	—	79
$Me_3CCH{=}CHCH_2CO_2^-$	60	40	—	15
	60	40	—	45
$Me_2CH{=}CHCH_2CO_2^-$	65	—	36	42
	76	24	—	29

[a]10–150 mmol were dissolved in 25–100 mL methanol, neutralized to 8–50% with triethylamine and electrolyzed in an undivided cell at platinum electrodes at 400–800 mA cm^{-2} with change of polarity of the electrodes until pH = 8 was reached.

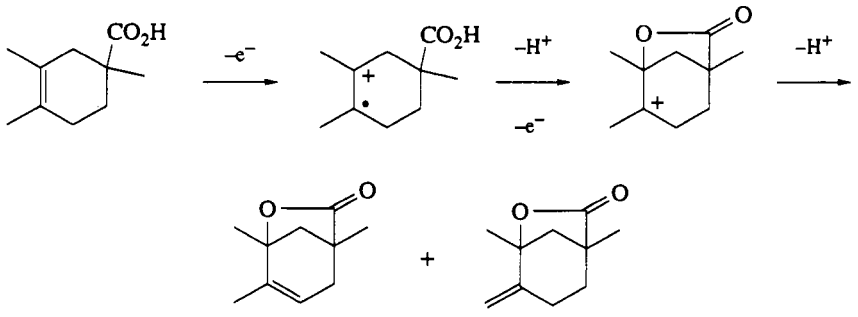


Scheme 5



(19)

In unsaturated carboxylic acids, where the oxidation of the double bond is facilitated by alkyl substitution, the double bond rather than the carboxylic group is oxidized, and a lactone is formed (Scheme 6).[111]



Scheme 6

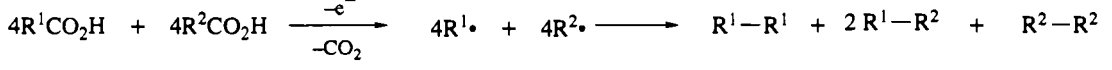
Other alkenoic acids that have been coupled without change of the double bond configuration are oleic acid (24% yield of dimer), elaidic acid (44%)[112] and erucic acid.[113]

2.8.4.1 Experimental Procedure for Symmetrical Kolbe Electrolysis — Preparation of Dimethyl Hexadecanedioate

A solution of 55 g (0.27 mol) of methyl azelate in 350 mL methanol, neutralized to the extent of 6% with KOH in methanol, is electrolyzed in a flow-through cell (Figure 1) at 35–40 °C at a cell voltage of 40 V between a platinum anode (area = 17 cm^2) and a steel cathode at a current density of 200 mA cm^{-2} until 1.2 F m^{-1} were consumed. The methanol is then evaporated, and the residue is dissolved in 500 mL ether and extracted with a saturated aqueous $NaHCO_3$ solution (3 × 100 mL) and subsequently washed with water. After drying ($MgSO_4$) and removal of the ether, fractionated distillation affords at b.p. 107–113 °C/0.02 Torr, 34.14 g (80%) dimethyl hexadecanedioate.[113] For the preparation of dimethyl decanedioate from methyl adipate see ref. 114.

2.8.5 CROSS-COUPLING REACTIONS OF DIFFERENT CARBOXYLIC ACIDS

Cross-coupling reactions of two carboxylates with different alkyl groups by anodic decarboxylation (mixed Kolbe electrolysis) is an electrochemical method that allows the synthesis of unsymmetrical compounds (Scheme 7).



Scheme 7

A disadvantage of this reaction is the statistical coupling of the intermediate radicals. This results in the additional formation of two symmetrical dimers as major side products. However, by taking the less costly acid in excess the number of products is lowered to two, the unsymmetrical product and one symmetrical dimer. When the chain length of the two acids is properly chosen, the two products can usually be separated by distillation. Furthermore, the more costly acid is incorporated to a major extent into the mixed dimer. The calculated yields for mixed couplings are listed in Table 4, and the experimental results for the coupling of methyl azelate with pentanoate are shown in Table 5.[113]

When one of the two acids is used in excess and the acidity of the two acids differs strongly, the salt-deficit method should be used with caution, as one of the acids might be preferentially converted into the carboxylate. In such a case it is useful to neutralize both acids completely.

For the selective preparation of unsymmetrical coupling products on a small scale, the photolysis of peroxides is a favorable alternative to the mixed Kolbe electrolysis. By photolysis of unsymmetrical diacyl peroxides at –60 to –70 °C in the solid state two different alkyl groups can be joined selectively.[115]

Table 4 Calculated Theoretical Yields for Mixed Coupling Reactions Products R^1—R^2

Ratio R^1CO_2H	R^2CO_2H	*Yield of* R^1—R^2 (%)[a]
1	1	50
1	2	66
1	4	80
1	6	86
1	8	89

[a]Calculated according to Yield (%) = $100n/(1 + n)$ with $1{:}n$ as ratio of $R^1CO_2H{:}R^2CO_2H$.

Table 5 Yield of Methyl Dodecanoate in the Cross-coupling Reactions of Methyl Azelate and Valerate[113]

Ratio $HO_2C(CH_2)_7CO_2Me$	$Me(CH_2)_3CO_2H$	*Yield of* $MeO_2C(CH_2)_{10}Me$ *in MeOH* (%)
1	2	56
1	4	72
1	8	83

Problems with passivation, that is, the coverage of the anode with insulating films which increase the cell voltage, or with the competitive oxidation to carbenium ions, are often less pronounced in crossed coupling.[113,116]

The mixed Kolbe electrolysis has turned out to be a widely used synthetic method, despite its disadvantage that at least one symmetrical dimer is formed as major side product, which has to be separated and which consumes a greater part of the coacid. Crossed Kolbe electrolyses have been used for the efficient synthesis of rare fatty acids and related compounds, of pheromones and of chiral building blocks. Weedon *et al.* during the 1950s and 1960s did much of the pioneering work in these type of syntheses.[5] Selected examples from the numerous reactions that have been published are compiled in Tables 6 and 7 and in the formulae (**20**)–(**39**). In some of the formulae the end-product of several transformations is shown; the bond formed in the mixed Kolbe electrolysis is marked by an arrow and the yield is indicated. Further examples of crossed couplings can be found in refs. 8 and 12.

Table 6 Cross-coupling Reactions by Kolbe Electrolysis of Unsubstituted (A) with Substituted Carboxylic Acids (B)

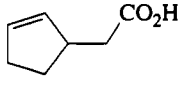
Carboxylic acids A—CO_2H	B—CO_2H	*Yield of cross-coupling product (A—B) (%)*	*Ref.*
$Me(CH_2)_6CO_2H$	$MeO_2C(CH_2)_4C{\equiv}C(CH_2)_4CO_2H$	23	117
$Me(CH_2)_{14}CO_2H$	Me_2CHCO_2H	40	118
$Me(CH_2)_5CO_2H$	(*E*)-$Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	37	118
CD_3CO_2H	CF_3CO_2H	68	119
CD_3CO_2H	$CF_3CF_2CO_2H$	75	119
$MeCO_2H$	$HC{\equiv}C(CH_2)_8CO_2H$	36	120
$MeCH_2CO_2H$	$Ph(CH_2)_2CO_2H$	44	121
$Me(CH_2)_3CO_2H$	$MeO_2C(CH_2)_7CO_2H$	69	113
$Me(CH_2)_5CO_2H$	$MeO_2C(CH_2)_7CO_2H$	61	113
$Me(CH_2)_2CO_2H$	$MeO_2CCH(OCOMe)CO_2H$	29	122
$Me(CH_2)_2CO_2H$	$MeCO(CH_2)_4CO_2H$	62	123
Methylhexadecanoic acid	$MeO_2C(CH_2)_4CO_2H$	42	124
$Me(CH_2)_8CO_2H$	$MeO_2C(CH_2)_4CO_2H$	38	125
$Me(CH_2)_2CO_2H$	$MeO_2CCH_2CHMeCH_2CO_2H$	30	126
	$MeO_2C(CH_2)_{11}CO_2H$	30	127
$Bu^t(CH_2)_2CHMeCH_2CO_2H$	$MeO_2CCH_2CHEtCH_2CO_2H$	15	128
$Me(CH_2)_{10}CO_2H$	$MeO_2CCH(OMe)CH_2CO_2H$	21	129
$Me(CH_2)_7CHMeCH_2CO_2H$	$MeO_2C(CH_2)_7CO_2H$	30	130
$Me(CH_2)_mCO_2H$	$MeO_2C(CH_2)_nCO_2H$		
$m = 8$–16, 18	$n = 4, 7, 8, 12$–20	—	131
$Me_2CHCH_2CO_2H$	$Et_2C(CO_2Et)CO_2H$	38	132

Table 7 Cross-coupling Reactions by Kolbe Electrolysis of Substituted Carboxylic Acids (A) with Substituted Carboxylic Acids (B)

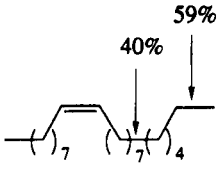
Carboxylic acids A—CO_2H	B—CO_2H	*Yield of cross-coupling product (A—B) (%)*	*Ref.*
$CH_2{=}CH(CH_2)_2CO_2H$	$MeO_2C(CH_2)_{10}CO_2H$	68	133
$Me_2CHCH{=}CHCH_2CO_2H$	$MeO_2C(CH_2)_nCO_2H$ $n = 1, 2, 4$	Good	134a
(Z)-$MeO_2C(CH_2)_2CH{=}CH(CH_2)_2CO_2H$	$Me(CH_2)_2CO_2H$	30	134b
$CH_2{=}CH(CH_2)_8CO_2H$	$MeO_2C(CH_2)_2CO_2H$	52	134c
$RC{\equiv}C(CH_2)_3CO_2H$ R = Et, Pr, Bu	$MeO_2C(CH_2)_nCO_2H$ $n = 2, 3, 4, 6$	45–59	135
(Z)-$Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	$MeO_2C(CH_2)_2CO_2H$	15–20	136
$CF_3CF_2OCF_2CO_2H$	$MeO_2C(CF_2)_nCO_2H$ $n = 1–3$	24–34	137
$CF_3OCF_2CF_2CO_2H$	$MeO_2C(CF_2)_nCO_2H$ $n = 1–3$	24–34	137
CF_3CO_2H	$MeO_2CCH_2CO_2H$	46	138
$Br(CH_2)_{10}CO_2H$	$MeO_2C(CH_2)_7CO_2H$	50	113
$Br(CH_2)_{10}CO_2H$	$EtO_2C(CH_2)_8CO_2H$	54	139
$Br(CH_2)_{10}CO_2H$	$MeO_2C(CH_2)_4CO_2H$	37	30b
$AcO(CH_2)_4CO_2H$	$EtO_2C(CH_2)_{10}CO_2H$	27–32	140, 141
$Me_3SiCH_2CO_2H$	$MeO_2C(CH_2)_nCO_2H$ $n = 4, 7$	71–76	142
$MeO_2C(CH_2)_{11}CO_2H$	$MeO_2C(CH_2)_4CO_2H$	—	143
$MeO_2C(CH_2)_{10}CO_2H$	$MeO_2C(CH_2)_4CO_2H$	—	144
$MeO_2C(CF_2)_nCO_2H$ $n = m = 1–4$	$MeO_2C(CF_2)_mCO_2H$	25–38	82
$MeCO(CH_2)_2CO_2H$	$MeCO(CH_2)_4CO_2H$	31	145
$MeCO(CH_2)_8CO_2H$	$MeO_2C(CH_2)_4CO_2H$	32	146

Tables 6 and 7 contain the syntheses of esters of trialkylacetic acids, specifically deuterated carboxylic acids, of branched acids, of enoic and ynoic acids, of ω-halo-, acetoxy- or trimethylsilyl-carboxylic acids, of perfluorinated 1,*n*-diacids, of keto esters and of diketones.

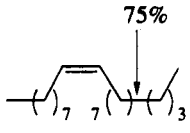
Crossed coupling has also been applied to the extension of the carbon chain in fatty acids. Extension by two carbon atoms is achieved with succinate half esters,[120,147–149] whereby separation problems can be simplified by using the benzyl half ester.[148a] Expansion by the propane unit has been accomplished with methyl glutarate,[150] by the isoprene unit with ethyl 3-methyladipate,[151] by four carbons with methyl adipate,[112] by the pentane unit with methyl pimelate,[152] and by six carbon atoms with methyl suberate.[153]

A variety of pheromones have been prepared in few steps using the crossed coupling reaction. Muscalure (**20**), the pheromone of the housefly, becomes available from the natural pool of unsaturated fatty acids, namely oleic or erucic acid.[154–156] The synergist of muscalure, (*Z*)-11-heneicosene (**21**), was similarly prepared.[155] Methyl (*Z*)-4-octenedioate, which is accessible from (*Z,Z*)-1,5-cyclooctadiene by partial ozonolysis, is a valuable starting acid to prepare (**22**),[134b] a precursor of the cabbage looper pheromone, or disparlure (**23**),[157] the sex attractant of the gypsy moth. The optically active *Trogoderma* pheromones (*E*)- and (*Z*)-(**24**) have been synthesized using 4-pentynoic acid and (*S*)-citronellic acid as precursor from the chiral pool.[158] Alkatrienes (**25**), which are sex attractants of certain *Lepidoptera*, become accessible in a one step synthesis using linolenic acid from the pool of polyunsaturated fatty acids.[159] Compound (**26**), the pheromone of the German cockroach *Blattela germanica*, was obtained from 3-methyl heneicosanoic acid.[160] The bromide (**29**), which is an important intermediate for the synthesis of natural α-tocopherol has been synthesized starting from (*R*)-(+)-citronellic acid.[161] The coelectrolysis of (*Z*)-4-nonenoic acid with methyl glutarate provided an alternative approach to looplure (**31**),[162] the pheromone of the Cabbage looper. Similarly the pheromone of the fruit pest insect *Dacus cucurbitae* (**32**)[163] and of the false codling moth (**33**)[164] became accessible by crossed coupling. Brevicomin (**34**), the sex attractant of the western pine beetle, became available in a short route by mixed Kolbe electrolysis of (*E*)-3-hexenoic acid with levulinic acid.[165] Besides (**23**), a number of other compounds have been prepared by successive cross couplings. (±)-Tuberculostearic acid (**27**) has been obtained in two consecutive Kolbe electrolyses from 2-methylsuccinate.[166] 10,16-Dimethylicosanoic acid (**28**) was synthesized in three subsequent Kolbe electrolyses.[147] The alkane (**30**) with three quaternary carbon atoms was prepared in two successive crossed couplings.[91] Pure (*E*)- or (*Z*)-configurated unsaturated pheromones are accessible by mixed coupling with 5-alkynoic acids and subsequent selective hydrogenation (Table 7).[135] The mixed Kolbe electrolysis of protected L- or D-glutamic acids provides access to dicarba analogs of cystine peptides (**35**).[167] Enantiomerically pure β-hydroxybutyric

acid derivatives have been converted into the useful chiral building blocks (**36**)–(**38**).[168] Chiral γ-lactones (**39**) could be obtained from (*R*)-3-cyclohexene-1-carboxylic acid.[169]



(**20**)



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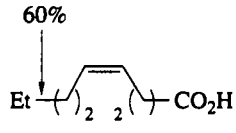

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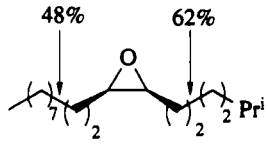

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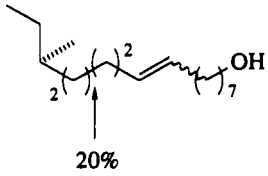
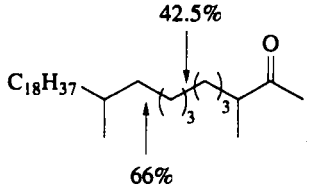


(**24**)

(**25**) R = Et, Pr^n, Bu^n



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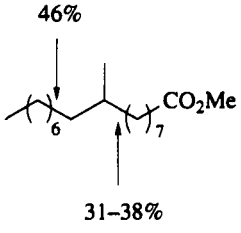
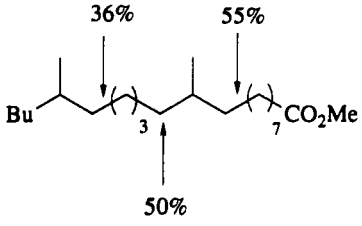
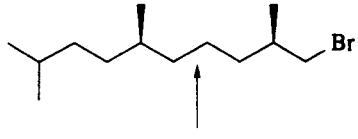


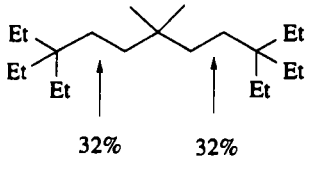
(**27**)



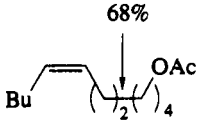
(**28**)



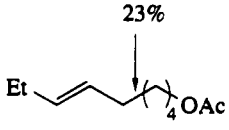
(**29**)



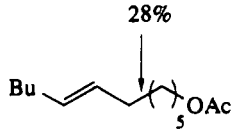
(**30**)



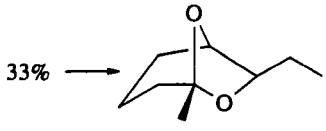
(**31**)



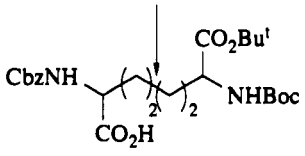
(**32**)



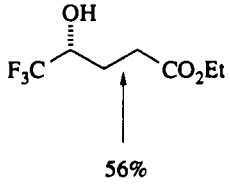
(**33**)



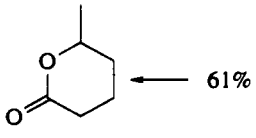
(**34**)



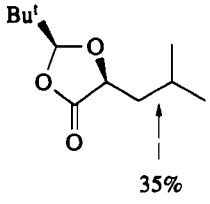
(**35**)



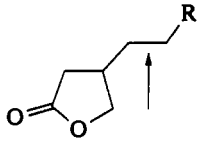
(**36**)



(**37**)



(**38**)



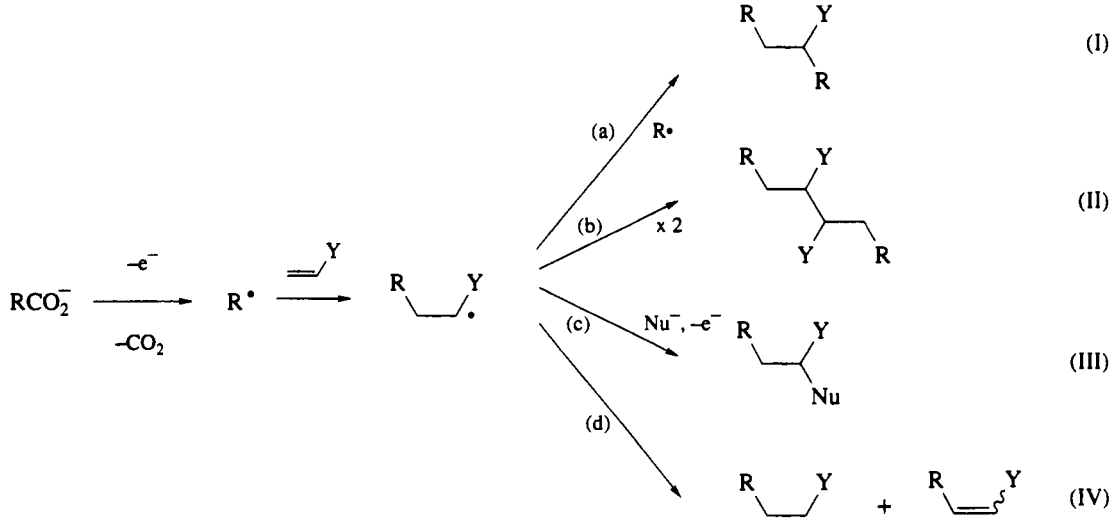
(**39**) R = Me, high yield; R = C_8H_{17}, 21%

2.8.5.1 Experimental Procedure for Mixed Kolbe Electrolysis — Preparation of 11-Hexadecynoic Acid

In a beaker-type cell (Figure 2) equipped with two platinum electrodes (area 10 cm^2, thickness 0.05 mm, supported on a teflon frame), a solution of 14.3 mmol 5-decynoic acid and 86 mmol methyl suberate in 40 mL methanol, neutralized to 5% with KOH, was electrolyzed at 22 °C and a current density of 100 mA cm^{-2}, provided from a regulated d.c. power supply, until a pH of 8–9 was reached. After evaporation of the methanol the crude product was refluxed with equimolar amounts of KOH in 100–200 mL methanol for 24 h; thereafter the mixture was evaporated to dryness and extracted with petroleum ether. The remaining salt was dissolved in water, acidified with 15% HCl, and continuously extracted with petroleum ether. The precipitated tetradecanoic dicarboxylic acid (72%, m.p. 126 °C) was filtered off, and after evaporation of the petroleum ether 8.43 mmol (59%) 11-hexadecynoic acid was isolated by bulb to bulb distillation; m.p. (from pentane) 40–41 °C.[135]

2.8.6 ADDITION OF KOLBE RADICALS TO DOUBLE BONDS

The radicals generated by anodic decarboxylation of carboxylic acids can be intercepted by alkenes that are present in the electrolyte. The adduct radical can couple with the radical generated from the carboxylate to form an additive monomer I (Scheme 8 path a), it can dimerize to form an additive dimer II (path b), it can be further oxidized to a cation, which reacts with a nucleophile to form III (path c), or it can disproportionate (path d).



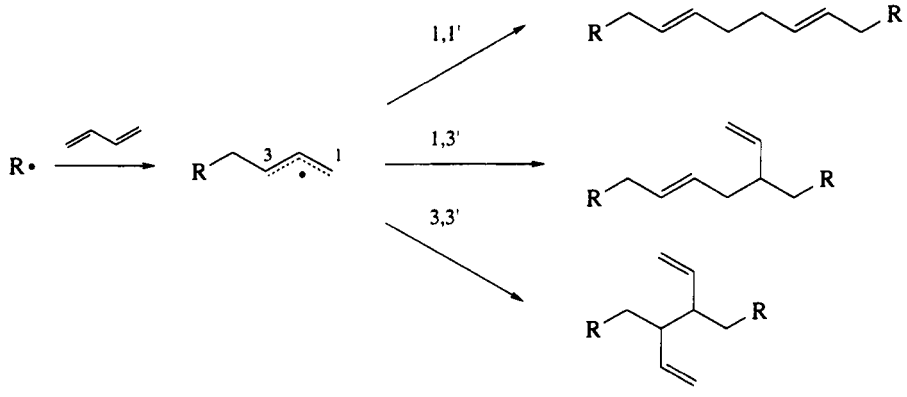
Scheme 8

As the reactive intermediates in electrolyses are confined to narrow reaction layers in front of the electrode, the radical concentration is much higher there than in homogeneous radical reactions. Therefore the propagation step of a polymerization is suppressed and the termination step leading to products I and II predominates. The products I and II appear to be exclusive products of electrolysis.

The high radical concentration at the anode, on the other hand, favors the dimerization of the radical generated from the carboxylate, which leads in the case of less reactive alkenes, like cyclohexene or 2-methylpropene (Table 8, entry 11), to low yields of adducts and the predominant formation of Kolbe dimers. With reactive alkenes (butadiene, isoprene, styrene) the yields of adducts are in general good (Table 8, entries 1–10). However, in the case of unreactive ethylene high adduct yields have also been claimed (Table 8, entry 12). Higher yields are found in the reaction of nucleophilic radicals with electrophilic alkenes (Table 8, entries 17–22) or *vice versa* (Table 8, entries 23–27). The ratio of additive monomer I Scheme 8 to additive dimer II can be controlled to some extent by the current density. High current densities aid the formation of I, low ones that of II (Table 8, entries 4 and 5). These results can be interpreted according to Scheme 8. When high current densities prevail, which correspond to high radical concentrations in the reaction layer, the alkene can trap only some of the radicals generated from the carboxylate (Kolbe radicals). This leads to their preferred combination with the primary adduct leading

to I and their dimerization to the Kolbe dimer. At low current densities, on the other hand, the major proportion of the Kolbe radicals are trapped by the alkene, which leads to a preferential formation of II.

In the addition of Kolbe radicals to 1,3-dienes allyl radicals are intermediates, that can then couple to form 1,1'-, 1,3'- and 3,3'-dimers (Scheme 9). In general, the reactivity of the allyl radical is two to three times higher at C-1 than at C-3, so that the 1,1'-dimer predominates.[170] Besides the examples given in Table 8, further additions of Kolbe radicals to dienes can be found in refs. 33, 179 and 191.

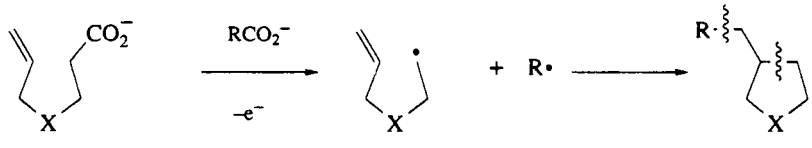


Scheme 9

The addition of the 5-pentanoate radical from methyl adipate to butadiene has been intensively investigated, because in this way long chain 1,*n*-diacids are easily accessible; a total yield of 96% has been claimed for this reaction (Table 8, entry 7). Different Kolbe radicals from acetic acid, monochloroacetic acid, trichloroacetic acid, oxalic acid, methyl adipate and methyl glutarate have been added to ethylene, propylene, fluoroalkenes and dimethyl maleate.[177] In this detailed study the influence of current density, alkene type and alkene concentration on the product yields and product ratios have been discussed.

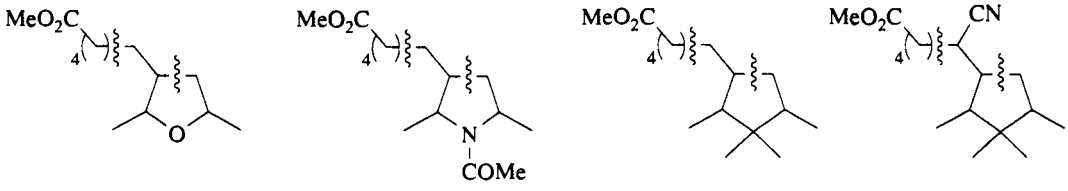
In some cases reactive alkenes can be polymerized with Kolbe radicals as initiators, *e.g.* styrene,[176] acrylonitrile,[176] vinyl acetate,[192] methyl acrylate,[192] acrylic acid,[193] acrylamide[194] or vinyl chloride.[193] The addition of Kolbe radicals to pyridine,[195] benzotrifluoride or benzonitrile[196] affords only low yields.

The addition of alkyl radicals to less reactive alkenes becomes more efficient if the addition is conducted intramolecularly. The Kolbe electrolysis of $\Delta^{6,7}$- and $\Delta^{7,8}$-unsaturated carboxylates produces five- and six-membered rings in a 5- or 6-*exo-trig*-cyclization.[108] Such a cyclization was first observed by Weedon[107] and later studied in more detail.[109] By intramolecular addition of appropriate precursors, 3-substituted tetrahydrofurans (Scheme 10; **40**, 41%),[197] pyrrolidines (**41**, 53%),[198] and cyclopentanes (**42**, 74%), and (**43**, 75%)[199] are obtained. In the reactions leading to cyclopentanes the extent of cyclization



X = O, NCOR, CMe_2

Scheme 10



(40) **(41)** **(42)** **(43)**

Table 8 Addition of Kolbe Radicals to Alkenes

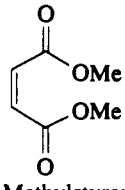
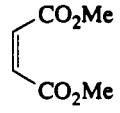
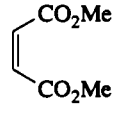
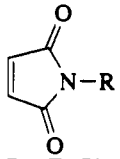
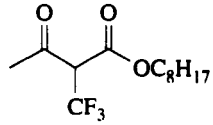
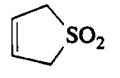
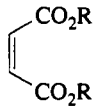
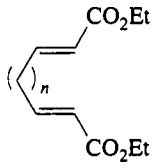
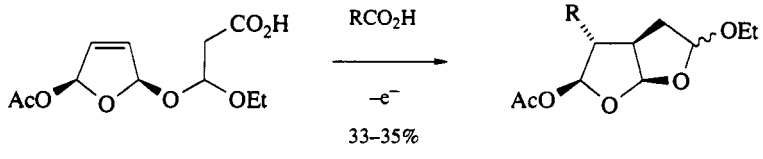
Entry	*Carboxylic acid*	*Alkene*	*Yield of additive monomer (%)*	*Yield of additive dimer (%)*	*Ref.*
1	$MeO_2CCH_2CO_2H$	Styrene	4	38[a]	170
2	$MeO_2CCH_2CO_2H$	Butadiene	17	18	170
3	$MeO_2CCH_2CO_2H$	Isoprene	1	43	170
4	EtO_2CCO_2H	Butadiene ($i = 0.025$ A cm^{-2})	4	66	170, 171
5	EtO_2CCO_2H	Butadiene ($i = 0.66$ A cm^{-2})	15	8	170
6	EtO_2CCO_2H	Isoprene	8	59	170
7	$MeO_2C(CH_2)_4CO_2H$	Butadiene	48	48	172, 173
8a	HO_2CCO_2H	Butadiene	—	20	174
8b	HO_2CCO_2H		62	34	175
9	$MeO_2CCH_2CO_2H$	α-Methylstyrene	—	46[b]	107b
10	$MeCO_2H$	Styrene		15	176
11	EtO_2CCO_2H	Isobutene	9		170
12	$MeCO_2H$	$CH_2{=}CH_2$	≈70		177
13	Cl_3CCO_2H	$CH_2{=}CH_2$	—	—	178
14	HO_2CCO_2H	$CH_2{=}CH_2$	25	46	177
15	$MeO_2C(CH_2)_4CO_2H$	$CH_2{=}CH_2$	15		177
16	$MeCO_2H$	$Bu^tCH{=}CH_2$	46	—	179
17	$MeCO_2H$	$CH_2{=}CMeCHO$	—	80	180
18	$MeCO_2H$	$CH_2{=}CHCO_2Et$	—	70	180
19	$MeCO_2H$		21–high	—	181, 182
20	$PhCH_2CO_2H$		24	—	183
21	$MeCO_2H$	 R = Et, Ph	80–88	—	182, 183
22	RCO_2H, R = Me, Et, Bu^i	$PhSO_2CH{=}CH_2$	37–69		184
23	CF_3CO_2H	$MeC(OAc){=}CHCO_2C_8H_{17}$	 64	185	
24	$MeO_2CCH_2CO_2H$	$CH_2{=}CHOEt$	—	35	186
25	CF_3CO_2H	1-Pentene	—	40	187
26	CF_3CO_2H	$CH_2{=}C(Me)OAc$	18[a]		188
27	CF_3CO_2H		31	—	189
28	CF_3CO_2H	$CH_2{=}CHCO_2Me$	5	50	187
29	CF_3CO_2H	$CH_2{=}CHCO_2H$	17	28	138
30	CF_3CO_2H	$CH_2{=}CHCF_3$		40	177
31	CF_3CO_2H	$CHF{=}CF_2$		30	177

Table 8 Addition of Kolbe Radicals to Alkenes (*continued*)

Entry	*Carboxylic acid*	*Alkene*	*Yield of additive monomer (%)*	*Yield of additive dimer (%)*	*Ref.*
32	CF_3CO_2H	 R = Me, Et	30	10	177
			41	27	189
33	CF_3CO_2H	 n = 0–3	4–42		190

[a]Additional 16% disproportionation product. [b]6% Product type IV, Scheme 8.

can be considerably increased by lowering the current density (300 mA cm^{-2}, ratio of cyclized:uncyclized product = 32:35; 10 mA cm^{-2} ratio = 74:8). The intramolecular cyclization has also been applied to the stereoselective synthesis of a prostaglandine precursor (equation 2).[200] The bonds formed in the Kolbe radical reactions are shown in (**40**)–(**43**).



(2)

R = Me, $(CH_2)_2CO_2Me$

Compared to chemical radical cyclizations,[201] the ring closures *via* Kolbe radicals have the advantage that here two carbon–carbon bonds can be joined in one step, whilst in the majority of chemical alternatives only one carbon–carbon bond is formed. Furthermore electrolysis avoids the toxic tributyltin hydride, that is usually needed as initiator or reagent in chemical radical cyclizations.

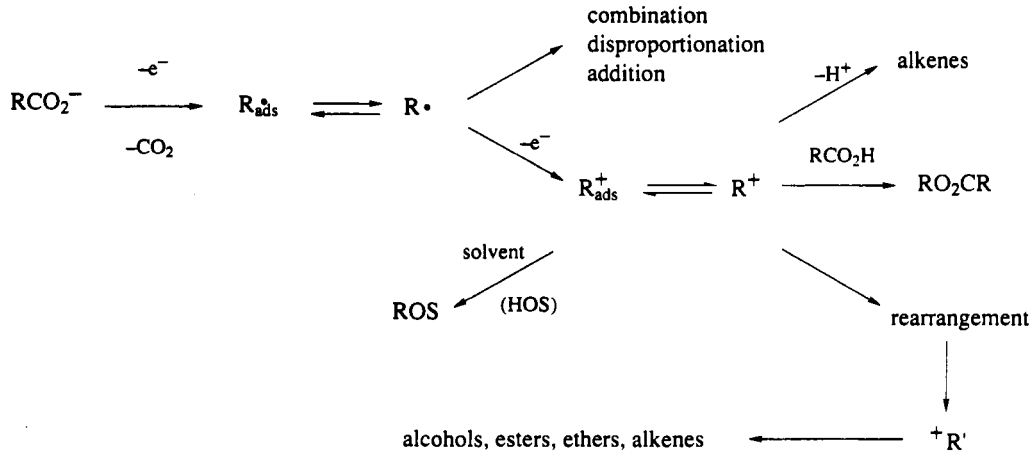
2.8.7 THE NONKOLBE ELECTROLYSIS

Besides the aforementioned Kolbe dimers, alcohols, esters or ethers can become the major products in the electrolysis of carboxylic acids. These results have suggested that in anodic decarboxylation the intermediate radicals were further oxidized to carbocations that yielded solvolysis and elimination products.[202] This part of the anodic decarboxylation, which leads to carbenium ions, is frequently called nonKolbe electrolysis. Applications of the nonKolbe electrolysis to synthesis and to mechanistic investigation of carbocations are summarized in refs. 8, 19, 20 and 23 .

The oxidation of carboxylates to radicals (Scheme 2) has to be extended by the additional steps, shown in Scheme 11. The radical is further oxidized to a carbocation, which can solvolyze to ethers, alcohols or esters, can lose a proton to form an alkene or can undergo rearrangement or solvolysis prior to those reactions.

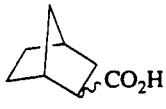
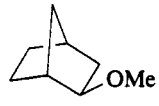
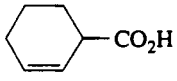
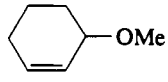
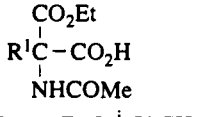
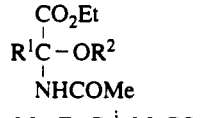
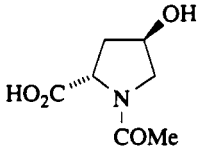
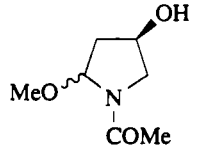
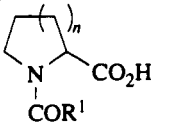
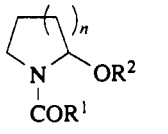
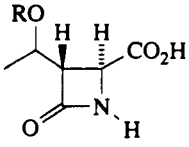
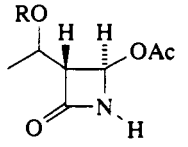
The formation of alcohols or ethers is favored by low current densities,[8,24] porous graphite as anode material,[203–205,206b] a solvent such as water/pyridine[206] instead of methanol, a pH of the electrolyte above 7 and anions, such as bicarbonate, sulfate or perchlorate, as additives.[24] Electron-donating substituents at C-2 of the carboxylic acid favor the oxidation of the intermediate radical. Thus α-alkyl, α-cycloalkyl[207,208] α-chloro,[209] α-bromo, α-amino, α-alkoxy, α-hydroxy, α-acyloxy and α,α-diphenyl substituents more or less promote the formation of nonKolbe products.

The nonKolbe electrolysis can lead to complex product mixtures, especially when there are equilibrating carbenium ions of about equal energy involved. On the other hand, the conversion of carboxylic acids to ethers, acetals, esters or alkenes can become very selective when the intermediate carbocation is



Scheme 11

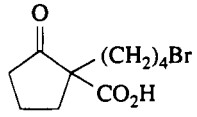
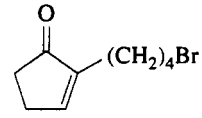
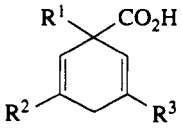
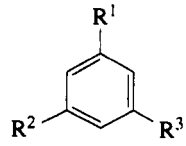
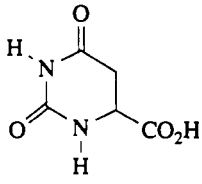
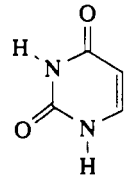
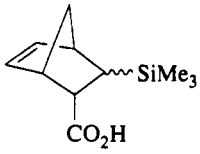
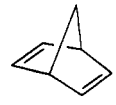
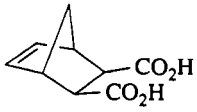
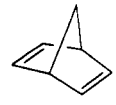
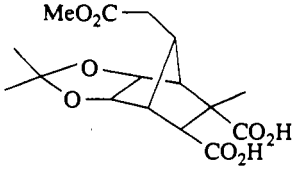
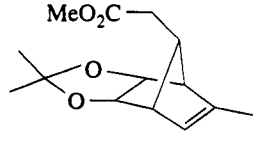
Table 9 Preparation of Ethers, Esters and Alcohols by NonKolbe Electrolysis of Carboxylates

Entry	*Carboxylate*	*Conditions*	*Product*	*Yield (%)*	*Ref.*
1	 *exo* or *endo*	MeOH, Pt		35–40	202c
2		MeOH		100	66
3	 R^1 = H, Me, Et, Pr^i, $PhCH_2$	R^2OH	 R^2 = Me, Et, Pr^i, MeCO	79–96	210c
4		MeOH, Pt		97	210b
5	$Me(CH_2)_nCH(SPh)CO_2H$ n = 2, 7	MeOH, $LiClO_4$, Pt	$Me(CH_2)_nCH(OMe)_2$	72–98	211
6	 n = 1, 2; R^1 = H, Me, Ph, OEt R^2 = Me, Et, H, Pr^i	R^2OH		75–98	212
7		AcOH, NaOAc, MeCN		84	213

stabilized, and either solvolysis or elimination can be favored. This is substantiated below with some selected examples. Suitably substituted carboxylates can be converted into ethers or acetals (Table 9).

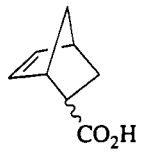
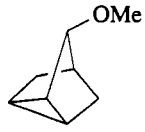
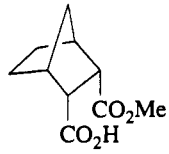
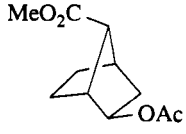
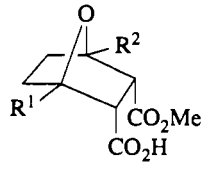
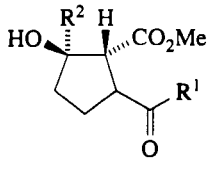
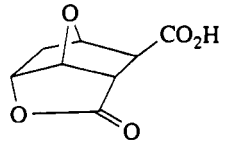
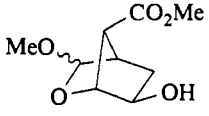
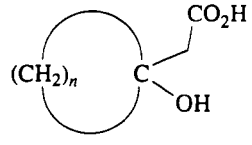
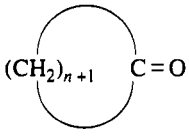
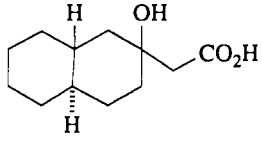
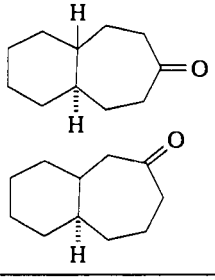
Both *exo*- and *endo*-norbornane-2-carboxylic acids are converted to the *exo*-2-methyl ethers, indicating that a bridged norbornyl cation is the intermediate (Table 9, entry 1). 2-Cyclohexene-1-carboxylic acid yields quantitatively 2-cyclohexen-1-yl methyl ether (Table 9, entry 2). Substituted *N*-acetylaminomalonic half esters are transformed in high yields into the corresponding aminoacetals (Table 9, entry 3). 4-Hydroxy-L-proline is converted into the corresponding 2-methoxypyrrolidine (Table 9, entry 4), which can be used to prepare optically active 2-substituted pyrrolidines.[210c] α-Phenylthio carboxylates are converted with loss of one carbon to dimethyl acetals (Table 9, entry 5). Cyclic acetals of β-ketocarboxylic acids react to form 2-methoxy-1,4-dioxacycloalkanes, that subsequently can be converted to 1,4-dioxenes. 4-Acetoxyazetidinone can be prepared by nonKolbe electrolysis of the corresponding carboxylic acid (Table 9, entry 7); it can serve as a valuable intermediate for the synthesis of β-lactams.

Table 10 Conversion of Carboxylic Acids into Alkenes

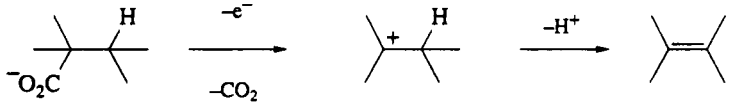
Entry	*Carboxylic acid*	*Reaction condition*	*Product*	*Yield (%)*	*Ref.*
1		H_2O, KOH		50	73b, 214
2	 $R^1 = Pr^i$; R^2 = Me, MeO; R^3 = H $R^1 = Me(CH_2)_4$; $R^2 = R^3$ = OMe	MeOH, NaOMe		60–70	215
3		C anode, NaOMe, MeOH		91	216
4		MeCN, EtOH, C anode		76	217
5		90% pyridine/H_2O		15	218
6		MeOH, NaOMe, Pt anode		50	219

Carboxylic acids can be transformed into alkenes when they contain a leaving group like H (Scheme 12), $SiMe_3$, SPh or CO_2H in the β-position. The alkene is formed by an *E*1-elimination from the intermediate carbocation. Some examples are summarized in Table 10. The decarboxylative elimination of 1,4-cyclohexadiene-6-carboxylic acids (Table 10, entry 2) is part of a useful method for the alkylation of aromatic compounds. This involves first a reductive alkylation using a Birch reduction, which is then fol-

Table 11 Rearrangements by NonKolbe Electrolysis

Entry	*Carboxylic acid*	*Reaction conditions*	*Product*	*Yield (%)*	*Ref.*
1	 *exo* or *endo*	MeOH, Et_3N		56	202c
2		AcOH, Bu^tOH, Et_3N		56	220
3	 $R^1 = R^2$ = Me, H	MeOH, NaOMe		87	221
4		MeOH, NaOMe		49–58	222
5		Pt anode, MeCN			
			$n = 4$	54–63	202c
			$n = 5$	54–63	202c
		C anode, pyridine/H_2O	$n = 9$	82	223
			$n = 11$	82	223
6		C anode, DMF		56	224

lowed by a nonKolbe electrolysis. 1,4-Cyclohexadienes are obtained from β-trimethylsilylcarboxylic acids (Table 10, entry 4); the latter are prepared by a Diels–Alder reaction of dienes with β-trimethylsilylacrylic acid or its derivatives. Vicinal dicarboxylates can be converted into alkenes by bisdecarboxylation (Table 10, entries 5 and 6). The reaction can be combined with a [4 + 2] or [2 + 2] cycloaddition, *e.g.* with maleic anhydride, whereby polycyclic hydrocarbons can be prepared in few steps.

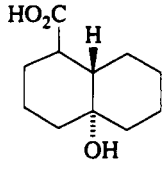
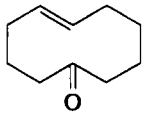
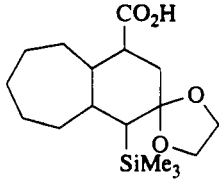
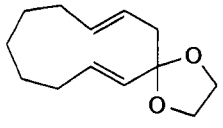
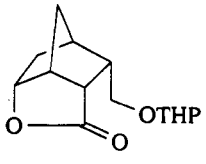
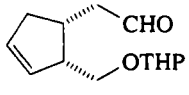
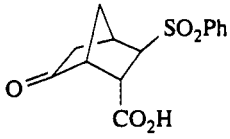
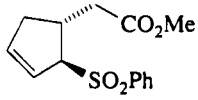


Scheme 12

The carbocations generated by nonKolbe electrolysis can rearrange by alkyl, phenyl or oxygen migration. Some examples are given in Table 11. The carbocations generated from *exo*- or *endo*-5-norbornene-2-carboxylic acid react by double bond participation and subsequent rearrangement to 3-methoxynortricyclene (Table 11, entry 1); the same compounds were also obtained by solvolysis.[225] The product in Table 11 (entry 2) has been used in a methyl (±)-jasmonate synthesis. Stereospecifically substituted cyclopentanes can be prepared by decarboxylation of oxabicycloheptanecarboxylic acids (Table 11, entries 3 and 4). A one-carbon ring extension of cyclic ketones is possible by first converting the ketones to β-hydroxycarboxylic acids by way of a Reformatzky reaction, and then subjecting these to a nonKolbe electrolysis (Table 11, entries 5 and 6).

The nonKolbe electrolysis of carboxylic acids can be used for a selective fragmentation, when the carbocation formed initially is stabilized in the γ-position by a hydroxy or trimethylsilyl group. This way the reaction can be used for a four-carbon ring extension (Table 12, entries 1 and 2). Furthermore it can be applied for the stereospecific construction of *cis*- or *trans*-disubstituted cyclopentenes from 6-hydroxynorbornane-2-carboxylic acids (Table 12, entries 3 and 4).

Table 12 Fragmentation of Carboxylic Acids by NonKolbe Electrolysis

Entry	*Carboxylic acid*	*Reaction conditions*	*Product*	*Yield (%)*	*Ref.*
1		MeOH		44 35	226 223
2		C anode, MeCN, EtOH		85	15
3		C anode, MeCN, EtOH		38	227
4		MeOH, C anode		63	227

2.8.7.1 Experimental Procedure for NonKolbe Electrolysis — Preparation of Methyl 2-(*t*-2-Phenylsulfonyl-3-cyclopenten-*r*-1-yl)acetate

A solution of 0.5 g (1.69 mmol) 6-oxo-*c*-3-phenylsulfonylbicyclo[2.2.1]heptane-*t*-2-carboxylic acid in methanol (50 mL), neutralized to 100% with 1 M NaOH in methanol, was electrolyzed at graphite electrodes (anode area 15 cm^2) in an undivided cell (Figure 2) with a current density of 100 mA cm^{-2} at 0 °C until consumption of 4 F mol^{-1}. The solution was then evaporated to dryness, treated with a saturated NaCl solution and extracted five times with CH_2Cl_2. After drying ($MgSO_4$) and removal of the CH_2Cl_2, 0.3 g (1.07 mmol, 63%) methyl 2-(*t*-2-phenylsulfonyl-3-cyclopenten-*r*-1-yl)acetate was obtained as a colorless oil by column filtration (silica gel, petroleum ether:ether = 2:1). Acidification of the aqueous phase with concentrated HCl to pH 1 and threefold extraction with CH_2Cl_2 afforded 0.04 g (9%) starting acid.[227]

2.8.8 CONCLUSIONS

Carboxylic acids can be converted by anodic decarboxylation into radicals and/or carbocations. The reaction conditions are simple; an undivided beaker-type cell as reaction vessel, controlled current supplied from an inexpensive d.c. power supply and methanol as solvent are in most cases sufficient. A scale-up is fairly easy and the yields are in general good. By the radical pathway 1,*n*-diesters, -diketones, -dienes and -dihalides, chiral intermediates for synthesis, pheromones and unusual fatty acids are accessible in just a few steps. The addition of the intermediate radicals to double bonds affords additive dimers, whereby four building units, two alkyl radicals from the carboxylates and two alkenes, can be coupled in one step. Five-membered hetero- or carbo-cyclic compounds can be prepared by intramolecular addition starting from unsaturated carboxylic acids.

The cationic pathway allows the conversion of carboxylic acids into ethers and acetals. The decarboxylative elimination of vicinal diacids or β-silylcarboxylic acids in combination with cycloaddition reactions leads efficiently to cyclobutenes or cyclohexadienes. Cationic rearrangements or fragmentations initiated by anodic decarboxylation allow the synthesis of specifically substituted cyclopentanes and ring extensions by one or four carbon atoms.

2.8.9 REFERENCES

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2.9
Oxidative Coupling of Phenols and Phenol Ethers

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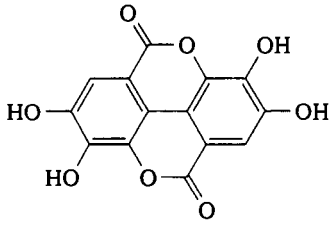
2.9.1 INTRODUCTION

2.9.1.1 General

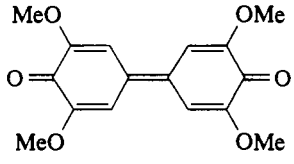
The ready oxidation of phenols to dimeric products has been well known for more than a century. The invaluable survey of the area by Musso[1] lists over 20 papers published before 1900 on, for example: the

formation of the dilactone (**1**) from gallic acid[2] and its derivatives (1871);[3] the production of both *para–para* and *ortho–ortho* coupled dimers from 1-naphthol (1873);[4] the synthesis of the diphenoquinone (**2**),[5] in 97% yield, from 2,5-dimethoxyphenol (1878); and the preparation of 2,2′-dihydroxybiphenyl from phenol itself (1878).[6] Reagents used in such early work include iron(III) salts, potassium ferricyanide, oxygen and the halogens; electrochemical methods were also known, and enzyme-catalyzed reactions were reported in, for example, the oxidative dimerization of eugenol (1896).[7] Extensive chemical investigations into this major reaction continued this century and further momentum was gained from the recognition of the role of oxidative coupling in biogenesis, signalled by the important and influential papers of Barton and Cohen,[8] and of Erdtman and Wachtmeister.[9] Subsequent biosynthetic investigations have confirmed the significance of the title reaction in the *in vivo* formation of many aromatic natural products including alkaloids (Battersby[1] estimated that such coupling was involved in *ca.* 10% of known alkaloids), lignans, lignin, tannins, and plant and insect pigments. Many biomimetic studies of oxidative phenolic coupling were made, either for synthetic ends or to demonstrate possibilities in biological processes. Low chemical yields were often reported in such work, particularly in certain well-known alkaloid cases, and attention was turned to new reagents, *e.g.* manganese(III), vanadium(V) and thallium(III), which generally proved more effective. Further, oxidants such as vanadium(V) were found to effect coupling of phenol ethers, and interest was revived in the anodic oxidation of such aromatic substrates. The oxidation of phenol ethers has proved a valuable synthetic process, often more predictable and higher yielding than the corresponding phenol oxidations, and this reaction has been employed in recent years in a number of notable natural product syntheses.

A number of good reviews of the oxidation of phenols have appeared;[1,10–19] the most recent covers the literature to mid-1980. These offer historical perspective and coverage of the biosynthetic aspects of the area, both inappropriate in the present article. This chapter focuses entirely on synthetic uses of the reaction and sets out: (i) to survey the main types of reaction stemming from oxidation of phenols and phenol ethers; and (ii) to offer selected examples of reactions showing satisfactory yield and regioselectivity.



(1)



(2)

2.9.1.2 Mechanistic Possibilities

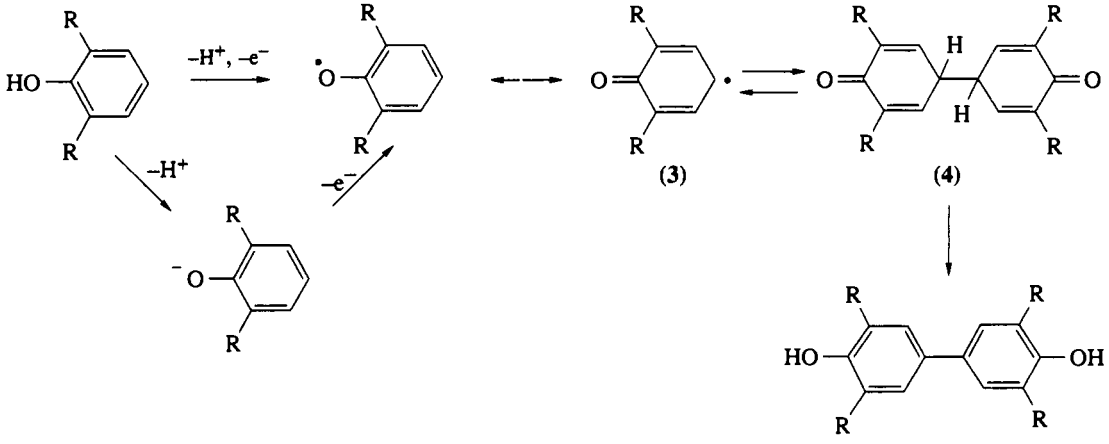
A wide variety of mechanistic pathways[16,20] present themselves for consideration, and since awareness of these ramifications aids synthetic planning they are outlined here. The major variables are as follows. (i) Substrate — either an un-ionized phenol or a phenolate anion may be oxidized, leading to different intermediates. Also the products after coupling may be new substrates for oxidation. (ii) Reagent — both homogeneous and heterogeneous reagents are employed covering a range of oxidation potential. Metal complexes are often implicated, which sometimes appear to be precipitated. Both inner-sphere and outer-sphere electron transfer processes can be involved. (iii) Pathway — overall two electrons and two protons are removed in a typical oxidation, and various sequences are thus possible. Two single-electron steps may occur, or one two-electron step, leading to radical or ionic processes. Species with carbon–metal or oxygen–metal bonds may intervene. The route may involve oxidation of one phenolic nucleus to quinone or quinone methide followed by a nonoxidative coupling step.

The main reaction pathways thus available for this process are summarized in the following schemes. For an excellent full discussion see ref. 20.

2.9.1.2.1 Coupling of aryloxy radicals

Scheme 1 illustrates this mechanism, which is the most generally accepted and widely discussed, for the *para–para* self-coupling of a simple phenol. Oxidation to the radical (**3**) may proceed from the phenol or phenolate anion according to pH, *etc.* The formation of such radicals is well attested, for example

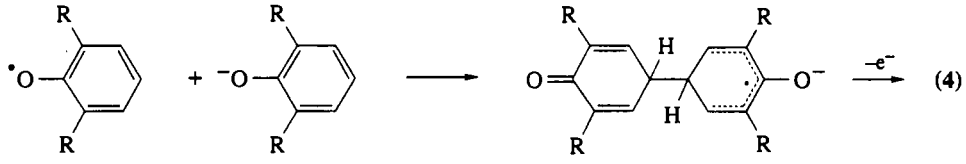
by ESR,[21-23] and it has been shown[24] that the subsequent dimerization fits a diffusion-controlled model. The coupling step (3) → (4) may be reversible, and in the absence of acid the enolization of (4) to produce biphenyl may be slow and rate determining.



Scheme 1

2.9.1.2.2 Radical substitution

While the above mechanism certainly operates in many systems, it is not universal. If each radical is surrounded by unoxidized phenol or phenolate anion molecules, then aromatic substitution becomes possible, and this becomes more likely in intramolecular cases where two units of different reduction potential are held in proximity. Scheme 2 shows the likely pathway with radical insertion into a phenoxide and the second one-electron transfer following coupling, and such a mechanism has been shown to operate in the oxidation of 2,3,4′-trihydroxybenzophenone to 2,6-dihydroxyxanthone (ref. 20, p. 114).



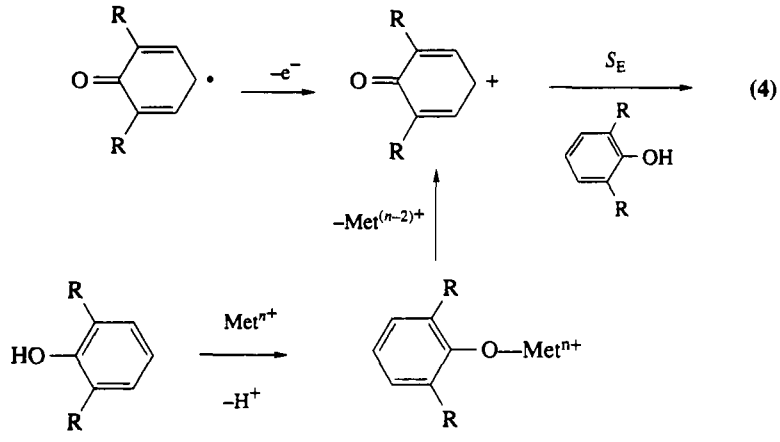
Scheme 2

2.9.1.2.3 Heterolytic substitution

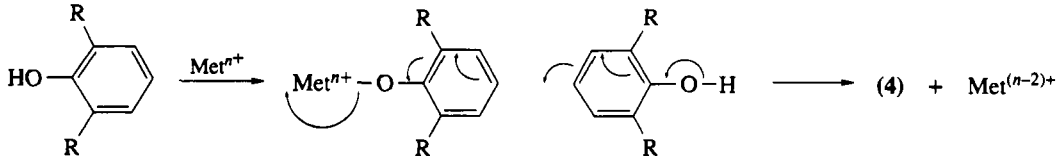
Scheme 3 shows that a second one-electron oxidation of an aryloxy radical yields an aryloxonium species, which could lead to a coupled product by electrophilic substitution. Although a less probable reaction course because of the energetics for two successive one-electron transfers, it cannot be discounted, since such transfers have been observed by polarography. Also phenoxy cations have been isolated as fluoroborate salts, and react rapidly with nucleophiles. Alternatively a single two-electron transfer to a suitable metal ion can be envisaged (Scheme 3), also leading to a cation. In this case no radical intermediates are involved. 2,3-Dichloro-2,6-dicyanobenzoquinone is thought to effect phenolic coupling by hydride transfer to an aryloxonium species.[25]

2.9.1.2.4 Concerted coupling and electron transfer

Scheme 4 shows the ionic substitution of a phenol by a metal phenolate compound, by a concerted mechanism. Although similar to Scheme 3, a phenoxonium ion is avoided, with probable energetic advantages: thallium(III) oxidations of phenols may follow such a path.



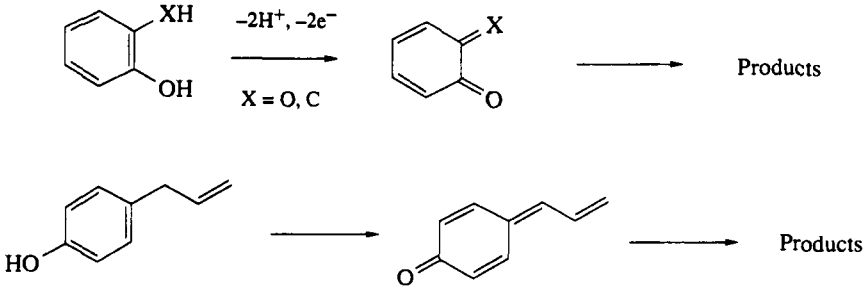
Scheme 3



Scheme 4

2.9.1.2.5 Postoxidative coupling

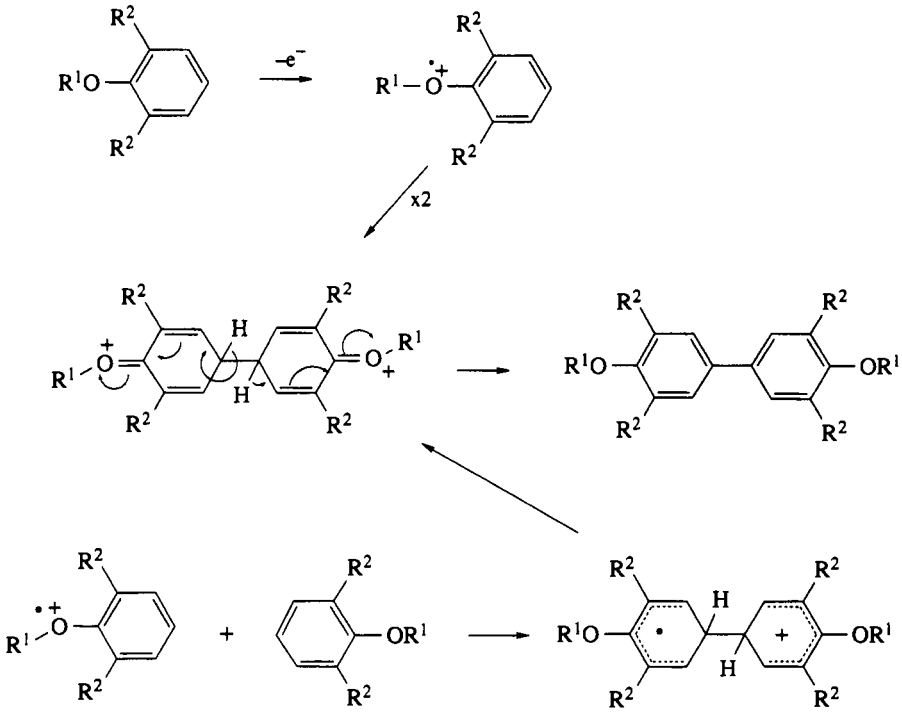
In some instances it has been demonstrated that oxidation is complete before coupling occurs, the second step thus being nonoxidative. Such cases (Scheme 5) involve oxidation to a quinone or a quinone methide whose further reactions may involve nucleophilic addition, *e.g.* by phenol, or cycloaddition. Examples are given below.



Scheme 5

2.9.1.2.6 Radical cation reactions

One-electron oxidation of an aryl ether, for example at the anode, gives rise to a radical cation whose fate may be radical coupling (shown as dimerization) or substitution into a neutral phenol ether; both paths are shown in Scheme 6 and converge to a biaryl product. Other products are possible if coupling at a quaternary center takes place. Mechanisms of this type must operate for the important couplings of phenol ethers with phenol ethers, and phenols with phenol ethers; possibly they should not be neglected for phenol–phenol coupling also, in certain cases.



Scheme 6

2.9.1.3 Product Types and Chapter Organization

Inter- or intra-molecular carbon–carbon coupling of phenols at two unsubstituted ring carbons leads to the corresponding biaryl. The product may then be further oxidized, for example to a diphenoquinone. Oxygen-unsubstituted ring carbon coupling gives an aryl ether. If coupling involves a substituted ring site then a cyclohexadienone results, which in intramolecular cases will be a spirodienone. Further reactions, for example with nucleophiles, may ensue.

In phenols with *ortho* or *para* unsaturated side chains, coupling reactions may occur outside the aryl ring, and may form new carbon–carbon or carbon–oxygen bonds. Benzylic radicals may also be generated, perhaps by hydrogen atom abstraction, and lead to coupling at this position. Finally the products arising from quinones, quinone ketals, or quinone methides may dominate.

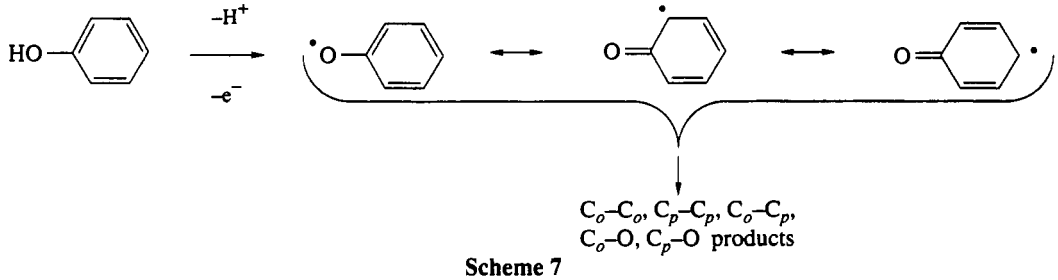
The survey of reactions presented here is divided first into the main product types above. Thus Sections 2.9.2 and 2.9.3 deal with the synthesis of biaryls and spirodienones respectively, by C—C bond formation. Section 2.9.4 covers the preparation of ethers through C—O bond making. The coupling of phenols through side chain sites is dealt with in Section 2.9.5. Section 2.9.6 contains a miscellany; post-oxidative cycloaddition reactions, coupling through benzyl radicals, and some examples of C—N bond forming. Within sections, material is divided firstly by reactant type and secondly by reagent type.

2.9.2 SYNTHESIS OF BIARYLS AND RELATIVES

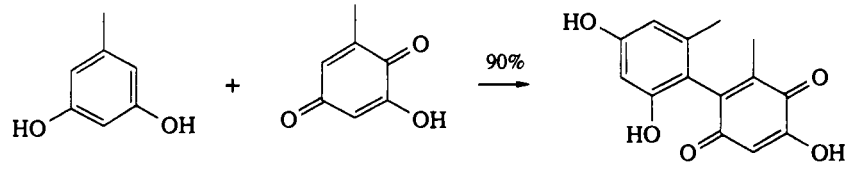
2.9.2.1 Phenol–Phenol C—C Coupling

This is the best known and most quoted chemistry in this area. Oxidation of a phenol as in Scheme 7, with loss of one proton and one electron, provides an aryloxy radical, which may dimerize: three modes of C—C union are possible, and two modes of C—O bonding. Spin density is greatest, in general, in the *para* position, but coupling is reversible (before intermediate dienone phenolization) and product ratios depend on pH, temperature, concentration and oxidant, for a given phenol.[26] Mixtures of isomeric dimers may, and often do, result. If different phenols are present then potential products are numerous. A survey of the literature indicates that reasonable chemospecificity is most likely observed either in cases of phe-

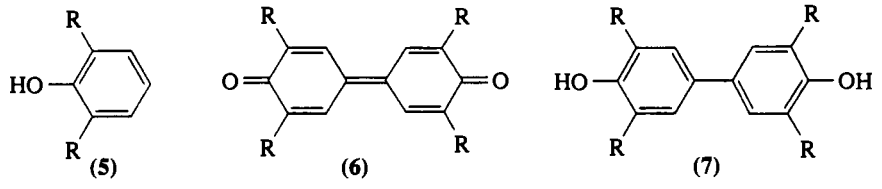
nol self-coupling where one or two of the *ortho*/*para* sites are substituted, or in intramolecular examples. The intermolecular coupling of different phenols can also be successful, but often involves a polyhydroxy compound which can be oxidized to a quinone. The coupling step is then nonoxidative, involving addition of phenol to quinone. The feasibility of this reaction is shown by the example in Scheme 8; the initial product is oxidized to a new quinone under the reaction conditions.[27] *o,o*-Disubstituted phenols (**5**) give excellent yields of *para–para* coupled products, *e.g.* the formation of (**2**). Essentially quantitative yields of the diphenoquinone (**6**), with R = various alkyl groups, were obtained from the corresponding phenol (**5**) by refluxing in benzene with silver carbonate–celite;[28] conversion of (**5**; R = Bu^t) to (**6**; R = Bu^t) was also quantitative, and complete in a few minutes at room temperature with hydrogen hexacyanoferrate(III) in methanol;[29] and (**6**; R = Me) was prepared in 92% yield using triphenylbismuth carbonate.[30] Many other oxidants have been investigated,[31] and for (**5**; R = Me) the biphenol (**7**) could be obtained with a silver nitrate–potassium persulfate reagent (27%),[31] or manganese(III) acetylacetonate (45%).[32] Phenol yielded the 4,4′-dihydroxybiphenyl (**7**; R = H; 34%) on oxidation with vanadium tetrachloride,[33] together with the 2,4′-isomer (17%). Vanadium oxytrichloride oxidized 1-naphthol to the *para–para* coupled binaphthyl (**8**; R = H; 56%). The tetrahydroxybinaphthyl (**8**; R = OH), a metabolite of *Daldinia concentrica*, was synthesized[34] by treatment of 1,8-dihydroxynaphthalene with potassium ferricyanide.

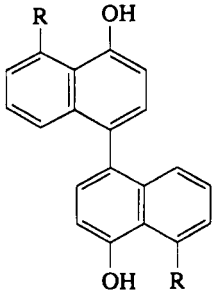


Scheme 7



Scheme 8

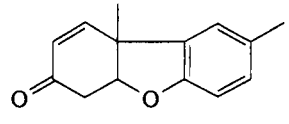




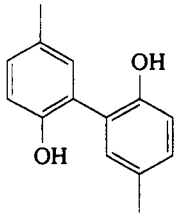
(8)

Para-substituted phenols may still couple through the *para* position and products may be formed in good yield, especially if stable. Thus *p*-cresol gives Pummerer's ketone (**9**; 63%) on treatment with silver

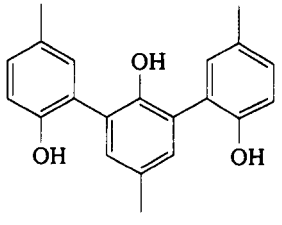
carbonate;[26] only the *o–p* coupled intermediate can cyclize to (**9**), which is then not subject to phenolic oxidation. In contrast *p*-cresol with iron(III) chloride gives at least 10 products including (**9**), and the biphenyl and terphenyl products of *o–o* coupling (**10**) and (**11**).[35] Simple *o–o* linking can be the major pathway, *e.g.* alkaline potassium ferricyanide oxidation of totarol (**12**; R = Me) in benzene–water afforded podototarin (**13**; R = Me) in 43% yield; and ethylmacrophyllate (**13**; R = CO_2Et) was the major product from similar oxidation of (**12**; R = CO_2Et).[36] An aqueous alkali–organic solvent two-phase system is usually favored for ferricyanide oxidation since the products may be separated from the oxidant. The naphthol (**14**) dimerizes quantitatively on heating (215 °C) in air to the bisnaphthol (**15**; R = H), which contains the gossypol nucleus. *O*-Methylation of (**15**; R = H) gave apogossypol hexamethyl ether (**15**; R = Me).[37] The allylguaiacol (**16**) was oxidized quantitatively at a platinum anode to the biphenol (**17**), using an alkaline electrolyte,[38] although to very different products in neutral media (*vide infra*). The trimethyltetralol (**18**) gave the dimer (**19**) in 46% yield using a copper(II)–amine complex.[39] The oxidation of a similar chiral reactant (**20**) has been examined from the stereochemical viewpoint.[40] The (±)-tetrahydroisoquinoline (**20**) on oxidation with potassium ferricyanide, or with oxygen over platinum, provided three stereoisomers of (**21**); a *meso* (*R,S*) form, and two separable rotamers of the (*S,S*)/(*R,R*) racemate. However, on electrooxidation at a graphite anode only one stereomer was formed (69%), the rotamer shown (**21**) of the (*S,S*)/(*R,R*) form. Separate oxidations of the (*S*)- and (*R*)-enantiomers of (**20**) afforded only the (*S,S*) (62%) and the (*R,R*) (66%) isomers, both as a single rotamer.



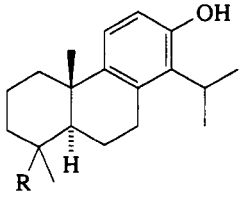
(**9**)



(**10**)

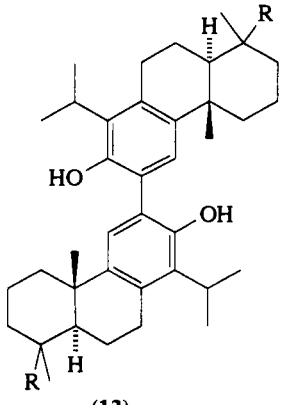


(**11**)

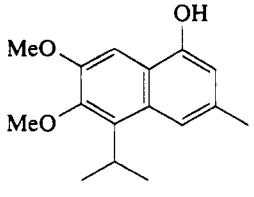


(**12**)

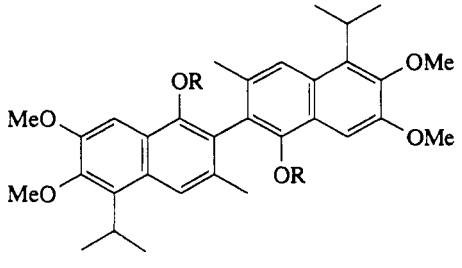
2-Naphthol can successfully be dimerized oxidatively, selectively through the *o*-site to give (**22**) using copper(II)–amine complexes (70%)[39] or manganese(III) acetylacetonate (69%),[32] and *o–o* coupling is the major pathway (90%) on ferricyanide oxidation of the trisubstituted phenol (**23**) to the orthodiphenoquinone (**24**).[41] In this context it is of interest that a compound obtained (74%) on ferricyanide oxidation of



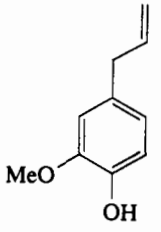
(**13**)



(**14**)



(**15**)



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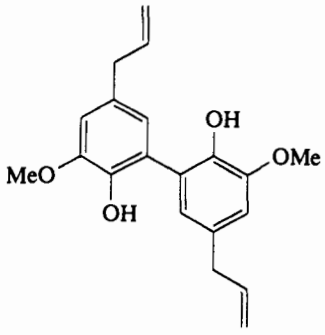

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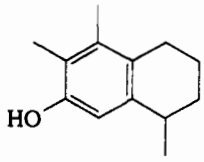

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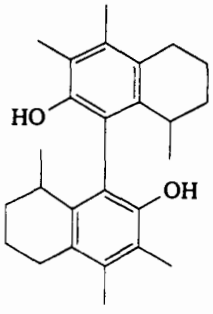

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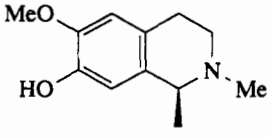

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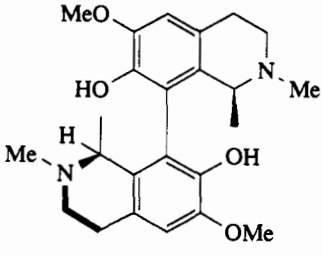
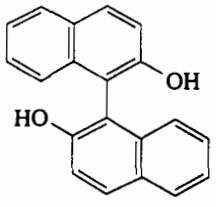


(21)

the 2,2′-dihydroxybiphenyl (**25**) proved to be the oxepinobenzofuran (**26**)[42] rather than the benzoxete (**27**) as originally formulated.[43] The intermediate orthodiphenoquinone (**28**) rearranges as shown. Another case of *o–o* dimerization is that of the anodic oxidation (graphite anode, acetonitrile–water, 0.3 V) of the sodium salt of the *p*-hydroxybenzyltetrahydroisoquinoline (**29**), which selectively gave product (**30**; 45%).[44] The *N*-ethoxycarbonyl substituent is necessary in this example to prevent oxidation at nitrogen; with NH or NMe analogs fragmentation supersedes coupling, as pictured in (**31**), leading to initial products (**32**) and (**33**).



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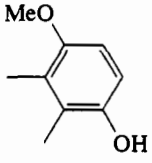

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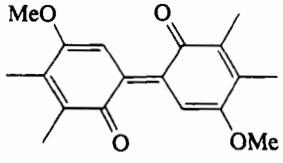

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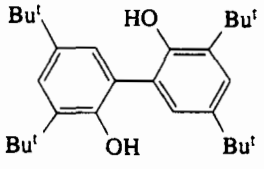

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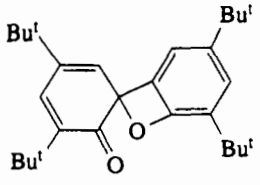
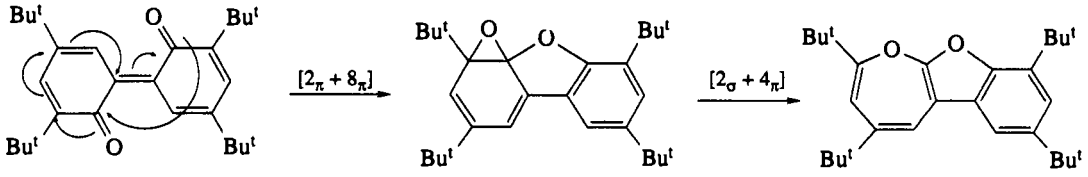
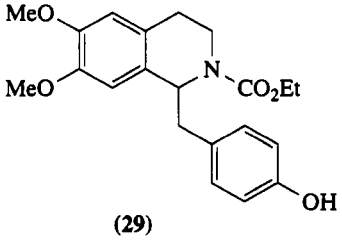


(27)

The question of cross-coupling of different phenols was alluded to above. An interesting example[45] of selectivity is shown in Scheme 9; the major product, shown, forms a relatively stable radical anion under the reaction conditions. To what extent this thermodynamic factor controls product ratios is not clear.



(28) (26)



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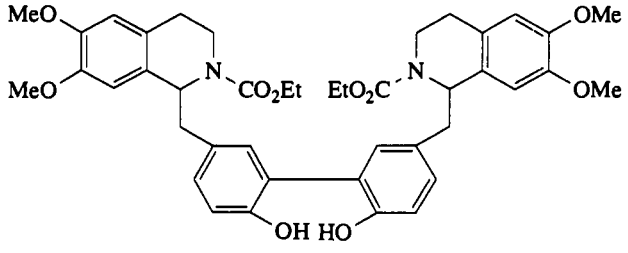

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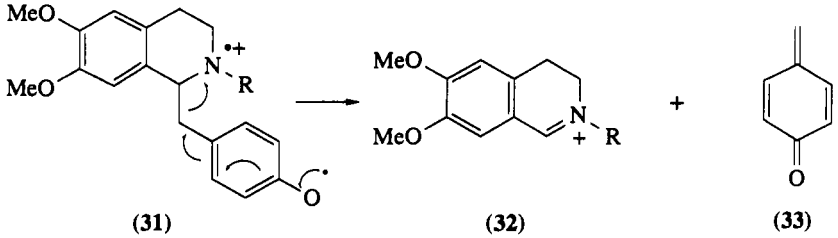
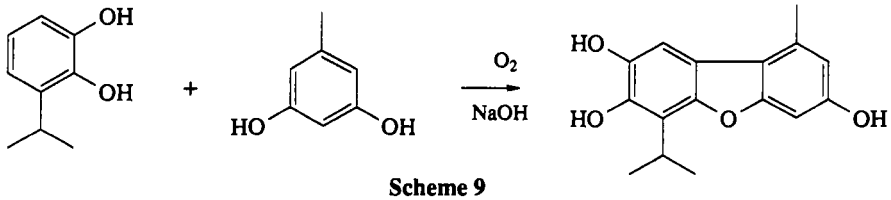


(31) (32) (33)

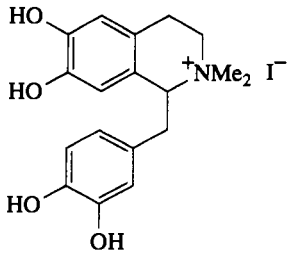
Few such cases have been described and it does not seem possible to make reliable predictions of such cross-coupling reactions on the basis of present knowledge.



Scheme 9

Intermolecular coupling has been displayed in the foregoing reactions. Intramolecular cases are of interest, potentially offering greater product selectivity, and many have been investigated as models of biogenetic significance. A high proportion of these proceed in poor yield and have limited synthetic value. However there are some rewarding examples. Thus laudanosoline methiodide (**34**) underwent preferential *o–p* linking to (**35**; 62%), with aqueous iron(III) chloride at room temperature.[46] Dihydropiceatannol (**36**) was also selectively oxidized to a 9,10-dihydrophenanthrene, isolated (66%) as its tetraacetate (**37**) after reductive acetylation.[47] It is possible but unproven that in both these cases an *o*-benzoquinone intermediate is generated. Such a pathway appears very likely in the following reaction[48] in which the tetrahydroisoquinoline (**38**) was treated with diphenyl selenoxide in methanol at ambient temperature to afford in 80% yield the coupled product (**39**), *N*-trifluoroacetylwilsonirine. This reagent cleanly oxidizes catechols to *o*-quinones *via* an intermediate seleno acetal (**40**). The arylethyltetrahydroisoquinoline (**41**) is similarly intracoupled,[48] forming a new seven-membered ring in product (**42**).

Finally in this section it is worth noting that the oxidative coupling of phenols may be extended to form interesting polymers. Thus electrooxidative polymerization of phenol using basal-plane pyrolytic graphite electrodes gives thin black polymer films which are electrically conducting.[49]



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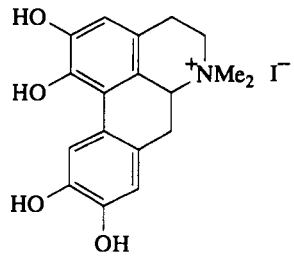

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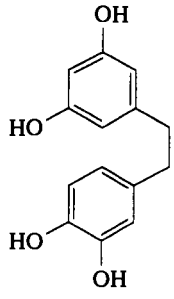

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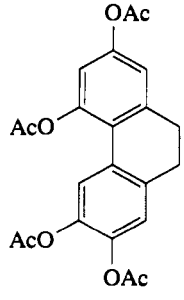

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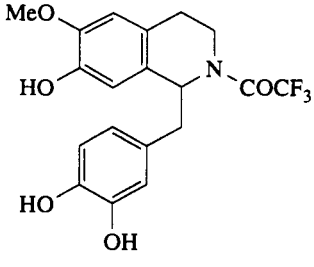

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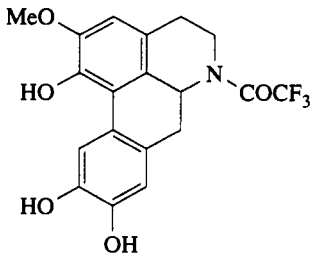

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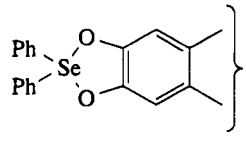

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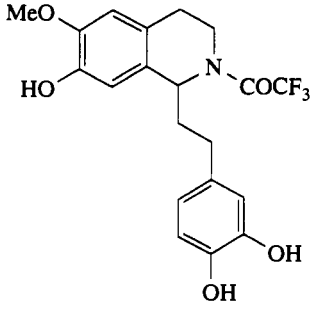

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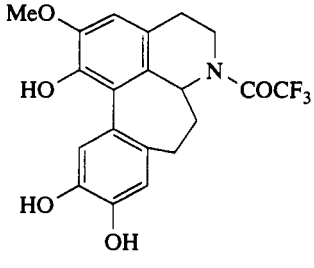


(42)

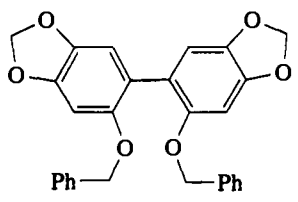
2.9.2.2 Biaryls Formed in Phenol Ether Couplings

This section covers the union of two aryl moieties, one of which is a fully alkylated phenol, and the other is either a free phenol or a phenol ether. Clearly, radical dimerization is not operative in such reactions. An early example is to be found in the work of Fitcher and Dietrich (1924)[50] who showed that 3,3′,4,4′-tetramethoxybiphenyl was among the products of electrolytic oxidation of veratrole in sulfuric acid using a lead dioxide anode; the biaryl was formed in about 20% yield based on reacted veratrole.

The potential of such syntheses was not realized for several decades. (The following account is not historical.)

The intermolecular examples of synthetic value are self-couplings, *e.g.* formation of the dimer (**43**) from benzylsesamol,[51] in 85% yield using vanadium oxytrifluoride; preparation of the biaryl (**44**; 95%), from 4-methylveratrole, employing iron(III) chloride supported on silica;[52] and synthesis of 4,4′-dimethoxybiphenyl (69%) from anisole by oxidation with thallium(III) trifluoroacetate in the presence of catalytic palladium(II) acetate.[53] This approach has been used in a natural product synthesis. The dimers (**45**) and (**46**) were prepared from appropriate derivatives of gallic acid, and transformed into schizandrin C (**47**) and an isomer respectively.[54,55]

Recently the conditions have been defined under which trimerization of some phenol ethers is viable; these require anodic oxidation in a flow cell with porous electrodes, using acetonitrile or trifluoroacetic acid–methylene chloride.[56] Catechol derivative (**48**) and 1,2-methylenedioxybenzene were thus converted into trimers (**49**) and (**50**) respectively, in *ca.* 30% yield.



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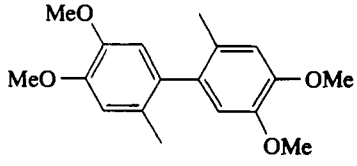

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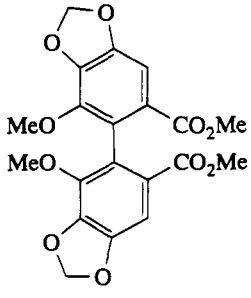

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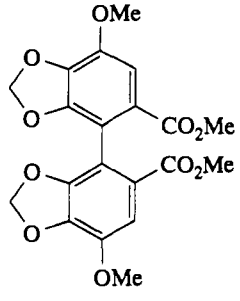

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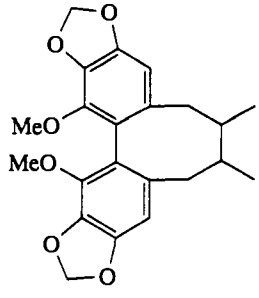

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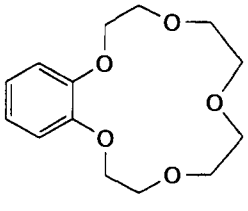

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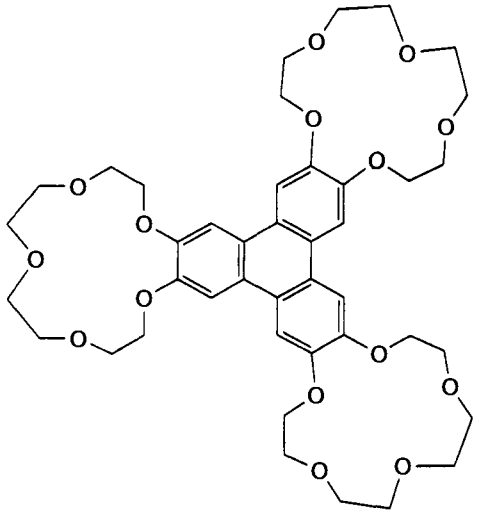

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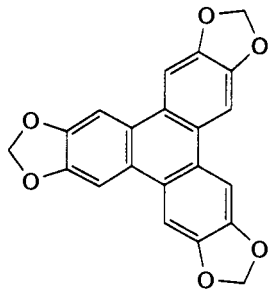


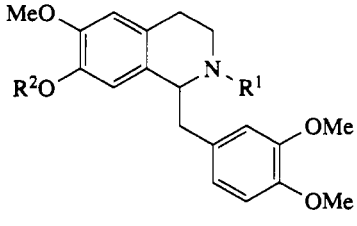
(50)

The intramolecular versions of this reaction have been widely exploited particularly for the synthesis of alkaloids and lignans. New six-, seven- and eight-membered rings are readily formed and there are some cases involving macrocycles.[57]

Starting with six-membered ring formation, it has been shown that (±)-laudanosine (**51**; $R^1 = R^2 = Me$) can be oxidized with vanadium oxytrifluoride in trifluoroacetic acid–fluorosulfonic acid to (±)-glaucine (**52**; $R^1 = R^2 = Me$; 43%).[57a] The same oxidant also effected phenol–phenol ether coupling in this alkaloid series, with *N*-trifluoroacetylcodamine (**51**; $R^1 = COCF_3$, $R^2 = H$) yielding the aporphine (±)-*N*-trifluoroacetylwilsonirine (**52**; $R^1 = COCF_3$, $R^2 = H$). The benzyltetrahydroisoquinoline (**53**) was intracoupled to (±)-ocoteine (= thalicmine; **54**) in 46% yield employing thallium trifluoroacetate at –40 °C, with catalytic boron trifluoride.[58]

To exemplify phenol–phenol ether coupling the benzylisoquinoline (**55**) was oxidized with a range of reagents, to form the novel quinonoid oxaporphine (**56**) with generation of the quinone methide after coupling; best yields were obtained with vanadium oxytrifluoride in trifluoroacetic acid (59%) and molybdenum oxytetrachloride (62%).[59] The former reagent was also very effective in converting the (non-natural) system (**57**) to (**58**; 70%); no further product oxidation was observed here, possibly because of reduced thermodynamic drive.[60]

Returning to phenol ether–phenol ether coupling, synthetic septicine (**59**) gave (±)-tylophorine (**60**) on treatment with thallium trifluoroacetate, and the same reagent converted synthetic julandine (**61**) to (±)-cryptopleurine (**62**; 69%).[61] In another synthesis of tylophorine the lactam (**63**) was transformed with va-



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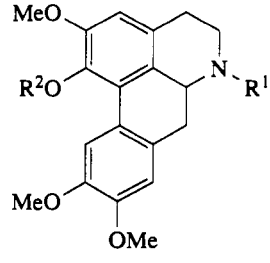

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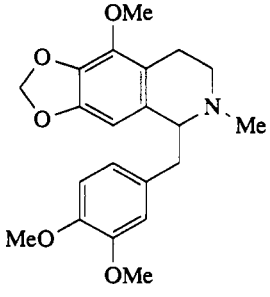

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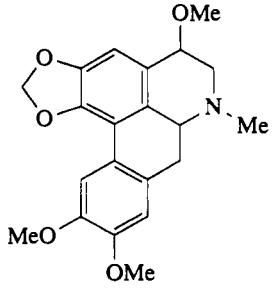

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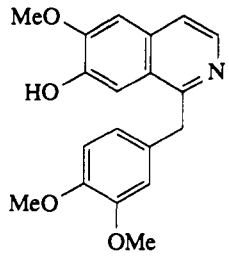

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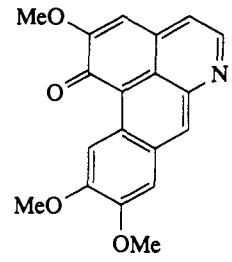

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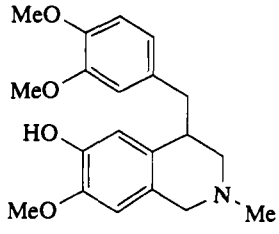

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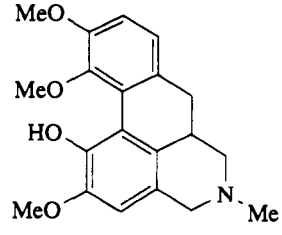
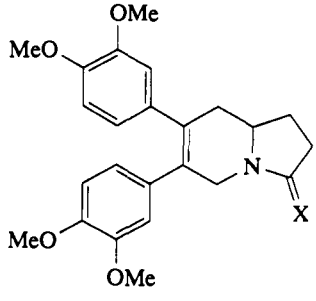


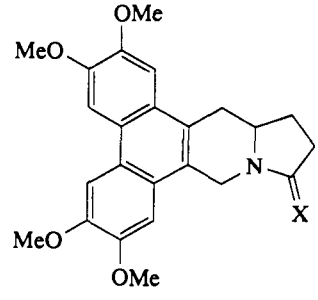
(58)

nadium oxytrifluoride to (**64**; 59%); reduction with diborane (85%) completed the sequence to tylophorine (**60**).[62]

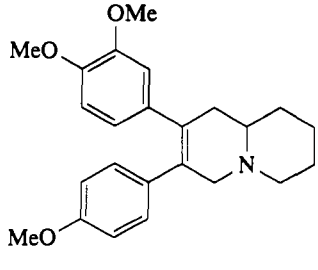
Electrooxidation is also viable for phenol ether–phenol ether coupling and has been thoroughly investigated. For example a range of compounds (**65**) with R = H or Me, Z = CH_2 or O, n = 1 or 2, reacted at the anode to give fair yields of the corresponding biaryls (**66**),[63] together with spirodienone products (see Section 2.9.3.2).



(**59**) X = H_2
(**63**) X = O



(**60**) X = H_2
(**64**) X = O



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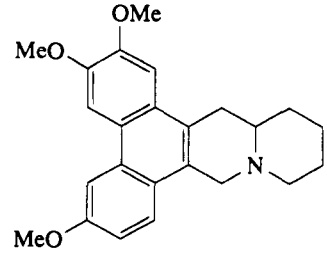

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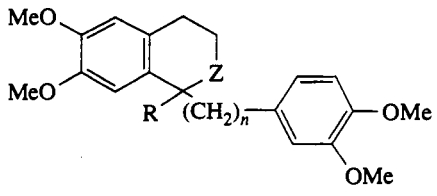

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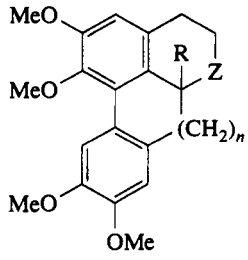
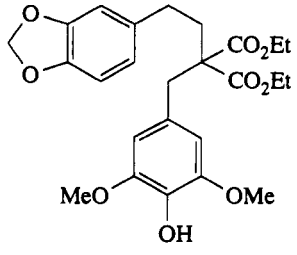


(66)

Aryl coupling to a benzylic site has also been observed: the monophenol (**67**) yielded the aryltetralin (**68**; 55%), with thallium trifluoroacetate–boron trifluoride.[64] Probably oxidation to quinone methide precedes the ring closure. Separate oxidation and cyclization steps were employed in the synthesis of (±)-thaliphorphine acetate. (±)-Codamine (**69**) underwent Wessely oxidation with lead tetraacetate to the acetoxycyclohexadienone (**70**), which closed in acetic anhydride–acid to (±)-thaliphorphine acetate (**71**), albeit in modest overall yield (14%).[65]



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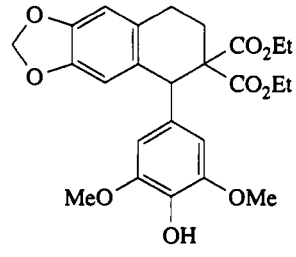

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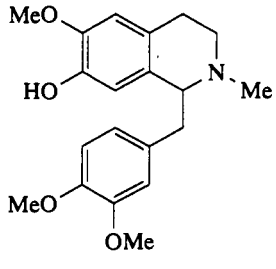
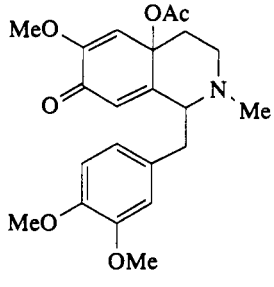
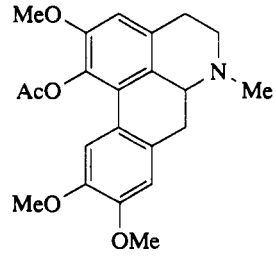


(69)



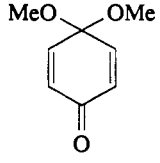
(70)



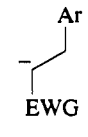
(71)

It is worth noting an alternative strategy for intracoupling to biaryls,[66] in which the quinone monoketal (**72**) undergoes addition by a suitable carbanion (**73**); the resulting tertiary alcohols, *e.g.* (**74**) and (**75**), could be cyclized with acid (conditions of low nucleophilicity), to biaryls (**76**; 77%), and (**77**; 61%), respectively. The new C—C bond forms *meta* to methoxy of the new aryl ring, thus complementing the oxidative approach. The formation of a five-membered ring is worthy of note.

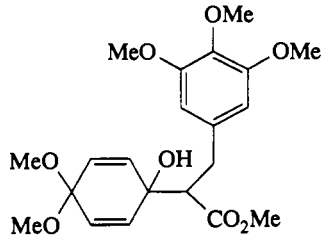
Closure to seven-membered rings has been demonstrated a number of times. Thus the 1,3-bisarylpropane (**78**) was oxidized anodically to the bridged biaryl (**79**; 72%). In a thorough study[67] of the effects of



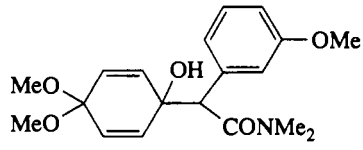
(72)



(73)



(74)



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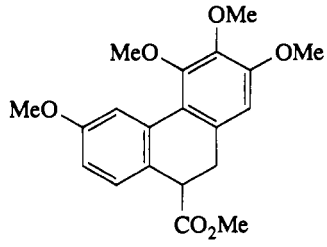

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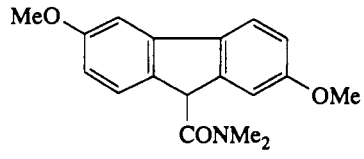
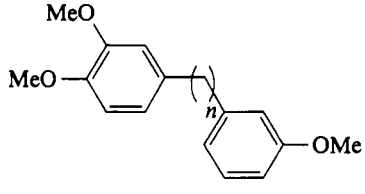


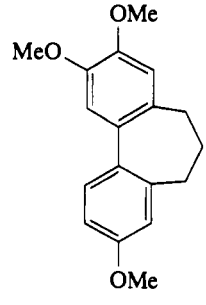
(77)

variations in conditions and in substrate structure on the competition between cyclization and dimerization it was concluded that intermolecular processes were favored at low anode potential, and conditions were given for dimerization of the 1,2-bisarylethane (**80**), to (**81**; 61%). It was concluded that, in the full range of examples studied, both cation radical couplings, and electrophilic substitution by cation radicals on unoxidized rings, were operating. Anodic oxidation was used to prepare homoglaucine (**83**) from homolaudanosine (**82**; 34%).[68]

Thallium trifluoroacetate has proved an excellent reagent for similar oxidations, *e.g.* of (**84**) and (**85**) to the bridged biaryls (**86**) and (**87**), 80% and 81%, respectively,[58,69] and this reagent was selected for a crucial step in a total synthesis of (±)-steganone.[70] Thus the (*E*)-2-benzylcinnamate (**88**) provided the bis-



(**78**) $n = 3$
(**80**) $n = 2$



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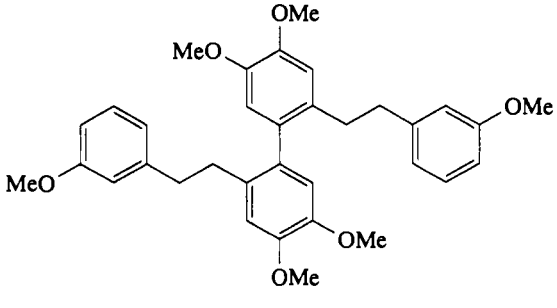

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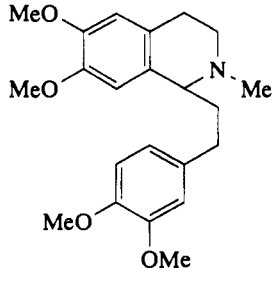

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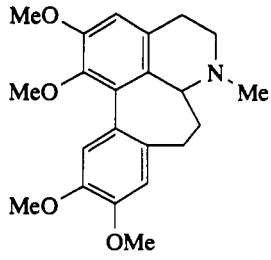
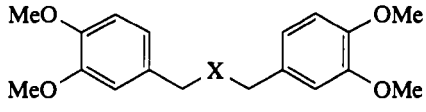


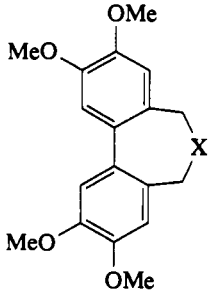
(83)

benzocycloheptatriene (**89**; 81%), at –18 °C in trifluoroacetic acid. Reduction of the methoxycarbonyl function and Simmons–Smith methylation then generated the cyclopropane (**90**; R = CH_2OH) from which (±)-steganone (**91**) could be generated *via* ring expansion with the correct biaryl twist, relative to lactone fusion. Alternatively the cyclopropane (**92**) could be cyclized (45%) to (**90**; R = CO_2Me). Interestingly it was not possible to induce biaryl formation with an eight-membered ring by treatment of (**93**) with thallium trifluoroacetate.[70b] Much synthetic interest has been shown in steganone and its relatives, induced by the anticancer properties of this group of lignans.

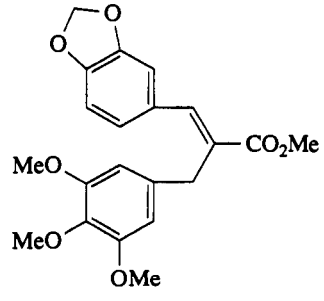
Although the bisarylbutene (**93**) proved unamenable to oxidative cyclization, eight-membered rings have been constructed successfully using substrates with saturated interaryl links. Several relatives of steganone have been prepared in this way. Thus (±)-steganacin was synthesized[71] using intracoupling of the malonate-derived bisaryl butane (**94**) to (**95**), in 45% yield, using vanadium oxytrifluoride at 25 °C,



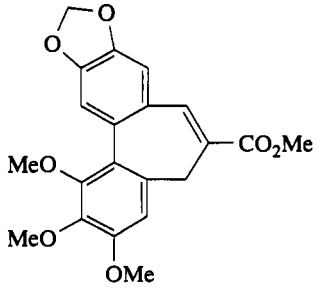
(**84**) X = O
(**85**) X = CH_2



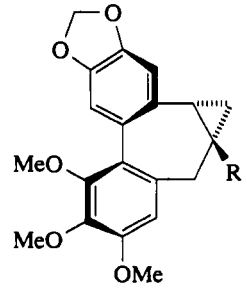
(**86**) X = O
(**87**) X = CH_2



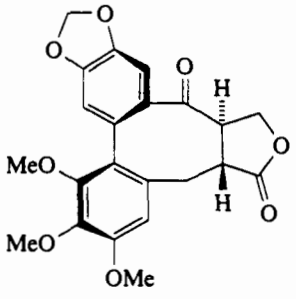
(**88**)



(**89**)



(**90**)



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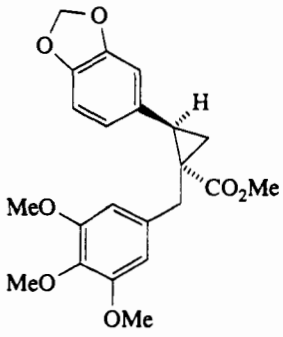
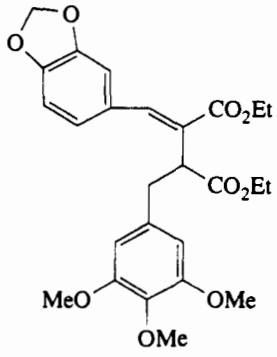
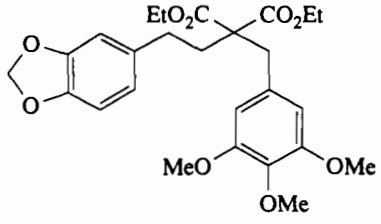


(92)

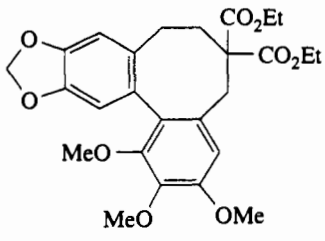


(93)

and (±)-isostegane (**96**) was obtained[72] in good yields (65–70%) by oxidation of the (±)-bisbenzylbutyrolactone (**97**), employing the same reagent at 45 °C. (–)-Isostegane (**96**) was similarly prepared[73] (61%) from (+)-deoxypodorhizone (**97**) (from enantiospecific synthesis), and converted into (+)-stegane and (+)-steganacin (**98**), the enantiomer of natural (–)-steganacin. This sequence demonstrated absolute stereochemistry in the sequence.[73] A related, but not natural, steganane (**99**) was obtained[74] from natural dimethylmatairesinol (**100**), effected by thallium tristrifluoroacetate in methylene chloride at room temperature; the reaction was accelerated by boron trifluoride and yields up to 90% were recorded.



(94)



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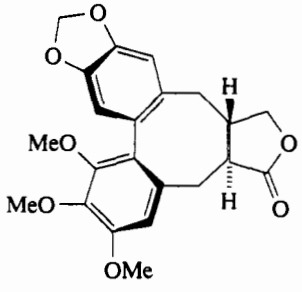
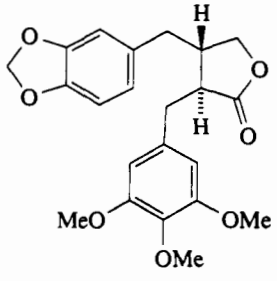


(96)



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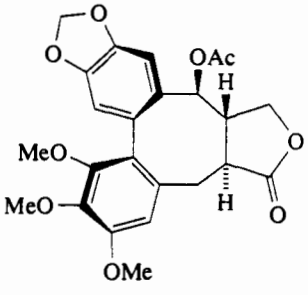

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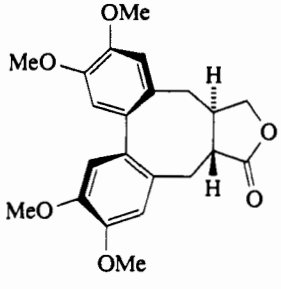

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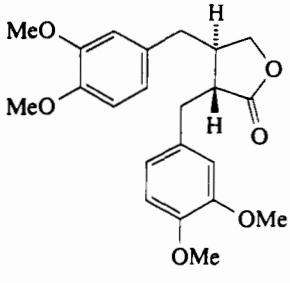
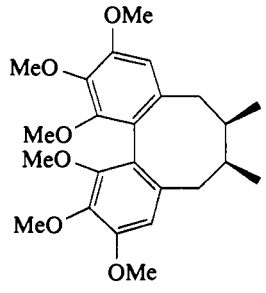
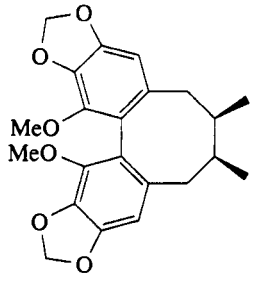


(100)

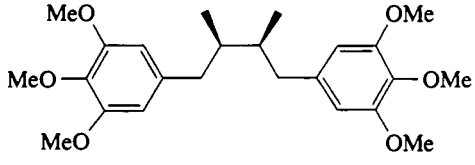
Some simpler lignans of the dibenzocyclooctadiene group have been prepared by related couplings, *e.g.* (±)-deoxyschizandrin (**101**; *ca.* 50%) and (±)-wuweizisu-C (**102**; yield unstated) from precursors (**103**) and (**104**), using low temperature vanadium oxytrifluoride oxidations[75,76] A reinvestigation[77] of the last two syntheses, comparing various reagents, concluded that iron(III) reagents were most effective although the yields reported were only fair, 32% and 46% for (**101**) and (**102**), utilizing iron(III) perchlorate hexahydrate in acetonitrile. Finally the successful formation is worth noting of the eight-membered nitrogen heterocycles (**105**) and (**106**) by anodic oxidations (platinum anode) of the precursor amides (**107**; 45%) and (**108**; 60%).[78]



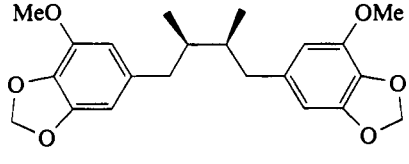
(**101**)



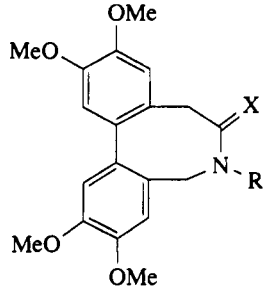
(**102**)



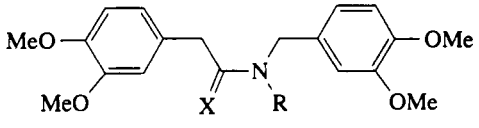
(**103**)



(**104**)



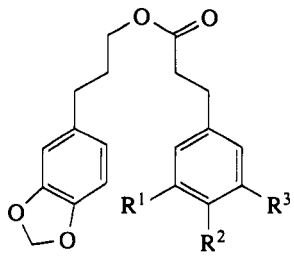
(**105**) X = O, R = Me
(**106**) X = H_2, R = Ac



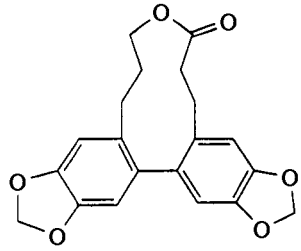
(**107**) X = O, R = Me,
(**108**) X = H_2, R = Ac

A few coupling reactions to afford macrocycles have been uncovered.[79] The ester (**109**), on treatment with thallium tristrifluoroacetate for 3 min at room temperature, yielded the 11-membered lactone (**110**; 14%), *via para–para* linking. Longer (10 min) reaction of the related ester (**111**), with water quenching, afforded the 13-membered lactone (**112**), by way of coupling, *para* to a methoxylated site, and loss of a benzylic hydrogen to intermediate (**113**), which was rearomatized in allylic hydrolysis. In studies on anodic oxidations of substrates (**78**), cyclization to biaryls with bridges as long as $n = 16$, *i.e.* 20-membered rings, have been observed, although in low yield.[80]

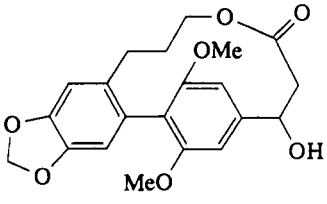
In concluding this section it is worth noting that in these nonphenolic aryl couplings, the new bond is usually formed between sites *para* to ether oxygen, in accord with electron density calculations on methoxybenzene cation radicals, and with their ESR spectra.



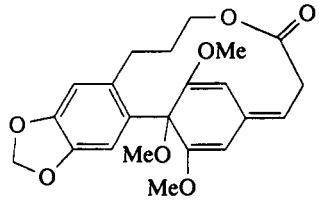
(**109**) $R^1 = H$, $R^2 = R^3 = OCH_2O$
(**111**) $R^1 = R^2 = R^3 = OMe$



(**110**)



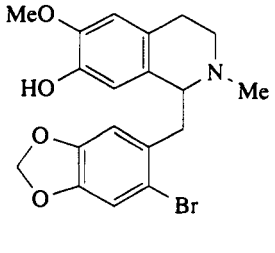
(**112**)



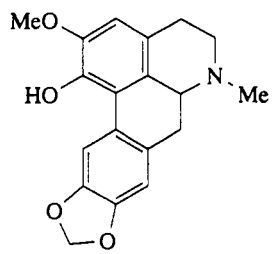
(**113**)

2.9.2.3 Biaryls Formed by Aryl Radical Insertion

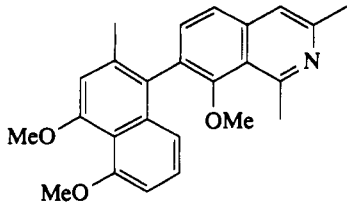
In the introduction it was pointed out that phenolic coupling may involve addition of a carbon radical to a phenolate anion, and nonphenolic coupling may proceed by way of radical cation attack on an unoxidized aromatic unit. A closely related group of transformations involve generation of an aryl radical which then inserts into a second aryl unit. A few examples are given here, since the process can supplement the direct oxidation approach. A representative reaction is the photochemical transformation,[81] under basic conditions (sodamide–dimethylformamide), of the bromophenol (**114**) into (±)-domesticine (**115**; 31%), with formation of a six-membered ring. The first synthesis[82] of a naphthylisoquinoline alkaloid, *O*-methyltetradehydrotriphyophylline (**116**) used irradiation (254 nm) of bromide (**117**) as the key step, forming the pentacycle (**118**; 15%) for conversion to (**116**). An aryl radical may also be generated by reductive cleavage of halide at the cathode; the bromobenzoylaniline (**119**) gave the biaryl (**120**) in this way.[83] In another example[84] the bromobenzoylnaphthylamine (**121**) afforded the arylnaphthalene (**122**; 44%), by closure and rearrangement through the spiro radical (**123**). Seven-membered rings are amenable to formation in such reactions; irradiation of the iodobenzylamine (**124**) in dilute acid gave the dibenzoazepine (**125**) in 57% yield,[85] and photolysis in dilute alkali of the bromophenol (**126**) yielded the homoaporphine (**127**)[86] albeit in only 55%. Two examples of intracoupling to eight-membered rings complete this brief survey; photolysis of the iodide (**128**)[87] and the bromide (**129**)[85] gave the dibenzoazacyclooctadienes (**130**; 21%) and (**131**; 22%). The former is an apogalanthamine analog.



(**114**)



(**115**)



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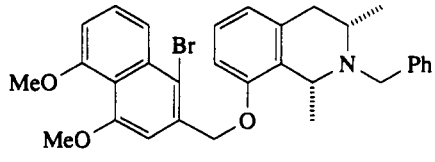

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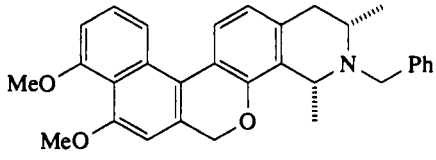

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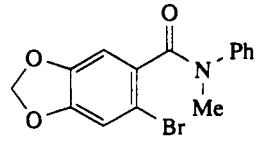

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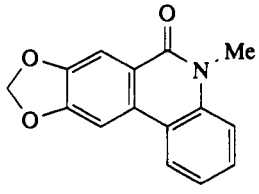

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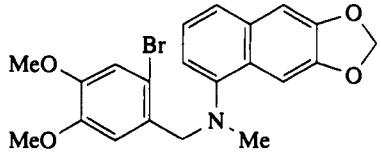

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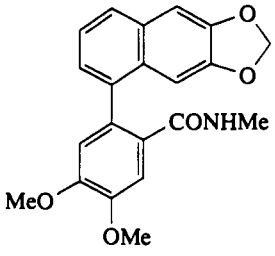

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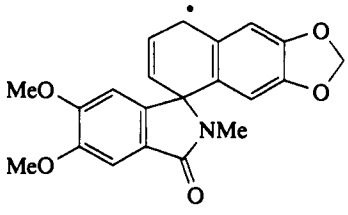

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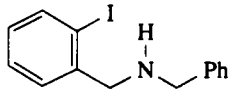

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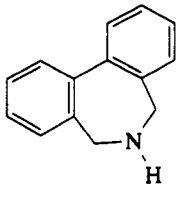

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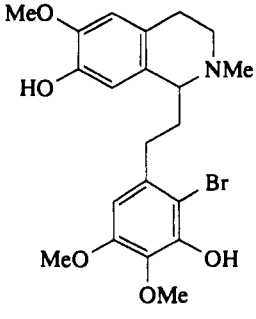

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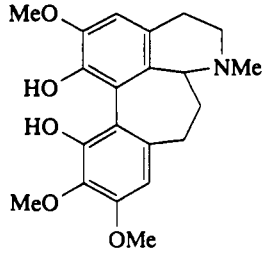

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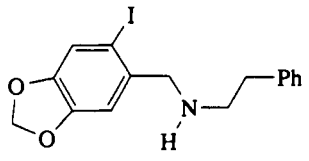

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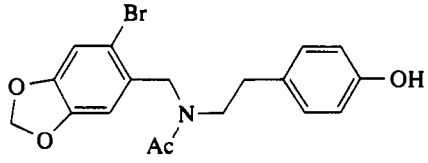

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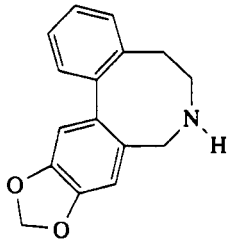

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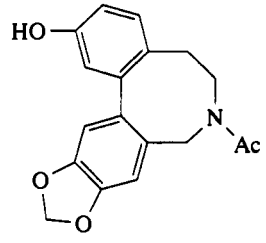


(131)

2.9.3 SYNTHESIS OF SPIRODIENONES

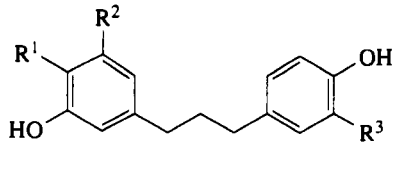
2.9.3.1 Spirodienones *via* Phenol–Phenol C—C Coupling

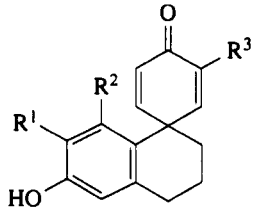
If, in an intramolecular phenolic coupling process, one of the preferred coupling sites (most usually *para* to OH) is already substituted, then a spirodienone product may form, and may be favored over coupling at another unsubstituted site. In practice good yields of spirodienones have often been isolated in such cases. Spirodienones are prone to undergo dienone–phenol rearrangement (see Chapter 3.5, Whiting, this volume) and occasionally reorganize under the reaction conditions; it is not always clear from products whether or not a dienone has intervened.

The clearest examples are suitably substituted 1,3-diarylpropanes. The 3,4′-dihydroxy compound (**132**) on treatment at –78 °C in ether with vanadium oxytrichloride yielded (75%) the tricyclic dienone (**133**),[88] and the methoxylated relatives (**134**) and (**135**) both cyclized in parallel fashion to (**136**) and (**137**), in 67% yield, using an iron(III) complex reagent.[89] The amide (**138**) formed the spiro-linked benzazepine (**139**; 50%) on oxidation with vanadium oxytrichloride,[90] showing that a seven-membered ring may form. Generation of five-membered rings is also satisfactory, as evidenced by the synthesis of picrolichenic acid (**140**) by manganese dioxide oxidation of the aryl ester (**141**), in 25% (max.) yield.[91]

These couplings are of major importance in the alkaloid area, where they may be biomimetic, and there has been a considerable quantity of work on the 1-benzyl- and 1-phenylethyl-tetrahydroquinoline alkaloids, which has been reviewed.[1,17,19]

One major preoccupation was the realization of a laboratory analogy for the intracoupling of relatives of reticuline (**142**) to the morphine group *via* *p–o* (4a–3′) linking. In various studies *p–p* coupling (4a–7′) and *o–p* (8–7′) of (±)-reticuline were achieved, leading to (±)-isosalutaridine (**143**) and (±)-isoboldine





(**132**) $R^1 = R^2 = R^3 = H$

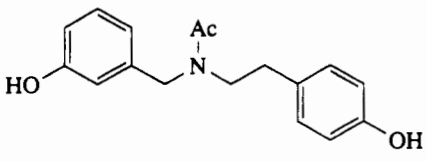
(**133**) $R^1 = R^2 = R^3 = H$

(**134**) $R^1 = R^2 = R^3 = OMe$

(**136**) $R^1 = R^2 = R^3 = OMe$

(**135**) $R^1 = R^3 = OMe$, $R^2 = H$

(**137**) $R^1 = R^3 = OMe$, $R^2 = H$



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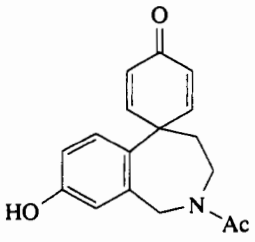

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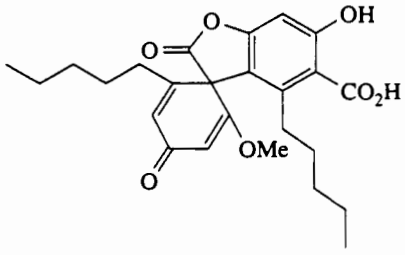

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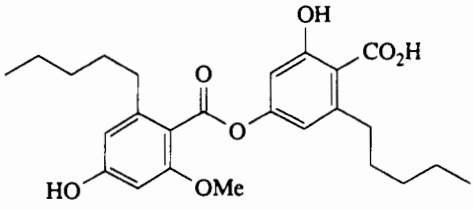
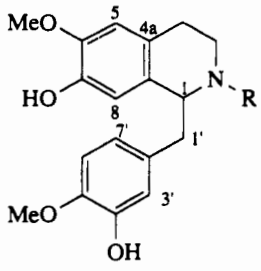
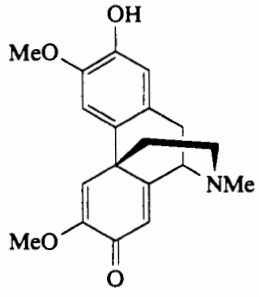


(141)

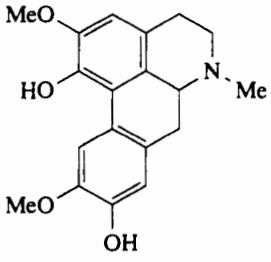
(**144**) respectively, in reactions of considerable biosynthetic interest, but little preparative value. The long-sought *p–o* linking (4a–3′) was eventually realized using thallium tristrifluoroacetate as oxidant at low temperature; in this way the *N*-ethoxycarbonyl relative (**145**) provided the spirodienone (**146**) in 23% yield.[92] Lithium aluminum hydride reduction gave alcohol (**147**), which closed in acid to (±)-thebaine (**148**).



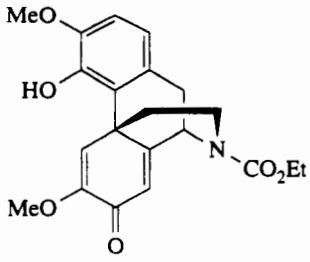
(**142**) R = Me
(**145**) R = CO_2Et



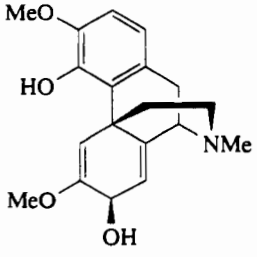
(**143**)



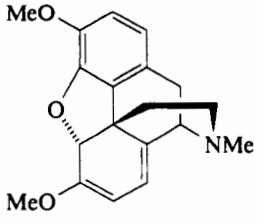
(**144**)



(**146**)

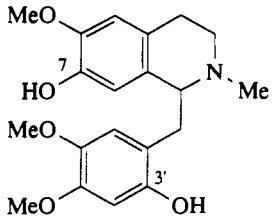


(**147**)

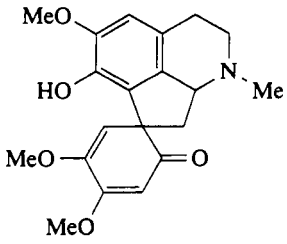


(**148**)

The (±)-benzyltetrahydroisoquinoline (**149**), with 3′,7- rather than 4′,7-dihydroxylation as in (**142**), was coupled[93] using potassium ferricyanide to the spiroketone (**150**), as a pair of diastereoisomers (up to 50% yield). One stereoisomer, on reduction of carbonyl and aqueous acid treatment, was converted to the new spirodienone (**151**), the alkaloid orientalone.



(149)



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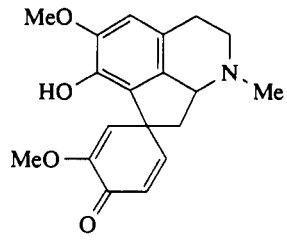
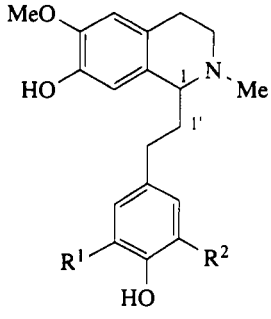
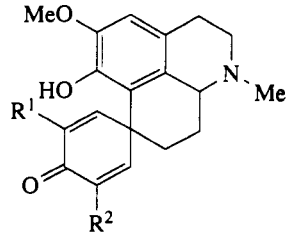


(151)

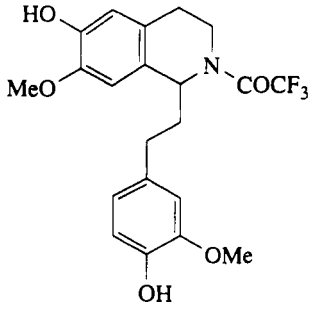
In the 1-arylethyltetrahydroisoquinoline series, the 6′,7-dihydroxy example (**152**) underwent *o–p* coupling (49%) with ferricyanide;[94] the product, (**153**), was rearranged into (±)-multifloramine (see Chapter 3.5, this volume). Similarly the dimethoxy analog (**154**) was oxidized to (±)-(**155**; two diastereomers), in 36% at a graphite anode,[95] and in 68% with vanadium oxytrifluoride;[68] one of the stereoisomers was kreysiginone. With a 6,6′-dihydroxy pattern, as in (**156**), *p–p* coupling was induced by the last named reagent to provide the spiro tetracycle (**157**).[68]



(**152**) $R^1 = R^2 = OMe$
(**154**) $R^1 = H$, $R^2 = OMe$



(**153**) $R^1 = R^2 = OMe$
(**155**) $R^1 = H$, $R^2 = OMe$



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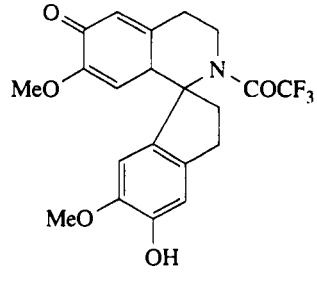
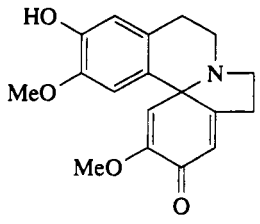


(157)

In a biomimetic synthesis of erysodienone (**158**), the bis(arylethyl)amine (**159**) was oxidized with alkaline ferricyanide to give the desired natural product in 35% yield.[96] The reaction probably involves *p–p* coupling, oxidation to the diphenoquinone (**160**), and intra-Michael addition; in support similar oxidation[97] of the bridged biaryl (**161**) also gave erysodienone, 80%. The key intermediate (**161**), both in *in vitro* and *in vivo* formation of (**158**), has also been prepared by oxidative coupling of the benzylisoquinoline (**162**) by vanadium oxytrifluoride at –10 °C. The product dienone (**163**; 40%) fragmented on base deacylation, and reduction of the product imine gave (**161**).[98]

The arylethylbenzylamine derivative (**164**) with one blocked *para* position was smoothly oxidized with alkaline ferricyanide to the spirodienone (**165**),[99] related to the Amaryllidaceae alkaloid system.

In recent work Kende and his coworkers[100] have explored intramolecular oxidative coupling between phenolate and enolate, rather than between two phenolates. This proved a viable process for certain carbonyl enolates, and for nitro-stabilized anions. Thus potassium ferricyanide oxidations of the indandione



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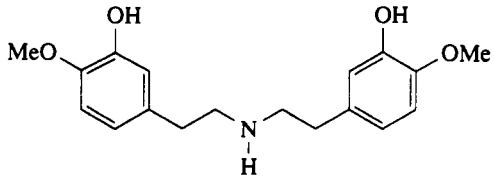

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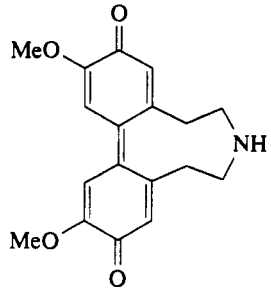

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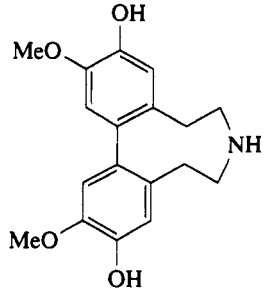

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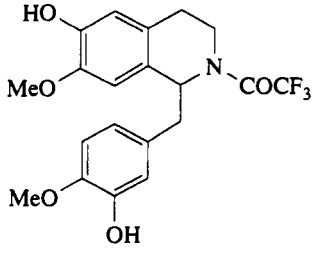

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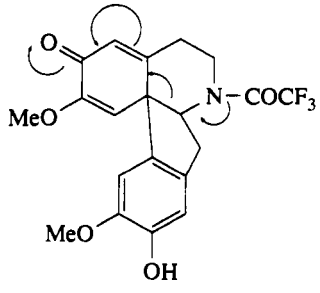
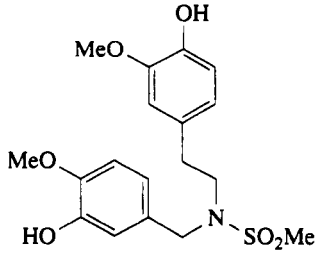


(163)

derivative (**166**) and 4-(ω-nitropentyl)phenol (**167**) gave the product spirodienones (**168**) and (**169**) in 88% and 83% yields respectively, while reaction of the coumarin (**170**) with dipotassium hexachloroiridate effected cyclization to (**171**; 33%).

For recent examples of intramolecular phenolic coupling to spirodienones, see refs. 164 and 165.



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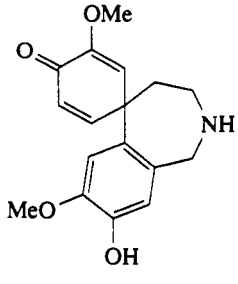

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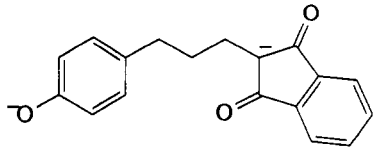

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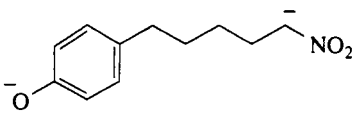

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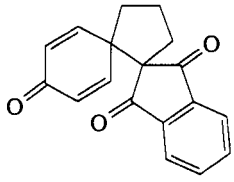

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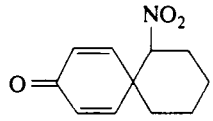

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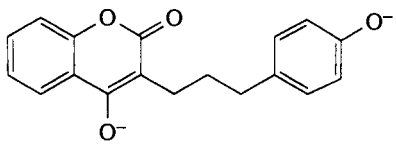

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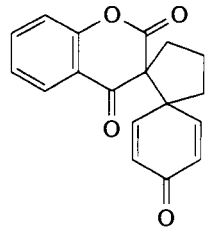
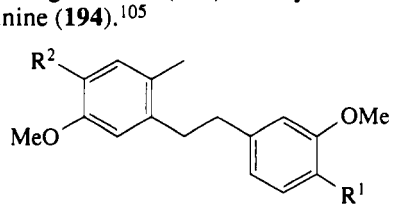


(171)

2.9.3.2 Cyclohexadienones *via* Phenol Ether Coupling

A number of interesting and useful reactions involve cyclization, forming six- to eight-membered rings, between the two aryl units separated by a short chain. Thus the bisarylethane (**172**) gave, on anodic oxidation, the tricyclic dienone (**173**) in 90% yield, arising from intracoupling followed by 1,2-shift.[101] Similarly the analog (**174**) afforded dienone (**175**; 98%), using silica-supported iron(III) chloride as oxidant.[52] The 1,2-shift was not observed with the example (**176**) with monooxygenated aryls, which gave the steroidal tricycle (**177**) at the anode (22%) or on reaction with vanadium oxytrifluoride (30%). With suitably substituted diarylpropanes formation of a spirodienone is feasible. Thus vanadium oxytrichloride treatment of (**178**) led to tricyclic spirodienone (**179**; 70%);[90] only 18% of the dibenzocycloheptadiene alternative (**180**) was formed. The parallel monophenolic coupling (**181**) → (**179**)[90] was also effected at –78 °C with the same reagent (97% yield); also, both thallium and silver trifluoroacetates induced the coupling. Such monophenolic coupling, using electrooxidation, was employed for transformation[102] of the biarylpropane (**182**) into the spirodienone (**183**; 80%); the latter was subjected to cyclopropanation, followed by fragmentation and ring expansion to the tropolone (**184**), a key intermediate in a colchicine synthesis. Another example involves monophenolic coupling in the acetal (**185**) using bistrifluoroacetyloxyiodobenzene;[103] the product (**186**), only obtained in 13% yield, was converted on to 6a-epipretazettine.

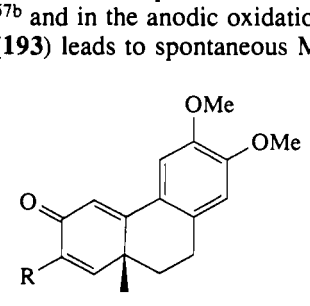
An original biomimetic synthesis[104] of the Amaryllidaceae alkaloid narwedine involved oxidation of the arylethylbenzylamine (**187**) with lithium tetrachloropalladate to generate the arylpalladium species (**188**); the course of further oxidation with thallium tristrifluoroacetate could be controlled to lead either to the bisspirodienone complex (**189**; 1′–1″ coupling) or to narwedine (**190**; 51%; 1′–2″ coupling). Seven-membered rings were also formed in the monophenolic oxidation of (**191**; vanadium oxytrifluoride–thallium tristrifluoroacetate, 88%)[57b] and in the anodic oxidation (62%) of (**192**),[105] in both cases yielding dienone (**193**). Deacylation of (**193**) leads to spontaneous Michael addition, forming (±)-oxocrinine (**194**).[105]



(**172**) $R^1 = R^2 = OMe$

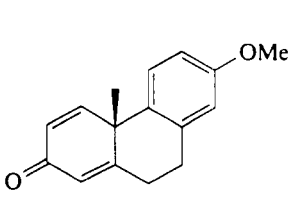
(**174**) $R^1 = OMe$, $R^2 = OEt$

(**176**) $R^1 = R^2 = H$

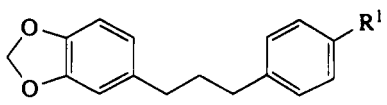


(**173**) R = OMe

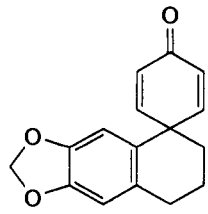
(**175**) R = OEt



(**177**)



(178) R^1 = OMe
(181) R^1 = OH



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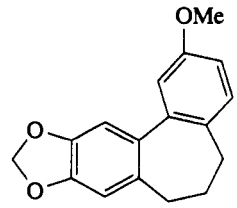

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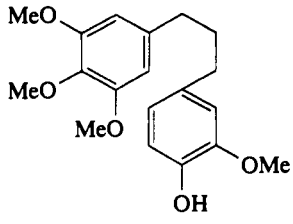

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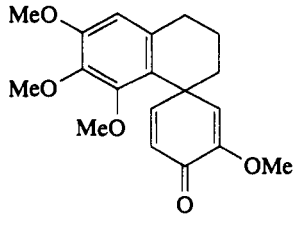

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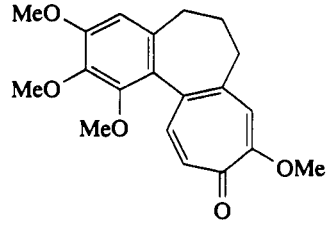
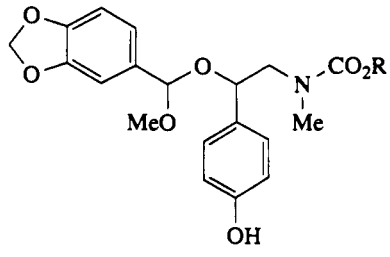
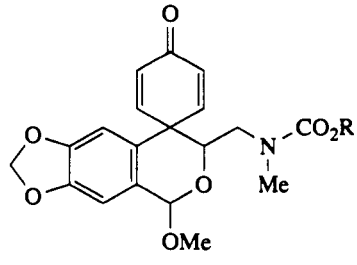


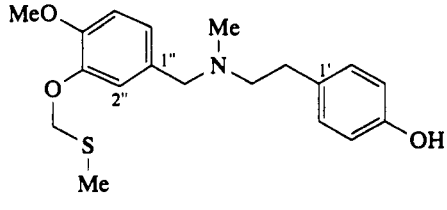
(184)



(185)



(186)



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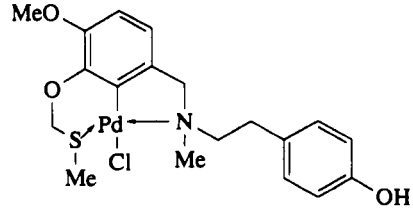

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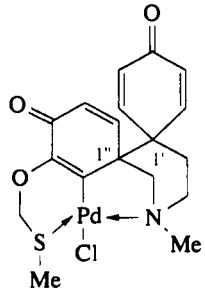

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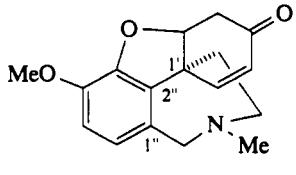

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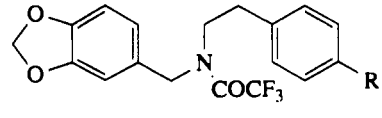
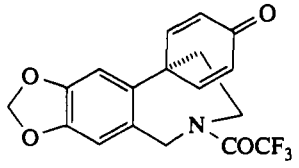


(191) R = OH
(192) R = OMe



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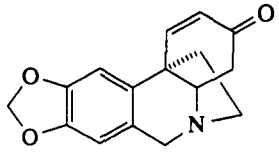
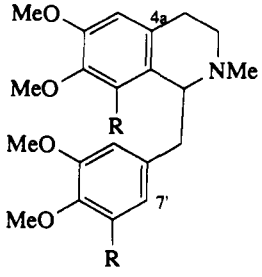
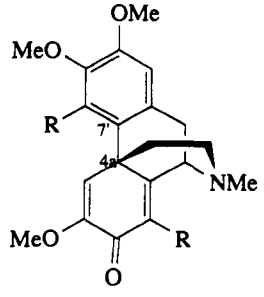


(194)

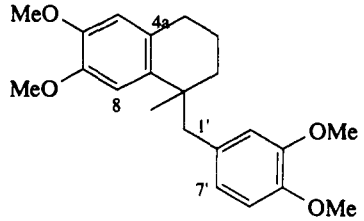
Benzyltetrahydroisoquinolines have been thoroughly investigated for reasons discussed above. (±)-Laudanosine (**195**) was oxidized at a platinum anode to yield methylflavinantine (**196**) in 52% yield[106] (4a–7′ coupling), and a similar reaction proceeds with a number of relatives including 6′,8-dimethoxylaudanosine (**197**), which provided protostephanone (**198**; 35%).[107] An enantioselective synthesis of (*R*)-laudanosine enabled preparation of (*R*)-methylflavinantine by anodic oxidation,[108] with reported yields 70–90%. Various analogs of the benzylisoquinoline system have been examined. Among these, oxidative coupling of the benzyltetralin (**199**) is of interest;[63] varying the conditions of anodic oxidation, *i.e.* solvent, temperature and pH, it was found possible to obtain either the dienone (**200**; 4a–7′ coupling, 71%) or the biaryl (**201**; 7′–8 coupling, 45%). The benzyl lactone (**202**) was electrooxidized to the spirolactone



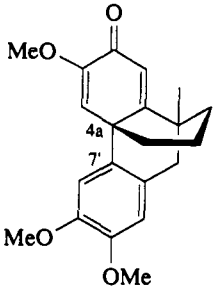
(**195**) R = H
(**197**) R = OMe



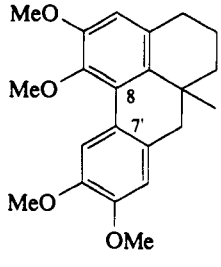
(**196**) R = H
(**198**) R = OMe



(**199**)



(**200**)



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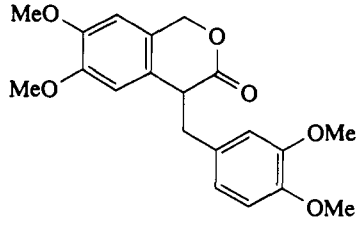

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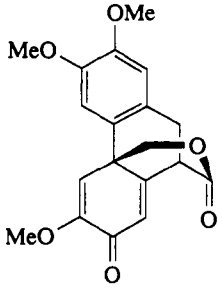

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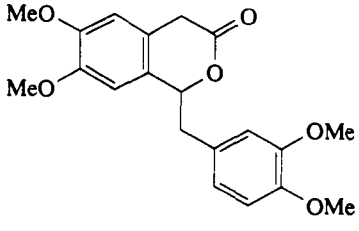

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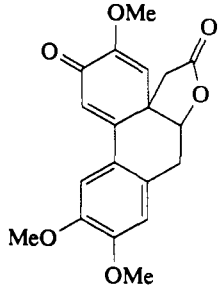

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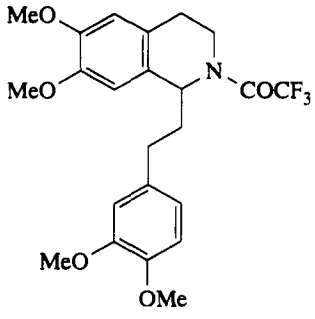

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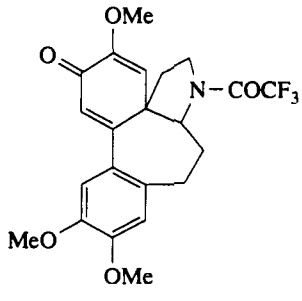
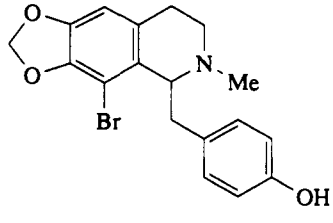


(207)

(203),[78] in parallel with the last two cases, but the isomeric lactone (**204**) afforded a rearranged spirolactone (**205**),[109] both with vanadium(V) reagents (59%) and at the anode (33%). The arylethylisoquinoline (**206**) also afforded a similarly rearranged spirodienone (**207**; 64%), on intracoupling, using vanadium oxytrifluoride.[68]

2.9.3.3 Spirodienones *via* Aryl Radical Insertion

Two examples suffice to illustrate this reaction type, both involving 1-benzyltetrahydroisoquinolines. The 8-bromo structure (**208**) was photolyzed under alkaline conditions to (±)-mecambrine (**209**), in 10% yield,[81] and the 7′-bromo relative (**210**) afforded dienone (**211**), 34% isolated, on the way to synthesis of (±)-boldine.[110]



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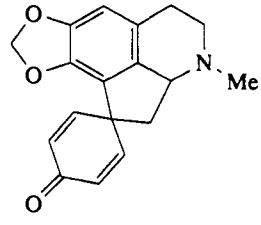

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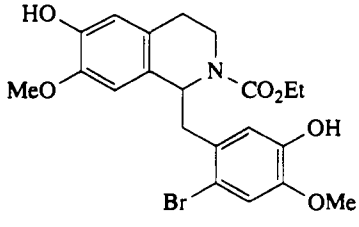

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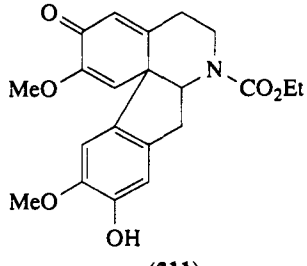


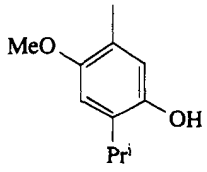
(211)

2.9.4 FORMATION OF CARBON–OXYGEN BONDS

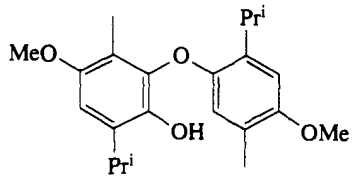
2.9.4.1 Synthesis of Aryl Ethers

An early example[111] was the surprisingly selective oxidation of methoxythymol (**212**) with alkaline ferricyanide to libocedrol (**213**; 49%); further cross-coupling of the latter with more monomer using the same reagent yielded (46%) the trimeric libocedroxythymoquinone (**214**; 46%). Lophocerine (**215**) also formed a dimer, isopilocereine (**216**; 32%), on exposure to ferricyanide, together with traces of the

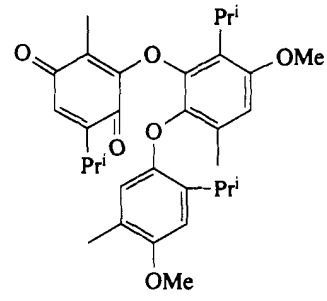
trimeric pilocerine (**217**).[112] Magnocurarine methiodide (**218**) was similarly dimerized (15%) to the model (**219**) for certain dimeric benzylisoquinoline alkaloids;[113] and in the same series, phenol (**220**)[44] was coupled at a graphite anode to a product which was transformed by *O*-protection, reduction, and deprotection to (±)-dauricine (**221**), 8% overall. Yet another benzylisoquinoline (**222**) gave the unusual macrocyclic dehydrodimer (**223**) on treatment with diphenyl selenoxide[48] followed by permethylation.



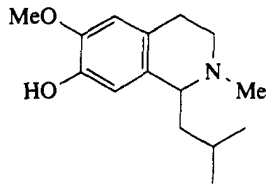
(**212**)



(**213**)



(**214**)



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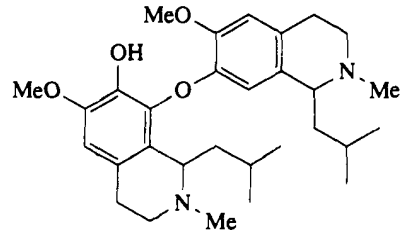
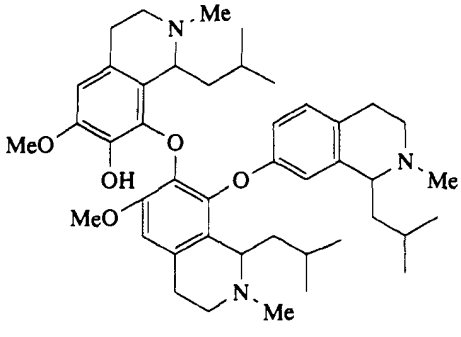


(**216**)



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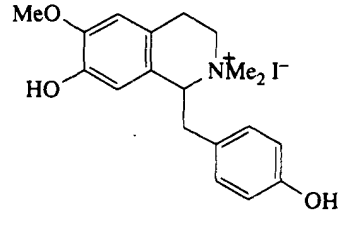

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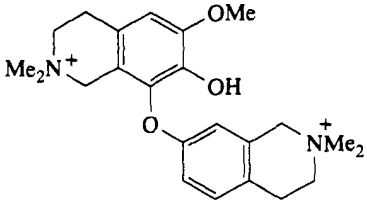

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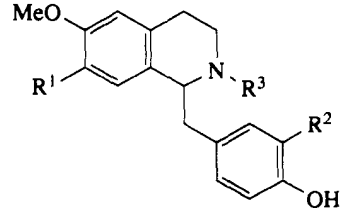
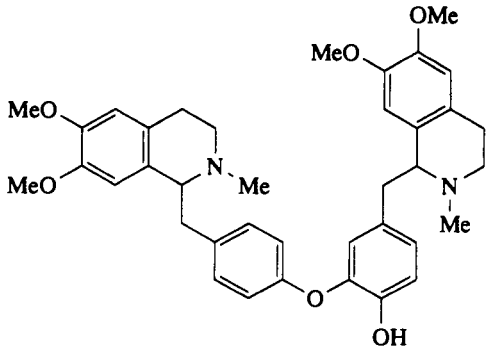


(**220**) R^1 = OMe, R^2 = H, R^3 = CO_2Et

(**222**) R^1 = R^2 = OH, R^3 = $COCF_3$



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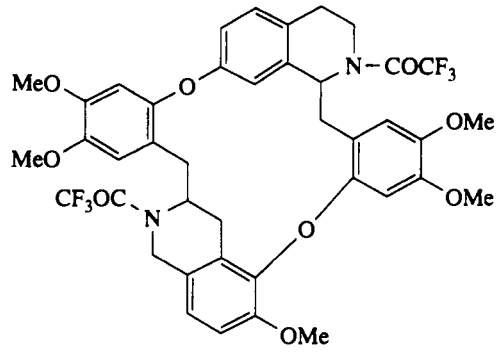
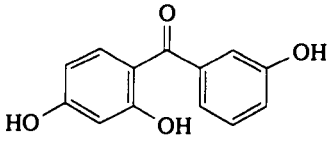
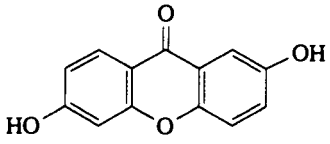


(223)

A number of intramolecular variations are documented, some of biogenetic interest. The benzophenone (**224**) was cyclized in good yield (83%) to 2,6-dihydroxyxanthone (**225**) with ferricyanide,[114] and the synthetic depside (**226**) yielded diploicin (**227**) on manganese dioxide oxidation.[115] Finally the diarylheptanoid (**228**) afforded the macrocyclic ether (**229**) on reaction with thallium tristrifluoroacetate; similar ethers, *e.g.* acerogenin, occur naturally.[116]



(224)



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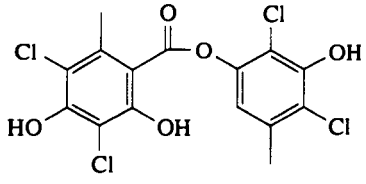

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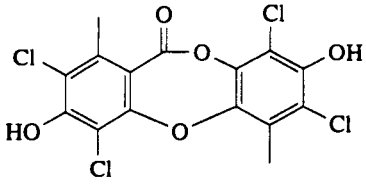

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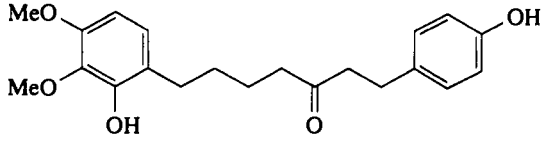
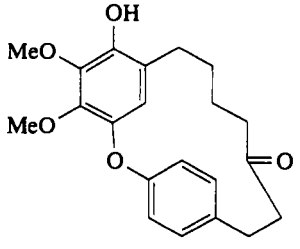


(228)

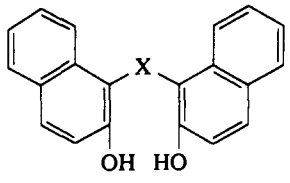


(229)

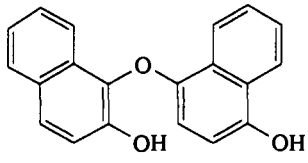
2.9.4.2 Spiroethers

Ring systems containing cyclohexadienones spiro-linked to a cyclic ether can be constructed by oxidative C—O bond connection in the intramolecular mode. Five-membered ring formation is well documented, and the reactions may be efficient. For example, the linked bisnaphthols (**230**), (**231**) and (**232**)

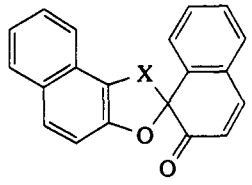
formed spirodienones (**233**),[117] (**234**)[117] and (**235**)[118] on treatment with sodium hypochlorite (*ca.* 60% yield), alkaline ferricyanide (60%), and dichlorodicyanobenzoquinone ('quantitative'), respectively. A well-known reaction in this area is the oxidation of griseophenone A (**236**) to dehydrogriseofulvin (**237**),[119] which has been induced with various reagents, potassium ferricyanide, lead dioxide and manganese dioxide, and quantitative yields have been reported. Copper(II) salt–amine complexes are also effective[120] and, using (–)-α-phenylethylamine, dehydrogriseofulvin with a small enantiomeric excess was obtained. The oxygen atom participating in C—O bond formation may derive from a function other than phenol. Thus the arylpropanoic acids (**238**) and (**239**) gave the spirodienones (**240**) and (**241**) at a platinum anode, in modest yield, while the acid (**242**) yielded (**243**; 40%), with buffered *N*-bromosuccinimide.[121] In view of the disparity between oxidation potentials of the interacting functions it is unlikely that these reactions involve radical–radical coupling. The same is true for the oxidative cyclization of phenolic oximes, *e.g.* (**244**) to the spirooxazoline (**245**; 62%), using manganese(III) acetylacetonate.[122] The reaction, a model for the biosynthesis of aerothionin, probably proceeds *via* an incipient phenoxonium ion (see Scheme 3).



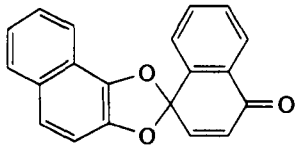
(**230**) X = CH_2
(**231**) X = S



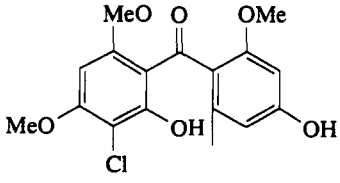
(**232**)



(**233**) X = CH_2
(**234**) X = S



(**235**)



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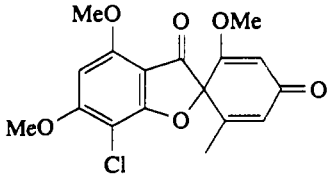
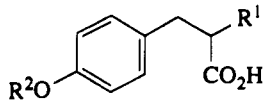
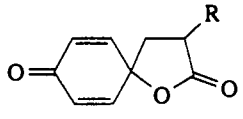


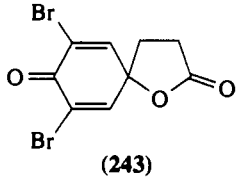
(**237**)



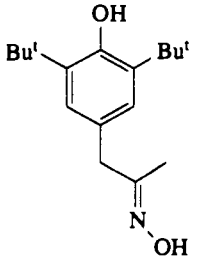
(**238**) $R^1 = R^2 = H$
(**239**) $R^1 = NHCO_2Me$, $R^2 = H$
(**242**) $R^1 = H$, $R^2 = Me$



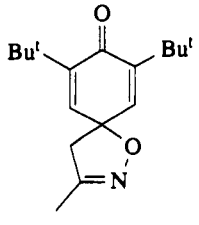
(**240**) R = H
(**241**) R = $NHCO_2Me$



(**243**)



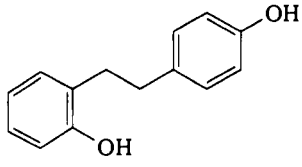
(**244**)



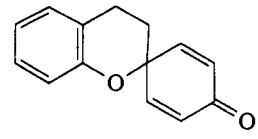
(**245**)

Few examples, in this class, of phenol–phenol coupling generating six-membered rings, are available: the bisarylethane (**246**) gave (**247**) only in 11% yield.[123] However biomimetic oxidation of phenolic

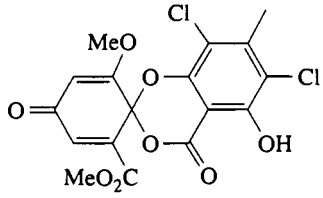
acids offers several high yielding examples, *e.g.* the formation of geodoxin (**248**) from geodin (**249**),[124] employing lead dioxide, 88% yield; and the oxidation of the acid (**250**) to dehydrogriseofulvoxin (**251**), 85% with manganese dioxide.[114] A striking case of successful intramolecular coupling[125] is the formation of the 17-membered cyclic ether (**252**) from the phenolic tripeptide (**253**) on oxidation with thallium trinitrate in methanol. Presumably a dibromospirodienone is formed, which suffers allylic displacement of bromine by methanol. Dienone ether (**252**) was transformed into the cyclic bisaryl ether peptide (**254**), an aminopeptidase inhibitor.



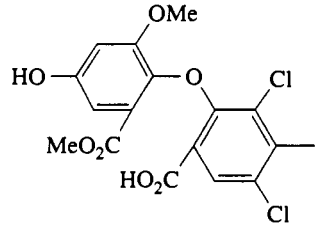
(**246**)



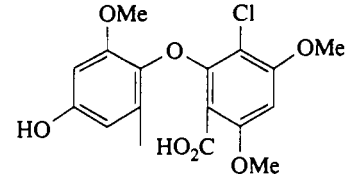
(**247**)



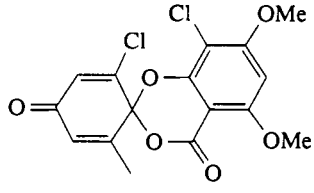
(**248**)



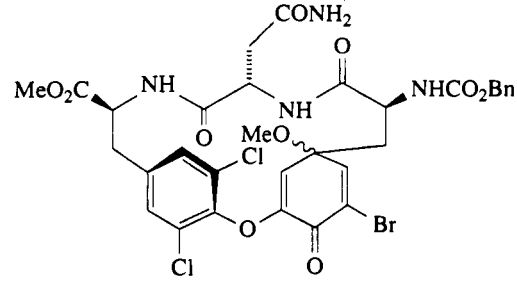
(**249**)



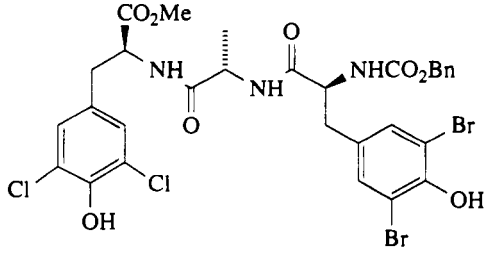
(**250**)



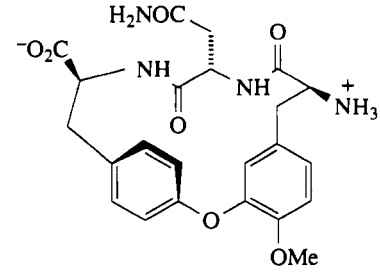
(**251**)



(**252**)



(**253**)

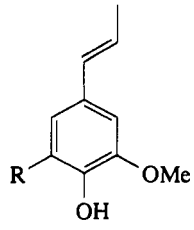


(**254**)

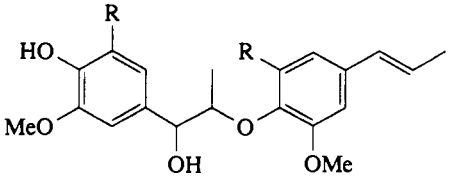
2.9.4.3 Aryl Alkyl Ethers *via* C—O Coupling

Two useful groups of related reactions may be discerned here, both of which are observed for propenyl-phenols. The first type is illustrated by the oxidation of isoeugenol (**255**) with aqueous iron(III) chloride,[126] which yields the *threo*- and *erythro*-stereomers (55%) of the hydroxy ether (**256**), presum-

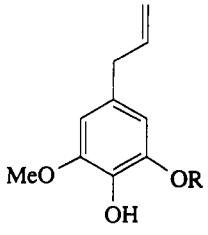
ably by O—C_β linking of the initial phenoxyl radical, and addition of water to the resulting intermediate quinone methide. A similar reaction[127] of the phenol (**257**), but using silver oxide, provided (**258**), isolated (62%) as a monomethyl ether; *threo*-(**258**) was (±)-virolin. Cross-coupling is also possible in an efficient manner; thus silver oxide treatment of a mixture of the propenylphenol (**255**) and the allylphenol (**259**; R = Me) yielded[127] an intermediate quinone methide which was reduced *in situ* and methylated to afford the neolignan (**260**), overall in 80% yield. Cross-coupling of (**259**) with (*Z*)-isoeugenol at a platinum anode gave stereoisomers of the ether (**261**; 34%).[128] Related examples are known.[129–131] It has been demonstrated[127] that oxidation of the allylphenol (**259**) with silver oxide in the absence of other phenols or nucleophiles yielded, in solution, the relatively stable quinone methide (**262**); addition of nucleophiles, *e.g.* *p*-methoxyphenol, proceeded smoothly to give ether (**263**), 71% overall.



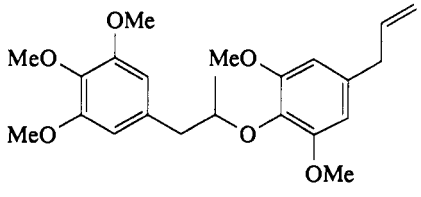
(**255**) R = OMe
(**257**) R = H



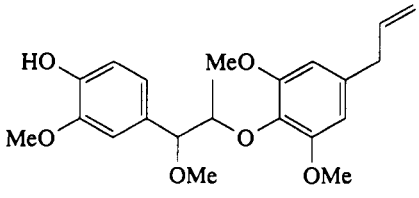
(**256**) R = OMe
(**258**) R = H



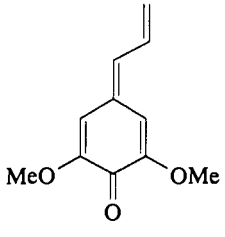
(**259**)



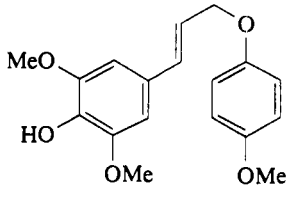
(**260**)



(**261**)

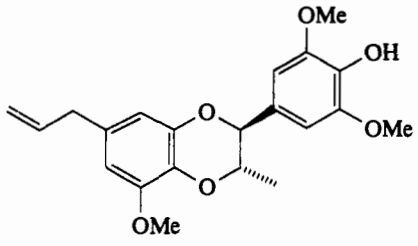


(**262**)



(**263**)

If, in this type of reaction, a suitable catechol component is present, then the major products may be benzodioxanes, *e.g.* silver oxide treatment (benzene, r.t.) of a mixture of propenylphenol (**255**) and allylphenol (**259**; R = H), gave the (±)-product (**264**)[132] in 'good yield', which on methylation formed the neolignan eusiderin. Coumarinolignans have been synthesized in a parallel way, *e.g.* cross-coupling[133] of fraxetin (**265**) with coniferyl alcohol (**266**) using silver oxide or horseradish peroxidase, leads to both cleomiscosin A (**267**) and its regioisomer (**268**), cleomiscosin B. Other members of this class, *i.e.* propacin, aquillochin, and daphneticin were prepared in parallel fashion. The interesting antihepatotoxic flavonolignan silybin (**269**) was obtained from (2*R*,3*R*)-dihydroquerctin (**270**) and coniferyl alcohol; again the regioisomer, isosilybin (**271**), was also produced.[134] These natural products occur as mixtures of stereoisomers, all (2*R*,3*R*) in the chromanone unit but differing in the geometry of the benzodioxane section. The same coupling may be effected enzymically,[135] and peroxidases induce coupling in other vinyl catechols.[136]



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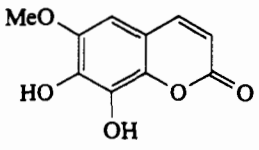

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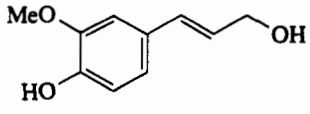

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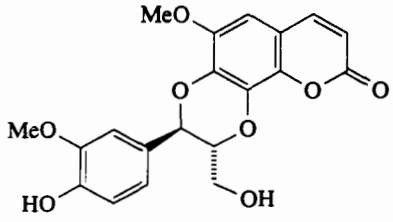

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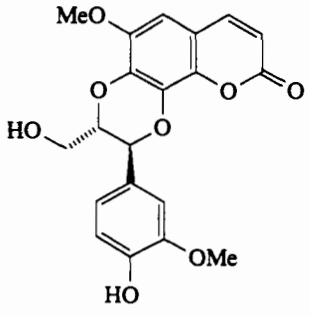

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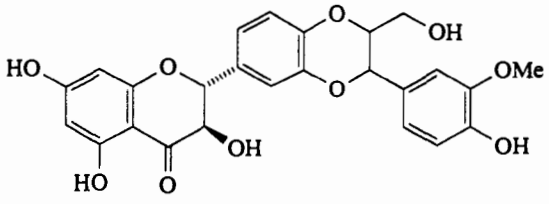

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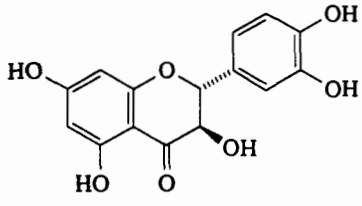

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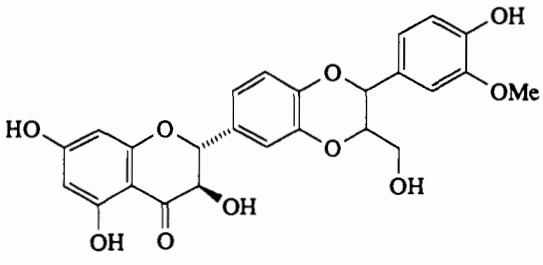


(271)

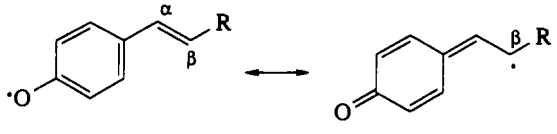
2.9.5 C—C COUPLING THROUGH ARYL CONJUGATED DOUBLE BONDS

In structures which contain an *o*- or *p*-hydroxystyryl subunit, the radical from phenolic oxidation is delocalized through the aromatic ring and the side chain (**272**), and couplings may thus involve the β-carbon. The charted reactions which fall into this class can be subdivided into three sets, with products derived from: (i) C_β—C_β coupling; (ii) C_β—C_{AR} coupling; and (iii) both modes of coupling.

In the first category the best known cases are those in which a hydroxycinnamic acid is dimerized oxidatively to a bisaryldilactone. A range of examples are known.[137] Typical reactions are the oxidation of sinapic acid (**273**) to the dilactone (**274**), in 65% yield using oxygen–iron(III) chloride,[138] and in 60%

yield using a high acid concentration at a glossy carbon anode,[139] and the oxidation of ferulic acid (**275**) to 'dehydrodiferulic acid' (**276**), with iron(III) chloride–air (22%)[140] and with a iron(III) chloride–dimethylformamide reagent.[89] A range of nonphenolic cinnamic acids have been oxidized with thallium tristrifluoroacetate–boron trifluoride to dilactones analogous to (**274**);[141] a nonradical mechanism is preferred whose key step is shown in cipher (**277**). If a *p*-hydroxycinnamate ester is employed, rather than acid, then C_β—C_β coupling can be followed by trapping of quinone methide intermediates with water, as in the formation of the tetrahydrofuran (**278**) from methyl dibromoferulate (**279**), with iron(III) chloride in aqueous acetone.[142] One stereoisomer of the diester (**278**) was obtained, albeit in modest yield; further reduction steps gave the lignan (±)-veraguensin. *p*-Hydroxycinnamyl alcohols can be oxidized to bisaryldioxabicyclo[3.3.0]octanes, *e.g.* syringin (**280**) is both hydrolyzed and oxidized by crude almond emulsion to (±)-syringaresinol (**281**), in up to 68% yield.[143] A cross-coupling between ferulic acid and coniferyl alcohol was used to synthesize, in low yield but in one step, the (±)-natural lactone (**282**).[144] Propenylphenols may also be induced to undergo C_β—C_β coupling, *e.g.* the phenol (**283**) on electrooxidation in methanol[128] afforded the cyclic ether (**284**; 47%), as well as some primary coupled product (**285**; 16%).

The formation of C_β—C_{AR} bonds is illustrated by the generation of 'dehydrodiisoeugenol' (**286**) from (*E*)-isoeugenol (**257**), enzymically with a mushroom juice[145] (45%) yield, with horseradish peroxidase (65%),[130] with iron(III) chloride[146] (53%), by photooxidation (20%)[129] and by (–)-α-phenylethylamine–copper(II) nitrate (21%). In the last case a low enantiomeric excess was recorded.[120b] Coniferyl alcohol can be oxidized to 'dehydrodiconiferyl alcohol' (**287**) with various enzyme oxidases.[147–149] The *cis*



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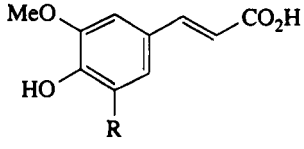
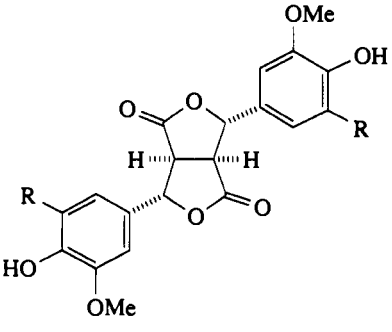
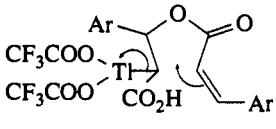


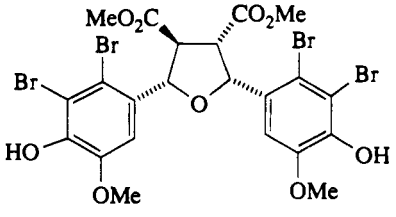
(**273**) R = OMe
(**275**) R = H



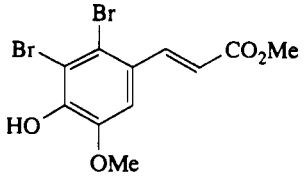
(**274**) R = OMe
(**276**) R = H



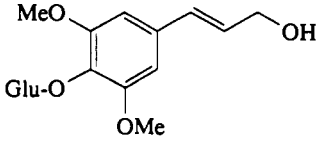
(**277**)



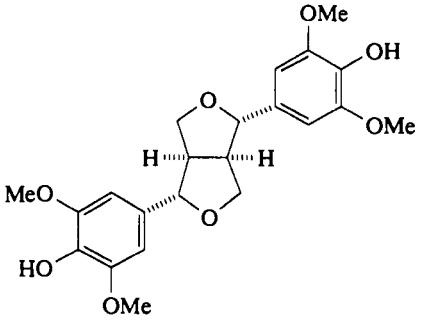
(**278**)



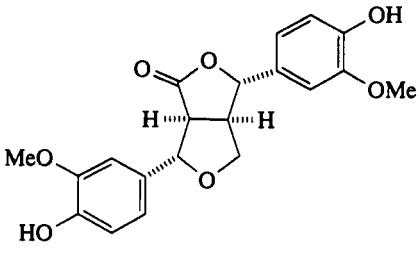
(**279**)



(**280**)



(**281**)



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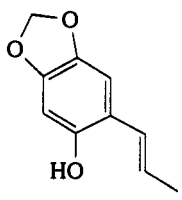

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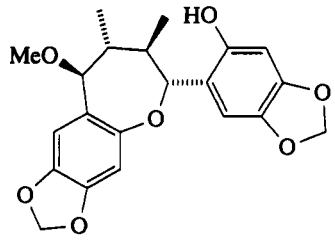

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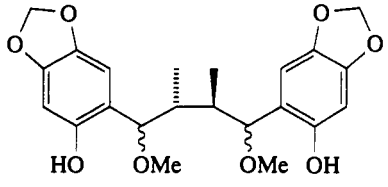
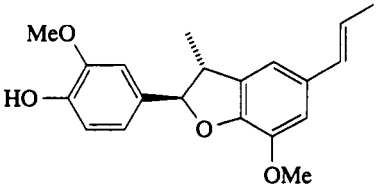


(285)

stereochemistry, for the dihydrobenzofuran ring substituents, was specifically formed in one case.[148] When horseradish peroxidase was used in a reaction mixture saturated with β-cyclodextrin, it is claimed[149] that the product was formed enantiospecifically. Sensitized photooxidation of methyl ferulate[150] afforded a related 2-aryldihydrobenzofuran (**288**).[150]

An unusual C_β—C_{AR} coupling was observed on anodic oxidation, in acetic and trifluoroacetic acids, of a mixture of (*E*)-isosafrole (**289**) and the allylphenol (**290**).[151] Various interesting products were characterized, among them the cyclohexadienone (**291**). Although only formed in 4% yield, this product was readily converted by successive alkali and acid reactions, into the neolignan derivative denudatin A (**292**).



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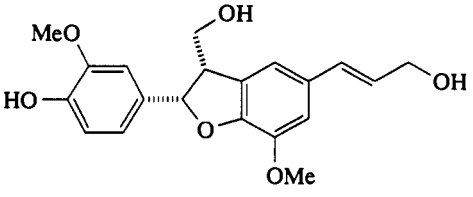

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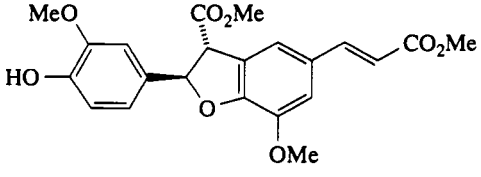

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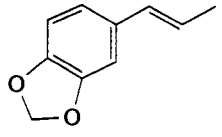

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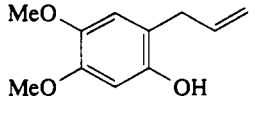

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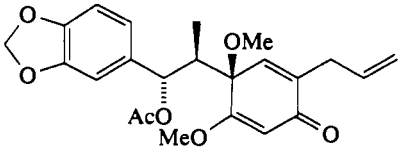

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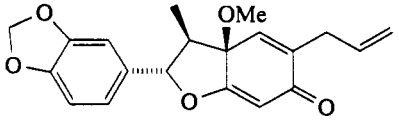

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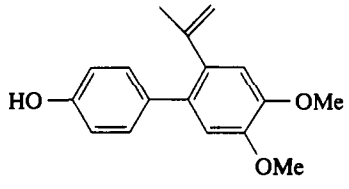
Intramolecular C_β—C_{AR} couplings have been observed in the anodic oxidation of a series of 4-hydroxy-2-vinylbiphenyls, (*e.g.* **293**),[152] which afforded the corresponding spirodienones (*e.g.* **294**; 92% from **293**). Another C_β—C_{AR} linkage resulted from the brief oxidation of the dihydrocinnamyl cinnamate (**295**) with thallium tristrifluoroacetate–catalytic boron trifluoride (water-quench), when the eight-membered lactone (**296**) was formed.[79]

There has been much interest in the synthesis of lignan lactones of the aryl tetralin type, induced by the antitumour activity of podophyllotoxin relatives, and some short oxidative routes into the series have been pursued. In a typical reaction, in which both C_β—C_β and C_β—C_{AR} couplings occur, the cinnamyl cinnamate (**297**) was treated for 30 s with chromium trioxide–fluoroboric acid in acetonitrile.[153] Three tetracyclic products were obtained, the lactones (**298**; 19%) and (**299**; 7%), and (±)-isopodophyllotoxone



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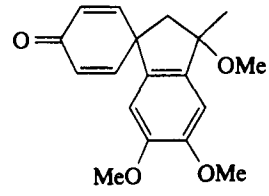

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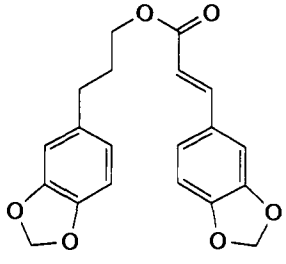

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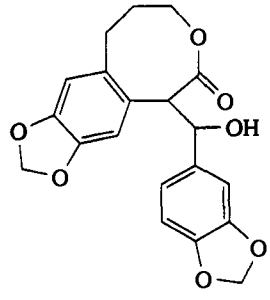

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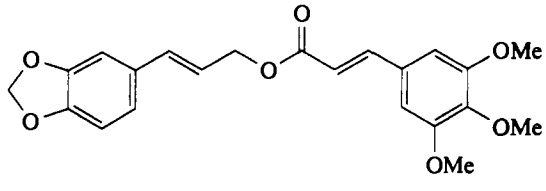

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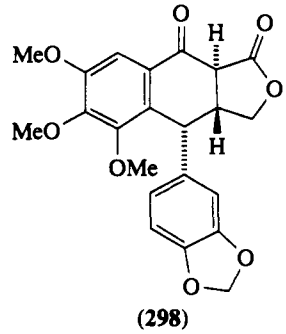

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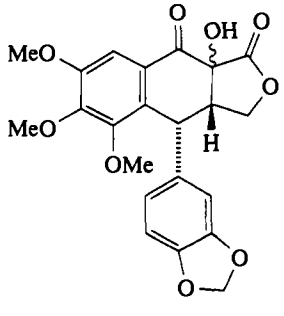

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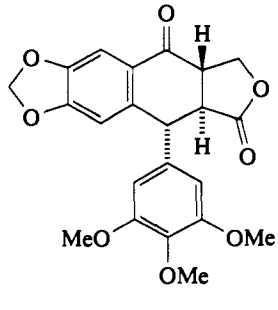

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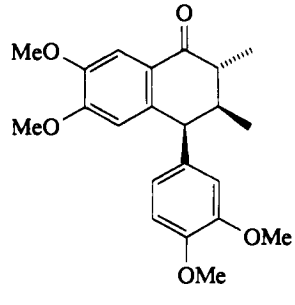


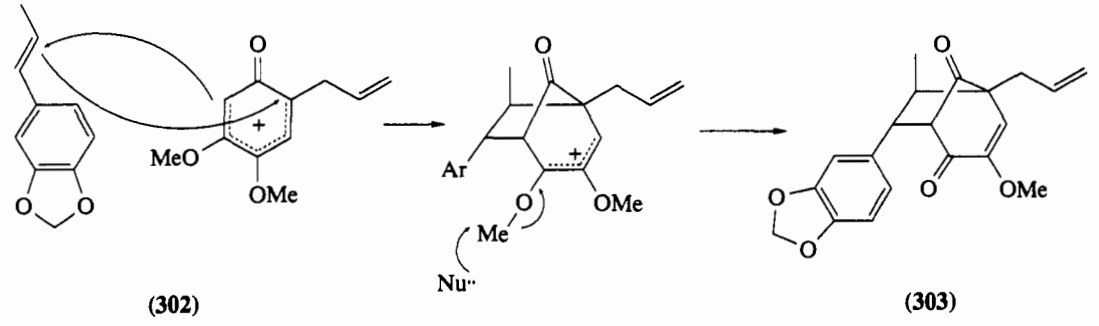
(301)

(**300**; 16.3%), which was epimerized (80%) to the *cis* ring fused natural isomer (±)-picropodophyllone. The same reagent converted *O*-methylisoeugenol (3,4-dimethoxyphenyl-1-propene) directly into the tetralone (**301**; 16%), which on deoxygenation gave the lignan (±)-galbulin.[154]

2.9.6 MISCELLANEOUS OXIDATIVE COUPLINGS

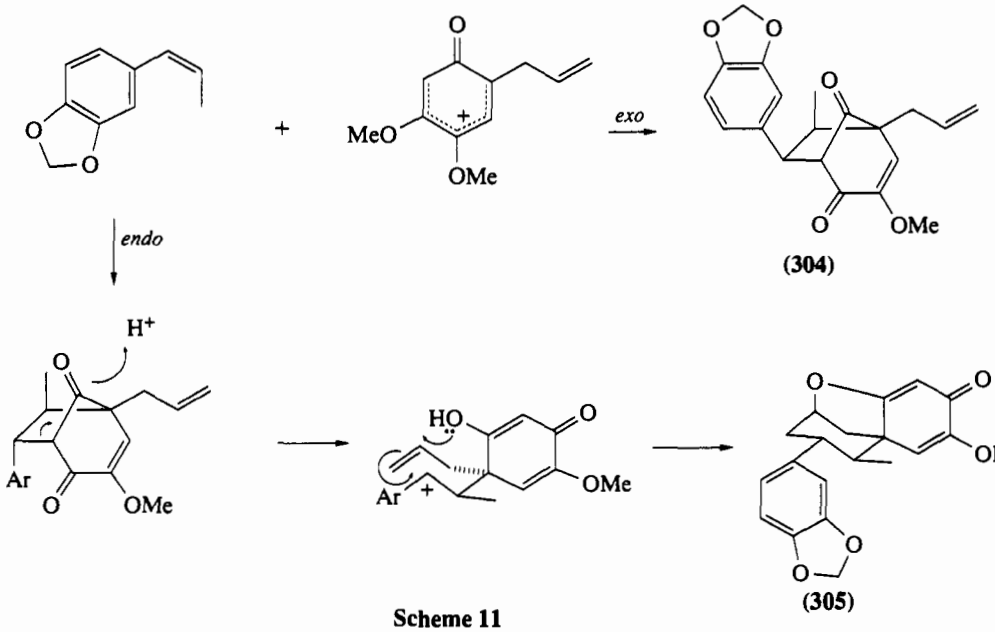
2.9.6.1 Couplings Involving Cycloadditions

The anodic coupling of (*E*)-isosafrole (**289**) and the allylphenol (**290**), in acidic medium was discussed above (see Section 2.9.5). The reaction took a different course under less acidic conditions (methanol–acetic acid) as illustrated in Scheme 10.[151] Two single-electron transfers from the phenol lead to the phenoxonium cation (**302**), which underwent [3 + 2] cycloaddition with the electron-rich alkene; demethylation of the product cation gave the neolignan (**303**; 81%), which occurs naturally in an *Aniba* species. (*E*)-Isosafrole could be replaced by a protected 4-hydroxy-3-methoxyphenylpropene, to form analogous compounds. Using (*Z*)-isosafrole in the reaction, and adding trifluoroacetic acid to the medium, led to isolation of two products, the stereoisomer (**304**) of the *Aniba* neolignan (**303**), and futoene (**305**; 15%), another unusual neolignan. As shown in Scheme 11, the former product arose from *exo* [3 + 2] cycloaddition, while futoene probably was formed by acid-catalyzed rearrangement of the initial *endo* cycloadduct.[151]



(**302**) (**303**)

Scheme 10

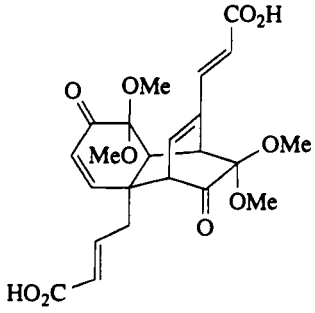


(**304**) (**305**)

Scheme 11

The electrooxidations of allyl- and propenyl-phenols may follow even more different pathways leading to a rich diversity of products. At a carbon anode in methanol–lithium perchlorate, ferulic acid formed the tricyclic diacid (**306**; *cf.* Section 2.9.5), in a concentration-dependent process[139] probably involving [4 + 2] dimerization of the primary oxidation product, the dienone acetal (**307**).

