COMPREHENSIVE ORGANIC SYNTHESIS

Selectivity, Strategy & Efficiency in Modern Organic Chemistry

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Volume 2

ADDITIONS TO C—X π-BONDS, PART 2

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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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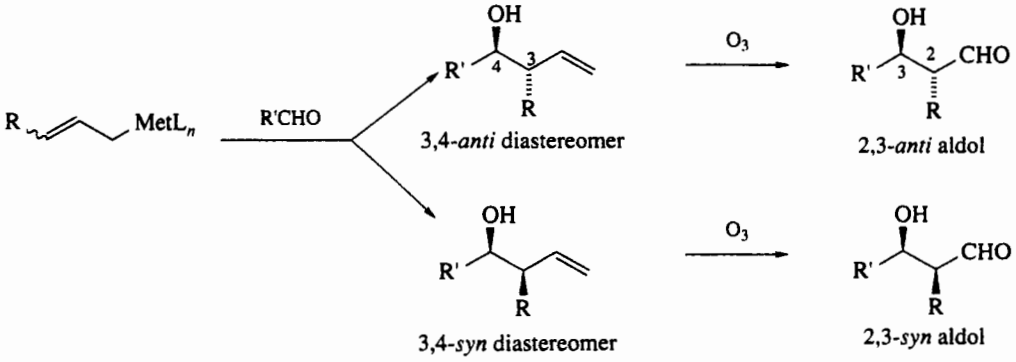
1.1.1 INTRODUCTION

The widespread occurrence and biological significance of the macrolide ansamycin and polyether antibiotics, and of polyhydroxylated natural products, including rare carbohydrates, among others, has stimulated considerable interest in the development of concise, efficient synthetic methodology for the stereo- and enantio-selective construction of stereochemically adorned acyclic molecules.[1,2] Indeed, considerable effort has been devoted towards the development of highly stereoselective syntheses of the so-called propionate (*e.g.*—CHMe—CHOH—CHMe—CHOH—), acetate (*e.g.*—CHOH—CH_2CHOH—CH_2—)

and glycolate (*e.g.*—CHOH—CHOH—CHOH—) segments that are commonly found in these natural products.[3]

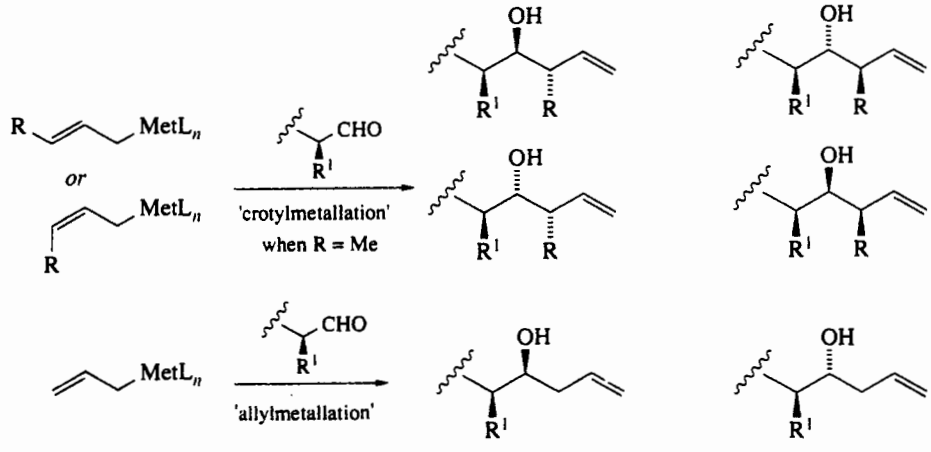
Methods that involve C—C bond formation with the establishment of two new stereogenic centers are of considerable interest in this context. The aldol reaction has proven very useful in this regard, particularly in view of the development of powerful chiral enolates capable of controlling the stereochemical course of reactions with chiral aldehydes *via* the principle of double asymmetric synthesis.[4,5]

The reactions of allyl metal reagents and carbonyl compounds offer a complementary approach to the aldol reaction for acyclic stereocontrol.[6] Many allyl metal reagents are known, many react with high stereoselectivity with carbonyl compounds and imines, and in nearly all cases the reactions are operationally straightforward. Additional synthetic versatility is provided by the ease of preparation of many substituted and highly functionalized allyl organometallic reagents, and the ability to store many of these (*e.g.* B, Si and Sn based reagents) until needed. Besides serving as 'aldol equivalents', the homoallylic alcohol products are easily manipulated to other useful synthetic intermediates by transformations of the double bond (Scheme 1).



Scheme 1

Several factors must be considered in selecting a crotyl metal or allyl metal reagent for use in an acyclic stereoselective synthesis. First, it is necessary that the new stereocenters generated in concert with the new C—C bond (Scheme 1) be formed with a high degree of stereoselectivity. This is the problem of simple diastereoselectivity. Two diastereomeric products may be produced, and in this chapter Masamune's *syn/anti* nomenclature system will be used to describe them.[7] Second, the issue of diastereofacial selectivity is encountered if the aldehyde (or other C=X reaction partner) is chiral. This is a problem of relative diastereoselectivity, and four products may be produced in the reactions of the crotyl organometallics (Scheme 2). The diastereofacial selectivity issue is also critical in the reactions of allyl metal reagents and chiral C=X electrophiles.



Scheme 2

A major goal of research in the allyl metal area has been the development of a family of allyl organometallic reagents that provide highly selective access to each of the four possible crotyl adducts and the two possible allyl adducts indicated in Scheme 2. While many crotyl organometallic solutions exist to the problem of simple diastereoselection, the issue of aldehyde diastereofacial selectivity (relative diastereoselection) has been much more difficult to solve. Although specific cases have been reported, and are reviewed here, that proceed with excellent selectivity, these are exceptions to the general rule that poor to moderate diastereofacial selectivity is obtained in reactions of chiral aldehydes and achiral allyl or crotyl metal compounds. Thus, recourse to the powerful technique of double asymmetric synthesis is generally required to achieve synthetically useful levels of selectivity in reactions of the type summarized in Scheme 2.

The purpose of this review is to provide a summary (through to the end of 1988) of the uncatalyzed reactions of type I and type III allyl organometallics with C=X electrophiles. Most of the examples involve aldehydes and ketones, but the reactions of allyl organometallics with imines are also covered. Because the focus of this review is on selectivity and synthetic efficiency, this review is not intended to be as comprehensive as an 'Organic Reactions' chapter or a *Chemical Reviews* article. Rather, we have attempted to define and illustrate the factors that influence stereoselectivity, to provide access to the most pertinent literature, and, most importantly, to provide a basis for selection of an allyl organometallic reagent for application in specific synthetic problems.

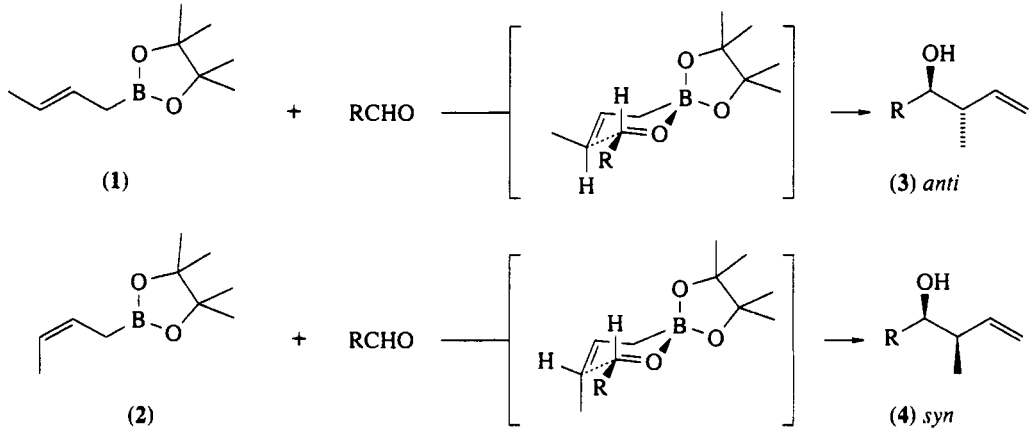
1.1.2 SIMPLE DIASTEREOSELECTION

1.1.2.1 General Considerations

1.1.2.1.1 Mechanistic classification of crotyl organometallics

The reactions of carbonyl compounds and imines with allyl metal and crotyl metal reagents derived from a variety of metals, including aluminum, antimony, bismuth, boron, cadmium, chromium, cerium, copper, indium, lithium, magnesium, manganese, molybdenum, potassium, silicon, tin, titanium, zinc and zirconium, among others, have been investigated.[6] Prior to approximately 1978 the major interest was in controlling the S_E2 or S_E2' regioselectivity in the coupling of allylic organometallics and electrophiles.[6a] Roughly 10 years ago, however, significant synthetic interest began to emerge in the control of the stereochemistry of the C—C bond formed in the reactions with carbonyl electrophiles.[8] Heathcock reported in 1978 that the Hiyama (*E*)-crotylchromium(II) reagent undergoes highly *anti* selective additions to aldehydes,[9] and in 1979 Hoffmann reported that (*Z*)-crotylboronates provide the *syn*-homoallylic alcohol products stereoselectively.[10]

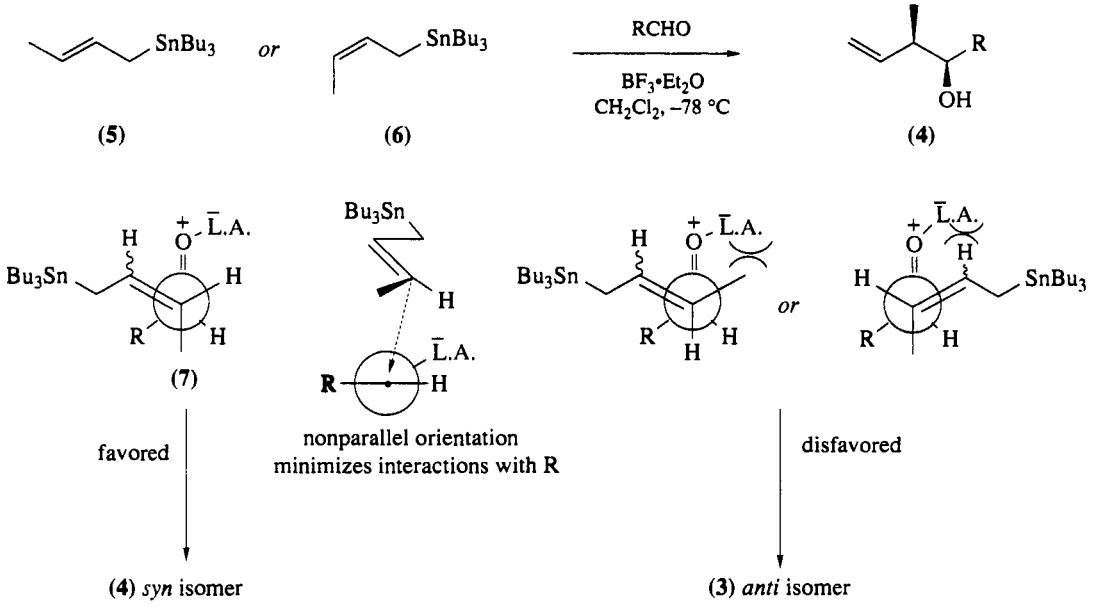
Three classes of crotyl organometallics have now been identified, based on mechanistic and stereochemical preferences.[11]



Scheme 3 Type I aldehyde addition reactions of crotylboronic esters

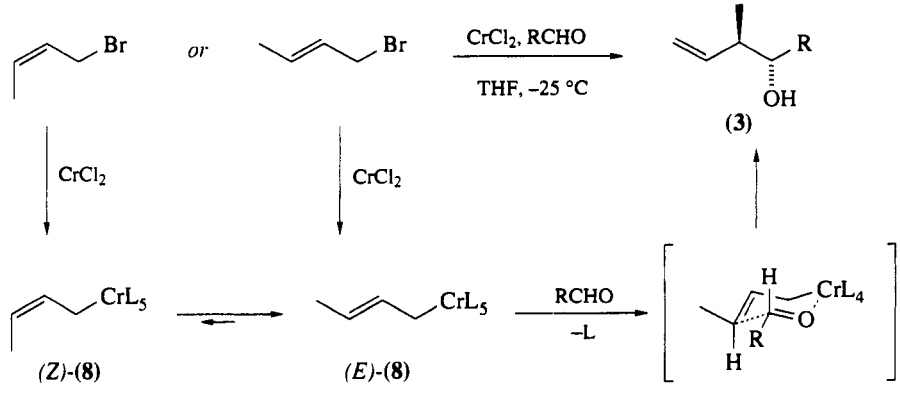
Type I crotyl organometallics react with aldehydes, presumably *via* chair-like transition states, such that the stereochemical information present in the reagent is transmitted to an *anti* (from (*E*)-alkene precursors) or a *syn* (from (*Z*)-alkene precursors) relationship about the new C—C bond of the product (Scheme 3). A detailed analysis of possible transition states appears in a subsequent section. Type I stereoselectivity has been observed for crotyl organometallics incorporating boron, aluminum, silicon and tin (thermal reactions).

Type II crotyl organometallic reagents undergo Lewis acid catalyzed carbonyl additions *via* pathways that tend to be stereoconvergent. That is, both geometric isomers of the reagent preferentially lead to the same (*syn*) product diastereomer (Scheme 4). Reagents based on tin, silicon and titanium, among others,[14b] belong in this category.[12–14]



Scheme 4 Type II Lewis acid catalyzed aldehyde addition reactions of crotylstannanes

The stereoconvergence of the Lewis acid catalyzed reactions of aldehydes and crotylstannanes (**5**) and (**6**) is particularly striking, with very high *syn* selectivity being realized with either reagent and $BF_3{\cdot}Et_2O$ as catalyst.[12a,c] These reactions have been reported to proceed through open, acyclic transition states in which the carbonyl oxygen is coordinated with a Lewis acid and the reagent double bond approaches the carbonyl oxygen in an antiperiplanar fashion.[12a] However, stereochemical studies performed by Denmark suggest that a synclinal orientation may be preferred.[15] The stereoconvergence is most easily ra-



Scheme 5 Type III reactivity of crotylchromium(II) reagents

tionalized if it is assumed that the two reactants approach in a nonparallel manner so as to minimize interactions between the allyl metal reagent and R (see 7 in Scheme 4).[16]

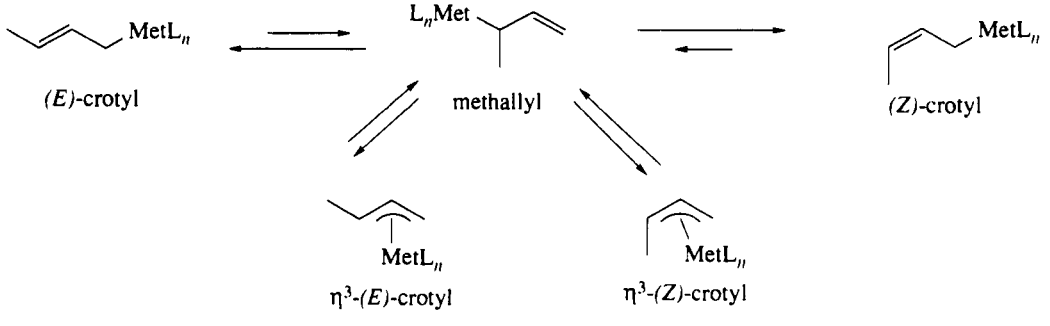
The type II Lewis acid catalyzed additions of allyl organometallics with C=X electrophiles are not covered in this chapter, since this is the topic of a separate survey elsewhere in this volume (see Chapter 2.2).

Type III crotyl organometallics react with aldehydes to give mainly the *anti* addition product regardless of the alkene geometry of the reagent (or its precursors).[9b,c,17–19] Type III crotyl metal reagents typically are generated *in situ* and presumably equilibrate to the more stable and/or more reactive (*E*)-isomer, which then reacts *via* a cyclic transition state to give the *anti* adduct (Scheme 5). This is strikingly demonstrated by the reactions of the crotylchromium reagent (**8**) generated either from (*E*)- or (*Z*)-crotyl bromide and $CrCl_2$: both experiments provide the *anti*-homoallyl alcohol (**3**) from PhCHO with very high diastereoselectivity.[9b,c] Other well-studied, synthetically useful type III crotyl organometallics are based on Ti and Zr.[17–19]

1.1.2.1.2 Configurational stability of crotyl organometallics

The principal difference between type I and type III crotyl organometallics is their configurational stability (type I), or lack thereof (type III), under the conditions of the reactions with C=X electrophiles. The stereochemical integrity of type I allyl organometallics is obviously critical to their successful application in synthesis, since any (*E*) to (*Z*) isomerization prior to reaction will have a detrimental effect on the ratio of 3,4-*anti*/*syn* product diastereomers. It is obviously necessary as well that they be accessible by highly stereoselective synthetic routes, and preferably also be stable to storage. The lack of configurational stability of type III reagents, however, means that high stereochemical control need not be exercised over the construction of allylic halide or other organometallic precursors. Thus, for example, many type III crotyl-titanium and -zirconium reagents are prepared from crotyllithium or crotylmagnesium bromide, which exist as mixtures of rapidly equilibrating (*E*)- and (*Z*)-isomers,[20] since the (*Z*)-crotyl-titanium or -zirconium species equilibrates rapidly to the (*E*)-isomer, which is either highly favored at equilibrium or the more reactive of the two.[17,19] Crotyllithium or crotylmagnesium bromide, however, cannot be used in the preparation of type I crotyl organometallics since mixtures of (*E*)- and (*Z*)-isomers will be produced. One route to configurationally defined type I crotyl organometallics thus involves the (*E*)- and (*Z*)-crotylpotassiums that can be generated with high isomeric purity and are configurationally stable in the absence of traces of O_2.[20a,21]

Allyl metal compounds can exist in either the monohapto η^1- or trihapto η^3-forms. Crotyl metal compounds that exist in the η^1-form, including those classified as type I reagents, are generally sensitive to metallotropic rearrangements (sequential 1,3-shifts) which affect (*E*) to (*Z*) isomerization *via* the intermediacy of the methallyl metal isomer (Scheme 6). Trihapto, or π-bound, allyl metal reagents can exist in either of two forms: the extended or (*E*)-isomer, and the U-shaped or (*Z*)-isomer. These η^3-reagents can also isomerize if a pathway for interconversion with the η^1-methallyl intermediate is energetically accessible.



Scheme 6

Allylboron compounds have been the most widely studied of the type I allyl organometallics.[6b] Of these, the dialkylcrotylboranes isomerize most readily and often require handling at temperatures below −78 °C for isomerization to be suppressed.[22] Thus, it is probably more appropriate to view such compounds (*e.g.* crotyl-9-BBN) as type III crotyl organometallics. The boratropic isomerization of dialkylcrotylboranes, however, is sensitive to steric factors. For example, the (*E*)- and

(*Z*)-crotyldiisopinocampheylboranes undergo highly stereoselective additions to aldehydes at –78 °C.[23] Nevertheless, these reagents are too labile to be prepared and stored for subsequent use.[23c] The boratropic shift may also be suppressed by replacing the alkyl ligands on boron with electron-donating alkoxy or amino groups that stabilize the electrophilic boron atom by resonance. Replacement of one alkyl ligand of an allyldialkylborane with an alkoxy group stabilizes the reagent at temperatures up to –20 °C, but using an amino ligand suppresses the boratropic rearrangement at temperatures up to 150 °C.[24] Replacement of both alkyl ligands with alkoxy groups gives allylboronic acid esters that can be handled at room temperature without isomerization; many have been distilled and their isomeric purity determined by capillary GC analysis.[25] These heteroatom-stabilized allylboron reagents, however, readily isomerize in the presence of Lewis acids.[10b,26]

Type I crotyl metal reagents based on silicon and tin have also proven useful synthetically. Crotyltrimethylsilane is reported to be configurationally stable at elevated temperatures,[27] but only type II carbonyl addition reactions (Lewis acid catalyzed) have been reported for this compound. Type I reactivity has been demonstrated for pentacoordinate crotyl silicates, and available stereochemical evidence suggests that these reagents are configurationally stable.[28] The crotyltrialkylstannanes, on the other hand, undergo carbonyl additions either thermally (type I reactivity)[8a] or in the presence of Lewis acid catalysts (type II reactivity).[12] These compounds readily isomerize in the presence of Lewis acids,[12c,29] and there are also indications that they may spontaneously isomerize (uncatalyzed) at temperatures below 100 °C.[30] Configurational instability, however, has not been demonstrated under the conditions of thermal additions to aldehydes.[8] Crotylstannanes such as (crotyl)SnX_3 and (crotyl)SnR_nX_{3-n} are more reactive than the trialkylcrotylstannanes,[31] and are probably highly prone to isomerization because of the Lewis acidity of the tin atom.[29,32]

Configurational lability is desirable in type III reagents, in as much as one geometric isomer is more reactive and/or highly favored at equilibrium. η^1-Crotyl-chromium, -titanium and -zirconium compounds apparently satisfy these requirements,[9,17,18] while η^3-crotyltitanium reagents such as dicyclopentadienylcrotyltitanium appear to be configurationally stable.[19] η^3-Cyclopentadienylcrotylmolybdenum complexes also appear to be stable.[33]

Many other crotyl organometallics that would be classified as type III reagents based on their configurational instability, including crotyl-cadmium, -lithium, -magnesium and -zinc, are not generally useful for diastereoselective synthetic conversions since mixtures of *syn*- and *anti*-homoallyl alcohols are obtained in reactions with achiral aldehydes.[6d] The equilibrium between the (*E*)- and (*Z*)-crotyl isomers is not highly biased in these cases,[20] consequently the poor diastereoselectivity suggests that the two isomers have comparable reactivity towards carbonyl electrophiles. Synthetically useful results have been obtained with reagents containing these metals only in cases where the crotyl metal compound is sterically biased or contains chelating substituents such that one geometric isomer is substantially favored at equilibrium.[34]

1.1.2.1.3 Transition states for the reactions of type I and type III crotyl organometallics with C=X electrophiles

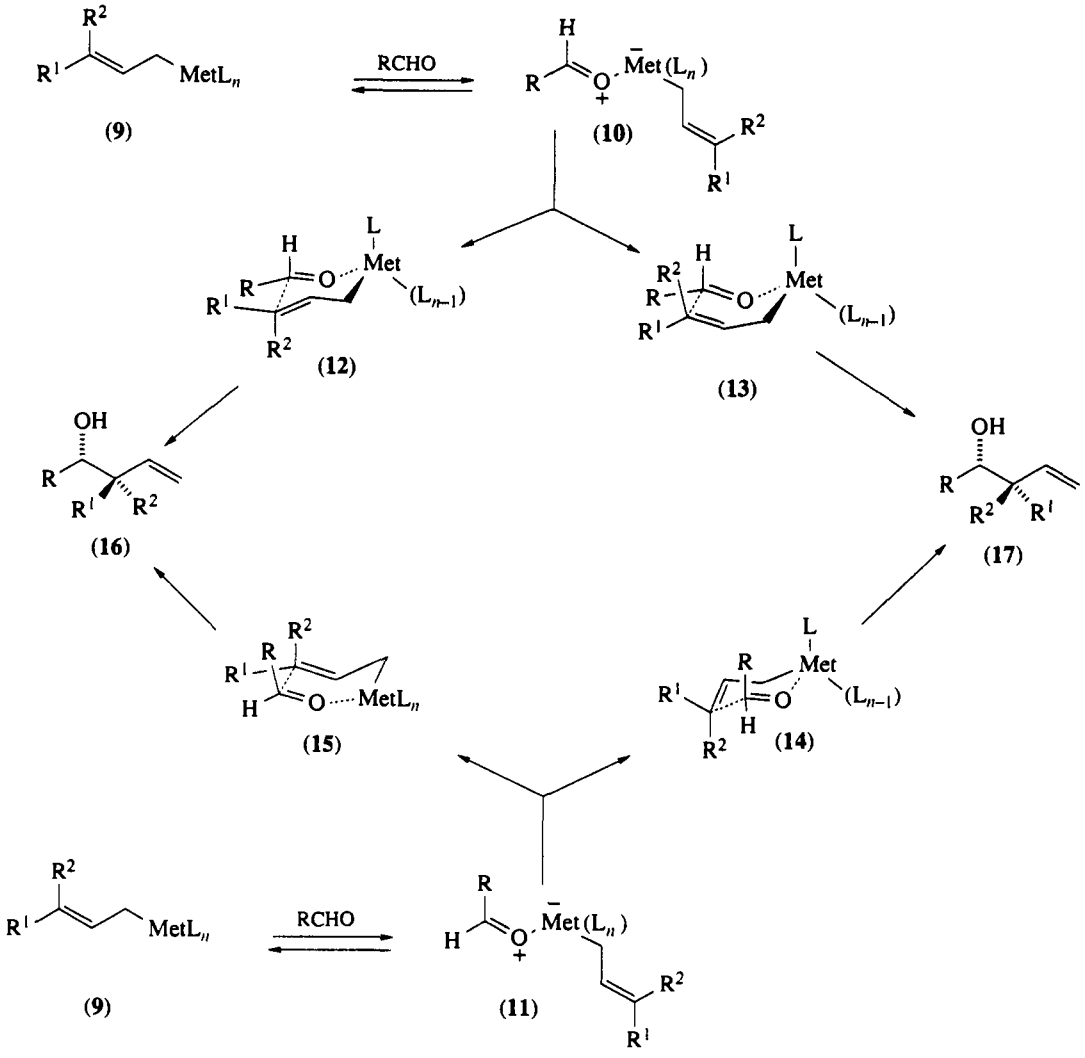
Another factor that influences the diastereoselectivity of the C—C bond-forming process concerns the selectivity for reaction through a single transition state. Clearly, if two or more diastereomeric transition states are accessible, the reaction diastereoselectivity will suffer.

Possible transition states for the reactions of type I and III crotyl organometallics with aldehydes are depicted in Scheme 7. Most of the available stereochemical evidence suggests that these reactions proceed preferentially through transition state (**12**) in which the metal is coordinated to the carbonyl oxygen *syn* to the smallest carbonyl substituent, H. This necessitates that R of RCHO adopt an equatorial position if the transition state is chair-like, an arrangement that is structurally similar to the Zimmerman–Traxler model commonly invoked for many aldol reactions.[4a] Transition states (**13**) and (**14**), however, may potentially intervene and are frequently cited to rationalize the production of minor diastereomers (**17**).

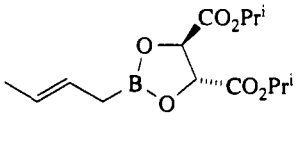
These reactions are probably initiated by the coordination of the carbonyl group with the Lewis acidic metal center (see structures **10** and **11**). Complex (**10**) should be highly favored as suggested by solution and X-ray structural investigations of Lewis acid aldehyde complexes.[35] It is productive then to view the conversion of complex (**10**) (or **11**) to products as a [3,3] sigmatropic rearrangement of a 2-oxa-3-metalla-1,5-diene system. It would be expected then that chair-like transition state (**12**) would be favored over boat-like (**13**) for the same reasons that acyclic Claisen and other [3,3] sigmatropic rearrangements are usually highly chair selective.[36] The alternative chair-like transition state (**14**) is usually viewed as unfa-

vorable owing to the interactions of the axial R of RCHO with the axial metal ligand. It should be noted further that the pathway *via* (**14**) is also kinetically disfavored owing to the location of the metal unit in the more highly sterically congested position *syn* to R in (**11**).

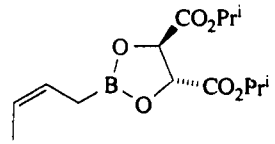
It is difficult to assess the relative importance of transition states (**12**)–(**15**) in the reactions of type III crotyl organometallics since their configurational instability provides an alternative set of pathways for generation of the minor diastereomer (**17**). This question can be addressed more easily with configurationally stable type I reagents as long as the isomeric purity of the reagent is known. In a recent detailed study of the stereochemistry of the reactions of tartrate crotylboronates (**18**) and (**19**) with achiral aldehydes, for example, it has been shown that in most cases the (*E*)-crotyl reagent (**18**) of 98% isomeric purity provides the 3,4-*anti* diastereomer (**16**; R^1 = Me, R^2 = H) with ≥98% diastereoselectivity, while



Scheme 7



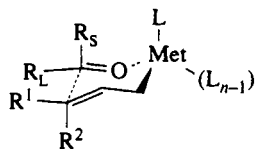
(R,R)-(**18**)



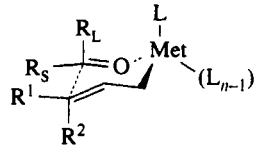
(R,R)-(**19**)

with ≥98% pure (*Z*)-crotyl reagent (**19**) the 3,4-*syn* diastereomer (**16**; R^1 = H, R^2 = Me) is usually obtained with at least 97% selectivity.[37] These reactions thus are highly selective for transition state (**12**), providing evidence that (**13**)–(**15**) must be highly disfavored.

The diastereoselectivity of the reactions of crotyl metal reagents with ketones is frequently lower than with aldehydes, owing presumably to greater competition between transition states (**20**) and (**21**) analogous to (**12**) and (**14**). The possibility that boat-like transition states similar to (**13**) and (**15**) may also be accessible, however, cannot be ruled out.

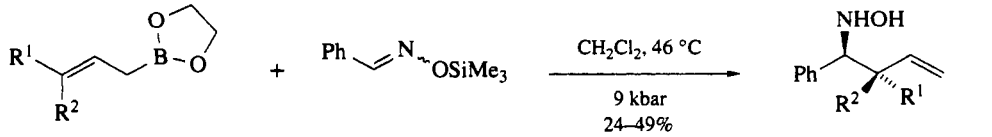


(**20**)



(**21**)

Additional insight into the competition between the various cyclic transition states is provided by a recent study of the reactions of crotylboronates (**22**) and (**23**) with the two isomers of oxime silyl ether (**24**; Scheme 8).[38] The stereoselectivities of these reactions were found to be independent of the geometry of (**24**), both isomers of which were shown to be configurationally stable under the reaction conditions. Since the oxime stereochemistry defines the site of coordination to the boron atom, it seems likely that the (*Z*)-oxime isomer reacts preferentially through the chair-like transition state (**28**), while the (*E*)-oxime reactions proceed preferentially *via* boat-like transition state (**27**). Evidently, the chair-like arrangement

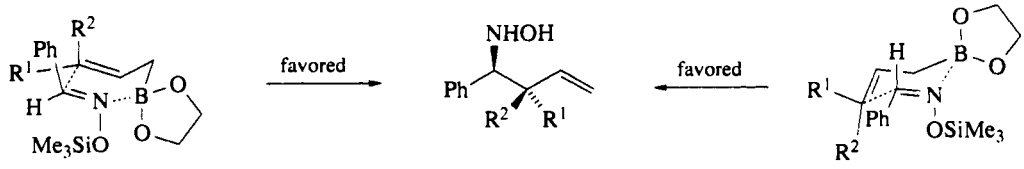


(**22**) R^1 = Me, R^2 = H
(**23**) R^1 = Me, R^2 = Me

(**24**)

(**25**) R^1 = Me, R^2 = H
(**26**) R^1 = H, R^2 = Me

Crotyl boronate	*Oxime ether*	*(25):(26)*
(**22**)	(**24**) *(E)*	95:5
(**22**)	(**24**) *(Z)*	95:5
(**23**)	(**24**) *(E)*	13:87
(**23**)	(**24**) *(Z)*	15:85



(**27**) *(E)*-oxime

(**25**) R^1 = Me, R^2 = H
(**26**) R^1 = H, R^2 = Me

(**28**) *(Z)*-oxime

(**29**)

(**30**)

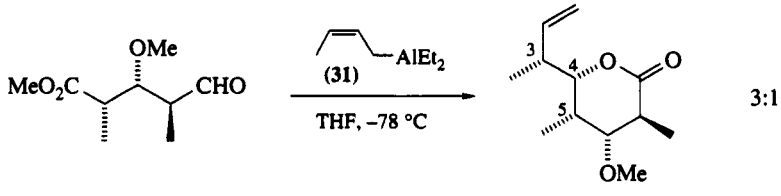
Scheme 8

(**29**) is destabilized by the 1,3-interaction between the axial phenyl group and the axial alkoxy ligand on boron. It may be inferred, therefore, that transition state (**14**) in Scheme 7 is less stable than (**15**), and consequently also that any stereochemical leakage in the reactions of type I crotyl organometallics with aldehydes probably occurs *via* boat transition state (**13**).

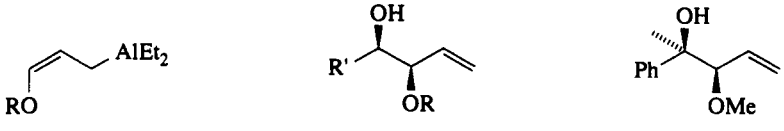
1.1.2.2 Reactions of Type I Crotyl Metal Reagents with Achiral Aldehydes, Ketones and Imines

1.1.2.2.1 Reagents based on aluminum

The parent crotylaluminum reagents have not been thoroughly investigated. (*Z*)-Crotyldiethylaluminum (**31**) has been generated at –78 °C by the reaction of (*Z*)-crotylpotassium with diethylaluminum chloride.[39] The reaction of (**31**) with (**32**) displayed good 3,4-*syn* selectivity, as expected for a type I (*Z*)-crotyl metal reagent, and 3:1 diastereofacial selectivity with respect to the preexisting chirality of (**31**).

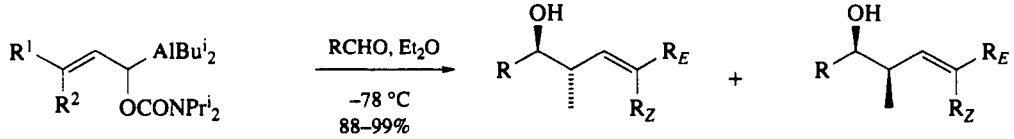


(**32**) (**33**)



(**34**) R = Me
(**35**) R = CMe_2OMe

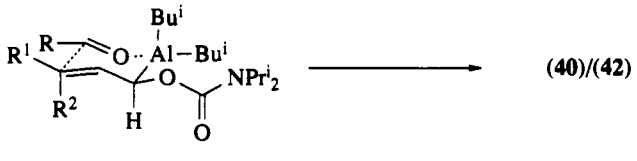
(**36**) (**37**)



(**38**) R^1 = Me, R^2 = H
(**39**) R^1 = H, R^2 = Me

(**40**) $R_E = OCONPr^i_2$, R_Z = H (**42**)
(**41**) R_E = H, $R_Z = OCONPr^i_2$ (**43**)

Reagent	*R*	*(40)*:	*(41)*:	*(42)*:	*(43)*	*anti*:*syn*
(**38**)	Ph	77	6	16	<1	83:17
(**38**)	Me	78	13	8	<1	91:9
(**38**)	Pr^i	90	4	5	<1	94:6
(**38**)	Bu^t	87	10	2	<1	97:3
(**39**)	Ph	8	2	87	3	10:90
(**39**)	Me	8	7	79	6	15:85
(**39**)	Pr^i	7	7	80	6	14:86



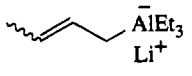
Scheme 9

The stereochemical outcome of this reaction is surprising because it is opposite to the diastereofacial selectivity observed in reactions of (*Z*)-crotylboronates and α-methyl chiral aldehydes. Rather, the preferential production of (**33**) parallels the results observed in the type II Lewis acid catalyzed additions of tributylcrotylstannanes and α-methyl chiral aldehydes.[12b,40]

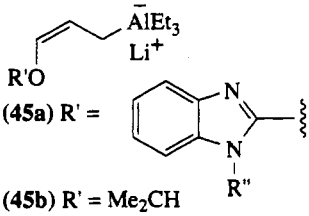
Alkoxy-substituted allylaluminum reagents (**34**) and (**35**) have been prepared by treatment of the corresponding alkoxyallyllithiums with Et_2AlCl in THF at –78 °C.[41] These species provided *syn* diastereomers (**36**) with 9–11:1 selectivity in reactions with aldehydes at –78 °C, while (**37**) was obtained with 4:1 selectivity from the reaction of (**34**) and acetophenone.

(*E*)- and (*Z*)-crotylaluminum reagents (**38**) and (**39**) have been generated at low temperature by treating the corresponding crotyllithium reagents with either Bu^i_2AlCl or Bu^i_2AlOMe.[42] These reagents display reasonable levels of stereoselectivity in reactions with aliphatic aldehydes (Scheme 9), and type I diastereoselection is clearly evident in the data. These reactions occur presumably *via* cyclic transition states with preferential equatorial placement of the allylic $OCONPr^i_2$ substituent. Diastereomer (**41**) is available with much greater stereoselectivity by using the corresponding titanium reagent.[43]

Ate complex (**44**) generated from crotyllithium and triethylaluminum displayed poor diastereoselectivity (56:44, *anti:syn*) in a reaction with benzaldehyde.[44] Heterosubstituted aluminate complexes such as (**45**), however, give good diastereoselectivity in aldehyde addition reactions.[45] The reactions of (**45a**) with aldehydes at –100 °C give the *syn*-3,4-diol monoether (**36**) with ≥95% diastereoselectivity and ≥80% regioselectivity.[45a] Reagents (**45b**) and (**45c**) are significantly more regioselective at –78 °C and show >99% *syn* selectivity with aliphatic aldehydes; the *syn:anti* selectivity with PhCHO, however, is somewhat lower (92:8).[45b] The heteroatom-substituted ate complexes (**46**) have also been examined, but their reactions with aldehydes are not as selective as those of alkoxy substituted reagents (**45**).[45b] The reagent generated by treatment of trimethylsilylallyllithium and $EtAlCl_2$, however, shows excellent selectivity for the *anti* diastereomer (86–100%).[46]

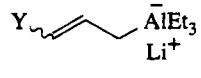


(**44**)



(**45a**) R' =

(**45b**) R' = Me_2CH
(**45c**) R' = $MeOCH_2O$

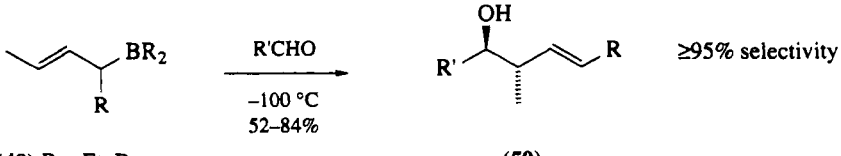


(**46**) Y = SPr^i, SePh, $SiMe_3$

1.1.2.2.2 Reagents based on boron

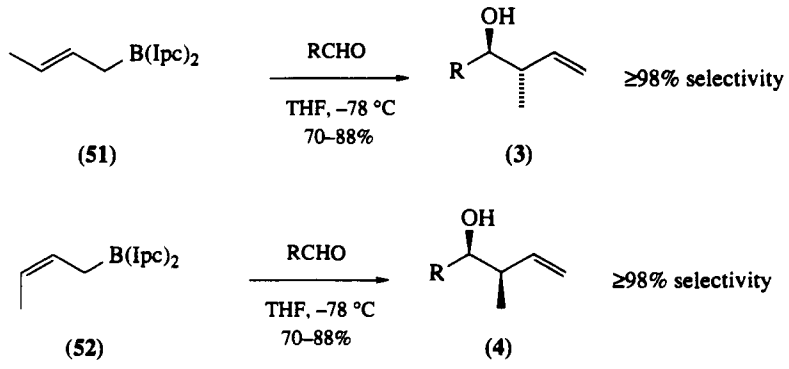
(i) Reactions with aldehydes and ketones

The dialkylcrotylboranes are the most reactive but also the least configurationally stable of the allylboron reagents.[22] Mixtures of *anti*- and *syn*-homoallyl alcohols, enriched in the *anti* isomer, are obtained in the reactions of aldehydes with crotyl-9-BBN (**47**) and other $R_2BCH_2CH{=}CHR$ (**48**) reagents. For example, the reactions of (**47**) and glyoxylate esters provide the *anti* diastereomer with up to 3:1 selectivity,[47] while the reactions of (**48**; R = Et, Bu) with various aldehydes at –78 °C provide the *anti* diastereomer with 61–88% selectivity.[48] Mixtures of *anti* and *syn* diastereomers are similarly obtained when (**49**) is treated with aldehydes at –78 °C.[22c] When (**49**) is generated and used at –100 °C, however, the *anti* diastereomer (**50**) is obtained with >95% diastereoselectivity. The boratropic shift is also sensitive to and retarded by steric factors, as evidenced by the crotyldiisopinocampheylboranes (**51**) and (**52**) that are generated at –78 °C and undergo highly diastereoselective additions to aldehydes at that temperature.[23]

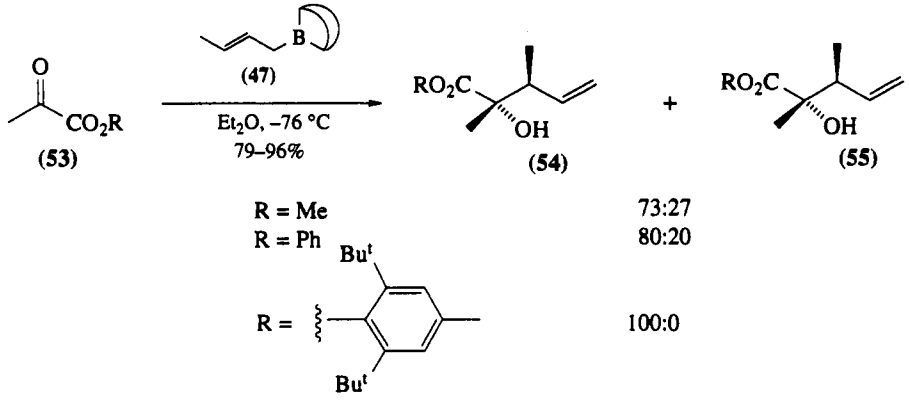


(**49**) R = Et, Bu

(**50**)

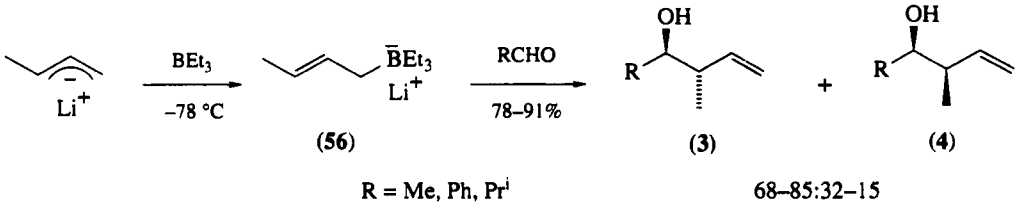


The reactions of crotyl-9-BBN (**47**) and pyruvate esters have been studied.[49] As was observed in reactions with glyoxylates,[47] stereoselectivity depends on the steric bulk of the ester group (Scheme 10). Interestingly, the stereochemistry of the major product (**54**) suggests that the CO_2R substituent adopts an equatorial position in the cyclic transition state like (**20**).



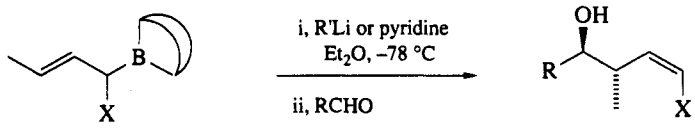
Scheme 10

The reactions of aldehydes with crotylboron ate complexes have also been investigated. Ate complex (**56**), generated by the addition of Et_3B to crotyllithium, exists mainly as the (*E*)-isomer and displays moderate selectivity (68–85%) for the *anti* diastereomer in reactions with various aldehydes (Scheme 11).[44] Greater selectivity has been achieved by using ate complexes generated *in situ* from (**57**; Scheme 12).[50] Diastereoselectivity is extremely high (>98:2) in reactions in which (**57**) is first treated with *n*-butyl- or *s*-butyl-lithium, but yields are only moderate (50–62%) due to competitive transfer of the alkyl group introduced as RLi. Yields of (**58**) are generally improved when pyridine is the additive, but overall stereoselectivity is somewhat lower (typically 88–92%).



Scheme 11

Yamamoto has rationalized these results by invoking cyclic transition states such as (**59**) for the reactions of (**57**).[44,50] This transition state seems unlikely, however, since the boron atom in the ate complex has a full octet and so no association with the carbonyl oxygen is possible prior to the transition state. A concerted pathway in which the new C—C and B—O bonds form as the allylic C—B bond

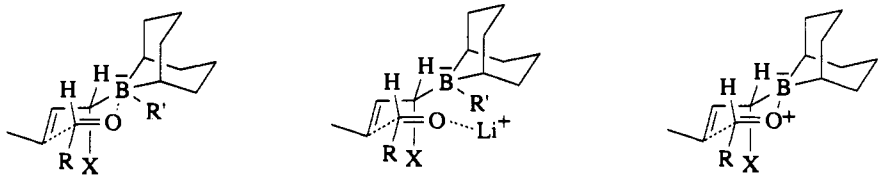


(57) a: X = $SiMe_3$; b: X = $SnMe_3$ **(58)**

Reagent	*R*	*Additive*	*Yield (%)*	*(58):Others*
(57a)	Ph	Bu^nLi	50	>98:2
(57a)	Ph	Bu^sLi	56	>98:2
(57a)	Bu^n	Bu^nLi	62	>98:2
(57a)	Ph	Pyridine	75–90	88–92:12–8
(57b)	Ph	Pyridine	90	Not determined
(57a)	Bu^n	Pyridine	70	90:10

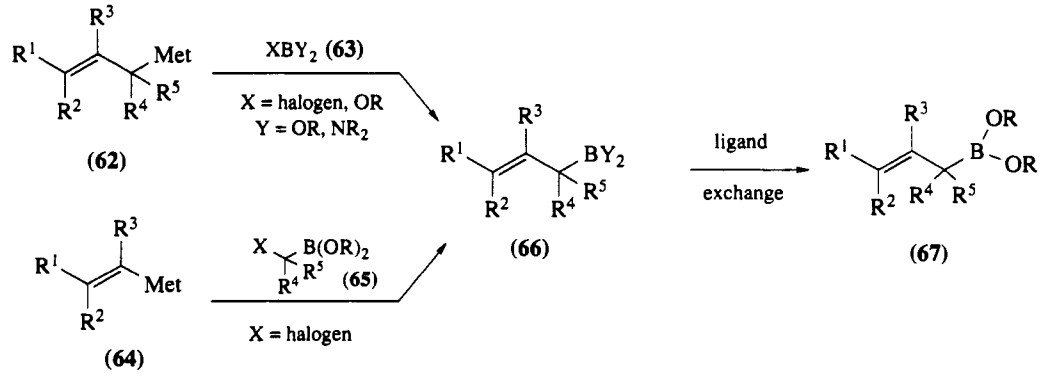
Scheme 12

breaks is also unreasonable for stereoelectronic reasons, since this would constitute an S_N2 reaction at boron with an angle of *ca.* 110° relating the incoming and departing groups. An alternative explanation involves a synclinal transition state such as (**60**) in which the carbonyl group is coordinated to a lithium cation that is held in close proximity to the negatively charged boron atom.[51] The X substituent will preferentially adopt a conformation in the plane of the C=C double bond so as to minimize interactions with the 9-BBN unit, which in turn reinforces a much higher preference for an (*E*)-alkene in the reactions of (**57**) than (**56**), which lacks a bulky allylic X group. The reactions of (**57**) in the presence of pyridine are adequately explained by cyclic transition state (**61**), since the carbonyl group should be capable of displacing pyridine as a ligand on boron.



(59) **(60)** **(61)**

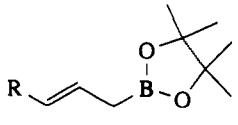
In contrast to the crotylboranes, crotylboronates have found widespread application in acyclic diastereoselective synthesis owing to their ease of preparation, configurational stability and highly stereoselective reactions with aldehydes.[3,6b,10,25] Substituted allylboronates are accessible by one of two general routes: (i) functionalization of a configurationally defined allyl anion (**62**) with an electrophilic boron reagent (**63**); or (ii) substitution of an α-haloalkylboronate (**65**) with a vinyl organometallic reagent (**64**; Scheme 13).



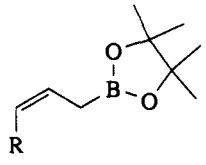
Scheme 13

Crotylboronates such as (**1**) and (**2**) are best prepared starting from (*E*)- and (*Z*)-crotylpotassium.[21] The crotylpotassiums have been functionalized with electrophilic boranes including $FB(OMe)_2$,[21,25] $ClB(NEt_2)_2$[10] and $B(OPr^i)_3$,[37] the products of which are either hydrolyzed to the crotylboronic acids and then treated with the appropriate diol[25,37] or directly transesterified as in the $ClB(NEt_2)_2$ procedure.[10] An advantage to the $FB(OMe)_2$ method is that crotylboronates (**68**) and (**69**) are generated *in situ* and may be directly treated with an aldehyde in a one-pot operation.[21] Substituted crotylboronates (**70**)–(**72**), among others, have also been prepared in this way.[21c,52] Recent optimization studies involving the synthesis of tartrate crotylboronates (**18**) and (**19**), however, have revealed that the yield (14–35%) and isomeric purity (92–96%) drop substantially as the $FB(OMe)_2$ procedure is scaled up.[37] Consistently good results have been obtained when the crotylpotassiums are treated with $(Pr^iO)_3B$ (70–75% yields of **18** and **19**, ≥98% isomeric purity), and it is this procedure that should be adopted for the large-scale preparation of achiral crotylboronates such as (**1**) and (**2**).

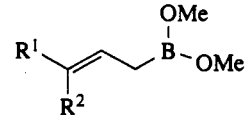
Substituted allylboronates (**73**)–(**79**) have been prepared by using similar methods. Of these, only the (*E*)-γ-alkoxyallylboronates (**73**) and (**75**) have proven particularly troublesome to prepare owing to the difficulty of generating (*E*)-alkoxyallylpotassium with high isomeric purity.[53]



(**1**) R = Me
(**73**) R = OMe
(**75**) R = $OCH_2CH_2SiMe_3$
(**78**) R = $SiMe_3$

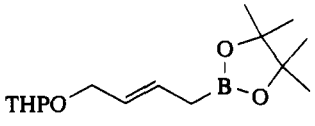


(**2**) R = Me
(**74**) R = OMe
(**76**) R = $OCH_2CH_2SiMe_3$
(**77**) R = OMOM
(**79**) R = SMe

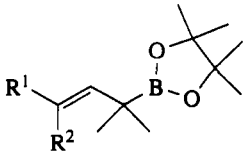


(**68**) R^1 = Me, R^2 = H
(**69**) R^1 = H, R^2 = Me
(**70**) R^1 = H, R^2 = Et
(**71**) R^1 = CH=CHMe (*Z*), R^2 = H
(**72**) R^1 = H, R^2 = CH=CHMe (*E*)

The α-halomethylboronate alkylation method (Scheme 13) is extremely useful for the preparation of substituted allylboronates that cannot be prepared *via* the allyl anion route. Notable examples that fall into this category are (**80**)–(**82**).[10,25,56] The only limitation to this method as a preparative route is the occasional coproduction of alkenylboronates that presumably arise *via* an α-elimination pathway involving the ate complex generated upon addition of (**64**) to (**65**).[25,57]



(**80**)



(**81**) R^1 = Me, R^2 = H
(**82**) R^1 = H, R^2 = Me

Results of representative reactions of substituted allylboronates and achiral aldehydes are summarized in Table 1. It is noteworthy that in the majority of cases the reaction diastereoselectivity closely parallels the isomeric purity of the reagents, thus underscoring the requirement that the allylboronate synthesis be highly stereoselective. Dimethyl crotylboronates (**68**) and (**69**) are more reactive than (**1**) and (**2**), as indicated by the fact that the reactions of (**68**) and (**69**) are complete within a few hours at –78 °C while those of (**1**) and (**2**) include an overnight period at room temperature.[59] Reagents (**73**)–(**79**) are even less reactive than (**1**) and (**2**), their reactions requiring several days at room temperature to reach completion.[60] A detailed study of the temperature dependence of diastereoselectivity, however, has not been reported to date.

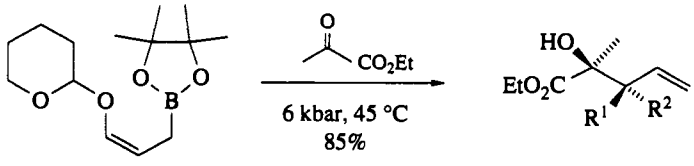
Several studies have noted that (*E*)-allylic boronates are more reactive than their (*Z*)-alkene isomers.[10,25,53,55,58] Thus, by using an (*E*)-allylic boronate as the excess reagent, it is possible to achieve a kinetic enhancement of the reaction diastereoselectively. This is nicely illustrated by the data in entries 15–19 of Table 1: reagents (**73**) and (**75**) of *ca.* 90% isomeric purity were treated with 0.9 equiv. of aldehyde and the *anti* diastereomer (**83**) was obtained with 94 to >98% selectivity.[53] Similarly, Schlosser has

Table 1 Diastereoselectivity in the Reactions of Aldehydes and Substituted Allyboronates

(**83**) (**84**)

Entry	*RCHO*	*Reagent*	R_E	R_Z	*Isomeric purity*	*Yield (%)*	(**83**):(**84**)	*Ref.*
1	PhCHO	(**1**)	Me	H	93:7	80	94:6	10
2	PhCHO	(**68**)	Me	H	a	50[b]	99:1	21c
3	MeCHO	(**1**)	Me	H	93:7	40	93:7	10
4	EtCHO	(**1**)	Me	H	93:7	62	93:7	10
5	EtCHO	(**68**)	Me	H	a	61[b]	97:3	21c
6	Me_2CHCHO	(**1**)	Me	H	93:7	59	94:6	10
7	$C_5H_{11}CHO$	(**80**)	$THPOCH_2$	H	93:7	86	93:7	56a
8	$AcOCH_2CH_2CHO$	(**80**)	$THPOCH_2$	H	93:7	71	93:7	56a
9	PhCHO	(**2**)	H	Me	5:95	80	5:95	56a
10	PhCHO	(**2**)	H	Me	5:>95	22	6:94	10
11	PhCHO	(**69**)	H	Me	a	40[b]	4:96	21c
12	MeCHO	(**2**)	H	Me	5:>95	20	7:93	10
13	EtCHO	(**2**)	H	Me	5:>95	26	7:93	10
14	EtCHO	(**69**)	H	Me	a	62[b]	2–4:96–98	21c,58
15	Me_2CHCHO	(**2**)	H	Me	5:>95	51	6:94	10
16	PhCHO	(**73**)	MeO	H	~90:10	87	95:5	53
17	PhCHO	(**75**)	$Me_3SiCH_2CH_2O$	H	~90:10	92	94:6	53
18	EtCHO	(**73**)	MeO	H	~90:10	68	95:5	53
19	Me_2CHCHO	(**73**)	MeO	H	~90:10	77	>98:2	53
20	Me_2CHCHO	(**75**)	$Me_3SiCH_2CH_2O$	H	~90:10	86	>95:5	53
21	PhCHO	(**74**)	H	MeO	5:>95	86	5:>95	53
22	PhCHO	(**76**)	H	$Me_3SiCH_2CH_2O$	5:>95	98	5:>95	53
23	EtCHO	(**74**)	H	MeO	5:>95	94	8:92	53
24	Me_2CHCHO	(**74**)	H	MeO	5:>95	94	11:89	53
25	Me_2CHCHO	(**76**)	H	$Me_3SiCH_2CH_2O$	5:>95	76	11:89	53
26	Me_2CHCHO	(**77**)	H	MOMO	5:>95	90	20:80	53
27	PhCHO	(**78**)	Me_3Si	H	a	89	>98:2	54
28	$n\text{-}C_7H_{15}CHO$	(**78**)	Me_3Si	H	a	78	>98:2	54
29	$AcO(CH_2)_8CHO$	(**78**)	Me_3Si	H	a	92	>98:2	54
30	PhCHO	(**79**)	H	MeS	5:>95	95	2:98	55
31	Me_2CHCHO	(**79**)	H	MeS	5:>95	90	5:95	55

[a]Isomeric purity was not determined. [b]The indicated yields include the preparation of the substituted allylboronate that was generated *in situ*. Yields in all other cases are for experiments in which purified allylboronates were used.



(**85**)

(**86a**) R^1 = OTHP, R^2 = H

(**86b**) R^1 = H, R^2 = OTHP

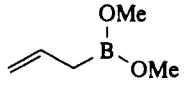
noted that the diastereoselectivity of the reactions of (*Z*)-crotylboronate (**69**) can be enhanced by first treating the reagent with 0.05–0.1 equiv. of acetaldehyde to consume any contaminating (*E*)-crotyl isomer.

The only reactions in Table 1 where diastereoselectivity deviates markedly from the reagent isomeric purity involve the (*Z*)-γ-alkoxyallylboronates (entries 21–26), and then only when a sterically demanding aldehyde (isobutyraldehyde, entries 24–26) or a bulky protecting group is employed.[53] Under these circumstances it appears that boat-like transition state (**13**) becomes competitive with the otherwise favored chair arrangement (**12**; Figure 7).

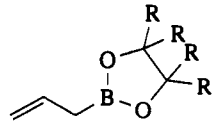
Relatively few studies of the reactions of allylboronates and ketones have appeared.[61] The reaction of (**85**) and ethyl pyruvate, for example, was conducted under 6 kbar pressure at 45 °C for 80 h to give a 9:1 mixture of diastereomers (**86a**) and (**86b**). The stereochemistry of this reaction parallels that seen with crotyl-9-BBN (Figure 10) in that the structure of the major isomer is consistent with a transition state in which the —CO_2Et unit adopts an equatorial position. The same result could occur, however, *via* a boat-like transition state with an axial —CO_2Et group.

(ii) Reactions with C=N electrophiles

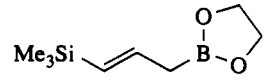
Reactions of allylboronates (**87**)–(**89**) and aldoximes,[62] imines[62a] and sulfenimides[63] have been described. These reactions are considerably slower than those of aldehydes, and consequently reagents (**87**) and (**88**) are generally used in preference to the less reactive pinacol ester (**89**). The reactions of imines and (**87**) proceed at room temperature, while those of (**88**) and oximes and sulfenimides generally require heating in refluxing CCl_4 or toluene. The reaction of (**88**) and oximes can be performed at room temperature if a pressure of several kilobars is applied.[62a]



(**87**)

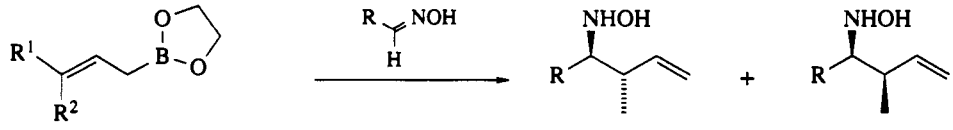


(**88**) R = H
(**89**) R = Me



(**90**)

The stereochemistry of the reactions of oxime ethers and crotylboronates (**22**) and (**23**) have been discussed earlier (Scheme 8).[38] The reactions of the corresponding oximes with (**22**) and (**23**) appear to follow a similar stereochemical course (Scheme 14).[38] Stereoselectivity, however, is not as high with the isobutyraldehyde and pentanal oximes as it is with phenylaldoxime. The reaction of Me_3Si-substituted allylboronate (**90**) and acetaldehyde oxime performed in refluxing CCl_4 similarly provides a 79:21 mixture of the *anti* and *syn* product diastereomers (Me_3Si replacing Me in **25** and **26**).[64] Excellent stereoselectivity for *syn*-homoallylamines has been achieved *via* the Lewis acid catalyzed reactions of aldimines and crotyltributylstannane.[65]



(**22**) R^1 = Me, R^2 = H
(**23**) R^1 = H, R^2 = Me

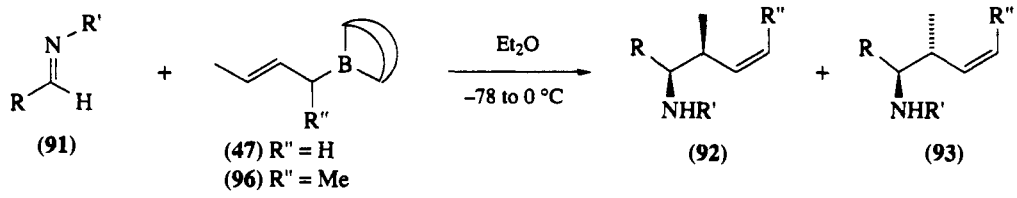
(**25**) (**26**)

Reagent	*R*	*Pressure* (kbar)	*Temp.* (°C)	*Yield* (%)	*(25):(26)*
(**22**)	Ph	9	46	64	95:5
(**22**)	Pr^i	9	46	81	81:19
(**22**)	Bu^n	4	25	84	75:25
(**23**)	Ph	9	46	38	12:88
(**23**)	Pr^i	9	46	65	20:80
(**23**)	Bu^n	9	46	60	30:70

Scheme 14

Yamamoto and coworkers have studied the reactions of crotyl-9-BBN (**47**) and achiral aldimines (Scheme 15).[66] These reactions occur at much lower temperature than those involving crotylboronates because of the greater reactivity of (**47**). No clear stereochemical pattern, however, is apparent in the data. Assuming that (**47**) reacts preferentially as the (*E*)-crotyl isomer, one would expect *anti* diastereomer (**93**) to be the major product *via* transition state (**95a**; Scheme 16) by analogy to Hoffmann's results with oximes and oxime ethers (Schemes 8 and 14).[38] Only in entries 1, 6, 7 and 8 of Scheme 15, however, is this stereochemical result realized. Yamamoto argues that *syn* diastereomer (**92**), the major

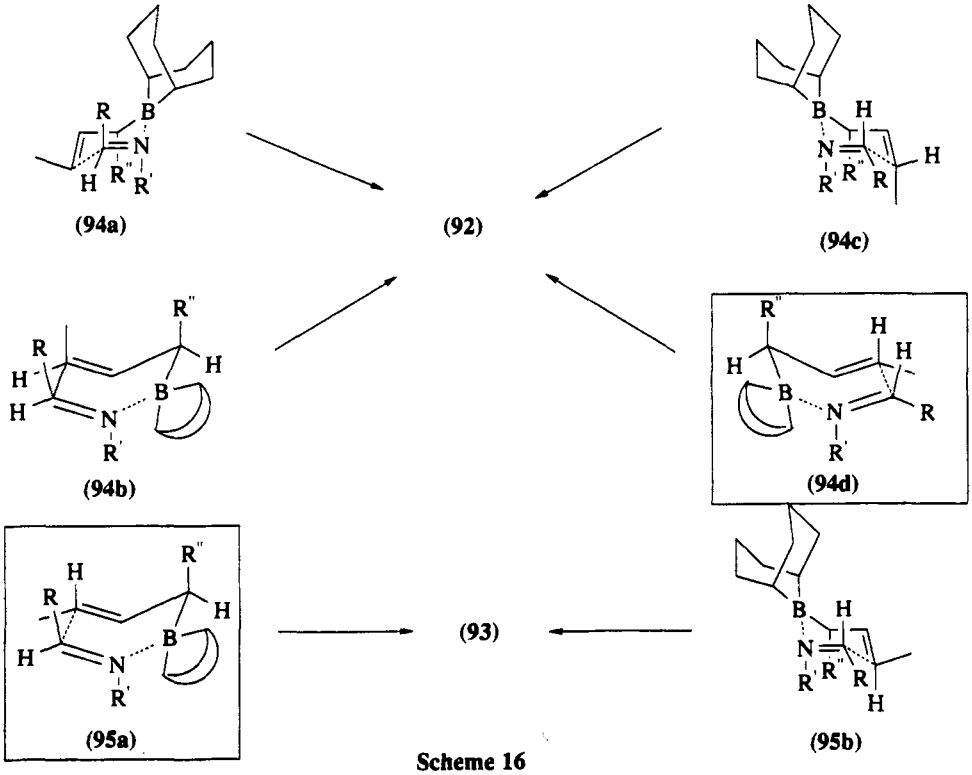
product in entries 2–5 and 9–11, is formed by way of chair-like transition state (**94a**). This seems unlikely, however, since the analogous transition state (**29**) is highly disfavored in the reactions of oximes and crotylboronates (Figure 8). The interactions involving the axial R and the 9-BBN unit in (**94a**) are probably more serious than those involving the axial OR group in (**29**). Thus, (**92**) is probably produced *via*



(**91**) + (**47**) R" = H, (**96**) R" = Me → (**92**) + (**93**)

Entry	*R*	*R'*	*R"*	*Yield (%)*	*(92):(93)*
1	Ph	Ph	H	93	0:100
2	Ph	Pr^n	H	95	85:15
3	Ph	Pr^i	H	79	65:35
4	Pr^n	Pr^n	H	90	75:25
5	Pr^n	Pr^i	H	97	100:0
6	Pr^i	Pr^n	H	95	34:66
7	Pr^i	Pr^i	H	60	30:70
8	Ph	Ph	Me	90	8:92
9	Ph	Pr^n	Me	84	100:0
10	Pr^n	Pr^i	Me	75	100:0
11	Pr^i	Pr^n	Me	78	85:15

Scheme 15



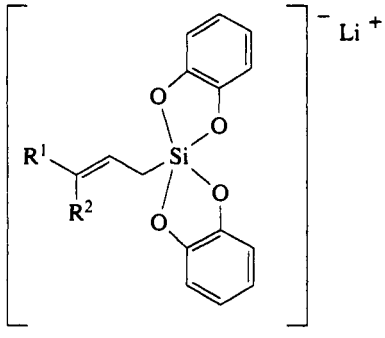
Scheme 16

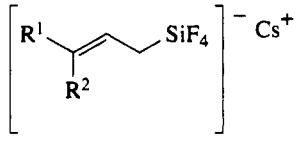
one of the alternative transition states (**94b**) in which the crotylborane has (*Z*)-configuration, (**94c**) in which the imine has isomerized and the crotyl unit is (*Z*), or (**94d**) in which only the imine has isomerized. It is likely that (**94d**) is the most important one in view of the exclusive generation of (**92**) in the reaction of (**96**; R″ = Me): transition states (**94b**) and (**94c**) clearly suffer from serious interactions involving R″.

In the final analysis, it appears that the diastereoselectivity of the reactions of imines and crotylboranes (**47**, **96**) depends on the relative rates of crotyl transfer (*e.g.* **95a** → **93**) *versus* imine isomerization that leads to competitive pathways (*e.g.* **94d** → **92**). When R′ is an aryl group, the rate of crotyl transfer is probably faster than competitive imine isomerization. When R′ is an alkyl group, however, the relative rates are probably inverted. The driving force for imine isomerization is probably that complex (**95a**) is not very stable owing to the bulky 9-BBN unit positioned *syn* to R, while the complex of crotyl-9-BBN (**47**) and a (*Z*)-aldimine (*e.g.* **94d**) is probably much more stable. It is conceivable, therefore, that the overall rate of reaction *via* (**94d**) can be much faster than *via* (**95a**) even though the (*Z*)-imine cannot be detected in solution. Additional research is clearly needed to clarify the stereochemical course of these reactions.

1.1.2.2.3 Reagents based on silicon

Stereoselective reactions of crotylsilicates (**97**)–(**100**) and aldehydes have been described (Scheme 17).[28] These reactions readily proceed at room temperature in the absence of a Lewis acid catalyst, and type I diastereoselection is clearly evident. Evidence supporting a cyclic transition state has been provided through studies of optically active crotylsilicates such as (**101**; Scheme 18).[67] The absolute stereochemistry of the products requires that the reaction is suprafacial with respect to the allylsilane moiety, in contrast to the *anti* stereochemical outcome of S_E' reactions of allylsilanes.[68] Cyclic transition states are also implicated in the reactions of the crotyltrifluorosilanes and CsF, but the crotyltrifluorosilane/Bu_4NF reaction apparently proceeds *via* an uncomplexed allyl anion species.[67]



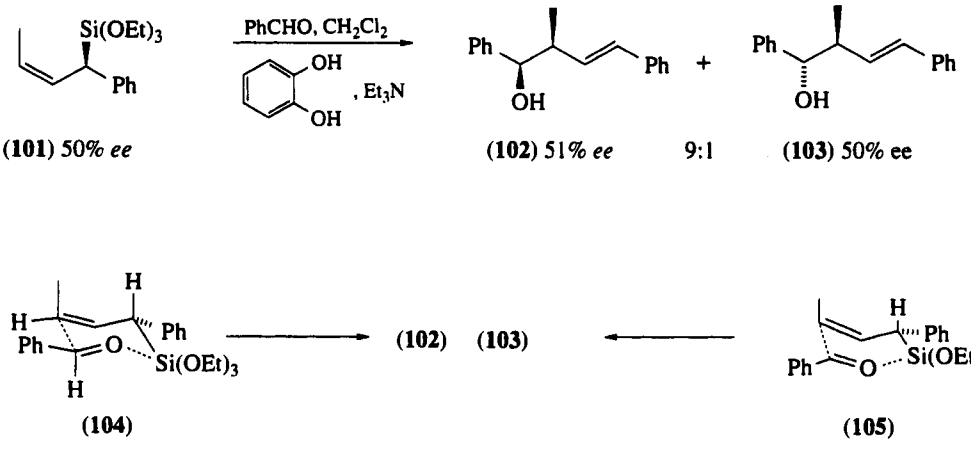


(**97**) R^1 = Me, R^2 = H
(**98**) R^1 = H, R^2 = Me

(**99**) R^1 = Me, R^2 = H
(**100**) R^1 = H, R^2 = Me

RCHO	*Reagent*	*Isomeric purity*	*Yield (%)*	*(3):(4)*	*Ref.*
PhCHO	(**97**)	88:12	82	88:12	28b
PhCHO	(**98**)	21:79	91	22:78	28b
PhCHO	(**99**)	99:1	92	99:1	28d
PhCHO	(**100**)	1:99	96	1:99	28d
n-C_8H_{17}CHO	(**99**)	99:1	96	99:1	28d
n-C_8H_{17}CHO	(**100**)	1:99	89	2:98	28d

Scheme 17



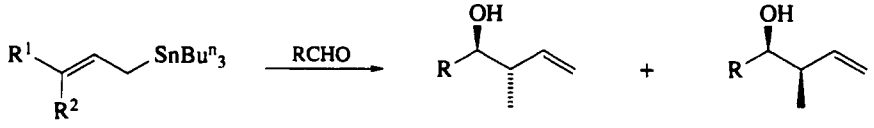
(101) 50% *ee* (102) 51% *ee* 9:1 (103) 50% ee

(104) (102) (103) (105)

Scheme 18

1.1.2.2.4 Reagents based on tin

Type I reactions of aldehydes and trialkylcrotylstannanes have been reported to occur both thermally (20–200 °C) and under high pressure (10 kbar). The first investigation of the thermal reaction was performed with isomerically impure crotyltributylstannanes (**5**; Scheme 19).[8a] A subsequent investigation of the reaction of chloral and isomerically pure (**6**) showed this reaction to be highly selective for the *syn* diastereomer (**4**).[30b]



(**5**) R^1 = Me, R^2 = H
(**6**) R^1 = H, R^2 = Me

(3) (4)

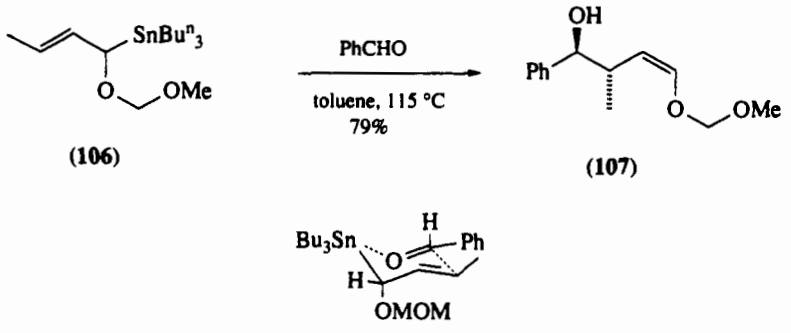
R	*Reagent*	*Isomeric purity*	*Temp. (°C)*	(3):(4)
CCl_3	(**5**)	90:10	20	90:10
CCl_3	(**5**)	65:35	20	67:33
CCl_3	(**6**)	0:100	25	1:99
Ph	(**5**)	92:8	200	87:13
Ph	(**5**)	60:40	200	62:38

Scheme 19

Yamamoto has reported that the reactions of aldehydes less activated than chloral occur at 23 °C using high pressures (10 kbar).[69] The diastereoselectivity of the reactions of (**5**) and aryl aldehydes, however, is only 65–80% in favor of the *anti* diastereomer.

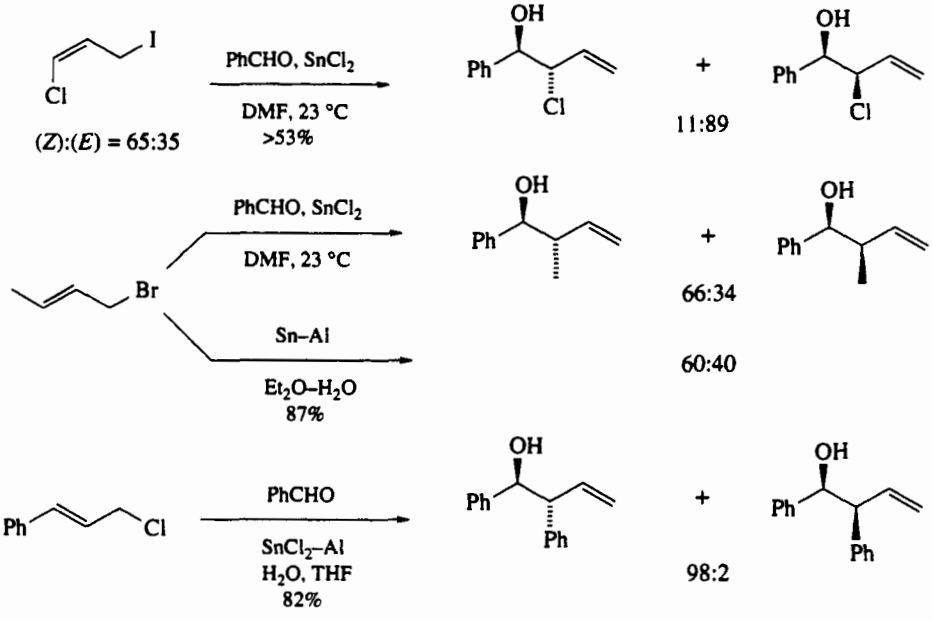
Thomas and coworkers have reported that the readily accessible alkoxy-substituted stannane (**106**) displays excellent *anti* diastereoselectivity in the thermal reactions with a range of aromatic and aliphatic aldehydes.[70] The reaction of benzaldehyde in Scheme 20 is representative. Marshall, however, has reported that the diastereoselectivity of the reactions of $Bu^tMe_2SiO(CH_2)_3C{\equiv}CCHO$ and (**106**) is only 56:44 in favor of the *anti* diastereomer, and that the reaction with β,β-disubstituted acroleins fails altogether.[71]

The thermal reactivity of the crotylstannanes is strongly influenced by the substituents on tin. The reactions of (crotyl)SnX_3 and (crotyl)(butyl)$_n SnX_{3-n}$ with aldehydes have been described, but in no cases has high stereoselectivity been clearly demonstrated.[31] Crotylstannanes of the general structure (crotyl)SnX_nY_{3-n} have also been generated *via* the reactions of allyl halides and SnF_2,[72] allylic acetates,[73] carbonates,[74] and alcohols[75] with $PdCl_2(PhCN)_2$–$SnCl_2$ and allylic phosphates with SnF_2–Et_2AlCl or



(106) (107) (108)

Scheme 20



Scheme 21

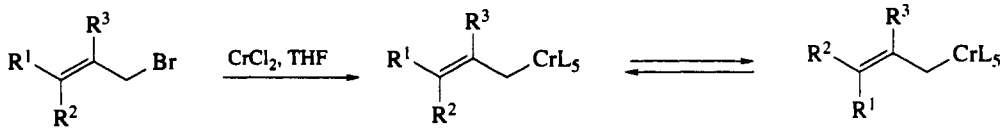
Bu$^n_3$SnLi–Et$_2$AlCl.[76] In none of these cases, however, has diastereoselectivity exceeded 75:25. It is probable that these reagents are configurationally unstable, as implied by the results summarized in Scheme 21.[32b,77] It is noteworthy that cinnamyl halides display very high *anti* selectivity with $SnCl_2$–Al[77a] and Sn–Al[77b] in contrast to the poor results obtained with the crotyl systems.[32b,77c]

1.1.2.3 Reactions of Type III Crotyl Organometallics with Achiral Aldehydes and Ketones

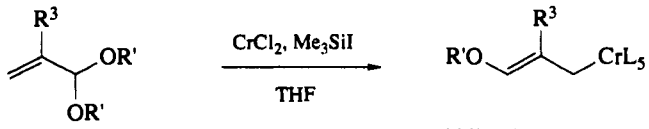
1.1.2.3.1 Reagents based on chromium

Crotylchromium reagents (**8**) are among the most selective and most widely applied of the type III crotyl organometallics.[9] Allylchromiums are typically generated by the reduction of an allylic halide using $CrCl_2$ in THF; the diastereoselectivity decreases in other solvents such as DMF.[9b,c] Commercially available $CrCl_2$ is often used, but several cases have been reported where selectivity is substantially better when $CrCl_2$ is generated *via* the $LiAlH_4$ reduction of $CrCl_3$. Other methods of generating $CrCl_2$ *in situ* lead to crotylchromium reagents that show diminished stereoselectivity.[78] Allylchromium reagents con-

taining vinyl or allylic halides,[9c,79] vinyl sulfones[34c] and even carboalkoxy[80] or cyano[81] substituents have been prepared from suitable allyl halide precursors, while γ-alkoxyallylchromiums have been generated by the reduction of acrolein acetals with $CrCl_2$ in the presence of Me_3SiI (Scheme 22).[82] Stereoconvergence has been demonstrated in several instances, indicating that the isomeric purity and geometry of the allylchromium precursor is not a factor that influences diastereoselectivity.[9b,c,80]



(**8**) R^1 = Me; $R^2 = R^3$ = H
(**109**) R^1 = Me or Bu; R^2 = H; $R^3 = SO_2Ph$
(**110**) R^1 = Me, Bu or Ph; R^2 = H; $R^3 = CO_2Me$



(**111**) R' = Me or Bzl; R^3 = H
(**112**) R' = Bzl; R^3 = Me

Scheme 22

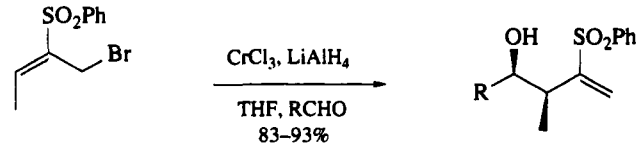
The reaction of aldehydes and substituted allylchromiums (**8**), (**111**) and (**112**) are generally highly selective for the *anti* product diastereomer (Table 2),[9b,c,82] except for the reactions with pivalaldehyde that provide the *syn* diastereomer with modest selectivity. This result has been attributed to the involvement of a boat transition state (**13**; Scheme 7),[9c] although the same product could also be produced *via* a chair transition state (**12**; R^1 = H, R^2 = Me) if the (*Z*)-crotylchromium intermediate is more reactive than the (*E*)-isomer. We favor the latter interpretation, since tartrate (*Z*)-crotylboronate (**19**) is more reactive than the (*E*)-crotyl isomer (**18**) towards pivalaldehyde — the only documented case of a (*Z*)-crotyl metal reagent exhibiting greater reactivity than the (*E*)-isomer.[37a] Boat-like transition states with internal coordination of Cr by the (*Z*)-γ-alkoxy substituent have been invoked to rationalize the *anti* diastereoselectivity of the reactions of (**111**),[82] although here again the stereochemistry is consistent with a chair-like transition state (**12**) and an (*E*)-geometry for (**111**).

Table 2 Diastereoselectivity of the Reactions of Substituted Allylchromiums (**8**) and (**111**) with RCHO[a]

RCHO	*Reagent*	*Yield (%)*	*Diastereoselectivity anti:syn*[b]
PhCHO	(**8**)	96	100:0
PhCHO	(**111**)	98	88:12[c]
Pr^nCHO	(**8**)	59	93:7
n-$C_8H_{17}CHO$	(**111**)	95	87:13
Pr^iCHO	(**8**)	81	97:3
c-$C_6H_{11}CHO$	(**111**)	93	88:12
Bu^tCHO	(**8**)	64	35:65
Bu^tCHO	(**111**)	91	33:67

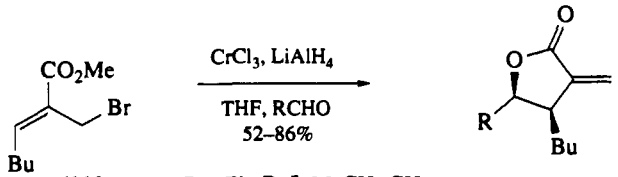
[a]Reactions of (**8**) were performed at 23 °C, while those of (**111**) were performed at –30 °C. Data for (**111**) are for R' = Bzl. [b]Ratio of *anti:syn* homoallyl alcohols. [c]Identical selectivity was obtained for (**111**) with R' = Me or Bzl.

In contrast to these results, *syn* diastereoselectivity is observed in the reactions of (**109**) and (**110**) with aldehydes.[34c,80,81] The stereochemistry in these cases leaves little doubt that it is the (*Z*)-allylchromium species that is involved, presumably as a result of a destabilizing interaction between the R^1 and bulky R^3 substituents in the (*E*)-isomer (Scheme 23). In the case of methallyl derivative (**113**), however, *anti* diastereoselection is realized in this interesting macrocyclization (Scheme 24).[83]



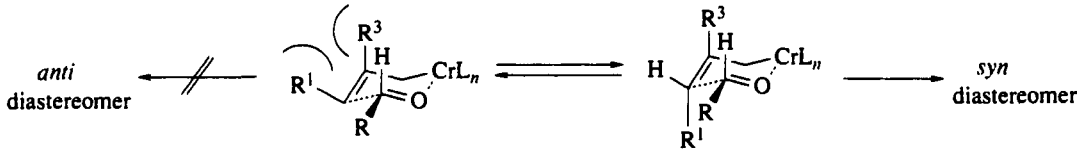
(ref. 80)

(109) R = Bu^i, MeCH=CH, Bu^t

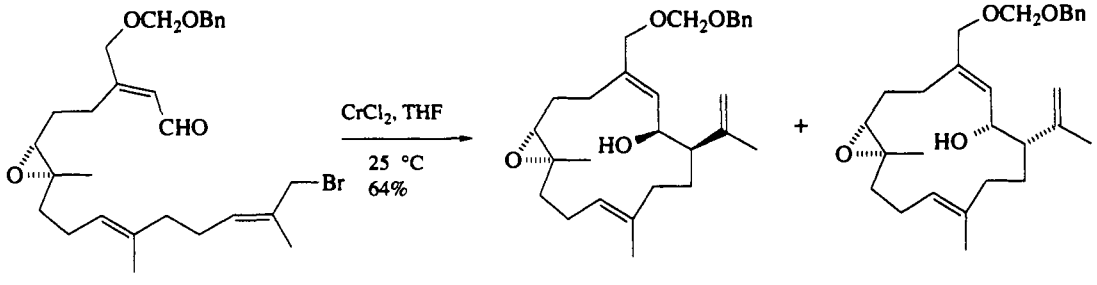


(ref. 81a)

(110) R = Ph, Bu^n, MeCH=CH



Scheme 23

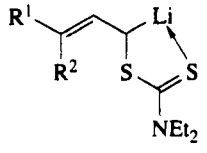


(113)

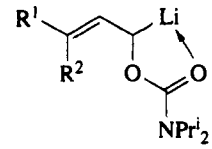
Scheme 24

1.1.2.3.2 Reagents based on lithium

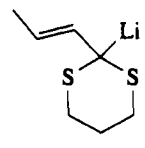
Crotyllithium is configurationally unstable[20] and shows poor regio- and stereo-selectivity in reactions with aldehydes.[6d,84] Regio- and stereo-chemical control has been achieved, however, by using substituted allyllithiums such as (**114**)–(**118**).[34a,b,43b,85] Reagents (**114**)–(**117**) are stabilized by chelation that helps to maintain their isomeric integrity, and type I diastereoselectivity has been demonstrated in reactions with aldehydes.[43b,85] Stereoselectivity is further improved by transmetallation to the corresponding aluminum or titanium reagents (*cf.* Scheme 9).[42,43] Reagent (**118**) reacts preferentially as the (*E*)-crotyl isomer, presumably since the (*Z*)-isomer is destabilized by interactions between Me and an axial S atom in the transition state corresponding to (**12**; Scheme 7, R^1 = Me, R^2 = H).[34a,b]



(**114**) R^1 = Me; R^2 = H
(**115**) R^1 = H; R^2 = Me



(**116**) R^1 = Me; R^2 = H
(**117**) R^1 = H; R^2 = Me

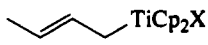


(**118**)

1.1.2.3.3 Reagents based on titanium

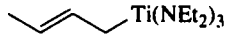
η^1-Crotyltitanium reagents (**119**)–(**121**), prepared by treatment of Cp_2TiX_2, $(RO)_3TiCl$ or $(Et_2N)_3TiCl$ with crotylmagnesium halides, react with aldehydes to give the *anti* diastereomer preferentially.[17] Greatest stereoselectivity in reactions with aldehydes has been achieved by using (**119a**) with X = Br. Reagent (**120a**) with R = Ph is more selective than other alkoxy- or amino-substituted titanium derivatives, including (**120b**) and (**121**; Table 3). Ate complexes (**122**) have also been studied,[17e] but seem to have no particular advantage relative to (**119**)–(**121**). Interestingly, however, the ate complex generated by the addition of allylmagnesium bromide to $Ti(NEt_2)_4$ reacts faster with ketones than aldehydes.[86] The reactions of a number of γ-heteroatom-substituted allyltitanium reagents have also been described.[45b,87]

α-Substituted crotyltitanium reagent (**123**) displays exceptional levels of diastereoselectivity, and is much more selective than the corresponding lithium or aluminum derivatives.[42b,43]

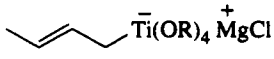


(**119a**) X = Br
(**119b**) X = Cl

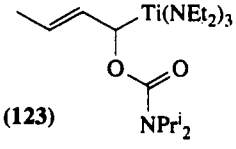
(**120a**) R = Ph
(**120b**) R = Pr^i



(**121**)



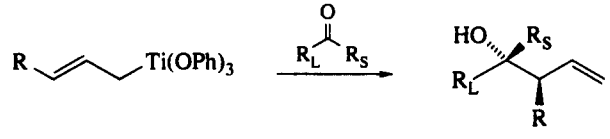
(**122a**) R = Pr^i
(**122b**) R = Ph



(**123**)

Table 3 Diastereoselectivity of Aldehyde Addition Reactions of (**119**)–(**121**)

Reagent	*RCHO*	*Diastereoselectivity (3):(4)*	*Ref.*
(**119a**)	PhCHO	99:1	17a
(**119b**)	PhCHO	60:40	17a
(**119a**)	EtCHO	96:4	17a
(**119a**)	Pr^iCHO	99:1	17a
(**120a**)	PhCHO	85:15	17c
(**120a**)	Pr^iCHO	96:4	17c
(**120b**)	Pr^iCHO	88:12	17c
(**121**)	PhCHO	69:31	17e



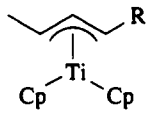
(**120a**) (**124**)

R_L	R_S	*Diastereoselectivity, R =* *Me*	*Bu^n*	*Pr^i*
Ph	Me	88:12	87:13	87:13
Ph	C≡CMe	72:28	77:23	77:23
Bu^t	Me	>98:<2		
Bu^t	Ph	>98:<2		
c-C_6H_{11}	Me	87:13		
c-C_6H_{11}	Et	60:40		

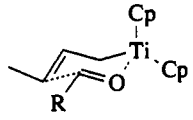
Scheme 25

Seebach has shown that various 2-alkenyltitanium triphenoxides, including (**120a**), display useful levels of diastereoselectivity with ketones, especially when the size difference between the two carbonyl substituents is pronounced (Scheme 25).[17b,d] The major diastereomer (**124**) presumably arises *via* transition state (**20**).

The reactions of η^3-crotyltitanium reagents (**125**) and aldehydes have been studied by Sato and coworkers.[19a,88] These reactions proceed in good yield and with high *anti* diastereoselectivity. For example, the reactions of (**125**; R = H) with propionaldehyde and benzaldehyde are 93–95% selective for the *anti*-homoallyl alcohol.[19a] The stereochemical course is consistent with the reaction proceeding by way of the usual chair-like transition state (**126**).



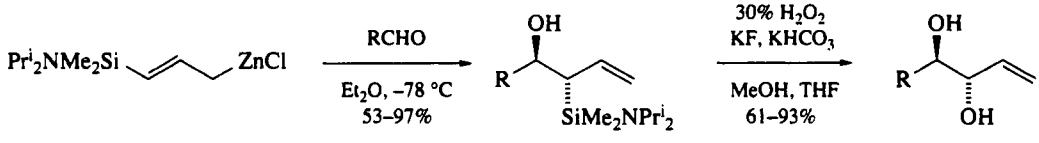
(**125**) R = H, $SiMe_3$, OPh, SPh



(**126**)

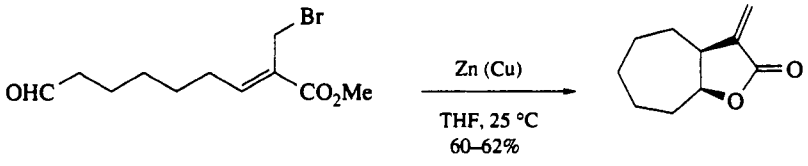
1.1.2.3.4 Reagents based on zinc[89]

Crotylzinc, like crotyllithium, is configurationally unstable and provides a mixture of *syn* and *anti* diastereomers upon reaction with aldehydes.[6d] Stereoselectivity improves, however, as the size of R of RCHO or the steric requirements of R′ of R′CH=CHCH$_2$ZnX increases.[6d,90] For example, cinnamylzinc provides up to 87:13 selectivity for the *anti* diastereomer in reactions with benzaldehyde,[90a] while the silicon-substituted allylzinc (**127**), generated *in situ* from the corresponding allyllithium and $ZnCl_2$, provides *anti* diastereomer (**128**) with excellent selectivity in all cases examined except heptanal (4:1 selectivity).[90b] Oxidation of (**128**) as indicated provides diols (**129**) that are of interest as intermediates in the synthesis of carbohydrates. The allylzinc species generated by treatment of allyllithium (**118**) with $ZnCl_2$ is much more selective than (**118**) in reactions with ethyl pyruvate, a result attributed to the greater ability of the zinc cation to coordinate to the —CO_2Et residue in the transition state.[34a]



(**127**) (**128**) (**129**)

R = n-C_6H_{13}	4:1
R = c-C_6H_{11}	one isomer
R = Ph	one isomer

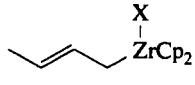


(**130**) (**131**)

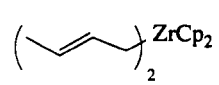
The presence of a substituent at C-2 of the allyl unit also influences the stereoselectivity of allylzinc reactions, in the same way that C-2 substituents influence the reactions of allylchromium (**109**) and (**110**) (Schemes 22 and 23). For example, the —ZnBr derivative corresponding to (**109**) displays *syn* diastereoselectivity comparable in the best cases to that realized with (**109**).[34c] The reaction of (**130**) with Zn(Cu) in dilute solution similarly provides (**131**) with *syn* stereochemistry about the new C—C bond. Type III diastereoselectivity has been demonstrated in this series, as the (*E*)-isomer of (**130**) provides a 3.8:1 mixture of (**131**) and the corresponding *trans*-fused lactone.[91]

1.1.2.3.5 Reagents based on zirconium

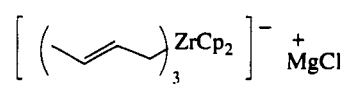
Crotylzirconiums (**132**)–(**134**) have been generated *in situ* by the addition of one, two and three equivalents of crotyllithium or crotylmagnesium chloride to Cp_2ZrCl_2 in THF, and exhibit a preference for the *anti*-homoallyl alcohol (**3**) in reactions with aldehydes (87–95% yield; Scheme 26).[18] Variable temperature NMR experiments have shown (**133**) to be a 60:40 mixture of (*E*)- and (*Z*)-isomers at 30 °C and an 87:13 mixture at –70 °C.[18a] Reagents (**132**) and (**134**) were similarly determined to be 85:15 and 55:45 mixtures of isomers at –70 °C. Thus, the reaction diastereoselectivity closely parallels the isomeric composition of these crotylzirconium species in solution. Crotylzirconium species of the general structure (crotyl)$Zr(OR)_3$, prepared by the addition of crotylmagnesium chloride and $Zr(OR)_4$, have also been studied, but in general are less diastereoselective than (**132**)–(**134**) or the comparable crotyltitanium complexes (**123**).[18a] The most selective of the alkoxy-substituted zirconium reagents is (**135**).



(**132**) X = Cl
(**135**) X = OC_5H_{11}



(**133**)



(**134**)

Diastereoselectivity (3):(4)

Reagent	*Temp.* (°C)	*PhCHO*	*MeCHO*	*EtCHO*	*Pr^{i}CHO*	*Ref.*
(**132**)	–78	86:14	73:27	86:14	88:12	18a
	–78	–	77:23	78:22	74:26	18b
(**133**)	30	–	78:22	79:21	72:28	18a
	0	–	80:20	81:19	77:23	18a
	–78	85:15	88:12	89:11	82:18	18a
	–110	–	91:9	92:8	86:14	18a
(**134**)	–78	–	58:42	66:34	55:45	18a
(**135**)	–78	–	90:10	90:10	89:11	18a

Scheme 26

1.1.2.3.6 Other type III crotyl metal reagents

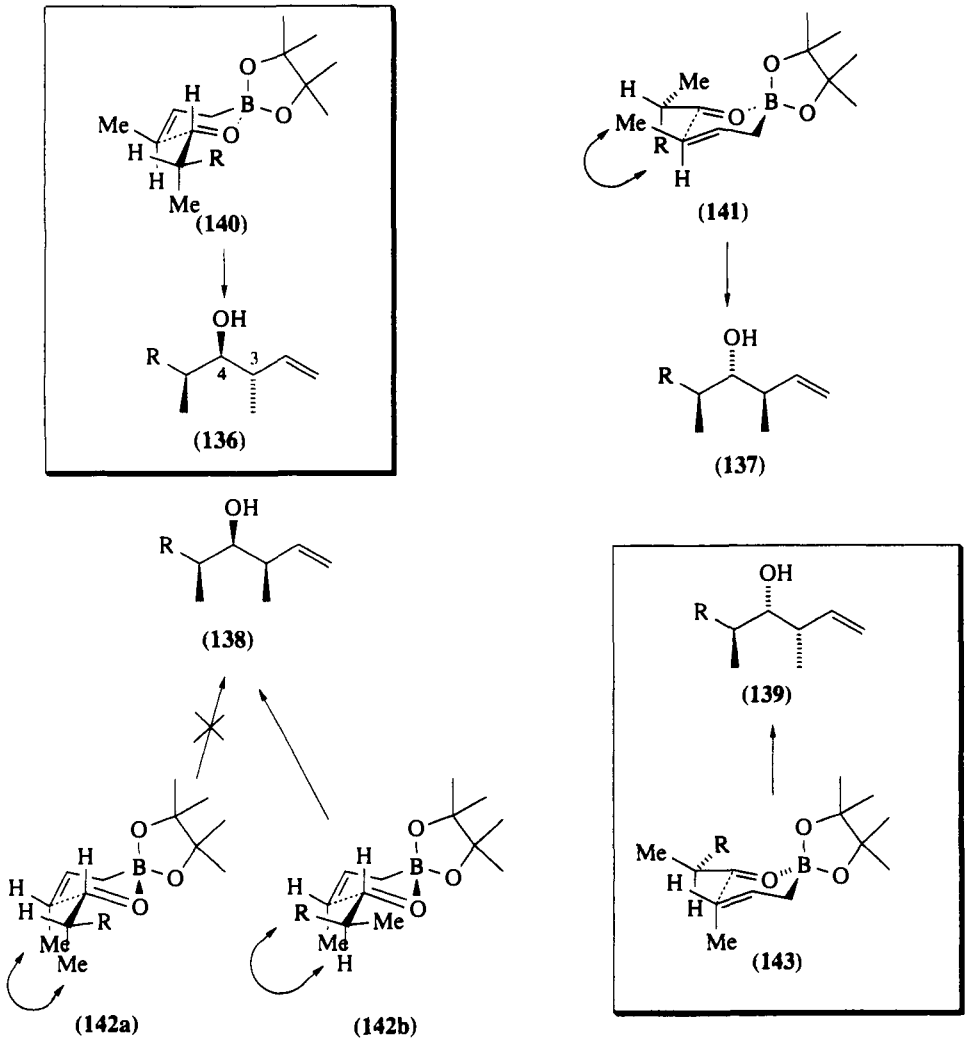
Crotyl metal reagents based on antimony,[92] bismuth,[93] indium[94] and manganese[95] have also been described. These reagents display moderate preferences for the *syn* diastereomer (**4**) in reactions with aromatic aldehydes (antimony, up to 75:25; bismuth, 85:15; indium, 66:34; manganese, 65:35). Too few examples have yet been reported, however, to fully assess the potential of these systems as reagents for organic synthesis.

1.1.3 RELATIVE DIASTEREOSELECTION

1.1.3.1 Reactions with Chiral Aldehydes

The stereochemistry of the reactions of chiral carbonyl compounds with nucleophiles has been a topic of considerable theoretical and synthetic interest since the pioneering study by Cram appeared in 1952.[96] The available predictive models focus entirely on the conformational and stereoelectronic demands of the chiral carbonyl substrate, the implicit assumption being that the relative stabilities of the competing transition states are determined only by stereoelectronics and the minimization of nonbonded interactions between the substituents on the chiral center and the nucleophile. These models totally ignore the possibility, however, that the geometric requirements of the nucleophile may also have an effect on reaction diastereoselectivity. Considerable evidence is now available, particularly in the reactions of Type I (*Z*)-crotylboronates and *Z*(*O*)-metal enolates, that the stereochemistry of the nucleophile is indeed an important issue that must be considered when assessing reaction diastereoselectivity.

Consider the reactions of pinacol crotylboronates (**1**) and (**2**) with a chiral aldehyde, RCHMeCHO (Scheme 27). The four diastereomeric products (**136**)–(**139**) arise *via* the indicated transition states (**140**)–(**143**). According either to the Cram rule or the Felkin–Anh paradigm, the 3,4-*anti*-4,5-*syn* diastereomer (**136**) should be favored over *anti,anti*-(**137**) in the reactions of the (*E*)-crotyl isomer (**1**), a result that is in fact observed experimentally.[97,98] The same reasoning leads to the prediction that *syn,syn* diastereomer (**138**) should be the major product of the reactions of (*Z*)-crotylboronate (**2**). In this case, however, it is the 3,4-*syn*-4,5-*anti* diastereomer (**139**) that is produced preferentially.[97,98] The reason that the reactions of (*Z*)-crotylboronates fail to follow the Felkin–Anh paradigm is probably that transition state (**142a**) is destabilized by the indicated 1,5-interaction between methyl groups. Although (**138**) can also arise *via* (**142b**) in which the 1,5-Me–Me interaction of (**142a**) is relieved, this transition state still suffers from a relatively large nonbonded interaction between Me and R. Transition state (**143**), on the other hand, allows for fewer interactions between the crotyl unit and the substituents at C-2 of the chiral aldehyde substrate and consequently is favored even though it corresponds to an 'anti-Felkin' arrangement. Similar 'anti-Felkin' diastereoselectivity has been observed in reactions of various *Z*(*O*)-boron and -lithium enolates with α-methyl chiral aldehydes, undoubtedly for similar reasons.[4a,5,99]

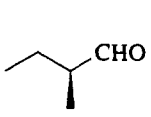
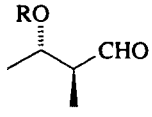
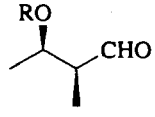


Scheme 27

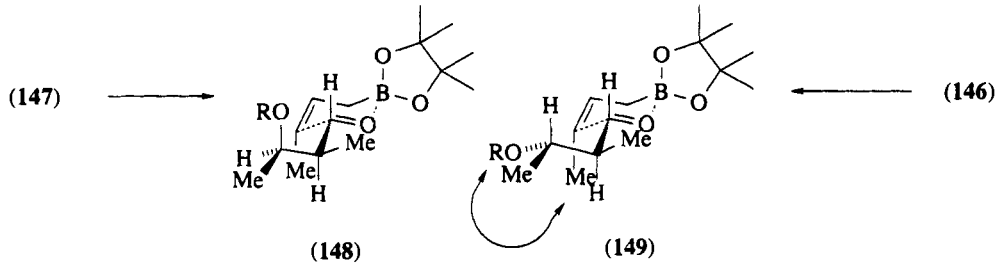
It is to be expected that the extent of relative diastereoselection will depend on the difference in size of the R substituent relative to Me. The examples summarized in Table 4 are generally supportive of this thesis, particularly the reactions of (**1**) with aldehydes (**146**) and (**147**) that are much more selective than with the structurally less complex aldehyde (**145**).[97] The data cited for reactions of pinacol allylboronate

(**144**) and (*Z*)-crotylboronate (**2**), however, also show that diastereoselectivity depends on the stereochemistry at C-3 of (**146**) and (**147**). This can be rationalized by inspecting transition states (**148**) and (**149**) that correspond to (**142b**) of Scheme 27. Aldehyde (**147**) can easily adopt the conformation indicated in (**148**) that minimizes the interactions between C-3 and the crotyl unit. These interactions are only slightly greater than the methyl/methyl interactions in the favored transition state (**143**). With aldehyde (**146**), however, the interactions between the C-3 substituents and the crotyl unit are envisaged to be much more serious due to the conformation indicated in (**149**). The R substituent of (**146**) thus behaves as a more sterically demanding unit than in (**147**), and consequently the diastereoselectivity of the reaction of (**146**) is greater.

Table 4 Relative Diastereoselection in the Reactions of Allylboronates and α-Methyl Chiral Aldehydes: Ratios of 4,5-*Syn* to 4,5-*Anti* Products[97]

			
Reagent	(**145**)	(**146**)	(**147**)[a]
Pinacol (*E*)-crotylboronate (**1**)[b]	83:17	95:5 (R = TBDMS) 89:11 (R = MOM)	98:2 (R = TBDMS) 94:6 (R = MOM)
Pinacol allylboronate (**144**)	62:38	49:51 (R = TBDMS) 61:39 (R = MOM)	79:21 (R = TBDMS) 79:21 (R = MOM)
Pinacol (*Z*)-crotylboronate (**2**)[c]	30:70	9:91 (R = TBDMS) 22:78 (R = MOM)	40:60 (R = TBDMS) 41:59 (R = MOM)

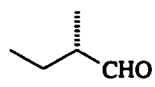
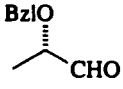
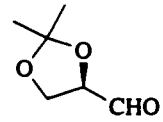
[a]The enantiomeric aldehyde was actually used (ref. 97a). [b]4,5-*Syn* diastereomer (**136**) is the major product. [c]4,5-*Anti* diastereomer (**139**) is the major product.

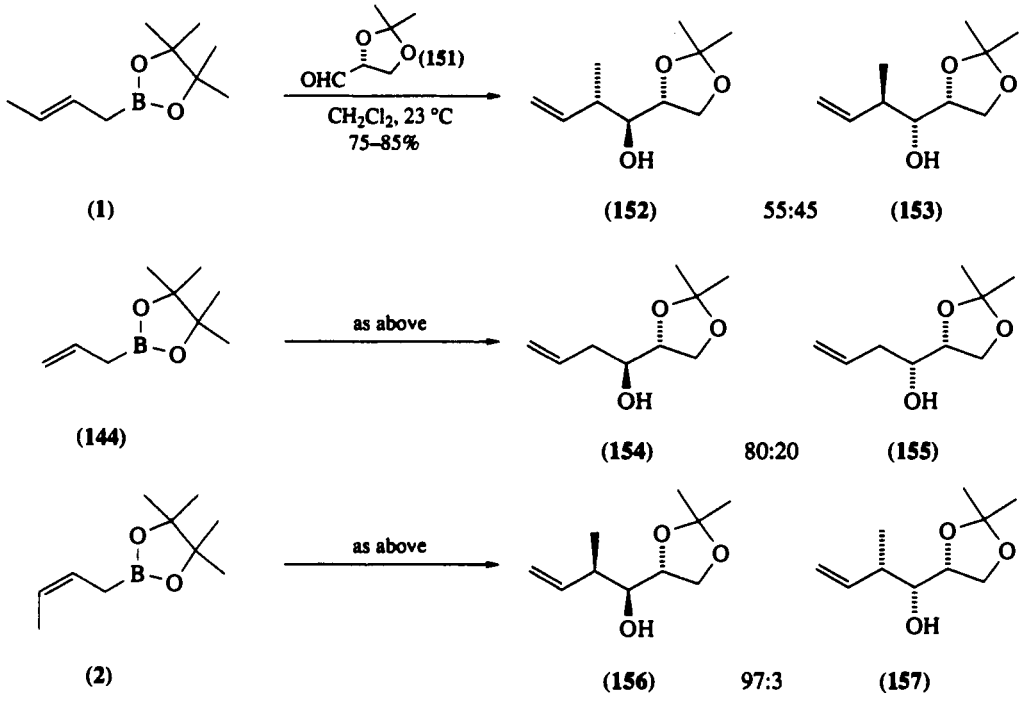


A more complete picture of relative diastereoselection in the reactions of allylboronates and chiral aldehydes is given in Table 5; structures of the products in the glyceraldehyde acetonide (**151**) series are given in Scheme 28.[25,100–102] The data for (**150**) and (**151**) reconfirm the conclusion of Table 4 that diastereoselectivity is dependent on the geometry and substitution pattern of the allylboronate. In addition, however, the data in Table 5 also show that diastereoselectivity depends strikingly on the aldehyde, with greater selectivity for the 4,5-*anti* diastereomer being realized as one moves across any row of the table. This is strongly suggestive of an electronic effect, particularly since it is believed, for example, that the reactions of (*Z*)-γ-substituted allylboronates (**2**) and (**74**) proceed preferentially *via* the same transition states: (**143**) for α-methyl chiral aldehydes and (**158**) for the α-oxygenated aldehydes.[25,100a] Transition state (**158**) corresponds to the Cornforth model and the increased diastereoselection in the reactions of (**2**) and (**74**) with oxygenated aldehydes *versus* the reactions of (**2**) with aldehydes like (**145**) has been attributed to the electronic stabilization of (**158**) relative to competitive diastereomeric arrangements.[25] The usually invoked Felkin–Anh arrangement (**159**) is probably not involved in the reactions of (*Z*)-allyl-boronates (**2**) and (**74**) owing to serious steric interactions between R of the allylboronate and the alkyl substituent at C-2 of the chiral aldehyde substrate.

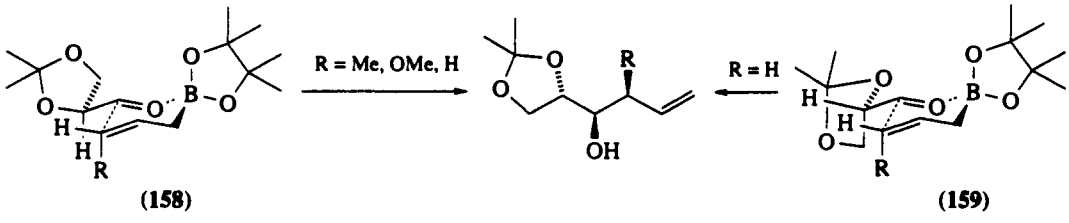
Electronic effects are also clearly operational in the reactions of allylboronate (**144**) since the diastereofacial preference switches upon moving from an α-methyl chiral aldehyde (**145**) to an oxygenated aldehyde such as (**150**) or (**151**). The identity of the major transition state(s) is less clear with (**144**), however, since at least two reasonable possibilities exist in every case (those resembling (**142a**) or (**142b**) in reactions with α-methyl chiral aldehydes and (**158**) or (**159**) with oxygenated aldehydes).

Table 5 Relative Diastereoselection in the Reactions of Substituted Allyboronates and Chiral Aldehydes (***145***), (***150***) and (***151***): Ratios of 4,5-*Anti* to 4,5-*Syn* Products

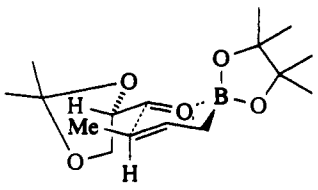
Reagent	 (**145**)	 (**150**)	 (**151**)
Pinacol (*E*)-crotylboronate (**1**)	17:83[97]	—	55:45[25]
Pinacol (*E*)-γ-methoxyallylboronate (**73**)	—	40:60	—
Pinacol allylboronate (**144**)	38:62[97]	65:35[100a] (55:45)[25]	80:20[25,101]
Pinacol (*Z*)-crotylboronate (**2**)	70:30[97]	—	97:3[25]
Pinacol (*Z*)-γ-methoxyallylboronate (**74**)	—	82:18[100a] (90:10)[100b]	>95:5[25,102]



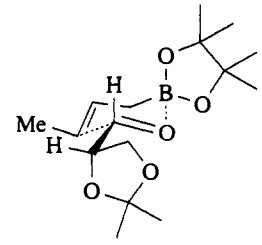
Scheme 28



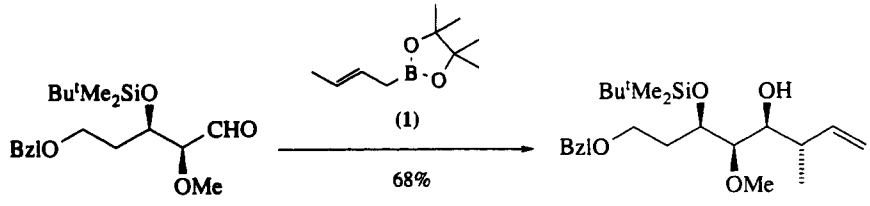
Electronic arguments have been presented to rationalize the poor diastereoselectivity of the reactions of (**1**) and (**151**).[25] It may be argued that even though transition state (**160**) has greater nonbonded interactions than (**161**) (which corresponds to (**140**), the major pathway in the reactions with α-methyl chiral aldehydes, Scheme 27), the electronic effect (Felkin activation) is sufficient to lower the energy of (**160**) so that it is slightly more accessible than (**161**). This result probably represents a special case, however, since C-3 of (**151**) is not very sterically demanding in (**160**), owing to the acetonide unit that minimizes



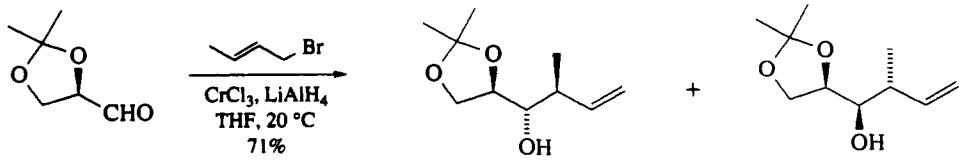
(160) → (152)



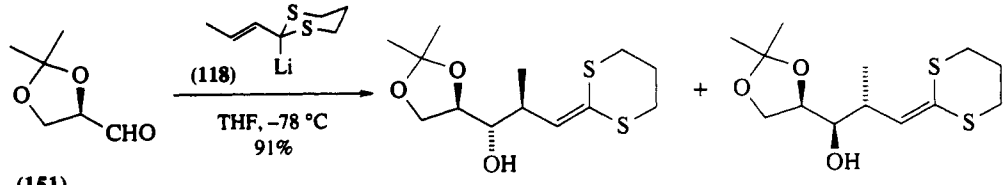
(161) → (153)



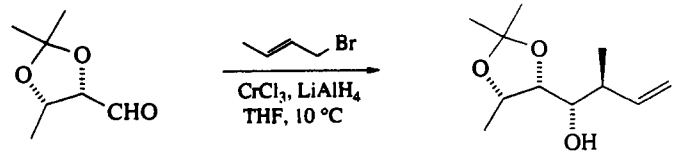
(162) → (163) >99:1 selectivity



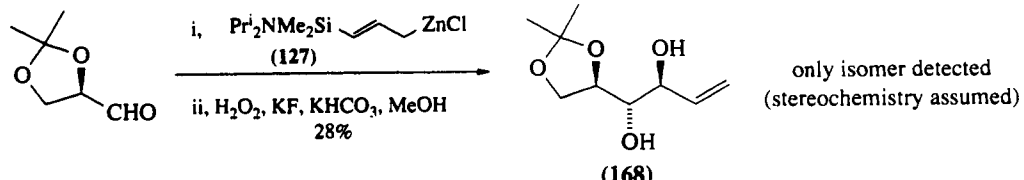
(151) → (152) 54:44:2 (156) (153)



(151) → (164) 44:43:13 (3,4-*syn*) (165)



(166) → (167) 96:4 selectivity



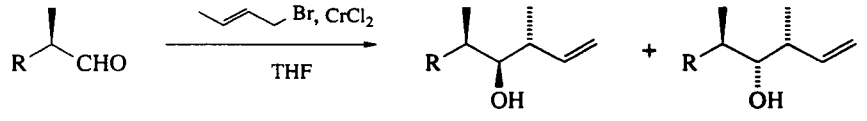
(151) → (168) only isomer detected (stereochemistry assumed)

Scheme 29

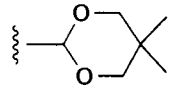
interactions of the C-3 alkoxy group with the crotyl unit. Indeed, the reaction of differentially protected α,β-dialkoxyaldehyde (**162**) and (*E*)-crotylboronate (**1**) provided (**163**) with very high diastereoselectivity *via* a transition state corresponding to (**161**).[103] Thus, increased steric interactions are sufficient to destabilize (**160**) relative to (**161**).

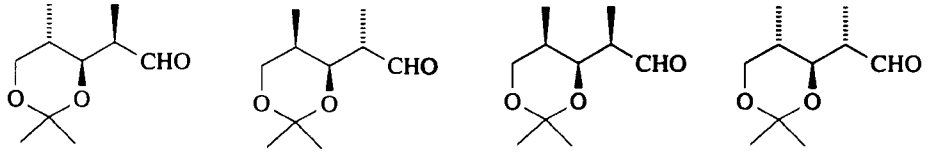
The aldehyde diastereofacial selectivity realized in the reactions of many other type I and III crotyl metal reagents closely parallels the results summarized above for the crotylboronates. For example, the reactions of glyceraldehyde acetonide (**151**) either with the crotylchromium reagent[104] or with allyllithium (**118**; Scheme 29)[34a] provide mixtures of diastereomers strikingly similar to those realized in the reaction of (**151**) and (*E*)-crotylboronate (**1**). Steric effects certainly have an effect on diastereoselectivity, as evidenced by the reaction of (**166**) and crotylchromium (**8**) that provides (**167**) with excellent stereoselectivity.[105] In contrast, however, the reaction of (**151**) and substituted allylzinc reagent (**127**) is reported to provide (**168**), but stereochemistry was not rigorously assigned in this case.[90b]

Reactions of the crotylchromium reagent (**8**) and α-methyl chiral aldehydes are summarized in Scheme 30.[9a,c,106] The results with (**169**)–(**173**) demonstrate that diastereoselectivity *via* a transition state analogous to (**140**) increases as the steric demands of R increase, while the data for (**174**)–(**177**) indicate that diastereoselectivity in these more stereochemically complicated cases depends subtly on the stereochemistry of the centers at C-3 and C-4 relative to C-2. This effect undoubtedly is related to the conformational preferences of the C(2)—C(3) bond, which influences the nonbonded interactions involving the

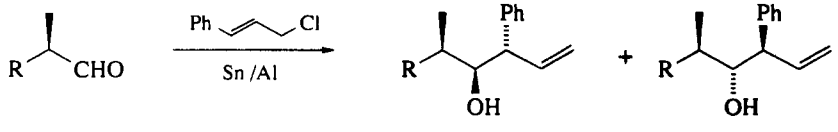


(**135**) (**136**)

(**169**) R = CH_2OTHP	50:50
(**170**) R = CH_2OBzl	61:39
(**171**) R = Et	69:31 (ref. 9c)
(**172**) R = Ph	72:28 (ref. 9a)
(**173**) R = 	92:8



(**174**) 80:20 (**175**) 80:20 (**176**) 92:8 (**177**) 95:5

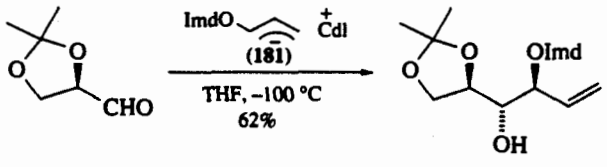


(**179**) (**180**)

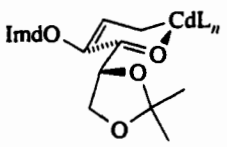
(**171**)	R = Et	75:25
(**172**)	R = Ph	80:20
(**178**)	R = CH_2Bu^t	100:0

Scheme 30

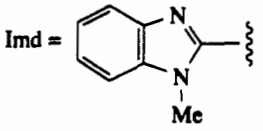
bulky R unit in the disfavored transition state (**141**).[106a] Interestingly, the reaction of (*E*)-crotylboronate (**1**) with (**170**) provides (**135**) and (**136**) in a ratio of 68:32,[98] while the reaction of (**172**) and (crotyl)$ZrCp_2Cl$ (**132**) provides (**135**) and (**136**) in the ratio of 73:27,[18b,107] diastereoselectivities very

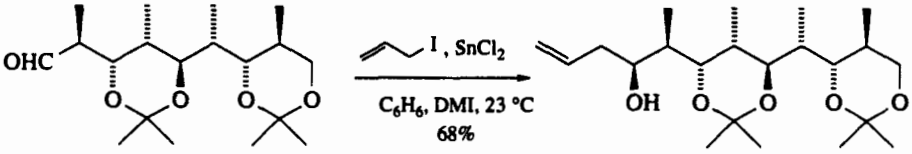


(**151**) (**182**)

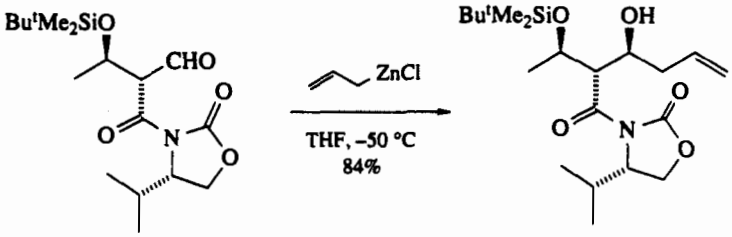


(**183**)

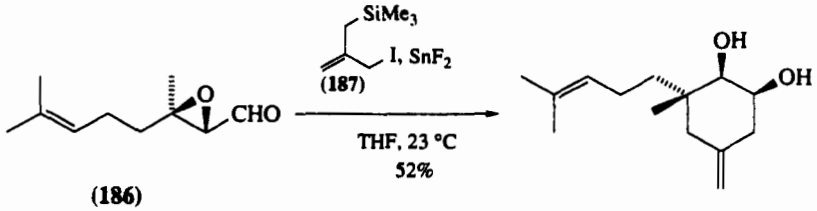




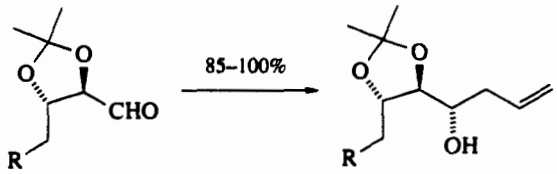
(**184**) 20:1 (ref. 106b)



(**185**) 97:3 (ref. 110)

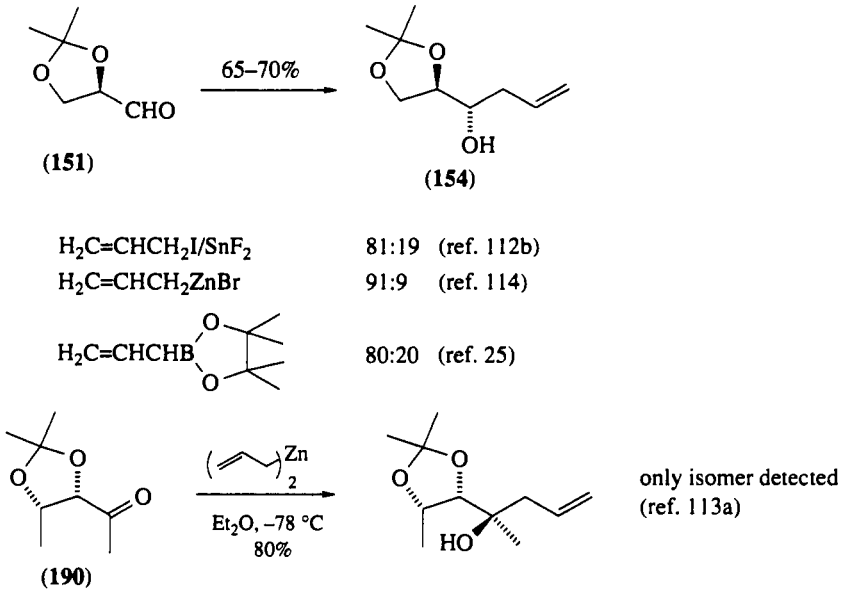


(**186**) 9:1 (ref. 111)



(**188**)	R = OBzl	$H_2C{=}CHCH_2I/SnF_2$	90:10 (ref. 112a)
(**189**)	R = H	$H_2C{=}CHCH_2ZnBr$	95:5 (ref. 113)
	R = H	$H_2C{=}CHCH_2B$(O)(O)	90:10 (ref. 25)

Scheme 31



Scheme 31 *(continued)*

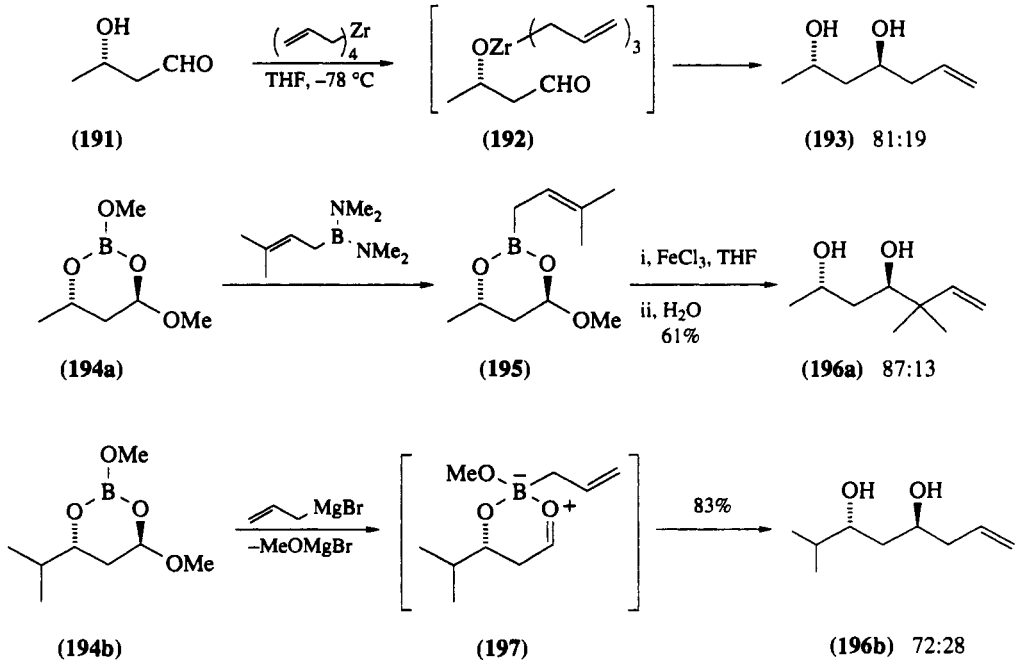
similar to those obtained with the crotylchromium reagent (**8**). The reactions of aldehyde (**171**), (**172**) and (**178**) and the cinnamyltin reagent also proceed *via* a transition state analogous to (**140**), again with diastereoselectivity increasing as the steric requirements of R increase.[77b,106b,108]

Several sets of experimental data have been reported that deviate from the stereochemical picture summarized above. The first involves the reaction of aldehyde (**32**) and (*Z*)-crotyldiethylalane (**31**) that provides *syn,syn* diastereomer (**33**) with 3:1 selectivity (Section 1.1.2.2.1).[39] This is the only example reported to date of a type I (*Z*)-crotyl metal reagent that reacts preferentially through transition states (**142a**) or (**142b**). Perhaps Felkin–Anh stereoelectronic considerations are more significant in this case because of the greater nucleophilicity of (**31**) compared to the (*Z*)-crotylboronates. In addition, the longer C—Al and Al—O bonds relative to the boron reactions may result in a longer developing C—C bond that further minimizes the magnitude of the nonbonded interactions noted in (**142a**) and (**142b**). Further experimentation is necessary, however, to establish the validity of these conclusions.

A second example concerns the reaction of glyceraldehyde acetonide (**151**) and γ-alkoxyallylcadmium reagent (**181**).[109] This reaction apparently proceeds preferentially by way of a Felkin–Anh transition state (**183**) analagous to (**160**) in the reactions of (*E*)-crotylboronates,[25] because of the smaller steric requirements of the γ-alkoxy group in (**181**). Here again, additional experimental data are required to verify this hypothesis. The reaction of (**151**) and allylzine reagent (**127**) appears also to be in disagreement with this stereochemical model (Scheme 29).

Numerous reactions of chiral aldehydes and allyl metal reagents have been reported. Some of the more highly selective examples are summarized in Scheme 31. The stereochemistry of the reaction of (**184**)[106b] and the allyl iodide/$SnCl_2$ reagent are typical of reactions of α-methyl chiral aldehydes: the 4,5-*syn* diastereomer predominates, but usually not with the level of stereoselection seen in this example.[97,98,107] Similar diastereoselection is realized in the reaction of (**185**) and allylzinc chloride, with the exception that in this case it is the imide function that appears to function as the largest substituent.[110,115] The allyltin intermediate generated from (**187**) displays very good levels of *anti* diastereoselectivity in the reactions with epoxy aldehydes such as (**186**),[111] a result in good agreement with those obtained in the addition of various allyl metal derivatives to α,β-dialkoxy aldehydes (**151**), (**188**) and (**189**).[25,112–114] The general agreement of the results with the different allyl metal reagents, especially those involving allylboronate (**144**), suggests that chelated transition states are not involved, as is often assumed by many investigators.[114a,116] Allylzinc chloride and allylmagnesium bromide also add with excellent stereoselectivity to methyl ketone (**190**), one of the rare, highly selective examples of the reaction of a chiral ketone with an allyl metal reagent.[113a]

The reactions of β-alkoxy-α-unsubstituted aldehydes are generally not highly diastereoselective, except in cases where the allyl metal addition occurs *via* a chelated transition state.[107,117] An interesting example along these lines is the reaction of aldol (**191**) and $Zr(allyl)_4$ that evidently proceeds with intra-



Scheme 32

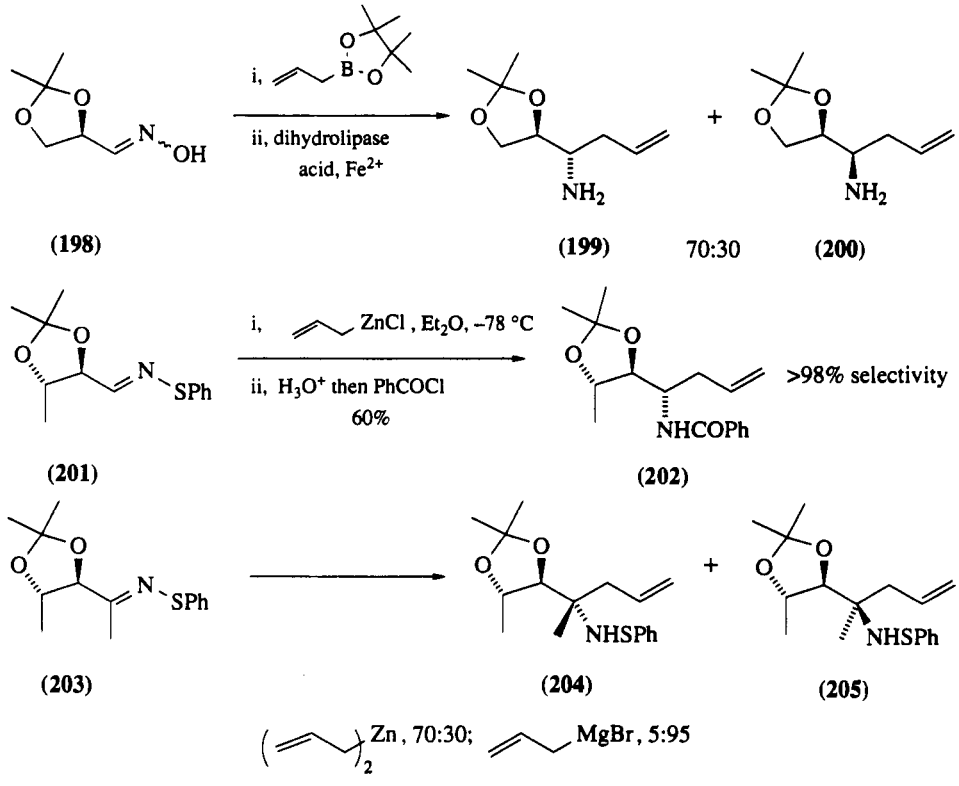
molecular transfer of an allyl unit *via* intermediate (**192**), producing (**193**) as the major product of an 81:19 mixture (Scheme 32).[117] A related process involves the reactions of 1,3,2-dioxaborinanes (**194**) with suitable allyl donors that provide *anti* (*threo*)-1,3-diols (**196**) with 70–87% diastereoselectivity *via* intermediates like (**197**).[118]

1.1.3.2 Reactions with Chiral C=N Electrophiles

Diastereoselective reactions of oxime (**198**) and phenylsulfenimines such as (**201**) with allyl metal reagents have been described (Scheme 33). The reaction of (**198**) and allylboronate (**144**) provides (**199**) with modest selectivity,[62a] while excellent diastereoselectivity was realized in the reactions of (**201**) and its C-2 epimer with the allylzinc reagent.[119] The corresponding ketone derivatives, however, gave 70:30 mixtures of (**204**) and (**205**) upon reaction with diallylzinc, while with allyl Grignard, (**205**) is almost the exclusive product.[119b] The latter result is suggestive of a chelated transition state.

Yamamoto and coworkers have studied the reactions of various allyl metal reagents and chiral aldimines.[6a,120] The reactions of (**206**) with allyl-9-BBN and other allyl metal reagents are highly selective for (**207**; Scheme 34).[120a] In contrast, however, the reactions of (**206**) and crotyl metal reagents do not exhibit such outstanding selectivity. Interestingly, the stereochemistry of the reactions of alkoxy-substituted imines (**209**) and (**210**) can be controlled within reasonable limits by selecting the appropriate reagent: the aluminum ate complex apparently reacts by way of chelated transition states, while those of allyl-9-BBN and (allyl)Ti(OPr^i)$_3$ proceed *via* conventional cyclic transition states.[120b]

Asymmetric induction from a stereocenter in a chiral group bound to N has also been studied, and good to excellent levels of relative diastereoselection have been observed (Scheme 35).[120a] Interestingly, incorporation of a *N*-phenethyl unit of appropriate absolute stereochemistry into (**214**) resulted in substantially improved selectivity for the 1,3-*syn* product diastereomer (compare results with **210**, Scheme 34).[120b] This is an example of double stereodifferentiation, a synthetic strategy that is discussed in Section 1.1.5.



Scheme 33

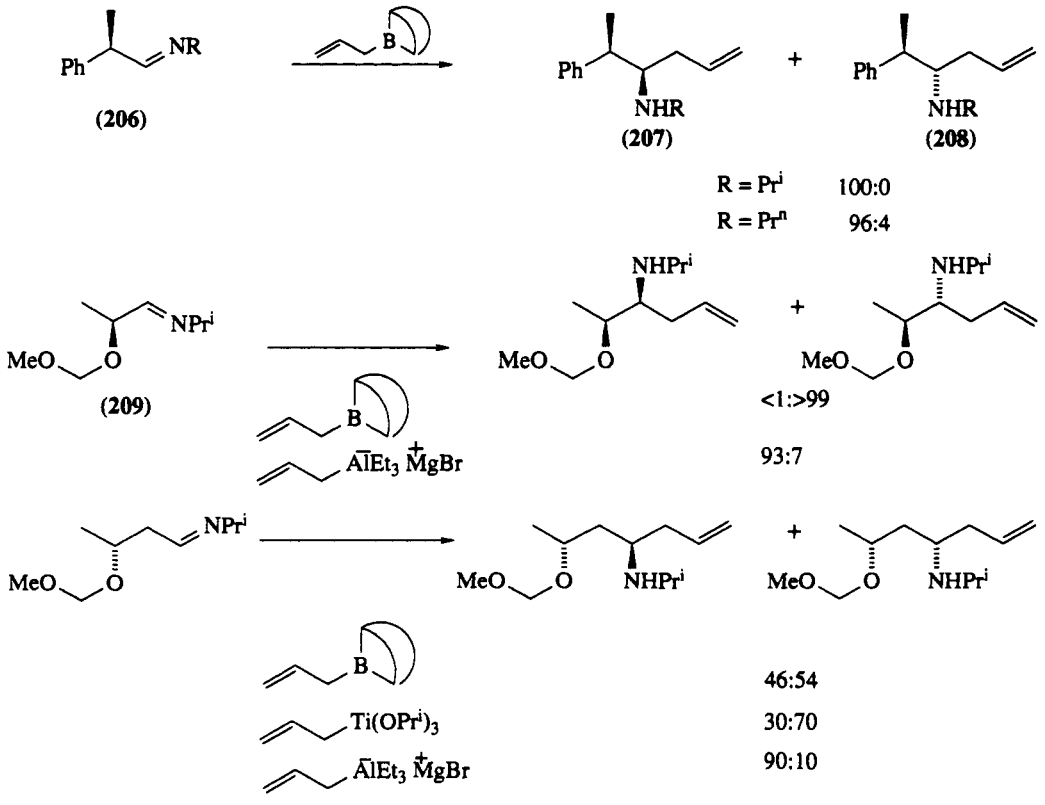
1.1.4 SINGLE ASYMMETRIC SYNTHESIS: REACTIONS OF ACHIRAL ALDEHYDES AND CHIRAL ALLYL ORGANOMETALLICS

A number of highly enantioselective chiral allyl organometallic reagents have been described in the literature. These are of considerable interest both for the asymmetric synthesis of homoallyl alcohols as well as in double asymmetric reactions with chiral C=X electrophiles.[3,5] Two distinct groups of chiral allyl metal reagents can be identified: those with conventional, easily introduced chiral auxiliaries and ones in which the center of chirality is a structural component of the reagent (*e.g.* allyl metal compounds with substituents at C-1). These are discussed separately in the sections that follow.

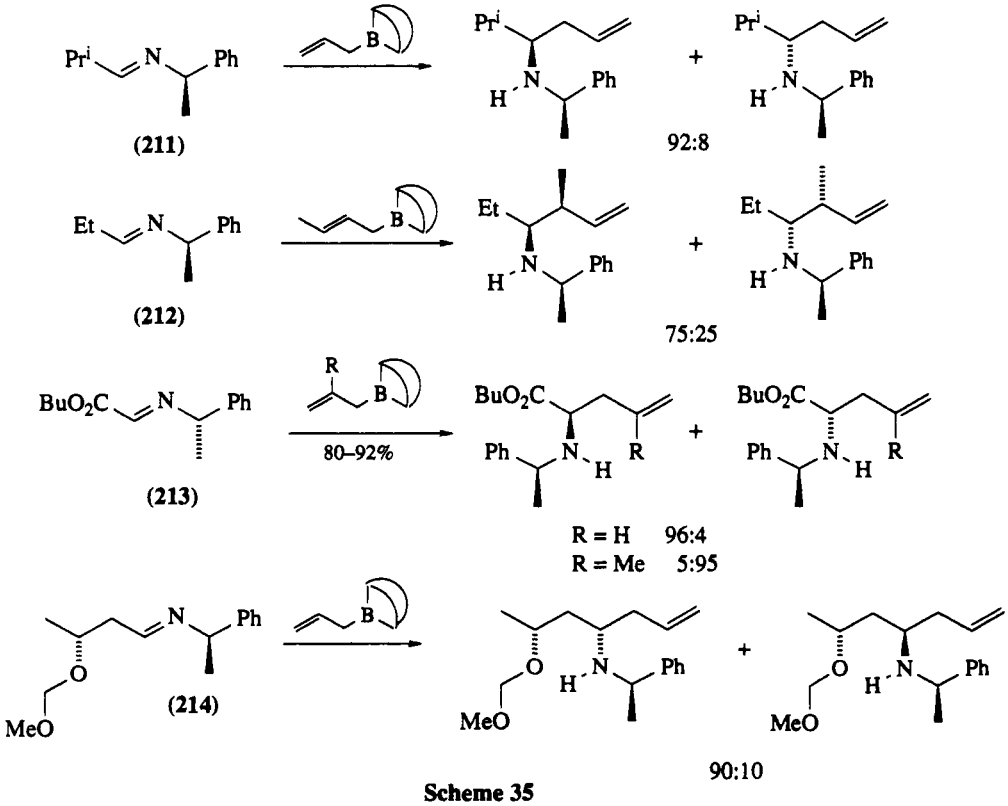
1.1.4.1 Chiral Allyl Organometallics with Conventional Auxiliaries

The most highly enantioselective type I and type III allyl metal reagents that fall into this category are listed in Scheme 36. Reagents (**215**)–(**217**), developed by Hoffmann, are of historical significance since they were the first chiral allyl metal compounds to be studied, and were also among the first chiral reagents of any sort shown to be capable of increasing the stereoselectivity of moderately diastereoselective reactions of chiral aldehydes (*i.e.* matched double asymmetric synthesis).[97b,121] Allyl reagent (**215**) gives 86% *ee* (enantiomeric excess) in the reaction with acetaldehyde at –90 °C, but for most other aldehydes the selectivity is in the range of 36% *ee* (PhCHO) to 72% *ee* (PrCHO) for reactions at –40 °C. The allylborane (**218**) recently described by Reetz is substantially improved and gives 88–96% *ee* with a range of aldehydes at –78 °C.[122] The corresponding crotyl reagent, however, has not yet been described.

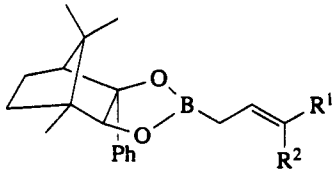
The allyldiisopinocampheylboranes (**51**), (**52**), (**219**) and (**220**) developed by Brown give consistently excellent results (83–96% *ee*) in reactions with aldehydes (Scheme 37).[23c,123] The homoallyl alcohols have (*R*) absolute configuration at the carbinol center, assuming that the allyl group transferred has priority over the R substituent of the aldehyde and that the Ipc_2B unit derives from (+)-α-pinene as indicated in Scheme 37. The analogous allylboranes prepared from (+)-3-carene show even greater levels of enantioselectivity.[123] The crotyl-*trans*-2,5-dimethylborolanes (**221**) and (**222**) are among the most highly



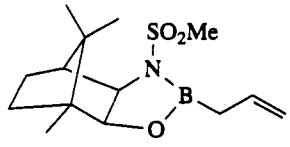
Scheme 34



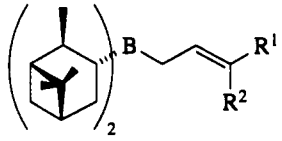
Scheme 35



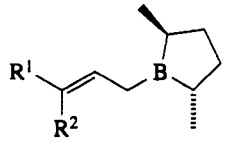
(215) $R^1 = R^2 = H$
(216) $R^1 = Me$; $R^2 = H$
(217) $R^1 = H$; $R^2 = Me$



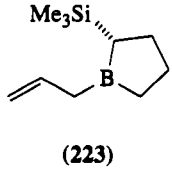
(218)



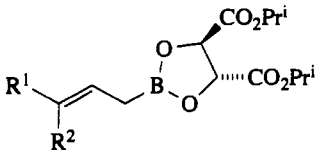
(219) $R^1 = R^2 = H$
(51) $R^1 = Me$; $R^2 = H$
(52) $R^1 = H$; $R^2 = Me$
(220) $R^1 = H$; $R^2 = OMe$



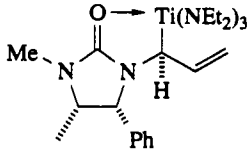
(221) $R^1 = Me$; $R^2 = H$
(222) $R^1 = H$; $R^2 = Me$



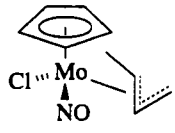
(223)



(224) $R^1 = R^2 = H$
(18) $R^1 = Me$; $R^2 = H$
(19) $R^1 = H$; $R^2 = Me$



(225)



(226)

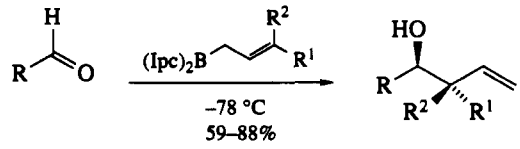
Scheme 36

enantioselective crotyl metal reagents yet described: in five of the six examples reported the enantioselectivity is 93–97% *ee* (simple diastereoselectivity is 93–96%).[124a] However, the difficult synthesis of the β-methoxy-2,5-dimethylborolane precursor renders these reagents unattractive for synthetic applications. Allylborane (**223**) has recently been reported to be an exceptionally enantioselective allyl transfer reagent (92–97% *ee*).[124b]

The tartrate ester modified allylboronates (**224**), (**18**) and (**19**) are attractive alternatives to the (allyl)B(Ipc)$_2$ reagents, owing to their ease of preparation and stability to storage.[37,125] In the best cases the tartrate allylboronates are about as enantioselective as Brown's allylboranes (82–88% *ee* with unhindered aliphatic aldehydes), but with hindered aliphatic, aromatic, α,β-unsaturated and most α- and β-alkoxy aldehydes the enantioselectivity falls to a level of 55–75% *ee* (Scheme 38). Enantioselectivity is highly dependent on reaction solvent, with best results being obtained in toluene for all substrates except aromatic ones for which the % *ee* is highest in THF. An electronic origin of asymmetry has been proposed (Scheme 39), and on this basis reagent (**228**) was designed and found to be significantly more enantioselective than the corresponding tartrate ester derivative (**224**; see data in Scheme 38).[126] Allylboronate (**228**), however, is less reactive and less soluble than (**224**), and consequently is less attractive, especially for large-scale work in spite of its enhanced enantioselectivity.

Allyltitanium reagent (**225**) undergoes highly diastereoselective reactions with aldehydes and even a ketone as indicated in Scheme 40.[127] It is interesting that (**225**) possesses a stereocenter at C-1 of the allyl unit, but unlike the other C-1 chiral reagents discussed in the following section this center is introduced in a very simple manner by the metallation of allylurea (**229**). The η^3-crotylmolybdenum reagent (**226**) undergoes a highly enantio- and diastereo-selective reaction with benzaldehyde (Scheme 41), but the full scope of this methodology has not yet been reported.[33]

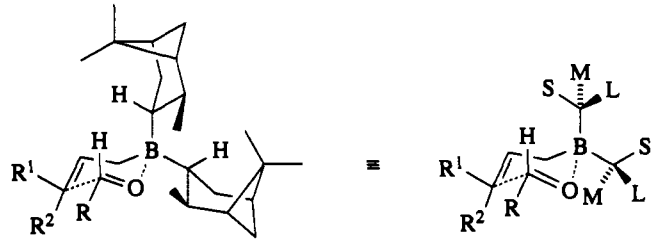
Several additional chiral type I and III allyl metal reagents based on boron,[128] chromium,[129] tin[130] and titanium[131] have been reported. The most selective of these are the chiral γ-alkoxyallylboronate (**231**) developed by Wuts for application in a synthesis of (–)-*exo*-brevicomin,[128] and the allyltin reagent gener-



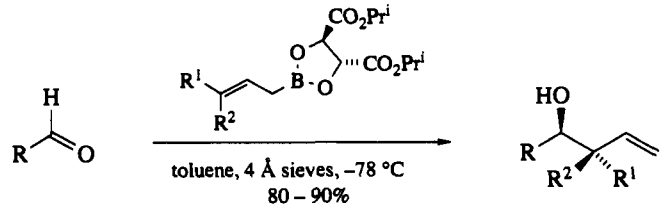
Enantioselectivity (% ee)

	(219)	*(51)**	*(52)**	*(220)**
MeCHO	93	90	90	90
EtCHO	86	90	90	88
Pr^iCHO	90	–	–	88
Bu^tCHO	83	–	–	–
H_2C=CHCHO	–	90	90	88
PhCHO	96	88	88	90

*Simple diastereoselectivity ≥ 98%



Scheme 37



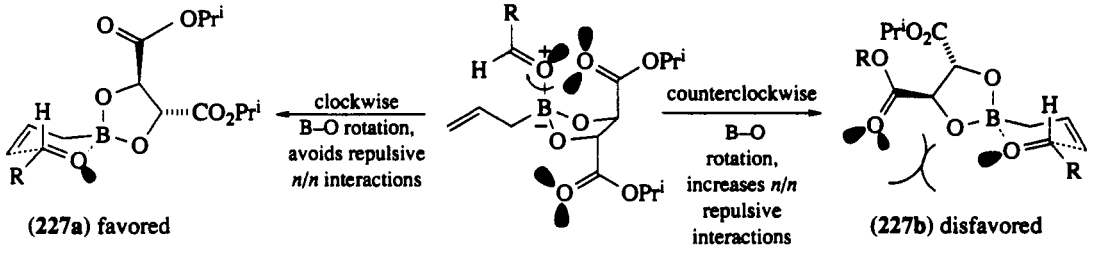
Enantioselectivity (% ee)

R	*(18)**	*(19)**	*(224)*	*(228)*
n-C_9H_{19}	87	82	86	–
C_6H_{11}	87	86	87	97
$Bu^tPh_2SiOCH_2CH_2CH_2$	–	–	82	94
$Bu^tMe_2SiOCH_2CH_2$	85	72	60	–
$BzlOCH_2$	–	–	60	85
Bu^t	73	70	86	96
(E)-$C_7H_{15}CH$=CH	74	62	60	–
Ph (THF)	67	55	72	85

*Simple diastereoselectivity ≥97%

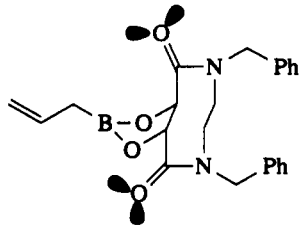
Scheme 38

ated *in situ* from $Sn(OTf)_2$, H_2C=$CHCH_2AlBu^i_2$ and the chiral diamine (**233**) reported by Mukaiyama (Scheme 42).[130] It is interesting to speculate that asymmetric induction with (**231**) may be a consequence of the *exo* anomeric effect, a stereoelectronically favored conformation that places the aglycone O—C bond antiperiplanar to the pyran C(1)—C(2) bond.[132] Related asymmetric induction has been observed in the reactions of the THP ether corresponding to (**231**).[61]



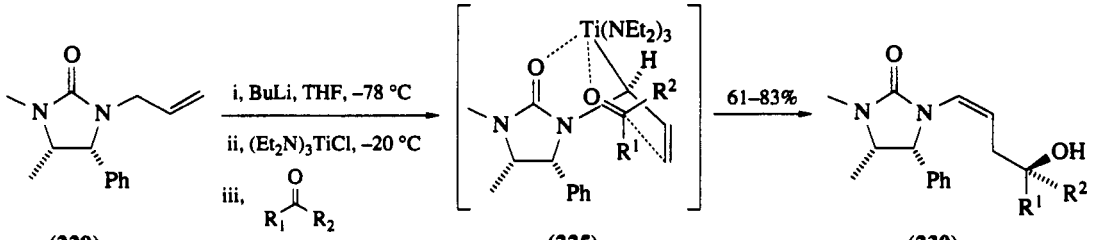
(**227a**) favored

(**227b**) disfavored



(R,R)-(**228**)

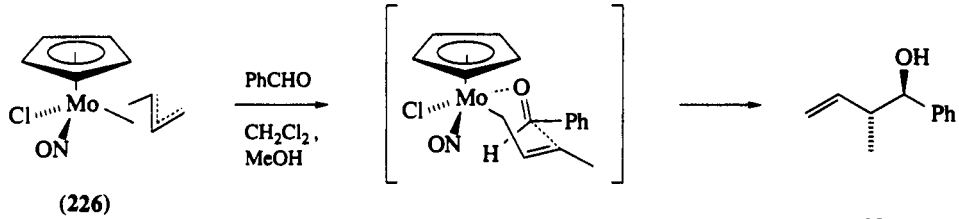
Scheme 39



(**229**) (**225**) (**230**)

R^1	R^2	*Diastereoselectivity* (%)
n-C_8H_7	H	88
Et	H	92
Pr^i	H	92
Pr^i	Me	96

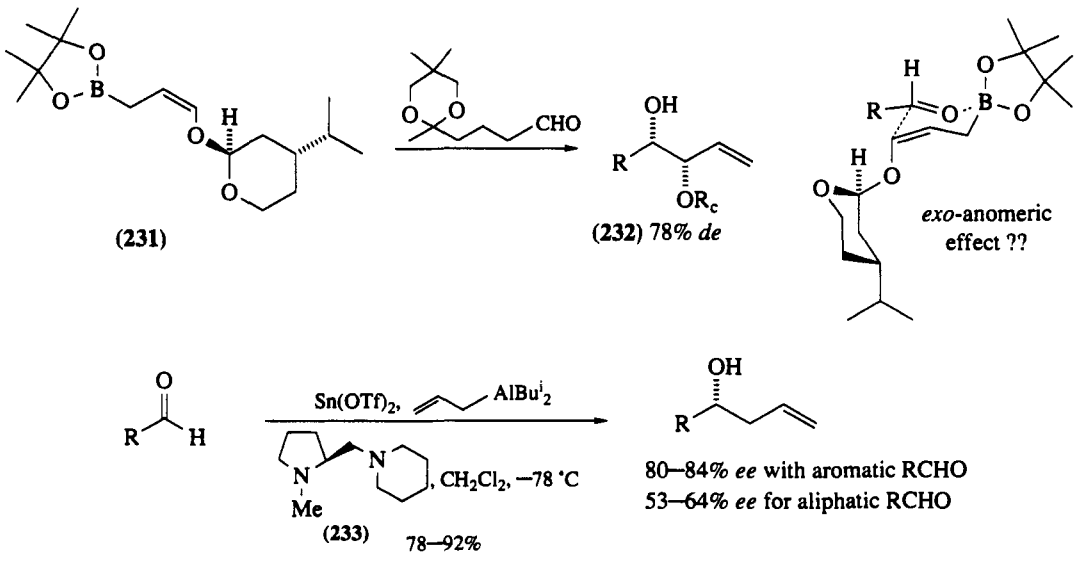
Scheme 40



(**226**)

>98% *ee*
(96:4 *anti*:*syn*)

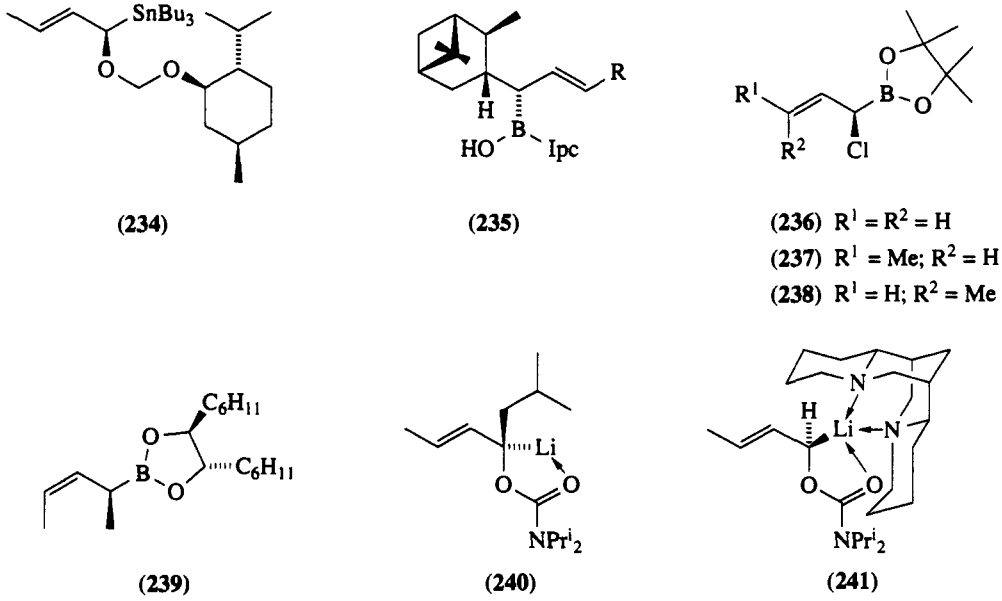
Scheme 41



Scheme 42

1.1.4.2 Chiral Allyl Organometallics with Stereocenters at C-1 or C-4

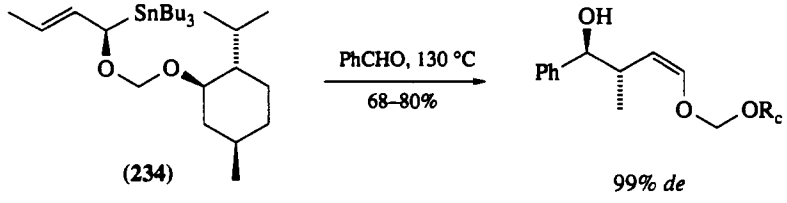
Allyl organometallics with stereocenters at either C-1 or C-4 of the allyl/crotyl unit have been described. For such compounds to be useful in single or double asymmetric reactions it is necessary that they be accessible with a high degree of enantiomeric purity. Such reagents are frequently less convenient to synthesize than those with conventional auxiliaries, but the trade off is that the reactions with aldehydes often occur with nearly 100% asymmetric induction. Chiral, nonracemic reagents that fall into this category are (**101**; Scheme 18)[67] and (**234–240**; Scheme 43). Of these, (**235**)[133] and (**240**)[134a] provide homoallyl alcohols with the lowest enantiomeric purity, (**235**) because of the method of synthesis and (**240**) presumably due to racemization; examples of their reactions will not be discussed in this chapter. The interesting, easily prepared chiral crotyllithium reagent (**241**), however, undergoes transmetallation



Scheme 43

with $Ti(OPr^i)_4$ at –70 °C to give a reagent that reacts with aldehydes with reasonable levels of enantioselectivity (80–84% *ee*).[134b]

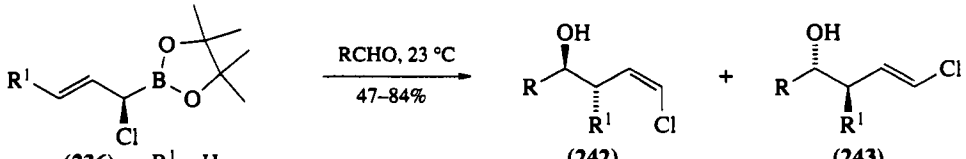
Thomas and coworkers have shown that the chiral crotylstannane (**234**) undergoes highly diastereoselective reactions with benzaldehyde, cinnamaldehyde and cyclohexanecarbaldehyde (Scheme 44).[135] These reactions occur by way of transition state (**108**; Scheme 20) with the α-alkoxy unit occupying an axial position so as to avoid nonbonded interactions with the butyl substituents on tin. Reagent (**234**) was prepared by the addition of Bu_3SnLi to crotonaldehyde and resolved by the reaction with chloromethyl (–)-menthyl ether. The menthyl unit probably has little to do with the asymmetric induction in aldehyde reactions, since diastereoselection is identical to that obtained with the racemic reagent (**106**; Scheme 20). Consequently, recent reports that α,β-unsaturated acylstannanes undergo highly enantioselective reductions with BINAL-H should provide an alternative preparative route to nonracemic crotylstannanes of this class.[136]



(**234**) 99% *de*

Scheme 44

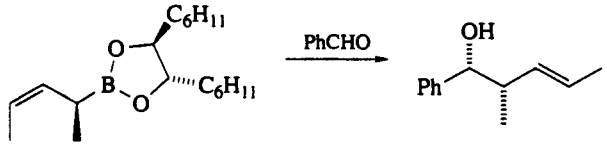
The α-chiral allyl- and crotyl-boronates (**236**)–(**239**) have been developed and studied extensively by Hoffmann and his coworkers.[137] Reagents (**236**) (92% *ee*) and (**239**) (>95% *ee*) are synthesized by using the Matteson α-haloalkylboronate alkylation procedure,[138] while (**237**) (95–98% *ee*) is prepared by hydroboration of 3-butyn-2-yl trimethylsilyl ether followed by an allylic rearrangement with $SOCl_2$.[139] (*Z*)-α-Chlorocrotylboronate (**238**) has so far been studied only as the racemate.[137b] Allylboronate (**236**)[140] and (*E*)-crotylboronate (**237**) provide roughly 95:5 mixtures of (**242**) and (**243**) in reactions with aldehydes, with the enantiomeric purity of the major isomer (**242**) closely paralleling the enantiomeric purity of the starting materials.[137a,b] (*Z*)-α-Methylcrotylboronate (**239**) also undergoes an exceptionally enanti-



(**236**) R^1 = H
(**237**) R^1 = Me

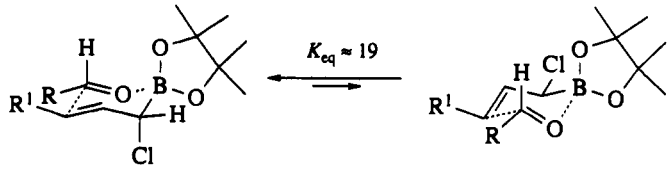
(**242**) (**243**)

	via (236)		*via (237)*	
R	*(242):(243)*	*(242) % ee*	*(242):(243)*	*(242) % ee*
Me	95:5	92	95:5	95
Et	96:4	89	95:5	96
Pr^i	95:5	92	95:5	96
Ph	94:6	92	95:5	98

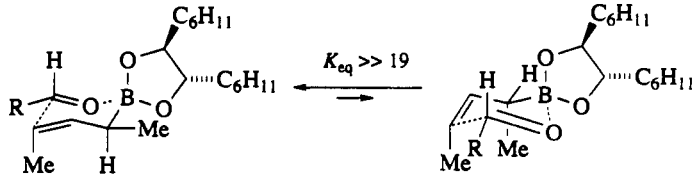


(**239**) (**244**) 99% *ee*

oselective reaction with benzaldehyde.[137c] α-Chloroallyl- and α-chlorocrotyl-boronates (**236**) and (**237**) react preferentially *via* transition state (**245**) with an axial orientation of the chloro substituent that is favored apparently for steric and/or stereoelectronic reasons (Scheme 45).[141] With (**238**) and (**239**), however, the α-substituent prefers an equatorial position as indicated in (**246**) in order to avoid 1,3-interactions with the (*Z*)-Me group.



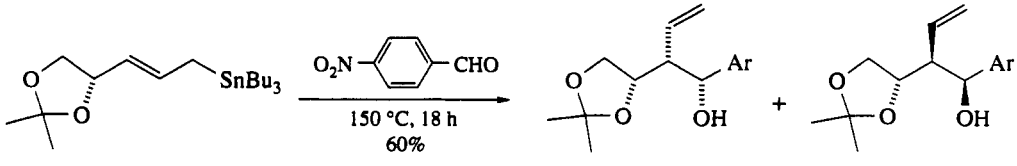
(**245**)



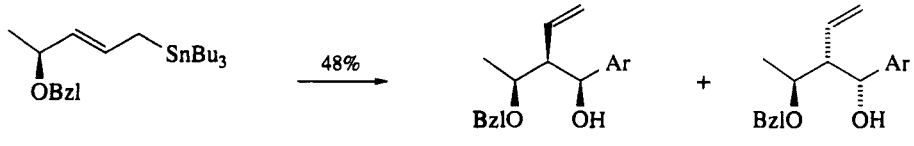
(**246**)

Scheme 45

Finally, Thomas has reported that allylstannanes (**247**) and (**248**) possessing stereocenters at C-4 undergo moderately diastereoselective reactions with *p*-nitrobenzaldehyde (Scheme 46).[142] The origin of asymmetric induction in these cases is probably related to that presented in Section 1.1.3.1 for the reactions of achiral allyl metal compounds and chiral aldehydes (*e.g.* Scheme 27).



(**247**) 82:18



(**248**) 73:27

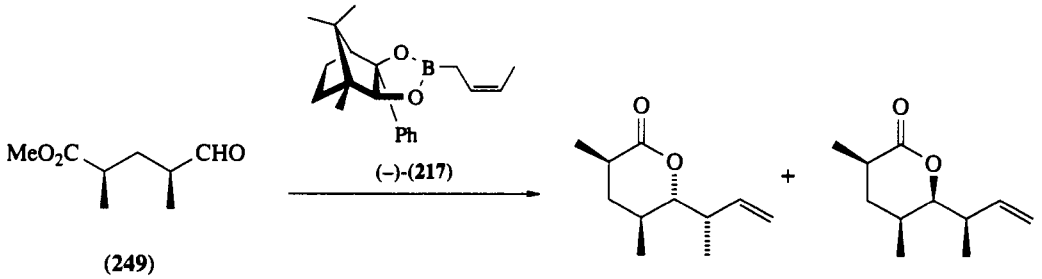
Scheme 46

1.1.5 DOUBLE ASYMMETRIC SYNTHESIS: REACTIONS OF CHIRAL C=X ELECTROPHILES AND CHIRAL ALLYL ORGANOMETALLICS

We have seen in Section 1.1.3 that reactions of many allyl organometallics and chiral C=X electrophiles proceed with only modest levels of relative diastereoselection. Significant improvement in diastereoselectivity is possible, however, by using double asymmetric synthesis,[5] that is, by using the highly enantioselective allyl metal reagents described in Section 1.1.4 rather than the less diastereoface-selective achiral allyl metal compounds discussed in Section 1.1.3. Double asymmetric synthesis is also

referred to as 'double stereodifferentiation'. Two types of double asymmetric reactions are possible: those in which the intrinsic diastereofacial preferences of the C=X electrophile and the chiral allyl metal reagent are cooperative, each favoring the production of the same product diastereomer, 'matched double asymmetric synthesis', and those in which the intrinsic diastereofacial preferences of the two reactants are dissonant, each favoring different stereochemical outcomes, 'mismatched double asymmetric synthesis'. If the chiral reagent has a larger diastereofacial preference than the chiral C=X electrophile, and as long as the transition state of the double asymmetric reaction is similar to that involved in single asymmetric induction experiments, the reagent will dominate the stereochemical course and the otherwise intrinsically disfavored product diastereomer will be formed preferentially. It is almost always more difficult to achieve high diastereoselection in mismatched than in matched double asymmetric reactions since the reagent is always fighting against the intrinsic diastereofacial preference of the C=X electrophile, and the larger that preference the more difficult the goal. Consequently, highly enantioselective reagents should be used, the more selective the better. On the other hand, high levels of diastereoselection are relatively easy to achieve in matched double asymmetric reactions since the intrinsic face selectivity of the substrate reinforces that of the reagent, and in many cases it has been possible to achieve synthetically useful levels of matched diastereoselection by using only moderately enantioselective reagents. Finally, it is worth reminding the reader that both components of double asymmetric reactions need to be chiral and nonracemic in order for the maximum diastereoselectivity to be realized.

Chiral crotylboronates (**216**) and (**217**) were among the first chiral allyl metal reagents to be used in double asymmetric reactions.[97b,121a] The example in Scheme 47, however, shows that (**217**) induces only modest changes in the stereoselectivity of the reactions of (**249**), thus underscoring the need for highly enantioselective chiral reagents.



(–)-(**217**)	32:68
(**2**)	60:40
(+)-(**217**)	81:19

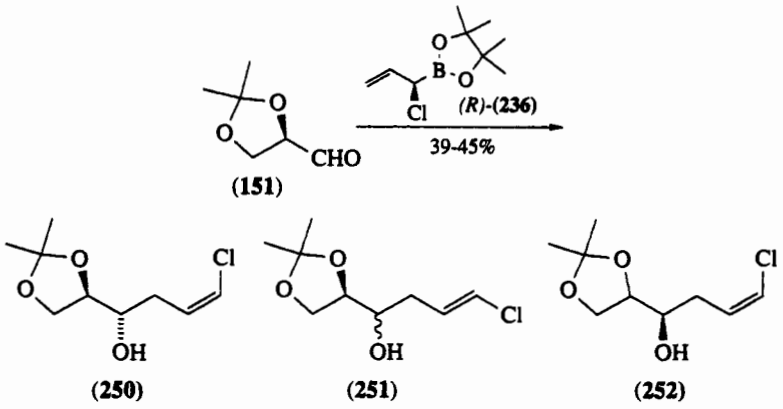
Scheme 47

The first examples of highly diastereoselective double asymmetric reactions involving chiral allyl metal reagents were obtained in reactions with D-glyceraldehyde acetonide (**151**; Table 6). Aldehyde (**151**) displays an 80:20 preference for (**154**) in reactions with the achiral pinacol allylboronate (**144**; entry 4),[25,101] and the selectivity for (**154**) improves to 96–98% with reagents (–)-(**215**) and (*R,R*)-(**224**).[101,125,143] With (*R,R*)-(**228**) the diastereoselectivity is 300:1, which is the highest selectivity yet documented for a reaction of a chiral allyl metal reagent.[126] Tartrate allylboronate (*S,S*)-(**224**) undergoes a highly diastereoselective mismatched double asymmetric reaction with D-(**151**), providing the 4,5-*syn* (*threo*) diastereomer (**155**) with 92% selectivity. Here again, diastereoselectivity for (**155**) increases to 98:2 by using the more enantioselective allylboronate (*S,S*)-**228**. Matched double diastereoselectivity is

Table 6 Reactions of D-Glyceraldehyde Acetonide (**151**) and Chiral Allyl Metal Reagents

Reagent	*Yield (%)*	*(154):(155)*	*Ref.*
(*R,R*)-(**224**)	90	98:2	125
(*R,R*)-(**228**)	81	99.7:0.3	125
(–)-(**215**)	87	96:4	101
(**144**)	75	80:20	25,101
(*S,S*)-(**224**)	85	8:92	125
(*S,S*)-(**228**)	84	2:98	126

also very good (94%) by using α-chloroallylboronate (*R*)-(**236**), but mismatched diastereoselection using (*S*)-(**236**), leading to (**252**), is considerably lower (77%) than that realized with tartrate allylboronate (*S,S*)-(**224**) (Scheme 48).[137a]



(*R*)-(**236**) 94:2:4
(*S*)-(**236**) 11:12:77

Scheme 48

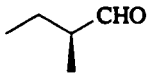
Excellent double diastereoselection has also been realized in the reactions of (**151**) and chiral crotylboron reagents (Table 7). Interestingly, the best selectivity for diastereomers (**153**) and (**156**) is obtained by using the tartrate crotylboronates (*S,S*)-(**18**) and (*R,R*)-(**19**), respectively (entries 2 and 3),[144,145] while Masamune's 2,5-dimethylborolane reagents (*R,R*)-(**221**) and (*S,S*)-(**222**) provide the greatest selectivity for diastereomers (**152**) and (**157**; entries 7 and 10).[124] Comparative data for the diastereoselectivity obtained with the achiral crotylboronates (**1**) and (**2**) appear in the last two entries of Table 7.

Table 7 Reactions of D-Glyceraldehyde Acetonide (**151**) and Chiral Crotyl Metal Reagents

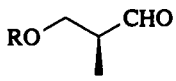
Reagent	*Yield (%)*	*(152)*	*(153)*	*(156)*	*(157)*	*Ref.*
(*R,R*)-(**18**)	87	87	9	4	—	144
(*S,S*)-(**18**)	85	2	96	2	—	144
(*R,R*)-(**19**)	84	1	—	99	—	145
(*S,S*)-(**19**)	90	7	2	76	15	145
(–)-(**216**)	85	72	28	—	—	101
(–)-(**217**)	86	—	—	>98	<2	101
(*R,R*)-(**221**)	71	96	3	1	—	124
(*S,S*)-(**221**)	74	12	86	—	2	124
(*R,R*)-(**222**)	66	4	2	92	2	124
(*S,S*)-(**222**)	65	—	2	16	82	124
(**1**)	75	52	42	6	—	25
(**2**)	85	5	1	91	5	25

Results of reactions of chiral α-methyl aldehydes and several chiral crotyl- and allyl-boron reagents are summarized in Tables 8 and 9. It is apparent from these data that the Brown $(Ipc)_2B$(crotyl) and $(Ipc)_2B$(allyl) reagents (**51**), (**52**) and (**219**) consistently give excellent results for the synthesis of each product diastereomer (Table 8, entries 3–6, 11, 16, 20, and 24; Table 9, entries 1, 2, 10 and 18). This is true also for their reactions with chiral α- and β-alkoxy aldehydes (Scheme 49).[146,148–150] The tartrate crotylboronates (**18**) and (**19**) also display excellent selectivity in the synthesis of crotyl diastereomers (**136**), (**137**) and (**139**) (Table 8, entries 7, 10, 13, 17, 25 and 28), but are much less selective for the synthesis of crotyl diastereomer (**138**), especially from β-alkoxy-substituted aldehydes such as (**253**).[98] Tartrate allylboronate (**224**) is also less effective than $(Ipc)_2$Ballyl (**219**) for the synthesis of (**257**) and (**258**) in Table 9,[98] and of (**266**) and (**267**) in Scheme 49.[149] Substantial improvements in selectivity have been realized by using the tartramide-based allylboronate (**228**), and the results with this reagent (Table 9, entries 4, 7, 9, 12, 14, 17, 20 and 22) compare very favorably with those obtained with (**219**).[126] The data

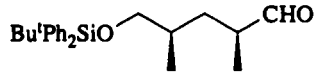
Table 8 Reactions of α-Methyl Chiral Aldehydes and Chiral Crotylboron Reagents



(145)



(253a) R = Bu^tMe_2Si
(253b) R = Bu^tPh_2Si
(253c) R = Bzl

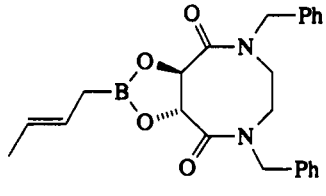


(254)

Entry	*RCHO*	*Reagent*[a]	*Yield (%)*	*Reaction products*[b,c] *(136)*	*(137)*	*(139)*	*(138)*	*Ref.*
1	(145)	(–)-(216)	74	92	8	—	—	97b
2	(145)	(–)-(217)	99	—	—	45	55	97b
3	(145)	(*d*)-(51)	75	96	4	—	—	146
4	(145)	(*l*)-(51)	70	9	91	—	—	146
5	(145)	(*d*)-(52)	79	—	—	96	4	146
6	(145)	(*l*)-(52)	73	—	—	18	82	146
7	(253a)	(*R,R*)-(18)	80	97	3	—	—	98
8	(253b)	(*R,R*)-(18)	—	82	15	1	2	98
9	(253b)	(*R,R*)-(255)	26	92	7	1	—	147
10	(253c)	(*R,R*)-(18)	—	93	5	1	1	98
11	(253c)	(*d*)-(51)	—	98	2	—	—	146b
12	(253a)	(*S,S*)-(18)	—	16	81	3	—	98
13	(253b)	(*S,S*)-(18)	85	10	90	—	—	98
14	(253b)	(*S,S*)-(255)	27	4	96	—	—	147
15	(253c)	(*S,S*)-(18)	—	14	85	1	—	98
16	(253c)	(*l*)-(51)	—	5	95	—	—	146b
17	(253a)	(*S,S*)-(19)	71	—	4	95	1	98
18	(253b)	(*S,S*)-(19)	—	—	4	85	12	98
19	(253c)	(*S,S*)-(19)	—	—	3	88	9	98
20	(253c)	(*l*)-(52)	—	—	—	95	5	146b
21	(253a)	(*R,R*)-(19)	—	12	2	45	41	98
22	(253b)	(*R,R*)-(19)	—	9	3	24	64	98
23	(253c)	(*R,R*)-(19)	—	8	2	45	45	98
24	(253c)	(*d*)-(52)	—	—	—	8	92	146b
25	(254)	(*R,R*)-(18)	56	>98	<2	—	—	147
26	(254)	(*S,S*)-(18)	55	16	84	—	—	147
27	(254)	(*S,S*)-(255)	51	12	88	—	—	147
28	(254)	(*S,S*)-(19)	63	—	—	94	6	147
29	(254)	(*R,R*)-(19)	55	6	—	16	78	147

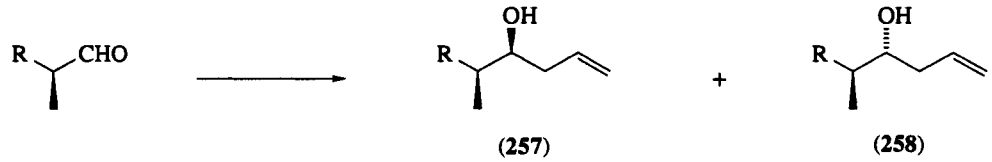
[a]Reagents (–)-(216) and (–)-(217) are prepared from (1*R*,2*S*,3*S*,4*S*)-3-*endo*-phenyl-bornane-2-*exo*-3-*exo*-diol, whileq (*d*)-(51) and (*d*)-(52) are prepared from (+)-α-pinene. [b]Refer to Figure 27 for structures. [c]Additional minor diastereomers are produced in the reactions of (51), (52), (216) and (217), but only the amounts of the two most predominant products are cited in the original literature.

summarized in entries 9, 14 and 27 of Table 8 (compare entries 8, 13 and 26) also indicate that stereoselectivity may be improved in the crotyl series by using tartramide crotylboronate (255).[147]



(*R,R*)-(255)

Table 9 Reactions of α-Methyl Chiral Aldehydes and Chiral Allylboron Reagents



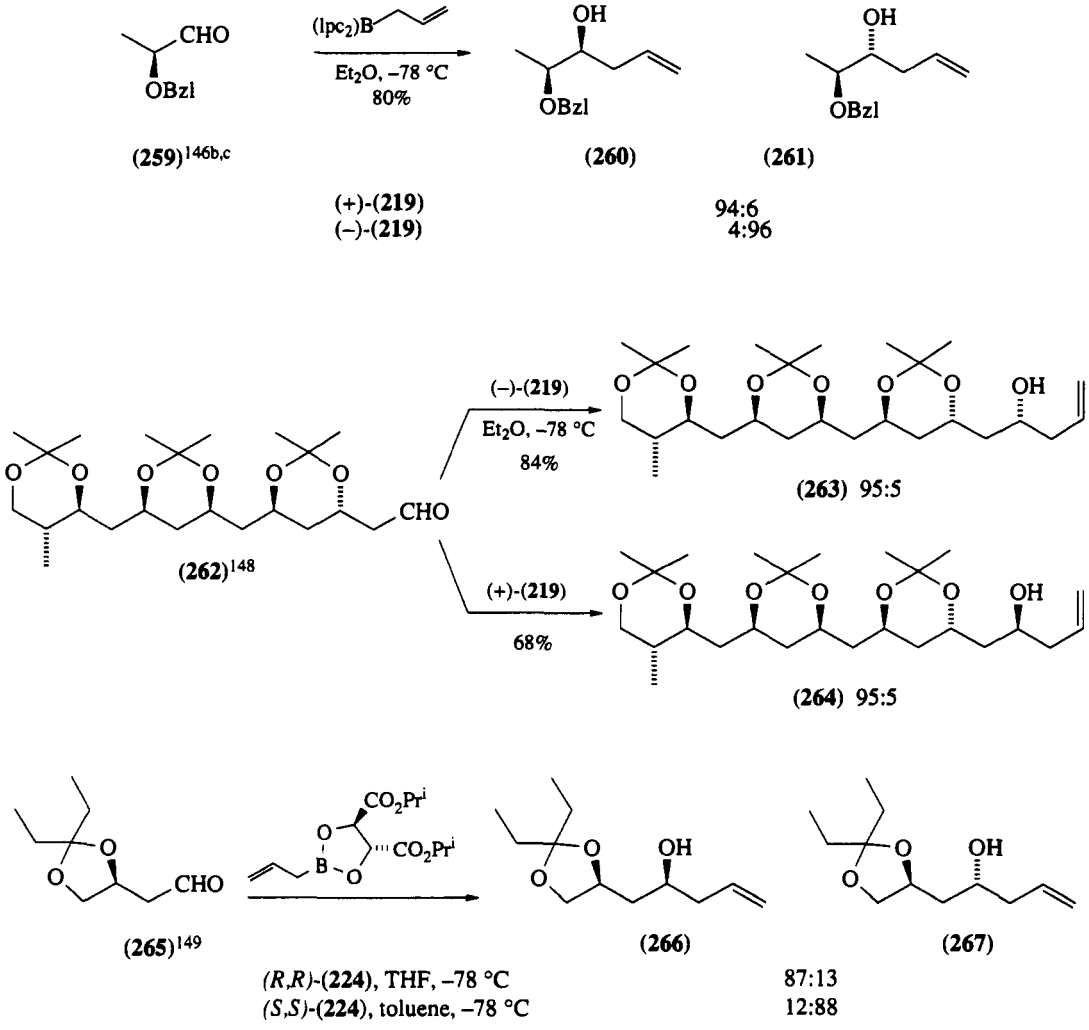
(257) (258)

Entry	*RCHO*	*Reagent*[a,b]	*Temperature* (°C)[c]	*Yield* (%)	*(257)*	*(258)*	*Ref.*
1	(145)	(*d*)-(219)		81	96	4	146b,c
2	(145)	(*l*)-(219)		—	5	95	146b,c
3	(253a)	(*R,R*)-(224)		71	89	11	98
4	(253a)	(*R,R*)-(228)		46	97	3	126
5	(253a)	(*R,R*)-(228)	–50	76	95	5	126
6	(253b)	(*R,R*)-(224)		—	79	21	98
7	(253b)	(*R,R*)-(228)		48	95	5	126
8	(253c)	(*R,R*)-(224)		—	83	17	98
9	(253c)	(*R,R*)-(228)	–50	56	93	7	126
10	(253c)	(*d*)-(219)		—	95	5	146b
11	(253a)	(*S,S*)-(224)		—	19	81	98
12	(253a)	(*S,S*)-(228)		43	3	97	126
13	(253b)	(*S,S*)-(224)		72	13	87	98
14	(253b)	(*S,S*)-(228)		35	3	97	126
15	(253b)	(*S,S*)-(228)	–50	68	4	95	126
16	(253c)	(*S,S*)-(224)		—	20	80	98
17	(253c)	(*S,S*)-(228)	–50	53	7	93	126
18	(253c)	(*l*)-(219)		—	2	98	146b
19	(254)	(*R,R*)-(224)		91	92	8	147
20	(254)	(*R,R*)-(228)		82	97	3	147
21	(254)	(*S,S*)-(224)		—	13	87	147
22	(254)	(*S,S*)-(228)		76	7	93	147

[a]Allylborane (*d*)-(219) is prepared from (+)-α-pinene. [b]The reactions in entries 4, 5, 7, 9, 12, 14, 15 and 17 involving (**228**) were actually performed with the enantiomers of (**253**) and (**228**) indicated here (ref. 126). The data are presented in the enantiomeric series only for the convenience of the structural representations. [c]All reactions were performed at –78 °C unless indicated otherwise.

Excellent results have also been obtained in double asymmetric reactions by using Hoffmann's α-substituted crotylboronates (**237**), (**268**) and (**238**) (Scheme 50).[137c,151] Aldehyde (**145**) and reagent (*R*)-(**237**) are a matched pair and react to provide (**269**) with >98:2 selectivity. The mismatched double asymmetric reaction of (**145**) and (*S*)-(**237**) is more difficult, and provides (**271**) with modest levels of selectivity. This reaction is improved, however, by using the α-methoxy-substituted reagent (*S*)-(**268**), providing (**271**) with *ca.* 95% selectivity.[151a] Evidently, the methoxy group has a much greater preference for an axial orientation in the transition state (refer to Scheme 45), resulting in (**268**) being more selective than (**237**). Finally, (**249**) and (*S*)-(**238**) are a matched pair and provide (**273**) with >95% selectivity.[137c] It should be noted, however, that even though the results obtained with these chiral α-substituted crotylboronates are excellent, the greater difficulty of their preparation compared to the $(Ipc)_2$crotylboranes (**51**)/(**52**) and the tartrate crotylboronates (**18**)/(**19**) does not warrant their use, especially in matched double asymmetric reactions where (**51**)/(**52**) and (**18**)/(**19**) are comparably selective.

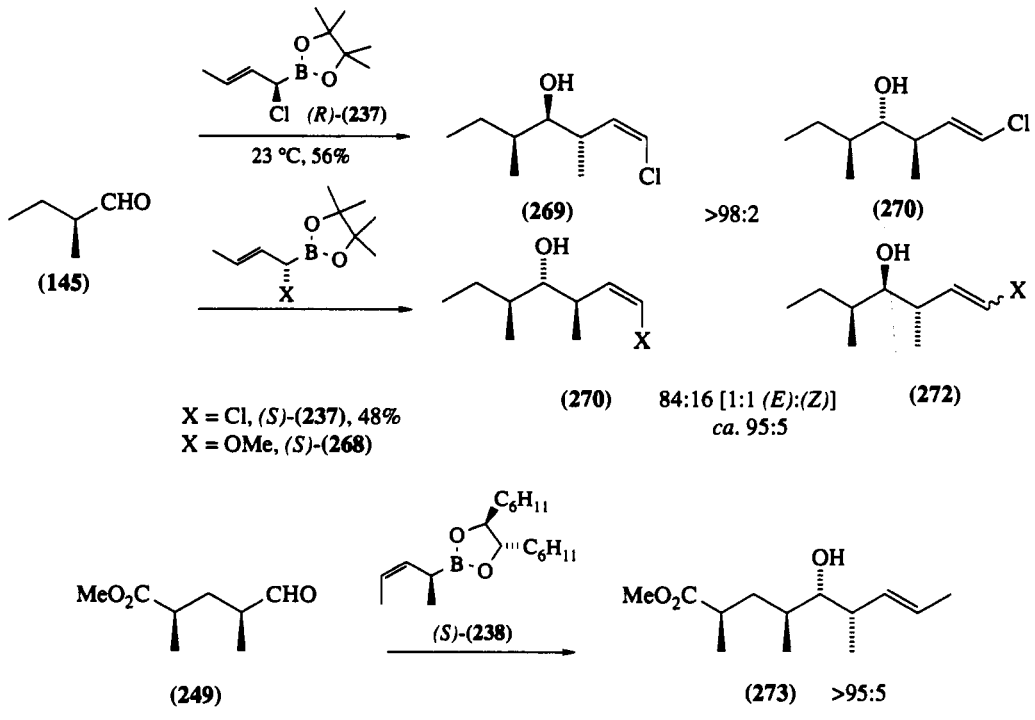
It was noted at the beginning of this section that as the intrinsic diastereofacial selectivity of the chiral aldehyde increases, the ease of accomplishing highly diastereoselective matched double asymmetric reactions increases and, correspondingly, the difficulty of achieving success in the mismatched pair also increases. The intrinsicially favored products of reactions of α-methyl chiral aldehydes and (*E*)- and (*Z*)-crotyl metal reagents are diastereomers (**136**) and (**139**), respectively (Scheme 27 and Table 4), and it is this pair of diastereomers that will always be easily prepared with very high diastereoselection by using matched double asymmetric reactions (Table 8; see also **269** and **273**, Scheme 50). Diastereomers (**137**), (**271**) and (**138**), however, are the intrinsicially disfavored set of products, and it is these that are the most difficult to access with synthetically useful levels of mismatched double diastereoselectivity, especially as the intrinsic diastereofacial selectivity of the aldehyde increases. The examples presented in



Scheme 49

Scheme 51 illustrate this point.[115] First, the mismatched double asymmetric reaction of (**274**) and (*S,S*)-(**18**) provides the 3,4-*anti*-4,5-*anti* diastereomer (**276**) (*cf.*, **137**) with only 73% selectivity. This is a substantial drop in stereoselectivity compared to the mismatched reaction of (*S,S*)-(**18**) and (**254**) that provides (**137**) with 84% selectivity (Table 8, entry 26). Substrate (**277**) is even more problematic: diastereomer (**278**) predominates with >95:5 selectivity from the reaction with (*R,R*)-(**18**), while (**279**) was the 'expected' product based on the stereochemical preferences of (*R,R*)-(**18**). Thus, the intrinsic diastereofacial selectivity of (**277**) totally overwhelmed that of (*R,R*)-(**18**) in this attempted mismatched double asymmetric reaction.

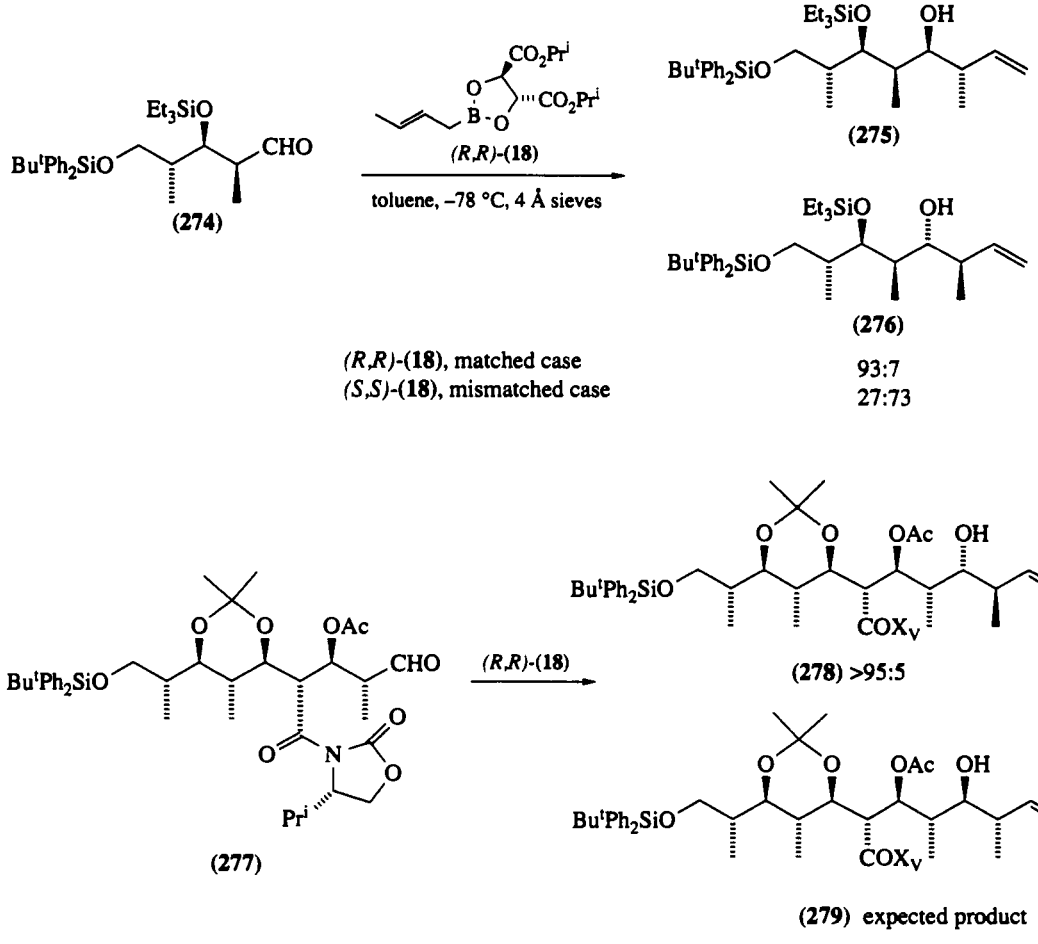
Of all the chiral allyl metal reagents reported to date, the one that is most effective in demanding cases of mismatched double diastereoselection is the α-methoxycrotylboronate (**268**) developed by Hoffmann.[151] Two illustrative cases are presented in Scheme 52. First, the reaction of (**280**) and (*R*)-(**268**) provides the 3,4-*anti*-4,5-*anti* diastereomer (**281**) with roughly 84% stereoselectivity. This is remarkable in view of the very high intrinsic diastereofacial selectivity (98:2) for the 3,4-*anti*-4,5-*syn* diastereomer exhibited by the structurally related aldehyde (**147**; Table 4). The second involves (**283**), which with (*S*)-(**268**) provides 3,4-*anti*-4,5-*anti* (**284**) with 73% stereoselection. By way of comparison, the α-chlorocrotylboronate (*S*)-(**237**) is incapable of overriding the intrinsic diastereofacial preference of (**283**), giving 3,4-*anti*-4,5-*syn* diastereomer (**E**)-(**285**) with 92% selectivity (compare also **277**, Scheme 51).



Scheme 50

1.1.6 SUMMARY

Tremendous progress has been realized in the past decade concerning the stereochemistry of the reactions of type I and type III allyl metal compounds with C=X electrophiles. Numerous reagents exist that provide excellent stereochemical control in reactions with achiral aldehydes and imines (simple diastereoselection, Section 1.1.2), and a clear stereochemical picture has emerged, particularly concerning the reactions with chiral aldehydes (relative diastereoselection, Section 1.1.3). Even more impressive has been the development of highly enantioselective chiral allyl metal reagents (Section 1.1.4) capable of enhancing, or reversing, depending on the absolute configurations of the two reactants, the diastereofacial selectivity of the chiral C=X electrophile *via* the strategy of double asymmetric synthesis (Section 1.1.5). Consequently, it is fair to say that the goal stated at the outset, namely the development of a family of allyl organometallics capable of providing highly selective access to each of the products depicted in Scheme 2, has been achieved. While room for improvement certainly exists, especially in terms of the discovery of allyl metal reagents that are both economical and practical as well as highly enantioselective, the state of the art of allyl organometallic chemistry is now at a sufficiently high level that significant opportunities exist for its application to the highly stereocontrolled synthesis of complex, biologically active molecules.[152]

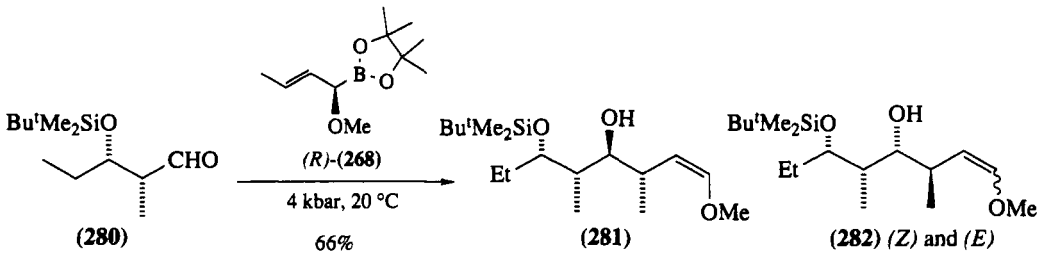


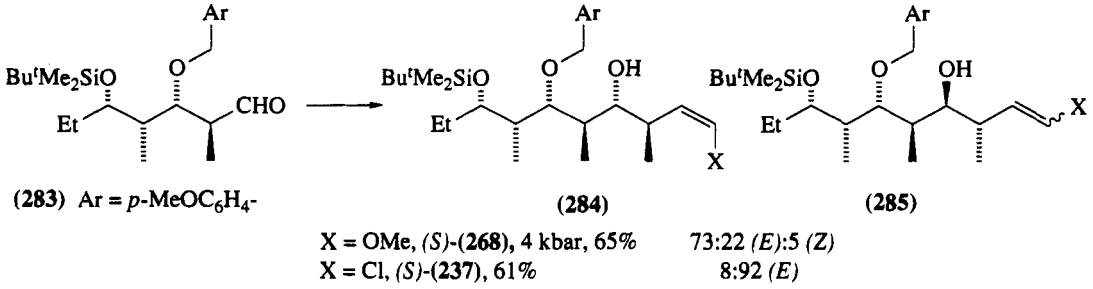
Scheme 51

1.1.7 ADDENDUM

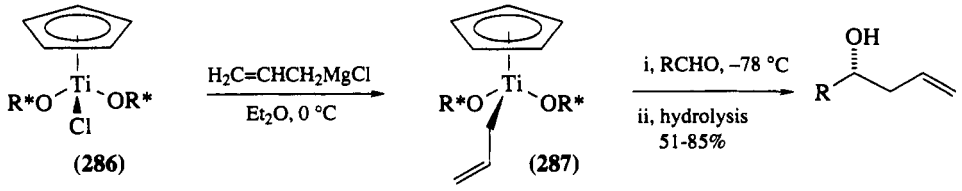
Several highly enantioselective chiral allyl metal reagents have been described in the literature since the original manuscript was submitted. Riediker and Duthaler have reported that the chiral allyltitanium reagent (**287**), prepared as indicated from (**286**), which incorporates two diacetone glucose residues as chiral auxiliaries, undergoes highly enantioselective reactions with aldehydes at –78 °C (Scheme 53).[153] The enantioselectivity ranges from 85 to 94% *ee* for 16 aldehydes that were examined, while lower levels of asymmetric induction are obtained in reactions with ketones (*ca.* 50% *ee*; 80% *ee* with acetophenone). Several substituted allyltitanium reagents were also described (*e.g.* (*E*)-crotyl, (*E*)-cinnamyl and (*E*)-pentadienyl) that provided the corresponding *anti* homoallyl alcohols in 83–90% *ee*.

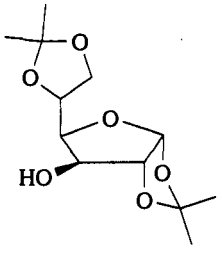
Corey and coworkers have described the preparation of allylborane (**289**) by the reaction of bromoborane (**288**) and allyltributylstannane and shown that (**289**) undergoes highly stereoselective reactions with both achiral (95–97% *ee*) and chiral aldehydes (Scheme 54).[154] The corresponding methallyl, (*E*)-crotyl and 2-chloro- and 2-bromo-allyl reagents were prepared by similar methods and shown to give excellent results in reactions with achiral aldehydes (84–99% *ee* in most cases).





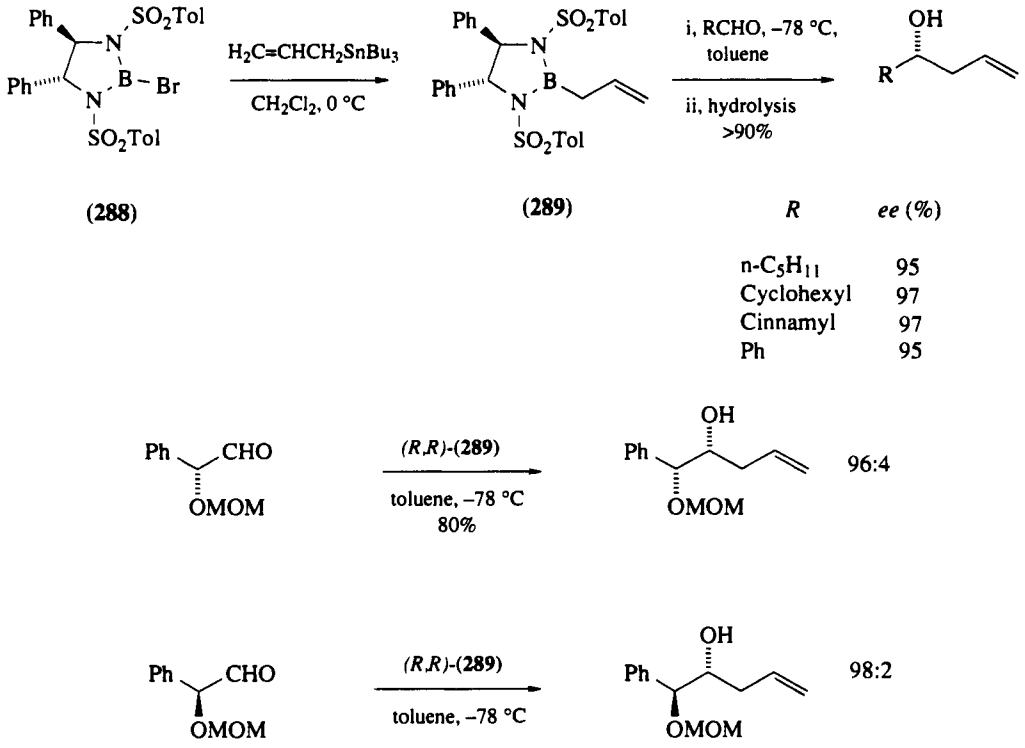
Scheme 52





R	*ee* (%)
Pr^n	93
Bu^i	85
Cyclohexyl	92
Bu^t	88
Vinyl	86
Styryl	90
Ph	90
9-Anthryl	94

Scheme 53



Scheme 54

1.1.8 REFERENCES

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1.2
Heteroatom-stabilized Allylic Anions

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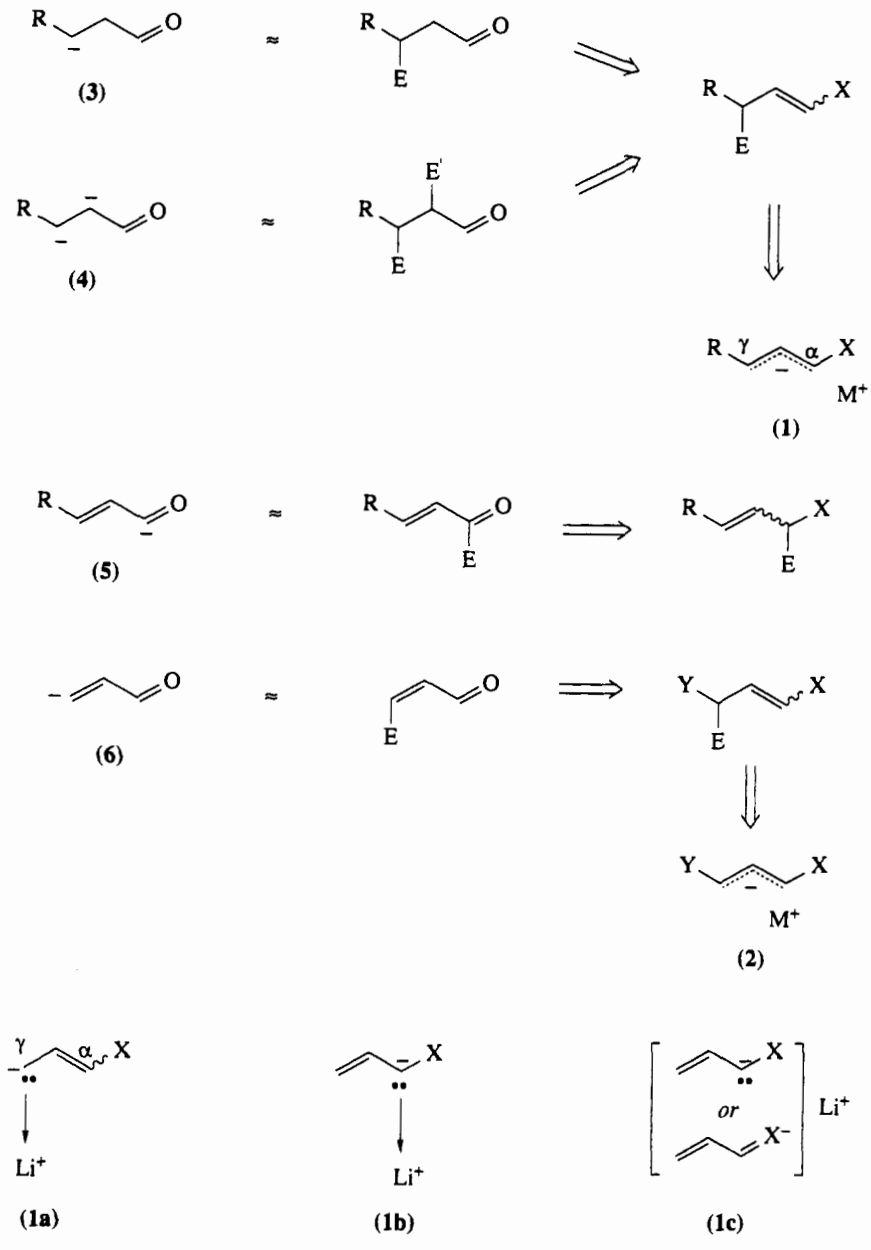
1.2.1 SYNTHETIC UTILITY

Heteroatom-stabilized allylic anions (**1** and **2**; X = Y = heteroatom) can be used as homoenolate anion synthons (**3**) and (**4**) or reversed polarity equivalents (**5**) and (**6**), as shown in Scheme 1. Homoenolates are important synthetic species since they are capable of converting aldehydes or ketones into γ-lactols or γ-lactones (Volume 2, Chapter 1.14). Acyl anion equivalents are also very important in organic synthesis.[1d] Electrophiles may react at either of the termini of allylic anions. A great deal of effort has been exerted to control the regioselectivity (α:γ ratio); regioselective attack at the γ-position of (**1**) leads to homoenolate anion equivalents, whereas the attack at the α-position leads to reversed polarity equivalents. The α/γ-selectivity is dictated by a number of factors, such as the nature of the heteroatom, the substituents attached to the heteroatom, the countercation, the type of electrophile, additives and solvent, reaction temperature, and reaction time.[1] The following rule of thumb is useful for predicting the regioselectivity of an allylic anion like (**1**; R = H, M = Li; Scheme 1),[2] in which lithium and the allylic anion are associated, thus free anions or anions bearing strong electron-withdrawing groups are excluded. When X is an anion-destabilizing substituent, higher electron density would be expected at the γ-position and (**1a**) would be preferred over (**1b**). Accordingly, alkyl halides and protons would react at the γ-position (the site of higher electron density), while carbonyl compounds would react at the α-position *via* a rearrangement process involving lithium. When X is an anion-stabilizing substituent, (**1b**) or (**1c**) would be preferred over (**1a**) and thus complementary regioselectivity would be observed. In fact, allylic anions substituted by anion-destabilizing groups (X = OR, NR_2, alkyl) undergo alkylation and protonation preferentially at the γ-position and react with carbonyl compounds predominantly at the α-position. Anions bearing anion-stabilizing groups (X = SR, BR_2) react with carbonyl compounds at the γ-position and with alkyl halides and protons at the α-position. However, these tendencies may be modified by a number of factors mentioned above.



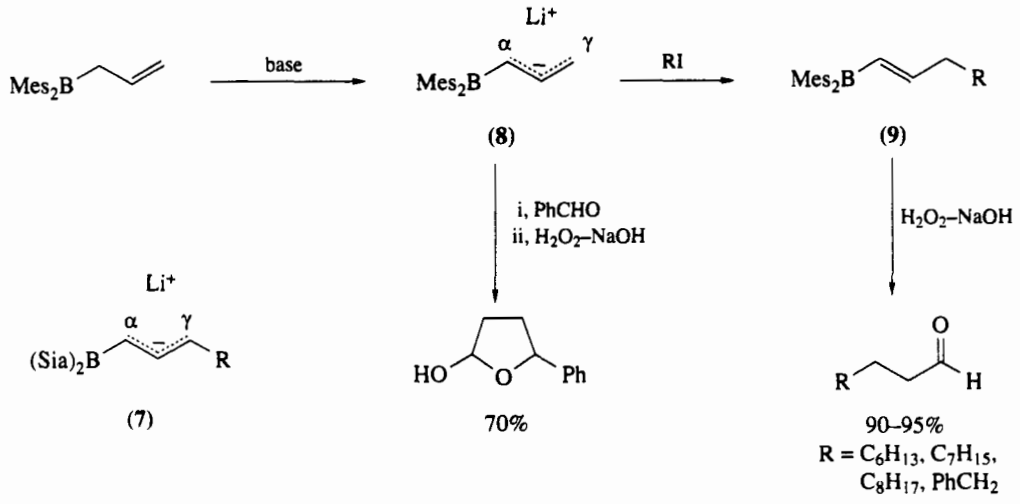
Scheme 1

The allylic anions are normally generated by deprotonation of the corresponding allylic derivatives with *n*-butyl- or *s*-butyl-lithium, often in conjunction with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA). Lithium dialkylamides are also employed. The deprotonation is usually performed in THF or ether at –65 °C or lower because of the high reactivity of both the lithium bases and the resulting allylic anions. Chloro-substituted allylic anions are most efficiently prepared by transmetallation of 3-chloroallyltriphenyllead with *n*-butyllithium.

1.2.2 BORON-SUBSTITUTED ALLYLIC ANIONS

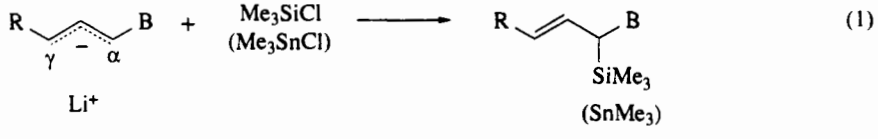
Although (**7**) reacts with methyl iodide and water predominantly at the α-carbon and with acetone mainly at the γ-carbon,[3] anion (**8**), which is readily prepared from the corresponding allyldimesitylborane by treatment with mesityllithium or lithium dicyclohexylamide, reacts with both alkyl halides and

benzaldehyde exclusively at the γ-position (Scheme 2).[4] The resulting alkenylborane (**9**) can be converted to the three-carbon-homologated aldehyde upon oxidation with H_2O_2–NaOH. The reaction of (**8**) with benzaldehyde followed by the usual oxidation gives the γ-lactol in 70% yield. The γ-regioselectivity exhibited by (**8**), regardless of the types of electrophiles, is presumably due to the steric bulkiness of the mesityl group. Unlike other allylic boranes, such as the precursor of (**7**), allyldimesitylborane is readily made from allylmagnesium bromide and fluorodimesitylborane, and is a crystalline compound, m.p. 68 °C, stable enough to be recrystallized from ethanol.



Scheme 2

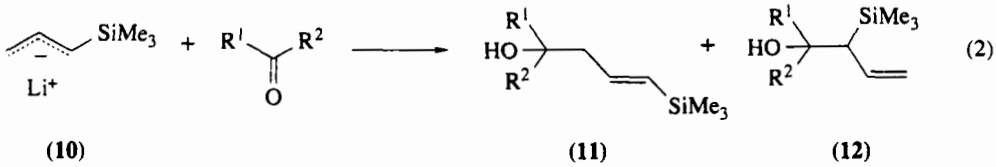
Although (**7**) reacts with trimethylsilyl chloride (TMS-Cl) at the γ-position because of the steric bulk of the siamyl group,[3] the 9-borabicyclo[3.3.1]nonyl (9-BBN) derivative (equation 1) gives the α-trimethylsilyl or α-trimethylstannyl allylic-9-BBN upon treatment with TMS-Cl or trimethyltin chloride.[5]



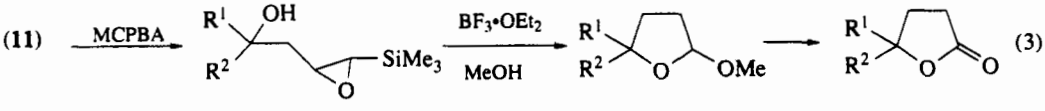
(1)

1.2.3 SILICON-SUBSTITUTED ALLYLIC ANIONS

The anion (**10**), prepared from allyltrimethylsilane and *s*-butyllithium in THF–TMEDA at –76 °C, reacts with a variety of aldehydes and ketones to give the γ-adducts (**11**).[6] The resulting vinylsilanes are converted to α,β-epoxysilanes by treatment with *m*-chloroperbenzoic acid (MCPBA). Ring opening with boron trifluoride etherate in methanol affords lactol ethers. Finally, γ-lactones are obtained from the lactols by Jones' reagent (equations 2 and 3). The γ-regioselectivity of carbonyl compounds can be converted to α-selectivity by changing the counterion to magnesium(II),[7] or by addition of triethylaluminum

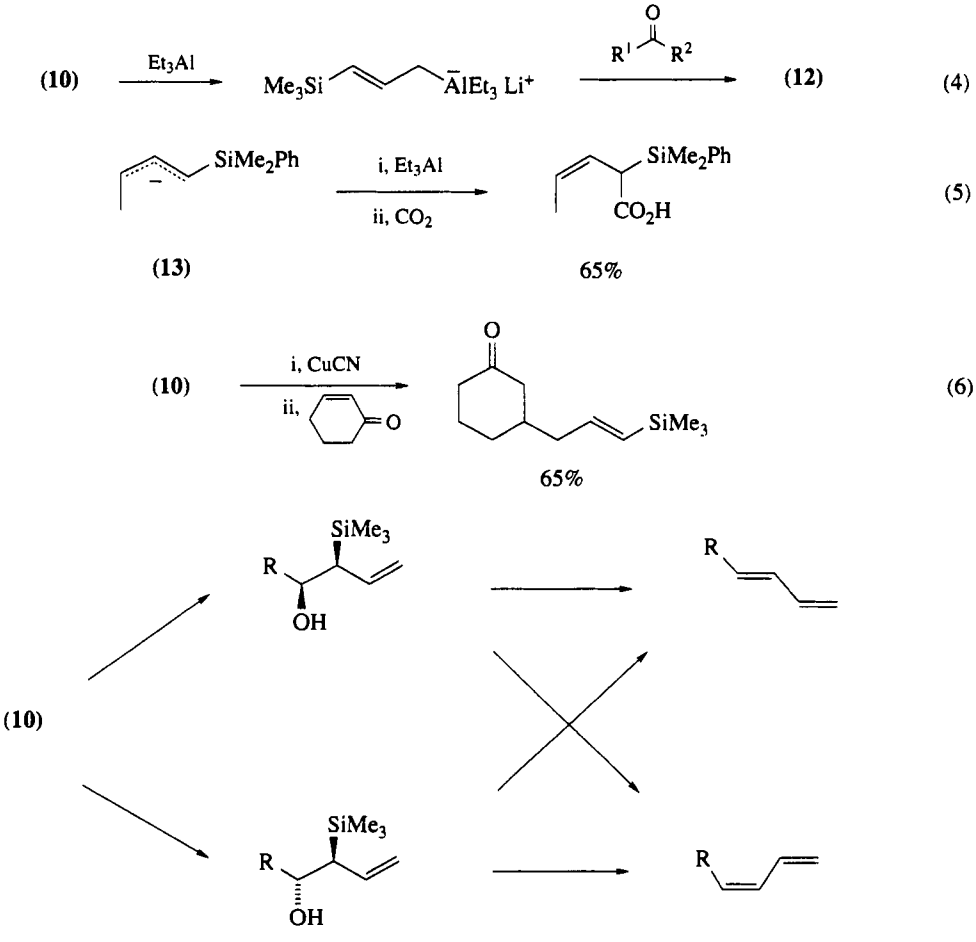


(2)



(3)

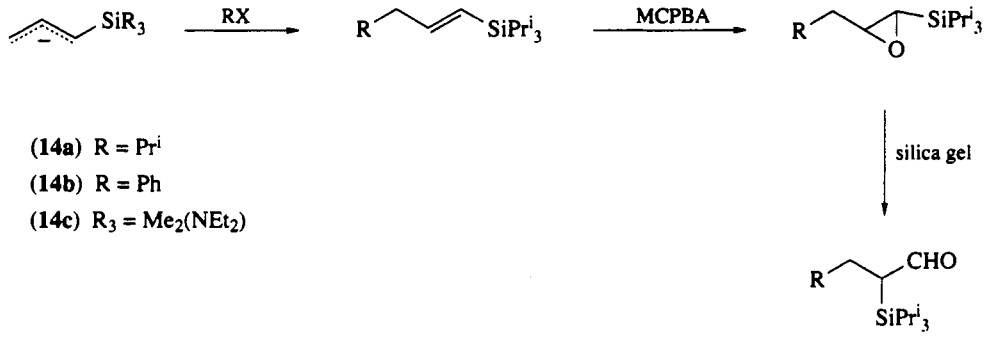
to form the aluminum ate complex (equation 4).[8] The ate complex of crotyl anion (**13**) reacts with carbon dioxide to give the α-silyl-substituted carboxylic acid (equation 5).[9] Carboxylation without triethylaluminum produces the γ-silylated-β,γ-unsaturated carboxylic acid. Other additives, such as R_3B, R_2BCl, $RBCl_2$, $RAlCl_2$, and R_3SnCl, direct aldehydes to the α-position.[10] Presumably, γ-silyl-substituted organometallics, like the aluminum ate complex, are formed *in situ*, and these reagents react with aldehydes with allylic rearrangement to give (**12**). Boron, aluminum and titanium complexation all induce *anti* selectivity, whereas the use of tin results in a *syn* preference, providing stereocontrolled routes to terminal dienes by Peterson alkenation. The α-adducts (**12**) can undergo the Peterson *syn* elimination of $OSiMe_3$ to give the 1,3-dienes (Scheme 3). Addition of copper(I) cyanide to (**10**) produces the copper complex, which reacts selectively at the γ-position with chloromethyl methyl ether and acetyl chloride to give the corresponding vinylsilanes.[11] Further, the copper complex adds to α,β-unsaturated ketones and esters in a highly regioselective γ-1,4-manner (equation 6). In contrast, α,β-unsaturated aldehydes give the γ-1,2-addition products.



Scheme 3

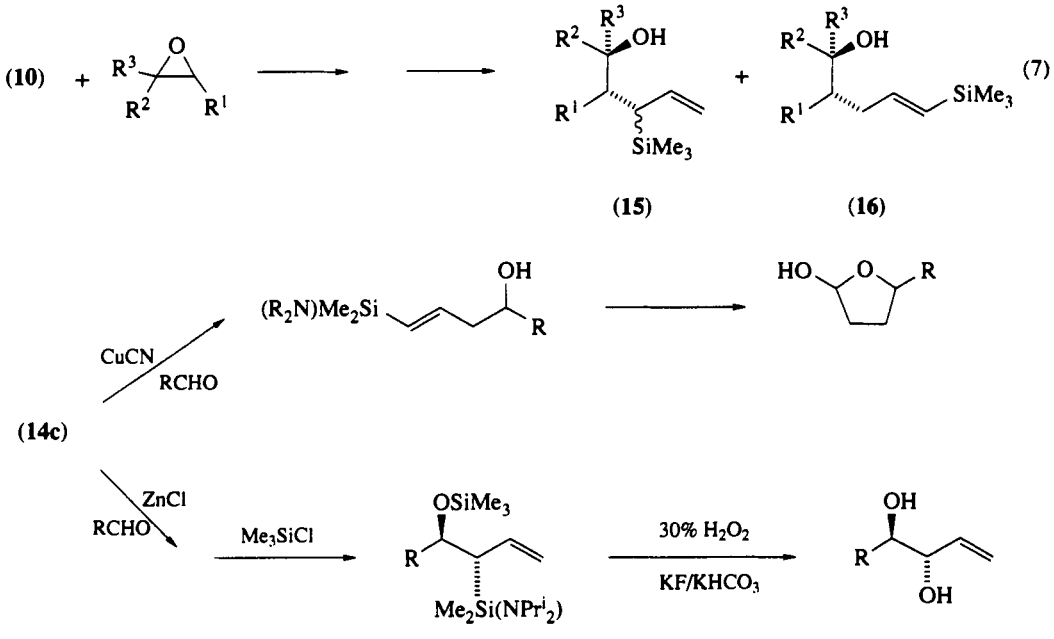
Regiocontrol has been satisfactorily accomplished in cases where carbonyl derivatives are the electrophiles. However, the reaction of (**10**) with simple alkyl halides produces a mixture of the α- and γ-alkylation products. The addition of various metal salts, such as MgX_2, ZnX_2 and CuX, does not induce appreciable change in the α:γ ratio. However, use of Bu^tOK/Bu^nLi in hexane as the proton-abstracting system enhances γ-selectivity (γ:α > 80:20).[12] A sterically demanding group on silicon such as in (**14a**) can increase the extent of γ-alkylation (γ:α = 80:20–99:1),[13] in which the deprotonation of allyltriisopropylsilane is carried out with the usual base (Bu^nLi–TMEDA). Epoxidation of the vinylsilanes, followed by treatment with silica gel affords α-triisopropylsilyl aldehydes (Scheme 4). The reaction of (**10**) with epoxides (equation 7) gives a mixture of (**15**) and (**16**).[14] Ethylene oxide and monosubstituted epoxides produce (**15**) predominantly, while 1,2-di- or 1,1,2-tri-substituted epoxides give (**16**) preferentially. The

γ-selectivity can be enhanced by addition of one-half equivalent of $CuBr{\cdot}SMe_2$, which produces the cuprate intermediate. Silicon-substituted allyl anions are normally prepared from 2-alkenylsilanes. Treatment of 1-propenyltriphenylsilane with Bu^nLi in THF–HMPA also produces (**14b**).[15] The triphenylgermyl-substituted allyl anion is produced similarly and exhibits a similar regioselectivity to (**14b**). Treatment of allyl(diethylamino)dimethylsilane with Bu^nLi/TMEDA produces (**14c**).[16] Addition of CuCN, followed by treatment with aldehydes gives δ-hydroxy vinylsilanes which can be converted to lactols (Scheme 5). Addition of $ZnCl_2$, $MgBr_2$ or $Ti(OPr^i)_4$ results in almost exclusive α-selectivity. The steroechemistry of the α-adducts is *anti*, and they may be converted to *anti* diols by oxidation of the Si—C bond.



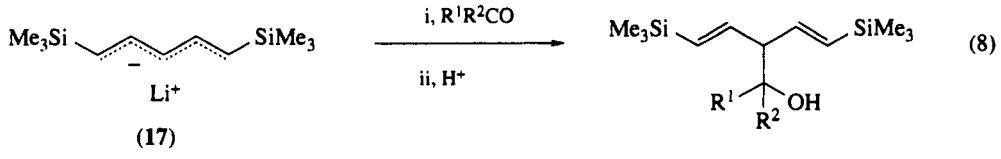
(**14a**) R = Pr^i
(**14b**) R = Ph
(**14c**) $R_3 = Me_2(NEt_2)$

Scheme 4



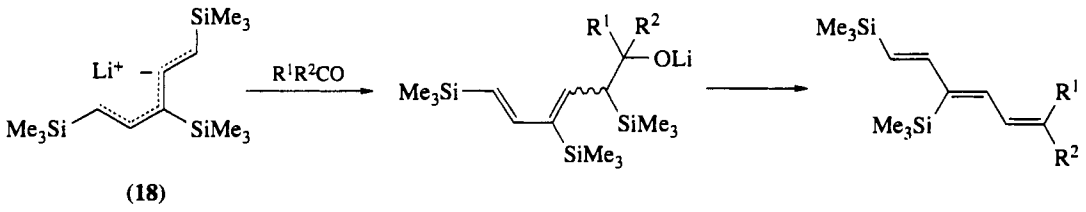
Scheme 5

Pentadienylation of simple aliphatic ketones or aldehydes by (**17**; equation 8) proceeds regioselectively at the C-3 position of the pentadienyl moiety, whereas the reaction with (**18**; Scheme 6) leads



(8)

(**17**)

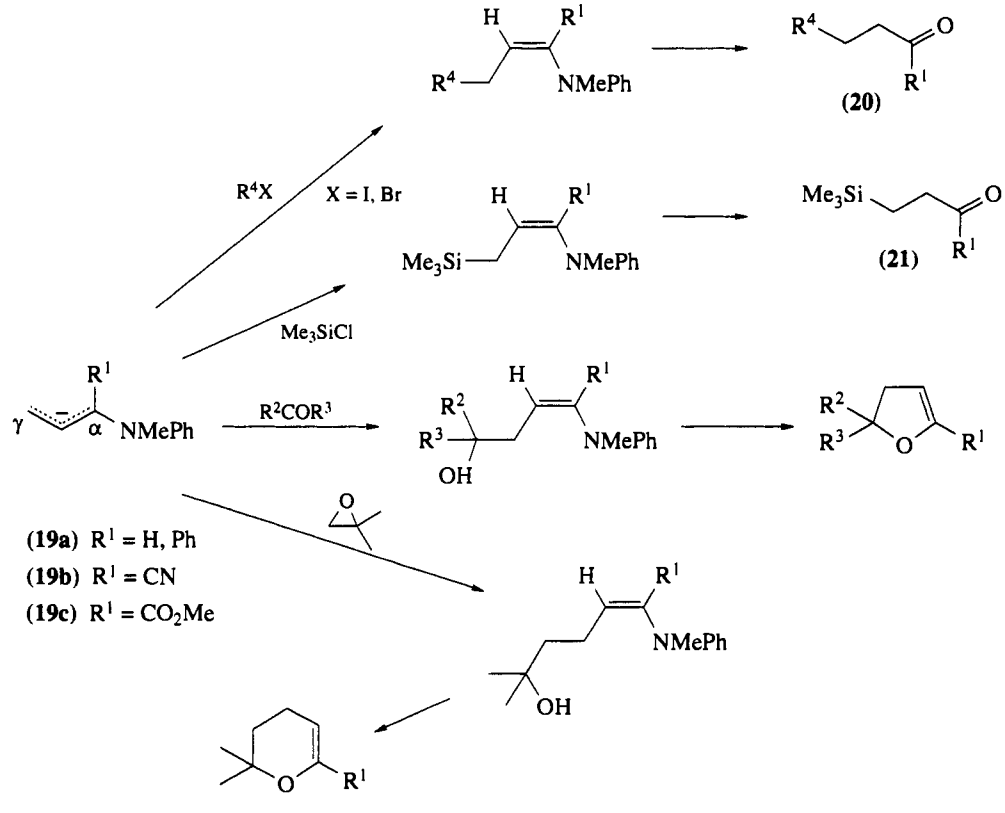


Scheme 6

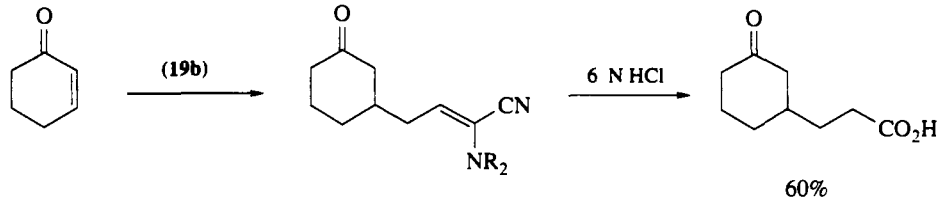
to preferential addition at the terminal carbon atom, resulting in conjugated trienes through Peterson elimination.[17] 1-Trimethylsilylpentadienyllithium generally gives a mixture of two regioisomers by competitive attack at the central (C-3) and terminal (C-1) carbons. Pentadienylation of α,β-unsaturated ketones or aldehydes with (**17**) or (**18**) occurs selectively in a 1,4-fashion at the C-3 position.

1.2.4 NITROGEN-SUBSTITUTED ALLYLIC ANIONS

Deprotonation of enamines or allylamines with bases such as Bu^nLi and Bu^tOK–Bu^tLi produces nitrogen-substituted allylic anions (**19a**; Scheme 7), which undergo protonation, alkylation, trimethylsilylation and reaction with carbonyl compounds and epoxides either exclusively or predominantly at the γ-position.[18] The resulting enamines can be hydrolyzed by dilute hydrochloric acid to give three-carbon-homologated carbonyl compounds (**20** and **21**). Reactions with carbonyl compounds and epoxides afford the corresponding hydroxy derivatives, which can be isolated as trimethylsilyl ethers. Upon heating, the hydroxy derivatives produce dihydrofurans or dihydropyrans (Scheme 7). Derivatives (**19b**) and (**19c**) also exhibit γ-regioselectivity. Alkylation of (**19c**) followed by hydrolysis produces 2-oxoalkanoic esters. Conjugate addition of (**19b**) to cyclohexenone gives the γ-1,4-adduct, which is converted to the carboxylic acid derivative after hydrolysis (Scheme 8).[18b]

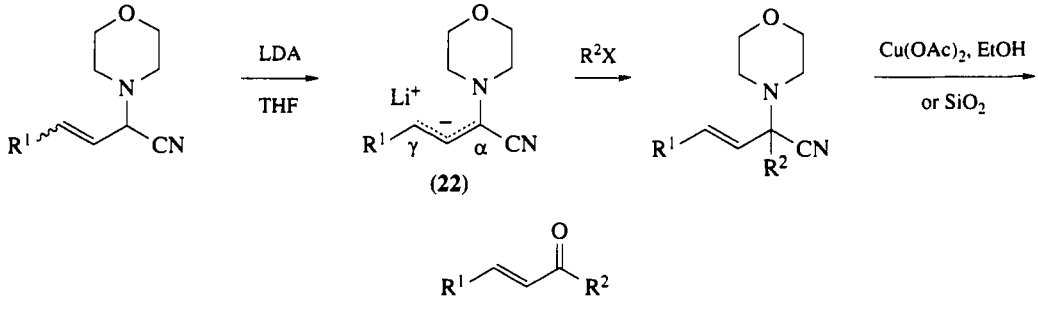


Scheme 7



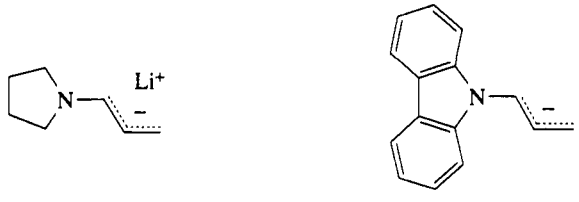
Scheme 8

On the other hand, allylic anions (**22**; Scheme 9) undergo alkylation at the α-position either exclusively or predominantly. Hydrolysis of the α-alkylation products gives α,β-unsaturated ketones in fair to good yields.[19] Allylpyrrolidine anion (**23**) and allylcarbazole anion (**24**) are alkylated at the γ-position with high regioselectivity, but additions of carbonyl compounds to (**23**) result in low regioselectivity.[1e] With zinc cations, almost exclusive α-addition of carbonyl compounds to (**23**) is accomplished. Treatment of (**23**) with triethylaluminum followed by addition of TMS-Cl produces the α-silylated allylpyrrolidine, though the direct reaction of (**23**) with TMS-Cl gives the γ-silylated enamine derivative.[8] The allylic anion (**25**; Scheme 10) produces the α-adduct upon treatment with ketones at –78 °C, while it gives the γ-adduct at 0 °C.[20] The γ-adduct can be converted to the three-carbon-annelation product. Thus, (**25**) can serve as either an acyl anion or a β-homoenolate equivalent, depending on the reaction conditions.