The allyl phenol (**259**; R = Me) at a platinum anode in methanol–sodium methoxide, gave a C—O coupled major product (see Section 2.9.4.3), but in aqueous methanol–sodium bicarbonate the adduct (**308**; 23%) was formed, by a cycloaddition mechanism whose course is not entirely clear, with a trace of the natural dione asatone (**309**).[131] The constitution of asatone suggests that it originates in [4 + 2] dimerization of the *o*-quinone acetal (**310**), and, in support, electrolysis of (**259**; R = Me) in neutral methanol gave acetal (**310**) which spontaneously dimerized at room temperature to asatone.[155] Further heating together of the quinone acetal (**310**) and asatone (**309**) gave the natural sesquilignans heterotropantrione (**311**) and isoheterotropantrione (**312**) by a further Diels–Alder process.[156] Bisdemethoxyasatone (**313**) can be prepared from 4-allyl-2-methoxyphenol (**16**), and on irradiation in hexane afforded demethoxyisoasatone (**314**) by [2 + 2] cycloaddition in the mode indicated.[38]



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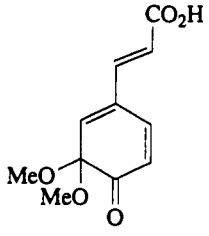

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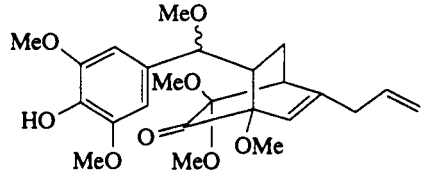

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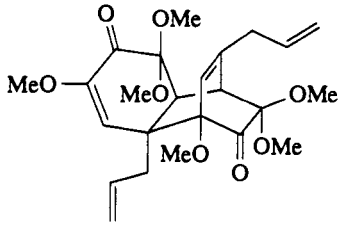

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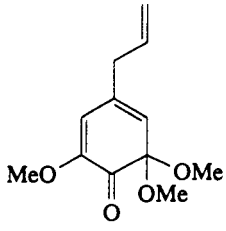

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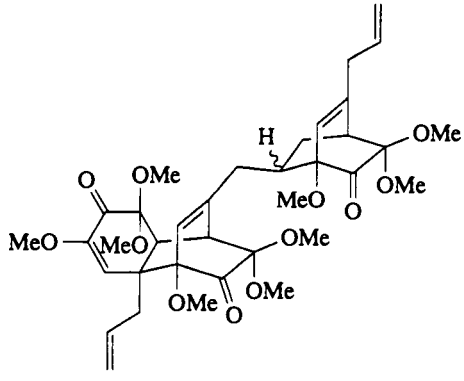
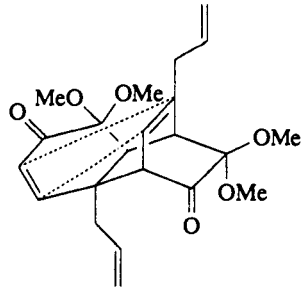


(311) β-H
(312) α-H



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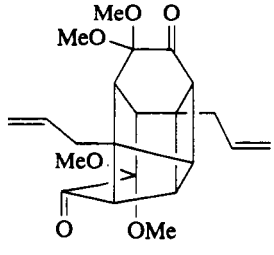
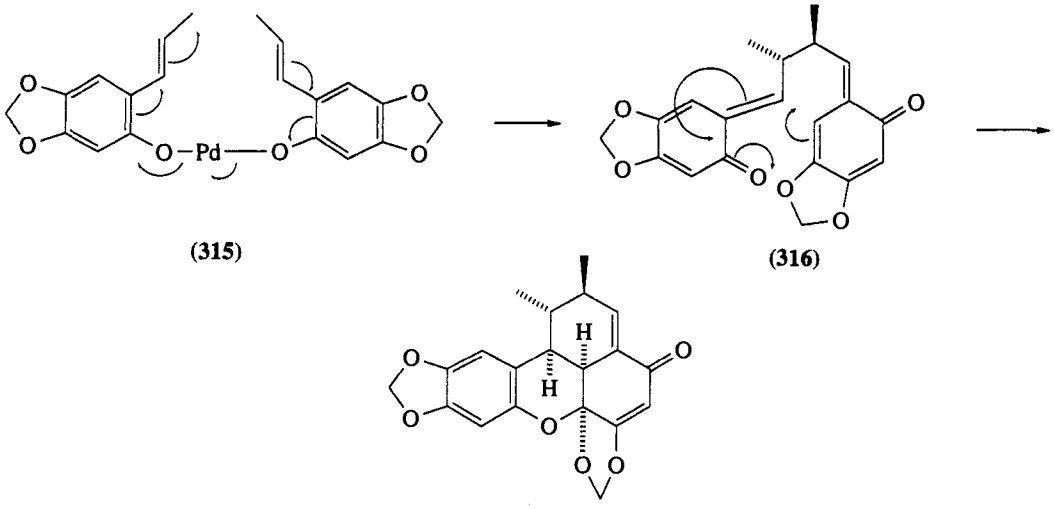


(314)

The methylenedioxypropenylphenol (**283**) undergoes another form of oxidative dimerization on treatment with palladium(II) chloride in aqueous methanol with sodium acetate. As shown in Scheme 12,

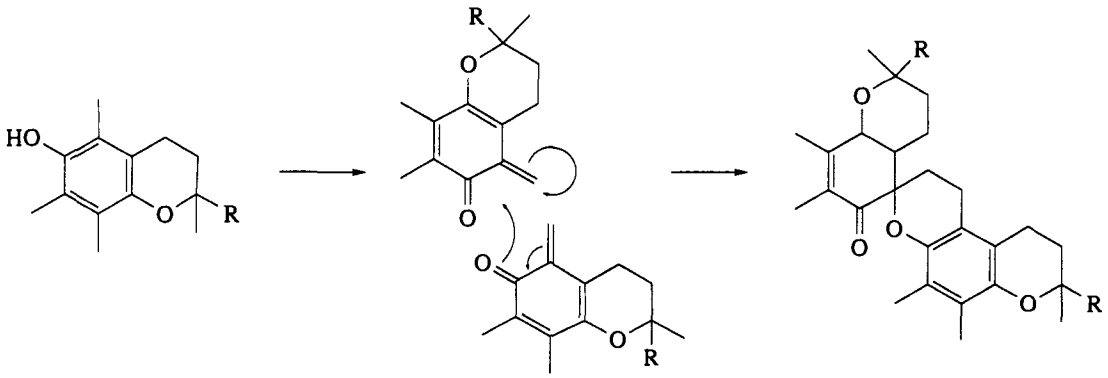
C_β—C_β coupling occurs, probably *via* the first-formed palladium phenolate (**315**) to give the bisquinone methide (**316**), and the latter spontaneously undergoes intramolecular Diels–Alder reaction to the natural lignan carpanone (**317**) in 46% yield, with stereocontrol at five chiral centers.[157a] High yields, up to 94%, have been recorded using oxygen as oxidant with a metal(II)–salen complex as catalyst, *e.g.* cobalt(II) salen.[157b] A low yield of carpanone was also obtained in electrooxidation.[128]



(**315**) (**316**) (**317**)

Scheme 12

Another case of oxidative coupling involving [4 + 2] cycloaddition is that of α-tocopherol (**318**). In alkaline ferricyanide the dehydrodimer (**319**) is formed, *ca.* 60%, by the sequence indicated in Scheme 13.[158] The chemistry was elucidated in the model coupling (**320**) → (**321**).[159]



(**318**) R = $C_{16}H_{33}$
(**320**) R = Me

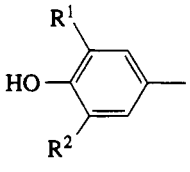
(**319**) R = $C_{16}H_{33}$
(**321**) R = Me

Scheme 13

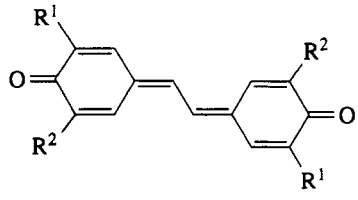
2.9.6.2 Coupling at Benzylic Carbon

A minor variant in the oxidative coupling process stems from generation of a benzylic radical and coupling at that site. The mechanistic course remains obscure, although it seems plausible to postulate primary oxidation at phenolic oxygen followed by hydrogen migration from a benzylic site. In practice excellent yields may be obtained, as illustrated by the oxidation of *p*-cresols (**322**) by silver oxide on Celite in refluxing dry benzene, forming the bisquinonemethides (**323**), *e.g.* with $R^1 = R^2$ = Me, 93% yield.[28] In a biomimetic conversion emodin anthrone (**324**) was oxidized in pyridine by oxygen to form the benzylically coupled dimer (**325**); on further oxidation conventional phenol coupling and dehydro-

genation lead through protohypericin (**327**) to the natural pigment hypericin (**328**). Penicillopsin (**326**) also reacted, on exposure to oxygen, by benzylic coupling to give protohypericin and then hypericin, in 50% overall yield.[160] As a final example, the lactone (**204**), the anodic oxidation (acidic medium) of which was discussed in Section 2.9.3.2, could be alternatively oxidized in neutral acetonitrile to the bridged lactone (**329**). Although the yield was only 20%, the reaction represents a novel C_{AR}—C benzylic bond formation.[109]



(322)



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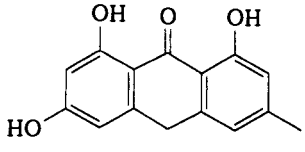

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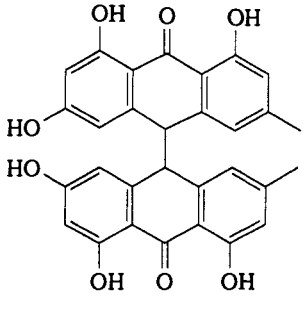

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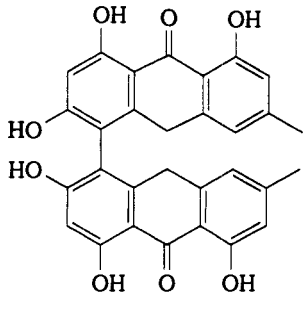

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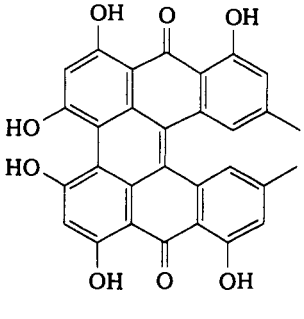

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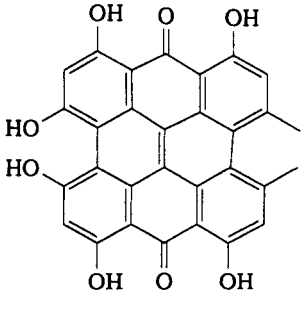

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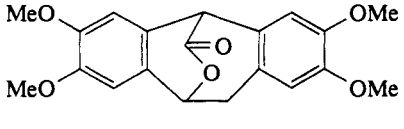
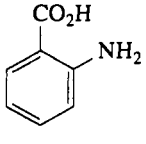


(329)

2.9.6.3 C—N Bond Formation

Coupling between aromatic amines and either phenols or other aromatic amino compounds is known and it is important in the production of azo polymers, and in the formation of azo dyes. Most of this work is outside the scope of this chapter; a number of reviews are cited in ref. 20. One or two examples will suffice here to illustrate the area. Thus anthranilic acid (**330**) forms phenazine-1,6-dicarboxylic acid (**331**) on treatment with manganese dioxide or lead dioxide in dry benzene or chloroform.[161] The mechanistic details are obscure. Excellent yields could be obtained in intramolecular cases,[162] *e.g.* amine (**332**)



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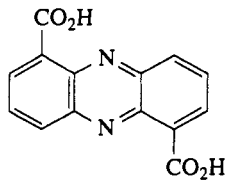

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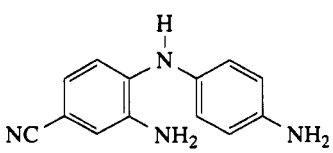

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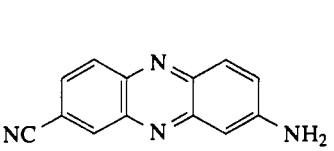

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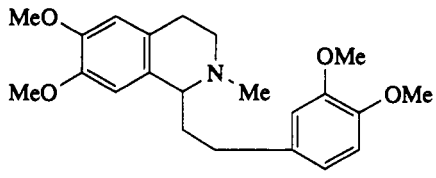

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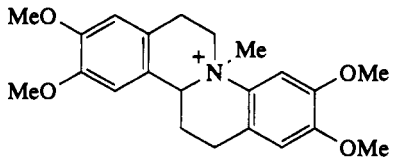

(335)

afforded phenazine (**333**) quantitatively on oxidation with iron(III) chloride. These studies comprise models for bacterial phenazine pigments. Lastly N—C (phenolic) linking is exemplified in the anodic conversion of the phenylethyltetrahydroisoquinoline (**334**) to the tetracyclic ammonium salt (**335**).[163]

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3.1
Wagner–Meerwein Rearrangements

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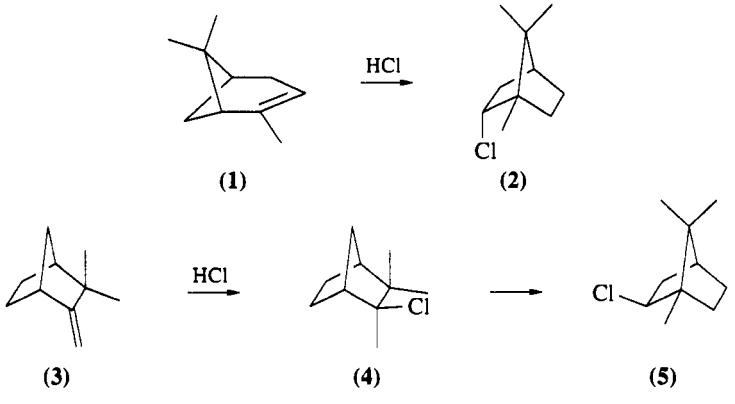
3.1.1 INTRODUCTION

Since the initial studies by Wagner at the turn of the century, the Wagner–Meerwein rearrangement has been the subject of almost continuous investigation.[1] The reaction was initially examined in terms of the rearrangement of α-pinene (**1**) to bornyl chloride (**2**; Scheme 1), and of camphene (**3**) *via* camphene hydrochloride (**4**) to isobornyl chloride (**5**).



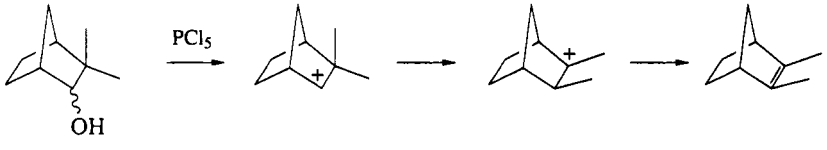
Scheme 1

The ionic nature of the rearrangement was first recognized by Meerwein in 1922.[2] These ideas replaced some earlier suggestions by Ruzicka.[3] However, in 1938 Bartlett questioned the intermediacy of the discrete ions proposed by Meerwein.[4] In the following year Wilson, in a remarkable study for the

period, suggested the possibility of a mesomeric delocalized carbocationic intermediate.[5] The subsequent controversy between Brown and Winstein in the 1950s and 1960s on the role of classical or nonclassical ions in the norbornyl series meant that the rearrangement and the nature of the intermediates became one of the most widely studied reactions. It is, however, beyond the scope of this chapter to review these mechanistic arguments.[6]

3.1.2 DEFINITION OF THE WAGNER–MEERWEIN REARRANGEMENT

The Wagner–Meerwein rearrangement involves the generation of a carbocation on a bicyclic system followed by the 1,2-shift of an adjacent skeletal C—C bond to generate a new carbocation.[7,8] The reaction is thus accompanied by a modification of the bicyclic skeleton. Although the Wagner–Meerwein rearrangement strictly involves the migration of a skeletal bond, the term is sometimes widened to embrace the migration of a substituent such as a methyl group as in the related Nametkin rearrangement. The latter may be exemplified by the conversion of camphenilol (**6**) to santene (**7**; Scheme 2)



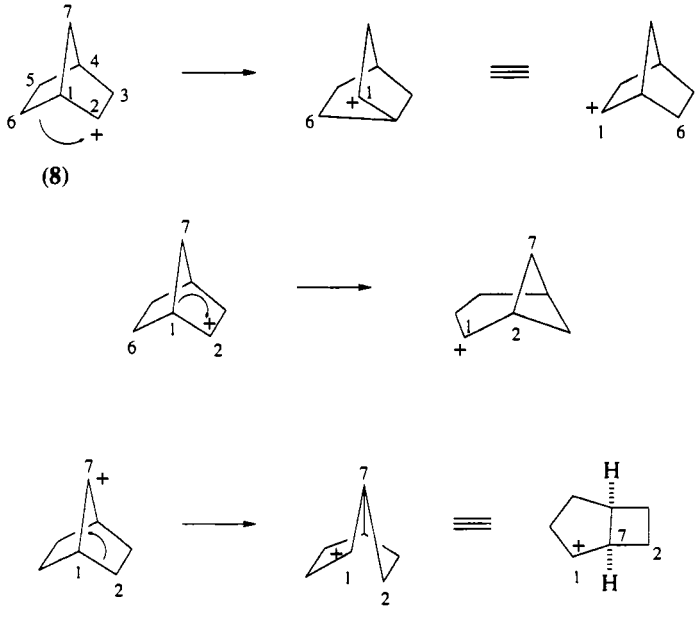
(**6**) (**7**)

Scheme 2

Since its discovery in the context of the reactions of the monoterpenoids, examples of the rearrangement have been found in many other systems. Therefore, for the purposes of this chapter, which is concerned with the synthetic utility of the Wagner–Meerwein type of rearrangement, some reactions involving substituents migrating will be included as well as examples of skeletal rearrangement in polycyclic systems.

3.1.3 WAGNER–MEERWEIN PATHWAYS IN BICYCLIC SYSTEMS

The branched chain of the terpenoids and the consequent number of tertiary centers that these natural products contain lead to many cationic rearrangements. Not unexpectedly the majority of the examples

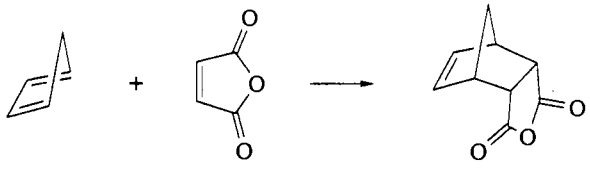


(**8**)

Scheme 3

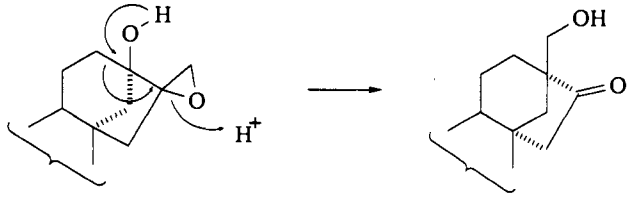
of the Wagner–Meerwein rearrangement come within this area,[9,10] and it is also here that its synthetic utility has been exploited. In the first instance, in order to assess the value of the reaction, it will be helpful to examine the consequences of the rearrangement in terms of the reactions of a simple bicyclo[2.2.1]heptyl (norbornyl) carbocation (**8**; Scheme 3).

These examples illustrate both the utility and the limitations of the rearrangement as part of a synthetic strategy. These may be summarized in the following terms. Firstly, there are many powerful methods with well-established regiospecificity that lead to the bridged ring system of defined stereochemistry, for example the Diels–Alder strategy (Scheme 4).



Scheme 4

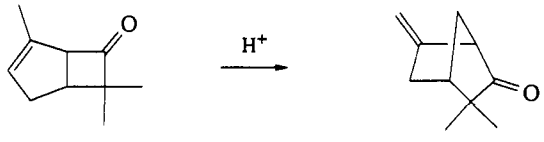
Such reactions may form part of a convergent synthesis and by their very nature place a functional group adjacent to the bridge. Secondly, the rearrangement may lead to the possibility of placing a functional group in a relatively inaccessible position. For example the rearrangement of the epoxide (**9**) affords the primary alcohol (**10**; Scheme 5).



(**9**) (**10**)

Scheme 5

However, the existence of many competing pathways as illustrated by Scheme 3 implies significant limitations on the generality of a strategy based on a particular Wagner–Meerwein rearrangement. Indeed the need to build features into a molecule which will drive the rearrangement along a specific pathway is a significant constraint. The tendency is for the carbocation to rearrange to the most stable structure. Thus 1,2-shifts tend to afford five- or six-membered rings rather than three- or four-membered rings. An example is given by the the rearrangement of the cyclobutanone (**11**), obtained from geronic acid, to the bicycloheptenone (**12**).[11] Secondly a bridge carbon bearing a positive charge or a double

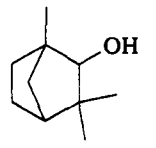


(**11**) (**12**)

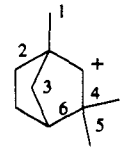
(**13**) (**14**)

bond is unstable. On the other hand conjugative or hyperconjugative stabilization may favor a particular carbocation. Furthermore a carbocation may collapse by fragmentation rather than by rearrangement as exemplified by the formation of α-terpineol (**13**) and limonene (**14**) from α- and β-pinene in the presence of aqueous mineral acid.[12]

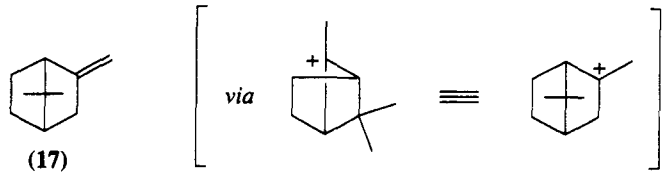
The dehydration of fenchyl alcohol (**15**) demonstrates the many structural possibilities that a Wagner–Meerwein rearrangement may afford (see Scheme 6).[13] The initial carbocation might in principle rearrange by the 1,2-shift of any one of six groups indicated on (**16**). Shift 1 would produce a bridgehead



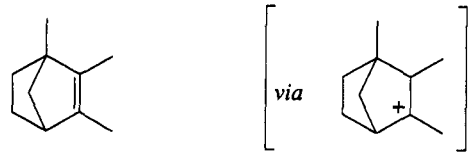
(**15**)



(**16**)

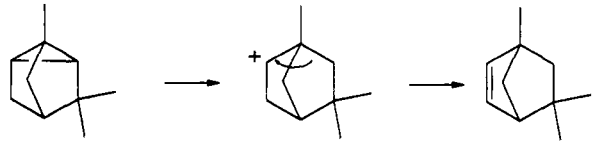


(**17**)

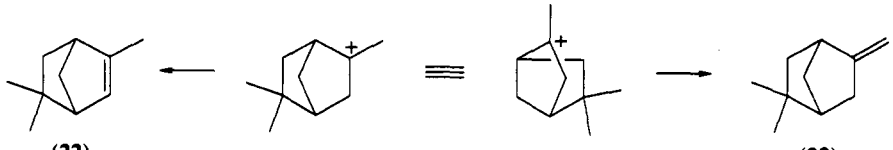


(**18**) (**19**)

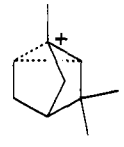
Scheme 6



(**20**) (**21**)



(**22**) (**23**)



(**24**)

Scheme 7

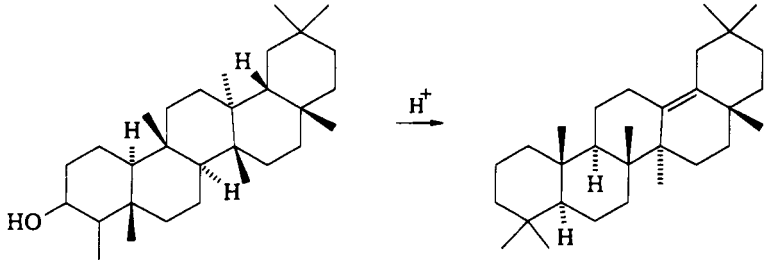
carbocation, whereas shifts 3 or 6 would form less stable rings. On the other hand shifts 2 and 4 are feasible and produce α-fenchene (**17**) and ε-fenchene (**18**).

The ion (**19**) plays an important role in the formation of ε-fenchene; however, the reaction is more complex. In addition to the α- and ε-fenchenes, small amounts of cyclofenchene (**20**), β-fenchene (**23**), γ-fenchene (**22**) and δ-fenchene (**21**) are also formed. Cyclofenchene (**20**) represents the key to the formation of these substances (see Scheme 7). It may arise by the loss of a proton from the carbocation (**24**). Reprotonation of the cyclopropane ring may lead to a new carbocation from which the alkenes may be derived.

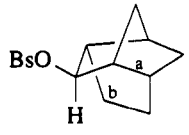
This intricacy, whilst revealing the limitations of a Wagner–Meerwein reaction, also indicates another aspect of the rearrangement as part of a synthetic strategy. The cyclopropyl system exemplified by cyclofenchene (**20**) may be accessed by a range of synthetic routes, for example the addition of diazo ketones across alkenes, and the resultant cyclopropane may then be subjected to the conditions of the Wagner–Meerwein rearrangement to afford a more stable ring system.

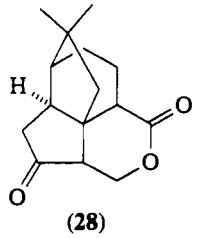
3.1.4 STEREOELECTRONIC FEATURES OF THE WAGNER–MEERWEIN REARRANGEMENT IN SYNTHESIS

The course of the Wagner–Meerwein rearrangement is markedly influenced by stereoelectronic effects.[14,15] In particular for a concerted Wagner–Meerwein rearrangement to occur the leaving and migrating groups should be antiperiplanar — the so-called sp^3-alignment factor. The rigid polycyclic triterpenoid and steroidal skeleta often provide a framework for a cascade of Wagner–Meerwein 1,2-shifts in which antiperiplanar groups, typically axially oriented hydrogen atoms and alkyl groups, migrate. These backbone rearrangements have been explored in many systems and are exemplified by the conversion of friedelin (**25**) to olean-13(18)-ene (**26**).[16] Many other examples in which the reaction is initiated by the cleavage of an epoxide or the protonation of a tertiary alcohol are found in the steroid series (*e.g.* a C-5 alcohol, in the Westphalen rearrangement).



(**25**) (**26**)

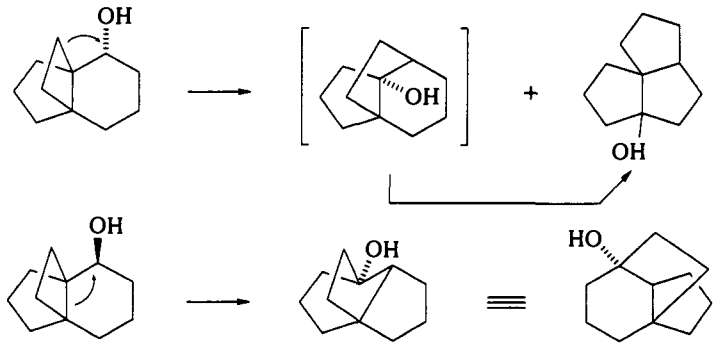




(**27**) (**28**)

For a nonconcerted rearrangement to a carbocationic site to occur, the migrating group and the receptor *p*-orbital should ideally be in a plane. These features have been explored in the acetolysis of *exo*-twistbrendan-2-ol brosylate (**27**). sp^3-Alignment clearly favors the migration of bond 'a', whilst sp^2-alignment favors the migration of bond 'b'. Solvolysis in acetic acid buffered with potassium acetate gave products consistent with sp^3 bond alignment being the dominant factor.

The importance of stereoelectronic factors in a synthetic context have been examined as part of a program directed at the synthesis of quadrone (**28**). A series of model 4,3,2-propellanols (see Scheme 8) were examined and shown to undergo concerted rearrangements involving initial 1,2-alkyl shift of the best-aligned cyclobutyl bond.[17] However, a number of the reactions were then accompanied by secondary rearrangements, again revealing limitations in the use of the rearrangement in a synthetic strategy. Nevertheless this approach has led to a successful synthesis of quadrone (**28**).[18]

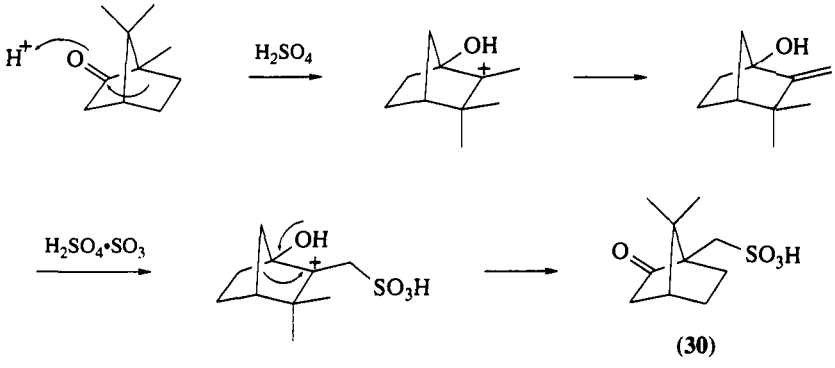


Scheme 8

3.1.5 EXAMPLES OF THE USE OF THE WAGNER–MEERWEIN REARRANGEMENT

3.1.5.1 Syntheses Based on Camphor

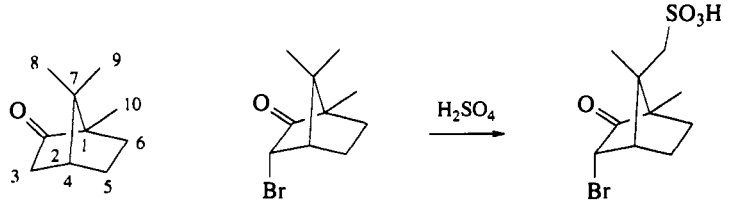
Since α-pinene is a readily available monoterpene, it forms the source of many monoterpenes, including those of the bornane skeleton through a Wagner–Meerwein rearrangement.[19] Camphor (**29**) itself has formed the starting material for a number of syntheses in which Wagner–Meerwein rearrangements have played an important part (for an excellent detailed review see ref. 20). The propensity of this skeleton to undergo Wagner–Meerwein rearrangements enables substituents to be introduced at C-3, C-5, C-8, C-9 and C-10. An example of this is shown in the formation of camphor-10-sulfonic acid (**30**; Scheme 9).[20] A variety of other substituents may then be introduced in place of the sulfonic acid group.



(30)

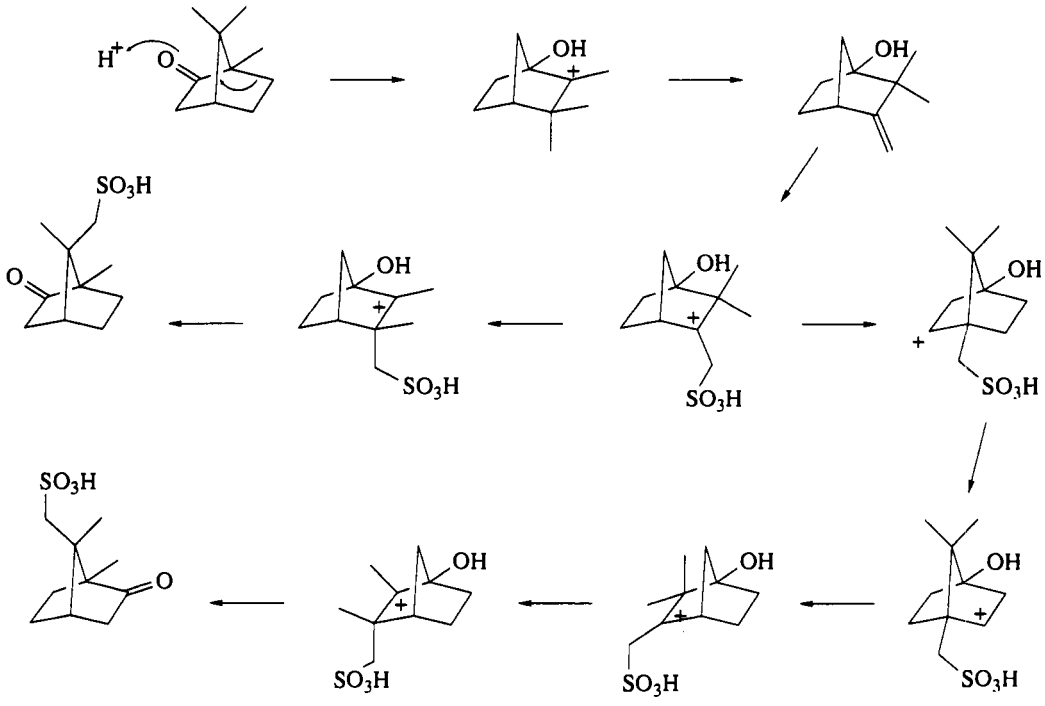
Scheme 9

Functionalization at C-9 (see Scheme 10) in camphor illustrates not only the complexity of the pathways when the possibility of Nametkin (2,3-methyl shift) and 2,6-hydride shifts are taken into account, but also one of the solutions to the simplification of the rearrangement.[21] The product is a mixture of (+)- and (–)-camphor-9-sulfonic acids, *i.e.* the pathway allows for racemization. Indeed camphor itself can be racemized in concentrated sulfuric acid by a similar pathway involving both Wagner–Meerwein and

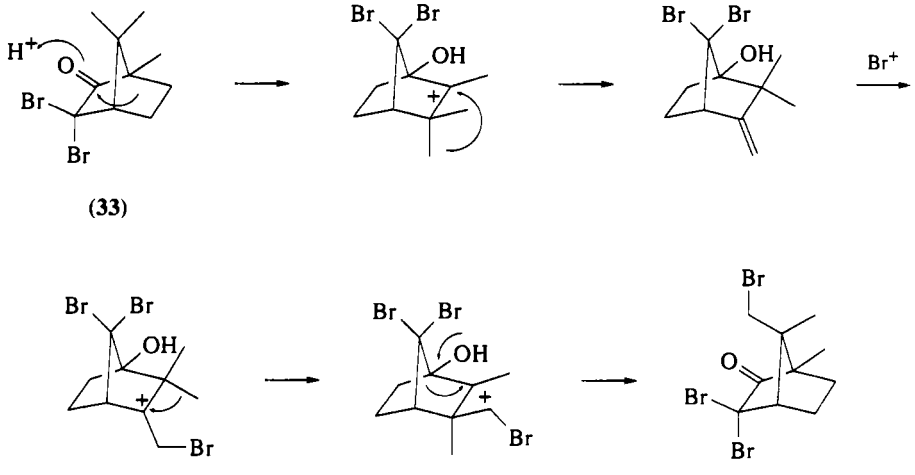


(29) **(31)** **(32)**

Nametkin rearrangements. A method of avoiding racemization was to use (+)-3-*endo*-bromocamphor (**31**), when only the (+)-3-*endo*-bromocamphor-9-sulfonic acid (**32**) was formed.[22] This problem of racemization has arisen in other situations, for example in syntheses in the alkene series.[23]

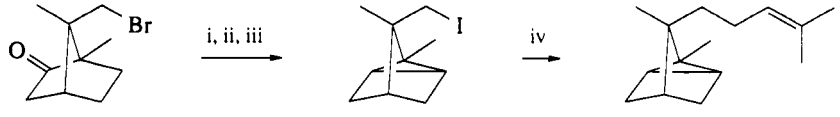


Scheme 10



(**33**)

Scheme 11

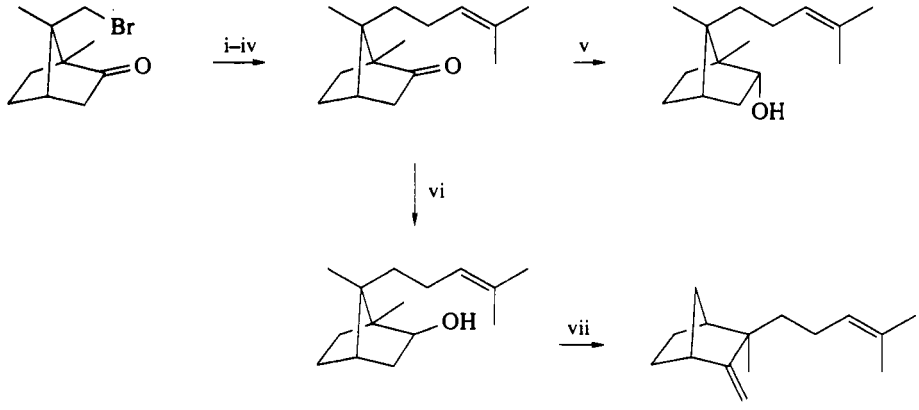


i, N_2H_4; ii, HgO, heat; iii, NaI, DMSO; iv, $(Me_2C{=}CHCH_2NiBr)_2$, DMF

Scheme 12

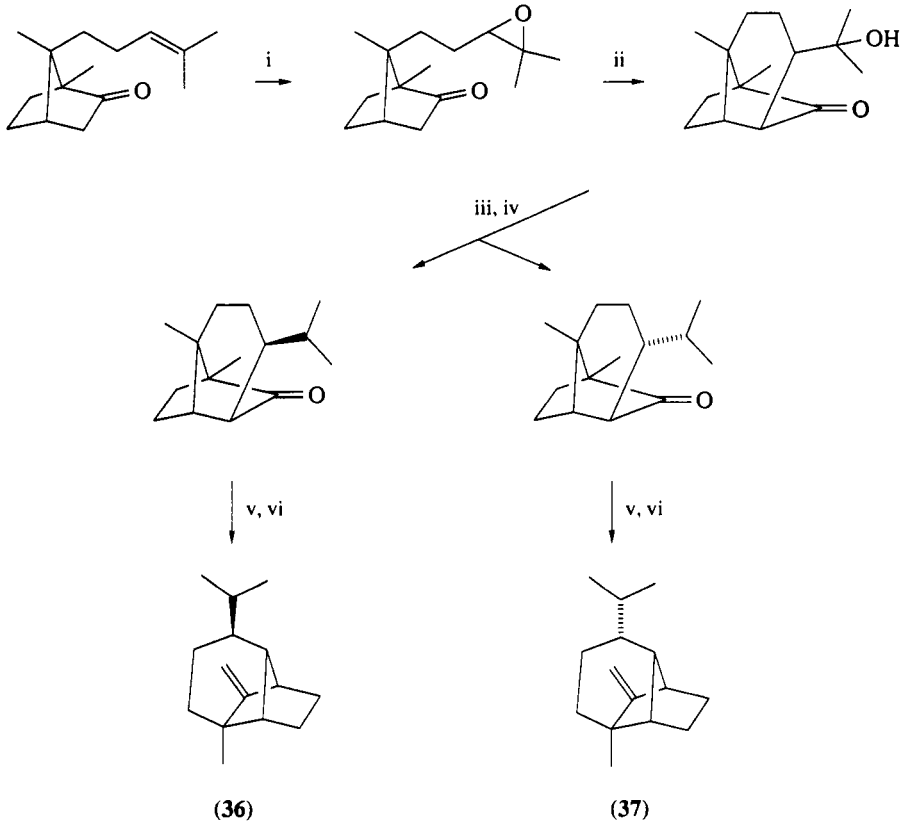
The C-8-substituted derivatives of camphor are formed by a route from 3,3-dibromocamphor (**33**) outlined in Scheme 11.[24] This involves a series of Wagner–Meerwein rearrangements.

These variously substituted camphor derivatives have in turn been used in a number of syntheses of natural products, some of which also involve Wagner–Meerwein rearrangements in their later stages. Examples drawn from the syntheses of (+)-α-santalene (**34**),[25] (–)-β-santalene (**35**),[26] (–)-copacamphene (**36**)[26] and (–)-sativene (**37**)[26] are given in Schemes 12–14.



i, NaI, HMPA; ii, $(CH_2OH)_2$, H^+; iii, $(Me_2C{=}CHCH_2NiBr)_2$, DMF; iv, Me_2CO, HCl; v, Na, Pr^iOH; vi, $LiAl(OMe)_3H$, THF; vii, TsCl, pyridine

Scheme 13

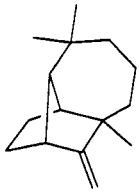


(**36**) (**37**)

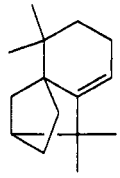
i, $ClC_6H_4CO_3H$, benzene; ii, Bu^tOK, Bu^tOH; iii, $SOCl_2$, pyridine; iv, H_2, Pt; v, $LiAlH_4$; vi, $MeSO_2Cl$, pyridine

Scheme 14

A number of aspects of longifolene chemistry may be understood in terms of Wagner–Meerwein rearrangements that have their parallel in the camphene series.[27] However, these rearrangements are often of a more deep-seated character, as in the conversion of longifolene (**38**) to isolongifolene (**39**), and have consequently found less application in a purely synthetic context. The intense activity that has surrounded sesquiterpenoid synthesis has involved many other examples of Wagner–Meerwein rearrangements.[28]



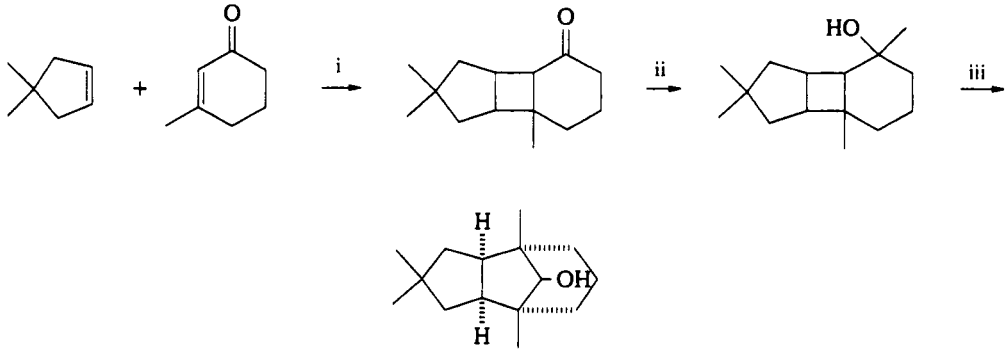
(**38**)



(**39**)

3.1.5.2 Ring Expansion Reactions

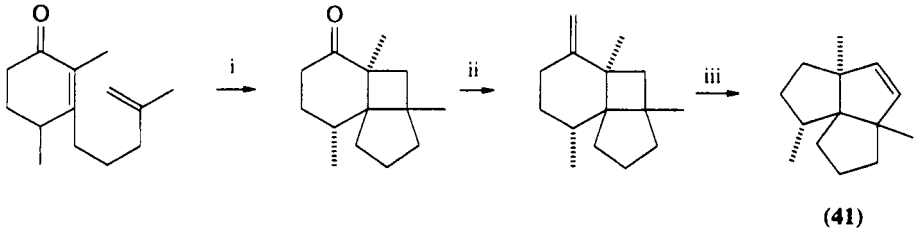
The ready availability of four-membered rings of defined stereochemistry from enone–alkene photocycloadditions has been the origin of several syntheses which employ Wagner–Meerwein rearrangements in subsequent steps. This is exemplified by a neat and very short synthesis of α-caryophyllene alcohol (**40**) from cyclopentene and 3-methylcyclohexenone which was described some years ago (see Scheme 15).[29] The rearrangement in 40% sulfuric acid proceeded remarkably smoothly. A short synthesis of isocomene (**41**; Scheme 16) also illustrates this strategy.[30]



(**40**)

i, *h*ν; ii, MeLi; iii, 40% H_2SO_4

Scheme 15

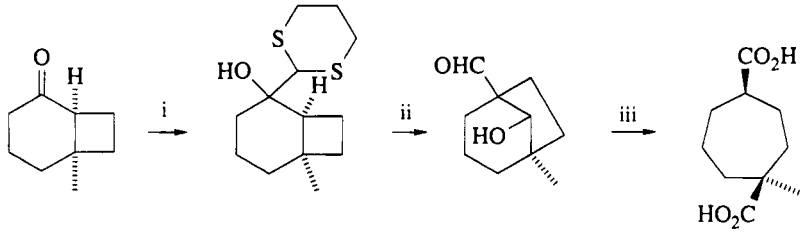


(**41**)

i, *h*ν; ii, $Ph_3\overset{+}{P}\overset{-}{C}H_2$; iii, TsOH, benzene

Scheme 16

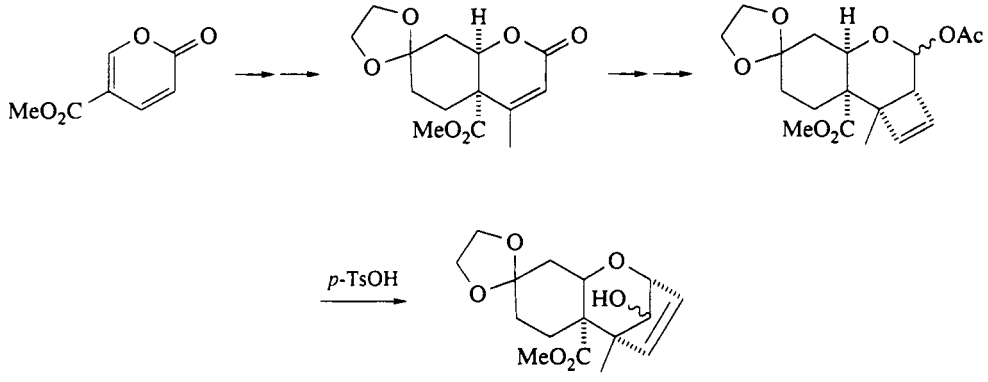
The defined geometry of these steps has permitted the synthesis of some cycloheptane acids related to terpenoid natural products. The key reaction was the rearrangement of a suitably substituted bicyclo[4.2.0]octane. Thus the photoaddition of ethylene to 3-methylcyclohexenone gave the ketone (**42**), which was converted to the alcohol (**43**). On treatment with HgO and HBF_4 this gave the unstable hydroxy aldehyde (**44**), which was readily oxidized to the dicarboxylic acid (**45**; Scheme 17).[31] Ring expansion methodology was also used in an approach to the synthesis of the trichothecenes (see Scheme 18).[32]



(**42**) (**43**) (**44**) (**45**)

i, 1,3-dithiane, BuLi; ii, HgO, HBF_4, aq. THF; iii, CrO_3, H_2SO_4

Scheme 17



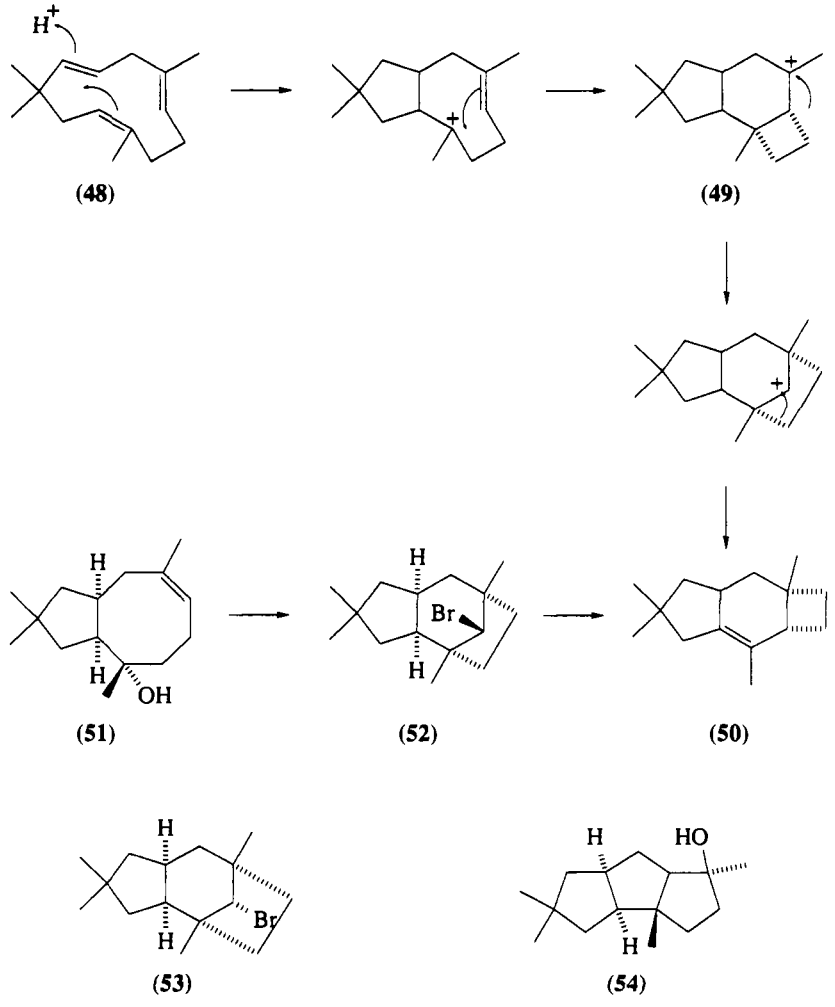
Scheme 18

Whereas this synthesis places an oxygen function on a bridge, an oxygen function of this type may also be the source of a ring contraction as exemplified by the conversion of (**46**) to (**47**).[33]

(**46**) (**47**)

3.1.5.3 Biomimetic Syntheses

A number of biomimetic syntheses have included Wagner–Meerwein rearrangements.[34] A chemical conversion of humulene (**48**) to sterpurene (**50**) involved an interesting series of Wagner–Meerwein rearrangements (see Scheme 19).[35] Humulene (**48**) was converted to the cyclooctenol (**51**) and thence to the bromide (**52**) *via* the protoilludyl cation (**49**). Treatment of (**52**) with silver acetate in acetic acid gave racemic sterpurene (**50**). In contrast the epimeric bromide (**53**) gave (**54**).



Scheme 19

3.1.5.4 Syntheses of the Tetracyclic Diterpenoids

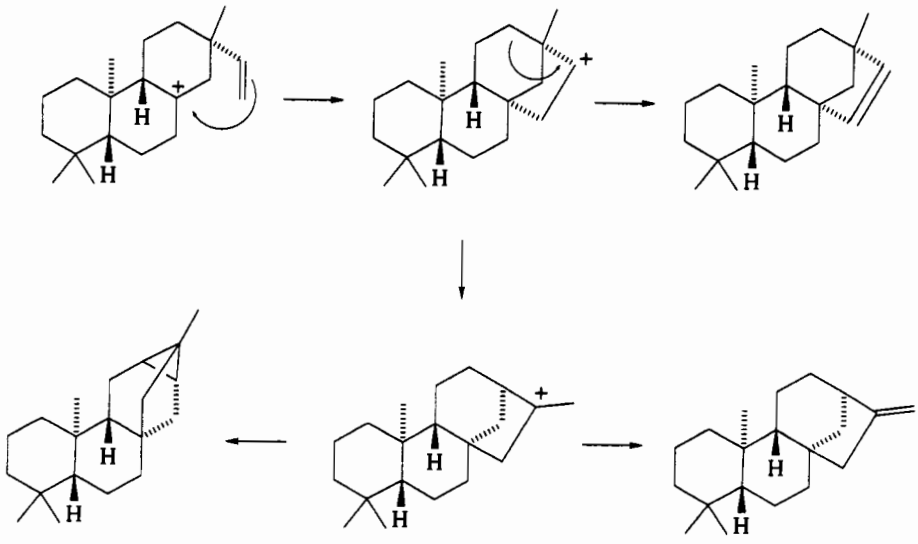
A possible biogenetic relationship between the pimaradienes and the tetra- and penta-carbocyclic diterpenoids was suggested by Wenkert.[36] Implicit in this scheme (see Scheme 20) are a number of rearrangements. There have been many investigations aimed at simulating aspects of this scheme. In particular the beyerene–kaurene rearrangement takes place quite readily. Thus solvolysis of the beyeran-16β-yl toluene-*p*-sulfonate (**55**) affords a mixture of kaurene (**57**), isokaurene (**58**), kauranol (**59**), and beyer-15-ene (**56**; Scheme 21).[37]

An allied rearrangement of the epoxide (**60**) has been used in partial syntheses in both the kaurene and gibberellin series to place oxygen functions at the relatively inaccessible C-14 position (*e.g.* **61**).[38] This type of rearrangement was also used in the final stages of one of the early gibberellin syntheses.[39,40]

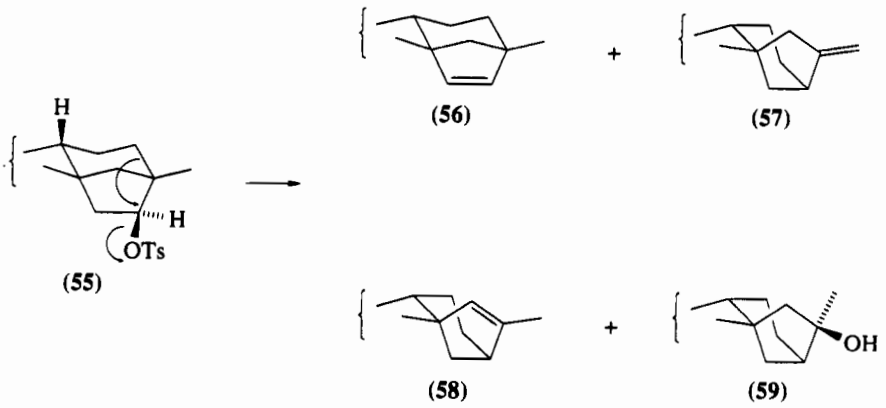
The reverse rearrangement, involving the conversion of the kaurene skeleton to that of the beyerene series, is found in the steviol–isosteviol and gibberellin–8,13-isogibberellin rearrangements (see Scheme 22).[41] Apart from their mechanistic interest, these rearrangements were used in partial syntheses directed at structural correlations.

Prior to the advent of simple methods for radical deoxygenation, a double Wagner–Meerwein rearrangement (Scheme 23) was used as a method for removing a bridgehead hydroxy group in this series.[42] The success of this sequence indicates the subtle balance of stabilities in this series.

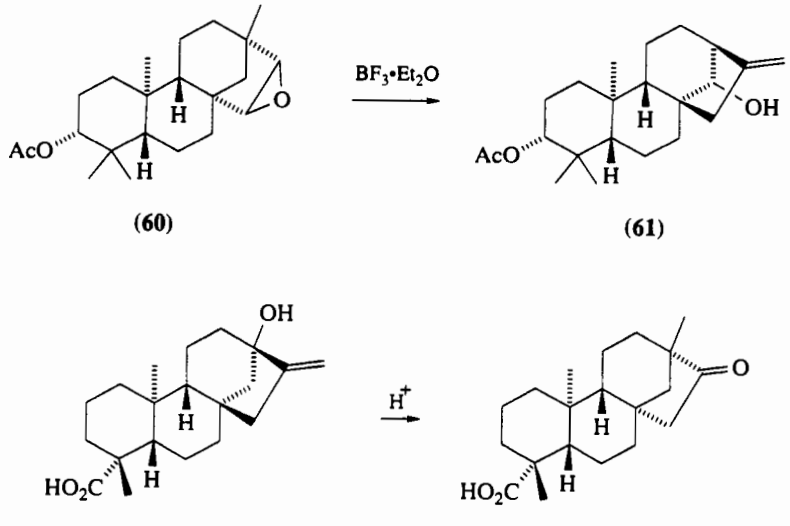
Interrelationships between the kaurene and atiserene series have also been established by a Wagner–Meerwein rearrangement. For example treatment of isokaurene epoxide (**62**) with acid gave atisiran-15-one (**63**), possibly through the sequence shown in Scheme 24.[43]



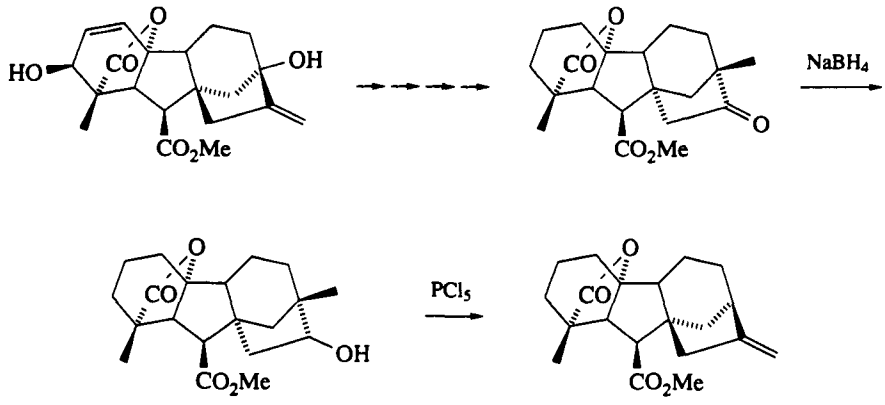
Scheme 20



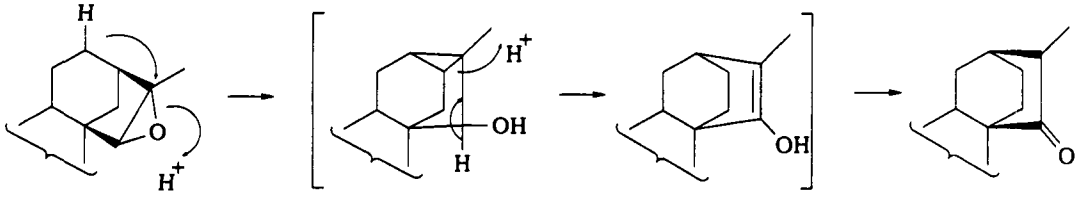
Scheme 21



Scheme 22

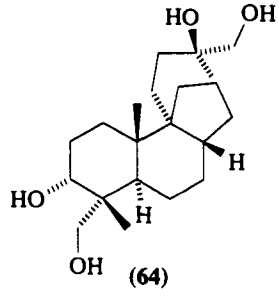


Scheme 23

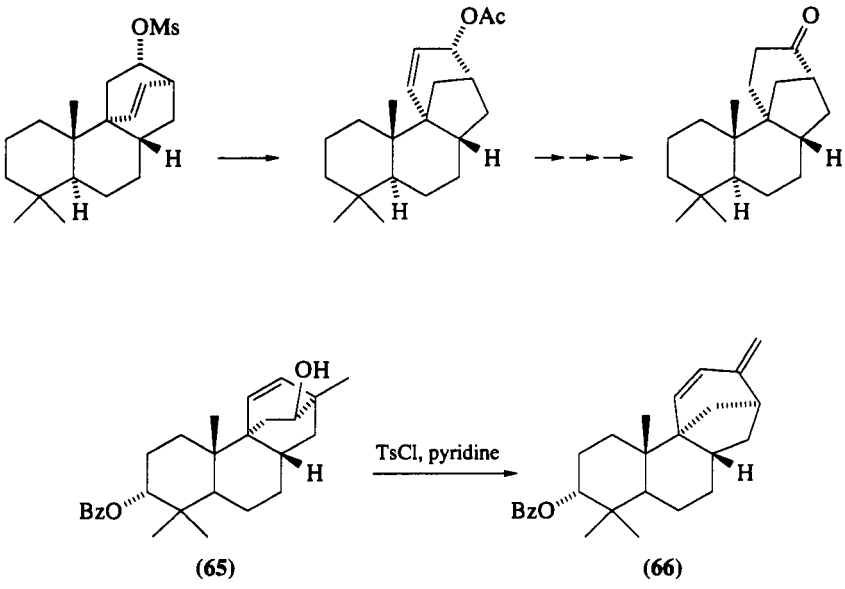


Scheme 24

The biologically important diterpenoid aphidicolin (**64**) and its relatives stemodin and maritimol have been the targets of several synthetic studies employing Wagner–Meerwein rearrangements at key steps in the construction of the carbon skeleton. One such strategy involves the solvolytic rearrangement of suitably oriented bicyclo[2.2.2]octenyl methanesulfonates exemplified by Scheme 25.[44] A synthesis of maritimol involved a similar [2.2.2] → [3.2.1] skeletal rearrangement of (**65**) to (**66**).[45] The rearrangement was induced by treatment of the alcohol with excess toluene-*p*-sulfonyl chloride in pyridine.



In conclusion, the Wagner–Meerwein rearrangement can be a useful component of a synthetic strategy provided its stereoelectronic requirements can be met and the possible pathways are limited. It has been of particular value in the synthesis of bridged ring systems in which the strategy requires the modification of the skeletal framework.



(65) (66)

Scheme 25

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3.2
The Pinacol Rearrangement

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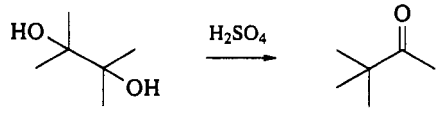
3.2.1 INTRODUCTION

The acid-catalyzed reaction of vicinal diols, which results in dehydration and the migration of an alkyl or aryl group, or a hydrogen atom, to form an aldehyde or ketone is known as the Pinacol rearrangement.[1] The name is derived from the material used in the earliest recorded example. Although the structures of both the starting material and product were unknown when the experiment was published in 1860, Fittig[2] found that treatment of pinacol (**1**) with sulfuric acid gave pinacolone (**2**; equation 1).



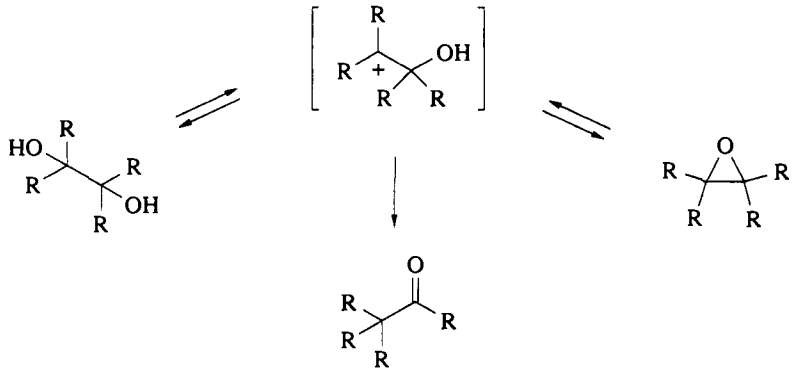
(1)

(1) **(2)**

All classes of vicinal diols (primary, secondary, tertiary, alkyl- or aryl-substituted) will undergo the pinacol rearrangement, and many acids and solvents have been used for this purpose. Various procedural modifications have been introduced over the years for particular glycols, but sulfuric acid remains the most commonly employed catalyst. The use of 25% H_2SO_4, as recommended in the procedure of Adams,[3] affords pinacolone in essentially quantitative yield. In some instances better results are obtained when cold concentrated acid is used as the solvent. The choice of reagents and conditions is important, and can completely alter the course of the reaction. For example, pinacol also serves as the starting material for the synthesis of 2,3-dimethylbutadiene, formed by slow distillation of a mixture of the diol and catalytic HBr.[4]

The pinacol rearrangement and the acid-catalyzed rearrangement of epoxides (see this volume, Chapter 3.3) may be closely related, depending upon the substrates, reagents and conditions employed. Epoxides have on occasion been isolated from diols under pinacol rearrangement conditions,[5] and they are implicated as reactive intermediates in many other instances. Similarly, the treatment of an epoxide with aqueous acid may cause opening to the vicinal diol either prior to, or in competition with, rearrangement. The two substrates (diol and epoxide) are equivalent for most purposes if the equilibrium shown in Scheme 1 is established more rapidly than rearrangement can occur. The use of strong acids and substrates which bear cation-stabilizing groups will encourage the merger of the two processes shown in Scheme 1 *via* a common carbenium ion intermediate. Conversely, mild acids and good nucleophiles will favor covalent bond-forming reactions, *e.g.* the formation of a halohydrin upon treatment of an epoxide

with HX. These covalently bonded materials may be stable and isolable, or may serve as reactive intermediates which lead to rearranged products under the conditions used for their formation. The rearrangement step itself can be regarded as the interaction of an intramolecular nucleophile (the migrating group and its bonding electron pair) with an adjacent electrophilic center. The latter may range from a formal carbocation to a carbon which bears a leaving group suitable for S_N2 displacement. These distinctions can be helpful in designing experiments to take advantage of the versatility of epoxides as starting materials.

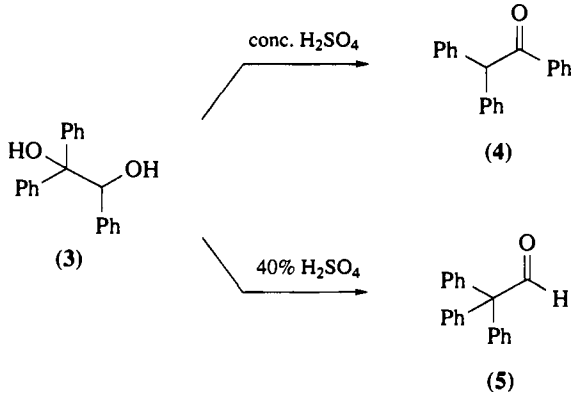


Scheme 1

Other methods of generating β-hydroxy carbocations lead to similar or identical products. The reaction of β-amino alcohols with nitrous acid, one variant of the semipinacol rearrangement (or Tiffeneau–Demjanov ring expansion if used for this purpose), is a familiar example.[6] Another is the so-called α-ketol rearrangement, in which the hydroxy and carbonyl groups of an acyloin exchange positions with concurrent migration of a substituent.[6] Many of the general features described here also apply to these related reactions (see this volume, Chapter 3.4).

3.2.2 MECHANISTIC FEATURES

Given the range of substrates and reagents that have been used in pinacol rearrangements, it is not surprising that very few mechanistic conclusions are general for all diols under all conditions. Indeed, the same substrate may give different products when subjected to apparently similar conditions. A classic illustration is provided by the diol (**3**), which gives the ketone (**4**) when treated with concentrated sulfuric acid, but mostly the aldehyde (**5**) when 40% acid is used (equation 2). Close mechanistic examination of this reaction with ^{14}C-labeled material showed that the kinetically controlled ratio of (**4**) to (**5**) does depend to some extent on the solvent and acid employed, but is further complicated by the conversion of the aldehyde (**5**) to the ketone (**4**) under the reaction conditions.



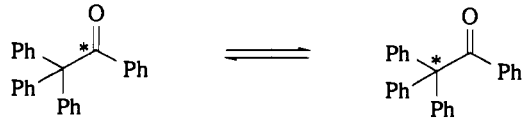
(2)

Other detailed mechanistic examples are described in two reviews by Collins.[6,7] Although published two decades ago, these require little updating in content, and appear to be unchallenged in general mechanistic conclusions, which can be summarized as follows: (i) pinacol rearrangements are exclusively intramolecular; (ii) the course of the pinacol rearrangement usually depends on which OH group is most easily removed, as predicted by consideration of the stability of the intermediate carbenium ion; (iii) the group which preferentially migrates is that which is better able to stabilize a positive charge, although complications may arise due to stereochemical and conformational effects, rapid equilibration of intermediate carbenium ions or interconversion of products; and (iv) either inversion or racemization may be observed at the migration terminus; racemization may occur either at the stage of an intermediate cation or by further reaction of the product.

It appears that the stereochemistry at the migrating center has not been explicitly examined in a pinacol rearrangement but, as seen in related 1,2-migrations, retention of configuration is expected.

Pinacol rearrangements are effectively irreversible in the sense that carbonyl products have not been shown to revert to diols. However, the products may be in equilibrium with the same cationic intermediates that are generated from the diol. This feature emerges clearly under strongly acid conditions, where the 1,2-carbonyl transposition of aldehydes and ketones is observed (*cf.* equation 2). An especially pertinent example comes from the work of Fry,[8] who found that pinacolone itself undergoes the ^{14}C-label redistribution shown in equation (3). Benzpinacolone, isotopically labeled at the carbonyl carbon, gives material with the label transposed as shown in equation (4).[9] These and related observations can be explained by invoking two or more carbenium ion intermediates connected by 1,2-migrations. The label exchange in equation (4) requires oxygen migration, presumably *via* an epoxide (or protonated epoxide) intermediate.

(3)



(4)

Many other 1,2-carbonyl transpositions with skeletal rearrangement are known.[6] In general, aldehydes react more rapidly than ketones; the rearrangement of a ketone to form an aldehyde appears to be unknown, but ketones can be converted to other ketones. A few examples from the early work of Venus-Danilova[10] are illustrated. Thus cyclobutane- and cyclopentane-carbaldehyde both gave the simple ring-expanded ketones as shown in equations (5) and (6), upon treatment with concentrated sulfuric acid.

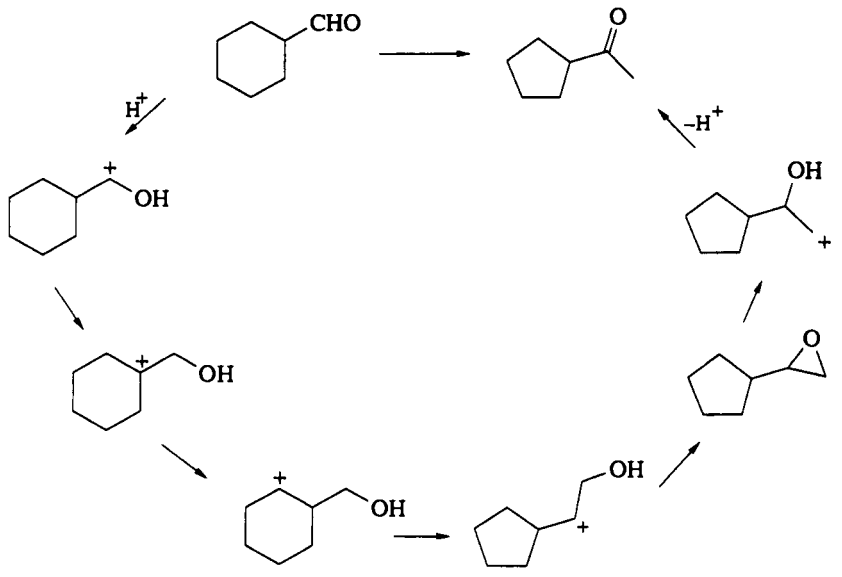
(5)

(6)

A more complex sequence, such as that suggested in Scheme 2, must be invoked to explain the formation of the ring-contracted methyl cyclopentyl ketone from cyclohexanecarbaldehyde.[10]

In general, 1,2-carbonyl transpositions require more vigorous conditions (stronger acid, higher temperatures) than pinacol rearrangements in which the same carbenium ion intermediates may be generated. However, harsher conditions than actually required have frequently been used to carry out pinacol rearrangements, and care must be taken to avoid over-interpretation of the mechanism from examination of the products.

The evidence for carbocation intermediates in the pinacol rearrangement is compelling for some substrates and conditions. Bunton[11] found that pinacol itself that was recovered from ^{18}O-enriched aqueous sulfuric acid had incorporated an appreciable amount of solvent oxygen. Under these conditions the reaction goes to completion, *i.e.* the incorporation cannot be due to reversible formation of diol from pina-

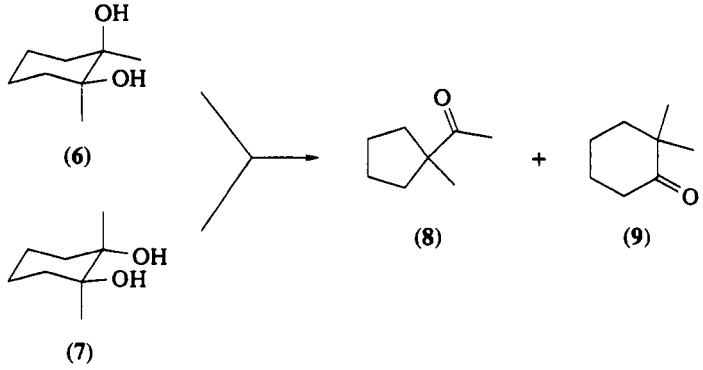


Scheme 2

colone. A common carbenium ion intermediate was proposed for both solvent incorporation and rearrangement. Similarly, Collins[12] found that the *threo* and *erythro* isomers of a triaryl-substituted diol, when treated with sulfuric acid in aqueous ethanol, were interconverted more rapidly than either isomer rearranged.

An early report that the *threo* and *erythro* isomers of 1,2-diphenyl-1,2-di(1-naphthyl)ethanediol gave two different products (a ketone and an unidentified substance)[13] could not be substantiated by other workers,[14] who also found that the *threo* and *erythro* isomers of 1,2-bis(2-chlorophenyl)-1,2-diphenylethanediol both gave the same ketone (phenyl migration).[14] Yields were not recorded, precluding substantive mechanistic interpretation.

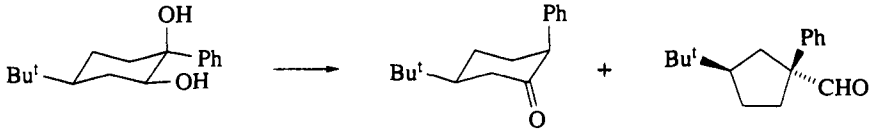
The *cis* (**6**) and *trans* (**7**) isomers of 1,2-dimethyl-1,2-cyclohexanediol have been examined by several research groups, but a clear understanding of this system did not emerge until modern analytical tools were employed. The very thorough study of Bunton and Carr[15] provides evidence for a carbenium ion intermediate common to both isomers. In *ca.* 1–3 M aqueous perchloric acid at 60 °C the isomeric diols are partially interconverted, and solvent oxygen is incorporated. The ring-contracted ketone (**8**) is the major product from both diols, but a small amount of 2,2-dimethylcyclohexanone (**9**) is also formed (equation 7). A carbenium ion intermediate with sufficient lifetime to undergo chair–chair equilibration would lead to identical product ratios from both diol isomers. The slightly different ratios which were found (from (**6**), (**8**):(**9**) = 93:7; from (**7**), (**8**):(**9**) = 97:3) presumably reflect a small stereochemical memory effect in one or both of the isomers, but the initial stereochemistry of the center which bears the departing hydroxy group clearly does not dominate the stereochemical course of these reactions. Larger differences in reactivity and product composition are found for the five-membered ring analogs.[16]



(7)

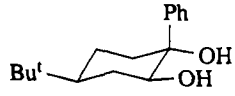
Earlier studies[17] of these diols, with one exception[18] which was later shown[17b] to be erroneous, differ only marginally in stereochemical conclusions, probably because the minor isomer could not be detected by the analytical methods used.

Another aspect of stereoselectivity has been probed by Berti and coworkers,[19] who used the *t*-butyl group to control the conformational populations of the diols depicted in equations (8) to (11). The results are informative, although atypical conditions ($BF_3{\cdot}OEt_2$ in benzene) for pinacol rearrangement were used, and the generality of the observations is unknown. The products of all four reactions are ascribed to initial loss of the benzylic OH group, with formation of a planar carbenium ion at C-1. The close similarity of the ratios of products for equations (8) and (9), or equations (10) and (11), respectively, supports the view that the departing OH group has at most a very slight influence on the outcome. Formal backside (equation 8) and frontside (equation 9) hydride migrations are involved in the formation of the ketone (**11**). In contrast, the stereochemistry at C-2 plays a controlling role, as shown by the formation of (**11**) as the exclusive ketone from (**10**) and (**13**), while (**15**) is the only ketone formed from the axial 2-hydroxy substrates (equations 10 and 11). The formation of the single stereoisomer of aldehyde (**12**) in all four reactions is in keeping with ring contraction *via* the planar carbenium ion held in the chair conformation of the starting materials.



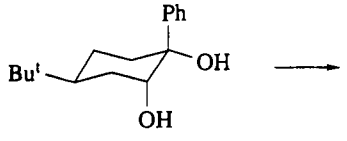
(8)

(**10**) (**11**) 93% (**12**) 7%



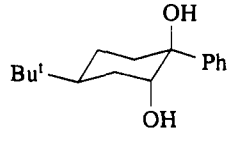
(**13**)

(**11**) 90% + (**12**) 10% (9)



+ (**12**) 33% (10)

(**14**) (**15**) 67%



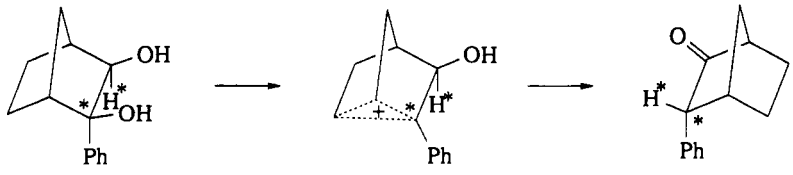
(**16**)

(**15**) 61% + (**12**) 39% (11)

Carbenium ion intermediates are implicated not only for diols in which one or both carbinol centers are tertiary, but also in less-substituted substrates. Alexander and Dittmer[20] found that the *meso* and (±)-isomers of 2,3-butanediol both gave 2-butanone and isobutyraldehyde when refluxed in 60% phosphoric acid, but the ratios were different, ruling out exclusive reaction *via* a single common intermediate. More recently, Herlihy[21] has reported the results of a thorough kinetic analysis of the rearrangement of optically active 1,2-propanediol in aqueous perchloric acid. The rate of racemization exceeded the rate of rearrangement, in keeping with a mechanism involving a carbenium ion intermediate. The rate of exchange of ^{18}O-enriched substrate was also examined, and found to be half as fast as racemization; a significant memory effect, *e.g.* shielding of one face of the cation by the departing water molecule, can be used to rationalize this rather S_N2-like behavior. Arguments against the involvement of an epoxide intermediate were presented, although rigorous exclusion of any role for epoxide is difficult. The ratio of racemization/rearrangement was found to be dependent on the acid concentration, an effect attributed to the influence of acidity on partitioning of the carbocation. The mechanistic conclusions for this system parallel those reached earlier[11] for pinacol itself. The nearly exclusive product from 1,2-propanediol is propanal (which does not survive the reaction conditions), but interestingly, a small amount of acetone is also formed.

Although inversion at the migration terminus has been observed in several pinacol rearrangements, the dramatic rate effects (anchimeric assistance) sometimes associated with neighboring group participation have not been observed or documented. The choice of a proper model to establish a baseline rate for comparison remains a problem. Alcohols are not suitable for this purpose, since diols are significantly less reactive than their monohydroxy analogs, presumably because of the inductive effect of the second OH group.[11,21]

Most detailed studies of pinacol rearrangements support the view that carbenium ion formation precedes migration, but occasionally stereoselectivity is observed when not anticipated from this perspective. The results of three separate labeling and stereochemical experiments carried out by Collins *et al.*[22] are incorporated in the depiction (equation 12) of the rearrangement of diol (**17**) to the ketone (**19**). The course of this reaction can be explained by considering the bridged ion (**18**) as an intermediate, even though the tertiary and benzylic nature of the corresponding classical ion makes it a poor candidate for nonclassical participation.



(17) (18) (19) (12)

Aqueous or concentrated acids are the most commonly used catalysts, but several other acidic materials can cause pinacol rearrangement, as noted in a recent review of the dehydration reactions of diols.[23]

Few generalizations can be made about the 'migratory aptitudes' of substituents in pinacol rearrangements, but some observations are worth noting. Phenyl and hydrogen appear to be similar in rate of migration, and hydrogen is some 20 times faster than methyl. The *t*-butyl group has been reported to shift much more rapidly than other simple alkyl groups (*t*-butyl:ethyl:methyl = >4000:17:1).[24] Cyclopropyl substituents migrate more readily than simple alkyl groups, and do so without ring opening, as illustrated in equation (13).[25]

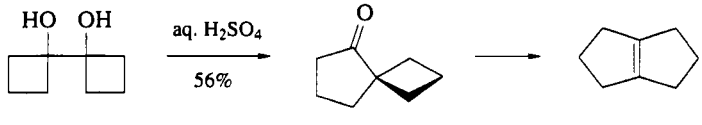
(13)

R = Me, Pr^i, cyclopropyl

3.2.3 APPLICATIONS

In order to maximize the synthetic utility of pinacol rearrangements, it is necessary to exclude competing processes, and control both regio- and stereo-selectivity. The two factors which influence regioselectivity — which OH is lost, and which adjacent group migrates — are at least marginally predictable and, in favorable circumstances, controllable. Control of stereoselectivity is more problematic, as noted above. Because of these complications and the difficulties associated with the preparation of complex diols, the pinacol rearrangement has not been widely used in multistep syntheses, in spite of its capacity for generating some unusual structural features.

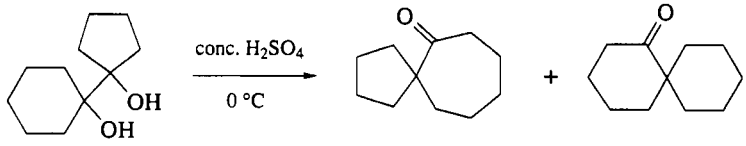
Both ring expansions and contractions are well documented. Ring size can strongly influence the course of the reaction. For example, Vogel[26] found that the diol (**20**), obtained by reductive dimerization of cyclobutanone, cleanly rearranged to the ketone (**21**) on warming in dilute sulfuric acid; (**21**) was subsequently used to prepare the novel pentalene (**22**; equation 14).



(20) (21) (22) (14)

The symmetrical diols derived from cyclopentanone[27] and cyclohexanone[28] can similarly be converted to ring-expanded ketones in good yield. The diols from reductive coupling of cycloheptanone and cyclooctanone give mainly the corresponding dienes in aqueous acid,[28] especially when heated, but Christol[29] found that pinacol rearrangement is strongly favored even for these materials when cold concentrated sulfuric acid is used as the solvent.

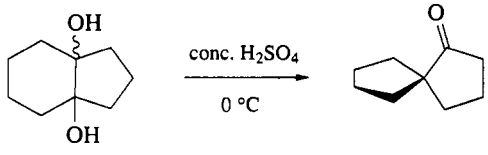
Results which follow the mechanistic generalizations given above have been obtained from examination of similar unsymmetrical diols. The formation of (**24**) as the major product from (**23**) can be explained by more rapid development of the carbenium ion in the five-membered ring (equation 15).



(**23**) (**24**) 60% (**25**) 40% (15)

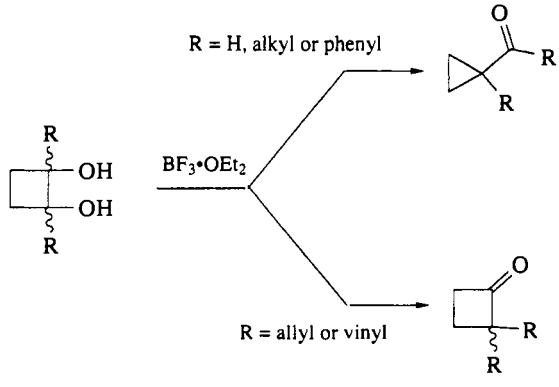
Other unsymmetrical diols, prepared (inefficiently) by the coupling of mixtures of ketones, have been studied.[28–30] The 'preferred cation' argument is also found to be applicable to mixed medium-ring analogs, *i.e.* the kinetically favored pinacol rearrangement product is that predicted by consideration of the relative stabilities of the two possible, initially formed, carbocations.[30] Earlier work[28] with these compounds may have given misleading results due to product instability. To illustrate, Mundy[30] observed that (**24**) is converted to (**25**) as the temperature is increased.

The *cis*- and *trans*-hydrindandiols (**26**) are both converted exclusively to the spiro ketone (**27**) on brief treatment with cold concentrated sulfuric acid (equation 16).[31] Plausible alternative products, the epoxide and spiro[5.3]nonanone, could not be ruled out as intermediates, since both were prepared by independent routes and found to give (**27**) under the reaction conditions.



(**26**) (**27**) (16)

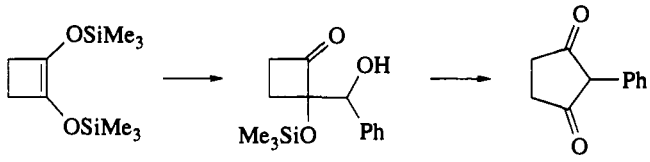
The pinacol rearrangements of several cyclobutanediols, mostly induced by BF_3·OEt_2, have been examined by Conia.[32] The reactions of symmetrically substituted materials occurred with high specificity and yield. Both isomers (*cis* and *trans*) gave the same product in instances where this question was examined. As shown in equation (17), for the substituents R = H, alkyl or phenyl, only ring contraction was observed, while equally regiospecific formation of the cyclobutanone product was found for the substituents R = allyl or vinyl.



(17)

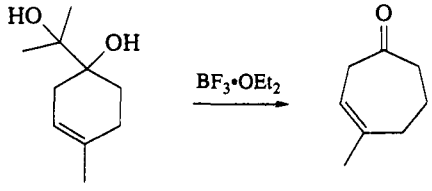
The strained four-membered ring has been used in a different way by Kuwajima.[33] Bis(trimethylsilyl)succinoin (**28**) when treated with benzaldehyde in the presence of $TiCl_4$ afforded the intermediate (**29**), which gave the ring-expanded product (**30**) on treatment with trifluoroacetic acid (equation 18). An

analogous reaction of (**28**) with ketals, catalyzed by $BF_3{\cdot}OEt_2$, led to good yields of 2,2-disubstituted-1,3-cyclopentanediones. These reactions illustrate the facile migration of an acyl group.



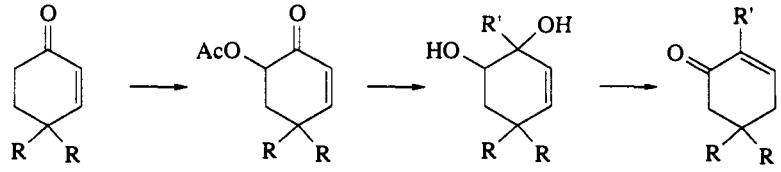
(**28**) (**29**) (**30**) (18)

An unusual observation was made when diol (**31**) was treated with $BF_3{\cdot}OEt_2$. The ring-enlarged terpene karahanaenone (**32**) was formed (along with a double-bond positional isomer); the authors[34] reported that other catalysts gave little or no ring-expanded product (equation 19).



(**31**) (**32**) (19)

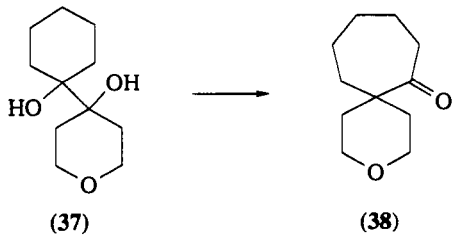
When one of the diol centers bears a vinyl group, a preference for initial formation of an allylic carbenium ion is anticipated. Oppolzer and coworkers[35] made use of this feature to develop a cyclohexenone 1,2-carbonyl transposition reaction, illustrated by the sequence shown in equation (20). Oxidation of (**33**) with $Pb(OAc)_4$ was used to introduce the acetoxy group in (**34**); subsequent reduction or addition of an organometallic reagent (*e.g.* R'Li) followed by hydroysis gave the diol (**35**). The pinacol rearrangement was best catalyzed by *p*-toluenesulfonic acid in refluxing benzene, which also caused migration of the double bond into conjugation. Moderate overall yields of the transposed cyclohexenone (**36**) were obtained.



(**33**) (**34**) (**35**) (**36**) (20)

Dana *et al.*[36] examined some similarly unsaturated acyclic diols under pinacol rearrangement conditions. With few exceptions these gave rather complex mixtures of products, and it appears that the synthetic utility of this method is limited.

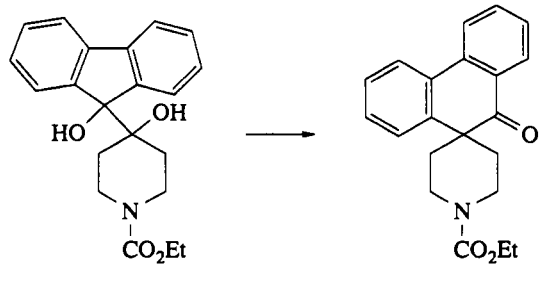
Some diols of heterocycles have been subjected to pinacol rearrangement. Mundy[37] found that (**37**) gave only (**38**) when treated with cold concentrated sulfuric acid (equation 21). It was noted that (**38**) is *not* the product expected from initial cation stability arguments based on anticipated heteroatom dipole effects. The basis for this selectivity remains unclear. An attempt to detect alternative products at short reaction times failed to shed light on this question.



(**37**) (**38**) (21)

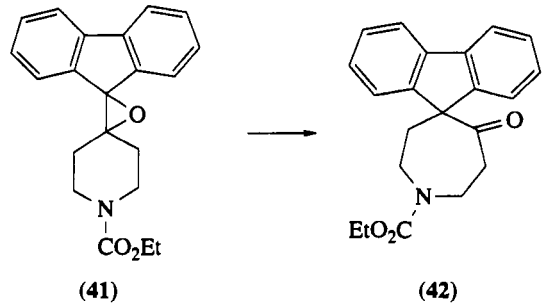
Diols obtained by osmium tetroxide treatment of porphyrins constitute some of the more complex structures which have been subjected to pinacol rearrangement.[38] These reactions left the polycyclic framework intact, and the oxochlorin products were formed by rearrangements which followed normal migratory aptitudes (*e.g.* H, Et > Me).

The diol (**39**) gave (**40**; 49%) when treated with $ZnCl_2$ in acetic anhydride (equation 22).[39] Interestingly, the analogous epoxide (**41**) gave the alternative expanded heterocycle azepinone (**42**) when subjected to $BF_3{\cdot}OEt_2$ in benzene (equation 23).



(22)

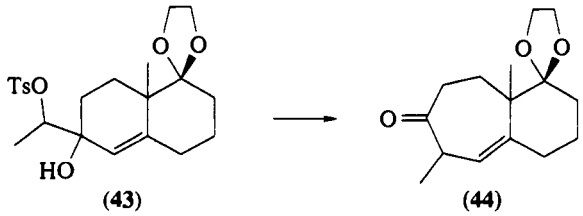
(**39**) (**40**)



(23)

(**41**) (**42**)

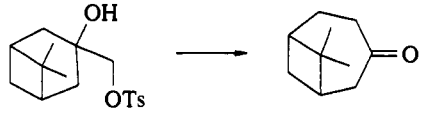
The distinction between the pinacol and semipinacol rearrangements is blurred in instances where the starting material is a diol, but steps are taken to form a derivative in order to control the regiochemistry of the reaction. For example, it is sometimes possible to take advantage of differential alcohol reactivity (primary > secondary > tertiary) to form a specific derivative, such that solvolysis will lead to migration to the less-substituted center.[7b] Corey *et al.*[40] used this approach to effect the ring expansion of (**43**) to (**44**) (note the preference for vinyl over alkyl migration), a key step in a synthesis of the sesquiterpene longifolene (equation 24).



(24)

(**43**) (**44**)

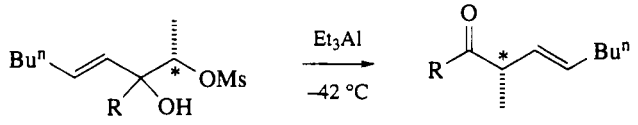
Migration to a primary center has also been effected, as shown by the conversion of (**45**) to (**46**; equation 25).[41] Conditions for these reactions are quite mild, consisting of solvolysis in tetrahydrofuran/$LiClO_4$, with $CaCO_3$ present to neutralize the *p*-toluenesulfonic acid that is formed.



(25)

(**45**) (**46**)

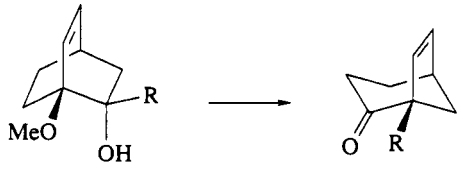
Tsuchihashi and coworkers used methanesulfonate esters in a novel variant.[42] An unusual feature is the use of alanes (Et_3Al or Et_2AlCl) in CH_2Cl_2 solvent at low temperatures to promote the rearrangement. Aryl and vinyl groups migrated more rapidly than alkyl substituents, and the more acidic Et_2AlCl was needed for good results with the latter. Some noteworthy features of this procedure are: (i) migration of vinyl groups with retention of (*E,Z*)-configuration; (ii) clean inversion of configuration at the migration terminus; and (iii) the formation of rather sensitive optically active materials, as illustrated in equation (26).[42b] The authors invoke a 'push–pull' mechanism involving initial formation of an aluminum alkoxide by reaction at the free hydroxy group.



(47) R = alkyl (48) (26)

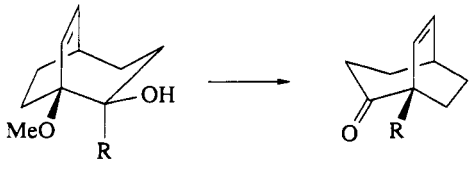
A similar reaction of vicinal diol monoacetates promoted by alanes has been reported.[43] Higher temperatures are needed with these substrates, and in some instances the rearrangement product (ketone) was alkylated (or alkynylated) by the alane promoter. The use of Et_2AlSPh avoided this complication.

Bicyclic systems have provided an interesting framework for examination of stereochemical preferences in the rearrangements of diol monoethers. Monti *et al.*[44] found that the *anti* (double bond and hydroxy group) isomer of the [2.2.2] bicyclic substrate (**49**) gave (**50**) stereospecifically, whereas the *syn* isomer gave a mixture of products (equation 27).



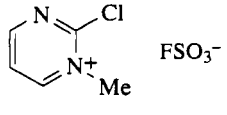
(49) (50) (27)

Surprisingly, the [3.2.2] bicyclic analogs gave contrasting results, with the *syn* isomer (**51**; equation 28) rearranging cleanly to (**52**), whereas the *anti* isomer gave a mixture derived from migration of both the saturated and unsaturated two-carbon bridges.[45] The remarkable net retention at the migration terminus in the formation of (**52**) has been ascribed to conformational effects, which also caused the *syn* substrate to react more rapidly that its *anti* counterpart.



(51) (52) (28)

Although its utility appears to be limited, Mukaiyama *et al.*[46] found that the chloropyrimidinium fluorosulfate (**53**) can effect both functionalization and subsequent pinacol rearrangement in a one-pot procedure. Unsymmetrical secondary–tertiary diols give the products expected of derivatization at the secondary hydroxy group. A major side reaction is elimination.



(53)

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3.3
Acid-catalyzed Rearrangements of Epoxides

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3.3.1 INTRODUCTION

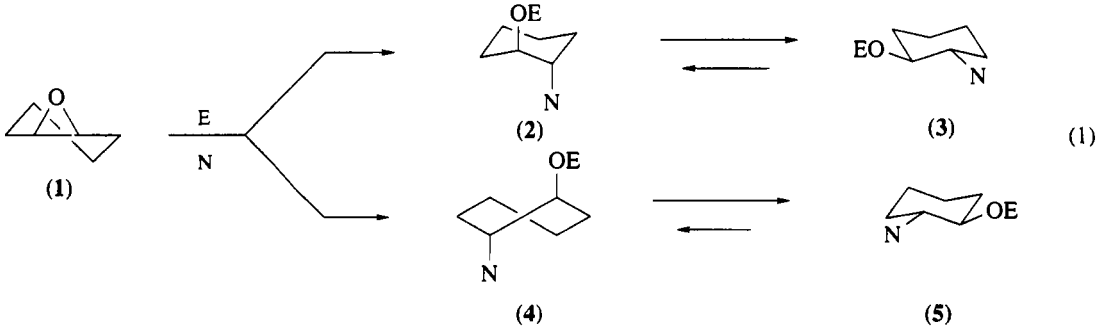
The parallels between acid-catalyzed reactions of epoxides and the pinacol rearrangement are noted in Chapter 3.2 of this volume. Epoxides react more or less readily with acids, but they are at least moderately stable to all but the strongest of bases. It is difficult to find a persuasive instance of epoxide opening, even under basic conditions, that does not involve some probable form of electrophilic assistance, and a case can be made for the view that electrophile bonding/coordination to oxygen is required in order to cleave an epoxide. This electrophilic assistance may be as mild as hydrogen bonding by water in the opening of epoxides with aqueous amines, or as strong as the interactions that occur with concentrated H_2SO_4 or powerful Lewis acids.

3.3.2 STEREOCHEMISTRY OF EPOXIDE OPENING

The stereochemical outcome is known for many epoxide-opening reactions. Examination of the effects of substituents and conditions on stereochemistry can provide insight into the mechanisms of the rearrangements which are the focus of this section. The words *syn* and *anti* are used here to describe mechanistic features, with the terms *cis* and *trans* retained as structural descriptors. The vast majority of epoxide-opening reactions occur with *anti* stereospecificity, *i.e.* backside displacement of the cleaved C—O bond.[1] *Anti* preference dominates sufficiently to warrant calling this the 'normal' stereochemical outcome.

The stereoelectronic aspects of *anti* opening have been explored in studies of cyclohexene oxides, *e.g.* (**1**; equation 1), including steroidal epoxides.[2] For the few reagents which have been examined in detail,

it has been found that an antiperiplanar array of the attacking nucleophile (N in equation 1), the two carbons of the oxirane ring and the epoxy oxygen (bonded to the electrophile E) is very strongly preferred. This antiperiplanar array is feasible with concurrent formation of either a chair (**2**) or twist boat (**4**) cyclohexane skeleton. The appreciable difference in $\Delta\Delta G^{\ddagger}$, which typically favors opening *via* (**2**) over (**4**), suggests that a significant portion of the chair *versus* twist boat energy difference is experienced in the transition states, *i.e.* these reactions are thought to have product-like transition states.



(1)

The chair antiperiplanar mode leads initially to the *trans* diaxial product (**2**), which typically will equilibrate *via* chair–chair interconversion with the *trans* diequatorial conformer (**3**). The twist boat antiperiplanar initial product (**4**) will commonly undergo rotation to form the more stable chair conformer (**5**). Thus both the upper and lower pathways of equation (1) can result in *trans* diequatorial products. Structures (**3**) and (**5**) are enantiomeric; these pathways can be distinguished through the use of an appropriate stereochemical marker (substituent).

Strong preference for chair over twist boat development appears to be general, and is often referred to as the rule of diaxial opening or the Furst–Plattner rule. Twist boat processes can be encouraged by suitable substitution,[3] but in the absence of such special features there are no known examples of cyclohexene oxides which give appreciable amounts of twist boat opened products (sometimes called diequatorial-opening products). The lone apparent exception[4] has been shown[5] to be an artifact caused by an impurity.

Although kinetic control typically favors the *trans* diaxial product, the *trans* diequatorial product is commonly thermodynamically preferred. If the epoxide can be regenerated due to reversibility under particular reaction conditions, a small amount of competing twist boat opening can in principle allow eventual product equilibration. An analogy is found in the classical steroid diaxial to diequatorial dibromide interconversion that is believed to occur *via* reversible formation of a bromonium ion intermediate that slowly drains to the thermodynamically favored product through the kinetically disfavored antiperiplanar twist boat intermediate.[6]

The preference for *anti* opening of epoxides by reagents which function both as an electrophile and a nucleophile is critical to the selectivity observed in some of the rearrangements elaborated below.

Syn (abnormal) opening[7] of epoxides appears to be closely associated with the formation of carbenium ion intermediates, and thus is typically observed when substituents, reagents or conditions favor the formation of carbocations. Increasing solvent polarity and acid strength can lead to *syn* opening. Most of the documented examples involve phenyl-substituted epoxides,[8] although an alkyl[9] or alkynyl[10] group at a tertiary center can be sufficient. *Syn* openings of bicyclic alkene oxides have also been observed.[11] The isolation of *syn*-opening products, *e.g.* the *cis*-diol from 1-phenylcyclohexene oxide, requires the use of a solvent, such as water, which is sufficiently nucleophilic to trap the intermediate carbenium ion before pinacol-like rearrangement can occur.

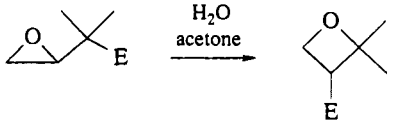
Apparent *syn* opening may also be the result of epimerization after normal *anti* opening. Examples have been identified in the cyanide opening of an anhydro sugar[12] and in the opening of steroidal epoxides by hydrogen fluoride.[13]

3.3.3 PROTIC ACID CATALYZED REARRANGEMENTS

The conjugate base of a protic acid is often sufficiently nucleophilic to prevent rearrangements in epoxide-opening reactions. As a consequence, most studies aimed at examining rearrangements have utilized aprotic Lewis acids, especially BF_3. Many such studies have compared protic and aprotic acids;

examples in this section are restricted to those in which the protic acid proved superior, or was the sole reagent used.

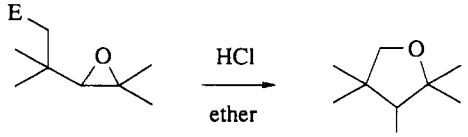
Acidic treatment of epoxides has provided a wealth of unusual rearrangements, many of which involve participation of a remote substituent with the incipient positive center. Conversely, the oxirane ring itself may function as a neighboring group, although this phenomenon has been little studied. Richey and Kinsman[14] examined the solvolyses of substrates such as (**6**; equation 2), and concluded that conversion to (**7**) was probably accelerated by the oxirane. Similar participation may be involved in the acid-catalyzed rearrangement of (**8**) to (**9**; equation 3).[15] On the other hand, Hornback[16] concluded that there was no anchimeric assistance in the acetolyses of the *cis*- and *trans*-tosylates (**10**; equation 4). Both isomers gave mixtures of products derived mainly from acetolysis of the epoxide ring of inverted acetates (**11**).



(2)

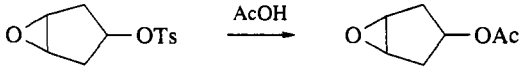
(**6**) (**7**)

E = 3,5-dinitrobenzoate



(3)

(**8**) E = isobutyrate (**9**)

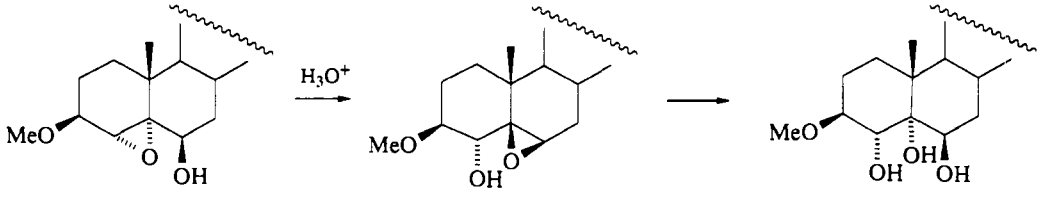


(4)

(**10**) (**11**)

Transannular hydride shifts, first detected by Cope and coworkers[17] in solvolyses of cyclooctene oxide, have subsequently been found in a number of related systems, *e.g.* cyclooctadiene monoepoxides,[18] *exo*-bicyclo[3.3.1]non-2-ene epoxide[19] and 1-oxaspiro[2.6]nonane.[20] In general these reactions do not involve skeletal rearrangements, and they will not be discussed in detail.

Hydroxy groups which are β to the oxirane ring readily participate in opening if the geometrical features are favorable. This, the Payne rearrangement, serves to interconvert two epoxy alcohols with inversion of the central carbon. In the simplest case, that of 2,3-epoxypropan-1-ol, the reaction constitutes a mechanism for racemization. Although usually carried out under basic conditions if the rearranged epoxide is to be isolated, the reaction may also be facile under acidic conditions, as illustrated by an example from the steroid literature (equation 5).[21] In this instance, Payne rearrangement effects the interconversion of (**12**) and (**13**), and normal *anti* opening of the latter by solvent then gives the formal *syn*-opening (from **12**) product, triol (**14**).

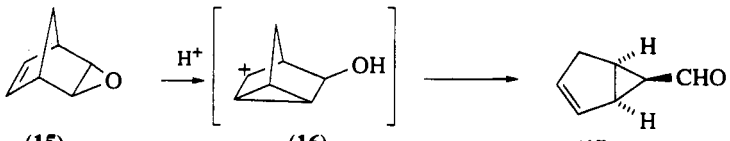


(5)

(**12**) (**13**) (**14**)

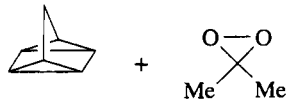
When the hydroxy group is further removed from the oxirane it may still participate in opening, but these reactions have been studied mainly under basic[22] conditions or with Lewis acids, as described in the next section.

Remote double bonds often participate in epoxide openings, sometimes with extensive skeletal changes. *exo*-Norbornadiene oxide (**15**; equation 6) provides an interesting example. Meinwald *et al.*[23] found that this very acid-sensitive material rearranged simply on standing to give the *endo*-aldehyde (**17**), presumably *via* the intermediate nortricyclanol ion (**16**).



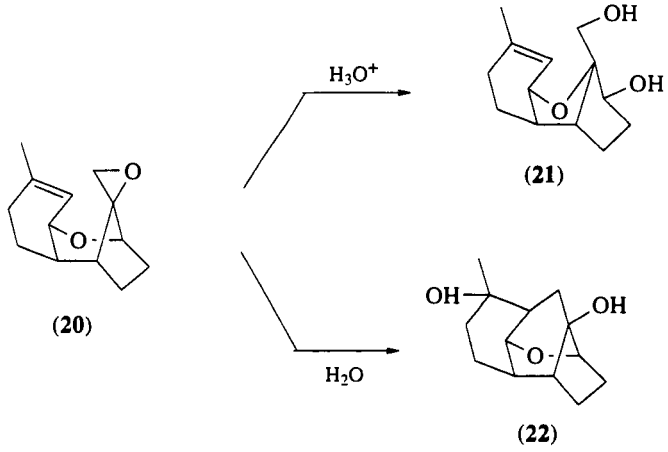
(15) (16) (17) (6)

Murray and coworkers[24] extended their studies of the novel oxidant dimethyldioxirane (**19**) to the reaction of quadricyclane (**18**; equation 7). The epoxide (**15**) was the nearly exclusive monooxidation product when the acetone solution of the oxidant was carefully dried, but in the presence of water a considerable amount of (**17**) was formed.



(18) (19) (15) + (17) (7)

Competition between an alkene and an ether oxygen for participation in epoxide opening is evident in the reactions of trichothecenes (illustrated by the skeletal structure **20**; equation 8). In aqueous acid, participation of the ether oxygen is favored and (**21**) is formed, probably due to preferred cleavage at the tertiary center under the more electrophilic conditions. Under neutral or basic conditions, the diminished role of intermolecular electrophile (water) results in unusual scission of the primary epoxide bond, with formation of (**22**).[25]

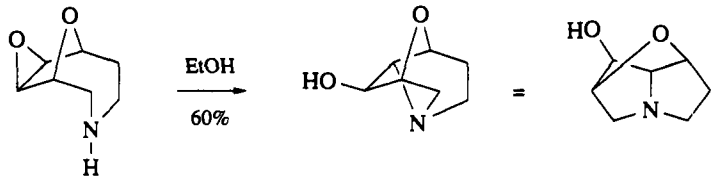


(20) (21) (22) (8)

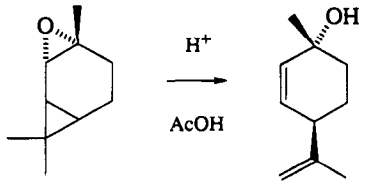
Detailed mechanistic studies of epoxide reactions in aqueous acid led Pocker *et al.* to conclude that protonated epoxide is an intermediate, distinguishable from the ring-opened carbocation (the latter leads to pinacol rearrangement),[26] and more recently a neutral solution zwitterion intermediate has been proposed for reactions in solutions of high ionic strength.[27] Solvent hydrogen bonding of the zwitterion would appear to be equivalent to calling upon water as the electrophile in 'spontaneous' openings such as that shown in equation (8).

An interesting approach to the pyrrolizidine ring system was developed by Glass *et al.*,[28] who found that transannular displacement of the epoxide (**23**; equation 9) could be effected simply by heating in ethanol.

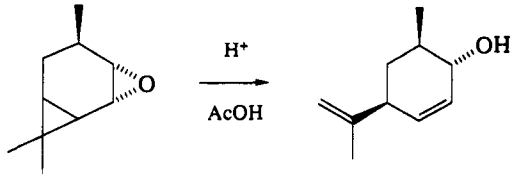
Cyclopropanes can also participate in epoxide openings, much like double bonds. The work of Ohloff and Giersch[29] with carene epoxides illustrates this behavior, *e.g.* (**25**; equation 10) is converted to (**26**) and related carbenium ion derived products, and (**27**; equation 11) similarly forms (**28**).



(23) (24) (9)

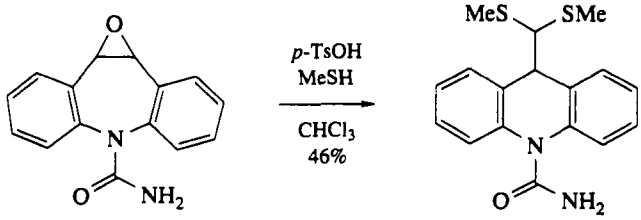


(25) (26) (10)



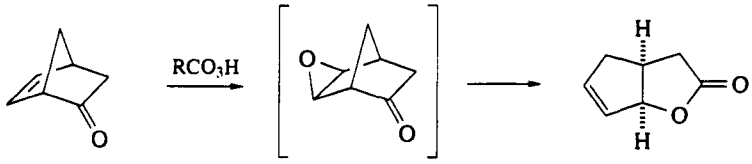
(27) (28) (11)

When the carbamazepin epoxide (**29**; equation 12) is treated with *p*-toluenesulfonic acid in chloroform solvent in the presence of methanethiol, the dithioacetal (**30**) is formed.[30] Apparently, rearrangement to ring-contracted aldehyde occurs more rapidly than normal thiol opening of the epoxide.

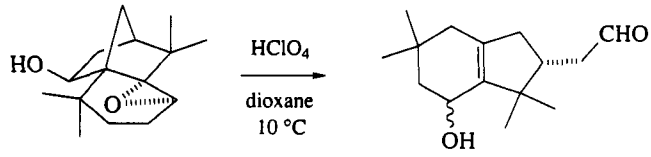


(29) (30) (12)

Attempted peroxy acid epoxidation of the bicyclic ketone (**31**; equation 13) gave the lactone (**33**), instead of several possible rational alternatives.[31] The epoxide (**32**) was implicated as an intermediate when it was independently synthesized from the epoxy alcohol, and shown to give (**33**) on treatment with aqueous acid.[32] A mechanism involving scission of the acyl bridgehead bond *via* the hydrated 1,1-diol form of the ketone was proposed to account for the formation of this unexpected product. The rearrangement of the isolongifolene derivative (**34**; equation 14) appears to be mechanistically related. The product (**35**) is formed by brief treatment with dilute $HClO_4$ in dioxane as a mixture of isomers believed to arise by acid-catalyzed epimerization of the carbinol center.[33]



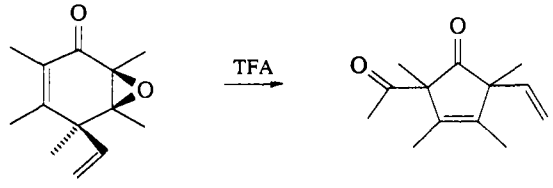
(31) (32) (33) (13)



(14)

(34) (35)

Hart and coworkers[34] used trifluoroacetic acid to catalyze some deep-seated epoxide rearrangements, illustrated by the examples in equations (15) and (16). An unusual mechanism involving scission of the epoxide C—C bond was suggested for the conversion of (**38**) to (**39**), in order to accommodate deuterium-labeling results.



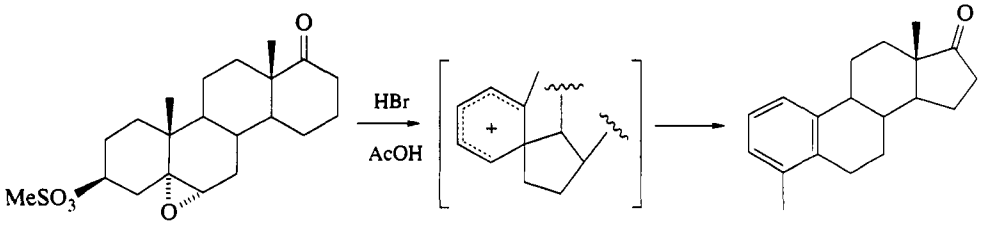
(15)

(36) (37)

(16)

(38) (39)

HBr in HOAc has been used to effect the rearrangement/aromatization of the androstenone epoxide (**40**). The use of DBr/DOAc and ^{13}C NMR analysis led to the conclusion that the reaction takes place *via* the phenonium ion (**41**) shown in equation (17).[35]



(17)

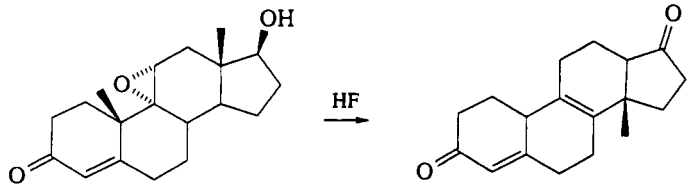
(40) (41) (42)

One of the few (intentional) applications of HF to epoxide rearrangement is found in an informative study by Audouin and Levisalles,[36] who isolated fluorohydrin and diene products on mild treatment of (**43**; equation 18); these proposed intermediates were converted to the dione (**44**) when resubjected to the reaction conditions.

Some α-substituted epoxides exhibit predictable and synthetically useful behavior when subjected to acids. Others are thermally unstable, and appear to rearrange by different mechanisms in the presence and absence of acids.

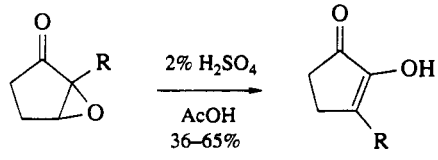
Lewis acid induced reactions of α-carbonyl epoxides have been extensively studied, but protic acid reactions in general have not found favor. An exception is shown in equation (19). The protic acid mixture shown was found to be superior to BF_3 etherate for the desired rearrangement.[37]

In the Darzens' aldehyde synthesis the α-substituent is a carboxyl(ate) group, which is lost during or subsequent to rearrangement. The normal mode of reaction of glycidic acids generates the new carbonyl group at the point of the original carboxyl group attachment, as shown in equation (20). However, when



(18)

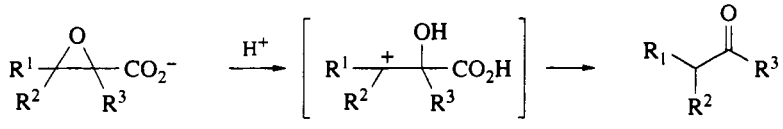
(43) (44)



(19)

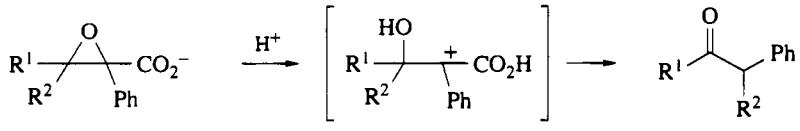
(45) R = alkyl (46)

the α-cation is stabilized by phenyl substitution as in (**49**), the product (**50**), derived from abnormal α-opening, may dominate (equation 21), depending upon the β-substituents.[38]



(20)

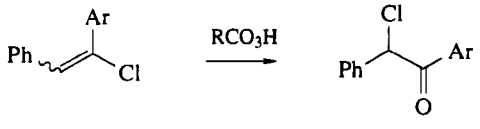
(47) R^3 = H or alkyl (48)



(21)

(49) (50)

Epoxides derived from vinyl halides and vinyl acetates tend to rearrange readily on heating. McDonald and his coworkers uncovered several mechanistically intriguing examples of thermal rearrangements involving α-chloro epoxides. In some instances the epoxides could not be isolated, but presumably are reactive intermediates, *e.g.* in the peroxy acid reaction of chlorostilbenes.[39] A common intermediate was proposed to account for the formation of the same (chlorine-migrated) product from both geometrical isomers of (**51**; equation 22).



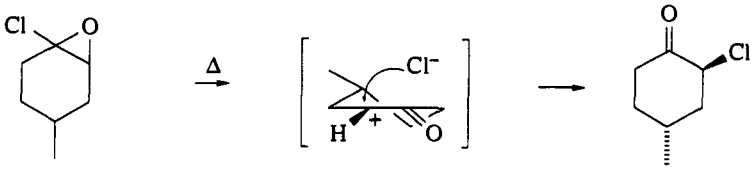
(22)

(51) *(E) or (Z)* (52)

The *cis* and *trans* isomers of (**53**) both gave (**54**) as the kinetically controlled product (equation 23).[40] These results, and those obtained in a study of (+)-2-chloronorbornene *exo*-oxide,[41] led the authors to conclude that the thermal reaction occurs by way of intermediate α-ketocarbenium–chloride ion pairs; preferential axial attack results in the formation of (**54**) as shown.

The role of acid in some of these rearrangements is not obvious. Kirrmann and coworkers[42] determined that thermal and acid-catalyzed reactions of α-chloro epoxides give different products in some instances. Again, preferred migration of chlorine was observed in thermal reactions.

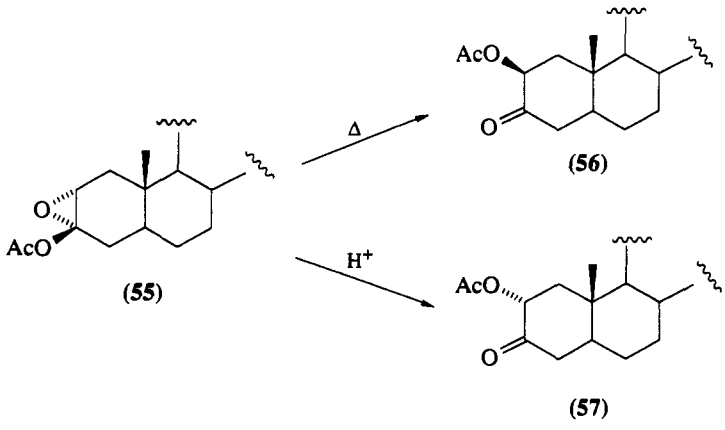
Different mechanisms for thermal and acid-catalyzed rearrangements of steroidal α-acetoxy epoxides have also been proposed.[43] On heating (**55**; equation 24), intramolecular migration of the acetate group occurs, with stereospecific inversion of the cleaved epoxide center leading to (**56**). Treatment of (**55**)



(53) *cis* or *trans* (54)

(23)

with acid results in formation of the more stable equatorial acetate (**57**). From rate studies, it was demonstrated that (**56**) is not an intermediate in the acid-catalyzed formation of (**57**). Although (**56**) does rearrange to (**57**) under the acidic reaction conditions, it does so much more slowly than the direct conversion of (**55**) to (**57**). The acyclic analog (**58**) gave the aldehyde (**59**) both thermally and under acid catalysis (equation 25). Several other reagents and conditions were examined in an effort to clarify the mechanisms of various reactions of (**58**), but some uncertainty remains.[44]



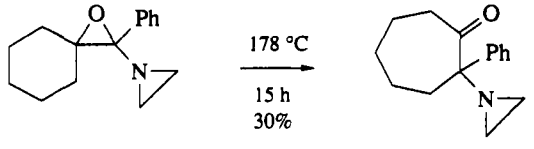
(55) (56) (57)

(24)

(58) R = alkyl, Ph (59)

(25)

Stevens and Pillai[45] prepared and isolated the azirane (**60**; equation 26), a rare example of an α-amino epoxide. This remarkably stable material required vigorous heating in *o*-dichlorobenzene to effect the ring expansion to (**61**); the remainder was converted to polymeric material.

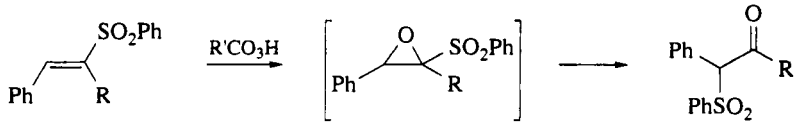


(60) (61)

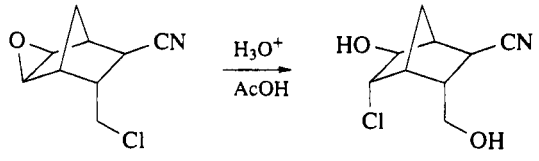
(26)

Yamamoto *et al.*[46] pointed out potential utility as an 'acyl anion' equivalent for the reaction shown in equation (27). The reaction of (**62**) with *m*-chloroperbenzoic acid was carried out in refluxing CCl_4. The presumed intermediate epoxide (**63**) rearranged directly under these conditions to give the product (**64**) in excellent yield.

More remote substituents may also participate in epoxide opening/rearrangement. Christol and coworkers examined several 5,(6)-substituted-2,3-norbornene *exo*-oxides under acidic conditions, and found that certain 5-*endo* substituents played a part in oxirane opening. For example, oxa rings were formed in reactions of substrates bearing 5-*endo*-methoxycarbonyl or -hydroxymethyl groups.[47] A novel 1,4-migration of chloride was also detected (equation 28).[48]

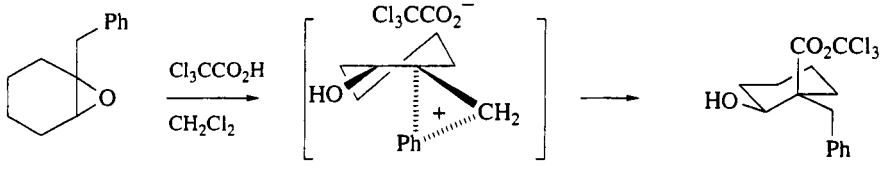


(62) (63) (64) (27)



(65) (66) (28)

Macchia *et al.*[49] observed that the proportion of *syn* opening of 1-benzylcyclohexene oxide increased as the nucleophilicity of the acid/solvent decreased, and became the major pathway when trichloroacetic acid in methylene chloride was employed (equation 29). The relative amount of *syn* opening was greater for (**67**) than for 1-methylcyclohexene oxide under the same conditions. The authors concluded that a phenonium ion intermediate, *i.e.* (**68**), was generated, even though no product involving phenyl migration was detected.

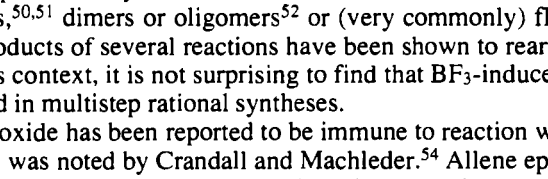


(67) (68) (69) (29)

3.3.4 BF_3-INDUCED REARRANGEMENTS

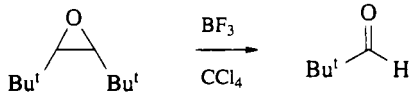
Scores of epoxides have been subjected to BF_3 (mostly as the etherate), and this appears to be the most widely used Lewis acid for rearrangement. The BF_3 is often consumed or altered in the course of these reactions, and is thus a reagent rather than a catalyst, although less than an equivalent is effective in some instances. Steroidal and terpene epoxides have been favorite substrates for study. In spite of the very extensive literature in this area, it is difficult to make product predictions with confidence. Some processes are clean and occur in high yield; many others give low yields and multicomponent mixtures. There is no single recommended standard set of conditions, and many solvent, temperature and time combinations have been described. Products range from simple hydride shift carbonyl isomers to structures formed by multistep rearrangement. Epoxides may also be converted, with or without skeletal rearrangement, to unsaturated alcohols,[50] dienes,[50,51] dimers or oligomers[52] or (very commonly) fluorohydrins.[53] To complicate matters further, the products of several reactions have been shown to rearrange to other materials on longer exposure. Given this context, it is not surprising to find that BF_3-induced rearrangements of epoxides are not commonly used in multistep rational syntheses.

On the other hand, no epoxide has been reported to be immune to reaction with BF_3, although an interesting example of inertness was noted by Crandall and Machleder.[54] Allene epoxides are usually too sensitive to acids to be isolable from peroxy acid epoxidations, but the bulky *t*-butyl groups on (**70**; equation 30) make it exceptionally unreactive. Several hours of reflux with BF_3 in ether were required to effect the conversion to (**71**).



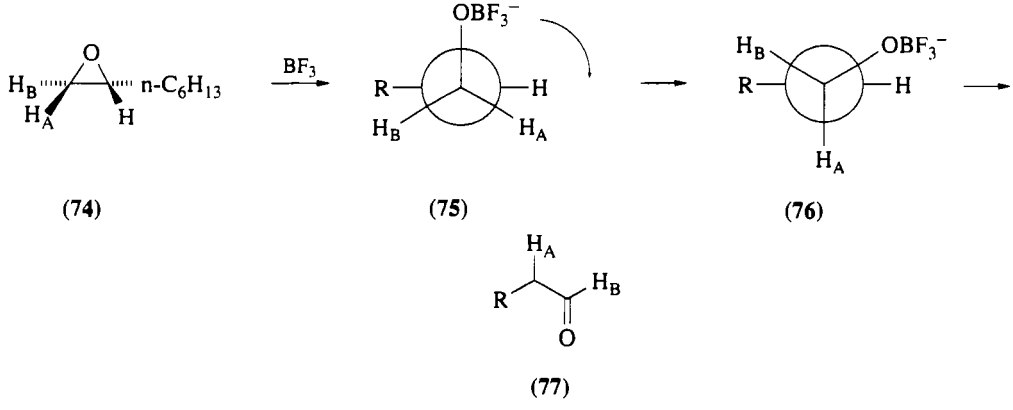
(70) (71) (30)

Steric effects are presumably also responsible for the formation of pivalaldehyde (**73**) when (**72**) is treated with ether-free BF_3 in CCl_4 (equation 31).[55] Although both isomers (*E* and *Z*) of (**72**) form pivalaldehyde as the major product under these conditions, a sharp distinction between the isomers was noted in ether solvent. The (*E*)-isomer was recovered unchanged from conditions that with the (*Z*)-isomer gave fluorohydrin in good yield.[55]

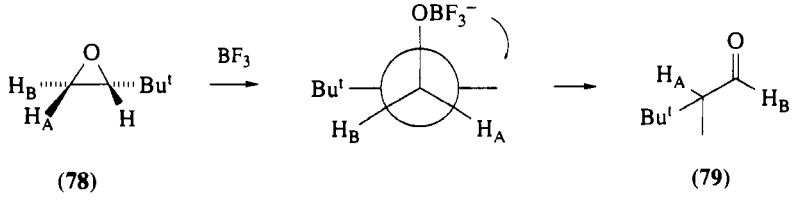


(72) (73) (31)

Mechanistic details are rarely obvious in BF_3–epoxide reactions, and various views ranging from concerted rearrangement to free carbenium ion intermediate processes have been put forward. The bulk of evidence, especially that obtained in elegant experiments carried out in the laboratory of Coxon and coworkers in New Zealand, supports a general mechanism involving carbenium ions which retain modest stereochemical memories. Coxon has introduced the perspective of relatively slow epoxide opening to give a carbenium ion which is then subject to rapid migration of adjacent groups, at rates which can be somewhat faster than conformer equilibration in the cleaved complex. Preferential direction of rotation to give a conformer which is stereoelectronically suitable for a 1,2-shift is dictated by steric interactions between the OBF_3 moiety and groups on the adjacent carbocation center. Rotation towards the smaller of these groups correctly predicts the results obtained with simple aliphatic epoxides. For example, by use of deuterium labeling with corrections for isotope effects, it was found that H_A migrates 1.4 times more readily than H_B in 1,2-epoxyoctane (**74**; equation 32).[56] This outcome was attributed to preferred rotation, as shown in the initial conformer (**75**), towards the smaller group (H *versus* alkyl) at the carbenium ion center. As a conformer with suitable orbital overlap features arises, (**76**), migration of this bond (H_A) must take place at a rate greater than or equal to that for continued rotation, in order to account for the formation of (**77**) as the major product. Similar results were obtained with epoxide (**78**; equation 33), which exhibited a preference of $H_A/H_B = 1.9$ for the formation of the aldehyde (**79**).[57]

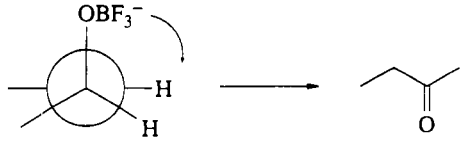


(74) (75) (76) (77) (32)

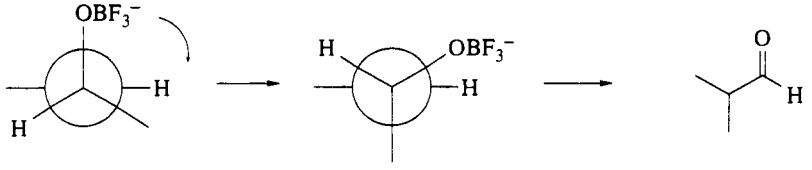


(78) (79) (33)

This mechanistic view can be used to rationalize other epoxide rearrangements. For example, the observation[55] that BF_3 treatment of (*Z*)-2,3-epoxybutane gives only 2-butanone (equation 34) is nicely accommodated. The (*E*)-isomer gives some isobutyraldehyde (2-butanone:aldehyde = 3:1), which again may be rationalized by this model. Preferred rotation (as in **82**) leads to conformer (**83**), in which the poorer intrinsic migratory aptitude of the methyl group (compared to H) prevents migration from being much faster than further rotation (equation 35).

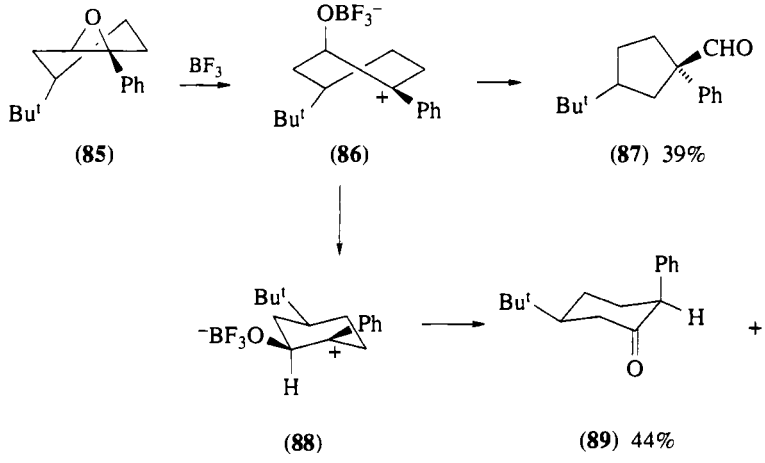


(80) (81) (34)



(82) (83) (84) minor product (35)

The important study of Berti *et al.*[58] (also discussed in the context of the pinacol rearrangement: see equations 8 to 11 of Chapter 3.2 in this volume) included BF_3-induced reactions of the *cis*- and *trans*-epoxides (**85**; equation 36) and (**91**; equation 37), respectively. These very informative reactions show that, at least under the particular reaction conditions used in this work (benzene as solvent), the Coxon mechanism must be expanded to include an appreciable antiperiplanar geometrical feature. Unlike the pinacol rearrangements of the related diols, which gave only ketone (**89**) and aldehyde (**90**) under the same conditions, epoxide (**85**) gives, in addition to these same products, a significant amount of aldehyde (**87**). This appears to require the involvement of the twist boat conformer (**86**), which is the expected intermediate if the shown starting material conformer opens at the tertiary benzylic center with antiperiplanar constraints. Subsequent rotation of (**86**) to the chair conformer (**88**) allows formation of the ketone (**89**) and the aldehyde (**90**).



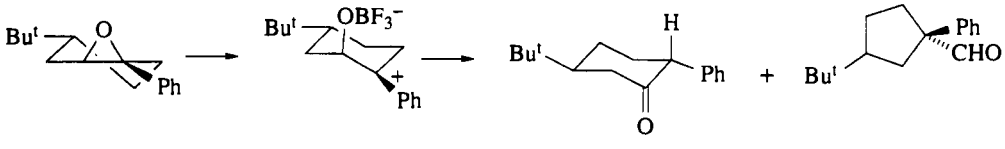
(85) (86) (87) 39%

(88) (89) 44% (90) 17% (36)

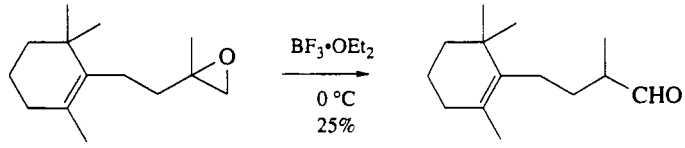
This view is reinforced by the reaction of isomer (**91**; equation 37). In this case antiperiplanar opening would occur directly to give a chair (**92**), which can then produce ketone (**93**) and aldehyde (**90**). The striking feature here is the preponderance of aldehyde relative to ketone, not expected based on migratory aptitude considerations, and quite different from the pinacol rearrangement of the related diols. Whatever the cause of this stereocontrol, it signifies fairly strong preference for migration to the back side of the cleaved epoxide center. It should be noted that some possible antiperiplanar-opening intermediates, *e.g. trans*-fluorohydrins, will not serve to rationalize this intriguing behavior.

The formation of aldehydes from 1,1-disubstituted epoxides has occasionally found use in synthesis, although simpler aldehydes in particular tend to form dioxolane dimers by BF_3-induced reaction with epoxide.[57] Hill *et al.*[59] converted the epoxide (**94**), which had been prepared from a β-ionone derivative, into luciferin aldehyde (**95**) by treatment with cold BF_3 etherate (equation 38).

Coxon and coworkers[60] found a small but consistent bias favoring the product involving inversion of the cleaved center when eight epoxides (four pairs of α- and β-isomers) derived from *exo*-methylene steroids were subjected to BF_3 etherate in benzene at room temperature. A carbenium ion intermediate was

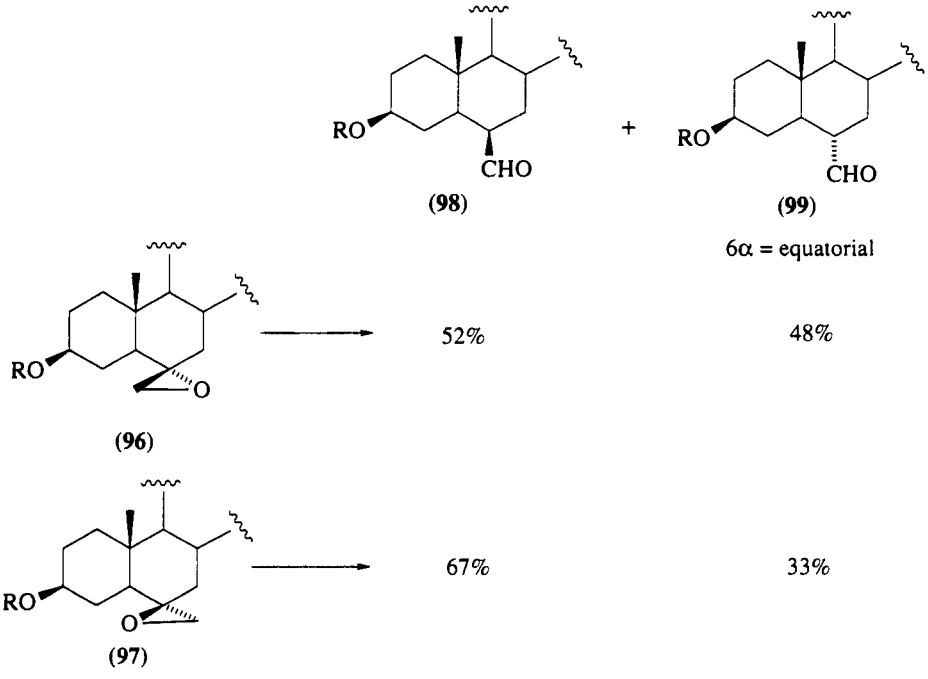


(91) (92) (93) 12% (90) 88% (37)



(94) (95) 25% (38)

proposed, and appears to be required to account for the nearly identical mixtures of epimeric aldehydes obtained from the stereoisomeric pairs of epoxides. This result is not due to equilibration, which would strongly favor the equatorial aldehyde. One isomeric pair is used to illustrate these features (equation 39).

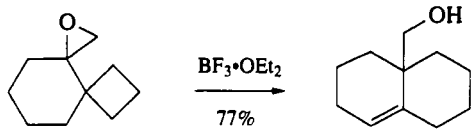


(39)

The 1,1-disubstituted epoxide (**100**; equation 40) undergoes ring expansion rather than hydride migration, to afford materials such as (**101**) and related products.[61] It is conceivable that an aldehyde was generated in this instance, which then rearranged to the isolated products. This kind of behavior is seen with (**102**; equation 41) which upon brief treatment with BF_3 afforded aldehyde (**103**) and ketone (**104**) in nearly equal amounts. When resubjected to the reaction conditions the aldehyde (**103**) gave a new ketone (**105**). Compound (**103**) was used as a precursor to the hydrocarbon cuparene, which has the structure of (**103**) modified by reduction of CHO to Me; in spite of the modest yield, this proved a convenient approach to a structure with two adjacent quaternary carbons.[62]

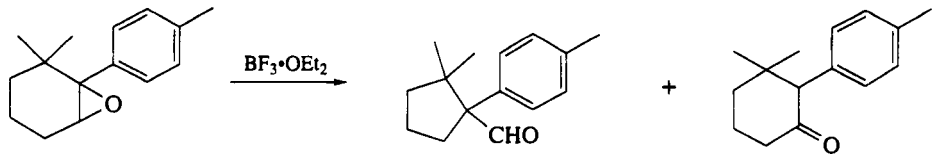
Some unsymmetrical tetrasubstituted alkenes (and hence epoxides) have become more available since the advent of McMurry low-valent Ti reductive-coupling procedures and related reactions, but relatively little use has been made of this in epoxide rearrangement studies. An exception involves the cycloheptyl derivative (**106**; equation 42) which was found to rearrange cleanly to ketone (**107**).[63]

Rearrangement of a tetrasubstituted epoxide is a key step (equation 43) in a recent approach to the taxane ring system.[64]

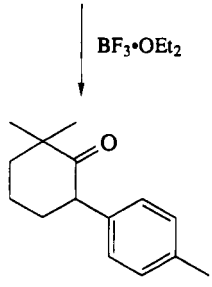


(40)

(100) **(101)**

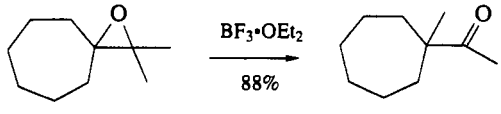


(102) **(103)** 22% **(104)** 25%



(41)

(105)



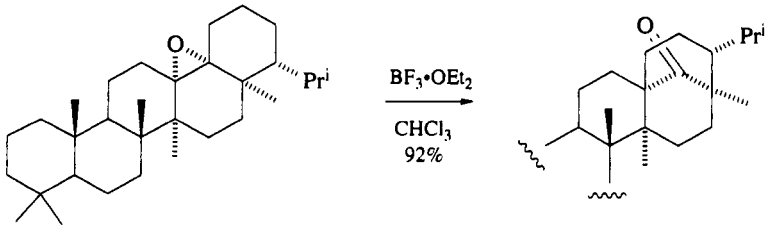
(42)

(106) **(107)**

(43)

(108) **(109)**

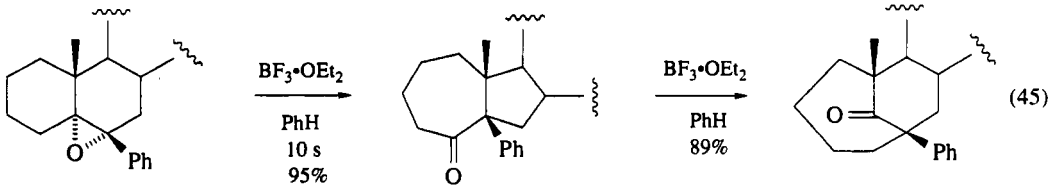
Berti *et al.*[65] found that the tetrasubstituted epoxide derivative (**110**; equation 44) of the triterpene hopane gave an efficient rearrangement to the ketone (**111**).



(44)

(110) **(111)**

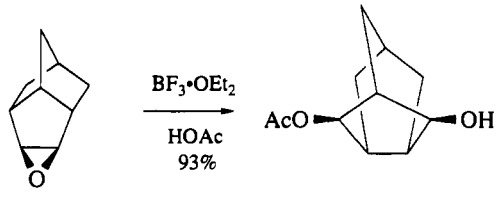
The phenyl substituent appears to be a major factor leading to the interesting results displayed in equation (45).[66] The timing needed to obtain the excellent yield of (**113**) is noteworthy, and indicates just how easy it can be to miss interesting chemistry associated with such rapid reactions.



(45)

(**112**) (**113**) (**114**)

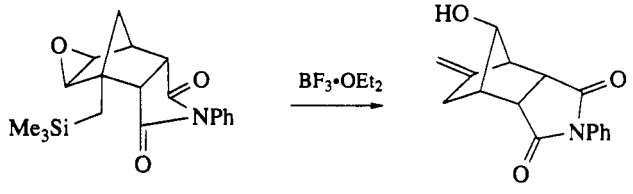
Disubstituted epoxides tend to give mixtures of products when treated with BF_3. An interesting exception is found in the novel approach to the noradamantane ring developed by Majerski and Hamersak.[67] The epoxide (**115**; equation 46) gives an excellent yield of this ring system with other acids as well, but BF_3 in HOAc offers the added advantage of directly differentiating the two alcohol functions in the formation of (**116**).



(46)

(**115**) (**116**)

The β-cation-stabilizing influence of the trimethylsilyl group probably assists in the rearrangement of (**117**) to (**118**; equation 47).[68]



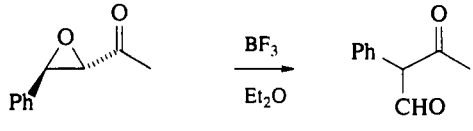
(47)

(**117**) (**118**)

Reactions of BF_3 and epoxides bearing an α-electron-withdrawing group (EWG) have been extensively studied. Often the course of such reactions can be predicted by assuming formation of a carbenium ion β to the EWG (avoidance of positive charge adjacent to the EWG dipole). When this occurs, facile migration of the EWG may take place.

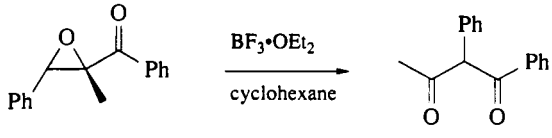
House and Reif examined certain heavily substituted acyclic keto epoxides, and found diverse behavior as illustrated by equations (48) to (51).[69]

The reaction of (**119**; equation 48) follows what may be regarded as normal behavior, *i.e.* the product is that predicted by β-cleavage followed by migration of the acyl group. Rearrangement of (**121**; equation 49) can be similarly explained. The formation of (**124**; equation 50) from (**123**) is most expediently regarded as involving β-cleavage, but with aryl migration occurring more rapidly than benzoyl migra-

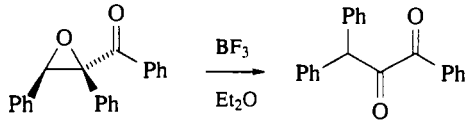


(48)

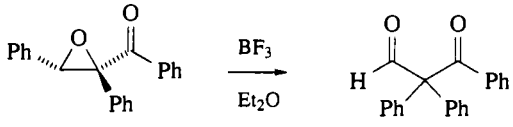
(**119**) (**120**)



(121) (122) (49)



(123) (124) (50)

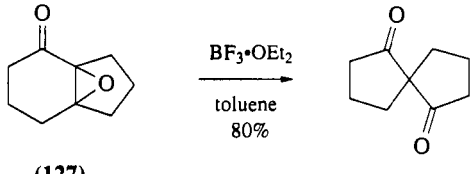


(125) (126) (51)

tion. This order of migratory aptitude appears to be in keeping with observations in other rearrangements. The (*Z*)-isomer (**125**; equation 51) gave an unexpected product, (**126**). The formation of this aldehyde requires cleavage of the epoxide α to the EWG. These early examples served to frame some of the important mechanistic questions.

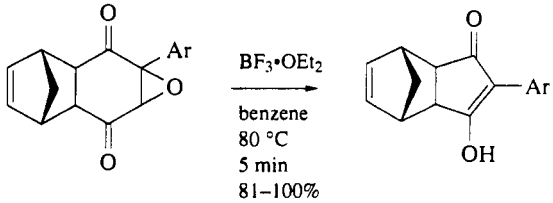
Kagan *et al.*[70] examined a series of 3-phenylglycidic esters (EWG = ethoxycarbonyl) and observed migratory preferences which parallel those developed in other studies. However, one important caveat arose from examination of variations in acid, solvent and temperature: the course of the reactions proved to be highly dependent on these variables, leading Kagan to disavow predictability based on structural features alone.

Nonetheless, acyl epoxides and related materials have given useful results when subjected to BF_3. The interesting spiro diketone (**128**; equation 52) for example, is readily prepared by BF_3 etherate treatment of the epoxide (**127**).[71]



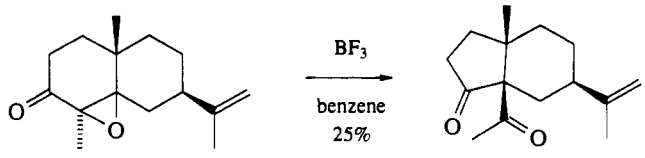
(127) (128) (52)

When the initially formed rearrangement product is a β-keto aldehyde, facile loss of the formyl group is sometimes observed (retro-aldol). An interesting example is found in the reactions of the quinone derivative (**129**; equation 53) Rearrangement accompanied by deformylation occurred under a variety of acidic conditions, but the BF_3-induced reaction was especially efficient.[72]



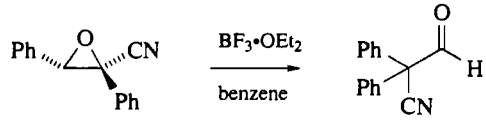
(129) (130) (53)

An example from the terpene literature[73] is shown in equation (54). The corresponding epoxy alcohol in this instance gave a complex mixture from which no product could be isolated. The formation of a second carbonyl group may help to stabilize the product *via* complex formation, as discussed by House.[69]

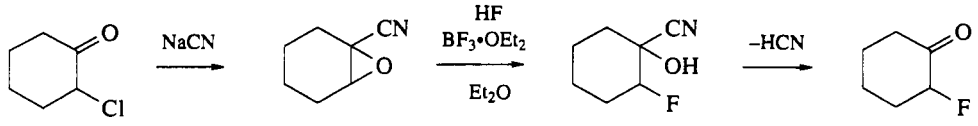


(131) (132) (54)

McDonald and Hill[74] found that α-cleavage is a common feature of aromatic epoxynitriles such as (**133**), which gave (**134**) in excellent yield (equation 55). In simpler systems the nitrile group typically leads to β-cleavage, a feature that has been used for the synthesis of fluoro ketones as shown by the example in equation (56).[75]

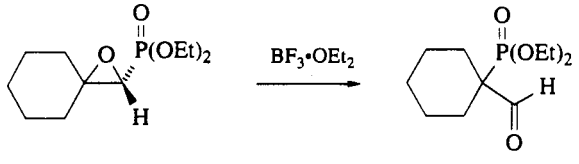


(133) (134) (55)

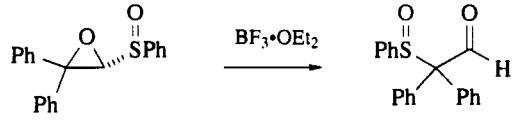


(135) (136) (137) (138) (56)

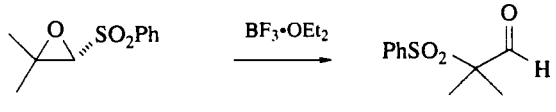
Other EWG which migrate readily upon β-cleavage of an epoxide include the phosphonate ester[76] (equation 57), sulfoxide (equation 58)[77] and sulfone (equation 59).[78]



(139) (140) (57)



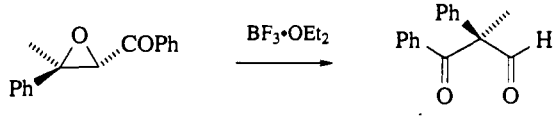
(141) (142) (58)



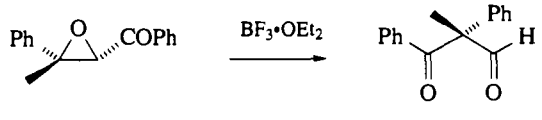
(143) (144) (59)

Bach and Domagala have demonstrated that the acyl migrations which occur when diastereomers (**145**; equation 60) and (**147**; equation 61) are treated with BF_3[79] (and in the case of (**145**), the analogous

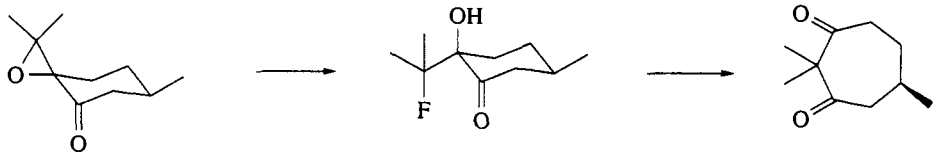
thermal[80] reaction) are stereospecific, in each instance taking place with complete inversion at the migration terminus, yielding the enantiomers (**146**) and (**148**), respectively. It was noted that such behavior is more in keeping with a concerted rearrangement than a carbenium ion process. The contrast to the modest levels of inversion discussed previously is appreciable, but it is not clear if this signals a fundamental change in mechanism or some feature of the carbonyl group which allows especially favorable interaction with the developing positive center. Bach suggested that the carbonyl group may have a conformational requirement for migration, and explored this idea with the systems shown below.[81] It was found that fluorohydrin formation occurred very rapidly with (**149**; equation 62) and (**152**; equation 63), although none was detected with (**154**; equation 64) under conditions where rearrangement to (**155**) took place. The fluorohydrins (**150**) and (**153**) both rearranged to diones rapidly in refluxing benzene containing BF_3. It was thus established that the fluorohydrins are viable but not necessarily required precursors to the dione product. The authors suggested that fluorohydrin formation occurred because acyl migration was geometrically retarded, and that the fluorohydrin in an appropriate conformation could serve as the immediate precursor to the dione. If the fluorohydrins are formed by normal *anti* opening of the epoxides, one would expect retention at the migration terminus in these reactions, an interesting possibility that remains to be tested on a suitably designed substrate.



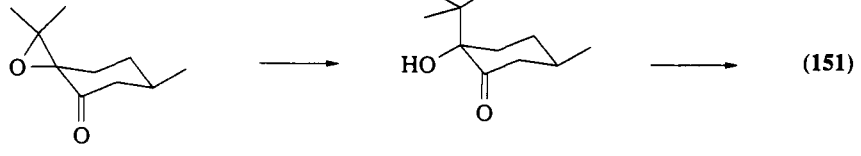
(145) (146) (60)



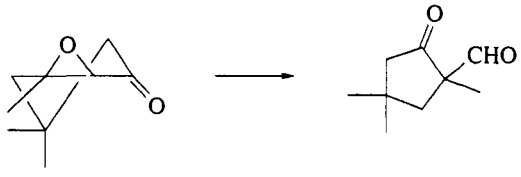
(147) (148) (61)



(149) (150) (151) (62)



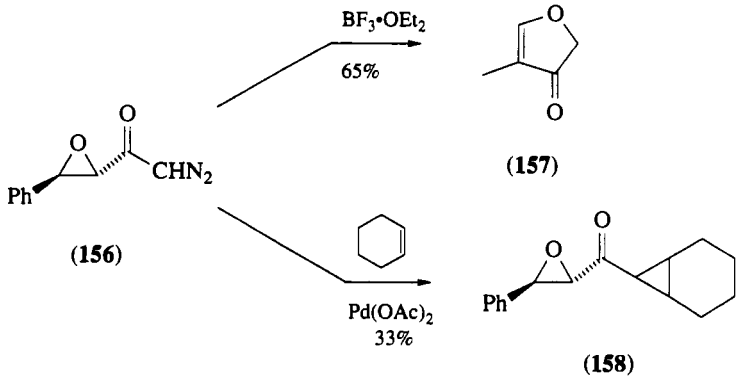
(152) (153) (151) (63)



(154) (155) (64)

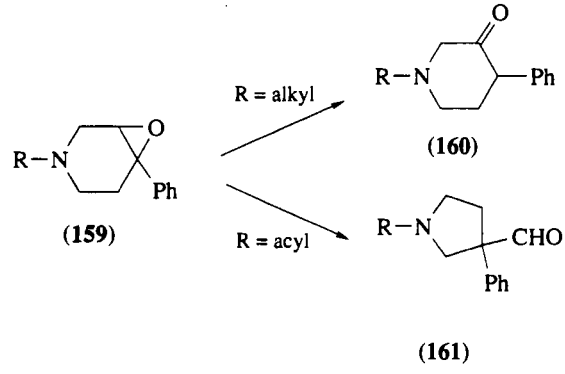
Zwanenburg *et al.* examined keto epoxides which contained an acid-sensitive diazomethyl group, *e.g.* (**156**; equation 65), and found conditions for selective initial reaction at both sites. BF_3 treatment gave the heterocycle (**157**), presumably by epoxide rearrangement followed by a carbene reaction with the

carbonyl group.[82] $Pd(OAc)_2$ catalysis was used to retain the epoxide function while carrying out typical carbenoid reactions, illustrated by the formation of (**158**).[83]



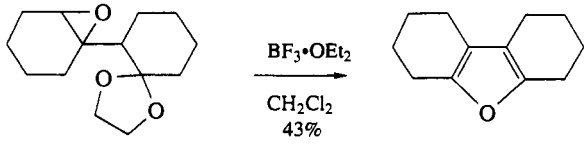
(65)

A subtle substituent effect is evident in the reactions of (**159**; equation 66); when the amine (R = alkyl) is subjected to acid-induced rearrangement it gives the hydride migration product (**160**), whereas the amide (R = acyl) reacts almost exclusively by ring contraction.[84]



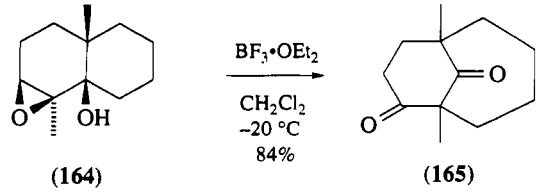
(66)

The epoxy ketal (**162**; equation 67) gave a modest yield of the furan (**163**) along with several other unidentified products.[85]



(67)

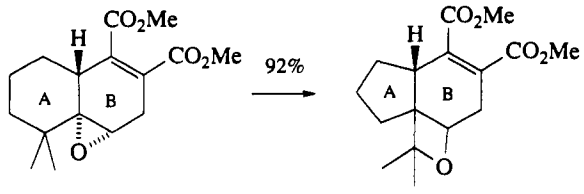
An effort to use an adjacent hydroxy group to force the conversion of a [4.4.0] derivative (**164**; equation 68) to the [5.3.0] ring system was thwarted by an alternative high yield rearrangement to the [4.3.1] bicyclic product (**165**).[86]



(68)

Another example of a rational synthetic plan going awry occurred with (**166**; equation 69). In this instance the desired reaction was simple methyl migration followed by loss of a proton, but instead

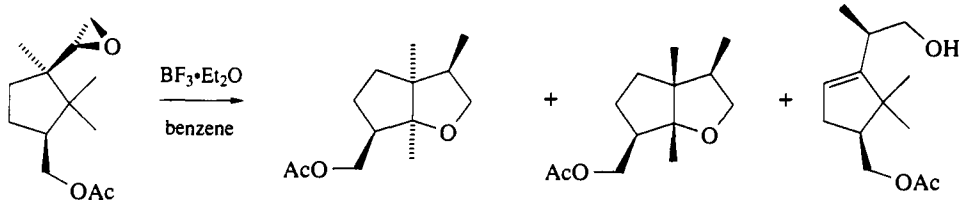
contraction of ring A took place. A high yield of oxetane (**167**) was isolated in this example. The stereochemistry of this product was attributed to a mechanism involving opening and reclosure of ring B.[87]



(69)

(**166**) (**167**)

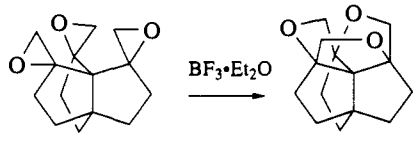
The epoxy oxygen reappears in the furanoid rings of (**169**) and (**170**) when (**168**) is subjected to typical rearrangement conditions (equation 70). The stereochemical relationships of these products support a stepwise carbenium ion process.[88]



(70)

(**168**) (**169**) 38% (**170**) 13% (**171**) 42%

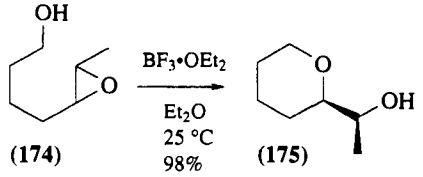
The remarkable, highly symmetrical compound (**173**) is generated when the triepoxide (**172**; equation 71) is treated with BF_3 etherate.[89]



(71)

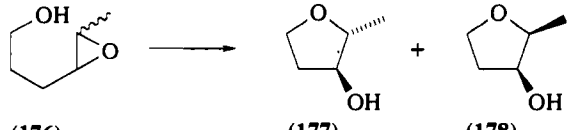
(**172**) (**173**)

Remote hydroxy groups participate in various epoxide openings. Coxon *et al.*[90] observed the formation of cyclic products in the peroxy acid epoxidation of some unsaturated alcohols, and examined the process in greater detail using BF_3 in ether. These reactions exhibited a ring size preference: 5 > 6 > 7. The reactions of *cis*- and *trans*-5,6-epoxyheptan-1-ol and *cis*- and *trans*-4,5-epoxyhexan-1-ol appeared to be stereospecific, with inversion of the cleaved center as expected for opening with participation of the hydroxy group. In contrast, the reactions of *cis*- and *trans*-3,4-epoxypentan-1-ol were not stereospecific, in spite of the apparently favored formation of five-membered ring products. Some of these features are illustrated in equations (72) and (73).



(72)

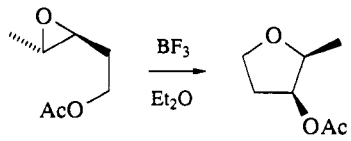
(**174**) (**175**)



(73)

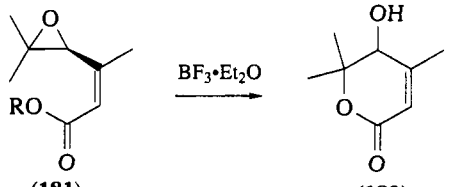
(**176**)	(**177**)	(**178**)
cis	86%	8%
trans	35%	3%

A novel mechanism involving an orthoester intermediate was proposed to account for the stereochemical features of reactions like that shown in equation (74), in which the relative configuration of the epoxide is retained.[91]



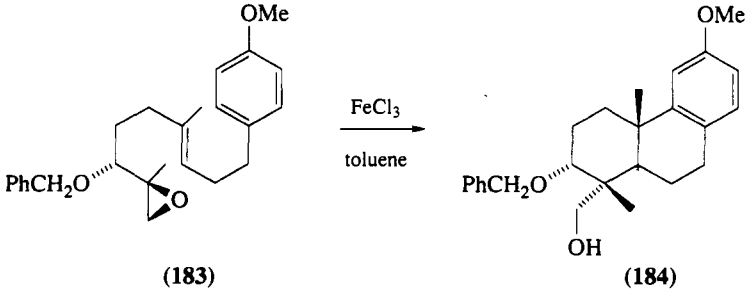
(179) (180) (74)

Suitably positioned carbonyl groups may cause ring closure, leading to either five- or six-membered ring lactones. BF_3 etherate proved to be more selective than protic acids in a study of unsaturated epoxides, giving exclusively the larger ring size, as illustrated in equation (75).[92]

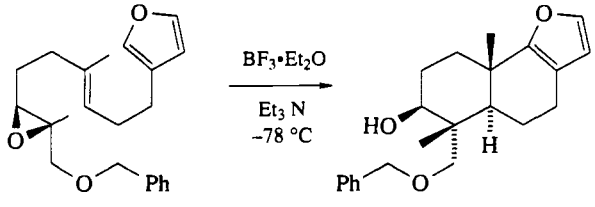


(181) (182) (75)

Among the best-known epoxide rearrangements are those which utilize remote double bonds in biomimetic reactions.[93] Two recent syntheses of aphidocolin illustrate variants of this concept. The application described by Van Tamelen *et al.*[94] is outlined in equation (76), while the Tanis *et al.*[95] alternative is shown in equation (77). These reactions tend to be highly stereoselective. Efforts are usually made to avoid nucleophilic gegenions which can disrupt the desired reaction cascade; a wide variety of catalysts in addition to BF_3 have been explored. In the conversion of (**185**) to (**186**), for example, an unusual 2:1 ratio of $BF_3{\cdot}OEt_2$ and triethylamine in a three component solvent was found to give the best yield.



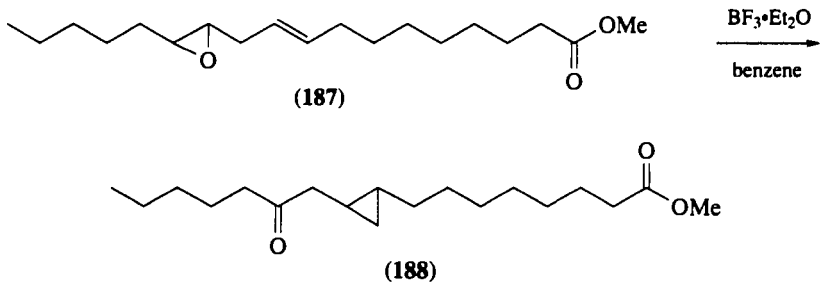
(183) (184) (76)



(185) (186) (77)

Conacher and Gunstone[96] reported the novel conversion of the diene monoepoxide methyl vernolate (**187**; equation 78) to the cyclopropyl keto isomer (**188**). Later Italian work[97] supported this conclusion, and furnished additional examples of cyclopropane formation.

Excellent yields of bi- or poly-cyclic materials may be obtained if the starting material contains significant portions of the desired product structure. Thus the isogermacrone epoxide (**189**; equation 79) is transformed into (**190**) by brief treatment with BF_3 etherate, while longer contact causes further rearrangements.[98] Similarly, epoxide (**191**; equation 80) with two six-membered rings already in place,

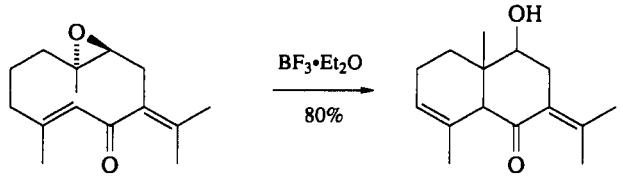


(187)

(188)

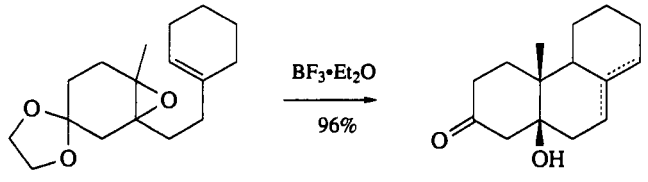
(78)

affords a nearly quantitative yield of the hydrophenanthrene derivative (**192**), isolated after hydrolytic work-up as a mixture of the two double-bond isomers.[99]



(189) (190)

(79)



(191) (192)

(80)

Cyclopropane participation occurs in the reaction of (**193**; equation 81) which rearranges exclusively to the aldehyde (**194**), although the latter is unstable to the reaction conditions. The *endo* (cyclopropyl) isomer was also examined in this study,[100] and gave mostly polymeric product.

(193) (194)

(81)

Epoxides may be generated as reactive intermediates when unsaturated materials are treated with BF_3/trifluoroperacetic acid, a powerful oxidation/rearrangement mixture developed by Hart.[101] The products from numerous alkenes and aromatic substrates, to the extent that comparisons can be made, are those expected from epoxide/carbenium ion rearrangements.

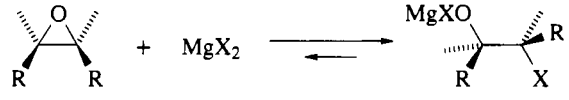
Although infrequently used, sodium cyanotrihydroborate in the presence of BF_3 has been shown to reduce epoxides with interesting regio- and stereo-chemical results.[102] For example, 1-methylcyclohexene oxide is converted in high yield to *cis*-2-methylcyclohexanol contaminated with only small amounts of the *trans* and 1-methylcyclohexanol isomers.

Acyloins are sometimes formed in moderate yield when 1,2-disubstituted epoxides are treated with BF_3 in dimethyl sulfoxide solvent.[103] A curious report[104] of highly temperature dependent nonoxidative rearrangement of 2,3-epoxycyclododecanone indicates that a 1,2-dione is formed at 85 °C, whereas a 1,3-dione is the product at 150 °C. All of these applications require heating, since the Lewis acidity of BF_3 is strongly attenuated in dimethyl sulfoxide.[105]

3.3.5 MAGNESIUM HALIDE CATALYSIS

French work over 60 years ago first led to the recognition that skeletal rearrangement can take place when epoxides are treated with Grignard reagents. By the 1940s the involvement of halohydrin salt intermediates was considered proven, and general stereochemical features were understood, *i.e.* preference for a *trans* relationship between the migrating group and the departing halide.[106] Geissman and Akawie[107] provided additional evidence relating cyclic halohydrin stereochemistry with the course of rearrangement. This work reinforced the view that a *trans* relationship was preferred for rearrangement, but also showed that the same rearrangement product could be formed (in low yield) from the 'wrong' halohydrin stereoisomer. Subsequent studies support the view that epoxide/Grignard and related reactions rarely provide clearcut mechanistic features, and that mixtures of products not explicable by a single pathway are commonly encountered.

Halohydrins are often the major products isolated (after hydrolysis) from epoxide/Grignard reagent mixtures. The magnesiohalide salt of the halohydrin (**196**; equation 82) is assumed to be the species present in solution, formed by reaction of the MgX_2 that is present from Schlenk equilibrium. *Anti* opening of the epoxide (**195**) is also usually assumed; there is experimental evidence in several instances to support this conclusion. The alternative (*syn* opening) halohydrin has rarely been ruled out, however, especially as a minor product. The magnesiohalide salts appear to be reasonably stable in ether solutions. Unlike the lithium salt analogs discussed in the next section, (re)closure of (**196**) to the epoxide does not appear to be thermodynamically favorable, and is known to be relatively slow in instances where this question has been addressed.

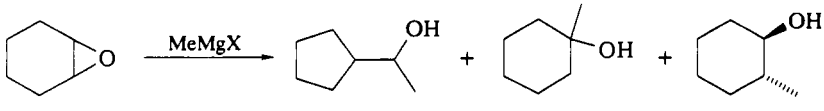


(82)

(**195**) (**196**)

Rearrangements of halohydrin salts usually require prolonged treatment of ether solutions at ambient temperature or heating in a less polar solvent, but there are some interesting exceptions. The 'standard' conditions consist of formation of the magnesiohalide salt in ether, followed by solvent replacement by benzene and short term reflux. House[108] found that residual ether can significantly influence the course of a reaction, and since this variable appears not to have been carefully controlled in most experiments, comparisons may have limited significance.

The reaction of cyclohexene oxide with MeMgX was reexamined in 1969, in work which clearly established the importance of the halide.[109] Standard conditions (1 h at 80 °C) were employed with 1.4 equiv. of the organometallic, to give the yields listed under equation (83). Only minor amounts of the 'normal' displacement product (**200**) are formed from the chloride and bromide, and none from the iodide. The iodide and bromide give extensive rearrangement, with the bromide being more selective in the sense that product (**198**) is expected on the basis of stereoelectronic considerations (backside displacement of halide) from the *trans*-halohydrin. The unusual product from this perspective is (**199**). It must arise either from the *cis*-halohydrin or a process which is not subject to the same stereoelectronic controls, *e.g. via* a carbenium ion.



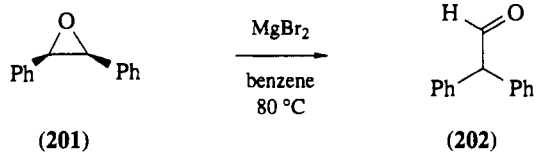
(83)

(**197**) (**198**) (**199**) (**200**)

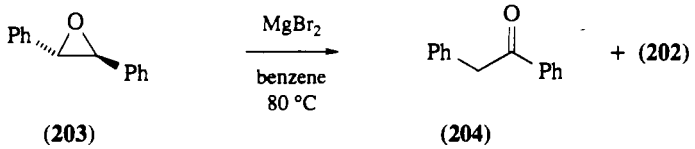
X			
I	43%	22%	–
Br	54%	3%	5%
Cl	5%	–	8%

Treatment of (**197**) with MgX_2 (X = I or Br) in ether gave high yields of the corresponding *trans*-halohydrins, with no sign of the *cis* isomers. When heated as in the Grignard reagent experiments, cyclopentanecarbaldehyde and cyclohexanone were formed in ratios of *ca.* 2:1 for the iodide, and 9:1 for the bromide. Based on these observations, the authors suggested that (**199**), or more precisely its precursor cyclohexanone, arises from the carbenium ion generated by loss of halide from the halohydrin salt, and that this process is more favorable with X = I than Br.

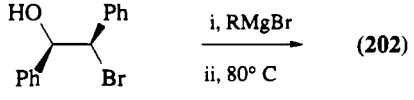
House[108] had earlier reached the same conclusion (competing concerted and carbenium ion pathways) from a study of the reactions of *cis*- and *trans*-stilbene oxide with $MgBr_2$ in refluxing benzene. The *cis*-epoxide (**201**; equation 84) gave diphenylacetaldehyde (**202**) with traces of deoxybenzoin (**204**), while the *trans*-epoxide (**203**; equation 85) gave a mixture of (**202**) and (**204**). The significance of these observations follows from the rearrangements of the corresponding independently prepared bromohydrins (**205**; equation 86) and (**206**; equation 87). When treated with RMgBr to form the magnesiobromide salts and then heated as before, *threo*-(**205**) gave only (**202**), while *erythro*-(**206**) gave only (**204**).



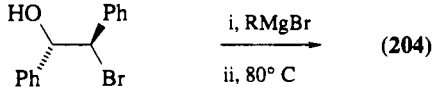
(201) (202) (84)



(203) (204) (85)



(205) (86)



(206) (87)

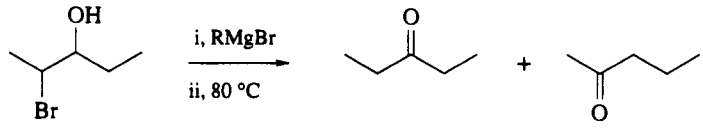
The cleaner reactions of the halohydrins show that these, if formed by *anti* opening and not subsequently epimerized, cannot account for the product mixtures from the epoxides. House proposed a competing carbenium ion route for both epoxides, leading to the normal pinacol rearrangement (carbenium ion) product, the aldehyde (**202**).