R^1 = Me, Ph; R^2 = Me, Et, hexyl

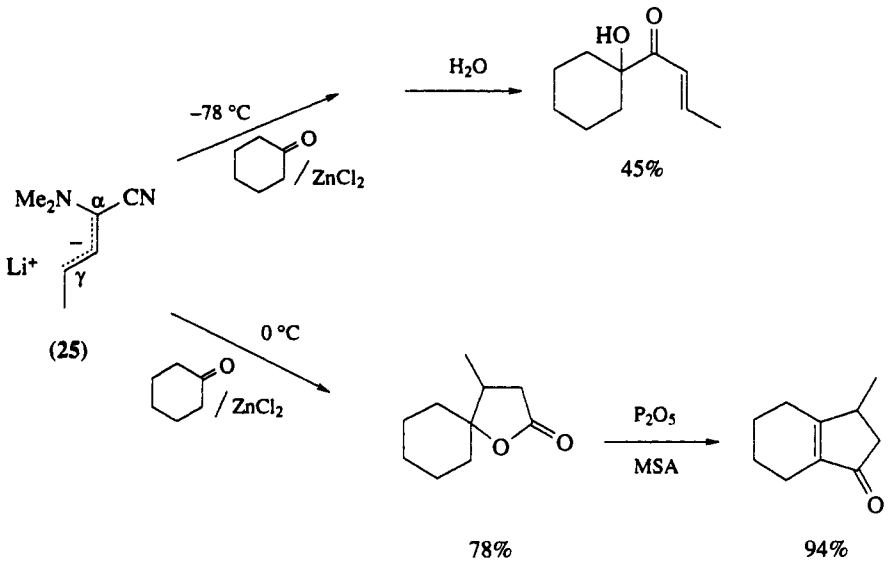
Scheme 9



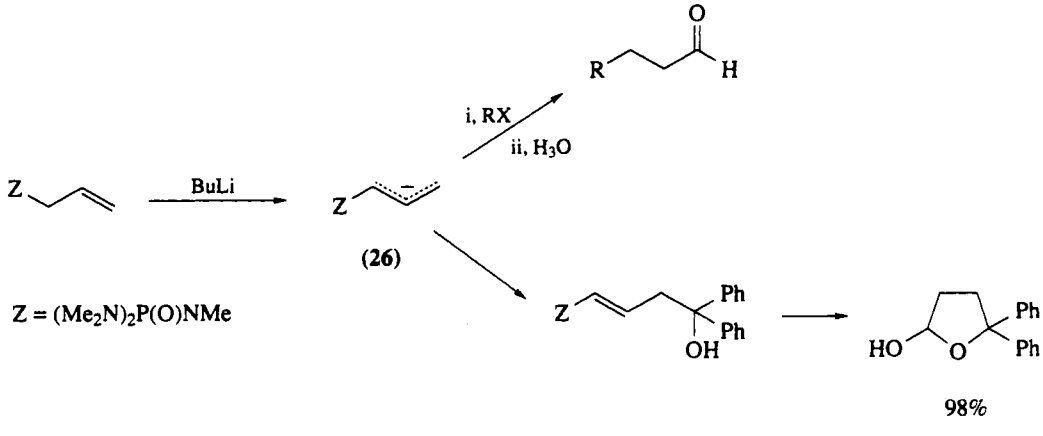
(**23**) (**24**)

Treatment of *N*-methyl-*N*-allylphosphoramide with Bu^nLi at –50 °C, followed by an alkyl halide results in γ-alkylation of the intermediate anion (**26**; Scheme 11). Acid-catalyzed hydrolysis gives the corresponding aldehydes. Although the reaction of (**26**) with benzophenone produces a mixture of the α- and γ-adducts, replacement of the lithium cation by magnesium leads almost exclusively to γ-substitution.[21] Acid hydrolysis affords the lactol almost quantitatively, but such a high yield is not realized with other ketones. The phosphoramide group is a convenient mask, since it is easily introduced to allylic structures and it is easily removed after the reaction. Although (**27a**) gives a mixture of the α- and γ-adducts, (**27b**) produces γ-adducts exclusively upon treatment with alkyl halides or carbonyl compounds. Replacement of lithium by less electropositive metals (Mg, Zn, Cd) leads to increased α-reactivity.[1d] The dilithiated anion (**28**) derived from deprotonation of the corresponding *N*-allylamide with two equivalents of lithium diisopropylamide (LDA) gives the γ-adduct with high regioselectivity.[1e] *N*-Nitroso-*N*-

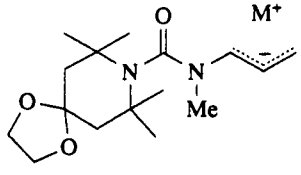
alkyl-*N*-allyl anions (**29**) show kinetically favored α-addition, but the addition of carbonyl compounds is essentially reversible and thus the γ-adducts become favorable under thermodynamic control.[1e] Metallated chiral allylamines (**30**; M = Li, K) are used as chiral homoenolate equivalents and allow, after alkylation and acid hydrolysis, asymmetric C—C bond formation to β-substituted aldehydes in up to 67% *ee*.[18d]



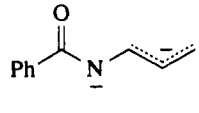
Scheme 10



Scheme 11



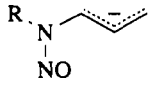
(**27a**) M = Li
(**27b**) M = MgX



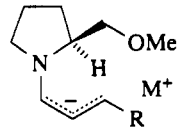
(**28**)

A stereo- and regio-selective synthesis of *trans*-2,5-dialkylpyrroline structures is accomplished *via* the *N*-substituted allylic anion intermediates (Scheme 12).[22a] The α-regioselective alkylation is presumably due to the presence of the electron-withdrawing methoxycarbonyl group. The piperidine ring system

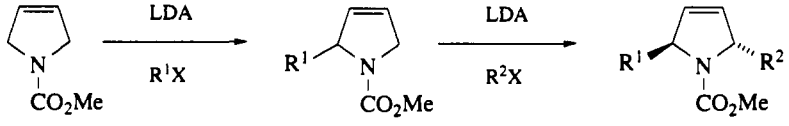
(Scheme 13), the cyclic analog of (**25**), gives α-products upon treatment with alkyl halides, protons or sterically unhindered aldehydes, whereas it affords γ-adducts upon treatment with bulkier electrophiles such as pivaloyl chloride and benzaldehyde.[22b]



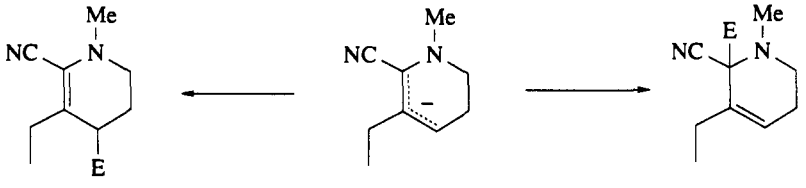
(**29**)



(**30**)



Scheme 12

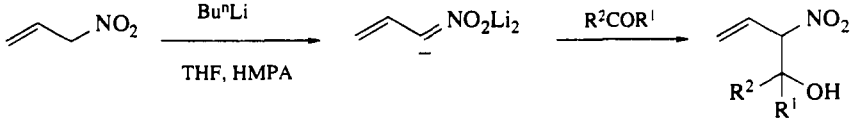


E = MeCO, PhS, PhCH(OH)

E = D, Me, Pr^i, Pr^{n}CH(OH), C(O)Me

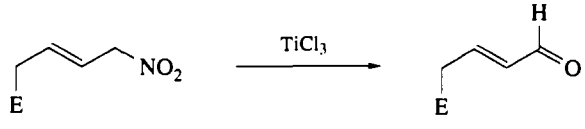
Scheme 13

3-Nitropropene (Scheme 14) undergoes α,α-double-deprotonation to give a dianion that reacts with carbonyl compounds at the α-nitro carbon to form nitro alcohols, whereas 4-nitro-1-butene (Scheme 15) produces an α,β-abstraction product that reacts with alkyl halides and carbonyl compounds to give a mixture of the β- and δ-adducts.[23] The δ-isomer can be separated and converted to an α,β-unsaturated aldehyde by Nef reaction with $TiCl_3$ (equation 9).



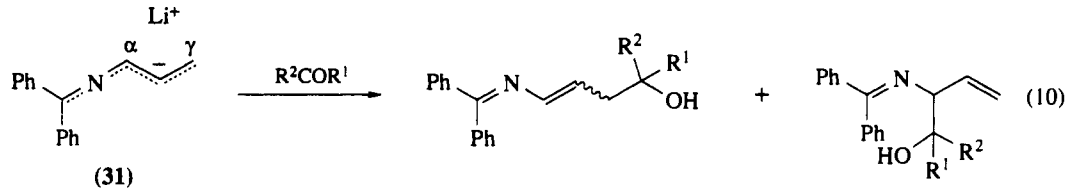
Scheme 14

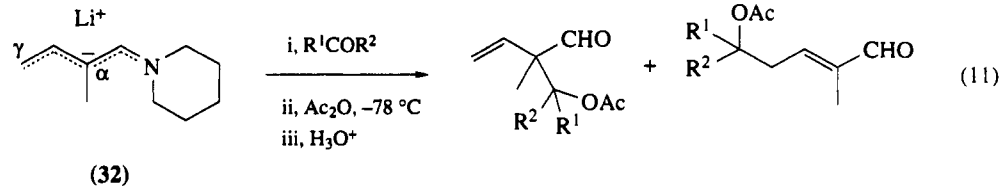
Scheme 15



(9)

E = Pr^i, Bn



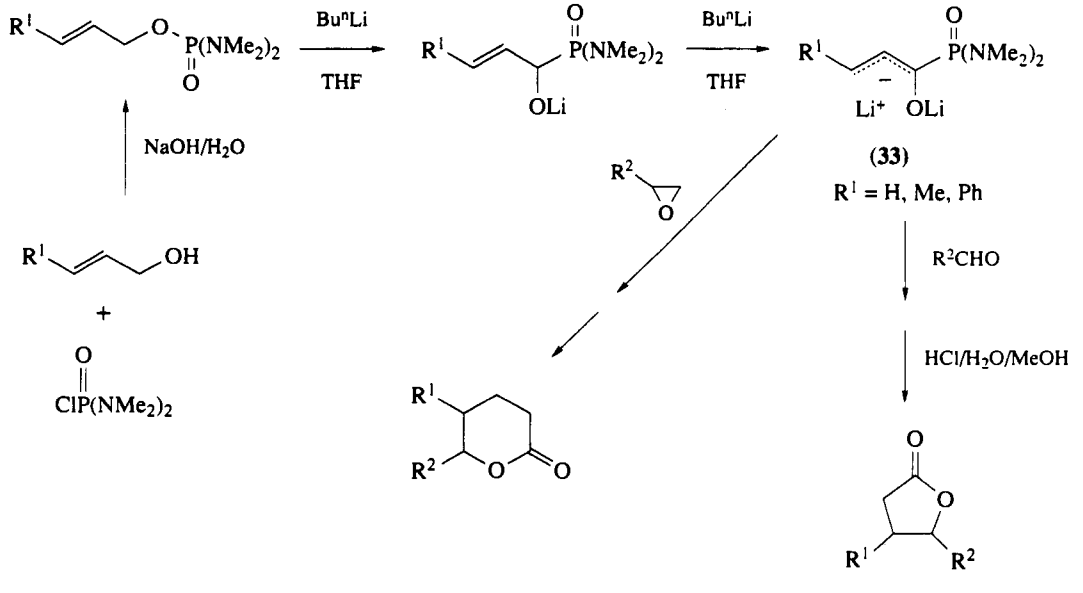


2-Azapentadienyl anion (**31**), readily prepared by deprotonation of the *N*-allylimine, reacts with carbonyl compounds at either the α- or the γ-position (equation 10).[24] The regioselectivity depends upon the reaction conditions. 1-Azapentadienyl anion (**32**; equation 11), prepared from the cyclohexylimine of tiglaldehyde and LDA, reacts with aldehydes and ketones to give the γ-capture products in the presence of HMPA or the α-capture products in the absence of HMPA.[25]

1.2.5 PHOSPHINE-SUBSTITUTED ALLYLIC ANIONS

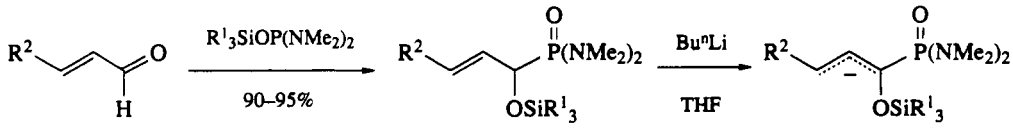
Deprotonation of allyl tetramethylphosphorodiamidate, readily prepared from allyl alcohol, induces the migration of phosphorus from oxygen to carbon. A second deprotonation then occurs to give the dianion (**33**; Scheme 16).[26] Alkylation with 1-iodopropane takes place at the γ-position to give hexanoic acid after hydrolysis. Reaction of (**33**) with aldehydes and ketones followed by hydrolysis gives γ-lactones, and a similar sequence with epoxides produces δ-lactones.

1,2-Addition of trivalent phosphorus siloxanes with α,β-unsaturated aldehydes gives high yields of (**34**), which can be easily deprotonated to give (**35**; Scheme 17). Here again, electrophiles react at the γ-position either exclusively or predominantly. The dianion (**33**; R = Ph; equation 12) reacts with excess methyl iodide and subsequent methanolysis affords a mixture of (**36**) and (**37**). Thus, (**36**) most closely approximates the binucleophilic homoenolate synthon (**4**; Scheme 1).[27]



Scheme 16

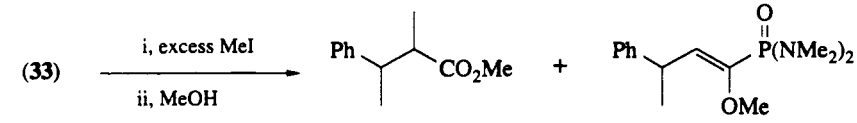
Allyl anions (**38a**),[28] (**38b**)[29] and (**38c**)[30] exhibit a similar regioselectivity toward electrophiles, and thus serve as homoenolate synthons. Addition of titanium tetraisopropoxide to (**39**) followed by condensation with aldehydes gives the *anti* adducts exclusively, which can be converted to the (*Z*)-1,3-dienes upon treatment with methyl iodide (Scheme 18).[31] The (*E*)-1,3-dienes can be prepared from the lithiated allyldiphenylphosphine oxide. The stabilized allylic phosphonate anion (**40**) condenses with carbonyl



(**34**) (**35**)

R^1 = Me, Et; R^2 = H, Me, Ph

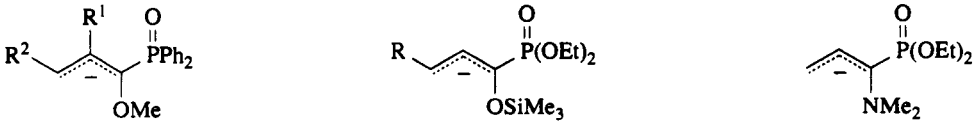
Scheme 17



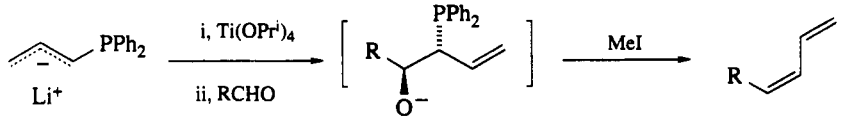
(12)

R^1 = Ph

(**36**) (**37**)



(**38a**) (**38b**) (**38c**)

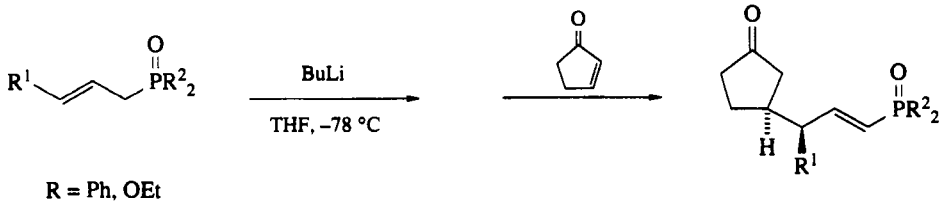


(**39**)

Scheme 18

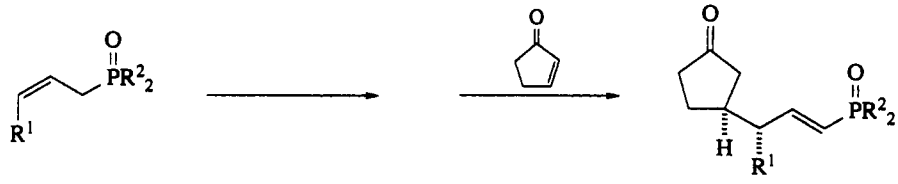
(13)

(**40**)



R = Ph, OEt

Scheme 19



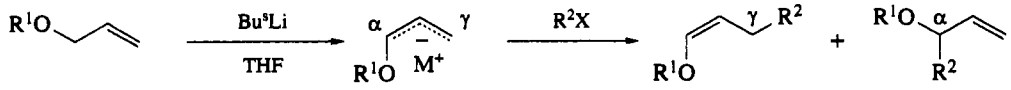
Scheme 20

compounds regioselectively at the phosphorus-bearing carbon atom to give stereospecifically the corresponding (2*E*,4*E*)-dienoate (equation 13).[32]

Lithiated (*E*)- and (*Z*)-2-alkenylphosphine oxides and phosphonates react with cyclic enones in a 1,4-conjugate addition manner (Schemes 19 and 20). The (*E*)- and (*Z*)-allylic anions react in highly diastereoselective fashion to deliver respectively *syn* and *anti* vinylic phosphine oxides and phosphonates.[33] Chiral allylphosphonyl anions undergo enantioselective 1,4-addition with cyclic enones of varying size.[34]

1.2.6 OXYGEN-SUBSTITUTED ALLYLIC ANIONS

Allyl ethers are readily deprotonated by *s*-butyllithium in THF at –65 °C in essentially quantitative yield (Scheme 21). At these temperatures, the allylic anion (**41a**) exhibits no tendency to undergo Wittig rearrangement, a reaction characteristic of these species at higher temperature. The reaction of (**41a**) with alkyl halides produces mixtures of enol ethers (γ-attack products) and allyl ethers (α-attack products).[35] With *t*-butyl allyl ether (**41a**; R^1 = Bu^t), the ratio of γ:α for R^2 = n-C_6H_{13} is 89:11. Allyl triethylsilyl ether derivative (**41c**) gives similar results;[36] the ratio of γ:α for R^2 = Me is 97:3. More bulky alkyl halides, such as *s*-propyl iodide and cyclohexyl iodide, give more of the α-alkylation product. Five-membered ring chelation (**42**) in the γ-lithio allylic derivatives (**41a, 41c**) may explain the (*Z*)-stereochemistry of the enol ether product. The importance of chelation is shown in the fact that the allylic anions derived from phenyl allyl ether (Scheme 22) and from phenyl (*Z*)-1-propenyl ether (Scheme 23) give different product ratios upon methylation.[37] The former presumably produces a mixture of (*Z*)-chelated and (*E*)-nonchelated lithium derivatives, while the latter affords an all-(*Z*)-chelated lithium intermediate.



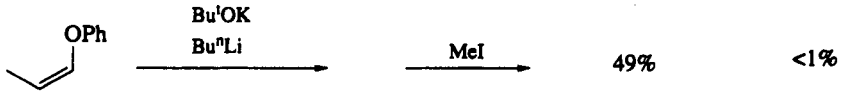
(41a) R^1 = alkyl; M = Li
(41b) R^1 = alkyl; M = Zn^{2+}
(41c) R^1 = $SiEt_3$; M = Li
(41d) R^1 = $SiMe_3$; M = Li

(42)

Scheme 21

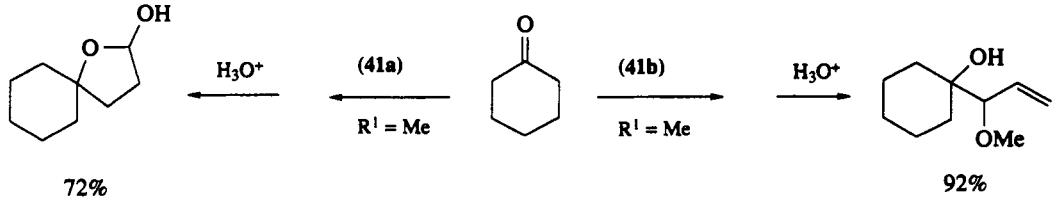
Scheme 22

The reaction of carbonyl groups produces the opposite regioselectivity. The reaction of (**41c**) with cyclohexanone gives predominantly the α-adduct (α:γ = 71:29). The lithium salt of the trimethylsilyl derivative (**41d**) in THF–HMPA produces the α-adduct in reactions with a variety of aldehydes and ketones (98–100% regioselectivity).[2] Mild acid hydrolysis of the product monosilyl ethers affords 3,4-dihydroxy-

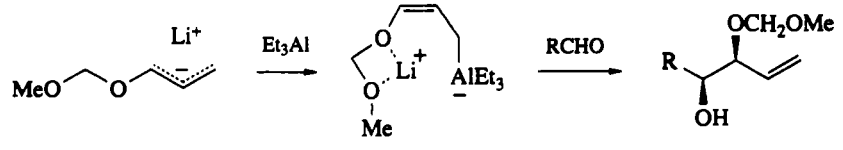


Scheme 23

1-alkenes in high yields. Although the butyl ether (**41a**; R^1 = Bu^t) gives mostly α-adducts, the γ-adducts are predominantly obtained when the smallest group is present in ether (**41a**; R^1 = Me; Scheme 24). The corresponding allylzinc reagents (**41b**; Scheme 24) are useful for effecting regiospecific α-attack on ketones.[34] The addition of triethylaluminum to (**41a**) also directs electrophiles to the α-position (Scheme 25).[8,38] Further, *syn* stereospecific condensation is accomplished *via* the aluminum ate complexes. By this method, (±)-*exo*-brevicomin is synthesized stereoselectively.

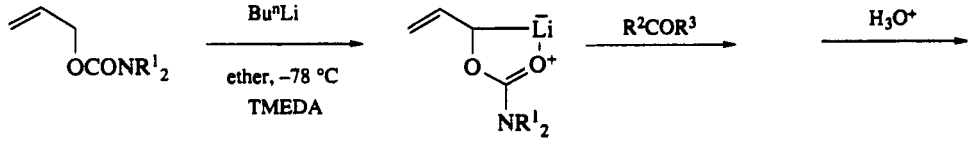


Scheme 24

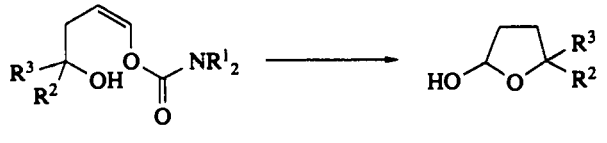


Scheme 25

The α-chelating anions (**43**) from allyl *N,N*-dialkylcarbamate esters react with carbonyl compounds at the γ-position with very high regioselectivity (in most cases >95%) to afford γ-hydroxyenol carbamates.[1d] Solvolysis gives a lactol which is readily oxidized to a lactone (Scheme 26). The γ-selectivity increases with increasing γ-substitution and with decreasing α-substitution in (**43**), and also with decreasing reactivity of the carbonyl group in the electrophiles. Ketones are better in this regard than aldehydes. In contrast to carbonyl addition, the regiochemistry of alkylation and silylation is largely controlled by the position of the alkyl groups present in the allylic system. The carbamoyl group has very little influence. Thus, the reaction of (**43**) itself with TMS-Cl gives a mixture of the γ- and α-products in the ratio of 41:59.

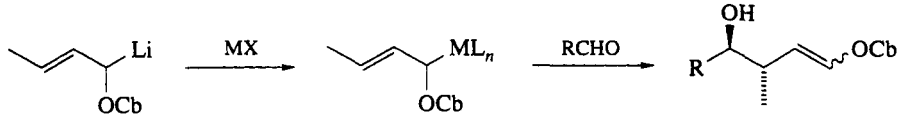


(**43**) R^1 = Pr^i, Et



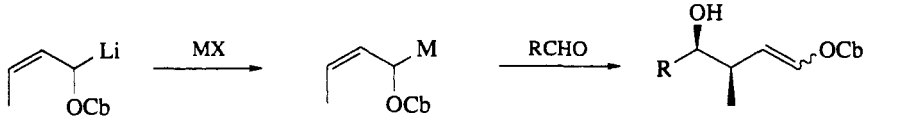
Scheme 26

The anions from crotyl carbamates (*E*)-(**44**) and (*Z*)-(**44**) are useful for diastereoselective homoaldol reactions.[1d] Diastereoselection with the lithium reagents (*E*)-(**44**) and (*Z*)-(**44**) is low, as expected from the results on crotyl organometallic condensation reactions.[39] The diastereoselectivity is improved by metal exchange. Addition of tris(dimethylamino)titanium chloride [$(Et_2N)_3TiCl$] to (*E*)-(**44**) gives the (*Z*)-*anti* adduct almost exclusively,[40] and addition of Bu^i_2AlCl produces the (*E*)-*anti* adduct predominantly (Scheme 27). The addition of diisobutylaluminum methanesulfonate (Bu^i_2AlOMs) to (*Z*)-(**44**) gives the (*E*)-*syn* adduct with variable selectivity, and in general the derivatives of (*Z*)-(**44**) result in low diastereoselectivity (Scheme 28). The α-chiral anion (**45**) reacts with 2-methylpropanal to give the optically active (*Z*)-(–)-*anti* adduct (24% yield, 52% *ee*) and the (*Z*)-(–)-*syn* isomer (29% yield, ≥25% *ee*). The metal exchange from lithium to titanium by treatment with $(Et_2N)_3TiCl$ followed by addition of the same aldehyde produces only one adduct, the (*Z*)-(+)-*anti* isomer (36% yield, 35% *ee*).[41] Therefore, the lithium–titanium exchange in (**45**) presumably takes place with inversion. Highly optically active 3-phenylalkanals are obtained by the reaction of alkyl halides and the chiral anion (**46**).[42] After exchange of lithium in (**47**) with Bu^i_2AlOMs, the addition of an aldehyde proceeds with high *anti* diastereoselectivity, affording (*E*)-(**48**), whereas exchange with tris(dimethylamino)titanium chloride produces (*Z*)-(**48**).[43] Peterson elimination introduces the second double bond either with (3*E*)- or with (3*Z*)-configuration.



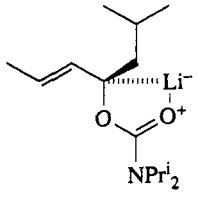
(*E*)-(**44**) M = Al, Ti (*E*)- and (*Z*)-*anti*

Scheme 27

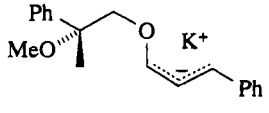


(*Z*)-(**44**) (*E*)- and (*Z*)-*syn* ; Cb = $C(O)NPr^i_2$

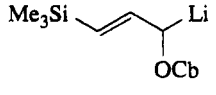
Scheme 28



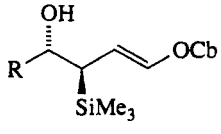
(**45**)



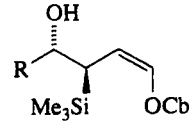
(**46**)



(**47**)

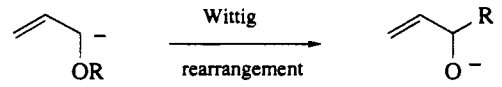


(*E*)-(**48**)

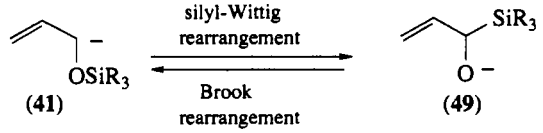


(*Z*)-(**48**)

1-Oxyallyl anions are prone to rearrangement, such as Wittig and Brook rearrangements as well as acyl and phosphoryl migration (equations 14 to 17).[1d] Although allyloxy carbanions (**41**) are in rapid equilibrium with (**49**; equation 15), the alkylation generally proceeds at the γ-position *via* (**41**).[36] Hard electrophiles such as Me_3SiCl, chloroformates, diphenyl carbonate and protons react at oxygen either exclusively or predominantly (equation 18).[44] The anion (**50a**, **50b**), prepared by treatment of the cyanohy-

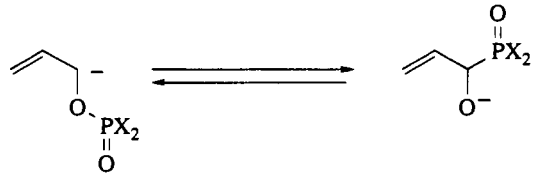


(14)



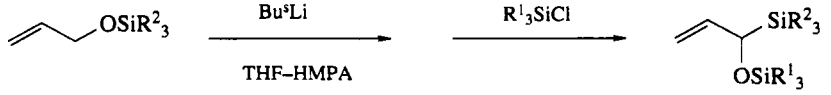
(15)

(16)

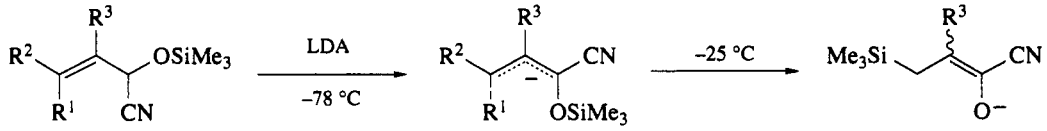


(17)

drin ethers (**51**) with LDA at –78 °C, undergoes 1,3-silyl migration at –25 °C (Scheme 29).[45] Reactions of (**50**) with alkyl halides at –78 °C give the α-alkylation products.



(18)



(**51**)

(**50a**) $R^1 = R^2 = R^3 = H$

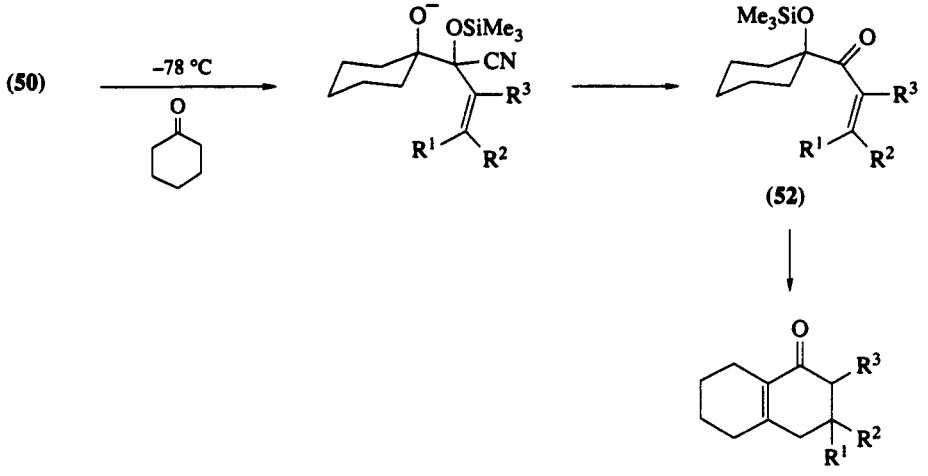
(**50b**) $R^1 = R^2 = H$; $R^3 = Me$

(**50c**) $R^1 = R^3 = H$; $R^2 = Me$

Scheme 29

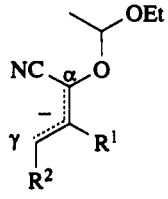
Reaction of (**50**) with alkyl halides gives exclusive α-alkylation. With aldehydes and ketones, α-addition again takes place to give (**52**) *via* intramolecular silyl transfer with concomitant loss of lithium cyanide (*cf.* **25**; Scheme 30).[46] Treatment of (**52**) with *p*-TsOH·H_2O gives the cyclopentenone annelation product. The allylic cyanohydrin anion (**53**) also gives α-adducts upon treatment with aldehydes and ketones at –78 °C, whereas reaction with electrophiles at 0 °C affords γ-adducts (*cf.* **25**).

Lithium anion (**54**) gives predominantly α-adducts with aldehydes and ketones, whereas alkylation or trialkylsilylation produces γ-adducts preferentially.[47] Here also, the zinc anion leads to exclusive α-attack of carbonyl compounds (*cf.* **41b**). The pentadienyl anion (**55**) reacts with ketones at the terminal (γ) position, and thus serves as a convenient C_5 unit.[48] On alkylation, however, the undesired α-attack is competitive. Reaction of (**55**) with dimethyl disulfide produces (**56**) regioselectively. The methylthio substituent of (**56**) not only facilitates deprotonation to (**57**), but also directs the alkylation of (**57**) toward the desired γ-products: the alkylation takes place exclusively at the carbon bearing the sulfur group. The anion (**58**), generated from 4*H*-1,3-dioxin, reacts with various alkyl halides, ketones, aldehydes and ethylene oxide to give (**59**) in good to high yields (Scheme 31).[49] Reflux of (**59**) in toluene produces α,β-

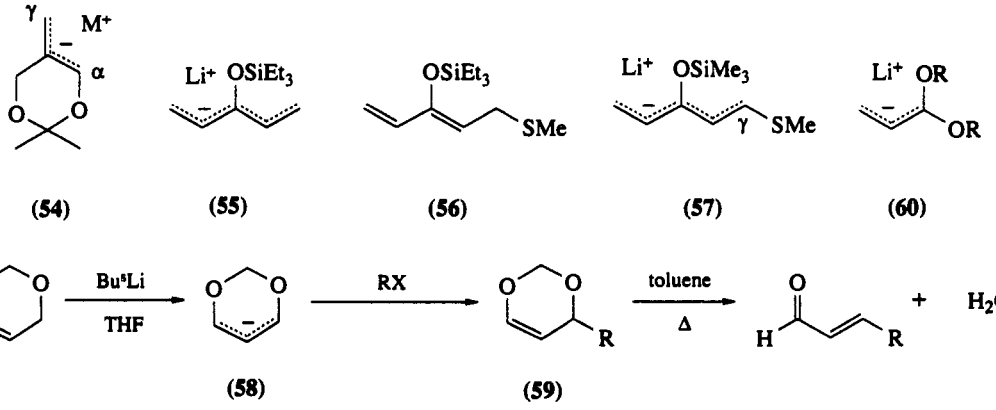


Scheme 30

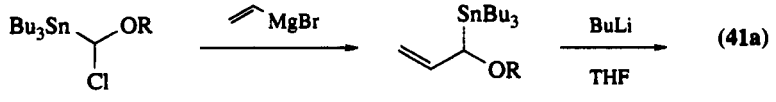
unsaturated aldehydes, and thus (**58**) serves as a β-acylvinyl anion equivalent (**6**). The reaction of Bu^{s}Li with acrolein dialkyl acetals results in the formation of (**60**), which reacts with organosilicon and organotin chlorides at the γ-position to give the corresponding ketone acetals.[50] Treatment of 6-methoxy-1-indanone with two equivalents of LDA produces the dianion, which reacts with ethyl iodide to give 3-ethyl-1-indanone with very high regioselectivity.[51] Reaction of 2-allyloxybenzimidazoles with butyllithium followed by addition of cadmium iodide generates the metallated allylic ethers, which react with aldehydes to give the α-adducts selectively.[52] The adducts are converted to vinyloxiranes in good yields on treatment with sodium hydride.



(**53**)



Scheme 31

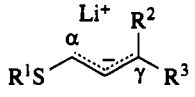


Scheme 32

Normally, anions like (**41**) are prepared by deprotonation of allyl ethers. Another method to generate (**41a**) is transmetallation of a C—Sn bond to a C—Li bond (Scheme 32). Treatment of an α-alkoxyallyltin with *n*-butyllithium gives (**41a**).[53] However, this is an inconvenient method for the preparation of the allyl anions, compared to the ordinary way.

1.2.7 SULFUR-SUBSTITUTED ALLYLIC ANIONS

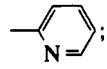
The thioallyl anions (**61**), prepared by treatment of the corresponding sulfides with Bu^nLi in THF at −30 °C in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), react with alkyl halides predominantly at the α-position.[1c] Anions (**61b**) and (**61c**), which are more highly substituted at the γ-position, show a higher α-selectivity (85–100%). The reaction of (**61b**) with acetone in THF produces the γ-adduct in 100% yield, while (**61b**) in the presence of cryptand[2.2.2] gives only the α-adduct.[1c] The former reaction involves intimate ion pairs, whereas the latter proceeds through dissociated ion pairs. Carbanions derived from benzyl allyl ethers ($R^1 = CH_2Ph$ in **61**) undergo complex rearrangements and thus are useless in organic synthesis.[54]

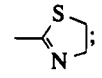


(**61a**) R^1 = Ar; $R^2 = R^3 = H$

(**61b**) R^1 = Ph; $R^2 = R^3$ = Me

(**61c**) R^1 = Et; $R^2 = R^3$ = Me

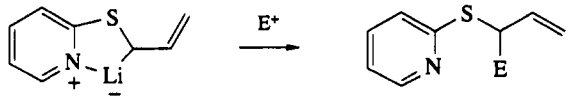
(**61d**) R^1 =  ; $R^2 = R^3 = H$

(**61e**) R^1 =  ; $R^2 = R^3 = H$

(**61f**) $R^1 = Pr^i$; $R^2 = R^3 = H$

(**61g**) $R^1 = Pr^i$; $R^2 = H$; R^3 = Me

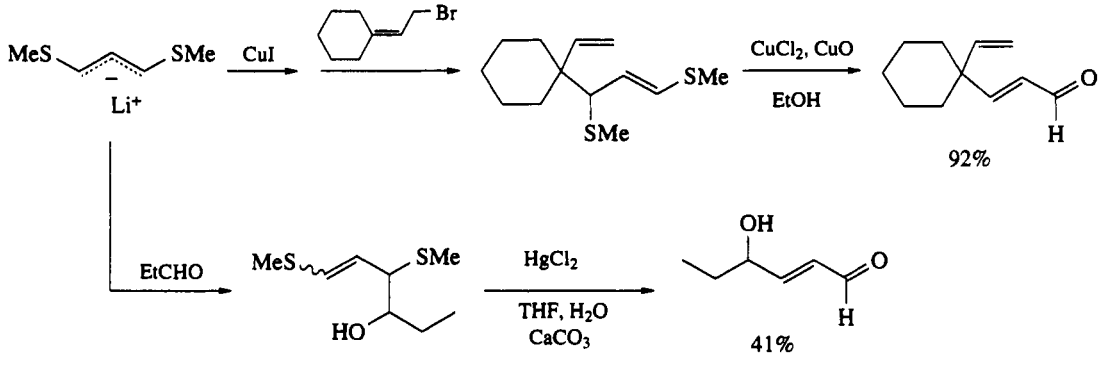
Intramolecular chelation of the lithium to the heteroaromatic ring may direct electrophiles to the α-position (equation 19). In fact, alkylation of (**61d**) and (**61e**) gives the α-product in the ratio of 99:1.[55]



(19)

Addition of triethylaluminum or triethylborane to (**61f**) produces the ate complexes, which react with aldehydes at the α-position.[8] In contrast to the ate complex of the oxygen-substituted anion, the ate complex of (**61f**) produces low diastereoselectivity. Reaction of the boron ate complex with γ,γ-dimethylallyl chloride and bromide occurs at the α-position with inversion of the allyl unit.

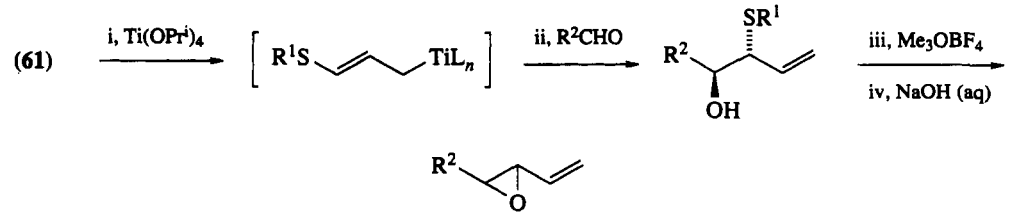
The addition of copper iodide to (**61f**), followed by alkylation with allylic halides, gives γ-allylation products with inversion of the allyl unit, whereas reaction with acetone yields predominantly the α-ad-



Scheme 33

duct: therefore, selectivity of the copper derivative is opposite to that of the lithio reagent (**61f**).[56] The copper derivative of 1,3-di(methylthio)allyl anion reacts with the allylic bromide with allylic rearrangement (Scheme 33). The hydrolysis and elimination of sulfur may be accomplished with thiophilic metal salts, including silver nitrate, mercury(II) chloride[57] or copper(II) chloride.[56] By using this procedure, α,β-unsaturated aldehydes can be prepared. 3-Alkyl- and 2,4-dialkyl-furans are prepared *via* similar condensation with aldehydes (Scheme 33).[58]

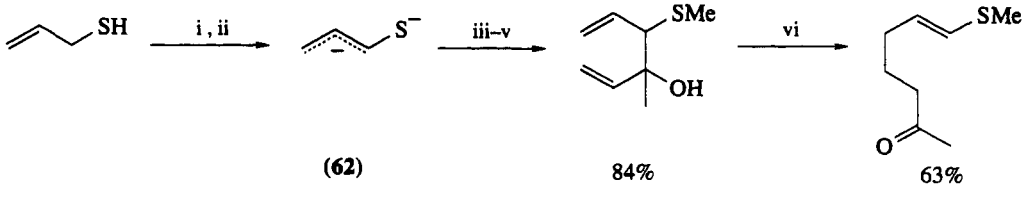
Addition of titanium tetraisopropoxide to the anion (**61**; $R^2 = R^3 = H$) produces a 3-(alkylthio)allyltitanium reagent that condenses with aldehydes to give *anti*-β-hydroxy sulfides in a highly regio- and stereo-selective manner (Scheme 34).[59] *Anti*-β-hydroxy sulfides are transformed stereoselectively to *trans*-vinyloxiranes or 1,3-alkadienes. In contrast, the titanium[59] and lithium[8] reagents from crotyl ethyl sulfide react with aldehydes affording δ-hydroxyvinyl sulfides exclusively.



Scheme 34

Substitution on the aromatic ring in (**61a**) has little effect on the α:γ ratio.[60] However, substituents on the allyl group cause dramatic changes in the regioselectivity, as shown in Table 1.

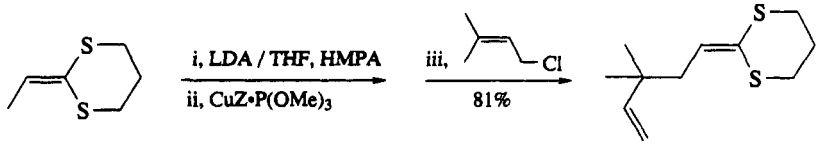
The dianion (**62**; Scheme 35), prepared from alkenethiols, gives good γ-selectivity toward both alkylation and carbonyl addition.[78] The γ-products (enol sulfides) may be converted to dimethylacetals by treatment with mercury(II) chloride in methanol. When (**62**) is associated with magnesium dibromide, the addition of carbonyl compounds produces the α-adducts with regioselectivity greater than 90%. The reaction with methyl vinyl ketone, followed by a Cope rearrangement, results in reattachment at the original γ-position.



i, Bu^{n}Li, 0 °C, TMEDA–THF; ii, HMPA, –50 °C, Bu^{t}OK; iii, $MgBr_2$; iv, ; v, MeI; vi, KH, THF, HMPA

Scheme 35

Ketene dithioacetals are deprotonated with LDA–HMPA and complexed with copper(I) iodide (Scheme 36). This reagent reacts with allylic halides exclusively at the γ-position with allylic rearrangement (S_N2').[79] The reaction of the lithium reagent with simple alkylating reagents gives mostly α-attack. Ketene dithioacetals can be converted to esters by aqueous mercury(II) chloride.



$S_N2':S_N2 = 80:20$

Scheme 36

Table 1 Reaction of Sulfur-substituted Allylic Anions with Electrophiles

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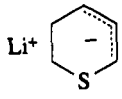
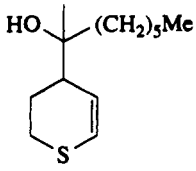
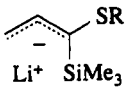
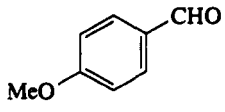
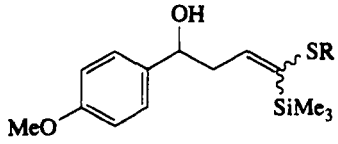
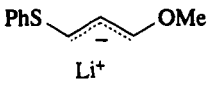
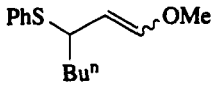
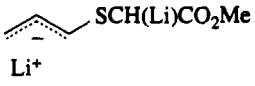
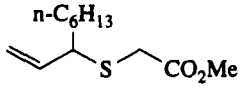
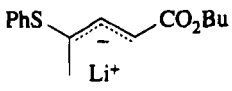
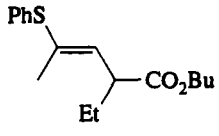
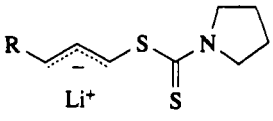
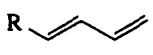
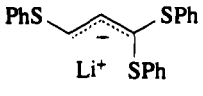
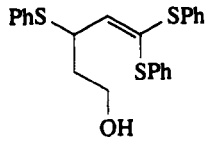
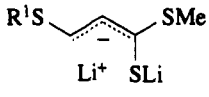
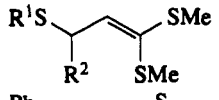
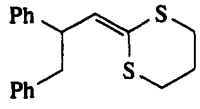
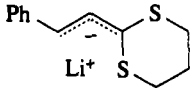
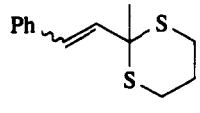
	$Me(CH_2)_5COMe$		73	61
			72	62
	Bu^nI		80	63
	$n\text{-}C_6H_{13}Br$		75	64
	EtI	 *(E)* only	88	65
	i, Me_3SiCH_2I ii, MeI/LiF, Li_2CO_3			66
			72	67
	i, R^2X ii, MeI			68
	$PhCH_2I$		60	
	Me_2SO_4		55	69

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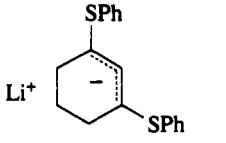
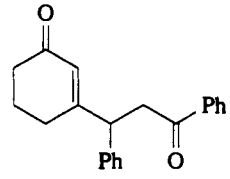
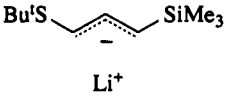
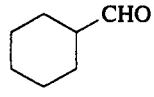
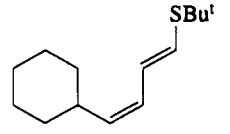
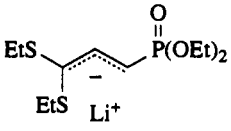
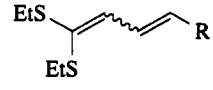
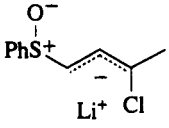
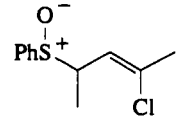
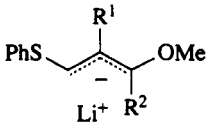
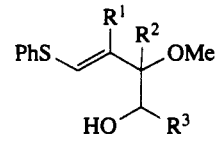
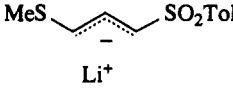
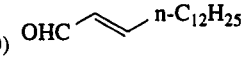
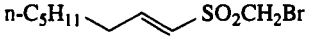
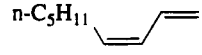
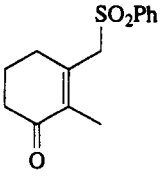
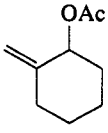
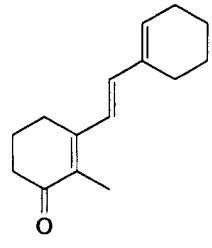
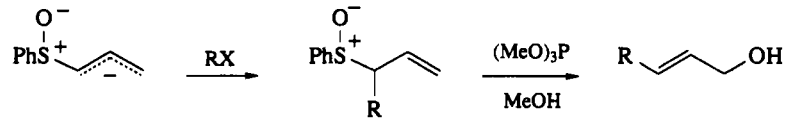
	i, PhCH=CHCOPh ii, Cu^+, H_2O, MeCN		59	70
	i, $Ti(OPr^i)_4$			
	ii, 		62	71
	RCHO			72
	MeI		65	73
	R^3CHO			74
	i, $n\text{-}C_{12}H_{25}Br$ ii, $TiCl_4$, $CuCl_2$ (H_2O) iii, K_2CO_3		73	75
	2.5 equiv. Bu^tOK Bu^tOH/THF	 *Z*:*E* = 83:17	59	76
	i, NaH ii,  $Pd(PPh_3)_4$ (cat.) THF–HMPA iii, DBU, 80 °C		77	77

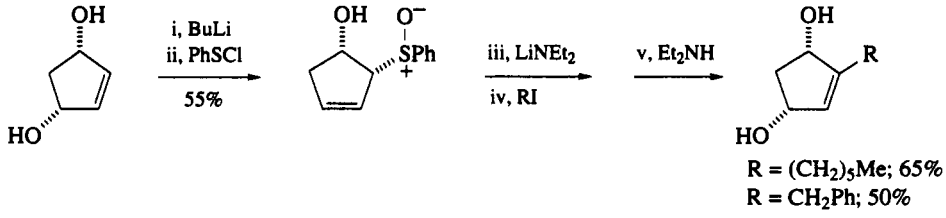
Anion (**63**), prepared from an allyl sulfoxide and LDA, reacts with alkyl halides at the α-position to give α-alkylated sulfoxides, which undergo rearrangement upon treatment with a thiophile, resulting in formation of allylic alcohols (Scheme 37).[55] This method can be applied to the synthesis of cyclic allylic alcohols (Scheme 38). The reaction of (**63**) with aldehydes produces a mixture of regioisomers and thus it is less synthetically useful.

Although allylic sulfoxides produce allyl anions like (**63**) upon treatment with bases, 1-alkenyl sulfoxides afford α-lithiated derivatives with LDA (Scheme 39).[80] *N,N*-Dimethyl-3-(phenylthio)-2-propenylamine also undergoes lithiation at the sp^2 carbon next to sulfur.

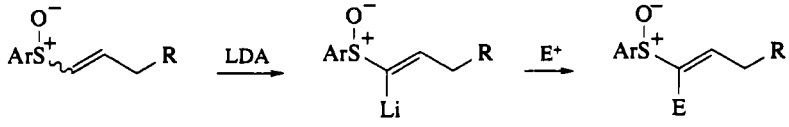


(63)

Scheme 37

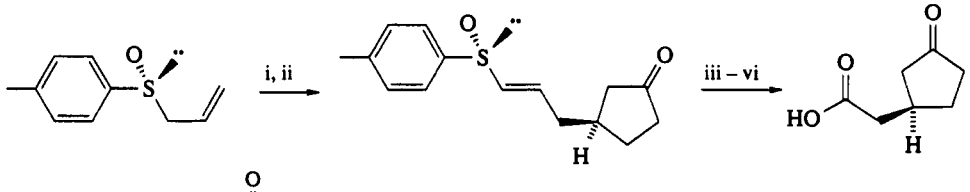


Scheme 38



Scheme 39

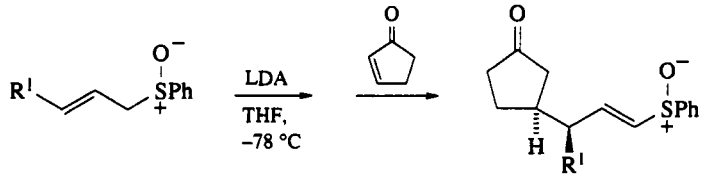
Treatment of (+)-(*R*)-allyl *p*-tolyl sulfoxide with LDA in THF at –78 °C followed by one equivalent each of HMPA and 2-cyclopentenone provides the 1,4-adduct in 90% yield with 96% *ee*.[81] The adduct is converted to (+)-(*R*)-3-oxocyclopentaneacetic acid (Scheme 40). Lithiated (*E*)- and (*Z*)-2-alkenyl sulfoxides, derived from the corresponding allylic sulfoxides and LDA, undergo highly diastereoselective conjugate addition to cyclopentenone, producing *syn* and *anti* vinylic sulfoxides respectively (Schemes 41 and 42).[33] Therefore, the addition takes place at C-3 (C_γ) of the allylic sulfoxide anions. The reaction of lithiated allylic phenyl sulfides with cyclopentenones in THF at –78 °C proceeds with 1,2-addition and gives regioisomeric mixtures of vinylic and allylic sulfides, whereas the reaction in the presence of HMPA in THF at –78 °C involves conjugate addition to afford allylic sulfides arising from reaction at C-1 (C_α) of the allylic anions.[82a] Lithiated allylic sulfones react in the same way as lithiated allylic sulfides in that HMPA causes kinetic conjugate addition to give allylic sulfones as mixtures of diastereomers.[82b]



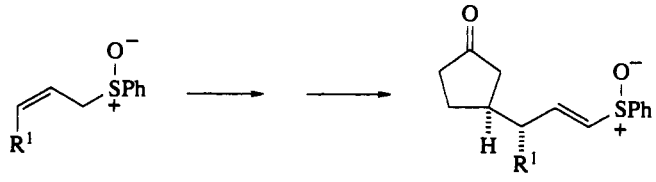
i, LDA; ii, ; iii, Zn–AcOH; iv, $HO(CH_2)_2OH$, pyridinium tosylate; v, O_3;

vi, Bu_4NMnO_4, $NaHSO_3$–HCl

Scheme 40

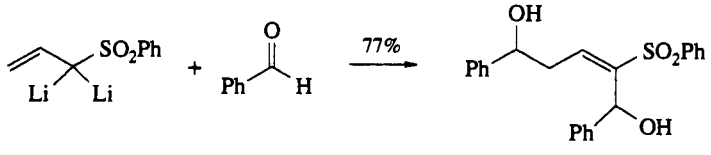


Scheme 41



Scheme 42

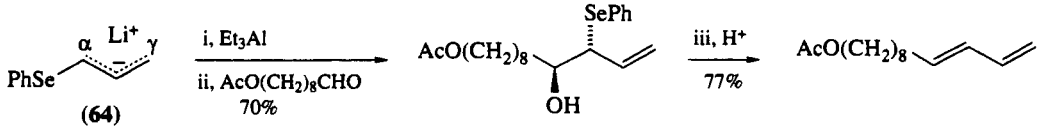
Allylic sulfonyl carbanions react with electrophiles such as alkyl halides[83a] and aldehydes[83b] at the α-position. Although relatively strong bases like Bu^{n}Li and LDA are usually used for deprotonation of allylic sulfur compounds, including sulfones, a catalytic two-phase system that consists of a concentrated aqueous NaOH solution and a quaternary ammonium salt can be used to generate allylic sulfonyl carbanions.[83a] 1,1-Dilithiated allyl phenyl sulfone (equation 20) reacts with excess benzaldehyde to afford the 1,3-(*E*)-diadduct, while 1,*ortho*-dilithiated allyl phenyl sulfone gives the 1,*ortho*-diadduct predominantly.[84] Other examples of sulfur-substituted allylic anions are summarized in Table 1.



(20)

1.2.8 SELENIUM-SUBSTITUTED ALLYLIC ANIONS

Anion (**64**) generally reacts with carbonyl compounds at the γ-position, whereas it reacts with alkyl halides at the α-position. The triethylaluminum ate complex of (**64**) exhibits reversed regioselectivity: propanal and 2-methylpropanal give exclusively the α-adducts.[8] The *anti* isomers are produced predominantly. Organic halides and trimethylsilyl chloride do not react with the aluminum ate complex. 9,11-Dodecadien-1-yl acetate, a pheromone of *Diparopsis castanea*, is prepared by condensation of 9-oxonon-1-yl acetate *via* the ate complex (Scheme 43).

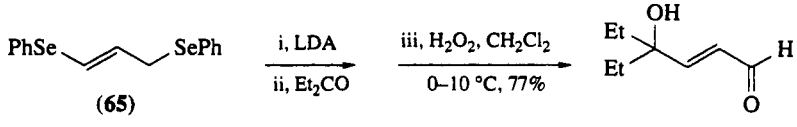


Scheme 43

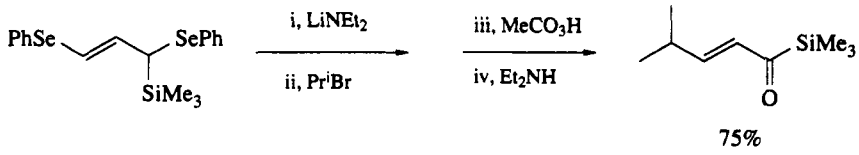
The regioselectivity of (**64**) depends on the nature of the electrophile:[85] TMS-Cl produces an α:γ ratio of 82:18, but $PhSiMe_2Cl$ gives an α:γ ratio of 41:59. Furthermore, substituents on the allylic unit exert a strong influence on the regioselectivity; α-selectivity increases with substituents at the γ-position.

Although (**64**) is produced by treatment of the corresponding allyl selenide with LDA or lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF, treatment with *n*-butyl- or methyl-lithium leads to rapid transmetallation at –78 °C, giving the allyllithium and alkyl phenyl selenides.[86]

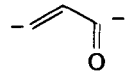
The selenium group can be removed under very mild oxidative conditions (Scheme 44).[87] Treatment of the anion of (**65**) with TMS-Cl gives another reagent that can be deprotonated and used with various electrophiles to prepare vinyl silyl ketones (Scheme 45). Therefore, (**65**) can be used as synthons of (**6**) and (**66**), like the 1,3-di(methylthio)allyl anions.[57]



Scheme 44



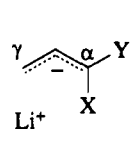
Scheme 45



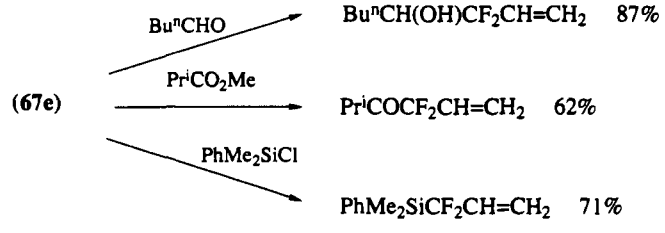
(66)

1.2.9 HALOGEN-SUBSTITUTED ALLYLIC ANIONS

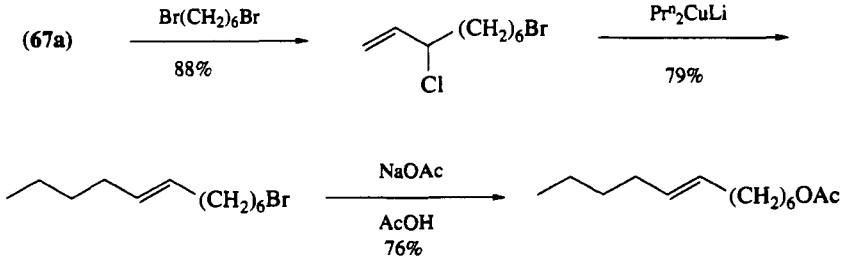
The anions (**67c**)–(**67e**) are prepared by the low temperature transmetallation reactions of *n*-butyllithium with the corresponding allylic tin or lead compounds. The addition of (**67d**) to aldehydes and ketones proceeds with C—C bond formation at either terminus. Dialkyl ketones give the α-products, while benzaldehydes and benzophenone afford the γ-products. Aliphatic aldehydes, acetophenone and substituted acetophenones give both types of products.[88] The anion (**67e**) is not stable in solution even at –95 °C and cannot be preformed prior to its reaction with the desired substrate; (**67e**) may be generated by Li–Br exchange between *n*-butyllithium and 3,3-difluoro-3-bromopropene at –95 °C. When this preparation is performed in the presence of chlorosilanes, aldehydes, ketones, and esters, the α-products are obtained, often in good yields (Scheme 46).[89] Reactions of (**67c**) with TMS-Cl and benzaldehyde afford γ-adducts, whereas those with methyl iodide, acetophenone and pentanal produce α-adducts predominantly.[90] Anions (**67a**) and (**67b**) give α-alkylation products with aliphatic halides and TMS-Cl, but afford γ-adducts with iminium salts.[91]



(**67a**) X = Cl, Y = H
(**67b**) X = Cl, Y = Me
(**67c**) X = Cl, Y = $SiMe_3$
(**67d**) X = Y = Cl
(**67e**) X = Y = F



Scheme 46

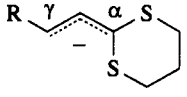


Scheme 47

Treatment of (**67a**) with 1,6-dibromohexane gives the α-product, which is reacted with di-*n*-propylcuprate, resulting in formation of 7-dodecenyl bromide by S_N2' displacement at the allylic position.[92] Conversion of this bromide into the corresponding acetate completes the synthesis of the *A. leucotreta* sex pheromone (Scheme 47).

1.2.10 ADDENDUM

The dithio-substituted cinnamyllithium (**68a**) reacts predominantly at the α-site with aldehydes and ketones in the presence of $BF_3{\cdot}OEt_2$.[93] No selectivity is found when the reaction is carried out in the absence of $BF_3{\cdot}OEt_2$. The reactions of (**68a**) and (**68b**) with three- to six-membered cyclic ethers take place exclusively at α-carbons in the presence of $BF_3{\cdot}OEt_2$.[94]



(**68a**) R = Ph
(**68b**) R = Me

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1.3
Propargyl and Allenyl Organometallics

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1.3.1 INTRODUCTION

The chemistry of acetylene and allene has seen a phenomenal expansion during the past two decades. The alkynic and allenic intermediates employed in these studies are frequently assembled by the reaction of propargyl and allenyl organometallics.[1] Unfortunately, the utility of this methodology is limited by the tendency of propargylic metal derivatives to combine with carbonyl compounds (and other electrophiles) to produce both allenic and alkynic products. This regiochemical ambiguity arises from the fact that these species generally exist as an equilibrium mixture of allenic and propargylic organometallic derivatives.

1.3.2 PREPARATION OF PROPARGYL AND ALLENYL ORGANOMETALLICS

Organometallics of allenic structure are usually prepared by the reactions of metals with propargylic or allenic halides, or by metallation with alkyllithiums of the corresponding hydrocarbons.[1] The first preparation of allenylmagnesium bromide was accomplished by Prevost in 1950.[2,3] Allenylzinc bromide is easily obtained by the direct reaction of the metal with propargyl bromide at −100 °C in anhydrous tetrahydrofuran. The yield is greater than 80%.[4]

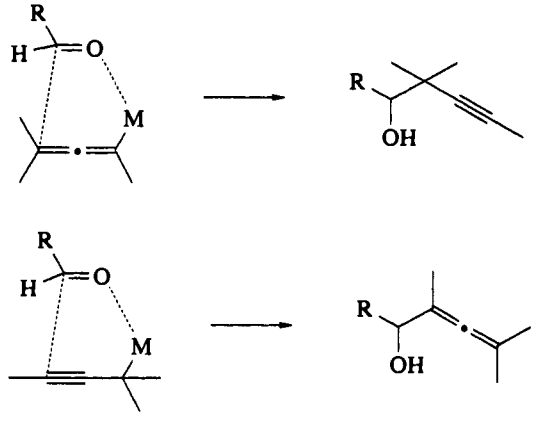
1.3.3 STRUCTURE AND PHYSICAL PROPERTIES

The structure of the propargyl Grignard reagent has been investigated over a considerable period of time, and it is known to be correctly represented by the allenic structure.[5] NMR studies on the Grignard

reagents obtained from various propargylic bromides show in all cases a rapid equilibrium between the allenic and alkynic forms.[1a]

1.3.4 REGIOSELECTIVE REACTIONS

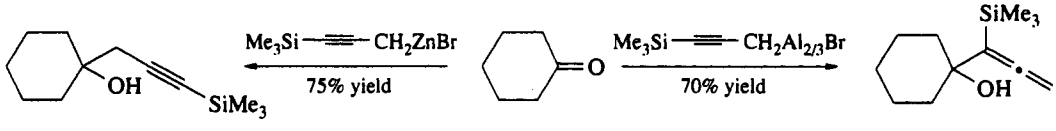
Reactions of the allenic Grignard derivative with most electrophiles give mainly or exclusively alkynic products. This behavior is rationalized by attack at the 3-position, which may be interpreted as an S_E2' (or S_Ei') reaction of allenyl Grignard compounds. For example, organometallic derivatives combine with carbonyl compounds by the S_E2' pathway to afford homopropargylic and allenic alcohols from the corresponding allenyl or propargyl organometallics, respectively (Scheme 1). The product distribution of these reactions is determined by the position of the equilibrium between the two organometallic intermediates and by their relative rates of addition to carbonyl compounds.[1]



Scheme 1

1.3.4.1 Non-heteroatom-substituted Propargyl or Allenyl Organometallics

The organometallic reagent produced by reaction of trimethylsilylpropargyl bromide with aluminum amalgam in anhydrous tetrahydrofuran condenses readily with aldehydes and ketones to give allenic alcohols resulting from coupling α to the trimethylsilyl substituent (Scheme 2). Dramatically divergent behavior is observed with the zinc reagent, which gives the corresponding homopropargylic alcohols.[6]

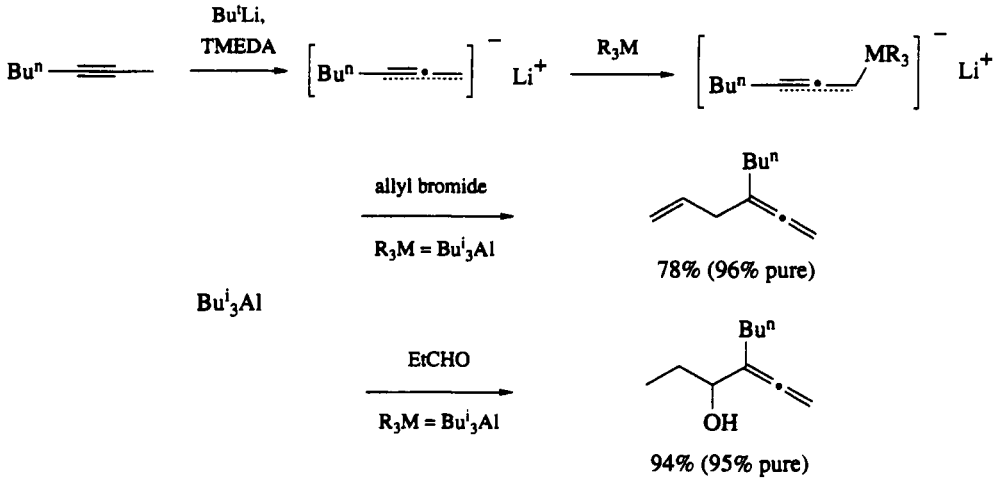


Scheme 2

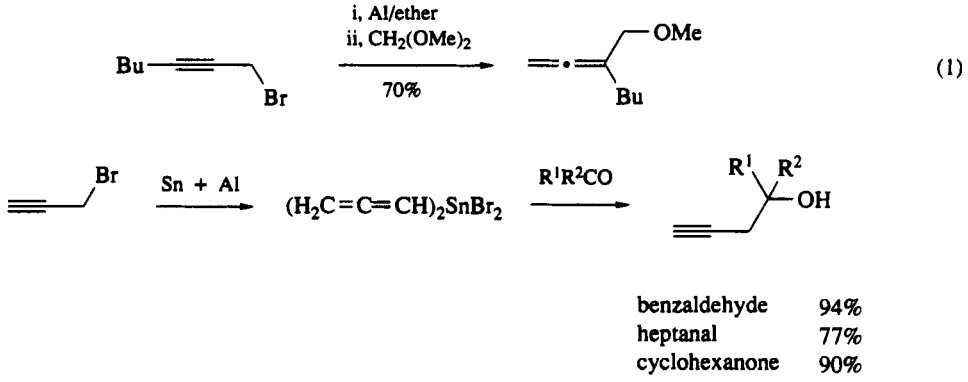
Propargylic lithium alanates or lithium borates react with allylic halides or with carbonyl compounds in a regioselective manner to furnish 1,1-disubstituted allenes (Scheme 3).[7]

The reaction between alkyl halides and aluminum metal is the basis of the oldest method for the synthesis of organoaluminum compounds. For example, propargylic bromides react with aluminum in ether giving organoaluminum compounds that on treatment with acetals yield solely α-allenic ethers (equation 1).[8] However, the reaction of simple alkyl halides with aluminum metal requires a long reaction time.

Diallenyltin dibromide, prepared by treatment of propargyl bromide with metallic tin in the presence of metallic aluminum in dry tetrahydrofuran, reacts with aldehydes and ketones to afford β-alkynic alcohols selectively (Scheme 4).[9] This result is different from a previous report in which an α-allenic alcohol was found to be a major product from a propargyltin reagent prepared from a tin(II) halide.[10] On the other hand, β-alkynic and α-allenic alcohols were synthesized selectively by the reaction of aldehydes and ketones with bis(trimethylsilylpropargyl)tin diiodide using different solvent systems (Scheme 5).[10]

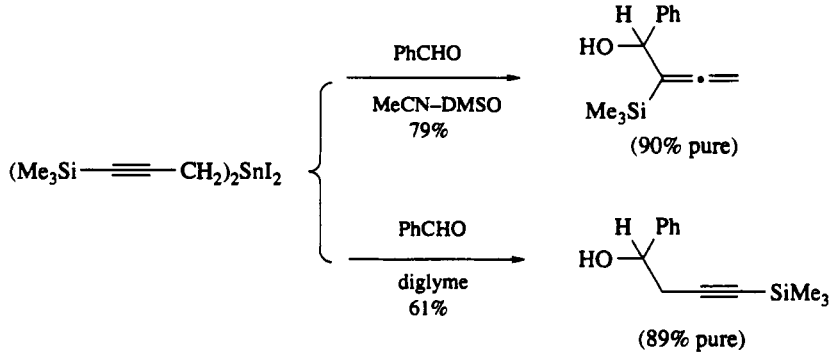


Scheme 3



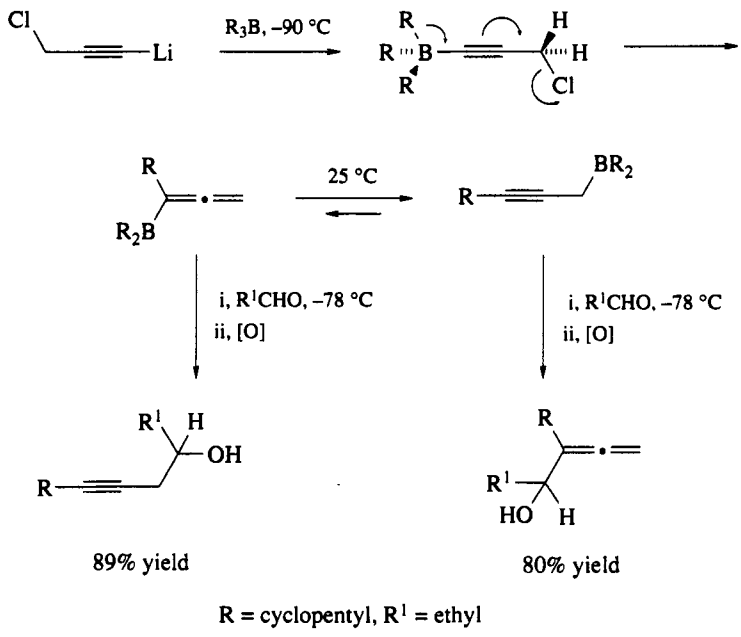
(1)

Scheme 4



Scheme 5

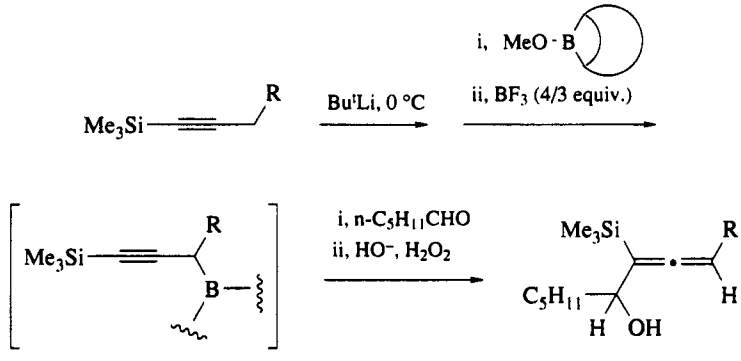
The ate complex of an organoborane reagent, formed by reaction of a trialkylborane with lithium chloropropargylide at –90 °C, undergoes a spontaneous anionotropic rearrangement in which one alkyl group migrates from boron to the adjacent carbon concomitant with an electron pair shift and loss of chloride to produce the allenic borane. Treatment of the allenic borane with an aldehyde results in an allenic–propargylic rearrangement to give, after oxidative work-up, a homopropargylic alcohol. However, if the allenic borane initially formed is allowed to warm, it rearranges to the thermodynamically more stable propargylic borane. This in turn reacts with the carbonyl group of an aldehyde, with boron transposition, to produce an α-allenic alcohol (Scheme 6).[11]



R = cyclopentyl, R^1 = ethyl

Scheme 6

Propargylic organoboranes derived from the corresponding lithium reagents react with aldehydes and certain ketones with high regioselectivity to give trimethylsilyl-substituted α-allenic alcohols (Scheme 7).[12]



R = H; 82%

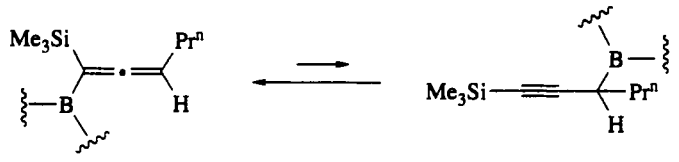
R = Pr^n; 78%

allene:alkyne = 88:12

Scheme 7

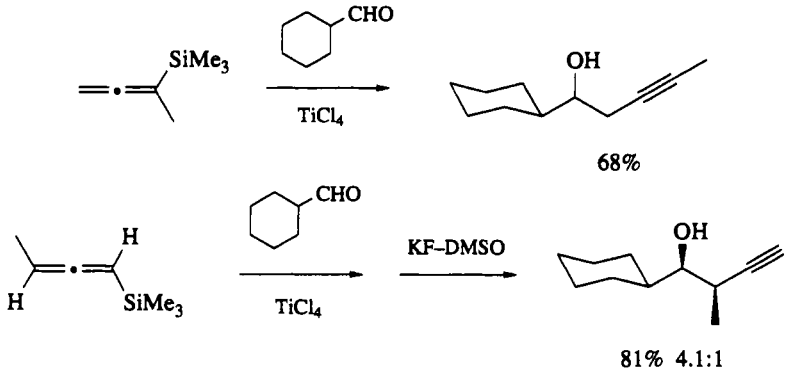
The high regioselectivity in the formation of α-allenic alcohols from boron reagents at low temperature is markedly different from that seen with the titanium reagent derived from 1-trimethylsilyl-1-butyne, in which exclusive formation of β-alkynic alcohols is observed.[47] This result was explained by a rapid exchange between the allenic and alkynic structures, as shown in equation (2). The alkynic structure is thermodynamically less stable and kinetically more reactive than that of the allenic form. At lower temperature, the rate of equilibrum becomes faster than the subsequent reaction with aldehydes and thus the alkynic species becomes the major reaction form.

The reaction of trimethylsilylallenes with aldehydes and ketones in the presence of titanium tetrachloride provides a regiocontrolled route to homopropargylic alcohols of a variety of substitution types. Thus, the addition of 1-alkyl-substituted trimethylsilylallenes to carbonyl compounds furnishes the desired alkynes directly, whereas reactions involving allenylsilanes initially produce mixtures of alkynes



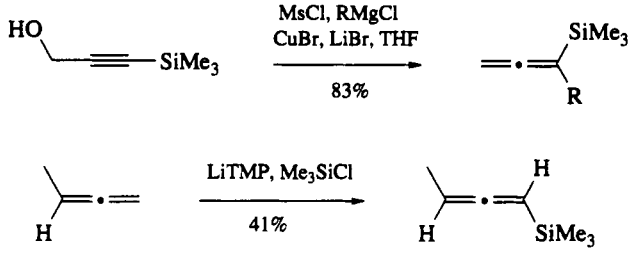
(2)

and trimethylsilylvinyl chloride derivatives. Exposure of these mixtures to the action of potassium fluoride in DMSO generates the desired homopropargylic alcohols (Scheme 8).[13]



Scheme 8

The requisite allenylsilanes are prepared selectively by the method of copper-catalyzed addition or by direct silylation of the lithium derivative of 1,2-butadiene (Scheme 9).[14]



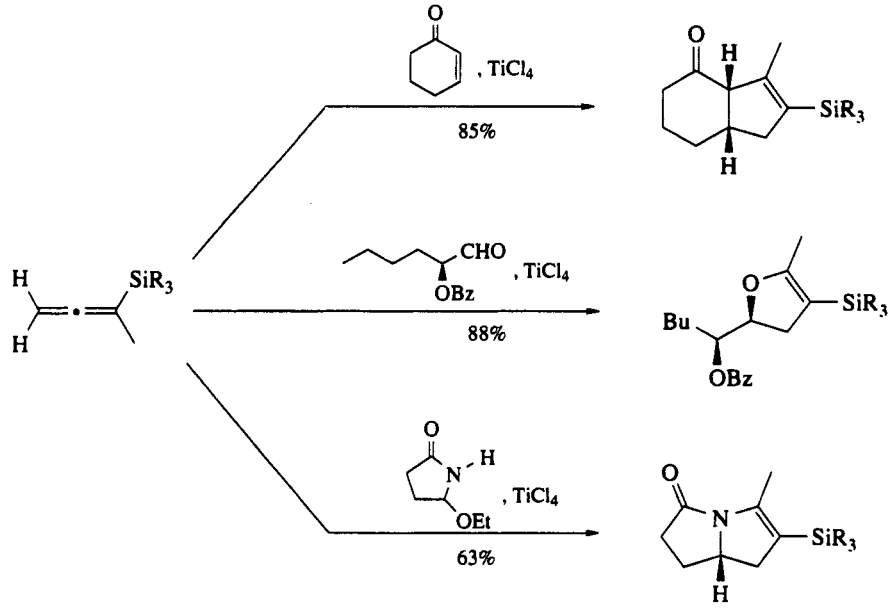
Scheme 9

Allenylsilanes combine with electron-deficient alkenes or alkynes regio- and stereo-selectively to afford highly substituted and functionalized cyclopentenes (Scheme 10). The [3 + 2] annulation reaction has been used for heteroannulation approaches to five-membered oxygen and nitrogen heterocycles.[15,16] One particularly useful application of the method is that readily available tropylium salts can function as allenophiles in a general [3 + 2] annulation route to substituted azulenes (equation 3).[17]

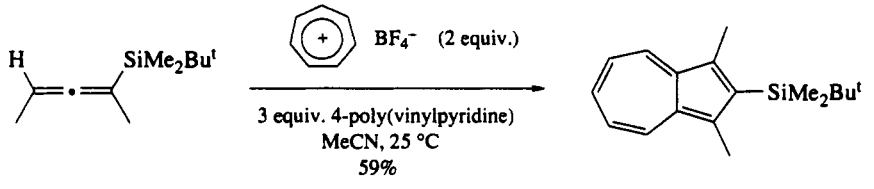
The condensation of propargyltrimethylsilane with acyl cyanide gives good yields of γ-allenic acyl cyanides (equation 4).[18]

Allenylsilver(I) compounds are prepared *in situ* by deprotonation of the allenic hydrocarbon with *n*-butyllithium and subsequent treatment with silver bromide (equation 5).[19] Allenylsilver compounds afford allenic derivatives when treated with a variety of electrophiles, without significant isomerization to the propargyl system (equation 6).[19,20] Reaction of the allenylsilver compound with carbon disulfide results in an interesting transformation to β,γ-unsaturated-γ-dithiolactones presumably by way of silver salts (Scheme 11).[19,21]

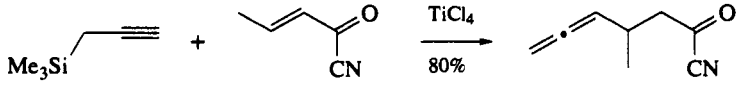
Convenient methods for the preparation of propargylic and allenic mercurials have been reported and their halogenation affords a route to the corresponding rearranged allenic and propargylic bromides and iodides (Scheme 12).[22] These organomercurials undergo facile acylation with rearrangement to afford the corresponding allenic and propargylic ketones in high yields (Scheme 13).[23]



Scheme 10



(3)



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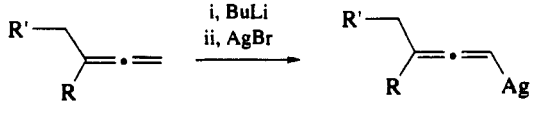

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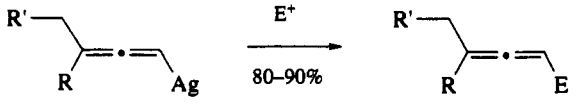
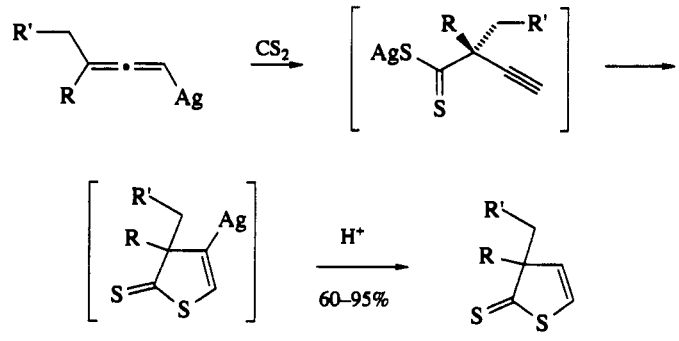


(6)

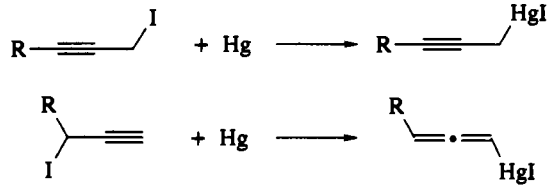
E	*Reagent*	*E*	*Reagent*
Br	BrCN	Br	NBS
MeS	$MeSSO_2Me$	Cl	NCS
CH_2=$CHCH_2$	Allyl bromide	CO_2H	CO_2
Me_3Si	TMS-Cl		

Allenyllithium compounds can function as nucleophiles for the synthesis of quinolines. The reaction of 3-methyl-1,2-butadienyllithium with phenyl isothiocyanate in THF at –70 °C produces the allenyl thiocarboximidate, which can be thermally cyclized to 2-methylthioquinoline (Scheme 14).[24]

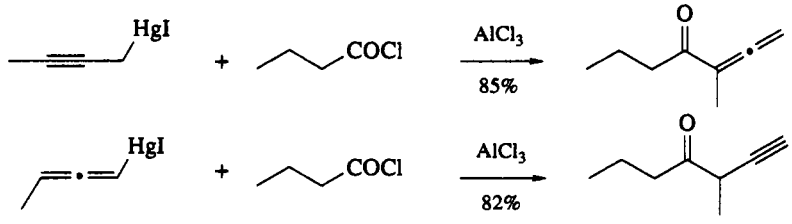
Reactions of allenyltin reagents with isoquinoline in the presence of chloroformate esters as acylating agents give 2-alkoxycarbonyl-1-(2-alkynyl)-1,2-dihydroisoquinolines in good to excellent yields (equation 7). Similarly, reactions with quinoline give 1-alkoxycarbonyl-2-(2-alkynyl)-1,2-dihydroquinolines exclusively.[25] Quinoxaline when treated with an excess of the allenylmagnesium bromide affords the di-



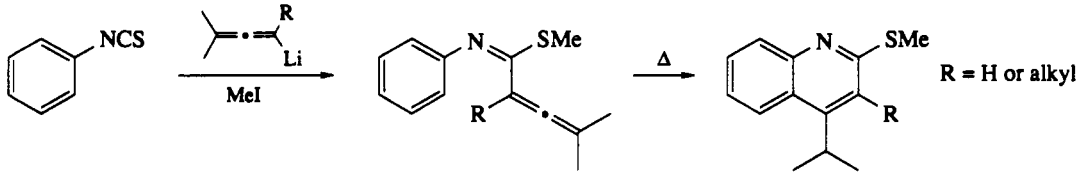
Scheme 11



Scheme 12

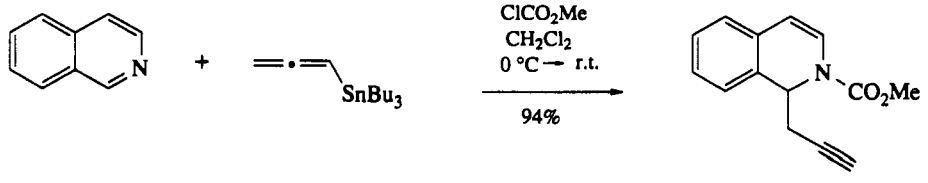


Scheme 13

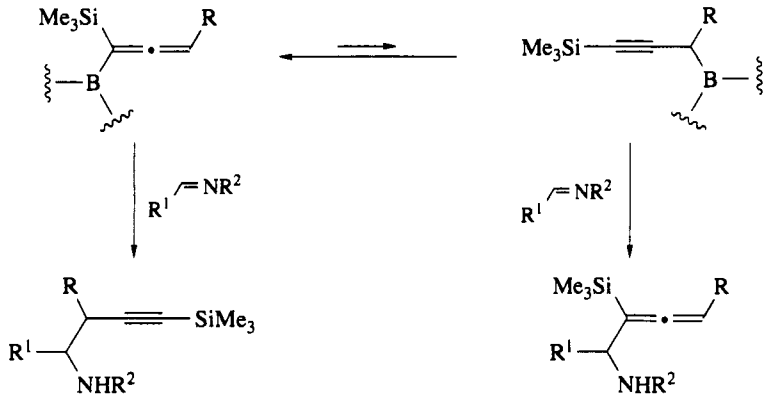


Scheme 14

methylpropargyldihydroquinoxaline, accompanied by small amounts of the bis-addition product.[26] Similarly, 2-chlorobenzoxazole reacts rapidly and cleanly with the Grignard reagents from propargyl bromide, 1-methylpropargyl bromide and 1,1-dimethylpropargyl bromide, giving high to excellent yields of 2-allenylbenzoxazole, 2-(1-methylpropargyl)benzoxazole and 2-(1,1-dimethylpropargyl)benzoxazole, respectively. Thus, the substitution pattern influences the allene/alkyne product distribution significantly.[27]



Nikam and Wang have reported a related boron reagent addition to C=N bonds. Reactions were carried out by adding imines to the organoboranes derived from 1-trimethylsilyl-1-alkynes. After oxidative work-up, the condensation adducts are isolated. The allenic/alkynic distribution is strongly influenced by the structures of both the imine and the organoborane reagent. Since imines are much less reactive toward the boron reagent than aldehydes, the regioselectivity of this reaction is simply determined by the difference of the energy barriers of the two subsequent condensation reaction pathways (Scheme 15).[28]



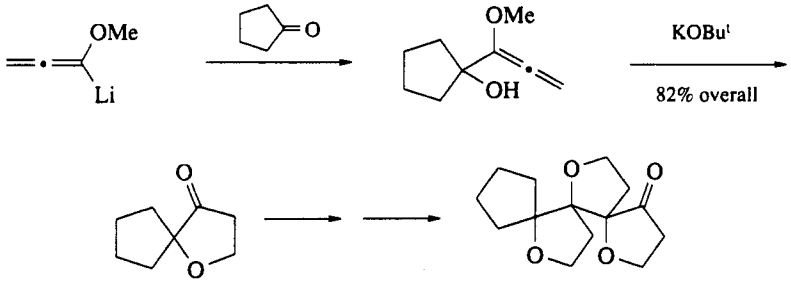
R	*R*^{1}	*R*^{2}	*Alkyne:allene*
H	Ph	Pr^n	<1:99
Pr^n	Ph	Pr^n	<1:99
Pr^n	Ph	Ph	>99:1
Pr^n	Pr^i	c-Hexyl	>99:1

Scheme 15

1.3.4.2 Heteroatom-substituted Propargyl and Allenyl Organometallics

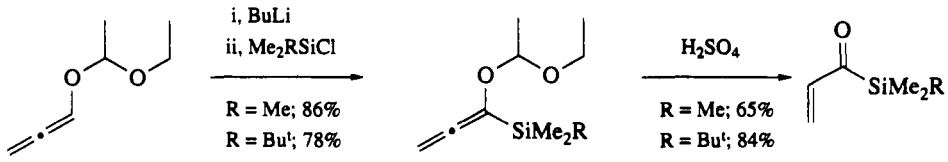
Heterosubstituted allenes are versatile synthetic intermediates. Direct substitution of a heteroatom on the allene confers upon the system an electronic bias that allows the molecule to be deprotonated easily using an organolithium reagent, and also permits regioselective reaction with carbonyl compounds.

The reaction of α-lithio-α-methoxyallene with cyclopentanone gives an allenic carbinol. Treatment of this material with potassium *t*-butoxide in *t*-butyl alcohol containing 18-crown-6 heated at reflux for 15 h provides the dihydrofuran derivative, which, after acid hydrolysis, gives a spirodihydrofuranone. The method has been utilized as an iterative process for the synthesis of helical molecules (Scheme 16).[29]

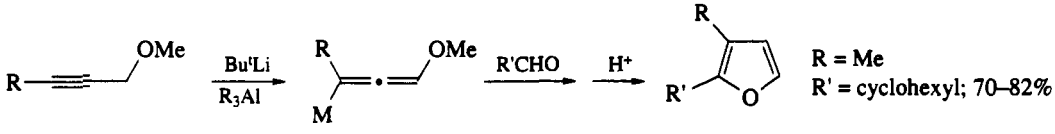


Scheme 16

Vinyl silyl ketones have been prepared from alkoxyallenes as shown in Scheme 17. Deprotonation and silylation afford the corresponding allenylsilanes, which are hydrolyzed to vinyl silyl ketones.[30,31,32] The regioisomeric organoaluminum reagents react with aldehydes to give furans after acid hydrolysis (Scheme 18).[33]

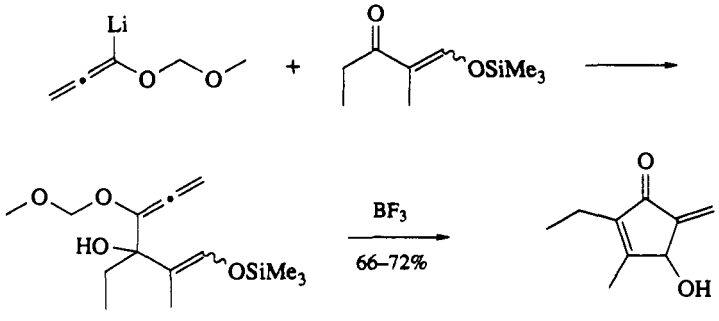


Scheme 17



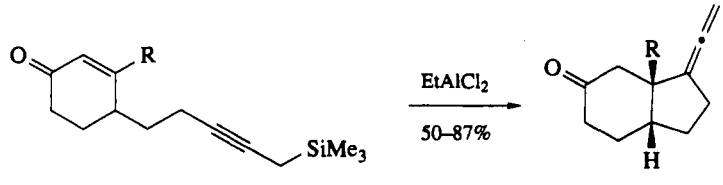
Scheme 18

The alkoxyallene adducts of *O*-trimethylsilyl hydroxymethylene ketones undergo a facile acid-catalyzed cyclization to produce functionalized cyclopentanones. Of various allene ether derivatives, methoxymethoxyallene gave the most satisfactory results (Scheme 19).[34]



Scheme 19

The intramolecular addition of propargylic silanes to cyclic enones proceeds smoothly under mild conditions, yielding functionalized exocyclic allenes (Scheme 20). This useful process has been reviewed by Schinzer.[35]



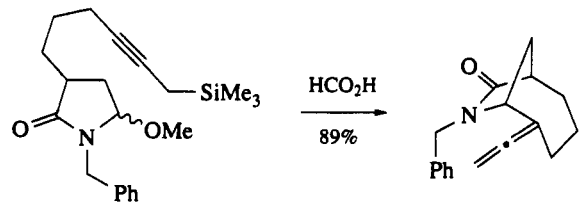
R = H or Me

Scheme 20

Reaction of propargyltrimethylsilane with ω-ethoxylactams under the influence of boron trifluoride affords ω-allenyllactams.[36] The intramolecular version of this process gives rise to bridged azabicyclic systems containing the uncommon α-allenic amide functionality (equation 8).[37]

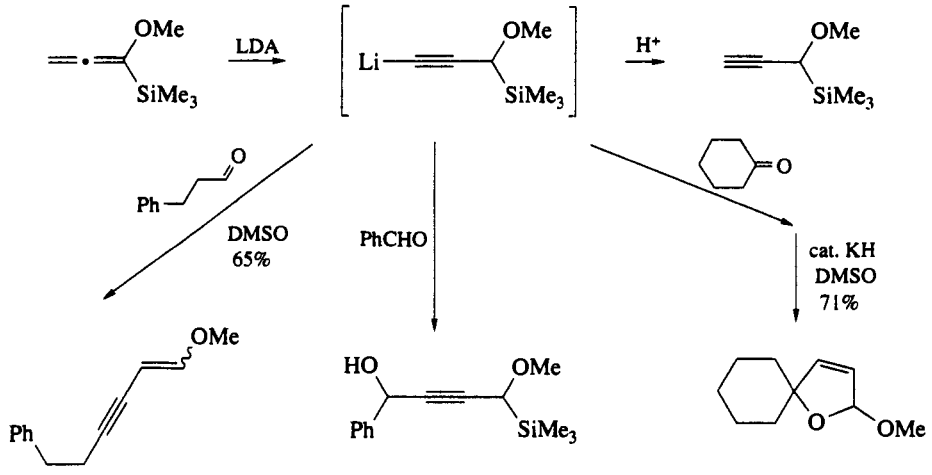
On treatment with LDA, methyl 1-trimethylsilylallenyl ether isomerizes to methyl 3-lithio-1-trimethylsilylpropargyl ether, which can be used efficiently for the preparation of 1-methoxy-1-alken-3-ynes and 2-methoxy-2,5-dihydrofurans. The isomerization in the first step may proceed through a sequence of deprotonation and protonation processes with LDA and diisopropylamine, respectively, since it does not take place under the influence of butyllithium (Scheme 21).[38]

A 3-*t*-butyldimethylsiloxyallenyllithium reagent generated quantitatively from the 1-silylpropargyl alcohol can be used as a synthetic equivalent of an α,β-unsaturated ketone having nucleophilic character at

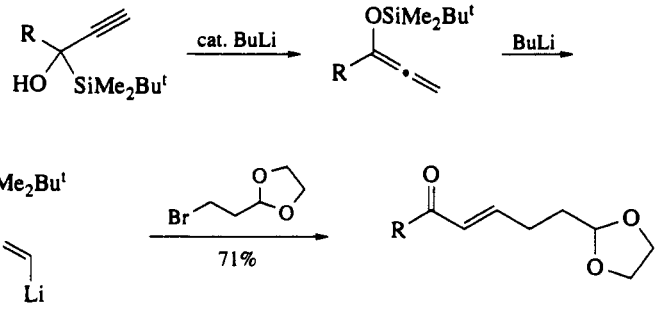


(8)

its β-position (Scheme 22). Both alkylation with alkyl halides and addition to carbonyl compounds proceed in good yields.[39]

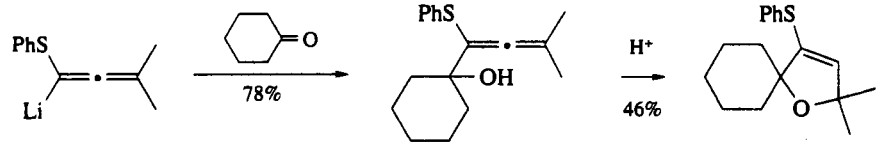


Scheme 21



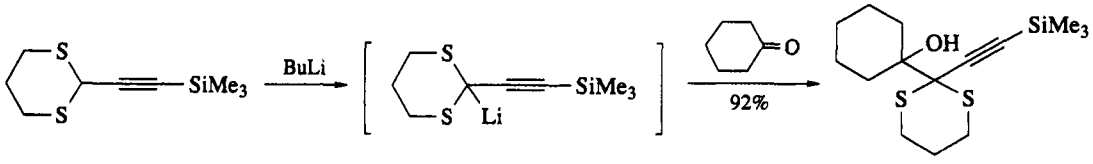
Scheme 22

3,3-Dialkyl-1-lithio-1-phenylthioallenes add efficiently to ketones only on warming to –20 °C or above; the adducts are readily cyclized by acid, or several other electrophiles, to produce highly substituted 2,5-dihydrofurans (Scheme 23).[40]



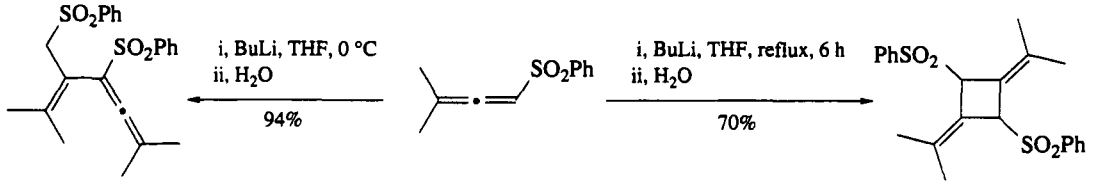
Scheme 23

2-Ethynyl-1,3-dithiane and several of its silyl and lithio derivatives have been reported (Scheme 24). The α-lithio-γ-silyl derivative is a particularly useful carbon nucleophile giving efficient α-alkylation with a variety of electrophiles (H_2O, D_2O, Me_3SiCl, MeI, allyl chlorides, R_2CO and RCHO).[41]



Scheme 24

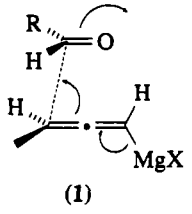
Treatment of a solution of γ,γ-dimethylallenyl phenyl sulfone with one-half equivalent of *n*-butyllithium at 0 °C results in dimerization of the substrate. However, if the same reaction is carried out at reflux temperature for 6 h, the cyclodimer is obtained (Scheme 25).[42]



Scheme 25

1.3.5 DIASTEREOSELECTIVE REACTIONS

The mechanism of the condensation between allenyl organometallics and carbonyl groups is thought to be a cyclic S_Ei' (or S_E2') process. In the reaction of aldehydes with 1,2-butadienylmagnesium halides, the *anti:syn* product ratio depends on the size of substitutent group of the aldehyde and may be rationalized as shown in (**1**).[43]



(**1**)

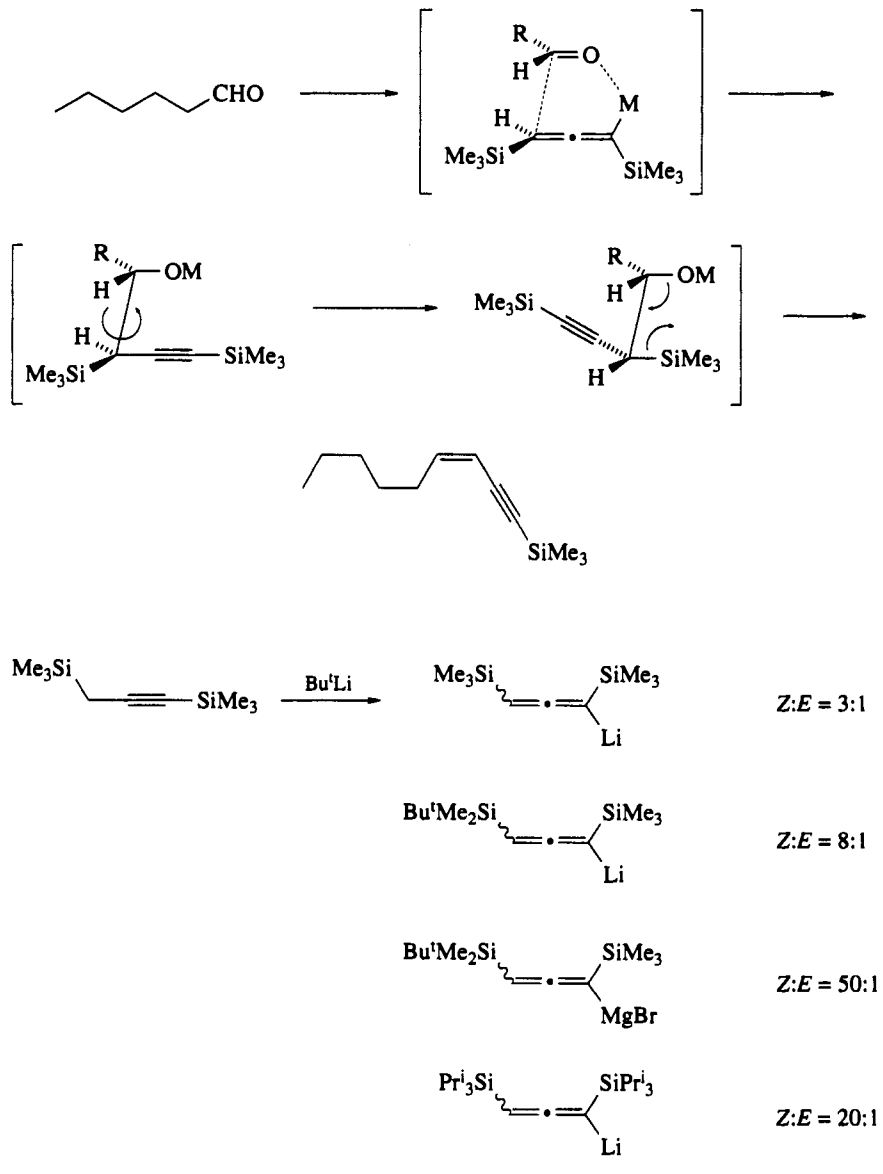
R	*threo:erythro*
Me	76:24
Et	82:18
Pr^i	90:10
Bu^t	95:5

The stereoselectivity of the reaction is also sensitive to the metal and to the bulk of the substituent on the allene (Scheme 26). For example, the lithium anion of 1,3-bis(trimethylsilyl)propyne reacts with aliphatic aldehydes and ketones to give a mixture of (*Z*)- and (*E*)-1,3-enynes in a ratio of about 1:3. Use of the anion of 3-*t*-butyldimethylsilyl-1-trimethylsilylpropyne results in a ratio of approximately 8:1. The corresponding allenylmagnesium reagent reacts with aldehydes to give enynes with exclusive formation of the (*Z*)-isomer (50:1).[44] High (*Z*)-selectivity is also observed in reactions of the anion derived from 1,3-bis(triisopropylsilyl)propyne, in which the (Z):(E) ratio is about 20:1.[45] The reagent apparently prefers the allenic structure and reacts *anti* selectively, the adduct undergoing a *syn* stereospecific elimination under the reaction conditions.

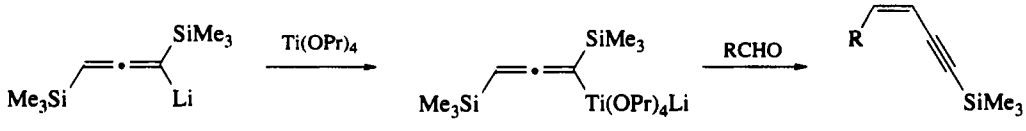
Similarly, the corresponding titanium reagents react with aldehydes in a one-pot procedure to provide (*Z*)-isomers exclusively (Scheme 27).[46,47]

Allenylzinc reagents react with aldehydes in a highly regio- and diastereo-selective manner to produce *anti* homopropargylic alcohols with diastereomeric purities of 96–99% (Scheme 28).[48]

Metallation of 1-methoxy-2-butyne with *n*-butyllithium at –78 °C, followed by the addition of one equivalent of zinc chloride, generates the very reactive and unisolable organozinc intermediate. Reaction of this zinc reagent with cyclohexenone affords the alkynic alcohol in 95% yield as a 65:35 mixture of diastereomers. Subsequent reduction of the triple bond provides either the *trans* alkene or the *cis* alkene, depending on the reaction conditions. A modified oxy-Cope rearrangement thus provides the diastereomeric ketones, which have been used for the synthesis of juvabione (Scheme 29).[49]

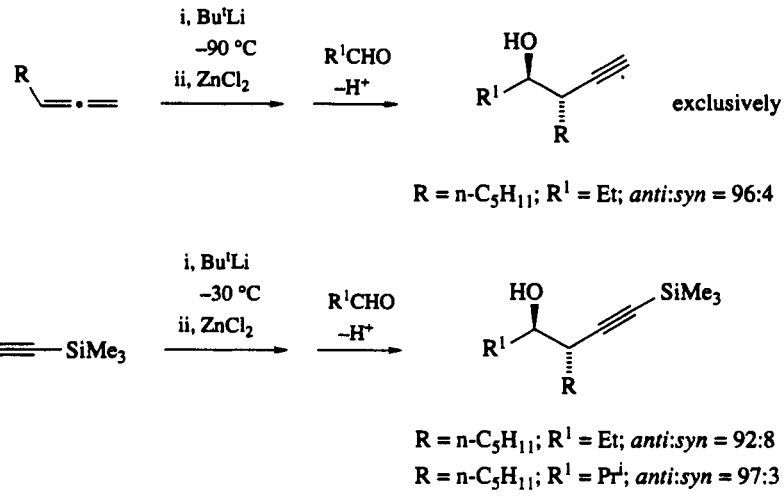


Scheme 26

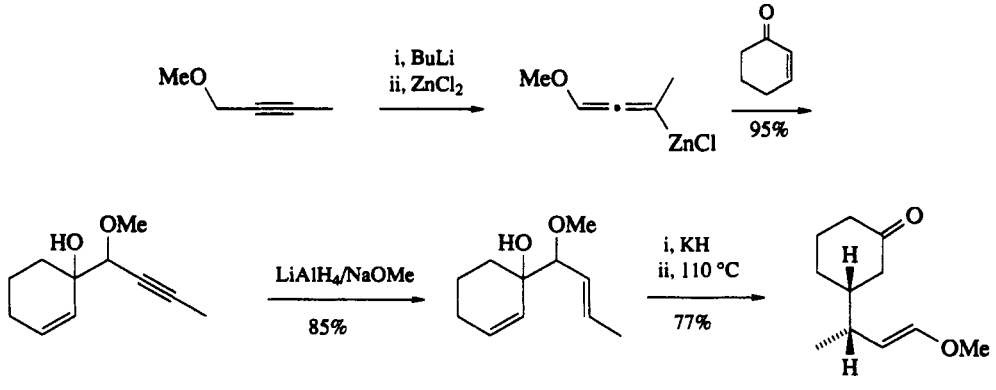


Scheme 27

The propargyltitanium reagents derived from 2-alkynes condense with aldehydes to give α-allenyl alcohols, whereas the allenyltitanium reagents generated from 3-alkynes give β-alkynic alcohols. In both cases, the reactions proceed with high regioselectivity. The observed site selectivity may be explained as follows. Titanation of the propargylic anion takes place with extremely high regioselectivity to produce allenic or alkynic titanium derivatives, depending on the substitution pattern of the original alkynes. Indeed, the IR spectrum of the titanium reagent in THF derived from 1-trimethylsilyl-1-butyne shows a strong absorption at 1898 cm^{-1}, characteristic of the allenic structure, while that of the reagent derived

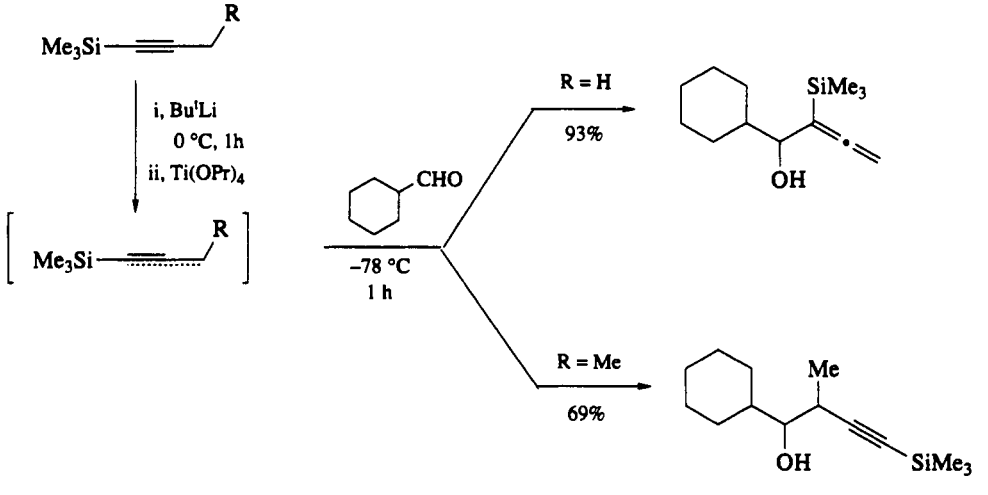


Scheme 28

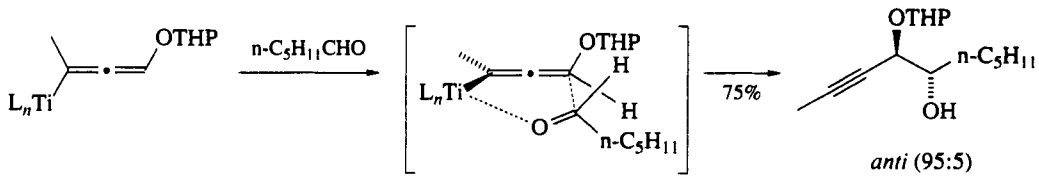


Scheme 29

from 1-trimethylsilylpropyne reveals only alkynic absorption at 2092 cm^{-1}, in accord with the foregoing speculation. Subsequent reaction with the electrophile then occurs in the usual S_Ei' (or S_E2') manner (Scheme 30).[46,47]

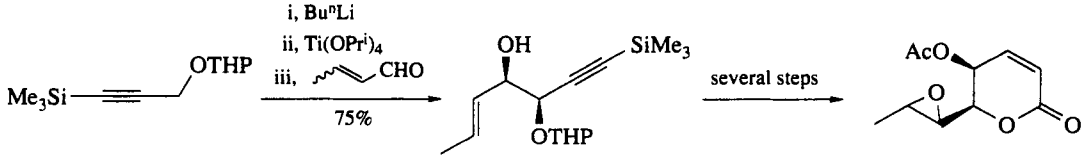


Scheme 30



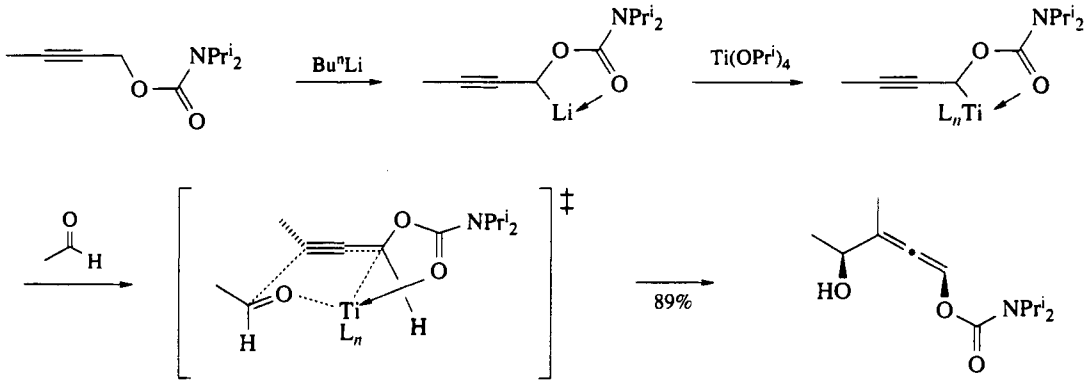
Scheme 31

The titanium reagents add to aldehydes to give *anti* vicinal diols. For example, the allenyltitanium reagent generated from 1-alkyl-1-butyne derivatives gives *anti* β-alkynic alcohols with high diastereoselectivities (Scheme 31). This method has been applied in a stereocontrolled synthesis of (±)-asperlin and related compounds (Scheme 32).[50]



Scheme 32

N,N-Diisopropyl-2-alkynyl carbamates are deprotonated by *n*-butyllithium to form lithium compounds. After exchange of the cation, the resulting titanium reagents add highly regio- and diastereo-selectively to aldehydes with the formation of *syn* allenyl alcohols (Scheme 33). Thus, in contrast to metallated 2-alkynyl ethers, the titanium reagent exhibits high γ-regioselectivity due to the powerful chelating carbamoyl group.[51]

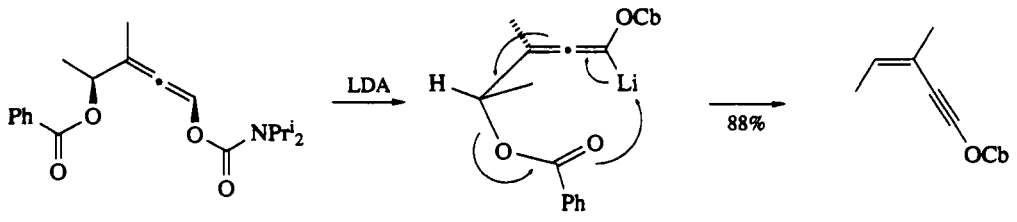


allene:acetylene = >95:5 *syn*:*anti* = >95:5

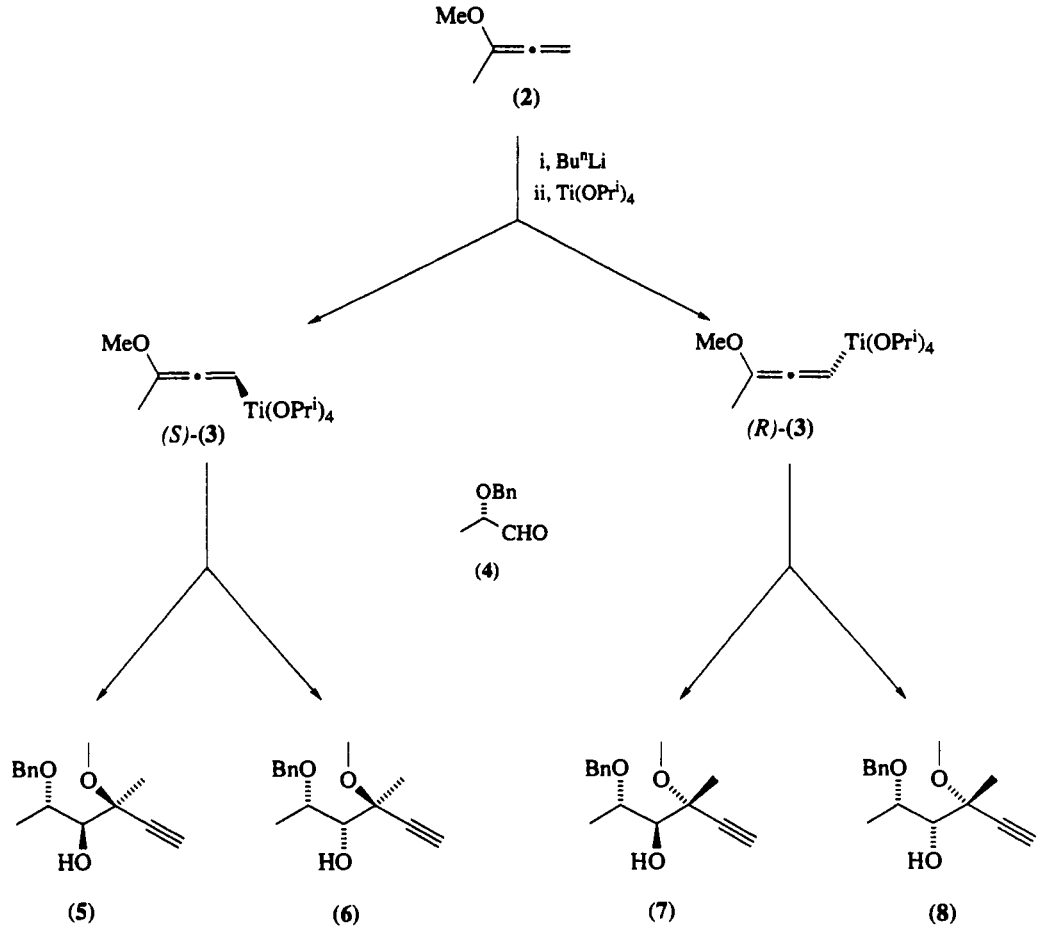
Scheme 33

The carbamate-stabilized allenyl anion was shown to have moderate configurational stability. Thus, when the 4-benzoate derivative of the allenyl compound is lithiated, 1,4-elimination of lithium benzoate occurs to form the very reactive 3-alken-1-ynyl carbamates stereospecifically (Scheme 34).[52]

Information about the degree of configurational stability of allenyltitanium compounds has been provided by Hoffmann and Hoppe (Scheme 35).[53] Racemic allenyltitanium reagent (**3**) is prepared by sequential treatment of 3-methoxy-1,2-butadiene (**2**) with *n*-butyllithium and titanium tetraisopropoxide. In the reaction of the racemate with one equivalent of (*S*)-(**4**) or its racemate, products (**5**)–(**8**) are formed in 70–90% total yield in the ratios shown in Scheme 35. Since the product ratios from the two experiments are different, the equilibrium between the enantiomers of (**3**) must be slow compared to the rate of reaction of (**3**) with (**4**). Thus, (*S*)-(**3**) leads to (**5**) + (**6**) and (*R*)-(**3**) leads to (**7**) + (**8**) (*i.e.* 51:49). From experiment B, the combinations (*S*)-(**3**) + (*S*)-(**4**) and (*R*)-(**3**) + (*R*)-(**4**) are shown to react considerably more rapidly than that of the (*R*)/(*S*) pairs (mutual kinetic resolution).[54]



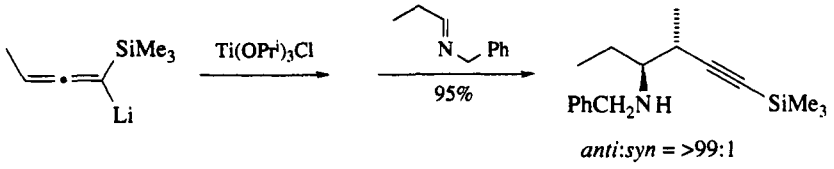
Scheme 34



A: (*S*)-(**4**)	(**5**)		(**6**)		(**7**)		(**8**)
	50	:	1	:	35	:	14
B: rac-(**4**)	*rac*-(**5**)		*rac*-(**6**)		*rac*-(**7**)		*rac*-(**8**)
	92	:	< 1	:	6	:	2

Scheme 35

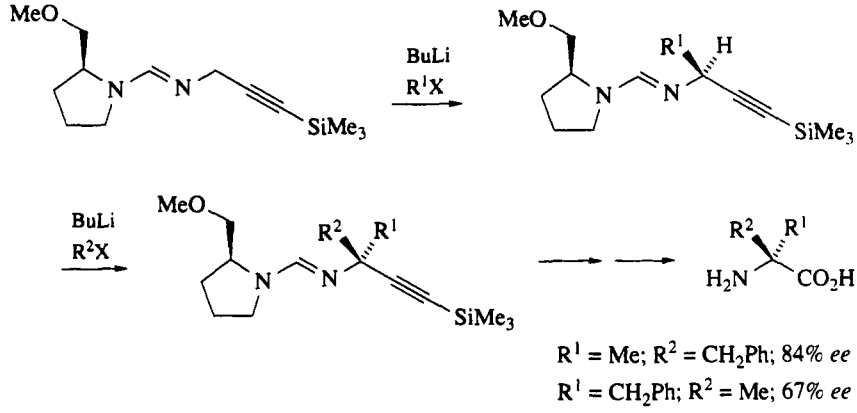
The reaction between the imines and allenic titanium reagents give the *anti* adducts with high stereoselectivity (Scheme 36). The observed stereoselectivity can be explained by a cyclic transition state in which the metal coordinates to the lone pair of the nitrogen atoms.[55]



Scheme 36

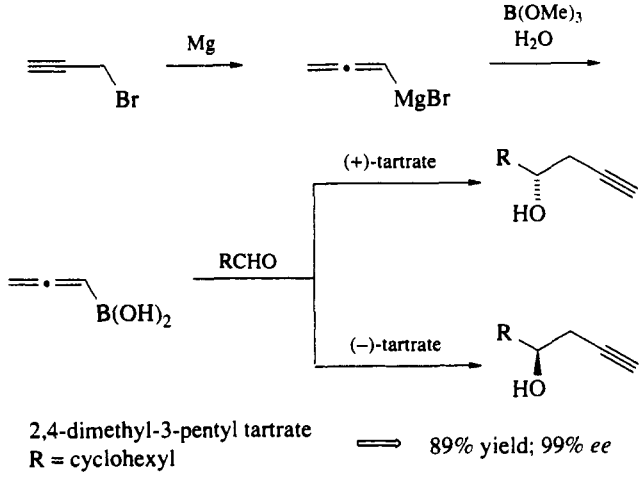
1.3.6 ENANTIOSELECTIVE REACTIONS

Diastereoselective carbon–carbon bond formation at the α-position to the amine nitrogen may be accomplished as shown in Scheme 37. Propargylamine is converted into the silylated amidine, which is metallated with *n*-butyllithium. After alkylation, the metallation and alkylation are repeated with a second alkyl halide to obtain the fully alkylated derivative. Thus, optically active α-substituted propargylamines and amino acids are obtained by hydrolysis of the amidine function and oxidative cleavage.[56]



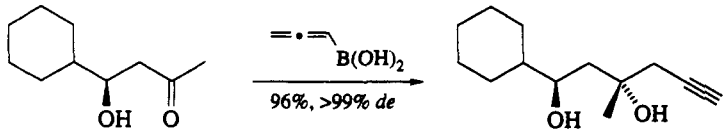
Scheme 37

Treatment of the propargyl Grignard reagent with trimethyl borate followed by acidic work-up gives the crystalline allenylboronic acid.[1] Reactions of this material with cyclohexanecarbaldehyde in the presence of various tartrate esters gives the homopropargyl alcohols. The greatest enantioselectivity was found with the tartrates of 2,4-dimethyl-3-pentanol or cyclododecanol (Scheme 38).[57,58]



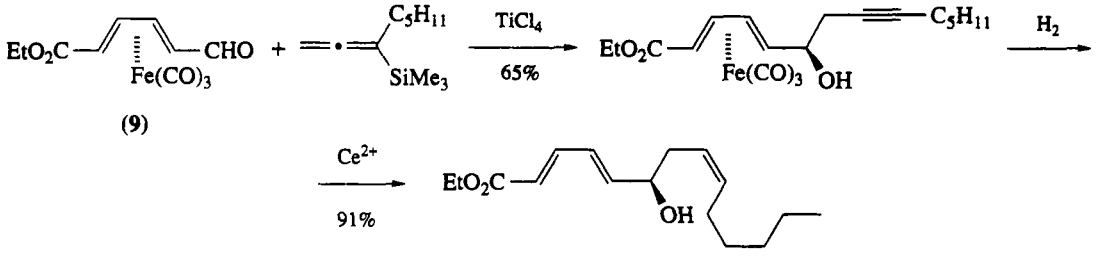
Scheme 38

Reaction of allenylboronic acid with β-hydroxy ketones in anhydrous ether at room temperature in the presence of 5A molecular sieves for 20 h, followed by treatment with basic hydrogen peroxide, yields 1,3-diols with high 1,3-asymmetric induction (>99%) (equation 9).[59]



(9)

Reaction of allenylsilanes with the easily accessible iron tricarbonyl complex (**9**) in the presence of $TiCl_4$ at –78 °C gives the homopropargyl alcohol in 65% yield, and leads to only the *Ψ-endo* derivative with the (*R*)-configuration at the secondary alcohol function (Scheme 39). It is noteworthy that $Fe(CO)_3$ acts here as an efficient protecting group.[60]



(**9**)

Scheme 39

1.3.7 REFERENCES

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1.4
Formation of Enolates

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1.4.1 INTRODUCTION

Enolates, or oxyallyl anions, are versatile reagents for the formation of α-substituted carbonyl compounds and are therefore important intermediates for the synthesis of complex molecules. The stereochemical outcome of an enolate reaction often depends on the geometry of the enolate and therefore the selective formation of enolates is a key step in many bond-forming processes.[1]

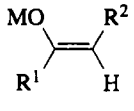
The counterion of an enolate has a pronounced influence on competing transition states of enolate reactions. The effect is often the result of cation chelation by the carbonyl oxygen atom and one or more additional basic portions of the reactants. For example, alkylation of chiral enolates may lead to more or less diastereomerically pure products and selectivity often depends on the countercation. The importance of the countercation in controlling enolate reaction product distributions requires that the synthetic chemist has at hand stereoselective methods for the preparation of enolate anions with a wide variety of counterions. This chapter is divided into several sections. The 10 following sections describe important current methods for preparing Li, Mg, B, Al, Sn, Ti, Zr, Cu, Zn and other transition metal enolates.

Enolates occur commonly in only two forms: the metal may be found either closer to the oxygen or closer to the carbon atom. Groups I, II and III enolates exist as O–metal tautomers. These strongly electropositive metals bind closely to the oxygen atom. Among transition metal enolates both types of

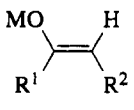
enolates are observed. In a few transition metal enolates the cation is associated with a delocalized enolate anion (η^3-enolate complexes).

The structures of enolates have been examined through magnetic resonance studies (NMR) and with X-ray crystallography.[2–12] It has been observed that solvated enolates exist as dimers, tetramers or hexamers, depending on the enolate structure, the nature of the cation and the solvent.

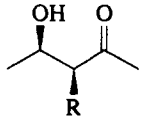
The following nomenclature for enolate stereoisomers is adopted throughout this chapter: the (*E*)/(*Z*) nomenclature is used according to the Cahn–Ingold–Prelog rules, with one change. At the carbonyl C-atom, the OM (oxy–metal) group is defined to be of highest priority without regard to the nature of the metal,[1] *e.g.* (**1**) and (**2**). This has the advantage that changing the metal associated with a given enolate does not affect the (*E*)/(*Z*) nomenclature.



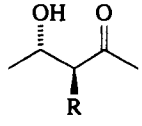
(**1**) (*Z*)



(**2**) (*E*)



(**3**) *syn/erythro*



(**4**) *anti/threo*

In the work cited here, the (*E*)/(*Z*) geometry of the enolate is sometimes not known or is not specified by the original authors. When this is the case, a wavy line is used in the representation of the enolate. Unfortunately, despite the importance of enolate geometry, many authors provide little direct information on this point. The exact nature of the countercation is also not always specified or known. Where the counterions are rather obvious but not certainly known, they are included in the formulas but placed in brackets [ ].

For aldol products many types of nomenclature have been proposed. Throughout this chapter the *syn/anti* nomenclature of Masamune[13] is adopted and defined as shown in (**3**) and (**4**).

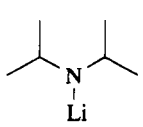
This chapter is restricted to the formation of metal and metalloid enolates that are more or less anionic and which can react with carbonyl groups without a catalyst. Silicon derivatives are therefore not described.

1.4.2 ALKALI METAL ENOLATES

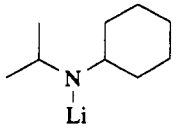
The alkali metal enolates are the most commonly employed and most useful of all enolates. Among alkali elements, lithium enolates are of greatest importance because these can often be formed under kinetic or thermodynamic conditions, as desired, and side reactions can be minimized since lithium is a small, tightly bound cation. Sodium and potassium countercations are more likely to support enolate equilibration, which is sometimes desired, but often undesired. This section is subdivided, based on the different methods of enolate formation.

1.4.2.1 Alkali Metal Enolates by Deprotonation of Carbonyl Compounds

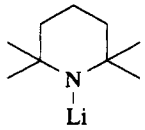
Deprotonation of carbonyl compounds by lithium dialkylamide bases is the single most common method of forming alkali enolates. Four excellent reviews have already been published.[1,14–16] Sterically hindered amide bases are employed to retard nucleophilic attack on the carbonyl group. The most common and generally useful bases are: (i) lithium diisopropylamide (LDA; **5**); (ii) lithium isopropylcyclohexylamide (LICA; **6**); (iii) lithium 2,2,6,6-tetramethylpiperidide (LITMP; **7**); (iv) lithium hexamethyldisilylamide (LHMDS; **8**); and (v) lithium tetramethyldiphenyldisilylamide (LTDDS; **9**). Bases that are not amides include sodium hydride, potassium hydride and triphenylmethyllithium.



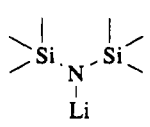
(**5**)



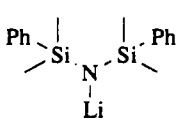
(**6**)



(**7**)



(**8**)



(**9**)

For ketone enolates the question of the regioselectivity of deprotonation arises.[1,17] Under kinetic conditions (low temperature, typically –78 °C, excess base, small cation), the less-substituted enolate is formed. More-hindered bases give higher selectivity. Under conditions designed to provide an equilibrium mixture of product enolates ('higher' temperature, excess ketone, larger cation) the more-substituted enolate is usually formed.

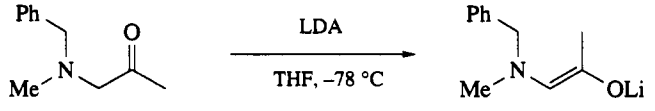
Aldehyde enolates and aldehydes are extremely reactive and therefore, to avoid undesirable side reactions, fast and quantitative conversion of aldehydes to enolates is necessary. Strong bases are needed, *e.g.* potassium amide in liquid ammonia[18] or potassium hydride in THF.[19] Aldehyde enolates are very rarely used in organic synthesis.

Ester enolates are less reactive than aldehyde enolates but rapid and quantitative deprotonation is still necessary because of the possibility of Claisen condensation side reactions.

For all enolates, (*E*)- and (*Z*)-geometry is possible. Much effort has been expended to determine the geometry of enolates and to define rules to predict the outcome of carbonyl group deprotonations.[1,14–16] This knowledge is relevant to the aldol reaction because (*Z*)-enolates tend to give *syn* products, whereas (*E*)-enolates tend to give *anti* products with varying degrees of stereoselectivity.

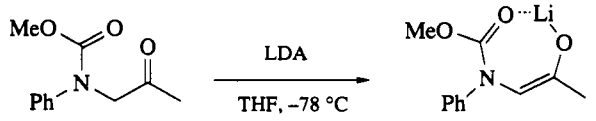
Under product-equilibrating conditions the (*Z*)-enolate is always the major product (except in smaller ring systems, three to nine membered, where the (*E*)-enolate is favored). Under conditions of kinetic product control, a closer study of reactants and bases is necessary. Reactions of ketones, esters or thioesters with lithium dialkylamides like LDA, LICA or LITMP in THF give predominantly the (*E*)-enolate. Larger, bulkier bases give better (*E*)-selectivity. However, if a bulky group (*e.g.* *t*-butyl, phenyl) is attached directly to the carbonyl group, the (*Z*)-enolate is preferred. If lithium dialkylamide bases are used in a mixture of THF and HMPA, or if silylamide bases are employed, the (*Z*)-enolates are found to be the major products. Carboxylic acid amides always give (*Z*)-enolates with high selectivity. Ireland *et al.*[20] proposed a cyclic six-membered transition state between the carbonyl and the dialkylamide base to explain these results. Recently, Moreland and Dauben[21] presented theoretical calculations that support this model.

Deprotonation of α-heteroatom-substituted carbonyl compounds (at the carbon bearing the substituent) has been less studied. In several cases it has been observed that, if chelation of the counterion by the enolate is possible, the (*Z*)-enolate is the preferred compound. Garst and coworkers reported two examples in which an α-dialkylamino ketone gives (*E*)-enolates selectively, whereas the corresponding



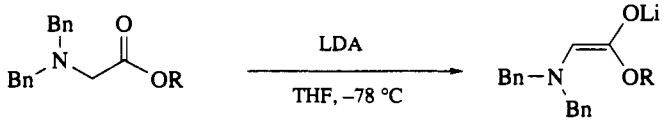
(1)

(E):*(Z)* > 98:2



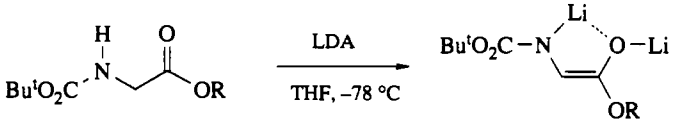
(2)

(Z):*(E)* = 80:20



(3)

(E):*(Z)* = 58:42

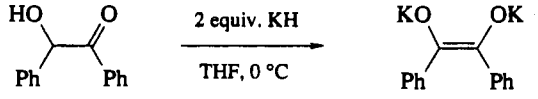


(4)

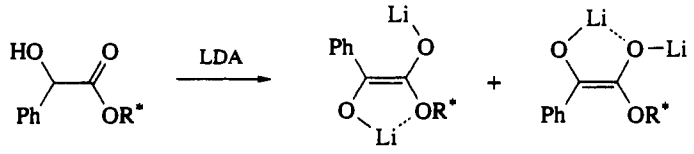
(Z) > 90%

urethane gives predominantly the (*Z*)-enolate (equations 1 and 2).[22] Ireland found a similar effect with α-amino esters (equations 3 and 4).[20]

α-Hydroxy ketones give (*Z*)-enolates (equation 5),[23] but if α-hydroxy esters are deprotonated, the prediction of (*E*)/(*Z*) selectivity is more difficult because both enolates can be stabilized through chelation. For the reaction shown in equation (6),[24] the (*E*):(*Z*) ratio is not known.

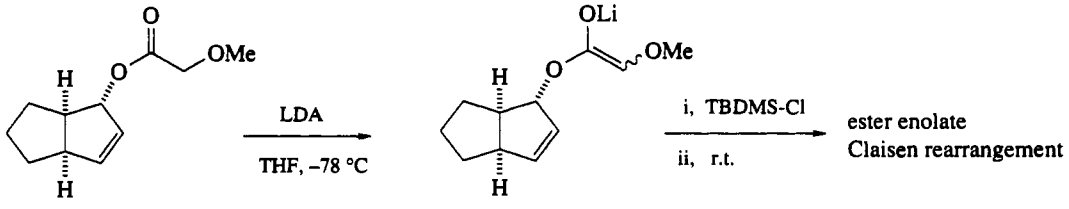


(*Z*) > 95% (5)

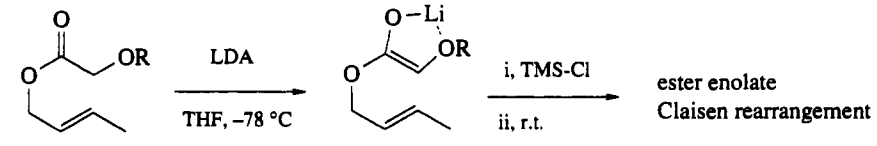


R* = 1-menthyl (*E*) (*Z*) (6)

α-Alkoxy esters would give (*Z*)-enolates if chelation effects dominated but the experimental results are inconsistent. Whitesell and Helbling[25] deprotonated an α-methoxy ester with LDA to get both diastereomers in roughly equal amounts (Scheme 1), but Kallmerten and Gould[26] obtained the chelated (*Z*)-enolate predominantly (Scheme 2). Ireland *et al.*[27] used a cyclic α-alkoxy ester and obtained a 5:1 mixture of enolates with LDA (in favor of the chelated (*Z*)-enolate) and a 1:1 mixture with LDA–HMPA. This latter change in selectivity can be explained by loss of the chelation effect (Scheme 3).

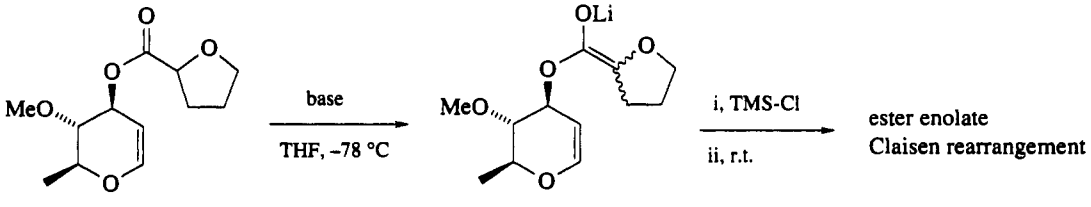


Scheme 1



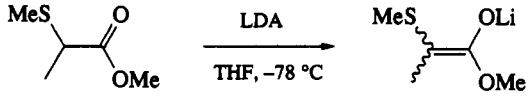
R = Me, CH_2Ph

Scheme 2



Base:LDA 5:1
LDA:HMPA 1:1

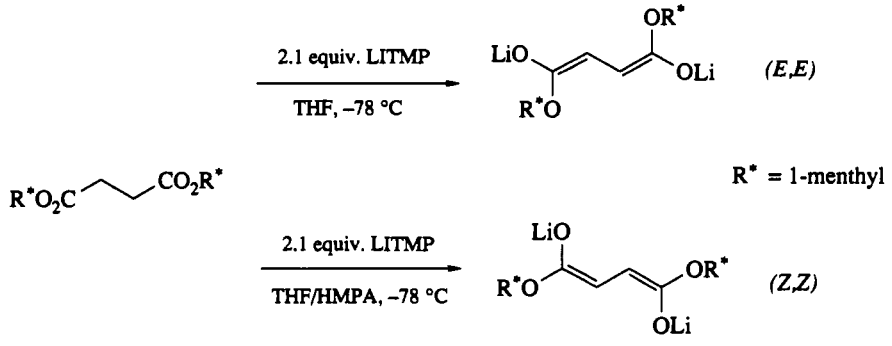
Scheme 3



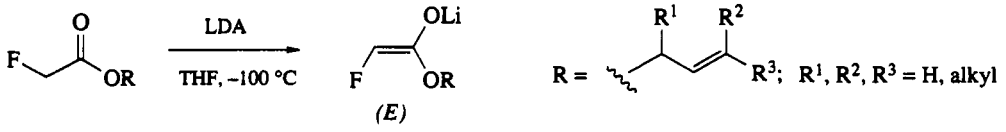
(7)

Deprotonation of one α-methylthio ester is reported to give a 75:25 diastereomer mixture, but it is not known if the (*E*)- or (*Z*)-isomer is the major product (equation 7).[28]

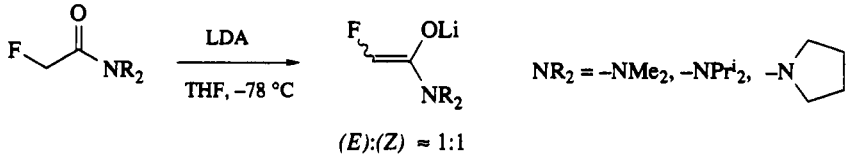
Dianion enolates of succinate diesters show the same stereochemical behavior as simple ester enolates: deprotonation with LITMP in THF gives the (*E,E*)-enolate and deprotonation in THF–HMPA gives the (*Z,Z*)-enolate (Scheme 4).[29] No mixed enolates are observed. The corresponding diamides seem to give (*Z,Z*)-enolates.[1,30]



Scheme 4



Scheme 5



Scheme 6

Welch *et al.* reported successful generation of α-fluoro enolates.[31,32] Deprotonation of ester enolates in THF gave the (*E*)-enolate as expected (Scheme 5), but no effect of HMPA on the enolate geometry was observed. The α-fluoroamides reacted unselectively (Scheme 6).

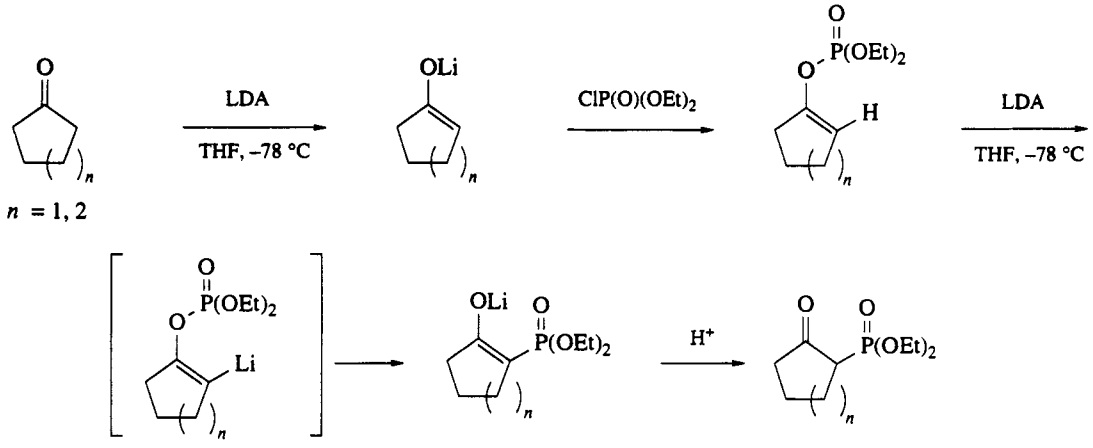
A versatile method to generate β-ketophosphonates that cannot be generated through the Arbuzov reaction has been developed: α-phosphonate enolates of cyclic ketones are obtained through sequential treatment of ketones with LDA, diethyl phosphorochloridate and LDA (Scheme 7).[33,34]

Acyclic β-ketophosphonates can also be formed from α-bromo ketones (Scheme 8)[35] and in a similar reaction α-trialkylsilyl enolates can also be obtained (Scheme 9).[35,36]

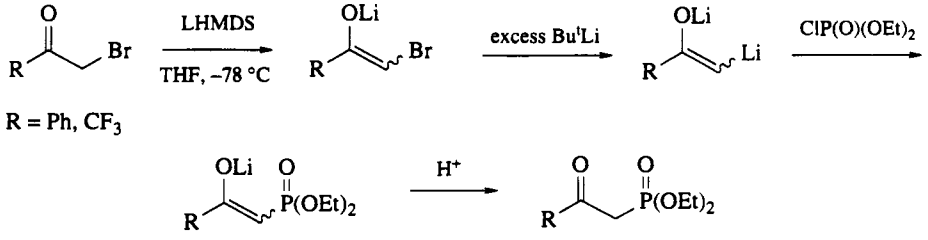
Kuwajima and Takeda employed the reaction of α-phenylselenylvinyl silyl ethers with lithium and dimethylaminonaphthalene (DMAN) to generate α-silyl enolates (Scheme 10).[37]

In these reactions (Schemes 7, 9 and 10) it is interesting that a strong P—O or Si—O bond is broken to get a less stable P—C or Si—C bond. The effect is apparently more than offset by the fact that a very unstable vinyl anion is converted to a relatively stable enolate anion.

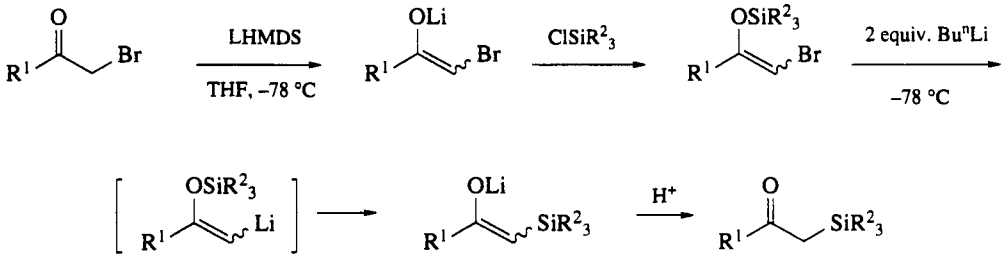
The reaction of esters and γ-lactone enolates with diphenylmethylsilyl chloride is reported to be atypical and to give the *C*-silylated product (Scheme 11).[38]



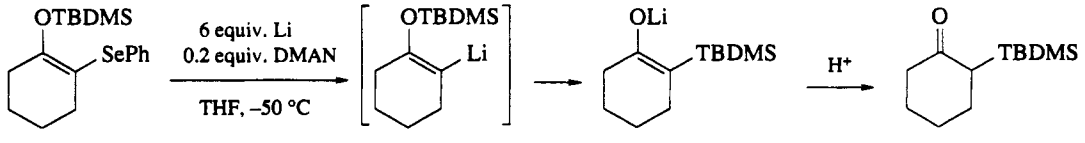
Scheme 7



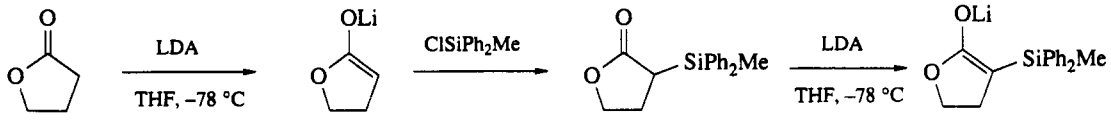
Scheme 8



Scheme 9

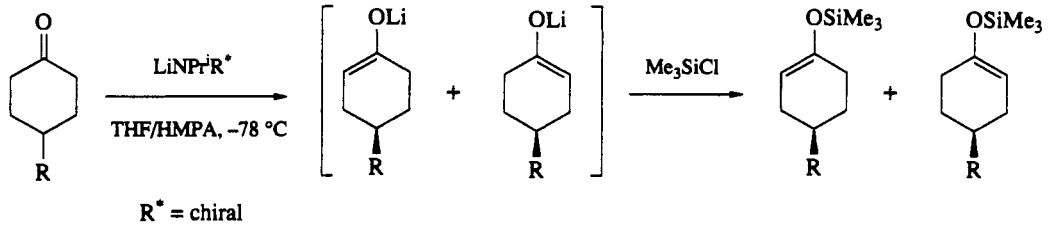


Scheme 10



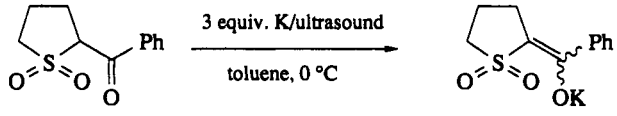
Scheme 11

Enantioselective deprotonation by chiral lithium amide bases has been reported. The degree of asymmetric induction depends on the base and on the bulkiness of the alkyl group in the cyclohexanone (Scheme 12).[39]



Scheme 12

Very recently, two examples of generating enolates with metallic potassium appeared. In one case potassium was dispersed ultrasonically, in the other 18-crown-6 was added to the potassium metal (equations 8 and 9).[40,41]



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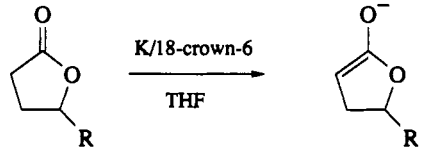
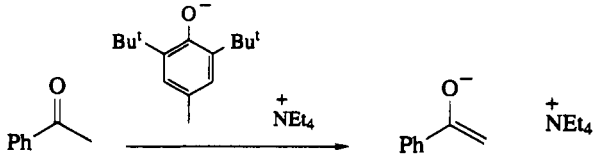


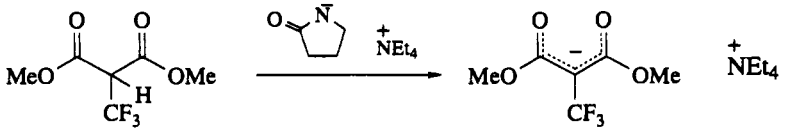
(9)

R = H, Me

Fuchigami and coworkers have formed enolates with electrogenerated bases (equations 10 and 11).[42,43] The basic anions of 2,6-di-*t*-butyl-*p*-cresol and α-pyrrolidone were obtained by cathodic reduction. Countercations with a weak affinity for the fluorine atom (*e.g.* quaternary ammonium, phosphonium or tertiary sulfonium cations) had to be used in the example shown in equation (11) in order to impede defluorination.

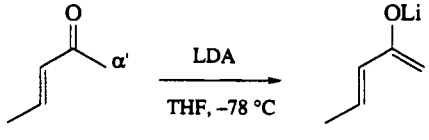


(10)

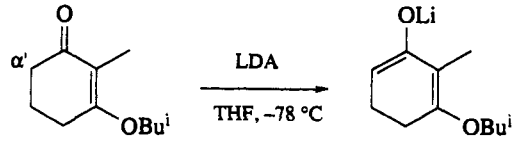


(11)

α,β-Unsaturated ketones can be deprotonated in two positions.[17] Under thermodynamic conditions the major product is that afforded by deprotonation at the γ-position, whereas under kinetic conditions the hydrogen in the α′-position is usually abstracted (equations 12 and 13).[44,45]

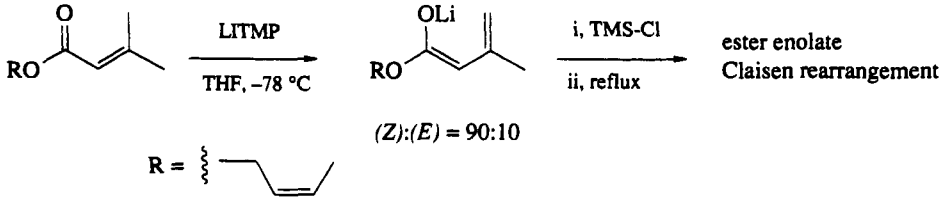


(12)

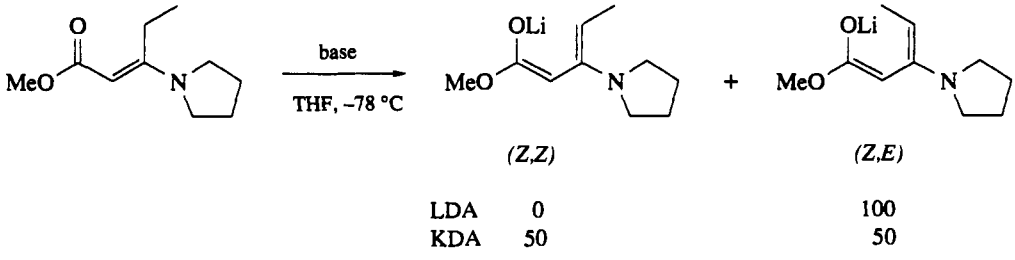


(13)

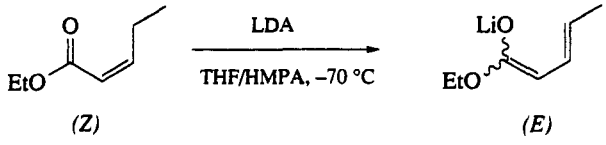
Little is known about the (*E*)/(*Z*) stereoselectivity of the enolate double bond and the newly generated Δ^3 double bond. Two experiments indicate that esters may give preferentially (*Z*)-enolates under kinetic conditions (Schemes 13 and 14).[46,47] If the Δ^2 double bond in an α,β-unsaturated ester has only alkyl ligands, (*Z*)-esters seem to give only enolates with (*E*)-geometry on the Δ^3 double bond and (*E*)-esters afford (*Z*)-Δ^3 double bonds (equation 14).[48,49]



Scheme 13



Scheme 14

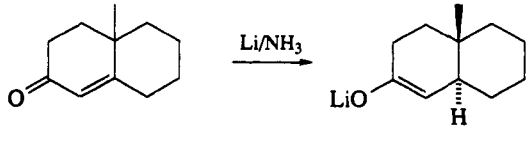


(14)

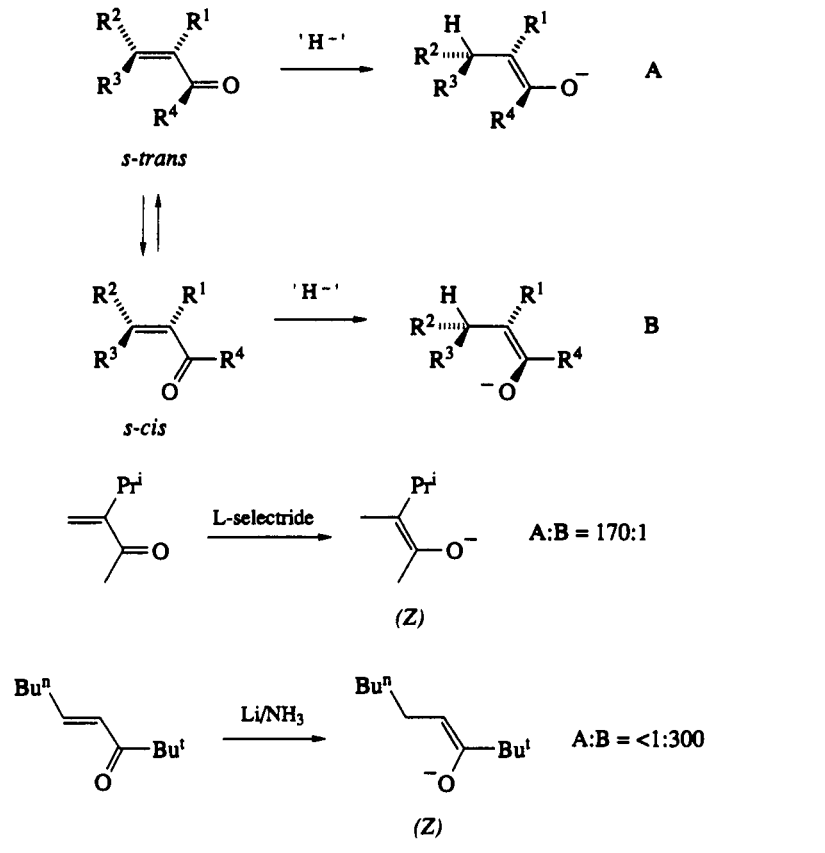
1.4.2.2 Alkali Metal Enolates by Addition to α,β-Unsaturated Carbonyl Compounds

The reduction of α,β-unsaturated carbonyls with lithium in ammonia is a versatile reaction of great utility.[17,50–52] The advantage of this method is that regiospecific enolates are obtained that are sometimes not accessible by other routes. This technique finds important applications in steroid-like systems (equation 15).[50]

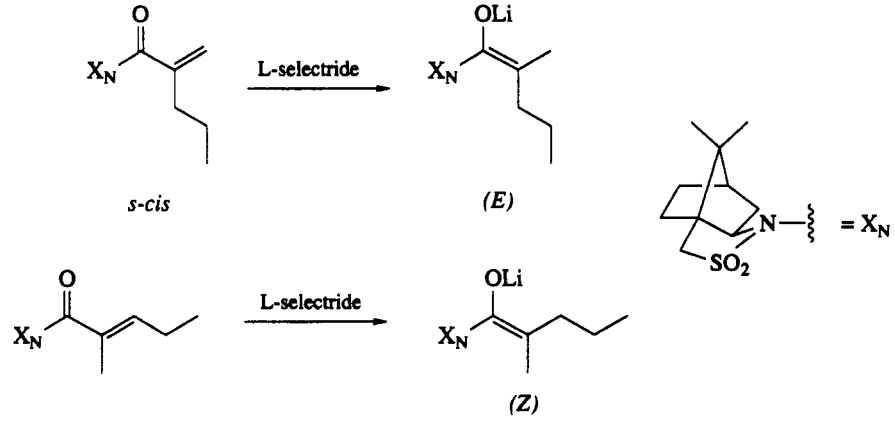
Chamberlin and Reich investigated hydride additions to α,β-unsaturated ketones and the correlation of conformational preferences in enones with the (*E*)/(*Z*) stereoselectivity in formation of the corresponding enolates. They found that in acyclic systems *s-trans* enones gave enolates A and *s-cis* enones gave enolates B (Scheme 15).[53] The reduction of α,β-unsaturated amides with L-selectride gave the same stereochemical results (Scheme 16).[54]



(15)



Scheme 15



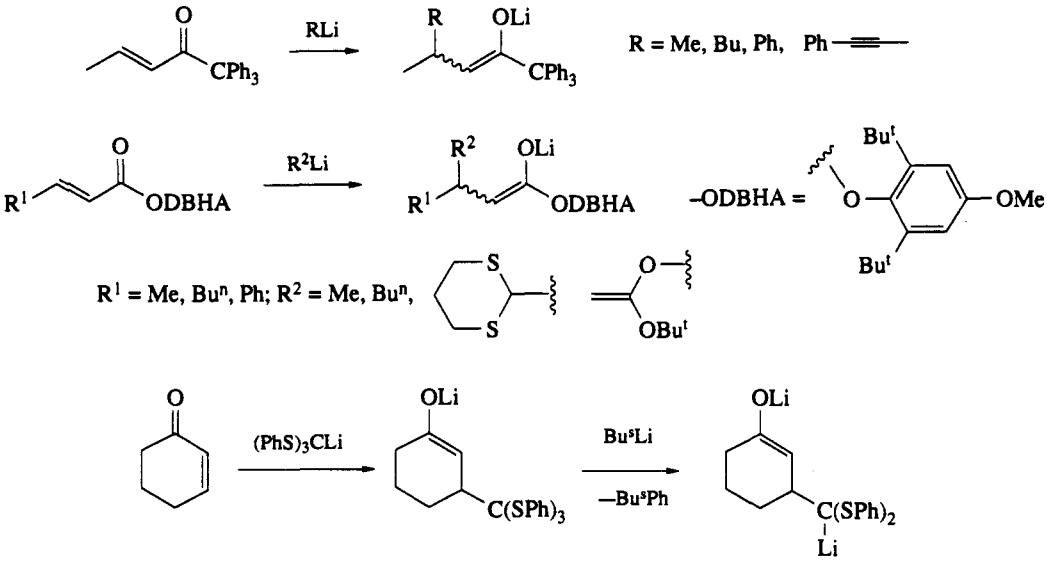
Scheme 16

Alkyllithium reagents normally react with α,β-unsaturated carbonyls in a 1,2-fashion, but with sterically hindered substrates or reagents 1,4-addition is preferred (Scheme 17).[55–57] Of course, the presence of other metals can also affect this preference. Other examples of 1,4-additions will be seen in later sections.

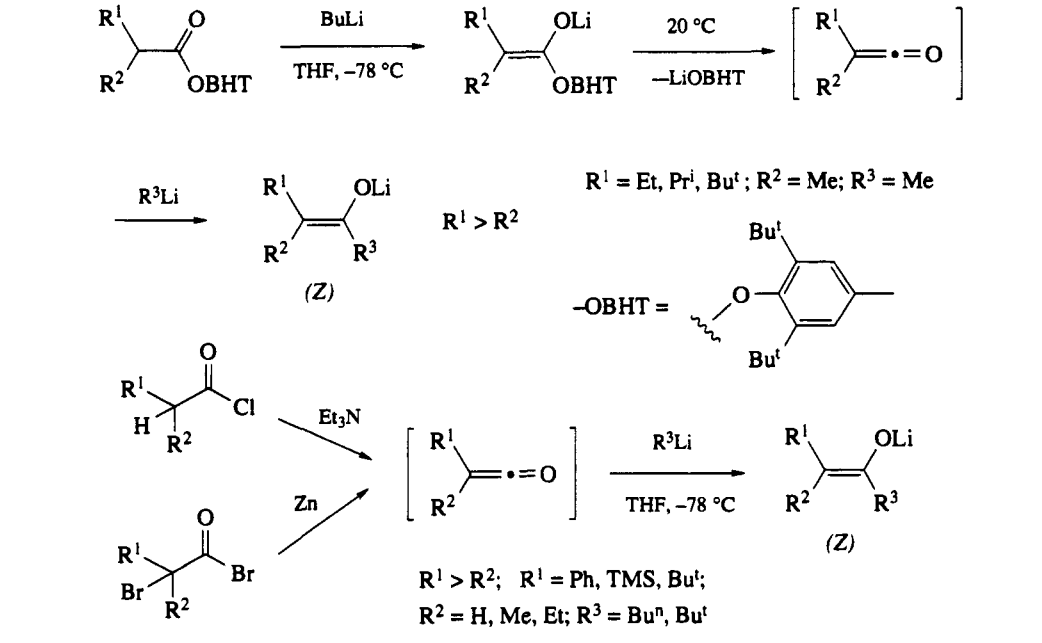
1.4.2.3 Alkali Metal Enolates from Ketenes

The formation of enolates from ketenes generates tetrasubstituted enolates regio- and stereo-selectively.[58–61] Deprotonation of the corresponding ketones gives mixtures of enolates. Ketenes are produced

from sterically hindered esters, from α-bromoacyl bromides and zinc, or from acid chlorides and triethylamine. Alkyllithium reagents add to the ketenes from the less-hindered side to give only (*Z*)-enolates (Scheme 18).[58,60]



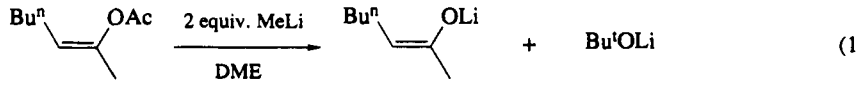
Scheme 17



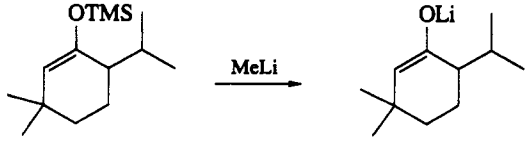
Scheme 18

1.4.2.4 Alkali Metal Enolates from Enol Acetates and Silyl Enol Ethers

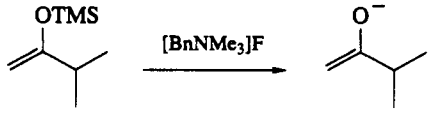
Enol acetates and silyl enol ethers may be prepared from enolates. This is sometimes advantageous because they are stable enolate equivalents.[17] Enol acetates can be cleaved with 2 equiv. of methyllithium



(16)



(17)



(18)

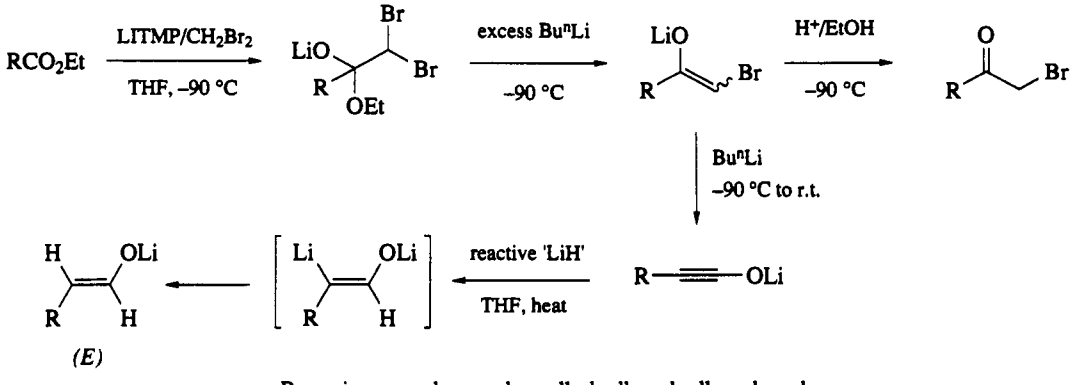
(equation 16).[62] Silyl enol ethers can be cleaved with methyllithium (equation 17),[63] with lithium or sodium amide,[64] or with benzyltrimethylammonium fluoride (equation 18).[65] These enolate formations occur without isomerization.

1.4.2.5 Alkali Metal Enolates by Miscellaneous Methods

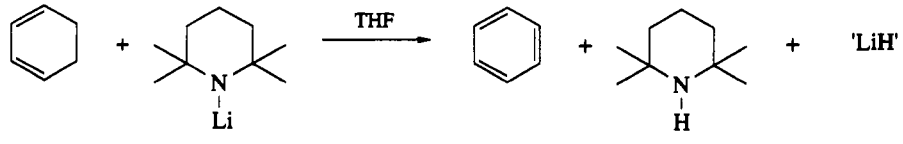
Kowalski *et al.*[66–69] employed dibromomethyllithium (prepared *in situ*) to prepare an α-bromo ketone enolate at low temperatures. At higher temperatures and under extremely basic conditions, this enolate rearranged to give an ynolate. A mixture of 1,3-cyclohexadiene and LITMP transformed the ynolate to an aldehyde (*E*)-enolate (Scheme 19).

Reaction of benzil with (benzenesulfonyl)methylenedilithium gives an enolate by an insertion process (Scheme 20).[70]

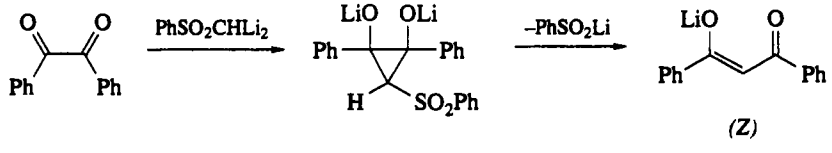
Lithium allenolates are obtained from 2,2-dimethyl-4-methylene-1,3-dioxolane and 2 equiv. of *s*-butyllithium. These allenolates can further undergo aldol reactions (Scheme 21).[71]



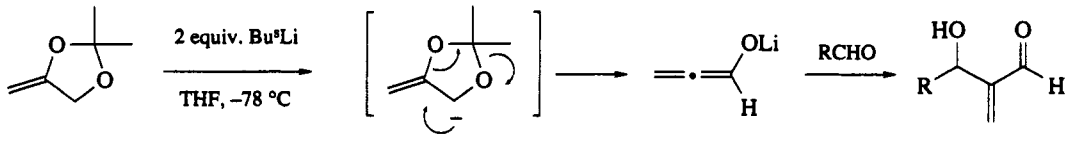
R = primary and secondary alkyl, alkenyl, alkynyl, aryl



Scheme 19



Scheme 20

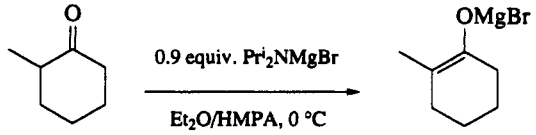


Scheme 21

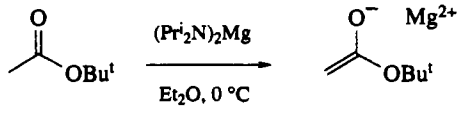
1.4.3 MAGNESIUM ENOLATES

Magnesium enolates are similar to alkali metal enolates. For example, often the same stereoselectivity is observed in their formation and in the aldol reactions of these enolates.

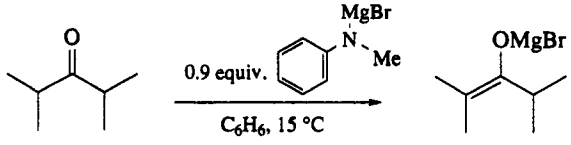
Carbonyl compounds can be deprotonated with magnesium dialkylamides, which are generated from Grignard reagents and are thus free of lithium. Again, the more-substituted enolate is obtained under thermodynamic conditions (equations 19 to 21).[72–74]



(19)

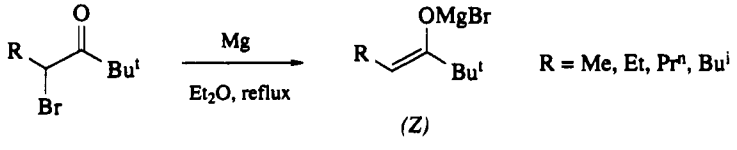


(20)



(21)

α-Bromocarbonyl compounds react with magnesium to give bromomagnesium enolates (equations 22 and 23),[75,76] and silyl enol ethers can be cleaved with methylmagnesium bromide (equation 24).[63]



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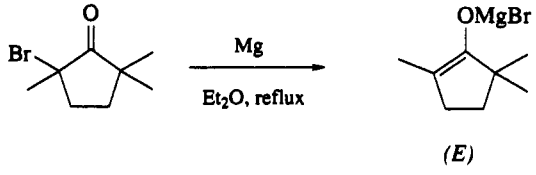

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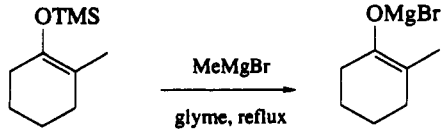
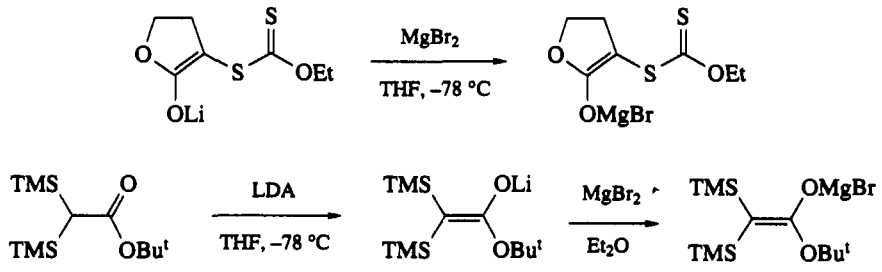
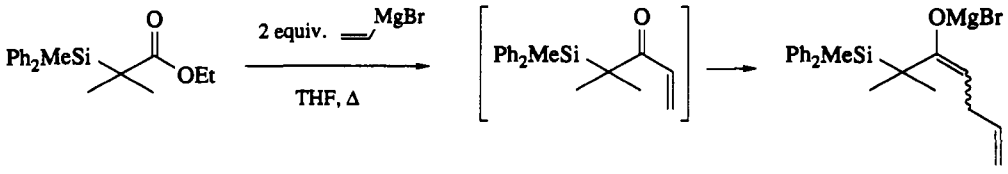


(24)



Scheme 22



Scheme 23

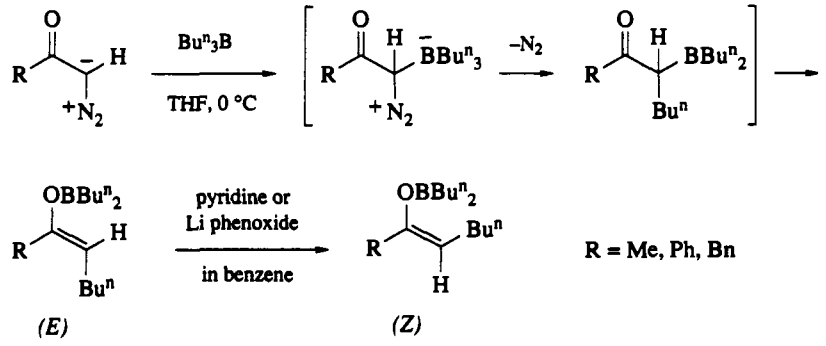
An important practical route involves the transmetallation reaction between lithium enolates and $MgCl_2$ or $MgBr_2$ (Scheme 22).[77,78] However, in such cases the true nature of the reactant (Li or Mg or both?) is obscured.

A different type of reaction is the addition of two equivalents of vinyl Grignard reagent to an ester. This involves a conjugate addition to a sterically hindered ketone in the second step (Scheme 23).[79]

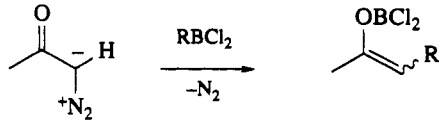
1.4.4 BORON ENOLATES

Boron enolates (other names are vinyloxyboranes, enol borinates, or boron enol ethers) are often employed in the aldol reaction because they show higher stereoselectivity than alkali and magnesium enolates. Extensive developmental work in this area has been carried out by Evans, Masamune and Mukaiyama, and their respective coworkers.[14–16,80,81] The correspondence between enolate geometry and aldol stereochemistry is exceptional: (*Z*)-enolates give *syn/erythro* aldol products, whereas (*E*)-enolates give *anti/threo* aldol products, albeit with slightly lower selectivity.

Hooz *et al.* produced boron enolates by treating α-diazo ketones with substituted boranes. Tri-*n*-butylborane gave almost exclusively the (*E*)-enolate, which could be isomerized quantitatively to the (*Z*)-enolate by a catalytic amount of pyridine or lithium phenoxide (Scheme 24).[82] This method has the disadvantage that only one of the three alkyl groups is utilized. If boranes with different substituents are employed, the question arises as to which substituent has the highest 'migration aptitude'. It was found that the order is aryl > alkyl > Cl (equation 25).[83] A hydride can be transferred, if a dialkylborane is used. Dicyclohexylborane proved to be the most efficient reagent to synthesize regiospecifically a terminal enolate (equation 26).[84] In a similar reaction, boron enolates can be obtained from α-halogen alkali enolates[85,86] and sulfur ylides.[87]



Scheme 24



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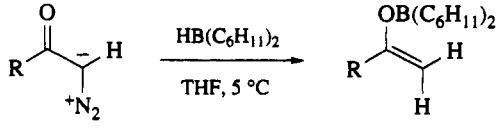

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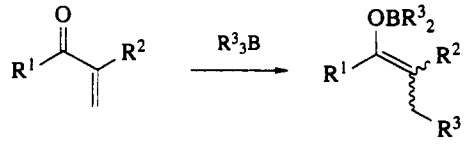

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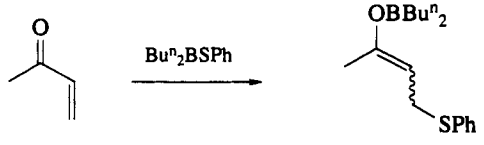
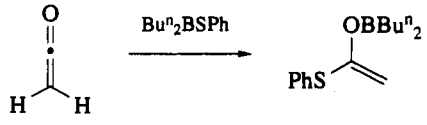


(28)

α,β-Unsaturated carbonyl compounds react with boron reagents solely through conjugate addition (equations 27 and 28).[88–90] The enolate stereochemistry, (*E*) or (*Z*), depends on the enone substituents but without useful trends in stereochemical control.[89]

Boron enolates can be formed with good stereoselectivity by the reaction of ketenes with dibutylthioborinates (equations 29 and 30).[90–92]



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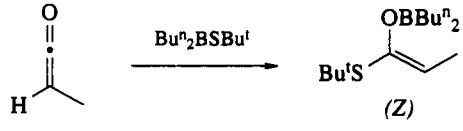
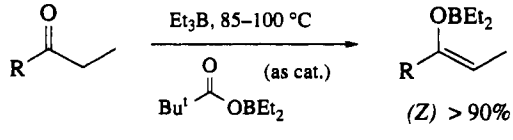


(30)

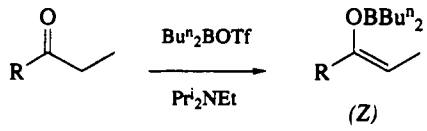
The most common route to boron enolates uses the method of carbonyl enolization. Köster and coworkers employed triethylborane with diethylboryl pivalate as a catalyst under vigorous conditions, which probably led to the thermodynamic enolates (equation 31).[93,94]



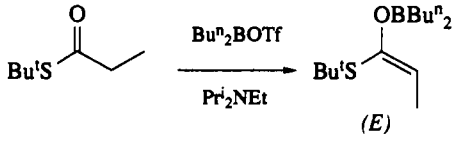
(31)

In an important experiment, Mukaiyama and coworkers enolized carbonyl compounds under much milder conditions (low temperatures) with dialkylboryl triflate and a sterically hindered tertiary amine base such as 2,6-lutidine (2,6-dimethylpyridine) or diisopropylethylamine (DPEA).[95–97] Less-hindered bases led to formation of a stable borane–amide complex (Lewis acid–Lewis base) and prevented the reaction with the carbonyl compound. Masamune *et al.*[98] and Evans *et al.*[99,100] carried out a study to investigate the reasons for the selective enolate formation. They showed that it depends on the boron ligand, base, solvent and the group attached to the carbonyl moiety. Ketones give (*Z*)-enolates with often excellent selectivity, whereas *t*-butyl thiolates give selectively the (*E*)-enolates (equations 32 and 33).[100,101] Evans suggests that reactions with 9-BBN triflate are often under thermodynamic control.[15] In equation

(34), the (*Z*)-enolate could well have arisen by equilibration of the kinetic (*E*)-enolate.[102–104] Recent examples of this type of reaction often employ chiral carbonyl compounds or chiral boranes to get enantioselective aldol products (equations 35 and 36).[105–110]



R = Et, Bu^s, Ph, Bu^t (32)



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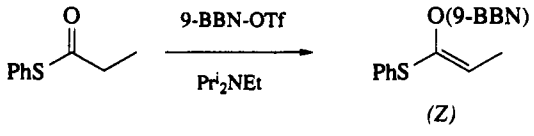

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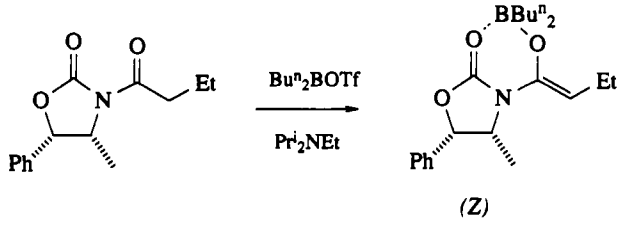
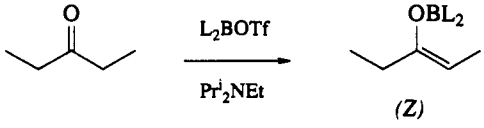
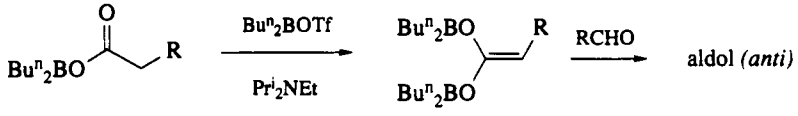


(35)

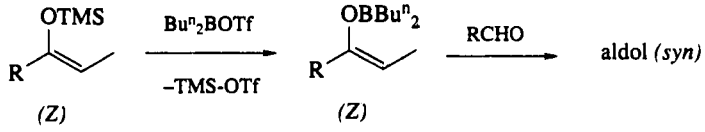


L$_2$BOTf = (–)-(Ipc)$_2$BOTf
(+)-(Ipc)$_2$BOTf
Ipc = diisopinocampheyl (36)

Simple alkyl esters do not react with boryl triflate reagents, but acyloxyboranes give diborane enediolates under these conditions (Scheme 25).[15] These diborane enediolates usually give more *anti* aldol than *syn* aldol product. Because aldol geometry depends on enolate geometry, it can be inferred that (*E*)-boron enolates are somewhat more reactive than the (*Z*)-isomers.



Scheme 25

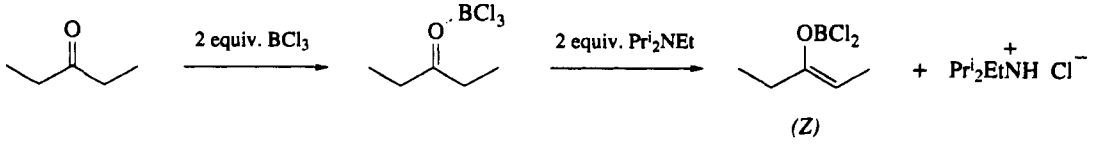


Scheme 26

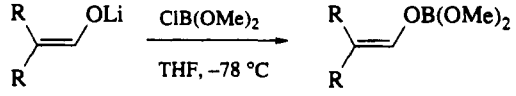
Trimethylsilyl enol ethers react rapidly with boryl triflate reagents (Scheme 26).[111,112] Subsequent aldol reaction occurs with apparent stereospecificity provided that the by-product trimethylsilyl triflate is

removed before the addition of the aldehyde. This seems to be a useful reaction for the synthesis of boron enolates that are not accessible by other methods, but the boryl triflate reagents are ineffective with trimethylsilyl enol ethers of amides and esters.

Trichloroborane reacts with ketones to form a complex. Subsequent addition of DPEA leads to a dichloroboron enolate (Scheme 27).[114] If the trichloroborane and DPEA are added at the same time, direct complex formation will preclude reaction of the ketone.



Scheme 27

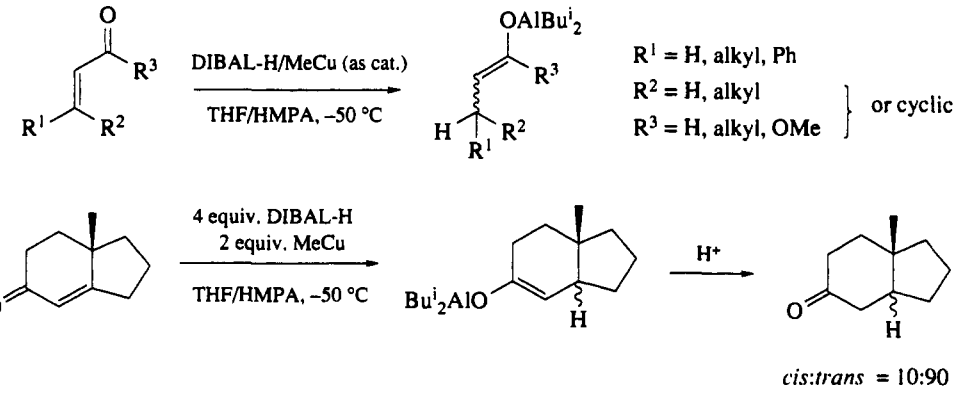


(37)

Lithium enolates react with chlorodimethoxyborane to give dimethoxyboron enolates (equation 37).[113]

1.4.5 ALUMINUM ENOLATES

Aluminum enolates can be formed by conjugate addition with diisobutylaluminum hydride (DIBAL-H) and a catalytic amount of methylcopper in a mixture of THF and HMPA (Scheme 28).[115–117] The role of copper and HMPA is crucial, for without these 1,2-reduction of the carbonyl group takes place. The effect of copper(I) on conjugate addition is not unexpected. In regard to the solvents it is suggested that HMPA functions not as a cosolvent but as an essential ligand. Treatment of an α,β-unsaturated ketone with trimethylaluminum and a catalyst leads to a dimethylaluminum enolate with moderate (*E*)/(*Z*) selectivity. The (*Z*)-enolate reacts with diphenylketene to give another enolate (Scheme 29).[118,119]

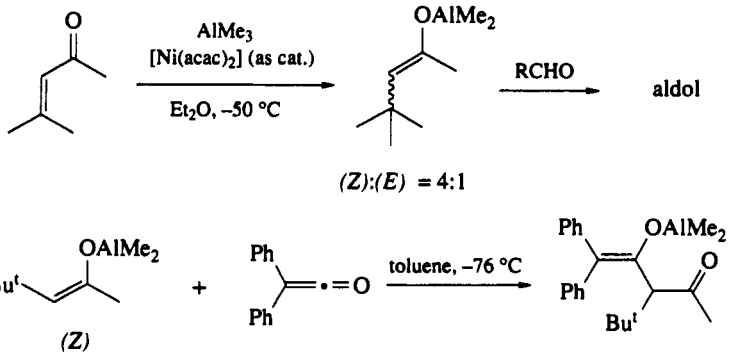


Scheme 28

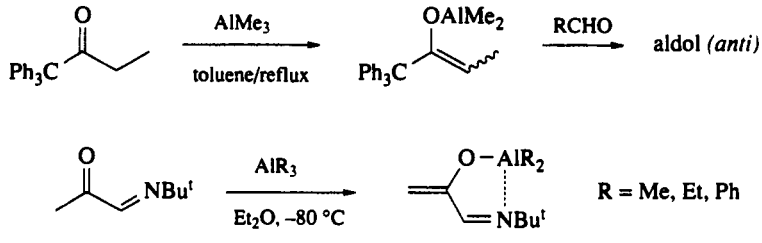
Another route to aluminum enolates is through the reaction of ketones with a trialkylaluminum, usually trimethylaluminum (Scheme 30).[120,121]

Aluminum enolates can be obtained also by transmetallation of lithium enolates (Scheme 31).[73]

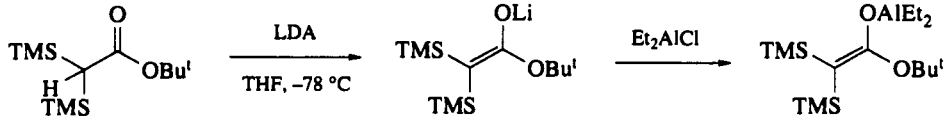
Diethylaluminum enolates can be produced regiospecifically through reaction of diethylaluminum chloride and zinc dust with α-bromo ketones and esters (Scheme 32).[122] Obviously zinc is involved in this reaction, but the mild conditions are in sharp contrast to the Reformatsky reaction and support the existence of an aluminum enolate in this process. The same type of enolate can be obtained from *t*-butyl acetates and diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), which is generated *in situ* from diethylaluminum chloride and LITMP (Scheme 33).[123]



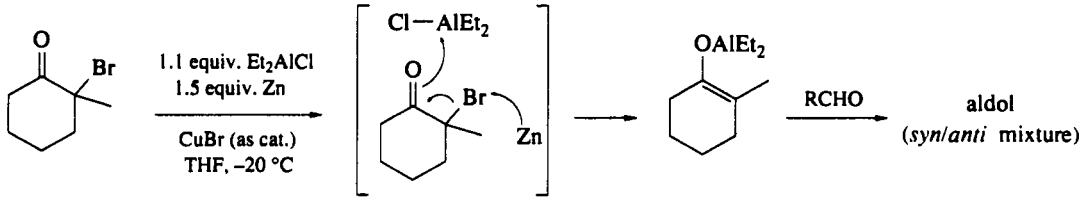
Scheme 29



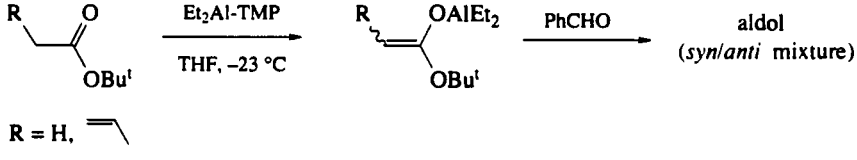
Scheme 30



Scheme 31

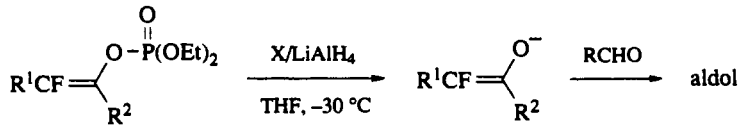


Scheme 32

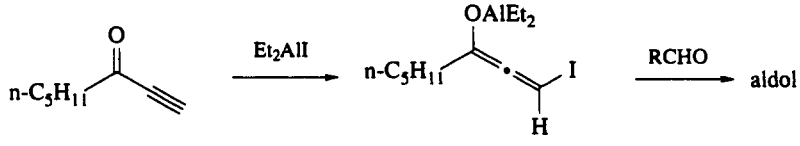


Scheme 33

Fluorinated enolates are generally difficult to form. Ishihara and coworkers used fluorovinyl phosphates, which can be prepared from α-fluoro ketones and sodium diethyl phosphite. Reaction of these fluorinated enol phosphates with a reagent prepared from lithium aluminum hydride ($LiAlH_4$) and copper(II) bromide, zinc(II) chloride, tin(II) chloride or bromine afforded the enolate (Scheme 34).[124] The reaction of the enol phosphate with the reagents mentioned above suggests that the metal cation of the enolate is an aluminum species, though its actual structure is not known at present.



Scheme 34

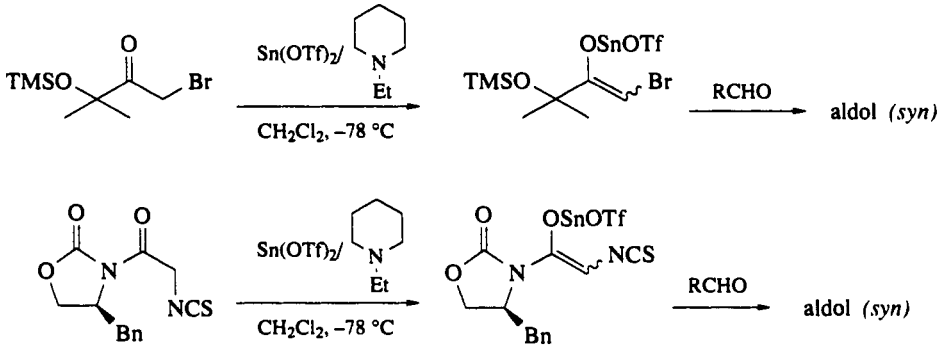


Scheme 35

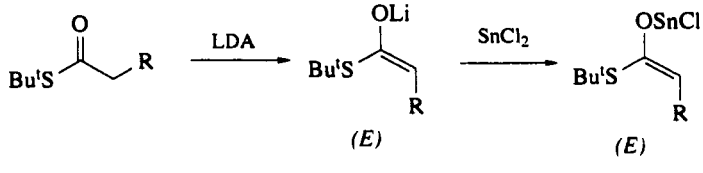
The reaction of α,β-alkynic ketones with diethylaluminum iodide gives allenolates by 1,4-addition (Scheme 35).[125] These intermediates can react with aldehydes to give aldol-type products.

1.4.6 TIN ENOLATES

Tin(II) enolates can be generated by more than one method (for reviews see refs. 75 and 126). The most common is the method of Mukaiyama:[127-141] ketones and amides react with tin(II) triflate and *N*-ethylpiperidine in methylene chloride at low temperatures to give tin(II) enolates which can have various substituents in the α-position. These divalent tin enolates have either (*Z*) or unknown configuration and produce predominantly the *syn/erythro* aldol products (Scheme 36).[127-136]

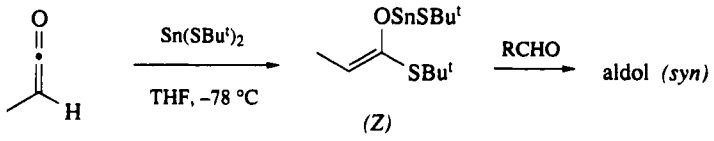


Scheme 36

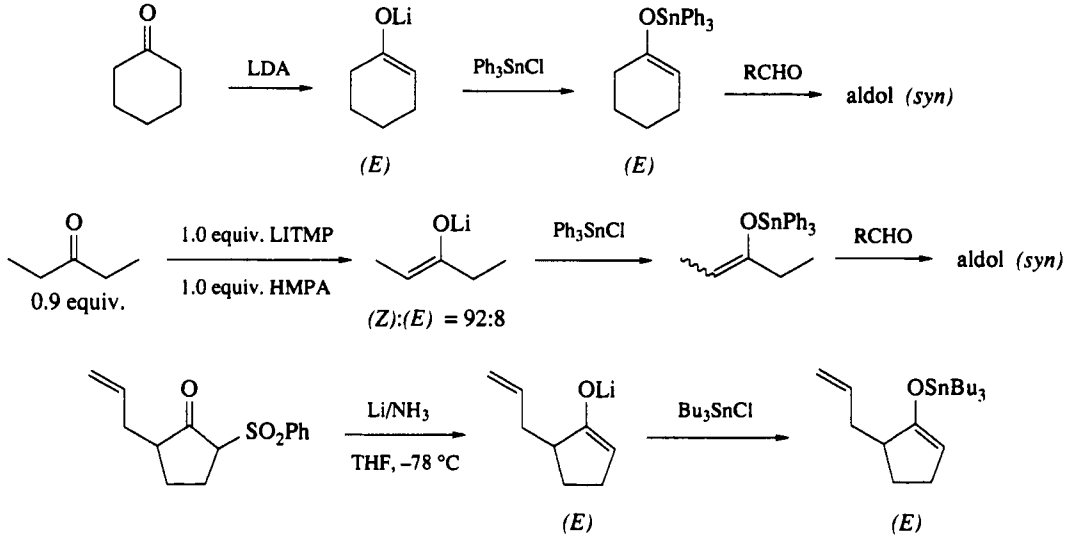


Scheme 37

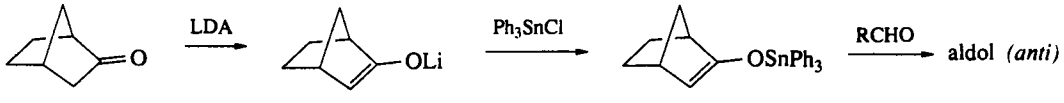
Another method is the reaction of lithium enolates with tin(II) chloride, tin(II) bromide or tin(II) triflate (Scheme 37).[142,143] During the transmetallation reaction, the geometry of the enolate is believed to be unchanged.[143]



Scheme 38



Scheme 39



Scheme 40

The reaction of ketenes with tin(II) thiolates gives tin(II) thioester enolates with (*Z*)-configuration (Scheme 38).[144,145]

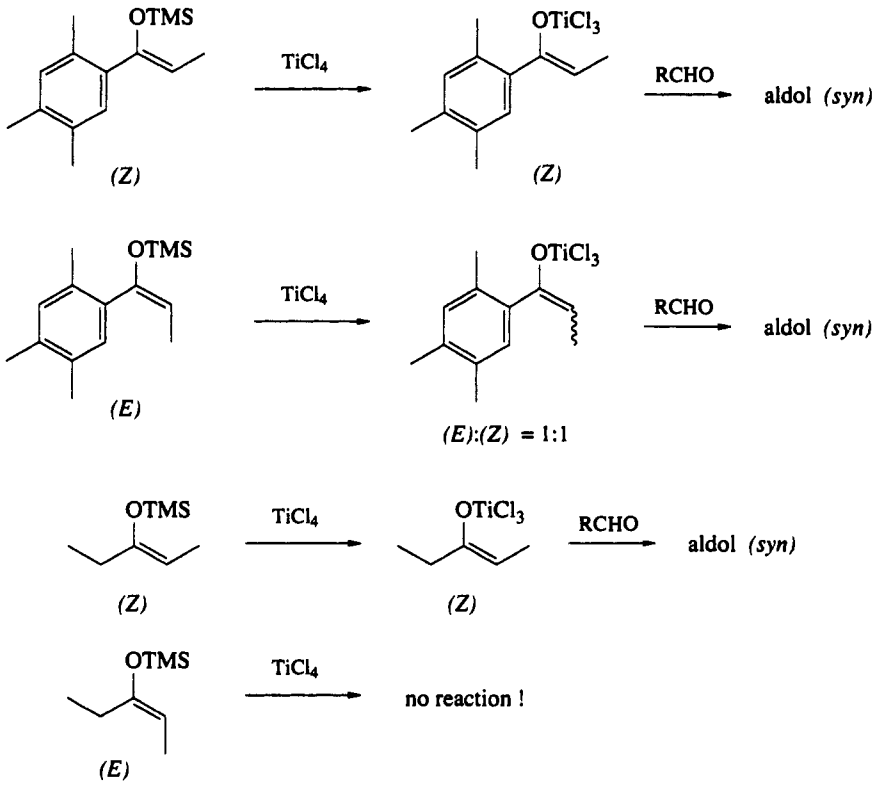
Tin(IV) enolates are generated by the reaction of lithium enolates with trialkyltin chlorides.[77,136,146,147] The best stereoselectivity in the aldol reaction with tin(IV) enolates has been achieved by employing triphenyltin chloride. *Syn/erythro* aldol products were predominantly produced irrespective of the geometry of the starting enolates (Scheme 39).[146,147] However, the aldol condensation *via* the enolate derived from norbornanone gave the *anti/threo* product predominantly (Scheme 40).[146]

1.4.7 TITANIUM ENOLATES

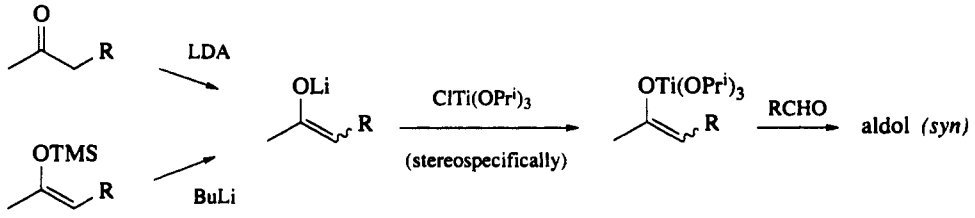
The Mukaiyama version of the aldol reaction is well known:[75] a carbonyl–titanium tetrachloride complex reacts with a trimethylsilyl enol ether. Under these conditions there is *no* titanium enolate involved. Another procedure has been reported:[148–150] a trimethylsilyl enol ether reacts with titanium tetrachloride to give the titanium enolate; addition of the carbonyl compound generates the aldol product (although with slightly lower diastereoselectivity than with Mukaiyama's procedure). (*Z*)-Enolsilanes from acyclic ketones react rapidly and stereospecifically with $TiCl_4$ to form (*Z*)-configured Cl_3Ti enolates, while the (*E*)-isomers react slowly to afford low yields of mixtures of (*E*)- and (*Z*)-Cl_3Ti enolates (Scheme 41).[149]

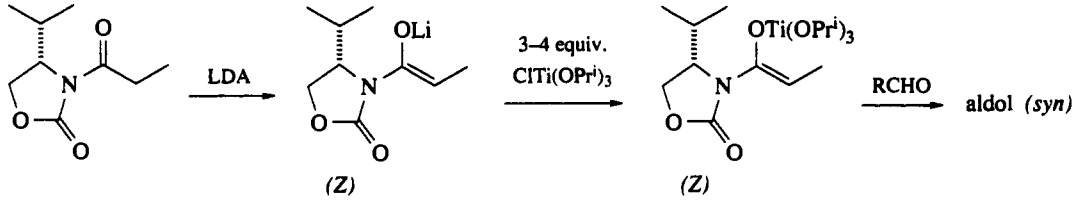
Another way of generating titanium enolates is the reaction of lithium enolates with titanium salts [$ClTi(OPr^i)_3$;[151–154] $ClTi(NEt_2)_3$;[153] $ClTi(NMe_2)_3$[153]]. The ratio of (*E*)- and (*Z*)-enolate remains unchanged in the exchange process (Scheme 42).

Titanium enolates generated with bis(cyclopentadienyl)titanium dichloride show *anti/threo* selectivity (Scheme 43),[155] although the corresponding zirconium enolates (*vide infra*) react *syn* selectively.

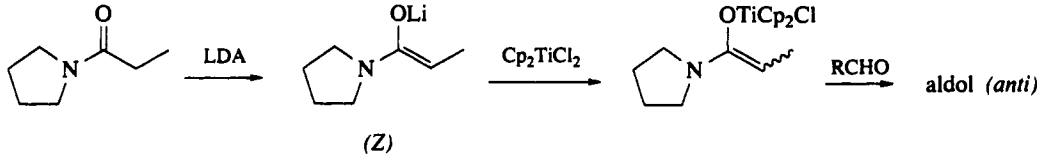


Scheme 41





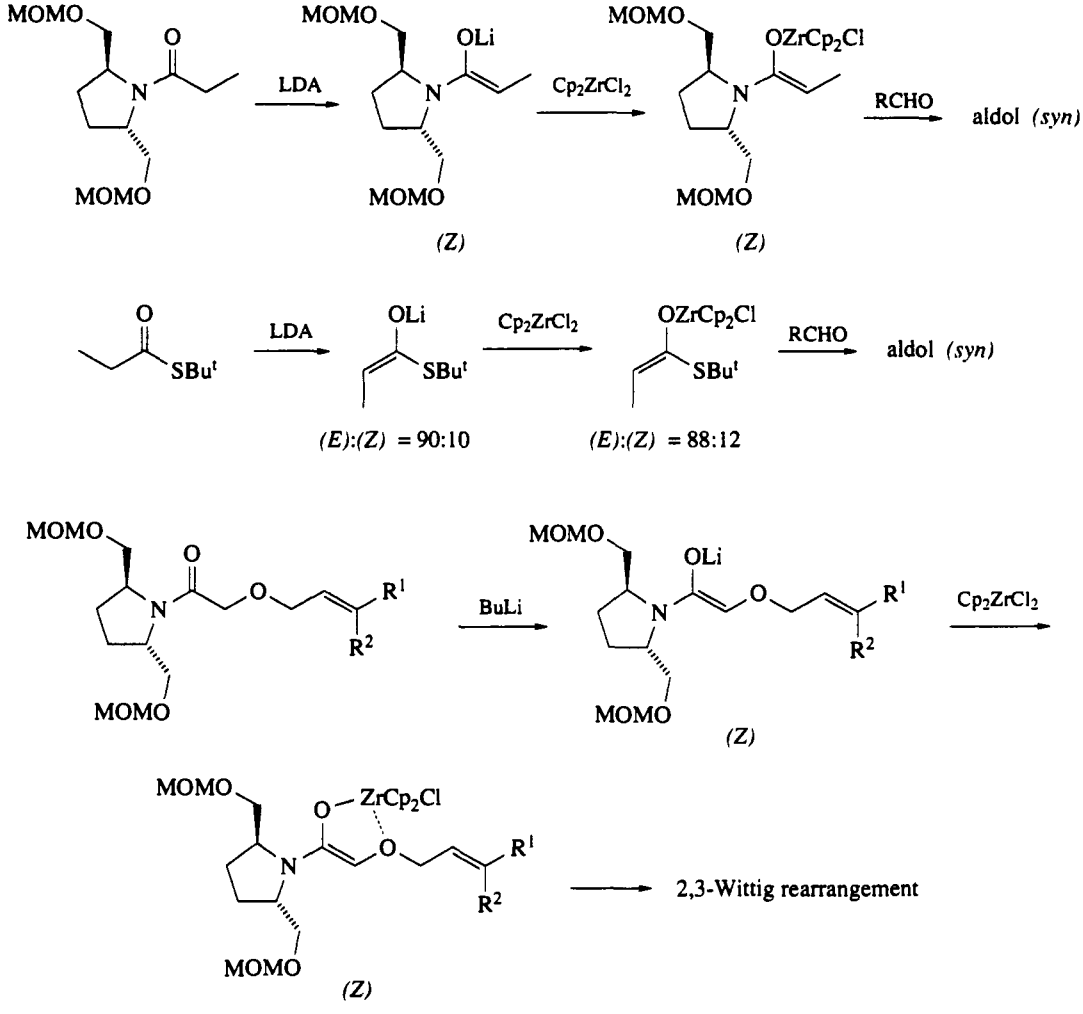
Scheme 42



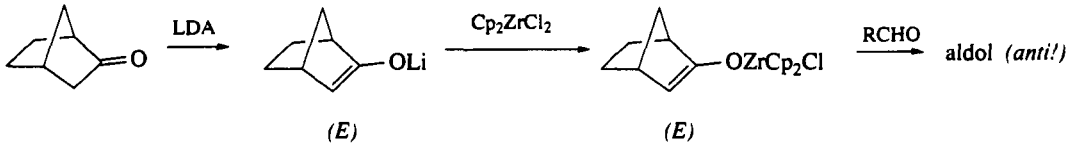
Scheme 43

1.4.8 ZIRCONIUM ENOLATES

Zirconium enolates are formed by reaction of the corresponding lithium enolates with bis(cyclopentadienyl)zirconium dichloride.[146,156–163] Complete retention of enolate geometry accompanies the metal exchange.[156,157] Both (*E*)- and (*Z*)-zirconium enolates have been shown to undergo selective kinetic aldol condensation to give mainly *syn/erythro* products (Scheme 44).[156–160] Again, the enolate derived from norbornanone provides an exception to the rule (Scheme 45).[146]



Scheme 44

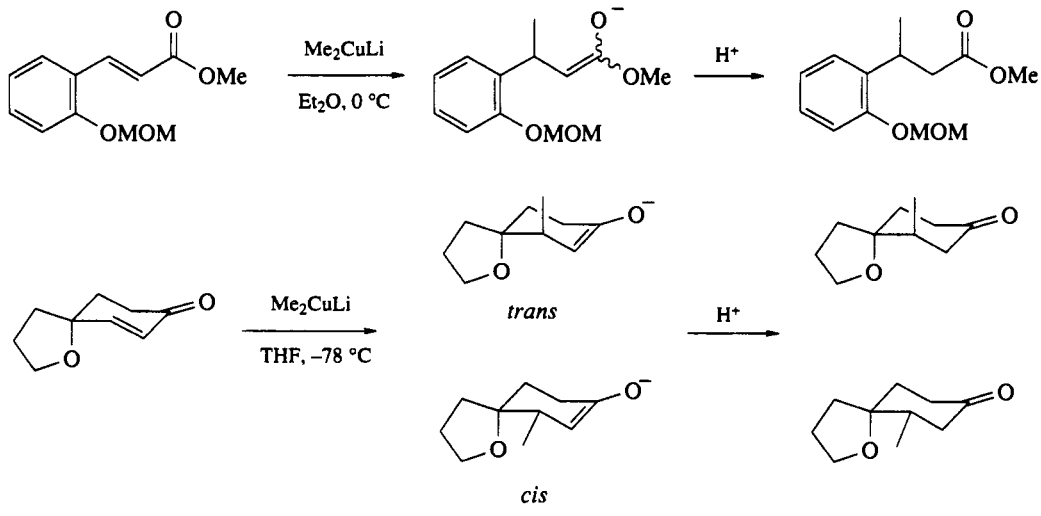


Scheme 45

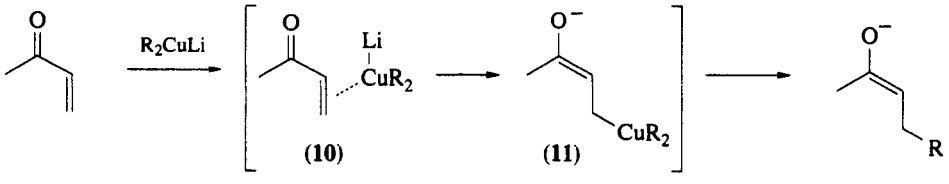
1.4.9 COPPER ENOLATES AND ENOLATES FROM CUPRATES

Conjugate addition to an α,β-unsaturated carbonyl compound is achieved routinely by using a lithium organocopper reagent or a copper-catalyzed Grignard reaction.[164–168] It should be noted that in many of these examples, and in particular in the case of lithium diorganocuprates, the resultant enolate has

properties most consistent with a lithium enolate, and the reactivity of these enolates is unaffected by soluble copper(I) salts.[169] The chemist who desires to generate authentic copper enolates would better avoid the use of lithium- or magnesium-ion-containing reagents. In this section, however, some discussion of lithiocuprate reagents is included. The reagent Me_2CuLi is often used (Scheme 46).[171,173] There has been considerable work done to reveal the mechanism of this reaction (Scheme 47). Now it seems to be certain that the first intermediate between the α,β-unsaturated carbonyl and the cuprate is a *d,p**-complex (**10**), and this is followed by a copper(III) β-adduct (**11**).[170–174]

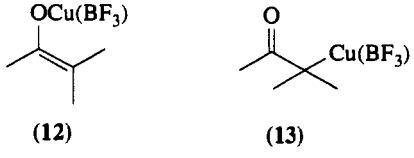


Scheme 46



Scheme 47

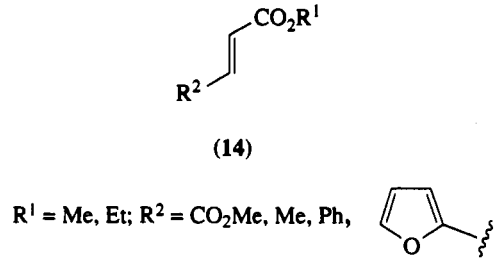
An authentic copper enolate can be prepared by an alternative route, which involves the conjugate addition of $BuCu(BF_3)$.[175] Experimental results indicate clearly that the intermediate is a copper-bonded enolate (**12**) rather than an α-cupriocarbonyl derivative (**13**).



The addition of lithium diallylcuprate to α,β-unsaturated carbonyl compounds is highly substrate dependent. Good yields can only be obtained with doubly activated esters as shown in (**14**) and (**15**).[176,177]

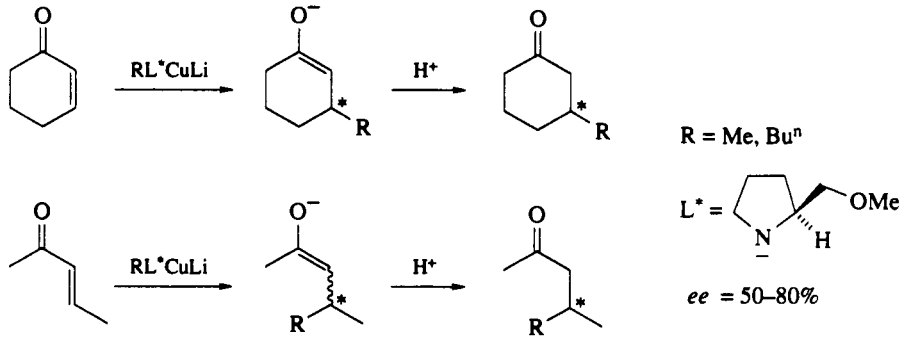
The importance of the conjugate addition has prompted numerous searches for procedures and methods to effect asymmetric induction.[178–182] One recent example is the use of (*S*)-2-(methoxymethyl)pyrrolidine as a chiral copper ligand (Scheme 48).[181]

One of the mildest and most efficient reactions for effecting conjugate addition to α,β-unsaturated ketones is the use of the so-called 'mixed higher order cuprates' $R_2Cu(CN)Li_2$ and $RMeCu(CN)Li_2$. The latter have the advantage that 100% of the alkyl groups can be transferred (Scheme 49).[183–186]

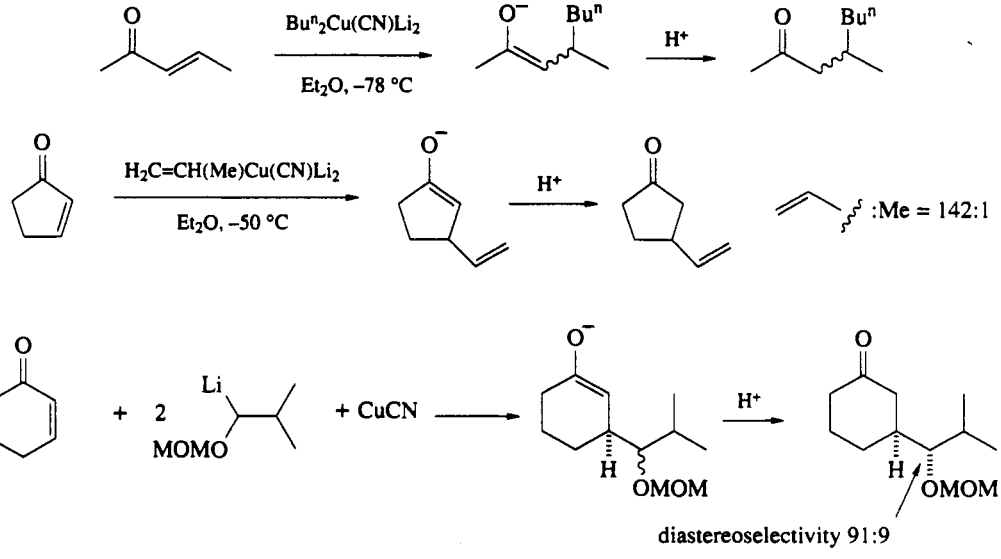


(14) (15)

R^1 = Me, Et; R^2 = CO_2Me, Me, Ph,



Scheme 48

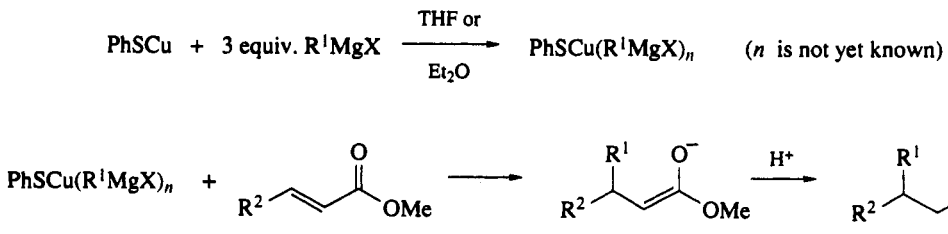


Scheme 49

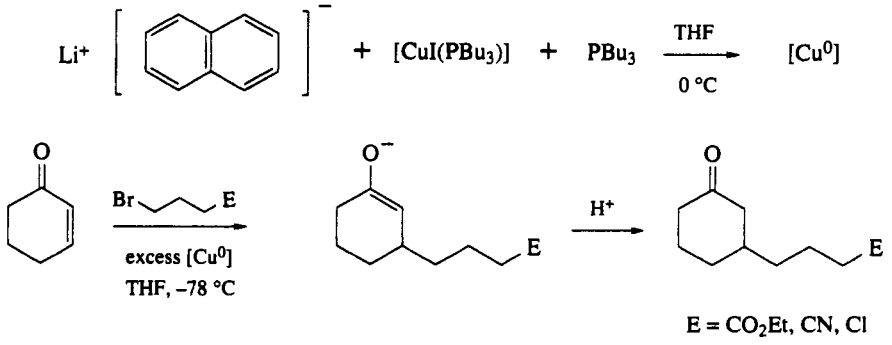
The use of the mixed lithium phenylthio(alkyl)cuprates, PhSCuRLi, for conjugate addition to α,β-unsaturated carbonyl compounds is well known.[187,188] The reaction of phenylthiocuprates derived from Grignard reagents with cinnamates and crotonates has also been reported (Scheme 50).[189]

Another method to generate copper enolates through conjugate addition is the use of alkyl bromides and highly reactive zerovalent copper prepared by lithium naphthalide reduction of the CuI–PBu_3 complex (Scheme 51).[190,191] The activated copper inserts directly into the carbon–halogen bond. The exact nature of the active copper and of the subsequent organocopper species is unknown. The advantage of this method is that the alkyl bromides can contain remote ester, nitrile, or chloride functionalities.

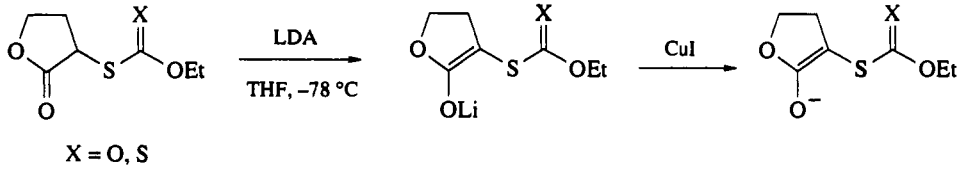
Finally, copper enolates of an α-thio lactone have been generated by the reaction of a lithium enolate with copper iodide (Scheme 52).[77]



Scheme 50



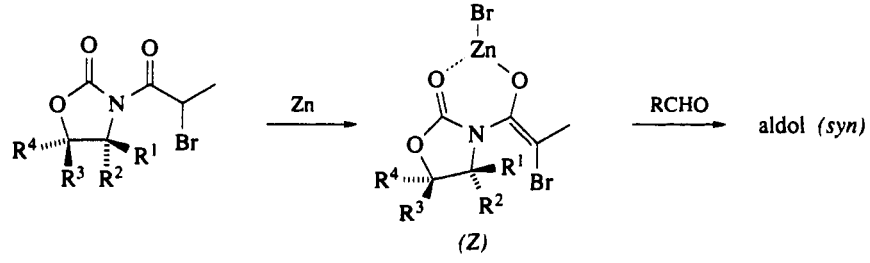
Scheme 51



Scheme 52

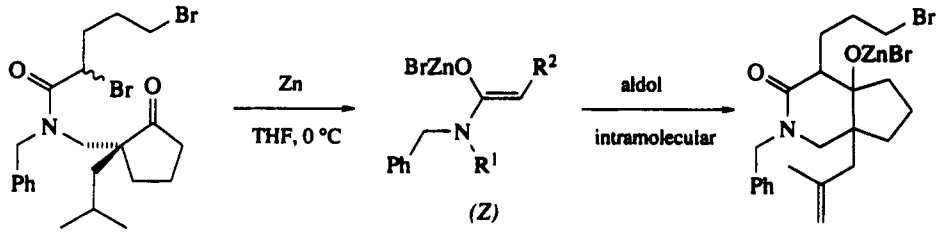
1.4.10 ZINC ENOLATES

The Reformatsky reaction has been known for over 100 years: α-bromo esters, ketones and amides react with activated zinc dust to give zinc enolates, which can react with carbonyl compounds to give aldol-type products.[192–194] Recent examples include the reactions with sterically crowded oxazolidone



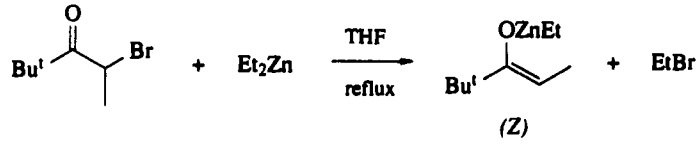
Scheme 53

derivatives, which give predominantly *syn* aldol products (Scheme 53),[197,198] and an intramolecular reaction (Scheme 54).[199] A zinc ester enolate has been observed to have a dimeric structure containing both Zn—O and Zn—C bonds.[195,196]

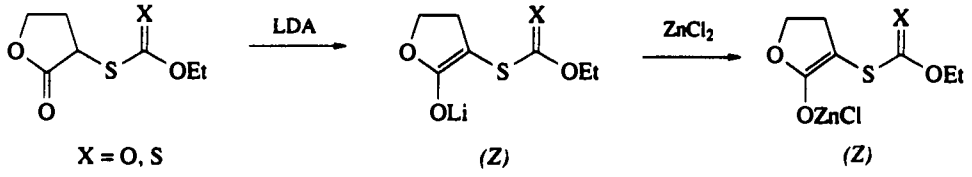


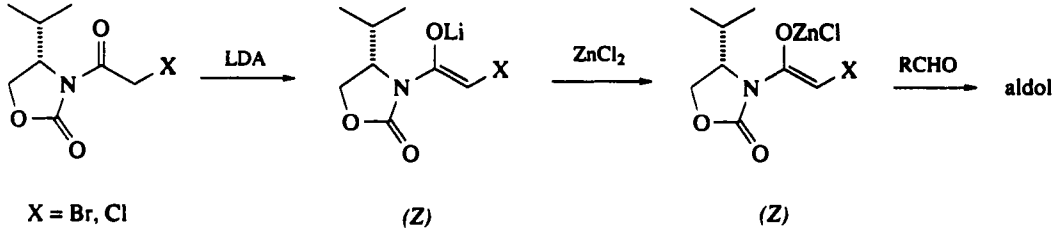
Scheme 54

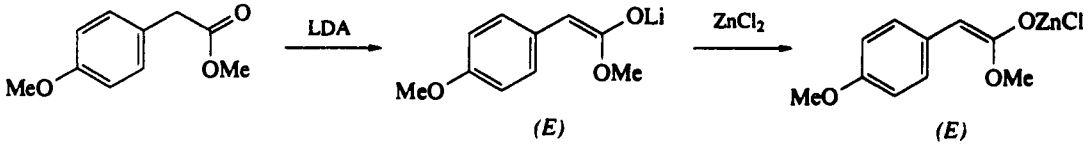
The reaction of α-bromo ketones with diethylzinc leads to an ethylzinc enolate (equation 38).[200]

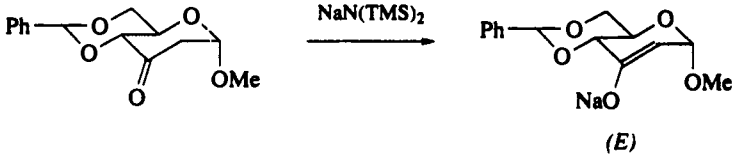


(38)





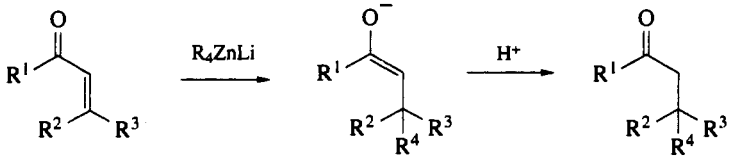




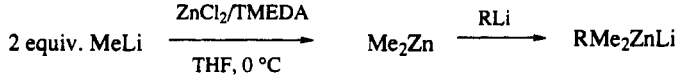
Scheme 55

A common way to generate zinc enolates, introduced by House,[201] is the reaction of (usually) lithium enolates with zinc chloride or zinc bromide (Scheme 55).[77,136,202,203] Boersma's experiments showed that the second chlorine atom could not be replaced with an excess of lithium enolate.[204]

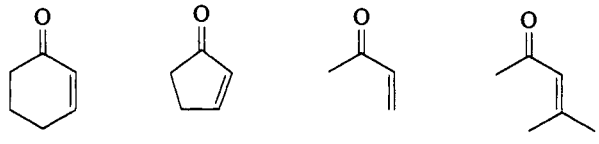
Lithium triorganozincates, R_3ZnLi, are known to effect 1,4-addition of alkyl groups to α,β-unsaturated ketones (Scheme 56).[205–208] They are an attractive alternative to the lithium diorganocuprates because of their solubility and thermal stability. A disadvantage of this method is that only one alkyl ligand can be transferred; the other two are lost. Mixed zincates of the type $R^1R^2_2ZnLi$, where R^2 is methyl, are very effective for circumventing this problem.[209] The R^1 group undergoes efficient 1,4-addition to α,β-unsaturated ketones, but the methyl groups (R^2) remain untransferred. The reactions with ketones (**16**) to (**18**) work well, when the transferring ligand is *n*-butyl or *s*-butyl, but ketones that are disubstituted on the β-carbon (**19**) give no 1,4-adduct. The mixed zincates are generated from methyllithium, zinc chloride and the lithiated transfer group (Scheme 57).[209]



Scheme 56

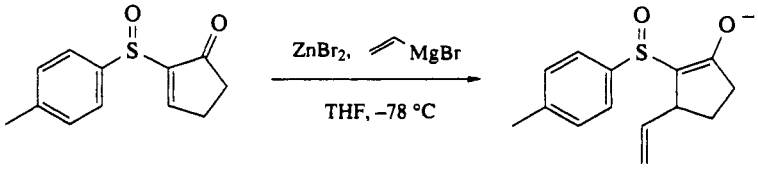


Scheme 57

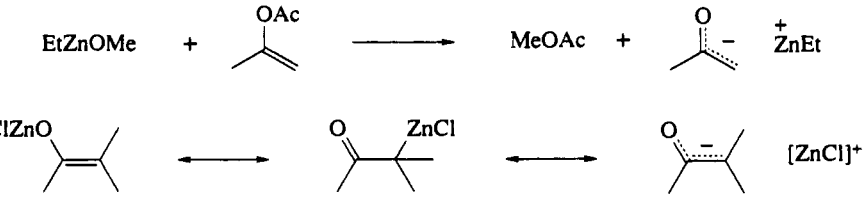


(16) **(17)** **(18)** **(19)**

A similar type of reaction has been conducted with $ZnCl_2$–TMEDA and 3 equiv. of a variety of Grignard reagents.[210] The experiments offer no real evidence for the existence of R_3ZnMgX (X = Cl, Br). The formula 'R_3ZnMgX' denotes only the stoichiometry involved in preparing the solutions used. Reactions of ketones (**16**) to (**18**) with 'R_3ZnMgX' (R = *n*-butyl, isopropyl, phenyl) give excellent yields of 1,4-adduct and usually less than 3% 1,2-adduct. Ketone (**19**) fails to react here, too (see above). An example with similar reagents to achieve 1,4-addition is shown in equation (39).[211]



(39)



(40)

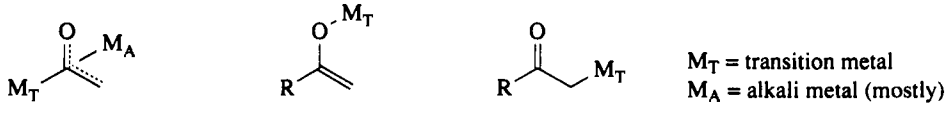
Scheme 58

The exchange reaction between ethylzinc methoxide and enol acetates affords ethylzinc enolates, which decompose by polymerization or by reaction with the methyl acetate produced in the exchange reaction (equation 40).[204]

Although zinc ketone enolates are generally considered to exist with an oxygen-bound rather than a carbon-bound metal, there is still some controversy. Boersma assumes that they contain both zinc–carbon and zinc–oxygen bonds (Scheme 58).[204] One indication that they contain only an oxygen–metal bond in solution is that the ^{13}C NMR data for zinc enolates are similar to the data for alkali metal enolates.[200]

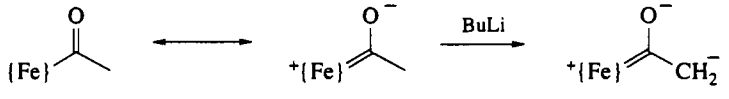
1.4.11 OTHER TRANSITION METAL ENOLATES

Three different types of transition metal enolates are known:[212,213] metallaenolates (**20**); enolates with *O*-bonded (**21**) metals; and enolates with *C*-bonded (**22**) metals.