It is by no means obvious why these acyclic halohydrins should give mutually exclusive products. Simple stereoelectronic and steric considerations do not provide explanations. House suggested that the OMgX substituent might have abnormally large spatial requirements. A similar observation was made by Curtin and Meislich, who proposed large differences in solvation for two alternative transition states to rationalize an even more subtle distinction (migration of Ph *versus* *p*-ClC_6H_4 in two diastereomers).[110] These suggestions appear reasonable especially when aggregation effects are taken into consideration.

Similar experiments with *cis*- and *trans*-2,3-epoxybutane and the corresponding bromohydrins all gave a single product, 2-butanone.[111] Thus the unusual factors in the aryl-substituted materials failed to appear in the simpler aliphatic materials. Here the product can be rationalized simply by assuming that hydride migration occurs more readily than methyl migration. Of course, this may be true for both concerted and carbenium ion processes, and the existence of a dual mechanism may be hidden in this example. The cyclohexene oxide results cited above suggest that this is plausible, and perhaps probable.

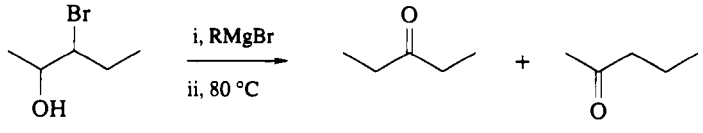
In all of these reactions halohydrin salts were implicated as the reactive species, since no rearrangement occurred when the halohydrins were treated with $MgBr_2$.

House also examined analogous reactions of 2-bromo-3-pentanol (**207**; equation 88) and 3-bromo-2-pentanol (**210**; equation 89), presumed to be mixtures of diastereomers obtained by $NaBH_4$ reduction of the corresponding bromo ketones. Each system gave some of the oxygen-shifted ketone, as shown in equations (88) and (89), presumably *via* the epoxides, with reopening leading to the opposite regioisomer. This work is significant in showing that such interconversions can occur, even though epoxide formation in these systems must be slower than rearrangement. Other examples of oxygen shifts which appear to require formation of an epoxide intermediate are known.[112]



(88)

(**207**) (**208**) 95% (**209**) 5%

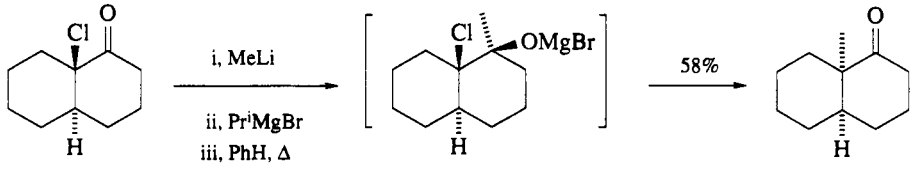


(89)

(**210**) (**208**) 20% (**209**) 80%

Cleavage of an epoxide by MgX_2 is only one of several ways by which halohydrins can be made. Other significant methods are reduction of halo ketones, addition of HOX to alkenes, bromination of alcohols and addition of RMgX or RLi to halo ketones. Some offer the advantage of controlling the regiochemistry of the halohydrin. Because of this diversity of approaches, MgX_2-catalyzed rearrangements of halohydrins have been studied more extensively than analogous reactions of epoxides.

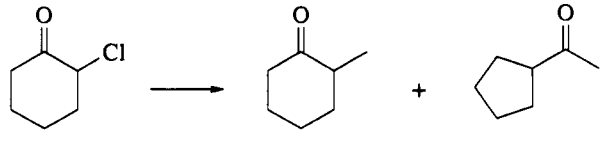
The addition of Grignard reagents to α-halo ketones can give a variety of products, including enolates generated either by dehalogenation or deprotonation.[113] Substitution of the halide by the organometallic R group has also been known for over half a century. Tiffeneau was the first to recognize that this product resulted from rearrangement of an initially formed halohydrin salt.[114] The halohydrin configuration that produces this skeletally unrearranged material is apparently formed preferentially because of addition to the carbonyl face away from the halide. However, these reactions rarely give pure products or high yields. An angular methylation application developed by Sisti and Vitale[115] illustrates the stereochemical features (equation 90).



(90)

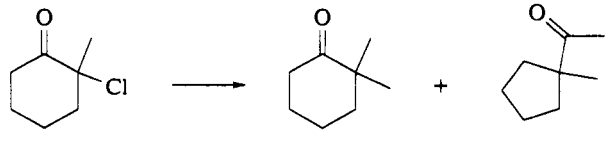
(**211**) (**212**) (**213**)

Simpler α-chloro ketones have also been examined,[115] and exhibit negligible selectivity. The mixtures of products shown in equations (91) and (92) may be the result of formation of both *cis*- and *trans*-halohydrin isomers in the addition step or, less likely with the chloride, a carbenium ion mechanism. The effect of varying the halide in such reactions has not been systematically investigated.



(91)

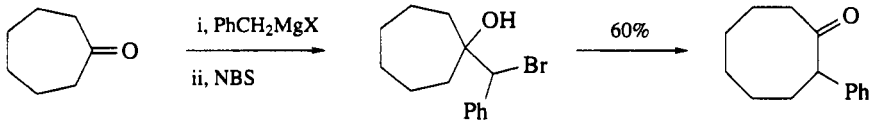
(**135**) (**214**) 32% (**215**) 22%



(92)

(**216**) (**217**) 26% (**218**) 40%

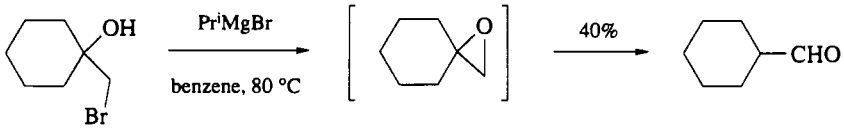
Sisti has also explored the potential utility of halohydrin rearrangements for ring expansions. A few examples are outlined. Ring-expanded α-phenyl ketones of product ring size six to nine were prepared in 60–80% yields by the sequence shown in equation (93).[116]



(93)

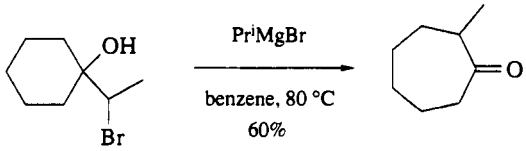
(219) (220) (221)

The reactions of bromohydrins shown in equation (94) to (96) are especially informative. No cycloheptanone was obtained from the primary halide (**222**; equation 94),[117] whereas the secondary (**225**; equation 95)[118] and tertiary (**227**; equation 96)[119] halides both gave good yields of ring-expanded products. These results reinforce the observation made earlier by Geissman[107] that facile rearrangement is associated with ease of carbenium ion formation. It would thus be misleading to view the rearrangement process as a simple S_N2-like displacement, in spite of the apparent operation of stereoelectronic control features. More complex halohydrins have also been examined; these tend to give mixtures of products.[120]



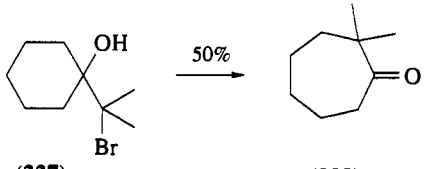
(94)

(222) (223) (224)



(95)

(225) (226)



(96)

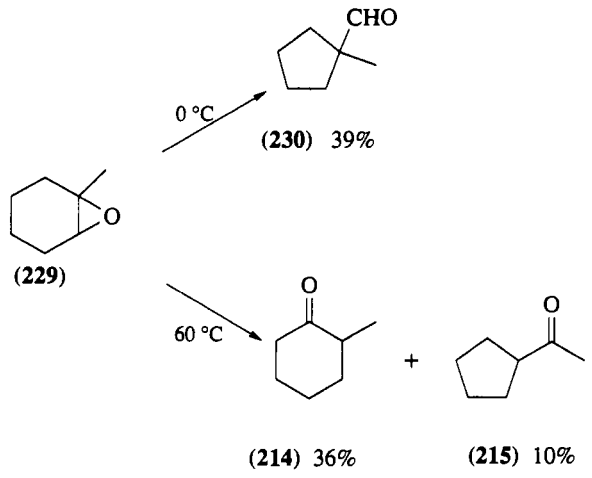
(227) (228)

Enhanced reactivity associated with a tertiary center appears to be a factor in the observations made by Naqvi *et al.*[121] on treatment of 1-methylcyclohexene oxide (**229**; equation 97) with $MgBr_2$. At 0 °C, conditions which give only halohydrin with cyclohexene oxide, (**229**) was converted into the aldehyde (**230**). Conversely, when (**229**) was added to a solution of $MgBr_2$ at 60 °C, only ketone rearrangement products were isolated. The modest yields prevent mechanistic conclusions.

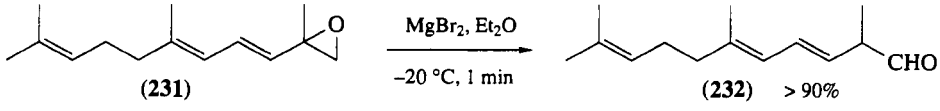
A striking example of enhanced reactivity is found in the vitamin A related studies of Rosenberger *et al.*[122] The example shown (equation 98) and several other analogous high yield reactions almost certainly proceed *via* the stabilized carbocation (tertiary and dienyl in this instance). Higher temperatures were detrimental to these applications, probably because of product instability.

Matsuda and Sugishita[123] found that cyclooctatetraene monoepoxide (**233**; equation 99) gave only skeletally rearranged products, *e.g.* (**234**), when treated with Grignard reagents. In an effort to isolate the presumed intermediate cycloheptatrienecarbaldehyde, (**233**) was subjected to a catalytic amount of $MgBr_2$, but this resulted in the formation of phenylacetaldehyde.

The stereochemistry of the product obtained when β-2,3-epoxycholestane is treated with MeMgI is in keeping with a mechanism involving initial diaxial opening to form an iodohydrin salt (equation 100), followed by rearrangement with backside displacement of the iodide *via* a twist boat conformer. Addition of MeMgI to the A-norsteroid aldehyde formed in this manner would then result in the two alcohols (epimeric at the carbinol center), which were isolated.[124]



(97)



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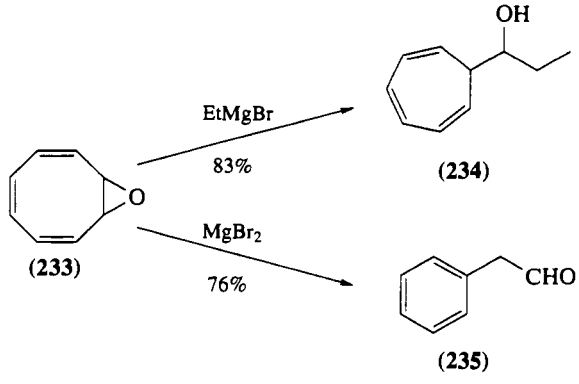

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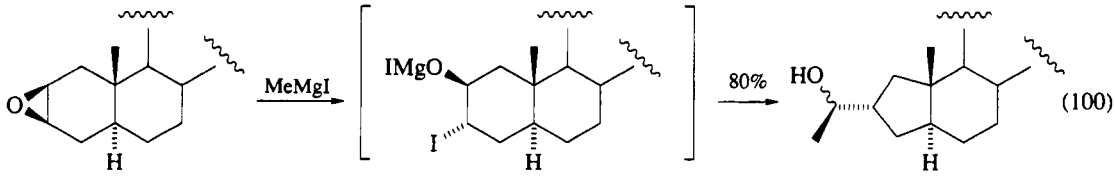
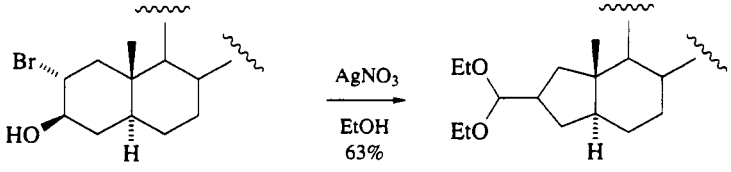


(100)

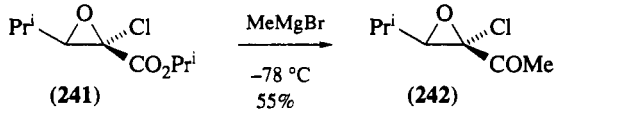
Although indirectly related to the present topic, a common alternative method of inducing rearrangement of halohydrins utilizes a soluble silver salt. It is interesting that the bromohydrin which is regioisomeric to the intermediate iodohydrin proposed in equation (100), when treated with $AgNO_3$ in refluxing ethanol, delivered the analogous aldehyde (of unknown stereochemistry) in protected form (equation 101).[125]



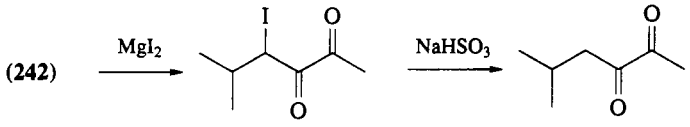
(101)

An unusual (for MgX_2) rearrangement of an epoxide to an allylic alcohol has been described in the terpene literature.[126]

Several epoxides substituted by α-EWG or other substituents have been treated with RMgX and/or MgX_2, generally to give products derived from initial β-cleavage. These substituents include chloride,[127] nitrile[128] and chloride/ester combined. The latter easily prepared substrates offer an attractive route to pyruvates and 1,2-diones. Chloro epoxy esters such as (**241**; equation 102) react with Grignard reagents at low temperature at the ester group, without opening the epoxide, to furnish epoxy ketones, *e.g.* (**242**), in modest yield.[129] This outcome is somewhat unusual, since ketones are rarely isolated in significant amounts from ester/Grignard reagent reactions; it appears that the electronegative substituents improve the stability of the initially formed intermediate. Subsequent treatment of (**242**) with MgI_2 gave the interesting iododione (**243**; equation 103) which could be reduced to the dione (**244**) by treatment with aqueous $NaHSO_3$.[130] In this sequence, facile loss of chloride from the iodohydrin (salt) intermediate prevents rearrangement from occurring.

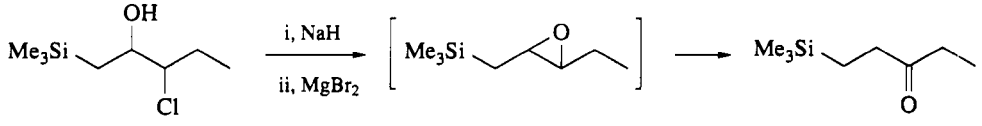


(241) (242) (102)



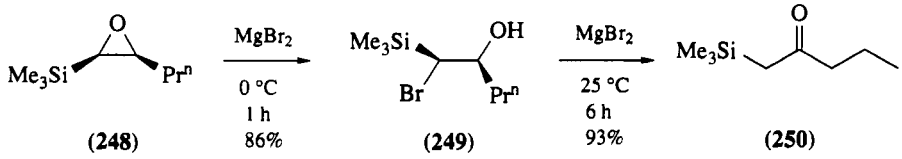
(243) (244) (103)

Attempts to prepare β-trimethylsilyl epoxides by closure of halohydrins resulted instead in the formation of aldehydes or ketones.[131] Epoxides are thought to be involved as intermediates, and the addition of $MgBr_2$ improved the overall conversion illustrated in equation (104). The potent β-cation-stabilizing capacity of β-trimethylsilyl groups was invoked to explain the high reactivity of the intermediate epoxides. Only hydride migration products were found. Application to tertiary halide halohydrins, which would require carbon migration to effect rearrangement, has apparently not been done.

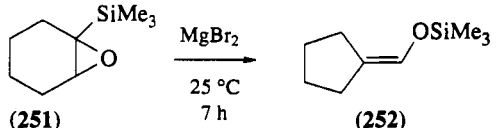


(245) (246) (247) (104)

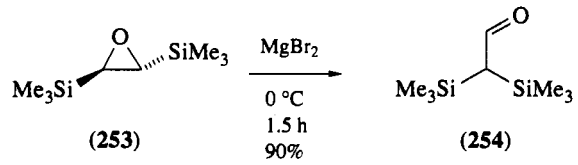
α-Trimethylsilyl epoxides have been more extensively studied, particularly by Hudrlik and coworkers. Reactions have been carried out with both $MgBr_2$[132] and MgI_2.[133] The products obtained arise from nucleophilic attack at the carbon adjacent to the silicon.[132,134] Depending upon the other substituents, the resulting bromohydrin (salt) may be stable and isolable, or rearrangement may occur to form β-keto-(aldehydo)silanes, or enol trimethylsilyl ethers derived from these carbonyl primary products. These features are illustrated in equations (105) to (107).



(248) (249) (250) (105)



(251) (252) (106)

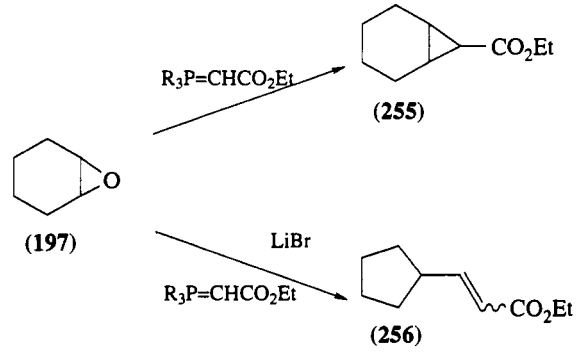


(253) (254) (107)

The stereochemistry shown in the bromohydrin (**249**; equation 105) has been proven (in analogs) by isolation and stereospecific conversion to vinyl bromide.[135] The reaction of (**251**; equation 106) to give exclusively ring-contracted product also supports the intermediacy of a bromohydrin (salt), and suggests the importance of normal stereoelectronic factors in the rearrangement. The preferential migration of a trimethysilyl group (over H) in equation (107) is noteworthy. The ketosilanes (and *in situ* Grignard reagent trapped aldehyde analogs[135]) are useful synthons.

3.3.6 LITHIUM SALT CATALYSIS

An attempt[136] to repeat, with presumably a minor modification, an established procedure[137] for the conversion of cyclohexene oxide to the cyclopropane (**255**; equation 108) gave instead the ring-contracted isomer (**256**). This reaction is fairly general and constitutes a convenient method for the preparation of acrylate esters, including some not easily made in other ways.



(108)

The key difference between the literature procedure[137] and the acrylate-forming reaction proved to be the use of a phosphonium bromide and BuLi to form the ylide in the latter. This gave a combination of ingredients (LiBr, ylide and/or R_3PO) and conditions (benzene solvent, reflux) which caused rapid rearrangement of epoxides to carbonyl compounds. Subsequent study provided the first unequivocal evidence[138] that LiBr as well as some other lithium salts can cause epoxide rearrangements.

In contrast to Grignard reagent/epoxide reactions in which MgX_2 (X = Br, I) is clearly responsible for many skeletal or hydride shift rearrangements, organolithium reactions usually do not exhibit these features, although some exceptions are known.[139] Heeren *et al.*[140] found that LiI altered the (complex) product mixture from treatment of cyclohexene oxide with MeLi in refluxing ether. One of the products (1-cyclopentylethanol) formed in the presence of LiI requires skeletal rearrangement. This material was not produced in the reaction with MeLi prepared from MeBr, *i.e.* LiBr did not cause similar rearrangement. We now recognize that this reflects the relative rates of competing reactions, and the dampening effect of ethereal solvents on the rearrangement process.

A systematic study[141] of epoxide/lithium salt reactions established the following general features: (i) LiI[138] is more reactive than LiBr. LiCl does not cause rearrangements, perhaps due to insolubility; (ii) LiBr is insoluble in benzene, and does not cause rearrangement unless a solubilizing agent is present (in controlled amounts). Phosphorus ylides (equation 108), tri-n-butylphosphine oxide and hexamethylphosphoramide (HMPA) will function as solubilizers; and (iii) $LiClO_4$ is insoluble in benzene but is partially solubilized by epoxides. Substrates susceptible to carbenium ion formation rearrange readily. Solubilizers and other Lewis bases diminish the rates of $LiClO_4$ reactions.

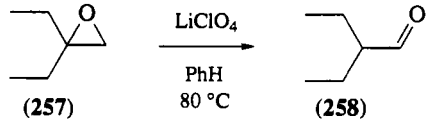
The effects of epoxide structure on rates and product distributions indicate that $LiClO_4$ reactions occur by a carbenium ion mechanism. Conversely, the LiBr-catalyzed reactions involve bromohydrin salts as precursors to rearrangement products. These are sharp distinctions, and provide the cleanest examples of the two extreme mechanisms for epoxide–carbonyl rearrangement.

3.3.6.1 $LiClO_4$ Catalysis

Certain epoxides rearrange readily in refluxing benzene in the presence of solid $LiClO_4$. When any epoxide (reactive or not) is added, the salt slowly disappears from the bottom of the flask, and is redeposited as a ring at the surface of the boiling liquid.[141] This phenomenon is presumably associated with a strong Lewis acid/base interaction between the lithium cation and ether oxygen. Pocker and Buchholz[142] carried out detailed studies of solutions of $LiClO_4$ in diethyl ether (up to 6 M solutions can be made), which exhibited various phenomena verifying a strong interaction. Solid mono- and di-etherate phases were also identified. It was noted that hydrated $LiClO_4$ has very low solubility in ether, in contrast to the anhydrous material. Hydration is also expected to diminish catalytic activity, although this has not been specifically demonstrated. A relatively simple procedure for purifying and drying $LiClO_4$ (vacuum, 160 °C, 8 h) is described in this work.[142]

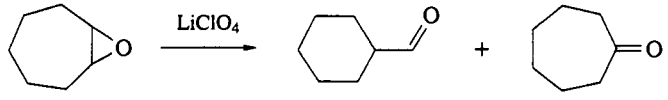
The evidence that $LiClO_4$ catalysis involves carbenium ion intermediates arises from consideration of the structures that undergo reaction and the products that are formed. For example, all epoxides with a tertiary oxirane center rearrange readily, and the products are those expected from tertiary carbenium ion formation.[141] Thus 1-methylcyclohexene oxide gives 80% of 2-methylcyclohexanone (hydride migration) and 20% of the ring-contracted product, 1-methylcyclopentanecarbaldehyde. The products from 1,2-dimethylcyclohexene oxide are identical in structure and proportion to those found by Bunton and Carr[143] in the pinacol rearrangement of 1,2-dimethyl-1,2-cyclohexanediol (see equation 7 of Chapter 3.2 in this volume). This is a remarkable outcome given the differences in conditions (particularly solvent, benzene *versus* aqueous perchloric acid), and strongly supports a similar mechanism for both processes. Presumably ions present or generated in the nonpolar medium exist as ion pairs or higher aggregates, but they appear to react in traditional ways.

Facile rearrangement is observed with 1,1-disubstituted epoxides and $LiClO_4$. For example, (**257**; equation 109) gives the aldehyde (**258**) exclusively.[141]



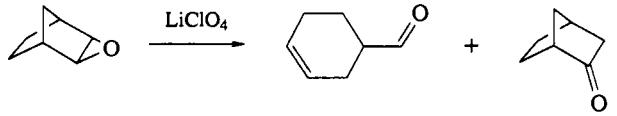
(**257**) (**258**) (109)

Although cyclopentene oxide was unreactive and cyclohexene oxide reacted very slowly to give mostly nonvolatile products, some other 1,2-disubstituted epoxides will rearrange, but at a diminished rate. Cycloheptene oxide provides an interesting illustration; treatment with $LiClO_4$ (equation 110) affords mainly the ring-contracted aldehyde along with some ketone formed by hydride migration.[141]



(**259**) (**224**) 83% (**219**) 17% (110)

Norbornene oxide (equation 111) rearranges with apparent nonclassical ion involvement, to give a similar ratio of aldehyde (**261**) and norbornanone (**262**).[141]

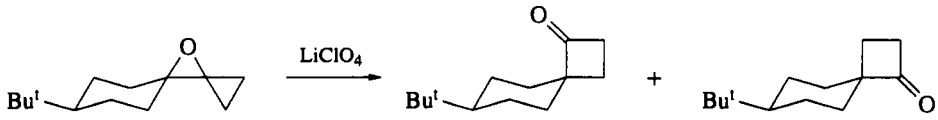


(**260**) (**261**) 83% (**262**) 17% (111)

The reaction of styrene oxide is noteworthy, not because phenylacetaldehyde (only) is formed, but because this reactive product appears to be reasonably stable to the reaction conditions.[141] This illustrates one of the advantages of using a catalyst which is only slightly soluble and contains an especially nonnucleophilic, nonbasic gegenion. Much of the work that has been done using BF_3 to catalyze epoxide rearrangements might benefit from reexamination with $LiClO_4$.

Trost and Bogdanowicz[144] examined several acidic catalysts for the rearrangement of oxaspiropentanes to cyclobutanones, and found the $LiClO_4$ method to be the most generally useful for this transformation. The reaction of (**263**), which is converted quantitatively to the ketones as shown in equation

(112), illustrates a tendency for migration with inversion at the cleaved center, reminiscent of some BF_3-induced reactions discussed previously.



(112)

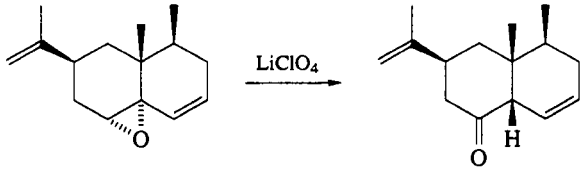
(263) **(264)** 91% **(265)** 9%

Synthetic utility depends upon compatibility with other functional groups, and although $LiClO_4$ has not been extensively tested in this regard, the method appears to be suitable for those groups examined to date. Thus a remote alkene does not interfere (equation 113).[144]

(113)

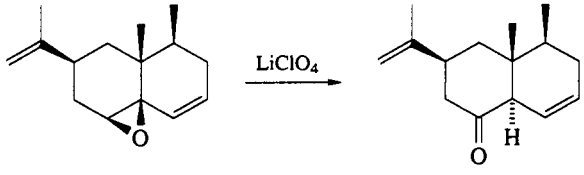
(266) **(267)**

Allylic epoxides seem to behave normally. Stereospecific hydride migrations were observed in the McMurry *et al.* synthesis of eremophilone.[145] Treatment of the isomeric epoxides (**268**) and (**270**) under standard conditions resulted in the exclusive formation of the rearranged ketones, as illustrated in equations (114) and (115).



(114)

(268) **(269)**



(115)

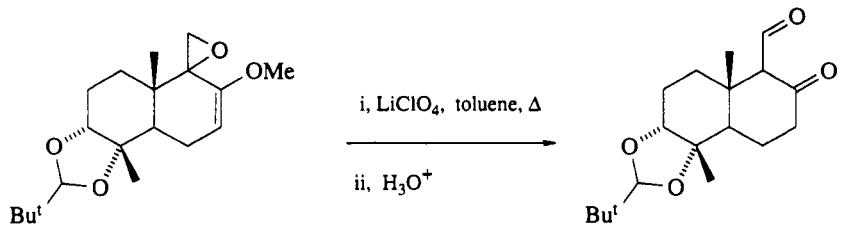
(270) **(271)**

Details are lacking, but the amide group apparently does not interfere with $LiClO_4$-catalyzed rearrangement of compound (**159**; equation 66), which gave the same product as BF_3 catalysis.[84]

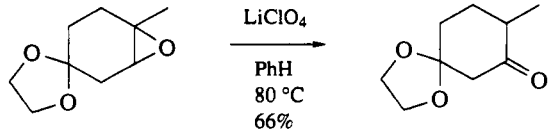
Two interesting applications show that $LiClO_4$ is compatible with at least some acetal groups. The reaction shown in equation (116) was used in the Corey *et al.* synthesis of aphidicolin.[146]

Burge *et al.*[147] reported that (**274**; equation 117) is cleanly converted to ketone (**275**) by $LiClO_4$ under the standard refluxing benzene conditions. Apparently the ketal group helps to prevent the small amount of ring contraction that accompanies analogous ketone formation in the parent system.[141]

Kennedy and Buse[148] used a $LiClO_4$–$LiClO_3$ eutectic mixture as a molten salt phase in a GLC column at 280 °C for rearrangement of a few model epoxides. Those with tertiary centers gave lower product selectivity than in the typical solution reaction, but the harsher conditions did cause cyclohexene oxide to rearrange, giving cyclopentanecarbaldehyde as the major product.



(272) (273) (116)



(274) (275) (117)

3.3.6.2 Lithium Halide Catalysis

Both LiBr and LiI have been widely used to effect epoxide–carbonyl rearrangements. These salts differ significantly in reactivity,[138] although no systematic comparison has been made. LiBr in benzene (or toluene) solvent requires a solubilizer (unlike $LiClO_4$, for which the epoxide itself is sufficient). LiI does not require a solubilizer, and has been used in several solvents, most often CH_2Cl_2; the possible role that solubilizer or solvent may play in LiI reactions has not been addressed. LiI is often employed as a hydrate, but occasionally 'anhydrous' salt is specified, although the purity of this difficult to dry material may be questioned.

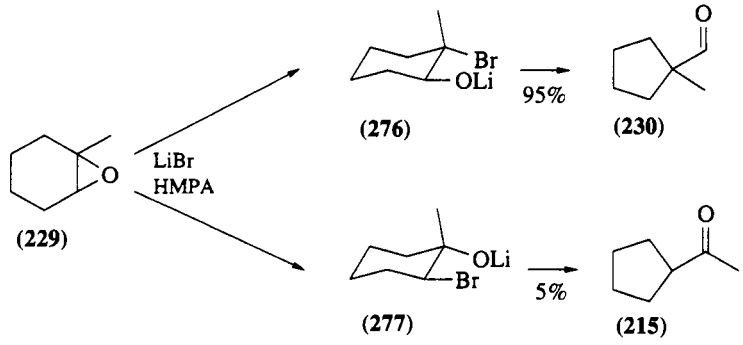
Various addends have been used to bring LiBr into solution. Hexamethylphosphoramide (HMPA) has been most widely used, although its reputation as a carcinogen provides interest in identifying alternatives. Magnusson *et al.*[149] found that tetramethylurea (TMU) is a suitable replacement for some highly oxygenated epoxides derived from sugars. It is not yet clear what role the addend plays in the determination of products. Magnusson found that TMU and HMPA gave essentially the same product mixtures, whereas some differences were observed in an earlier comparison of HMPA and Bu^n_3PO.[138,141]

Only products which can be attributed to bromohydrin (salt) intermediates are formed when epoxides are treated with LiBr (solubilizer) in refluxing benzene. Any apparent exceptions to this generalization are believed to be due to interconversion of halohydrin stereoisomers, as discussed below. The bromohydrin is formed by traditional *anti* opening (antiperiplanar, probably nearly exclusively *trans* diaxial). It has been established[141] that a model epoxide (1-methylcyclohexene oxide) reacts by a process that is kinetically first order in a 1:1 complex of LiBr–HMPA, but the state of aggregation [*n* in the formula $(LiBr{\cdot}HMPA)_n$] is not known.[150] The nature of the epoxide–$(LiBr{\cdot}HMPA)_n$ interaction that allows bromide to attack (exclusively) in the *anti* mode is not known, but must require fairly extensive ion pair (aggregate) reorganization.

Solid complexes of defined stoichiometry have been prepared for all the lithium halides with HMPA.[151] For LiBr, both $[LiBr(HMPA)_2]$ and $[LiBr(HMPA)_4]$ have been obtained as solids of defined m.p., but the 1:1 complex, the kinetically active species for epoxide rearrangement, has not been isolated. The rate of epoxide loss and solubility of LiBr increased proportionately with added solubilizer (HMPA), to a maximum rate at a 1:1 ratio of addend:LiBr.[141] Additional HMPA beyond this ratio caused the rate to decrease even though all the LiBr remained in solution. At an addend:LiBr ratio of 2:1, the reaction effectively ceased. These observations allow the conclusions that $[LiBr(HMPA)_2]$ is more stable than the reactive 1:1 complex in benzene, and that only the latter is kinetically competent.[141]

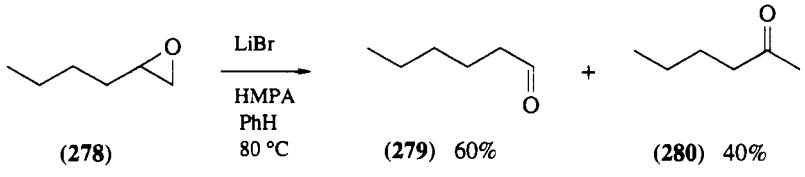
1-Methylcyclohexene oxide (equation 118) provides a useful model system for mechanistic discussion. It is important that no 2-methylcyclohexanone is formed, since this rules out carbenium ion pathways. The major product is derived from the bromohydrin (**276**), formed by bromide attack at the tertiary center (followed by chair–chair interconversion), but care must be taken to avoid overinterpretation of this observation. Thus, if the bromohydrins are rapidly interconverting *via* the epoxide, the product distribution would be determined not only by the equilibrium ratio of (**276**) and (**277**), but also by the respective rate constants for rearrangement to (**230**) and (**215**). Although cyclohexene bromohydrin is immediately converted to the epoxide by treatment with Bu^nLi in benzene,[138] the possible effect of HMPA on the bromohydrin(salt)/epoxide equilibrium is not known. The rearrangement rates would be Br^t (**276**) > Br^s

(**277**) if parallels with MgX_2-catalyzed halohydrin–carbonyl rates can be drawn. The rates for the final rearrangement steps rather than the rates of initial bromohydrin formation may thus control the product ratio.



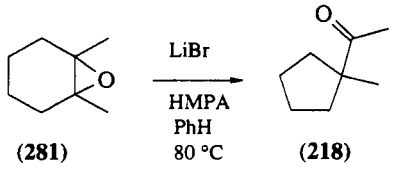
(118)

Rate constants were obtained[141] for rearrangement of a variety of epoxides with LiBr·HMPA in refluxing benzene, and an inverse relationship between degree of epoxide substitution and reactivity is evident. Terminal alkene epoxides are the most reactive, followed by 1,2-disubstituted, which are in turn more reactive than 1,1-disubstituted, while trisubstituted and tetrasubstituted epoxides react even more slowly. While this appears to parallel S_N2 reactivity, the expected ease of bromide attack is not reflected in the products of many of these reactions. For example, the terminal epoxide (**278**; equation 119) is among the most reactive examined but it gives a mixture of products, the major one requiring attack of bromide at the secondary center. Both rates and product ratios thus appear to be associated with more subtle features of the actual rearrangement step, as suggested above.



(119)

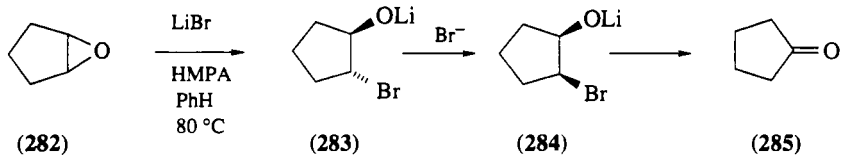
The reaction of cyclohexene oxide with LiBr·HMPA in refluxing benzene leads exclusively to cyclopentanecarbaldehyde, but, like other enolizable aldehydes, the product is not indefinitely stable to the reaction conditions. The rearrangement of 1,2-dimethylcyclohexene oxide, although much slower, gives only the ketone (**218**) as shown in equation (120). This result is especially difficult to rationalize by any mechanism other than one requiring a bromohydrin intermediate.



(120)

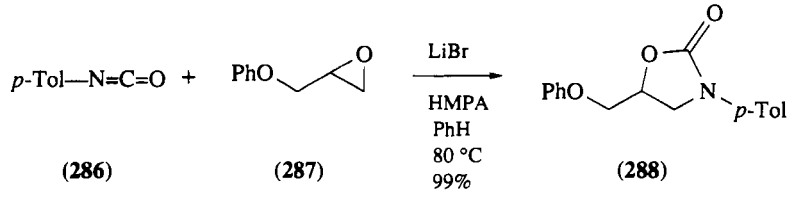
Styrene oxide reacted rapidly but gave no volatile material, perhaps because of aldol polymerization of phenylacetaldehyde (the probable initial product). Norbornene oxide gave no detectable reaction, either because *endo* attack of bromide is especially unfavorable, or because the bromohydrin salt has no geometrically accessible alternative other than to return to epoxide.

Cyclopentene oxide is very unreactive ($k \leq 10^{-3} k_{\text{cyclohexene oxide}}$), an observation clearly not in accord with expected S_N2 reactivity; it gives cyclopentanone as the only observed product. This ketone cannot be formed by antiperiplanar hydride displacement of bromide from the *trans*-bromohydrin, whereas the *cis*-bromohydrin could easily adopt the necessary conformation for hydride migration. Almost certainly the latter is formed by slow, perhaps rate-determining S_N2 attack by bromide on the initially formed *trans*-bromohydrin salt, as outlined in equation (121). This secondary reaction may be more important with LiI than with LiBr, although this has not been proven (see also equation 83 and discussion of MgX_2-catalyzed reactions).



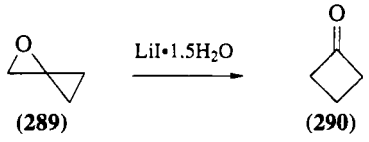
(282) (283) (284) (285) (121)

LiBr solubilized by Bu^n_3PO (or HMPA) was found[152] to catalyze the formation of 2-oxazolidones from organic isocyanates and terminal alkene epoxides. The epoxide substituent appears at the 5-position of the product as shown in equation (122). This outcome is in keeping with rapid trapping by the isocyanate of the halohydrin salt formed by attack of bromide at the primary center. This interpretation requires that oxazolidone formation be faster than epoxide rearrangement; data are not available to confirm this point.



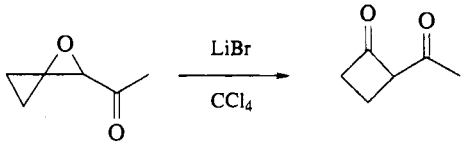
(286) (287) (288) (122)

Rearrangements of epoxides catalyzed by LiBr·HMPA or LiI have figured in a number of natural product syntheses in which ring expansions to cyclopentanones are required. Both salts were earlier shown to effect the especially facile rearrangements of the small ring spiro epoxides which serve as models for these processes. Thus (**289**; equation 123) was found by Salaun and Conia[153] to rearrange rapidly and in excellent yield to cyclobutanone, simply on exposure to commercial hydrated LiI.



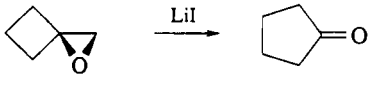
(289) (290) (123)

Conia and coworkers[154] later examined the rearrangements of acylated derivatives such as (**291**; equation 124) which undergo analogous ring expansion to give unstable diones. Rearrangement of (**291**) was effected by LiBr in CCl_4, reflecting not only high reactivity but perhaps also the ability of the keto epoxide to solubilize the salt.

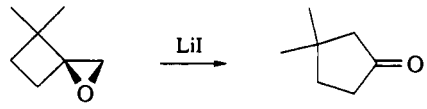


(291) (292) (124)

Leriverend and Leriverend[155] used LiI hydrate in refluxing CH_2Cl_2 to examine the conversion of the unsubstituted homolog (**293**; equation 125) into cyclopentanone. Analogs with methyl substituents on the cyclobutane ring reacted more slowly (up to 75 h as opposed to 6 h for **293**) and, interestingly, exhibited a strong preference for migration of the more-substituted carbon. Thus (**294**; equation 126) gave exclusively (**295**).[155] This kind of selectivity appears in a number of spiro epoxide rearrangements discussed below, although usually smaller in magnitude.

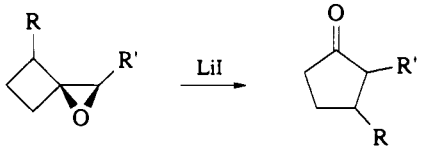


(293) (285) (125)



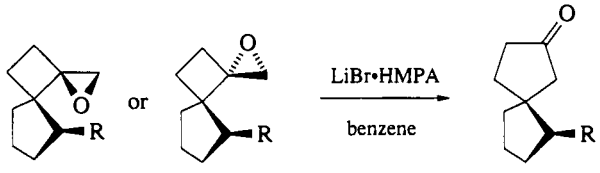
(294) (295) (126)

Halazy and Krief[156] showed that substituents on the epoxide ring are tolerated, and analogous migration selectivity was exhibited by substrates having one substituent on the cyclobutane and one on the epoxide (equation 127). Substrates with more than two substituents at the pertinent positions have apparently not been examined.



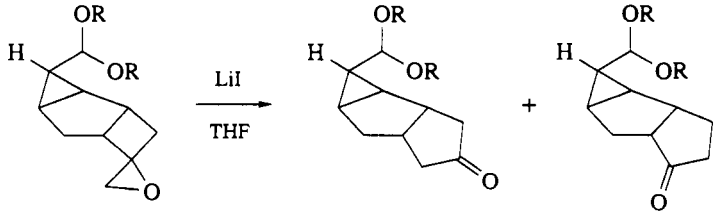
(296) (297) (127)

Trost and Latimer's approach to gibberellins[157] made use of the rearrangement shown in equation (128). Migration of the more-substituted center is evident in the conversion of (**298**) to (**299**; 65%), and even more so in the isomer of (**298**), epimeric at the epoxide center, which gave (**299**) in even higher yield (equation 128).



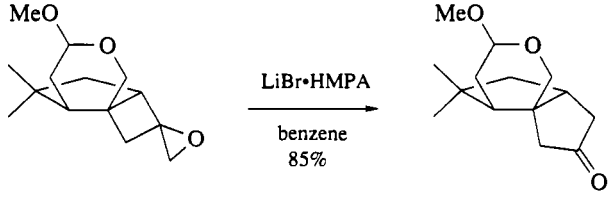
(**298**) R = $CH_2CH_2OPh_3$ (**299**) (128)

Related selectivity is also evident in the reaction of (**300**; equation 129), used as an undetermined mixture of epimers at the epoxide center. Ketones (**301**) and (**302**) were formed in a 9:1 ratio.[158] The use of THF solvent for this and some other anhydrous LiI-catalyzed reactions is worth noting, since ethers have been shown to inhibit reactions of LiBr.



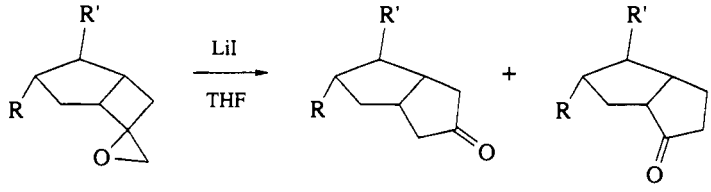
(**300**) (**301**) (**302**) (129)

High migration selectivity is again demonstrated in the efficient conversion of (**303**; equation 130) to (**304**), a key step in a synthesis of a pentalenolactone G.[159]

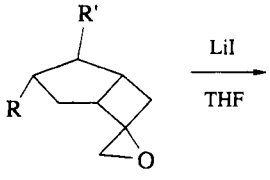


(**303**) (**304**) (130)

Only one exception to this otherwise general selectivity feature has been reported. In prostacyclin synthon studies, Hart and Comte[160] separately examined the two epimeric epoxides (**305**) and (**308**). Both gave only modest selectivity when treated with LiI in THF, with (**305**) showing the normal preference for migration of the more highly substituted center. In a slower reaction, (**308**) rearranged with the opposite selectivity, giving mainly the product (**307**) formed by migration of the methylene carbon (equation 131). This 'abnormal' behavior may be associated with an adverse steric interaction between the R group and the iodine in the conformation of the halohydrin needed for migration of the more-substituted center.



(**305**) R = $OSiMe_2Bu^t$ (**306**) 68% (**307**) 10%

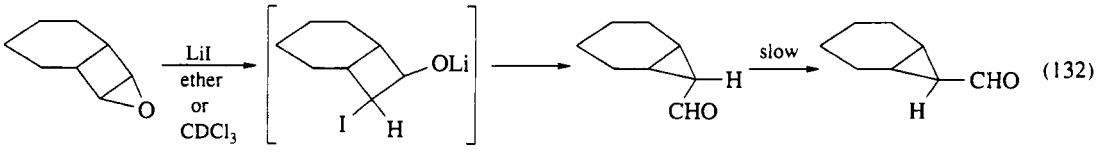


<10% 71%

(131)

(**308**)

Ring contraction from cyclobutyl to cyclopropyl will also occur if other structural features permit; thus conversion of an epoxide ring to a carbonyl group more than compensates for any free energy cost associated with the change in carbocyclic ring size. Garin's work[161] nicely proves the stereochemical features of this kind of rearrangement, and provides convincing evidence for the intermediacy of a halohydrin. Halohydrins formally derived from cyclobutene are known[162] to undergo facile ring contraction. The slow conversion of the initially formed *endo* aldehyde (**311**) to the more stable *exo*-(**312**) form is typical behavior of enolizable aldehydes under LiX epoxide rearrangement conditions (equation 132). Garin also made the interesting observation that lithium thiocyanate could be used in place of LiI to effect this epoxide rearrangement.[161] There is no record in the literature of LiSCN causing the rearrangement of any other epoxide, so generality remains doubtful.



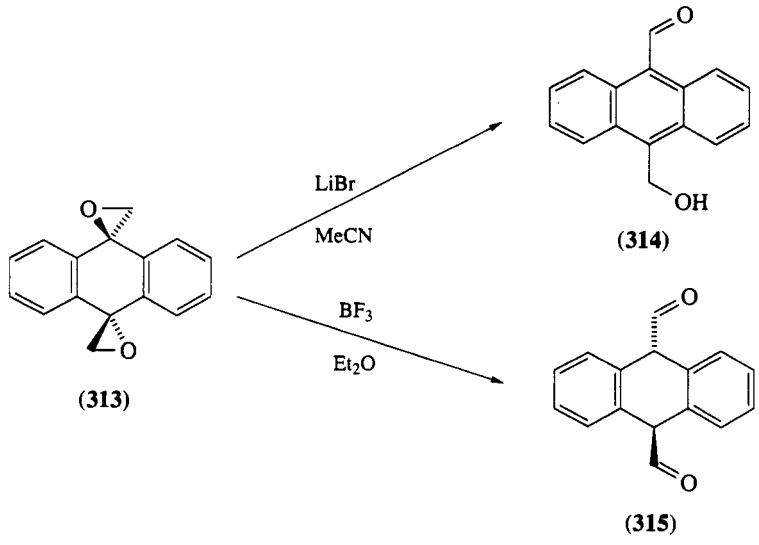
(132)

(**309**) (**310**) (**311**) (**312**)

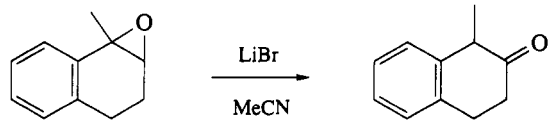
Lin and coworkers[163] used LiBr in acetonitrile to carry out the conversion of the *trans*-diepoxide (**313**) to (**314**); in this instance the enol(ate) generated after the initial aldehyde formation causes aromatization and opening of the other epoxide in an elimination-type reaction (equation 133). The use of BF_3 in ether allowed isolation of the dialdehyde (**315**). It is worth noting that the more acidic conditions cause epoxide rearrangement to occur more rapidly than enolization reactions of this sensitive substrate.

Banks and Ziffer[164] used LiBr in both acetonitrile and in benzene/HMPA in attempts to cause carbon migration (ring contraction) of epoxides such as (**316**; equation 134), but in all instances only ketones formed by hydride migration were obtained. The authors noted the lability caused by the tertiary benzylic center, and suggested that this could account for the failure of normal stereoelectronic features with these substrates. Ring contraction was also thwarted in substrates lacking a suitable hydride for migration; instead, relatively slow elimination with loss of a proton from the exocyclic methyl group occurred.

The work of Magnusson and his colleagues[165] with epoxides derived from allylic alcohols has provided important mechanistic insights as well as useful synthetic procedures. These reactions require the

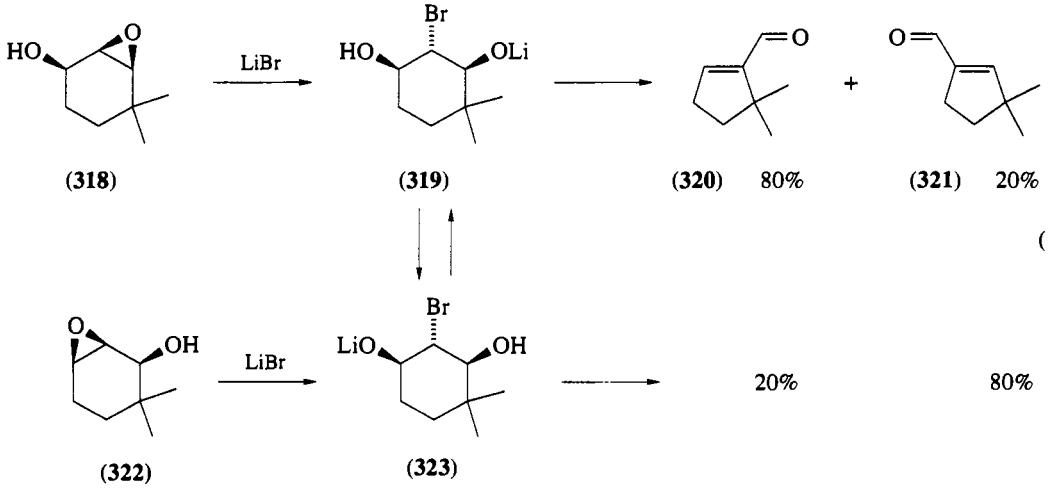


(313) (314) (315) (133)



(316) (317) (134)

use of stoichiometric or greater amounts of LiBr·HMPA to obtain high yields, presumably because the water that is formed inhibits the catalytic power of the salt. The formation of the two isomeric aldehydes (**320**) and (**321**) from both epoxides (**318**) and (**322**) was shown to occur by interconversion of the bromohydrin salts (**319**) and (**323**), as depicted in equation (135). The fact that the two epoxides give different ratios of the two aldehydes conversely shows that this halohydrin salt interconversion is not rapid compared to rearrangement. Since the interconversion of (**319**) and (**323**) appears to require only proton (and lithium ion) exchange, this is a surprising observation, and suggests that the mechanism may be more complex than depicted here. These intriguing mechanistic points were demonstrated by carrying out the reactions with specifically deuterated substrates.



(318) (319) (320) 80% (321) 20% (135)

(322) (323)

Similar bromohydrin interconversions were demonstrated in sugar-based epoxide rearrangements.[149] The unsaturated aldehydes formed in these reactions are useful for further elaboration, as shown in a recent synthesis of botryodiplodin.[166]

A one-step homologation/ring expansion has been reported,[167] in which a ketone is treated with CH_2I_2 and Li metal. The epoxides that could conceivably be generated from the presumed iodohydrin salts

formed in this process generally do not ring-expand with other lithium salts. Thus if this reaction involves intermediate iodohydrin salts, rearrangement must take place more rapidly than closure to epoxide. Acyclic aldehydes apparently give isolable homologated epoxides from similar treatment.

Kennedy and Buse[148] examined the rearrangement of a series of epoxides on molten salt (LiBr + RbBr) at 280 °C. At this temperature the epoxides also undergo thermal rearrangement, and it is difficult to separate out the effects of the salt-catalyzed process. In general, these reactions are much less selective than the 80 °C LiBr·HMPA solution analogs, and some of the products appear to require formation of the alternative halohydrin stereoisomer or carbenium ion intermediates.

Another interesting LiBr variant was recently discovered by Suga and Miyake,[168] who reported that LiBr coated on alumina (LiCl and $MgBr_2$ were also effective, as was LiBr on silica gel) is an effective catalyst for use either in the gas phase or as a solid added to refluxing toluene, affording 80% of cyclopentanecarbaldehyde from cyclohexene oxide. This reagent (LiBr–alumina) promises to be useful, especially for the formation of large amounts of volatile aldehydes by a continuous stream gas phase process.

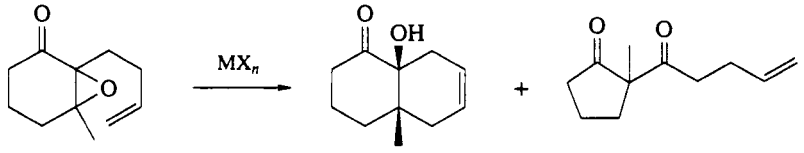
There are many different variations for epoxide–carbonyl rearrangements that utilize lithium salts. Unfortunately, there are very few controlled comparisons of the sort needed to determine the best choice of LiX, solvent, addend and conditions for a particular application.

3.3.7 OTHER CATALYSTS

Most common Lewis acids have at one time or another been examined as prospective catalysts for epoxide rearrangements. Relatively few cause skeletal changes, although formal hydride migration leading to ketones is often observed.

Epoxides have occasionally been used in Friedel–Crafts reactions, and some interesting stereochemical observations have been made in this context. Quite unlike secondary alcohols which give almost fully racemized product, it has been shown[169] that optically pure propylene oxide with $AlCl_3$ and benzene gives optically pure 2-phenyl-1-propanol with inversion of configuration at the cleaved center. $AlBr_3$ leads to much lower levels of optical purity; it was demonstrated that both starting material and product are optically stable to the reaction conditions, and therefore partial racemization is intrinsic to the mechanism with $AlBr_3$. It is nonetheless clear from these and other results that even powerful Lewis acids do not assure reaction *via* simple planar carbenium ions.

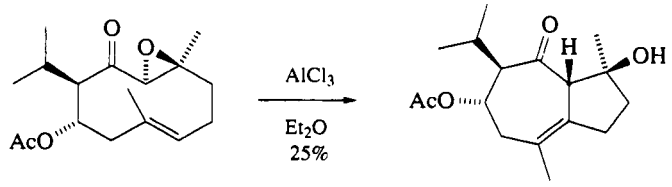
Strong Lewis acids are often chosen for use with epoxides when the goal is intramolecular addition to an alkene or aromatic system. In an informative study, Sutherland *et al.*[170] compared the effect of different catalysts on the ratio of cyclization (**325**) to ring contraction (**326**) for the system shown in equation (136). A positive correlation between Lewis acid strength and cyclization was noted. Thus $AlCl_3$ was reasonably effective in this regard (ratio (**325**):(**326**) = 3:1) but it was inferior to $TiCl_4$ which gave only cyclized product (55%). Other catalysts (ratio) are: $FeCl_3$ (1.1); $SnCl_4$ (0.6); $BF_3{\cdot}Et_2O$ (0.8); and $ZnCl_2$ (0.3).



(136)

(**324**) (**325**) (**326**)

$AlCl_3$ in ether has been used to explore intramolecular cyclization of some germacrones, and gives a [5.3.0] bicyclic derivative in one instance, illustrated in equation (137).[171]

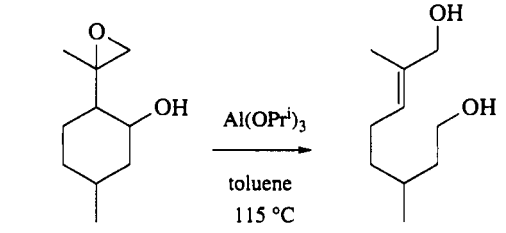


(137)

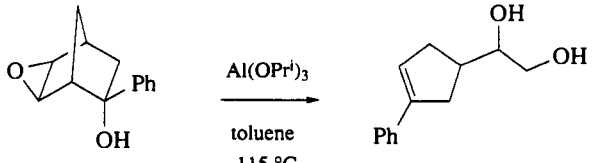
(**327**) (**328**)

An organoaluminum compound in hydrocarbon solvent caused rearrangement of an acid-sensitive diene monoepoxide, but a change to ether solvent mediated this (undesired) reaction.[172]

The modest Lewis acid properties of $Al(OPr^i)_3$ are needed for the fragmentation reactions of epoxides derived from homoallylic alcohols described recently by Waddell and Ross.[173] Carbonyl groups in the initial fragmentation products are reduced by $Al(OPr^i)_3$ to give the materials shown in equations (138) and (139).

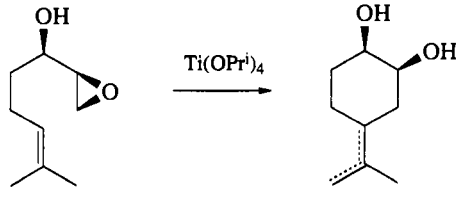


(329) (330) ($E + Z$) (138)



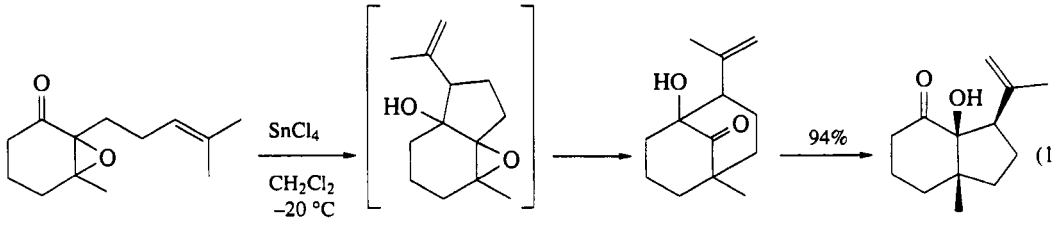
(331) (332) (139)

$Al(OPr^i)_3$ was less satisfactory than $Ti(OPr^i)_4$ for the hydroxy-influenced cyclizations examined by Sharpless *et al.*[174] The relative stereochemistry of the hydroxy group and epoxide proved critical for this process, leading to the suggestion that an intramolecular metal alkoxide was the active catalyst (equation 140).



(333) (334) (140)

$SnCl_4$ was used with epoxide (**335**), and resulted in a deep-seated rearrangement. The mechanism proposed by Scovell and Sutherland[175] is shown in equation (141).

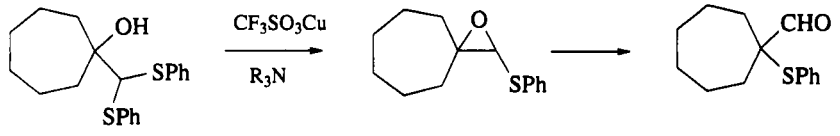


(335) (336) (337) (338) (141)

$FeCl_3$ is infrequently used to initiate epoxide rearrangements. It has been shown to give chlorohydrins rapidly with a range of oxiranes, simply by brief mixing in ether followed by an aqueous wash.[176] Other rarely used reagents for rearrangement are $SbCl_5$,[177] $Me_2SO + Pr^nI$,[178] various clays,[179] $[Rh_2Cl_2(CO)_4]$[180] and $[Mo(CO)_6]$,[181] each of which has either demonstrated or potential Lewis acid properties. Probably not in this category but worthy of note as a useful synthetic method is the Pd^0-catalyzed conversion of

2,3-epoxy ketones to 1,3-diones.[182] Some epoxides are rearranged to allylic alcohols by diborane, with subsequent reaction (addition, oxidation) typically leading to diols.[183]

An epoxide has been identified as an intermediate in the copper(I) triflate-catalyzed reaction outlined in equation (142).[184]

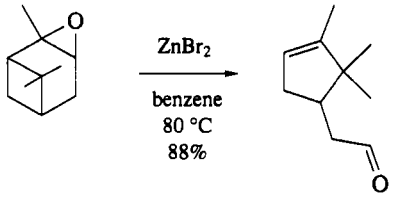


(142)

(339) (340) (341)

The zinc halides have a mixed reputation in the field of epoxide chemistry. ZnI_2 is recommended as a catalyst for epoxide opening, without rearrangement, in the addition of thiosilanes[185] and selenosilanes.[186] Conversely, rearrangements catalyzed by zinc salts have been clearly documented for several epoxides. Sutherland's comparison[170] suggests that $ZnCl_2$ should be rated on the weaker end of the strong acid scale.

Terpene oxides have been favorite substrates for $ZnBr_2$-catalyzed reactions, probably because early work indicated that certain reactions afforded high yields of unusual materials. Indeed some of these claims have held up well to later analytical scrutiny. For example, α-pinene oxide (**342**; equation 143) yields essentially pure (**343**; 88%) upon brief treatment with $ZnBr_2$ (catalytic amount) in refluxing benzene.[187]



(143)

(342) (343)

More typically, mixtures of products are formed. Terpene epoxides that have been subjected to $ZnBr_2$-catalyzed rearrangement include the oxiranes derived from limonene,[188] carvomenthene,[188] other pinenes,[189] 2,3-carvene,[190] pulegone[191] and piperitone.[191] $ZnCl_2$ is rarely employed, but has been compared with $AlCl_3$ in a study involving several epoxides.[192] In most instances there appears to be no evidence for special advantages of zinc halides compared with other more commonly used Lewis acids.

3.3.8 REFERENCES

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3.4
The Semipinacol and Other Rearrangements

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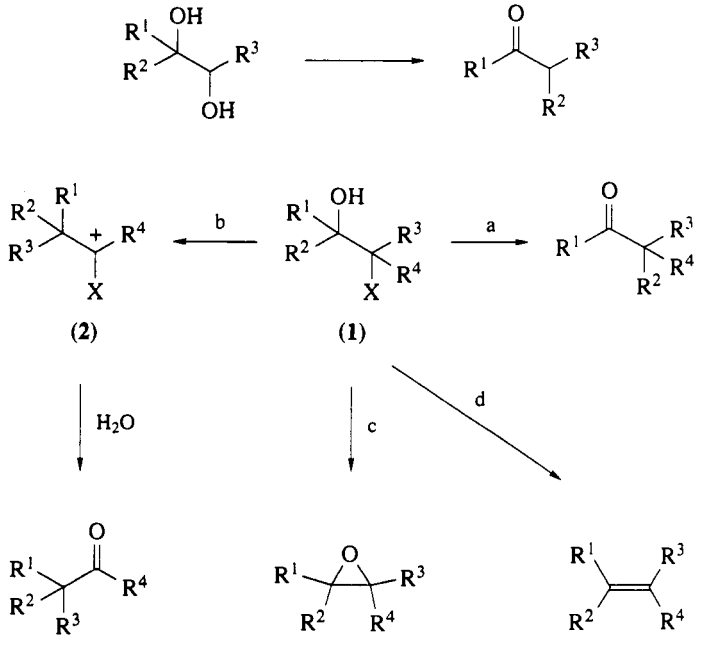
3.4.1 INTRODUCTION

3.4.1.1 Semipinacol Rearrangements

The semipinacol rearrangement was originally defined as a special case of the pinacol rearrangement, in which migration occurred towards the secondary center of a tertiary, secondary diol (equation 1), *i.e.* the reverse of the regiochemistry observed in the pinacol rearrangement. However, the term 'semipinacol' is now used generally to describe all such rearrangements which are related to, or reminiscent of, the pinacol rearrangement.[1] The largest class of semipinacol rearrangements are those derived from 2-heterosubstituted alcohols (**1**), such as halohydrins (**1**; X = Cl, Br), 2-amino alcohols (**1**; X = NH_2), 2-hydroxy sulfides (**1**; X = SR) and 2-hydroxy selenides (**1**; X = SeR).

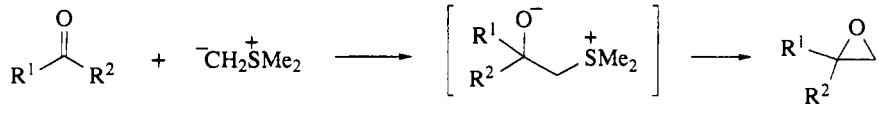
The normal pathway for rearrangement of the substrates (**1**) is *via* loss of the heteroatom substituent with migration of an adjacent alkyl (or aryl) group, and concomitant ketone formation (Scheme 1, path a). An alternative migration (path b), is occasionally observed in protic media, *i.e.* protonation of the alcohol (**1**) and migration with loss of water generates the stabilized carbocation (**2**), which is then hydrolyzed.



(1)

Scheme 1

Epoxide formation (path c) is an important side reaction which can become the dominant pathway. For example, the addition of sulfur ylides to ketones (equation 2) constitutes a general synthesis of epoxides,[2] while 2-hydroxy sulfides undergo the semipinacol rearrangement under certain conditions (equation 3).[3] Elimination (path d) is observed in some special cases such as 2-hydroxysilanes (**1**; X = SiR_3; the Peterson alkenation)[4] and 2-hydroxyphosphonium species (**1**; X = PR_3^+ ; Wittig intermediates).[5]

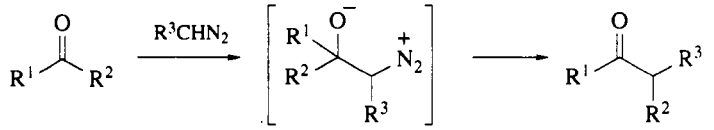


(2)

(3)

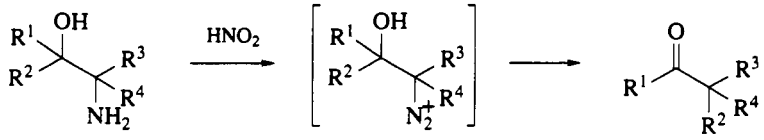
The semipinacol rearrangement is not restricted to 2-heterosubstituted alcohols. Thus, the addition of diazoalkanes to ketones yields homologated ketones (equation 4), *via* rearrangement of the adduct (**3**). This process is closely related to the rearrangement of 2-amino alcohols on treatment with nitrous acid (equation 5). Similarly, 2-hydroxyimines undergo rearrangement to 2-amino ketones in a related process (equation 6).

The rearrangement of acetals of 2-haloalkyl aryl ketones is a well-documented process yielding esters of 2-arylalkanoic acids by 1,2-aryl shift (equation 7).[6] The mechanism of this rearrangement is reminiscent of other semipinacol rearrangements. Loss of the halogen (usually assisted by Lewis acid), yields a carbocation (**4**), which then undergoes a 1,2-aryl shift with carbonyl group formation.



(4)

(**3**)



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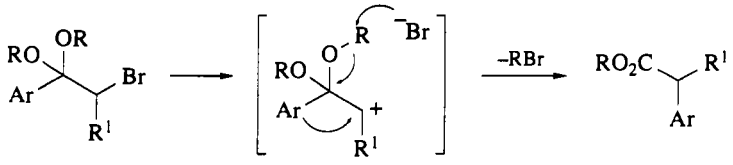
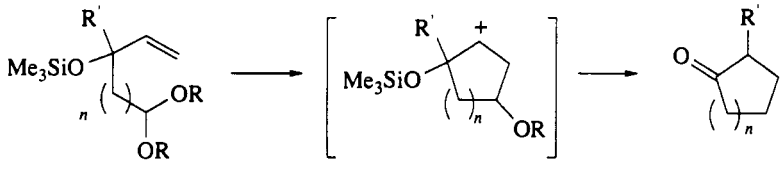


(7)

(4)

A number of tandem cyclization–semipinacol rearrangements have been reported,[7] whereby cyclization is initiated by an acetal and terminated by a semipinacol rearrangement (equation 8).

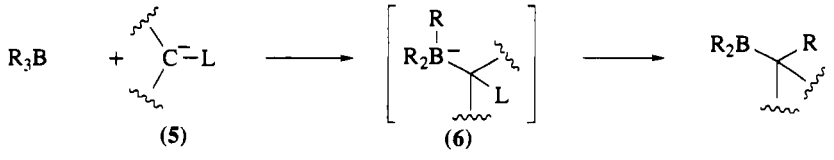


(8)

In general, semipinacol rearrangements are more selective than the classical pinacol rearrangement in terms of regiochemistry and mildness of conditions. Consequently there have been many applications of the semipinacol rearrangement in the formation of carbon–carbon bonds. The carbon atom bearing the migrating group is usually tertiary, while the carbon receiving the migrating group can be primary, secondary or tertiary. Migratory aptitude is not an important factor in semipinacol rearrangements. Electronic factors, the relief of ring strain and the stereochemistry of the substrate all influence the course of migration. Inversion of configuration is observed in most cases, and this feature has been utilized in chiral synthesis. With some exceptions, the mechanism of semipinacol rearrangements has not been examined in detail. Most investigations have centered on the synthetic utility of the rearrangement.

3.4.1.2 Boron Rearrangements

Organoboranes undergo rearrangements with the formation of carbon–carbon σ-bonds. The boron atom plays a pivotal role in the rearrangement by accepting a nucleophile (**5**) to produce an intermediate four-coordinate organoborate species (**6**). Migration from boron to carbon occurs if a leaving group is positioned on the carbon center α to boron (equation 9), yielding a new neutral organoborane. For example, ylides of sulfur (**5**; L = SMe_2^+) and nitrogen (**5**; L = NMe_3^+) add to triorganylboranes to yield rearranged products; anions of haloalkanes (**5**; L = halogen) effect a similar transformation.

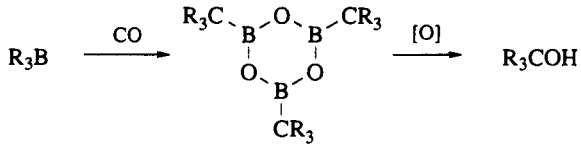


(9)

(5) (6)

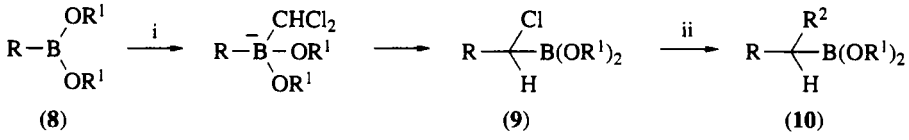
The carbonylation of triorganylboranes is well documented,[8] and provides a unique route to tertiary alcohols. Thus, triorganylboranes react with carbon monoxide to yield a trimeric product (**7**) which is read-

ily oxidized to a tertiary alcohol (Scheme 2). The exact mechanism of this process is not clear, but it is known to proceed by three sequential rearrangements from boron to carbon.



Scheme 2

Boronic esters (**8**) react with dichloromethyllithium to form intermediate borate complexes which then undergo rearrangement to form 2-haloboronic esters (**9**). When treated with a Grignard reagent, the 2-haloboronic esters (**9**) rearrange to secondary alkylboronic esters (**10**; Scheme 3).

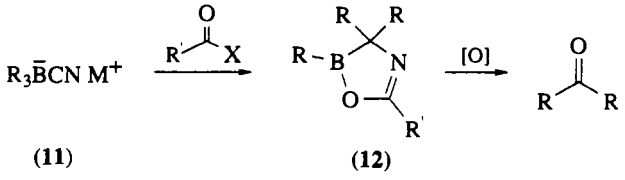


i, $LiCHCl_2$; ii, R^2MgX

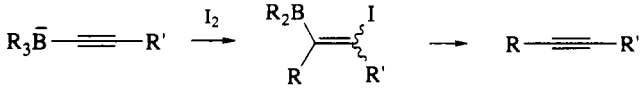
Scheme 3

This iterative procedure has been utilized with great effect in asymmetric synthesis *via* chiral boronic esters derived from chiral alcohols.[9]

Certain tetraorganylborate salts are stable isolable species, and undergo rearrangement by migration from boron to carbon when treated with electrophiles. For example, the cyanoborates (**11**), when treated with acylating agents, yield the heterocyclic intermediate (**12**) by two successive rearrangements (Scheme 4). Oxidation of the intermediate (**12**) yields ketones. Similarly, alkynylborates produce alkynes when treated with iodine, *via* rearrangement and elimination (equation 10).



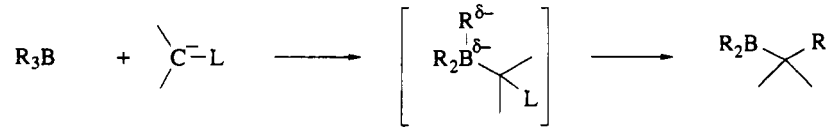
Scheme 4



(10)

There are many applications of boron rearrangements in organic synthesis and the subject has been comprehensively reviewed.[10] This methodology offers considerable scope in the formation of carbon–carbon bonds.

A common mechanism involved in these rearrangements is one whereby an organic group migrates from a four-coordinate, electron-rich boron center, to an electron-deficient α-carbon center. In general, primary groups migrate before secondary, which migrate before tertiary. This migratory aptitude can be rationalized by consideration of a partial negative charge on the nucleophilic migrating group (equation 11), and hence reflects the relative stabilization of negative charge.

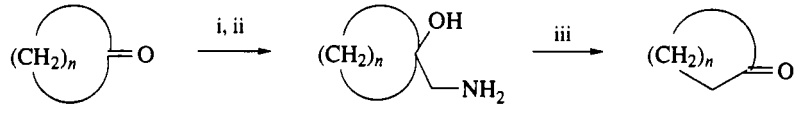


(11)

3.4.2 SEMIPINACOL REARRANGEMENTS

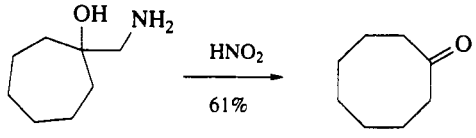
3.4.2.1 Rearrangements of 2-Amino Alcohols

The semipinacol rearrangement of primary 2-amino alcohols on exposure to nitrous acid is known generally as the Tiffeneau–Demjanov rearrangement. The reaction is well documented and is often associated with ring enlargement[11] and, to a lesser extent, ring contraction. Thus, a cyclic ketone may be homologated in a three-step sequence *via* cyanohydrin formation, followed by reduction to an aminomethylcycloalkanol and rearrangement (Scheme 5). This sequence has been applied to the formation of five- to eight-membered rings, for example in the preparation of cyclooctanone (equation 12).[12] Trimethylsilyl cyanide forms cyanohydrin *O*-silyl ethers of ketones resistant to HCN treatment, and has been recommended for the preparation of 2-amino alcohols.[13]



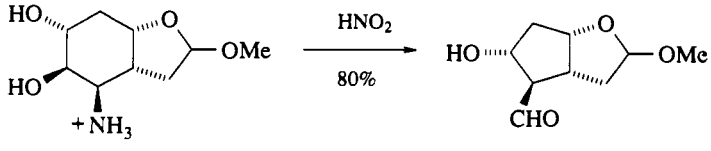
i, HCN; ii, $LiAlH_4$ or PtO_2 / H_2; iii, HNO_2

Scheme 5



(12)

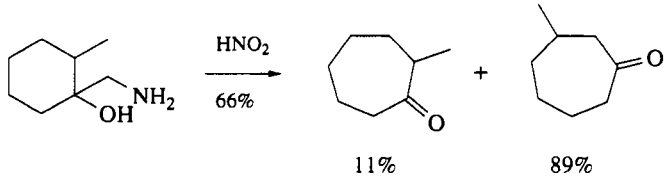
In general, the rearrangement is most effective when the hydroxy group is tertiary. However, rearrangement is possible with a secondary hydroxy group, as Woodward *et al.*[14] have demonstrated in the ring contraction of the bicyclic acetal (**13**; equation 13), used in a synthesis of prostaglandin $F_{2\alpha}$. The degree of substitution at the carbon bearing the primary amino group is variable, but an aryl group has been shown to inhibit rearrangement.[15]



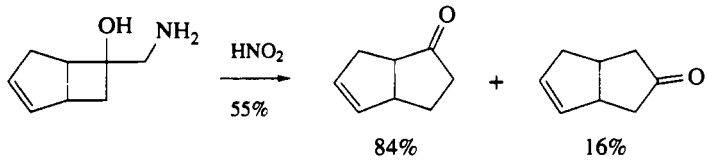
(13)

(13)

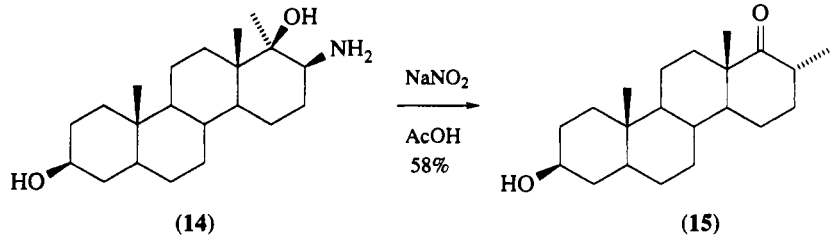
In ring expansion reactions, the least-substituted group shows a greater tendency to migrate (equations 14 and 15), although the selectivity may be attributable to conformational effects. The importance of conformational effects has been amply demonstrated in the rigid steroidal framework. Thus, the D-ring homosteroid (**14**) rearranges to the ketone (**15**; equation 16),[17] while the alcohol epimer (**16**) does not rearrange under the same conditions, but instead forms the epoxide (**17**; equation 17).[18] In marked contrast, the homosteroid (**18**), which is diastereoisomeric with (**14**) at the amino alcohol function, undergoes ring contraction (equation 18).[19] In these rigid systems it is the group that is *trans* coperiplanar to the amino function which migrates. In the case of the amino alcohol (**16**) the hydroxy group is *trans* coperiplanar, and epoxide formation is favored (Scheme 6).



(14)[15]

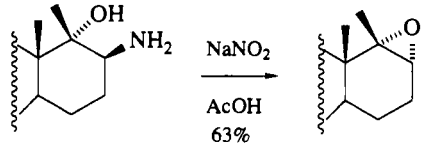


(15)[16]



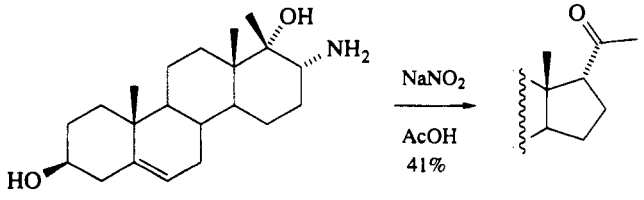
(14) (15)

(16)



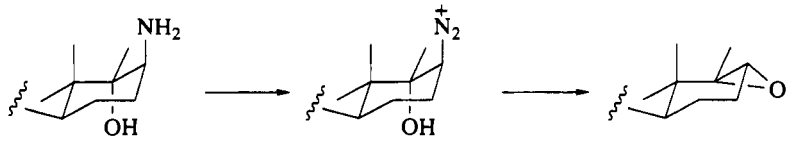
(16) (17)

(17)



(18)

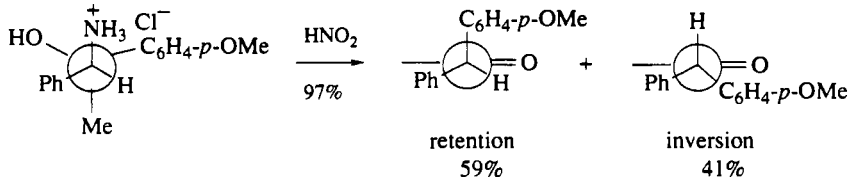
(18)



(16) (17)

Scheme 6

Inversion of configuration is normally observed on rearrangement of cyclic 2-amino alcohol substrates. Collins *et al.*[20] have examined in detail the stereochemical course of the Tiffeneau–Demjanov rearrangement in acyclic substrates. In a series of 2-amino-1,2-diaryl alcohols studied, variable amounts of inversion were observed, while in some cases retention of configuration predominated (equation 19). This complexity can be attributed to the flexibility of such acyclic substrates where several conformations are possible in the transition states.

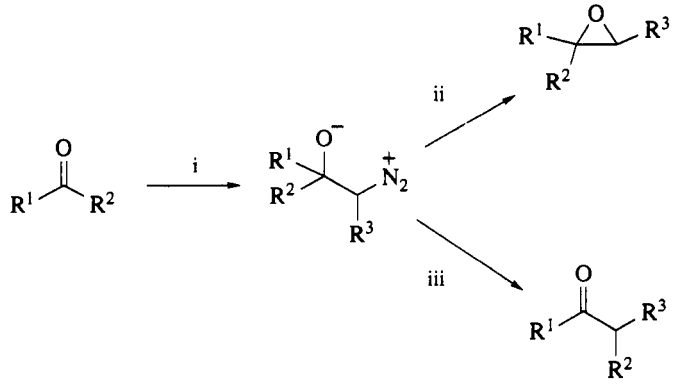


(19)

retention 59% inversion 41%

3.4.2.2 Additions of Diazoalkanes to Ketones

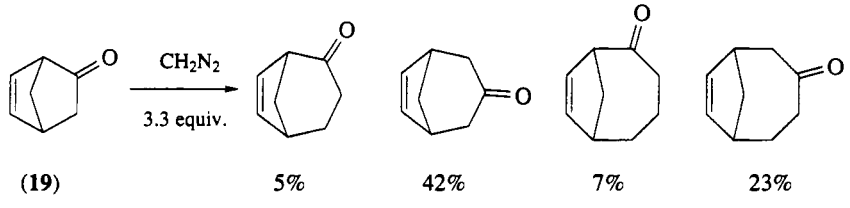
The homologation of ketones by the addition of diazoalkanes complements the Tiffeneau–Demjanov rearrangement. Epoxide formation is a side reaction which can be minimized if polar aprotic solvents are avoided (Scheme 7). Rearrangement (*i.e.* homologation) is maximized in ether solvents or by Lewis acid catalysis.[21] The reaction is most effective in the ring expansion of cyclic ketones.



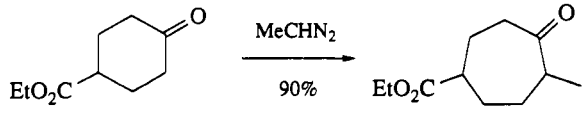
i R^3CHNH_2; ii, aprotic solvents; iii, ether solvents or Lewis acid

Scheme 7

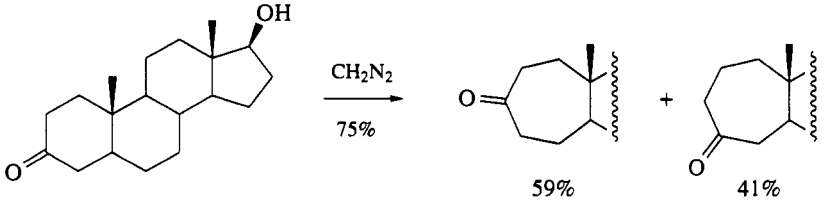
In the addition of simple diazoalkanes to ketones, the product homologated ketone is often an effective substrate for further homologation. For example, norbornenone (**19**), when treated with an excess of diazomethane, yields a complex mixture of homologated ketones (equation 20).[22] However, high yields of a desired homologated ketone can be obtained, as in the preparation of 5-ethoxycarbonyl-2-methylcycloheptanone from 4-ethoxycarbonylcyclohexanone (equation 21).[23] With unsymmetrical ketones a mixture, due to migration of either group, is obtained (equation 22),[24] and the degree of substitution of either group appears to be of little importance.[25] However, 2-halo ketones undergo rearrangement with exclusive migration of the nonhalogenated group, and this selectivity has been utilized in a regioselective synthesis of ketones (Scheme 8).[26]



(**19**) 5% 42% 7% 23% (20)

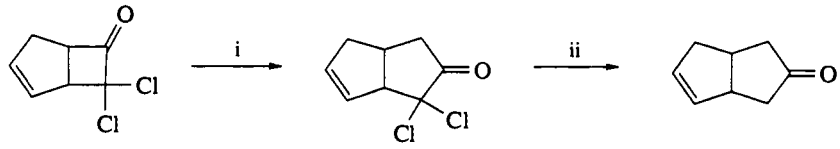


(21)



59% 41% (22)

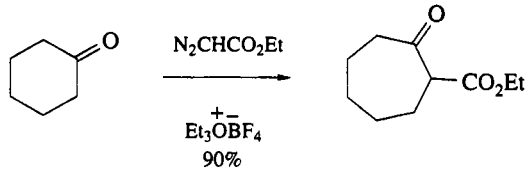
Ethyl diazoacetate has been used extensively in the homologation of ketones to 3-keto esters. Lewis acid is required for the reaction (equation 23).[105] There is a tendency for the least-substituted group to migrate, particularly if one group is fully substituted (equation 24).[27] In a total synthesis of (±)-aplysin (**20**) this selective rearrangement was applied (Scheme 9),[28] and a similar approach was used in a synthesis of (+)-hirsutic acid.[29] Ethyl diazoacetate has also been used in the homologation of acyclic



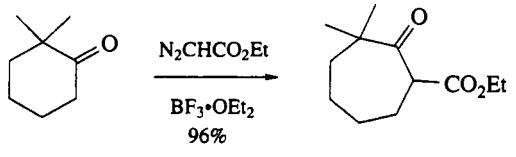
i, CH_2N_2; ii, Zn, AcOH, 70% (2 steps)

Scheme 8

ketones. The presence of a 2-halogen promotes selective migration of the nonhalogenated group. The halogen 'protection' and the ethoxycarbonyl group can be removed reductively in one operation (Scheme 10).[30] The anion of ethyl diazoacetate adds to ketones to produce isolable 3-hydroxy-2-diazo esters, which rearrange to 3-keto esters when exposed to metal salt catalysis (Scheme 11).[31]



(23)



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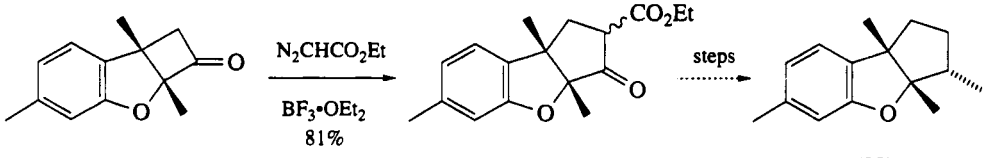
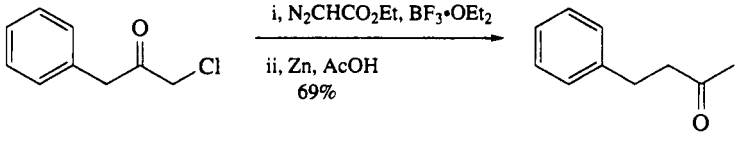
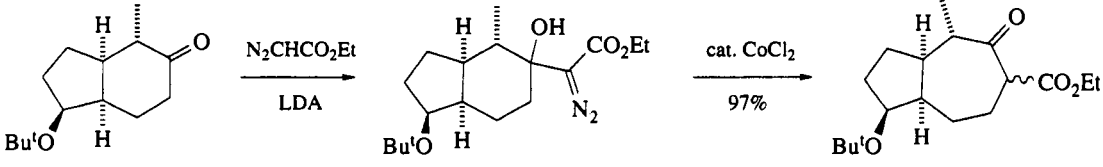


(20)

Scheme 9



Scheme 10

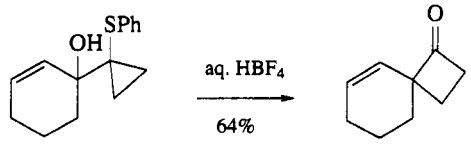


Scheme 11

3.4.2.3 Rearrangements of 2-Hydroxy Sulfides

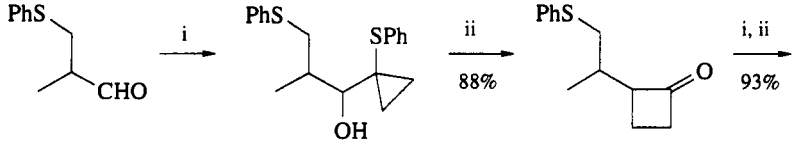
2-Hydroxy sulfides rearrange to ketones under a variety of conditions. In aqueous acid it is the carbon bearing the sulfur group which ultimately becomes the carbonyl carbon. The rearrangement proceeds *via* protonation of the hydroxy group (Scheme 1, path b), and appears to be restricted to the expansion of

small rings, particularly cyclopropanes (equation 25).[32] Trost and coworkers have developed this method, whereby the anion of cyclopropyl phenyl sulfide adds to a ketone and the adduct then rearranges to a cyclobutanone.[32,33]

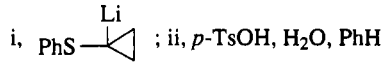


(25)

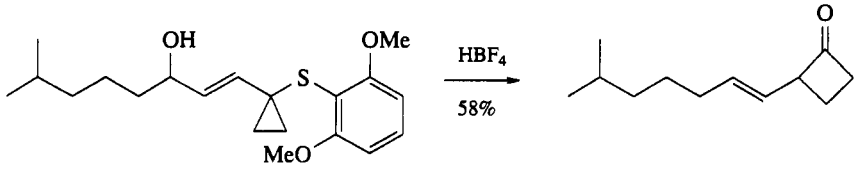
Two such rearrangements were used in the preparation of the cyclobutanone (**21**), a key intermediate in a synthesis of grandisol (**22**; Scheme 12).[33] A similar rearrangement is observed if the alcohol is allylic to the sulfide (equation 26),[34] and the formation of cyclobutanones from 1-thiophenyl-1-vinylcyclopropanes[35] is a closely related process.



(**21**) (**22**)

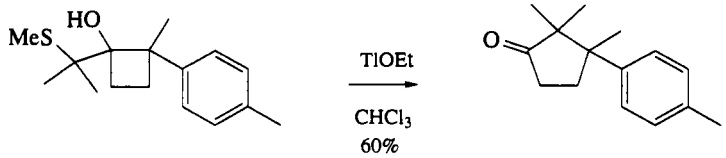


Scheme 12



(26)

When exposed to soft electrophiles such as dichlorocarbene (generated *in situ*), 2-hydroxy sulfides rearrange with loss of the sulfur group and ketone formation at the hydroxy-bearing carbon,[3,36] as in the synthesis of cuparenone (**23**; equation 27).[3]

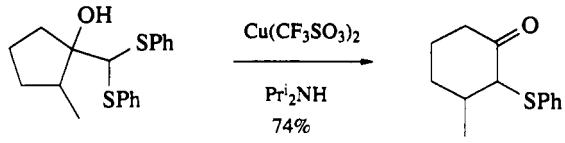


(27)

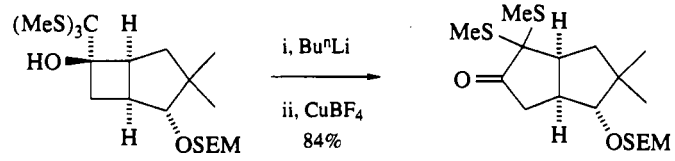
(**23**)

The anion of 1,1-dithiophenoxymethane adds to cyclic ketones and the adduct then rearranges to a ring-expanded ketone on metal salt catalysis (equation 28).[36a] The least-substituted group migrates in this case, as in the trithioalkyl derivative (**24**; equation 29), which was utilized in a synthesis of coriolin.[36b]

In a similar vein, the adducts derived from the anion of methoxymethyl phenyl sulfone and cyclic ketones rearrange on Lewis acid catalysis (Scheme 13).[37] This rearrangement is quite stereospecific, in that a single diastereoisomer is formed and it is the most substituted group which migrates. Similar results were obtained with adducts derived from phenyl thiomethyl phenyl sulfone (Scheme 14).[37]

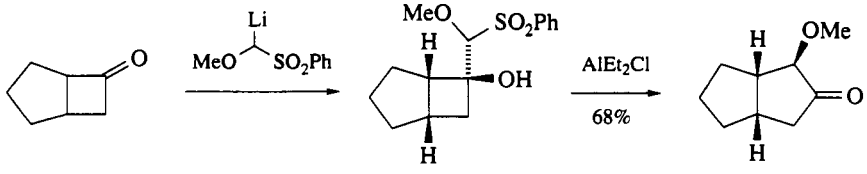


(28)

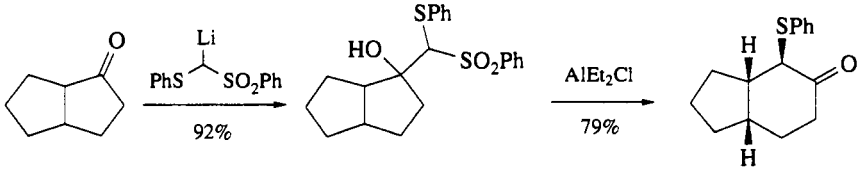


(29)

(24)

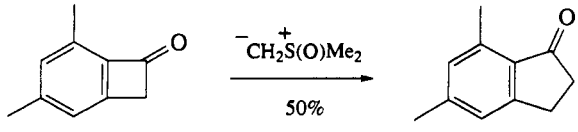


Scheme 13



Scheme 14

Rearrangement is sometimes observed on the addition of sulfur ylides to ketones, yielding a homologated ketone rather than the expected epoxide (equation 30).[38] Hydroxy sulfides can undergo elimination to form alkenes, but the conditions are quite specific and require derivatization at oxygen[39] or sulfur.[40]



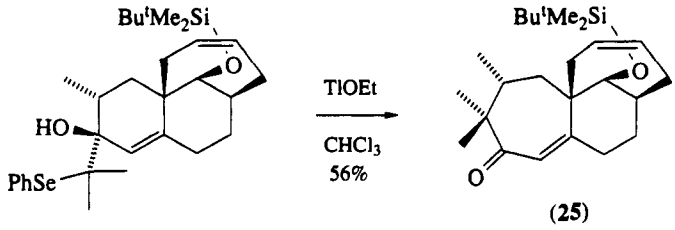
(30)

3.4.2.4 Rearrangements of 2-Hydroxy Selenides

The semipinacolic rearrangements of 2-hydroxy selenides are closely related to those of 2-hydroxy sulfides, but they have not been studied as extensively, and the use of selenium does not seem to offer any advantages over sulfur. The rearrangement has been applied mainly to the ring expansion of cyclic ketones *via* the addition of α-selenoalkyl anions.

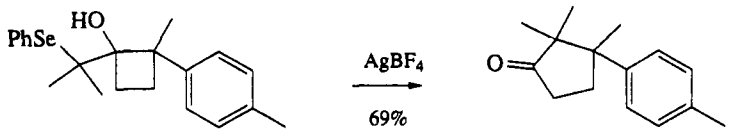
Paquette *et al.*[41] prepared the complex tricyclic ketone (**25**) by a selective rearrangement of a 2-hydroxy selenide (equation 31). In this case, it was the alkyl rather than the vinyl group which migrated. However, this preference is not as marked in a less rigid system.[41] A similar selectivity was noted in a cyclobutene derivative,[42] and Krief *et al.*[43] found that selectivity was highly dependent on ring size and the degree of substitution at the migrating center.

Dichlorocarbene (generated *in situ*), is generally used to induce migration, but silver tetrafluoroborate has also been used, as in the preparation of cuparenone (**23**; equation 32).[44] Rearrangement occurs only if the selenyl moiety is attached to a fully substituted carbon. For example, the hydroxy selenide (**26**) does not rearrange but instead yields the epoxide (**27**; equation 33).[44]



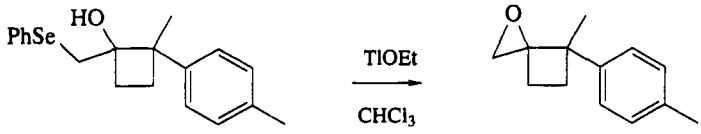
(31)

(25)



(32)

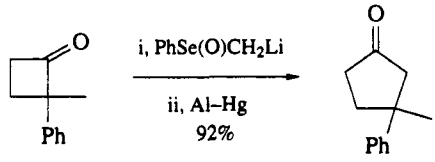
(23)



(33)

(26) (27)

This limitation can be overcome using the anion of alkyl phenyl selenoxides which add to ketones and rearrange *in situ* (equation 34).[45] The amalgam reduction is required to remove the small amount of α-phenyl selenated ketones formed in the reaction.

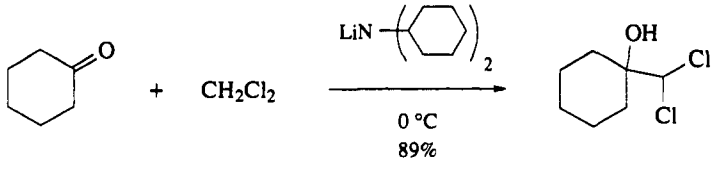


(34)

2-Hydroxy selenides undergo elimination to alkenes when treated with an excess of methanesulfonyl chloride, but elimination is not an important side reaction in rearrangement reactions.[46]

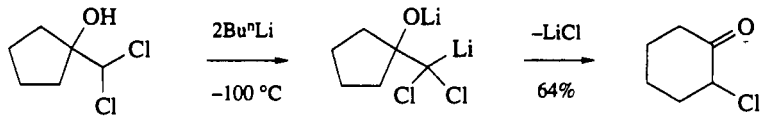
3.4.2.5 Rearrangements of Halohydrins

Halohydrins undergo semipinacolic rearrangement when exposed to base. The rearrangement of epoxides with metal halides is a closely related process and both rearrangements have been described in Chapter 3.3. However, the adducts of ketones and polyhalomethyllithium undergo rearrangements analagous to halohydrins, but by a quite different mechanism. The adducts are easily prepared by treating a mixture of polyhalomethane and ketone with an *N,N*-disubstituted lithium amide (equation 35).[47] When a dichloromethylcycloalkanol is treated with 2 equiv. of *n*-butyllithium, a dilithiated species (**28**) is formed, which then rearranges to form a homologated 2-chloro ketone (Scheme 15).[48]



(35)

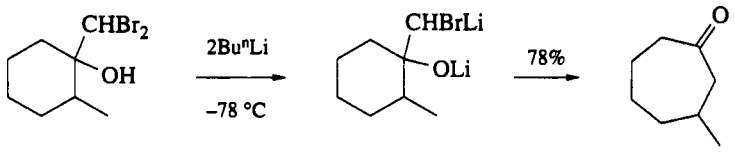
A dibromomethylcycloalkanol rearranges in a similar fashion, except that a different dilithio intermediate is formed *via* halogen–metal exchange rather than deprotonation (Scheme 16).[48] With unsymmetrical ketones, the more substituted group migrates. This selectivity has been applied to a synthesis of (±)-muscone (**29**; Scheme 17).[48] Substituted polyhalomethyllithium species can be used in the prepara-



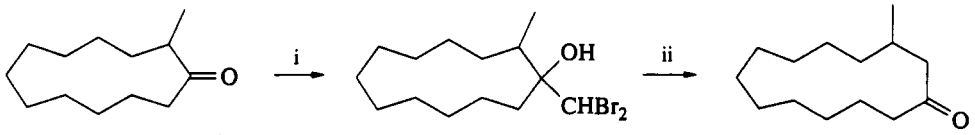
(28)

Scheme 15

tion of 2-substituted homologated ketones (Scheme 18).[49] The *O*-silyl ethers of dihaloalkylcarbinols do not rearrange when treated with *n*-butyllithium but instead eliminate to form vinyl halides.[50]



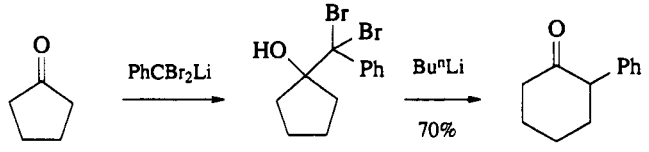
Scheme 16



(29)

i, LiCHBr$_2$, 78%; ii, Bu^{n}Li, 76%

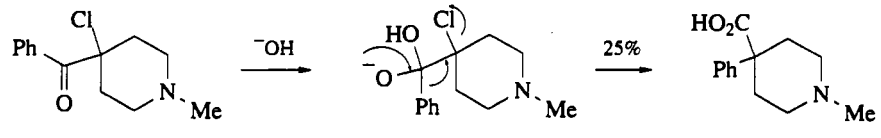
Scheme 17



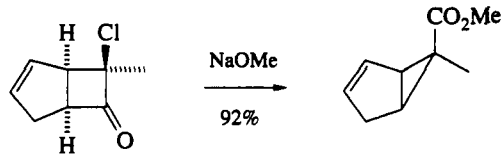
Scheme 18

3.4.2.6 Rearrangements of 2-Halo Ketones and Acetals

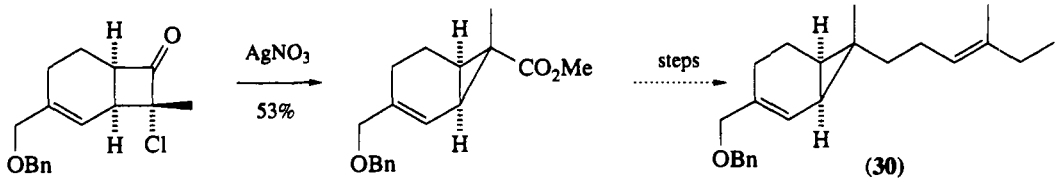
The semipinacolic rearrangement of 2-halo ketones and acetals to esters or acids is a valuable synthetic procedure, and the reaction has attracted considerable interest in the synthesis of 2-arylalkanoic acids,[6] several of which are valuable pharmaceuticals. The rearrangement is related to the Favorskii rearrangement and is sometimes referred to as the 'quasi-Favorskii' rearrangement. Under basic conditions, the semipinacolic mechanism applies with 2-halo ketones where the cyclopropanone intermediate of the Favorskii rearrangement cannot form. Such examples are ketones which do not have an α′-hydrogen (Scheme 19),[51] or certain cyclobutanones (equation 36).[52] Low yields in the base-induced rearrangement are often due to preferential displacement of the halogen by hydroxide ion. However, the rearrangement can be induced under milder conditions, such as silver nitrate in methanol, which was used in the chlorocyclobutanone ring contraction step in a recent synthesis of (±)-sirenin (**30**; Scheme 20).[53] Lewis acid is equally effective in the rearrangement of aryl bromoalkyl ketones (equation 37),[54] which is limited to secondary or tertiary bromides and to an electron-rich aromatic ring.



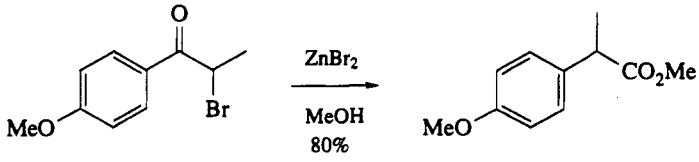
Scheme 19



(36)

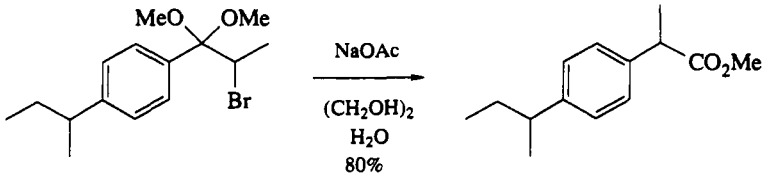


Scheme 20

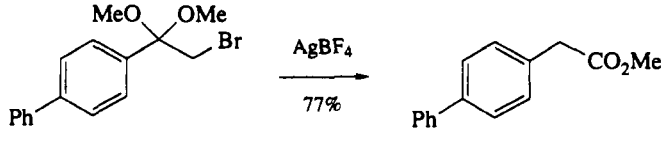


(37)

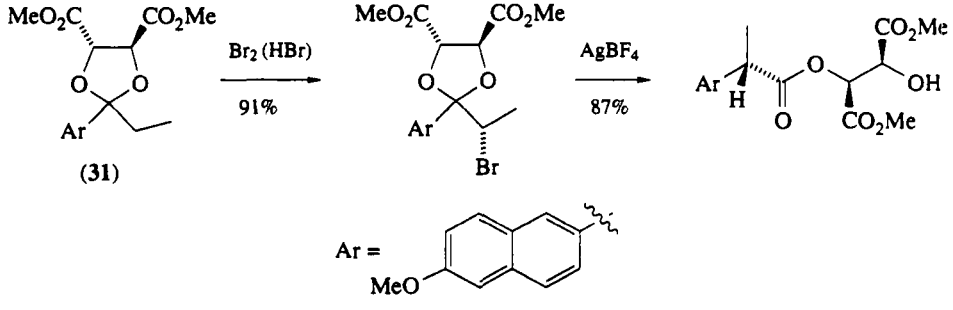
The acetals of 2-haloalkyl aryl ketones rearrange to esters of 2-arylalkanoic acids under a wide range of conditions.[6] Simply heating these substrates in aqueous alcohol containing sodium acetate provides the ester in high yield (equation 38).[55] Primary halides or electron-deficient arenes do not rearrange under these conditions. The use of silver salts in alcoholic media is more general (equation 39).[56] The rearrangement proceeds with inversion of configuration and an asymmetric synthesis of (+)-naproxen highlighting this feature has been described (Scheme 21).[57] Thus, the acetal (**31**), derived from (2*R*,3*R*)-tartaric acid, undergoes stereospecific bromination to yield a bromo acetal, which rearranges in high yield to the ester of (+)-naproxen. Yamauchi *et al.*[70] have demonstrated the similarity of these rearrangements by preparing esters of 2-arylalkanoic acids from ketones, acetals or enol ethers, using iodine, iodine monochloride or iodine trichloride in trimethylorthoformate solution (Scheme 22).



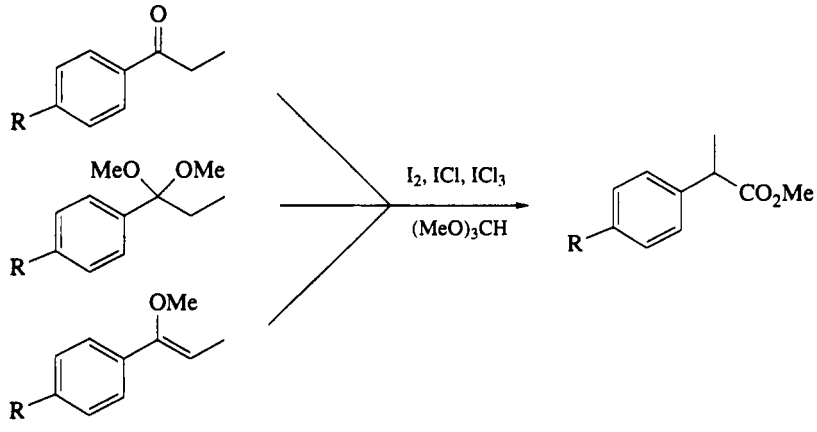
(38)



(39)



Scheme 21

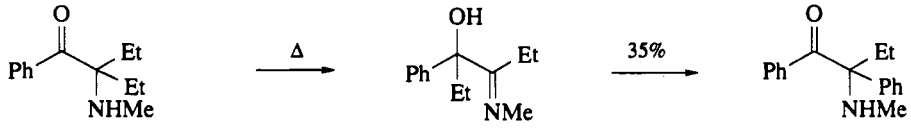


R = MeO, Bu^i, H, Br, F

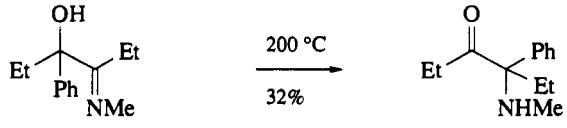
Scheme 22

3.4.2.7 Rearrangements of 2-Amino Ketones and 2-Hydroxyimines

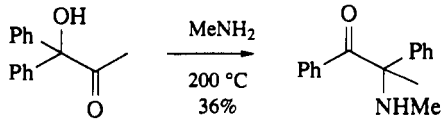
Certain 2-amino ketones undergo rearrangement on thermolysis to produce new 2-amino ketones. The reaction proceeds by an initial 1,2-shift to yield a hydroxyimine, followed by a second 1,2-shift to the observed product (Scheme 23).[58] The amine must be primary or secondary and attached to a tertiary center. As would be expected, 2-hydroxyimines rearrange to 2-amino ketones (equation 40).[58] Similarly, 2-hydroxy ketones when heated with amines form rearranged 2-amino ketones *via* 2-hydroxyimines (equation 41).[58] This reaction has been applied in the synthesis of a D-ring homosteroid (equation 42).[59]



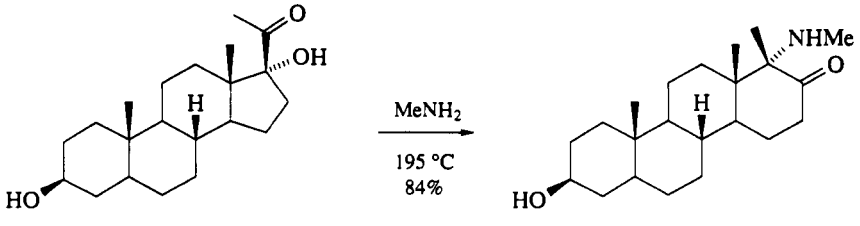
Scheme 23



(40)

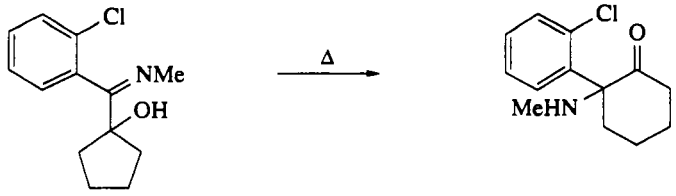


(41)

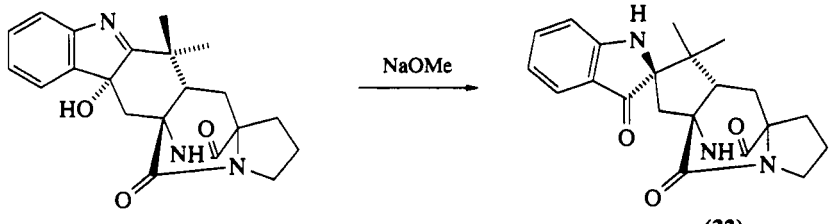


(42)

The semipinacolic rearrangement of 2-hydroxyimines has also been applied to the synthesis of 2-amino ketones which are not easily available by other methods (equation 43).[60] An impressive example is the biomemetic formation of the spiroindoxyl brevianamide A (**32**; equation 44).[61]



(43)

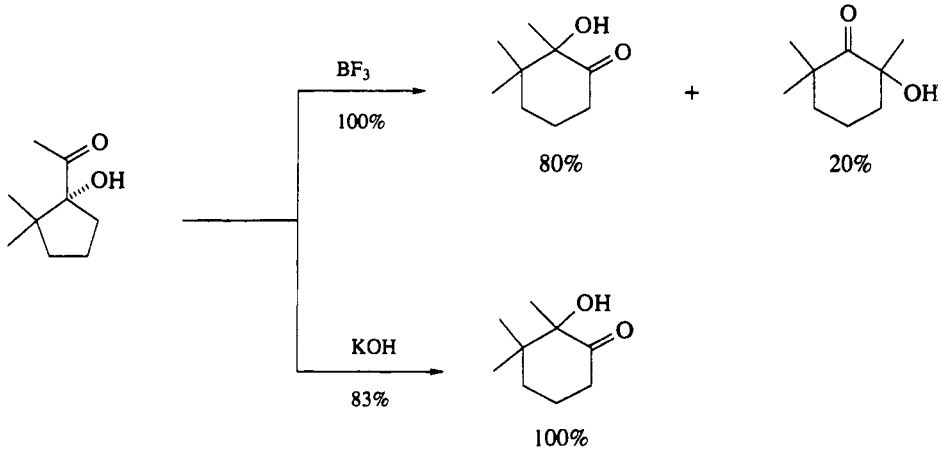


(44)

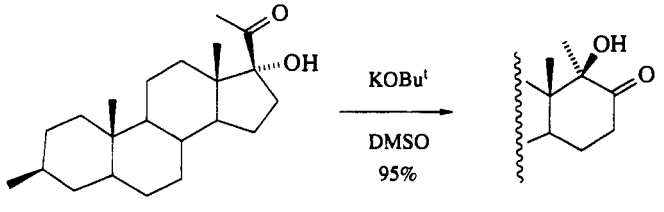
(32)

3.4.2.8 Rearrangements of 2-Hydroxy Ketones

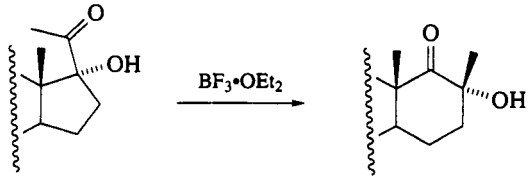
The rearrangement of 2-hydroxy ketones is analagous to the rearrangement of 2-hydroxyimines, and is termed the acyloin rearrangement. The reaction is of limited use, however, and has not found wide application. The rearrangement is initiated by base or Lewis acid (Scheme 24).[62] With unsymmetrical ketones it is possible for either group to migrate, depending on the conditions. With 3β,17α-dihydroxy-5α-pregnan-20-one, the more substituted group migrates under basic conditions (equation 45),[63] while Lewis acids promote migration of the least substituted group (equation 46).[62] Ring contraction is also possible, as in the case of the steroidal substrate (**33**; equation 47).[64]



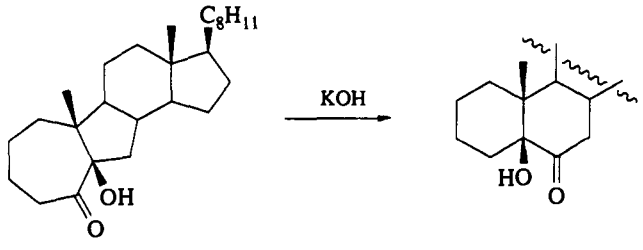
Scheme 24



(45)



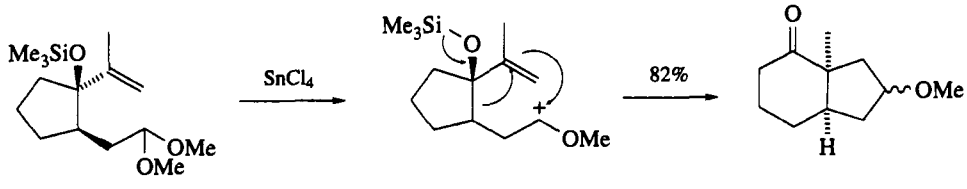
(46)



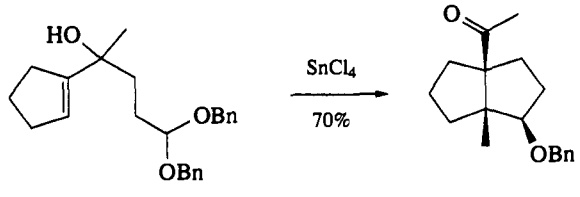
(33) (47)

3.4.2.9 Tandem Cyclization–Semipinacol Rearrangements

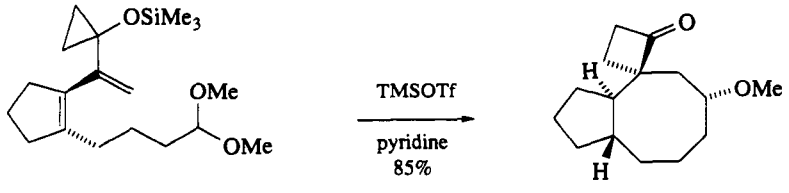
A semipinacol rearrangement in tandem with a cyclization has been shown to be a powerful method for the construction of carbocyclic rings. Here the cyclization is initiated by an acetal function and terminated by a semipinacol rearrangement (Scheme 25).[7] In some cases, the cyclization has been found to be stereospecific at the acetal center (equation 48),[65] and up to four chiral centers can be generated in a single step (equation 49).[66] Highly substituted tetrahydrofurans are obtained from cyclic acetals (Scheme 26),[67] and stereoselective tetrahydrofuran annelations are possible using bicyclic acetals (Scheme 27).[68]



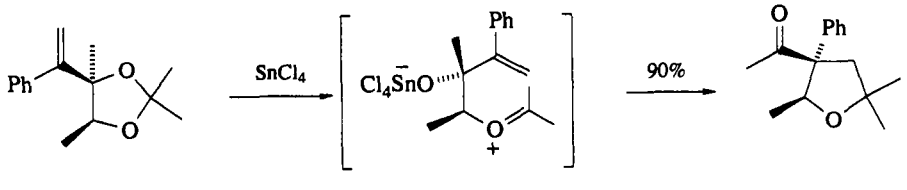
Scheme 25



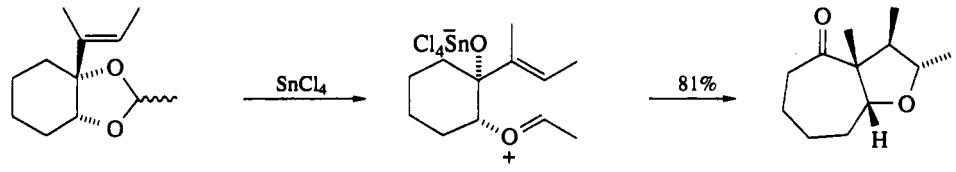
(48)



(49)



Scheme 26

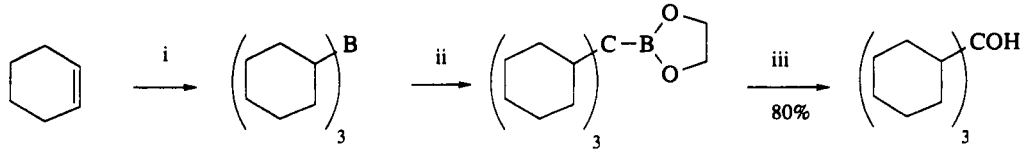


Scheme 27

3.4.3 ORGANOBORON REARRANGEMENTS

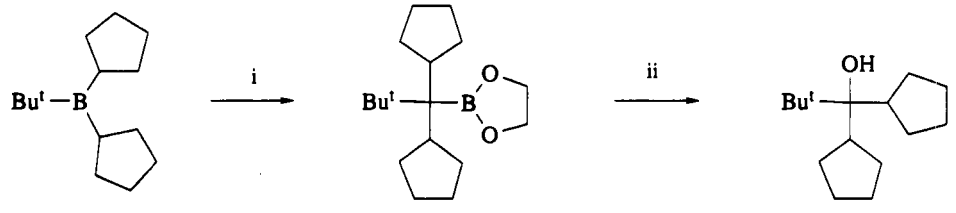
3.4.3.1 Rearrangements of Triorganylboranes

Trialkylboranes react with carbon monoxide in the presence of ethylene glycol to yield tertiary alkylboronic esters (Scheme 28), which on oxidation yield trialkylmethanols.[8,69] The presence of ethylene glycol is not necessary for this rearrangement but it greatly facilitates the oxidation reaction. The alkyl groups can be primary, secondary or tertiary, but tertiary groups do not migrate easily and more vigorous conditions are required (Scheme 29).[71]



i, BH_3 ; ii, CO, $(CH_2OH)_2$, 100 °C; iii, NaOH, H_2O_2

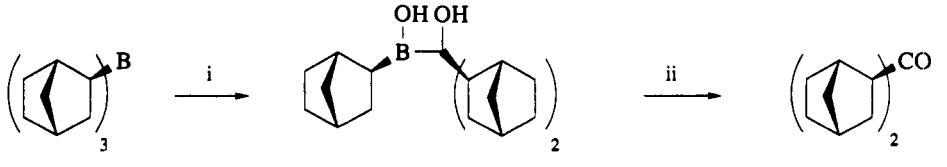
Scheme 28



i, CO (70 atm), $(CH_2OH)_2$, 150 °C; ii, NaOH, H_2O_2, 60% (2 steps)

Scheme 29

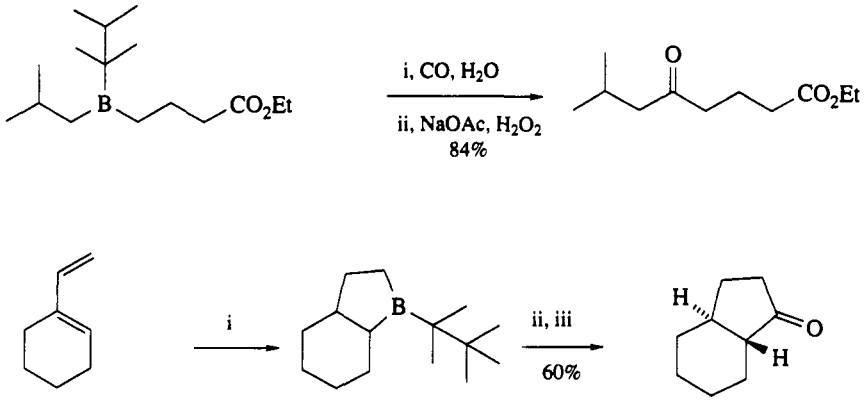
If water is present in the carbonylation reaction, rearrangement of the third group is inhibited and ketones instead are obtained on oxidation (Scheme 30).[72] The mechanism of this sequence is not clear but the reaction proceeds *via* the intermediate (**34**). Unsymmetrical ketones are available from thexyldialkylboranes (equation 50),[73] since the thexyl group does not migrate easily. Cyclic ketones are also available by this route (Scheme 31).[74] When the carbonylation is performed in the presence of reducing agents, only one alkyl group migrates. Aldehydes and alcohols are then available by this method.[8,75]



(**34**)

i, CO, H_2O, 100 °C; ii, NaOH, H_2O_2, 82%

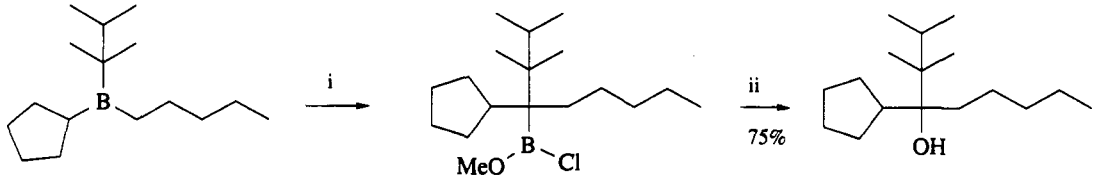
Scheme 30



i, $Me_2CHMe_2CBH_2$; ii, CO, H_2O; iii, H_2O_2, NaOAc

Scheme 31

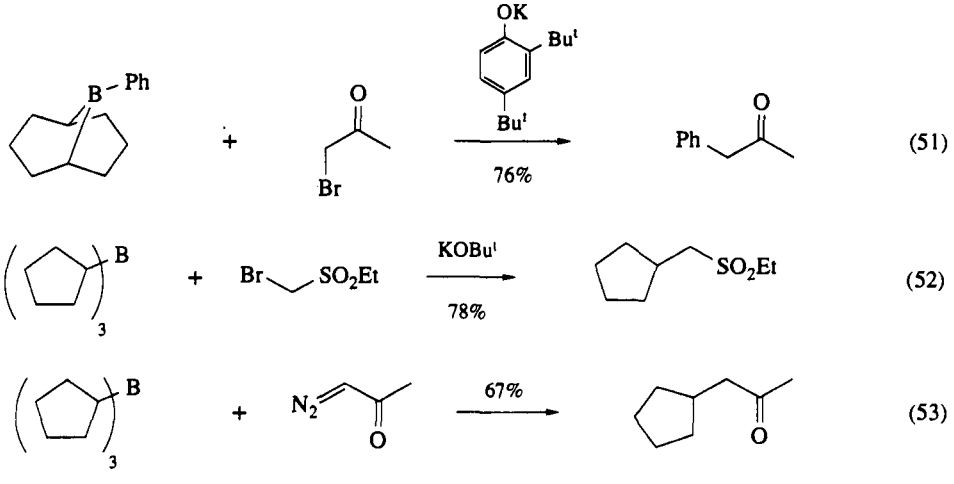
There are certain disadvantages to the carbonylation reaction, such as high temperature and pressure. An alternative preparation of trialkylmethanols is the use of the anion of dichloromethyl methyl ether. Addition of this anion to a trialkylborane is followed by three successive migrations to yield the trialkylmethanol on oxidation. The reaction takes place at room temperature, and tertiary groups migrate without difficulty (Scheme 32).[76]



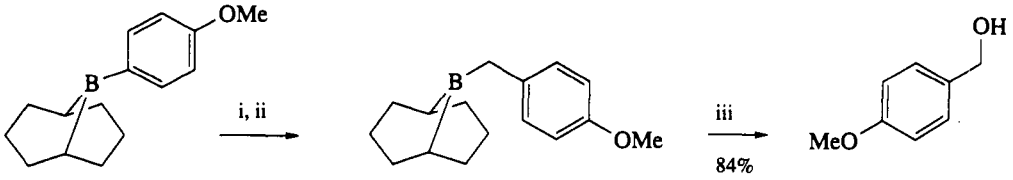
i, $CHCl_2OMe$, Et_3COK; ii, $(CH_2OH)_2$, NaOH, H_2O_2

Scheme 32

2-Halocarbonyl compounds react with triorganylboranes to yield 2-alkylated derivatives. 9-Alkyl- or 9-aryl-borabicyclononane derivatives yield the 9-alkyl/aryl group selectively (equation 51).[77] Sequential dialkylation of dichloroacetonitrile is feasible by this method.[78] Trialkylboranes also react with halo sulfones (equation 52)[79] and diazo ketones (equation 53),[80] in a similar fashion.



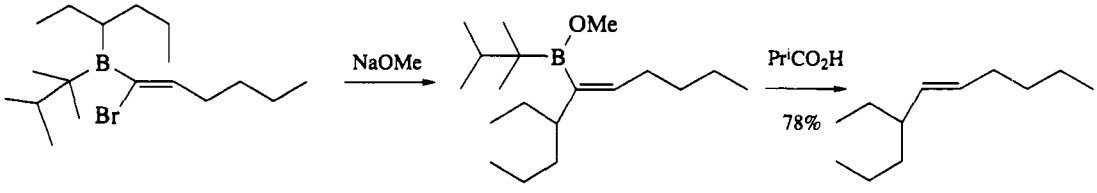
The reactions between ylides of sulfur and nitrogen, and triorganylboranes have not proved to be synthetically useful. A major side reaction is the competitive reaction between the product and the starting ylide. This complication can be overcome in the case of sulfur, by first reacting the borane with the anion of a sulfide and inducing rearrangement of the tetraorganylborate with an electrophile (Scheme 33), to yield a homologated borane.[81] The rearrangements of alkenylboranes yield either (*E*)- or (*Z*)-alkenes of high geometric purity by the judicious choice of substrate and conditions.



i, $LiCH_2SMe$; ii, MeI; iii, NaOH, H_2O_2

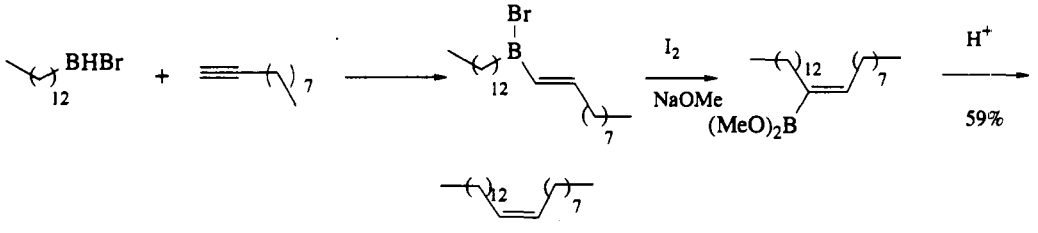
Scheme 33

Alkylbromoalkenylthexylboranes are available from thexylborane by sequential hydroboration of alkenes and bromoalkynes, and they rearrange to borinic esters when treated with methoxide. Protonation yields (*E*)-alkenes of high purity (Scheme 34).[82] Rearrangement takes place with inversion of configuration at the halogen center, while protonation proceeds with retention of configuration.



Scheme 34

Monoalkylbromoboranes hydroborate terminal alkynes to yield alkylalkenylbromoboranes, which then rearrange to yield (*Z*)-alkenes after protonation; this useful procedure has been applied to the preparation of muscalure (**35**; Scheme 35).[83] (*E*)-Alkenes are available by a similar sequence if 1-bromoalkynes are employed at the hydroboration stage.[84] Similarly, dialkenylthexylboranes yield dienes on rearrangement and protonation.[85]



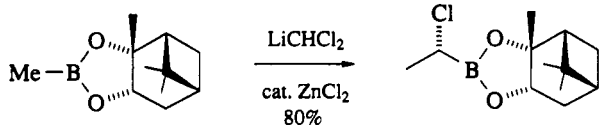
(35)

Scheme 35

The rearrangements of triorganylboranes have focused on the use of alkyl and alkenyl groups, due to the availability of these substrates by hydroboration. However, aryl groups are equally effective for rearrangement and this aspect warrants further study. There are many variants of the rearrangements of triorganylboranes which constitute a wide and varied methodology,[8,10a,75,86,87] some of which have not been fully exploited in synthesis.

3.4.3.2 Rearrangements of Boronic Esters

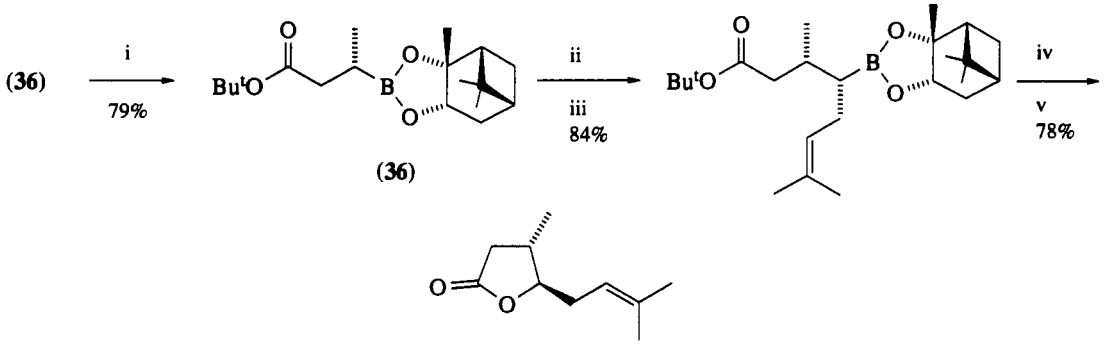
Boronic esters are not as reactive as triorganylboranes towards nucleophiles; however, rearrangement does take place if the boronic ester is treated with an α-halocarbanion (equation 54).[88] In this case, the 1-chloroethylboronate (**36**) can be obtained in 95% *de* due to the diastereofacial influence of the chiral pinanediol. Similarly, chloro- or bromo-alkylboronic esters react with Grignards reagents, alkyllithiums and enolates leading to rearranged products.[9,88]



(54)

(36)

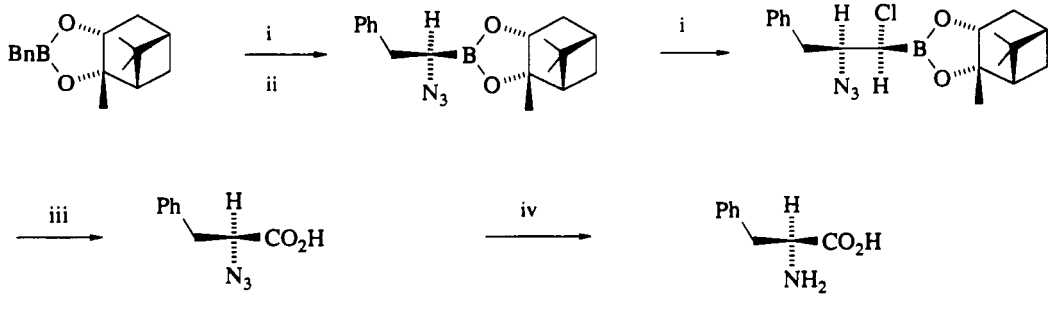
This methodology has been developed by Matteson and coworkers,[9,87] with particular emphasis on chiral boronic esters derived from pinanediol. Sequential chiral centers can be assembled by an iterative procedure with excellent enantiomeric excess at each step. The two chiral centers in eldanolide (**37**), for example, were assembled in this manner (Scheme 36).[88]



i, $Bu^tO_2CCH_2Li$; ii, $LiCHCl_2$, cat. $ZnCl_2$; iii,$Me_2C{=}CHCH_2MgCl$; iv, H_2O_2; v, TFA

Scheme 36

L-α-Amino acids can also be prepared by this method. Thus, heteronucleophiles, such as azide ion, react with the chloroalkylboronic ester *via* a four-coordinate boronate, as with carbon nucleophiles (Scheme 37).[89]

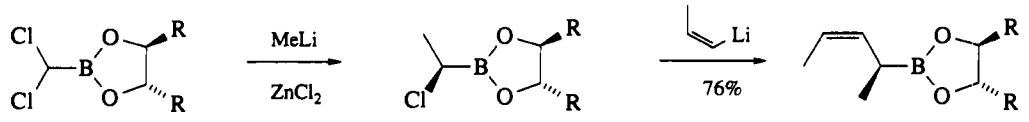


i, $LiCHCl_2$, cat. $ZnCl_2$; ii, NaN_3; iii, $NaClO_2$; iv, H_2, Pd/C, 63% (5 steps)

Scheme 37

The C_2 symmetry present in the boronic ester (**38**) derived from (*S*,*S*)-1,2-dicyclohexylethanediol allows the stereoselective displacement of each chlorine atom to yield the chiral pentenylboronic ester

(**39**), a key intermediate which has been used in a synthesis of the macrolide mycinomycin (Scheme 38).[90]

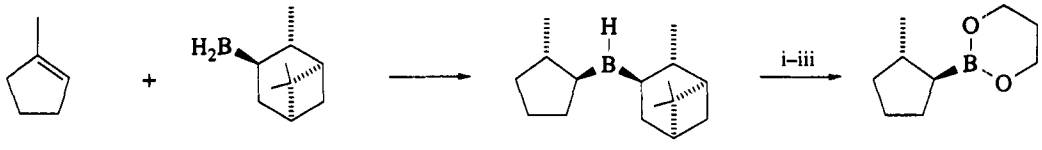


R = cyclohexyl (**39**)

Scheme 38

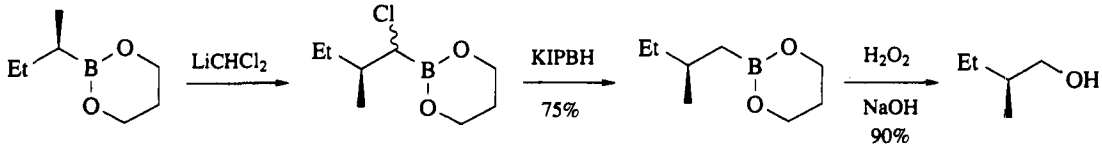
(*S,S*)-Diisopropylethanediol and (*R,R*)-2,3-butanediol are also effective chiral 'directors' in boronic ester rearrangements.[9] Both of these vicinal diols are C_2 symmetric and the butanediolboronic esters are readily hydrolyzed to boronic acids, which can then be reesterified if a change in chiral direction is required.

Brown and coworkers[75] have described an alternative synthesis of chiral alkylboronic esters. In this synthesis prochiral alkenes are hydroborated with monoisopinocamphenylborane to yield isopinocamphenylalkylboranes which are then readily transformed to chiral alkylboronic esters (Scheme 39).[91] Homologation with dichloromethyllithium, followed by reduction with potassium triisopropoxyborohydride (KIPBH) and oxidation, finally yields β-chiral alcohols (Scheme 40).[92] These alcohols are not easily prepared by other methods. Aldehydes can be prepared by homologation from chiral alkylboronic esters with LiCH(OMe)SPh and oxidation (Scheme 41).[91]

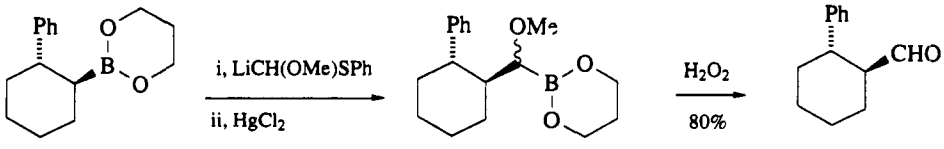


i, MeCHO; ii, NaOH; iii, $HOCH_2CH_2CH_2OH$, 85% (3 steps)

Scheme 39



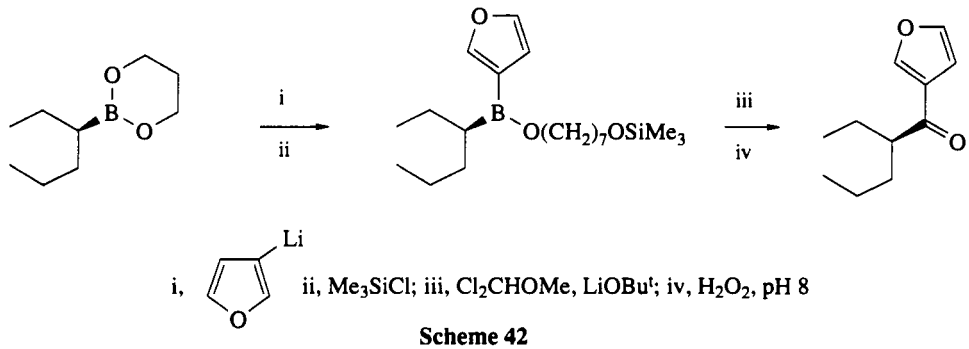
Scheme 40



Scheme 41

Chiral boronic esters react with organolithium reagents to form diorganylalkoxyboranes (borinic esters).[93] Subsequent reaction with the anion of dichloromethyl methyl ether then yields chiral ketones by rearrangement of both of the groups on boron (Scheme 42).[93] No racemization is observed in this sequence and alkyl-, aryl-[93] or alkynyl-lithium[94] reagents can be used.

The rearrangements of boronic esters frequently offer advantages over those of triorganylboranes. The presence of only one organic group for migration, for example, contrasts with triorganylboranes where selectivity is often a problem. In addition, the use of boronic esters derived from chiral diols is a powerful technique in chiral synthesis. Finally, the use of alkyl, alkenyl and aryl groups in rearrangements of boronic esters has been demonstrated. All of these features have resulted in the wide application of boronic esters in synthesis.[9,86,87,95]

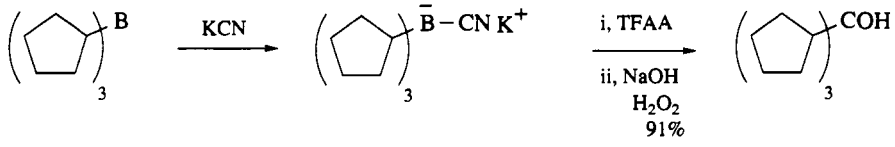


Scheme 42

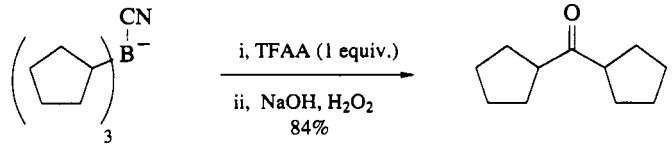
3.4.3.3 Rearrangements of Tetraorganylboronates

Triorganylboranes have been shown to react with certain carbon nucleophiles to produce stable, isolable tetraorganylboronate salts. On exposure to electrophiles, these boronates then rearrange, producing neutral triorganylboranes.[10b,95]

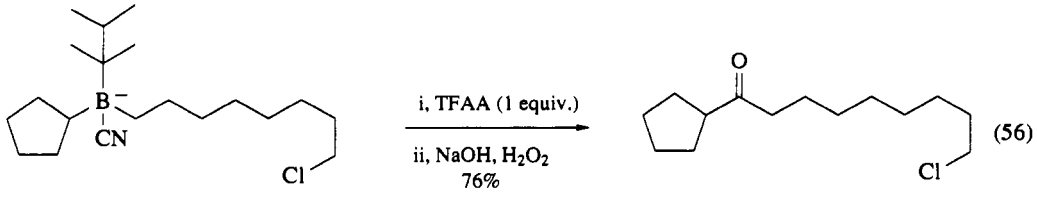
Cyanoboronates are prepared by the treatment of triorganylboranes with cyanide ion. When treated with an excess of TFAA, all three groups in the triorganylborane migrate to the cyanide carbon, leading to tertiary alcohols on oxidation (Scheme 43).[96] This transformation is closely related to the carbonylation of triorganylboranes (see Section 3.4.3.1). In the presence of 1 equiv. of TFAA, the third group does not migrate and ketones are obtained instead (equation 55).[97] Unsymmetrical ketones are available from thexyldialkylcyanoboronates since the bulky thexyl group does not migrate (equation 56);[97] cyclic ketones can also be prepared by this method (Scheme 44).



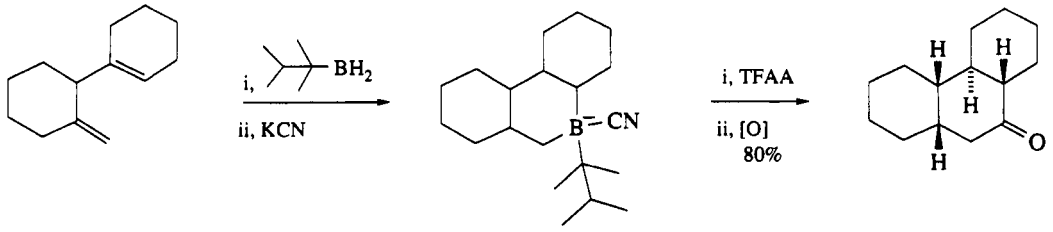
Scheme 43



(55)

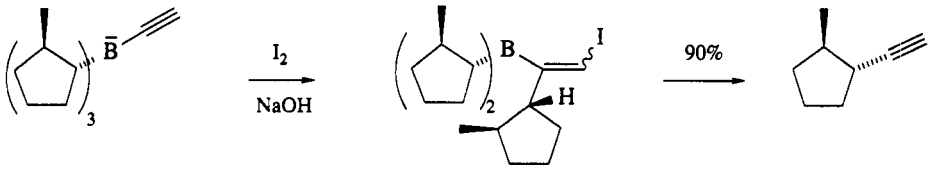


(56)

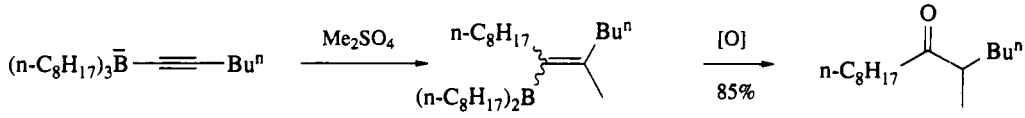


Scheme 44

Triorganylboranes react with alkynide ion to yield alkynylborates. When exposed to iodine and hydroxide, rearrangement to an alkylated alkyne then takes place (Scheme 45).[98] When alkynylborates are treated with alkylating agents such as dimethyl sulfate, rearrangement and concomitant alkylation takes place. The resulting alkenylborane can then be hydrolyzed to an (*E*)/(*Z*) mixture of alkenes or oxidized to ketones (Scheme 46).[99] This alkylation–rearrangement reaction has been used, for example, in a synthesis of propylure.[100]

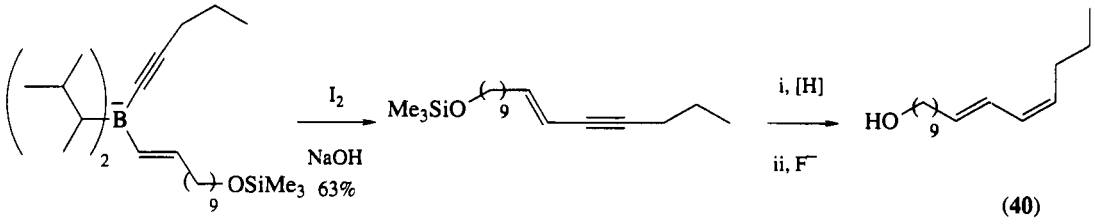


Scheme 45



Scheme 46

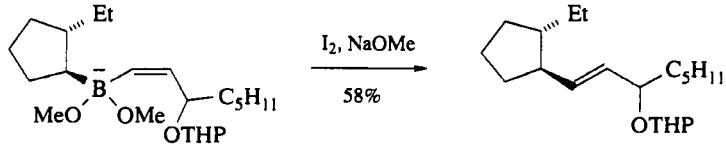
Alkenylalkynyldi(1,2-dimethylpropyl)boronates, when exposed to iodine and hydroxide, rearrange with selective migration of the alkenyl group to the alkynyl group. The pheromone bombykol (**40**) has been synthesized *via* this key reaction (Scheme 47).[101]



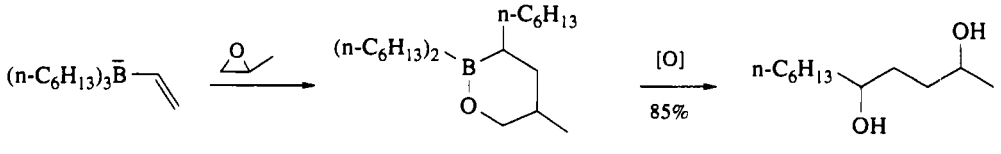
(**40**)

Scheme 47

Alkenylalkyldimethoxyboronates have been shown to rearrange with inversion of geometry, leading to substituted alkenes (equation 57),[102] and alkenyltrialkylboronates react with epoxides to yield 1,4-diols after oxidation (Scheme 48).[103]



(57)



Scheme 48

Tetraorganylboronates offer some advantages over triorganylboranes, particularly in the preparation of ketones from cyanoborates. Where a direct comparison has been made, the cyanoborate method was found to be superior.[104]

3.4.4 REFERENCES

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3.5
Dienone–Phenol Rearrangements and Related Reactions

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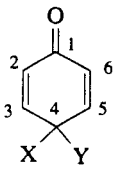
3.5.1 INTRODUCTION

Dienone–phenol rearrangements involve cyclohexadienones in the great majority of cases, although other variations are possible, *e.g.* ring contractions of tropolones to phenols. Cyclohexadienones can be either cross conjugated as in the 2,5-dienones (**1**), or linearly conjugated as in the 2,4-dienones (**2**). These forms are often referred to as the '*para*' and '*ortho*' dienones respectively, and they are available synthetically from a number of reactions, including oxidative coupling of phenols, electrophilic substitution of phenols, oxidation of phenols, other aromatic rearrangements and dehydrogenation of cyclohexanones.

The cross-conjugated structures are generally more stable than their linearly conjugated isomers, but both types rearrange readily to a phenol (**3**) with migration of a substituent X or Y from C-4 (**1**) or C-6 (**2**). Both substituents X and Y may shift. If the migrating group moves to a site on the ring which aromatizes, as in (**3**), the rearrangement is termed 'intracyclic', but if a group migrates to a position outside the ring, as in (**4**), then the reorganization is referred to as 'extracyclic'.

Dienone–phenol rearrangements are mechanistically diverse. They may involve: 1,2-shifts of the Wagner–Meerwein type, or of the benzil–benzilic acid kind; 1,3-shifts by a Claisen–Cope mechanism; 1,5-sigmatropic shifts; Favorskii-like reactions; and other types. They may also be induced photochemically. A number of reviews are available,[1] which discuss mechanistic aspects in detail. In this chapter emphasis is put on preparative aspects of these reactions and the examples are organized on a structural basis, stressing the new bond(s) formed.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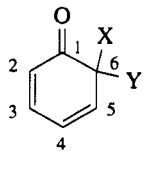
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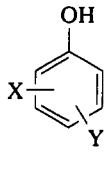
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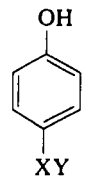

(4)

3.5.2 INTRACYCLIC MIGRATION

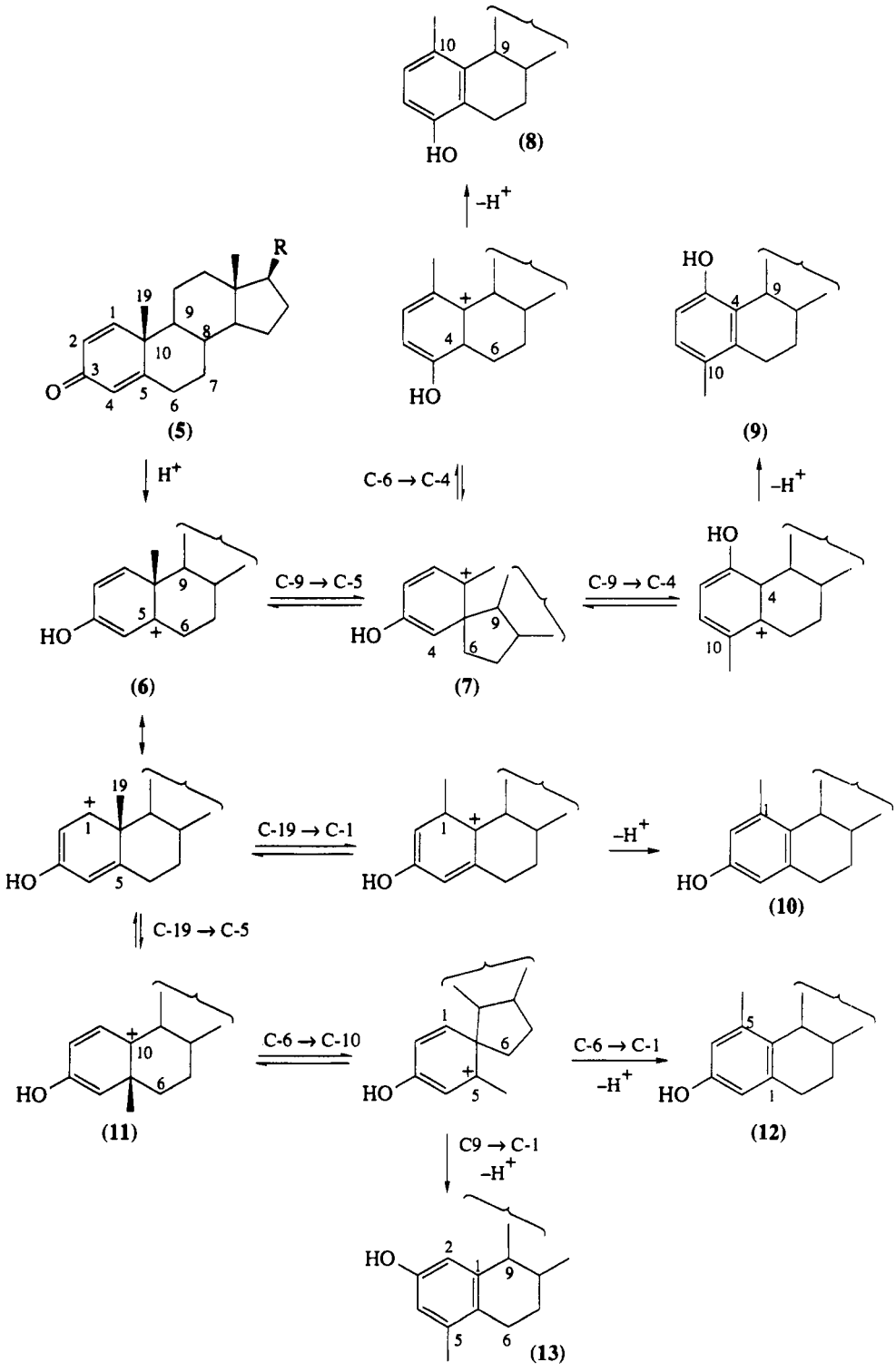
3.5.2.1 Formation of New C—C Bonds

The major ramifications of carbon migration in the dienone–phenol rearrangement are shown in Scheme 1, for a steroid ring A dienone (**5**). Several hundred of such acid-catalyzed reactions have been described[2] and five different pathways can be discerned. Protonation at oxygen in the dienone (**5**) leads to cation (**6**), and three different carbon shifts may follow. C-9 migration to C-5 leads to a new cation (**7**) which can reach an aromatic system either by migration of C-6, leading to phenol (**8**) or by shift of C-9, giving rise to phenol (**9**). Going back to cation (**6**), two courses are possible for a methyl (C-19) shift; 1,2-migration to C-1 yields phenol (**10**), while shift to C-5 affords another cation (**11**). Intermediate (**11**) can undergo either a C-6 → C-10, C-6 → C-1 sequence to arrive at phenol (**12**), or a C-6 → C-10, C-9 → C-1 routine to yield phenol (**13**). Of the five phenol products, (**10**) and (**12**) are structurally identical as shown, but represent different bond reorganizations. All these pathways have been observed. The choice between, for example, the migration of methyl or methine from C-10 is finely balanced and is sensitive to reagents and conditions.[3] The migration of the potentially most stable carbocation is expected to be kinetically preferred, *i.e.* the pathway which leads to (**9**). However, the shifts are reversible, and other factors may intervene, so that although product (**9**) may predominate, phenols of structures (**8**) and (**10**) are often the major products. The reader is referred to mechanistic reviews for a discussion of the controlling features. The examples collected in this chapter are organized on a structural basis, and it should be pointed out that a mechanism cannot always be reliably deduced from product structure.

3.5.2.1.1 Rearrangements forming one new C—C bond

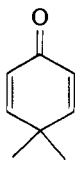
Alkyl shifts in simple cyclohexadienones can be induced with strong acids at room temperature. Thus 4,4-dimethylcyclohexadienone (**14**) rearranges to 3,4-dimethylphenol (**15**) at 25 °C with 70% perchloric acid, in 90% yield.[4] The 4-methyl-4-ethyl homolog (**16**) smoothly rearranges in trifluoroacetic acid, with preferential ethyl shift, to 3-ethyl-4-methylphenol (**17**).[5,6] Preferred ethyl shift is also seen in the *o*-dienone (**18**), which rearranges to the 3-ethyl-2-methylphenol (**19**) with loss of a *t*-butyl group.[7] In the 4-hydroxy-4-methyldienone (**20**), methyl group shift dominates when boron trifluoride etherate is used as acid (but see Section 3.5.3) to yield methyl hydroquinone (**21**; 55%).[8] Vinyl groups[9] and ethoxycarbonyl groups[5] migrate in preference to methyl. Electron-withdrawing groups adjacent to reacting centers slow down the reaction so that the dichloromethyl-substituted dienone (**22**) requires long treatment at 50 °C with concentrated sulfuric acid for conversion (84%) to 4-hydroxy-2-methylbenzaldehyde (**23**), with methyl migration, and concomitant hydrolysis of the *gem*-dichloride.[10] In the decalindienone group the rearrangement of santonin (**24**) in acid to desmotroposantonin (**25**) is an example of historical interest.[11] The parent ring system (**26**) has been investigated systematically.[3,12] With (**26**; R = Me) fairly good yields (50–60%) of the methyltetralol (**27**) were obtained using aqueous hydrochloric or sulfuric acid as catalyst; a small proportion (10%) of the isomeric tetralol (**28**; R = Me) was also obtained. Apparent 1,2-shift of the methyl is the major pathway. With other angular alkyls, *e.g.* (**26**; R = Pr^n), in which both potential migrating centers are methylene, the product of 1,2-shift dominates even more *i.e.* (**27**; R = Pr^n):(**28**; R = Pr^n) = 98:2, on rearrangement with 10 M sulfuric acid.

In the steroid series the androstadiendione (**29**) reacts slowly with 48% hydrobromic acid at room temperature; after 5 d the main product (55%) is 1-methylestrone (**30**) with its isomer (**31**) in minor amount (11%).[3] The ring bond shifts are inhibited in the 11-ketodienone (**32**) which essentially reacts exclusively by 1,2-methyl shift in perchloric acid–acetic anhydride to provide the 2-methyl steroid (**33**), with parallel peracetylation.[13] An 11-hydroxy function has a different effect (see Section 3.5.2.1.2). The 1,2-methyl



Scheme 1

shift becomes the major pathway when C-4 is blocked, and when C-6 is an sp^2-hybrid. Thus the 4-methylandrostadienone (**34**) yields the phenol (**35**; 73%) after saponification with acetic anhydride–*p*-toluenesulfonic acid,[14] and the same reagents effect the parallel conversion of the Δ^6-dienone (**36**) to the phenol acetate (**37**).[15]



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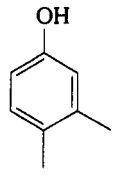

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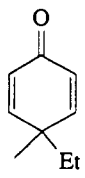

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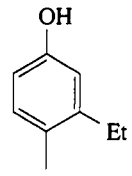

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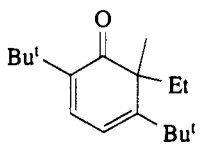

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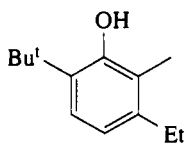

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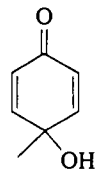

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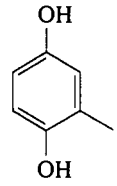

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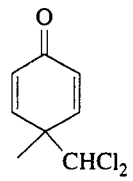

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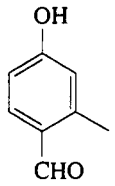

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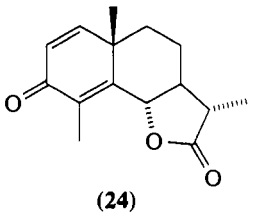

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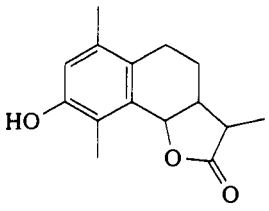

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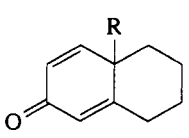

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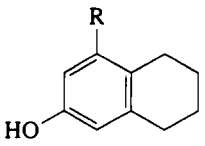

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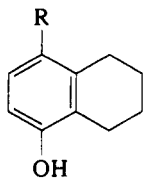

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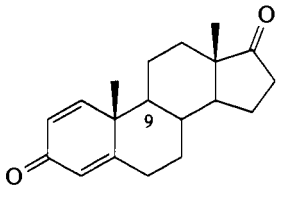

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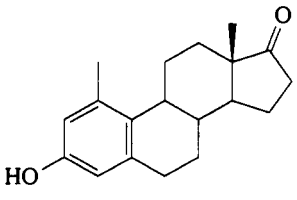

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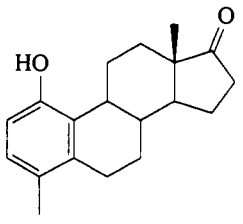

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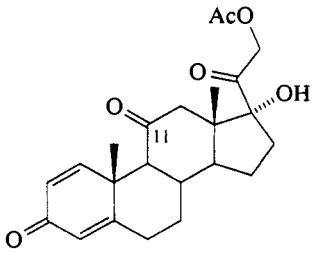

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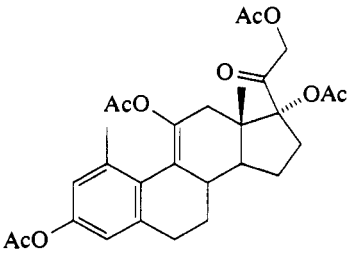

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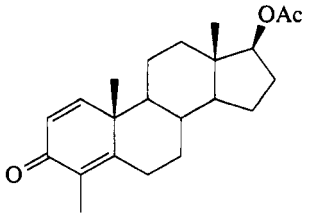
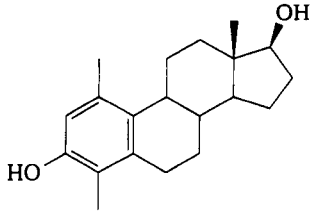


(34)

Not all dienone–phenol rearrangements are acid catalyzed. The 4-hydroxy-4-methyl-2,5-cyclohexadienones (**38**; R = H) and (**38**; R = Me) react in refluxing aqueous alkali to afford the methylhydroquinones (**39**; R = H) and (**39**; R = Me; 95%), respectively.[16] This is understandable as migration in an electron-rich, vinylogous α-ketol system (**40**). A different mechanism operates in the rearrangement of the decaladienone (**41**), induced by sodium hydroxide–aqueous methanol, to the tetralindiol (**42**; 76%) which appears to proceed by a retro-aldol–aldol sequence, by way of the aldehyde (**43**).[17]

The acid-catalyzed reactions so far listed in this section all involve shift of an alkyl residue. In bicyclic spirodienones, a related ring bond shift leads to ring expansion, and rearrangement to a fused bicycle. Thus the spirooxetane (**44**) is converted quantitatively into the hydroxydihydrobenzofuran (**45**) on treatment with ethanolic hydrogen chloride (preferred carbon migration),[18] and expansion of a four- to a five-membered ring is also seen in the spontaneous benzylic migration of the lactam (**46**), yielding (**47**; 62%).[19] Five- to six-membered ring size increase is observed in the conversion of the dienone (**48**) to the octahydrophenanthrol (**49**; 95%) with acetic anhydride–sulfuric acid,[20] and in the transformation of the dienone (**50**) to the tetralone derivative (**51**), with migration of the undeactivated methylene.[21] Six- to seven-membered ring expansion occurs in the reaction of the dienone oxime (**52**) with acetic anhydride–sulfuric acid, which yields the phenolic amine diacetate (**53**; 75%). This sequence probably involves addition (of acetate) then elimination to afford a spirodienimine (**54**) which reacts analogously to a dienone.[22] Interestingly the spirodienone (**55**) in aqueous citric acid reacts by a different mode of ring expansion, yielding the tropone (**56**; 80%), presumably through a tricyclic intermediary (**57**).[23]



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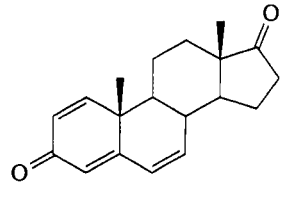

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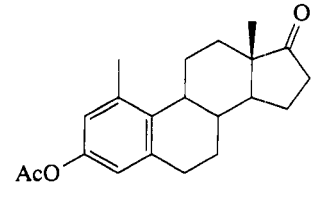

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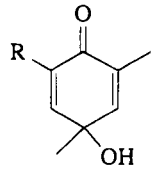

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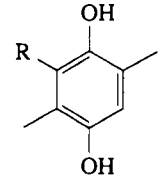

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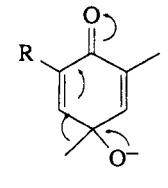

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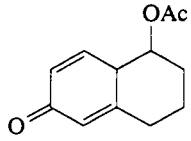

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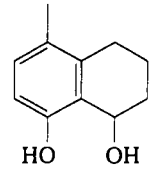

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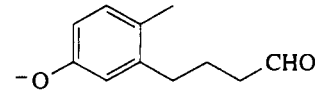
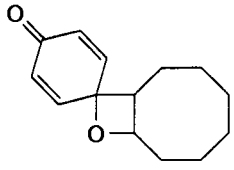


(43)

1,2-Aryl shifts are preferred, as expected, to competing alkyl shifts. Thus the 2,4-dienone (**58**) aromatizes quantitatively by phenyl migration, to trimethylphenylphenol (**59**),[24] and the 2,5-dienone (**60**) gives the biaryl (**61**; 51%),[25] in both cases with acetic anhydride–sulfuric acid. Suitable spirodienones react similarly, *e.g.* (**62**) yields the triphenylene derivative (**63**; 83%),[26] and the quinamide (**64**) rearranges sluggishly to the biaryl (**65**), with slow aryl migration in the protonated system.[27] Aryl shifts feature in the best-known applications of the dienone–phenol rearrangement for natural product synthesis, in the alkaloid area. Thus synthetic (±)-orientalinone (**66**) was converted into (±)-corydine (**67**) with dry methanolic hydrogen chloride (through preliminary hemiketalization) and into (±)-isocorytuberine (**68**) with an acetic acid–hydrochloric acid mixture.[28–30] Synthetic spirodienone (**69**) gave (±)-multifloramine (**70**; 45%) with concentrated sulfuric acid,[31] and its relative (**71**) rearranged with boron trifluoride to the homoaporphine (**72**) in 93% yield.[32] The dienone (**73**) also reacts by 1,2-aryl shift to give homoaporphine (**74**),[33] and the demethyl homolog (**75**) is similarly transformed to (**76**; 75%),[34] using boron trifluoride as catalyst in both cases. The homoaporphine series can also be reached from another variation on the spirodienone structure in this series (**77**), which affords (**78**) by boron trifluoride induced ring bond and aryl shifts.[33] Finally, it is worth noting the concurrent fragmentation–aryl migration involved in the transformation of (**79**) to (**80**) in a colchicine synthesis.[35]



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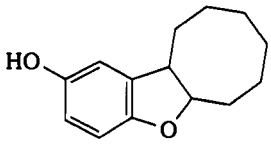

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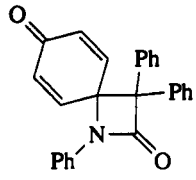

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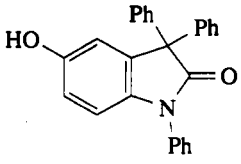

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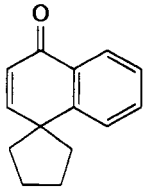

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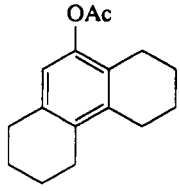

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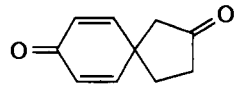

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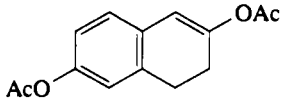

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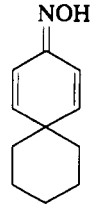

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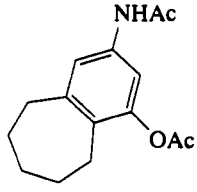

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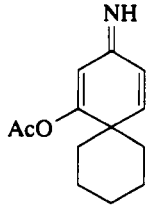

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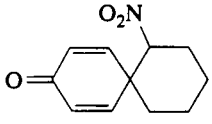

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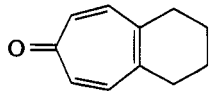

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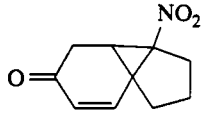

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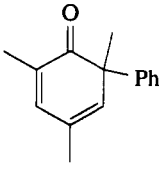

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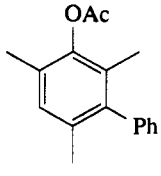

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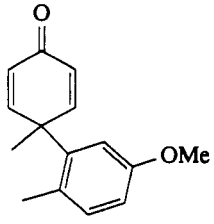

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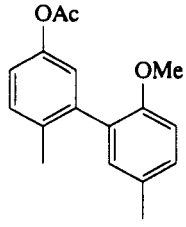

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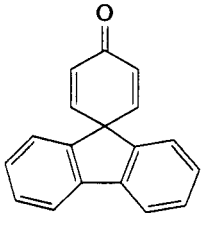

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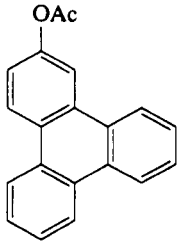

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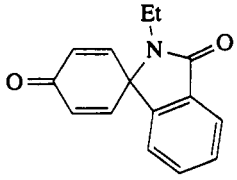

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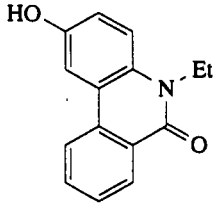

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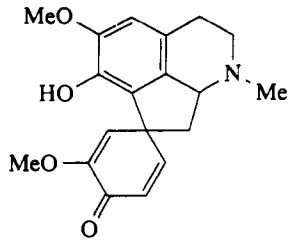

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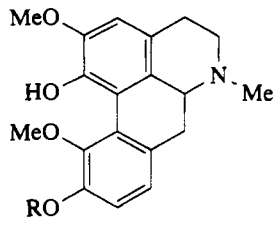
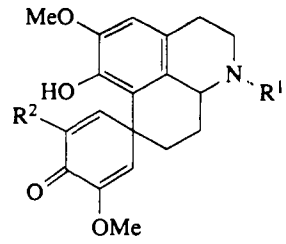
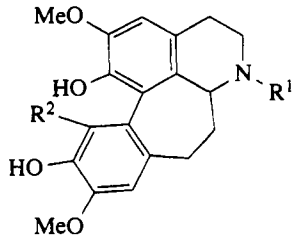


(67) R = Me
(68) R = H



(69) R^1 = Me, R^2 = OMe
(71) R^1 = $COCF_3$, R^2 = H



(70) R^1 = Me, R^2 = OMe
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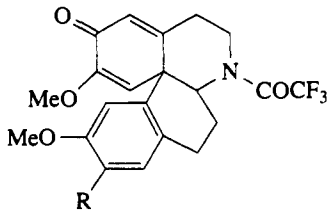

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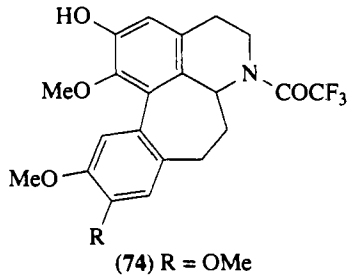

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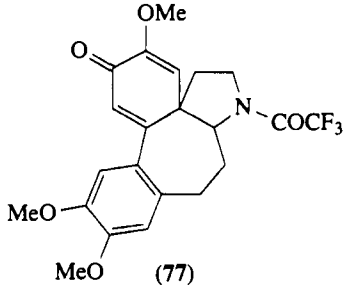

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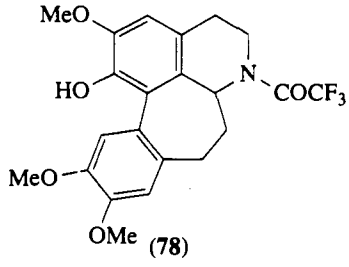

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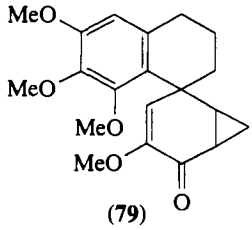

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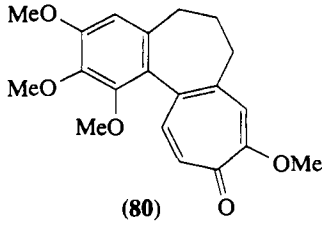
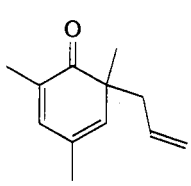


(80)

The last topic in this section concerns allyl shifts. This is a mechanistically complex area, in which migrations may proceed by one or more 1,2-shifts to cationic centers, or by 1,3- or 1,5-sigmatropic shifts, thermal or acid catalyzed. It is interesting that carbon–carbon bond formation is generally preferred to carbon–oxygen bond formation, even where the latter would be favored by aromaticity,[1b] as in the thermal reactions of dienones (**81**) and (**82**) which lead at *ca.* 100 °C to the new dienones (**83**) and (**84**), but not detectably to the corresponding *O*-allylphenols, *e.g.* (**85**). The 2,5-dienone (**86**) reacts rapidly in acid to give a mixture of phenols (**87:88** = 2:1),[36] the first by an acid-catalyzed Claisen–Cope reaction, and the second *via* a Wagner–Meerwein shift. The 1,3-shift is blocked in the 2,5-dienone (**83**), and 1,2-migration is induced on an acidic clay surface yielding (**89**; 98%).[37] Rearrangement of the 2,5-dienone (**90**) proceeds by two sequential 1,2-shifts, rather than a 1,3, yielding (**91**).[38] 1,3-Shifts are observed in the aromatization of the 2,4-dienone (**92**) in trifluoroacetic acid, yielding (**93**; 63%),[39] with its homolog (**94**) in sulfuric acid–acetic acid, giving (**95**; 83%),[36] and with the androstadienone (**96**),[40] which yields both phenols (**97:98** = 3:2), essentially quantitatively and stereospecifically.

In synthetic work towards tetracyclines the tricyclic dienone (**99**) was rearranged at 0 °C using boron trifluoride, to the anthraquinone (**100**; 65%) apparently by a direct 1,5-shift.[41] The quinamine (**101**) undergoes facile reorganization in hydrochloric acid to the biaryl (**102**)[42] in an aza-Claisen-like process.

Lastly, aromatization of the dienone (**103**), in sodium acetate–acetic anhydride at 140 °C, proceeds by a Favorskii-style mechanism, to afford (**104**).[43]



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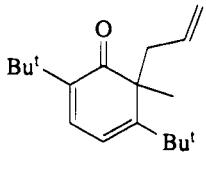

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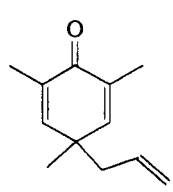
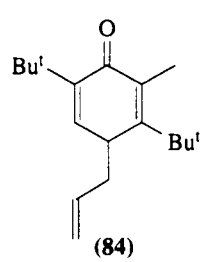


(**83**)



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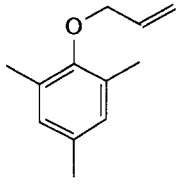

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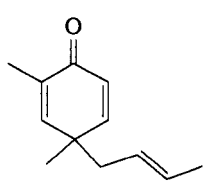

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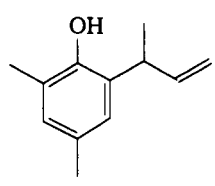

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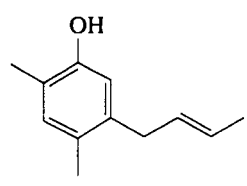

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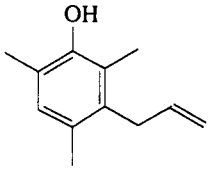

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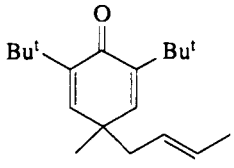
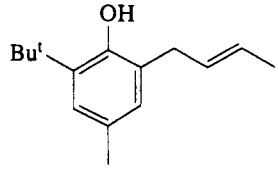


(**90**)



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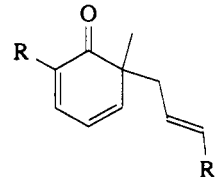
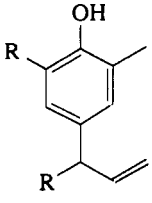
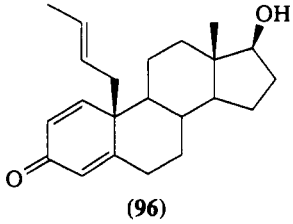


(**92**) R = H
(**94**) R = Me



(**93**) R = H
(**95**) R = Me



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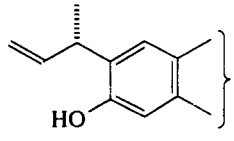

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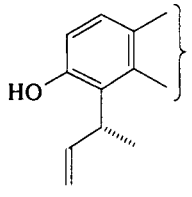
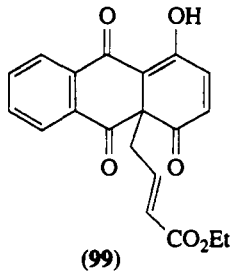


(**98**)

3.5.2.1.2 Rearrangements forming more than one new C—C bond

Aromatization through sequential ring bond shifts is exhibited in the acid-catalyzed conversion of the decaladienone (**105**; R = Me) to the methyltetralol (**106**; R = Me; 57%)[44] at room temperature with acetic anhydride–sulfuric acid; lactone (**107**) very similarly rearranges to (**108**; 69%).[45] Decaladienones with an angular hydroxy, *e.g.* (**105**; R = OH), react in parallel fashion, to give, for example, (**106**; R = OH),[46,47] although their acetyl derivatives undergo oxygen migration, *vide infra*. In the steroid series the androstadienedione (**109**) rearranges in acetic anhydride–zinc chloride, with two shifts of C-9 (methine), to the 1-hydroxyandrosta-1,3,5-trienone (**110**) in 92% yield.[48] A number of similar reactions are cataloged in valuable reviews.[2] 10-Hydroxy steroids can also rearrange in this way, *e.g.* (**111**) to (**112**).[49] Although a 6,7 double bond usually impresses 1,2-methyl shifts, the androstatrienone (**113**) was converted by superacid into the ring bond rearranged product (**114**; 75%).[50] In the tetracycle (**115**) shifts of a methylene from the quaternary center, and then of a benzylic carbon, lead to the phenol acetate (**116**)[51] in 88% conversion.