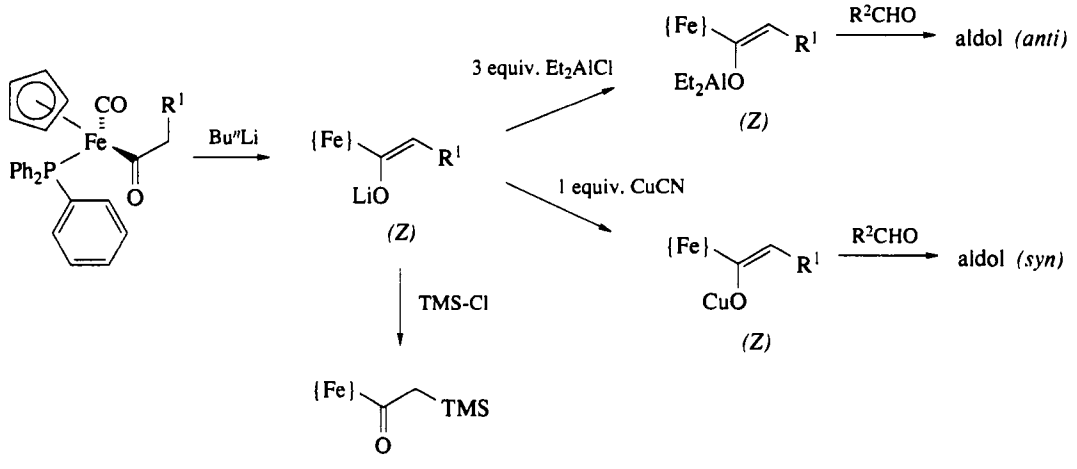


(20) **(21)** **(22)**

Metal–acyl complexes of iron, cobalt and rhenium have been reported to react with strong bases (BuLi or LDA) to give lithium enolates. Reaction of these enolates with various metal salts generates enolates with different countercations through transmetallation. These enolates are called metallaenolates (**20**). They are somewhat different from the usual enolates:[214–216] (i) they undergo *C*- rather than *O*-silylation; and (ii) very strong bases are needed to generate them, indicating that an ionic resonance form makes a significant contribution to the structure (Scheme 59).

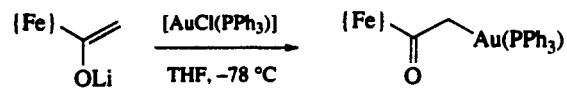


Scheme 59

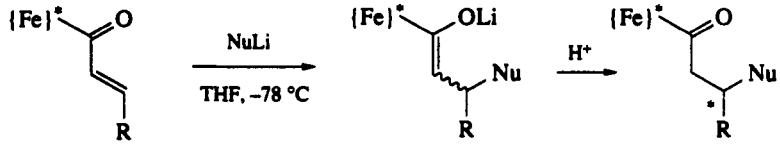


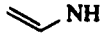
Scheme 60

Enolates of iron–acyl complexes have been studied extensively, especially by Davies and Liebeskind and their respective coworkers. The chiral complex [η^5-CpFe(PPh$_3$)(CO)COCH$_2$R] is usually used; it can be prepared in racemic or optically active form. The enolate usually has the *anti* conformation with regard to CO and O$^-$.[217–223] Copper (*Z*)-enolates give predominantly *syn* aldols, whereas diethylaluminum (*Z*)-enolates produce *anti* aldols (Scheme 60).[224,225] If R^1 = H, the terms *syn* and *anti* make no sense

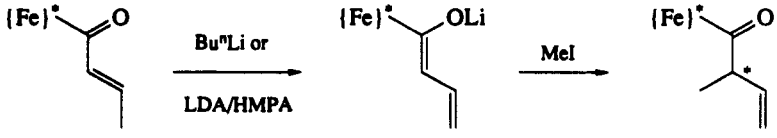


(41)



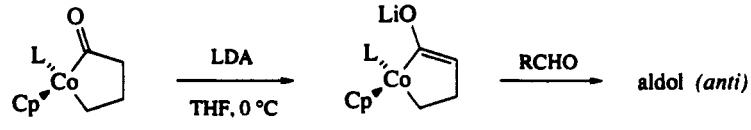
Nu = Bu, Ph, BnNH, 

Scheme 61

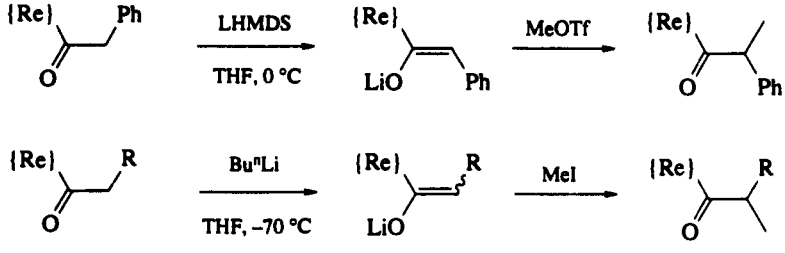


(Z) major

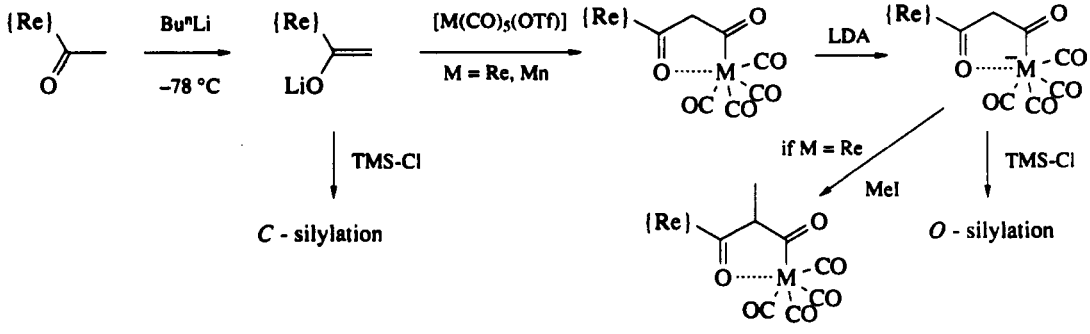
Scheme 62



Scheme 63



R = H, Ph

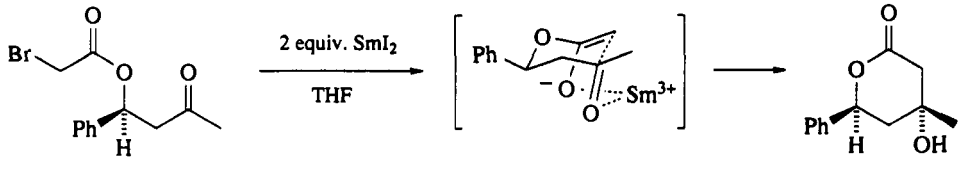


Scheme 64

anymore, but two diastereomers are distinguishable.[226–228] Bu^i_2Al, ClSn and BrSn enolates produce one diastereomer with good selectivity. A *C*-bonded enolate of an iron–acyl complex can be generated with [AuCl(PPh3)] (equation 41).[229] Another way to these enolates is the diastereoselective conjugate addition of nucleophiles to chiral α,β-unsaturated acyl complexes of [η^5-CpFe(PPh3)(CO)] (Scheme 61)[230] or the deprotonation of these with Bu^nLi or LDA–HMPA (Scheme 62).[231,232]

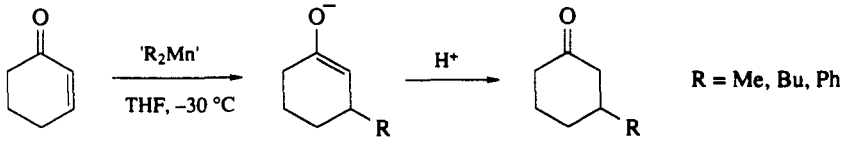
Cyclic cobalt–acyl complexes can be deprotonated, and subsequent reaction of these enolates with aldehydes gives predominantly the *anti/threo* product (Scheme 63).[233] Rhenium–acyl complexes can be deprotonated in the same manner. These lithium enolates can be alkylated or can react with [$M(CO)_5(OTf)$] (M = Re, Mn) to give the corresponding enolates (Scheme 64).[234,235]

Many transition metal enolates of type (**21**) or (**22**) are known,[212,213,236] but only a few have shown 'normal enolate behavior', *e.g.* aldol reaction, reaction with alkyl halides, *etc.* Particularly useful examples have been developed by Molander. In a process analogous to the Reformatsky reaction, an α-bromo ester may be reduced with SmI_2 to provide excellent yields of condensation products (Scheme 65) which are generated through intermediacy of a samarium(III) enolate.[237]



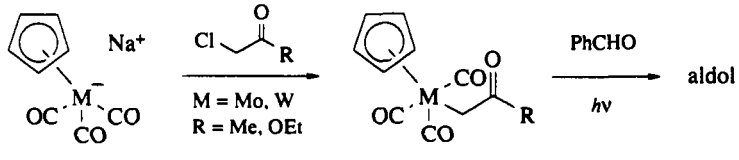
Scheme 65

A manganese reagent prepared from RLi or RMgCl and $MnCl_2$ reacts with cyclohexenone in a 1,4-addition (Scheme 66).[238,239] The structure of the reagent is not known and the formula (*e.g.* 'R_2Mn') is attributed based upon the ratio of the reactants.

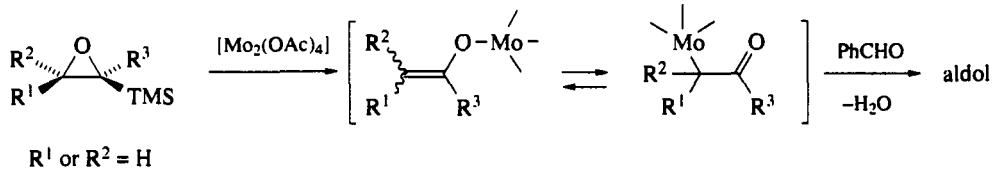


Scheme 66

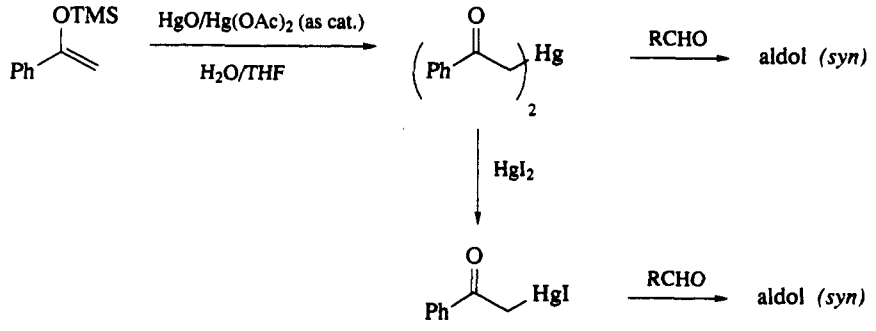
Molybdenum and tungsten *C*-enolates can be generated by reaction of complexes with α-chlorocarbonyls (Scheme 67).[212,213] These 2-oxaallyl(η^1-*C*-enolate) complexes react with aldehydes in a photoreaction to produce aldol products, by way of the η^3-enolate.



Scheme 67



Scheme 68



Scheme 69

α,β-Epoxysilanes react with molybdenum(II) acetate dimer to give presumably an enolate intermediate, which can subsequently undergo aldol reaction (Scheme 68).[240]

α-Mercurio ketones (*C*-bonded enolates) can be generated by the reaction of trimethylsilyl vinyl ethers with mercury(II) oxide, followed sometimes by further reaction with mercury(II) iodide (Scheme 69).[241,242]

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1.5
The Aldol Reaction: Acid and General Base Catalysis

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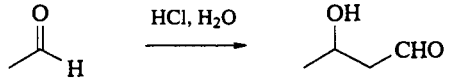
1.5.1 INTRODUCTION

An 'aldol' reaction is the reaction of one carbonyl compound, acting as a nucleophile in the form of its enol or enolate derivative, with another, acting as an electrophile. The two carbonyl compounds may or may not be the same. The general reaction is subject to either acid or base catalysis. The initial product is a β-hydroxycarbonyl compound. Under some conditions, this primary product undergoes dehydration, resulting in an α,β-unsaturated carbonyl compound. In this chapter, we summarize the aldol reaction from a historical perspective and point out the limitations of the reaction as it was generally used prior to about 15 years ago.[1] Succeeding chapters treat the aldol reaction as it is usually practiced today, in a 'directed' manner, using 'preformed' enolates.[2] As will be seen in the sequel, an understanding of the fac-

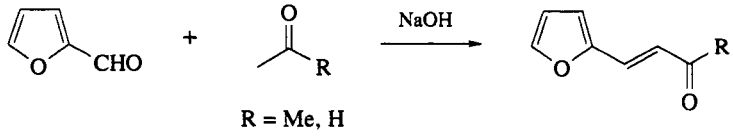
tors regulating the stereochemistry of the aldol reaction has been largely responsible for the rebirth of this venerable reaction in the last 15 years.[3]

1.5.2 BACKGROUND

The trivial name of the reaction was applied by Wurtz in 1872, and stems from the trivial name of the dimer resulting from the acid-catalyzed self-reaction of acetaldehyde (equation 1).[4] In time, the term came to be applied to the analogous self-condensation reactions of ketones, the first known example of which was the acid-mediated dimerization of acetone, discovered in 1838.[5] The first use of a base as a catalyst for the aldol reaction was in the reaction of furfural with acetaldehyde or acetone (equation 2).[6] This example also illustrates the first example of a 'mixed' aldol reaction, a process that came to be known as the Claisen–Schmidt condensation.[7]



(1)



R = Me, H

(2)

As implied in equations (1) and (2), the general reaction may give rise to a β-hydroxycarbonyl compound or to its dehydration product, the corresponding α,β-unsaturated carbonyl compound. For the first century after its christening, both processes were generally referred to as the 'aldol condensation'.[1] More recently, the latter term has been reserved for reactions leading to α,β-unsaturated carbonyl products, in keeping with the more general usage of 'condensation'.[8] In this treatise, we use the terms aldol *addition* reaction[9] for processes leading to β-hydroxycarbonyl compounds (*e.g.* equation 1) and the term aldol *condensation* for processes leading to α,β-unsaturated carbonyl compounds (*e.g.* equation 2); the term aldol reactions is used generically to apply to either kind of process.

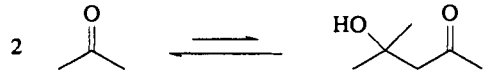
1.5.3 REVERSIBILITY OF THE ALDOL REACTION

One of the most important characteristics of the aldol reaction is its easy reversibility under many conditions. Since this factor has such a generally profound effect, we briefly introduce the topic here. For an aldol addition reaction that is carried out under the influence of a catalytic amount of acid or base in protic medium ΔH° and ΔG° can be estimated from thermochemical data. Guthrie has estimated ΔH° and ΔG° for the aldol addition depicted in equation (3) to be –9.8 kcal mol^{-1} and –2.4 kcal mol^{-1}, respectively (1 cal = 4.18 J).[10] The thermochemical values used in this estimation, and the derived values of ΔH° and ΔG°, refer to species at equilibrium with the covalently hydrated aldehydes. It is not expected that values for the free aldehydes would be greatly different. The equilibrium constant for equation (3) is 400 M^{-1}.

A similar estimate for the dimerization of acetone (equation 4) leads to an estimated ΔG° of +2 kcal mol^{-1}.[11] Other values of ΔG° for selected aldol equilibria are presented in Table 1.

The data in Table 1 are in qualitative accord with our experience with the aldol addition reaction on two counts: (1) aldol reactions in which aldehydes are receptors are often easily reversible under mild conditions; (2) aldol reactions in which ketones are receptors are invariably more easily reversible than

(3)



(4)

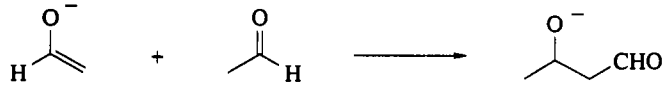
Table 1 Equilibrium Constants for Aldol Addition Equilibria[a]

Nucleophile	*Electrophile*	$\Delta G°$ (kcal mol^{-1})	K (M^{-1})
MeCHO	CH_2O	–6.32	
	MeCHO	–3.55	400
	PhCHO	–2.18	
	Me_2CO	–0.02	
	PhCOMe	+2.31	
Me_2CO	CH_2O	–4.58	
	MeCHO	–1.75	
	PhCHO	–1.27	8.5
	Me_2CO	+1.92	0.039
	PhCOMe	+4.08	
PhCOMe	CH_2O	–3.30	
	MeCHO	–0.47	
	PhCHO	+0.16	0.76
	Me_2CO	+3.00	
	PhCOMe	+5.37	
$MeCO_2H$	CH_2O	–9.84	
	MeCHO	–6.94	
	PhCHO	–6.35	
	Me_2CO	–3.39	

[a]Values for $\Delta G°$ are mostly calculated from free energies of formation of reactants. Values for K are experimental values. For more details, see ref. 12.

analogous reactions with aldehydes. The available evidence suggests that the aldol addition reaction has only a modest driving force in most cases, and in some is actually endothermic. The main structural factor that favors reversibility is steric compression in the aldol. As seen in the difference between equations (3) and (4), branching at the hydroxy carbon in the aldol results in a less favorable $\Delta H°$. Similarly, branching at the carbon between the hydroxy and carbonyl functions in the aldol promotes reversal.

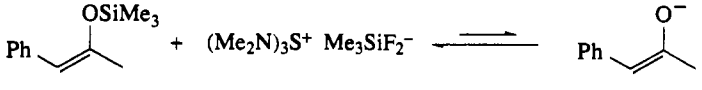
The foregoing value of $\Delta G°$ for the catalytic aldol addition reaction shows that the strong O—H bond in the product provides a significant fraction of the driving force for the reaction. For example, in equation (3) about 60% of the driving force comes from exchange of one of the acetaldehyde C—H bonds for the aldol O—H bond; this approximation assumes $\Delta H°$ for the C—H and O—H bonds to be 98 kcal mol^{-1} and 104 kcal mol^{-1}, respectively. It follows that an aldol addition reaction carried out with a preformed acetaldehyde enolate in nonprotic medium (equation 5) will be less exothermic than the catalytic version by 6 kcal mol^{-1}. In addition, one must consider the relative basicities of the two anions (or relative acidities of the corresponding conjugate acids). These are taken to be pK_a 20 for a methyl ketone and pK_a 18 for a secondary alcohol. The difference of 2 pK units contributes an additional –2.7 kcal mol^{-1} to $\Delta H°$ at room temperature. If we take the actual $\Delta G°$ of equation (3) to be –10 kcal mol^{-1}, then we can estimate that $\Delta G°$ of equation (5) is of the order of –1 kcal mol^{-1}. The preformed enolate version of equation (4) is estimated to be endothermic by about 5 kcal mol^{-1}.



(5)

Of course, under many conditions, the preformed enolate aldol reaction appears to be significantly exothermic. The additional driving force is presumably provided by the enthalpy of coordination of the ambident aldolate ion with a cation. The importance of cation solvation in providing a driving force for the aldol reaction has been elegantly demonstrated by Noyori and coworkers.[12] In this important experiment, the tris(dimethylamino)sulfonium (TAS^+) enolate of 1-phenyl-2-propanone was prepared as shown in equation (6). The 'naked enolate' was obtained as a yellow crystalline material, free of trimethylsilyl fluoride, by concentration of the THF solution.

The TAS^+ enolate reacts rapidly with acetic anhydride in THF to give the enol acetate, and with methyl iodide to give the *C*-methylated product. However, addition of benzaldehyde to the THF solution



(6)

of the naked enolate, followed by aqueous work-up, gives no aldol! If trimethylsilyl fluoride is added to the enolate + benzaldehyde solution prior to work-up, the silylated aldol is obtained. The most straightforward rationale for these observations is that the aldol addition reaction of the TAS^+ enolate is endothermic. The successful reaction in the presence of trimethylsilyl fluoride results from silylation of a small, equilibrium amount of aldolate. The driving force in this case is presumably formation of F^- and the strong Si—O bond in the reaction of the aldolate with Me_3SiF. Note that this rationale requires that the aldolate react with Me_3SiF considerably more rapidly than the enolate.

Although we do not know the precise ΔG° for preformed enolate aldol additions, the available evidence implies that such reactions are only modestly exothermic in many cases, particularly with Group I and Group II cations. As in the catalytic aldol addition, there are a number of structural features that can make the reaction less exothermic. One of these factors, demonstrated vividly in the Noyori experiment, is a weakly coordinated cation. Thus, it is found that sodium and potassium aldolates are more prone to reversal than are their lithium counterparts. Conversely, a strongly coordinated cation provides a greater driving force for reaction; examples are seen in the increased stability of boron and zinc aldolates relative to Group I analogs. Steric compression in the aldolate is another factor that makes the reaction more easily reversible. Use of a more basic enolate results in a more exothermic process, for an obvious reason. Aldolates derived from amide enolates are less prone to reversal than those derived from ketone or ester enolates. Aldol reactions involving preformed enolates are discussed in succeeding chapters in this volume.

For aldol reactions carried out under catalytic conditions, dehydration of the initial aldol may provide an additional driving force, due to formation of water (with two strong O—H bonds) and the enone system. Such reactions are almost always thermodynamically favorable.

After this chapter had been completed, there appeared a paper describing the first determination of the thermochemistry of an aldol reaction of a preformed enolate (E. M. Arnett, F. J. Fisher, M. A. Nichols and A. A. Ribeiro, *J. Am. Chem. Soc.*, 1989, **111**, 748). The enthalpy of reaction of the hexameric lithium enolate of pinacolone with pivalaldehyde in hexane at 25 °C is -30.19 ± 0.76 kcal mol^{-1}. With one equivalent of various added ligands, enthalpies of reaction are: -17.94 ± 0.36 kcal mol^{-1} in tetrahydrofuran (THF); -20.85 ± 0.72 kcal mol^{-1} in tetramethylethylenediamine (TMEDA); and -19.05 ± 0.44 kcal mol^{-1} in dimethoxyethane (DME). The product is believed to be a tetrameric lithium aldolate in each case. In view of the discussion given in this section, these reactions are surprisingly exothermic. Note, however, that one equivalent of THF makes the reaction about 10 kcal mol^{-1} *less* exothermic. The enthalpy of reaction in pure THF has yet to be determined experimentally.

1.5.4 OVERVIEW: REACTIONS UNDER PROTIC CONDITIONS

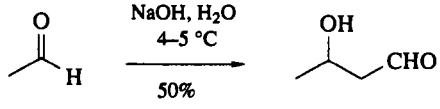
Traditionally, aldol reactions were carried out under conditions wherein the enol or enolate is generated reversibly in the presence of the electrophilic carbonyl component. Typical conditions employed sodium hydroxide in aqueous solvents, alkali metal alkoxides in the corresponding alcoholic solvents, or protic acids. Stronger bases (*e.g.* aluminum tri-*t*-butoxide) were sometimes used, but usually in the presence of both the aldol donor and acceptor molecules. When the reaction is carried out under these enol- or enolate-equilibrating conditions, there are several serious limitations, as follows: (1) Because of the modest intrinsic driving force for the reaction, self-addition processes often proceed in low yield. (2) Under enol- or enolate-equilibrating conditions, 'mixed' aldol reactions often give complex mixtures of products. This is especially true if the two reactants have α-hydrogens of comparable acidity and if the two carbonyl groups are of comparable electrophilicity. (3) Dehydration of the initially formed aldol presents a complication, especially with acid catalysis. However, this dehydration provides a significant driving force, and the formation of α,β-unsaturated aldehydes and ketones by the aldol condensation under conditions of catalytic acid or base is often an excellent preparative method.

1.5.5 SELF-REACTIONS OF ALDEHYDES

Base-catalyzed self-addition of aldehydes to form β-hydroxy aldehydes is successful under mild conditions, but only with relatively low molecular weight aldehydes; examples are presented in equations (7) and (8).[13,14] The rule of thumb is that aldehydes of up to about six carbons can be dimerized in aqueous and alcoholic medium by such methods.[15] Attempts to force the addition reaction of higher molecular weight aldehydes by using more vigorous conditions result in dehydration of the initial aldols, with for-

mation of the corresponding α,β-unsaturated aldehydes. These products are often available by this method in reasonable yield (*e.g.* equation 9).[16]

2,4,6-Trimethylphenoxymagnesium bromide catalyzes aldol condensation of aliphatic aldehydes to form α,β-unsaturated aldehydes in excellent yield if the reaction is carried out in benzene (Scheme 1).[17] In hexamethylphosphoric triamide (HMPA), the diol monoesters (**1**) and (**2**) are produced, also in nearly quantitative yield. Compounds (**1**) and (**2**) arise from a process known as the 'Tischtschenko reaction' (*vide infra*).



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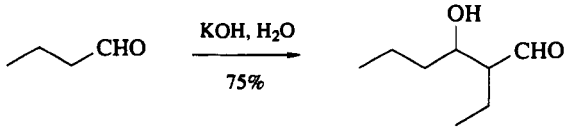

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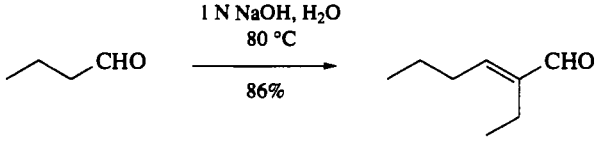

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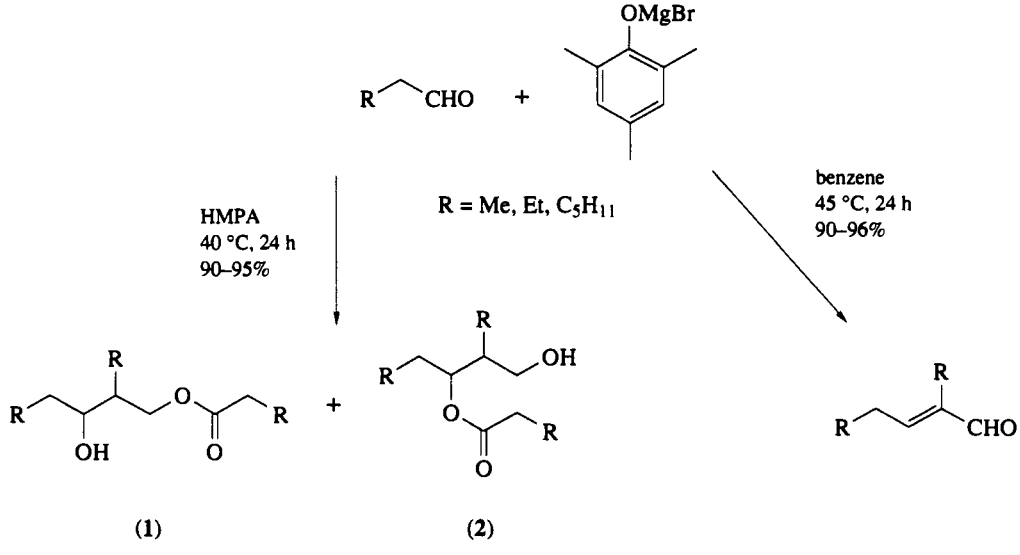
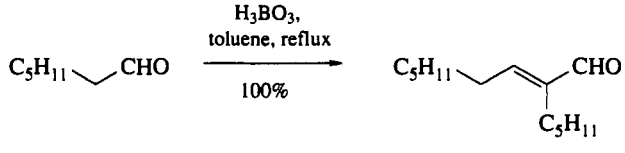


(1) (2)

Scheme 1



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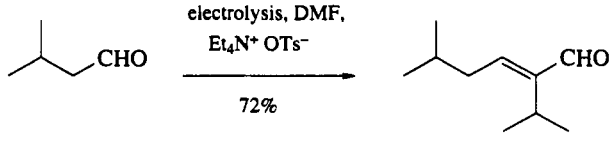


(11)

Offenhauer and Nelsen discovered that boric acid is an excellent catalyst for aldol condensations; treatment of heptanal with boric acid in refluxing toluene under a Dean–Stark trap gives the condensation product in quantitative yield (equation 10).[18] The authors suggested an intermediate enol borate; this was probably the first example of a boron enolate aldol reaction.

Shono and coworkers have shown that aliphatic aldehydes may be condensed electrochemically (equation 11).[19] Current efficiency for the reaction in equation (11) was found to be $0.96 \times 10^4\%$.

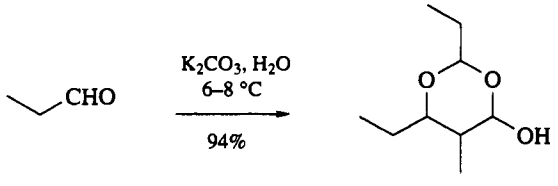
Aldehydes may be dimerized, either to β-hydroxy aldehydes or to α,β-unsaturated aldehydes, by the use of the anion-exchange resins Amberlite and Dowex.[20]

Catalytic aldol dimerizations of aldehydes sometimes lead to unexpected products. An example is shown in equation (12), where the initial aldol has formed an 'aldoxan' derivative by interacting with a third equivalent of propionaldehyde.[21] Although the aldoxan is dissociated to 1 mol each of the aldol and aldehyde upon distillation, the reaction effectively limits the yield of the aldol addition reaction itself to 66.7%.

A related phenomenon is the easy dimerization of some aldols upon standing; an example is the conversion of aldol itself into paraldol (equation 13).[22] Again, aldol can be regenerated by distillation of the dimer.

A more complex oligomer is obtained by treatment of butanal with KOH or NaOH in aqueous ethanol. This reaction has been shown to produce the tetramers (**3**)–(**5**) and trimer (**6**; equation 14), some in respectable yield, depending on the exact reaction conditions.[23,16] Compound (**3**) is produced as a mixture of four diastereomers and probably arises from dimerization of the initial aldol condensation product, 2-ethylhexenal. Diol (**4**), also obtained as a mixture of four stereoisomers, appears to be a Cannizarro reduction product of (**3**). Lactones (**5**) and (**6**) can reasonably arise by mechanisms involving hydride transfer from a cyclic hemiacetal.

Hydride transfer is also involved in the Tischtschenko reaction, wherein an aliphatic aldehyde is dimerized under the influence of aluminum tri-*t*-butoxide to the corresponding ester (equation 15).[24] Tischtschenko reaction products are sometimes observed as side products in aldol reactions. Under proper conditions, rather complex esters may be prepared in excellent yield (*e.g.* equations 16 and 17).[25]



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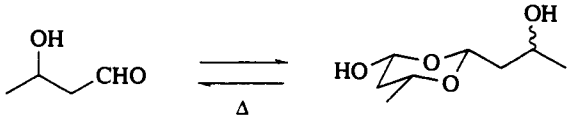

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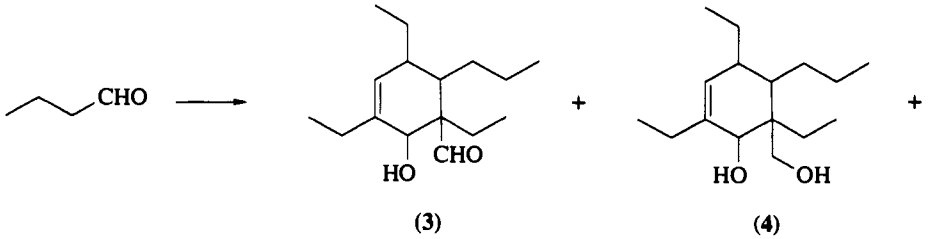

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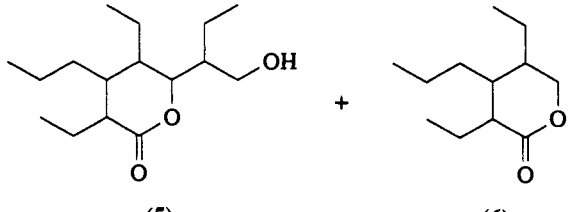

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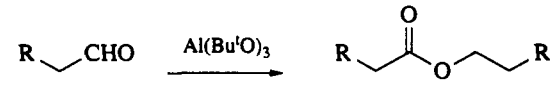

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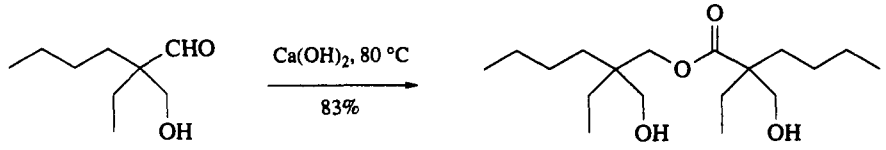

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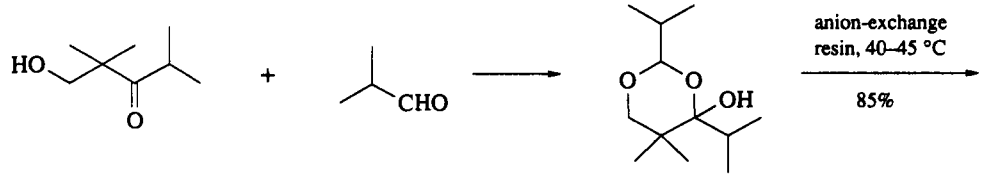

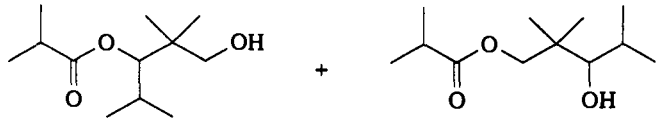

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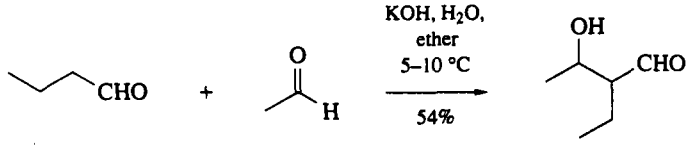

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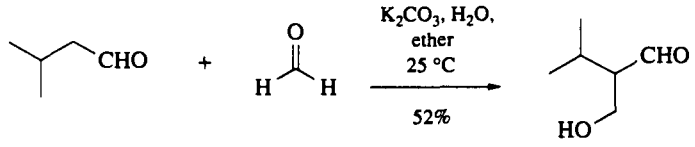


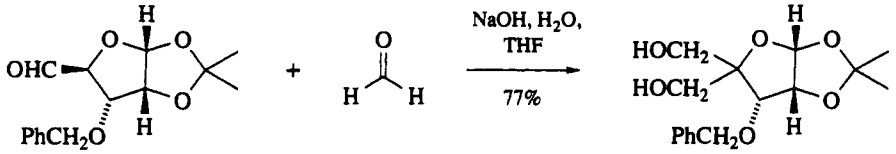
(19)

1.5.6 MIXED REACTIONS OF ALDEHYDES

Mixed aldol reactions between two different aldehydes generally give mixtures when each aldehyde can function both as enolate precursor and electrophilic component. In fortunate cases, one of the four possible aldols may predominate. An early generalization (Lieben's rule)[26] stated that the major aldol results from attachment of the carbonyl carbon of the aldehyde with the lesser number of α-substituents to the α-carbon of the aldehyde having the greater number of α-substituents (*e.g.* equation 18).[13]

An extreme case of the foregoing generalization is the reaction of formaldehyde with other aliphatic aldehydes, known as Tollen's reaction.[27] In this reaction it is possible to introduce only one hydroxymethyl group in certain exceptional cases (equation 19).[28] Generally, however, all available α-hydrogens are replaced by hydroxymethyl groups. Unless the reaction conditions are carefully controlled, the aldehyde function of the final aldehyde is reduced by formaldehyde (crossed Cannizzaro reaction), leading to a diol, triol or tetraol (*e.g.* equations 20 and 21).[27a,29] Ho has used this method for a convenient synthesis of branched sugars (equation 22).[30]

The other category of mixed aldehyde reactions that is generally successful is the reaction of an aromatic aldehyde with an aliphatic one. Although the aldol addition products have only rarely been isolated, the method is often acceptable for the preparation of β-aryl-α,β-unsaturated aldehydes (*e.g.* equations 23–25).[31–33]



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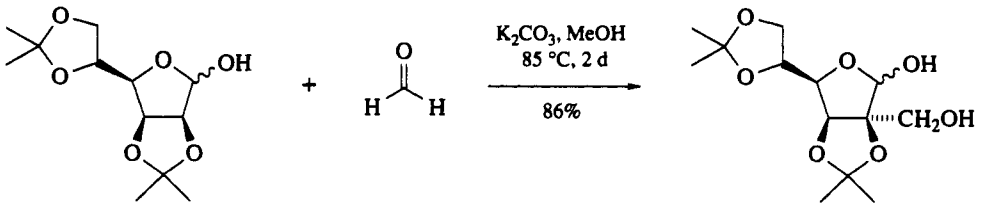

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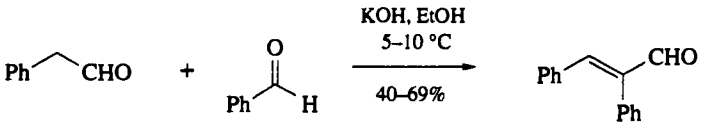

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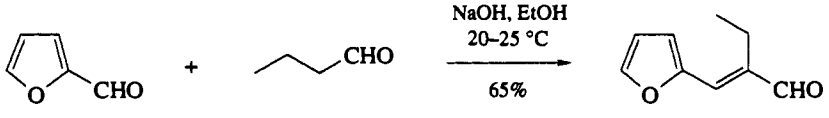

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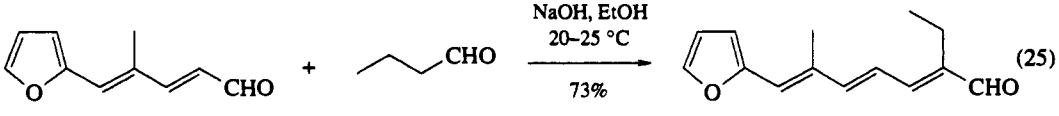
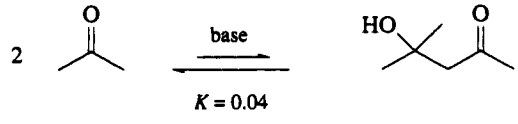


(25)

1.5.7 SELF-REACTIONS OF KETONES

Aldol addition reactions of ketones are rarely successful, since they are usually endoergonic. For example, the base-mediated aldolization of acetone provides only a few percent of the aldol, 'diacetone alcohol' (equation 26).[11,34] However, the conversion may be accomplished in 75% yield by refluxing acetone under a Soxhlet extractor containing calcium or barium hydroxide.[13,35] On the other hand, dimethoxyacetone dimerizes under basic conditions to the aldol, with an equilibrium constant significantly greater than unity (K = 10 dm^3 mol^{-1}; equation 27).[36] The difference in equilibrium constants of equations (26) and (27) parallels the equilibrium constants for hydration of the two ketones, and results from the inductive effect of the methoxy groups.



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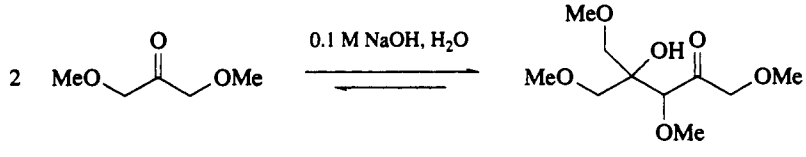

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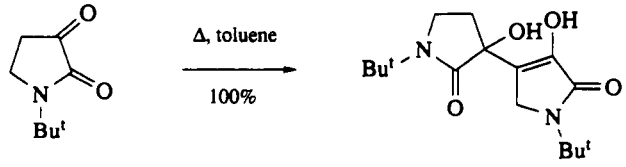
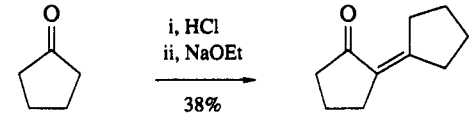


(28)

Cyclic ketones cannot usually be dimerized to the corresponding β-hydroxy ketones under protic conditions. An exception to this generalization is shown in equation (28).[37] The 2,3-dioxopyrrolidine is quantitatively dimerized by being warmed briefly with ethanolic pyridine, or by attempted recrystallization from warm toluene. In this case, as in equation (27), the favorable equilibrium constant is no doubt related to the inductive effect of the amide C=O, which favors hydration and other addition reactions of the ketonic carbonyl.

A number of methods may be used for self-condensation of ketones to give α,β-unsaturated ketones. Cyclic ketones are especially prone to aldol condensation, and the product from cyclopentanone (equation 29)[38] is frequently encountered as a by-product in reactions that involve exposure of cyclopentanone to acid or base. In the example shown in equation (29), the aldol addition reaction is carried out with gaseous HCl, leading to an intermediate β-chloro ketone that is dehydrochlorinated by treatment with base. It has recently been shown that basic alumina is an effective catalyst for the aldol condensation of ketones.[39]

Aldol condensations of monoketones can lead to trimeric products if the reaction is carried out under more vigorous conditions. The prototypical example of this behavior is acetone, which can give rise to mesityl ketone (**7**), phorone (**8**) and isophorone (**9**; equation 30). An example is seen in the treatment of acetone with aluminum tri-*t*-butoxide in toluene (equation 31).[40] Isophorone is frequently obtained as a by-product in base treatment of acetone;[41] it may be formed from the phorone enolate by an electrocyclization mechanism (equation 32).



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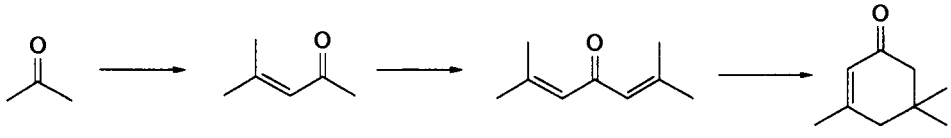
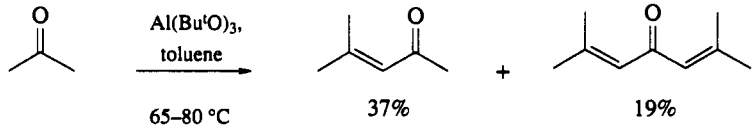


(7) (8) (9)

(30)



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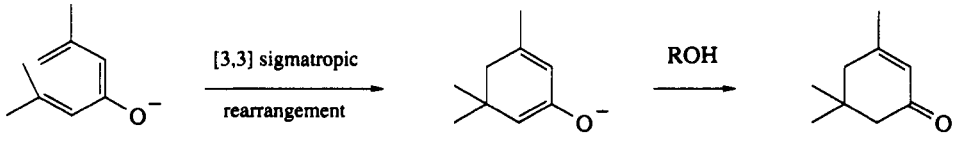
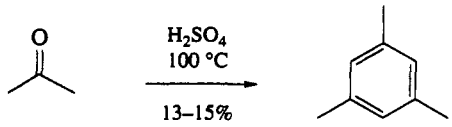


(32)

Acid-catalyzed aldol condensation of ketones can give rise to aromatic products. Examples are the trimerization of acetone to mesitylene (equation 33)[42] and the analogous conversion of 1-indanone to the heptacyclic product (**10**; equation 34).[43]



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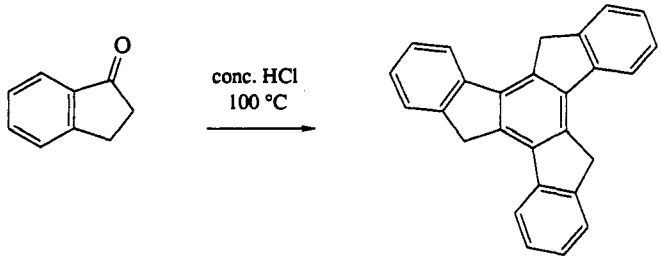

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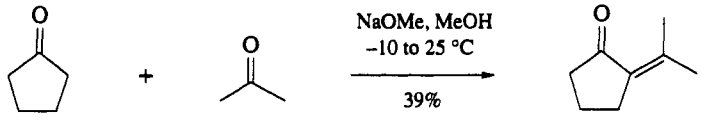
(10)

1.5.8 MIXED REACTIONS OF KETONES

Mixed condensations of two ketones are rarely preparatively useful. The factors that determine which of the four possible products will predominate include the relative concentrations and relative acidities of the two ketones, the relative rates of addition of the two carbonyl groups, and the relative rates of dehydration of the intermediate aldols. The examples shown in equations (35)[44] and (36)[45] demonstrate that only minor structural changes can greatly affect the product distribution.

Benzil and its derivatives condense with aliphatic ketones to give 4-hydroxycyclopentenones in good yield (equation 37).[46] Although this reaction is not usually observed with aliphatic diketones, a recent example has been reported.[47] A special version of this reaction involves the use of dibenzyl ketone. In such cases the initial 4-hydroxycyclopentenone dehydrates to form the tetraphenylcyclopentadienone ('tetracyclone'; equation 38).[48]



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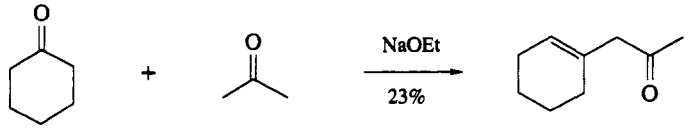

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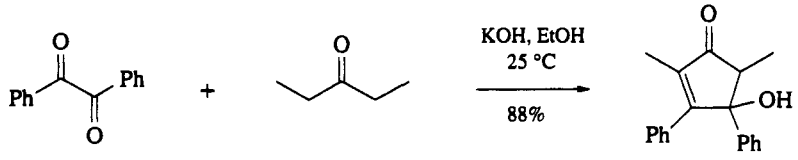

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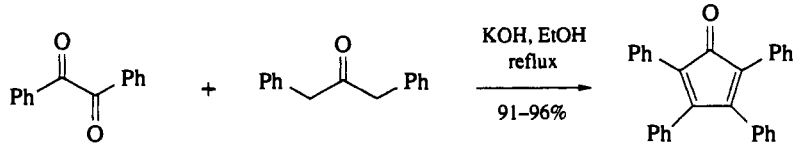


(38)

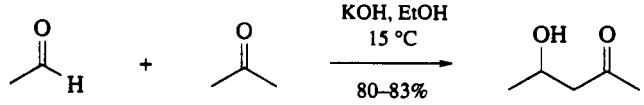
1.5.9 REACTIONS OF KETONES WITH ALDEHYDES

Mixed aldol reactions between ketones and aldehydes are frequently successful because one of the competing side reactions, self-reaction of the ketone, is endothermic. Most commonly, these mixed aldol reactions are carried out under conditions that lead to the α,β-unsaturated ketone product. The principal side reaction is usually aldehyde dimerization.

1.5.9.1 Acyclic Ketones

The condensation of aliphatic aldehydes with acetone to give methyl vinyl ketone derivatives is rather common. The reaction can be carried out to the ketol stage (equations 39 and 40),[49,50] or under conditions that lead to the α,β-unsaturated ketone (equations 41 and 42).[51,52] By adjusting the stoichiometry, bis-condensation products can often be obtained in excellent yield (equations 43 and 44).[53,54]

Similar transformations can be obtained in the reactions of acetone with aromatic aldehydes, the classic Claisen–Schmidt reaction. These reactions invariably give the α,β-unsaturated ketone products. Either the mono- or bis-condensation product may be obtained by suitable adjustment of the reaction conditions (equation 45 and 46).[55,56]



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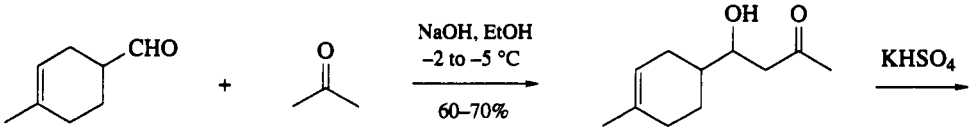

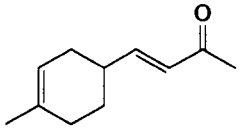

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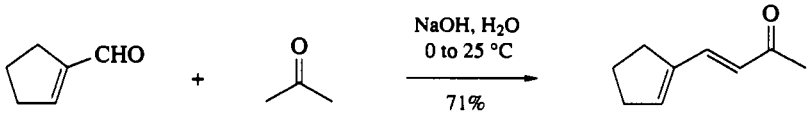

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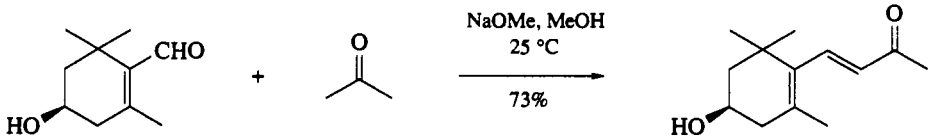

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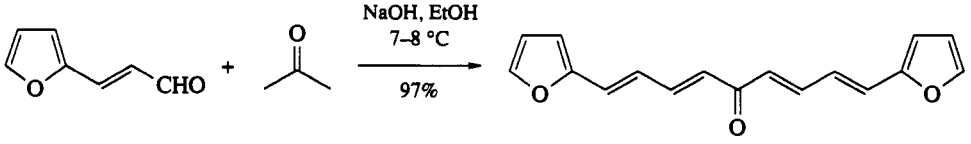

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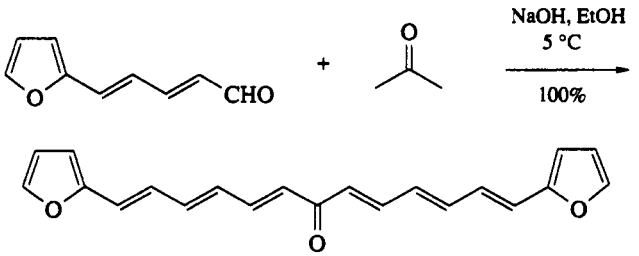

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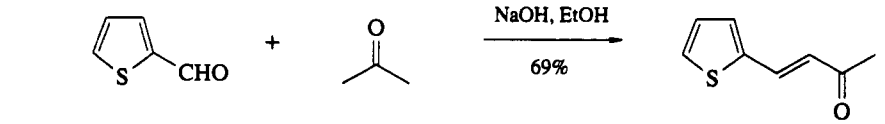

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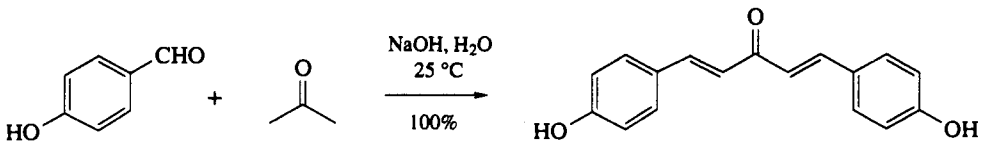
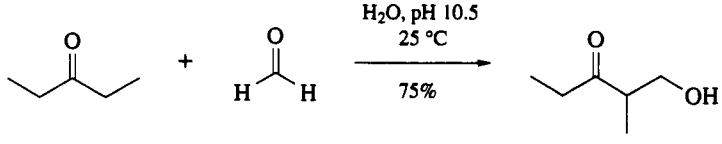


(46)

3-Pentanone is similar to acetone in its behavior, and 1:1 adducts may be obtained from aliphatic aldehydes in good yield (equations 47 and 48).[57,58] 4-Heptanone and higher symmetrical ketones are much less reactive and give very poor yields of aldols with simple aldehydes. However, the reactions of these ketones with *o*-phthalaldehyde often provide benzotropone derivatives in excellent yield (*e.g.* equation 49).[59] Diisopropyl ketone and diisobutyl ketone do not give mixed adducts with aldehydes under the normal protic conditions.



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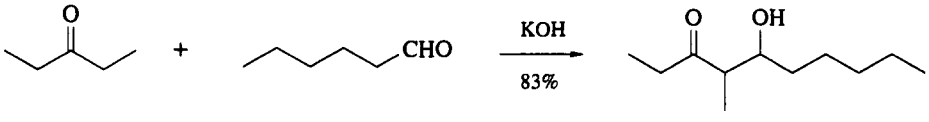

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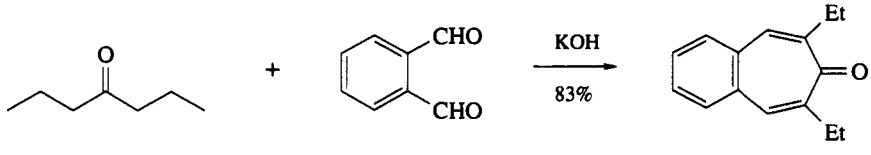

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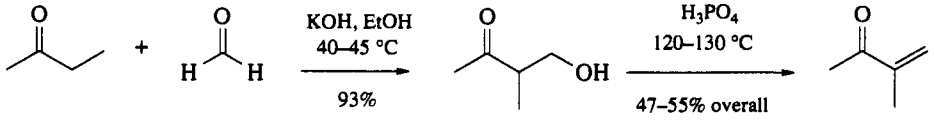


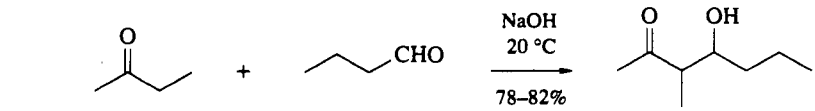
(50)

With unsymmetrical aliphatic ketones there is a regiochemical feature. The situation is complicated, and the actual product obtained seems to depend on catalyst, solvent and the structures of both the aldehyde and ketone. Some representative examples are presented in the following paragraphs.

Butanone reacts with formaldehyde and other aliphatic aldehydes under mildly basic conditions to give monosubstitution products at C-3 (*e.g.* equations 50 and 51).[60,61] The behavior of aromatic aldehydes with this ketone is complex; condensation at both C-1 and C-3 has been reported.

Dubois and Fellmann have studied the kinetic regioselectivity in the base-promoted reactions of 2-butanone and 2-pentanone with a series of aliphatic aldehydes (equation 52);[62] results are summarized in Table 2. The data indicate that steric effects play a subtle role in the determination of aldol regiochemistry in unsymmetrical ketones. Although reaction at C-3 is favored for 2-butanone with all of the aldehydes, pivalaldehyde gives more reaction at C-1 than the other aldehydes studied. Selectivity for reaction at C-3 in 2-pentanone is significantly less with all aldehydes, especially pivalaldehyde.

A similar trend may be seen in a study of the reaction of chloral with unsymmetrical ketones (equation 53; Table 3).[63] Reactions were carried out in glacial acetic acid with or without added sodium acetate as catalyst. Several control experiments showed that the isomer ratios obtained were kinetic. The lack of reversibility in this reaction implies that ΔG° is much more negative than for the simple aldol reactions discussed previously. This is presumably because of the inductive effect of the chlorines, which is known to favor hydration and other nucleophilic additions to chloral.



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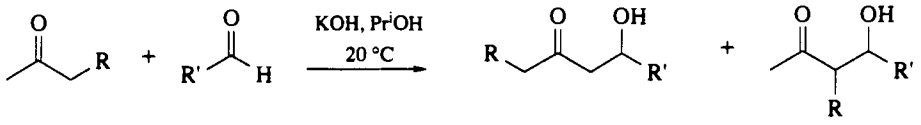
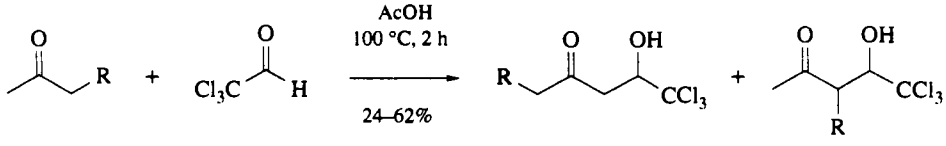


(52)

Table 2 Regiochemistry of Aldol Reactions with 2-Alkanones (equation 52)

Aldehyde R′:	*Me*	*Et*	*Percent reaction at C-3 of the ketone* Pr^i	Bu^t	Pr^n	Bu^i	*neo-Pe*
2-Butanone (R = Me)	93	90	86	70	88	90	88
2-Pentanone (R = Et)	78	75	56	17	71	71	70

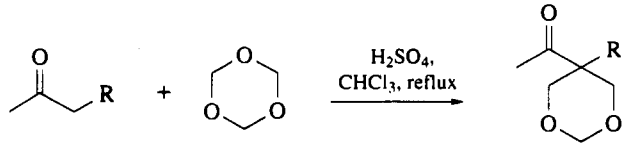
The data in Tables 2 and 3 show common qualitative trends, although chloral appears to have a greater proclivity for reaction at C-1. This preference for reaction at C-1 is actually enhanced in the reactions conducted without added sodium acetate, in contrast to the normal generalization that methyl alkyl ketones undergo acid-catalyzed reactions preferentially at C-3.[64] Kiehlmann has reported that the rates of deuteration of the ketones shown in equation (53) are much faster than the rates of the aldol reactions, supporting a mechanism in which carbon–carbon bond formation is the rate-limiting step. This is also true in the Dubois study (equation 52; Table 2). The difference is presumably due to the greater steric bulk of chloral, leading to a greater C-1:C-3 ratio.



(53)

Table 3 Regiochemistry of Aldol Reactions of Chloral with 2-Alkanones (equation 53)

R	*Percent reaction at C-3* *NaOAc/HOAc*	*HOAc*
Me	56	15
Et	23	11
Pr^n	28	15
Bu^n	22	11
Pr^i or Bu^t	0	0



(54)

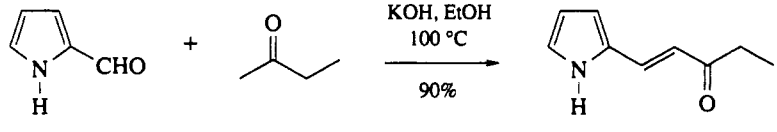
Table 4 Regiochemistry of Aldol Reactions of Formaldehyde with 2-Alkanones (equation 54)

R	*Yield (%)*	*C-3:C-1*
H	3	n/a
Me	98	100:0
Et	80	100:0
Pr^n	79	100:0
Pr^i	43	86:14
Bu^t	6	n/a

Wesslén has investigated the acid-catalyzed reactions of trioxane with methyl alkyl ketones to give dioxanes; representative data are shown in equation (54) and Table 4.[65] These data show a strong preference for reaction at a more substituted position. Indeed, the examples presented where reaction *must* occur at a methyl group (acetone and pinacolone) give very low yields of product.

Base-promoted reactions of unsymmetrical methyl ketones often give C-1 substituted products in high yield; an example of such a case is shown in equation (55).[66] A clue to the source of this behavior is seen in the two aldol reactions presented in equations (56) and (57). Under the milder set of conditions, benzaldehyde reacts with butanone to give a mixture of aldols resulting from attack at C-1 and C-3 (equation 56).[67] When the reaction is carried out at higher temperature and for a longer period, the C-1 condensation product is obtained in nearly quantitative yield (equation 57).[68]

The indication is that, in basic medium, the aldol addition reaction has a preference for formation of the more-substituted addition product. Under the more forcing conditions that lead to the enone, aldol reversal must occur, and formation of the C-1 condensation product must be favored over formation of the C-3 condensation product. This preference may be the result of more facile dehydration of the C-1 addition product.



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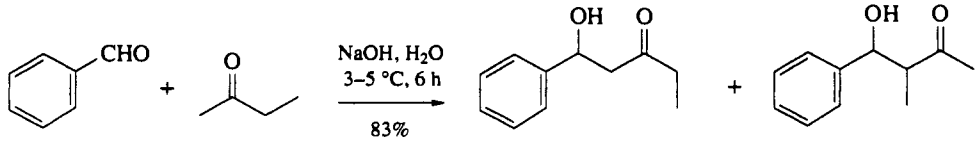

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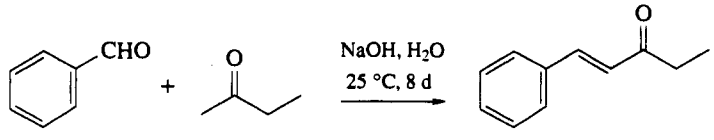
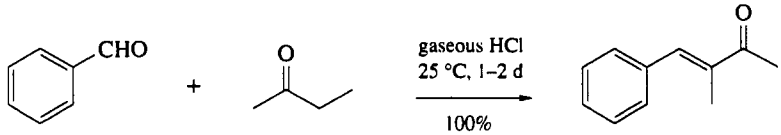


(57)

Under acidic conditions, benzaldehyde reacts with butanone to give exclusively the C-3 condensation product (equation 58).[69] In this example, we are presumably seeing the normal acid-mediated preference for aldol addition at C-3, followed by rapid acid-mediated dehydration. The latter reaction is probably irreversible under the reaction conditions.

Citral undergoes base-catalyzed aldol condensation with 2-butanone to give the methylpseudoionones in excellent yield; the C-3:C-1 ratio is 2:1 (equation 59).[70]

McKervey and coworkers have used lithium iodide as a catalyst for mixed aldol reactions; several examples are shown in equation (60).[71] In all cases studied, 2-butanone reacts solely at C-1. The process is also applicable to other ketones, but they react much more slowly than do methyl ketones. For



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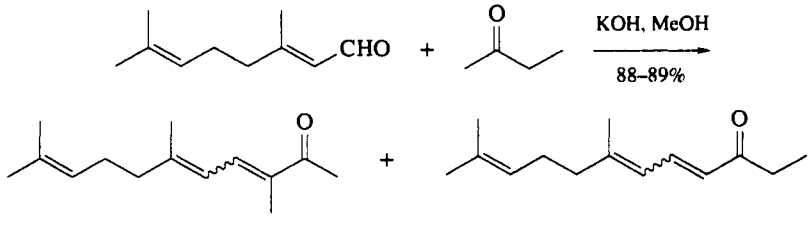

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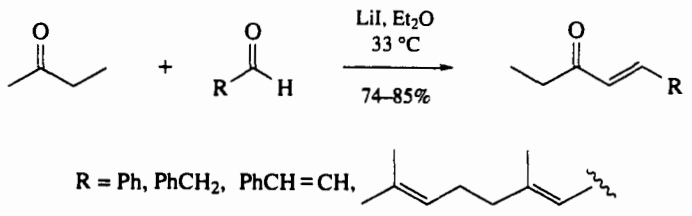
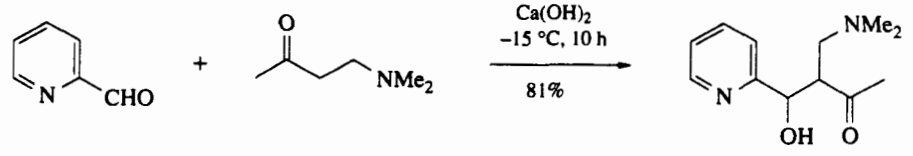


(60)

example, whereas *p*-methoxybenzaldehyde reacts with 2-butanone in 7 h, the comparable reaction with 3-pentanone requires 72 h. Cyclohexanone is comparable to 2-butanone and acetone in reactivity.

In contrast to the foregoing examples, 2-pyridinecarbaldehyde reacts with 4-*N*,*N*-dimethylamino-2-butanone to give only the C-3 substitution product (equation 61).[72] In this case, the inductive effect of the C-4 heteroatom must play a role, perhaps by favoring enolization toward C-3.



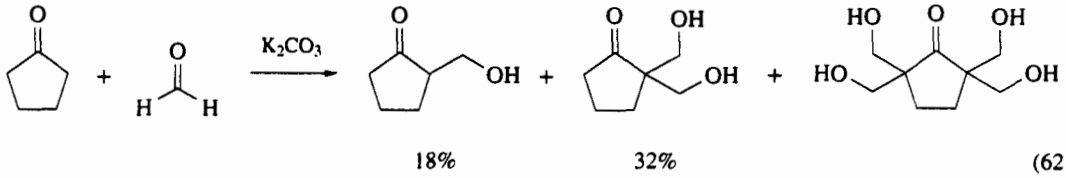
(61)

1.5.9.2 Cyclic Ketones

The base-catalyzed aldol addition reaction of cyclic ketones with formaldehyde is limited by the propensity of the initial hydroxymethyl products to undergo subsequent reactions (*e.g.* equations 62 and 63).[73,74] Similar problems occur with enolizable aliphatic aldehydes.

On the other hand, cyclic ketones react well with nonenolizable aldehydes (equations 64–66).[75,76] As shown in equation (65), mild conditions lead to the aldol (as a diastereomeric mixture). More forcing conditions provide the α-benzylidine derivatives (equations 64 and 65). By adjusting the stoichiometry, α,α′-bisarylidine derivatives may be obtained in excellent yield from cyclohexanone or cyclopentanone (*e.g.* equation 66).[77]

With unsymmetrical cyclic ketones, regioisomers may be formed. However, if one of the enolizable positions is substituted, or if other structural features favor enolization in a given direction, good yields of aldol products may be realized. 2-Substituted cycloalkanones undergo condensation reactions at the



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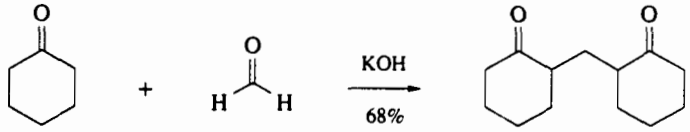

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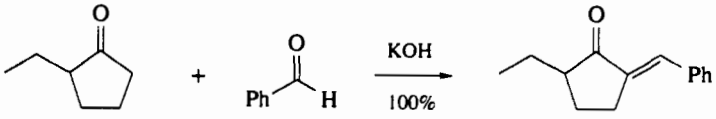

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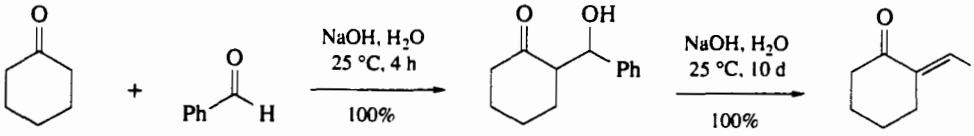

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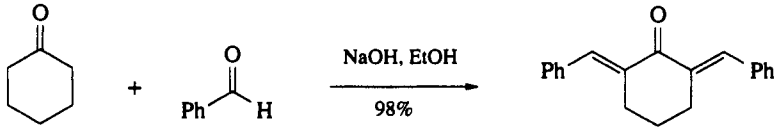
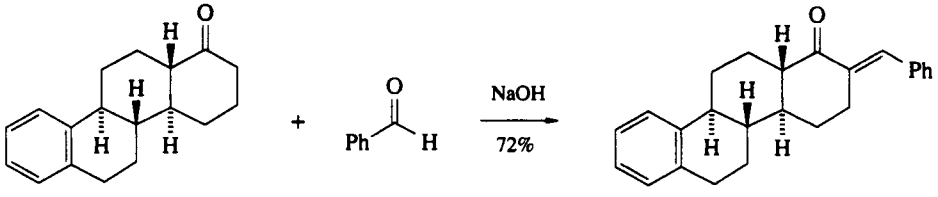


(66)

unsubstituted α-position under dehydrating conditions (equations 64 and 67).[78] The example shown in equation (68) is regioselective, presumably because of steric hindrance to reaction at the neopentyl center.[79]



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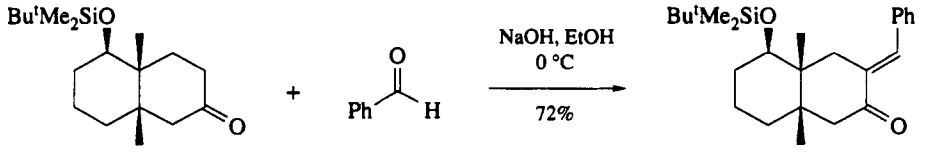
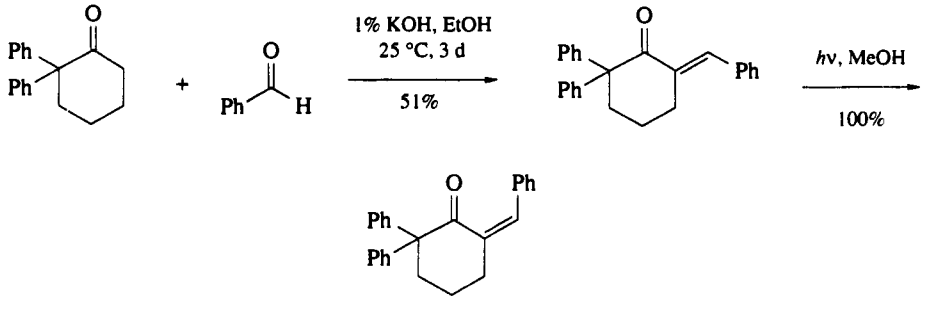


(68)

As shown in many of the foregoing examples, aldol condensation of an aromatic aldehyde with a ketone normally provides the (*E*)-α,β-unsaturated ketone. This stereochemical generalization has been investigated by Hassner and Mead.[80] It was found that even very hindered ketones such as 2,2-diphenylcyclohexanone give the (*E*)-enone under mild conditions (equation 69).[81] The (*Z*)-enone is obtained quantitatively by irradiation in alcoholic solution, but this isomer is easily transformed back to the (*E*)-isomer.

Acid-catalyzed reactions with cyclic ketones sometimes give products of further reactions (*e.g.* equations 70 and 71).[82]



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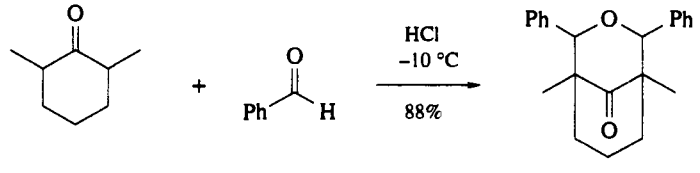

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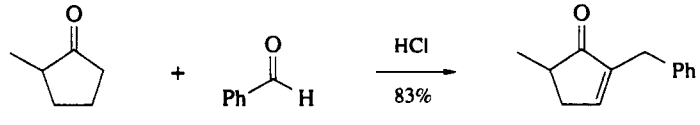
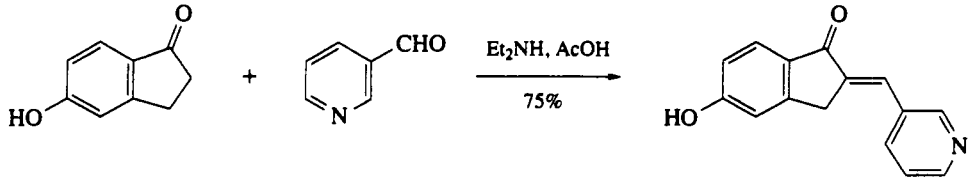


(71)

There are an immense number of examples of aldol condensations of aromatic carbocyclic ketones with aromatic aldehydes. These systems usually give excellent yields of aldol condensation products, because the starting ketone can usually enolize in only one direction and because the ketones do not afford



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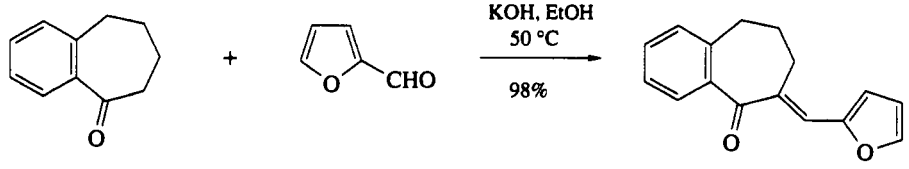

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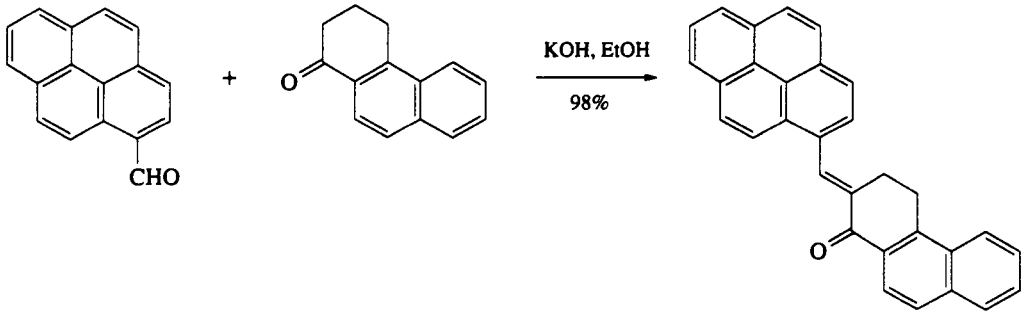

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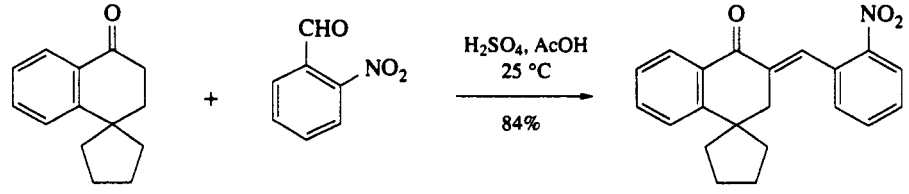

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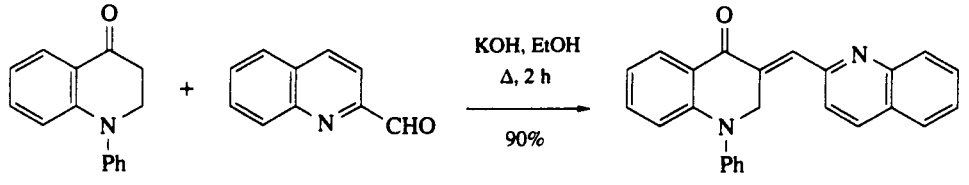

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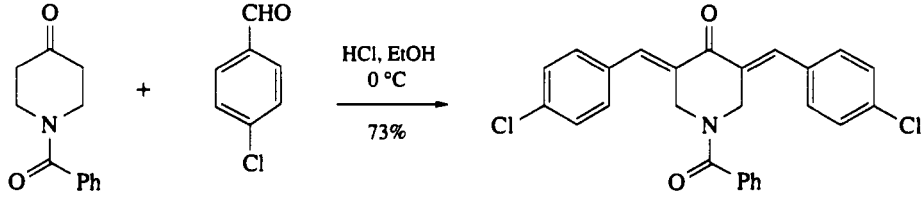
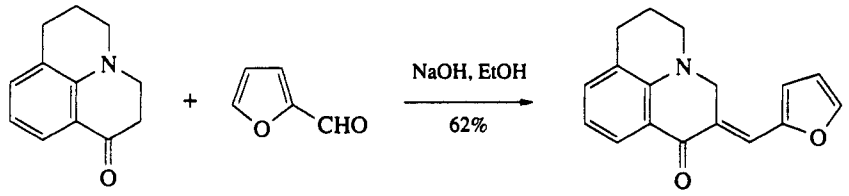


(77)

stable self-condensation products. A few high-yielding examples from the older literature are given in equations (72)–(75);[83–86] the reader is directed to the Nielsen–Houlihan review for a a much more extensive compilation of examples.[87]

Saturated heterocyclic ketones are also good substrates for mixed aldol condensations with aromatic aldehydes. Again, a selection of high-yielding examples is presented in equations (76)–(80).[88–92] These



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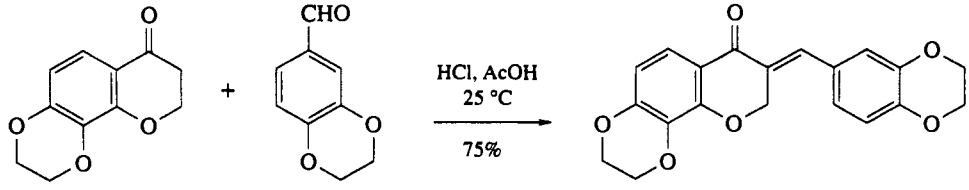

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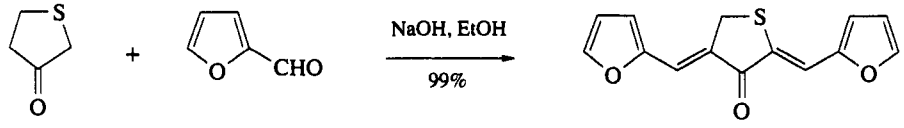


(80)

examples illustrate base catalysis and acid catalysis, and include examples of oxygen, nitrogen and sulfur heterocyclic ketones. Note that in each case β-elimination of the heteroatom might have provided a complication.

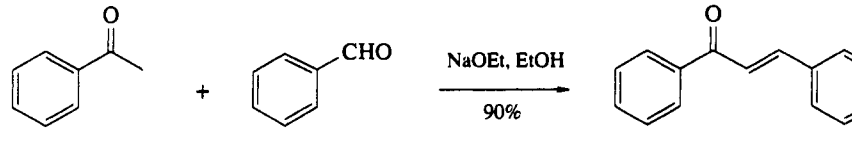
1.5.9.3 Alkylaryl and Related Ketones

In this section, we discuss a useful version of mixed ketone–aldehyde condensation, the reaction of aromatic methyl ketones with nonenolizable (usually aromatic) aldehydes. The prototype reaction is the condensation of acetophenone with benzaldehyde, leading to 1,3-diphenylprop-2-en-1-one, 'chalcone' (equation 81).[7b] The scope of this reaction is exceedingly broad; the Nielsen–Houlihan review enumerates hundreds of examples comprising almost every imaginable combination of substituted acetophenone and aromatic aldehyde.[93]

It has recently been found that chalcone formation may be carried out under the influence of copper(II) 2,2′-bipyridyl[94] or a complex of cobalt(II) acetate and a 4-vinylpyridine–styrene–divinylbenzene copolymer; chalcone is obtained in high yield and the catalyst may be recovered and reused.[95]

A recently reported procedure calls for addition of sodium hydroxide pellets to a rapidly stirring solution of the ketone and aldehyde in absolute ethanol at room temperature. The crystalline chalcones are isolated by simple filtration. Yields are reported to be in the range 72–99%; an example is shown in equation (82).[96]

Becher and coworkers have studied the aldolization of 3-formyl-2(1*H*)-pyridinethiones.[97] Aldehyde (**11**) reacts with *p*-chloropropiophenone to give a single diastereomeric aldol, shown by X-ray analysis to have the *syn* structure (**12**), in 83% yield (equation 83). Several other examples, all apparently highly



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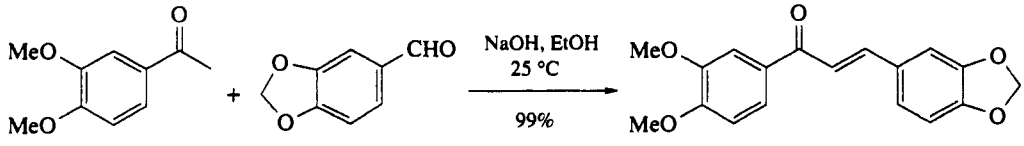

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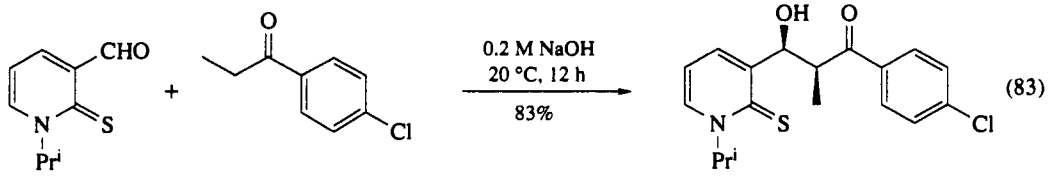
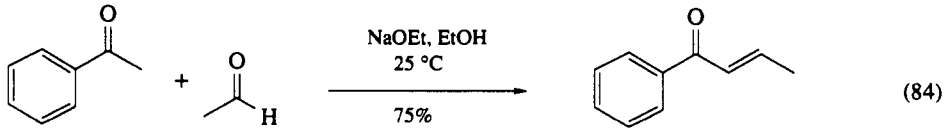
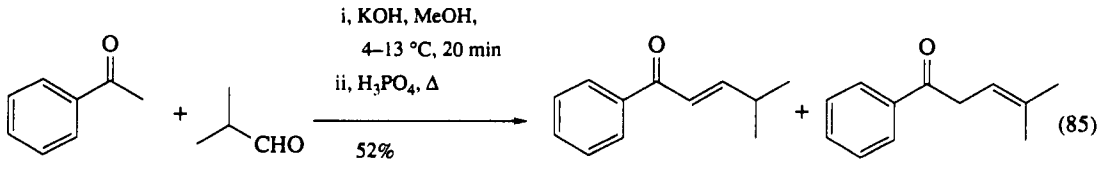


(11) (12)





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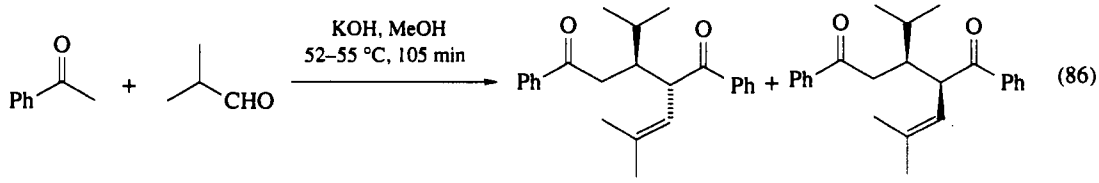
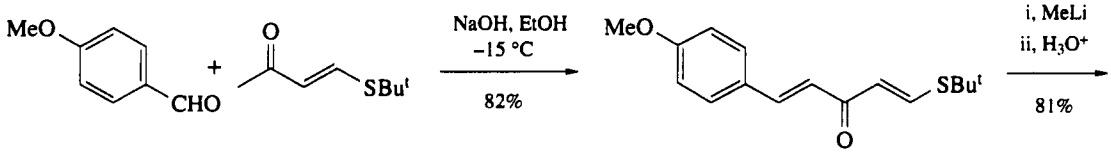
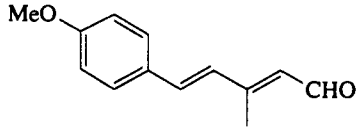


(13) 60% (14) 9%



(15) (16)



(17)

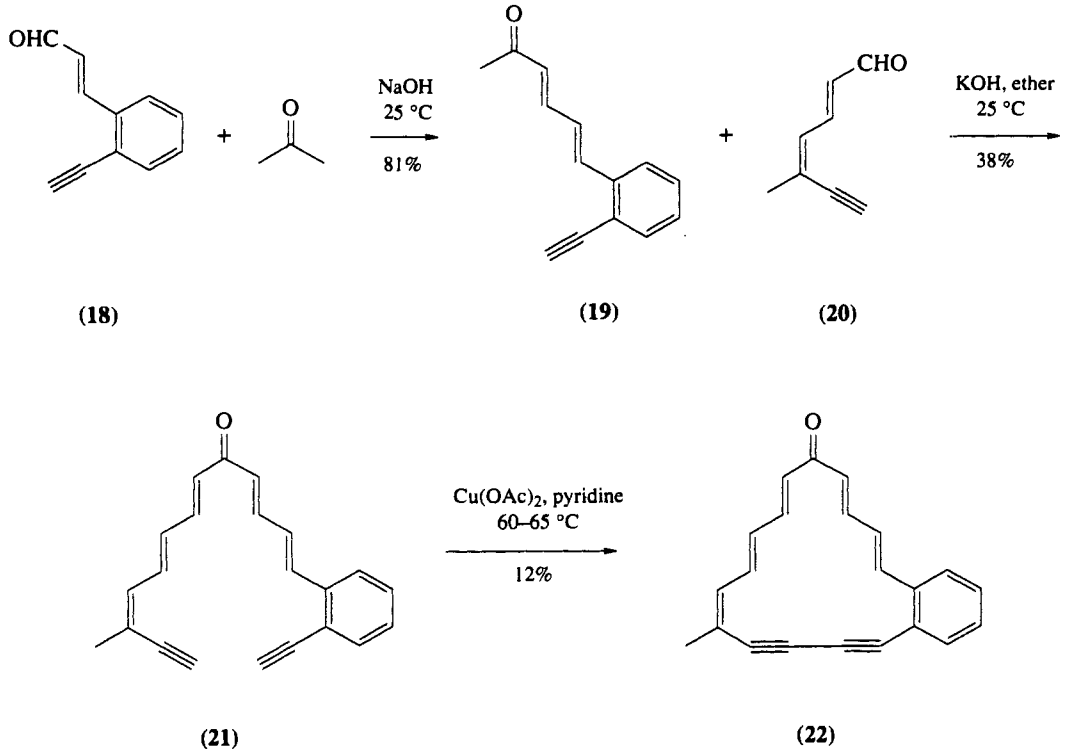
stereoselective, were reported. Such stereoselective aldol reactions are highly unusual under protic conditions. Oxoamides corresponding to (**11**) were found to give the α,β-unsaturated ketone products.

Condensations of acetophenones with aliphatic aldehydes are often complicated by side reactions, although some simple cases are known to proceed in good yield (*e.g.* equation 84).[96] An example of the kind of complications that may arise in such cases is seen in the reaction of acetophenone with isobutyraldehyde. Base-mediated reaction at low temperature gives a crude aldol that is dehydrated by heating with phosphoric acid to obtain a 3:1 mixture of α,β- and β,γ-unsaturated ketones (equation 85).[98] If the reaction is carried out under more traditional conditions, by heating an alcoholic solution of the reactants

with potassium hydroxide, the main products are diones (**13**) and (**14**), resulting from subsequent Michael addition of the initially formed enones (equation 86).[98,99]

Some methyl vinyl ketones behave similarly to acetophenones in aldol condensations, a primary requirement being that the vinyl ketone not be particularly susceptible to Michael addition or base-catalyzed polymerization processes. A recent example utilizes the vinylogous β-keto sulfide (**15**), which undergoes smooth condensation with benzaldehyde and its derivatives (equation 87).[100] The product of this aldol condensation, enone (**16**), may be converted by a straightforward sequence of steps into the dienal (**17**), which is obtained as a 4:1 mixture of (*E*)- and (*Z*)-isomers at the C(2)=C(3) double bond. A number of other examples of this useful process are reported in the primary publication.

An annulenone synthesis that employs aldol condensations in two key steps is outlined in Scheme 2.[101] Condensation of *o*-ethynylcinnamaldehyde (**18**) with acetone provides (**19**), which is condensed with aldehyde (**20**) to obtain ketone (**21**). Intramolecular oxidative coupling of the two alkyne functions affords annulenone (**22**).

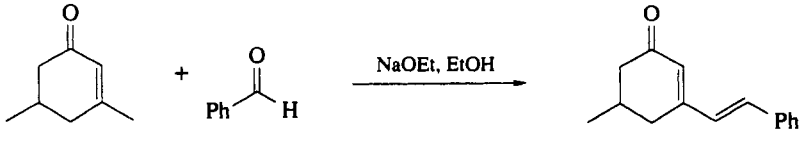


(**18**) (**19**) (**20**) (**21**) (**22**)

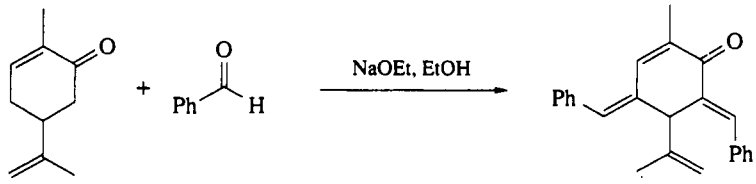
Scheme 2

1.5.9.4 Vinylogous Enolates

There have been frequent reports of the condensation of cyclic α,β-unsaturated ketones at the γ-position; an example is seen in equation (88).[102] Other 3-methylcyclohexenones have been reported to undergo similar reactions.[103] Unfortunately, the original literature does not report yields for these transformations. These reactions would bear reinvestigation with modern methods of analysis. Other cyclohexenones have also been found to undergo aldol condensation at the γ-position. For example, carvone condenses with two equivalents of benzaldehyde (equation 89).[104]



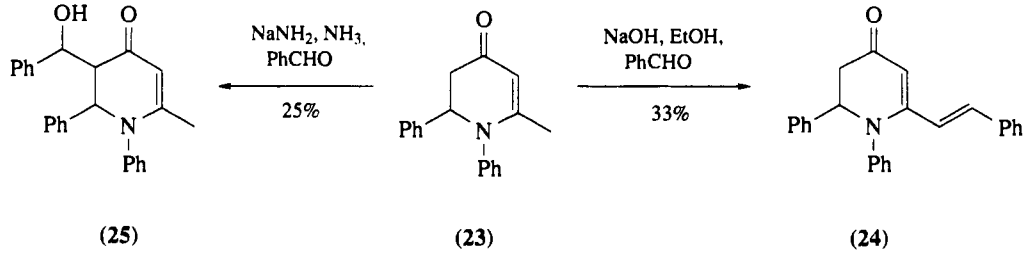
(88)



(89)

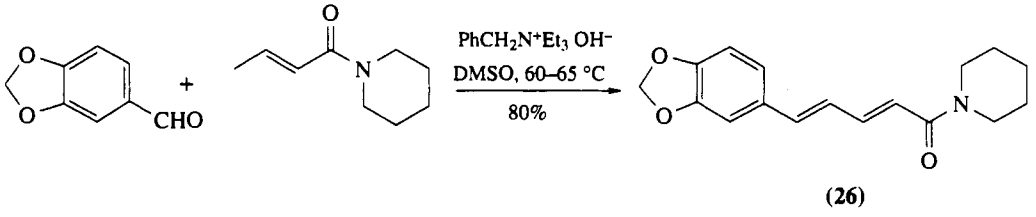
A similar phenomenon has been reported by Sugiyama and coworkers, who found that the vinylogous amide (**23**) reacts with benzaldehyde to give (**24**) as the sole product (equation 90).[105] When (**23**) is treated with two equivalents of sodium amide in ammonia, followed by treatment with benzaldehyde, aldol (**25**) is formed in 25% yield. Although the authors invoke a dianion in the latter reaction, it is unlikely that one could be formed under the reaction conditions used. Instead, it is likely that deprotonation at the endocyclic α-position is preferred kinetically, and that this leads to the product observed with $NaNH_2/NH_3$ (irreversible enolate formation). Reaction of this enolate must be slow, for steric reasons, as witnessed by the low yield in the aldol reaction. Under conditions of enolate equilibration, the more stable extended dienolate is produced.

Schulze and Oediger have used such a reaction in the synthesis of piperine (**26**), the sharp principle of black pepper. Condensation of piperonal with *N*-crotonylpiperidine in DMSO in the presence of benzyltriethylammonium hydroxide provides piperine in 80% yield (equation 91).[106]



(25) (23) (24)

(90)



(26)

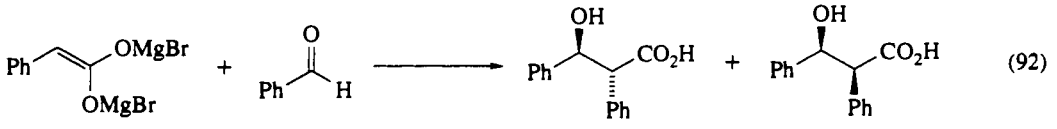
(91)

1.5.9.5 Stereochemistry

One of the features of the aldol addition reaction that limited its usefulness prior to the early 1970s was an imperfect understanding of its stereochemistry. Indeed, the methods of analysis prior to the advent of ^1H NMR spectroscopy were not especially appropriate for distinguishing diastereomers. Reactions such as those depicted in equations (8), (14), (18), (40), (48), (51), (56), and (65) give mixtures of diastereomers, but this issue was largely ignored because it was not conveniently addressed.

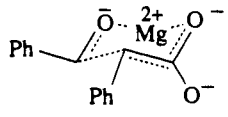
One of the first attempts to study this issue came from Zimmerman and Traxler, in a 1952 paper on the Ivanov reaction. It was observed in this work that the preformed magnesium dianion of phenylacetic acid reacts with benzaldehyde to give the '*threo*' and '*erythro*' β-hydroxy acids (**27**) and (**28**) in a ratio of 3:1 (equation 92).[107] It was proposed that the reaction proceeds through transition state (**29**), in which the magnesium cation is chelated by the benzaldehyde oxygen and one oxygen of the carboxylate. The same proposal was later advanced by Toromanoff in a paper dealing with the general topic of perpendicular attack by nucleophiles on carbonyl groups.[108]

In a 1964 paper, Stiles and coworkers isolated and identified diastereomeric aldols.[109] However, the first person to address the question of aldolization stereochemistry in a serious manner was the French physical organic chemist J.-E. Dubois.[110] His first study was of the KOH-promoted aldolization of cyclopentanone with several aliphatic aldehydes (equation 93);[111] the results are summarized in Table 5. In this discussion of the Dubois work, we use the stereochemical descriptors '*threo*' and '*erythro*' in the same sense that they were employed in the original Dubois papers, in order to avoid confusion for those



(92)

(27) 69% (28) 22%



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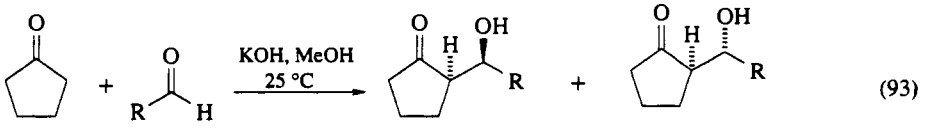


(93)

erythro *threo*

Table 5 Stereochemistry of Aldol Reactions of Cyclopentanone with Aliphatic Aldehydes (equation 93)

R	*Threo* (%)	*Erythro* (%)
Me	43	57
Et	38	62
Pr^i	32	68
Bu^t	13	87
neo-C_5H_{11}	35	65

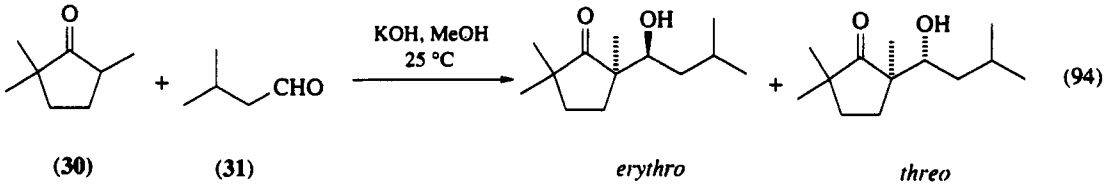
who wish to consult the original publications for more detail. It was established by appropriate control experiments that the reactions were under thermodynamic control.

In a later series of papers, Dubois and Fort studied the stereochemistry of the reaction of 2,2,5-trimethylcyclopentanone with isovaleraldehyde (equation 94).[112] In this study, it was shown that, whereas the *erythro* diastereomer is thermodynamically preferred, the *threo* isomer is formed more rapidly under certain conditions.

The concentrations of *erythro* and *threo* aldols as a function of time are presented in Figure 1(a) for a relatively nonpolar solvent (90:10 THF–MeOH) and in Figure 1(b) for a polar solvent (pure MeOH). In the nonpolar solvent the *threo* aldol is formed more rapidly than the *erythro* isomer. However, as a result of the reversibility of the system, its concentration peaks and then diminishes to eventually reach an equilibrium value. In pure MeOH, on the other hand, the *erythro:threo* equilibrium composition is maintained throughout the reaction. Thus, the reaction is under thermodynamic control in the polar solvent and under kinetic control in the less polar one.

Dubois defined a quantity called the 'restoring energy', E_r, that measures the difference between kinetic and thermodynamic stereoselectivity. The idea in this concept is that, for easily reversible reactions under kinetic control, the reverse reactions, whose rate constant ratio is related to E_r, restores the diastereomeric system to its equilibrium composition. This is illustrated with the generic reaction coordinate diagram for equation (94), presented in Figure 2. Figure 2 ignores the deprotonation step, which is common for the two competing reactions, and subsequent protonation of the aldolates. It may be seen in this figure that the reaction of (**30**) and (**31**) is under kinetic control, with formation of the *threo* diastereomer being more rapid. However, because neither of the competing reactions is very exothermic (ΔG° for these reactions can be estimated to be only a few kcal mol^{-1}) the activation energies for the reverse reactions are only slightly greater than those for the forward reactions. In addition, Figure 2 shows that the more rapidly formed *threo* diastereomer will reverse more rapidly than the more slowly formed *erythro* diastereomer. Thus, $E_r = \Delta G^{\ddagger}_{-E} - \Delta G^{\ddagger}_{-T}$. From the known *threo–erythro* equilibrium constant, and a careful measurement of the activation parameters for the forward reactions, Dubois

evaluated the effect of various parameters on E_r. For the two conditions depicted in Figure 1, E_r was found to have values of 1.95 kcal mol^{-1} (90:10 THF–MeOH) and 0.01 kcal mol^{-1} (pure MeOH).



(30) (31) *erythro* *threo*

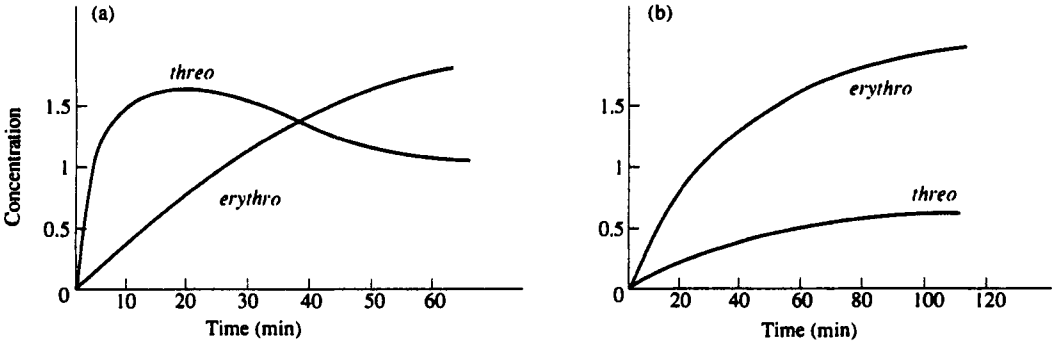


Figure 1 Concentration of *threo* and *erythro* aldols as a function of time for equation (94). (a) 90:10 THF:MeOH; (b) pure MeOH

For E_r to be zero, as it is in the reaction of (**30**) and (**31**) in methanol, $\Delta G^{\ddagger}_{-E}$ must be equal to $\Delta G^{\ddagger}_{-T}$, and the reaction is under pure thermodymanic control. It follows that interactions in the transition states and products are similar. This was found to be the case in polar solvents (H_2O, MeOH, DMSO) and in less polar solvents (90:10 THF–MeOH) when the cation is highly dissociating (Me_4N^+). Dubois postulated that reactions with significant positive E_r proceed through Zimmerman–Traxler transition states, in which the cation is chelated by the two partially negative oxygens (Figure 3). Of these, the *erythro* transition state is presumed to be the less stable, because it brings the aldehyde R group into interaction with the cyclopentanone ring. For reactions with negligible E_r, it was proposed that an open transition state

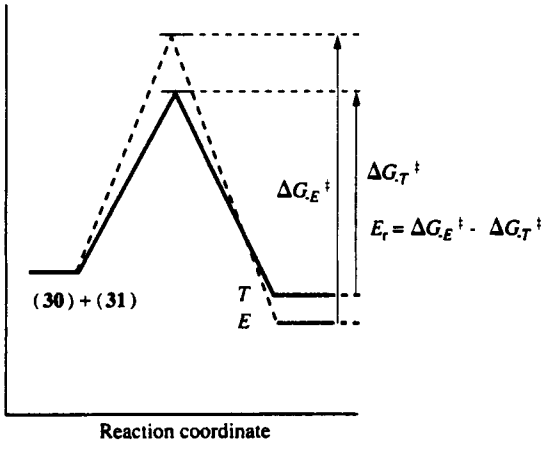
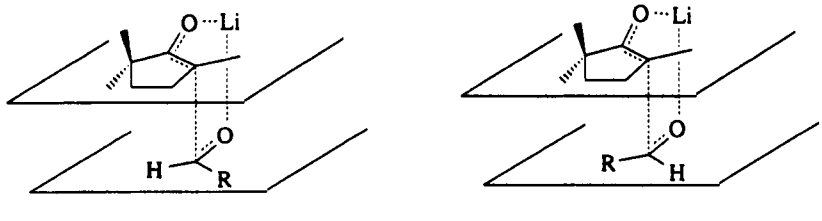


Figure 2 Potential energy diagram for the aold reaction of ketone (**30**) and aldehyde (**31**) (equation 94)



threo transition state *erythro* transition state

Figure 3 Chelated transition states for equation (94)

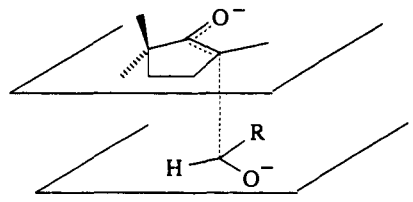


Figure 4 Open transition states for equation (94)

prevails (Figure 4). In this case, the *threo* and *erythro* transition states would have steric interactions that mirror those found in the aldols themselves. This is the case when the solvent is polar or when the cation is dissociating.

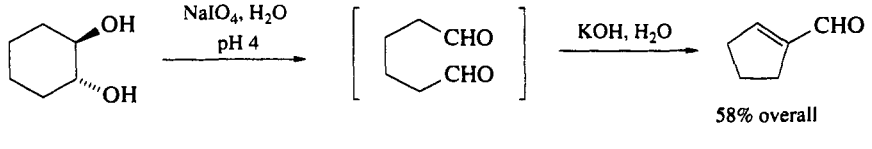
These important papers by Dubois and his coworkers laid the groundwork for an understanding of the factors governing the stereochemistry of the aldol reaction. Further studies were greatly facilitated by the introduction, in the 1970s, of reliable methods for the use of preformed enolates in the aldol reaction. This subject is discussed at length in succeeding chapters in this volume.

1.5.10 INTRAMOLECULAR ALDOL REACTIONS

Examples of intramolecular aldol reaction are legion, mainly in the context of the Robinson annelation reaction. Because this process has been the subject of recent reviews,[113] we do not here attempt an exhaustive survey. Emphasis in this chapter is placed on representative examples, to show the scope of the reaction, and questions of regio- and stereo-selectivity.

1.5.10.1 Dialdehydes

Intramolecular condensation of alkane dialdehydes gives cycloalkenecarbaldehydes under conditions of acid or base; cyclizations of symmetrical dialdehydes leading to five-, six- and seven-membered rings are depicted in equations (95)–(97).[114–116]



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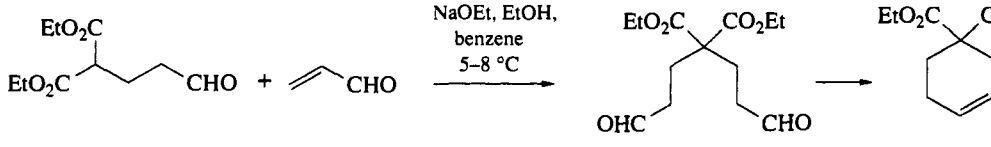

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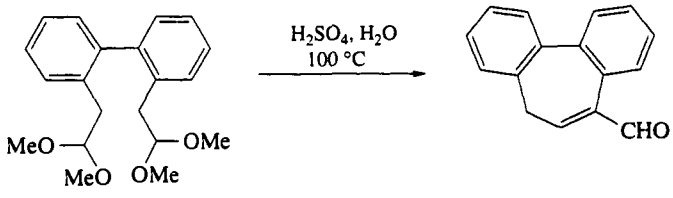


(97)

With unsymmetrical dialdehydes, a regiochemical issue exists. The first study of such a situation came as a part of Woodward's steroid synthesis.[117] Dialdehyde (**32**) is cyclized by piperidinium acetate, *via* an intermediate enamine, to give predominantly the cyclopentenecarbaldehyde (**33**; equation 98). It was proposed that the β-aldehyde (that is, CHO of the C-14 formylmethyl group) is less hindered and therefore more susceptible to intramolecular attack by an enamine derived from the more encumbered aldehyde.

In connection with a total synthesis of gibberellic acid, Corey and coworkers used dibenzylammonium trifluoroacetate to accomplish a regioselective aldol condensation (equation 99).[118] The success of this

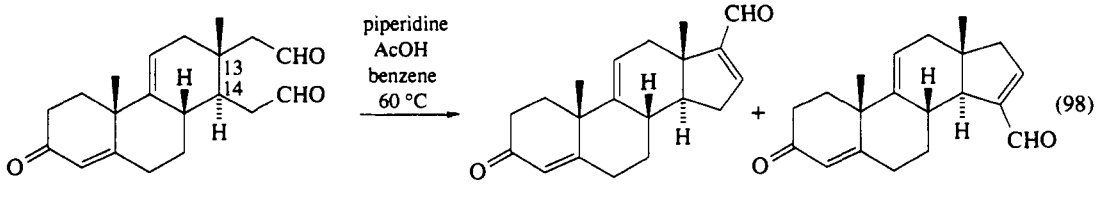
transformation was rationalized by the authors on the basis of activation of the less hindered formyl group as its enamine by a 'not-too-basic, sterically discriminating secondary amine under almost neutral aprotic conditions'.

Inubushi and coworkers have studied a similar unsymmetrical dialdehyde in the context of their fawcettimine synthesis.[119] Dialdehyde (**34**) cyclizes under various conditions to give a mixture of enals (**35** and **36**; equation 100). Unexpectedly, both the Woodward and Corey methods give the same major product, providing (**35**):(**36**) ratios of 21:1 (80% yield) and 19:1 (62% yield), respectively. The opposite regioselectivity is obtained by using morpholine and camphoric acid in ether–HMPA solvent; under these conditions, the (**35**):(**36**) ratio is 1:25 and the yield is 54%.

Büchi and coworkers have applied the Woodward conditions for the completely regioselective cyclization of dialdehyde (**37**) to (**38**) (equation 101).[120] As in the earlier examples, the cyclization appears to occur by the enamine of the more hindered aldehyde reacting with the less hindered aldehyde.

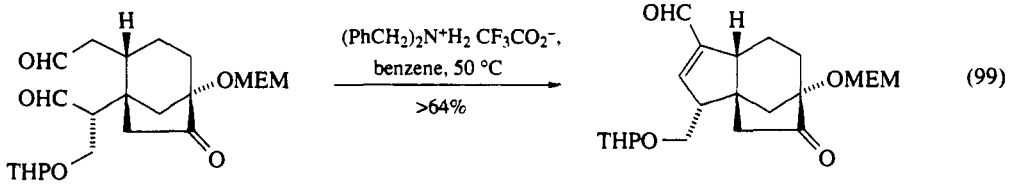
Nakane and Hutchinson have further shown that the aldol step in this cyclization is stereoselective as well as regioselective. Treatment of (**39**) with Hunig's base, acetic anhydride and 4-(*N,N*-dimethylamino)pyridine (DMAP), followed by sodium borohydride reduction of the intermediate β-hydroxy aldehyde, gives diol (**40**) in 48% yield; no diastereomeric diols were detected (equation 102).[121]

An exception to the generalization that the enamine of the more hindered aldehyde acts as the nucleophilic arm in intramolecular aldol reactions of unsymmetrical dialdehydes is seen in equation (103).[122] The regioselectivity of this cyclization is apparently very high; none of the other isomer was detectable by HPLC or NMR; the 57% yield quoted is the overall yield of the alcohol obtained by sodium borohy-

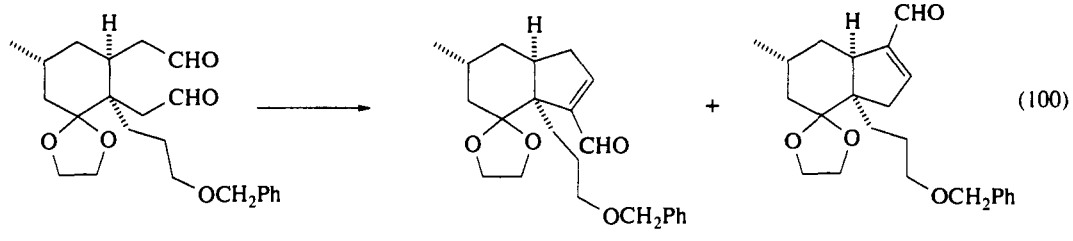


(98)

(**32**) (**33**) 66% very little

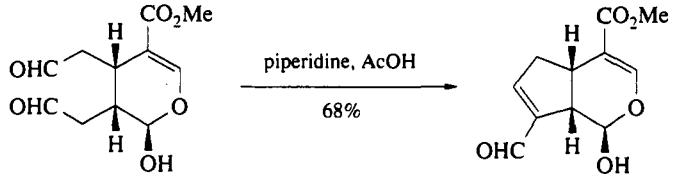


(99)



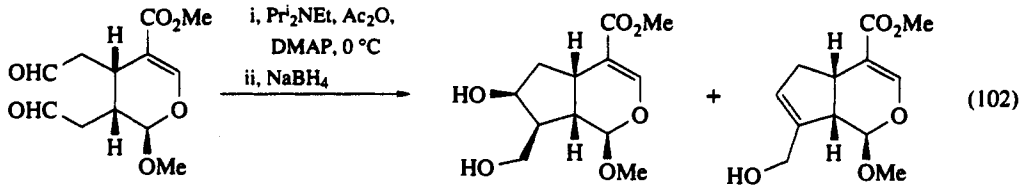
(100)

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



(101)

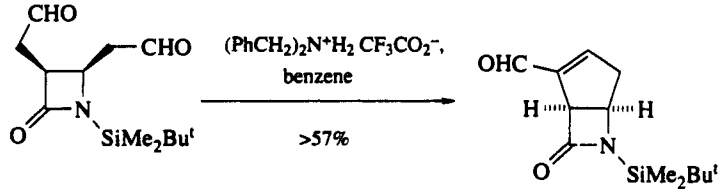
(**37**) (**38**)



(102)

(39) (40) 48% (41) 5%

dride reduction of (43). The Woodward procedure was also highly regioselective, but gave (43) in low yield (16% of the derived alcohol); the Inubushi method in this case gave the two regioisomeric enals in a 1:1 ratio.



(103)

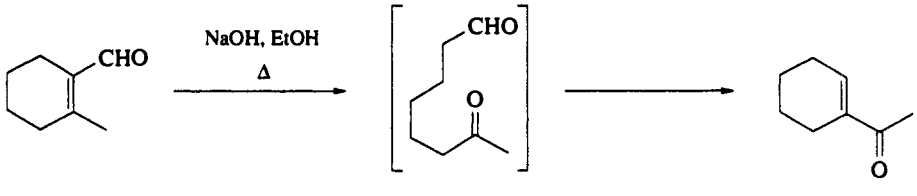
(42) (43)

1.5.10.2 Keto Aldehydes

Keto aldehydes are intrinsically unsymmetrical, and at least two isomeric products are usually possible. Conditions are known in which either the ketone or the aldehyde can function as the nucleophilic component. Aqueous or alcoholic base generally results in addition of the ketone enolate to the aldehyde, as shown in equation (104).[123] This example also illustrates the general preference for formation of an α,β-unsaturated ketone, rather than an isomeric α,β-unsaturated aldehyde under equilibrating conditions.

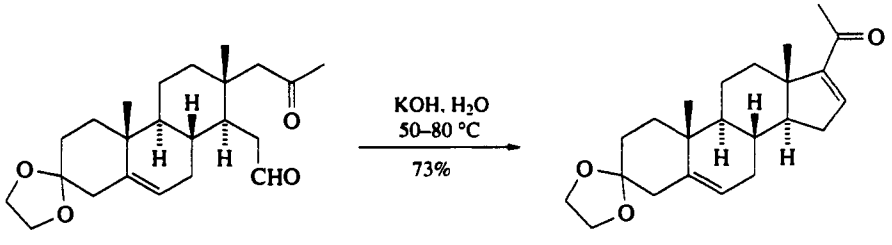
Aldol cyclization of keto aldehyde intermediates has been used in several steroid syntheses, as part of a strategy for conversion of a six-membered D-ring into a five-membered ring. An example is seen in equation (105), a step in the Sarett steroid synthesis.[124] A similar transformation has been utilized by Johnson and coworkers in a steroid synthesis.[125]

Corey and Nozoe cyclized a keto aldehyde as one step in a total synthesis of helminthosphoral (equation 106).[126] In this case, note that the aldehyde enolate adds to the more hindered ketone carbonyl to form a five-membered ring. The alternative addition of the ketone enolate to the aldehyde would give a seven-membered ring.



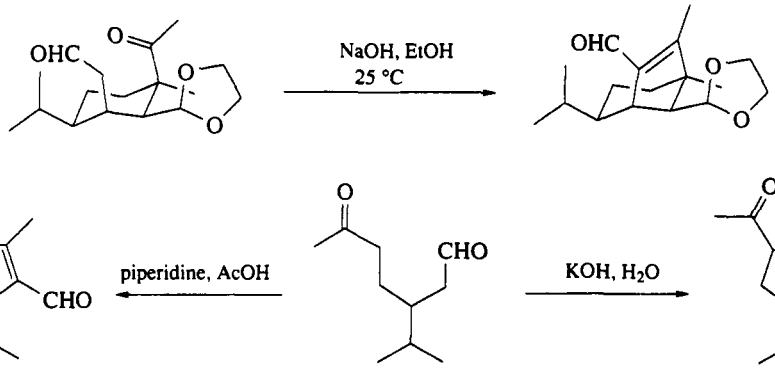
(104)

68%



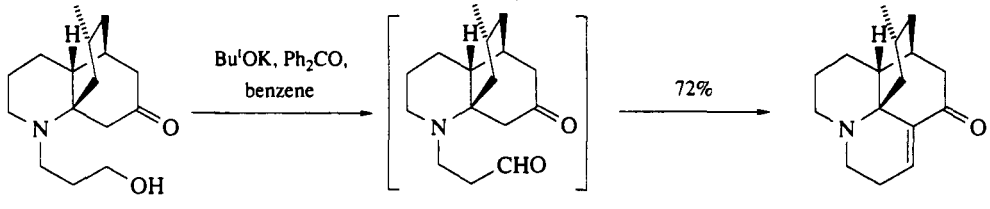
(105)

Lalande and coworkers have studied the regiochemistry of cyclization of keto aldehyde (**44**; equation 107).[127] In this system, aqueous KOH gives exclusively the cyclopentenyl methyl ketone (**45**), while piperidinium acetate leads to cyclopentenecarbaldehyde (**46**). Similar results were obtained by Wolinsky with the isopropenyl analog of (**44**).[128] These examples also demonstrate the preference for formation of a five- over a seven-membered ring.

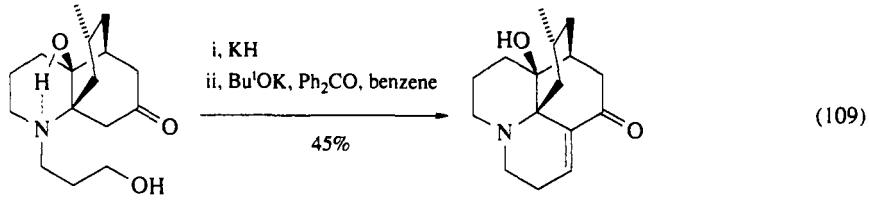


(**46**) (**44**) (**45**)

The cyclization depicted in equation (108) was a key step in a total synthesis of lycopodine.[129] Oppenauer oxidation of keto alcohol (**47**) gives keto aldehyde (**48**), which is cyclized under the reaction conditions to provide dehydrolycopodine (**49**). The transformation failed with keto diol (**50**). It was reasoned that, in this case, the tertiary hydroxy group acts as a general acid, protonating the nitrogen and allowing the intermediate β-amino aldehyde to undergo elimination. To remove this side reaction, compound (**50**) was deprotonated with KH prior to the Oppenauer reaction. Under these modified conditions, enone (**51**) is obtained in reasonable yield (equation 109).[130]

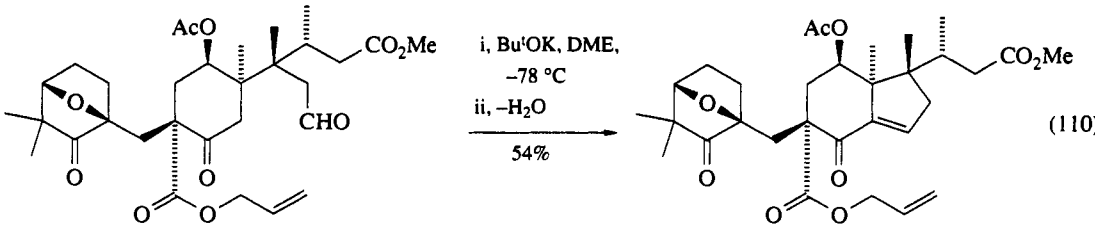


(**47**) (**48**) (**49**)



(**50**) (**51**)

Murai and coworkers carried out the intramolecular aldolization of intermediate (**52**) as one of the key steps in a synthesis of glycinoeclepin A (equation 110).[131] This example is more complicated than it may appear at first glance. There are four functions that may reasonably be deprotonated (two esters, the ketone and the aldehyde). Of these, the aldehyde is probably the most acidic. Although addition of the aldehyde enolate to the ketone is expected to be reversible, it could have undergone acylation by the side chain ester group (five-membered ring) or by the acetoxy group (six-membered ring).

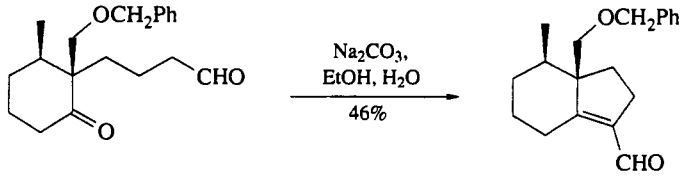


(110)

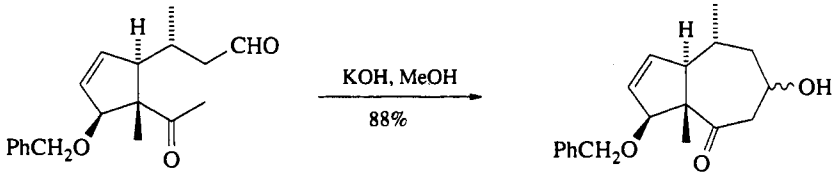
(52) (53)

When the preferred cyclization of the ketone enolate to the aldehyde is disfavored, the alternate mode of cyclization is observed; an example in which a cyclopentenecarbaldehyde is formed from a 1,6-keto aldehyde is shown in equation (111).[132]

Grieco and coworkers have utilized intramolecular aldolization of keto aldehydes to form seven-membered rings. In a synthesis of (±)-helenalin, keto aldehyde (**54**) was cyclized to aldol (**55**; equation 112).[133] In a later modification of the basic approach, keto aldehyde (**56**) was cyclized to cycloheptenone (**57**; equation 113).[134] The success of these cyclizations is related to the fact that the normally preferred five-membered ring closure would yield a strained *trans*-fused bicyclo[3.3.0]octene system.[135]

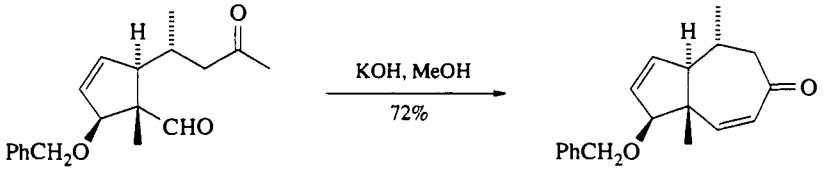


(111)



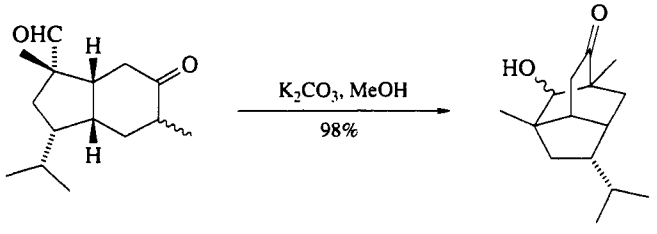
(112)

(54) (55)

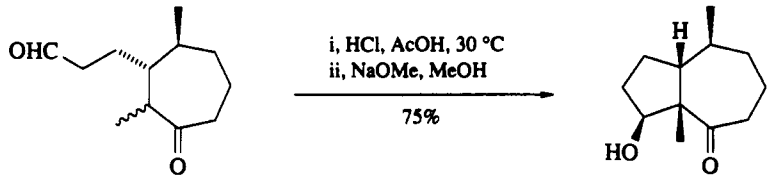


(113)

(56) (57)



(114)



(115)

Keto aldehydes are often observed to cyclize to aldols that cannot undergo dehydration. An example is taken from Corey's synthesis of (±)-2-isocyanopupukeanane (equation 114).[136]

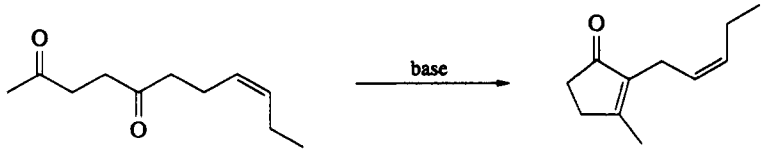
Keto aldehydes may also be cyclized under acidic conditions, as is shown by the transformation in equation (115), a step in the total synthesis of (±)-parthenin.[137] The aldol ester that is produced in the initial reaction is saponified by treatment with methanolic sodium methoxide.

1.5.10.3 Diketones

Aldol cyclization of 1,4-diketones yields cyclopentenones. Indeed, this excellent cyclization has been employed dozens of times in syntheses of the perfumery material *cis*-jasmone (**58**; equation 116).[138]

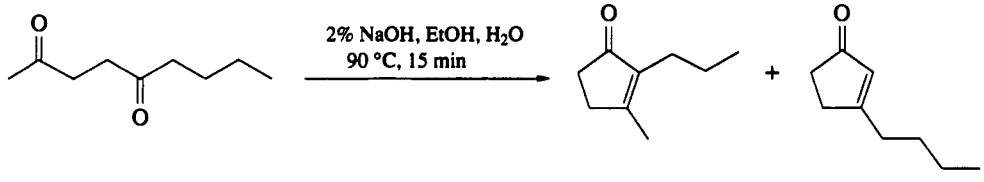
McCurry has investigated the regiochemistry of unsymmetrical 1,4-diketone cyclizations.[139] 2,5-Nonanedione undergoes cyclization under weakly basic conditions to give cyclopentenones (**59**) and (**60**) in a ratio of 94:6 (equation 117). Under the reaction conditions, independently synthesized (**60**) was not converted into (**59**). However, it was found that such trisubstituted alkenes *are* rearranged to the more stable tetrasubstituted isomers under more drastic conditions (equation 118).

Aldol cyclization can be used as a method of annulating a cyclopentenone ring onto another ring, provided the necessary 1,4-diketone is readily available. A pertinent example is seen in equation (119) in the



(116)

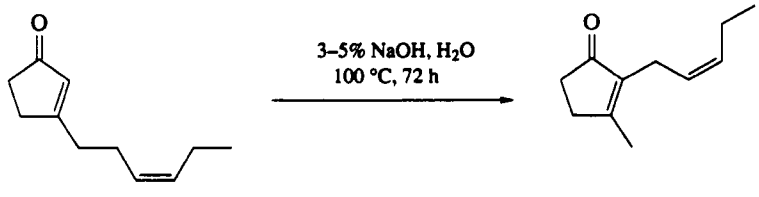
(**58**)



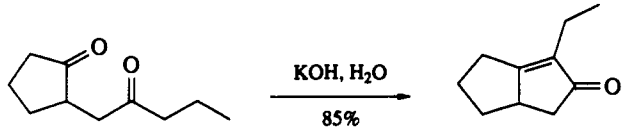
(117)

(**59**) (**60**)

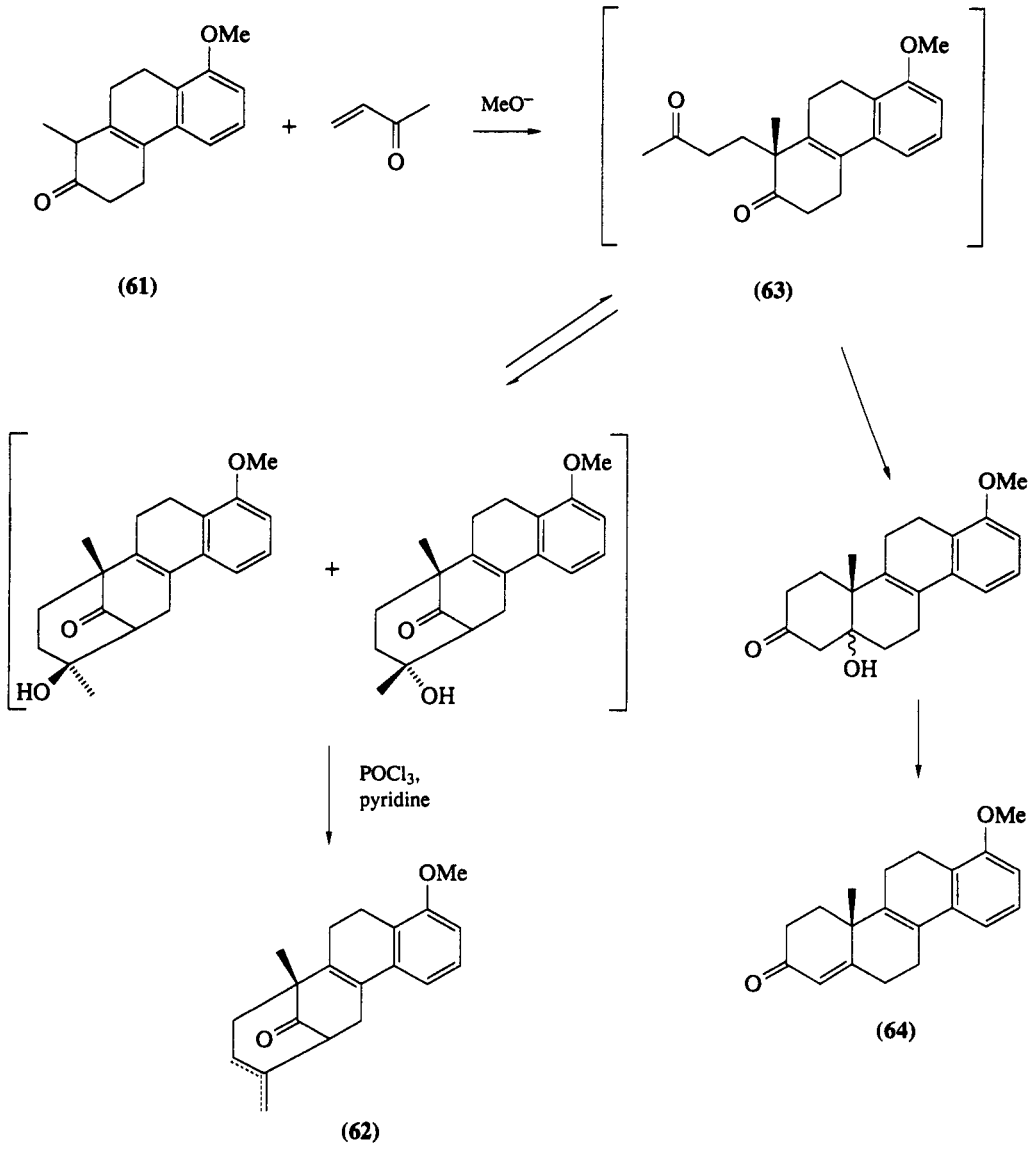
94:6



(118)



(119)



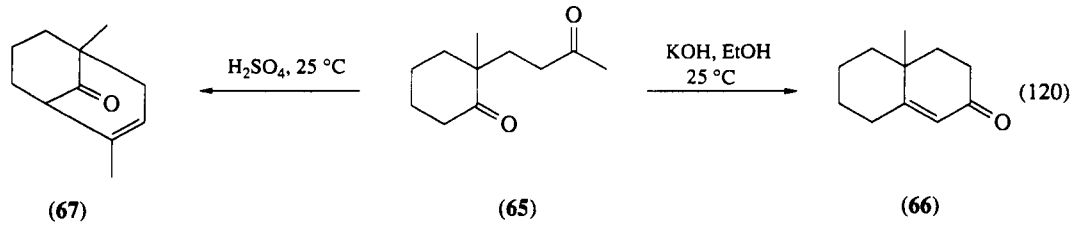
Scheme 3

formation of a bicyclo[3.3.0]octenone derivative.[140] However, the unsubstituted bicyclo[3.3.0]octenone cannot be prepared by this straightforward method.[141]

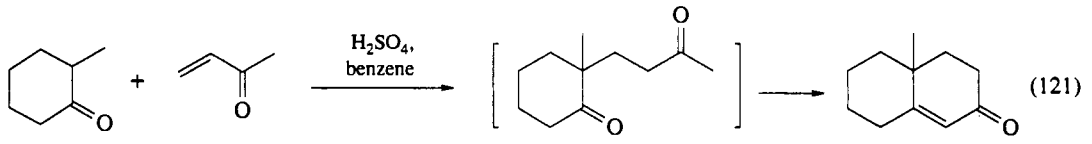
1,5-Diketones condense to give cyclohexenones. There are an enormous number of examples of such cyclizations, as this is one of the two steps in the Robinson annelation reaction.[113] In the annelation of a cyclohexenone onto a preexisting ring, the intermediate 1,5-diketone is unsymmetrical, and there is a question of regiochemistry. This issue was addressed by W. S. Johnson and coworkers in the context of steroid total synthesis.[142] As shown in Scheme 3, Robinson annelation of β,γ-unsaturated ketone (**61**) with methyl vinyl ketone affords a mixture of two bridged ketols. Dehydration of the separated isomers provides a mixture of β,γ-unsaturated ketones (**62**). However, treatment of the original ketol mixture under more vigorous basic conditions leads to the α,β-unsaturated ketone (**64**). Presumably, the kinetically formed ketols are in equilibrium with dione (**63**), which cyclizes, *via* the isomeric ketols, to (**64**).

Similar behavior with the simpler 1,5-diketone (**65**) has been documented by Marshall and Schaeffer.[143] As shown in equation (120), diketone (**65**) cyclizes to octalone (**66**) under basic conditions and to the bicyclo[3.3.1]nonenone (**67**) under acidic conditions. The regiochemistry of ring closure in this system is sensitive to the exact reaction conditions. For example, diketone (**65**), an intermediate in the acid-mediated Robinson annelation process, cyclizes to octalone (**66**; equation 121).[144] In this example, it is

possible that enones (**66**) and (**67**) are actually in equilibrium, and that the former is favored on thermodynamic grounds.

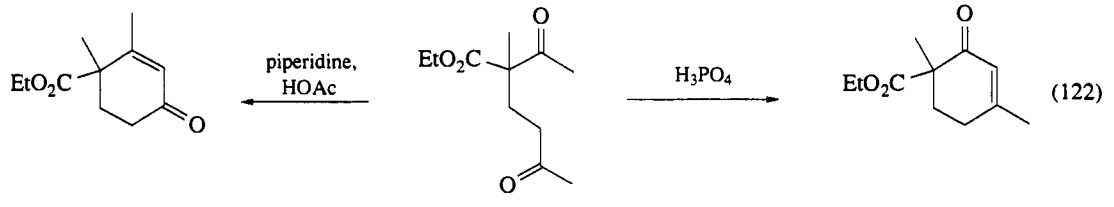


(**67**) (**65**) (**66**)



(**65**) (**66**) 60%

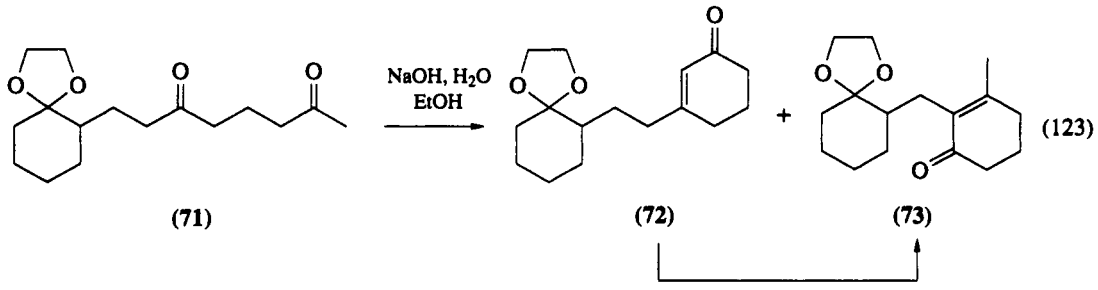
Several groups have examined the regiochemistry of cyclizations of acyclic 1,5-diketones. One of the first investigations was carried out by Plieninger and Suchiro, who studied the regiochemistry of cyclization of diketone (**68**; equation 122).[145] It was found that acidic conditions lead to the cyclohexenone (**69**), a reaction in which the enol of the more hindered ketone has condensed with the less hindered ketone. With piperidine and acetic acid (enamine conditions), the enamine of the less hindered ketone appears to add to the more hindered carbonyl group. This cyclization has been studied in detail by Kreiser and Below, who investigated compound (**68**) and eight of its analogs.[146] The best reagent for cyclization to (**69**) was found to be a mixture of HCl and trimethylsilyl chloride; compound (**69**) and its analogs are obtained in 70–92% yield after 16 h at room temperature. Piperidine and acetic acid in refluxing benzene for 12 h provides (**70**) in 65–94% yield. Similar investigations have been reported by Koga and coworkers[147] and by Frater and coworkers.[148]



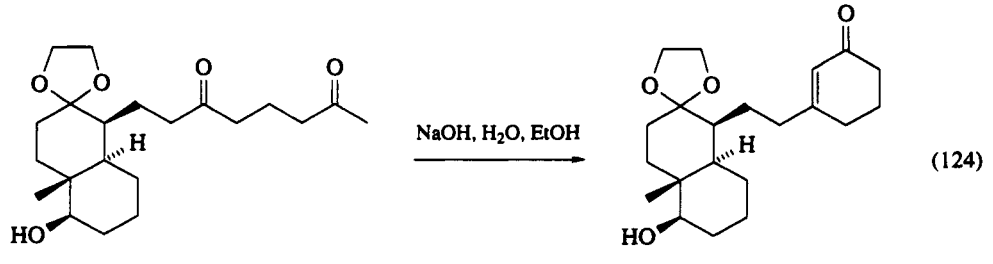
(**70**) (**68**) (**69**)

Danishefsky examined the regiochemistry of 1,5-diketone cyclization in the context of a steroid synthesis.[149] Diketone (**71**) cyclizes in aqueous ethanolic base to give a mixture of isomeric cyclohexenones (**72**) and (**73**) (equation 123). If the reaction is carried out at room temperature, the (**72**):(**73**) ratio is 77:23; after refluxing for 50 h, the ratio is 21:79. Furthermore, pure (**72**) is converted into (**73**) under the latter reaction conditions. With diketone (**74**), cyclohexenone (**75**) is the only product seen under either conditions (equation 124).

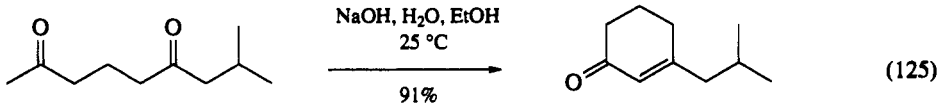
The foregoing work suggests that the 3-substituted cyclohexenones (**72**) and (**75**) are kinetically favored in the cyclization of diketones (**71**) and (**74**), but that sufficiently vigorous conditions might cause isomerization to the 2,3-disubstituted cyclohexenone (*e.g.* **72** → **73**). The fact that (**75**) does not undergo this further isomerization suggests that chain branching might perturb the equilibrium ratio in favor of the 3-substituted isomer. The effect of chain branching was verified in a further investigation.[150] Diketone (**76**) cyclizes at room temperature to give the 3-substituted product (**77**) as the only detected product in 91% yield (equation 125). Under identical conditions, the unbranched diketone (**78**) affords isomers (**79**) and (**80**) in a ratio of 17–19:1 (equation 126). The effect of branching is attenuated when the branch point is moved away from the carbonyl group, as shown in equation (127). The data in this equation suggest that, in the absence of branching, there is no intrinsic preference for formation of either the trisubstituted or tetrasubstituted alkene. Branching near one of the carbonyl groups causes a pref-



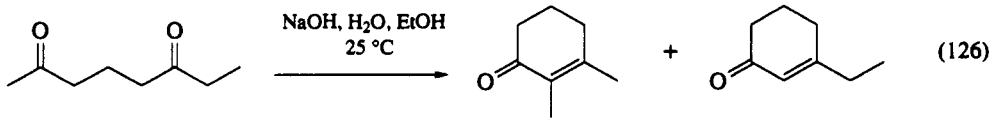
(71) (72) (73) (123)



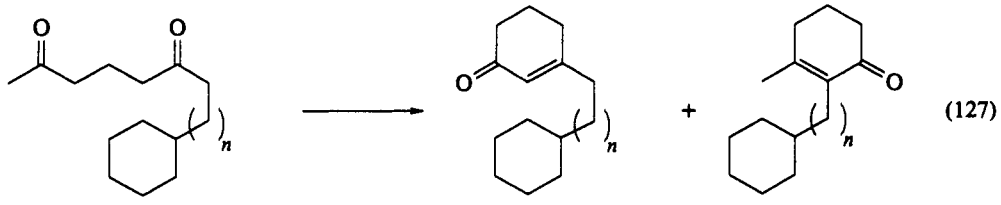
(74) (75) (124)



(76) (77) (125)



(78) (79) 79% (80) 4.5% (126)

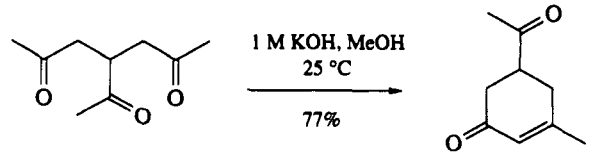


(81) (82) (83) (127)

n	(82):(83)
0	> 30:1
1	8.1:1
2	1.3:1
3	1.3:1
4	1.1:1

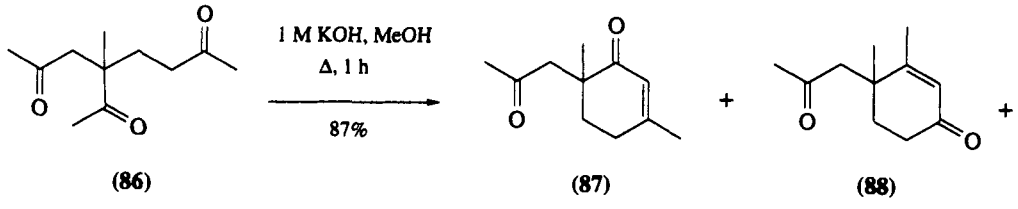
erence for formation of isomer (**82**), with the effect being stronger the nearer the branch point is to the carbonyl group.

Baldwin and Lusch have studied several triketones that could, in principle, undergo intramolecular aldol condensation to give several different enones.[151] Triketone (**84**), which is both a 1,4- and a 1,5-diketone, reacts under mild basic conditions to give only the corresponding cyclohexenone (**85**); neither of the two possible cyclopentenones are produced (equation 128). Triketone (**86**) is a more complex case, since it embodies 1,4-, 1,5- and 1,6-diketone relationships. In principle, this material can cyclize to five-, six- or seven-membered aldol products, in a total of eight different ways. However, when an aqueous alcoholic basic solution of (**86**) is refluxed, only two of these eight modes of cyclization are observed (equation 129). Cyclohexenones (**87**) and (**88**) are formed in a ratio of 85:15 (*cf.* equation 122), along with smaller amounts of the bicyclic aldols (**89**) and (**90**), shown to be secondary products arising from (**87**) and (**88**). Triketone (**91**) is a somewhat simpler case, in that it may cyclize to a cyclohexenone or to three different cyclopentenones. In the event, (**91**) was found to give only cyclohexenone (**92**; equation 130). This work clearly shows that six-membered rings are formed in preference to five- or seven-membered rings by intramolecular aldolization under condensation conditions.

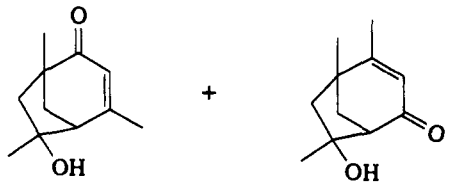


(128)

(**84**) (**85**)

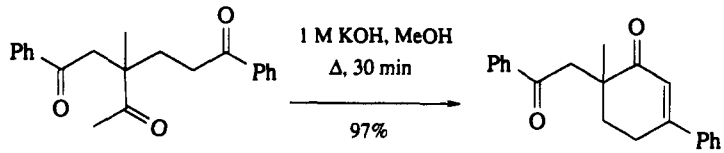


(**86**) (**87**) (**88**)



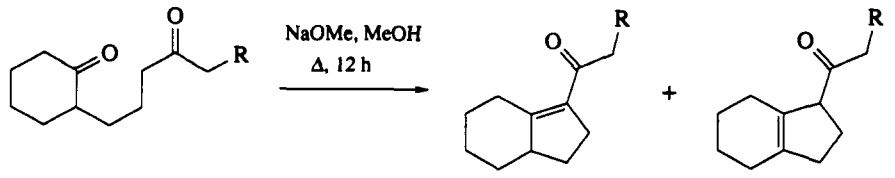
(129)

(**89**) (**90**)



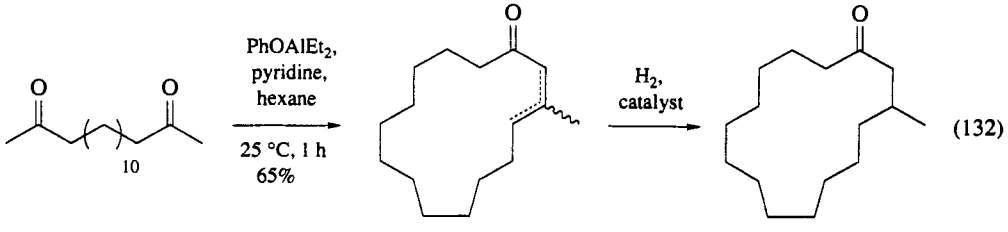
(130)

(**91**) (**92**)

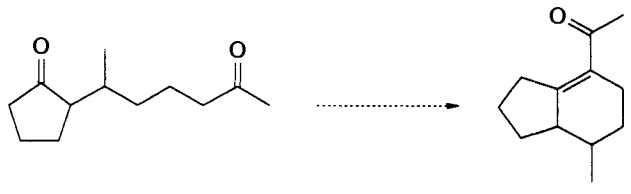


(131)

(**93**) (**94**) (**95**)

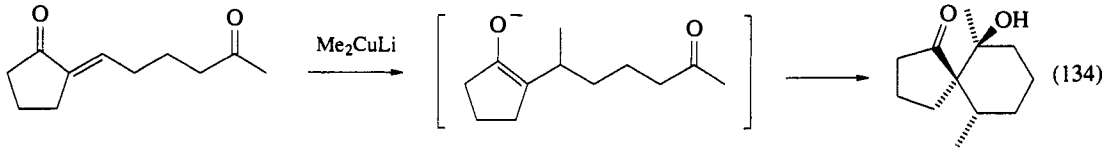


(132)



(133)

(96) (97)



(134)

(98) (99) (100)

Two other research groups have also examined the relative ease of formation of five- and seven-membered aldol condensation products from 1,6-diketones.[152,153] In one study, diketone (**93**; equation 131; R = H) was found to cyclize to give solely (**94**). In another investigation, (**93**; R = Me) was employed and the product was carefully examined for minor amounts of seven-membered ring isomers. None could be detected, although an unspecified amount of the β,γ-unsaturated isomer (**95**) was found.

Tsuji and coworkers have developed diisobutylaluminum phenoxide–pyridine as an effective aldol condensation catalyst and applied it to the macrocyclization of 2,15-hexadecanedione (equation 132).[154] Addition of the diketone at high dilution to a solution of the catalyst in hexane provides a mixture of *cis* and *trans* isomers of the Δ^2 and Δ^3 enones. Catalytic hydrogenation of the mixture affords (±)-muscone. The authors explain the regioselectivity of the process by assuming that the aluminum phenoxide functions as a Lewis acid, coordinating to the carbonyl group. Pyridine functions as a base to remove a proton from the less hindered methyl group.

As will be seen in the following chapter, the use of strong amide bases for preforming enolates allows a considerable measure of control in defining the regiochemistry of aldol reactions. This technique, however, is more often applied in intermolecular aldol additions than in intramolecular ones. Näf and coworkers have reported an interesting way to control regiochemistry.[155] Diketone (**96**) would presumably cyclize under dehydrating conditions to give the acetylcyclohexene (**97**; equation 133). However, if the unsaturated diketone (**98**) is treated with lithium dimethylcopper, enolate (**99**) is formed and cyclizes to give the spirocyclic aldol (**100**; equation 134).

1.5.10.4 Stereochemistry of Aldol Cyclizations

There are few cases in which the stereochemistry of cyclic aldol addition reactions has been carefully examined. The situation is complicated by the problem of retro-aldolization and by the propensity of such aldols to dehydrate to the enone. There is a suggestion that under strictly kinetic conditions, aldols in which the carbonyl and hydroxy groups can chelate a metal cation are favored. However, in protic medium, it does not appear that the kinetic product is generally the more stable one. A particularly instructive example is seen in equation (135).[156] The complex keto aldehyde (**101**) was treated with dilute KOH in methanol for 15 min at various temperatures. At –20 °C, +25 °C, and +65 °C, the (**102**):(**103**) ratios were 93:7, 50:50 and 0:100, respectively.

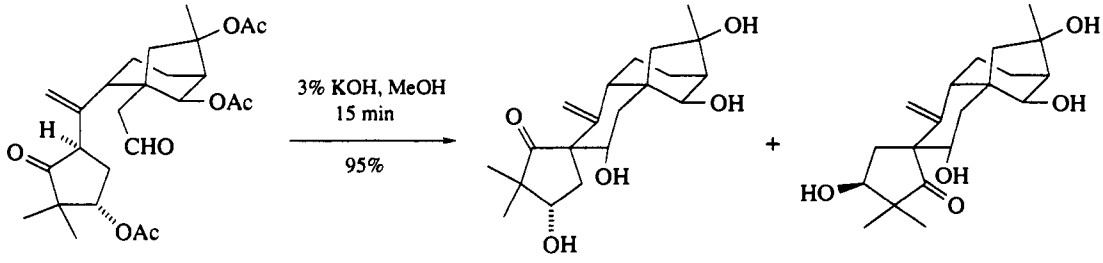
Similar behavior is seen in the cyclization of dialdehyde (**104**), an intermediate in the dimerization of 2-ethyl-2-hexenal; the resulting mixture of aldol products contains 99% of isomer (**105**; equation 136).[23a-b]

Cyclizations that are carried out under equilibrating conditions often give mixtures of stereoisomeric aldols. An example of this behavior is seen in aldolization of keto aldehyde (**106**) with potassium *t*-butoxide in benzene; aldols (**107**) and (**108**) are formed in a ratio of 2:3 (equation 137).[157]

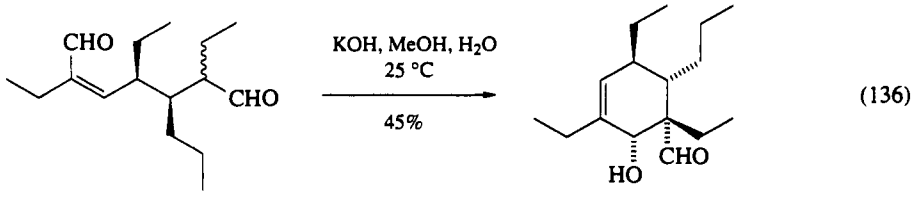
However, other structural features can provide a thermodynamic selection of one stereoisomer. Intramolecular aldolization of 2,2′-*O*-methylene-bis-D-glycerose (**109**) under weakly basic conditions affords only two of the four possible aldols, (**110**) and (**111**) (Scheme 4).[158] The (**110**):(**111**) ratio greatly favors the former, and conditions were found under which only isomer (**110**) is produced. It was proposed that the aldol cyclization is under thermodynamic control, and that the initial products are trapped as their intramolecular hemiacetals (**112**) and (**113**). The other two possible aldols cannot form such hemiacetals. Isomer (**112**) is presumably favored over (**113**) because of the normal equatorial preference of a hydroxy group that is hydrogen-bonded to water.

In 1971, groups at Hoffmann–La Roche and Schering AG reported the exceedingly useful discovery that symmetric triketones such as (**114**), in which the two cyclopentanone carbonyl groups are enantiotropic, undergo aldolization in the presence of L-proline to give aldols (**115**) in high enantiomeric excess (equation 138).[159,160] Using (**114**; R = Me), the aldol is produced in quantitative yield with 93.4% *ee*; with (**114**; R = Et), the aldol is obtained in 70–76% yield with 99.5% *ee*. Dehydration of the aldols provides the synthetically useful hydrindenediones (**116**; R = Me or Et). The method was subsequently extended to the synthesis of enantiomerically homogeneous Wieland–Miescher diketone (**117**; equation 139).[161] Takano and coworkers have used the procedure with an indanedione derivative to prepare the gibbane framework in enantiomerically pure form (equation 140).[162]

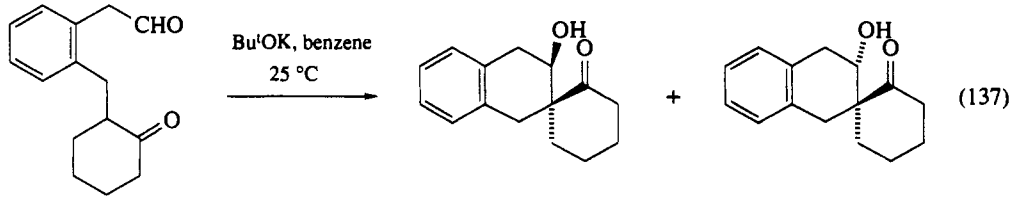
Danishefsky and Cain examined several amino acids for asymmetric aldolization of trione (**118**; equation 141).[163] With L-proline, the hydrindenedione (**119**) was obtained in only 27% *ee*. However, L-phenylalanine was more effective, giving (**119**) with 85% *ee*. Other amino acids (tyrosine *O*-methyl ether,



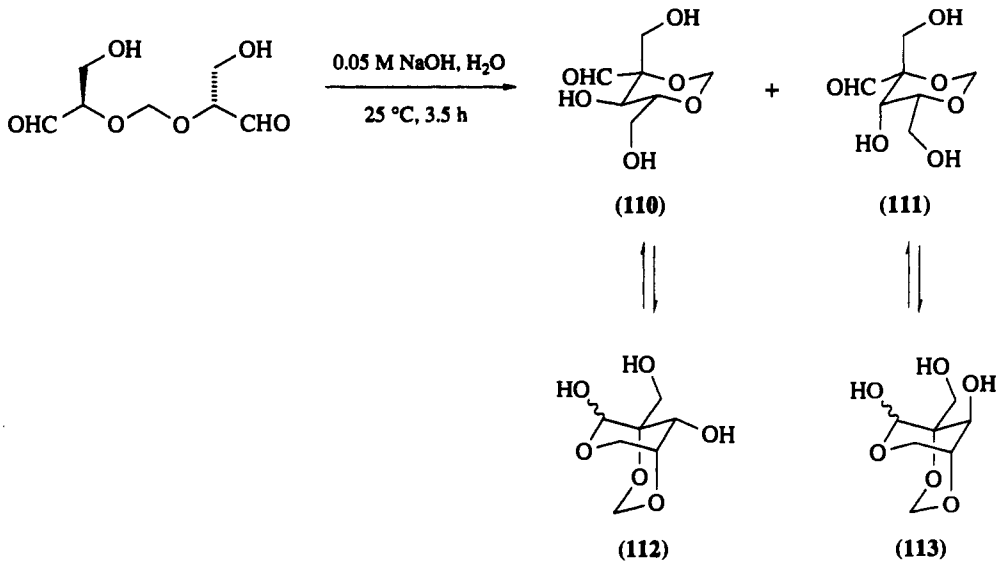
(**101**) (**102**) (**103**) (135)



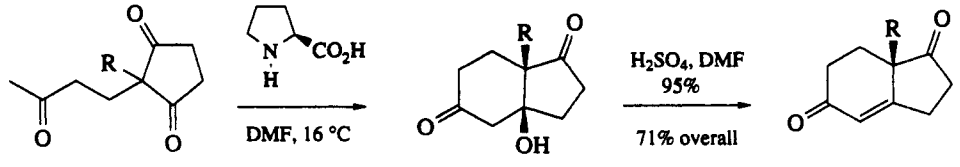
(**104**) (**105**) (136)



(**106**) (**107**) 21% (**108**) 30% (137)

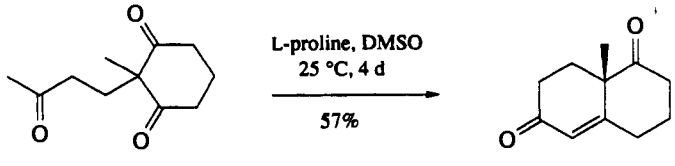


Scheme 4



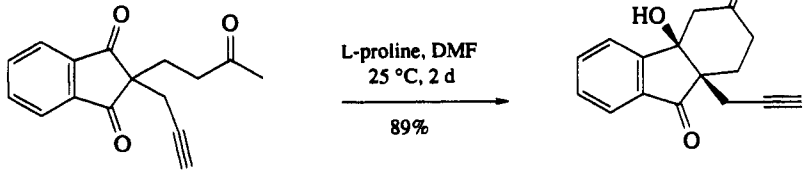
(138)

(114) R = Me, Et **(115)** R = Me, Et **(116)** R = Me, Et

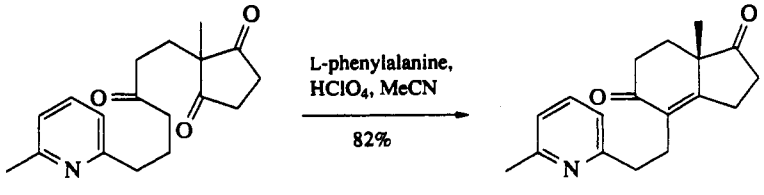


(139)

(117)



(140)



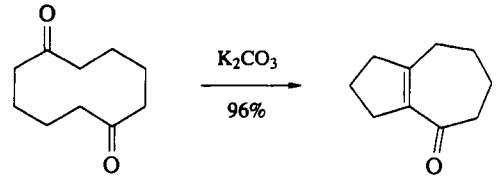
(141)

(118) **(119)** 85% *ee*

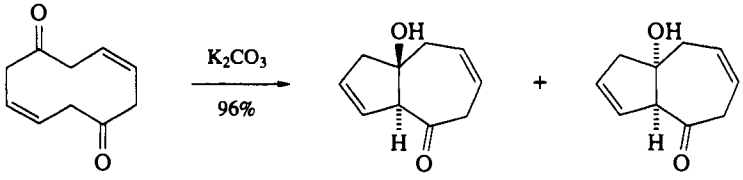
tryptophan, serine and valine) also gave cyclized products, with enantiomeric excesses of 84%, 78%, 35% and 21%, respectively.

1.5.10.5 Transannular Cyclizations

Macrocyclic diketones can undergo transannular aldol cyclization reactions, giving bicyclic aldols. A representative example is seen in the cyclization of 1,6-cyclodecanedione to the corresponding hydroazulenone (equation 142).[164] Aldolization of the related cyclodecadienedione (**120**) has also been examined; under mildly basic conditions aldols (**121**) and (**122**) are the main products, being formed in a ratio of 1:4 (equation 143).[165] Control experiments with the pure aldols showed that this is the thermodynamic ratio of isomers.



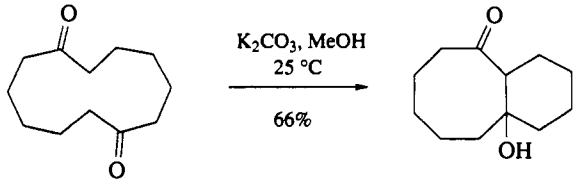
(142)



(143)

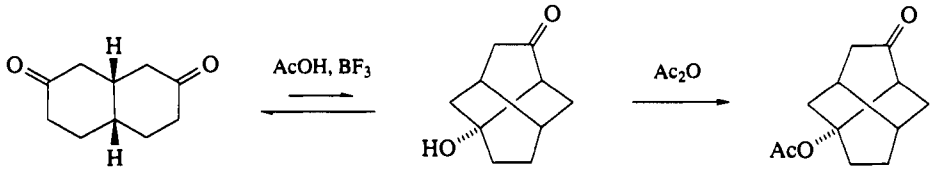
(**120**) (**121**) (**122**)

Aldolization of 1,7-cyclododecanedione proceeds smoothly to produce a crystalline aldol in 66% yield (equation 144).[166] Although the stereochemistry of this product has not been elucidated, its sharp melting point (70–71 °C) suggests that it may be a single isomer.



(144)

Related cyclizations are observed in certain bicyclic diketones, converting them into tricyclic aldols. Deslongchamps and coworkers discovered that *cis*-bicyclo[4.4.0]decane-3,9-dione is the minor isomer in equilibrium with its intramolecular aldol, the twistane derivative (**123**; equation 145).[167] The equilibrium could be shifted completely to the aldol by acetylation.

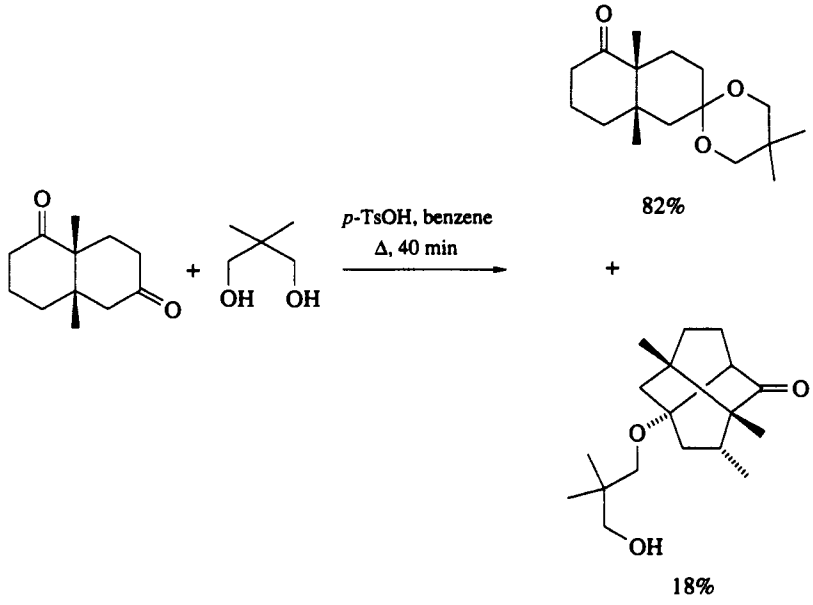


(145)

(**123**) (**124**)

Yordy and Reusch observed a similar intramolecular aldolization in a decalindione. As shown in equation (146), dione (**125**) is in equilibrium with aldol (**126**) under basic conditions ($K = 2.3$).[168] Aldol (**126**) may be obtained as a crystalline substance, but it is easily converted back into dione (**125**) (*e.g.* under

(125) (126) (146)

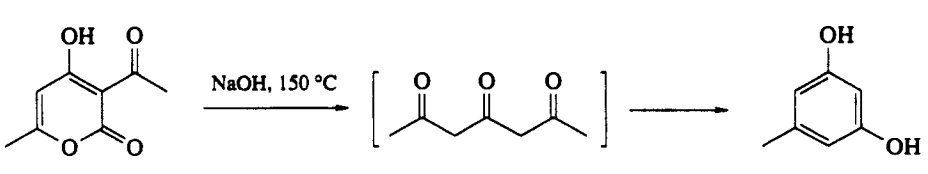


(147)

acidic conditions). Similar intramolecular aldolizations can sometimes give rise to quite unexpected products (equation 147).[169]

1.5.10.6 Polyketides

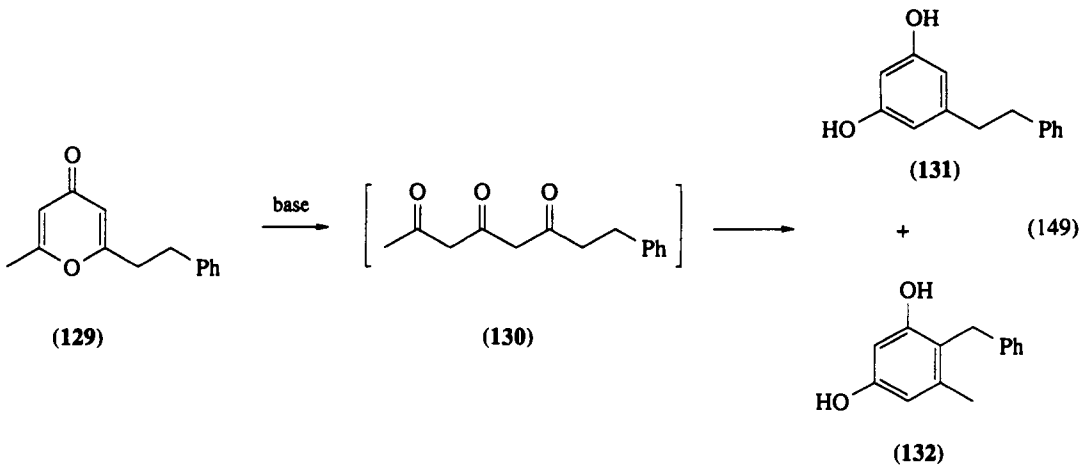
In 1907, Collie showed that dehydroacetic acid is converted into orcinol (**128**) on treatment with base.[170] It was presumed that this transformation proceeds through triketone (**127**; equation 148). On the basis of this reaction, Collie suggested the 'polyacetate' biogenesis of naturally occurring phenolic compounds. In later work, it was shown that trione (**127**) is converted by acid into phenol (**128**).[171,172]

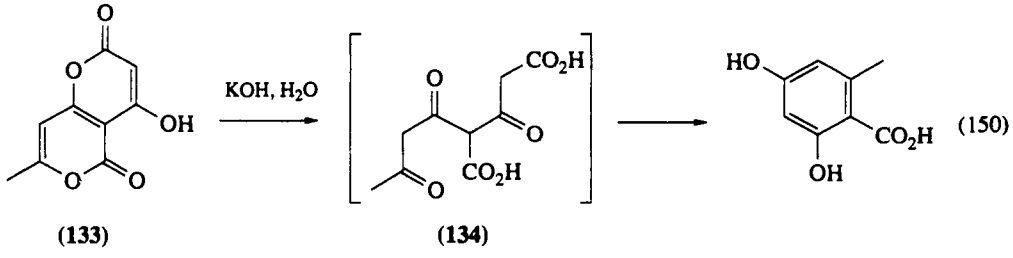


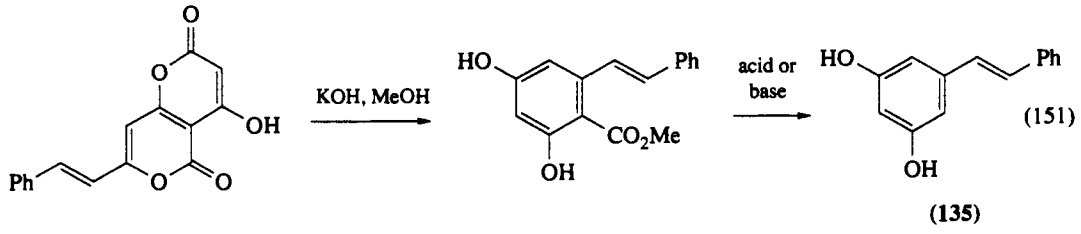
(127) (128) (148)

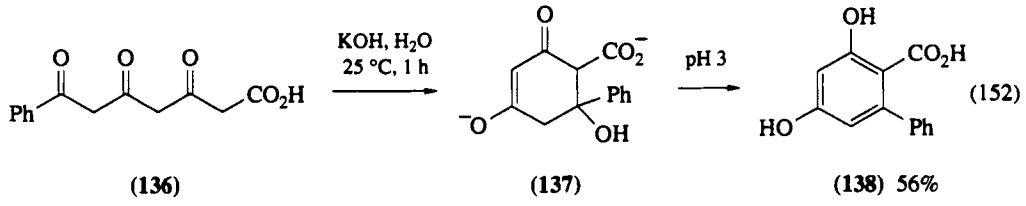
Birch and coworkers fully elaborated the polyketide hypothesis and examined possible biomimetic syntheses. In one example, treatment of γ-pyrone (**129**) with base was found to give a mixture of resorcinols (**131**; dihydropinosylvin) and (**132**), presumably from the two modes of intramolecular aldolization of triketone (**130**; equation 149).[173]

Money, Scott and coworkers utilized a similar strategy of protecting the labile polyketone as a pyrone ring. As shown in equation (150), pyranopyrone (**133**) reacts with aqueous base to give orsellinic acid, presumably by way of the intermediate triketo diacid (**134**).[174] The procedure was found to be quite general; equation (151) shows a further application in the synthesis of pinosylvin, (**135**).[175]





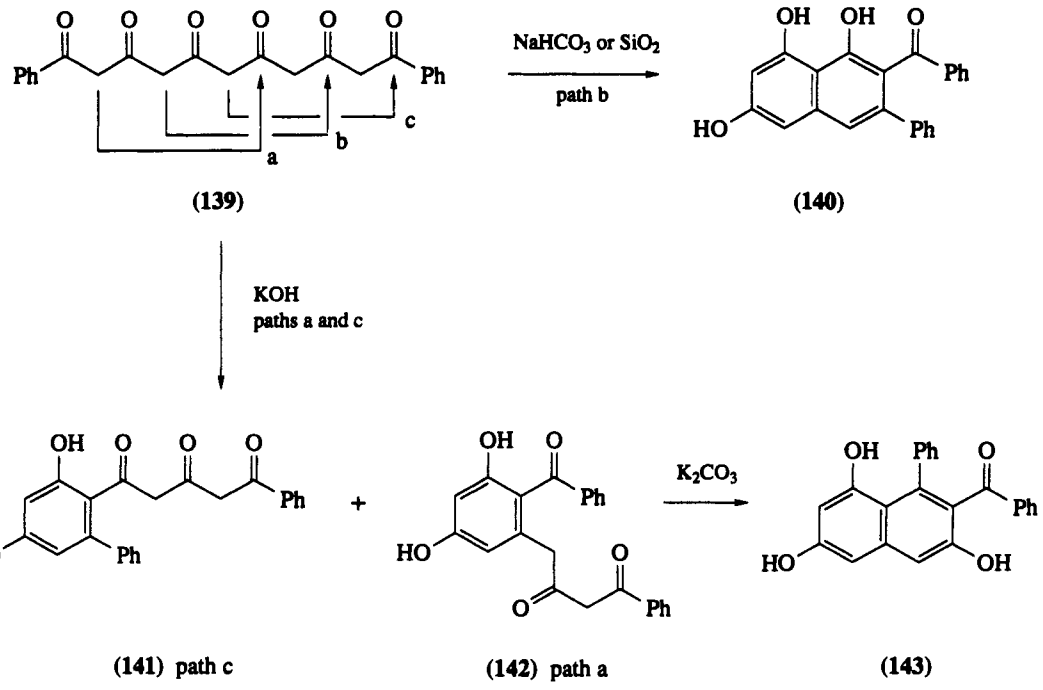




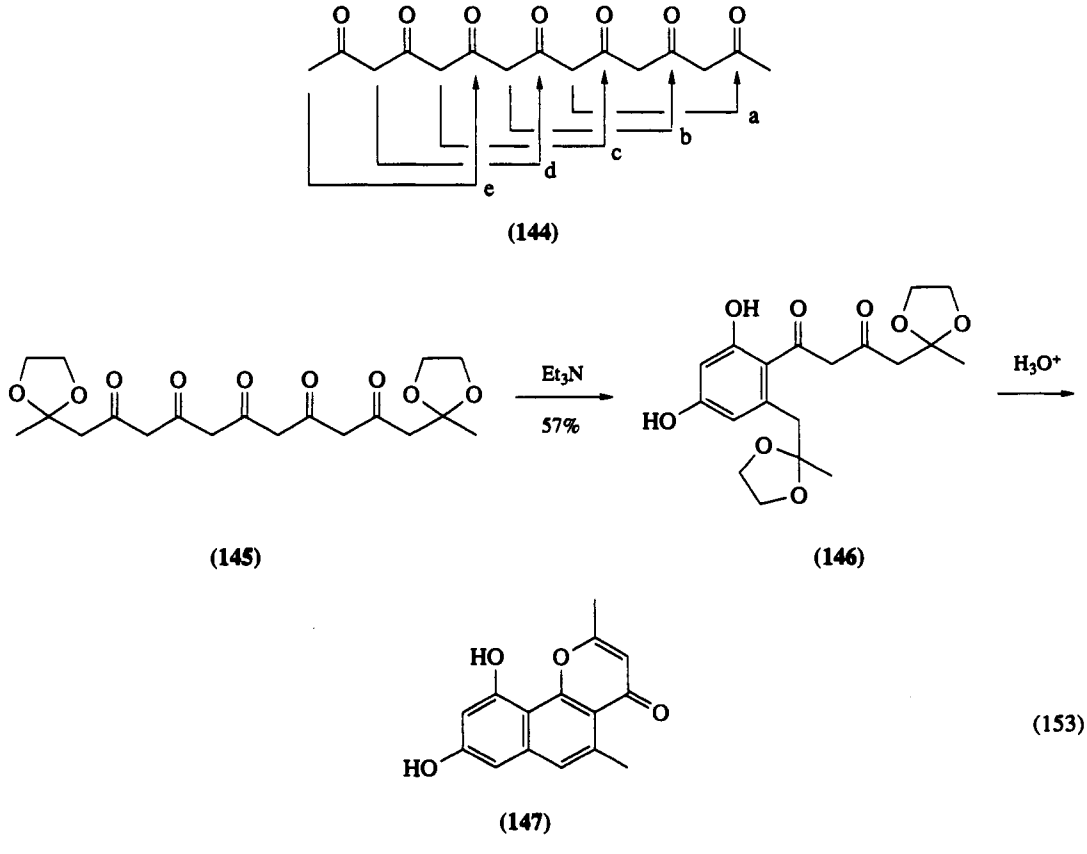
Harris and coworkers have developed ways to prepare polyketones and have carried out extensive studies on their intramolecular aldol reactions.[176] A simple and representative example of this work is shown in equation (152); treatment of triketo acid (**136**) with aqueous base at room temperature gives (**137**), the dianion of a 1,3-cyclohexanedionecarboxylic acid.[177] Although (**137**) is stable for several days in basic solution, acidification results in rapid dehydration to give the resorcylic acid (**138**).

A more complex substrate is hexaketone (**139**), which has three possible initial aldolization modes (Scheme 5; a, b and c). Treatment of this material with sodium bicarbonate or silica gel provides naphthalene derivative (**140**), the result of mode b aldolization.[178] On the other hand, use of aqueous KOH gives resorcinol derivatives (**141**) and (**142**), resulting from aldolization modes a and c. Further aldolization of (**142**) to (**143**) is achieved by treatment with potassium carbonate.

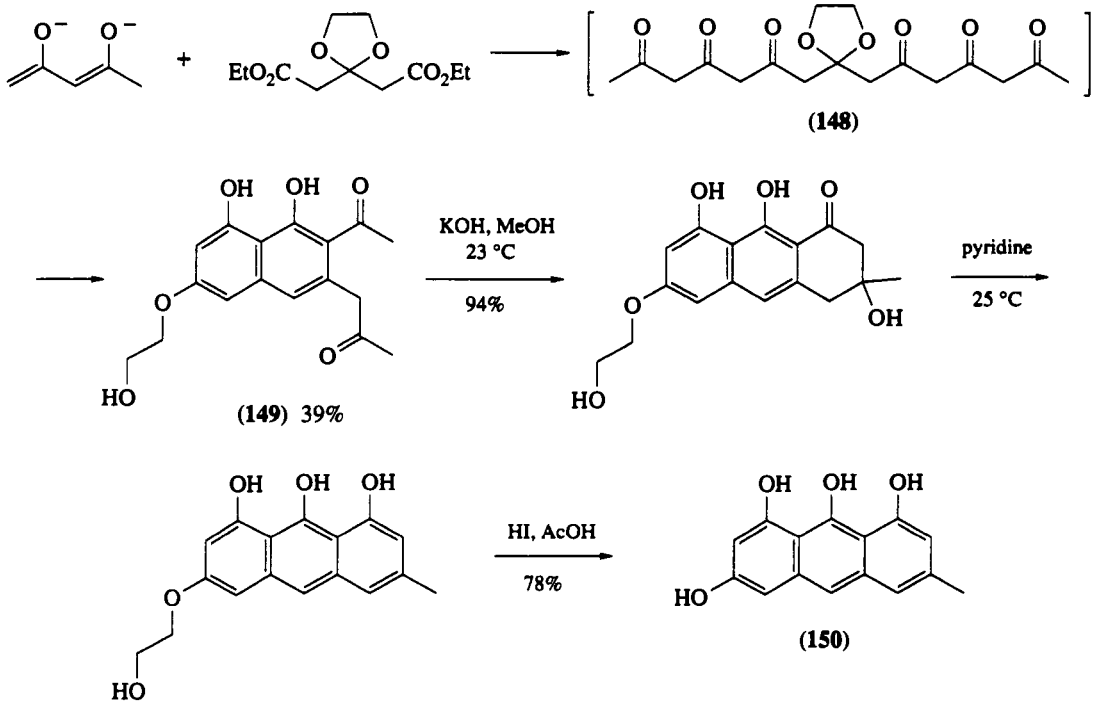
In extending these biomimetic studies to higher polyketones, one encounters a plethora of possible aldol reactions. For example, 2,4,6,8,10,12,14-pentadecaneheptone can undergo five possible initial cyclizations leading to six-membered rings (**144**). To reduce the number of possible reactions, Harris and Wittek prepared the diketal (**145**). Cyclization of this material occurs mainly by mode b to give (**146**), which further cyclizes on acidification to provide eleutherinol (**147**); equation 153).[179]


NaHCO3 or SiO2
path b
KOH
paths a and c
K2CO3
(139)
(140)
(141) path c
(142) path a
(143)

Scheme 5


(144)
Et3N
57%
H3O+
(145)
(146)
(147)
(153)

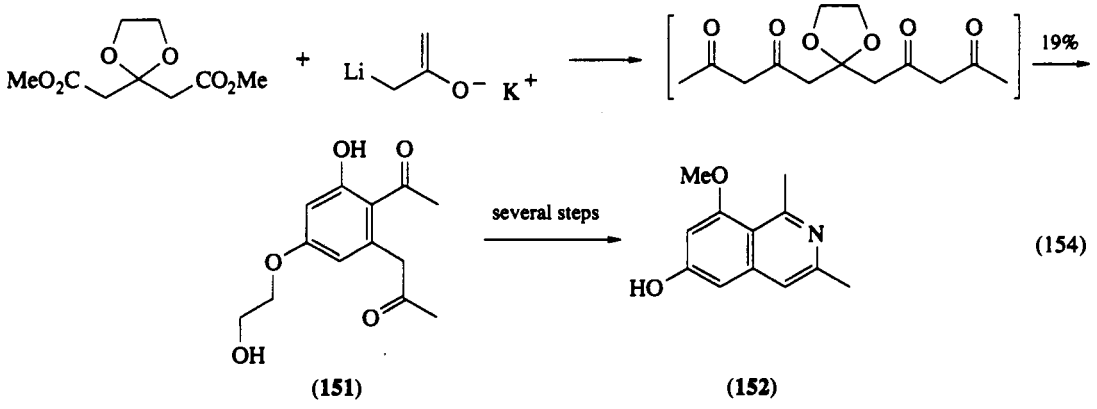
To achieve type c aldolization, the monoprotected heptaketone (**148**) was prepared as shown in Scheme 6.[180] Condensation of the dianion of 2,4-pentanedione with the ethylene ketal of diethyl 3-oxoglutarate presumably affords (**148**). However, the substance eludes isolation or even spectral identification. Instead, naphthalene derivative (**149**) is obtained in 39% yield. Further aldolization, dehydration, and removal of the ethylene glycol moiety provides the naturally occurring anthrone (**150**).



Scheme 6

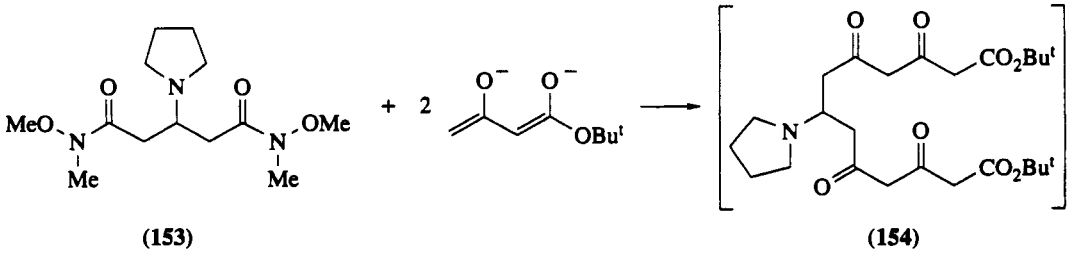
Bringmann has reported a similar cyclization.[181] Reaction of lithiopotassioacetone with the ethylene ketal of dimethyl 3-oxoglutarate provides phenol (**151**) in 19% yield (equation 154). Again, the intermediate tetraketone eludes isolation. A series of transformations serves to convert (**151**) into the isoquinoline (**152**).

One of the most complex molecules yet prepared by these biomimetic approaches is the pretetramid (**158**; Scheme 7).[182] The 3-pyrrolidinoglutaric acid diamide (**153**) is condensed with two equivalents of the dianion of *t*-butyl acetoacetate. The putative intermediate (**154**) undergoes spontaneous cyclization to provide the naphthalene derivative (**155**). This substance is transformed by a sequence of steps into naphthalenopyrone (**156**), which is extended by reaction with an isoxazole dianion. Spontaneous aldolization again occurs, yielding the anthracene derivative (**157**). Closure of the final ring ensues when (**157**) is treated with HI.

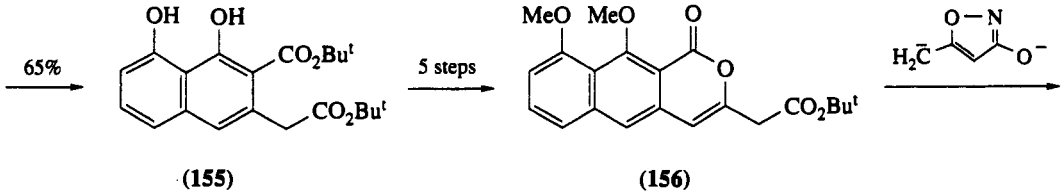


(154)

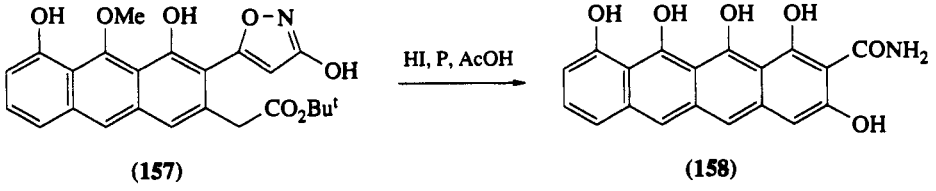
Yamaguchi has reported the preparation of polyketone compounds by addition of the dianion of methyl acetoacetate to *N,N,N',N'*-tetramethylsuccinamide in the presence of boron trifluoride etherate (equation 155).[183] Treatment of the resulting tetraketo diester with aqueous acid provides the hydrindanone (**159**) in 67% overall yield. *N,N,N',N'*-Tetramethylglutaramide is treated similarly to obtain the tetralone (**160**; equation 156). The homologous tetraketo diester (**161**) fails to undergo the aldolization reaction under the normal conditions. However, cyclization is brought about in 40% yield by manganese acetate in refluxing methanol (equation 157). A metal template effect has been invoked to explain this reaction.



(153) (154)

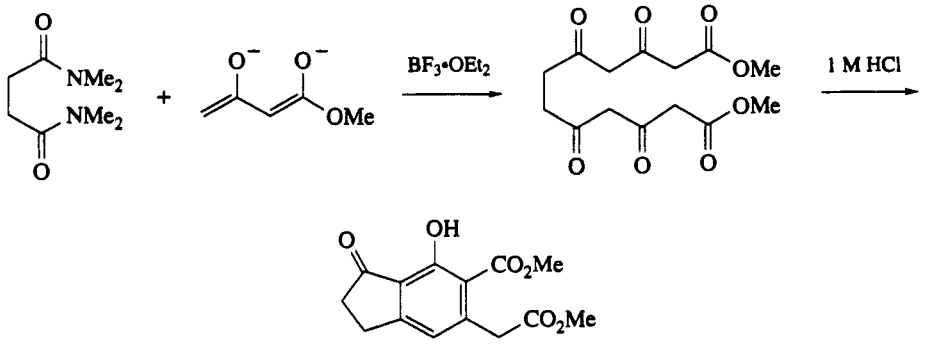


(155) (156)



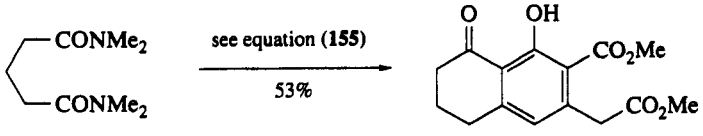
(157) (158)

Scheme 7



(155)

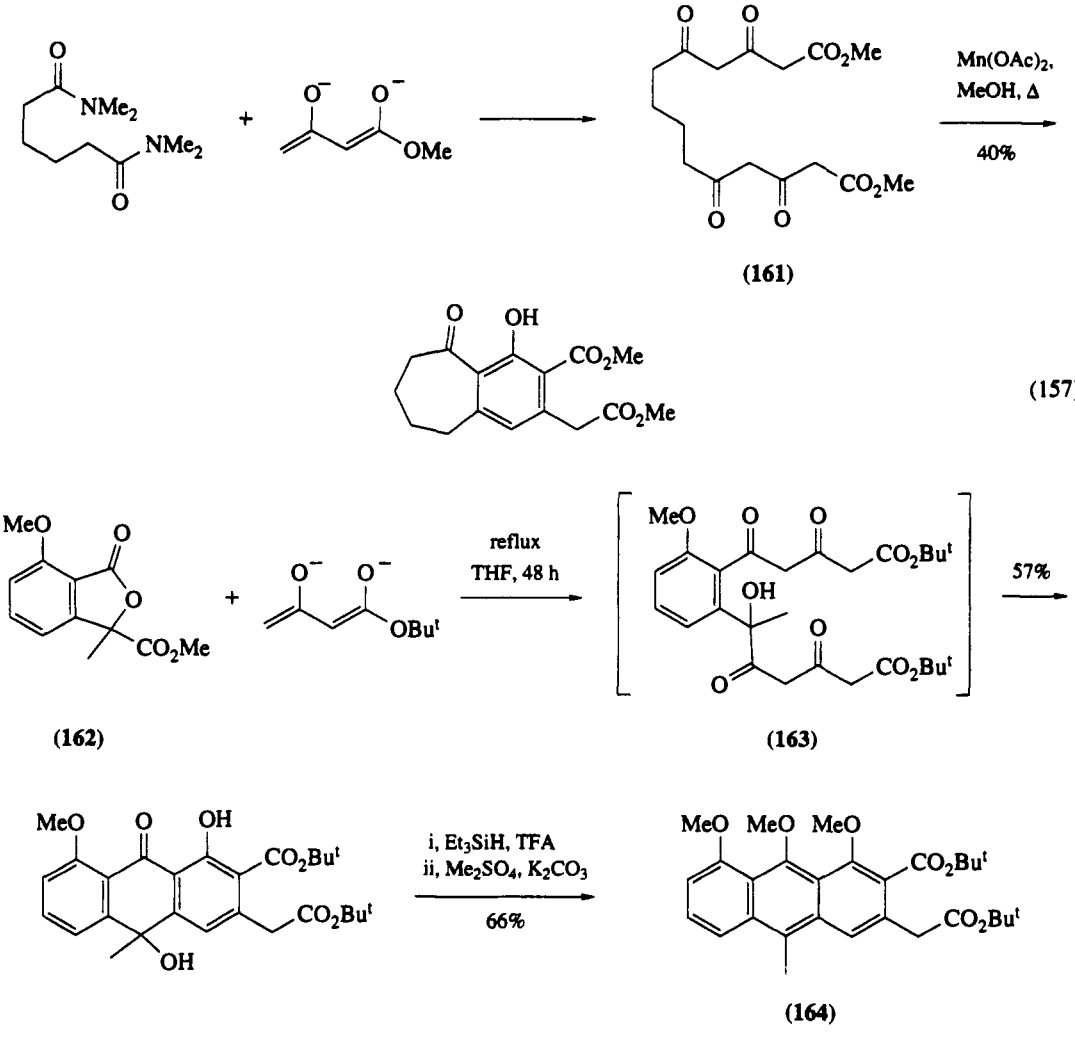
(159) 67% overall



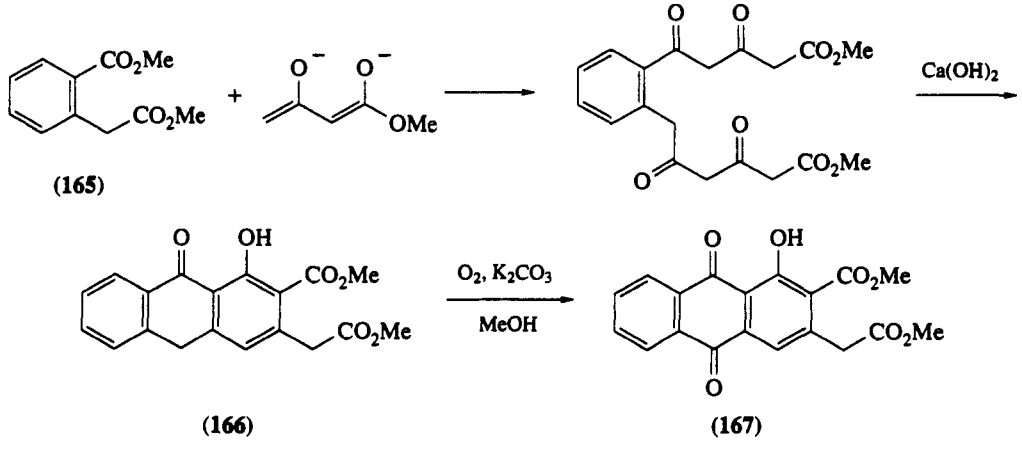
(156)

(160)

Starting with a preformed A-ring, in the form of phthalide (**162**), Harris and coworkers assembled the anthracene derivative (**164**) as shown in Scheme 8.[184] The intermediate tetraketo diester (**163**) closes spontaneously under the conditions of its synthesis from (**162**) and the dianion of *t*-butyl acetoacetate.



Scheme 8



Scheme 9

Yamaguchi has reported a related biomimetic synthesis of anthraquinones, summarized in Scheme 9.[185] Reaction of diester (**165**) with methyl acetoacetate dianion provides a tetraketo diester which is cyclized by calcium hydroxide to obtain anthrone (**166**). Air oxidation in basic medium affords the anthraquinone (**167**).

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1.6
The Aldol Reaction: Group I and Group II Enolates

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1.6.1 INTRODUCTION

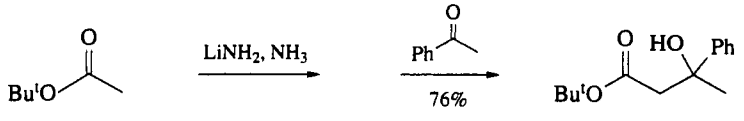
Traditionally, aldol reactions were carried out under protic conditions, such that the enolate was formed reversibly (see Volume 2, Chapter 1.5). An added measure of control is possible if one uses a sufficiently strong base that the enolate may be quantitatively formed prior to addition of the electrophile. The renaissance that has occurred in the aldol reaction in the last two decades has been mainly due to the development of methods for the formation and use of preformed enolates. The simplest enolates to prepare are those associated with lithium and magnesium, and there now exists a considerable literature documenting certain aspects of lithium and magnesium enolate aldol chemistry. This chapter summarizes the aldol chemistry of preformed enolates of these Group I and Group II metals. Other chapters in this volume deal with boron enolates, zinc enolates, transition metal enolates and the related chemistry of silyl and stannyl enol ethers.

1.6.2 FORMATION AND ALDOL REACTIONS OF REGIO-DEFINED ENOLATES

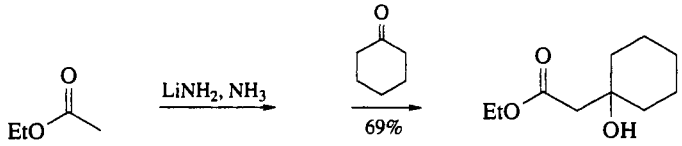
The great power of the aldol addition reaction lies in the ability to generate and use structurally defined enolates. In this section, the emphasis is on the formation of regio-defined enolates, and the aldol reactions of these enolates. Stereochemical issues are dealt with in Sections 1.6.2–1.6.4.

1.6.2.1 Stoichiometric Deprotonation of Carbonyl Compounds

The first use of preformed enolates for synthesis appears to have been by Hauser and coworkers, who converted *t*-butyl and ethyl acetate into the lithium enolates by reaction with $LiNH_2$ in liquid ammonia; the resulting enolates were found to react with aldehydes and ketones to give β-hydroxy esters (equations 1 and 2).[1]



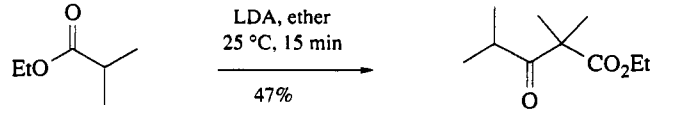
(1)



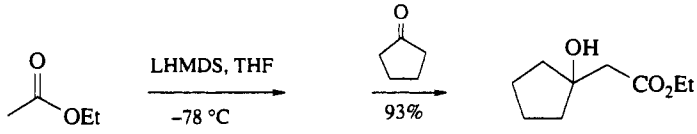
(2)

It was later found that dialkyl- and disilyl-amides have several attractive advantages, relative to the unsubstituted amides. Firstly, because they are relatively hydrophobic, these bases dissolve readily in organic solvents such as ether, tetrahydrofuran (THF), benzene and toluene. Secondly, the steric hindrance of the nitrogen atom reduces the nucleophilicity of the amide, thus ameliorating one of the principal side reactions of $LiNH_2$ and $NaNH_2$ with esters.[2]

One of these important bases, diisopropylaminomagnesium bromide, was first introduced by Frostick and Hauser in 1949 as a catalyst for the Claisen condensation.[3] However, the most generally useful base has turned out to be lithium diisopropylamide (LDA), which was first used by Hamell and Levine for the same purpose in 1950 (equation 3).[4] After the introduction of LDA, it was more than 10 years before it was used by Wittig for the stoichiometric deprotonation of aldimines in what has come to be known as the 'Wittig directed aldol condensation.'[5] In a seminal paper in 1970, Rathke reported that the lithium enolate of ethyl acetate is formed by reaction of the ester with lithium hexamethyldisilazane in THF.[6,7] Rathke found that THF solutions of the lithium enolate are stable indefinitely at –78 °C, and that the enolate reacts smoothly with aldehydes and ketones to give β-hydroxy esters (equation 4).



(3)



(4)

In a 1971 paper, Rathke and Lindert reported that lithium *N*-isopropylcyclohexylamide (LICA) is a superior reagent for the generation of ester enolates.[8] Subsequent workers, however, have found that LDA works just as well.[9] This base has the added virtue of being derived from a relatively volatile amine (the b.p. of diisopropylamine is 84 °C).

Lithium 2,2,6,6-tetramethylpiperidide (LITMP) was introduced by Olofson and Dougherty in 1973.[10] This base appears to be significantly more hindered than LDA, and is useful for regioselective enolate formation in cases where a very bulky base is desirable.[9c] Another very hindered base is lithium *t*-butyl-*t*-octylamide, introduced by Corey and Gross.[11]

Lithium, sodium and potassium hexamethyldisilazanes are available from the corresponding amine, bis(trimethylsilyl)amine. (This amine has a multitude of traditional common names, the most common of

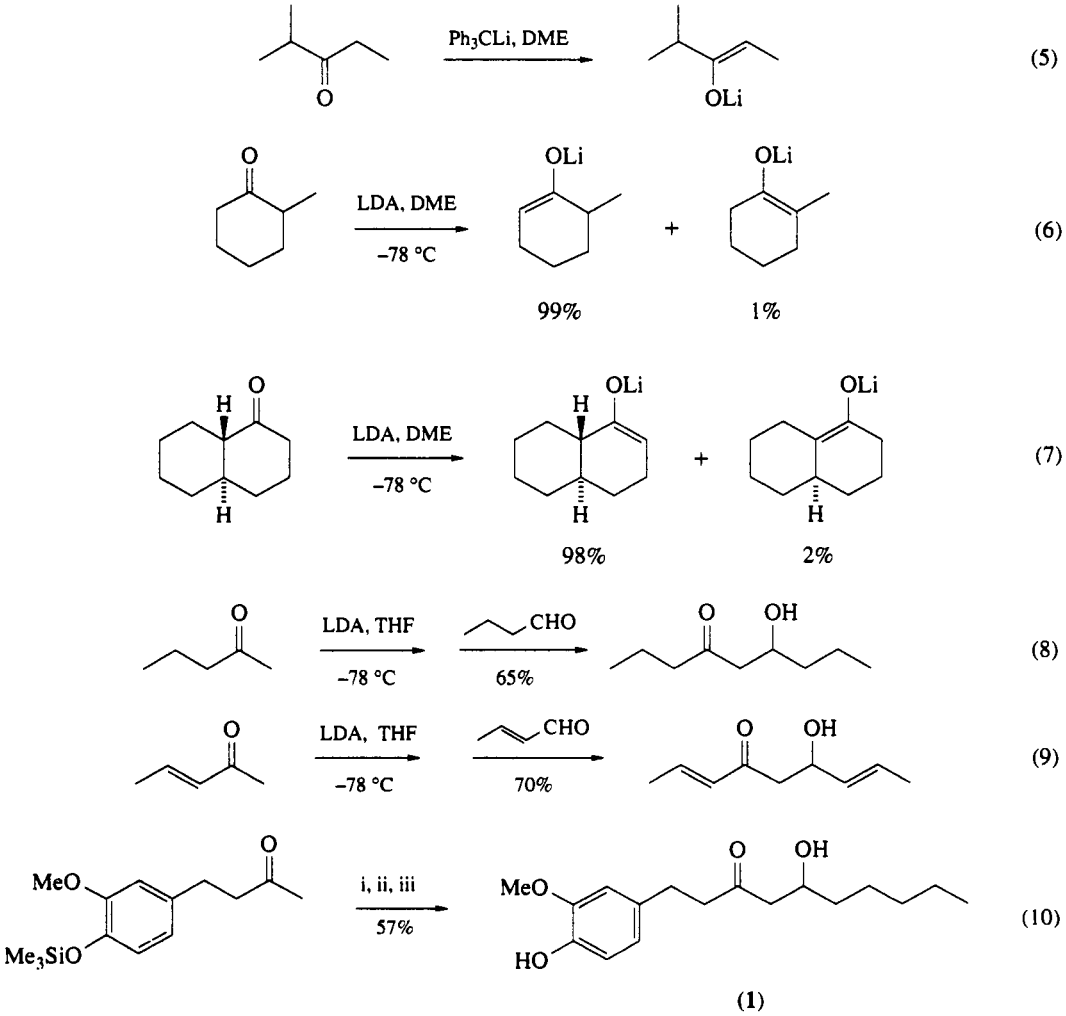
which are 'hexamethyldisilazine' and 'hexamethyldisilazane.' Its conjugate base has been called 'hexamethyldisilazide' and 'hexamethyldisilazane,' among other things. Although these names are somewhat confusing to the uninitiated, they are firmly entrenched in the literature. In this volume, we will use hexamethyldisilazane, abbreviated HMDS.) The lithium base may be formed by treatment of the amine with an alkyllithium in an ether solvent;[12] the sodium and potassium bases are produced by reaction of the amine with $NaNH_2$ or KNH_2.[7,13] All three of the hexamethyldisilazanes are also commercially available.

Triphenylmethylpotassium[14] and triphenylmethyllithium[15,16] were once used for stoichiometric deprotonation of ketones, but these bases offer no significant advantages over the foregoing amide bases, and they are rarely used now.

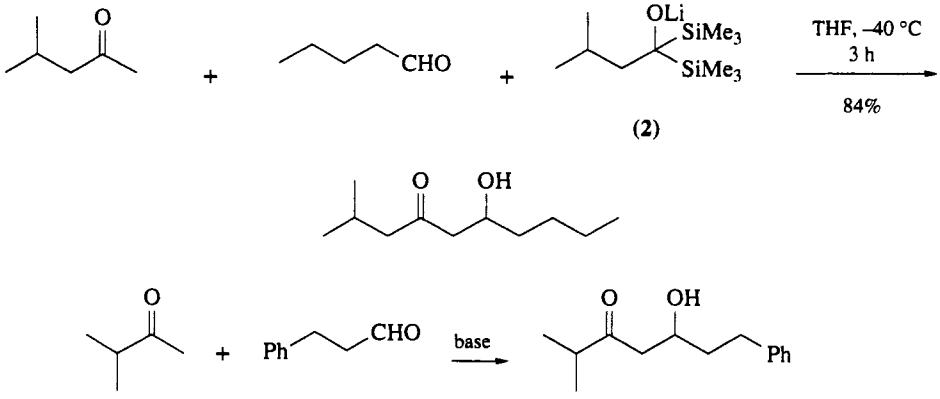
1.6.2.2 Regioselective Deprotonation of Ketones

The introduction of the foregoing bases opened the way for the preparation of structurally defined enolates; examples are seen in equations (5) to (7).[16,17] The first examples of the use of these regio-defined enolates in crossed aldol reactions were reported by Stork, Kraus and Garcia in 1974; representative examples are shown in equations (8) and (9).[18,19]

An application of this process is seen in the synthesis of (±)-[6]-gingerol (**1**; equation 10).[20] In this example, the regioselectivity of deprotonation is 92% at C-1 and 8% at C-3. With the weaker base lithium hexamethyldisilazane, the C-1:C-3 ratio is only 3:1. The method has also been used to prepare nine other (±)-gingerols.



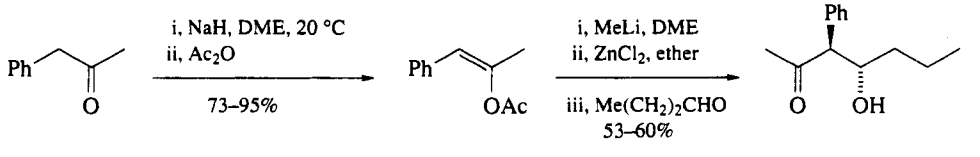
i, LDA, DME, -78 °C; ii, $Me(CH_2)_4CHO$; iii, H_3O^+

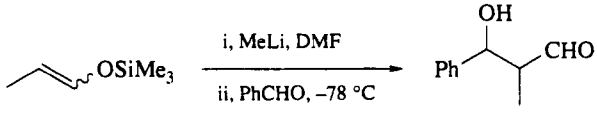


Kuwajima and coworkers used very hindered bases such as (**2**) to deprotonate methyl alkyl ketones regioselectively *in the presence of enolizable aldehydes.*[21] One example of this amazing process is shown in equation (11); the reaction is reported to work equally well with other methyl ketones, including 2-pentanone. The process was also demonstrated with other bases in the reaction of 3-methyl-2-butanone with dihydrocinnamaldehyde (equation 12). Among the bases that are effective are LDA, lithium hexamethyldisilazane, lithium *t*-butoxide and even lithium ethoxide. However, base (**2**) is superior, giving the aldol in 83% yield.

1.6.2.3 Enolates from Enol Esters and Silyl Enol Ethers

Enolates can also be prepared by reaction of enol esters[16,22,23] or silyl enol ethers[16,24] with alkyllithium reagents. House has worked out a protocol wherein these enolates are allowed to react with aldehydes to give the corresponding aldols.[25] Higher yields of aldol products are obtained when the lithium enolate is generated in ether or 1,2-dimethoxyethane (DME) by reaction of an enol acetate with methyllithium. Lower yields are obtained if the enolate is produced by reaction of a silyl enol ether with methyllithium. For the aldol reaction, ether or mixtures of ether and DME are superior to THF. Acceptable yields of aldol adducts are obtained in ether at low temperatures (–20 to –50 °C). In the more polar solvents DME or THF, the addition of anhydrous $ZnCl_2$ or $MgBr_2$ results in higher yields. An example is seen in equation (13).[25b] The stereochemistry of this process is discussed in Section 1.6.5.



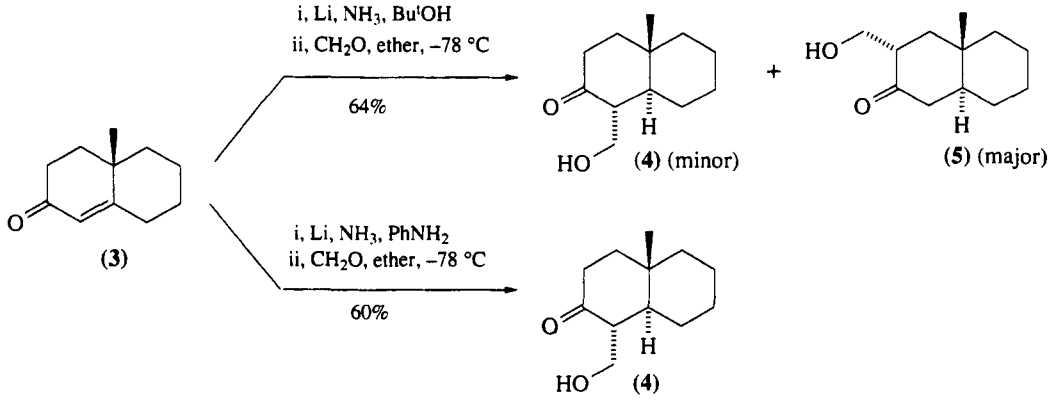


The enol ester or silyl enol ether route to enolates has advantages over direct deprotonation in certain cases. If direct deprotonation provides a mixture of regio- or stereo-isomers, it is often possible to trap the enolate mixture by esterification or silylation, separate the desired enol ester or silyl enol ether and regenerate the enolate by reaction with methyllithium. It is also useful for preparation of enolates from substances that are so electrophilic that direct deprotonation is complicated by self-aldolization. For example, aldehyde enolates have been prepared in this manner (equation 14).[9c]

1.6.2.4 Enolates from Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

A classic method for generating regio-defined enolates is metal–ammonia reduction of an enone.[26] Stork and d'Angelo found that the enolate resulting from lithium–ammonia–*t*-butyl alcohol reduction of octalone (**3**), followed by evaporation of ammonia, suspension of the enolate in ether and treatment with

gaseous formaldehyde, provides a mixture of hydroxy ketones (**4**) and (**5**), with the latter predominating (equation 15).[27] Enolate equilibration can be suppressed by use of aniline, rather than *t*-butyl alcohol, as the proton source in the reduction step (equation 15). However, the yield of hydroxymethyl ketone is only 60%. A much better overall yield (90%) is realized by trapping the original enolate as the trimethylsilyl enol ether and regenerating the enolate in the absence of any proton donors (*vide infra*).



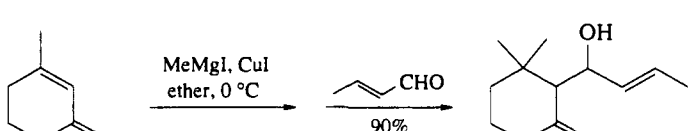
(15)

As shown in equation (15), the necessary presence of a proton source in the reaction medium that is used to generate specific enolates by metal–ammonia reduction limits the use of these enolates for regio-defined aldol reactions. The enolates resulting from conjugate additions of Grignard reagents or Gilman reagents to α,β-unsaturated carbonyl compounds do not suffer from this limitation, and have frequently been employed for aldol reactions.

Two papers that appeared in 1974 were the first to demonstrate the preparation and aldol reaction of a regio-defined magnesium enolate from copper(I)-mediated conjugate addition of a Grignard reagent to an enone.[27,28] As shown in equation (16), 3-methylcyclohexenone reacts with methylmagnesium iodide to give an enolate that reacts smoothly with crotonaldehyde, producing an aldol as a mixture of diastereomers in excellent yield.

A nice example of the foregoing stratagem is seen in equation (17); enone (**6**) undergoes copper(I)-catalyzed reaction with vinylmagnesium bromide from its less-hindered face to give an enolate that reacts with formaldehyde from the opposite face to provide decalone (**7**), an intermediate in the synthesis of insect antifeedants.[29] Yoshida and coworkers have used this method for the stereospecific generation of tetrasubstituted thioamide enolates, which undergo remarkably stereoselective aldol reactions (equation 18).[30] The stereochemistry of this process is discussed in Section 1.6.3.6.

Heng and Smith found that the regio-defined enolates resulting from conjugate addition of lithium dialkylcuprates to enones undergo acceptable aldol additions under the House conditions.[31] One of the



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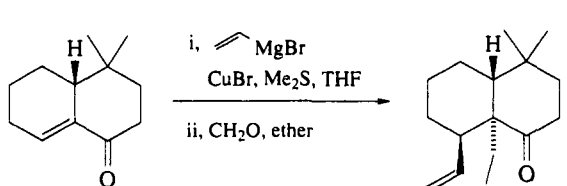

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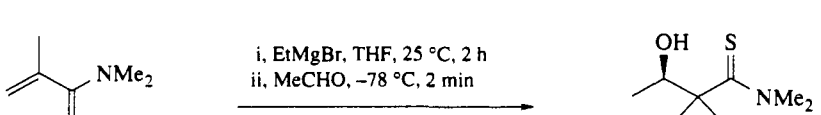

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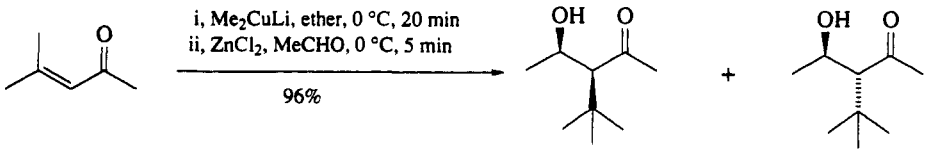

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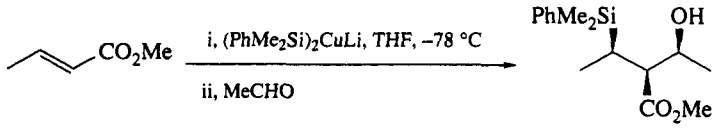


(20)

many examples reported in this investigation is shown in equation (19). The stereochemistry of these reactions is discussed in Section 1.6.3.2.

Fleming has generated enolates by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to α,β-unsaturated esters.[32] The intermediate (*Z*)-enolates undergo stereoselective aldol addition, providing adducts having three contiguous stereocenters; one example of this process is seen in equation (20).[33]

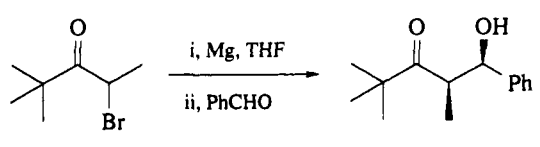
1.6.2.5 Enolates from Reduction of α-Heteroatom-substituted Carbonyl Compounds

Several workers have observed aldol reactions with enolates prepared by reductive removal of an α-heteroatom from a carbonyl compound. The classic example is the Reformatsky reaction, which is reviewed in Volume 2, Chapter 1.8. Dubois and coworkers have employed this method for the preparation of magnesium enolates.[34] An important example from this study, which stimulated much of the subsequent work on aldol stereoselectivity, is shown in equation (21).

Clark and coworkers have used a similar process for generation and aldol reactions of a cyclobutanone enolate; one example of many is illustrated in equation (22).[35] Direct formation of the enolate in this case gives aldols in low yield.

Trost has used α,α-disulfenylated lactones as enolate precursors.[36] As shown in equation (23), α,α-di-(phenylthio)-γ-butyrolactone is treated sequentially with ethylmagnesium bromide and acetaldehyde to obtain β-hydroxy lactone (**8**) in virtually quantitative yield. Oxidation of the phenylthio group and subsequent elimination of the resulting sulfoxide provides the unsaturated hydroxy lactone (**9**). The process was employed with more complex lactones in a total synthesis of iridoids. The method fails with α,α-disulfenylated ketones unless a catalytic amount of copper(I) bromide is included in the reaction mixture.

Reaction of γ-butyrolactone with LDA and bis[methoxy(thiocarbonyl)] disulfide in THF at –78 °C provides an enolate that reacts with heptanal to give the (*E*)-α-heptylidine-γ-butyrolactone (**10**), contaminated by only 4% of the (*Z*)-isomer (**11**; equation 24).[37] If the aldol step is carried out in the presence



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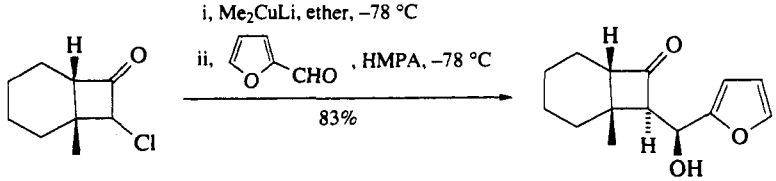

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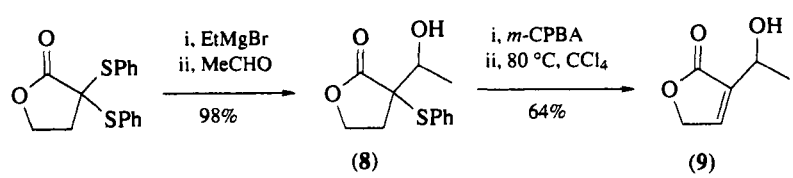
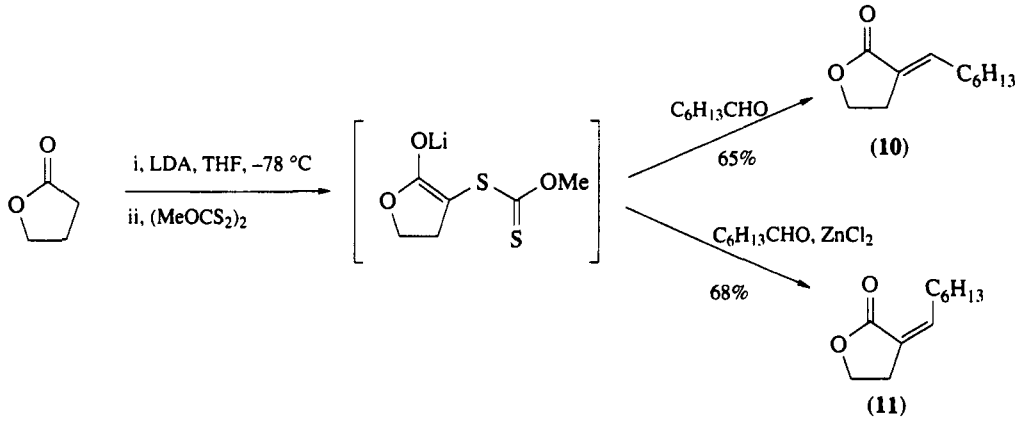


(23)

(**8**) (**9**)

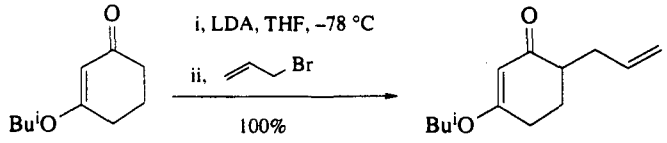


(24)

of $ZnCl_2$, compounds (**11**) and (**10**) are formed in a ratio of 85:15. The reaction apparently proceeds through an intermediate episulfide, and the double-bond geometry is a function of the initial aldol stereochemistry. The process illustrated in equation (24) seems to be quite general; the original reference should be consulted for numerous other examples.

1.6.2.6 Enolates of α,β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds can present two regiochemical problems. With ketones that have hydrogens at the γ- and α′-position, there is a regiochemical issue in the deprotonation reaction itself. Stork and Danheiser have shown that α′-deprotonation is favored over γ-deprotonation, and that the resulting enolates may be alkylated without the complication of proton transfer (equation 25).[38] Stork and Kraus extended this method to aldol reactions, as shown in equation (26).[39,40] Although the original



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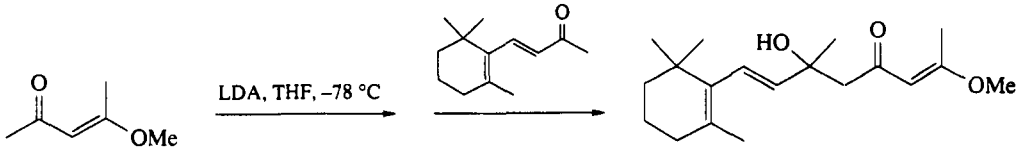
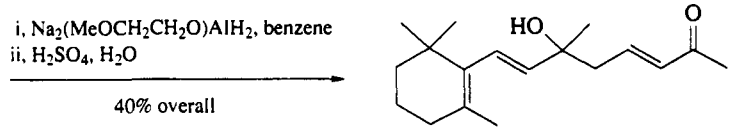
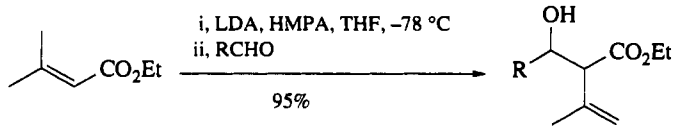




(26)

aldol reaction occurs exclusively at the α′-position of the vinylogous ester, the product after reduction and acid hydrolysis of the initial aldol is the one that would result from aldol reaction at the γ-position of 3-penten-2-one.

α,β-Unsaturated carbonyl compounds that do not have enolizable hydrogens at the α′-position give ambident enolates that can react with electrophiles at two sites—α or γ.[41] Reaction at either position has been observed. Instructive examples are seen in the different behaviors of ethyl 3-methylcrotonate and ethyl 2-methylcrotonate (equations 27 and 28).[42,43] Control experiments showed that both enolates undergo alkylation exclusively at the α-position. It is likely that both also undergo kinetic aldol addition at this position, but that the more substituted α-substituted aldolate from ethyl 2-methylcrotonate equilibrates with the less-congested γ-substituted isomer.



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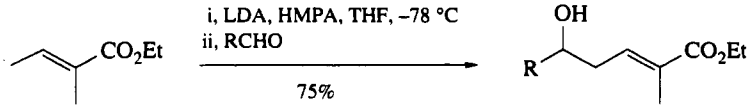
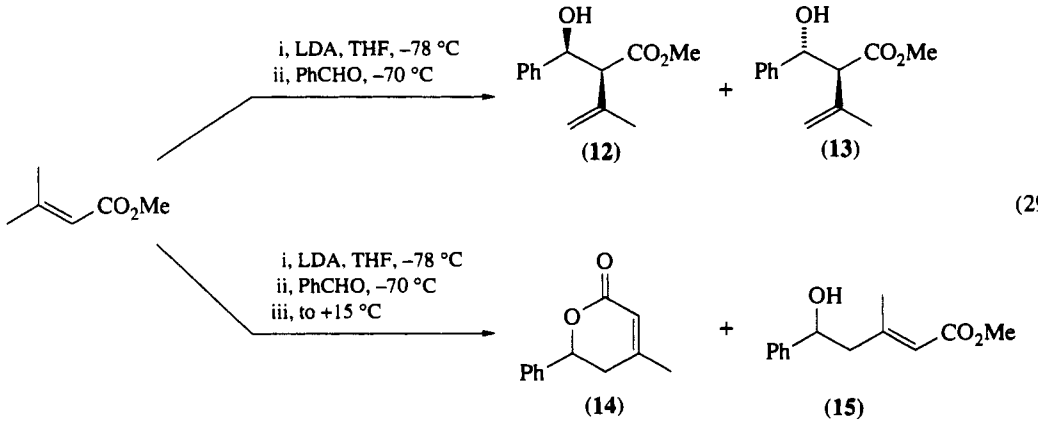


(28)

Heathcock and Dugger examined the enolate derived from methyl 3-methylcrotonate (equation 29).[44] When the aldol reaction with benzaldehyde is carried out at –70 °C and quenched at this temperature, diastereomeric aldols (**12**) and (**13**) are formed in a ratio of 3:2. However, if the aldolate is warmed to 15 °C prior to work-up, lactone (**14**; 80%) and hydroxy ester (**15**; 12%) are produced. These results con-



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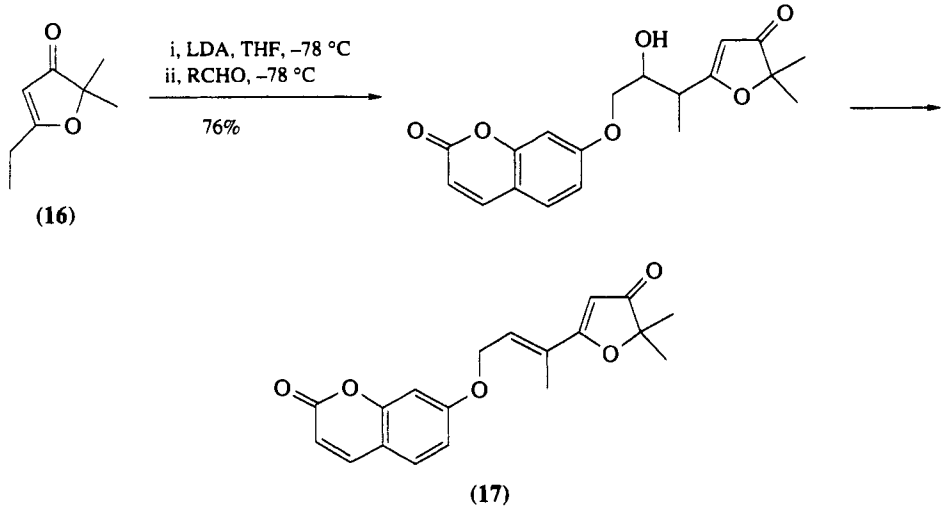

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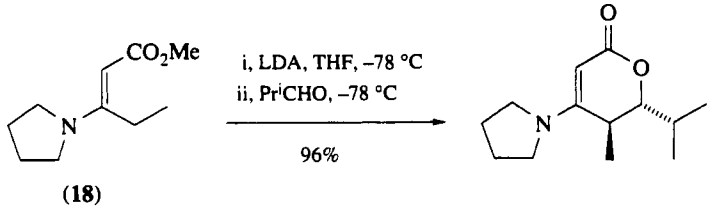


(31)

clusively demonstrate that such dienolates react kinetically at the α-position, and that the initial aldolate isomerizes to the more stable γ-substituted isomer at elevated temperatures.

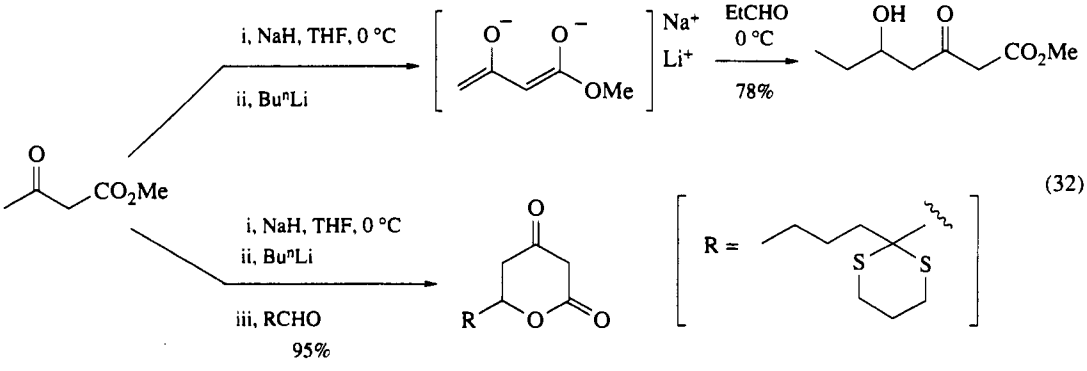
3(2*H*)-Furanone (**16**) gives a dienolate that shows a proclivity for reaction with electrophiles at the exocyclic γ-position (equation 30).[45] Dehydration of the mixture of diastereomeric aldols gives a 1:1 mixture of geiparvarin (**17**) and its geometric isomer.

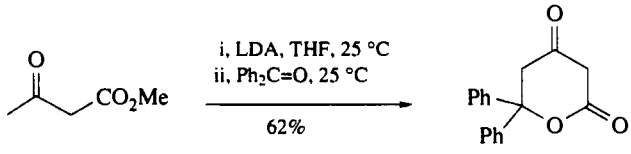
Schlessinger and coworkers have studied the aldol reactions of the dienolates derived from the vinylogous carbamate (**18**); in all cases, reaction occurs solely at the γ-position, as shown in equation (31).[46] Various evidence has been adduced that (**18**) reacts kinetically at the γ-position, in contrast to the behavior of crotonate enolates (*vide supra*). The process has been used to synthesize the Prelog–Djerassi lactonic acid and a chiral version of (**18**) has been used to synthesize a fragment of the antibiotic virginiamycin M_2 (*vide infra*).[47]

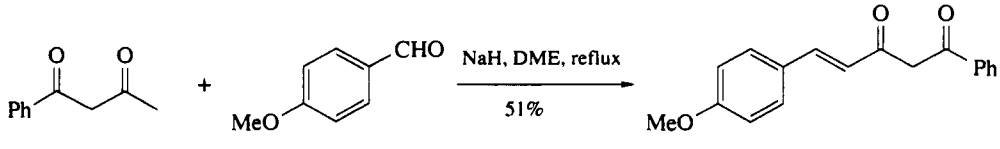
1.6.2.7 Dianions of Diketones and Keto Esters

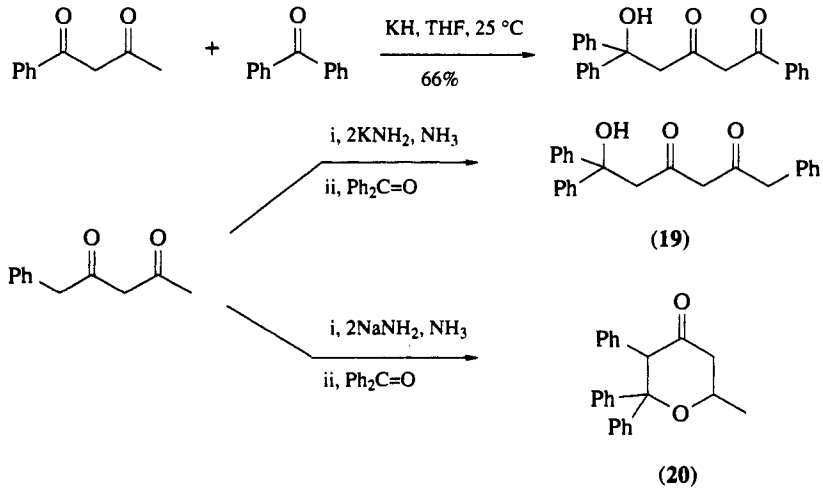
β-Dicarbonyl compounds may be converted into dianions, which react with electrophiles at the more basic site.[48] Huckin and Weiler found that β-keto ester dianions undergo aldol addition reactions at the more basic methyl position (equation 32).[49] The lithium/sodium dianion shows surprisingly weak reactivity, giving the aldol in only 11% yield after 1 h at −78 °C! In contrast, the lithium enolates of simple ketones and esters, which should be much less basic than the β-keto ester dianion, react with aldehydes to give nearly quantitative yields of aldols in THF in seconds at −78 °C.[50] Seebach and Meyer also studied this reaction, and obtained the oxolactone (equation 33).[51] Simple diastereoselection in the reaction of β-keto ester dianions has also been studied (*vide infra*).

Hauser and coworkers have extensively developed the chemistry of 1,3-diketone dianions.[52] In a 1965 paper, it was reported that treatment of a refluxing DME solution of benzoylacetone with NaH and various aromatic aldehydes and ketones gives unsaturated β-diketones in fair yield (equation 34).[53] Although this result suggests the intermediacy of the dianion, control experiments showed that benzoylacetone is converted only into the monoanion under the reaction conditions. Wolfe and coworkers reexamined this reaction with KH and found that, indeed, treatment of a THF solution of benzoylacetone with 4 equiv. of KH at 25 °C gives only 1.1 equiv. of hydrogen, corresponding to the formation of only 10% dianion. However, upon addition of benzophenone to the reaction mixture, the remaining 0.9 equiv. of hydrogen is rapidly evolved. Upon work-up, the aldol is obtained in 66% yield (equation 35).[54] The reason for this unusual behavior is still not clear.









(35)

(19)

(36)

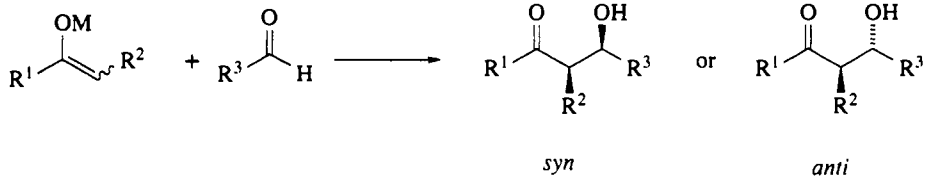
(20)

When 1-phenyl-2,4-pentanedione is doubly deprotonated with potassium amide in ammonia, the ensuing aldol reaction with benzophenone gives the expected aldol (**19**).[55] However, if sodium amide is employed to generate the dianion, the reaction product with benzophenone is the dihydro-γ-pyrone (**20**; equation 36).[56] This result suggests the intermediacy in the latter reaction of a dianion involving the benzylic position. Further study of this interesting reaction is warranted.