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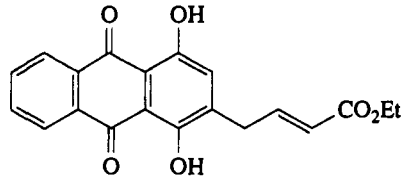

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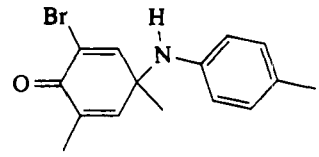

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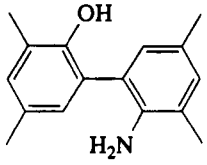

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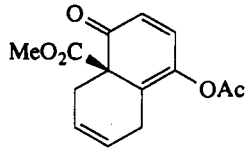

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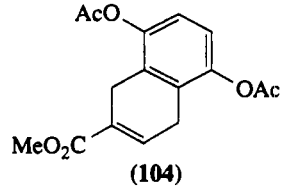

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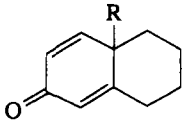

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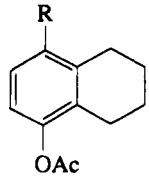

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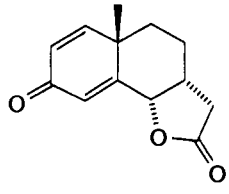

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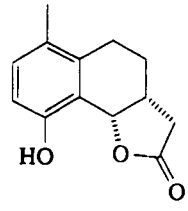

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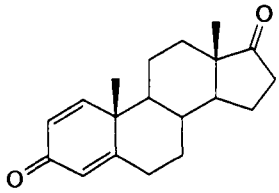

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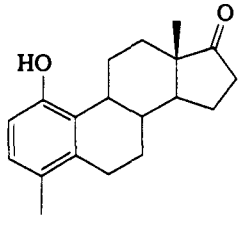

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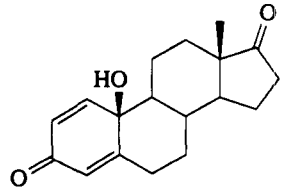

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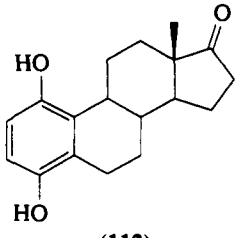

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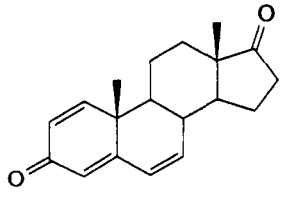

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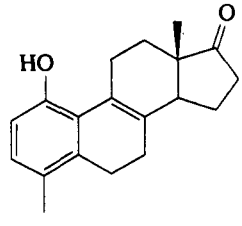

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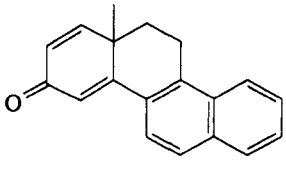

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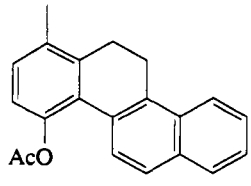
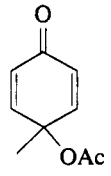


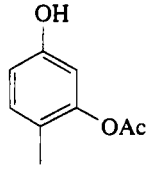
(116)

3.5.2.2 Formation of a New C—O Bond

The migration of oxygen from a quaternary center in a cyclohexadienone may be preferred to a carbon shift, when present as an ether or ester function rather than free hydroxy. Thus the *p*-quinol acetate (**117**) yields the orcinol monoacetate (**118**; 79%) on treatment at room temperature with trifluoroacetic anhydride,[52] and the *p*-quinol ether (**119**) forms the resorcinol diethyl ether (**120**; 71%) in ethanolic sulfuric acid. In the second case, hemiketalization must intervene; also some methyl shift (12%) is observed.[53] With the quinol (**121**), treatment with acetic anhydride–sulfuric acid leads to the lactone (**122**); acetylation or lactonization probably precedes oxygen shift.[54] A number of related examples can be found in the steroid area.[2,55] Thermal 1,3-shifts of *p*-quinol acetates can also be induced; acetate (**117**) yields catechol acetate (**123**; 50–60%, 45 °C) by way of isomerization of the first-formed acetate (**124**).[56] In the *o*-quinol acetate series, 1,2-acetoxy shift is seen in (**125**) → (**126**; 92%)[57] and in (**127**) → (**128**; 90%),[58] both in acetic anhydride with acid catalyst. In the 2,4-dienone (**129**), two 1,2-acetoxy shifts are required for aromatization, leading to the hydroquinone diacetate (**130**).[54]



(**117**)



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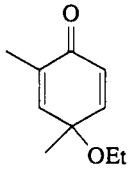

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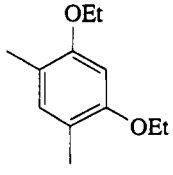

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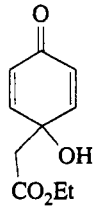

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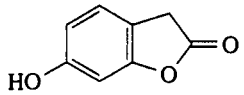
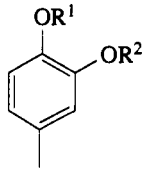
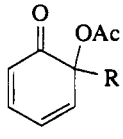


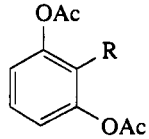
(**122**)



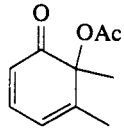
(**123**) R^1 = Ac, R^2 = H
(**124**) R^1 = H, R^2 = Ac



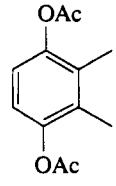
(**125**) R = Et
(**127**) R = Ph



(**126**) R = Et
(**128**) R = Ph

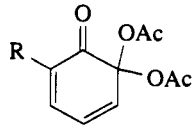


(**129**)

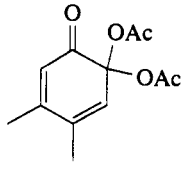


(**130**)

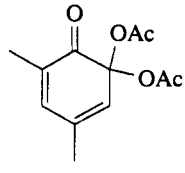
A number of *o*-quinol diacetates have been prepared and they rearrange smoothly to triacetoxybenzenes;[59] *o* → *o'* migration is preferred unless the latter position is blocked or sterically crowded, when acetoxy shift is directed to another aryl site. The range of possibilities is indicated by the conversions of the *o*-quinol diacetates (**131**)–(**134**) to the 1,2,3- or 1,2,4-triacetoxybenzenes (**135**)–(**138**), in 56–90% yields.



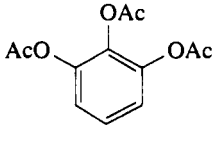
(**131**) R = H
(**132**) R = Me



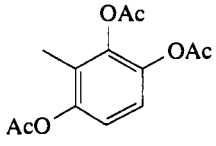
(**133**)



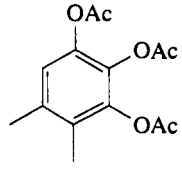
(**134**)



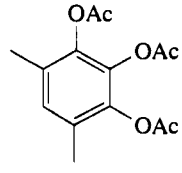
(**135**)



(**136**)



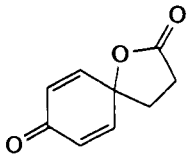
(**137**)



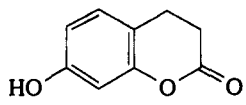
(**138**)

The reactions in this section represent useful ways of introducing oxygen into aromatic rings, for which methodology is limited, and of reaching certain substitution patterns.

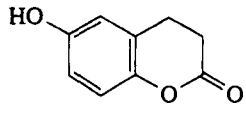
Oxygen migration may be observed in spirodienones. Thus the lactone (**139**) affords dihydrocoumarins (**140**) and (**141**) in 90% and 10% yields, respectively, in acetic acid–sulfuric acid; change of reagent to dilute sulfuric acid changes the yields to 5% and 95%, respectively, nicely illustrating the fine balance between pathways in these reactions.[60] The spirodienone (**142**) undergoes *O*-shift in acid, but *C*-shift in alkali, yielding either (**143**) or (**144**).[61]



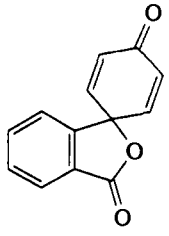
(**139**)



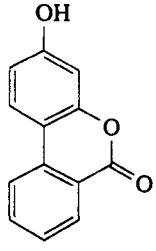
(**140**)



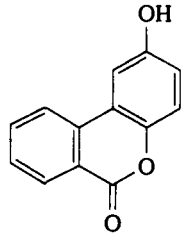
(**141**)



(**142**)

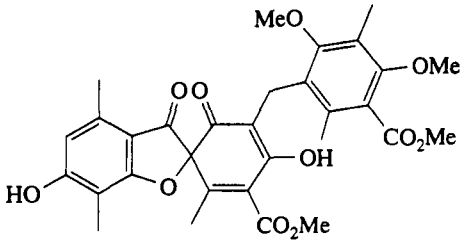


(**143**)

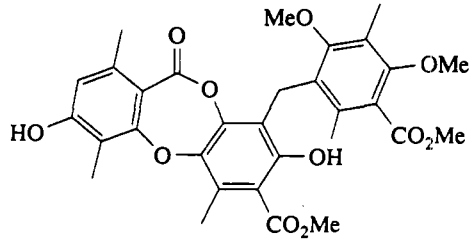


(**144**)

Finally a rare example of C—O bond formation by migration of carbon to oxygen is found in the pyrolysis of the complex spirodienone (**145**) at 205 °C, which affords the depside (**146**; 91%).[62]



(**145**)



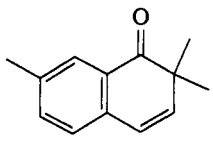
(**146**)

3.5.2.3 Formation of New C—C and C—O Bonds

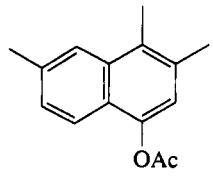
In a number of cyclohexadienone aromatizations both new C—C and C—O bonds are formed, in multistep reactions which may still be high yielding. Thus the tetralenone (**147**) gives the trimethylnaphthol acetate (**148**; 95%) in acetic acid.[63] Both of the spiroketones (**149**) and (**150**) reorganize under acetylating conditions to the tetrahydrophenanthrol acetate (**151**).[64] The allylquinol acetates (**152**; R = H) and (**152**; R = Me) reorganize to the monacetylallylcatechols (**153**) on heating at 180–190 °C, through an initial 1,5-acetyl shift to (**154**), followed by 1,3-allyl shift and acetyl transfer between oxygens.[65]

3.5.3 EXTRACYCLIC BOND MIGRATION

The conventional dienone–phenol rearrangements of *o*-quinol acetates are described above. An alternative mode of restructuring to an aromatic system has been observed, exemplified by the quantitative conversion of the 2,4-dienone (**155**) on heating at 110 °C in acetic acid to the benzylic acetate (**156**).[66] The related 2,4-dienone (**157**) rearranges at 70–80 °C in dimethyl sulfoxide–sodium bicarbonate to the



(147)



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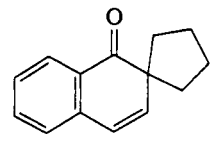

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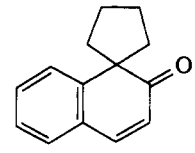

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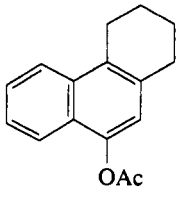

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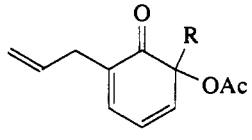

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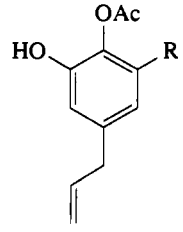
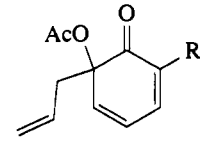
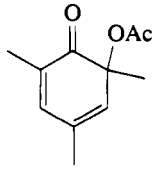


(153)

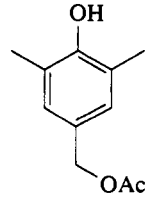


(154)

m-hydroxybenzaldehyde (**158**), in 45% yield.[67] The mechanisms by which the benzylic positions are oxidized are not known. Interestingly, pyrolysis of (**155**) at 450 °C gave the diarylethane (**159**; 37%), with some of the corresponding stilbene,[68] suggesting formation of benzylic radicals. Similar halogen migrations have been recorded. Thus the *p*-bromodienone (**160**) quantitatively converts to the benzylic bromide (**161**) on standing at 0 °C, and the di-*t*-butyl analog (**162**) similarly rearranges on brief warming, to give (**163**; 70%).[69] Related reactions occur with polyhalomethyl groups. Thus the 2,5-cyclohexadienone (**164**) yields the benzoate (**165**) on heating with benzoyl chloride to 140 °C.[70] If phosphorus pentachloride is used then the product is the trichloroethylaryl chloride (**166**; 89%), but in polyphosphoric acid the acid (**167**) is the major product (56%).[71] Again mechanisms remain obscure.



(155)



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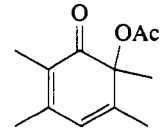

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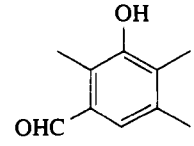

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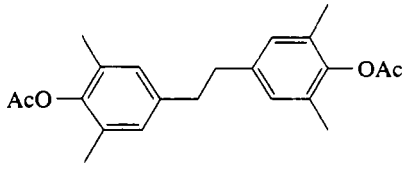

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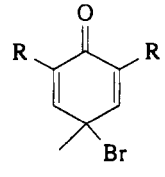
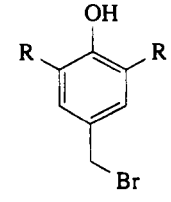
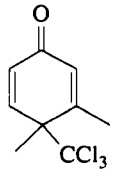


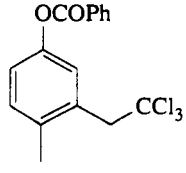
(160) R = Me
(162) R = Bu^t



(161) R = Me
(163) R = Bu^t



(164)



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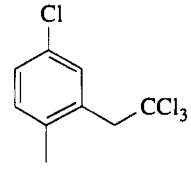

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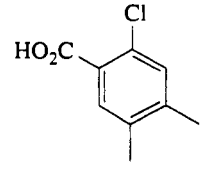
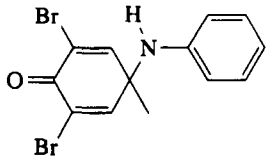
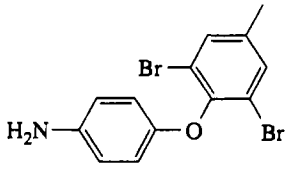


(167)

The last example in this section is the facile and quantitative rearrangement of the quinamine (**168**) in 10^{-5} M hydrochloric acid, to the aminoaryl ether (**169**), with extracyclic shift of aryl to oxygen.[72] A number of examples are known and the mechanism appears similar to the benzidine rearrangement.



(**168**)

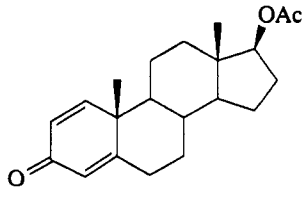


(**169**)

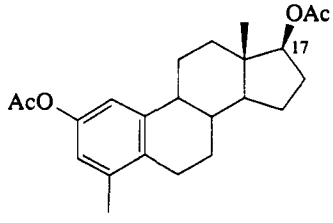
3.5.4 PHOTOCHEMICAL AROMATIZATION

The photochemistry of cyclohexadienones is a complex topic, which has been reviewed[73] and is discussed in detail elsewhere in this series. It is only appropriate here to point out that aromatization to a phenol is a possible outcome of such reactions, and indicate a very few synthetically useful examples.

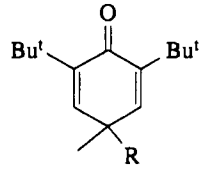
The steroidal dienone (**170**) can be induced to undergo the relatively unusual reorganization to the 2-hydroxy-4-methylandrosta-1,3,5-triene (**171**), by irradiation in refluxing acetic acid;[74] although only 48% of the acetate (**171**) was isolated, the related 17-ketone (36%) was also formed. The *p*-dienones (**172**) and (**173**) are restructured on irradiation in cyclohexane with net relocation of methyl and *t*-butyl groups to afford the phenols (**174**) and (**175**) in 55% and 73% yield, respectively.[75,76] A photo-induced aryl shift in the benzylisoquinoline dienone (**176**) was employed to prepare the aporphine (**177**; 44%) *en route* to (±)-boldine.[77] The *p*-dienones (**178**; X = Cl, X = N_3) aromatize on irradiation to yield the alkylated p-hydroxybenzoates (**179**; *e.g.* X = N_3, 57%) as well as minor quantities of their isomers (**180**).[78] Mechanistic aspects of these reactions are discussed in the literature cited.



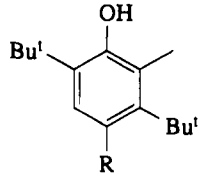
(**170**)



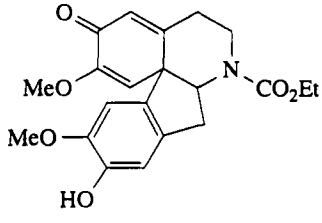
(**171**)



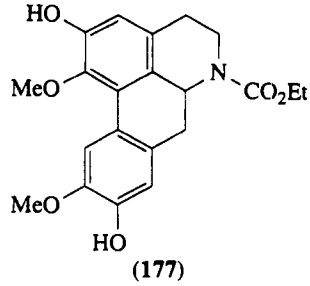
(**172**) R = $CH_2CH{=}CH_2$
(**173**) R = Bu^t



(**174**) R = $CH_2CH{=}CH_2$
(**175**) R = H



(**176**)



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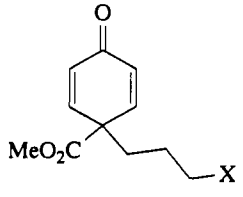

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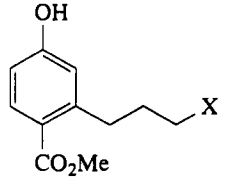

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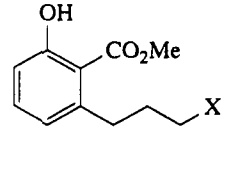
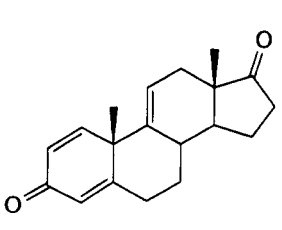


(**180**)

3.5.5 MISCELLANEOUS AROMATIZATION

3.5.5.1 Dienone Aromatization with Bond Cleavage

A group of predominantly steroid reactions involve a ring A or ring B dienone which aromatizes under reductive conditions with cleavage of a carbon fragment. In most cases[79] the angular A/B methyl is removed, as in the case of the androstatrienedione (**181**) which suffers reductive demethylation to the phenol (**182**) on brief refluxing with zinc in aqueous pyridine,[79a] in 93% yield. Less commonly, fragmentation of the C(9)—C(10) ring bond is engineered, as in the reductive elimination of the 11-hydroxy derivative (**183**) with samarium diiodide to the B-secophenol (**184**; 38%).[80] Fragmentations have also been ingeniously employed in alkaloid syntheses. Thus the spirodienone (**185**) aromatized during alkaline deacylation; *in situ* reduction of the resulting imine gave the *o,o'*-bridged biaryl (**186**; 80%), a key intermediate in both *in vivo* and *in vitro* formation of erysodienone.[81] The ketal (**187**), formed conventionally from the corresponding dienone, fragments (increased *N*-basicity) during reduction of the formamide function with lithium aluminum hydride to the *N*-methyl compound, to yield *O*-methylerybidine (**188**; 81%).[82] In a synthesis of L-tyrosine, the precursor (**189**), from L-glutamic acid was aromatized in dilute alkali, with decarboxylation, to form *N*-BOC-Tyr (**190**; 98%).[83] Outside the natural product area the spirodienone (**191**) achieved aromaticity in acid with C—C cleavage, giving (**192**; 40%),[84] and the epoxide (**193**) rearranged with C—O cleavage to yield naphthaldehyde (**194**; 92%).[85]



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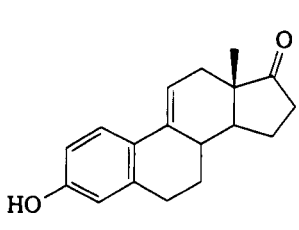

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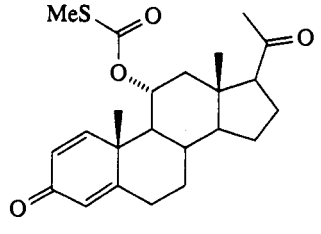

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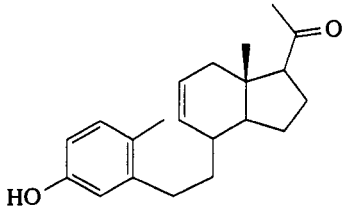

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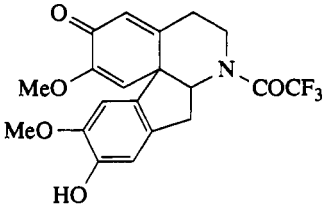

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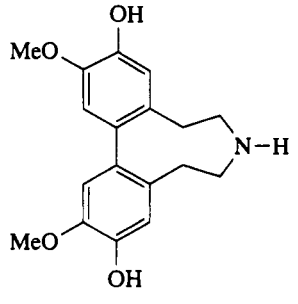

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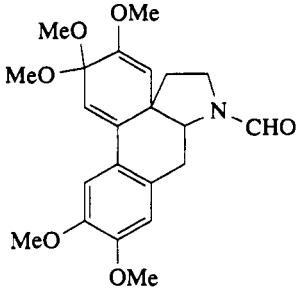

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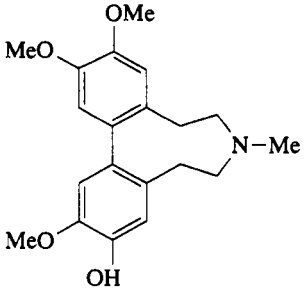

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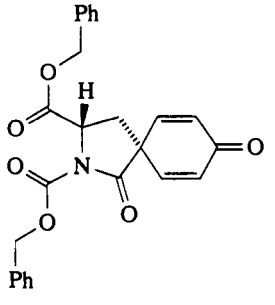

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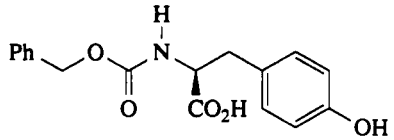

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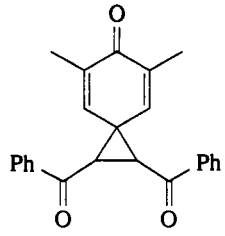

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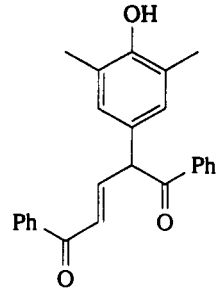

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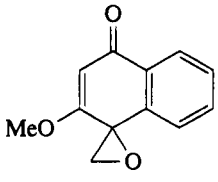

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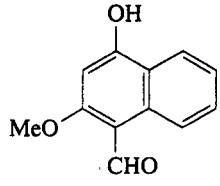
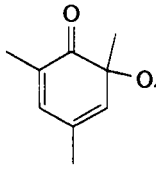


(194)

3.5.5.2 Rearrangements in Dienone Reactions with Nucleophiles

Cyclohexadienones containing a leaving group, such as *o*- or *p*-quinol acetates, undergo various reactions with nucleophiles, most often involving an addition–elimination sequence to form a phenolic product with nucleophile as a substituent. Thus the *o*-quinol acetate (**195**) reacts with secondary amines, cyanide ion, or diethyl sodiomalonate to give the phenols (**196**; X = NR_2),[86] (**196**; X = CN),[87] and (**196**; X = CH $(CO_2Et)_2$);[88] Wittig reagents behave similarly.[89] The site of attack may be modified by other functions, *e.g.* azide ion adds to C-2 in aldehyde (**197**) yielding azidophenol (**198**) as product.[90] Thiols behave in a different fashion from other nucleophiles, for example thiophenol substitutes the dienone acetate (**199**) at C-4 rather than C-3, to afford (**200**) as the major product;[91] various mechanisms are possible, including S_N2' substitution–enolization. More complex sequences occur when the dienone carbaldehydes (**201**) and (**197**) are treated with cyanide. In the first case, methanolic cyanide affords the cyano ester (**202**), but cyanide in dimethylformamide gives the aldehyde (**203**), in good yield in both cases.[92] The isomer (**197**) reacts with cyanide in methanol to provide the ester (**204**; 85%) without incorporating cyanide.[92] For mechanistic discussions see ref. 1b. Related transformations occur with *p*-dienones, *e.g.* (**205**) yields cyanophenol (**206**), on addition–elimination with cyanide ion.[87] Different patterns of reactivity emerge with different nucleophiles; thus (**205**) reacts with phenyl- or methyl-magnesium bromide to afford phenols (**207**; R = Ph and R = Me) respectively. This is a result of 1,2-addition



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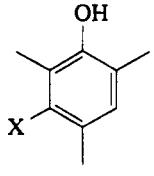

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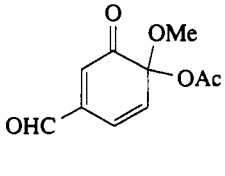

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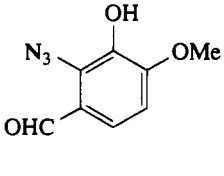

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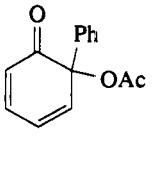

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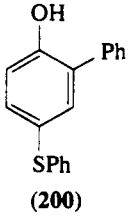

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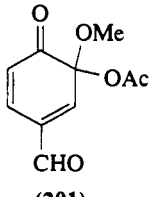

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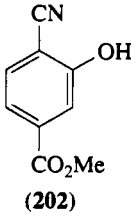

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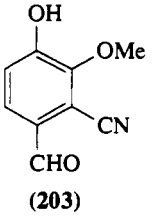

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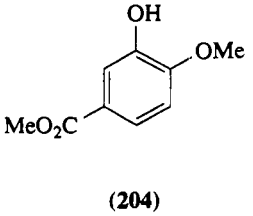
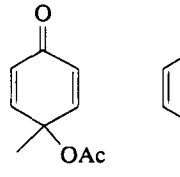


(204)

followed by loss of acetate and 1,2-shift of phenyl (or methyl), whereas (**205**) and phenyllithium yield (**208**) *via* 1,2-addition, deacylation, loss of benzylic oxygen function and 1,2-methyl shift.[93] Another interesting conversion occurs when the spirodienone (**209**) is treated with diacetyl sulfide and boron trifluoride, giving rise to the thiolactone (**210**), in a useful C—S bond-forming process.[94] Finally in this section we remark on the curious transformation of the dichloromethyldienone (**211**) into the acid (**212**) by hydroxide ion in ethanol;[95] an intermediate (**213**) is implicated. The conversion (**214**) → (**215**) also requires a bridged intermediate.[96]

3.5.5.3 Tropolone–Phenol Rearrangements

A number of cases are known of ring contraction of tropolones to phenols, with extrusion of the carbonyl group as carboxylate or carbon dioxide. Examples are the conversions of the benzotropolone (**216**) to the naphthol ester (**217**; 73%) with methanolic potash;[96] the pyridinotropolone (**218**) to the quinoline (**219**; 50%) in dilute alkali;[97] the aminotropolone (**220**) to the methylsalicyclic acid (**221**; 82%) on diazotization;[98] and the tropolonecarboxylate (**222**) to the dicarboxylic acid (**223**; 78%) on brief alkali fusion.[99]



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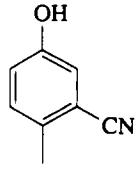

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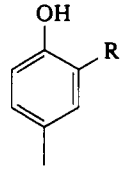

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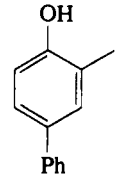

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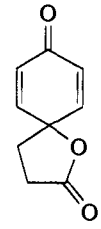

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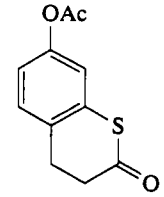

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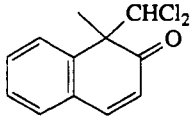

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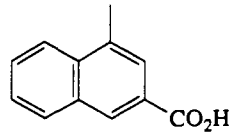

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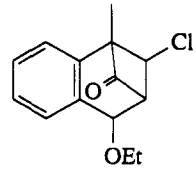

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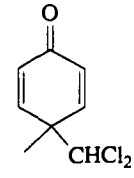

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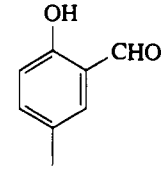

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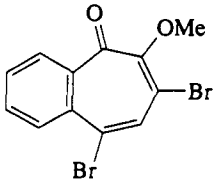

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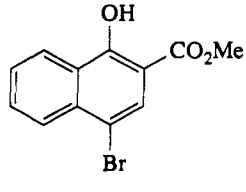

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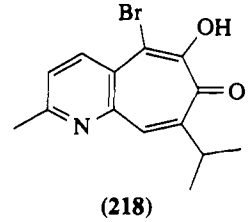
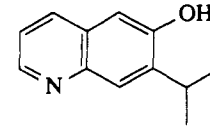


(**218**)



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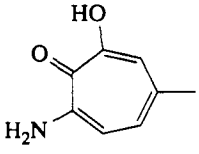
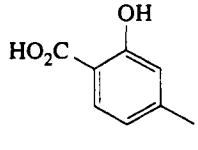
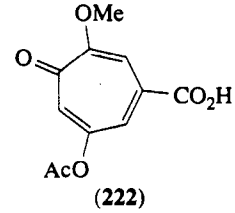


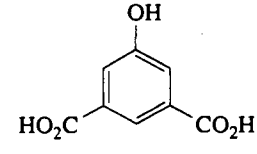
(**220**)



(**221**)



(**222**)



(**223**)

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3.6
Benzil–Benzilic Acid Rearrangements

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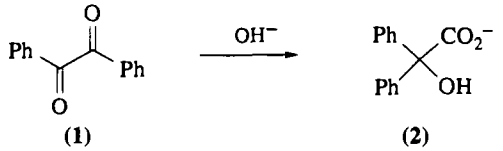
3.6.1 INTRODUCTION

In 1838 von Liebig[1] described the hydroxide ion induced transformation of an α-diketone, benzil (**1**), into the salt of an α-hydroxy acid, benzilic acid (**2**; equation 1). This process is probably the first molecular rearrangement reaction to be recognized, and hence occupies a special place in both synthetic organic and physical organic chemistry. In its strictest sense the benzil–benzilic acid rearrangement refers to the reaction of bisaryl α-diketones with hydroxide ion leading to aryl migration. Generally, however, the reaction is chronicled in a wider sense to include the migrations of other groups (*e.g.* alkyl, acyl, nitrogen), which result from the treatment of vicinal dicarbonyl systems with hydroxide, methoxide, *t*-butoxide and other bases. This wider interpretation is used in this chapter.

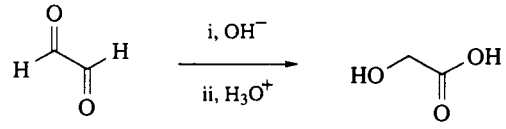


(1) (2) (1)

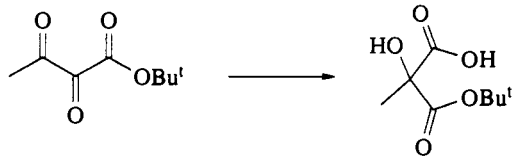
3.6.2 SCOPE AND MECHANISM

3.6.2.1 Benzilic Acid Type Rearrangements

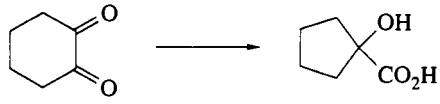
The prototype reaction is the conversion of glyoxal into glycolic acid (equation 2),[2] and here the benzilic acid rearrangement mechanism coincides with that for an intramolecular Cannizzaro reaction. The reaction is observed with other purely aliphatic α-diketones such as *t*-butyl 2,3-dioxobutyrate[3] and cyclohexane-1,2-dione (equations 3 and 4),[4] but the scope is limited in the aliphatic series by competing (*e.g.* aldol) reactions. Suitably constructed heterocyclic systems also rearrange, and the conversion of alloxan (**3**) into alloxanic acid (**4**) was among the first of the benzilic acid rearrangements to be discovered (equation 5).[5]



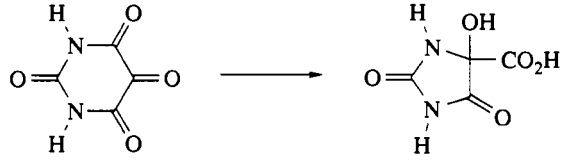
(2)



(3)



(4)

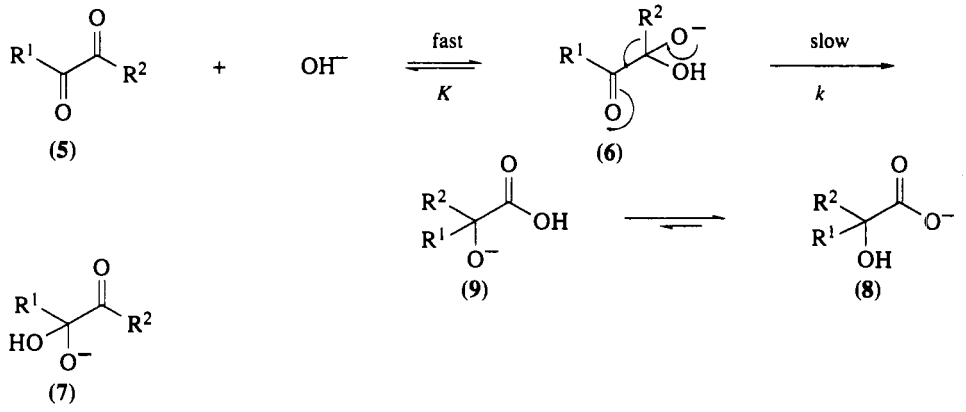


(5)

(**3**) (**4**)

Much of the definitive mechanistic evidence has been provided by studies of the reaction of hydroxide ion with benzil (**1**) and substituted benzils.[6] The presently accepted mechanism is that which was proposed by Ingold[7] as early as 1928, and is shown in Scheme 1; see, however, Section 3.6.2.2. The initial step involves the fast reversible addition of hydroxide to one of the carbonyl groups. In unsymmetrical α-diketones (**5**) the more electrophilic carbonyl (*i.e.* the one with the lower LUMO) is attacked preferentially. Thus, if R^2 in (**5**) is more electron withdrawing than R^1, the concentration of intermediate (**6**) greatly exceeds that of (**7**), and the rearrangement follows the (**6**) → (**9**) → (**8**) pathway. In physical organic terms, the observed rate constant (k_{obs}) is the product of the equilibrium constant (K) for the first step, and the rate constant (k) for the rate-determining second step. Thus $k_{obs} = Kk$ and, of the two variables, the key term is K, since the rate-limiting transition state is not far along the reaction coordinate leading from (**6**) to (**9**). It follows, therefore, that it is the more electron-withdrawing substituent R^2 which migrates (in the absence of steric problems).[6,8]

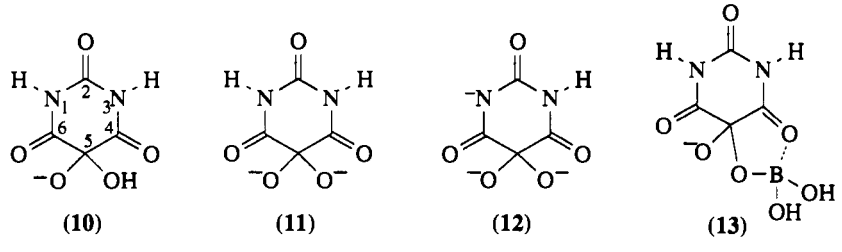
With simple unsymmetrical α-diketones (**5**) it appears to be immaterial which substituent migrates, for the product structure is the same. Much of the information concerning migratory aptitudes has come from studies of benzils possessing one $^{14}C{=}O$ group.[6] Hydroxide ion attack at the labeled center results in the migration of the attached aryl substituent with the production of carboxy-labeled benzilic acid. The rearrangement is irreversible. Similar labeling studies in other α-dicarbonyl systems[3,9–13] have indicated the preferential migration of H over Ph, Ph over Me, $CONH_2$ over Ph, CO_2R over CO_2^-, and CO_2R or CO_2^- over cyclopropyl. These results are all consistent with initial hydroxide ion addition to the more electrophilic C=O group.



Scheme 1

When R^1 and/or R^2 in (**5**) possess a chiral center, both the initial attack of hydroxide ion and the subsequent migration can be stereoselective, regioselective and stereospecific. Steroidal α-diketones are suitable vehicles for such studies, and their chemistry is considered later (see Section 3.6.3.5).

The results obtained for alloxan (**3**)[9] and related N-heterocycles[14] are much more complex. The central of the three contiguous C=O groups is the most electrophilic part of the molecule (**3**) and, indeed, alloxan readily forms a stable hydrate through the addition of water to this center. In alkaline solution, and depending on pH, the mono-, di- and tri-anions (**10**)–(**12**) exist; (**10**) is much more stable than the corresponding species for benzil and does not rearrange. Thus, isotopic labeling of this C-5 carbon atom affords, on rearrangement in aqueous alkali, C-4 ring-labeled alloxanic acid. The carboxylic acid group contains none of the isotope, which would be the requirement if (**10**) was involved directly in the rate-determining rearrangement to the anion of (**4**). Furthermore, analysis of the products of alkaline rearrangement of C-4 labeled (**3**), and its methyl- and phenyl-substituted derivatives, is consistent with the exclusive shift of nitrogen over carbon. In the rearrangement of *N*-phenyl[4-^{14}C]alloxan the shift of NPh occurs to the exclusion of NH, whereas in the case of *N*-methyl[4-^{14}C]alloxan the migration ratio of NMe to NH is about 4:1. Clearly, then, C-5 is the migration terminus, and rearrangement is triggered by hydroxide ion attack at C-4 (or the symmetry related C-6 position). Specific catalysts such as borate, which is ineffective for the benzil–benzilic acid transformation, enhance the electrophilicity of C-4 by coordinating the carbonyl oxygen atom, as shown in formula (**13**).

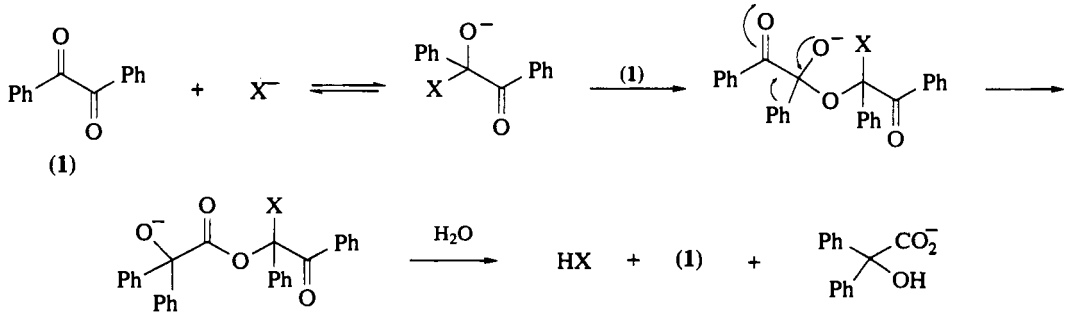


3.6.2.2 The Benzilic Ester Rearrangement

A somewhat confusing situation existed in the early literature concerning the precise timing of the migration and proton transfer steps and the apparent specificity of hydroxide ion, because of the failure of alkoxides to give benzilic esters.[6] However, benzil is a good oxidizing agent for alcohols in the presence of their alkoxides,[15] and Doering and Urban showed[16] that the failure of the rearrangement with primary and secondary alkoxide ions was due to competitive hydride transfers (a Meerwein–Ponndorf–Verley–Oppenauer type of reaction). Nevertheless, boiling anhydrous methanolic sodium methoxide gave methyl benzilate (68%), benzoin (9.6%) a product of the above redox reaction, and benzilic acid (9.7%) which probably arose from a $B_{AL}2$ mechanism (*i.e.* S_N2 attack by methoxide on the methyl carbon atom of methyl benzilate). The reaction of (**1**) with sodium ethoxide in dry ethanol at reflux gave a mixture of rearrangement, oxidation and cleavage products. The reaction of (**1**) with potassium *t*-butoxide in boiling benzene is especially clean, affording *t*-butyl benzilate in 90% yield. The reaction fails with the weakly

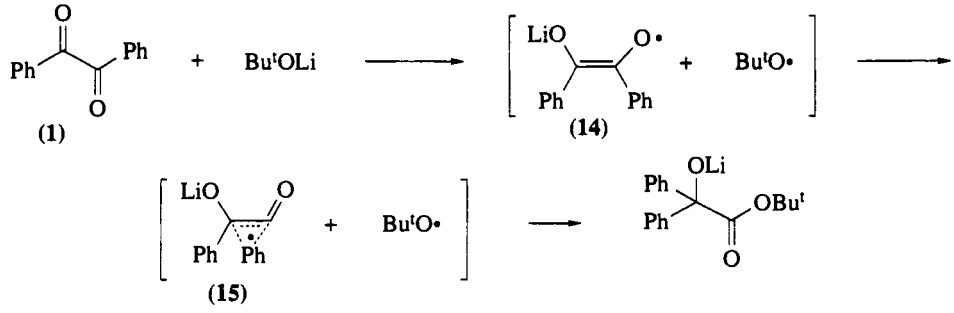
basic phenoxides, presumably because of an unfavorable equilibrium (*cf.* the formation of **6**) in the initial attack on the α-diketone.

Rearrangement of benzil in nonhydroxylic solvents by nonoxygen bases such as sodium amide[17] or acetylide,[18] followed by mild hydrolytic work-up, afforded not the expected benzilamide or 1,1-diphenyl-2-oxobut-3-yn-1-ol but rather benzilic acid itself. As the mild conditions were insufficient to bring about the hydrolysis of the amide, and the only source of the required oxygen atom was another molecule of benzil, Selman and Eastham[6] suggested the mechanism given in Scheme 2. The consistent recovery of starting material in these reactions is accounted for by the mechanism — which was also suggested as a pathway by which benzilic acid could form in some of the alkoxide-initiated processes (X = OR).



Scheme 2

In recent years, single-electron transfer (SET) mechanisms have been suggested for a number of organic processes, including a number of base-catalyzed reactions. These include the Wittig 1,2-rearrangement (see Chapter 3.11, this volume), the Cannizzaro reaction,[19] Meerwein–Ponndorf–Verley reductions,[20] and also the benzilic acid (or ester) rearrangement.[21] Benzil is not rearranged by lithium dialkylamides (Scheme 2; X = NEt_2, NPr^i_2), but these bases are of low nucleophilicity. Reaction with lithium *t*-butoxide in benzene–THF gives intense violet-colored paramagnetic solutions which exhibit an ESR spectrum consistent with the presence of the lithium semidione of benzil (**14**). On the basis of this evidence the SET mechanism given in Scheme 3 was proposed.[21] Although the Bu^tOLi reaction gave *t*-butyl benzilate in high yield (96%), similar reaction using LiOEt failed to cause rearrangement, but the semidione was detected. In a somewhat related case, the condensation products of 3-amino-2,4-dicyanocrotonic esters with benzils (see Section 3.6.3.2) undergo a benzilic acid type rearrangement in aqueous alkali, and ^{1}H NMR–CIDNP experiments support the assumption of a partial radical character for the processes.[22] Hence, the SET mechanisms do deserve careful consideration, but the problem is that such proposals are highly controversial at the present time,[23] and it is not yet clear if the SET mechanism for benzilic acid rearrangements will achieve general acceptance. The mechanism raises a number of questions on interpretation. For example, the semidione species is a radical anion, four canonical forms of which are shown in formulae (**14a–d**). It is not yet clear if the electron density distribution in (**14a–d**) finds a satisfactory parallel in the experimentally determined migratory aptitudes of the substituents R^1 and R^2. Likewise, it is not clear why phenoxide anions, which are efficient one-electron transfer agents, fail to promote the rearrangement.



Scheme 3

(14a) (14b) (14c) (14d)

Hence, although the presence of radicals has been demonstrated, it has yet to be shown that the SET pathway is more than a minor competitive reaction, and for the remainder of this review the anionic mechanism set out in Scheme 1 will be assumed to apply.

3.6.3 THE CHEMISTRY OF BENZILIC ACID REARRANGEMENTS

3.6.3.1 Reaction Conditions

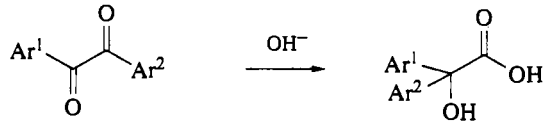
The sensitivity, or otherwise, of the α-dicarbonyl substrate determines the reaction conditions. However, variations in conditions are not especially large. Although 1 equiv. of base may be used, more usually an excess is employed — sometimes 10 equiv. or more to accelerate the reaction. Studies on the reaction of hydroxides with benzil indicate that the rate depends to some extent on the cation,[24a] and it can be advantageous to use $Ba(OH)_2$ rather than the more usual NaOH or KOH.[24b] With hydroxide ion, favored solvents are water and aqueous ethanol. Heterogeneous conditions, for example potassium hydroxide and diethyl ether[25] or sodamide and toluene,[17,26] have also been employed. The reactions are conducted at room temperature (sometimes requiring up to 4 d) or under reflux (10 min–24 h). With methoxide or *t*-butoxide the corresponding anhydrous alcohol or benzene are employed as solvents.[16,21]

3.6.3.2 Bisaryl α-Diketones

A detailed *Organic Synthesis* procedure is available for the conversion of benzil into benzilic acid.[27a] It is advantageous to isolate the acid as its potassium salt, for this enables the removal of the more soluble potassium benzoate, which results from a competitive cleavage reaction. Benzilic acid is then obtained in 77–79% yield by acidifying an aqueous solution of potassium benzilate. Since benzil is usually obtained by the oxidation of benzoin, both this conversion and rearrangement can be performed in tandem by using alkaline sodium bromate.[27b] Thus, benzilic acid is obtained in 84–90% yield from benzaldehyde *via* benzoin.

The rearrangement of substituted benzils is facilitated by electron-withdrawing substituents in the *meta* or *para* positions ($m > p$); steric hindrance retards the rate of rearrangement of *ortho*-substituted aryl groups. Some typical examples of the rearrangement of simple bisaryl α-diketones are summarized in Table 1. The very high reactivity of decafluorobenzil is noteworthy; quite exceptionally the rate of the benzilic acid rearrangement exceeds that for hydride transfer reduction by ethoxide ion (see Section 3.6.2.2) and ethyl decafluorobenzilate is obtained in 90% yield in the benzilic ester rearrangement.[32] The analogous reaction with sodium methoxide was found to occur at –78 °C. The similar reaction of

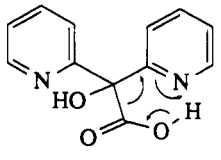
Table 1 Rearrangement of Substituted Benzils



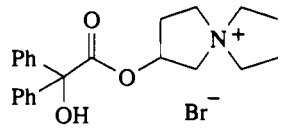
Ar^1	Ar^2	*Temperature* (°C)	*Time (h)*	*Yield (%)*	*Ref.*
Ph	4-ClC_6H_4	25	72	70	28
Ph	2-MeC_6H_4	80	0.17	80	29
Ph	4-$MeOC_6H_4$	80	0.17	60	28, 30
4-$Pr^iC_6H_4$	4-$Pr^iC_6H_4$	80	—	70	31
2-OH-5-BrC_6H_3	2-OH-5-BrC_6H_3	100	17	68	24
C_6F_5	C_6F_5	25	0.08	83	32
2-Furyl	2-Furyl	25	24	88	25

decafluorobenzil with pentafluorophenyllithium gave the pentafluorophenyl migration product, $(C_6F_5)_2C(OH)COC_6F_5$, after low temperature hydrolysis (see Section 3.6.3.7).

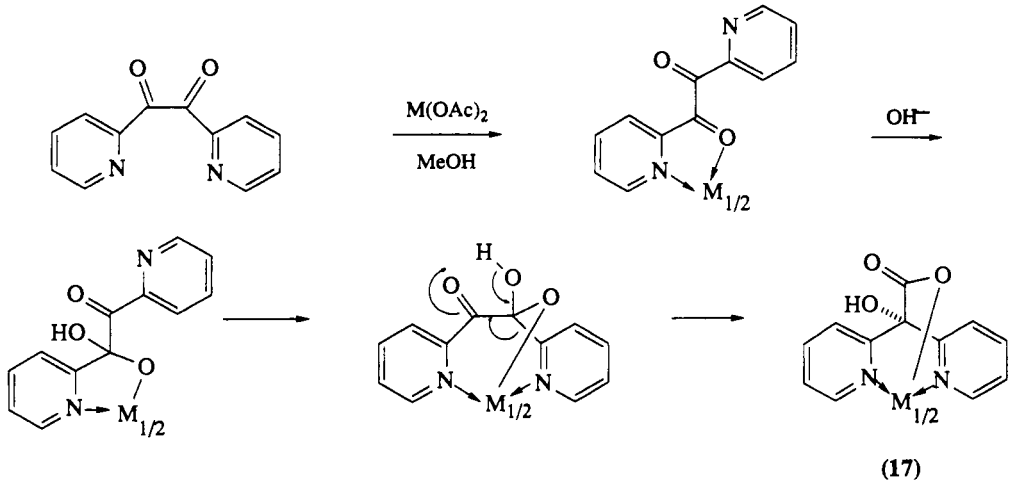
The generality of the rearrangement is further illustrated by the reaction of 2,2′-furil with hydroxide ion in dry ether (Table 1).[25] Likewise, 2,2′-pyridil is rearranged in hot methanol solution (40 min) to give the sodium salt of 2,2′-pyridilic acid (86%).[33] Acidification, however, affords bis(2-pyridyl)methanol by decarboxylation since 2,2′-pyridilic acid (**16**) is structurally similar to a β-keto acid. Benzilic rearrangement of 2,2′-pyridil with methanolic nickel(II) and cobalt(II) acetates results in the formation of metal complexes of 2,2′-pyridilic acid (**17**; 92%). A plausible mechanism is summarized in Scheme 4.[34] Rearrangement is also observed with 2,2′-quinaldil, but benzil, 2,2′-furil or 1-phenyl-2-(2′-pyridyl)ethane-1,2-dione are not susceptible to these metal template reactions.



(16)



(18)

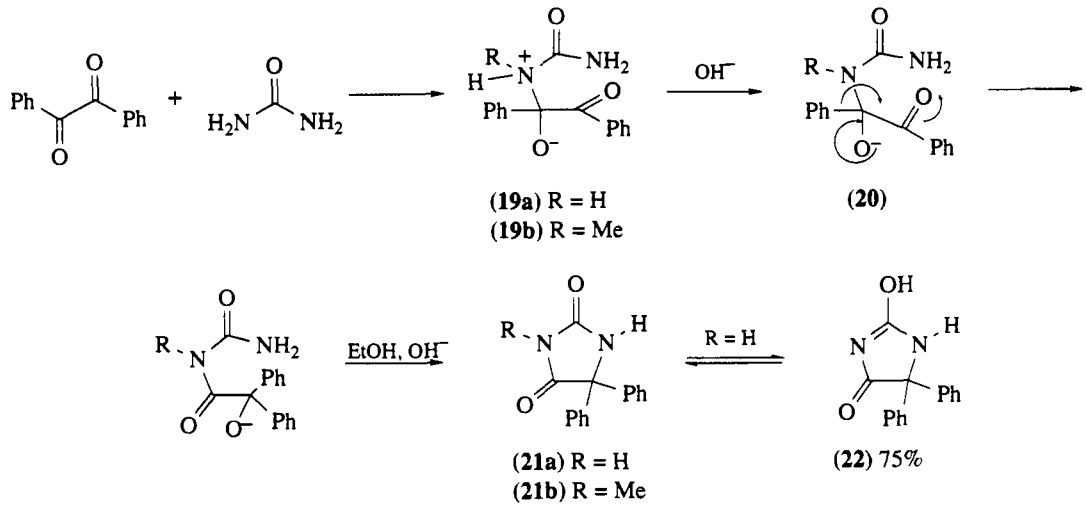


(17)

Scheme 4

Simple benzilic acid derivatives frequently show pronounced pharmacological activity.[35] For example, the ester (**18**) is an anticholinergenic and spasmolytic agent (Minelsin, Ortyn). The reaction of benzil with urea in ethanol in the presence of potassium hydroxide affords 5,5′-diphenylhydantoin (**22**),[36] the sodium salt of which is the anticonvulsant Dilantin. The probable mechanism is shown in Scheme 5, the function of the hydroxide ion being the deprotonation of the initial adduct (**19a**), thereby triggering the benzilic rearrangement of the anion (**20**). The corresponding reaction with *N*-methylurea gives 3-methyl-5,5-diphenylhydantoin (**21b**; 95%), the regioselectivity resulting from the preferential formation of (**19b**) through the attack by the more nucleophilic nitrogen center. Substituted benzils[37] and ureas[36] or thioureas[38] generally react to give analogous hydantoins; however, condensation reactions without rearrangement compete in some cases.

In somewhat similar chemistry, a one-step synthesis of 4-cyano-3,3-diaryl-5-methyl-2-oxo-2,3-dihydropyrroles (**23**) is available through the reaction of benzils with acetonitrile in the presence of sodium hydride (Scheme 6).[39] Likewise, the base-catalyzed addition of malononitrile to benzil[40] yields 2-benzoyl-2-phenylethylene-1,1′-dicarbonitrile (**24**) which, in the presence of aqueous alkali, undergoes 1,2-aryl migration (Scheme 7) and cyclization, yielding the succinimide (**25**).[41] Condensation of benzils with 3-amino-2,4-dicyanocrotonic esters gives the ylidene cyanoacetates (**26**), which rearrange to the ylidene pyrrolidines (**27**) in the presence of aqueous alkali (Scheme 8); ^{1}H NMR–CIDNP experiments indicate that radical intermediates are formed under the rearrangement conditions.[22] The regiochemistry of the initial condensation is determined by the more electrophilic of the two carbonyl groups of the benzil.



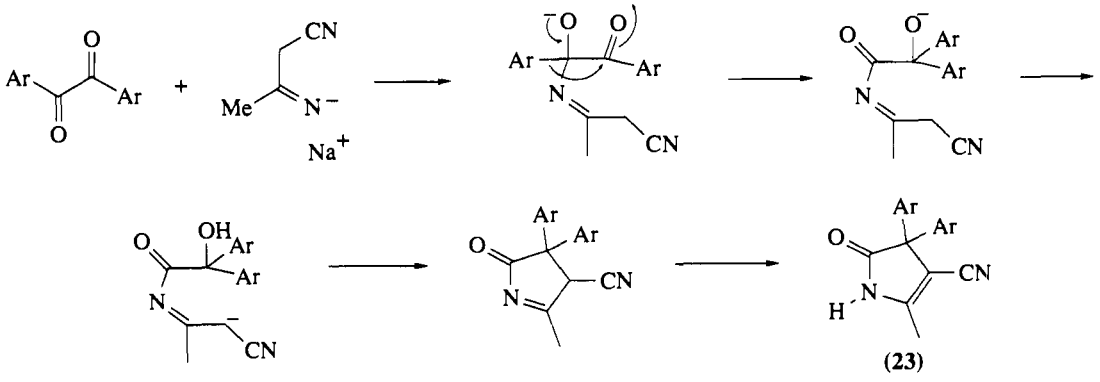
(19a) R = H
(19b) R = Me

(20)

(21a) R = H
(21b) R = Me

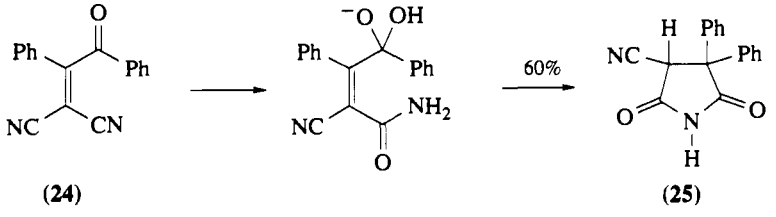
(22) 75%

Scheme 5



(23)

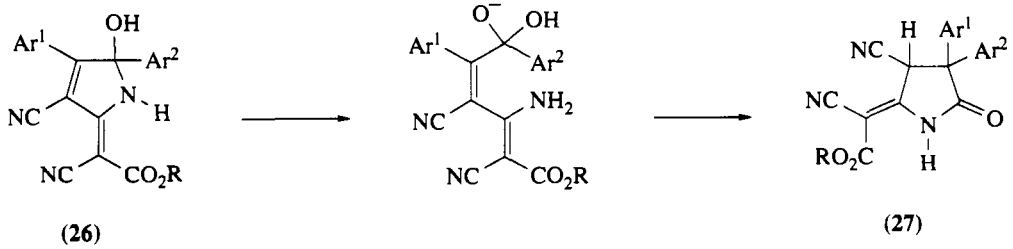
Scheme 6



(24)

(25)

Scheme 7



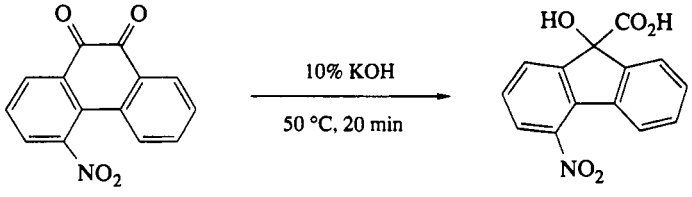
(26)

(27)

Scheme 8

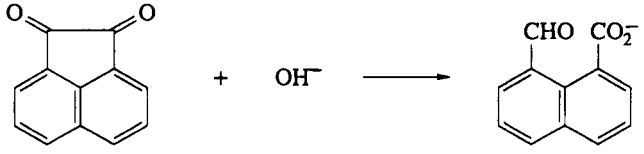
3.6.3.3 Quinones

The benzilic rearrangement of an *o*-quinone results in ring contraction. Among the earliest recorded examples is the synthetically useful conversion of phenanthroquinones into 9-hydroxyfluorenecarboxylic acids (equation 6).[42–46] As with the benzilic acids, compounds such as (**28**) are susceptible to oxidative decarboxylation, especially under acidic conditions. Simply boiling a solution of (**28**) in oxygenated water gives the 9-fluorenone derivative.[44] The phenanthroquinones are readily prepared through the chromium(VI) oxidation of phenanthrenes. When phenanthrene derivatives are oxidized with alkaline permanganate, oxidation to the quinone and benzilic acid rearrangement occur in tandem; furthermore, permanganate cleaves α-hydroxy acids, and the 9-fluorenone is thus obtained directly.[45]



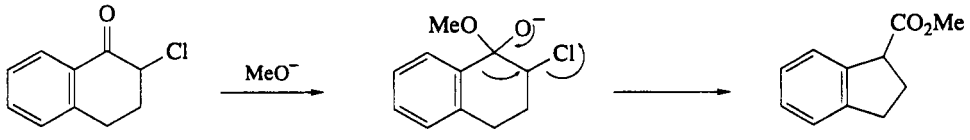
(6)

(**28**)



(7)

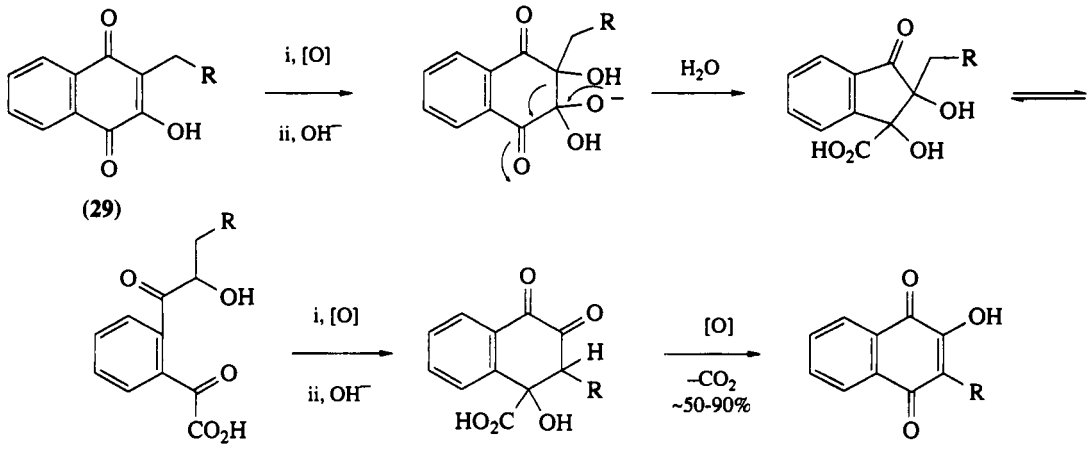
The outcome of the reaction of acenaphthoquinone with hydroxide ion is quite different. Benzilic rearrangement, which would lead to a highly strained four-membered ring, is not observed. Instead, simple cleavage occurs to give naphthaldehyde-9-carboxylate (equation 7).[24a] Despite the fact that the benzilic acid and ester rearrangements have been shown to be irreversible, they apparently cannot be employed routinely in the construction of strained rings (see Section 3.6.3.5). This contrasts with the semibenzilic mechanism (*e.g.* Scheme 9)[47] which operates in certain base-induced rearrangements of α-halo ketones when the conventional Favorskii mechanism is not possible (see Section 3.6.3.7).



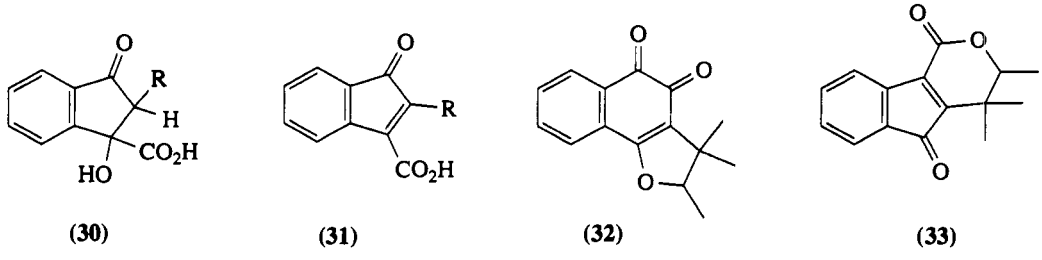
Scheme 9

Annelated quinones such as phenanthroquinone are best regarded simply as bisaryl α-diketones. The benzilic acid rearrangement mechanism does not figure large in the chemistry of the simpler benzoquinones, presumably because there are too many other opportunities for reaction, such as oxidation and reduction, condensation, Michael addition and retro-aldol cleavage. However, benzilic rearrangements do occur, and may not be uncommon in the oxidative rearrangements of hydroxyquinones.[48] The Hooker oxidation of 2-hydroxy-3-alkyl-1,4-naphthoquinones by alkaline permanganate gives the next lower homolog, and it has been shown[49] that the alkyl and hydroxy groups exchange places. The mechanism shown in part in Scheme 10 has been proposed for the Hooker oxidation (and the related H_2O_2/OH^- oxidation),[49,50] and contains a benzilic acid ring contraction step. The R group in (**29**) is usually saturated, but examples in which R contains unsaturation, alcohol, ether or carboxylic acid functionality have also been studied. When R is a large group (*t*-butyl or cyclohexyl), treatment with 5% aqueous alkali in the absence of oxygen leads to the formation of 2-alkylindenone-3-carboxylic acids (**31**) in high yield *via* the benzilic acids (**30**), which may be isolated under buffered conditions.[51,52] An analogous transformation is involved in the base-promoted rearrangement of the natural pigment dunnione (**32**) into allodunnione (**33**).[53]

The rearrangements of hydroxy-1,4-benzoquinones in alkali are more complex.[48] Under conditions in which polyporic acid (**34**) is converted, by way of retro-aldol ring cleavage and benzilic rearrangement, into α-benzyl-β-phenylsuccinic acid, *cis*- and *trans*-α-benzylcinnamic acid and oxalic acid, atromentin

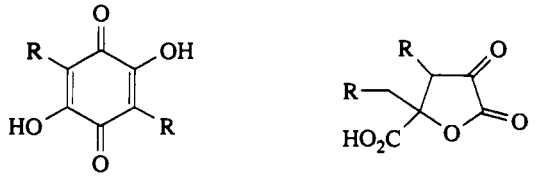


Scheme 10



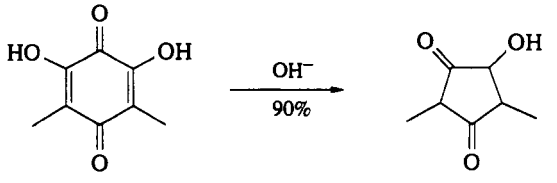
(30) (31) (32) (33)

(35) gives the lactone (36), which affords the analogous cinnamic acid only on boiling in 50% alkali.[54,55] Analogously, 4-hydroxycyclopentane-1,3-diones are available in good yield from 2,6-dihydroxy-1,4-benzoquinones by base-induced benzilic rearrangement followed by decarboxylation; equation (8) is fairly typical.[48,55]



(34) R = Ph
(35) R = 4-HOC$_6$H$_4$

(36) R = 4-HOC$_6$H$_4$

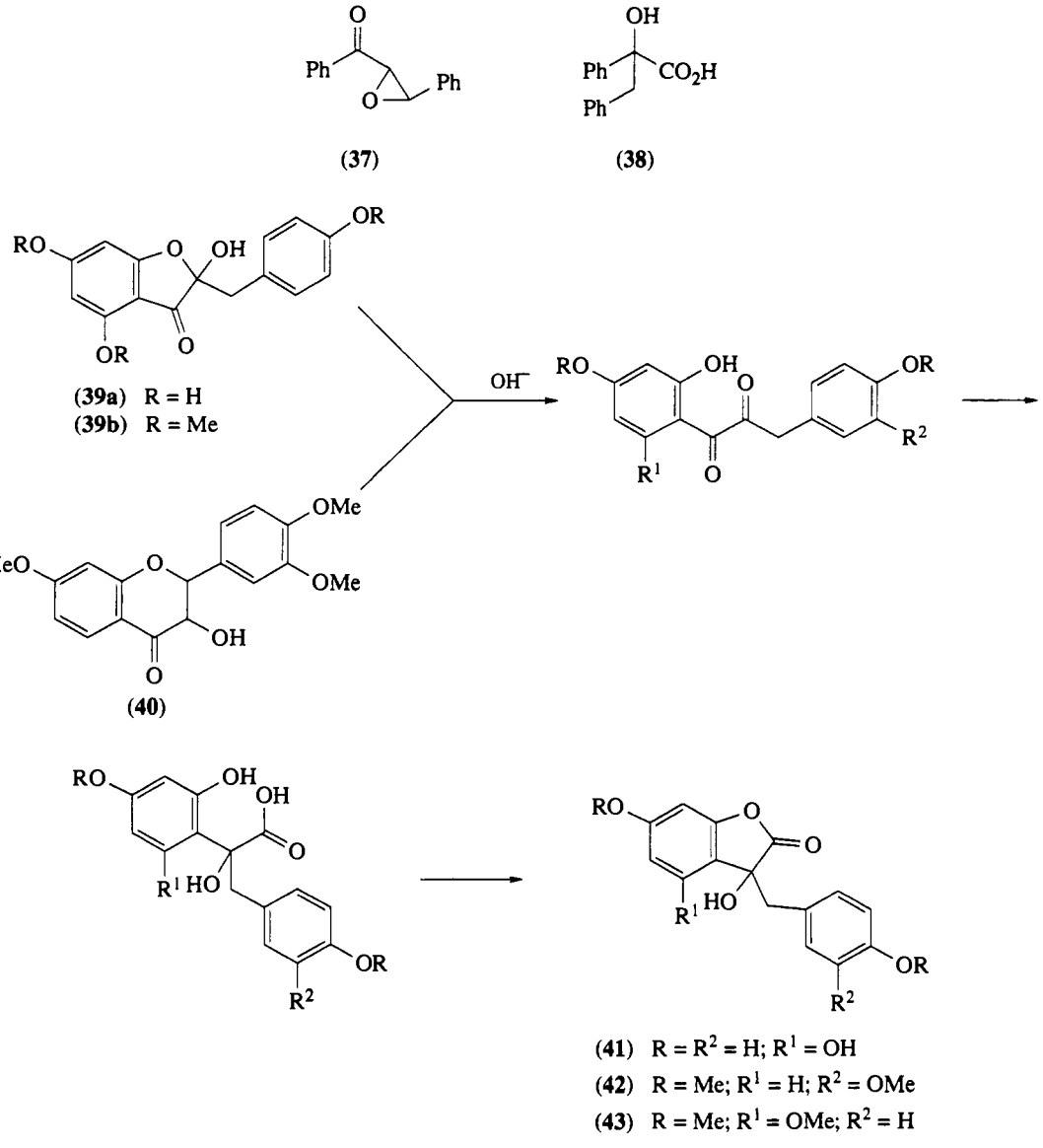


(8)

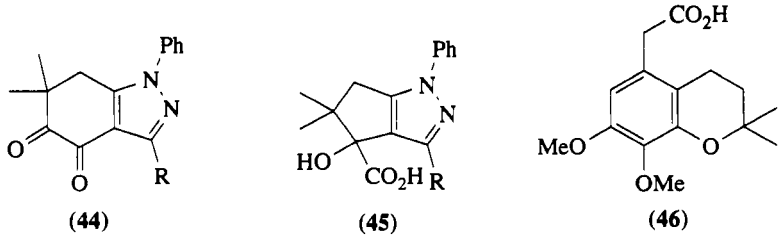
3.6.3.4 1-Alkyl-2-aryl-1,2-dicarbonyl Systems

The simplest of such systems is phenylglyoxal (PhCOCHO), which undergoes H migration to give mandelic acid (PhCHOHCO$_2$H; 72.5%) on reaction with barium hydroxide.[13,56] Likewise, the reaction of α-(4-isobutylphenyl) β-methyl diketone with 10% aqueous sodium hydroxide–xylene mixture at 100 °C for 5 h affords a 96% yield of α-(4-isobutylphenyl)-α-hydroxypropionic acid (4-Me$_2$CHCH$_2$C$_6$H$_4$C(Me)OHCO$_2$H) on work-up.[57] The rearrangement of both methyl phenyl diketone and α,α-dibromopropiophenone (PhCOCBr$_2$Me) occurs with 100% phenyl migration;[10] the yield of

atrolactic acid ($PhC(Me)OHCO_2H$) is rather low since aldol condensation competes. It is essential, therefore, to keep the concentration of the diketone low to limit the rate of the competing bimolecular reaction.



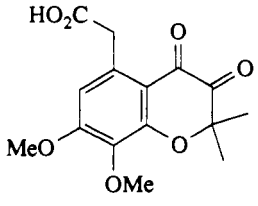
Scheme 11



The reaction of benzylideneacetophenone oxide (**37**) with aqueous sodium hydroxide in ethanol at reflux for 1.5 h affords, on work-up, a 72% yield of the acid (**38**). The reaction proceeds *via* benzyl phenyl diketone, and isotopic labeling indicates that exclusive benzyl migration occurs.[58] Benzyl 2-hydroxyphe-

nyl diketones are available through the base-promoted ring scission of 2-benzyl-2-hydroxy-2*H*-benzo[*b*]furan-3-ones (*e.g.* the hardwood extract maesopsin **39a**)[59] and 3-hydroxyflavanones (*e.g.* **40**).[60] Hence, under alkaline conditions rearrangement products are formed (*i.e.* 3-benzyl-3-hydroxy-3*H*-benzo[*b*]furan-2-ones, respectively **41** and **42**) as shown in Scheme 11. A photochemical equivalent of the benzilic acid rearrangement has also been observed in this series. Thus, irradiation of 4,4′,6-tri-*O*-methylmaesopsin (**39b**) in THF–water at 350 nm afforded the rearrangement product (**43**) in modest yield.[61]

The cyclopentapyrazoles (**45**; R = H, Me) are obtained in 67% and 54% yields, respectively, by benzilic acid rearrangement of the corresponding indazolediones (**44**).[62] This ring contraction has many analogs in the next section, and may occur during alkaline permanganate oxidations of suitable substrates. For example, oxidation of fuscinic acid dimethyl ether (**46**) affords (**48**) and (**49**), implicating the α-diketone (**47**) as a common intermediate.[63]



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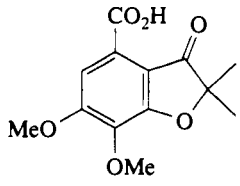
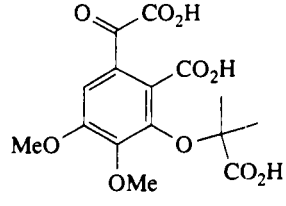


(48)

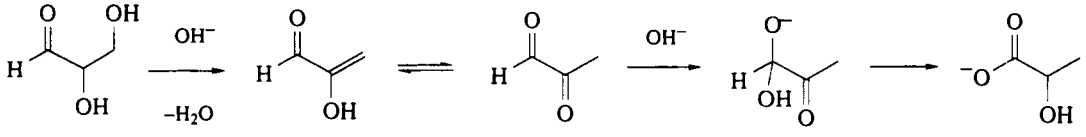


(49)

3.6.3.5 Aliphatic and Alicyclic α-Diketones

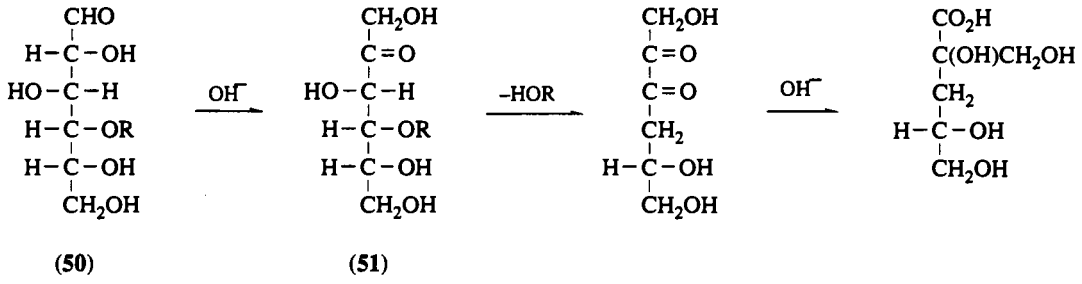
Glyoxal is the simplest member, and is readily rearranged in aqueous alkali to glycolic acid (equation 2).[2] This and similar rearrangements of simple aliphatic α,β-dicarbonyl and α,β,γ-tricarbonyl systems are of mechanistic rather than synthetic interest and importance. However, in handling such compounds for other synthetic purposes it is necessary to recognize their lability to base. In the rearrangement of *t*-butyl α,β-dioxobutyrate, which exists in aqueous solution as the hydrate $MeCOC(OH)_2CO_2Bu^t$, exclusive 1,2-shift of the CO_2Bu^t group occurs (equation 3).[3] Likewise, in alkaline medium ethyl cyclopropane-2,3-dioxopropionate is transformed into $Pr^nC(OH)(CO_2H)_2$ by rearrangement only of CO_2Et or CO_2^- (not cyclopropyl)[12] and only $CONH_2$ migration occurs with the compounds $ArCH_2COC(OH)_2CONH_2$.[12]

Compounds which are converted into α-diketones by base are susceptible to benzilic acid rearrangement. Especially common is the base-catalyzed dehydration of α,β-dihydroxycarbonyl compounds, and the transformation of glyceraldehyde into lactic acid (Scheme 12) is a simple example of α-hydroxy acid formation by this route.[64] The higher carbohydrates also undergo similar alkali-induced degradative rearrangements,[65] but here an α-ketol rearrangement (see Section 3.6.3.7), for example (**50**) → (**51**) in Scheme 13,[66] precedes the formation and benzilic rearrangement of the α-diketone. α,β-Dihydroxy ketones are also formed in the ring opening of α,β-epoxy ketones by hydroxide, and hence produce the rearranged α-hydroxy acids by way of the intermediate α-diketone; an example, (**37**) → (**38**), was given earlier.[58]



Scheme 12

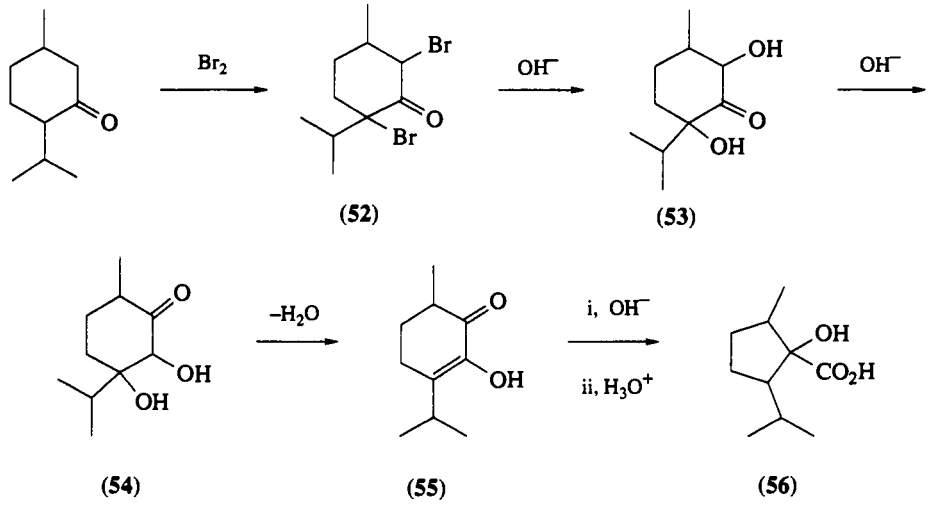
The ring contraction rearrangement of alicyclic α-diketones is much more valuable from the synthetic viewpoint (*e.g.* equation 4). There are several routes available for the synthesis of α-diketones from monoketones. These include: direct oxidation using selenium dioxide; permanganate or osmium tetroxide addition across the double bond of an enone followed by base-promoted elimination of water; bromination to give the dibromo ketone followed by hydrolysis; condensation with 4-nitroso-*N*,*N*-dimethylaniline followed by acidic hydrolysis — but there are many others. The bromination–hydrolysis route has been extensively studied by Wallach.[4] The conversion of menthone into 1-hydroxy-



(50) **(51)**

Scheme 13

2-isopropyl-5-methylcyclopentanecarboxylic acid (**56**) is fairly typical. In the dibromination of menthone it was proven that the bromine atoms are not attached to the same carbon atom, but rather the dibromide has the structure (**52**). The dihydroxy ketone formed in the initial hydrolysis step (**53**) presumably is transformed (*cf.* ref. 4) into the necessary α-diketone (**55**; shown in a monoenolic form, a diosphenol) by sequential α-ketol rearrangement (**53**) → (**54**) and dehydration (**54**) → (**55**; Scheme 14). The same acid (**56**) is formed in the cognate reaction of carvomenthone, the reaction also proceeding *via* α-diketone (**55**).

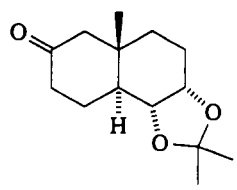


(52) **(53)** **(54)** **(55)** **(56)**

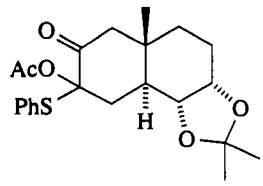
Scheme 14

The general strategy for ring contraction also works well with more elaborate molecules. Regiospecific sulfenylation of the diketone (**57**) followed by acetoxylation afforded the α-acetoxy sulfide (**58**; 68%).[67] Hydrolysis and *in situ* rearrangement was effected with aqueous potassium hydroxide, and oxidative cleavage of the crude α-hydroxy acid (**59**) gave the perhydroindanone (**60**; 50%), a potential intermediate in the synthesis of taxanes. Relatively unstrained cage ketones can also be ring-contracted by employing the benzilic acid rearrangement strategy (for example equation 9).[68a] There are few examples of the production of strained rings. However, cyclobutane-1,2-diones have been shown to undergo ring contraction to α-hydroxycyclopropanecarboxylic acids and derivatives.[68b] Relatively little attention has been paid to the use of other bases for promoting rearrangement. Cyclohexane-1,2-dione reacts in this manner with arylbiguanides (**61**) and with *N*-amidino-*O*-alkylisoureas (**62**) to give the heterocyclic derivatives (**63**) in fair yield (*cf.* Scheme 5).[69]

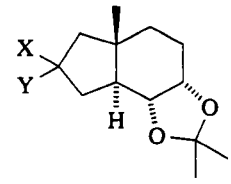
Considerable interest has been shown in the rearrangement of the α-diketones of steroids and of di- and tri-terpenoids. Of particular interest is the abutment of the reaction center to a chiral system of rigid stereochemistry. This allows an examination of the regiochemistry and the stereospecificity and stereoselectivity of the reaction with alkali. The isomeric diosphenols (**64**) and (**65**), respectively 3-hydroxy-5α-cholest-3-en-2-one and 2-hydroxy-5α-cholest-1-en-3-one, are interconvertible in the presence of acid or base. On reaction of either with potassium hydroxide in propanol a single benzilic acid rearrangement



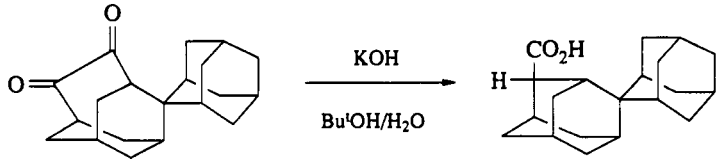
(57)



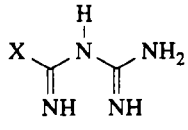
(58)

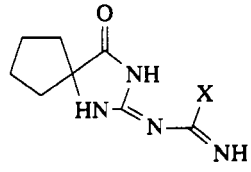


(59) X = OH; Y = CO_2H
(60) X = Y = O



(9)



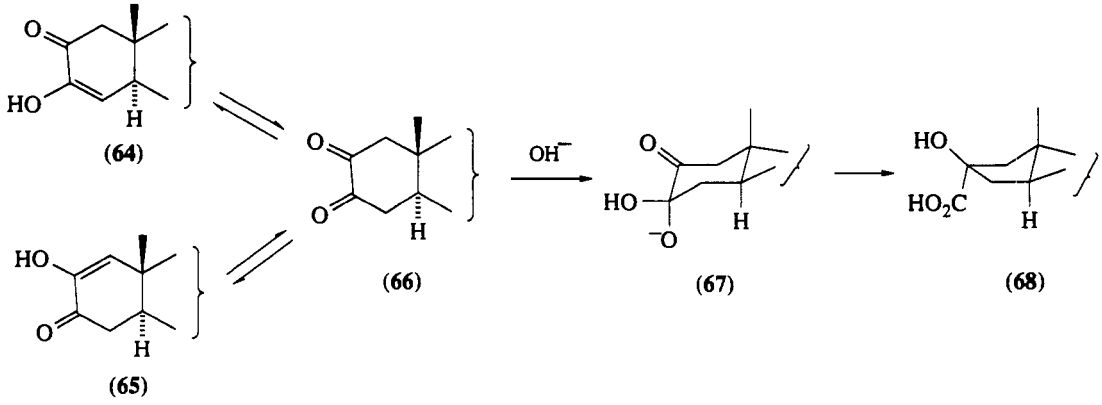


(61) X = 4-RC_6H_4NH
(62) X = RO

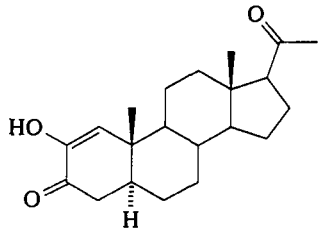
(63)

product, A-nor-5α-cholestan-2-ol-2-carboxylic acid, was obtained.[70] The necessary common intermediate is presumably the α-diketone (**66**; Scheme 15) which can yield four possible hydroxide addition products arising from α- or β-attack at either of the two carbonyl groups. It was thought that of these (**67**) should be the most stable through the minimization of 1,3-diaxial interactions and oxygen–oxygen dipolar repulsions, and by stereospecific rearrangement should give 2β-hydroxy-2α-carboxy-A-nor-5α-cholestane (**68**). However, the configuration of the single product was not determined. Likewise, the diosphenol (**69**), 5α-pregn-1-en-2-ol-3,20-dione, was rearranged by treatment with potassium hydroxide in ethanol or propanol to give a single product, A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid (90%).[71] The configuration of the substituents at C-2 in the hydroxy acid (**70**) was tentatively assigned as 2β-hydroxy-2α-carboxy on the basis of similar reasoning to the above. There have been several other reports in this area of benzilic acid rearrangements in which only a single α-hydroxycarboxylic acid was isolated.[70]

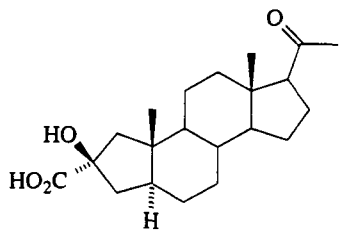
Reaction of a solution of 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (**71**) in aqueous propanol with potassium hydroxide, followed by an acidic work-up, afforded the lactone (**75**; 76%). Three events are involved in this transformation (Scheme 16), namely retro-aldol equilibration to give the *cis*-fused C–D-ring system (**72**) → (**73**), stereoselective benzilic acid rearrangement (**73**) → (**74**) to



Scheme 15

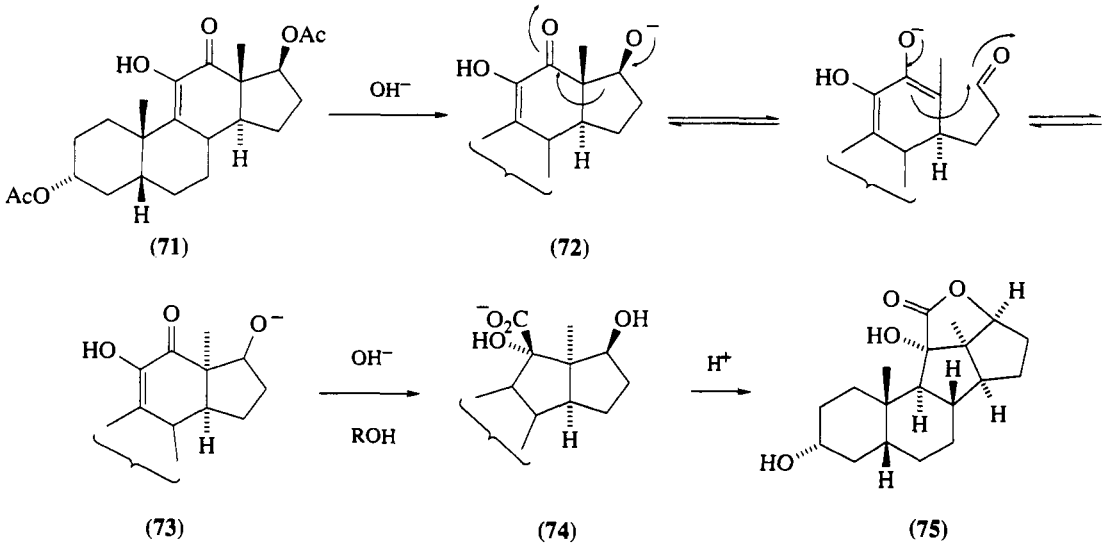


(69)



(70)

provide the 11β-carboxylic acid function, and finally lactonization (**74**) → (**75**).[72] Since the benzilic acid rearrangement has been shown to be irreversible,[6,73] the formation of the lactone (**75**) indicates that the transformation (**73**) → (**74**) is a highly stereoselective process.



(71) (72)

(73) (74) (75)

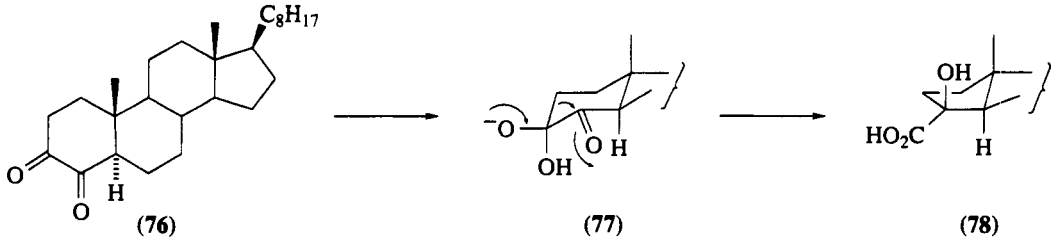
Scheme 16

The major product of the rearrangement of 5α-cholestane-3,4-dione (**76**) was shown to be 3α-carboxy-A-nor-5α-cholestan-3β-ol (**78**). By using (**76**) labeled with ^{14}C at C-4, it was shown that the carboxy group of (**78**) arose from C-3 of (**76**). The evidence, and the steric constraints imposed by the steroidal system, favors stereo- and regio-specific α-attack by hydroxide to give (**77**) and stereoselective rearrangement *via* a chair-like transition state to give the product (**78**; Scheme 17).[11] Rearrangement of 4,4-dimethyl-5α-cholestane-2,3-dione (**79**) gave only the hydroxy acid (**81**) with the carboxy group α. Labeling experiments indicated that 94% of the benzilic rearrangement resulted from attack at the C-3 carbonyl through a quasi-chair transition state. The remaining 6% of the rearrangement resulted from attack at the C-2 carbonyl through a quasi-boat transition state.[74] The similar reaction of 5α-cholestane-2,3-dione (**80**) gave the two hydroxy acids (**82**; 85%) and its epimer at C-2 (15%). Labeling studies reveal a more complex regio- and stereo-chemical situation than for the conversion of (**79**) into (**81**).[75]

The stereochemistry of the hydroxy diacid obtained by the rearrangement of the dioxo ester (**83**), itself derived from (–)-abietic acid, has been determined unequivocally, and is as shown in (**84**).[76] Other stereospecific benzilic acid rearrangements have been reported, including ring contraction of a D-homo-17,17a-dione,[77] and contraction of ring A in ursolinic acid[78] and betulinic acid.[79]

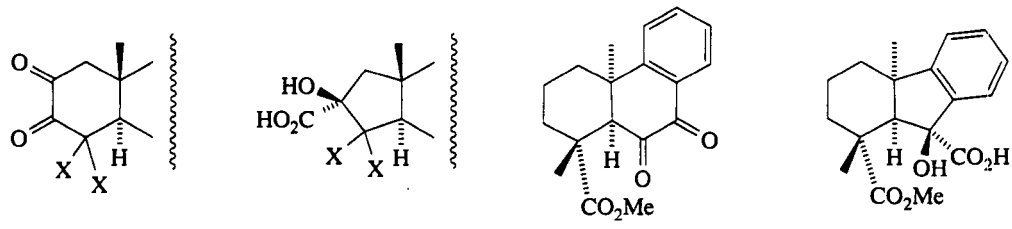
3.6.3.6 Heterocyclic Systems

Relatively little attention has been paid to this important area, and much of the definitive work has centered upon studies of the rearrangement of alloxan[5] and substituted alloxans[9] (equation 5). The essen-



(76) (77) (78)

Scheme 17

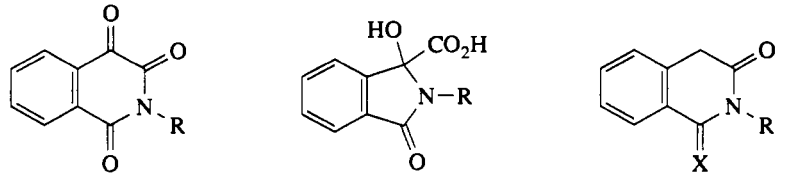


(79) X = Me
(80) X = H

(81) X = Me
(82) X = H

(83) (84)

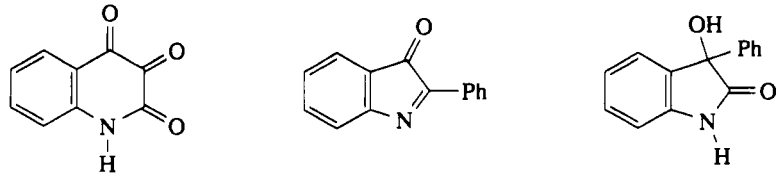
tial features concerning mechanism and regiochemistry were covered in Section 3.6.2.1. These studies indicated the exclusive shift of nitrogen over carbon. A similar situation is found in the reactions of the phthalonimides (**85**) and (**86**) with aqueous alkali to give 3-hydroxyphthalimidine-3-carboxylic acids (**87**).[14] Indeed, the ring-shrinking process can be conducted on the 1,3(2,4)-isoquinolinediones (**88**) or their monothio analogs (**89**), and their substituted derivatives, by the expedient of using excess hydrogen peroxide in aqueous alkali at room temperature (*ca.* 3 h or less). The phthalonimide intermediates (**85**) and (**86**) are converted rapidly under the reaction conditions into the hydroxy acids (**87**). These can be isolated provided that the excess peroxide is destroyed before acidification (46–81%), otherwise oxidative decarboxylation occurs and the corresponding phthalimides are formed. Kinetic measurements on the amide quinisatine (**90**) have also revealed that the rearrangement involves the shift of the carboxyamide group.[12b] The base-promoted conversion of 2-phenylindolone (**91**) into 3-phenyldioxindole (**92**), which occurs readily, may also be classified as a benzilic acid type rearrangement.[24,80]



(85) R = H
(86) R = Me

(87)

(88) R = H, Me; X = O
(89) R = H, Me; X = S

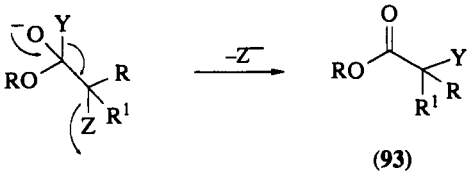


(90) (91) (92)

3.6.3.7 Related Rearrangements

The key steps in several additional rearrangements can be represented as in equations (10) and (11), and they are effectively the 'back-end' and the 'front-end' respectively of the benzilic acid rearrangement itself. Selman and Eastham[6] and others[8,81] have provided a brief analysis of such processes, and their scope. These reactions are referred to by a variety of names; for equation (10) Selman and Eastham suggest they be called 'α-oxo alcohol rearrangements', but the 'tertiary α-ketol rearrangement' or 'acyloin rearrangement'[81] are more common labels. Equation (11) differs from a benzilic acid rearrangement only inasmuch as the displacement occurs on a σ-bonding electron pair rather than the π-bonding electron pair of a carbonyl group, and has been referred to earlier as a 'semibenzilic rearrangement' (see Scheme 9). Z^- is a stable anion such as halide or tosylate, and the reaction may operate when the Favorskii mechanism is not possible. The subsequent loss of the carboxylate proton from (**93**; R = H) under the basic conditions of equation (11) renders the process irreversible. However, even with alkoxides as bases (*e.g.* **93**; R = Me) the inherent stability of the carboxylic ester function and the lack of electron pressure on the α-carbon atom, makes the reaction irreversible in the general sense. No such situation exists for equation (10), and its reversible nature frequently leads to the formation of mixtures of products. The tertiary α-ketol rearrangement occurs upon treatment of a tertiary alcohol containing an α-oxo group with base, or by reaction of an α-diketone with 1 equiv. of a Grignard reagent. The base-catalyzed reactions of α-hydroxyketosteroids have been especially well-studied. The reader is referred to the above-mentioned review articles for further insights into this area.

(10)



(11)

(**93**)

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3.7
The Favorskii Rearrangement

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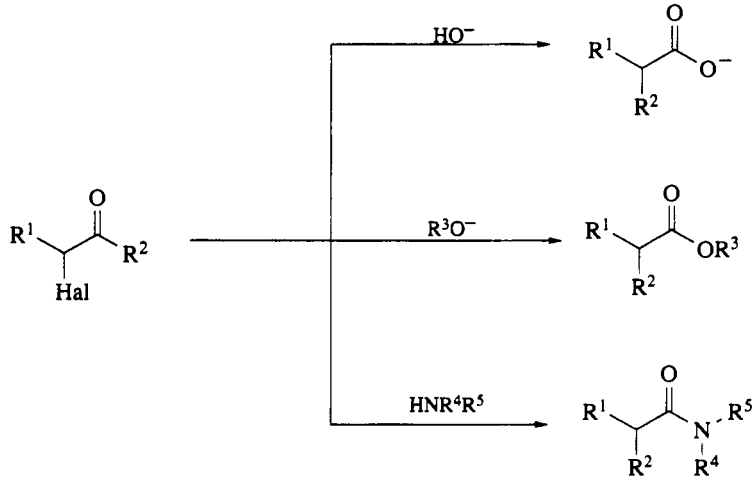
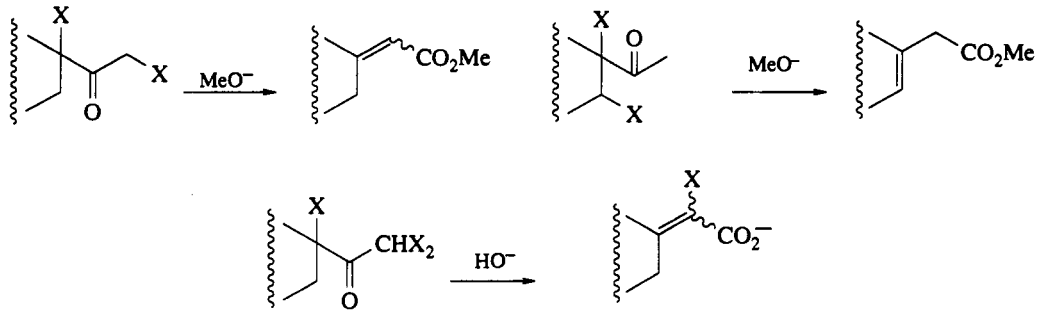
3.7.1 INTRODUCTION

The rearrangement of α-halo ketones under the influence of base was first described by Favorskii in 1892,[1,2] and the general scope of the reaction and the mechanistic implications have been the subject of a number of reviews.[3–12] In its most generally useful form, α-halo ketones undergo skeletal rearrangement when treated with a nucleophilic base (hydroxide, alkoxide or amine) to produce salts, esters and amides respectively (Scheme 1). With polyhalogenated ketones unsaturated acid derivatives are produced, as shown in Scheme 2.

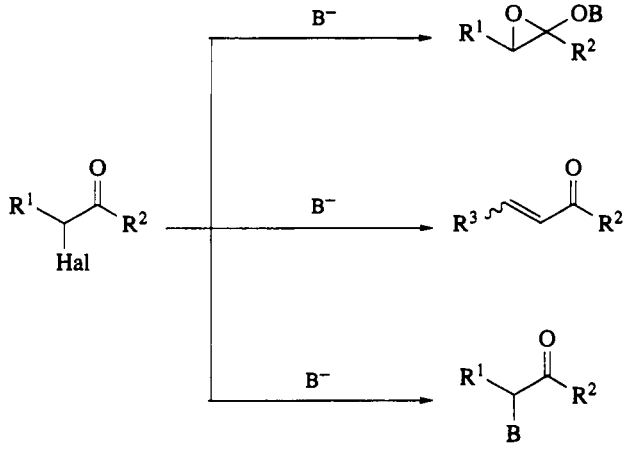


Scheme 1



Scheme 2

The reactions are usually carried out by adding the halo ketone to a solution or suspension of the base in either a protic solvent (water, alcohols) or an ether (diethyl ether, dioxane, dimethoxyethane). The bases employed include: hydroxides of Group I and Group II metals; alkoxides, carbonates and hydrogen-carbonates of Group I metals; ammonia, and amines. There is no one recommended set of experimental conditions, because both the mechanism of the reactions and the type of products obtained depend upon the initial choice of α-halo ketones. In addition, since the halo ketones are highly reactive molecules, side products are inevitably obtained; those most commonly produced are shown in Scheme 3.



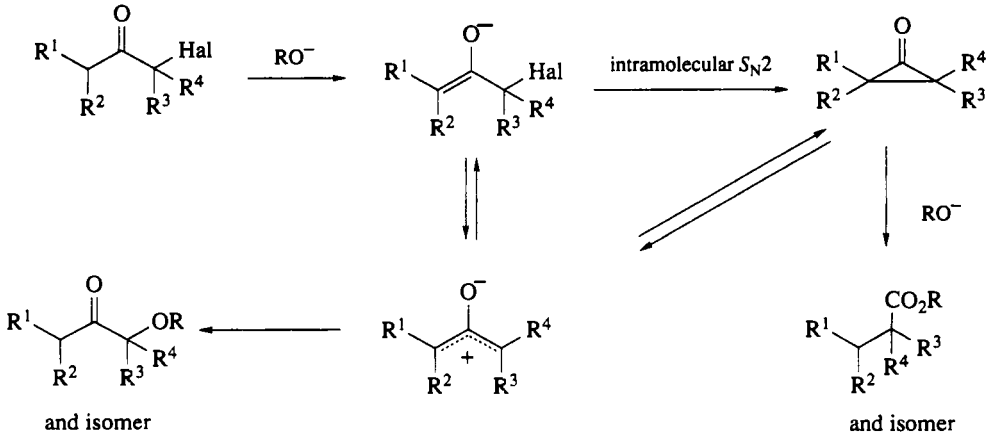
Scheme 3

3.7.2 MECHANISM

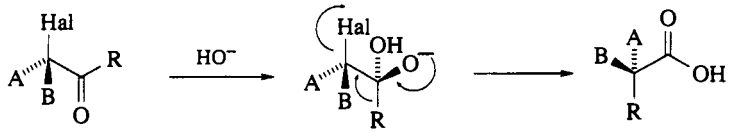
The various mechanisms that have been proposed for the rearrangement have been discussed in full,[12] and only a brief summary will be given here. Two main reaction mechanisms have been established: (i) a symmetrical mechanism, also known as the cyclopropanone pathway; and (ii) an unsymmetrical mechanism or semibenzylic pathway (Schemes 4 and 5).

The symmetrical mechanism necessitates an acidic hydrogen at the α′-center, and the intermediacy of a cyclopropanone or zwitterion/oxyallyl cation (Scheme 4). The likely existence of a symmetrical intermediate was first suggested by McPhee and Klingsberg[13] when they showed that the two ketones (**1**) and (**3**) rearranged to yield the same ester (**2**; Scheme 6). More cogent experimental support was provided by Loftfield[14] who reacted [1,2-$^{14}C_2$]-2-chlorocyclohexanone with sodium pentylate and obtained two ring-contracted products. These had an identical isotope distribution to the starting ketone (Scheme 7).

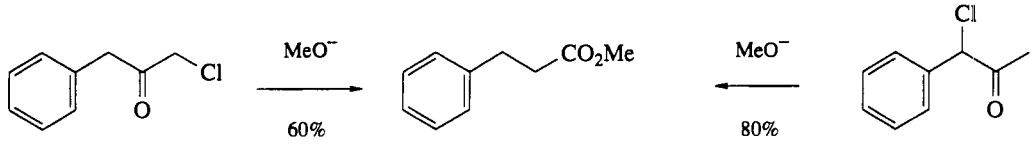
Numerous more recent experiments (reviewed in ref. 12) have confirmed the general accuracy of the mechanism shown in Scheme 4, and the actual intermediate involved depends upon the relative stabilities of the zwitterions/oxyallyl cations and the corresponding cyclopropanones. These will be affected by the choice of solvent and structural features of the starting ketone, such as the degree of substitution and ring strain (in cyclic halo ketones). A recent example in which an oxyallyl intermediate and a cyclopropanone intermediate were both intercepted is shown in Scheme 8.[15]



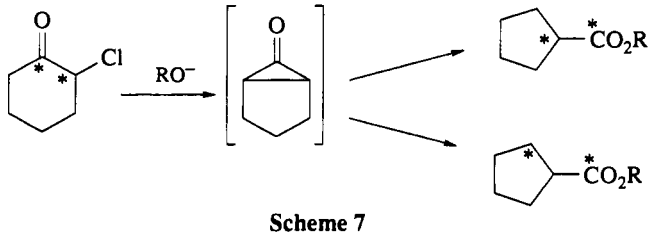
Scheme 4



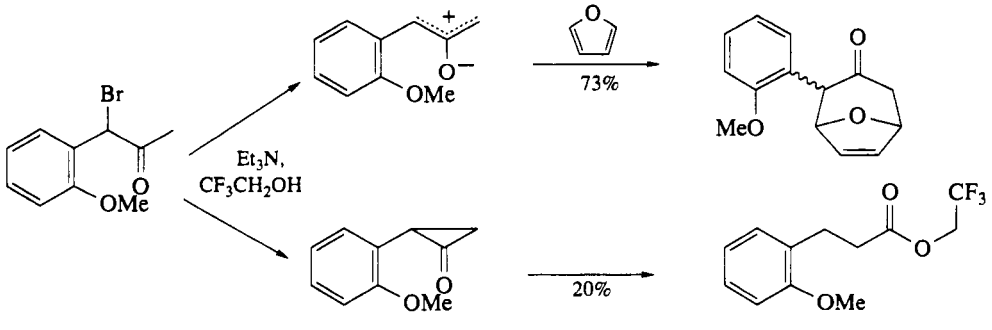
Scheme 5



Scheme 6



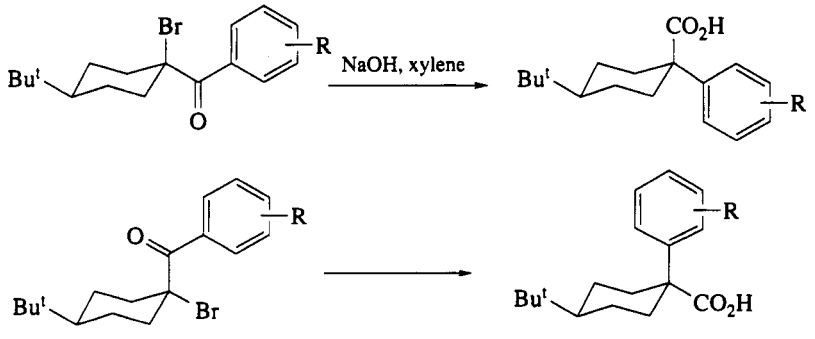
Scheme 7



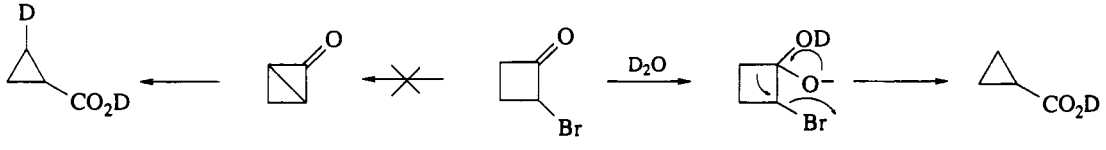
Scheme 8

In the semibenzylic pathway there is a nucleophilic attack by the base at the carbonyl carbon, followed by a concerted 1,2-migration of a carbanionic moiety with concomitant expulsion of halide. Implicit in this mechanism is the requirement for an antiparallel arrangement of the C—C bond that is broken and the carbon–halogen bond. This further requires an inversion of configuration at the carbon center initially bonded to the halogen atom, and an elegant demonstration of this feature has been provided by Charpentier and coworkers (Scheme 9).[16]

In cyclic systems where ring strain may be large for the cyclopropanone pathway, the semibenzylic pathway is preferred, and a good example of this is shown in Scheme 10.[17] Even when the ring strain is less severe, the semibenzylic pathway will be favored if there is a pseudo-equatorial halogen, thus allowing the new C—C bond to form from the pseudo-axial direction.



Scheme 9

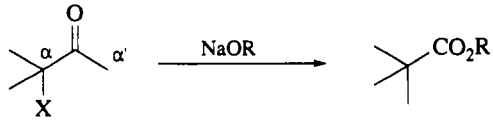


Scheme 10

3.7.3 SYNTHETIC UTILITY

3.7.3.1 Acyclic α-Halo Ketones

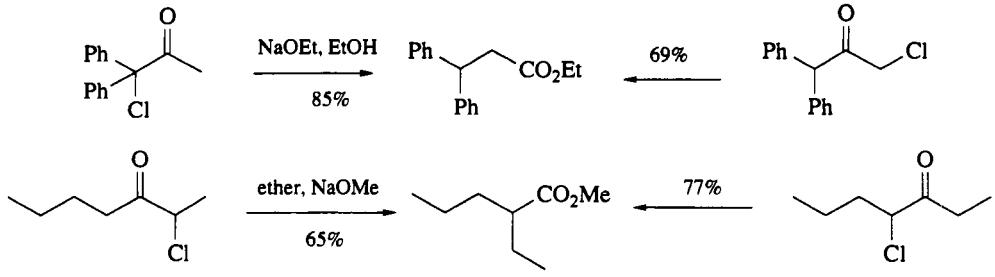
The Favorskii rearrangement of α-monohalo ketones is of primary utility for the synthesis of branched-chain aliphatic acid derivatives, and a typical example is shown in equation (1).[18,19] With increasing substitution at the α-carbon center, the rearrangement is favored since competing side reactions are suppressed; increasing the substitution at the α′-carbon center disfavors the rearrangement due to steric hindrance.



(1)

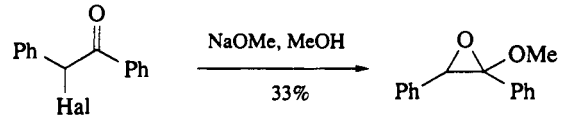
R	Me	Et	Pr^i	Ph
X	Br	Br	Br	Cl
%	39	61	64	47

The structural equivalence of the starting materials with respect to their common rearrangement product has already been mentioned, and two further examples are illustrated in Scheme 11.[20,21] In practice this often means that the ketone can be halogenated, and the mixture of halo ketones used directly in the Favorskii rearrangement.

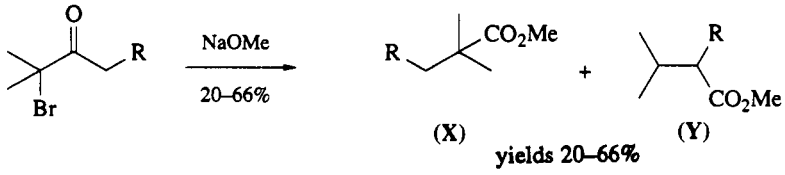


Scheme 11

Aryl groups generally have a labilizing effect on the substrate, and the rearrangements are particularly facile, often requiring only weak bases for their initiation. However, if aryl groups are present on both α- and α′-centers, alkoxy epoxides are formed in preference to the Favorskii products (equation 2).[22,23] Complications can also arise if an alkyl group is present at the α-center, of which the results shown in Scheme 12[24] are examples. It appears that the rearrangements are subject to the competitive influences of carbanion stability (secondary more stable than tertiary) and steric factors. The proportions of the two products also vary with the steric bulk of the base.



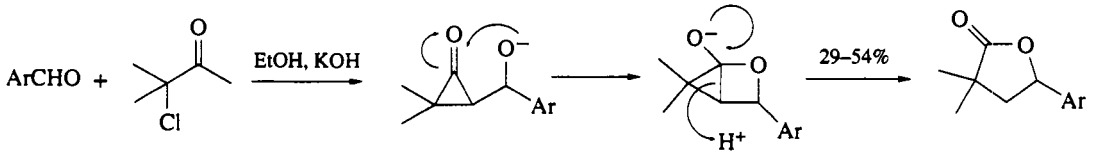
(2)



percentage of (**Y**) in the product mixture increases from 16 to 80% as R changes from Me to Et to Pr^{i}

Scheme 12

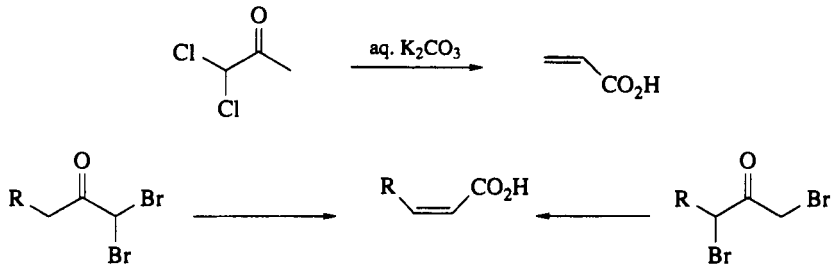
When the Favorskii rearrangement is carried out on a substrate which contains an internal nucleophile, this can attack the cyclopropanone intermediate to yield cyclic products. The reaction shown in Scheme 13[25] provides a route to polysubstituted γ-butyrolactones by this kind of mechanism.



Scheme 13

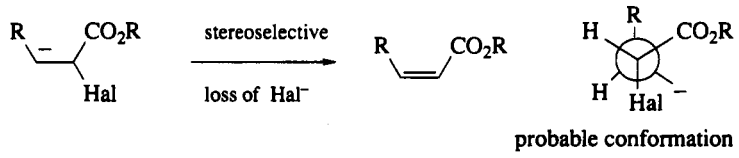
The reaction of a polyhalo ketone with base (equation 3)[26] was described several years before Favorskii described a similar rearrangement (equation 4).[27] Simple α,α- and α,α′-dihalo ketones yield the same product (Scheme 14),[28] so dibromination can be followed by Favorskii rearrangement without purification. These rearrangements are usually stereospecific, though subsequent *cis* to *trans* isomerization, under the influence of base, often obscures this feature. Various explanations have been provided for this stereospecificity, but the one due to Rappe (illustrated in Scheme 15) seems most plausible.[29]

(3)



(4)

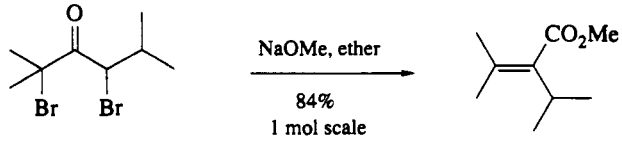
Scheme 14



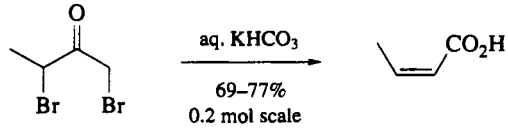
probable conformation

Scheme 15

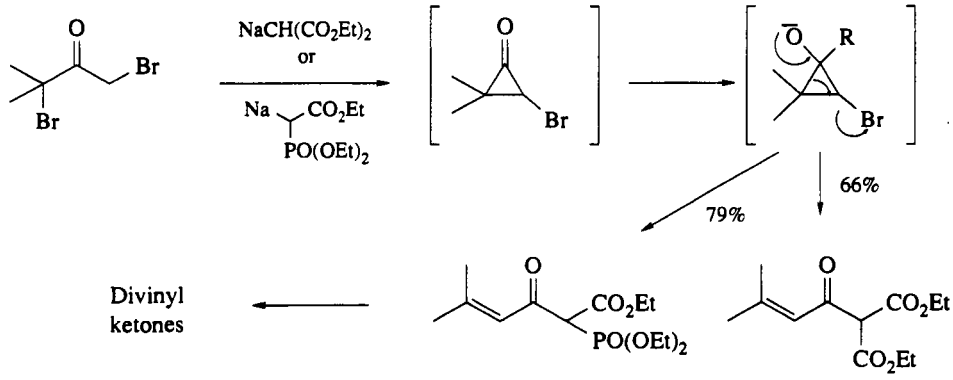
The reactions of polyhalo ketones often proceed in good yield, and the examples shown in equations (5) and (6) are typical.[30,31] Favorskii-type rearrangements of α,α′-dihalo ketones with enolates of diethoxyphosphinylacetic esters[32] or with sodiomalonates,[33] have provided useful routes to divinyl ketones and conjugated enones respectively (Scheme 16). Most of this chemistry is of a general nature, but a reaction that provides a key intermediate for the elaboration of an analog of obtusilactone (**4**) is shown in Scheme 17.[34] These analogs are of interest because the parent lactone (R = H) has antitumor activity. Finally, the tribromo ketones (**5**) undergo base-induced rearrangement and elimination to yield conjugated dienes (**6**) with a high (*Z*)-stereoselectivity (Scheme 18).[35]



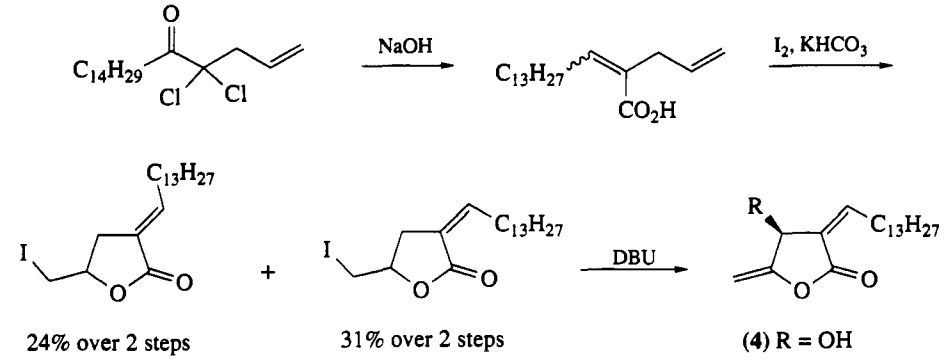
(5)



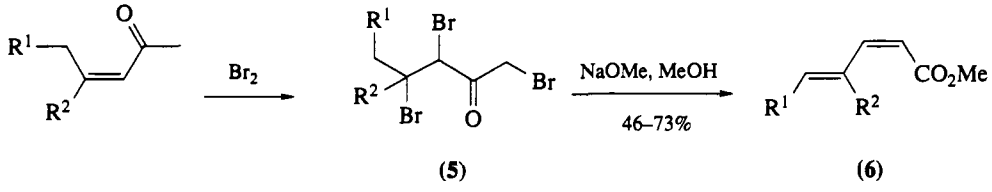
(6)



Scheme 16



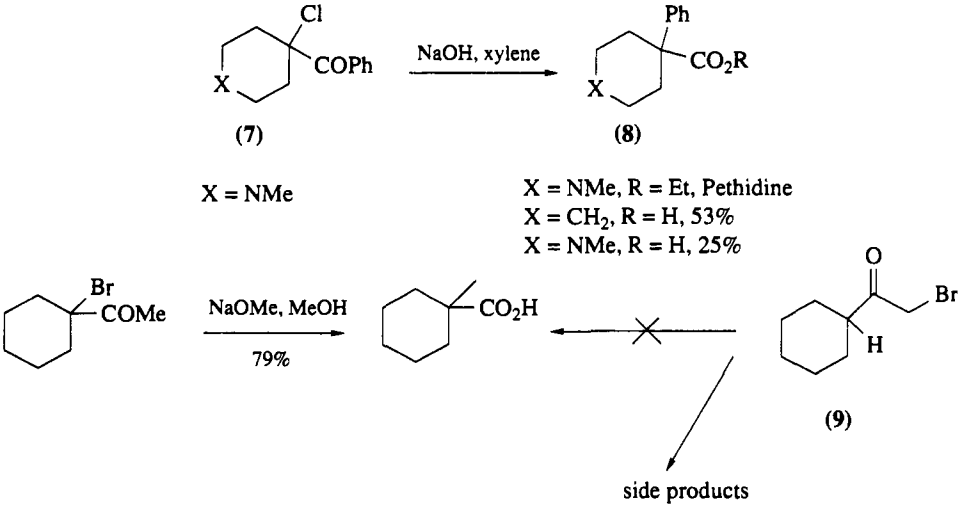
Scheme 17



Scheme 18

3.7.3.2 α-Halocycloalkyl Ketones

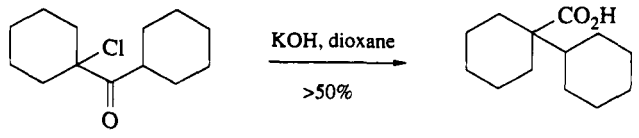
The reactions of monohalocycloalkyl ketones are of considerable interest because they allow access to cycloalkylcarboxylic acids; the rearrangements shown in Scheme 19 are examples. When pure stereoisomers were employed, complete racemization resulted, suggesting the intermediacy of ion pairs.[36] This methodology has been used for the synthesis of the potent analgesic pethidine (**8**) from the piperidyl ketone (**7**).[37] The lack of products from bromomethyl cyclohexyl ketone (**9**) was ascribed to a slow (rate-determining) removal of hydrogen to produce a tertiary carbanion, thus allowing competing side reactions to occur.[38]



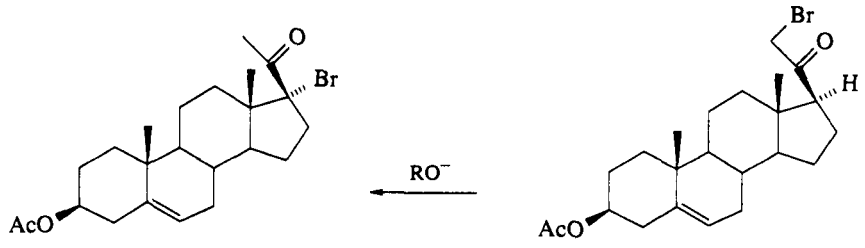
Scheme 19

Relatively inaccessible cycloalkylcarboxylic acids can be produced *via* these Favorskii rearrangements (for example equation 7),[39] and they have been especially useful for the introduction of alkyl groups at C-17 of the steroid nucleus. Thus the pregnenolones (**10**) and (**11**) can be converted into mixtures of rearrangement products (**12**) and (**13**), with the latter usually predominating in polar, protic solvents (Scheme

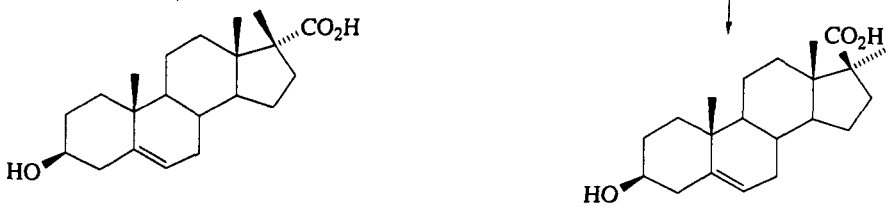
20).[40] The potent progestin (**14**) and the relatively inactive cortisone analog (**15**) have been prepared *via* this strategy.[41,42]



(7)



(**10**) (**11**)



(**12**) (**13**)

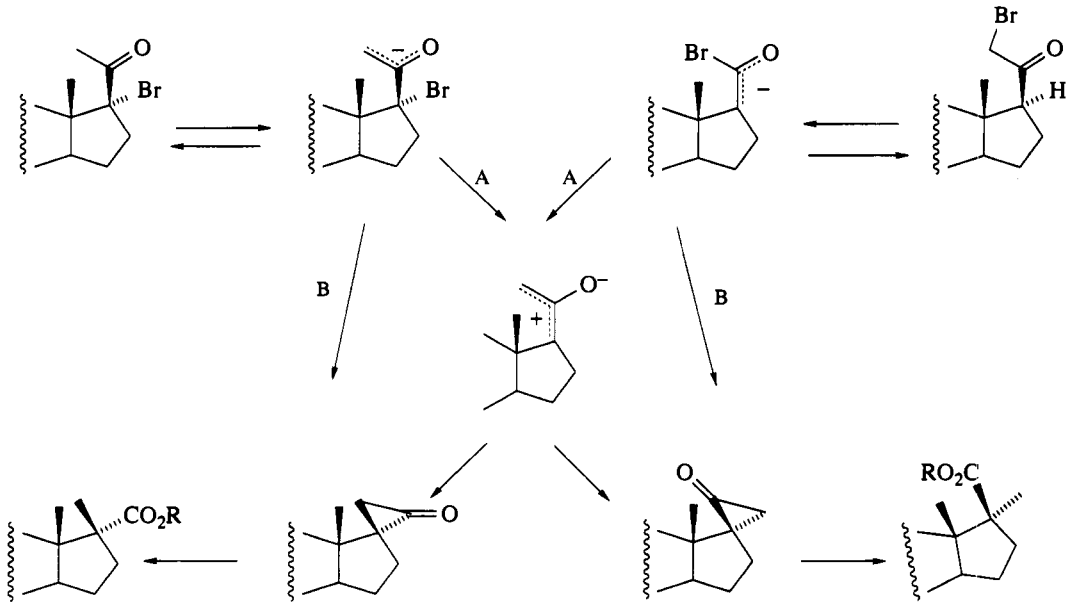
(**14**) (**15**)

Scheme 20

When a nonprotic, though relatively polar, solvent, such as dimethoxyethane, was employed, the 17-α-bromopregnenolone yielded primarily the 17-β-methyl product; these results have been rationalized as shown in Scheme 21.[43] The 17-α-bromo steroid and the 21-bromo steroid are converted *via* separate concerted processes into discrete stereoisomeric cyclopropanones; these transformations are in competition with the formation of the common dipolar species which can yield both stereoisomers. However, one of these will usually be favored on steric grounds, and the rearrangement can thus proceed with a high degree of stereoselectivity. The steric effect of having a 12-α-substituent or substituents at C-16 has been probed, and the result is a lowering of stereoselectivity observed in polar aprotic solvents.[44,45]

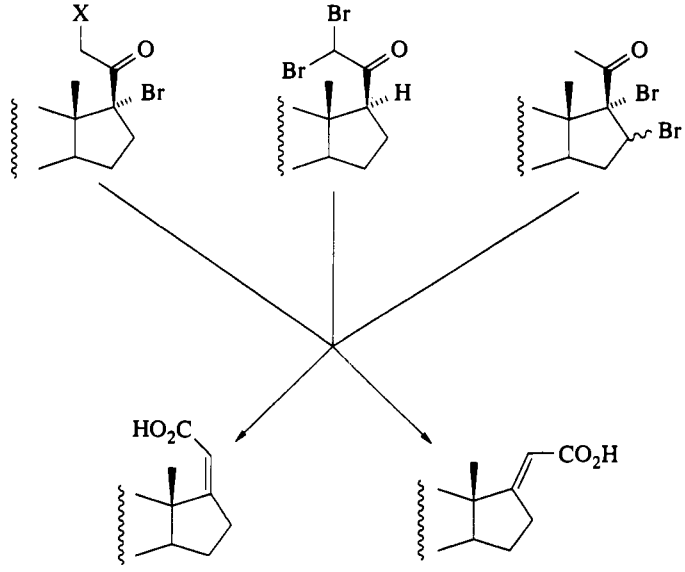
With dihalogenated analogs of these steroids, rearrangement yields the anticipated products in high yield (Scheme 22),[46] and these unsaturated acids are appropriately substituted for elaboration of the steroid side chain.

Finally, the related trihalogenated steroids produce α-bromo acids, and the example shown in equation (8) is representative.[47]

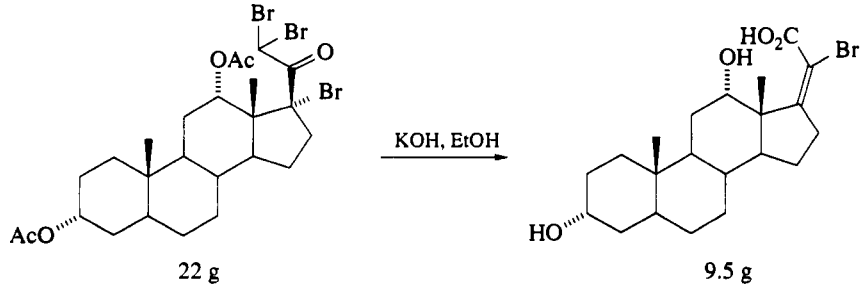


A is a polar, protic solvent; B is an aprotic, medium polarity solvent

Scheme 21



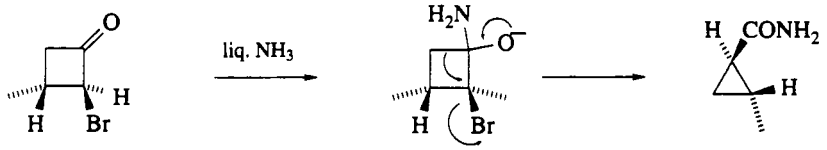
Scheme 22



22 g 9.5 g (8)

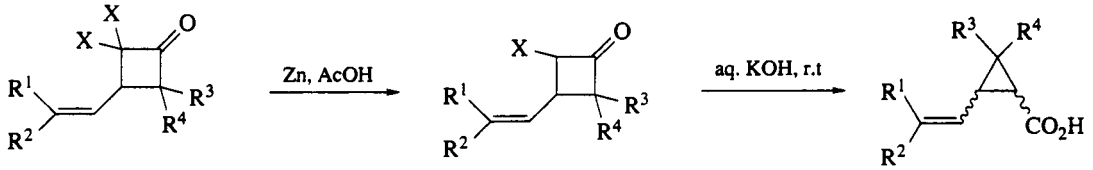
3.7.3.3 Monocyclic Halo Ketones

Favorskii rearrangements have been reported with alicyclic and heterocyclic bromocycloalkanones containing 4–13 (but not 5) atoms in the rings. The important mechanistic studies with 2-bromocyclobutanone have already been mentioned (Scheme 10),[17] and Scheme 23 contains a summary of other results obtained by Conia and coworkers.[17,48] Of particular note is the fact that the rearrangement will even proceed with water as reagent, and that the stereospecificity observed is consistent with a mechanism involving (as expected) inversion of configuration at the carbon center initially attached to the bromine atom.

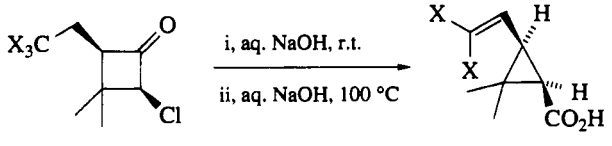


Scheme 23

Reactions of this type have been much employed for the construction of cyclopropane carboxylic acids that are appropriately functionalized for elaboration into the commercially important pyrethroid insecticides (Scheme 24 and equation 9).[49,50] The stereospecificity observed in the second report is of particular note given the superior potency of the *cis*-pyrethroids.



Scheme 24

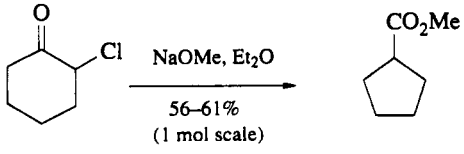


(9)

X	%	*cis:trans*
Cl	86	83:17
Br	84	85:15

No Favorskii rearrangement products are produced when α-halocyclopentanones are treated with base, and products of aldol, substitution and dehydrohalogenation reactions are produced. However, when an α-halocyclopentanone is part of certain condensed systems, cubane derivatives may be obtained (see Section 3.7.3.5).

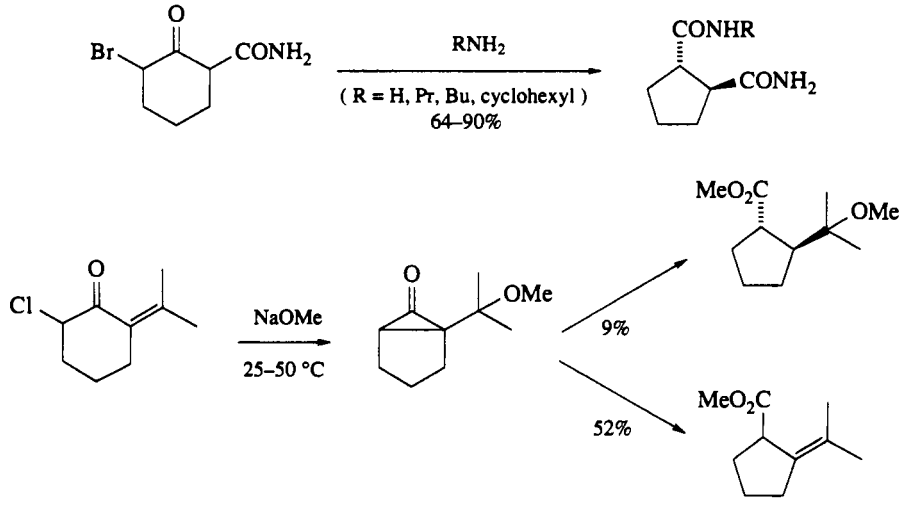
The reactions of α-halocyclohexanones have been most thoroughly studied, and the reaction shown in equation (10),[51] carried out on the molar scale, is an example. In general the chloro compounds provide larger yields than the bromo and fluoro analogs, and branched-chain aliphatic alkoxides are claimed to be the most effective bases.[7]



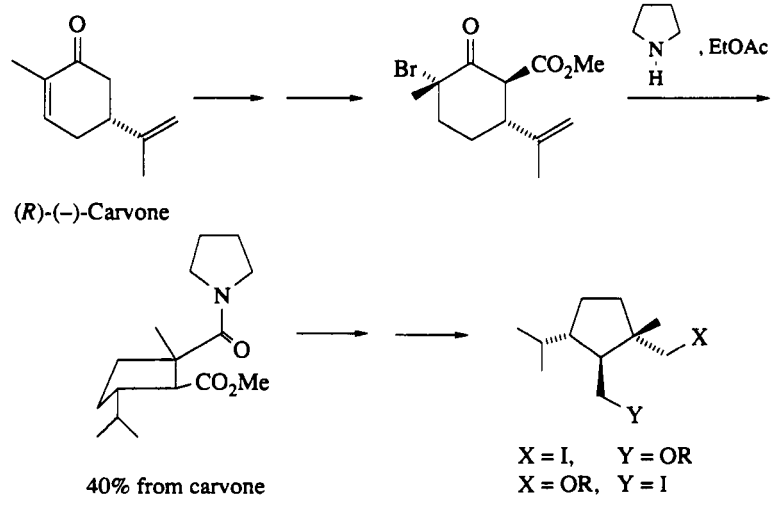
(10)

The synthetic potential of these reactions can be illustrated by their use for the construction of polyfunctionalized cyclopentanecarboxylic acids and derivatives (Scheme 25).[52–54a] The Michael-induced

Favorskii rearrangement is of note, as is the use of carvone as a chiral starting material,[54b] and the annelation procedure that follows the rearrangement shown in Scheme 26.[55]

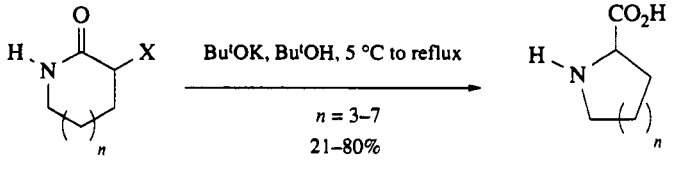


Scheme 25



Scheme 26

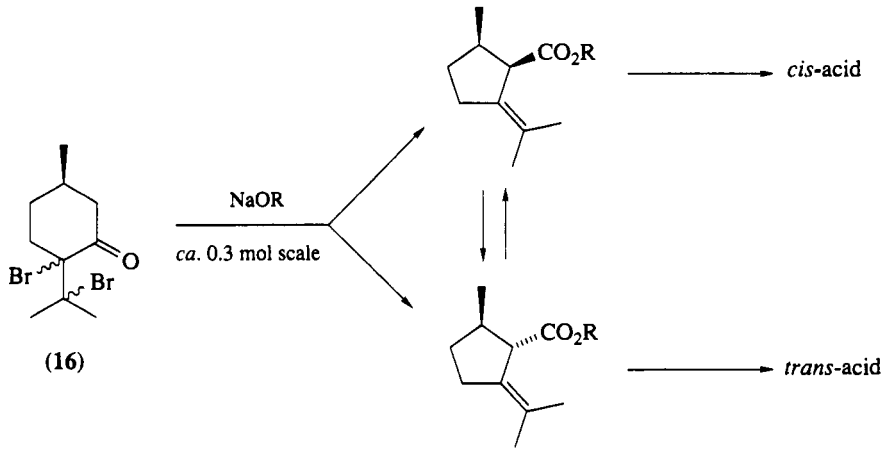
The corresponding rearrangements of higher homologs are also well documented (*e.g.* 2-chlorocyclododecadienone[56] and 2-bromocycloundecanone)[57] as are the base-induced rearrangements of heterocyclic haloalkanones, such as the conversion of halolactams into proline and homologs (equation 11).[58] In addition, the rearrangement of 2-chlorocaprolactam has been reported on the 3.5 mol scale.[59]



(11)

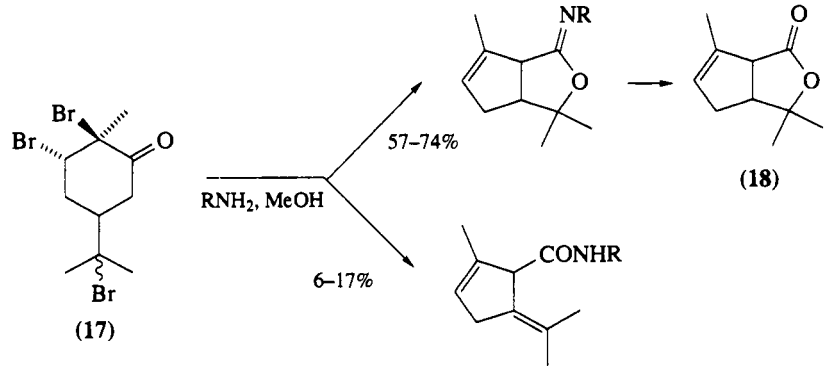
When polyhalocycloalkanones are employed the anticipated products are almost invariably obtained, and the reactions of polybromomonoterpenes are of particular synthetic value. Dibromination of pulegone produced dibromo ketone (**16**), and reaction of this (on a 0.3 mol scale) produced the results shown in Scheme 27.[60] The *trans*-acid usually predominates because there are steric constraints to the hydrolysis of the *cis*-ester. The related tribromomonoterpene (**17**) provides access to carvenolide (**18**;

Scheme 28)[61] and both rearrangement processes have potential utility for the construction of cyclopentanoid monoterpenes, *e.g.* the iridolactones which are important as constituents of insect defensive secretions.



aq. NaOH, *cis*:*trans* ≈ 1:1; NaOEt, EtOH, *cis*:*trans* ≈ 0:100

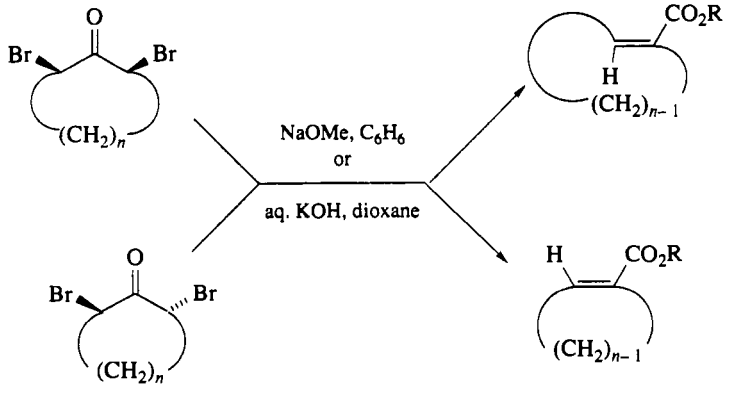
Scheme 27



R = Et, Pr^i, Pr^n, allyl, cyclohexyl

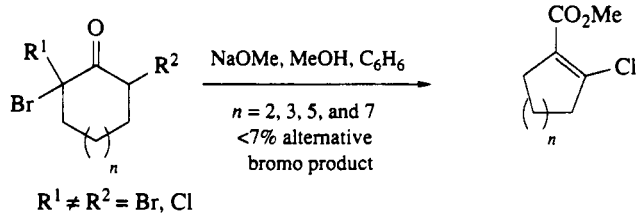
Scheme 28

Larger ring polyhalocycloalkanones behave in a predicatable fashion. Thus 2,8-dibromocyclooctanone yields cyclohept-1-enecarboxylic acid in 96% yield when treated with aqueous NaOH, and 2,2,8-tribro-



Scheme 29

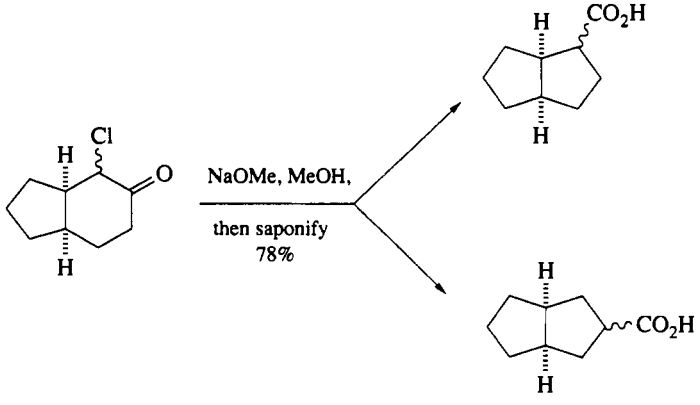
mocyclooctanone when treated with ethanolic sodium ethoxide yields 2-bromocyclohept-1-enecarboxylic acid in 83% yield.[62] The results obtained with dibromo- undecanones and -dodecanones are shown in Scheme 29.[63] Finally, when various dibromomonochlorocycloalkanones are treated with sodium methoxide, there is an almost exclusive preference for displacement of bromide rather than chloride (equation 12).[64]



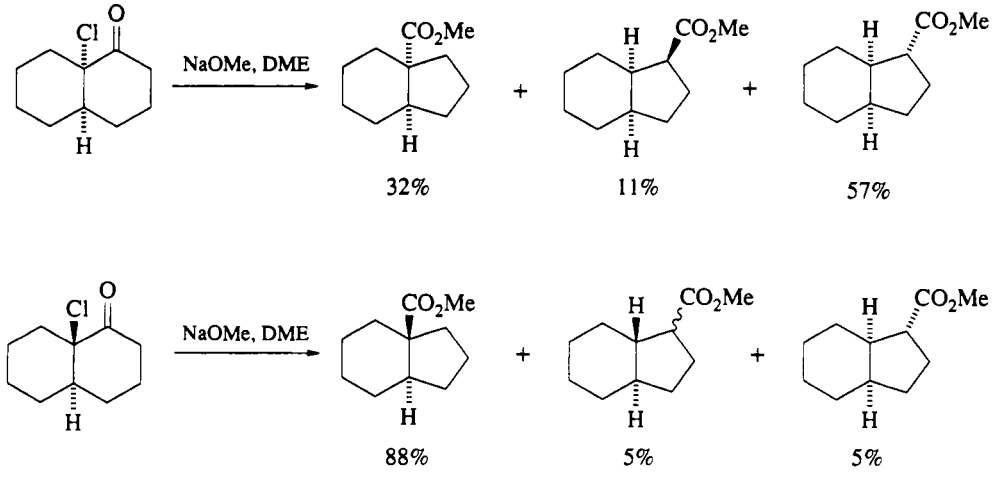
(12)

3.7.3.4 Bicyclic Halo Ketones

Cis-fused 5,6- and *cis*-fused 6,6-bicyclic halo ketones undergo Favorskii rearrangements to produce 5,5- and 6,5-bicyclic ring systems, respectively. The *trans*-5,6-bicyclic system does not yield rearranged products, presumably due to steric constraints. Representative examples are shown in Schemes 30 and 31,[65,66] and the high degree of retention of stereochemistry at the bridging centers is noteworthy.



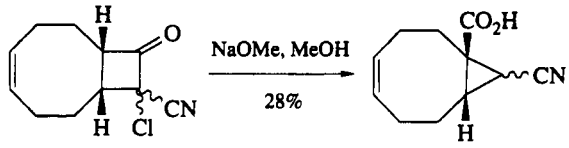
Scheme 30



Scheme 31

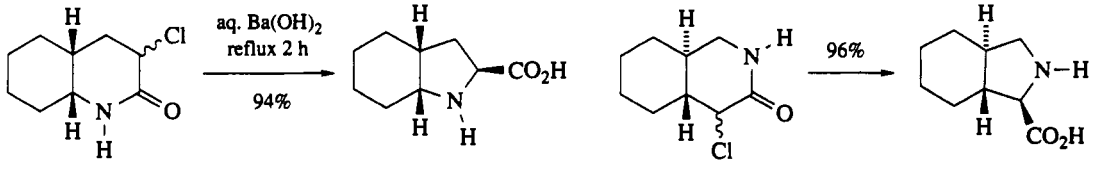
An interesting syn thesis of bicyclo[*n*.1.0] systems is shown in equation (13),[67] though the yields for $n = 6$ are rather poor. Of more preparative use is the chemistry illustrated in Scheme 32,[68] by which bicy-

clic analogs of proline may be prepared. These were required as components of potential inhibitors of angiotensin-converting enzyme. Once again a high degree of diastereoselectivity was observed.



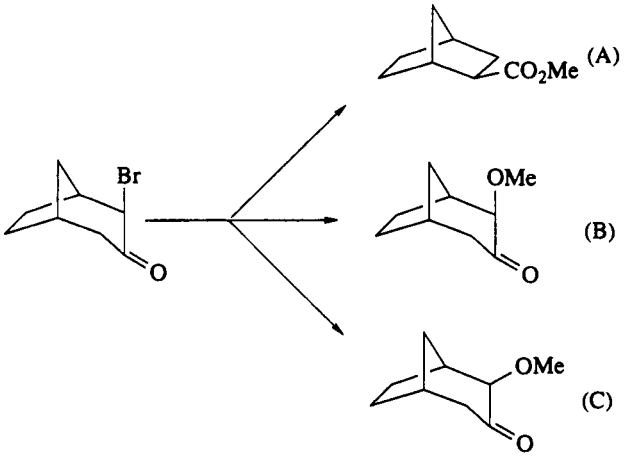
(13)

Saturated 6,4-system, 62%
Saturated 8,4-system, 12%



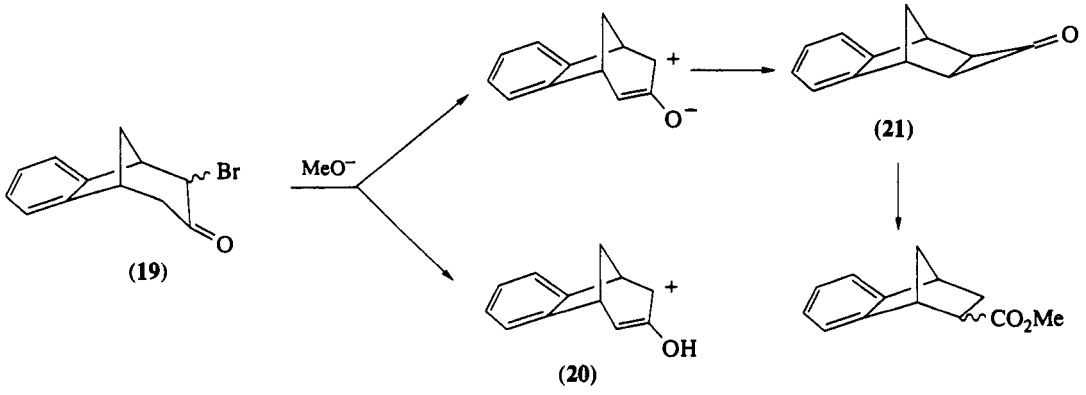
Scheme 32

With nonfused bicyclic systems, most reactions have been carried out with compounds containing a bridgehead halogen; though the chemistry of 2-bromobicyclo[3.2.1]octan-3-ones has provided interest-



NaOMe, MeOH, A, 10%, B, 5%, C, 74%; NaOMe, DME, A, 76%, *endo* ester, 24%

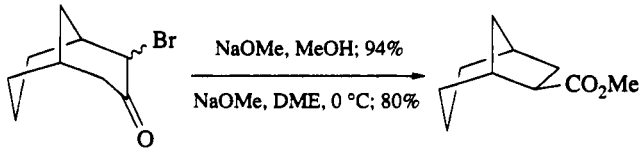
Scheme 33



Scheme 34

ing mechanistic results (Scheme 33).[69,70] A preponderance of the solvolysis products is obtained when methanol is used as solvent, whilst dimethoxyethane favors the Favorskii rearrangement. Protonation of the intervening enolate or zwitterion would disfavor formation of a cyclopropanone, and favor attack at the carbocation by methoxide. Interestingly, both equatorial and axial bromides of the related fused benzobicyclo[3.2.1]octanone (**19**) react with sodium methoxide to provide good yields of Favorskii rearrangement products (Scheme 34).[71] The greater facility of this reaction has been attributed to the inherent instability of the bishomoantiaromatic carbocation (**20**), which would favor the alternative formation of the cyclopropanone (**21**), and resultant Favorskii rearrangement.

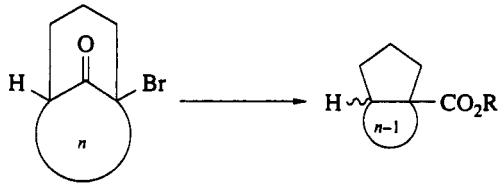
A mixture of the 2-bromobicyclo[3.3.1]nonan-3-ones (**22**) rearranges with great stereoselectivity and good yield to the *exo*-ester (**23**; equation 14).[72]



(14)

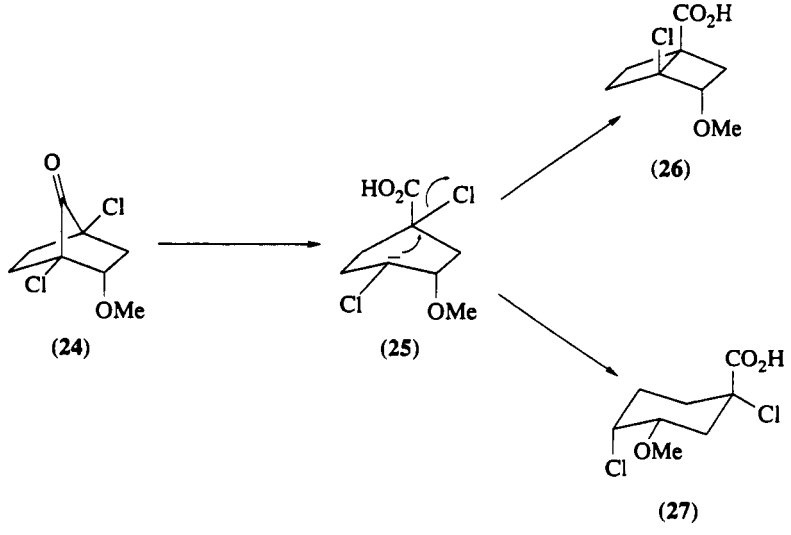
(**22**) (**23**)

Most other systems studied have bridgehead halogens, and special attention has been paid to the reactions of the kind shown in Scheme 35. The yields of rearrangement products are uniformly good, and deuterium incorporation results imply that the semibenzilic mechanism operates for the smaller ring



i, n = 6, Bu^{t}OK, Bu^{t}OD; R = Bu^t, 94%, 0.026 atoms D incorporated
ii, n = 7, NaOMe, MeOD; R = Me, 96%, 0.00 atoms D incorporated
n = 7, Bu^{t}OK, Bu^{t}OD; R = Bu^t, 67%, 0.83 atoms D incorporated
iii, n = 8, NaOD, EtOD, D_2O; R = H, 88%, 0.90 atoms D incorporated

Scheme 35



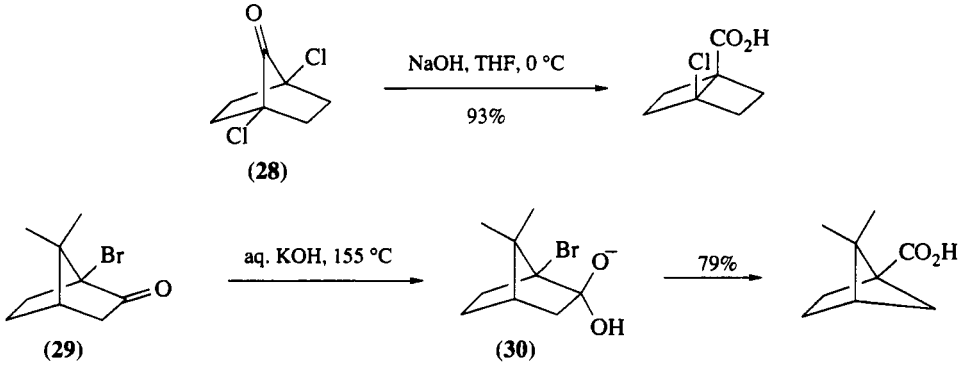
NaOH, THF, (**26**):(**27**) = 89:11
aq. NaOH, (**26**):(**27**) = 64:36

Scheme 36

sizes, whilst a cyclopropanone is implicated for the larger ring size (*cf.* Schemes 4 and 5). This is reasonable since Bredt's rule would suggest a difficult enolization for the ring systems with $n = 6$ and 7. When stronger base (*t*-butoxide) was employed, the cyclopropanone pathway apparently also operates for the system with $n = 7$.[73]

Compound (**24**), with two bridgehead chlorines, yields the bicyclo[2.2.0] acid (**26**) and the cyclohexanecarboxylic acid (**27**). The relative proportion of the latter was increased when water was present, presumably because there was more quenching of the intermediate anion (**25**; Scheme 36).[74]

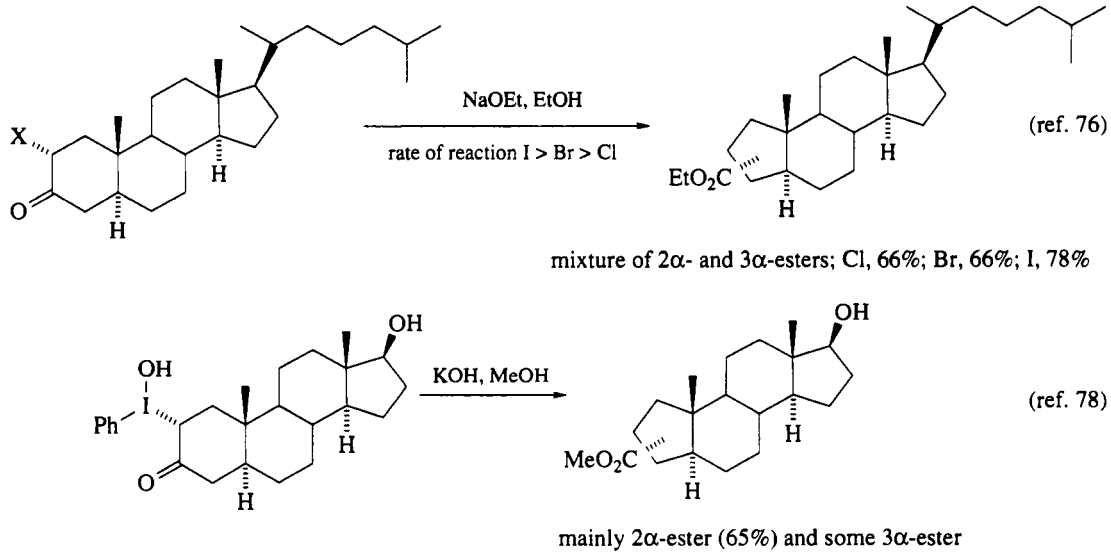
The related dihalo ketone (**28**) rearranges smoothly at 0 °C, whilst bromo ketone (**29**) requires prolonged heating at 155 °C (Scheme 37).[75] This is anticipated, since formation of the intermediate (**30**) required for the semibenzilic mechanism is sterically disfavored.



Scheme 37

3.7.3.5 Polycyclic Halo Ketones

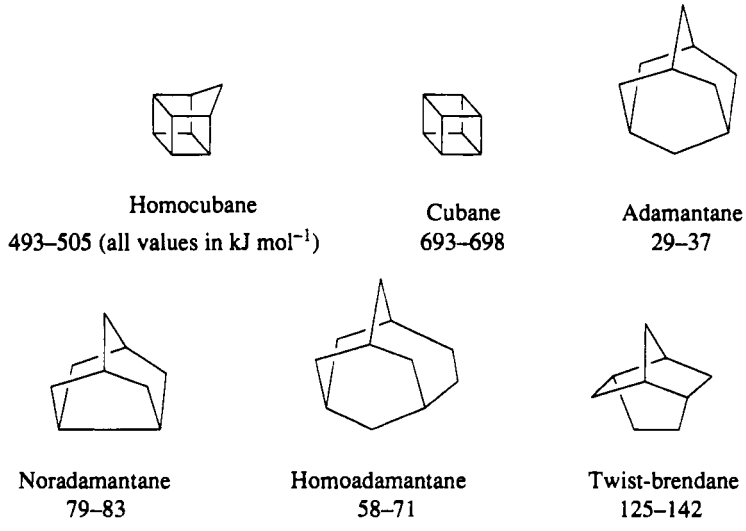
In terms of synthetic utility these rearrangements fall into two major classes: (i) reactions of halo steroids and related systems; and (ii) reactions that yield cage-like structures. Reactions of the first type are exemplified by the rearrangements illustrated in Scheme 38.[76–78]



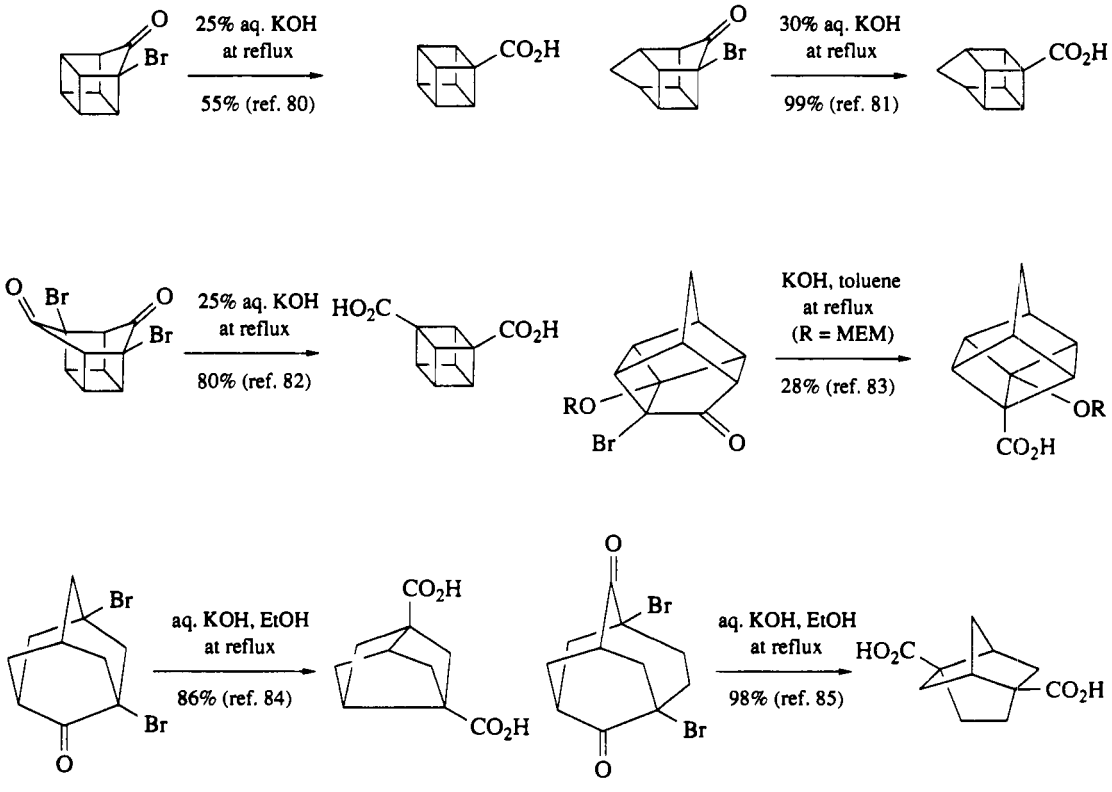
Scheme 38

The rearrangements of cage-like structures have been discussed in some detail in refs. 11 and 12, and can be divided into three main classes: (i) homocubane to cubane; (ii) adamantane to noradamantane; and (iii) homoadamantane to twist-brendane; and these are depicted (together with strain energy estimations from ref. 79) in Scheme 39. It can be seen that in each case rearrangement provides a system with

greater strain, and the Favorskii reaction thus allows access to strained structures that would be otherwise inaccessible. Typical examples are shown in Scheme 40.[80–85]

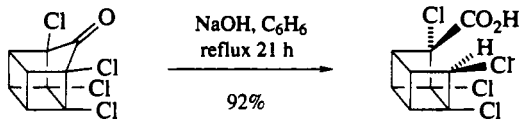


Scheme 39



Scheme 40

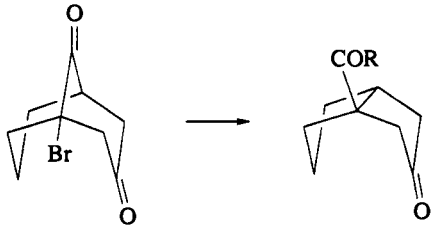
It is interesting to note that with the homocubane derivatives it is the cyclopentanone ring that contracts, whilst this process has never been observed in simple halocyclopentanones. A semibenzilic mechanism probably operates in most cases, since the requisite cyclopropanones are unlikely to be produced. Ring-opened products are not infrequent side products, and they are favored products when highly halogenated precursors are employed (Scheme 41).[86] The intermediate carbanions are stabilized by the electron-withdrawing halogens, and these lead to products that are less strained than the usual cage products.



Scheme 41

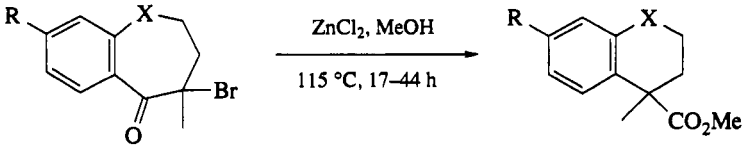
3.7.3.6 Miscellaneous

All of the examples described thus far have involved the use of bases to initiate the Favorskii rearrangements. However various Lewis acids have also been used for this purpose. An early example of this methodology is shown in Scheme 42.[87] The Lewis acid promoted ring contractions depicted in Scheme 43[88] and Scheme 44[89] are also Favorskii-type rearrangements.



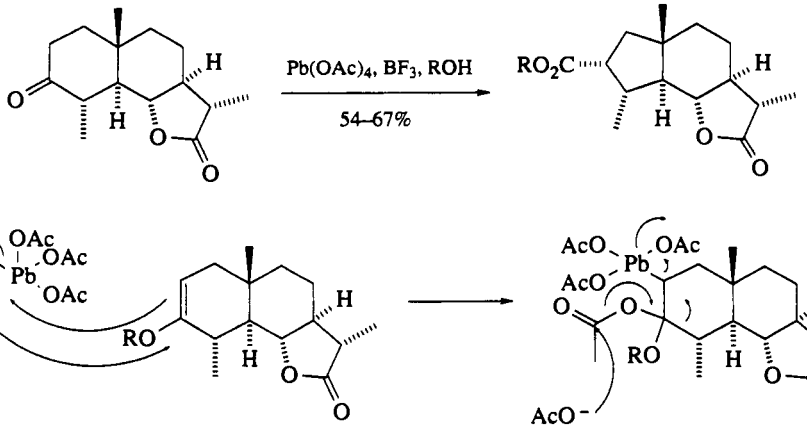
KOH, Et_2O, R = OH, 34%; Na, liq. NH_3, R = NH_2, 68%; $AgNO_3$, aq. EtOH, R = Et, 11%; R = OH, 61%; $Hg(OAc)_2$, EtOH, R = Et, 71%

Scheme 42



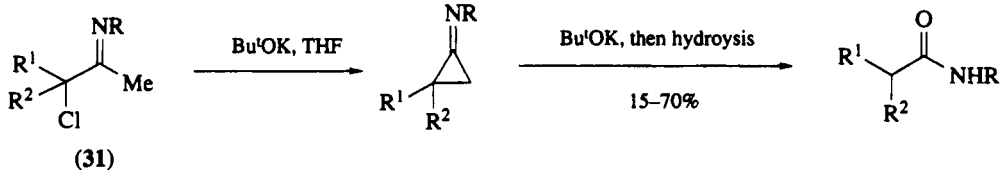
R	OMe	H	OMe	H
X	CH_2	CH_2	O	O
%	61	91	44	22

Scheme 43



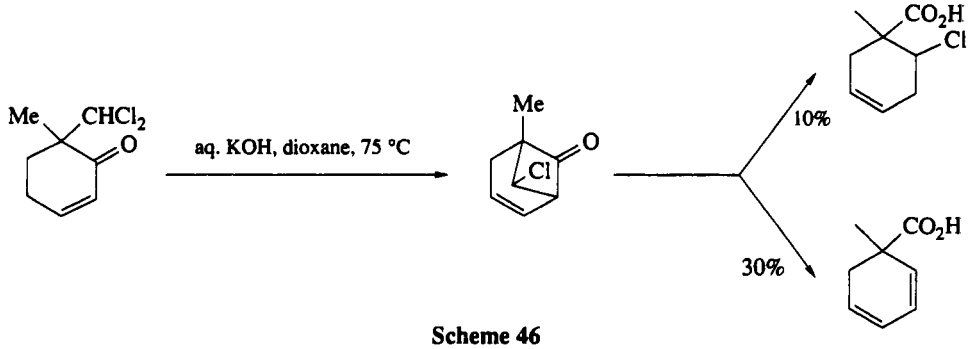
Scheme 44

The Favorskii-type rearrangements of chloroenamines such as (**31**) have received some investigation, and key results are presented in Scheme 45.[90] Finally, the so-called homo-Favorskii rearrangement has been probed, and an example from the original work of Wenkert and coworkers is illustrated in Scheme 46.[91] A partially successful homo-Favorskii rearrangement carried out on the diterpenoid (**32**; a derivative of virescenol A) is shown in Scheme 47,[92] but the synthetic potential of this variant of the Favorskii rearrangement remains to be established.

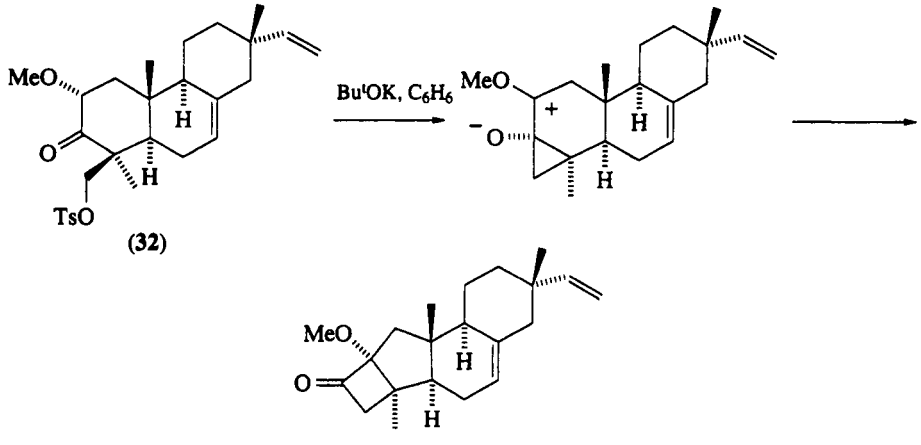


R^1 = Me, Ph; R^2 = H, Me; R = Pr^i, Bu^t, Ph, cyclohexyl

Scheme 45



Scheme 46



Scheme 47

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3.8
The Ramberg–Bäcklund Rearrangement

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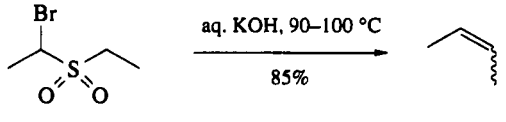
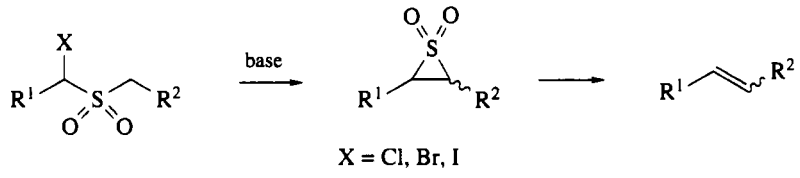
3.8.1 INTRODUCTION

In 1940, Ramberg and Bäcklund reported a new and surprising reaction, *i.e.* that on treatment with an excess of aqueous KOH, α-bromoethyl ethyl sulfone was converted in high yield into 2-butene (equation 1).[1] α-Chloroethyl ethyl sulfone reacts in the same way, although more slowly. Also surprising was the stereoselectivity of this reaction; bromination of the 2-butene was found to give racemic 2,3-dibromobutane, showing that the (*Z*)-isomer predominated. Since that time, this transformation, now known as the Ramberg–Bäcklund rearrangement, or simply as the Ramberg–Bäcklund reaction, has been used to synthesize a wide variety of alkenes. It is now understood to take place *via* 1,3-elimination of halide from the sulfone α-anion, and loss of SO_2 from the resulting thiirane 1,1-dioxide (Scheme 1).



(1)



Scheme 1

The Ramberg–Bäcklund reaction has been reviewed several times previously,[2] and brief reviews have appeared as recently as 1988.[3] The classic and most comprehensive review was written by Paquette in 1977[4] and, though still extremely useful, particularly with respect to mechanism and the preparation of the α-halo sulfone precursors, it is now, of course, rather out of date. Two older reviews[5,6] are still worth citing because they discuss the mechanism of the reaction in great detail.

3.8.2 SCOPE AND IMPORTANT USES OF THE REACTION

The Ramberg–Bäcklund reaction can be used to synthesize mono-, 1,1- or 1,2-di-, tri- and tetra-substituted alkenes, including alkenes substituted with a variety of functional groups. Despite the (*Z*)-stereoselectivity obtained with acyclic α-halo sulfones under the original conditions of Ramberg and Bäcklund, the reaction is most useful where stereoisomeric alkenes cannot occur because high stereocontrol is not a general feature. Nevertheless, very high (*E*)-stereoselectivity can be achieved in favorable circumstances, especially with functionalized alkenes.

One of the great strengths of the reaction is that there is no ambiguity about the position of the newly introduced double bond; it is fixed by the position of the sulfone group in the precursor, and never migrates under the reaction conditions. Good examples are shown in equations (3) and (29), and in Scheme 20.

The reaction is extremely useful for preparing strained cycloalkenes, particularly cyclobutenes. The success of such reactions stems from the fact that they are not ring forming, but involve contraction of a less-strained saturated ring.

Thiols may be converted into alkenes with one extra carbon atom by successive chloromethylation, oxidation at sulfur, and Ramberg–Bäcklund rearrangement. If the original thiol is prepared by free radical addition of H_2S to an alkene, the sequence constitutes a one-carbon homologation of alkenes. Although these transformations were at one time important applications of the Ramberg–Bäcklund reaction,[4,5] they have hardly been used in recent years.

Incorporation of deuterium at the vinylic positions of alkenes can be carried out very efficiently by performing the Ramberg–Bäcklund reaction in D_2O. Finally, the recently developed 'Michael-induced' and 'vinylogous' modifications of the Ramberg–Bäcklund reaction offer useful approaches to conjugated dienes and polyenes.

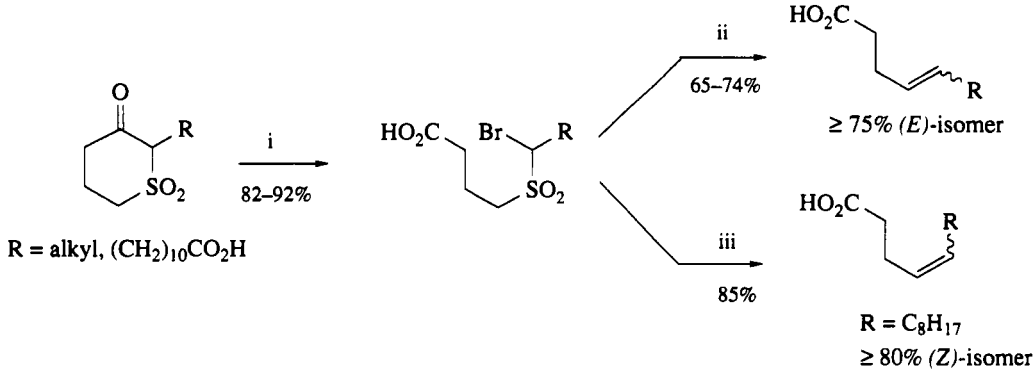
3.8.3 PREPARATION OF PRECURSORS: α-HALO SULFONES

α-Halo sulfones are most commonly prepared by successive oxidation and halogenation (or *vice versa*) of the corresponding sulfides. These, and other methods, have been described in detail by Paquette,[4] while more recent reviews give numerous ways to prepare sulfones[7] and α-halo sulfides.[8] Representative pathways to α-halo sulfones are shown in the schemes throughout this review.

3.8.4 REACTION CONDITIONS

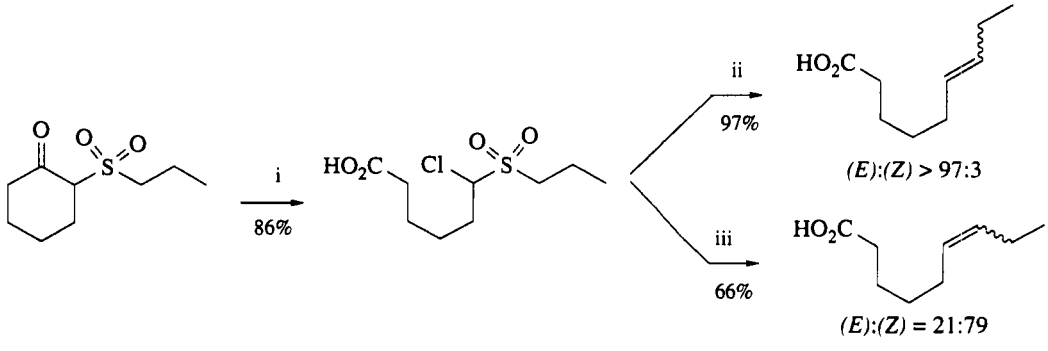
The first rearrangements of α-halo sulfones were performed using aqueous hydroxide, and these conditions are still frequently used. However, the rearrangement takes place in a wide variety of base–solvent systems and the yield and stereochemical outcome are often strongly dependent on the conditions chosen. The work of Scholz, in which he uses the reaction to prepare a variety of alkenes with remote carboxy groups, usefully illustrates this point. Examples are shown in Schemes 2[9] and 3.[10,11] In each case, treatment of a cyclic β-keto sulfone with a hypohalite produces a ring-opened α-halo sulfone bearing a carboxy group; Ramberg–Bäcklund rearrangement then furnishes the unsaturated carboxylic acid.

A systematic survey showed that the stereochemical outcome of these Ramberg–Bäcklund reactions is highly dependent on both the base and the solvent used, while the temperature is relatively unimportant.[11] Whereas aqueous hydroxide favors the (*Z*)-alkenes, very high (*E*)-stereoselectivity can be achieved in favorable circumstances using Bu^{t}OK in DMSO. Scholz has also reported reactions analogous to those shown in Scheme 3 involving five- or seven-membered cyclic substrates.[12] An acyclic version gives simple alkenes as products, since the carboxy group is lost during halogenation.[13]



i, Br_2, aq. NaOH, 0 °C, 2 h; ii, Bu^{t}OK, Bu^{t}OH, reflux, 4 h; iii, aq. KOH, 100 °C, 3 h

Scheme 2

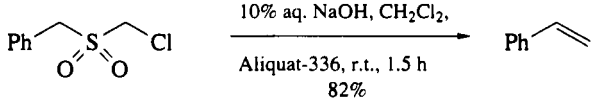


i, NaOCl, NaOH, aq. EtOH, 0 °C to r.t., 15 h; ii, Bu^{t}OK, DMSO, r.t., 12 h; iii, 0.5 M aq. NaOH, 100 °C, 18 h

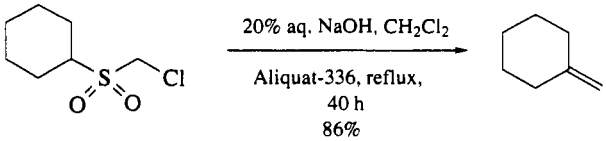
Scheme 3

The Ramberg–Bäcklund reaction using hydroxide as base can also be performed under phase-transfer conditions, the rate of reaction varying markedly from one substrate to another (equations 2 and 3).[14] One advantage of using these conditions is that ester groups are not hydrolyzed (equation 4; compare equation 46).

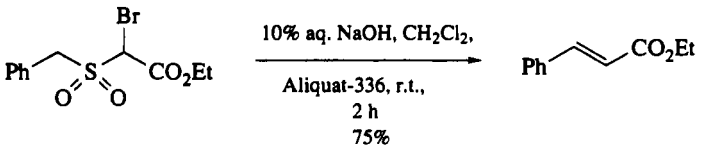
Without doubt, the most important modification of the Ramberg–Bäcklund reaction is the result of the work of Meyers. In 1969, he reported that a suspension of powdered KOH in a mixture of CCl_4 and Bu^{t}OH is a powerful chlorinating system for a variety of compounds with acidic methylene groups.[15]



(2)



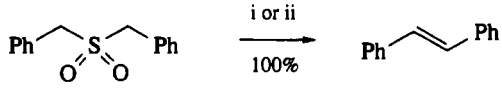
(3)



(4)

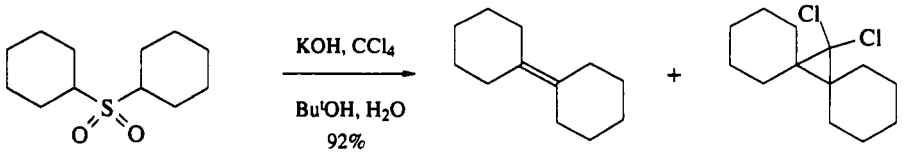
Sulfones with α-hydrogens, for example, are converted into α-chloro sulfones on treatment with this mixture of reagents. More interesting, however, is the observation that α-chloro sulfones are formed but cannot be isolated from reactions of sulfones with both α- and α′-hydrogens; instead, further reaction, often Ramberg–Bäcklund rearrangement, takes place in the basic reaction medium. Clearly, the ability to convert sulfones into alkenes in one operation, circumventing a separate halogenation step, is extremely useful. Furthermore, the reagents required for this reaction are easy to handle, readily available and are easily separated from the reaction products. For these reasons, Meyers' variant of the Ramberg–Bäcklund reaction has been used with great frequency, and many examples appear later in this chapter. Meyers himself has written two excellent reviews on this subject.[16,17]

Numerous experiments support the following mechanism for the chlorination of sulfones under Meyers' conditions. Reaction takes place at the surface of the KOH, where a small concentration of Bu^{t}OK is maintained and is responsible for converting the sulfone into its α-anion. This anion transfers an electron to a molecule of CCl_4 to form an intimate 'caged' radical/radical anion pair in which transfer of a chlorine atom is effected by nucleophilic attack of the substrate radical on a chlorine of the CCl_4 radical anion. The by-product of this process is the trichloromethyl anion, which can eject chloride to give dichlorocarbene. If the α-chloro sulfone has an α′-hydrogen, further reaction takes place, the course of which depends on the relative rates of 1,3-elimination (which leads *via* a thiirane 1,1-dioxide to the Ramberg–Bäcklund alkenes) and further chlorination (which leads *via* an α,α-dichloro sulfone to the salt of an alkenesulfonic acid).[18] With dibenzyl sulfones, 1,3-elimination clearly predominates since they are converted in high yield into stilbenes (equation 5).[15,19] Di-*s*-alkyl sulfones give tetrasubstituted alkenes, although these often react further with dichlorocarbene to give dichlorocyclopropanes (equation 6).[15] Fortunately, this side reaction can be suppressed by the addition of a suitable carbene trap such as phenol or an inexpensive nucleophilic alkene. Simple acyclic di-primary-alkyl sulfones normally give alkenesulfonates rather than the Ramberg–Bäcklund products (equation 7),[17,20] although branching at the β-position can divert the course of the reaction to give alkenes (Scheme 4).[21] Primary- or *s*-alkyl benzhydryl sulfones give 1,1-diarylalkenes very efficiently, while primary-alkyl benzyl sulfones give mixtures of β-alkylstyrenes and alkenesulfonates.[22] Whichever type of sulfone is used as substrate, carbonyl and primary or secondary hydroxy groups must be protected since they are reactive under Meyers' chlorinating conditions.[15,16,23]



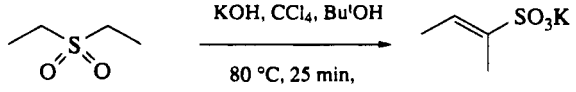
(5)

i, KOH, CCl_4, Bu^{t}OH, H_2O, 60–80 °C, 10–60 min (ref. 15); ii, KOH, CCl_4, CH_2Cl_2, H_2O, cat. $(PhCH_2)Et_3N^+Cl^-$, 24 h (ref. 24)

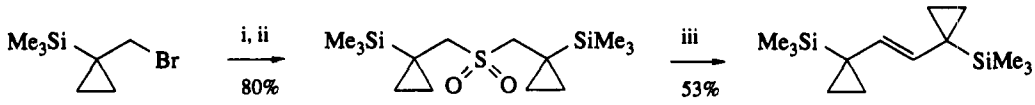


35% 65%

(6)



(7)

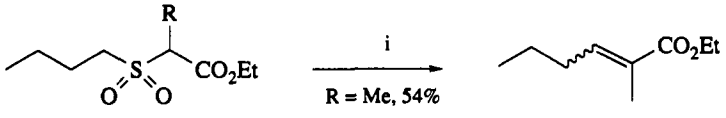


i, $Na_2S{\cdot}9H_2O$, EtOH, heat; ii, MCPBA, $NaHCO_3$, $CHCl_3$; iii, KOH, CCl_4, Bu^tOH, 50 °C

Scheme 4

Meyers' method has been modified to allow it to be operated under phase-transfer conditions.[14,24] This is a convenient way of converting dibenzyl sulfones directly into (*E*)-stilbenes (equation 5), but it is not so useful for less reactive substrates.

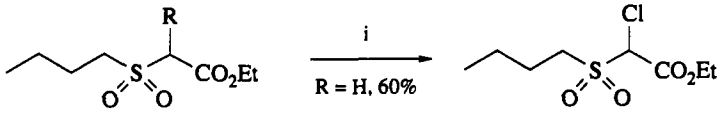
Vedejs has developed a method for the conversion of α-substituted-α-alkoxycarbonyl sulfones directly into α,β-unsaturated esters, whereby chlorination and Ramberg–Bäcklund rearrangement occur consecutively in the same reaction vessel (equation 8).[25] The α-substituent is crucial; without it, the reaction stops after chlorination, presumably because formation of the wrong anion is so strongly favored (equation 9).[25] Cyclic α-alkoxycarbonyl sulfones are particularly good substrates for this reaction (equation 10)[25] and several examples have been reported.[26] In some cases, the rearrangement is slow, and yields are improved if the α-alkoxycarbonyl-α-chloro sulfone is isolated and treated with Bu^tOK in a separate step.[25,27] Although similar to Meyers' variant of the Ramberg–Bäcklund reaction, Vedejs' method is not applicable to simple unactivated sulfones, which are recovered unchanged.



(8)

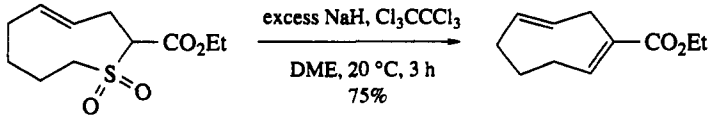
(E):*(Z)* = 1:1

i, excess NaH, Cl_3CCCl_3, DME, 20 °C



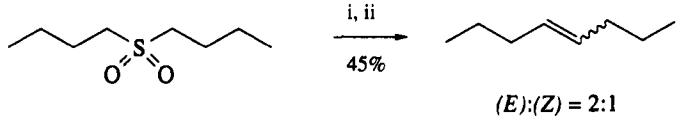
(9)

i, excess NaH, Cl_3CCCl_3, DME, 20 °C



(10)

Sulfones may also be converted directly into alkenes by oxidation of their α,α′-dianions with copper(II) chloride; the intermediate thiirane 1,1-dioxides extrude SO_2 under the reaction conditions (equation 11; compare equation 47).[28]



(11)

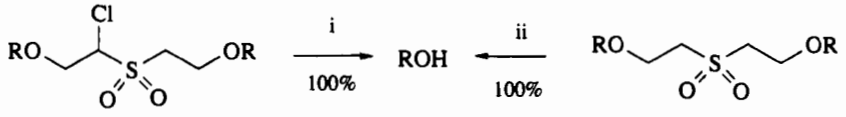
(E):*(Z)* = 2:1

i, 5 equiv. Bu^nLi, DME, 0 °C or below; ii, 5 equiv. $CuCl_2$, r.t.

3.8.5 COMPATIBILITY OF FUNCTIONAL GROUPS

Ramberg–Bäcklund reactions are always performed under basic conditions, and sulfones containing incompatible functional groups must obviously be protected. Carbonyl groups, for example, may be

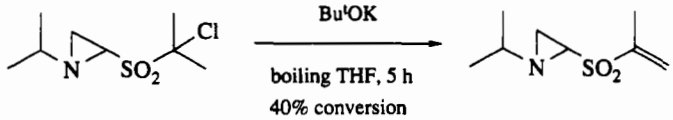
protected as acetals (*e.g.* Scheme 21). Certain functional groups may undergo 1,2-elimination under the reaction conditions (*e.g.* equation 24), and if this affects the α-halo sulfone, Ramberg–Bäcklund rearrangement may be prevented from taking place (Scheme 5[29] and equation 12[30]). Further examples of undesirable competing 1,2-elimination are shown in Scheme 18 and equation (25). The α-chloro sulfone (**1**) undergoes 1,2-elimination when treated with an excess of KOH, but with 1 equiv. an intriguing Ramberg–Bäcklund-like rearrangement involving a 1,7- (instead of the usual 1,3-) elimination step takes place (Scheme 6).[16,17,31]



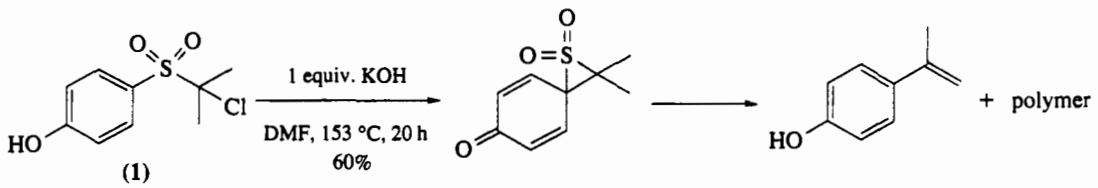
R = n-$C_{12}H_{25}$

i, Bu^{t}OK or NaOMe or NaOH in THF, 0 °C; ii, Bu^{t}OK, CCl_4, THF

Scheme 5



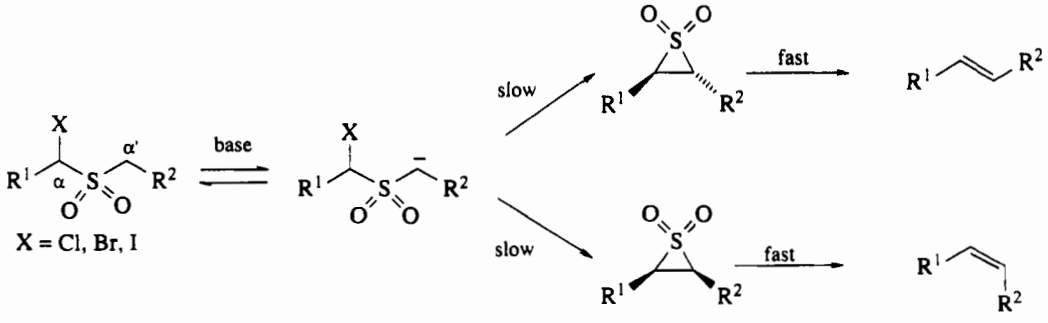
(12)



Scheme 6

3.8.6 MECHANISM OF THE REACTION

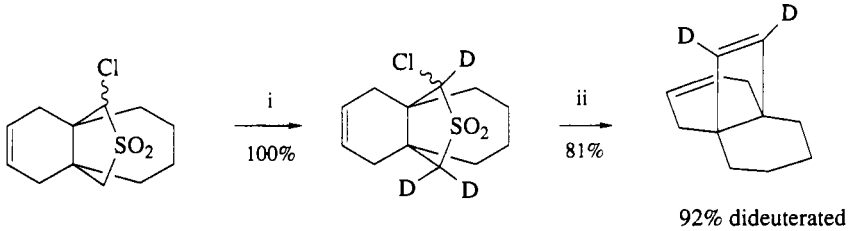
It is now widely accepted that α-halo sulfones are converted into alkenes under the basic conditions of the Ramberg–Bäcklund reaction *via* intermediate thiirane 1,1-dioxides (Scheme 7). Experimental data in support of this mechanism were first put forward by Bordwell in 1951,[32] and extensive studies carried out since that time, particularly by Bordwell and Paquette in the late 1960s and early 1970s, have substantiated this overall scheme and have provided further insight into the mechanisms of the individual steps. Very little additional work concerning the mechanism of the reaction has been published since 1975. Consequently, only a summary of the essential features is presented here, and readers are referred to the detailed reviews, written by the leaders of the key research groups themselves, for the full data which support the following broad outline.[4–6]



Scheme 7

The transformation of an α-halo sulfone into an alkene takes place in three steps (Scheme 7). Step 1 involves reversible formation of the α′-anion. Under the basic reaction conditions, there is a rapid equilibration of the α-halo sulfone with its α- and α′-anions. Only the α′-anion leads to step 2 which is intramolecular displacement of a halide ion to give a thiirane 1,1-dioxide, generally as a mixture of *cis* and *trans* isomers. This is the rate-limiting step. Finally, in step 3, the thiirane dioxides lose SO_2 to give the stereoisomeric alkenes. This transformation can take place *via* two distinct pathways; one is thermal, while the other involves base catalysis. Both pathways are stereospecific; *trans*- or *cis*-thiirane 1,1-dioxides give only (*E*)- or (*Z*)-alkenes, respectively. Consequently, the stereochemical outcome of the overall reaction is determined at the ring-forming step 2.

Strongest evidence for a rapid equilibration of the α-halo sulfone with its α- and α′-anions comes from reactions performed in D_2O. If such reactions are interrupted before they are complete, the recovered α-halo sulfones are almost fully deuterated at both the α- and α′-positions. Furthermore, the alkene products are also essentially fully deuterated, this time at the vinylic positions. When allowed to run to completion, this forms the basis of a very useful preparative method for deuterium-labeled alkenes (Scheme 8[33] and equation 24). Not only is a high percentage incorporation possible, but the source of deuterium is very cheap.



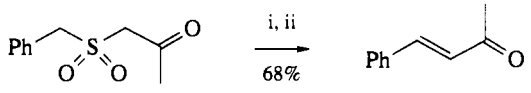
92% dideuterated

i, NaOD, D_2O, dioxane, reflux, 72 h; ii, Bu^tOK, THF, reflux, 4 h

Scheme 8

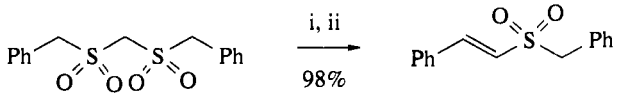
Halogens of α-halo sulfones are remarkably resistant to intermolecular nucleophilic substitution due to a combination of steric effects and the large negative field of the oxygen atoms of the sulfonyl group.[34] However, during the Ramberg–Bäcklund reaction, displacement of halide occurs in an intramolecular sense, leading to diastereomeric thiirane 1,1-dioxides. These intermediates are not normally deprotonated under the reaction conditions. However, if one or both of the groups R^1 or R^2 (Scheme 7) stabilizes an adjacent negative charge, or if a very strong base is used, reversible deprotonation and hence equilibration of the diastereoisomeric thiirane dioxides can occur. Under such circumstances, the ratio of (*E*)- to (*Z*)-alkenes does not reflect the ratio of first-formed thiirane dioxides. Instead, (*E*)-stereoselectivity can be rather high, the simple result of the greater stability of the *trans*-thiirane dioxide intermediate. For example, α,β-unsaturated ketones, sulfones and acids of (*E*)-configuration are formed when the appropriate sulfone precursors are successively brominated and treated with alkoxide (equations 13–15).[35]

The precise mechanisms by which thiirane 1,1-dioxides are converted stereospecifically into alkenes and SO_2 (or products derived from SO_2) are not clear.[6,36,37] In typical Ramberg–Bäcklund reactions both thermal and base-catalyzed mechanisms are likely to be in operation, with the latter generally predominating. The importance of the base-catalyzed pathway accounts for the fact that thiirane 1,1-dioxides



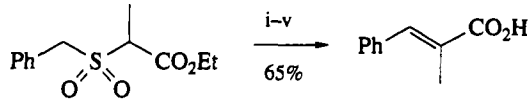
(13)

i, Br_2, aq. K_2CO_3, $CHCl_3$; ii, NaOMe, MeOH, reflux, 0.5 h



(14)

i, Br_2, aq. K_2CO_3, $CHCl_3$; ii, NaOMe, MeOH, reflux, 0.5 h



(15)

i, NaH, benzene, reflux, 10 min; ii, Br_2, benzene, 10 °C; iii, NaOEt, EtOH, reflux, 0.5 h; iv, KOH, EtOH, reflux, 10 min; v, H_3O^+

have never been isolated from Ramberg–Bäcklund reactions. Nevertheless, they can be prepared by quite independent methods,[38] and it is samples obtained in this way which have allowed their properties, such as the stereospecificity of their decomposition to alkenes, to be established.

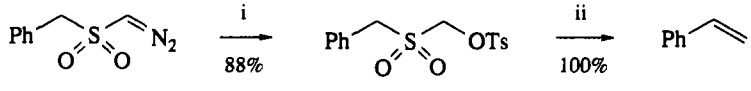
Finally, no definitive mechanistic explanation has been given for one of the most intriguing aspects of the Ramberg–Bäcklund reaction, the fact that acyclic α-halo sulfones consistently give products rich in the (*Z*)-isomer.[4,6]

3.8.7 RELATED REACTIONS

3.8.7.1 Replacement of the Halide

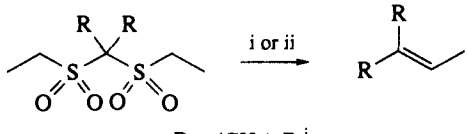
Variations of the Ramberg–Bäcklund reaction have been described in which the usual halide ion is replaced by *p*-toluenesulfonate or *p*-toluene-, alkane- or trifluoromethane-sulfinate leaving groups. For example, Meyers has described a single transformation of the Ramberg–Bäcklund type of an α-tosyloxy sulfone (Scheme 9).[39] The reaction is surprisingly slow, nearly 1000 times slower than that of the corresponding α-chloro sulfone under the same conditions, and this, of course, limits its value in synthesis. Another problem is the fact that the precursors are not easy to prepare.

An example of sulfinate functioning as a leaving group is shown in equation (16),[40] while another forms the basis of a useful synthesis of 3-cyclopentenones (Scheme 22). Zwanenburg has reported a transformation related to the Ramberg–Bäcklund reaction in which the halide leaving group is replaced by sulfinate and, in addition, the usual sulfone is replaced by sulfoxide.[41]



i, *p*-TsOH, $ClCH_2CH_2Cl$, 25 °C, 2 h; ii, Bu^tOK, Bu^tOH, 25 °C

Scheme 9



$R = (CH_2)_2Pr^i$

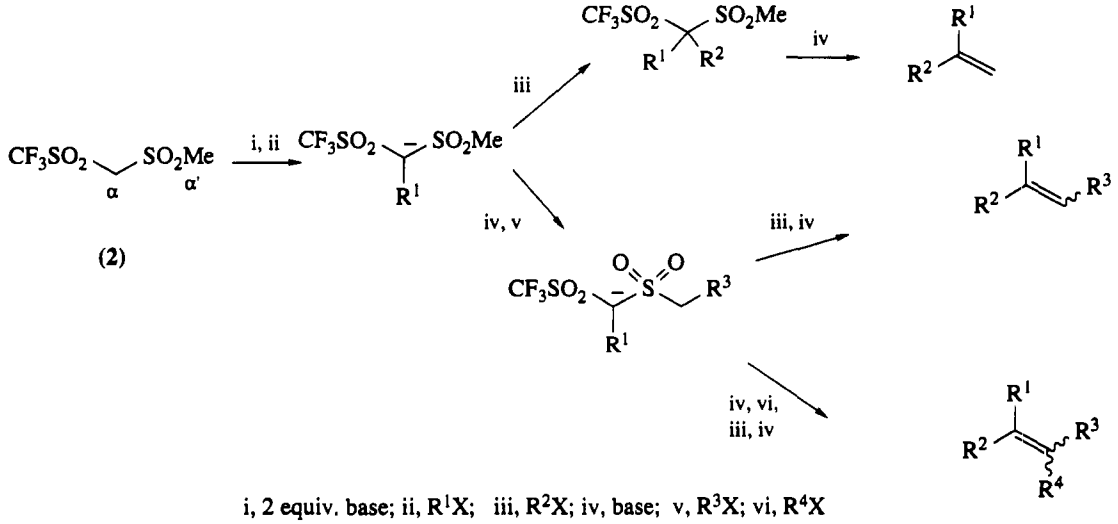
(16)

i, 10% aq. NaOH, 250 °C, 24 h (33%); ii, $LiAlH_4$, Et_2O, 24 h (61%)

More useful from a synthetic point of view than any of these variations is the discovery by Hendrickson that trifluoromethanesulfinate ('triflinate') is a very effective leaving group in Ramberg–Bäcklund reactions.[42–44] The reaction succeeds only if the precursors, α-triflyl sulfones, are fully substituted at the α-position; if they are not, simple deprotonation occurs under the basic reaction conditions because the triflyl group is so strongly electron withdrawing. Consequently, this approach is applicable only to the synthesis of 1,1-di-, tri- and tetra-substituted alkenes.

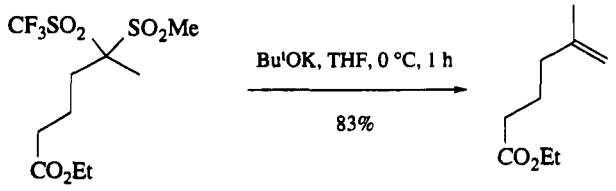
The precursors for this reaction can be prepared by multiple alkylations of mesyltriflone (**2**); this can be carried out with a high degree of regiocontrol and, in fact, is facile enough to allow several successive operations in one vessel (Scheme 10).[44] The α-proton of mesyltriflone is so acidic that treatment with

1 equiv. of base (*e.g.* K_2CO_3) leaves an α-monoanion which is very stable and difficult to alkylate. Interestingly, a second equivalent of base (usually Bu^nLi) abstracts the second α-hydrogen in preference to an α′-hydrogen to give an α,α-dianion which can be monoalkylated without danger of over reaction. If required, further successive treatments with Bu^nLi and alkyl halides can be used to introduce either one or two alkyl groups at the α′-position, the α-anion protecting the molecule from premature Ramberg–Bäcklund rearrangement when the α′-anions are formed. Alternatively, the α,α′-dianions can be acylated at the α′-position in high yield by reaction with acid chlorides, anhydrides, esters or chloroformates. (In these reactions, an extra equivalent of base, typically LDA, is added since the β-keto sulfone products are more acidic than the starting sulfones.) Finally, the second α-position is alkylated (this can be performed only with very reactive alkylating agents and requires elevated temperatures), and treatment with another equivalent of base triggers the Ramberg–Bäcklund rearrangement. Optimum conditions depend on the nature of the substrate. For simple alkylated compounds, Bu^tOK is generally the base of choice (equation 17). Formation of cyclic disulfones as by-products can be a problem, especially with trialkyl compounds (equation 18).[44] For α′-acylated substrates, the reaction proceeds smoothly on heating with K_2CO_3 (*e.g.* Scheme 11, which shows a synthesis of dihydrojasmone),[43] or on treatment with sodium hydroxide under phase-transfer conditions (*e.g.* Scheme 12, which shows the simplest reported synthesis of artemisia ketone).[44]

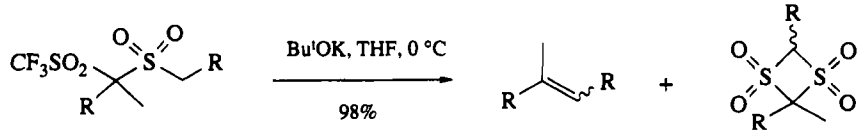


i, 2 equiv. base; ii, R^1X; iii, R^2X; iv, base; v, R^3X; vi, R^4X

Scheme 10



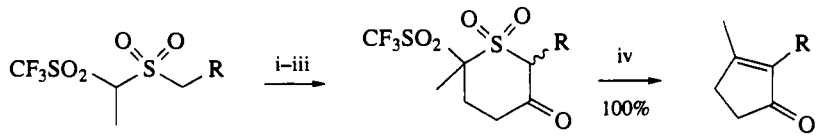
(17)



(18)

R = *n*-pentyl

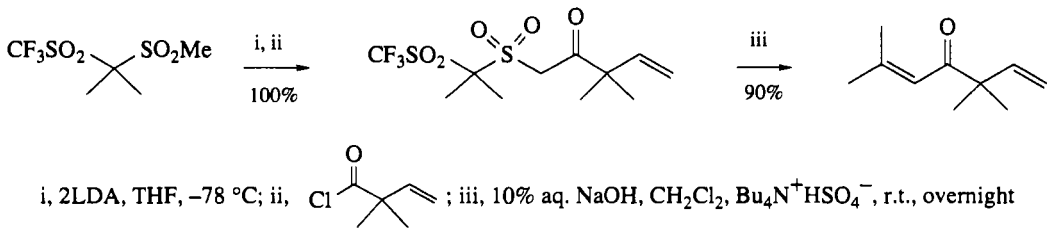
(*E*):(*Z*) = 2.2:1; 46% *trans*:*cis* = 3:2; 54%



R = *n*-pentyl

i, 2 equiv. Bu^{n}Li, THF, –78 °C; ii, H_2C=CHCHO; iii, CrO_3, aq. acetone, 0 to 5 °C; iv, 2 equiv. K_2CO_3, THF, reflux, 3 to 5 h

Scheme 11



i, 2LDA, THF, –78 °C; ii, ; iii, 10% aq. NaOH, CH_2Cl_2, $Bu_4N^+HSO_4^-$, r.t., overnight

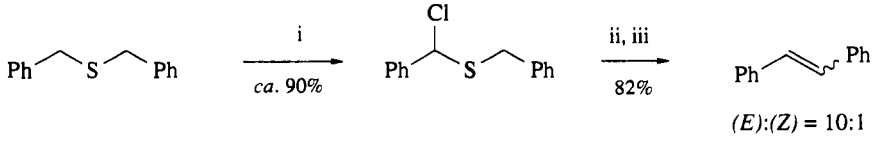
Scheme 12

As usual, no significant stereocontrol is observed with these transformations. The alkylation of the mesyltriflone (**2**), although highly regioselective, generally gives diastereoisomeric mixtures of products, which are converted during the Ramberg–Bäcklund reaction into (*E*)/(*Z*)-mixtures of alkenes. Consequently, the sequence is most useful for the synthesis of compounds where stereoisomers are not possible, such as 1,1-disubstituted alkenes and five- or six-membered cycloalkenes.

3.8.7.2 Replacement of the Sulfone Group

In simple terms, the function of the sulfone group in Ramberg–Bäcklund reactions is first to stabilize an α-anion and then, following 1,3-elimination of halide, to be extruded efficiently from the intermediate thiirane 1,1-dioxide to yield an alkene. In fact, the sulfone group is not unique in its ability to perform these tasks: transformations related to the Ramberg–Bäcklund reaction have been described in which sulfide, sulfoxide, sulfoximine, phosphine oxide,[45] or phosphinate[46] groups replace the familiar sulfone group. On occasions, even α-halo ketones can be diverted from their usual Favorskii rearrangement to give alkenes instead of carboxylic acids. Reactions which are useful for the synthesis of alkenes are discussed in more detail in the following paragraphs.

Mitchell has reported that benzyl α-chlorobenzyl sulfides are cleanly converted into stilbenes on successive treatment with PPh_3 and Bu^{t}OK (Scheme 13).[47] Desulfurization of an intermediate thiirane by PPh_3 is a likely pathway for this reaction. Benzyl α,α-dichlorobenzyl sulfides are converted into diphenylacetylenes under the same conditions.[48] Viehe has reported that pyrolysis of α-halo-α-alkylthio esters, ketones and nitriles under reduced pressure furnishes α,β-unsaturated esters, ketones and nitriles respectively; it is probable that these reactions also take place *via* intermediate thiiranes.[49] α-Chlorophenacyl phenacyl sulfide is converted into (*E*)-dibenzoylethylene on treatment with Et_3N.[50]



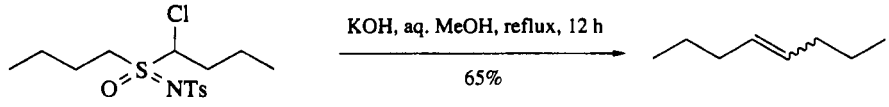
i, SO_2Cl_2, CCl_4; ii, PPh_3, THF; iii, Bu^{t}OK, THF, reflux, 24 to 36 h

Scheme 13

Cyclobutenes can sometimes be prepared more efficiently from five-membered cyclic α-chloro sulfoxides rather than from the corresponding sulfones (*e.g.* Scheme 17).

Johnson has shown that α-halo-*N*-tosylsulfoximines with an α′-hydrogen atom, on treatment with KOH in refluxing methanol, undergo rearrangement to alkenes by analogy with the Ramberg–Bäcklund

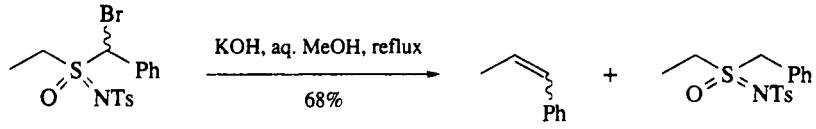
reaction.[51] Surprisingly, alkenes are not formed from the corresponding *N*-H- or *N*-methyl-sulfoximines under these conditions. Two types of *N*-tosylsulfoximine were examined. The first, alkyl-α-chloroalkylsulfoximines, give alkenes as approximately 1:1 mixtures of geometric isomers (equation 19). By contrast, alkyl- or benzyl-α-bromobenzylsulfoximines give predominantly (*Z*)-alkenes, together with significant quantities of sulfoximines resulting from debromination (equation 20). This (*Z*)-stereoselectivity probably stems from equilibration *via* deprotonation of the intermediate 2-phenylepisulfoximines in favor of the isomer in which substituents at the 2- and 3-positions are both *trans* to the bulky tosyl group.



(19)

single unidentified diastereoisomer

(E):*(Z)* = 52:48

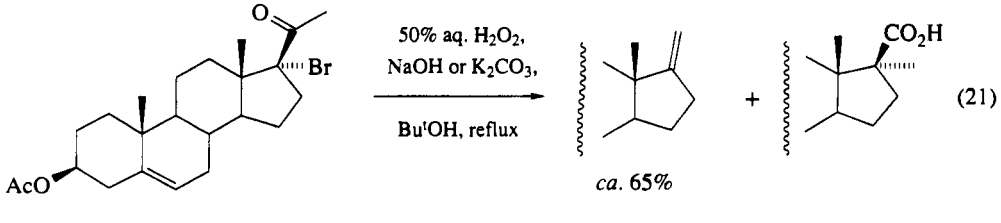


(20)

1:1 mixture of diastereoisomers

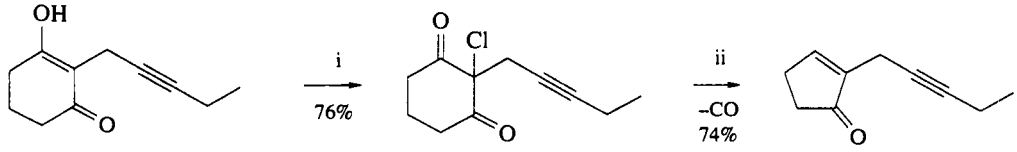
72% *(E)*:*(Z)* = 8:92 28%

Under basic conditions, α-halo ketones with an α′-hydrogen atom generally undergo Favorskii rearrangement *via* cyclopropanones to carboxylic acids. It is clear that while the ring closure step of this transformation resembles that of the Ramberg–Bäcklund reaction, the subsequent ring-opening step does not. However, under certain conditions and with particular substrates, α-halo ketones can be redirected to give alkenes *via* (in some cases formal) loss of carbon monoxide from the intermediate cyclopropanones. An isolated example is shown in equation (21).[52] In this case, the intermediate cyclopropanone reacts with hydroperoxide anion to form an adduct which collapses to the alkene with loss of carbon dioxide and hydroxide ion; the Favorskii acid is a by-product. Far more useful is a preparative method for 2-cyclopentenones based on the ring contraction of 2-chloro-1,3-cyclohexanediones which was discovered by Büchi (Scheme 14)[53] and has since been applied on numerous occasions.[54] The success of this reaction depends on the use of a non-nucleophilic base, which avoids simple dechlorination of the substrate; a systematic survey showed that Na_2CO_3 is the reagent of choice.



(21)

ca. 65%



i, Bu^tOCl, $CHCl_3$, −15 °C; ii, Na_2CO_3, boiling xylene, 12 h

Scheme 14

3.8.8 SYNTHESIS OF CYCLOALKENES

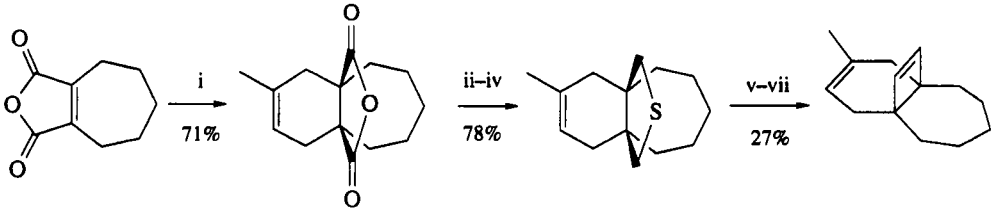
3.8.8.1 Cyclobutenes

In spite of an unpromising early report,[55] the Ramberg–Bäcklund rection has been applied with great success since the early 1970s to the synthesis of cyclobutenes, particularly by Paquette and Weinges. Al-

though yields are often only moderate or low, the reaction still compares favorably with other possible approaches to these strained compounds.

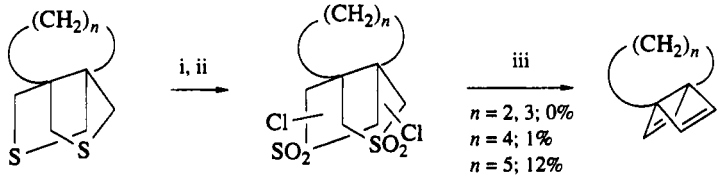
The following general remarks may be made concerning the use of the Ramberg–Bäcklund reaction to prepare cyclobutenes. It is usually performed by treating α-chloro sulfones with an excess of Bu^{t}OK in THF or, less commonly, in dioxane. These precursors are almost always prepared by successive chlorination and oxidation of the corresponding substituted tetrahydrothiophenes. Since the intermediate α-chloro sulfides and α-chloro sulfones are frequently formed as mixtures of regio- and stereo-isomers, it is convenient to use them in a crude form, and to withhold purification until after the Ramberg–Bäcklund reaction itself. The reaction is particularly suitable for the synthesis of cyclobutenes which are unsubstituted at the vinylic positions and fully substituted at the 3- and 4-positions, and the products of the reactions in the following examples are mostly compounds of this type. Meyers' method for the direct conversion of sulfones into alkenes appears not to have been applied to the synthesis of cyclobutenes.[24]

A Diels–Alder reaction with a substituted maleic anhydride followed by a Ramberg–Bäcklund rearrangement are key steps in a reaction sequence which Paquette has used frequently for the synthesis of fused cyclobutenes.[56–58] An example is shown in Scheme 15.[58] Weinges has prepared 1,4-bridged Dewar benzenes using double Ramberg–Bäcklund reactions which introduce both double bonds simultaneously (Scheme 16).[59] Although yields are low, these compounds are difficult to prepare by other methods. The interesting tetracyclic hydrocarbon pterodactyladiene was prepared for the first time using another double Ramberg–Bäcklund reaction (equation 22).[60]



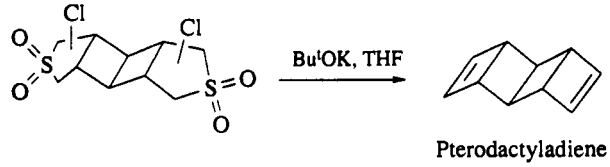
i, isoprene, hydroquinone, dioxane, 170 °C, 68 h; ii, $LiAlH_4$, THF; iii, $MeSO_2Cl$, Py, 0 °C; iv, Na_2S, HMPA, 130 °C, 20 h; v, NCS, CCl_4, reflux, 1 h; vi, monoperphthalic acid, Et_2O, –78 to 0°C; vii, Bu^{t}OK, THF, –78 to 0 °C

Scheme 15



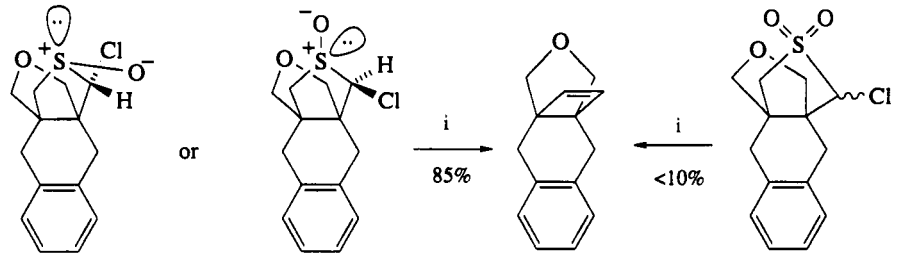
i, NCS, CCl_4, 0 °C, 4 h; ii, monoperphthalic acid, Et_2O, r.t., 2 to 3 d; iii, Bu^{t}OK, THF: for n = 4, –15 °C, 24 h; for n = 5, r.t., 18 h, then reflux, 2 h

Scheme 16



Pterodactyladiene (22)

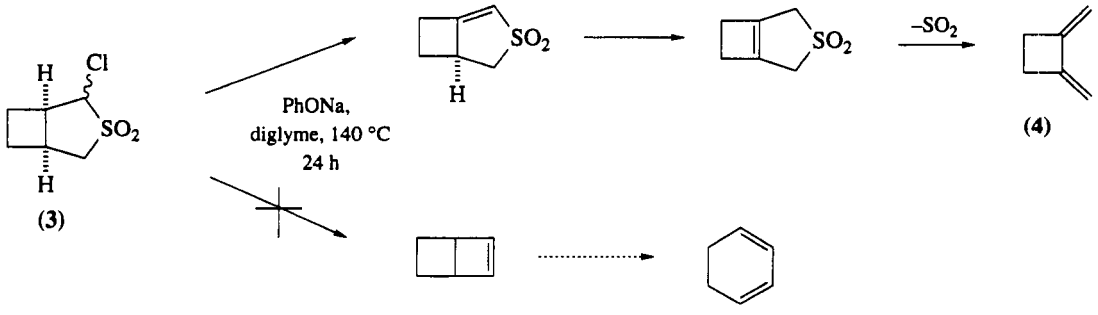
Weinges has discovered that, on occasions, cyclobutenes can be prepared far more efficiently using α-chloro sulfoxides rather than the conventional α-chloro sulfones as precursors (Scheme 17).[61] The course of these reactions is analogous to the usual Ramberg–Bäcklund reaction, proceeding *via* base-catalyzed or thermal elimination of sulfur monoxide from thiirane 1-oxide intermediates.[37] In fact, Weinges was able to isolate such intermediates from some reactions and these were converted into cyclobutenes by treatment with Bu^{t}OK in refluxing THF[62] or with LAH in THF at 55 °C.[63] It is not clear why sulfoxides give better yields than sulfones in these reactions.



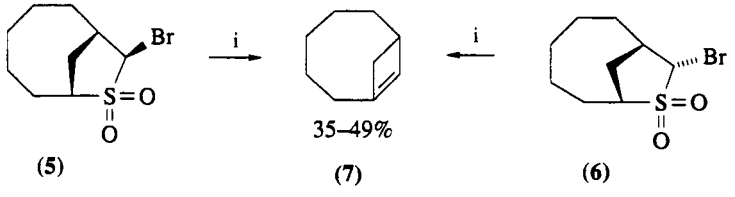
i, Bu^{t}OK, THF, –70 °C to r.t. over 2 h, then 55 °C, 2 h

Scheme 17

As the preceding examples illustrate, most successful applications of the Ramberg–Bäcklund reaction to the synthesis of cyclobutenes involve as precursors 2-halotetrahydrothiophene 1,1-dioxides which are fully substituted at the 3- and 4-positions. Where this is not the case, simple 1,2-elimination of hydrogen halide can compete with the required 1,3-elimination. For example, the simple substrate (**3**) is converted into 1,2-dimethylenecyclobutane (**4**), the product of 1,2-elimination of HCl, rather than the product expected from Ramberg–Bäcklund rearrangement (Scheme 18).[64] Nevertheless, on treatment with Bu^{t}OK, either of the epimeric α-bromo sulfones (**5**) and (**6**) are converted with surprising efficiency into the highly strained cyclobutene (**7**). It is postulated that competing 1,2-elimination of HBr does not occur in these instances because of unfavorable dihedral angles.[65]

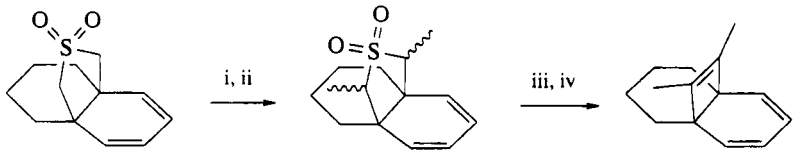


Scheme 18



i, Bu^{t}OK, THF, 5 h at –75 °C then warm to room temperature

Cyclobutenes prepared by the Ramberg–Bäcklund reaction are almost always unsubstituted at the vinylic positions. In 1974, Paquette introduced a related and complementary ring contraction which is particularly suitable for the synthesis of 1,2-dialkylcyclobutenes.[33,57,66,67] The reaction takes place when carbanions of five-membered cyclic sulfones are treated with LAH in refluxing dioxane (Scheme 19).[66] The mechanism of the reaction is not clear. Good yields are obtained only when the sulfone is 2,5-dialkylated; in the absence of these groups, simple reduction of sulfone to sulfide becomes a serious side reaction. Dibenzyl sulfone is converted into a mixture of stereoisomeric stilbenes (56%) and dibenzyl sulfide (23%) under the same conditions.[66]



57% overall yield

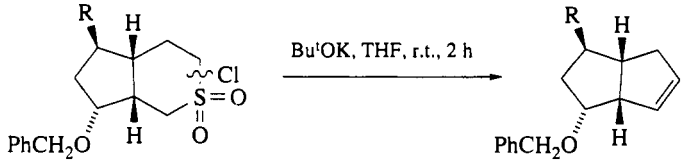
i, 2 equiv. Bu^nLi, THF, –80 °C; ii, excess MeI; iii, Bu^nLi, dioxane, 0 °C; iv, $LiAlH_4$, dioxane, reflux, 6 h

Scheme 19

3.8.8.2 Cyclopentenes, Cyclopentadienes and Cyclopentenones

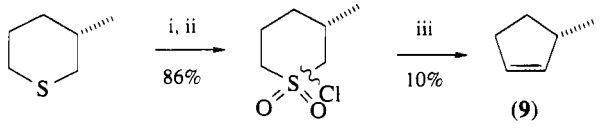
Since the late 1970s, the Ramberg–Bäcklund reaction has been used to convert a wide variety of six-membered cyclic α-halo sulfones into cyclopentenes, often in high yield; and useful regioselective syntheses of both 2- and 3-cyclopentenones, using sequences in which the Ramberg–Bäcklund reaction is the key step, have also been reported. Bu^tOK in THF, diethyl ether or DME are the preferred conditions for these reactions and, in addition, Meyers' method has been used to convert six-membered cyclic sulfones directly into cyclopentenes. Examples of these reactions follow.

Weinges has used the reaction to prepare the stereochemically pure intermediates (**8**), which are useful for the synthesis of cyclopentenoid natural products (equation 23).[68] In contrast to his observations when preparing cyclobutenes (*e.g.* Scheme 17), he found that in these cases, α-chloro sulfoxides give only low yields of cyclopentenes and numerous by-products on treatment with Bu^tOK. The Ramberg–Bäcklund reaction has been used to prepare (–)-(*S*)-3-methylcyclopentene (**9**; Scheme 20) as well as its enantiomer.[69] Although the yield is low, this method is very attractive because the product is free from double bond regioisomers. Paquette treated the trihalo sulfone (**10**) with an excess of Bu^tOK at low temperatures in a mixture of THF and D_2O to perform a remarkable simultaneous double dehydrobromination and Ramberg–Bäcklund reaction with deuterium incorporation to give the unstable tricyclodecatriene (**11**; equation 24).[70] Bicyclo[2.1.1]hexenes, which, though less elaborate, are related compounds, can be made from 1,3-cyclobutanedicarboxylic acids in a sequence incorporating the Ramberg–Bäcklund reaction.[71] In rigid fused-ring systems, unfavorable geometry can lead to 1,2-elimination of hydrogen halide to give a vinyl sulfone (equation 25) instead of the Ramberg–Bäcklund alkene (equation 26).[65]



(23)

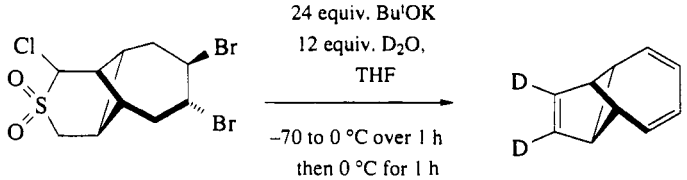
R = H; 66%; R = $PhCH_2O$; 71% (**8**)



(**9**)

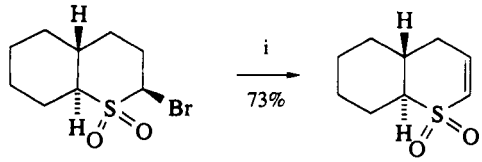
i, NCS, CCl_4, heat, 1 h; ii, MCPBA, Et_2O, 12 h; iii, Bu^tOK, Et_2O, 0 °C, 2 h, then reflux, 6 h

Scheme 20



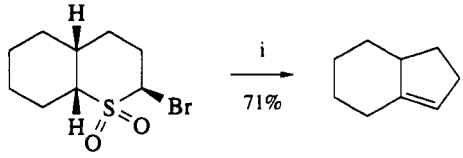
(**10**) (**11**)

(24)



(25)

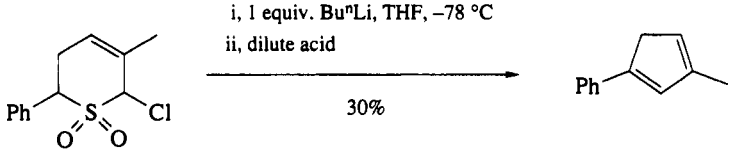
i, Bu^{t}OK, THF, –15 °C, 6 h, then r.t., 18 h



(26)

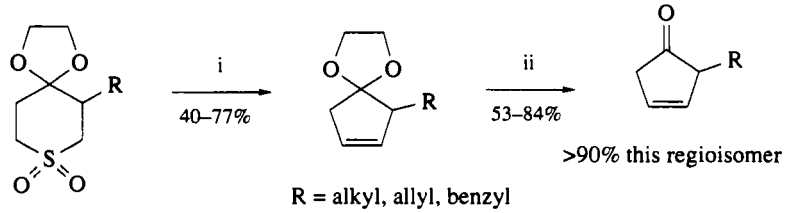
i, Bu^{t}OK, THF, –15 °C, 6 h, then r.t., 18 h

The Ramberg–Bäcklund reaction has also been applied to the synthesis of cyclopentadienes. For example, the α-chloro sulfone (**12**), a single unidentified diastereoisomer, was converted regiospecifically into the cyclopentadiene (**13**).[72] In principle, the acidity of the product requires the use of at least 2 equiv. of base for optimum yields, but, in practice, more than 1 equiv. of Bu^{n}Li causes appreciable polymerization.



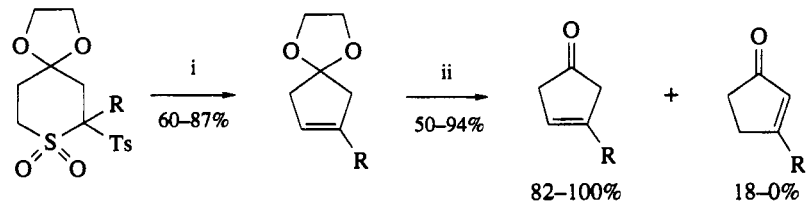
(**12**) (**13**)

Matsuyama and Taylor have reported that the Ramberg–Bäcklund reaction may be used to prepare a variety of 2-substituted-3-cyclopentenones (Scheme 21),[73,74] 3-substituted-3-cyclopentenones (Scheme 22)[74,75] and 2,3-disubstituted-2- or -3-cyclopentenones (Scheme 23).[76] De Waard has applied similar chemistry to the synthesis of the D-ring of a steroid.[77] In each case, the carbonyl group is protected as an acetal during the ring contraction, and careful hydrolysis is essential if migration of the carbon–carbon double bond into conjugation with the carbonyl group is to be avoided. If 2-cyclopentenones are required, hydrolysis and migration can be performed simultaneously under more strongly acidic conditions (Scheme 23). Other noteworthy features of these reactions are the use of sulfones with Meyers' one-pot basic chlorination conditions in the synthesis of 2-substituted-3-cyclopentenones (Scheme 21) and the use of 4-toluenesulfinate instead of the usual halide leaving group during the synthesis of 3-substituted-3-cyclopentenones (Scheme 22). 2-Cyclopentenones, as well as cyclopentenes, can be prepared very efficiently using Hendrickson's variant of the Ramberg–Bäcklund reaction in which trifluoromethanesulfinate functions as the leaving group (*e.g.* Scheme 11). Furthermore, 2-cyclopentenones can be prepared by ring-contraction of 2-chloro-1,3-cyclohexanediones (*e.g.* Scheme 14).



i, Bu^{t}OK, CCl_4, Bu^{t}OH, 50 °C, 20 h; ii, *p*-TsOH•Py, aq. acetone, reflux, 22 h

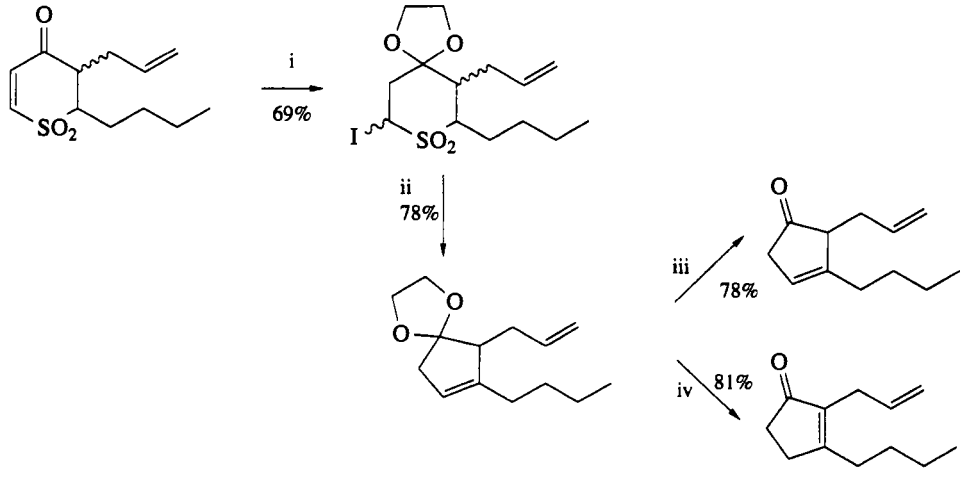
Scheme 21



R = alkyl

i, 2.5 to 3.0 equiv. NaH, 0.1 equiv. KH, DMSO, 20 to 30 °C, 24 h; ii, *p*-TsOH•Py, aq. acetone, reflux

Scheme 22

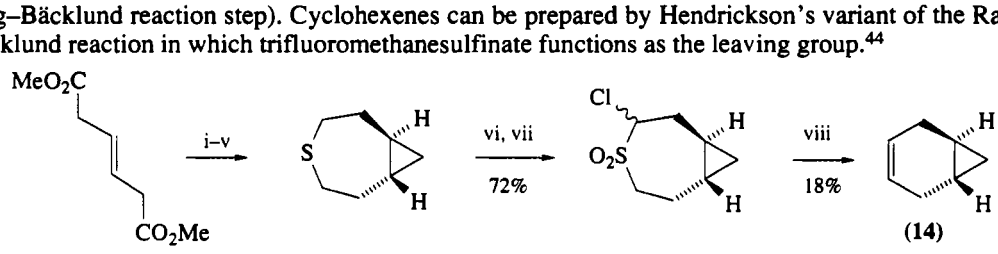


i, Me_3SiI, $HOCH_2CH_2OH$; ii, Bu^tOK, −78 °C, 0.5 h; iii, *p*-TsOH•Py, aq. acetone; iv, 5% aq. HCl

Scheme 23

3.8.8.3 Cyclohexenes and Phenanthrenes

The Ramberg–Bäcklund reaction has not been applied frequently to the synthesis of six-membered rings, but it has nevertheless proved useful where the target compounds are strained. Gassman chose to use the reaction to prepare *trans*-bicyclo[4.1.0]hept-3-ene (**14**), a strained hydrocarbon which slowly isomerizes to the more stable *cis* isomer at 120 °C (Scheme 24).[78] The 7-methyl[79] and 7,7-dimethyl derivatives[80] were prepared by similar methods (with yields of 20% and 45% respectively at the Ramberg–Bäcklund reaction step). Cyclohexenes can be prepared by Hendrickson's variant of the Ramberg–Bäcklund reaction in which trifluoromethanesulfinate functions as the leaving group.[44]

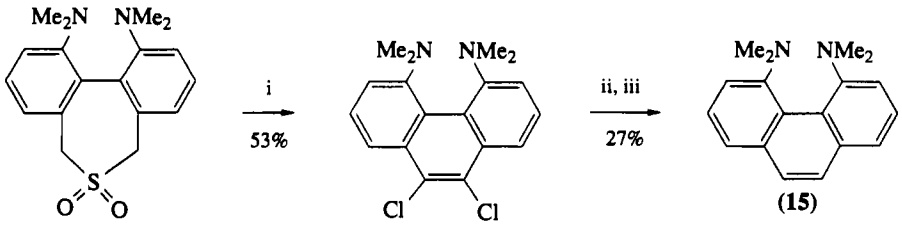


i, Zn–Cu, CH_2I_2; ii, $LiAlH_4$; iii, TsCl, Py; iv, LiBr; v, Na_2S, high dilution; vi, NCS, CCl_4, reflux; vii, MCPBA, CH_2Cl_2, 0 to 25 °C; viii, Bu^tOK, Et_2O, 0 °C

Scheme 24

In 1964, Paquette reported that although the 9,10-double bond of simple phenanthrenes can be formed using the Ramberg–Bäcklund reaction (NaOH in aqueous dioxane), the sterically crowded 4,5-dimethylphenanthrene cannot be made by this method.[81] Staab has now shown that the highly strained 'proton sponge' 4,5-bis(dimethylamino)phenanthrene (**15**) can be prepared using Meyers' modification of the re-

action, although over-chlorination under these conditions necessitates an extra reduction step (Scheme 25).[82]

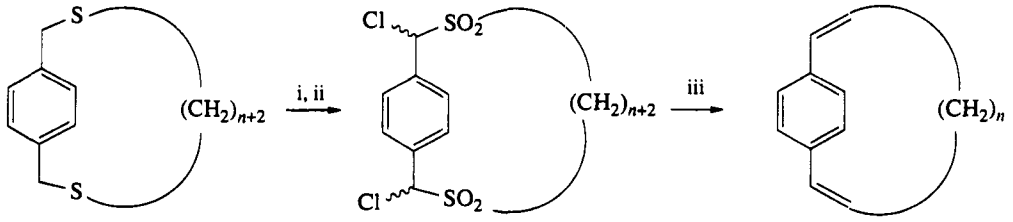


i, KOH, CCl_4, Bu^{t}OH, 0 to 20 °C, 1 h; ii, Li, THF, –55 to –35 °C, 1.5 h; iii, MeOH

Scheme 25

3.8.8.4 Large Ring Systems

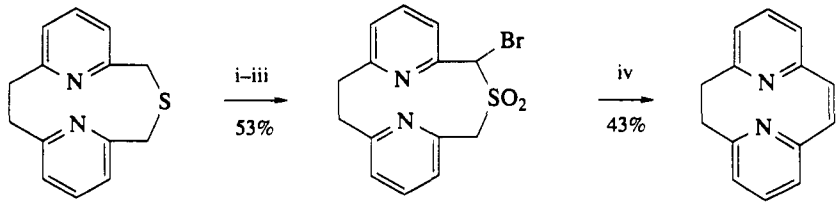
The Ramberg–Bäcklund reaction has been used to synthesize unsaturated cyclophanes and related bridged systems. However, it does not always compare favorably with the alternative methods for the conversion of similar precursors into the same products, namely: (i) the Wittig rearrangement of sulfides followed by repeated methylation and Hofmann elimination;[83] (ii) the Stevens rearrangement of sulfur ylides followed by quaternization and Hofmann elimination;[84] or (iii) the benzyne–Stevens rearrangement of sulfides followed by oxidation and pyrolysis.[85] The major problem with this application of the Ramberg–Bäcklund reaction is the preparation of the appropriate α-halo sulfones; the precursors are frequently benzylic sulfones and it has proved difficult to oxidize these to α-halo sulfones without over-halogenation. When α-halo sulfones can be obtained, the Ramberg–Bäcklund reaction itself takes place in moderate yield (Schemes 26[86] and 27[87]). One way of circumventing these problems is to allow sulfones to react under Meyers' conditions (equation 27).[88] Yields are sometimes low, and over-chlorination can still occur (leading, for example, after dehydrochlorination, to alkynes; equation 28),[89] but despite these drawbacks, the ability of the reaction to introduce a double bond regiospecifically can be extremely valuable. For example, the [3.3]paracyclophanediene (**16**), prepared in just 2% yield by the



yield from disulfide: $n = 5$; 29%
$n = 7$; 55%

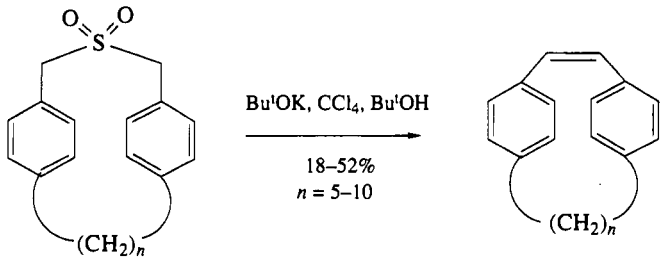
i, NCS, CCl_4; ii, MCPBA, CH_2Cl_2; iii, 4 equiv. Bu^{t}OK, DME

Scheme 26

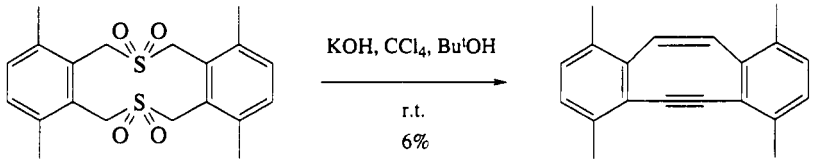


i, H_2O_2, cat. tungstic acid, aq. THF, 50 to 60 °C, 1 h; ii, Bu^{n}Li, THF, –78 °C; iii, Br_2, –78 °C; iv, NaOH, aq. dioxane, r.t., 2 h

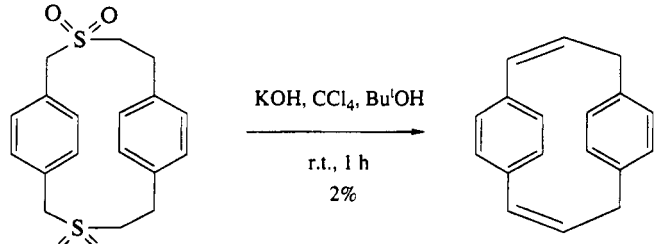
Scheme 27



(27)



(28)



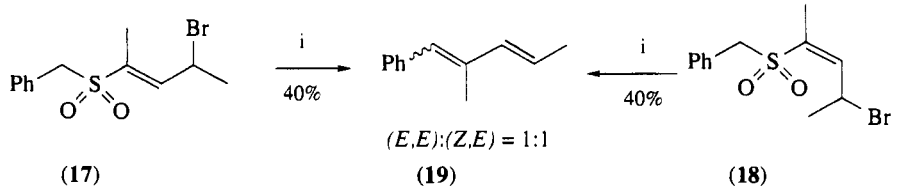
(29)

(16)

Ramberg–Bäcklund reaction (equation 29),[90] can be prepared in higher yield using the benzyne–Stevens rearrangement, but, when this approach is used, it is always contaminated with an equal amount of the inseparable regioisomeric [3.3]paracyclophanediene.

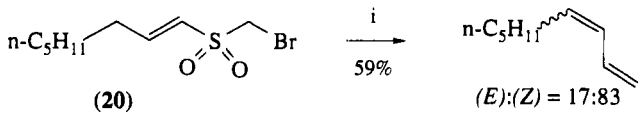
3.8.9 SYNTHESIS OF CONJUGATED DIENES, ENYNES AND POLYENES

In 1975, it was reported that treatment of each of the stereoisomeric α,β-unsaturated γ-bromo sulfones (**17**) and (**18**) with Bu^{t}OK leads *via* a vinylogous Ramberg–Bäcklund reaction to the same mixture of stereoisomeric 1,3-dienes (**19**).[91] More recently, Block has demonstrated that α,β-unsaturated α′-bromo sulfones are alternative and versatile precursors for vinylogous Ramberg–Bäcklund reactions, and he has developed this concept into an extremely useful method for the synthesis of dienes and polyenes. Examples are shown in equations (30)–(32).[92–95] The (*Z*)-stereoselectivity of the transformation shown in equation (30) stems from an attractive interaction between the developing negative charge at the α-position and the methylene group at the δ-position of the (*E*)-sulfone (**20**), which favors the transition state leading to the (*Z*)-isomer. With the corresponding (*Z*)-sulfone (**21**); steric effects disfavor the transition state which leads to the (*Z*)-isomer and the (*E*)-diene is the predominant product (equation 31). In a more extreme case (equation 32), the (*E*)-isomer is the exclusive product.



(17) **(19)** **(18)**

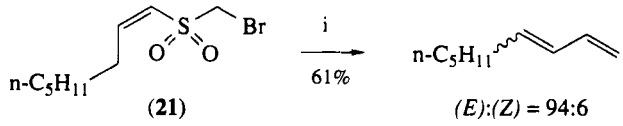
i, Bu^{t}OK, Bu^{t}OH, r.t., 12 h



(20) (30)

(E):(Z) = 17:83

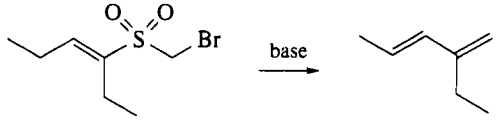
i, 2.5 equiv. Bu^{t}OK, Bu^{t}OH:THF (7:3), –20 °C, 1 h



(21) (31)

(E):(Z) = 94:6

i, 2.5 equiv. Bu^{t}OK, Bu^{t}OH:THF (7:3), –20 °C, 1 h

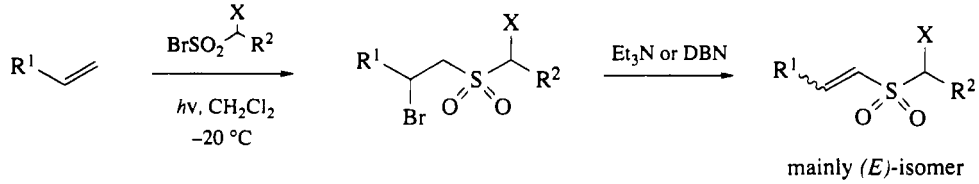


(32)

>99% *(E)*-isomer
[58% yield from *(E)*-3-hexene]

An attractive feature of Block's vinylogous Ramberg–Bäcklund reaction is that the precursors are easily prepared by the addition of α-haloalkanesulfonyl bromides to alkenes followed by elimination of the elements of HBr (Scheme 28). The addition, which takes place for a wide range of alkenes, is almost certainly a free radical chain reaction and is regiospecific for mono-, 1,1-di- and tri-substituted alkenes, with the formation of products consistent with the addition of the sulfonyl radical first to give the more stabilized radical intermediate. Even unsymmetrical 1,2-disubstituted alkenes show a high degree of regioselectivity, and in the case of compounds with both 1,1-di- and tri-substituted double bonds, addition occurs exclusively at the less-hindered disubstituted double bond. The general procedure involves treatment of the crude addition product with Et_3N in CH_2Cl_2 at 0 °C, which gives α,β-unsaturated α′-bromo sulfones as stereoisomeric mixtures in which the *(E)*-isomer predominates.[92,94] Taken sequentially, these addition and elimination steps and the vinylogous Ramberg–Bäcklund reaction allow an alkene to be converted into a 1,3-diene. Due to incomplete stereocontrol, during both the elimination and the rearrangement, the sequence is most useful where geometric isomers cannot occur, or for specific classes of compounds where high stereoselectivity has been observed. Several examples are shown in equations (33)–(38).[93,94] In each case, the initial alkene was treated in three successive steps with $BrCH_2SO_2Br$, Et_3N and Bu^{t}OK without separating stereoisomeric intermediates. Particularly noteworthy are the transformations shown in equations (33) and (34), which illustrate how the sequence allows a methylene group to be attached to interior atoms in chains or rings. 1-Methylcyclohexene gives 1,2-dimethylenecyclohexane as the predominant product (equation 36),[96] indicating that Bu^{t}OK preferentially abstracts a proton from the methyl rather than the methylene position of the intermediate unsaturated sulfone. Block has studied the regioselectivity of this deprotonation with Bu^{t}OK and Bu^{t}OLi for a selection of substrates. His results can be rationalized in terms of two effects: (i) abstraction at the less-hindered position is favored with both bases; and (ii) coordination of the cations by sulfonyl oxygen favors deprotonation *syn* to the sulfonyl group, and this effect is far more significant with lithium than potassium. Examples are shown in equations (39) and (40).[94,97]

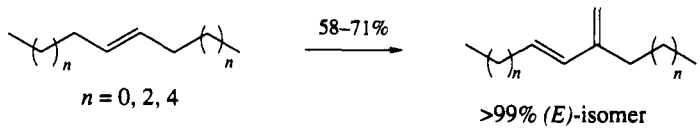
Conjugated trienes can also be synthesized *via* the vinylogous Ramberg–Bäcklund reaction (Scheme 29).[94] However, it is not possible to convert conjugated trienes into conjugated tetraenes using Block's procedure: conjugated trienes fail to give adducts with $BrCH_2SO_2Br$, probably because the intermediate



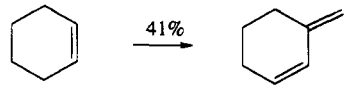
mainly *(E)*-isomer

X = Cl, Br, I; R^1 = alkyl, allyl, benzyl, *etc.*; R^2 = H, Me

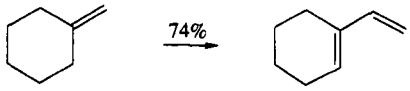
Scheme 28



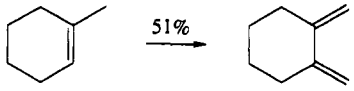
(33)



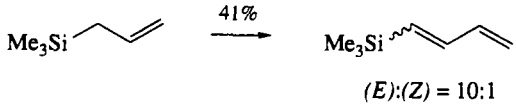
(34)



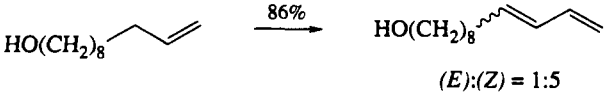
(35)



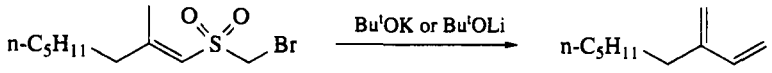
(36)



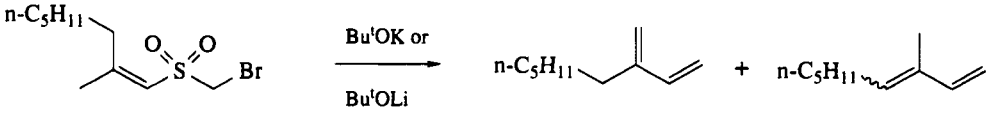
(37)



(38)



(39)

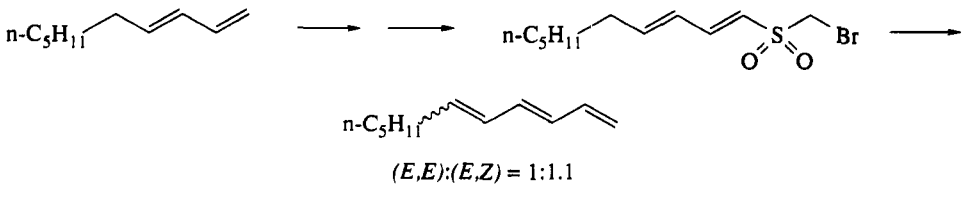


(40)

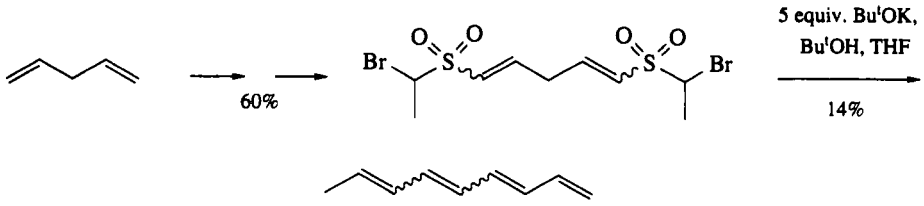
pentadienyl radical is too stable to abstract a bromine atom from $BrCH_2SO_2Br$. Nevertheless, conjugated tetraenes can be made by the alternative procedure shown in Scheme 30, a process which involves a Ramberg–Bäcklund rearrangement through three intervening double bonds! Furthermore, terminal or internal alkynes are converted into 1,3-enynes under appropriate conditions (equations 41 and 42).[94]

Block has described a further use for α-haloalkanesulfonyl bromides; radical addition to silyl enol ethers followed by simple Ramberg–Bäcklund rearrangement yields α,β-unsaturated ketones (Scheme 31).[94,98] Ethylene oxide, an acid scavenger, is used as solvent for the radical addition to prevent hydrolysis of the silyl enol ether.

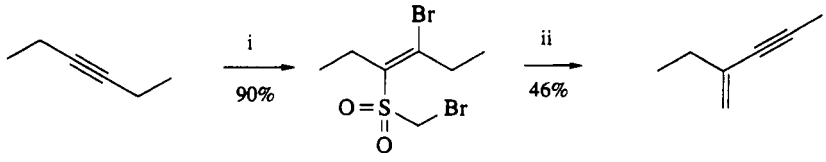
De Waard has developed a modification of the Ramberg–Bäcklund rearrangement in which the intermediate α-sulfonyl carbanion is generated by 1,4-addition of a nucleophile to a vinyl sulfone: the 'Mi-



Scheme 29

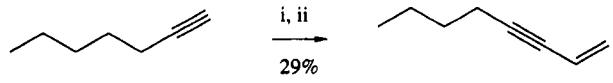


Scheme 30



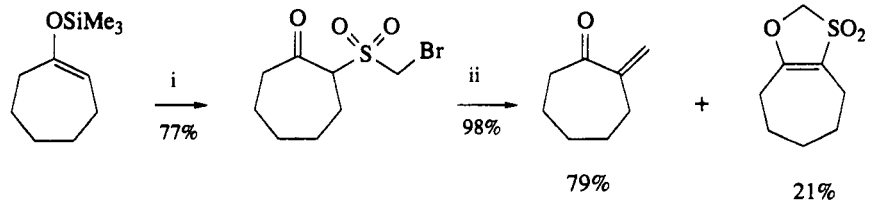
(41)

i, 0.5 equiv. $BrCH_2SO_2Br$, *hν*, CH_2Cl_2, –20 °C; ii, 4 equiv. Bu^{t}OK, Bu^{t}OH, THF



(42)

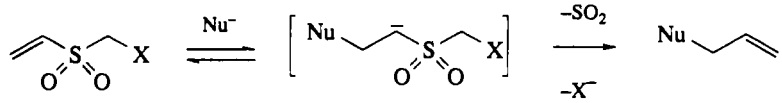
i, 0.5 equiv. $BrCH_2SO_2Br$, *hν*, CH_2Cl_2, –20 °C; ii, 4 equiv. Bu^{t}OK, Bu^{t}OH, THF



i, $BrCH_2SO_2Br$, ethylene oxide, *hν*, –15 °C; ii, DBN, CH_2Cl_2, –78 °C, 2 h, then 23 °C, 0.5 h

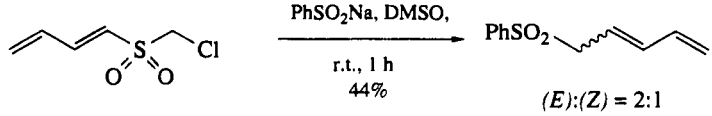
Scheme 31

chael-induced Ramberg–Bäcklund reaction'.[99] Scheme 32 shows this transformation in its simplest form, though in practice it appears that butadienyl sulfones have been used universally, perhaps because the equilibrium shown does not favor the sulfone α-anion with simple vinyl sulfones (compare Scheme 5). Examples from de Waard[99] and from Block[94] are shown in equations (43) and (44), respectively.



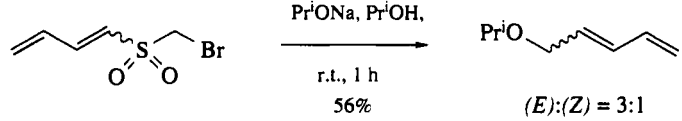
X = Cl, Br; $Nu^- = RSO_2^-, RO^-$

Scheme 32



(E):*(Z)* = 2:1

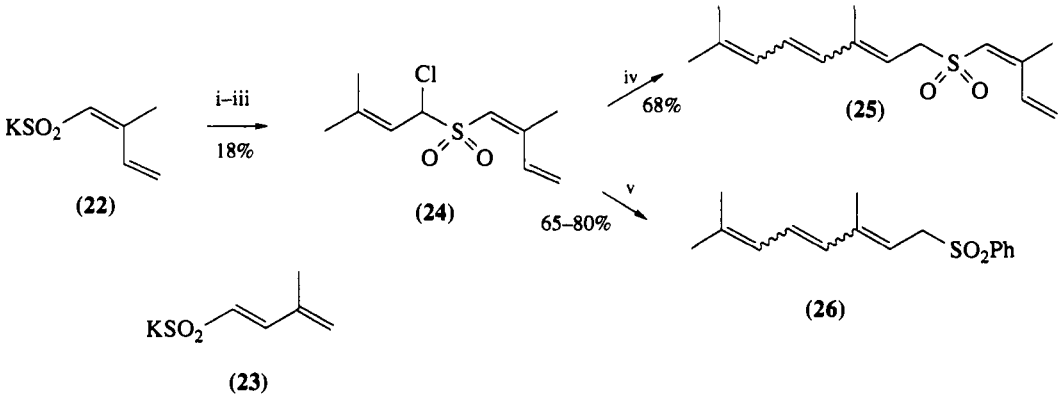
(43)



(E):*(Z)* = 3:1

(44)

De Waard has focused on the use of the reaction for the synthesis of conjugated isoprenoids (Scheme 33);[100] the regioisomeric sulfinates (**22**) and (**23**) or their stereoisomers function as the key five-carbon building blocks. Reaction of the sulfinate (**22**) with prenyl chloride followed by chlorination[101] gives the α-chloro sulfone (**24**), precursor for the Michael-induced reaction. Further treatment with the sulfinate (**22**) then gives the stereoisomeric 'head-to-tail' linked pentaenes (**25**), ready for rechlorination and for the cycle to be repeated. Use of the alternative isoprene synthon (**23**) results in 'tail-to-tail' coupling of the isoprene units. When the polyisoprenoid chain reaches the required length, phenylsulfinate is allowed to trigger the rearrangement and gives an allyl phenyl sulfone, *e.g.* the conversion of (**24**) into the stereoisomeric trienes (**26**), from which the phenylsulfonyl group may be removed by reduction.

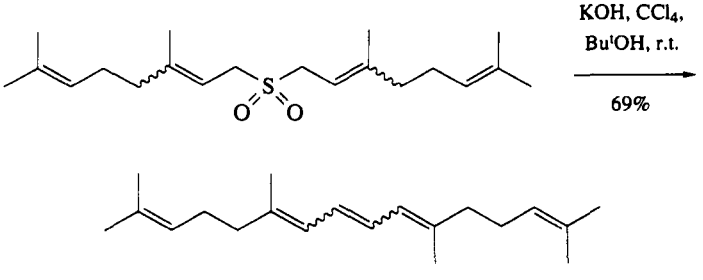


i, prenyl chloride, DMSO, r.t., 40 h; ii, LDA, THF, –78 °C; iii, Cl_3CCCl_3, –78 °C to r.t.; iv, (**22**), DMSO, r.t., 68 h; v, $PhSO_2Na$, DMSO, r.t., 0.5 h

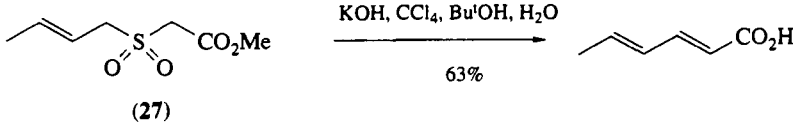
Scheme 33

The least attractive feature of the Michael-induced Ramberg–Bäcklund reaction is the absence of any useful stereocontrol; where several isomeric products are possible, they are all formed. In fact, both stereoisomers of the α-chloro sulfone (**24**) give the same mixture of trienes (**26**) on treatment with sodium phenylsulfinate.[100] The reaction is presumably most useful if the required isomer can be obtained by equilibration of the complex mixture in a subsequent step.

Bisallylic sulfones are converted into conjugated trienes under Meyers' conditions;[102–104] an example is shown in equation (45).[102] Although experiments with isomerically pure substrates have not been performed, there are indications that the geometry of the allyl groups is conserved during the rearrangement while the newly introduced double bond has mainly the (*E*)-configuration.[104] Meyers' conditions also allow unsaturated β-sulfonyl esters such as (**27**) to be converted into (*E,E*)-dienoic acids, hydrolysis accompanying the rearrangement (equation 46; compare equation 4). An all-(*E*)-trienoic acid was made by the same method.[105]



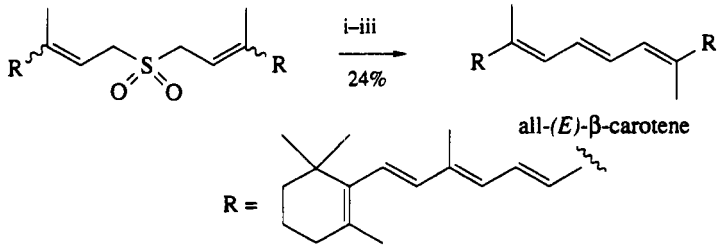
(45)



(46)

(**27**)

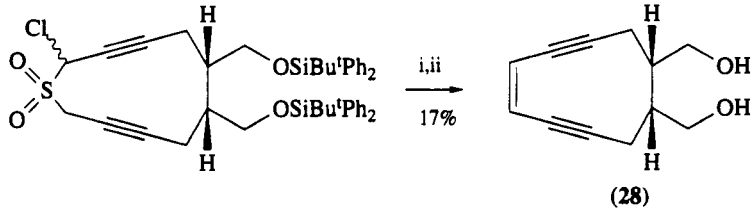
β-Carotene has been prepared by treatment of an appropriate sulfone α,α′-dianion with bromine or iodine (equation 47).[102] This transformation may be regarded either as proceeding through a conventional α-halo sulfone α′-anion, or *via* a two-electron oxidation to the intermediate thiirane 1,1-dioxide (compare equation 11).



(47)

i, 2 equiv. Bu^nLi, THF, 0 °C; ii, I_2 or Br_2; iii, thermal or I_2–catalyzed stereomutation

The reactive cyclodecenediyne ring system found in the calicheamicins has recently been synthesized for the first time, together with a homologous series of larger (11- to 16-membered) rings containing the same enediyne unit.[106] The synthesis of the first derivative (**28**) with DNA-cleaving properties by the same approach (equation 48) was reported soon afterwards.[107]



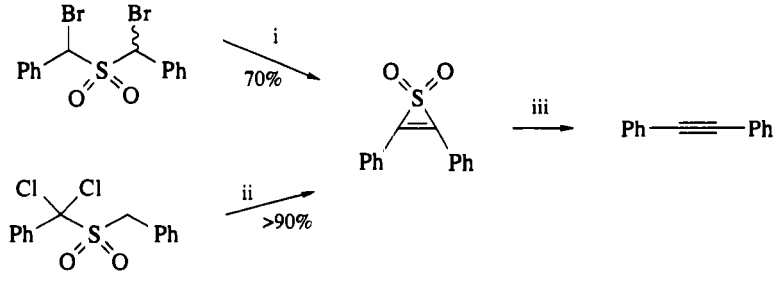
(48)

(28)

i, 1.2 equiv. MeLi, Et_2O, –78 °C, 15 min (20% yield); ii, Bu^n_4NF, THF, 1 h (84% yield)

3.8.10 SYNTHESIS OF ALKYNES

On treatment with appropriate tertiary amines, both α,α-[108] and α,α′-dihalodibenzyl sulfones[109] are converted into diphenylthiirene 1,1-dioxides which, although far more stable than the corresponding thiirane dioxides, extrude SO_2 on heating to give diphenylacetylenes (Scheme 34).[37] The highly strained alkyne acenaphthyne, isolated in the form of its trimer, has been prepared in this way.[110] α-Chloroneopentyl neopentyl sulfone reacts under Meyers' basic chlorinating conditions (KOH, CCl_4, Bu^{t}OH) at above 40 °C to give di-*t*-butylacetylene in yields of up to 90%.[16,17]



i, Et_3N, CH_2Cl_2, reflux, 3 h; ii, triethylenediamine, DMSO, r.t.; iii, boiling benzene, several hours, or melt

Scheme 34

3.8.11 REFERENCES

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3.9
The Wolff Rearrangement

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3.9.1 INTRODUCTION

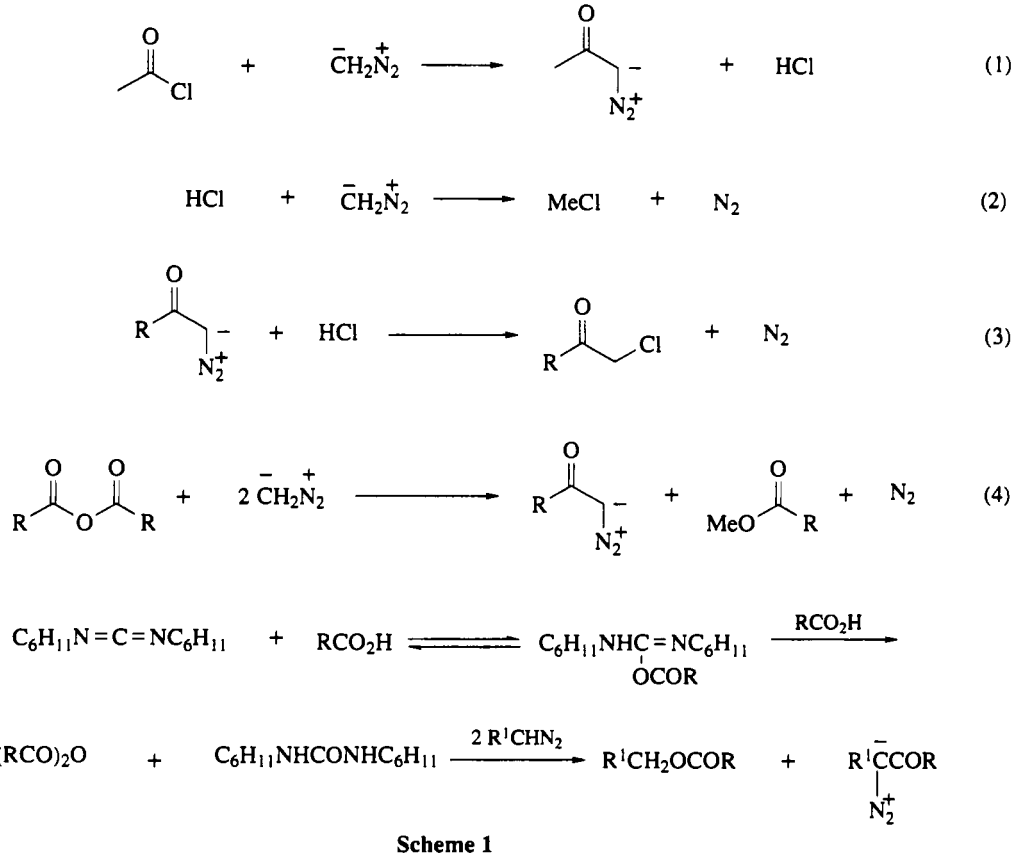
3.9.1.1 Historical

During a study of the chemistry of α-diazo ketones at about the turn of the century, Wolff found, for example, that treatment of diazoacetophenone ($PhCOCHN_2$) with water and silver oxide gave not the hydroxy ketone ($PhCOCH_2OH$), but rather the rearrangement product phenylacetic acid ($PhCH_2CO_2H$).[1a] When aqueous ammonia was present in the reaction medium, the corresponding amide ($PhCH_2CONH_2$) was formed in good yield, even in the cold. A few years later, but independently of Wolff, Schröter[1b] published his results of an analogous study. Occasionally, therefore, such transformations of α-diazo ketones are also called the Wolff–Schröter rearrangement.

In a sense the discoveries of Wolff and Schröter were ahead of their time, for over 20 years were to pass before convenient methods for the preparation of the diazo ketones became available. Hence, synthetic applications largely date from the early 1930s. Periodically since then a number of substantial reviews of the Wolff rearrangement have been published,[2–11] testifying to the importance that the reaction has achieved in preparative organic chemistry. Diazo ketone chemistry has achieved modern commercial importance in the photolithography industry.[12]

3.9.1.2 Preparative Routes to α-Diazo Ketones

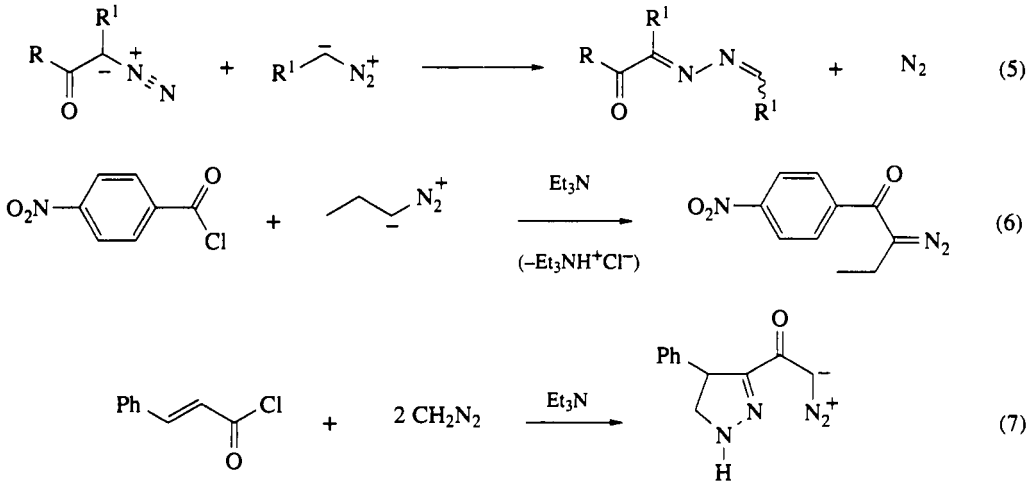
Several methods are now available for the preparation of α-diazo ketones. Of these, the Arndt–Eistert procedure is the most versatile and popular.[2–4,8,10,13,14] In essence, the method involves the *C*-acylation of a primary diazoalkane ($RCHN_2$), usually diazomethane (*i.e.* R = H), with acid chlorides or, less commonly, with acid anhydrides.[15] In practice, it is essential to realize that diazo ketones are decomposed by acid. Hence, the acid chloride should be freshly purified and distilled, and precautions taken to exclude moisture. Any carboxylic acid present is converted by diazomethane into the methyl ester which contaminates the product, reducing the yield. In the classical Arndt–Eistert procedure the diazo ketones are formed in nearly quantitative yield by the slow addition of the acid chloride (1 equiv.) to an ice-cold dry ethereal (or CH_2Cl_2) solution of diazomethane (2 equiv.; for higher homologs, see below). The second equivalent of diazomethane combines with the hydrogen halide formed in the first step to give the gaseous by-products methyl chloride and nitrogen (equations 1 and 2). In the absence of the second equivalent of diazomethane,[16] the HCl protonates the diazo ketone and an α-chloro ketone is then formed by the S_N2 displacement of nitrogen (equation 3).[3] Triethylamine may frequently be used to take on the role of the second molecule of diazomethane in neutralizing the HCl.[17] With acid anhydrides the reaction produces equimolar quantities of the diazo ketone and the methyl ester (equation 4). The addition of a mixture of a carboxylic acid (1 equiv.) and dicyclohexylcarbodiimide (1 equiv.) in ether to ice-cold ethereal diazomethane (1.25 equiv.) or diazoethane (1.25 equiv.) affords the corresponding diazoketones (max. yield 50%) by way of acid anhydride intermediates (Scheme 1).[18] This route may be applicable in thoses cases where the conventional Arndt–Eistert method fails.



Scheme 1

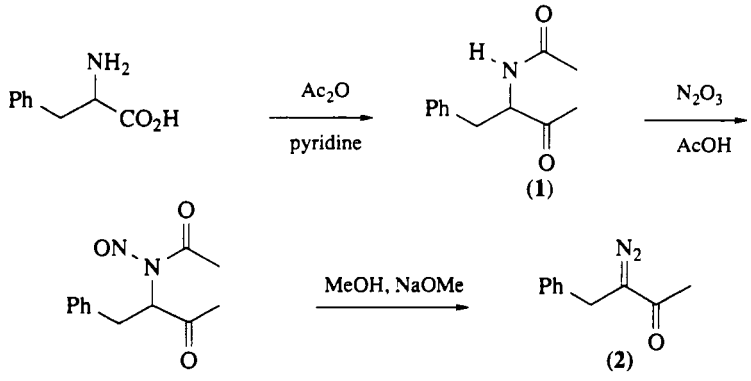
Reaction conditions for the acylation of higher diazoalkanes by acid chlorides are more critical.[19,20] Since azo coupling of the diazo ketone with the diazoalkane can occur to give azines (equation 5),[21] it is essential to avoid an excess of the diazoalkane and to carry out the acylation at lower temperatures. Typically, the acid chloride (1 equiv.) in ether is added to a stirred solution of the diazoalkane (1 equiv.) and triethylamine (1 equiv.) in ether at –40 °C. Yields of the diazoketones are then *ca.* 74–91%, and equation (6) is fairly representative.[20]

There are a few, mainly obvious, limitations to the Arndt–Eistert acylation procedure, in that other functional groups in the acid chloride which react with the diazoalkane require suitable protection. Be-



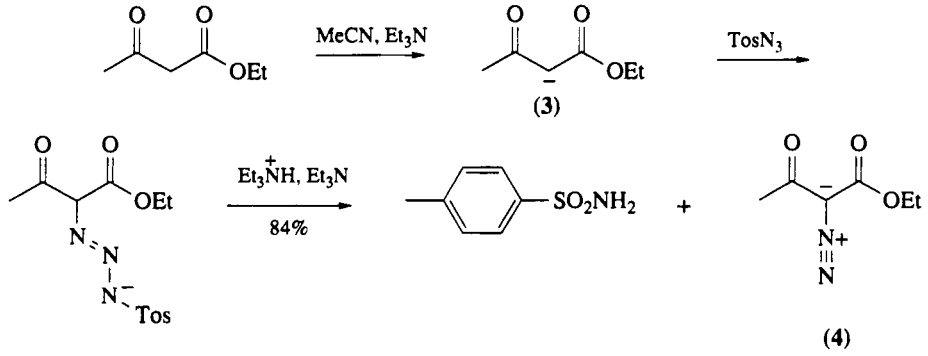
cause diazomethane is a fairly reactive 1,3-dipole, activated alkenes (dipolarophiles) afford cycloaddition products. Hence, α,β-unsaturated acid chlorides react with diazomethane at both the carbonyl carbon atom and at the double bond (*e.g.* equation 7).[22,23] A more remote, unactivated double bond does not usually inhibit diazo ketone formation. On the whole, therefore, the *C*-acylation of primary diazo compounds is a widely applicable procedure.[6,10]

The Dakin–West reaction[24] provides a source of *N*-acyl-α-amino ketones (*e.g.* **1**), which Franzen[20] has exploited for the synthesis of secondary diazo ketones, thereby avoiding the need to use the higher homologs of diazomethane (Scheme 2). The ketoamide (**1**) is first nitrosated using N_2O_3 in glacial acetic acid. The oily *N*-nitroso derivative is separated and then decomposed with sodium methoxide in methanol to give the diazo ketone (**2**); yields are about 50–60%.



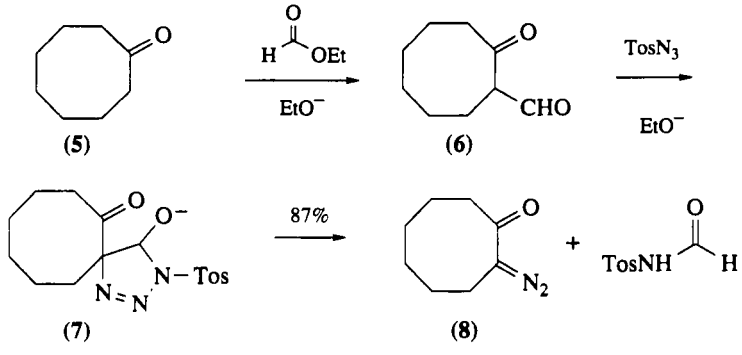
Scheme 2

The synthesis of α-diazocarbonyl compounds by the transfer of a diazo group from an organic azide to a suitable substrate containing an active methylene group was studied extensively in the 1960s and 1970s, but the origins of the basic reaction are much older.[10,25] Tosyl azide is now used almost exclusively as the diazo group transfer agent since it is stable and easily prepared, and because tosyl amide (a coproduct) is readily removed. The presence of a base is necessary, for it is the enolate anion which reacts with the tosyl azide. Commonly used solvent/base combinations are ethanol and potassium hydroxide, triethylamine, or potassium ethoxide; methanol and sodium methoxide; acetonitrile and triethylamine; and dichloromethane and piperidine. The choice of the base is, of course, dictated by the pK_a of the active methylene group in the substrate; hence the presence of two Z-groups (*i.e.* COR, CO_2R, CN, NO_2, SO_2R, *etc.*) is essential. The preparation of ethyl acetodiazoacetate (**4**) is illustrated in Scheme 3.[26] Since α-diazo-β,β′-dicarbonyl compounds such as (**4**), but more especially those formed from β-diketones, have a highly electrophilic diazo group, it can be difficult to completely suppress azo coupling with the enolate ion (**3**).[25] The yields of the α-diazocarbonyl compounds can be improved by employing phase-transfer catalysis. Thus, reaction of ethyl acetoacetate with tosyl azide in a mixture of pentane and saturated aqueous sodium carbonate containing tetrabutyl ammonium bromide, afforded (**4**) in 90% yield.[27]



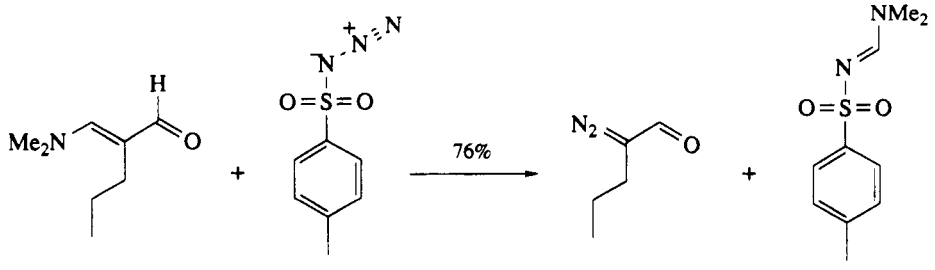
Scheme 3

The diazo-transfer reaction strategy has to be modified for the preparation of simple diazo monoketones (*e.g.* **8**). The presence of only one activating Z-group is circumvented by the temporary introduction of a formyl group by means of a Claisen reaction (Scheme 4; **5** → **6**).[28] The formyl derivative is either preformed and then treated with tosyl azide and a tertiary amine, or the initial ketone is reacted with ethyl formate and sodium ethoxide in ethanol and then the tosyl azide is added to the Claisen adduct. Yields are generally in the range 55–90%,[25] and deformylative group transfer renders a wide range of α-diazocarbonyl compounds accessible; even α,β-unsaturated diazo ketones can be prepared by this route.[29]



Scheme 4

The need for proton-activating Z-groups may be dispensed with by employing diazo group transfer to enamines of suitable structure. The initial addition is regiospecific (*cf.* **7**), and the triazoline so-formed decomposes spontaneously to give the diazo compound and a tosyl amidine. Although α-diazo ketones can be prepared in this manner, the other routes outlined above are generally superior. However, the method is useful for α-diazoaldehydes, and an example is given in equation (8).[30]



(8)

Various other procedures have been developed for the synthesis of α-diazo ketones and, although less popular in modern organic chemistry, may occasionally be valuable for the preparation of specific compounds.[7,10,25] These routes include the oxidation of α-ketoximes with chloramine,[31] the oxidation of α-ketohydrazones with yellow mercury(II) oxide[32] or manganese dioxide,[33] the hydroxide ion assisted decomposition of tosylhydrazones,[34] and the diazotization of α-amino ketones.[1,35]

3.9.1.3 Methods for Initiating the Wolff Rearrangement

The Wolff rearrangement may be initiated thermally, by transition metal catalysts, or by photolysis. Thermolysis is used less frequently than the other two procedures since solution temperatures in the region of 180 °C are often required, and this can be counter-productive if the rearrangement results in the formation of a strained ring. Additionally, under thermal control nucleophiles can displace the diazo group without causing rearrangement.[1,36] Nevertheless, the ketene intermediate produced by the rearrangement (see Section 3.9.2.1) can often be intercepted efficiently by employing a high boiling point amine or alcohol as solvent (*e.g.* aniline[1,37] and benzyl alcohol[19] which, respectively, afford the anilide and benzyl ester).

The use of transition metal species can lower appreciably the decomposition temperature of α-diazocarbonyl compounds; they can also alter the reactivity of the carbene intermediate (resulting from the initial nitrogen elimination; see Section 3.9.2.1) by complex formation. Hence, the Wolff rearrangement may occur with difficulty or, usually, not at all. Thus, some copper species (excepting, for example, CuI),[38] or Rh and Pd catalysts are inappropriate. Freshly prepared silver(I) oxide has been used most frequently, but silver salts (especially silver benzoate) are sometimes preferred.[1,2,37,39] Silver-based catalysts are usually employed in combination with an alkaline reagent (*e.g.* sodium carbonate or a tertiary amine). Even under silver catalysis competing reactions may be observed, and sometimes the products of Wolff rearrangement may not be obtained (see Section 3.9.2.3).

Photolysis[40] is often successful when the thermal or catalytic procedures fail and, increasingly, has become the method of choice. The UV spectra of simple diazo ketones show two absorption bands; one in the 240–270 nm region, and a lower intensity (forbidden) band in the 270–310 nm region. Protic solvents diminish the intensity of the first band relative to the second.[41a] Excitation of this second band accesses the lowest energy excited singlet state (^1S) of the diazo ketone by way of a $\pi \rightarrow \sigma^*$ overlap-forbidden transition.[41b] This may be achieved by use of a medium-pressure mercury arc. Since ^1S is only moderately reactive it may be necessary to excite the higher intensity, higher energy $\pi \rightarrow \pi^*$ band by use of a low-pressure mercury arc, but this may lead to increased amounts of by-products. The photochemical procedure fails if the reaction product itself is photolabile under the reaction conditions. Since moderately low temperatures are usual (*e.g.* 0 °C), problems of thermal lability can be avoided. The presence of triplet sensitizers tends to suppress the Wolff rearrangement but other, carbene-mediated, processes may occur. Rearrangements of α-diazo ketones have also been observed under electron impact in the mass spectrometer.[42]

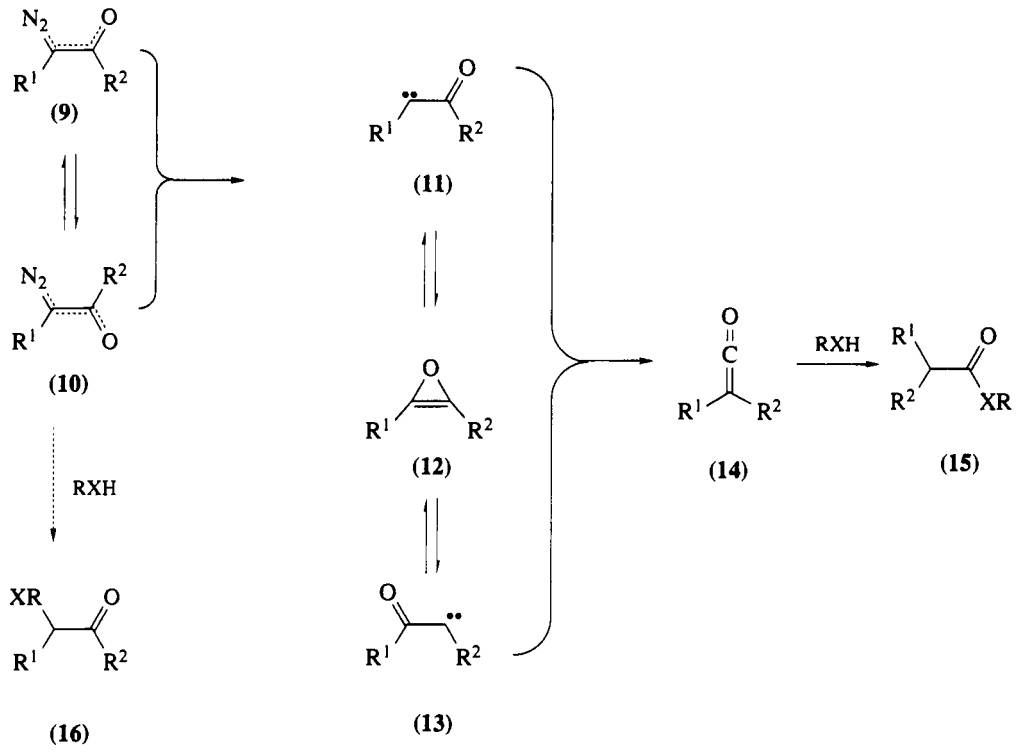
3.9.2 MECHANISM, STEREOCHEMISTRY AND COMPETING REACTIONS

3.9.2.1 Mechanism

Even after more than 75 years, theoretical and mechanistic interest in the Wolff rearrangement continues unabated.[43] There is as yet no general agreement on all of the mechanistic detail connecting reactant to product, and it is probable that there is not a single mechanistic description for all Wolff rearrangements. Scheme 5 summarizes the main features; most of the disagreements concern the exact placement of the interconnecting arrows and the participation of the reactive intermediates (**11**)–(**13**).

Two features of the mechanism are regarded as secure. Firstly, an acyclic α-diazo ketone exists as an equilibrium mixture of the *s*-(*Z*) and *s*-(*E*) forms (**9**) and (**10**), respectively. The central C—C bond possesses double bond character, and the rotational barrier is approximately 9–18 kcal mol^{-1} (1 kcal = 4.18 kJ).[44] The substituents R^1 and R^2 influence the balance of the equilibrium, and it is possible to favor entirely the *s*-(*Z*) form (*e.g.* R^1,R^2 = small ring) or the *s*-(*E*) form (*e.g.* $R^1 = R^2 = t$-butyl). Secondly, the rearrangement leads to the ketene intermediate (**14**),[1b,40] which is usually trapped by a weak acid RXH (*e.g.* water, alcohols and amines) to give the product (**15**); stronger acids protonate the diazo ketone, and nucleophilic displacement of nitrogen occurs without rearrangement to give the product (**16**).

In the *s*-(*Z*) form (**9**) the leaving group (N_2) and the migrating group (R^2) are deployed in an ideal antiperiplanar geometry for concerted extrusion/rearrangement (*i.e.* **9** → **14**). Indeed, the concerted mechanism has been proposed to account for the conformational control observed in the photolysis and thermolysis of some α-diazo ketones.[44] Product ratios obtained in direct and triplet-sensitized photolyses have led to the proposal of a concerted component from (**9**) and a nonconcerted (carbenic) component from (**10**).[45] Likewise, CIDNP studies indicate that the photochemical rearrangement of diazoacetone is concerted.[46] However, the observation of conformational control in the Wolff rearrangement is not



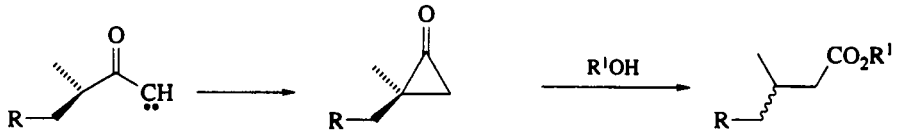
Scheme 5

regarded[47] as proof *per se* for a concerted mechanism, and compelling evidence for the intermediacy of α-ketocarbenes[43] and for the oxirene (**12**)[48] has been advanced. The oxirene appears neither to be formed directly from the diazo ketone nor to rearrange directly to the ketene, but a 'symmetrical' species is needed to explain the scrambling of isotopic label which has been observed in some reactions. A wide variety of groups R^1 or R^2 in the carbenes (**11**) or (**13**) are able to migrate. For thermal reactions the migratory aptitudes fall in the series: H > Ph > Me > NR_2 > OR. Under photochemical control Ph and Me exchange places.[11]

There are undoubtedly appreciable mechanistic differences in the transition metal catalyzed reactions.[7,11] For example, Newman and Beal have suggested that a radical chain process is involved in the silver benzoate/triethylamine-promoted rearrangement of diazomethyl ketones.[39]

3.9.2.2 Stereochemistry

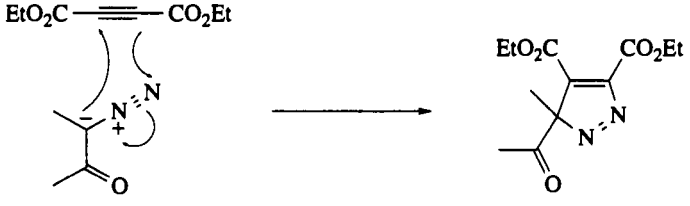
The Wolff rearrangement, irrespective of the method employed for initiation, appears to occur by the intramolecular transfer of the migrating group. By and large, all stereochemical information at the migrating center is conserved. Thus, studies with optically active diazo ketones have shown predominant or complete retention of configuration of the migrating group.[49–51] The loss, or partial loss, of stereochemical integrity has only been observed when the migrating center is a secondary carbon atom. This centre is adjacent to the C=O group of the diazo ketone, and hence partial racemization through enolization could result during diazo ketone synthesis or storage, or under the conditions of the Wolff rearrangement, as well as during the rearrangement itself. From their results on the rearrangement of *s*-butyldiazomethyl compounds ($RCH_2CH(Me)COCHN_2$; R = H, Ph) photochemically or by a variety of silver ion catalyzed methods, Wiberg and Hutton[51] concluded that either the diazo ketone was partially racemized under the reaction conditions, or racemization occurred during the rearrangement. An alternative explanation for the racemization based on a minor pathway involving C—H insertion by the carbene intermediate (Scheme 6) seems unattractive in view of the known chemistry of cyclopropanones (*i.e.* cleavage requires a strong base and takes place in the direction towards the less-substituted carbon atom).[52]



Scheme 6

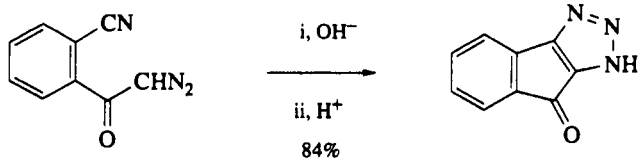
3.9.2.3 Competing Reactions

Diazo ketones are reactive substances. The problems of compatibility towards functional groups in the same molecule are discussed in Section 3.9.1.2. Clearly, there will be a similar incompatibility in intermolecular processes if certain other compounds are present in the reaction medium during Wolff rearrangement. α-Diazo ketones are 1,3-dipoles but, according to Huisgen's index of reactivity for diazo compounds (*i.e.* CH_2N_2 > Ph_2CN_2 > EtO_2CCHN_2 > $RCOC(N_2)R^1$ > $RCOC(N_2)CO_2Et$), they are only moderately reactive.[53a] Since dipolarophile reactivity of Z-group-activated alkenes falls in the series CO_2Ph > CO_2Et > CN > COMe > $C_6H_4NO_2$ > Ph,[53b] then loss of diazo ketone through 1,3-dipolar cycloaddition is generally only important for the more electron-deficient alkenes and alkynes. Thus, for example, cycloaddition of 2-diazo-3-oxobutane to diethyl acetylenedicarboxylate affords 5-acetyl-3,4-diethoxycarbonyl-5-methyl-5*H*-pyrazole (**16**; equation 9).[54] Analogous intramolecular cycloaddition occurs across the nitrile group in (**17**) under alkaline conditions; on acidification the initial adduct undergoes prototropic rearrangement to give the triazole (**18**; equation 10).[55] The triazole (**18**) is converted by acidic hydrolysis into 2-diazoindane-1,3-dione (80%).



(9)

(**16**)

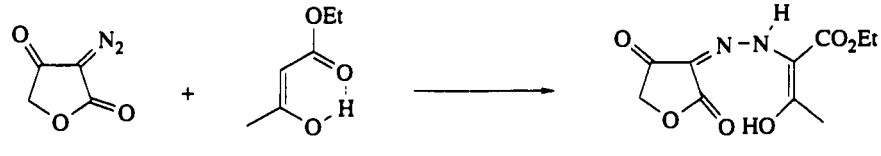


(10)

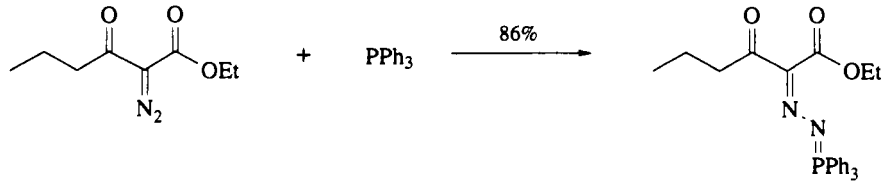
(**17**) (**18**)

Diazo ketones also possess an electrophilic diazo group, and hence are susceptible to diazo-coupling reactions with suitable soft nucleophiles. Examples are given in equations (11)[1a] and (12).[56] Phosphazines such as (**19**) are useful synthetic intermediates in their own right. The carbon terminus of the 1,3-dipole possesses nucleophilic properties and can participate in aldol-type reactions with the particularly electrophilic carbonyl groups in 1,2-di- and 1,2,3-tri-carbonyl compounds.[25] Intramolecular condensations occur with greater ease (equation 13).[57] Reaction of diazo ketones of the type summarized in equations (9)–(12) have been thoroughly reviewed.[4,6,8]

Prevention of the Wolff rearrangement is much more likely to occur through alternative reactions of the ketocarbene intermediate (**11**; Scheme 5). Lack of rearrangement to the ketene (**14**) may be due to a structural feature present in the ketocarbene (*e.g.* functional groups α to the C=O interfere with the Wolff rearrangement, or lead to secondary reactions)[7–11] but, not infrequently, it can be the result of an

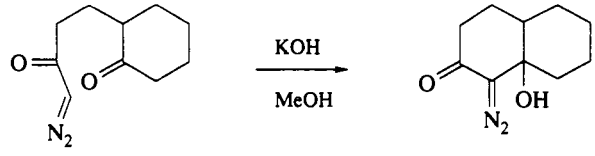


(11)



(12)

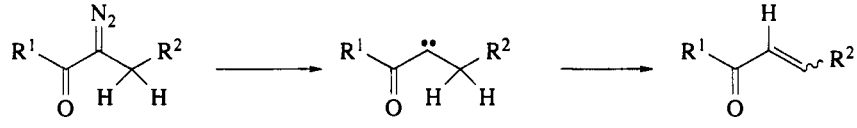
(19)



(13)

inappropriate choice of reaction conditions. Hence, it is often worthwhile investigating the photochemical decomposition of the α-diazocarbonyl compound if the thermal or transition metal catalyzed procedures fail to effect rearrangement. Likewise, changes in temperature, solvent or coreactants should be considered.

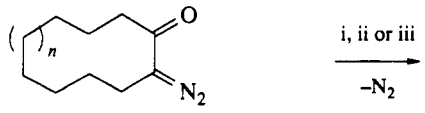
Ketocarbenes of type (**21**) obtained from acyclic and medium to large ring alicyclic α-diazo ketones (**20**) are prone to react by way of an intramolecular [1,2] H-shift, especially under catalytic conditions, to afford α,β-unsaturated ketones (**22**).[1,20,58–60] Franzen[20] has shown that the Wolff rearrangement of diazo ketones (**20**) is favored if temperatures in excess of 100 °C are used in the photochemical or Ag_2O-promoted decompositions. Related [1,2] methyl shifts can also occur, and this pathway is the principal decomposition route of 4-diazo-2,2,5,5-tetramethyl-3-hexanone.[61]

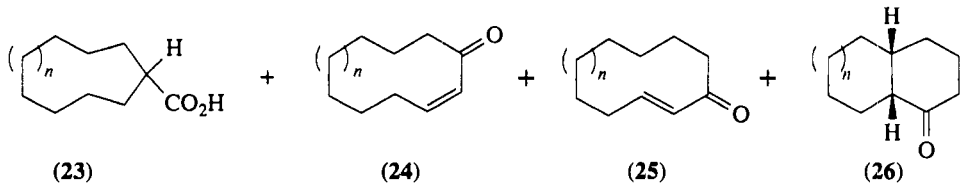


(**20**) (**21**) (**22**)

The transient ketocarbene is also able to effect both intramolecular and intermolecular H-abstraction. The fact that a triplet state of the carbene is often implicated follows from observations that sensitized photolyses frequently enhance the abstraction pathway.[6,9] Abstraction and radical combination results in the formal insertion of the carbene into the C—H (or S—H, N—H, *etc.*) bond. Insertions may also occur into C—C, C—O, C—S, C—Hal, *etc.* bonds; the mechanisms are often not known, but a singlet state of the ketocarbene is probably involved in many cases. Reactions at soft basic centers (*e.g.* —S: or —Br:) generally proceed by the preliminary formation of an ylide. The multiplicity of the possible pathways is illustrated in Scheme 7,[58] equation (14) (photolysis in dioxane affords only **27**, 57% and **28**, 43%),[62] and Scheme 8.[63]

The electron deficiency in the ketocarbene intermediate can be satisfied through various types of addition reactions. Cyclopropane derivatives are the result of inter- or intra-molecular cycloaddition to alkenic double bonds. In the case of Z-group-activated C=C, the initial reaction of the diazo ketone is usually a 1,3-dipolar cycloaddition to give a pyrazoline derivative (see equation 9); on heating these decompose with nitrogen elimination, resulting in cyclopropane formation (*e.g.* **29** → **30** → **31**).[64] The electrophilic ketocarbenes generated by photolysis or under thermal control normally undergo the Wolff rearrangement with too great a rapidity to allow trapping by a nucleophilic double bond, even in the same molecule. Hence, the formation of the tricyclo[1.1.1.$0^{4,5}$]pentane skeleton by this means (equation 15) is quite exceptional.[65] Silver benzoate catalysis, however, affords only the Wolff rearrangement product (**32**). The production of cyclopropanes is of some importance in synthesis, and hence there have been a number of studies directed towards inhibition of the rearrangement pathway.[9] Photolysis of diazo esters affords alkoxycarbonylcarbenes which rearrange relatively slowly and, accordingly, cyclopropanation reactions have been observed in both direct and sensitized irradiations.[6] The *exo* addition route is favored (*e.g.* equation 16).[66] Similar results may be achieved by copper-catalyzed decomposition of the



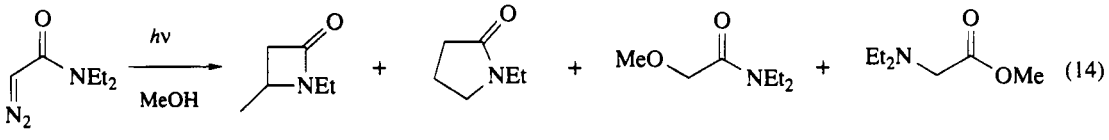


(23) **(24)** **(25)** **(26)**

(i)	$n = 1$	62%	–	–	–
	$n = 2$	35%	–	–	–
(ii)	$n = 1$	5%	57%	–	–
	$n = 2$	2%	30%	30%	–
(iii)	$n = 1$	–	39%	–	13%
	$n = 2$	–	20%	15%	–

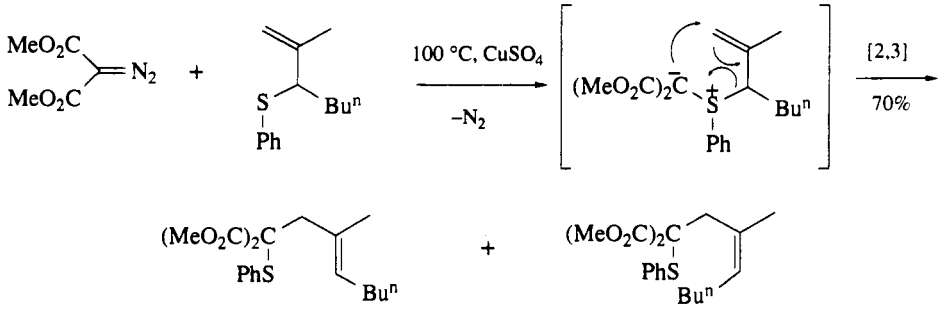
i, *hν*, THF/H_2O; ii, Ag_2O, THF/H_2O; iii, CuO, Δ, hexanes

Scheme 7



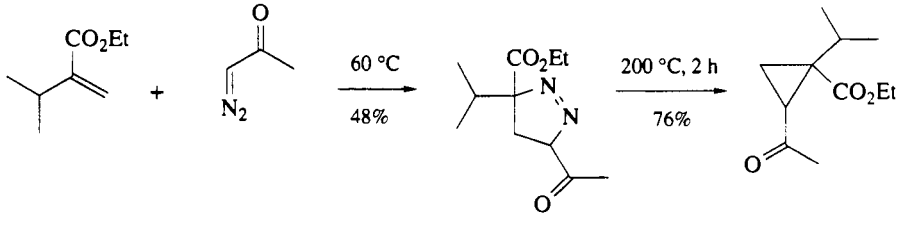
(14)

(27) 43% **(28)** 5% 34% 18%

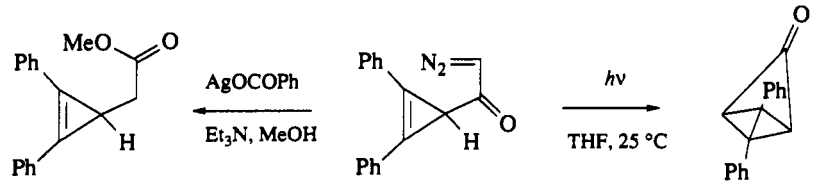


90:10

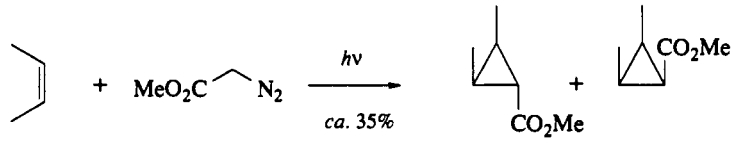
Scheme 8



(29) **(30)** **(31)**

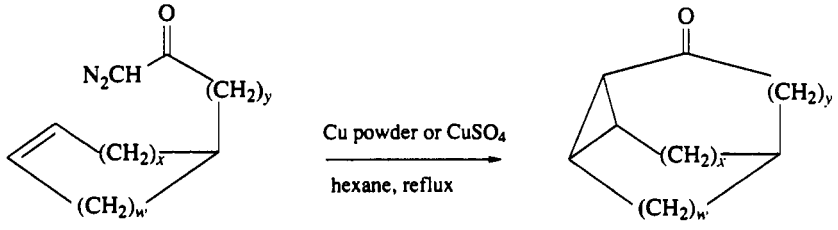


(32) (15)

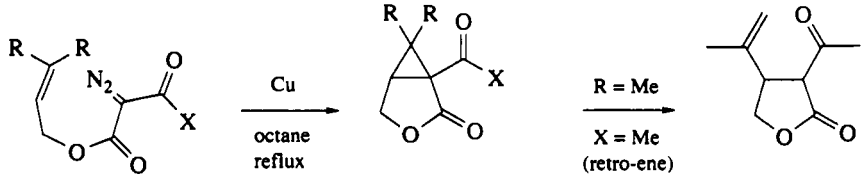


(33) 71.4:28.6 (34) (16)

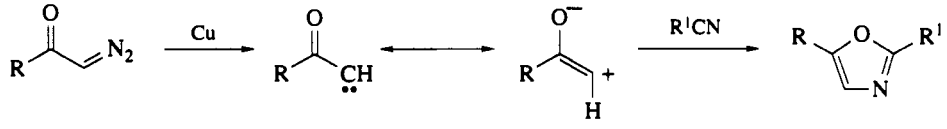
diazo ester,[67] but loss of the metallocarbene can occur through dimerization (*e.g.* to form dimethyl fumarate as well as **33** and **34**).[66] The rearrangement of ketocarbenes is greatly inhibited through complexation by copper. Copper powder and anhydrous copper(II) sulfate are the favored catalysts, and intramolecular trapping of the metallocarbene is relatively efficient. Equations (17) (w = 1–4, x = 0–2, y = 0–1; yields *ca.* 50%)[68] and (18) (R = H, Me; X = Me, OEt; yields 30–50%)[69] hopefully indicate the scope.[9] Allylic C—H insertion may occur in competition with cyclopropanation and Wolff rearrangement, but by the appropriate choice of the transition metal catalyst (and its ligands), a degree of control may be achieved.[9,70] Similar reactions occur with other multiple bonds, but with nitriles, for example, formal 1,3-dipolar cycloaddition occurs to give oxazoles; yields are improved by copper catalysts (*e.g.* equation 19).[71] In the absence of such trapping agents, and the use of inert solvents and copper(II) oxide as catalyst, symmetrical diacylethylenes are obtained by dimerization of the carbenone.[6,7,72] Sometimes azines (*e.g.* RCOCH=N—N=CHCOR) are obtained by the reaction of the carbene with the original diazo compound.[7]



(17)



(18)



(19)

In the light of the large number of ways in which the reaction of α-diazocarbonyl compounds can be deflected away from the Wolff rearrangement pathway to give the ketene intermediate, it is clear that, in practice, careful thought has to be given to the choice of reaction conditions. Nevertheless, the Wolff rearrangement is a synthetic tool of very wide scope, and in the following sections only a flavor of a large body of chemistry can be given.

3.9.3 THE CHEMISTRY OF WOLFF REARRANGEMENTS

The essence of the Wolff rearrangement is the production of the ketene intermediate (**14**; Scheme 5). The fate of the ketene is determined by its structure and the reaction conditions. Usually the ketene is trapped *in situ* with a weak acid (RXH) to give the addition product (**15**). A variety of weak acids can be employed, but water, alcohols, ammonia, or primary or secondary amines are the most popular reagents (*i.e.* XR = OH, OR, NH_2, NHR, NHOH, NR_2, SR). The structure of the carboxylic acid or derivative (**15**) thus formed is inevitably linked to the nature of the groups R^1 and R^2 in the original α-diazocarbonyl compound (**9**). If R^1 = H, then the overall transformation is, in effect, a one-carbon homologation (*i.e.* $R^2CO_2H \rightarrow R^2COCl \rightarrow R^2COCHN_2 \rightarrow R^2CH_2COXR$). This is the Arndt–Eistert synthesis,[2–11,73] and is the principal application of the Wolff rearrangement, since it represents a rapid, efficient and economical method, of wide scope, for effecting homologation. When $R^1 \neq H$, then the ultimate product (**15**) is an α-substituted carboxylic acid or derivative, and the overall change represents an extension to the Arndt–Eistert synthesis. However, the Wolff rearrangement, (**11**) → (**14**), may be less efficient here because of competing decomposition pathways for the carbene intermediate (**11**); see Section 3.9.2.3. Hence, very much less attention has been focused on the case $R^1 \neq H$. These two aspects of the Arndt–Eistert synthesis are covered in Section 3.9.3.1.

A third possibility arises when R^1 and R^2 are directly linked such that (**9**) is a cyclic α-diazo ketone. Rearrangement to (**14**) therefore represents a ring contraction, and trapping by RXH affords the ring-contracted carboxylic acid derivative (**15**). This area is covered in Section 3.9.3.2.

Occasionally the ketene (**14**) is sufficiently stable to allow its isolation in the absence of the coreactant RXH (*e.g.* $R^1 = R^2$ = aryl).[1b] In hydrocarbon solvents, however, the ketene is usually lost through self-dimerization or through inter- or intra-molecular cycloaddition reaction with alkenic double bonds. This aspect of the Wolff rearrangement is covered in Section 3.9.3.3. Extensions to the Wolff rearrangement strategy are covered in the concluding sections.

3.9.3.1 Homologations and Related Reactions

In the usual Arndt–Eistert homologation strategy, (**9**) → (**14**) → (**15**), the nonmigrating group R^1 is a hydrogen atom and the starting material is an α-diazomethyl ketone or ester. In principle, the ketene (**14**) could also be generated from an α-diazo aldehyde ($R^1C(N_2)CHO$) in which the migrating group (R^2 in **9**) is a hydrogen atom. However, the lack of such examples is indicative of the greater reactivity and poorer accessibility of α-diazo aldehydes.[30] Table 1 and the accompanying formulae provide a short summary of the many hundreds of examples of the Arndt–Eistert synthesis that have been published. Silver ion catalysis or photolysis are the favored methods for effecting the reaction. In the preparation of carboxylic acids (*i.e.* RXH = H_2O), solubility problems usually dictate the use of water as a diluant rather than as the main solvent. Hence, it can be more efficient to trap the ketene with an alcohol or amine, and subsequently hydrolyze the ester or amide obtained. The preparation of the peptides (**52**) and (**55**) indicates that the trapping agent RXH can be a fairly sophisticated molecule in its own right. In several of these examples it can be seen that migration of R^2 occurs with complete retention of configuration.

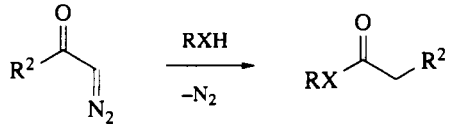
The migratory aptitude of R^2 in (**11**) varies widely with its structure (see Section 3.9.2.1), the shift of an alkoxy group being among the slowest. The formation of alkoxyketenes in the photolysis of alkyl diazoacetates is a fairly recent discovery.[9] The major competing reactions of the carbene precursor are insertions into the C—H and O—H bonds of alcohols employed as solvents and ketene traps. The extent of Wolff rearrangement varies with structure: ethyl diazoacetate (20–25%), phenyl diazoacetate (45–60%), and *N*-methyldiazoacetamide (30%).[94] These reactions are of limited synthetic interest at present.

The value of the Arndt–Eistert method in synthesis rests with the versatility of the products obtained, and there have been a number of developments which increase the overall appeal. One of these allows the direct synthesis of homologous aldehydes by the reduction of the *N*-methylanilide with lithium aluminum hydride, or the thiol ester using Raney nickel (Scheme 9).[4,76]

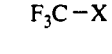
Table 2 surveys some of the results of the Arndt–Eistert method for higher order α-diazocarbonyl systems (*i.e.* **9**; R^1, $R^2 \neq$ H). The mildness of the photochemical procedure under neutral conditions is nicely demonstrated by the isolation of β-keto acids from the photolysis of α-diazo-β-keto thiol esters in the presence of water (entry 6).[73,91] This work indicates that the migratory aptitude of RS is greater than RO, and occurs exclusively. Likewise, it has been shown that in the rearrangement of methyl 3-diazo-2,4-dioxopentanoate (*i.e.* $MeCOC(N_2)COCO_2Me$) the migratory aptitudes fall in the series Me > $MeCO_2$ > MeO.[92] Hence, although the decomposition of an unsymmetrical 2-diazo-1,3-dicarbonyl compound can give two different ketenes, one pathway usually predominates and the procedure shows sufficient

selectivity to be of value in synthesis.[11] The reactions in which R^1 represents a sulfonyl or phosphonate group are also of interest in this respect.

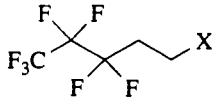
Table 1 Arndt–Eistert Homologations



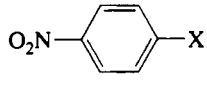
Diazo ketone	*RXH*	*Activation*	*Solvent/conditions*	*Product*	*Yield (%)*	*Ref.*
(**35a**)	EtOH	Ag_2O	EtOH, reflux, 18 h	(**35b**)	40	74
(**36a**)	NH_3	$AgNO_3$	aq. NH_3, reflux, 2 h	(**36b**)	33	75
(**37a**)	Bu^tOH	AgOCOPh	Bu^tOH, reflux, 1.25 h	(**37b**)	57	39
(**38a**)	EtSH	*hν*	Et_2O, 8 h	(**38b**)	67	76
(**38a**)	PhNHMe	*hν*	PhH, 3 d	(**38c**)	45	76
(**39a**)	H_2O	Ag_2O	aq. dioxane, 65 °C, 2.5 h	(**39b**)	64	77
(**40a**)	EtOH	AgOCOPh	EtOH, reflux, 1 h	(**40b**)	88	78
(**41a**)	H_2O	Ag_2O	aq. dioxane, 25 °C, 1 h	(**41b**)	33	79
(**42a**)	H_2O	Ag_2O	H_2O, 50 °C	(**42b**)	68	49
(**43a**)	MeOH	AgOCOPh	MeOH, 25 °C, 15 min	(**43b**)	55	80
(**44a**)	H_2O	Ag_2O	aq. dioxane, reflux, 2 h	(**44b**)	33	81
(**45a**)	EtOH	Ag_2O	EtOH, reflux, 1 h	(**45b**)	68	82
(**46a**)	H_2O	Ag_2O	aq. dioxane, 70 °C, 1.5 h	(**46b**)	81	83
(**47a**)	H_2O	*hν*	aq. dioxane, 2.75 h	(**47b**)	58	84
(**48a**)	MeOH	Ag_2O	MeOH, 100 °C, 13 h	(**48b**)	65	85
(**49a**)	MeOH	*hν*	MeOH, 6–8 h	(**49b**)	70	86
(**50**)	(**51**)	Ag_2O	dioxane, 60 °C	(**52**)	62	87
(**53**)	(**54**)	Ag_2O	dioxane, 65 °C, 10 min	(**55**)	45	88



(**35a**) X = $COCHN_2$
(**35b**) X = CH_2CO_2Et

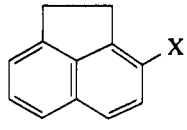


(**36a**) X = $COCHN_2$
(**36b**) X = CH_2CONH_2

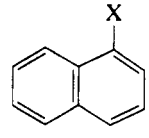


(**37a**) X = $COCHN_2$
(**37b**) X = $CH_2CO_2Bu^t$

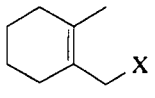
(**38a**) X = $COCHN_2$
(**38b**) X = CH_2COSEt
(**38c**) X = $CH_2CON(Me)Ph$



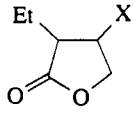
(**39a**) X = $COCHN_2$
(**39b**) X = CH_2CO_2H



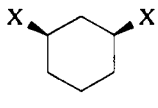
(**40a**) X = $COCHN_2$
(**40b**) X = CH_2CO_2Et



(**41a**) X = $COCHN_2$
(**41b**) X = CH_2CO_2H

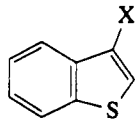


(**42a**) X = $COCHN_2$
(**42b**) X = CH_2CO_2H

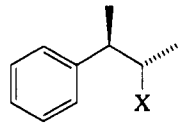


(**43a**) X = $COCHN_2$
(**43b**) X = CH_2CO_2Me

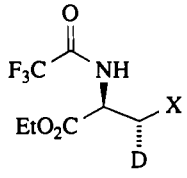
(**44a**) X = $COCHN_2$
(**44b**) X = CH_2CO_2H



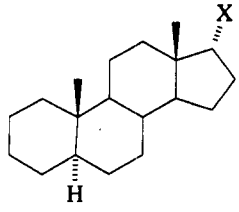
(**45a**) X = $COCHN_2$
(**45b**) X = CH_2CO_2H



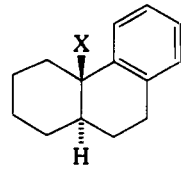
(**46a**) X = $COCHN_2$
(**46b**) X = CH_2CO_2H



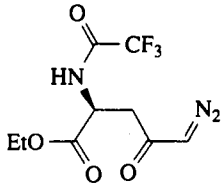
(**47a**) X = $COCHN_2$
(**47b**) X = CH_2CO_2H



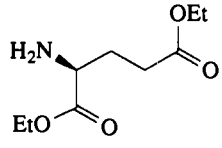
(**48a**) X = $COCHN_2$
(**48b**) X = CH_2CO_2Me



(**49a**) X = $COCHN_2$
(**49b**) X = CH_2CO_2Me



(**50**)



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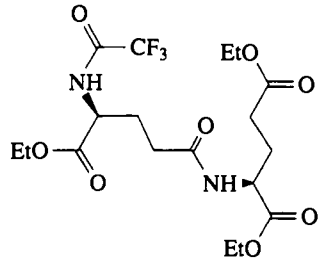
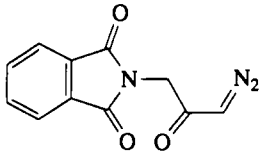


(**52**)



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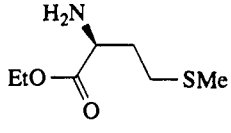
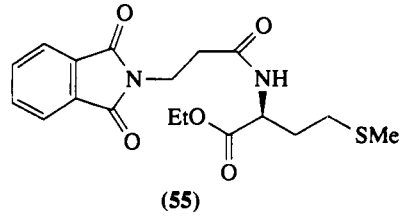


(**54**)



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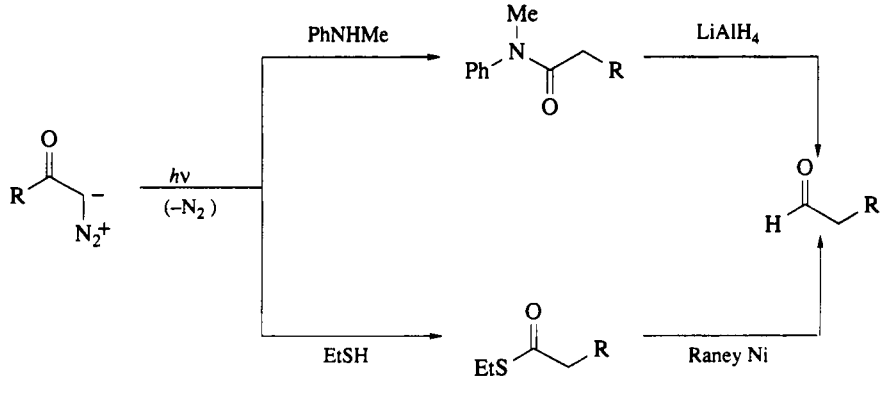
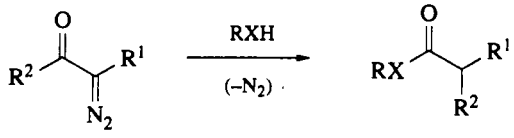
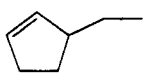
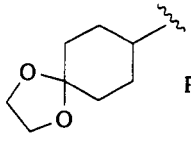


Scheme 9

Table 2 Rearrangements Leading to α-Substituted Carboxylic Acids and Derivatives



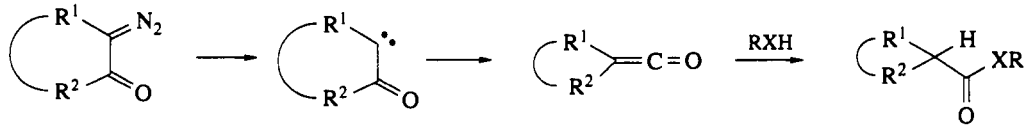
R^2	R^1	*RXH*	*Activation*	*Solvent/conditions*	*Yield (%)*	*Ref.*
4-ClC_6H_4	Me	$PhCH_2OH$	190 °C	$PhCH_2OH$, isoquinoline, 5 min	87	19
$PhCH_2$	Et	NH_3	$AgNO_3$	aq. NH_3, 80 °C, 2 h	60	89
Ph	$(CH_2)_3CO_2Me$	$PhNH_2$	150 °C	$PhNH_2$, 5 min	55	59
Me_2CH	SO_2CH_2Ph	$PhCH_2OH$	110 °C	PhMe, 2 h	86	90
Ph	SO_2CH_2Ph	$PhCH_2OH$	110 °C	PhMe, 4 h	92	90
$H_2C{=}CHCH_2S$	CO_2Me	H_2O	*hν*	PhH, 3 h	70	91
MeO_2C	CO_2Me	MeOH	*hν*	PhH, 4 h	83	92
Me	$COCO_2Me$	MeOH	*hν*	PhH, 6 h	—	92
	$PO(OMe)_2$	EtOH	*hν*	CH_2Cl_2, 2–3 h	81	93
	$PO(OMe)_2$	EtOH	*hν*	CH_2Cl_2, 2–3 h	66	93

3.9.3.2 Ring Contractions

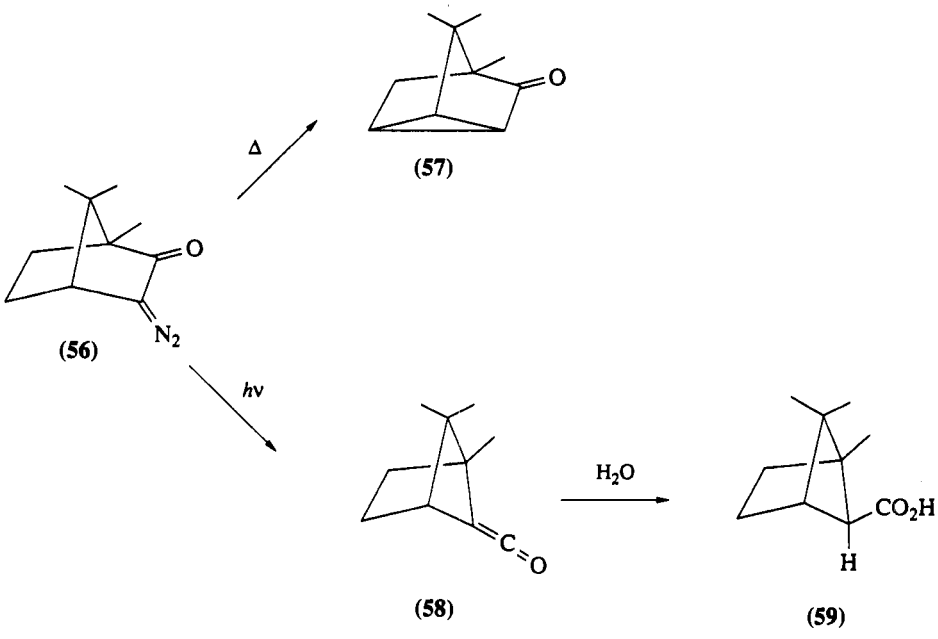
When the groups R^1 and R^2 of (**9**; Scheme 5) are directly linked to give a cyclic α-diazocarbonyl system, then Wolff rearrangement results in ring contraction (Scheme 10). It is in this area especially that the photochemical method comes into its own. In processes involving thermal control or transition metal catalysis, competing reaction pathways are frequently a serious problem. Application of the Wolff rearrangement to ring contraction is relatively recent, and post-dates Horner's pioneering work on the photochemical method.[40] Thus, although diazocamphor (**56**) yields the tricyclic ketone (**57**) upon heating,[1a] photolysis in aqueous dioxane affords *exo*-1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (**59**) through kinetically controlled hydration of the ketene intermediate (**58**) at its least-hindered *endo* face (Scheme 11).[95] This study laid the groundwork for a protocol in synthesis which has since been widely exploited, especially for the construction of strained rings since ring size imposes few restrictions on the Wolff rearrangement. This area has been reviewed previously.[4–11,96]

There are very few examples of ring contraction from cyclobutyl to cyclopropyl. Irradiation of a benzene solution of 2-diazo-3,4-bis(diphenylmethylene)cyclobutanone (**60**) in the presence of water, methanol, 2-propanol or aniline afforded the carboxylic acid derivatives (**61**) in 13, 87, 75 and 45% yield respectively. Thermolysis of an aqueous dioxane solution of (**60**) surprisingly gave (**61**; XR = OH) in higher yield (**52%**; equation 20).[97]

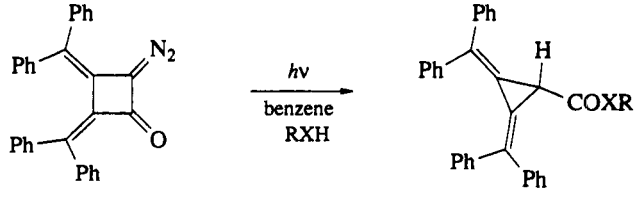
α-Diazocyclopentanones are much easier to prepare, and consequently much more attention has been given to the contraction of cyclopentanes to cyclobutanes. Several bicyclo[2.1.1]hexane derivatives have been prepared from α-diazobicyclo[2.2.1]heptanones following similar chemistry to the transformation (**56** → **59**; Scheme 11).[98] Frequently the 5-carboxylate derivatives are formed as a mixture of *endo* and



Scheme 10

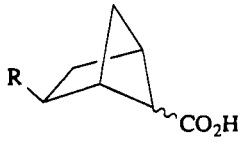


Scheme 11

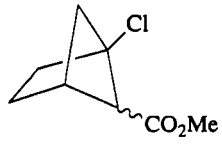


(60) (61) (20)

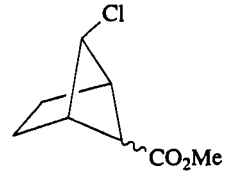
exo isomers as a result of kinetically controlled addition of RXH to each of the two faces of the ketene intermediates. The *endo:exo* ratio reflects the ease of access on steric grounds. When XR represents a large grouping, however, thermodynamic control may apply and the least-hindered carboxylic acid derivative is then formed predominantly. The derivatives (**62**)–(**66**) have been prepared by the photolysis of the analogous α-diazo ketones in the presence of the appropriate trapping agent RXH. Product ratios, where given, are in the sense *endo:exo*.



(**62a**) R = H (ref. 99)
(**62b**) R = OAc; 90:10 (ref. 100)

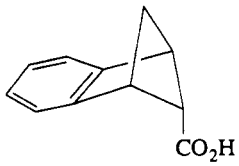


(**63**) (ref. 101)

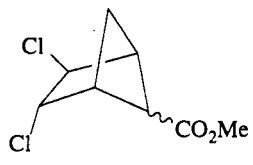


(**64a**) XR = OH; 20:80 (ref. 102)
(**64b**) XR = NHBu^t; 16.7:83.3 (ref. 102)

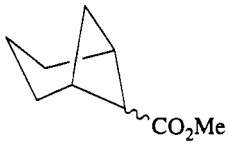
Similar procedures are also successful in the construction of cyclobutane rings in other stereochemical environments, including the formation of bicyclo[3.1.1]heptane (**67**)[105] and bridged tricyclic systems such as (**68**),[106] (**69**)[107] and (**70**).[108] A variety of annelated cyclobutanes have been prepared by the photochemical procedure; as above, yields are sometimes poor or only moderate. Examples include bicyclo[2.1.0]pentanes (**71**),[109] bicyclo[2.2.0]hexanes (**72**)[110] and cyclobuteno aromatics (*e.g.* **73**),[111] D-nor-steroids (*e.g.* **74**),[112] A-bisnorsteroids[113] and triterpenes[114] as well as the highly strained tricyclo[4.2.0.0^{1,4}]octane system (**75**),[115] and the [4.4.4.5]fenestrane (**76**).[116]



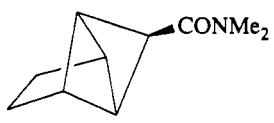
(**65**) (ref. 103)



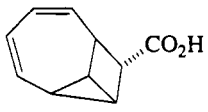
(**66**) 85:15 (ref. 104)



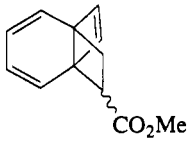
(**67**) 96:4, 75%



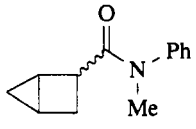
(**68**) 3%



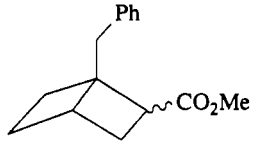
(**69**) 43%



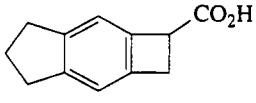
(**70**) 11%



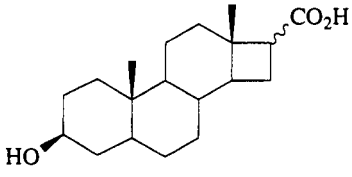
(**71**) 80:20



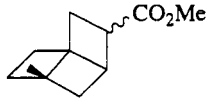
(**72**) 75:25, 68%



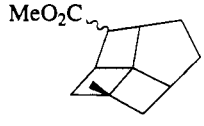
(**73**) 46%



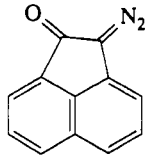
(**74**) 75%



(**75**) 84.6:15.4, 80%



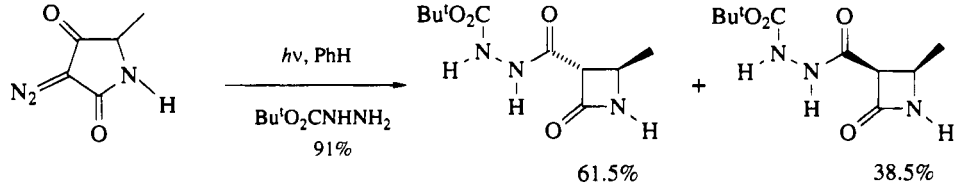
(**76**) 75:25, 20%



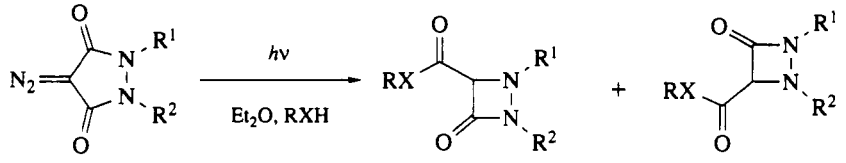
(**77**)

The ring contraction of 2-diazo-1-oxonaphthenes is very difficult because of a large increase in in-plane strain. The parent compound (**77**) failed to undergo Wolff rearrangement on thermolysis, instead giving the ketazine (81%; *cf.* equation 5).[117] Chapman and coworkers[43a] have observed the photochemical extrusion of nitrogen from (**77**) and related compounds in an argon matrix at 10–15 K. The α-ketocarbenes were characterized spectroscopically and by trapping; excitation (T_0–T_1) led to ring contraction, the rates paralleling the increase in strain of ketene formation. In solution-phase preparative chemistry such α-ketocarbenes are, presumably, simply too reactive to survive encounters with the solvent or unreacted diazoketone.

Applications of the Wolff rearrangement in the synthesis of four-membered heterocycles have been much more limited, and have largely been directed towards the simpler mono- and bi-cyclic systems. Ring contraction of 3-diazopyrrolidine-2,4-diones affords a relatively simple route to β-lactams;[118] carbon migrates in preference to nitrogen (*e.g.* equation 21).[118a] The photochemical decomposition of 4-diazopyrazolidine-3,5-diones analogously yields aza-β-lactams. Unsymmetrically substituted substrates give rise to a mixture of regioisomers (equation 22).[119] Relative migratory aptitudes fall in the series NPh > $NCHPh_2$ ≈ NCH_2Ph ≈ NMe > NCH_2CO_2Et; yields were in the range 30–72% and regioselectivities varied from *ca.* 1:1 to 2.8:1. Earlier work on 2,2,5,5-tetraalkyl-4-diazotetrahydro-3-oxofurans had shown that rearrangement to oxetane-3-carboxylates occurred in good yield under photochemical, thermal or Ag_2O-promoted conditions.[7]

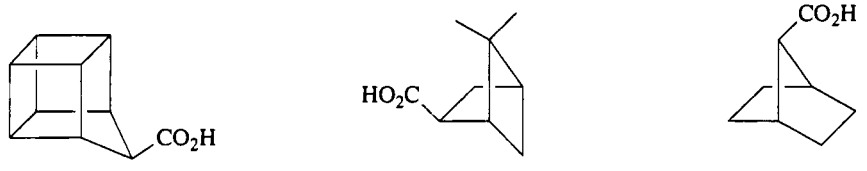


(21)

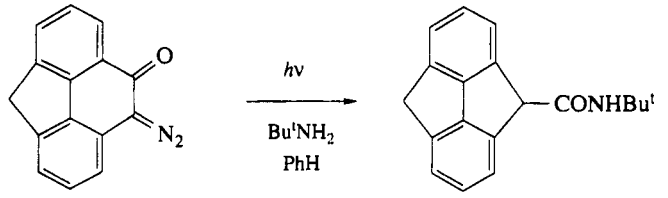


(22)

There are a considerable number of examples of great variety for the construction of cyclopentane rings by ring contraction.[4–11,96] Six-membered rings in highly strained polycyclic systems are amenable to contraction, as shown by the synthesis of homocubanecarboxylic acid (**78**),[120] but there have been few applications in this area. Among bicyclic systems, photolysis of the appropriate diazo ketones resulted in efficient conversion into the bicyclo[2.1.1]hexane-2-carboxylic acid (**79**)[99] and bicyclo[2.2.1]heptane-7-carboxylic acid (**80**).[121] In view of the earlier discussion concerning diazo ketone (**77**), the very low yield of ring-contracted product from photolysis of the phenanthrene derivative (**81**; equation 23), is not too surprising. A dihydrobenzofuran is the major product, resulting from an unprecedented reaction of the ketocarbene (or 1,3-dipole) with the aromatic solvent. On the other hand, Wolff rearrangement of 9-diazo-10-oxophenanthrene itself proceeds efficiently.[122]



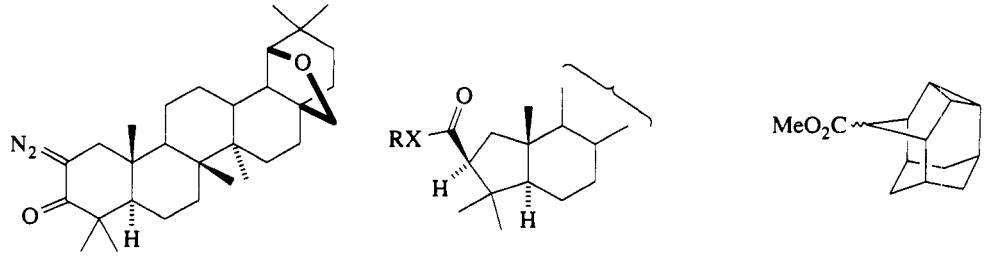
(**78**) 47% (**79**) 68% (**80**) 82%



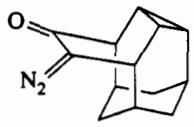
(**81**) 2%

(23)

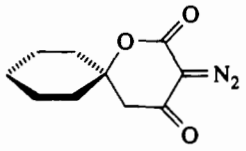
Simple 2-diazocyclohexanones are readily converted by photolysis in methanol, for example, into methyl cyclopentanecarboxylates.[123] However, the Favorskii method for ring contraction (see Volume 3, Chapter 3.7) is usually more convenient in these systems since the necessary starting materials are more readily prepared. Applications have been found in the synthesis of A-norsteroids[113,124] and A-nortriterpenes. For example, photolysis of 2-diazoallobetulone (**82**) in the presence of weak acids RXH affords mainly the 2β-carboxy-A-nor derivative (**83**).[114] The 3,12-cycloiceane esters (**84**) are obtained in 52% yield from the photolysis of the diazo ketone (**85**) in methanol.[125] Wolff rearrangement of cyclic 2-diazo-1,3-dicarbonyl systems gives ring-contracted β-keto carboxylic acid derivatives.[126,127] The predominant or exclusive product of rearrangement of an unsymmetrical diazo compound can be predicted from the relative migratory aptitude data discussed previously (see Sections 3.9.2.1 and 3.9.3.1). Thus, for example, exclusive carbon migration occurs in the conversion of the spirocyclic diazo compound (**86**) into (**87**; 69%).[128]



(**82**) (**83**) (**84**)



(85)



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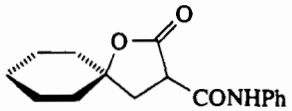
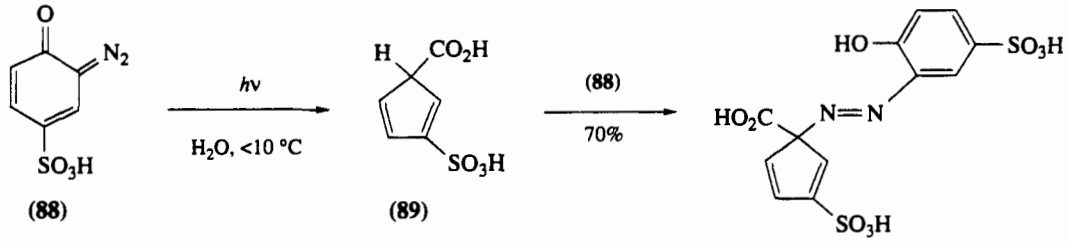
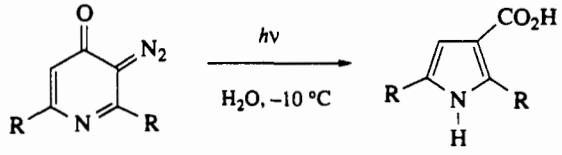


(87)

The photochemical decomposition of *o*-diazo oxides ('*o*-quinone diazides') is of both preparative and commercial interest and importance. Wolff rearrangement with ring contraction gives access to the cyclopentadiene system (including heterocyclic analogs). Since the *o*-diazo oxides are usually prepared from *o*-aminophenols, the process is remarkable in that it represents the shrinking of a benzene ring. However, the products are prone to undergo diazo coupling with unreacted starting material (*e.g.* **88** → **89** → **90**),[129] but this chemistry has been exploited in the Diazotype offset photocopying process.[130] Reduction of pH inhibits the coupling process, hence the photolyses for preparative ring contraction are often conducted in acidic solvents (*e.g.* aq. AcOH). Reaction of benzene derivatives is decidedly more difficult than for *o*-diazo oxides based on naphthalene and higher aromatics where stabilization is not so great. Thermolysis can be used for the latter systems, but an intense UV source is necessary for benzenoid *o*-diazo oxides to enhance the rate of rearrangement. An indication of the variety of the synthetic applications is given in equations (24),[131] (25),[131] (26)[132,133] and (27).[133] The migration of sp^2 nitrogen (equation 25) is particularly noteworthy. Similar routes have been used for the synthesis of a variety of indenecarboxylic acids (yields *ca.* 20–60%),[131] related systems[134] and pentalenes such as (**105**; 75%).[135]

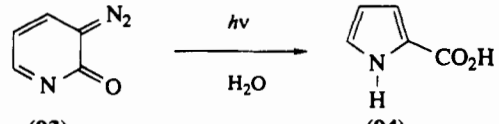


(88) → (89) → (90)



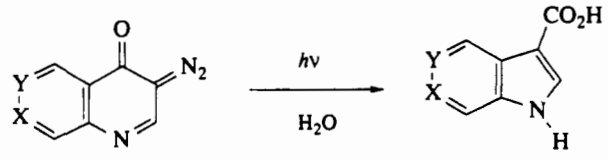
(24)

(91) R = H, Me (92) R = H, Me



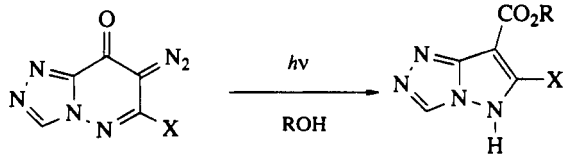
(25)

(93) (94)

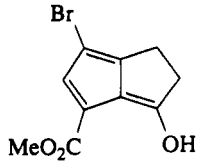


(26)

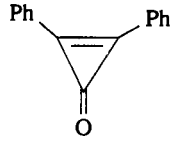
(95)	X = Y = CH	(96)
(97)	X = CH, Y = CCl	(98)
(99)	X = N, Y = CH	(100)
(101)	X = CH, Y = N	(102)
(103)	X = CMe, Y = CH	(104)



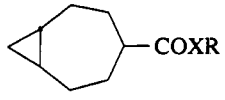
X = Me, Ph (27)



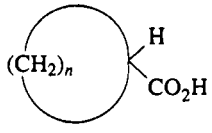
(105)



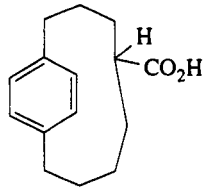
(106)



(107)



(108)



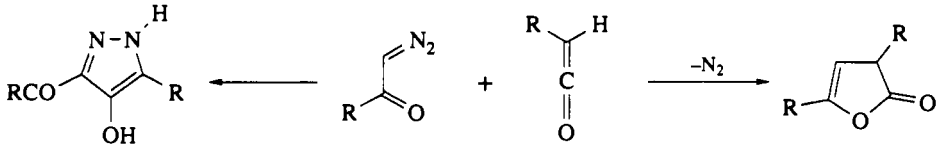
(109)

Irradiation of 1,3-bisdiazocyclohexan-2-ones in hydroxylic solvents affords cyclopentene-1-carboxylic acids and esters; regiochemical control is only moderate.[9,136] Although the course of the reactions could be accommodated by sequential Wolff rearrangement and [1,2] H-shift, studies on 1,3-bisdiazo-1,3-diphenylpropan-2-one indicate the formation of the cyclopropenone intermediate (**106**).[137]

There have been relatively few applications to the contraction of larger rings. Irradiation of solutions of 4-diazo-*trans*-bicyclo[6.1.0]nonan-5-one afforded the strained carboxylate derivatives (**107**; XR = OH, OMe) in *ca.* 22–45% yield.[138] Small to medium ring diazo ketones afford the ring-contracted carboxylic acids (**108**; n = 4–10) in 25–95% yield on photolysis in dioxane–H_2O[139] or THF–H_2O.[58] Thermolysis of the diazo ketones in aniline at 150–160 °C gave the anilides of (**108**) in 78–91% yield.[28] Transannular reactions of the ketocarbene intermediates can be a complication under some conditions.[28,139] 4-Carboxy[8]paracyclophane (**109**) has been prepared (25%) by the photochemical method.[140]

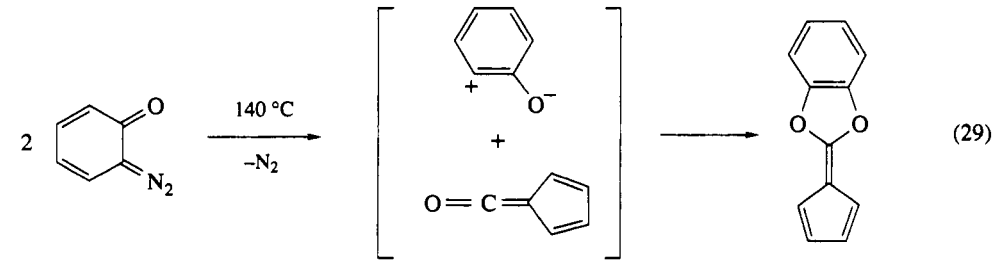
3.9.3.3 Cycloaddition Reactions

When the Wolff rearrangement is conducted in inert solvents (*i.e.* in the absence of weak acids, RXH) it is possible, in principle, to intercept the ketene intermediate; stabilized ketenes can be isolated.[1b] Their [2 + 2] cycloadditions to activated alkenes and dienes is a valuable synthetic procedure.[141] However, such reactions are relatively slow, and the generation of ketenes from α-diazo ketones provides a number of other species capable of acting as trapping agents. Thus, the rather labile aldoketenes react with intact α-diazo ketone to give butenolides or pyrazoles (equation 28).[7,9,11] The *o*-diazo oxides on thermolysis afford dioxofulvalenes, resulting from the formal [1,3] dipolar cycloaddition of the ketocarbene intermediate to the ketene (equation 29).[9,11] Nevertheless, trapping the ketene by cycloaddition to C=C, C=N, N=N and the C=O bonds of *o*-quinones has been achieved frequently.[9,11] but such reactions have been studied mainly from a general interest viewpoint rather than for specific purposes in synthesis. Various

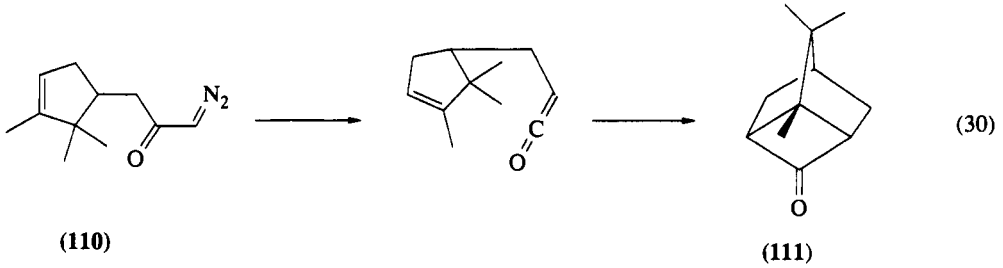


(28)

examples of intramolecular trapping by a strategically located C=C in the molecule are also known. A particularly remarkable case is shown in equation (30).[142] The major product of decomposition of diazo ketone (**110**) is 6,7,7-trimethyltricyclo[3.2.1.$0^{3,6}$]octan-4-one (**111**), even in boiling aqueous dioxane. On the other hand, decomposition of the more rigid diazo ketone (**112**) partitions between intramolecular trapping of the carbene to give (**113**) and the ketene to give (**114**) by way of a Cope rearrangement.[143] The pathway to (**114**) *via* the ketene is favored in the photolytic reaction, whereas copper-catalyzed decomposition affords (**113**) preferentially. By-and-large, therefore, this area of diazo ketone chemistry has scarcely been over-exploited.

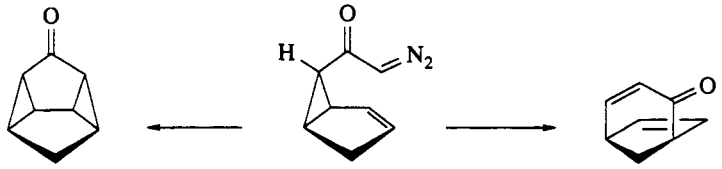


(29)



(30)

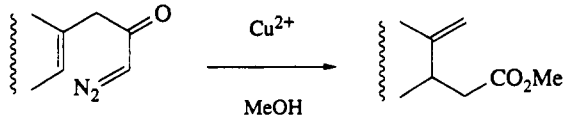
(**110**) (**111**)



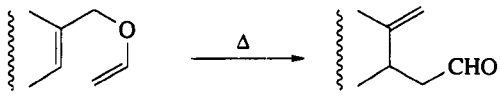
(**113**) (**112**) (**114**)

3.9.3.4 The Vinylogous Wolff Rearrangement

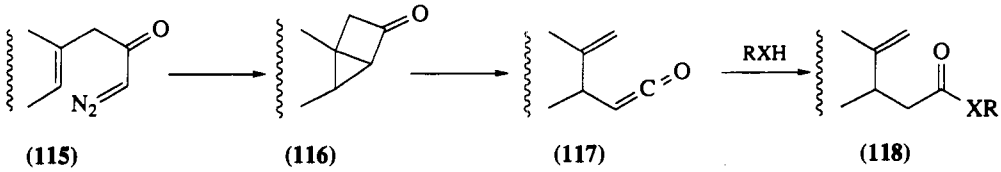
This name has been applied[144] to the decomposition of β,γ-unsaturated diazo ketones (**115**) by copper salts in the presence of alcohols, leading to skeletally rearranged γ,δ-unsaturated esters, and is a comparatively recent discovery.[144,145] The transformation represents a synthetic alternative to Claisen type rearrangements (compare equations 31 and 32). The allylic transposition of the acetate residue is thought to occur by way of a bicyclo[2.1.0]pentan-2-one (**116**), which is formed by intramolecular trapping of the ketocarbenoid (Scheme 12). Fragmentation of the bicyclo[2.1.0]pentan-2-one gives rise to a β,γ-unsaturated ketene (**117**), which is captured by the added nucleophile to afford the observed γ,δ-unsaturated carboxylic acid derivative (**118**). Similar decomposition of (**115**) by thermolysis, photolysis or by silver ion catalysis gives mixtures of rearranged product and the normal Wolff product, respectively (**118**) and (**119**); mixture compositions vary, but the normal product (**119**) generally predominates. In contrast, copper(II) ion catalysis affords mainly rearranged products (**118**), and $Cu(OTf)_2$ and benzyl alcohol give the best results. Although the initial insertion step leading to (**116**) seems to be stereoselective, the fragmentation reaction appears to proceed with loss of this initial stereoselectivity, hence mixtures of stereoisomers are usually produced. Illustrative examples of the reaction are given in equations (33)–(35);[144] the reactions were carried out in boiling cyclohexane for 4 h. In equation (35) it can be seen that the vinylogous Wolff rearrangement leading to (**121**), a 1:1 mixture of stereoisomers, competes effectively with cyclopropanation of the γ,δ-double bond, giving a 1:1 mixture of the stereoisomers of (**120**), when the β,γ-double bond is at least equally activated.



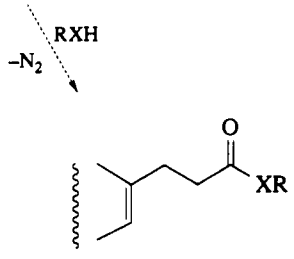
(115) (31)



(32)

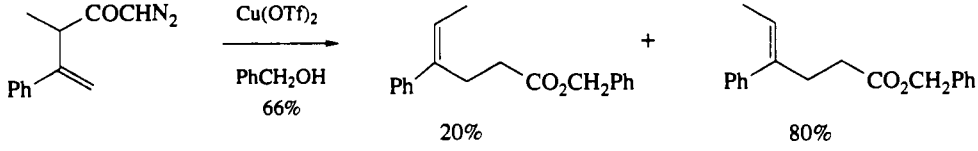


(115) (116) (117) (118)

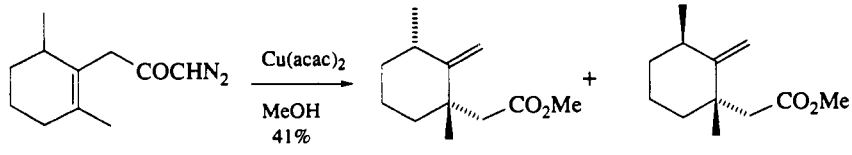


(119)

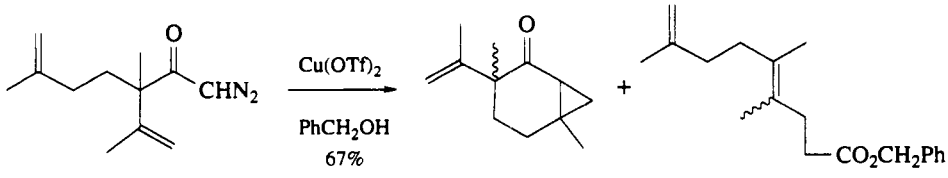
Scheme 12



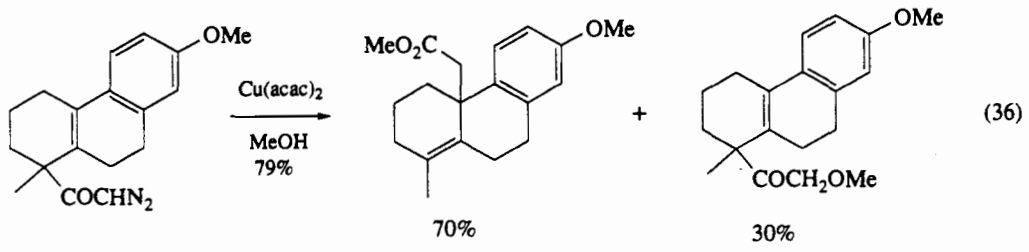
20% 80% (33)



10% 90% (34)



(120) 25% (121) 75% (35)

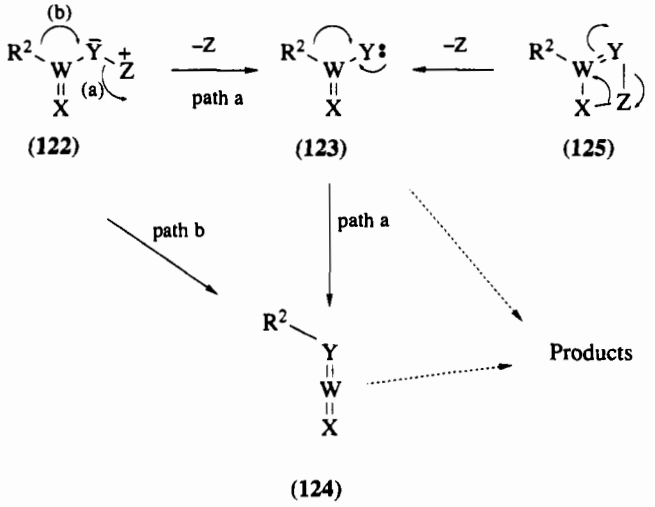


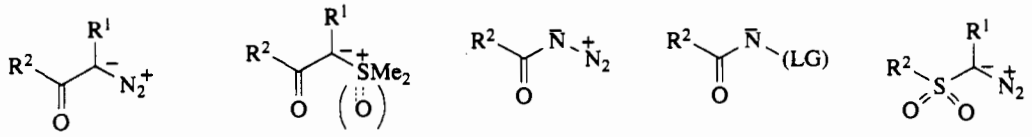
(36)

In a recent application, the vinylogous Wolff rearrangement has been used to provide angular functionalization in annelated polycyclic systems (*e.g.* equation 36).[146]

3.9.3.5 Related Reactions

The Wolff rearrangement has much broader horizons than the decomposition pathway for α-diazocarbonyl compounds, and a generalized mechanistic route is given in Scheme 13. This allows for both a stepwise pathway (a) and concerted decomposition (b). Thus, although sometimes α-diazo ketones (**122a**) appear to give the ketene (**124**) by path b, in the majority of reactions there is strong evidence for a ketocarbene intermediate (**123**) preceding the ketene. Acyl azides (**122c**), on the other hand, suffer concerted rearrangement to isocyanates (**124**) on thermolysis (Curtius rearrangement); there is no evidence for nitrene intermediates in the rearrangement pathway.[147,148] The related Schmidt, Lossen and Hofmann





(122a) (122b) (122c) (122d) (122e)

(122f) (125a) (125b) (125c)

Scheme 13

reactions, which proceed *via* (**122c**; Schmidt) or (**122d**; LG = leaving group such as Br or OAc) also follow path b but, because of the reaction conditions, products derived from the isocyanate, rather than the isocyanate itself, are isolated.[147]

The electronic make-up of the assemblage WXYZ of (**122**) can be fulfilled in a number of other ways, as indicated by the selection of structures (**122b**)–(**122f**). Although in simple α-diazo ketones there does not appear to be a strong direct electronic interaction between the carbonyl oxygen atom (X in **122**) and the terminal diazo nitrogen atom (Z in **122**), when X is a softer base (*e.g.* NR, S, Se) the cyclic form (**125**) is more stable. Thus, the intermediate (**123**) can be accessed from (**125a**)–(**125c**), further broadening the scope. Studies on these other variants of (**122**) and (**125**) have been much more limited. Reaction pathways are determined by reaction conditions, but products arising from Wolff-type rearrangements have been observed in the thermolysis or pyrolysis of acylsulfonium ylides,[149] β-ketosulfoxonium ylides (**122b**),[150] α-diazosulfones (**122e**),[151] α-diazophosphine oxides (**122f**),[152,153] 1,2,3-triazoles (**125a**),[154] 1,2,3-thiadiazoles (**125b**),[155] and 1,2,3-selenadiazoles (**125c**).[156]

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3.10
The Stevens and Related Rearrangements

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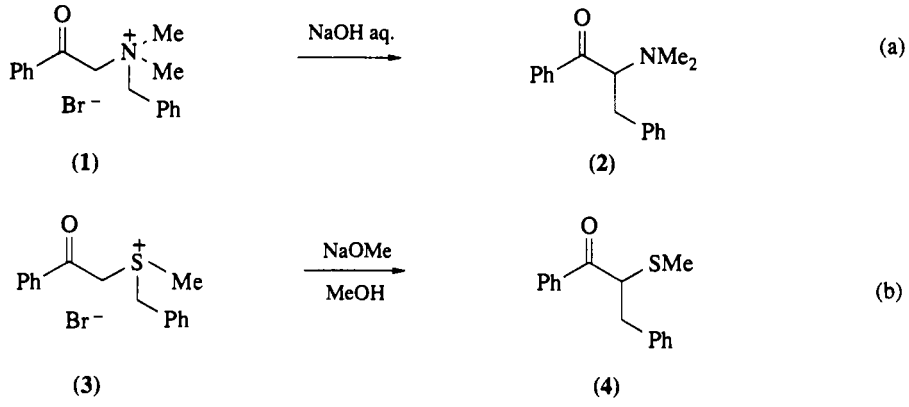
3.10.1 INTRODUCTION

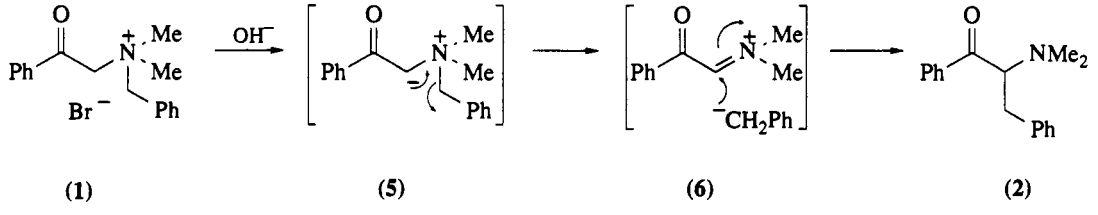
Nitrogen and especially sulfur ylides are used extensively in synthetic organic chemistry. Our understanding of the sigmatropic rearrangements of these ylidic intermediates has matured over the last few decades. These rearrangements, which often proceed with high regio-, stereo- and enantio-selectivities, have become a powerful synthetic tool.

In 1928, T. S. Stevens reported the first example of a reaction which was later to be called the Stevens rearrangement.[1] He found that, upon treatment with aqueous alkali, phenacylbenzyldimethylammonium bromide (**1**) was converted into 1-benzoyl-2-benzyldimethylamine (**2**) in high yield (Scheme 1, equation a). Soon after, in 1932, Stevens reported the analogous rearrangement of the corresponding sulfonium derivative.[2] The sulfonium bromide (**3**) was smoothly transformed into a sulfide, which was initially formulated as structure (**4**), when (**3**) was treated with hot alkali (Scheme 1, equation b). Subsequent work, however, established that the correct structure of the rearranged material was (**84**) (Scheme 19).