1.6.3 SIMPLE DIASTEREOSELECTION

1.6.3.1 General Overview

The principal factor that was responsible for the rebirth of the venerable aldol reaction as a modern method of synthesis was the discovery that its stereochemistry can be controlled quite effectively through the use of preformed enolates.[57] In this section is discussed 'simple diastereoselection,' reactions between prochiral enolates and prochiral aldehydes (equation 37); the *syn/anti* stereochemical notation is employed.[58]

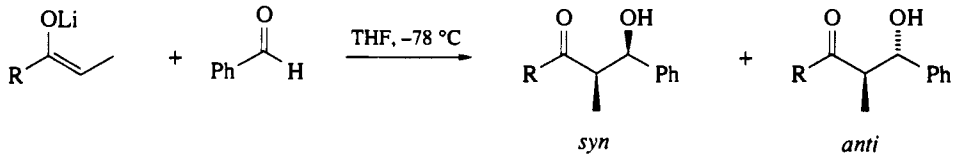


(37)

Before commencing this discussion, it is appropriate to consider briefly the issue of kinetic *versus* thermodynamic control in the reactions of preformed Group I and Group II enolates and to summarize the structure–stereoselectivity generalizations that have emerged to date. It is now well established that preformed lithium, sodium, potassium and magnesium enolates react with aldehydes in ethereal solvents at low temperatures (typically –78 °C) with a very low activation barrier. For example, reactions can often be quenched within seconds of the addition of an aldehyde to a solution of a lithium enolate.[9c]

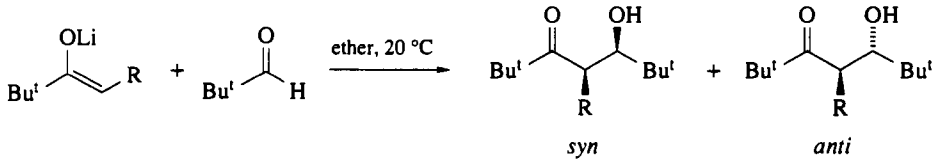
The kinetic stereoselectivity of the aldol is a function of the enolate stereochemistry *and* its structure. One often reads the over-generalization that '(*Z*)-enolates gives *syn* aldols and (*E*)-enolates give *anti* aldols.' However, the situation is much more complex than this; in addition to enolate geometry, several variables are involved. The following generalizations may be made at this time (refer to equation 37 for definition of R^1, R^2 and R^3).

(Z)-Enolates. If R^1 is large, (*Z*)-enolates give *syn* aldols; for moderate R^1, (*Z*)-enolates are still fairly *syn* selective; but for very small R^1, they are stereorandom. Examples are shown in equation (38).[9c] Another apparent structural effect is the size of R^2 (equation 37). As this is increased in size, there is a greater propensity for formation of the *anti* aldol; examples are seen in equation (39).[59]



(38)

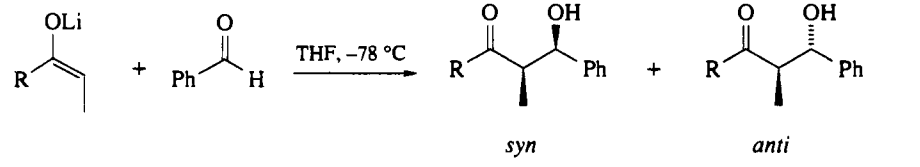
R	*syn:anti*	*R*	*syn:anti*
Bu^t	98.7:1.3	Et	90:10
Pr^i	90:10	H	50:50



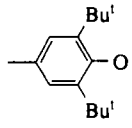
(39)

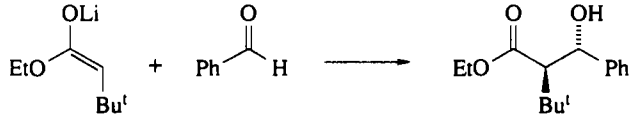
R	*syn:anti*	*R*	*syn:anti*
Me	100:0	Bu^i	97:3
Et	100:0	Pr^i	29:71
Pr^n	98:2	Bu^t	0:100

(E)-Enolates. For large R^1, high *anti* selectivity is seen but (*E*)-enolates with medium-sized and small R^1 groups are stereorandom (equation 40).[9c] The effect of the size of R^2 on (*E*)-enolate stereoselectivity has not been systematically investigated. However, if one extrapolates from the behavior of (*Z*)-enolates, it is likely that the (*E*)-enolate of an ester like ethyl 3,3-dimethylbutanoate might react with aldehydes to give rather high *anti* selectivity (equation 41).



(40)

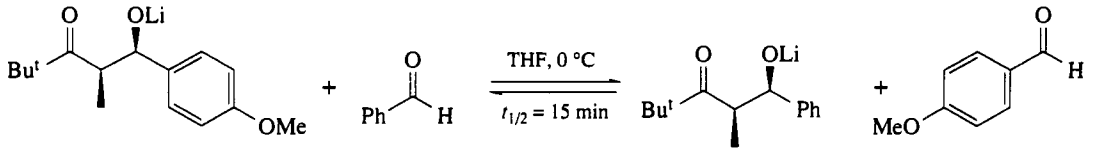
R	*anti:syn*	*R*	*anti:syn*
	>98:2	MeO	60:40
		Et	60:40
		Pr^i	50:50
		H	60:40



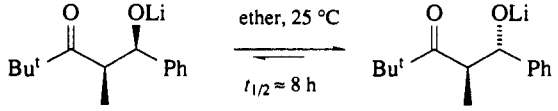
(41)

In addition to the foregoing structural effects, it is clear that the nature of the enolate cation affects aldol stereoselectivity. Since the kinetic stereoselectivity of the aldol reaction seems to result from a rather tightly organized, six-center transition state,[60] cations that are effectively chelated tend to give higher stereoselectivity. Although the question has not yet been carefully investigated, magnesium enolates appear to give somewhat higher stereoselectivity than comparable lithium enolates. As is discussed in Volume 2, Chapter 1.7, boron enolates give even higher simple diastereoselection.

Although most aldol reactions of preformed Group I and Group II enolates are quite rapid, even at –78 °C, the ΔG° of reaction is not normally very negative. Thus, aldol reversal is possible under relatively mild conditions. In such cases, the observed stereochemistry is governed partially or fully by the thermodynamic properties of the diastereomeric aldolates. Some of the factors that promote aldol reversal are



(21) (22) (42)



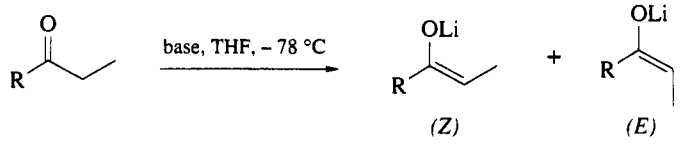
(22) (23) (43)

discussed in Volume 2, Section 1.5.3. For the purpose of the following discussion, the most important factor is the basicity of the enolate. In general, the more basic the enolate, the less likely is aldol reversal. Amide and ester aldolates show little tendency toward reversal, whereas ketone aldolates often undergo reversal under very mild conditions. Of course, the occurrence of a retroaldol process need not be reflected in rapid erosion of stereochemical homogeneity. For example, the *syn* aldolate (**21**) derived from ethyl *t*-butyl ketone and *p*-anisaldehyde reacts with benzaldehyde to give aldolate (**22**) with a half-life of only 15 min at 0 °C (equation 42). However, aldolate (**22**) equilibrates to its *anti* diastereomer (**23**) in ether with a half-life of approximately 8 h at 25 °C (equation 43).[9c] The reason for this discrepancy is that the (*Z*)-enolate that results from the retroaldol reaction of (**21**) or (**22**) shows a very high kinetic stereoselectivity (*ca.* 80:1). Thus, on average, aldol reversal must occur 80 times in order for one molecule of (**22**) to be converted into one molecule of (**23**).

1.6.3.2 Ketone Enolates

Enolates of acyclic ketones can be prepared stereoselectively with a fair amount of control by varying the base that is used for deprotonation. Some representative data are shown in equation (44) and Table 1.[9c] In discussing the stereochemistry of enolates, the (*E*)/(*Z*) notational format suggested by Evans (ref. 2c) is followed. Thus, in naming an enolate derived from an ester $R^2CH_2CO_2R^1$, OM is assigned higher priority than OR^1, regardless of the metal. It is clear from this table that there is an intrinsic preference for esters and ketones with small R groups to give the (*E*)-enolate, regardless of base. As R is increased in size an increasing amount of (*Z*)-enolate results. On the other hand, a more bulky base gives relatively more of the (*E*)-enolate (*i.e.* LITMP *versus* LDA).

Masamune and coworkers studied the deprotonation of 3-pentanone and ethyl cyclohexyl ketone with various bases.[6l] These workers confirmed that lithium hexamethyldisilazane gives more (*Z*)-isomer than



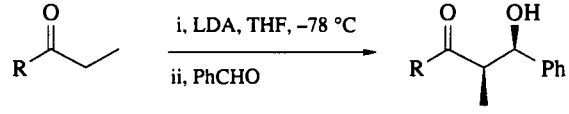
(*Z*) (*E*) (44)

Table 1 Enolate Stereochemistry (equation 44)

R	*(Z)-Isomer (%)* *LITMP*	*LDA*	*LHMDS*
MeO	—	5	—
2,4,6-$Me_3C_6H_2$	4	8	87
Et	16	30	66
Pr^i	32	56	>97
Pr^i_2N	52	81	—
Ph	>97	>97	>97
Bu^t	>97	>97	>97

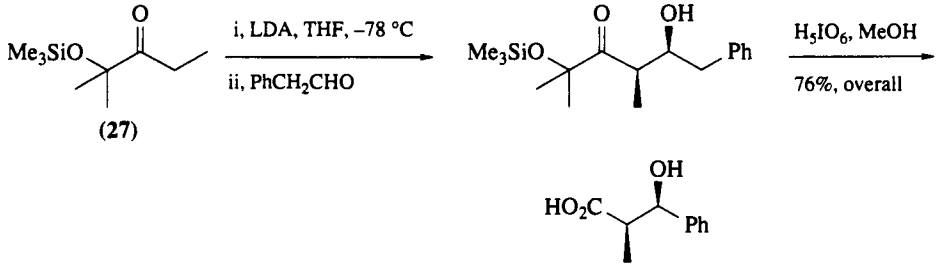
does LDA and found that other bis(trialkylsilyl)amides are even more (*Z*)-selective. The best base studied was lithium hexamethyldisilazane, which gives >99% (*Z*)-isomer with both ketones.

Certain (*Z*)-ketone enolates react with aldehydes to give *syn* aldols with excellent stereoselectivity. As shown in equation (45), the (*Z*)-enolates of ethyl *t*-butyl ketone, ethyl 1-adamantyl ketone and ethyl mesityl ketone all react with benzaldehyde to give *syn:anti* ratios of >50:1.[9c,62] The bulky *t*-butyl, adamantyl and mesityl groups assure that (*Z*)-enolates are formed with high selectivity and organize the transition state so as to maximize formation of the *syn* aldol. To capitalize on this discovery, various ketone reagents have been devised that have bulky alkyl groups that can be removed oxidatively or reductively. One such reagent is the α-trimethylsilyloxy ketone (**27**; equation 46).[9c,63] A related reagent, compound (**28**), also gives high *syn* selectivity in its aldol reactions. The resulting β-hydroxy ketone may be reduced to a diol that is oxidatively cleaved by lead tetraacetate to an aldehyde (equation 47).[64] Trityl ketone (**29**) functions predictably, giving *syn* aldol with excellent stereoselectivity and in high yield (equation 48).[65] These aldols may be reductively cleaved with lithium triethylborohydride, after protection of the secondary alcohol. The (*Z*)-lithium enolate of ketone (**30**), formed with lithium hexamethyl-



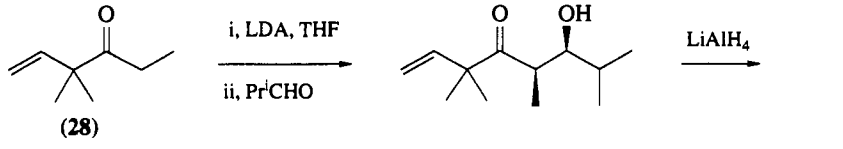
(45)

(**24**) R = Bu^t
(**25**) R = 1-adamantyl
(**26**) R = 2,4,6-$Me_3C_6H_2$



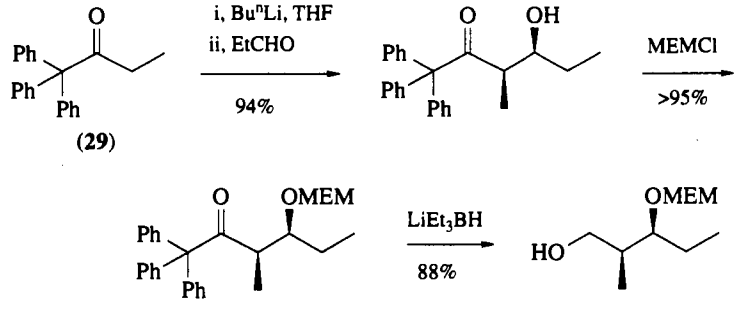
(**27**)

(46)



(**28**)

(47)

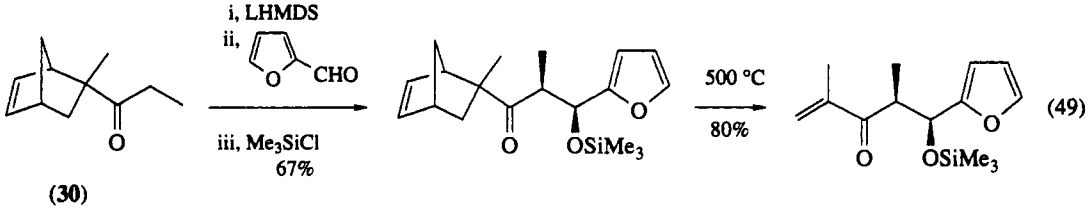


(**29**)

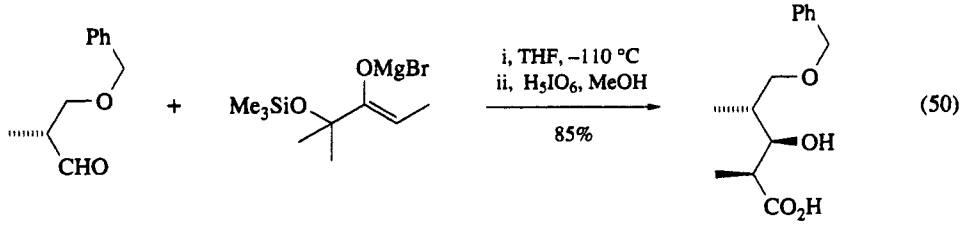
(48)

disilazane, gives *syn* aldols with several aldehydes. Flash vacuum pyrolysis of the aldol silyl ether expels cyclopentadiene by a retro-Diels–Alder reaction, providing the *syn* aldol of an α,β-unsaturated ketone (equation 49).[66]

Ketone (**27**) and reagents related to it have been used in synthesis. In equation (50) is shown an application of the magnesium enolate in Still's synthesis of monensin; the facial selectivity in this case is 5:1 and the reaction proceeds in 85% yield.[67] The lithium enolate of (**27**) has been employed in a synthesis of the C-1,C-7 segment of erythronolide A (equation 51); the facial selectivity in this case is 6:1.[68] Ketone (**31**) was used in a synthesis of the basic nucleus of crassin acetate (equation 52).[69] The aldol reaction of (**31**) with (**32**), derived from geraniol, occurs in 58% yield to give only one isomer. Four further



(**30**) (49)



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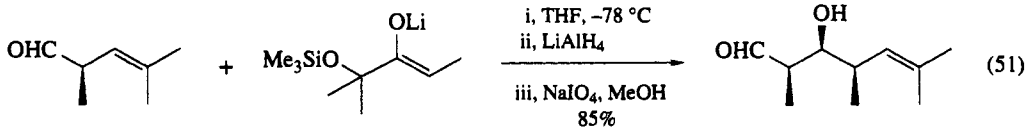

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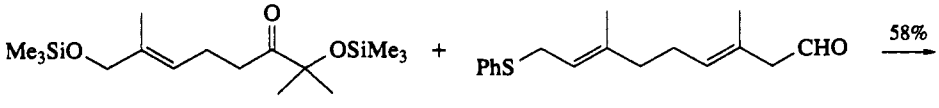
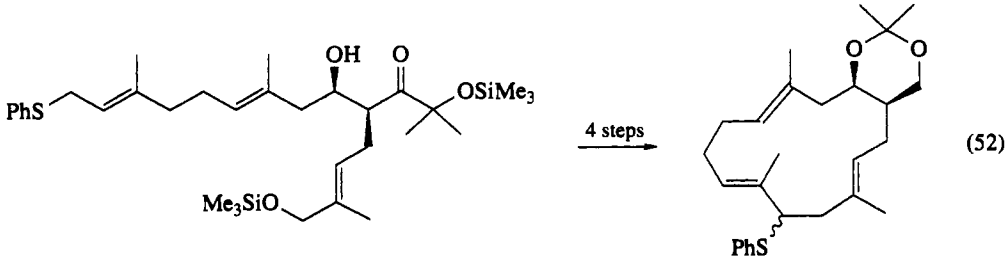
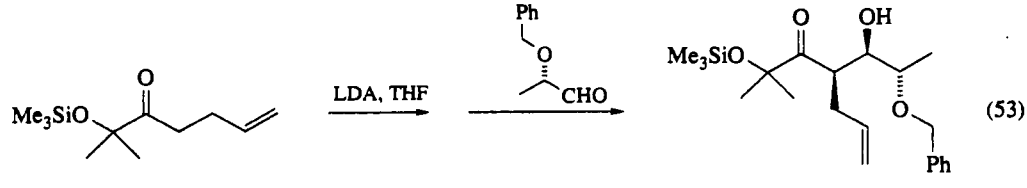


(**31**) (**32**)



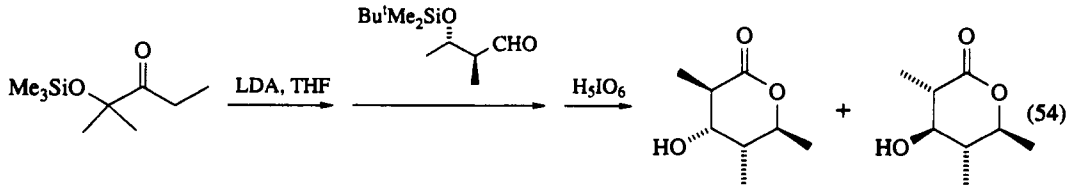
(52)



(53)

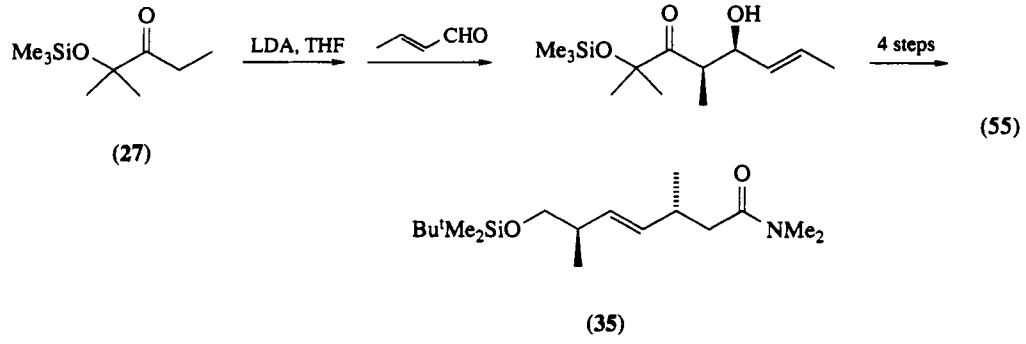
(**33**) (**34**)

steps converted the aldol into the 14-membered crassin ring. (±)-Ristosamine was synthesized starting with ketone (**33**), which adds to (*S*)-*O*-benzyllactaldehyde to give the *syn* aldol (**34**; equation 53); the facial selectivity in this reaction is 4:1 and the total yield is 97%.[70] Ketone (**27**) has been used in a similar manner to prepare the C-29,C-37 fragment of amphotericin B and nyastatin (equation 54).[71]

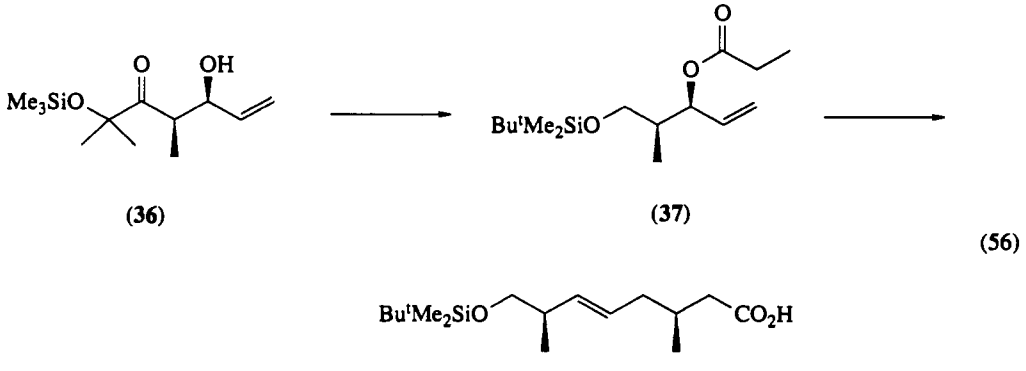


(**27**) 40% 15%

Reaction of reagent (**27**) with crotonaldehyde provides a *syn* aldol, which is transformed by a four-step sequence including a Claisen rearrangement into (**35**; equation 55).[72] Aldol (**36**), obtained from (**27**) and acrolein, was converted *via* propionate (**37**) into (**38**), a building block for the vitamin E side chain (equation 56).[72b,73] The strategy of parlaying the 1,2 relative stereochemistry obtainable from the aldol reaction into 1,5 relative stereochemistry by use of a Claisen rearrangement has also been used to prepare the C_{40} archaebacterial diol and one of its stereoisomers.[72b,74]



(**27**) (**35**) (55)

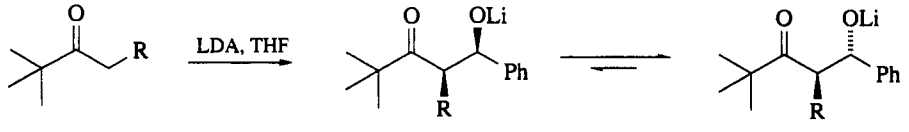


(**36**) (**37**) (**38**) (56)

A study of ethyl *t*-butyl ketone (**39**) and its homologs (**40**) to (**42**) (equation 57) revealed several interesting differences.[75] Firstly, there is a significant steric effect on the rate of deprotonation in this series. Whereas ketone (**39**) (0.2 M in THF) is deprotonated completely by LDA in 20 min at –20 °C, ketone (**42**) requires 4 h for deprotonation at this temperature. Aldol reactions of (**39**) to (**42**) with benzaldehyde were compared in THF and in pentane. All four ketones give exclusively the *syn* aldol in THF at –78 °C. In pentane, (**40**) to (**42**) give some *anti* aldol under the normal reaction conditions, with the amount of *anti* product being greater with increasing size of R. With ketone (**42**), reaction for 30 min at room temperature provides aldols with an *anti:syn* ratio of >50:1. The formation of *anti* aldols in pentane solution

was shown to result from equilibration of the kinetic *syn* product to the more stable *anti* aldolate. Whereas the equilibration of *syn* aldolate (**43**) to *anti* aldolate (**44**) has a half-life in ether solution at 25 °C of approximately 8 h (*vide supra*), this reaction has a half-life in pentane at 25 °C of only 45 min. As expected, steric bulk in the aldolate promotes the retroaldol reaction; the half-life for equilibration of (**45**) to (**46**) in pentane at 25 °C is only 7 min; the *n*-propyl and *n*-butyl aldolates undergo *syn* to *anti* equilibration under the same conditions with a half-life of less than 4 min.

Although a considerable amount of data exists pertaining to simple diastereoselection with trisubstituted enolates, very little is known about reactions of fully substituted enolates, principally because of a dearth of methods for the stereospecific generation of such enolates. (Ester enolates that are substituted at the α-position by heteroatoms constitute a special exception to this generalization; these fully substituted enolates are discussed in Section 1.6.3.3.) Two research groups have recently reported an interesting approach to the generation of such enolates, which is summarized in equation (58).[76] The method is based on the discovery that amine-free enolates of 2,6-di-*t*-butyl-4-methylphenol ('butylated hydroxytoluene', or BHT) decompose by ejection of phenoxide upon being warmed from –78 °C to room temperature (the onset of decomposition is believed to be at about –20 °C). If this decomposition occurs in the presence of an alkyllithium species, the ketene produced is trapped to give a regio-defined enolate. If the ester has two α-substituents of differing size, the enolate produced is also stereochemically defined because the alkyllithium reagent attacks the ketene preferentially *syn* to R^S, the smaller of the two substituent groups. Consequently, a (*Z*)-ketone enolate is generated preferentially, the stereoselectivity of the process depending upon the difference in size between R^S and R^L. The enolate mixture so generated may

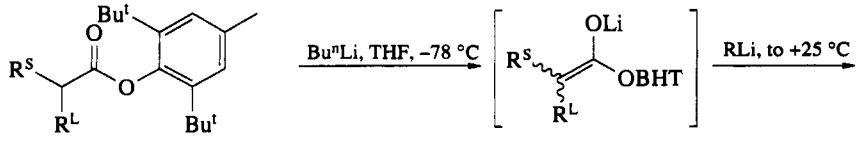


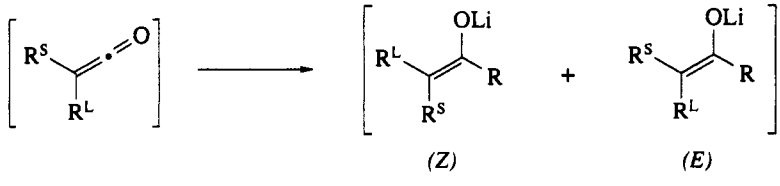
(57)

(**39**) R = Me
(**40**) R = Et
(**41**) R = Pr^n
(**42**) R = Bu^n

(**43**) R = Me
(**45**) R = Et

(**44**) R = Me
(**46**) R = Et





(58)

(*Z*) (*E*)

Table 2 Enolate Stereochemistry (equation 58)

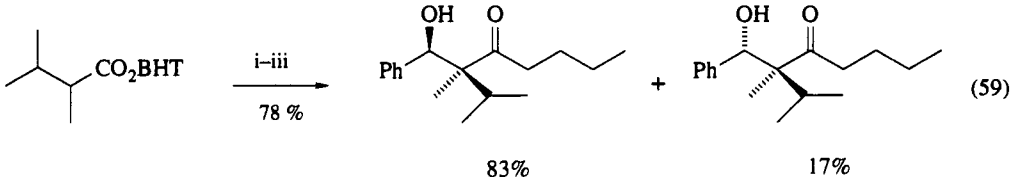
R^S	R^L	*R*	*Yield* (%)[a]	(*Z*):(*E*)
Me	Et	Me		1.7:1
Me	Pr^i	Me		7:1
Me	Bu^t	Me		>99:1
Et	Me_3Si	Bu^n	77	>99:1
Me	Ph	Bu^n	50	>99:1
Et	Ph	Bu^n	76	>99:1
H	Bu^t	Bu^t	62	>99:1

[a]Yield of the trimethylsilyl enol ether.

be trapped with trimethylsilyl chloride to give a mixture of stereoisomeric silyl enol ethers, which reflects the stereoselectivity of enolate formation; data for three different esters are summarized in Table 2. As is shown in the table, there is a little stereoselectivity in enolate formation when R^S and R^L are Me and Et, moderate stereoselectivity when the two groups are Me and Pr^i, and excellent stereoselectivity with Me and Bu^t.

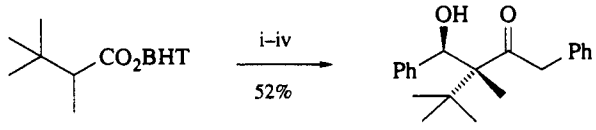
The substituted enolates produced in the foregoing manner may be trapped with aldehydes; one example is shown in equation (59). In this case, the aldol ratio, assigned as shown without rigorous proof, corresponds closely to the enolate ratio (Table 2). A related enolate, in which R^S and R^L are Me and Bu^t, gives a sole aldol (equation 60); unexpectedly, this aldol was found to have the indicated structure by X-ray analysis.[77] This result is understood in terms of the Zimmerman–Traxler transition state, if one assumes that the *gauche* interaction between the phenyl of the aldehyde and the bulky *t*-butyl group strongly destabilizes the normal chair-like transition state with phenyl equatorial.[78] [The stereochemical outcome of this reaction is also in accord with the results of Dubois and Fellmann on 2-*t*-butyl-5,5-dimethylcyclopentanone (*vide infra*, equation 67).] In the light of this result, the stereochemical assignment of the aldols shown in equation (59) should probably be regarded as tentative.

The degree of stereoselectivity of aldol reactions of simple cyclohexanone enolates has been a subject of some confusion. For cyclohexanone itself, it has been reported that reaction of the lithium enolate with benzaldehyde gives the two isomeric aldols (Scheme 1) in ratios of 52:48 in THF at –78 °C[9c] and 50:50 in dimethoxyethane at –20 °C.[79] On the other hand, Seebach reports ratios of 79:21 at –78 °C and 85:15 at –150 °C.[80] Hirama and coworkers reinvestigated the reaction of the lithium enolate of cyclohexanone with benzaldehyde (Scheme 1) and found *anti:syn* ratios of about 82:18 at –78 °C.[81] The ratio is



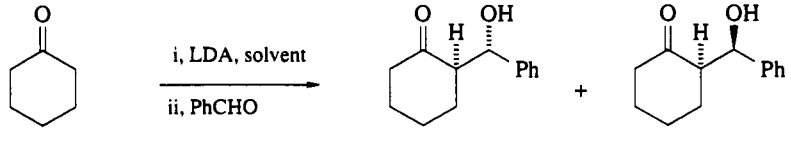
(59)

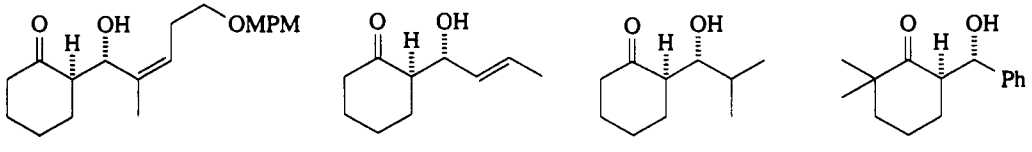
i, 2 equiv.Bu^nLi, THF, –78 °C; ii, warm to +25 °C; iii, PhCHO



(60)

i, Bu^nLi, THF, –78 °C; ii, $PhCH_2Li$; iii, warm to +25 °C; iv, PhCHO





(49) **(50)** **(51)** **(52)**

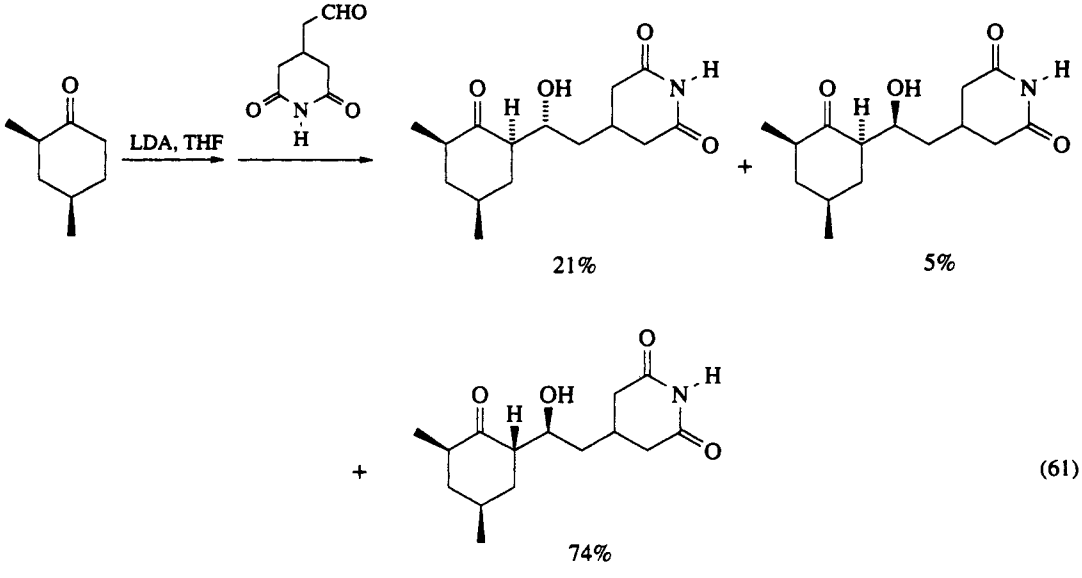
Scheme 1

also 82:18 at –50 °C if the reaction is worked up after 3 s, but falls to 60:40 if worked up after 5 min. Careful temperature monitoring showed that there is a significant rise (up to 5 °C) at the moment of addition of benzaldehyde to the enolate solution, even if the aldehyde is precooled. Hirama and coworkers also observed high *anti* selectivity in the preparation from cyclohexanone of aldols (**49**; 100% *anti*),[82] (**50**; 88% *anti*) and (**51**; 96% *anti*). The lithium enolate of 2,2-dimethylcyclohexanone reacts with benzaldehyde to produce aldol (**52**; 88% *anti*).[9c,83]

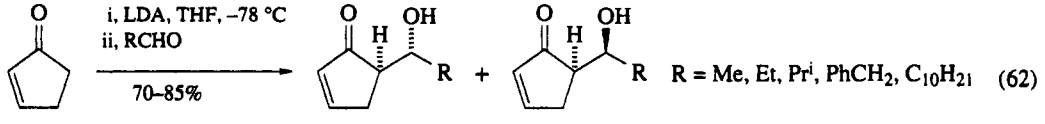
The lithium enolate of (2*R*,4*R*)-2,4-dimethylcyclohexanone has been condensed with an appropriate aldehyde to prepare several isomers of the antibiotic cycloheximide (equation 61).[84] The major isomer results from reaction on the unsubstituted face of the cyclohexanone ring, and has the same relative stereochemistry at the two new stereocenters as the major isomer in Scheme 1. The second most abundant isomer is also a *syn* aldol, and results from attack on the more-substituted face of the dimethylcyclohexanone.

The α′-enolate of cyclopentenone reacts with aldehydes to give *anti* and *syn* aldols in ratios of 70:30 to 95:5, with the degree of stereoselectivity being related to the size of R (equation 62).[85] Similar yields, with reversed diastereoselectivity, are observed with the corresponding zirconium enolates.

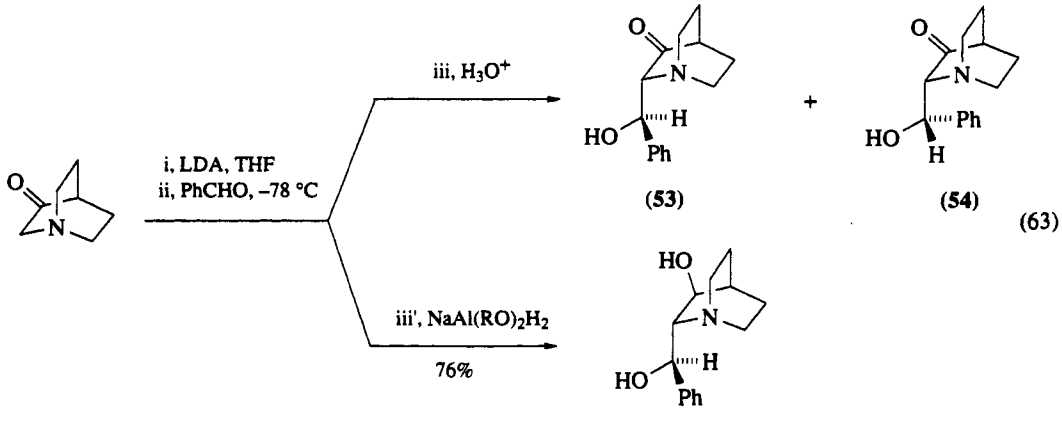
Stotter has reported a study that suggests that the low stereoselectivity sometimes observed in aldol reactions of cyclohexanones results from significant aldolate equilibration.[86] As shown in equation (63), the lithium enolate of 1-azabicyclo[2.2.2]octan-3-one reacts with benzaldehyde to give, after normal



(61)



(62)

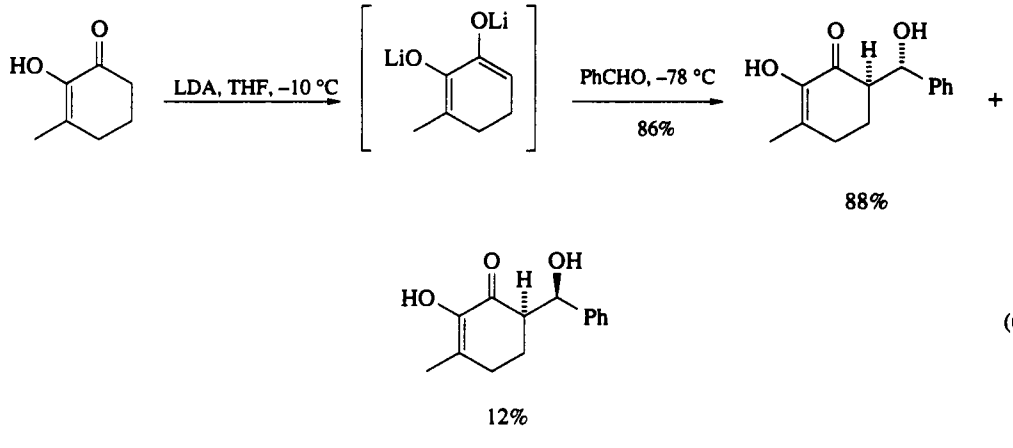


(63)

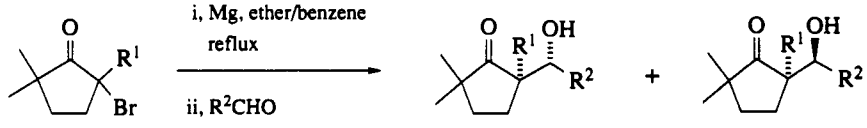
work-up, aldols (**53**) and (**54**) in a ratio of about 90:10. Aldol (**53**) was found to be exceedingly sensitive with respect to conversion to (**54**), particularly in solution. If the initial aldolate was reduced prior to work-up, a single diol was obtained, suggesting that the aldol reaction itself proceeds with nearly 100% diastereoselectivity.

Dianions derived from 1,2-cyclohexanediones react with aldehydes rather stereoselectively, as shown in equation (64).[87] The *anti:syn* ratio of about 8:1 was shown to be kinetic rather than thermodynamic in nature, and was found to be independent of the alkyl group at C-3. The *anti* stereoselectivity is even higher with α-branched aldehydes (*e.g.* >99:1 with isobutyraldehyde).

Dubois and Fellmann have carried out a careful investigation of the reaction of magnesium enolates of substituted cyclopentanones with various aldehydes (Scheme 2).[59] Data from this important study are summarized in Table 3. As shown in entries 1–6, the α-unsubstituted cyclopentanone enolate shows *anti* selectivity, with the magnitude of stereoselectivity increasing with the degree of branching at the α-position of the aldehyde; branching at the β-position of the aldehyde has essentially no effect. Substitution at the enolate carbon has an interesting effect, *reducing the amount of* anti *diastereomer as the size of* R^1 *increases* (Table 3, entries 7–11). This study also revealed that the magnesium enolate is somewhat more stereoselective than the corresponding lithium enolate. With the lithium enolate only minor medium-effects are observed.



(64)



(**55**) (**56**)

(**A**) (**B**)

(**55**) (**56**)

Scheme 2

Table 3 Aldol Stereochemistry (Scheme 2)

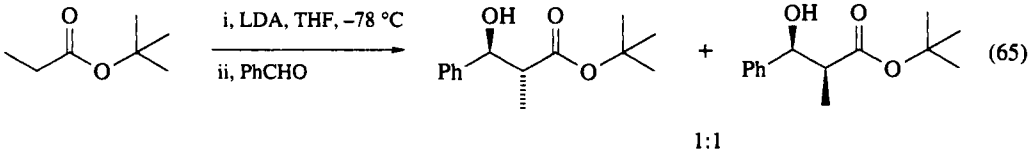
Entry	R^1	R^2	*(55):(56)*
1	H	Me	93.5:6.5
2	H	Et	94:6
3	H	Bu^i	93.5:6.5
4	H	neo-Pe[a]	94:6
5	H	Pr^i	97:3
6	H	Bu^t	>99:1
7	Me	Me	93.5:6.5
8	Et	Me	87.5:12.5
9	Bu^i	Me	80:20
10	Pr^i	Me	46:54
11	Bu^t	Me	29:71

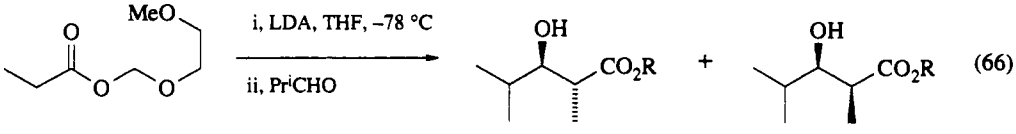
[a]neo-Pe = neopentyl.

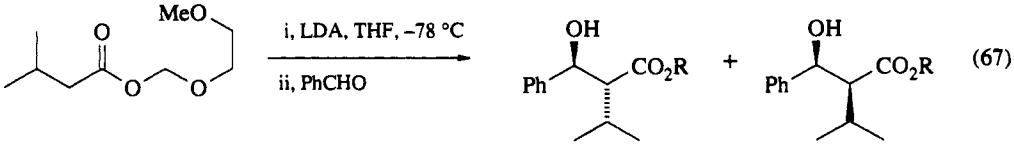
The foregoing results are in accord with the transition state structures depicted in Scheme 2. The usual Zimmerman–Traxler chelates (**A**) and (**B**) lead to aldols (**55**) and (**56**), respectively. With small R^1, (**A**) is favored over (**B**), because the latter transition state brings group R^2 into interaction with the cyclopentane ring; this interaction is more serious with larger R^2 groups. If group R^1 is larger, the *gauche* R^1:R^2 interaction disfavors (**A**) and leads to more reaction through transition state (**B**). Note that these results are precisely in accord with the observations by Seebach and coworkers with an acyclic (*Z*)-tetrasubstituted enolate (*vide supra*, equation 60).

1.6.3.3 Ester and Lactone Enolates

Deprotonation of esters with lithium dialkylamides gives rise to (*E*)-enolates.[9c,88] However, with normal alkyl propionates there is little or no stereoselectivity in additions to aldehydes (equation 65).[9c] It was found by Meyers and Reider that certain esters that contain additional ether oxygens in the alcohol moiety give reasonably high *anti* selectivity (equation 66).[89] Unfortunately, this high selectivity is not general, as is shown by the example in equation (67).[9c]

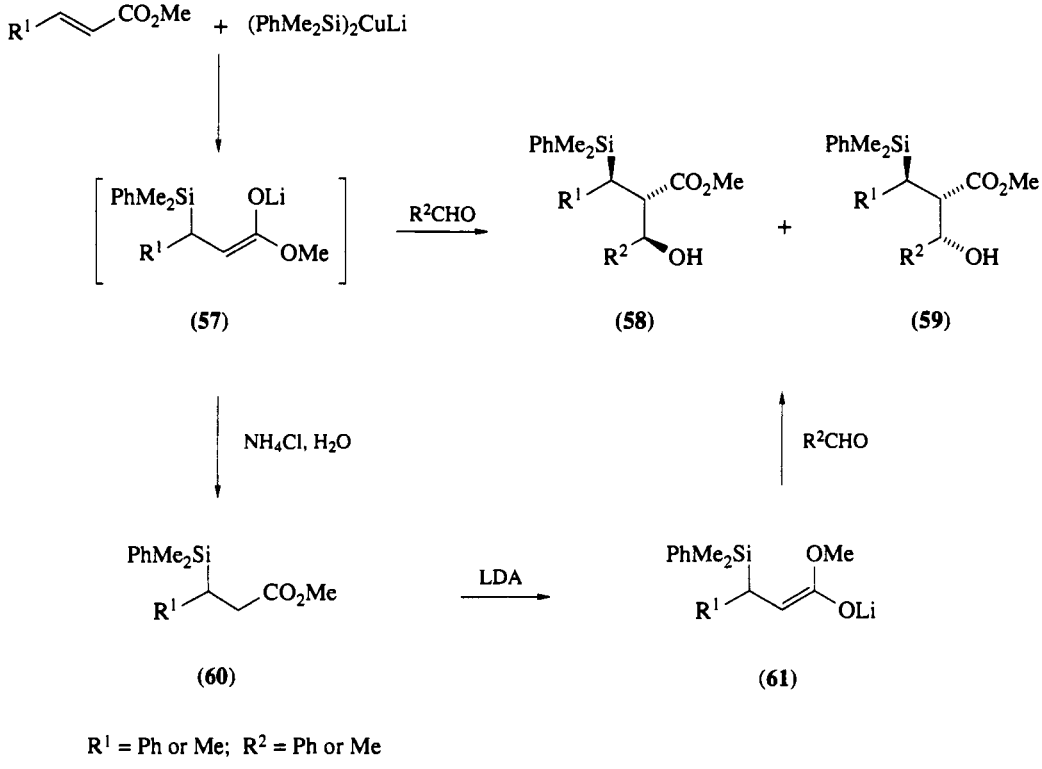






As shown in Scheme 3, (*Z*)-enolate (**57**), prepared by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to methyl crotonate or methyl cinnamate, reacts with acetaldehyde or benzaldehyde to give a mixture of two diastereomeric aldols, (**58**) and (**59**), with excellent diastereomeric excess favoring (**58**) (ratios of 85:15 to 94:6).[90] On the other hand, deprotonation of ester (**60**) by LDA provides the (*E*)-enolate (**61**), which reacts with the same two aldehydes to give the aldol (**59**) as the major product

(ratios of 89:11 to 94:6). Enolates (**57**) and (**61**) both show exceptional diastereofacial preferences, in the same sense. If one assumes enolate homogeneity, the simple diastereoselection observed (6:1 to 16:1) is remarkable. The sense of simple diastereoselection is the same as is observed for other stereoselective enolates [(*Z*)-enolate (**57**) gives the 2,3-*anti* aldol and (*E*)-enolate (**61**) gives the 2,3-*syn* aldol]. This process has been used in a synthesis of the antibiotic thienamycin.[91]



Scheme 3

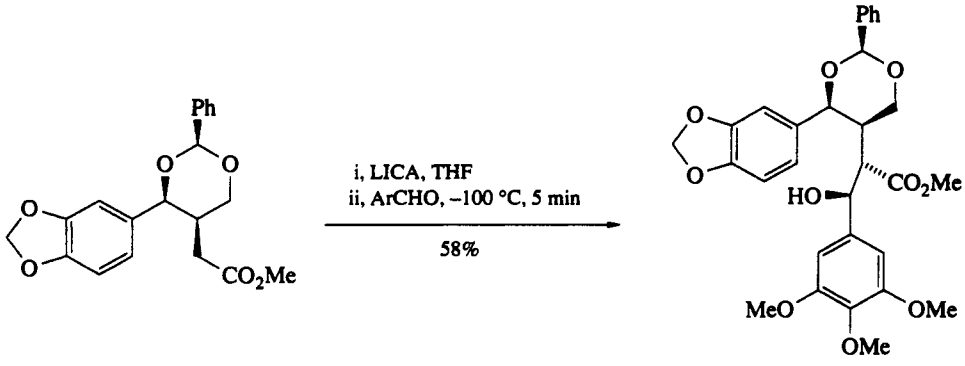
In connection with the synthesis of podophyllum lignans, ester (**62**) was deprotonated and the resulting enolate condensed with 3,4,5-trimethoxybenzaldehyde to give a 1:1 mixture of diastereomeric aldols (equation 68).[92] The structure of (**63**) was established by X-ray analysis; the other diastereomer was assigned the 2,3-*anti* relative stereochemistry (**64**) on circumstantial evidence. It was suggested that the 1:1 mixture of isomeric products results from a 1:1 mixture of the (*E*)- and (*Z*)-enolate, each of which shows complete simple and diastereofacial selectivity in its reactions with 3,4,5-trimethoxybenzaldehyde. For this to be true, it is also necessary that the (*E*)-enolate reacts through a 'non-Zimmerman', boat-like transition state, whereas the (*Z*)-enolate reacts through the normal chair-like transition state.

The hindered aryl esters (**65**) to (**71**) (Scheme 4) have been shown to be effective reagents for the preparation of 2,3-*anti* aldols.[93] Aldol additions with the enolates of these esters give predominantly 2,3-*anti* aldols (Table 4). The DMP esters (**65**), (**66**) and (**67**) give *anti:syn* ratios of 6:1 to 10:1 with aromatic aldehydes and α-unbranched aliphatic aldehydes (Table 4, entries 1, 2, 7 and 8) and pure *anti* products with α-branched aliphatic aldehydes (entries 3–6, 9). The BHT and DBHA esters (**68**) to (**71**) give only *anti* aldols with all aldehydes (Table 4, entries 10–20). The DMP, BHT and DBHA esters are conveniently prepared from commercially available phenols. The DMP aldols may be hydrolyzed to obtain the corresponding β-hydroxy acids. The DMP reagents are limited, however, since high stereoselectivity is only observed with α-branched aldehydes. The BHT reagents do not have this limitation, and have the added virtue that the product aldols are often nicely crystalline solids. However, the BHT aldols may not be hydrolyzed, because of the severe steric hindrance of the carbonyl group. The DBHA reagents show the same high stereoselectivity as their BHT analogs. With this reagent, the DBHA moiety may be removed oxidatively, thus permitting access to the β-hydroxy acid.

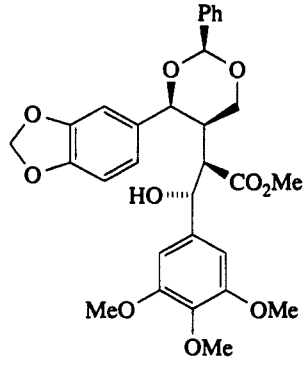
The foregoing *anti* selective aldol reagents have been employed for several synthetic purposes. Paterson used reagent (**65**) to convert aldehyde (**72**) into β-hydroxy ester (**73**); the yield in this reaction is 92%

and the diastereomer ratio at −100 °C is 13:1 (equation 69).[94] Aggarwal and Warren employed (**65**) to convert aldehyde (**74**) into aldol (**75**) (equation 70, stereoselectivity = 95:5) and the related acyclic aldehyde (**76**) into aldol (**77**) (equation 71).[95] In the latter example, the aldol stereoselectivity (C-2,C-3) is complete and the diastereofacial selectivity (C-3,C-4) is 10:1.

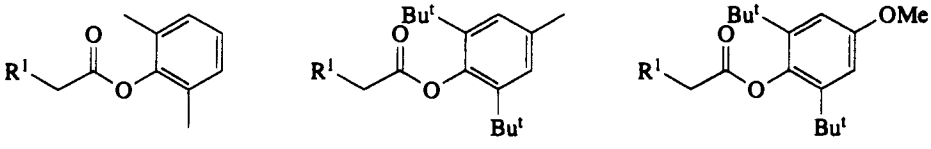
In the course of a synthesis of davanone, Bartlett and Holmes utilized ester (**68**) to convert aldehyde (**78**) into aldol (**79**); the stereochemical purity of the product is 97.6% (equation 72).[96] Sato and co-



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



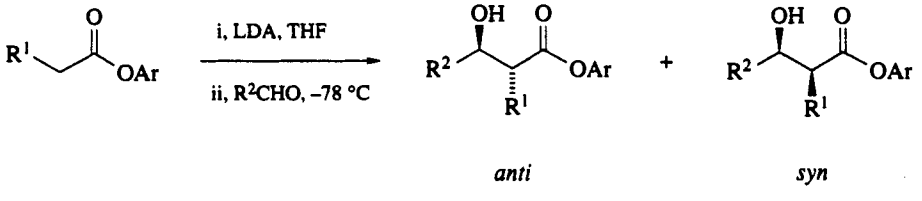
(**64**) (68)



(**65**) R^1 = Me
(**66**) R^1 = Et
(**67**) R^1 = H_2C=$CHCH_2$

(**68**) R^1 = Me
(**69**) R^1 = H_2C=$CHCH_2$

(**70**) R^1 = Me
(**71**) R^1 = Et



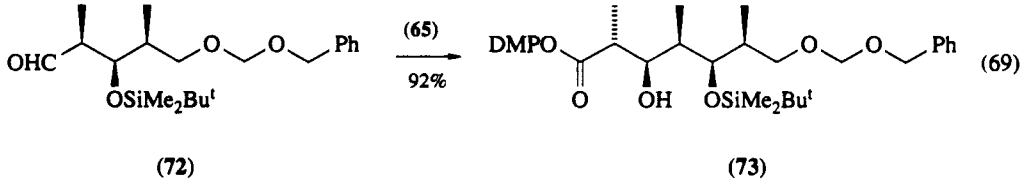
anti *syn*

Scheme 4

Table 4 Aldol Stereochemistry (Scheme 4)

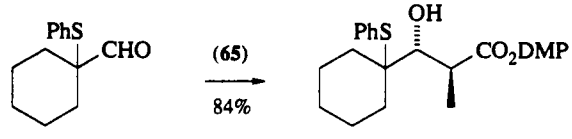
Entry	*Ester*	*Aldehyde*	*Yield* (%)	*Anti:syn*
1	(65)	PhCHO	72	88:12
2	(65)	n-C_5H_{11}CHO	70	86:14
3	(65)	Pr^iCHO	78	>98:2
4	(65)	Bu^tCHO	82	>98:2
5	(65)	Ph(Me)CHCHO	81	>98:2[a]
6	(66)	Pr^iCHO	93	>98:2
7	(67)	PhCHO	87	91:9
8	(67)	EtCHO	67	84:16
9	(67)	Pr^iCHO	77	>98:2
10	(68)	PhCHO	96	>98:2
11	(68)	Pr^iCHO	100	>98:2
12	(68)	Ph(Me)CHCHO	100	>98:2[a]
13	(69)	PhCHO	76	>94:6
14	(69)	EtCHO	81	>98:2
15	(69)	Pr^iCHO	60	>96:4
16	(70)	EtCHO	75	>98:2
17	(70)	n-C_5H_{11}CHO	70	>98:2
18	(70)	Pr^iCHO	79	>98:2
19	(70)	Bu^tCHO	77	>98:2
20	(71)	Pr^iCHO	68	>98:2

[a]4:1 mixture of C-3,C-4 diastereomers.



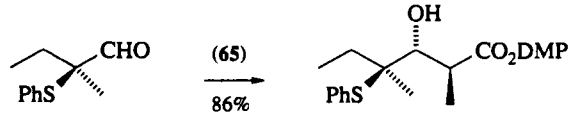
(69)

(72) (73)



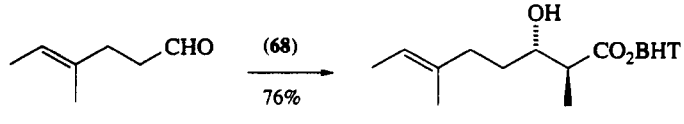
(70)

(74) (75)



(71)

(76) (77)

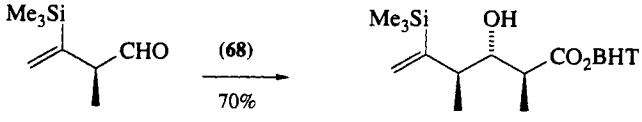


(72)

(78) (79)

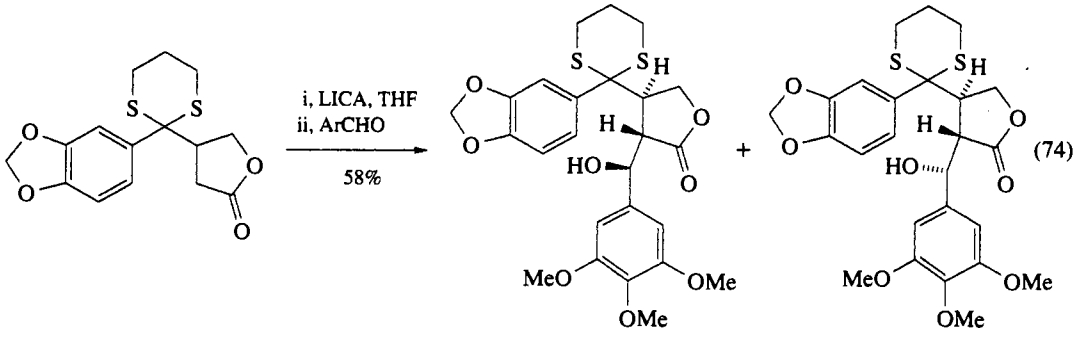
workers added (**68**) to the β,γ-unsaturated aldehyde (**80**) to obtain aldol (**81**), of at least 97% stereochemical purity (equation 73).[97]

Lactone enolates typically show poor simple diastereoselection. For example, in connection with a synthesis of (±)-podorhizol, Ziegler and Schwartz added the lithium enolate of butyrolactone (**82**) to 3,4,5-trimethoxybenzaldehyde (equation 74). Although the diastereofacial selectivity of the chiral enolate is complete, aldols (**83**) and (**84**) are formed in a ratio of 50:50 in THF and 25:75 in an equimolar mixture of dimethoxyethane and ether.[98]



(73)

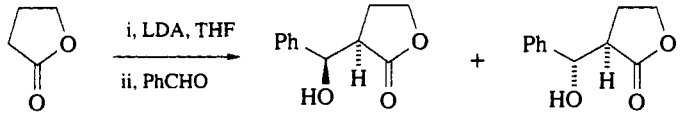
(**80**) (**81**)



(74)

(**82**) (**83**) (**84**)

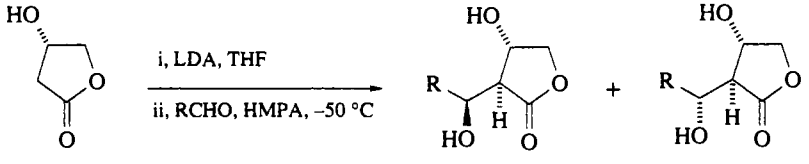
Widdowson and coworkers investigated aldol reactions of butyrolactone itself with benzaldehyde (equation 75).[99] The lithium enolate gives diastereomers (**85**) and (**86**) in a ratio of 40:60 to 30:70, depending upon reaction temperature. If 0.5 mol equiv. $ZnCl_2$ is added to the reaction mixture prior to enolate formation, the (**85**):(**86**) ratio is 56:44 to 70:30, depending upon reaction temperature.



(75)

(**85**) (**86**)

The dianion of the hydroxybutyrolactone (**87**) reacts with aldehydes with high diastereofacial selectivity to give mixtures of dihydroxy lactones (**88**) and (**89**) (equation 76; Table 5).[100] The lithium enolate shows little simple stereoselection with the sterically undemanding aldehydes phenylacetaldehyde and tetradecanal. Significant stereoselectivity is seen in the reaction with benzaldehyde, and pivalaldehyde gives only a single product. Because the aldol relative stereochemistry in the reactions with benzalde-



(76)

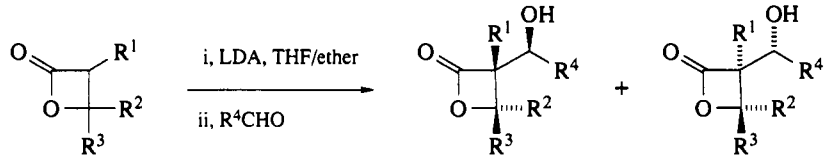
(**87**) (**88**) (**89**)

Table 5 Aldol Stereochemistry (equation 76)

R	*Without $ZnCl_2$* (88):(89)	Yield (%)	*With $ZnCl_2$* (88):(89)	Yield (%)
Ph	90:10	43	80:20	85
$PhCH_2$	57:43	45	42:58	89
Bu^t	>100:1	34	>100:1	48
n-$C_{13}H_{27}$	50:50	48	45:55	60

hyde and pivalaldehyde is different from that normally observed with (*E*)-enolates, the authors postulate an open transition state to explain the results. As in the previous example, the stereoselectivity is not very much affected by the addition of $ZnCl_2$, although yields are improved significantly.

β-Propiolactone enolates that are substituted at C-2 show excellent simple and diastereofacial selectivity in their reactions with aldehydes.[101] As shown in equation (77) and Table 6, the reaction is quite general; yields are in the range 85–95%. In only one case (Table 6, entry 2) is an isomer detected; in this case the (**90**):(**91**) ratio is 85:15. (The data in Table 6 are taken from the preliminary communication (ref. 101a). In this publication, structures (**90**) and (**91**) were tentatively advanced. In ref. 101b, it is reported that the structure of the major product (**90**) had been determined by X-ray crystallography. This was presumably done on the major product of Table 6, entry 1, although this is not clear from ref. 101b. In addition, in ref. 101b, it is stated that the reactions in equation (77) all proceed with >88% enantioselectivity, presumably referring to the degree of simple diastereoselection. No experimental details for the preparation of aldol (**90**) were given in this full paper.)



(77)

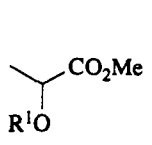
(**90**) (**91**)

Table 6 Aldol Stereochemistry (equation 77)

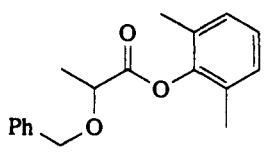
Entry	R^1	R^2	R^3	R^4	*Isomer ratio*
1	Bu^t	H	Ph	Ph	Only one
2	Bu^t	H	Ph	Me	85:15
3	Bu^t	H	Ph	H	Only one
4	Pr^i	H	Ph	Ph	Only one
5	Pr^i	H	Ph	Me	Only one
6	Pr^i	H	Ph	H	Only one
7	Pr^i	H	H	H	Only one
8		$(CH_2)_4$	Ph	Ph	Only one
9		$(CH_2)_4$	Ph	Me	Only one
10	Bu^t	H	Me	Ph	Only one

An extensive study of the aldol reactions of α-alkoxypropionate esters has been carried out.[102] The results of this investigation are summarized in Scheme 5 and Table 7. The trend that emerges from an examination of the data in Table 7 is that aldols of structure (**99**) are favored by small R^2, while aldols of structure (**100**) are favored by large R^2. The size of R^3, the aldehyde ligand, is also important; the larger this group, the more aldol of structure (**100**) is produced (compare entries 13–17, 18–19 and 20–23, Table 7). The ethers of methyl lactate (**92**) to (**94**) show only modest preferences for aldol structure (**99**). An exception to this generalization is seen in the reaction of methyl *O*-methyllactate (**92**), which gives a single isomer in its reactions with α-branched aliphatic aldehydes (Table 7, entries 2 and 3). The excellent complementary stereoselectivity observed with this reagent and the corresponding BHT ester (**97**) is striking (entries 24–26). It is also noteworthy that 2-phenylpropanal shows perfect diastereofacial selectivity in its reaction with the latter reagent.

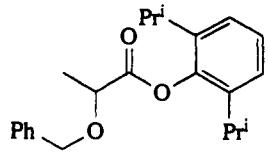
Reagent (**98**) has been employed in syntheses of the C-1,C-7 and C-8,C-15 segments of erythronolide A.[103,104] Reaction of the lithium enolate of (**98**) with aldehyde (**101**) provides aldols (**102**) and (**103**) in a



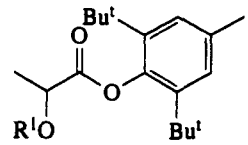
(92) R^1 = Me
(93) R^1 = $PhCH_2$
(94) R^1 = $MeOCH_2CH_2OCH_2$



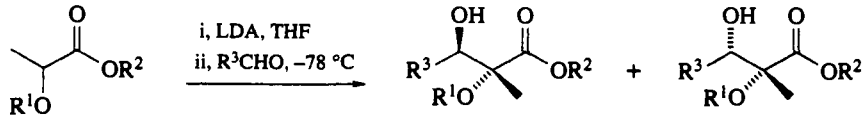
(95)



(96)



(97) R^1 = Me
(98) R^1 = $PhCH_2$



(99) (100)

Scheme 5

Table 7 Aldol Stereochemistry (Scheme 5)

Entry	*Ester*	*Aldehyde*	*Yield (%)*	*(99):(100)*
1	(92)	EtCHO	99	70:30
2	(92)	Pr^iCHO	98	>97:3
3	(92)	Bu^tCHO	84	>97:3
4	(92)	PhCHO	85	>75:25
5	(93)	EtCHO	87	70:30
6	(93)	Pr^iCHO	85	70:30
7	(93)	Bu^tCHO	80	70:30
8	(93)	PhCHO	100	70:30
9	(94)	EtCHO	60	82:18
10	(94)	Pr^iCHO	83	85:15
11	(94)	Bu^tCHO	73	88:12
12	(94)	PhCHO	95	85:15
13	(95)	CH_2=CHCHO	65	64:36
14	(95)	EtCHO	50	78:22
15	(95)	Pr^iCHO	77	83:17
16	(95)	Bu^tCHO	30	<3:97
17	(95)	PhCHO	65	25:75
18	(96)	Pr^iCHO	73	33:67
19	(96)	PhCHO	73	10:90
20	(98)	EtCHO	57	17:83
21	(98)	Pr^iCHO	89	<3:97
22	(98)	Bu^tCHO	0	—
23	(98)	PhCHO	62	<3:97
24	(97)	Pr^iCHO	84	<3:97
25	(97)	PhCHO	91	<3:97
26	(97)	Ph(Me)CHCHO	59	<3:97[a]

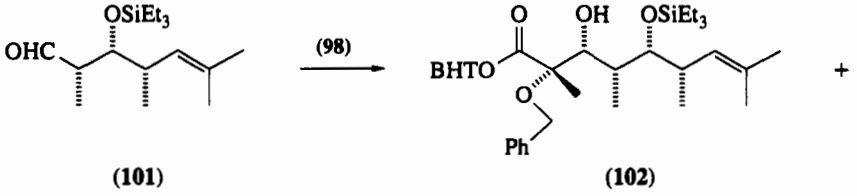
[a]A single diastereofacial isomer is produced in this reaction.

ratio of 85:15 (equation 78).[103] With the β,γ-unsaturated aldehyde (**104**), ester (**98**) gives a single aldol (equation 79).[104]

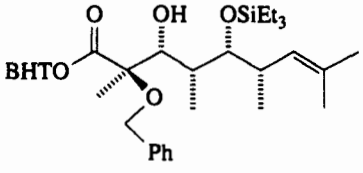
The enolate of α,β-dialkoxy ester (**105**) reacts with acetone to give (**106**) in good yield (equation 80); the product has been converted into (+)-viridifloric acid.[105]

The enolates of dioxolanones (**107**) react with aldehydes to give aldols (**108**) and (**109**) with, at most, a 3:1 preference for the former (equation 81).[102b] This modest preference is of the same magnitude, and in

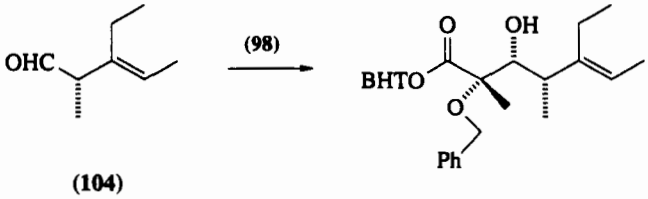
the same sense, as the preference seen with the lithium enolate of butyrolactone (equation 75, *vide supra*). However, Seebach and coworkers have carried out aldol reactions with chiral dioxolanone (**110**) and have observed high diastereofacial preference, as well as high simple diastereoselection in some cases (equation 82, Table 8).[106] The enolate of (**110**) also adds, in excellent yield and with essentially perfect diastereofacial selectivity, to ketones (cyclohexanone, acetone, acetophenone and benzophenone).



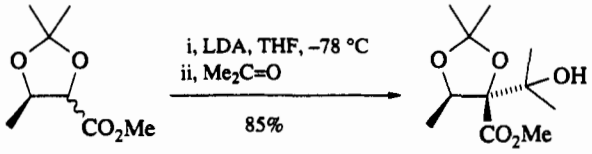
(**101**) (**102**)



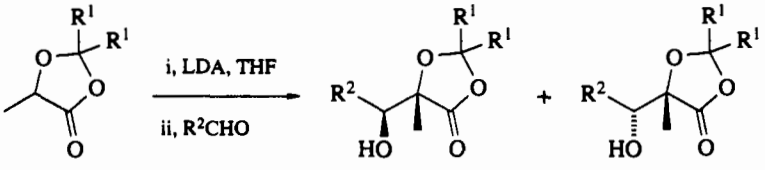
(**103**) (78)



(**104**) (79)

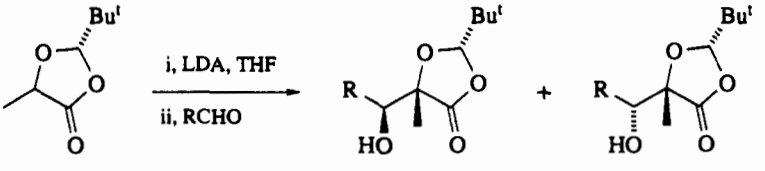


(**105**) (**106**) (80)



(**107**) (**108**) (**109**) (81)

R^1 = H, Me; R^2 = Et, Pr^i, Bu^t, Ph

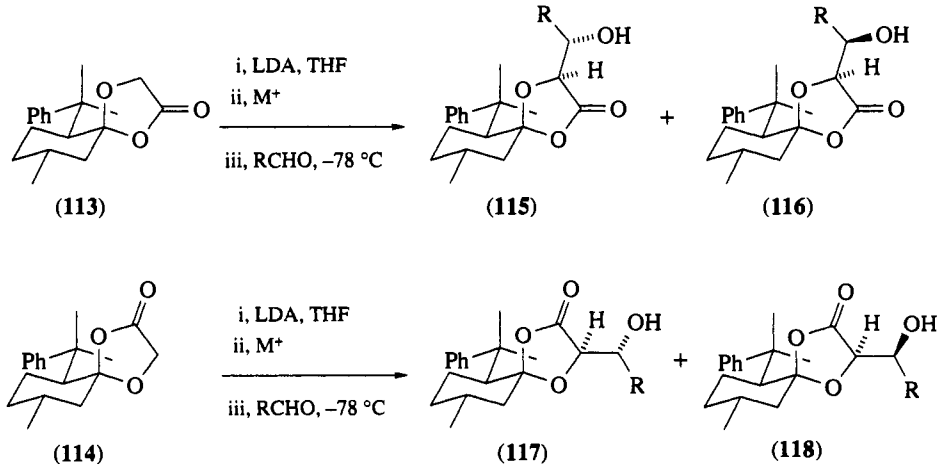


(**110**) (**111**) (**112**) (82)

Table 8 Aldol Stereochemistry (equation 82)

Entry	*R*	*Yield (%)*	*(111):(112)*
1	Me	84	82:18
2	Et	80	85:15
3	Bu^t	83	53:47
4	Ph	85	84:16
5	2,4,6-$Me_3C_6H_2$	65	78:22
6	CH=CHPh	66	64:40

Aldol reactions of chiral dioxolanones (**113**) and (**114**) are summarized in Scheme 6 and Table 9.[107] With both (**113**) and (**114**), essentially perfect diasterofacial selectivity is observed. The simple diastereoselection is modest to good, and is dependent on the enolate counterion. For the lithium and magnesium enolates, the sense of simple diastereoselection is the same as is observed with the achiral dioxolanone (**107**) and the chiral dioxolanone (**110**). Use of the zirconium enolate generally reverses the sense of simple diastereoselection, although the isomer ratios are not very high in some cases.



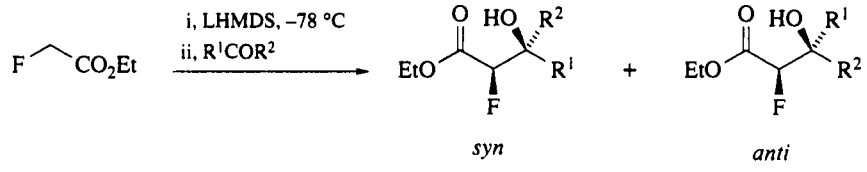
Scheme 6

Table 9 Aldol Stereochemistry (Scheme 6)

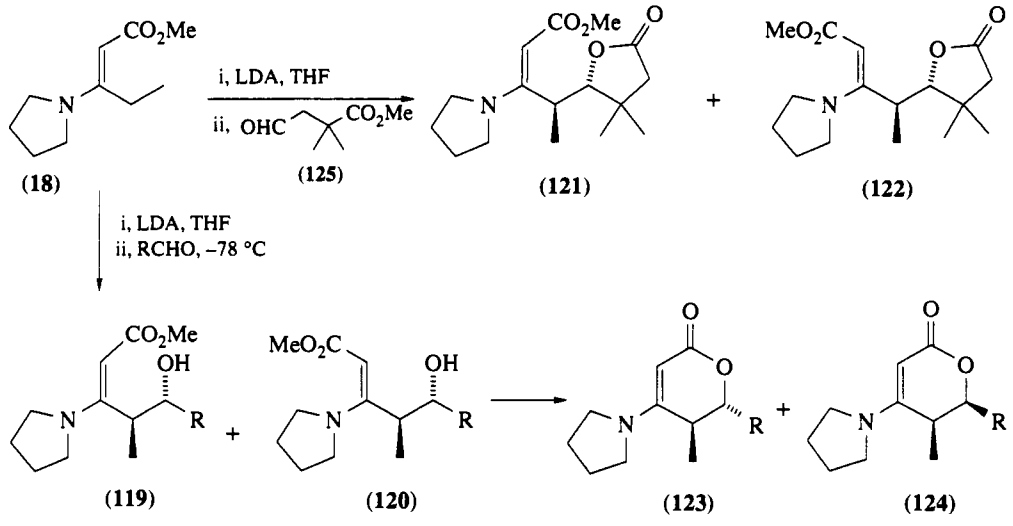
Entry	*Dioxolanone*	M^{+a}	*R*	*Yield (%)*	*(115):(116)*	*(117):(118)*
1	(**113**)	Li^+	Ph	92	68:32	—
2	(**113**)	Mg^{2+}	Ph	92	83:17	—
3	(**113**)	Zr^{4+}	Ph	95	19:81	—
4	(**113**)	Li^+	Pr^n	93	96:4	—
5	(**113**)	Mg^{2+}	Pr^n	86	90:10	—
6	(**113**)	Zr^{4+}	Pr^n	97	45:55	—
7	(**113**)	Li^+	Pr^i	85	90:10	—
8	(**113**)	Mg^{2+}	Pr^i	86	73:27	—
9	(**113**)	Zr^{4+}	Pr^i	91	24:76	—
10	(**114**)	Li^+	Ph	99	—	68:32
11	(**114**)	Mg^{2+}	Ph	89	—	75:25
12	(**114**)	Zr^{4+}	Ph	91	—	18:82
13	(**114**)	Li^+	Pr^n	96	—	88:12
14	(**114**)	Mg^{2+}	Pr^n	92	—	74:26
15	(**114**)	Zr^{4+}	Pr^n	91	—	37:63
16	(**114**)	Li^+	Pr^i	86	—	96:4
17	(**114**)	Mg^{2+}	Pr^i	89	—	89:11
18	(**114**)	Zr^{4+}	Pr^i	89	—	17:83

[a]For $M^+ = Li^+$, no extra salt was used; for $M^+ = Mg^{2+}$ or Zr^{4+}, 1.0 equiv. of $MgBr_2$ or Cp_2ZrCl_2 was added.

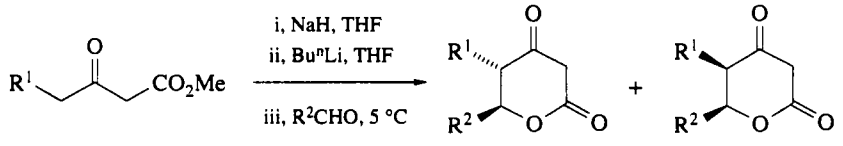
Ethyl fluoroacetate gives a 1:1 mixture of the (*E*)- and (*Z*)-enolate, which reacts with aldehydes and ketones to give mixtures of *syn* and *anti* aldols (equation 83).[108] Stereoselectivity is generally low, the *syn:anti* ratio ranging from 50:50 for 2-butanone to 4:1 for ethyl *t*-butyl ketone. However, since a mixture of enolates was employed in this study, there remains the possibility that one of the enolates is highly stereoselective, whereas the other one is stereorandom.



(83)



Scheme 7



(84)

Schlessinger and coworkers have investigated vinylogous ester enolates derived from enamino ester (**18**).[46] As shown in Scheme 7, the lithium enolate of (**18**) reacts with isobutyraldehyde or pivalaldehyde at –78 °C to give two adducts, (**119**) and (**120**), that both have the *anti* relative configuration at the new stereocenters. If the initial aldolate solution from the reaction of (**18**) with isobutyraldehyde is kept for an extended period of time at –78 °C, or warmed to 0 °C for 5 min, cyclization occurs, providing lactones (**123**) and (**124**) in a ratio of 20:1 under both conditions. However, the pivalaldehyde adduct gives (**123**) and (**124**) in a ratio of 18:1 at –78 °C or 7.8:1 at 0 °C. If the enolate of (**18**) is treated with aldehyde (**125**), the only products obtained are lactones (**121**) and (**122**), both having the *anti* relative configuration at the new stereocenters. The foregoing evidence is taken to indicate that the enolate of (**18**) reacts kinetically at C-4, in contrast to simple crotonate esters, which undergo aldolization at C-2. Cyclization of the original aldolate must involve geometric isomerization of the double bond, and may be complicated by reverse aldolization, particularly with the pivalaldehyde adduct at 0 °C.

The foregoing reactions bear a resemblance to the reactions of β-keto ester dianions (*vide supra*, equation 32), in that reaction occurs at C-4 instead of C-2. The only study of simple diastereoselection in the aldol reactions of β-keto ester dianions shows a stereochemical similarity as well. As shown in equation (84), the dianions of a series of β-keto esters react with aldehydes to give largely the *trans* lactone (**126**); data are summarized in Table 10.[109]

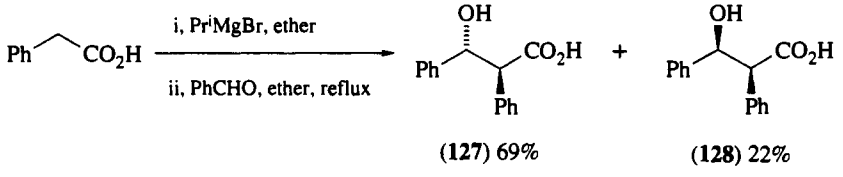
Table 10 Aldol Stereochemistry (equation 84)

Entry	R^1	R^{2a}	*Yield (%)*	***(125):(126)***
1	$PhCH_2$	Me	94	100:0[b]
2	$PhCH_2$	n-C_3H_7	96	100:0[b]
3	$PhCH_2$	n-C_7H_{15}	82	100:0
4	$PhCH_2$	c-C_6H_{11}	91	100:0
5	$PhCH_2$	c-C_8H_{15}	85	89:11
6	$PhCH_2$	Ph	78	87:13
7	*m*-$MeOC_6H_4CH_2$	c-C_6H_{11}	21	100:0
8	*p*-$MeC_6H_4CH_2$	n-C_3H_7	26	100:0[b]
9	$CH_2{=}CHCH_2$	c-C_6H_{11}	84	79:21
10	$CH_2{=}C(CH_3)CH_2$	c-C_6H_{11}	94	100:0[b]
11	Bu	Ph	83	63:37

[a]c-C_6H_{11} = cyclohexyl; c-C_8H_{15} = cyclooctyl. [b] Although a single diastereomer was obtained, the NMR spectra did not allow definite stereochemical assignment.

1.6.3.4 Carboxylic Acid Dianions (Ivanov Reaction)

The Ivanov reaction is the preparation of a β-hydroxy acid by reaction of the magnesium dianion of a carboxylic acid with an aldehyde or ketone.[110] In a seminal paper, Zimmerman and Traxler investigated the Ivanov reaction of phenylacetic acid and benzaldehyde and obtained *anti* and *syn* β-hydroxy acids (**127**) and (**128**) in 69% and 22% yields, respectively (equation 85).[111] The observed stereochemistry was rationalized with a cyclic, chair-like transition state in which a magnesium cation is chelated by one oxygen each of the carboxylate enolate and the aldehyde (the 'Zimmerman–Traxler transition state').



(85)

(**127**) 69% (**128**) 22%

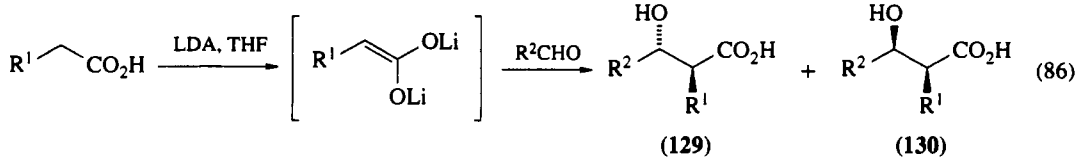
Table 11 Aldol Stereochemistry (equation 86)

Entry	R^1	R^2	*Method A*[a] *Yield (%)*	*Method A*[a] ***(129):(130)***	*Method B*[b] *Yield (%)*	*Method B*[b] ***(129):(130)***
1	Me	Bu^t	70	50:50	68	50:50
2	Me	Ph	75	55:45	75	55:45
3	Et	Ph	73	52:48	75	55:45
4	Pr^i	Ph	80	55:45	73	58:42
5	Bu^t	Pr^i	78	79:21	75	90:10
6	Bu^t	$PhCH_2CH_2$	70	67:33	65	67:33
7	Bu^t	Bu^t	85	80:20	83	>98:2
8	Bu^t	Ph	73	60:40	70	88:12
9	Ph	Ph	88	71:29	90	92:8
10	Ph	1-Naphthyl	85	73:27	80	92:8
11	Ph	2-Thienyl	75	70:30	68	91:9
12	Ph	2-Furyl	68	71:29	60	92:8
13	Ph	$PhCH{=}CH$	88	71:29	79	92:8
14	Bu^t	Mesityl	68	64:36	60	93:7
15	Mesityl	Mesityl	95	91:9	85	>98:2
16	1-Adamantyl	Bu^t	80	>95:5	77	>95:5
17	Ph	Bu^t	95	66:34	90	>98:2
18	Ph	Pr^i	83	66:34	77	93:7
19	Ph	Et	70	58:42	70	64:36
20	Ph	Me	65	58:42	60	64:36

[a]Method A: –50 °C, 10 min. [b]Method B: 50 °C, 3 d.

Blagoy *et al.* examined the effect of the counterion on the stereochemistry of this reaction.[112] With the bis(bromomagnesium) salt, a (**127**):(**128**) ratio of about 60:40, similar to that observed by Zimmerman and Traxler, is obtained. With the disodium salt, the sole isomer obtained (in 40% yield) is (**127**).

Mulzer and coworkers have examined the reactions of dilithium salts of carboxylic acids (equation 86, Table 11).[113] Products were assayed under kinetic conditions (10 min at –50 °C), and after 3 d at 50 °C. The compounds studied fall into two categories. For one set of reactions (*e.g.* Table 11, entries 1–4), the diastereomer ratios under the two conditions are essentially the same, showing that there is no equilibration after prolonged reaction time at elevated temperature. On the other hand, if the combined steric bulk of R^1 and R^2 is great enough, there is significant equilibration to isomer (**129**) under the more vigorous reaction conditions (*e.g.* Table 11, entries 7–15).

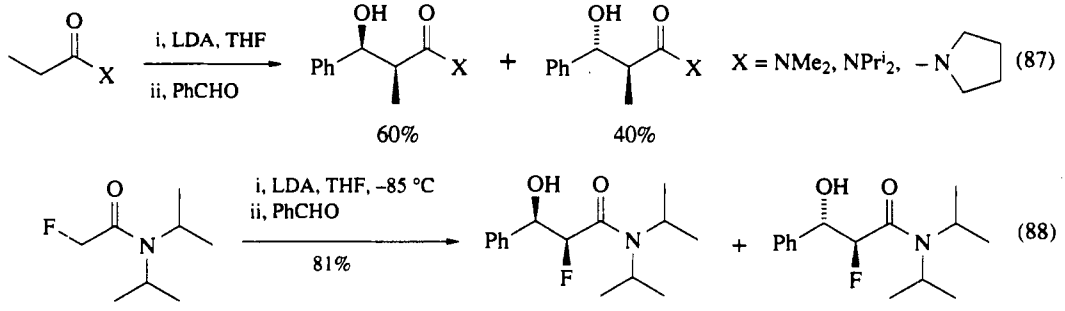


(86)

(**129**) (**130**)

1.6.3.5 Amide and Lactam Enolates

Simple amide enolates give poor stereoselection as shown by the examples in equation (87).[9c,114,115] This low degree of simple stereoselection appears to result from differences in the diastereomeric transition states, since *N*-propionylpyrrolidine gives a single enolate.[114] Welch found that the lithium enolates of fluoroacetamides give mixtures of *syn* and *anti* aldols, and that the lack of stereoselectivity is due to the fact that enolate mixtures are obtained; a typical example is shown in equation (88).[116] On the other hand, *N*-acyl derivatives of 2,3-dihydro-4*H*-1,4-benzothiazine and phenothiazine react with a variety of aldehydes to give *syn*-β-hydroxy amides (equations 89–90).[117]

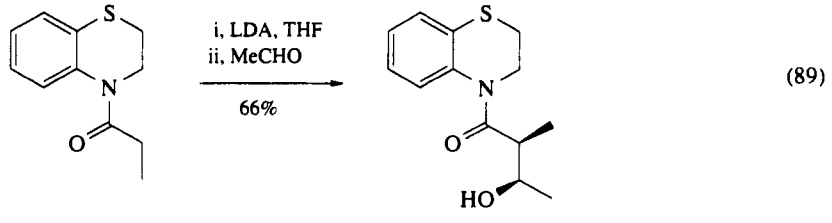


(87)

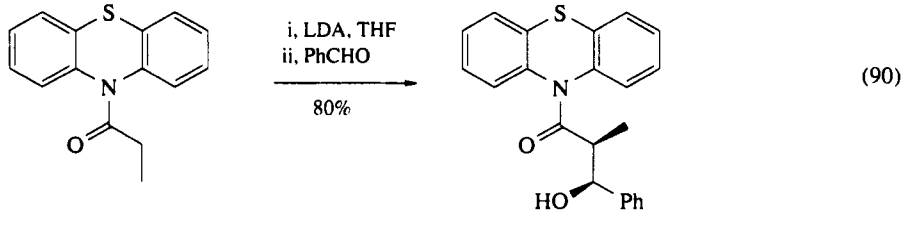
60% 40%

(88)

62% 38%



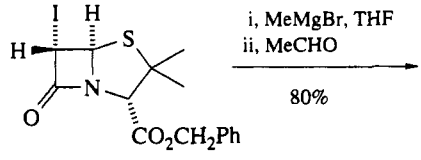
(89)

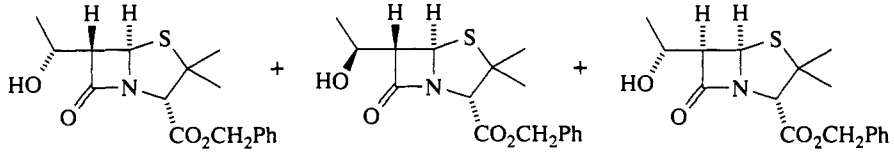


(90)

The antibiotic thienamycin has stimulated considerable interest in aldol reactions of β-lactams. In one of the first papers on this subject, DiNinno and coworkers examined various versions of this aldol reaction, one of which is shown in equation (91).[118] The magnesium enolate of the β-lactam, prepared by metallation of the 6-iodo derivative in THF, gives isomers (**131**) to (**133**) in a ratio of 24:49:27. In this reaction, the facial preference of the chiral β-lactam and the simple diastereoselection (*anti:syn*) are both modest (3:1). If metallation is carried out with *n*-butyllithium in ether, the ratio of the three isomers is 47:35:18, corresponding to a facial preference of 4:1 and an *anti:syn* ratio of 1:1. The stereochemistry of aldol reactions of the 6-bromopenam enolate derived from metallation of 6,6-dibromopenams has also been studied.[118,119] If the metallation is carried out in THF, either with *n*-butyllithium or methylmagnesium bromide, there is a surprising preference for reaction on the more congested concave face of the β-lactam; with the magnesium enolate, aldol (**134**) is isolated in 67% yield (equation 92). Metallation of the dibromo-β-lactam (**135**) with methylmagnesium bromide, followed by reaction of the magnesium enolate with acetaldehyde, gives aldol (**136**) as a single isomer in excellent yield (equation 93).[120] Again, the aldehyde attacks the concave face of the bicyclic system.

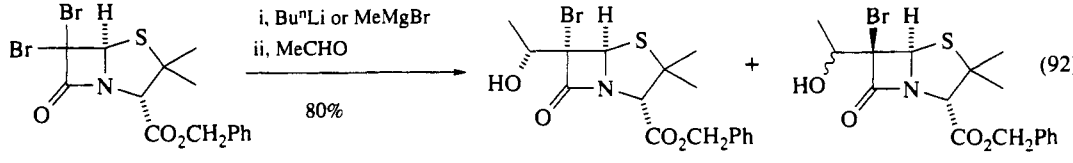
Several groups have studied aldol reactions of simpler β-lactam enolates. Diarylazetidinones such as (**137**) react as their lithium enolates to give completely or largely one of the four possible stereoisomers (**138**); a typical reaction is shown in equation (94).[121] [The interpretation of this paper is complicated by





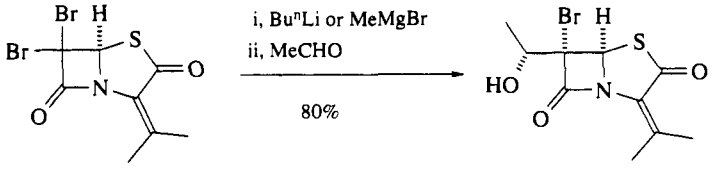
(91)

(**131**) (**132**) (**133**)



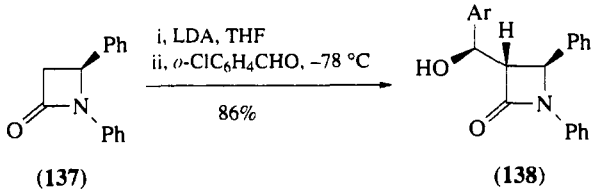
(92)

(**134**)



(93)

(**135**) (**136**)

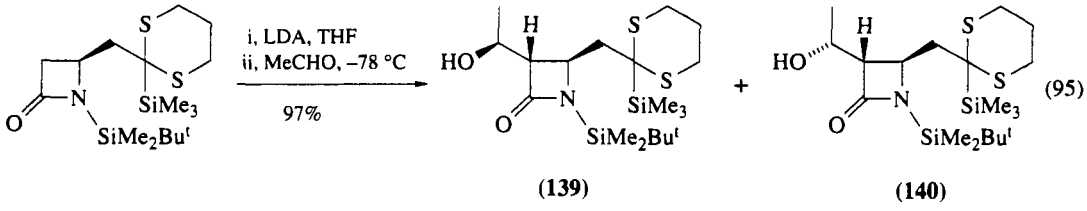


(94)

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

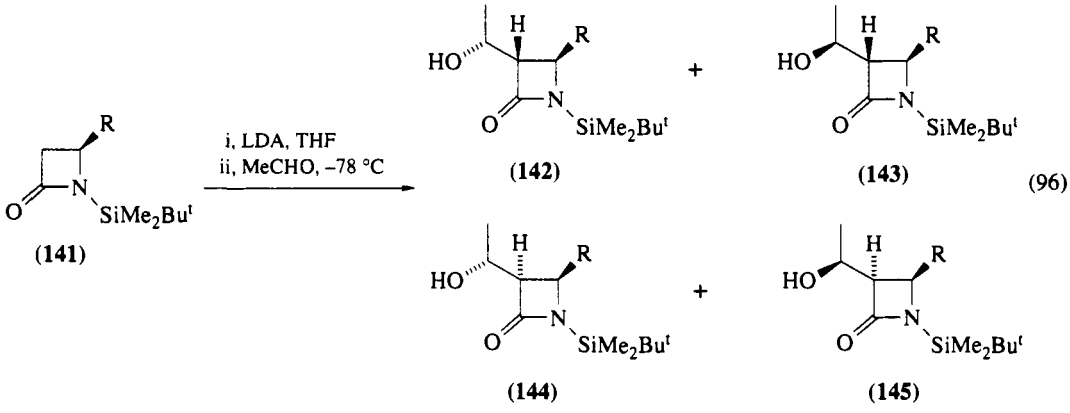
an error in nomenclature; product (**92**) and a number of structural analogs are incorrectly designated as (α*S**,3*S**,4*R**), rather than as (α*R**,3*S**,4*S**) or (α*S**,3*R**,4*R**).] The aldol product has the *anti* configuration at the two new stereocenters, as expected for an (*E*)-enolate. In a few cases, minor amounts of the *syn* product were isolated.

On the other hand, it has been found that β-lactams having other substituents at C-1 and C-4 give complex isomer mixtures.[122–124] A typical example is shown in equation (95); *anti* and *syn* aldols (**139**) and (**140**) are formed in excellent yield, but in a ratio of 1:1.[122] Another example is seen in the reaction of β-lactam (**141**; R = SPh); aldols (**142**) to (**145**) are produced in a ratio of 34:27:11:23 (equation 96).[125] Similar results are obtained with the 4-trityl derivative (**141**; R = CPh_3); aldols (**142**) to (**145**) are formed in a ratio of 32:39:12:17.[126] However, the lithium enolate of β-lactam (**146**) reacts with acetaldehyde to give a single aldol (**147**) in 80% yield (equation 97)! The implication from these results is that the methoxymethyl group in (**146**) effects the stereoselectivity, both facial and simple, by coordination of the lithium cation. Again, (**147**) has *anti* aldol stereochemistry, as is expected for an (*E*)-enolate.



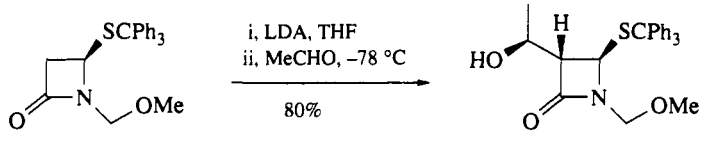
(95)

(**139**) (**140**)



(96)

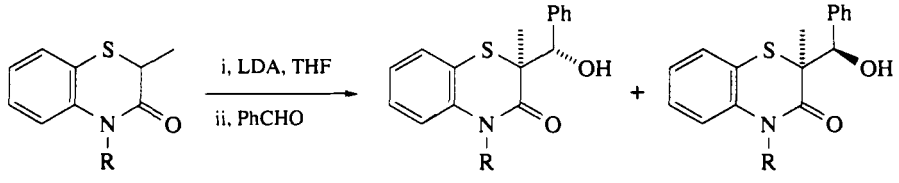
(**141**) (**142**) (**143**) (**144**) (**145**)



(97)

(**146**) (**147**)

The lithium enolate of lactam (**148**; R = Me) reacts with aromatic aldehydes to give the diastereomeric aldols (**149**) and (**150**) in ratios of 6:1 to 9:1 (equation 98); stereoselectivity is reduced with (**148**; R = H), and with aliphatic aldehydes.[127]



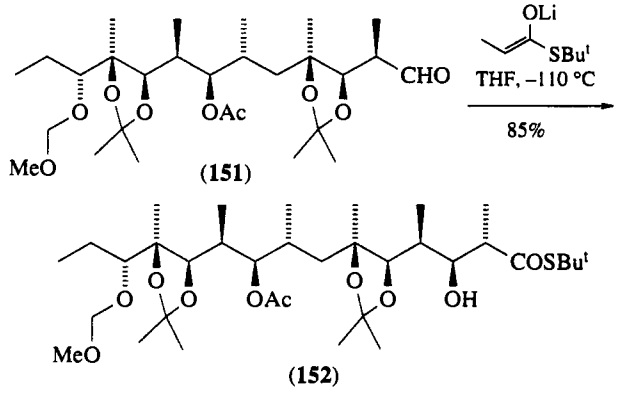
(98)

(**148**) (**149**) (**150**)

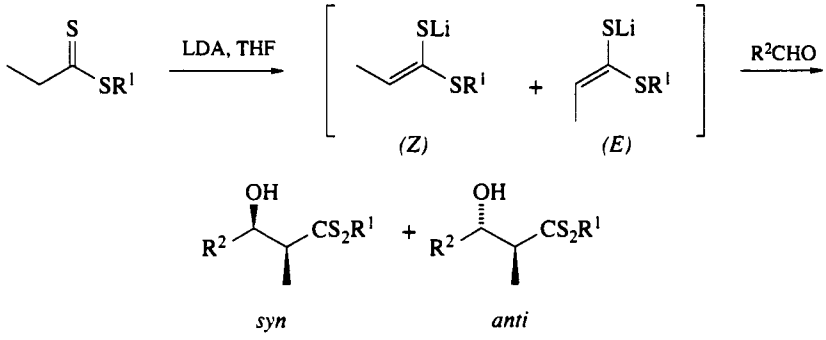
1.6.3.6 Thioester and Thioamide Enolates

In the Woodward erythromycin synthesis, the lithium enolate of *t*-butyl thiopropionate[128] was added to aldehyde (**151**); aldol (**152**) was obtained in 85% yield (equation 99).[129] The remarkable diastereofacial selectivity observed in this reaction may be a general property of thioester enolates (*vide infra*).

Dithiopropionate esters are deprotonated by LDA in THF to give mixtures of the (*Z*)- and (*E*)-enolate, favoring the former.[130] [As with ester enolates, the Evans (*E*)/(*Z*) notational format (ref. 2c) is followed. Thus, in naming an enolate derived from a dithioester $R^2CH_2CS_2R^1$, SM is assigned higher priority than SR^1, regardless of the metal.] The reactions of these enolate mixtures with aldehydes have been studied (equation 100; Table 12).[131,132] The data in Table 12 suggest a relationship between enolate geometry and aldol stereochemistry, at least for (*Z*)-enolates of dithioesters with moderately large R^1 groups. The simple diastereoselection seen with the sterically encumbered aldehydes 2-phenylpropanal and 2-cyclohexylpropanal (Table 12, entries 3 and 4) is exceptional in light of the fact that the enolate ratio is



(99)



(100)

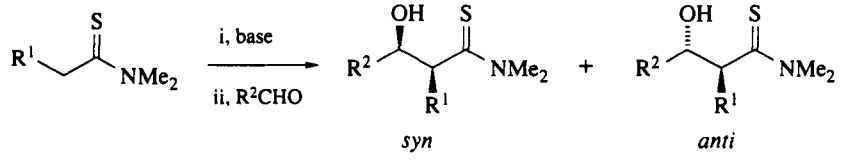
Table 12 Aldol Stereochemistry (equation 100)

Entry	R^1	*(Z):(E)*[a]	R^2	*Temperature* (°C)	*Yield* (%)[d]	*Syn:anti*	*Ref.*
1	Me	75:25	Ph	−78	84	57:43	131
2	Et	b	Ph	−120	50–60	46:54	132
3	Et	b	Ph(Me)CH	−120	50–60	95:5	132
4	Et	b	c-C_6H_{13}(Me)CH	−120	50–60	84:16	132
5	Pr^i	81:19	Et	−78	85[e]	82:18	131
6	Pr^i	81:19	Pr^i	−78	50[f]	83:17	131
7	Bu^t	84:16	Ph	−78	40	77:23	131
8	Bu^t	84:16	Et	−78	60	76:24	131
9	CH_2OMe	86:14	Et	−78	50	77:23	131
10	Ph	87:13	Ph	−78	35	74:26	131
11	Ph	87:13	Et	−78	15[f]	81:19	131
12	Pr^i	44:56[c]	Ph	−78	60	64:36	131

[a]Enolate ratio obtained with LDA in THF at −78 °C. [b]The enolate ratio was not determined in this study. [c]Enolate ratio obtained with LHMDS or LITMP. [d]Yield after 10 s reaction time, unless stated. [e]Reaction time 30 s; yield after 10 s was 47%. [f]Reaction time 2 min.

probably of the order of 75:25. This high stereoselectivity, apparently independent of enolate geometry, has been interpreted by Meyers and Walkup as indicative of an open transition state.

Thioamides of secondary amines give (*Z*)-enolates that react with aldehydes to give *syn* aldols with good stereoselectivity (equation 101; Table 13).[115,133] The stereoselectivity is slightly greater with the magnesium enolate than with the lithium enolate (Table 13, entries 2 and 3) and is strongly influenced by conditions (entries 6 and 7). The poor stereoselectivity observed with the thioamide of valeric acid (Table 13, entries 10 and 11) is attributed to the formation of a mixture of enolate geometric isomers.



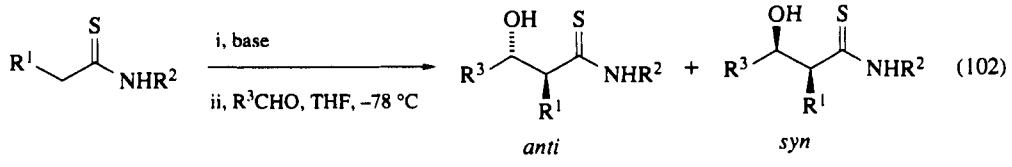
(101)

Table 13 Aldol Stereochemistry (equation 101)

Entry	R^1	R^2	*Base*	*Temperature* (°C)	*Time* (min)	*Syn:anti*[a]	*Ref.*
1	Me	Pr^i	Pr^{i}MgBr	−78	30	95:5	115
2	Me	Ph	Pr^{i}MgBr	−78	2	93:7	115
3	Me	Ph	Bu^{n}Li	−78	2	87:13	115
4	Me	Et	Bu^{n}Li	−78	10	90:10	115
5	Me	CH_2=CH	Pr^{i}MgBr	−78	30	89:11	115
6	Ph	Pr^i	Pr^{i}MgBr	−78	2	72:28	115
7	Ph	Pr^i	Pr^{i}MgBr	+25	60	3:97	115
8	Ph	CH_2=CMe	Pr^{i}MgBr	−78	10	73:27	115
9	PhS	Pr^i	Pr^{i}MgBr	−78	10	66:34	115
10	Pr^i	Ph	Pr^{i}MgBr	−78	2	34:66	133
11	Pr^i	$PhCH_2CH_2$	Bu^{n}Li	−78	2	32:68	133

[a]Combined isolated yields = 85–100%.

Thioamides of primary amines react with two equivalents of *n*-butyllithium or isopropylmagnesium bromide to give dianions that have been shown to have the (*Z*)-configuration. These species react with aldehydes to afford predominantly *anti* aldols (equation 102; Table 14).[134] Again, the magnesium dianions generally show superior stereoselectivity. In certain cases, the degree of stereoselectivity is excellent. This procedure provides a convenient complement to the *syn* selectivity obtained with thioamides of secondary amines.



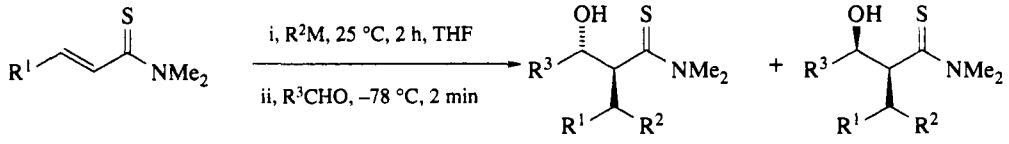
(102)

Table 14 Aldol Stereochemistry (equation 102)

Entry	R^1	R^2	R^3	*Base*	*Anti:syn*[a]
1	Me	Ph	Me	Bu^{n}Li	69:31
2	Me	Ph	Pr^i	Bu^{n}Li	88:12
3	Me	Ph	Ph	Bu^{n}Li	62:38
4	Pr^i	Ph	Pr^i	Bu^{n}Li	93:7
5	Pr^i	Ph	Ph	Bu^{n}Li	69:31
6	Ph	Me	Pr^i	Bu^{n}Li	78:22
7	Ph	Me	Pr^i	Pr^{i}MgBr	98:2
8	Ph	Me	Ph	Bu^{n}Li	71:29
9	Ph	Me	Ph	Pr^{i}MgBr	94:6
10	Ph	CH_2CH_2OMe	Ph	Bu^{n}Li	94:6
11	Ph	CH_2CH_2OMe	Ph	Pr^{i}MgBr	97:3

[a]Combined isolated yields = 75–99%.

Thioamide enolates may be prepared by conjugate addition of organometallics to α,β-unsaturated thioamides. Reaction of these enolates with aldehydes affords *anti* aldols, often in excellent diastereomeric excess (equation 103; Table 15).[133] It is believed that the conjugate addition reactions provide (*Z*)-enolates, *via* a cyclic, six-centered transition state.[135] The *anti* stereochemistry observed in the aldol reactions of these (*Z*)-enolates would result from a boat-like, chelated transition state. The transition state has boat-like character to avoid a serious *gauche* interaction between R^3 and the bulky secondary alkyl group in the thioamide enolate. Several of the intermediate enolates in this study (*e.g.* Table 15,

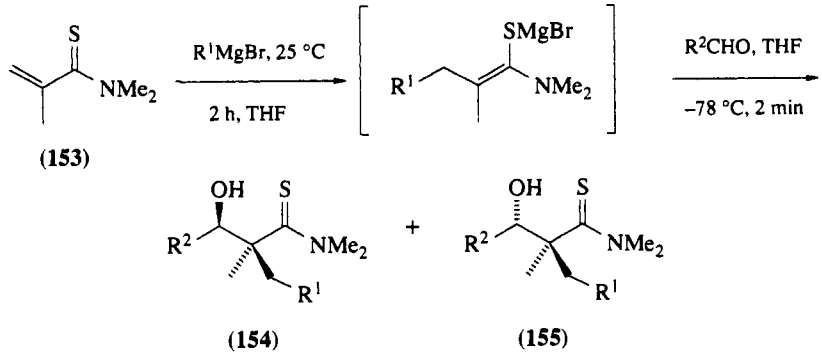


(103)

Table 15 Aldol Stereochemistry (equation 103)

Entry	R^1	R^2-*Metal*	R^3	*Anti:syn*[a]
1	Me	MeMgI	Me	96:4
2	Me	MeLi	Me	90:10
3	Me	MeMgI	Pr^i	>99:1
4	Me	MeMgI	Ph	94:6
5	Me	EtMgBr	Ph	85:15
6	Me	Bu^nLi	Ph	87:13
7	Me	Pr^iMgBr	Me	74:26
8	Me	Pr^iMgBr	Pr^i	>99:1
9	MeCH=CH	MeMgI	Pr^i	>99:1
12	MeCH=CH	Pr^iMgBr	Me	89:11
13	MeCH=CH	Pr^iMgBr	Pr^i	>99:1
14	Ph	Pr^iMgBr	Me	82:18

[a]Combined isolated yields = 70–88%.



(104)

Table 16 Aldol Stereochemistry (equation 104)

Entry	R^1	R^2	*Temperature* (°C)	*Time* (min)	***(154):(155)***	*Yield* (%)
1	Et	Me	–78	2	>99:1	85
2	Et	Pr^i	–78	2	>99:1	86
3	Pr^i	Me	–78	2	>99:1	95
4	Pr^i	Et	–78	2	>99:1	86
5	Ph	Me	–78	2	>99:1	24
6	Ph	MeCH=CH	–78	2	>99:1	25
7	Ph	PhCH=CH	–78	2	>99:1	48
8	Et	Ph	–78	2	41:59	80
9	Et	Ph	+25	1080	8:92	80
10	Pr^i	Ph	–78	2	33:67	83
11	Ph	Ph	–78	2	17:83	81

entries 5–8, 12–14) are chiral. However, no information pertaining to the diastereofacial selectivity, if any, has been provided.

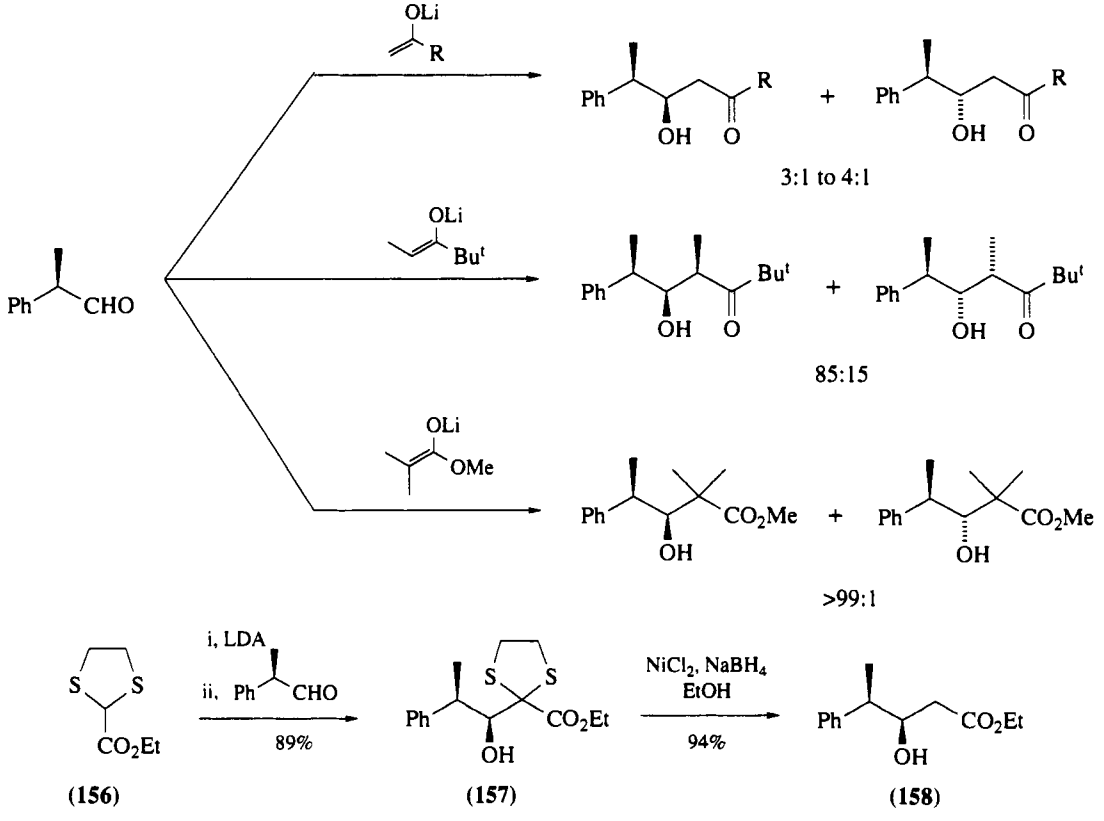
Conjugate addition to thioamide (**153**) gives tetrasubstituted enolates, presumably having the (*Z*)-configuration.[30] Reaction of these enolates with aliphatic aldehydes gives aldols of high stereochemical purity (equation 104; Table 16).[136] This is a relatively uncommon example of a stereoselective aldol reaction involving a tetrasubstituted enolate. Note that the use of benzaldehyde as the electrophile leads to stereochemical reversal, which is strongest under conditions of thermodynamic control (Table 16, entries 8–11).

1.6.4 DIASTEREOFACIAL SELECTIVITY

In this section are treated aldol reactions of preformed lithium and magnesium enolates in which one or both of the reaction partners are chiral.

1.6.4.1 Chiral Substrates

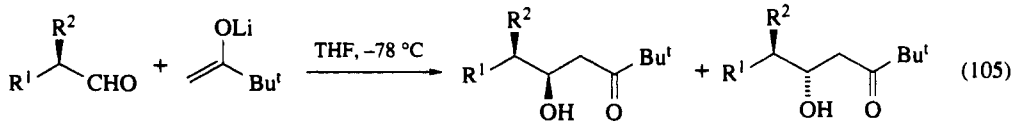
The two faces of a chiral aldehyde are diastereotopic, and reaction with an achiral enolate can therefore give two diastereomeric products. Qualitatively, the major and minor products of such a reaction are determined by the intrinsic diastereofacial preference of the chiral aldehyde, which may be evaluated by the use of Cram's rule or one of its more modern derivatives.[137] Quantitatively, the diastereomeric ratio in such a reaction is a function of the enolate. An example is seen in Scheme 8. 2-Phenylpropanal reacts with the lithium enolates of acetone, pinacolone, methyl acetate and *N,N*-dimethylacetamide to give 3,4-*syn* and 3,4-*anti* diastereomers in ratios of 3:1 to 4:1.[138] With ethyl ketones and propionate esters, the diastereofacial ratio is approximately 6:1,[9c] and with methyl isobutyrate only a single isomeric product is produced.[139] This tendency of more bulky nucleophiles to give higher diastereofacial ratios in reactions



Scheme 8

with chiral aldehydes has been exploited as shown in Scheme 8; addition of the enolate of ester (**156**) to 2-phenylpropanal gives a single adduct (**157**), which is desulfurized to obtain β-hydroxy ester (**158**).[140]

Data for the addition of the lithium enolate of pinacolone to a variety of α-chiral aldehydes are presented in equation (105) and Table 17.[141] The results in the table show that the diastereofacial preference of a chiral aldehyde is a function of the steric bulk and the electronic nature of the groups attached to the stereocenter. In a purely empirical manner, the major isomer may be correctly predicted by the

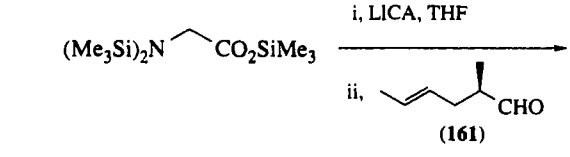


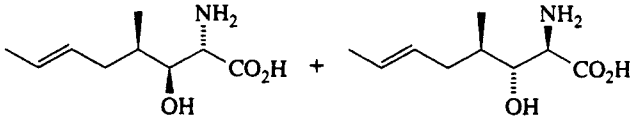
(105)

Table 17 Aldol Stereochemistry (equation 105)

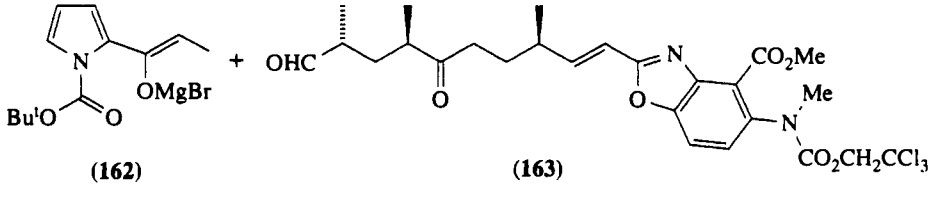
Entry	R^1	R^2	*(159):(160)*[a]
1	Ph	Me	78:22
2	Ph	Et	86:14
3	Ph	Pr^i	70:30
4	Ph	Bu^t	37:63
5	Ph	OMe	17:83
6	Me	OMe	42:58
7	Et	OMe	24:76
8	Pr^i	OMe	8:92
9	Bu^t	OMe	7:93

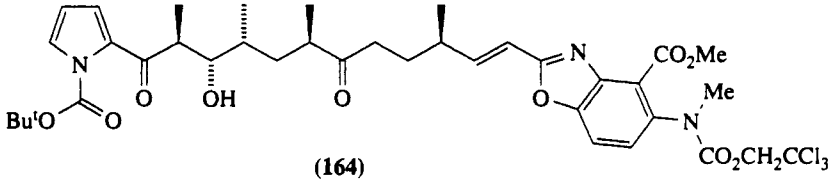
[a]Each ratio is the average of three independent determinations.





(106)



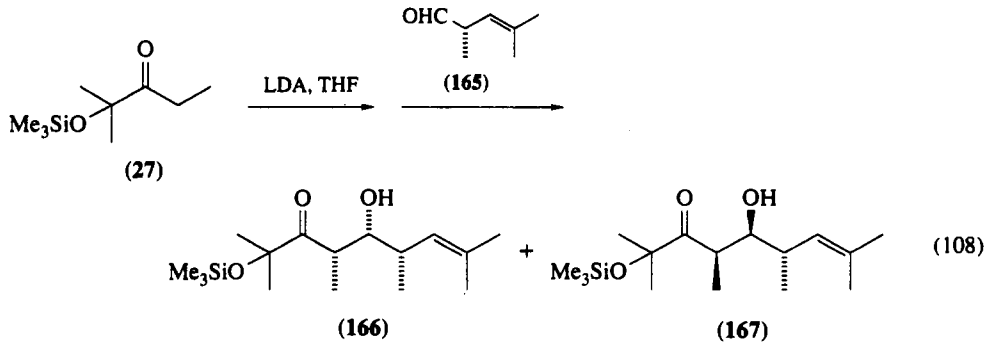


(107)

Felkin model for asymmetric induction if one uses the order of ligand preferences for the *anti* position: MeO > Bu^t > Ph > Pr^i > Et > Me > H. Note that the major isomers produced in reactions of the α-methoxy aldehydes (Table 17, entries 5–9) are not those expected from a chelation-controlled process.

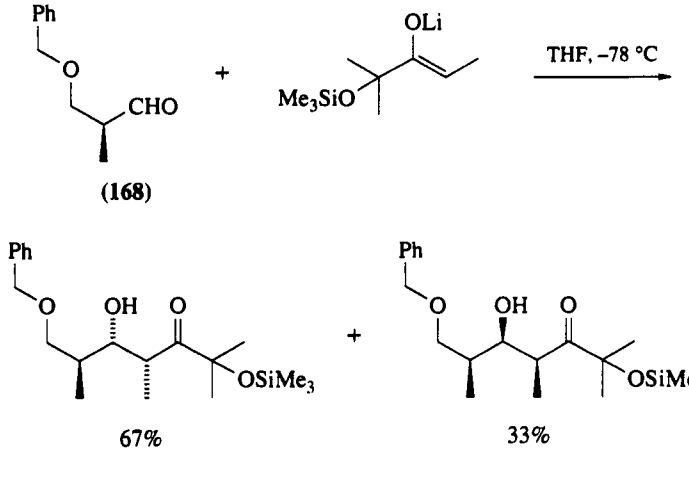
It is often necessary in a synthetic project to carry out an aldol addition on a chiral aldehyde in which the α-ligands are hydrogen, methyl and an alkyl group. In the synthesis of MeBMT, the characteristic amino acid of the antibiotic cyclosporin, the lithium enolate of *N,N,O*-tris(trimethylsilyl)glycine is added to aldehyde (**161**) to give, after deprotection, two hydroxy amino acids in a ratio of 3:1 (equation 106).[142] One step in a total synthesis of the polyether antibiotic A23187 (calcimycin) is the aldol reaction of the magnesium enolate (**162**) with aldehyde (**163**); β-hydroxy ketone (**164**) is obtained in 61% yield, along with 16% of a stereoisomer (equation 107).[143] For other examples of such reactions, see equations (50) and (51), (69), (73) and (78) and (79).

Reagent (**27**) has been used in a synthesis of the C-1,C-7 segment of erythronolide A, as shown in equation (108).[144] Addition of the lithium enolate of (**27**) to chiral aldehyde (**165**) provides aldols (**166**) and (**167**) in a ratio of approximately 6:1. [The initial report that this aldol reaction gives a stereoisomer ratio of approximately 15:1 was subsequently found to be in error (ref. 144b).]

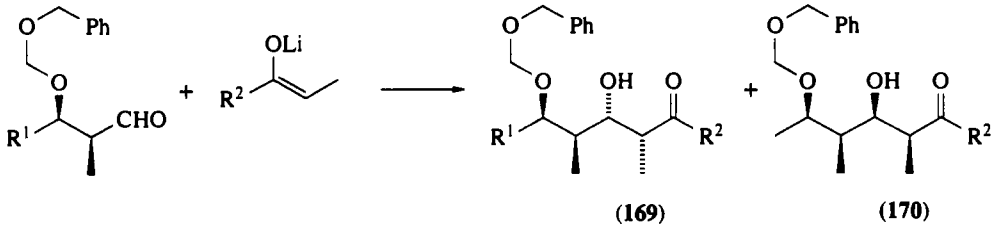


(108)

The major and minor products obtained in aldol reactions of chiral aldehyde (**168**; equation 109) are not those predicted by Cram's rule, presumably because the lithium cation is chelated by the alkoxy and aldehyde oxygens, leading to a rigid six-membered intermediate that undergoes attack primarily from its unsubstituted face.[68] Similar behavior, with somewhat higher diastereofacial selectivity (5:1), is seen with the magnesium enolate (equation 50).



(109)

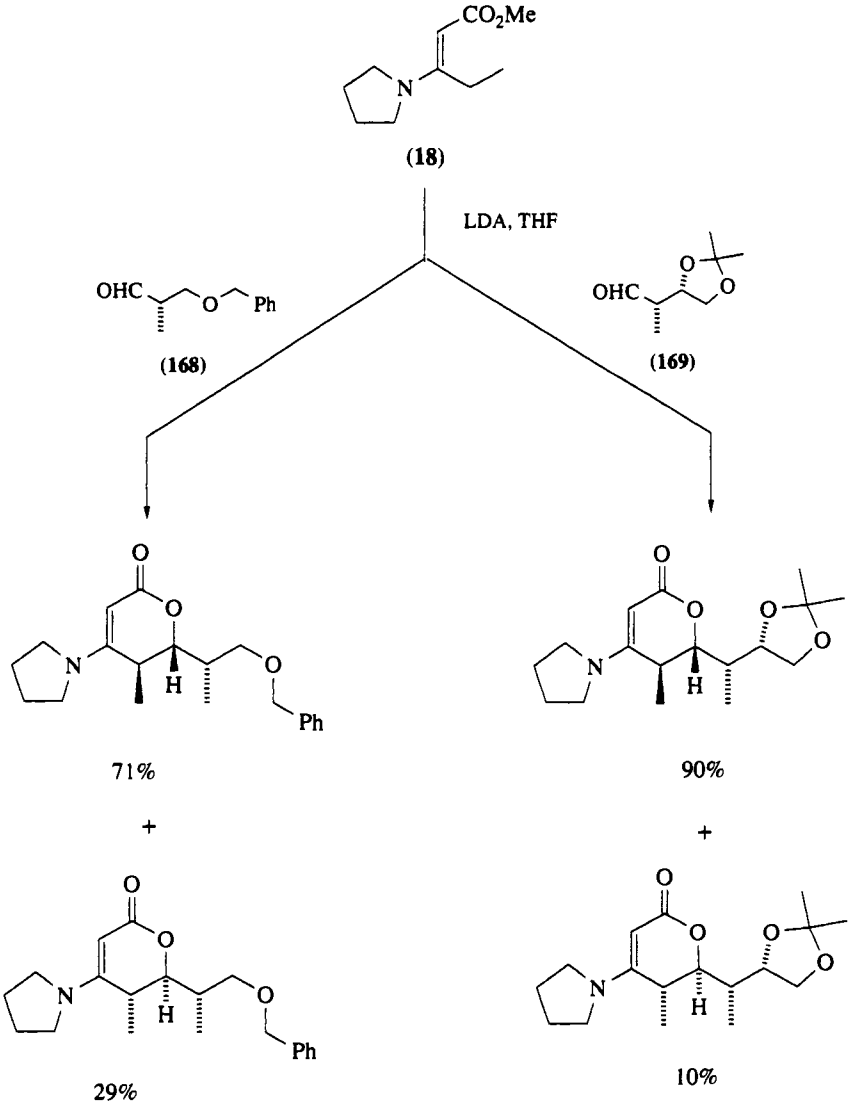


(110)

Table 18 Aldol Stereochemistry (equation 110)

R^1	R^2	*(169):(170)*	*Yield (%)*
H	Et	80:20	87
H	Cy[a]	78:22	79
Et	Et	83:17	81
Et	Cy	90:10	79
$PhCD_2$	Et	85:15	71
$PhCD_2$	Cy	90:10	70
Pr^i	Et	87:13	75
Pr^i	Cy	92:8	68
$Bu^tMe_2SiOCH_2CH_2$	Et	93:7	82
$Bu^tMe_2SiOCH_2CH_2$	Cy	95:5	79

[a]Cy = cyclohexyl.

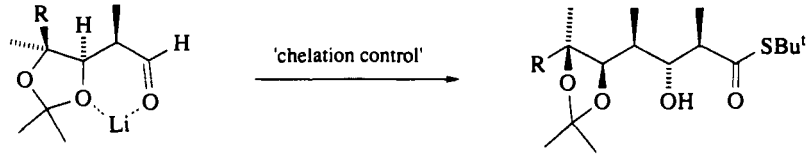


Scheme 9

Masamune and coworkers have examined the facial selectivity of the (*Z*)-lithium enolates of 3-pentanone and ethyl cyclohexyl ketone with a series of β-alkoxy aldehydes having stereocenters at both the α- and β-position (equation 110; Table 18).[61] In the six-membered chelate, the methyl and R^1 groups are on the same side of the ring, and it may be seen from the data in Table 18 that the nature of R^1 influences the facial preference of the chiral aldehyde. Another example of this effect is seen in equation (54).

However, such chelation effects are not always observed. For example, in the Woodward erythromycin A synthesis (equation 99), the facial preference of aldehyde (**151**) is that predicted by application of Cram's rule, even though there is an alkoxy group at the β-position. Addition to a chelated carbonyl group in this case would amount to a choice between addition to the convex or concave face of a bicyclo[4.3.0]nonane structure (equation 111).

Other cases in which chelation control is not involved in addition to a chiral β-alkoxy aldehyde are shown in equations (69) and (78); in these cases, it might be argued that the *t*-butyldimethylsilyloxy and triethylsilyloxy groups are not good ligands for steric reasons. Yet other examples are seen in the two reactions summarized in Scheme 9.[46a] Here, the lithium enolate of the vinylogous ester (**18**) adds to aldehyde (**168**) to give predominantly the Cram-predicted isomer; with aldehyde (**169**), the Cram diastereofacial preference is even greater.

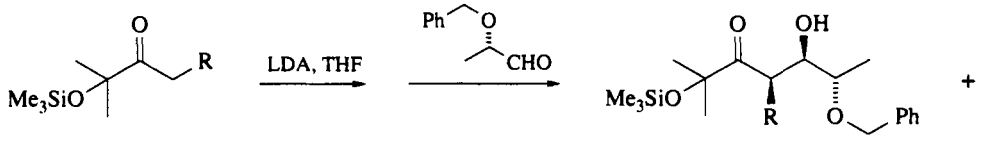


(111)

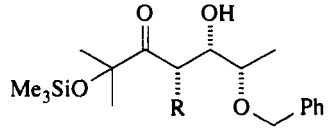
(**151**)

Additions to chiral aldehydes in which the stereocenter ligands are H, methyl and alkoxy are also relatively common. With lithium enolates, these aldehydes show diastereofacial preferences that suggest that the major product does not involve addition to an intermediate chelate (*vide supra*). However, diastereomer ratios are often rather low. For example, in equation (112) the diastereofacial preference with reagent (**27**) is 65:35,[145] and that with reagent (**33**) is 78:22.[70]

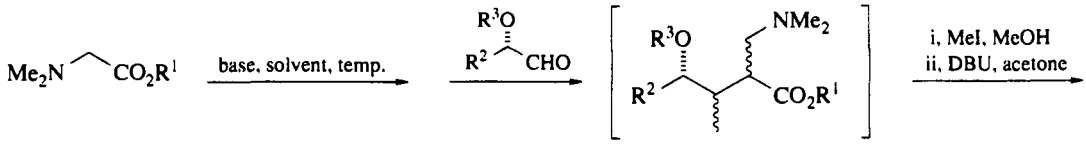
A detailed study has been carried out with the lithium enolates of methyl and *t*-butyl *N,N*-dimethylglycinate (equation 113).[146] Selected data from this study are presented in Table 19. The data show that the

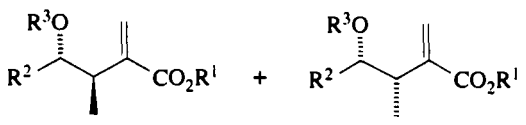


(**27**) R = Me
(**33**) R = H_2C=$CHCH_2$



(112)





(113)

(**170**) (**171**)

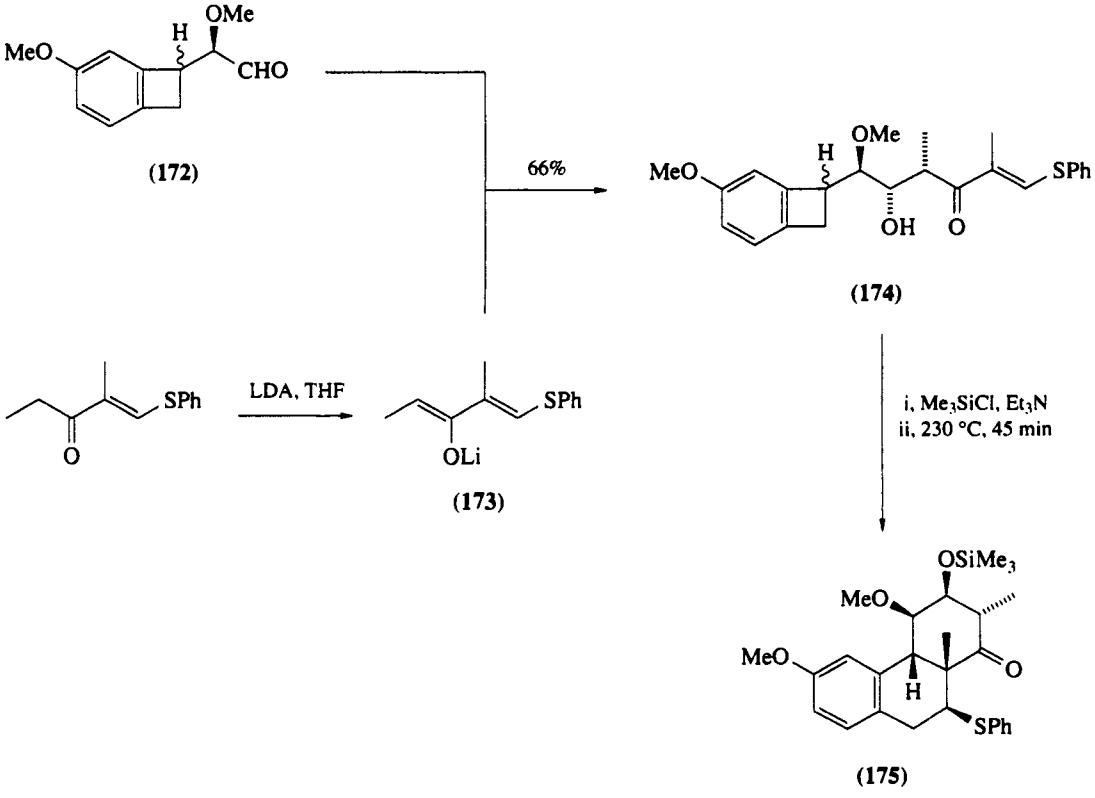
size of R^1 has a significant effect, whereas that of R^2 or R^3 is not very important. The solvent, temperature and period of metallation strongly affect the diastereomer ratio, suggesting that enolate equilibration may be occurring. This was confirmed by trapping the enolate as its *t*-butyldimethylsilyl enol ether. Deprotonation at –78 °C with LDA in THF gives two enolates in a ratio of 67:33, whereas the use of LDA in ether at 0 °C for 4 h leads to a ratio of 14:86.

Table 19 Aldol Stereochemistry (equation 113)

Entry	R^1	R^2	R^3	*Solvent*	*Metallation temperature* (°C)[a]	*Yield* (%)	*Anti:syn*
1	Me	Me	$PhCH_2OCH_2$	THF	–78	55	65:35
2	Bu^t	Me	$PhCH_2OCH_2$	THF	–78	68	80:20
3	Me	Me	$MeOCH_2$	THF	–78	42	77:23
4	Bu^t	Me	$MeOCH_2$	THF	–78	47	83:17
5	Me	Me	$MeOCH_2CH_2OCH_2$	THF	–78	52	65:35
6	Bu^t	n-C_6H_{13}	$PhCH_2OCH_2$	THF	–78	72	79:21
7	Me	n-C_6H_{13}	$MeOCH_2$	THF	–78	60	73:27
8	Bu^t	n-C_6H_{13}	$MeOCH_2$	THF	–78	69	82:18
9	Bu^t	n-C_6H_{13}	$MeOCH_2$	THF/HMPA	–78	—[c]	63:37
10	Bu^t	n-C_6H_{13}	Me	THF	–78	71	80:20
11	Bu^t	n-C_6H_{13}	Me	THF	–30	—[c]	87:13
12	Bu^t	n-C_6H_{13}	Me	THF	0	—[c]	88:12
13	Bu^t	n-C_6H_{13}	Me	Ether	–30	—[c]	92:8
14	Bu^t	n-C_6H_{13}	Me	Ether	0	—[c]	93:7
15	Bu^t	n-C_6H_{13}	Me	Ether	0[b]	—[c]	96:4

[a]Metallation was carried out at the indicated temperature for 1 h, unless otherwise noted. [b]Metallation was carried out for 4 h in this case. [c]Yields were not given for these cases.

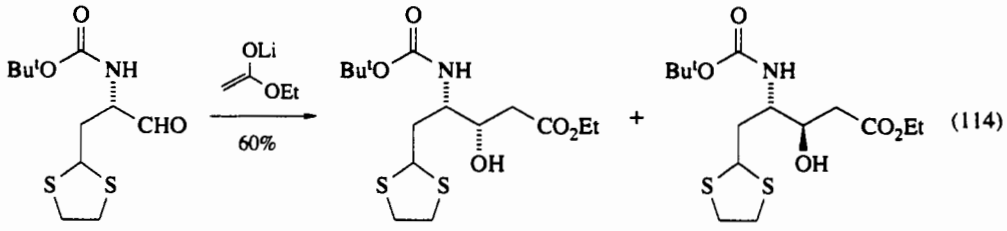
Scheme 10 summarizes what appears to be a highly stereoselective addition to an α-methoxy aldehyde.[147] The (*Z*)-lithium enolate (**173**), formed from the enone by reaction with lithium hexamethyldisilazane, reacts with benzaldehyde to give *syn* and *anti* aldols in a ratio of 8:1. Reaction of (**173**) with



Scheme 10

aldehyde (**172**), a diastereomeric mixture, gives diastereomeric aldols (**174**). These isomers must have the same relative stereochemistry at C_α, C_β and C_γ because the intramolecular Diels–Alder reaction that occurs upon heating the trimethylsilyl ethers of (**174**) gives a single product, (**175**).

Much less is known about aldol additions to chiral aldehydes that have heteroatoms other than oxygen at the α-stereocenter. In connection with a synthesis of statine analogs, α-amino aldehyde (**176**) was allowed to react with ethyl lithioacetate to obtain (**177**) and (**178**) in a ratio of 60:40 (equation 114).[148]



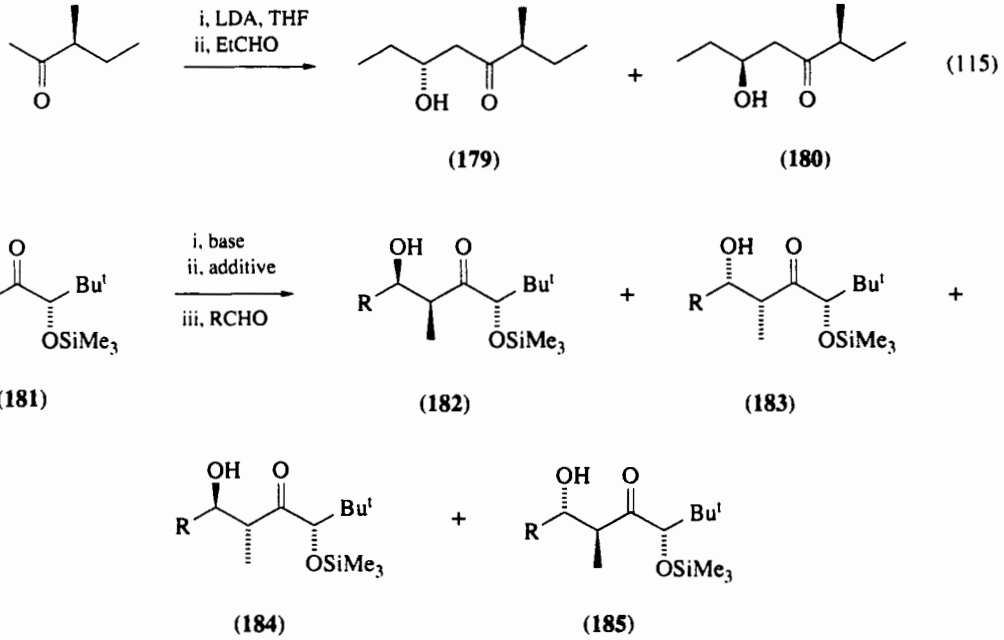
(**176**) (**177**) (**178**)

1.6.4.2 Chiral Enolates

In this section are discussed aldol reactions of achiral aldehydes with chiral enolates. In previous sections, many such examples have already been given for enolates derived from rigid cyclic ketones, lactones and lactams. The emphasis here is on reactions of the enolates of conformationally flexible, achiral ketones, esters and amides.

In one of the first such examples, the lithium enolate of (*S*)-3-methyl-2-pentanone was allowed to react with several aldehydes; in the case of propanal, the two products are formed in 15% diastereomeric excess, favoring (**179**; equation 115).[149] The di-*n*-butylboron enolate of this ketone has been studied and found to give (**179**) and (**180**) in a ratio of 63:37 in CH_2Cl_2 and 64:36 in pentane.[150]

In the interest of asymmetric synthesis, there has been a considerable effort to develop chiral ketones, esters and amides that will undergo aldol reactions with high diastereofacial preference. One such reagent is ketone (**181**), available in three steps from (*S*)-*t*-butylglycine.[151] [For a discussion of the use of the racemic version of ketone (**181**) for aldol reactions, see ref. 57d, pp. 181–184.] Aldol reactions of several different enolates of (**181**) have been studied with benzaldehyde (Scheme 11; Table 20).[150c,d] The



(**179**) (**180**)

(**181**) (**182**) (**183**)

(**184**) (**185**)

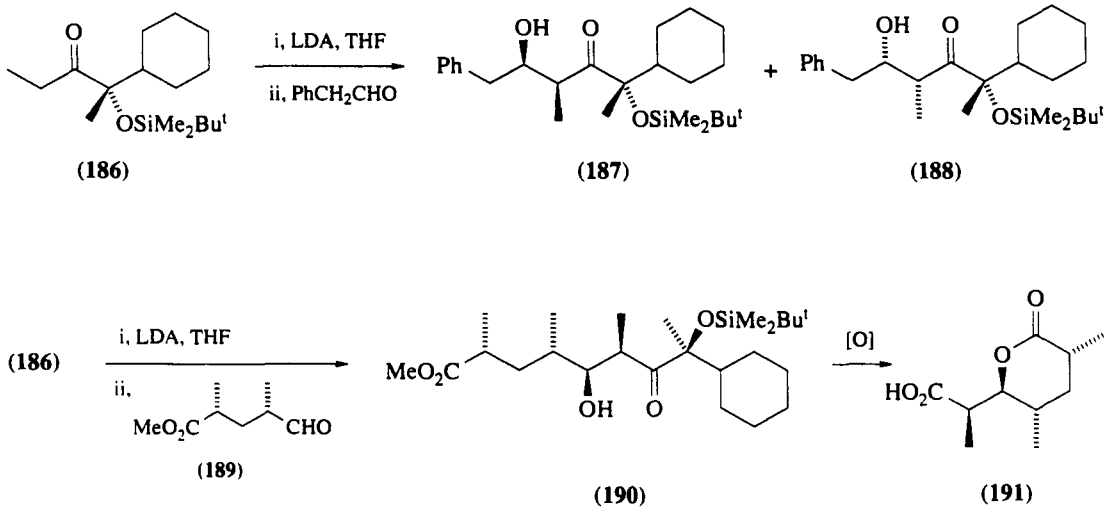
Scheme 11

Table 20 Aldol Stereochemistry (Scheme 11)

Entry	*Enolization Conditions*	*Enolate (Z):(E)*	*R*	*(182)*	*(183)*	*(184)*	*(185)*	*Yield (%)*
1	LDA, THF, -78 °C	>98:2	Ph	>95	<5	0	0	80
2	LDA, THF, -78 °C	>98:2	Pr^i	>95	<5	0	0	70
3	Bu_2BOTf, R_3N, CH_2Cl_2	>98:2	Ph	<5	>95	0	0	85
4	Bu_2BOTf, R_3N, CH_2Cl_2	>98:2	Pr^i	<5	>95	0	0	70
5	Pr^i_2NMgBr, THF, -78 °C	<4:96	Ph	0	0	95	5	80
6	Pr^i_2NMgBr, THF, -78 °C	<4:96	Pr	0	0	95	5	75
7	i, Pr^i_2NMgBr, THF, -78 °C, ii, $(Pr^iO)_3TiCl$, sonicate	<4:96	Ph	0	0	20	80	80
8	i, Pr^i_2NMgBr, THF, -78 °C, ii, $(Pr^iO)_3TiCl$, sonicate	<4:96	Ph	0	0	<5	>95	80

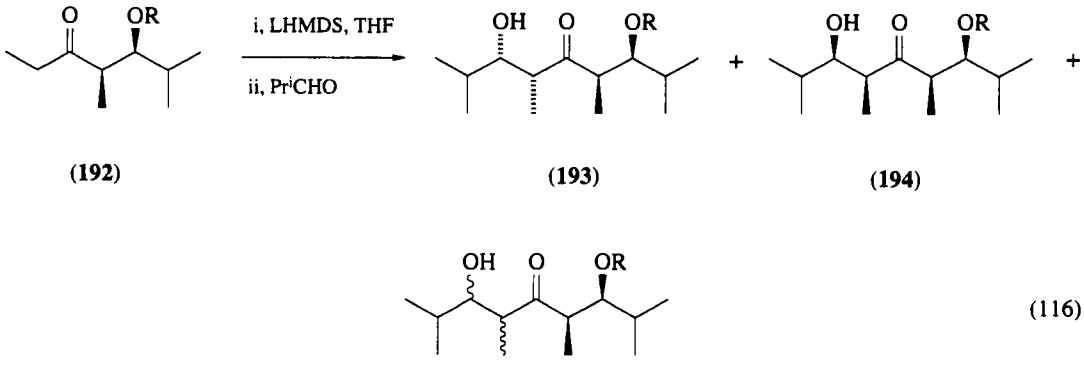
lithium and di-*n*-butylboron enolates both have the (*Z*)-configuration. However, they have opposite diastereofacial preferences because lithium can be coordinated by three oxygens in the aldol transition state, whereas boron cannot. Deprotonation of (**181**) with bromomagnesium diisopropylamide gives the (*E*)-enolate, which has the same diastereofacial preference as the lithium enolate. Finally, treatment of the (*E*)-bromomagnesium enolate with tris(isopropoxy)titanium chloride[152] affords the (*E*)-titanium enolate, which reacts with the same diastereofacial preference as does the (*Z*)-boron enolate, leading predominantly to isomer (**185**). Thus, by appropriate choice of reaction conditions, all four stereoisomeric aldols can be obtained from the same chiral reactant.

A related reagent (**186**) is prepared in three steps from (*S*)-atrolactic acid.[153] The lithium enolate of (**186**) reacts with phenylacetaldehyde to give two aldols in a ratio of 94:6 (Scheme 12). [The full relative stereochemistry of aldols (**187**) and (**188**) was not rigorously determined, but may be deduced from the stereochemistry of (**190**). It is surprising that the lithium enolate of (**186**) has a diastereofacial preference that is *opposite* that of the related ketone (**181**).] Compound (**186**) has been used in a synthesis of the Prelog–Djerassi lactonic acid (**191**), as shown in Scheme 12. Reagents related to (**181**) and (**186**) have been used as their boron enolates for other synthetic purposes (see Chapter 1.7, this volume).



Scheme 12

The diastereofacial preferences of keto ethers (**192**) are summarized in equation (116) and Table 21. The (*Z*)-lithium enolate of (**192**), prepared by reaction of the keto ether with lithium hexamethyldisilazane, reacts with isobutyraldehyde to give *syn* aldols (**193**) and (**194**), along with small amounts of an *anti* aldol of undefined stereochemistry (**195**).[154] The results of this investigation demonstrate that the facial preference of a chiral β-hydroxy ketone can be affected to some extent by the hydroxy-protecting group.

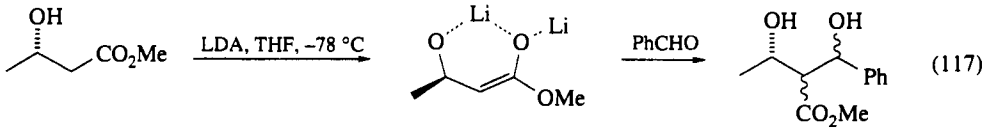


(192) (193) (194) (195) (unknown *anti*) (116)

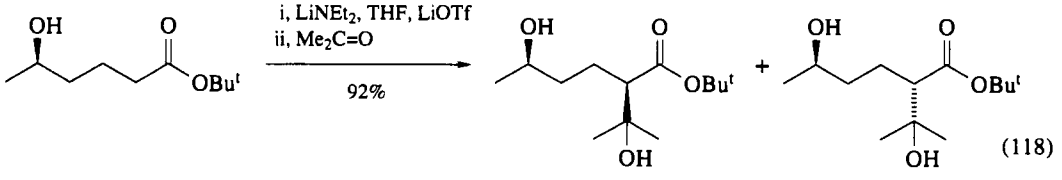
Table 21 Aldol Stereochemistry (equation 116)

Entry	*R*	*(193)*	*(194)*	*(195)*	*Yield (%)*
1	H	26	54	20	75
2	$PhCH_2$	52	48	0	79
3	$MeOCH_2CH_2OCH_2$	56	40	4	73
4	$PhCH_2OCH_2$	63	31	6	81
5	Bu^tMe_2Si	76	17	7	85
6	Me_3Si	78	13	9	66
7	Et_3Si	78	12	10	74

Although alkylation of β-hydroxy ester dianions occurs with high diastereofacial selectivity, the aldol reaction of the dianion obtained from methyl 3-hydroxybutanoate with benzaldehyde gives all four diastereomeric aldols in a ratio of 43:34:14:9 (equation 117).[155] On the other hand, dianions of δ-hydroxy esters show rather good diastereofacial preferences under the proper conditions. Deprotonation of *t*-butyl-5-hydroxyhexanoate with lithium diethylamide in the presence of lithium triflate gives an enolate that reacts with benzaldehyde to give aldols (**196**) and (**197**) in a ratio of 91:9 (equation 118).[156] Use of the *t*-butyldimethylsilyl ether instead of the alcohol resulted in no facial preference.



(117)

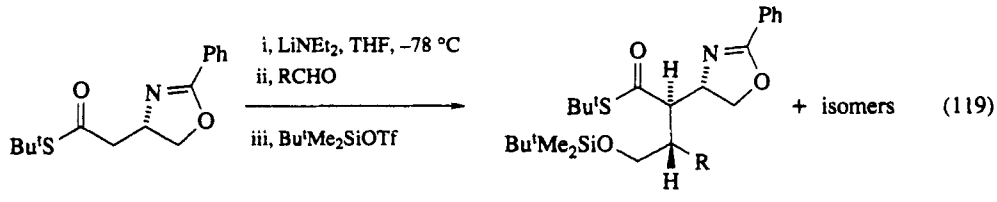


(118)

(196) (197)

The chiral β-amino thiol ester (**198**) gives a lithium enolate that shows excellent diastereofacial preference in its reactions with α,β-unsaturated and aryl aldehydes (equation 119; Table 22).[154] The stereochemistry of the major isomer (**199**) is consistent with attack of the aldehyde on a relatively rigid enolate chelate.

In an early attempt to achieve useful levels of asymmetric induction in aldol reactions of chiral esters, Solladié and coworkers examined the reaction of menthyl acetate with several aryl ketones in the presence of bromomagnesium diethylamide (equation 120).[157] After hydrolytic removal of the chiral au-



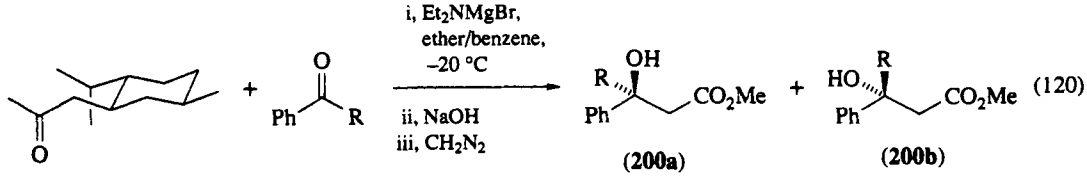
(198) (199)

Table 22 Aldol Stereochemistry (equation 119)

Entry	*RCHO*	*Yield (%)*	*(199):(isomers)*[a]
1	EtCHO	70	77:(18:5)
2	$Bu^tMe_2SiOCH_2CH_2CHO$	67	79:(21)
3	PhCHO	89	>50:(1)
4	$3,4,5\text{-}(MeO)_3C_6H_2CHO$	99	87:(13)
5	$4\text{-}NO_2C_6H_4CHO$	92	95:(3:1:1)
6	$CH_2{=}CHCHO$	95	>50:(1)
7	(*E*)-PhSCH=CHCHO	>40	84:(13:3)
8	(*E*)-$Me_3SiCH{=}CHCHO$	91	20:(1)

[a]Ratio of isomer (**199**) and other detectable isomers.

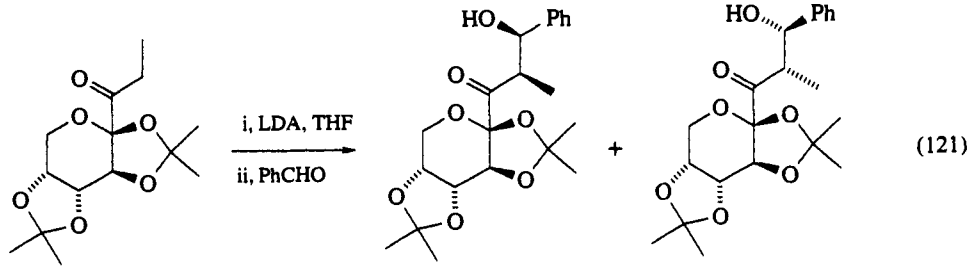
xiliary and methylation of the resulting β-hydroxy acid, the β-hydroxy esters are obtained in 48–58% enantiomeric excess, favoring enantiomer (**200a**).



R = Me, Et, Pr^i, Bu^t

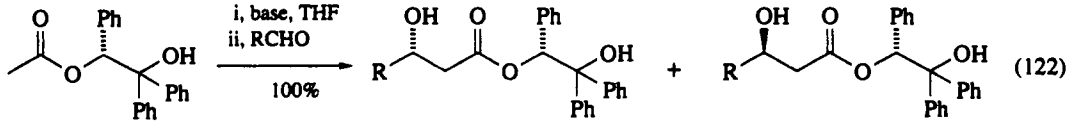
(200a) (200b)

A number of ethyl ketones and propionate esters derived from carbohydrates have been investigated in the aldol reaction.[158] None of the compounds studied give useful levels of stereoselection. The most selective compound from this study is ketone (**201**; equation 121); *syn* aldols (**202**) and (**203**) are produced in a ratio of 79:21.



(201) (202) (203)

Chiral acetate (**204**) shows excellent diastereofacial selectivity and has obvious utility as a reagent for asymmetric aldol reactions.[159] As shown in equation (122), reaction of (**204**) with benzaldehyde provides diastereomers (**205**) and (**206**). As shown in Table 23, entry 1, the diastereoselectivity is 83% if the lithium enolate is formed in the conventional manner and the aldol reaction is carried out in THF at −78 °C. A significant improvement is obtained by using the magnesium enolate (Table 23, entry 5), and diastereoselectivity of up to 98% is obtained by the use of very low reaction temperatures (Table 23, entries 10–13).



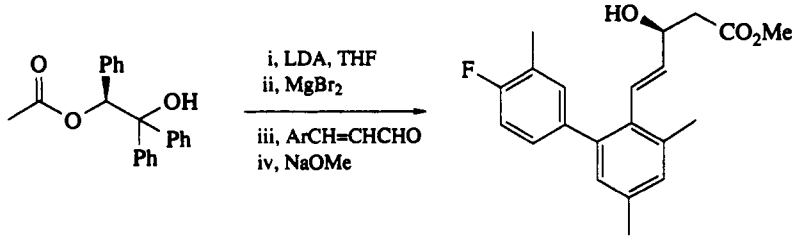
(122)

(204) (205) (206)

Table 23 Aldol Stereochemistry (equation 122)

Entry	*Temperature* (°C)	*Solvent*	*Base*	*Additive*	*(205):(206)*
1	−78	THF	LDA	None	83:17
2	−78	THF	Me_3SiCH_2K	None	59:41
3	0	THF	LDA	$ZnCl_2$	60:40
4	−78	THF	LDA	$(Pr^iO)_3TiCl$	85:15
5	−78	THF	LDA	$MgBr_2$	88:12
6	−78	DME	LDA	$MgBr_2$	84:16
7	−78	Ether	LDA	$MgBr_2$	59:41
8	−150	2-MeTHF	LDA	$MgBr_2$	55:45
9	−78	THF	Pr^i_2NMgBr	None	60:40
10	−135	THF/Me_2O	LDA	$MgCl_2$	94:6
11	−135	THF/Me_2O	LDA	$MgCl_2$	96:4
12	−130	THF/2-methylbutane	LDA	$MgBr_2$	97:3
13	−135	THF/Me_2O	LDA	MgI_2	98:2

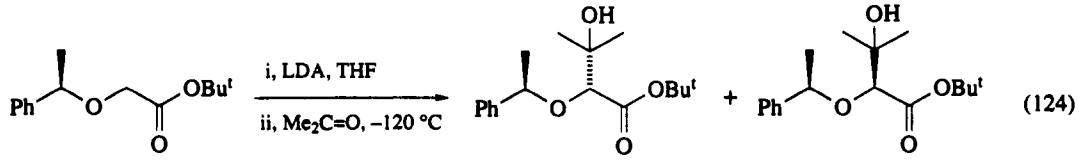
One of the virtues of the Braun reagent is that both enantiomers are available, since the chiral diol is made by reaction of phenylmagnesium bromide with (*R*)- or (*S*)-methylmandelate. An application of the (*S*)-enantiomer is shown in equation (123).[160] The initial aldol reaction was carried out with the magnesium enolate in THF at −78 °C to give the diastereomeric aldols in a ratio of 97:3. Transesterification with methanol gives β-hydroxy ester (**207**) in 94% enantiomeric excess.



(123)

(207)

Aldol reactions of the lithium enolates of chiral α-alkoxy esters have also been studied. Ester (**208**) reacts with acetone to give diastereomers (**209**) and (**210**) in a ratio of 85:15 in THF at −120 °C (equation 124); the ratio is only 64:36 in THF at −78 °C.[161] Even higher facial selectivity is obtained with the mesityl analog of (**208**); the lithium enolate of this ester reacts with acetone in THF at −120 °C to give the aldols corresponding to (**209**) and (**210**) in a ratio of 94:6. The Seebach and Pearson methods to accomplish this same goal have already been discussed (*vide supra*, Schemes 6 and 7).



(124)

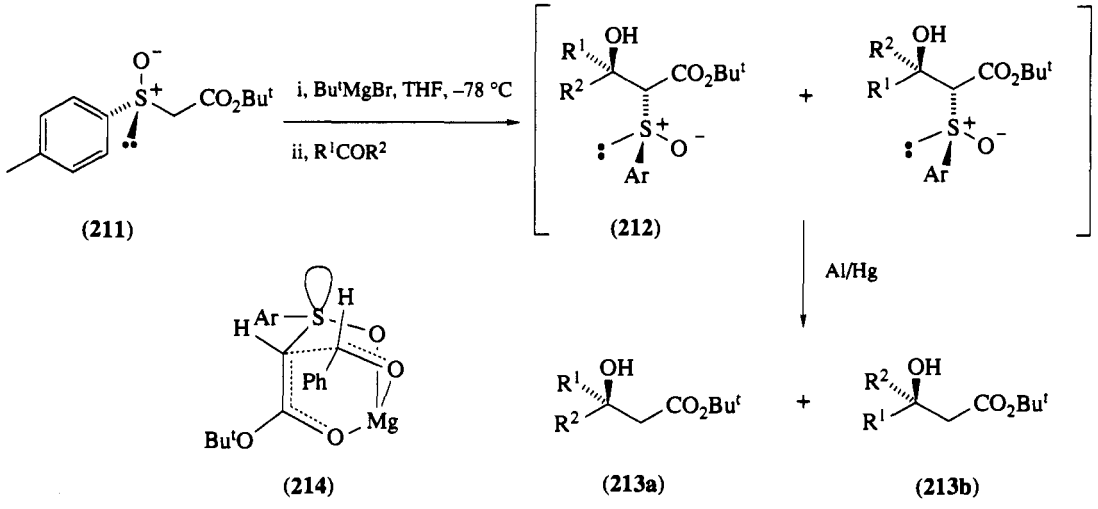
(208) (209) (210)

Solladié has introduced α-sulfinyl acetates as reagents for asymmetric aldol reactions.[162] Compound (**211**) is prepared in good optical purity from the menthyl ester of *p*-tolylsulfinic acid. The magnesium enolate of (**211**), prepared by reaction of the sulfinyl ester with *t*-butylmagnesium bromide, reacts with aldehydes and ketones to give diastereomeric mixtures of α-sulfinyl-β-hydroxy esters (Scheme 13). No

condensation results if *t*-butyllithium or sodium hydride is used as the base for formation of the enolate ion. Reductive removal of the chiral auxiliary provides the corresponding β-hydroxy esters (**213a**) and (**213b**): data are summarized in Table 24. The diastereofacial selectivity is excellent with aldehydes and with some ketones. The full stereochemistry of the intermediate α-sulfinyl-β-hydroxy ester was found to be as shown in (**212**) for the reaction with benzaldehyde. A transition state (**214**) in which the magnesium cation is chelated by three oxygens was invoked to explain the observed facial and simple stereoselectivity. Several applications of the Solladié reagent in synthesis have been reported.[163,164]

Attempts to extend this methodology to α-sulfinyl derivatives of other esters have been only moderately successful.[165] As shown in Scheme 14, ester (**215**) may be deprotonated by *t*-butylmagnesium bromide and added to aldehydes, although not to ketones. The intermediate β-hydroxy-α-sulfinyl esters, in each case a mixture of diastereomers, are reduced to obtain diastereomeric mixtures of β-hydroxy esters. The diastereomeric ratio of these materials does not reveal the degree of asymmetric induction in the original aldol reactions, because of the unknown stereochemistry of the desulfurization step. Aldols (**216**) were converted by a three-step process into secondary alcohols (**217**), which were found to have isomeric purities of 33.5% enantiomeric excess for R = Ph and 80% enantiomeric excess for R = *n*-heptyl.

The Solladié method has been extended to *N,N*-dimethylacetamide derivatives with good success (equation 125; Table 25).[166,167] The lithium enolate of (**218**) gives low overall stereoselectivity (Table



(**211**) (**212**) (**214**) (**213a**) (**213b**)

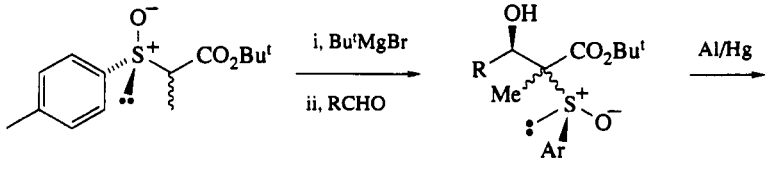
Scheme 13

Table 24 Aldol Stereochemistry (Scheme 13)

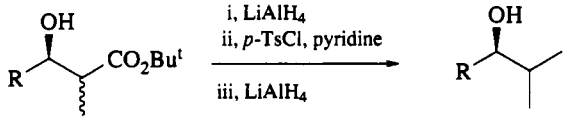
Entry	R^1	R^2	*Yield (%)*	*(213a):(213b)*
1	Ph	H	85	95:5
2	Ph	Me	75	84:16
3	Ph	CF_3	75	64:40
4	n-C_7H_{15}	H	80	93:7
5	$Pr^nCH{=}CH$	H	65	85:15
6	n-$C_{11}H_{23}$	H	74	90:10
7	n-C_8H_{17}	H	80	92:8
8	c-C_6H_{11}	Me	88	98:2
9	CO_2Et	Me	80	54:46
10	$CH(OMe)_2$	Me	80	55:45
11	$CH_2CH(OMe)_2$	Me	57	54:46
12	CH_2CH_2OAc	Me	90	(70:30)
13	$CH_2CH_2CO_2Me$	Me	63	75:25
14	$CH_2CH_2CH_2CO_2Me$	H	76	80:20
15	CH_2NMe_2	Me	0	—
16	$PhC{\equiv}C$	H	75	>95:5
17	$Pr^nC{\equiv}C$	H	73	95:5
18	n-$C_6H_{13}C{\equiv}C$	H	53	95:5
19	$Bu^tC{\equiv}C$	H	64	92:8

25, entries 1–9). The stereoisomer ratios observed seem to be kinetic, rather than thermodynamic, since the same yield and enantiomeric excess are observed at reaction times of 3 or 60 min (Table 25, entries 3 and 4). Stereoselectivity decreases as the size of R^2 increases (entries 1, 2, 3 and 6). Addition of HMPA has a deleterious effect on stereoselectivity. The magnesium enolate shows excellent diastereoselectivity. Again, stereoselectivity diminishes as the size of R^2 increases (Table 25, entries 10, 11, 14 and 16) and HMPA has a detrimental effect (entry 18). The analogous thioamide was prepared and studied, but it appears to offer no advantage over the oxoamide.[168]

Schneider and Simon prepared the α-sulfinyl ketones (**220**) and studied their aldol reactions with several aldehydes (equation 126).[169] In seven cases examined, the chiral secondary alcohols (**221**) were obtained in reasonable overall yield (40–67%), but with only modest stereoselectivity (54–78% *ee*).



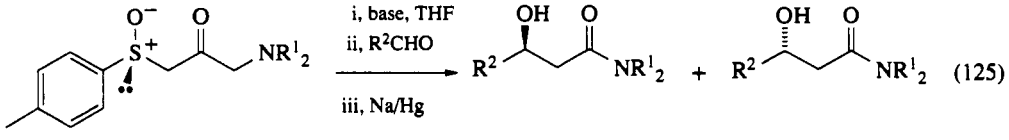
(**215**)



(**216**) (**217**)

R = Ph, n-C_7H_{15}

Scheme 14

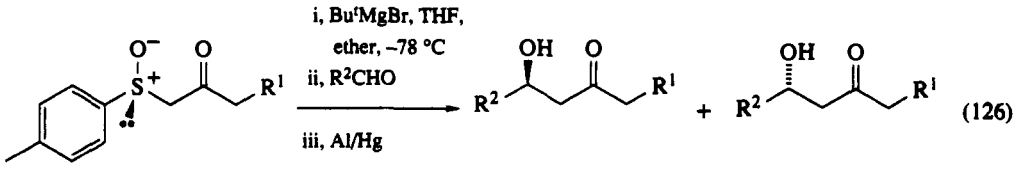


(**218**) (**219a**) (**219b**)

Table 25 Aldol Stereochemistry (equation 125)

Entry	R^1	*Base, mol equiv.*	*Reaction Time* (min)	R^2	*Yield* (%)	(*219a*):(*219b*)
1	Me	Bu^{n}Li, 1.1	3	Me	65	74:26
2	Me	Bu^{n}Li, 1.1	3	Bu^i	77	73:27
3	Me	Bu^{n}Li, 1.1	3	Pr^i	77	67:33
4	Me	Bu^{n}Li, 1.1	60	Pr^i	78	66:34
5	Me	Bu^{n}Li, 2.0	3	Pr^i	40	59:41
6	Me	Bu^{n}Li, 1.1	3	Bu^t	20	54:26
7	Me	Bu^{n}Li, 1.1	3	Pr^i	78	60:40[a]
8	Me	Bu^{n}Li, 0.55	60	Pr^i	74	64:36
9	Me	LDA, 1.1	60	Pr^i	70	67:33
10	Me	Bu^{t}MgBr, 0.55	60	Me	68	>99:1
11	Me	Bu^{t}MgBr, 0.55	60	Bu^i	71	99:1
12	Me	Bu^{t}MgBr, 1.1	3	Bu^i	73	95:5
13	Me	Bu^{t}MgBr, 0.55	3	Pr^i	62	93:7
14	Me	Bu^{t}MgBr, 0.55	60	Pr^i	66	98:2
15	Me	Bu^{t}MgBr, 1.1	3	Pr^i	63	85:15
16	Me	Bu^{t}MgBr, 0.55	60	Bu^t	56	95:5
17	Me	Bu^{t}MgBr, 0.1	60	Pr^i	31	64:40
18	Me	Bu^{t}MgBr, 0.55	60	Pr^i	31	76:24[a]

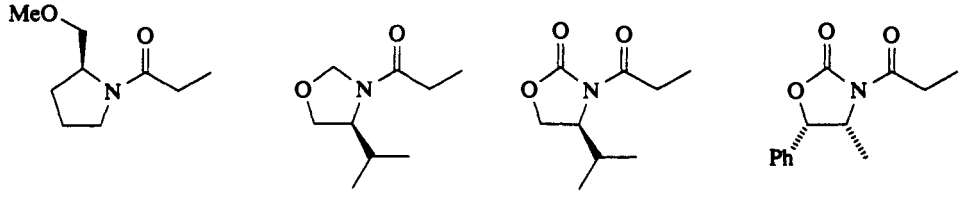
[a]In the presence of 3 mol equiv. of HMPA.



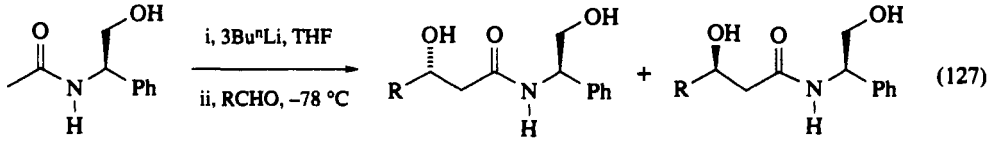
(126)

(220) (221a) (221b)

R^1 = H, Me; R^2 = Et, c-C_6H_{11}, Ph, $PhCH_2CH_2$



(222) (223) (224) (225)



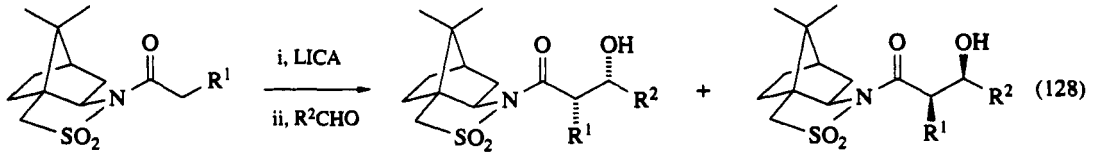
(127)

(226) (227) (228)

Table 26 Aldol Stereochemistry (equation 127)

Entry	*R*	*Yield* (%)	*(227):(228)*	*Yield* (%)[a]
1	Ph	96	80:20	43
2	Bu^t	98	85:15	35
3	Pr^i	82	77:23	24
4	Pr^n	93	78:22	25

[a]Yield of pure (227) after recrystallization.



(128)

(229) (230) (231)

Table 27 Aldol Stereochemistry (equation 128)

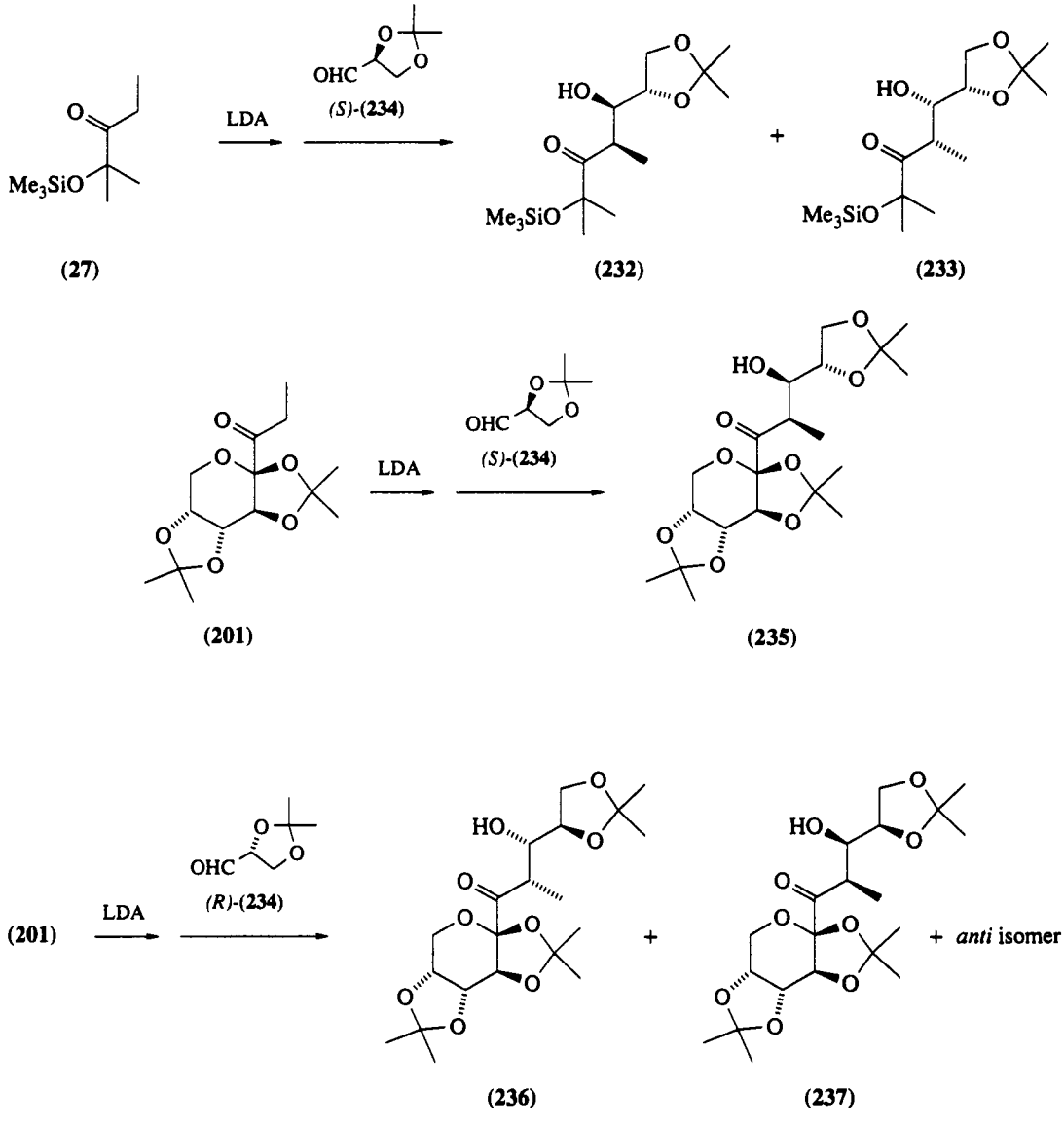
Entry	R^1	R^2	*(230):(231):other*	*Major product*[a] *Yield* (%)	*de* (%)
1	Me	Ph	8:85:(7)	72	>99
2	Me	Pr^i	6:86:(8)	70	>95
3	Et	Ph	9:88:(3)	51	>95
4	Me	Bu^t	7:88:(5)	51	>95

[a]Yield and purity of (231) after recrystallization or chromatography.

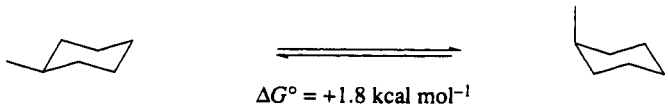
Chiral amides (**222**) and (**223**) and imides (**224**) and (**225**) have also been studied as reagents for asymmetric aldol reactions. These reagents show excellent diastereofacial preferences as their boron and zirconium enolates, but generally show poor selectivity as their lithium enolates. The reader is referred to other chapters in this volume for a discussion of these and related reagents.

The lithium enolate of amide (**226**) shows reasonable diastereofacial selectivity in its reactions with several aldehydes (equation 127; Table 26).[170] The hydroxymethyl group is important, as *N*-acetylphenethylamine has almost no diastereofacial preference.[171]

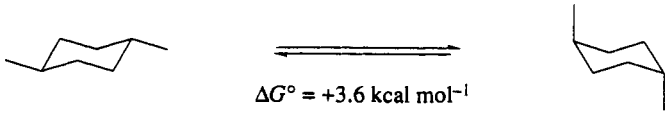
One of the more useful chiral auxiliaries that has been developed is illustrated in equation (128).[172] The lithium enolates of imides (**229**) react with aldehydes to give mainly the *syn* diastereomer (**230**), along with (**231**) and an *anti* isomer (Table 27). After purification, the major *syn* isomer is obtained in good yield and in good stereochemical purity. The results shown in Table 27 nicely complement the results obtained using the boron enolate. In this case, no *anti* products are observed and the (**231**):(**230**) ratio is >95:5 in all cases. Thus, acylsultam (**229**), like α-alkoxy ketone (**181**; Scheme 11), has opposite diastereofacial preference as its lithium and boron enolates.



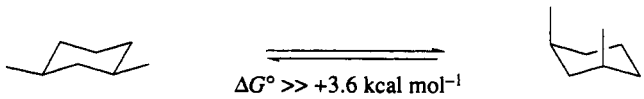
Scheme 15



$\Delta G° = +1.8$ kcal mol^{-1} (129)



$\Delta G° = +3.6$ kcal mol^{-1} (130)



$\Delta G° >> +3.6$ kcal mol^{-1} (131)

1.6.4.3 Double Diastereoselection

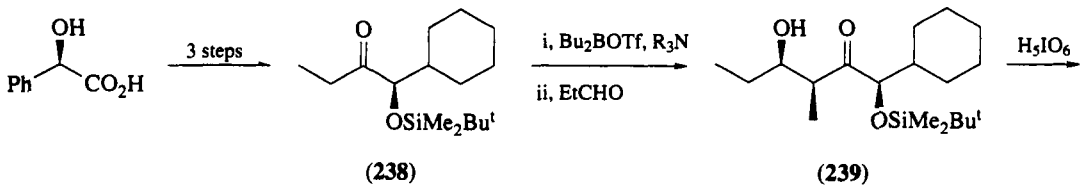
In this section is discussed the phenomenon of double diastereoselection (double asymmetric synthesis). If both partners in a reaction are chiral, each has its own intrinsic diastereofacial preference. New stereocenters that are created in such a process are, therefore, formed under the influence of both chiral reactants.[173–177] To a first approximation, one can think of the effects of the two stereodifferentiating reactants as being additive.[152,157,178] For example, as shown in equation (121) (*vide supra*), chiral ketone (**201**) reacts with benzaldehyde, a representative achiral aldehyde, to give aldols (**202**) and (**203**) in a ratio of 4:1. As shown in Scheme 15, chiral aldehyde (*S*)-(**234**) reacts with achiral ketone (**27**) to give aldols (**232**) and (**233**) in a ratio of 4.3:1. The two double stereodifferentiation experiments are also shown in Scheme 15. Reaction of ketone (**201**) with (*S*)-(**234**) gives a single aldol (**235**), whereas reaction of (**201**) with (*R*)-(**234**) gives *syn* aldols (**236**) and (**237**) and an *anti* aldol in a ratio of 5.5:2.5:1.[157] Similar experiments have been reported by several other workers.[152,169a,179] Double stereodifferentiation experiments such as those illustrated in Scheme 15 have been referred to as 'consonant' and 'dissonant' and as 'matched' and 'mismatched' pairs. If one of the reactants has an exceedingly high diastereofacial preference, it will totally dominate the situation and solely determine the stereochemistry at the new stereocenters.[180]

However, one should not always expect to see additivity in such double stereodifferentiation experiments, as is illustrated by the following logic.[181] For equation (129), $\Delta G° = +1.8$ kcal mol^{-1} (1 cal = 4.18 J); that is, an axial methyl group disfavors the conformation on the right by 1.8 kcal mol^{-1}. In equation (130), the effects of two axial methyl groups are additive, and $\Delta G° = 3.6$ kcal mol^{-1}. However, in equation (131), the effects of the two axial methyl groups are not additive, and $\Delta G° >> 3.6$ kcal mol^{-1}. Thus, we should expect that there will be cases in which the ideas of 'consonant' and 'dissonant' double stereodifferentiation will break down.[176,182]

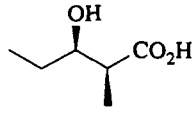
1.6.4.4 Chiral Auxiliaries

Some of the chiral reagents discussed in earlier sections have proven useful for preparation of enantiomerically pure aldols. From a practical viewpoint, the first level of asymmetric induction is that in which the chiral auxiliary is stoichiometrically consumed in the overall process. An example of this kind of 'first order' asymmetric induction is illustrated in equation (132).[183] Mandelic acid is converted by a three-step procedure into the enantiomerically homogeneous α-silyloxy ketone (**238**). The boron enolate of the latter substance shows excellent diastereofacial preference in reactions with aldehydes, giving aldol (**239**) in high purity (diastereoselectivity = 100:1). Desilylation of (**239**) and periodic acid cleavage of the resulting α,β-dihydroxy ketone provides the corresponding β-hydroxy acid (**240**) and cyclohexanecarbaldehyde. In this process, the chiral auxiliary is mandelic acid and at least 1 mol of this material is expended for each mole of hydroxy acid prepared. Other examples of this kind of 'immolative' process are the Solladié reagent (**211**) and the related amide (**218**) (*vide supra*).

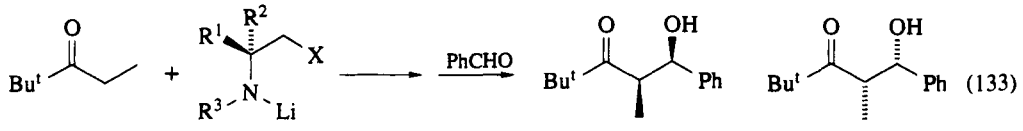
A more efficient process is one in which the chiral auxiliary, although still used stoichiometrically, can be recovered and reused. A notable example of a 'second order' chiral reagent is ester (**204**; equation 122). In this process, methyl mandelate is converted into chiral ester (**204**). After the aldol reaction, the product (**205**) is saponified and the chiral auxiliary may, in principle, be fully recovered and recycled. However, in practice, yields are never quantitative and the overall efficiency of auxiliary recovery is usually of the order of 50%.



(238) (239)



(240) (132)



(241) (242a) (242b) (133)

Table 28 Aldol Stereochemistry (equation 133)

Entry	*Ketone*	*Reagent ratios* (*241*)	*BunLi*	*Pri3NH*	*Temp.* (°C)	*Yield* (%)	(*242a*):(*242b*)
1	1.0	1.2	0.6		−10	89	49:51
2	1.0	1.2	1.2		−10	90	59:41
3	1.0	1.2	1.8		−10	52	79:21
4	1.0	1.2	2.2		−10	29	86:14
5	1.0	1.2	2.4	1.2	25	92	74:26
6	1.0	1.2	2.4	1.2	−10	93	84:16
7	1.0	1.2	2.4	1.2	−40	91	84:16
8	1.0	1.2	2.4	1.2	−70	88	67:33

The most efficient kind of asymmetric induction is one in which the chiral auxiliary is used catalytically. An outstanding example of such a process is the Monsanto procedure for enantioselective catalytic hydrogenation of dehydro amino acids.[184] So far, there has been no report of a highly efficient catalytic asymmetric aldol reaction of Group I or Group II enolates. There is one report of good asymmetric induction involving a noncovalently bound chiral auxiliary in an aldol reaction of a tin(II) enolate.[185] However, there is to date only one example of a truly *catalytic* asymmetric aldol addition reaction, the Ito–Hiyashi carbomethoxyisoxazoline synthesis, which proceeds through a gold(I) enolate.[186]

A number of chiral amines, diamines and amino ethers have been investigated, but only low degrees of asymmetric induction have been observed with lithium or magnesium enolates.[187,188] Recently, however, progress has been made.[189] The aldol reaction employed in this study was that between the lithium enolate of ethyl *t*-butyl ketone and benzaldehyde (equation 133); *syn* aldols (**242a**) and (**242b**) are produced in various ratios if the enolate is formed with a lithium amide derived from the chiral secondary amine (**241**). One of these amines (R^1 = Pr^i, R^2 = H, R^3 = Me and X = OMe) was utilized to optimize the reaction conditions; results are presented in Table 28. The data reveal a pronounced effect on stereoselectivity of the *amount of base*. Thus, when 1.2 equiv. of base are employed, the aldol yield is excellent, but the product is obtained in only 18% *ee* (Table 28, entry 2). If more base is used, enantioselectivity improves at the expense of yield (entries 3–4). These results suggest that the lithium amide derived from (**241**) is a more effective chiral auxiliary than the amine itself. In fact, if the reaction is carried out with excess *n*-butyllithium, along with a corresponding amount of the achiral diisopropylamine, the yield is excellent and the diastereomeric excess is a very respectable 68% (Table 28, entry 6). It is interesting to observe that the stereoselectivity diminishes, both at higher and lower temperatures (entries 5 and 8).

Table 29 Aldol Stereochemistry (equation 133)

Entry	R^1	R^2	R^3	*X*	*Yield (%)*	***(242a):(242b)***
1	Me	H	Pr^i	MeO	85	73:27
2	Pr^i	H	Me	MeO	77	53:47
3	Pr^i	H	Pr^i	MeO	93	84:16
4	Pr^i	H	Et_2CH	MeO	90	68:32
5	Pr^i	H	c-C_6H_{11}	MeO	89	79:21
6	Pr^i	H	Bu^tCH_2	MeO	93	56:44
7	H	Ph	Pr^i	H	80	17:83
8	H	Ph	Pr^i	MeO	92	16:84
9	H	Ph	Pr^i	Bu^tO	85	23:77
10	H	Ph	Pr^i	Me_2N	87	36:64
11	H	Ph	Pr^i	$(CH_2)_5N$	84	35:65
12	$PhCH_2$	H	Pr^i	MeO	80	72:28

Using the optimum conditions (Table 28, entry 6), a variety of chiral secondary amines have been investigated. The results are shown in Table 29. The most effective auxiliary for preparation of the enantiomeric aldol (**242b**) is the phenylglycine-derived amine (Table 29, entry 8).

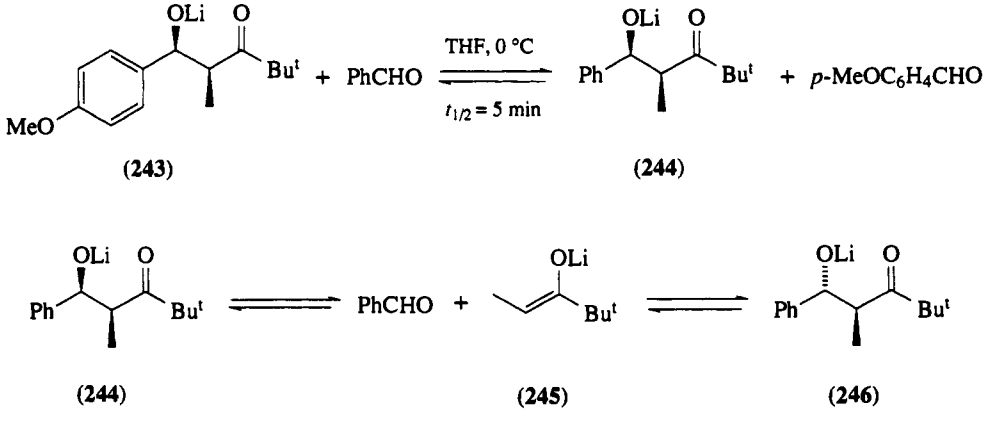
The foregoing results clearly constitute an encouraging lead, and represent the best that has yet been done with chiral auxiliaries for lithium enolate aldol reactions. Although the chiral auxiliary is not covalently attached to either reactant, it is still used stoichiometrically. Furthermore, the process has only been demonstrated with the aldol reaction in equation (133). It will be interesting to see if the efficacy of this method will extend to other enolates and aldehydes.

1.6.5 EQUILIBRATION; THERMODYNAMIC CONTROL

The bulk of this chapter has dealt with kinetically controlled aldol addition processes. However, one of the characteristics of aldol reactions involving Group I and Group II enolates is that they are frequently subject to ready reversibility (see Volume 2, Chapter 1.5). Under appropriate conditions, aldol reactions can be carried out under conditions of thermodynamic control. Furthermore, it is usually found that the stereoisomer ratio formed under equilibrating conditions is quite different from the kinetic isomer mixture.

In most cases, aldolate equilibration is to be avoided, since the result is usually to degrade the kinetically established stereoisomer ratio. A good example is seen in the reaction of the lithium enolate of cyclohexanone with benzaldehyde (Scheme 1, *vide supra*). If this reaction is carried out at –50 °C and worked up after 3 s, the diastereomer ratio is 82:18. If the reaction mixture is worked up after 5 min, however, the ratio is only 60:40.

In some cases, however, there is a significant bias in favor of the more stable aldolate. For example, the kinetic product mixture in the reaction of the bromomagnesium enolate of ethyl *t*-butyl ketone and

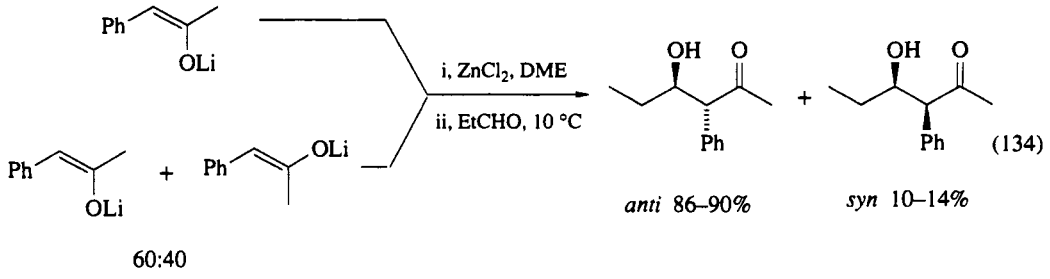


Scheme 16

benzaldehyde is *syn:anti* >95:5 (equation 21, *vide supra*).[34] However, under conditions of thermodynamic control the *anti:syn* ratio is >95:5.

Even when the retroaldol reaction is fairly facile, stereoisomer equilibration can be slow.[9c] This phenomenon is illustrated in Scheme 16. A solution of the lithium aldolate (**243**) and benzaldehyde equilibrates to (**244**) and *p*-anisaldehyde with a half-life of 15 min at 0 °C. However, the *syn* lithium aldolate (**244**) equilibrates with its *anti* diastereomer (**246**) with a half-life of approximately 8 h at room temperature. The reason for this apparent dichotomy is that enolate (**245**) is so stereoselective in its reactions with aldehydes. Since the kinetic *syn:anti* ratio is 98.7:1.3,[9c] the *syn* aldolate must dissociate approximately 75 times in order for one *syn* aldolate molecule to be converted into one *anti* aldolate molecule. Of course, for less stereoselective enolates, such as the cyclohexanone enolate referred to above, stereochemical isomerization will more nearly parallel the rate of actual aldol reversal.

The classic case of effective stereocontrol under equilibrating conditions is the House method, wherein the aldol reaction of the preformed lithium enolate is carried out in the presence of coordinating divalent metal ions, such as magnesium and zinc.[190] An example is seen in equation (134). The enolate of phenylacetone reacts with propionaldehyde to give 86–90% *anti* aldol, regardless of the original enolate geometry. Further discussion on zinc endates is found in Volume 2, Chapter 1.8.



(134)

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1.7
The Aldol Reaction: Group III Enolates

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1.7.1 INTRODUCTION

Over the past two decades the chemistry of boron-mediated aldol reactions has been the subject of intense studies and a wealth of information essential for mechanistic elucidation and synthetic applications is now available. Some general comments which highlight the differences between boron- and lithium-mediated aldol reactions are appropriate at the outset of this chapter. (i) The reacting boryl (boron) enolate species in solution appears to be homogeneous and uncomplicated in terms of aggregation, while the lithium counterparts exist in dimeric, tetrameric and hexameric forms. Characterization of the lithium species involved in product formation for some reaction systems is still required.[1] (ii) The B—O and B—C bonds are significantly shorter than the Li—O and Li—C bonds,[2] respectively, and the nucleophilicity of boryl enolates is generally less pronounced than that of the lithium enolates. These characteristics would predict a comparatively tight and organized transition state for the boron-mediated aldol reaction and, in fact, the stereochemical information embedded in the boryl enolates is 'faithfully' expressed in the aldol products on many occasions. These findings have provided incentive to explore the boron aldol methodology for the total synthesis of polyketide-type natural products such as macrolide and ionophore antibiotics. Many successful examples are recorded in the recent literature.

The only main Group III metal, other than boron, that has been utilized in the aldol reaction is aluminum, the enolates of which behave rather capriciously in terms of stereochemistry. The Al—C bond is relatively weak. However, aldol reactions with aluminum enolates derived from chiral acyl–iron complexes proceed with high asymmetric induction.

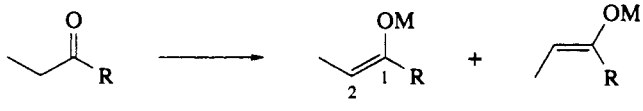
There are a number of excellent review articles on the subject of boron-mediated aldol reactions and related reactions.[2–7]

1.7.2 BORON-MEDIATED ALDOL REACTION

The chemistry of boron-mediated aldol reactions has developed in several stages. A variety of inorganic acids and bases, including boric acid and boron oxide, have long been known to catalyze aldol condensations of aldehydes and ketones.[8] An alkenyloxyborane was presumed to be involved as a reactive intermediate in the aldol reaction when boric acid was used as a catalyst.[9] In 1973 alkenyloxyboranes were recognized by Mukaiyama[10] as useful enolate reagents for the directed aldol reaction. Since then extensive studies have revealed that the (*E*)- or (*Z*)-stereochemistry of alkenyloxyboranes is directly reflected in the stereochemical outcome of the aldol reaction.[11] In the early 1980s, enantiomerically pure (homochiral) alkenyloxyboranes with significant facial selectivity were prepared for use in the aldol reaction. Thus boron-mediated aldol methodology has now become one of the most efficient methods for diastereoselective and enantioselective C—C bond formation.

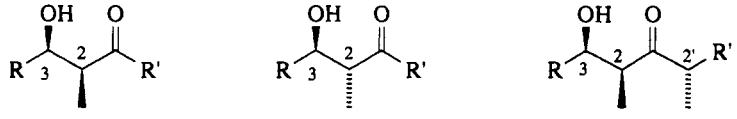
Alkenyloxyboranes formulated as $R^1R^2C{=}CR^3OBXY$ are perhaps more conventionally called boryl enolates and both terms are used in this article. Alkenyloxyboranes may be categorized as alkenyloxydialkylboranes, alkenyloxyalkylalkoxyboranes and alkenyloxydialkoxyboranes. To avoid confusion the terms 'borinyl', 'boronyl' and 'borate' are not used.[12] Although the majority of the stereoselective aldol reactions reported involve alkenyloxydialkylboranes, alkenyloxydialkoxyboranes have also been utilized. The stereochemical course of the latter aldol reaction has been evaluated both experimentally and computationally and is discussed separately in Section 1.7.2.4.

Before beginning the mechanistic discussion of aldol reactions involving boryl enolates, brief comments are in order on the stereochemical descriptors used below. The two possible stereoisomers derived by deprotonation of a carbonyl compound, *e.g.* (**1**) and (**2**) from (**3**) (Scheme 1), are designated *Z(O)* and *E(O)*,[13] instead of the usual (*Z*) and (*E*), so that enolates that have an identical stereochemical relationship between the C(2) and C(1)—OM substituents may be grouped together. According to this system, the OM substituent on C(1) always takes the higher priority regardless of the Cahn–Ingold–Prelog priority of the R group (consider the case when R = SiR'_3).



(**3**) (**1**) *Z(O)* (**2**) *E(O)*

Scheme 1



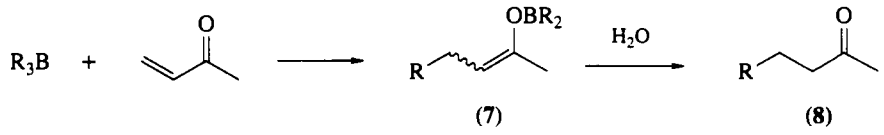
(**4**) 2,3-*syn* (**5**) 2,3-*anti* (**6**) 2,3-*syn*, 2,2'-*anti*, 2',3-*anti*

To describe the stereochemistry of the aldol products, the terms *syn* and *anti* are used to express the relative stereochemistry of the substituents attached to a main chain, whenever the chain is unambiguously identified and expressed in a zigzag fashion: *syn* describes two substituents on the same side of the plane defined by the chain (**4**), and *anti* is used when they are on opposite sides (**5**). The relative stereochemistry of distant stereogenic centers can also be described using this notation (**6**).

1.7.2.1 Preparation of Alkenyloxydialkylboranes

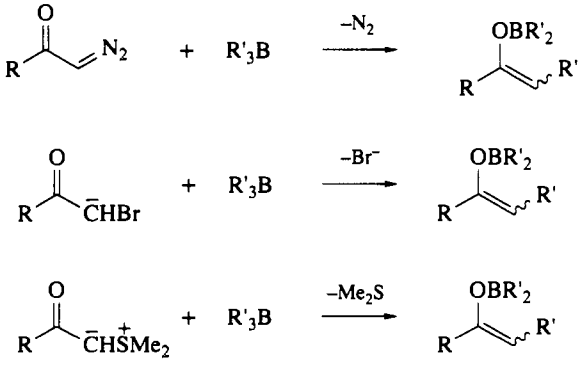
A variety of methods are now known for the preparation of alkenyloxydialkylboranes and are enumerated below more or less in chronological order. Stereochemical problems associated with dialkylboryl enolate formation and subsequent aldol reaction are discussed in the following two sections (1.7.2.2 and 1.7.2.3). It is interesting to note that most of the methods initially developed (before 1975) do not use direct enolization procedures.

The products (**8**) that result from the reaction of trialkylboranes with α,β-unsaturated carbonyl compounds followed by hydrolysis (Scheme 2),[14] provided the first strong evidence to permit assignment of the alkenyloxyborane structure to the precursors (**7**).

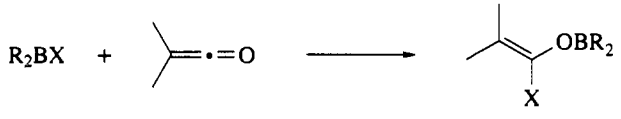


(**7**) (**8**)

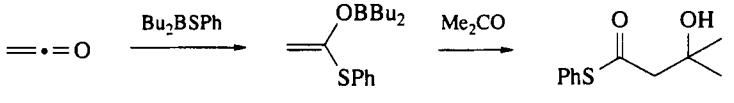
Scheme 2



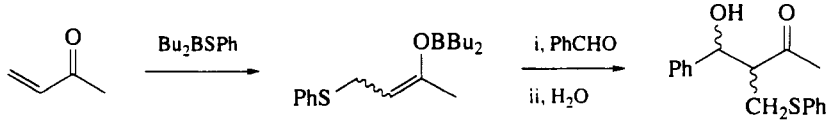
Scheme 3



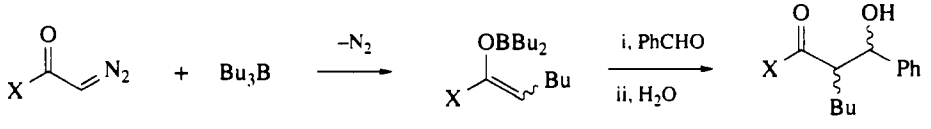
Scheme 4



(**9**)



3:1 diastereomeric mixture



X = Ph, OEt

X = Ph; 98% yield
X = OEt; 75% yield

Scheme 5

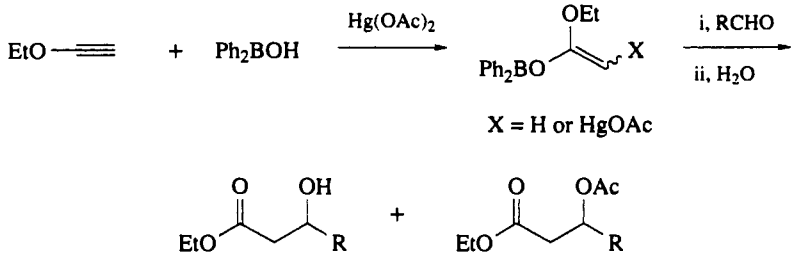
Reactions of α-diazocarbonyl compounds,[15] halogen-substituted enolates[14b,16] and sulfur ylides[17] with trialkylboranes were subsequently recorded and represent alternative methods of preparation (Scheme 3).

Addition of boron reagents (R_2BX; X = halogen, —SR′, *etc.*) across the C=O bond of ketenes also produces alkenyloxyboranes (Scheme 4).[18]

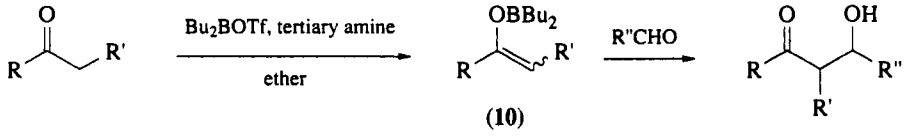
Mukaiyama *et al.* prepared boryl enolates from thiol esters in this way and unambiguously demonstrated that enolate (**9**) is capable of effecting directed aldol reactions.[10] Similarly, alkenyloxyboranes prepared in the two other ways mentioned above afford the expected aldol products, as shown in Scheme 5, confirming that alkenyloxyboranes are responsible for the directed aldol reactions.

A boryl enolate of an ester can be generated *in situ* by treatment of ethoxyacetylene with diphenylhydroxyborane in the presence of mercury(II) acetate, as shown in Scheme 6.[19]

Direct enolization of carbonyl compounds using dialkylboryl trifluoromethanesulfonate (dialkylboryl triflate; R_2BOTf) in the presence of a tertiary amine base is versatile and advantageous in many ways compared with the foregoing indirect methods (see Sections 1.7.2.3 and 1.7.2.4).[20] The resulting boryl enolates, *e.g.* (**10**), react cleanly with various aldehydes to provide high yields of crossed aldol products (Scheme 7).

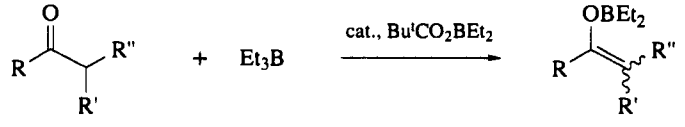


Scheme 6

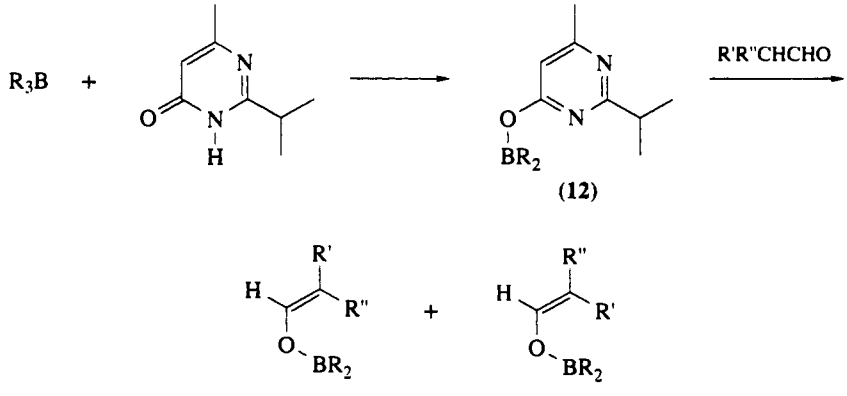


(10)

Scheme 7

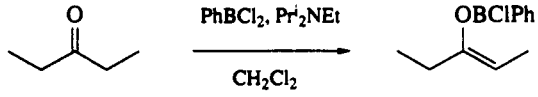


(11)

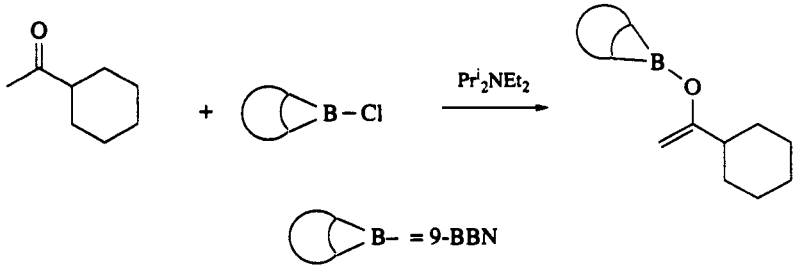


(12)

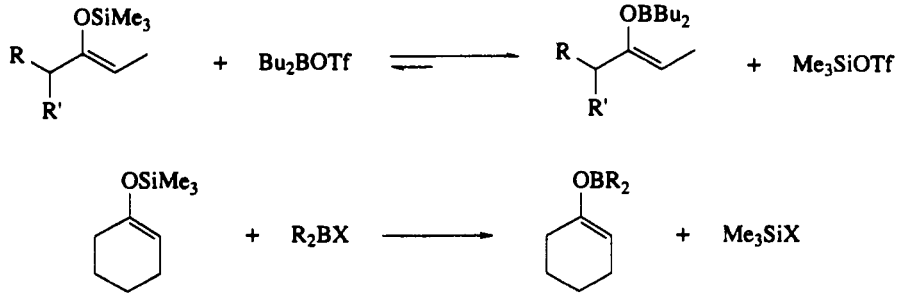
Scheme 8



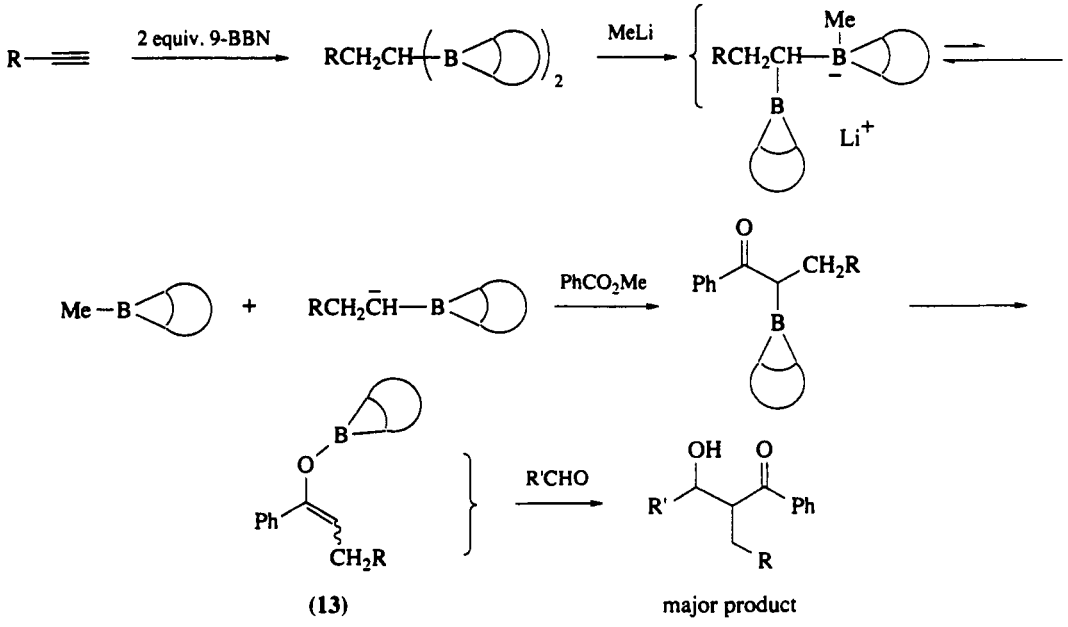
Scheme 9



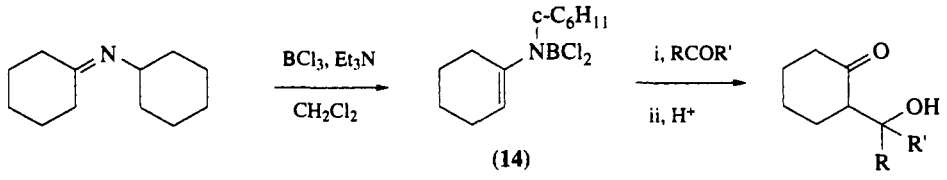
Scheme 10



Scheme 11



Scheme 12



Scheme 13

The reaction of triethylborane with a ketone in the presence of a catalytic amount of diethylboryl pivalate provides another direct route to the corresponding boryl enolate (**11**; Scheme 8).[11,21] This is probably the first time that the alkenyloxyborane was isolated and fully characterized.[21] Unfortunately this method requires rather vigorous reaction conditions and has not been used frequently. The stereochemistry of the resulting boryl enolates is probably controlled thermodynamically. 4-Dialkylboryloxy-2-isopropyl-6-methylpyrimidine (**12**) may be used specifically for the preparation of boryl enolates from aldehydes.[22]

Ethyl ketones have been enolized by Hamana *et al.* using dichlorophenylborane in the presence of a tertiary amine (Scheme 9).[23] Recently Chow and Seebach found that, under carefully controlled conditions, trichloroborane can also be used to prepare the corresponding alkenyloxydichloroboranes.[24]

Dialkylchloroboranes instead of dialkylboryl triflates can also be successfully utilized for the generation of alkenyloxyboranes, as exemplified in Scheme 10.[25] Dialkylchloroboranes are more easily manipulated than the corresponding triflates, offering an advantage as reagents for enolization. However, enolization using a dialkylchloroborane proceeds more slowly, resulting in self-condensation of certain unhindered methyl ketones (up to 30%).[26]

An exchange reaction of trimethylsilyl enolates with dialkylboryl triflates will provide the corresponding boron enolates (Scheme 11) after removal of trimethylsilyl triflate.[27]

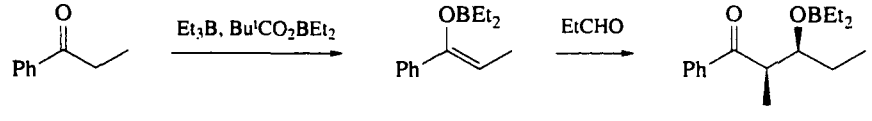
C(1)-Phenyl-substituted alkenyloxyboranes (**13**) may be prepared by the acylation of boron-stabilized carbanions with methyl benzoate (Scheme 12).[28]

Alkenylaminoboranes (**14**), though not in the category of alkenyloxyboranes, also undergo aldol reactions with carbonyl compounds (Scheme 13). Pure alkenylaminoboranes can be isolated from the reaction of a ketimine, boron trichloride and triethylamine in dichloromethane.[29]

1.7.2.2 Diastereoselective Aldol Reactions (2,3-Stereochemistry)

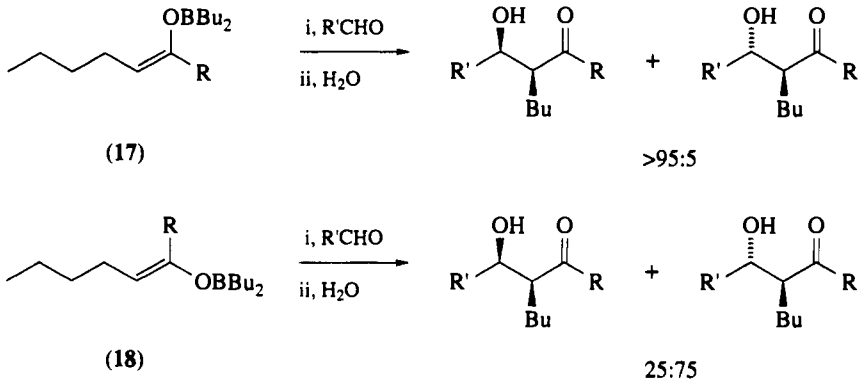
In 1975 Fenzl and Köster made some important observations which eventually led to the development of highly diastereoselective aldol reactions using alkenyloxyboranes.[11] The *Z*(*O*) and *E*(*O*) ratios of alkenyloxyboranes prepared from various ketones according to Scheme 8 in Section 1.7.2.1 apparently correspond to the diastereoselectivities of subsequent aldol reactions with aldehydes (Scheme 14).[11] Thus, the pure *Z*(*O*)-enolate (**15**) derived from propiophenone provides exclusively the *syn* aldol product (**16**) upon treatment with propanal. Although the enolates of only a few ketones were examined, the results strongly suggested a direct stereochemical correlation between alkenyloxyborane configuration and aldol product stereochemistry. Compound (**16**) and all other aldol products shown in this section are racemic.

A study on stereodefined boryl enolates that employed both pure (*Z*)- and (*E*)-dialkylboryl enolates has been carried out by Masamune *et al.*[30] Hooz' reaction involving α-diazocarbonyl compounds (Scheme 3) and a trialkylborane provides exclusively *E*(*O*)-alkenyloxyboranes, which can be isomerized cleanly to the corresponding *Z*(*O*)-isomers.[30] The *Z*(*O*)-dibutylboryl enolates (**17**) react with various aldehydes exhibiting uniformly high *syn* selectivities (*syn*:*anti* > 95:5), while the corresponding *E*(*O*)-isomers (**18**) are converted into the *anti* aldol products with somewhat lower selectivities (Scheme 15).



(**15**) 100% *Z*(*O*) (**16**)

Scheme 14



Scheme 15

Diastereoselective addition of a propionate unit to an achiral aldehyde is an important process in organic synthesis (see Section 1.7.2.3 for the reaction with chiral aldehydes). This process can be achieved with full control by the judicious choice of a thiol ester and a dialkylboryl triflate.[18b,20d] As shown in Scheme 16, the *E*(*O*)-enolate (**19**) generated from *S*-*t*-butyl propanethioate, dicyclopentylboryl triflate and diisopropylethylamine furnishes, upon reaction with an aldehyde, the *anti* aldol product (**20**). The *syn* product (**21**) is obtained from the *Z*(*O*)-enolate (**22**) derived from the reaction of *S*-phenyl propanethioate with 9-borabicyclo[3.3.1]non-9-yl triflate (9-BBNOTf).

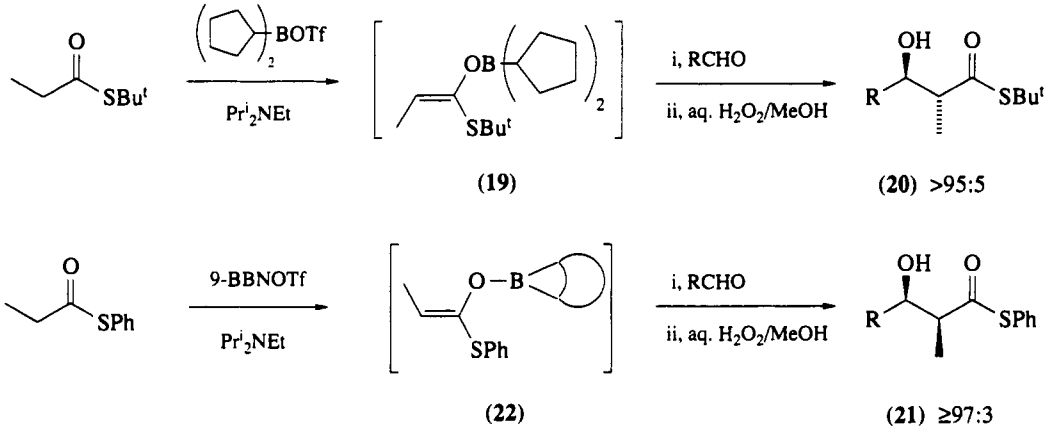
Van Horn and Masamune have shown that it is possible to prepare either boryl enolate stereoisomer from the same ketone by changing the steric demand of the dialkylboryl triflate (Scheme 17).[20e]

Evans *et al.* also carried out independent studies on the stereochemical course of these aldol reactions and demonstrated that dialkylboryl enolates were kinetically stable even at elevated temperatures.[20f,31] The results obtained from the Evans group also established that exceptionally high levels of aldol diastereoselection are governed by the stereochemistry of the dialkylboryl enolates (Table 1).

It has been shown by Evans *et al.* that the aldol reaction of diboryl enediolates (**23**), with one exception, exhibit varying degrees of *anti* stereoselection[31,32] (Scheme 18). This implies that (**23**) reacts more effectively as an *E*(*O*)-boryl enolate than as a *Z*(*O*)-enolate.[33]

When dichlorophenylborane in the presence of diisopropylethylamine is used to enolize ethyl ketones (see Scheme 9), excellent *syn* diastereoselectivity (>94:6) is observed (Scheme 19).[23] Similar *syn* selectivity ranging from 90 to 99% depending on the aldehyde employed is recorded by Chow and Seebach[24] when trichloroborane is used.

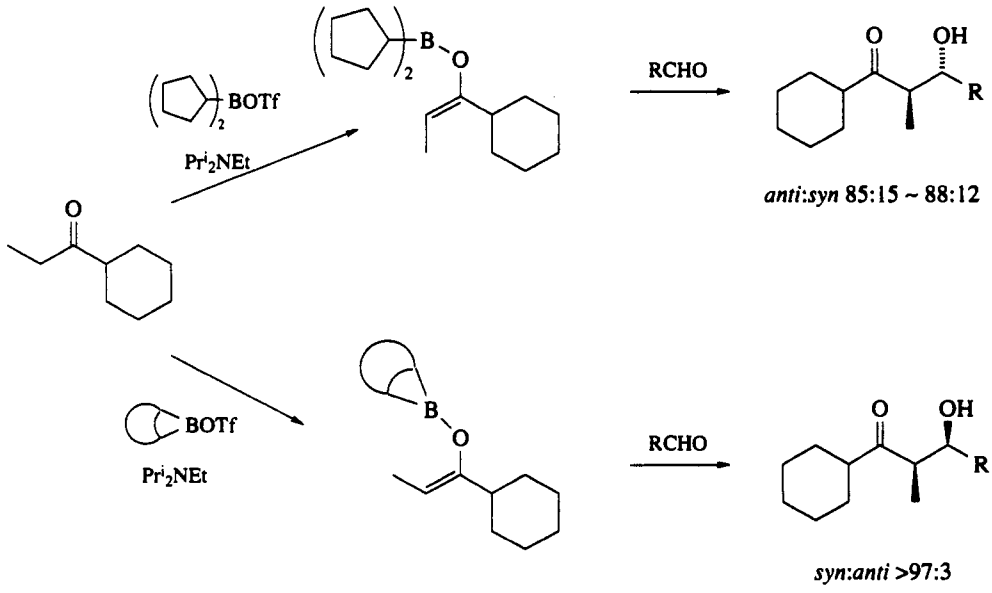
A metal exchange reaction between an alkenyloxysilane (silyl enolate) and a dialkylboryl triflate has already been described (Scheme 11).[27] When a mixture of a silyl enolate and dibutylboryl triflate is allowed to react with an aldehyde, aldol product diastereoselectivity is negligible, presumably because trimethylsilyl triflate promotes an aldol reaction of the silyl enolate. When trimethylsilyl triflate is com-



Scheme 16

pletely removed from the reaction mixture, the aldol reaction proceeds with high stereoselectivity to provide a 95:5 ratio of *syn:anti* aldol products from a 96:4 ratio of *Z(O)*-/*E(O)*-silyl enolates (Scheme 20).

Systematic studies by Evans *et al.*[31] and Masamune and coworkers,[18b,20d,20e,34] including experimental results discussed above, reveal several factors affecting the kinetic enolization involving boron reagents. At low temperature (–78 to 0°C) enolization is thought to be completely kinetically controlled. The struc-

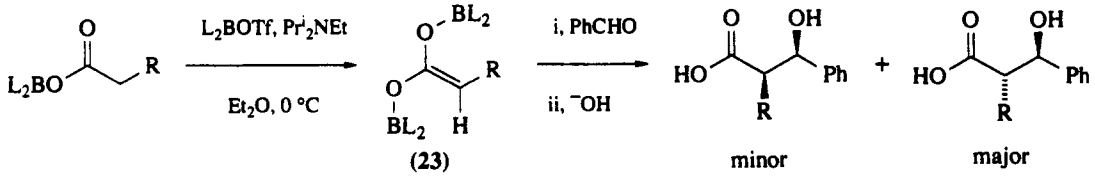


Scheme 17

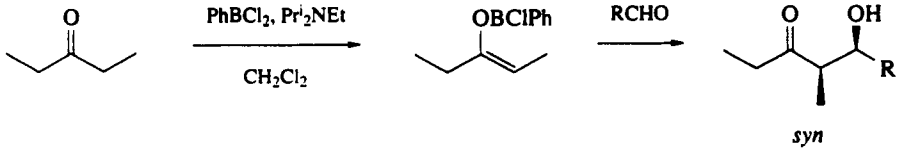
Table 1[20f,31] Kinetic Boron-mediated Aldol Reactions of Various Ketones with Representative Aldehydes[a]

Entry	*Carbonyl compound*	*Aldehyde*	*L in L_2BOTf*	*Z(O):E(O) ratio*	*Syn:anti ratio of aldol products*
1	EtCOEt	PhCHO	Bu^n	>97:3	>97:3
2	EtCOEt	Pr^{i}CHO	Bu^n	>97:3	>97:3
3	Pr^{i}COEt	PhCHO	Bu^n	45:55	44:56
4	Pr^{i}COEt	PhCHO	c-C_5H_9	19:81	18:82
5	EtC(O)SBu^t	Pr^{n}CHO	Bu^n	≤5:95	10:90
6	EtC(O)SBu^t	Pr^{i}CHO	Bu^n	≤5:95	9:91

[a]Enolization was carried out at –78 °C (entries 1–3) or at 0 °C (entries 4–6). In all cases Pr$^i_2$NEt was used as the base.



Scheme 18

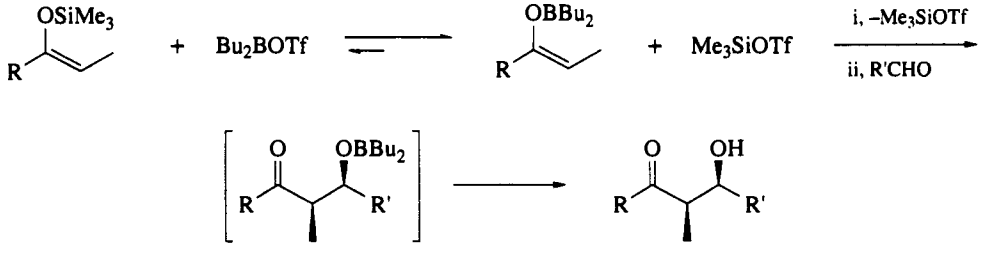


Scheme 19

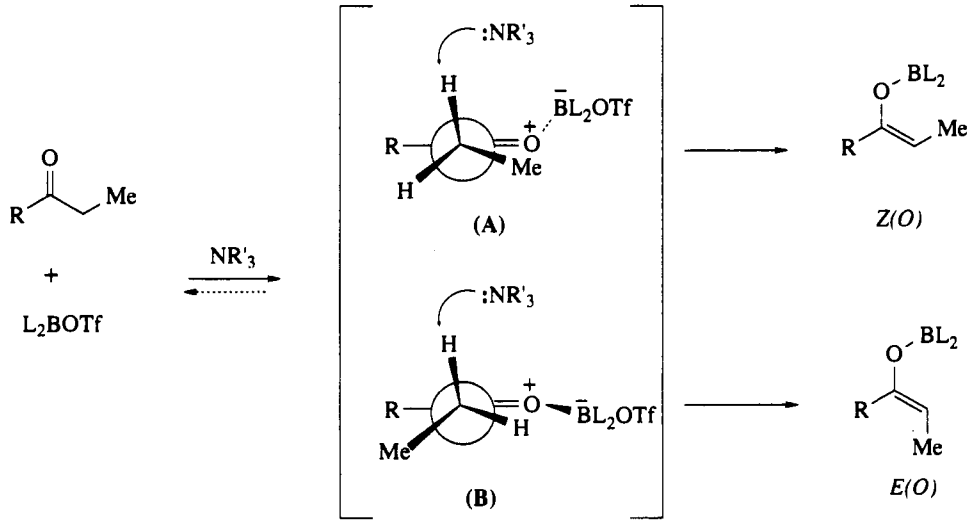
tural features of the carbonyl compound, tertiary amine and boryl triflate, individually contribute to the observed enolate stereoselection. Recently both experimental and computational studies by Reetz *et al.*[35] have shown that BF_3 forms an adduct with benzaldehyde such that the Lewis acid is placed *anti* to the phenyl ring. Thus, all four atoms of the C—C=O—B complex lie in a common plane. This Lewis acid complexation of the carbonyl group may be extrapolated into the discussion of the kinetic enolization, which utilizes a strongly Lewis acidic boron reagent. The discussion can be summarized as follows (Scheme 21): (i) *Z(O)*- and *E(O)*-enolates are derived from the deprotonation of two complexes (**A**) and (**B**), respectively. (ii) With all other factors equal, kinetic stereoselection is maximized with increased steric hindrance of the amine base.[20e,31,34] (iii) Several factors are involved in the kinetic enolization of a carbonyl compound using a boryl triflate. With a given base, when the steric interaction between R and the boron ligands is relatively small (see **22** in Scheme 16), complex (**A**) is preferred, leading to the formation of the *Z(O)*-enolate. However, if the steric interaction between R and the boron moiety becomes severe (see **19** in Scheme 16 and **91** in Section 1.7.2.3.1 iii), *E(O)*-enolate formation prevails through complex (**B**). If the interaction between R and Me becomes unendurably large with an extremely bulky R group (see **29** in Scheme 23 and **37** in Scheme 25), the boron reagent can only be complexed *syn* to R (complex **A**), resulting in the formation of the *Z(O)*-enolate. When both interactions between R and Me and R and the boron ligands are large, the enolate formation becomes sluggish (see Table 2).

An improvement in aldol diastereoselection for a given boron ligand is obtained when less polar solvents are employed, presumably due to 'transition state compression' in nonpolar solvents. This solvent effect is also significant in enolate chirality transfer in asymmetric aldol reactions.

Selective formation of either *Z(O)*- or *E(O)*-enolates from ethyl ketones has been accomplished by Brown *et al.*[82] by employing dialkylchloroborane as well as dialkylboryl triflate. The results of enolization with propiophenone and diethyl ketone are summarized in Table 1a. It is of note that *anti* aldol pro-



Scheme 20



Scheme 21

Table 1a Enolization of Propiophenone and Diethyl Ketone in the Presence of R_2BX and Amines at 0 °C

Reagent R_2BX	*Amine R_3N*	*Syn/anti ratio*	
		Propiophenone	*Diethyl ketone*
B-Cl-9-BBN	Et_3N	60:40	>99:1
	Pr^i_2EtN	95:5	>99:1
B-OTf-9-BBN	Et_3N	93:7	>99:1
	Pr^i_2EtN	95:5	>99:1
c-Hex_2BCl	Et_3N	5:95	21:79
	Pr^i_2EtN	51:49[a]	72:28
c-Hex_2BOTf	Et_3N	67:33[a]	80:20
	Pr^i_2EtN	98:2	93:7

[a]Ratios of enolates determined by ^1H NMR analysis.

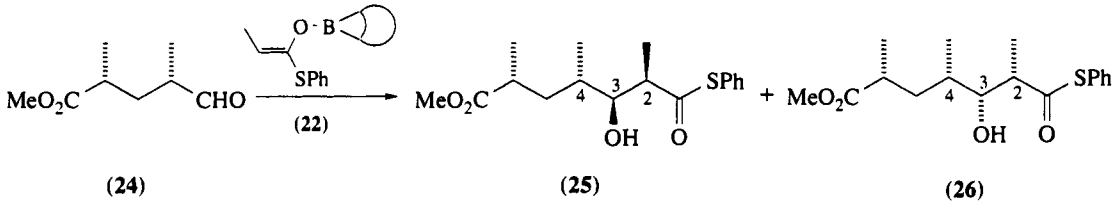
ducts of high diastereomeric purity (79–99%) can be obtained by the use of a combination of dicyclohexylchloroborane and triethylamine.