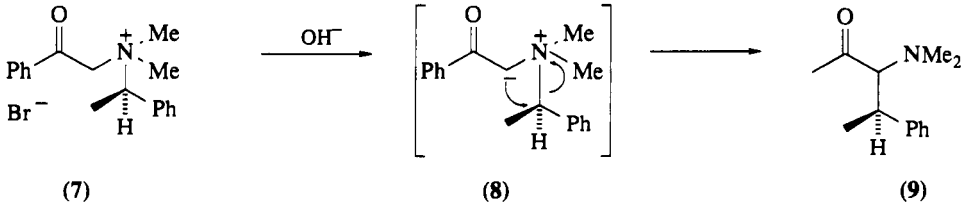


Scheme 1

A variety of groups, including allyl, propargyl and phenacyl, were also shown to be good migrating groups in ylidic rearrangements.[3] Mechanistic investigations, using ^{14}C-labeled starting material, as well as cross-over experiments, demonstrated the reaction to be intramolecular.[4] Subsequent studies of the effect of substituents on the phenyl ring on the migrating ability of the benzyl group in reactions of (**1**) gave the order *p*-NO_2 > *p*-Hal > *p*-Me > *p*-MeO.[5] This observation led Stevens to postulate that the reaction proceeded by initial formation of an ylidic intermediate (**5**) which, by heterolysis, yielded a benzylic anion and an iminium ion. This ion pair could then lead to the observed product (Scheme 2). Later, Kenyon showed that the migrating group retained its configuration during the course of the rearrangement.[6] The optically-active ammonium salt (**7**), for example, was converted into an optically-active amine (**9**) with retention of chirality at the benzylic chiral carbon atom. Wittig[7] and Hauser[8] then proposed that the reaction was a concerted intramolecular displacement of the migrating group by the carbanionic center of the ylidic intermediate (**8**; Scheme 3).



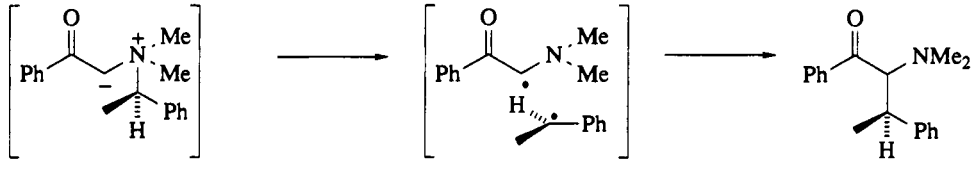
Scheme 2



Scheme 3

If the Stevens rearrangement is a concerted reaction, then the Woodward and Hoffmann rules of conservation of orbital symmetry demonstrate that it is a symmetry-forbidden reaction.[9] Later on, Ollis reinvestigated the reaction and demonstrated, in a very elegant manner, that the Stevens rearrangement proceeds by radical pair intermediates.[10] These radicals recombine quickly while being held within a solvent cage, a fact that explains the high intramolecularity and stereoselectivity observed in these rearrangements (Scheme 4).

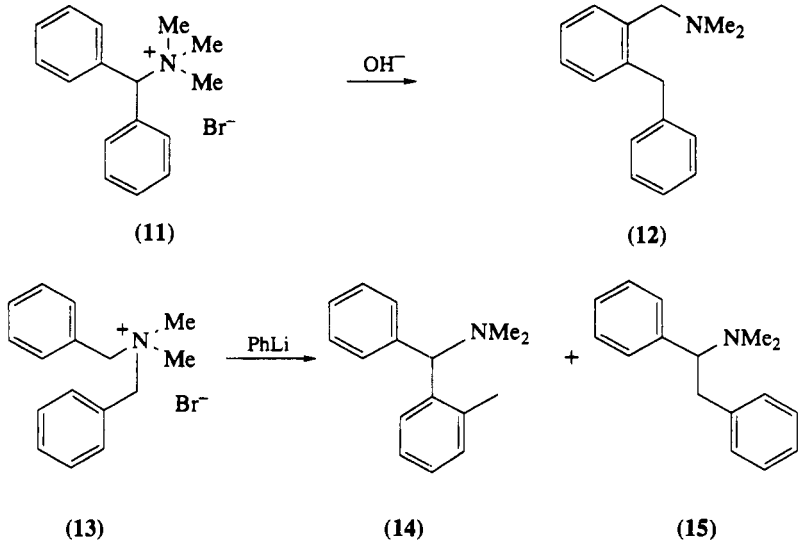
Another type of ylidic rearrangement, the Sommelet–Hauser rearrangement, was discovered later, in 1937, by Sommelet and studied extensively by Sommelet and by Hauser.[11,12] This transposition involves the base-promoted rearrangement of non stabilized ammonium and sulfonium ylides. Thus, the ammonium salt (**11**), when heated with alkali, gave cleanly the substituted diphenylmethane derivative (**12**; Scheme 5). Wittig found that the dibenzyl ammonium salt (**13**) reacted with phenyllithium giving two



(8) (10) (9)

Scheme 4

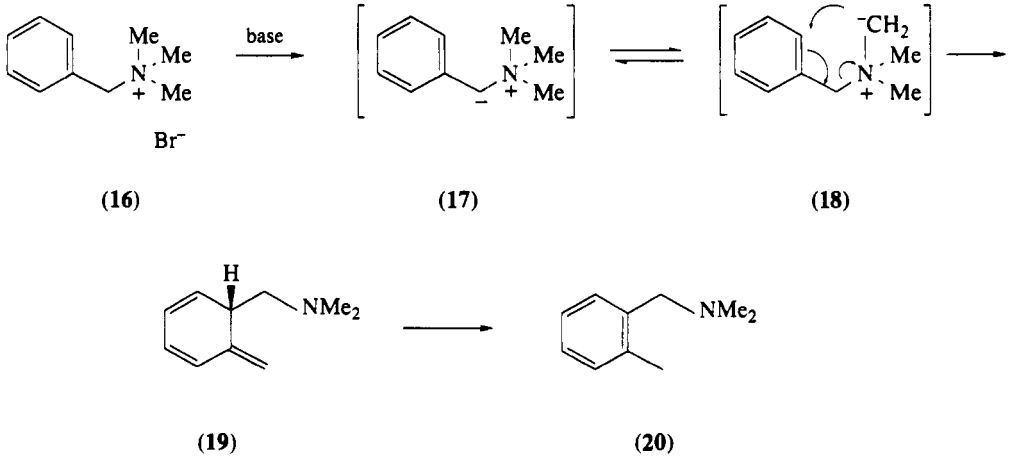
products, (**14**) and (**15**).[13] The product (**15**) is produced by a competing Stevens rearrangement. Subsequent work led to the proposed mechanism for the Sommelet–Hauser rearrangement as depicted in Scheme 6.[14] The ylide (**17**), formed upon base treatment of the ammonium salt (**16**), attacks the aromatic ring, leading to the unstable intermediate (**19**), which may be isomerized into the substituted aromatic derivative (**20**). It was also shown later that the two equilibrating ylides (**17**) and (**18**) were involved in these reactions; the ylide (**18**) being associated with the Sommelet–Hauser rearrangement.[15]



(11) (12)

(13) (14) (15)

Scheme 5



(16) (17) (18)

(19) (20)

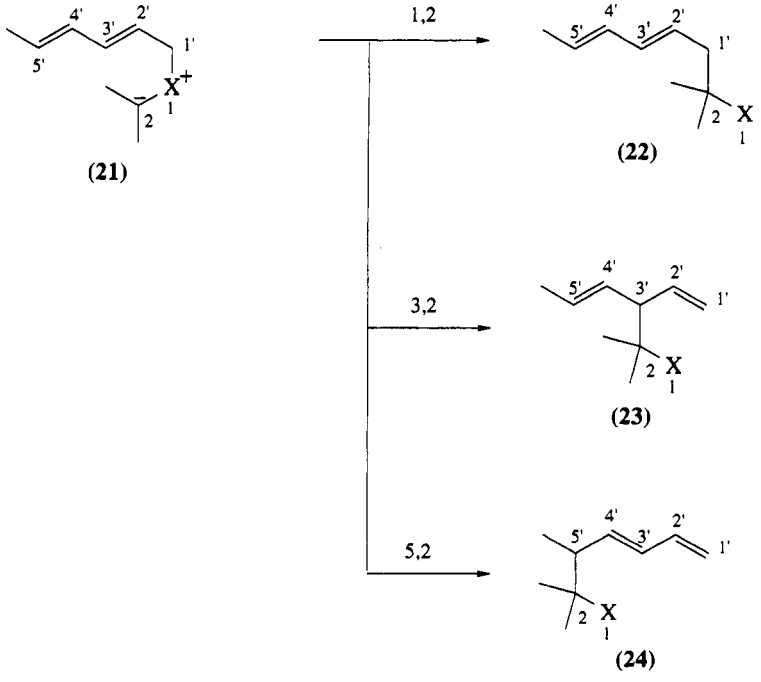
Scheme 6

In 1969, Ollis recognised that the rearrangement of allylic ammonium and sulfonium ylides was a facile process of considerable synthetic interest,[16] and Baldwin reported his generalization of the sigmatropic rearrangement processes.[17] Since then, numerous examples of the synthetic utility of ylidic rearrangements have been recorded in the chemical literature and this number is growing continuously.

3.10.2 DEFINITIONS

With some substrates, several types of ylidic rearrangements can occur simultaneously, though by judicious choice of experimental conditions, this competition can be controlled. This is of paramount importance in the utilization of these rearrangements in synthesis. The two examples described below illustrate this point.

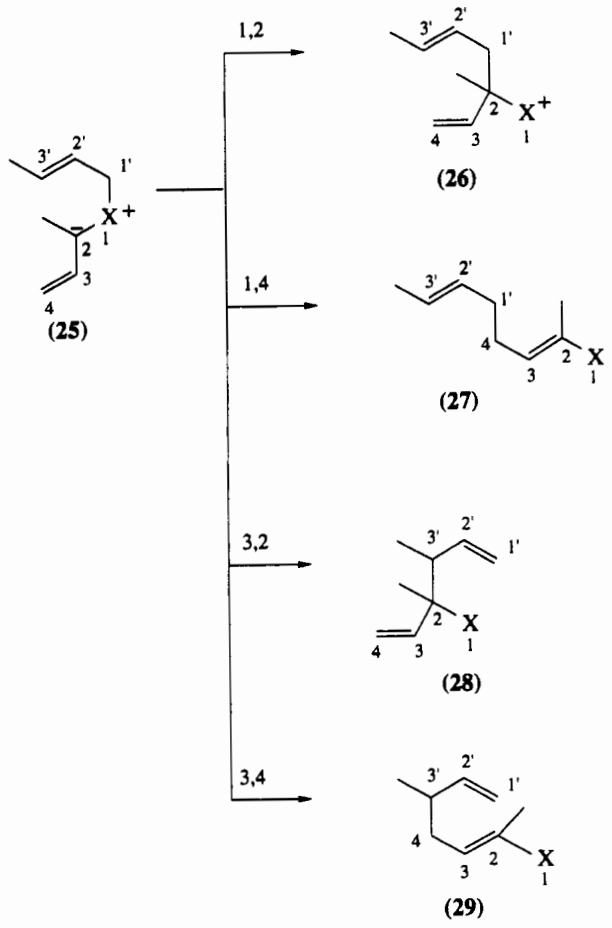
When the hypothetical ylide (**21**) is generated, then, in principle, a 1,2-, 3,2- or 5,2-rearrangement can occur, leading to the three products (**22**), (**23**) and (**24**) respectively (Scheme 7). [The 3,2-rearrangement is often reported in the literature as a 2,3-sigmatropic rearrangement. The author believes that, if the other reactions in Scheme 7 are called 1,2- and 5,2-sigmatropic rearrangements respectively, then logic would dictate that this reaction is a 3,2-sigmatropic rearrangement. We would like to encourage the use of the 'correct' 3,2 nomenclature rather than the 'incorrect', but popular, 2,3 one.] Similarly, when examining ylide (**25**), four different products (**26**), (**27**), (**28**) and (**29**) can, in principle, be identified: they are those derived from 1,2-, 1,4-, 3,2- and 3,4-sigmatropic rearrangement respectively (Scheme 8).



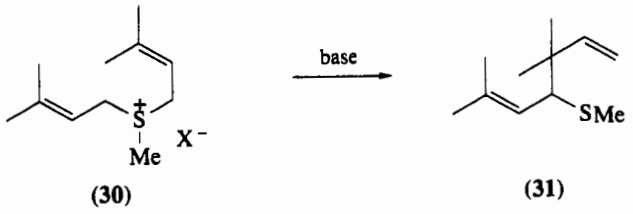
Scheme 7

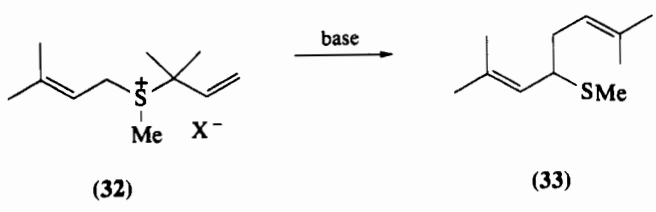
The 1,4- and 3,2-rearrangements are thermal, concerted, orbital symmetry allowed processes possessing suprafacial–suprafacial characteristics. They are facile reactions, occurring readily and under mild conditions. The 3,2-rearrangement will take place with allylic inversion, as demanded by orbital symmetry control. Thus, the sulfonium salt (**30**) gave the allylic sulfide (**31**), whereas (**32**) gave the isomerically pure (**33**; Scheme 9).[18]

The 1,4-rearrangement, though symmetry-allowed, is rarely observed.[19] The 1,2-, 5,2- and 3,4-rearrangements are symmetry-forbidden processes which would have to take place *via* a suprafacial–antarafacial mode. They have been shown to proceed by radical pair intermediates.[20]



Scheme 8



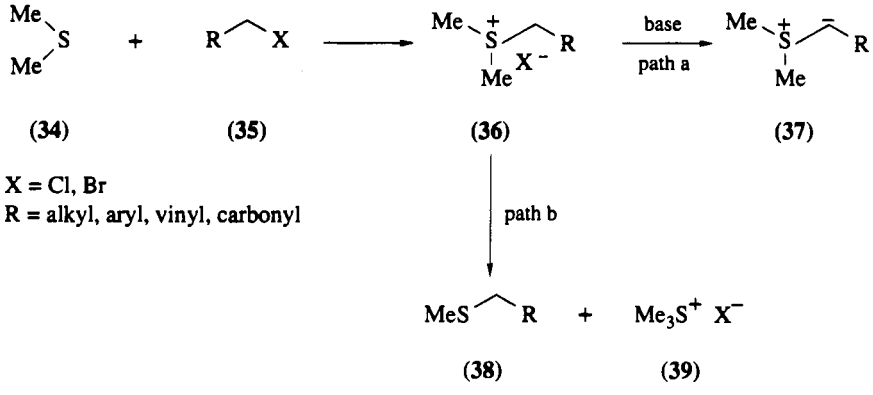


Scheme 9

3.10.3 PREPARATION OF NITROGEN AND SULFUR YLIDES

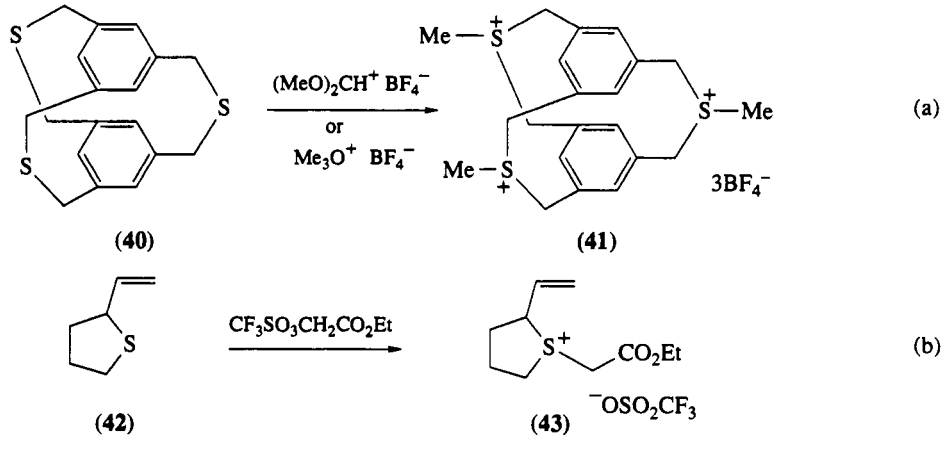
3.10.3.1 Indirect Methods

The oldest and most commonly used method for ylide preparation is the so-called 'salt-method', where a sulfonium or ammonium cation, generated by alkylation of the corresponding sulfide or amine, is deprotonated by a strong base (Scheme 10, path a). In general, an active alkylating agent is required. Primary allylic and benzylic halides, as well as α-halocarbonyl derivatives,[21] produce the ammonium or sulfonium salts fairly readily. A serious side reaction, which characterizes this method, is the competitive dealkylation of the salt by any nucleophilic halide ion produced (Scheme 10, path b).[22] Therefore, exchange of the halide ion for a non-nucleophilic counterion employing a metal salt, *e.g.* Ag^+, is performed routinely. Alternatively, the use of Meerwein salts,[23] *e.g.* $Me_3O^+BF_4^-$ (Scheme 11, equation a), or the more recently introduced triflate methodology[24] (Scheme 11, equation b) give directly the stable ammonium or sulfonium salts. The counterions in these cases, are poor nucleophiles unable to dealkylate the cations (Scheme 11).



(34) (35) (36) (37) (38) (39)

Scheme 10

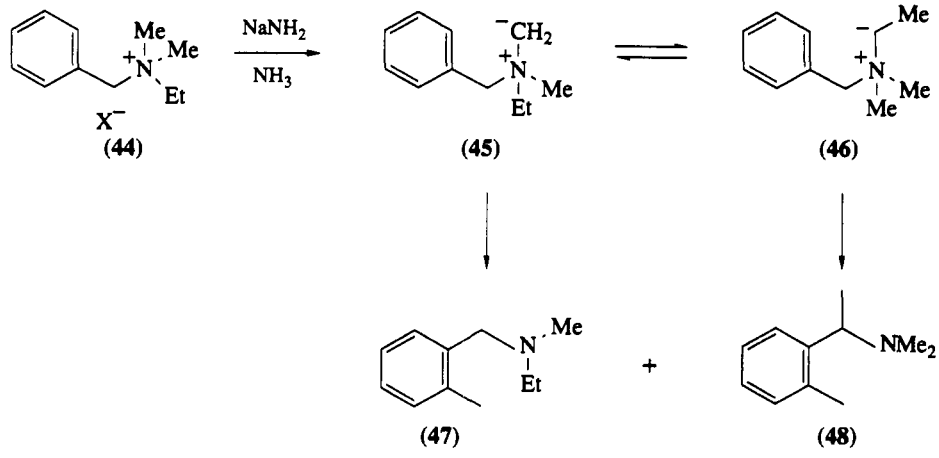


(40) (41) (42) (43)

Scheme 11

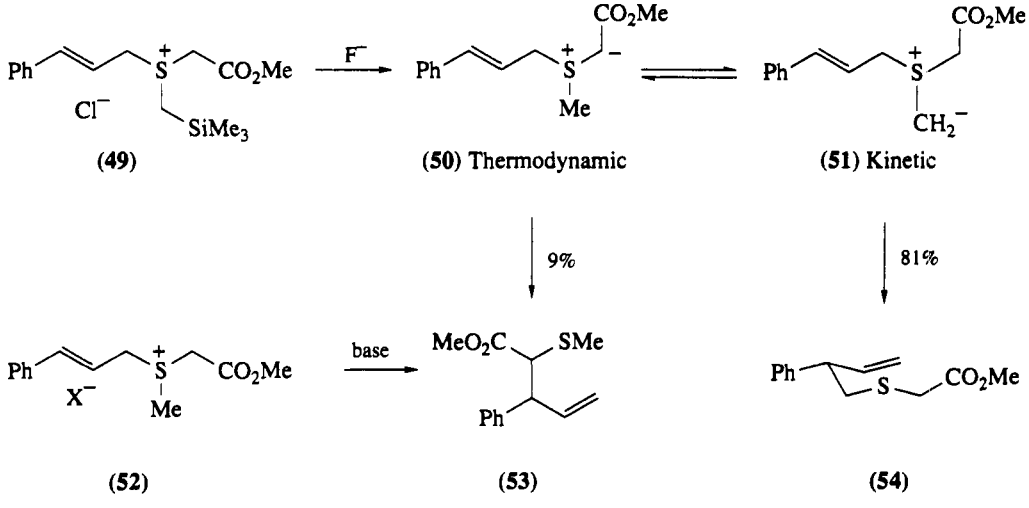
A second side reaction using this approach is the Hoffmann elimination of the sulfide or amine, during attempted deprotonation of the sulfonium or ammonium salt. This reaction is especially important in the case of ammonium ylides. Finally, another problem which surfaces during the deprotonation step is the formation of a mixture of ylides, *e.g.* (**45**) and (**46**) from (**44**), which undergo competing rearrangements to give (**47**) and (**48**; Scheme 12).[25]

An elegant solution to these problems was proposed independently by Vedejs[26] and Sato.[27] They generated ylides regiospecifically, under nonbasic conditions, using fluoride-catalyzed desilylation of



Scheme 12

trimethylsilyl ammonium or sulfonium salts. Not only is the extent of elimination considerably reduced, but also one reaction pathway predominates easily over the other one (Scheme 13).



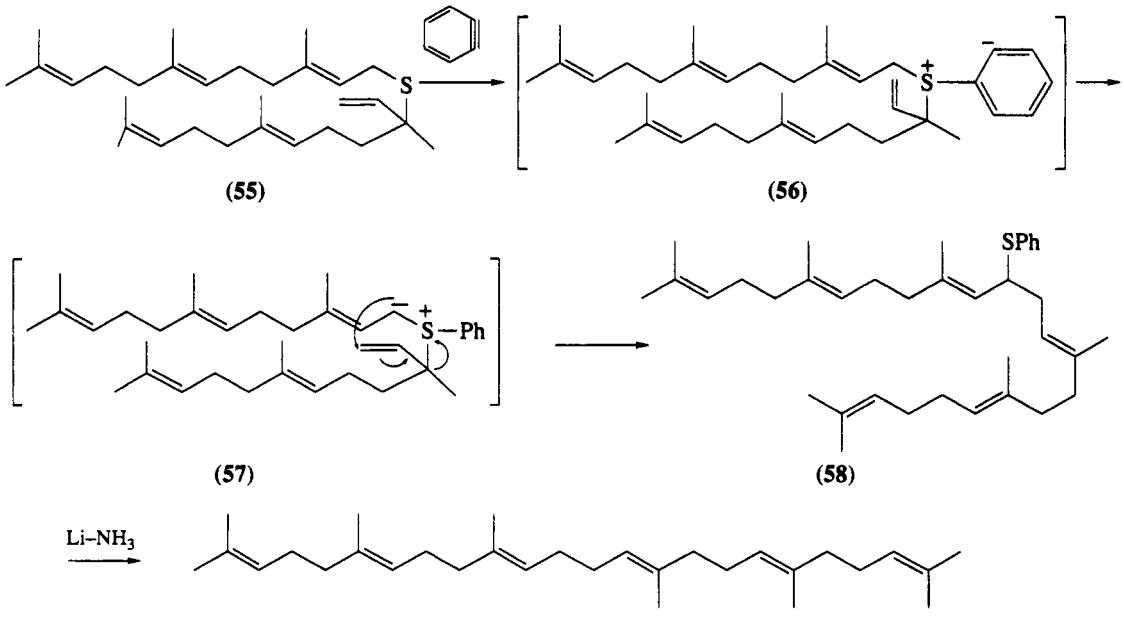
Scheme 13

3.10.3.2 Direct Formation of Ylides

The addition of a carbene or benzyne to a sulfide, and to a lesser extent to an amine, provides a direct route to ylides. Enormous progress has been realized with this approach, mainly as a result of the efforts of Ando[28] and Doyle.[29] Most noteworthy amongst examples using benzyne is the squalene synthesis reported by Ollis, in which the sulfide (**55**) was transformed by a 3,2-rearrangement into the squalene precursor (**58**) and eventually into squalene itself (Scheme 14).[30]

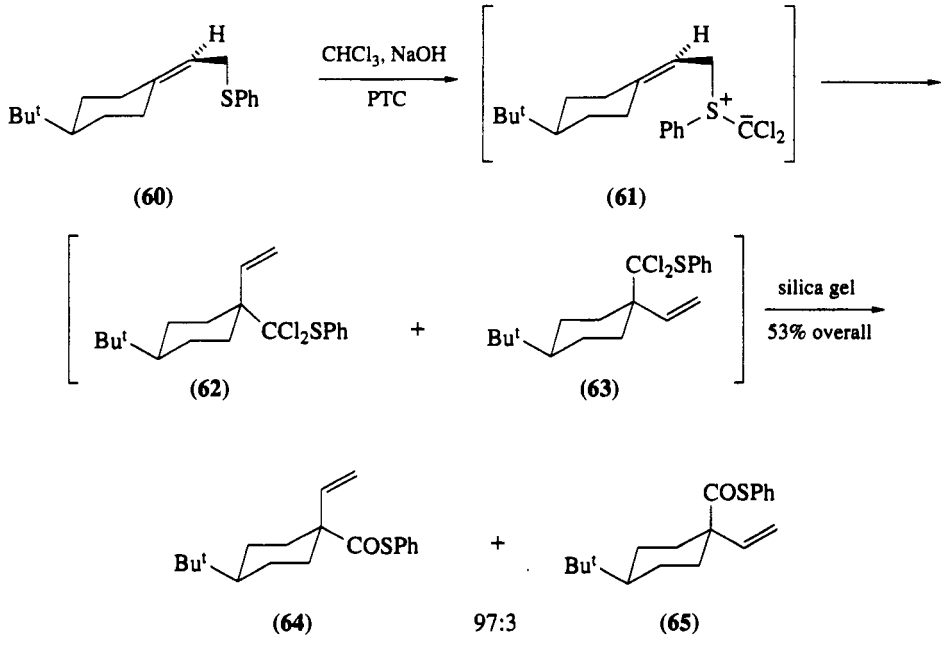
The stereospecific rearrangement of *exo*-methylenecyclohexane derivatives discovered by Evans employed dichlorocarbene, generated under phase transfer conditions (Scheme 15).[31]

An extremely versatile approach to ylides involves the light-promoted or metal-catalyzed generation of carbenes from diazonium salts. In most cases, metal-catalyzed reactions give better yields and cleaner reaction mixtures than do corresponding photolytic techniques (Scheme 16, equation a).[32] A classical example is to be found in penicillin chemistry (Scheme 16, equation b).[33] However, copper catalysts have their limitations in the generation of carbenoid intermediates. These limitations can be largely over-



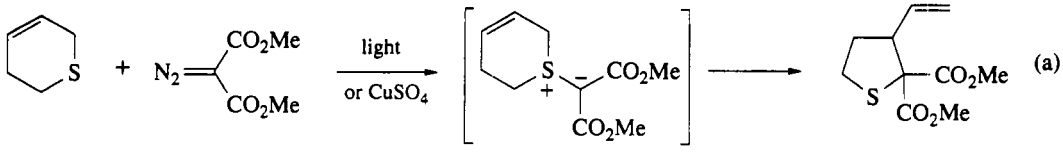
(59) Squalene

Scheme 14

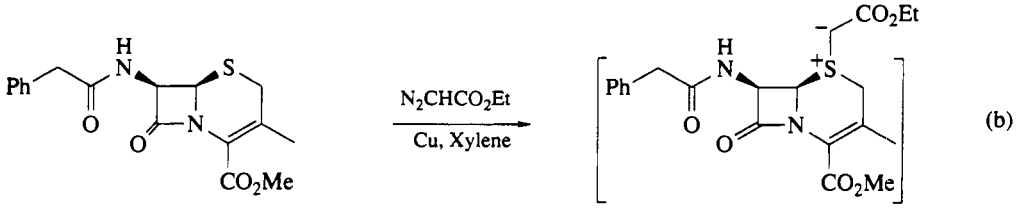


Scheme 15

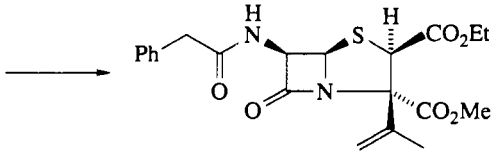
come by employing rhodium catalysts that not only afford the desired material when the copper catalysts fail to react, but also allow the reactions to be performed under much milder conditions. It is quite remarkable that rhodium catalysts allow the preparation and reaction of some oxonium and halonium ylides.[34] It is only recently that their synthetic use has started to be fully appreciated (Scheme 17).



(66) (67) (68) (69) light: 30%
$CuSO_4$: 68%

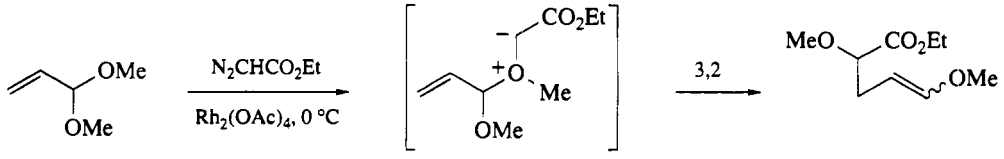


(70) (71)

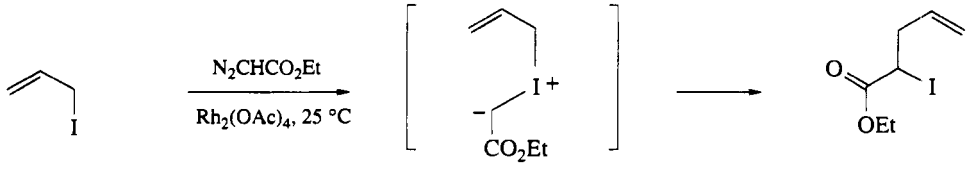


(72) 63%

Scheme 16



(73) (74) (75) 77%



(76) (77) (78) 98%

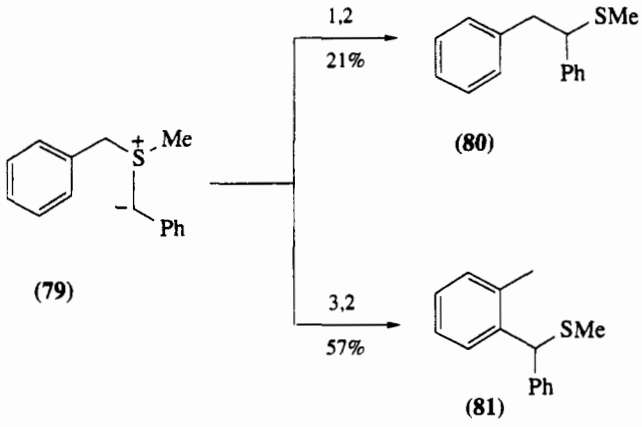
Scheme 17

3.10.4 1,2-SIGMATROPIC REARRANGEMENTS

3.10.4.1 Synthetic Applications of the Stevens Rearrangement

Although studied at great length from a mechanistic point of view, the Stevens reactions of nitrogen and sulfonium ylides have, so far, been applied in synthesis only to a limited extent. The details of the earlier work by Stevens have been summarized elsewhere,[35] and some excellent reviews on ylide chemistry mention a few synthetic uses of this rearrangement.[36] One of the classical problems associated with the 1,2-rearrangement is the co-ocurrence of competing reactions, including other rearrangements, *i.e.* 1,3 and 1,2 as well as elimination reactions (more frequent for nitrogen ylides than for sulfur ones). For

example, rearrangement of the ylide (**79**) gives the 1,2- and 3,2-products in 1:3 ratio, indicating the greater propensity for the concerted, symmetry-allowed 3,2-rearrangement to occur, in relation to the forbidden 1,2-rearrangement (Scheme 18).[37]

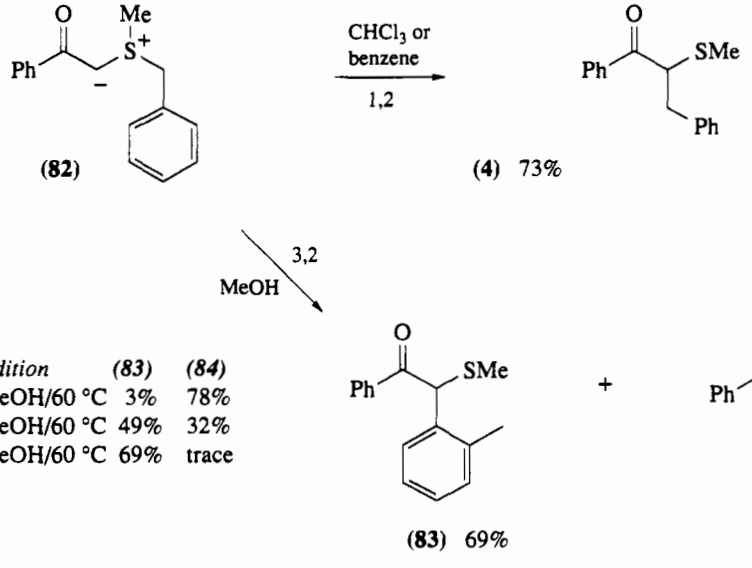


Scheme 18

An important breakthrough was the discovery that the ratio 1,2:3,2 was highly dependent upon the nature of the solvent and the concentration of the base. Under aprotic conditions, the Stevens rearrangement of ylide (**82**) takes place nearly exclusively,[35a,38] whereas the 3,2-rearrangement is favored under protic basic conditions (Scheme 19).[37,39] Not only can the 1,2:3,2 ratio be controlled, but the relative proportion of the 3,2-products (**83**) and (**84**) has been shown to depend strongly on the concentration of the base employed in these reactions.[37] This striking result can be understood if one looks at the fate of the primary product (**85**) obtained in the Sommelet–Hauser reaction. This intermediate can participate in two different pathways. Aromatization requires a 1,3-prototropic shift and, therefore, the presence of a proton source or protic solvent. In aprotic solvent, this transformation cannot take place and a competing homolysis will occur followed by a radical recombination giving the 1,2-product (Scheme 20).

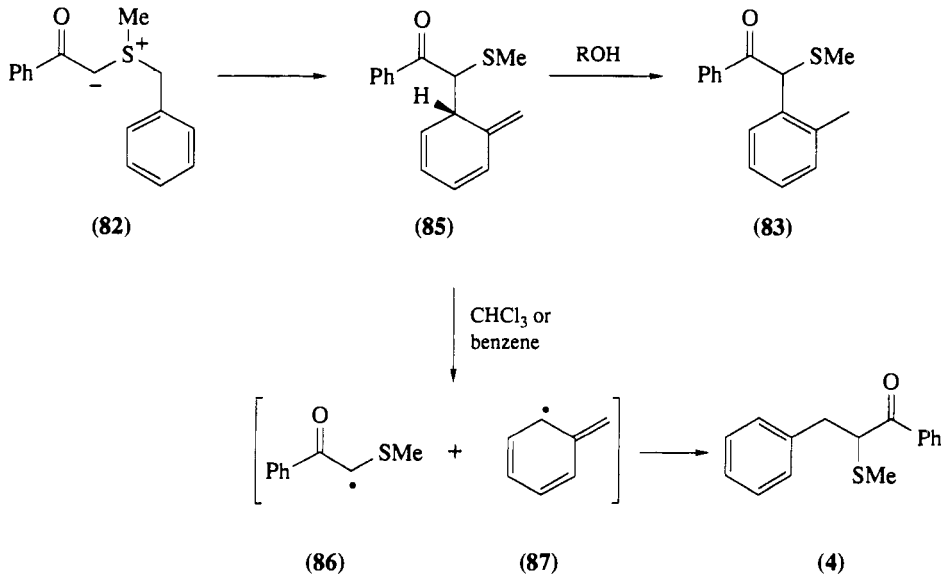
Intermediates such as (**85**) have been isolated and reacted under different conditions to give the expected rearrangement products.[37] A few examples of simple Stevens rearrangements are presented in Table 1.

More complex and synthetically useful applications of the Stevens rearrangement have been reported. Kondo, for example, has shown that the ylide (**89**), formed from (**88**) by an intramolecular carbene re-



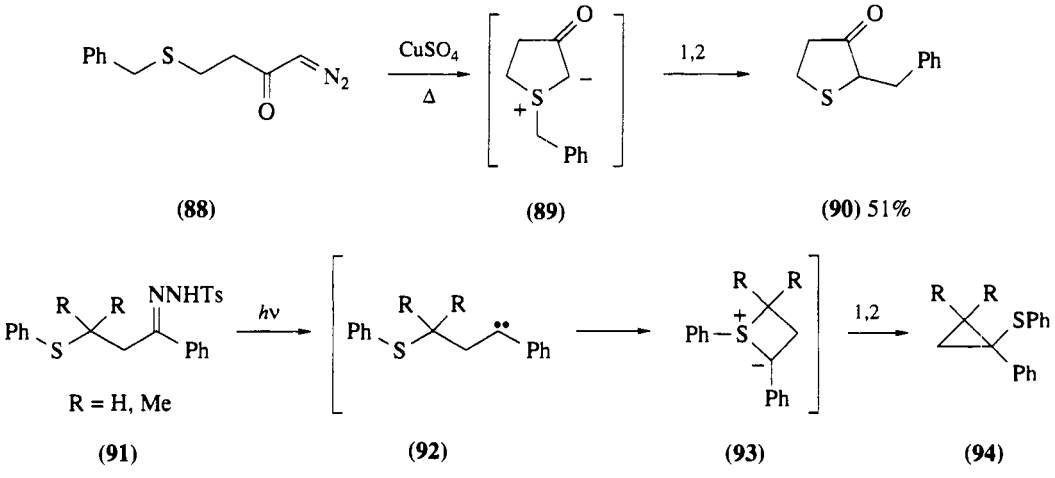
Condition	*(83)*	*(84)*
5% Na/MeOH/60 °C	3%	78%
10% Na/MeOH/60 °C	49%	32%
15% Na/MeOH/60 °C	69%	trace

Scheme 19



Scheme 20

action, undergoes a 1,2-sigmatropic shift to give the five-membered ring (**90**) in 51% yield.[42] Even smaller ring compounds, *e.g.* (**94**), can be prepared following this route (Scheme 21). When two ylides of similar stability can be formed and rearranged, poor selectivity is often observed. Thus, irradiation of (**95**) leads to the equilibrating ylides (**96**) and (**97**). It is therefore not too surprising that two Stevens products (**98** and **99**) are obtained from this reaction (Scheme 22).



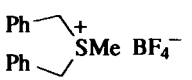
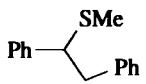
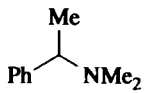
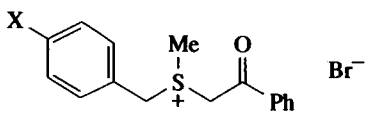
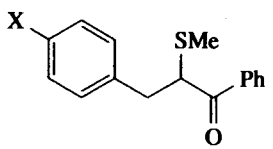
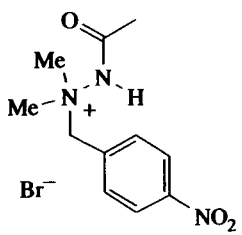
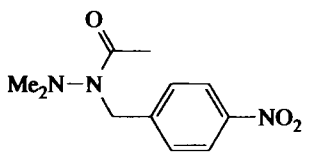
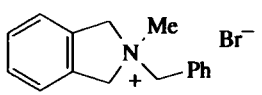
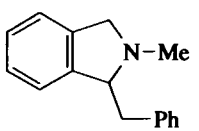
Scheme 21

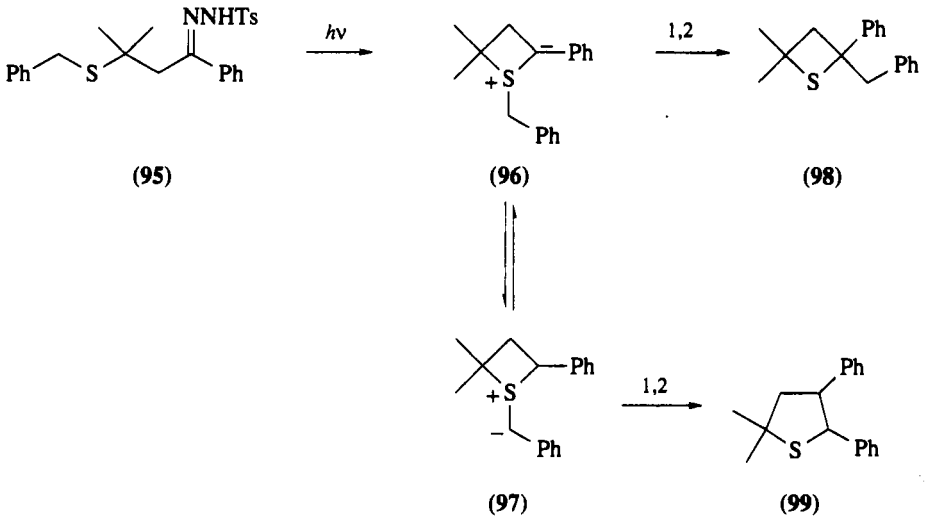
In some cases, the Stevens rearrangement can be used to form ring-expanded products. Thus, thietane (**100**) reacts with dimethyl diazomalonate in the presence of a copper catalyst to provide the functionalized tetrahydrothiophene (**102**).[43] A similar and most remarkable example, where a possible competing 3,2-rearrangement is not observed, is the ring expansion of dihydrothiophene (**103**) to (**105**; Scheme 23).[44] Clearly, the increase in strain in the transition state (**106**), which would lead to the 3,2-rearrangement product (**107**) is responsible for this interesting selectivity. In general, nitrogen ylides behave in an analogous manner though sometimes they can supersede sulfur ylides (Scheme 24).

Ollis has demonstrated that the successful transformation of the dihydropyrrole (**110**) into the tetrahydropyridine (**111**) is a fairly easy process.[45] In sharp contrast, the analogous sulfonium salt (**112**) does not form the expected Stevens product (**113**) but rather (**114**), a product of dimerization.

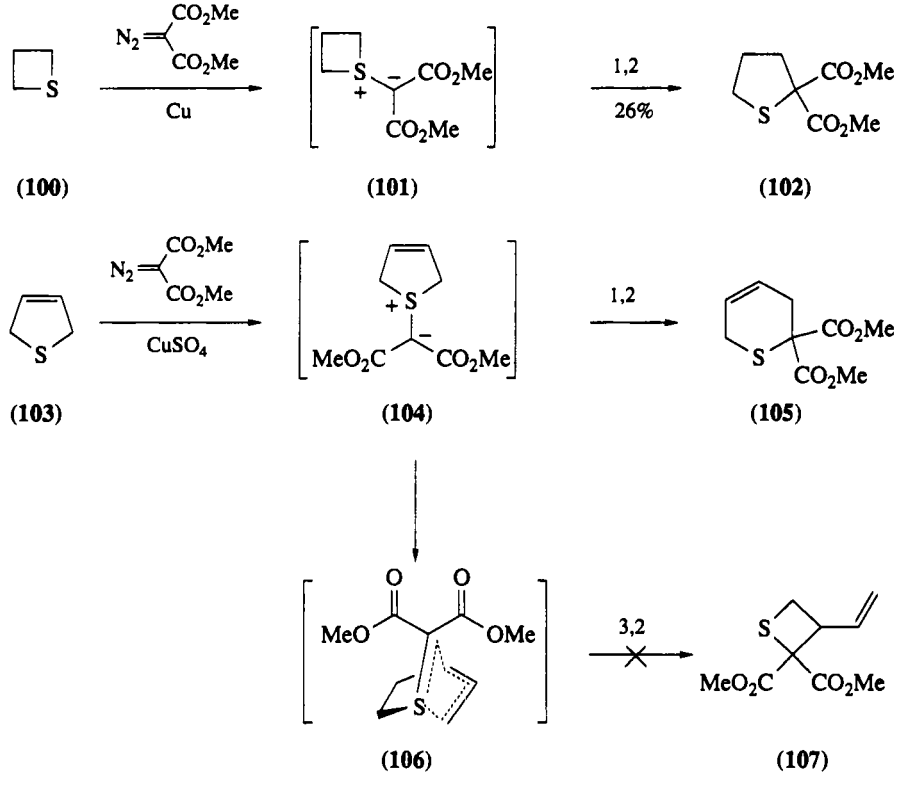
Recent and interesting examples of Stevens reactions were reported by Doyle who reacted dithianes with ethyl diazoacetate in the presence of a rhodium catalyst.[34b] Seven-membered ring bissulfides were

Table 1

Entry	*Salt*	*Conditions*	*Product*	*Yield (%)*	*Ref.*
1		NaOH, H_2O		21	37
2		PhLi		32	7
3		Δ, THF or acetone	 X = F, Cl or Br	70–80	35a
4		180 °C		50	40
5		3% Na, EtOH		75	41



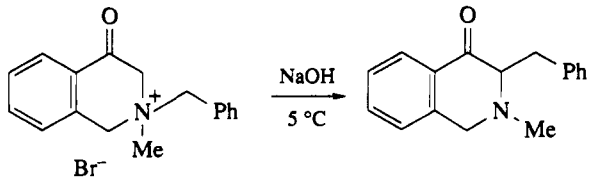
Scheme 22



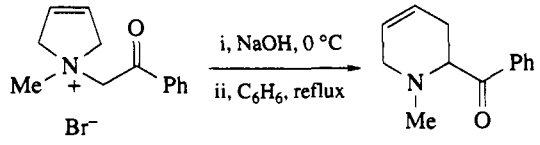
Scheme 23

obtained in variable yields, depending on the substituents present in the starting dithianes (Scheme 25). With 2-phenyl-1,3-dithiane (**115**), smooth Stevens 1,2-rearrangement gave (**116**). However, with 2-phenyl-2-methyl-1,3-dithiane (**117**), elimination becomes a competing process. In this case, the Stevens 1,2-rearrangement product (**119**) is the minor component of the reaction.

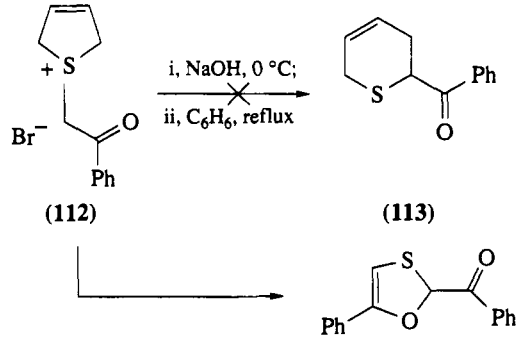
A most remarkable result is obtained when allylic halides are reacted with ethyl diazoacetate in the presence of metal catalysts.[34a] The 1,2-rearrangement product (**122**) and the 3,2-rearrangement product (**121**) can be isolated and their relative proportions shown to be related to the nature of the catalyst em-



(108) **(109)** 60%



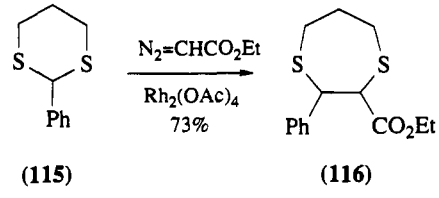
(110) **(111)** 85%



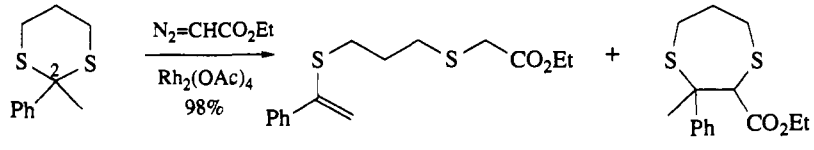
(112) **(113)**

(114) 60%

Scheme 24



(115) **(116)**

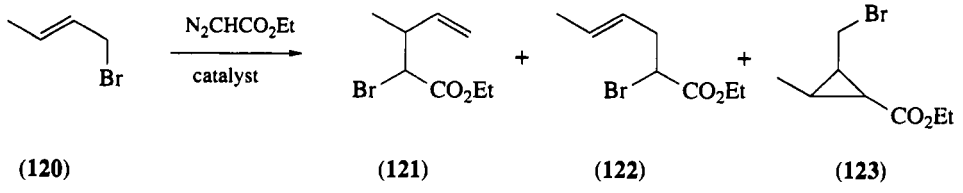


(117) **(118)** 4.6:1 **(119)**

Scheme 25

ployed (Scheme 26, equation a). A competing side reaction, cyclopropanation, is dependent upon the nature of the halogen atom (X) and it can be totally suppressed when X is iodide (Scheme 26, equation b).

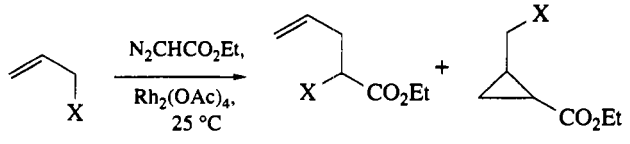
Stevens rearrangements are not limited only to heteroatom to carbon migrations; heteroatom to heteroatom shifts are also observed frequently. Two such examples are given in Scheme 27.[46,47] In this case



(a)

(120) (121) (122) (123)

Catalyst	(*121*)	(*122*)	(*123*)	*Yield* (%)
$Rh_2(OAc)_4$	76	0	24	82
$CuCl{\bullet}P(OPr^i)_3$	32	53	6	68



(b)

(124) (125) (126)

X	(*125*)	(*126*)	*Yield* (%)
I	100	0	98
Br	28	72	76
Cl	5	95	95

Scheme 26

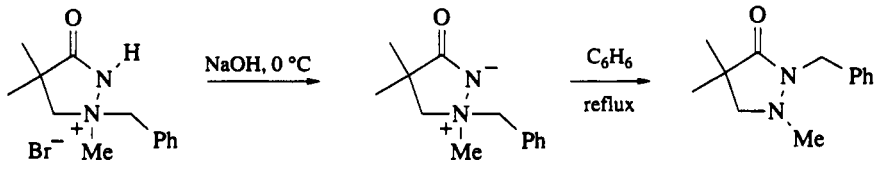
too, the 1,2- and 3,2-rearrangements are competing but their relative importance has been shown to be substituent dependent.

Despite extensive mechanistic investigations, the Stevens 1,2-rearrangement has found only a few applications in synthesis. Standing out, however, as a landmark in this area is the beautiful work of Boekelheide, who utilized the 1,2-rearrangement of sulfur-containing macrocycles in an elegant and general approach towards cyclophanes (Scheme 28).[48] This brilliantly conceived strategy has been applied in numerous cases and two recent examples are shown in Scheme 29.[49,50]

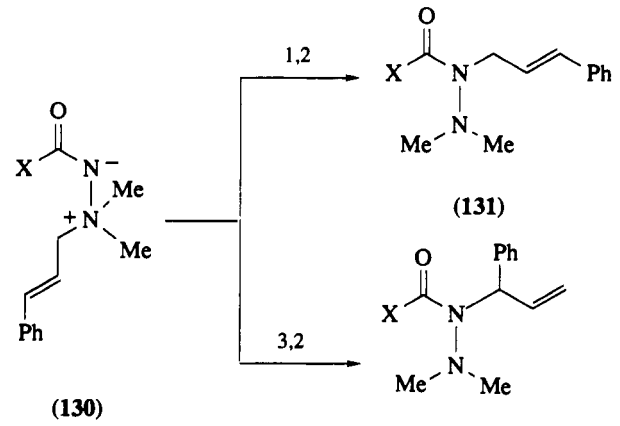
3.10.4.2 Transfer of Chirality

If the 1,2-rearrangement is a concerted process, then it is a disfavored one. As a consequence, there has been considerable interest in determining the stereochemistry of the migrating group. If the reaction proceeds *via* a suprafacial–antarafacial mode, inversion of configuration at the migrating center should result. In fact, a high degree of retention of configuration was observed by Kenyon[6] and Brewster[51] as early as 1952 (Scheme 30, equation a). Schollkopf[52] and Stevens[53] reinvestigated the reaction and found it to proceed with at least 95% *ee*. The same conclusion was reached by Lown several years later using optically active benzylamine (Scheme 30, equation b).[54] In 1962, Jenny and Bruey showed that retention of configuration was also very high for the analogous allylic system (Scheme 30, equation c).[55] Mislow reported the fascinating case where total transmission of configuration, from a center of chirality involving a nitrogen atom into a center of chirality involving a carbon atom, took place (Scheme 31).[56]

When the optically active diazepinium salt (**151**) was treated with phenyllithium, only the (*S*)-amine (**152**) was obtained. However, the (*S*)-amine (**152**) consists of an equilibrating mixture of (+) and (–) diastereomeric amines which interconvert by mutarotation upon heating. Similarly, Brewster demonstrated that the pure (*R*)-isomer of the spiro ammonium salt (**153**) was transformed into the alkaloid (**155**) having an (*S*) absolute configuration (Scheme 32).[57]



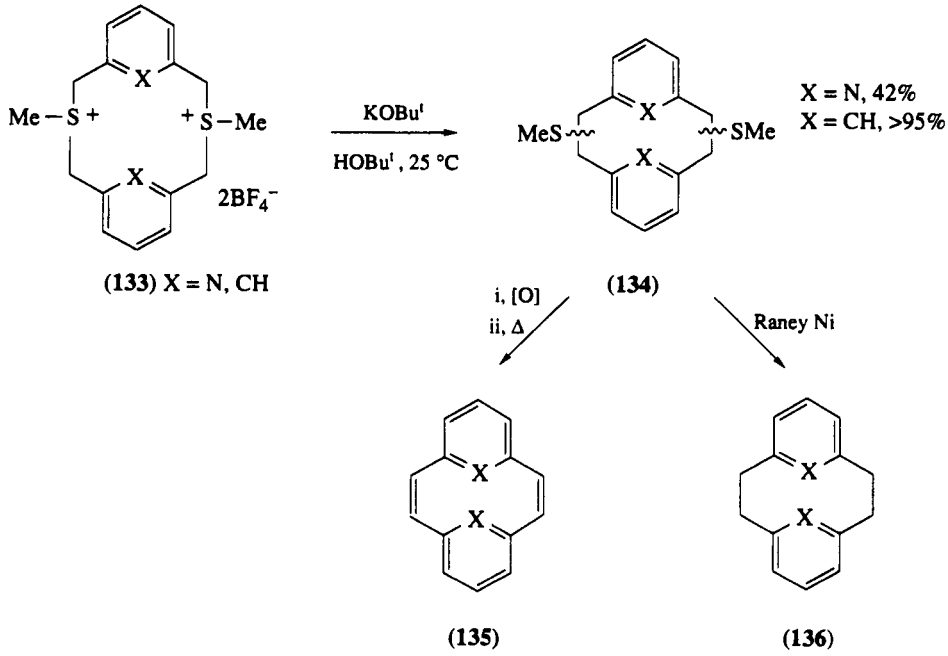
(127) (128) (129)



(130) (131) (132)

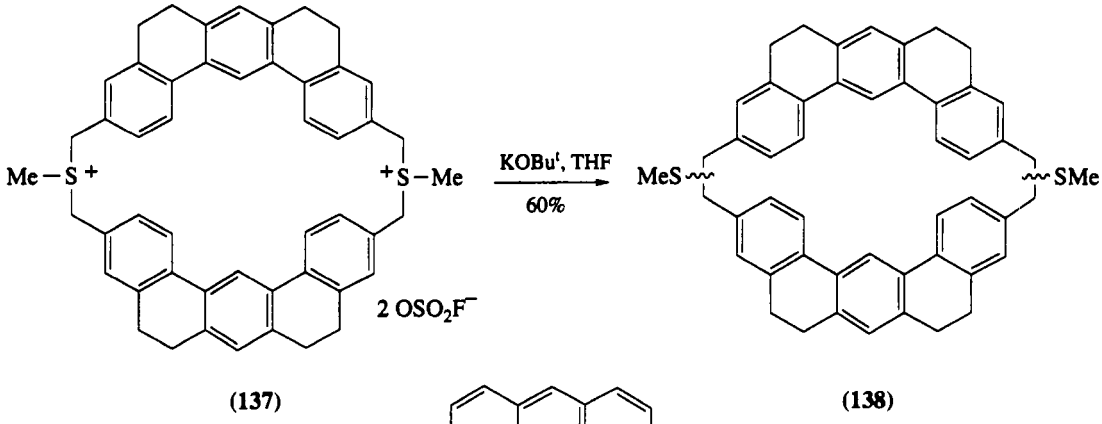
X	(*131*)	(*132*)
Ph	88	12
OEt	45	55
NHMe	40	60

Scheme 27

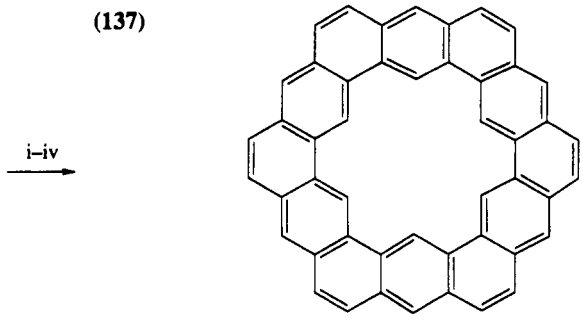


(133) X = N, CH (134) (135) (136)

Scheme 28

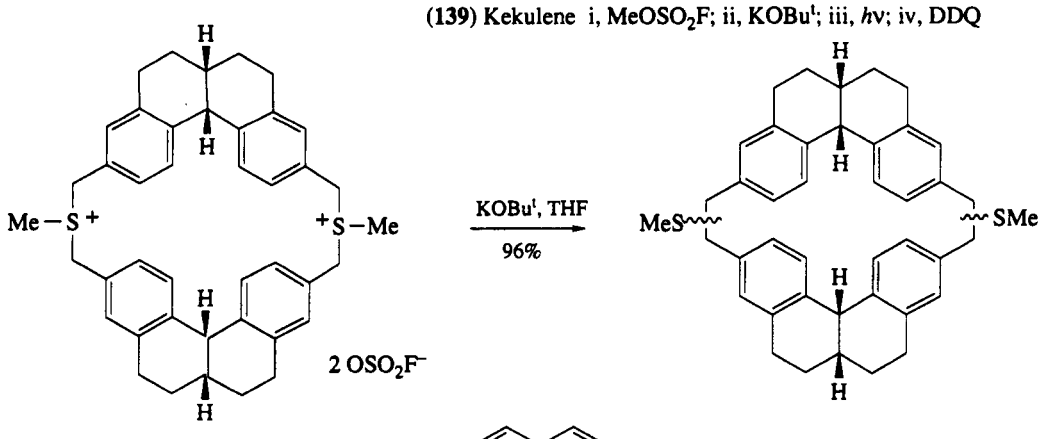


(137) (138)

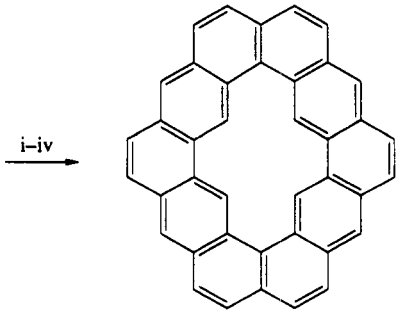


(a)

(139) Kekulene i, $MeOSO_2F$; ii, $KOBu^t$; iii, *hν*; iv, DDQ



(140) (141)

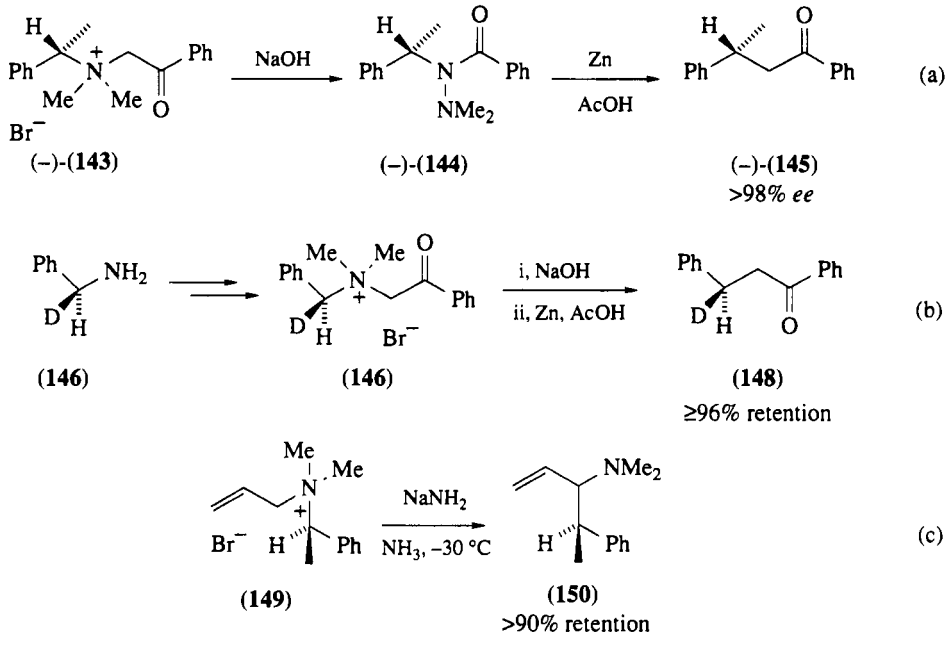


(b)

(142) i, MCPBA, CH_2Cl_2; ii, 170 °C; iii, *hν*; iv, DDQ

Scheme 29

Chan and Hill have studied the transmission of configuration in ammonium salts where the only chiral center is the quaternary nitrogen atom.[58] The Stevens rearrangement proceeded in poor yield; a competing 1,4-rearrangement product being surprisingly formed as the major product, and gave the amine (**157**) with 58% *ee* (Scheme 33).

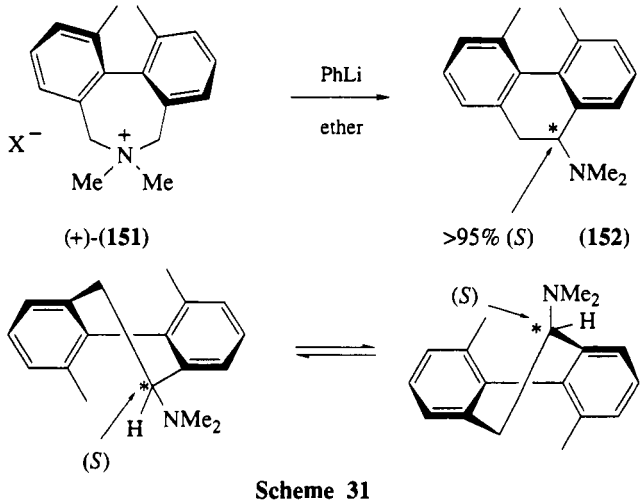


(–)-(**143**) (–)-(**144**) (–)-(**145**) >98% *ee* (a)

(**146**) (**146**) (**148**) ≥96% retention (b)

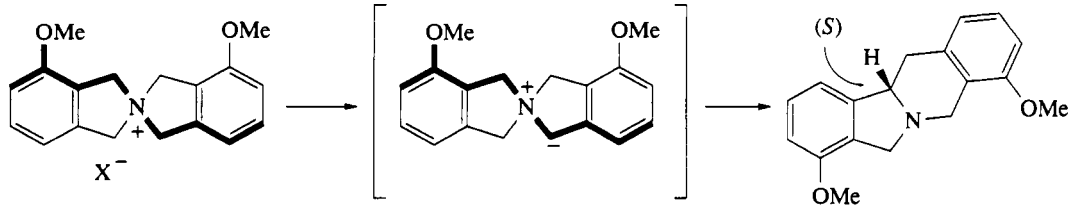
(**149**) (**150**) >90% retention (c)

Scheme 30



(+)-(**151**) >95% (*S*) (**152**)

Scheme 31



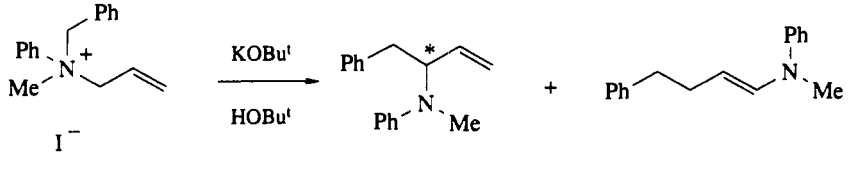
(*R*)-(–)-(**153**) (**154**) (*S*)-(–)-(**155**), 7-11%

Scheme 32

Ollis and coworkers reinvestigated the stereochemical outcome of the Stevens rearrangement and provided a detailed understanding of the mechanism of this reaction.[10,59] Rearrangement of the optically pure ammonium salt (**143**) gave three products, (**144**), (**159**) and (**160**) in a ratio of 80:11:5 (Scheme 34). The amine (**144**) was optically active and degradation studies proved that migration occurred with more

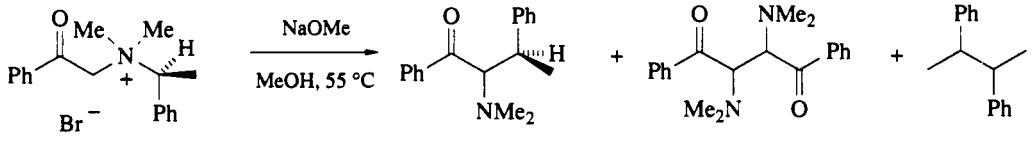
than 95% retention of the stereochemistry at the terminus of the migrating group. The diamine (**159**) (and similarly the alkane **160**) was a mixture of the racemate and the meso compound. Clearly, these products (**159**) and (**160**) arose from coupling of radicals which have escaped from the solvent cage. A few related examples are represented in Table 2.[10]

In all the cases discussed so far, retention of configuration at the terminus of the migrating group has been observed. The degree of retention was influenced strongly by the nature of the substituents present on the migrating group (Table 2, entries 1–3). It is also worth noting that the extent of retention of configuration in the case of sulfonium ylides (entry 4) is substantially lower than in the case of the ammonium analog. Comparison between entry 1 and entry 5 demonstrates how the nature of the substituent influences the enantiomeric excess. All these results can be explained by the mechanism, involving diastereomeric radical pairs, proposed by Ollis for the Stevens rearrangement and summarized in Scheme



(+)- (**156**) (*S*)-(−)-(**157**) 15% yield, 58% *ee* (**158**) 35% yield

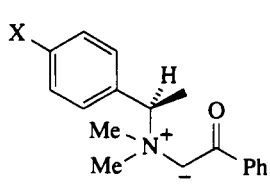
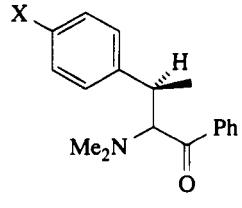
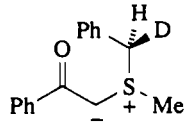
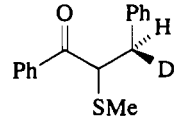
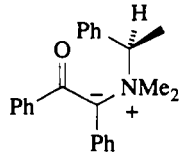
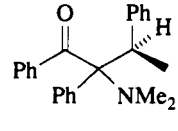
Scheme 33



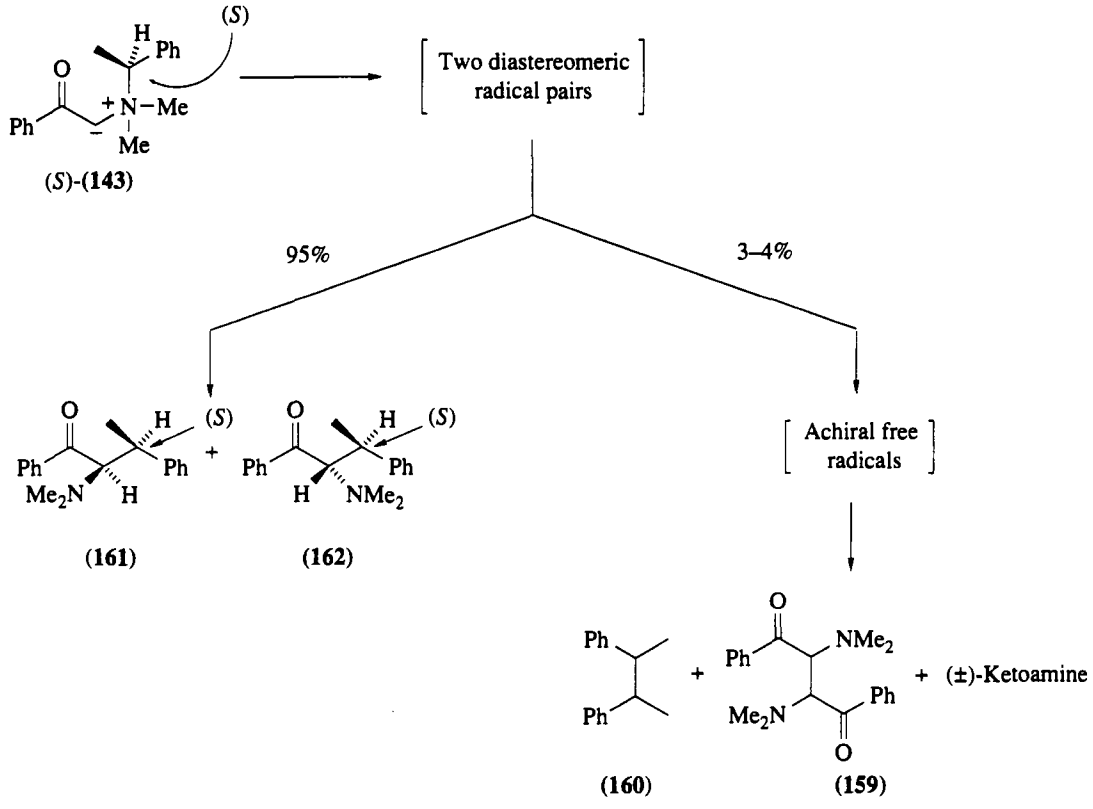
(*R*)-(+)-(**143**) (**144**) 80% yield, >95% *ee* (**159**) 11% (**160**) 5%

Scheme 34

Table 2

Entry	*Reactant*	*Product*	*ee* (%)
			
1	X = H		>95
2	X = OMe		87
3	X = NO_2		66
4			36
5			32

35.[60] Homolytic fission of the chiral ammonium ylide (**143**) generates two diastereomeric radical pairs which evolve by two different routes: (a) cage recombination leads to the two diastereomeric ketoamines (**161**) and (**162**), where the migrating center has retained its absolute stereochemistry; (b) radical escape gives achiral free radicals that combine to yield racemic products (Scheme 35).



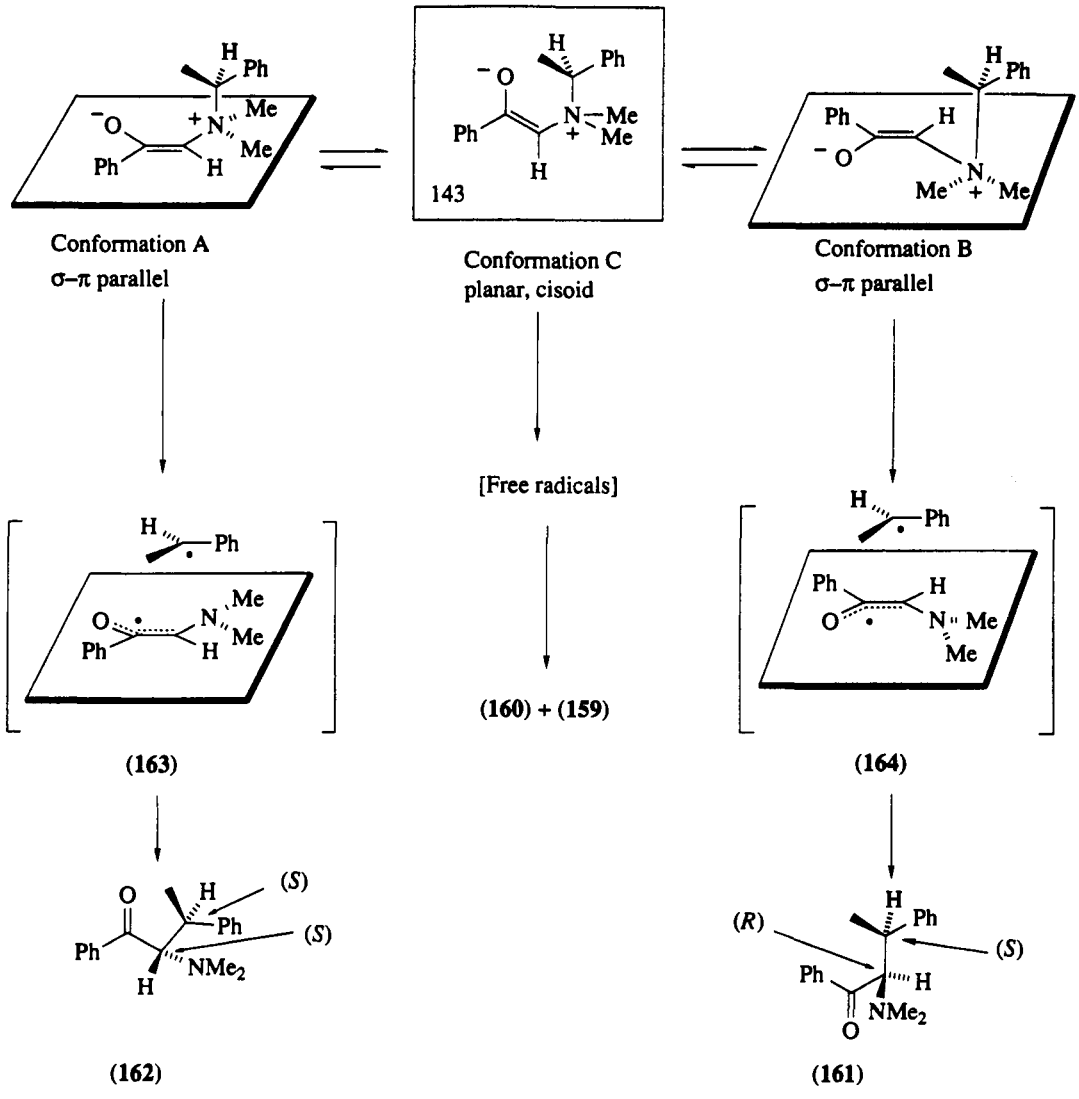
Scheme 35

The radical pair recombination is a very fast process. This explains the high intramolecularity of the Stevens 1,2-rearrangement as well as the high stereoselectivity observed. Retention of configuration is ensured by the absence of rotation of the radicals in the solvent cage. The formation of the two diastereoisomeric amines (**161**) and (**162**) can be explained by the presence of an equilibrium mixture of conformational isomers of the starting ylide.[60] Indeed, the ylide (**143**) exists in the planar cisoid conformation **C**, which is in equilibrium with the two orthogonal conformational isomers **A** and **B**. These are the conformations from which migration will occur, since the σ-bond to be broken is parallel to the π-system of the enolate, ensuring maximum stabilization of the radicals as they are formed. Conformation **A** will lead to the radical pair (**163**), which eventually collapses to form the diastereoisomer (**162**). The same process involving co nformation **B** leads to the diastereoisomer (**161**; Scheme 36).

3.10.5 3,2-SIGMATROPIC REARRANGEMENTS

3.10.5.1 Introduction

In sharp contrast with the Stevens 1,2-rearrangement, the 3,2-sigmatropic rearrangement of ylidic intermediates has been used extensively in organic synthesis. These rearrangements, being concerted symmetry-allowed processes, show high regio-, diastereo- and enantio-selectivities. It is, therefore, not too surprising that they have become rapidly accepted synthetic tools, since Baldwin published his important papers on the generalization of sigmatropic rearrangements.[17]

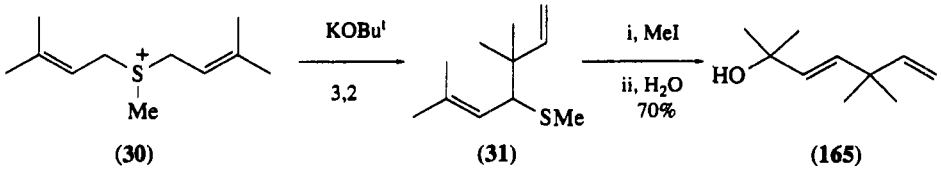


Scheme 36

3.10.5.2 Synthetic Applications in Alicyclic Systems

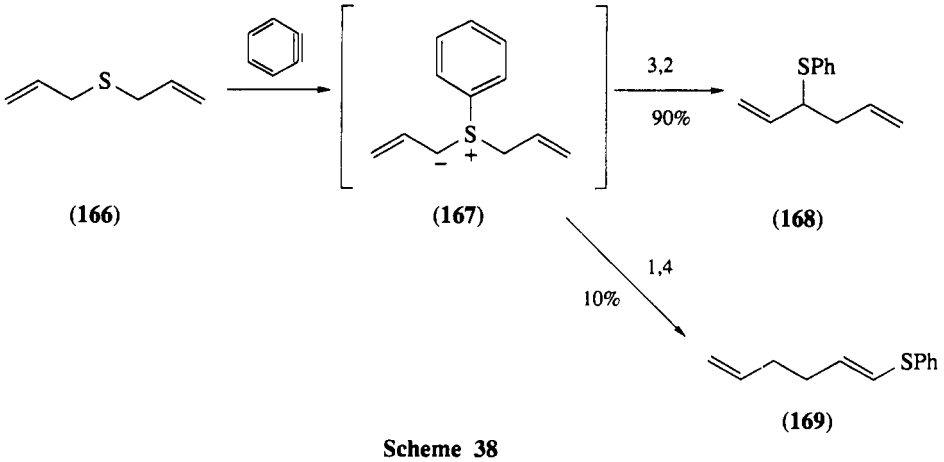
3,2-Rearrangements of ylidic intermediates proceed with allylic transposition. This useful property is the key feature of one of the best preparations of 1,5-dienes (Scheme 9). Trost has used this approach to synthesize yomogi alcohol (**165**) in a particularly simple way by *S*-alkylation of sulfide (**31**) and solvolysis of the resulting sulfonium ion (Scheme 37).[61]

One of the landmarks in the early use of the 3,2-rearrangement of sulfur ylides is the squalene synthesis reported by Ollis and already discussed in Section 3.10.4.[30] This approach used benzyne to generate the ylidic intermediate. Frequently, however, benzyne produces a mixture of products (Scheme 38).[62] The sulfide (**168**) may be formally regarded as the expected 3,2-sigmatropic rearrangement product, whereas (**169**) results from a competitive 1,4-rearrangement. Use of carbenes instead of benzyne gener-



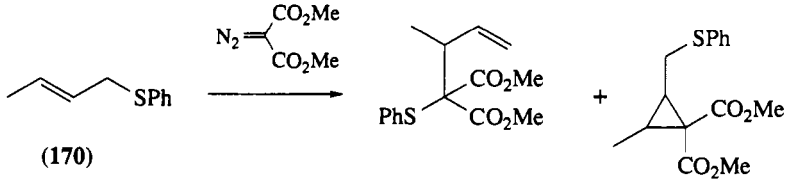
Scheme 37

ally gives higher yields of 3,2-rearrangement products. Ando has shown that crotyl phenyl sulfide (**170**) forms mainly the sulfide (**171**) when the carbene is generated using $CuSO_4$.[44,63] In contrast, the light-induced reaction affords the desired material in much lower yield (Scheme 39). Evans also used carbenes to generate sulfonium ylides of rigid systems in order to study the diastereoselectivity of the 3,2-rearrangement (Scheme 40).[31]



(**166**) (**167**) (**168**) (**169**)

Scheme 38



(**170**)

	(**171**)	(**172**)
hν	47%	10%
$CuSO_4$	90%	–

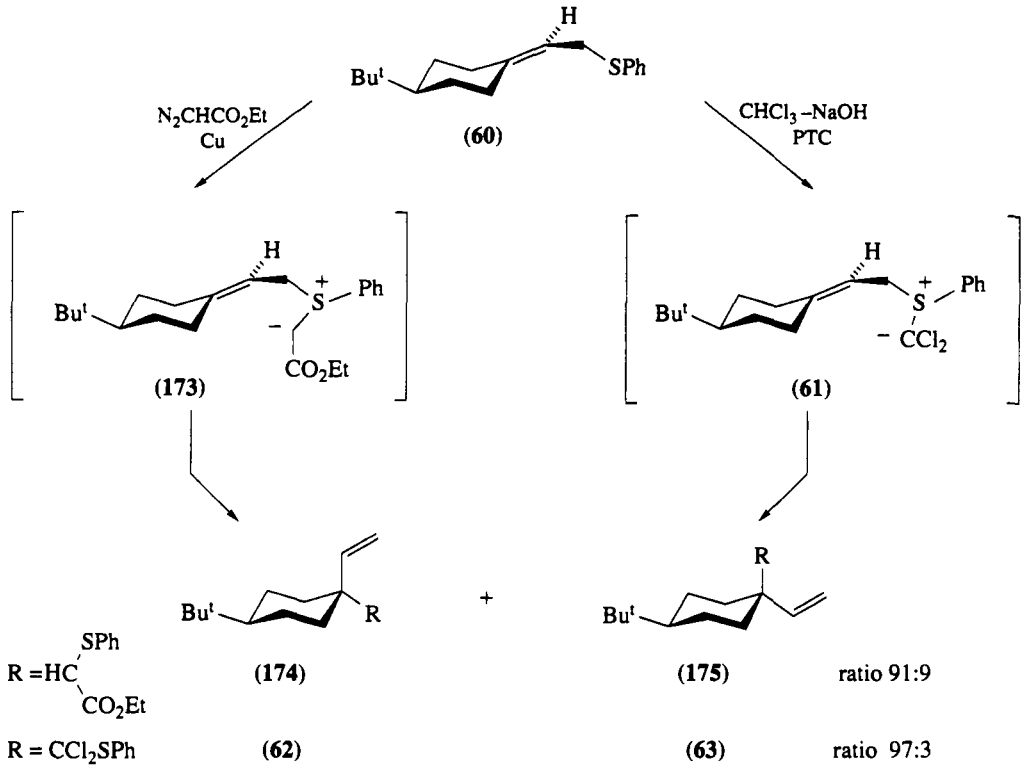
Scheme 39

John has investigated the BF_3–etherate and copper-catalyzed rearrangement of diazopenicillins in the presence of allylic sulfides and selenides.[64] The results are presented in Scheme 41. The reaction is believed to involve the initial formation of ylide (**177**) followed by a 3,2-sigmatropic rearrangement. Support for this mechanism came from utilization of substituted allylic sulfides which were shown to rearrange with net allylic transposition, a result expected on the basis of orbital symmetry considerations (Scheme 42). A similar rearrangement involving nitrogen ylides has been reported by Baldwin (Scheme 43).[65]

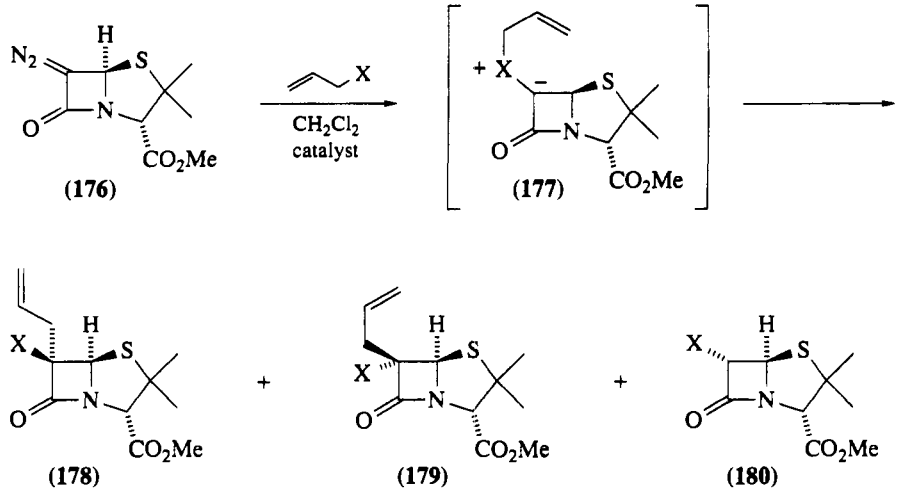
Doyle has shown that the rhodium-catalyzed reaction of allylic sulfides and amines with ethyl diazoacetate produced smoothly the products of 3,2-rearrangement.[34] In contrast with the copper-catalyzed reaction, allylic amines can be used and the yields are good to high (Scheme 44); virtually no cyclopropanation is observed. These observations demonstrate the superiority of rhodium catalysts compared with either copper ones or the use of light.

Vedejs has also discussed the inefficiency of copper catalysts in ylidic 3,2-sigmatropic processes.[66] Optimization of ring expansion reactions using diazomalonates were found to be unsatisfactory and analogous reactions using diazoketones were totally unsuccessful. Takano has taken advantage of a rhodium-promoted ylide formation followed by a 3,2-rearrangement, in a useful synthesis of γ,δ-unsaturated carbonyl compounds (Scheme 45).[67]

Julia, in a very elegant approach, has used sulfur ylidic 3,2-rearrangements to produce β,γ-unsaturated aldehydes (Scheme 46).[68] Following the same idea, Kociensky also used ylidic 3,2-sigmatropic rearrangements to prepare β,γ-unsaturated aldehydes; he employed sulfur ylides in conjunction with silicon substituents (Scheme 47).[69] In contrast, Mander used the nitrogen ylidic 3,2-rearrangement as an easy route towards the synthesis of β,γ-unsaturated aldehydes (Scheme 48).[70] It is noteworthy that better

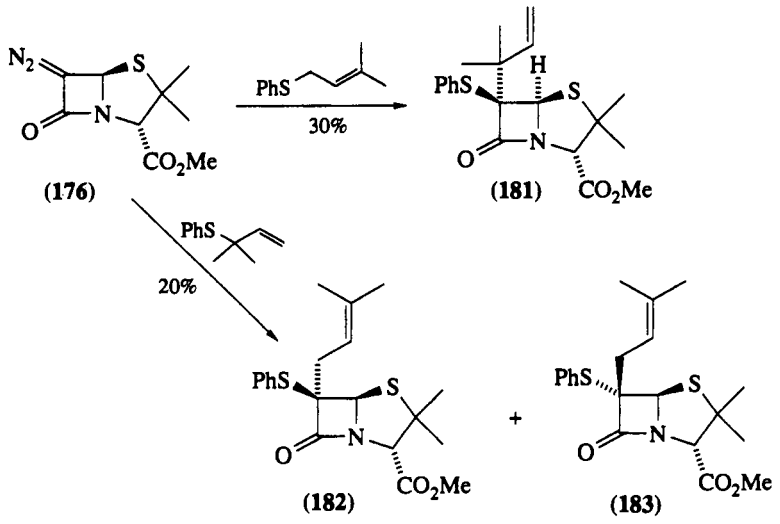


Scheme 40



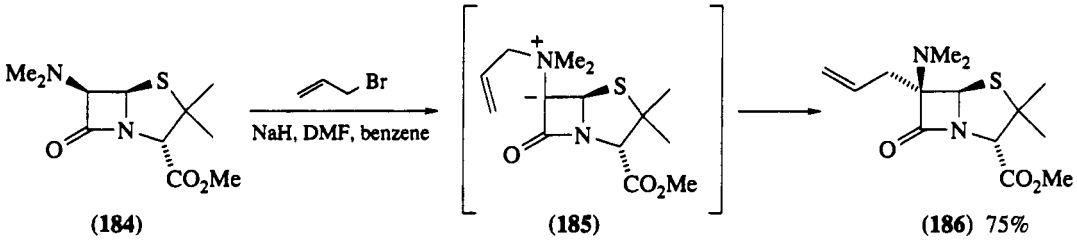
Entry	*X*	*Catalyst*	*(178)+(179)* (%)	*(178):(179)*	*(180)* (%)
1	PhS	$BF_3{\cdot}Et_2O$	47	56:44	5
2	MeS	$BF_3{\cdot}Et_2O$	49	80:20	16
3	PhSe	$BF_3{\cdot}Et_2O$	48	66:34	15
4	PhS	$Cu(acac)_2$	65	87:13	0
5	MeS	$Cu(acac)_2$	60	80:20	0
6	PhSe	$Cu(acac)_2$	64	50:50	0

Scheme 41

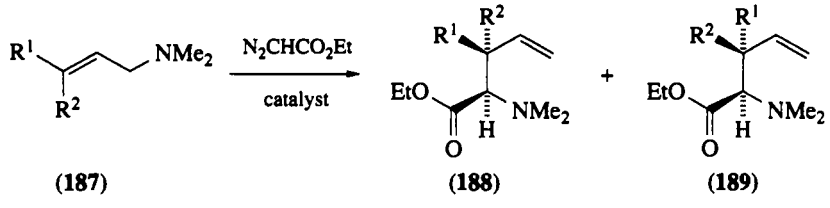


(182):(183) = 3:2

Scheme 42



Scheme 43

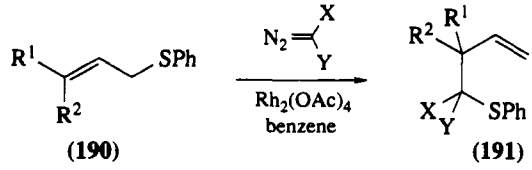


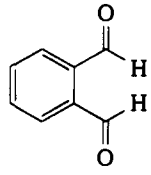
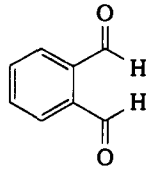
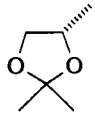
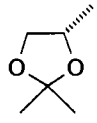
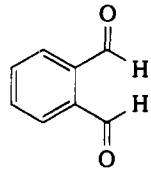
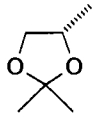
R^1	R^2	*Catalyst*	*Yield (%)*	*(188):(189)*
H	H	$Rh_2(OAc)_4$	82	-
Me	Me	$Rh_6(CO)_{16}$	49	-
Me	H	$Rh_2(OAc)_4$	79	75:25
Ph	H	$Rh_2(OAc)_4$	78	72:28

Scheme 44

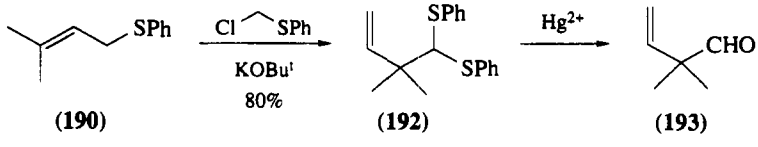
overall yields are obtained using ammonium rather than sulfonium ylides. Following the same theme, Lythgoe has used 1,3-dithiane as the masked aldehydic equivalent.[71] *S*-Alkylation of dithiane using allylic halides followed by a sulfur ylidic 3,2-rearrangement gave the homoallylic dithiane (**209**), which was hydrolyzed smoothly to the β,γ-unsaturated aldehyde (**199**; Scheme 49).

Büchi has used Mander's approach as a key step in his synthesis of α-sinensal (**212**; Scheme 50),[72] and Corey has applied the ylidic 3,2-rearrangement to the efficient preparation of 3-cyclopentenones.[73] Thus, base treatment of the sulfonium salt (**213**) first gave the rearranged product (**215**). Thermal vinylcyclopropane ring expansion then produced the spiro compound (**216**). Deprotection finally gave the nonconjugated cyclopentenone (**217**; Scheme 51).



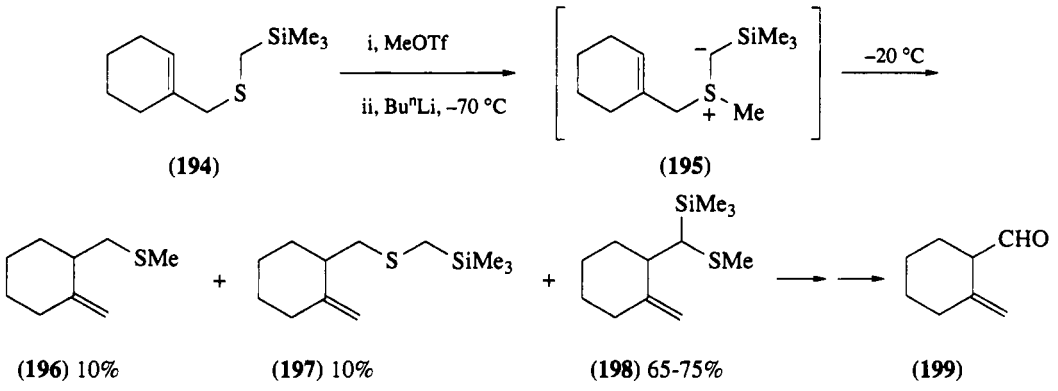
Entry	R^1	R^2	*X*	*Y*	*Yield (%)*
1	Me	Me	CO_2Et	CO_2Et	84.3
2	Me	Me			62.8
3	Me	Me	CO_2Et	$O{=}P(OEt)_2$	81.1
4	CH_2OBn	H	CO_2Et	CO_2Et	83.4
5	CH_2OBn	H			61.1
6	CH_2OBn	H	CO_2Et	$O{=}P(OEt)_2$	100
7		H	CO_2Et	CO_2Et	63
8		H			82.7
9		H	CO_2Et	$O{=}P(OEt)_2$	80.3

Scheme 45



Scheme 46

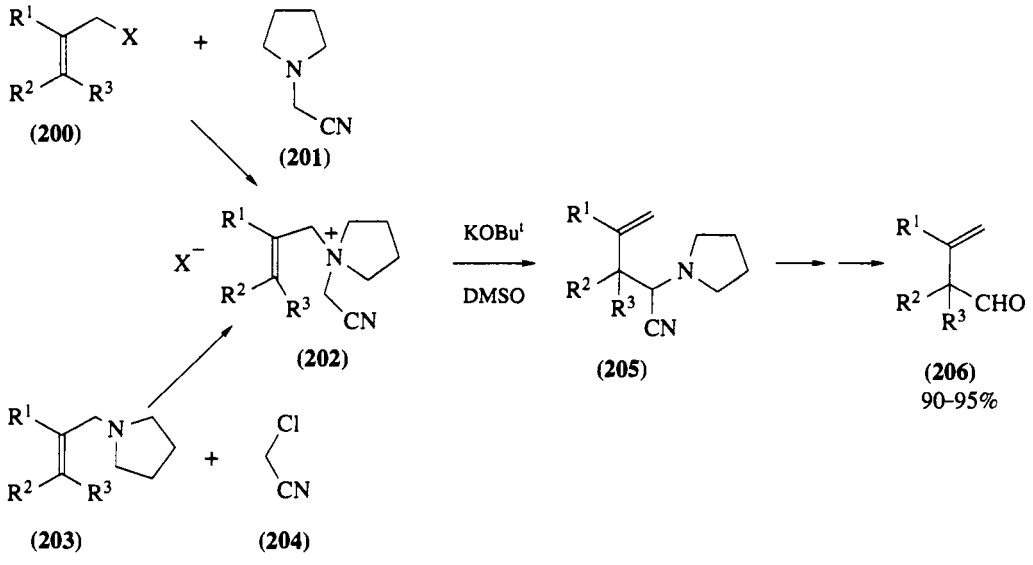
Cohen has used a soluble version of the Simmons–Smith reagent to promote the 3,2-rearrangement of allylic sulfides (Scheme 52).[74] He has also applied this methodology to the synthesis of sarkomycin (**225**).[75] The allylic sulfide (**221**), easily available *via* a Petrow reaction, was first alkylated and the sulfonium ylide was then generated by a fluoride-promoted desilylation. Rearrangement of the ylide (**223**) gave the homoallylic sulfide (**224**) which was eventually transformed into sarkomycin (Scheme 53).



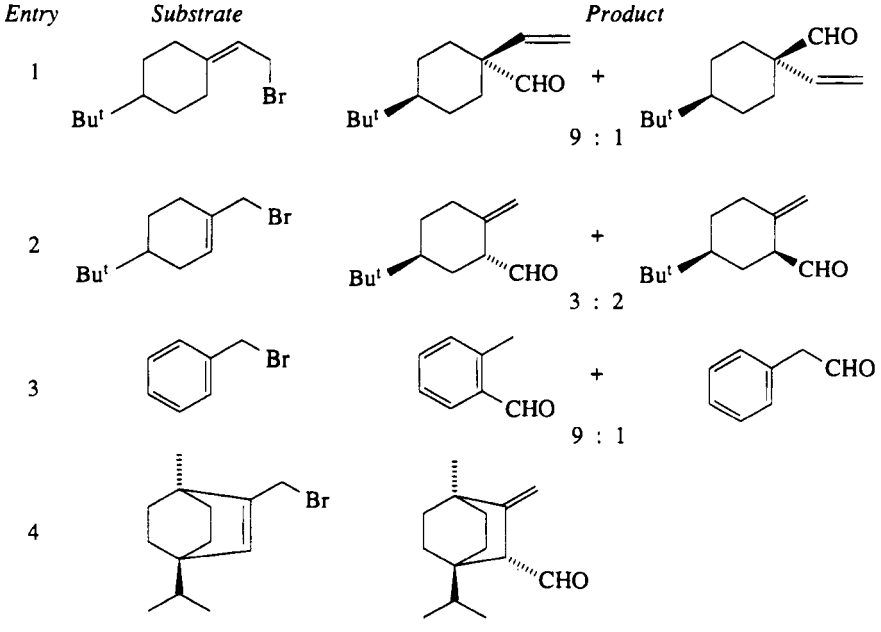
(194) **(195)**

(196) 10% **(197)** 10% **(198)** 65-75% **(199)**

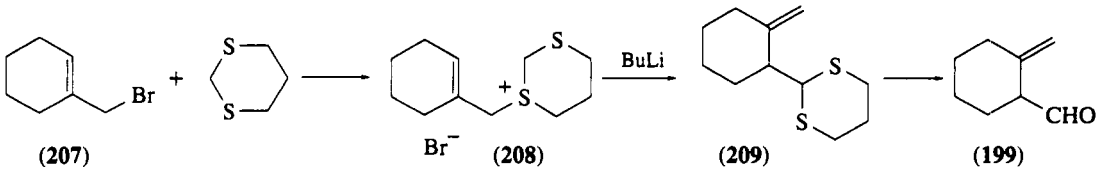
Scheme 47



(200) **(201)** **(202)** **(203)** **(204)** **(205)** **(206)** 90–95%

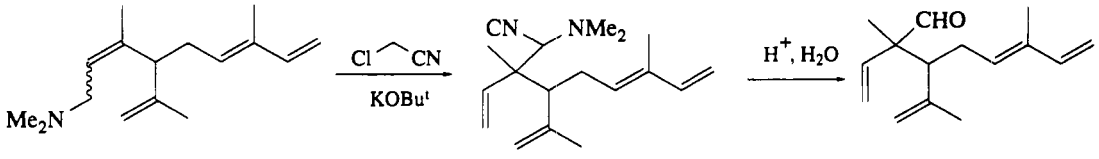


Scheme 48



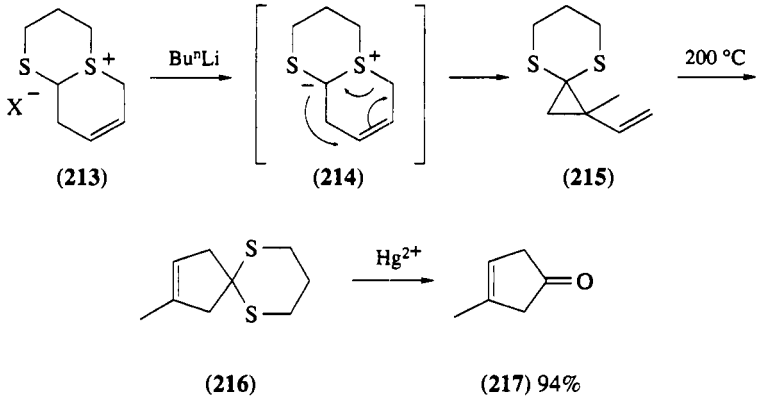
(207) (208) (209) (199)

Scheme 49



(210) (211) (212)

Scheme 50



(213) (214) (215)

(216) (217) 94%

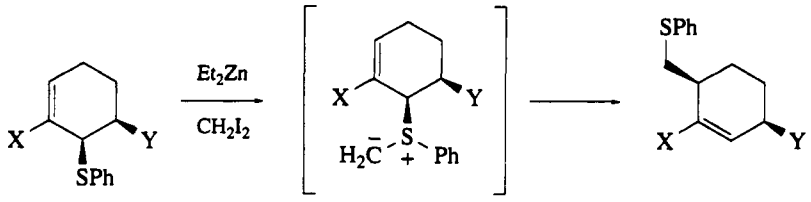
Scheme 51

The formation and 3,2-sigmatropic rearrangement of sulfonium and ammonium ylides, generated by fluoride-promoted desilylation, has also been actively investigated by Vedejs. He showed that ylides, produced under kinetic control, could be prepared using this technique and rearranged by a 3,2-sigmatropic process. This rearrangement can take place before equilibration to the thermodynamically more stable ylide occurs (Scheme 13). In yet another version, Zbiral has used silyl-stabilized ylides to produce homoallylic sulfides.[76] An initial Peterson reaction between the ylide (**227**) and a carbonyl compound (**228**) is followed by a deprotonation to generate another ylide (**229**). Equilibration of the thermodynamically more stable ylide (**229**) gives a small amount of the isomer (**230**), which undergoes rapid 3,2-sigmatropic rearrangement, leading to the observed reaction product (Scheme 54).

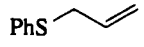
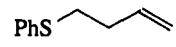
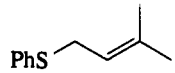
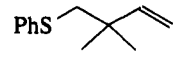
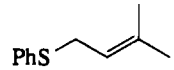
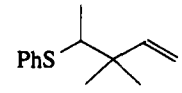
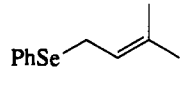
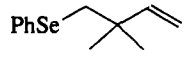
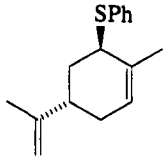
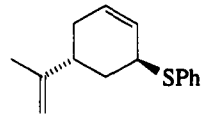
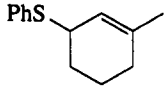
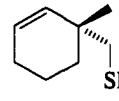
Ratts and Yao reported a particularly interesting preparation of enol ethers by a 3,2-sigmatropic transposition in which the carbonyl function of stabilized ylides participates in the rearrangement (Scheme 55).[39] The same starting sulfonium ylide is well known to give Stevens rearrangement products. The competition between the 1,2- and 3,2-pathways is strongly dependent on the reaction conditions and good yields of either product can be obtained by carefully selecting the base concentration (Scheme 56).

During his generalization of 3,2-sigmatropic rearrangements, Baldwin observed the interesting transformation depicted in Scheme 57.[77] Base treatment of the tosylhydrazone (**236**) generates, after loss of nitrogen, the carbene (**237**), which rearranges to the dithioester *via* a 3,2-sigmatropic transposition. A most elegant application of this reaction has been reported by Evans in his bakkenolide synthesis (Scheme 58).[78] Thus, base-promoted rearrangement of the tosylhydrazone (**239**) occurred from the less hindered face of the hydrindane system and gave stereospecifically the dithioester (**241**), which was subsequently transformed into bakkenolide (**242**).

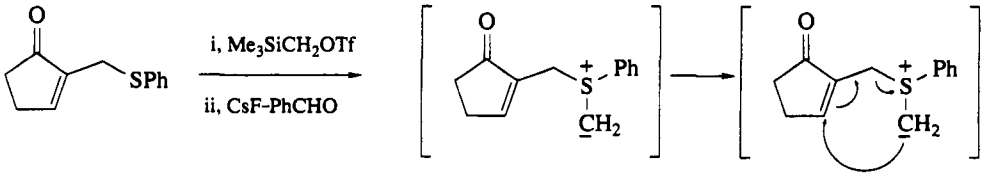
Sulfoxonium ylides also undergo 3,2-sigmatropic rearrangements.[79] A useful preparation of conjugated dienes is based on a 3,2-rearrangement followed by spontaneous elimination of methanesulfenic acid (Scheme 59, equation a). In some cases, the reaction proceeds without isolation of the intermediate ylide (Scheme 59, equation b).



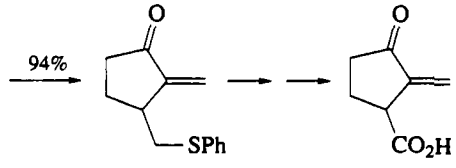
(218) **(219)** **(220)**

Entry	*Substrate*	*Reagent*	*Product*	*Yield (%)*
1		Et_2Zn-CH_2I_2		55
2		Et_2Zn-CH_2I_2		80
3		Et_2Zn-$EtCHI_2$		70
4		Et_2Zn-CH_2I_2		75
5		Et_2Zn-CH_2I_2		78
6		Et_2Zn-CH_2I_2		72

Scheme 52

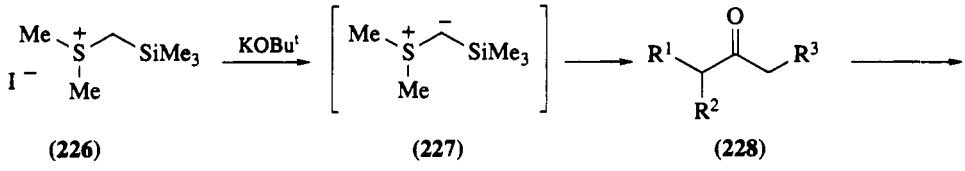


(221) **(222)** **(223)**

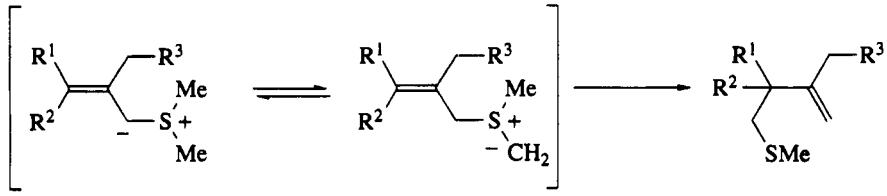


(224) **(225)**

Scheme 53



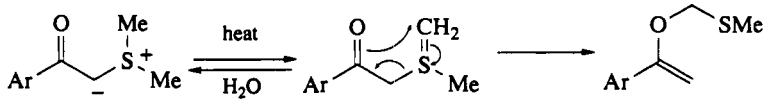
(226) (227) (228)



(229) (230) (231)

Entry	R^1	R^2	R^3	*Yield* (%)
1	Me	H	H	49
2	Pr^i	H	H	60
3	Me	Me	H	20
4	H	$-(CH_2)_2-$		20
5	H	$-(CH_2)_3-$		~20

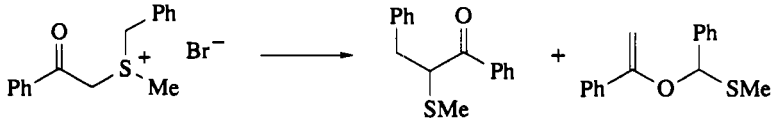
Scheme 54



(232) (233) (234)

Entry	*Ar*	*Yield* (%)
1	Ph	66
2	4-BrC_6H_4	50
3	4-ClC_6H_4	64
4	2-Naphthyl	57

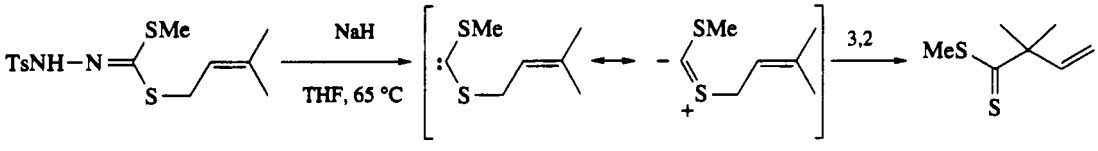
Scheme 55



(3) (4) (235)

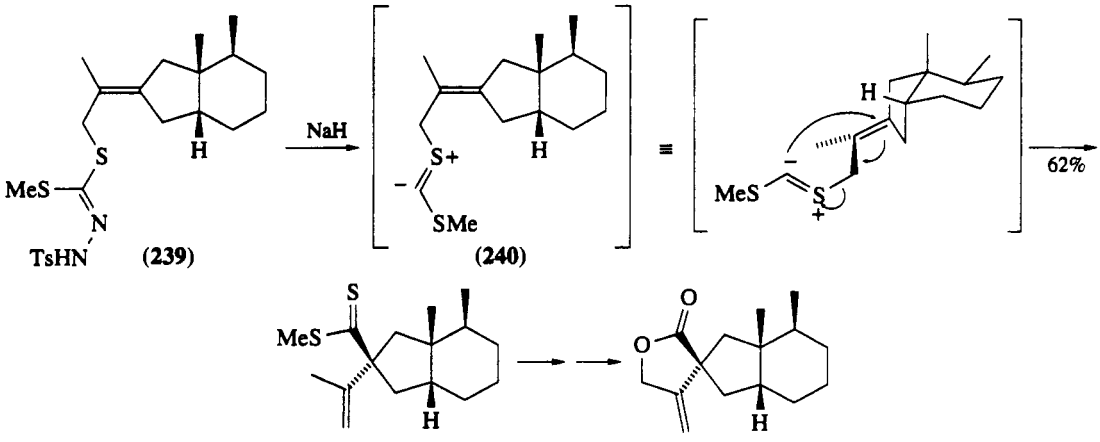
5% Na, MeOH, 60 °C :	3%	78%
10% Na, MeOH, 60 °C :	48%	32%
15% Na, MeOH, 60 °C :	69%	trace

Scheme 56



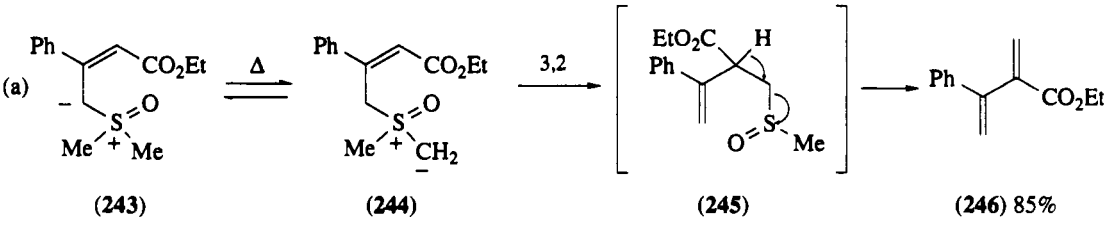
(236) (237) (237) (238)

Scheme 57

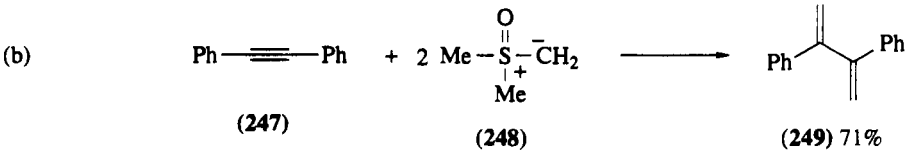


(239) (240) (241) (242)

Scheme 58



(243) (244) (245) (246) 85%

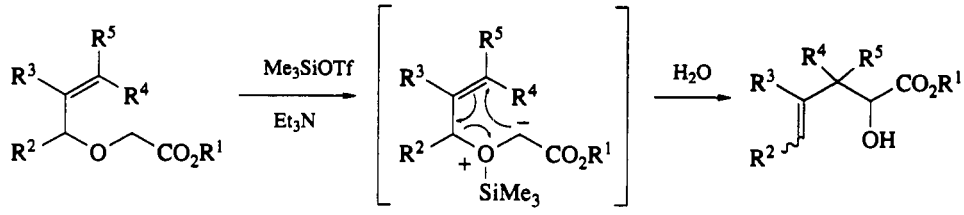


(247) (248) (249) 71%

Scheme 59

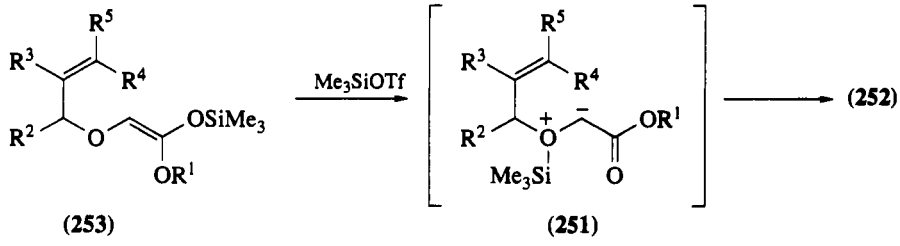
Despite the pioneering work of Ando and Doyle, few synthetic applications of oxonium ylidic rearrangements have been reported. However, three examples of synthetic relevance appeared recently (Schemes 60 to 62). When α-allyloxyacetic esters are reacted with trimethylsilyl triflate and a base, the transposed material (**252**), resulting from a 3,2-sigmatropic rearrangement of the transient ylide (**251**), could be isolated in good yields.[80] The same product ratio was also obtained upon treatment of the ketene acetal (**253**) with trimethylsilyl triflate. This second variant involves the direct formation of ylide (**251**) followed by its transformation into (**252**; Scheme 60).

Almost at the same time, Pirrung[81a] and Johnson[81b] independently described the rearrangement of oxonium ylides prepared by intramolecular rhodium-catalyzed carbene addition. The reaction appears to have a broad scope and gives an easy entry into complex oxygenated polycycles (Scheme 61). When the possibility arises, high levels of diastereocontrol are exercised (Scheme 62).



(250) (251) (252)

Entry	R^1	R^2	R^3	R^4	R^5	*(E)*	*(Z)*	*Syn:anti*	*Yield (%)*
1	Me	Me	H	H	H	31	69		93
2	Me	Me	Me	H	H	31	69	–	98
3	Me	H	H	H	Me	–	–	92:8	83
4	Me	H	H	Me	H	–	–	53:47	86
5	H	Me	H	H	H	43	57		85
6	H	H	H	H	Me	–	–	88:12	92
7	Pr^i	H	H	H	Me	–	–	95:5	86
8	Bu^t	H	H	H	Me	–	–	88:12	56



(253) (251)

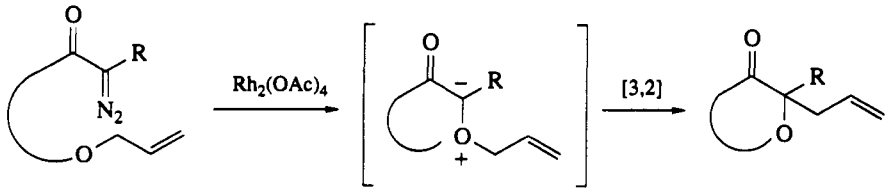
Scheme 60

3.10.5.3 Configuration of the Newly Formed Double Bond

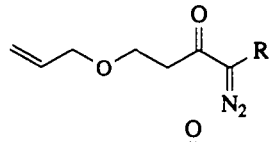
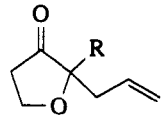
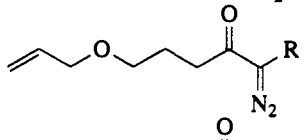
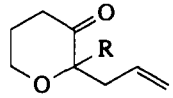
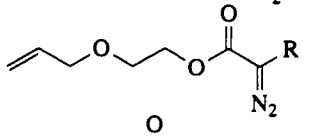
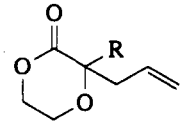
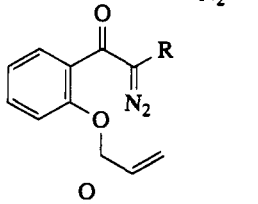
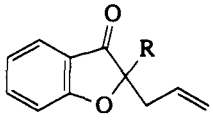
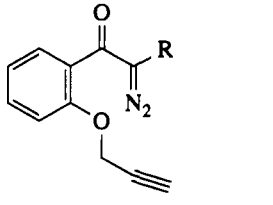
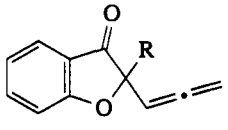
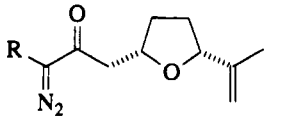
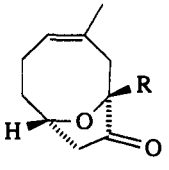
The 3,2-sigmatropic rearrangement of ylides proceeds in general with high stereocontrol at the newly formed carbon–carbon double bond. In the synthesis of squalene by Ollis for example, the sulfur ylide (**57**) rearranged into the sulfide (**58**) with a *trans* (*E*) double bond (Scheme 14). Grieco has also shown that rearrangement of the sulfide (**262**) gave a 9:1 ratio of (*E*)- to (*Z*)-alkenes (Scheme 63, equation a).[82] Hill demonstrated that ammonium ylide rearrangements proceed with >95% (*E*)-stereoselectivity (Scheme 63, equation b),[83] and Julia found that the sulfur ylide (**267**) gave the sulfide (**268**) as the pure (*E*)-isomer (Scheme 63, equation c).[84]

By analogy with the chair conformation invoked for the transition state of the 3,3-rearrangement, the transition state geometry of the 3,2-sigmatropic rearrangement could be analyzed in terms of the 'folded envelope', or puckered, conformation of cyclopentane.[85] This well-defined conformation should result in a high degree of stereocontrol of the alkene geometry and a high level of stereospecificity in the generation of chiral centers. In the absence of particular effects, examination of these puckered conformations for the transition states of the 3,2-sigmatropic rearrangement suggests that a substituent located on carbon C-1′ of the ylide (**269-T**, Scheme 64) would prefer to be pseudo-equatorial. This should lead preferentially to the formation of (*E*)-alkenes (Scheme 64).

Model studies have been carried out in order to compare the stereospecificity of different types of 3,2-rearrangements (Scheme 65). From these results, it appears that, in the absence of any special effect, the 3,2-ylidic rearrangement is (*E*)-selective. The Wittig rearrangement shows a greater tendency for (*Z*)-stereochemistry.[89] However, the energy difference between the cisoid (**270-C**) and transoid (**270-T**) transition states in a 3,2-sigmatropic rearrangement (Scheme 64) is not very large. These rearrangements will



(254) **(255)** **(256)**

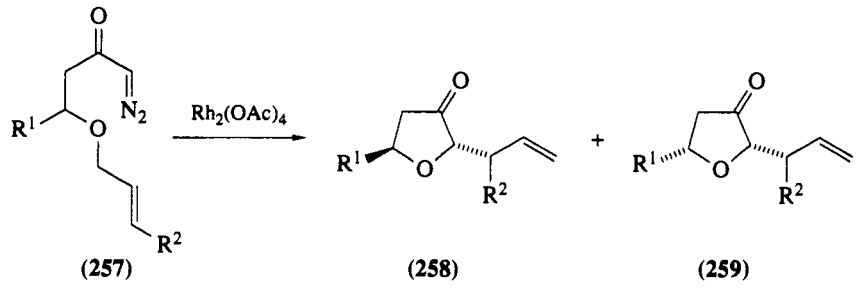
Entry	*Substrate*	*Product*	*Yield (%) R = H*	*R = CO_2Me*	*R = CO_2Et*
1			70	91	–
2			33	53	–
3			0	–	51
4			71	–	95
5			33	53	–
6			81	67	–

Scheme 61

occur readily even if they have to proceed *via* the less favored cisoid transition state (**270-C**). This is observed when the reacting double bond is incorporated into a ring, as shown in Scheme 66. However, if the ring size allows it, the products of the favored transoid transition state will be observed. The increase in strain associated with the formation of an (*E*)-alkene in a cyclic system might sometimes disfavor the transoid transition state (Scheme 67).[90]

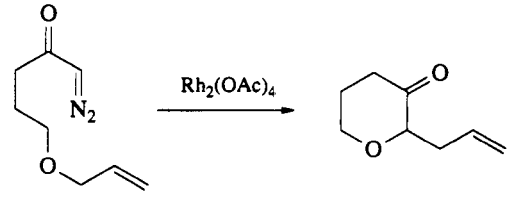
Rearrangement of the five-membered ring sulfonium ylide (**278**) gives the (*Z*)-sulfide (**279**) accompanied by a small amount of (*E*)-isomer. The homologous six-membered ring sulfonium ylide (**280**) reacts smoothly to give diastereomerically pure (*E*)-(**281**). In the formation of the sulfide (**279**), the transition state (**278-C**) leading to the (*Z*)-alkene suffers from an H–H steric interaction. However, the steric strain arising from the incipient *trans* double bond, in what will eventually become an eight-membered ring, is far more important and transition state (**278-C**) is preferred over (**278-T**; Scheme 68). The reverse holds true for the reaction of the ylide (**280**) where the transition state (**280-C**) leading to the (*Z*)-alkene is the more sterically encumbered one because of a severe H–H interaction (Scheme 69).

By placing substituents at suitable positions on the starting ylide, it may become possible to alter the stereochemical course of these reactions. Fava has actually been able to reverse completely the normal stereochemical trend in these 3,2-sigmatropic rearrangements (Scheme 70).[91] Ylide (**282**) rearranges



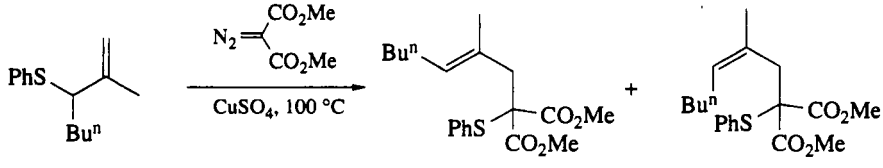
(257) (258) (259)

R^1 = Me, R^2 = H	60%	5%
R^1 = H, R^2 = Me	63%	–



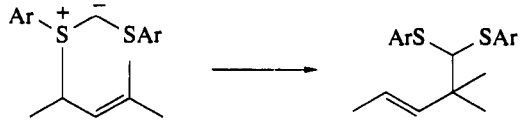
(260) (261) 61%

Scheme 62



(262) (263) 90 : (259) 10 (a)

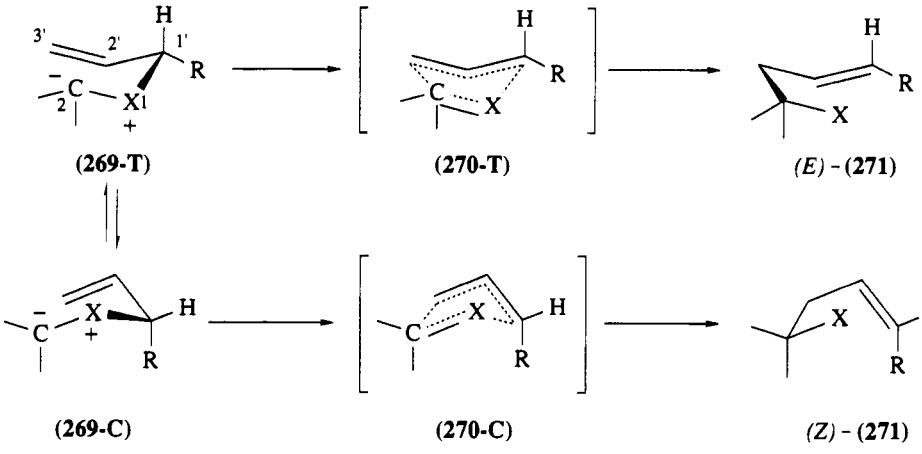
(265) (266) >95% *(E)* (b)



(267) (268) 100% *(E)* (c)

Scheme 63

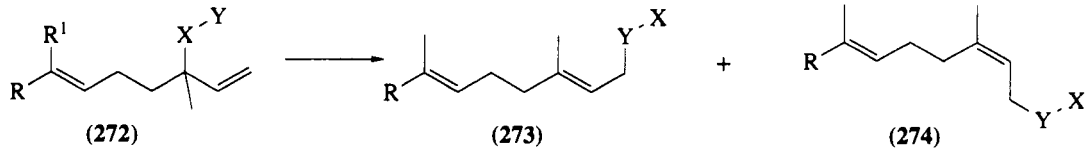
smoothly to the (*E*)-sulfide (**283**), which is contaminated by less than 2% of the (*Z*)-alkene. In the transition state (**282-C**) leading to the (*Z*)-product, a severe steric interaction can be observed between an axial hydrogen and one of the alkenic methyl groups. This interaction will destabilize transition state (**282-C**) relative to (**282-T**) and a product with (*E*)-stereochemistry will be obtained. Similarly, the ylide (**284**) rearranges to the (*Z*)-alkenic nine-membered sulfide (**285**; Scheme 71).



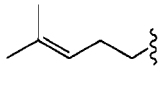
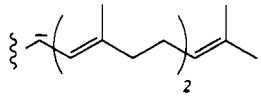
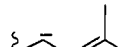
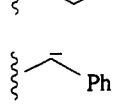
(269-T) (270-T) (*E*)-(271)

(269-C) (270-C) (*Z*)-(271)

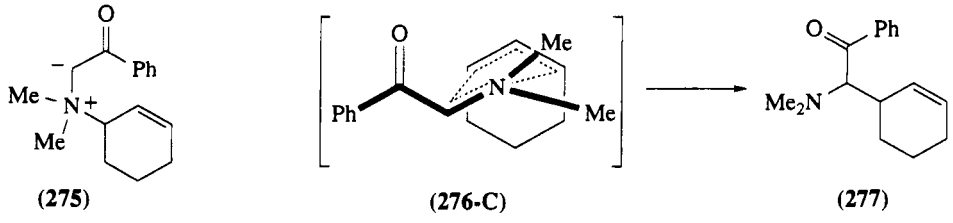
Scheme 64



(272) (273) (274)

R	*R*^{1}	*X*	*Y*	(*E*)	(*Z*)	*Ref.*
	Me	PhS^+		100	0	30
Me	H	PhS^+		9	1	86
Me	H	S		3	2	87
Me	H	O		1	1	88

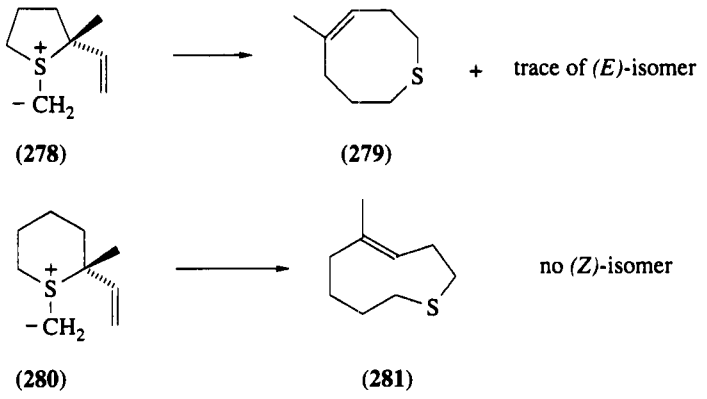
Scheme 65



(275) (276-C) (277)

Scheme 66

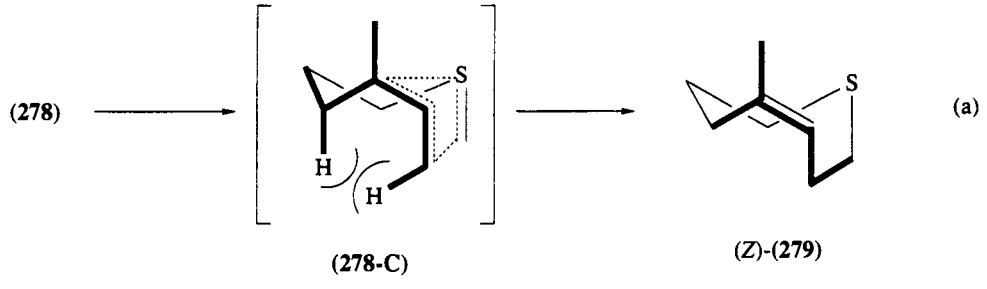
Transition state (**284-T**) reveals clearly a particularly destabilizing methyl–methyl interaction. It is therefore strongly disfavored compared with transition state (**284-C**), which shows only an axial methyl–methyl interaction. This approach has been used by Fava in a highly imaginative route to betweenanenes.[92] The sulfonium salt (**286**) is transformed by a stereospecific 3,2-sigmatropic rearrangement into the (*E*)-macrocycle (**287**). A Ramberg–Backlund reaction followed by catalytic hydrogenolysis then leads to betweenanene (**289**; Scheme 72, equation a). The epimeric sulfonium salt (**290**) rearranges smoothly to the (*Z*)-macrocycle. An identical methodology has been used by Nickon to prepare betweenanenes with enol sulfide functionalities.[93]

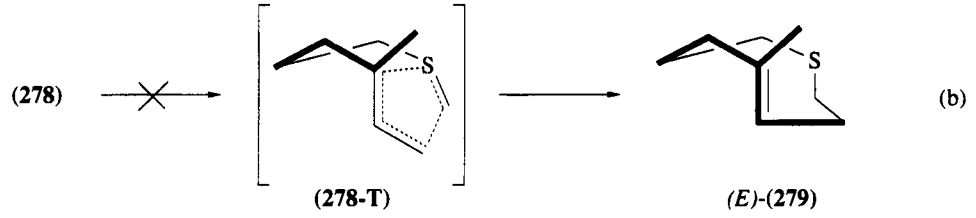


(278) (279)

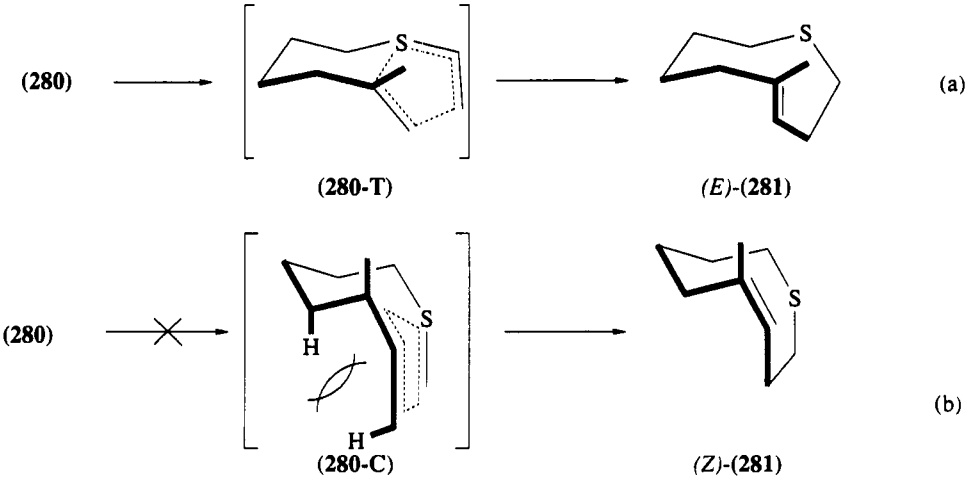
(280) (281)

Scheme 67

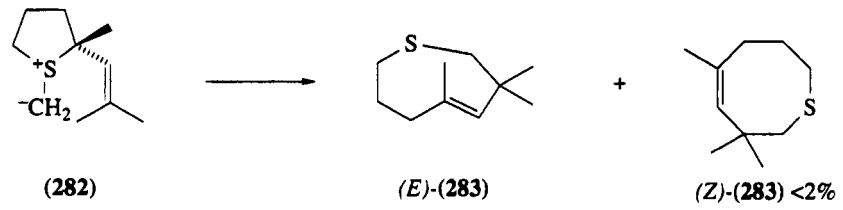




Scheme 68



Scheme 69

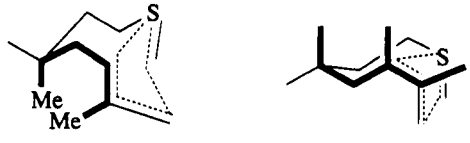


(282) (*E*)-(283) + (*Z*)-(283) <2% (a)

(282-T) → (*E*)-(283) (282-C) → (*Z*)-(283) (b)

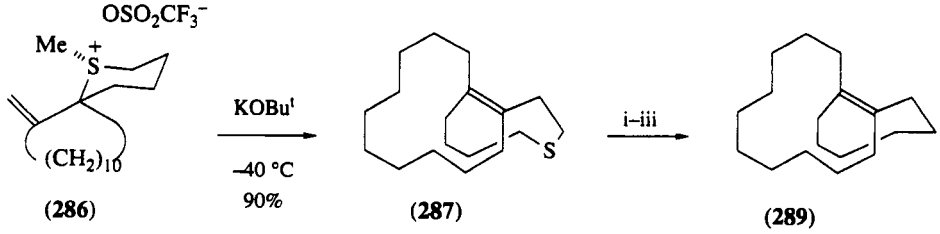
Scheme 70

(284) (*Z*)-(285) (a)

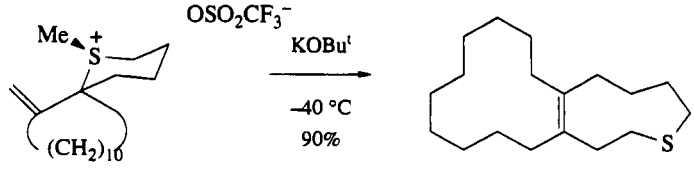


(284-T) → (*E*)-(285) (284-C) → (*Z*)-(285) (b)

Scheme 71



(286) (287) (289) (a)



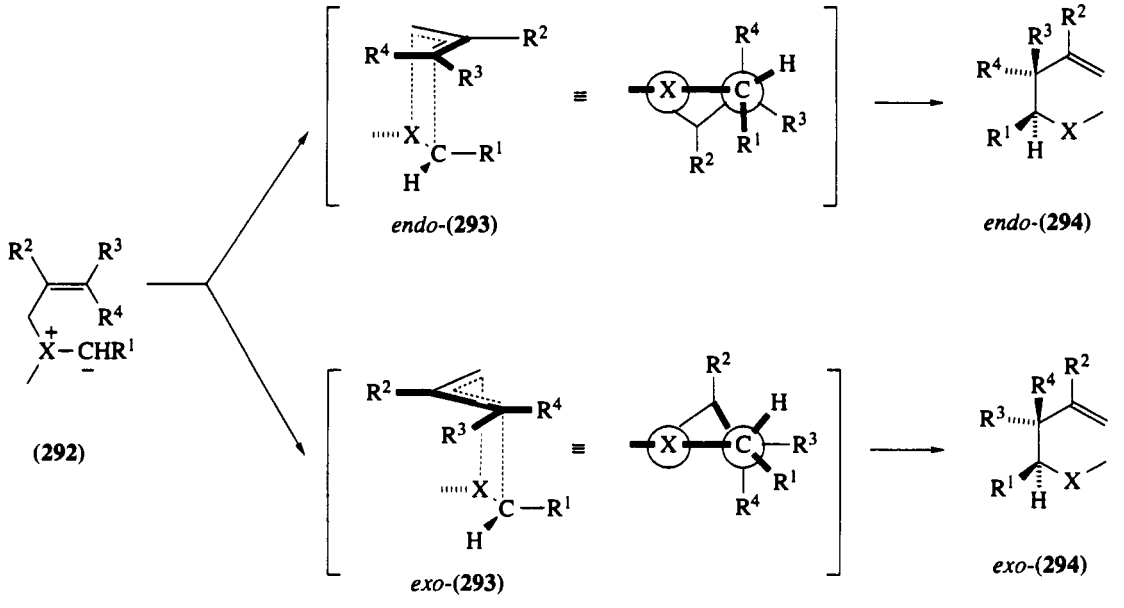
(290) (291) (b)

i, MCPBA; ii, NaH; iii, H_2–Pd–C

Scheme 72

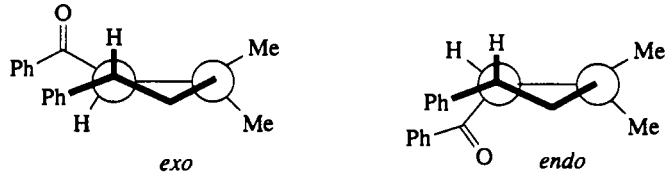
3.10.5.4 The Erythro–Threo Ratio

In 3,3-sigmatropic rearrangements, the ratio of diastereoisomers is controlled by the energy difference between boat and chair conformations. In general, this energy difference represents a significant quantity. For 3,2-sigmatropic rearrangements the diastereoisomeric ratio will be dependent upon the preference of a substituent to be located on the *exo* or *endo* position in the transition state. These are often only small energy differences and, therefore, mixtures occur frequently (Scheme 73).



Scheme 73

When sterically feasible, an *endo* transition state will however be favored.[94] Some examples are collected in Table 3.[94–97] From the results indicated in the table, a general pattern seems to emerge. Sulfur ylides and propargylic ammonium ylides undergo preferential 3,2-rearrangement *via* an *endo* transition state and the diastereoisomeric control is good to excellent. Acyclic, nonpropargylic ammonium ylides give a mixture of diastereoisomers and, in some cases, a strong *exo* preference is displayed (Table 4).[98] Examination of the envelope transition states reveals that the *exo* transition state is the least sterically congested and should, therefore, be the preferred one in these cases (Scheme 74).



Scheme 74

It can also be seen that an increase in the steric bulk of the ketone substituent (Ph replaced by Bu^t) should favor the *exo* transition state even more. This is indeed observed, since the *endo*:*exo* ratio rises from 1:5 to 1:9. It is, however, difficult to make some predictions since subtle effects which could be present could favor either one or the other of the transition states (compare entry 5 in Table 3 with entry 1 in Table 4). Sometimes, steric hindrance in one of the transition states is so overwhelming that prediction can be made rather safely.[99] This is the case for the ylide (**295**) which rearranges exclusively *via* an *exo* transition state *exo*-(**296**), the *endo* transition state *endo*-(**296**) being much too hindered to be attained (Scheme 75). Similarly, the ylide (**299**) gives the amine (**300**) as a single isomer in 88% yield (Scheme 76).[99]

Table 3

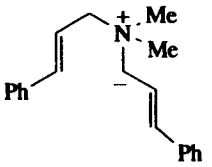
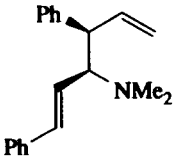
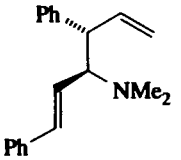
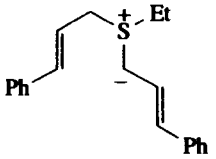
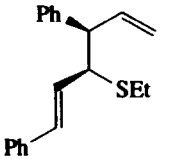
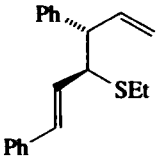
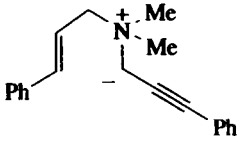
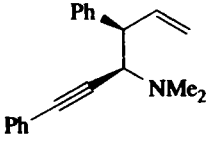
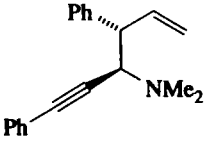
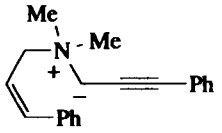
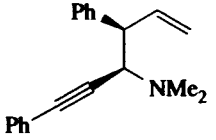
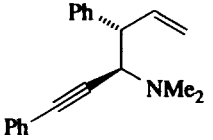
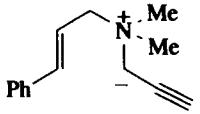
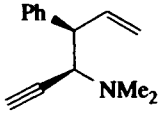
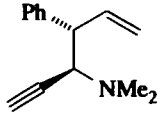
Entry	*Substrate*	*Products*		*Ratio*	*Transition state*
1				10:1	*Endo*
2				—	*Endo*
3				86:14	*Endo*
4				10:90	*Endo*
5				100:0	*Endo*

Table 3 *(continued)*

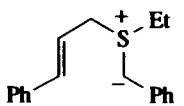
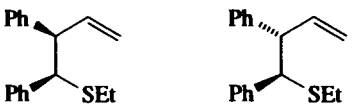
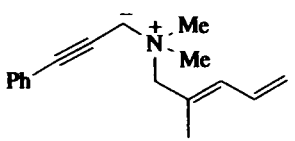
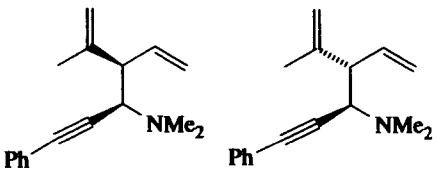
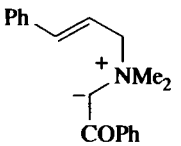
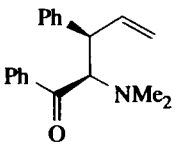
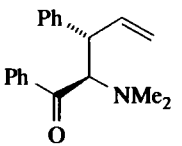
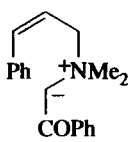
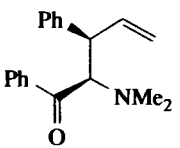
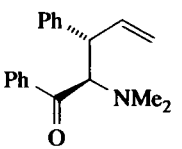
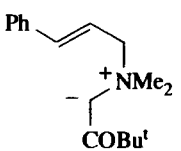
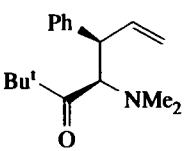
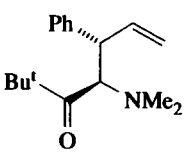
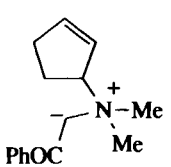
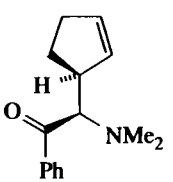
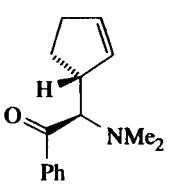
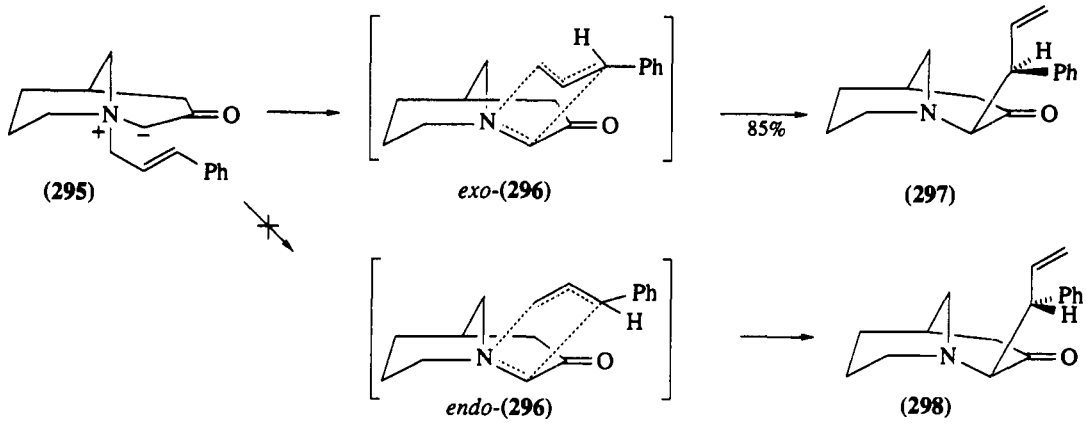
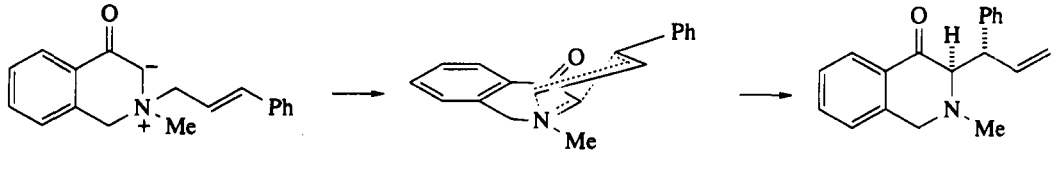
Entry	*Substrate*	*Products*	*Ratio*	*Transition state*
6			60:40	*Endo*
7			60:10	*Endo*

Table 4

Entry	*Substrate*	*Products*		*Ratio*	*Transition state*
1				1:5	*Exo*
2				2:1	*Endo*
3				1:9	*Exo*
4				2:1	*Endo*



Scheme 75



Scheme 76

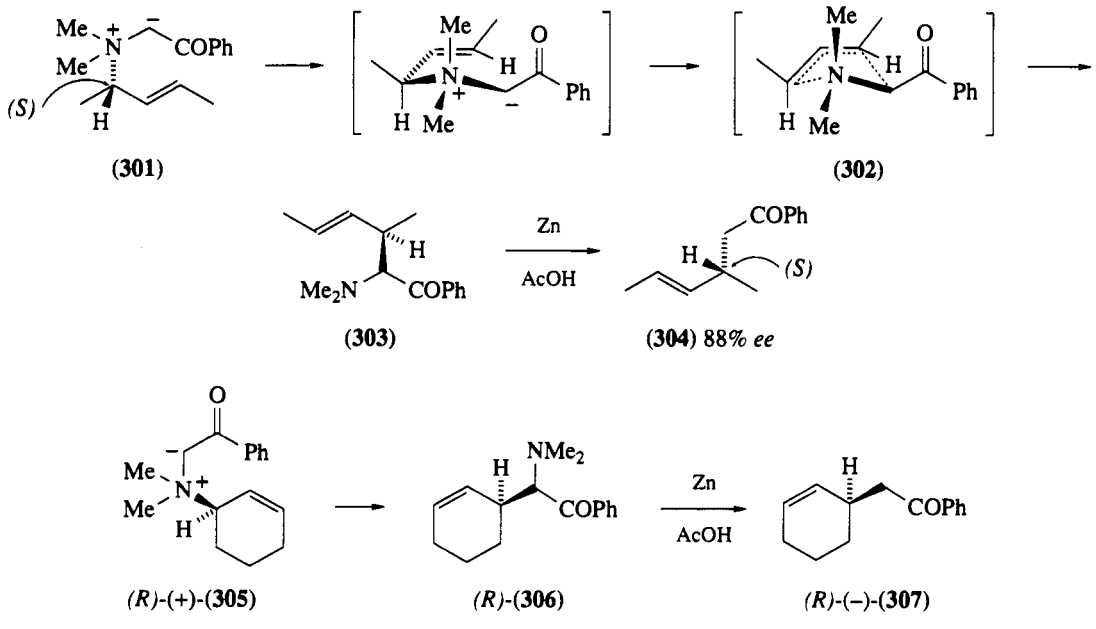
3.10.5.5 Transfer of Configuration

In a way similar to 3,3-rearrangements, the configuration of C-1 of the allylic group can be transferred to C-3 by a 3,2-sigmatropic rearrangement. The original chiral center and the double bond configuration will control, *via* the envelope transition state, the chirality and configuration of the product; an (*R*)-(*E*)-starting material usually leads to an (*S*)-(*E*)-product, whereas the use of a (*Z*)-substrate gives the opposite result: (*R*)-(*Z*). Hill has studied the chirality transfer of simple acyclic ammonium ylides and observed that transposition of the ylide (**301**), followed by reductive cleavage, gave the ketone (**304**; 88% *ee*).[83,100] The configuration of the carbon–carbon double bond is, as expected, retained. Similarly, the ylide (**305**) leads to the (*R*)-(–)-cyclic ketone (**307**; Scheme 77). In an analogous manner, rearrangement of the (*S*)-(*E*)-allylic alcohol (**308**) using the 'Buchi method' gives the (*Z*)-amide (**310**) of >99% *ee*, accompanied by ~13% of the (*S*)-(*Z*)-isomer resulting from the other envelope conformation.[101] In sharp contrast, the (*R*)-alcohol (**308**) gives only the (*R*)-(*E*)-amide (**310**; Scheme 78).

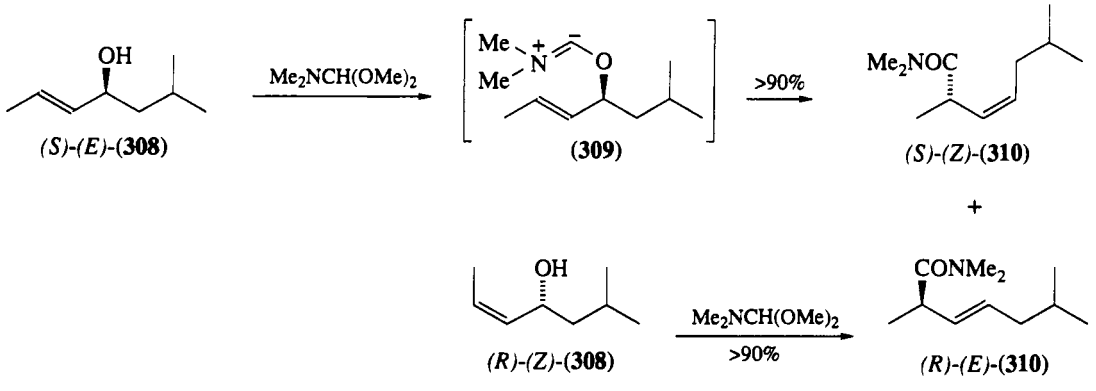
An interesting transfer of asymmetry from a chiral heteroatom to the newly formed carbon–carbon bond has been reported by Trost.[102] The sulfonium salt (**311**) gives the 3,2-rearrangement product (**312**) with 94% *ee* (Scheme 79, equation a). The high asymmetric induction obtained in this case can be rationalized by preferential rearrangement *via* transition state (**313**), containing a minimum of nonbonded interactions, rather than the more congested transition state (**315**; Scheme 79, equation b). This is, however, a rather exceptional example and, in general, the asymmetric induction remains low (Scheme 80).[103–105]

Asymmetric induction arising from remote chiral centers present in the ylide is yet another way of transferring chirality. Although only a few examples are known, an outstanding one has been described by Baldwin and Kaiser, who obtained the α-allyl penam derivative (**186**) as a single isomer upon rearrangement of the nitrogen ylide (**185**; Scheme 43).[65] Sulfonium and selenonium ylides proved to be much less efficient, as demonstrated by John (Scheme 41).[64]

The last, and probably most interesting, example of the approach towards chiral products derived from ylidic 3,2-rearrangements, involves the generation of a chiral ylide by enantioselective deprotonation of a prochiral sulfonium (ammonium) salt using a chiral base. Few attempts have been reported so far, the most noteworthy coming from the laboratory of Trost and involving the reaction of the sulfonium salt (**321**) with the chiral base (**322**; Scheme 81).[103] The asymmetric induction is rather poor and represents the extent of prochiral recognition by the chiral base.



Scheme 77

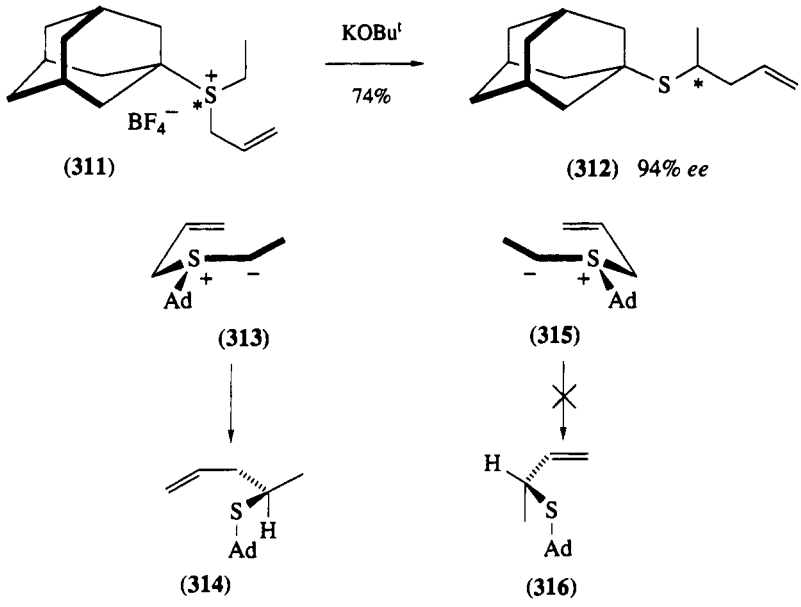


Scheme 78

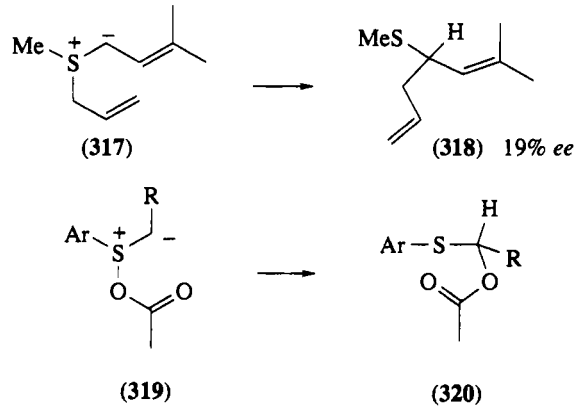
3.10.5.6 Ring Contraction Reactions

Ylidic 3,2-sigmatropic rearrangements have quite recently been used to promote ring contraction reactions, generally with high selectivity. One of the most famous examples involves the transformation of the cephalosporin derivative (**70**) into the penicillin derivative (**72**; Scheme 82).[33] A similar ring contraction was observed by Ando when the unsaturated sulfide (**66**) was reacted with diazomalonate under photolytic conditions.[44] The stable ylide (**68**) underwent 3,2-rearrangement only upon heating (Scheme 83, equation a).

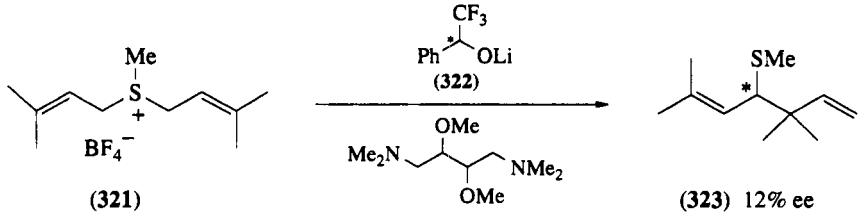
In sharp contrast, the ylide (**325**) rearranges spontaneously above –5 °C to give a mixture of *cis*- and *trans*-sulfides (**326**) and (**327**) in a 25:1 ratio.[98] The fact that the stereochemistry of the reaction products is under kinetic control was demonstrated by the base-catalyzed epimerization of (**326**) and (**327**) to a thermodynamic 1:19 ratio. Ammonium ylides also undergo ring contraction but with complete *cis* diastereoselectivity (Scheme 84).[98] Base-catalyzed equilibration affords some *trans* isomer. The high diastereoselectivities displayed in these reactions contrasts with the poor and rather unpredictable ones observed for acyclic ylide rearrangements (*cf.* Section 3.10.5.4). In all of the cases examined, the *endo* transition state *endo*-(**325**) is highly favored over the *exo* transition state *exo*-(**325**) (Scheme 85). A



Scheme 79



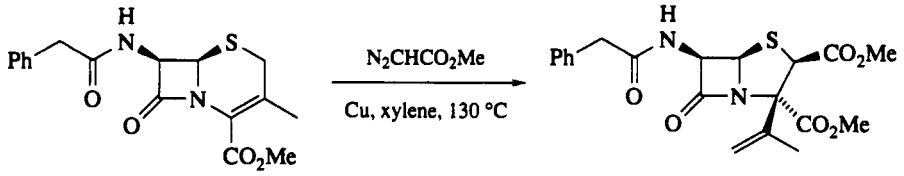
Scheme 80



Scheme 81

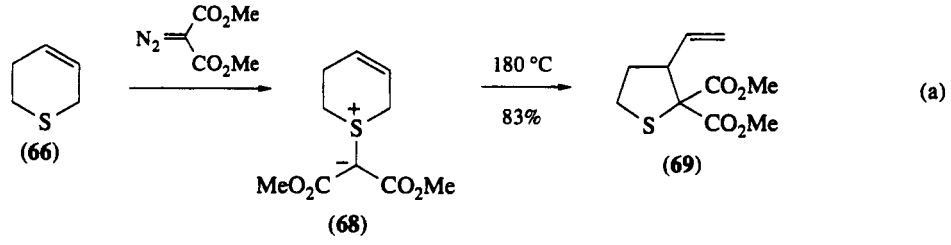
possible explanation invokes secondary orbital interactions, which can take place between the *endo* carbonyl group and the carbon–carbon double bond only in the *endo* transition state (**328**; Scheme 86).

Once again, ammonium ylides display higher diastereoselectivities than their sulfur counterparts. This observation formed the basis of a recent synthetic approach towards the alkaloid makomakine (**331**; Scheme 87) where the key step was the ring contraction of the azepine (**329**) into the *cis*-substituted piperidine ring (**330**).[106]

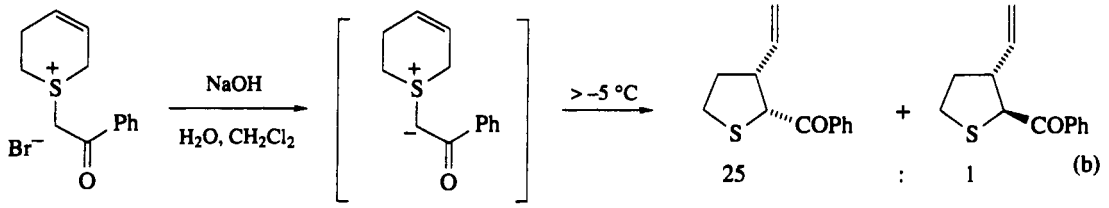


(70) (72) 63%

Scheme 82

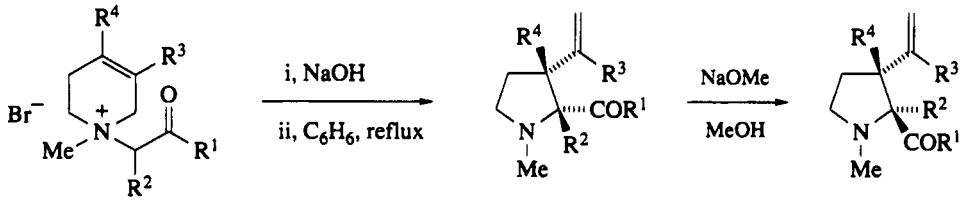


(66) (68) (69) (a)



(324) (325) (326) (327) (b)

Scheme 83

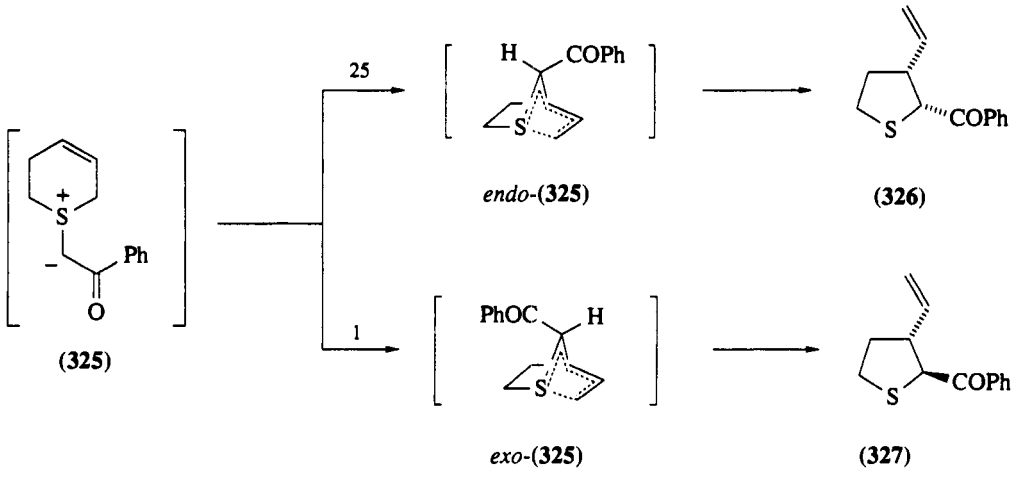


(328) (329) (330)

R^1	R^2	R^3	R^4	*(329):(330)*
Ph	H	H	H	100:0
Ph	H	Me	Me	100:0
Ph	H	H	Et	100:0
Ph	H	H	Bu^t	100:0
Ph	Ph	H	H	100:0
Bu^t	H	H	H	100:0

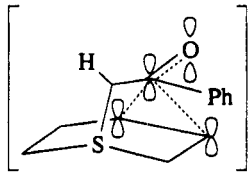
Scheme 84

Yoshikoshi has explored a novel strategy directed towards the enantioselective preparation of highly substituted butyrolactones, based on the 3,2-sigmatropic rearrangement of sulfur ylides (Scheme 88).[107] Intramolecular carbene trapping generated the eight-membered ring sulfur ylide (**334**), which then underwent ring contraction to give the complex lactone (**335**) as a single stereoisomer.



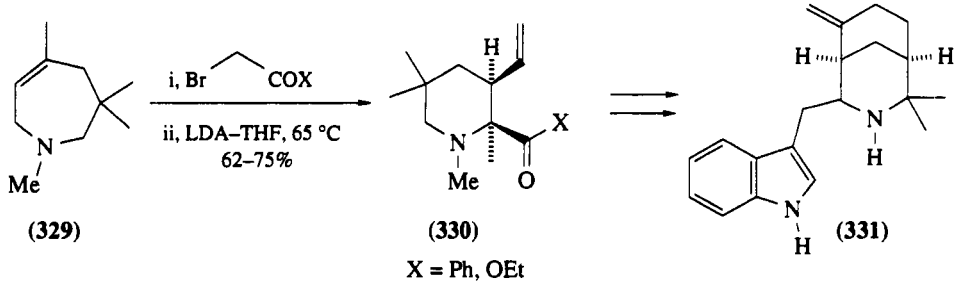
(325) *endo*-(325) (326) *exo*-(325) (327)

Scheme 85



(328)

Scheme 86

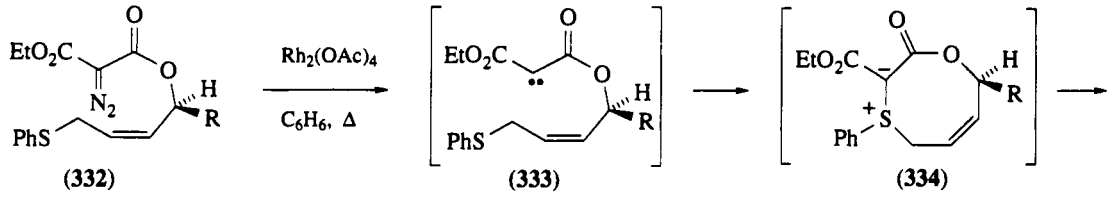


(329) (330) X = Ph, OEt (331)

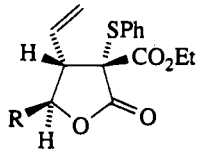
Scheme 87

3.10.5.7 Ring Expansion Reactions

One of the first ring expansion reactions of an ylidic intermediate was reported by Hauser and involves the Sommelet–Hauser reaction (see Section 3.10.5.9) of the nitrogen ylide (**336**; Scheme 89).[108] However, the recognition of the synthetic potential of ylidic 3,2-rearrangements for controlled ring expansions is due to Vedejs, who published in 1975 a novel 'ring-growing' reaction.[109] This was to be the beginning of a remarkable synthetic methodology, which eventually culminated in the preparation of numerous natural and non-natural products. The general strategy is summarized in Scheme 90.[110] Transformation of a cyclic α-vinyl sulfide (**338**) into a stabilized ylide (**340**) is followed by a 3,2-sigmatropic rearrangement to give the eight-membered ring sulfide (**341**) as a mixture of (*Z*) (major) and (*E*) (minor) isomers. Separation and Wittig reaction regenerates an α-vinyl sulfide (**343**) ready to undergo another ring expansion reaction. The original approach used stabilized ylides but required an extra Wittig reaction in order to become an iterative process. However, by using a nonstabilized allylic ylide such as (**346**), the ring expansion product (**347**) contains an exocyclic vinylic moiety and the process can be repeated again (Scheme 91).[111]



(332) (333) (334)



(335)

R	*Yield* (%)
Me	53
Pr^n	68
Pr^i	70
Pentyl	66
$PhCH_2$	63

Scheme 88

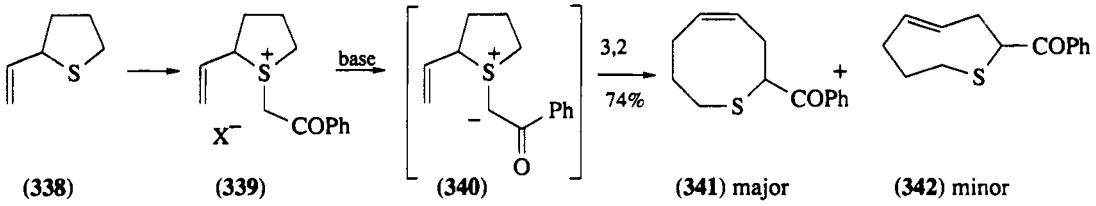
(336) (337)

Scheme 89

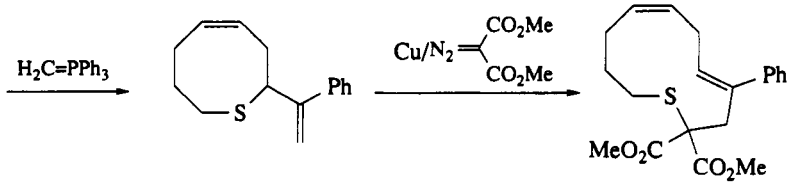
When comparing the examples described in Scheme 90 and 91, several important considerations surface. When employing nonstabilized ylides, the stereochemistry at the sulfur atom of the starting sulfonium salt can no longer be ignored. This is a real problem since the sulfonium salt, and therefore the ylide, has the vinyl group and alkyl group *trans* to each other, a result of kinetically-controlled alkylation at sulfur. The formation of (*Z*)-alkenes by a concerted 3,2-sigmatropic rearrangement requires a *cis* relationship between these two groups in order for it to take place. Fava has contributed extensively to the solving of this crucial problem.[112] He has shown that, with nonstabilized ylides, equilibration of the *cis* and *trans* sulfonium ions takes place more rapidly than deprotonation of the group present on sulfur (Scheme 92). The formation of *cis* sulfonium ylide by equilibration of the *trans* material then allows the concerted 3,2-rearrangement to take place. By blocking the epimerizable center, only the *cis* isomer rearranges smoothly, the *trans* one giving mostly the elimination product (**354**; Scheme 93).[90]

The expected high preference for (*E*)-alkenes (as compared with acyclic precursors) is conserved in the formation of the nine (and higher) membered rings,[66] but the formation of eight-membered rings, as already discussed in Section 3.10.5.3, is (*Z*)-selective. However, ammonium ylides behave differently in these reactions than their sulfur counterparts.[113] Both of the ylide isomers (**358**) and (**359**), derived from the ammonium salt (**357**) give smoothly the nine-membered ring amine (**360**; Scheme 94). Transition states (**358-C**) and (**358-T**) have been invoked to rationalize this result. If the piperidine ring is locked in a conformation in which the ylidic carbon center has to adopt an axial orientation, then only a *cis* macrocycle will be obtained (Scheme 95).[113]

Transition states (**363**) and (**364**) can be considered, with (**363**) possessing a correct bonding distance between the alkenic terminus and the ylidic carbon. In (**364**) this distance is too long for bonding and a conformational change to a boat form would be required for reaction to ensue. This is energetically too

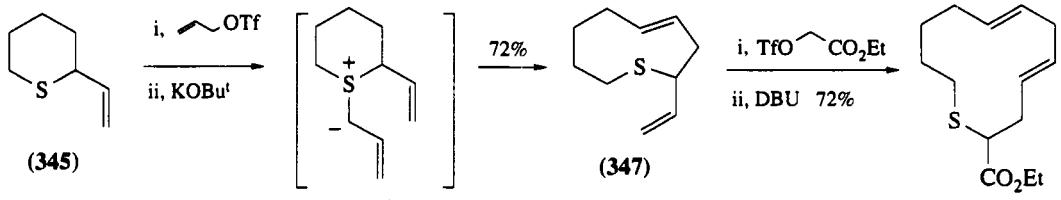


(338) (339) (340) (341) major (342) minor



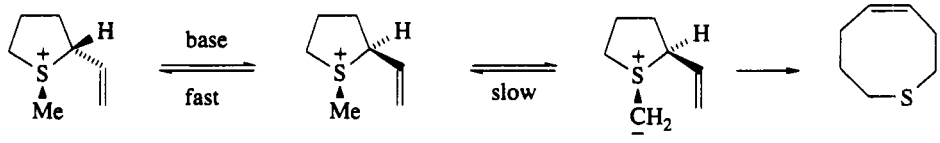
(343) (344)

Scheme 90



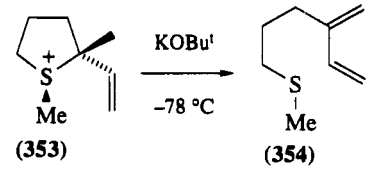
(345) (346) (347) (348)

Scheme 91

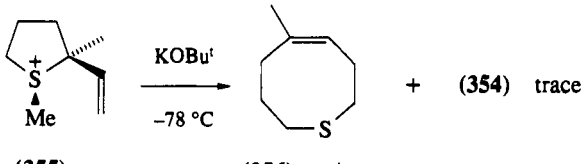


(349) (350) (351) (352)

Scheme 92

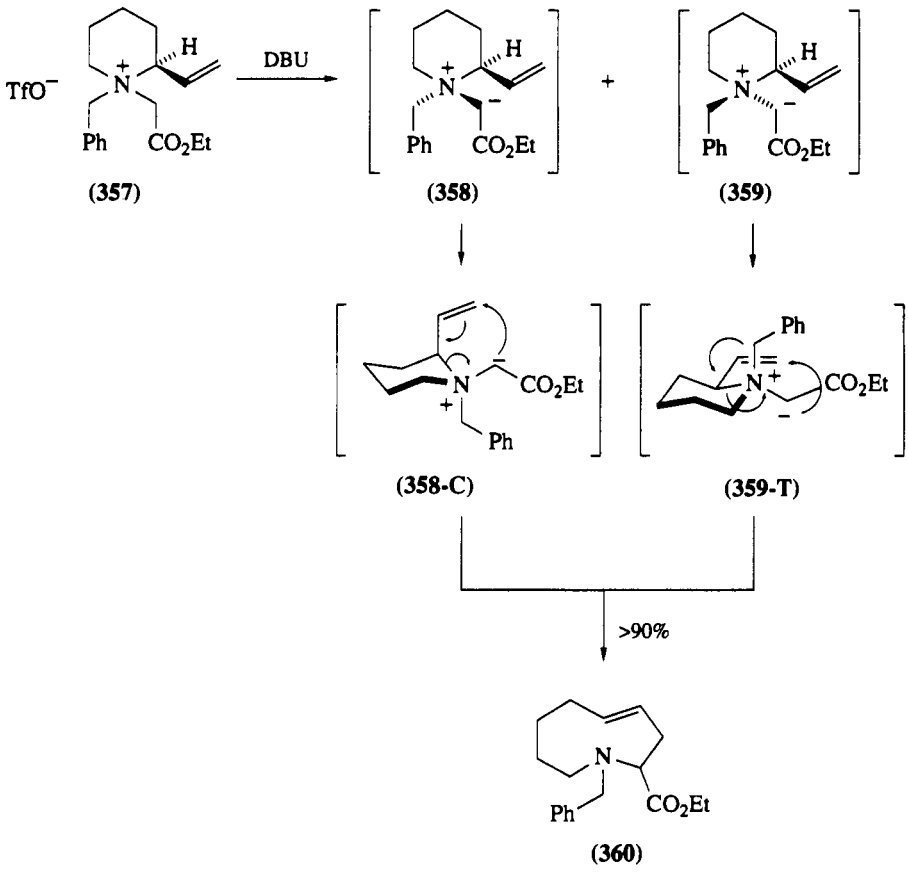


(353) (354)



(355) (356) major + (354) trace

Scheme 93

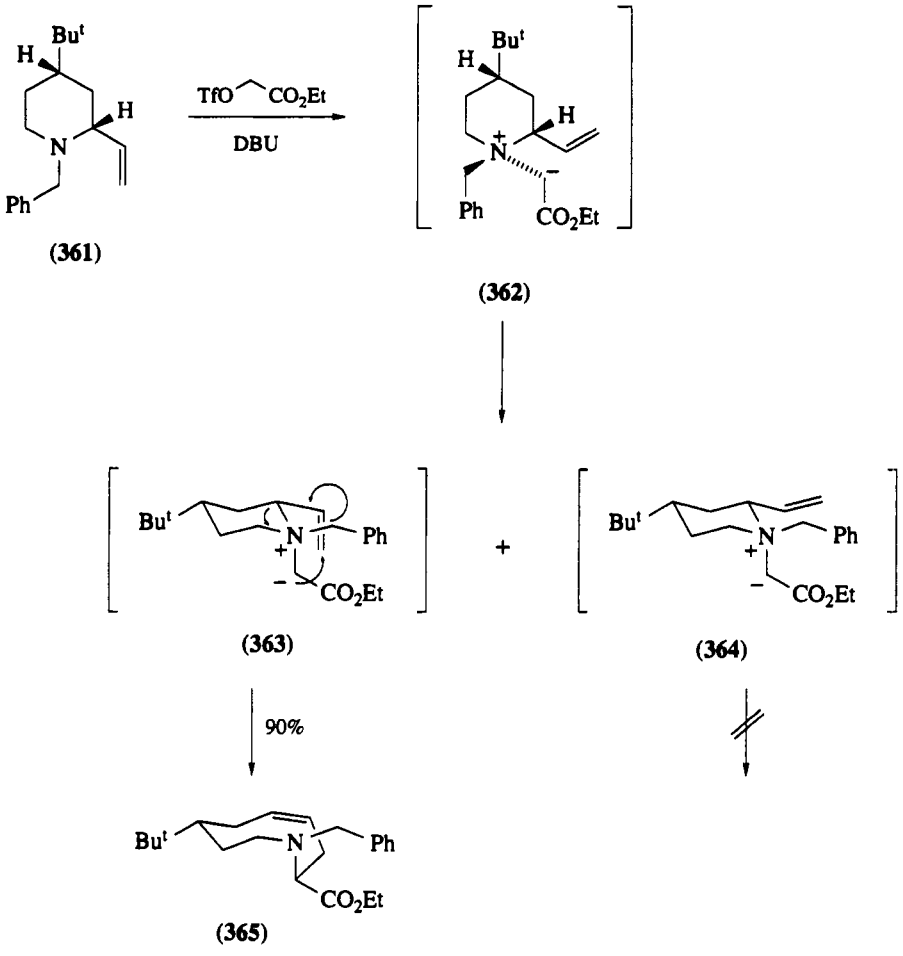


Scheme 94

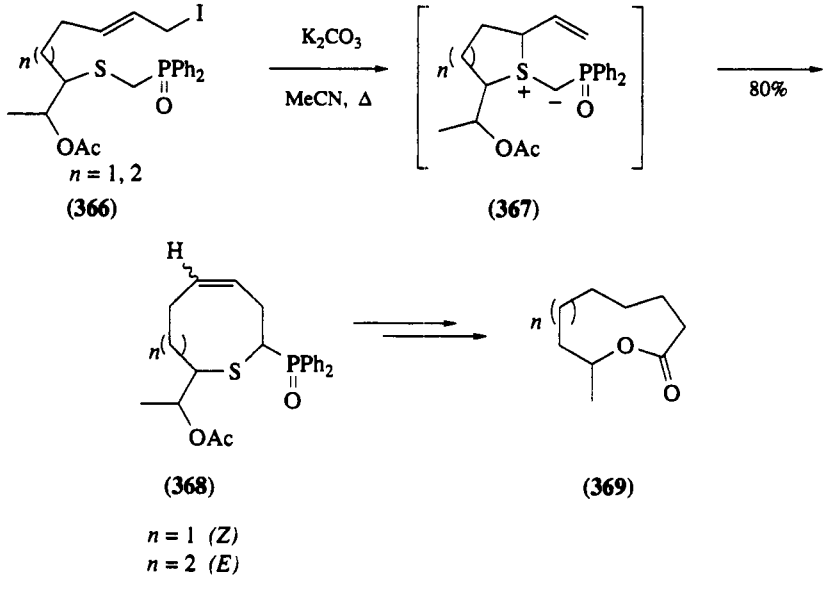
costly and no *trans*-alkene is observed. Vedejs has used this ring expansion methodology in the preparation of macrocyclic lactones and a typical example is recorded in Scheme 96.[114]

Intramolecular *S*-alkylation of (**366**) is followed by deprotonation to form the ylide (**367**), which rearranges to the sulfide (**368**). A few more steps are then required to obtain the nine- and ten-membered ring lactones, including a particularly interesting *S*- to *O*-acyl transfer. The efficient stereocontrol usually observed for 3,2-sigmatropic rearrangements was utilized in the synthesis of the C-1 to C-9 fragment (**373**) of the erythromycin family (Scheme 97).[115] This methodology was also used in a repetitive manner for methynolide synthesis (Scheme 98).[116] Thus, the 3,2-sigmatropic rearrangement of the ylide (**376**) initially gave the (*Z*)-sulfide (**377**) in 40% yield. This low yield is attributed to the impossibility for the second diastereoisomeric ylide to rearrange. In this case, equilibration through the usual proton transfer is prevented by the C-4 methyl group. Six more steps are then necessary to transform (**377**) into (**378**), ready to undergo another ring expansion reaction. The 3,2-rearrangement proceeded this time uneventfully and gave the 11-membered ring (**379**) in 80–85% yields. Only the (*E*)-alkene was obtained, as expected. More surprising was the kinetic 16:1 mixture of C-10 epimers isolated, even though (**378**) consisted of a 1:1 mixture of diastereoisomers. The strong conformational preference for the transoid vinyl rotamers of ylides (**381**) and (**382**) accounts for this observation.