1.7.2.3 Aldol Reactions Using Enantiomerically Homogeneous Alkenyloxydialkylboranes (3,4-Stereochemistry)

The reaction of a chiral aldehyde with an achiral enolate leads to the formation of two diastereomeric isomers in a proportion which largely reflects the facial selectivity inherent to the aldehyde. This proportion is often referred to as the Cram/anti-Cram ratio. The ratio is normally small for acyclic chiral aldehydes (ranging 1:1 ~ 1:5) and is often unpredictable, as exemplified below for the aldol reaction involving an achiral boron enolate (**22**) and the chiral aldehyde (**24**; Scheme 22).[3a,5b]

The observed 2,3-*syn* stereoselectivity of the products (**25**) and (**26**) reflects the *Z*(*O*)-configuration of the enolate (**22**), and the predominant product (**25**) is the anti-Cram product, indicated by the *anti* orientation of the C-3 and C-4 substituents. The control of the 3,4-stereoselectivity of the aldol reaction is a problem more generally associated with the apparent facial selectivity of a substrate in any reaction and has been a major challenge in organic synthesis of acyclic systems. As a solution to this problem a new strategy emerged based on the rule of double asymmetric synthesis.[5b] In the reaction of an enantiomerically pure aldehyde with an enantiomerically pure reagent, the use of an (*S*)- or (*R*)-reagent with a *large* facial selectivity either enhances the apparent facial selectivity of the substrate when the facial selectivities of both reactants are acting in concert (matched pair reaction), or overrides it when they are counteracting each other (mismatched pair reaction). In this way the stereochemical course of the reaction is controlled by the reagent. This reagent-controlled organic synthesis requires the design and preparation of reagents with exceedingly high enantioselectivities (>50:1), a term normally defined as the ratio of two enantiomers that result from the reaction of an achiral substrate with a chiral reagent (after removal of the chiral auxiliary group from the products), and a term synonymous with diastereofacial stereoselectivity (*DS*)[5b] of a chiral reactant. Such reagents (and catalysts) are now available for many organic reactions including boron-mediated aldol reactions.

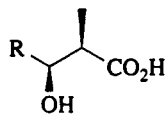
Over the past decade the enantio- and diastereo-selective aldol methodology has been developed mainly with the purpose of synthesizing polyketide-type natural products such as macrolides and ionophore antibiotics. These natural products have the basic structural units that result from propionate and acetate addition: α-methyl-β-hydroxycarbonyl (**27a–d**) and β-hydroxycarbonyl (**28a** and **28b**). Discussions on the construction of these units will be followed by comments on the stereoselective assembly



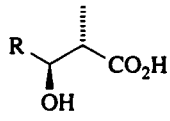
(**24**) (**25**) (**26**)

(**25**):(**26**) = 3:2

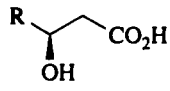
Scheme 22



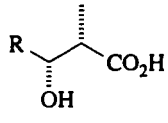
(27a)



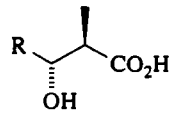
(27c)



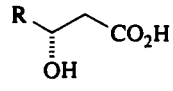
(28a)



(27b)



(27d)



(28b)

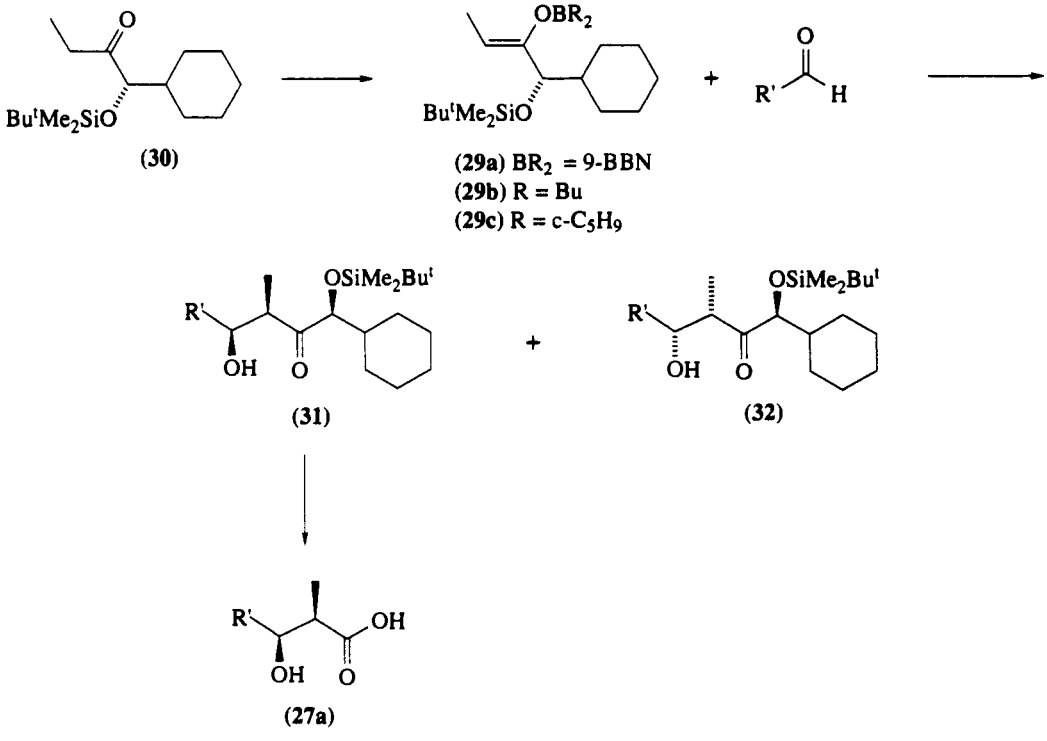
R = achiral or chiral

of two enantiomerically pure fragments by an aldol reaction. Some references pertinent to this section can be found in ref. 84.

1.7.2.3.1 Construction of α-methyl-β-hydroxycarbonyl units

(i) Syn-selective aldol reactions

The first highly enantioselective construction of α-methyl-β-hydroxycarbonyl units, described by Masamune *et al.*, used alkenyloxyboranes (**29**) prepared by enolization of ethyl ketone (**30**) derived in three steps from enantiomerically pure mandelic acid.[36] Various dialkylboryl triflates are used with diisopropylethylamine for enolization. The alkenyloxyboranes (**29**) exhibit striking stereoselectivity as chiral reagents in reactions with representative aldehydes. With judicious choice of the alkyl ligands on the



(30)

(29a) BR_2 = 9-BBN
(29b) R = Bu
(29c) R = c-C_5H_9

(31)

(32)

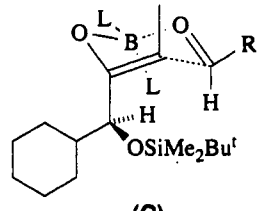
(27a)

Scheme 23

boron atom, diastereoselectivities (ratio of **31** to **32** in Scheme 23) exceed 100:1. Removal of the TBDMS group from the aldol products followed by $NaIO_4$ treatment provides the corresponding α-methyl-β-hydroxycarboxylic acids (**27a**) with enantiomeric excesses exceeding 98% (Table 2). This highly stereoselective aldol reaction can be rationalized by the Zimmerman–Traxler[37] six-membered chair-like transition state as shown in (**C**).

Table 2 Reaction of Aldehydes with Boron Enolate (**29**)

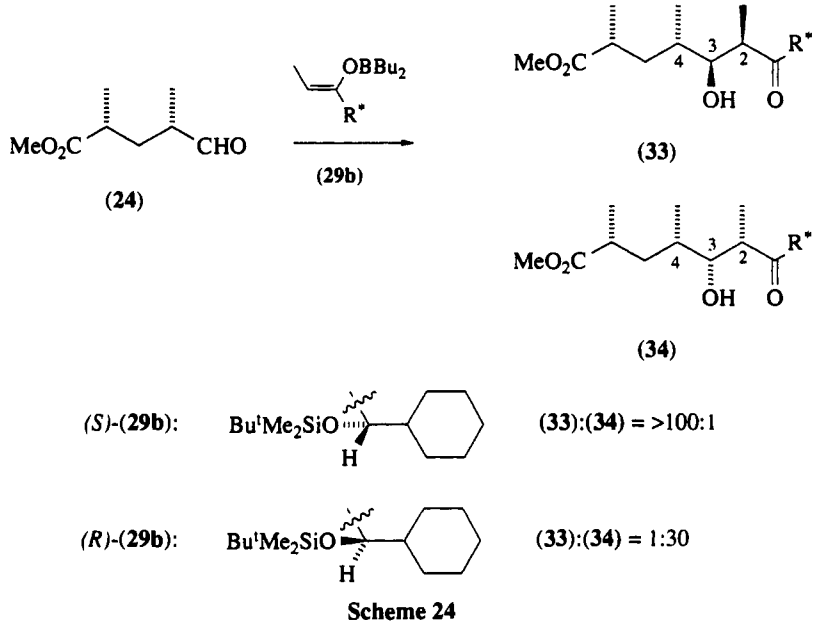
Aldehyde	*Boron enolate*	*Ratio of (31):(32)*
$BnOCH_2CH_2CHO$	(**29a**)	16:1
	(**29b**)	28:1
	(**29c**)	100:1
Pr^iCHO	(**29a**)	>100:1
	(**29b**)	>100:1
	(**29c**)	No reaction



(**C**)

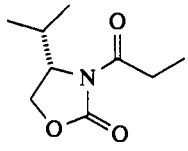
Since the stereochemical outcome of the aldol reaction with these enolates is predictable from the above results, selection of either (*S*)-(**29b**) or (*R*)-(**29b**) for a matched or mismatched pair can easily be made. Thus, in the reaction of chiral aldehyde (**24**) with (*S*)-(**29b**) (matched) the product ratio exceeds 100:1, favoring formation of (**33**), whereas when reagent (*R*)-(**29b**) is used, (**34**) becomes the predominant product with a respectable stereoselection (mismatched) (Scheme 24). Compared to the ratios observed for the reaction with an achiral enolate (Scheme 22), it is clear that the facial selectivity of the enolates dictates the 3,4-stereochemistry of the aldol reaction and either the 2,3-*syn*-3,4-*anti* or 2,3-*syn*-3,4-*syn* units can be constructed in a predictable manner.

Independent work on asymmetric aldol reactions by Evans *et al.* led to the development of alternative chiral boron enolates that exhibit >100:1 facial selectivity.[38] A pair of chiral *N*-acyl-2-oxazolidones (**35**)

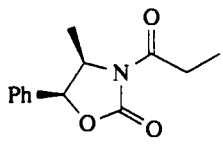


Scheme 24

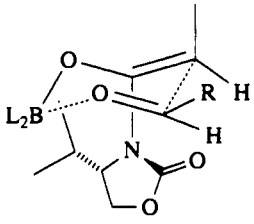
and (**36**), derived from (*S*)-valine and (1*S*,2*R*)-norephedrine, can be converted under standard (Mukaiyama) conditions into the corresponding boron enolates (**37**) and (**38**), respectively. Reaction of either (**37**) or (**38**) with a set of aldehydes provides a single 2,3-*syn* diastereomeric aldol product showing that both the enolate formation and the aldol reaction proceed with near perfect stereoselection (Table 3), as shown in Scheme 25. Treatment of the aldol products (**39**) and (**40**) with sodium methoxide (molar ratio 1:1) in methanol leads to the corresponding methyl esters (**41**) and (**42**) with >99% optical purity and opposite absolute stereochemistry. As in the case of enantiomerically homogeneous boryl enolates (**29**), the observed stereoselection can be explained by the Zimmerman–Traxler transition state model (**D**).



(**35**)



(**36**)

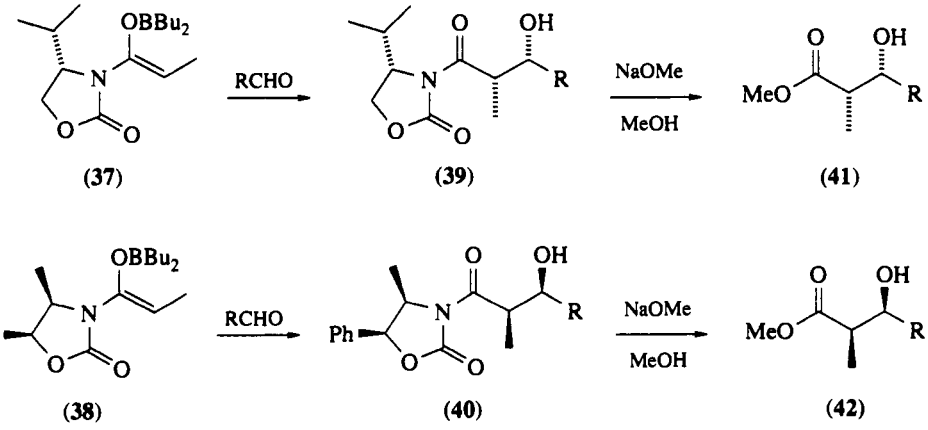


(**D**)

Table 3 Aldol Reactions of (**37**) and (**38**) with Representative Aldehydes (Scheme 25)[38]

Entry	*Boron enolate*	*Aldehyde*	*Ratio of syn diastereomers*[a]	*Aldol product*	*Yield (%)*	*Overall product*	*Overall Yield (%)*
1	(**37**)	Pr^iCHO	497:1	(**39**)	78	(**41**)	69
2	(**38**)	Pr^iCHO	<1:500	(**40**)	91	(**42**)	78
3	(**37**)	Bu^nCHO	141:1	(**39**)	75	(**41**)	68
4	(**38**)	Bu^nCHO	<1:500	(**40**)	95	(**42**)	71
5	(**37**)	PhCHO	>500:1	(**39**)	88	(**41**)	81
6	(**38**)	PhCHO	<1:500	(**40**)	89	(**42**)	60

[a]In all cases the *anti* aldol adducts constituted <1% of the total reaction mixture.

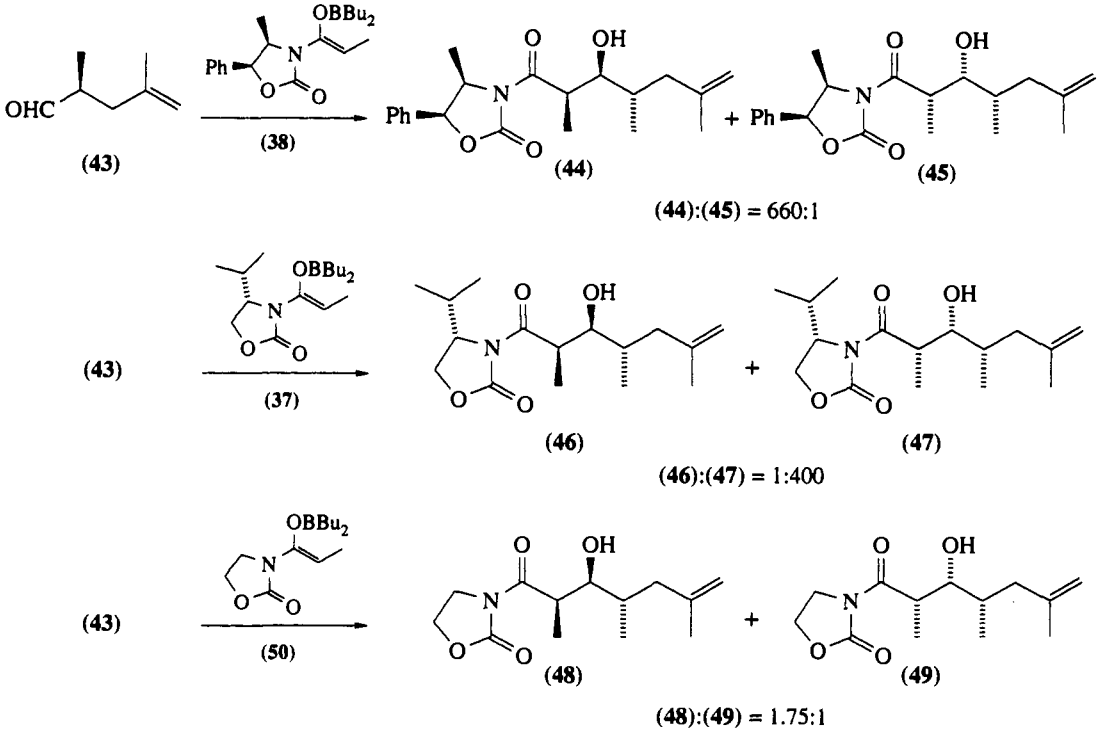


Scheme 25

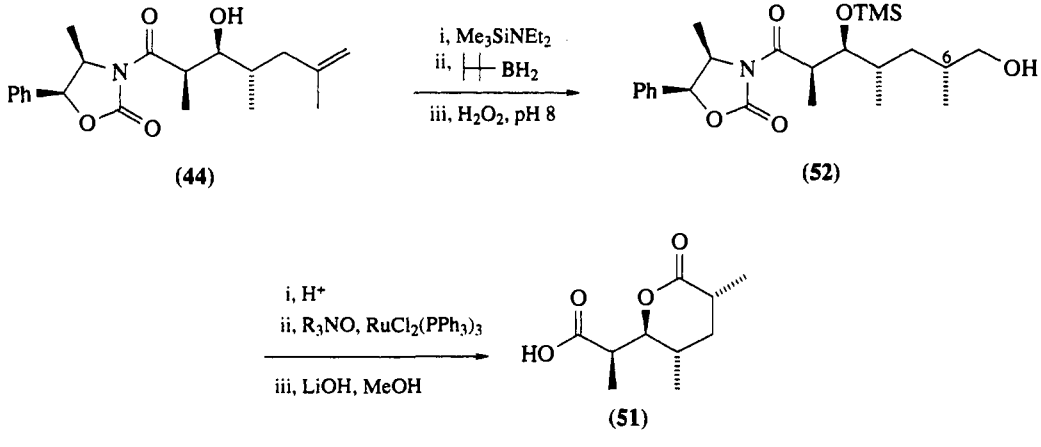
The reactions of chiral aldehyde (**43**) with reagents (**37**) and (**38**) represent a typical example of double asymmetric synthesis.[39] As shown in Scheme 26, the reactions provide exclusively (**44**) and (**47**), with stereoselection of 660:1 and 400:1, respectively.

The facial selectivity of (**43**) was found to be 1.75:1 from the ratio of aldol products (**48**) and (**49**) obtained by the reaction with the achiral boron enolate (**50**). The latter is structurally similar to reagents (**37**) and (**38**). These experiments confirm again the validity of the rule of double asymmetric synthesis. The product (**44**) can be further converted through a sequence of reactions to provide (+)-Prelog–Djerassi lactonic acid (**51**; Scheme 27): (i) trimethylsilylation; (ii) hydroboration with thexylborane (single asym-

metric induction with a 5.7:1 ratio in favor of the diastereomer (**52**), see C-6), followed by oxidative work-up; (iii) acid hydrolysis to remove the trimethylsilyl group of (**52**); (iv) ruthenium-catalyzed oxidation of the primary hydroxy group; and finally (v) hydrolytic removal of the chiral auxiliary.



Scheme 26

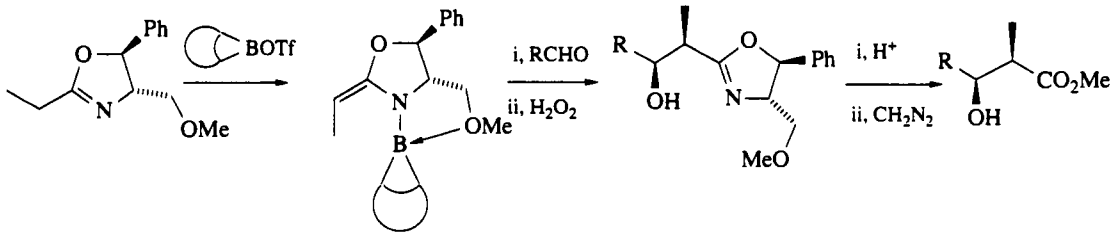


Scheme 27

Meyers *et al.*[40] reported the use of boron azaenolate (**53**), derived from enantiomerically homogeneous oxazoline (**54**) and 9-BBN triflate, for the preparation of 2,3-*syn* aldol units (**55**), as shown in Scheme 28. The resulting *syn*-3-hydroxy-2-methyl esters (**56**) are obtained with very high (95–98%) *syn* diastereoselectivities but modest enantiomeric excesses (29–71% *ee*).

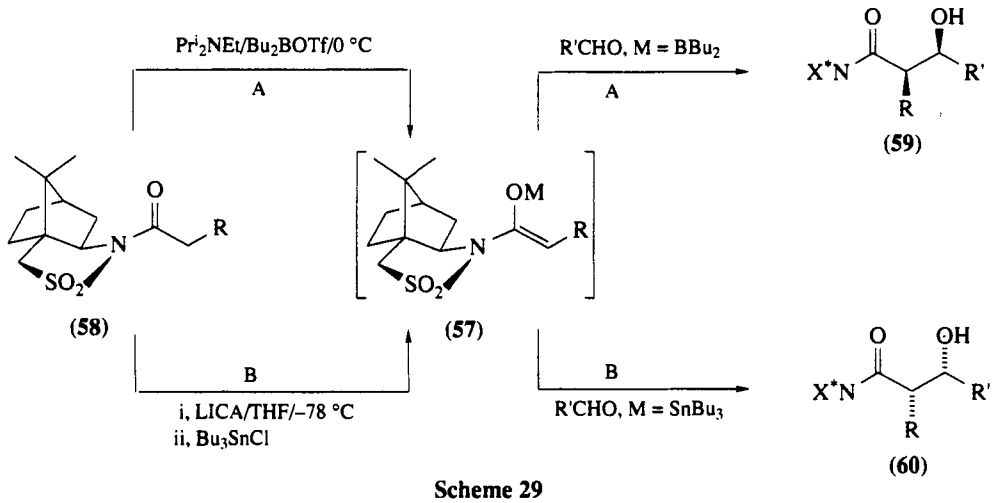
An interesting asymmetric aldol reaction utilizing enantiomerically homogeneous bornane sultam derived boron enolates has recently been reported by Oppolzer *et al.*[41] The reaction of aldehydes with boron enolates (**57**), generated from acyl sultams (**58**) under standard enolization conditions ($Pr^i_2NEt/Bu_2BOTf/0$ °C), provides *syn* aldol products (**59**) with extremely high ratios of (**59**) to (**60**) as shown in Scheme 29. Results from the aldol reactions with representative aldehydes are summarized in

Table 4. It is interesting to note that the tin enolate corresponding to (**57**), upon reaction with aldehydes, also provides *syn* aldol products (**60**), diastereomeric to (**59**), with high diastereoselection. This opposite sense of asymmetric induction is believed to be due to coordination of the sultam oxygen to the metal (Sn) in the transition state, which is absent in the boron counterpart. Notably, the products can be easily purified by flash chromatography and/or crystallized to nearly perfect (>99% *de*) diastereomeric purity.



(**54**) (**53**) (**55**) (**56**)

Scheme 28



(**58**) (**57**) (**59**) (**60**)

Scheme 29

Table 4 Aldol Reactions of Boron Enolates Derived from Enantiomerically Pure Acyl Sultam (**58**)[41]

R	*R'*	*Yield of the major product (%)*	*Product ratio*[a] (**59**):(**60**)	*After purification* (**59**):(**60**)
Me	Ph	78	>95:<5	>200:1
Me	Pr^i	48	>99:<1	>200:1
Me	Me (–100 °C)	48	>99:<1	>200:1
Et	Me (–100 °C)	69	>95:<5	>40:1
Et	Ph	63	>95:<5	>40:1
Et	Pr^i	72	>95:<5	>40:1

[a]No *anti* aldol products were obtained.

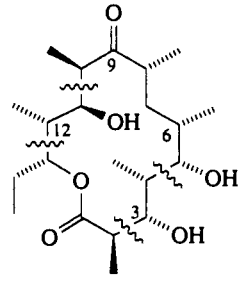
(ii) Application of the syn*-selective propionate aldol methodology to natural product synthesis*

The synthesis of 6-deoxyerythronolide B (**61**), accomplished by Masamune *et al.*[42] in 1981, was the first successful demonstration of double asymmetric synthesis applied to the construction of molecules of this stereochemical complexity, and manifests clearly the power of this new strategy using enantiomerically homogeneous reagents to control stereochemistry. The macrolide (**61**) is the lactone derived from 13-hydroxypentadecanoic acid (**62**), which consists of seven propionate building blocks (Scheme 30). Retrosynthetic analysis of the seco-acid (**62**) into fragments (**63**) and (**64**) immediately suggests the order of the aldol reactions to be used in the synthesis. Aldol reaction I (involving propanal and its enolate

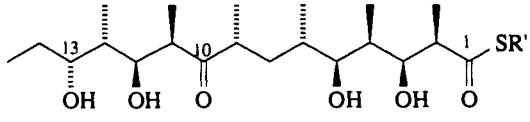
equivalent **65**) produces (**63**), while aldol reactions II (**65** and **66**) and III (**67** and **65'**; an enolate equivalent of propanethioate) complete the synthesis of fragment B. Finally, both fragments are combined *via* aldol reaction IV. Note that aldol reactions I, II, and III all concern the creation of 2,3-*syn* stereochemistry, a task that can be readily achieved with the *Z*(*O*)-enolates (**29**) described above.

In practice, eight stereogenic centers out of the 10 embedded in the target molecule have been created with remarkable efficiency and stereoselection *via* the aldol reactions I–III using (**29**). The overall yield was 30% and overall stereoselectivity approximately 90%. Many other natural product syntheses using the strategy outlined above are now on record.

Evans *et al.* utilized the chiral oxazolidones to prepare optically pure β-hydroxy-α-amino acids,[43] important constituents of peptides and β-lactams. As shown in Scheme 31, an asymmetric aldol reaction using the boron enolate derived from the *N*-(α-haloacyl)oxazolidone (**68**) provides the *syn*-β-hydroxy-α-halocarbonyl derivative (**69**), which is converted to the *anti*-β-hydroxy-α-azidocarbonyl derivative (**70**)



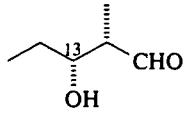
(**61**)



(**62**)

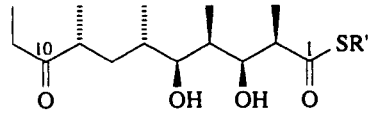
aldol IV

2,3-*syn*, 3,4-*anti*



(**63**) Fragment A

+



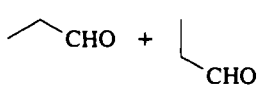
(**64**) Fragment B

aldol I

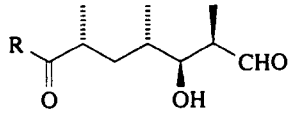
2,3-*syn*

aldol III

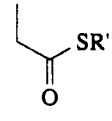
2,3-*syn* 3,4-*syn*



(**65**)



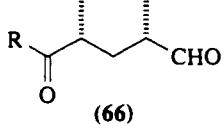
(**67**)



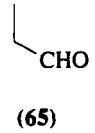
(**65'**)

aldol II

2,3-*syn* 3,4-*anti*



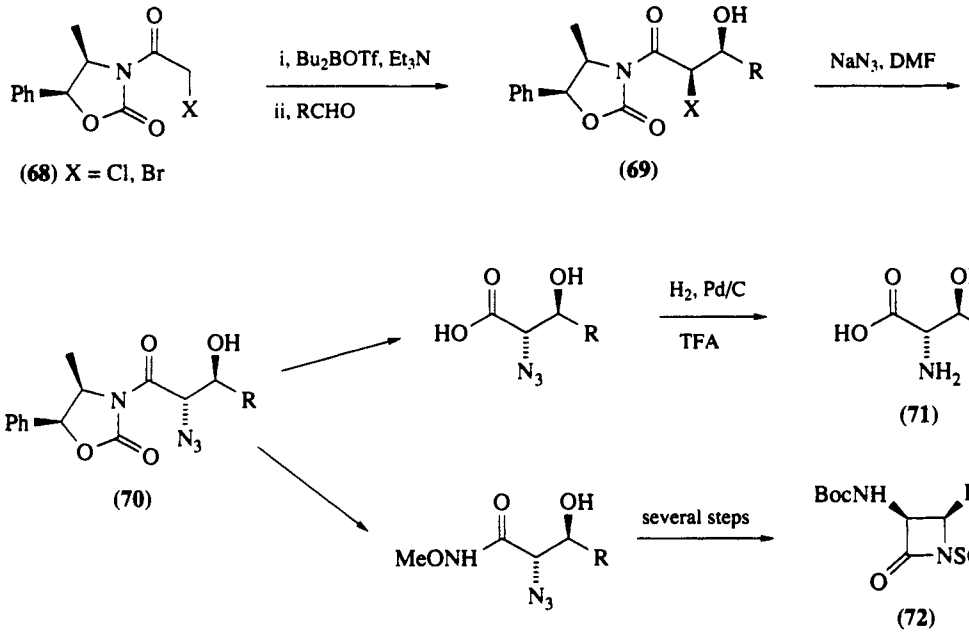
(**66**)



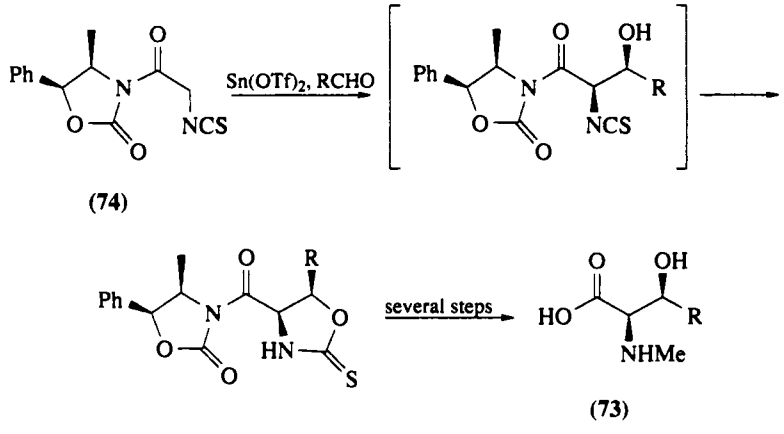
(**65**)

Scheme 30

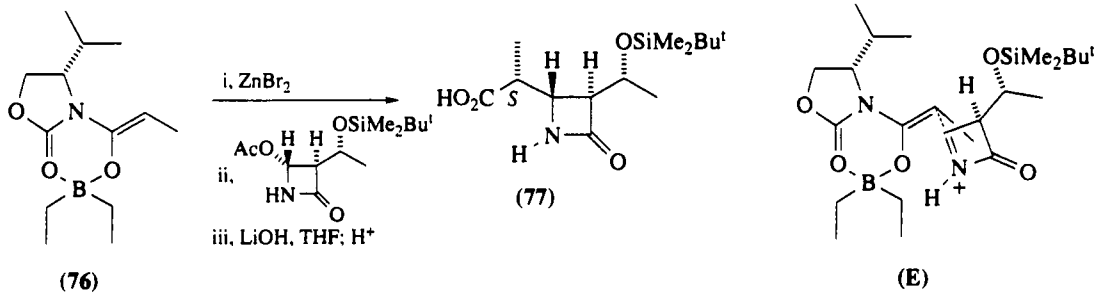
by an S_N2 displacement. Further synthetic transformations of (**70**) provide routes to β-hydroxy-α-amino acids (**71**) and β-lactams (**72**). Notably *syn*-β-hydroxy-α-amino acids (**73**) can be obtained by reaction of the tin enolate derived from (**74**) as shown in Scheme 32.[44]



Scheme 31

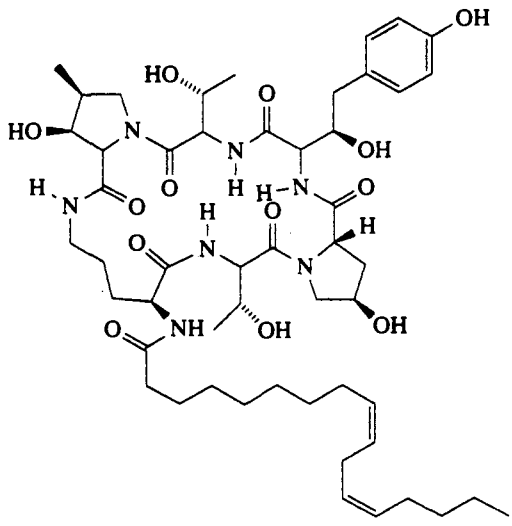


Scheme 32



S:*R* ≥ 99:1

Scheme 33



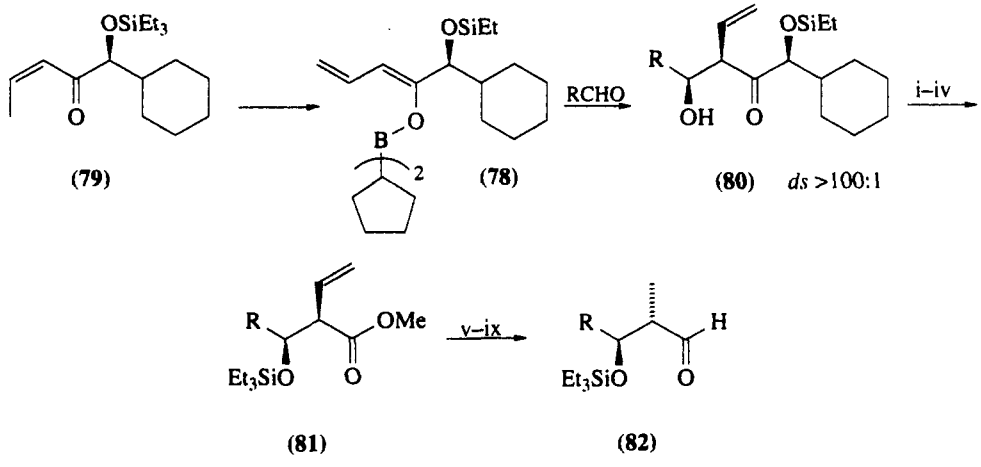
(**75**) Echinocandin D

The cyclic hexapeptide echinocandin D (**75**) has been successfully synthesized with the aid of the foregoing methods for the preparation of *syn*- and *anti*-β-hydroxy-α-amino acid units.[45]

Fuentes *et al.*[46] have also used boron-mediated aldol reactions to prepare enantiomerically homogeneous β-lactam moieties. In the presence of a Lewis acid ($ZnBr_2$), enantiomerically homogeneous boryl enolate (**76**) provides adduct (**77**) with high diastereoselectivity (see acyclic transition state **E**; Scheme 33).

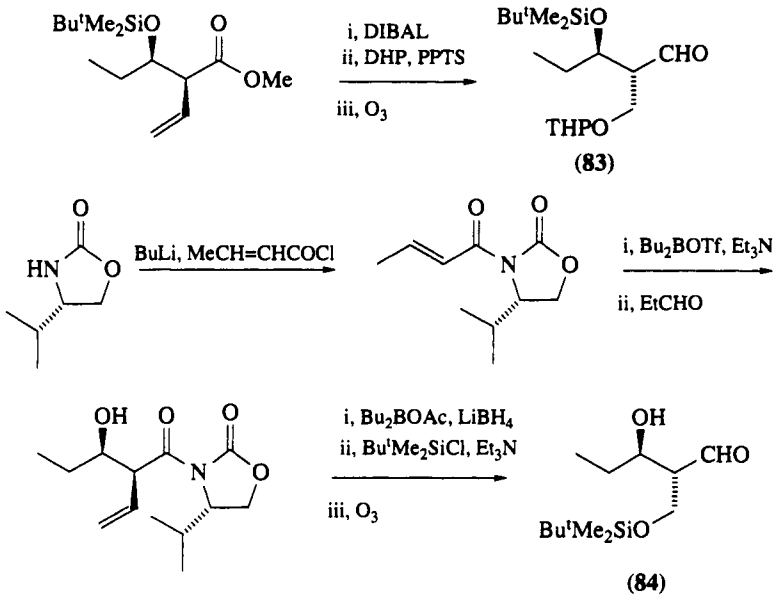
(iii) Anti-*selective aldol reactions*

(a) Earlier methods. Since *E(O)*-boron enolates with acceptably high facial selectivities were not available before 1985, the enantio- and diastereo-selective construction of 2,3-*anti*-α-methyl-β-hydroxycarbonyl units had to rely on indirect, circuitous approaches. Depicted in Scheme 34 is a typical example of such an approach.[13,47] The *Z(O)*-enolate (**78**) prepared from (*Z*)-enone (**79**) adds to an aldehyde in the expected manner (diastereoselection > 100:1) to provide the *syn* aldol product (**80**), which is converted into ester (**81**). Straightforward manipulation of the ester followed by ozonolysis of



i, HF; ii, $NaIO_4$; iii, CH_2N_2 ; iv, Et_3SiOTf ; v, DIBAL; vi, *p*-TsCl ; vii, NaI ; viii, $NaBH_3CN$; ix, O_3

Scheme 34

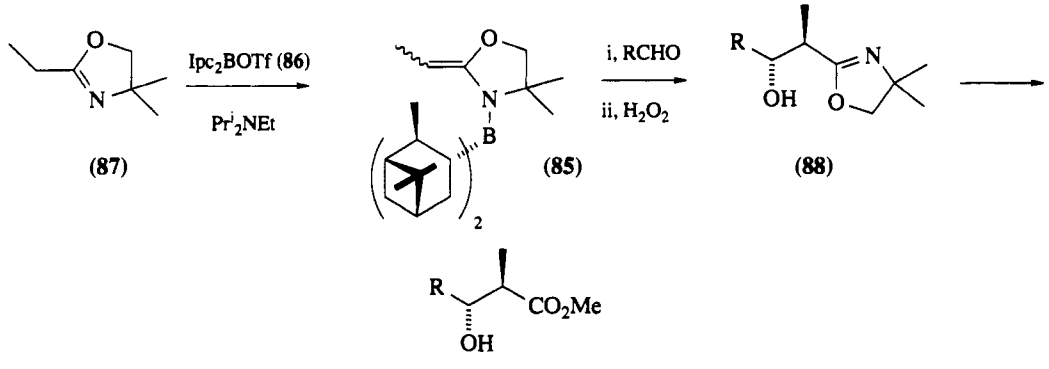


Scheme 35

the double bond furnishes the *anti* unit (**82**). This methodology was applied to the construction of β-hydroxy-α-(hydroxymethyl)carbonyl units (**83**) and (**84**) in Masamune's[13b,47] and Evans'[4a] tylonolide syntheses, respectively (Scheme 35).

(b) Preparation of anti-α-methyl-β-hydroxy units using external reagents. The aldol reactions with each of the synthetically useful enantiomerically homogeneous boron reagents discussed above (**29**, **37**, **38** and **57**) provide almost exclusively a single diastereoisomer in which the chiral auxiliary of the reagent is covalently attached to the remainder of the molecule. Reagents of this type are designated internal as opposed to external (chiral) reagents, where the auxiliary is detached from the product after usual work-up. The advantages of the external reagent over the internal are obvious and the crucial role of the external reagent becomes evident in the process of assembling two chiral fragments *via* an aldol reaction, as will be discussed in Section 1.7.2.3.4.

In 1981 Meyers and Yamamoto[40] reported the use of an external reagent in the construction of a 2,3-*anti* unit. The boron azaenolate (**85**), prepared from the chiral boron reagent (**86**; diisopinocampheylboryl triflate; Ipc$_2$BOTf) and the achiral oxazoline derivative (**87**), reacts with aldehydes in ether at –78 °C (Scheme 36). The direct products (**88**) are converted, after hydrolysis and esterification, to the corresponding α-methyl-β-hydroxycarboxyl derivatives (**89**), which are rich in the *anti* isomer (*anti*:*syn*

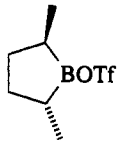


(**89**) *anti*

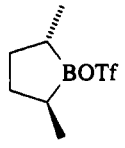
Scheme 36

ratio, 9:1–19:1) and have significant enantiomeric purity (77–85% *ee*). Unfortunately the overall conversion proceeds in low yield (22–36%), probably due to the rather harsh conditions (3 N sulfuric acid, 12 h) used to hydrolyze the oxazoline moiety.

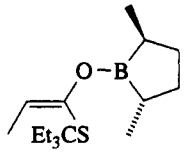
Masamune and coworkers[48] designed a set of chiral *trans*-2,5-dimethylborolane-based reagents that show remarkable enantioselectivities in hydroboration,[49] ketone reduction[50] and crotyl addition to aldehydes.[51] The chirality transfer also turns out to be highly efficient in the aldol reaction. Initial experiments were aimed at defining the structural parameters which affect the *E*(*O*):*Z*(*O*) ratios of the enolates prepared from various alkanethioates with 2,5-dimethylborolanyl triflate (**90**) under standard conditions



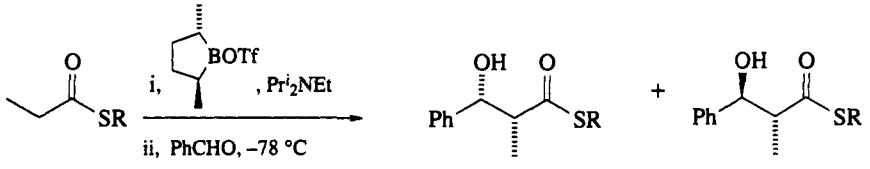
(2*R*,5*R*)-(**90**)



(2*S*,5*S*)-(**90**)



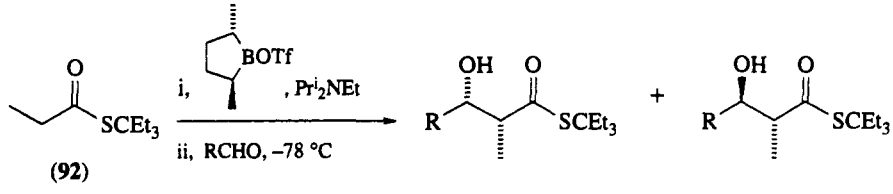
(2*S*,5*S*)-(**91**)



Scheme 37

Table 5 *Anti/Syn* Selectivity of the Aldol Reaction using (2*S*,5*S*)-(**90**)

Entry	*R in thiol esters*	*Combined yield (%)*	*Anti:syn ratio*
1	Pr^i	85	78:22
2	Bu^t	100	91:9
3	3-(3-Ethyl)pentyl	75	97:3
4	Ph	87	7:93
5	2-Naphthyl	83	5:95



Scheme 38

Table 6 Aldol Reaction of Thioate (**92**) using (2*S*,5*S*)-(**90**) with Representative Aldehydes

Entry	*Aldehyde*	*Yield (%)*	*Anti:syn ratio*	*ee of Anti product (%)*	*Configuration*
1	Pr^nCHO	91	33:1	97.9	(2*R*,3*R*)
2	Pr^iCHO	85	30:1	99.5	(2*R*,3*R*)
3	Bu^tCHO	95	30:1	99.9	(2*R*,3*S*)
4	c-$C_6H_{11}CHO$	87	32:1	98.0	(2*R*,3*R*)
5	PhCHO	71	33:1	99.8	(2*R*,3*S*)
6	$BnO(CH_2)_2CHO$	93	30:1	>97.1	(2*R*,3*R*)

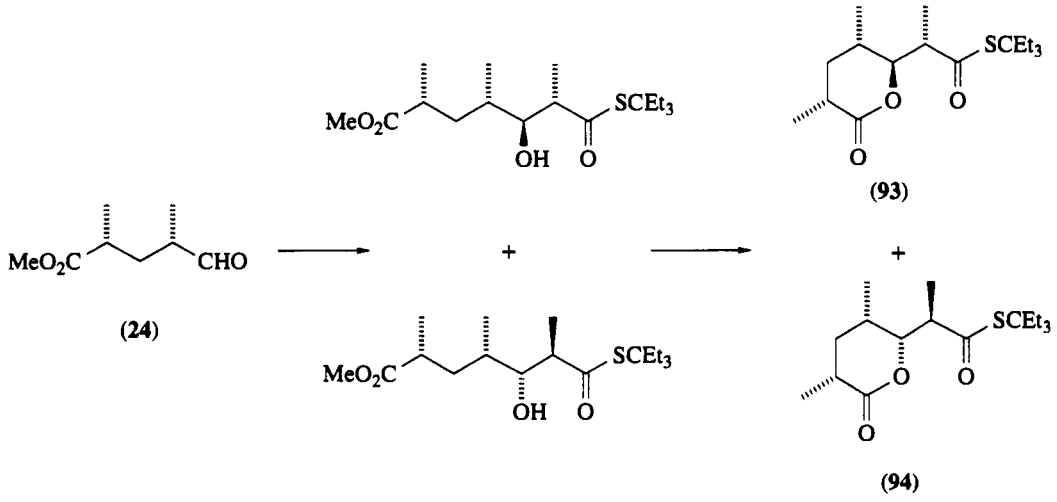
(Scheme 37). It is clear from Table 5 that the *E(O)*:*Z(O)* ratio increases with the size of the alkanethiol moiety, whereas formation of the *Z(O)*-enolate prevails with *S*-aryl thioates.

The *E(O)*-reagent (**91**) is formed almost exclusively from *S*-3-(3-ethyl)pentyl propanethioate (**92**) and borolanyl triflate (**90**). Despite its apparent steric demand, (**91**) still retains a high degree of reactivity towards aldehydes (in Scheme 21 the interaction between R and Me is not exceedingly large). Summarized in Table 6 are the results obtained from aldol reactions of representative aldehydes with (**91**; Scheme 38). All reactions proceed smoothly at −78 °C and the major products have the 2,3-*anti* stereochemistry (*anti*:*syn* > 30:1). With (2*S*,5*S*)-(**90**) the aldehydes examined provide, in most cases, the (2*R*) aldol products with more than 98% *ee*. It is important to note that the external chiral moiety can be recovered as its 2,2-dimethylaminoethanol complex, and that the aldol products are equipped with a versatile thioate functionality for further synthetic transformation.

The boron enolates prepared from propanethioate (**92**) and borolanyl triflate (**90**) were examined in reactions with enantiomerically homogeneous aldehydes and proved to follow the rule of double asymmetric synthesis (Scheme 39).[52] As shown in Table 7, the results obtained from a set of lactonization experiments are fully consistent with the approximate multiplicativity rule for double asymmetric synthesis.

The two other aldol products that can be derived *via* propionate addition to (**24**) are the Prelog–Djerassi lactonic acid diastereomers, both of which were prepared successfully with the internal chiral boron enolates discussed earlier in this section. Thus this work completes a set of chiral reagents that can control the relative stereochemistry at the 2, 3 and 4 positions of aldol products.

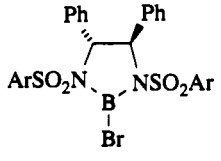
Another C_2 symmetric chiral borane reagent has been utilized by Corey *et al.*[83] for the construction of *syn* aldol products in a highly enantioselective manner. When an enolate prepared from *S*-phenyl pro-



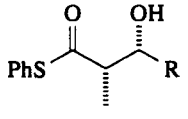
Scheme 39

Table 7 Aldol Reactions of (**24**) and Ent-(**24**) with Enolate (**91**) Followed by Lactonization

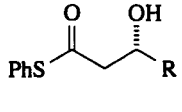
Entry	*Aldehyde*	*Products after lactonization*		*3,4-Anti*:*syn ratio*	*Yield (%)*
		3,4-anti	*3,4-syn*	*(corrected)*	
1	(**24**)	(**93**)	(**94**)	200:1	90
2	Ent-(**24**)	Ent-(**93**)	Ent-(**94**)	1:55	83



(R,R)-(**i**)



(**ii**)



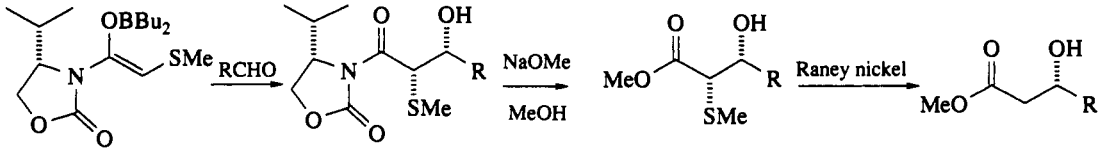
(**iii**)

panethioate and the chiral borane reagent (*R,R*)-(**i**) in the presence of Pr^i_2EtN is allowed to react with benzaldehyde or isobutyraldehyde, highly *syn* selective aldol products (**ii**) (*syn/anti* 95:5 and 98:2, respectively) are obtained with very high enatioselectivities (95 and 97% *ee*, respectively). Likewise, the aldol reaction of acetate derivatives using a similar chiral borane reagent proved to be very enantioselective. The enolate prepared from phenyl thioacetate and the chiral borane reagent in the presence of triethylamine provided, upon reaction with benzaldehyde or isobutyraldehyde at –90 °C, the aldol products (**iii**) of 91% and 83% *ee*, respectively.

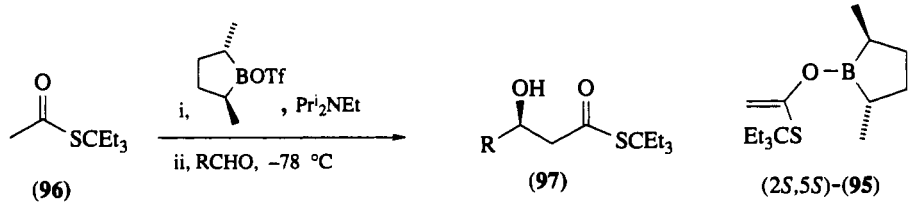
1.7.2.3.2 Construction of α-unsubstituted-β-hydroxycarbonyl units

The synthesis of enantiomerically homogeneous α-unsubstituted-β-hydroxycarbonyl compounds by the aldol reaction has been a difficult challenge. Nor analogs of the chiral boron enolates developed for the highly *syn* selective propionate aldol reaction have given disappointingly low degrees of stereoselection with representative aldehydes. Several attempts have been made to overcome this problem. These efforts include aldol reactions of boron enolates which incorporate at the α-position a 'dummy' group which is removed after the reaction. Using this technique high levels of asymmetric induction have been recorded as shown in Scheme 40.[5e,38]

Various other methods not involving boron enolates have been developed to achieve high asymmetric induction in acetate addition and are discussed elsewhere in this volume.



Scheme 40



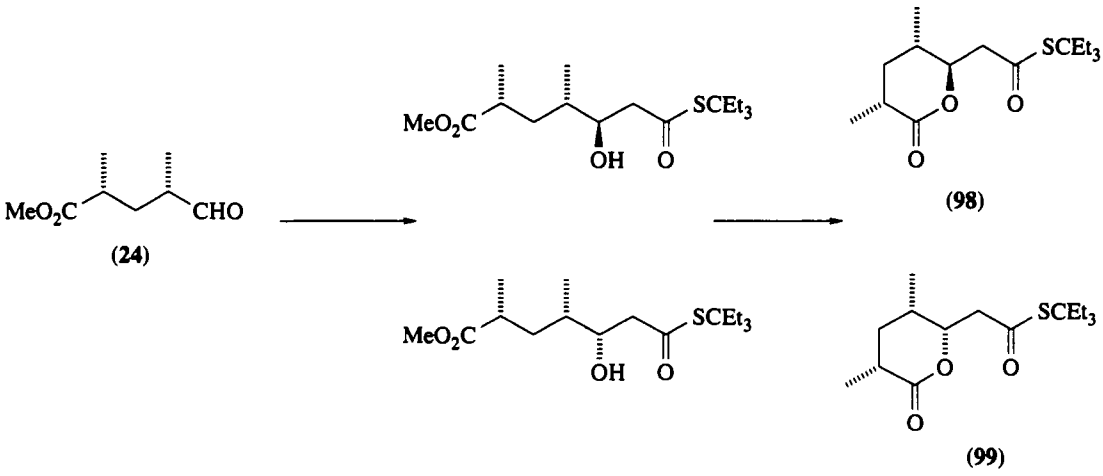
Scheme 41

Table 8 Synthesis of 3-Hydroxy Thioesters (**97**)

Entry	*Aldehyde*	*Yield (%)*	*Corrected ee (%)*	*Configuration*
1	Pr^nCHO	82	91.2	(*R*)
2	Bu^iCHO	81	91.5	(*S*)
3	Bu^tCHO	71	98.4	(*S*)
4	$c\text{-}C_6H_{11}CHO$	95	90.1	(*S*)
5	PhCHO	78	92.2	(*S*)
6	$BnO(CH_2)_2CHO$	93	89.1	(*R*)

Table 9 Aldol Reactions of (**24**) and Ent-(**24**) with Enolate (**95**) Followed by Lactonization

Entry	*Aldehyde*	*Products after lactonization*		*3,4-Anti:syn ratio (corrected)*	*Yield (%)*
		3,4-anti	*3,4-syn*		
1	(**24**)	(**98**)	(**99**)	13:1	81
2	Ent-(**24**)	Ent-(**98**)	Ent-(**99**)	1:7	83



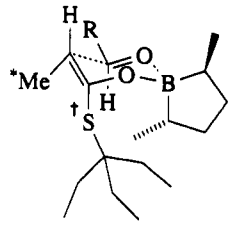
Scheme 42

In contrast to all known chiral boron enolates, the external reagent (**95**) derived from ethanethioate (**96**) and 2,5-dimethylborolanyl triflate (2*S*,5*S*)-(**90**) effects asymmetric induction in the aldol reaction to provide β-hydroxy thioesters of approximately 90% *ee* for most aldehydes (Scheme 41; Table 8).[48]

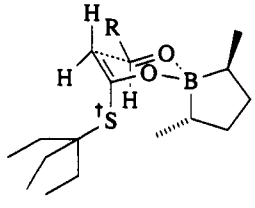
The 10% decrease in enantiomeric excess compared with that observed for the propionate enolate (**91**) is reflected in the double asymmetric synthesis outlined in Scheme 42 and Table 9 (see Table 7 for comparison).[52]

1.7.2.3.3 Comments on the facial selectivities of the chiral alkenyloxydialkylboranes

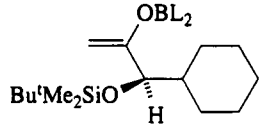
For many aldol reactions, a Zimmerman–Traxler model[37] is most conveniently used to rationalize the stereochemical outcome of these reactions. It may be used here again to explain the higher enantioselectivities exhibited by (**91**) compared to (**95**). In transition state (**F**) for the reaction of an aldehyde with re-



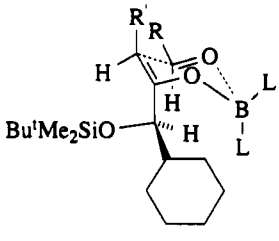
(F)



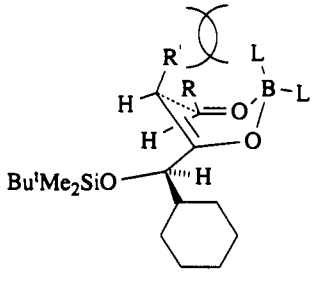
(G)



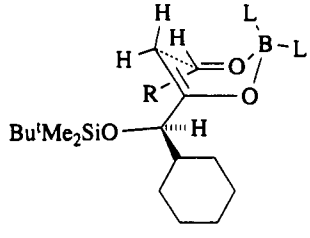
(100)



(C)



(H)



(I)

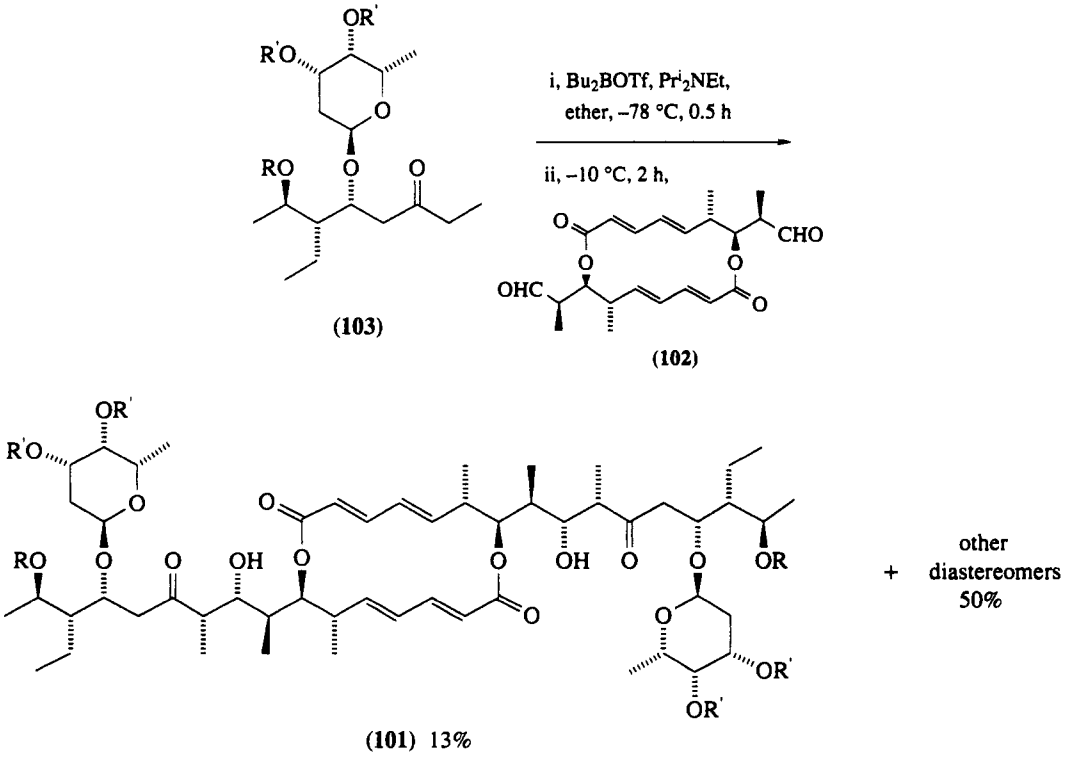
agent (**91**), the asterisked methyl group steers the 3-ethyl-3-pentanethiol group toward the borolane moiety, effectively transferring the chirality. In the absence of this 'steering effect', as may be the case for transition state (**G**), depicting the reaction of reagent (**95**), the enantioselection of the reaction decreases. The supposition that both reactions proceed through a chair-form transition state is of great interest in that both (**91**) and (**95**) have no *Z*(*O*)-methyl substituent. The nor analog (**100**) of reagent (**29**), previously discussed in Section 1.7.2.3.1, provides an approximately 1:1 mixture of two diastereomeric aldol products.[53]

While the preferred transition state for reaction with (**29**) is (**C**) (rather than (**H**) where the steric hindrance between the *Z*(*O*)-methyl group (R′) and the ligand (L) attached to the boron atom is prohibitively severe), the reaction with (**100**) may well proceed through the boat-form transition states (**H**; R′ = H) and/or (**I**). Transition states (**H**) and (**I**) would be expected to be of approximately equal energy, differing only in the orientation of the reacting aldehyde with respect to (**100**), as shown. The reaction thus proceeds stereorandomly. In contrast, the 3-ethyl-3-pentanethiol group in (**F**) and (**G**), despite its steric bulk, is conformationally more flexible and free to rotate about the axis of the carbon–sulfur bond, indicated by the dagger. (Note: the carbon–sulfur bond is long.) Thus, this large group can be accommodated within the chair-form framework.

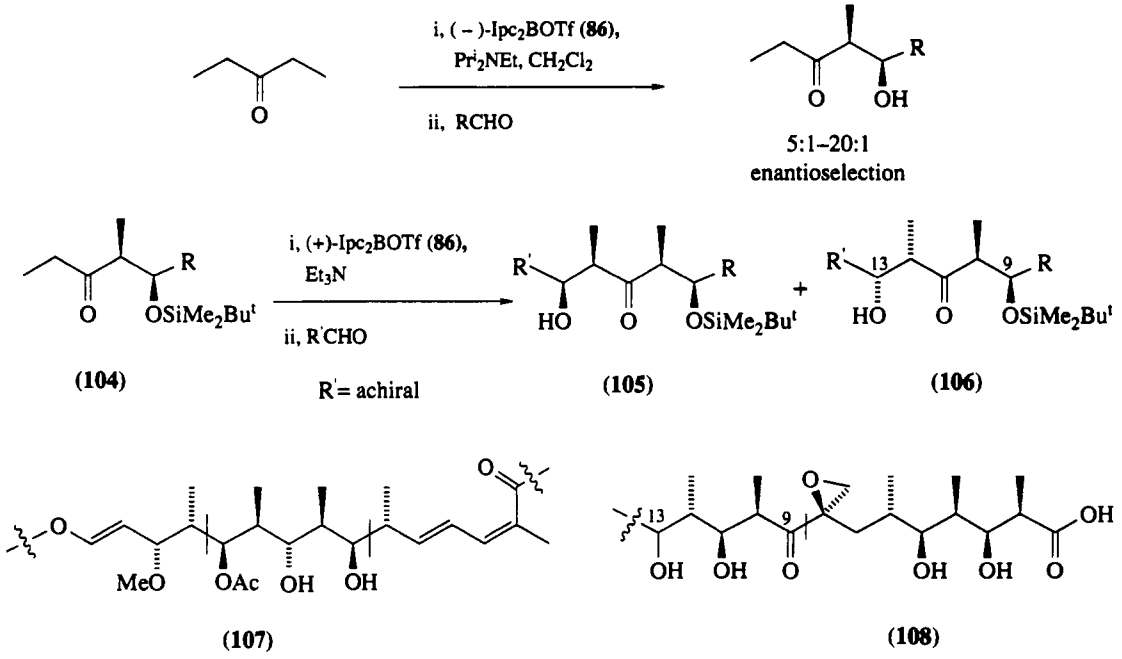
1.7.2.3.4 External chiral reagents for the aldol reaction of ketones

(i) Aldol reactions of ethyl ketones

The aldol reaction has been recognized as a useful reaction for assembling two large fragments with concomitant creation of a stereogenic center or centers in the convergent synthesis of many natural products. Stereocenters embedded in the fragments necessarily correspond to those of a target molecule, and the stereoselectivity of the coupling reaction heavily depends on the diastereoselectivities of the two reactants, *e.g.* an enolate and an aldehyde, derived from the two fragments, if an aldol reaction is used. Diastereofacial selectivities are predetermined but are normally unpredictable in both magnitude and



Scheme 43



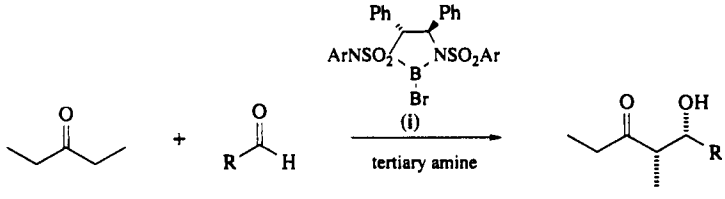
Scheme 44

sense. The coupling often constitutes the least stereoselective step in the total synthesis unless the two reactants fall into a matched pair favoring the formation of the desired stereochemistry.

Depicted in Scheme 43 is an example of an apparently mismatched, but otherwise highly convergent, set of two simultaneous coupling reactions used by Kinoshita and coworkers[54] in their synthesis of elaiophylin (azalomycin B; **101**; R = R′ = H), a C(2)-symmetrical 16-membered macrodiolide. When the aldehyde (**102**) is treated with the dibutylboryl enolate of (**103**), generated in a standard fashion, the desired diastereomer (**101**) is obtained in 13% yield. This crucial closing stage of the total synthesis is enfeebled by a 2:1 preponderance of the unwanted 'Cram' product over the desired 'anti-Cram' product (**101**). The latter upon removal of the protecting groups R and R′ provides azalomycin B. A similar situation where the selectivity is solely dependent upon the inherent facial selectivity of two coupling substrates has arisen in the final stage of a recent total synthesis of ionophore X-206 by Evans.[55]

How can we gain stereocontrol over aldol reactions used for coupling? One solution is to alter, or ideally overpower, the diastereofacial selectivities of the enolates derived from chiral ketones by using an external chiral boron reagent, *e.g.* Ipc_2BOTf (**86**) and 2,5-*trans*-dimethylborolanyl triflate (**90**), instead of the achiral reagent (Bu_2BOTf) exemplified above in the azalomycin B synthesis. In this way, the stereochemical course of the coupling reaction may be analyzed in terms of three diastereofacial selectivities, that of the chiral ligands attached to the boron reagent and those of the two chiral fragments. The boron reagent can be designed, selected and serve as a controlling component.

Paterson *et al.*[56] have prepared the enolate of 3-pentanone, an achiral ketone, with (+)- or (–)-Ipc_2BOTf and have found that its aldol reactions with various aldehydes proceed with high *syn:anti* ratios (>9:1) and respectable enantioselectivities (5:1–20:1) (Scheme 44). High degrees of asymmetric induction are noted with unhindered aldehydes. The combination of the chiral ethyl ketone (**104**) and (+)-Ipc_2BOTf constitutes a matched pair, which enhances the diastereofacial selectivity of the resulting enolate (compared to that obtained with an achiral boron reagent), and provides *via* aldol reactions high



Scheme A

ratios (30:1–47:1) of the products (**105**) and (**106**). The product (**105**) is an intermediate that can be converted to the ansa chain (**107**) of rifamycin S.[57] Attempts to prepare (**106**) as the major product were made for the purpose of preparing (**108**), the seco-acid of oleandomycin. The use of (–)-(**86**) and (**104**) (mismatched pair) results in a decrease of the (**105**):(**106**) ratio to 3:1 but not in the predominant formation of (**106**). Apparently the diastereofacial selectivity of (+)- or (–)-Ipc_2BOTf is smaller than that intrinsic to (**104**).

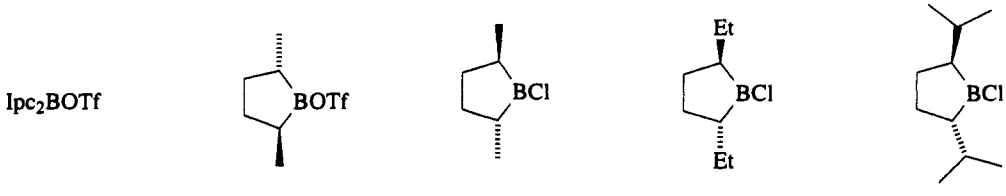
Highly enantioselective aldol reactions of diethyl ketone have been recorded with the use of the chiral borane reagent (**i**).[83] As shown in Scheme A, *syn* aldol products of 95–98% *ee* have been obtained upon reaction with various aldehydes with 94–98% diastereoselectivities.

(ii) Aldol reactions of methyl ketones

Achievement of high asymmetric induction in boron-mediated aldol reactions of methyl ketones turns out to be an exceedingly challenging task, and chiral reagents capable of meeting this challenge are yet to be designed and synthesized. This section briefly summarizes the endeavors of the Masamune group toward this aim, with the hope that the data shown below are of some use for the future development of this methodology.

Diastereofacial selectivities have been examined for a set of external chiral boron reagents using a standard sequence of processes: (i) preparation of the enolates of methyl cyclohexyl ketone, pinacolone and methyl neopentyl ketone with the boron reagents, (ii) aldol reactions with isobutyraldehyde and (iii) determinations of enantiomer ratios. Selected examples are shown in Table 10. The diastereofacial selectivities (or enantioselectivities) of (**86**), (2*S*,5*S*)-(**90**), (2*R*,5*R*)-(**90a**), (**109**) and (**110**) are not significantly high; mostly in the range of 3:1–8:1 (50–70% *ee*), except for that shown in entry 6. These results suggest that use of the foregoing chiral reagents in the assembly of two chiral fragments will effectively enhance the stereoselectivity of the reaction in a matched case, but will not reverse its stereochemical course. Several trends are predictable: (i) when Ipc_2BOTf (**86**; entries 4 and 6) is used, the aldol reactions must be carried out at an elevated temperature (0 °C instead of –78 °C) to provide reasonable yields of products; and (ii) for a given boron reagent, *e.g.* (**86**) and (**90**), the more highly hindered ketone (pinacolone) undergoes aldol reactions with lower asymmetric inductions (compare entries 1 and 5, and 4 and 6).

Application of the external chiral boron reagent (**90**) in the total synthesis of bryostatin, a natural product, is shown in Scheme 45.[58] The convergent approach adopted involves coupling of the boron enolate derived from (**111**) with aldehyde (**112**). The reaction mediated by an achiral boron reagent (Et_2BOTf) provides only a 2:1 preference for the formation of the desired isomer (11*S*) in adduct (**113**). The use of chiral (2*R*,5*R*)-dimethylborolanyl triflate in this reaction increases the selectivity to a 6:1 preference as



(**86**) (2*S*,5*S*)-(**90**) (2*R*,5*R*)-(**90a**) (**109**) (**110**)

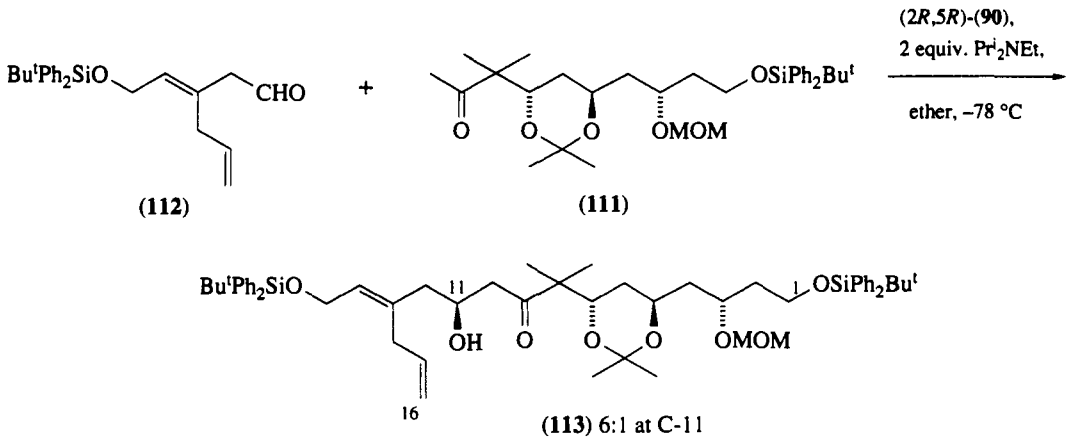
Table 10 Asymmetric Aldol Reaction of Ketones with Various Boron Reagents[a]

Entry	*Ketone*	*Boron reagent*	*Solvent*	*Reaction conditions*	*Isolated yield (%)*	*Configuration*	*Ee (%)*
1	MeCOc-C_6H_{11}	(*S*,*S*)-(**90**)	Pentane	–78 °C, 2 h	68	(*S*)	60
2	MeCOc-C_6H_{11}	(*R*,*R*)-(**110**)	Pentane	–78 to –65 °C, 7 h	76	(*R*)	56
3	MeCOc-C_6H_{11}	(*R*,*R*)-(**109**)	Pentane	–78 °C, 4.5 h	72	(*R*)	61
4	MeCOc-C_6H_{11}	(**86**)[b]	Pentane	0 °C, 2 h	54	(*R*)	77
5	$MeCOBu^t$	(*S*,*S*)-(**90**)	Pentane	–78 °C, 4 h	91	(*S*)	50
6	$MeCOBu^t$	(**86**)[b]	CH_2Cl_2	0 °C, 2 h	66	(*R*)	23
7	$MeCOCH_2Bu^t$	(*R*,*R*)-(**90a**)	CH_2Cl_2	–78 °C, 3 h	86	(*R*)	64

[a]Unless otherwise noted, the enolates are prepared by adding the boron reagent (1.2 equiv.) to a mixture of the ketone (1.0 equiv., 0.15–0.20 M) and Pr^i_2NEt (1.2 equiv.), isobutyraldehyde (1.5 equiv.) is then added to the enolate. [b]Prepared from (α)-(+)-pinene.

predicted for this matched reaction. In contrast, the mismatched reaction using the (2*S*,5*S*)-dimethylborolanyl triflate produces a 1:2 preference for the formation of the (11*R*) isomer.

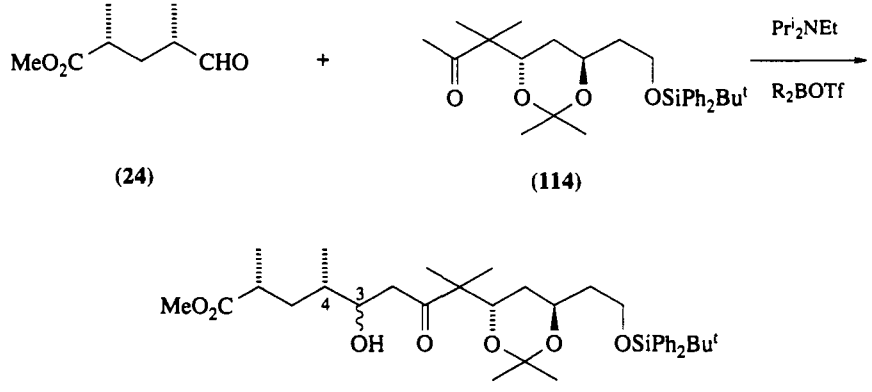
The stereochemical outcome for the assembly of the C(1)–C(16) fragment of bryostatin outlined above is consistent with the rule of double asymmetric synthesis. This suggests that the approximate multiplicativity of *ds* values may even apply to a reaction system involving three chiral components (triple asymmetric synthesis). To examine this possibility, Masamune *et al.*[59] have selected an aldol reaction involving (–)-aldehyde (**24**) and ketone (**114**) (enolate precursor), both of which are 3,4-*anti* selective, and each has a *ds* of *ca.* 2:1. As expected, the reaction with achiral diethylboryl triflate provides the aldol products (**115**) with a 7:1 *anti:syn* selection (Scheme 46). The chiral reagent (2*R*,5*R*)-(**90**) is matched with both (**24**) and (**114**) and its utilization in the aldol reaction enhances the above selection to 25:1, whereas the mismatched reaction of (2*S*,5*S*)-(**90**) leads to a 1:1 ratio of diastereomers. These results also support the approximate multiplicativity rule for triple asymmetric synthesis and assure that the fragment assembly can be stereocontrolled to secure either isomer with an external chiral reagent possessing a higher *ds*. The *ds* of (**90**) is approximated to be 5:1 in aldol reactions using methyl ketone enolates.



(**112**) (**111**)

(**113**) 6:1 at C-11

Scheme 45



(**24**) (**114**)

(**115**)

	3,4-anti:*3,4-syn*
$R_2BOTf = Et_2BOTf$	7:1
(2*R*,5*R*)-(**90**)	25:1
(2*S*,5*S*)-(**90**)	1:1

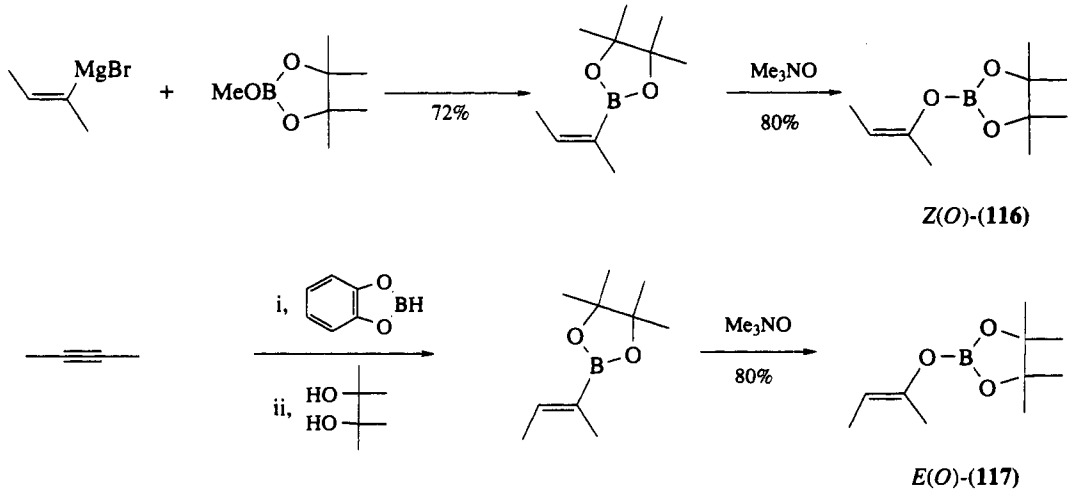
Scheme 46

1.7.2.4 Aldol Reactions Mediated by Alkenyloxydialkoxyboranes

The high degree of stereoselectivity achieved with alkenyloxydialkylboranes due to the tightness of the six-membered transition states has been amply discussed in an earlier section of this chapter. Hoffmann and Ditrich[60] investigated aldol reactions of alkenyloxydialkoxyboranes with the assumption that a decrease in the Lewis acidity of these reactants may lead to an even tighter transition state at a later stage of the reaction pathway. Either of the two stereoisomeric enolates can be prepared using different routes. The *Z(O)*-enolate (**116**) can be derived from (*Z*)-2-bromo-2-butene *via* a Grignard reaction as shown in Scheme 47. The preparation of *E(O)*-enolate (**117**) is achieved through a sequence of reactions involving hydroboration of 2-butyne with catecholborane, transesterification of the dialkoxyborane with pinacol and oxidation to (**117**). Aldol reactions of aldehydes with *Z(O)*-enolate (**116**) proceed very slowly (10–75 h at 25 °C) compared to those with typical alkenyloxydialkylboranes (several hours at –78 °C). The *Z(O)*-enolate (**116**) as expected yields *syn* products with aldehydes after work-up with triethanolamine (Table 11, entries 1–3). Unexpectedly, the *E(O)*-enolate (**117**) also provides *syn* diastereomers with a much enhanced rate ($t_{1/2} \approx 20$ min at –60 °C) as shown in entries 4–6. Thus, aldol reactions with (**116**) and (**117**) are stereoconvergent.

Alkenyloxydialkoxyboranes can also be generated from the corresponding silyl enolates, either directly or *via* the lithium enolates.[60] The slow reaction of *Z(O)*-enolate (**116**) with aldehydes can be accelerated with the aid of a catalytic amount (10–20 mol %) of trimethoxyborane.[60] This acceleration is presumably due to a facile transesterification that converts (**116**) into the more reactive alkenyloxydimethoxyborane.

Several reports by Gennari *et al.*[61] describe the generation of enolates directly from carbonyl compounds by using ethylenedioxychloroborane (*B*-chloro-2,5-dioxaborolane; **118**) in the presence of diisopropylethylamine. Reactions of these enolates, derived from ketones and thiol esters, with aldehydes provide good yields (60–85%) of aldol adducts, whereas esters give unsatisfactory yields (~30%). When ethyl ketones or propanethioates are employed, *Z(O)*-enolates (**119**) can be formed exclusively using specific reaction conditions,[62] and excellent *syn* selectivities (92:8 to 99:1) are observed (Scheme 48).



Scheme 47

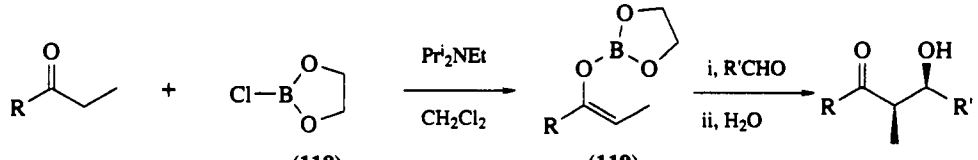
Table 11 *Syn:Anti* Ratios of Aldol Products From the Reaction of *Z(O)*- and *E(O)*-Alkenyloxydialkoxyboranes with Representative Aldehydes

Entry	*Dialkoxyboryl enolate*	*Aldehyde*	*Yield (%)*	*Syn:anti ratio*
1	*Z(O)*-(**116**)	PhCHO	89	>95:5
2	*Z(O)*-(**116**)	Pr^{i}CHO	85	91:9
3	*Z(O)*-(**116**)	EtCHO	88	88:12
4	*E(O)*-(**117**)	PhCHO	79	95:5
5	*E(O)*-(**117**)	Pr^{i}CHO	86	90:10
6	*E(O)*-(**117**)	EtCHO	82	90:10

Z(*O*)-Enolates are readily equilibrated to the corresponding *E*(*O*)-isomers in the presence of a protonated amine.

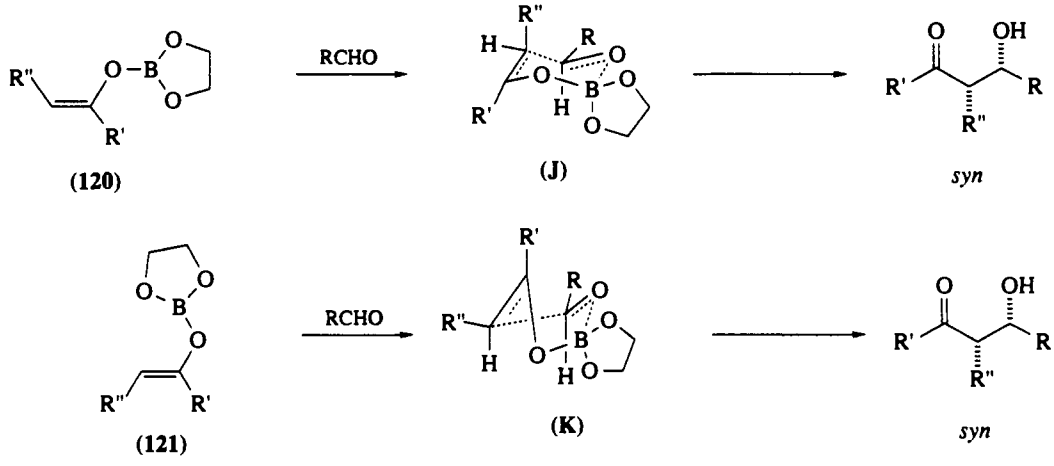
To explain the *syn* selectivity for the reactions of both *Z*(*O*)- and *E*(*O*)-enolates derived from (**118**), Gennari *et al.* suggested a chair-like transition state (**J**) for *Z*(*O*)-enolates and a boat-like transition state (**K**) for *E*(*O*)-enolates (Scheme 49).[62,63] Computational studies undertaken later by the same group[64] on aldol reactions using enolates (**120**) and (**121**), as well as dialkylboryl enolates, provided a set of data that was consistent with the experimental results and further corroborated the proposed mechanism. Thus: (i) The ground-state conformations of the enolates are important in determining the different reactivities of *Z*(*O*)-enolates (**120**) and *E*(*O*)-enolates (**121**), the latter are much more reactive than the former. (ii) The energy requirements for the reactions with aldehydes indicate that *Z*(*O*)-enolates prefer half-chair transition states, while *E*(*O*)-enolates favor half-boat transition states. Both transition states lead to the formation of *syn* aldol products. (iii) In contrast, when dialkylboryl enolates are used, bulky substituents on the boron atom disfavor the twist-boat for both *E*(*O*)- and *Z*(*O*)-enolates, resulting in the formation of *anti* and *syn* isomers, respectively (Section 1.7.2.2).

An attempt to accomplish asymmetric induction using a dialkoxyboryl enolate has been made by Chow and Seebach.[24] Reaction of the alkenyloxydialkoxyborane (**122**) derived from (–)-(*S*)-1,1′-bi-2-



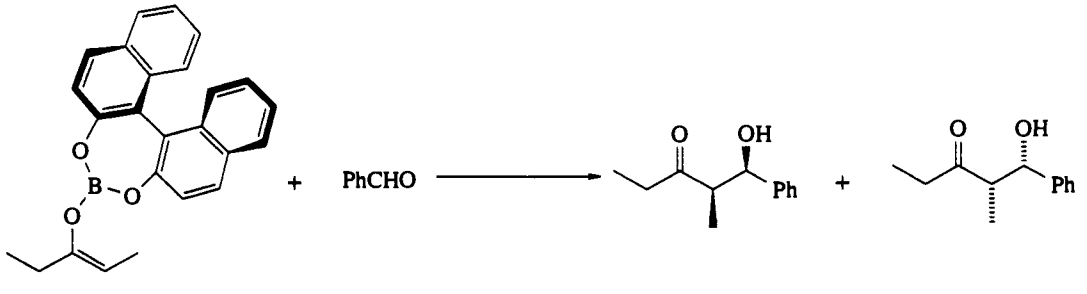
(**118**) (**119**)

Scheme 48



(**120**) (**J**) (**121**) (**K**)

Scheme 49



(**122**)

Scheme 50

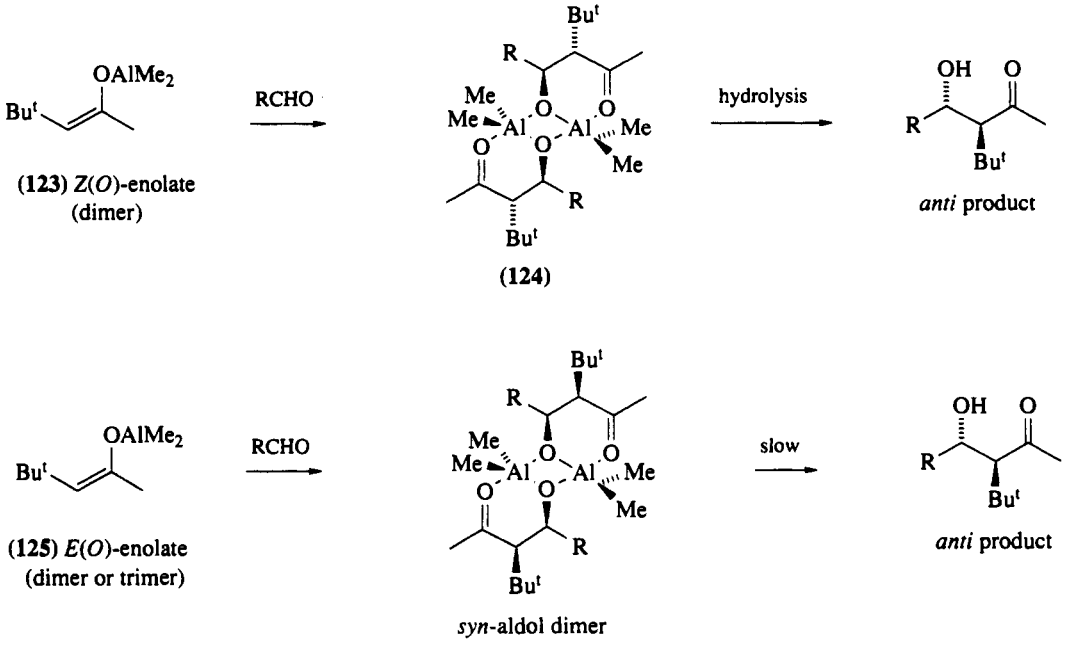
naphthol with benzaldehyde provides the *syn* aldol product in 47% *ee* (Scheme 50). The absolute configuration of this product is not recorded.

1.7.3 ALUMINUM-MEDIATED ALDOL REACTION

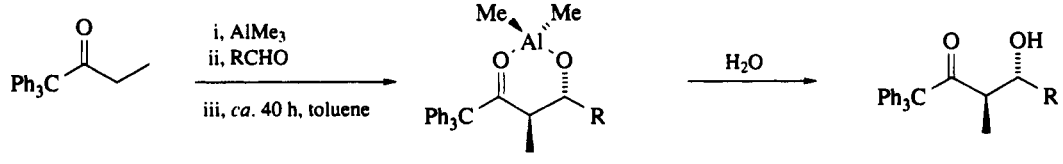
1.7.3.1 Preparation of Alkenyloxyalanes and Subsequent Aldol Reactions

Aluminum oxide has been one of the most frequently used reagents for self-condensation of ketones and aldehydes.[65] However applications of aluminum-mediated aldol reactions to cross-coupling have appeared only recently in the literature. Aluminum reagents, in common with other Lewis acids, form aldol product chelates so that unwanted side reactions such as dehydration or secondary condensation may be avoided.[66]

In 1974, Jeffery *et al.* reported the first use of well-defined dimeric or trimeric aluminum enolates in the aldol reaction.[67,68] Reaction of dimethyl-*Z*(*O*)-4,4-dimethylpent-2-en-2-oxyalane (**123**) with acetaldehyde or benzaldehyde provides the *anti* aldol products (**124**) as chelated dimers involving five-coordinate aluminum atoms, as shown in Scheme 51. However, the corresponding *E*(*O*)-enolate (**125**) gives dimeric products of *syn* configuration which undergo isomerization, if not hydrolyzed immediately, to provide the same *anti* products.[69] This *syn–anti* isomerization is much more facile with benzaldehyde, and is in sharp contrast to aldol reactions mediated by boron.



Scheme 51



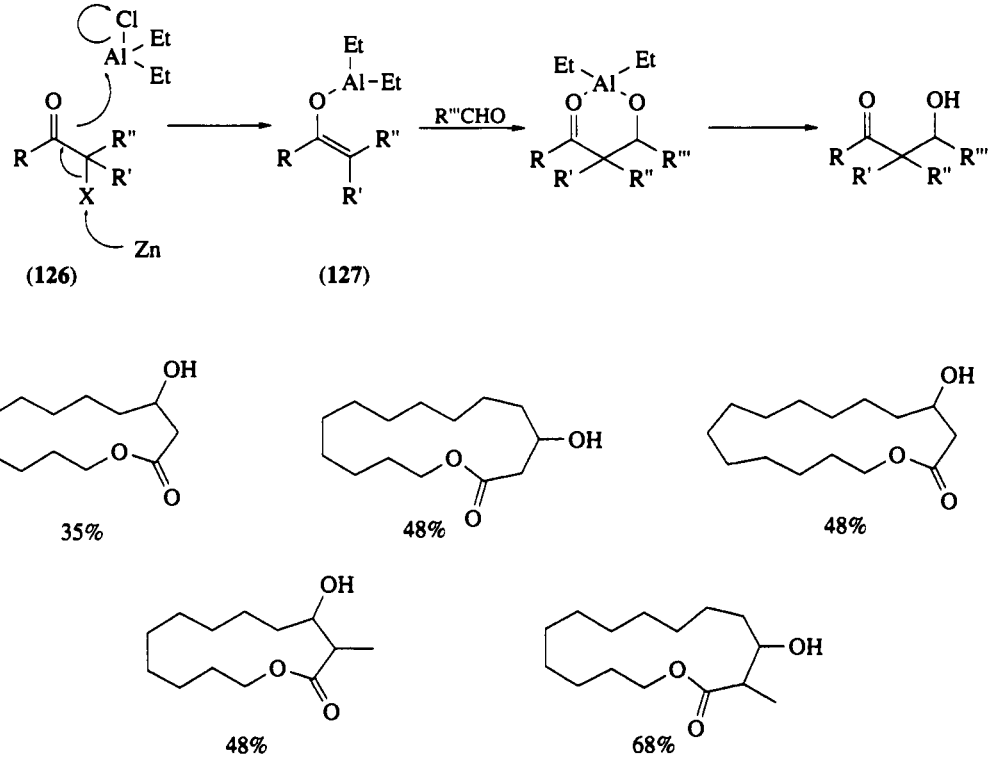
Scheme 52

Ertas and Seebach[70] have studied the *syn–anti* isomerization of aldol adducts chelated to aluminum for the reaction of ethyl trityl ketone with aldehydes in the presence of trimethylaluminum (Scheme 52).

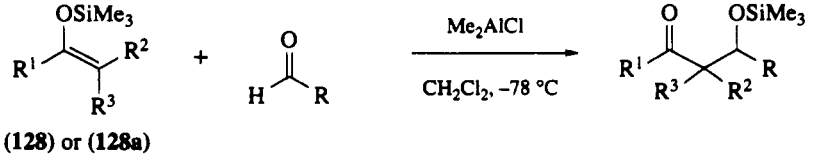
Aldol reactions involving aluminum species are considered to be of less synthetic value because of the ambiguous isomerization of the aldol products, under the influence of the Lewis-acidic aluminum species. Efforts have been made to generate an aluminum enolate in a regiospecific manner. Addition of dialkylchloroalane and zinc to a mixture of an α-halo ketone (**126**) and an aldehyde leads to the formation of enolate (**127**), which subsequently reacts with the aldehyde, as shown in Scheme 53.[71] This method is applicable to the construction of medium to large rings by intramolecular aldol cyclization of various α-bromocarboxylates of ω-hydroxy aldehydes (*e.g.* $BrCHRCO_2(CH_2)_nCHO$ where $n = 9$, 11 or 12 and R = H or Me). The macrolactonization proceeds in reasonable yield, as shown in Scheme 53.

A new procedure for the preparation of β-trimethylsilyloxy ketones and esters from silyl enolates (**128**) and silyl ketene acetals (**128a**; $R^1 = OPr^i$) has been developed by Yamamoto *et al.* (Scheme 54).[72] Good to excellent yields of protected aldol products are obtained using a catalytic amount (0.05–0.1 equiv.) of dimethylaluminum chloride. However, only a small degree of diastereoselectivity is obtained even when silyl enolates of high stereochemical purity are used.

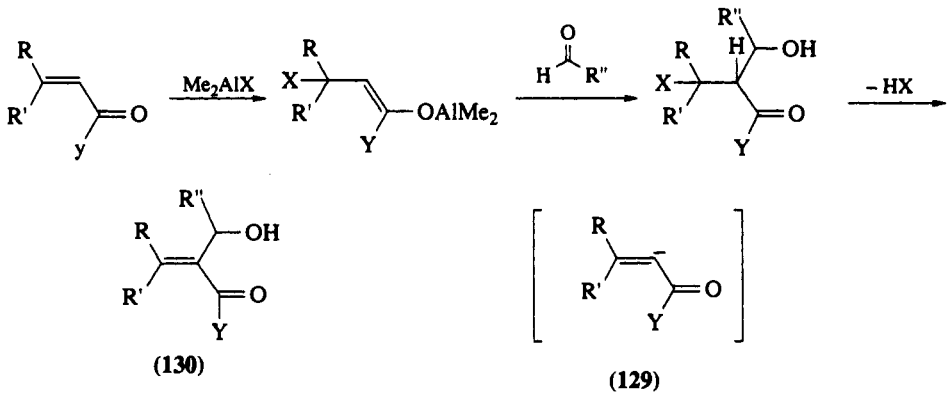
In a manner analogous to the earlier boron work (Section 1.7.2.1), an effort has been made to generate alkenyloxyalanes from α,β-unsaturated carbonyl compounds by 1,4-addition of aluminum reagents.[73] The addition of Me_2AlSPh or $Me_2AlSeMe$ to an α,β-unsaturated carbonyl compound produces a 3-substituted alkenyloxyalane derivative, which upon reaction with an aldehyde gives a crossed aldol product,



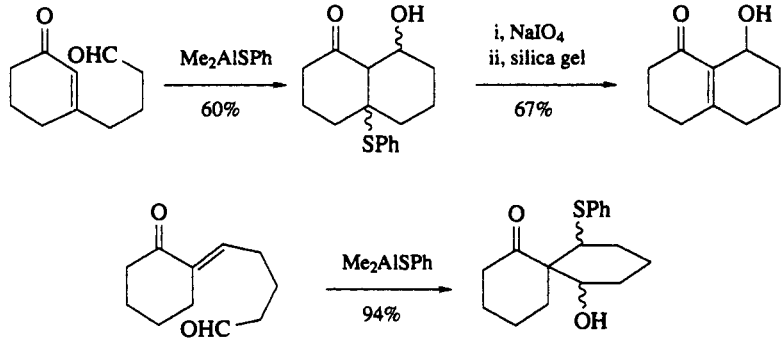
Scheme 53



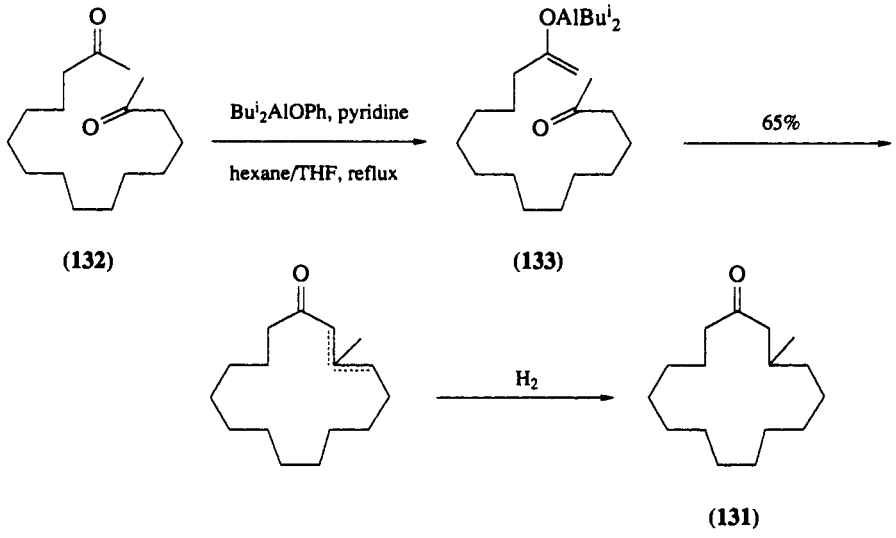
Scheme 54



Scheme 55



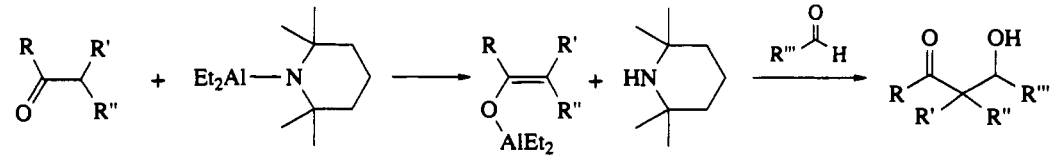
Scheme 56



Scheme 57

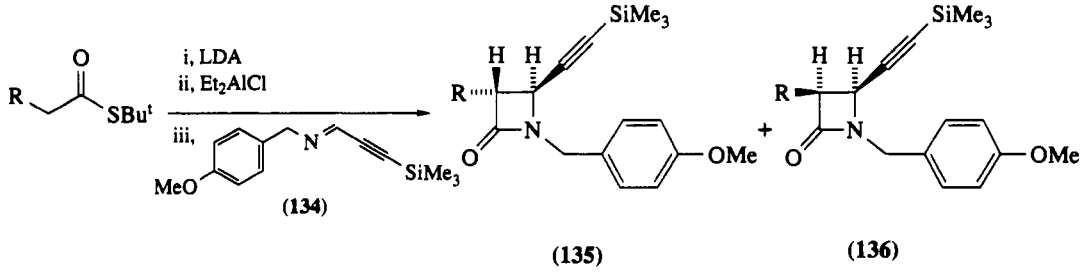
as shown in Scheme 55. The overall transformation is viewed as addition of the acylethenyl anion (**129**) to the aldehyde to form (**130**). The application of this method is exemplified in Scheme 56.

Regioselective aldol reactions can be achieved with organoaluminum reagents, and a good example of this application is in the synthesis of muscone (**131**; Scheme 57).[74] The key step involves macrocycli-



55–92% yields

Scheme 58



anti:*syn* 3:1 ~ 4:1

Scheme 59

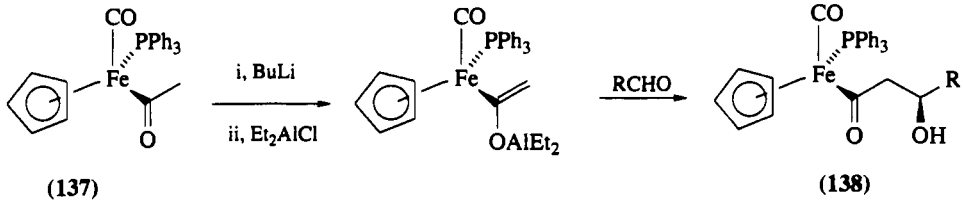
zation of the diketone (**132**), which uses diisobutylphenoxyalane and pyridine to furnish the kinetic enolate (**133**). The desired intramolecular aldol reaction of (**132**) is difficult to achieve by other methods.

A similar method for the formation of enolates derived from esters and ketones uses diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), as shown in Scheme 58.[75]

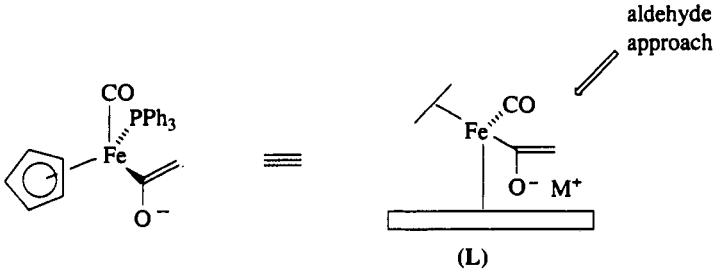
Reaction of an alkenyloxydiethylalane with an imine has been reported by Iwasaki and Shibasaki (Scheme 59).[76] The diethylaluminum enolate derived from *S*-*t*-butyl alkanethioate, upon reaction with imine (**134**), furnishes β-lactams (**135**) and (**136**) in an *anti* selective manner.

1.7.3.2 Aldol Reactions Using Enantiomerically Homogeneous Alkenyloxydialkylalanes

Davies[77] and Liebeskind[78] independently prepared chiral aluminum enolates from enantiomerically homogeneous acyl–iron complexes (**137**) and recorded the first aluminum-mediated asymmetric aldol reactions. Although the lithium enolate of the chiral iron complex (CHIRAC) provides aldol products with



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



(**L**)

Scheme 60

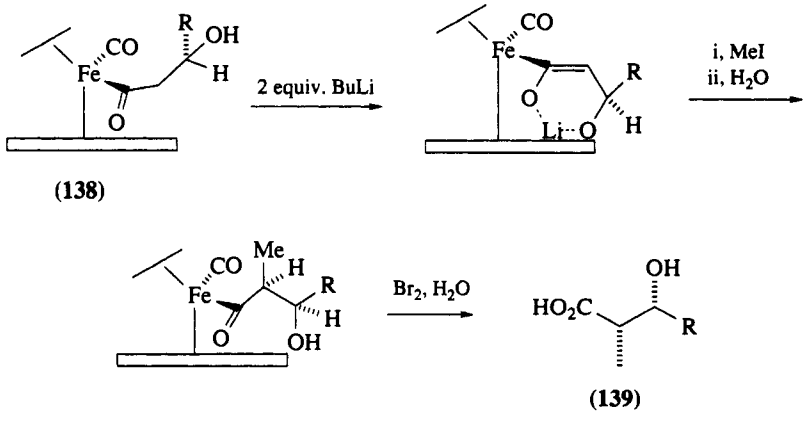
low diastereoselectivity, the corresponding aluminum enolate species prepared by adding chlorodiethylalane to the lithium enolate gives aldol products (**138**) with high selectivity (~20:1 to 100:1). A rationale for the observed high selectivity is based on the facial selectivity of the enolate of the enantiomerically homogeneous iron complex as shown in Scheme 60 (conformation **L**).

This facial selectivity can also be utilized in alkylation reactions of the β-hydroxy aldol products (**138**), so that overall a chiral propionate aldol unit is formed, as shown in Scheme 61.[77,79] The final products are *syn*-α-methyl-β-hydroxycarboxylic acids (**139**).

Asymmetric aldol reactions are also possible with chiral propanoyl–iron complexes, as shown in Scheme 62.[80] Good to excellent stereoselectivities for *anti* aldol products (**140**) are obtained when the lithium enolate of the propanoyl–iron complex is treated with 3 equiv. of Et_2AlCl at –40 °C, followed by an aldehyde at –100 °C. Interestingly the same reaction using CuCN instead of Et_2AlCl provides exclusively *syn* aldol products (**141**).

Recently Ojima and Kwon[81] reported aldol reactions of a chiral iron–acyl complex possessing a pentafluorophenyl group on the phosphine ligand. In contrast with the CHIRAC complex, this newer complex, $[(C_6F_5)Ph_2P](CO)CpFeCOMe$ (PFCHIRAC) provides, upon reaction with aldehydes, product (**142**) with high stereoselectivity (89–99% *de*) regardless of the metal enolate species (Scheme 63). Furthermore, while an aluminum enolate prepared by direct metal exchange exhibits moderate selectivity (8:1) in the aldol reaction with benzaldehyde, addition of the lithium enolate to a mixture of an aldehyde and chlorodiethylalane greatly enhances the diastereoselectivity of the reaction.

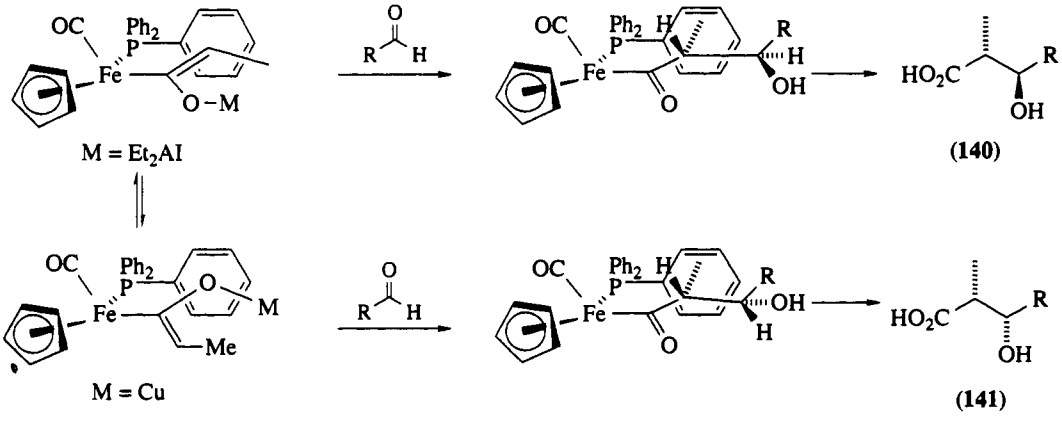
A variable temperature NMR (^1H, ^{19}F and ^{31}P) study on the dynamic behavior of PFCHIRAC has allowed a rationalization of the unique stereodifferentiation and opposite sense of asymmetric induction observed with this complex, compared to the CHIRAC complex. Thus, a highly selective generation of the *endo* (or *syn*) enolate (**143**) in the PFCHIRAC system is suggested to be due to an electron donor—



(**138**)

(**139**)

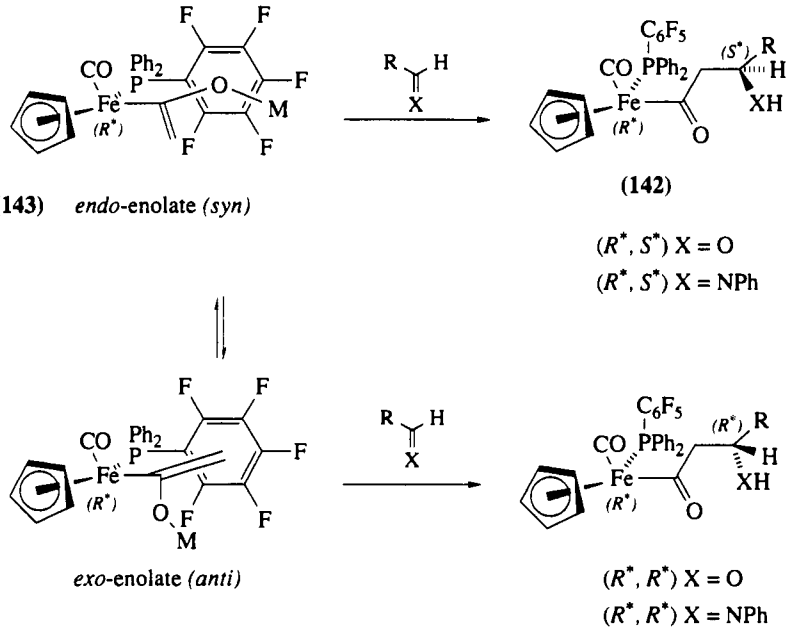
Scheme 61



(**140**)

(**141**)

Scheme 62



Scheme 63

acceptor type attractive interaction between the pentafluorophenyl moiety (electron acceptor) and the enolate oxygen (electron donor).

1.7.4 REFERENCES

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1.8
Zinc Enolates: the Reformatsky and Blaise Reactions

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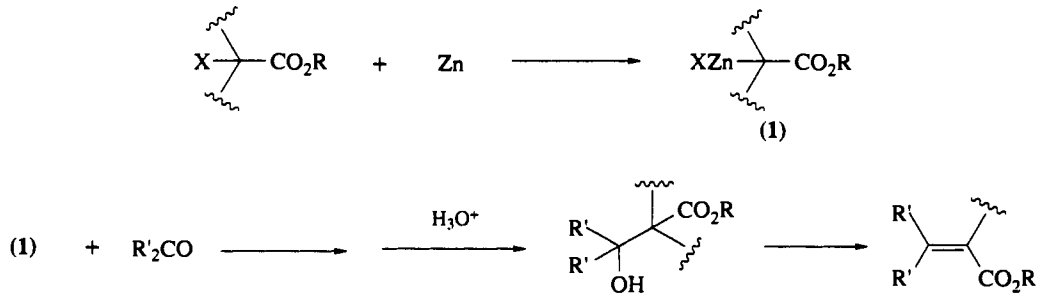
1.8.1 INTRODUCTION

The Reformatsky reaction is the reaction of an α-halo ester with an aldehyde or ketone in the presence of zinc metal as shown in Scheme 1. The usual product of the reaction is a β-hydroxy ester, which may be dehydrated in subsequent steps to give an unsaturated ester. A zinc ester enolate (**1**), the so-called Reformatsky reagent, is an intermediate in the reaction and the sequence is thus classified as an aldol condensation. Compared to the usual base-promoted aldol procedures, the distinguishing features of the Reformatsky reaction are the use of a metal–halogen redox reaction rather than an acid–base reaction to form the enolate, and the fact that the counterion of the enolate is zinc.

Assuming ready availability of the α-halo ester component, the Reformatsky reaction is often a convenient and economical alternative to base-promoted aldol procedures. Since its discovery in 1887,[1] over 500 research articles and six reviews[2–7] of the reaction have been published. Heathcock has recently reviewed the stereochemistry of the reaction of a variety of zinc enolates with aldehydes and ketones.[8]



Scheme 1

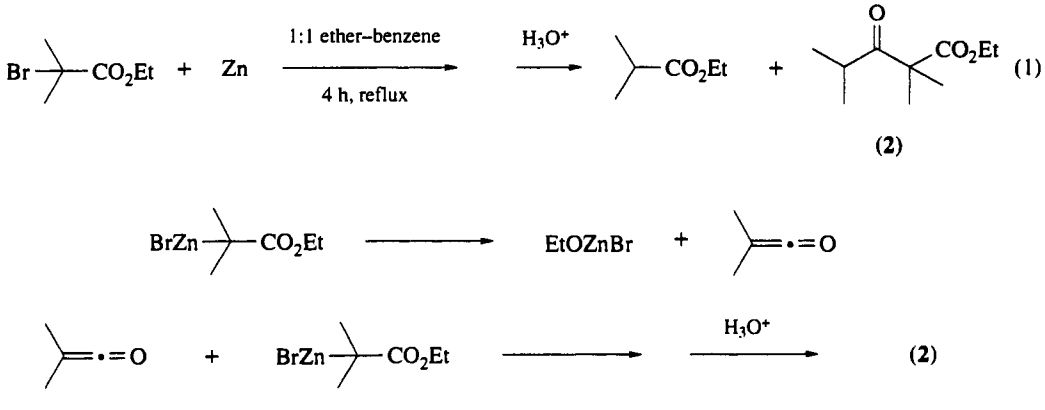
This chapter summarizes studies on the nature of the Reformatsky reagent as well as other, related, zinc enolates and outlines the synthetic aspects of the reaction with aldehydes and ketones. In addition, reactions of the Reformatsky reagent with imines and nitriles (the Blaise reaction) are described.

1.8.2 NATURE OF THE REFORMATSKY REAGENT

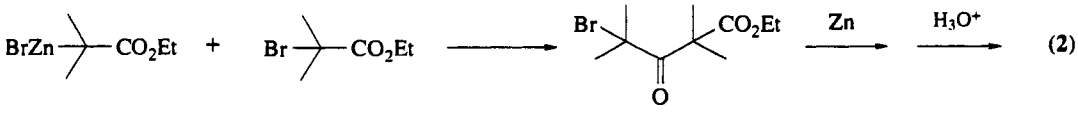
1.8.2.1 Isolation and Stability of Zinc Enolates

The Reformatsky reaction is most commonly conducted in a single step by addition of a mixture of α-halo ester and carbonyl substrate to a suspension of zinc in a suitable solvent. This one-stage procedure clearly minimizes any problems due to instability of the Reformatsky reagent. Since 1953,[9] solutions of the reagent have occasionally been prepared, with varying degrees of success, by reaction of the α-halo ester with zinc in an initial separate step of a two-stage procedure.

The first detailed examination of a Reformatsky reagent was described in 1965 by Vaughan and co-workers,[10] who prepared a solution of the reagent from ethyl α-bromoisobutyrate. Hydrolysis of the freshly prepared solution gave ethyl isobutyrate (from the Reformatsky reagent) and the so-called 'condensed ester', ethyl isobutrylisobutyrate (**2**; equation 1). Refluxing the reaction mixture for longer periods prior to hydrolysis gave a gradual decrease in ethyl isobutyrate and a corresponding increase in (**2**). Vaughan[11] proposed that the zinc ester enolate decomposed by loss of EtOZnBr to form a ketene intermediate, which subsequently formed condensed ester (Scheme 2). A similar formation of ketenes from



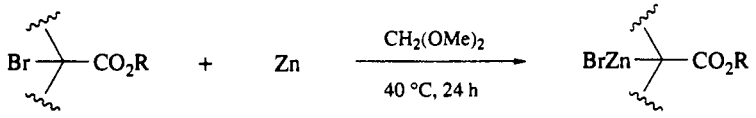
Scheme 2



Scheme 3

lithium ester enolates has been well documented.[12,13] It is also possible that at least some of the condensed ester is produced by a direct condensation as suggested earlier by Newman and Hussey (Scheme 3).[14]

According to Gaudemar and Curé,[5,15] dimethoxymethane is an especially useful solvent for two-stage reactions and they report yields of 70–80% for the Reformatsky reagents derived from a variety of α-bromo esters (equation 2); however, the procedure was unsatisfactory with ethyl α-bromopropionate, methyl α-bromophenylacetate and phenyl α-bromoisobutyrate. The zinc enolates were generally used shortly after preparation and no data on their stability in this solvent were reported.

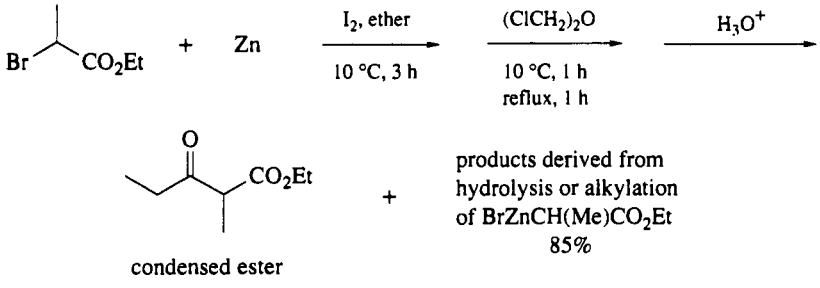


(2)

Orsini and coworkers[16,17] obtained $BrZnCH_2CO_2Bu^t \cdot THF$ in 80% yield as a colorless crystalline solid by reaction in THF at 25–35 °C. They described the reagent as mostly unchanged after 4–6 d in a number of solvents, with a slow hydrolysis to *t*-butyl acetate and a gradual formation of Bu^tOZnBr. Using the same procedure, $BrZnCHMeCO_2Bu^t$ and $BrZnCMe_2CO_2Bu^t$ were isolated as THF complexes. They were described as stable in THF for a few hours and in pyridine and in DMSO for about 10–15 min, after which time an abundant precipitate of $BrZnOBu^t$ was present.

Orsini and coworkers[16] obtained primarily 'condensed ester' from the reaction of methyl α-bromopropionate with zinc in a variety of solvents; however, Johnson and Zitsman[18] evidently obtained the reagent from ethyl α-bromopropionate in good yield by conducting the reaction at a lower temperature in ether (equation 3).

It seems likely that many simple α-bromo esters can be reacted with zinc to produce the Reformatsky reagent nearly quantitatively, and that the reagent forms condensed ester primarily in a subsequent step. A successful synthesis of a Reformatsky reagent should then depend strongly on the time and temperature required for the preparation. Recently, a number of methods, including ultrasound promotion[19] and the use of highly active forms of zinc,[20] have allowed completion of the Reformatsky sequence in



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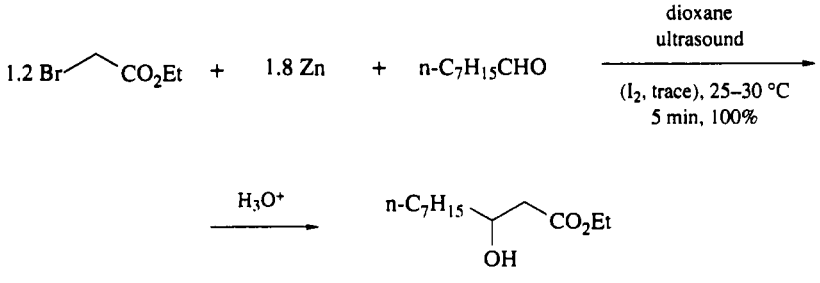

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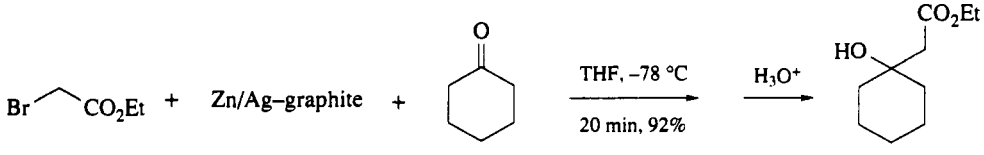
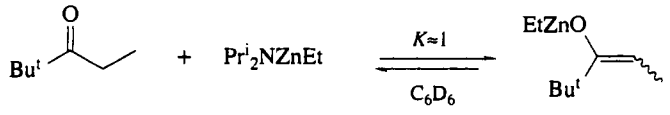


(5)

$$MeCO_2Bu^t \xrightarrow[\text{ii, } ZnCl_2\text{, ether, } -70\ ^\circ C]{\text{i, } NaNH_2\text{, } NH_3\ (l)} ClZn\diagup\!\!\diagdown CO_2Bu^t \qquad (6)$$



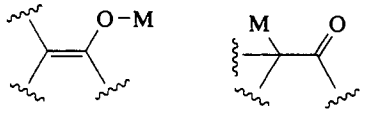
(7)

remarkably short times and at low temperatures. However, these methods have so far been applied only to one-stage procedures (equations 4[19] and 5[21]).

Zinc ester enolates may also be obtained by the addition of ZnX_2 to lithium or sodium enolates as first described by Hauser and Puterbaugh (equation 6).[22] This approach has so far received little attention but similar reactions have been used to obtain zinc ketone enolates.[22,23] In this regard, it should be noted that Heathcock and coworkers[24] have shown that deprotonation reactions of ketones with zinc dialkylamide bases reach equilibrium at only about 50% conversion (equation 7). This result implies that attempts to prepare zinc enolates from solutions of amide-generated lithium enolates will be successful only when the lithium enolate is made amine-free.

1.8.2.2 Structure of Zinc Enolates

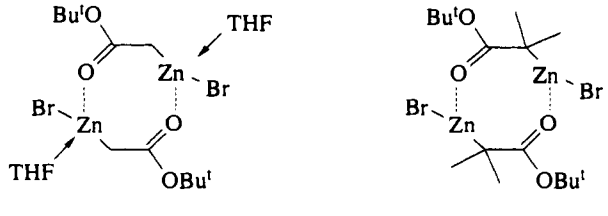
Metal enolates may have structures with either a metal–oxygen (**3**) or a metal–carbon (**4**) bond. Lithium enolates typically have oxygen-bonded structures,[25] while mercury enolates are usually assumed to have carbon-bonded structures.[26]



(3) (4)

From a crystallographic study of the Reformatsky reagent obtained from *t*-butyl α-bromoacetate, Boersma and coworkers[27] reported the carbon-bonded dimeric structure (**5**). Based on ebulliometric and cryoscopic molecular weight measurements, the dimeric structure persists in solvents of medium coordinating power (THF, DME, dioxane, dimethoxymethane and pyridine), but the reagent is monomeric in strongly coordinating solvents (HMPA and DMSO). Spectral data[16] are also consistent with a carbon-bonded structure for the reagent in solution (Table 1). The spectral differences observed between the solvents THF and DMSO are consistent with the presence (THF solution) or absence (DMSO solution) of zinc coordination to the carbonyl oxygen of a carbon-bonded structure, as first suggested by Gaudemar and Martin.[28] In strongly coordinating solvents, the carbonyl frequency of a variety of Reformatsky reagents appears just below 1700 cm^{-1}, close to the normal value for ester carbonyls.[28] It is interesting to note that a dimeric structure (**6**) completely analogous to (**5**) was considered in 1970 for the Reformatsky reagent obtained from ethyl α-bromoisobutyrate and discarded, based on the failure of the reagent to react with Grignard reagents.[11] Clearly, with sufficient ionic character to the metal bonds, the reactivity of a carbon-bonded enolate to any reagent must approach that of the corresponding oxygen-bonded enolate.

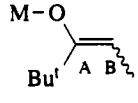
No crystallographic structure has been reported for zinc ketone enolates. Although carbon-bonded structures analogous to (**5**) have been proposed,[27] spectral data obtained for the bromozinc and ethylzinc



(5) (6)

Table 1 Spectral Data for $BrZnCH_2CO_2Bu^t$

Spectrum	*Solvent*	*Signal (assignment)*
^1H NMR $BrZnCH_2CO_2C(CH_3)_3$ A B		p.p.m. relative to Me_4Si
	THF	1.88 (A), 1.40 (B)
	DMSO	1.04 (A), 1.30 (B)
^{13}C NMR $BrZnCH_2CO_2C(CH_3)_3$ A B C D		p.p.m. relative to Me_4Si
	THF	22.7 (A), 186.2 (B), 80.4 (C), 27.6 (D), $J(C_1—H_\alpha)$ 132 Hz
	DMSO	20.8 (A), 177.4 (B), 75.3 (C), 28.6 (D) $J(C_1—H_\alpha)$ 128.6 Hz
IR		cm^{-1}
	THF	1580 (C=O)
	DMSO	1660 (C=O)



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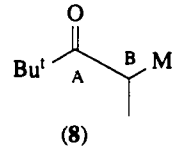
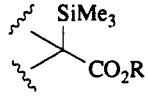


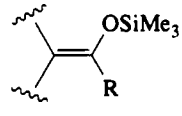
(8)

Table 2 NMR Spectral Data for Enolates (7) and (8)

M	*Solvent*	*Chemical shifts (p.p.m.)* C_A	C_B	H_α	$J(C_B—H_\alpha)$ *(Hz)*	*Ref.*
ZnEt	THF-d_8	165.5	93.0	4.41	155	24
ZnBr	THF	164.7	96.6	—	—	29
MgBr	Ether	162.4	95.5	4.54	154	30
Li	Benzene	169	84	—	—	31
HgBr	Benzene	213	51	—	140	31



(9)



(10)

enolates of 2,2-dimethyl-3-pentanone seem most consistent with oxygen-bonded (7) rather than carbon-bonded (8) structures. The chemical shifts and C—H coupling constants are close to the oxygen-bonded lithium or magnesium enolates and not to the presumably carbon-bonded mercury enolates (Table 2).[24]

The preference of zinc ester enolates for carbon-bonded structures and zinc ketone enolates for oxygen-bonded structures is reminiscent of the situation with silicon. A carbon-bonded structure (9) is the thermodynamically more stable form for the trimethylsilyl derivatives of esters, while the oxygen-bonded structure (10) is the more stable form for ketone derivatives. This has been attributed to the greater resonance stability of ester compared to ketone carbonyls.[32]

1.8.3 REACTION WITH ALDEHYDE AND KETONE SUBSTRATES

1.8.3.1 Scope and Procedures

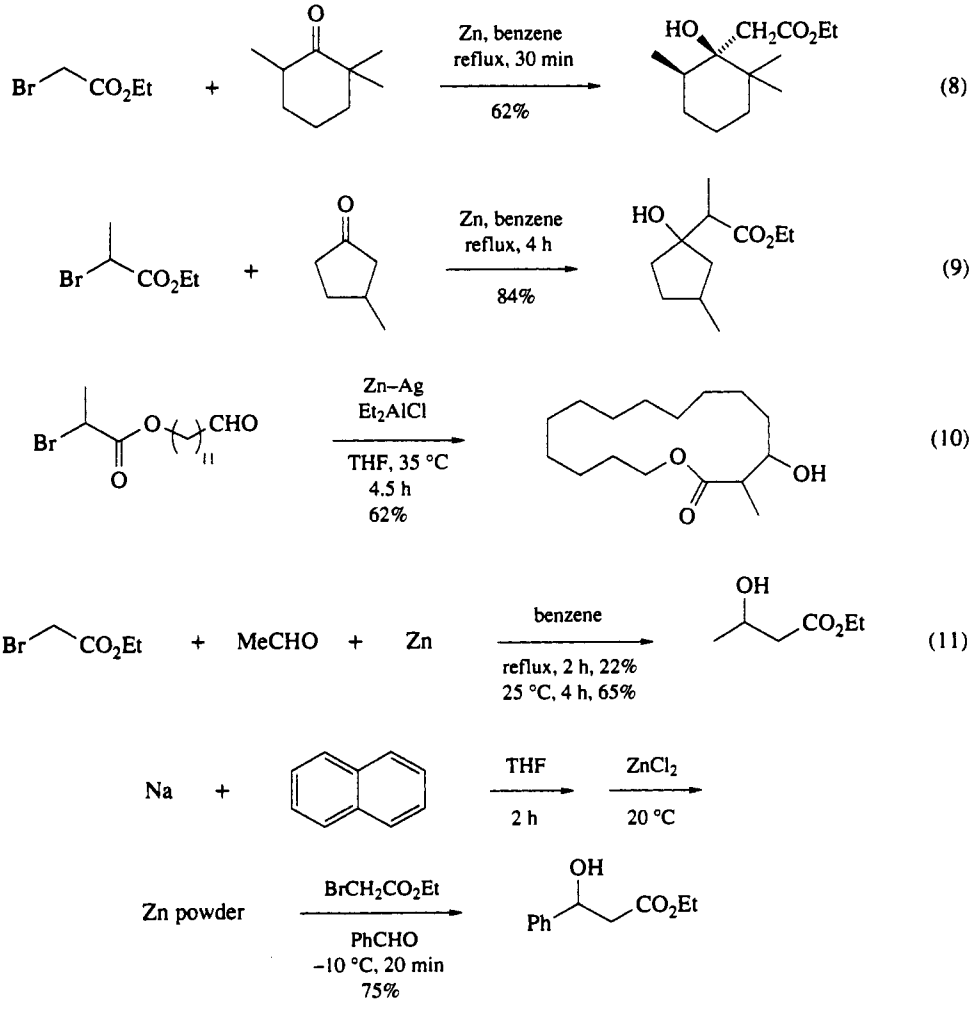
Reformatsky reactions of more than 500 different aldehydes and ketones have been tabulated.[2,5,7] One of the significant features of the Reformatsky reaction is that it succeeds even with highly hindered

ketones (equation 8).[33] It is one of the few successful methods[34] for the addition of carbon nucleophiles to the readily enolized cyclopentanone ring system (equation 9).[35]

Because the Reformatsky sequence allows the generation of an ester enolate in the presence of an enolizable aldehyde or ketone, it is uniquely suited for intramolecular aldol reactions.[36–40] The transformation shown in equation (10) would be difficult to accomplish by conventional base-promoted aldol methods.[40]

Single-stage procedures are most commonly used for the Reformatsky reaction with aldehydes and ketones. A mixture of α-halo ester and carbonyl substrate is added to a suspension of zinc at a rate sufficient to maintain the reaction. In the original procedure of Reformatsky,[1] no solvent was used but modern practice is to use benzene or an ether solvent such as diethyl ether, THF, glyme or dimethoxymethane. The reaction is often conducted at reflux temperature, probably to avoid surges from the highly exothermic nature of the reaction. However, in a comparison with a number of aldehydes and ketones, much higher yields were obtained at room temperature than at reflux in benzene (equation 11).[41]

The zinc metal is typically activated before use and methods for accomplishing this have been reviewed.[20] The use of highly reactive forms of zinc (Reike powders), obtained by reduction of zinc salts with an alkali metal, detracts from the convenience of the classical procedure but much higher yields have been obtained, at least with the simple substrates that have so far been examined. One of the most convenient preparations of a Reike powder uses sodium naphthalide, as shown in Scheme 4.[42] Reactive zinc powders also allow the use of α-chloro esters which are unsatisfactory with the usual forms of zinc.[20]

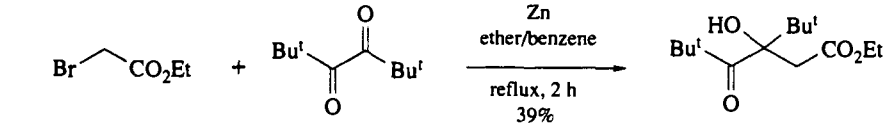


Scheme 4

1.8.3.2 Chemoselectivity

In addition to aldehydes and ketones, organic compounds which are known to react with Reformatsky reagents include: esters,[43] nitriles,[44] acid chlorides,[43] organic halides,[17,45] epoxides,[46] nitrones,[47] azirenes[48] and imines.[49] This section describes the selectivity reported for Reformatsky reactions with functionally substituted aldehydes or ketones.

Symmetrical diketones react normally with either one (equation 12)[50] or two (equation 13)[51] equivalents of the Reformatsky reagent. There are no reports of selective reaction at a single carbonyl of an unsymmetrical substrate, although this has been accomplished by selective acetal protection (Scheme 5).[52]



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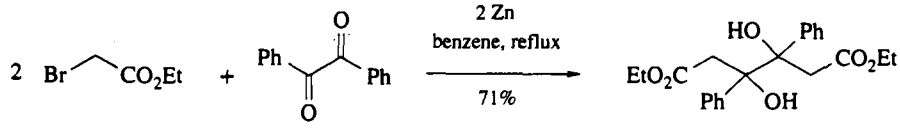

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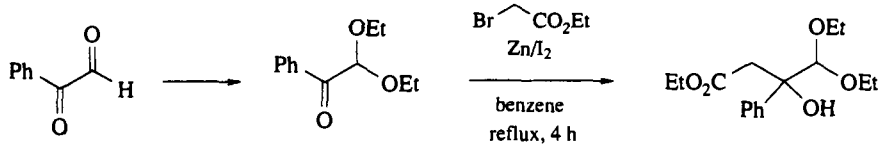
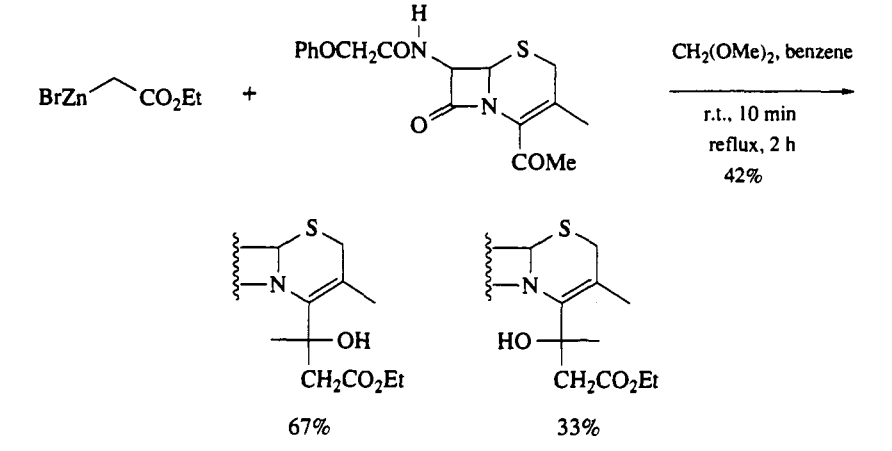
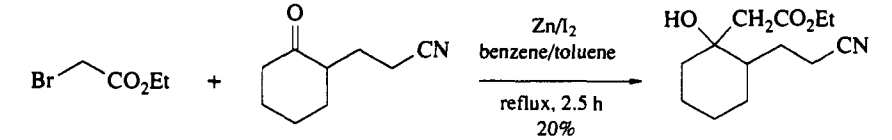


Scheme 5



(14)



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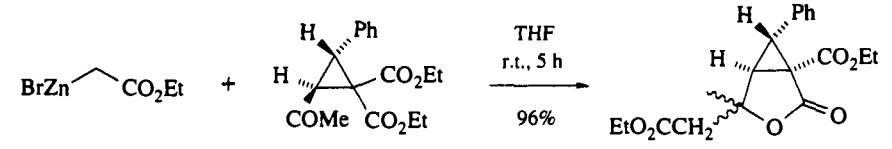
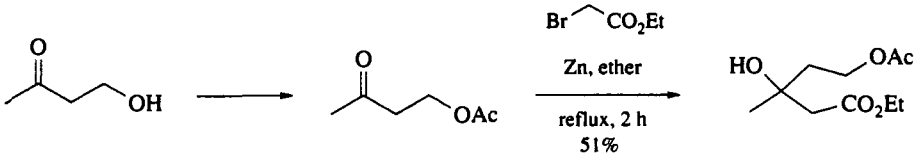


(16)

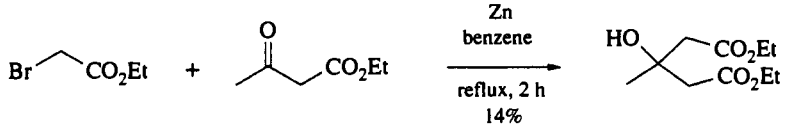
Ketoamides,[53] ketonitriles[54] and keto esters[55] may all be reacted selectively at the ketone function (equations 14–16). In fact, esterification was found to be the best of several hydroxy-protecting methods for the transformation shown in Scheme 6.[56]

Ethyl acetoacetate gave only low yields in a Reformatsky reaction[57] but even this is remarkable considering its acidic nature (equation 17). β-Keto esters that lack acidic hydrogens react in good yield (equation 18).[58]

Halogen can be tolerated either in the carbonyl substrate or in the bromo ester component of the Reformatsky reaction. It is noteworthy that the intermediate zinc aldolate (**11**) does not internally substitute halogen until HMPA is added (Scheme 7).[39] For reactions with α-halo ketone substrates in a Δ^1-buten-



Scheme 6



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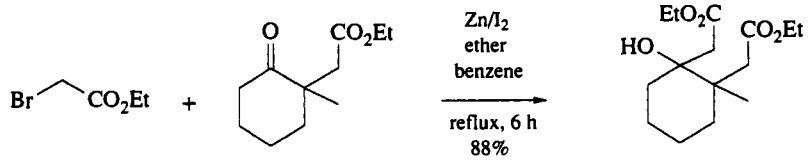

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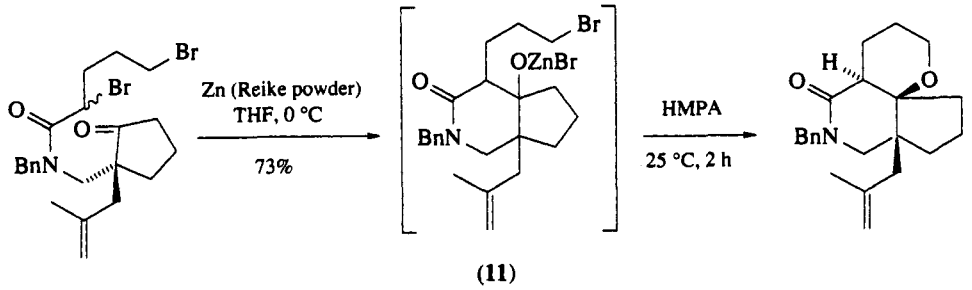
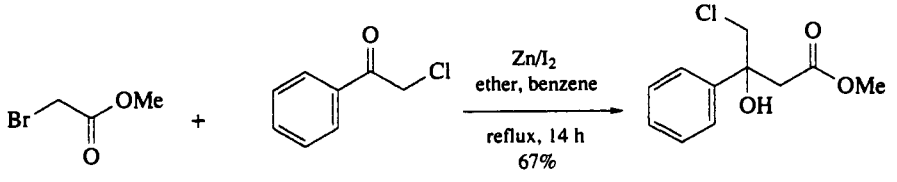


(**11**)

Scheme 7



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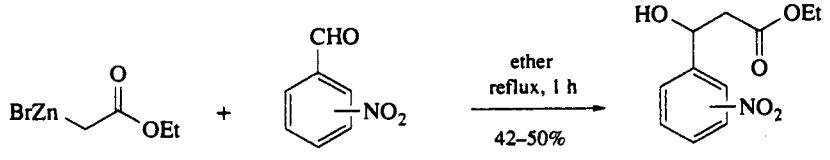


(20)

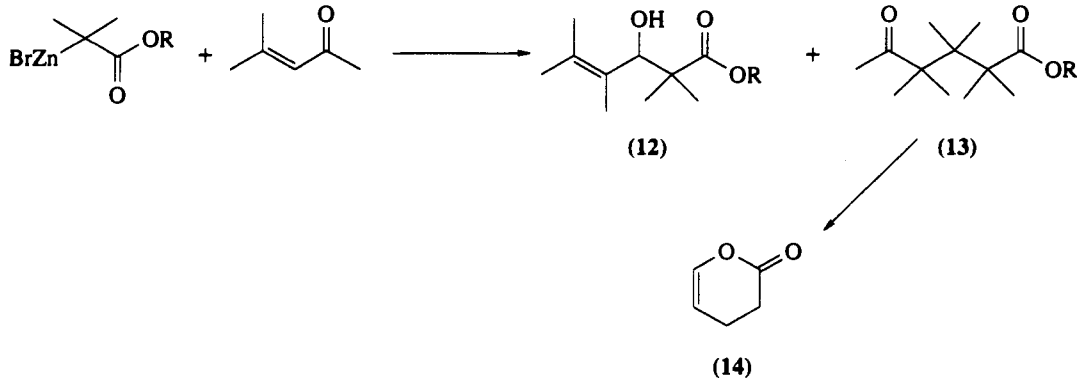
olide synthesis,[59] the use of α-chloro rather than α-bromo ketones was recommended to avoid formation of a zinc ketone enolate (equation 19).

The two-stage Reformatsky procedure was originally devised to avoid the reduction of quinone substrates by zinc, which was observed in a single-stage sequence.[9] A two-stage sequence also allows successful reaction with nitrobenzaldehydes (equation 20),[60] although in this case the problem is a marked inhibition of the reaction of zinc with the bromo ester by nitro aromatics.

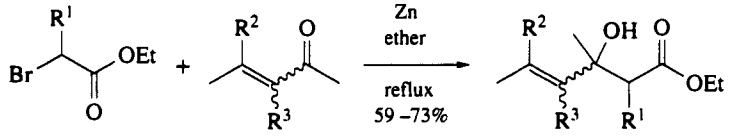
1.8.3.3 Regioselectivity

1.8.3.3.1 Reaction of zinc ester enolates with conjugated enones

Reaction of zinc ester enolates with a conjugated enone can give either β-hydroxy esters (**12**) from 1,2-addition, or δ-keto esters (**13**) from 1,4-addition, as shown in Scheme 8. Cyclization of the 1,4-product to the corresponding δ-lactone (**14**) is occasionally observed.

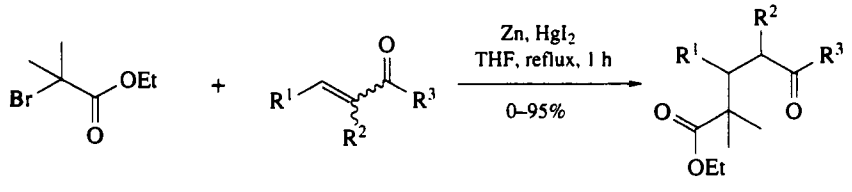


Scheme 8

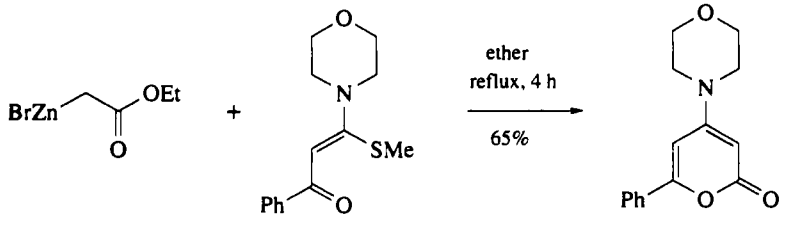


(21)

R^1 = H, Me, Et; R^2 = H, Me; R^3 = H, Me



(22)



(23)

Reaction of a variety of unsaturated methyl ketones with relatively unhindered bromo esters in refluxing ether gave only 1,2-addition products (equation 21).[61] A similar study in refluxing THF with the more hindered ethyl α-bromoisobutyrate gave exclusively 1,4-addition products; however, the conditions of work-up were such that 1,2-addition products would not have been isolated (equation 22).[62]

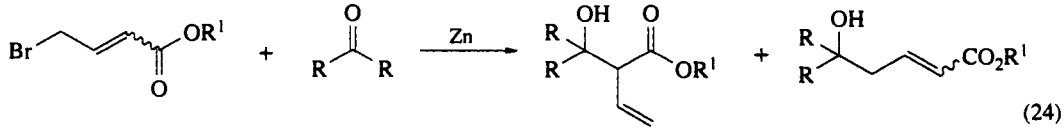
There has been no systematic study of the Reformatsky reaction of conjugated enones under conditions where both 1,2- and 1,4-products could be determined. In general, only 1,2-addition products are obtained with α-bromoacetates. However, in one favorable case, exclusive 1,4-addition was observed (equation 23).[63] Reactions with α-bromoisobutyrates commonly give 1,4-addition products. It is not known whether these are the result of a kinetically or thermodynamically controlled process. Low temperature reactions of conjugated enones with preformed Reformatsky reagents of α-bromoisobutyrates, conditions most favorable for a kinetically controlled process, have apparently never been reported.

1.8.3.3.2 Reaction of zinc ester dienolates with simple aldehydes and ketones

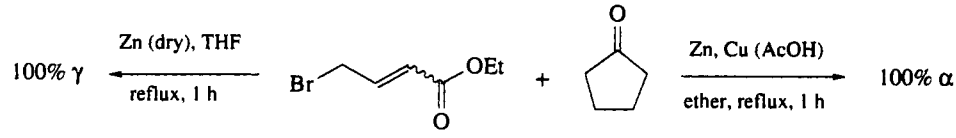
The Reformatsky reaction of 4-bromocrotonate esters can give either α- or γ-products as shown in equation (24). Hudlicky and coworkers[64] have suggested that the high γ-selectivity usually observed for the reaction may be due to the instability of the α-products to isolation procedures. They examined the reaction of ethyl 4-bromocrotonate with 10 carbonyl substrates and defined conditions for obtaining either α- or γ-products with generally good selectivity (Scheme 9). In at least one case, these results were shown[34] to be the result of a selection between kinetic control, leading to α-product, and thermodynamic control, leading to γ-product (equation 25).

In a similar study of the reaction of trimethylsilyl esters of 4-bromocrotonic and 4-bromosenecioic acids with benzaldehyde, low temperatures favored α-products, while higher temperatures or longer reaction times favored γ-products (equation 26).[65]

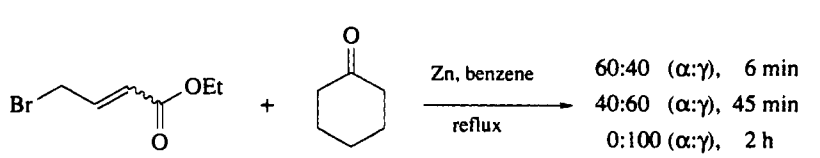
It seems reasonable to conclude that, as originally proposed by Gaudemar,[66] one-stage Reformatsky reactions of zinc ester dienolates will produce mainly α-products in kinetically controlled processes, and



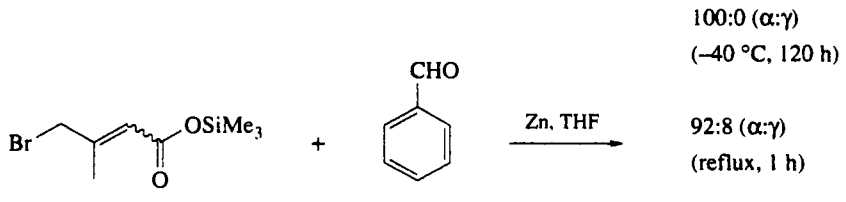
(24)



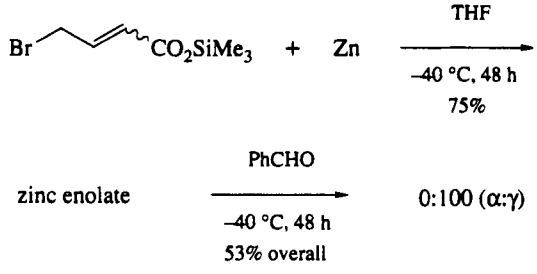
Scheme 9



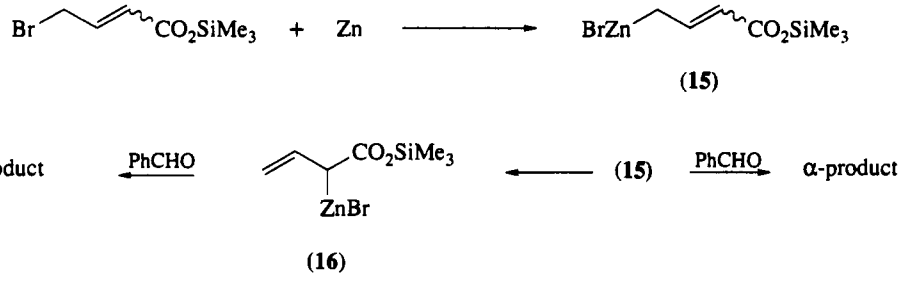
(25)



(26)



Scheme 10



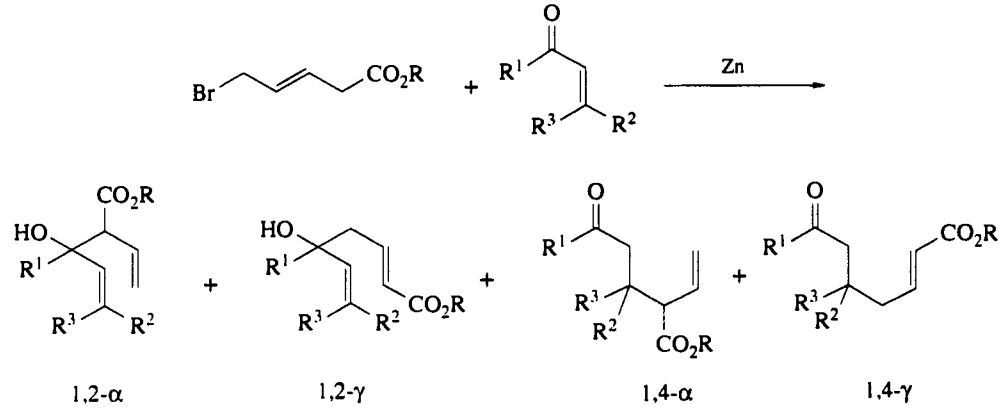
Scheme 11

mainly γ-products in thermodynamically controlled processes. Similar conclusions were reached for the corresponding reactions of lithium ester dienolates.[67] It is therefore surprising that two-stage Reformatsky reactions, completed under conditions where the α-product is stable, gave exclusively γ-products (Scheme 10).[65] The existence of two different zinc dienolates was proposed to explain these results, as shown in Scheme 11. In one-stage reactions, the initially formed enolate (**15**) is trapped to give α-products. In two-stage reactions, (**15**) rearranges to a second enolate (**16**), which then reacts to give γ-products.

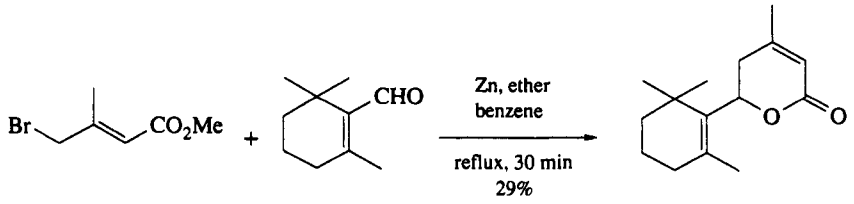
1.8.3.3.3 Reaction of zinc ester dienolates with conjugated enones

The Reformatsky reaction of 4-bromocrotonate esters with conjugated enones can conceivably give four regioisomers, as shown in equation (27). Several workers have applied such reactions to the synthesis of vitamin A and related compounds.[7] In most cases, δ-lactones derived from 1,2-γ-adducts were obtained, as exemplified by results with β-cyclocitral (equation 28).[68]

In a study of the reaction of ethyl 4-bromocrotonate with a variety of conjugated enones, Hudlicky and coworkers[34] observed almost exclusive formation of 1,2-α-products at very short reaction times in

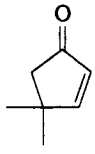
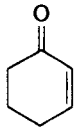
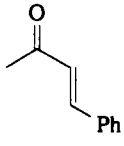
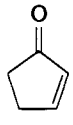
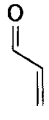
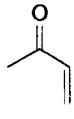


refluxing ether. Longer reaction times produced increasing amounts of 1,2-γ- and 1,4-γ-products. Reaction for several hours in refluxing THF gave, with ketones, exclusively the 1,4-γ-product and, with the single aldehyde examined, exclusively the 1,2-γ-product. Selected data are shown in Table 3. Interestingly, the lithium enolate of ethyl crotonate gave primarily the 1,4-α-product with cyclohexenone (entry 7), a regioisomer not observed with any of the Reformatsky reactions of Table 3.



(28)

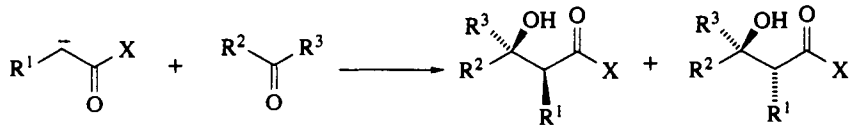
Table 3 Regioselectivity in the Reformatsky Reaction (equation 27)

Unsaturated carbonyl compound	*Reaction conditions*	*Product distribution (%)*			
		1,2α	*1,2γ*	*1,4α*	*1,4γ*
	Zn/Cu (HOAc)/Et_2O, 3 min	>95			
	Zn/Cu (HOAc)/Et_2O, 1 h	28	26		46
	Zn, THF, 4 h	10			90
	Zn/Cu (HOAc)/Et_2O, <1 min	>90			<10
	Zn/Cu (HOAc)/Et_2O, 45 min	53	17		30
	Zn, THF, 6 h				>90
	LDA, –78 °C, THF, $MeCHCHCO_2Et$			75	25
	Zn/Cu (HOAc)/Et_2O, 1 min	100			
	Zn/Cu (HOAc)/Et_2O, 1 h	16	26		58
	Zn, THF, 4 h				>90
	Zn/Cu (HOAc)/Et_2O, 3 min	>96			
	Zn, THF, 2 h	15			85
	Zn/Cu (HOAc)/Et_2O, 30 s	100			
	Zn/Cu (HOAc)/Et_2O, 1 h	41	59		
	Zn, THF, 2 h		100		
	Zn/Cu (HOAc)/Et_2O	35	55		<10

1.8.3.4 Stereoselectivity

1.8.3.4.1 Introduction

Reaction of an α-substituted enolate with an aldehyde or ketone can give two pairs of aldol diastereomers, which are conveniently designated as the *syn* form (**17**) and the *anti* form (**18**), where R^2 is part of the parent chain in IUPAC nomenclature (equation 29). For simplicity, only one enantiomer of each pair will usually be shown throughout this section. The *syn/anti* notation for aldol diastereomers has been described in detail by Heathcock.[8]



(29)

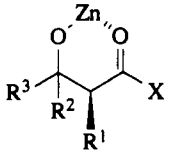
(**17**) *syn*-aldol (**18**) *anti*-aldol

1.8.3.4.2 Thermodynamic stereoselection

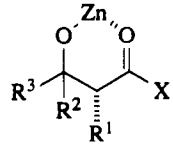
Aldol condensations of zinc enolates under conditions of thermodynamic control are reasonably discussed in terms of the relative stability of the two chelated aldolates; (**19**), which leads to the *syn* aldol, and (**20**), which leads to the *anti* aldol. If R^2 is larger than R^3, the *anti* chelate, with R^1 and R^2 *trans* in a six-atom ring, is expected to be the more stable form. Heathcock[8] has noted that the most common mechanism for equilibration of aldolate stereochemistry is reverse aldolization (reversal of equation 29). Aldolates obtained by reaction of an enolate with ketone substrates are expected to undergo reverse aldolization at a faster rate than those obtained with aldehyde substrates, in part for steric reasons. Similarly, aldolates derived from ketone enolates are expected to undergo reverse aldolization at a faster rate than those derived from the more basic ester or amide enolates.

Chelated structures analogous to (**19**) and (**20**) were first proposed by House and coworkers[23] to explain the increased *anti* selectivity observed for lithium ketone enolates following addition of $ZnCl_2$ (equation 30). Heathcock and coworkers[69] determined the rate of equilibration as well as the equilibrium composition for a number of aldolates derived from benzaldehyde and zinc ketone enolates (equation 31). Again, the preference for *anti* aldolates is in accord with zinc-chelated structures.

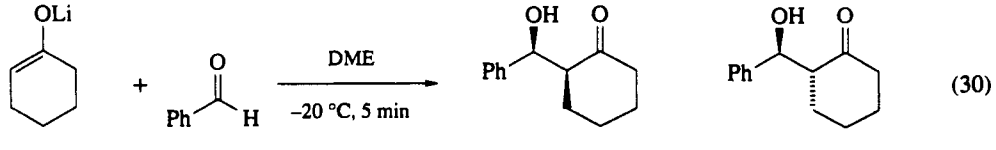
Jacques and coworkers[70] examined the Reformatsky reaction of a series of α-alkyl-substituted bromo esters. In refluxing benzene, the zinc aldolates derived from aromatic ketones, but not from aromatic



(**19**) *syn*-chelate



(**20**) *anti*-chelate

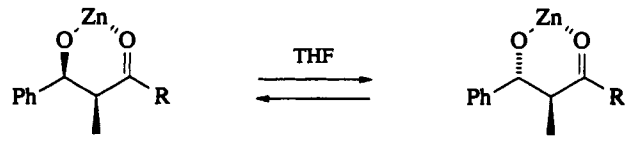


(30)

syn 50% (25%)

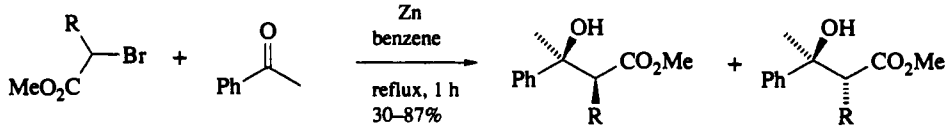
anti 50% (75%)

($ZnCl_2$, –5 °C)

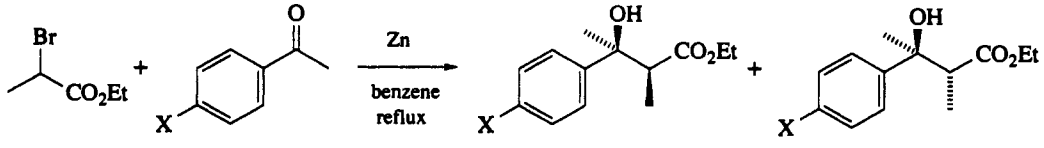


syn *anti* (31)

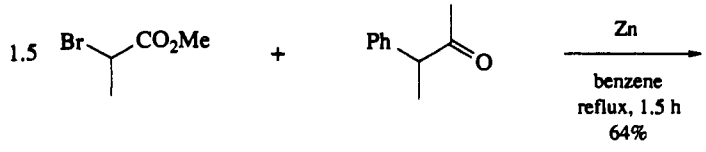
25%	$T_{1/2}$ = 4 min, –10 °C	75%	R = Ph
9%	$T_{1/2}$ = 0.5 min, –78 °C	91%	R = mesityl
—	$T_{1/2}$ = 210 min, 25 °C	—	R = Bu^t



syn *anti* (32)

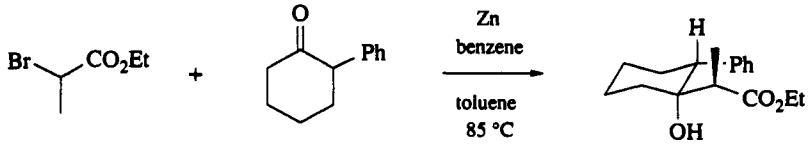


X = OMe, H, Cl *syn* *anti* (33)

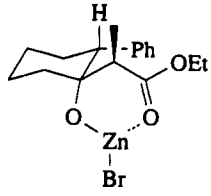


(21) 10% **(22)** 0%

(23) 75% **(24)** 15% (34)



(25) (35)



(26)

aldehydes, were found to equilibrate. *Syn:anti* ratios increased with increasing size of R and ranged from 30:67 (R = Me) to 17:83 (R = Pr^i) (equation 32). Balsamo and coworkers[71] observed a similar equilibration in the reaction of ethyl α-bromopropionate with substituted acetophenones in refluxing benzene (equation 33). Equilibration of stereochemistry was fastest with X = OMe (complete equilibration in 1 h) and slowest with X = Cl (complete equilibration in 5 h). All three substrates gave approximately the same equilibrium *syn:anti* ratio of 30:70.

Other studies of the Reformatsky reaction in refluxing benzene with ketone substrates are readily explained in terms of equilibrated zinc aldolates, although direct evidence for equilibration was not obtained. Matsumoto and coworkers[72] examined the reaction of 3-phenyl-2-butanone with methyl α-bromopropionate and observed a net *syn:anti* ratio [(**21** + **22**):(**23** + **24**)] of 10:90, in harmony with equilibrated zinc aldolates (equation 34).

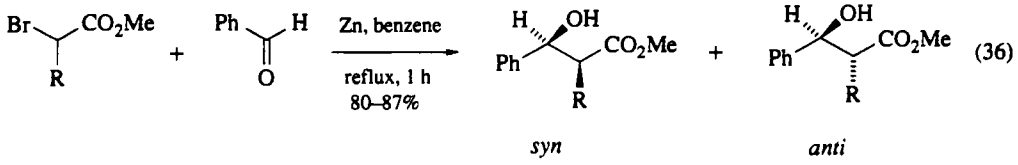
Thomas and coworkers[73] examined the reaction of 2-phenylcyclohexanone with a number of nucleophiles. The highest stereoselectivity was observed with a Reformatsky reaction of ethyl α-bromopropionate (equation 35). The exclusive product (**25**) corresponds to that expected from the most stable zinc aldolate (**26**) with the α-methyl away from the phenyl group.

1.8.3.4.3 Kinetic stereoselection

Because of conflicting reports or inadequate controls, the question of kinetic or thermodynamic control of stereochemistry for reported Reformatsky reactions often has no satisfactory answer. Jacques and coworkers[70] have concluded that Reformatsky reactions of benzaldehyde in refluxing benzene can be completed with kinetic stereoselection. The relatively high *syn:anti* ratios they observed, at least with small R groups (equation 36 and Table 4), are not those expected for equilibrated zinc chelates.

Matsumoto and coworkers[74] observed a similar high *syn:anti* ratio for the Reformatsky reaction of a chiral aldehyde in refluxing benzene [*syn:anti* = (**27** + **28**):(**29** + **30**) = 71:29] (equation 37).

The optimum approach to kinetic stereoselection in the Reformatsky reaction would appear to be the use of two-stage procedures, which allows the zinc aldolates to be formed at the lowest possible temperature. Gaudemar-Bardone and Gaudemar[75] prepared a variety of zinc ester enolates in dimethoxymethane at 40 °C which were then reacted at lower temperatures with benzaldehyde or with acetophenone (equation 38). Selected data from their study are shown in Table 5. If these data are the result of total kinetic control, as concluded by the authors, it is clear that the reactions exhibit only a modest kinetic stereoselectivity.



(36)

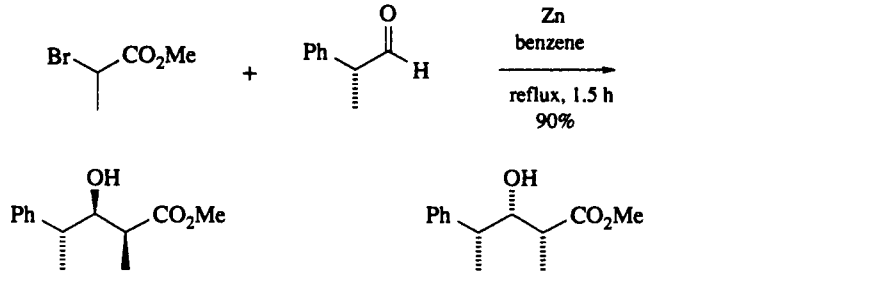
Table 4 *Syn:Anti* Ratios (equation 36)

R	*Syn:anti*	*R*	*Syn:anti*
Me	63:37	c-C_6H_{11}	50:50
Et	54:46	Bu^t	31:69
Pr^i	47:53	Ph	24:76

Gaudemar and Curé[76] examined a two-stage procedure for condensing α-bromoamides with aldehydes and ketones. Again, no significant stereoselectivity was observed (*syn:anti* ratios ranged from 52:48, R = Me, to 72:28, R = Pr^i; Scheme 12).

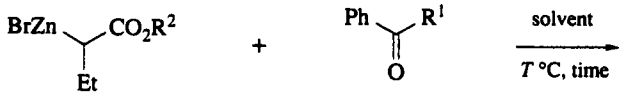
Ito and Terashima[77] obtained good *syn* selectivity for a two-stage condensation of 3-(2-bromopropionyl)-2-oxazolidone derivatives and zinc dust with aldehydes (Scheme 13). *Syn:anti* ratios as high as 98:2 were obtained.

Although zinc–carbon bonded structures have been established for zinc ester enolates, it is conceivable that the alternate zinc–oxygen bonded structure is the reactive form in aldol condensations. Two research groups[78,79] have observed a modest degree of optical activity in the products from reaction of benzalde-



(27) 16% (28) 55% (37)

(29) 5% (30) 24%



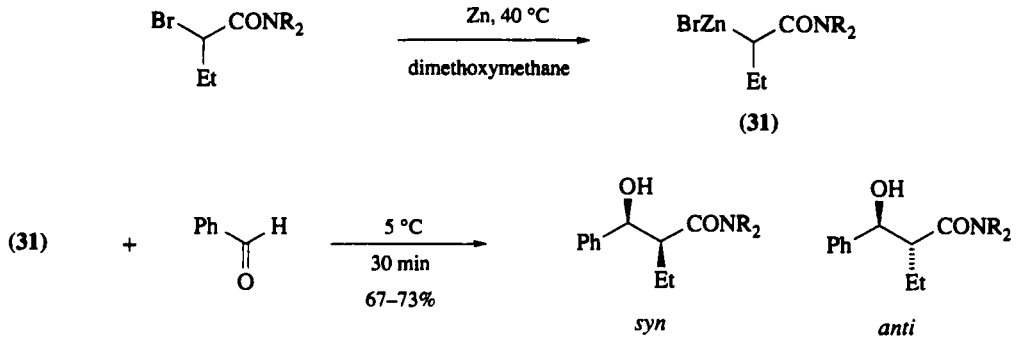
(38)

syn *anti*

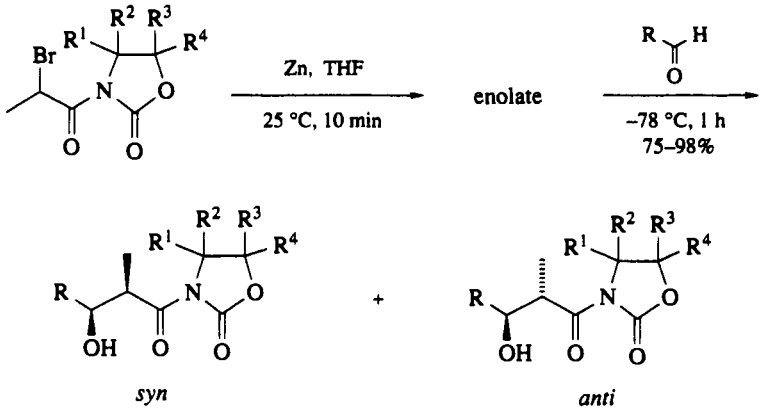
Table 5 Syn:Anti Ratios (equation 38)

R^1	R^2	*Syn:anti*		
		Dimethoxymethane (−75 °C, 24 h)	*Dimethoxymethane (−10 °C, 0.5 h)*	*DMSO (−10 °C, 0.5 h)*
Me	Me	62:38	29:71	60:40
Me	Et	50:50	25:75	52:48
Me	Pr^i	30:70	21:79	50:50
Me	Bu^t	15:85	15:85	40:60
H	Me	50:50	50:50	68:32
H	Et	44:56	51:49	66:34
H	Pr^i	38:62	42:58	68:32
H	Bu^t	47:53	44:56	68:32

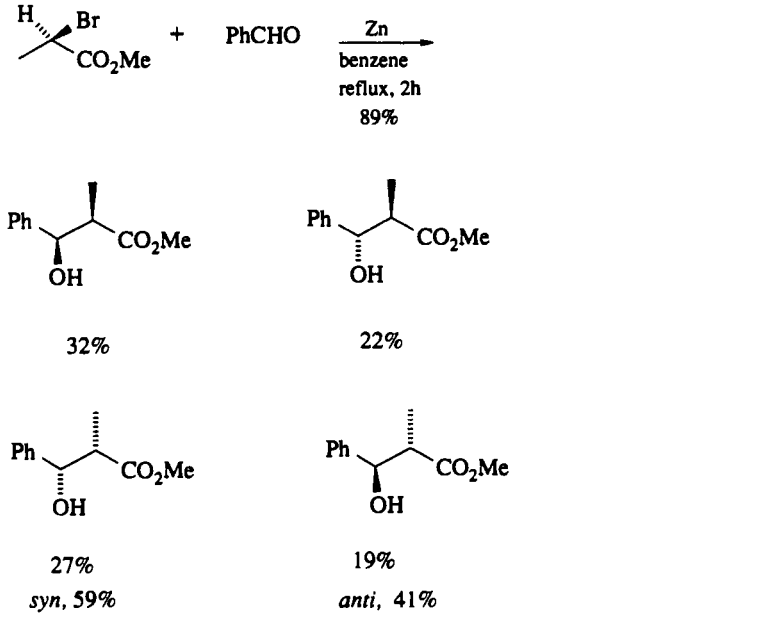
hyde with optically active methyl α-bromopropionate (equation 39), and this result is most simply explained by reaction of a zinc–carbon bonded enolate.



Scheme 12



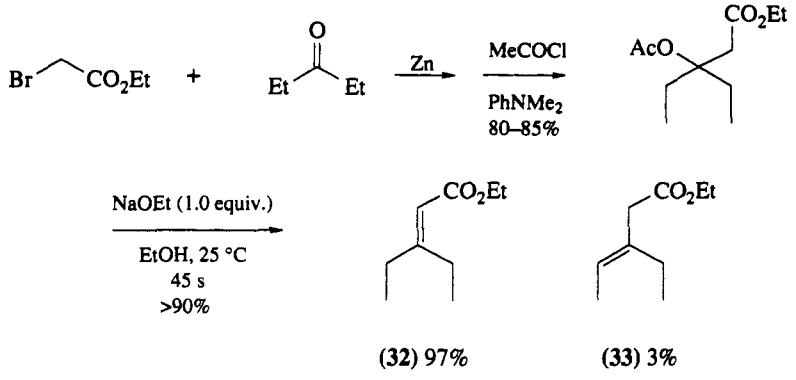
Scheme 13



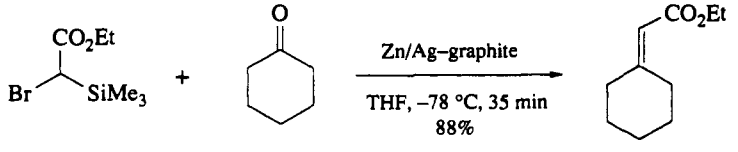
(39)

1.8.3.5 Preparation of Unsaturated Esters

Dehydration of the aldol products of a Reformatsky reaction does not normally occur under the usual reaction conditions but is often accomplished in a separate step to prepare unsaturated esters. Acid-promoted dehydration of β-hydroxy esters can give significant amounts of nonconjugated unsaturated esters by either kinetic or thermodynamic control.[2] Mirrington and coworkers[80] found that acetates can be prepared directly from Reformatsky reaction mixtures by addition of acetyl chloride. Base-promoted elimination of the acetates produced conjugated esters in high yield. For the reaction shown in Scheme 14, the thermodynamic ratio of products (**32**):(**33**) is 40:60 and four different acid-promoted dehydration procedures gave at best a 68:32 ratio of products.[2]



Scheme 14

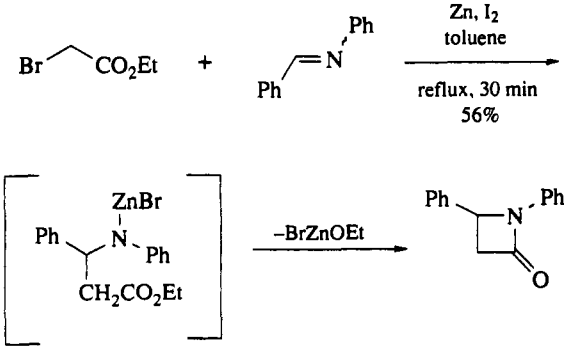


(40)

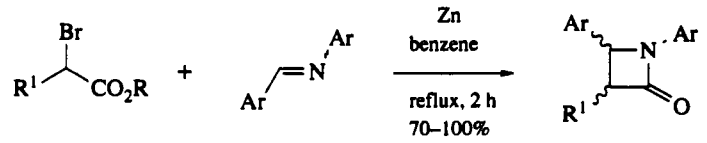
Reformatsky reactions of α-trimethylsilyl esters have been used to obtain α,β-unsaturated esters directly from carbonyl substrates in a Peterson-type alkenation,[81] as shown in equation (40).

1.8.4 REACTION WITH IMINES

The reaction of imines with Reformatsky reagents was first examined by Gilman and Speeter[82] in 1943 with benzalaniline. The product of the reaction was a β-lactam, formed by cyclization of an intermediate zinc salt (Scheme 15). The stereoselectivity of the reaction of α-alkyl-substituted bromo esters with a variety of benzalanilines was examined by both Luche and Kagan,[83] and Gaudemar and coworkers.[84] Condensations conducted at reflux temperatures gave a mixture of *cis* and *trans* β-lactams (equation 41).

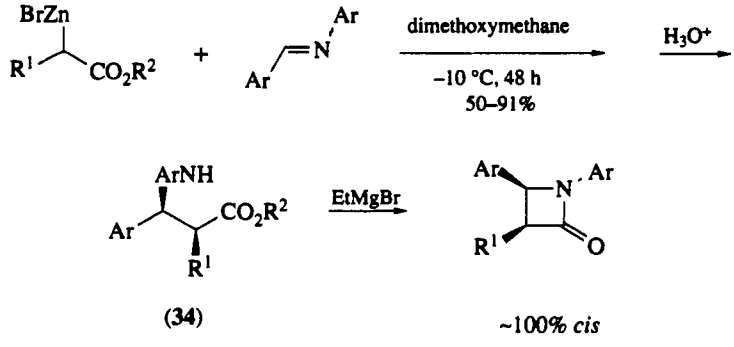


Scheme 15



(41)

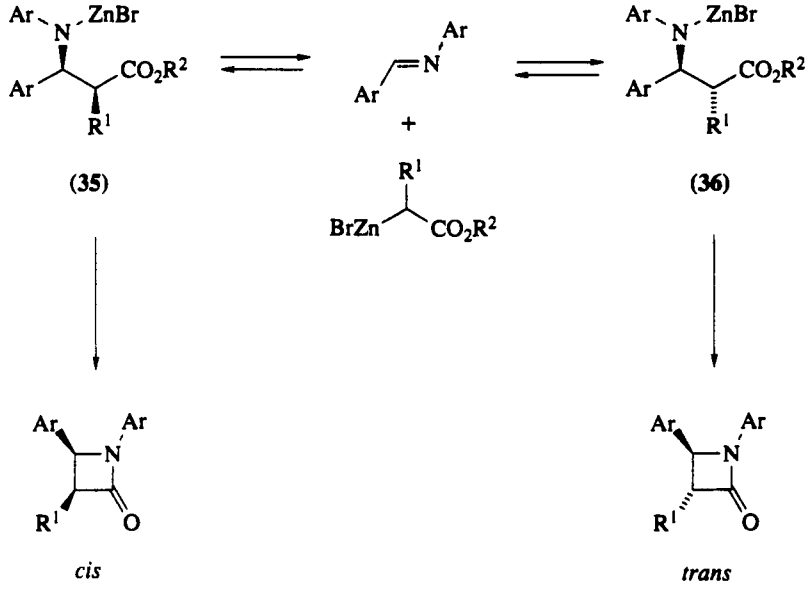
cis and *trans*



(34)

~100% *cis*

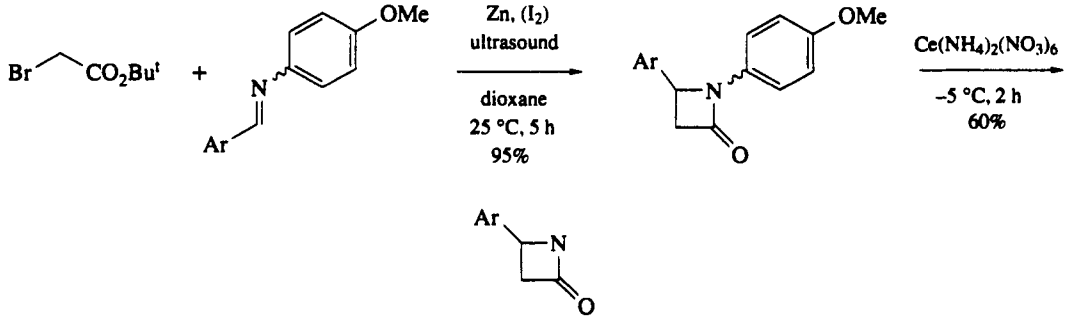
Scheme 16



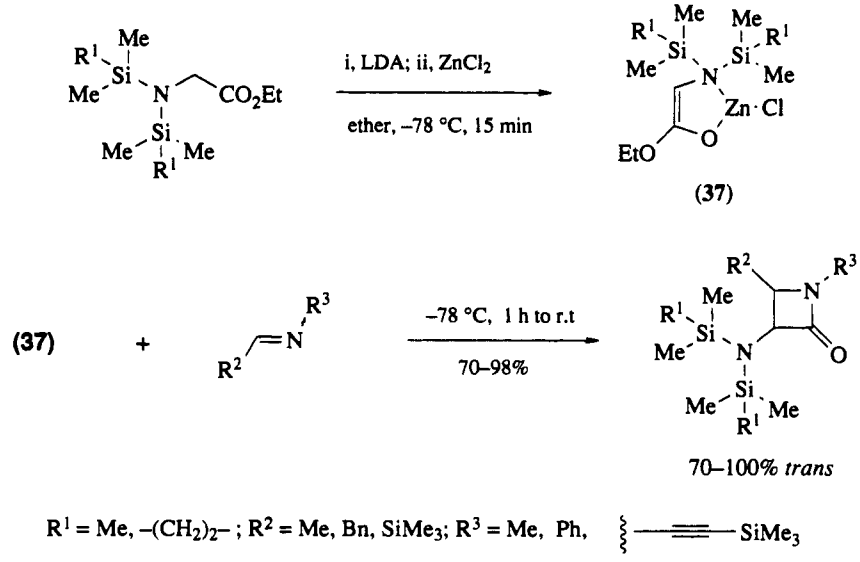
(35) (36)

cis *trans*

Scheme 17



Scheme 18



Scheme 19

Condensations conducted at low temperatures using preformed Reformatsky reagents gave β-amino esters that have almost exclusively the *syn* configuration (**34**; Scheme 16). These may be cyclized by forming the magnesium salt to give the pure *cis*-β-lactam. It was concluded that the first step of the reaction is reversible at reflux temperature and equilibration of *syn* and *anti* zinc salts, (**35**) and (**36**), is competitive with irreversible cyclization, as shown in Scheme 17.[84]

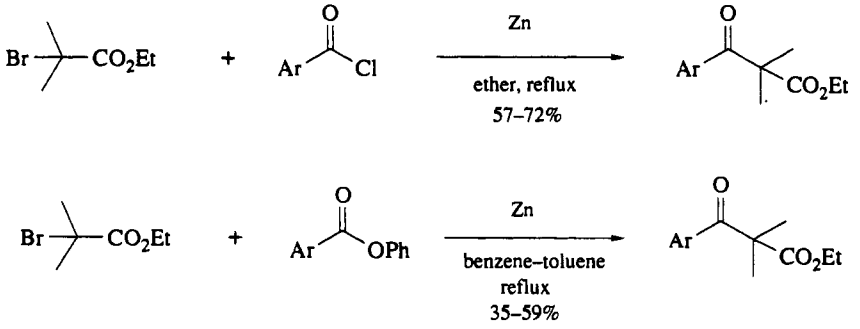
Bose and coworkers[85] have reported that the condensation of ethyl bromoacetate with a variety of imines can be completed in a few hours at room temperature by means of ultrasound activation. Oxidative removal of a *N*-(*p*-methoxyphenyl) group gave *N*-unsubstituted β-lactams, which are useful intermediates in the preparation of β-lactam antibiotics (Scheme 18).

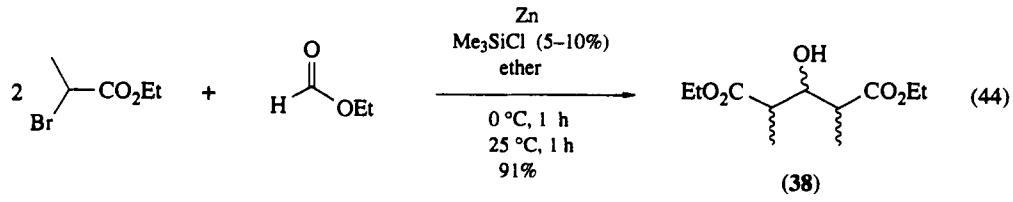
Van Koten and coworkers[86] prepared zinc ester enolates of *N*-protected α-amino esters from the corresponding lithium enolates and allowed them to react with imines at low temperature to obtain *trans*-3-amino-β-lactams, often with high stereoselectivity as shown in Scheme 19. Interestingly, the authors interpreted their results in terms of an internally chelated zinc–oxygen bonded enolate (**37**).

1.8.5 REACTION WITH ACYLATING AGENTS

1.8.5.1 Reaction with Esters and Acid Chlorides

Reactions of Reformatsky reagents with esters or with acid chlorides generally give only low yields of β-keto esters.[2] Hauser reported that ethyl α-bromoisobutyrate could be acylated in reasonable yields with either the acid chlorides[43] or the phenyl esters[87] of aromatic acids, but the reaction fails with acylating

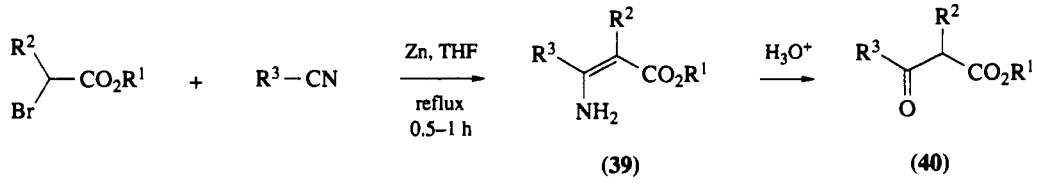




agents or with bromo esters which possess α-hydrogens (equations 42 and 43). It is interesting to note that Reformatsky himself[88] reported a reasonably successful synthesis (41% yield) of the tandem aldol product (**38**) by reaction of ethyl formate with two equivalents of ethyl α-bromopropionate. Recently, with zinc metal activated with Me_3SiCl,[89] the same product was obtained in 91% yield (equation 44).

1.8.5.2 Reaction with Nitriles, the Blaise Reaction

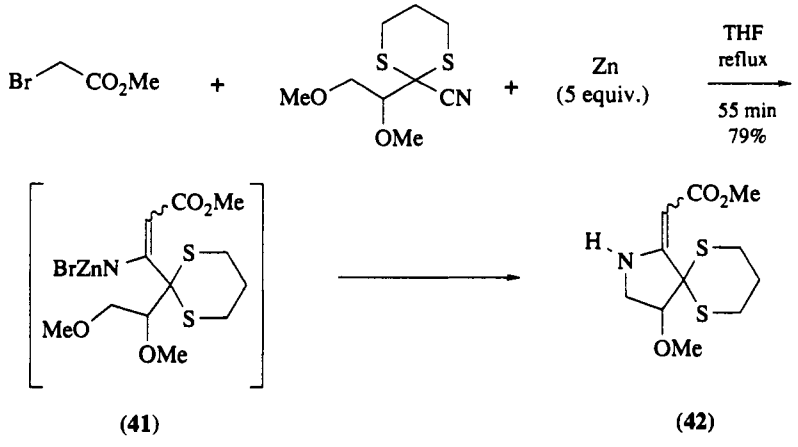
The most successful acylations of Reformatsky reagents have been obtained with nitriles. This reaction, first reported in 1901 by Blaise,[90] was little used until Kagan and Suen[91] reported that slow addition of a benzene solution of α-bromo esters to a refluxing mixture of zinc and the nitrile gave good yields (70–83%) of α,α-disubstituted β-keto esters. Hannick and Kishi[92] reported that a similar proce-



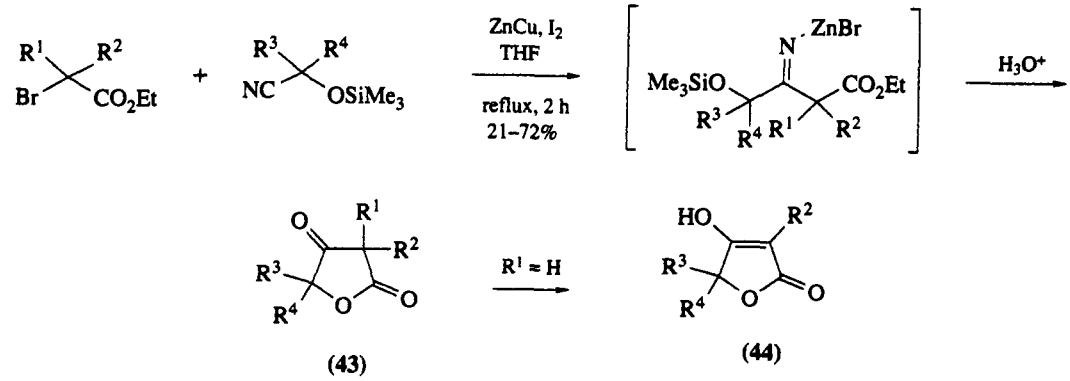
Scheme 20

Table 6 Yield of Enamino Esters (**39**) or β-Keto Esters (**40**) (Scheme 20)

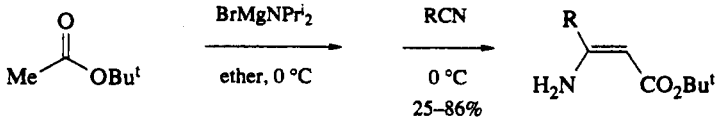
R^1	R^2	R^3	*(38) (%)*	*(39) (%)*
Me	H	$(CH_2)_4Cl$	95	85
Bu^t	H	$(CH_2)_4Cl$	87	83
Me	H	$C(CH_3)_2(CH_2)_2Cl$	70	62
Me	H	Ph	88	82
Me	Me	Ph	84	79
Me	Me	$(CH_2)_4Cl$	54	84



Scheme 21



Scheme 22



Scheme 23

dure using activated zinc dust in refluxing THF was substantially better for the preparation of both α-monosubstituted or α-unsubstituted β-keto esters (Scheme 20 and Table 6).

Hannick and Kishi[92] cyclized an intermediate bromozinc enamino ester (**41**; Scheme 21) to obtain the heterocycle (**42**), used for the synthesis of saxitoxins. The Kishi procedure for the Blaise reaction has been applied[44] to a facile synthesis of β-keto-δ-butyrolactones (**43**), or tetronic acids (**44**; Scheme 22).

It is useful to note that Hiyama and Kobayashi[93] have reported successful reactions of nitriles with a magnesium ester enolate (Scheme 23), whereas the corresponding lithium ester enolate failed to react.

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1.9
The Aldol Reaction: Transition Metal Enolates

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1.9.1 INTRODUCTION

The application of transition metal and lanthanide metal enolates to the aldol reaction is a recent development. There are significant potential advantages to be gained in selectivity over the aldol addition reactions of their main group counterparts: the use of less electropositive metals leads to reduced enolate basicity; stabilization of the aldolate by transition metal coordination can lead to improved conversion and avoidance of retroaldolization, thus ensuring kinetic control of reaction; greater stereochemical control arising from sterically demanding transition metal centers; moreover, enantioselective aldol reactions are possible by the introduction of chiral ligands on the metal or a chiral metal center. Correspondingly, the aldol reactions of specific transition metal enolates, where a marked improvement in selectivity over the main group reactions has been realized in practice, will be emphasized here. While mercury with a d^{10} electronic configuration is not normally considered as a transition metal, it is convenient to deal with its aldol chemistry in this section. The aldol reactions of the enolates of acyl–transition metal complexes are also included in this section, even though their reactivity is largely governed by the enolate counterion and not the transition metal itself.

To facilitate an analysis of enolate reactivity and as an aid to the rationalization of the stereochemical outcome of the aldol reaction, a consideration of the enolate structure is necessary.[1] For convenience, the following classification of transition metal and lanthanide metal enolates will be used here: η^1-*O*-bound metal enolates (**1**) of carbonyl compounds; η^1-*C*-bound metal enolates (**2**) and η^3-metal enolates (**3**) of

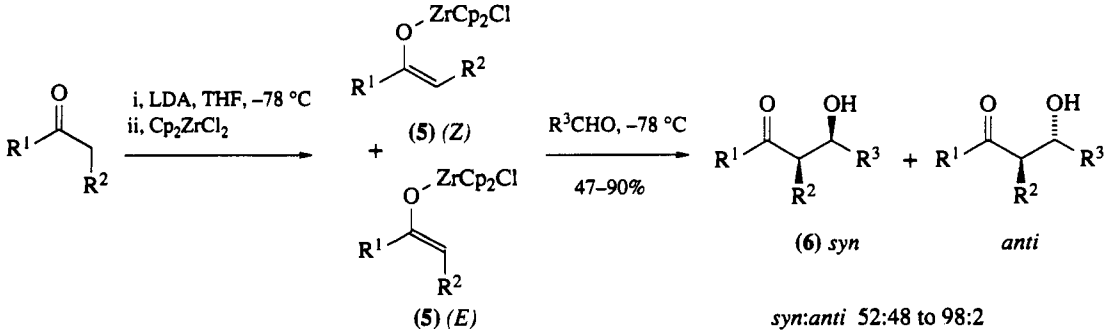
(1) (2) (3) (4)

carbonyl compounds; main group metal enolates of acyl–transition metal complexes (**4**). Other important considerations include: the metal oxidation state; the nature of the ligands; type of ligand–metal coordination; and ligand- and metal-centered chirality.

1.9.2 ALDOL REACTIONS OF η^1-*O*-BOUND METAL ENOLATES

1.9.2.1 Zirconium

The aldol reactions mediated by the early transition metals zirconium and titanium are characterized by high *syn* stereoselectivity and good yields. They usually involve formation of the required enolate intermediate by a transmetallation reaction of a preformed lithium enolate with the appropriate transition metal halide. An important feature is that, unlike the situation with lithium and boron enolates, high *syn* stereoselectivity in additions to aldehydes is generally obtained for acyclic carbonyl compounds regardless of enolate geometry. The enolate geometry, therefore, does not need to be controlled at the enolization stage to ensure useful levels of stereocontrol in the aldol step. For example, the di(cyclopentadienyl)chlorozirconium enolates (**5**) of ethyl ketones, propionate esters and thioesters, and propionamides, prepared by transmetallation of the preformed lithium enolates with Cp_2ZrCl_2, undergo aldol additions to aldehydes in THF at –78 °C with moderate to high levels of diastereoselectivity favoring the *syn* adduct (**6**; Scheme 1 for R^2 = Me and Table 1, entries 1–14).[2,3] In contrast, the corresponding lithium enolate precursors usually show much lower levels of stereoselectivity even when a single enolate geometry is involved (Volume 2, Chapter 1.5). Evans and McGee have demonstrated that these zirconium-mediated aldol reactions proceed under kinetic control, and, to explain the stereochemical convergency operating, propose that the (*Z*)-enolates favor reaction with the aldehyde *via* a chair-like transition state (**7**) to give (**6**), whereas the (*E*)-enolates favor reaction *via* a boat-like transition state (**8**) to also give (**6**).[2] Acyclic transition states have also been proposed for these reactions.[3] Either way, the steric effect of the ligands on the metal plays a significant role in controlling the stereochemistry. Cyclic ketones (Table 1, entries 15 and 16), which can only give the (*E*)-enolate, also produce the *syn* aldols *via* the zirconium enolate in moderate selectivity.[3] Here the lithium enolates lead to mainly *anti* aldol pro-



Scheme 1

(7) (8)

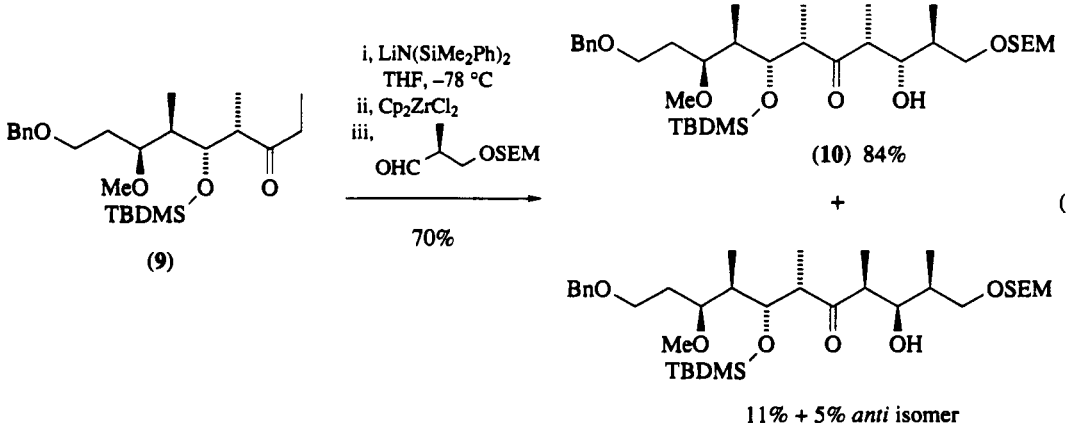
Table 1 *Syn:Anti* Selectivity in the Aldol Reactions of Di(cyclopentadienyl)chlorozirconium Enolates (Scheme 1)

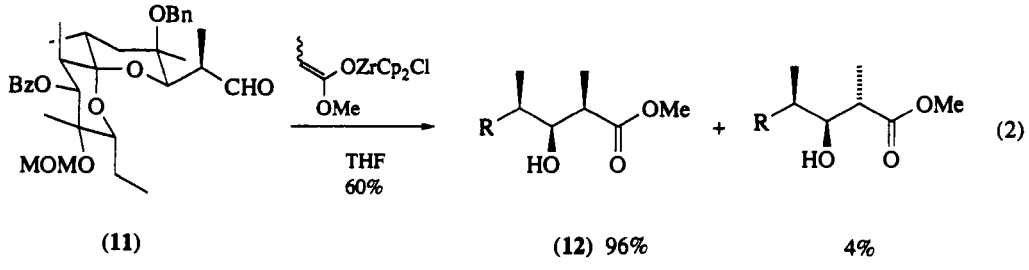
Entry	R^1	R^2	R^3	*(Z):(E)*	*Syn:Anti*	*Yield (%)*	*Ref.*
1	Bu^tS	Me	Ph	10:90	93:7	70	2
2	MeO	Me	Ph	5:95	87:13	80	2
3	Bu^tO	Me	Ph	5:95	72:28	—	2
4	Ph	Me	Ph	>98:2	90:10	62	2
5	Et	Me	Ph	92:8	67:33	86	3
6	Et	Me	Ph	14:86	88:12	70	3
7	$Pr^i{}_2N$	Me	Ph	81:19	>98:2	87	2
8	$Pr^i{}_2N$	Me	Pr^n	81:19	98:2	80–90	2
9	$Pr^i{}_2N$	Me	Pr^i	81:19	97:3	80–90	2
10	$Pr^i{}_2N$	Me	$H_2C{=}CMe$	81:19	95:5	80–90	2
11	c-$(CH_2)_4N^a$	Me	Ph	>95:5	95:5	80	2
12	c-$(CH_2)_4N$	Me	Pr^n	>95:5	94:6	80–90	2
13	c-$(CH_2)_4N$	Me	Pr^i	>95:5	95:5	80–90	2
14	c-$(CH_2)_4N$	Me	$H_2C{=}CMe$	>95:5	90:10	80–90	2
15	—$(CH_2)_3$—		Ph	0:100	74:26	82	3
16	—$(CH_2)_4$—		Ph	0:100	64:36	75	3
17	—$CH{=}CH(CH_2)_2$—		Ph	0:100	75:25	65	4
18	—$CH{=}CH(CH_2)_2$—		Bu^n	0:100	52:48	55	4
19	—$CH{=}CHCH_2$—		Ph	0:100	85:15	65	4
20	—$CH{=}CHCH_2$—		Bu^n	0:100	57:43	47	4

[a] c-$(CH_2)_4N$ = 1-pyrrolidinyl.

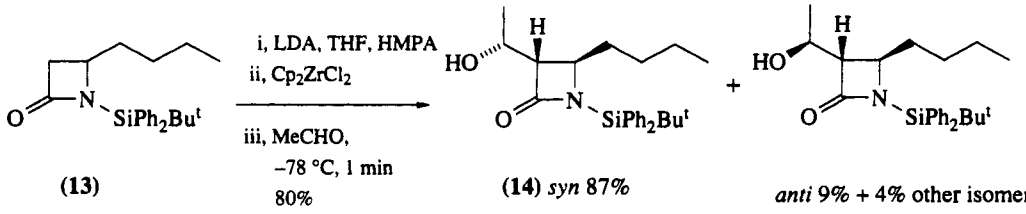
ducts. Moderate levels of *syn* selectivity have also been found in the aldol reactions of the zirconium dienolates derived from 2-cyclohexenone and 2-cyclopentenone (Table 1, entries 17–20).[4]

The high *syn* stereoselectivity attained in zirconium enolate aldol reactions has proved useful in complex natural product synthesis. The zirconium-mediated aldol reaction of the chiral ethyl ketone (**9**) with a chiral aldehyde has been used by Masamune *et al.* to give selectively adduct (**10**), which was further elaborated into the ansa chain of rifamycin S (equation 1).[5] Good enolate diastereofacial selectivity is also obtained here and leads to a predominance of one of the two possible *syn* adducts. A zirconium enolate aldol reaction also features in the Deslongchamps formal total synthesis of erythromycin A, where the di(cyclopentadienyl)chlorozirconium enolate from methyl propionate adds with high levels of Cram selectivity to the chiral aldehyde (**11**) to give the *syn* adduct (**12**; equation 2).[6] A further example is





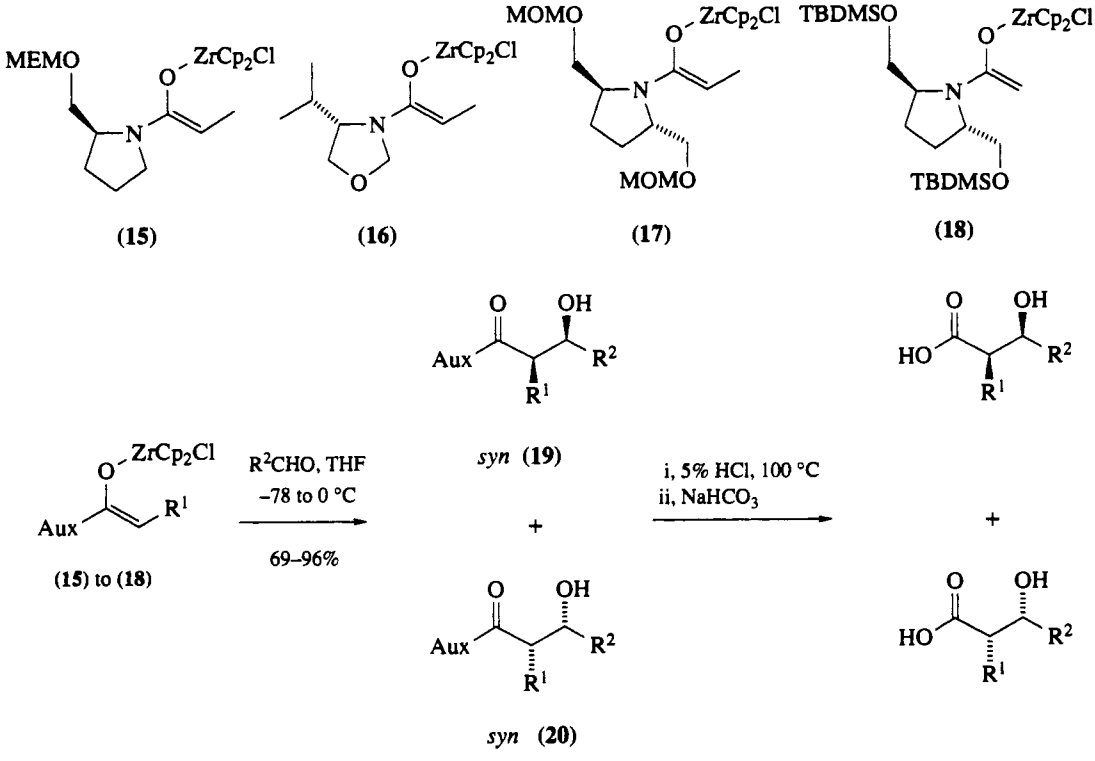
the aldol reaction of the β-lactam (**13**), which sets up the stereochemistry in the *syn* adduct (**14**), as required for a projected thienamycin synthesis (equation 3).[7]



(13) (14) *syn* 87% *anti* 9% + 4% other isomers (3)

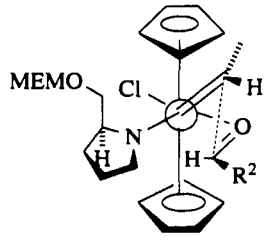
Highly stereoselective aldol reactions have been developed using the zirconium enolates (**15**) to (**18**), which now have a chiral auxiliary attached to the enolate.[8,9] Evans and McGee have described the use of the amino acid derived zirconium enolates (**15**) and (**16**) for stereoregulated aldol reactions, which proceed to give the *syn* isomers (**19**) and (**20**) respectively in >96% diastereoselectivity for R^1 = Me (Scheme 2 and Table 2, entries 1–8).[8] The overall result, after auxiliary removal to give the *syn*-α-methyl-β-hydroxycarboxylic acid, is equivalent to an enantioselective aldol reaction of a propionate enolate. Note that a (*Z*)-substituent in the enolate is a prerequisite for good diastereofacial selection as the analogous acetate enolates show virtually no selectivity. A preferred chair-like transition state (**21**) for the reaction has been proposed based on minimizing steric interactions between the enolate substituents and the bulky cyclopentadienyl ligands on the metal.

The diastereofacial selectivities of these enolates are greatly superior to those of most chiral aldehydes, such that the reaction can also be used to control the aldol addition to a chiral aldehyde (Table 2, entries



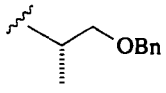
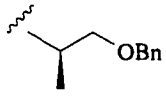
(**19**):(**20**) ≥ 96:4 for (**15**) or (**17**), R^1 = Me
(**20**):(**19**) ≥ 96:4 for (**16**), R^1 = Me
(**19**):(**20**) ≥ 89:11 for (**18**), R^1 = H

Scheme 2



(21)

Table 2 Stereoselectivity in the Aldol Reactions of Chiral Di(cyclopentadienyl)chlorozirconium Enolates (Scheme 2)

Entry	*Enolate*	R^1	R^2	*Syn* (**19**) *(%)*	*Syn* (**20**) *(%)*	*Anti (%)*	*Yield (%)*	*Ref.*
1	(**15**)	Me	Bu^n	96	2	2	69	8
2	(**16**)	Me	Bu^n	1	97	2	96	8
3	(**15**)	Me	Pr^i	96	2	2	77	8
4	(**16**)	Me	Pr^i	0.5	97.5	2	77	8
5	(**15**)	Me	Ph	96	1	3	71	8
6	(**16**)	Me	Ph	1.5	94.5	4	71	8
7	(**16**)	Me		0.9	98.7	0.4	—	8
8	(**16**)	Me		1.7	94.5	3.8	—	8
9	(**17**)	Me	Pr^i	>99	<1		85	9
10	(**17**)	Me	Et	>99	<1		92	9
11	(**18**) + Et_2NH	H	Ph	84	16		62	9
12	(**18**) + $BuNH_2$	H	Ph	89.5	10.5		20	9

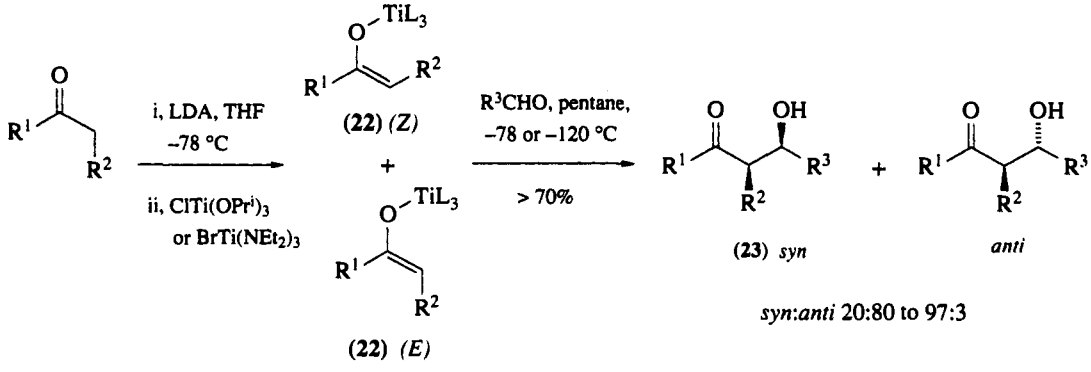
7 and 8). For acid-stable adducts, amide hydrolysis by boiling in 5% hydrochloric acid leads to the corresponding β-hydroxycarboxylic acid without appreciable epimerization. However, such conditions for auxiliary removal are probably incompatible with application to the synthesis of complex acid-sensitive structures. Similar results have been obtained by Katsuki and Yamaguchi for the zirconium enolate (**17**), which gives the aldol product (**19**) with both high diastereofacial selectivity and *syn* diastereoselectivity (Table 2, entries 9 and 10).[9] Again, acid hydrolysis is required for auxiliary removal, which restricts its application to acid-tolerant aldol products. This chemistry can also be extended to some extent to give a chiral acetate enolate equivalent (**18**; Table 2, entries 11 and 12), but much better reagents are available.[10]

1.9.2.2 Titanium

The aldol reactions of titanium enolates have been the best studied of all the transition metal enolates.[11,12] In many cases they show higher stereoselectivity and chemoselectivity in their reactions than lithium enolates and are easily prepared using inexpensive reagents. They also promote high levels of diastereofacial selectivity in reactions of chiral reactants. The Lewis acidity of the titanium metal center can be easily manipulated by variation of the ligands (chloro, alkoxy, amino, cyclopentadienyl, *etc.*) attached to titanium, which leads to enhanced selectivity in appropriate cases. Moreover, the incorporation of chiral ligands on titanium makes possible efficient enantioselective aldol reactions.

Titanium enolates of cyclic and acyclic ketones, like their zirconium counterparts, usually give rise to *syn* aldol products irrespective of enolate geometry. Tri(alkoxy)- or tri(dialkylamino)-titanium enolates

(**22**) are prepared (Scheme 3) from lithium enolates by an exchange reaction with $ClTi(OPr^i)_3$ or $BrTi(NEt_2)_3$ in THF at –78 °C and can be isolated by evaporating the solvent at room temperature.[13] The subsequent aldol reactions are carried out in pentane at –78 °C or –120 °C. Useful levels of diastereoselectivity towards the *syn* adduct (**23**) are usually obtained in the aldol reactions of acyclic ketones and cyclohexanone using these titanium enolates (Table 3, entries 1–16).[13] Poorer selectivities are obtained in only a few cases (Table 3, entries 17 and 18). This is probably the best method available for obtaining high *syn* selectivity in the aldol reactions of five- to seven-membered cyclic ketones (Table 3 entries 11–



Scheme 3

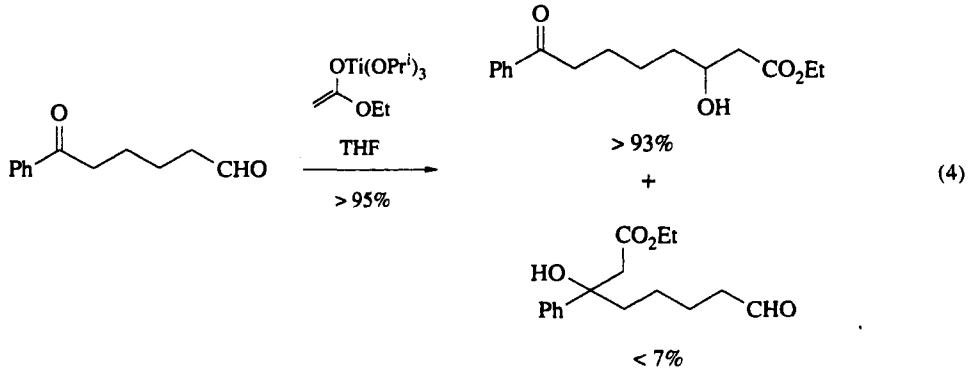


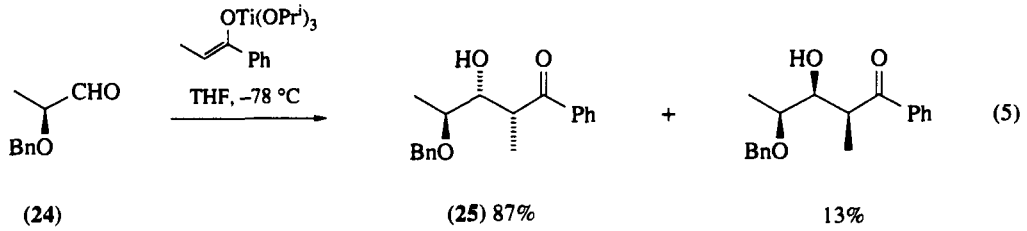
Table 3 *Syn:Anti* Selectivity in the Aldol Reactions of Tri(isopropoxy)- and Tri(diethylamino)-titanium Enolates (Scheme 3)[13]

Entry	R^1	R^2	R^3	*L*	*Temperature (°C)*	*(Z):(E)*	*Syn:Anti*
1	Et	Me	Ph	Pr^iO	–120	36:64	89:11
2	Et	Me	Ph	Pr^iO	–120	92:8	88:12
3	Et	Me	Ph	Et_2N	–78	36:64	76:24
4	Me	Me	Ph	Et_2N	–78	5:95	74:26
5	Et	Me	c-C_6H_{11}	Pr^iO	–120	36:64	77:23
6	Et	Me	Bu^t	Pr^iO	–120	36:64	81:19
7	Bu^t	Me	Ph	Pr^iO	–120	>98:2	87:13
8	Ph	Me	Ph	Pr^iO	–120	>98:2	87:13
9	Ph	Me	Et	Pr^iO	–120	>98:2	89:11
10	Mesityl	Me	Ph	Pr^iO	–120	87:13	90:10
11	—$(CH_2)_3$—		Ph	Et_2N	–78	0:100	85:15
12	—$(CH_2)_4$—		Ph	Et_2N	–78	0:100	97:3
13	—$(CH_2)_4$—		Ph	Pr^iO	–120	0:100	86:14
14	—$(CH_2)_4$—		Pr^i	Pr^iO	–120	0:100	96:4
15	—$(CH_2)_5$—		Ph	Et_2N	–78	0:100	97:3
16	—$(CH_2)_5$—		Ph	Pr^iO	–120	0:100	91:9
17	Mesityl	Me	Ph	Pr^iO	–120	5:95	20:80
18	Et	Me	Ph	Et_2N	–78	92:8	41:59

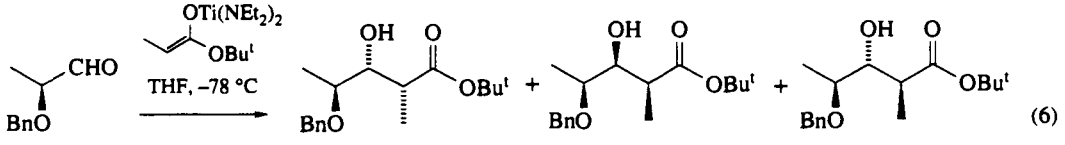
16). A similar chair and boat dual transition state model to that for zirconium enolates has been used by Reetz and Peter to explain the *syn* stereoselectivity, although acyclic transition states may also be operative.

These tri(alkoxy)titanium enolates, which have low Lewis acidity, are known to react chemoselectively with an aldehyde group in the presence of a ketone (equation 4).[14] Other uses described by Reetz *et al.* include the diastereofacially selective additions of ketone and ester enolates to chiral α-alkoxy aldehydes with nonchelation control.[15,16] For example, aldol addition of the tri(isopropoxy)titanium enolate of propiophenone to the aldehyde (**24**) leads to only the two *syn* diastereomers, with the nonchelation adduct (**25**) favored (equation 5); *i.e.* Felkin–Anh selectivity is operating. In the case of aldol addition of *t*-butyl propionate to the same aldehyde (equation 6), highest stereoselectivity for the isomer (**26**) is obtained using the tri(diethylamino)titanium enolate.[17] Very high levels of nonchelation stereoselectivity can also be obtained in the aldol addition to chiral α-siloxy or α-benzyloxy ketones if a titanium enolate of low Lewis acidity is employed, as in equation (7).[18]

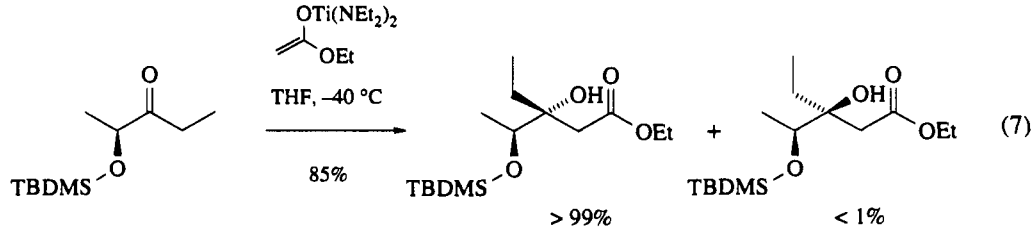
In some cases titanium enolates give as good, if not better, stereoselectivity as the corresponding boron enolate aldol reactions (Volume 2, Chapter 1.7). For example, the tri(isopropoxy)titanium enolate of the chiral ethyl ketone (**27**) has been found to undergo aldol reactions with aldehydes with very high dia-



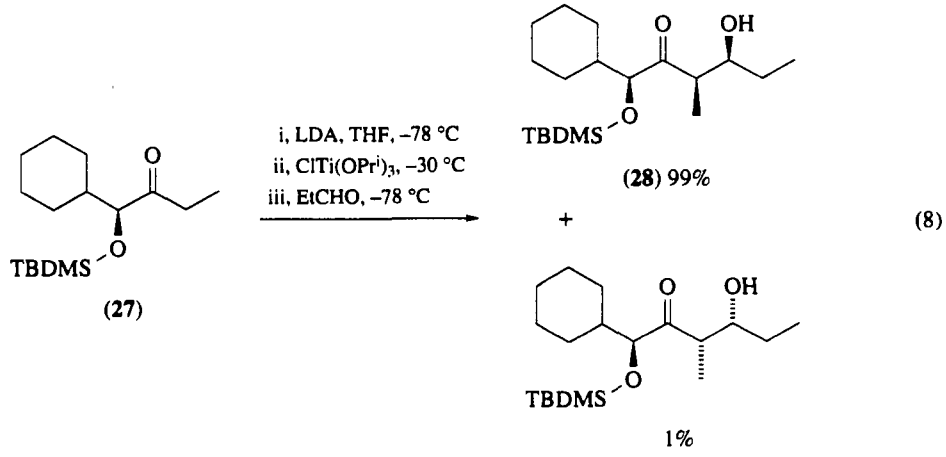
(**24**) (**25**) 87% 13%



(**24**) (**26**) 85% 7% 8%



> 99% < 1%

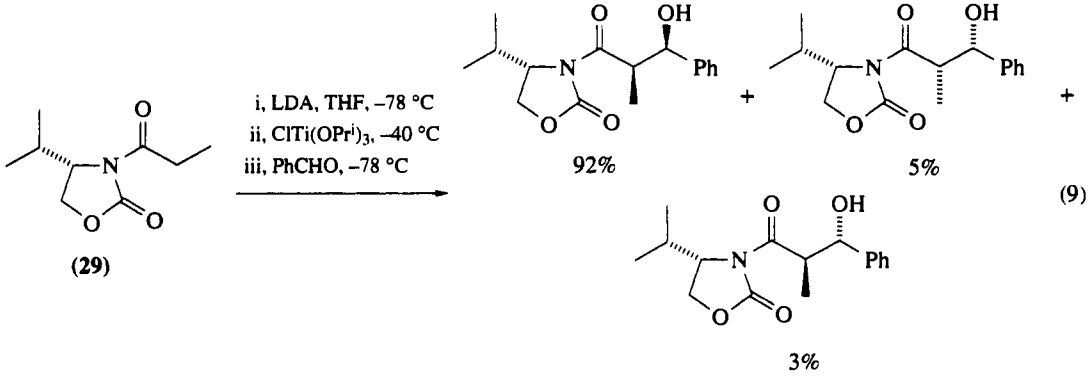


(**27**) (**28**) 99%

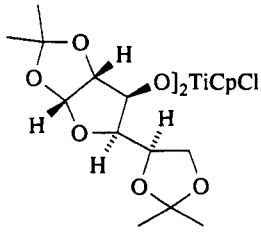
1%

stereofacial selectivity at the 99% level (equation 8).[19] The titanium enolate is easily prepared in THF from the preformed lithium enolate. Highest selectivity requires the use of three equivalents of $ClTi(OPr^i)_3$, presumably ensuring complete Li → Ti exchange in the enolate, and produces the same major *syn* isomer (**28**) as that from the corresponding boron enolate reaction. The aldol products may be oxidatively converted into *syn*-α-methyl-β-hydroxycarboxylic acids in optically pure form.[20] An advantage of the use of titanium with this chiral propionate enolate equivalent is that the reagent is inexpensive and no oxidative work-up is now needed compared to the boron reaction described by Masamune *et al.*[20] Nerz-Stormes and Thornton have reported a similar study for the aldol reactions of the Evans chiral imide reagent (**29**; equation 9).[21] However, this time the diastereofacial selectivity is poorer for titanium than boron; but of more interest, it is in the opposite direction, which has been explained by invoking a chelated chair transition state.

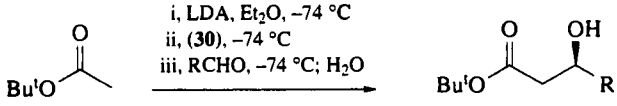
An important development is the use of D-glucose-derived alkoxy ligands on titanium in cyclopentadienyldi(alkoxy)titanium enolates, which undergo efficient enantioselective aldol reactions with aldehydes. The chiral titanium reagent (**30**), prepared from reaction of cyclopentadienyltitanium trichloride with two equivalents of (1,2;5,6)-di-*O*-isopropylidene-α-D-glucofuranose,[22] can be used to transmetallate the lithium enolate of *t*-butyl acetate in ether solution (equation 10).[23] The titanium enolate generated is then



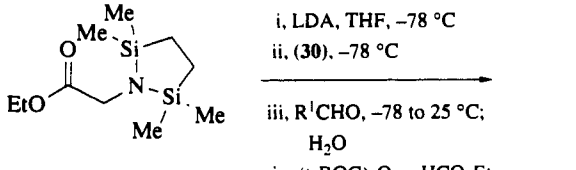
(29) (9)



(30)



(31) 90–96% *ee* (10)



(32) (33) (11)

syn:*anti* ≥ 96:4
87–98% *ee*

reacted at –74 °C with an aldehyde *in situ*, which after hydrolytic work-up gives the β-hydroxy ester adduct (**31**) in 90–96% *ee*. Duthaler *et al.* have shown that the reaction is applicable to a wide range of aldehydes (Table 4) and that the carbohydrate ligand can be recycled.[23] The use of other ligands should make available the enantiomeric adducts, while application of this method to the enantioselective aldol reactions of other carbonyl compounds should also be feasible. For instance, the method has also been applied to the enantioselective synthesis of *N*-protected *syn*-β-hydroxy-α-amino acids (**33**) by aldol reaction of the titanium enolate of the glycine derivative (**32**; equation 11).[24] Here high *syn* diastereoselectivity is obtained as expected from titanium, while the attached chiral ligands induce a high level of enolate π-face selectivity in addition to aldehydes (Table 5).

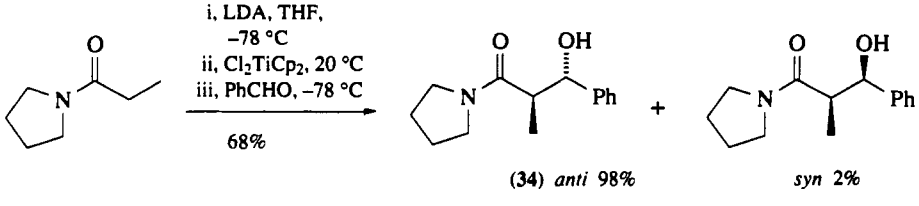
Table 4 Enantioselective Aldol Reactions of the Chiral Titanium Enolate of *t*-Butyl Acetate with Aldehydes (equation 10)[23]

Entry	*R*	*Ee (%)*	*Yield (%)*
1	Pr^n	94	51
2	$Me(CH_2)_{11}$	94	70
3	Bu^i	94	81
4	Pr^i	95	66
5	$c\text{-}C_6H_{11}$	92	70
6	Bu^t	91	80
7	(*E*)-$Pr^nCH{=}CH$	91	81
8	(*E*)-$MeCH{=}CH$	92	58
9	$H_2C{=}CMe$	96	81
10	Ph	95	69
11	2-Furyl	90	62

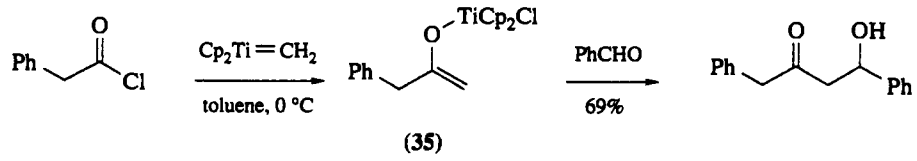
Table 5 Enantioselective Aldol Reactions of the Chiral Titanium Enolate Derived from (**32**) with Aldehydes (equation 11)[24]

Entry	R^1	R^2	*Syn:Anti*	*Ee (%)*	*Yield (%)*
1	Me	BOC	≥98:2	97	53
2	Pr^n	BOC	≥98:2	98	66
3	Bu^t	BOC	≥96:4	96	43
4	$H_2C{=}CH$	BOC	≥97:3	97	48
5	$H_2C{=}CMe$	BOC	99:1	98	57
6	Ph	BOC	≥96:4	97	60
7	Bu^tO_2C	CHO	≥96:4	87	66

The formation and aldol reactions of di(cyclopentadienyl)chlorotitanium enolates have also been studied. The aldol reaction of *N*-propionylpyrrolidine proceeds with *anti* selectivity (equation 12) by using the di(cyclopentadienyl)chlorotitanium enolate prepared from the lithium enolate and Cp_2TiCl_2.[25] Procter and coworkers have found that high selectivity for the *anti* isomer (**34**) requires ageing of the titanocene enolate solution in THF at room temperature, which probably facilitates some enolate equilibration process, followed by addition of the aldehyde and quenching of the aldol reaction at –78 °C. This result further illustrates the fine tuning which is possible in transition metal mediated aldol reactions, since the corresponding di(cyclopentadienyl)chloro*zirconium* enolate (**5**) gives the reverse diastereoselectivity favoring the formation of the *syn* adduct (Table 1, entries 11–14). Rationalization of these contrasting results, however, is hampered by the lack of detailed information on the enolate structures. Other methods for the formation of titanocene enolates are also available. The di(cyclopentadienyl)chlorotitanium enolates of methyl ketones, *e.g.* (**35**), can be formed regiospecifically by reaction of an acid chloride with the di(cyclopentadienyl)titanocene methylene complex (Scheme 4).[26] These titanium enolates are regiostable and undergo aldol addition exclusively at the methyl position.

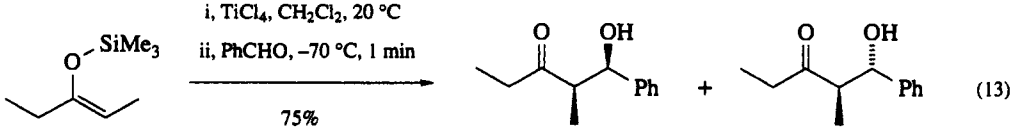


(**34**) *anti* 98% *syn* 2% (12)



(35)

Scheme 4



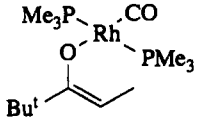
syn 81% *anti* 19% (13)

Trichlorotitanium enolates are formed in variable yield from trimethylsilyl enol ethers and an equivalent of $TiCl_4$ in dichloromethane at 20–35 °C.[27] These highly Lewis acidic preformed enolates then undergo aldol reactions at −70 °C to give moderate levels of *syn* selectivity, as in equation (13).[28] Trichlorotitanium enolates have also been used by Reetz *et al.* in their studies on diastereofacially selective aldol additions to α-alkoxy aldehydes.[15,16] Trichlorotitanium enolates are formed *in situ* in the aldol reaction of aromatic ketones and aldehydes using $TiCl_4$ and Et_3N.[29]

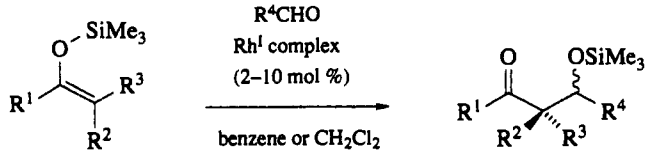
1.9.2.3 Rhodium

The aldol reactions of rhodium enolates have limited synthetic utility when employed stoichiometrically. *O*-Bound rhodium enolates of ketones, *e.g.* (**36**), have been prepared in high yield by reaction of preformed potassium enolates with carbonyldi(trimethylphosphine)rhodium(I) chloride or fluoride.[30] However, the basic nature of these particular enolates restricts their aldol reactions to nonenolizable aldehydes.

If rhodium enolates are used in a catalytic cycle they can promote aldol reactions under reasonably mild conditions. For example, the aldol reactions of trimethylsilyl enol ethers and ketene silyl acetals (**37**) with aldehydes can be catalyzed by various rhodium(I) complexes, under essentially neutral conditions, to give β-trimethylsiloxy ketones and esters (**38**; equation 14 and Table 6).[31,32] The study of Matsuda and coworkers[31] suggests that use of the rhodium complex $Rh_4(CO)_{12}$ (**39**; at 2 mol %) in benzene at 100 °C gives best results for the formation of adduct (**38**; Table 6, entries 1–7). There is negligible diastereoselectivity in most cases. Various cationic rhodium complexes such as (**40**) also catalyze the reaction. Reetz and Vougioukas have found that this aldol reaction proceeds well with the more reactive ketene silyl acetals, (**37**) for R^1 = OMe or OEt, in CH_2Cl_2 at room temperature (Table 6, entries 8–13).[32] The intermediacy of an η^1-*O*-bound rhodium enolate, such as (**41**), in the catalytic cycle is like-



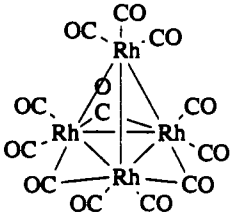
(36)



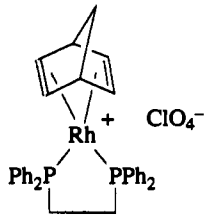
(37) (38) (14)

Table 6 Rh^{I}-catalyzed Aldol Reactions of Enol Silanes with Aldehydes (equation 14)

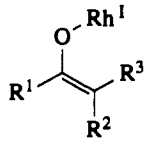
Entry	R^1	R^2	R^3	R^4	*Catalyst*	*Temperature (°C)*	*Yield (%)*	*Ref.*
1	Me	H	H	n-C_5H_{11}	(**39**)	100	71	31
2	Me	H	H	c-C_6H_{11}	(**39**)	100	35	31
3	Me	H	H	Ph	(**39**)	100	61	31
4	—$(CH_2)_4$—		H	n-C_5H_{11}	(**39**)	100	71	31
5	—$(CH_2)_4$—		H	c-C_6H_{11}	(**39**)	100	52	31
6	—$(CH_2)_4$—		H	Ph	(**39**)	100	83	31
7	Et	Me	H	Ph	(**39**)	100	54	31
8	MeO	Me	Me	Ph	(**40**)	22	75	32
9	MeO	Me	Me	n-C_6H_{13}	(**40**)	22	71	32
10	EtO	$OSiMe_3$	OEt	Ph	(**40**)	22	92	32
11	EtO	$OSiMe_3$	OEt	Pr^n	(**40**)	22	91	32
12	EtO	$OSiMe_3$	OEt	n-C_6H_{13}	(**40**)	22	82	32
13	EtO	$OSiMe_3$	OEt	$CH_2{=}CH(CH_2)_8$	(**40**)	22	74	32
14	Et	Ph	H	H	(**40**)	22	35	32



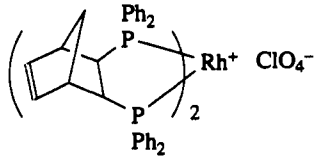
(**39**)



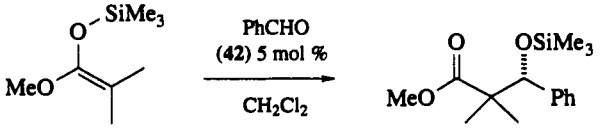
(**40**)



(**41**)



(**42**)



(**43**) 12% *ee*

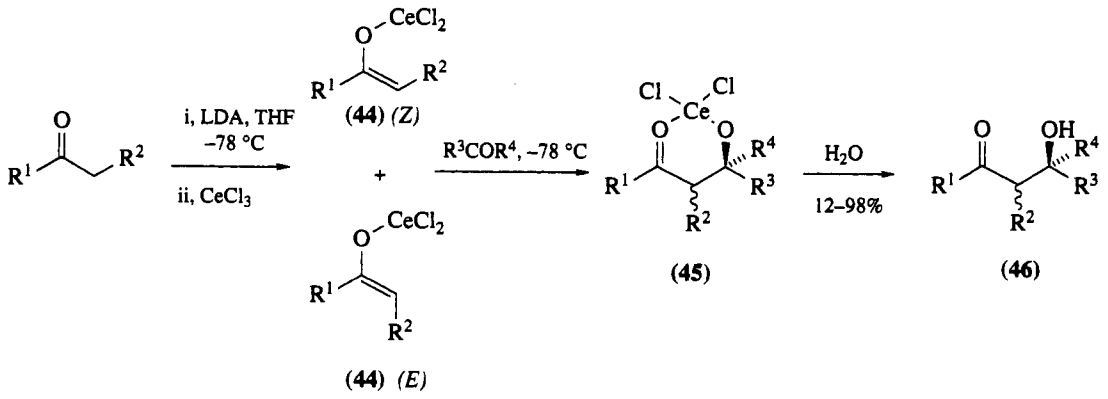
(15)

ly in these reactions. Support for this comes from the related work of Slough, Bergman and Heathcock, who have also developed a rhodium-catalyzed aldol reaction with benzaldehyde involving silyl enol ethers and ketene silyl acetals.[30]

Preliminary examples of catalytic enantioselective aldol additions using rhodium complexes with chiral phosphine ligands attached, *e.g.* (**42**), have been disclosed by Reetz and Vougioukas (equation 15);[32] although the low level of asymmetric induction so far obtained in the silylated aldol adduct (**43**) requires substantial enhancement before this reaction has any synthetic value. However, there is ample scope for future improvement by the use of more effective chiral diphosphine–rhodium complexes.

1.9.2.4 Cerium

The use of lanthanide metal enolates in the aldol reaction has, to date, only been developed to a synthetically useful level in the case of cerium (Scheme 5 and Table 7). Stereoselectivities are no better than those of lithium enolates, but the cerium enolates of ketones work well in crossed aldol additions to ketones (Table 7, entries 1–7) and sterically hindered aldehydes (Table 7, entries 9 and 10). Such crossed aldol reactions do not often work well with lithium enolates as enolate equilibration, retroaldolization and steric retardation of addition occur. Imamoto *et al.* have shown that cerium enolates (**44**), formed from anhydrous $CeCl_3$ (1.2 equiv.) and the preformed lithium enolates of ketones in THF at –78 °C, undergo such aldol reactions to give the corresponding β-hydroxy ketones (**46**), usually in high yield.[33] The cerium suppresses the retroaldol reaction by efficient chelation of the aldolate (**45**). A similar effect is known for zinc halide mediated aldol reactions (Volume 2, Chapter 1.8).[34] The stereoselectivity of the



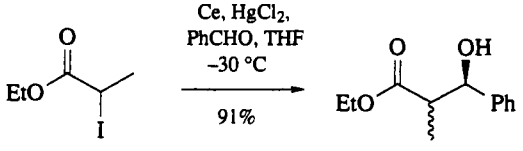
Scheme 5

Table 7 Aldol Reactions of Ketone Cerium Enolates with Aldehydes and Ketones (Scheme 5)[33]

Entry	R^1	R^2	R^3	R^4	*Diastereoselectivity*	*Yield (%)*
1	Ph	Me	—$(CH_2)_5$—			79
2	Ph	Me	—$(CH_2)_4$—			45
3	Ph	Me	Me	Et	40:60	62
4	Mesityl	Me	—$(CH_2)_5$—			56
5	Mesityl	Me	—$(CH_2)_4$—			12
6	Ph	H	*p*-ClC_6H_4	Me		60
7	Ph	Br	—$(CH_2)_5$—			75
8	Ph	Me	Ph	H	18:82	98
9	Ph	Me	Mesityl	H	20:80	93
10	Mesityl	Me	Mesityl	H	7:93	91
11	Mesityl	Me	Ph	H	9:91	94
12	—$(CH_2)_4$—		Ph	H	50:50	95
13	Ph	Br	Ph	H		74

cerium enolate addition parallels that of the lithium enolate and, therefore, can be rationalized by the conventional chair-like transition state.

Cerium enolates may also be generated reductively in THF from α-iodo or α-bromo esters in the presence of an aldehyde or ketone using cerium metal turnings and catalytic $HgCl_2$ (or cerium amalgam).[35] This leads to a Reformatsky-type reaction (Volume 2, Chapter 1.7) producing the β-hydroxy ester (**47**) as a mixture of diastereomers (equation 16).



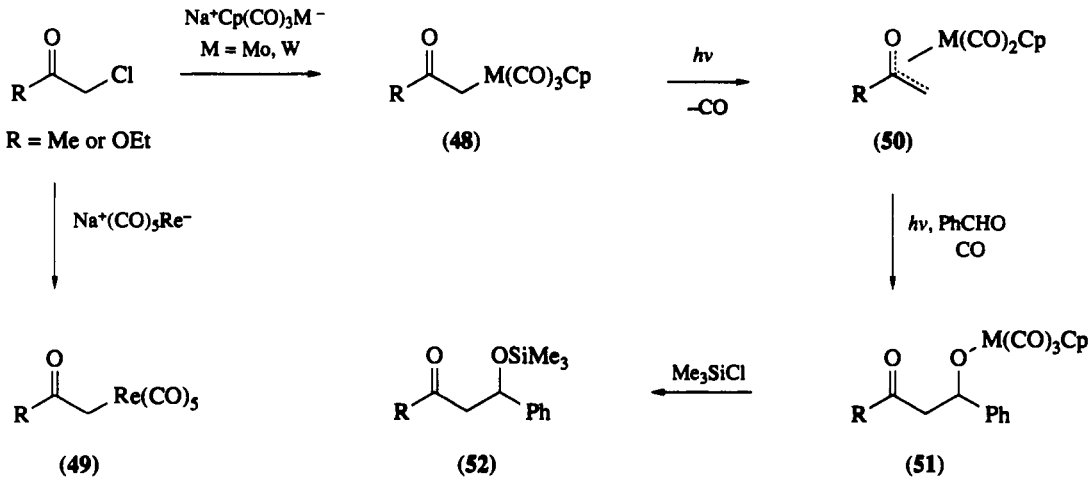
(16)

(**47**) *syn* : *anti* 50 : 50

1.9.3 ALDOL REACTIONS OF η^1-*C*-BOUND METAL ENOLATES AND η^3-METAL ENOLATES

1.9.3.1 Tungsten, Molybdenum and Rhenium

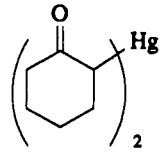
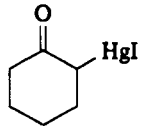
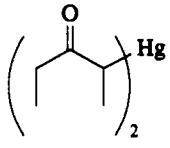
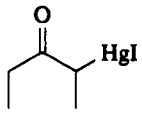
The enolates (**48**) and (**49**) of the transition metals tungsten, rhenium and molybdenum can be successfully prepared by the nucleophilic displacement of α-chloro ketones and α-chloro esters with the appropriate transition metal anion (Scheme 6). They are isolated as *C*-bound enolate derivatives and, except for the rhenium enolate (**49**), do not undergo thermal aldol additions to benzaldehyde. However, Bergman and Heathcock *et al.* have found that an aldol reaction of complex (**48**) with benzaldehyde can occur on irradiation *via* the rearranged η^3-oxaallyl derivative (**50**), where the metal aldolate (**51**) can then be



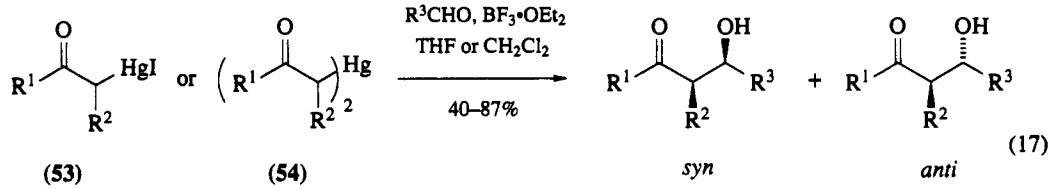
Scheme 6

converted *in situ* into the β-trimethylsiloxy ketone or ester (**52**).[36] These reactions have no real synthetic value at present; however, if it is possible to establish viable catalytic cycles in such photochemical transition metal enolate aldol reactions, then catalytic enantioselective aldol reactions might become accessible by using chiral phosphine ligands on the metal.[37] Some success has already been reported in this area using rhodium enolates (Section 1.9.2.3).

Table 8 *Syn:Anti* Selectivity in the $BF_3{\cdot}OEt_2$-catalyzed Aldol Reactions of α-Mercurio Ketones with Aldehydes (equation 17)[38]

Entry	*Substrate*	R^3	*Solvent*	*Temperature (°C)*	*Time*	*Syn:Anti*	*Yield (%)*
1		Ph	THF	r.t.[a]	2 h	80:20	85
2		Ph	THF	r.t.	7 h	90:10	60
3		Ph	CH_2Cl_2	0	2 min	>98:2	35
4		Ph	THF	r.t.	10 min	74:26	82
5		Ph	THF	r.t.	13 h	74:26	85
6		Ph	CH_2Cl_2	0	1 min	96:4	56
7		Ph	CH_2Cl_2	0	2 h	89:11	87
8		Bu^n	THF	r.t.	2 h	72:28	75
9		Bu^n	CH_2Cl_2	0	2 min	73:27	70
10		Ph	THF	r.t.	2 h	90:10	40

[a] r.t. = room temperature.



(53) (54) (17)

syn:*anti* 72:28 to > 98:2

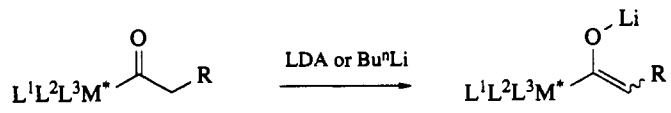
1.9.3.2 Mercury

The aldol reactions of *C*-bound mercury enolates (**53** or **54**; *i.e.* α-mercurio ketones) with aldehydes take place with *syn* selectivity in CH_2Cl_2 or THF under Lewis acid catalysis (equation 17 and Table 8).[38] The level of diastereoselectivity compares well with that obtained for zirconium and titanium enolates, but their preparation is more involved and so they are unlikely to be as useful in synthesis. Yamamoto and Maruyama have found that an equivalent of the Lewis acid $BF_3{\cdot}OEt_2$ is required to promote the reaction, although this has no apparent effect on the stereoselectivity (*i.e.* Hg → B exchange is assumed not to be operating). *Syn*:*anti* ratios are very high for short reaction times in CH_2Cl_2 (Table 8, entries 3 and 6), but some equilibration towards the thermodynamic *anti* isomer takes place on longer reaction times (Table 8, entry 7). The very high *syn* selectivity of >98% recorded for the kinetic aldol reaction between α-iodomercuriocyclohexanone and benzaldehyde (Table 8, entry 3) is comparable to that found for the corresponding titanium-mediated reaction of cyclohexanone (Table 3, entry 13). An acyclic transition state model involving an S_E-type reaction of the C—Hg bond has been proposed to account for this selectivity.

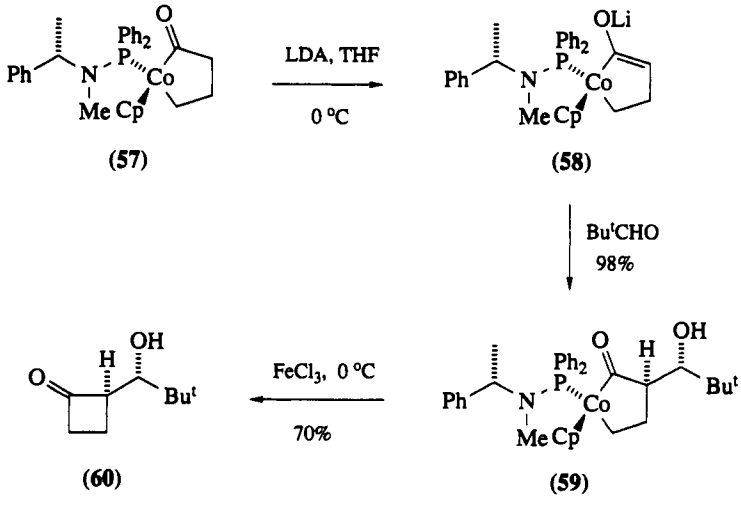
1.9.4 ALDOL REACTIONS OF METAL ENOLATES OF ACYL–TRANSITION METAL COMPLEXES

1.9.4.1 Cobalt

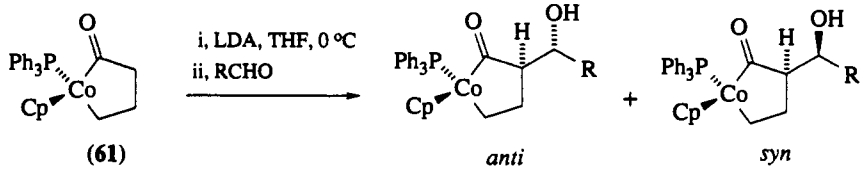
Organotransition metal acyls (**55**) are readily prepared by acylation of transition metal anions, migratory insertion in alkyl metal–carbonyl complexes or by attack of carbanions at metal-bound carbon monoxide. Their conversion into reactive lithium enolates (**56**) by deprotonation by strong base (LDA or Bu^nLi in THF) has been demonstrated for various cobalt– and iron–acyl complexes (equation 18). These lithium enolates, like simple ester enolates, undergo aldol reactions with aldehydes and ketones. The important attribute of these systems is that transition metal centered chirality can be introduced to exert high levels of diastereofacial selectivity in aldehyde or ketone attack on the enolate. The transition metal group can then function as a removable chiral auxiliary giving rise to chiral enolate equivalents. For example, Bergman and coworkers have shown that the optically pure lithium enolate (**58**), derived from the resolved acyl–cobalt complex (**57**), undergoes an aldol addition with pivaldehyde to give the *anti* adduct (**59**) as a single isomer (Scheme 7).[39] The very high stereoselectivity in this reaction is explained by the large steric bias for electrophilic attack on the face of the metallocyclopentanone enolate (**58**) opposite the bulky phosphine ligand and the operation of a chair-like aldol transition state, *viz.* (*E*)-enolate → *anti* aldol. The chiral auxiliary may then be removed oxidatively by $FeCl_3$ treatment to give the cyclobutanone (**60**) in enantiomerically pure form. Other less sterically demanding aldehydes give more modest *anti*:*syn* ratios using the simpler system (**61**; equation 19). However, conversion of the lithium enolate into a different metal enolate derivative might enhance this selectivity further.



(55) (56) (18)



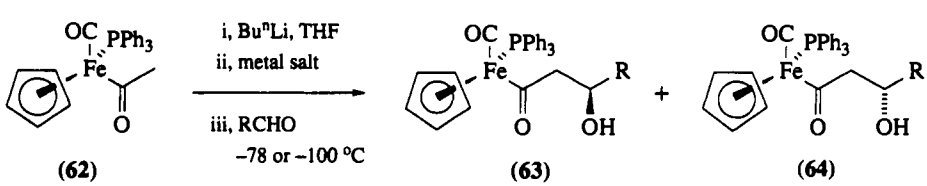
Scheme 7



(19)

1.9.4.2 Iron

Related aldol chemistry has been developed independently by the groups of Liebeskind and Davies based on acyclic chiral acyl–iron complexes,[40–46] which can be prepared in optically pure form. In the case of the acetyl system (**62**), the derived lithium enolate shows negligible diastereofacial selectivity in additions to aldehydes (equation 20 and Table 9, entry 1).[40–42] However, >97% diastereofacial selectivity is possible *via* the diethylaluminum enolate under carefully controlled conditions, *i.e.* when 2 equiv. of Bu^nLi are first used to generate the lithium enolate and an excess of Et_2AlCl (5 equiv.) is then added before addition of the aldehyde at ≤–95 °C (Table 9, entries 6–12).[42,43] Small changes in stoichiometry in this reaction lead to much poorer selectivity for isomer (**63**),[43] such that the Et_2AlCl may also be functioning as a Lewis acid for the aldehyde. Oxidative removal of the iron group then gives the β-hydroxy ester in high *ee*, if enantiomerically pure iron complex (**62**) is used. Note, however, that the results in Table 9 were obtained for the racemic complex (**62**). In principle, this method provides a highly selective chiral acetate enolate equivalent for aldol additions. The enolate face selectivity can also be reversed to produce adduct (**64**) as the major diastereomer if the corresponding tin(II) enolate is used (Table 9, entry 2).[41,43] Moreover, Ojima and Kwon[47] have subsequently shown that high aldol stereoselectivities (98:2 for benzaldehyde) can easily be obtained using the lithium enolate itself if one of the phenyl groups is replaced by a pentafluorophenyl group, as in the iron–acyl complex (**65**). The sense of the stereoselectivity

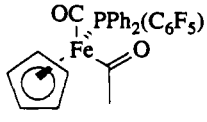


(20)

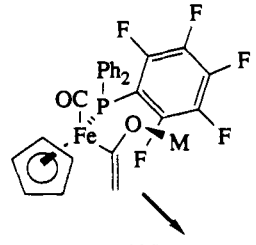
is now unaffected by variation of the metal counterion. This high π-face selection has been interpreted by the preferred formation and reaction of the enolate *via* conformation (**66**), which is favored by a stabilizing electrostatic interaction between the enolate oxygen and the electron-deficient pentafluorophenyl group.[47]

Table 9 Diastereofacial Selectivity in the Aldol Reactions of Chiral Acetyliron Enolates (equation 20)

Entry	*Metal salt*	*R*	*Temperature (°C)*	*Stereoselectivity*	*Yield (%)*	*Ref.*
1	None	Pr^i	−78	58:42	—	42
2	$SnCl_2$	Pr^i	−78	8:92	74	41, 43
3	CuCN	Et	−100	45:55	—	42
4	$(Pr^iO)_3TiCl$	Et	−100	87:13	—	42
5	$Bu^i{}_2AlCl$	Pr^i	−78	89:11	76	41, 43
6	Et_2AlCl	Pr^i	−100	>99:1	86–90	42
7	Et_2AlCl	Pr^i	−95	97:3	85	43
8	Et_2AlCl	Me	−100	96:4	86–90	42
9	Et_2AlCl	Et	−100	>99:1	86–90	42
10	Et_2AlCl	$PhCH_2$	−100	>95:5	86–90	42
11	Et_2AlCl	Bu^t	−100	>99:1	86–90	42
12	Et_2AlCl	Ph	−100	>95:5	86–90	42



(**65**)



(**66**)

The corresponding chiral propionate enolate from (**67**) can be used to produce *anti* adducts (**68**) with high selectivity by this aluminum-mediated aldol reaction (equation 21 and Table 10, entries 1–4).[44] Again, carefully controlled experimental conditions are probably required for optimum selectivity. Using optically active reagents, this reaction has been applied by Davies and coworkers to the enantiocontrolled synthesis of (**72**), a degradation product of the marine norterpene sigmosceptrellin.[45] If the lithium enolate is converted instead into the copper(I) enolate by reaction with copper cyanide in THF at −40 °C, the major product in the aldol reaction with aldehydes is the *syn* isomer (**69**; Table 10, entries 5–9).[44] When this copper(I) enolate is reacted with symmetrical cyclic ketones, the aldol adduct (**73**) is obtained with high stereoselectivity (≥95:5).[46] A working model for this selectivity is suggested by consideration of structure (**74**) as the reacting conformation of the enolate. The important feature of these reactions is that the enolate reacts with the aldehyde, *via* a chair or boat transition state, on its π-face opposite the sterically demanding PPh_3 group.

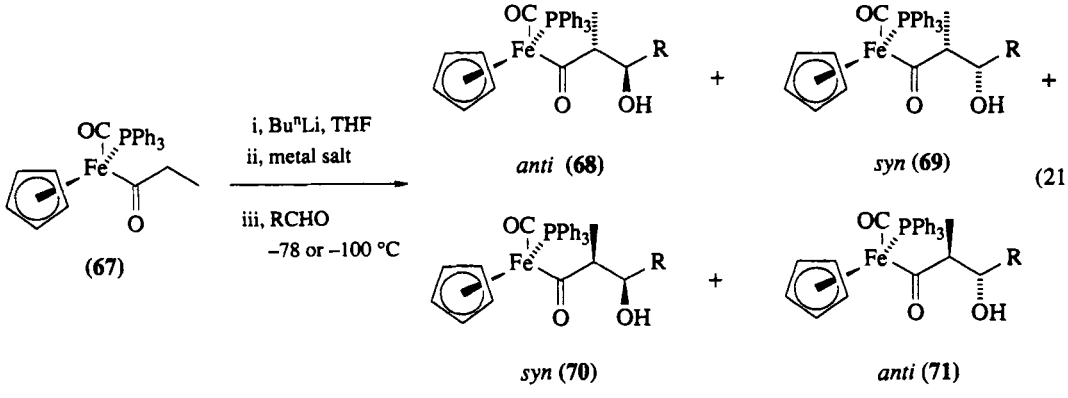
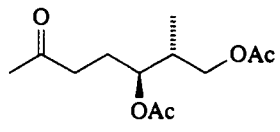


Table 10 Stereoselectivity in the Aldol Reactions of Chiral Propionyliron Enolates (equation 21)[44]

Entry	*Metal salt*	*R*	*Temperature (°C)*	*Anti (68)*	*Syn (69)*	*Syn (70)*	*Anti (71)*
1	Et_2AlCl	Me	−100	91	0	6	3
2	Et_2AlCl	Et	−100	88	0	12	0
3	Et_2AlCl	Pr^i	−100	90	0	9	<1
4	Et_2AlCl	Bu^t	−100	100	0	0	0
5	CuCN	Me	−78	12	87	<1	0
6	CuCN	Et	−78	9	90	<1	0
7	CuCN	Pr^i	−78	6	93	<1	0
8	CuCN	Bu^t	−78	4	96	0	0
9	CuCN	Ph	−78	4	95	<1	0



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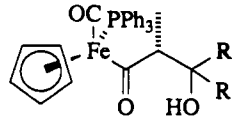

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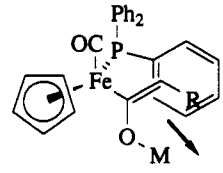
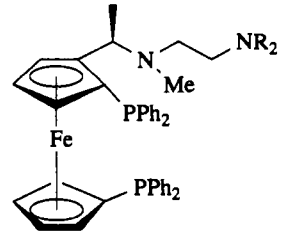
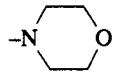


(74)

1.9.5 OTHER ASYMMETRIC ALDOL REACTIONS INVOLVING TRANSITION METALS

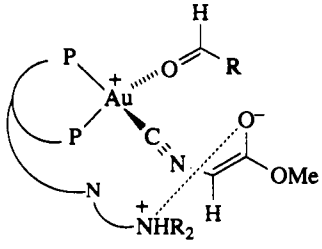
A significant advance in the development of catalytic enantioselective aldol reactions has been made by the use of rationally designed chiral ferrocenylphosphine ligands like (**75**) and (**76**) in the presence of the cationic gold(I) complex (**77**).[48,49] Ito *et al.* have found that the gold-catalyzed aldol reaction of methyl isocyanoacetate with aldehydes, using 1 mol % of ligands (**75**) or (**76**) in CH_2Cl_2 at 25 °C, leads to *trans* oxazolines (**78**) in up to 96% *ee* with high diastereoselectivity (equation 22 and Table 11). Acid hydrolysis of the oxazoline aldol product gives *syn*-α-amino-β-hydroxycarboxylic acids like L-threonine (Table 11, entry 2 and equation 23).[49] Overall, this reaction then corresponds to the enantioselective aldol reaction of a glycine enolate equivalent and gives comparable selectivity to that obtained using chiral titanium enolates (Section 1.9.2.2). The impressive selectivity in this aldol reaction has been interpreted by coordination of the ammonium enolate of the isocyanoacetate and aldehyde to the gold in the preferred transition state (**79**). Other metals, as well as other chiral phosphine ligands, are found to give



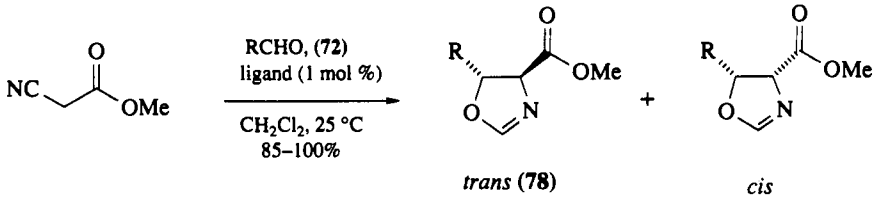
(**75**) $NR_2 = NEt_2$ (**76**) $NR_2 =$ 

$[Au(c\text{-}C_6H_{11}NC)_2]^+ BF_4^-$

(**77**)



(**79**)



(22)

trans (**78**)

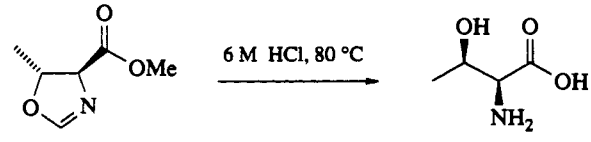
72–97% *ee*

cis

trans:*cis* 84:16 to 100:0

Table 11 Enantioselectivity and Diastereoselectivity in the Aldol Reactions of Methyl Isocyanoacetate Under Catalysis by Chiral Ferrocenylphosphine–Gold Complexes (equation 22)

Entry	*Phosphine*	*R*	*Trans:Cis*	*Ee/trans (%)*	*Yield (%)*	*Ref.*
1	(**75**)	Me	84:16	72	100	48
2	(**76**)	Me	89:11	89	99	49
3	(**75**)	Pr^i	98:2	90	99	48, 49
4	(**76**)	Pr^i	99:1	92	100	48
5	(**76**)	(*E*)-$Pr^nCH{=}CH_2$	87:13	92	85	48
6	(**75**)	Ph	89:11	93	98	48
7	(**76**)	Ph	95:5	95	93	48
8	(**75**)	c-C_6H_{13}	97:3	95	90	48
9	(**75**)	Bu^i	100:0	97	100	48



(23)

much lower selectivity. The nature of the terminal amine, as well as the length of the connecting chain to the ferrocene nucleus, is also critical.

Future significant developments in the catalytic enantioselective and diastereoselective aldol reactions of a wide range of carbonyl compounds are anticipated by the design of other new and efficient chiral transition metal reagents.

1.9.6 ADDENDUM

A highly effective method for the direct generation of trichlorotitanium enolates from acyclic ketones has been developed by the Evans group,[50] which relies on precomplexing with $TiCl_4$ followed by enolization with diisopropylethylamine at -10 °C in dichloromethane. The (*Z*)-enolates produced in this way then undergo a *syn* selective aldol reaction on addition of aldehydes (*c.f.* Scheme 3). The stereochemical control is comparable to that using boron enolates, which indicates that this simple titanium-mediated aldol reaction will have wide utility. Furthermore, high levels of diastereofacial selectivity can be obtained using α-chiral ethyl ketones.

The titanium carbohydrate complex (**30**) has been used to transmetallate the (*E*) lithium enolate of 2,6-dimethylphenyl propionate to aldol addition to aldehydes.[51] This provides access to either *syn* aldols in 91-97 % *ee* (reaction at -78 °C throughout) or *anti* aldols in 94–98% *ee* (warming the enolate to -30 °C) with good diasteroselectivity in many cases. This highly unusual situation, that is that the kinetically generated (*E*)-enolate → *syn* adduct and the isomerized (*Z*)-enolate → *anti* adduct, has been rationalized by Duthaler and coworkers by invoking boat transition states for both reactions. Together with the earlier aldol reactions described using D-glucose-derived titanium enolates (equations 10 and 11), these additions all lead to attack at the *re*-face of the aldehyde. This method is clearly useful for enantioselective ester–aldehyde aldol reactions in many situations. Moreover, it suggests that boat transition states may be more important in titanium aldol reactions than previously recognized.

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1.10
The Henry (Nitroaldol) Reaction

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1.10.1 INTRODUCTION

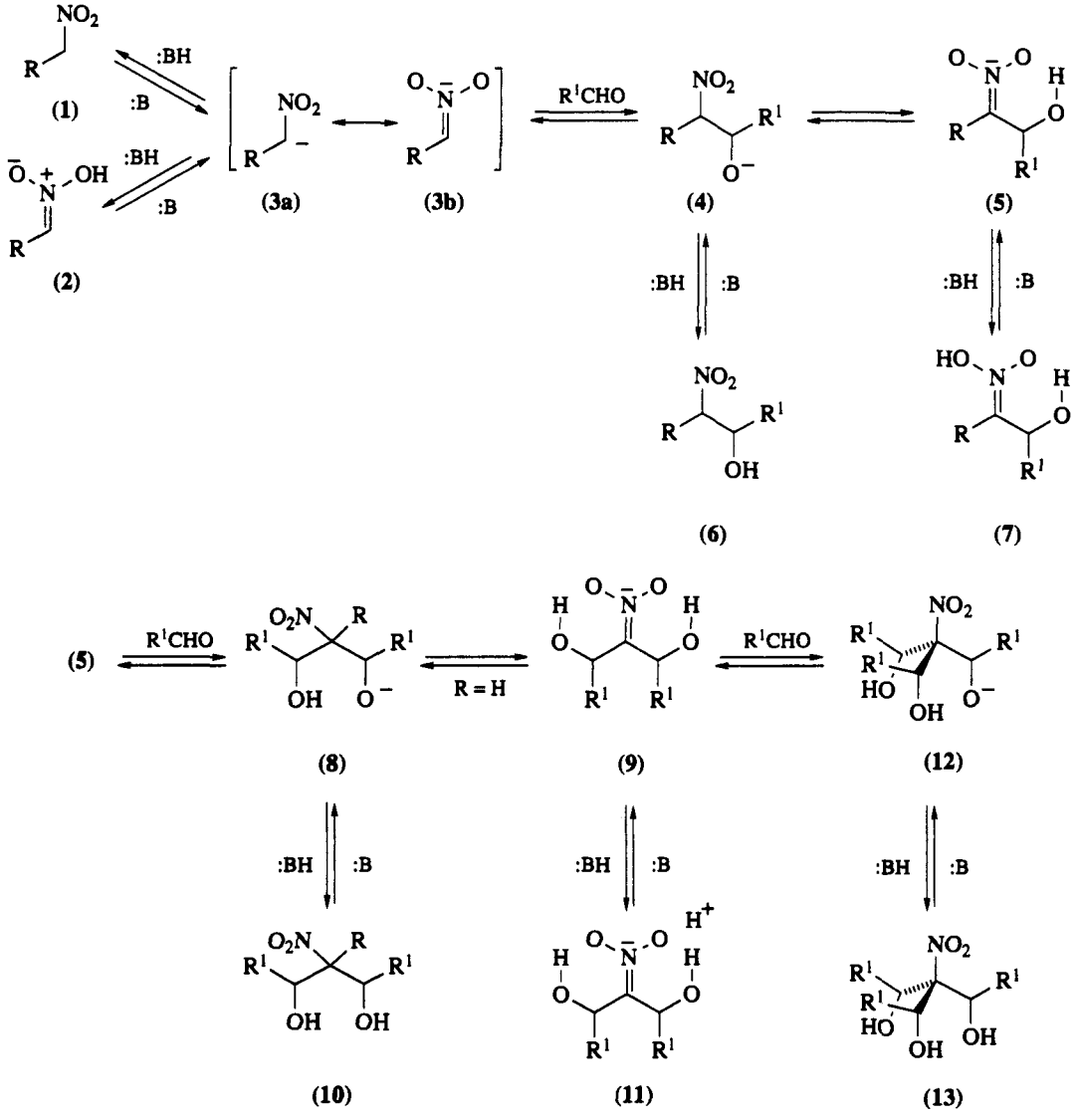
The utilization of carbanions stabilized by various electron-withdrawing groups to effect carbon–carbon bond formation occupies a central position in organic synthesis. This chapter focuses on the reactions of nitro-stabilized carbanions (nitronate anions or their equivalents) with aldehydes and ketones. This route for the coupling of a carbonyl and a nitroalkane component, leading to vicinal nitro alcohols, was discovered in 1895 by Henry[1] and is currently known as the Henry or nitroaldol reaction.

At the end of the 19th century, nitroalkanes were the center of very important achievements made by organic chemists. During 1872, Victor Meyer[2] produced the first mononitroalkane and a few months later Kolbe[3] prepared nitromethane from sodium nitrite and chloroacetate. It was 23 years later that Louis Henry discovered his reaction, and within the next year J. U. Nef prepared the first nitronic ester and discovered the conversion of nitro group to carbonyl group,[4] one of the most important transformations of nitroalkanes, which now bears his name. Since the original work of Henry, shortly before the turn of the century, the nitroaldol reaction has been depicted as a classical chain-lengthening reaction and, in common with a number of other classical reactions, there is a vast literature. The vigorous development of organic chemistry over the past decades reveals an ever-increasing interest in the utilization of nitroalkanes in synthesis; the Henry reaction and some of its recent improvements have found numerous applications in assembling carbon atoms and functional groups to build natural product structures with high chemo- and regio-selectivity.

There are several important general reviews on the utility of nitro aliphatic compounds and the Henry reaction in organic synthesis.[5–19] Several of these are quite recent reviews and give further evidence for renewed interest in this area of chemistry.

1.10.2 GENERAL CONSIDERATIONS ON THE NITROALDOL REACTION AND ITS UTILITY IN ORGANIC SYNTHESIS

The Henry reaction (nitroaldol addition) is one of the classical C—C bond-forming processes by which diastereomeric mixtures of 2-nitro alcohols are formed on treatment of primary and secondary nitroalkanes and carbonyl derivatives (more frequently aldehydes) with a base. It is clear that the Henry reaction (Scheme 1) is an aldol-type reaction and the deprotonation of primary and secondary nitroalkanes with a whole range of different bases for generating the corresponding nitronate monoanions constitutes the first step of the sequence. The nitro group is particularly effective in stabilizing a negative charge on the adjacent carbon. Nitroalkanes (**1**) have pK_a values of approximately 9–10; the corresponding nitronic acids (**2**), or *aci*-nitro compounds, resemble carboxylic acids in their acid strength (pK_a 2–6), and thus they are readily deprotonated to give a nitronate salt. Then the nitro and *aci*-nitro forms, related by the nitro–*aci*-nitro tautomerism, share a common anion (**3**). These stabilized carbanions are ambident nucleophiles as implied in the canonical forms of (**3**). Since oxygen is the more electronegative 'end' of the delocalized system, such ions might have been expected to undergo *O*-alkylation rather than the exclusive *C*-alkylation. The fact is that these reagents are rather poor C-nucleophiles and normally they undergo predominant *O*-alkylation with electrophiles.



Scheme 1

Scheme 1 illustrates the equilibria involved in a base-catalyzed nitroaldol reaction consisting of: deprotonation of a nitroalkane to give the anion (**3**); nucleophilic attack at the carbonyl group leading to the formation of the hydroxyalkylated nitroalkane anion (**4**), as well as its corresponding α-hydroxy nitronate (**5**); and protonation of these latter systems to give a diastereomeric mixture of the 2-nitro alcohol (**6**), its α-hydroxynitronic acid (**7**) and the regenerated free base. However, in the case of primary nitroalkanes and nitromethane the product of this reaction sequence still contains an acidic hydrogen, and the process may thus be repeated giving the dihydroxyalkyl derivatives (**8**) and (**9**) of the starting nitroalkane. The second hydroxyalkylation may be more difficult than the first because the first hydroxyalkyl substituent introduced, being electron repulsive, will reduce the acidity of the adjacent hydrogen, and the corresponding carbanion will, in any case, be more sterically hindered than its parent analog. Trihydroxyalkylation is a peculiar reaction of nitromethane with aldehydes.

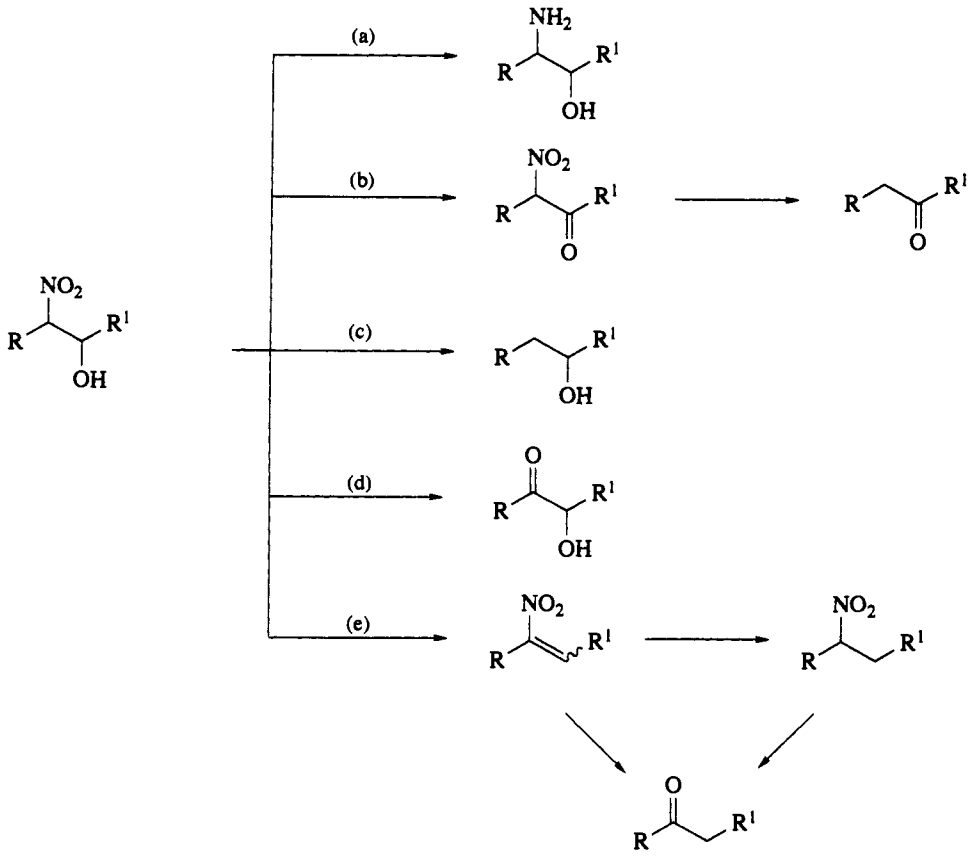
It is well known[20] that the tautomerization of a nitronic acid to its parent nitroalkane through a nitronate anion proceeds essentially to completion for most simple nitroalkanes because of the relatively weaker acidity of a nitroalkane compared to its corresponding nitronic acid or *aci* form. Inductive effects exhibit predictable behavior in relation to ionization constants, which affect tautomerization rates. Electron-withdrawing groups (*e.g.* halogen and nitro groups) increase the strength of nitronic acids and the tautomerization rate, while electron-releasing groups such as methyl decrease both acidity and tautomerization rate. Slow tautomerization of nitronic acids to the nitro forms has been observed when resonance-stabilized nitronate anions (*e.g.* fluorene-9-nitronic acid is very stable) are involved. These findings reveal[20] the relatively slow *C*-protonation of resonance-stabilized nitronic acids. However, it is worth noting that tautomerization may be slowed down by the hydrogen-bonded stabilization of the nitronate intermediate in spite of the enhanced acidity. This effect is of great importance in the Henry reaction where vicinal nitro alcohols are formed. This stabilizing effect increases with the number of hydrogen-bonding groups and significantly influences the equilibria of Scheme 1 involving compounds (**6**), (**7**), (**10**), (**11**) and (**13**) as products of mono-, di- and tri-hydroxyalkylation reactions. For example, 2-*aci*-nitropropane-1,3-diol (**11**; R′ = H), where two hydroxy groups are available, has been isolated in 73% yield from nitromethane and paraformaldehyde in a 1:2 ratio under fluoride ion catalysis.[21]

It will become apparent in the subsequent discussion that the success of most of the preparatively useful reactions involving the Henry reaction is attributable to the selection of appropriate reaction conditions to avoid concomitant or further transformations of the initial 2-nitro alcohol product.

By examining Scheme 1 it is possible to verify the key role of the base as catalyst for the overall process and to justify the lack of stereoselectivity which, in general, has been observed in nitroaldol additions. In fact, the reversibility of the nitroaldol process, as well as the difficulty of a stereoselective protonation of the stereogenic center of the nitronate intermediates, leads to a mixture of diastereomeric 2-nitro alcohols.

The potential utility of the Henry reaction as a chain-lengthening tool can be illustrated by the great importance of 2-nitro alcohols as pivotal synthetic intermediates in synthesis (Scheme 2). They can be converted into 2-amino alcohols by reduction of the nitro group with lithium aluminum hydride,[22] aluminum amalgam,[23] hydrogen and palladium on carbon,[24,25] hydrogen and platinum[7] or by using Raney nickel.[7,26–30] This route to such useful compounds is in addition to a number of different synthetic procedures[31,32] including, *inter alia*, reduction of α-amino ketones, ring-opening of epoxides with amines or amine precursors, oxyamination of alkenes and other methods. Vicinal amino alcohols have a broad significance in organic chemistry and their biological relevance can be seen in the structures of epinephrine (adrenalin) and related mediators of the sympathetic nervous system,[33] as well as in the chemistry and biochemistry of sphingolipids[34] and in the structures of some carbohydrate components of a group of biologically important anthracycline antibiotics. L-Daunosamine, L-ristosamine, L-acosamine and L-vancosamine are typical compounds of this family of amino sugars.[28–30,35]

2-Nitro alcohols can be oxidized to give the corresponding 2-nitro ketones. In the past, this kind of reaction has been performed with strong oxidizing agents and in strong acidic media.[36,37] However, more recently, several very mild and efficient procedures have been devised to effect this conversion. Pyridinium chlorochromate[38] in dichloromethane, and chromium reagents under phase-transfer conditions[39] were shown to be sufficiently mild and also gave good results with substrates which are acid or base sensitive. The utility of linear α-nitro ketones has been increased recently by the discovery of some direct[17] and indirect[19] procedures to effect the replacement of the nitro group by hydrogen. These reductive denitration reactions have opened up new routes to nitroalkanes. In fact, one synthetic utility of such a transformation consists in the possibility of using primary nitroalkanes as synthons for alkyl anions. Several functionalized nitroalkanes have been reported to be useful functionalized alkyl anion synthons in the synthesis of natural products *via* 2-nitro alcohol and α-nitro ketone intermediates.[17,19] In some cases it has also been possible to effect a direct reductive denitration of the 2-nitro alcohol itself to obtain the

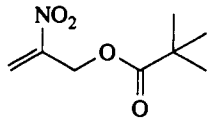


Scheme 2

corresponding alcohol.[40] However, the conversion of 2-nitro alcohols into conjugate nitroalkenes can be considered by far the most important. This reaction can be accomplished by dehydration with several reagents including dicyclohexylcarbodiimide, methanesulfonyl chloride, pivaloyl chloride and acetic or phthalic anhydride. Conjugated nitroalkenes are intermediates of a certain importance; there are a wide range of efficient methods for their transformations into other functionalities. Among them, the selective reduction to nitroalkanes[18] and the conversion of the latter into their corresponding ketones by the Nef reaction[4,19] play a very important role. This key reaction, which effectively reverses the polarity of the neighboring carbon from a potentially nucleophilic to an electrophilic one, is of great strategic importance, and can also be performed by working on the α-nitroalkene itself.[18] The wide range of new methods for carrying out the Nef reaction, together with the nitroaldol reaction, has led synthetic chemists to consider primary nitroalkanes as useful and convenient reagents for acyl anion synthons.[12,19] This double possibility for using primary nitroalkanes as versatile starting material and reagents for alkyl anion synthons (equation 1), as reported before, and for acyl anion synthons (equation 2) has significantly increased the synthetic potential of nitroalkane derivatives in the building of organic structures in a predictable way. In any case, both these possibilities stem from the central role of the Henry reaction in C—C bond formation.

(1)

(2)



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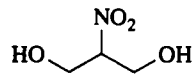


(15)

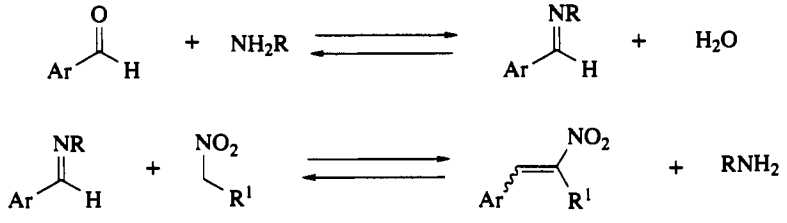
The vast preparative potential of nitroalkenes has been the subject of recent excellent reviews,[8,14–16,18] some of them highly focused on synthetic aspects. It is worthy of note that conjugate nitroalkenes, being good activated alkenes, are also very efficient dienophiles in Diels–Alder reactions[15] and their use, in some cases, can be considered complementary to that of other classical dienophiles in the regiochemistry of cyclization. In addition, they are very good acceptors of C-nucleophiles as well as S-, O- and N-nucleophiles[9,15] and a number of heteroatom-substituted nitro compounds have been reported,[14] in particular, the condensation reactions of conjugated nitroalkenes with enol silanes,[14,15] carboxylic acid dianions, ester enolates and monoanions derived from β-dicarbonyl compounds to give 1,4-dicarbonyl derivatives.[15]

Reactions of metal-activated nucleophiles with conjugated nitroalkenes, dialkylcuprates, Grignard reagents and alkyllithium derivatives gave unsatisfactory yields of alkylated products, owing to both the high reactivity and the basic properties of these organometallic reagents. Nevertheless, more recently it was reported that triorganoallanes (AlR_3, AlR_2R') and the corresponding etherate complexes are very effective reagents in conjugate alkyl, aryl, alkenyl and alkynyl group transfer to α-nitroalkenes.[41,42]

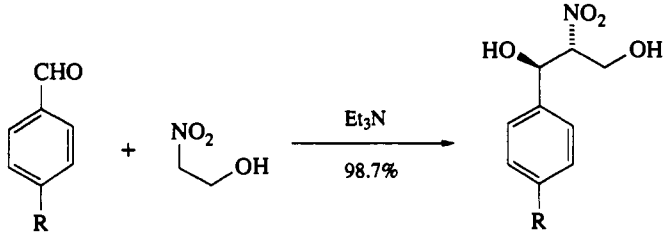
Finally, it has been shown that the pivalate of 2-nitro-2-propen-1-ol (**14**; NPP),[43] a nitroalkene with an allylic leaving group, can be used as a versatile *multiple coupling reagent* by selective sequential reactions with several nucleophiles as varied as anilines, indoles, enolates and organolithium compounds. The preparation of NPP has been reported on a 50 g scale from nitromethane and formaldehyde through the nitropropanediol (**15**), deriving from two consecutive nitroaldol reactions. Due to the multitude of conversions of the nitro group, NPP[43] and its analogs[44,45] provide access to a great variety of structures without NO_2 and constitute very important multiple coupling reagents for convergent syntheses.

1.10.3 CLASSICAL NITROALDOL PROCEDURES AND THEIR LIMITATIONS

The Henry reaction is routinely performed in the presence of only catalytic quantities of a base. Several base catalysts including alkali metal hydroxides, carbonates, bicarbonates, alkoxides, calcium and barium hydroxides and magnesium and aluminum ethoxides have been used. Anion-exchange resins and, among organic bases, primary and tertiary amines and ammonium acetate and fluoride have proven to be

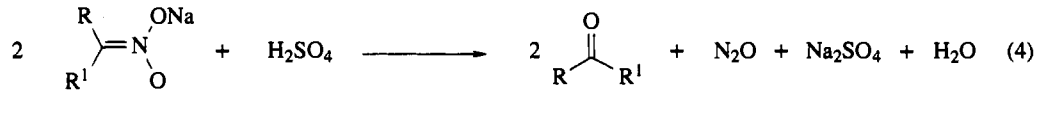


Scheme 3

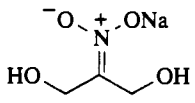


(3)

(**16**) R = H
(**17**) R = NO_2



(4)



(18)

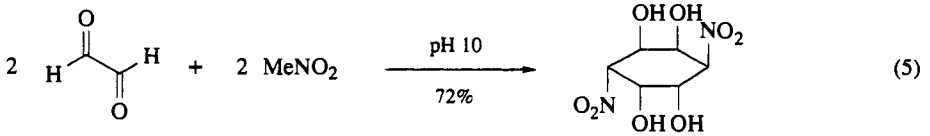
useful. Since basic reagents are also catalysts for the aldol condensation and for the Cannizzaro reaction when aldehydes are used as carbonyl sources, it is necessary to adopt experimental conditions to suppress these competitive reactions.[5–9] To obtain better yields of 2-nitro alcohols, it is necessary to carefully control the basicity of the reaction medium. The concentration of carbonyl component also has to be kept to a minimum for a sufficient rate of reaction avoiding aldol condensation and the Cannizzaro reaction. Furthermore, 2-nitro alcohols formed in the Henry reaction may undergo base-catalyzed elimination of water to give α-nitroalkenes which readily polymerize. This elimination is difficult to avoid when aryl aldehydes and ketones are used. The use of primary amines as base catalysts improves yields of β-nitrostyrenes, presumably *via* the formation of an imine intermediate (Scheme 3).[6,9] However, when benzaldehyde was treated with 2-nitroethanol in the presence of triethylamine as catalyst DL-*threo*-1-phenyl-2-nitropropane-1,3-diol (**16**; equation 3) was obtained in 98.7% yield with >95% *ds*; compound (**17**) is important as an intermediate in an industrial synthesis of the antibiotic chloroamphenicol.[12,46] It was found that inorganic bases, such as sodium and potassium hydroxides and sodium alkoxides could be used with some success in the preparation of 1-aryl-1-hydroxy-2-nitroalkanes if their alkali salts are acidified with acetic acid or by slow addition of mineral acids. In the presence of strong acids, a fast, acid-catalyzed dehydration occurs, giving β-nitrostyrene derivatives in high yields.

In general, it would be better to remove the base catalyst before working up the reaction mixture. This operation must be done with sufficient care to avoid, if this is not desired, the Nef reaction (equation 4) on the salt of the *aci* tautomer of the product as well as of the starting nitroalkane present at the equilibrium. Anyway, since base-catalyzed aerobic oxidation of nitroalkanes can give products formed by a free radical chain reaction, it is necessary to keep the temperature of the nitroaldol reaction at a practical minimum. Aliphatic aldehydes, and formaldehyde in particular, are more prone than ketones to undergo the Henry reaction. Nitromethane reacts more easily to give multiple addition products (**10**), (**11**) and (**13**). Primary nitroalkanes also may react with two equivalents of formaldehyde but, in general, the reaction tends to stop with only one aldehyde condensed when homologs of nitromethane and formaldehyde are used and when the ratio of reagents has been chosen with care. Secondary nitroalkanes react more sluggishly than primary ones, while tertiary nitroalkanes obviously do not react at all.

In some cases, a stoichiometric amount of the base was employed to facilitate isolation of the product by precipitation of its salt. For instance, the sodium salt of 2-*aci*-nitropropane-1,3-diol (**18**) was prepared in >95% yield of isolated product starting from nitromethane and paraformaldehyde in a 1:2 ratio by using 1.2 equiv. of sodium methoxide in methanol. The successive protonation of (**18**) was achieved in 75% yield by quick addition of salicylic acid in *t*-butyl methyl ether. These highly satisfying results in preparing 2-nitropropane-1,3-diol (**15**),[43] key intermediate for NPP synthesis, stem also from adequate control of temperatures and reaction times, dilution of the reaction mixtures and choice of solvents.

1.10.3.1 Nitroaldol Reactions with Dialdehydes

Reaction of nitromethane in aqueous sodium carbonate with glyoxal led to cyclization (equation 5).[7] A substance soon precipitated (72% yield), to which was assigned the structure of 1,4-dideoxy-1,4-dinitro-

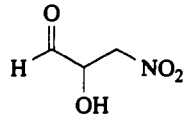


(5)

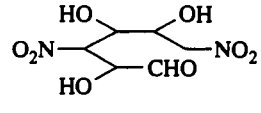
(19)

neo-inositol (**19**), one of the 14 theoretically possible configurations. 3-Nitrolactaldehyde (**20**) was demonstrated to be a key intermediate, probably together with (**21**), in the cyclization of glyoxal with nitromethane.

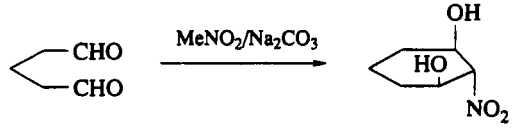
Two consecutive nitroaldol reactions were observed when nitromethane, or one of its higher homologs, was treated with 1,4-, 1,5- and 1,6-dialdehydes in the presence of catalytic or stoichiometric amounts of a base. This sequence consists of a cyclization process where a faster intramolecular nitroaldol reaction follows the first intermolecular one and the methyl group of the nitromethane is incorporated into the ring. This reaction leads to five-, six- and seven-membered rings and is equally applicable to aliphatic, aromatic and sugar dialdehydes.[7,9] Three-atom tethers offer the best results. In the case of glutaraldehyde and nitromethane, nitrodiol (**22**; equation 6) was readily obtained as a single *trans,trans* diastereomer. This compound represented a useful system for model studies of synthetic and stereochemical problems implicated in the more complex chemistry of nitro sugars. The pioneering studies of Fisher and Lichtenthaler were useful to Seebach and coworkers[45] in the preparation of enantiomerically pure derivatives of cyclic 2-nitroallylic alcohols, which are important chiral multiple coupling reagents. *trans,trans*-2-Nitrocyclohexane-1,3-diol (**23a**), 3,4,5,6-tetrahydro-4-nitro-2*H*-pyran-3,5-diol (**23b**), 4-nitrothiane-3,5-diol (**23c**) and some of their derivatives (Scheme 4) were easily prepared from methanolic solutions of the starting dialdehydes and nitromethane or nitroethane (1.5 equiv.) in the presence of cata-



(**20**)

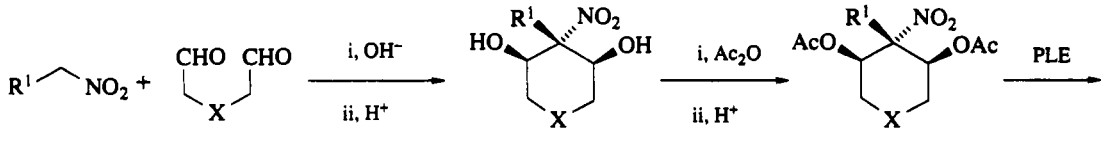


(**21**)

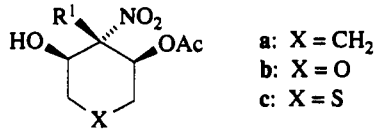


(6)

(**22**)

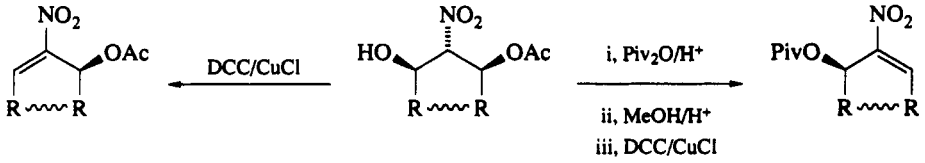


(**23a–c**) (**24a–c**)



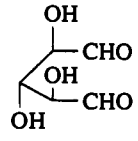
(**25a–c**)

Scheme 4

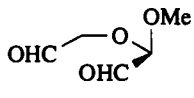


Scheme 5

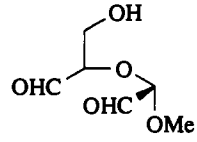
lytic amounts of 2 M NaOH and then converted into the corresponding diacetates (**24a–c**). The reproducible enantioselective saponification of the corresponding diacetates with pig liver esterase (PLE) gave monoacetates (**25a–c**) of >95% *ee*. The *pro-(R)* enantiotopic acetate group appeared to be saponified preferentially and the open chain diacetate of *meso*-2-nitropropane-1,3-diols also gave satisfying results. Enantiomerically pure derivatives of nitroallylic alcohols were obtained by elimination of water or acetic acid from the hydroxy acetates (Scheme 5). The cyclization reaction of nitromethane with aldehydic diglycol derivatives of monosaccharides formed by periodate oxidation, 'sugar dialdehydes', has been depicted as an excellent procedure to synthesize 3-amino sugars.[7,9] 'Sugar dialdehydes' (**26**) to (**34**) are the most used in cyclization reactions with nitromethane to prepare 3-amino-3-deoxy derivatives of, *inter*



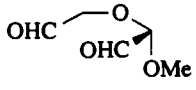
(**26**)



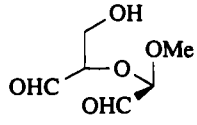
(**27**)



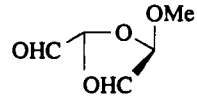
(**28**)



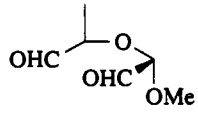
(**29**)



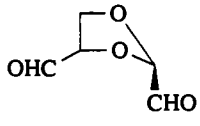
(**30**)



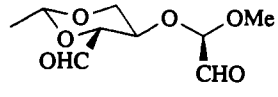
(**31**)



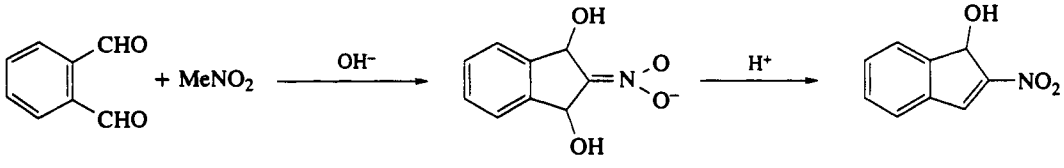
(**32**)



(**33**)

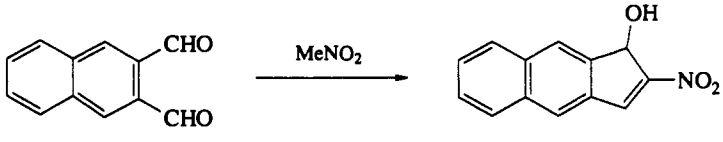


(**34**)

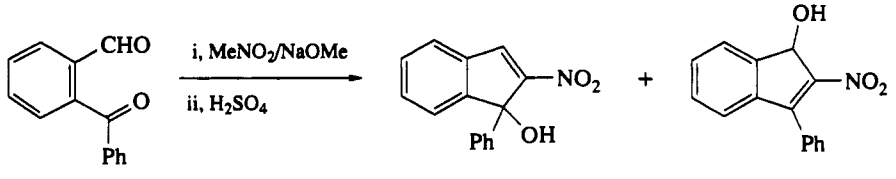


(**35**)

Scheme 6

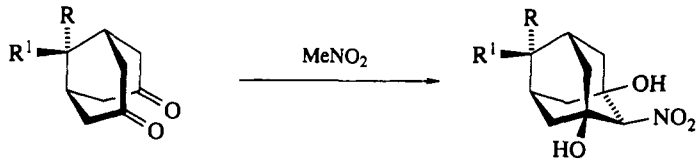


(7)



(8)

(**36**) (**37**)



(9)

alia, glucose, mannose, talose, 3-amino-3,6-dideoxyglucosides of the D and L series and 3-amino derivatives of 3-deoxyheptopyranoses.

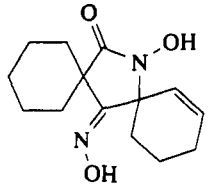
In the case of aromatic dialdehydes, the cyclization is frequently accompanied by dehydration.[7,9] Thus, *o*-phthalaldehyde cyclizes when treated with nitromethane in the presence of alcoholic potassium hydroxide (Scheme 6) to give the *aci*-nitro salt that undergoes dehydration by acidification with mineral acid to form 2-nitroinden-1-ol (**35**). This reaction was discovered in 1910 by Thiele and Weitz and can be considered the first demonstrated example of the cyclization of a dialdehyde with nitromethane. Like *o*-phthalaldehyde, naphthalene-2,3-dicarbaldehyde and *o*-benzoylbenzaldehyde[47] undergo ready cyclization with nitromethane under similar reaction conditions to form respectively, 2-nitrobenzinden-1-ol (equation 7) and two isomeric *o*-nitrohydroxyindenes (**36**) and (**37**) (equation 8) upon acidification with mineral acid. The cyclization with nitromethane also works well with suitable diketones such as bicyclo[3.3.1]nonane-3,7-diones where the carbonyl groups are favorably oriented for cyclization: on treatment with nitromethane and sodium methoxide the corresponding 2-nitroadamantane-1,3-diols (equation 9) are obtained in fair to good yields.

1.10.3.2 Nitroaldol Reactions with Ketones

It has been observed that 'the nitroaldol reaction becomes less and less satisfactory as more substituents are attached to the C atoms to be linked together'.[48]

The Henry reaction of ketones is sensitive to steric factors and yields of 2-nitro alcohols normally are very low except for those reactions involving nitromethane.[9–12] For instance, nitromethane reacts with cyclohexanone and its 3- and 4-methyl derivatives, with sodium ethoxide as the catalyst, to form the corresponding 1-nitromethylcyclohexan-1-ols in, respectively, 33.7% (36 h), 29% (79 h) and 42% (one week) yields after reaction times indicated in parentheses. Nevertheless, under the same reaction conditions, nitroethane and 1-nitropropane did not react when sodium ethoxide was used but, with piperidine as the catalyst, reacted with 3- and 4-methylcyclohexanone to give the corresponding 2-nitroalkylcyclohexanols in 5–13% yield after two weeks at room temperature. 2-Methylcyclohexanone, a more sterically hindered ketone, did not react at all by using these procedures. Moreover, when nitromethane and alicyclic ketones of five to eight carbons in the ring were treated in refluxing solution in the presence of piperidine or secondary aliphatic amines, oximes of azadispiro ketocyclic hydroxamic acids (**38** for cyclohexanone) were obtained as by-products.[49] However, yields were observed ranging from low to good with significant effect due to the amount and type of amine catalyst used.

More recently, the use of high pressure with tetra-*n*-butylammonium fluoride as catalyst allowed these reactions to be accomplished with cyclic ketones.[50] Thus, the Henry reaction of nitroalkanes with 3- and 4-methylcyclohexanones in THF at 30 °C and 9 kbar (1 bar = 100 kPa) afforded fair to high yields (60–90% after 4 d) of the corresponding nitro alcohols, while with 2-methylcyclohexanones it was possible to obtain addition products, although in moderate yields. These facts explain the modest utility of the Henry reaction as a chain-lengthening reaction when the carbonyl component is a ketone, but also show the difference in reactivity of aldehyde and ketone C=O groups with respect to nitromethane, primary and secondary nitroalkanes in the presence of a base as catalyst. Such a difference in reactivity can be considered as the most evident chemoselectivity of this reaction.

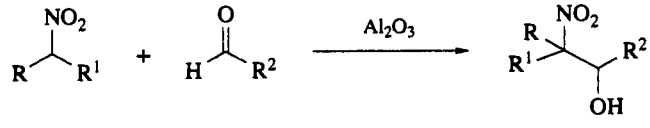


(**38**)

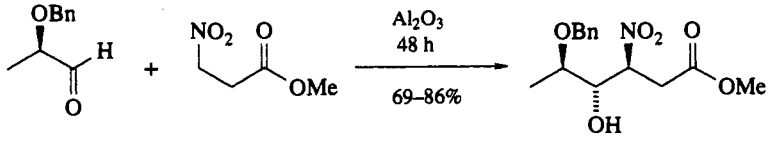
1.10.3.3 Nitroaldol Reactions by Heterogeneous Phase Methods

Recently, several improved methods have been devised to overcome many drawbacks of Henry reactions by increasing their chemo-, regio- and, in some specific cases, stereo-selectivity. The Henry reaction performed by using commercial chromatographic alumina in the absence of solvent gave[51] mixtures of diastereomeric 2-nitro alcohols in fair to high yields after 24 h of reaction at room temperature (equation 10). This heterogeneous, solvent-free method is mild and convenient. Good results could also be obtained with substrates which are acid- or base-sensitive and the method was shown to be useful in multistep syntheses of natural products.[19] A very important application of the alumina procedure concerns the total synthesis of biologically important aminodeoxy sugars *via* the nitroaldol reaction. Treatment of *O*-benzyl-D-lactaldehyde with methyl 3-nitropropionate (equation 11) in the presence of chromatographic alumina without solvent[30] led to a mixture of three nitroaldol products from which the predominant crystalline D-*ribo* isomer (**39**) was formed and easily isolated as the major component (*ribo:xylo:arabino* = 15.0:1.5:1). Stereoselectivity was much lower when the nitroaldol reaction was performed by using catalytic amounts of potassium *t*-butoxide in THF at 0 °C or with stoichiometric quantities of potassium *t*-butoxide in THF at 0 °C in the presence of various salts of divalent metals.

The preparation of 2-nitro alcohols was also achieved by reaction of equimolar amounts of nitroalkanes and aldehydes in the presence of alumina-supported potassium fluoride without solvent (equation 12).[52] A peculiar feature of this method were reactions performed with aromatic aldehydes, such as benzaldehyde and furaldehyde, which allowed preparation of the corresponding 2-nitro alcohols without dehydration of these into nitroalkenes, as observed when nitroaldol reactions were performed with organic bases in homogeneous medium or with alumina alone.

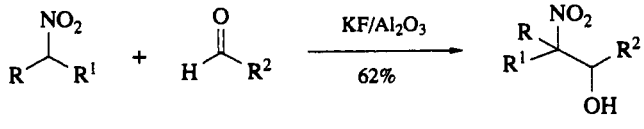


(10)



(11)

(**39**) major isomer



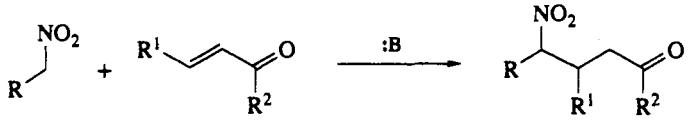
(12)

1.10.3.4 Regio- and Stereo-selectivity in the Nitroaldol Reaction with α,β-Unsaturated Aldehydes and Ketones

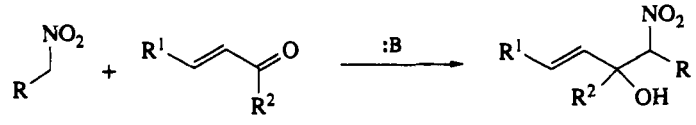
Another kind of reaction competes with the nitroaldol reaction when primary and secondary nitroalkanes, as well as α-nitroalkanones, undergo base-catalyzed reaction with α,β-unsaturated aldehydes and ketones. The reaction of these latter systems with a stabilized carbanion (nitronate anion) will be expected to give either a 1,4-addition to the conjugate system (Michael reaction) or 1,2-addition to the carbonyl group (Henry reaction). The Michael reaction is another classic C—C bond-forming reaction of primary and secondary nitroalkanes with several conjugate systems such as aldehydes, ketones, nitriles, esters, sulfones and sulfoxides. These reactions are typically run in homogeneous systems using organic bases such as tetramethylguanidine (TMG), diisopropylamine, tri-*n*-butylphosphine, triphenylphosphine, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetra-*n*-butylammonium fluoride and potassium *t*-butoxide, as well as inorganic bases such as potassium fluoride/18-crown-6, sodium hydroxide/18-crown-6 and, more recently, chromatographic alumina under solvent-free conditions.[17,19] Several applications of the conjugate addition of nitroalkanes to α,β-unsaturated compounds have concerned, *inter alia*, the synthesis of prostaglandins, monomerine I and quercus lactone, the preparation of α,β-unsaturated aldehydes, 1,4-dicar-

bonyl compounds and jasmonoids, 1,5-dicarbonyl derivatives, 2-substituted-2-nitrocycloalkanones and spiroacetal pheromones.[19]

Of the two types of reactions (equations 13 and 14), nitroaldol reaction and conjugate addition at the β-position, the latter is prevalent especially with β-substituted-α,β-unsaturated ketones. In the case of α,β-unsaturated aldehydes the Michael addition seems to proceed better but the selective conditions of these two reaction pathways have not been well established.

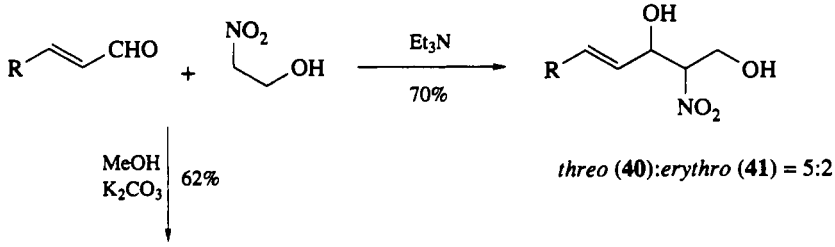


(13)

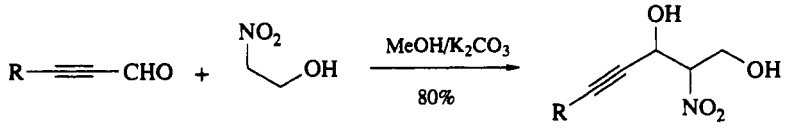


(14)

A recent paper, however, revealed a successful attempt to control the regioselectivity of the reaction to prepare racemic *erythro*-sphingosine and ceramids. Hino *et al.*[23] reported that the reaction of (*E*)-hexadec-2-enal with 2-nitroethanol in triethylamine at room temperature gave a diastereomeric mixture of 1,2-addition products (**40**) and (**41**) in 70% overall yield, while the reaction in methanol–potassium carbonate gave a mixture of compounds (**42**; 50%) and (**43**; 12%). Both these compounds are derived from a Michael adduct intermediate (Scheme 7). Previously, it was observed[53] that the reaction of hexadec-2-ynal with 2-nitroethanol (equation 15) in methanol in the presence of potassium carbonate at room temperature gave a mixture of diastereomeric nitrodiols (**44**) and (**45**) in 80% yield.



Scheme 7



(15)

1.10.3.5 Significant Functionalized Nitroalkanes Used in Nitroaldol Reactions

Although the Henry reaction has been known for over 90 years and is considered as a classic carbon–carbon bond-forming process, its utilization has so far been limited to simple nitroalkanes and the more

Table 1 Significant Functionalized Nitroalkanes Used in Nitroaldol Reactions

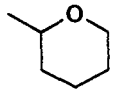
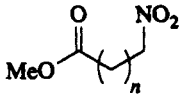
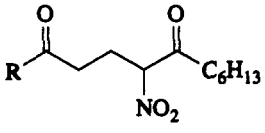
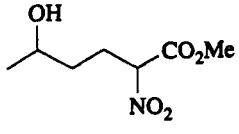
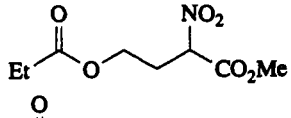
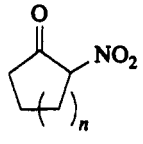
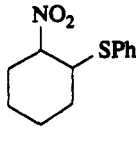
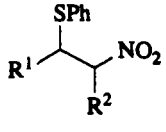
Nitroalkane		*Ref.*
$BrCH_2NO_2$		54
$CF_3CH_2NO_2$		55
$CHF_2CH_2NO_2$		55
$ArSO_2CH_2NO_2$		56
$PhSCH_2NO_2$		57
$RO(CH_2)_2NO_2$	R = H	23, 46, 53, 58
	R = 	51, 58, 59
	R = –CH(Me)OBu^n	51
$MeCH(OH)(CH_2)_2NO_2$		51
	n = 1	30, 60, 61
	n = 2	51
	n = 6	19
$R(NO_2)CHCO_2Et$	R = H	62
	R = Me	63
	R = Et	63
	R = Pr^n	63
	R = Pr^i	63
	R = Bu^n	63
	R = Me	63
	R = OMe	63
		63
		63
	n = 1	63
	n = 2	63
	n = 3	63
		64
	R^1 R^2 / H Me / H Et / H Bu^n / H n-C_7H_{13} / Ph Me / Et Me / Pr^i Me / Me Ph / Ph H / Me H	64

Table 1 *(continued)*

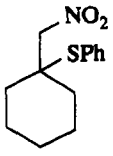
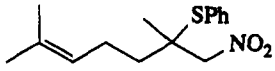
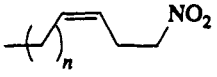
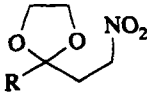
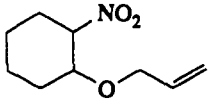
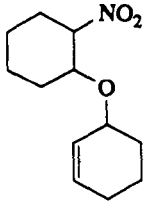
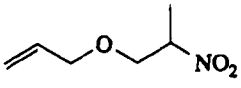
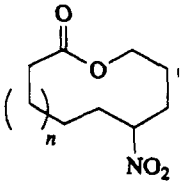
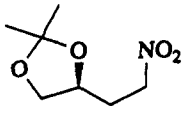
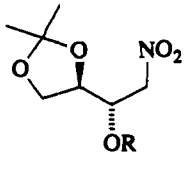
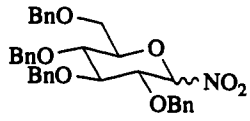
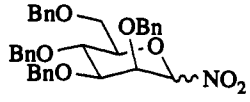
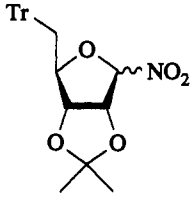
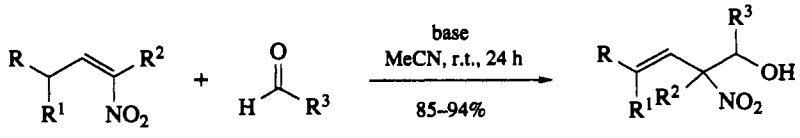
Nitroalkane		*Ref.*
		64
		64
	$n = 1$ $n = 4$	19 19
	R = H R = Me	19, 25 19, 51
		65
		65
		65
	$n = 1$ $n = 7$	66 66
		28
	R = H R = THP	58 58

Table 1 *(continued)*

Nitroalkane	*Ref.*
	40, 67
	40
	40

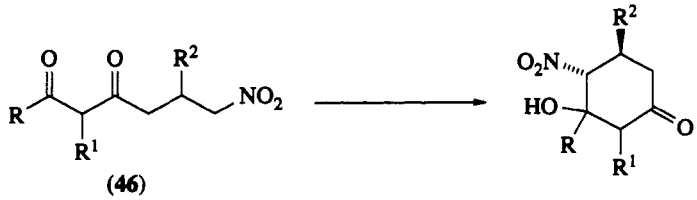
common carbonyl compounds. Because recent studies have developed new methodologies and disclosed the use of new catalysts to improve regio-, chemo- and stereo-selectivity of nitroaldol reactions, an ever-increasing utilization of the reaction has been observed. During the last few decades, functionalized nitroalkanes have been used more as building blocks in organic syntheses by nitroaldol reactions. Among them, the compounds in Table 1 are the most important. α-Nitroalkenes are also good substrates for nitroaldol reactions when they have at least one allylic hydrogen.[68] In fact, treatment of α,β-unsaturated nitro compounds with base results in the formation of allylic carbanions that react with aldehydes regioselectively at the position α to the nitro group (equation 16). The choice of base is important in this reaction, which is useful for preparing γ,δ-unsaturated-β-nitro alcohols. When R^2 is not hydrogen, the reaction is limited to formaldehyde.



(16)

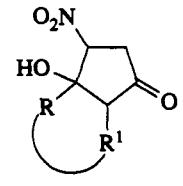
base = NEt_3, NPr^iEt_2, 1,4-diazabicyclo[2.2.0]octane (DABCO)

Intramolecular nitroaldol reactions of 6-nitro-1,3-dicarbonyl compounds (**46**) have been the focus of attention for their peculiar aspects. Seebach *et al.*[69,70] reported the cyclization of these (equation 17), yielding highly functionalized and substituted six-membered rings in diastereomerically pure form. Cyclization of the corresponding 5-nitro-1,3-dicarbonyl compounds (equation 18) has been performed by adding a tetrahydrofuran solution of them and diisopropylamine to hydrochloric acid/borate buffer solution. Compounds (**47**) and (**48**), certainly formed as intermediates in all these reactions as one stereoisomer, were not very stable and an easy elimination of nitrous acid from (**47**) gave (**48**), which completely rearranged to the more stable isomer (**49**).

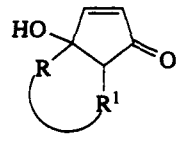


(46)

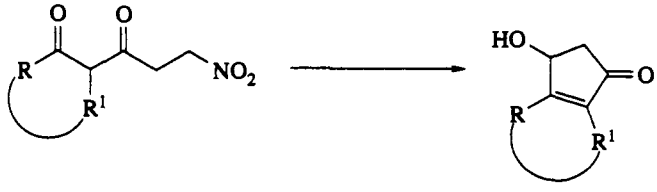
(17)



(47)



(48)



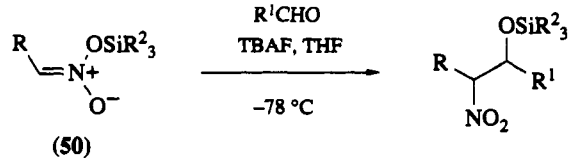
(18)

(49)

1.10.4 NITROALDOL REACTIONS WITH SILYL NITRONATES AND WITH α,α DOUBLY DEPROTONATED NITROALKANES

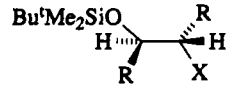
Significant improvements to the Henry reaction have been achieved by using silyl nitronates[71] and catalytic amounts of fluoride ion or, alternatively, α,α doubly deprotonated primary nitroalkanes.[48] Both of these procedures, discovered by the Seebach group, have proved to be useful for the stereoselective preparation of vicinal amino alcohols.

Trialkylsilyl nitronates can be prepared in good yields from primary nitroalkanes by consecutive treatment at –78 °C in THF with lithium diisopropylamide and trimethylsilyl or *t*-butyldimethylsilyl chloride. Again at –78 °C in THF, and in the presence of catalytic amounts of tetra-*n*-butylammonium fluoride (TBAF), the reaction between (**50**) and a wide range of aliphatic and aromatic aldehydes gave the trialkylsilyl ethers of 2-nitro alcohols in fair to excellent yields (equation 19). Highly pure *erythro* nitro ethers (**51**; >98% *ds*) are obtained in yields of about 60% from aliphatic aldehydes if the *t*-butyldimethylsilyl nitronates are used.[26] Among the most important factors to ensure reproducible diastereoselectivity are the use of tetrabutylammonium fluoride freshly dried over molecular sieves in a THF solution, careful control of the reaction temperature at low enough values and avoiding reaction mixtures being kept too long at room temperature before work-up. With aromatic aldehydes reduced diastereoselectivity (≈80% *ds*) is observed.



(19)

(50)



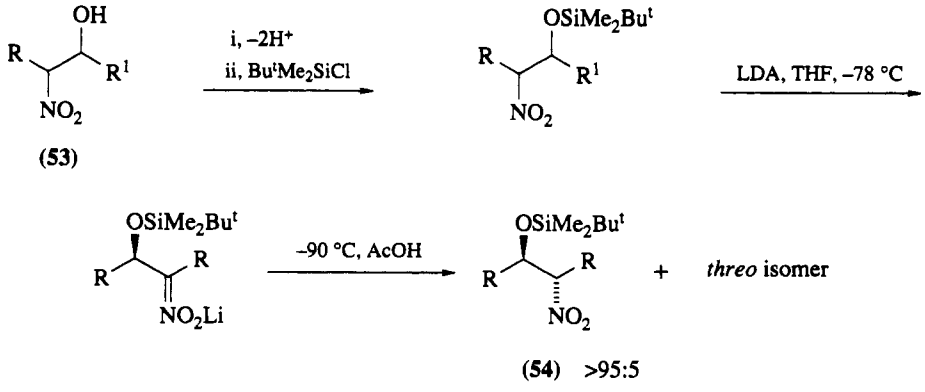
(51) X = NO_2
(52) X = NH_2

Secondary nitroalkanes are converted into the corresponding silyl nitronates in lower yields and only those with *t*-butyldimethylsilyl groups are sufficiently stable to be available for the next reaction. However, their fluoride-catalyzed *O*-silylnitroaldol addition gives only free nitro alcohols which can be subsequently silylated.

O-*t*-Butyldimethylsilylnitroaldols show a peculiar reactivity with respect to the corresponding free vicinal nitro alcohols and play a central role in the synthesis of *erythro*-1,2-amino alcohols (**52**). In fact, the diastereomeric enrichment of (**51**) can be preserved during reduction by Raney nickel. Thus, almost

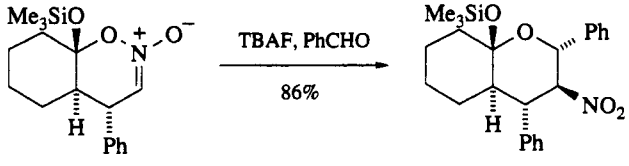
pure (*RS,SR*) diastereomers of *O*-protected β-amino alcohols can be prepared with retention of configurational purity. The ensuing deprotection by $LiAlH_4$ in diethyl ether or TBAF in tetrahydrofuran or aqueous HF occurs again with retention of configuration giving (*RS,SR*)-β-amino alcohols. On the contrary, direct reductive treatment of (**53**) with $LiAlH_4$ produces free β-amino alcohols but stereochemical integrity is lost.

Diastereomeric mixtures of vicinal nitro alcohols obtained by a classical Henry reaction with low diastereoselectivity can be easily silylated to give the corresponding mixture of *O*-*t*-butyldimethylsilyl ethers.[26] The latter undergoes an enrichment of the *erythro* isomer (**54**; up to >95:5) by treatment with LDA and successive protonation of the corresponding lithium salts (Scheme 8), which occurs with high diastereoselectivity.



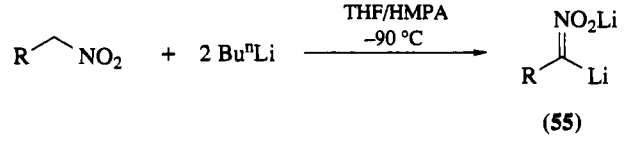
Scheme 8

A stereoselective Henry reaction has also been observed between bicyclic trimethylsilyl nitronates and benzaldehyde with fluoride ion as the catalyst. The reaction results in the formation in high yield of a cyclic hemiacetal (equation 20) and is highly diastereoselective (95% *ds*).[72]



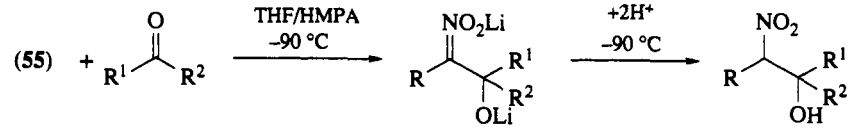
(20)

Ketones do not undergo fluoride-mediated reactions with silyl nitronates. However, enhancement of the C-nucleophilicity of nitronates has been achieved by double deprotonation at –90 °C with *n*-butyllithium in THF in the presence of at least 2 equiv. of HMPA (equation 21). Under these conditions, the residual proton of the monolithium salt, the acidity of which has been indicated to be in the same range as that of diisopropylamine, is metallated to give the dianion.



(21)

α,α Doubly deprotonated primary nitroalkanes show enhanced C-nucleophilicity with respect to that of the corresponding nitronate monoanions. They undergo acylation with carboxylic acid esters, anhydrides and acyl chlorides; *C*-alkylation with alkyl bromides and iodides; and hydroxyalkylation with aldehydes and ketones (Scheme 9).[48] This variant of the nitroaldol reaction proceeds in better yields than classical Henry procedures, especially in cases with steric hindrance. Benzophenone reacts with (**55**) and the stability of the dianion (**56**), greater than that of the corresponding monoanion, suppresses the reversibility of the addition process. Clean reactions and satisfactory yields depend on careful control of the temperature of these reactions at –90 °C. Under these conditions, the addition of α,α doubly deprotonated primary nitroalkanes to aromatic and aliphatic aldehydes leads to a *threo*-enriched product. The de-



(56)

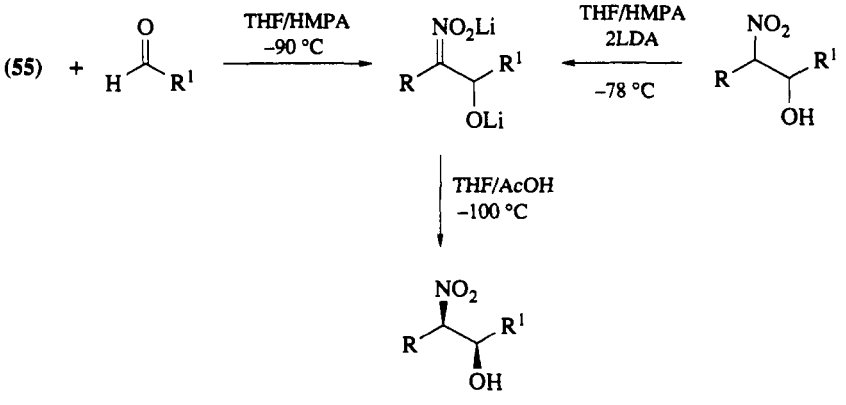
Scheme 9

gree of stereoselectivity depends strongly upon the presence of HMPA and is highest in the case of nitroaldols from aromatic aldehydes. When a diastereomeric mixture of nitroaldols is obtained by classical Henry procedures, with low or no stereoselectivity, double deprotonation under the foregoing reaction conditions gives the same dilithio derivative as that formed by addition of (**55**) to an aldehyde. Subsequent double protonation in the presence of HMPA furnishes *threo* nitro alcohols in ≈50% yields and good to high stereoselectivity (75% to 94%). This procedure also avoids the easy epimerization at the nitro-substituted C-atom. (Scheme 10).

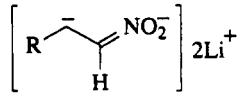
Using the simple trick devised by Seebach *et al.*, all nitro alcohol derivatives can be prepared diastereoselectively in a complementary fashion, and even β-amino alcohols, which cannot be prepared by oxyamination of alkenes, are accessible.

Tetrahydropyranyl-protected nitroethanol and other protected vicinal nitro alcohols can be doubly deprotonated to lithium lithionitronates without β-elimination of the pyranyloxy group.

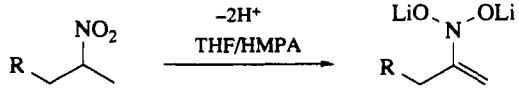
The double deprotonation of 2-arylnitroethanes followed by treatment with electrophiles led to 2-substituted-2-arylnitroethanes.[73] This fact suggested that the strong base sequentially abstracted α- and then β-protons of these substrates giving α,β-dianions (**57**). The same behavior has been observed with primary nitroalkanes having a vinyl or carbonyl group on the β-carbon. If there is only one α-nitro CH as in open-chain and cyclic secondary nitroalkanes, bis(lithioxy)enamines (**58**) and (**59**) (dianion derivatives of α-nitroalkenes, also called super enamines) are generated and exclusively those with a terminal double bond in the case of 2-nitroalkanes (equations 22 and 23). These dianion derivatives react with aromatic and aliphatic aldehydes as well as ketones to give 1,3-difunctional derivatives. In contrast to the lack of



Scheme 10

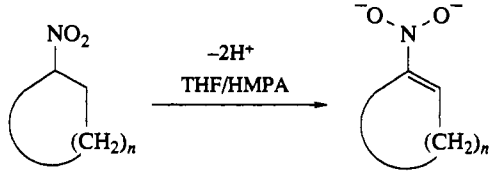


(**57**) R = Ph, vinyl, COR^1



(22)

(**58**)



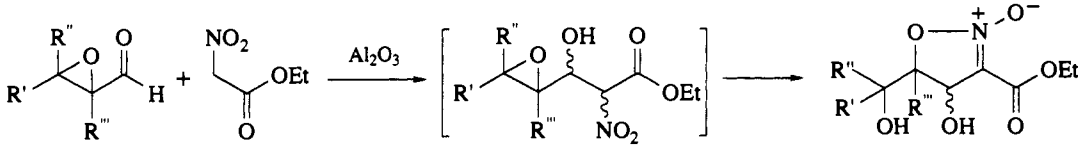
(23)

(59)

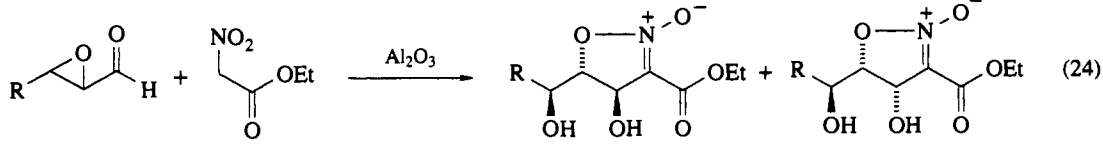
stereoselectivity observed in reactions between secondary open-chain nitroalkanes, 'super-enamines' of cyclic secondary nitroalkanes produce stereoselectively (60% to more than 95% *ds*) derivatives with three newly formed centers of chirality.[74]

1.10.5 ADDENDUM

Stereochemical control in nitroaldol reactions continues to be a challenge for organic chemists. Barrett and coworkers recently have discovered an experimentally simple procedure for stereoselective preparation of *erythro*-2-nitroalkanols.[75] The procedure consists of the treatment of alkyl nitronates formed by the action of *n*-butyllithium on nitroalkanes in THF solution with aldehydes in the presence of isopropoxytitanium trichloride at room temperature. The method works well in the case of electron-deficient aromatic aldehydes but is less efficient with aliphatic aldehydes. Another interesting reaction uses alumina without a solvent. In the course of studies of the synthesis of polyhydroxylated α-amino acids it was discovered[76] that equimolar mixtures of 2,3-epoxy aldehydes and ethyl nitroacetate furnished 3-ethoxycarbonyl-4-hydroxy-5-(1-hydroxyalkyl)-2-isoxazoline 2-oxides when absorbed with commercial chromatographic alumina without solvent at room tempeature for 2 to 24 h. The reaction was depicted as a base-catalyzed tandem nitroaldol addition–cyclization in which the carbon–carbon bond forming step affords a 2-nitroalkanol and/or the corresponding *aci*-nitro form as a transient species that undergoes a fast epoxide ring-opening cyclization (Scheme 11). The method is of particular interest in that 3-*trans*-monosubstituted substrates gave C(4),C(5)-*trans* and *cis* isomers (*dr* = 1.5) with C(5),C(6)-*anti* configuration (equation 24), whereas 3-*cis*-monosubstituted 2,3-epoxy aldehydes give C(4),C(5)-*trans* and *cis* derivatives with a much higher diastereoselectivity (*dr* = 20) and C(5),C(6)-*syn* configuration (equation 25). 5-*Exo* cyclization rather than the 6-*endo* one has been observed even though the cyclization to 2-isoxazoline 2-oxides involves intramolecular nucleophilic attack to the more substituted end of the oxirane. Since homochiral 2,3-epoxy aldehydes are easily available from the corresponding (*E*)- and (*Z*)-allylic alcohols by a Sharpless asymmetric epoxidation–oxidation sequence[77] and 2-isoxazoline 2-oxides can be converted into 2-isoxazolines, which are central intermediates in organic synthesis,[78] this stereoselective reaction can be considered as a useful tool in the construction of polyhydroxylated linear structures in a controlled and predictable way.



Scheme 11



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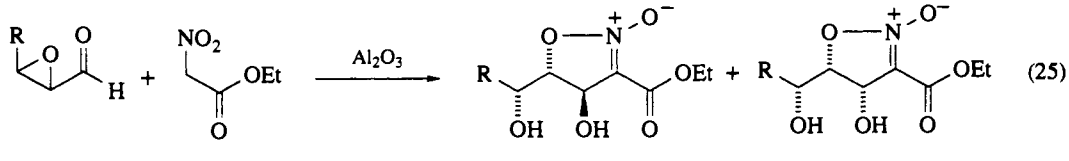

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1.11
The Knoevenagel Reaction

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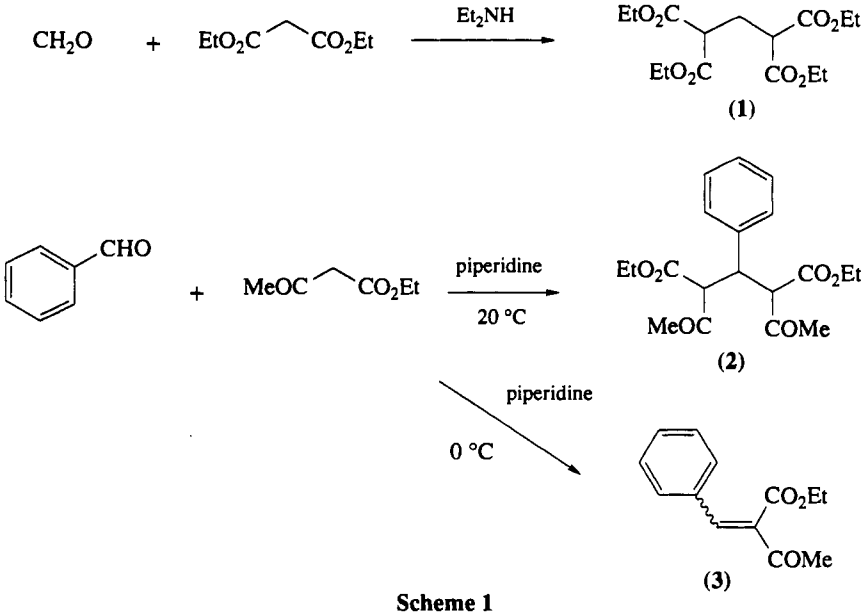
1.11.1 INTRODUCTION

In 1894 Knoevenagel published a paper in the journal *Chemische Berichte* on the reaction of formaldehyde and diethyl malonate in the presence of diethylamine as catalyst.[1] He obtained the bis adduct (1).

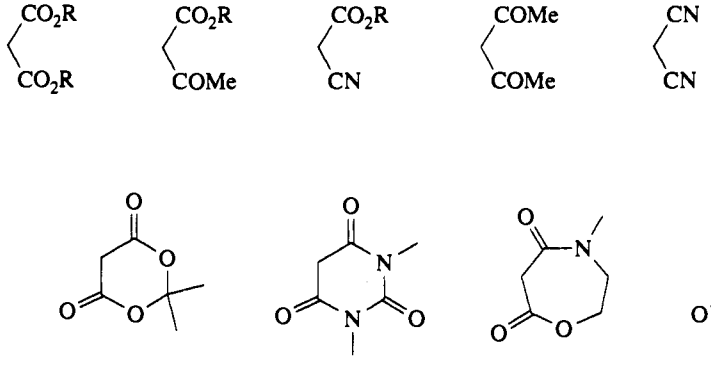
Two years later he was able to show that the reaction of benzaldehyde and ethyl acetoacetate in the presence of piperidine gives the bis adduct (**2**) at room temperature and at 0 °C the benzylidene-1,3-dicarbonyl (**3**; Scheme 1).[2]



Scheme 1

The Knoevenagel condensation[3–7] covers reactions of aldehydes and ketones with active methylene compounds in the presence of a weak base, *e.g.* an amine, to give alkylidene- or benzylidene-dicarbonyls or analogous compounds (Knoevenagel products). Usually methylene groups activated by two electron-withdrawing moieties are employed; the reaction of an aldehyde or a ketone with nitroalkanes in the presence of a weak base is, however, also considered a variant of the Knoevenagel condensation. This reaction (the Henry reaction) is treated elsewhere in this volume (Chapter 1.9). The active methylene compounds used most often are acyclic 1,3-dicarbonyls and analogous substances such as malonates, acetoacetates, acetonitriles, acetylacetone and malonodinitrile, though cyclic compounds like 1,3-cyclohexanediones, Meldrum's acid, barbituric acids, oxazepanediones and 4-hydroxycoumarins are also frequently employed (Scheme 2). With the latter compounds, it is often difficult to isolate the Knoevenagel product, since a fast Michael addition with a second molecule of the methylene component to give a bis adduct takes place. It should also be noted that isomerization of the initial α,β-unsaturated dicarbonyl to a β,γ-unsaturated system frequently takes place. In the case of unsymmetrical 1,3-dicarbonyls and analogous compounds two diastereomeric products can be formed and some of these transformations show a pronounced stereoselectivity.

The aldehydes used in the reaction can be varied over a wide range; chiral compounds such as sugar aldehydes have been employed to some extent. The use of ketones is limited due to their lower reactivity.



Scheme 2

On the other hand the catalyst is of great importance; primary, secondary or tertiary amines or their corresponding ammonium salts are usually used, but many other catalysts such as phase transfer catalysts, Lewis acids or potassium fluoride can also be applied. The most widely employed catalysts are pyridine, with or without added piperidine, and ammonium salts, such as ammonium or piperidinium acetate. Condensations that employ strong bases or preformed metal salts of the methylene component are not covered here since transformations under these conditions are not usually considered to be Knoevenagel reactions.

Several mechanisms may operate. In some cases there is probably first a reaction between the aldehyde and the amine to give an imine or an iminium salt, which, rather than the free aldehyde, reacts with the anion derived from the active methylene compound.

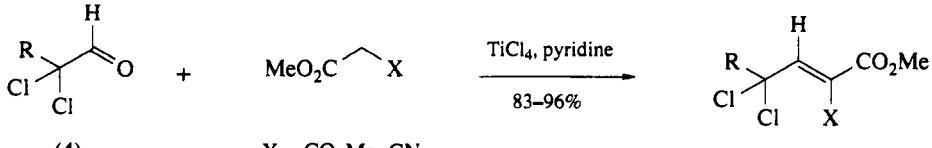
1.11.2 GENERAL ASPECTS

1.11.2.1 Reaction Conditions

The Knoevenagel condensation is effected by treating a carbonyl compound with an active methylene compound in the presence of at least catalytic amounts of a base and an acid. It is appropriate in these reactions to remove the water formed either azeotropically or by addition of molecular sieves or sodium sulfate. As the methylene compounds are more acidic than the aldehydes and ketones used in the aldol reaction, the bases employed as catalysts are usually weaker than those needed to effect the aldol condensation. Ammonia, primary, secondary and tertiary amines, as the free bases or their salts, are effective catalysts.[3] The condensation of aliphatic and heterocyclic aldehydes with ethyl cyanoacetate can be brought about by secondary amines like piperidine or diethylamine.[8] Another possibility is the use of ammonium salts or amines of organic acids, such as ammonium acetate, ethylenediammonium diacetate or piperidinium acetate, usually in an acetic acid solution or in other organic solvents like dioxane, dichloromethane or benzene. Acetamide, which is usually contaminated with ammonium acetate, can also be used. The condensation of ketones with ethyl cyanoacetate can be performed under similar conditions.[9] Piperidinium acetate has become one of the most popular catalysts in Knoevenagel condensations. ε-Aminocaproic acid, α-aminophenylacetic acid, β-alanine and *p*-aminophenol are also very efficient catalysts for the condensation of various ketones with malonodinitrile and ethyl cyanoacetate.[10] Alkali metal fluorides have found wide application in base-catalyzed reactions.[11,12] In particular, potassium fluoride is a useful catalyst for the Knoevenagel reaction because of its adequate basicity, its high affinity to water and its low cost. A comparison of the activity of the various alkali metal fluorides in the Knoevenagel condensation of benzaldehyde and cyclohexanone with malonodinitrile, ethyl cyanoacetate and ethyl malonate has shown that potassium fluoride, in less than equivalent amounts, is an effective catalyst and that rubidium and cesium fluoride are even better, while lithium fluoride and sodium fluoride are ineffective. This is probably due to an increase in solubility from LiF to CsF in polar solvents. It can be assumed that the fluoride anion acts as a base to promote the deprotonation of the methylene compound.[13]

As a new generally applicable catalyst for the Knoevenagel condensation, a mixture of titanium tetrachloride and a tertiary organic base in solvents like tetrahydrofuran or dioxane was introduced by Lehnert.[14] The procedure is often superior to standard methods in reactions of sensitive compounds because it can be performed at low temperature. As an example, the reaction of the aldehyde (**4**) with malonate or cyanoacetate in the presence of titanium tetrachloride and pyridine gives the desired products (**5**) in high yield, whereas the classical method using piperidine acetate fails (Scheme 3).[15]

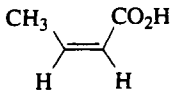
In recent years the use of inorganic solids and solid supports as reagents or reaction media has rapidly increased as these reactions often involve milder conditions, easier workup and higher selectivity than



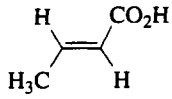
(**4**) X = CO_2Me, CN (**5**)

Scheme 3

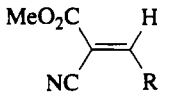
similar reactions in solution. Foucaud *et al.* found that Knoevenagel condensations can be achieved in the presence of dry alumina without organic solvents under mild conditions. Condensations with aldehydes are generally very fast, but reactions with ketones are more difficult to accomplish.[16,17] Knoevena-



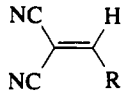
^3J (CO_2H,H-*trans*) = 14.5 Hz
^3J (CH_3,H-*trans*) = 9.40 Hz



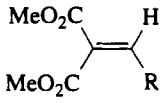
^3J (CO_2H,H-*cis*) =6.78 Hz
^3J (CH_3,H-*cis*) = 6.30 Hz



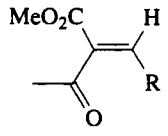
^3J (CO_2Me,H-*cis*)= 6.25 Hz
^3J (CN,H-*trans*) = 13.4 Hz



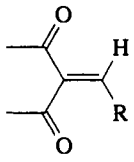
^3J (CN,H-*cis*) = 7.90 Hz
^3J (CN,H-*trans*) = 14.0 Hz



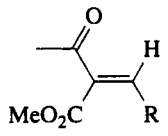
^3J (CO_2Me,H-*cis*) = 7.60 Hz
^3J (CO_2Me,H-*trans*) = 12.1 Hz



^3J (CO_2Me,H-*cis*) = 7.40 Hz
^3J (COMe,H-*trans*) = 9.75 Hz

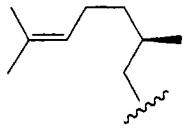


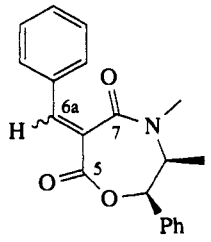
^3J (COMe,H-*cis*) = 7.05 Hz
^3J (COMe,H-*trans*) = 10.2 Hz



^3J (COMe,H-*cis*) = 6.25 Hz
^3J (CO Me,H-*trans*) = 12.7 Hz

R =





(*Z*) ^3J (C-7,6a-H) = 12.0 Hz
^3J (C-5,6a-H) = 7.5 Hz

(*E*) ^3J (C-7,6a-H) = 7.5 Hz
^3J (C-5,6a-H) = 10.5 Hz

Scheme 4

gel condensations in solid–liquid systems with magnesium oxide or zinc oxide as catalyst occur at room temperature.[17] Another inorganic catalyst that can be used in the absence of a solvent is aluminum phosphate/aluminum oxide. It was established that the reaction mechanism under these conditions is the same as that in solution.[18] Knoevenagel condensations can also be achieved employing catalytic amounts of xonotlite, or xonotlite doped with potassium *t*-butoxide at ambient temperature.[19] Recently, silica gel functionalized with amino groups has found application as a catalyst.[20] In addition, successful catalysis by ion-exchange resins has been known for a long time.[21,22] The use of dibenzo-18-crown-6 supported on a polymer in condensations of aromatic aldehydes has been studied recently.[23] Copper(II) chloride catalyzes the Knoevenagel condensation of aldehydes or their tosylhydrazones with 2,4-pentanedione under neutral conditions at room temperature;[24] zinc acetate in the presence of defined quantities of water can be also used.[25]

The Knoevenagel reaction is strongly solvent-dependent. The first step, the formation of the enolate from the 1,3-dicarbonyl and its addition to the carbonyl (or imine) is facilitated in solvents of high polarity and the second step, 1,2-elimination, is inhibited by protic solvents. Thus, dipolar aprotic solvents such as dimethylformamide are especially useful in Knoevenagel condensations.[26,27]

It must be emphasized that the scope and limitations of many of the new Knoevenagel catalysts have not been explored sufficiently. From the practising chemist's point of view the situation is somewhat confusing and the search for the appropriate reaction conditions is still largely a process of trial and error.

1.11.2.2 Spectroscopy and Physical Properties

NMR spectroscopy is the most widely used method to investigate both the configuration and conformation of Knoevenagel products. The configuration of acrylic or cinnamic acids obtained by condensation of aldehydes with malonic acid and other 1,2-disubstituted alkenes can be determined from the value of the vicinal coupling constant $^3J_{H,H}$ (between the protons of the double bond) on the basis of the relationship $^3J_{H,H\text{-}trans} > {}^3J_{H,H\text{-}cis}$. If only one isomer is available, the electronegativity of the substituents has to be considered.[28] This method, however, is not applicable to 1,2-disubstituted alkenes where the chemical shifts of the alkenic protons are similar, or to tri- and tetra-substituted alkenes. Allylic and homoallylic coupling constants ($^4J_{H,H}$ and $^5J_{H,H}$) have been used to determine the geometry of alkenes, but they are less reliable than the vicinal coupling constants for this purpose.[28,29]

Analysis of $^3J_{C,H}$ coupling constants is a powerful, generally applicable tool for establishing double bond configuration in di- and tri-substituted Knoevenagel products.[30–32] It is even possible to apply this method without separating mixtures of isomers. Examples of $^3J_{C,H}$ coupling constants in di- and tri-substituted Knoevenagel products are given in Scheme 4.[30,33,34] The analysis of vicinal coupling constants is not restricted to H,H and C,H couplings, but can also be applied to couplings between vinylic protons and other nuclei having a magnetic moment. The values of $^3J_{P,H}$ coupling constants for trisubstituted Knoevenagel products obtained from phosphonatoacetates have been determined.[35]

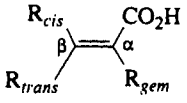
Since the chemical shift of an alkenic proton or carbon depends on the nature and position of the other alkenic substituents, this property can be used for configurational assignment. It can be evaluated by the empirical relation shown in equation (1), which is based on additive shielding increments (*Z*) that have been extracted from a large number of alkenes.[28,36,37] This 'differential shielding method' is especially useful for the determination of configuration in alkenes containing highly anisotropic substituents like carbonyl groups.[28,38] The method has been applied successfully to elucidate the double bond configuration of Knoevenagel products between aldehydes or ketones and cyanoacetates. The β-vinylic proton and the protons of β-substituents are more deshielded when they are *cis* to the ester group (Scheme 5).[39–42]

$$\delta_H \text{ (p.p.m.)} = 5.28 + Z_{cis} + Z_{trans} + Z_{gem} \quad (1)$$

Scheme 5

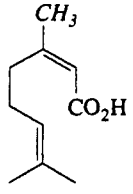
From the data shown it is clear that both isomers must be available to allow unambiguous stereochemical assignments.

There is also a correlation of ^{13}C NMR chemical shifts of the α- and β-carbons of di- and tri-substituted α,β-unsaturated acids, represented by the empirical relation in equations (2a) and (2b), which relies on the additive shielding increments Z_i.[28,43] Another method used for the determination of double bond configuration makes use of effects induced by benzene or other aromatic solvents on the chemical shifts of double bond substituents; preferential shielding of protons or alkyl groups *trans* to the polar groups is usually observed. An example of the use of this method is the determination of the stereochemistry of the double bond in (*Z*)- and (*E*)-geranic acids (**6** and **7**; Scheme 6).[44]

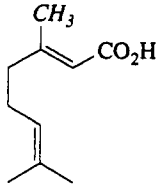


$$\delta_\alpha = -64 + \sum_i Z_i^\alpha \text{ (p.p.m.)} \quad (2a)$$

$$\delta_\beta = -60 + \sum_i Z_i^\beta \text{ (p.p.m.)} \quad (2b)$$



(**6**)



(**7**)

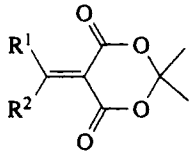
δ (CCl_4) = 1.96 p.p.m.
Δ (C_6H_6/CCl_4) = 0.45 p.p.m.

δ (CCl_4) = 2.18 p.p.m.
Δ (C_6H_6/CCl_4) = 0.13 p.p.m.

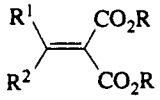
Scheme 6

Spectroscopic methods have also been used to characterize the conformational properties of Knoevenagel products from acyclic[39,45] and cyclic[46,47] active methylene compounds.

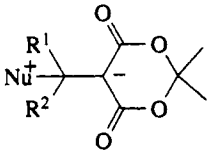
Knoevenagel products display interesting physical properties, the most striking of which is their Lewis acidity.[48] The strength of these neutral organic Lewis acids increases with increasing strength of the electron-withdrawing groups and with increasing planarity of the system. Thus, the Lewis acidity of the nearly coplanar methylene derivatives of Meldrum's acid (**8**) exceeds that of the corresponding methylenemalonates (**9**), in which one ester group is probably out of the general plane of the conjugated system.



(**8**)

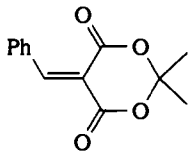


(**9**)

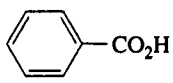


(**10**)

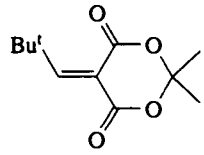
The acidity of these products cannot be determined by means of direct pH determination. However, the virtual acidity constant, K'_L, is accessible from optical and electrochemical measurements. Comparison of the pK'_L values of selected Knoevenagel products and the p*K* values of some typical carboxylic acids in methanol establishes that they exhibit comparable acidity (Scheme 7). Using the σ^+-values, the pK'_L values of benzylidene derivatives of Meldrum's acid are in good accordance with the Hammett equation. The Lewis acidity of Knoevenagel products is due to the formation of labile pseudobase adducts, the so-called anbadons (**10**), upon reaction with nucleophiles. Structures of the anbadons have



$pK'_L = 9.2$



$pK = 9.4$



$pK'_L = 8.4$

$MeCO_2H$

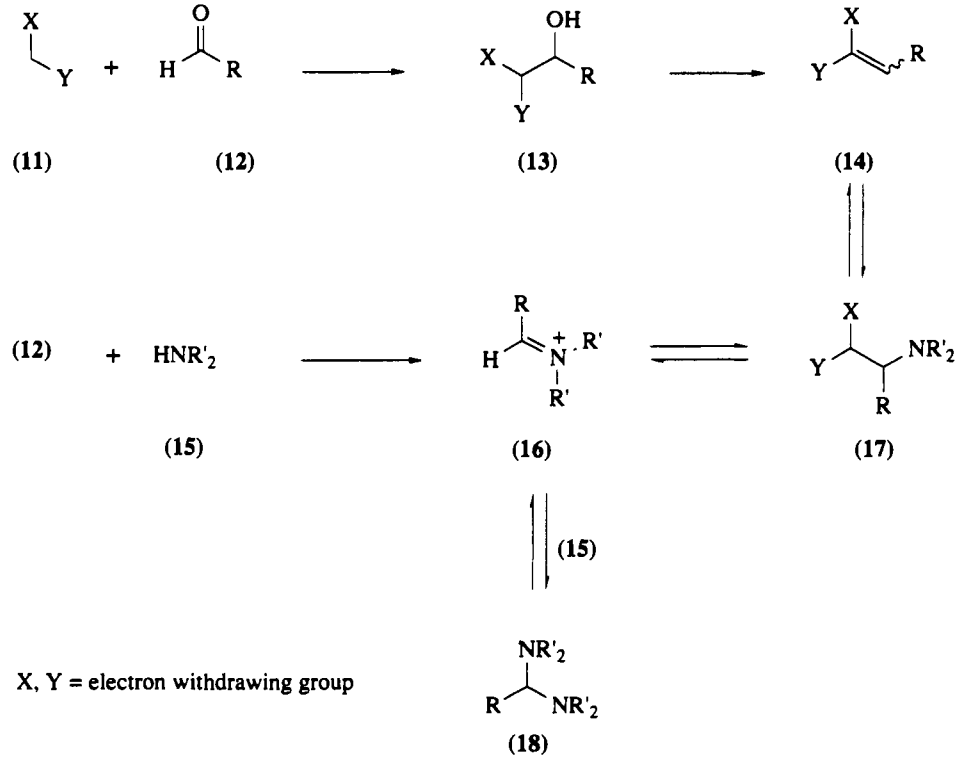
$pK = 9.65$

Scheme 7

been established by means of NMR and UV spectroscopy as well as by chemical methods. The alkenic protons of the Knoevenagel products in question absorb in the range $\delta = 7–9$ in different solvents like CD_3OD, CCl_4 or $CDCl_3$. The signal for this proton disappears on addition of CD_3ONa and a new absorption appears in the range $\delta = 3.8–5.5$.[48]

1.11.2.3 Mechanism

The Knoevenagel reaction belongs to the general class of base-catalyzed aldol-type condensations, where a carbanion adds to a carbonyl or heterocarbonyl group. Two different mechanisms, mainly depending on the base used, have been proposed for the reaction of (**11**) and (**12**) to give (**14**; Scheme 8). In the Hann–Lapworth[49] mechanism the intermediacy of a β-hydroxydicarbonyl compound (**13**) is assumed; this certainly holds true when using tertiary amines such as pyridines by reaction of (**12**). (**13**) is also formed as an intermediate with the sodium salt of (**11**); however, this transformation is not classified as a Knoevenagel reaction. Employing secondary and primary amines as catalysts, Knoevenagel[50] has shown that a condensation of the aldehyde (**12**) and the amine (**15**) takes place to give an iminium salt (**16**), which then forms the alkylidene- or benzylidene-1,3-dicarbonyl product (**14**). Since an elimination step is involved in both mechanisms, the final product would be the same. Kinetics of several

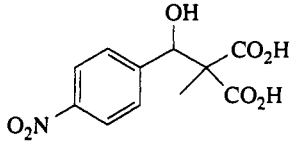


Scheme 8

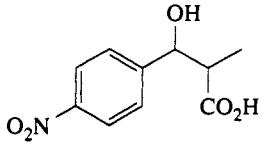
Knoevenagel reactions have been measured. Patai *et al.* and others have studied the effect the catalyst has on the reaction mechanism.[51–53] For the reaction of malonodinitrile and 3-methylcyclohexanone in benzene with triethylamine or piperidine, the rate of the reaction was found to be first order in amine, ketone and nitrile[54] and was interpreted in terms of basic catalysis by the amine. Using a mixture of triethylamine or piperidine and an acid like acetic acid or benzoic acid, general acid catalysis was observed, but its effect on the overall rate of the reaction was small since the acid lowers the concentration of free amine. With mixtures of primary amines like hexylamine and acetic acid in the reaction of 3-methylcyclohexanone with malonodinitrile the rate is zero order in malonodinitrile. It was argued that in the rate-determining acid-catalyzed step hexylamine forms an imine with cyclohexanone. This imine then reacts rapidly with malonodinitrile. When employing hexylamine without acid, a complex rate law indicates that hexylamine acts mainly as a basic catalyst and the reaction proceeds according to the Hann–Lapworth mechanism.[54] Furthermore, it has been shown that weak bases producing solutions having a pH of 7.5–8.0 are most efficient. With β-alanine the energy of activation is 7.6 kcal mol^{-1}, compared to 11 kcal mol^{-1} for the uncatalyzed reaction.[55] Although stronger bases such as KF or piperidine cause even more rapid condensation, the yield is lower because of telomerization of malonodinitrile.

Various aromatic aldehydes react with active methylene compounds in the presence of piperidine to give the corresponding dipiperidines (**18**), which are in equilibrium with the iminium ion (**16**) under the reaction conditions (Scheme 8). In addition, the primary reaction products (**17**) of iminium ions (**16**) with the active methylene compound (**11**) can also be isolated.[56] In the reaction of *N,N*-dimethylbarbituric acid and citronellal using catalytic amounts of ethylenediammonium diacetate, the β-hydroxy-1,3-dicarbonyl has been identified by NMR spectroscopy.[57]

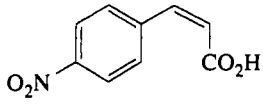
In a valuable variation of the Knoevenagel reaction, malonic, cyanoacetic and acetoacetic acids are used as active methylene compounds. The reaction is accompanied by decarboxylation to give α,β-unsaturated esters, nitriles or ketones. The transformation could either proceed *via* β-hydroxy or β-amino intermediates followed by decarboxylation and elimination or *vice versa*. To elucidate this mechanism, Knoevenagel reactions of *p*-nitrobenzaldehyde with methylmalonic acid in the presence of a secondary or a tertiary amine have been carried out with NMR observation.[58–60] In the presence of pyridine the concentration of the β-hydroxy intermediate (**19**) reaches a maximum in about 3.5 h and the decarboxylation product (**20**) begins to appear after 24 h.[58] It seems clear that the reaction between the starting materials and intermediate (**19**) is reversible.[61] The α,β-unsaturated acid (**21**) was not observed. In contrast, in the presence of piperidine, depending on the concentration of the amine, compounds (**19**)–(**21**) are obtained. Since (**21**) is not formed *via* (**19**) or (**20**), another pathway, namely the Knoevenagel mechanism, is implicated. Here, a bisdialkylamino derivative and an iminium salt are formed. It is of interest that the formation of the bisdialkylamino derivative depends on the type of secondary base. Thus, with piperidine and morpholine the formation of (**21**) *via* the Knoevenagel mechanism is preferred, whereas with diethylamine and dicyclohexylamine mainly (**20**) *via* the Hann–Lapworth mechanism is formed.[58]



(**19**)

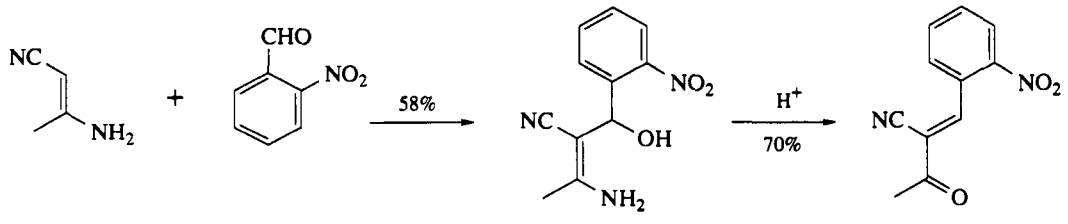


(**20**)



(**21**)

The generalization can be made that in the presence of tertiary amines, with and without acids, the Knoevenagel reaction always proceeds according to the Hann–Lapworth mechanism through a β-hydroxy intermediate. With secondary and primary amines, the Hann–Lapworth and Knoevenagel mechanisms can compete. The formation of an imine intermediate mainly depends on the bulkiness of the amine and the carbonyl compound. With ketones and piperidine as catalyst, with or without acid, normal basic catalysis is found, whereas with hexylamine in the presence of an acid, an intermediate imine is formed. With aldehydes and piperidine, an intermediate imine is observed, whereas with diisopropylamine, the chief intermediate is the β-hydroxy adduct. However, using only catalytic amounts of secondary or primary bases the β-hydroxy compound is clearly the intermediate.[58] In some cases β-hydroxy-1,3-dicarbonyls have been isolated in the Knoevenagel reaction.[62,63] Crystalline adduct (**24**) is obtained by condensation of *o*-nitrobenzaldehyde (**23**) and aminocrotononitrile (**22**) in basic or neutral media; the structure was elucidated by X-ray crystallography. In ethanolic hydrochloric acid the corresponding ketonitrile (**25**) is formed (Scheme 9).[64] The influence of pressure on the Knoevenagel reaction has also been investigated. As expected, pressure increases the reaction rate.[65]

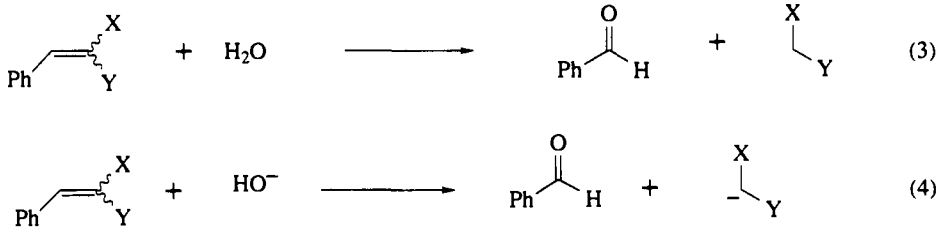


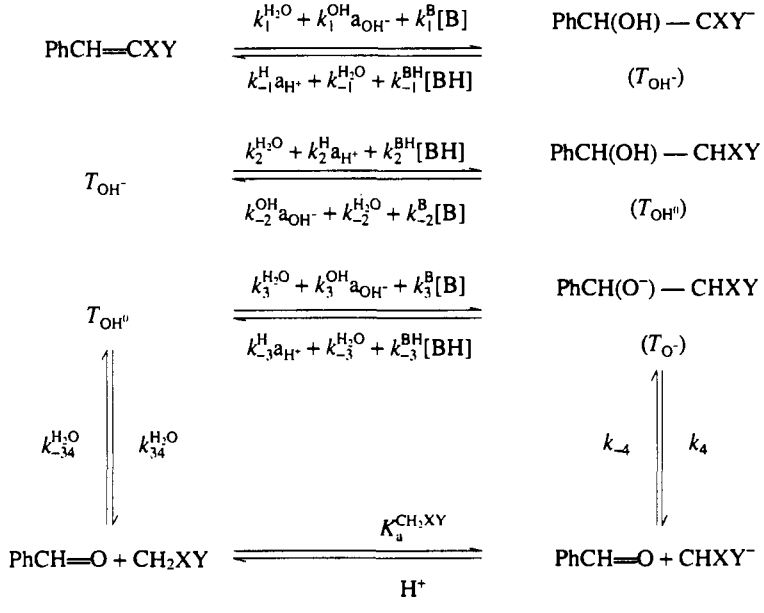
(22) (23) (24) (25)

Scheme 9

1.11.2.4 The Retro-Knoevenagel Reaction

The rate of the hydrolytic cleavage of Knoevenagel products (retro-Knoevenagel reaction)[5] strongly depends on the pH of the aqueous solution[66,67] as well as on cosolvents such as DMSO[68] and additional nucleophiles such as amines.[69] The hydrolysis of these alkenes to CH_2XY can be presented by equation (3) at pH < $pK_a^{CH_2XY}$ and by equation (4) at pH > $pK_a^{CH_2XY}$. Although the kinetics are related to the nature of Y and X, the mechanism is basically the same for all Knoevenagel products. Detailed studies have been performed for the hydrolysis of benzylidene-Meldrum's acid, benzylidenemalonodinitrile, benzylidene-1,3-indandione, benzylideneacetylacetone and 1,1-dinitro-2,2-diphenylethylene. Below pH 3 an aqueous solution of benzylidene-Meldrum's acid is relatively stable (half-life ≈ 35 min). With increasing pH the decomposition increases rapidly and shows a rate maximum near pH 6 (half-life ≈ 2 min). The hydrolysis rate decreases above pH 6 with a minimum around pH 8–9 (half-life at pH 8 ≈ 60 min). Above pH 9 cleavage takes place due to attack of hydroxide ion at one of the carbonyl groups. The different cleavage rates can easily be explained by assuming four consecutive steps (Scheme 10).[67–69]





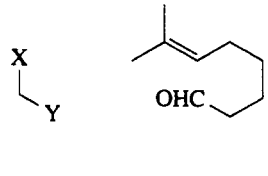
Scheme 10

(i) Attack of water or OH^- at the β-carbon to form an adduct (T_{OH^-}) subject to a weak general base catalysis; (ii) protonation of the α-carbon of T_{OH^-} to form $T_{OH}{}^0$; (iii) deprotonation of the OH group of $T_{OH}{}^0$ to form the tetrahedral intermediate T_{O^-}; and (iv) breakdown of T_{O^-} into the aldehyde and the anion of the 1,3-dicarbonyl compound.

At high pH (pH > 6) protonation of T_{OH^-} is rate limiting, whereas at low pH (pH ≤ 6) deprotonation of the OH group in the neutral adduct $T_{OH}{}^0$ is rate limiting. The breakdown of the tetrahedral intermediate T_{O^-} must be at least in the order of 10^{10} s^{-1}. Since carbanions are generally considered to be sluggish nucleofuges, the high rate for the last step is astounding.

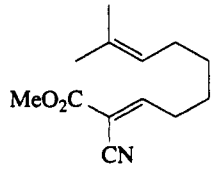
1.11.2.5 Stereochemistry

Geometrical isomers can be obtained in the Knoevenagel reactions of compounds (**11**) when X and Y are different. The selectivity in these reactions is mainly governed by steric effects. Condensations of cyanoacetate with aliphatic and aromatic aldehydes give (*E*)-products almost exclusively.[40,70] Thus, reaction of methyl cyanoacetate and aldehyde (**26**) in the presence of piperidinium acetate in CH_2Cl_2 affords the (*E*)-isomer (**27**) in 82% yield after chromatography.[71] With (**28**) as the methylene component (*E*)-alkenes (**29**) are obtained, in which the β-substituent is *anti* to the more bulky methanesulfonyl group.[72] If the electron-withdrawing groups X and Y in (**11**) are of similar size, a mixture of the two diastereomeric Knoevenagel products is formed. Thus, condensation of methyl acetoacetate with an aliphatic aldehyde like 7-methyl-6-octenal (**26**) gives (*E*)-(**30**) and (*Z*)-(**30**) in a 40:60 ratio. Although the diastereomers can be separated by chromatography, they isomerize slowly at 0 °C.[71] It is noteworthy that 1,3-dicarbonyl compounds in which one group is COPh undergo highly stereoselective Knoevenagel reactions. Thus, condensation of benzaldehyde with (**31**) and (**32**) gives the products (**33**) and (**34**), respectively, in which the phenyl group derived from benzaldehyde is *trans* to the COPh group (99:1).[73]

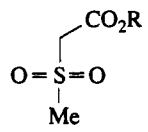


(**11**)

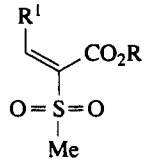
(**26**)



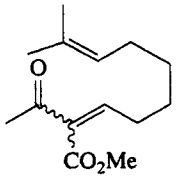
(**27**)



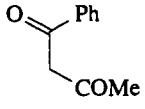
(**28**)



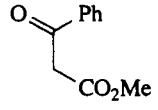
(**29**)



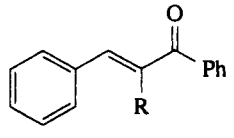
(*E*/*Z*)-(**30**)



(**31**)

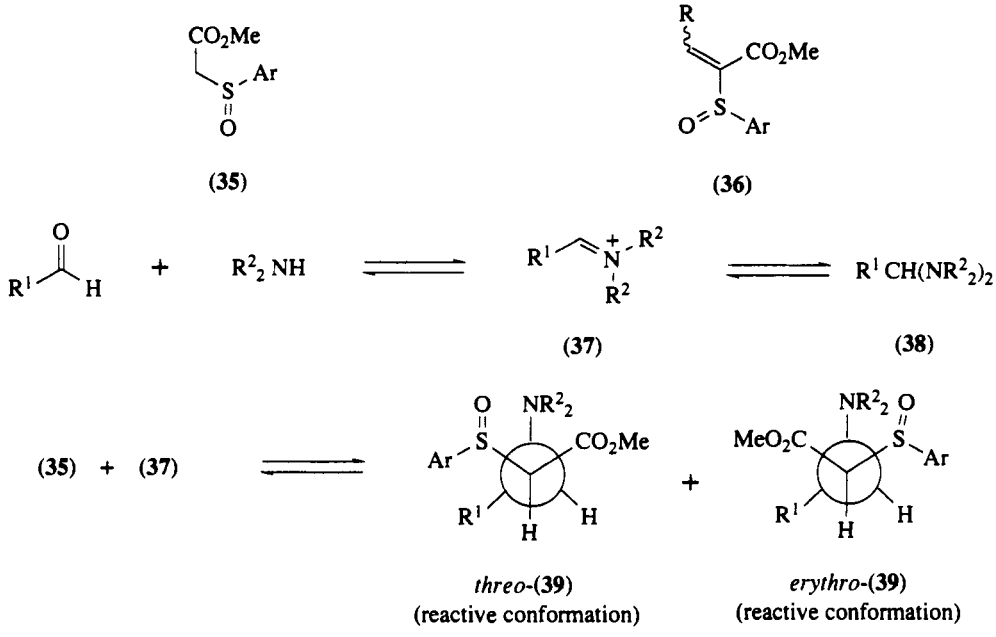


(**32**)



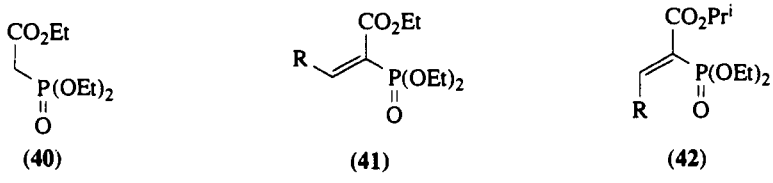
(**33**) R = COMe
(**34**) R = CO_2Me

The stereochemical course of the Knoevenagel reaction of methyl arene-sulfinylacetate (**35**) with aliphatic and aromatic aldehydes has been investigated in detail.[74] In the presence of catalytic amounts of piperidine, methyl (*E*)-3-alkyl- and methyl (*E*)-3-arene-sulfinylalk-2-enoates (*E*)-(**36**) are formed exclusively. It is of interest that the sodium and lithium enolates of (**35**) do not react with aldehydes. However, using the magnesium or zinc salts it is possible to drive the equilibrium towards the condensation products.[75–77] Primary and tertiary amines are not effective as catalysts either. This is a strong hint that an iminium salt (**37**) is an intermediate in this reaction. Also, (**39**), which is an adduct of the proposed iminium salt (**37**) and methyl arenesulfinylacetate (**35**), can be obtained in crystalline form either from (**38**) and (**35**) or from the aldehyde and (**35**); (Scheme 11). The *erythro*/*threo* ratio of (**39**) depends on the secondary amine used (R^1 = phenyl; *threo*/*erythro* ratio for dimethylamine is 0:100; for pyrrolidine is 0:100; and for 2-methylpiperidine is 30:70). The ratio is clearly related to the relative bulkiness of the groups CO_2Me, SOAr, R^1 and NR^2_2. In acetic acid a stereospecific *anti* elimination is found to give (*E*)-(**36**) from *threo*-(**39**) and (*Z*)-(**36**) from *erythro*-(**39**). However, a different mechanism operates under Knoevenagel conditions, where the thermodynamically more stable alkene (*E*)-(**36**) is obtained from both diastereomers (**39**) *via* an intermediate carbanion.[74] One has always to keep in mind though, that isomerization of the Knoevenagel product is possible.

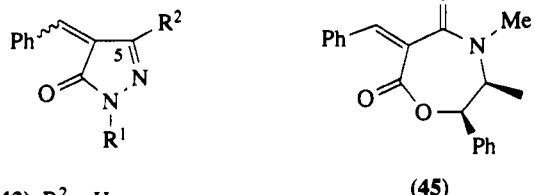


Scheme 11

In the Knoevenagel reaction, the thermodynamically more stable compounds are usually formed. However, a closely related transformation provides access to compounds of opposite stereochemistry. Condensation of phosphonoacetate (**40**) with aliphatic and aromatic aldehydes in the presence of *N*-methylmorpholine/$TiCl_4$ yields product (**41**) with the thermodynamically more stable (*E*)-configuration.[78] In contrast, titanated (**40**), obtained from the reaction of the sodium salt of (**40**) with $ClTi(OCHMe_2)_3$ reacts with aldehydes to give preferentially the thermodynamically less stable (*Z*)-isomer (**42**).[35]



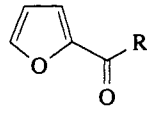
Unsymmetrical cyclic active methylenes such as pyrazolones, isoxazolones and oxazepane-5,7-diones can also undergo stereoselective condensation with aldehydes. Benzylidenepyrazolones (**43**) with a hydrogen at C-5 are more stable in the (*E*)-configuration, whereas the corresponding compounds (**44**) with an alkyl or aryl substituent at C-5 have the (*Z*)-configuration.[79–81] Knoevenagel condensation of benzaldehyde with oxazepane-5,7-diones in the presence of $TiCl_4$, ethylenediammonium diacetate or piperidine/acetic acid leads mainly to the Knoevenagel product (**45**) with a (*Z*)-configuration,[34] contrary to earlier descriptions in the literature.[82] The pronounced selectivity is rationalized by the pseudo-boat conformation of the seven-membered ring with an upwards flexion of the lactone carbonyl of 57.4° and of the amide carbonyl of 31.5°. Thus, the benzylidene compound with the (*Z*)-configuration should be sterically less hindered.[34]



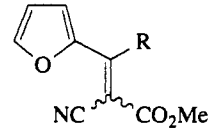
(**43**) R^2 = H

(**44**) R^2 = alkyl, Ph

Condensation of unsymmetrical ketones with methyl cyanoacetate usually gives a mixture of (*E*)- and (*Z*)-isomers in which the isomer with a *trans* relationship between the bulkier substituent and the carboalkoxy group predominates. Thus, condensation of alkyl 2-furyl ketones (**46**) and (**47**) affords a mixture of (*E*)- and (*Z*)-isomers of (**48**) and (**49**) with the (*E*)-isomer predominating (Scheme 12).[39]



(**46**) R = Me
(**47**) R = Pr^i

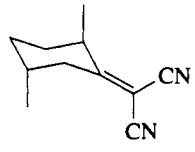


(**48**) R = Me *(E)*:*(Z)* = 5:1
(**49**) R = Pr^i *(E)*:*(Z)* = 1.1:1

Scheme 12

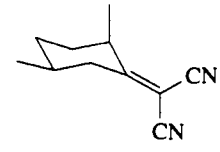
Knoevenagel products of cyclic ketones such as cyclohexanone show a pronounced preference in adopting a chair conformation with an axial orientation of substituents in the α-position. Condensation of *trans*-2,5-dimethylcyclohexanone (**50**) with malonodinitrile under neutral or weakly basic conditions leads, as expected, to (**51**); under the same conditions the *cis*-2,5-dimethylcyclohexanone (**52**) affords (**53**). It is remarkable that the *cis* product (**53**) is thermodynamically more stable than (**51**), whereas the ketone (**50**) with *trans* orientated methyl groups is more stable than (**52**). The unexpected difference in stability is due to the necessity of the α-substituent in the Knoevenagel products (**51**) and (**53**) to adopt an axial orientation. In the conformation with an equatorial α-methyl group a severe steric interaction would occur because of a coplanar arrangement of the methyl and the dicyanomethylene moiety.[83]

(**50**)



(**51**)

(**52**)

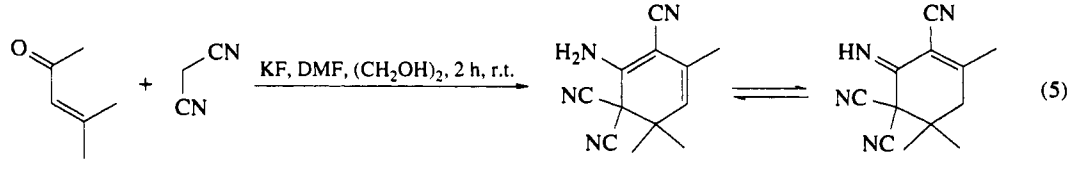


(**53**)

Instead of α,β-unsaturated acids, (*E*)-β,γ-unsaturated acids can be obtained in the Knoevenagel condensation if the reaction is performed in boiling xylene with an excess of malonic acid.[84]

1.11.2.6 Competitive Reactions

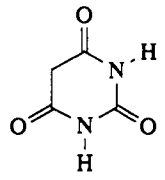
The main problem inherent in the application of the Knoevenagel condensation for synthesis is the undesired formation of the so-called bis adduct or Michael adduct, resulting from the Michael addition of a second molecule of the active methylene compound to the initial Knoevenagel product.[3,5,85] In the reaction of α,β-unsaturated ketones and malonodinitrile it has been found that the ratio of Knoevenagel and Michael products depends on steric factors. As an example, in the reaction of mesityl oxide (**54**), Knoevenagel condensation is followed by conjugate addition and finally by intramolecular condensation to yield the trinitrile (**55**; equation 5).[86] Whereas the reaction of barbituric acid (**56**) and *N*,*N*-dimethylbarbituric acid (**57**) yield Knoevenagel products with nearly every type of aldehyde,[3,87,88] Meldrum's acid (**58**) and its derivatives give Knoevenagel products only with aromatic aldehydes and ketones and with hindered aliphatic aldehydes, but yield Michael products upon reaction with simple aliphatic aldehydes.[89] An unusual Michael product (**60**) is formed by the reaction of Meldrum's acid with *n*-butanal.[90] Finally, dimedone (**59**) and similar cyclic 1,3-diketones yield Michael adducts exclusively with every type of aldehyde.[3,91,92] This property of dimedone (**59**) has been used traditionally in analytical chemistry for the qualitative and quantitative determination of aldehydes (see Section 1.11.2.7).[93] The different be-



(5)

(**54**) (**55**)

havior of various Knoevenagel products upon reaction with active methylenes has been correlated with their calculated Lewis acid strength.[48]



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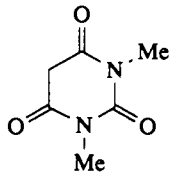

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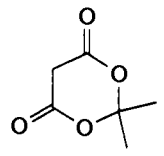

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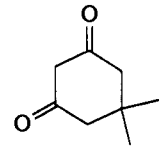
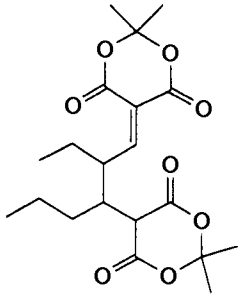
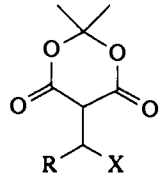


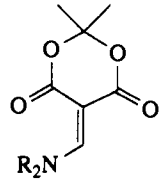
(59)



(60)

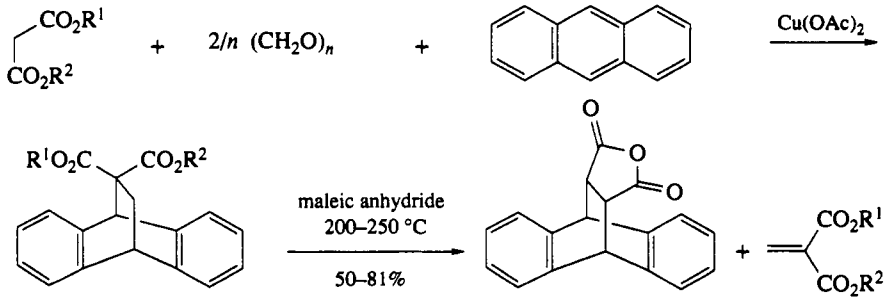


(61) X = OR^-
(62) X = NR_2
(63) X = SPh



(64)

Formation of the undesired Michael adducts can be avoided by trapping the Knoevenagel product with methoxide,[94] secondary amines,[95] or thiols[90] to give the 3-heterosubstituted alkyl-1,3-dicarbonyls (**61**), (**62**) and (**63**), respectively, from which the alkene may be generated by acid or in the case of the thio compound by an oxidative base-catalyzed hydrolysis. In some cases the adduct (**63**) shows a reactivity similar to the alkylidene-Meldrum's acid, *e.g.* yielding the corresponding epoxide with H_2O_2.[90] Alkylidene-Meldrum's acid can also be prepared by addition of metal organic reagents[96] to the easily available aminomethylidene-Meldrum's acids (**64**),[97] or by oxidative elimination of selenoalkylated Meldrum's acid.[98] A novel method for preparation of the highly reactive methylidenemalonates on a multigram level involves trapping them as Diels–Alder adducts with anthracene and their liberation by a subsequent retro-Diels–Alder thermolysis.[99] Thus, heating symmetric or unsymmetric malonates with paraformaldehyde, copper(II) acetate and anthracene in a mixture of xylene and acetic acid affords the crystalline Diels–Alder adducts (**66**), which generate the alkenic material (**65**) by thermolysis at 200–250 °C in the presence of maleic anhydride (Scheme 13).[99] In contrast, di-*t*-butyl methylenemalonate, a stable clear liquid, can be prepared by normal Knoevenagel condensation of di-*t*-butyl malonate and paraformaldehyde in acetic acid in the presence of potassium acetate and copper(II) acetate.[100]



(66) (65)

Scheme 13

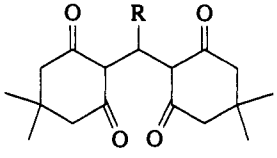
With some methylene active compounds ($NCCH_2PO(OEt)_2$) competition between Knoevenagel and Wittig–Horner reactions has been observed; the ratio of Knoevenagel and Wittig–Horner products is dependent upon the reaction conditions.[16,17]

Another non-trivial problem with Knoevenagel compounds that contain a γ-hydrogen atom is their tendency to undergo isomerization to β,γ-unsaturated products.[101,102] It has been observed that the ratio

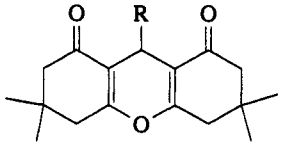
of α,β- and β,γ-isomers is dependent upon the nature of the amine catalyst used. Separation of α,β- and β,γ-isomers is usually difficult, but has been achieved in a few cases.[71,103]

1.11.2.7 Analytical Applications

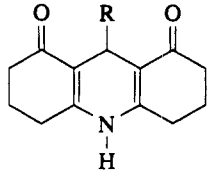
The Knoevenagel condensation with 1,3-dicarbonyls followed by a Michael reaction of a second molecule of the methylene compound, with or without addition of an amine or ammonia, may be used for the qualitative and quantitative determination of aldehydes even in the presence of ketones. Thus, cyclic β-diketones such as dimedone (**59**) react with aldehydes but not with ketones in the absence of a catalyst. For the characterization the bis(2,6-dioxo-4,4-dimethylcyclohexyl)methanes (**67**) or the 4,6-dioxo-2,2,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-9*H*-xanthene (**68**) may be used.[93,104,105]



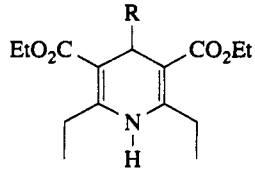
(**67**)



(**68**)



(**69**)



(**70**)

For fluorimetric measurements aldehydes are transformed to 9-substituted-1,8-dioxodecahydroacridines (**69**) by reaction with 1,3-cyclohexanedione and ammonia in aqueous acetic acid.[106] The acridine derivative (**69**) obtained from acetaldehyde absorbs at λ_{max} = 360 nm and emits at 470 nm in acidic medium, allowing the detection of as little as 0.2 μg of aldehyde. Finally, aldehydes can also be selectively determined in the presence of ketones by reaction with diethyl 3-oxoglutarate and ammonia to give dihydropyridines (**70**), which show a strong absorption at λ_{max} = 340 nm.[107] The difference in reactivity of ketones and aldehydes in the Knoevenagel reaction can be used to purify ketones. This process has some economical relevance and has been used to separate a mixture of glucose and fructose obtained by hydrolysis of sucrose over a cation exchanger. Stirring of the mixture with ethyl acetoacetate in the presence of $CaCl_2$ gives a solid glucose adduct; fructose can be obtained as a syrup of >95% purity.[108]

1.11.3 SCOPE AND LIMITATION

1.11.3.1 Variation of the Active Methylene Compound

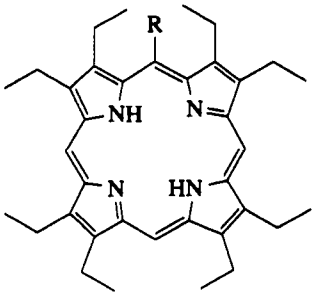
The active methylene compounds XCH_2Y can be divided into cyclic and acyclic, into symmetrical and unsymmetrical compounds and into compounds that contain either carbon or heteroatoms at positions 1 and 3. The groups X and Y can be CO_2R, $CONR_2$, COR, CN, $CNNR_2$, Ar, NO_2,[109] $PO(OR)_2$, SO_2OR, SO_2NR_2, SO_2R, SOR, SR and SiR_3 or similar functional groups (R = H, alkyl, aryl). General overviews on the variation of active methylene compounds[3] and on malonodinitrile[110,111] have appeared.

1.11.3.1.1 Malonic esters

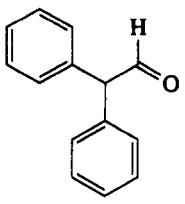
Most aldehydes easily undergo Knoevenagel condensation using secondary amines or their salts as a catalyst.[3] Under standard conditions, reaction of simple unbranched aliphatic aldehydes and of most ketones is difficult. However, the use of $TiCl_4$/amine allows reaction even of refractory aldehydes and a multitude of ketones in good to very good yields.[112,113] For example, the synthesis of Knoevenagel adducts (**72**) from 5-formyl-octaethylporphyrin (**71**) and different malonic esters in the presence of $TiCl_4$/pyridine at 0 °C has been achieved in 75–94% yield.[114]

Usually the Knoevenagel condensation yields the unsaturated product, but, with appropriate aldehydes, β-hydroxymalonates can be isolated.[62] The unusual formation of an α-naphthol (**74**) has been reported from the reaction of diphenylacetaldehyde (**73**) with diethyl malonate under Knoevenagel conditions.[115] Condensation of salicylaldehydes and other aromatic *o*-hydroxy aldehydes with malonates is still in use for the synthesis of the corresponding coumarin-3-carboxylic esters (**75**).[3,116–118] Reduction

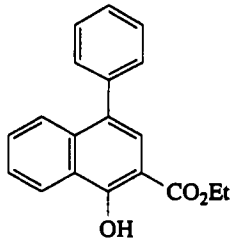
of several coumarins (**75**) to yield 3-substituted-3,4-dihydrocoumarin-3-carboxylic esters has been achieved using boranes.[118] Steroidal α-pyrones (**77**) have been obtained in one step from α-ketohydroxymethylene compounds (**76**) in a $TiCl_4$-mediated Knoevenagel condensation with dimethyl malonate followed by intramolecular cyclization.[119]



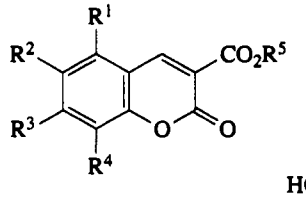
(**71**) R = CHO
(**72**) R = HC=C(CO$_2$R^1)$_2$



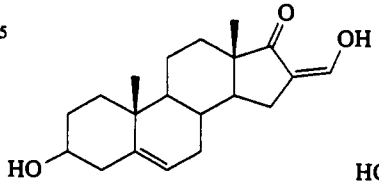
(**73**)



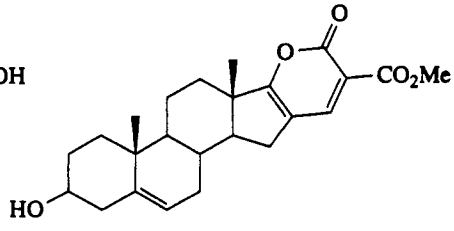
(**74**)



(**75**)



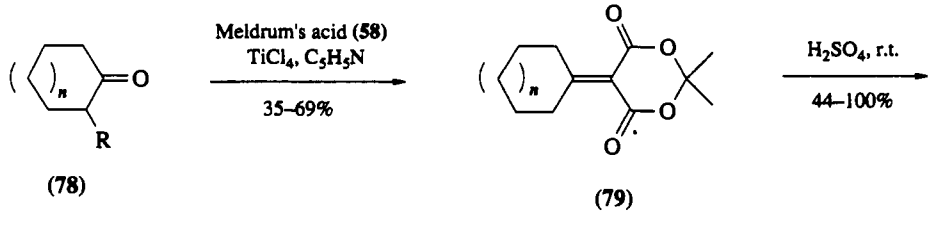
(**76**)



(**77**)

1.11.3.1.2 Meldrum's acid and derivatives

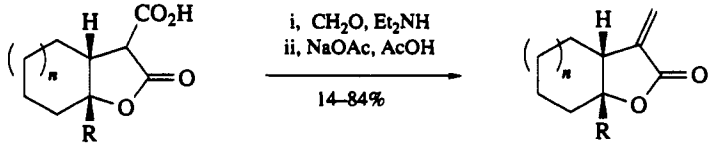
Meldrum's acid undergoes standard Knoevenagel condensations with aromatic and heteroaromatic aldehydes,[120,121] with hindered aliphatic aldehydes $R^1R^2R^3CCHO$[48] and with reactive, simple aliphatic ketones.[121–123] Condensation with less reactive ketones can be performed in the presence of $TiCl_4$/amine[124,125] or by prior conversion of the ketone into the corresponding ketimine.[48] The reaction with simple aliphatic aldehydes under standard conditions usually gives the corresponding Michael products as described in Section 1.11.2.6. Knoevenagel condensations of some other cyclic esters of malonic acid have also been reported.[126,127]



(**78**)

(**79**)

R = H, alkyl; n = 0, 1, 2



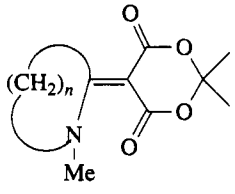
(**81**)

(**80**)

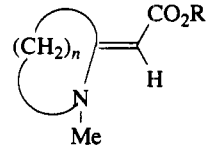
Scheme 14

The 1,4-addition of nucleophiles to Knoevenagel products of Meldrum's acid has been widely used synthetically. The products of the addition of Grignard reagents can be degraded to yield monocarboxylic acids and monocarboxylic esters, respectively.[128] Although hydrolysis of Knoevenagel products in aqueous methanol yields Meldrum's acid and the corresponding aldehyde or ketone, with a trace of hydrochloric acid in ethanol half-esters of 2-methylenemalonates are obtained.[66,120]

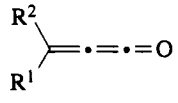
An interesting route to α-carboxy-δ-lactones (**81**) and α-methylenelactones (**80**), based on hydrolysis of Knoevenagel products (**79**) of Meldrum's acid with cyclic aliphatic ketones (**78**), has been developed (Scheme 14).[129] Reduction of 5-methylene derivatives of Meldrum's acid has been performed catalytically[130] or by use of LAH.[48] Imidoylation reaction of Meldrum's acid and subsequent solvolysis of the resulting (**82**) yields β-enamino esters (**83**) in good yields.[131,132] Flash vacuum pyrolysis of alkylidene derivatives of Meldrum's acid can be used to prepare methylene ketenes (**84**), a class of compounds difficult to prepare by conventional methods. By this procedure, methylene ketenes are obtained from aromatic aldehydes and ketones and from aliphatic ketones in only two steps.[133,134] Intramolecular trapping of the methylene ketene obtained from the ketone (**85**) has been used successfully in the synthesis of the naphthol (**86**).[133]



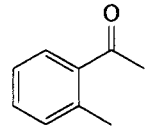
(**82**)



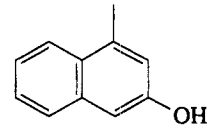
(**83**)



(**84**)



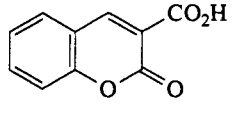
(**85**)



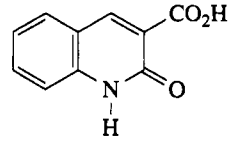
(**86**)

1.11.3.1.3 Malonic acid

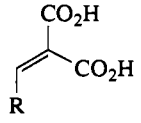
Malonic acid undergoes Knoevenagel condensations with nearly every type of aldehyde and with very reactive ketones.[3] If condensations with malonic acid are performed in ethanolic ammonia below 70 °C, the methylenemalonic acids are usually obtained. If, however, the condensations are performed in pyridine (Doebner modification), decarboxylation normally takes place and the acrylic or cinnamic acid is



(**87**)

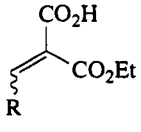


(**88**)

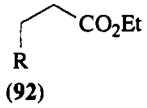


(**89**)

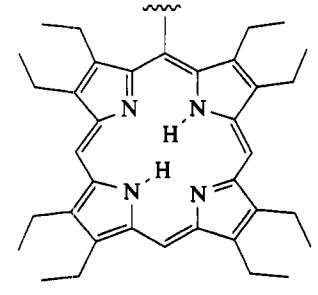
(**90**)



(**91**)



(**92**)

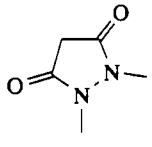


R

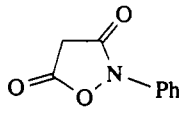
formed (see also Section 1.11.2.3). In these reactions the double bond isomer with the carboxyl group *trans* to the larger substituent is usually obtained (see also Section 1.11.2.5).[3,135,136] A problem with condensations of malonic acid is the isomerization of the α,β-isomer to the β,γ-isomer.[3,84] Coumarin-3-carboxylic acid (**87**) and related compounds are obtained in the reaction of salicylaldehyde and other 3-hydroxy aldehydes with malonic acid.[3,26,117] Finally, reaction of *o*-aminobenzaldehyde with malonic acid yields 2(1*H*)-quinolone (**88**).[3] The condensation of aldehydes with 2-alkylmalonic acids is of limited synthetic value as the reaction is susceptible to steric hindrance.[3] In these cases the β-hydroxy acids instead of α-alkyl-α,β-unsaturated acids can be obtained, depending on the reaction conditions.[58,60,137] An example from the porphyrin field illustrates the problem of prediction in chemical reactivity. Condensation of 5-formyloctaethylporphyrin with malonic acid delivers compound (**89**) which is double decarboxylated under conditions of catalytic hydrogenation to give (**90**). The desired compound (**92**), however, is obtained by hydrogenation of half-ester (**91**).[114] Monoalkyl malonates, obtained by partial hydrolysis of dialkyl malonates, show a reactivity similar to malonic acid. The Knoevenagel reaction is usually accompanied by decarboxylation, giving a cinnamic ester.[138,139] Addition of halogen to the double bond with subsequent dehydrohalogenation is a method for the preparation of alkynic acid esters.[140]

1.11.3.1.4 Mono- and di-amides of 1,3-diacids

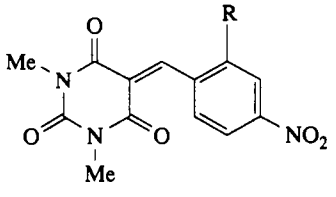
Malonomonoamides can be condensed with aldehydes to give acrylamides or cinnanamides, but condensation with malonodiamides is of only minor importance.[3] In contrast to Meldrum's acid (**58**), Knoevenagel reactions of barbituric acid (**56**) and *N,N*-dimethylbarbituric acid have been less explored. However, several aliphatic, aromatic and heteroaromatic aldehydes are known to react easily and with high yields in most cases.[57,87,88] Reactions of 1,2-dimethyl-3,5-pyrazolidinedione (**93**) with several aliphatic and aromatic aldehydes using standard conditions yield Knoevenagel products in good yield.[141] A similar reactivity is observed with 2-phenyl-3,5-dioxoisoxazolidine (**94**)[142] and oxazepanediones (**45**; see Section 1.11.2.5).[34,82] Recently, the oxidations of alcohols to carbonyl compounds and thiols to disulfides with 5-arylidene-1,3-dimethylbarbituric acids (**95**) have been described. Mechanistically (**95**) mimics enzymic oxidation by flavin adenine dinucletide (FAD).[143]



(**93**)



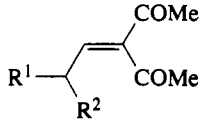
(**94**)



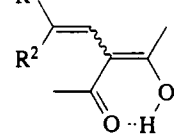
(**95**) R = H, NO_2

1.11.3.1.5 1,3-Diketones

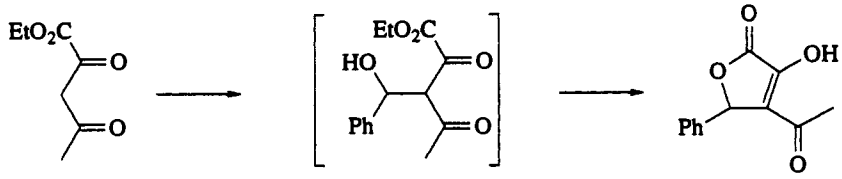
Aromatic aldehydes condense with acyclic 1,3-diketones to yield the α,β-unsaturated Knoevenagel products exclusively.[3,144–148] With aliphatic aldehydes, particularly those that are α-branched, the situation is somewhat more complex as the α,β-unsaturated Knoevenagel products (**96**) tend to isomerize to enolic β,γ-unsaturated products (**97**) that are stabilized by intramolecular chelation.[3,14,71,102,103,145] At higher temperatures or with prolonged reaction times Michael addition products are formed.[3] However, to bring about Knoevenagel condensations with 1,3-diphenyl-1,3-propanedione and similar compounds, higher temperatures must usually be employed.[146] In the reaction of the ethyl acylpyruvate (**98**) with benzaldehyde γ-lactone (**100**) is obtained, probably *via* intermediate (**99**).[149] The condensation of 1,1,1-trifluoroacetylacetone with aromatic aldehydes using piperidine/AcOH is a relatively slow reaction, and gives not only the expected product (**101**), but (**102**) as well.[150]



(**96**)

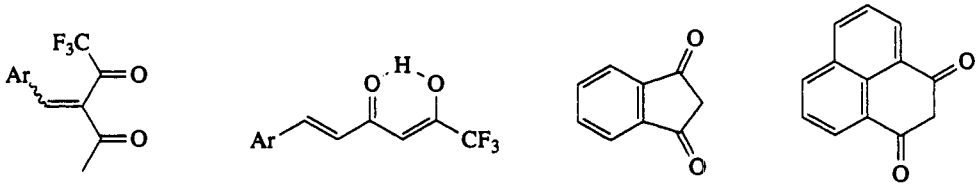


(**97**)



(98) (99) (100)

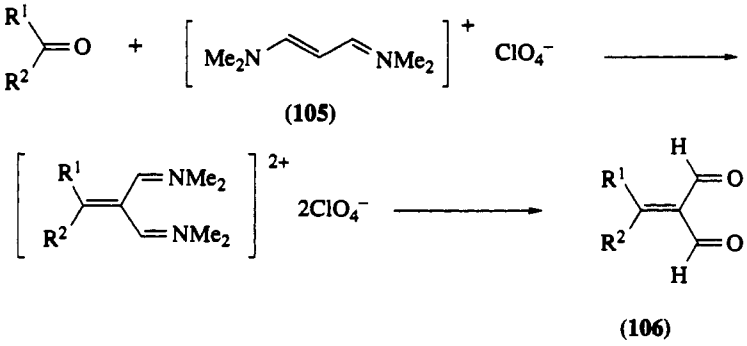
Hydrogenation of Knoevenagel products of 2,4-alkanediones over Raney nickel provides a simple route to 3-substituted 2,4-diones.[145] Alternatively, reductive deacetylation can be accomplished using tetracarbonylhydridoferrate(0) in ethanol to prepare alkyl ketones. If the reaction is carried out in THF or acetone, exclusive reduction of the α,β-unsaturated double bond is observed.[146,151] Reactions of aldehydes with cyclic 1,3-diketones generally lead to the formation of Michael adducts under standard conditions.[91] Indane-1,3-dione (**103**) yields Knoevenagel products with different aldehydes, ketones and ketimines, whereas perinaphthindane-1,3-dione (**104**) gives the Michael adducts.[48]



(101) (102) (103) (104)

1.11.3.1.6 Malondialdehyde

Stable and isolable derivatives of methylene malondialdehydes are not accessible using standard Knoevenagel methodology.[152] However, they have been prepared *in situ* in the synthesis of cephalosporin C,[153] iridoids and secoiridoids.[154,155] Arnold *et al.* have recently succeeded in the synthesis, isolation and characterization of methylenemalondialdehydes (**106**) by exploitation of the reactivity of polymethinium salts (**105**) toward electrophilic reagents as shown in Scheme 15. Detailed studies have revealed that reaction takes place with aromatic, heteroaromatic, aliphatic unsaturated aldehydes and different types of dialdehydes. The method has also been used for the synthesis of diarylmethylene aldehydes. The reactivity of these compounds is governed by the strongly electron-deficient β-carbon atom. Michael additions with a series of CH-acidic compounds, amines, phosphines and different inorganic anions such as CN^-, CNO^- and N_3^-, have been studied.[156,157]



(105)

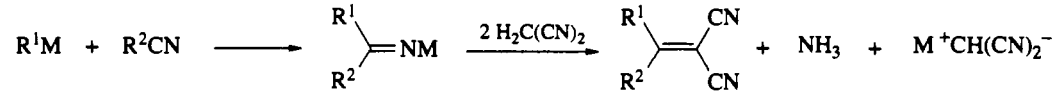
(106)

Scheme 15

1.11.3.1.7 Malonodinitrile

Syntheses with malonodinitrile, including Knoevenagel condensations, have been reviewed extensively[3,110,111] Malonodinitrile is one of the most reactive methylene compounds employed in the Knoevenagel condensation and alkylidene and arylidene malonodinitriles are readily available. In many cases the condensation proceeds satisfactorily without any added catalyst, although it is efficiently catalyzed by weak bases like ammonium acetate and piperidinium acetate or amino acids like β-alanine.[10] Several

other catalysts, including potassium fluoride[11,12], aluminum oxide,[16] aluminum phosphate/aluminum oxide[18] and xonotlite–potassium *t*-butoxide,[19] have also been used. Recently, ylidene malonodinitriles have been prepared by reaction of an organometallic reagent (**107**) with a nitrile (**108**) to produce a metal ketimate intermediate (**109**), which gives the desired ylidene malonodinitrile (**110**) upon treatment with 2 equiv. of malonodinitrile (Scheme 16).[158] The Knoevenagel condensation of malonodinitrile with aldehydes and ketones followed by cyclization has been used widely for the synthesis of a multitude of carbocycles and heterocyclic compounds (see Section 1.11.5.1).[110,111]



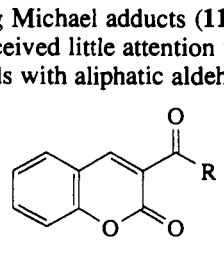
(**107**) (**108**) (**109**) (**110**)

Scheme 16

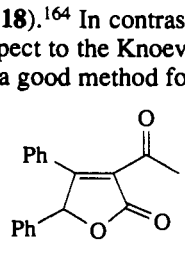
Ylidene malonodinitriles are known to undergo 1,4-addition reactions with a wide range of nucleophiles.[3,110,111,159] Reduction of the double bond can be performed by the Meerwein–Ponndorf–Verley reaction, $NaBH_4$, $LiBH_4$ or *N*-alkyl-1,4-dihydronicotinamides, to give the corresponding substituted malonodinitriles.[3,159] Conjugate addition of Grignard reagents to methylidenemalonodinitriles gives 2-substituted malonodinitriles.[160] Reaction at the δ-position of alkylidene malonodinitriles can be accomplished with secondary amines and orthoformates to provide access to 4-amino-1,1-dicyano-1,3-butadienes in moderate to good yields.[161]

1.11.3.1.8 β-Keto esters and β-keto acids

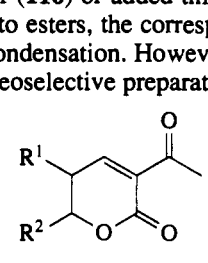
A wide range of catalysts and reaction conditions have been developed to bring about Knoevenagel condensations of β-keto esters.[3,162] A useful procedure involves the use of $TiCl_4$/pyridine in THF at low temperatures, which allows formation of methyleneacetoacetates from aliphatic, aromatic and heteroaromatic aldehydes.[162] Knoevenagel reactions of β-keto esters with hydroxy aldehydes and ketones are followed by ring closure to give 3-acylcoumarins (**111**), acylfuranones (**112**) and dihydropyranones (**113**).[3] Similar reactions have been reported with *o*-aminobenzaldehydes.[3] The tendency of the alkylidene-β-keto esters to form Michael adducts with carbonyl compounds at elevated temperatures has been widely exploited in the synthesis of 1,5-diketones (**114**) that can cyclize to give cyclohexenones (Scheme 17).[163] Reaction between aromatic aldehydes and 4-hydroxy-6-methyl-2-pyrone (**116**) affords the Knoevenagel product only as an intermediate that reacts with a second molecule of (**116**) or added thiols to yield the corresponding Michael adducts (**117**) or (**118**).[164] In contrast to β-keto esters, the corresponding β-keto acids have received little attention with respect to the Knoevenagel condensation. However, the reaction of β-keto acids with aliphatic aldehydes is a good method for the stereoselective preparation of (*E*)-α,β-



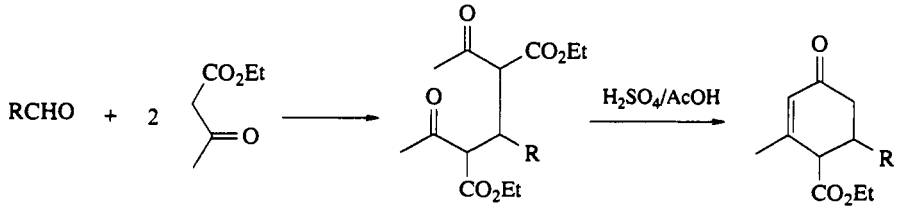
(**111**)



(**112**)

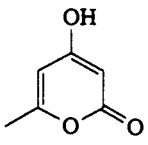


(**113**)



(**114**) (**115**)

Scheme 17



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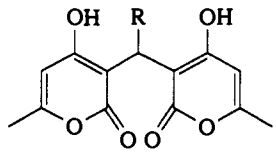

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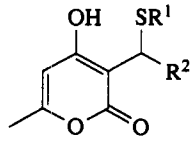


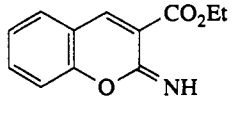
(118)

unsaturated ketones. Aromatic aldehydes are less reactive and give β-ketols in some cases.[165a] Formyl acetate can not be used for Knoevenagel reactions because of its instability. However, 4,4,4-trichloro-3-oxobutanal may be employed as an equivalent.[165b]

1.11.3.1.9 Cyanoacetic esters, cyanoacetic acid and isocyanoacetic esters

Like malonodinitrile, cyanoacetic esters are sufficiently reactive to undergo Knoevenagel condensation with a wide variety of aldehydes and ketones. In contrast to the reaction with malonodinitrile, only the Knoevenagel products and usually no Michael adducts are obtained under standard conditions. Nearly all known Knoevenagel catalysts can be successfully employed.

Condensations with aldehydes are stereoselective, yielding the stereoisomer in which the β-alkyl or β-aryl group is *cis* to the smaller cyano function (see Section 1.11.2.5). Some side products that originate from the reaction of benzaldehydes with ethyl cyanoacetate are formed.[166] Reaction of *o*-hydroxybenzaldehyde with ethyl cyanoacetate affords (**119**), arising from attack of the phenol oxygen at the cyano group. The imino lactone (**119**) thus obtained can be hydrolyzed to yield lactone (**120**).[16,18] The synthesis of substituted dihydrothiophenes has been accomplished starting with the unsaturated (*Z*)-aldehyde (*Z*)-(**121**). Michael addition of a second molecule of cyanoacetate to the initially formed Knoevenagel product (*Z*)-(**122**), followed by elimination of HCN, yields (**123**). With the (*E*)-aldehyde (*E*)-(**121**) the reaction stops at (*E*)-(**122**).[167] Stereoselective cyclopropane formation is accomplished by reaction of the α-anions of compounds containing allylic or benzylic nitro groups with alkylidene and benzylidene cyanoacetates (Scheme 18).[168] α-Naphthols are formed by heating the Knoevenagel products of ethyl cyanoacetate and benzyl ketones.[3,169] Mixtures of stereoisomers of α,β-unsaturated nitriles are obtained under Krapcho conditions from alkylidene cyanoacetates.[170] Reduction of the methylene cyanoacetates has been performed by using $NaBH_4$[171] and by catalytic hydrogenation[171,172] to yield substituted cyanoacetates or by LAH to yield amino alcohols.[173] The conversion of Knoevenagel products from steroidal ketones and ethyl cyanoacetate to the corresponding α-keto esters is possible.[171]



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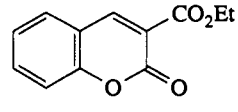

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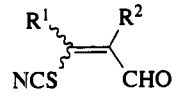

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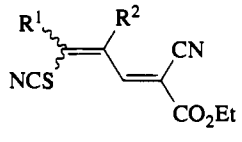

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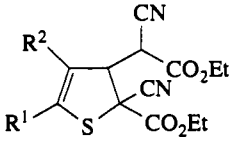

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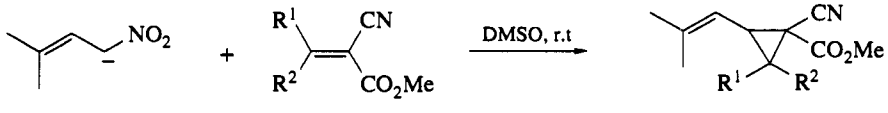
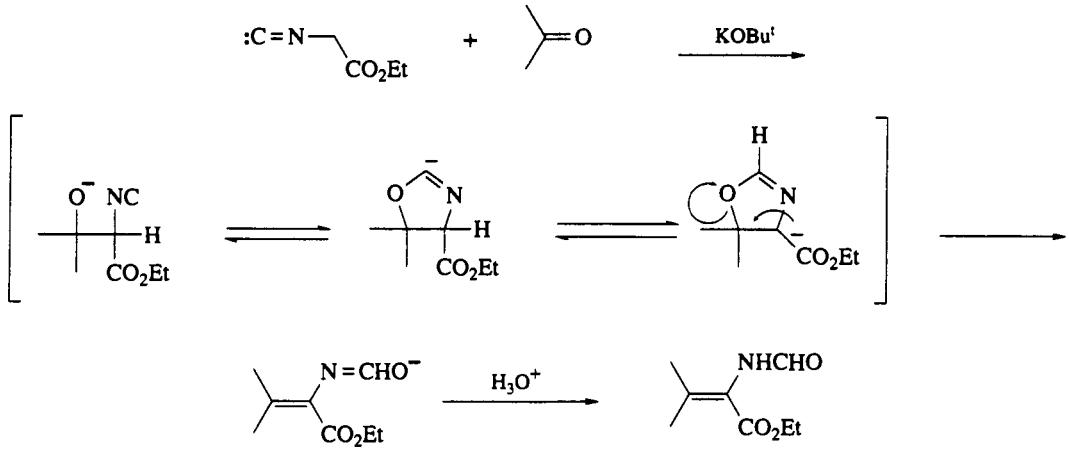


Scheme 18

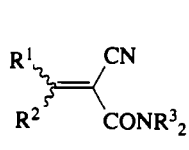
No substantial developments on Knoevenagel condensations with cyanoacetic acid have emerged in the last few years. As in the reaction with cyanoacetates, Knoevenagel products can be obtained from aldehydes and different ketones using ammonia and ammonium salts, primary and secondary amines and their salts, amino acids and ion-exchange resins as catalysts. α,β-Unsaturated nitriles are obtained when pyridine or pyridine/piperidine is used as the catalyst at a higher temperature.[3] The isocyanide group also has an activating effect on the α-methylene group. Thus, isocyanoacetates react with aldehydes or ketones in the presence of bases such as DBU or Bu^{t}OK. Instead of the normal Knoevenagel products, α-formylaminoacrylates are formed (Scheme 19).[174,175]



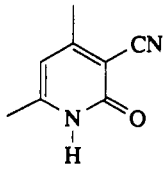
Scheme 19

1.11.3.1.10 Cyanoacetamides, thiocyanoacetamides and β-keto nitriles

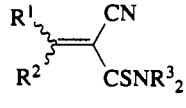
Cyanoacetamides yield α-cyanoacrylamides (**124**) stereoselectively upon reaction with aldehydes and nonselectively with ketones under standard Knoevenagel conditions.[3] α-Cyanoacrylamides (**124**) are also obtained by partial hydrolysis of methylenemalonodinitriles.[158] With 1,3-diketones, *e.g.* acetylacetone, pyridones like (**125**) are formed upon reaction with cyanoacetamides.[176] Base-catalyzed dimerization of α-cyanoacrylamides (**124**) yields piperidones.[176]



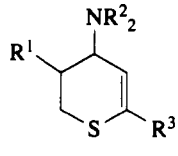
(**124**)



(**125**)

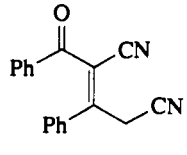


(**126**)

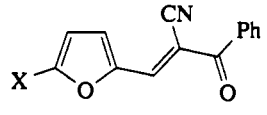


(**127**)

The Knoevenagel reaction of aromatic and heteroaromatic aldehydes with cyanothioacetamides affords α-cyanothioacrylamides (**126**), which easily undergo thermal dimerization to 3,4-dihydro-2*H*-thiopyrans (**127**).[177] α-Keto-substituted acrylonitriles are synthesized by condensation of β-keto nitriles with aldehydes or ketones.[3,178] Benzoylacetonitrile self-condenses to afford (**128**), which can be transformed



(**128**)

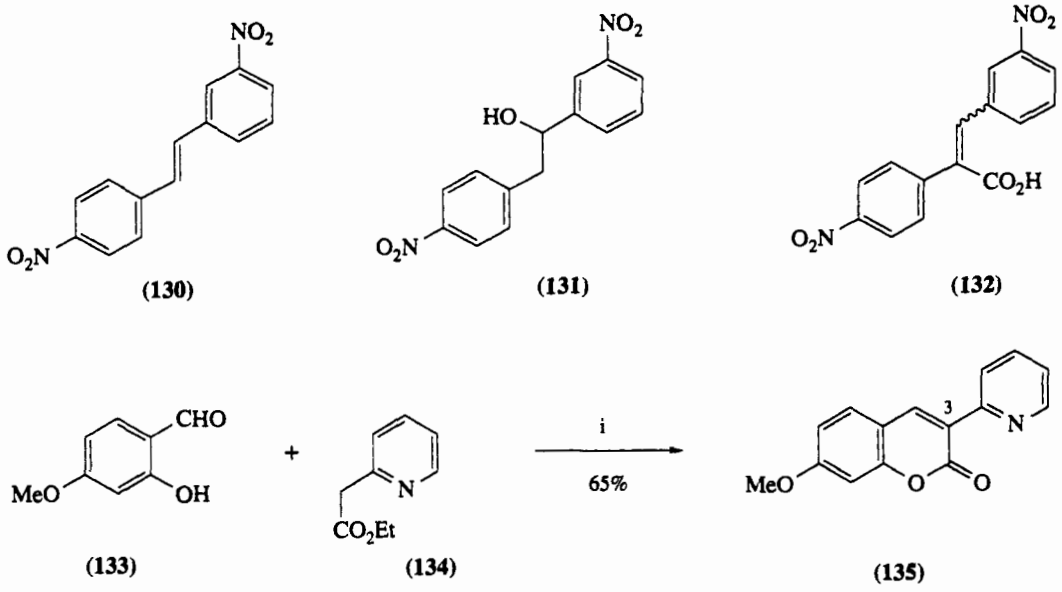


(**129**) X = NO_2, Br, PhS, $PhSO_2$

to different heterocycles such as pyrazoles and pyridazines.[179] Substituted furancarbaldehydes react with benzoylacetonitrile and other activated acetonitriles to give Knoevenagel products (**129**) in good yield.[180]

1.11.3.1.11 Derivatives of arylacetic acid

Condensations of arylacetic acids, arylacetates and arylacetonitriles with aromatic aldehydes and ketones proceed under standard Knoevenagel conditions, providing access to stilbenes or substituted stilbenes.[3,59,181–184] Thus 3-nitrobenzaldehyde and 4-nitrophenylacetic acid react in the presence of different amines to give (**130**), (**131**) and (**132**). The ratio of the products varies greatly with the amine used. (**131**) and (**132**) could easily be transformed into (**130**) in high yield.[59] Reaction of arylacetates with *o*-hydroxybenzaldehydes yields the corresponding coumarins.[3] The condensation of 2-hydroxy-4-methoxybenzaldehyde (**133**) with pyridylacetates like (**134**) yields 7-methoxy-3-pyridylcoumarins like (**135**); (Scheme 20).[184]

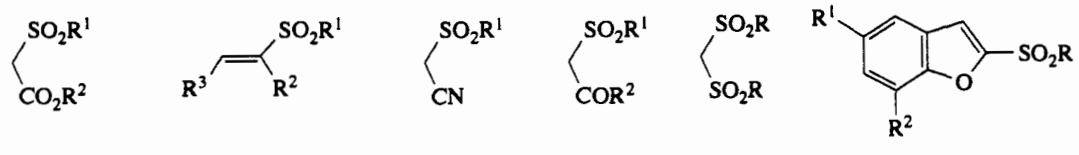


i, pyridine, isopropyl alcohol, reflux, 8 h

Scheme 20

1.11.3.1.12 Methylenes activated by sulfur-containing functional groups

Knoevenagel condensations with methylenes activated by sulfur-containing functionalities have been less explored than reactions with typical 1,3-dicarbonyl compounds. Mostly sulfones and sulfoxides, but also sulfonic acid derivatives, have been used.[185] Aliphatic and aromatic aldehydes react with sulfonylacetates (**136**) to give α-sulfonyl-α,β-unsaturated esters in good yields using piperidine as catalyst.[56,186] The (*E*)-configuration of the products has been proven (see Section 1.11.2.5). Dealkoxycarbonylation of Knoevenagel products (**138**) with LiI in DMF provides a useful route to (*E*)-α,β-unsaturated sulfones



(**136**) R^2 = alkyl
(**137**) R^2 = H

(**138**) R^2 = CO_2R
(**139**) R^2 = H

(**140**)

(**141**)

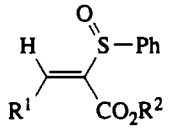
(**142**)

(**143**)

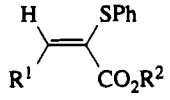
(**139**), which cannot be obtained in reasonable yield by direct condensation with sulfonylacetic acid (**137**).[72]

Knoevenagel condensations have also been performed with unsymmetrical active methylenes like (**140**), (**141**)[56,186,187] and symmetrical compounds (**142**).[188,189] Reaction of (**142**) with aliphatic aldehydes affords only the β,γ-unsaturated condensation products.[188] Reaction of (**142**) with salicylaldehydes in the presence of piperidine followed by acidification yields 2-alkylsulfonylbenzofurans (**143**).[189]

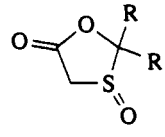
The condensation of aromatic and aliphatic aldehydes with sulfoxide-activated methylenes like phenylsulfinylacetonitriles and phenylsulfinylacetates selectively forms α-sulfinyl-α,β-unsaturated carbonyl compounds (**144**) with the alkyl or aryl group *trans* to the sulfinyl group (see Section 1.11.2.5).[52,73,186,187] Oxidations of (**144**) with *m*-chloroperbenzoic acid yield the unsaturated (*E*)-sulfones (**138**) and reductions with NaI/$(CF_3CO)_2O$ give (*E*)-α-phenylthioacrylates (**145**).[56] With cyclic sulfoxides (**146**) and (**147**), however, benzylidene products with (*Z*)-configurated double bonds are obtained on reaction with aromatic aldehydes.[190] α-Phenylsulfinylacrylates (**148**) undergo acid-induced vinylogous Pummerer rearrangement yielding γ-oxygen-functionalized products (**149**).[191] Michael reactions involving enantiomerically pure α-sulfinyl-α,β-unsaturated carbonyl compounds are of particular interest, as they provide access to optically active addition products. This approach has been applied for the preparation of enantiomerically pure β-substituted cyclopentanones, β-alkylcarboxylic acids and other useful intermediates for the synthesis of natural products. However, it must be pointed out that optically active α,β-ethylenic sulfoxides have not been prepared by the Knoevenagel condensation.[192]



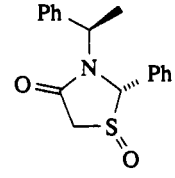
(**144**)



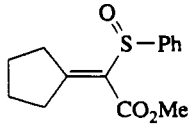
(**145**)



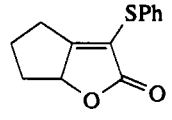
(**146**)



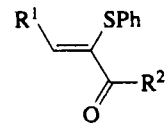
(**147**)



(**148**)



(**149**)

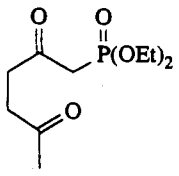


(**150**)

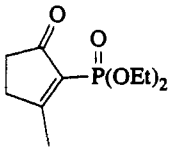
Knoevenagel condensations of β-carbonyl aryl sulfides and similar compounds have been little studied.[186,193,194] β-Cyano aryl sulfides undergo condensation with a number of aromatic aldehydes and ketones in modest yield, but β-ethoxycarbonyl aryl sulfides fail to form Knoevenagel products.[186,193] In contrast to the results obtained with sulfonyl- and sulfinyl-containing active methylenes, condensations with β-keto sulfides yield α-sulfenyl-α,β-unsaturated compounds (**150**) with the (*Z*)-configuration at the double bond, that is, with the alkyl group *cis* to the sulfinyl moiety.[56] Oxidation of these compounds gives access to unsaturated sulfines and sulfones with the (*Z*)-configuration.[56]

1.11.3.1.13 Phosphonates

The anions of cyanophosphonates and alkoxycarbonylphosphonates are generally used for Wittig–Horner alkenation. However, under appropriate conditions, Knoevenagel condensations can be observed.[16,17] Reactions of triethylphosphonoacetic acid with aliphatic aldehydes, aromatic aldehydes, or aromatic ketones in the presence of $TiCl_4$/*N*-methylmorpholine yield Knoevenagel condensation products with the thermodynamically more stable (*E*)-configuration (**41**).[78] The corresponding (*Z*)-configured products (**42**) can be obtained using titanated triethylphosphonoacetate (**38**) (see Section 1.11.2.5).[35] In an intramolecular Knoevenagel condensation phosphonate (**151**) affords cyclopentenone (**152**).[195] Vinylic phosphonates undergo a variety of reactions.[8,196–200] Tetraalkyl alkylidene- and benzylidene-diphosphonates (**153**) can be prepared from tetraalkyl diphosphonates and aromatic or α-substituted aliphatic aldehydes using $TiCl_4$/amine as the condensing reagent.[78] A preparation of methylidenediphosphonates has also been reported.[201]



(151)



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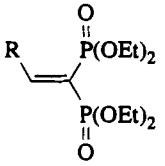


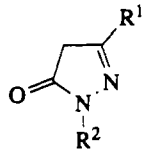
(153)

1.11.3.1.14 Methylenes activated by nitro groups

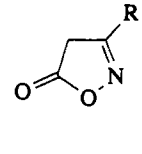
Reactions of carbonyl compounds with nitroalkanes like nitromethane (Henry reaction) are described in Volume 2, Chapter 1.10. The doubly activated ethyl nitroacetate readily reacts with aliphatic, aromatic and heteroaromatic aldehydes to give α,β-unsaturated-α-nitrocarboxylic acid esters in the presence of $TiCl_4$/*N*-methylmorpholine as mixtures of *cis* and *trans* isomers.[162]

1.11.3.1.15 Pyrazolones and isoxazolones

Pyrazolones (**154**) and isoxazolones (**155**) can also be used in the Knoevenagel reaction. Thus condensations with aliphatic aldehydes, aromatic aldehydes and ketones in the presence of ethylenediammonium diacetate or other typical catalysts provide the corresponding alkylidene and benzylidene compounds in good yields (for stereochemistry see Section 1.11.2.5).[79–81,202,203] A new method involves the use of dicyclohexylcarbodiimide at 20 °C without an additional catalyst.[204]



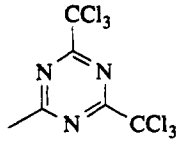
(154)



(155)

1.11.3.1.16 Methylenes activated by heterocycles

Certain heteroaromatic compounds that have acidic methyl groups are effective in the Knoevenagel condensation. 6-Methyl-1,3,5-triazine (**156**), 2-methylpyridine *N*-oxides (**157**), quinolines and pyrimidines all condense with aromatic aldehydes in the presence of the usual catalysts. An example of a doubly activated methylene compound in which one activation group is a heterocycle is the 2-oxopropylthiazole (**158**), which condenses with a number of aldehydes.[205–207]



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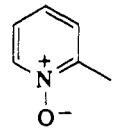

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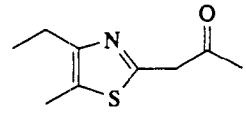
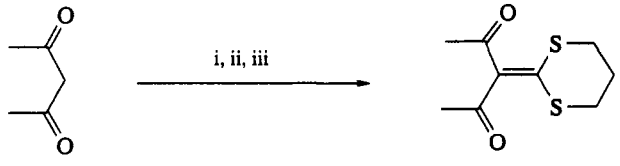


(158)

1.11.3.2 Variation of the Carbonyl Compound

There is almost no restriction in the choice of an appropriate electrophile in the Knoevenagel reaction. Aldehydes, ketones, thioketones, imines, enamines, acetals and orthoesters have been used. With less reactive methylene groups, however, drastic reaction conditions may be necessary. Steric effects have a significant influence on the rate and unexpected compounds are often obtained as a result of secondary reactions. Reaction of 1,3-dicarbonyl compounds with carbon disulfide followed by dialkylation with an alkyl halide give diacylketene-*S*,*S*-acetals (**159**). However, even with highly acidic dicarbonyl com-

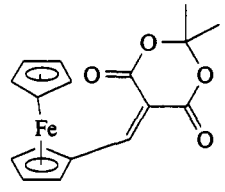
pounds, strong bases such as sodium hydride in DMF must be used for this reaction (Scheme 21).[208–210] The reactivity of the electrophilic reactant decreases in the order aldimine > aldehyde > ketimine > enamine > ketone. Branched compounds are generally less reactive than the unbranched analogs. In accord with the second-order kinetics observed for the reaction of malonodinitrile with benzaldehyde in alcohol, the reaction rate decreases in the order *p*-nitrobenzaldehyde > benzaldehyde > 4-methoxybenzaldehyde.[211] Similar results are obtained with ethyl cyanoacetate in boiling ethanolic triethylamine.[212] As mentioned already, using highly reactive 1,3-dicarbonyl compounds such as Meldrum's acid, the main deleterious side reaction is Michael addition. However, condensation of Meldrum's acid with aliphatic aldehydes having less than two hydrogens at the α-position with piperidine or pyridine and a small amount of acetic acid gives excellent yields of condensation products. Similarly, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups and a variety of heteroaromatic aldehydes (furan, pyrrole, indole, pyridine) readily react with Meldrum's acid. Even ferrocenylcarbaldehyde (**160**) gives 91% yield of the desired product. In contrast, α-unbranched aldehydes do not afford the Knoevenagel products (see Section 1.11.2.6).[48]



(159)

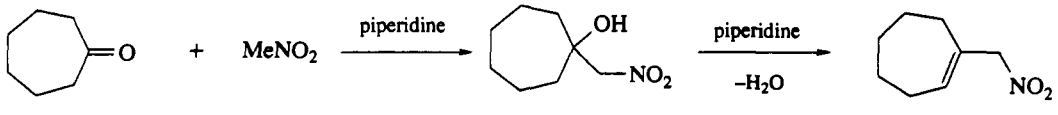
i, NaH; ii, CS_2; iii, $Br(CH_2)_3Br$

Scheme 21



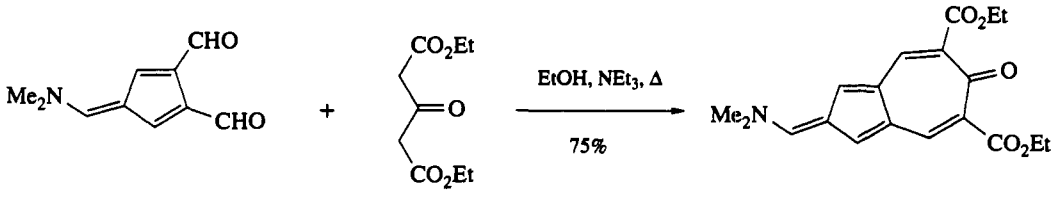
(160)

α,β-Unsaturated aldehydes react with 1,3-dicarbonyl compounds in the presence of piperidine or triethylamine to give the Knoevenagel adducts in only modest yield (42–74%).[213–215] Crotonaldehyde reacts with malonic acid in acetic acid to give the expected alkylidenemalonic acid, but if the reaction is carried out in pyridine hexadienoic acid is formed in 30% yield.[95] Alkynic aldehydes such as trimethylsilyl-2-propynal can also be used.[214] Aromatic aldehydes with electron-donating or electron-withdrawing groups give good yields in most Knoevenagel condensations. Many reactions of this type are known and the procedure is widely used for the construction of heterocyclic systems (see Section 1.11.5.1). The reactions of aldehydes with nitroalkanes to give nitro alcohols are usually rapid, but elimination of water to give nitroalkenes takes place only upon acidification of the reaction mixture or azeotropic removal of water in the presence of piperidine. By the latter method 1-nitromethylcycloheptene (**161**) has been prepared in 60% yield from cycloheptanone and nitromethane (Scheme 22).[215,216] With $ZnCl_2$ as catalyst, aromatic and heteroaromatic aldehydes can be transformed directly to β-nitrostyrene derivatives. Thus, benzaldehyde and nitromethane at 160 °C give 56% of β-nitrostyrene.[217] Dialdehydes may also be used



(161)

Scheme 22

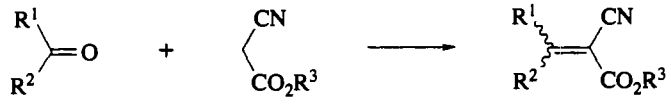


(162) (163) (164)

Scheme 23

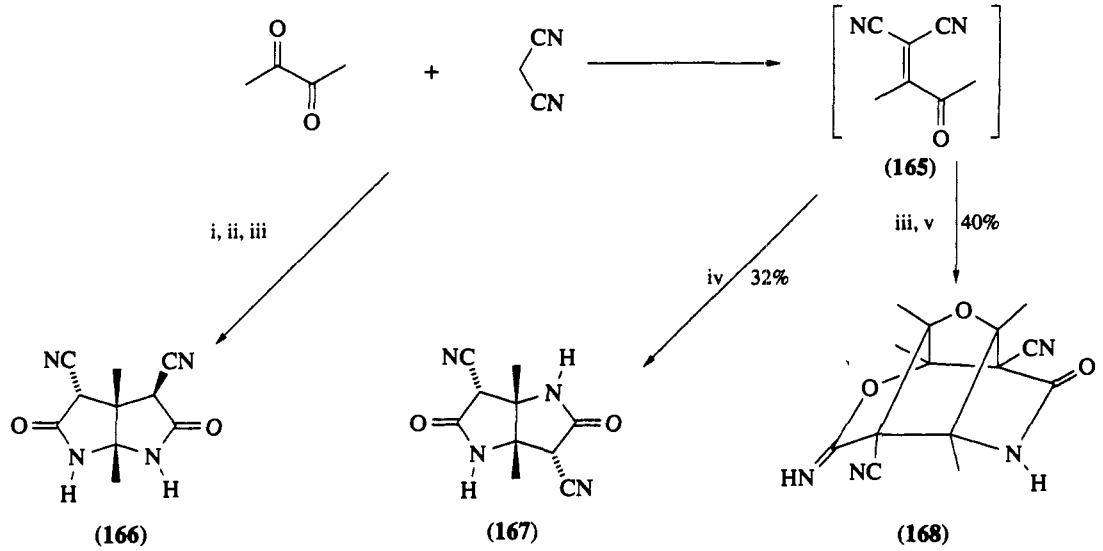
in the Knoevenagel condensation. An interesting example is the reaction of 2,3-diformyl-6-dimethylaminofulvene (**162**) with diethyl 3-ketoglutarate (**163**) to give 2-methylene-6-oxo-2,6-dihydroazulene (**164**; Scheme 23). If the reaction is carried out at room temperature with piperidine as catalyst the bis-Knoevenagel product is produced.[218]

Simple aliphatic ketones react with unhindered 1,3-dicarbonyl compounds and analogous compounds to give good yields of the condensation products in most cases. Thus, with cyanoacetate in the presence of piperidine, piperidinium acetate or zinc chloride in acetic anhydride, alkylidenecyanoacetates are obtained nonstereoselectively (Scheme 24). However, with branched ketones the yields decrease dramatically and camphor does not react at all.[219,220] Condensations of the less reactive malonates with ketones except acetone, cyclohexanone or similar compounds give low yields or do not proceed. Electron-deficient ketones such as hexafluoroacetone give best results with malonodinitrile in the presence of zinc chloride. In this case the reaction stops at the stage of the β-hydroxydinitrile, which can be transformed in a second step employing P_4O_{10} to afford the corresponding alkylidene.[221]



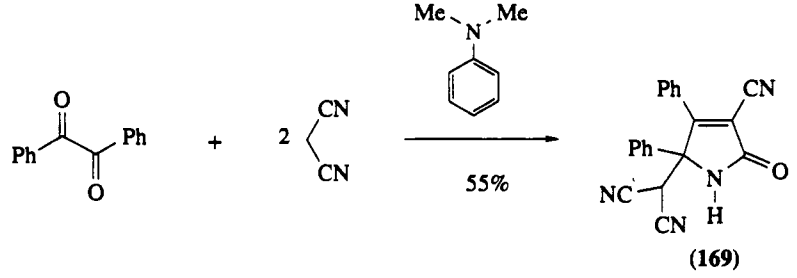
Scheme 24

It is of interest that a methyl group in compounds bonded to a 1,2-dicarbonyl moiety, such as in pyruvaldehyde (2-oxopropanal), displays the same reactivity as the methyl group in acetaldehyde; however,



i, NaOEt/EtOH, 0 °C, 4 h; ii, HCl; iii, $CH_2(CN)_2$; iv, H_2O, $CH_2(CN)_2$; v, MeCOCOMe

Scheme 25

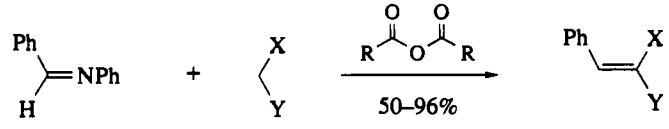


(169)

Scheme 26

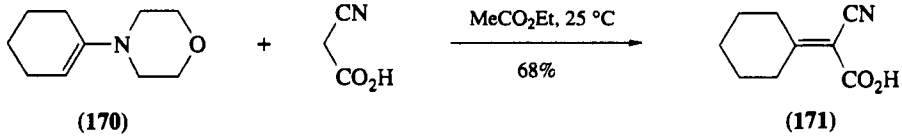
the reactivity of the formyl group is enhanced.[222] Aliphatic and aromatic 1,2-diketones are reactive carbonyl components in the Knoevenagel reaction with malonodinitrile. Depending on the 1,2-diketone, the catalyst used and the ratio of the reagents, one gets either simple Knoevenagel products or substituted γ-lactams. Reaction of 2,3-butanedione with malonodinitrile in the presence of piperidine leads to a complex mixture of 32% of the bislactam (**167**) and 40% of the bridged compound (**168**), whereas with sodium methoxide bislactam (**166**) is obtained. Compounds (**167**) and (**168**) are presumably formed *via* the alkylidenemalonodinitrile (**165**; Scheme 25).[223] With benzil the mono-Knoevenagel product is obtained using *N,N*-dimethylaniline or *N,N*-diethylaniline as catalyst.[224,225] However, by increasing the proportion of the amine, a γ-lactam (**169**) is formed in 55% yield (Scheme 26).[226]

In some cases it is appropriate to use an imine[48,227–229] instead of a carbonyl compound. Thus, benzalaniline reacts with activated methylenes in the presence of carbocyclic acid anhydrides to give the corresponding Knoevenagel products (Scheme 27).[229] Similarly, the enamine (**170**) reacts with cyanoacetic acid in ethyl acetate[230] or dimethylformamide[231] to afford the cyclohexylidene compound (**171**; Scheme 28). Acetals may be employed instead of the free ketones. An example is the reaction of fluorenone cyclic acetal (**172**) with malonodinitrile, which occurs in butanol without added catalyst to af-



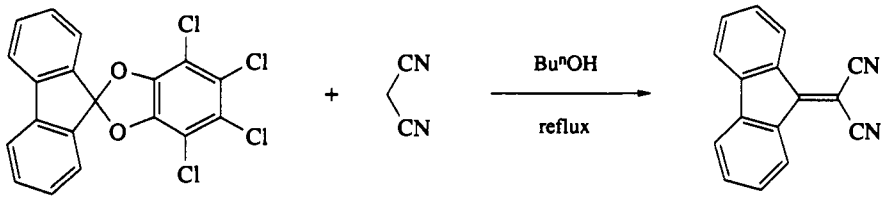
X, Y = CO_2H, CO_2Et, CN, COMe, NO_2, SO_2Ph

Scheme 27



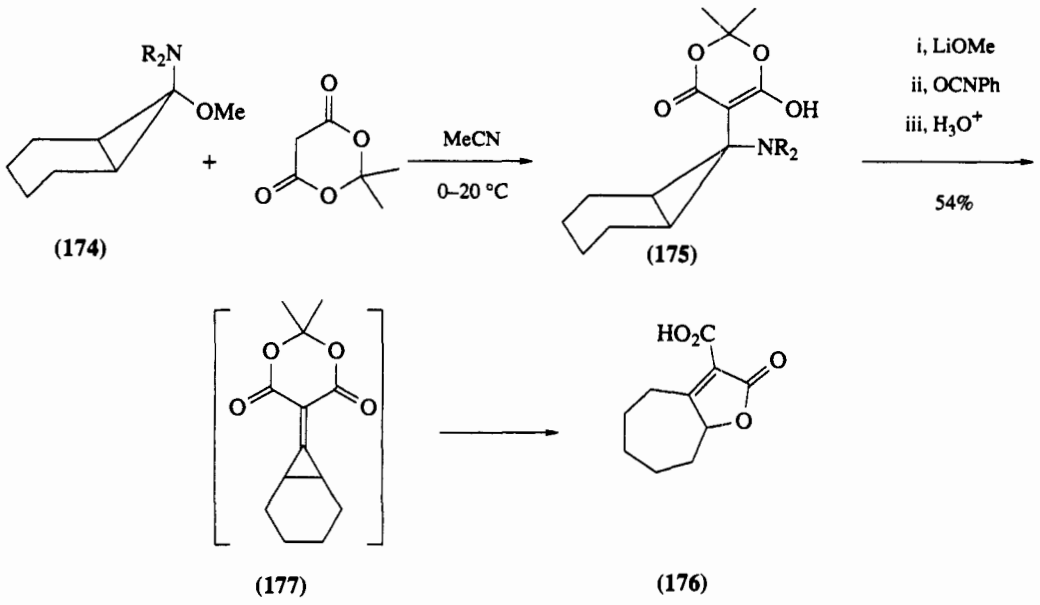
(**170**) (**171**)

Scheme 28



(**172**) (**173**)

Scheme 29

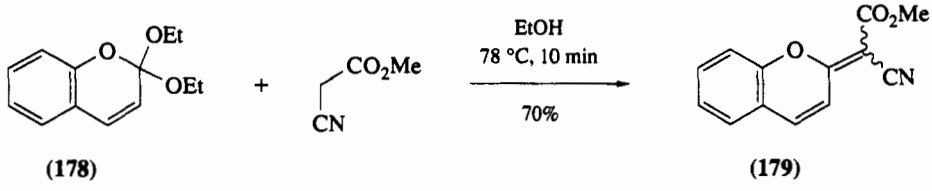


(174) (175) (177) (176)

Scheme 30

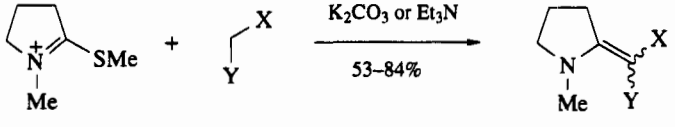
ford (**173**; Scheme 29).[232] α-Amino ethers derived from bicyclo[4.1.0]heptanone and bicyclo[5.1.0]octanone react with Meldrum's acid and dimedone. Reaction of (**174**) with Meldrum's acid gives adduct (**175**), which is dehydrated to give the unsaturated lactone (**176**) *via* the unstable methylenecyclopropane derivative (**177**; Scheme 30).[233]

Orthoesters and carbonic acid derivatives can be employed in lieu of carbonyl compounds.[234–239] For example, 2,2-diethoxy-2*H*-chromene (**178**) and methyl cyanoacetate give the 2*H*-chromene derivative (**179**; Scheme 31).[234] (Methylthio)alkylideniminium salts (**180**) react with active methylene compounds under basic conditions (K_2CO_3 or Et_3N) to give the corresponding condensation products (**181**; Scheme 32).[240] This method is an alternative to the Eschenmoser procedure[241] for synthesizing vinylogous lactams and urethanes. *N*-Alkyl and *N*-acylpyridinium salts can also serve as electrophiles in the Knoevenagel condensation with activated methylenes.[242–244] Suitably activated nitriles (R^1CN) such as trichloroacetonitrile or ethyl cyanoformate react with various 1,3-dicarbonyl compounds to afford (**182**) in the presence of catalytic amounts of metal acetylacetonates [$M(acac)_n$]. In the presence of $TiCl_4$ non-



(178) (179)

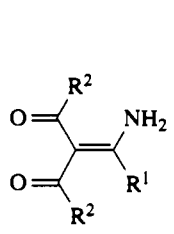
Scheme 31



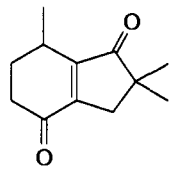
(180) (181)

X, Y = H, NO_2; CO_2Me, CO_2Me; CO_2Et, CO_2Et; COMe, CO_2Bu^t; CO_2Et, CN; CO_2Et, COMe; COMe, COMe

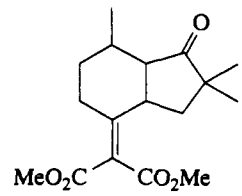
Scheme 32



(182)



(183)



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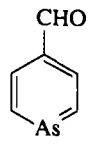

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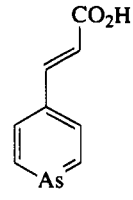
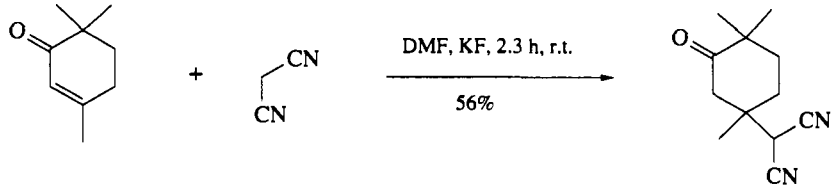


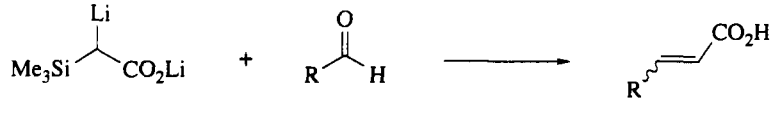
(186)

activated nitriles give the corresponding enamines (**182**) with a few 1,3-dicarbonyl compounds, including dimethyl malonate.[245]

As has been mentioned already, steric effects have a great influence on the rate of Knoevenagel reactions. Thus, a selective condensation of the less sterically congested carbonyl group in (**183**) with dimethyl malonate using $TiCl_4$/pyridine as catalyst affords the alkylidene product (**184**) in 74% yield.[246] If the carbonyl group of an α,β-unsaturated ketone is hindered, preferential formation of the Michael product is observed. On the other hand, compounds with an unhindered α,β-unsaturated carbonyl tend to undergo an initial Knoevenagel reaction that may or may not be followed by further reaction (Scheme 33).[86,247] Interesting chemoselectivity is observed in the Knoevenagel reaction of arsabenzaldehyde (**185**), which yields exclusively the (*E*)-arsacinnamic acid (**186**) upon reaction with malonic acid in pyridine. In contrast, with PhMgBr addition at the C=As bond occurs.[248] Finally, an alternative route to α,β-unsaturated acids[249] and cyanides[250] is the reaction with trimethylsilylacetic acid or trimethylsilylacetonitrile[250] and derivatives.[251] Addition of the dianion (**187**) to aldehydes gives trimethylsilylalkoxides, which undergo Peterson elimination to give the α,β-unsaturated acids (**188**).[249]



Scheme 33



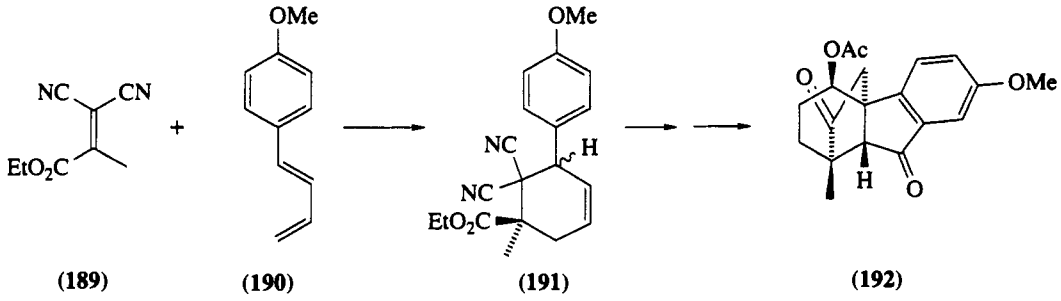
(187) (188)

1.11.4 SEQUENTIAL REACTIONS

Knoevenagel products are highly reactive compounds because of their low energy LUMO. They can act as dienophiles in the normal Diels–Alder reaction,[48,252] as heterodienes in the hetero Diels–Alder reaction with inverse electron demand,[253] as dipolarophiles in 1,3-dipolar cycloadditions,[48,254] as enophiles in the ene reaction[255a] and as acceptors for the addition of allylsilanes.[255b] Sigmatropic rearrangements and photochemical reactions have been described.

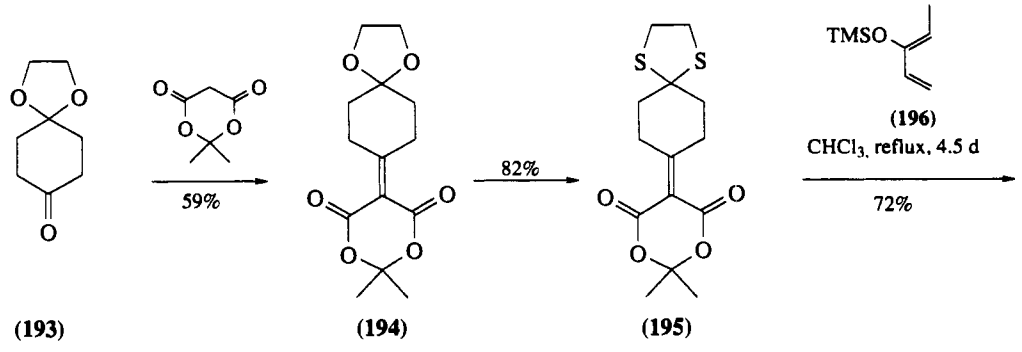
The Knoevenagel product (**189**), obtained from the reaction of ethyl pyruvate and malonodinitrile in the presence of β-alanine, undergoes a normal Diels–Alder reaction with 1-(*p*-methoxyphenyl)butadiene (**190**) to give cycloadduct (**191**), which has been transformed into (**192**), a promising precursor for the synthesis of C_{19}-gibberellins (plant-growth hormones; Scheme 34).[256,257] In a similar way, (**195**), obtained in 48% overall yield from Meldrum's acid and the ketone (**193**) *via* (**194**), reacts with diene (**196**) to give regioisomers (**197**) and (**198**) as a 3:2 mixture (Scheme 35).[258] δ-Damascone (**201**) has been synthesized by a Knoevenagel condensation of Meldrum's acid and acetone to give (**199**), followed by a Diels–Alder reaction with 1,3-pentanediene. Treatment of adduct (**200**) with allyllithium and isomerization of the double bond with NH_4Cl affords δ-damascone (**201**) in 18% overall yield (Scheme 36).[259] An intramolecular cycloaddition was accomplished by condensation of the aldehyde (**202**) with different 1,3-dicarbonyl compounds. Thus, reaction of (**202**) with dimethyl malonate affords the corresponding Knoevenagel product, which cyclizes upon heating at 150 °C to the *trans*-hydrindene (**203**).[260]

The Knoevenagel products of sufficiently reactive acyclic as well as cyclic 1,3-dicarbonyls can act as oxadienes in hetero Diels–Alder reactions with enol ethers and enamines. Alkenes may be used as dienophiles if the reaction is performed in an intramolecular mode.[253] The cycloadditions of ethyl vinyl ether

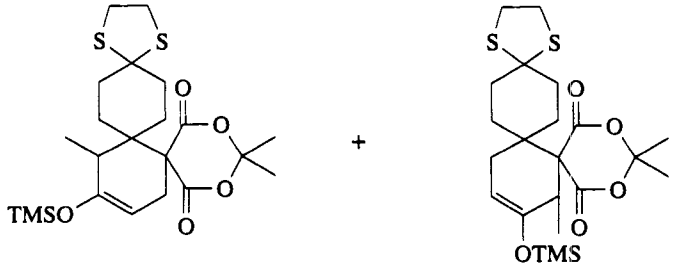


(**189**) (**190**) (**191**) (**192**)

Scheme 34

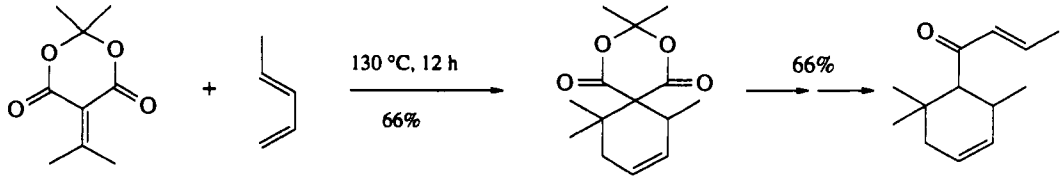


(**193**) (**194**) (**195**)



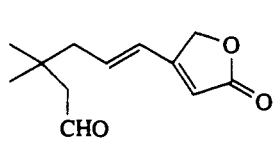
(**197**) 60% (**198**) 40%

Scheme 35

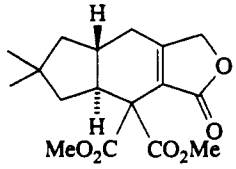


(199) (200) (201)

Scheme 36

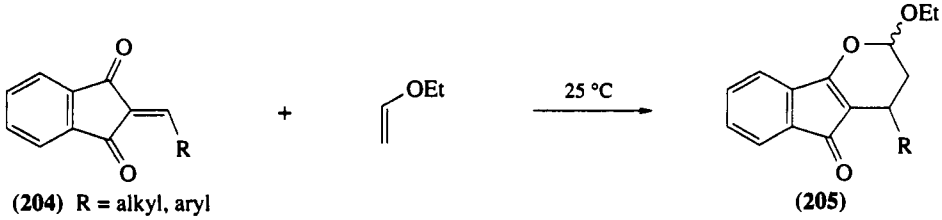


(202)



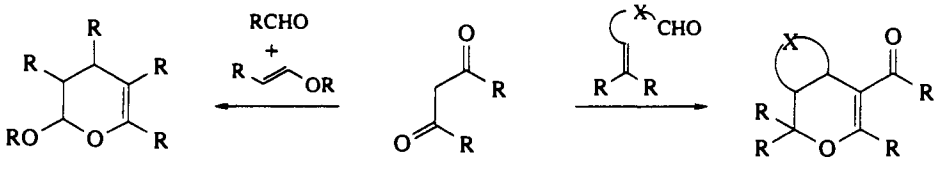
(203)

and the alkylidene or benzylidene compounds (**204**) give adducts (**205**) as mixtures of diastereomers in good yields (Scheme 37).[261] The Knoevenagel products of Meldrum's acid are even more reactive. The tandem-Knoevenagel–hetero-Diels–Alder reaction, first introduced in 1980, is especially useful.[262] Here, the initial alkylidene or benzylidene compound is not isolated but is directly transformed into the cycloadducts. The reaction can be carried out as a two- or three-component transformation (Scheme 38).[253] An example of a three-component reaction is the condensation of malondialdehyde, a monoprotected malondialdehyde and an enol ether to give a dihydropyran ring system with the skeleton and relative configuration of secologanin.[154,155] In the two-component transformation using aldehydes that contain a dienophile moiety a high induced and noninduced diastereoselectivity is observed in the final intramolecular cycloaddition step. Thus, the sequential reaction of citronellal (**206**) leads nearly exclusively to the cycloadduct (**207**) as one of four possible stereoisomers (Scheme 39).[57,263] The *cis* annulated compounds are obtained exclusively by using appropriate aromatic aldehydes[264] and asymmetric induction with *de* >99% is found by employing enantiomerically pure 1,3-dicarbonyls such as oxazepanediones derived from ephedrine.[34] In addition to the six-membered ring systems, cyclopentane and cycloheptane derivatives as well as novel heterocycles have been synthesized by the tandem-Knoevenagel–hetero-Diels–Alder reaction.[264,265]

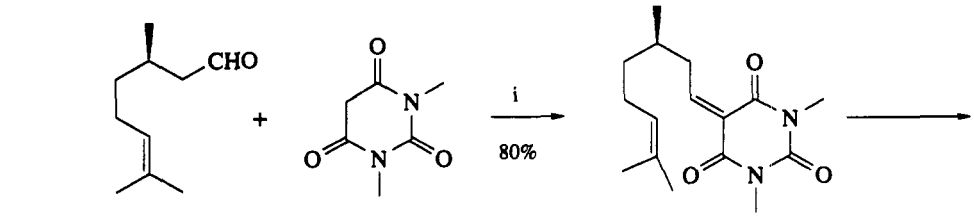


(**204**) R = alkyl, aryl (**205**)

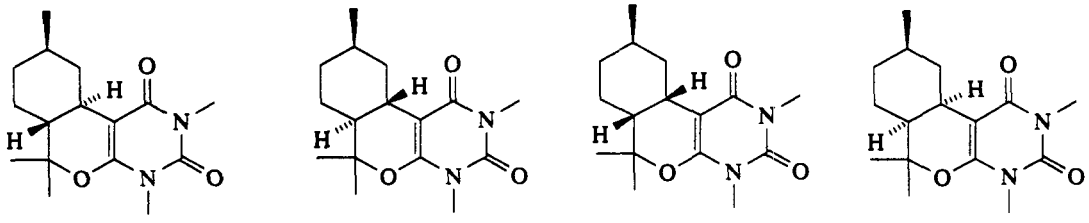
Scheme 37



Scheme 38



(206)

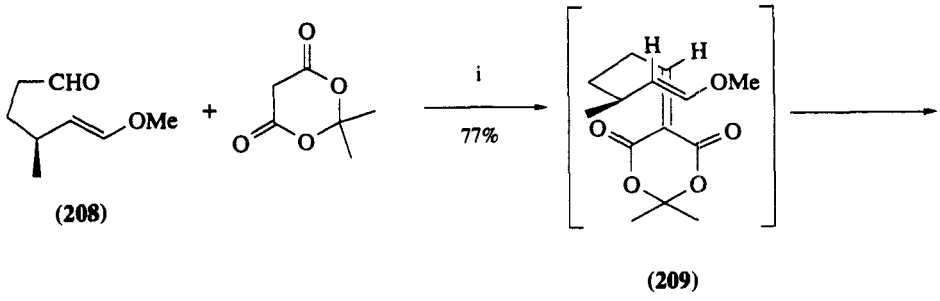


(207) 95.2% 3.6% 0.7% 0.5%

i, ethylenediammonium diacetate, acetonitrile, 3 h, 20 °C

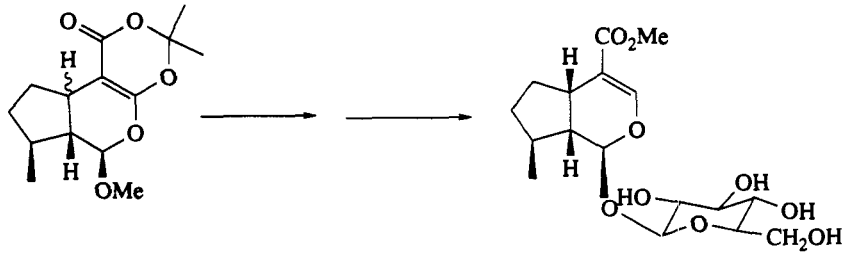
Scheme 39

Several natural products such as cannabinoids,[253] iridoids,[266] indole alkaloids,[267–269] furofuran lignans[270] and other compounds[271] have been synthesized using this methodology. Deoxyloganin (**210**) was obtained by condensation of the enantiomerically pure aldehyde (**208**) with Meldrum's acid in the presence of ethylenediammonium diacetate to give the Knoevenagel product (**209**), which cyclizes immediately, yielding the cycloadducts (**211**) and (**212**) in a 10:1 ratio (Scheme 40).[266] (–)-Ajmalicine



(208)

(209)



(211) β-H
(212) α-H

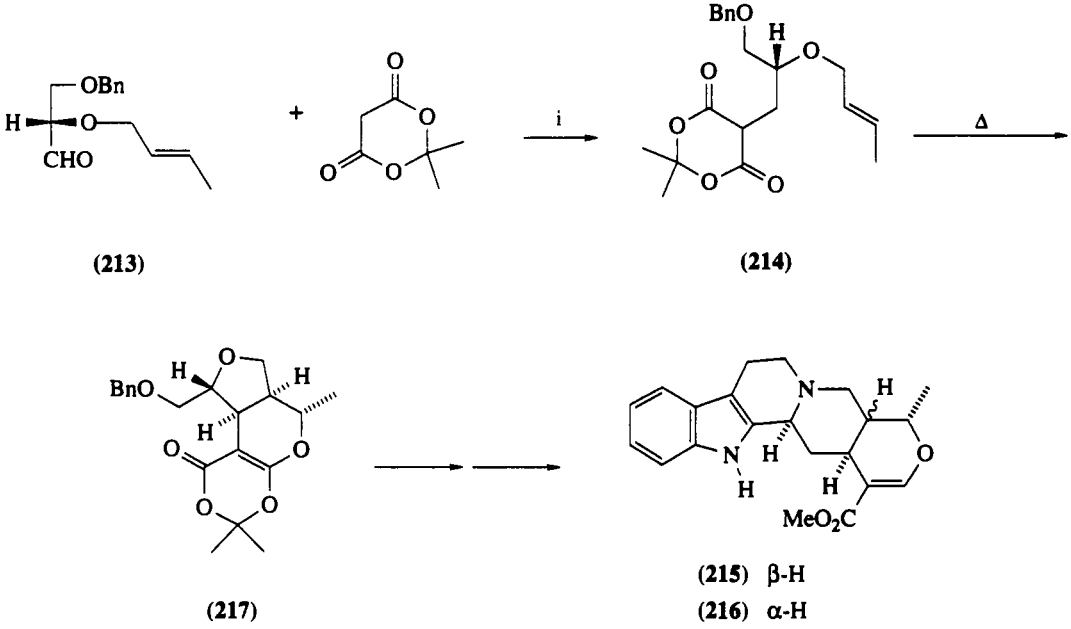
(210)

i, ethylenediammonium diacetate, toluene, Na_2SO_4, 20 °C, 2 h

Scheme 40

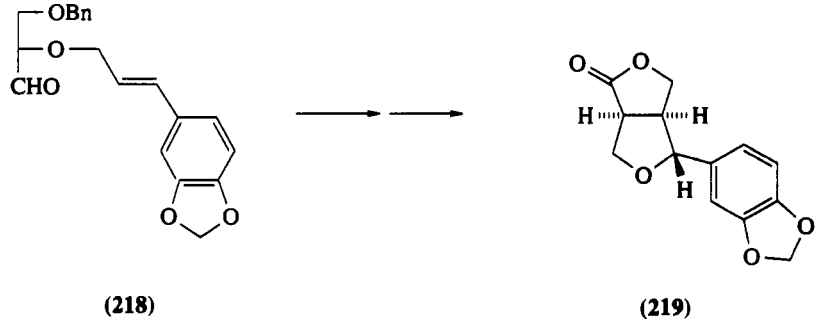
(**215**) and (–)-tetrahydroalstonine (**216**), which possess *trans*- and *cis*-fused D/E ring systems, respectively, have been synthesized from the single cycloadduct (**217**), which is obtained by a Knoevenagel condensation of the enantiomerically pure aldehyde (**213**) with Meldrum's acid followed by a hetero-Diels–Alder reaction of the intermediate (**214**; Scheme 41).[267,268] By a similar sequence the furofuran lignans (–)-sesamolin, (–)-sesamine and (–)-acuminatolide (**219**) have been prepared from aldehyde (**218**) and Meldrum's acid (Scheme 42).[270] A novel synthetic entry to indole alkaloids along a biosynthetic pathway has been developed using strictosidine derivatives (**221**). These compounds were constructed by a three-component tandem-Knoevenagel–hetero-Diels–Alder reaction of aldehyde (**220**), dimethylbarbituric acid and an enol ether (Scheme 43).[269]

The alkylidene-1,3-dicarbonyl moiety is also a highly reactive enophile. Thus, the Knoevenagel adduct (**223**) obtained from aldehyde (**222**) and dimethyl malonate in the presence of piperidinium acetate, cyclizes by treatment with Lewis acids such as $FeCl_3$ on Al_2O_3 exclusively to the *trans*-substituted cyclohexane (**224**; *trans:cis* > 99.5:0.5; Scheme 44).[71,103,272] The sesquiterpene veticadinol (**225**) has been synthesized in enantiomerically pure form by this method.[273] Contrary to the expectation, *trans*-substituted cyclopentanes can also be obtained with excellent induced and noninduced diastereoselectivities.[274] Similarly, aldehydes containing an allylsilane moiety[274] can be used for a highly stereoselective formation of *trans*-1,2-disubstituted cyclopentanes and cyclohexanes by a Knoevenagel

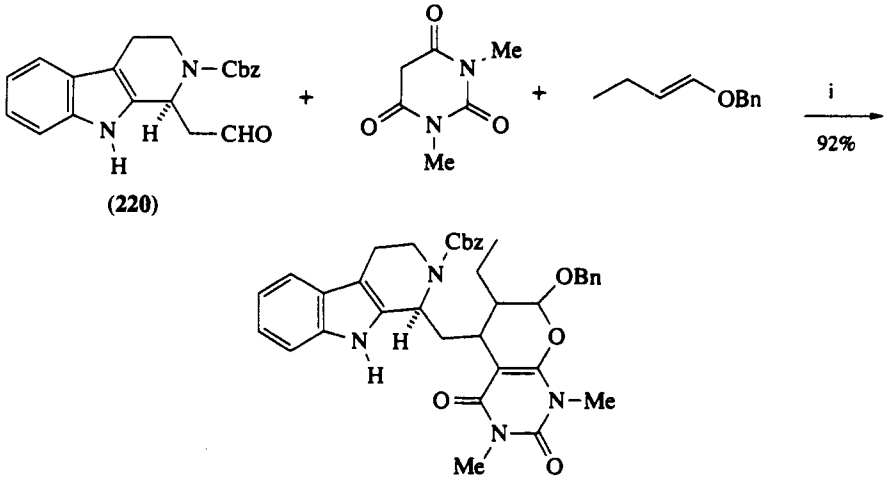


i, ethylenediammonium diacetate, MeOH, 0–20 °C

Scheme 41



Scheme 42



(220)

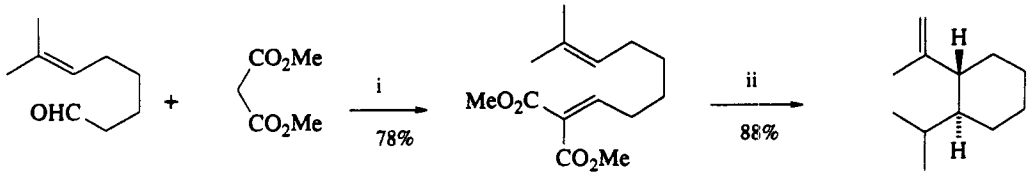
(221)

i, ethylenediammonium diacetate, ultrasound, 50–60 °C, 4 h

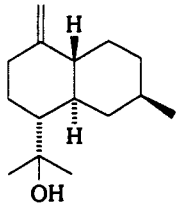
Scheme 43

condensation with 1,3-dicarbonyl compounds, followed by a Lewis acid promoted cyclization.[255b] An interesting transformation is the tandem-Knoevenagel [2,3] sigmatropic rearrangement, which leads to γ-hydroxy-α,β-unsaturated acid derivatives (**230**; Scheme 45).[275,276] Knoevenagel condensation of the sulfoxides (**226**) yields the (*E*)-condensation products (**227**), which can be converted, *via* (**228**) and (**229**), into the allyl alcohols (**230**) by treatment with piperidine. The reaction can also be carried out with enantiomerically pure sulfoxides.[276,277]

Knoevenagel products of aliphatic aldehydes do not undergo photochemically induced [2 + 2] cycloaddition with alkenes, but are isomerized instead to the β,γ-unsaturated isomers. On the other hand, benzylidene-Meldrum's acids give two isomeric cycloadducts upon irradiation in the presence of cyclohexene.[48] Unsymmetrical Knoevenagel products such as the benzylidenepyrazolones undergo *cis/trans* isomerization on irradiation. The photostationary state of (**231**) is (*E*):(*Z*) = 2:1, whereas the thermo-



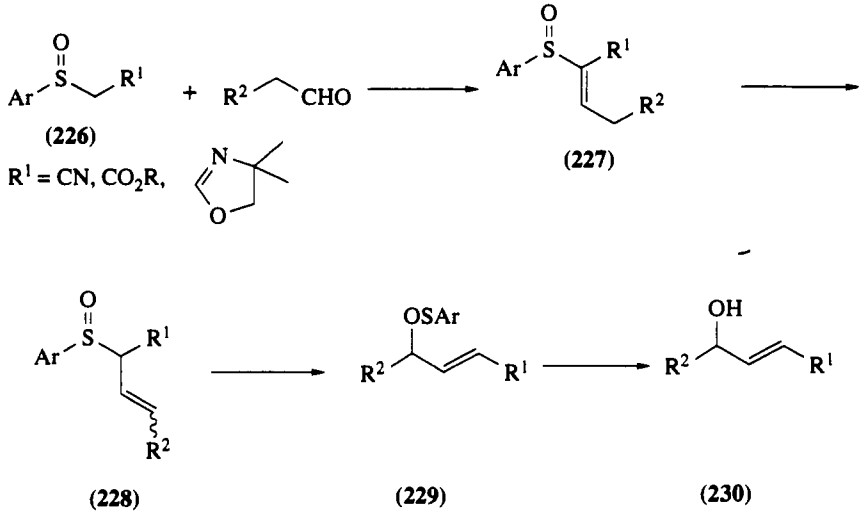
(222) (223) (224)



(225)

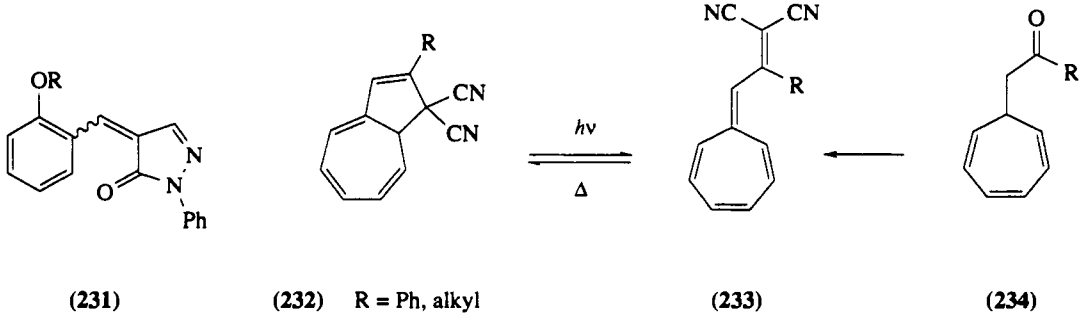
i, piperidinium acetate, CH_2Cl_2, 20 °C, 1 h; ii, $ZnBr_2$, CH_2Cl_2, 20 °C, 30 min

Scheme 44



Scheme 45

dynamic equilibrium is (*E*):(*Z*) = 10:1.[81] An interesting new aspect in the photochemistry of Knoevenagel products is the interconversion of pairs of compounds with photochromic behavior. Irradiation of the dihydroazulene (**232**) with visible light affords the vinylheptafulvene (**233**), which can be thermically reconverted to (**232**). Compound (**233**) is synthesized by a Knoevenagel condensation of malonodinitrile and the ketone (**234**) in the presence of ammonium acetate/acetic acid followed by oxidation with DDQ or hydride abstraction with triphenylmethyl tetrafluoroborate (Scheme 46).[278]



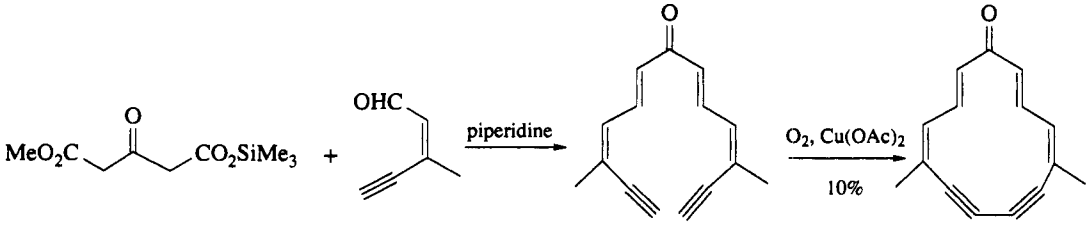
Scheme 46

1.11.5 SYNTHETIC APPLICATIONS

The Knoevenagel reaction is a synthetic method with a broad scope. The educts are simple and cheap, reaction conditions are mild, and a wide variety of solvents can be used. In addition, the Knoevenagel products are reactive compounds and may be employed in sequential transformations (see also Section 1.1.1.4). This is why the Knoevenagel reaction is widely employed, especially in the formation of heterocycles. The most used active methylene in these reactions is malonodinitrile. In many syntheses of natural products, drugs, dyes and other compounds, the condensation of a carbonyl group with an activated methylene compound is found. It is beyond the scope of this review to discuss all examples described in the literature, so only a few recent examples are given in this section.