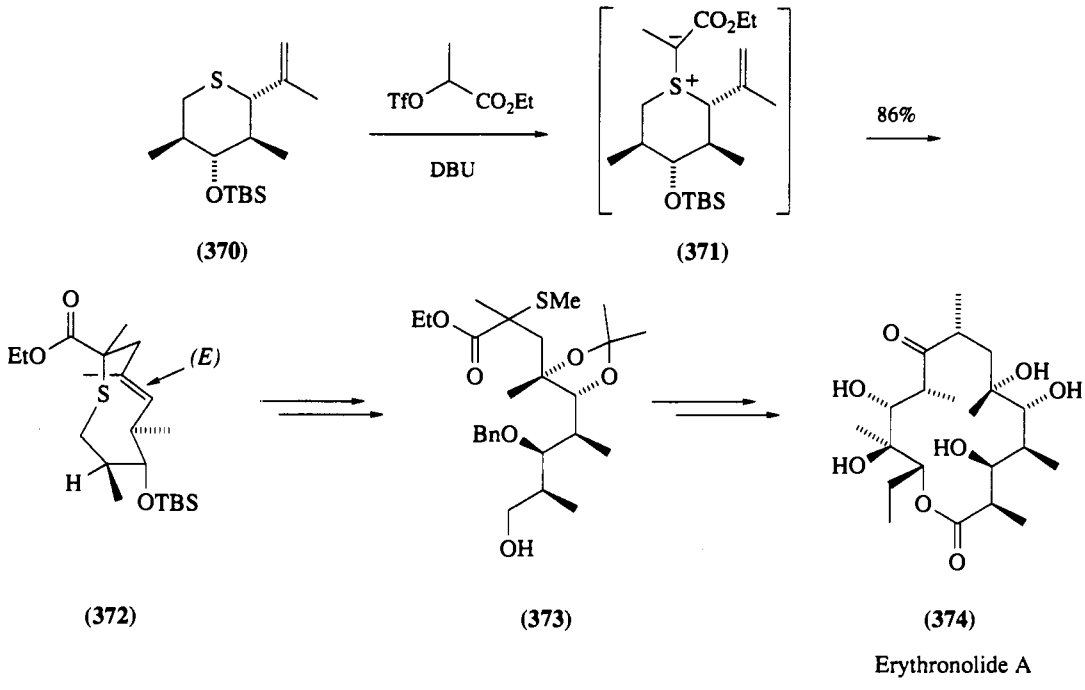
Particularly outstanding examples of the high degree of stereocontrol that can be exercised using ylidic 3,2-sigmatropic rearrangements are demonstrated in the cytochalasin (**387**)[117] and zygosporin (**388**)[118] syntheses (Scheme 99). The allylic halide (**384**) was obtained with high regio- and stereo-selectivity from the lactam (**383**). The key 3,2-sigmatropic rearrangement was performed by heating the chloride (**384**) with sodium iodide and K_2CO_3. A 1.3:1 mixture of epimeric sulfides (**386**) was obtained in 60% yield. Both isomers have the crucial (*E*)-double bond geometry. The rest of the synthesis then involved desulfurization and allylic transposition. The preparation of the highly elaborated zygosporin (**388**) followed essentially the same route.



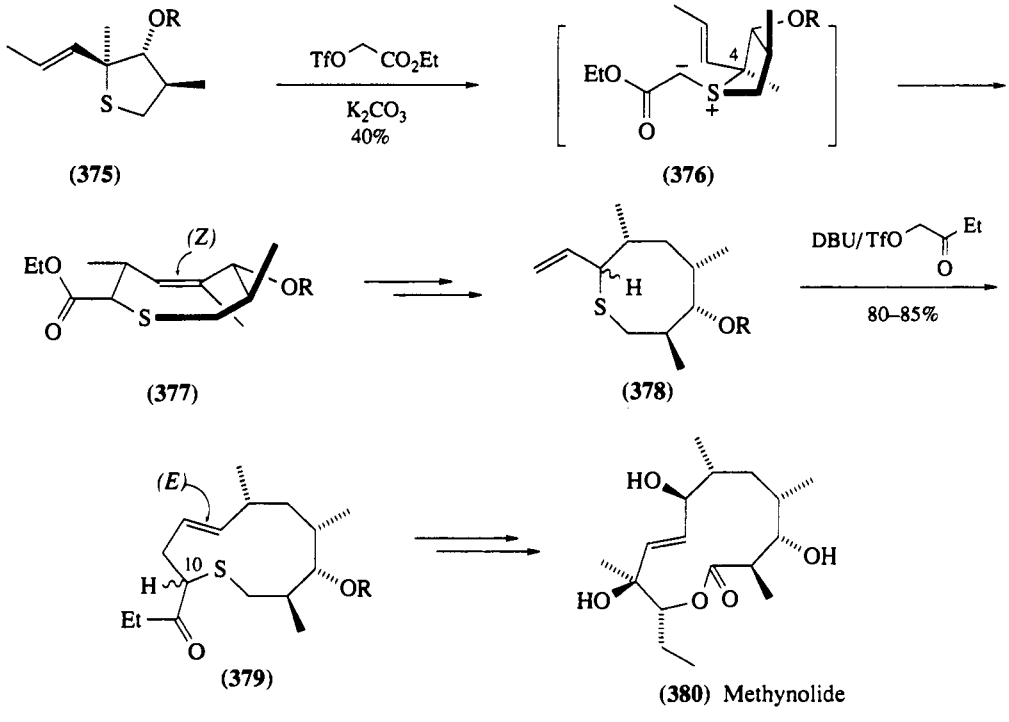
Scheme 95



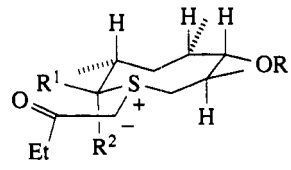
Scheme 96



Scheme 97

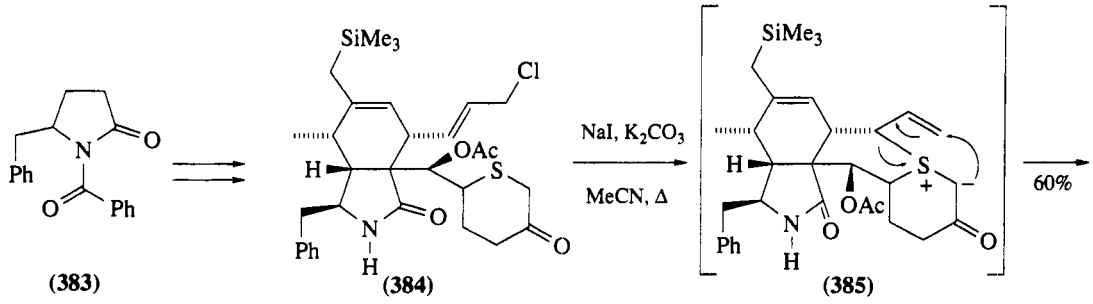


Scheme 98

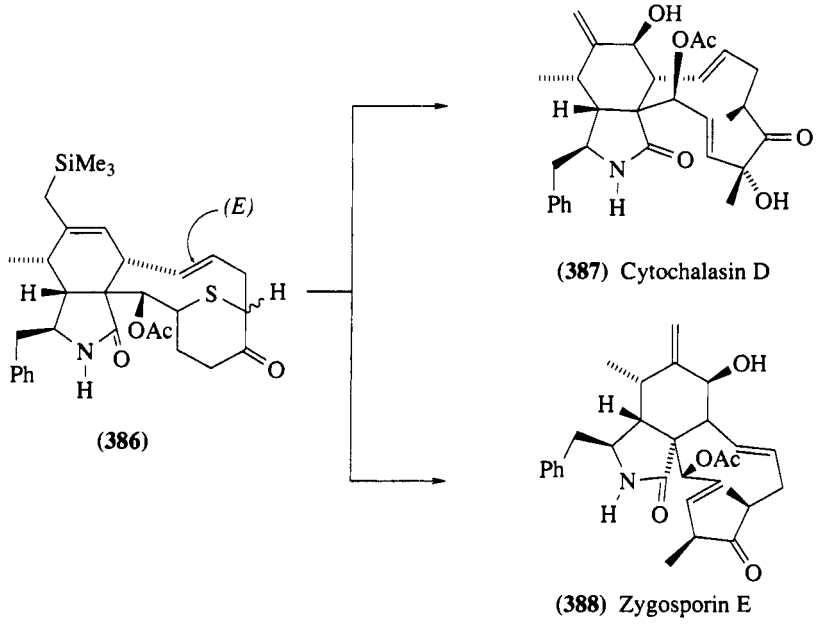


(**381**): $R^1 = -CH{=}CH_2$, $R^2 = H$

(**382**): $R^1 = H$, $R^2 = -CH{=}CH_2$



(**383**) (**384**) (**385**)



(**386**) (**387**) Cytochalasin D (**388**) Zygosporin E

Scheme 99

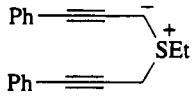
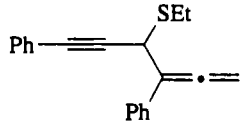
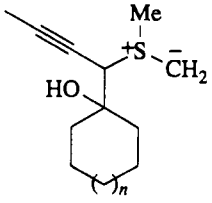
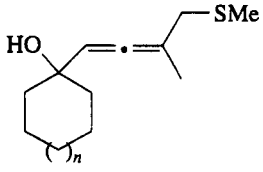
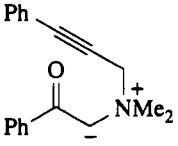
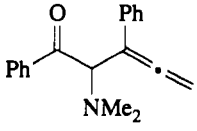
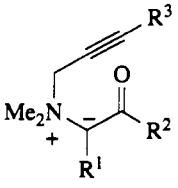
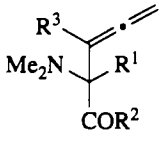
3.10.5.8 Ylidic Rearrangements Involving Alkynes and Allenes

Allenes can be easily prepared using the 3,2-sigmatropic rearrangement of ylidic intermediates. This methodology also provides a general route towards the synthesis of cumulenes. Some examples using sulfonium and ammonium ylides are collected in Table 5.[119–122]

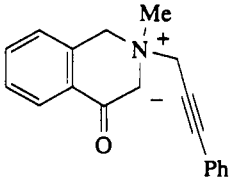
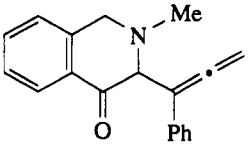
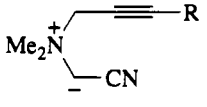
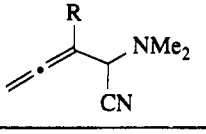
Ketene dithioacetals have been prepared by Julia by isomerization of the initially formed allene (Scheme 100),[123] and Viehe has utilized this approach to obtain capto-datively substituted dienes (Scheme 101).[124] The latter reaction can be stopped before isomerization is complete and the allene can be detected along with some diene. The analogous cyanodienes are also easily accessible *via* this route (Scheme 102).

The striking difference in behavior between nitrogen and sulfur ylides is illustrated once again with the examples collected in Scheme 103.[124] In most of the cases involving the rearrangement of propargylic ammonium ylides, the allene (initial reaction product) can be isolated or identified as a component of the

Table 5

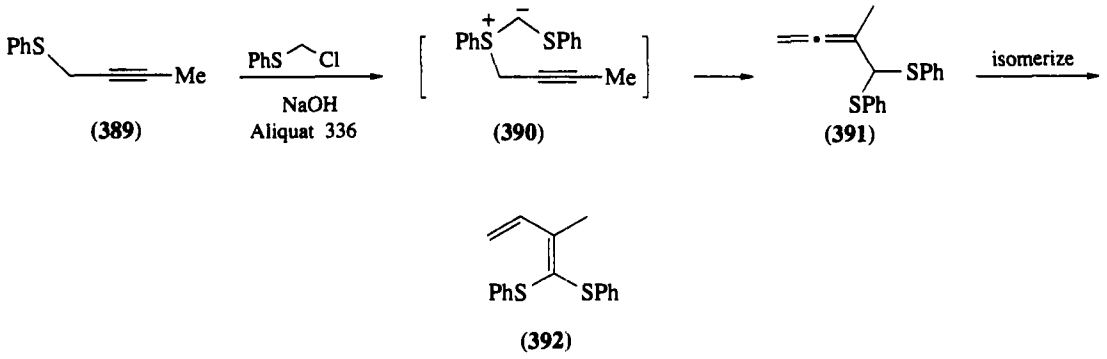
Ylide	*Product*		*Yield (%)*
			—
		$n = 0$ $n = 1$	61 43
			83
			

R^1	R^2	R^3	
H	Bu^t	Ph	60
H	OMe	Ph	56
H	Me	Ph	80
Ph	Ph	H	19
Ph	Ph	Ph	7

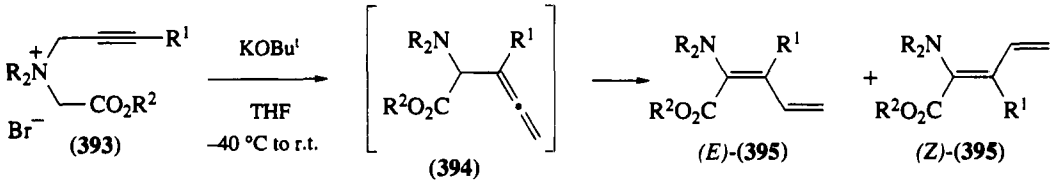
			86
		R = H R = Me	50 54

reaction mixture. When the substituent at C-2 is an amino group, the allene (**400**) is the only isolable product. Its isomerization to the diene does not occur under the reaction conditions (Scheme 103, equation a). However, in the case of the sulfur ylides, the allene cannot be detected, even after a very short period of time (Scheme 103, equation b).[125]

Very few synthetic applications have appeared in this area, the most noteworthy being the extremely short synthesis of artemesia ketone (**408**) starting from the allyl sulfide (**404**; Scheme 104).[123] If an alkyne unit can replace a carbon–carbon double bond without apparent deleterious effect on the 3,2-rearrangement, so also can an allene unit. Dienes are then produced (Scheme 105).[126]

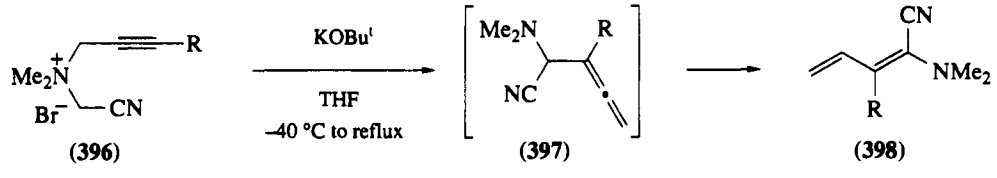


Scheme 100



R, *R*	R^1	R^2	*Yield* (%)	(*E*)	(*Z*)
Me, Me	H	Me	87	–	100
Me, Me	Me	Me	80	55	45
Me, Me	H	Et	79	–	100
Me, Me	Me	Et	79	45	55
$-(CH_2)_2O(CH_2)_2-$	H	Me	62	–	100
$-(CH_2)_4-$	H	Me	48	85	15
$-(CH_2)_4-$	Me	Me	57	–	–

Scheme 101

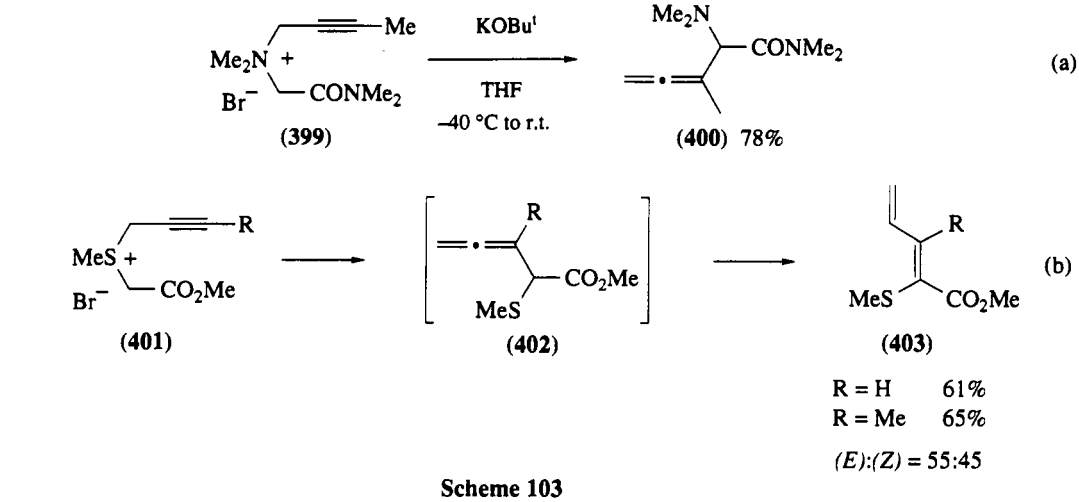


R	*Yield* (%)	(*E*)	(*Z*)
H	60	100	0
Me	64	25	75

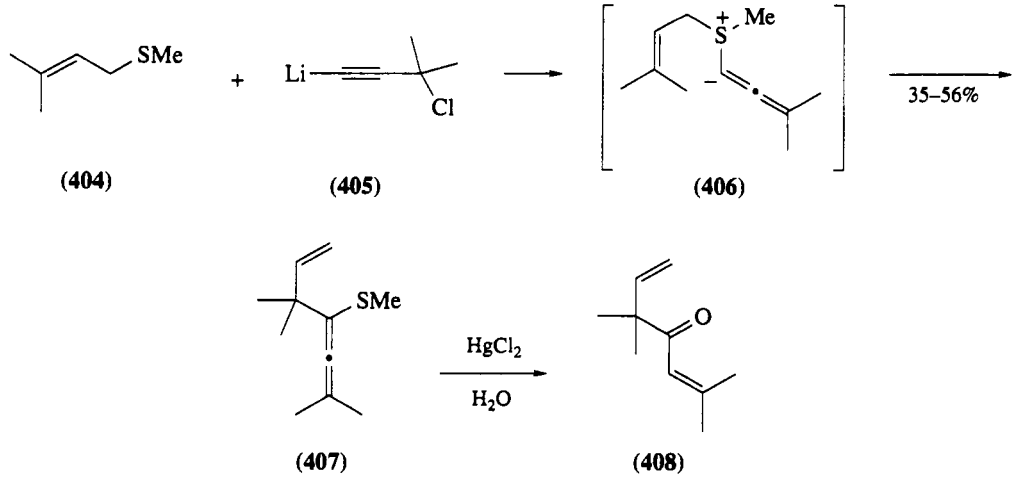
Scheme 102

3.10.5.9 Sommelet–Hauser Rearrangement

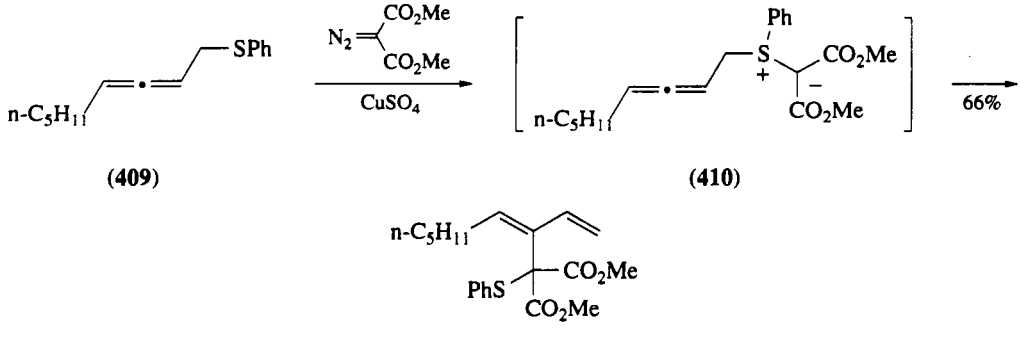
In 1930, Ingold and Jessop reported the rearrangement of the fluorenyl ylide (**412**).[127] Compound (**414**) was obtained in what can be considered as the first example of a Sommelet–Hauser reaction (Scheme 106). In 1937, Sommelet described the base-catalyzed transformation of the benzhydryl ammonium bromide (**415**) into the substituted benzylic amine (**416**; Scheme 107, equation a).[11] Wittig found later that reacting the salt (**417**) with phenyllithium produced two amines, (**418**) and (**419**).[13] The former is derived from a Sommelet–Hauser 3,2-rearrangement, whereas the latter comes from a Stevens



Scheme 103

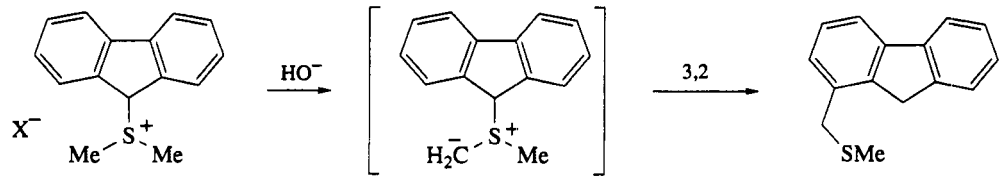


Scheme 104



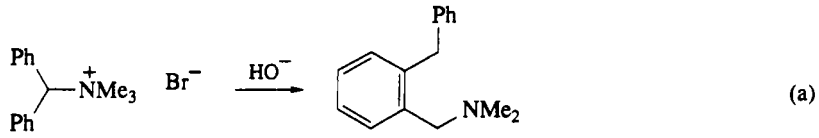
Scheme 105

1,2-rearrangement (Scheme 107, equation b). The Stevens rearrangement often competes with the Sommelet–Hauser rearrangement. However, in protic solvents, Sommelet–Hauser rearrangements usually predominate.

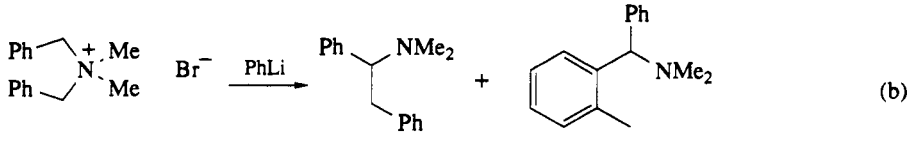


(412) (413) (414)

Scheme 106



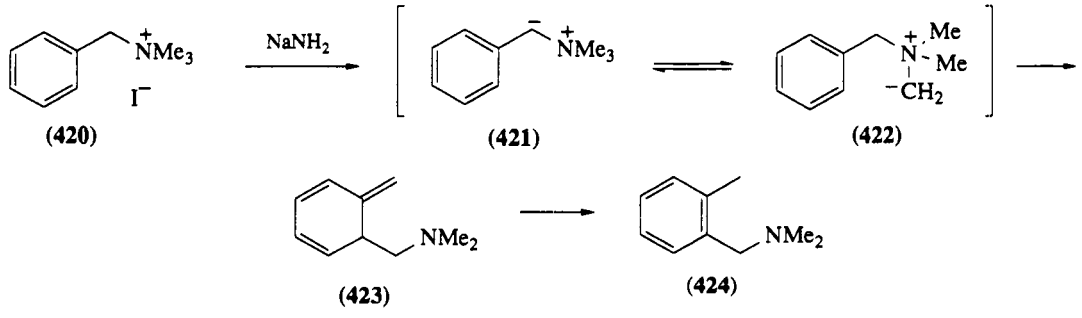
(415) (416) (a)



(417) (418) (419) (b)

Scheme 107

Initial work on the Sommelet–Hauser rearrangement was mechanistically inspired. Hauser and Kantor provided a major contribution to the understanding of this transformation.[14] They showed that two ylides were involved in the rearrangement. The more stable ylide (**421**) is initially generated but equilibrates with the less stabilized one (**422**). The latter ylide then undergoes a concerted, symmetry-allowed 3,2-sigmatropic shift, giving the triene (**423**). Aromatization finally affords the *ortho*-substituted benzylic amine (**424**; Scheme 108).

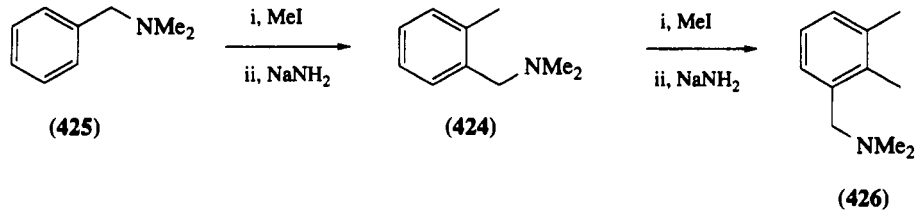


(420) (421) (422) (423) (424)

Scheme 108

Similar rearrangements also occur in the case of sulfur analogs. Since the product of a Sommelet–Hauser rearrangement is a benzylic tertiary amine (or sulfide), just as the starting material was a benzylic amine (or sulfide), the process can be repeated and is a unique method to move substituents around the periphery of aromatic rings (Scheme 109).

Several limitations of this base-promoted rearrangement are worthy of mentioning: (a) when structurally feasible, both Stevens and Sommelet–Hauser reactions will compete; (b) certain substituents on the aromatic ring, *e.g.* Cl, CN, NO_2, prevent the formation of the ylide and no rearrangement takes place; (c) if a β-hydrogen is present on the ammonium salt, elimination becomes yet another undesirable side reaction. In an attempt to overcome these limitations, Sato has utilized the fluoride-induced desilylation of

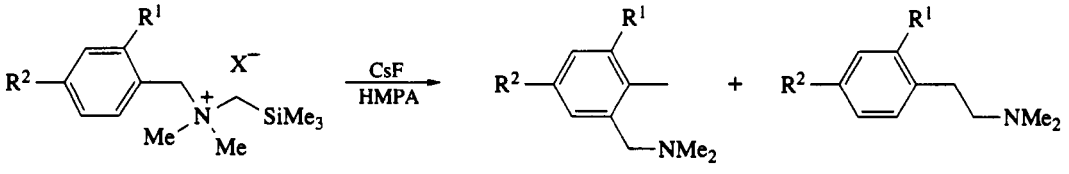


(425) (424) (426)

Scheme 109

triorganosilylmethyl ammonium salts (**427**).[128] This provided a new route for effecting the Sommelet-Hauser rearrangement under non-basic conditions (Table 6). Remarkably, the Stevens product was obtained in small amounts in most cases, except when strong electron-withdrawing groups (COR, NO_2, CN) were present on the aromatic substituent. Sato also found that, under the fluoride-induced desilylation conditions, minimum competitive Hoffmann elimination was observed (Table 7).[129] The lack of elimination products can be rationalized by the absence of ylide equilibration under fluoride-induced Sommelet–Hauser reaction conditions as compared with the base-promoted rearrangement. Desilylation affords ylide (**435**) which undergoes the 3,2-sigmatropic rearrangement faster than equilibration with the other ylides (**434**) and (**436**; Scheme 110).

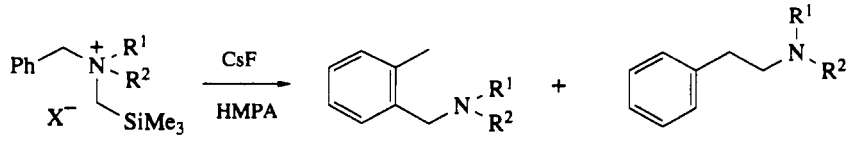
Table 6



(427) (428) (429)

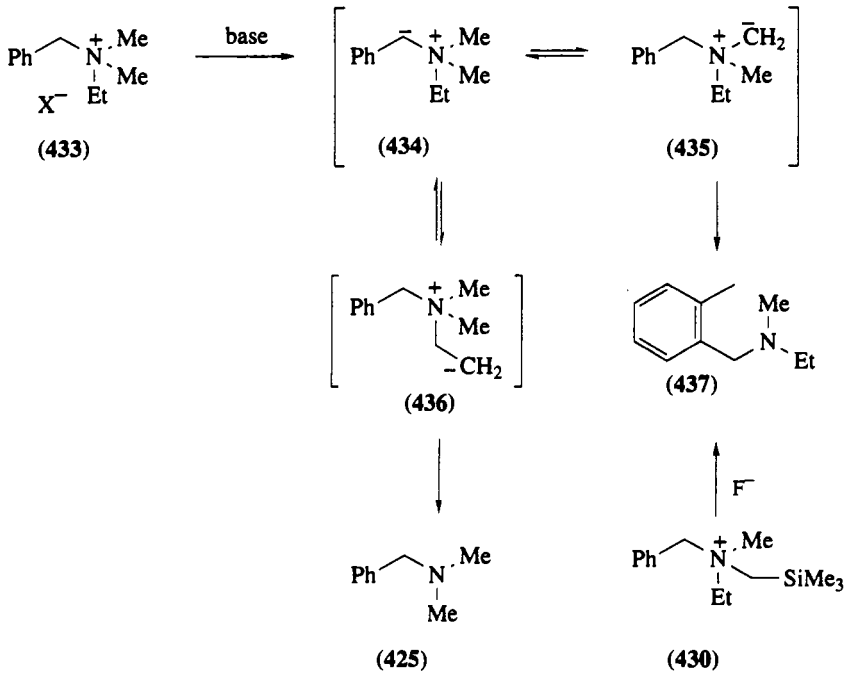
Entry	R^1	R^2	*Yield (%)*	(**428**):(**429**)
1	H	H	84	97:3
2	Me	H	84	96:4
3	H	Me	77	96:4
4	H	OAc	72	99:1
5	Cl	H	69	94:6
6	H	Cl	84	>99:<1
7	CoMe	H	54	42:58
8	No_2	H	80	<1:>99

Table 7



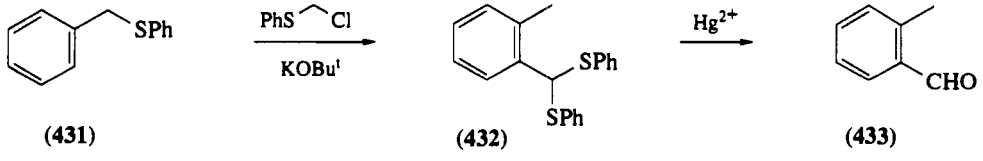
(430) (431) (432)

Entry	R^1	R^2	(**431**):(**432**)
1	Me	Et	97:3
2	Pr^i	Me	93:7
3	Bu^t	Me	65:35
4	Cyclohexyl	Me	89:11
5	Et	Et	91:9
6	—$(CH_2)_4$—		98:2
7	—$(CH_2)_5$—		97:3



Scheme 110

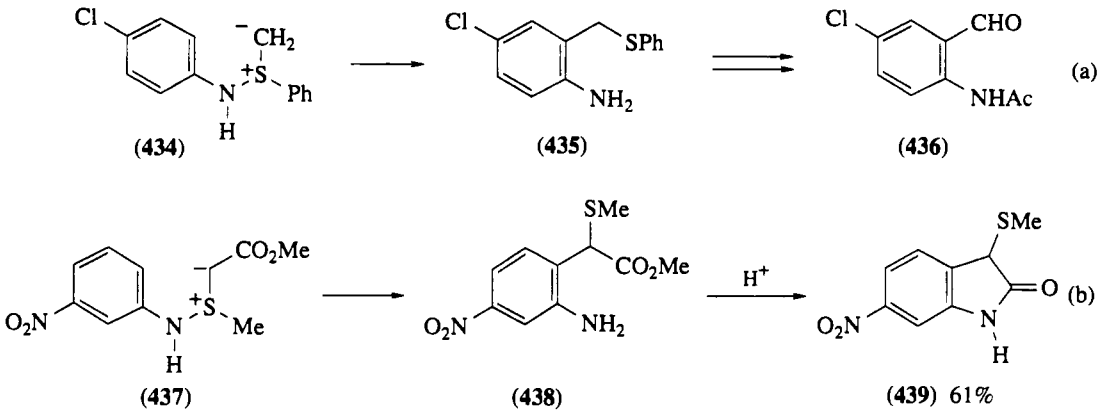
The Sommelet–Hauser rearrangement has been mostly employed for aromatic functionalization and ring expansion. Julia for example has reported an elegant formylation using a sulfonium ylide rearrangement (Scheme 111).[130] The reaction provides an easy entry into orthoformylation of aromatics. It is interesting to note that alkylation of the thioacetal (**432**) followed by hydrolysis could lead to ketone preparation. Gassman has used a similar approach to formylate aniline derivatives (Scheme 112, equation a),[131] and has extended his method to the useful preparation of substituted oxindoles (Scheme 112, equation b).[132] Gammill, in his synthetic approach towards khellin, used the sulfonium ylide 3,2-sigmatropic rearrangement to transfer functionality from C-6 to C-7 in the key intermediate (**441**; Scheme 113).[133] Warpehoski employed Gassman's procedure as an important step in his synthetic route towards the indole alkaloid CC-1065 (Scheme 114).[134]



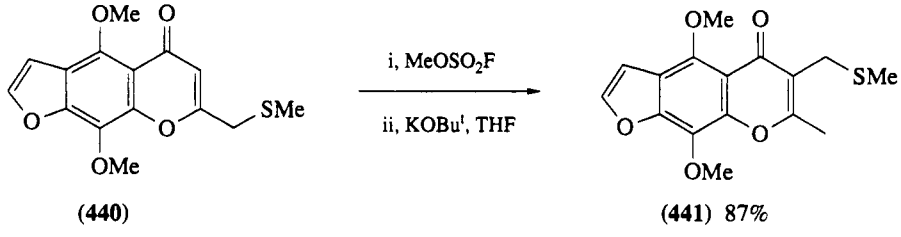
Scheme 111

Aromatic functionalization coupled with ring expansion has also been applied to produce macrocyclic amines. Lednicer and Hauser for example reported the Sommelet–Hauser rearrangement of ammonium salt (**336**) to give the macrocycle (**337**; Scheme 89).[108] Sato reinvestigated this reaction and was able, using his silicon methodology, to isolate the intermediate triene (**446**).[135] Surprisingly enough, compound (**446**) is fairly stable and can be stored for several weeks. It reacts readily with dienophiles to provide interesting adducts (Scheme 115).

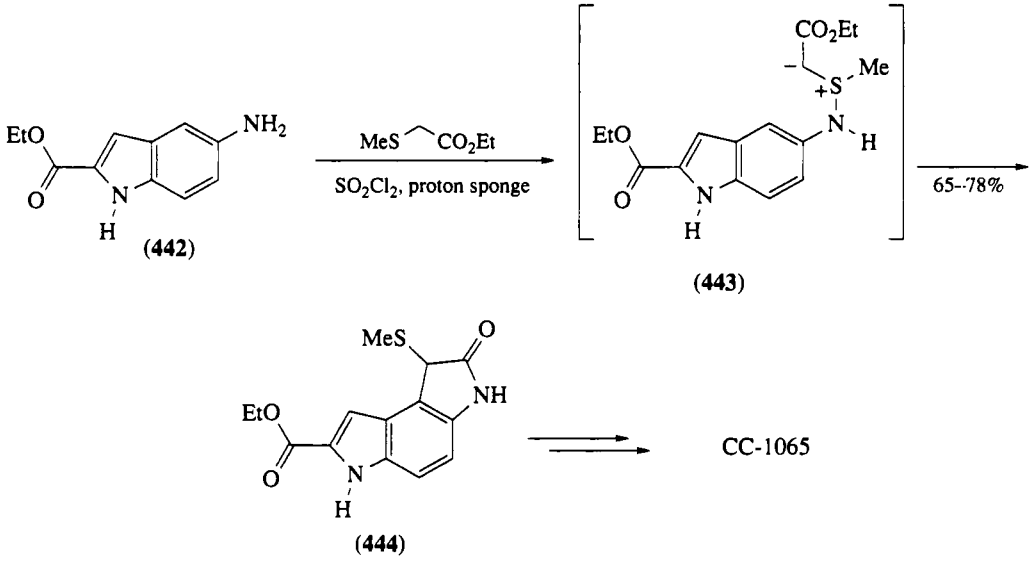
Finally, attempts have been made to induce asymmetry in the Sommelet–Hauser rearrangement, but with limited success. Campbell rearranged the optically active sulfonium salt (**449**) and obtained a mixture of the two Sommelet–Hauser products (**450**) and (**451**).[136] The chiral product (**451**) displayed only low optical activity (Scheme 116).



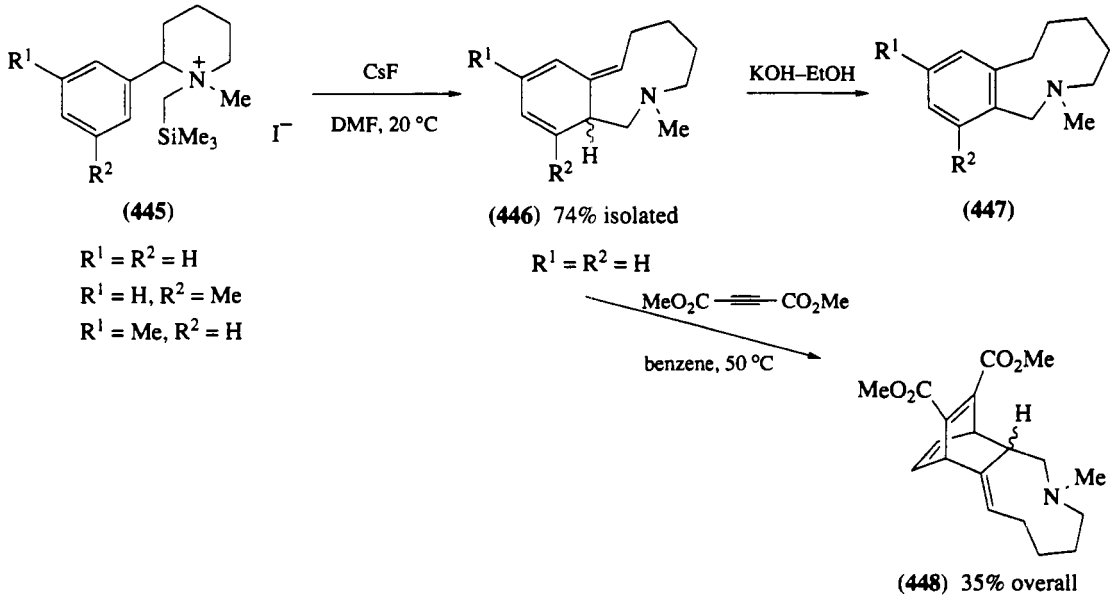
Scheme 112



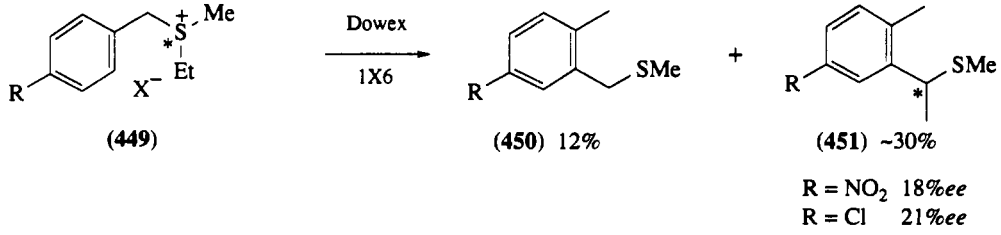
Scheme 113



Scheme 114



Scheme 115



Scheme 116

3.10.6 CONCLUSIONS

Enormous progress has been realized in the last two decades both in the preparation of ylidic intermediates and in the mechanistic understanding of ylidic sigmatropic rearrangements. The Stevens 1,2-sigmatropic rearrangement has been shown to proceed *via* radical pair intermediates, whereas the 3,2-sigmatropic rearrangements have been demonstrated to be concerted processes. Unfortunately, competition between these and other related rearrangements often takes place, and this has always placed a severe limitation on the use of ylidic rearrangements in synthesis. However, as a result of contemporary mechanistic insights, suitable experimental conditions have been defined that allow one of these processes to predominate largely, if not solely, over the other one. The 3,2-sigmatropic rearrangement of ylidic intermediates has been shown to be a particularly efficient and versatile synthetic tool, mainly because of the remarkable contributions by Vedejs and his group. In sharp contrast, the Stevens 1,2-sigmatropic rearrangement has, so far, led to very few synthetic applications.

ACKNOWLEDGEMENTS

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3.11
The Wittig Rearrangement

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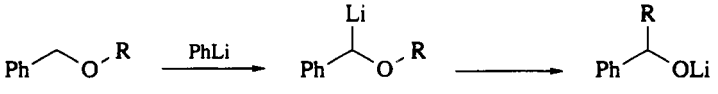
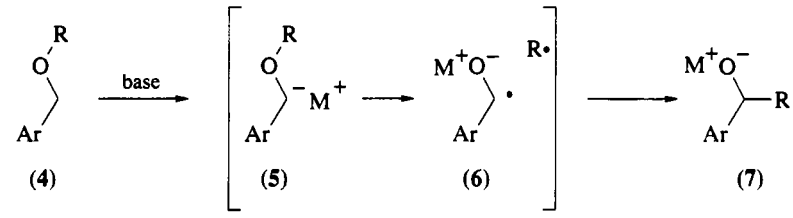
3.11.1 INTRODUCTION

3.11.1.1 Historical Development

In 1942 Wittig and Löhmann described the isomerization of α-lithiated ethers (**2**; R = Me or CH_2Ph) to skeletally rearranged lithio alkoxides (**3**; equation 1).[1] Subsequent work by Wittig and others established that a variety of ethers undergo the Wittig rearrangement, provided the α-anion is stabilized by an aryl substituent. Of the several mechanisms proposed for this reaction a sequence involving homolysis of the anion intermediate (**5**), followed by recombination of the radical and radical anion fragments (equation 2) best accommodates the experimental findings.[1–4]

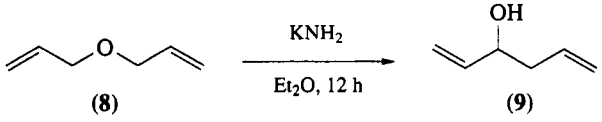


(1) (2) (3) (1)

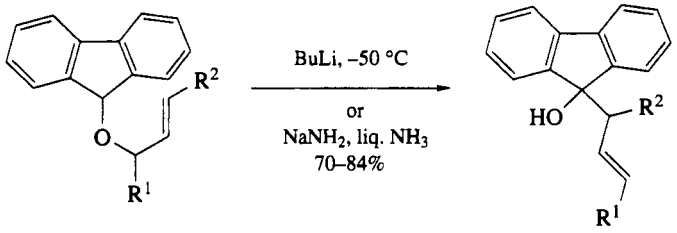


(4) (5) (6) (7) (2)

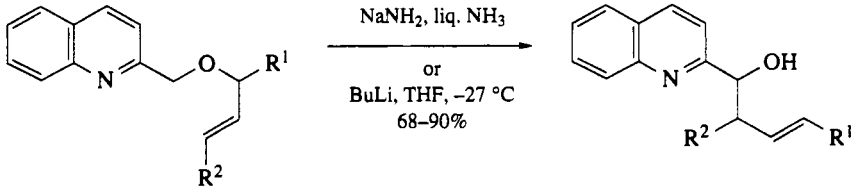
Hauser noted that diallyl ether (**8**) also undergoes Wittig rearrangement upon base treatment and suggested that product formation could involve either a 1,2-shift or a 'cyclic mechanism' (equation 3).[2] Later studies by Schöllkopf[5] and Makisumi[6] with substituted allylic ethers (**10**, **11** and **14–16**; equations 4 and 5) pointed to a cyclic (S_Ni') mechanism; a process allowed by the Woodward–Hoffmann rules.[7] The diastereoselectivity of the reaction was not determined in these cases, but Schöllkopf subsequently found that benzyl *trans*-crotyl ether (**20**; equation 6) affords mainly the *anti* products upon rearrangement of ether (**20**) with BuLi in THF.[8] Rautenstrauch observed a 1:1 mixture of *syn* and *anti* products upon rearrangement of ether (**20**) in the presence of TMEDA, whereas the *cis* isomer (**23**) gave only the *syn* product (**22**; equation 7).[9]



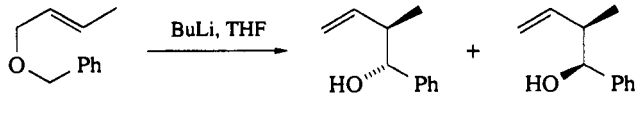
(**8**) (**9**) (3)



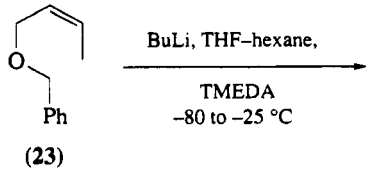
(**10**) R^1 = Me, R^2 = H
(**11**) R^1 = H, R^2 = Me
(**12**) R^1 = Me, R^2 = H >99% (*E*)
(**13**) R^1 = H, R^2 = Me
(4)



(**14**) $R^1 = R^2$ = H
(**15**) R^1 = H, R^2 = Me
(**16**) R^1 = Me, R^2 = H
(**17**) $R^1 = R^2$ = H
(**18**) R^1 = H, R^2 = Me
(**19**) R^1 = Me, R^2 = H
(5)



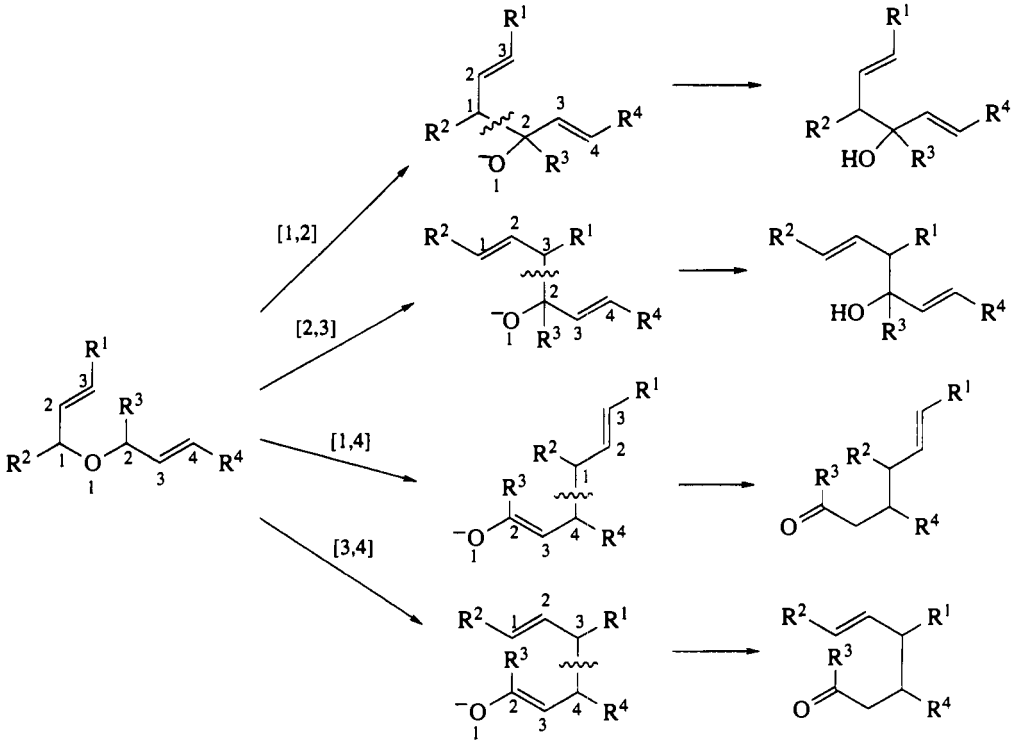
(**20**) (**21**) 66% (**22**) 33% (6)



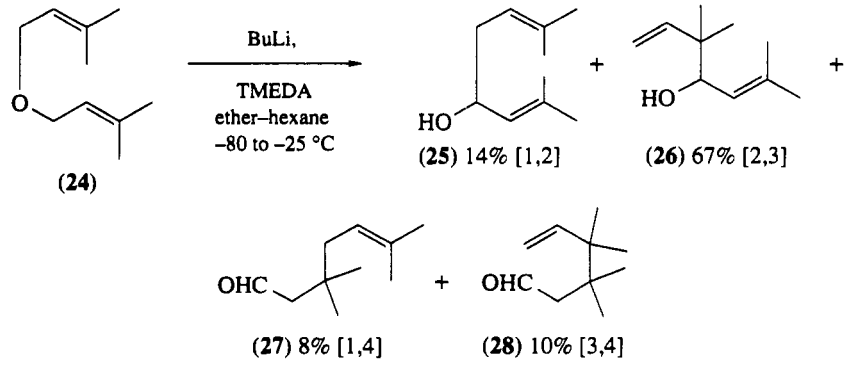
(**23**) (**21**) 0% (**22**) 100% (7)

3.11.1.2 Rearrangement Pathways

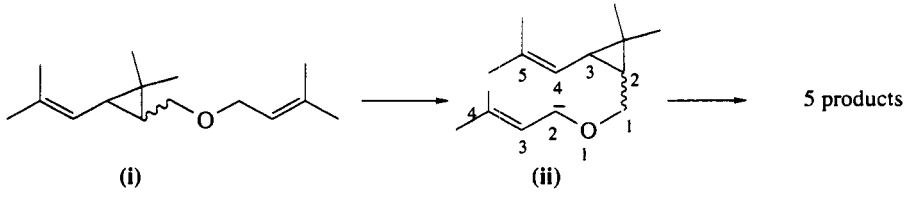
Rearrangements of allylic ethers can follow several pathways (Scheme 1). The 2,3- and 1,4-routes are symmetry allowed concerted processes, whereas the 1,2- and 3,4-rearrangements proceed in a stepwise manner through radical dissociation and recombination (equation 2). In fact, all four pathways have been experimentally observed with bis-γ,γ-(dimethyl)allyl ether (**24**; equation 8).[9] Anions derived from allyl vinylcyclopropylmethyl ethers (*e.g.* **i**) rearrange by competing, 1,2, 1,4, homo-2,5, homo-4,5 and radical dissociation–recombination pathways.[9a] Nakai has shown that 1,4-rearrangement proceeds with retention of stereochemistry in the cyclohexenyl system (**29**; equation 9), as required by orbital symmetry considerations.[10]

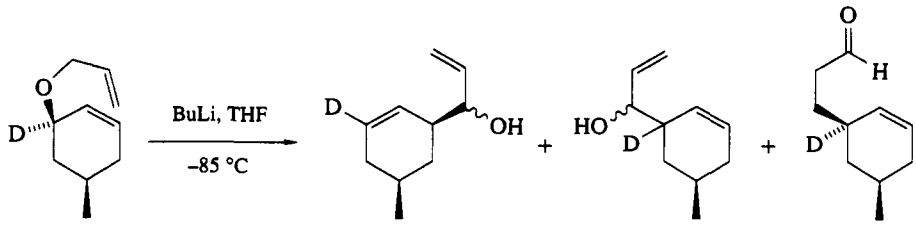


Scheme 1 Rearrangement pathways for allylic ether anions



(8)



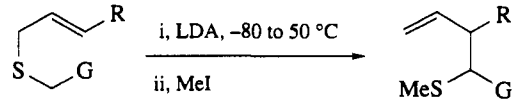


(9)

(29) (30) 41% [2,3] (31) 20% [1,2] (32) 14% [1,4]

3.11.1.3 Heterologs

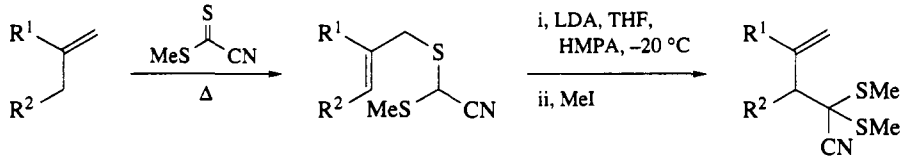
Sulfides undergo 2,3-Wittig rearrangement, but at a slower rate than their oxygen counterparts (equation 10). This rate retardation has been attributed to a decrease in the energy of the anion HOMO as a consequence of the greater stabilizing influence of sulfur.[7c] Snider prepared the α-thiomethylcyanomethyl sulfides (**36**) through ene reaction of alkenes with methyl cyanodithioformate, and observed facile 2,3-rearrangement upon treatment with BuLi or LDA in THF–HMPA (equation 11).[11] In the absence of HMPA the α-cyano anions are stable and can be readily C-methylated with iodomethane. Representative examples are shown in Table 1.



(10)

(33) (34)

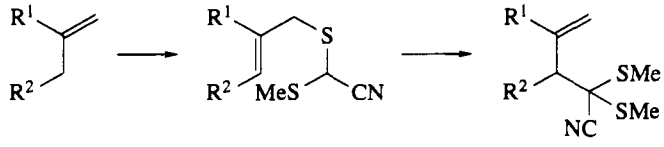
G = Ph, CO_2Li, CN, CO_2Et, COMe; R = Ph, H, Me



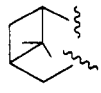
(11)

(35) (36) (37)

Table 1 Formation and 2,3-Rearrangement of Sulfides



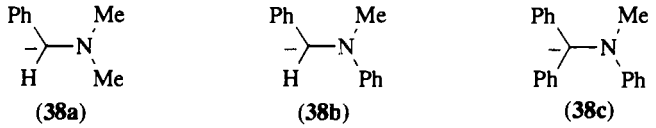
(35) (36) (37)

Alkene (**35**)	R^1	R^2	*Yield* (%) (**36**)	(**37**)
(**35a**)	Et	Me	72	86
(**35b**)	H	Pr	43	56
(**35c**)		$(CH_2)_4$	76	70
(**35d**)		a	22	77
(**35e**)			83	72

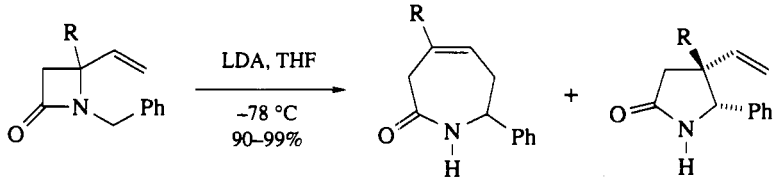
[a] $(CH_2)_2CH(CH_2OCO_2Me)CH_2$.

The amine α-anions (**38a–c**) failed to rearrange under conditions employed for the analogous ethers.[2] The corresponding ammonium salts, on the other hand, readily isomerize *via* the derived ylides (Stevens rearrangement) in a process analogous to the 1,2-Wittig rearrangement.[12]

The *N*-benzyl β-lactams (**39**) and (**40**) undergo facile rearrangement upon base treatment.[13] In the former case only the 2,3-product (**41**) is observed, whereas the latter affords a mixture of 2,3- and 1,2-products (**42**) and (**44**; equation 12). The methyl substituent of (**40**) evidently facilitates homolysis of the intermediate benzylic anion. The phenyl-substituted β-lactams (**45**) and (**46**) yield the 1,2-rearrangement products (**47**) and (**48**) exclusively under comparable conditions (equation 13). These rearrangements undoubtedly derive considerable driving force from relief of ring strain. Thus *N,N*-allylbenzylbenzamide, an acyclic counterpart of lactam (**39**), is recovered unchanged upon exposure to strong base.



(**38a**) (**38b**) (**38c**)

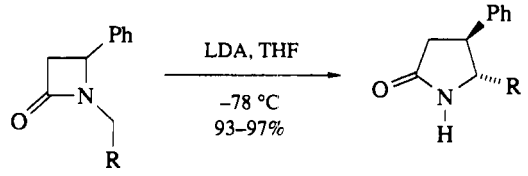


(12)

(**39**) R = H
(**40**) R = Me

(**41**) R = H; 100%
(**42**) R = Me; 60%

(**43**) R = H; 0%
(**44**) R = Me; 40%



(13)

(**45**) R = Ph
(**46**) R = $CH{=}CH_2$

(**47**) R = Ph
(**48**) R = $CH{=}CH_2$

3.11.2 1,2-REARRANGEMENTS

Early work on the 1,2-Wittig rearrangement was mechanistically inspired. As indicated in Table 2, yields of products tended to be moderate and harsh conditions were often employed. The effects of structural variation on reaction rates and product composition can be accommodated by a pathway involving homolysis of an α-anion intermediate and recombination of the radical and radical anion fragments (equation 2). In a more recent study, Schöllkopf found that the optically active benzyl ethers (**51**) and (**52**) afford the alcohols (**53**) and (**54**) of predominately retained configuration in 20% and 80% enantiomeric excess (equation 14). This finding further supports a dissociative mechanism.[4] A concerted one-step rearrangement should proceed with inversion of the migrating center according to orbital symmetry considerations.

In the first purely synthetic application of the reaction, Schreiber employed the 1,2-Wittig rearrangement to synthesize 1,3-diol monoethers (equation 15).[14] The *syn* products (**56**) were obtained in 14–32% yield with 90–95% diastereoselectivity (Table 3). The 1,4-product (**57**) was found to predominate at low temperature, whereas at 0 °C the 1,2-product was favored but the absolute yield did not increase.

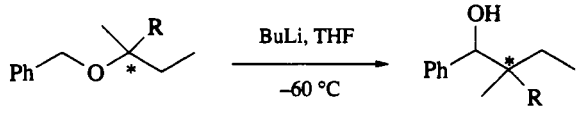
The nonracemic secondary ethers (**58**) and (**60**) rearrange with over 90% retention of stereochemistry at the migrating center (equations 16 and 17). A lithium-bridged diradical species (**63**; Scheme 2) is postulated to account for the observed diastereoselectivity. Recombination of the radical pair must occur more rapidly than inversion of the radical center, judging from the high degree of retention observed with (**58**) and (**60**). A two-directional application of this rearrangement was used to prepare the *syn*-skipped polyols (**66**) and (**68**; Scheme 3).

Table 2 1,2-Wittig Rearrangement of Benzyl Ethers

(49) **(50)**

R	*Conditions*	*Time* (h)	*Yield* (%)	*Ref.*
$PhCH_2$	a	15	61–67	2
$CH_2{=}CHCH_2$	a	15	65 (mixture)	2
Bu^s	a	140	27	2
Ph	a	18	0 (recovered ether)	2
Et	a	19	0 (40% $PhCH_2OH$)	2
$CH_2{=}CH(CH_2)_2$	b	24	67	3
$c\text{-}C_4H_7$	b	24	68	3
Bu^t	c	48	50	3
1-Adamantyl	c	48	54	3

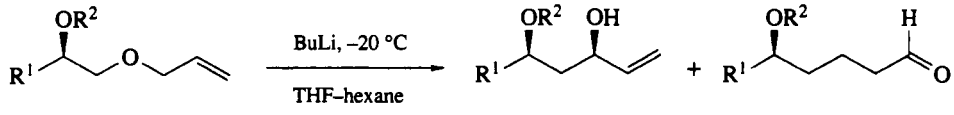
[a] $2KNH_2$, Et_2O, reflux. [b] 2MeLi, THF, r.t. [c] 5MeLi, THF, r.t.



(14)

(51) R = H
(52) R = Ph

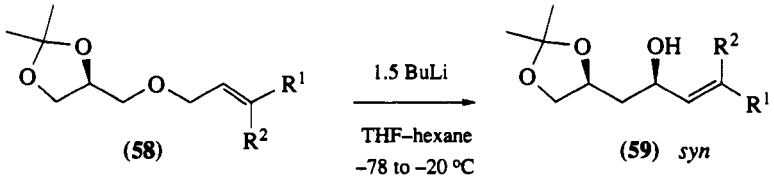
(53) R = H
(54) R = Ph



(15)

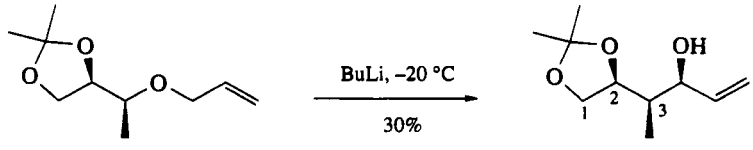
(55) **(56)** [1,2] **(57)** [1,4]

Table 3 1,2-Wittig Rearrangement of Glyceryl Allyl Ethers



(58) **(59)** *syn*

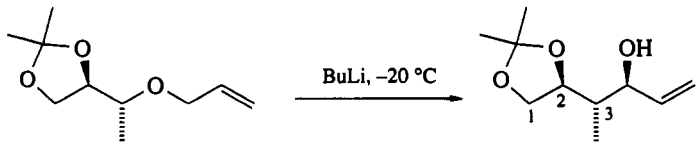
R^1	R^2	*Syn/anti*	*Yield* (%)
H	H	92:8	32
Me	H	91:9	30
Ph	H	90:10	25
Me	Me	90:10	14



(16)

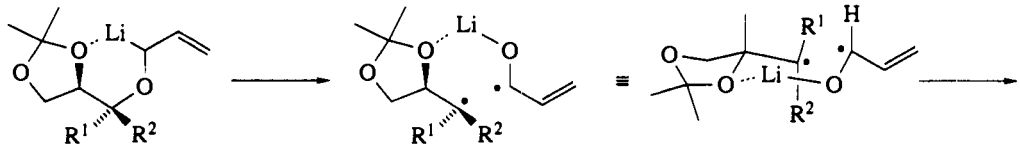
(58)

(59) 91:9 *syn:anti*
94% retention at C-3

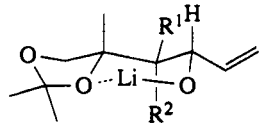


(60) (61) 91:9 *syn:anti*
93% retention at C–3

(17)

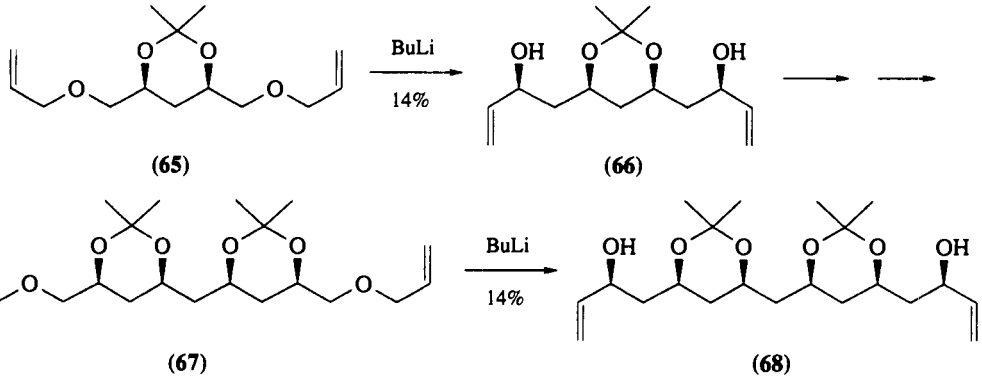


(62) (63) (63)



(64)

Scheme 2 Chelation-controlled 1,2-rearrangement of glyceryl allyl ethers



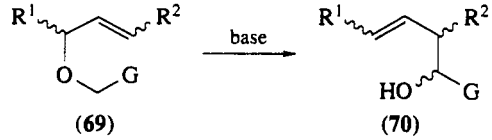
(65) (66) (67) (68)

Scheme 3

3.11.3 2,3-REARRANGEMENTS

3.11.3.1 Overview

The 2,3-Wittig rearrangement (equation 18) proceeds under milder conditions and gives higher yields of products than its 1,2-counterpart. Furthermore, a greater degree of structural variation is possible in the starting ether. For these reasons, the 2,3-rearrangement offers considerable promise as a synthetic method. The reaction effects an interchange of sp^2 and sp^3 stereochemistry such that both (*E*)/(*Z*) and *syn*/*anti* isomerism are possible in appropriately substituted systems. Furthermore, in nonracemic ethers

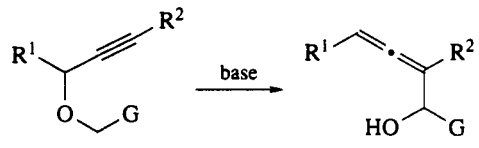


(69) (70)

G = C≡CH, Ph, HC=CH_2, COZ, CN

(18)

the concerted nature of the rearrangement allows for control of absolute stereochemistry. In most applications, various functional groups (G) are employed to promote formation of the intermediate anion. In principle, propargylic ethers could undergo 2,3-rearrangement analogously leading to allenes (equation 19). In practice such rearrangements have infrequently been observed.



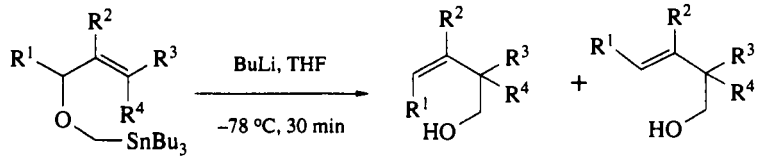
(71) (72) (19)

3.11.3.2 2,3-Rearrangements of Allyl Lithiomethyl Ethers

A unique variant of the 2,3-Wittig rearrangement employs an unstabilized lithiomethyl allylic ether generated *in situ* through lithiation of a (trialkylstannyl)methyl allylic ether (equation 20). This version, first introduced by Still,[15] has proven exceedingly useful owing to its efficiency and potential for high stereoselectivity. Applications to acyclic systems are summarized in Table 4. The rearrangement proceeds under mild conditions to give high yields of products. Interestingly, the stereochemistry of the rearranged double bond depends upon the substitution pattern of the allylic ether. In rearrangements of secondary allylic ethers R^2-substituents favor (*Z*)-products (**76**) whereas R^4-substituents are highly (*E*)-directing. These trends are accommodated by the envelope transition states (**A**) and (**B**) in Scheme 4. Unfavorable steric interactions between R^1 and R^2 in (**A**) are alleviated in (**B**), thereby favoring formation of the (*Z*)-alkenic product. Transition state (**B**), on the other hand, imposes unfavorable 1,3-*syn* steric strain on substituents R^1 and R^4. This strain is lacking in (**A**). When 1,2- and 1,3-interactions are both present, or when they are both absent ($R^2 = R^3 = R^4 = H$), a mixture of (*Z*)- and (*E*)-rearranged products is obtained.

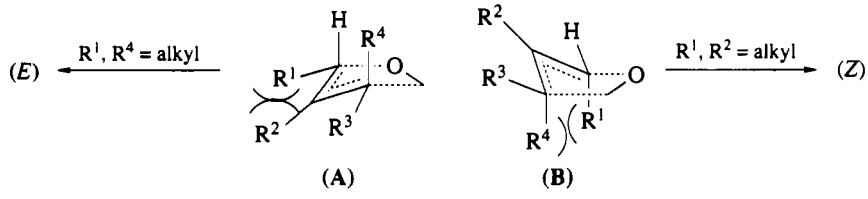
(73) (74) (20)

Table 4 2,3-Wittig Rearrangement of Lithiomethyl Allyl Ethers



(75) (76) (*Z*) (77) (*E*)

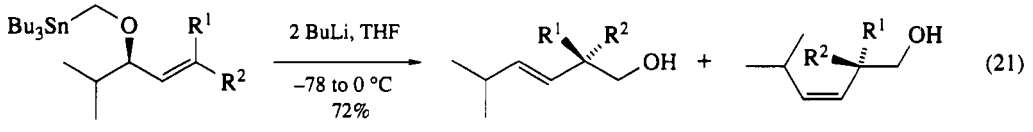
R^1	R^2	R^3	R^4	*Yield* (%)	(*Z*):(*E*)
n-C_7H_{15}	H	H	H	95	60:40
n-C_7H_{15}	H	Me	H	96	65:35
n-C_7H_{15}	H	H	Me	91	0:100
Bu^n	Me	H	H	95	97:3



(A) (B)

Scheme 4 Transition states for lithiomethyl allyl ether rearrangements

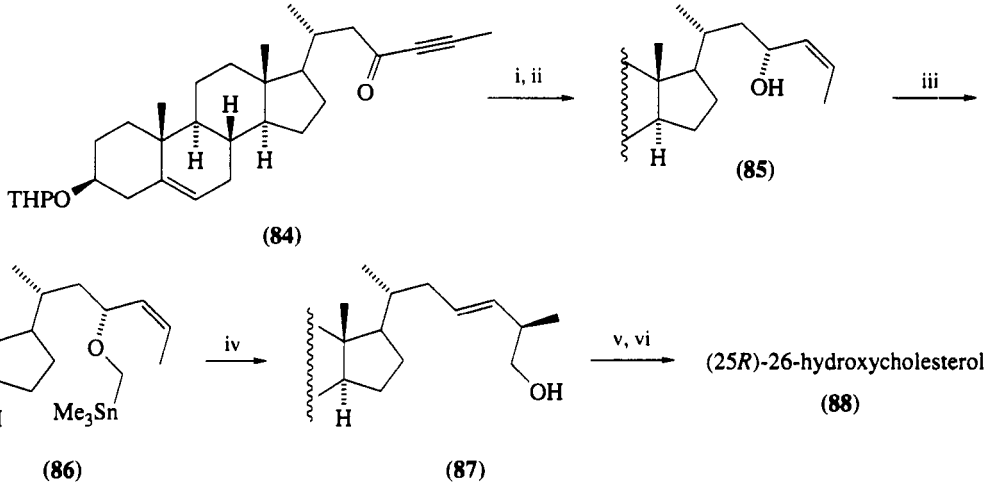
An additional example of such geometric control was recently observed by Midland and Kwon in the isomeric allylic ethers (**78**) and (**79**; equation 21).[16] The (*Z*)-isomer (**78**) gave the (*E*)-rearranged alcohol (**80**) exclusively, in accord with transition state (**A**), whereas the (*E*)-allylic ether (**79**) yielded a 53:47 mixture of (*E*)- and (*Z*)-products (**81**) and (**83**). In both cases rearrangement proceeded with retention of sp^3 stereochemistry, as expected for a concerted suprafacial process. In related work, 2,3-rearrangement of the steroidal (23*R*)-ether (**86**) afforded (25*R*)-26-hydroxycholesterol (**88**), an important intermediate in bile acid biosynthesis (Scheme 5). Again, the key rearrangement step proceeded with complete (>120:1) 1,3-*syn* stereoselectivity.[17] A similar application led to the 25,28-dihydroxylated ergosterol derivatives (**91**) and (**92**; equation 22).[18]



(21)

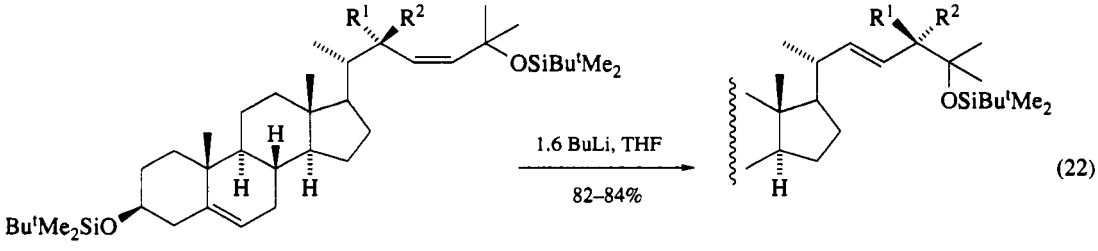
(**78**) R^1 = Me, R^2 = H (**80**) R^1 = Me, R^2 = H (100%) (**82**) R^1 = Me, R^2 = H (0%)

(**79**) R^1 = H, R^2 = Me (**81**) R^1 = H, R^2 = Me (53%) (**83**) R^1 = H, R^2 = Me (47%)



i, (*R*)-alpine borane, 92%, 92% *ee*; ii, H_2, Lindlar catalyst; iii, NaH, Me_3SnCH_2I, 62%; iv, 2.3 BuLi, THF, –78 to 0 °C, 80%; v, H_2/Pd–C; vi, AcOH, H_2O, THF

Scheme 5



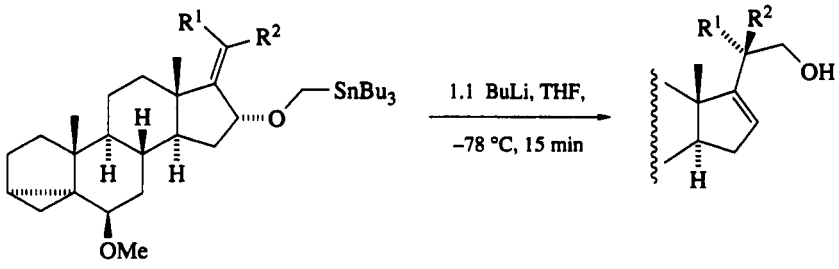
(22)

(**89**) R^1 = H, R^2 = OCH_2SnMe_3 (**91**) R^1 = H, R^2 = CH_2OH

(**90**) R^1 = OCH_2SnMe_3, R^2 = H (**92**) R^1 = CH_2OH, R^2 = H

Still–Wittig rearrangement of the (*E*)- and (*Z*)-17-ethylidene-16α ethers (**93**) and (**94**) afforded the 20α- and 20β-methyl steroids (**95**) and (**96**) with complete stereochemical control (equation 23).[19] As in other examples, sp^3 stereochemistry depends upon double bond geometry in the starting allylic ether.

Still–Wittig rearrangements have been used to introduce an allylic hydroxymethyl substituent to a cyclohexene ring (equations 24 and 25).[20,21] These reactions proceed with retention of stereochemistry. Al-

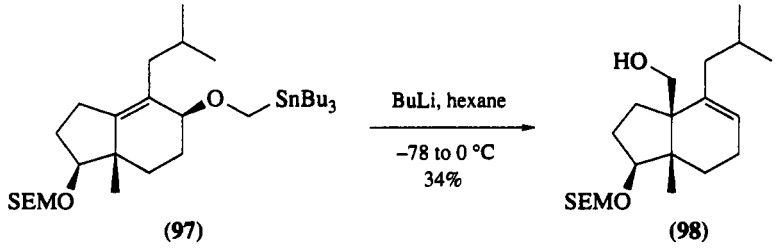


(23)

(**93**) R^1 = Me, R^2 = H
(**94**) R^1 = H, R^2 = Me

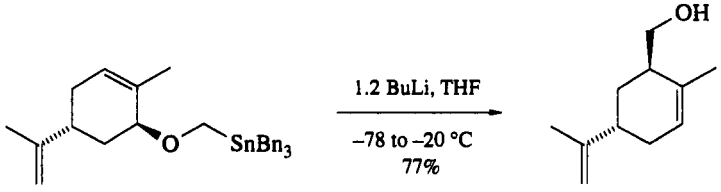
(**95**) R^1 = Me, R^2 = H (83%)
(**96**) R^1 = H, R^2 = Me (70%)

cohol (**98**) was employed in the total synthesis of (–)-punctatin A, a sesquiterpene antibiotic.[20] Alcohol (**100**) is a precursor of a synthetic intermediate for 1α, 25-dihydroxy vitamin D_3.[21]



(**97**) (**98**)

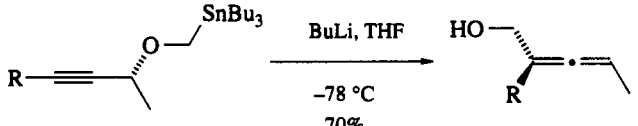
(24)



(**99**) (**100**)

(25)

Still–Wittig rearrangement of the nonracemic (*R*)-propargylic ethers (**100a**) and (**100b**) has been found to give the (*R*)-allenes (**100c**) and (**100d**) with complete asymmetric transfer (equation 25a).[21a] The stereochemistry is consistent with a five-membered cyclic transition state.



(**100a**) R = Bu
(**100b**) R = C_7H_{15}

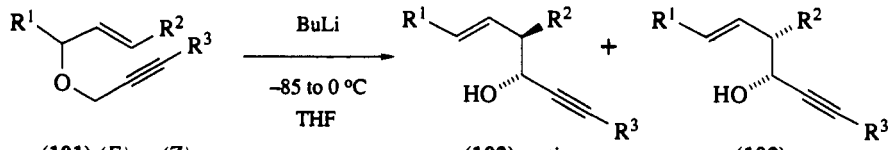
(**100c**) R = Bu
(**100d**) R = C_7H_{15}

(25a)

3.11.3.3 2,3-Wittig Rearrangement of Allyl Propargyl Ethers

Allyl propargyl ethers are selectively deprotonated at the propargylic position to give anions which readily undergo 2,3-rearrangement. Typically *n*-butyllithium is employed as the base in THF or THF–hexane at –85 to 0 °C. In substituted allylic systems a high degree of diastereoselectivity is often seen, particularly with (*Z*)-allylic ethers (Table 5). In general, (*E*)-allylic ethers afford *anti* homoallylic alcohols (**102**), and (*Z*)-allylic ethers rearrange to *syn* homoallylic alcohols (**103**) as major 2,3-products. The TMS-propargyl (*E*)-allylic ethers (entries 3 and 4) are exceptional, giving rise to a predominance of *syn* products.[22,23] However, the TMS-propargyl (*Z*)-allylic ether (entry 12) behaves normally to give the rearranged *syn* alcohol.[22] When allylic substituents are present, as in (**101**; $R^1 \neq H$), (*E*)/(*Z*)-isomerism is possible in the rearranged products. The examples in Table 5 (entries 5–9 and 13–15) afford only the (*E*)-products within the limits of detection.

Table 5 2,3-Wittig Rearrangement of Allyl Propargyl Ethers

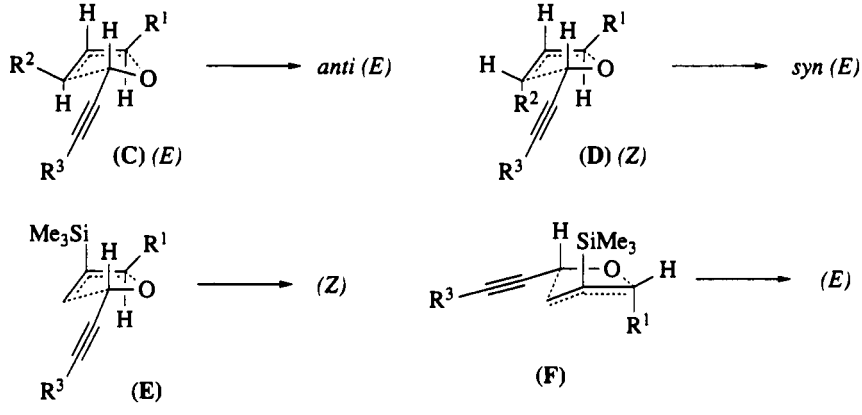


(**101**) (*E*) or (*Z*) (**102**) *anti* (**103**) *syn*

Entry	R^1	R^2	R^3	*(E)/(Z)*	*Anti:syn*	*Yield (%)*	*Ref.*
1	H	Me	H	(*E*)	99:1	72	22
2	H	Me	Me	(*E*)	99:1	65	22
3	H	Me	TMS	(*E*)	27:73	72	22
4	H	TMS	TMS	(*E*)	3:97	91	23
5	Me	Me	H	(*E*)	91:9	62	22
6	Me	Me	H	(*E*)	88:12[a]	b	22
7	Me	TMS	TMS	(*E*)	96:4	85	23
8	Et	TMS	TMS	(*E*)	97:3	80	23
9	Bu	TMS	TMS	(*E*)	89:11	61	23
10	H	Me	H	(*Z*)	10:90	56	22
11	H	Me	Me	(*Z*)	0:100	55	22
12	H	Me	TMS	(*Z*)	0:100	74	22
13	Me	Me	TMS	(*Z*)	1:99	64	22
14	Me	Bu	TMS	(*Z*)	1:99	96	24
15	Bu	Me	TMS	(*Z*)	1:99	b	25
16	H	OTBS	TMS	(*Z*)[c]	98:2	79	25a
17	H	OTBS	TMS	(*Z*)[d]	95:5	66	25a

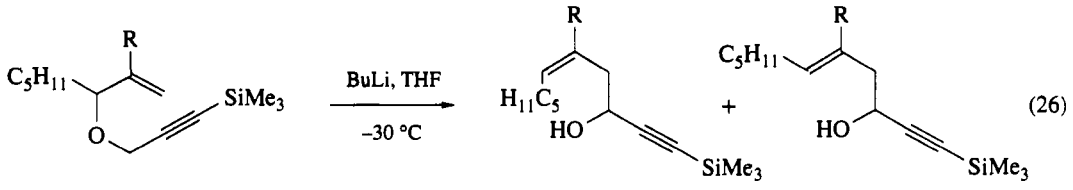
[a]1:1 THF–hexane. [b]Not reported. [c]65:35. [d]95:5.

An envelope transition state in which the alkynyl grouping assumes an equatorial-like orientation has been proposed to accommodate these observations (Scheme 6).[26a] The orientation of R^2 is fixed by the (*E*)/(*Z*)-geometry of the starting allylic ether. When allylic (R^1) substituents are present they likewise adopt an equatorial position as in (**C**) and (**D**), thereby favoring the (*E*)-double bond geometry in the rearrangement product.[26b]



Scheme 6 Envelope transition states for 2,3-Wittig rearrangements of propargyl allyl ethers

The TMS-propargyl ether (**104**) rearranges to an 80:20 mixture of the (*E*)- and (*Z*)-isomers (**106**) and (**108**) in an apparent violation of this transition state proposal (equation 26).[27] (Note that because of the stereochemical descriptor rules the sense of (*E*) and (*Z*) is inverted by the TMS substituent.) However, replacement of the vinylic TMS grouping by hydrogen led 'almost exclusively' to the (*E*)-product (**109**). Evidently, the normally favored transition state (**E**) is destabilized by steric interactions between the vinylic TMS substituent and the *n*-pentyl grouping (R^1). The alternative conformation (**F**) lacks this interaction. The situation is analogous to that noted by Still in the rearrangement of lithiomethyl allyl ethers (Scheme 4).



(26)

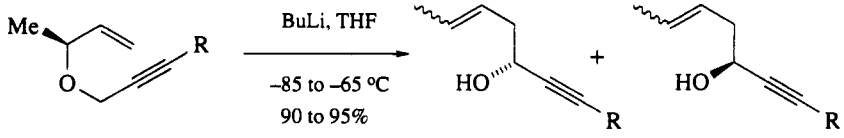
(**104**) R = SiMe$_3$
(**105**) R = H

(**106**) R = SiMe$_3$ (80%)
(**107**) R = H

(**108**) R = SiMe$_3$ (20%)
(**109**) R = H (~100%)

The 2,3-rearrangement of nonracemic propargylic ethers proceeds enantioselectively, as might be expected considering the concerted nature of the reaction and its high diastereoselectivity. Nakai examined the (*S*)-2-butenyl propargyl ethers (**110**; Table 6).[28] In each case a rearranged product of high stereochemical integrity was obtained in near quantitative yield. The stereochemistry of these rearrangements reflects the equatorial preference of substituents in the envelope transition state (**G**; R^1 = Me, R^2 = H) as depicted in Scheme 7.

Table 6 2,3-Wittig Rearrangement of Chiral Allyl Propargyl Ethers



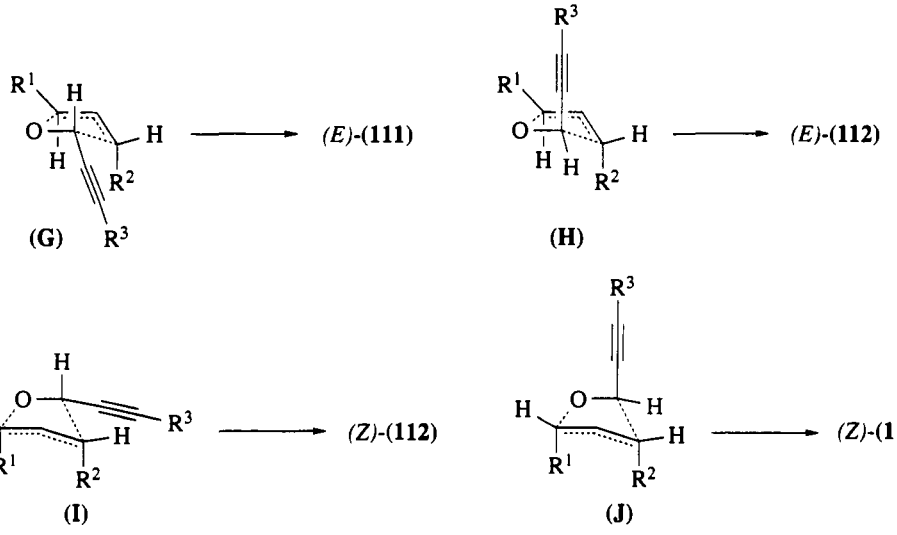
(**110**)

(**111**) *(R) (E)/(Z)*

(**112**) *(S) (E)/(Z)*

R	*(E)/(Z)*	*(R)/(S)*[a]
H	98:2	96:4
TMS	93:7	90:10
Me	97:3	94:6

[a]Major isomer.

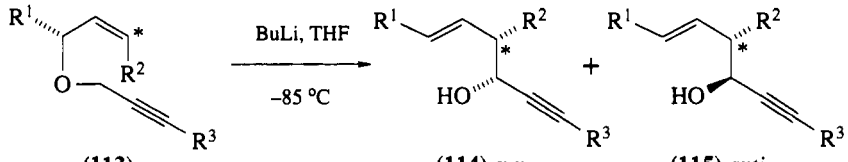


Scheme 7 Transition states for 2,3-Wittig rearrangements of chiral propargyl allyl ethers

Nonracemic (*Z*)-allylic propargyl ethers likewise rearrange with excellent enantioselectivity (Table 7). In these examples the configuration of the starred center in (**114**) and (**115**) should be opposite for (*E*)- and (*Z*)-products owing to the concerted suprafacial nature of the rearrangement. The stereochemistry at the carbinyl center is related to the equatorial/axial preference of the alkynyl grouping (Scheme 7). It should be noted that the (*E*)-products (**114**) and (**115**) are greatly favored because of repulsive *syn*-1,3 in-

teractions between R^1 and R^2 in the transition states (**I**) and (**J**) leading to (*Z*)-products (Scheme 7). The (*E*)-allylic ether (**116**), lacking this 1,3-interaction, rearranges with complete chirality transfer but yields a mixture of *syn/anti* and (*E*)/(*Z*)-isomers (equation 27).[29]

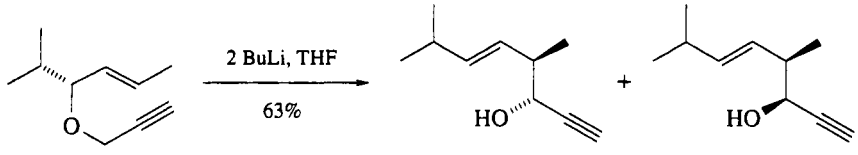
Table 7 2,3-Wittig Rearrangement of Chiral (*Z*)-Allyl Propargyl Ethers



(**113**) (**114**) *syn* (**115**) *anti*

R^1	R^2	R^3	*Yield (%)*	*Syn:anti*	*Enantioselectivity*	*Ref.*
Pr^i	Me	H	89	91:9	100	29
Pr^i	Me	TMS	62	98:2	100	29
Pr^{ia}	CH_2OTBS	TMS	b	98:2[a]	100	30
Me	Bu	TMS	96	99:1	100	24
Me[a]	Me	TMS	64	99:1[a]	100	31

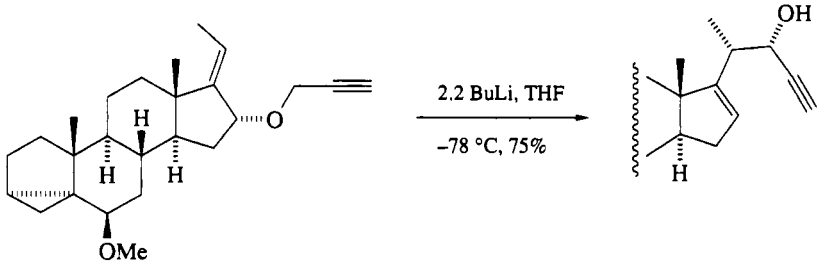
[a]The enantiomer of the depicted compound was employed. [b]Not reported.



(27)

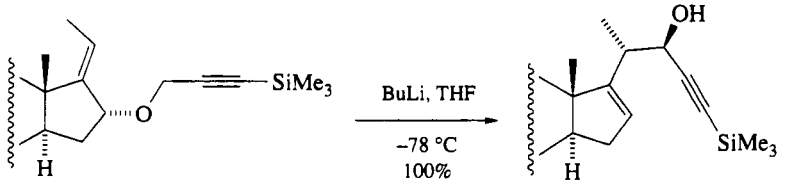
(**116**) (**117**) 82% (**118**) 10% 8%

Nakai has employed the propargylic 2,3-Wittig rearrangement for elaboration of side chains in steroidal systems. The (*E*)-17-ethylidene-16α ether (**119**) rearranges to the expected alcohol (**120**) on base treatment (equation 28).[32] Remarkably, the TMS derivative (**121**) of ether (**119**) rearranges with even greater facility to give the diastereomeric alcohol (**122**; equation 29).[33] The isomeric (*Z*)-17-ethylidene-16β TMS-propargyl ether (**123**) yields the same alcohol (equation 30). These results indicate that attack by the propargylic anion derived from the 16α ether (**121**) takes place with orientation of the TMS-ethynyl grouping toward the c-ring of the steroid as in (**K**; Scheme 8). In the 16β-(*Z*)-isomer (**123**) the TMS-



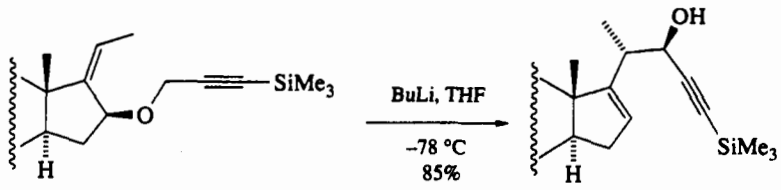
(28)

(**119**) (**120**)

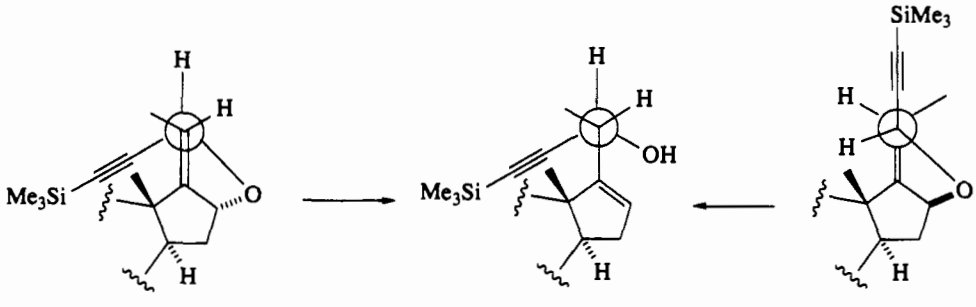


(29)

(**121**) (**122**)



(123) (122) (30)



(K) (122) (L)

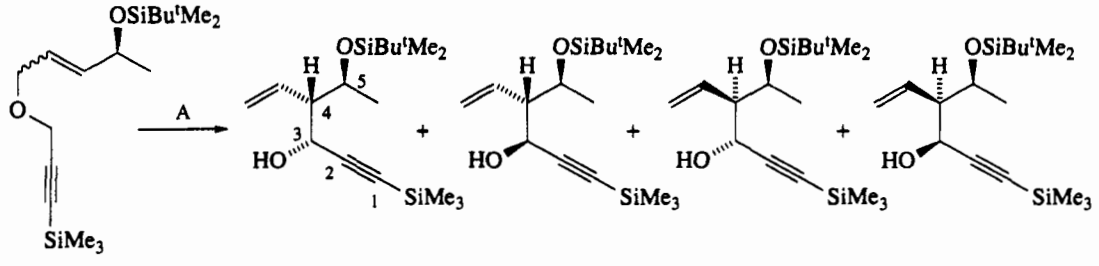
Scheme 8 2,3-rearrangment of steroial 17-ethylidene-16-trimethylsilyl-propargyl ethers

ethynyl grouping adopts the opposite orientation (**L**), also leading to the (22*R*)-alcohol (**122**). The ethynyl anion must assume the same relative orientation as in (**L**) but on the α-face of the double bond *en route* to the (22*S*)-alcohol (**120**).

The effect of a stereocenter at the δ-allylic position of allyl propargyl ethers has been examined by Nakai.[33a] The (*Z*)-ethers show particularly high 3,4-diastereoselectivity (Tables 7a and 7b).

The high asymmetric induction of these rearrangements is explained by transition states (**La**) and (**Lb**) as shown in Scheme 8a. The allylic oxygen substituents adopt an orientation perpendicular to the plane of the double bond to minimize allylic 1,3-repulsion. The propargylic anion attacks the double bond preferentially *anti* to these oxygens.

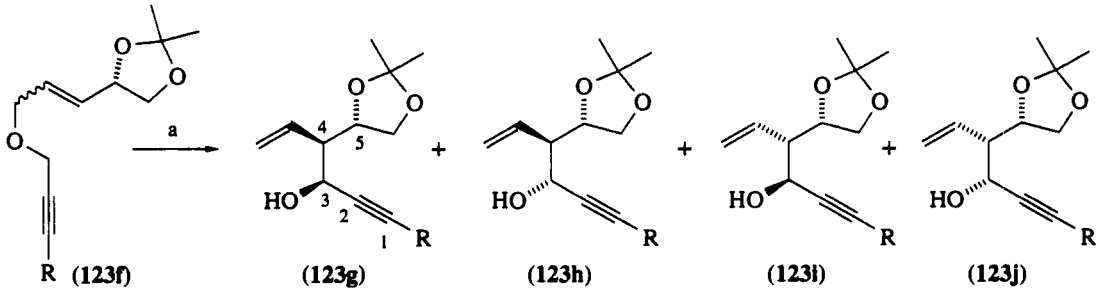
Table 7a 2,3-Wittig Rearrangement of Nonracemic Allylic Propargylic Ethers Derived from (*S*)-Lactaldehyde.



(123a) (123b) (123c) (123d) (123e)

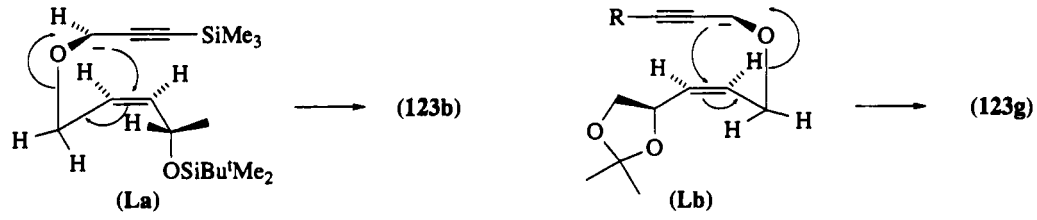
(123a)	A	Yield (%)	Product distribution (123b)	(123c)	(123d)	(123e)
(*Z*)	BuLi, THF, –78 °C	77	94	1	4	1
(*E*)	BuLi, THF, –78 °C	93	10	21	80	19
(*E*)	LDA ,THF–HMPA	74	3	3	87	7

Table 7b 2,3-Wittig Rearrangement of Nonracemic Allylic Propargylic Ethers Derived from (*R*)-Glyceraldehyde Acetonide



(123f)	R	Yield (%)	Product distribution (123g)	(123h)	(123i)	(123j)
(*Z*)	TMS	77	>99	0	0	0
(*Z*)	Me	62	98	0	0	2
(*E*)	TMS	86	12	81	3	4
(*E*)	Me	73	7	77	16	0

[a]$BuLi, THF, –78 °C, 5 h.

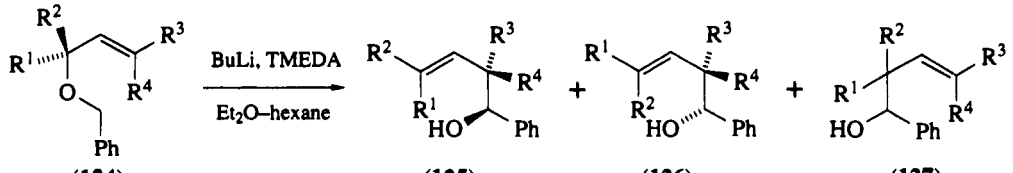


Scheme 8a

3.11.3.4 2,3-Wittig Rearrangement of Allyl Benzyl Ethers

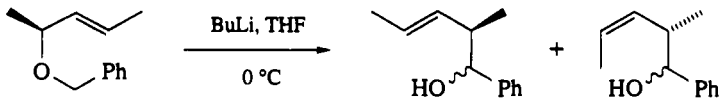
As noted in Section 3.11.1, some of the earliest mechanistic work on the 2,3-Wittig rearrangement was carried out with allyl benzyl ethers. Selective benzyl deprotonation is typically effected with *n*-butyllithium in THF or THF–TMEDA at low temperature. Rautenstrauch's studies, summarized in Table 8, clearly showed that lower temperature favors 2,3- over 1,2-rearrangement, and established the potential

Table 8 2,3-Wittig Rearrangement of Allyl Benzyl Ethers



R^1	R^2	R^3	R^4	T (°C)	(125):(126):(127)	Ref.
H	H	Me	H	–80 to –25	50:50:0	9
H	H	H	Me	–80 to –25	100:0:0	9
Me[a]	H	H	H	–80 to –25	0:100:0	9
H	H	Me	Me	–80 to –25	(89)[b]:11	9
H	H	Me	Me	23	(86)[b]:14	9
Me	Me	H	H	–25	(60)[b]:40	9
H	H	H	OTBS[c]	–65	18:82[d]	25a
H	H	H	OTBS[e]	–65	23:77[d]	25a

[a]Racemic. [b](125) = (126). [c]71:29 (*Z*):(*E*). [d](125):(126). [e]93:7 (*Z*):(*E*).

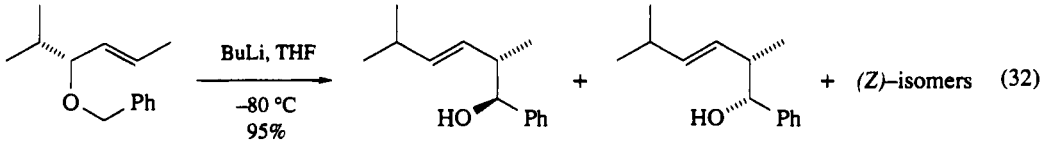


(31)

(**128**) (**129**) 83% 72% *ee* (**130**) 17% 62% *ee*

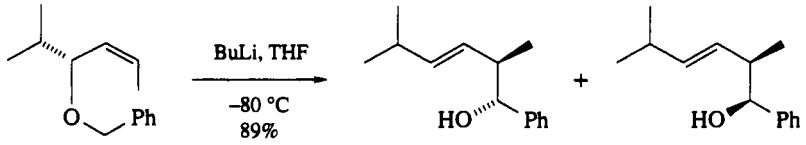
for (*E*)/(*Z*) and *syn*/*anti* stereoselectivity in the former.[9] Baldwin and Patrick examined the chiral (*S*)-(*E*)-1-methyl-2-butenyl ether (**128**) and concluded that the 2,3-rearrangement is 100% suprafacial (equation 31).[34] A second pathway, involving nonconcerted homolysis and supported by deuterium labeling studies, was proposed to account for some 28% of racemic (*E*)-product (**129**). The configuration of the carbinyl center was not determined.

In connection with studies on chirality transfer in 2,3-Wittig rearrangements, Tsai and Midland examined the (*E*)- and (*Z*)-(*R*)-1-isopropyl-2-butenyl benzyl ethers (**131**; equation 32) and (**135**; equation 33).[29] Both ethers rearranged with essentially complete suprafaciality, but the (*Z*)-isomer (**135**) showed considerably higher (*E*)/(*Z*) and *syn*/*anti* selectivity in accord with transition state considerations previously discussed for the analogous propargylic ethers (Scheme 7).



(32)

(**131**) (**132**) 62% (**133**) 20% (**134**) 18%

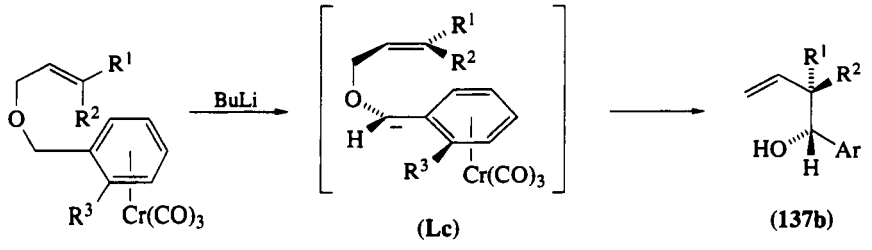


(33)

(**135**) (**136**) 7% (**137**) 93%

A novel approach to stereocontrol in 2,3-Wittig rearrangements involves the use of chiral chromium tricarbonyl complexes (Table 8a).[34a] The reactions, which were carried out with racemic ethers, show excellent diastereoselectivity as a consequence of a preferred transition state in which the benzylic oxygen and the R^3-substituent and the vinylic grouping and $Cr(CO)_3$ grouping adopt *anti* orientations (**Lc**).

Table 8a 2,3-Wittig Rearrangement of $Cr(CO)_3$-complexed Benzyl Allyl Ethers



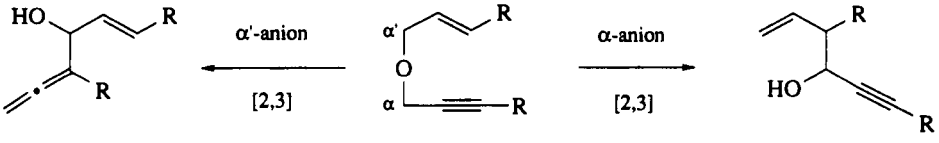
(**137a**) (**Lc**) (**137b**)

R^1	R^2	R^3	*Yield* (%)
H	H	H	98
H	H	Me	82
Me	H	Me	90[a]
H	Me	H	90[a]
Me	Me	Me	88

[a]An 80:20 mixture of (*E*) and (*Z*) ethers yielded an 80:20 mixture of *syn* and *anti* products.

3.11.3.5 2,3-Rearrangement of Dipropargyl Ethers

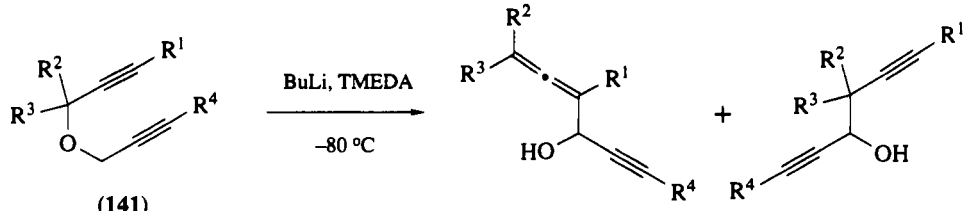
As noted in Section 3.11.3.3, allyl propargyl ethers undergo highly selective 2,3-rearrangement through the propargylic anion intermediate. Allenic products (**138**) arising from 2,3-rearrangement of the allylic anion are not observed (equation 34). This regioselectivity may result from preferred formation of the propargylic anion or from the unfavorable geometry associated with a five-membered allenic transition state. Dipropargylic ethers lack this ambiguity. In fact, such ethers afford mixtures of 2,3- and 1,2-rearrangement products on base treatment (Table 9).[35] A methyl substituent at the propargylic position significantly retards 2,3- in favor of 1,2-rearrangement whereas geminal substituents defeat both processes. Neither the mono- nor the di-methylated propargyl allyl ethers (**144**) and (**145**) gave an allenic rearrangement product (**147**). In the former case only the propargyl alcohol (**146**) and traces of aldehyde were isolated, whereas the latter yielded no rearranged products (equation 35).



(34)

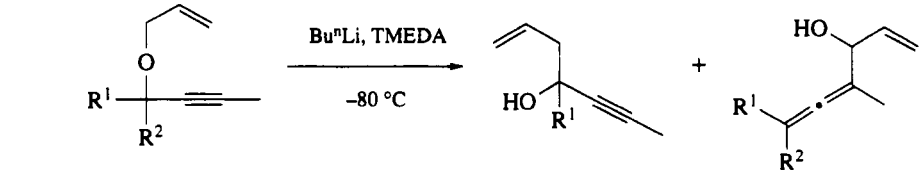
(**138**) (**139**) (**140**)

Table 9 Wittig Rearrangement of Dipropargylic Ethers



(**141**) (**142**) [2,3] (**143**) [1,2]

R^1	R^2	R^3	R^4	(**142**) (%)	(**143**) (%)
H	H	H	H	10	0
Me	H	H	Me	64	0
TMS	H	H	TMS	52	0
Me	Me	H	Me	9	31
Me	Me	Me	H	0	0
H	Me	Me	H	0	0



(35)

(**144**) R^1 = Me, R^2 = H
(**145**) R^1 = R^2 = Me

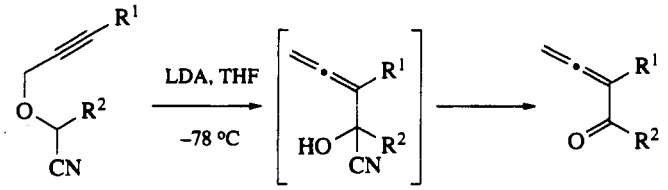
(**146**) R^1 = Me (**147**)

Allenic products are formed in the anion-initiated rearrangement of cyanohydrin propargylic ethers (**148**; Table 10).[36] The intermediate cyanohydrins (**149**) are converted to allenyl ketones (**150**) upon work-up.

3.11.3.6 2,3-Rearrangement of Diallyl Ethers

Unsymmetrical diallyl ethers, like their propargyl allyl counterparts, can theoretically yield isomeric 2,3-rearrangement products depending upon the site of deprotonation. In the first systematic study of

Table 10 2,3-Wittig Rearrangement of Cyanohydrin Propargylic Ethers

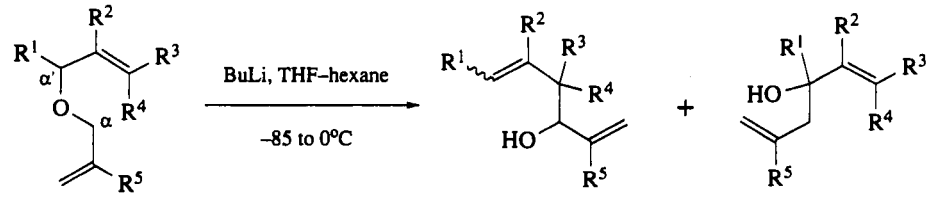


(148) (149) (150)

R^1	R^2	*LDA* (equiv.)	*Yield* (%)
H	Bu^n	3.5	48
H	Bu^i	4	51
Me	Bu^n	2.2	54
Et	Bu^n	2.2	61

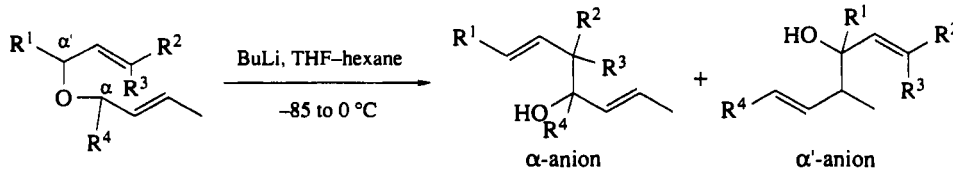
such reactions, Nakai and coworkers found that the regioselectivity of the rearrangement is related to the stability of the presumed allylic anion intermediate (Table 11).[37] Thus allyl or methallyl are deprotonated more readily than crotyl or 1-methyl-2-propenyl (Table 11, entries 1 and 3–7). Allyl and methallyl, on the other hand, are deprotonated with comparable ease (entry 2). In general the less-substituted allylic anion is preferred (equation 36). (*Z*)-Allylic ethers afford *syn* products with high diastereoselectivity (Table 11, entries 4 and 7), whereas (*E*)-allylic ethers yield *anti* products, but less selectively (entries 3 and 6). Ethers with α′-substituents rearrange to (*E*)-products nearly exclusively (entries 1 and 5). Further investigations by Nakai and coworkers confirmed and extended these findings (Table 12).[38]

Table 11 2,3-Wittig Rearrangement of Unsymmetrical Diallylic Ethers



(151) (152) α-anion (153) α′-anion

Entry	R^1	R^2	R^3	R^4	R^5	*Yield* (%)	α:α′	*Anti*:*syn*	(*E*):(*Z*)
1	Me	H	H	H	H	79	100:0		>95:5
2	H	Me	H	H	H	77	55:54		
3	H	H	Me	H	H	81	100:0	84:16	
4	H	H	H	Me	H	88	100:0	8:92	
5	Me	H	H	H	Me	60	100:0		>95:5
6	H	H	Me	H	Me	70	100:0	72:28	
7	H	H	H	Me	Me	71	100:0	5:95	



(36)

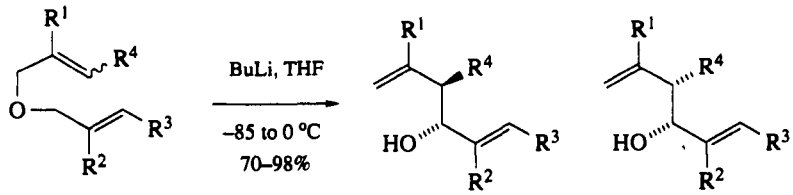
α-anion α′-anion

(**154a**) R^1 = Me, R^2 = R^3 = R^4 = H (**155a**) 33% (**156a**) 66%

(**154b**) R^1 = R^4 = H, R^2 = R^3 = Me (**155b**) 100% (**156b**) 0%

(**154c**) R^1 = H, R^2 = R^3 = R^4 = Me (**155c**) 100% (**156c**) 0%

Table 12 Diastereoselectivity in 2,3-Wittig Rearrangement of Diallylic Ethers

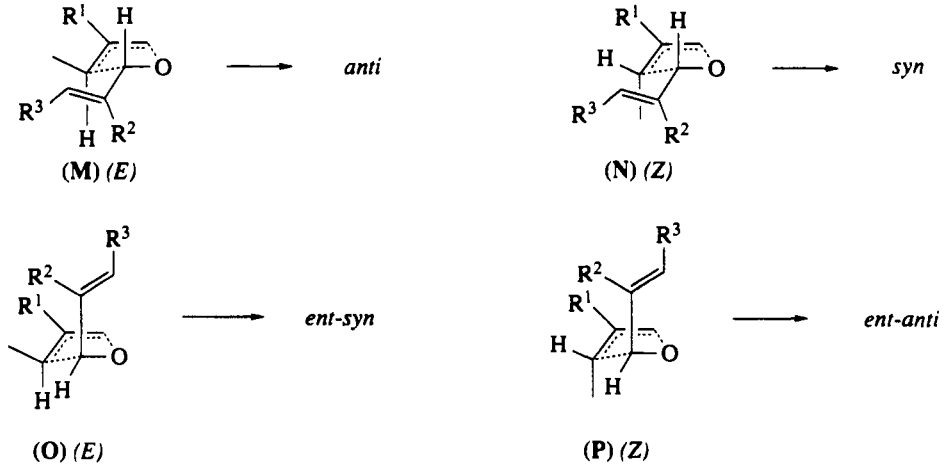


(157) *(E)* or *(Z)* **(158)** *anti* **(159)** *syn*

Entry	R^1	R^2	R^3	R^4	*(E)or(Z)*	*Anti:syn*	*Ref.*
1	H	H	H	Me	(*E*)	84:16	38
2	H	Me	H	Me	(*E*)	72:28	38
3	TMS	Me	H	Me	(*Z*)[a]	91:9	38
4	H	TMS	H	Me	(*E*)	70:30	38
5	H	H	Ph	Me	(*E*)	74:26	38
6	H	H	H	Me	(*Z*)	8:92	38
7	H	Me	H	Me	(*Z*)	5:95	38
8	H	H	Ph	Me	(*Z*)	28:72	38
9	H	H	H	OTBS	(*Z*)[b]	95:5	25a
10	H	Me	H	OTBS	(*Z*)[b]	91:1	25a

[a]Artefact of sequence rule priority change. [b]70:30 (*Z*):(*E*).

A transition state model was formulated (Scheme 9) in which the anion-stabilizing vinyl substituent adopts the lower energy equatorial orientation in the envelope conformation (**M**) for the (*E*)-allylic ether and (**N**) for the (*Z*)-allylic ether.[38] The alternative higher energy axial disposition of this grouping as in (**O**) and (**P**) would lead to the *syn* and *anti* products, respectively. [It should be noted that these products are enantiomers of the *syn* and *anti* products derived from (**N**) and (**M**).] Presumably, interactions between the vinyl substituent and the equatorial (Me) grouping at the migration terminus raises the energy of this transition state slightly in the (*E*)-allylic ethers, resulting in lower diastereoselectivity. R^1-substituents destabilize the axial vinylic grouping in transition state (**O**) in favor of (**M**) leading to an enhanced *anti:syn* ratio (Table 12, entry 3). The lower *syn:anti* ratio seen in entry 8 for the (*E*)-3-phenylallyl ether may stem from unfavorable interactions between the Me grouping at the migration terminus and the R^3-phenyl substituent in transition state (**N**).



(**M**) *(E)* (**N**) *(Z)*

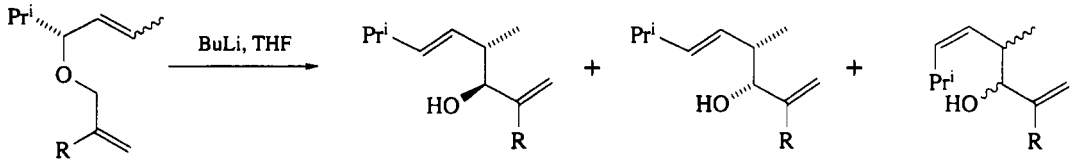
(**O**) *(E)* (**P**) *(Z)*

Scheme 9 Envelope transition states for 2,3-Wittig rearrangements of diallylic ethers leading to diastereomeric and enantiomeric products

The question of conformational preferences at the nonmigrating carbinyl center was addressed by Tsai and Midland (Table 13).[29] Their results are consistent with the previously described transition state pic-

ture for lithiomethyl and propargyl allyl ethers (Schemes 4 and 6). Accordingly, (*Z*)-allylic ethers rearrange to *syn* (*E*)-products with high diastereoselectivity and (*E*)-allylic ethers favor *anti* (*E*)-products. The rearrangement proceeds with complete 1,3-*syn* stereocontrol as expected for a concerted suprafacial process. The Nakai transition state (Scheme 6) with an equatorial-like isopropyl substituent (R^1) accommodates these results.

Table 13 Stereoselectivity of 2,3-Wittig Rearrangement of Chiral Diallylic Ethers

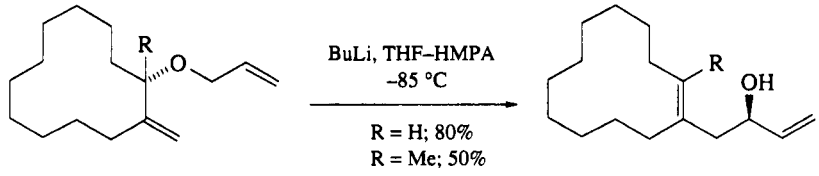


(160) **(161)** *anti* **(162)** *syn* **(163)** *(Z)*

R	*(E) or (Z)*	*Yield (%)*	*Anti:syn:(Z)*
H	(*E*)	75	60:40:0
Me	(*E*)	89	50:40:10
H	(*Z*)	84	8:92:0[a]
Me	(*Z*)	93	7:93:0[a]

[a] *ent*-(**161**)/(**162**).

Studies on the nonracemic methylenecyclododecyl ethers (**164**; equation 37) led to similar conclusions.[39] With HMPA as a cosolvent the secondary allylic ether (**164a**) afforded mainly (86:14) the (*E*)-homoallylic alcohol (**165a**) of 95% *ee*. The tertiary ether (**164b**) yielded a 98:2 (*E*):(*Z*) mixture, but the major product (**165b**) was 40% racemic. A dissociative rearrangement process could account for this result. Without HMPA both ethers rearranged in poor yield (5–30%) to nearly 1:1 mixtures of (*E*)- and (*Z*)-cycloalkenes.



(37)

(164a) R = H
(164b) R = Me

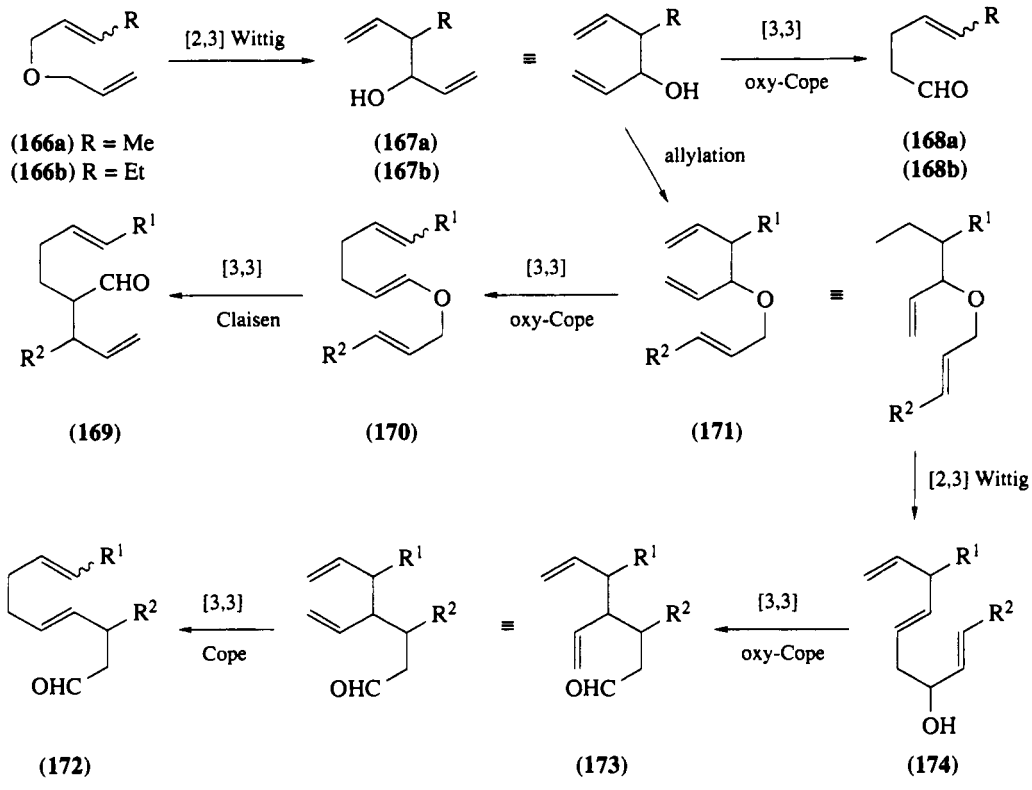
(165a)
(165b)

3.11.3.7 Tandem and Sequential 2,3-Wittig–3,3-Sigmatropic Rearrangements

The 1,5-dien-3-ols produced by 2,3-Wittig rearrangement of diallylic ethers can serve as pivotal intermediates for further elaboration through tandem or sequential 3,3-sigmatropic reactions.[40,41] The three sequences examined to date are summarized in Scheme 10.

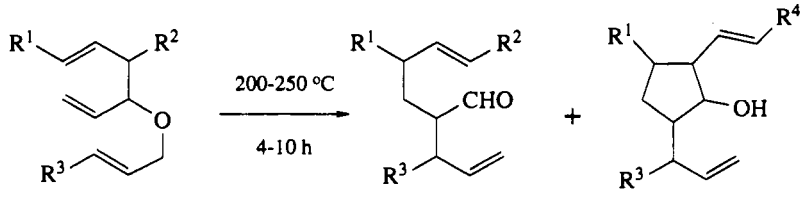
2,3-Wittig rearrangement of the (*E*)- and (*Z*)-diallylic ethers (**166a**) and (**166b**) afforded mixtures of the 1,5-dienes (**167a**) and (**167b**) enriched in the *anti* [from (*E*)] and *syn* [from (*Z*)] isomers, respectively. Subsequent oxy-Cope rearrangement of these dienes gave the enals (**168a**) and (**168b**) as mixtures of (*E*)- and (*Z*)-isomers whose composition depended upon the oxy-Cope reaction conditions, but not the *syn:anti* ratios of the precursor 1,5-dienes (**167**).[42] Best results were obtained in refluxing decane, whereupon (*E*)-enals (**168**) of 90–95% isomeric purity were produced.

Allylation of the 2,3-Wittig products (**167**) leads to diallylic ethers (**171**) in which one of the allylic double bonds is part of a 1,5-diene system. These ethers undergo 3,3-oxy-Cope rearrangement to afford vinyl allyl ethers (**170**), which rearrange *in situ* by a 3,3-Claisen process to yield the (*E*)-dienals (**169**).[43] Some typical results are summarized in Table 14. The cyclopentanols (**175**) were shown to arise from aldehydes (**169**) by an intramolecular thermal ene reaction.[44]



Scheme 10 Tandem and sequential 2,3–Wittig–3,3-sigmatropic rearrangements

Table 14 Tandem Oxy-Cope–Claisen Rearrangements of 1,5-Dien-3-ol Allylic Ethers

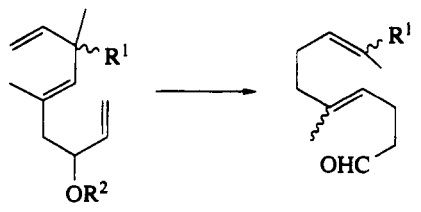


R^1	R^2	R^3	R^4	(171) *Anti:syn*	(169) (%)	(175) (%)
H	Me	Me	H	79:21	36	20
H	$CH_2{=}CH(CH_2)_3$	Me		80:20	45	0
H	$CH_2{=}CH(CH_2)_3$	H	a	80:20	45	13
Me	H	H			41	

[a] $(CH_2)_2CH{=}CH_2$.

A third variant of tandem rearrangements employs the dienyl allylic ether (**171**) in a second regioselective 2,3-Wittig rearrangement leading to the 1,5-dienol (**174**), which undergoes sequential oxy-Cope–Cope rearrangement to the dienal (**172**). Examples of the latter steps of this sequence are collected in Table 15. In the oxy-Cope rearrangement of the methyl derivative (**174**; R^1 = Me) the silyl ether proved superior to the free alcohol (entries 1 *versus* 2). No such improvement was realized with the geranyl-derived silyl ether (**174**; entries 3 *versus* 4). The ratio of isomeric products (**172**) was independent of the diastereomeric composition of the starting allylic ethers (**171**).

Table 15 Tandem Oxy-Cope–Cope Rearrangements



(174) (172)

Entry	R^1	R^2	*Temperature* (°C)	*Yield* (%)	*(E):(Z)* (172)
1	Me	H	202 (NMP)	41	67:33
2	Me	TMS	250 (neat)	86	a
3	$CH_2CH{=}CMe_2$	H	202 (NMP)	46	b
4	$CH_2CH{=}CMe_2$	TMS	250 (neat)	46	b

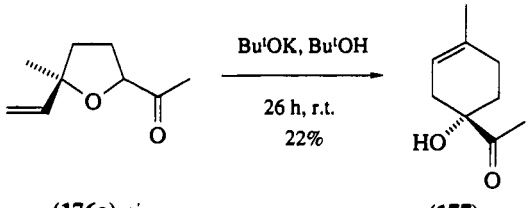
[a]Not determined. [b]Mixture of all four geometric isomers.

3.11.3.8 Rearrangement of α-Allyloxy Enolates

The anion that initiates a 2,3-Wittig rearrangement can be derived from α-allyloxy or α-propargyloxy ketones, nitriles (cyanohydrins), acids, esters and amides. Such anions have the virtue of being more easily formed under milder conditions than their methyl, benzyl, propargyl and allyl counterparts. In addition, they lead to more highly functionalized products with greater potential for synthetic applications. Furthermore, through changes in counterion or incorporation of chiral auxilliary groupings, better control of relative and absolute stereochemistry can often be realized.

3.11.3.8.1 α-Allyloxy ketones

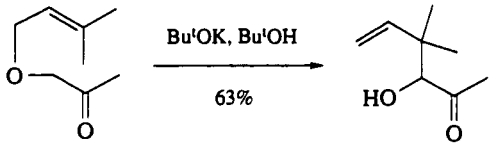
One of the earliest observations of ketone enolate 2,3-rearrangement was made in connection with attempts to add Grignard reagents to the tetrahydrofurfuryl ketone (**176**).[45] Instead of the expected adduct, the hydroxy ketone (**177**) was obtained (equation 38). Both *cis* and *trans* ketones (**176a**) and (**176b**) rearranged to this product. Concordant with a concerted 2,3-process, the nonracemic ketone (**177**) was produced from optically active ether (**176**). The acyclic ether (**178**) also underwent 2,3-rearrangement upon base treatment (equation 39). An analogous α-allyloxy ketone (**180**) was found to follow a 3,3-rearrangement pathway[43] exclusively with KOMe–KH or NaOMe–NaH in toluene or THF (Scheme 11).[46] With LiOMe–LiH as the base an 80:20 mixture of the 3,3- and 2,3-products (**183**) and (**182**) was produced.



(38)

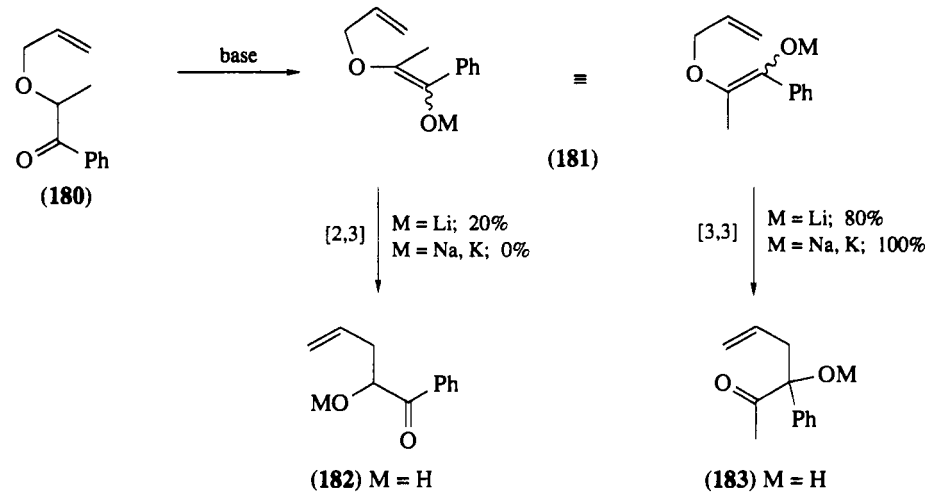
(**176a**) *cis*
(**176b**) *trans*

(**177**)



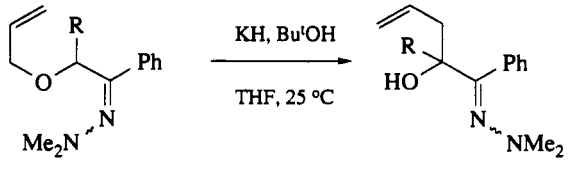
(39)

(**178**) (**179**)



Scheme 11 Competing 3,3- and 2,3-rearrangement pathways for a ketone enolate

The dimethylhydrazone derivatives of α-allyloxy ketones undergo exclusive 2,3-Wittig rearrangement upon deprotonation with excess KH in *t*-butyl alcohol (equation 39a).[46a] The lack of competing 3,3-rearrangement is ascribed to the higher charge density on carbon in the anion as a result of the diminished electronegativity of the hydrazone nitrogen. In the case of (**183b**) only the (*E*)-hydrazone isomer rearranged. The apparent unreactivity of the (*Z*)-isomer is thought to stem from greater steric hindrance to deprotonation.

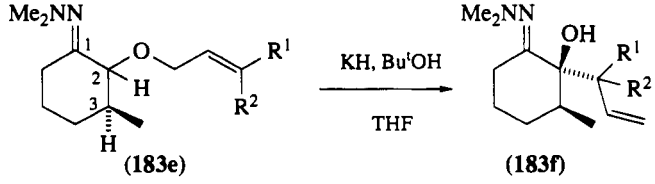


(39a)

(**183a**) R = H (*E*:*Z* = 1:3)
(**183b**) R = Me (*E*:*Z* = 2.9:1)
(**183c**) 95% yield
(**183d**) 73% yield

The cyclohexanone hydrazones (**183e**) rearrange similarly (Table 15a). The *cis* isomers (entries 2 and 4) required elevated temperatures for deprotonation owing to the stereoelectronically disfavored equatorial disposition of the α-proton (H-2). The diastereofacial selectivity of the rearrangement was high in all cases examined but the diastereoselectivity at the allylic center was poor (entries 3–5).

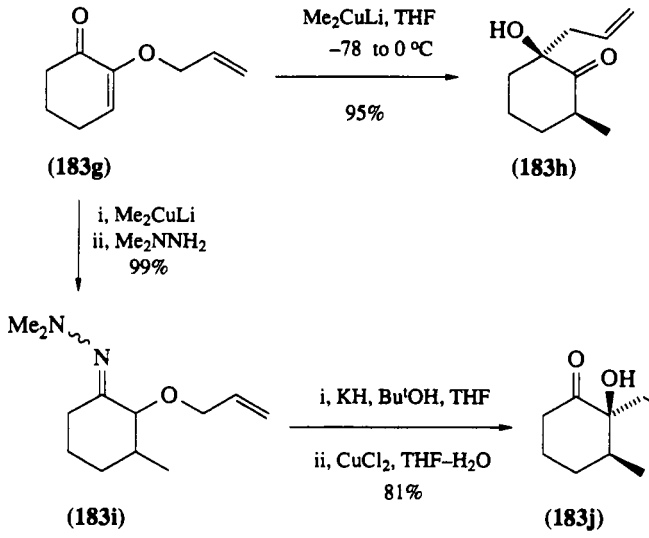
Table 15a 2,3-Wittig Rearrangement of Cyclohexanone Hydrazone Derivatives



(**183e**) (**183f**)

Entry	R^1	R^2	*(E)/(Z)*	*H-2/H-3*	*Yield (%)*
1	H	H	>50:1	*Trans*	91
2	H	H	4:1	*Cis*	92
3	Me	H	>50:1	*Trans*	88 (1.4:1)
4	Me	H	6:1	*Cis*	45 (1.1:1)
5	H	Me	>50:1	*Trans*	81 (1.25:1)

The complimentarity of hydrazone and ketone enolate rearrangements is illustrated in equation (39b).

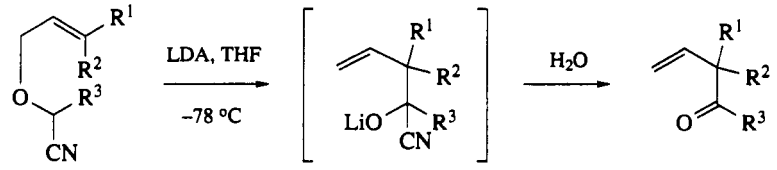


(39b)

3.11.3.8.2 O-*Allyl cyanohydrins*

Allylic ethers of cyanohydrins are easily prepared through phase transfer allylation.[47] Deprotonation of these ethers with LDA in THF at −78 °C effects 2,3-rearrangement to transient β,γ-unsaturated ketone cyanohydrins, which are transformed during work-up to the ketones (Table 16).[48] In an extension of this work, the mixed acetal cyanohydrin ethers (**187**), prepared by mild acid treatment of the cyanohydrins with 2-methoxy-1,3-butadiene or 1-*t*-butoxyallene, rearranged to the keto enol ethers (**189**; equation 40).[49] Hydrolysis of the enol ethers (**189**) leads to 1,4-dicarbonyl compounds, which can be cyclized to cyclopentenones.

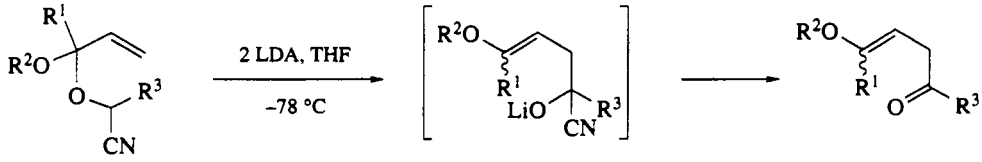
Table 16 2,3-Rearrangement of *O*-Allyl Cyanohydrins



(**184**) (**185**) (**186**)

R^1	R^2	R^3	*Yield* (%) (**184**)	(**186**)
H	H	Bu^i	46	76
Me[a]	H	Bu^i	45	65
Me	Me	Bu^i	57	75
Me	Me	Me	32	36
b	Me[c]	Bu^i	48	58
b	Me[c]	Me	15	36

[a]85:15 (*E*):(*Z*). [b]$Me_2C=CHCH_2CH_2$. [c]90:10 (*E*):(*Z*).



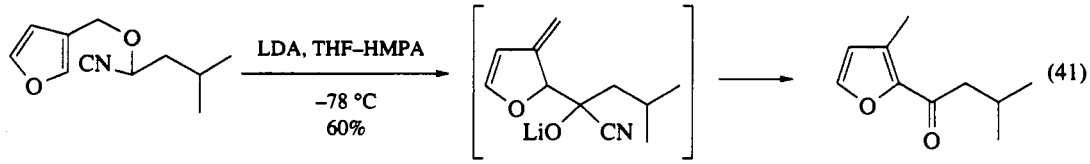
(40)

(**187a**) R^1 = H, R^2 = Bu^t, R^3 = Bu^i; 84%
(**187b**) R^1 = H, R^2 = Bu^t, R^3 = n-C_6H_{13}; 80%
(**187c**) R^1 = Me, R^2 = Me, R^3 = n-C_6H_{13}; 63%

(**188**)

(**189a**) 90%
(**189b**) 89%
(**189c**) 83%

Base treatment of the cyanoisopentyl β-furfurylmethyl ether (**190**; equation 41) affords Elsholtzia ketone (**192**), a naturally occurring monoterpene.[50] Even though it disrupts the aromatic furan ring, this rearrangement proceeds readily, illustrating the potency of cyanohydrin anions as 2,3-Wittig initiators.

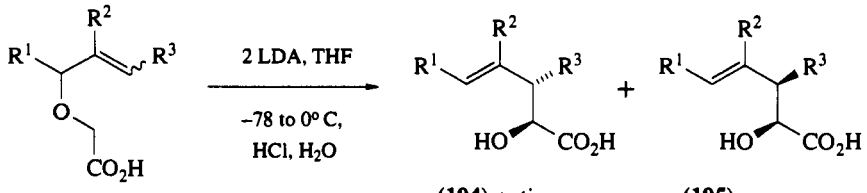


(**190**) (**191**) (**192**)

3.11.3.8.3 α-Allyloxycarboxylic acids

2,3-Wittig rearrangement of α-allyloxycarboxylic acid dianions and allyl propargylic dianions (Section 3.11.3.3) might be expected to proceed analogously. In fact, the same high preference for (*E*)-products is observed, but the diastereoselectivity is reversed (Table 17, entries 5 *versus* 6).[51] A chelated bicyclo [3.3.0] transition state readily explains the *anti* selectivity of (*Z*)-allylic ethers [Scheme 12, compare (**R**) with (**T**)]. The basis for *syn* selectivity observed with (*E*)-allylic ethers (**Q**) *versus* (**S**) is less clear.

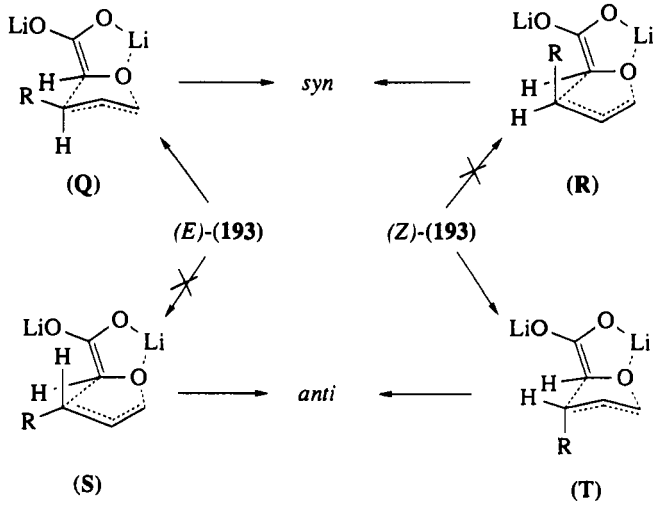
Table 17 2,3-Wittig Rearrangement of α-Allyloxycarboxylic Acids



(**193**) (**194**) *anti* (**195**) *syn*

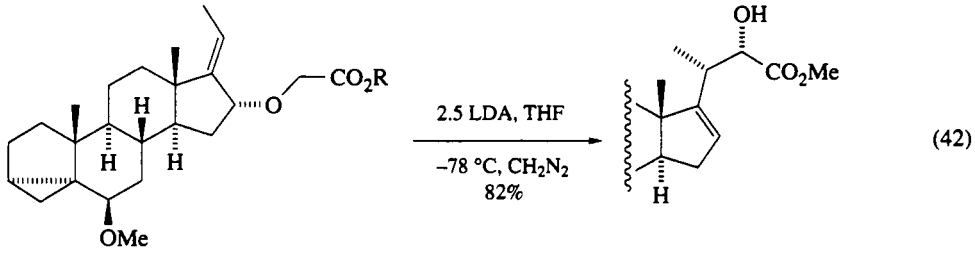
Entry	R^1	R^2	R^3	*(E) or (Z)*	*Yield (%)*
1	n-C_7H_{15}	H	H		80[a]
2	n-C_5H_{11}	H	H		64[a]
3	Me	H	H		87[a]
4	n-C_5H_{11}	Me	H		74[a]
5	H	H	Me	(*E*)	60[b]
6	H	H	Me	(*Z*)	73[c]

[a]>95% (*E*). [b]92:8 *syn:anti*. [c]79:21 *anti:syn*.

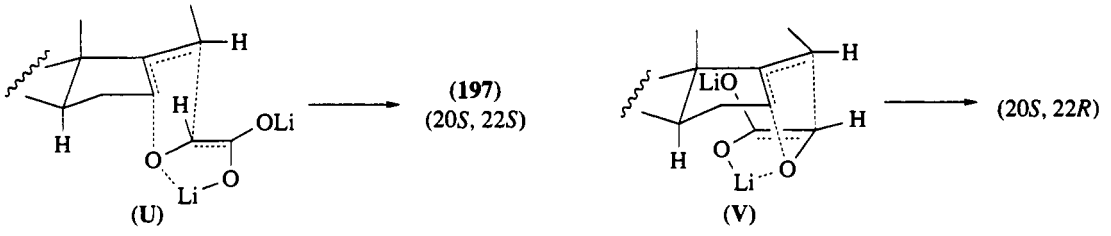


Scheme 12 Envelope transition states for 2,3-rearrangement of α-allyloxycarboxylic acid dianions

The carboxylic acid variant of the 2,3-Wittig rearrangement has been used in steroidal systems to elaborate the 22-hydroxy substituent found in ecdysone and brassinolide natural products (equation 42).[52] Whereas the ethyl ester (**196**; R = Et) gave a mixture of products, acid (**196**) was cleanly converted to the (22*S*)-alcohol (**197**) at –78 °C *via* the dianion followed by acidification and esterification.[53] The stereochemistry of this rearrangement is analogous to that observed for the corresponding propargylic ether (**119**) and opposite to that of the acyclic *trans* crotyl analog (Table 17, entry 5). The preference for (**197**) can be clearly seen by comparison of transition states (**U**) and (**V**) in Scheme 13.

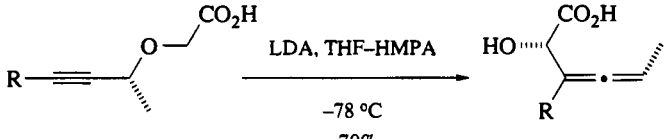


(196) R = H (197) (42)



Scheme 13 Diastereomeric transition states for carboxylic acid dianion 2,3-rearrangement of a steroidal 17-ethylidene-16α ether

2,3-Wittig rearrangement of the nonracemic (*R*)-propargylic glycolic acid ethers (**197d**) and (**197e**) to the (*R,S*)-α-hydroxy acids (**197f**) and (**197g**) proceeds with complete chirality transfer and 94% diastereoselectivity (equation 42a).[51b]

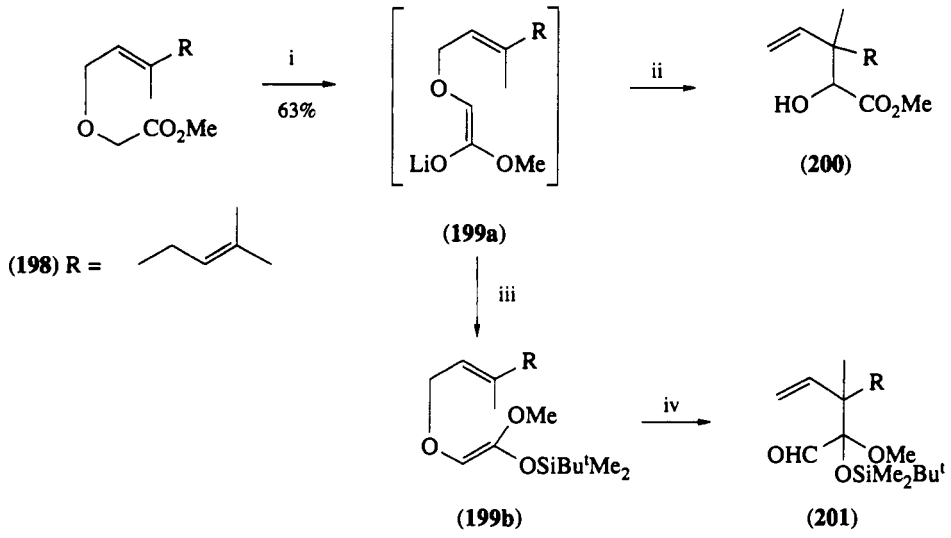


(197d) R = Bu (197f) (42a)
(197e) R = C_7H_{15} (197g)

3.11.3.8.4 α-Allyloxycarboxylic esters

It was previously noted that enolates of α-allyloxy ketones were capable of either 2,3- or 3,3-rearrangement, depending upon counterion, reaction conditions and substituents.[46] Ester enolates show a greater propensity for the 2,3-pathway, as illustrated by the geraniol-derived alkoxyacetate (**198**) which afforded hydroxy ester (**200**) as the sole product upon treatment with LDA in THF at –78 to 0 °C.[54] The 3,3-product (**201**) could be obtained by addition of TBDMS-Cl and HMPA to the enolate at –78 °C and thermal rearrangement of the TBS enol ether (**199b**; Scheme 14).[43]

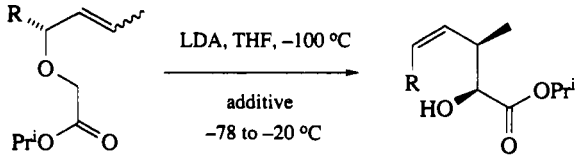
Zirconium enolates offer a number of advantages in the 2,3-Wittig rearrangement of α-allyloxyacetic esters. Although both lithium and zirconium enolates afford predominantly *syn* (*Z*)-products, regardless of initial allyl geometry, reactions of the latter tend to be more efficient and more selective (Table 18, entries 1, 3 and 5 *versus* 2, 4 and 6).[55] In addition, nonracemic secondary allyloxyacetates rearrange with high 1,3-suprafaciality (entries 6–9). These trends reflect steric interactions between the coordinated metal and the substituent R in a bicyclo [3.3.0] folded transition state (Scheme 15). Of the four possible arrangements, (**U**) offers the best steric environment for an R-substituent. When the allylic position is primary (R = H), then (**U**) and (**X**) are enantiomeric, as are (**V**) and (**W**).



i, LDA, THF, –78 °C; ii, –78 to 0 °C, H_2O; iii, –78 °C, THF, HMPA, Bu^tMe_2SiCl; iv, 110 °C

Scheme 14

Table 18 2,3-Wittig Rearrangement of α-Allyloxyacetic Ester Enolates



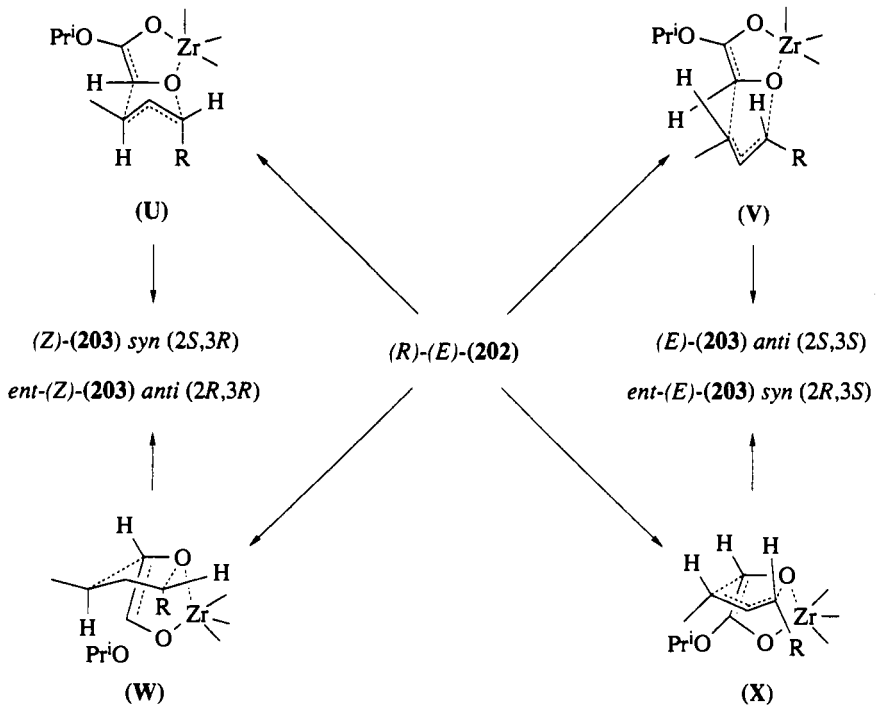
Entry	*R*	*(E)/(Z)*	*Additive*	*Yield (%)*	*Syn:anti*	*ee (%)*
1	H	(Z)	None	20	67:33	
2	H	(Z)	Cp_2ZrCl_2	15	86:12	
3	H	(E)	None	14	82:18	
4	H	(E)	Cp_2ZrCl_2	47	98:2	
5	Me	(E)	None	72	80:20	
6	Me[a]	(E)	Cp_2ZrCl_2	91	99:1	>96[a]
7	Bu^n	(E)	Cp_2ZrCl_2	81	98:2	>96
8	n-C_8H_{17}	(E)	Cp_2ZrCl_2	70	99:1	>96
9	Pr^i	(E)	Cp_2ZrCl_2	26	98:2	>96
10	CH_2OBn	(E)	Cp_2TiCl_2	72	98:2[b]	
11	CH_2OBn	(E)	Cp_2HfCl_2	37	97:3[b]	
12	$(CH_2)_2OBn$	(E)	Cp_2ZrCl_2	62	98:2	
13	$(CH_2)_3OBn$	(E)	Cp_2ZrCl_2	57	98:2	
14	$(CH_2)_3OBn$	(E)	Cp_2TiCl_2	37	79:21[c]	

[a]Enantiomer of depicted structure. [b]The (*E*) product formed predominantly. [c]*Ca.* 2:1 mixture of (*E*) and (*Z*).

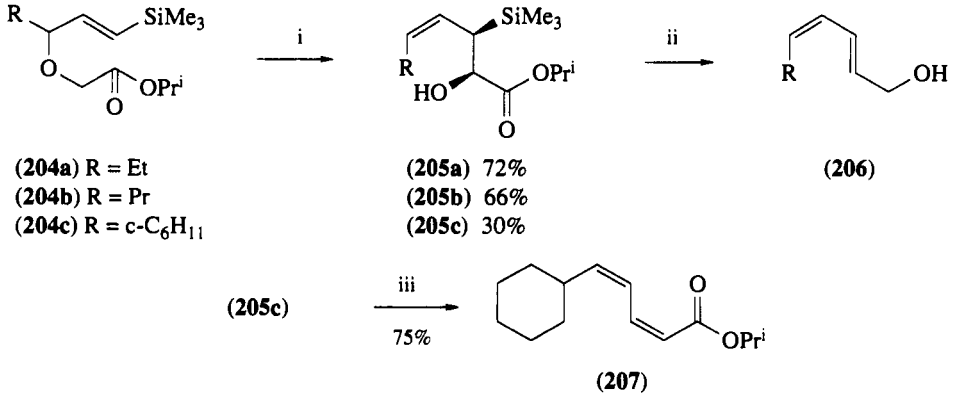
The presence of a benzyloxymethyl substituent at the allylic position of ester (**202**) leads to a predominance of the (*E*)-*syn* rearranged product with Hf and Ti enolates (Table 18, entries 10 and 11). In these cases favorable chelation between the ester enolate and the benzyloxy oxygen stabilizes transition state (**X**; Scheme 15). When the benzyloxy substituent is more remote (Table 18, entries 12–14) such chelation is less favorable and the reaction proceeds through transition state (**U**).

2,3-Rearrangement of the γ-TMS-allyloxy system (**204**) gave the (*Z*)-*syn*-β-TMS-α-hydroxy esters (**205a–c**) as single isomers.[56] These were transformed through reduction and basic elimination to the (*Z,E*)-dienols (**206a–c**). Lewis acid promoted elimination converted ester (**205c**) to the (*Z,Z*)-dienoate (**207**; Scheme 16).

Chiral auxilliaries have been employed to direct stereochemistry in 2,3-rearrangements of ester enolates. The (–)-8-phenylmenthyl α-allyloxyacetates (**208**) rearrange *via* their lithium enolates to the *syn*



Scheme 15 Envelope transition states for 2,3-rearrangement of α-allyloxyacetate zirconium enolates



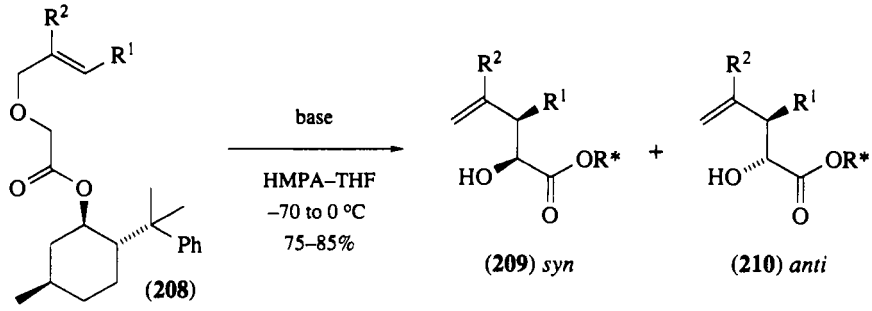
i, LDA, Cp_2ZrCl_2, THF; ii, DHP, PPTS, $LiAlH_4$, PPTS, MeOH, NaH; iii, $Et_2O{\cdot}BF_3$, CH_2Cl_2

Scheme 16

(2*S*, 3*R*)-hydroxy esters (**209**) with generally high diastereo- and enantio-selectivity (Table 19).[57] Best results are obtained with allylic ethers possessing substituents at the γ-position (compare entries 1–4 with 5 and 6). The observed enantioselectivity is in accord with the envelope transition state (**Y**) in which the double bond approaches the enolate from the *si* face to avoid steric confrontation with the bulk of the 8-phenylmenthyl grouping (Scheme 17). Substituents (R^1, R^2) on the allylic double bond accentuate this steric interaction, thereby enhancing the enantioselectivity.

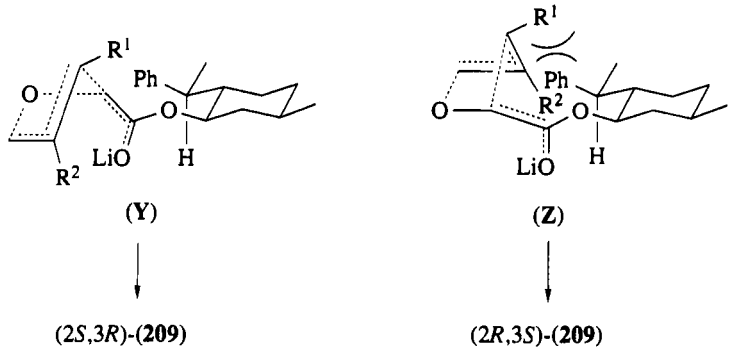
Substituents at the δ-position of the allylic ether have also been found to influence diastereoselectivity in α-allyloxyacetate enolate 2,3-rearrangements. The acetonide (**211**) afforded the α-hydroxy ester (**212**) containing less than 2% of isomeric rearrangement products (equation 43).[58] In a closely related example, an analog of (**211**), R = Bu_3Sn, but with an (*E*) double bond, rearranged upon lithiation to an 86:14 mixture of diastereoisomers. These results can be explained by transition state (**AA**) in which the oxygen of the acetonide aligns perpendicular to the double bond, thereby lowering the LUMO of the allylic system through π*/σ*-orbital overlap (equation 44).

Table 19 2,3-Wittig Rearrangement of (–)-8-Phenylmenthyl α-Allyloxyacetates

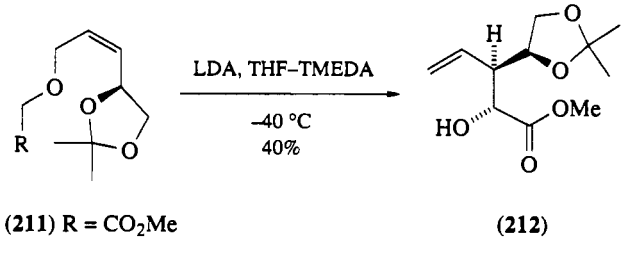


Entry	R^1	R^2	*Base*	*Syn:anti*	*ee* (%)[a]
1	Me	H	LDA	90:10	97
2	Me	H	LHDS	93:7	96
3	Me	H	LTMP	92:8	97
4	Bu	H	LDA	92:8	95
5	H	H	LDA		11
6	H	Me	LDA		4

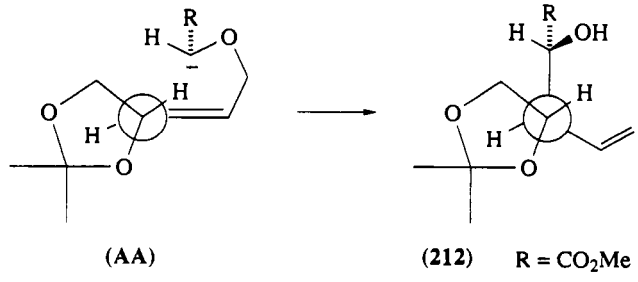
[a]Major isomer.



Scheme 17 Diastereomeric transition states for 2,3-rearrangement of (–)-8-phenylmenthyl α-allyloxyacetates



(43)

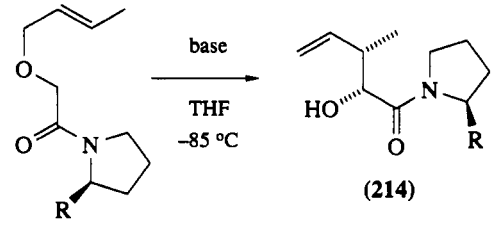


(44)

3.11.3.8.5 α-Allyloxycarboxamides

The 2,3-rearrangement of α-allyloxyacetamide enolates proceeds readily. (*E*)-Crotyl ethers (**213**) show high *syn* diastereoselectivity (Table 20) in accord with acid and ester analogs (**193**) and (**208**). Amides of homochiral pyrrolidines derived from (*S*)-proline undergo moderately enantioselective rearrangement (entries 5–8).[59] 2,5-Disubstituted pyrrolidine amides, on the other hand, rearrange with appreciably higher enantioselectivity but with generally lower diastereoselectivity.[60] The (*E*)-allylic ether zirconium enolate (Table 21, entry 3) gives the best overall result. In contrast, rearrangement of the isomeric (*Z*)-allylic ether zirconium enolate is unselective (entry 5). The diastereomeric cyclohexyl-substituted allylic ethers (**215**; R^1 = c-C_6H_{11}, R^2 = H) exhibit double stereodifferentiation. At low conversion (Table 21, entry 7) product of 87% *ee* is isolated, indicating preferential rearrangement of one diastereomeric amide enolate over the second. At 70% conversion (entry 8) rearrangement of the mismatched diastereoisomer results in a product of lower *ee*.

Table 20 2,3-Rearrangement of α-Crotyloxyacetamides

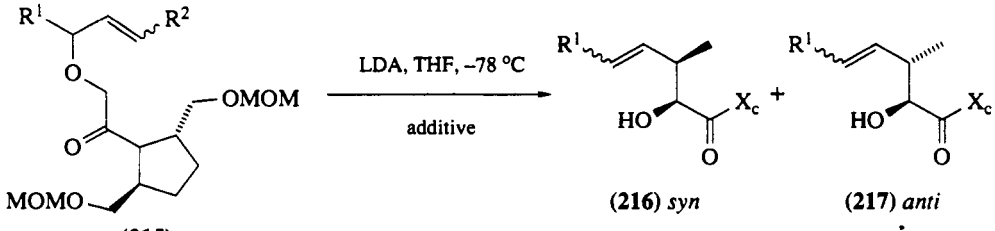


(**213**) (**214**)

Entry	*R*	*Base*	*Yield* (%)	*Syn:anti*	*ee* (%)[a]
1	H	LDA	98	96:4	
2	H	LHMDS	96	96:4	
3	H	LDA[b]	98	96:4	
4	H	KHMDS	88	96:4	
5	CH_2OH	LDA	c	95:5	52
6	CH_2OH	LHMDS	c	95:5	20
7	CH_2OMEM	LDA	c	97:3	20
8	CH_2OMEM	d	c	95:5	12[e]

[a]Major isomer. [b]THF–HMPA solvent. [c]'70–80%'. [d]LDA, –100 °C; Cp_2ZrCl_2. [e]Enantiomer at C-2,C-3 of depicted structure.

Table 21 2,3-Rearrangement of Chiral α-Allyloxyacetamides

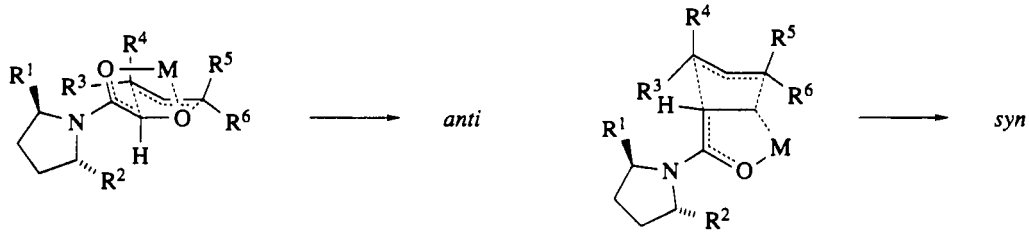


(**215**) (**216**) *syn* (**217**) *anti*

Entry	R^1	R^2	*(E)/(Z)*	*Additive*	*Yield* (%)	*Syn:anti*	*ee* (%)[a]
1	H	H		None	61		96
2	H	Et	(*E*)	None	75	67:33	92
3	H	Et	(*E*)	Cp_2ZrCl_2	65	97:3	96
4	H	Et	(*Z*)	None	33	22:78	90
5	H	Et	(*Z*)	Cp_2ZrCl_2	7	50:50	92
6	n-C_7H_{15}	H		None	82		67[b]
7	c-C_6H_{11}	H		Cp_2ZrCl_2	25		87[b]
8	c-C_6H_{11}	H		Cp_2ZrCl_2	70		41[b]

[a]Major isomer. [b](*E*):(*Z*) ratio not determined.

These results are consistent with the chelated transition states depicted in Scheme 18. Steric interactions between the substituent R^3 and the carboxamide favor (**AC**) for (*E*)-allylic ethers. The R^4-substituent of a (*Z*)-allylic ether, though less affected by this interaction, still experiences a certain degree of steric strain in the *anti* transition state (**AB**) thus diminishing *anti* selectivity. Enantioselectivity is controlled by the substituents R^1 and R^2 on the pyrrolidine ring. As pictured in Scheme 18, bonding occurs preferentially on the face of the enolate *anti* to R^1. For the diastereomeric secondary allylic ethers (Table 21, entries 6–8) transition state (**AB**) represents the matched arrangement for R^5 = H and R^6 = alkyl, whereas (**AC**) is matched for R^5 = alkyl and R^6 = H. The former arrangement would lead to an (*E*)-product and the latter to a (*Z*)-product.



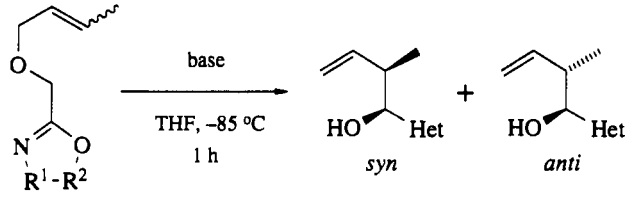
(**AB**) (**AC**)

Scheme 18 Diastereomeric transition states for 2,3-rearrangement of α-allyloxyacetamide enolates

3.11.3.8.6 Allyloxymethyl-oxazolines and -1,3-oxazines

2-Oxazolines (**218a**) and 5,6-dihydro-1,3-oxazines (**218b**) with C-2 allyloxymethyl substituents, readily undergo 2,3-rearrangement *via* their imino-stabilized anions (Table 22).[61] The (*E*)-crotyl ethers afford the *syn* products (**219a**) and (**219b**) and the oxazoline ether (*Z*)-(**218a**) yields mainly the *anti* product (**220a**). Surprisingly, the 1,3-oxazine analog (*Z*)-(**218b**) gives the *syn* product (**219b**) predominantly.

Table 22 2,3-Rearrangement of Oxazoline and 1,3-Oxazine Crotyloxymethyl Anions



(**218a**) (**219a**) (**220a**)
(**218b**) (**219b**) (**220b**)

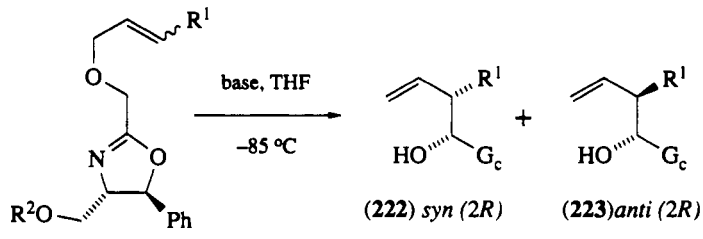
Entry	*System*	*(E)/(Z)*	*Base*	*Yield (%)*	*Syn:anti*
1	(**218a**)[a]	(*E*)	BuLi	98	66:34
2	(**218a**)[a]	(*E*)	LDA	80	84:16
3	(**218a**)[a]	(*Z*)	LDA	80	22:78
4	(**218b**)[b]	(*E*)	BuLi	92	98:2
5	(**218b**)[b]	(*E*)	LDA	86	96:4
6	(**218b**)[b]	(*Z*)	LDA	82	65:35

[a] R^1—R^2 = Me_2C—CH_2. [b] R^1—R^2 = Me_2C—CH_2CHMe.

These findings have been extended to nonracemic oxazolines (**221**; Table 23).[62,63] The methoxymethyl-substituted derivatives (entries 1–3) rearrange with moderate enantioselectivity and high *syn* diastereoselectivity (entries 2 and 3). The hydroxymethyl analogs, on the other hand, rearrange with excellent enantioselectivity when KH is used as the base (entries 4, 6 and 8–10). However, the crotyl ethers show poor diastereoselectivity (entries 6, 9 and 10).

The foregoing results for the most part parallel those observed with carboxamides (Section 3.11.3.8.5) and an analogous chelated transition state has been proposed (Scheme 19). Accordingly (**AD**) represents the lowest energy rearrangement pathway for (*E*)-allylic ethers. The alternative (**AF**) places the R^1-sub-

Table 23 2,3-Rearrangement of Chiral Oxazoline Allyloxymethyl Anions

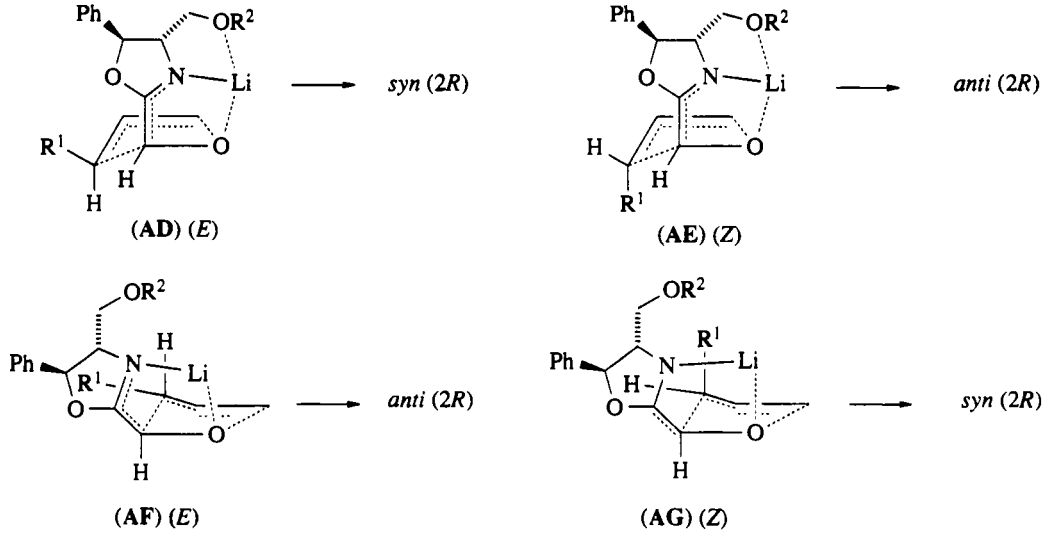


(221) (222) *syn* (2*R*) (223) *anti* (2*R*)

Entry	R^1	R^2	(*E*)/(*Z*)	*Base*	*Syn:anti*	*ee* (%)	*Configuration*
1	H	Me		BuLi		38	(2*R*)
2	Me	Me	(*E*)	BuLi	90:10	78[a]	(2*R*)
3	Me	Me	(*E*)	LDA	84:16	64[a]	(2*R*)
4	H	H		KH		84	(2*S*)
5	H	H		BuLi		8	(2*R*)
6	Me	H	(*E*)	KH	41:59	74[a] 0[b],	(2*S*)
7	Me	H	(*E*)	BuLi	89:11	0[a]	
8	H	H		KH–18-crown-6		96	(2*R*)
9	Me	H	(*E*)	KH–18-crown-6	46:54	84[a] 86[b]	(2*R*)[a] (2*R*)[b]
10	Me	H	(*Z*)	KH–18-crown-6	54:46	86[a] 86[b]	(2*R*)[a] (2*R*)[b]

[a]Major isomer. [b]Minor isomer.

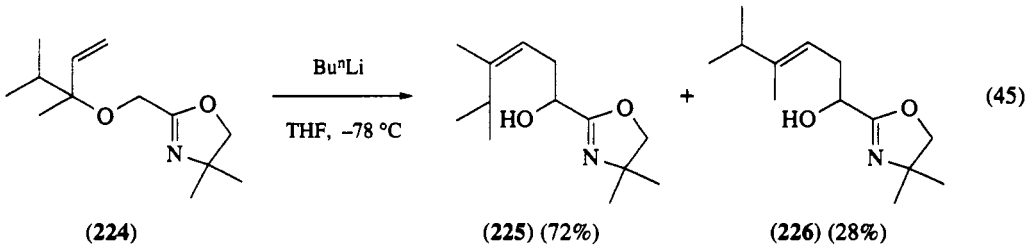
stituent closer to the oxazoline ring. Interactions between the R^1-substituent and the oxazoline ring must also exist to a degree in (**AD**) as evidenced by the lower enantioselectivity of rearrangements in systems lacking this substituent (Table 23, entries 1 *versus* 2). Evidently the methoxymethyl- and hydroxymethyl-substituted oxazoline systems (**221**; R^2 = Me or H) rearrange through different transition states. The potassium counterion plays a major role in the latter cases (Table 23, compare entries 4 and 6 with 5 and 7). The possibility of a preferred (*Z*)-enolate has been suggested to explain the enantioselectivity of rearrangements carried out with KH–18-crown-6 (Table 23, compare entries 4 with 8 and 6 with 9).



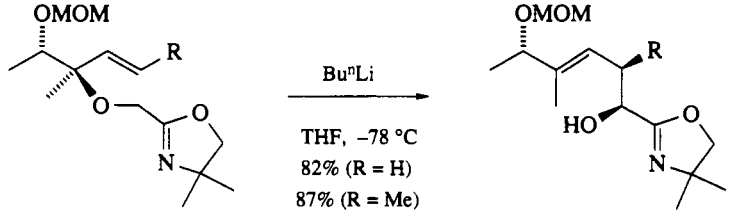
Scheme 19 Transition states for 2,3-rearrangement of oxazoline allyloxy anions

The role of chelation by lithium cations in 2,3-rearrangements of oxazoline allyloxymethyl anions is exemplified by the contrasting behavior of the two tertiary ethers (**224**; equation 45) and (**227**; equation

46).[64] Rearrangement of the former affords a 72:28 mixture of (*Z*)- and (*E*)-products (**225**) and (**226**), whereas the methoxymethoxy analog (**227**) yields the (*E*)-isomer (**229**) as the sole product. The epimeric tertiary allylic methoxymethoxy-substituted ether (**231**; equation 47), on the other hand, gives rise to a 64:36 mixture of rearranged products favoring the (*E*)-isomer (**233**).

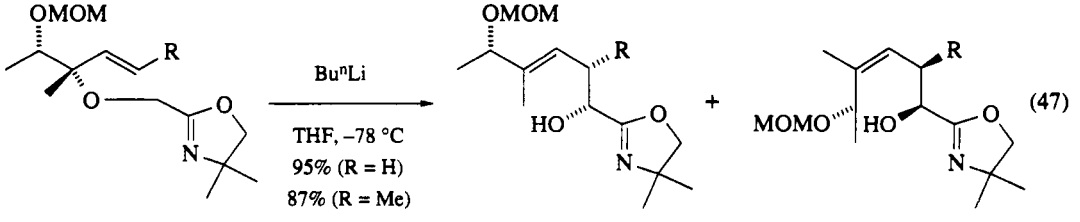


(**224**) (**225**) (72%) + (**226**) (28%) (45)



(**227**) R = H
(**228**) R = Me

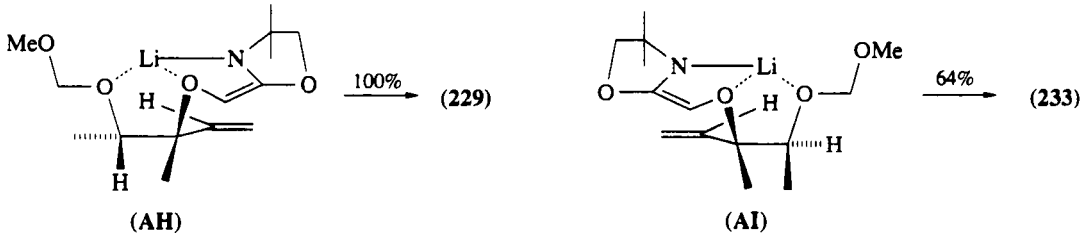
(**229**) R = H (100%)
(**228**) R = Me (98.5%) (46)



(**231**) R = H
(**232**) R = Me

(**233**) R = H (64%)
(**234**) R = Me (69%) + (**235**) R = H (36%)
(**236**) R = Me (31%) (47)

The high (*E*)-preference observed with ether (**227**) can be accounted for by the chelated transition state (**AH**) in which the oxazolidine enamide is held in close proximity to the allylic double bond terminus in the *s-trans* conformation (Scheme 20). The analogous transition state (**AI**) for the epimer (**231**) suffers from an eclipsing interaction between the two adjacent carbinyl methyl groupings. Accordingly, the rearrangement of (**231**) takes place, in part, *via* a nonchelated *s-cis* conformer to give a mixture of (*E*)- and (*Z*)-products. The crotyl ether (**228**) likewise rearranges with high (*E*)-selectivity, whereas the epimeric ether (**232**) gives rise to a mixture of isomers favoring the (*E*)-product (**234**). Selectivity for the cooperative diethers (**227**) and (**228**) decreases dramatically (to 90:10 and 55:45, respectively) in the presence of HMPA, owing to competitive coordination of the lithium cation with this cosolvent.



(**AH**) (**AI**)

Scheme 20 Chelated transition states for 2,3-rearrangement of epimeric tertiary alkoxyallyl oxazolines

Greatly enhanced ratios of the (*E*)/(*Z*)-products (**234**):(**236**) (>99:1) can be realized by using MeMgBr as the base for rearrangement of the uncooperative diether (**232**), but the yield is only 20%. Presumably,

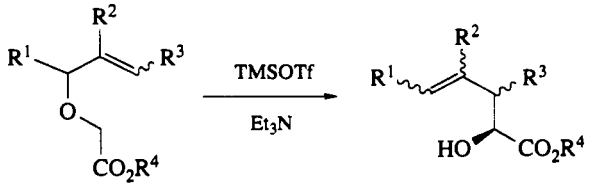
chelation is strong with a Mg counterion, but the anionic character of the resulting enamide is relatively weak.