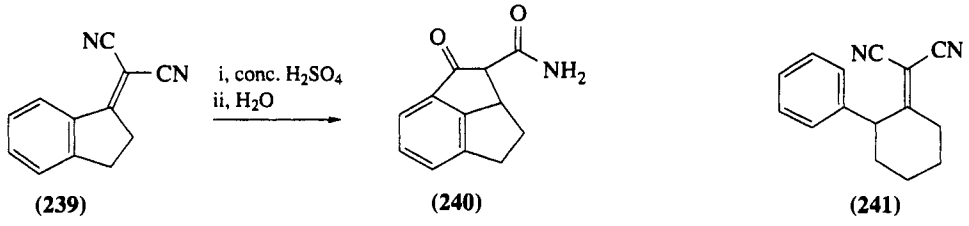
1.11.5.1 Carbocycles and Heterocycles

An interesting approach to the substituted 6,8-bisdehydro[13]annulenone (**238**) includes a double Knoevenagel reaction of the mixed acetonedicarboxylic ester (**235**) with aldehyde (**236**) in the presence of piperidine to give (**237**). Oxidative coupling of the acetylene moieties in (**237**) with $Cu(OAc)_2$ in pyridine affords (**238**) in 10% yield (Scheme 47).[279] α,β-Unsaturated malonodinitriles are suitable intermediates for the synthesis of a variety of carbocyclic systems. Cyclization of the benzylidene malonodinitrile (**239**) to form a five-membered carbocyclic ring (**240**) can be achieved upon treatment with acid and subsequent hydrolysis (Scheme 48).[158] A similar cyclization of (**241**) affords six-membered carbocyclic ring systems.[158,169]



(**235**) (**236**) (**237**) (**238**)

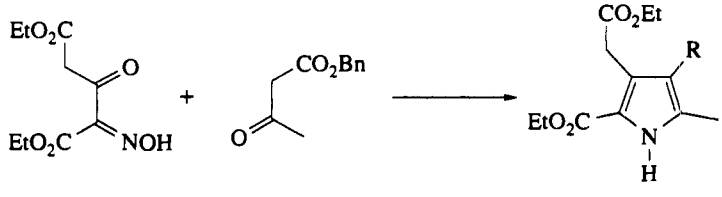
Scheme 47



(**239**) (**240**) (**241**)

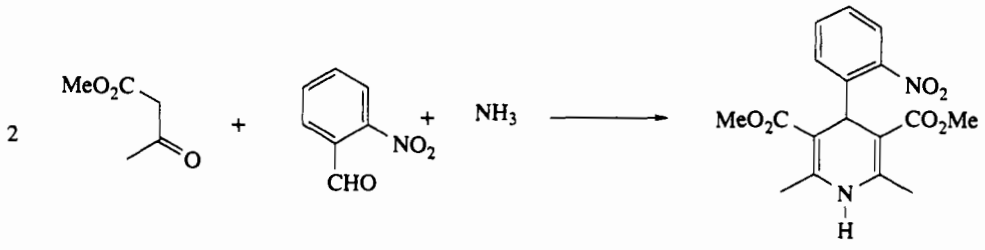
Scheme 48

Knoevenagel reactions are used in the synthesis of a wide variety of O- and N-heterocycles. In the typical Knorr pyrrole synthesis, a 1,3-dicarbonyl compound is condensed with an oximino- or azimino-1,3-dicarbonyl compound followed by reductive cyclization. Thus, catalytic hydrogenation of benzyl acetoacetate (**243**) and diethyl oximinoacetonedicarboxylate (**242**) affords pyrrole (**244**), which is transformed to (**245**) by another Knoevenagel reaction (Scheme 49). A rational synthesis of all four uroporphyrines has been achieved by cyclization of appropriate pyrroles such as (**245**).[280] Another typical preparation of a heterocycle that involves a Knoevenagel condensation is the Hantzsch 1,4-dihydropyridine synthesis. Here, an aldehyde and two molecules of a 1,3-dicarbonyl compound react in the



(**242**) (**243**) (**244**) R = CO_2H
(**245**) R = $CH_2CH_2CO_2Et$

Scheme 49

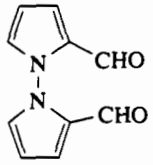


(246)

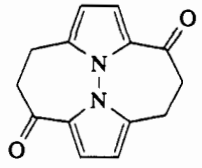
Scheme 50

presence of ammonia or an amine. Newer methods use the condensation of an aldehyde, a 1,3-dicarbonyl compound and an enamine of a second 1,3-dicarbonyl compound. The reaction is used in the preparation of the important calcium antagonist nifedepin (**246**; Scheme 50).[281,282]

Compound (**248**), a relative of [14] annulene containing a hydrazine bridge, has been synthesized by a Knoevenagel condensation of the [1,1′-bipyrrole]-2,2′-dicarbaldehyde (**247**) and *t*-butyl cyanoacetate, followed by reduction of the *exo* double bond with diisobutylhaluminum hydride, acid-catalyzed cyclization, and decarboxylation.[283]

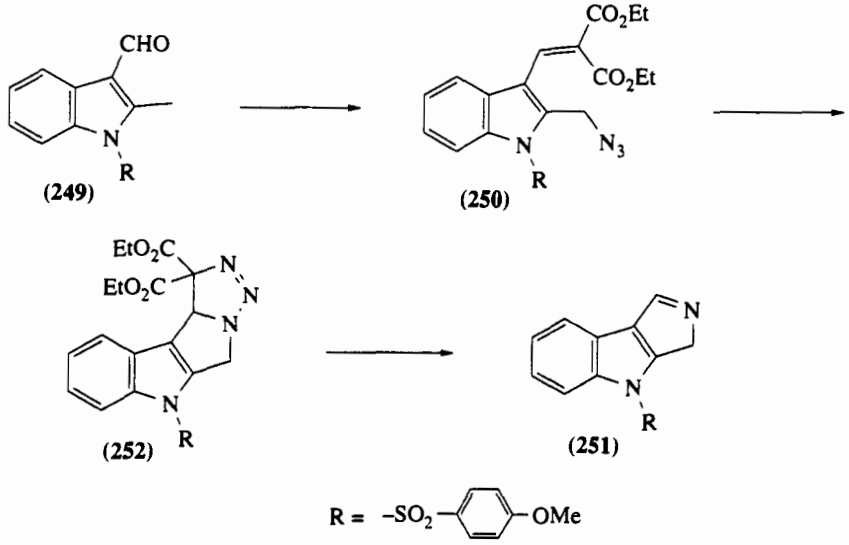


(247)

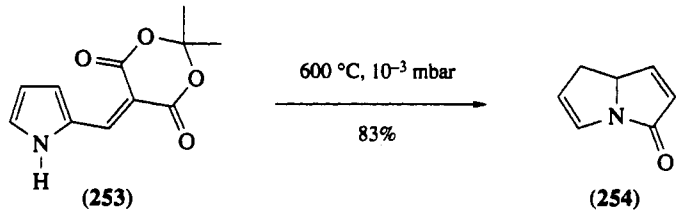


(248)

As part of a project to synthesize stable analogs of the indole-2,3-quinodimethane system, the 2,4-dihydropyrrolo[3,4]indole (**251**) has been prepared from formylindole (**249**). Knoevenagel condensation with ethyl malonate followed by bromination and nucleophilic substitution of the bromide with azide yields (**250**), which immediately undergoes intramolecular 1,3-dipolar cycloaddition to give the triazoline (**252**). Treatment of (**252**) with toluene-*p*-sulfonic acid affords diethyl diazomalonate and (**251**;



Scheme 51

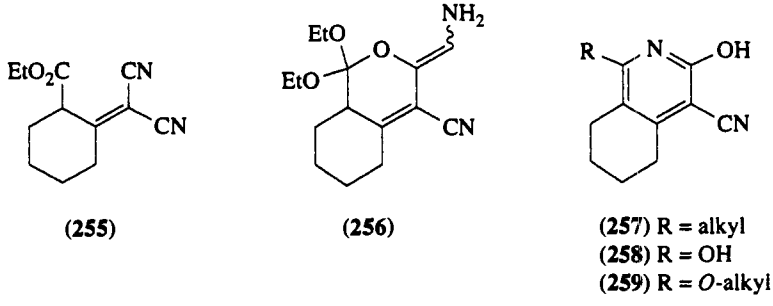


(253) (254) (6)

Scheme 51).[284] The annulated dihydropyrrole (**254**) is formed by gas phase pyrolysis of the Knoevenagel product (**253**; equation 6).[285]

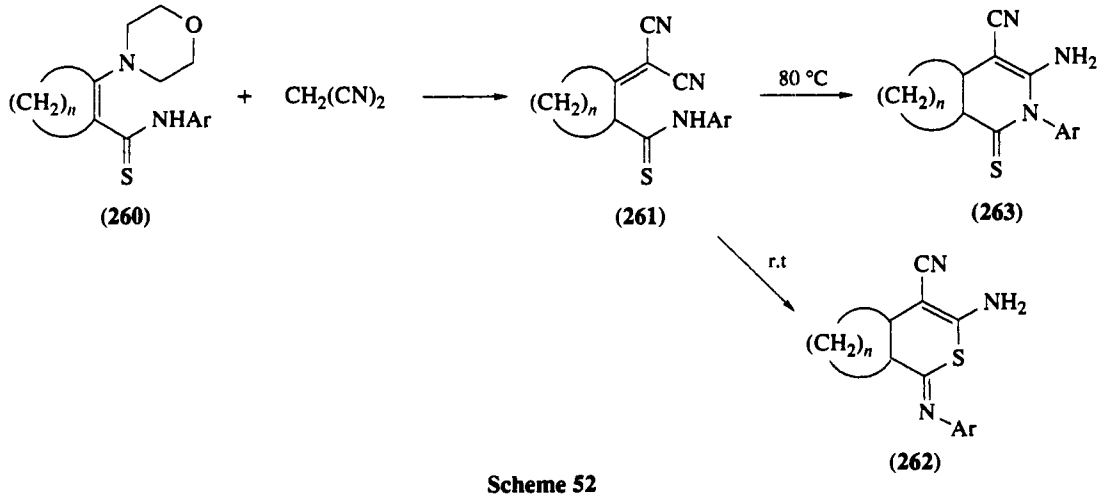
Another interesting transformation starting from 3-methylthiophene-2-carbaldehyde yields 5*H*-thieno [2,3-*c*]pyrrole *via* a Knoevenagel reaction with malonate and a Staudinger reaction.[286]

For the synthesis of pyridine derivatives, the Knoevenagel condensation with malonodinitrile, cyanoacetamide or cyanoacetates followed by an intramolecular addition of an amino function to a C≡N triple bond has found wide application. Hence, the formation of 2-hydroxypyridines like (**257**) is accomplished by Knoevenagel reaction of 1,3-diketones with cyanoacetamide, cyanoacetate and malonodinitrile, and that of 2,6-dihydroxypyridines like (**258**) by reaction with β-keto esters and cyanoacetamide followed by direct cyclization. With malonodinitrile, the reaction with β-keto esters usually stops at the Knoevenagel stage (**255**). However, with a mixture of ammonium acetate and acetic acid as catalyst, the 6-alkoxy-2-hydroxypyridines (**259**) are formed exclusively.[287–291] Pyran (**256**) is an intermediate in the latter process.[287] Enamines of 1,3-dicarbonyl compounds and their thio analogs may also be used in this transformation. Thus, reaction of (**260**) with malonodinitrile gives thiopyran (**262**) at room temperature and thiopyridone (**263**) at 80 °C, presumably *via* the Knoevenagel adduct (**261**; Scheme 52).[292] Knoevenagel condensation of phthalic anhydride with ethyl cyanoacetate in the presence of triethylamine in toluene yields highly reactive benzofulvene (**265**), which can be transformed into the indenopyridine-1,3-dione (**266**) with base or into indenopyridazine-3,9-diones and indenopyran-1,9-diones



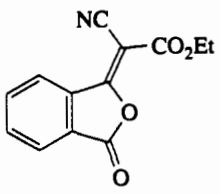
(**255**) (**256**)

(**257**) R = alkyl
(**258**) R = OH
(**259**) R = *O*-alkyl



(**260**) (**261**) (**263**) (**262**)

Scheme 52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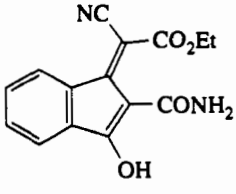
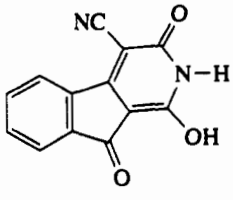
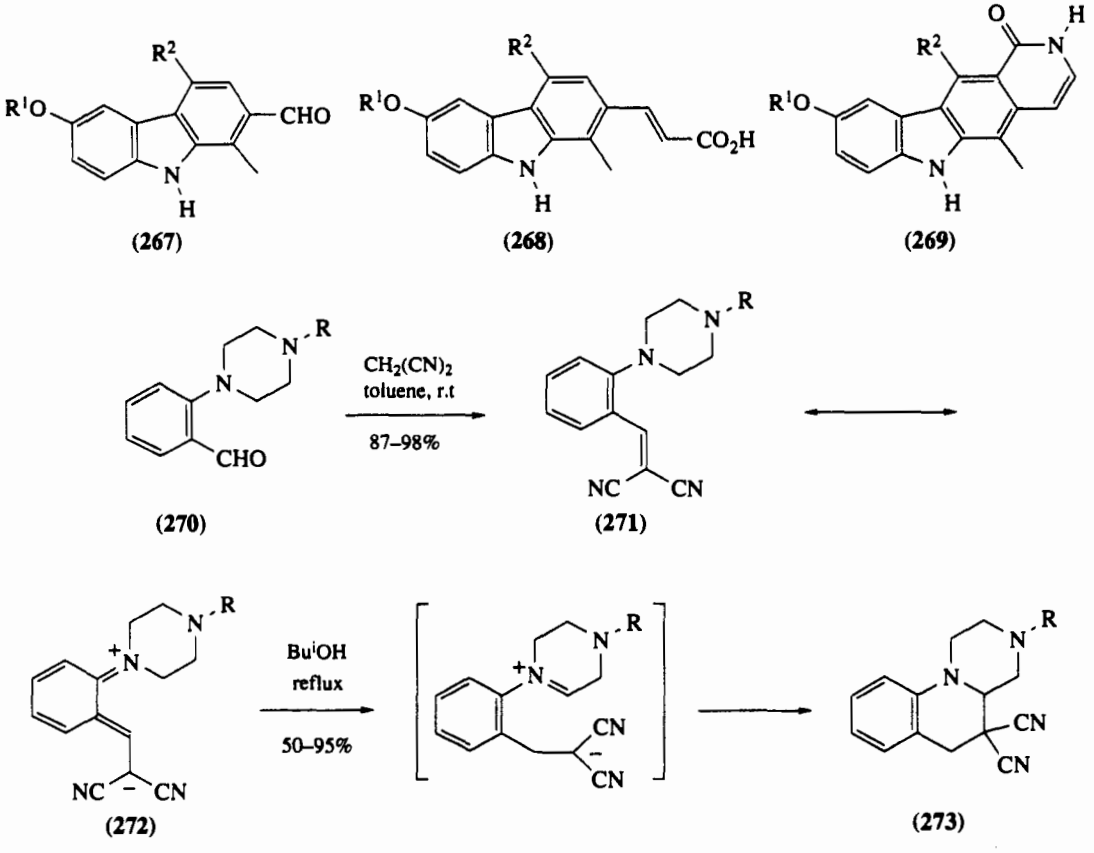

(265)


(266)

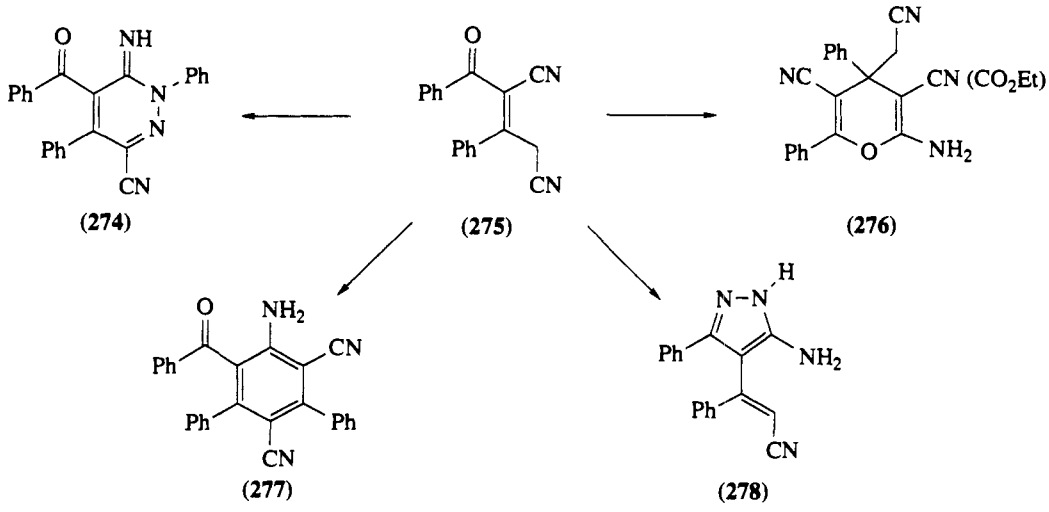
under other conditions. Knoevenagel product (**264**) is not formed if an amine is used as catalyst, whereas with sodium 9% of (**264**) can be isolated.[293]

Pyrido[4,3-*b*]carbazole (**269**), an intermediate for the synthesis of ellipticine analogs, has been prepared by a Knoevenagel condensation of the aldehydes (**267**) with malonic acid to give (**268**). The derived acyl azides are thermolyzed to obtain (**269**).[294] An interesting synthesis of hexahydropyrazino[1,2-*a*]quinolines (**273**) is summarized in Scheme 53.[295] The transformation involves a Knoevenagel reaction of aldehyde (**270**) with malonodinitrile to yield (**271**) ↔ (**272**), which cyclizes in refluxing 1-butanol after a [1,5] H shift to give (**273**). The Knoevenagel self-condensation product of benzoylacetonitrile (**275**) can be transformed into a variety of heterocyclic compounds, such as pyridazine (**274**), pyran (**276**), benzene derivative (**277**), or pyrazole (**278**) by treatment with benzenediazonium chloride, malonodinitrile or acetoacetate, benzoylacetonitrile, or hydrazine, respectively (Scheme 54).[296] Condensation of 1,4-diketones with malonodinitrile using ammonium acetate/acetic acid as catalyst affords the cyclopentadiene derivatives (**279**) *via* the intermediate bis-Knoevenagel products. Acid-catalyzed cyclization of (**279**) yields the pentalenes (**280**), whereas in basic medium the pyridines (**281**) are formed. With succindialdehyde, however, a bicyclo[3.2.1]octene is obtained exclusively.[297]

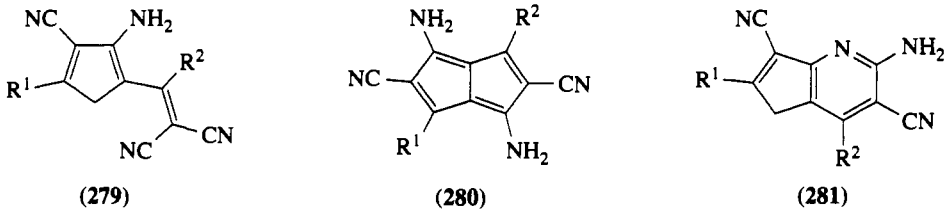
4-Flavones and their thia anologs (**282**) undergo Knoevenagel condensation with malonodinitrile to give the corresponding 4,4-dicyanomethylene derivatives (**283**). These compounds give ready access to



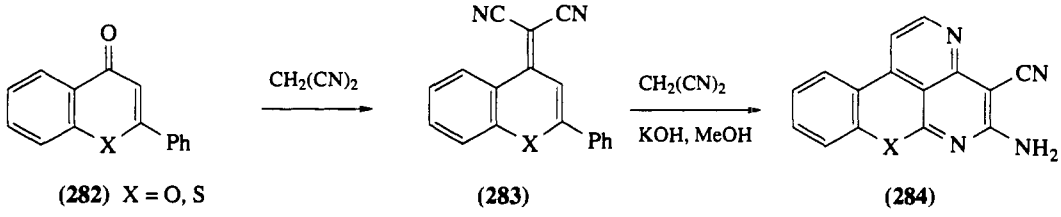
Scheme 53



Scheme 54

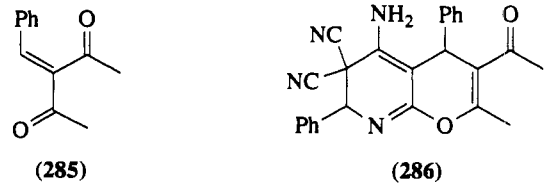


pyranonaphthyridine (**284**; X = O) and its thia analog (**284**; X = S) by condensation with a second equivalent of malonodinitrile (Scheme 55).[298]



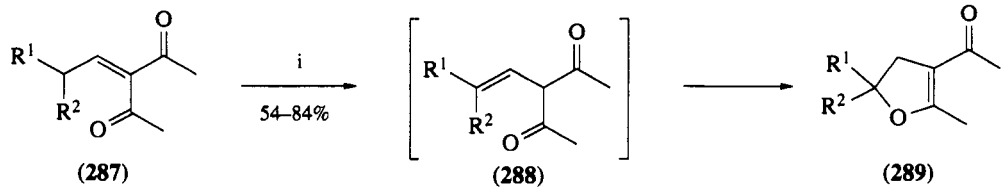
Scheme 55

Pyrano[2,3-*b*]pyridines (**286**) are obtained in a one-pot procedure from the Knoevenagel product (**285**) and malonodinitrile.[299]



O-Heterocycles such as furan and pyran derivatives can easily be constructed from Knoevenagel products either after double bond isomerization or functionalization at the γ- or δ-position. Hence, acid-catalyzed ring closure of (**287**) affords the 4,5-dihydrofurans (**289**), presumably *via* the double bond isomer (**288**; Scheme 56).[102] Knoevenagel condensation of acrolein and malonic acid in the presence of

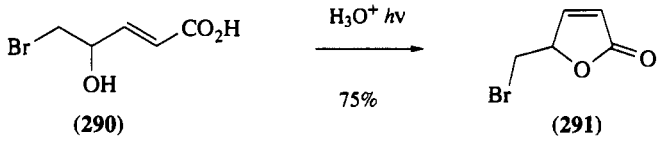
pyridine gives 70% of (*E*)-pentadienoic acid which, after formation of the bromohydrin (**290**), undergoes photochemically mediated isomerization and acid-catalyzed cyclization to give the substituted α,β-butenolide (**291**; equation 7).[300]



(**287**) (**288**) (**289**)

i, conc. H_2SO_4, 20 °C, 12 h; or HCl, DMF, 140 °C, 24 h; or *p*-TsOH, xylene, 140 °C, 12 h

Scheme 56



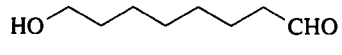
(**290**) (**291**) (7)

Unsaturated δ-lactones are biologically active structural elements in many natural products. The synthesis of this heterocyclic moiety can be achieved by a Knoevenagel condensation of 3-hydroxy aldehydes with active methylene in the presence of $TiCl_4$/pyridine or under standard conditions.[301–303]

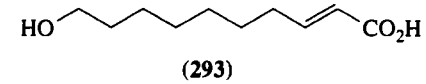
1.11.5.2 Natural Products and Biologically Active Compounds

In nature, the intramolecular condensation of a 1,3-dicarbonyl moiety with a keto group in polyketides is an important step in the biosynthesis of aromatic compounds. Biomimetic transformations of this type have been intensively investigated by Harris.[303] (For a discussion, see Chapter 1.5, this volume.) In the following, the synthesis of some natural products and biologically active compounds using the Knoevenagel reaction will be described.

An efficient and short synthesis of (*E*)-10-hydroxy-2-decenoic acid (**293**), the major component of the royal jelly of the common honey bee (*Apis mellifera*) uses the Knoevenagel condensation of aldehyde (**292**) with malonic acid in the presence of pyridine to give 61% of (**293**).[304] For the synthesis of stable prostacyclin analogs (**297**), the hemiacetal (**294**) is condensed with active methylenes containing one sulfenyl or sulfinyl group to give adducts (**295**) and (**296**), respectively. Thermal elimination of the sulfoxides (**296**), either obtained directly or by oxidation of the sulfides (**295**), affords (**297**; Scheme 57).[305] A simple process that yields carbocyclic analogs of prostacyclines starts with a sequential Knoevenagel–Michael reaction of 2 equiv. of dimethyl acetonedicarboxylate and 1 equiv. of glyoxal with sodium hydroxide in methanol to give the bicyclo[3.3.0]octadiene (**298**).[306,307] This compound can be transformed into (**299**), which is a starting material for the highly active prostacyclin analogs iloprost and cicaprost.[308]



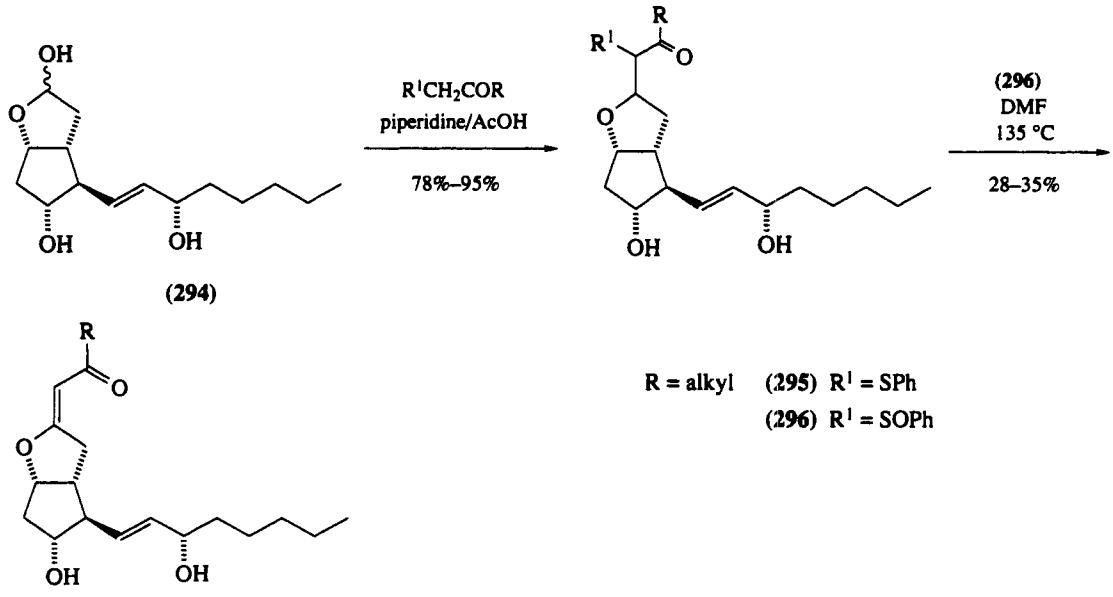
(**292**)



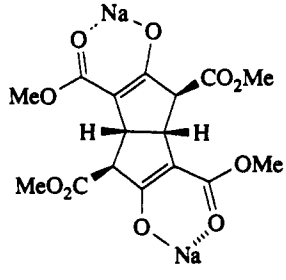
(**293**)

A synthesis of cyclobutane derivative (**301**), which may be a useful substrate in an approach to podophyllotoxin, involves Knoevenagel reaction of an aromatic aldehyde with cyanoacetate to give (**300**) followed by a Michael addition, demethylcarbonylation, intramolecular alkylation and exchange of a cyano group with acetate.[309]

In connection with a synthesis of the hydroazulenic sesquiterpene kessanol (**304**), Knoevenagel condensation of photocitral-A (**302**) with ethyl cyanoacetate was found to give (**303**) as a single isomer. The following sequence includes an intramolecular Prins reaction initiated with $SnCl_4$.[310] In Isobe's synthesis of vernolepin (**307**) the two carbons of the γ-lactone are introduced by a Knoevenagel condensation. Reaction of ketone (**305**) with di-*t*-butyl malonate followed by treatment with DBU affords (**306**), which is transformed to the α,α′-dihydroxy compound (**308**). Hydrolysis of the esters followed by decarboxylation, formation of the γ-lactone, Mannich reaction and elimination yields vernolepin (**307**; Scheme 58).[311]



Scheme 57



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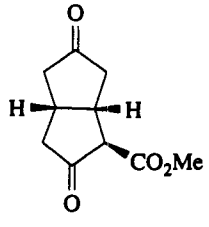

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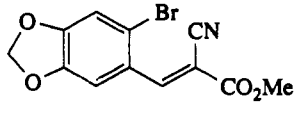

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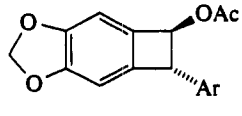

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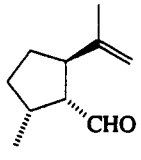
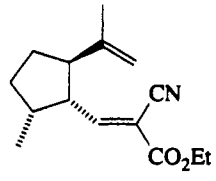


(302)



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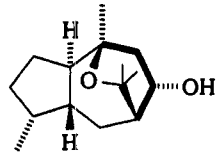
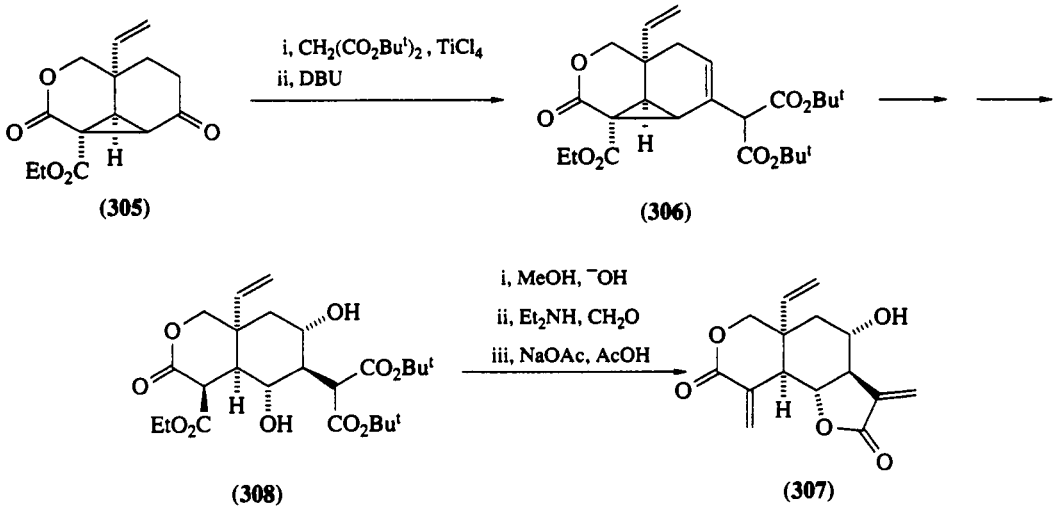


(304)

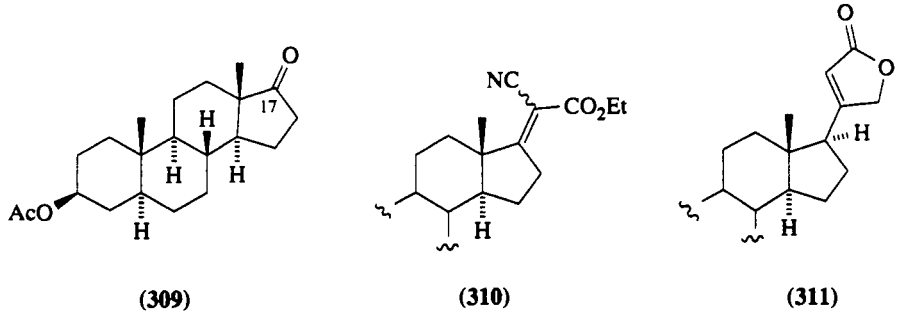
Steroidal ketones have been used extensively in the Knoevenagel reaction.[312–315] Thus, the transformation of 17-oxoandrostane derivatives (**309**), which are readily available by microbiological degradation of sitosterin, are employed for the synthesis of enantiomerically pure cardiotonic steroids such as bufadienolide and cardenolide (**311**). In both syntheses the substitutent at C-17 is introduced by a Knoevenagel reaction of the 17-oxoandrostane derivative (**309**) with ethyl cyanoacetate in the presence of ammonium acetate to give the cyano ester (**310**), presumably as a mixture of the (*E*)- and (*Z*)-isomers, in 89% yield.[315]

The Knoevenagel reaction has also been used in the synthesis of alkaloids. In a preparation of yohimbane derivatives, 2-cyano-4′-methoxycinnamic acid, the Knoevenagel product of *p*-anisaldehyde and

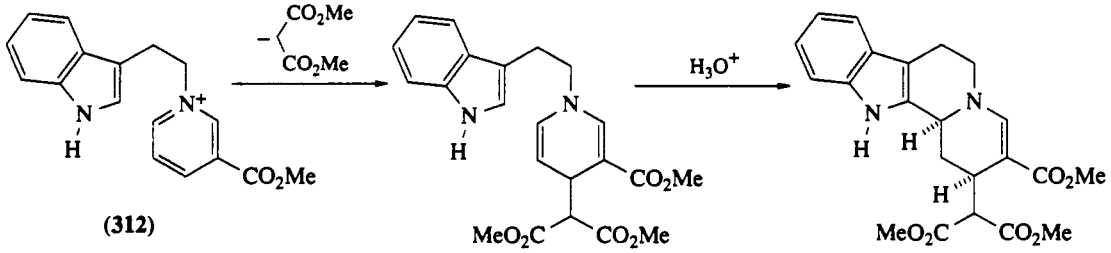


(305) (306) (308) (307)

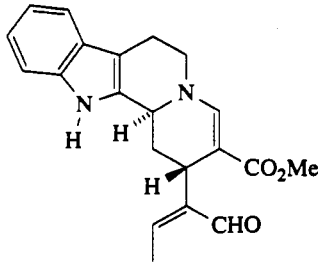
Scheme 58



(309) (310) (311)



(312) (313) (315)

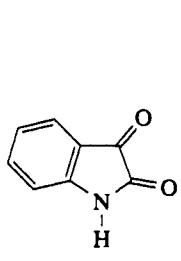


(314)

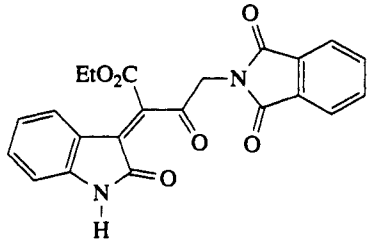
Scheme 59

cyanoacetic acid, was employed as the starting material.[316] A new synthesis of indole alkaloids involves sequential addition of a carbanion such as the sodium salt of dimethyl malonate to a tryptophylpyridinium salt (**312**), followed by hydronium ion catalyzed cyclization of the product (**313**), to give the β-carboline (**315**) in 28% yield (Scheme 59).[317] It has recently been shown in the synthesis of the indole alkaloid vallesiachotamine (**314**) that the yield can be improved by using the lithium salt of ethyl trimethylsilylacetate as the active methylene component.[318]

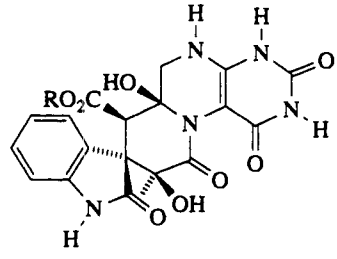
Surugatoxin (**319**), with its unique spirooxindole moiety connected to a tetrahydropteridine ring, is an interesting marine natural product. Inoue *et al.* have synthesized the pentacyclic ring system (**318**) of surugatoxin in 10 steps from the oxindole derivative (**317**), which is obtained in 79% yield by a Knoevenagel condensation of isatin (**316**) and 4-phthalimidoacetoacetate.[319]



(**316**)

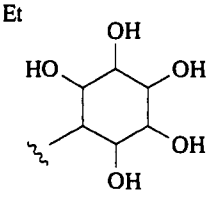


(**317**)

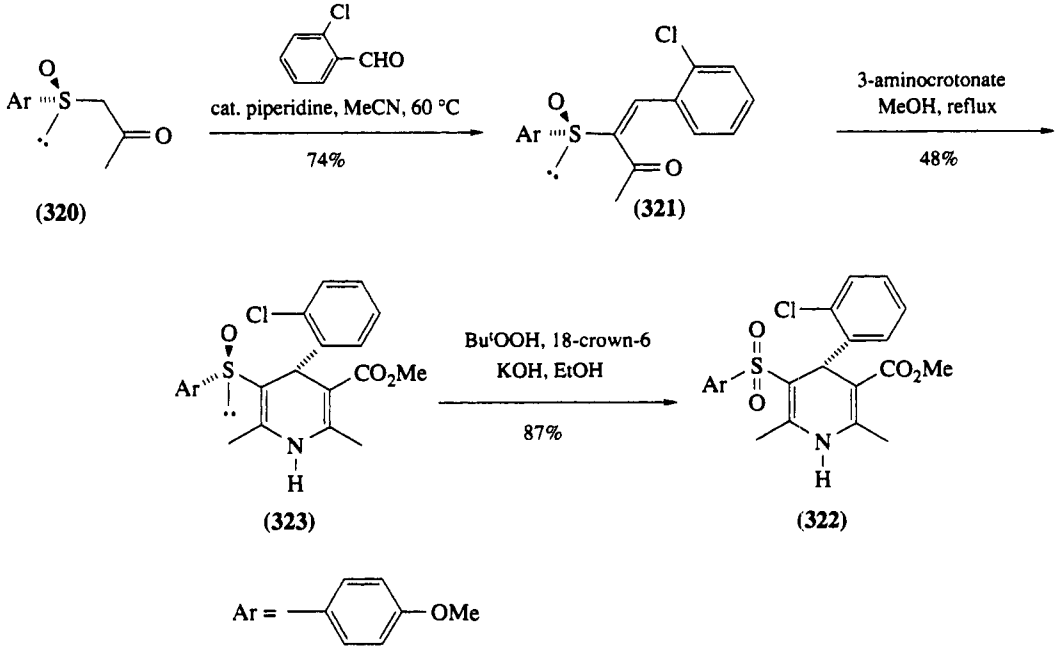


(**318**) R = Et

(**319**) R =

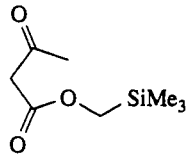


In addition to natural products, a multitude of biologically active unnatural compounds have also been synthesized using the Knoevenagel condensation. A few recent examples are given here. In an attempt to obtain enantiomerically pure 1,4-dihydropyridines as calcium channel antagonists,[281] (*R*)-sulfinylpropanone (**320**) was condensed with 2-chlorobenzaldehyde in acetonitrile with piperidine as catalyst to provide exclusively the (*E*)-benzylidene compound (**321**). Formation of the (*S*)-1,4-dihydropyridine (**323**) as a

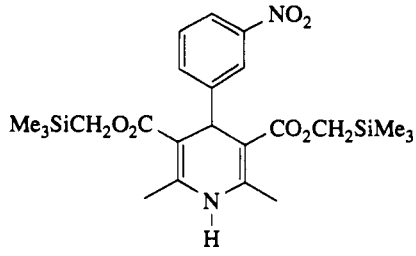


(**320**) (**321**) (**323**) (**322**)

Scheme 60



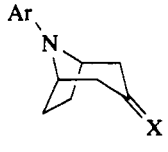
(324)



(325)

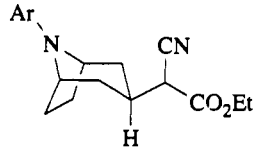
single diastereomer as a result of an asymmetrically induced Michael addition has been achieved by reaction with methyl 3-aminocrotonate according to Hantzsch (Scheme 60).[320] A sila-substituted nifedipine-like 1,4-dihydropyridine (**325**) has been synthesized by condensation of the Knoevenagel product obtained from 3-nitrobenzaldehyde and β-keto ester (**324**) with the β-aminocrotonic ester derived from (**324**).[321]

Compound (**329**), a potent inhibitor of dihydrofolate reductase, was synthesized by a Knoevenagel condensation of the ketone (**326**) with ethyl cyanoacetate to afford (**327**) in 28–81% yield. Catalytic hydrogenation of (**327**) over Pd/C gave almost exclusively the undesired *endo* isomer, whereas with lithium in liquid ammonia and phenol as proton donor the desired *exo* compound (**328**) was obtained in 71% yield.[322] Knoevenagel condensation of benzaldehydes with malonodinitrile in the presence of a base leads to benzylidenemalonodinitriles. These compounds, especially the 2-chlorobenzylidenemalonodinitrile (CS, **330**), are used as riot-control agents (sneeze and tear gas).[323,324]

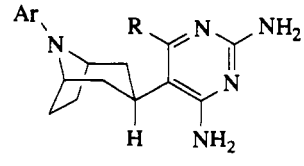


(326) X = O

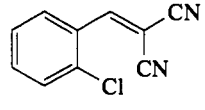
(327) X =



(328)



(329)

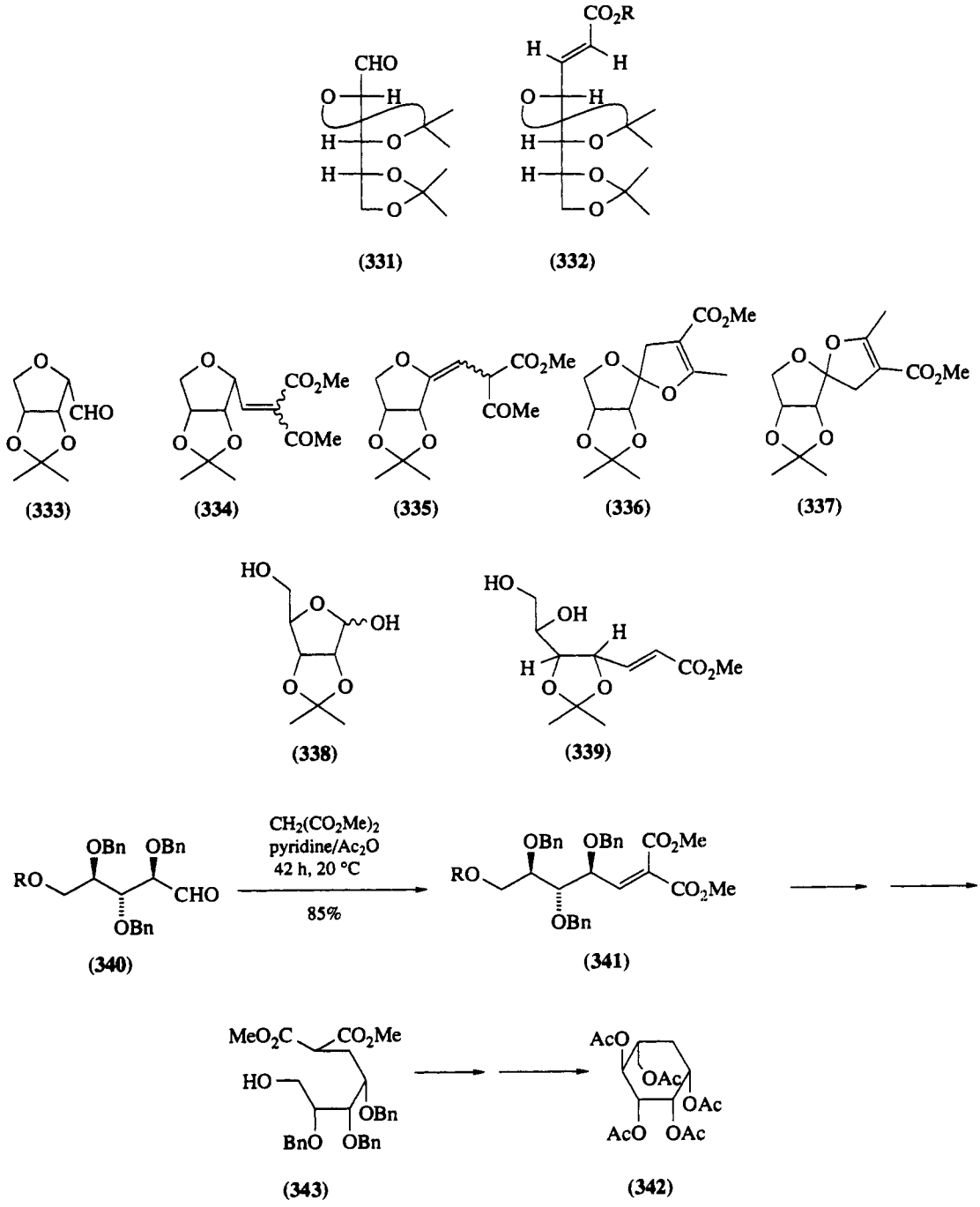


(330)

1.11.5.3 Transformation of Sugars

The Knoevenagel condensation of sugar aldehydes with different 1,3-dicarbonyl compounds is a useful method for chain elongation of carbohydrates. Thus, condensation of isopropylidene-2-arabinose (**331**) with alkyl hydrogen malonates in the presence of pyridine (Knoevenagel–Doebner modification) stereoselectively yields alkyl (*E*)-3-polyhydroxyalkylacrylates (**332**).[325–328] It is noteworthy that the Wittig reaction of (**331**) gives a mixture of (*E*)- and (*Z*)-acrylates. Compound (**332**) can be hydroxylated and reduced to give heptoses. Hexuloses, deoxyhexuloses and branched-chain sugars have been synthesized in a similar manner. For the latter reaction, monoethyl methylmalonate and α-methylacetoacetic acid are used. As an example, the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde gives the corresponding alkylidene compounds with cyanoacetate, benzoylacetate and benzoylacetone using piperidine as catalyst.[328] With the 2,5-anhydroarabinose derivative (**333**) and methyl acetoacetate, the β,γ isomer (**335**; mixture of 1,3-dicarbonyl and enol form) is obtained in addition to the Knoevenagel product (**334**). Treatment of (**335**) with acid results in the formation of a mixture of the spiro derivatives (**336**) and

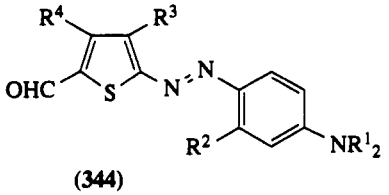
(**337**), leading to the thermodynamically more stable compound (**337**) after prolonged reaction time.[329] In the Knoevenagel reaction of the 2,3-*O*-isopropylidene derivatives of D-ribofuranose (**338**) with monomethyl malonate, using pyridine as catalyst, the epimer with the *threo* arrangement at C-4 and C-5 (**339**) is obtained, due to the stronger reaction conditions. The isomerization takes place either in the starting material or in an intermediate, since the compound with the *erythro* configuration shows no tendency to epimerize.[330] An interesting example of a sugar transformation involving the Knoevenagel reaction is the synthesis of pseudopyranoses with a cyclohexane skeleton (**342**) from D-ribose *via* (**343**). One of the key steps is condensation of (**340**) and dimethyl malonate to give (**341**) using pyridine and acetic anhydride (Scheme 61).[331]



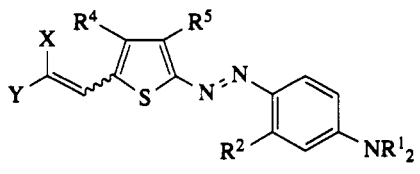
Scheme 61

1.11.5.4 Dyes and Polymers

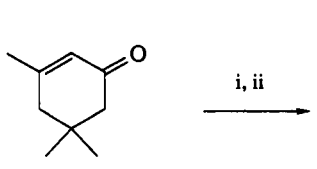
The Knoevenagel condensation has been used in the synthesis of different types of dyes. Thiophene derivatives (**345**), which may be useful for dyeing synthetic fibers or plastic, have been prepared by condensation of the azo aldehydes (**344**) with a variety of methylene compounds.[332] Dyes (**347**) exhibiting positive solvatochromatical and negative thermochromatical properties are prepared by Knoevenagel reaction of isophorone (**346**) and malonodinitrile followed by an aldol condensation with substituted benzaldehydes (Scheme 62). Similar reactions have been performed using *N,N*-diethylthiobarbituric acid as the active methylene compound.[27] In the course of investigations directed at the preparation of synthetic oxygen carriers, tetraphenylporphyrins (**349**) containing a long chain alkylimidazole moiety were synthesized. A step in this approach was the Knoevenagel condensation of the aldehyde (**348**) with malonic acid.[333]



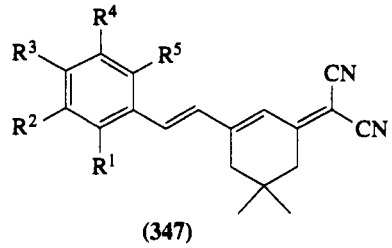
(**344**)



(**345**)

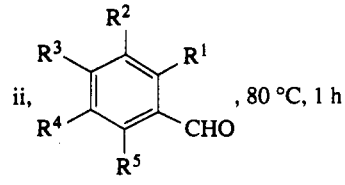


(**346**)

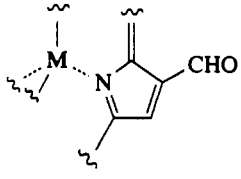


(**347**)

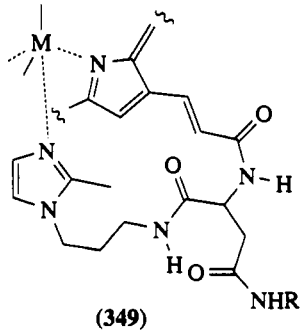
i, $CH_2(CN)_2$, DMF, piperidine, AcOH, Ac_2O, 80 °C, 14 h;



Scheme 62



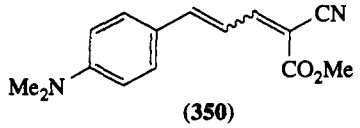
(**348**)

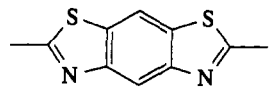


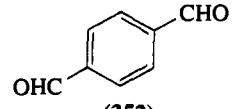
(**349**)

With respect to the formation of polymers, the Knoevenagel condensation is usually employed to prepare the monomers.[334–337] Thus, 4-(*N,N*-dimethylamino)cinnamaldehyde is condensed with methyl cyanoacetate to give the corresponding Knoevenagel product (**350**), which is copolymerized with terephthalate and ethylene glycol to give a brilliant yellow polyester.[337] On the other hand, the Knoevenagel

reaction has been successfully used to perform the polycondensation step itself. Hence, poly(arylenalkenylene)s and poly(heteroarylenalkenylene)s have been synthesized by a Knoevenagel condensation of bifunctional active methylene compounds like (**351**) and bifunctional aldehydes such as (**352**).[338,339]


(**350**)

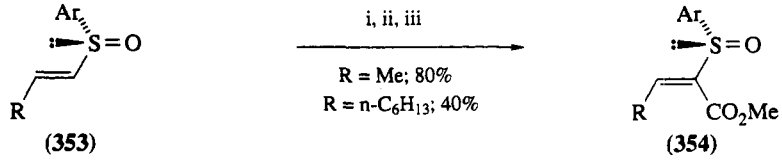

(**351**)


(**352**)

1.11.6 SYNTHETIC ALTERNATIVES

The Knoevenagel condensation is the method of choice for the preparation of α,β-unsaturated dicarbonyl compounds and related compounds and only a few alternative methods have been developed. However, with the traditional Knoevenagel condensation there are problems with the reactivity of ketones, with the competitive Michael addition occuring in the reaction of some active methylene compounds. There is also a problem with stereocontrol in the synthesis of Knoevenagel products from unsymmetrical 1,3-dicarbonyl compounds. An alternative method is the addition of Grignard reagents to vinylogous carbamates (see Section 11.2.6).[96] Another possibility is the reaction of a metal ketimate with malonodinitrile to yield ylidenemalonodinitriles (see Section 11.3.1.7).[158]

A way to synthesize enantiomerically pure α,β-unsaturated-α-sulfinylcarboxylic esters (**354**) is based on reaction of the lithiated enantiomerically pure α,β-unsaturated sulfoxide (**353**) with carbon dioxide, followed by esterification (Scheme 63).[192] Similarly, procedures involving α-vinyl anions are known for the synthesis of α,β-unsaturated α-keto esters and α,β-unsaturated-α-formylcarboxylic acids.[340]



i, Pr^i_2NLi, THF, –78 °C; ii, CO_2, –78 °C; iii, MeI, HMPA

Scheme 63

A general alternative to obtain Knoevenagel products is the dehydrogenation of β-dicarbonyl and related compounds. In practice, however, the yields using classical dehydrogenation protocols like DDQ oxidation or α-halogenation/dehydrohalogenation are usually modest.[341] Sulfinyl compounds with at least one β-hydrogen are known to undergo *syn* elimination on pyrolysis to yield alkenes. By using this method α,β-unsaturated dicarbonyl compounds can be obtained by pyrolysis of 1,3-dicarbonyl-2-phenylsulfinyls.[342–344] Similarly, α-selenodicarbonyl compounds easily undergo oxidative *syn* elimination to afford the α,β-unsaturated-1,3-dicarbonyls. Several methods have been developed to synthesize the α-selenodicarbonyls.[345]

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1.12
The Perkin Reaction

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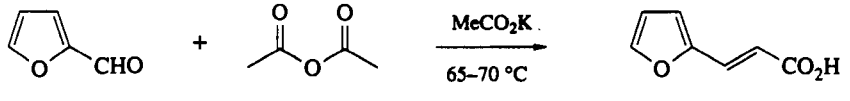
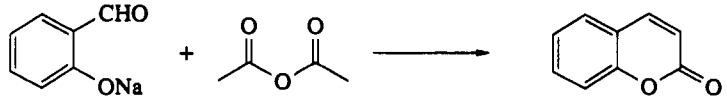
1.12.1 INTRODUCTION

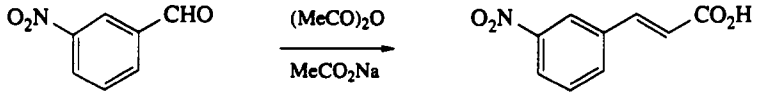
The Perkin reaction involves the condensation of a carboxylic acid anhydride and an aldehyde in the presence of a weak base, often the sodium or potassium salt of the acid or triethylamine, to give unsaturated carboxylic acids (equation 1).[1] The first example of this reaction was described by Perkin in 1868 and involves a synthesis of coumarin by heating the sodium salt of salicylaldehyde with acetic anhydride (equation 2).[2] The reaction is generally applicable only to aromatic aldehydes and is particularly useful for the preparation of substituted cinnamic acids, as illustrated by equation (3).[3]



(1)

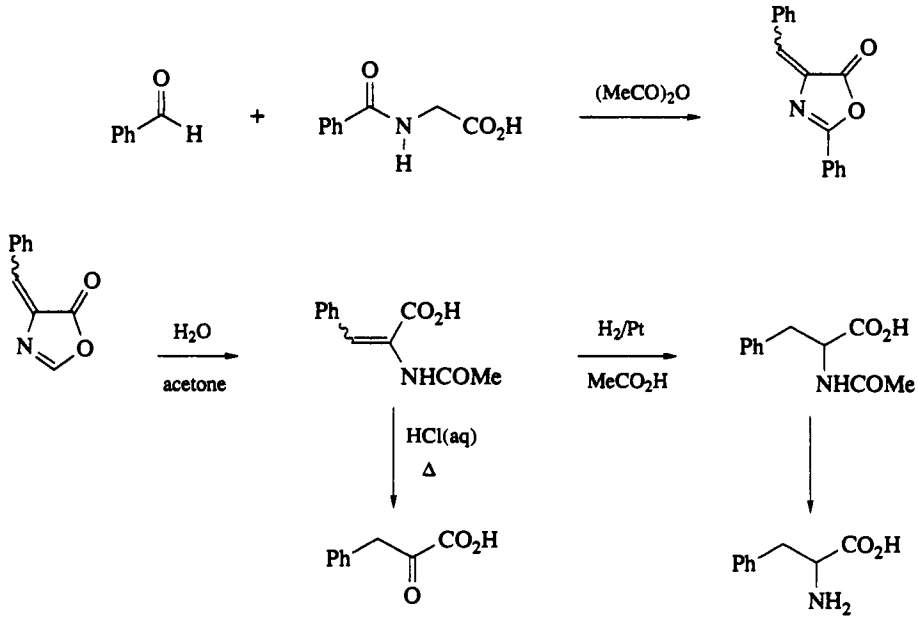


(2)



(3)

In 1883, an important variation of the reaction was reported by Plöchl, involving the condensation of benzaldehyde and hippuric acid in the presence of acetic anhydride.[4] It was Erlenmeyer, however, who determined the azalactone structure of the product (equation 4) and extended its scope to include other

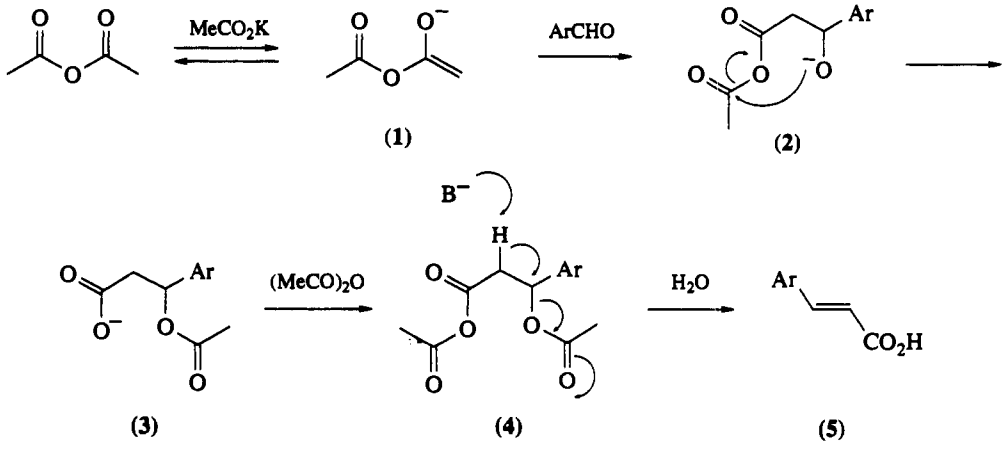


Scheme 1

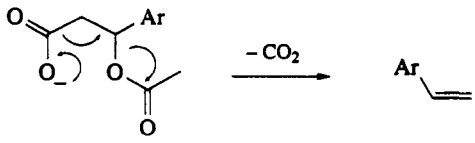
aldehydes; this modification of the reaction, utilizing acylglycine derivatives, is usually referred to as the Erlenmeyer azalactone synthesis.[5,6] Azalactones (also referred to as oxazolones) serve as important intermediates for the synthesis of α-amino acids and α-keto acids (Scheme 1).[7] Interestingly, penicillin was initially assigned an incorrect thiazolidine–oxazolone structure, and much information regarding the chemistry and properties of azalactones was developed from penicillin research during the Second World War.[8] In this chapter, the scope of the Perkin condensation is examined with an emphasis on modifications that have extended its utility beyond the synthesis of cinnamic acids.

1.12.2 MECHANISTIC CONSIDERATIONS

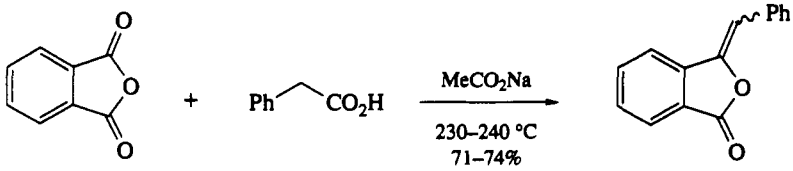
The generally accepted mechanism for the Perkin reaction is shown in Scheme 2. Much of the early work leading to this view, which was the result of numerous investigations spanning a period of greater than 50 years, has been reviewed in some detail.[1] Formation of the anhydride enolate (**1**) and aldol-type condensation generates the alkoxide anhydride (**2**). Intramolecular acylation provides an acetoxycarboxylate (**3**), which forms a mixed anhydride; elimination of acetic acid and hydrolysis affords the unsatu-



Scheme 2



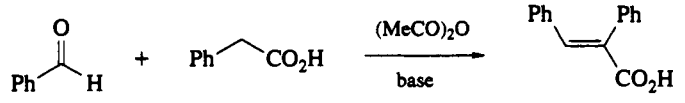
(3) (5)



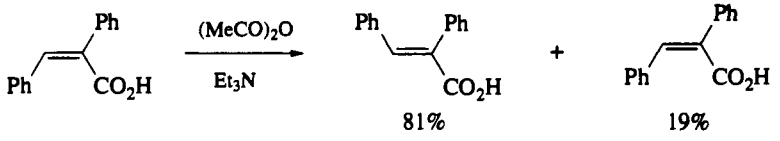
(6)

rated acid (**5**). A potential side reaction involves decarboxylative elimination of (**3**) to form an alkene (equation 5). This side reaction is generally minor, although higher temperatures and/or activating substituents may facilitate this pathway (equation 6;[9] compare this reaction to conditions and outcome shown in equation 12).

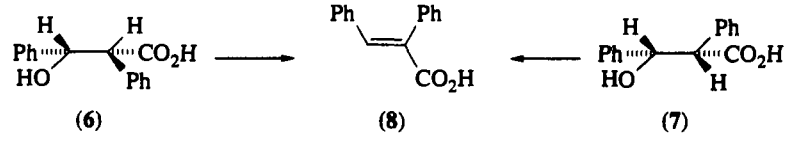
The Perkin reaction of an aromatic aldehyde with phenylacetic acid affords preferentially the α-phenylcinnamic acid stereoisomer in which the phenyl groups are in a *cis* relationship (equation 7).[10] This product was also shown to be favored thermodynamically; heating α-phenyl-*cis*-cinnamic acid in a dilute solution of acetic anhydride–triethylamine affords an equilibrium mixture containing 81% of the (*E*)-cinnamic acid and 19% of the (*Z*) isomer (equation 8). Zimmerman and Ahramjian studied this reaction in some detail, and through a series of elegant experiments found evidence indicating that the condensation step of the sequence is not reversible.[10] The lack of reversibility is suggested to result from rapid acetylation of the β-alkoxide substituent in the intermediate analogous to (**2**; Scheme 2). Furthermore, the elimination of each of the diastereomeric 3-hydroxy-2,3-diphenylpropionic acids (**6**) and (**7**) under Perkin conditions (acetic anhydride, Et_3N, reflux, 35 min), affords products consisting of 99 ± 2% of α-phenyl-*trans*-cinnamic acid (**8**; Scheme 3); under the same relatively mild conditions, the Perkin condensation of benzaldehyde and phenylacetic acid affords products consisting of 96% of (**8**). Thus, a significantly greater proportion of the stable isomer is obtained than is accountable on simply a thermodynamic basis. The observed product ratios apparently reflect a kinetic preference. The authors postulate that the stere-



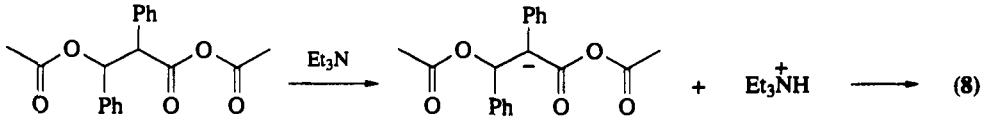
(7)



(8)

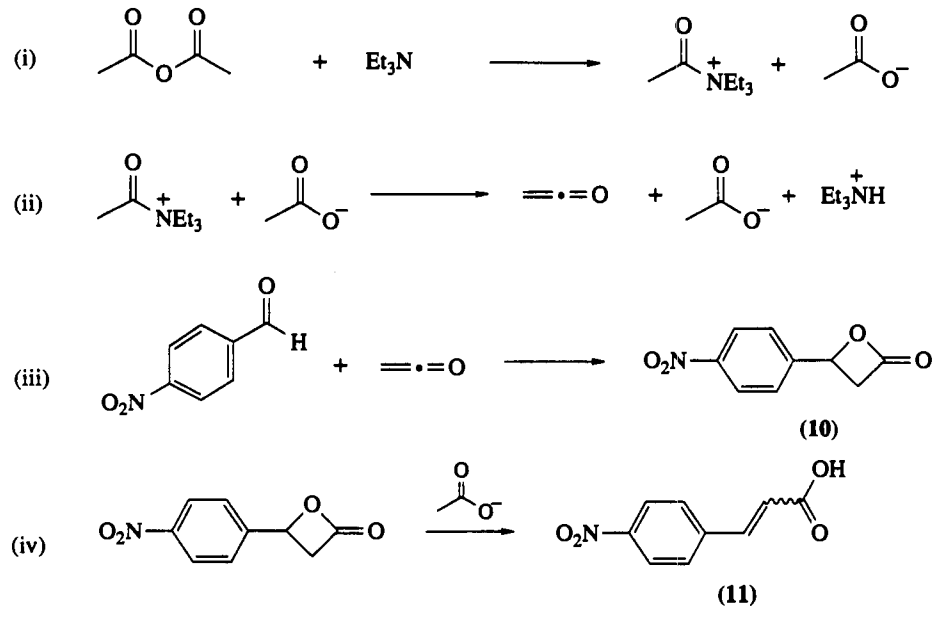


Scheme 3



erythro or *threo* (**9**)

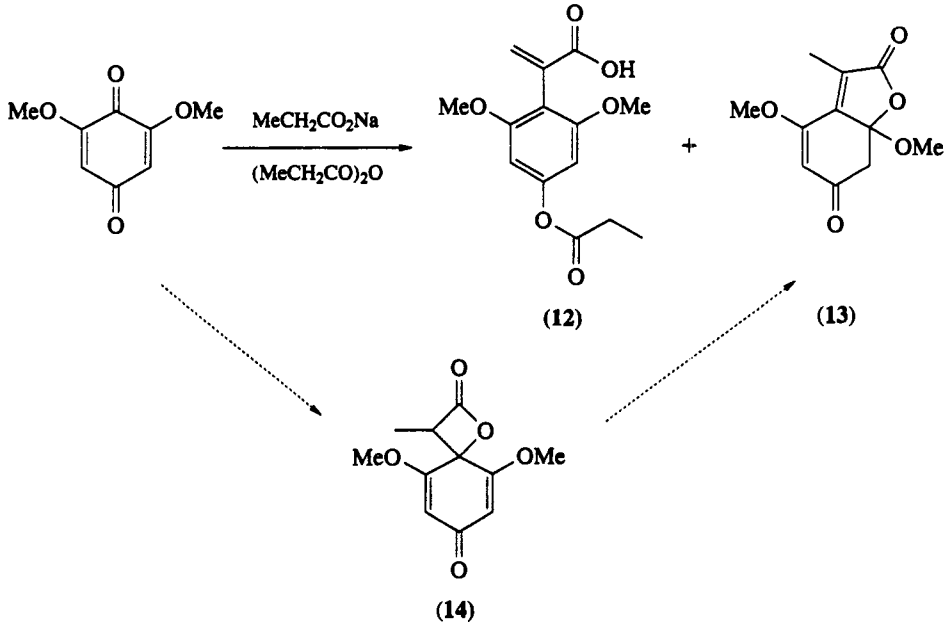
Scheme 4



Scheme 5

ochemical outcome of the reaction is determined by the conformations of the presumed intermediates (**9**) that allow maximum conjugation between the carboxyl group, the double bond being formed and the β-phenyl substituent in the transition state leading to (**8**) (overlap control; Scheme 4).[11] Applying this underlying driving force, the authors present a series of arguments explaining the preference of both diastereomers (**9**) to afford a single geometric isomer (**8**). Kinetic data, concluding that the condensation step is the slowest step in the Perkin reaction, have also been reported.[12]

More recently, results have been published indicating that the initial condensation, at least in the presence of triethylamine, may not be only of the aldol type but also include a pathway involving the formation and subsequent cycloaddition of ketene to form a β-lactone intermediate that cleaves to provide



Scheme 6

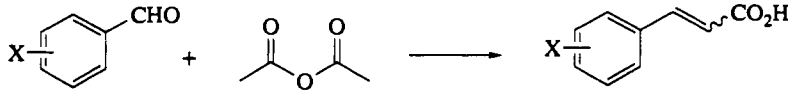
the cinnamic acid (**11**; Scheme 5).[13] Spectroscopic (IR, NMR) evidence is provided for the formation of a β-lactone intermediate (as suggested in 1936 by Hurd and Williams) in the reaction of *p*-nitrobenzaldehyde with ketene to afford the Perkin product, cinnamic acid. Subsequently, the reaction between *p*-nitrobenzaldehyde, acetic anhydride and triethylamine was investigated, and the β-lactone (**10**) was observed by IR spectroscopy under these conditions. Furthermore, it was shown that independently prepared (**10**) treated with acetic anhydride and triethylamine affords *p*-nitrocinnamic acid (**11**). It was also found that decomposition of (**10**) in dioxane to afford (**11**) is catalyzed by acetate ion, while amine catalyzes the decomposition of (**10**) to a series of minor products rather than (**11**), leading the authors to propose the mechanism shown in Scheme 5.

Analogous results were reported earlier concerning the Perkin reaction of quinones.[14] Treatment of 2,6-dimethoxy-*p*-benzoquinone with propionic anhydride in the presence of sodium propionate affords a mixture of condensation-derived products (**12**) and (**13**) (Scheme 6). However, when the reaction is carried out under milder conditions, among the products isolated is the β-lactone (**14**). Compound (**14**) can be converted under Perkin conditions to (**12**) and (**13**). It is noted that (**14**) could be in equilibrium with dimethoxybenzoquinone and methylketene; its isolation does not prove with certainty its intermediacy in the formation of (**12**) and (**13**). Thus, the actual mechanism of this condensation is not necessarily as simple as indicated in Scheme 2 and may involve more than one distinct pathway, depending on the exact nature of the particular substrate or base employed.

1.12.3 REACTION SCOPE

1.12.3.1 Preparation of Cinnamic Acids and Related Aromatic Derivatives

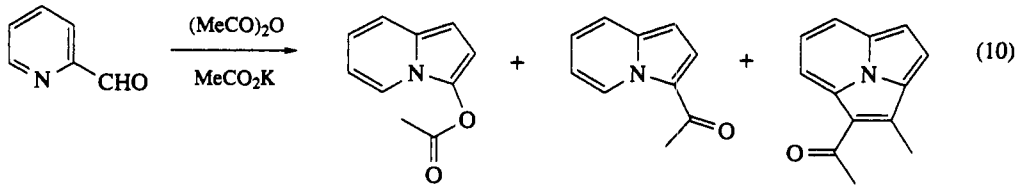
The Perkin condensation is a primary method for the synthesis of substituted cinnamic acids (equation 9), and several examples are illustrated in Table 1.[1,15,16] Interestingly, 2,6-dimethylbenzaldehyde (entry i) fails to react under the conditions employed, while 2,6-dichlorobenzaldehyde (entry j; similar steric situation) affords the corresponding cinnamic acid in excellent yield, illustrating the activating effect of the electron-withdrawing chloro substituents. The reaction is limited to acetic acid and monosubstituted acetic acids, as two α-hydrogen atoms must necessarily be eliminated to form the α,β-unsaturation. The reaction typically requires relatively high temperatures (>150 °C). The aromatic dialdehydes phthalaldehyde,[17] isophthalaldehyde[18] and terephthaldehyde[19] also undergo the transformation, affording the corresponding benzenediacrylic acids in 20–80% yields. Heteroaromatic aldehydes such as furfural[20] (equation 1) and 2-thiophenecarbaldehyde[21] also take part in the reaction. 2-Pyridinecarbaldehyde, on the other hand, does not afford the Perkin product, 3-(2-pyridyl)acrylic acid.[22] Instead, it gives a mixture of indolizine derivatives as shown in equation (10). Detailed mechanistic discussions for these and related transformations are found in the original work. Cinnamaldehyde affords β-styrylacrylic acid under Perkin conditions (equation 11).[23] An extensive list of cinnamic acids formed in this reaction is found in ref. 1.



(9)

Table 1 Preparation of Cinnamic Acids from Substituted Benzaldehydes[1,15,16]

Entry	*Substituent*	*Yield of cinnamic acid (%)*
a	H	70–75
b	4-Me	33
c	2-Cl	71
d	4-Cl	52
e	2-MeO	55
f	4-MeO	30
g	2-NO_2	75
h	4-NO_2	82
i	2,6-Me_2	0
j	2,6-Cl_2	82



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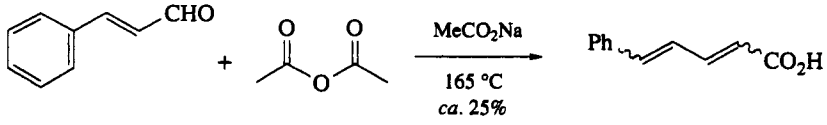
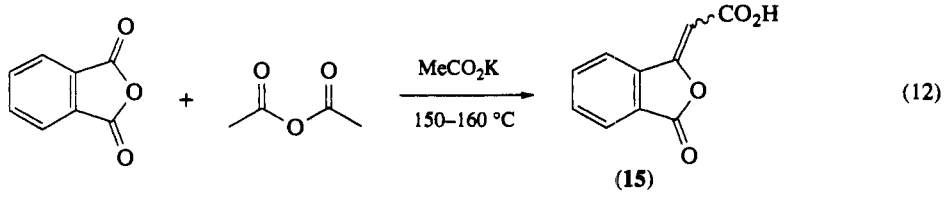


(11)

Phthalic anhydride, when used as the carbonyl component in the Perkin reaction, affords, on treatment with acetic anhydride and potassium acetate, phthalylacetic acid (**15**; equation 12).[24] α-Arylacetic acids also react with aromatic aldehydes to afford α-arylcinnamic acids (Ogliaro modification of the Perkin condensation, equation 7);[1] this type of reaction presumably involves the formation of the mixed anhydride of phenylacetic acid and acetic acid and/or phenylacetic anhydride. This modification is also illustrative of the equilibrium that is established between acid, acid salt and acid anhydrides under the conditions of the reaction.

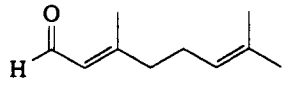


(12)

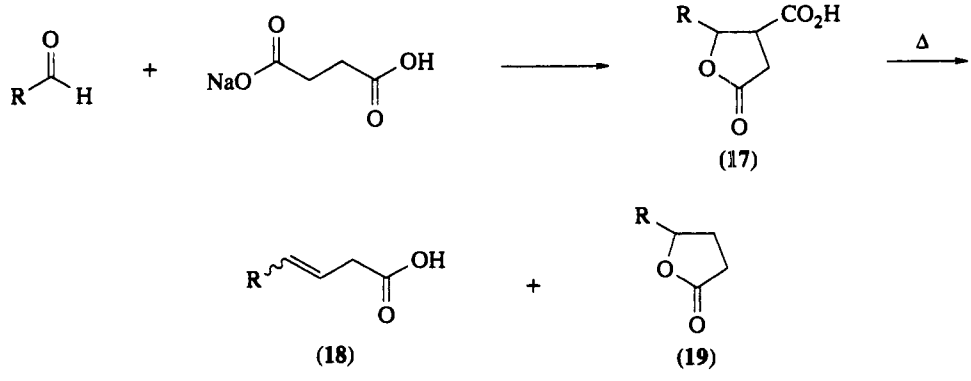
(**15**)

1.12.3.2 Aliphatic Aldehydes and Ketones

Simple aliphatic or aromatic ketones are not suitable substrates in the Perkin transformation. Similarly, aliphatic aldehydes are not generally acceptable components in this reaction. This long-known limitation was studied by Crawford and Little.[25] They demonstrated that many aliphatic aldehydes give diacetates and enol acetates when heated with acetic anhydride, with or without sodium acetate, suggesting this side reaction causes the typical Perkin process to fail. Semmeler had previously obtained similar results.[26] They did show, however, that several short chain aldehydes, as well as *trans*-citral (**16**), undergo the Perkin condensation with *p*-nitrophenylacetic anhydride; the *p*-nitrophenyl substituent activates the anhy-



(**16**)



(**17**)

(**18**) (**19**)

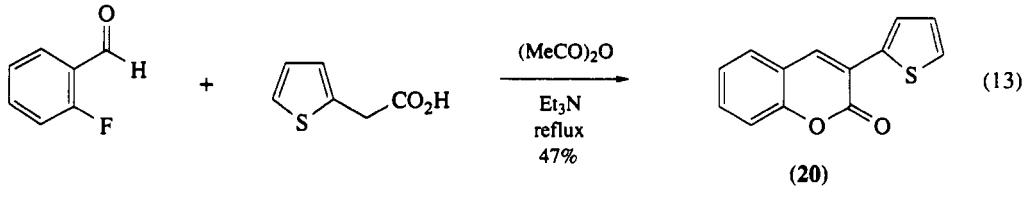
Scheme 7

dride, and these reactions are carried out at 35–55 °C. Higher aldehydes and *cis*-citral do not give Perkin products under these conditions, presumably because of increased hindrance due to the side chain sterically interfering with the reactivity of the carbonyl group. It is also suggested that a principal factor in the decreased reactivity of aliphatic aldehydes is the reduced rate in the elimination step relative to the aromatic systems in which this process is facilitated by conjugation of the newly forming double bond and the aromatic π-system in the transition state. Thus, from a practical standpoint, the Perkin condensation remains limited in scope to the use of aromatic aldehydes.

Related condensations involving the replacement of the anhydride component with succinic acid (Fittig synthesis)[27] or with malonic acid (Knoevenagel condensation, see Volume 2, Chapter 1.11) provide complementary preparative methods which are useful for both aromatic and aliphatic systems. The Fittig extension of the Perkin transformation involves heating an aliphatic or aromatic aldehyde with sodium succinate and acetic anhydride to give the condensation products (**17**), which lose carbon dioxide to afford β,γ-unsaturated carboxylic acids (**18**), accompanied by small amounts of the corresponding γ-butyrolactones (**19**; Scheme 7).[27]

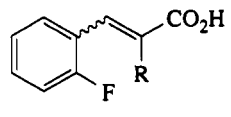
1.12.3.3 Preparation of Coumarins

As exemplified by equation (2), the Perkin condensation of *o*-hydroxybenzaldehydes is an important method for the synthesis of substituted coumarins. An interesting variation on this procedure has been reported recently.[28] Heating a mixture of *o*-fluorobenzaldehyde, 2-thiopheneacetic acid, acetic anhydride and triethylamine affords directly the coumarin (**20**; equation 13) instead of the expected cinnamic acid (**21**). The reaction proceeds similarly with several arylacetic acids. The reaction presumably proceeds through the cinnamic acids (**21**). The observed product can conceivably arise by direct nucleophilic displacement involving the carboxylate or by an elimination/addition (benzyne) mechanism. The authors note that when 2-fluorobenzaldehyde is replaced by its 2-bromo analog in this reaction, the substituted cinnamic acid (**22**) is the major product and the corresponding coumarin (**20**) is obtained only in low yield. It is suggested that since it is known that fluoride is displaced more rapidly in nucleophilic aromatic substitution reactions, while bromo aromatic compounds form benzynes more rapidly, this result is consistent with a nucleophilic displacement mechanism.

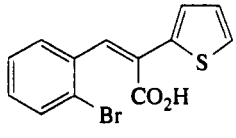


(13)

(**20**)

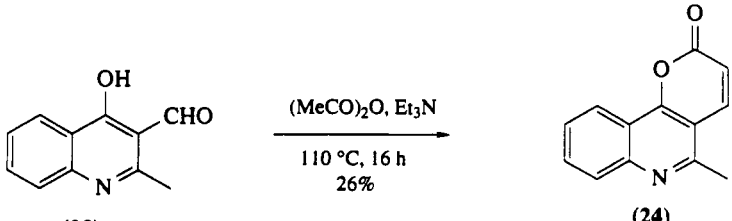


(**21**) R = 2-thienyl



(**22**)

Analogous to the preparation of coumarins (equation 2), treatment of 2-methyl-3-formyl-4-hydroxyquinoline (**23**) with acetic anhydride and triethylamine affords the pyranoquinoline (**24**; equation 14).[29] When sodium acetate was employed as the base, instead of triethylamine, no pure (**24**) could be isolated.



(**23**)

(**24**)

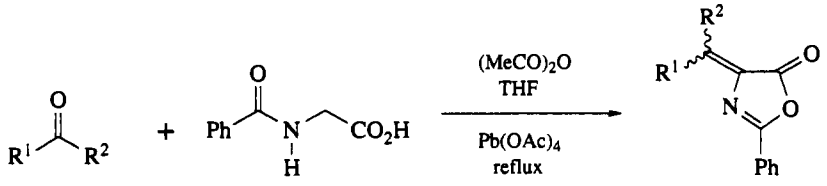
(14)

Recently, it has been reported that significantly higher yields are obtained and shorter reaction times required in the Perkin synthesis of cinnamic acids when sodium acetate is replaced by cesium acetate.[30]

1.12.4 ERLENMEYER AZALACTONE SYNTHESIS

1.12.4.1 General and Mechanistic Considerations

An important variation of the Perkin reaction is the Erlenmeyer azalactone synthesis exemplified by equation (4), involving condensation of an aldehyde and an *N*-acylglycine derivative in the presence of acetic anhydride and sodium acetate.[6] Although this reaction, analogous to the classical Perkin condensation, was initially limited to the use of aromatic aldehydes, Baltazzi and Robinson reported[31] that the use of lead acetate and THF allowed the preparation of several azalactones derived from aliphatic aldehydes (equation 15). The results for the condensation of several aldehydes and ketones with hippuric acid (**28**) under these conditions are shown in Table 2. The reaction proceeds through the intermediate (**26**) (intramolecular condensation of **25**), which reacts with the aldehyde in Perkin fashion to provide the so-called azalactone product (Scheme 8). It is the formation of such oxazolones from acylamino acids which is be-

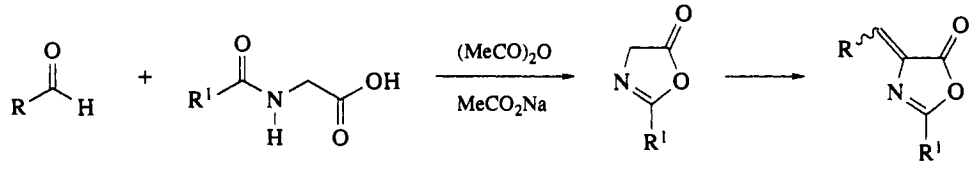


(15)

(28) (29)

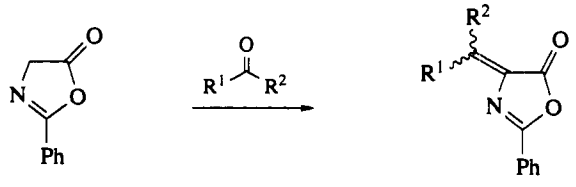
Table 2 Erlenmeyer Reaction in the Presence of $Pb(OAc)_4$[31]

R^1R^2CO	*Reflux time* (h)	*Yield of* (**29**) (%)
Propanal	4	55
Isobutyraldehyde	4	61
Cinnamaldehyde	4.5	78
Cyclohexanone	22	70
2-Methylcyclohexanone	22	5–6
Fluorenone	22	71



(25) (26)

Scheme 8



(16)

(26) (30)

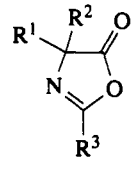
lieved to be primarily responsible for racemization during peptide synthesis using activated esters.[32] Crawford and Little, in a key mechanistic study, demonstrated that independently prepared 2-phenyloxazol-5-one (**26**) reacts with aldehydes in the absence of both acetic anhydride and sodium acetate to provide Perkin products (**30**; equation 16).[33]

The oxazolone (**26**) is highly activated and acts as the equivalent of the anhydride reagent in the normal Perkin condensation. Compound (**26**) may be thought of as the anhydride of the parent α-acylamino acid and may be generated from acylamino acids using cyclodehydrating agents other than acetic anhydride such as carbodiimides[34] or ethyl chloroformate.[35] Yields in the condensation of (**26**) and carbonyl compounds are improved by the addition of lead acetate or acetic anhydride, perhaps facilitating the elimination step. The results for the reaction of (**26**) with several carbonyl compounds are shown in Table 3.[33] Aromatic aldehydes (entries a–d) react quite well and afford (**30**) in good yields. Lower aldehydes (entries e–g) give moderate to good yields of product, particularly in the presence of lead acetate; heptanal, octanal, 2-methylpropanal and 2-ethylbutanal fail to provide (**30**) under these conditions. Acetone and cyclohexanone also afford condensation products in this reaction. Thus, the similarity between the Perkin condensation and the Erlenmeyer reaction lies in the analogy between the role of the acid anhydride in the former case and the intermediate oxazolone (**26**) in the latter, each condensing with aldehydes to generate a new carbon–carbon double bond. It should be noted that there has been significant effort directed toward the synthesis of saturated azalactones of the general structure (**31**), including the development of methodology for the preparation of compounds possessing high enantiomeric purity at C-2,[36] this center being highly prone to racemization, as well as the development of alternative methods for the synthesis of this heterocyclic system; the reader is referred to earlier reviews in these areas.[6,37]

Table 3 Condensation of 2-Phenyloxazol-5-one with Aldehydes and Ketones[33]

Entry	*Carbonyl compound*	*Yield of (30) (%)*
a	Benzaldehyde	63[a]
b	Anisaldehyde	55[a]
c	Furfuraldehyde	82[a]
d	Cinnamaldehyde	72[a]
e	Ethanal	58[b]
f	Propanal	55[b]
g	Butanal	34[b]
h	Acetone	35[b]
i	Cyclohexanone	74[b]

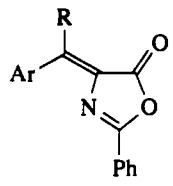
[a]Based on equimolar quantities of the reactants. Much higher yields can be obtained by using an excess of either component.
[b]Reaction carried out in the presence of lead acetate.



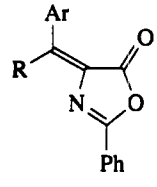
(**31**)

1.12.4.2 Geometric Isomers of Oxazolone Products

The Erlenmeyer azalactone synthesis generally affords predominantly, and often exclusively, (*Z*) isomers (**32**).[38] However, a simple method for the synthesis of (*E*) isomers (**33**), obtained previously by separation of isomeric mixtures or isomerization procedures, has been reported.[39] Aromatic aldehydes condense with hippuric acid when heated in polyphosphoric acid (PPA) to afford (**33**) in 80–90% yields (equation 17; Table 4). Alternatively, the (*Z*) isomers may be heated in PPA to afford the corresponding (*E*) isomers in excellent yield. The authors note that hippuric acid is not converted to (**26**) in PPA, the generally accepted intermediate in the Erlenmeyer synthesis. Furthermore, both isomers of 2-(benzamidoyl)cinnamic acid, (**34**) and (**35**), obtained by the alkaline hydrolysis of (**32**; R = H, Ar = Ph) and (**33**; R = H, Ar = Ph), respectively are converted to (**33**; R = H, Ar = Ph) in PPA (Scheme 9). The authors therefore suggest a mechanism involving condensation, first of the aldehyde and hippuric acid followed by

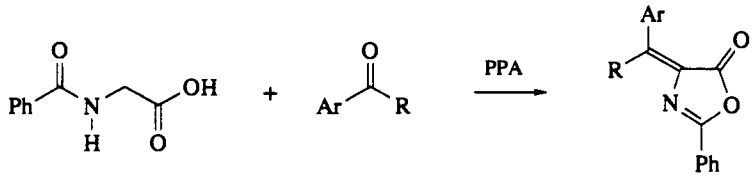


(32)



(33)

cyclodehydration. However, it is not clear what factors control the interesting stereochemical outcome of the overall transformation. It should be noted that it is also possible that (**26**) is indeed formed in this reaction, however under these conditions it exists only in low steady-state concentrations (in equilibrium with hippuric acid) and is therefore still a potential intermediate. The (*E*) isomers are converted to the (*Z*) isomers by heating with pyridine.[6c] A report has also appeared describing the use of ion-exchange resins in the Erlenmeyer synthesis to obtain (*E*) isomers of the product azalactones.[40]

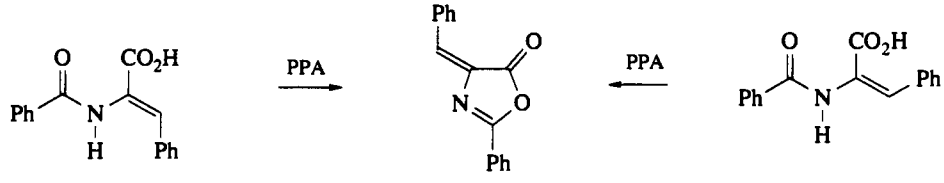


(17)

(33)

Table 4 Preparation of (*E*)-4-Arylmethylene-2-oxazolin-5-ones (*33*)[39]

Ar	*R*	*Yield of (33) (%)*
4-ClC_6H_4	H	85
4-$MeOC_6H_4$	H	90
4-MeC_6H_4	H	80
3,4-$(MeO)_2C_6H_3$	H	82
4-HOC_6H_4	H	80
2-HOC_6H_4	H	70
Ph	Me	80
4-ClC_6H_4	Me	52
4-$MeOC_6H_4$	Me	50
4-$NO_2C_6H_4$	Me	88
4-MeC_6H_4	Me	70



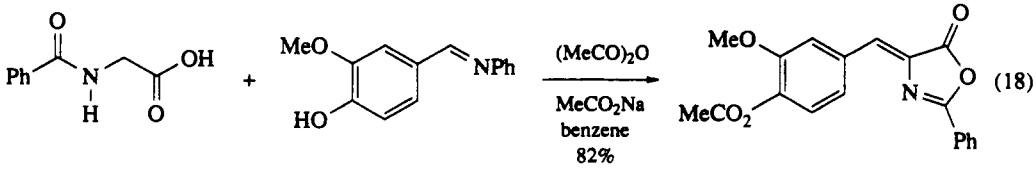
(34) (33) Ar = Ph; R = H (35)

Scheme 9

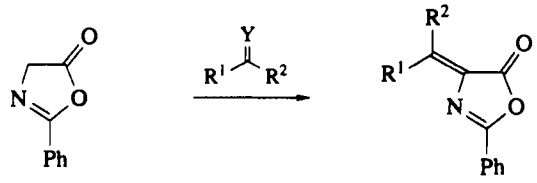
1.12.4.3 Imines as Substrates

The condensation is also reported to proceed with aromatic Schiff bases, as shown in equation (18).[41] In a more recent publication, the condensation of 2-substituted oxazolones with imines was compared to the corresponding reaction with the parent aldehydes and ketones.[42] When aldehydes are employed in place of imines, better or comparable yields of condensation product (**36**) are obtained. Two ketones, acetophenone and cyclohexanone, were investigated in this study. In both of these cases, significantly

improved yields of (**36**) are obtained with the corresponding ketone imine (equation 19; Table 5). The authors also note that in the ring cleavage of (**36**) with aniline, the products maintain the stereochemistry of the carbon–carbon double bond (equation 20). The same authors have also published work describing the preparation and conversion of several azalactones of the general structure (**36**), by 1,5-bond cleavage with amines, hydroxide and alkoxides, to afford *N*-substituted 2-acylamino-2-alkenamides (**37**)[43] or 2-acylamino-2-alkenoic acids (or esters) (**38**),[44] respectively (Scheme 10); these cleavage reactions afford alkenes that maintain the initial (*Z*) stereochemistry of the oxazolones (**36**). From a practical standpoint, it has been suggested that α-acetamido compounds are preferable to the corresponding α-benzamido derivatives when the ultimate target (such as in the case of the preparation of amino acids) requires



(18)



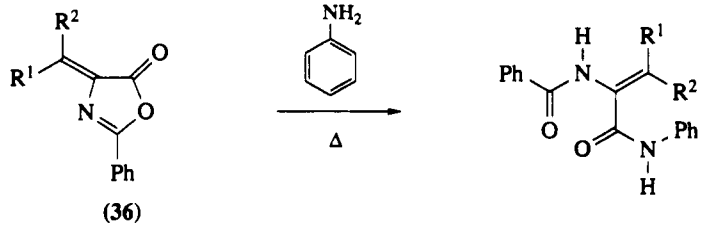
(19)

(**36**)

Table 5 Condensation of Oxazolones with Carbonyl Compounds and Their Corresponding Imines[42]

R^1	*R*^{2}	*Y*	*Yield of* (**36**) (%)[a]
Ph	H	O	77
Ph	H	*N*-Ph	60
Ph	Me	O	0
Ph	Me	*N*-Ph	42
—$(CH_2)_5$—		O	8.4[b], 25[c]
—$(CH_2)_5$—		*N*-Ph	50

[a]Reaction mixtures heated on water bath for *ca.* 10 min. [b]Reaction mixture heated for 20 h. [c]Reaction mixture heated with *p*-TsOH (catalyst) for 20 h.



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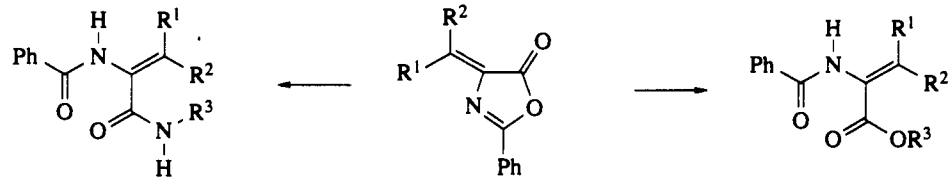
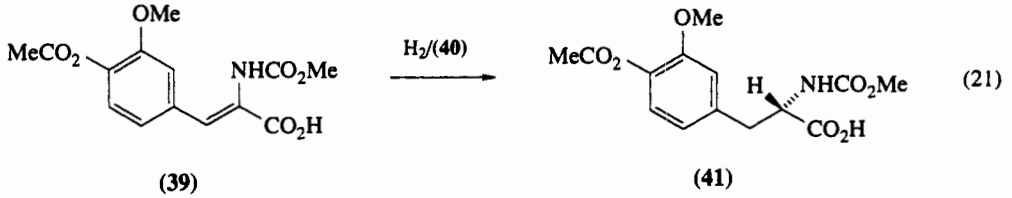


(**37**) (**36**) (**38**)

Scheme 10

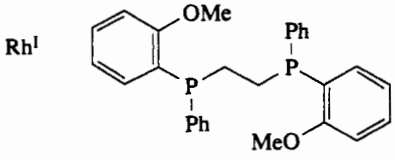
cleavage of this moiety, since they are more readily hydrolyzed;[1] it is also suggested that it is generally simpler to separate the hydrolysis products from acetic acid than from benzoic acid.[6b] Meléndez and coworkers have also reported related work on the cleavage of oxazolones to give stereospecifically (*Z*) and (*E*) isomers of dehydroacylamino acids and amides.[45] The mechanism of the hydrolysis of (*Z*)-4-benzylidene-2-methyloxazolin-5-one and (*Z*)-4-benzylidene-2-phenyloxazolin-5-one derivatives has been investigated, and the results indicate that under alkaline conditions hydrolysis occurs through nucleophilic attack at the carbonyl carbon of the substrate, while acidic hydrolysis involves attack at the imine carbon.[46]

Dehydroamino acids are important synthetic intermediates in that their reduction provides a route to α-amino acids. There has been a large volume of research examining the hydrogenation of such compounds, mediated by asymmetric homogeneous catalysts, to provide amino acids with varying degrees of optical purity.[47] For example, a key step in an industrial procedure for the manufacture of L-DOPA is reported to involve the hydrogenation of (**39**) in the presence of the bisphosphine rhodium catalyst (**40**) to provide (**41**) in 94% optical yield (equation 21).



(21)

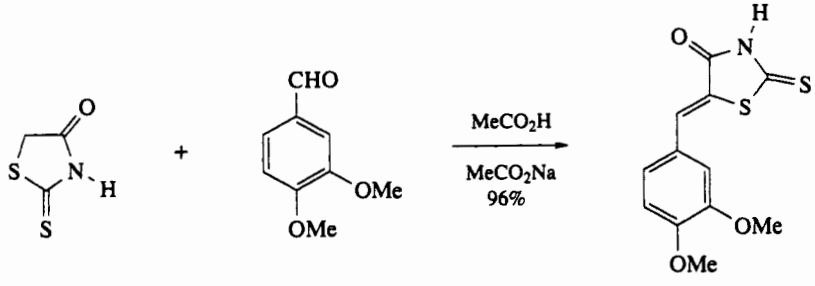
(**39**) (**41**)



(**40**)

1.12.4.4 Rhodanine and Hydantoin Derivatives

The condensation of rhodanine (**42**) with aldehydes is an important reaction closely related to the Erlenmeyer azalactone synthesis (equation 22);[48] the resulting condensation products are particularly useful intermediates for the preparation of various functionalized arylacetic acids and derivatives *via* standard manipulations of the nitrile (**43**), which is available as illustrated in Scheme 11.[48] Similarly, aldehydes



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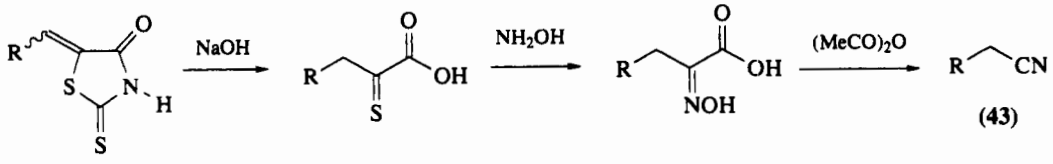
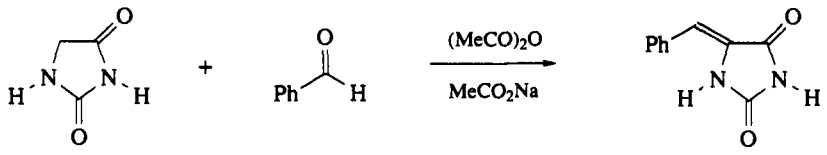


(**43**)

Scheme 11



(23)

condense with hydantoin under Perkin conditions (equation 23);[49] these condensation products, analogous to azalactones, may be converted to α-amino acids.

1.12.5 REFERENCES

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1.13
Darzens Glycidic Ester Condensation

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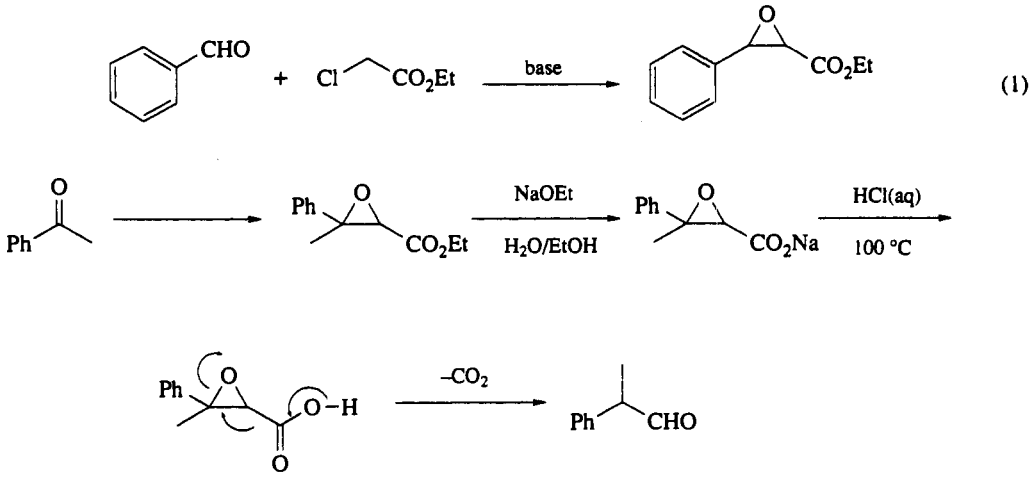
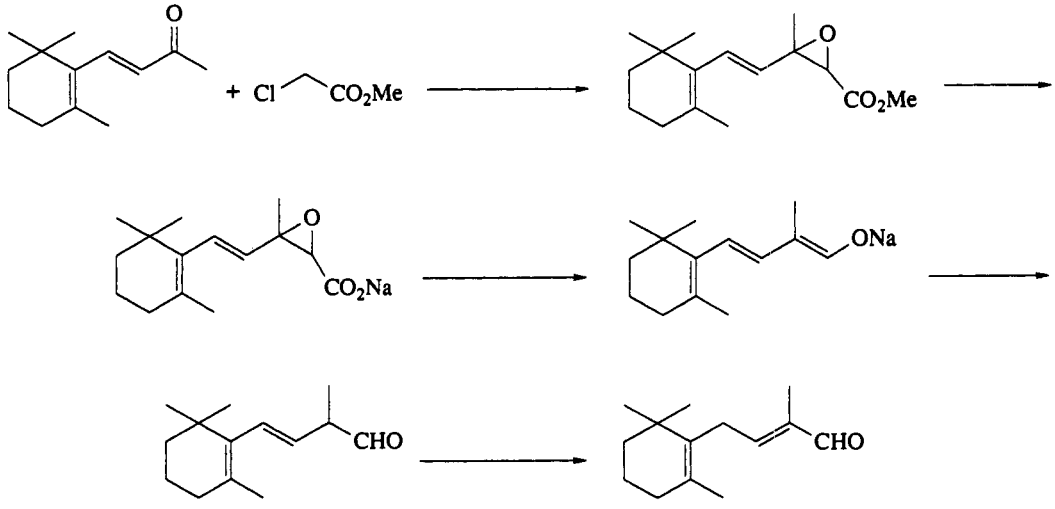
1.13.1 INTRODUCTION

The Darzens glycidic ester condensation involves the condensation of an aldehyde or ketone with an α-halo ester, in the presence of a base, to afford an α,β-epoxy ester (a 'glycidic ester'). The first synthesis of a glycidic ester was reported by Erlenmeyer in 1892 and is illustrative of the general reaction, as shown in equation (1).[1] The reaction was subsequently developed and generalized by Darzens.[2] Glycidic esters, in addition to undergoing transformations normally associated with epoxides, afford upon hydro-

lysis glycidic acids, which subsequently decompose to provide aldehydes or ketones (Scheme 1).[3] The reaction is thus pivotal in a general method for the one-carbon homologation of aldehydes and ketones.[4] An illustration of the classic reaction is found in one of the major industrial achievements of the 1940s, the commercial synthesis of vitamin A.[5] A key step in this process involves the Darzens condensation of methyl chloroacetate and β-ionone to give the corresponding glycidic ester, which upon sequential hydrolysis, decarboxylation and basic treatment affords the thermodynamically favored α,β-unsaturated aldehyde, subsequently converted to vitamin A (Scheme 2). The mechanism and stereochemical course of the reaction have been studied extensively and have been the subject of some controversy;[2,6] the scope of its applicability has been broadened beyond the use of α-halo esters to include α-halo compounds that are activated by a variety of electron-withdrawing substituents.



Scheme 1



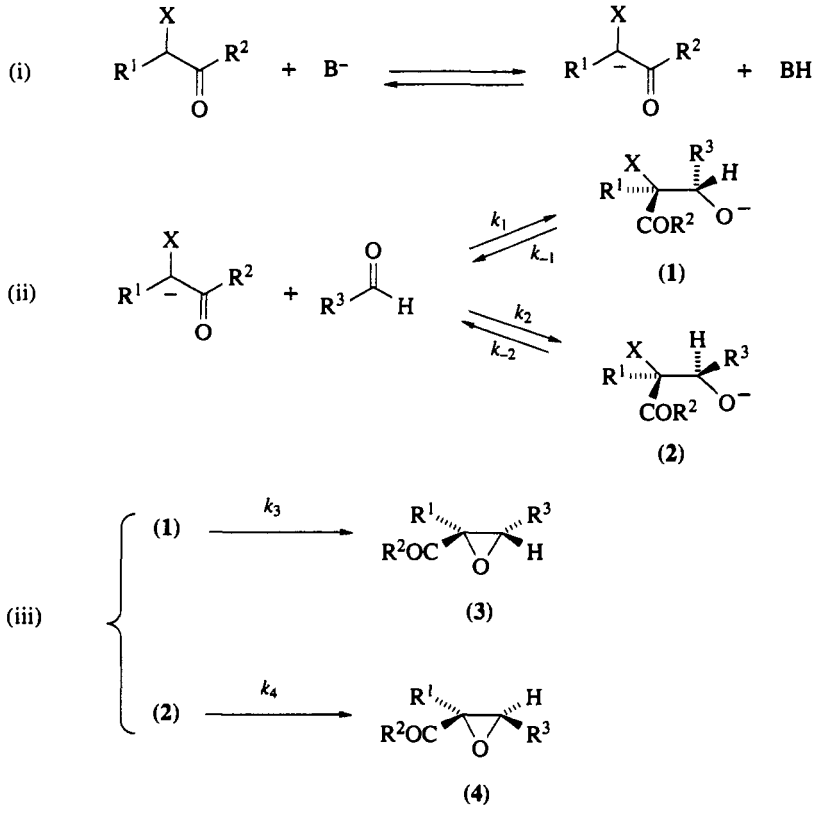
Scheme 2

In this chapter, key studies which have led to the current understanding of the mechanism of this transformation will be discussed, as a basis for dealing with issues of selectivity and choice of experimental variables in subsequent sections. Since the initial development of this reaction, it has evolved in scope to become a primary method for the stereoselective synthesis of epoxides to which an electronegative substituent is directly attached. Several recent variations on the initial protocol which afford functionally diverse molecules are the subject of Section 1.13.3. Section 1.13.5 examines related reactions that afford substituted aziridines instead of epoxides, and Section 1.13.6 examines some recent variants of the re-

action using multiphase systems. This section also discusses Darzens condensations involving α,β-unsaturated carbonyl systems and an extension of the reaction that provides methodology for the synthesis of substituted cyclopropanes. Section 1.13.7 is concerned with several studies aimed at developing enantioselective variants of the reaction.

1.13.2 GENERAL AND MECHANISTIC CONSIDERATIONS

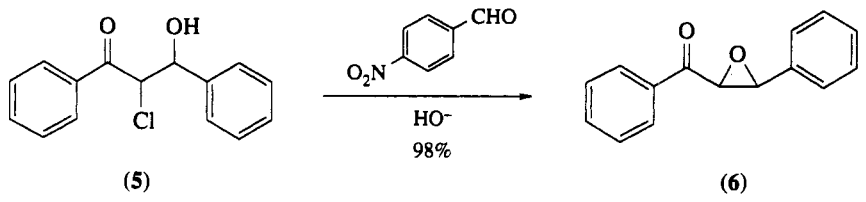
The mechanism of the Darzens condensation has been studied extensively; for discussions of early mechanistic proposals, some of which have been ruled out, reference is made to previous reviews.[2,6] The generally accepted mechanism for this transformation is shown in Scheme 3.



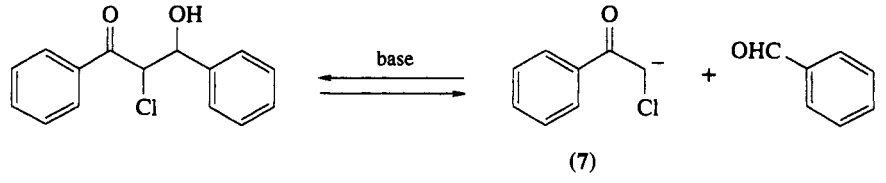
Scheme 3

The reaction involves generation of the carbanion of an activated halide (step i) and subsequent addition to an aldehyde or ketone to generate the diastereomeric aldolates (**1** and **2**; step ii), which cyclize (internal S_N2) to afford the stereoisomeric epoxides (**3** and **4**), respectively (step iii). The α-halo aldolates (**1**) and (**2**), or the related halohydrins, are not normally isolated, although this has been done with α-fluoro esters[7] as well as with α-chloro esters.[8] The isolation of these products is amongst the evidence which rules out carbene intermediates, which were invoked in earlier mechanistic proposals.

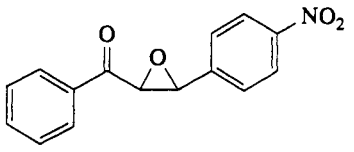
The ratio of diastereomers (**3**) and (**4**) can vary greatly, depending on the structures of the reactants, the solvent and the base. The stereochemistry of the product epoxide is determined by the configuration of the intermediate α-halo aldolate (step ii), and its control may be the result of kinetic or thermodynamic factors, depending on the relative rates of cyclization (k_3 and k_4) and retroaddition (k_{-1} and k_{-2}). Either step (ii) or step (iii) can be the rate-determining step. For example, treatment of the isolated halohydrin (**5**), derived from the reaction of benzaldehyde and phenacyl chloride, with hydroxide in the presence of *p*-nitrobenzaldehyde affords the epoxy ketone (**6**) in 98% yield (equation 2).[2b] This result has been interpreted as indicating that aldolization (step ii), in this case, is the rate-determining step and that cyclization (step iii) is fast. If cyclization was the slow step, the aldol–retroaldol preequilibrium would generate



(5) (6) (2)



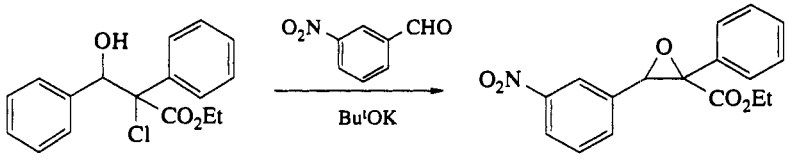
(7) (3)



(8)

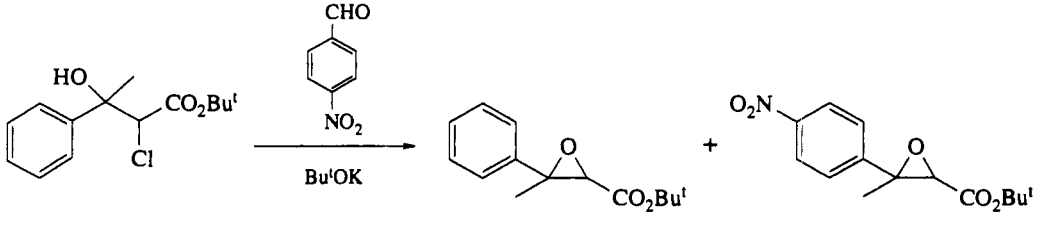
the carbanion (**7**; equation 3), which would be expected to condense with the highly reactive aldehyde acceptor *p*-nitrobenzaldehyde to afford the epoxy ketone (**8**), which is not observed.

In contrast to this result, Zimmerman and Ahramjian have reported that treatment of the halohydrin (**9**; a single diastereomer, unknown relative stereochemistry) with potassium *t*-butoxide in the presence of *m*-nitrobenzaldehyde affords only the glycidic ester (**10**; equation 4), indicating that in this case the rate-limiting step is cyclization.[9]



(9) (10) (4)

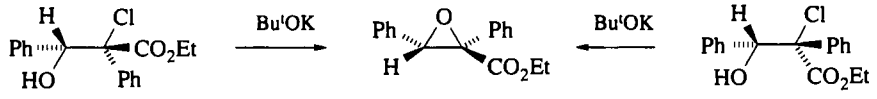
In a similar trapping experiment, Bachelor and Bansal identified a Darzens condensation in which the rates for the aldol–retroaldol preequilibrium and cyclization steps are similar.[10] Treatment of the diastereomeric mixture of halohydrins, derived from acetophenone and *t*-butyl chloroacetate, with potassium *t*-butoxide in the presence of *p*-nitrobenzaldehyde gives a mixture of products consisting of 87% from direct cyclization (**11**) and 13% from condensation with *p*-nitrobenzaldehyde (**12**; equation 5).



(**11**) 87% GLC (**12**) 13% (5)

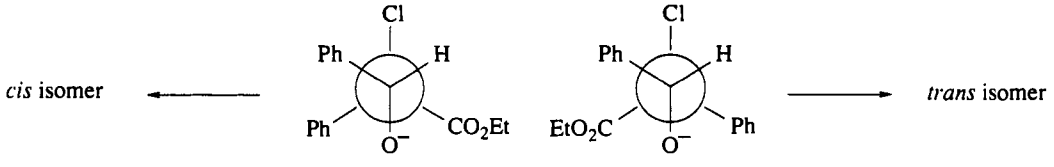
Thus far, this discussion has neglected the issue of stereochemistry and its control, and implications concerning mechanism. However, the stereochemical outcome of the Darzens condensation has been central to mechanistic studies. As part of a key mechanistic study, it was shown that treatment of each of

the diastereomeric halohydrins (**13**) and (**14**) with potassium *t*-butoxide furnishes ethyl *cis*-2,3-diphenyl-2,3-epoxypropionate (**15**) as the only isolable product (Scheme 4); this stereoisomer is also the product obtained from the Darzens condensation itself.[9] Earlier mechanistic proposals do not explain this experimental observation.[11,12] Based on the reasonable assumption that the intramolecular displacement must occur with inversion, the result is interpreted to indicate a rapid aldol–retroaldol preequilibrium (interconverting **13** and **14**), followed by a rate-limiting cyclization (Scheme 5); furthermore, the transition state barrier for the cyclization of the alkoxide of (**13**) must be of lower energy than that for the cyclization of the alkoxide of (**14**) which would lead to the *trans*-epoxide. Simple steric arguments do not explain the observed product. In order to achieve an antiperiplanar relationship for displacement to afford (**15**), the two phenyl substituents must experience a van der Waals repulsive interaction, whereas this interaction is not present in the analogous transition state leading to the *trans* isomer. The driving force advanced to explain the stereochemical outcome is overlap control; that is, stabilization of the transition state occurs by delocalization of electrons from the relatively electron rich *p*-orbital on C-2 to the ester carbonyl π-orbital (Figure 1). This overlap is possible only when the newly forming carbon–oxygen bond and the breaking carbon–chlorine bond are both perpendicular to the plane of the ester function. Such a conformation is easily attainable in the transition state leading to the *cis* product, as the carboethoxy group is unhindered. Models indicate that the proper conformation for such overlap is less easily obtainable in the transition state leading to the *trans* isomer due to steric interactions between the ester and phenyl substituents. Thus, this mechanism predicts that for condensations in which the rate-limiting step is cyclization, the major isomer is that in which the carbonyl group is *trans* to the larger group on the epoxide. It should be noted that this type of orbital overlap has been invoked as an influencing factor in determining a favored transition state for other transformations, such as the base-catalyzed dehydration of aldol products.



(**13**) (**15**) (**14**)

Scheme 4



alkoxide of (**13**) alkoxide of (**14**)

Scheme 5

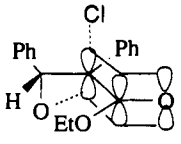
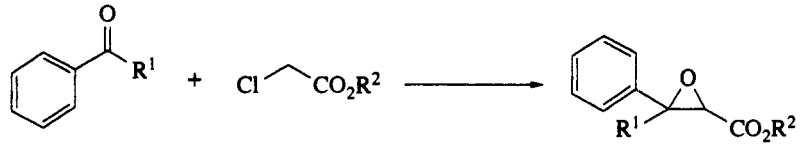


Figure 1 Overlap control as an explanation for the stereochemical control of the Darzens condensation

Bachelor and Bansal observed that in the condensation between acetophenone and *t*-butyl chloroacetate, the major product is that in which the carboalkoxy group is *cis* to the phenyl group, in contrast to the results predicted by the previous mechanism.[10] A series of glycidic esters was prepared using benzaldehyde, acetophenone and butyrophenone as the carbonyl component and the methyl, ethyl, isopropyl and *t*-butyl esters of chloroacetic acid as the carbanion source (equation 6). Potassium *t*-butoxide/*t*-butyl alcohol was used as the base/solvent system. The results are shown in Table 1. Two general trends are apparent. As the size of R^1 or R^2 increases, the *cis:trans* isomer ratio increases. Furthermore, epimerization of the glycidic esters was ruled out as a controlling factor. Based on these results, it is concluded that in

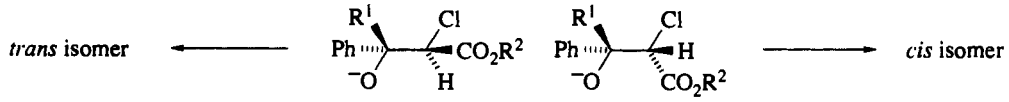
this series, the stereochemistry of the final product is fixed by the aldol step. A primary consideration in this premise involves the consideration of the preferred conformations of the α-chloro aldolates required for cyclization (**16** and **17**; Scheme 6). It is proposed that since increasing the size of R^2 enhances the predominance of *cis*-epoxide (*via* **17**), cyclization must be rapid compared with the aldol step. The authors postulate an interesting controlling factor in this step, involving optimal overlap of the developing oxyanion and the π-orbital of the ester carbonyl which requires an eclipsed conformation (**18**) in the transition state. Increasing the size of R^1 or R^2 increases the repulsive energy of the eclipsed groups, and when this energy exceeds that gained by overlap, the favored conformation for attack becomes (**19**), in which the partial negative charge on the ester carbonyl oxygen and the developing alkoxide are as far apart as possible (*trans* coplanar); conformation (**19**) leads to the *cis*-epoxide after cyclization.



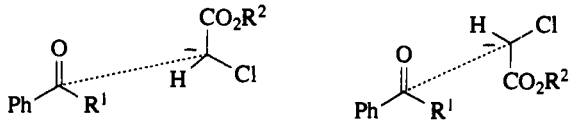
(6)

Table 1 *Cis:Trans* Isomer Ratios from Darzens Condensations[10]

R^1	R^2	*Cis* (%)	*Trans* (%)
H	Me	21	79
	Et	26	74
	Pr^i	33	67
	Bu^t	54	46
Me	Me	43	57
	Et	49	51
	Pr^i	60	40
	Bu^t	62	38
Pr^i	Me	73	27
	Et	75	25
	Pr^i	79	21
	Bu^t	75	25



Scheme 6



These stereochemical results obtained by Bachelor and Bansal, using *t*-butyl alcohol as solvent, differ from those observed in a study using hexamethylphosphoramide (HMPA).[13] In a subsequent paper, it is suggested that the differences must be attributed to differences in the degree of reversibility of the aldol step in the two solvents; when irreversible aldolization is ensured (by appropriate modification of reaction conditions), the stereochemical results obtained in HMPA, ether and *t*-butyl alcohol/ether are essentially the same.[14,15] In HMPA, it was found that this condition is reached at ambient temperature, however in *t*-butanol/ether the aldol step has a significant component of reversibility above –40 °C. Similar observations have been reported by Villieras and Combret in a study of the condensation of isobutyraldehyde with alkyl chloroacetates (equation 7).[16] The results of this study are summarized in Table 2. The results at room temperature are similar to those shown in Table 1; the ratio of *cis*-epoxide increases as the size of the ester substituent increases. However, at low temperature the corresponding ratios of

isomeric adducts (encompassing varying amounts of epoxide and the related uncyclized halohydrin) are essentially constant, independent of the size of R. Thus, it appears that the products obtained at room temperature do not accurately represent the kinetic steric course of the reaction, and the data indicate that the rate-limiting step for the ethyl and isopropyl ester cases is cyclization. In addition the data shown in Table 1, also at room temperature, may not reflect kinetic control and, as noted previously,[6] the subsequent mechanistic implications must be taken with caution. Indeed, it is clear that much of the early work attempting to define the factors influencing the stereochemical outcome of the Darzens condensation must be viewed similarly, as many of these experiments were carried out at room temperature. Although the work described thus far has increased the knowledge base concerning the mechanism of the Darzens reaction, a unifying interpretation of its steric course is still lacking. Additional mechanistic information and proposals are discussed subsequently, in the context of the specific studies involved in the more recent evolution of this reaction.

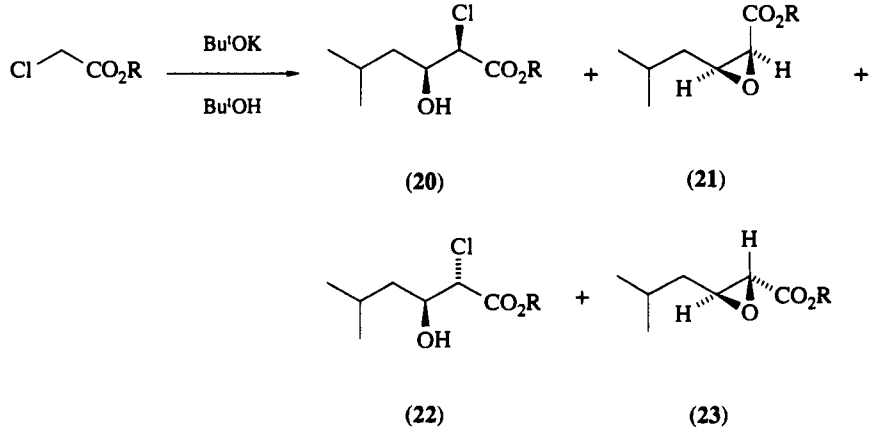


Table 2 Temperature Dependence of *Cis:Trans* Isomer Ratio in the Darzens Condensation[16]

R	*Composition at room temperature (%)* *(21);cis*	*(23);trans*	*Composition at −78 °C (%)* *(20) + (21)*	*(22) + (23)*
Et	16	84	72	28
Pr^i	20	80	73	27
Bu^t	70	30	70	30

It will be recognized by the reader that the aldol reaction has been one of the most intensely studied reactions (see Volume 2, Chapters 1.5–1.7) in contemporary organic chemistry, in terms of mechanism, stereochemical outcome and practical application, and therefore this work is relevant in the context of the Darzens condensation. Very recently, this technology has been applied to the Darzens condensation, making available a new asymmetric stereocontrolled epoxide synthesis, and this work is discussed in Section 1.13.7.2.

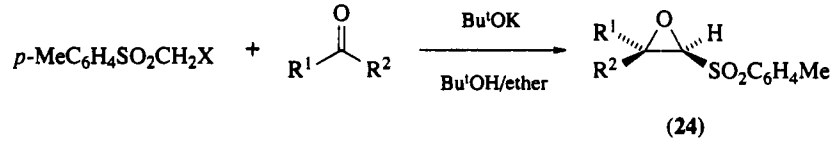
1.13.3 CONDENSATIONS EMPLOYING ANIONS STABILIZED BY SUBSTITUENTS OTHER THAN SIMPLE ESTERS

1.13.3.1 Sulfur-containing Groups

1.13.3.1.1 Sulfones

A large amount of effort has been devoted to studying Darzens condensations employing anions stabilized by substituents other than ester groups. Several sulfur-containing functional groups have been investigated. Chloro- and bromo-methyl *p*-tolyl sulfone condense with a variety of aldehydes and ketones in the presence of potassium *t*-butoxide to afford α,β-epoxy sulfones (**24**) in good to excellent yield

(equation 8; Table 3).[17] These reactions afford exclusively epoxides in which the sulfone group is *trans* to the larger group of the electrophile. It is postulated that the cyclization step is rate-determining (initial nucleophilic attack on aldehyde or ketone being rapidly reversible), and that the transition state (**25**) leading to the observed *trans* products is of lower energy than (**26**) for steric reasons. It is suggested that solvation of the highly polarized sulfonyl group also may be a contributing factor, pointing the *p*-tolyl group toward the *cis* substituent on the adjacent carbon atom and thereby enhancing the negative steric interaction in (**26**; Figure 2).

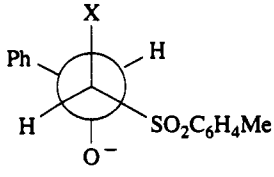


(8)

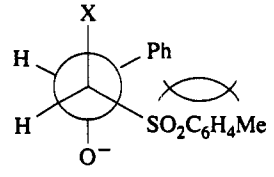
(**24**)

Table 3 Preparation of α,β-Epoxy Sulfones by the Darzens Condensation (equation 8)[17]

Halo sulfone	*Carbonyl compound*	*Yield of epoxy sulfone (24) (%)*
p-$MeC_6H_4SO_2CH_2Cl$	Benzaldehyde	95
p-$MeC_6H_4SO_2CH_2Cl$	Acetaldehyde	53
p-$MeC_6H_4SO_2CH_2Cl$	Acetone	80
p-$MeC_6H_4SO_2CH_2Cl$	Benzophenone	57
p-$MeC_6H_4SO_2CH_2Cl$	Cyclohexanone	77
p-$MeC_6H_4SO_2CH_2Br$	Benzaldehyde	92
p-$MeC_6H_4SO_2CH_2Br$	Benzaldehyde	91
p-$MeC_6H_4SO_2CHClMe$	Acetone	77



(**25**)



(**26**)

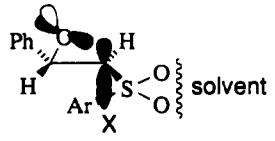
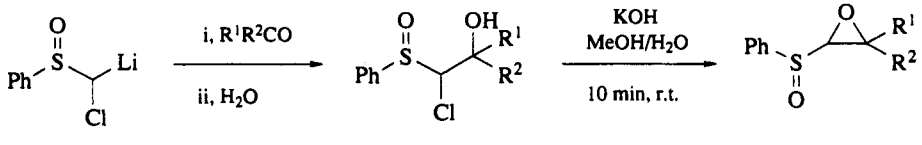


Figure 2 Solvation of the sulfonyl group, enhancing the negative steric interaction in (**26**)

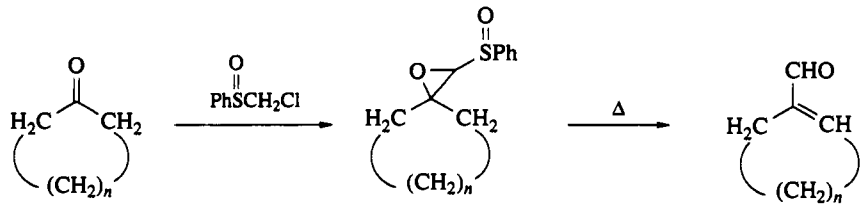
1.13.3.1.2 Sulfoxides

Generation of the sulfinyl carbanion of chloromethylphenyl sulfoxide (Bu^nLi/THF, −78 °C), followed by treatment with cyclohexanone, acetone or benzophenone, affords the corresponding chlorohydrin (**27**) in good yield (68–79%).[18] Treatment of the cyclohexanone or acetone adducts with methanolic KOH provides the α,β-epoxy sulfoxides in yields of greater than 90% (Scheme 7). Each of the halohydrin products appeared to be a single diastereomer, although the relative stereochemistry was not assigned.



(**27**) (**28**)

Scheme 7

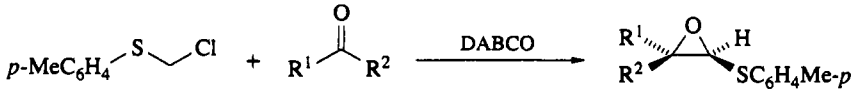


Scheme 8

The α,β-epoxy sulfoxides available using this protocol are important intermediates for several synthetic methodologies.[19] For example, they give upon thermal rearrangement α,β-unsaturated aldehydes and thus represent the pivotal intermediate in a two-step procedure for the one-carbon homologation of carbonyl compounds (Scheme 8).[20]

1.13.3.1.3 Sulfides

In an attempt to further extend the foregoing methodology to include the preparation of α,β-epoxy sulfides, the condensation of chloromethyl *p*-tolyl sulfide and benzaldehyde using a protocol similar to that employed successfully in the sulfone case (Bu^{t}OK) gave only poor conversion to the desired epoxide.[21] However, addition of the hindered amine base 1,4-diazabicyclo[2.2.2]octane (DABCO) results in the formation of the isomeric expoxides (**29**) in good yield (equation 9). In the case of benzaldehyde, the *cis*-epoxide predominates over the *trans*-epoxide (**29b**; 82% *versus* 18%), while in the corresponding condensation with pivalaldehyde, the only epoxy sulfide obtained is the *cis* isomer (**29c**). Several attempts to effect an analogous reaction with ketones were unsuccessful; formation of (**30**) (displacement–elimination) becomes the favored process (equation 10).

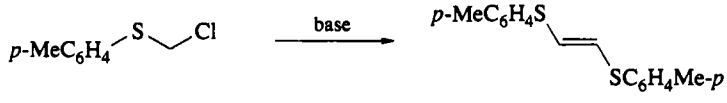


(9)

(**29a**) R^1 = Ph; R^2 = H

(**29b**) R^1 = H; R^2 = Ph

(**29c**) R^1 = H; R^2 = Bu^t

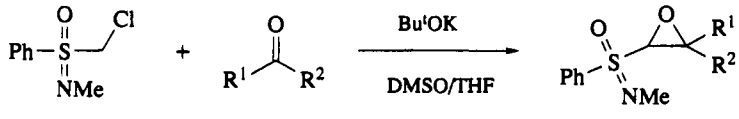


(10)

(**30**)

1.13.3.1.4 Sulfoximines

The α-halo sulfoximine (**31**) reacts with benzaldehyde and several ketones to afford epoxy sulfoximines (equation 11; Table 4).[22] The products (**32a**), (**32b**) and (**32c**) are each mixtures of two diastereomers due to the contiguous stereocenters at sulfur and the α-carbon atom. Product (**32c**) is a diastereomeric mixture in which the *t*-butyl and sulfoximino groups are predominantly (90%) *cis*. The epoxy sulfoximines (**32**) were viewed as potential intermediates in a homologation sequence for alde-

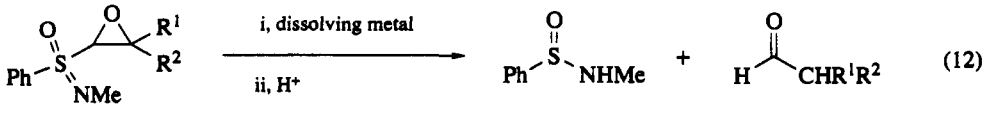


(11)

(**31**) (**32**)

Table 4 Condensations of (31) with Carbonyl Compounds Giving Epoxy Sulfoximines[22]

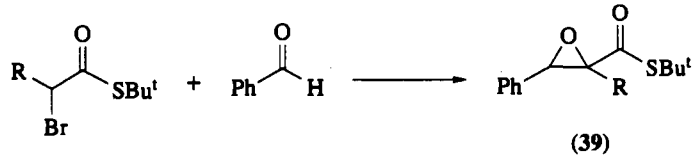
R^1	R^2	*Product*	*Yield* (%)
Me	Me	(32a)	81
—(CH$_2$)$_5$—		(32b)	75
—(CH$_2$)$_2$CHBu^t(CH$_2$)$_2$—		(32c)	50
H	Ph	(32d)	75

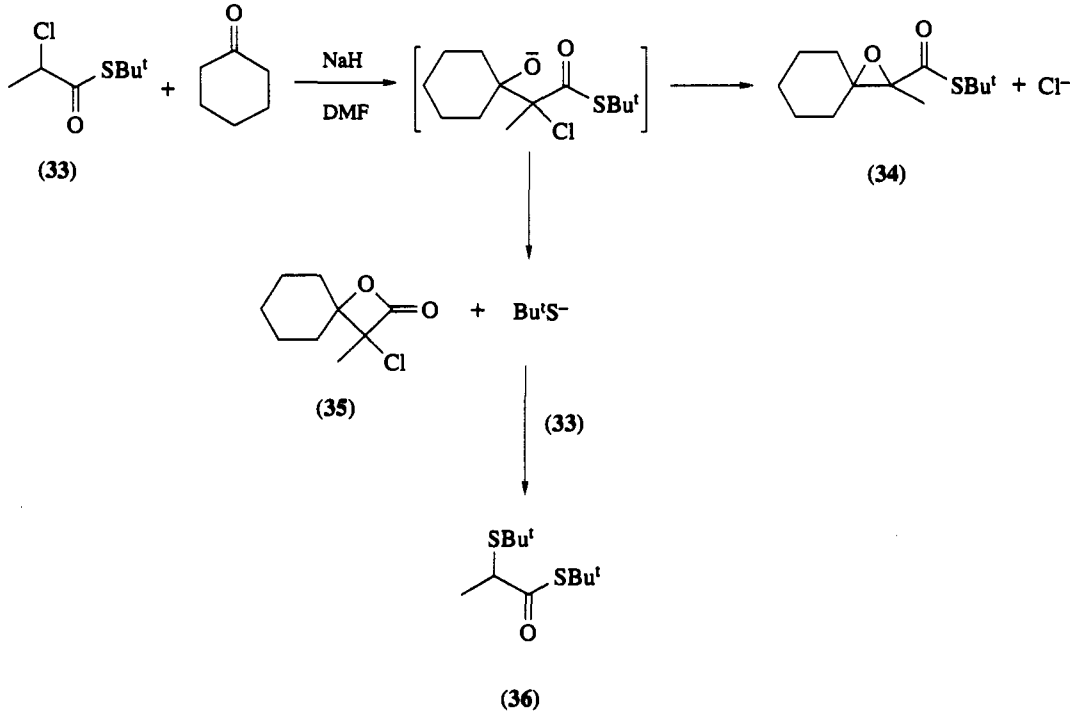


hydes and ketones (equation 12). Several attempts to achieve this transformation, however, were unsuccessful.

1.13.3.1.5 Thiol esters

α-Halo thiol esters also undergo Darzens condensations, providing a method for the synthesis of *S*-alkyl glycidic thiol esters (equation 13).[23] In the formation of glycidic thiol esters, it is important to use nonnucleophilic bases such as NaH or lithium hexamethyldisilylamide (LHMDS) and polar aprotic solvents such as THF or DMF. It is also noted that α-bromo thiol ester reactants are usually preferable to

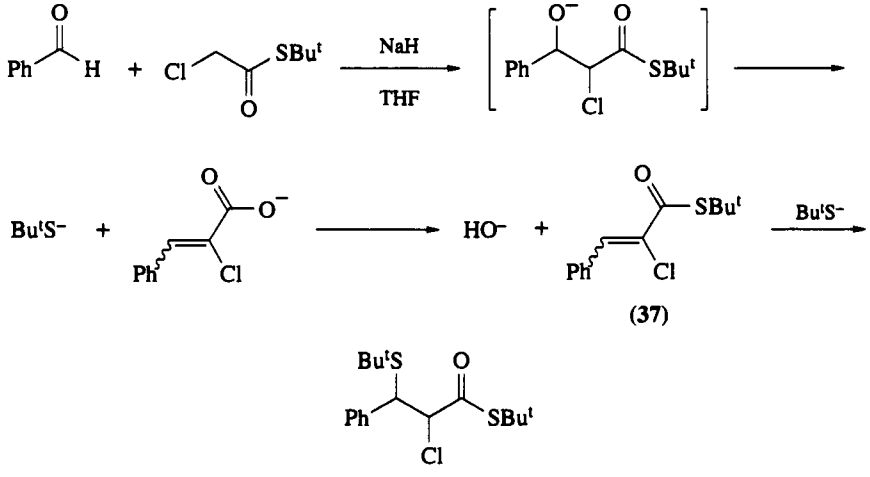




Scheme 9

the corresponding α-chloro thiol esters. In the reaction of cyclohexanone with *S*-*t*-butyl 2-chloropropanethioate (**33**) in NaH/DMF, the thioglycidate (**34**) is obtained in a yield of only 15% along with the two by-products (**35** and **36**; Scheme 9). The formation of the β-lactone (**35**) suggests that an intramolecular nucleophilic acyl substitution reaction is competitive with epoxide formation; the liberated thiolate anion is trapped by the starting substrate (**33**), resulting in the formation of (**36**). Replacing (**33**) with the corresponding α-bromo derivative results in an improved yield (60%) of the thioglycidate (**34**). Presumably, the enhanced leaving group ability of the bromide substituent enhances epoxide formation in the intermediate halo alkoxide relative to alternative reaction pathways. The competing intramolecular displacement of thiolate to afford a β-lactone, which is not a problem in the formation of glycidic (oxygen) esters, is a manifestation of the improved leaving group ability of thiolate relative to alkoxide.

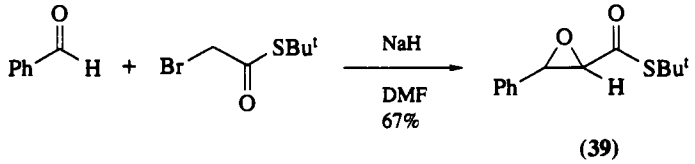
Another potential side reaction in the thiol ester version of this condensation may be more likely than in the simple ester analogy, due to the greater acidity of the α-protons in the thiol ester. The reaction of benzaldehyde with *S*-*t*-butyl 2-chloroethanethioate in NaH/THF gives several products, including 2-chlorocinnamic acid and a diastereomeric mixture of (**38**); (**38**) presumably arises from the elimination product (**37**). A competing elimination process may also explain the result that no thioglycidate (**39**) was obtained in the attempted condensation of benzaldehyde with *S*-*t*-butyl 2-chloroethanethioate using NaH/DMF (Scheme 10). In contrast, replacing 2-chloroethanethioate with the corresponding bromide affords the thioglycidate (**39**) in 67% yield (70:30, *cis*:*trans*; equation 14). Again, bromide presumably facilitates the epoxide-forming intramolecular cyclization at the expense of competing intermolecular side reactions.



(**37**)

(**38**)

Scheme 10

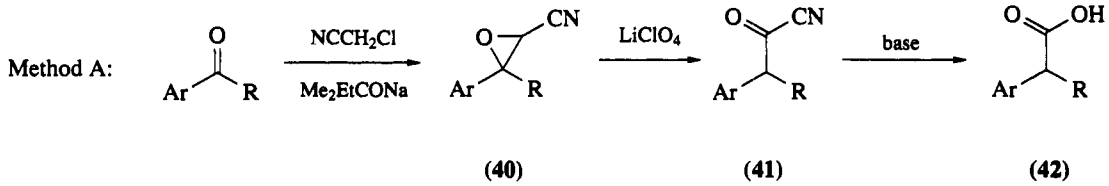


(**39**) (14)

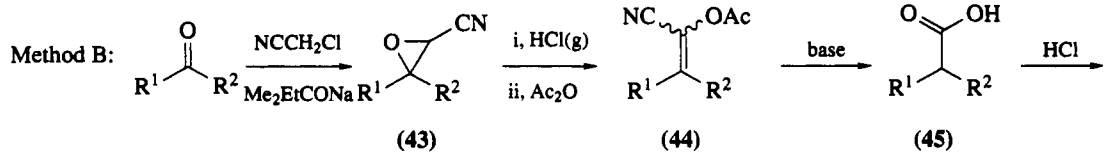
1.13.3.2 Nitriles

The Darzens condensation, as a source of glycidonitriles,[24] is a pivotal step in a method for the one-carbon homologation of ketones to afford carboxylic acids (Scheme 11).[25] Treatment of a ketone with chloroacetonitrile in the presence of sodium *t*-amyl oxide affords the corresponding glycidonitrile in excellent yield (greater than 95% after distillation). Crude β-arylglycidonitriles (**40**) are converted to α-ketonitriles upon treatment with lithium perchlorate; subsequent basic hydrolysis provides the acid (**42**; method A). Alternatively, heating (**41**) with an amine provides the corresponding amide. A less direct route is employed for aliphatic ketones. Exposure of the glycidonitrile (**43**) to dry HCl gives an α-hydroxy-β-chloronitrile which is acetylated and dehydrohalogenated to provide an α-acetoxyacrylonitrile (**44**). Basic hydrolysis affords the desired carboxylic acid (**45**; method B); the α-acetoxyacrylonitriles

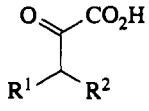
(**44**) may also be converted to α-keto carboxylic acids (**46**) upon treatment with cold mineral acid. The results for several ketones are shown in Table 5. In contrast to the clean addition of HCl to glycidonitriles, it was found that treatment of glycidic esters with HCl affords a mixture of α-hydroxy-β,γ-unsaturated esters and α-hydroxy-β-chloro esters (equation 15). It is suggested that this propensity for glycidic esters to form elimination products may be due to intramolecular deprotonation of the incipient tertiary carbonium ion by the carboalkoxy group.



(**40**) (**41**) (**42**)



(**43**) (**44**) (**45**)

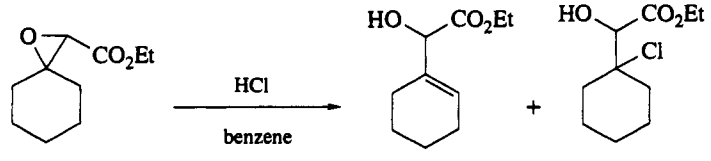


(**46**)

Scheme 11

Table 5 Carboxylic Acids Prepared from Ketones[25]

Ketone	*Product*	*Yield (%) Method A*	*Method B*
p-Isobutylacetophenone	2-(*p*-Isobutylphenyl)propionic acid	72	73
α-Tetralone	1,2,3,4-Tetrahydro-1-naphthoic acid	47	68
Cyclohexanone	Cyclohexanecarboxylic acid		57
Cyclopentanone	Cyclopentanecarboxylic acid		51
2-Pentanone	2-Methylpentanoic acid		57

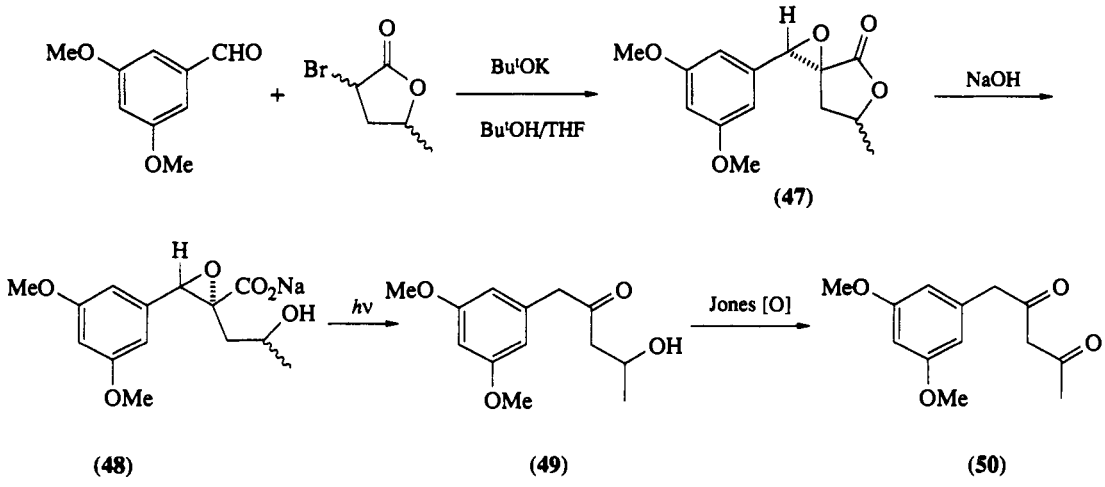


(15)

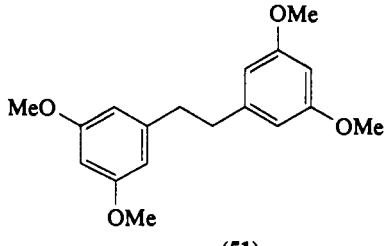
1.13.3.3 Lactones

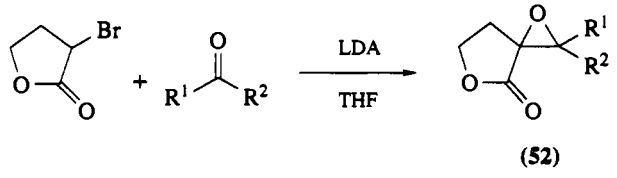
The Darzens condensation of aldehydes with α-halo lactones has been investigated as a method for a homologation of the type ArCHO → $ArCH_2COCH_2COMe$.[26] Addition of an equimolar mixture of 3,5-dimethoxybenzaldehyde and α-bromo-γ-valerolactone (mixture of *cis* and *trans* isomers) to a solution of Bu^tOK affords the epimeric mixture of lactones (**47**) in 78% yield with high stereoselectivity (addition to the carbonyl). Saponification followed by irradiation affords the decarboxylated β-hydroxy ketone (**49**) in 62% yield, accompanied by the secondary photolysis product (**51**).[27] Oxidation of (**49**) with Jones' reagent affords the diketone (**50**), characterized as its copper(II) chelate (Scheme 12). Methodology has

been described for the preparation of tetrasubstituted epoxy lactones (**52**) involving the Darzens reaction of α-bromobutyrolactone and ketones (equation 16).[28]



Scheme 12

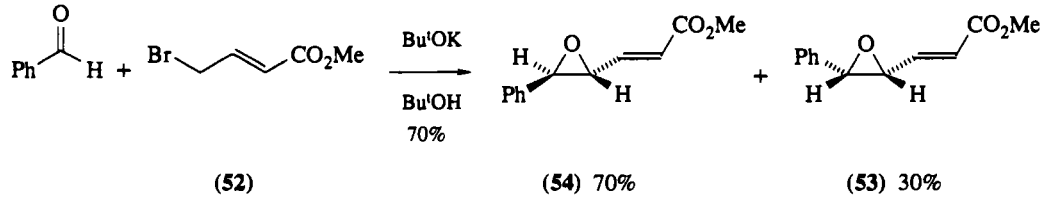




(16)

1.13.3.4 Vinylogous Esters

A vinylogous Darzens condensation has been reported.[29] Treatment of benzaldehyde and methyl 4-bromocrotonate with Bu'OK/Bu'OH (0 °C, 40 min) affords a mixture of the *cis*- and *trans*-epoxides (**53**) and (**54**) in 70% yield (equation 17). It is noted that compounds (**53**) and (**54**) could have been formed either by γ-alkylation of (**52**) or by α-alkylation followed by rearrangement. However, it is suggested that the lack of formation of the dihydrofuran derivatives (**55** and **56**; Scheme 13), as well as the prolonged reaction times and/or elevated temperature generally required to induce rearrangement, argue against the α-alkylation–rearrangement mechanism.



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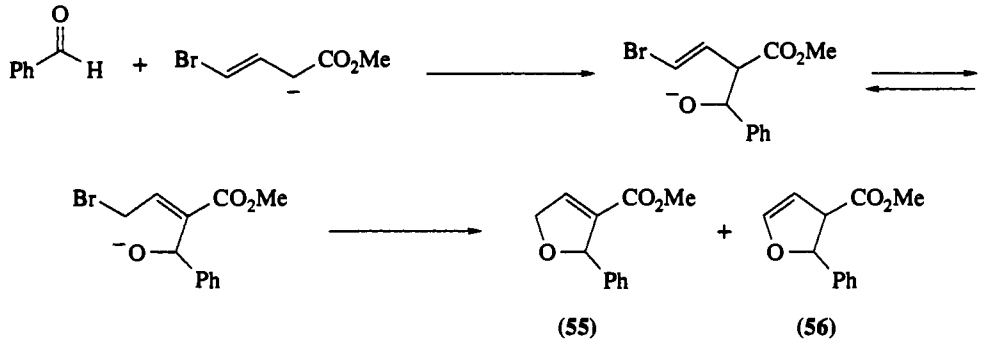
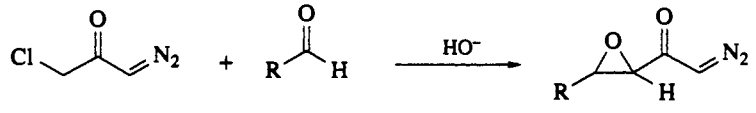


(55) (56)

Scheme 13

1.13.3.5 Diazo Ketones

The condensation of 1-chloro-3-diazopropanone (**57**) with aldehydes provides epoxy diazo ketones (equation 18).[30] Treatment of a methanolic solution of (**57**) and benzaldehyde, in a stoichiometric ratio, with aqueous sodium hydroxide furnishes 1-diazo-3,4-epoxy-4-phenyl-2-butanone (**59a**) in 69% yield; the *trans*-epoxide is obtained stereoselectively, analogous to the Darzens condensation of benzaldehyde and chloroacetone.[31] The reaction is reported to proceed to give also the diazo ketones (**59b–59e**), and the epoxides obtained are exclusively of the *trans* configuration.[30]



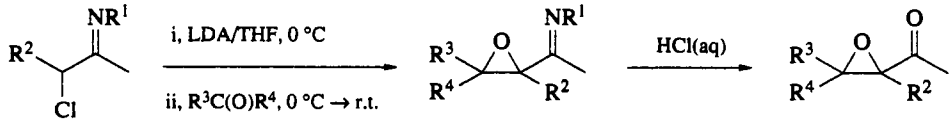
(18)

(**57**) (**58**)

(**59a**) R = Ph
(**59b**) R = *p*-$NO_2C_6H_4$
(**59c**) R = *p*-$MeOC_6H_4$
(**59d**) R = $PhCH\overset{t}{=}CH$
(**59e**) R = 2-thienyl

1.13.3.6 Imines

In general, α-halogenated ketones are poor substrates in the Darzens condensation, except when they lack α′-hydrogen atoms (for example, phenacyl halides). The unsuitability of α-halo ketones is due to their propensity to undergo undesirable side reactions such as the Favorskii rearrangement (*via* 1,3-dehydrohalogenation), elimination (1,2-dehydrohalogenation) or nucleophilic substitution under basic conditions. In an effort to circumvent these problems, *N*-alkyl-α-haloimines, which have been previously shown to be useful as masked α-halocarbonyl compounds,[32] were investigated for their utility in the Darzens condensation.[33] α-Chloroimines (**60**), prepared by condensation of the corresponding α-chloro ketones with a primary amine in the presence of titanium tetrachloride,[34] are converted into 1-aza-3-chloroallylic anions upon treatment with LDA.[32] These anions react cleanly with ketones and aldehydes, generating 2-imidoyloxiranes (**61**) in high yield (Scheme 14; Table 6); the intermediate noncyclized



(**60**) (**61**) (**62**)

Scheme 14

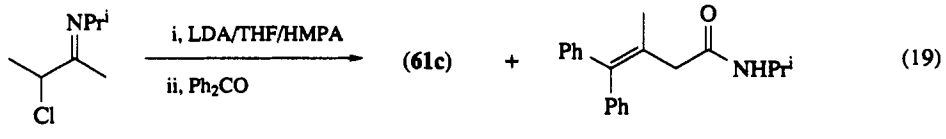
Table 6 Preparation of 2-Imidoyloxiranes (**61**)[33]

Entry	R^1	R^2	R^3	R^4	*Yield* (%)
(**61a**)	Pr^i	Me	Me	Me	80
(**61b**)	Pr^i	Me	Ph	H	81
(**61c**)	Pr^i	Me	Ph	Ph	80–90[a]
(**61d**)	Pr^i	Ph	Me	Me	92
(**61e**)	Pr^i	Ph	Me	Et	95[b]
(**61f**)	C_6H_{11}	Me	Ph	Ph	92

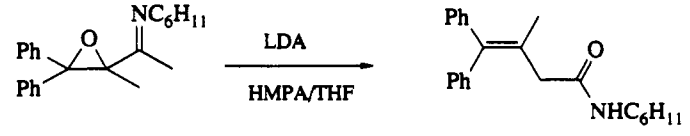
[a] In the presence of HMPA and greater than 100 mol % of LDA, compound (**63**) was also isolated. [b] A mixture (7:3) of *cis* and *trans* isomers is formed; isomeric assignments were not determined.

chloroimines could not be isolated. Treatment of the imidoyloxiranes with aqueous hydrochloric acid (2M HCl, r.t., 1 d) provides the corresponding 2-acyloxiranes (**62**).

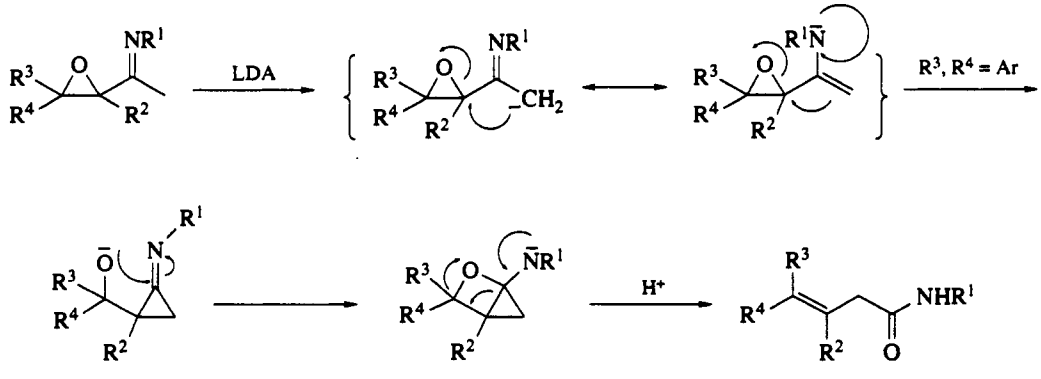
Formation of oxiranes (**61**) proceeds smoothly when aliphatic ketones or benzaldehyde are employed as the carbonyl substrates. When greater than 100 mol % of LDA is used for the deprotonation of (**60**; $R^1 = Pr^i$; R^2 = Me) in the presence of HMPA and 200 mol % of benzophenone is added to the resulting anion, the oxirane (**61c**; Table 6) is formed in 80% yield accompanied by the unsaturated amide (**63**), obtained in 15% yield (equation 19). Rearranged amides, such as (**63**), are formed only when benzophenones are used as the electrophiles; if only 100 mol % of LDA is employed in the deprotonation step, (**61c**) is obtained exclusively. When 200 mol % of LDA is utilized in this step, unsaturated amides, analogous to (**63**), are obtained in 26–65% yield; these butenamides are isolated in significant yield only if HMPA is present in the reaction medium. The geminal diphenyloxirane (**61g**) was shown to be a probable intermediate in the formation of the corresponding rearrangement product (**64**). Treatment of (**61g**) with LDA in HMPA/THF affords butenamide (**64**) in 25% yield as the only isolable product (equation 20).



(**60**) (**63**) (19)



(**61g**) (**64**) (20)

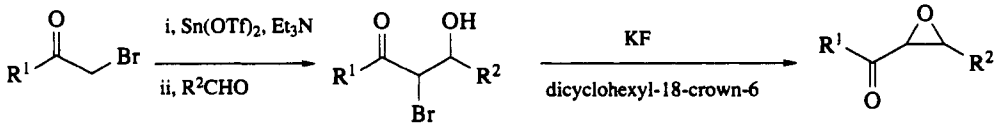


Scheme 15

A mechanistic rationale for the formation of the butenamides is shown in Scheme 15. Apparently, base-induced intramolecular cleavage of the oxirane does not occur in alkyl-substituted epoxides (**61**). However, this pathway becomes important for activated diaryl derivatives. The proposed process is somewhat analogous to the Favorskii rearrangement of α-halo ketones, in this case the geminal diaryl activated epoxide leaving group being analogous to the halogen leaving group. It is noted that α-halo imines[35] as well as α,β-epoxy ketones[36] have been shown to undergo base-induced Favorskii rearrangements.

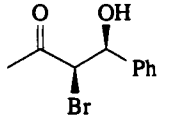
1.13.3.7 Ketones

trans-β-Substituted-α,β-epoxy ketones are obtained with reasonable facility by hydrogen peroxide epoxidation of α,β-unsaturated ketones; however, *cis*-β-substituted-α,β-epoxy ketones cannot be prepared by this procedure. Mukaiyama and coworkers have developed a two-step procedure for the synthesis of such *cis*-epoxides involving a tin-mediated aldol reaction between α-bromo ketones and aldehydes, followed by treatment of the adduct with KF/dicyclohexyl-18-crown-6 to effect cyclization (Scheme 16).[37]

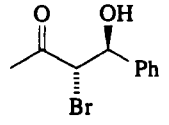


Scheme 16

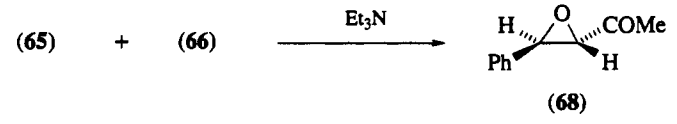
The stereoselectivity of the aldol reaction was initially investigated using bromoacetone and benzaldehyde, and it was found that THF is the best solvent for obtaining an optimum *syn:anti* ratio; the *syn*-bromohydrin (**65**; precursor to *cis*-epoxide) predominates in a ratio of 81:19. When the 81:19 mixture of (**65**) and (**66**) was treated with triethylamine, the *trans*-epoxide (**68**) was obtained exclusively in nearly quantitative yield (equation 21). After exploring several sets of reaction conditions aimed at avoiding the facile isomerization of (**65**) to the thermodynamically favored *anti* isomer (**66**), it was found that KF/dicyclohexyl-18-crown-6 induces cyclization with a minimum amount of isomerization. The overall results for the process of Scheme 16 for several reactants are shown in Table 7. It was found that, in each case, *cis*-epoxy ketones are obtained with moderate to high stereoselectivity.



(**65**)



(**66**)



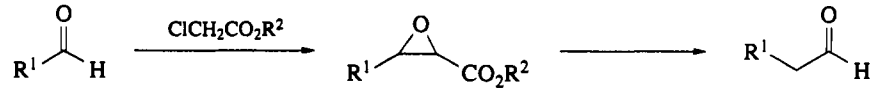
(**68**) (21)

Table 7 Synthesis of α,β-Epoxy Ketones *via* Divalent Tin Enolates[37]

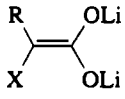
α-Bromo ketone	*Aldehyde*	*Yield of epoxy ketone (67) (%)*	*Cis (%)*	*Trans (%)*
$MeCOCH_2Br$	PhCHO	72	70	30
$MeCOCH_2Br$	$Ph(CH_2)_2CHO$	65	73	27
$PhCOCH_2Br$	$Ph(CH_2)_2CHO$	80	66	34
$PhCOCH_2Br$	Me_2CHCHO	80	65	35
Bu^tCOCH_2Br	PhCHO	64	>95	<5
Bu^tCOCH_2Br	$Ph(CH_2)_2CHO$	48	>95	<5
Bu^tCOCH_2Br	Me_2CHCHO	47	>95	<5

1.13.3.8 Carboxylic Acids

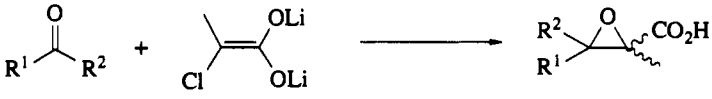
A major complication in the use of glycidic esters as precursors to aldehydes (homologation sequence shown in Scheme 17) involves premature epoxide cleavage during ester hydrolysis. In an effort to obviate this complication, the use of dianions of α-halocarboxylic acids in place of monoanions of esters was investigated. This procedure produces glycidic acids directly, avoiding the potential problems associated with the ester hydrolysis.[38] The dianions (**69**)–(**71**), generated using LDA in THF at –80 °C, were studied in condensation reactions with aldehydes and ketones. The results for the addition of (**70**) to several carbonyl compounds (equation 22) are shown in Table 8. The yields of product (**72**) shown are those for the isolation of the corresponding methyl glycidates obtained by treatment of (**72**) with diazomethane. The glycidic acids are difficult to isolate and purify; when used in a homologation sequence, they are decarboxylated directly with as little handling as possible. Dianion (**70**) reacts quite efficiently with acetophenone to afford, after methylation, methyl glycidate in 93% yield. If the reaction mixture, at –80 °C, is poured into aqueous acid 30 s after the addition of acetophenone, the only product isolated after work-up and methylation is the uncyclized α-chloro-β-hydroxy methyl ester (2:3 diastereomeric mixture, 90% yield). The alkoxide does not close to the epoxide at –80 °C, even after 4 h. When the reaction mixture is allowed to warm, epoxide begins to appear at *ca.* –15 °C, and almost complete conversion occurs by the time the reaction mixture reaches 25 °C. To assess steric effects, the condensations of (**70**) with diisopropyl ketone and di-*t*-butyl ketone were evaluated. Addition to diisopropyl ketone occurs reasonably efficiently, furnishing the corresponding methyl glycidate in 77% yield, after treatment with diazomethane. This yield is somewhat lower than that obtained with methyl ethyl ketone (96%), suggesting a steric effect. Di-*t*-butyl ketone fails to react. The yields (37–79%) obtained with the dianion (**71**) are consistently lower than those obtained with (**70**), perhaps reflecting the increased bulk of (**71**). Significantly lower yields (38–59%) are obtained with the dianion (**69**) relative to both (**70**) and (**71**). The decreased yields are due to an enhanced propensity for condensation of the dianion with the monoanion of α-chloroacetic acid as compared with the analogous reactions for (**70**) and (**71**).



Scheme 17



(**69**) R = H; X = Cl
(**70**) R = Me; X = Cl
(**71**) R = Pr^i; X = Br



(22)

(**70**) (**72**)

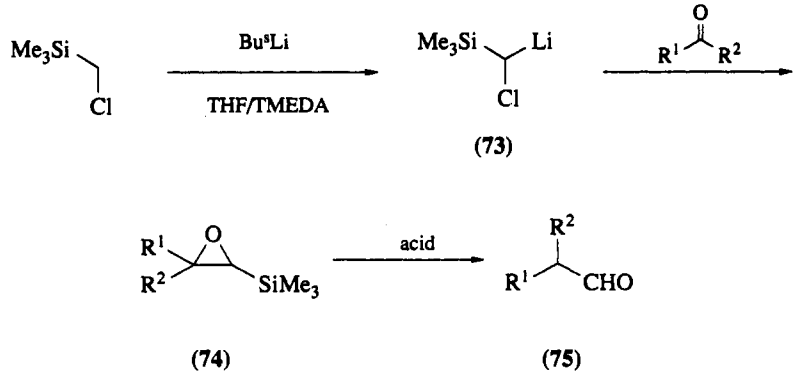
Table 8 Addition of Dianion (**70**) to Carbonyl Compounds[38]

Carbonyl compound		*Yield of methyl glycidate* (%)	*Cis* (%)	*Trans* (%)
R^1	R^2			
Ph	Me	93	65	35
Ph	Ph	76		
Et	Me	96	50	50
—(C_5H_{10})—		74		
—(C_4H_8)—		47		
Pr^i	Pr^i	77		
Bu^t	Bu^t	0		
Ph	H	90	4	96
Et	H	34	33	67

The decarboxylation of the glycidic acids obtained in this study was studied under various pyrolytic and catalytic conditions; although moderate to good yields of product could be obtained, the overall synthetic potential of the homologation sequence shown in Scheme 17 remains limited due to the lack of a general method for mild and rapid decarboxylation.

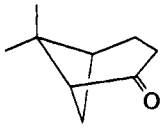
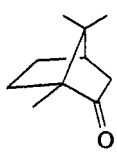
1.13.3.9 Silicon

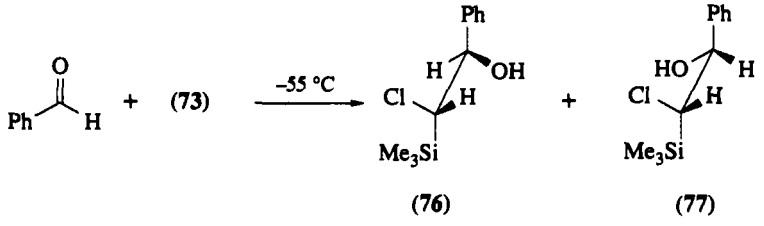
A very useful methodology that accomplishes the overall transformation envisaged in Scheme 17 involves the addition of an α-chloro-α-trimethylsilyl carbanion to carbonyl compounds in a Darzens-type condensation, followed by hydrolysis of the resulting α,β-epoxysilane (Scheme 18).[39] The anion (**73**) is generated by treatment of chloromethyltrimethylsilane with *s*-butyllithium in THF containing 100 mol % of TMEDA. Table 9 shows the results of the reaction of several carbonyl compounds with (**73**) to give epoxysilanes. If the reaction of (**73**) and benzaldehyde is quenched at –55 °C, a mixture of the chlorohydrins (**76**) and (**77**) is isolated (equation 23). The *threo* isomer (**77**) is the major component of this mixture; treatment of (**77**) with sodium hydride (THF, 50 °C) affords only the *cis*-epoxide (**79**). Elimination of trimethylsilanol, to afford vinyl chlorides, is not observed. Warming the mixture of (**73**) and benzaldehyde from –55 °C to 20 °C causes the initially formed chlorohydrins (**76**) and (**77**) to cyclize to the corresponding *trans*- and *cis*-epoxides (**78**) and (**79**), respectively (equation 24). The *threo*-chlorohydrin (**77**) is converted more slowly to the *cis*-epoxide (**79**) than the *erythro* isomer (**76**) is converted to the *trans*-



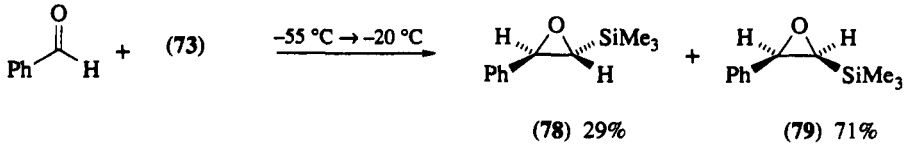
Scheme 18

Table 9 Epoxysilanes from the Condensation of α-Chloro-α-trimethylsilyl carbanion (**73**) and Carbonyl Compounds[39]

Carbonyl substrate	*Yield of epoxysilane (74) (%)*	*Carbonyl substrate*	*Yield of epoxysilane (74) (%)*
Benzaldehyde	≥95	Butanal	≥75
Benzophenone	≥95	9-Fluorenone	≥60
Cyclohexanone	≥95	Cyclododecanone	≥70
4-*t*-Butylcyclohexanone	≥95	2-Adamantanone	≥90
Cholestanone	≥95	Cyclohex-2-enone	≥80
		Cyclopentanone	≥90
	≈40		
	≥20		



(23)

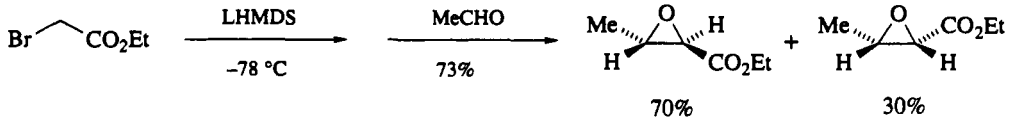


(24)

epoxide (**78**). All of the substrates shown in Table 9 react rapidly and cleanly with the anion (**73**) to give the corresponding α,β-epoxysilanes. The only limitations noted are that sterically hindered or easily enolizable carbonyl groups cause decreased yields. In all cases, hydrolysis of the α,β-epoxysilanes affords a clean rapid conversion to the corresponding aldehydes (**75**; Scheme 18), thus providing a simple and versatile homologation sequence.

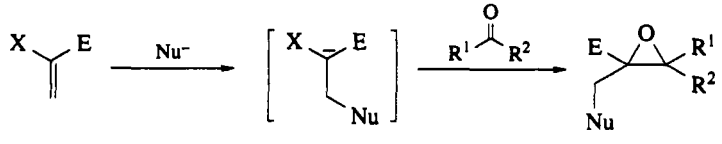
1.13.4 MISCELLANEOUS MODIFICATIONS

Early attempts to utilize acetaldehyde and monosubstituted acetaldehyde derivatives in the Darzens reaction were unsuccessful, presumably due to competitive base-catalyzed self-condensations of the aldehydes. It was subsequently reported that generation of the requisite bromo ester enolates with LHMDS at −78 °C provides a species which reacts with a variety of aldehydes and ketones to afford glycidic esters in good to excellent isolated yields (equation 25).[40]



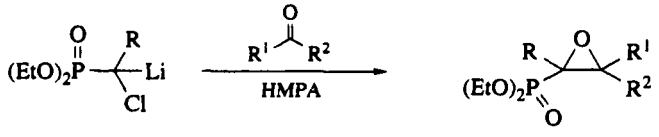
(25)

An interesting alternative procedure for the generation of Darzens intermediates is illustrated in equation (26).[41] In this method such anions are generated by the conjugate addition of a nucleophile to an activated alkene. In the presence of a carbonyl compound, an epoxide is formed. This process has been developed as an annulation procedure.



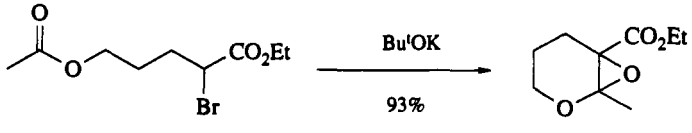
(26)

It has also been reported that diethyl 1-chloro-1-lithioalkanephosphonates react with carbonyl compounds in the presence of HMPA to give diethyl 1,2-epoxyalkanephosphonates (equation 27).[42]



(27)

An intramolecular variant of the Darzens reaction affords 2,7-dioxabicyclo[4.1.0]heptanes (equation 28).[43] Similar results are reported for nitrile, acetyl and sulfoxide derivatives.

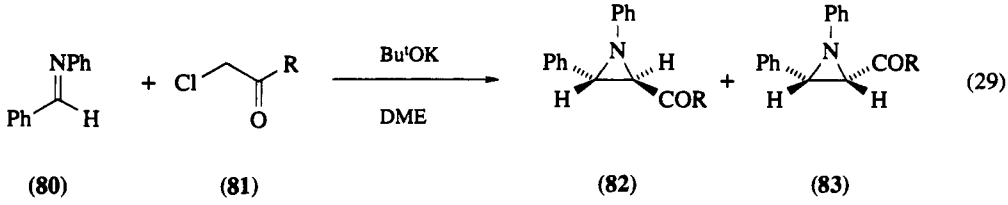


(28)

Studies on Darzens condensations involving substituted cyclohexanones have also been described.[44]

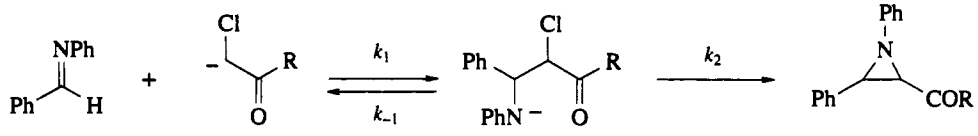
1.13.5 PREPARATION OF AZIRIDINES

A procedure has been developed which extends the Darzens synthesis to the preparation of aziridine esters and amides (equation 29).[45] Reaction of benzalaniline (**80**) and ethyl chloroacetate (in Bu^{t}OK/DME) results in the formation of the *trans*-aziridine (**82a**) in 29% yield; analysis of the crude reaction mixture showed no more than 10% of the isomeric *cis* adduct (**83a**). Similarly, condensation of 2-chloro-*N*,*N*-diethylacetamide and (**80**) affords aziridines (**82b**) and (**83b**) in 65% yield. However, in this case the *cis* isomer predominates (≈90:10, *cis:trans*). The formation of (**83a**; R = OEt) as the major product is consistent with the overlap control model suggested by Zimmerman. Apparently, the decreased stability of the amide (**81b**) enolate relative to the ester (**81a**) enolate causes k_2 (cyclization) to become greater than k_1 (addition; Scheme 19); it follows that the stereochemical outcome is determined in the initial aldol step, and steric arguments are advanced to explain this outcome.



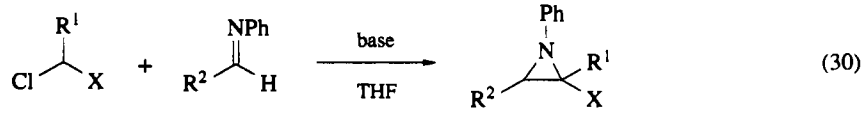
(**80**) (**81**) (**82**) (**83**)

a: R = OEt
b: R = NEt_2



Scheme 19

In a subsequent investigation, *t*-butyl esters were utilized to reduce competition from Claisen condensation; the more reactive *m*-chlorobenzalaniline was found to give slightly better yields of product than benzalaniline.[46] The reaction was also extended to the synthesis of nitrile derivatives (equation 30; Table 10). The stereochemical outcome of the reaction appears to be affected by the base (or corresponding cation) employed, depending on the X and R substituents. In the ester examples, when R^1 = H, only the



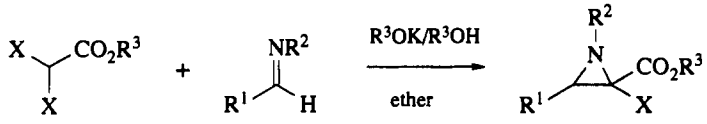
(**84**)

Table 10 Substituted Aziridines from Darzens Condensations[46]

R^1	R^2	X	*t* (°C)	*Yield* (%)	*Cis:trans ratio* (R^2 *and X substituents*) Bu^{t}OK	$(Me_3Si)_2NLi$
H	Ph	CO_2Bu^t	−50	85	30:70	>95:5
H	*m*-ClC_6H_4	CO_2Bu^t	−50	90	35:65	>95:5
Me	Ph	CO_2Bu^t	−15	60	30:70	30:70
Me	*m*-ClC_6H_4	CO_2Bu^t	−15	75	30:70	30:70
H	Ph	CN	−80	50	≈100% *cis*	80:20
H	*m*-ClC_6H_4	CN	−80	70	≈100% *cis*	80:20
Me	Ph	CN	−80	75	15:85	20:80
Me	*m*-ClC_6H_4	CN	−80	90	15:85	15:85

cis isomer is obtained with LHMDS, while the *trans* isomer predominates with Bu^{t}OK. In the nitrile examples, when R_1 = H, the *cis* isomer is formed exclusively with Bu^{t}OK and it is also predominant when LHMDS is the base. When R^1 = Me, the *trans* isomer is the major product in all examples, and the ratio is independent of the base. The mechanistic ramifications of these stereochemical results are not clear.

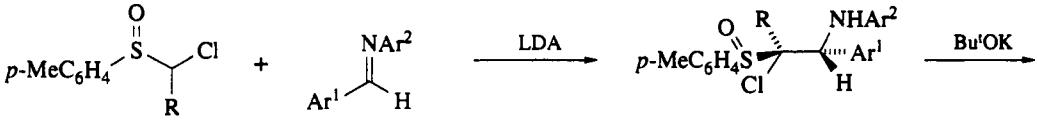
The reactions of aromatic imines with alkyl dichloroacetates in a protic medium afford highly functionalized 1,3-diarylaziridines (equation 31).[47] Excellent yields (65–96%) of 2-aziridine-2-chlorocarboxylic acid isopropyl esters (**87**; R^2 = Ph, R^3 = Pr^i, X = Cl) are obtained. However, the reaction is limited to aromatic imines in which both R^1 and R^2 are aryl substituents.



(31)

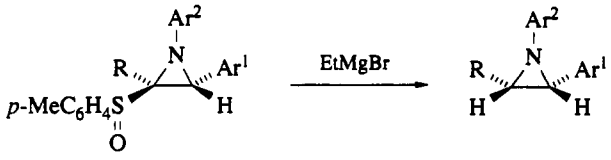
(87)

A method for the synthesis of *cis*-*N*-arylaziridines involves sequential condensation of a substituted chloro *p*-tolyl sulfoxide and an aromatic imine, cyclization with Bu^{t}OK and desulfinylation with ethylmagnesium bromide (Scheme 20).[48] Treatment of 1-chloroundecanyl *p*-tolyl sulfoxide with LDA (–40 °C) followed by benzalaniline (**89**; Ar^1 = Ar^2 = Ph) affords the corresponding crystalline adduct (**90**) as a single diastereomer (94% yield). Cyclization provides the sulfinylaziridine (**91**) in 87% yield; desulfinylation (–55 to –35 °C, 2 h) provides stereospecifically (retention) the *cis*-aziridine (**92**) in 95% yield. Several related examples are provided in which products are obtained stereospecifically in similar yields.



(88) (89) (90)

a: R = $Me(CH_2)_9$
b: R = $CH_2{=}CH(CH_2)_2$
c: R = Me



(91) (92)

Scheme 20

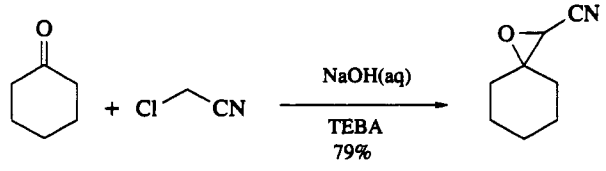
1.13.6 CONDENSATIONS UNDER MULTIPHASE CONDITIONS

1.13.6.1 Phase-transfer Conditions

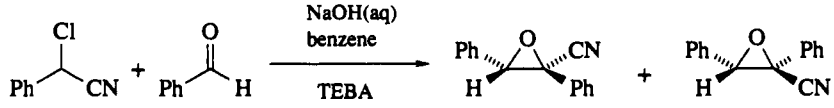
1.13.6.1.1 Esters, nitriles, sulfones and sulfonamides

Darzens condensation of chloroacetonitrile and carbonyl compounds to give glycidic nitriles can be carried out in the presence of aqueous sodium hydroxide and a quaternary ammonium catalyst, such as triethylbenzylammonium chloride (TEBA; equation 32).[49] In a subsequent study, interesting stereochemical control was obtained in an interfacial Darzens condensation.[50] Condensation of α-chlorophenylacetonitrile (**93**) with benzaldehyde, conducted in benzene in the presence of 50% aqueous sodium hydroxide and TEBA as a phase transfer catalyst, affords predominantly the *trans*-glycidonitrile (**94**) accompanied by the corresponding *cis* isomer (**95**; equation 33). Similar results are obtained when

catalytic dibenzo-18-crown-6 is employed instead of TEBA. In contrast, when the reaction is carried out without a quaternary ammonium salt, the *cis*- and *trans*-epoxides (**95**) and (**94**) are obtained in a ratio of approximately 1:1. The underlying rationale suggested for the observed stereoselectivity is shown in Scheme 21. It is proposed that the transition state (**96**) leading to the observed major *cis* product is stabilized to a larger extent relative to the corresponding transition state (**97**), leading to *trans*-epoxide at the phase boundary through interactions of the O^-, Cl and CN substituents located at the surface of the aqueous phase. This interpretation requires that the cyclization step is the rate-determining step for the reaction; the authors also note that in the two-phase condensation of chloroacetonitrile or α-chloropropionitrile with carbonyl compounds, in which the cyclization step is reportedly[51] the rapid step (under single-phase conditions), enhanced selectivity is not observed. It should be noted that one can also draw a transition state structure (**98**), leading to *trans* product (**94**), which appears to have stabilizing interactions similar to (**96**). However, (**98**) necessitates an interaction of a lipophilic phenyl substituent with the aqueous phase, perhaps destabilizing (**98**) relative to (**96**).

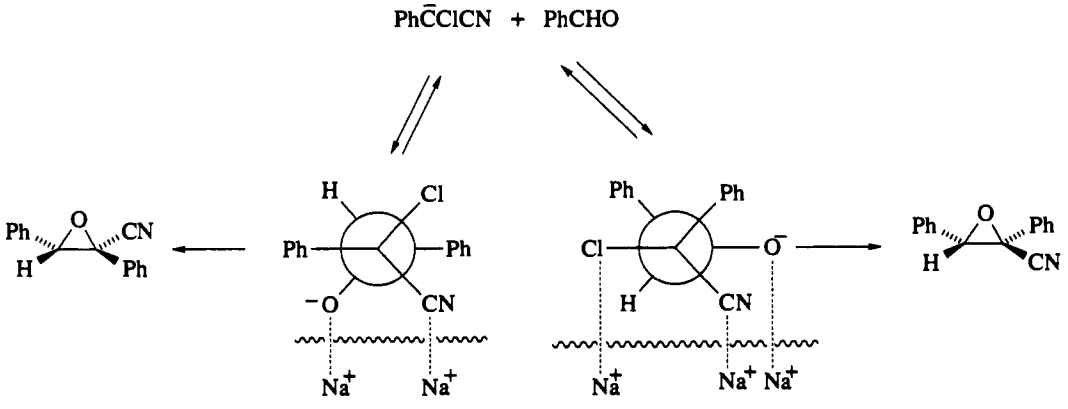


(32)



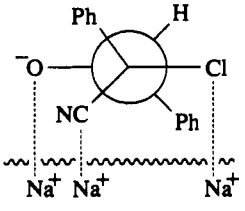
(33)

(**93**) (**94**) 90% (**95**) 10%



(**97**) (**96**)

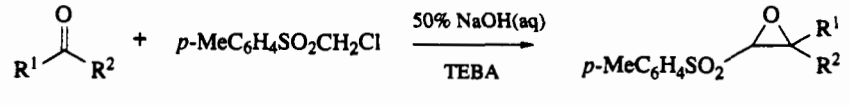
Scheme 21



(**98**)

α-Halo sulfones react with aldehydes and ketones under catalytic two-phase conditions (equation 34; Table 11) to give glycidic sulfones.[52a,53] For the aldehyde substrates employed, only *trans*-epoxides are

isolated. The sulfonamide (**100**) has also been shown to react in a highly stereoselective manner with aldehydes under phase-transfer conditions;[52b] only *trans*-1,2-epoxyalkanesulfonamides are obtained (equation 35).

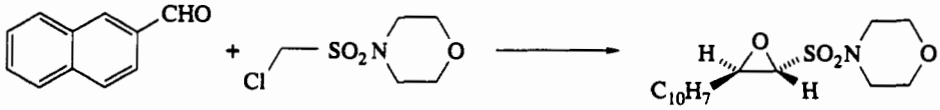


(34)

(**99**)

Table 11 Epoxy Sulfones (**99**) Obtained Under Phase-transfer Conditions[52a]

R^1	R^2	*Yield of (99) (%)*
Ph	Ph	90
Me	Me	91
Ph	H	60
Pr^i	H	65
—$(CH_2)_5$—		90

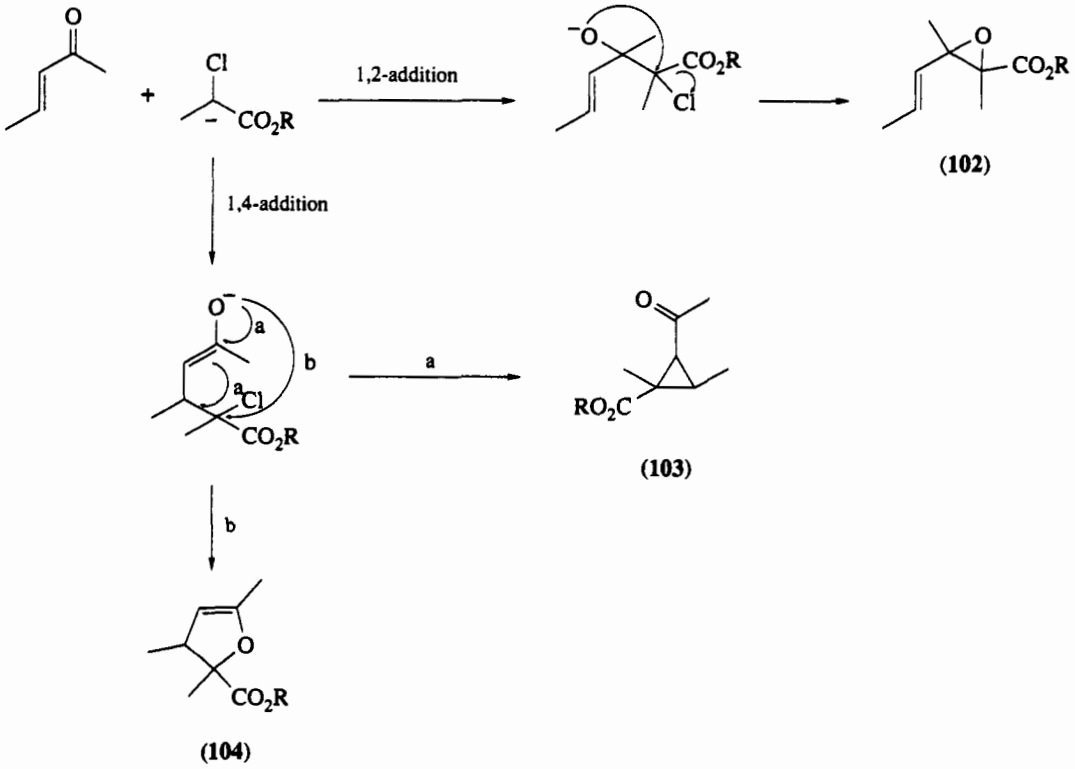


(35)

(**100**) (**101**)

1.13.6.1.2 Conjugated enones—preparation of cyclopropanes

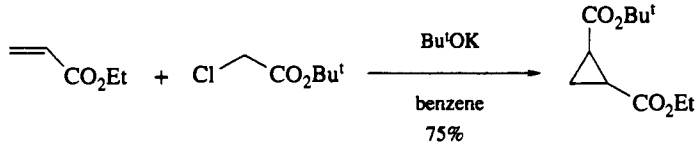
When conjugated enones are employed in Darzens-type condensations, three product types are possible, as shown in Scheme 22, depending on the initial site of addition as well as the mode of intra-



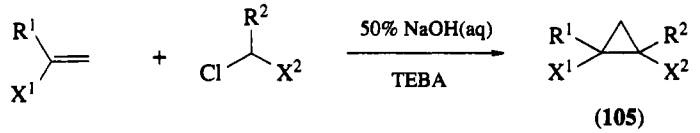
(**102**) (**103**) (**104**)

Scheme 22

molecular displacement.[54] In an early systematic investigation on this type of reaction,[55] it was found that under homogeneous conditions, simple α-halo esters afford cyclopropanes analogous to (**103**; equation 36). The reaction was demonstrated to give synthetically useful yields of substituted cyclopropanes from several electrophiles and a variety of α-halo esters. Subsequently, the reaction of electrophilic alkenes with α-chloronitriles and esters was investigated under phase-transfer catalytic conditions (equation 37).[56,57] The results are shown in Table 12. The cyclopropane derivatives are formed in good yield with a slight to moderate predominance of *trans* product. Normally, the Michael adducts cannot be isolated, because cyclization of the incipient carbanions is so rapid. However, phenyl vinyl sulfone and α-chloropropionitrile react under these conditions to afford primarily (**106**; 86% yield). The sulfone can be cyclized under more vigorous conditions.



(36)

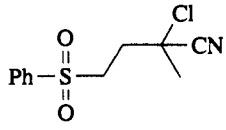


(37)

(**105**)

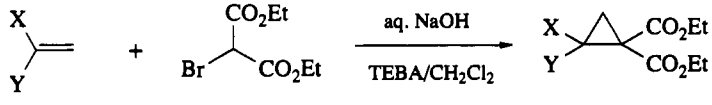
Table 12 Preparation of Cyclopropanes (***105***)[56]

R^1	R^2	X^1	X^2	*Yield of (**105**) (%)*	*Product ratio* *Cis (%)*	*Trans (%)*
H	H	CN	CO_2Bu^t	45	29	71
H	Me	CN	CN	75	46	54
H	Me	CO_2Ph	CN	67	24	76
H	Me	SO_2Ph	CN	7	32	68
Me	Me	CN	CN	75	45	55



(**106**)

The issue of 1,2- *versus* 1,4-addition, as shown in Scheme 22, in the phase transfer catalyzed (benzyltriethylammonium chloride; TEBA) version of this cyclopropanation reaction, was addressed in a more recent publication.[54] Simple α-halo esters do not react with acrolein, methyl vinyl ketone or 2-chloroacrylonitrile under the conditions examined. However several electrophilic alkenes do react with diethyl bromomalonate to give good yields of substituted cyclopropanes (equation 38; Table 13). The only side

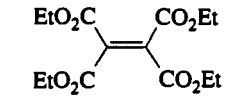


(38)

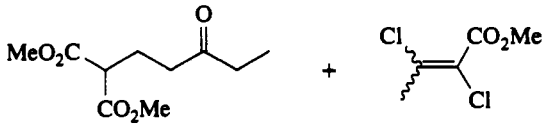
(**107**)

Table 13 Substituted Cyclopropanes from Diethyl Bromomalonate and Electrophilic Alkenes[54]

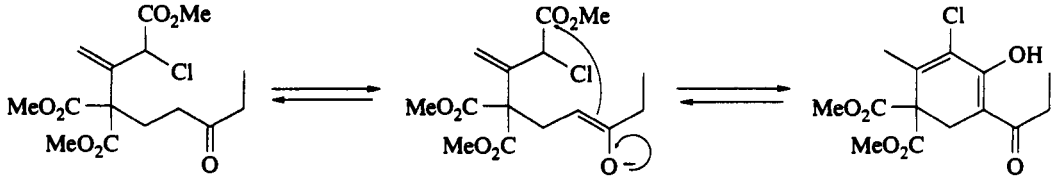
X	*Y*	*Yield of (**107**) (%)*
CHO	H	100
COMe	H	97
Cl	CN	75
Ph_3P^+	H	70
$(EtO)_2P(O)$	CO_2Me	65



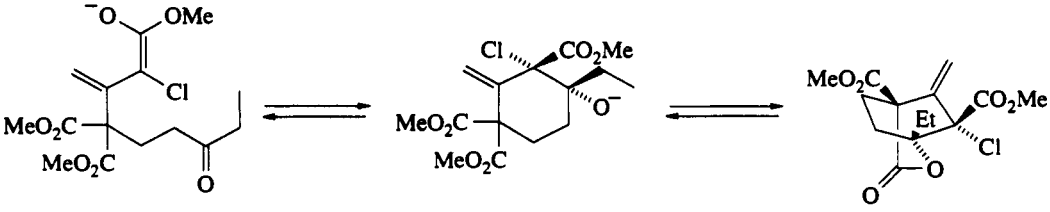
(108)



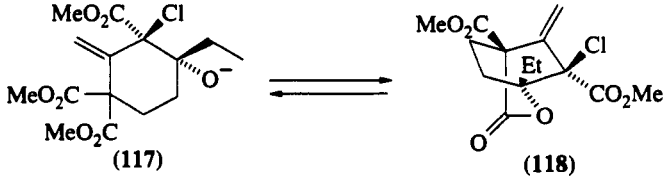
(109) (110)



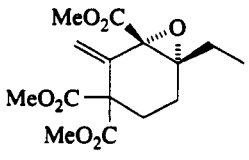
(111) (112) (113)



(114) (115) (116)



(117) (118)

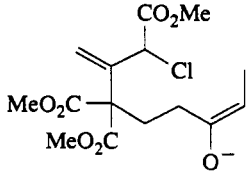


(119)

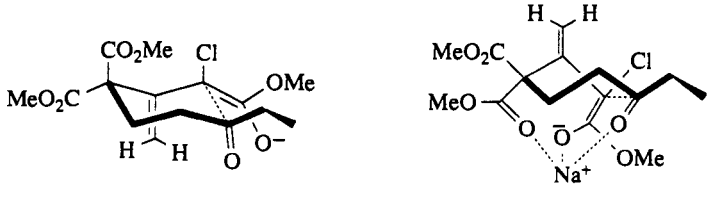
Scheme 23

product observed in these condensations is (**108**), derived from self-condensation of diethyl bromomalonate and subsequent dehydrobromination. Activated alkenes substituted at the β-position do not afford the desired cyclopropane products. Thus, this method, although useful for the preparation of certain substituted cyclopropanes, is somewhat limited due to lack of generality.

Another situation involving multiple electrophilic sites, although investigated under homogeneous conditions, emerged during the course of studies directed toward the synthesis of aklavinone, the aglycone of the potent antitumor antibiotic aclacinomycin.[58] The cyclohexadiene monoepoxide (**119**) was prepared as a potential synthon for the A ring of this natural product. The preparation of (**119**) utilized an intramolecular Darzens condensation as a key step and like the situation portrayed in Scheme 22, several viable regiochemical outcomes could be envisioned. The reaction (Scheme 23) was studied under several conditions, and its course was found to be highly dependent on the exact nature of the variables involved. Despite the complexities, the desired epoxide (**119**) is obtained efficiently under appropriate conditions. The Darzens reaction precursor (**111**) is obtained by condensation of the dichlorocrotonate (**110**) and ketomalonate (**109**) with potassium *t*-butoxide (70% yield). The solvent plays a critical role in determining the subsequent fate of this adduct. In the presence of methanol (**113**) is obtained as the major product; it is postulated that this outcome is due to stabilization of the ketone enolate (**112**) relative to the more delocalized ester dienolate (**114**) by the protic hydrogen-bonding solvent. Although the less-hindered enolate (**112a**) would also be predicted to be similarly stabilized under these conditions, no products derived from this species are observed, most likely because the malonate ester groups, six carbon atoms removed, are too sterically hindered. In polar aprotic solvents, such as DMF or DMSO which strongly solvate the counterion, the delocalized ester (**114**) is more stable than (**112**) or (**112a**). Steric factors thus determine the conformation of (**114**) and the transition states leading to (**115**) or (**117**). Molecular models indicate that steric interactions are minimized when (**114**) exists in the (*Z*)-(*S*)-*cis* conformation as shown in Figure 3a. In less polar solvents, such as diethyl ether or THF, the dienolate (**114**) is postulated to exist as a tight ion pair with the sodium cation, such that chelation of the cation by the ketone and ester carbonyl groups overcomes steric hindrance associated with the (*Z*)-(*S*)-*trans* dienolate. This chelation also controls the transition state conformation in the aldol addition (Figure 3b) leading to (**117**) in a boat conformation. Since the alkoxide and chloro substituents are not antiperiplanar, epoxide formation is precluded, and the lactone (**118**) is the major product. Chelation has a relatively lesser stabilizing effect on the transition states leading to (**116**) or (**119**), and only small quantities of these products are observed.



(**112a**)



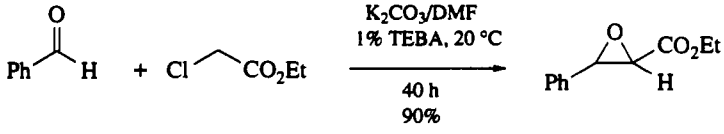
(a) (b)

Figure 3 (a) Transition state for (**114**) in polar solvents, leading to epoxide (**119**) through the chair conformation; (b) transition state for (**114**) in less-polar solvents, leading to lactone (**118**) through the boat conformation

1.13.6.2 Solid–Liquid Systems

Normally, the Darzens reaction of simple α-halo esters is carried out under anhydrous conditions, since in aqueous media or under phase-transfer catalysis conditions the esters are prone to hydrolysis. Saponification can be largely prevented by using *t*-butyl esters, but this strategy also poses potential problems, as hydrolysis of the resulting glycidic ester is often the next stage of a synthetic process. Recently, a procedure has been developed in which α-chloro esters are deprotonated by treatment with potassium

carbonate suspended in DMF in the presence of catalytic tetraalkylammonium salts.[59] Under these conditions, the α-halo esters are not hydrolyzed, and the derived carbanions react smoothly with aromatic aldehydes to give the corresponding glycidic esters in high yields (equation 39). The yields of glycidic esters are reduced in the case of aliphatic substrates, due to competitive self-condensation of the aldehydes. Aldehydes possessing only one α-hydrogen afford the oxirane derivatives in satisfactory yield. The conversion of ketones to glycidic esters under these conditions occurs less readily.

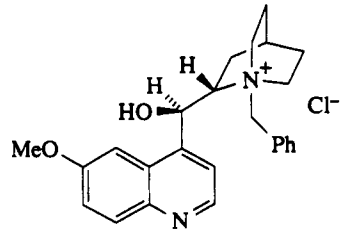


(39)

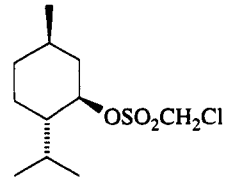
1.13.7 ASYMMETRIC VARIANTS OF THE DARZENS CONDENSATION

1.13.7.1 Asymmetric Catalysis

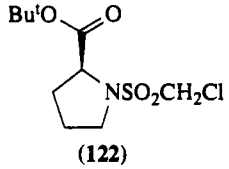
Until recently, little success had been achieved in developing a highly enantioselective version of the Darzens reaction. Several investigations of chiral phase-transfer catalysts for this condensation, in which low or modest asymmetric induction is obtained, have been reported. These include the use of *N*-alkyl-*N*-methylephedrinium halides,[60] the quinine-derived salt (**120**),[61] and polyamino acids.[62] A related study has examined the use of achiral phase-transfer catalysts in the condensations of carbonyl compounds and the asymmetric chloromethylsulfonate ester (**121**).[63a] The same group of researchers subsequently reported similar studies employing the sulfonamides (**122**)–(**124**).[63b]



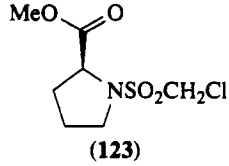
(**120**)



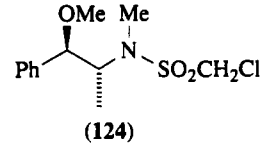
(**121**)



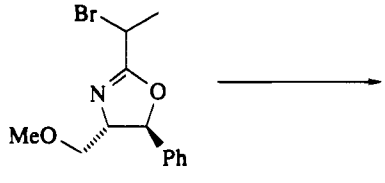
(**122**)



(**123**)



(**124**)



(**125**)

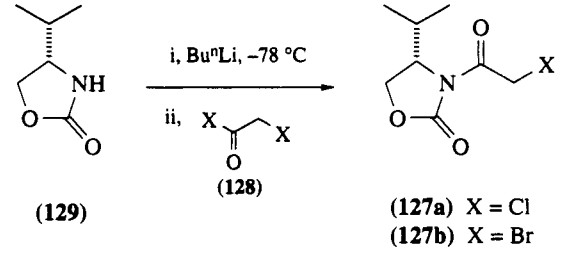
(**126**)

(40)

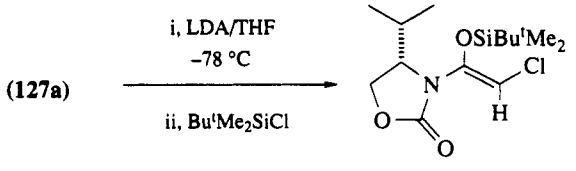
The condensation of the asymmetric oxazoline (**125**) and 2-propanone is reported to give the adduct (**126**; equation 40).[64] The Darzens condensation of aromatic aldehydes with phenacyl halides in the presence of catalytic bovine serum albumin affords epoxy ketones in optical yields as high as 62% *ee*.[65]

1.13.7.2 Condensations Employing Asymmetric *N*-(α-Haloacetyl)oxazolidinones

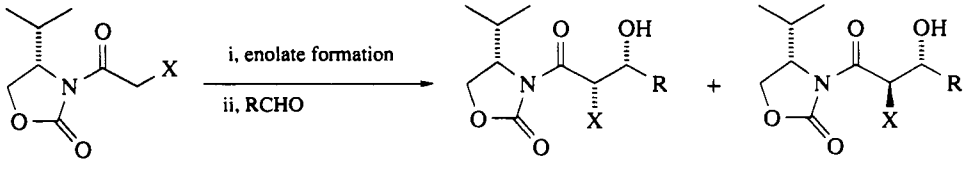
A comprehensive study involving a modified Darzens procedure which employs the aldol reaction of α-haloimides with aldehydes to afford ultimately enantiomerically pure benzyl *cis*-α,β-epoxycarboxylates has been carried out.[66] The research was based on the premise that since the initial phase of the Darzens condensation entails an aldol-type reaction, an asymmetric variant could be developed utilizing technology employed for enantioselective aldol condensations (see Volume 2, Chapters 1.5–1.7). In particular, the work was aimed at using the protocol developed by Evans[67] involving enolates of *N*-acyloxazolidinones, in this case requiring the use of enantiomerically homogeneous α-haloacyloxazolidinones in aldol-like reactions with aldehydes and cyclization of the derived halohydrins to give the desired epoxides. Initially, the effect of enolate countercations in affecting the stereochemical course of the reaction was investigated. The requisite *N*-(α-haloacetyl)oxazolidinones (**127**) are prepared from the corresponding α-haloacetyl halides (**128**) and (4*S*)-4-isopropyl-2-oxazolidinone (**129**; equation 41). Generation of the lithium enolate of (**127a**; LDA, –78 °C) and subsequent trapping with *t*-butyldimethylsilyl chloride affords the enol ether (**130**) as predominantly (>40:1) a single isomer (equation 42). Zn and Sn^{IV} enolates were obtained from lithium enolates by addition of ethereal solutions of $ZnCl_2$ or $SnBu^n_3Cl$, respectively. Sn^{II} enolates were obtained by treatment of lithium enolates with a THF solution of tin(II) triflate or by the procedure of Mukaiyama.[68] Boryl enolates were prepared by the method of Evans.[67] In all cases, the aldehyde was added to the enolate solution at –78 °C except for the Zn enolates; in these cases, the addition was done at –20 °C or at 0 °C. The general reaction is shown in equation (43). The diastereoselectivity of this transformation is consistent with earlier findings;[67] *syn* products (**131**) and (**132**) are obtained predominantly. The selectivity is generally moderate (2–3:1) for lithium enolates where X = Cl and somewhat better (3–19:1) for zinc and tin enolates. The boron enolates, however, exhibit exceptionally high diastereoselection (>50:1); no *anti* isomers are detected. Consistently, over the range of aldehydes studied, diastereoselectivity for zinc enolates is improved by a decreased molar ratio of zinc chloride (50 mol % *versus* 100 mol %). It is postulated that the enhanced selectivity is due to the capa-



(129) (127a) X = Cl (127b) X = Br (41)

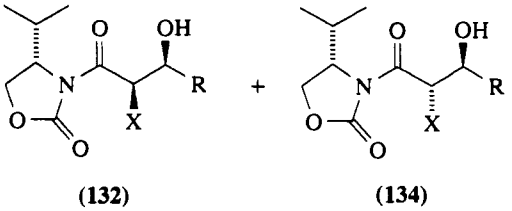


(127a) (130) (42)



(127) (131) (133) (43)

(135) R = n-C_5H_{11}
(136) R = Bu^i
(137) R = Pr^i



(132) (134)

bility of the zinc cation to bind intermolecularly two enolate molecules, thereby producing greater steric demand in the transition state. Diastereoselectivity in the tin(II) triflate-mediated reactions is dependent on the method used to generate the enolate. The α-chloro enolates generated by the Mukaiyama method [$Sn(OTf)_2$, tertiary amine, CH_2Cl_2, 0 °C][68] afford modest levels (3–4:1) of diastereoselectivity; in contrast, this selectivity is improved (6–13:1) by generating the lithium enolate prior to adding a THF solution of tin(II) triflate to the system (–78 °C). Generally, α-bromo enolates show enhanced selectivity relative to the corresponding chloro derivatives. Selectivity generally improves with increasing bulk in the aldehyde (**135** → **136** → **137**), although, as noted previously, the boron enolates afford only *syn* products regardless of the other variables investigated.

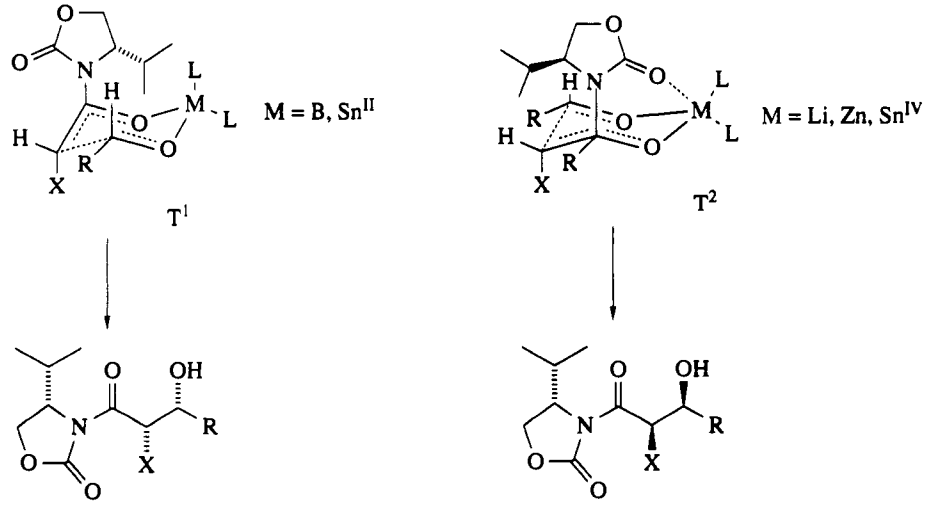
In addition to the excellent diastereofacial selectivity observed with the boron enolate, an unusual result was obtained concerning the absolute stereochemistry of the *syn* products (ratio of **131**:**132**). Interestingly, the stereochemistry of the newly formed chiral centers in the major products derived from tin(II) and boron enolates (**131**) is reversed from that obtained from lithium, tin(IV) and zinc enolates. Several examples of the reaction are shown in Table 14.

Table 14 Condensations of *N*-(α-Bromoacetyl)oxazolidinone Enolates and Aldehydes[66b]

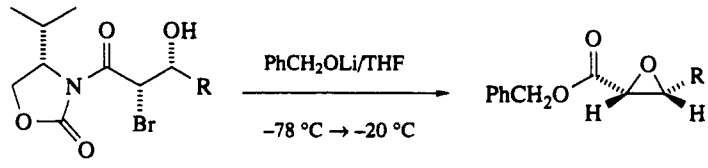
Aldehyde	*Metal*	*Yield (%)*	*Diastereoselection*		*Enantioselection*	
			Syn (%) (131) and (132)	*Anti (%) (133) and (134)*	*(131) (%)*	*(132) (%)*
n-C_5H_{11}CHO	B	55	>98	<2	>98	<2
n-C_5H_{11}CHO	Zn[a]	65	89	11	12	88
Bu^iCHO	B	48	>98	<2	>98	<2
Bu^iCHO	Zn[a]	72	91	9	17	83
Pr^iCHO	B	51	>98	<2	>98	<2
Pr^iCHO	Zn[a]	79	98	2	11	89

[a]50 mol %.

The origin of the cation dependence concerning the sense of enantioselectivity is not completely understood, although a possible explanation has been advanced. In this model (Scheme 24), it is postulated that a major stereocontrolling factor is the difference in orientation as represented by transition states T^1 and T^2; enantioselectivity is controlled through direction of attack of the enolate on the aldehyde, which is dependent upon, to a large extent, the orientation of the enolate face with respect to the oxazolidinone ring. Steric constraints cause the aldehyde to approach the enolate from the face remote to the ring isopropyl substituent. The enolate orientation in T^1 (*E*,*Z*), in which the ring carbonyl is *anti* to the enolate carbonyl leads to (**131**), the observed major product in the B- and Sn^{II}-mediated reactions. The alternative transition state T^2 (*Z*,*Z*) leads to (**132**), the observed major product in the Li-, Zn- and



Scheme 24



(44)

(131)

(45)

(132)

Sn^{IV}-mediated reactions. Apparently, Li, Zn and Sn^{IV} overcome thermodynamic dipolar forces which favor[69a] the (*E,Z*)-orientation through chelation[69b] involving the enolate and both carbonyl groups. Without loss of ligand (L), boron or Sn^{II} cannot bind simultaneously the three oxygen atoms from the enolate and the two carbonyls; in these cases, the reaction proceeds primarily through a template similar to T^{I} with the (*E,Z*)-orientation to provide predominantly (**131**).

syn-Bromohydrins (**131**) and (**132**) afford stereospecifically *cis*-benzyl-α,β-epoxy esters, in 70–74% yield, upon treatment with lithium benzyloxide,[70] with no evidence of epimerization to *trans*-epoxides (equations 44 and 45). Thus, the methodology provides overall a route to both enantiomers of α,β-epoxy esters from the same α-haloimide.

1.13.8 REFERENCES

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1.14
Metal Homoenolates

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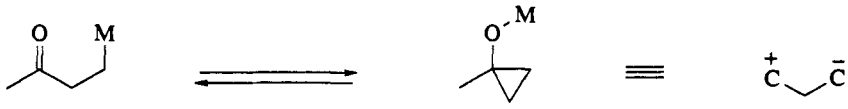
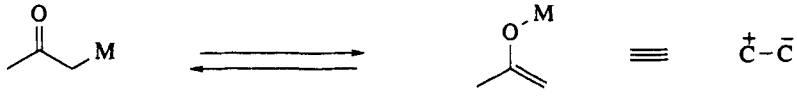
1.14.1 INTRODUCTION

This chapter describes the chemistry of carbanionic species having a carbonyl function at the β-position, relative newcomers among synthetically useful carbanionic species. The chemistry of homoenolates is complicated by the problem of tautomerism between oxyanionic and carbanionic isomers through a process that formally involves homoconjugation.[1] The synthetic problem caused by this tautomerism is much more severe in homoenolate chemistry (Scheme 1) than in enolate chemistry (Scheme 2), which also has a similar problem, since the carbanionic tautomer (**1**; Scheme 1) once formed often undergoes rapid and irreversible cyclization to the oxyanionic tautomer (**2**), and rarely acts as a carbon nucleophile. Until recently, therefore, chemists have not been able to make use of carbanionic homoenolates for organic syntheses.[2–4] However, a large number of useful homoenolate reactions have recently been discovered, and are described in this chapter.



(1) (2)

Scheme 1



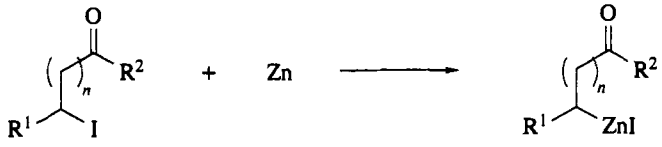
Scheme 2

Because of the convenience of the terminology, the term homoenolate has been used to describe the carbanionic tautomer (**1**). By using this term, trivial names such as homoenolate anion, zinc homoenolate and ester homoenolate may be used, along with more strict terms such as ethyl 3-lithiopropionate, *etc.*

The synthetic value of homoenolates, in exact analogy to that of enolates, stems from their amphoteric nature (equations 1 and 2). In addition, homoenolates represent archetypal synthons in the concept of 'umpolung',[5–7] acting as inverse polarity nucleophilic synthons of Michael acceptors.

(1)

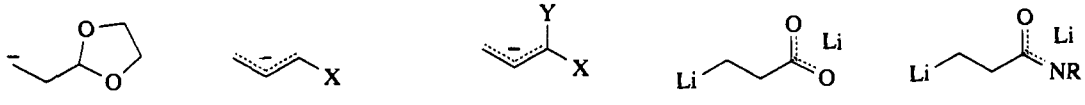
R^1 = hydrogen, alkyl, aryl, alkoxy



(2)

Because of the lack of appropriate synthetic entries to true homoenolates, many 'homoenolate equivalents' appeared in the early 1970s, and their prototypes are shown in formulae (**3**) to (**5**). Protection of the carbonyl group either as a ketal (**3**) or an enol derivative, *e.g.* (**4**) and (**5**), constitutes the main concept for the design of such synthetic equivalents.[7]

Dianions (**6**)[8] and (**7**)[9] illustrate the concept of *in situ* protection of the carbonyl group, representing another class of synthetic protocol. 3-Lithiated β-ketophosphonates, carboxamides and carboxylic acids have been generated and allowed to react with some electrophiles.



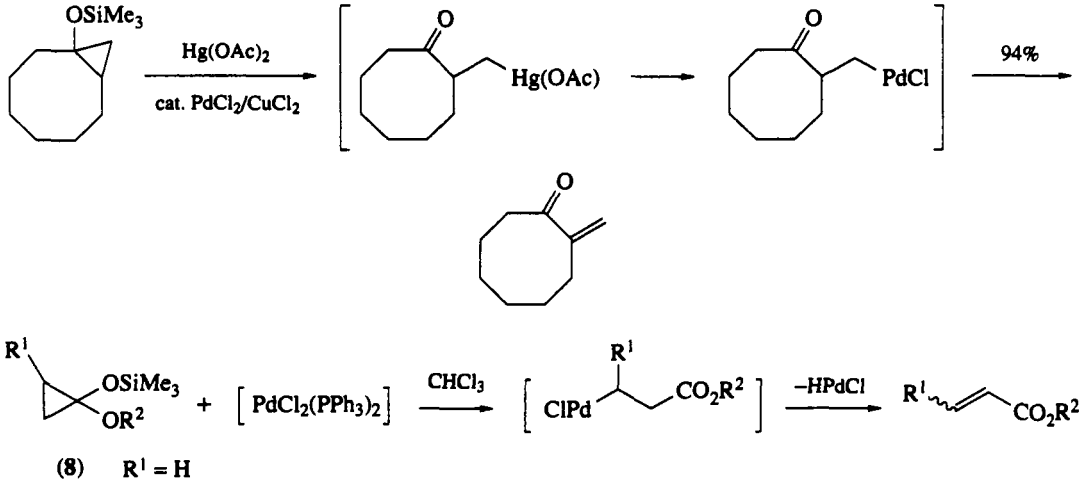
(3) (4) X = OR, NR_2, *etc.* (5) X, Y = OR, $P(O)X_2$, *etc.* (6) (7)

Since the mid-1970s, advances in organometallic chemistry have permitted the preparation and synthetic use of homoenolates. Major efforts have been expended for the exploration of a silyloxycyclopropane route,[10,11] in which silyloxycyclopropanes are cleaved by polyvalent metal salts to obtain reactive metal homoenolates (equation 1). Through such a route, a host of reactive ester,[10,12] ketone[11] and aldehyde homoenolates have been generated.

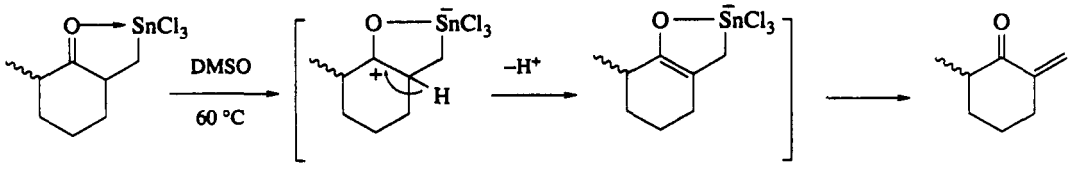
Reduction of 3-iodocarbonyl compounds (equation 2, $n = 1$) with a low-valent metal,[13,14] such as metallic zinc, generates homoenolates of esters, nitriles and ketones, and represents a convenient new entry to homoenolates. This reductive method also allows the preparation of higher homologs ($n > 2$).

1.14.2 ELIMINATION

Palladium homoenolates readily undergo β-elimination to give α,β-unsaturated carbonyl compounds. Treatment of a mercurio ketone with a catalytic amount of palladium(II) in the presence of $CuCl_2$ results in the formation of an enone *via* a 3-palladio ketone (Scheme 3).[15] Treatment of a silyloxycyclopropane (**8**) with $PdCl_2$ also generates *in situ* a palladium homoenolate which then undergoes β-elimination (Scheme 3). Heating a mixture of a 3-trichlorostannyl ketone[16] or aldehyde with DMSO results in the formation of an enone or an enal in excellent yield (Scheme 4).[17]



Scheme 3

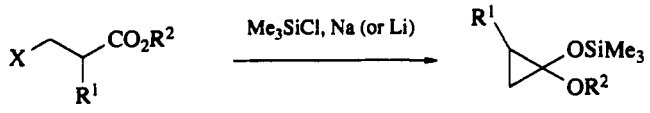


Scheme 4

1.14.3 FORMATION AND CLEAVAGE OF CYCLOPROPANE RINGS

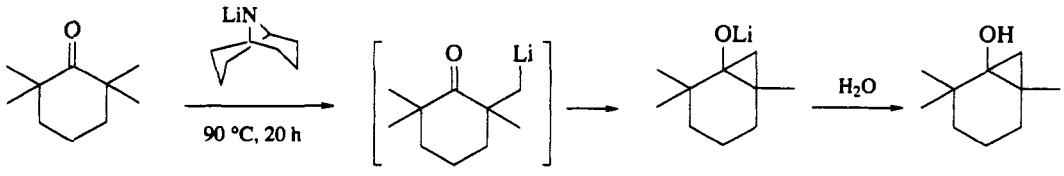
1.14.3.1 Cyclopropane Ring Formation

Internal nucleophilic cyclization is one of the most typical reactions of reactive metal homoenolates (equation 3 and Scheme 5),[1,2] and provides a convenient route to silyloxycyclopropanes (*e.g.* **8**) through cyclization of 3-halo esters.[18] Zinc homoenolates (**9**) also cyclize to cyclopropanes under suitable conditions. Treatment of the zinc homoenolate in $CHCl_3$ with an acid chloride at room temperature gives an *O*-acylation product (Scheme 6), instead of a 4-keto ester (see Section 1.14.7.1).[19] The reaction of the zinc homoenolate with Me_3SiCl in a polar solvent gives a silyloxycyclopropane (Scheme 6), providing a very mild route to silyloxycyclopropanes.[19]

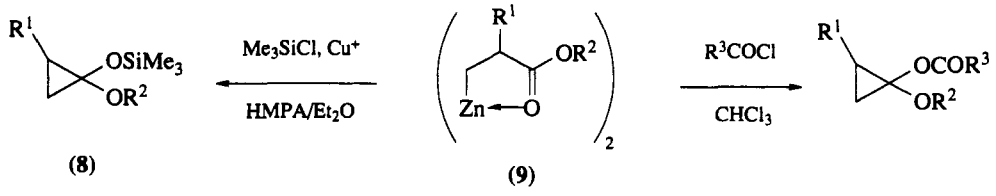


(3)

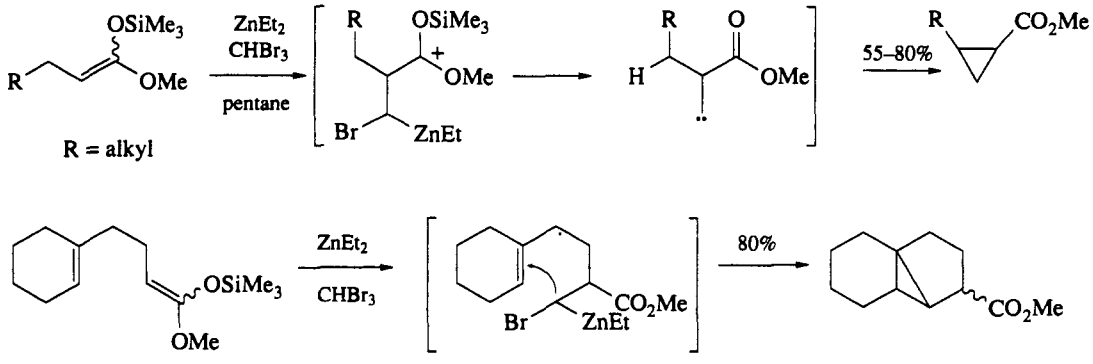
R^1 = H, alkyl; X = halogen (**8**)



Scheme 5



Scheme 6

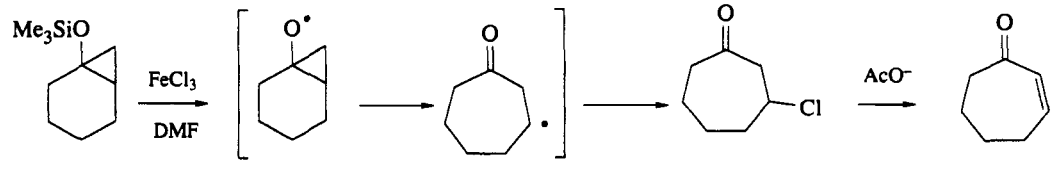


Scheme 7

Two types of cyclization reaction take place when a ketene silyl acetal is treated with a carbenoid generated from $CHBr_3$ and $ZnEt_2$.[20] When the substrate is aliphatic (Scheme 7), a cyclopropylcarboxylate is formed due to a CH insertion reaction of an intermediate zinc carbenoid. With substrates having an alkene in the vicinity of the carbenoid (Scheme 7), in particular those derived from δ,ε-unsaturated esters, internal cyclopropanation takes place.

1.14.3.2 Cyclopropane Ring Cleavage

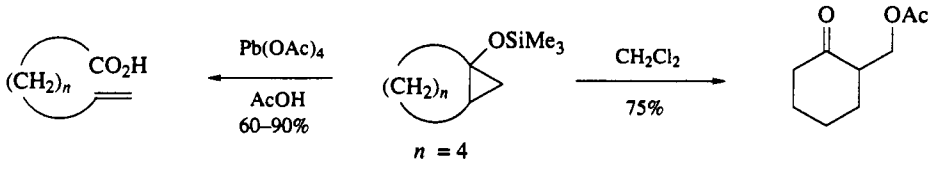
In most of the ring cleavage reactions of silyloxycyclopropanes described in this chapter, the reaction takes place in such a direction that the less alkyl-substituted bond directed to the silyloxy group is cleaved to give the more stable anionic species. Chlorination of a silyloxycyclopropane with $FeCl_3$ in DMF, however, provides a unique case of the cleavage in an opposite direction (Scheme 8).[21,22] Treatment of a silyloxycyclopropane having a bicyclo[*n*.1.0]alkane structure with $FeCl_3$ in DMF produces a 3-



Scheme 8

chloro ketone with cleavage of the internal bridging bond. Such regiochemistry is believed to be due to the radical character of the reaction, and it is presently unclear if a metal homoenolate is involved. The overall sequence of cyclopropanation, chlorination and elimination of HCl represents a useful one-carbon ring expansion method.