An application of this chemistry to the synthesis of the nargenicins has recently been reported.[64a]

3.11.3.9 Oxonium Ylide Rearrangements

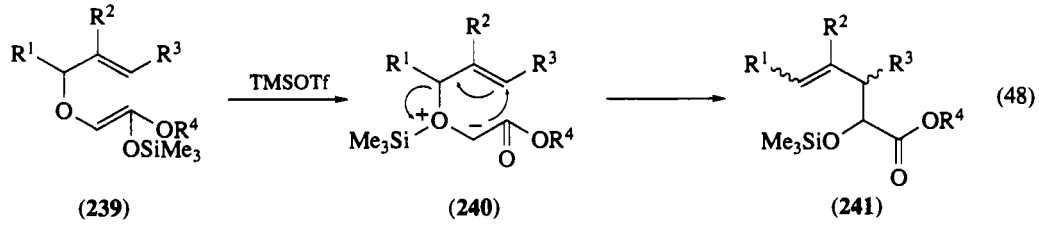
The 2,3-rearrangement of α-allyloxyacetic esters can be effected with TMSOTf and Et_3N (Table 24).[65–71] A pathway involving the trimethylsilyloxonium ylide (**240**; equation 48) has been proposed. Accordingly, treatment of the TMS ketone acetals (**239**; R^1 = Me, $R^2 = R^3$ = H; $R^1 = R^2$ = Me, R^3 = H; $R^1 = R^2$ = H, R^3 = Me) with 20 mol % of TMSOTf yields rearranged products (**241**) in ratios comparable to those obtained directly from the corresponding esters (**237**). The enhanced formation of (*Z*)-products is thought to reflect a preference for the *anti* (**AJ**) *versus syn* (**AK**) R^1/Me_3Si orientation in the oxonium intermediates (Scheme 21).

Table 24 Trimethylsilyl Triflate Promoted 2,3-Rearrangement of α-Allyloxyacetic Esters

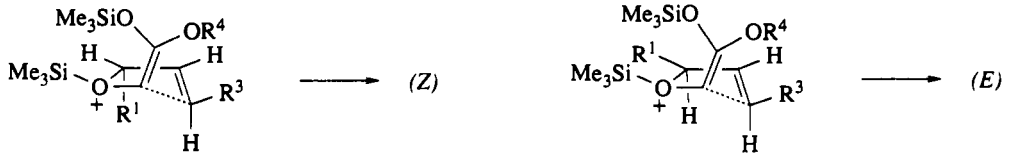


(**237**) (**238**)

R^1	R^2	R^3	R^4	(*E*) or (*Z*)	Yield (%)	(*E*):(*Z*)	Syn:anti
Me	H	H	Me		93	31:69	
Me	H	H	H		85	43:57	
Me	Me	H	Me		98	31:69	
H	H	Me	Me	(*E*)	83		92:8
H	H	Me	H	(*E*)	92		88:12
H	H	Me	Me	(*Z*)	86		53:47
H	H	Me	Pr^i	(*E*)	86		95:5
H	H	Me	Bu^t	(*E*)	56		88:12



(**239**) (**240**) (**241**)



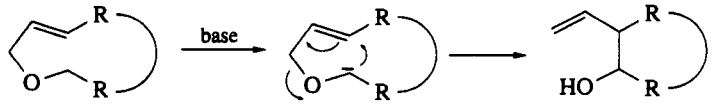
(**AJ**) *anti* (**AK**) *syn*

Scheme 21 Transition state orientations for trimethylsilyloxonium rearrangements

3.11.3.10 Cyclic 2,3-Rearrangement–Ring Contractions

In 1986 the groups of Takahashi[72] and Marshall[73] independently and simultaneously announced a new application of the 2,3-Wittig rearrangement for the construction of medium and large ring carbocycles (Scheme 22). The incorporation of the allylic ether into a cyclic structure (**AL**) ensures favorable

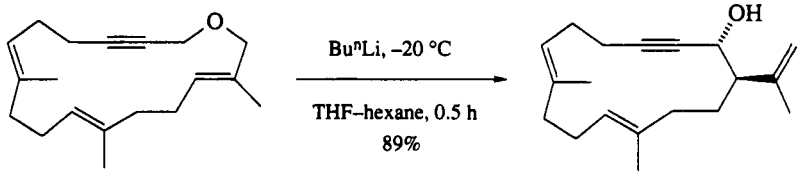
proximity of the reacting centers, as in (**AM**), thereby lowering the activation energy of the rearrangement considerably.



(**AL**) (**AM**) (**AN**)

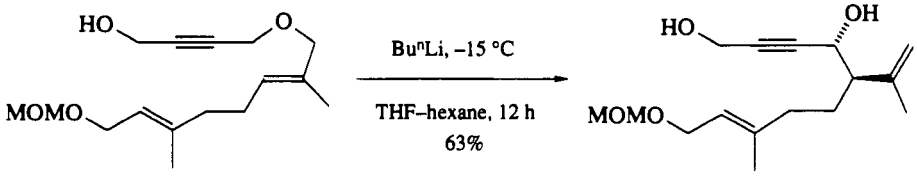
Scheme 22 2,3-Wittig ring contraction

Thus, for example, the cyclic propargylic allylic ether (**242**; equation 49) rearranges completely within 30 min upon treatment with Bu^{n}Li in THF–hexane at –20 °C, whereas the acyclic analog (**244**; equation 50) requires 12 h under comparable conditions. Alcohol (**243**) serves as a useful intermediate for the synthesis of cembranoid diterpenes.[74]



(49)

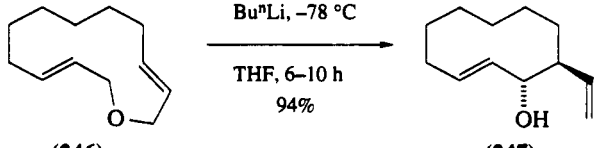
(**242**) (**243**) 80:20 *trans*:*cis*



(50)

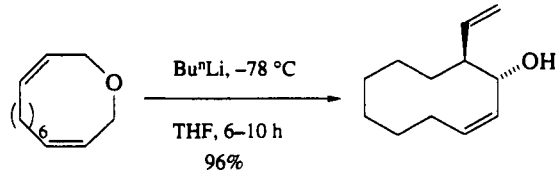
(**244**) (**245**) 67:33 *trans*:*cis*

Takahashi and coworkers studied 2,3-Wittig ring contractions of the isomeric 13-membered diallylic ethers (**246**), (**248**) and (**250**).[72] The (*E*,*E*)-diallylic ether (**246**; equation 51) rearranges to the (*E*)-*trans*-cyclodecenol (**247**). Interestingly, the (*Z*,*Z*)-ether (**248**; equation 52) yields the (*Z*)-*trans*-cyclodecenol (**247**) with the opposite relative stereochemistry from that observed with acyclic (*Z*)-allylic ethers (Table 12). The (*Z*,*E*)-diallylic ether (**250**; equation 53) is converted with high regioselectivity to a 9:91 mixture of (*E*)- and (*Z*)-products (**247**) and (**249**). The latter consists of a 50:41 mixture of *trans* and *cis* isomers. The contrasting diastereoselectivity of acyclic (*E*)-allylic ethers is again noteworthy (Table 12). Evidently, conformational factors in these cyclic diallylic ethers attenuate or override intrinsic transition state preferences of the acyclic analogs (Scheme 9).



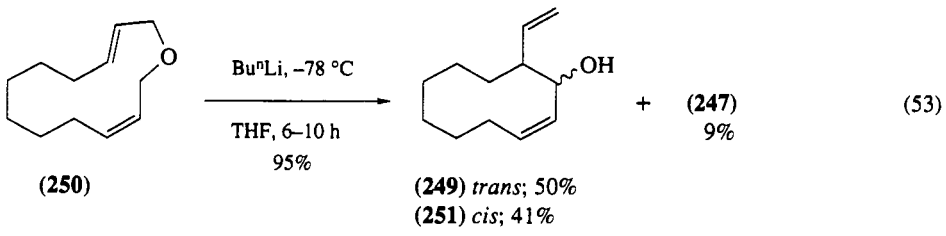
(51)

(**246**) (**247**)

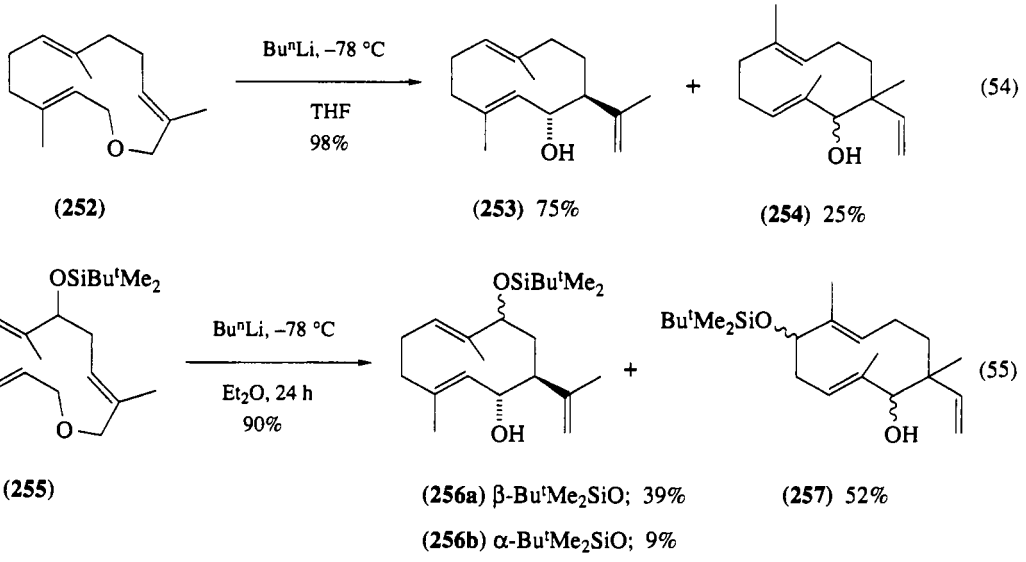


(52)

(**248**) (**249**)



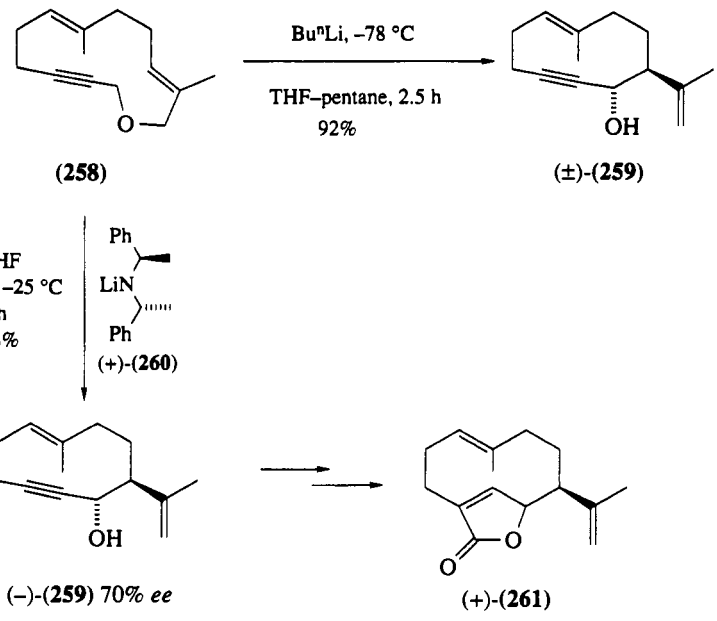
The isoprenoid (*E,E*)-diallylic ether (**252**; equation 54) affords a 75:25 mixture of the regioisomeric products (**253**) and (**254**) in 98% yield. The major isomer (**253**) was employed in a synthesis of racemic costunolide, a medium ring sesquiterpene. In a related application the TBS ether (**255**; equation 55) was converted to a 48:52 mixture of regioisomers (**256**) and (**257**) in 90% yield.[75] The former consists of a 81:19 mixture of diastereoisomers (**256a**) and (**256b**). Alcohol (**256a**) was converted to the sesquiterpene (±)-haagenolide, along lines developed in the costunolide synthesis.[72]



In contrast to the foregoing diallylic examples, the 13-membered allylic propargylic ether (**258**) rearranges to a single regioisomer (**259**).[74] The apparent preference for propargylic anion formation is in accord with analogous acyclic systems. In the first application of nonracemic chiral bases for 2,3-Wittig rearrangements, treatment of the allylic propargylic ether (**258**) with the lithio amide (+)-(**260**), prepared from (*R*)-(+)-1-phenylethylamine, afforded the (–)-alcohol (**259**) in 78% yield and 70% *ee*.[76] The enantiomeric base (–)-(**260**) gave rise to (+)-(**259**) in comparable yield and *ee*. These alcohols were converted to the germacranolide sesquiterpene aristolactone (+)-(**261**) and its enantiomer (Scheme 23). The bases (+)- and (–)-(**260**) also effect 2,3-Wittig rearrangement of the 17-membered allyl propargyl ether (**242**) to the cembranoid precursor (**243**) with an *ee* of 20–30%. The nine-membered diallylic ether (**262**; equation 56) afforded the optically active alcohol isopiperitenol (**263**) of 25% *ee* upon treatment with (–)-(**260**).[77] This rearrangement was considerably slower than those of the 13- and 17-membered ethers (**246**), (**252**), (**258**) and (**242**), indicative of a more highly strained transition state. The preferential formation of the *cis* diastereoisomer from the (*E*)-allylic ether moiety is contrary to results obtained with acyclic (*E*)-allylic ethers (Table 12). It should be noted that the diallylic ether (**262**) is incapable of rearranging to the regioisomeric product derived from α′-deprotonation because of the strain associated with a *trans*-cyclohexene product.

The acyclic ethers (**264a–c**; equation 57) failed to give optically active rearrangement products with the nonracemic amide base (–)-(**260**). Accordingly, the asymmetric induction observed in the rearrangements of ethers (**242**), (**258**) and (**262**) appears to depend upon the chiral environment provided by the cyclic array.

Macrocyclic ethers with remote sp^3 stereocenters can undergo diastereoselective 2,3-Wittig ring contractions. Thus, the alcohol (**266a**; equation 58) and several of its ether derivatives (**266b**) and (**266c**) upon treatment with Bu^{n}Li in pentane–THF–TMEDA afforded the four diastereomeric rearrangement

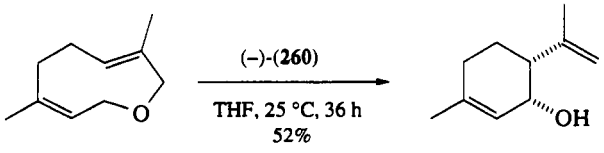


(258) (±)-(259)

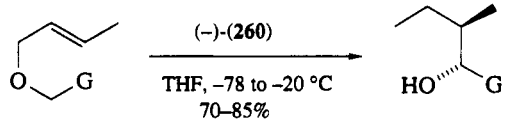
(+)-(260)

(–)-(259) 70% *ee* (+)-(261)

Scheme 23



(262) (263) (56)

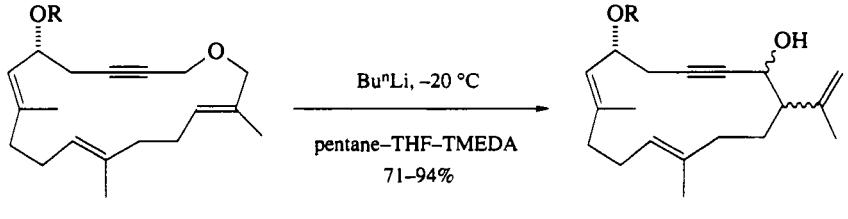


(264a) G = C≡CH (±)-(265) (57)

(264b) G = CO_2H

(264c) G = $CON(CH_2)_4$

products (267)–(270) in varying ratios (Table 25), depending upon the nature of the substituent OR.[78] Presumably, bulkier OR groupings tend to fix the conformation of the macrocyclic ether, thereby enhancing the diastereoselectivity of deprotonation and ensuing 2,3-rearrangement. Because the controlling substituent is well removed from the reaction center, this type of directing effect is referred to as remote



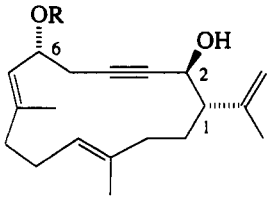
(266a) R = H (267)–(270) (58)

(266b) R = THP

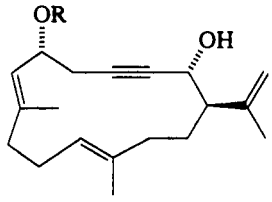
(266c) R = $SiBu^tMe_2$

diastereocontrol. A similar effect may be operational in the rearrangement of the 13-membered ether (**255**), although in this example the substituent is closer to one of the reacting centers and could therefore exert a direct steric effect.

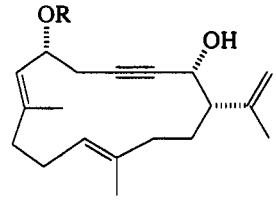
Table 25 Remote Diastereocontrol in Macrocyclic 2,3-Wittig Ring Contraction



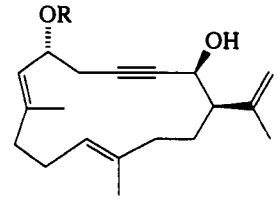
(**267a**) R=H
(**267b**) R=THP
(**267c**) R=TBS



(**268**)



(**269**)

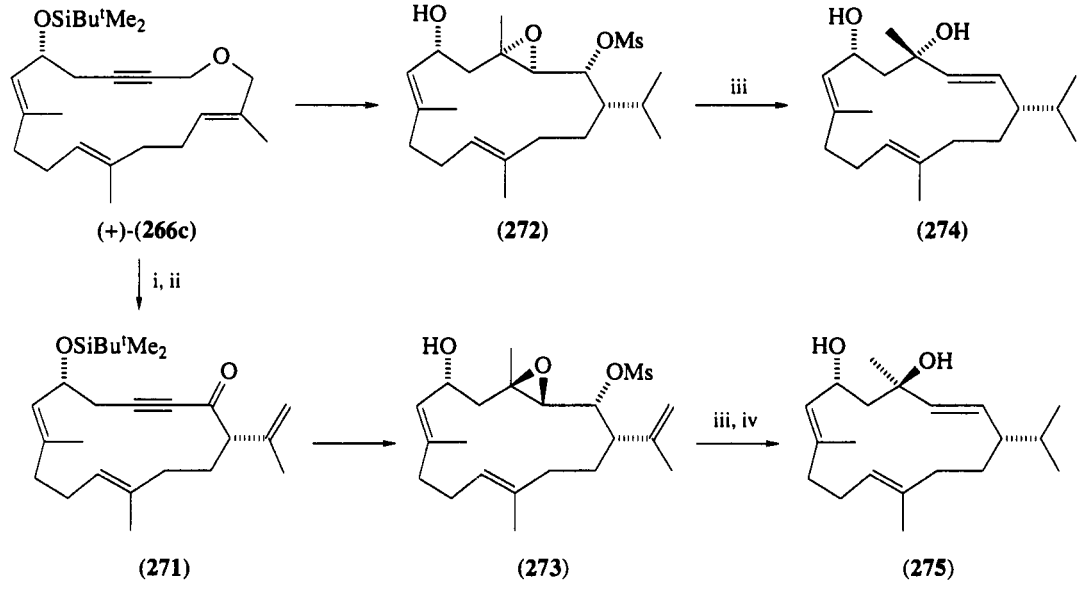


(**270**)

R	*Yield* (%)	(**267**)	(**268**)	(**269**)	(**270**)	*Trans/cis*[a]	*Syn/anti*[b]
H (a series)	71	20	29	39	12	49:51	59:41
THP (b series)	90	81	7	6	6	88:12	87:13
TBS (c series)	94	74	8	14	4	82:18	88:12

[a] C-1/C-2 relationship. [b] C-1/C-6 relationship.

Remote diastereocontrol can be used to effect chirality transfer in these macrocyclic systems. Thus ring contraction of the nonracemic propargyl ether (+)-(**266c**), followed by Swern oxidation, afforded the ketone (**271**) as a 9:1 mixture of *syn* and *anti* isomers in over 70% yield (Scheme 24). Further transformations led to α- and β-CBT (**274**) and (**275**), two tumor inhibitory constituents of tobacco.[79] The former was prepared in nonracemic form starting from (+)-(**266c**) of the indicated (*R*)-configuration.[80] The β-isomer (**275**) was obtained as the racemate starting from racemic (**266c**).



i, Bu^nLi, pentane, −78 °C; ii, $(COCl)_2$, Et_3N, DMSO; iii, Na, NH_3, THF; iv, $(PPh_3)RhCl$, H_2, C_6H_6, EtOH

Scheme 24

3.11.4 REFERENCES

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4.1
Carbonylation and Decarbonylation Reactions

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4.1.1 INTRODUCTION

Fifty years ago the first well-defined carbonylation reaction was discovered by Otto Roelen.[1] Whilst studying the high pressure, cobalt-catalyzed Fisher–Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen, he observed that addition of ethylene to the CO/H_2 feed gas led to formation of 1-propanal in high yield. This reaction, subsequently named hydroformylation, as it results in the addition of hydrogen to one end of the C=C double bond and a formyl group at the other, has been intensively studied over the years[2] and has formed the basis of several industrial processes, for example the synthesis of 1-butanal from propene, and acrylic acid from acetylene. Unfortunately, the reaction generally requires the use of high temperatures (100–300 °C) and pressures (100–1000 bar; 1 bar = 100 kPa), expensive autoclave equipment and the use of large quantities of toxic or unstable catalysts such as $[Ni(CO)_4]$, $[Fe(CO)_5]$ or $[HCo(CO)_4]$.

Subsequently, up until the early 1960s carbonylation chemistry was little considered as a synthetic method for the preparation of fine organic chemicals. In recent years, however, there has been a dramatic

change in this picture, mostly brought about by the discovery of stable but extremely active catalysts based on organophosphine complexes of palladium and rhodium. Many carbonylations can now be carried out below 100 °C at atmospheric pressure, using very small quantities of involatile, air-stable catalyst precursors, such as $[Pd(PPh_3)_2Cl_2]$ or $[RhCl(CO)(PPh_3)_2]$, which are converted to the active catalytic species *in situ*. Moreover, the scope and understanding of carbonylation has grown to such an extent that it can now be regarded, like catalytic hydrogenation, as one of the more generally useful techniques of synthetic organic chemistry, with a well-developed set of guidelines for choice of catalyst and reaction conditions. In most cases the functional group tolerances of catalysts and reaction conditions have been examined and selectivities between different functional groups established, so that reactions using new substrates can be carried out with a degree of confidence impossible a few years ago.

Even after 50 years of continuous development carbonylation chemistry has still not achieved its full potential and new reactions are still being discovered, a good recent example being double carbonylation leading to α-keto carboxylic acids, α-keto esters and α-keto amides.[3]

Whilst a large number of transition metal complexes have been studied for carbonylation reactions, most transformations can be carried out by selection from a relatively small number of accessible metal complexes (Table 1). Wherever possible, reactions described later in this chapter will avoid the use of volatile and toxic metal carbonyls, particularly $[Ni(CO)_4]$, and will concentrate on the use of readily available metal complex catalysts or reagents which can be used in apparatus familiar to the synthetic organic chemist.

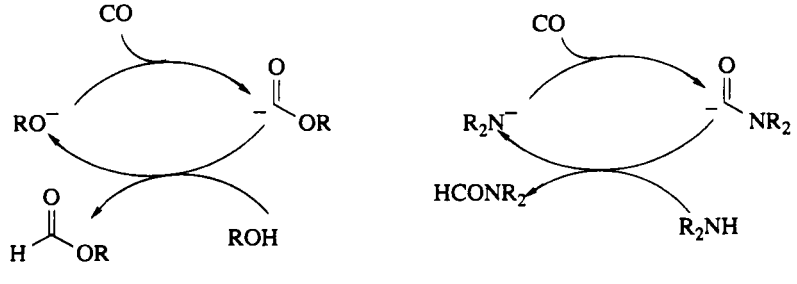
Table 1 Transition Metal Complexes Used in Carbonylation Reactions

From / *To*	*Aryl halide*	*Alkyl, vinyl halide*	*Alkene*	*Alkyne*
Aldehyde	a, b	d, f	d, e, g	—
Ketone	a, b, j	a, f	a, d, g	g
Carboxylic acid	a, h	f, g	g, h	g, h
Ester	a, h	a, f, g	g, h	c, h
Lactone	a, g	a, b, h	c, e	c
Lactam	a, g	a	e	—
Amide	a, g	a, h	—	—

[a] $[Pd(PPh_3)_2Cl_2]$. [b] $[Pd(PPh_3)_4]$. [c] $PdCl_2$. [d] $[PtCl_2(PPh_3)_2]$. [e] $[HRhCO(PPh_3)_3]$. [f] $[Fe(CO)_5]$, $Na_2[Fe(CO)_5]$. [g] $[Co_2(CO)_8]$, $Na[Co(CO)_4]$. [h] $[Ni(CO)_4]$. [j] $[Ni(CO)_2(PPh_3)_2]$.

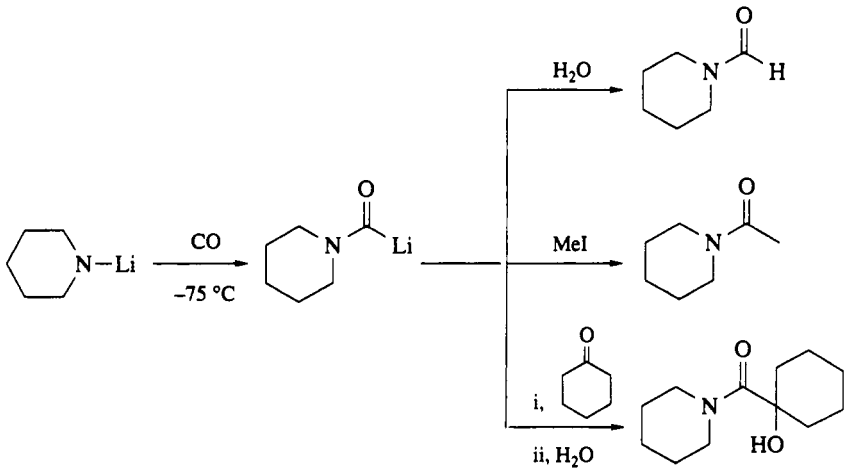
4.1.2 CARBONYLATION MECHANISMS

Despite the presence of a formally divalent carbon atom, CO is not in fact a particularly reactive molecule and much of its chemistry depends on the use of either extreme conditions, energetic reagents or some form of catalysis. Perhaps the simplest examples of such catalysis are found in the reactions of carbon monoxide with protic reagents such as alcohols or secondary amines, affording esters or amides of formic acid. These reactions are catalyzed by alkoxide or amide anions, respectively, and, as shown in Scheme 1, the key step is nucleophilic attack on CO by the catalyst to give a strongly basic alkoxyacyl or aminoacyl anion which is immediately trapped by proton transfer from the alcohol or amine, so generating the catalytic species.



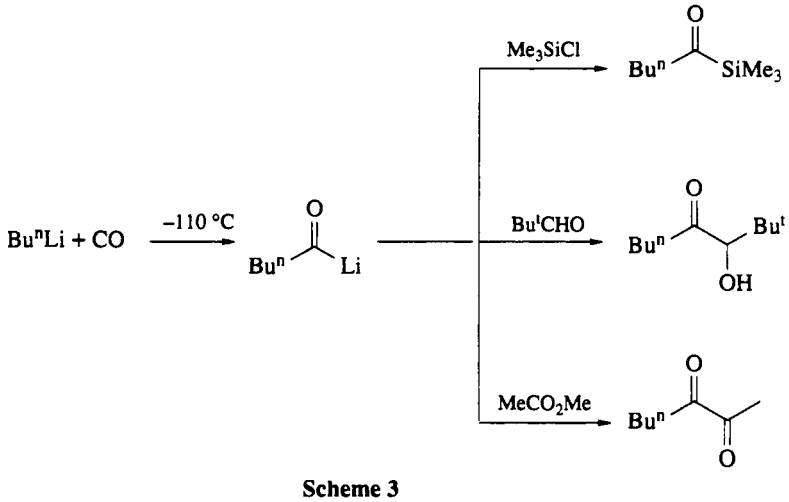
Scheme 1

The aminoacyl anions can also be generated as stoichiometric reagents in the form of lithium derivatives which are stable at –75 °C and react with a variety of electrophiles, including alkyl halides, aldehydes and ketones (Scheme 2).[4]



Scheme 2

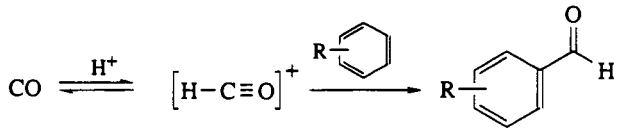
Organolithium reagents, like lithium amides, also react with carbon monoxide at low temperature (–100 °C) *via* a formal nucleophilic attack to give acyllithium species which can be trapped cleanly by reaction with alkyl or silyl halides. Other trapping agents can also be used; aldehydes and ketones afford α-hydroxy ketones, whereas esters give good yields of α-diketones (Scheme 3). In the absence of such trapping agents, however, complex mixtures of products tend to be obtained on hydrolytic work-up, so that although reaction of phenyllithium with CO yields benzophenone as the major product, appreciable quantities of benzoin, benzil, benzpinacol and benzhydrol are also formed.[5]



Scheme 3

Since the highest filled molecular orbital in carbon monoxide is the weakly antibonding carbon-centered 5σ-orbital, it would be reasonable to expect electrophilic reagents to attack CO at carbon and, indeed, powerful electrophiles such as carbenium ions do react to give acylium ions $[R_3CCO]^+$, which can be hydrolyzed to carboxylic acids *in situ* (the Koch reaction).[6] However, carbon monoxide is an extremely weak σ-donor and does not form stable complexes with more conventional Lewis acids such as BF_3 or $AlCl_3$, though there is good evidence for a transient protonated species (solvated $[HCO]^+$) in acid-catalyzed reactions of CO with aromatics (Gatterman–Koch synthesis, Scheme 4).[7]

In contrast, transition metals form a vast array of complexes containing coordinated CO. The effect of the metal coordination is to increase the susceptibility of CO towards nucleophilic attack, either by another ligand or by a noncoordinated nucleophile. A detailed description of the various transition metal catalyzed reactions is not appropriate here, especially as excellent reviews are available.[8] However, it is

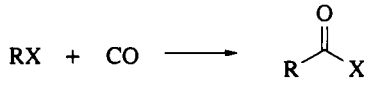


Scheme 4

worthwhile to outline the five major types of carbonylation which will describe nearly all the reactions to be detailed later.

4.1.2.1 Direct Carbonylation

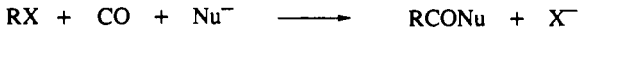
This is the simplest of all carbonylations and is best illustrated by the conversion of iodomethane to acetyl iodide,[9] a reaction crucial to the success of the low pressure Monsanto process for acetic acid production from methanol (equation 1).



(1)

4.1.2.2 Substitutive Carbonylation

Direct carbonylation of an organic halide is a rather rare synthetic process and systems in which halide ion is replaced by a nucleophile (equation 2) are much more frequently encountered. This is a particularly versatile type of reaction providing a wide range of 'acyl anion equivalents', which allow the synthesis of many carboxylic acid derivatives from organic halides. As an example, the elementary steps involved in the palladium-catalyzed carbonylation of a bromoarene are shown in Scheme 5, where oxidative addition is followed by CO insertion and reductive cleavage by whichever nucleophile (Nu = OH, OR, NR_2 or F) is present in the system. Substitutive carbonylation of aliphatic halides is also possible, but generally requires more vigorous conditions and the use of platinum–phosphine complexes, such as $[Pt(PPh_3)_2Cl_2]$.[10]



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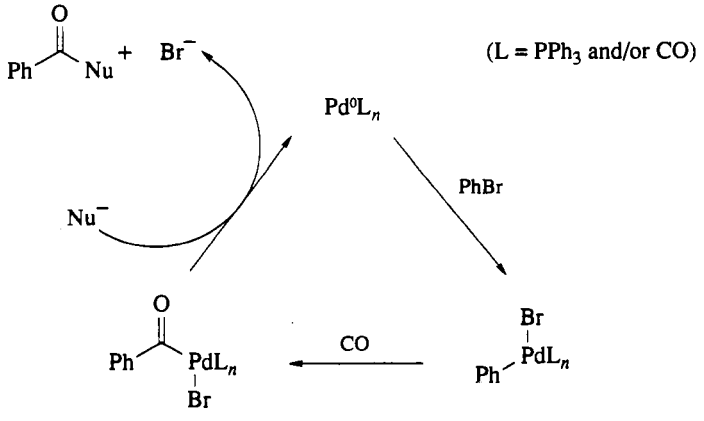
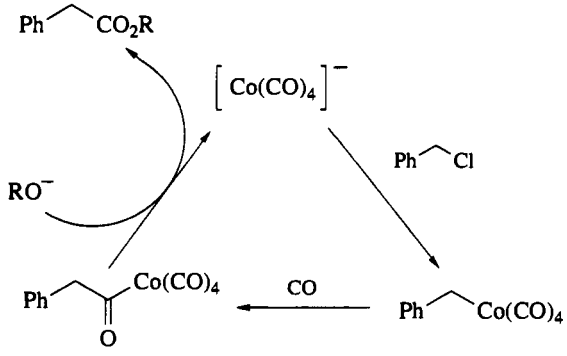


Scheme 5

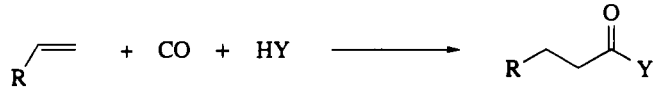
A rather different approach to carbonylation of aliphatic halides involves the carbonyl anion $[Co(CO)_4]^-$ which, being a kinetically stable 18-electron species, attacks the halide by nucleophilic displacement rather than by undergoing oxidative addition. A probable catalytic cycle for cobalt-catalyzed carbonylation of benzyl chloride is shown in Scheme 6.[11]



Scheme 6

4.1.2.3 Additive Carbonylation

As noted in the introduction this class of reaction includes hydroformylation (Y = H; equation 3), the first carbonylation to be discovered. Replacing hydrogen by water or an alcohol yields carboxylic acids (hydrocarboxylation) or esters (hydroesterification), respectively, and although different catalysts may be required the general mechanistic pattern is very similar in all three cases. The reaction is initiated by alkene insertion into a metal–hydride bond and the resulting alkyl ligand migrates to coordinated CO. In cobalt-catalyzed hydroformylation, oxidative addition of hydrogen to the metal is followed by reductive elimination of aldehyde, and the original metal hydride complex is thus regenerated (Scheme 7).



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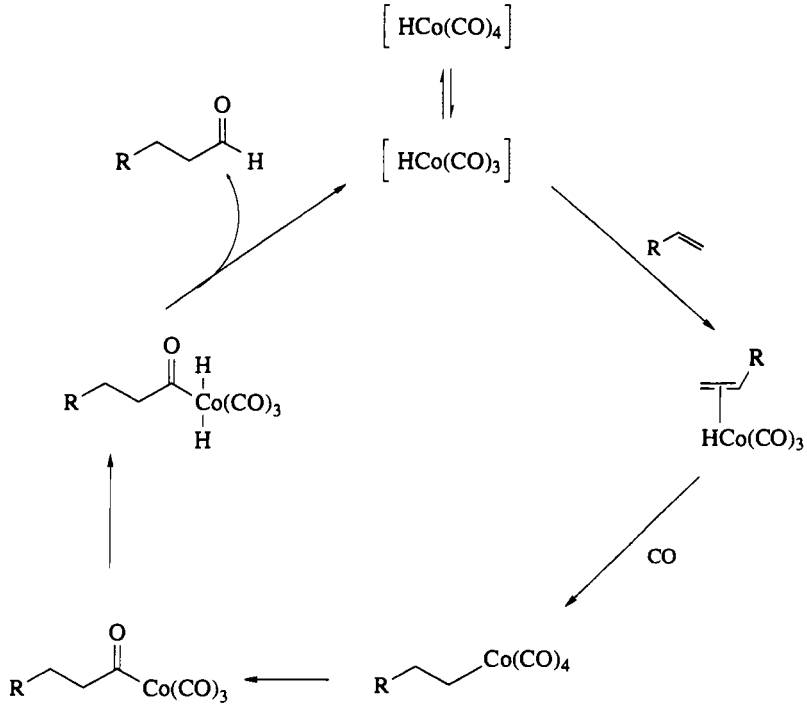
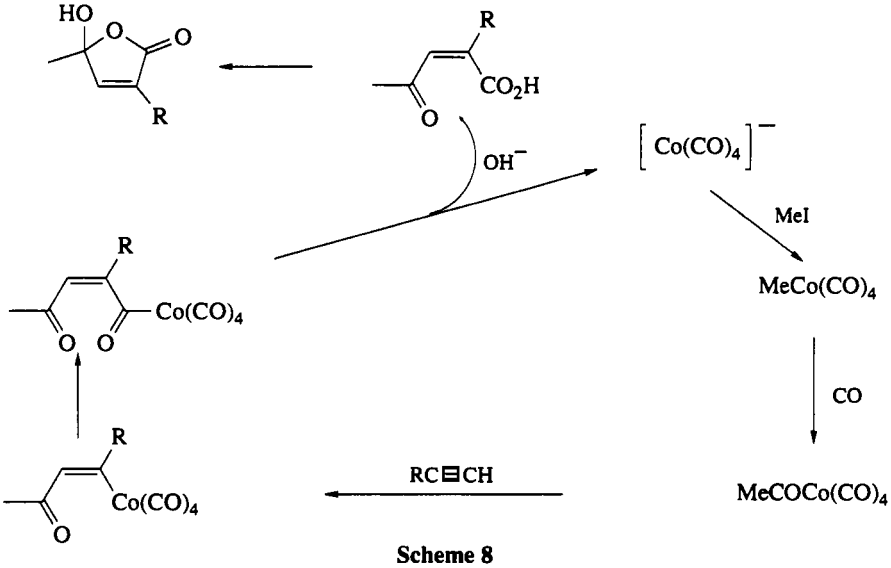


Scheme 7

4.1.2.4 Multicomponent Carbonylations

One of the best illustrations of the ability of homogeneous catalysts to assemble complex organic molecules by sequential insertions is the hydroxybutenolide synthesis shown in Scheme 8, where no fewer than five separate molecules (MeI, HC≡CR, H_2O and 2CO) combine under ambient conditions with high selectivity.[12]

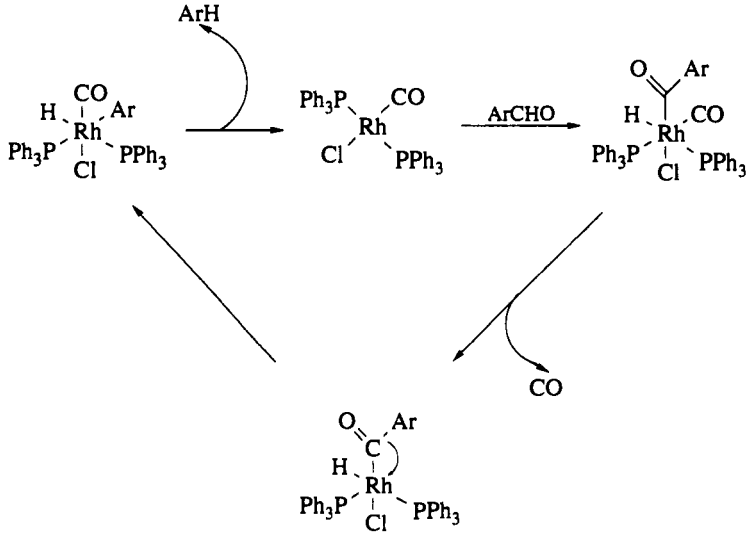


Scheme 8

4.1.2.5 Decarbonylation

Since most of the elementary reactions involved in carbonylation chemistry are readily reversible (equation 4), it is not surprising that metal complexes which catalyze carbonylation also catalyze decarbonylation under certain conditions. The catalytic decarbonylation of aldehydes by $[RhCl(CO)(PPh_3)_2]$, for example, is shown in Scheme 9.

$$RCOX \longrightarrow RX + CO \qquad (4)$$



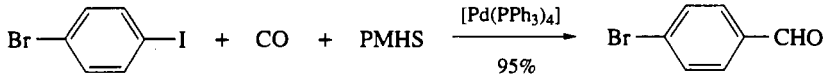
Scheme 9

4.1.3 FORMATION OF ALDEHYDES

The direct catalytic carbonylation of halides to aldehydes is not readily achieved. Aryl, heterocyclic and vinyl halides, for example, in the presence of $[Pd(PPh_3)_2Cl_2]$, a stoichiometric quantity of tertiary amine and synthesis gas (CO/H_2), are converted to aldehydes, but the conditions are somewhat drastic (80–100 bar, 80–150 °C).[13] Alkyl halides are even less suitable for this reaction as they tend to undergo dehydrohalogenation to form alkenes, rather than carbonylation. However, using the platinum catalyst $[PtCl_2(PPh_3)_2]$, primary alkyl iodides can be successfully carbonylated to aldehydes in good yield under moderate conditions (equation 5).[10]

$$RI + CO + H_2 \xrightarrow[K_2CO_3]{[PtCl_2(PPh_3)_2]} R\text{-}C(=O)\text{-}H \qquad (5)$$

Using poly(methylhydrosiloxane) (PMHS) as the hydrogen donor, aryl and benzyl halides can be carbonylated to aldehydes in the presence of $[Pd(PPh_3)_4]$ under mild conditions (3 bar, 80 °C).[14] The reaction only works for iodides; 4-bromophenyl iodide, for example, is converted to 4-bromobenzaldehyde in 95% yield (equation 6).



(6)

A more versatile palladium-catalyzed formylation of organic halides takes place using tributyltin hydride and carbon monoxide (equation 7).[15] The reaction works for a variety of substrates — aryl, benzyl and vinyl iodides, vinyl triflates and allyl halides. Reaction conditions are mild (1–3 bar CO, 50 °C), and a variety of functional groups can be tolerated. With unsymmetrical allyl halides formylation is regioselective, taking place at the less-substituted allylic position with retention of geometry at the allylic double bond.

$$RI + CO + Bu_3SnH \xrightarrow{[Pd(PPh_3)_4]} R\text{-}C(=O)\text{-}H \qquad (7)$$

Carbonylferrate salts, such as $K^+[HFe(CO)_4]^-$, which is readily prepared from $[Fe(CO)_5]$ and ethanolic KOH, react with alkyl bromides or iodides to form alkyliron complexes. Under ambient conditions these complexes undergo insertion of CO and, in the presence of excess CO, aldehyde is eliminated and $[Fe(CO)_5]$ is regenerated (Scheme 10).[16] Unfortunately, the reaction is not catalytic and the hydridocarbonylferrate salt must be prepared in a separate step. Using the commercially available salt $Na_2[Fe(CO)_4]$ a similar reaction takes place, but in this case the intermediate acyl complex is anionic and acid treatment is necessary to liberate the aldehyde (Scheme 11).[17]

$$KHFe(CO)_4 \xrightarrow{RX} R(H)Fe(CO)_4 \xrightarrow{CO} RCOFe(H)(CO)_4 \xrightarrow{CO} RCHO + [Fe(CO)_5]$$

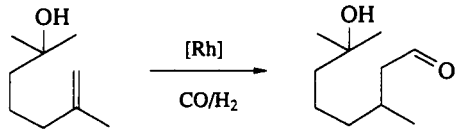
Scheme 10

$$Na_2Fe(CO)_4 \xrightarrow{RX} Na^+[RFe(CO)_4]^- \xrightarrow{CO} [RCOFe(CO)_4] \xrightarrow{H^+} RCHO + [Fe(CO)_5]$$

Scheme 11

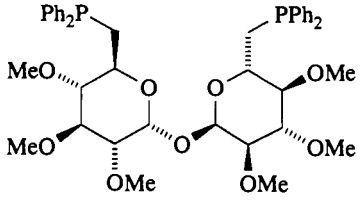
The cobalt-catalyzed reaction of carbon monoxide and hydrogen with an alkene, hydroformylation, is an extremely important industrial process, but it occurs under vigorous conditions (200–400 bar, 150–200 °C) and is not a particularly selective reaction. In the presence of ligand-modified rhodium catalysts, however, hydroformylation can be carried out under extremely mild conditions (1 bar, 25 °C). The catalytic activity of such rhodium complexes is in fact 10^3–10^4 times greater than that of cobalt complexes and side reactions, such as hydrogenation, are significantly reduced. The reactivity of alkenes in hydroformylation follows a similar pattern to that observed in other carbonylation reactions, *i.e.* linear terminal alkenes react more readily than linear internal alkenes, which in turn are more reactive than branched

alkenes. An interesting review describes the application of rhodium-catalyzed hydroformylation to the synthesis of a number of vitamins, terpenes and pharmacologically active compounds.[18] Hydroxycitronnellal (**1**), for example, can be produced by hydroformylation of 2,6-dimethyl-6-hepten-2-ol.



(1)

Rhodium complexes of the ligand α,α-TREDIP (**2**) give very high iso regioselectivity in the hydroformylation of styrene under mild conditions, and this has been extended to the synthesis of 2′-(2-methoxy-6-naphthyl)propanal (**3**), a precursor of the antiinflammatory drug naproxen.[19]



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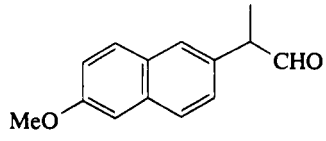
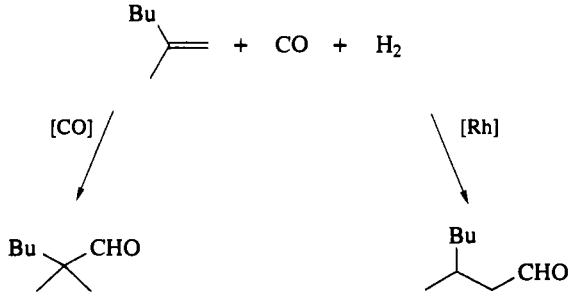


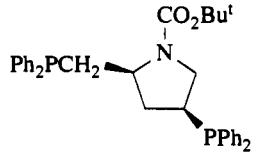
(3)

Using phosphite-modified rhodium catalysts, otherwise unreactive alkenes, such as 2-methyl-1-hexene, limonene and cyclohexene, are hydroformylated under mild conditions.[20] 2-Methyl-1-hexene, for example, yields almost exclusively 3-methylheptaldehyde, which is in contrast to the result of cobalt catalysis where a compound with a quaternary carbon is formed (Scheme 12).



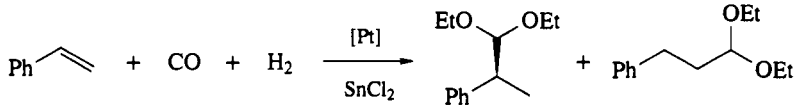
Scheme 12

Optically active aldehydes can be obtained by hydroformylation of prochiral alkenes, but few successful results have been obtained. One major problem appears to be that the product aldehydes are susceptible to racemization and hence the optical yield deteriorates as the reaction proceeds. Most progress has been made with rhodium catalysts, but platinum-catalyzed reactions have also shown promise. Hydroformylation of styrene, for example, using $PtCl_2/SnCl_2$ in the presence of the chiral ligand (–)-BPPM (**4**) and triethyl orthoformate gives the enantiomerically pure acetal of 2-phenylpropanal, together with the acetal of 3-phenylpropanal (equation 8).[21] A number of other chelating biphosphines, for example DIOP



(4)

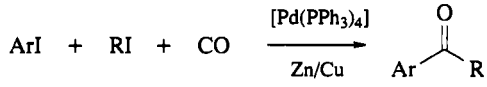
and CHIRAPHOS, have been used with rhodium and platinum systems but generally optical yields do not exceed 50%.[22]



(8)

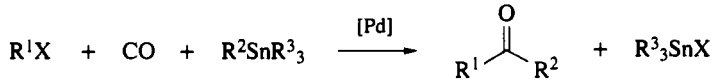
4.1.4 FORMATION OF KETONES

To date, only a limited number of methods for the synthesis of unsymmetrical ketones under carbonylation conditions have been described. Aryl iodides in the presence of stoichiometric amounts of a zinc–copper couple and a catalytic amount of $[Pd(PPh_3)_4]$ react with alkyl iodides in an atmosphere of CO to give unsymmetrical ketones in good yield (equation 9).[23] The reaction works best for aryl halides containing electron-donating substituents and can be applied to either primary or secondary alkyl halides.



(9)

The palladium-catalyzed carbonylative coupling reaction of organic halides with organotin compounds is a potentially useful route to unsymmetrical ketones (equation 10).[24] Diallyl ketones are synthesized by the reaction of allyl chlorides and allyltin reagents in the presence of CO and a palladium catalyst under mild conditions. This reaction has been used for the high yield synthesis of egomaketone from prenyl chloride and 3-furanyltrimethyltin (equation 11).[24] Vinyl iodides and vinyl triflates also react with vinyl-, alkenyl-, alkynyl- and phenyl-tin compounds in the presence of CO and a palladium catalyst to yield the corresponding ketone (equation 12).[24] The reaction tolerates carbonyl groups in both reagents as well as alkynic groups in the tin reagents. The (*E*)-configurations of the double bonds in the vinyl iodide and the stannate are retained in the product. The (*Z*)-configuration of the double bond in the stannate, however, is lost under the usual reaction conditions and the (*E*)-isomer of the product predominates. With vinyl triflates the presence of lithium chloride is essential to ensure that the reaction proceeds smoothly. This palladium-catalyzed coupling reaction of triflates with organostannates has been extended to aryl triflates,



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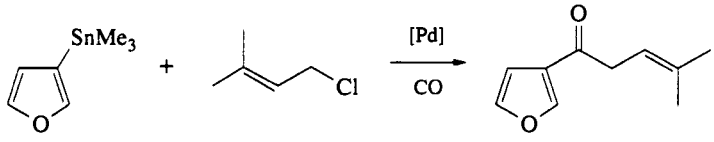

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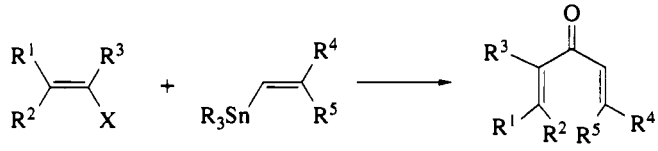
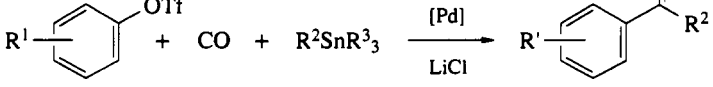


(12)

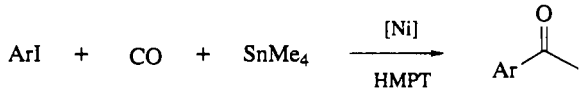
X = I, OTf



(13)

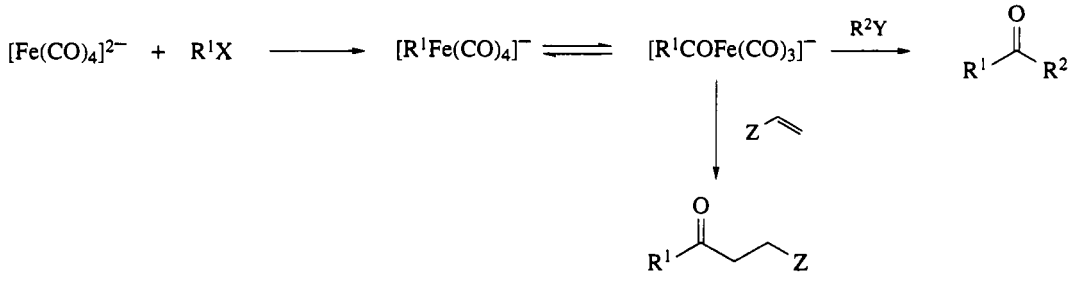
which react under mild conditions to give good yields of aryl ketones (equation 13).[25] The coupling takes place in the presence of functional groups such as alcohol, aldehyde and ester in the coupling reagents.

Methyl aryl ketones can be synthesized *via* carbonylation of aryl iodides and tetramethyltin in the presence of a nickel catalyst (equation 14).[26] Unfortunately the reaction cannot be extended to the synthesis of unsymmetrical diaryl ketones since tetraphenyltin does not react under these conditions.



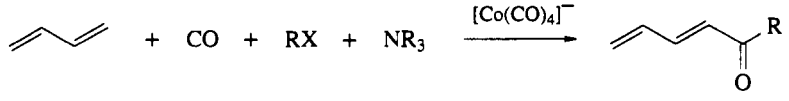
(14)

Reaction of alkyl halides or tosylates with the commercially available $Na_2[Fe(CO)_4]$ gives anionic alkyliron complexes, $[RFe(CO)_4]^-$, which can then react further with alkylating agents to give ketones in good yield (Scheme 13).[27] Whereas primary bromides, iodides and tosylates or secondary tosylates can be used in the first alkylation, only more reactive alkylating agents such as benzyl halides or primary iodides can be used in the second stage. Activated alkenes such as acrylonitrile or ethyl acrylate can also be used in the second step.[28]



Scheme 13

Acyl dienes can be prepared in good yield by reaction of alkyl or acyl halides with conjugated dienes and CO in the presence of catalytic quantities of $[Co(CO)_4]^-$ and a stoichiometric quantity of base (equation 15). By using a phase transfer method increased yields can be obtained under milder conditions (1 bar, 25 °C).[29] The reaction is highly stereo- and regio-specific since the acyl group is normally added to the least-substituted carbon atom of the least-substituted double bond, with exclusive formation of the *trans*-acyldiene. The (acyl-π-allyl)cobalt complex (**5**), an intermediate in this reaction, can also be reacted with stabilized carbanions resulting in alkylation of the unsubstituted π-allyl terminus to give the product (**6**).[30] In all cases studied the alkylation only took place at the unsubstituted π-allyl terminus.



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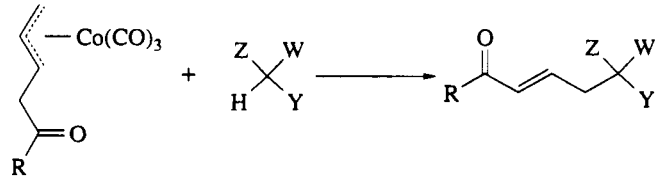
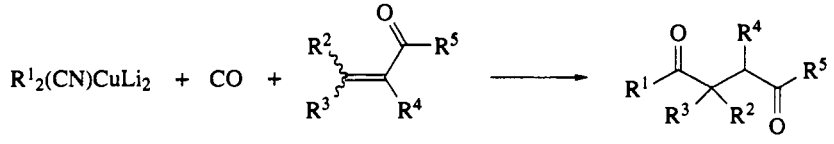


(**5**) Y, W = CO_2Me, COMe; Z = H, Me (**6**)

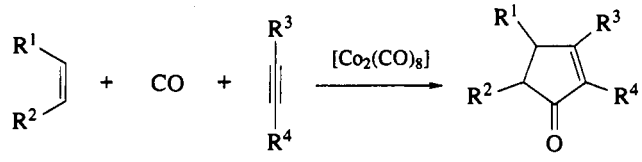
Carbonylation of the cuprate reagent, $R_2(CN)CuLi_2$, prepared from copper(I) cyanide and an alkyllithium, gives a product which can be used for the direct nucleophilic 1,4-acylation of α,β-unsaturated aldehydes and ketones (equation 16).[31] The reaction works particularly well with cyclic α,β-unsaturated ketones to give high yields of the expected 1,4-diketone.

A particularly useful synthesis of cyclopentanones involves the coupling of an alkene, an alkyne and carbon monoxide in the presence of dicobalt octacarbonyl (equation 17). The reaction proceeds *via* an alkyne–cobalt complex (**7**) and with relatively unreactive alkenes such as cyclopentene it is preferable to synthesize the complex in a separate step.[32] With highly strained alkenes such as norbornadiene, how-



(16)

ever, only catalytic quantities of $[Co_2(CO)_8]$ are required. Very volatile or gaseous alkenes require the use of an autoclave, but since the reaction proceeds at 1 bar pressure of CO/acetylene less volatile alkenes may be used in hydrocarbon solvents. Fused ring systems are equally readily synthesized by this route and the reaction has been extended to the synthesis of a number of natural products and oxygen heterocycles.[33] 3-Oxabicyclo[3.3.0]octa-6-en-7-ones, for example, are synthesized in moderate yields by intramolecular cyclization of the cobalt complexes of substituted allyl propargyl ethers (equation 18).[33a]



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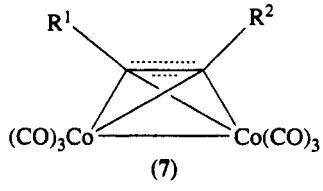

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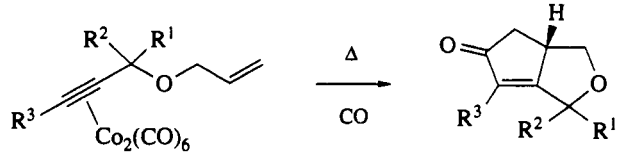
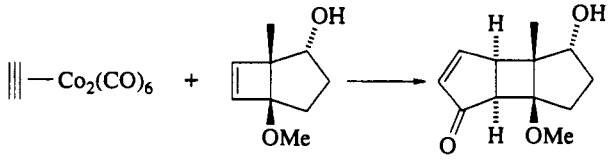


(18)

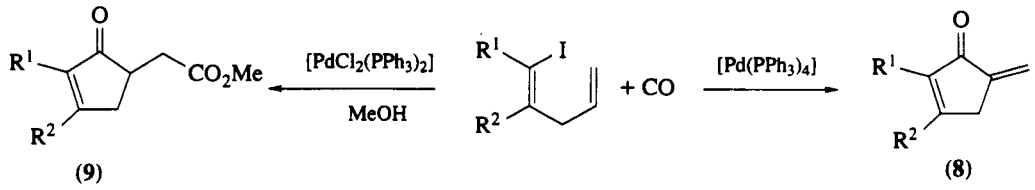
One major problem associated with this type of reaction is the formation of regioisomeric cyclopentenones when unsymmetrically substituted alkenes are used, although unsymmetrically substituted alkynes prefer an orientation which places the larger substituent in the α-position of the cyclopentenone.[33c] Several examples have been published which show that steric interactions can bias the regiochemical outcome of the intermolecular cycloaddition. Substituents in the allylic position, for example, exert a modest to excellent degree of regiocontrol (equation 19).[34] In this case the larger of the two ring fusion substituents becomes β to the new enone carbonyl.



(19)

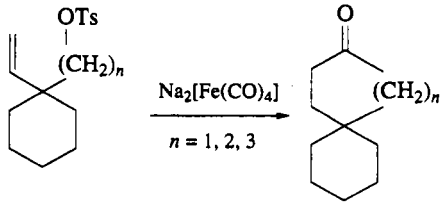
1-Iodo-1,4-dienes undergo carbonylation in the presence of stoichiometric amounts of $[Pd(PPh_3)_4]$ to give α-methylenecyclopentenones (**8**).[35] By varying the conditions the reaction can be made catalytic in palladium, but the reaction has to be performed in methanol and the product in this case is the methyl ester (**9**). The reaction is also applicable to the formation of cyclohexenones and spiro compounds, with good yields being obtained in all cases.

Alkenic tosylates undergo cyclization with concomitant carbonylation when treated with $Na_2[Fe(CO)_4]$ (equation 20).[36] The reaction is particularly effective for the synthesis of five- and six-membered rings but seven-membered rings can also be prepared, although in the latter case the reaction is not regiospecific and a mixture of products is obtained. The reaction appears to be limited to monosub-



(9) (8)

stituted alkenes since addition of a second substituent on either carbon of the double bond prevents cyclization.



(20)

4.1.5 FORMATION OF CARBOXYLIC ACIDS

Early work on the conversion of aryl halides to carboxylic acids was mostly concerned with the use of nickel tetracarbonyl, and although the reaction proceeds under mild conditions more effective and less hazardous syntheses can be achieved using palladium catalysts. In particular, aryl, benzyl, vinyl and heterocyclic halides can be converted to carboxylic acids under mild conditions in two-phase systems.[37] The carbonylation reaction is carried out by addition of the organic halide, triphenylphosphine, $[PdCl_2(NCPh)_2]$ and a phase transfer catalyst, such as $Bu^n_4N^+I^-$, to a two-phase system consisting of *p*-xylene and 50% aqueous sodium hydroxide, followed by stirring for several hours under CO at a pressure of 1–10 bar. A great advantage of this system is that continuous extraction of the product acid into the aqueous phase leaves the catalyst and any residual starting material in the organic layer, allowing easy product separation and effectively making heterogeneous the homogeneous catalyst. This procedure also allows selective monocarbonylation of polyhalogenated aromatic substrates such as 1,4-dibromobenzene, since transformation of the first C—X group to carboxy enables the product to be rapidly removed from the organic to the aqueous phase where it is no longer in contact with the catalyst.

A related biphasic synthesis uses $[Co(CO)_4]^-$ as the catalyst, but in this case the reaction is limited to substrates such as benzyl and naphthylmethyl halides which are susceptible to attack by the metal carbonyl anion.[38]

Iron pentacarbonyl is also an effective catalyst precursor allowing high yield carbonylation of alkyl and aralkyl halides under relatively mild biphasic conditions (equation 21).[39] This represents a very interesting and useful development of the earlier procedure which used stoichiometric quantities of the preformed reagent $Na_2[Fe(CO)_4]$. The reaction works equally well for bromides and chlorides.

$$RX + CO \xrightarrow[\text{base}]{[Fe(CO)_5]} RCO_2H \qquad (21)$$

Under conditions of photostimulation $[Co_2(CO)_8]$ in aqueous alkali will catalyze carbonylation of aryl and vinyl halides, including the normally less reactive aryl chlorides, at low pressures and with high efficiency. The active catalyst under these conditions is $[Co(CO)_4]^-$ and this can be generated *in situ* from simple cobalt salts such as $CoCl_2{\cdot}6H_2O$, thus avoiding any need to handle the highly air sensitive $[Co_2(CO)_8]$ or its derived anion (equation 22).[40]

$$ArX + CO + NaOH \xrightarrow[h\nu]{CoCl_2} ArCO_2Na \qquad (22)$$

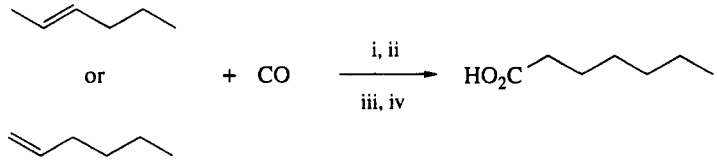
Arenediazonium salts react stoichiometrically with nickel and iron carbonyls to give aromatic carboxylic acids in moderate yield, but a more reliable procedure involves direct, catalytic carbonylation in the presence of palladium acetate.[41] The reaction proceeds at room temperature under CO pressure (9 bar)

and gives a mixed anhydride as the initial product. Hydrolytic work-up produces the aromatic acid in 50–90% yield (Scheme 14).

$$ArN_2^+ + CO + MeCO_2K \xrightarrow{Pd(OAc)_2} ArCO_2COMe \longrightarrow ArCO_2H + MeCO_2H$$

Scheme 14

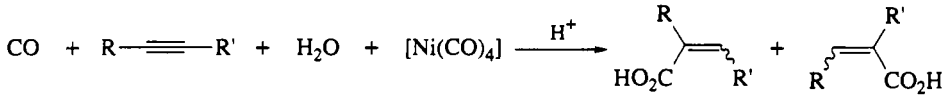
Addition of carbon monoxide and water to an alkene, *i.e.* hydrocarboxylation, is catalyzed by a variety of transition metal complexes, including $[Ni(CO)_4]$, $[Co_2(CO)_8]$ and $[H_2PtCl_6]$. Unfortunately this reaction usually leads to mixtures of products due to both metal-catalyzed alkene isomerization and the occurrence of both Markownikov and anti-Markownikov addition of the metal hydride intermediate to the alkene. The commercially available zirconium hydride $[(C_5H_5)_2Zr(H)Cl]$ can be used as a stoichiometric reagent for conversion of alkenes to carboxylic acids under mild conditions (equation 23).[42] In this case the reaction with linear alkenes gives exclusively terminal alkyl complexes even if the alkene double bond is internal. Insertion of CO followed by oxidative hydrolysis then leads to linear carboxylic acids in very good yield.



(23)

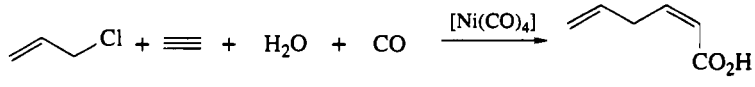
i, Cp_2ZrHCl; ii, CO; iii, NaOH; iv, H_2O_2

Alkynes react readily with stoichiometric quantities of $[Ni(CO)_4]$ under essentially ambient conditions to give, in the presence of aqueous acid, good yields of *cis*-α,β-unsaturated carboxylic acids (equation 24).[2] With monosubstituted alkynes the reaction rate decreases with increasing size of the substituent group and with alkyl substituents the branched product isomer usually predominates.



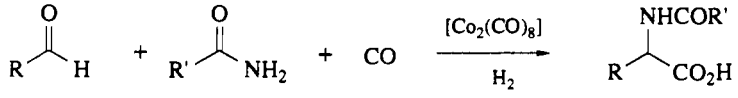
(24)

The nickel-catalyzed carbonylation of allyl halides in the presence of alkynes and water produces 2,5-dienoic acids in good yields under very mild conditions (equation 25).[43] This remarkable four-component reaction probably involves oxidative addition of the allyl chloride to the catalyst, followed by successive insertions of alkyne and CO, and finally hydrolysis. The carbon–carbon double bond derived from alkyne insertion is thus conjugated with the carbonyl group and generally has the (*Z*)-configuration.



(25)

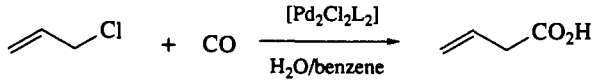
An interesting reaction discovered by Wakamatsu involves the cobalt-catalyzed carbonylation of aldehydes in the presence of primary amides to give *N*-acylamino acids in high yield (equation 26).[44] By combining this reaction with known catalytic routes to aldehydes, for example isomerization of allyl alcohols or hydroformylation of alkenes, it is possible to achieve the direct synthesis of *N*-acylamino acids from precursors other than aldehydes.[45]



(26)

By using a two-phase benzene/aqueous sodium hydroxide medium and a palladium catalyst, allyl chlorides can be converted into 3-butenoic acids in high yield at atmospheric pressure and room temperature (equation 27).[46] The reaction appears to go equally well using either water soluble or water insoluble

catalysts, but in the latter case some α,β-unsaturated acid is also produced. In the absence of a two-phase system the reaction requires high pressures of CO.



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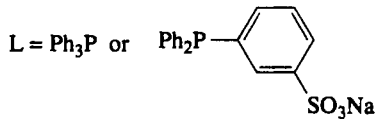
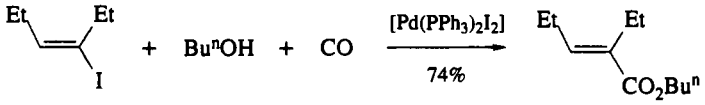


4.1.6 FORMATION OF ESTERS

Nickel tetracarbonyl is an efficient catalyst for the carboalkoxylation of aryl or vinyl halides, but a much better and safer route is *via* palladium-catalyzed synthesis. Bromides and iodides in the presence of 1–2 mol % $[Pd(PPh_3)_2Cl_2]$, the reactant alcohol as solvent and a tertiary amine as acid acceptor react at 60–100 °C and atmospheric pressure to produce the corresponding ester in good yield (equation 28).[47] With iodo compounds even palladium acetate, without any added phosphine, may be used as catalyst. The reaction is unaffected by the presence of a variety of functional groups (ester, ether, nitrile), and strong electron-donating or -withdrawing substituents do not affect the yield of aromatic esters to any significant extent. A more recent application of this reaction indicates that by conducting the reaction in benzyl alcohol aryl iodides are readily converted to the benzyl ester, which can then be easily cleaved to the acid by catalytic hydrogenation.[48]

$$RX + CO + R'OH \xrightarrow{[Pd]} RCO_2R' + HX \qquad (28)$$

At 60–80 °C vinyl halides can be carbonylated with almost complete retention of stereochemistry. For example, carbonylation of (*E*)-3-iodo-3-hexene in *n*-butanol gives 74% of the corresponding (*E*)-carbobutoxylated product (**10**), with only 6% of the (*Z*)-isomer.[47]



(10)

Iodoalkanes tend to undergo dehydrohalogenation rather than carbonylation, but more recently it has been shown that primary, secondary and even tertiary alkyl halides can be efficiently carbonylated to esters in the presence of platinum catalysts, under mild conditions, if the reaction takes place under UV irradiation (equation 29).[49] Alkyl bromides and chlorides are not carbonylated under these conditions and in the presence of visible light irradiation the reaction is very slow. Other transition metal carbonyls, such as $[Co_2(CO)_8]$, $[Ru_3(CO)_{12}]$, $[Os_3(CO)_{12}]$, $[Mn_2(CO)_{10}]$ and $[Re_2(CO)_{10}]$, also catalyze the reaction.

$$RI + R'OH + CO \xrightarrow[h\nu]{[Pt(CO)_2(PR_3)_2]} RCO_2R' \qquad (29)$$

Benzyl halides can be catalytically carbonylated to esters in the presence of $[Rh_2(CO)_4Cl_2]$[50] and $[Ni(PPh_3)_2(CO)_2]$.[47] Esters can also be obtained from alkyl and benzyl halides using stoichiometric quantities of $Na_2[Fe(CO)_4]$ (Scheme 15).[51] Although aryl halides do not react with this reagent, initial

$$RX + Na_2[Fe(CO)_4] \longrightarrow Na^+[RFe(CO)_4]^- \xrightarrow{I_2} RCOI \xrightarrow{R'OH} RCO_2R'$$

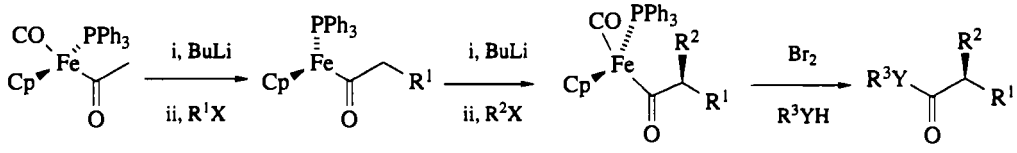
Scheme 15

preparation of a Grignard reagent, followed by reaction with $[Fe(CO)_5]$, produces an acyliron intermediate which on subsequent treatment with alcoholic halogen yields the ester (Scheme 16).[52]

$$ArX + Mg \longrightarrow ArMgX \xrightarrow{Fe(CO)_5} ArCOFe(CO)_4 \xrightarrow[ROH]{I_2} ArCO_2R$$

Scheme 16

Alkyliron complexes, $[(C_5H_5)Fe(CO)_2R]$, undergo carbonyl insertion on treatment with donor ligands, such as triphenylphosphine, to give iron acyls which are configurationally asymmetric. When resolved into their isomers such complexes allow extensive elaboration of the acyl ligand with essentially complete control of the stereochemistry at any new chiral center which may be formed (Scheme 17).[53] Moreover, chirality is almost invariably retained when the organic product (ester, acid or amide) is liberated by oxidative cleavage of the iron–acyl bond. Both enantiomers of the acetyl complex $[(C_5H_5)Fe(PPh_3)(CO)(COMe)]$ are now commercially available.



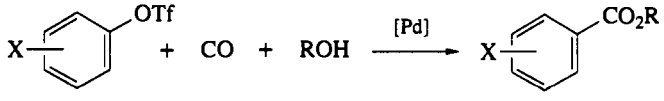
Cp = C_5H_5; Y = N, O

Scheme 17

Organohalides, such as iodoalkanes, alkyl chloroacetates and benzyl halides, which are highly susceptible to nucleophilic attack, are readily converted to esters by reaction with carbon monoxide and an alcohol in the presence of a base using $Na[Co(CO)_4]$ as catalyst (equation 30).[54] Reactions proceed under mild conditions (25 °C, 1 bar CO) and very good yields and selectivities can be obtained. With less reactive halides, however, higher temperatures are required leading to isomerization of the intermediate alkylcobalt complex and hence to a mixture of carbonylated products.

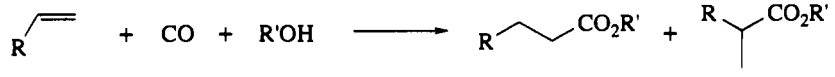
$$RX + CO + R'OH \xrightarrow{Na[Co(CO)_4]} RCO_2R' + HX \qquad (30)$$

By careful selection of the palladium catalyst, aryl trifluoromethanesulfonates can be converted directly to benzoate esters under mild conditions (70 °C, 1 bar CO; equation 31).[55] The best catalyst appears to be $Pd(OAc)_2$–1,3-bis(diphenylphosphino)propane and the best solvent DMF. With aromatic compounds bearing electron-withdrawing substituents carbonylations can be carried out under even milder conditions.



(31)

The synthesis of an ester by addition of carbon monoxide and an alcohol to an alkene, *i.e.* hydroesterification, has a fairly obvious relationship to the hydrocarboxylation described in Section 4.1.5, where water replaces the alcohol and a carboxylic acid is formed. Not surprisingly, therefore, the same types of catalysts, $[Co_2(CO)_8]$, $[H_2PtCl_6]$ and $[Pd(PPh_3)_2Cl_2]$, are effective for both reactions. Unfortunately, the reaction usually requires very high pressures (200 bar) and necessitates the use of an autoclave. By varying the catalyst and reaction conditions a variety of linear, branched and cyclic alkenes can be carbonylated under these conditions to give the product in good yield (equation 32).[56] Improved selectivity to the linear ester can be obtained by addition of $SnCl_2$ to the catalyst system.

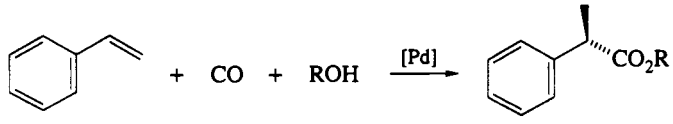


(32)

Stoichiometric hydroesterification can be carried out using the zirconium complex $[(C_5H_5)_2Zr(H)Cl]$, as described in Section 4.1.5 in the context of carboxylic acid synthesis, and, apart from the use of alcoholic rather than aqueous bromine in the final cleavage reaction, the same procedure is applicable (equation 33).[42]

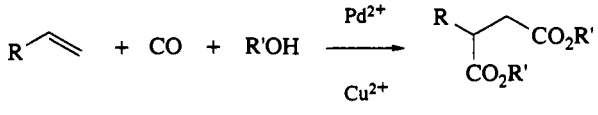
$$(C_5H_5)Zr(R)Cl \xrightarrow[\text{iii, R'OH}]{\text{i, CO}\\ \text{ii, } Br_2} RCO_2R' \qquad (33)$$

Palladium-catalyzed hydroesterification of styrene gives predominantly the branched ester, in which a new chiral center has been created at the 2-position (equation 34). Carrying out this reaction at low pressure (1–2 bar) in the presence of the bulky chiral phosphine neomenthyldiphenylphosphine and trifluoroacetic acid leads to significant asymmetric induction (50% *ee*);[57] this work seems to represent the only significant advance towards stereocontrol of catalytic hydroesterification reactions.



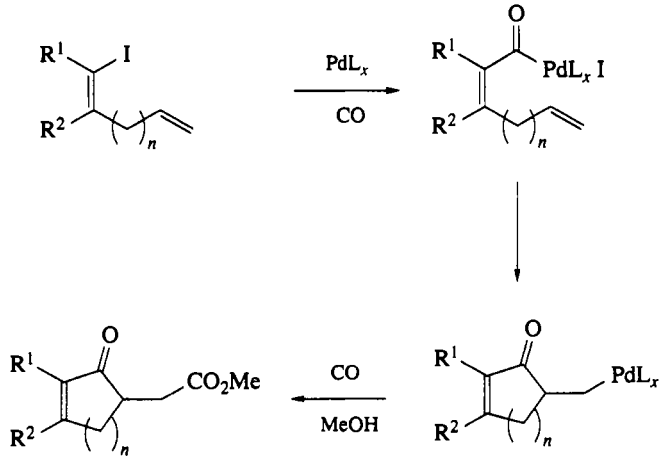
(34)

Palladium salts can bring about oxidative carbonylation of alkenes in the presence of copper(II) salts which can reoxidize Pd^0 to Pd^{II}. Oxidative carbonylation is favored over simple hydroesterification by the presence of bases and by low temperatures (25 °C) and low pressures (3–15 bar). The products can be α,β-unsaturated esters, dicarboxylic acid esters or β-alkoxy esters. By careful optimization of the conditions (25 °C, 4 bar CO, methanol solvent, $CuCl_2$ reoxidant and sodium butyrate buffer) high yields of diesters can be obtained (equation 35).[58]



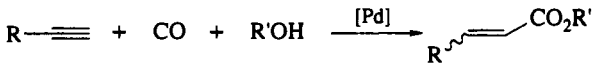
(35)

The carbonylation of 1-iodo-1,4-dienes in the presence of homogeneous palladium catalysts provides a good example of the ability of such catalysts to promote a complex sequence of metal-centered reactions yielding a single product with a high degree of specificity. Two carbonylation steps are involved, the first leading to formation of a cyclic ketoalkyl ligand and the second to the introduction of an ester function and release of the product from the metal (Scheme 18).[35]



Scheme 18

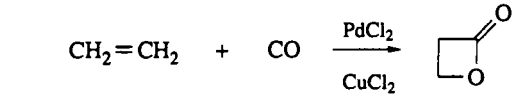
Alkynes undergo simple hydroesterification under mild conditions to give α,β-unsaturated esters. Addition of the ester function to terminal alkynes frequently occurs at the substituted carbon atom to give branched products, but linear esters may be obtained with high selectivity using palladium–tin catalysts (equation 36).[59] Under oxidative carbonylation conditions *cis*-diesters are formed.[60]



(36)

4.1.7 FORMATION OF LACTONES

β-Lactones can be obtained by oxidative carbonylation of alkenes in the presence of water. Ethylene, for example, is converted to β-propiolactone by carbonylation in aqueous acetonitrile at –20 °C using a catalytic amount of $PdCl_2$ and a stoichiometric quantity of copper(II) chloride (equation 37).[61] Palladium-catalyzed carbonylation of halides can also be used to prepare β-lactones under mild conditions. The reaction takes place at room temperature and pressure in the presence of $[PdCl_2(PPh_3)_2]$ and has been applied to both bromides and chlorides (equations 38 and 39).



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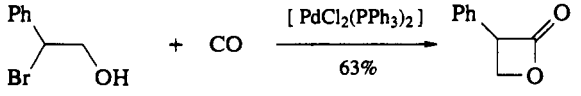

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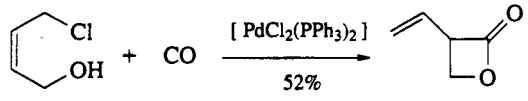
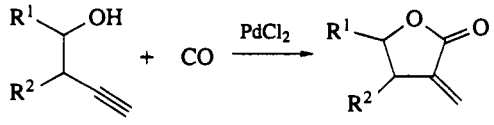
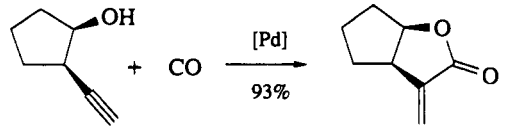


(39)

In recent years, one of the most useful and best-studied areas of transition metal mediated carbonylation reactions is the formation of γ-lactones. Carbonylation of ethynyl alcohols is a very attractive route to α-methylene-γ-lactones. Earlier methods used nickel carbonyl but a more recent method uses a palladium/thiourea catalyst (equation 40).[63] A further improvement in the catalytic system is to use $PdCl_2$ with 1 equiv. of anhydrous $SnCl_2$ and 2 equiv. of a tertiary phosphine in dry acetonitrile.[64] Using either of these methods a variety of α-methylenelactones have been synthesized in good yield, including fused ring products. Both *trans*- and *cis*-ethynyl alcohols readily give fused-ring methylenelactones of the corresponding stereochemistry (equation 41).

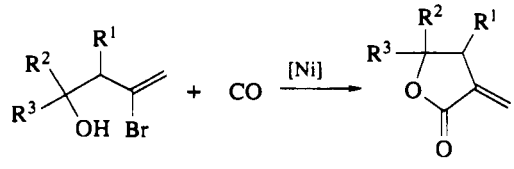


(40)

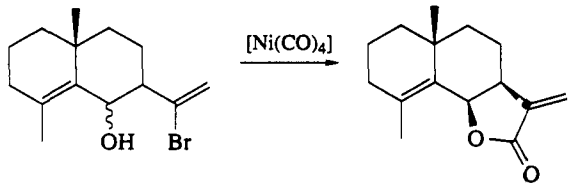


(41)

α-Methylenebutyrolactones can also be synthesized from homoallylic alcohols in the presence of a base (equation 42). Early work used $[Ni(CO)_4]$, but more recently the reaction has been shown to proceed in the presence of $[Ni(CO)_2(PPh_3)_2]$ and triethylamine.[65] Unfortunately neither of these reactions are catalytic but the homoallylic alcohol method has been used in the synthesis of the sesquiterpene frullanolide (**11**).[65b]

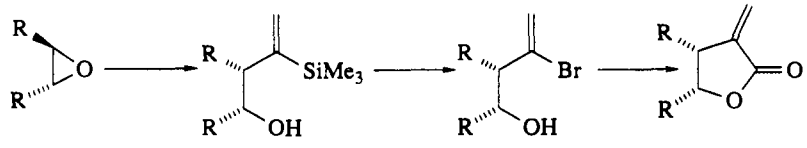


(42)



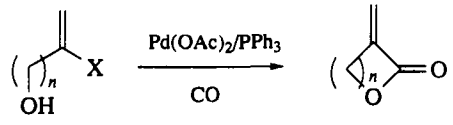
(11)

The conversion of hydroxy-substituted vinyl halides into α-methylenebutyrolactones can be performed catalytically in the presence of $[Pd(PPh_3)_4]$.[66] The starting materials for this reaction are prepared from epoxides and α-silylated vinyl Grignard reagents followed by the substitution of the silyl substituent by bromine. Due to the regio- and stereo-specific nature of the ring-opening reaction of the epoxide by the vinyl Grignard reagent, and the noninvolvement of asymmetric carbons in the carbocyclization reaction, the reaction can be extended to the synthesis of optically active lactones from the corresponding optically active epoxides (Scheme 19).



Scheme 19

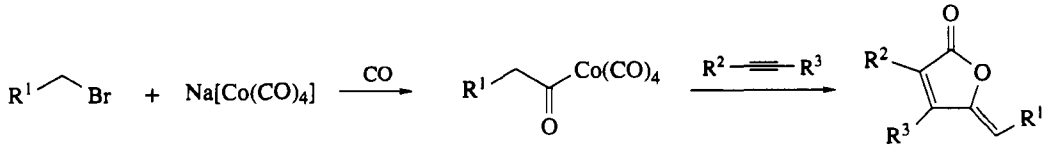
A further variation on this reaction is the cyclocarbonylation of hydroxy-substituted vinyl halides using a palladium acetate/triphenylphosphine catalyst system. Using this procedure five-, six- and seven-membered α-methylenelactones can be prepared (equation 43).[67]



(43)

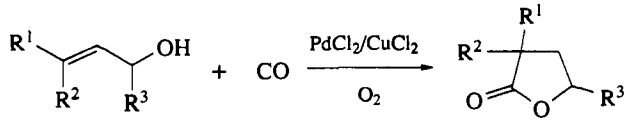
$n = 2, 3, 4$

Acylcobalt tetracarbonyl complexes, formed from $Na[Co(CO)_4]$ and alkyl or acyl halides, react with alkynes to give 2,4-pentadieno-4-lactones (Scheme 20).[68] The reaction is catalytic in cobalt and yields are around 60% for a variety of substituted alkynes and alkyl halides.



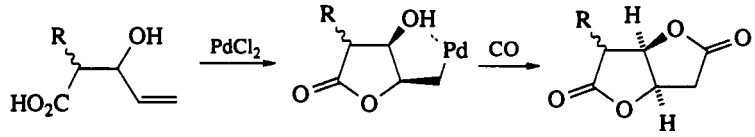
Scheme 20

Five-membered ring lactones are formed from the reaction of primary, secondary or tertiary allyl alcohols with carbon monoxide in the presence of a catalytic amount of $PdCl_2/CuCl_2$ (equation 44).[69] The reaction proceeds at room temperature under 1 bar of CO and yields are generally in the range 40–60%.



(44)

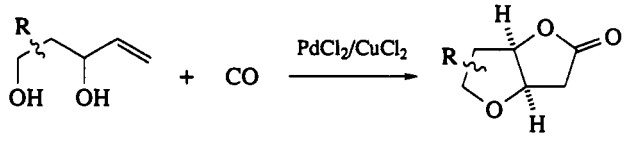
Dilactones can be synthesized by a palladium-catalyzed stereospecific intramolecular double cyclization of 3-hydroxy-4-pentenoic acids (Scheme 21).[70] The *cis* stereochemistry of the reaction is rationalized by assuming that attack of Pd^{II} on the alkene is directed by the allylic OH group, forming the intermediate (**12**).



(12)

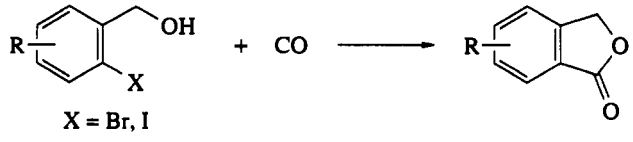
Scheme 21

cis-3-Hydroxytetrahydrofuranacetic acid lactones have been prepared in high yield by intramolecular palladium-catalyzed oxycarbonylation of 4-pentene-1,3-diols under mild conditions (equation 45).[71] A wide range of 4-pentene-1,3-diols can be prepared in essentially quantitative yield by the sequential aldol condensation (reaction of enolates, ketones, esters or lactones with unsaturated aldehydes in THF) and reduction with $LiAlH_4$ in ether at room temperature, thus allowing the ready synthesis of a number of lactones.



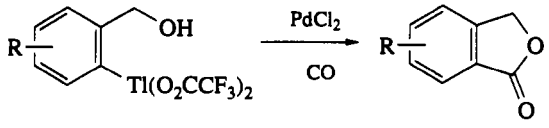
(45)

The catalytic carbonylation of halides can also be used to synthesize phthalides (equation 46). The reaction will proceed both in the presence of palladium[62] and cobalt[72] catalysts.



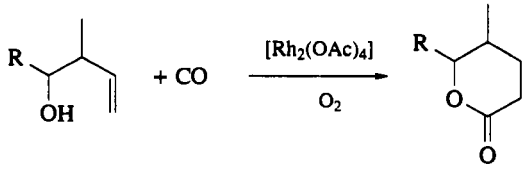
(46)

The direct carbonylation of arylthallium compounds usually requires high temperatures and pressures, but in the presence of palladium catalysts the reaction proceeds in high yield at room temperature and atmospheric pressure (equation 47).[73]

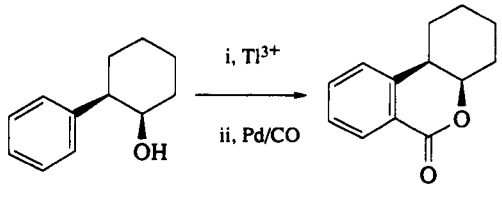


(47)

Compared with the synthesis of five-membered rings relatively little has been done on the synthesis of δ-lactones. Homoallylic alcohols can be converted into δ-lactones by rhodium-catalyzed hydroformylation followed by oxidation (equation 48).[74] The thallation and subsequent palladium-catalyzed carbonylation described earlier can also be used for the synthesis of six-membered rings (equation 49).[73]

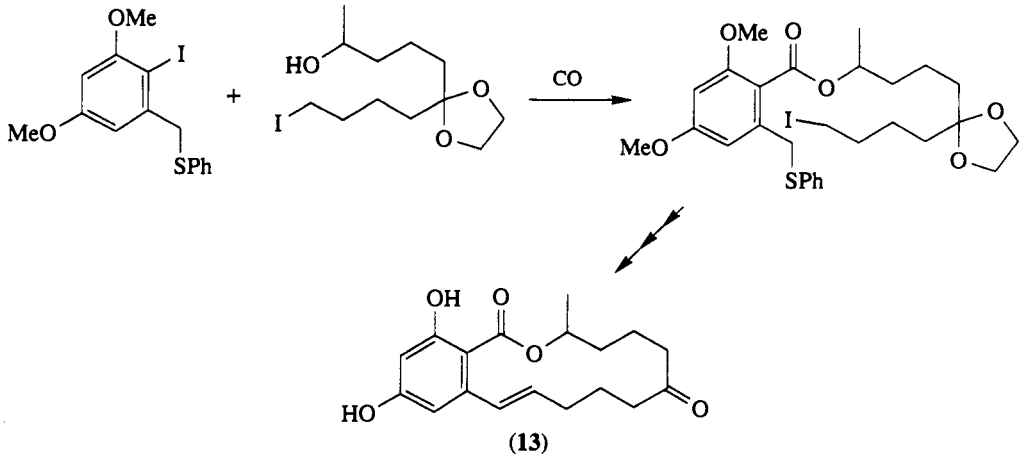


(48)



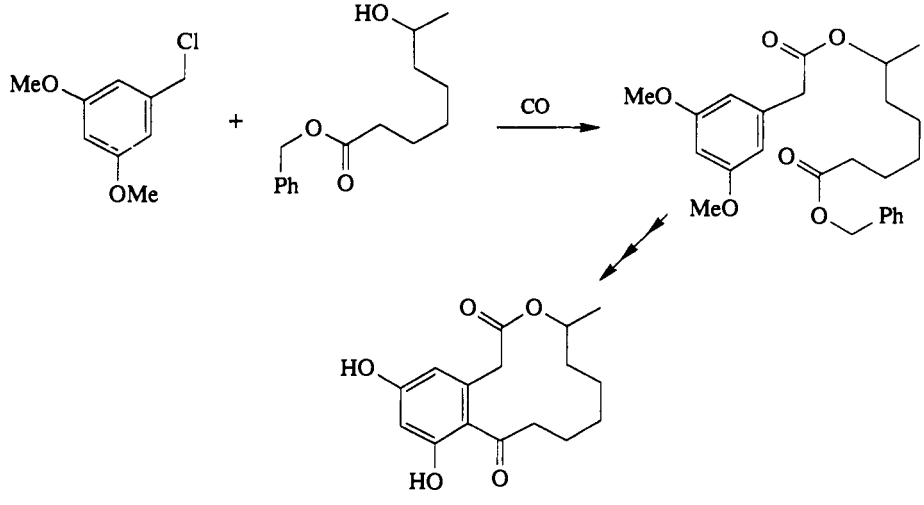
(49)

Palladium-catalyzed carbonylation of halides has been applied to the synthesis of natural products such as zearalenone (**13**; Scheme 22)[75] and curvulin (**14**; Scheme 23).[76] In both cases the yields for the carbonylation steps are 70%.



(13)

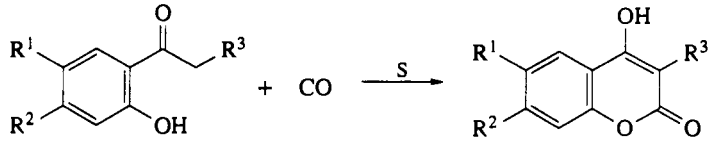
Scheme 22



(14)

Scheme 23

Whereas most carbonylation studies have focused on the use of transition metal catalysts, one recent report describes the facile synthesis of 4-hydroxycoumarins using sulfur-assisted carbonylation (equation 50).[77] Yields are good for a variety of substrates while reaction conditions are relatively mild.



(50)

4.1.8 FORMATION OF AMIDES

Reaction of organic halides with CO and amines using stoichiometric quantities of $[Ni(CO)_4]$ or $Na[Co(CO)_4]$ indicate that metal-promoted amidation is a feasible route to carboxylic amides, but of more use is a palladium-catalyzed synthesis (equation 51).[78] Aryl, vinyl or heterocyclic halides react with primary or secondary amines in the presence of $[Pd(PPh_3)_2Cl_2]$ under mild conditions (60–100 °C; 1 bar CO) to give high yields of the appropriate amide. The amidation reaction proceeds much more rapidly than the corresponding ester synthesis (Section 4.1.6) so that bromobenzene, for example, reacts with benzylamine and CO to give *N*-benzyl benzamide about 17 times faster than with 1-butanol under the

same conditions. Amidation also shows greater stereoselectivity than carboalkoxylation with *cis*- and *trans*- vinyl halides, giving amides with essentially complete retention of configuration.

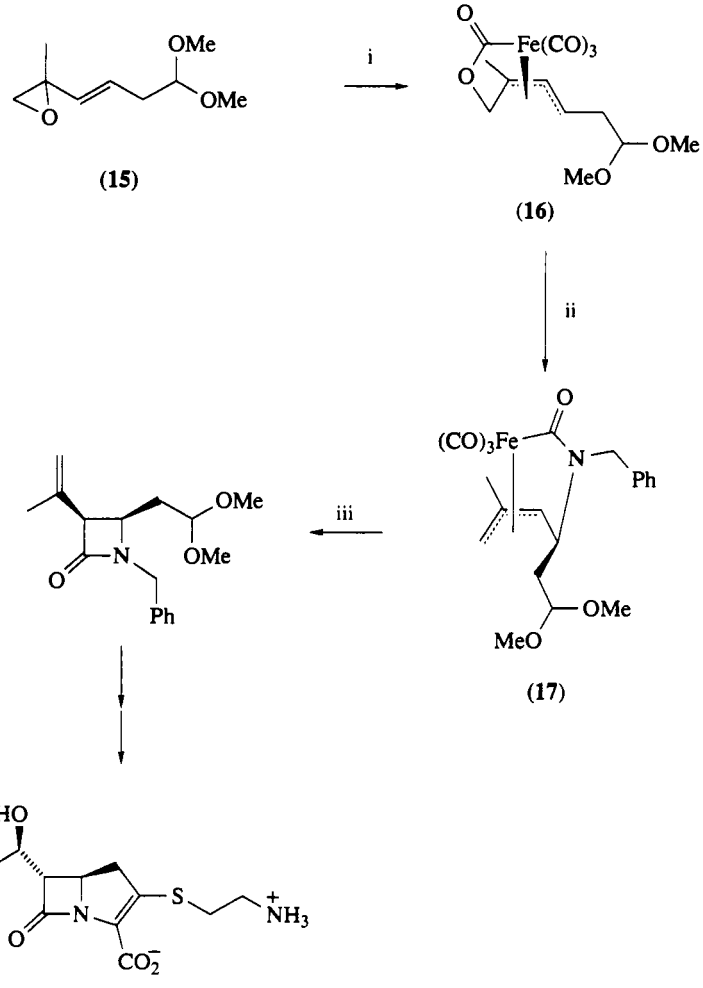
$$RX + CO + R'NH_2 \xrightarrow{[Pd(PPh_3)_2Cl_2]} \underset{R}{\overset{O}{\diagup\!\!\diagdown}}\!\!\underset{NHR'}{} + HX \qquad (51)$$

Vinyl and aryl esters of trifluoromethanesulfonic acid are readily converted to amides using a palladium–phosphine catalyst (equation 52).[79] The reaction proceeds under mild conditions (60 °C; 1 bar CO) to produce amides in excellent yield, but often appears to need the use of the exotic ligand 1,1′-bis(diphenylphosphino)ferrocene (DPPF).

$$R^1OTf + CO + R^2{}_2NH \xrightarrow[R^3{}_3P]{Pd(OAc)_2} \underset{R^1}{\overset{O}{\diagup\!\!\diagdown}}\!\!\underset{NHR^2{}_2}{} \qquad (52)$$

4.1.9 FORMATION OF LACTAMS AND RELATED *N*-HETEROCYCLES

The synthesis of β-lactams has been achieved using a variety of transition metal mediated reactions, many of which are specific to this type of compound. The vinyl epoxide (**15**) reacts with $[Fe_2(CO)_9]$ to



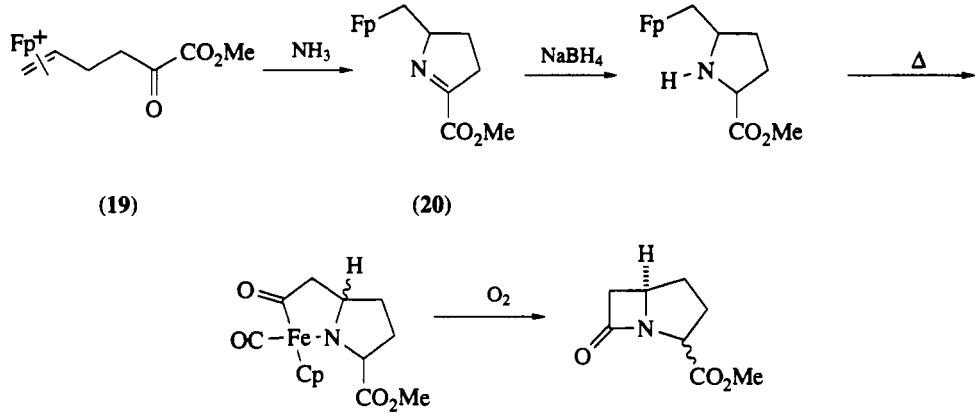
(**15**) (**16**) (**17**) (**18**)

i, $Fe_2(CO)_9$; ii, $PhCH_2NH_2$; iii, Ce^{4+}

Scheme 24

give the lactone complex (**16**), which then reacts with benzylamine to give the complex (**17**). Oxidation with cerium(IV) ammonium nitrate produces the β-lactam, in 64% yield, which can be further elaborated into the antibiotic thienamycin (**18**; Scheme 24).[80]

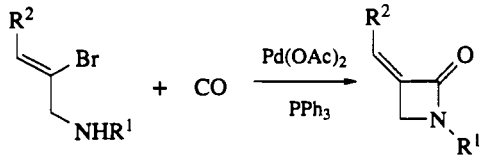
Iron–alkene complexes have also been used for the synthesis of β-lactams (Scheme 25).[81] The alkene complex (**19**) is transformed into the pyrroline complex (**20**) on exposure to ammonia. Reduction with $NaBH_4$ gives a mixture of stereoisomeric pyrrolidine complexes which are then converted on heating to the diastereomeric chelate (**21**). Oxidation with air or silver oxide produces the lactam (**22**).



Fp = $C_5H_5Fe(CO)_2$

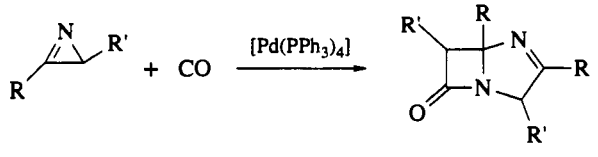
Scheme 25

A more conventional carbonylation route to β-lactams involves the palladium-catalyzed conversion of various 2-bromo-3-aminopropene derivatives into the corresponding α-methylene-β-lactams (equation 53).[82]

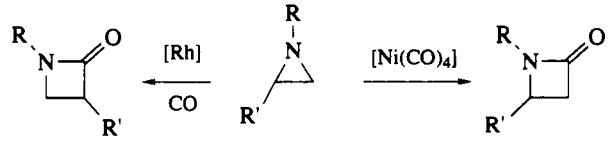


(53)

Exposure of an azirine to carbon monoxide in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ gives the bicyclic β-lactam (**23**) in reasonable yield.[83] Attempts to synthesize monocyclic β-lactams from azirines has so far failed, but aziridines can be carbonylated to β-lactams. Depending on the organometallic reagent used two different products can be obtained (Scheme 26). Using catalytic quantities of $[Rh_2(CO)_4Cl_2]$ carbon monoxide inserts selectively into the more-substituted C—N bond,[84] whereas using a stoichiometric amount of $[Ni(CO)_4]$ it is the less-substituted C—N bond that is carbonylated.[85]

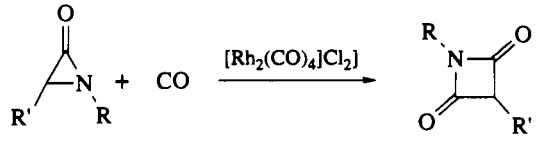


(**23**)



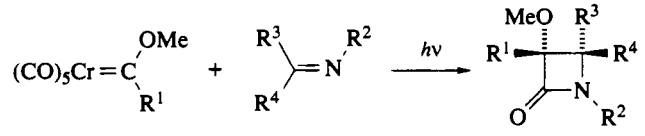
Scheme 26

Azetidine-2,4-diones can be prepared in good yield from aziridinones by carbonylation in the presence of a rhodium catalyst (equation 54).[86] This conversion can also be brought about using $[Co_2(CO)_8]$, but in this case the reaction is not catalytic.

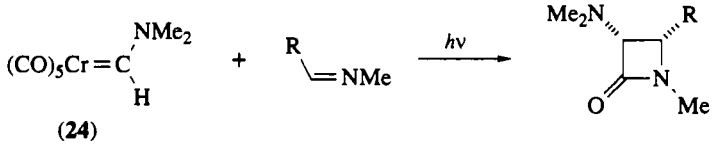


(54)

A somewhat different approach to the synthesis of mono- and bi-cyclic β-lactams involves the reaction of pentacarbonyl(methoxymethyl)chromium complexes with amines under sunlight irradiation (Scheme 27).[87] The chromium complexes are readily made by reaction of $[Cr(CO)_6]$ with alkyl- or aryl-lithium reagents, followed by alkylation with trimethyloxonium tetrafluoroborate. Sunlight photolysis is required for β-lactam formation, with the product being isolated in 40–76% yield. The reaction is applicable to a wide variety of imines and proceeds with high stereoselectivity. However, the reaction is sometimes limited by the stability of the alkoxycarbene complex and to overcome this the reaction has been extended by using the more stable aminocarbene complex (**24**). Photolytic reaction of these complexes with imines, oxazines, oxazolines, imidates, thiazines and thiazolines produces β-lactams in fair to good yield, with *trans* stereochemistry being observed in most cases (equation 55).



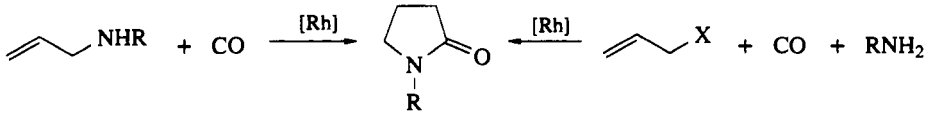
Scheme 27



(55)

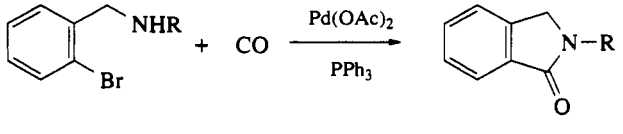
(**24**)

Carbonylation of allylamines can produce pyrrolidones, although relatively high pressures of CO are usually required. Homogeneous rhodium catalysts are preferred and, using similar catalysts, the pyrrolidones can be obtained from allylic halides, CO and ammonia (Scheme 28).[88]



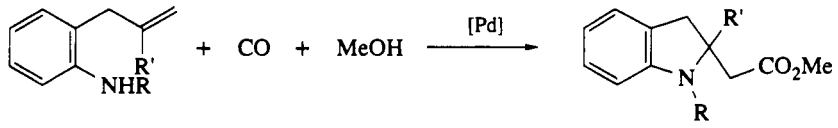
Scheme 28

The formation of *ortho* palladium products from α-aryl nitrogen derivatives and palladium salts is well known.[89] Complexes formed from azobenzene, Schiff bases, tertiary benzylamines and oximes readily undergo insertion of CO into the metal–carbon bond to give, after work-up, a variety of heterocyclic compounds. Unfortunately, such reactions use expensive palladium salts in stoichiometric quantities. However, a number of related reactions have been shown to proceed in the presence of only catalytic quantities of palladium. Isoindolinones, for example, can be synthesized in good yield by reaction of *o*-bromoaminoalkylbenzenes with CO (100 °C, 1 bar) in the presence of catalytic amounts of $Pd(OAc)_2$, PPh_3 and $Bu^n{}_3N$ (equation 56).[90]



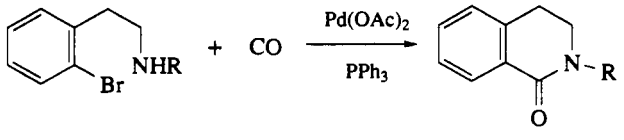
(56)

Cyclization of *N*-substituted-*o*-allylanilines in the presence of carbon monoxide, methanol and a palladium catalyst gives the dihydroindoleacetic acid ester (**25**) in 70% yield.[91]

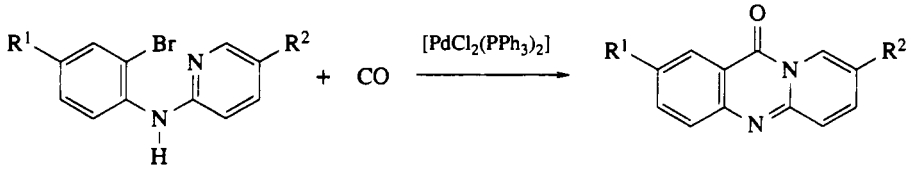


(**25**)

N-Substituted-1,2,3,4-tetrahydroisoquinolin-1-ones (**26**) can be prepared in good yield by carbonylation of *N*-alkyl-*o*-bromophenethylamines in the presence of catalytic amounts of $Pd(OAc)_2/PPh_3$.[90] Similarly substituted 2-(2-bromoanilino)pyridines undergo carbonyl insertion to produce pyrido[2,1-*b*]quinazoline derivatives in good yield (equation 57).[92]

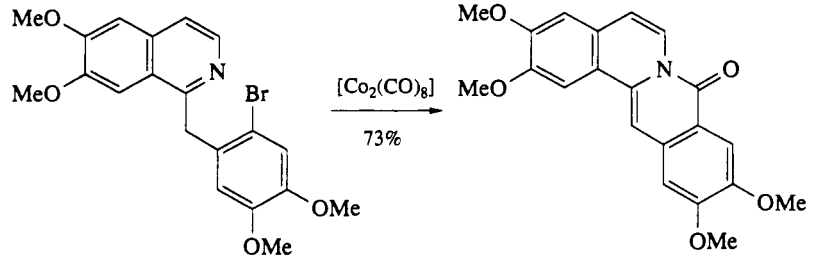


(**26**)



(57)

A number of berbin-8-ones have been synthesized from 2'-halogeno-1-benzylisoquinolines by reaction with metal carbonyls.[93] In order to optimize the yield of the required product and suppress the main side reaction, dehalogenation, it is important to choose the right metal carbonyl. In some cases $[Co_2(CO)_8]$ appears to be the right reagent (equation 58), whereas in other cases $[Fe_3(CO)_{12}]$ is more suitable (equation 59). The latter reaction can also be brought about by palladium-catalyzed carbonylation of the same starting material in 52% yield.[94]



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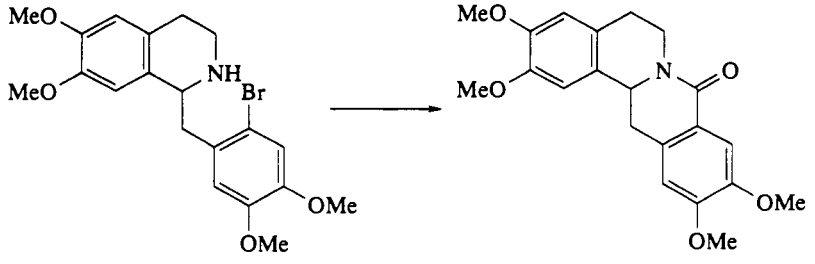
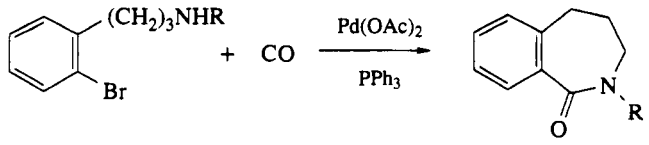
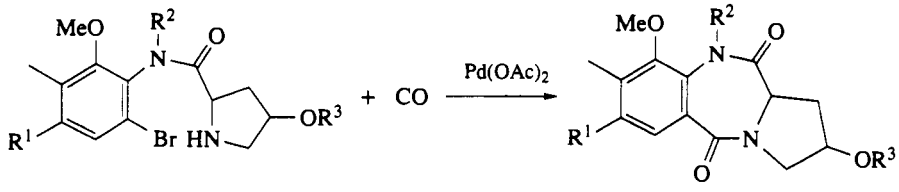


(59)

Using the same procedure as for the synthesis of the related five- and six-membered benzolactams, the benzoazepinone derivatives (**27**) have been synthesized in good yield.[90] This palladium-catalyzed procedure has more recently been extended to the synthesis of a number of antibiotics.[95] A key step in the synthesis of anthramycin, for example, is the palladium-catalyzed insertion of CO into the amine (**28**).[95b]



(27)



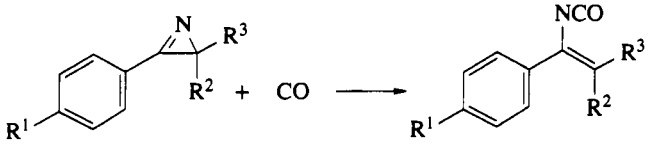
(28)

4.1.10 FORMATION OF ISOCYANATES

Aromatic nitro compounds can be carbonylated to isocyanates in the presence of palladium catalysts such as $PdCl_2$/pyridine (equation 60).[96] Although high conversions can be obtained the reaction conditions are somewhat vigorous (200 °C, 150 bar CO). Rhodium catalysts have also been shown to be active for this transformation.[97] From an industrial point of view, however, the simplicity of the reaction offers an attractive route to isocyanates, which are important intermediates for polyurethanes.[98]

$$ArNO_2 + 3CO \longrightarrow ArNCO + 2CO_2 \qquad (60)$$

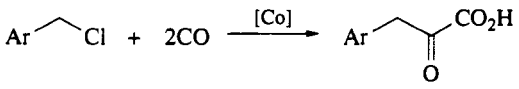
2-Arylazirines are carbonylated under very mild conditions (5 °C, 1 bar CO) in the presence of $[Rh_2(CO)_4Cl_2]$ to give arylvinyl isocyanates in high yield (equation 61).[99] These products can be isolated or more conveniently converted to carbamates or ureas by reaction with alcohols or amines, respectively.



(61)

4.1.11 DOUBLE CARBONYLATION

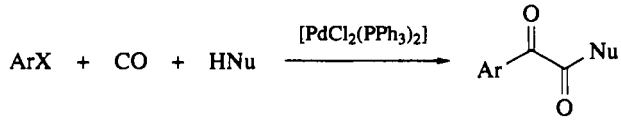
The realization that doubly carbonylated products can be formed in carbonylation reactions has only emerged in the last ten years, but specific syntheses of many α-keto acids, amides, esters and related products are being developed rapidly. Although many such syntheses depend on the use of CO pressures well above ambient, variation of other parameters such as catalyst, solvent and base can lead to efficient double carbonylation even at relatively low pressures. Selective, cobalt-catalyzed formation of phenylpyruvic acid (97% selectively at 85% yield) from benzyl chloride was thus achieved at 50 bar pressure of CO in propan-2-ol, but more recent work has shown that similar selectivity and an even higher yield can be obtained at less than 2 bar when 1,2-dimethoxyethane is used as solvent (equation 62).[100]



(62)

Palladium-catalyzed double carbonylations of aromatic halides have also been studied (equation 63).[101] As might be expected, higher pressure is favorable for both reaction rate and selectivity. Selectivity for the formation of keto esters is also maximized by the use of sterically hindered alcohols and solvents of low polarity.

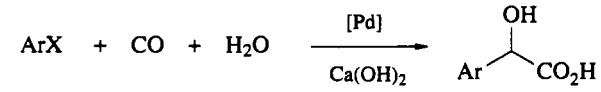
The above reactions take place in the presence of an organic tertiary amine as base, but in the presence of calcium hydroxide reductive double carbonylation takes place with the formation of α-hydroxy acids (equation 64).[102] To maximize the yield of hydroxy acid it is necessary to use isopropyl alcohol as



(63)

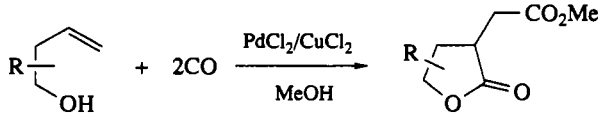
HNu = R_2NH, RNH_2, ROH, H_2O

solvent and a basic phosphine ligand, such as PMe_3, in combination with calcium hydroxide as the base. Formation of the α-hydroxy acid is rationalized in terms of a double carbonylation followed by Meerwein–Ponndorf-type reduction of the resulting α-keto acid by the isopropyl alcohol/calcium hydroxide mixture.



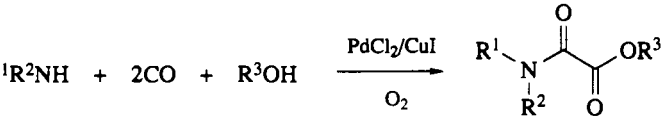
(64)

By careful selection of the reaction conditions 3-butenols undergo efficient dialkoxycarbonylation to produce γ-butyrolactone 2-acetic acid esters under 1 bar of CO (equation 65).[103] Although the roles of the additives are not fully understood, the presence of propylene oxide and ethyl orthoacetate is essential to ensure high selectivity to the double carbonylation product.

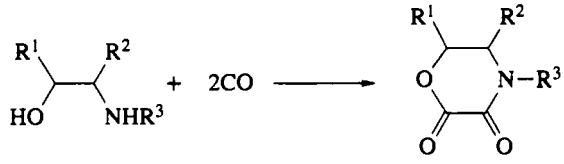


(65)

In the presence of catalytic amounts of $[PdCl_2(NCMe)_2]$/CuI under CO and O_2, amines react with alcohols to form oxamates (equation 66).[104] The reaction proceeds at room temperature and with β-amino alcohols the corresponding cyclic oxamate is produced (equation 67).



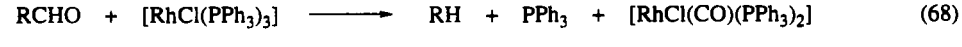
(66)



(67)

4.1.12 DECARBONYLATION

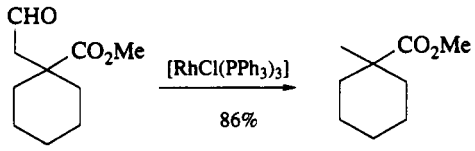
Since most of the elementary steps in carbonylation reactions are reversible, it is not surprising that transition metals and their complexes promote the decarbonylation of organic compounds in either a stoichiometric or a catalytic manner.[105] In stoichiometric reactions carbon monoxide removed from the organic compound is retained by the metal complex, as in equation (68), whereas for catalytic behavior this CO must be released, a reaction that often occurs only at high temperatures (>200 °C).



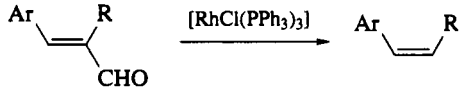
(68)

The rhodium complex $[RhCl(PPh_3)_3]$ readily brings about stoichiometric decarbonylation of aldehydes, acyl halides and diketones. A typical aldehyde decarbonylation is illustrated by equation (69).[106] α,β-Unsaturated aldehydes are decarbonylated stereospecifically (equation 70), while with chiral aldehydes the stereochemistry is largely retained (equation 71).[107]

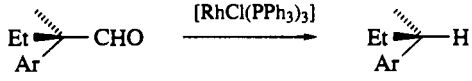
Acyl halides are decarbonylated under mild conditions, but halides containing β-hydrogens also undergo dehydrohalogenation and alkenes rather than alkanes are obtained.[108] Early reports suggested that aromatic acyl chlorides, bromides and fluorides could be decarbonylated, but more recent work indicates that the reaction is not as simple as first thought and variable results have been obtained.[109]



(69)

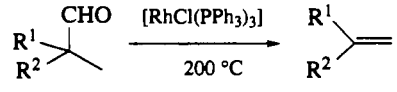


(70)

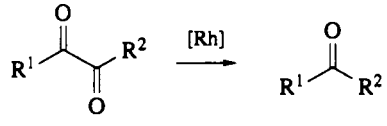


(71)

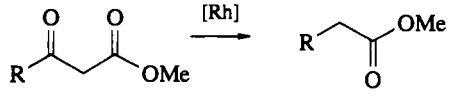
By heating above 200 °C catalytic decarbonylation is possible using $[RhCl(PPh_3)_3]$, and is particularly suitable for aromatic aldehydes since aliphatic aldehydes tend to dehalogenate under these conditions to form alkenes (equation 72). Cationic rhodium complexes, for example $[Rh(Ph_2P(CH_2)_2PPh_2)_2]^+$, are much more active catalysts and hence reactions can be carried out at below 100 °C.[110] Because of the milder conditions aliphatic aldehydes can be decarbonylated to the alkane using this catalyst system. Rhodium catalysts can also be used to decarbonylate α- and β-diketones and keto esters (equations 73 and 74).[111]



(72)

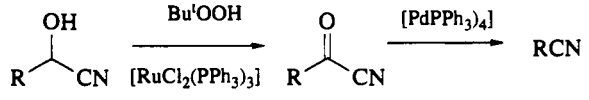


(73)



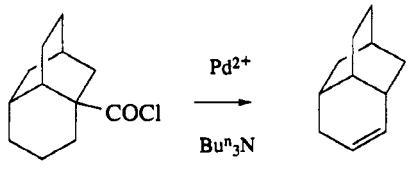
(74)

The palladium-catalyzed decarbonylation of aromatic acyl cyanides proceeds at 120 °C to give the corresponding nitriles in excellent yield.[112] Since acyl cyanides are readily prepared by the ruthenium-catalyzed oxidation of cyanohydrins with Bu^tOOH this represents a good method for the conversion of aldehydes to nitriles under mild conditions (Scheme 29).



Scheme 29

Decarbonylation of the tricyclic bridgehead acid chloride (**29**) with a palladium catalyst at 130 °C in the presence of tri-*n*-butylamine gives exclusively the disubstituted alkene (**30**) in essentially quantitative yield.[113] Under these conditions none of the bridgehead alkene is obtained, but it is assumed that this is an intermediate in the reaction.



(**29**) (**30**)

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4.2
Carbon–Carbon Bond Formation by C—H Insertion

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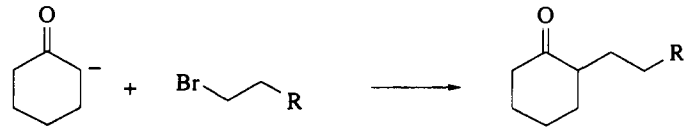
4.2.1 INTRODUCTION

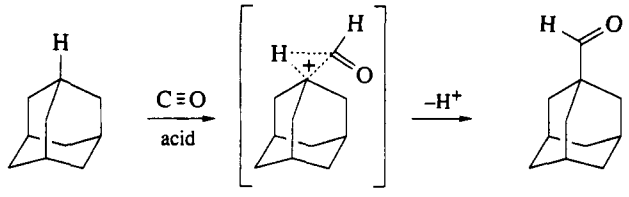
Traditionally, carbon–carbon bond forming processes have required that both organic fragments be specifically activated. This approach is exemplified by the alkylation of an enolate anion (**1**) with an alkyl halide (**2**; equation 1).



(1)

(1) (2) (3)

There are isolated reports of an alternative approach, in which the carbon–carbon bond is formed by direct insertion into an unactivated C—H bond. Often, these are special cases. The conditions under which carbonylation of adamantane (**4**; equation 2) is observed, for instance, would not be expected to be equally efficacious for cyclohexane.[1]



(2)

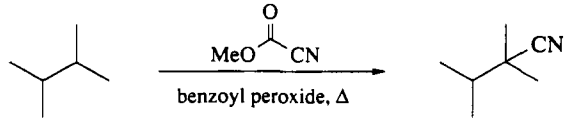
(4) (5) (6)

The purpose of this chapter is to review those methods for constructing C—C bonds from unactivated C—H bonds that appear to have some synthetic generality. Both intermolecular and intramolecular reactions will be considered.

4.2.2 INTERMOLECULAR C—H INSERTION

4.2.2.1 Abstraction–Recombination

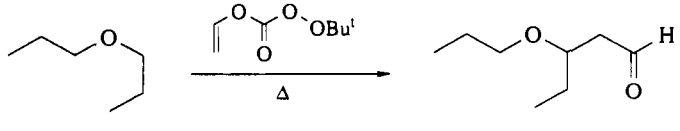
The most common strategy for laboratory-scale hydrocarbon functionalization is hydrogen atom abstraction followed by free radical recombination. This approach is exemplified by the method of Tanner for cyanation of hydrocarbon (**7**) to give (**8**; equation 3).[2]



(3)

(7) (8)

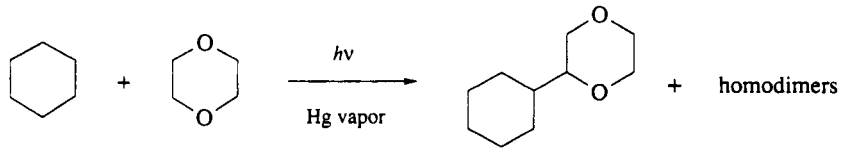
It is possible to achieve some selectivity using this method. As illustrated above, tertiary C—H sites are much more reactive than primary C—H sites. Radical-stabilizing functional groups also impart selectivity, as illustrated by the regioselective functionalization of (**9**; equation 4).[3]



(4)

(9) (10)

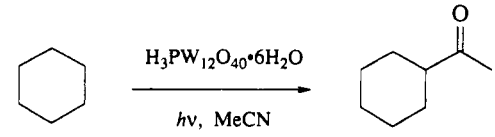
Crabtree, by combining ease of free radical generation with the site selectivity imparted by functional groups that stabilize adjacent free radicals, has developed a very practical approach to hydrocarbon carbafunctionalization, as illustrated by the conversion of cyclohexane to (**13**; equation 5).[4] The real elegance of this method is that it does not require highly reactive reagents. This photochemically initiated dimerization of hydrocarbons proceeds efficiently in the presence of even a very low concentration of mercury vapor.



(5)

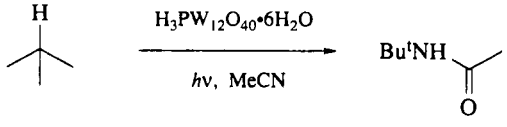
(**11**) (**12**) (**13**)

Hill has shown that the nature of the product formed in such an insertion reaction can vary with the substrate (equations 6 and 7).[5] It is thought that bond formation using the procedure he has developed also proceeds *via* a free radical intermediate. A secondary radical, as from (**14**), will react directly with acetonitrile to form a new carbon–carbon bond. A tertiary radical, as from (**16**), on the other hand, will be oxidized to the corresponding carbocation before reacting with acetonitrile.



(6)

(**14**) (**15**)

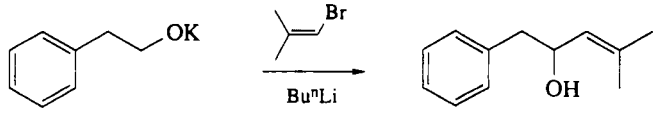


(7)

(**16**) (**17**)

4.2.2.2 Carbenoid Insertion

Intermolecular insertion of free carbenes or carbenoids into C—H bonds is not, in general, an efficient process. However, if the C—H is especially activated, as with an alkoxide such as (**18**; equation 8), the reaction can be preparatively useful.[6]



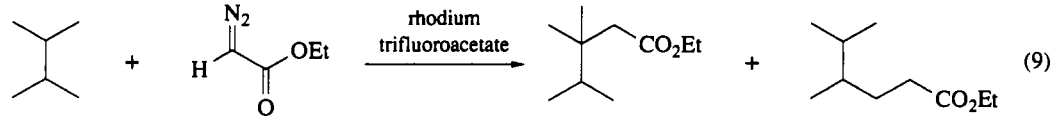
(8)

(**18**) (**19**)

4.2.2.3 Metallocarbene Insertion

In 1981, Noels reported that rhodium(II) carboxylates, originally developed as cyclopropanation catalysts, smoothly catalyze the addition of ethyl diazoacetate (**21**; equation 9) to a variety of alkanes.[7,8] While some differentiation between possible sites of insertion is observed, selectivity is not as high for this carbenoid process as it is for the free radical processes illustrated above.

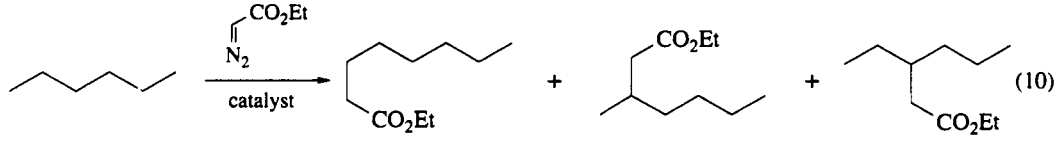
Rhodium-mediated intermolecular C—H insertion is thought to proceed *via* oxidative addition of an intermediate rhodium carbene into the alkane C—H bond. Evidence that the rhodium and its ligands are directly associated with the product-determining transition state has been put forward by Callot, who ob-



(9)

(20) (21) (22) 88% (23) 12%

served that the differential selectivity observed for C—H insertion into (**24**) is a function of the rhodium complex employed (equation 10).[9]



(10)

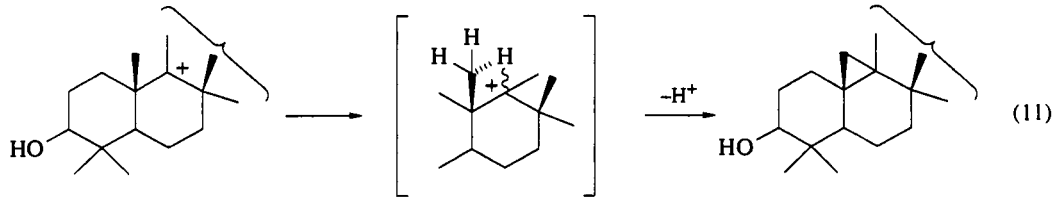
(24) (25) (26) (27)

Rh pivalate	5	62	33
Rh tetraphenylporphyrin	8	71	21
Rh tetra(trimethylphenyl)porphyrin	25	61	14

4.2.3 INTRAMOLECULAR C—H INSERTION: CARBACYCLES

4.2.3.1 Introduction

Unlike the intermolecular examples of C—H insertion mentioned above, most of which are relatively recent, intramolecular C—H insertion has long been recognized. In a late stage of the biosynthesis of cycloartenol (**29**), for instance, the cyclopropane ring is formed by such a process (equation 11).[10]

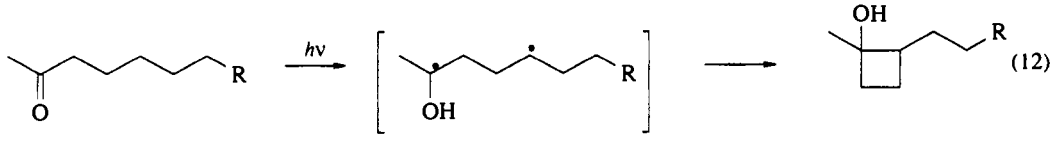


(11)

(28) (29)

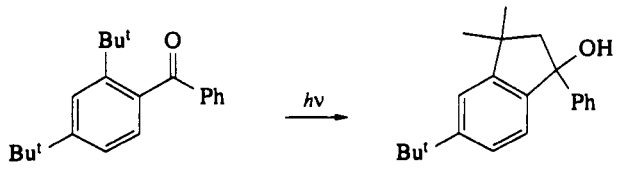
4.2.3.2 Photochemical

Photochemical C—H insertion of a ketone (**30**) will proceed by initial photoexcitation to give an excited state that can usefully be considered to be a 1,2-diradical. Intramolecular hydrogen atom abstraction then proceeds, to give a 1,4- or 1,5-diradical, which can collapse to form the new bond. This approach has been used to construct both four- and five-membered rings (equations 12–14).[11–13] Photochemically mediated cyclobutanol formation is known as the Norrish type II reaction.

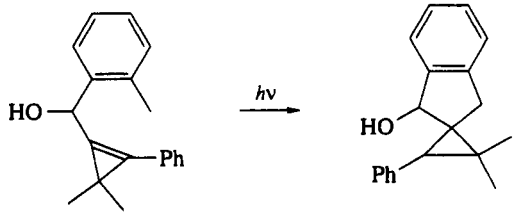


(12)

(30) (31)



(32) (33) (13)

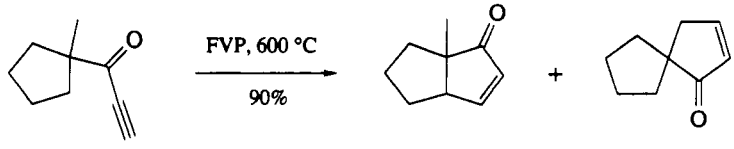


(34) (35) (14)

4.2.3.3 Alkylidene Carbenes

4.2.3.3.1 Alkynone pyrolysis

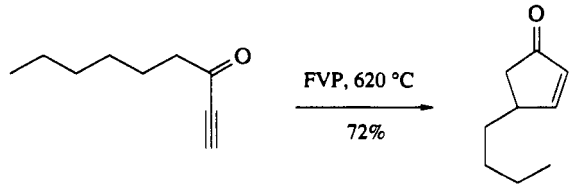
The first preparative use of intramolecular C—H insertion in organic synthesis was developed by Dreiding, who reported in 1979 that, on flash vacuum pyrolysis, a conjugated alkynyl ketone such as (**36**) is smoothly converted to a mixture of the cyclized enones (**37**) and (**38**) (equation 15).[14] This elegant reaction apparently proceeds *via* isomerization of the alkyne to the corresponding alkylidene carbene.



(**36**) (**37**) 92% (**38**) 8% (15)

It should be noted that despite a 3:2 statistical predominance of primary C—H bonds over secondary C—H bonds, a marked preference for insertion into the latter is observed.

In subsequent work, Dreiding demonstrated that the straight chain conjugated alkynone (**39**) cyclizes smoothly to the corresponding cyclopentenone (**40**; equation 16).[15]

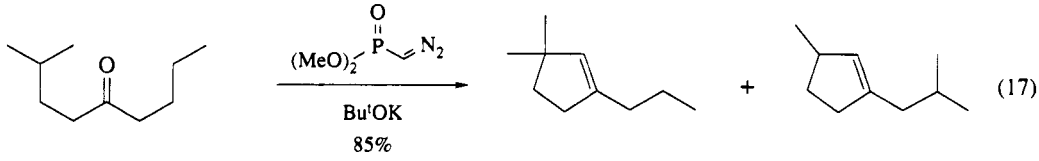


(**39**) (**40**) (16)

4.2.3.3.2 Diazoalkenes

In 1982, Gilbert reported that an aliphatic ketone or aldehyde on exposure to dimethyl (diazomethyl)phosphonate is converted to the corresponding cyclopentene (**41** → **42** and **43**; equation 17).[16]

This reaction apparently proceeds by way of the normal phosphonate condensation product, the diazoalkylidene, which then spontaneously loses nitrogen to form the transient alkylidene carbene.

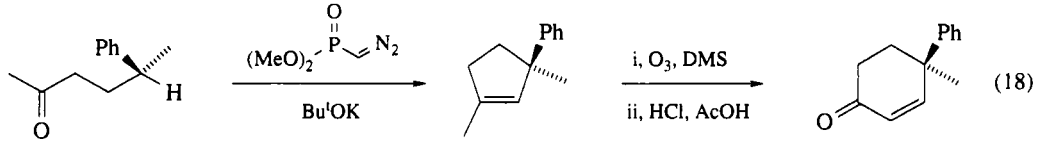


(17)

(41) (42) 90% (43) 10%

Careful work showed that, after statistical corrections were applied, the reactivity of a C—H bond toward insertion was approximately —CH_3 = 0.003; —CH_2— = 1.0; Ph—CH_2— = 7.5; R_3C—H = 18.6. These relative reactivities are very similar to those previously observed by Wolinsky for intramolecular C—H insertion by an alkylidene carbenoid generated from a vinyl bromide.[17]

In subsequent work, Gilbert showed that the alkylidene carbene insertion reaction proceeds with retention of absolute configuration.[18] Using this approach, cyclopentene (**45**) and cyclohexene (**46**) were prepared in high enantiomeric purity (equation 18).

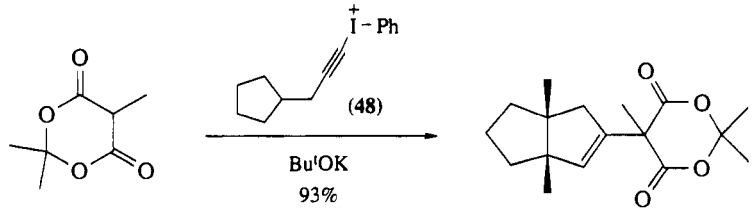


(18)

(44) (45) (46)

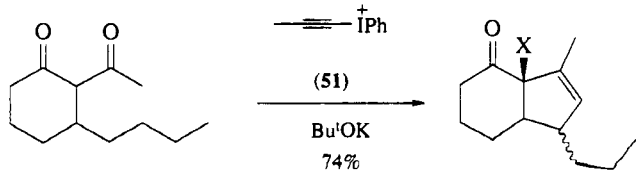
4.2.3.3.3 Alkylidene carbenoids

The insertion reactions described above probably proceed *via* the free alkylidene carbenes. The analogous alkylidene carbenoids also insert efficiently into remote C—H bonds. Ochiai has demonstrated that such alkylidene carbenoids are conveniently generated from the corresponding iodinium tosylates.[19] Depending on the substitution pattern employed, either [5 + 0] cyclization to give (**49**; equation 19), or [2 + 3] cyclization to give (**52**; equation 20), can be obtained.



(19)

(47) (49)



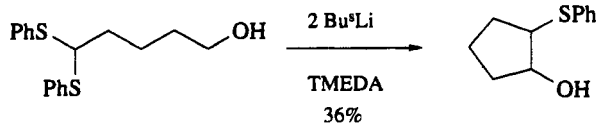
(20)

(50) (52) X = COMe

4.2.3.4 Alkyl Carbenoids

4.2.3.4.1 Thermal insertions

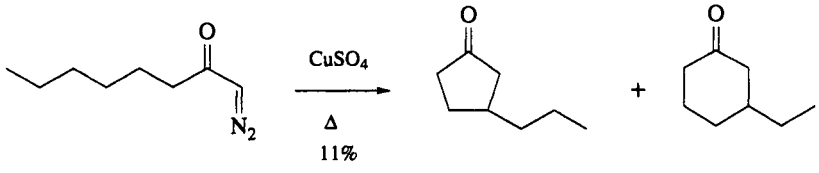
The simple thermal insertion of an unsubstituted alkyl carbene or carbenoid into a remote C—H bond is, in general, not a useful synthetic method. Activation of the C—H bond by an α-alkoxy group, as with the cyclization of (**53**) to (**54**) reported by Cohen, makes this process more efficient (equation 21).[20]



(53) (54) (21)

4.2.3.4.2 Copper-catalyzed diazo insertions

There are several isolated examples of conformationally constrained α-diazo ketones that, under catalysis by Cu salts, smoothly undergo intramolecular C—H insertion.[21] This cyclization was investigated in some detail by Wenkert, who found that it was not, in the acyclic series, a preparatively useful synthetic method (equation 22).[22]

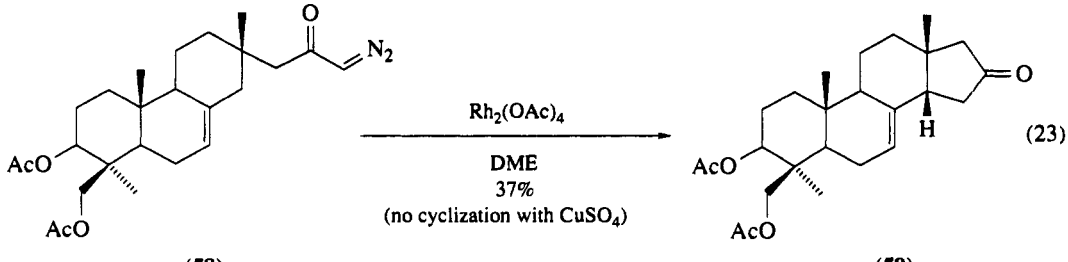


(55) (56) 82% (57) 18% (22)

4.2.3.4.3 Rhodium-catalyzed diazo insertions

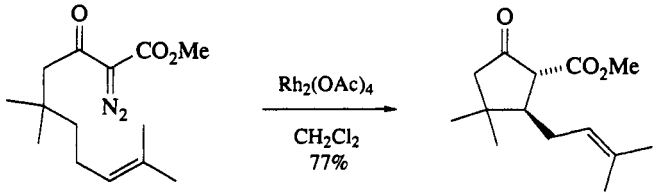
(i) Initial cyclization studies

Hubert in 1976 reported that rhodium acetate efficiently catalyzes diazo insertion into an alkene, to give the cyclopropane.[8] In 1979, Southgate and Ponsford reported that rhodium acetate also catalyzes diazo insertion into a C—H bond.[23] Prompted by these studies, Wenkert then demonstrated that cyclization of (**58**) to (**59**) proceeded much more efficiently with the rhodium carboxylates than it had with copper salt catalysis (equation 23).[22]



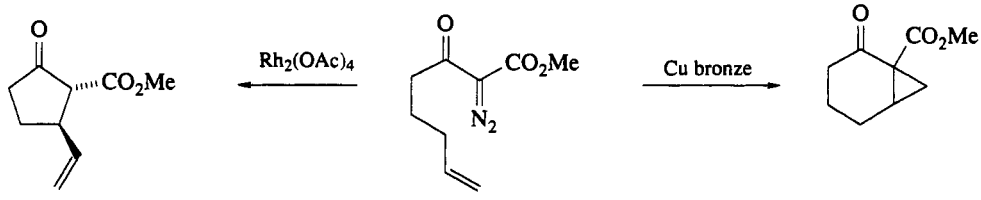
(58) (59) (23)

Concurrently, Noels had reported that rhodium carboxylates smoothly catalyze the intermolecular C—H insertion of ethyl diazoacetate into alkanes.[7] Following up on this report, Taber demonstrated that the open chain α-diazo β-keto ester (**60**) cyclizes smoothly under rhodium acetate catalysis to give the corresponding cyclopentane (**61**; equation 24).[24] In contrast to the copper-mediated cyclization cited above (equation 22), the six-membered ring product is not observed. The insertion shows significant electronic selectivity. Although there is a 3:1 statistical preference for methyl C—H, only the methylene C—H insertion product (**61**) is observed (equation 24).



(60) (61) (24)

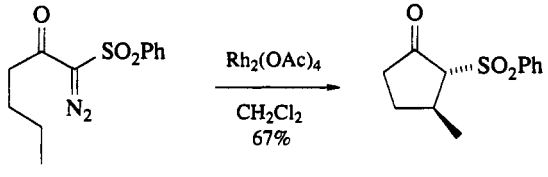
In a direct comparison, it has been found that with the same substrate (**62**), $Rh_2(OAc)_4$ directs the reaction toward C—H insertion, to give (**63**), whereas Cu bronze favors alkene insertion, to make the cyclopropane (**64**; Scheme 1).[24,25]



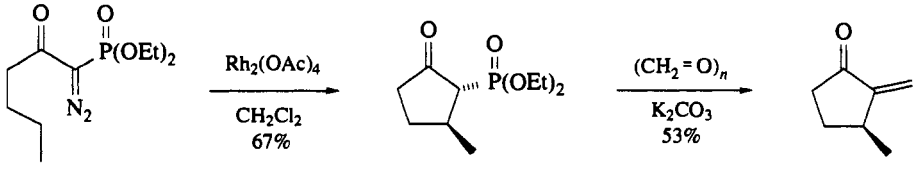
(63) (62) (64)

Scheme 1

Other electron-withdrawing groups are compatible with both diazo transfer and cyclization. Both the β-keto sulfone (**65**) and the β-keto phosphonate (**67**) have been cyclized using rhodium acetate catalysis (equations 25 and 26).[26,27] The cyclized keto phosphonate (**68**) can be further reacted with formaldehyde to make the α-alkylidenecyclopentanone (**69**; equation 26).[27]



(65) (66) (25)



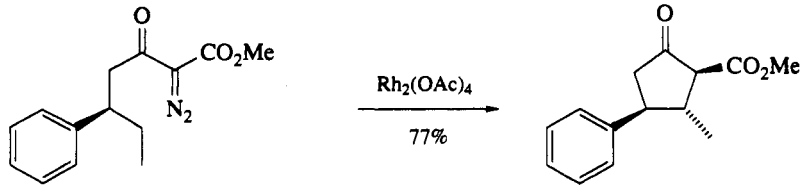
(67) (68) (69) (26)

(ii) Selectivity

Steric and electronic selectivity in the C—H insertion process has been studied in some detail.[28] The cyclization of (**70**) was shown to give (**71**) with high diastereoselectivity (equation 27).

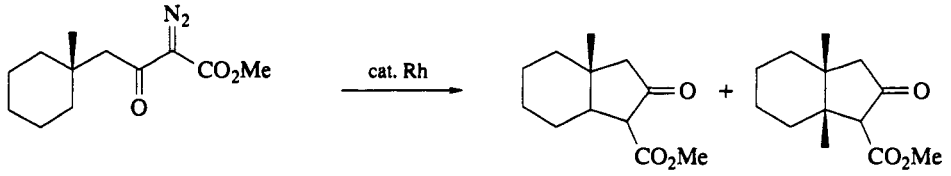
Wenkert demonstrated that cyclization of the diazomethyl ketone corresponding to (**72**)[22] proceeds to give predominantly the *trans*-hydrindan (equation 28).[22] Taber showed that the degree of diastereoselectivity in the cyclization of (**72**) to (**73**) and (**74**) is affected by the ligands on rhodium (equation 28).[28]

As with the work of Gilbert cited above, electronic selectivity can also be observed.[28] It is striking that cyclization of (**75**) proceeds to give preferentially (**76**) rather than (**77**; equation 29). The observation that



(27)

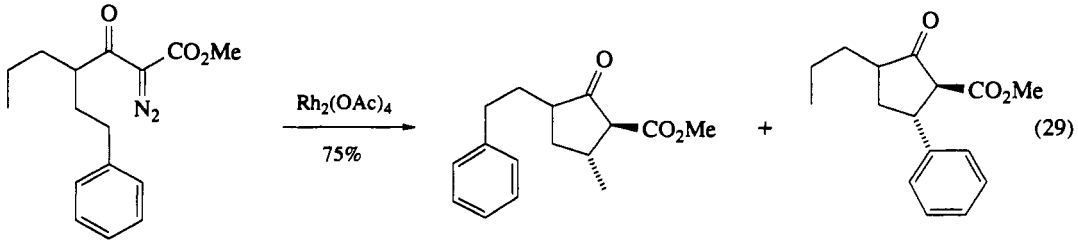
(70) (71) only product observed



(28)

(72) acetate 3:1, octanoate 5:1 (73) (74)

a benzylic —CH_2— is significantly less reactive than an aliphatic —CH_2—, in direct contrast to the 'free carbene' work of Gilbert and others,[16] led to the suggestion that the reaction is proceeding by complexation of a coordinatively unsaturated rhodium carbene complex with the electron density in the target C—H bond.[28] The phenyl substituent, being inductively electron-withdrawing, might then be expected to deactivate the benzylic methylene.



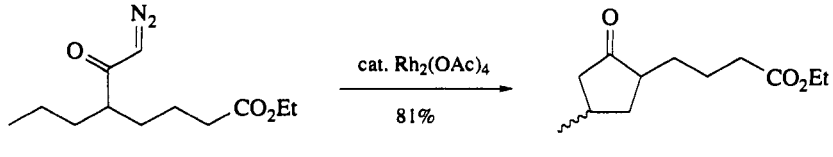
(29)

(75) (76) 77% (77) 23%

(iii) Mechanism

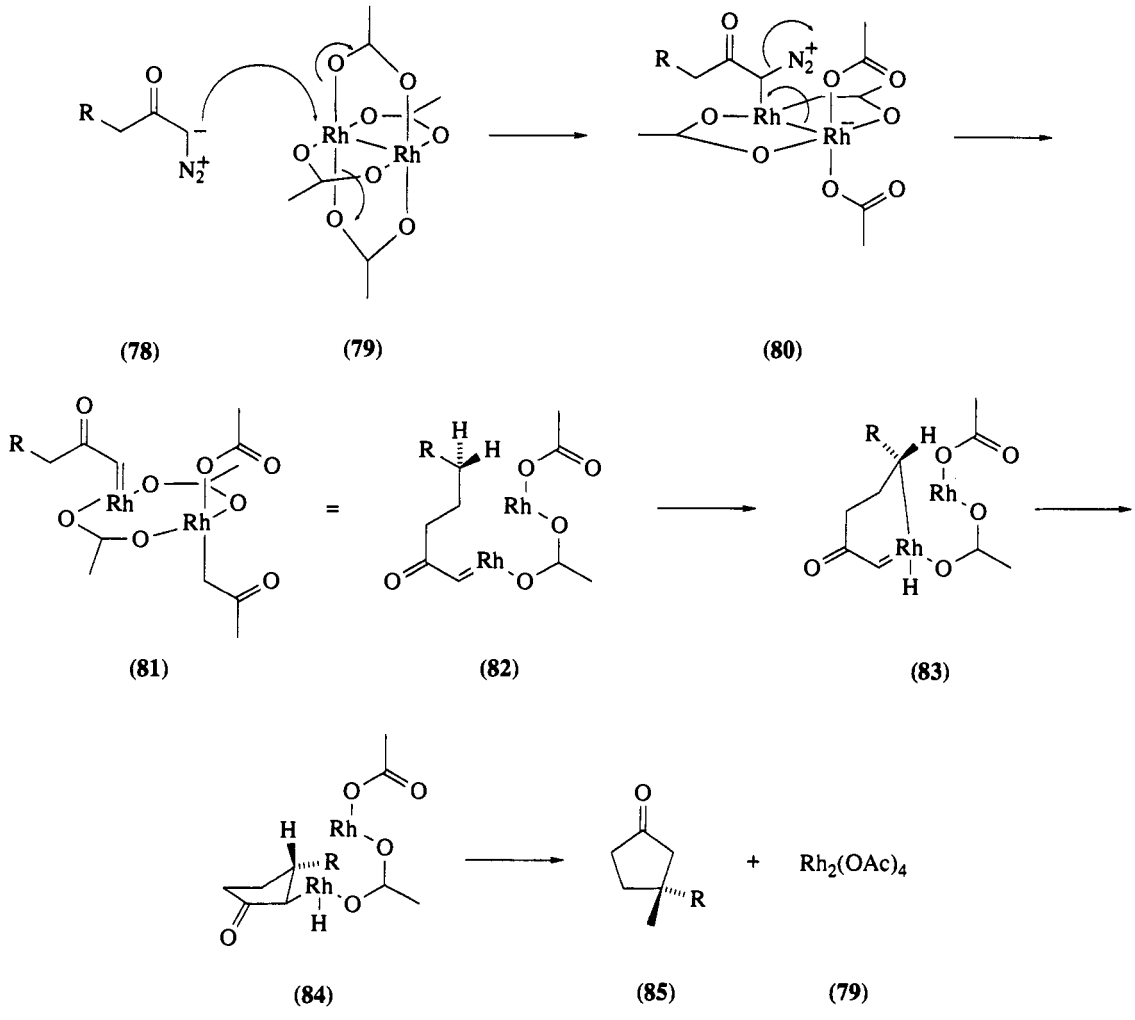
While the detailed mechanism of the rhodium-mediated cyclization is not known, a working hypothesis that accommodates all of the observations to date is that it proceeds *via* a Rh^I carbene complex such as (**82**; Scheme 2). Oxidative addition of the rhodium carbene into a remote C—H bond would give a metallacycle such as (**83**). Carbene rearrangement could then give (**84**), which could undergo reductive elimination to give the product (**85**), along with the regenerated catalyst (**79**).

This mechanistic hypothesis led to two predictions.[28] The first was that, since the product-determining step would seem to be oxidative addition of an electron deficient Rh center into the C—H bond, a C—H bond near an electron-withdrawing group should be less reactive than an isolated C—H bond. This prediction was borne out remarkably well by the work of Stork and Nakatani.[29] They demonstrated that cyclization of (**86**) proceeds to give exclusively (**87**; equation 30). Thus, a C—H bond even β to the electron-withdrawing carboxyl group is much less reactive toward rhodium-mediated C—H insertion than is an isolated aliphatic C—H bond.



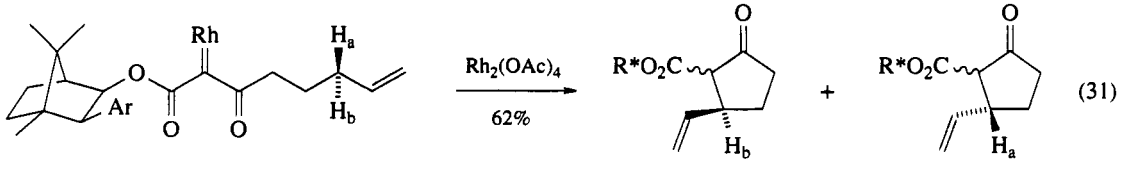
(30)

(86) (87) only product observed



Scheme 2

The other prediction stemmed from the expectation that in the transition state leading to C—H insertion, the forming ring would adopt a lowest energy, staggered, chair-like conformation. It followed that it might be possible to design an enantiomerically pure ester that would destabilize one of the two enantiomeric transition state conformations and thus direct the absolute stereochemistry of the cyclization. Indeed, even though the nearest stereogenic center in the directing alcohol is eight atoms removed from the C—H insertion site, cyclization of (**88**) to (**89**) and (**90**) proceeds with reasonably good selectivity (equation 31).[30] The cyclized esters are diastereomers and can be separated chromatographically.

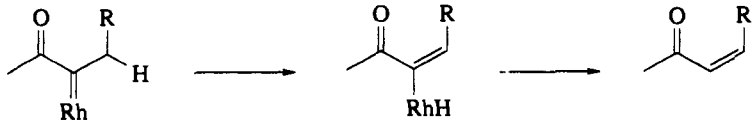


(**88**) Ar = 1-naphthyl (**89**) 92% (**90**) 8% (31)

(iv) Simple α-diazo ketones and esters

It could be expected that if a simple α-diazo ketone with β-C—H bonds were exposed to the rhodium catalyst, metallocarbene formation would proceed as usual, but that β-hydride elimination would com-

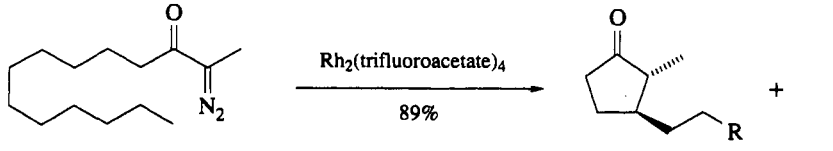
pete with the desired 1,5-insertion. Such a β-hydride elimination could, in fact, be viewed as a 1,2-insertion (**91** → **93**; equation 32).



(32)

(91) **(92)** **(93)**

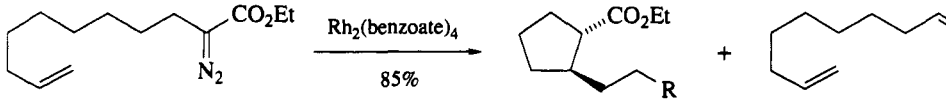
In recent work, Taber and Hennessy have found that simple α-diazo ketones and esters can, in fact, be induced to undergo 1,5-insertion in preparatively useful yields.[31] It was already known[28] that, in the rhodium-mediated insertion process, methyl C—H is electronically less reactive than methylene C—H or methine C—H. It therefore seemed likely that competing β-hydride elimination would be least likely with a diazoethyl ketone. In fact, on cyclization of (**94**), only a trace of the enone product from β-hydride elimination is observed (equation 33). The main side reaction competing with 1,5-insertion is dimer formation.



(33)

(94) **(95)** 77% **(96)** 23%

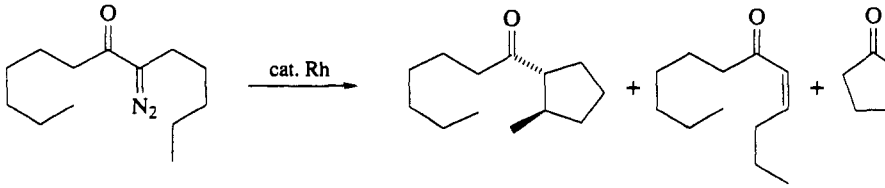
In a direct competition between 1,2- and 1,5-insertion into methylene C—H, the relative proportion of products depends on the rhodium carboxylate used. Rhodium benzoate is the most efficient catalyst so far found for the cyclization of α-diazo ester (**97**) to (**98**) (equation 34).[31]



(34)

(97) **(98)** 77% **(99)** 23%

With the long chain α-diazo ketone (**100**), 1,5-insertion could proceed to put the carbonyl outside the ring or to include it in the ring. In fact, only the product (**101**) from the first of these two cyclization modes is observed (equation 35).[31] The alternative cyclopentane (**103**) is not formed. As with the α-diazo ester, the relative proportion of 1,2- and 1,5-products depends on the rhodium carboxylate used. Throughout these studies, it has been observed that the alkene (**102**) obtained from 1,2-elimination is cleanly *cis*.[31,32]

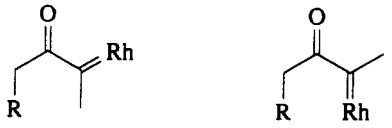


(35)

(100) **(101)** **(102)** **(103)**

acetate (86%)	70%	30%	0%
trifluoroacetate (87%)	38%	62%	0%

The complete absence of the cyclopentanone product (**103**) in the reaction above suggests that, in the intermediate rhodium carbenoid, there is a significant preference for the conformation (**104**), in which the ketone carbonyl and the rhodium center are *syn* to one another (equation 36).



(36)

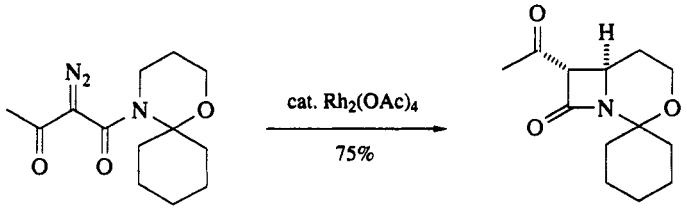
syn (**104**) *anti* (**105**)

4.2.4 INTRAMOLECULAR C—H INSERTION: HETEROCYCLES

4.2.4.1 Rhodium-mediated Cyclization

4.2.4.1.1 β-Lactam synthesis

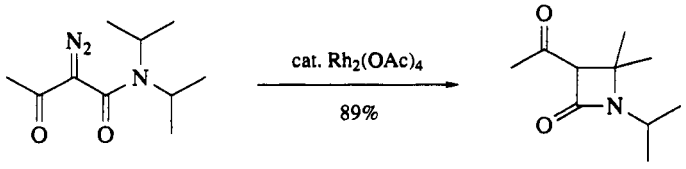
The first observation of rhodium-mediated intramolecular C—H insertion was by Southgate and Ponsford at Beecham Pharmaceuticals, who reported that (**106**) on exposure to a catalytic amount of rhodium acetate cyclizes cleanly to the β-lactam (**107**; equation 37).[23] This approach to thienamycin derivatives has been developed further by the Beecham group.[33,34]



(37)

(**106**) (**107**)

More recently, Doyle has shown that even an acyclic amide such as (**108**) can cyclize smoothly to the β-lactam (**109**; equation 38).[35] β-Lactam formation in these cases is surprising, since the electron-withdrawing heteroatom should direct insertion away from the α-C—H bond. It may be that in this situation, overlap between the filled orbital on the nitrogen atom and the C—H orbital can increase the electron density in the latter, thus making it more reactive. It may be pertinent that as (**108**) becomes more product-like, amide resonance decreases and the electron-donating ability of the nitrogen atom could increase.

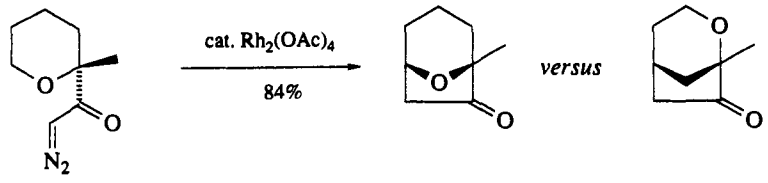


(38)

(**108**) (**109**)

4.2.4.1.2 Furanone synthesis

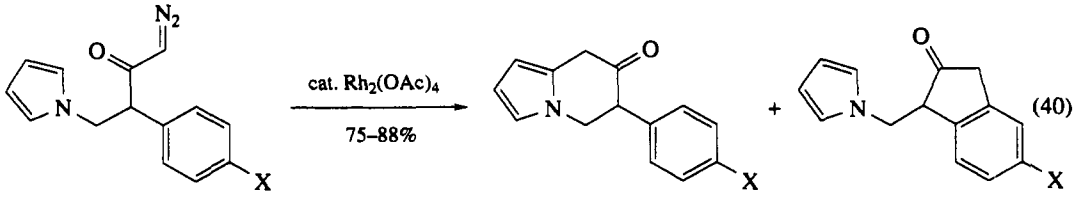
The cyclization of (**110**) to (**111**) reported by Adams is a particularly striking example of C—H activation by an adjacent heteroatom (equation 39).[36] Although the ring size would be the same, and conformational differences in the transition states leading to the two products should be minimal, none of the alternative bicyclic ketone (**112**) was observed.



(110) (111) 100% (112) 0%

4.2.4.1.3 Pyrrole synthesis

Rhodium-catalyzed intramolecular insertion into aromatic C—H bonds proceeds smoothly.[28,37] For instance, (**113**) cyclizes to a mixture of the heterocyclic product (**114**) and the carbacyclic product (**115**; equation 40).[37] From the product ratios observed, one could conclude that the substituent on the aromatic ring can accelerate or decelerate C—H insertion. As with the results cited above (Section 4.2.3.4.3), the differences in reactivity observed can be ascribed to greater or lesser electron density in the target C—H bond.



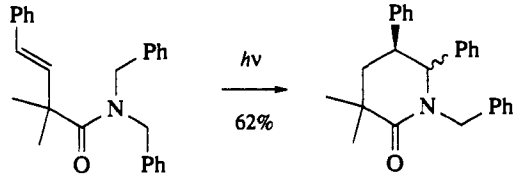
(113)

X	(114)	(115)
$-NO_2$	100%	0%
–H	83%	17%
–OMe	77%	22%

4.2.4.2 Photochemical Cyclization

4.2.4.2.1 γ-Lactam synthesis

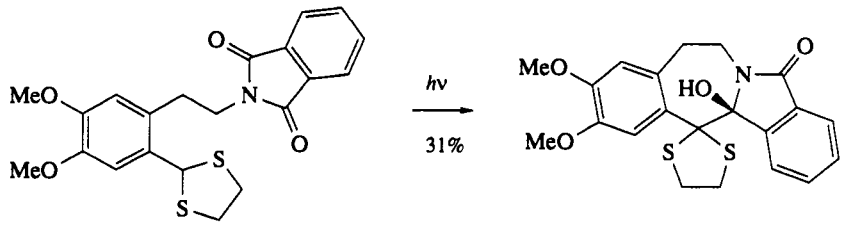
Photochemical C—H insertion, by abstraction–recombination, can also be used to construct heterocyclic rings. In the example illustrated, 1,5-hydrogen atom abstraction leads to the six-membered lactam (**117**; equation 41).[38]



(116) (117)

4.2.4.2.2 Macrolactam synthesis

In some cases, abstraction–recombination can lead to still larger rings. In the example illustrated, 1,8-hydrogen atom extraction leads to the formation of a seven-membered ring product (**119**; equation 42).[39] The 1,7-diradical would be thermodynamically favored because of the radical-stabilizing ability of the two sulfur atoms. The reaction may not, however, proceed by direct 1,8-abstraction. A 1,5-abstraction followed by a subsequent 1,4-abstraction would give the same product and would be sterically more reasonable.

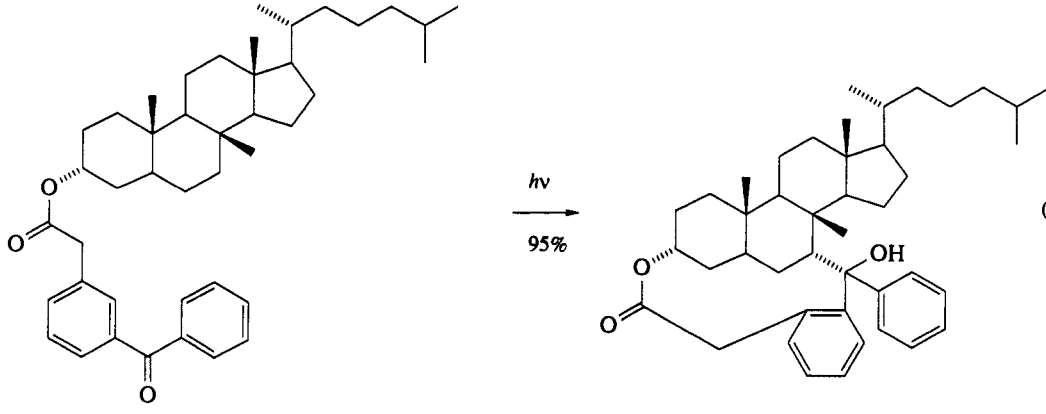


(42)

(118) (119)

4.2.4.2.3 Macrolide synthesis: remote functionalization

In sterically constrained cases, hydrogen atom abstraction over long distances has been unequivocally established. In the steroid functionalization work of Breslow, for instance, irradiation of (**120**) leads, by 1,13-abstraction, to clean formation of the 12-membered macrolide (**121**; equation 43).[40] The chapter on 'Remote Functionalization' (Volume 7, Chapter 1.3) contains a full discussion of this family of reactions.



(43)

(120) (121)

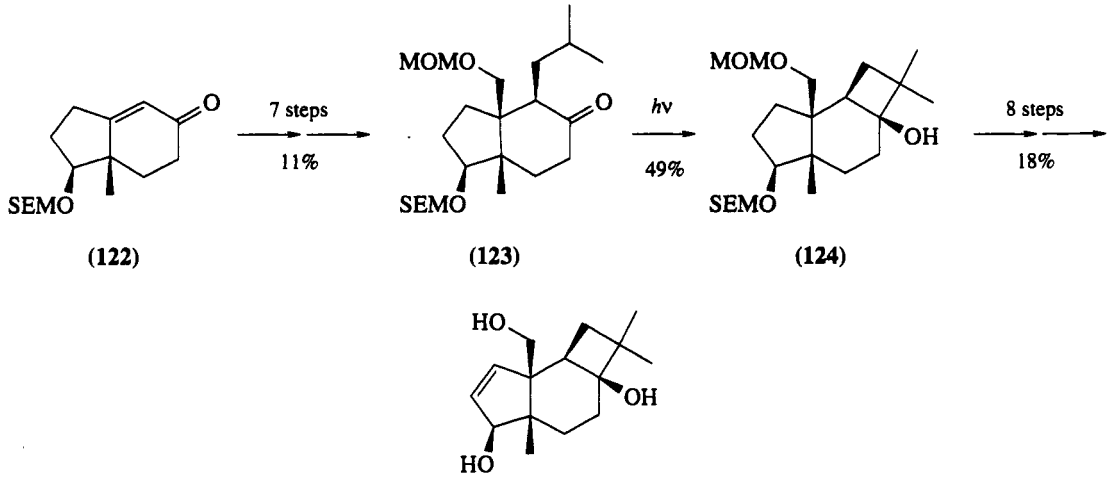
4.2.5 APPLICATIONS TO NATURAL PRODUCT SYNTHESIS

4.2.5.1 Photochemical: (–)-Punctatin A

The elegant route to (–)-punctatin A (**125**) developed by Paquette nicely illustrates the synthetic utility of photochemically mediated intramolecular C—H insertion (Scheme 3).[41] The excellent stereoselectivity observed in the four-membered ring forming process (**123**) → (**124**) was, in fact, predicted. The intermediate 1,4-diradical could cyclize to the equatorially fused *trans*-cyclobutane, as illustrated. The alternative cyclization mode, leading to the *cis*-fused cyclobutane, has a bad steric interaction with the angular alkoxymethyl group, and so is less favored.

4.2.5.2 Alkylidene Carbene: Clovene

Dreiding has used the conjugated alkynone flash vacuum pyrolysis he developed (Section 4.2.3.3) as the key step in several elegant natural product syntheses. The considerations that lead to regio- and stereo-chemical control are nicely illustrated by his approach to clovene (**130**; Scheme 4).[42] Thermolysis of the (symmetrical) alkynone (**126**) could lead to three different enones, two of which (**127** and **128**) are illustrated. In fact, only (**127**) is isolated, in 80% yield. The structure and stereochemistry of this product enone was confirmed by straightforward conversion to the tricyclic hydrocarbon clovene (**130**). The outcome of the thermolysis was anticipated, on the basis of previous observations that insertion is most

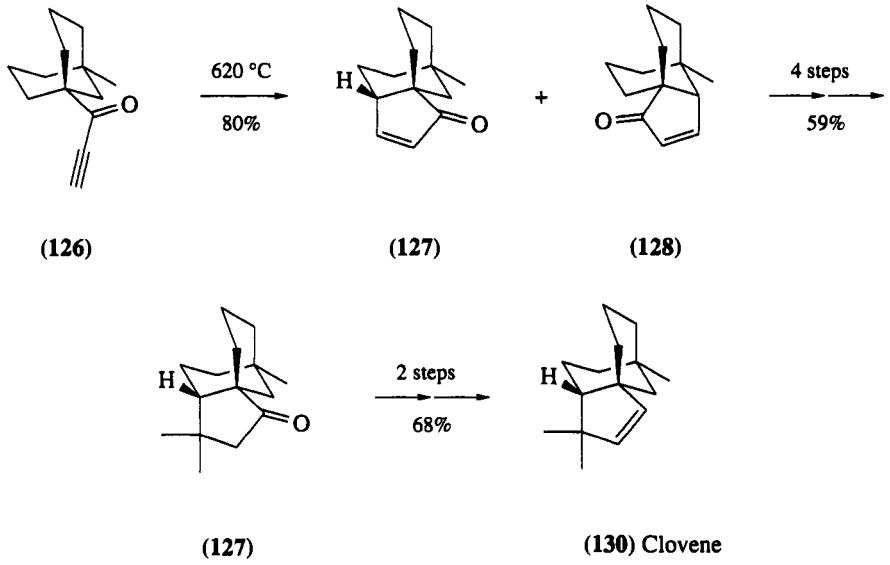


(122) (123) (124)

(125)

Scheme 3

facile when the intermediate alkylidene carbene can achieve coplanarity with the target C—H bond. In this system, such coplanarity is easily achieved only by insertion into the boat conformation of the more flexible of the two rings.



(126) (127) (128)

(127) (130) Clovene

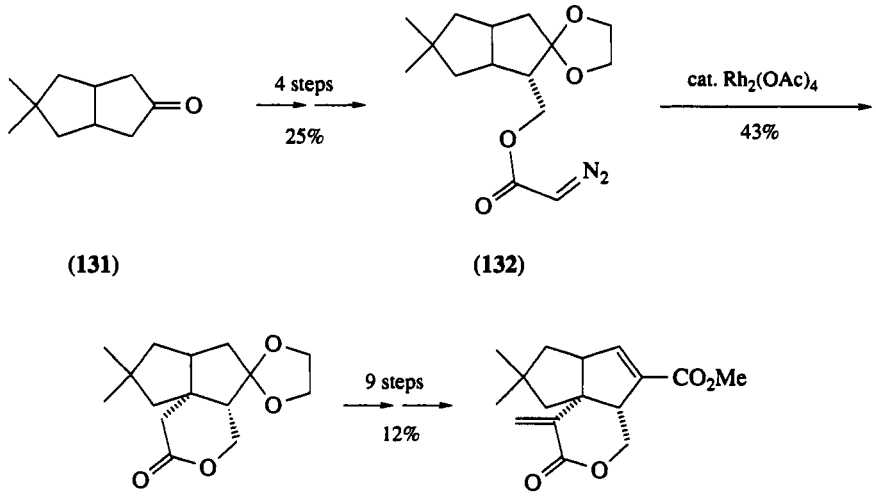
Scheme 4

4.2.5.3 Rhodium-mediated C—H Insertion

4.2.5.3.1 Pentalenolactone E (Cane)

After the initial observation by the Beecham group, the first detailed exploration of rhodium-mediated intramolecular C—H insertion in natural product synthesis was by Cane (Scheme 5).[25,43] Starting from the symmetrical bicyclooctanone (**131**), he elaborated the corresponding diazo ester (**132**). Rhodium-mediated methine insertion to give (**133**) then proceeded smoothly. The tricyclic lactone (**133**) so produced had already been converted, by Paquette, to pentalenolactone E (**134**). In the same article (not

illustrated here), Cane also reported that rhodium-mediated cyclization provides a viable route to substituted bicyclo[3.3.0]octanones.[43]



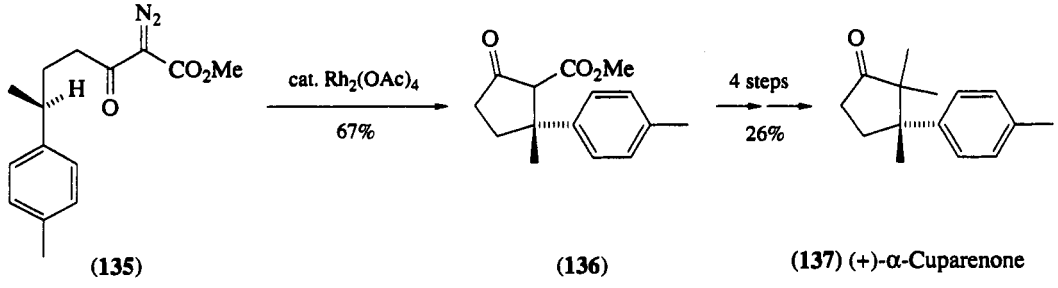
(131) (132)

(133) (134) Pentalenolactone E methyl ester

Scheme 5

4.2.5.3.2 (+)-α-Cuparenone

A powerful feature of intramolecular C—H insertion is the inherent ability to transform an acyclic ternary stereogenic center into a cyclic quaternary stereogenic center.[18] Taber has demonstrated that the rhodium-mediated cyclization of (**135**) to (**136**) indeed proceeds with retention of absolute configuration (Scheme 6).[44] The absolute stereochemistry of (**136**) was confirmed by conversion to the sesquiterpene (+)-α-cuparenone (**137**).

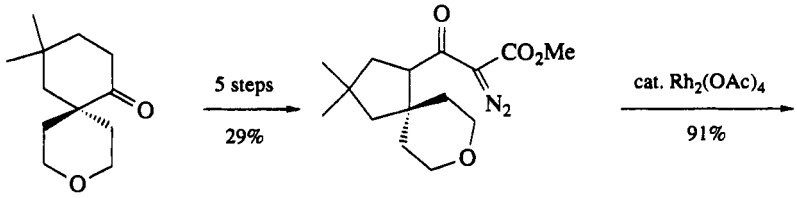


(135) (136) (137) (+)-α-Cuparenone

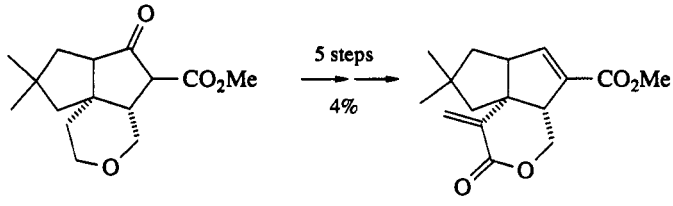
Scheme 6

4.2.5.3.3 Pentalenolactone E (Taber)

Intramolecular C—H insertion is, essentially, a method for specific remote functionalization of hydrocarbons. An important implication of this for synthetic strategy is that the C—H insertion process can dissolve symmetry, thus leading from a simple precursor to a much more complex product. Both the clovene synthesis, by Dreiding, and the pentalenolactone E synthesis, by Cane, take advantage of this idea. It is further illustrated by the pentalenolactone E synthesis reported by Taber (Scheme 7).[45] In the key step, β-keto ester (**139**), which has a single stereogenic center, is transformed into the tricyclic ketone (**140**), which has four stereogenic centers.



(138) **(139)**

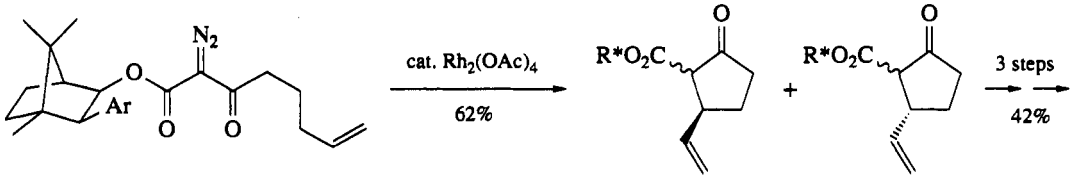


(140) **(134)** Pentalenolactone E methyl ester

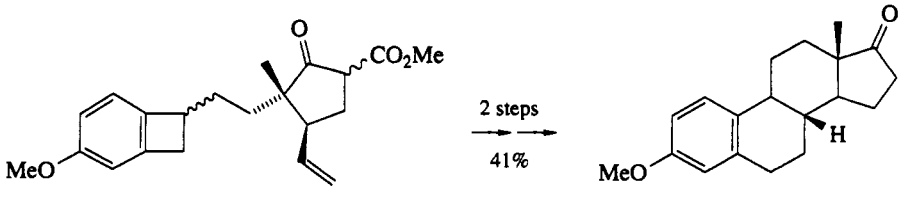
Scheme 7

4.2.5.3.4 (+)-Estrone methyl ether

The key step in the enantioselective synthesis of a polycyclic target is the establishment of the first cyclic stereogenic center. Further construction can then be directed by that initial center. This principle is nicely illustrated by a synthesis of (+)-estrone methyl ether (**145**), reported by Taber (Scheme 8).[46] The specifically designed naphthylbornyl ester (**141**) is used to direct C—H insertion selectively toward one of the two diastereotopic C—H bonds. The new ternary center so created then directs the formation of the adjacent quaternary center in the course of the alkylation. Finally, the chiral skew in the product cyclopentanone (**144**) directs the relative and absolute course of the intramolecular cycloaddition, to give the steroid carbon skeleton.



(141) Ar = 1-naphthyl **(142)** 92% **(143)** 8%



(144) **(145)** (+)-Estrone methyl ether

Scheme 8

4.2.6 DIRECTIONS FOR THE FUTURE

It is apparent that intermolecular C—C bond formation by C—H insertion can be effective for the preparative functionalization of hydrocarbons. A drawback to this approach is the substantial cost of the reagents, as compared to the relatively low value of the products. These factors are perhaps best balanced in the mercury-catalyzed photochemical process developed by Crabtree.[4]

Intramolecular C—H insertion, on the other hand, is already a practical alternative for the construction of cyclobutanols,[41] β-lactams[23,33–35] and of cyclopentane-containing targets. With regard to the latter, diazo transfer can be effected on a large scale with the inexpensive methanesulfonyl azide.[47] The rhodium carboxylate catalysts are effective at very low concentration (<1 mol %) and can easily be recovered from the reaction mixture, if desired.[31]

In the rhodium carboxylate catalyzed process, the transition state leading to C—H insertion is highly ordered.[30,46] Rhodium-mediated C—H insertion has further been shown to proceed with retention of absolute configuration.[44] It may likely be possible, therefore, to design enantiomerically pure ligands for rhodium that would direct the absolute course of insertion into a target methylene.

4.2.7 REFERENCES

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Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

Abbott, D. E., $6^{12,12c}$, 10^{40}, $573^{53,54}$

The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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