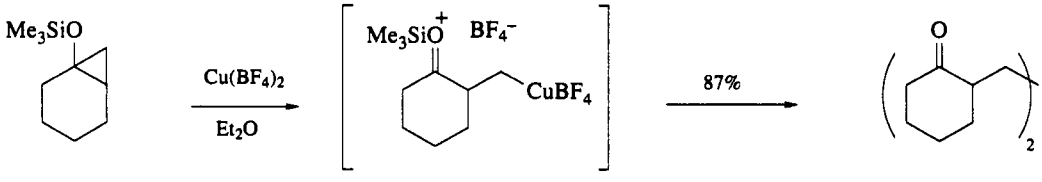
Fragmentation of a 1-silyloxybicyclo[*n*.1.0]alkane with $Pb(OAc)_4$ in acetic acid leads to two-bond cleavage to yield an alkenoic acid (Scheme 9).[23] The reaction involves fission of the two bonds connected to the carbon bearing a silyloxy group. The reaction is considered to involve prior conversion of the silyloxycyclopropane to the corresponding cyclopropanol. In fact, treatment of a silyloxycyclopropane under strictly aprotic conditions gives a product due to one-bond cleavage (Scheme 9).



Scheme 9

1.14.4 SYMMETRICAL COUPLING

Reaction of a silyloxycyclopropane and $Cu(BF_4)_2$ in ether results in symmetrical coupling of two homoenolate moieties (Scheme 10).[24] This reaction provides a convenient route to 1,6-diketones. Intermediacy of a copper(II) homoenolate has been suggested. $AgBF_4$ and CuF_2 effect the same reaction, albeit in lower yield.[25]



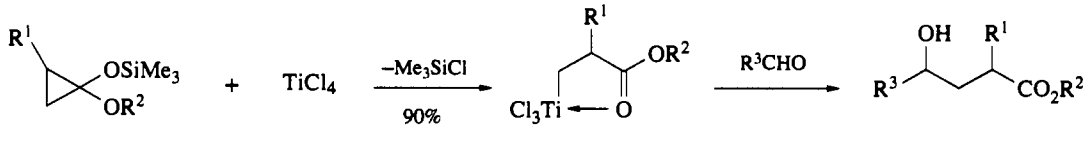
Scheme 10

1.14.5 CARBONYL ADDITION

Addition of a homoenolate to a carbonyl compound, which may be called a 'homoaldol reaction',[26] provides a straightforward route to 4-hydroxy esters and γ-lactones. Only two classes of well-characterized homoenolates that undergo nucleophilic addition to carbonyl compounds are known, namely titanium and zinc homoenolates of esters.

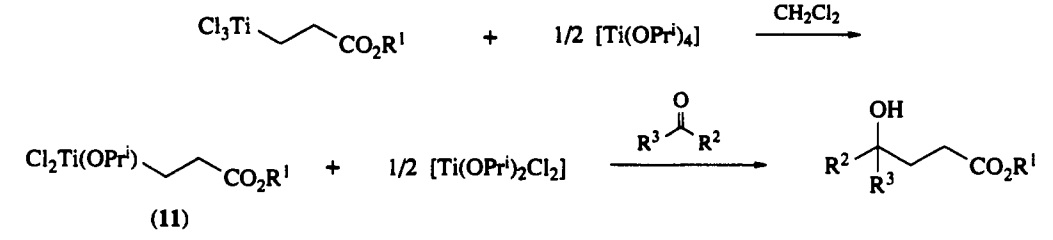
1.14.5.1 Titanium Homoenolates

Trichlorotitanium homoenolates[27,28] (**10**), which can be generated by the reaction of 1-alkoxy-1-silyloxycyclopropanes (**8**) with $TiCl_4$,[10] smoothly add to aldehydes at 0 °C (Scheme 11). They are not, however, sufficiently reactive to add to ketones.

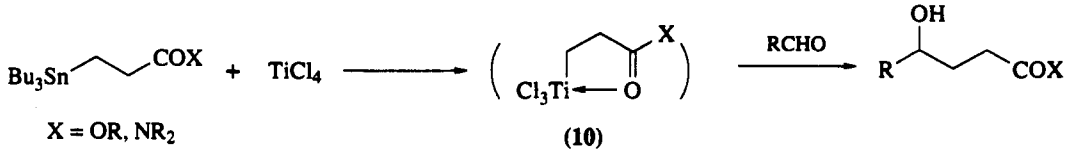


(8) **(10)**

Scheme 11



Scheme 12

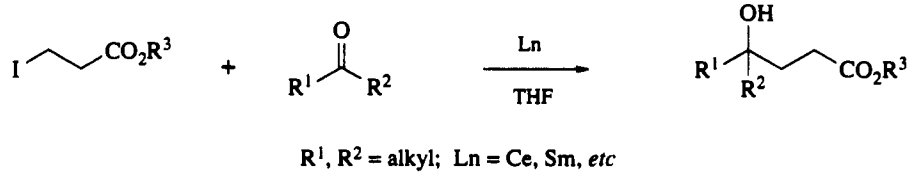


Scheme 13

Addition of 0.5 equiv. of $Ti(OPr^i)_4$ or $Ti(OBu^t)_4$ to the trichlorotitanium homoenolate (**10**) produces an alkoxytitanium species (**11**; Scheme 12) which readily adds to ketones.[28] The basic trend of the chemical behavior, stereo- and chemo-selectivities of (**11**) is similar to that of simple titanium alkyls.[29]

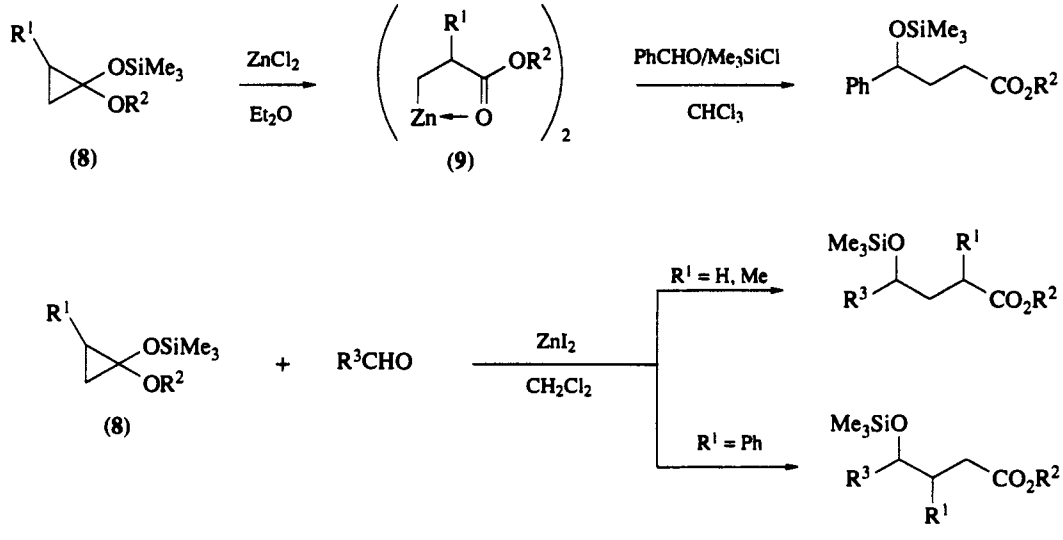
Titanium homoenolates can be prepared by transmetallation of 3-stannyl esters with $TiCl_4$ (Scheme 13).[30,31] The trichlorotitanium species (**10**), shows reactivity very similar to that obtained by the silyloxycyclopropane route.

An attractive alternative to the chemistry of titanium homoenolates is the use of highly nucleophilic lanthanide homoenolates, which can be prepared by reduction of 3-halopropionates (Scheme 14).[32]



R^1, R^2 = alkyl; Ln = Ce, Sm, *etc*

Scheme 14



Scheme 15

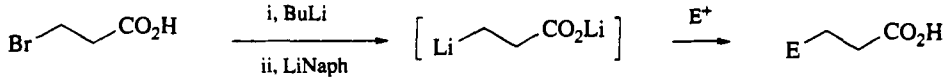
1.14.5.2 Zinc Homoenolates

In line with the chemistry of dialkylzincs, pure zinc homoenolates (**9**),[12] which can be generated by the reaction of a silyloxycyclopropane (**8**) with $ZnCl_2$, are inert to carbonyl compounds in ethereal solvents. By contrast, when the reaction is conducted in halomethanes in the presence of Me_3SiCl, rapid addition occurs.[19] The accelerating effect of the chlorosilane disappears in ethereal solvents (Scheme 15).[19]

A silyloxycyclopropane (**8**) and an aldehyde have been coupled directly in the presence of a catalytic amount of ZnI_2.[19] The reaction proceeds with regioselective cleavage of the cyclopropane ring (Scheme 15).

1.14.5.3 Other Metal Homoenolates

The preparation of a 3-lithiated propionic acid derivative was reported in 1978.[8] The carbonyl function was protected by prior conversion to the lithium carboxylate. Thus, treatment of the lithium 3-bromopropionate with lithium naphthalenide produces the desired dilithiated propionic acid (**6**), which reacts in moderate yield with carbonyl compounds (Scheme 16).

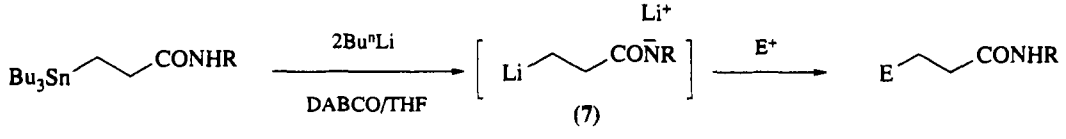


(**6**)

E^+ = carbonyl compound

Scheme 16

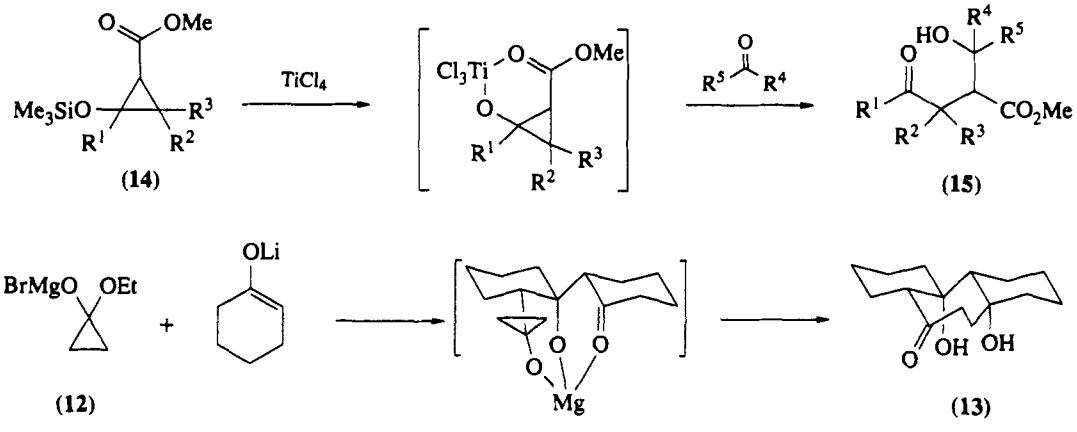
Treatment of a 3-stannylpropionamide with 2 equiv. of Bu^nLi at low temperature gives a dianionic homoenolate (**7**) which reacts with standard electrophiles (Scheme 17).[9,33] It is interesting to note that the tin–carbon bond to the propionate moiety, rather than one to a butyl group, is selectively cleaved during the tin–lithium exchange.



(**7**)

R = Ph E^+ = alkyl halide, Me_3SiCl, ketone

Scheme 17



(**14**) (**15**)

(**12**) (**13**)

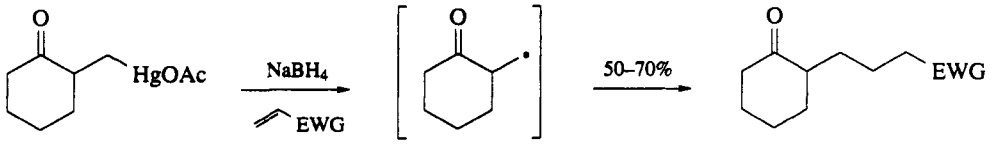
Scheme 18

In the presence of a Lewis acid, alkyl 2-silyloxycyclopropanecarboxylates (**14**) react with a wide range of carbonyl compounds to give a diester (**15**), which has been converted to a variety of furan derivatives (Scheme 18).[34,35] An interesting use of the oxyanionic tautomer of a homoenolate involves the reaction of a magnesium cyclopropanolate (**12**) with the lithium enolate of cyclohexanone, from which a tricyclic ring containing a functionalized cycloheptanone (**13**) is formed in a single step (Scheme 18).[36]

1.14.6 CONJUGATE ADDITION

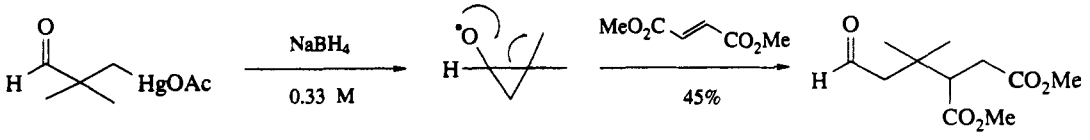
1.14.6.1 Homoenolate Radicals

The reaction of a mercurio ketone with $NaBH_4$ produces a radical species which can be trapped *in situ* by a reactive acceptor such as a vinyl ketone.[37,38] Treatment of a mixture of a mercurio ketone and an electron-deficient terminal alkene (or fumarate) in CH_2Cl_2 with concentrated aqueous $NaBH_4$ gives a conjugate adduct (Scheme 19). Isomerization of such a homoenolate radical, presumably *via* an intermediate cyclopropanoxy radical, has been observed in the reaction of a mercurio aldehyde (Scheme 20).[37,38] The direction of the isomerization is opposite to that observed in the reactions of anionic homoenolates. Such a rearrangement has been used for a ring expansion reaction.[39]



EWG = CO_2Et, CN, Ac

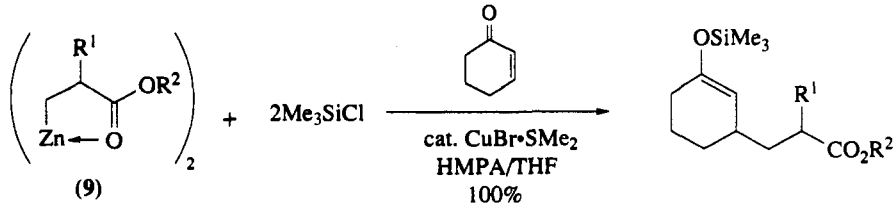
Scheme 19



Scheme 20

1.14.6.2 Zinc Homoenolates

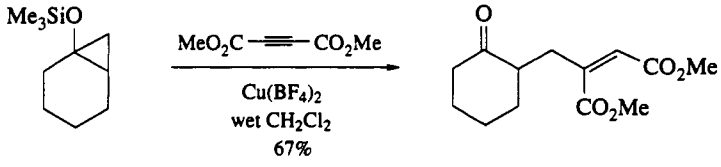
The copper(I)-catalyzed reaction of a zinc homoenolate (**9**) with a Michael acceptor provides a reliable method for the synthesis of 1,6-keto esters.[40,41] Successive addition of an enone, copper catalyst and HMPA to an ethereal solution of the zinc homoenolate (**9**) containing Me_3SiCl results in quantitative formation of a conjugate adduct as an enol silyl ether (Scheme 21).[19] Me_3SiCl strongly accelerates conjugate addition of the intermediate organocopper species.[42–46] $BF_3{\cdot}OEt_2$ also enhances the reaction rate, but the use of this catalyst may influence the stereochemistry of the reaction.[47] The conjugate addition also takes place with alkynic esters and ketones.



Scheme 21

1.14.6.3 Copper Homeonolates

Divalent copper has been found to be a good catalyst for the direct coupling of silyloxycyclopropanes with highly electron deficient alkynes. If a silyloxycyclopropane and copper(II) are allowed to react in the presence of dimethyl acetylenedicarboxylate or propynyl sulfone in wet CH_2Cl_2, a conjugate adduct is obtained in good yield (Scheme 22).[3] Strictly dry conditions lead to oxidative coupling products.



Scheme 22

1.14.7 SUBSTITUTION REACTIONS

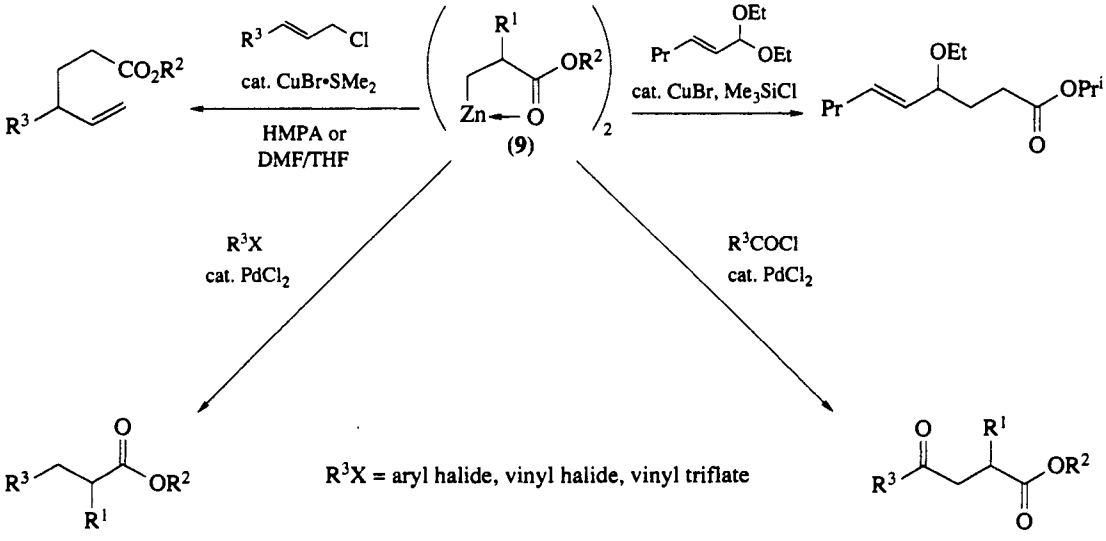
Copper(I) and metals of the nickel triad have been used to effect allylation, arylation, vinylation and acylation reactions of zinc homoenolates. Transient homoenolates generated under Pd catalysis and Ag catalysis have also been used for direct arylation and acylation of silyloxycyclopropanes.

1.14.7.1 Zinc Homoenolates

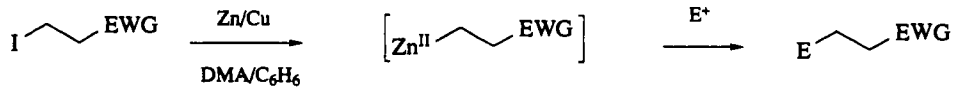
Zinc homoenolates (**9**) react with allyl halides and diene monoepoxides under copper catalysis.[19,48] Treatment of a zinc homoenolate (**9**) with a catalytic amount of copper(I) in a polar solvent (*e.g.* DMA) generates a copper species which undergoes S_N2' allylation (Scheme 23). Polar solvents accelerate the reaction and greatly improve the S_N2' selectivity. Copper-catalyzed reaction with the acetal of an unsaturated aldehyde proceeds without allylic isomerization (Scheme 23).[19]

Substitution reactions of sp^2 halides have been achieved with the aid of a palladium catalyst (Scheme 23).[14,19] A variety of aryl bromides and iodides serve as electrophiles. Reactions with vinyl halides are stereospecific. Vinyl trifluoromethanesulfonates (triflates) also react rapidly with homoenolates.

Zinc homoenolates (**9**) react rapidly with acid chlorides in ethereal solvents containing a dipolar aprotic solvent to give 1,4-keto esters in high yield (Scheme 23).[13,19] A palladium catalyst[49] (or, less effective, a copper catalyst)[40] accelerates the reaction, in contrast to cyclopropane formation in halomethane solvents (see Section 1.14.3.1).



Scheme 23



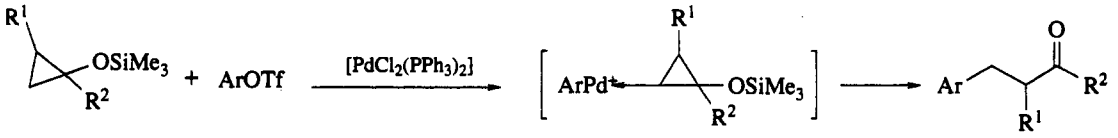
EWG = CO_2R, acyl, CN

Scheme 24

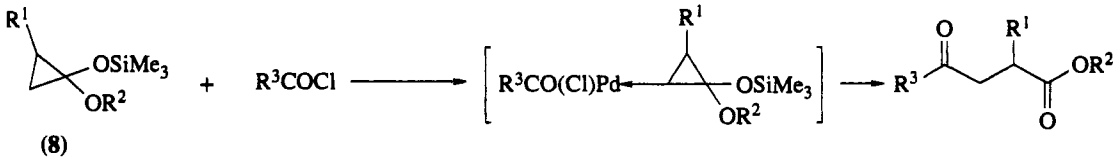
Reduction of 3-iodocarbonyl compounds with a zinc/copper couple in polar solvents (*e.g.* DMF, DMA)[13,14] generates homoenolates of esters, nitriles and ketones[50,51] (Scheme 24). These species are not well defined, but they appear to be very similar to those obtained by the silyloxycyclopropane route.

1.14.7.2 Palladium Homoenolates Generated *In Situ*

Silyloxycyclopropanes react with a $PdCl_2$–phosphine complex to give a transient complex which undergoes β-elimination (see Section 1.14.2.2). However, if the cyclopropane is treated with an $RPd^{II}X$ complex, where R is either aryl or acyl and X is a suitable electron-withdrawing heteroatom, the intermediate palladium homoenolate undergoes reductive elimination to produce a carbonyl compound having the R group at its 3-position (Scheme 25). Thus, heating a mixture of a cyclopropane and an aryl triflate in the presence of a palladium catalyst gives a 3-arylpropionate.[52] Silyloxycyclopropanes corresponding to ketone and aldehyde homoenolates (*e.g.* **3**) also undergo reaction with aryl triflates to give arylated products (Scheme 25). Diazonium salts also serve as arylating reagents.[52]



R^1, R^2 = H, alkyl, aryl

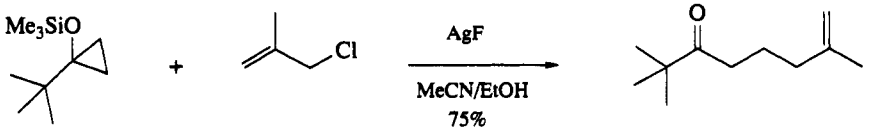


Scheme 25

Reaction of a silyloxycyclopropane (**8**) with an acid chloride in the presence of a palladium catalyst also proceeds cleanly to give 1,4-keto esters in high yield (Scheme 25).[53] A mechanism involving the interaction of (**8**) and an acylpalladium chloride complex in the rate-limiting step has been proposed on the basis of kinetic studies.

1.14.7.3 Silver Homoenolates

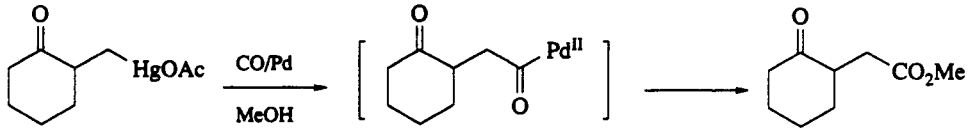
Silyloxycyclopropanes react with allyl chlorides in the presence of AgF in aqueous ethanol to give allylated products (equation 4).[54] The reaction is considered to involve cyclopropanols as initial intermediates.



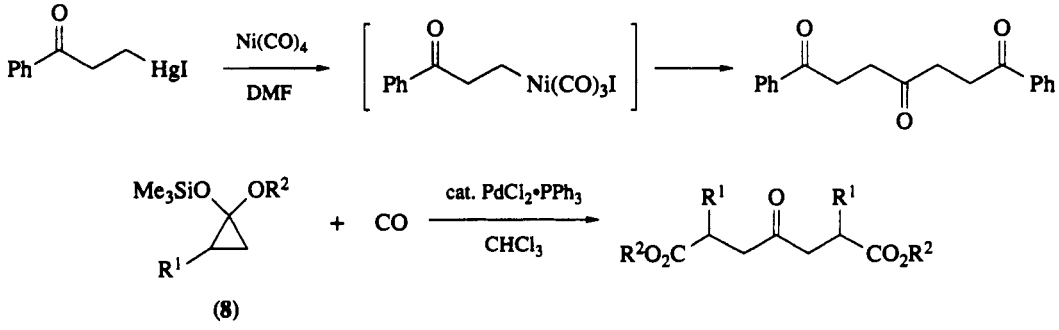
(4)

1.14.8 CARBONYLATION

The reaction of a mercurio ketone and carbon monoxide in the presence of a palladium catalyst in methanol (Scheme 26) results in the formation of a 1,4-keto ester with incorporation of one molecule of carbon monoxide.[15] Treatment of a mercurio ketone with $[Ni(CO)_4]$ results in symmetrical coupling with incorporation of one molecule of carbon monoxide to give a triketone, presumably *via* a 3-nickel-substituted ketone (Scheme 27).[55] Such symmetrical coupling reactions are general for alkylmercury compounds. If silyloxycyclopropane (**8**) is heated in $CHCl_3$ in the presence of a catalytic amount of a palladium–phosphine complex under CO, symmetrical coupling with incorporation of one molecule of CO takes place to give a 4-ketopimelate (Scheme 27).[56]



Scheme 26

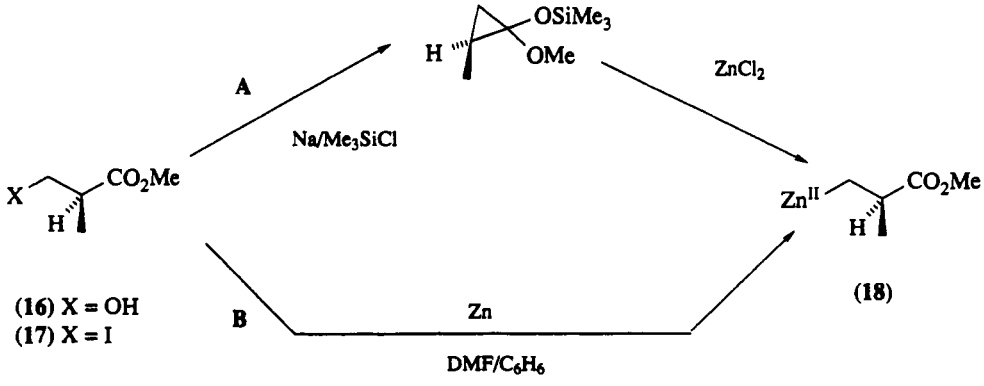


(**8**)

Scheme 27

1.14.9 SYNTHETIC APPLICATIONS

As shown in the preceding paragraphs, metal homoenolates represent a very useful nucleophilic species, and their chemistry provides a model for the design of various other functionalized nucleophilic species. Currently this chemistry is still in its infancy, and only a few examples of applications to total syntheses have been reported. However, the diversity of the reactions of metal homoenolates promises the appearance of many more applications.



Scheme 28

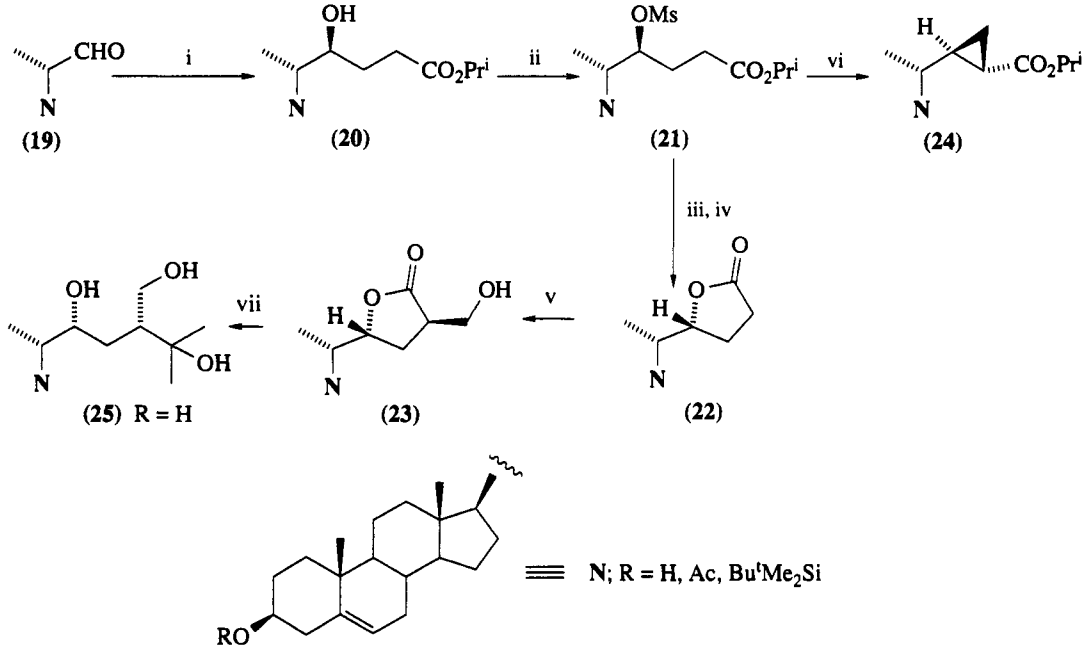
1.14.9.1 Chiral Ester Homoenolates

Commercially available methyl β-hydroxyisobutyrate (**16**) has been converted to the corresponding halide (**17**), then either *via* the silyloxycyclopropane route (A) or *via* the reductive route (B) to the chiral zinc homoenolate (**18**; Scheme 28). It is optically stable in ether and has been used for several standard carbon–carbon bond-forming reactions, *e.g.* carbonyl addition, arylation and acylation.[57]

1.14.9.2 Carbonyl Addition

Synthesis of a marine sterol, depresosterol (**25**), illustrates the utility of the homoenolate as a multifunctional, three-carbon building block.[58] Homo-Reformatsky reaction between an alkoxytitanium homoenolate (**11**; Section 1.14.5.1) and an aldehyde (**19**) afforded the undesired Cram product (**20**) in a ratio of >6:1 (Scheme 29). Inversion of the stereochemistry at the sterically hindered C-22 position was achieved through internal solvolysis by taking advantage of the terminal ester function. Stereoselective hydroxymethylation of the lactone (**22**) followed by introduction of the C-26 and C-27 methyl groups to (**23**) afforded depresosterol (**25**).

Treatment of the mesylate (**21**) with non-nucleophilic *t*-butoxide gives the cyclopropane (**24**), which serves as precursor to a marine sterol, demethylgorgosterol.

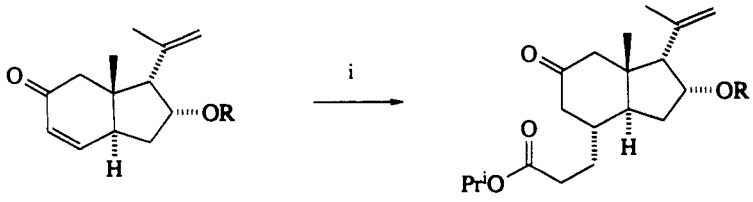


i, (**11**); ii, MsCl; iii, KOH; iv, *p*-TsOH; v, MeMgBr; vi, KOBu^t; vii, MeLi

Scheme 29

1.14.9.3 Conjugate Addition

Conjugate addition of a catalytically generated copper homoenolate (Section 1.14.6.2) has been used for one stage in the stereoselective synthesis of (±)-cortisone (Scheme 30).[47] BF_3·OEt_2-assisted conjugate addition of the copper homoenolate generated *in situ* from the zinc precursor gave the desired conjugate adduct (**26**) in greater than 95% α-selectivity at the newly created stereocenter, C-8.



R = Ac, Bu^{t}Me$_2$Si (26)

i, $Zn(CH_2CH_2CO_2Pr^i)_2$, cat. CuBr•SMe_2, BF_3•OEt_2, HMPA/THF

Scheme 30

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1.15

Use of Enzymatic Aldol Reactions in Synthesis

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1.15.1 INTRODUCTION

The development of methods for the stereoselective formation of carbon–carbon bonds using the aldol reaction is a current topic of interest in organic synthesis.[1–6] Many successful strategies rely on chiral auxiliaries[7–15] and a few employ nonbiological catalysts.[16] Zinc(II) complexes of amino acid esters, for example, catalyze the reaction of *p*-nitrobenzaldehyde with acetone.[17] Eu(DPPM)$_3$ catalyzes the condensation of ketene silyl acetals with benzaldehyde.[18] A chirotopic ferrocenyl phosphine–gold(I) complex catalyzes the reaction of isocyanoacetate with a number of simple aldehydes such as benzaldehyde, acetaldehyde and pivaldehyde.[19] These latter reactions show fair to good enantiofacial and diastereofacial selectivity, with the chiral gold complex giving the best results: 72–97% diastereomeric and enantiomeric excess.

Enzymes often provide products with still higher enantiomeric purity.[20,21] Their usefulness in organic synthesis is, however, only now being explored. This chapter discusses the utility of readily available carbon–carbon bond-forming enzymes as catalysts for the asymmetric aldol reaction.

1.15.2 ENZYMES AS CATALYSTS

Enzymes have been employed as catalysts in organic synthesis for many years, primarily for the construction of small chiral molecules.[22–27] Most synthetic chemists, however, perceive enzymes as being absolutely specific for their natural substrates and thus limited in their application to organic synthesis. The use of enzymes is also plagued by concerns of enzyme stability and requirements for the use of cofactors. Developments in biotechnology have, however, solved many of the problems associated with cofactor regeneration and enzyme stability.

Many enzymes do accept a wide range of substrates.[20–21] Although the reaction of unnatural substrates may be slower than that of the natural substrate, the specificity of many enzymes is broad enough to allow a wide range of compounds to be utilized at an acceptable rate. Lipase,[28] chymotrypsin,[29] lactate dehydrogenase,[30,31] acyclase I,[32] and aldolase[33,34] are only a few examples of enzymes useful in synthetic applications because of their broad substrate specificity. The development of techniques such as enzyme immobilization,[27,35–37] hollow-fiber reactors[38] and the use of membranes[39] allows increased stability, recovery and reuse of enzymes. Deactivation of enzymes by oxidation can also be avoided through the use of reducing agents.

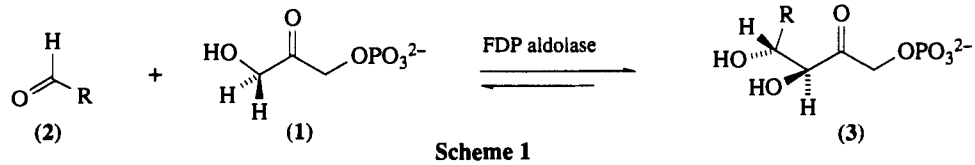
Several groups of enzymes do require cofactors. In many cases these cofactors are too expensive to use stoichiometrically and this was a major limitation for the use of enzymes in organic synthesis. This problem has now been solved through the development of regenerating systems, which allow for the use of catalytic amounts of cofactor. These systems have been extensively reviewed elsewhere.[40,41]

1.15.2.1 Enzymes That Form Carbon–Carbon Bonds

Three general types of enzymes have been applied for the formation of carbon–carbon bonds in organic synthesis: aldolases, synthetases and transketolases. Aldolases are a class of enzymes that catalyze the stereoselective construction and degradation of carbon–carbon bonds in monosaccharides.[42–46] Synthetases catalyze an irreversible aldol reaction of activated enols such as phosphoenol pyruvate (PEP) with aldoses to form complex monosaccharides;[47] transketolases catalyze the transfer of a hydroxyketo group of a keto sugar to an aldose.[48] These enzymes are discussed individually below with an outline of their use in organic synthesis.

1.15.3 D-FRUCTOSE-1,6-DIPHOSPHATE ALDOLASE

D-Fructose-1,6-diphosphate (FDP) aldolase (E.C. 4.1.2.13) from rabbit muscle, catalyzes the equilibrium condensation of dihydroxyacetone phosphate (**1**; DHAP) with D-glyceraldehyde 3-phosphate (**2**; G-3-P) to form D-fructose 1,6-diphosphate (**3**; FDP; Scheme 1).[42–44] The equilibrium constant for this reaction is $K = 10^4\ M^{-1}$ in favor of the formation of FDP. The stereoselectivity of the reaction is absolute; the configuration of the vicinal diols at C-3 and C-4 is always *threo* (*i.e.* D-*glycero*). Although there is a significant discrimination (20:1) between the antipodes of the natural substrate (*i.e.* D- and L-G-3-P), this selectivity extends to only a few unnatural substrates.[33]



Scheme 1

1.15.3.1 Substrate Specificity

FDP aldolase accepts a wide range of aldehydes in place of its natural substrate, G-3-P,[33] thus permitting for the synthesis of carbohydrates such as nitrogen-containing sugars,[34,49] deoxy sugars,[50,51] fluoro sugars[51] and C_8/C_9 sugars.[52] More than 75 aldehydes have been identified as substrates based on enzymatic assay and many of the aldol adducts have been isolated and characterized.[53–77] In general, unhindered aliphatic, α-heteroatom-substituted and differentially protected alkoxy aldehydes are substrates; severely hindered aliphatic aldehydes such as pivaldehyde do not react with FDP aldolase, nor do α,β-unsaturated aldehydes, although these compounds do not inhibit the enzyme. Aromatic aldehydes are either poor substrates or unreactive. Some examples are summarized in Table 1.

Table 1 Products Synthesized by Reacting the Substrate with Dihydroxyacetone Phosphate in the Presence of FDP Aldolase

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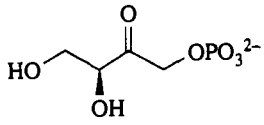
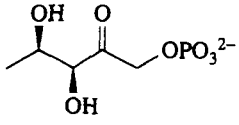
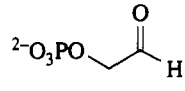
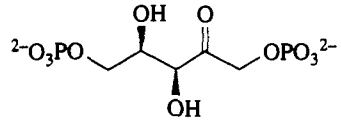
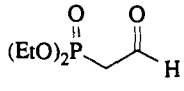
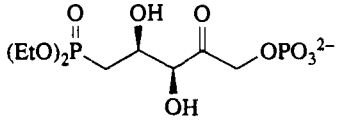
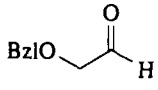
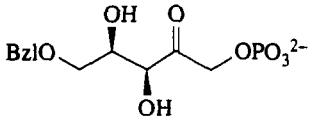
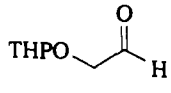
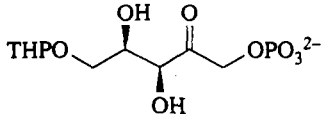
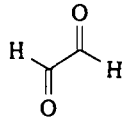
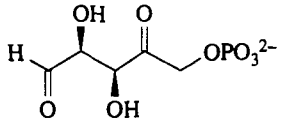
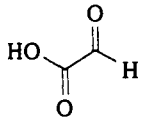
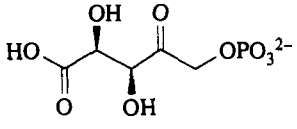
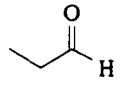
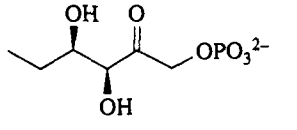
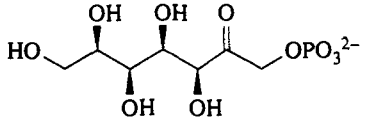
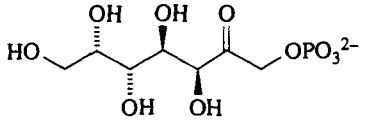
		33
		60, 69
		59, 70
		66
		33
		33
		66
		66
		33, 61, 72
D-Threose		60
L-Threose		55

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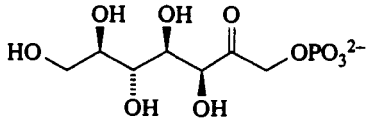
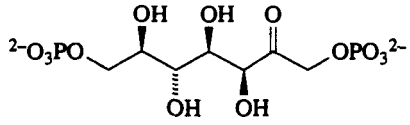
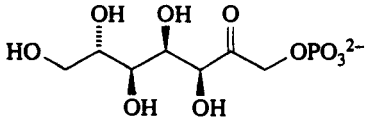
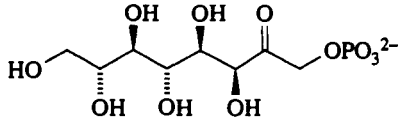
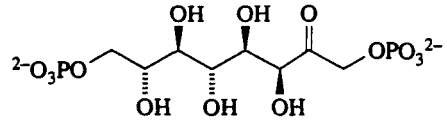
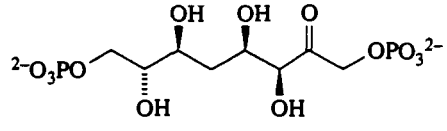
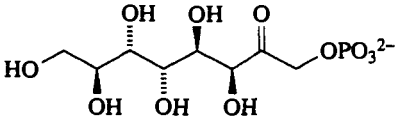
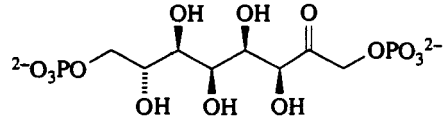
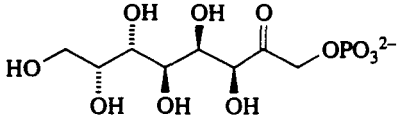
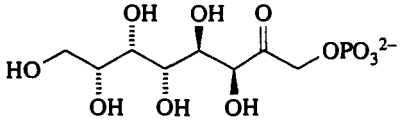
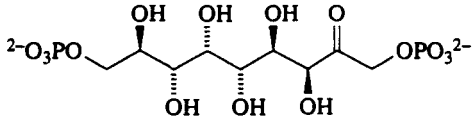
D-Erythrose		33, 59, 62, 65
D-Erythrose-4-P		71, 73
L-Erythrose		62
D-Ribose		53, 57
D-Ribose-5-P		52, 58, 59, 63
2-Deoxy-D-ribose-5-P		52
L-Arabinose		53
D-Arabinose-5-P		52, 58, 63
D-Lyxose		53
D-Xylose		53
D-Glucose-6-P		52

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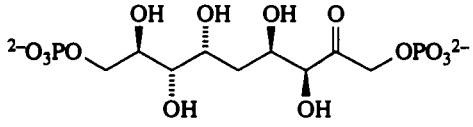
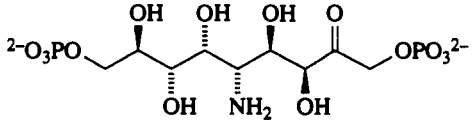
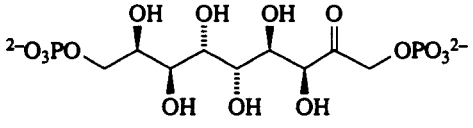
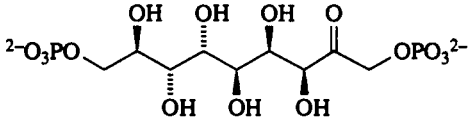
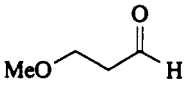
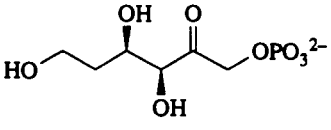
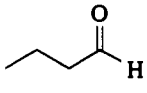
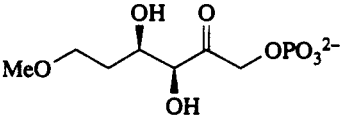
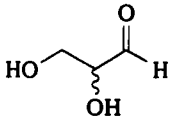
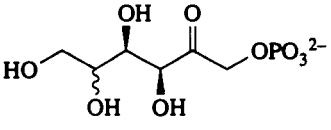
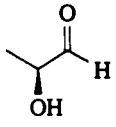
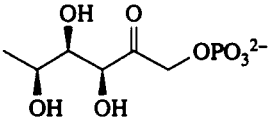
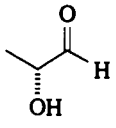
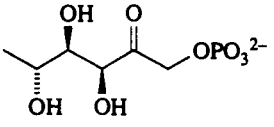
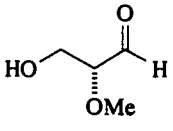
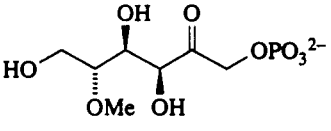
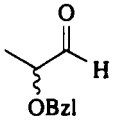
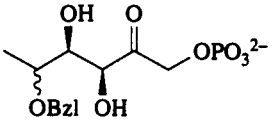
2-Deoxy-D-glucose-6-P		52
D-Glucosamine-6-P		52
D-Galactose-6-P		52
D-Mannose-6-P		52
		33
		72
		50
		33
		33
		33
		33

Table 1 *(continued)*

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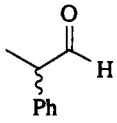
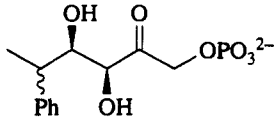
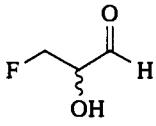
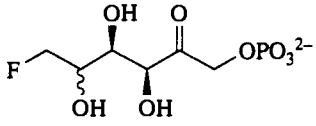
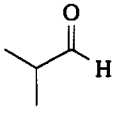
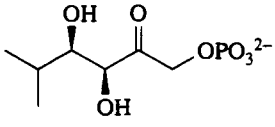
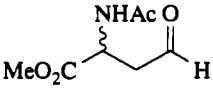
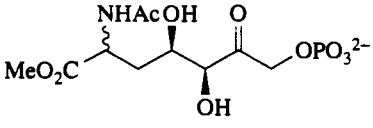
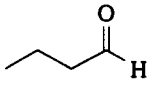
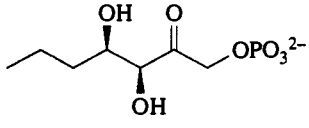
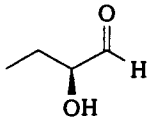
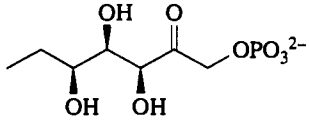
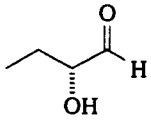
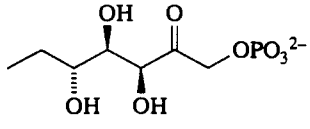
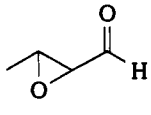
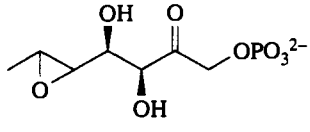
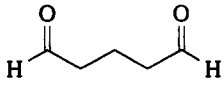
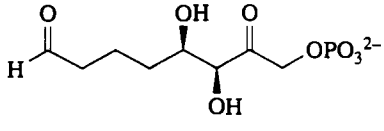
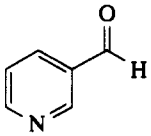
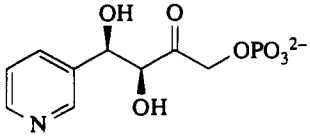
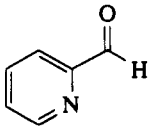
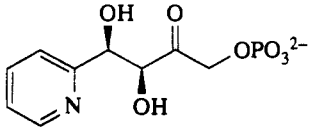
		33
		51
		66
		66
		66, 33
		51, 49, 68, 69
		49, 51, 68, 69
		66
		66
		33, 66
		33, 66

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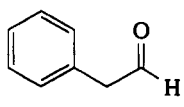
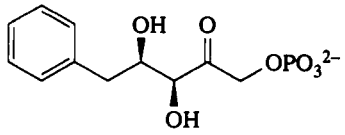
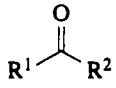
		33, 66

The requirement for the electrophilic component (DHAP) is much more stringent than for the nucleophilic component; so far investigations have demonstrated that only 1,3-dihydroxy-2-butanone 3-phosphate and 1,4-dihydroxy-3-butanone 1-phosphonate are substrates (Table 2).[33]

Table 2 Relative Rates of DHAP Analogs in FDP Aldolase Catalyzed Reactions using G-3-P as the Aldehyde Substrate



R^1	R^2	V_{rel}
$HOCH_2$	$CH_2OPO_3^{2-}$	100
$HOCH_2$	$CHMeOPO_3^{2-}$	10
$HOCH_2$	$CH_2CH_2PO_3^{2-}$	10
$HOCH_2$	CH_2SO_3H	<0.1
$HOCH_2$	CH_2OH	<0.1
Me	$CH_2OPO_3^{2-}$	<0.1
N_3CH_2	$CH_2OPO_3^{2-}$	<0.1
$AcNHCH_2$	$CH_2OPO_3^{2-}$	<0.1
$HOCH_2$	$CH_2OPO_3^{2-}$	<0.1
$ClCH_2$	$CH_2OPO_3^{2-}$	0
$BrCH_2$	$CH_2OPO_3^{2-}$	0

1.15.3.2 Preparation of DHAP

DHAP is an essential substrate of aldolase-catalyzed reactions and a simple preparation of this compound is essential for developing the use of this enzyme in asymetric synthesis. DHAP may be generated by three procedures: (i) *in situ* from fructose 1,6-diphosphate with the enzymes aldolase and triosephosphate isomerase (E.C. 5.3.1.1);[33] (ii) from the dimer of dihydroxyacetone by chemical phosphorylation with $POCl_3$;[33,66] and (iii) from dihydroxyacetone by enzymatic phosphorylation using PEP and glycerol kinase (E.C. 2.7.1.30).[33,50,76] The *in situ* generation of DHAP from FDP is the most convenient method. This reaction does not, however, go to completion and the presence of excess FDP can complicate the isolation of products that are negatively charged. In these cases the chemical synthesis of DHAP is the method of choice.

A mixture of dihydroxyacetone and inorganic arsenate may replace DHAP[49] and this mixture has been used in syntheses by Wong and coworkers. A dihydroxyacetone arsenate monoester probably forms in the rate-determining step, and is consumed in a fast, irreversible aldol reaction. The irreversibility imposed by this method may be useful with slowly reacting substrates, but the toxicity of arsenate limits its usefulness. Vanadate does not operate as a phosphate mimic in FDP aldolase catalyzed reactions.[49]

The phosphate group (derived from DHAP) of the aldol adducts facilitates the purification of aldol products by ion-exchange chromatography or by precipitation as their barium or silver salts. Either enzymatic methods using acid or alkaline phosphatase or chemical methods using acid or base also allow cleavage of this group.[33]

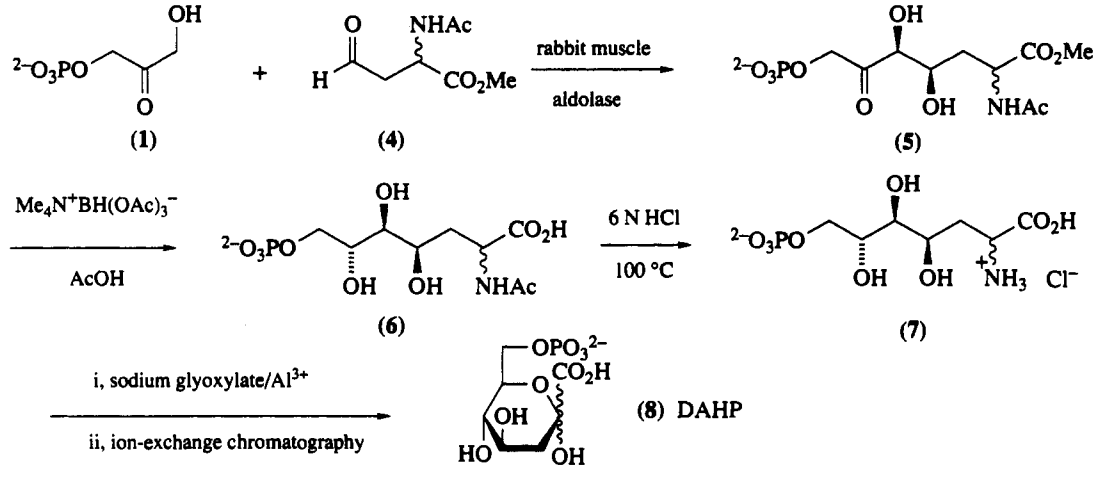
1.15.3.3 Enzyme Characteristics

Several characteristics of FDP aldolase make it a useful enzyme for use in synthesis. Commercial preparations of the enzyme are inexpensive (it costs \$0.04 to produce 1 mmol of product per minute, *i.e.* \$0.04 $unit^{-1}$ and it has a reasonable specific activity (60 unit mg^{-1} of protein). FDP aldolase requires no metal ions or cofactors and it is stable in the presence of oxygen and added organic cosolvents, and is not

inhibited to a significant extent by the natural product (*i.e.* FDP). The enzyme has been used in soluble or immobilized forms, or enclosed within a dialysis membrane.[33]

1.15.3.4 Examples of FDP Aldolase in Organic Synthesis

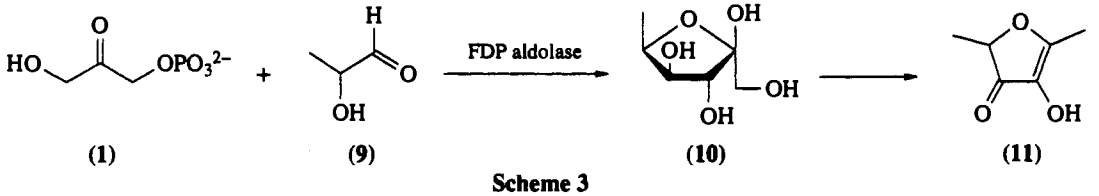
The biologically active monosaccharide 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (**8**; DAHP) is an important intermediate in the biosynthesis of aromatic amino acids in plants (the shikimate pathway). As shown in Scheme 2, this compound has been produced in a combined chemical and enzymatic synthesis from racemic *N*-acetylaspartate β-semialdehyde (**4**) and DHAP (**1**).[67] The four-step synthesis proceeds in an overall yield of 13% (37% for the aldolase reaction). The enzymatic step generates the required, enantiomerically pure, *syn* aldol adduct compound (**5**). In view of the broad range of substrates tolerated by FDP aldolase, this method may be applicable to the production of analogs of DAHP.



(1) (4) (5) (6) (7) (8) DAHP

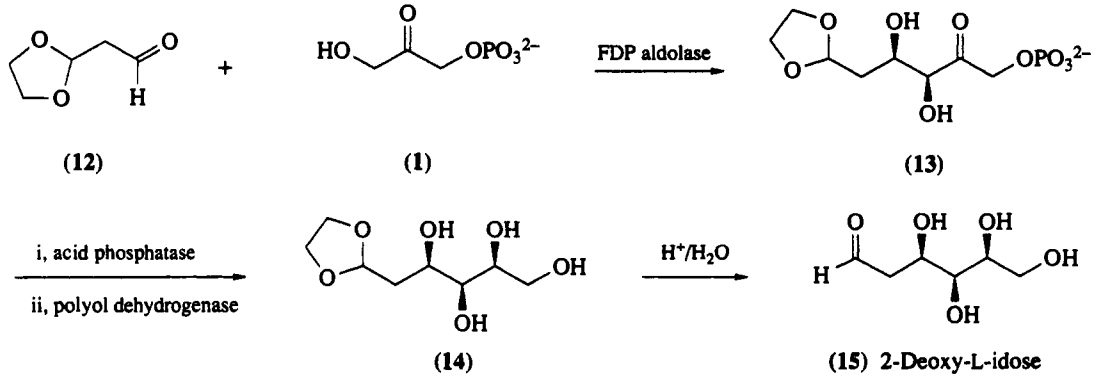
Scheme 2

Other monosaccharide derivatives have also been synthesized using FDP aldolase as a catalyst. Deoxyfructose derivatives such as compound (**10**) were, for example synthesized using FDP aldolase catalyzed addition of DHAP to lactaldehyde (**9**). The aldol adduct (**10**) was chemically converted to furaneol (**11**), an important flavoring agent (Scheme 3).[50] Other deoxy sugars such as 2-deoxy-L-idose (**15**) are also available using FDP aldolase. The condensation of aldehyde (**12**) with DHAP gives (**13**), which upon dephosphorylation, reduction and deprotection yields the deoxyidose (**15**; Scheme 4).[50,51] Two



(1) (9) (10) (11)

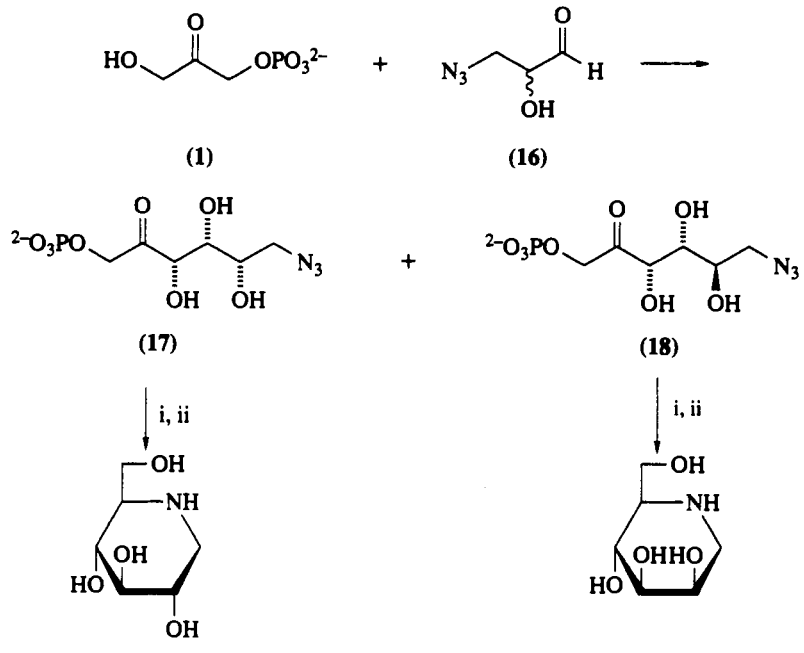
Scheme 3



(12) (1) (13) (14) (15) 2-Deoxy-L-idose

Scheme 4

groups have also used aldolase to synthesize alkaloids.[34,78] Aldehyde (**16**) was condensed with DHAP (**1**) using aldolase as a catalyst to give (**17**) and (**18**) respectively (Scheme 5). These compounds were chemically converted into deoxynojirimycin (**19**) and deoxymannonojimycin (**20**) as shown in Scheme 5.[79]

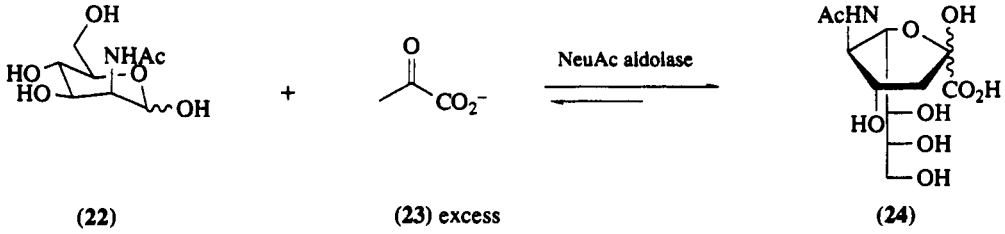


i, phosphatase (or H^+); ii, H_2/Pd

Scheme 5

1.15.4 *N*-ACETYLNEURAMINIC ACID ALDOLASE (E.C. 4.1.3.3)

N-Acetylneuraminic acid aldolase catalyzes the reversible aldol condensation of pyruvate (**23**) and *N*-acetylmannosamine (**22**; ManNAc) to form *N*-acetylneuraminic acid (**24**; NeuAc; *N*-acetyl-5-amino-3,5-dideoxy-D-glycerogalacto-2-nonulopyronic acid; Scheme 6).[80–83] *In vivo* the enzyme has a catabolic function and the equilibrium for this reaction is near unity; the presence of excess pyruvate can shift this equilibrium. NeuAc and other derivatives of neuraminic acid are termed sialic acids. These compounds are found at the termini of mammalian glycoconjugates and play an important role in cellular recognition.[84–89] The production of analogs of NeuAc is a point of great interest to synthetic and medicinal chemists. The enzymatic approach has not been fully explored but it may be a practical alternative to the chemical synthesis of certain sialic acids.[89]

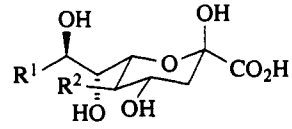


Scheme 6

Reactions catalyzed by NeuAc aldolase have produced several grams of NeuAc after purification by ion-exchange chromatography.[90–92] Although the specificity for pyruvate appears to be absolute, the re-

sults of enzymatic assays suggest that NeuAc aldolase accepts a range of substrates in place of ManNAc.[80,81,90–97] Several groups have taken advantage of this observation to synthesize and isolate derivatives of NeuAc. General observations from these syntheses and from assay results suggest that NeuAc aldolase will be useful in synthesis. Substitution at C-2 and C-6 is tolerated, and the enzyme exhibits only a slight preference for defined stereochemistry at other centers (Table 3).

Table 3 Sialic Acids Synthesized by Condensation of Pyruvate with Analogs of ManNAc in the Presence of NeuAc Aldosase



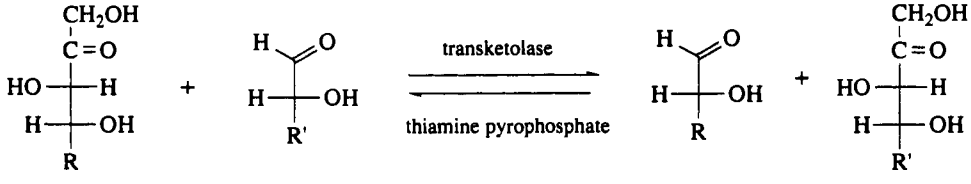
R^1	R^2	*Ref.*
CH_2OAc	NHAc	91
CH_2N_3	NHAc	97
CH_2OH	OH	95a,b
CH_2OH	H	95a,b
H	OH	95a,b
CH_2OH	N_3	96
CH_2OH	$NHCOCH_2OH$	95b
CH_2OMe	NHAc	95b
$CH_2OCOCH(OH)Me$	NHAc	95b
CH_2OAc	$NHCOCH_2OH$	95b
CH_2OH	N_3	95b
CH_2OH	$NHCOCH_2OCOMe$	95b

In addition to its acceptance of unnatural substrates, several other characteristics make NeuAc aldolase a useful synthesis catalyst. The cloning of the enzyme has reduced its cost and offers the potential to produce large quantities of new proteins with improved stability or with altered stereoselectivity.[98] This approach could be used to extend the chain of a variety of aldoses by two carbon units. Although the optimal pH for activity of NeuAc aldolase is near pH 7.5 at 37 °C, the enzyme is active at pH 7–9.[82,83] The protein is stable in the presence of oxygen and does not require added cofactors.[82,83] One drawback is that an excess of pyruvate (the less expensive reagent) must be used in synthetic reactions to shift the equilibrium towards the formation of product; approximately 7 equiv. of pyruvate are needed to attain 90% conversion of ManNAc to NeuAc at equilibrium. It may be possible to avoid the need for an excess of pyruvate by coupling the synthesis of NeuAc to a more thermodynamically favored process.

An advantage of the enzymatic route compared with the chemical route is that purification of NeuAc or its derivatives may be avoided. For example, an unpurified solution of NeuAc generated enzymatically from an unpurified solution of ManNAc was used in the enzymatic synthesis of cytidine 5′-monophospho-NeuAc (CMP-NeuAc).[89] The unpurified preparation of ManNAc was derived from base-catalyzed epimerization of the much less expensive starting material GlcNAc.

1.15.5 TRANSKETOLASE

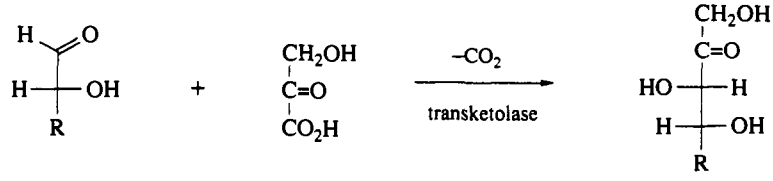
This enzyme catalyzes the reversible transfer of the hydroxyketo group of a ketose phosphate to an aldose phosphate.[99,100] The cofactor thiamine pyrophosphate (TPP) is associated with the enzyme and activates the ketose (Scheme 7). Most known donor ketoses (xylulose 5-phosphate, sedoheptulose 7-phosphate, fructose 6-phosphate, L-erythrose) have a *trans* arrangement of hydroxy groups at C-3 and C-4; hydroxypyruvate is an exception.[101] A range of aldehydes (such as D-glyceraldehyde 3-phosphate, D-ribose 5-phosphate, D-erythrose 4-phosphate, glycoaldehyde) are acceptors.[102] Transketolase has been



Scheme 7

used in synthesis with its natural substrates and has been used to prepare ^{14}C-labeled intermediates of the pentose pathway.[103,104]

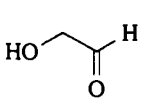
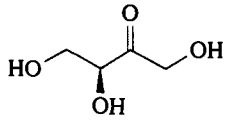
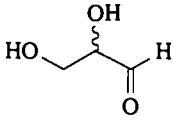
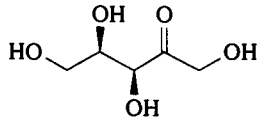
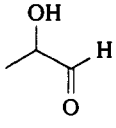
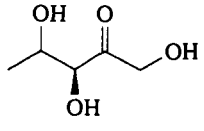
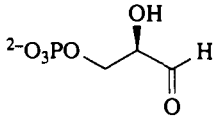
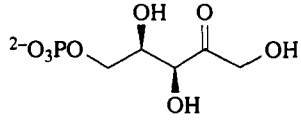
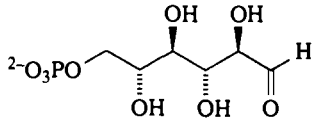
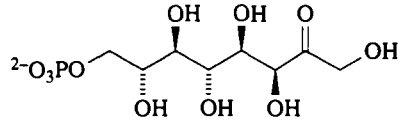
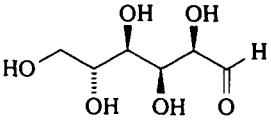
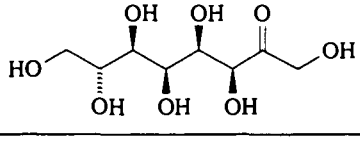
Although the substrate specificity of transketolase has not been thoroughly explored, it appears to be a promising catalyst for use in synthesis. The 2-hydroxypyruvate (**26**) can replace the ketose (**25**), providing a reactive hydroxyketo group after decarboxylation of hydroxypyruvate. This group is transferred to the acceptor aldehyde in an irreversible reaction (Scheme 8) to give (**27**).[102] This method has allowed the synthesis of a number of monosaccharides on scales of 2–5 mmol with yields ranging from 24 to 85% (Table 4).[102–104] The enzyme is commercially available and has also been immobilized.[102]



(**25**) (**26**) (**27**)

Scheme 8

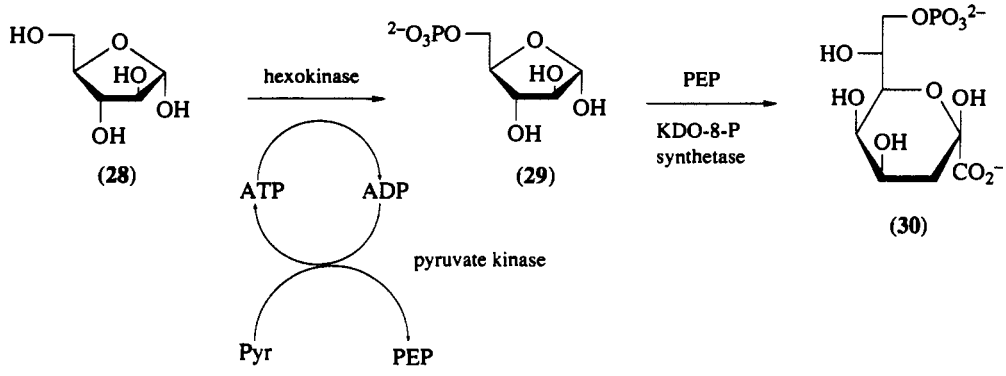
Table 4 Products Synthesized Using Transketolase as a Catalyst and Hydroxypyruvate as a Donor

Substrate	*Product*	*Ref.*
		102
		102
		102
		103
		104
		104

1.15.6 KDO SYNTHETASE

KDO synthetase catalyzes the reaction of arabinose 5-phosphate (**29**; Ara-5-P) and phosphoenol pyruvate (PEP) to form KDO-8-P (**30**; Scheme 9).[105] KDO synthetase is not commercially available but has been isolated from *E. coli* and used in the synthesis of KDO-8-P (63% from Ara-5-P, 38 mmol).[106] KDO-8-P is a key intermediate in the synthesis of the lipopolysaccharide region of Gram-negative bacteria (LPS). Inhibitors of LPS biosynthesis are targets for the design of antimicrobial drugs.[107,108]

The substrate specificity of this enzyme has not been thoroughly examined for synthetic application. In the example given below the expensive arabinose 5-phosphate was generated from arabinose by hexokinase-catalyzed phosphorylation (Scheme 9).



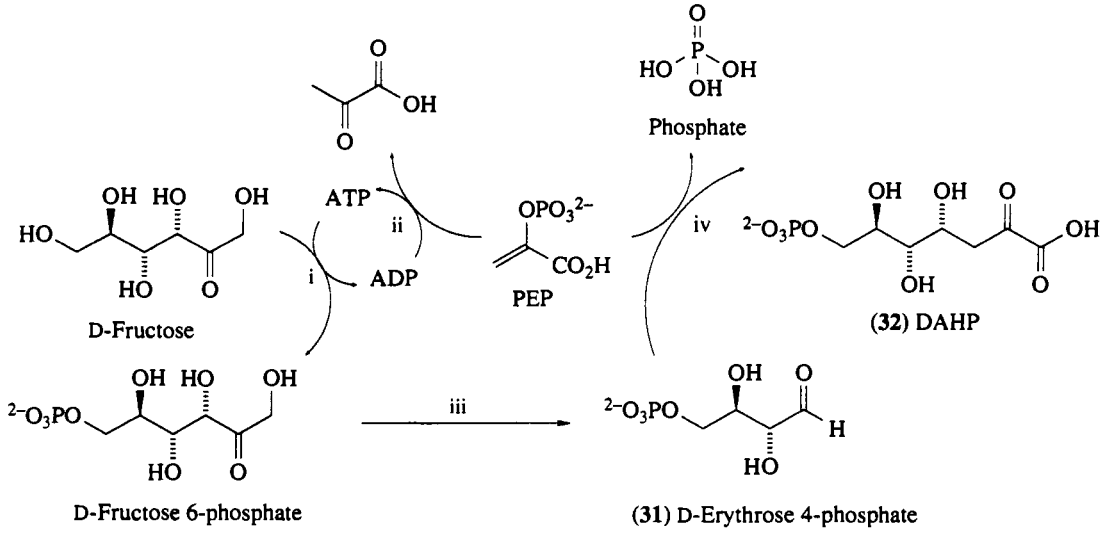
Scheme 9

1.15.7 DAHP SYNTHETASE

This enzyme produces 3-deoxy-D-*arabino*-heptulsonic acid 7-phosphate (**32**; DAHP) from D-erythrose 4-phosphate (**31**). The enzyme was used by Frost[109,110] to synthesize DAHP as an intermediate in the chemical synthesis of its phosphonate analog, 3-deoxy-D-*arabino*-heptulsonic acid 7-phosphonate (DAH phosphonate), a potential inhibitor of the shikimate pathway (Scheme 10).

1.15.8 CONCLUSION AND FUTURE PERSPECTIVES

A large number of other aldolases have been isolated and characterized (Table 5).[33,42,43,111-127] Limited explorations of substrate specificity have been made in many cases but these enzymes have not yet been used in synthetic organic chemistry. In terms of potential utility as catalysts, the aldolases of bacterial origin may be of more use than the enzymes from plant or animal sources because the former are more easily cloned and altered by genetic engineering than the latter. The alterations should prove to be useful for controlling the substrate specificity of these enzymes.



Enzymes: i, hexokinase; ii, pyruvate; iii, transketolase; iv, DAHP synthetase

Scheme 10

Table 5 Summary of the Different Aldolases Available for Use in Asymmetric Organic Synthesis

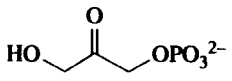
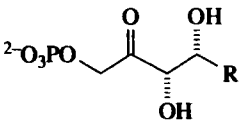
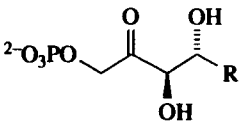
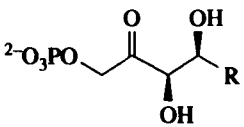
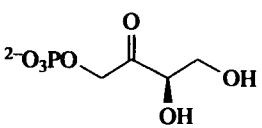
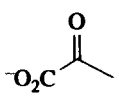
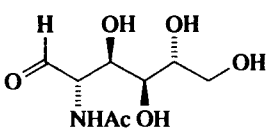
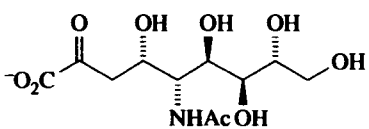
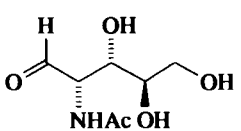
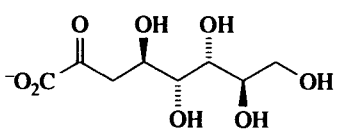
Nucleophile	*Electrophile*	*Enzyme*	*Product*	*Ref.*
		Fructose-1,5-diphosphate aldolase (E.C. 4.1.2.7)		42, 43, 111
		Fuculose-1-phosphate aldolase (E.C. 4.1.2.17)		112
		Rhamulose-1-phosphate aldolase (E.C. 4.1.2.19)		113
		Erythulose-1-phosphate aldolase (E.C. 4.1.2.2)		114
		Neuraminic acid aldolase (E.C. 4.1.3.3)		90, 115
		2-Keto-3-deoxyoctanoate aldolase (E.C. 4.1.2.23)		116

Table 5 *(continued)*

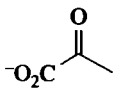
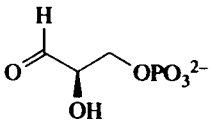
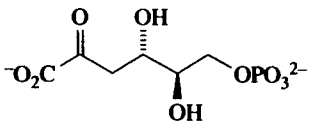
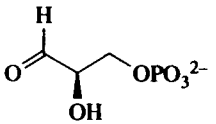
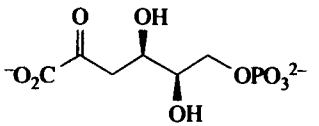
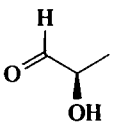
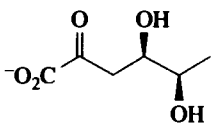
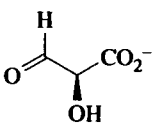
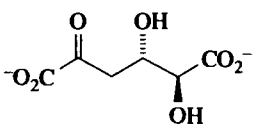
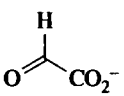
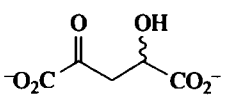
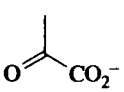
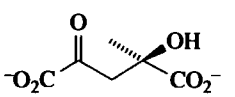
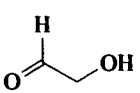
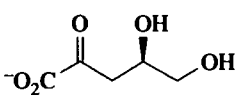
Nucleophile	*Electrophile*	*Enzyme*	*Product*	*Ref.*
		2-Keto-3-deoxy-6-phosphogluconate aldolase (E.C. 4.1.2.14)		117
		2-Keto-3-deoxy-6-phosphogalactonate aldolase (E.C. 4.1.2.21)		117
		2-Keto-3-deoxy-L-arabinoate aldolase (E.C. 4.1.2.18)		117
		2-Keto-3-deoxy-D-glucoarate aldolase (E.C. 4.1.2.20)		117
		2-Keto-4-hydroxyglutarate aldolase (E.C. 4.1.2.31)		117
		4-Methyl-4-hydroxy-2-ketoglutarate aldolase		117
		2-Keto-3-deoxy-L-arabinate aldolase (E.C. 4.1.2.18)		117

Table 5 *(continued)*

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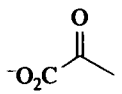
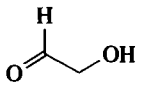
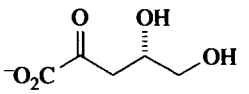
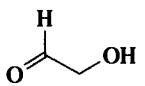
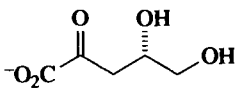
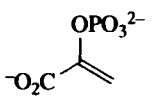
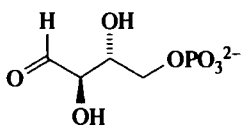
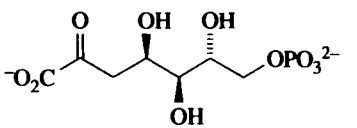
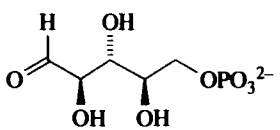
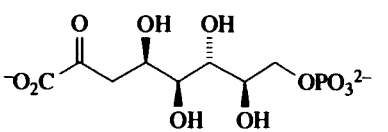
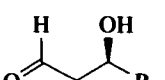
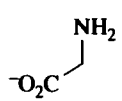
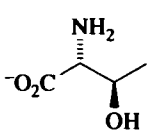
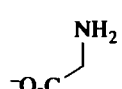
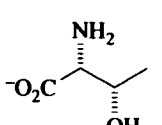
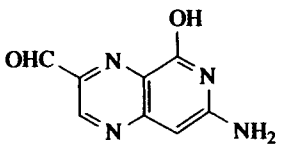
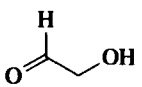
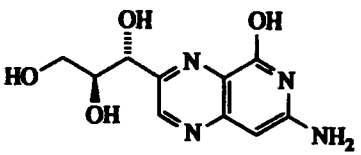
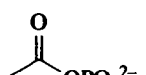
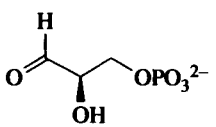
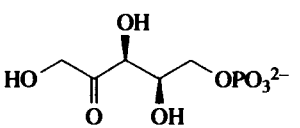
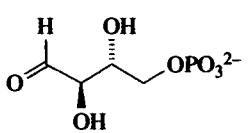
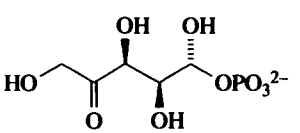
		2-Keto-3-deoxy-D-pentanoate aldolase (E.C. 4.1.2.28)		118
		Hydroxybutyrate aldolase (E.C. 4.2.1.1)		119
		Phosphono-2-keto-3-deoxyheptanoate aldolase (E.C. 4.2.1.15)		120
		Phosphono-2-keto-3-deoxyoctanoate aldolase (E.C. 4.2.1.16)		121
		Deoxyribose aldolase (E.C. 4.1.2.4)		122
		Threonine aldolase (E.C. 4.1.2.5)		123
		Serine hydroxymethyl transferase (allothreonine aldolase) (E.C. 4.1.2.6)		124

Table 5 *(continued)*

Nucleophile	*Electrophile*	*Enzyme*	*Product*	*Ref.*
		Dihyroneopterin aldolase (E.C. 4.1.2.25)		125
		Phosphoketolase (E.C. 4.1.2.9)		126
		Fructose-6-phosphate phosphoketolase (E.C. 4.1.2.22)		127

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1.16 Metalloenamines

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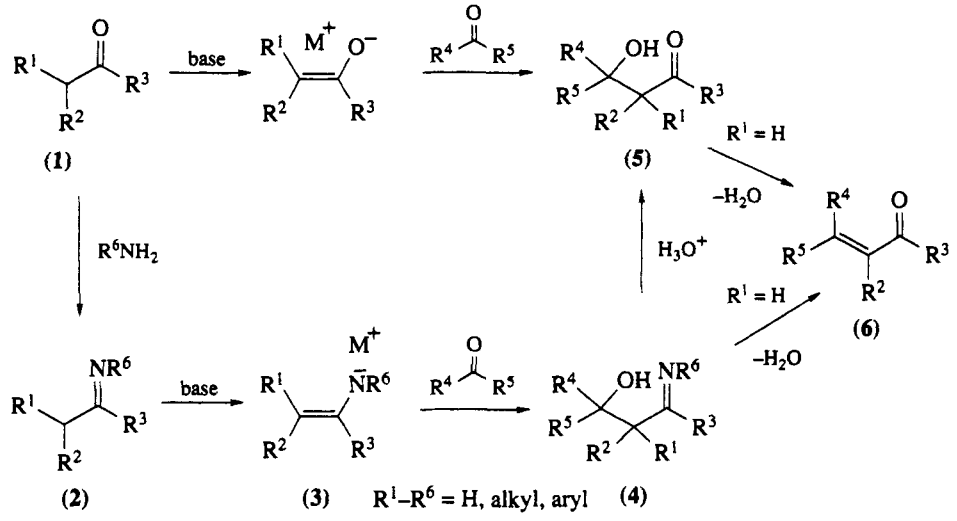
1.16.1 INTRODUCTION

The β-hydroxycarbonyl and α,β-unsaturated carbonyl functional arrays constitute important structural subunits present in a variety of synthetic targets of natural or unnatural origin and in key intermediates leading thereto. The aldol and related reactions stand as highly useful, classical methods for constructing such bifunctional moieties (Scheme 1).[1] One important variant of this reaction features the refunctionalization of the carbonyl group of the aldehyde or ketone (**1**) to the corresponding imine (**2**). Subsequent regioselective deprotonation of this imine with a suitable, nonnucleophilic base followed by the reaction of the intermediate imine anion (metalloenamine; **3**) with a carbonyl partner yields a β-hydroxyimine (**4**), which may be transformed by hydrolysis into the corresponding β-hydroxy aldehyde or ketone (**5**) or by hydrolysis and dehydration into the corresponding α,β-unsaturated carbonyl compound (**6**).[2] This overall process results in the two-carbon homologation[3] of the carbonyl group of the electrophilic partner R^4R^5CO to provide a structurally more complex product that may be further elaborated. Although an extra step is required for the conversion of the carbonyl function of the starting material into the corresponding imine, the enhanced nucleophilicity coupled with a low propensity to suffer proton transfer of

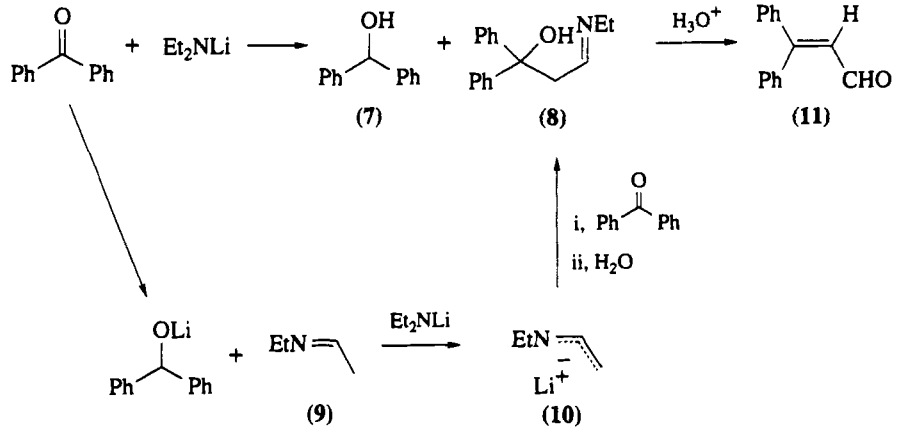
the resulting imine anions relative to the corresponding enolates often justifies the additional steps required. Moreover, the low electrophilicity of the azomethine group ensures that there will be no side reactions involving nucleophilic additions of the intermediate imine anions to either starting or product imines.



Scheme 1

The metallation of aldimines (**2**; R^3 = H) may be readily achieved using lithium dialkylamides and Grignard reagents as bases; alkyllithium reagents are not generally useful because of competing addition to the carbon–nitrogen double bond. Depending upon the experimental conditions (*e.g.* solvent, temperature and base) and the nature of the *N*-substituent, deprotonation of the unsymmetrical ketimines (**2**; R^3 = alkyl) may lead to either the less-substituted or more-substituted imine anion; these regiochemical issues have been previously examined in some detail.[4]

Interestingly, the discovery of imine anions as potentially useful synthetic intermediates was made serendipitously by Wittig approximately 30 years ago.[5] Acting upon an earlier discovery that lithium diethylamide may serve as a hydride donor to benzyne, Wittig examined the reaction of lithium diethylamide with benzophenone to ascertain whether the latter might also serve as a hydride acceptor. Surprisingly, the products observed from this reaction were benzhydrol (**7**) and the β-hydroxy aldimine (**8**) rather than the expected oxidation product (**9**). The sequence of reactions depicted in Scheme 2 was then proposed to account for this unexpected transformation. The initially produced aldimine (**9**) undergoes deprotonation with a second equivalent of lithium diethylamide to provide the imine anion (**10**),



Scheme 2

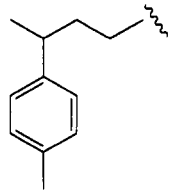
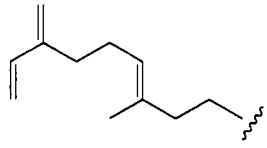
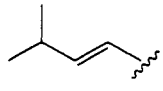
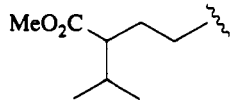
which adds to benzophenone to provide (**8**); hydrolysis and dehydration of (**8**) furnishes (**11**). The net result of this unexpected process is a 'directed aldol reaction' of acetaldehyde with benzophenone, a transformation that cannot otherwise be easily achieved.

1.16.2 DIRECTED ALDOL REACTIONS OF IMINE ANIONS

1.16.2.1 Reactions of Imine Anions Derived from Aldimines

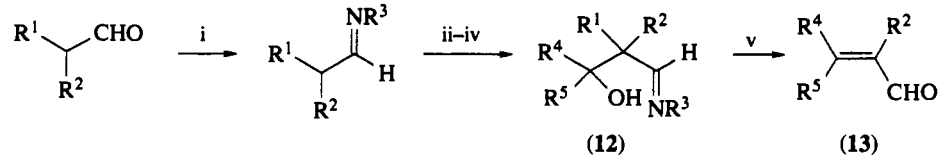
Following this exciting discovery Wittig, and subsequently others,[6–12] then explored the scope and limitations of this process, and the development of a highly useful directed aldol reaction evolved for the preparation of α,β-unsaturated aldehydes (**13**; Scheme 3); some representative results are collected in

Table 1 Directed Aldol Reactions of Metallated Aldimines with Carbonyl Compounds (Scheme 3)

R^1	R^2	R^3	R^4	R^5	*Yield of (12) (%)*	*Yield of (13) (%)*	*Ref.*
H	H	c-C_6H_{11}	Ph	Me	80	65	6
H	H	c-C_6H_{11}	Ph	H	94	77	6
H	H	c-C_6H_{11}		—$(CH_2)_5$—	92	58	6
H	H	c-C_6H_{11}	Pr^n	H	Not isolated	65	7
H	H	c-C_6H_{11}		Me	76	64	7
H	H	c-C_6H_{11}	Ph	Ph	92	100	7
H	Me	c-C_6H_{11}	Ph	Ph	91		7
H	Et	c-C_6H_{11}	Ph	Ph	71		7
Me	Me	c-C_6H_{11}	Ph	Ph	29		7
Et	Et	c-C_6H_{11}	Ph	Ph	0		7
H	Me	Bu^t		H	—	83[a]	8
H	Me	Bu^t		H		60	9
H	H	Bu^t		H		50	10
H	H	c-C_6H_{11}	—$(CH_2)_2CH{=}CMe$—		75	55[b]	11
H	H	c-C_6H_{11}	—$(CH_2)_2CMe{=}CH$—			57[c]	11
H	H	c-C_6H_{11}		Me		44[c,d]	12

[a](*E*)-isomer only. [b](*E*):(*Z*)=9:1. [c](*E*):(*Z*)=3:2. [d]Hydroxy aldehyde isolated in 77% yield and dehydration accompanied by retroaldol.

Table 1, examination of which provides ample support for the generality of the process. It is noteworthy that increased branching at the carbon α to the imine function leads to decreased yields of the desired adducts (**12**); the reason for this failure has not been addressed, but reversion by retroaldolization is one likely possibility. The base that was typically employed to effect the deprotonation of the intermediate aldimines was lithium diisopropylamide, since alkyllithiums were found to add to the carbon–nitrogen double bond of the aldimines. Wittig observed in a number of instances that the overall yields of α,β-unsaturated carbonyl compounds obtained according to this procedure were better than by the corresponding classical Wittig reaction.[7] Interestingly, the anion derived from the *t*-butylimine of isobutyraldehyde reacts with selected α,β-unsaturated ketones to give 1,4-adducts, whereas the corresponding hydrazone anions add to such ketones to provide the 1,2-adducts.[13]

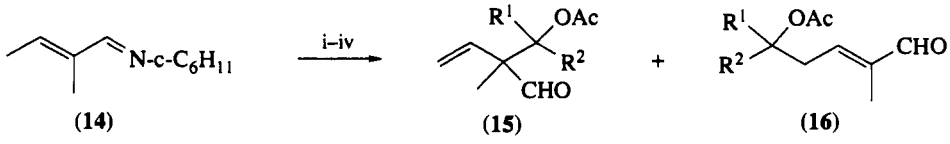


(12) (13)

i, R^3NH_2, $-H_2O$; ii, base; iii, R^4R^5CO; iv, H_2O; v, H_3O^+, $-H_2O$ with $R^1 = H$

Scheme 3

Anions derived from the aldimine of tiglaldehyde (**14**) react with carbonyl compounds preferentially at the α-position under conditions of kinetic control to give adducts (**15**), but products (**16**) derived from γ-attack are obtained under equilibrating conditions (Scheme 4).[14] Addition of HMPA to the reaction or adduct mixture is required to promote isomerization of the initially formed α-adduct to the γ-product. There is also an increasing preference for γ-capture of the unsaturated imine anion as the degree of substitution α to the carbonyl function increases as in α-branched aldehydes and ketones (Table 2). Efforts to isomerize the initial α-adduct formed from reaction of the aldimine derived from crotonaldehyde with cyclohexanecarbaldehyde gave complicated mixtures.



(14) (15) (16)

i, LDA, THF, 0 °C; ii, R^1R^2CO, HMPA, −78 °C; iii, Ac_2O, −78 °C; iv, H_3O^+

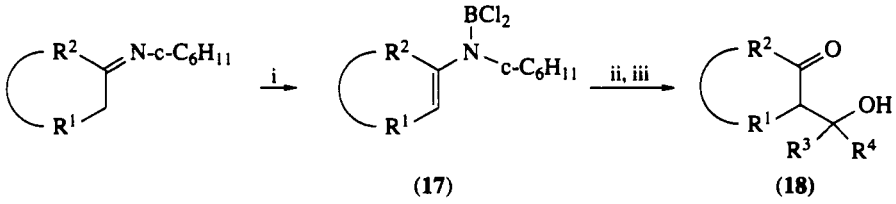
Scheme 4

Table 2 Additions of Metallated (**14**) to Carbonyl Compounds (Scheme 4)

R^1	R^2	(**15**) (%)	(**16**) (%)
c-C_6H_{11}	H	36[a] (6[b])	24[a] (73[b])
Ph	H	71[a] (<3[b])	<3[a] (70[b])
Pr^n	H	71[a] (<3[b])	11[a] (70[b])
$PhCH_2CH_2$	H	54[a] (15[b])	3[a] (66[b])
—$(CH_2)_5$—		<3[a]	70[a,c]

[b]In the absence of HMPA. [c]In the presence of HMPA. [d]Isolated free alcohol rather than acetate.

An interesting variant of the original reaction discovered by Wittig has been reported in which carbonyl compounds undergo reactions with vinylaminodichloroboranes (**17**) derived from ketimines to give, upon hydrolytic work-up, the expected aldol adducts (**18**; Scheme 5).[15] The reactions proceed in fair to good overall yields but with relatively poor diastereoselectivity (Table 3). The extension of this reaction



(17) (18)

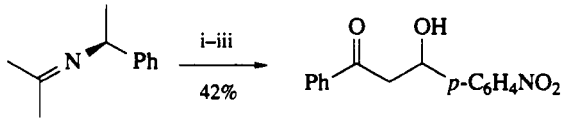
i, BCl_3, Et_3N, CH_2Cl_2, Δ; ii, R^3R^4CO, Δ; iii, H_3O^+

Scheme 5

Table 3 Directed Aldol Reactions of Vinylaminodichloroboranes (**17**) with Carbonyl Compounds (Scheme 5)

R^1	R^2	R^3	R^4	*Yield of (18) %*	*erythro:threo*
—$(CH_2)_4$—		Ph	H	71[a]	2
—$(CH_2)_4$—		$PhCH2CH_2$	H	52[a](39[b])	1
—$(CH_2)_4$—		Me	Me	31[a]	
—$(CH_2)_4$—		—(CH2)5—		28[a]	
Me	Et	p-$O_2NC_6H_4$	H	59[a]	3
—$(CH_2)_3CH(Me)$—		Ph	H	37[b]	
H	Ph	p-$O_2NC_6H_4$	H	46[b]	

[a]Overall yield based on carbonyl compound for two-step procedure with isolation of intermediate vinylaminodichloroborane.
[b]Isolated yield of aldol adduct according to one-pot procedure.



(19) 35% *ee*

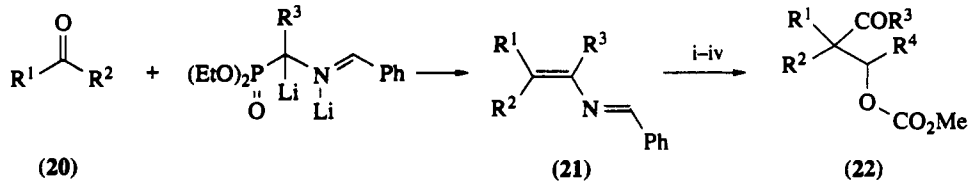
i, BCl_3, Et_3N; ii, p-$O_2NC_6H_4CHO$; iii, H_3O^+

Scheme 6

to the asymmetric synthesis of β-hydroxy ketones through the use of a chiral auxiliary on nitrogen has also been reported as illustrated in Scheme 6; however, these reactions proceeded with only modest chemical yields (30–42%) and enantioselectivity (35–48%).[16] The additions of the corresponding magnesium and lithium imine anions derived from (**19**) to p-nitrobenzaldehyde proceeded with even lower yields (6–15%) and enantiomeric excesses (19–7%).

1.16.2.2 Reactions of Imine Anions Derived from 2-Azadienes

Historically, imine anions have been typically prepared by deprotonation of the corresponding imines, but a highly useful alternative route to these reactive intermediates features the regioselective 1,2-addition of alkyllithium reagents to 2-azadienes (**21**).[17–19] Although the requisite 2-azadienes may be prepared by isomerization of either *N*-allylimines or the imines of α,β-unsaturated ketones,[19] one particularly useful procedure has been devised that involves alkenation of carbonyl compounds with the aminoalkylphosphonate reagent (**20**; Scheme 7).[17] Sequential reaction of the 2-azadienes (**21**) thus produced with *n*-butyllithium and an aldehyde affords intermediate adducts that may be trapped with methyl chloroformate to furnish protected β-hydroxycarbonyl compounds in very good overall yields (Table 4). This novel procedure for effecting the net geminal acylation/hydroxyalkylation of a carbonyl group has been nicely exploited for the formation of quaternary carbons bearing differentially functionalized alkyl appendages.

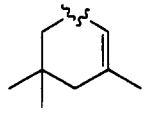


(20) (21) (22)

i, Bu^nLi; ii, R^4CHO; iii, MeO_2CCl; iv, H_3O^+

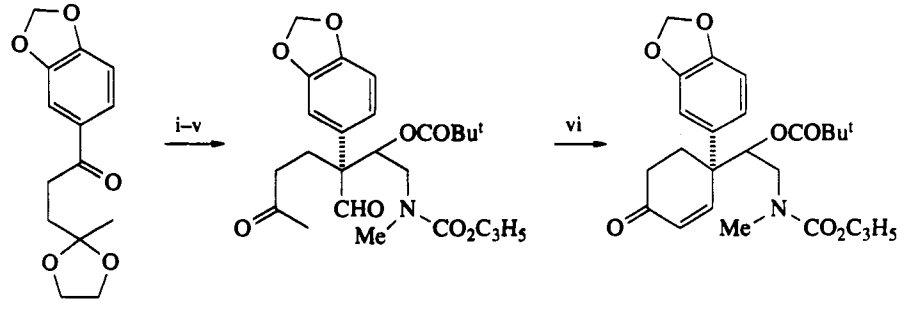
Scheme 7

Table 4 Geminal Acylation/Hydroxyalkylation of Carbonyl Compounds (Scheme 7)

R^1	R^2	R^3	R^4	*Overall yield of (22)* (%)
Pr^n	Pr^n	H	Ph	56
—$(CH_2)_5$—		H	Pr^n	45
—$(CH_2)_5$—		H	Ph	47
		H	Ph	59[a]
Ph	Me	H	Pr^n	49[a]
Ph	Me	H	Ph	62[a]
Ph	Me	Me	Ph	51[a]

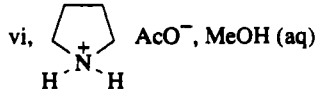
[a]Obtained as mixture of diastereomers 45:55–40:60.

The general utility of this method is nicely illustrated by its application to the synthesis of the cyclohexenone (**24**), a key synthetic intermediate in the synthesis of several of the *Amaryllidaceae* alkaloids, in 51% overall yield from (**23**) as a mixture (1.5:1) of diastereomers (Scheme 8).[18]



(23) (24)

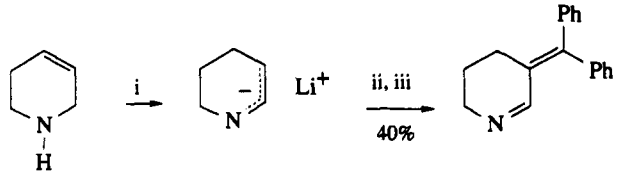
i, $(EtO)_2P(O)CH(Li)N{=}CHPh$; ii, Bu^nLi, $ZnCl_2$; iii, $CH_2{=}CHCH_2OCON(Me)CH_2CHO$; iv, Bu^tCOCl; v, H_3O^+;



Scheme 8

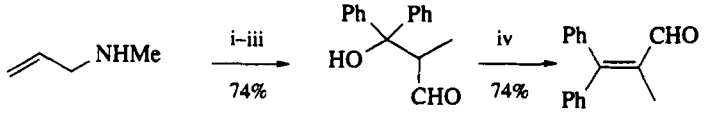
1.16.2.3 Reactions of Endocyclic Imine Anions Derived from Unsaturated Heterocycles

Imine anions obtained by isomerization of heterocyclic, secondary allylic amines[19] with *n*-butyllithium add to benzophenone (Schemes 9 and 10).[20] However, the generality of this process with respect to the allylamine starting material and the carbonyl partner remains to be established.



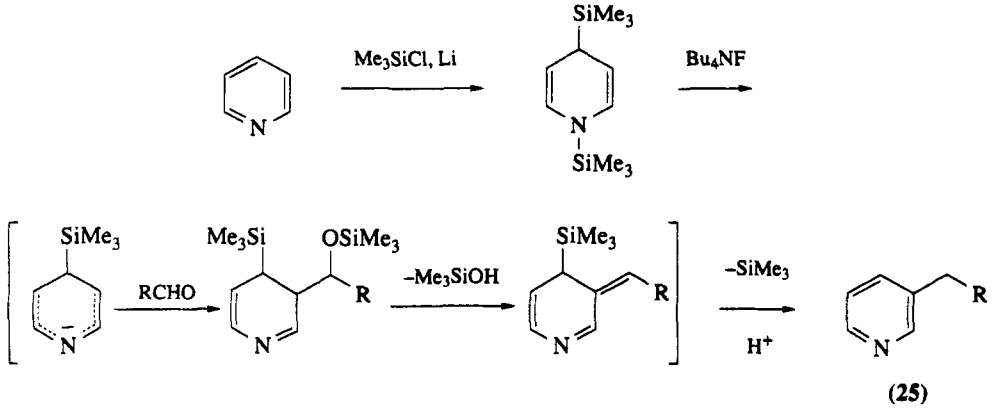
i, Bu^nLi, THF, r.t.; ii, Ph_2CO; iii, H_2O

Scheme 9

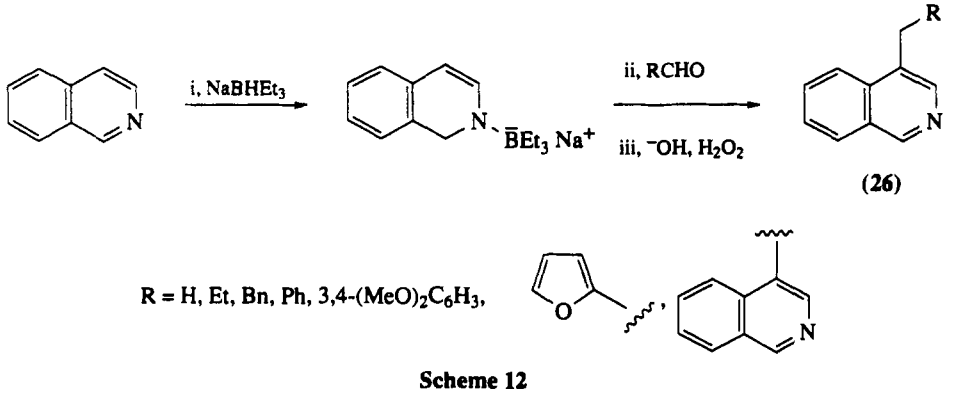


i, BuLi, THF, r.t.; ii, Ph_2CO; iii, H_3O^+; iv, $-H_2O$, Δ

Scheme 10



Scheme 11



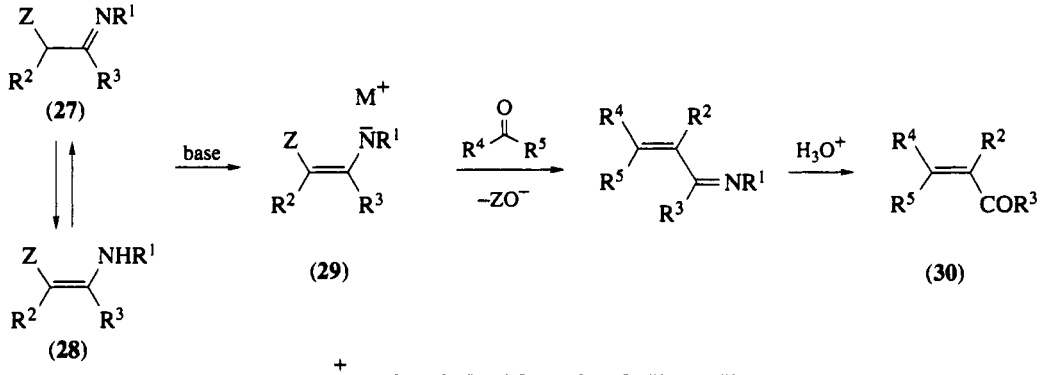
Scheme 12

Several routes to substituted heterocyclic systems have been devised that feature the reactions of unsaturated imine anions formed by reduction of the corresponding aromatic nitrogen heterocycles (Schemes 11 and 12).[21,22] Dehydration of the intermediate adducts gives the alkyl-substituted aromatic heterocycles. These procedures provide useful entries to 3-alkylpyridines (**25**; 15–77% overall yields)[21] and 4-alkylisoquinolines (**26**; 25–65% overall yields).[22]

1.16.3 ADDITION REACTIONS OF HETEROATOM-STABILIZED IMINE ANIONS

1.16.3.1 Phosphorus- and Silicon-stabilized Imine Anions

The discovery that imine anions (**29**) bearing either phosphorus- or silicon-derived anion-stabilizing groups α to the imine function also serve as nucleophilic partners in reactions with carbonyl compounds has led to the development of several useful synthetic methods for the preparation of α,β-unsaturated carbonyl compounds (Scheme 13). There is an equilibrium, which is a function of the substituent Z, between the imino and enamino tautomers, (**27**) and (**28**) respectively, of the starting material; when Z = $(EtO)_2P(O)$, the major isomer present in solution is (**28**). The starting imines or enamines for the formation of the anions (**29**) may be readily prepared upon condensation of the corresponding carbonyl compound with a suitable amine[23,24] or by nucleophilic addition of a primary amine to the corresponding alkynyl-1-phosphorus compounds.[25,28,29] Recently, however, more expeditious routes for the preparation of lithiated enamino alkylphosphonates [**29**; Z = $(EtO)_2P(O)$] have been devised.[26,27] The intermediate adducts formed upon the reaction of anions generated upon metallation of (**27**) or (**28**) with aldehydes and ketones typically undergo spontaneous elimination to provide α,β-unsaturated imines that may then be hydrolyzed to furnish α,β-unsaturated carbonyl compounds (**30**). The overall process results in the efficient two-carbon homologation of the carbonyl function of the electrophilic partner R^4R^5CO.



Z = $Ph_3\overset{+}{P}$, $(EtO)_2PO$, Ph_2PO, $(EtO)_2PS$, $SiMe_3$, $SiEt_3$, *etc.*

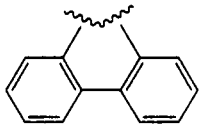
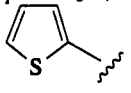
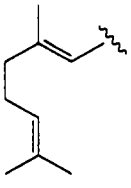
Scheme 13

Representative examples of this transformation are collected in Table 5. Examination of these results reveals that these processes generally proceed in good to very good overall yields, and a variety of aldehydes and ketones may be employed as the electrophiles. The overall yields are often best when the more nucleophilic anions derived from the phosphonates [**27/28**; Z = $(EtO)_2P(O)$] are employed rather than the anions of the phosphoranes (**27/28**; Z = Ph_3P^+). Indeed the phosphonate-derived reagents (**27/28**; Z = $(EtO)_2P(O)$; R^3 = H) are vastly superior to the phosphorane $Ph_3P{=}CHCHO$ for the conversion of aldehydes and ketones to α,β-unsaturated aldehydes.[24]

A useful alternative to the Wittig-type reactions of carbonyl compounds with the phosphorus-stabilized imine anions [**29**; Z = Ph_3P^+, $(EtO)_2P(O)$, $Ph_2P(O)$ and $(EtO)_2P(S)$] has been developed which features a variant of the Peterson alkenation.[31–37] This process involves the condensation of the related α-silyl anions (**29**; Z = R_3Si) with carbonyl partners. The reaction was originally developed using the α-trimethylsilyl analogs (**29**; Z = Me_3Si),[31–34] but there now appears to be a preference for the use of the corresponding α-triethylsilyl derivative (**29**; Z = Et_3Si).[36,37] Although reaction times using the latter reagents are somewhat longer than required for the corresponding trimethylsilyl analog, the starting α-triethylsilylimines are more readily available in pure form.[36] As may be seen from examination of Table 6, the overall yields of new α,β-unsaturated aldehydes and ketones prepared by this procedure are generally

very good to excellent, often better than the corresponding Wittig process. The one apparent drawback that is evident from early work in this area is that the (*E*):(*Z*) ratios were typically poor, ranging from 1:1 to 3:1. However, recently it has been discovered that treatment of (*E*)/(*Z*) mixtures of the intermediate α-methyl-α,β-unsaturated imines with anhydrous acid followed by hydrolysis affords the corresponding α,β-unsaturated aldehydes in ≥100:1 (*E*):(*Z*) ratios.[37]

Table 5 Reaction of α-Phosphorus-stabilized Imine Anions with Carbonyl Compounds (Scheme 13)

Z	R^1	R^2	R^3	R^4	R^5	*Overall yield of (30) (%)*[a]	*Ref.*
Ph_3P^+	c-C_6H_{11}	H	H	Ph	H	36[b]	23
	p-$Me_2NC_6H_4$	H	H	Ph	H	61[b]	
	p-$Me_2NC_6H_4$	H	H	PhCH=CH	H	20[b]	
	p-$Me_2NC_6H_4$	H	H			25[b]	
$(EtO)_2P(O)$	c-C_6H_{11}	H	H	—$(CH_2)_5$—		86	24
		Me	H	—$(CH_2)_5$—		66	
		Bn	H	—$(CH_2)_5$—		63	
		H	H	Ph	H	77	
		H	Pr^n	Ph	H	55	25
		H	Ph	*p*-$MeOC_6H_4$	H	53	
		H	Me	Ph	Me	46	
	Bu^n	H	Bu^n	Ph	H	65	
		H	Bu^n	—$(CH_2)_5$—		67	
	Bu^t	H	H	Ph	H	70	26
				$Ph(CH_2)_2$	H	73	
				c-C_6H_{11}	H	76	
				PhCH=CH—	H	67	
				—$(CH_2)_5$—		94	
				Pr^n	Pr^n	53	
				Ph	Ph	71	
				Pr^i	Me	72	
$(EtO)_2P(O)$	Ph	Me	H	Ph	H	71	27
		Pr^n	H	Ph	H	66	
		Et	H	*p*-MeC_6H_4	H	68	
		Me	H		H	47	
		Me	H	PhCH=CH—	H	45	
		Me	H	Et	H	42	
		Me	H	Pr^i	H	60	
		Me	H		H	32	
$Ph_2P(O)$	Bu^n	H	Bu^t	*p*-$MeOC_6H_4$	H	66	28
			Ph	Ph	H	57	
			Bu^t	Ph	H	61	
			Pr^n	Ph	H	63	
			c-C_5H_9	Ph	H	59	
			c-C_6H_{11}	Ph	H	70	
			Ph	Ph	Ph	62	
	Bn	H	Ph	—$(CH_2)_5$—		53	
$(EtO)_2P(S)$	Bu^n	H	n-C_6H_{13}	Ph	H	37	29

[a]Unless otherwise indicated, isolated as α,β-unsaturated carbonyl compound. [b]Isolated as α,β-unsaturated imine.

Table 6 Reactions of α-Trialkylsilyl-stabilized Imine Anions with Carbonyl Compounds (Scheme 13)

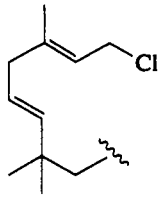
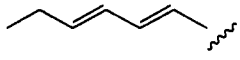
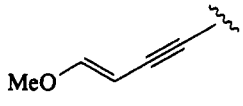
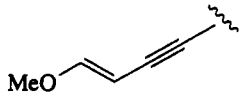
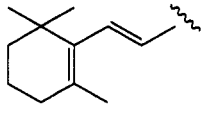
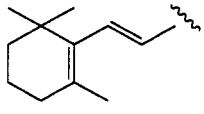
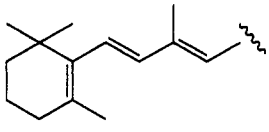
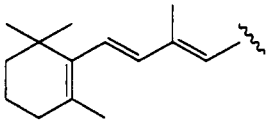
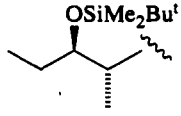
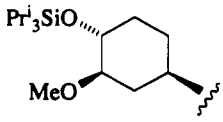
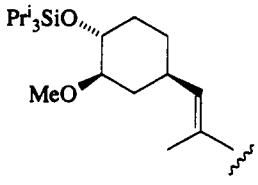
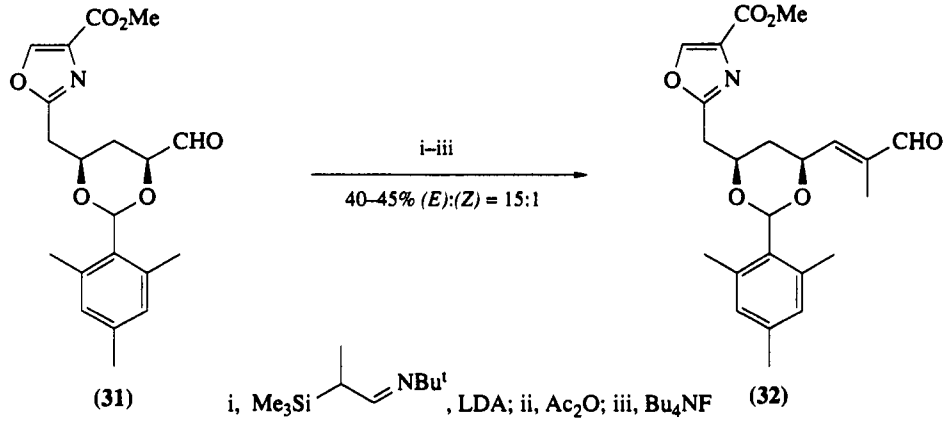
Z	R^1	R^2	R^3	R^4	R^5	*Overall yield of (30) (%)*[a]	*(E):(Z)*[b,c]	*Ref.*
Me_3Si	Bu^t	H	H	n-C_5H_{11}	H	94		31
					—$(CH_2)_5$—	90		
		Me	H	Pr^n	H	88		
					—$(CH_2)_5$—	90		
				Ph	H	90	1:1[b]	
					H	79	3:1[b]	32
		H	H		H	45	12:1[b]	33
					H	60		34
					Me	80		
		H	Me		Me	59	47:53[b]	35
		Me	Me		Me	52	17:83[b]	
		H	Me		H	65	62:38[b]	
	Bu^t	Me	Me		H	53	41:59[b]	
		H	Me	Ph	Me	58	59:41[b]	
		Me	Me	Ph	Me	<10		
		H	Me	Ph	H	81		
Et_3Si	Bu^t	Me	H		H	77		36

Table 6 (*continued*)

Z	R^1	R^2	R^3	R^4	R^5	*Overall yield of (30) (%)*[a]	*(E):(Z)*[b,c]	*Ref.*
Et_3Si	c-C_6H_{11}	Me	H		H	84 85	100:1[c] 2:1[b]	37
				Ph	H	91	>100:1[c]	
				n-C_7H_{15}	H	82 83	>100:1[c] 6:1[b]	
					H	68	>100:1[c]	

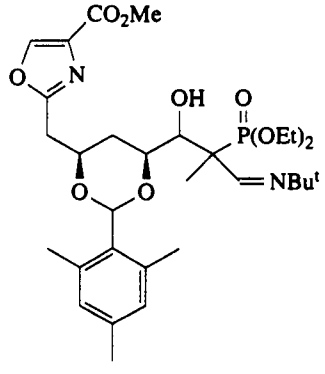
[a]Overall yield of α,β-unsaturated carbonyl compound. [b]Hydrolytic workup with aqueous acid. [c]Anhydrous isomerization with trifluoroacetic acid followed by hydrolytic work-up with aqueous acid.



(31)

i, Me_3Si NBu^t, LDA; ii, Ac_2O; iii, Bu_4NF

(32)



(33)

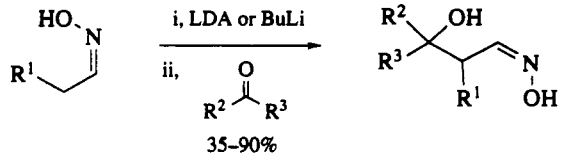
Scheme 14

The transformation outlined in Scheme 14 nicely illustrates some of the advantages associated with the Peterson alkenation relative to the Horner–Emmons reaction for the conversion of the aldehyde (**31**) into the α,β-unsaturated aldehyde (**32**). When the corresponding phosphonate reagent is used, only the β-hydroxy phosphonate (**33**) is isolated; elimination to form the α,β-unsaturated imine from (**33**) could not be induced under a variety of conditions.[30]

1.16.4 ADDITION REACTIONS OF METALLATED OXIME DERIVATIVES

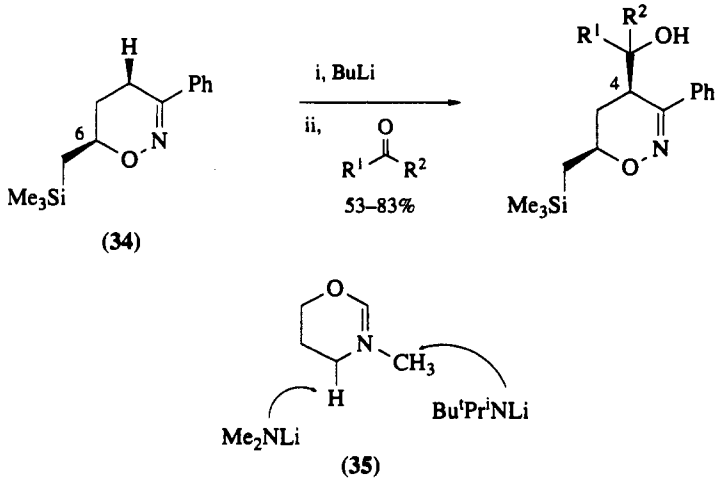
1.16.4.1 Acyclic and Cyclic Oxime Anions

The dianions of (*Z*)-oximes react with aldehydes and ketones to give β-hydroxy oximes in good to very good yields (Scheme 15);[38,39] no dianion formation occurs with (*E*)-aldoximes.



Scheme 15

Deprotonation of the chiral 1,2-oxazine (**34**) by *n*-butyllithium proceeds with a high degree of stereoselectivity *cis* to the C-6 substituent; subsequent capture of this carbanion with carbonyl compounds also proceeds *syn* to the C-6 substituent, so that the overall process occurs with retention of configuration at C-4 (Scheme 16).[40] Although the related 1,2-oxazine (**35**) has not been condensed with carbonyl compounds, it is useful to note that the regioselectivity of its deprotonation can be easily controlled by the size of the base employed. Bulky amide bases preferentially abstract the proton at the exocyclic methyl group, whereas small amide bases such as lithium dimethylamide preferentially abstract a proton at C-4.[41]

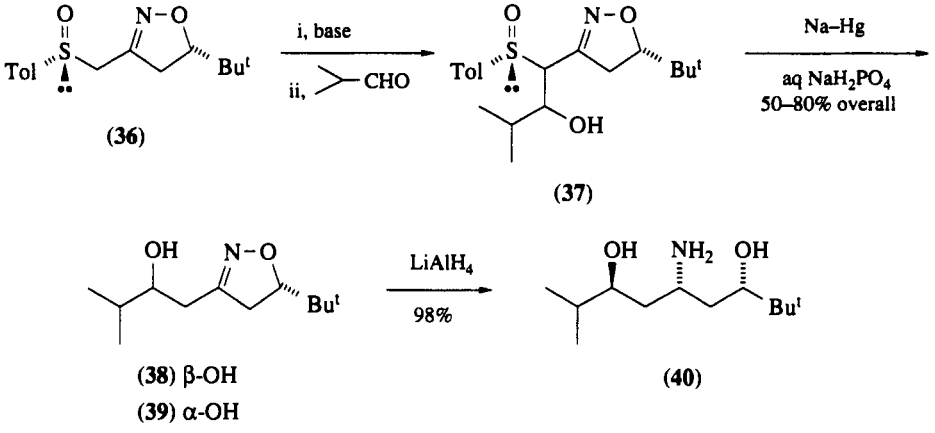


Scheme 16

1.16.4.2 Stabilized Oxime Anions

A useful protocol for effecting the stereoselective synthesis of masked β,β′-dihydroxy ketones and compounds derived therefrom has recently been developed (Schemes 17 and 18).[42] The process features the metallation of enantiomerically pure 3-*p*-tolylsulfinylmethyl-4,5-dihydroisoxazoles such as (**36**), followed by reaction with an aldehyde to give the intermediate adducts (**37**). The diastereomeric ratio of the

adducts obtained varies with the nature of the base used to deprotonate the starting arylsulfinylisoxazole (**36**). For example, when *t*-butylmagnesium bromide is the base, the diastereomeric ratio of the adducts (**37**) is 8:1, whereas when lithium diisopropylamide is the base, the ratio is 1.1:1; other bases give intermediate ratios of products. At least in the specific case illustrated in Scheme 17, the new stereocenter α to the sulfoxide group appears to be formed with a high degree of stereoselectivity, and the adducts are epimeric only at the hydroxy-bearing carbon. Based on other results (*vide infra*, Scheme 18), the major product obtained upon reductive removal of the sulfinyl group of diastereoisomers is (**38**). Subsequent reduction of (**38**) with lithium aluminum hydride gives the aminodiol (**40**) with >50:1 stereoselectivity.



(**36**)

(**37**)

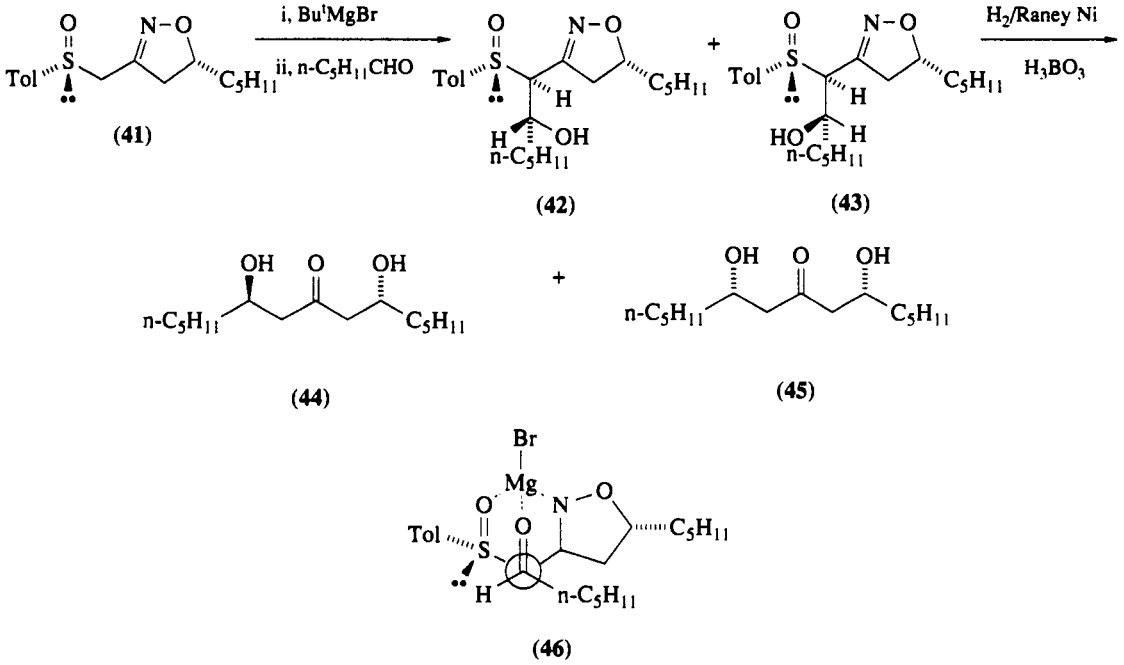
(**38**) β-OH

(**39**) α-OH

(**40**)

Scheme 17

The adducts obtained upon reaction of enantiomerically pure, metallated sulfinyl-4,5-dihydroisoxazoles with aldehydes can be converted into β,β′-dihydroxy ketones in what is the equivalent of a regiospecific double aldol condensation of a ketone with two different aldehydes (Scheme 18). For example, metallation of (**41**) with *t*-butylmagnesium bromide followed by quenching the intermediate anion with



(**41**)

(**42**)

(**43**)

(**44**)

(**45**)

(**46**)

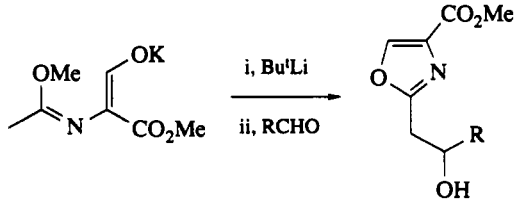
Scheme 18

n-hexanal gives a mixture (3:1) of diastereomers (**42**) and (**43**); hydrogenolysis and hydrolysis of the isoxazoline ring leads to a mixture (3:1) of the optically active dihydroxy ketone (**44**) and the *meso*-dihydroxy ketone (**45**). Based on the results of this experiment, a transition state was proposed for additions of metallated derivatives of (**36**) to aldehydes in which the aldehyde approaches the chiral azaenolate according to (**46**).

1.16.5 ADDITIONS OF METALLATED DERIVATIVES OF IMIDATES

1.16.5.1 Acyclic Imidates

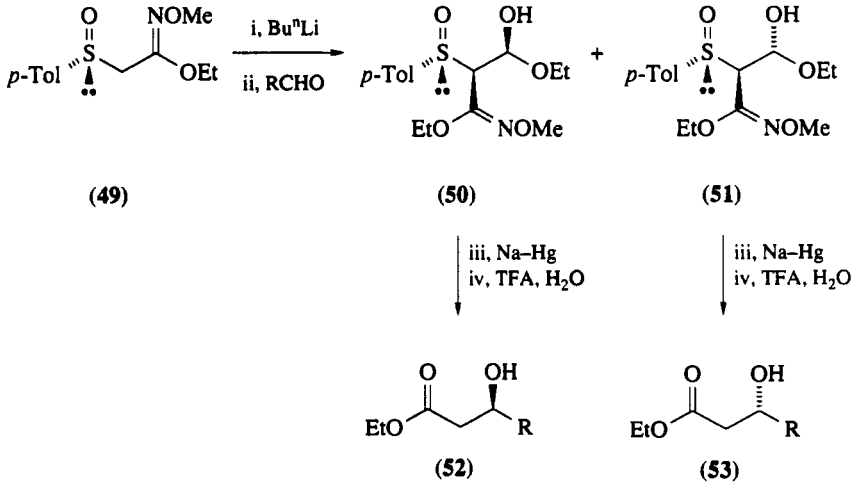
Metallation of the acyclic imidate salt (**47**) followed by reaction of the intermediate dianion with aldehydes leads to the production of the oxazoles (**48**; Scheme 19).[30] This procedure constitutes a useful modification of the Cornforth oxazole synthesis.



(**47**) (**48**)

Scheme 19

Metallation of the arylsulfinyl-*N*-methoxyacetimidate (**49**), which may be prepared in two steps from commercially available *N*-hydroxyacetimidate, followed by reaction with aldehydes provides adducts that after sequential desulfurization and hydrolysis may be converted into β-hydroxy esters with ≥80% enantiomeric excess (Scheme 20).[43] Thus, under kinetic conditions the reaction of the anion derived from (**49**) with aldehydes gives mixtures of the *syn* and *anti* products, (**50**) and (**51**) respectively, in nearly equal amounts. Under thermodynamic conditions, however, the more stable *anti* adducts (**51**) dominate, and after desulfurization and hydrolysis the β-hydroxy esters (**53**) are obtained in 75–94% enantiomeric excess. When the zinc enolate derived from (**49**) is condensed with aldehydes, the *anti* adducts (**51**) are again the major products and the β-hydroxy esters (**53**) can be isolated in 76–86% enantiomeric excess. On the other hand, the reaction of the zirconium enolate of (**49**), which is obtained by the addition of Cp_2ZrCl_2 to the corresponding lithium enolate, with aldehydes followed by desulfurization gives β-hy-



(**49**) (**50**) (**51**)

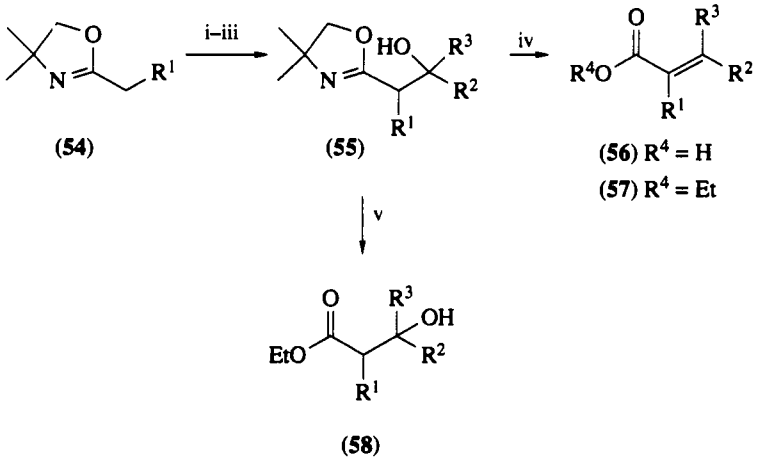
(**52**) (**53**)

Scheme 20

droxy esters (**52**) in 79–88% enantiomeric excess. The only drawback to the use of zirconium enolates is the lower chemical yields in the condensation reaction.

1.16.5.2 Metallated 2-Methyloxazolines

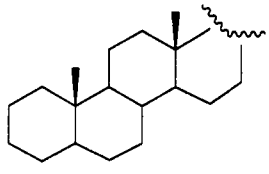
The reactions of metallated 2-methyloxazolines with carbonyl compounds to provide adducts constitute the key step in a general procedure for the conversion of carbonyl compounds into β-hydroxy carboxylic acids and esters or their α,β-unsaturated counterparts (Schemes 21–26).[44–50] For example, reaction of the lithiated derivative of (**54**) with carbonyl compounds provides the adducts (**55**) in high yield (Scheme 21). Subsequent acid-catalyzed hydrolysis provides the unsaturated carboxylic acids (**56**); depending upon the severity of the reaction conditions, acid-induced ethanolysis can be performed on the adducts (**55**) to provide either the unsaturated esters (**57**) or the β-hydroxy esters (**58**) in good yields (Table 7).[45] The main limitation of the method is that extensive retroaldolization occurs upon attempts to hydrolyze adducts (**55**; R^1 = alkyl), so α-alkyl-β-hydroxy esters and acids do not appear to be accessible.



i, BuLi; ii, R_2R_3CO; iii, H_2O; iv, R_4OH, H^+; v, EtOH, H^+

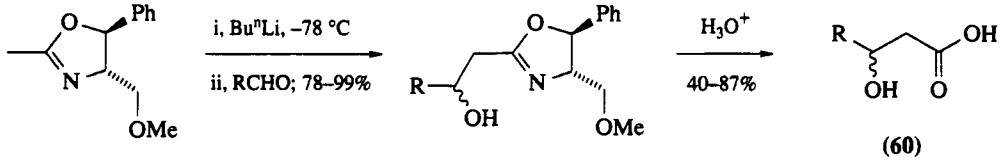
Scheme 21

Table 7 Reactions of Metallated Achiral 2-Alkyloxazolines (**54**) with Carbonyl Compounds (Scheme 21)[45]

R^1	R^2	R^3	(**56**) (%)	(**57**) (%)	(**58**) (%)
H	Me	Me			55
H	Pr^n	Pr^n		80[a]	91
H	—$(CH_2)_5$—		84	88	
H	—$(CH_2)_6$—		90[b]	69[c]	80
H			96		
Me	—$(CH_2)_6$—		88[d]		
Et	—$(CH_2)_5$—		[e]		
Et	Ph	H	[e]		

[a]Contained 54% of the β,γ-unsaturated isomer. [b]Contained 60–70% of the β,γ-unsaturated isomer. [c]Contained 78% of the β,γ-unsaturated isomer. [d]Contained 79% of the β,γ-unsaturated isomer. [e]Although initial 1,2-adduct formed in good yield, there was extensive reversion upon attempted acid-catalyzed hydrolysis of the oxazoline; only retroaldol under alkaline conditions.

After the lithiated chiral oxazoline (**59**) is allowed to react with different aldehydes, the adducts thus obtained can be hydrolyzed to provide optically enriched β-hydroxy acids (**60**), albeit with only poor enantiomeric excesses (18–25%; Scheme 22). When ketones are used as carbonyl partners, the β-hydroxy acids obtained are essentially racemic.[46]

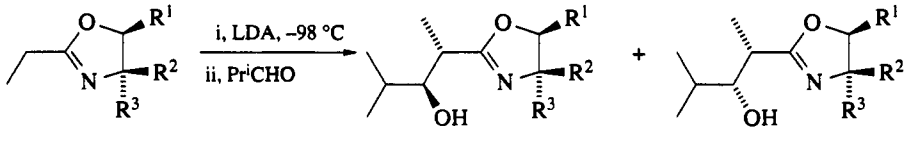


(**59**) (**60**)

R = Me, Et, Bu^t, n-C_6H_{13}, c-C_6H_{11}, Ph

Scheme 22

In a related process, reaction of the metallated derivatives of the 2-ethyloxazolines (**61a–c**) with isobutyraldehyde produces the diastereomeric adducts (**62a–c**) and (**63a–c**) (Scheme 23).[47] Although reaction of the anion derived from (**61a**) with isobutyraldehyde proceeds with low (56:44) *anti*:*syn* selectivity, the reaction of racemic (**61b**) with isobutyraldehyde proceeds with an acceptable level of *anti*:*syn* selectivity to give a mixture (9:1) of the adducts (**62b**) and (**63b**). When the enantiomerically pure oxazoline (**61c**) is lithiated and treated with isobutyraldehyde, four diastereomers are produced in a ratio of 18.3:1:2.4:2.2; the *anti*:*syn* ratio observed in this reaction is thus 82:18.



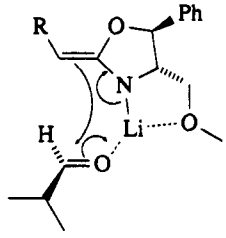
(**61a**)–(**61c**) (**62a**)–(**62c**) (**63a**)–(**63c**)

Series a: R^1 = H; R^2 = R^3 = Me
Series b: R^1 = R^2 = H; R^3 = CH_2OMe
Series c: R^1 = Ph; R^2 = H; R^3 = CH_2OMe

Scheme 23

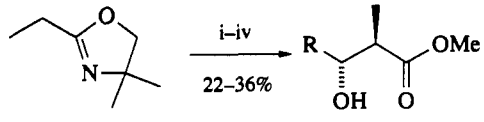
The diastereoselectivity observed during the addition of (**61c**) to isobutyraldehyde stands in marked contrast to the significantly lower selectivity (1.5:1) that was previously observed when the chiral 2-methyloxazoline (**59**) was used as the nucleophilic partner (*vide supra*). The enhanced diastereoselection in the reaction involving (**61c**) is presumably a consequence of internal lithium chelation, which enhances both the selectivity in the deprotonation step as well as the diastereofacial selectivity in the nucleophilic addition to the aldehyde. For example, in separate experiments it was determined that metallation of (**61c**) proceeded with a (*Z*):(*E*) diastereoselectivity of >9:1.[48] Subsequent reaction of this (*Z*)-azaenolate with isobutyraldehyde *via* the chelated, chair-like transition state depicted in (**64**; R = Me), in which steric interactions between the reacting residues are minimized, would lead preferentially to the *anti* isomer (**62c**).[47] For the additions involving (**59**), examination of the related transition state (**64**; R = H) clearly reveals that the facial selectivity should be somewhat less.

By judicious choice of chiral auxiliary–reagent pairs, it has been possible to extend this chemistry to the enantioselective synthesis of β-hydroxy-α-methyl-carboxylic acid derivatives having either *anti* or *syn* stereochemistry (Schemes 24 and 25).[49] For example, the boron azaenolate obtained upon reaction of (**65**) with diisopinocamphenylboryl triflate reacts with a series of aldehydes to provide adducts that are readily converted to the *anti* methyl esters (**66**) in good overall yields (Scheme 24). The *anti*:*syn* ratios for these reactions are typically >9:1, and the percentage enantiomeric excesses for the *anti* adducts are in the range of 77–85%. On the other hand, the boron azaenolate derived from oxazoline (**61c**) and 9-borabicyclononane triflate reacts with aldehydes to give adducts that can be converted into the methyl esters of the *syn*-carboxylic acids (**67**; Scheme 25). The *syn*:*anti* ratios in these reactions are typically



(**64**) R = H, Me

>97:3, but the percentage enantiomeric excesses for the *syn* isomer are only 40–60%. Although it appears that a single boron enolate is formed in the first step of each of these sequences, its geometry is not known. Furthermore, there is not a high correlation between the geometry of the intermediate boron azaenolates that are formed *in situ* and the enantioselectivity of the reaction. Further studies of this process are required to provide the necessary insights.

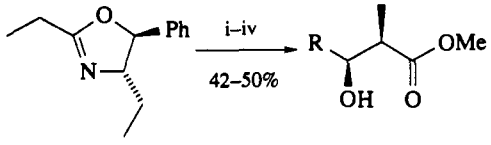


(**65**) (**66**)

i, Ipc_2BOTf; ii, RCHO; iii, H_3O^+, Δ; iv, CH_2N_2

R = Et, Pr^n, n-C_5H_{11}, Pr^i, c-C_6H_{11}, Bu^t

Scheme 24

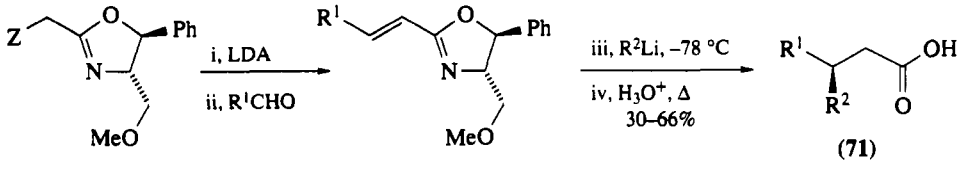


(**61c**) (**67**)

i, 9-BBN-OTf; ii, RCHO; iii, H_3O^+, Δ; iv, CH_2N_2

Scheme 25

The oxazolines (**68**) and (**69**) are useful synthetic intermediates for the preparation of α,β-unsaturated oxazolines (**70**; Scheme 26),[50] but the phosphonate-derived reagent (**69**) gives higher yields (80–93% *vs.* 37–65%) of (**70**) with higher (*E*):(*Z*) ratios (100:1 *vs.* 80:20 to 100:1). The subsequent nucleophilic addition of organolithium reagents to the chiral oxazolines (**70**) followed by hydrolysis of the intermediate adducts furnishes 3-substituted alkanoic acids (**71**) in >90% enantiomeric excess. By simply reversing the order of the introduction of the alkyl groups, the enantiomers of (**71**) can also be obtained. The high optical yields obtained by this process more than compensate for the modest chemical efficiency (overall



(**68**) Z = H
(**69**) Z = $(Pr^iO)_2P(O)$

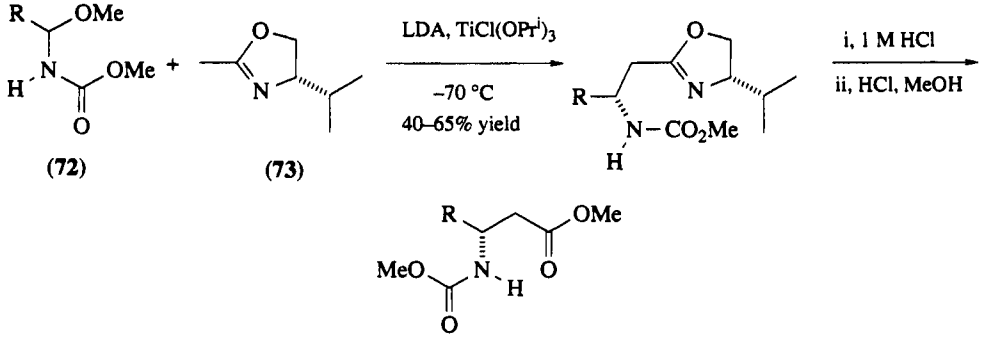
(**70**) R^1 = Me, Et, Ph; R^2 = Et, Bu^n, Ph

(**71**)

Scheme 26

yields 30–66%). Lower yields are generally observed in the 1,4-addition to (**70**) whenever R^1 is alkyl, because of competing deprotonation of the allylic hydrogen of the starting material.

The nucleophilic addition of anions derived from the enantiomerically pure 2-methyloxazoline (**73**) to the *N*-methoxycarbonylimines generated *in situ* from (**72**) provides adducts that may be readily converted into β-amino acid derivatives (**74**) in good overall chemical yield (40–65%) and 72–90% enantiomeric excess (Scheme 27).[51] This transformation has been featured as a key step in the enantioselective synthesis of carbapenem antibiotics.



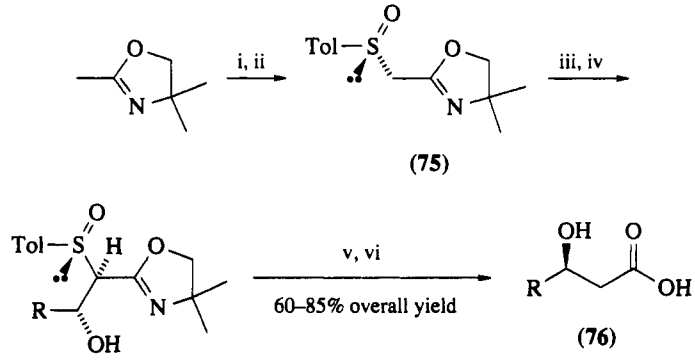
(**72**) (**73**)

(**74**)

R = Pr^i, Me, –$CH_2CH{=}CH_2$, –$CH_2CH_2OSiMe_2Bu^t$

Scheme 27

The reaction of simple aliphatic aldehydes with the lithiated derivative of the enantiomerically pure arylsulfinylmethyloxazoline (**75**) provides adducts which can be converted by sequential desulfurization and hydrolysis into the β-hydroxy acids (**76**) in 60–85% overall chemical yield, but with only modest (26–53%) enantiomeric excess (Scheme 28).[52]



(**75**) (**76**)

i, Bu^{n}Li; ii, (–)-(*S*)-menthyl-*p*-toluenesulfinate; iii, Bu^{n}Li, –90 °C; iv, RCHO; v, Na–Hg (MeOH–aq. NaH_2PO_4); vi, aq. H_2SO_4

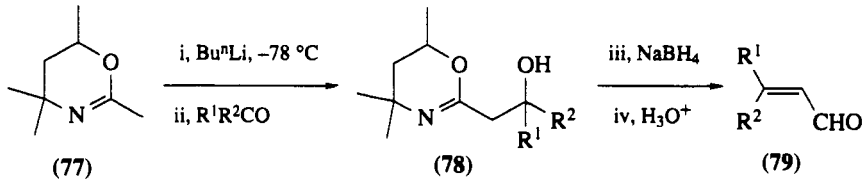
R = Me, Pr^n, Bu^i, Pr^i, Bu^t

Scheme 28

1.16.5.3 Metallated 2-Methyldihydro-1,3-oxazines

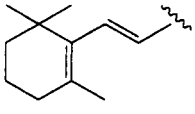
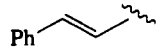
The anions derived from dihydro-1,3-oxazines have been nicely exploited as reagents to effect the two-carbon homologation of carbonyl compounds to provide α,β-unsaturated aldehydes, ketones and carboxylic acid derivatives.[53,54] For example, metallation of (**77**) followed by reaction with a wide variety of aldehydes and ketones provides adducts (**78**; Scheme 29). Although attempts to purify these adducts have been unsuccessful owing to facile retroaldolization, sequential reduction of (**78**) with sodium

borohydride followed by hydrolysis of the intermediate tetrahydro-1,3-oxazines provides the α,β-unsaturated aldehydes (**79**) in generally good overall yields (Table 8).[53]



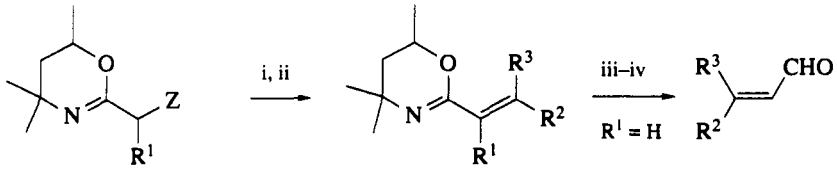
Scheme 29

Table 8 Two-carbon Homologation of Carbonyl Compounds to α,β-Unsaturated Aldehydes Using Dihydro-1,3-oxazines (**77**) (Scheme 29)[53]

R^1	R^2	*Overall yield of (79)* (%)
Me	Me	50
Et	Et	62
—$(CH_2)_4$—		63
—$(CH_2)_5$—		53
Ph	Ph	60
Ph	Me	49[a]
Ph	H	64
Pr^n	H	61
	Me	28[b]
Ph 	H	61

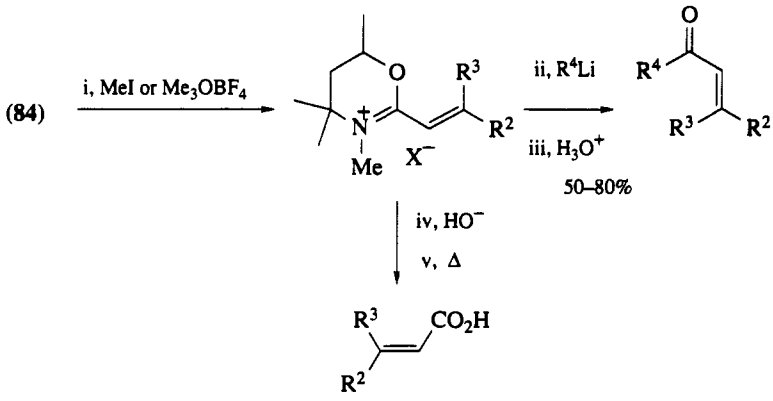
[a]*Cis:trans* ratio = 2:3. [b]Isolated in 54% yield as 2,4-DNPH derivative.

Although it is not possible to prepare α,β-unsaturated dihydro-1,3-oxazines (**84**) by mere dehydration of the adducts (**78**), these alkenes can be prepared in good overall yields by Wittig-type reactions of carbonyl compounds with the phosphorus-substituted dihydro-1,3-oxazines (**80–83**; Scheme 30).[54] Generally, better yields of (**84**) are obtained when aldehydes are employed as the reaction partners for the phosphoranes (**80**) and (**81**) and ketones are the reactants for the phosphonates (**82**) and (**83**). The α,β-unsaturated dihydrooxazines (**84**) are highly useful intermediates since they can be converted into α,β-unsaturated aldehydes (Scheme 30) as well as α,β-unsaturated ketones and carboxylic acids (Scheme 31).[54]



i, $KOBu^t$ or NaH; ii, R^2R^3CO; iii, MeI or Me_3OBF_4; iv, $NaBH_4$; v, H_3O^+

Scheme 30

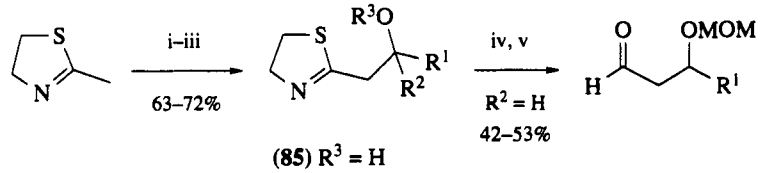


R^2 = Ph; R^3 = H
$R^2 = R^3$ = Me
$R^2, R^3 = (CH_2)_4$

Scheme 31

1.16.5.4 Metallated 2-Methylthiazolines

On a related front, the reactions of carbonyl compounds with metallated derivatives of 2-methylthiazoline furnish adducts (**85**). Although the initial nucleophilic addition occurs smoothly with a wide variety of aldehydes and ketones, the intermediate β-hydroxythiazolines (**85**) suffer thermal reversion upon attempted purification by distillation. Moreover, attempted cleavage of the corresponding β-hydroxythiazolidines, which are readily produced from (**85**) upon dissolving metal reduction (Al–Hg), leads to the formation of β-hydroxy aldehydes only in simple systems; numerous complications arising from dimerization, dehydration and retroaldol processes of the products usually intervene. Consequently it is necessary to protect the initial 1,2-adducts (**85**; R^2 = H) as the corresponding *O*-methoxymethyl ether derivatives (**86**; R^2 = MOM), which can then be easily transformed into protected β-hydroxy aldehydes by sequential reduction and hydrolysis (Scheme 32).[55]



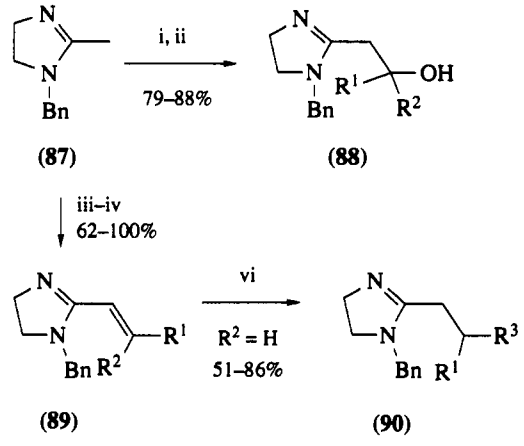
(**85**) R^3 = H
(**86**) R^3 = MOM

i, Bu^nLi, –78 °C; ii, R^1R^2CO; iii, $MeOCH_2Cl$; iv, Al–Hg; v, $HgCl_2$

Scheme 32

1.16.5.5 Metallated 2-Methylimidazolines

Similarly, the lithiated derivative of the 2-methylimidazoline (**87**) undergoes smooth addition to carbonyl compounds to provide the adducts (**88**; Scheme 33).[56] However, these substances undergo rapid reversal upon standing or heating; trapping with trimethylsilyl chloride is successful only when $R^1 = R^2$ = Me. On the other hand, the derived phosphonate reagent, which is prepared *in situ* from (**81**), reacts readily with aldehydes and ketones to give 2-alkenyl-2-imidazolines (**89**); subsequent reaction of these intermediates with alkyllithium reagents gives 2-alkylimidazolines (**90**), which may be converted into β-substituted carboxylic acids and ketones by known methods.[57]



(87) (88) (89) (90)

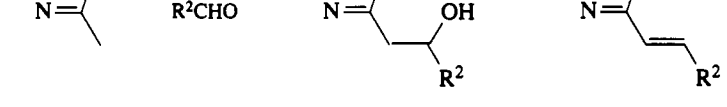
i, BuLi, –78 °C; ii, R^1R^2CO; iii, 2LDA; iv, $(EtO)_2P(O)Cl$; v, R^1R^2CO, r.t.; vi, R^3Li

Scheme 33

1.16.6. OTHER METALLATED AZOMETHINE DERIVATIVES

1.16.6.1 2-Methyl Azaheteroaromatic Compounds

Alkyl groups on the carbon atom adjacent to the ring nitrogen atom in nitrogen heteroaromatic compounds (**91**) are activated by the carbon–nitrogen double bond, and aldol-type reactions of such substances have been known for years. Indeed, the process outlined in Scheme 34 is one of the classical methods for preparing alkenyl-substituted heterocycles.[58–61] These condensations are typically catalyzed by $ZnCl_2$, Ac_2O/HOAc, KOMe, *etc.* Although the intermediate hydroxy compounds (**92**) may occasionally be isolated, dehydration normally proceeds spontaneously to give the alkenic products (**93**).



(91) (92) (93)

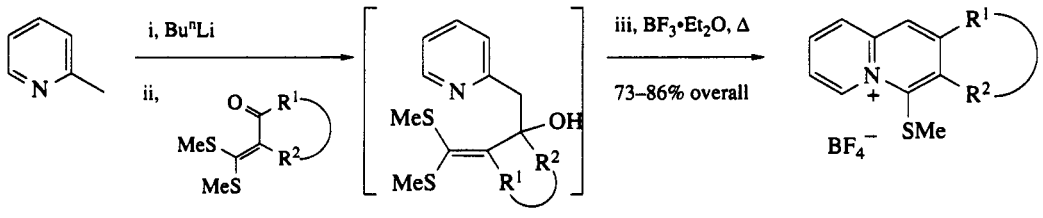
X = CH=CH, O, S, NR^1

Scheme 34

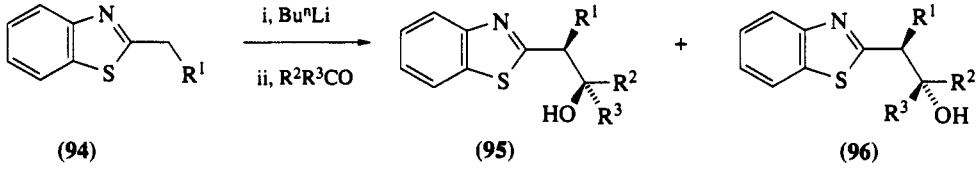
More recently, it has been discovered that metallation of the alkyl heterocycle with a strong base such as Bu^nLi followed by reaction of the intermediate anion with carbonyl compounds leads to the formation in high yields of adducts, which may either be isolated or subjected to chemical transformations (Schemes 35–37).[62–65]

Because of the ease with which the heterocyclic ring of benzothiazoles may be further elaborated into carbonyl compounds and carboxylic acid derivatives,[63,66] there has been considerable interest in the reactions of metallated 2-alkylbenzothiazoles (**94**) with aldehydes and ketones to give the adducts (**95**) and (**96**) (Scheme 36). As may be seen upon examination of the representative results in Table 9, the yields in these reactions are generally excellent when either aldehydes or ketones are employed as the electrophilic partners. When lithium is the counterion, the diastereoselection in the addition of (**94**; R^1 = alkyl) is only modest, giving mixtures of the *erythro* and *threo* adducts (**95**) and (**96**), with the latter predominating. However, the corresponding organotin reagents add to aldehydes with significant *erythro* selectivity.[64] When allyl anions are the nucleophilic reaction partners, the α-adduct is typically formed under

the conditions of kinetic control with *erythro:threo* diastereoselectivity varying from 2:1 to 9:1.[65] When these adducts are allowed to warm to room temperature prior to quenching, the γ-adducts are produced together with other by-products.[65]



Scheme 35[62]

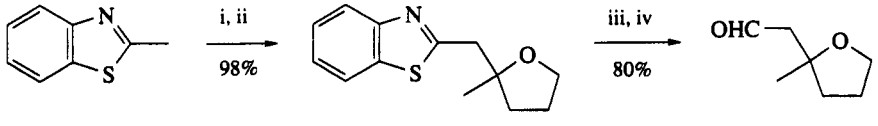


Scheme 36

Table 9 Reactions of Metallated 2-Alkylbenzothiazoles (**94**) with Carbonyl Compounds (Scheme 36)

R^1	R^2	R^3	(**95**):(**96**)	Yield (%)	Ref.
H	Et	H	—	98	63
H	Pr^i	H	—	98	
H	Bu^t	H	—	99	
H	Ph	H	—	95	
H	Ph	Me	—	98	
H	Bu^n	Bu^n	—	96	
H	CH=CH_2	Me	—	96	
Me	Ph	H	42:58[a]	88	64
Me	Ph	H	19:81[b]	90	
Me	Ph	H	72:28[c]	58	
Me	Pr^i	H	38:62[a]	62	
Et	Ph	H	43:57[a]	83	
Et	Ph	H	28:72[b]	68	
Et	Ph	H	80:20[c]	89	
Et	*p*-ClC_6H_4	H	>98[c]	84	
CH=CH_2	Ph	H	67:33[d]	95	65
CH=CH_2	Me	H	*ca.* 100:0[d]	95	

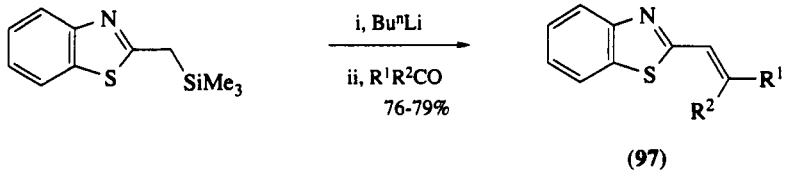
[a]Bu^{n}Li used as base in lithiation step. [b]LDA used as base in lithiation step. [c]From 2-trichlorostannane derivative. [d]α-Adduct obtained when reaction quenched at –78 °C.



i, Bu^{n}Li; ii, $MeCO(CH_2)_3Cl$; iii, MeI, DMF, Δ; iv, $NaBH_4$; v, $AgNO_3$ (aq), MeCN

Scheme 37[63]

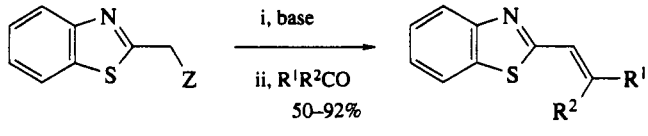
Although the adducts (**95**) and (**96**) can be dehydrated under a variety of conditions to provide the corresponding alkenes, the alternative application of the Peterson[66] (Scheme 38) or the Wittig and Horner–Emmons[67–69] (Schemes 39–41) reactions to the preparation of alkenyl heterocycles may often be preferred because of the mildness of the reaction conditions required. For example, such an alkenation



(97)

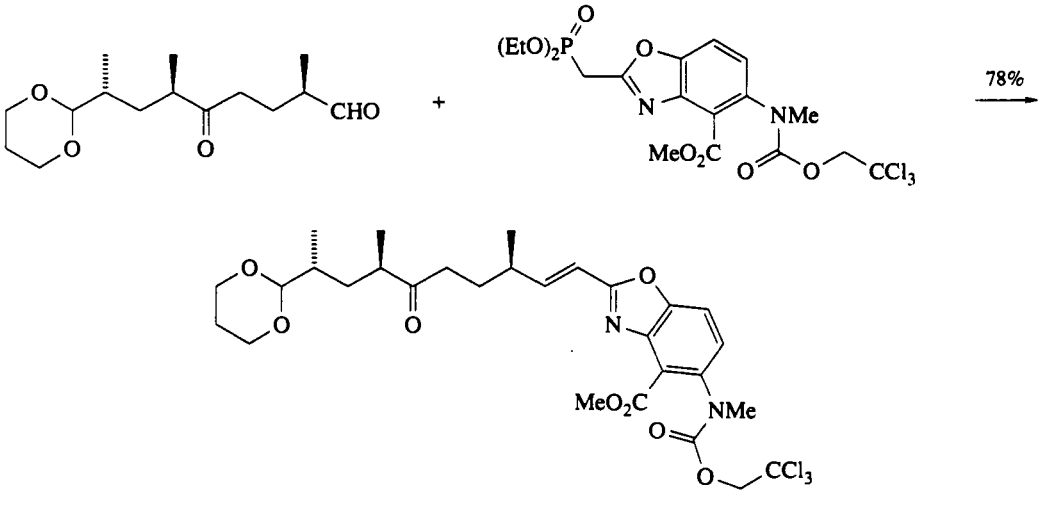
R^1 = alkyl, aryl; R^2 = H, alkyl

Scheme 38



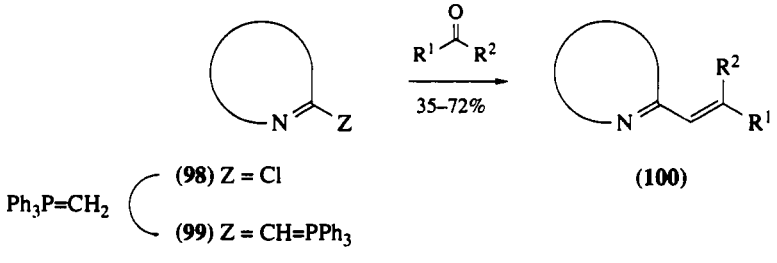
$Z = Br, \overset{+}{P}Ph_3, P(O)(OEt)_2$

Scheme 39[67]



Scheme 40

was recently used as the key step in the total synthesis of the polyether antibiotic calcimycin (Scheme 40).[68] The vinylbenzothiazoles (**97**) are useful synthetic intermediates since the thiazole ring may be unmasked to provide carbonyl derivatives by straightforward synthetic transformations.[66]



R^1 = Me, Pr^n, Ph; R^2 = H, Me, Ph

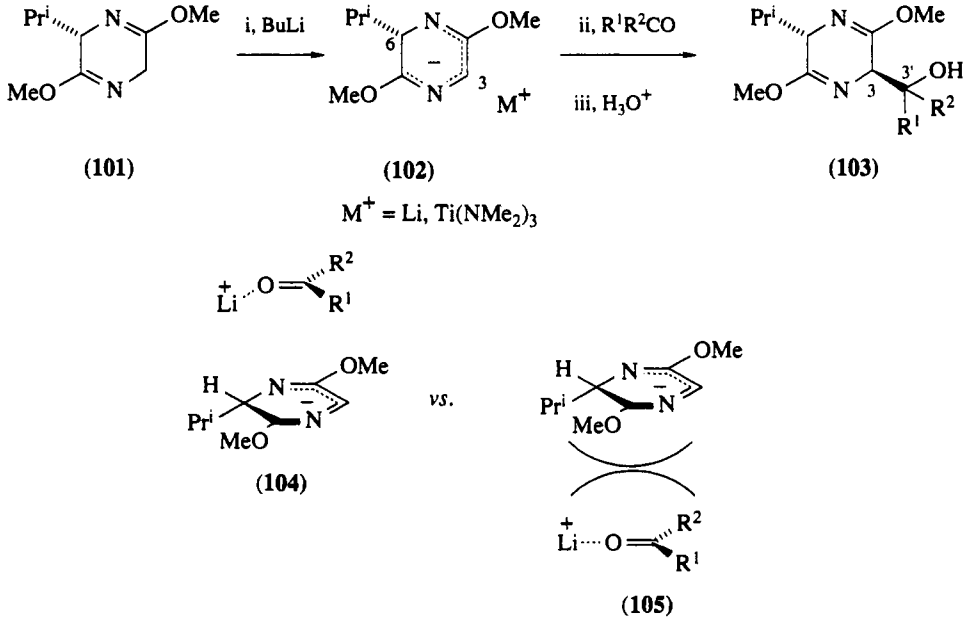
Scheme 41

A highly useful alternative entry to Wittig reagents of the general type (**99**) has been developed that features displacement of a chloride leaving group from the readily available chloroaza heterocycle (**98**) by an alkylidenephosphorane.[69] The intermediate phosphonium salt then undergoes transylidation with a second equivalent of the Wittig reagent to produce the heterocyclic ylide (**99**) which may be treated with a variety of carbonyl partners to furnish alkenyl-substituted heterocycles in good overall yields (Scheme 41). The process is applicable to a number of five- and six-membered systems as well as to monocyclic and polycyclic heterocyclic frameworks including pyridines, pyrazines, quinolines, isoquinolines, quinazolines, quinoxalines and benzoxazoles.

1.16.7 ADDITIONS OF METALLATED BIS-LACTIM ETHERS OF 2,5-DIKETOPIPERAZINES

1.16.7.1 Asymmetric Synthesis of Amino Acids

Over the past decade Schöllkopf and coworkers have worked toward the development of a general procedure for the synthesis of optically active, nonproteinogenic amino acids. The strategy underlying the approach is based upon the observation that metallated derivatives of bislactim ethers of 2,5-diketopiperazines, such as (**102**), undergo reactions with electrophiles at C-3 with a high degree of stereoselectivity from the face of the delocalized anion opposite to the isopropyl group at C-6.[70–79] This has proven to be a highly useful synthetic method for the asymmetric synthesis of amino acids. During the course of these investigations, Schöllkopf has demonstrated that carbonyl compounds admirably serve as electrophilic partners in reactions with (**102**) to give the adducts (**103**; Scheme 42), and some representative results are collected in Table 10.



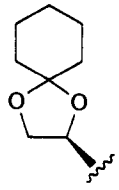
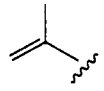
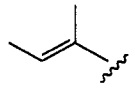
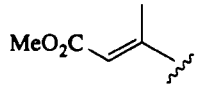
(**101**) (**102**) (**103**)

(**104**) (**105**)

Scheme 42

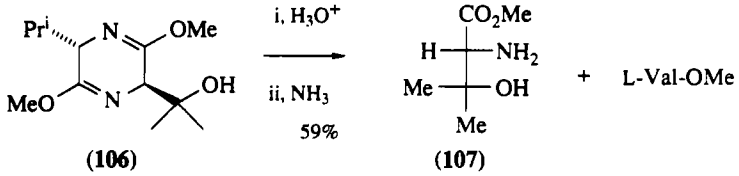
The diastereoselection at C-3 of (**103**) is uniformly high, generally exceeding 98%. The extent of asymmetric induction at this center does not depend very much upon the size of the alkyl groups R^1 and R^2. Clearly these groups must not play a decisive role in the transition state, and the primary factor determining the stereochemical course of these reactions would seem to involve the interactions between the isopropyl group at C-6 of the piperazine ring and the carbonyl oxygen in the two possible transition states (**104**) and (**105**). The stereoselectivity at C-3′ is generally somewhat less. However, it has been recently observed that the titanium derivative of the anion (**102**; M = $Ti(NMe_2)_3$) adds to aldehydes with very high (>95%) diastereoselectivity at both C-3 and C-3′.[75] Presumably, the titanium enforces a tighter transition state, which then results in increased diastereoselection in the addition.

Table 10 Diastereoselective Reactions of Metallated Piperazines (**102**) with Aldehydes and Ketones (Scheme 42)

R^1	R^2	*de (C-3)* (%)	*de (C-3')* (%)	*Yield* (%)	*Ref.*
Me	Me	>95		98	71
Ph	Me	>95	38	91	
H	H	80			
Ph	H	86	4	97	
$PhCH_2$	H	89	66	77	
Bu^t	H	92	56	96	
Pr^i	H	94	70	96	
Me	H	85	60	95	
Me	H	98[a]	97[a]	79	72
	H	66 95[a]	5 87[a]	69 73	73
$CH_2SiMe_2Bu^t$	H	>95	58	76	74
$CH(Me)SiMe_2Bu^t$	H	>95	0	80	
$C(Me)_2SiMe_2Bu^t$	H	>95	25	70	
	H	94 96[a]	51 >98[a]	85	75
	H	99[a]	99[a]	82	
	H	96[a]	95[a]	80	

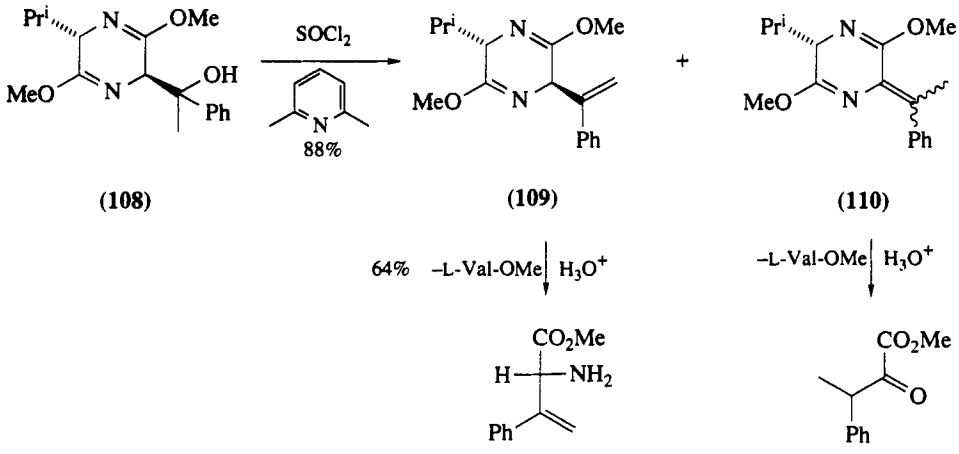
[a]Lithium anion was treated with $TiCl(NMe_2)_3$ prior to reaction with the aldehyde.

Of particular synthetic importance are the subsequent transformations of the initially formed adducts (**103**) and analogs thereof. For example, hydrolysis of (**106**) provides the β-hydroxy-α-amino acid ester (**107**) together with Val-OMe (Scheme 43).[76] On the other hand, dehydration of (**108**) with thionyl chloride in the presence of 2,6-lutidine furnishes a mixture (4:1) of (**109**) and (**110**); hydrolysis of the former led to the unsaturated amino acid (**111**; Scheme 44).[71] α-Alkenylglycine methyl esters may be also prepared from the silyl derivatives (**112**; Scheme 45).[74] An alternative route to α-alkenylglycines features the addition of the metallated derivative of (**101**) to thioketones followed by *S*-methylation to provide adducts (**113**), which undergo elimination of methanethiol upon reaction with Raney nickel (Scheme 46).[74]

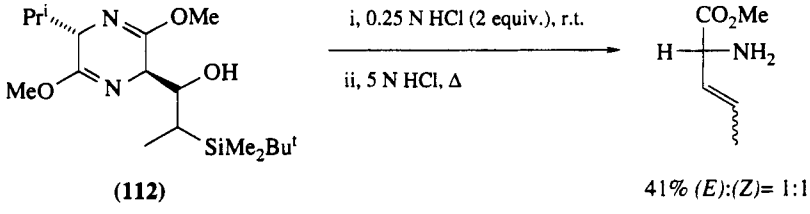


(**106**) (**107**)

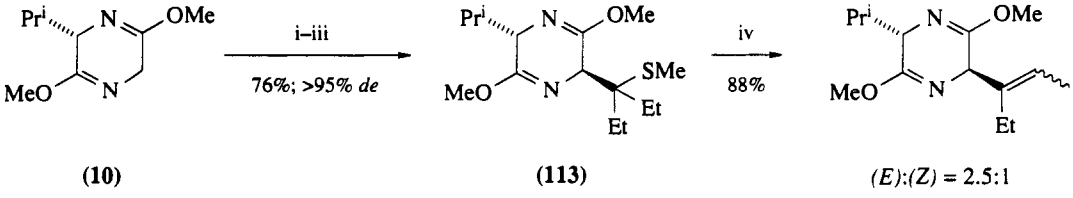
Scheme 43



Scheme 44

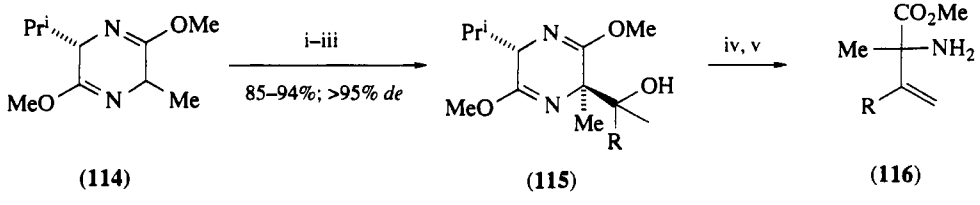


Scheme 45



i, Bu^{n}Li; ii, EtC(S)Et; iii, MeI; iv, Raney Ni, EtOH, Δ

Scheme 46



i, Bu^{n}Li; ii, MeCOR; iii, H$^+$, iv, SOCl$_2$, Py; v, H$_3$O$^+$

Scheme 47

When the bislactim ether of the diketopiperazine (**114**) is metallated with Bu^nLi, deprotonation occurs exclusively α to the methyl substituent to provide an anion that undergoes highly selective reaction with aldehydes and ketones to generate adducts of the general type (**115**). As before, these adducts undergo dehydration to form α-methyl-α-alkenylglycines (**116**; Scheme 47),[78] but attempted hydrolysis of these adducts gives a mixture of products because of preferential retroaldol reactions.

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1.17
Hydrazone Anions

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1.17.1 INTRODUCTION

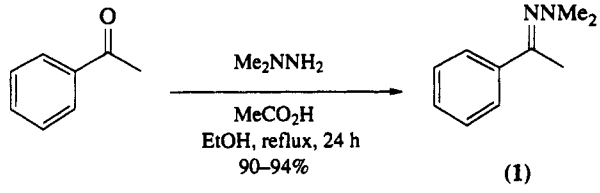
Carbanions derived from hydrazones are primarily used as equivalents of carbanions derived from ketones and aldehydes. Reactions that ultimately lead to electrophilically substituted carbonyl derivatives through hydrazone anions proceed through four separate steps. First, the hydrazone has to be prepared from the starting carbonyl compound. In most cases, this requires a simple, facile condensation reaction between a hydrazine derivative and a ketone or aldehyde. Second, the neutral hydrazone has to be converted into a nucleophile; typically this involves deprotonation with a strong base. Both regiochemical and stereochemical considerations affect this step. Third, the nucleophilic anion so formed undergoes electrophilic substitution. Various electrophiles can be used; the most common are sp^3-hybridized carbon electrophiles (*e.g.* alkyl halides) and sp^2-hybridized carbon electrophiles (*e.g.* carbonyl compounds). This chapter will concentrate on the latter reactions, introducing alkylations only when appropriate for discussions of regiochemistry and stereochemistry in anion generation. Finally, the product hydrazones produced in these electrophilic substitution reactions have to be converted back into carbonyl compounds, as hydrazones are rarely if ever the desired final product. In a few instances, one or both nitrogens of the hydrazone can be used for heterocycle formation. In such instances, the last step then becomes a more efficient convergent step in an overall synthetic strategy.

Since hydrazone anion chemistry is complementary to more conventional deprotonation–electrophilic substitutions effected with carbonyl derivatives such as ketones and aldehydes, and since hydrazone chemistry involves two additional synthetic operations, the use of hydrazones has to have some additional advantages. Compensating for the additional synthetic effort required to prepare and hydrolyze the

hydrazone derivatives is the greater synthetic utility of these intermediates. The reactivity of the intermediate azaallyl anions, the control over stereochemistry of the electrophilic substitution step afforded by the nitrogen substituent, and the considerable control of regiochemistry which can be attained using hydrazones, make them especially useful.

1.17.2 PREPARATION OF HYDRAZONES FROM ALDEHYDES AND KETONES

Formation of *N,N*-dialkylhydrazones from ketones and aldehydes is generally a facile reaction. In the case of most aldehydes, all that is required is stirring of the unsymmetrical *N,N*-dialkylhydrazine with the aldehyde in the presence of a drying agent. In some cases, these reactions can be carried out at room temperature. Ketones react similarly but can require more vigorous conditions. In the case of less-reactive carbonyl substrates, acid catalysts like *p*-toluenesulfonic acid or azeotropic distillation are commonly used to promote hydrazone formation. Formation of the aldehyde and ketone dimethylhydrazones and of the chiral hydrazone in equations (1)–(4) are examples of typical procedures.[1–4] Monosubstituted hydrazones such as (**6**) are prepared in a similar manner (equation 5).[5] These reactions often proceed in near-quantitative yield.



(1)

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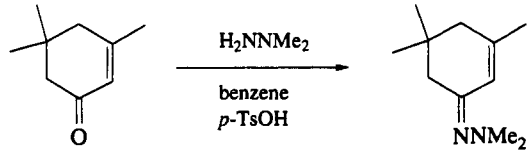

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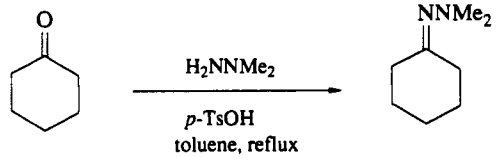

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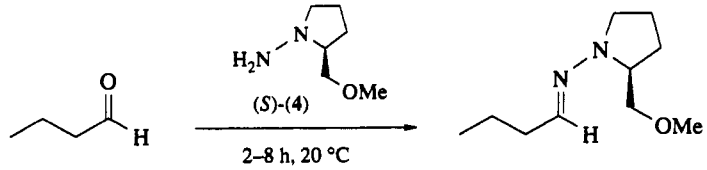

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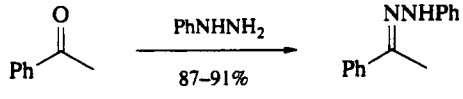

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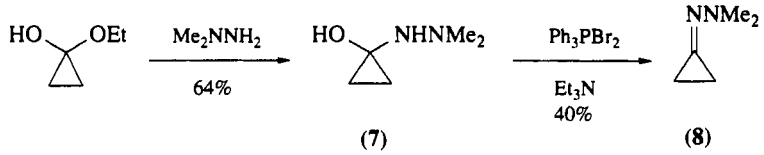
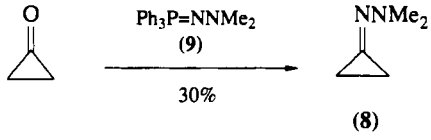
(6)



(6)



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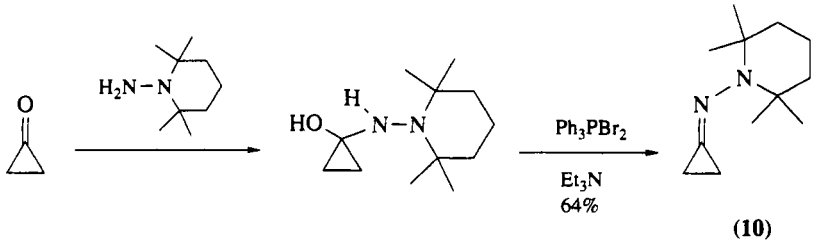
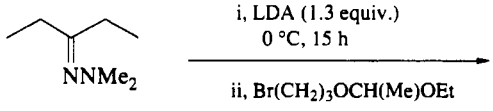


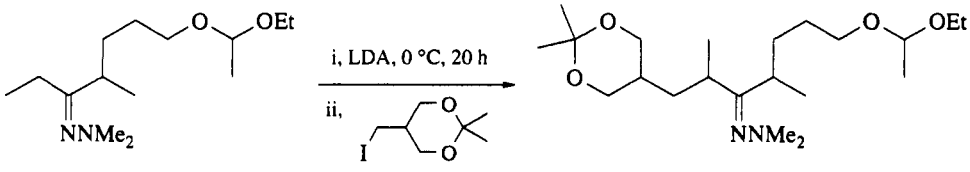
(8)

Cyclopropanone *N,N*-dialkylhydrazones such as (**8**) and (**10**) are examples of *N,N*-dialkylhydrazones that are formed with some difficulty,[6] as the high reactivity of cyclopropanone makes its use problematic. However, the *N,N*-dimethylhydrazone (**8**) can be prepared using one of two routes starting either with the ethyl acetal of cyclopropanone or cyclopropanone itself. Starting with the ethylacetal, the initial product is a hemiaminal (**7**; equation 6). This intermediate which normally could be converted to the hydrazone by acid catalysis instead undergoes ring opening with acid. However, dehydration to yield the hydrazone is still possible using triphenylphosphine dibromide. An interesting alternative route to the *N,N*-dimethylhydrazone (**8**) uses cyclopropanone and the nitrogen ylide (**9**; equation 7).[7] These procedures are also effective in preparation of the still more hindered *N,N*-dialkylhydrazone (**10**; equation 8).

In some cases, *N,N*-dimethylhydrazones (or other dialkylhydrazones) can be most easily prepared from simpler *N,N*-dimethylhydrazones by alkylation. Such reactions can be especially useful in controlling regiochemistry or stereochemistry at positions α to the carbonyl carbon. For example, Yamashita has emphasized the desirability of using acetone dimethylhydrazone as a precursor of unsymmetrical ketone dimethylhydrazones.[8] This strategy has been used successfully in various syntheses including Schreiber's synthesis of an ionomycin fragment precursor (**13**; equation 9) and a recent synthesis of (–)-gloeosporone.[9,10] Isotopically labeled hydrazones, *e.g.* (**14**; equation 10), are also conveniently available in this same manner.[11,12] Other examples using this strategy to prepare hydrazones of relatively unavailable ketones, that can then be used in addition reactions to sp^2-hybridized electrophiles, are included in some of the syntheses discussed below. Finally, α-functionalized aldehyde and ketone hydrazones can also be prepared *via* an intermediate azaallyllithium reagent (as an alternative to synthesis from the car-

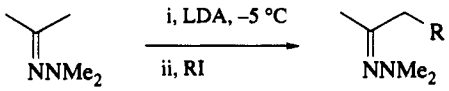


(11)



(9)

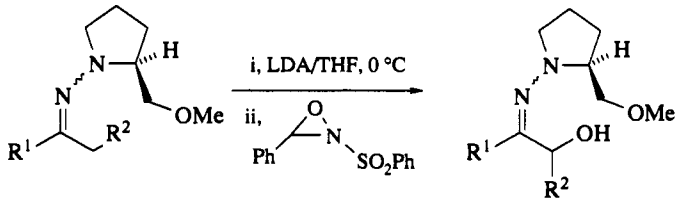
(12) (13)



(10)

(14a) R = $^{13}CH_3$

(14b) R = C^2H_3



(11)

R^1 = H, Me, Ph;

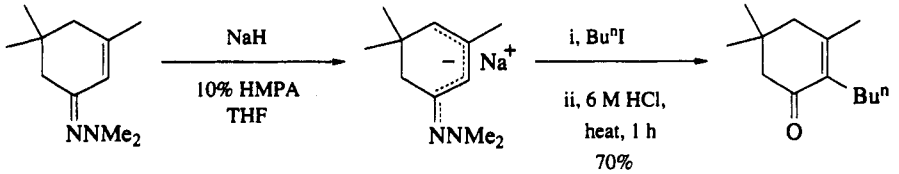
R^2 = Me, Ph, C_6H_{13}, $PhCH_2$

(15)

bonyl compound). This is illustrated in equation (11) by the asymmetric synthesis of α-hydroxy ketone and aldehyde hydrazones (**15**) by oxidation of a chiral hydrazone-derived azaallyllithium reagent.[13] Yields in equation (11) range from 60 to 85%. An additional advantage of this synthesis, like alkylation of similar chiral hydrazones, is that a new stereocenter is produced with very high enantioselectivity (*ee* > 93% in most cases).

1.17.3 FORMATION OF AZAALLYL METAL REAGENTS FROM HYDRAZONES

Once formed, dialkylhydrazones can be converted into nucleophilic anions using a number of strong bases. In one of the earliest examples of this chemistry, Stork and Benaim deprotonated α,β-unsaturated ketone dimethylhydrazones such as (**2**) with sodium hydride in THF in the presence of 10% HMPA.[2] A second α,β-unsaturated *N,N*-dimethylhydrazone derived from Δ^4-cholestenone was lithiated using *n*-butyllithium. In both cases, the deprotonation occurred regioselectively to yield the linearly conjugated anion (*e.g.* **16**). The final product in these cases was a new α,β-unsaturated carbonyl compound in which overall replacement of the α-vinyl proton by an alkyl group had occurred. Isomerization of the double bond back into conjugation presumably occurred during hydrazone hydrolysis (equation 12).



(12)

(2) **(16)**

Formation of nucleophilic carbanions from *N,N*-dialkylhydrazones is more often accomplished using LDA or alkyllithium reagents including both Bu^nLi and Bu^tLi.[14,15] The intermediate azaallyllithium reagents so formed are sometimes soluble in THF, the solvent most commonly used. In other cases such as with simple aldehyde dimethylhydrazones, the intermediate azaallyllithium reagents are insoluble unless a cosolvent like HMPA is added. Formation of dianions from monosubstituted hydrazones such as tosylhydrazones is accomplished most commonly through the use of Bu^nLi.[16] In each case, the azaallyllithium reagents generated are not isolated but are used immediately in synthesis.

Potassium diisopropylamide (KDA) has been advocated as an alternative to alkyllithium reagents and LDA as a means to form anions from *N,N*-dimethylhydrazones.[17] The KDA for this purpose is prepared most conveniently *in situ* from Bu^nLi, Bu^tOK and diisopropylamine. The principal advantage of KDA over lithium reagents is reportedly that its use produces anions from any hydrazone and generates them more rapidly.

Potassium salts of hydrazones are also available by other procedures. Potassium amide has been used to generate potassium salts of monoaryl ketone hydrazones.[18] The reactive intermediate generated in these cases is a dianion. Highly dispersed forms of potassium have also been reported to generate potassium salts from *N,N*-dimethylhydrazones at –60 °C.[19] The use of K/Al_2O_3 in metalation of aldehyde hydrazone anions produces modest yields of alkylated products in THF suspension. In hexane suspension, side reactions believed to include nitrile formation lead to lower synthetic yields of hydrazone products.

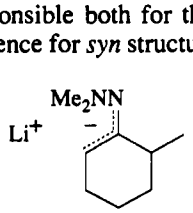
Potassium and sodium salts of hydrazone anions in which a second methoxycarbonyl or nitrile group stabilizes the anion have been prepared by metalation with potassium hydride and sodium hexamethyldisilazane, respectively.[20] Use of these bases affords clean solutions suitable for NMR structural studies. Other azaallyl metal derivatives of hydrazones, including copper(I) and magnesium derivatives, have been used in synthesis and are discussed below. These reagents are generally prepared from an azaallyllithium reagent by transmetalation with copper(I) iodide or with magnesium bromide.[21,22] Transmetalation starting with a lithium salt of a cyclohexanone dimethylhydrazone and chlorotitanium triisopropoxide, bromotitanium tris(diethylamine) or titanium tetraisopropoxide has been similarly used by Reetz to make azaallyltitanium reagents from hydrazones.[23]

Silylation of azaallyllithium reagents derived from hydrazones unlike silylation of enolates seems to occur mainly on carbon. While chiral (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) aldehyde hydrazones (*cf.* equation 4) alkylate to a greater extent on nitrogen to form an azaallylsilyl reagent, ketones give predominant *C*-silylation. In the case of chiral ketone hydrazones derived from (*S*)-(**4**), α-silylated ketone hydrazones are produced in these reactions with consistently high *ee* (≥96%).[24]

Side reactions can occur in formation of hydrazone anions and limit the thermal stability of these anions. Most commonly these side reactions involve addition at the carbonyl carbon or elimination of a dialkylamide anion and nitrile formation.[25] Normant has described both problems and has suggested that nitrile formation also occurs slowly in cases where HMPA has been added to azaallyllithium reagents derived from *N,N*-dimethylhydrazones. These problems are exacerbated in the case of aldehyde hydrazones when there is branching at the carbon α or β to the carbonyl carbon.

1.17.4 STRUCTURES OF AZAALLYL METAL REAGENTS DERIVED FROM HYDRAZONES

The structure of the intermediate azaallyllithium reagents typically used in hydrazone anion chemistry has been a subject of considerable speculation. Interest in the structure of these intermediates parallels related studies on other delocalized anions and has been sparked by advances in asymmetric syntheses that employ enolates and related species. Collum and Clardy have recently reported two X-ray structures of lithiated cyclohexanone dimethylhydrazone and lithiated 2-methoxycarbonylcyclohexanone dimethylhydrazone.[26,27] In the case of the simple lithiated cyclohexanone dimethylhydrazone (**17**), the azaallyllithium reagent was in the form of a polymer with an extended array of dimethylcyclohexanone anions and lithium in alternating η^1- and η^4-coordination. The η^4-coordination in this structure is unusual and serves to differentiate it from enolate structures described by others.[28] The C—C—N—N group coordinated to lithium is planar and the lithium is 1.64 Å from this plane. This same lithium is coordinated to the central anionic nitrogen of another C—C—N—N group in an η^1-fashion with a Li—N distance of 0.5 Å. The two C—C—N—N planes of alternating lithiated cyclohexanone dimethylhydrazones were disposed at an angle of 111° to one another. Collum and Clardy speculated that the η^4-coordination in this azaallyllithium reagent could be responsible both for the pronounced stereoselectivity in electrophilic alkylations and for the known preference for *syn* structures in these anions (*vide infra*).

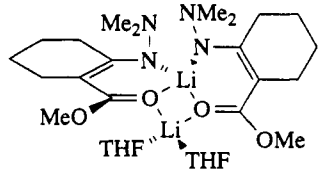


(**17**)

In the case of (**17**), Collum and Clardy were able to obtain some osmometric data about aggregation in solution. They found that (**17**) in THF had an apparent molecular weight of 515, which corresponds to a 3.5 degree of aggregation. Based on these results, and the independence of axial alkylation stereoselectivity with respect to the concentration of (**17**) or the nature of the metal ion and solvent, Collum and Clardy suggested that solvent free tetramers of (**17**) may be the predominant species in solution. Studies

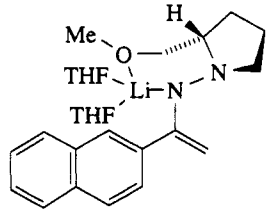
with models also suggested that cyclic tetramers with alternating η^4–η^1 Li–CCNN coordination are both plausible and that such an arrangement would have two sterically different faces for each anionic cyclohexanone dimethylhydrazone subunit.

Collum and Clardy have also described the X-ray crystal structure of (**18**).[27] Unlike (**17**), no C–Li interactions were present in the chelated structure (**18**). No definitive evidence of C–Li interactions was obtained with [^{6}Li]-labeled (**18**) either. Solution molecular weight studies with (**18**) showed that extensive dissociation occurred at high dilution. This dissociation could be due to dimer–monomer exchange (which would have to be fast to account for the temperature invariant NMR spectra) or could be due to solvent dissociation from (**18**). NMR studies with 3.0 equiv. of added THF in toluene-d_8 showed that exchange of free and coordinated THF was fast at all temperatures.



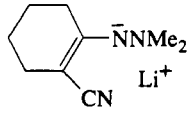
(**18**)

More recently, Enders' group has described the X-ray crystal structure of the chiral hydrazone anion (**19**).[29] This internally chelated chiral hydrazone crystallizes as the bis(tetrahydrofuran) monomeric adduct. The lithium in this structure is 17° out of the C—C—N plane and is predominantly associated with the anionic nitrogen (and the chelating methoxy group). Interactions with the $=CH_2$ carbon are minimal. Earlier studies by Bauer and Seebach had examined the association behavior of (**19**). They found that in THF this azaallyllithium reagent was monomeric.[30] While there is no η^3- or η^4-interaction with the azaallyl anion, the lithium in this structure is tetracoordinate and prochiral. Preferential coordination of lithium to an electrophile such as a carbonyl oxygen with selective replacement of one THF moiety could be involved in some of the asymmetric aldol reactions discussed below.

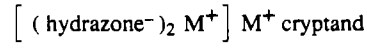


(**19**)

It is clear from these X-ray structures of dimethylhydrazone anions and from related studies carried out by a variety of other groups on related enolate and enolate-like species[28,30,31] that a variety of metal coordination and aggregation phenomena can be expected for these organometallic reagents. Simple monomeric species that do not include metal interactions are implausible and are not likely to be the species responsible for the chemistry seen with these reagents. However, identifying the major species present *in solution* and the major species of kinetic importance remains an especially challenging problem, both in enolate chemistry generally and for reactions of lithium dimethylhydrazone anions in particular. For example, detailed studies by Wanat and Collum have suggested that aggregation of cyclohexanone dimethylhydrazone lithio anions does occur, but that dissociation to a monomer may precede rate-determining alkylation.[32] In more recent work, Collum has carried out ^{6}Li and ^{23}Na NMR



(**20**)



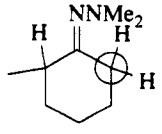
(**21**)

spectroscopic studies of (**17**), (**18**) and (**20**).[20] In these studies, ion triplets of general structure (**21**) were observed. Based on these results, it is equally possible that aggregated azaallyllithium reagents derived from hydrazones alkylate *via* ion triplets. Distinguishing between such ion triplets and the aforementioned tetramer–monomer dissociation in determining the true intermediates in alkylations would be difficult and was not attempted. In the case of stabilized hydrazone anions, the effects of cryptate lithium complexing agents suggest that alkylation stereoselectivities are not necessarily dependent on the metal counterion present. Extensions of these studies to the potentially more complicated case of additions to sp^2-hybridized electrophiles have not been reported.

These X-ray structures and detailed multinuclear studies of hydrazone anions are the most recent structural details available about these anions. While they are likely to prove invaluable in understanding the mechanistic basis of hydrazone selectivity in electrophilic substitution reactions, other questions of stereochemistry and regiochemistry in anion generation are of more immediate synthetic interest. Both questions have received considerable study within the last 10 years.

1.17.5 REGIOCHEMICAL AND STEREOCHEMICAL CONTROL IN HYDRAZONE DEPROTONATION

Regiochemical questions in hydrazone anion formation from ketone hydrazones center on two issues. First, if the starting hydrazone has two different types of acidic α-hydrogens, selectivity in proton removal is an important consideration if a synthetic sequence is to produce a single product. In the case of hydrazones, deprotonation regioselectivity of this sort is typically both high and predictable. For example, in the case of (**22**)–(**25**) the deprotonation occurs selectively at the circled carbon to produce alkylated products. In general, deprotonation occurs at the less-substituted carbon unless there is an anion stabilizing group present.[3,33] Hydrazones (**24**) and (**25**) are examples of this latter case.



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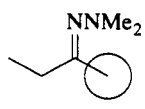
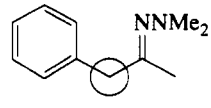
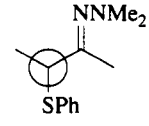


(**23**)

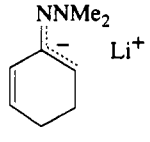


(**24**)

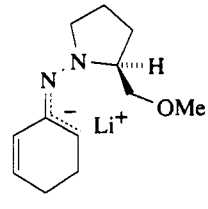


(**25**)

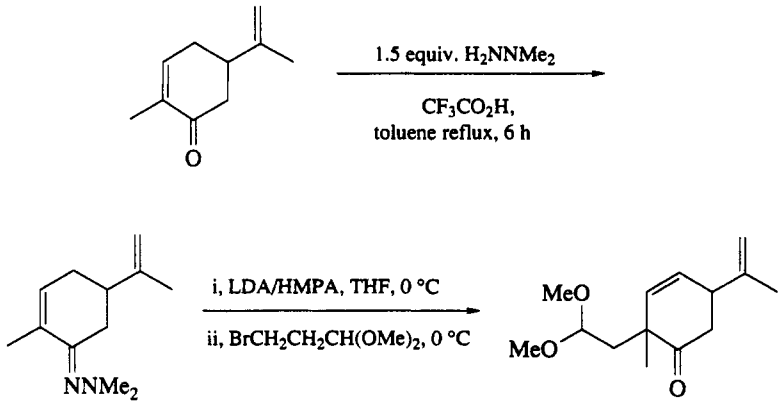
A second question concerns the regio- or stereo-selectivity of deprotonation of ketone hydrazones that contain two α-CH_2 groups. This question has been studied for several sorts of compounds. In an early report of the use of hydrazone anions,[2] Stork described deprotonation of α,β-unsaturated hydrazones such as (**2**). In this case, deprotonation could have occurred at either the α-CH_2 or the CH_2 group adjacent to the conjugated double bond. Based on the results of the alkylation shown in equation (12), the linearly conjugated anion evidently formed. It was not established whether these regioselective γ-deprotonations of α,β-unsaturated ketone hydrazones were the result of kinetic or thermodynamic factors, or whether the additional methyl groups on the ring affected the deprotonation regiochemistry. In subsequent work, the dimethylhydrazone of cyclohexenone and a chiral hydrazone of cyclohexenone were deprotonated regiospecifically so as to form anions (**26**) and (**27**).[3,34] However, regioselectivity like that noted by Stork was again seen in deprotonation and in electrophilic substitution to prepare (**28**; equation 13), a precursor in the total synthesis of picrotoxinin.[35] Based on these results it is evident that the substituents on the



(**26**)



(**27**)



(13)

(28)

cyclohexyl ring can significantly influence deprotonation regioselectivity of cyclic α,β-unsaturated ketones.

The kinetic selectivity of deprotonation in ketone dimethylhydrazones containing two —CH_2 groups differing only in their stereochemistry relative to the nitrogen —NMe_2 group is low. While there was some initial confusion in the literature, NMR studies using diastereomerically pure $^{13}CH_3$-labeled 3-pentanone dimethylhydrazone showed that deprotonation occurred at both —CH_2 groups.[11] Earlier reports had suggested that deprotonation occurred *anti* to the dimethylamino group.[36] A subsequent study further established that this lack of preference for deprotonation *syn* or *anti* to the dimethylamino group was not due to equilibration of the starting isomerically pure hydrazone through proton transfer reactions as suggested by others.[12,37] This resistance of hydrazones to proton transfer between a neutral ketone or aldehyde hydrazone and an azaallyllithium reagent is such that the half life of such equilibrations is of the order of 2 to >8 h. In contrast, deprotonations are typically complete within 30 min. In fact, this resistance to proton transfer (and subsequent formation of disubstituted products) is one of the major advantages of hydrazones in alkylation reactions.

Studies of deprotonation regioselectivity in mono-*N*-substituted ketone hydrazones have mainly dealt with the regiochemistry of ketone tosylhydrazone deprotonations. Deprotonation of these tosylhydrazones, as well as deprotonation of mono-*N*-alkyl- or mono-*N*-aryl-hydrazones, proceeds predominantly *syn* to the starting —NHR group.[16] This regioselectivity is plausibly similar to that reported for oxime and imine deprotonations.[38,39]

The stereochemistry of the intermediate azaallyl anions formed in ketone and aldehyde hydrazone deprotonation has been studied and is of interest, especially in the context of asymmetric synthesis. The first study of this sort demonstrated that the azaallyllithium reagents derived from hydrazones did not undergo rapid isomerization about the carbon–carbon bond of the C—C—N anion.[40,41] This study further established that the stereoselectivity of this deprotonation reaction could be varied, with an $(E)_{C-C}$ anion formed with LDA in THF, while a $(Z)_{C-C}$ anion formed using LDA in THF in the presence of 2 equiv. of HMPA. Subsequent ^1H NMR studies have shown that SAMP aldehyde hydrazones deprotonate with LDA to yield $(E)_{C-C}$,$(Z)_{C-N}$ anions and that deprotonation stereoselectivity is also altered by the addition of 2 equiv. of HMPA to become predominantly $(Z)_{C-C}$,$(E)_{C-N}$.[42] This latter study showed that use of these stereoisomeric intermediate azaallyllithium reagents produced enantiomeric products in alkylation reactions. Several groups have speculated that the same factors responsible for stereoselective enolate formation[43] are responsible for stereoselective hydrazone anion formation, though the explanations offered to explain HMPA's effects with ketones and esters cannot be valid in the case of aldehyde *N,N*-dialkylhydrazones.[40]

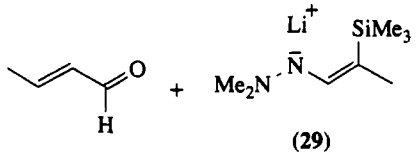
The stereospecificity of deprotonation of ketone *N,N*-dialkylhydrazones is less defined because of the problem of making unambiguous stereochemical assignments. However, based on the observed stereoselectivity of electrophilic substitutions on these anions, on ^{13}C chemical shift data and on analogies to enolate chemistry, it appears that $(E)_{C-C}$ stereochemistry again predominates, at least with LDA deprotonations.[44]

1.17.6 1,2-ADDITIONS TO ALDEHYDES AND KETONES

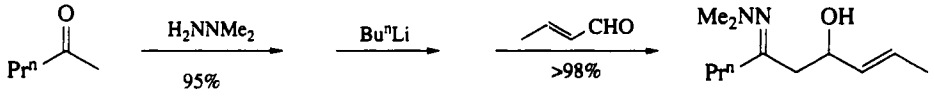
Dialkylhydrazone lithio anions readily react with aldehydes and ketones to generate aldol-like products. Depending on the procedures used, β-hydroxycarbonyl products or α,β-unsaturated carbonyls can be obtained. The regioselective control over dimethylhydrazone anion formation and the stereoselectivity afforded these anions by use of chiral nitrogen substituents are advantages of this alternative strategy for aldol reactions.

Corey, Enders and Bock were among the first to describe the utility of lithium dimethylhydrazone anions for crossed aldol reactions.[45] In the reaction shown in equation (14), an azaallyllithium reagent derived from an aldehyde dimethylhydrazone was first silylated with trimethylsilyl chloride to yield a silyl aldehyde dimethylhydrazone. Subsequent lithiation using lithium diethylamide at –20 °C for 1 h generated the silylated azaallyllithium reagent (**29**). Subsequent addition of one equivalent of an aldehyde or ketone at –78 °C and warming to –20 °C then yielded the product α,β-unsaturated aldehyde dimethylhydrazone in yields of 85–95%. Hydrolysis produced the unsaturated aldehyde in 75% overall yield.

The 1,2-addition of simple azaallyllithium reagents derived from ketone and aldehyde dimethylhydrazones to aldehydes and ketones was also first described by Corey and Enders.[14,21] Regioselective deprotonation of 2-pentanone dimethylhydrazone with Bu^nLi followed by addition of an aldehyde or



(29) (14)



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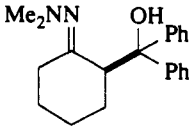

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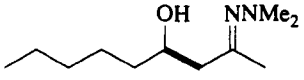

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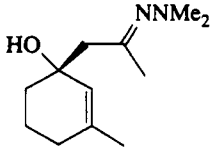

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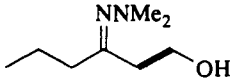

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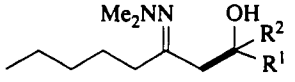
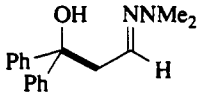
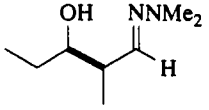


(**35**) $R^1 = R^2 = Ph$ 85%
(**36**) $R^1 = Ph$, $R^2 = H$ 95%
(**37**) $R^1 = Ph$, $R^2 = Me$ 80%



(38) 81%



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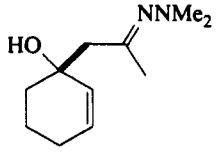
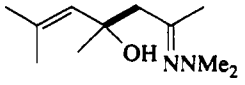


(40) 95%

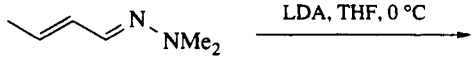


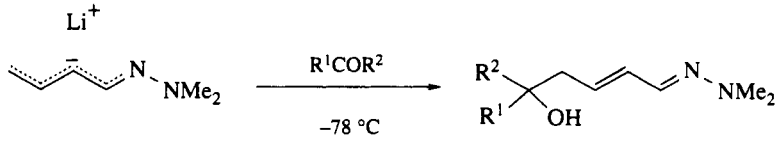
(41) 95%

Scheme 1

ketone yielded a β-hydroxy dimethylhydrazone in high yield. Oxidative cleavage of the dimethylhydrazone group using sodium periodate in methanol at pH 7 yielded the final product (equation 15). Examples of β-hydroxycarbonyl compounds prepared in this manner, together with yields, are shown in Scheme 1, with the carbon–carbon bond formed by the aldol addition highlighted. In each case, hydrolysis to the carbonyl derivative was effected without dehydration.

The azadienyllithium reagent derived from the *N,N*-dimethylhydrazone of crotonaldehyde when allowed to react with simple ketones yielded α,β-unsaturated-δ-hydroxy-*N,N*-dimethylhydrazone products, resulting from 1,2-addition at the γ-carbon. This is in contrast to alkylation which occurs at the α-carbon (*cf.* equation 13) and to the reactivity of (**42**; equation 16) with cyclohexenone which led to mixtures of Michael adducts arising from electrophilic substitution at both the α- and γ-carbons.[21]





(16)

(**42**)

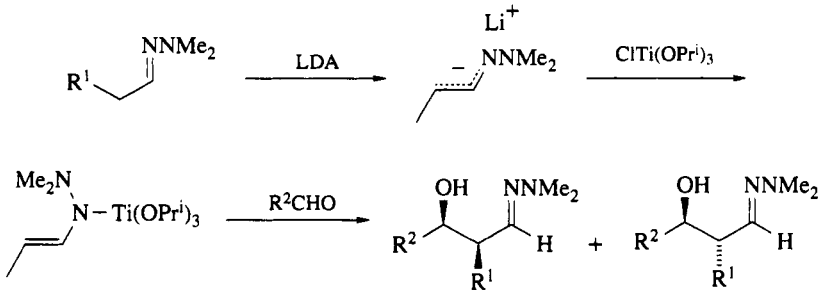
(**43a**) $R^1 = R^2 = Me$ (90%)

(**43b**) $R^1 = R^2 = -(CH_2)_5-$ (40%)

(**43c**) $R^1 = Bu^t$, $R^2 = Me$ (30%)

Aldol-type reactions are also feasible using trianions derived from simple hydrazones.[46] Thus, the hydrazone from acetophenone can be generated using Bu^nLi and added to benzophenone or 4-methylbenzophenone to yield an aldol product in modest yield. However, it does not appear that this method has any special advantages over the procedures using *N,N*-dimethylhydrazones described by Corey and Enders.

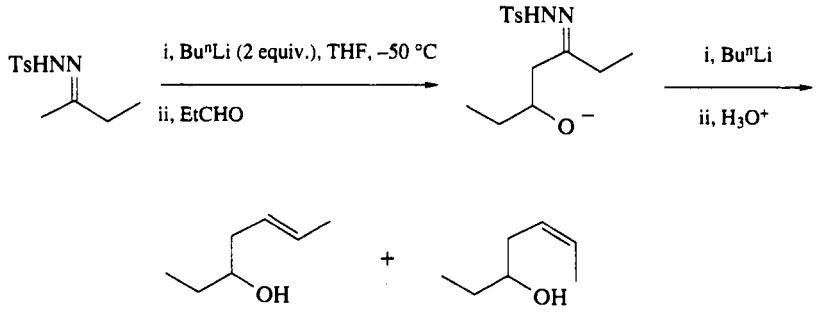
Syn selective aldol additions of titanated aldehyde hydrazones and ketone hydrazones have been reported by Reetz.[23] The observed *syn* selectivity parallels the *syn* selectivity seen in titanium ketone enolates,[47] and the intermediate titanium aldehyde hydrazone derivatives were seen to have $(E)_{C-C}$ geometry (equation 17).



(17)

syn *anti*

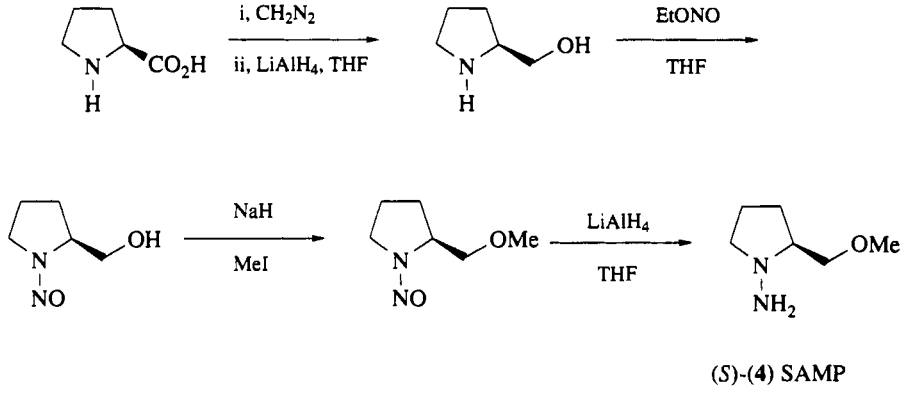
R^1	R^2	*syn:anti*
Me	Ph	91:9
Ph	p-$NO_2C_6H_4$	98:2
Ph	Pr^i	98:2
Pr^i	Ph	94:6
Me	Me	95:5
Me	Bu^t	93:7



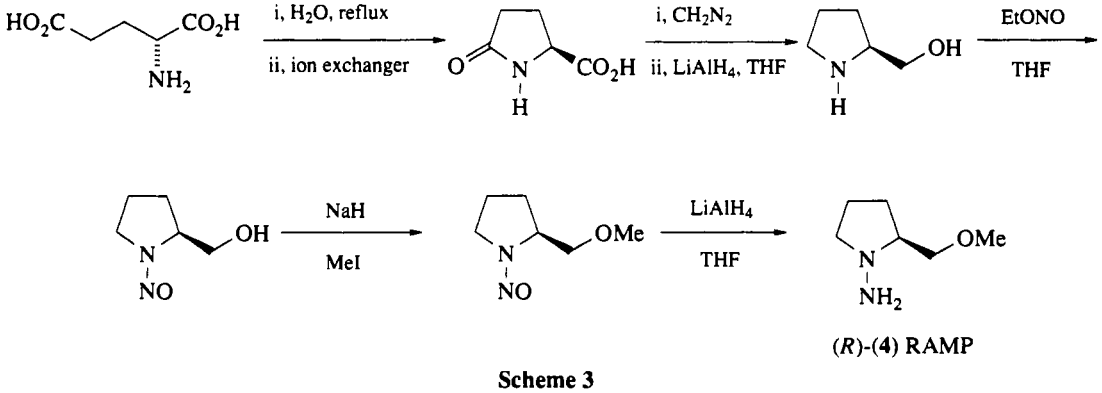
(18)

Aldol reactions between dilithio tosylhydrazone dianions and aldehydes and ketones afford good yields of β-hydroxy tosylhydrazones.[16] However, attempts to regenerate the ketone group from the tosylhydrazone either led to no reaction (basic conditions) or retro-aldol reactions (acidic conditions). While this potentially regioselective route to aldol products *via* tosylhydrazones was frustrated, the β-hydroxy tosylhydrazones could be converted in good yield into homoallylic alcohols using the Shapiro reaction, thus making use of the intermediate aldol product in equation (18). Tosylhydrazone dianions also react readily with chloroformates to yield ethyl esters. Thus, using a procedure analogous to that in equation (18) the dianion formed from the tosylhydrazone of cyclopentanone can be trapped with ethyl chloroformate to yield 73% of 2-ethoxycarbonylcyclopentanone tosylhydrazone.

β-Hydroxy tosylhydrazones, which are the products of a conventional aldol reaction between a dilithiated tosylhydrazone reagent and an aldehyde, can also be prepared by alternative routes. For example, Stork and Ponaras have described a procedure whereby an epoxy ketone is converted into an epoxy hydrazone. Subsequent addition of an alkyl- or aryl-magnesium bromide followed by hydrolysis yields either an α-alkylated- or α-arylated-β-hydroxy ketone or an α,β-unsaturated ketone. Since the attack of the Grignard reagent on the epoxide occurs with inversion at the α-carbon, this reaction can be used to



Scheme 2



Scheme 3

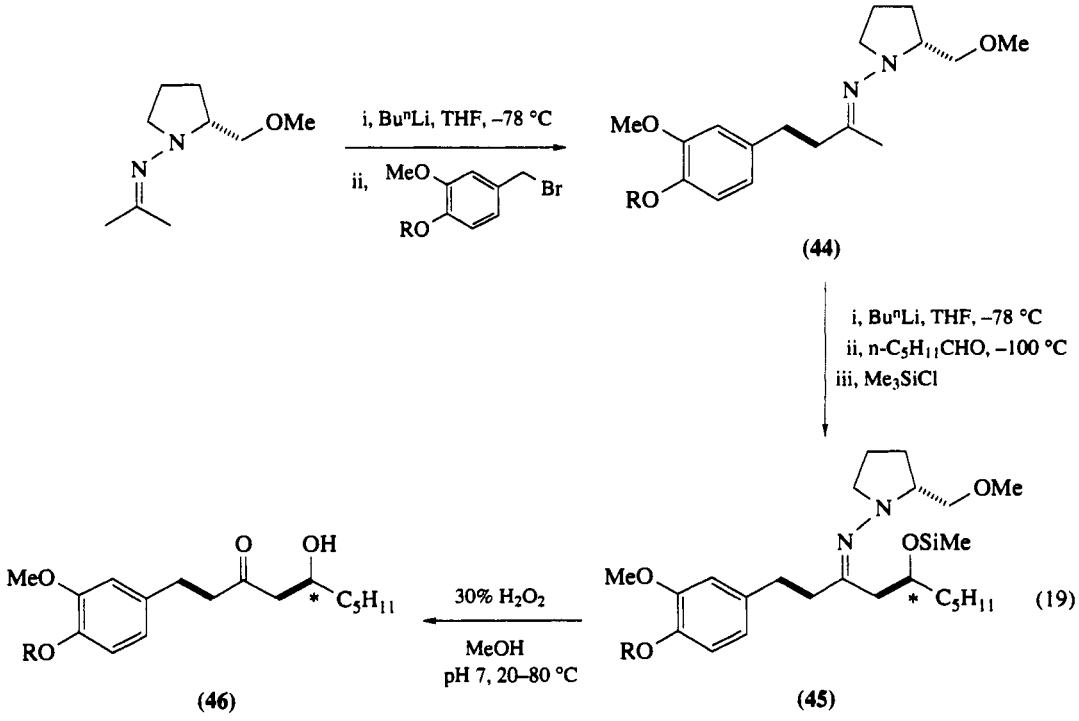
prepare a single diastereomer of a β-hydroxy hydrazone.[48] Similar reactions can also be carried out with α,β-epoxy tosylhydrazones and organocopper reagents.[49]

An advantage of using azaallyllithium reagents derived from aldehyde and ketone hydrazones is the potential for asymmetric synthesis. Enders' group has provided many elegant demonstrations of the practicality of this approach.[50] Enders' work in this area has relied on the use of (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine as a replacement for *N,N*-dimethylhydrazine. This chiral auxiliary is available commercially and can be prepared in the (*S*)-form starting with proline or in the (*R*)-form starting with glutamic acid (Scheme 2 and Scheme 3). These two chiral auxiliaries are often referred to as SAMP and RAMP respectively. Hydrazone formation with either enantiomer of this hydrazine follows the general procedures discussed above. These chiral hydrazines can be recycled when the product hydrazones are cleaved oxidatively and the resulting SAMP nitrosoamine is recovered. Large scale synthesis of chiral hydrazines including analogs of (*S*)-(**4**) in which the —CH_2OMe group is changed into more hindered groups such as —CMe_2OMe have recently been discussed by Enders and coworkers.[51]

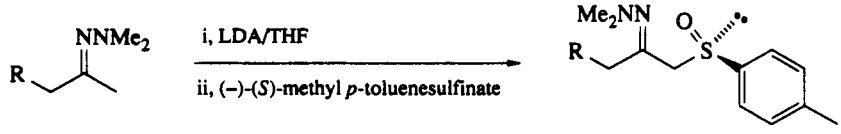
Initial applications of SAMP and RAMP hydrazones in regio- and enantio-specific aldol reactions were first reported by Enders' group.[52] In these initial studies, several methyl ketones were converted into SAMP hydrazones, deprotonated with Bu^nLi and then allowed to react with various aldehydes and methyl ketones. The diastereomeric hydrazone products of these reactions were then cleaved to form β-ketols in good chemical yields and with enantiomeric excesses of 31–62%.

Enders used SAMP and RAMP hydrazones in enantioselective aldol reactions leading to an efficient enantioselective synthesis of (+)-(*S*)-[6]-gingerol (**46**), the major pungent constituent of ginger.[53] Using the scheme shown in equation (19), the chiral acetone hydrazone prepared using RAMP was deprotonated and alkylated. A second regiospecific deprotonation followed by addition of *n*-hexanal at −100 °C yielded a hydroxy hydrazone which was protected with trimethylsilyl chloride. Oxidative hydrolysis followed by hydrogenolysis of the benzylic protecting group yielded the product (*S*)-(**46**). Through the use of azaallyllithium reagents derived from acetone RAMP hydrazone, acetone SAMP hydrazone and acetone dimethylhydrazone, it was possible similarly to prepare samples of both enantiomers of (**46**) as well as of racemic (**46**).

Stereospecific aldol syntheses can also be accomplished using chiral α-sulfinylhydrazones such as (**47**).[54] These reagents are prepared from dimethylhydrazone anions using (−)-(*S*)-methyl *p*-toluenesulfinate as an electrophile according to equation (20). The enantiomeric excess of the chiral sulfoxide so prepared can be measured by ^1H NMR using chiral shift reagents. The absolute configuration at sulfur was assigned as shown based on the assumption that the nucleophilic substitution at sulfur proceeds with inversion of configuration. Hydrolysis of these hydrazones yielded known 2-oxoalkyl sulfoxides and con-



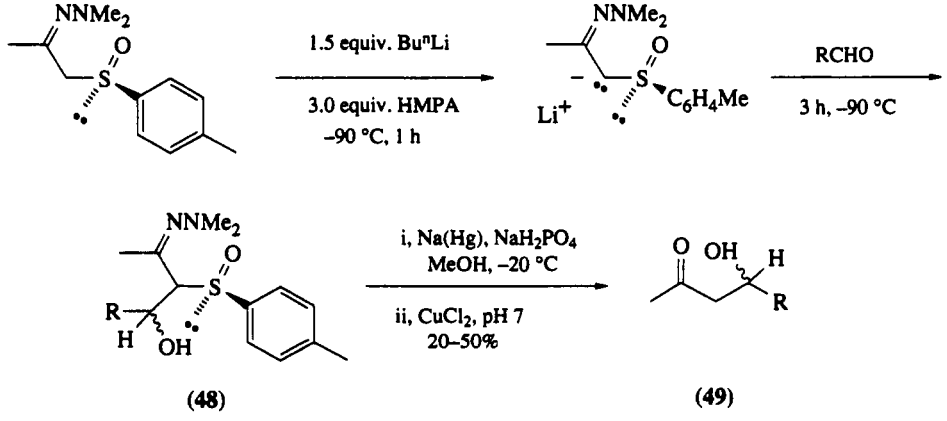
firmed the stereochemical assignments. Hydrolyses were, however, accompanied by some racemization and were unsuccessful in the case of aldehyde dimethylhydrazones. Unlike SAMP or RAMP hydrazones, the chirality of these hydrazones derives from the chirality at the attached sulfur atom.



(20)

(47)

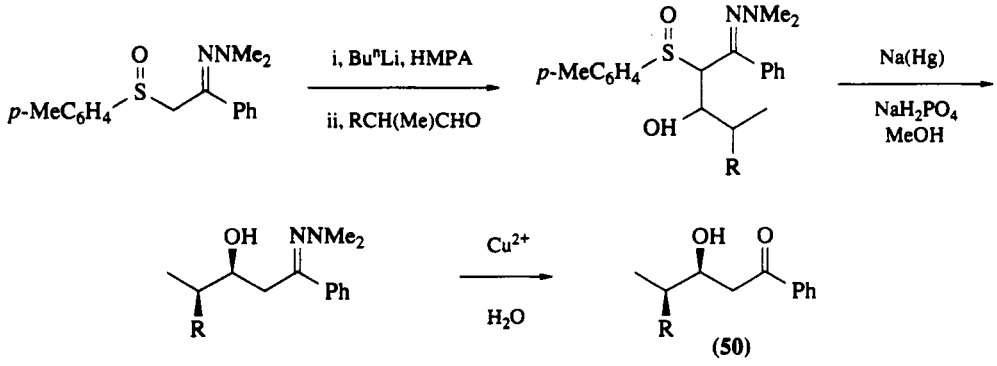
Chiral α-sulfinyl dimethylhydrazones form stabilized carbanions that can be used in enantioselective aldol reactions. A typical example is shown in equation (21).[55,56] Removal of the chiral sulfur auxiliary is accomplished by reductive desulfurization. Under these conditions recovery and reuse of the sulfur moiety is impossible. Synthetic and optical yields reported for these aldol reactions are modest in most cases. However, in a direct comparison to the SAMP/RAMP methodology, Annunziata has prepared (–)-(*R*)-[6]-gingerol in 60% *ee*.[57] Enders' prior synthesis had yielded this aldol product in 36% *ee*.[53]



(21)

(48) (49)

The effect of metalation conditions and the conditions under which 1,2-addition of sulfinylhydrazones occurs on the overall stereoselectivity of processes like that in equation (21) have been studied.[56] Optimi-



(22)

(50)

Ketol	*Yield* (%)	*Diastereoselectivity* (%)	*Enantioselectivity* (%)
(50a) R = Et	40	10	≥80
(50b) R = Pr^i	40	50	60
(50c) R = Pr^i	42	91	50
(50d) R = $PhCH_2$	46	10	≥90
(50e) R = $Me(CH_2)_4CH_2$	38	100	100

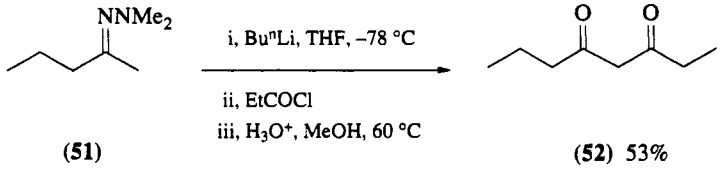
zation of these experimental variables produced enantiomeric excesses as high as 88% in one instance. However, the *ee* values were more generally in the range of 30–50%.

The reaction of anions derived from chiral α-sulfinyl hydrazones with chiral racemic aldehydes proceeds with both high diastereoselectivity and high enantioselectivity in certain cases.[58] The overall stereoselectivity of the reaction sequence in equation (22) was determined by HPLC and/or ^{1}H NMR analysis of the ratio of diastereomers and by the application of chiral shift reagents. The results seen both in equation (22) and with similar reactions employing α-alkyl- or α-aryl-α-alkoxy aldehydes show that the diastereoselectivity of these reactions is dependent on the size of the α-alkyl or α-aryl group. The enantioselectivity varied but again was highest with the most-hindered α-sulfinyl dimethylhydrazone, 2-phenylpropanal. Application of this chemistry led to a synthesis of manicone, (4*E*)-4,6-dimethyloct-4-en-3-one, an alarm pheromone of *Manica mutica* and *Manica bradleyi* in 11% *ee*.

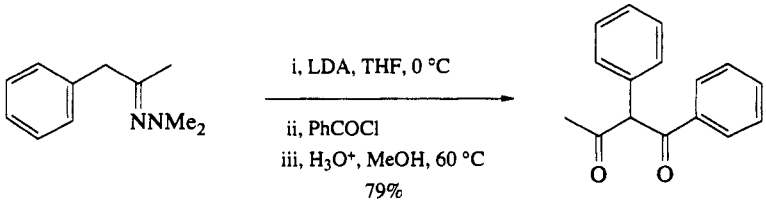
While the configuration of the predominant stereoisomer formed in reactions of α-alkoxy aldehydes with these azaallyllithio anions was not determined, ^{1}H NMR analysis was successful at assigning the configuration of the ketols in equation (22). Based on coupling constants, the predominant isomer formed was the *syn* isomer.

1.17.7 1,2-ADDITIONS TO CARBOXYLIC ACID DERIVATIVES

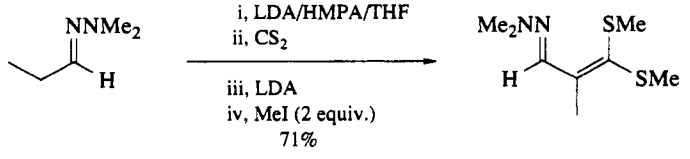
In additions to aldehydes and ketones, carboxylic acids and carboxylic acid derivatives also react with hydrazone anions in synthetically useful ways. In analogy to the Claisen reaction of ketone enolates and carboxylic acid derivatives, lithium dimethylhydrazone ketone anions can be used as nucleophiles in reactions with acid chlorides (equations 23 and 24).[59] LDA at 0 °C could also be used in place of Bu^{n}Li in these metalations. The resulting lithium dimethylhydrazone anion then reacted in a regiospecific manner with an acid chloride to afford on hydrolysis a 1,3-diketone. Overall yields in these reactions with various methyl ketone dimethylhydrazones ranged from 53 to 60%. Yields with 2-methylcyclopentanone and 2- or 3-methylcyclohexanone dimethylhydrazones ranged from 67 to 83%. With the exception of (**53**), all these reactions yielded products with overall substitution at the less-substituted α-carbon. Hydrolysis of the product hydrazone in these reactions only worked with acidic methanol and was a limiting step in the overall reaction scheme. Alternative dimethylhydrazone hydrolyses using 30% hydrogen peroxide, sodium metaperiodate and copper(II) chloride were not successful. Similar acylations using anhydrides, isocyanates, nitrile and carbon disulfide were also reported to work. However, specific examples were not reported.



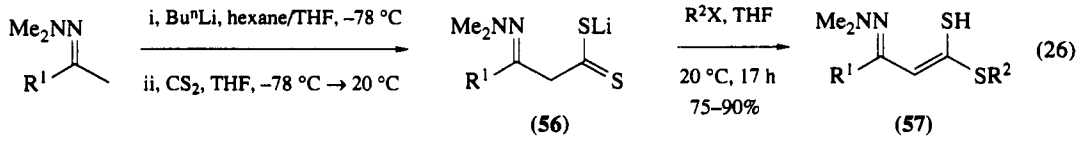
(**51**) (**52**) 53% (23)



(**53**) (**54**) (24)



(**55**) (25)



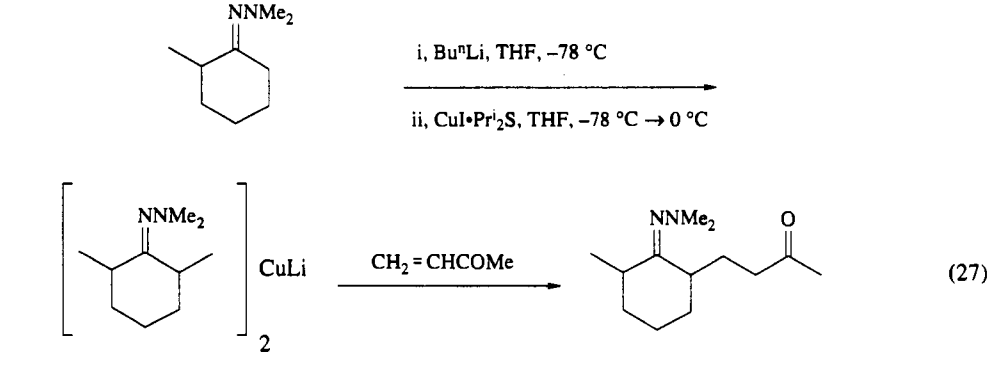
R^1 = Me, Ph; R^2 = Me, Et, Pr^n or $PhCH_2$

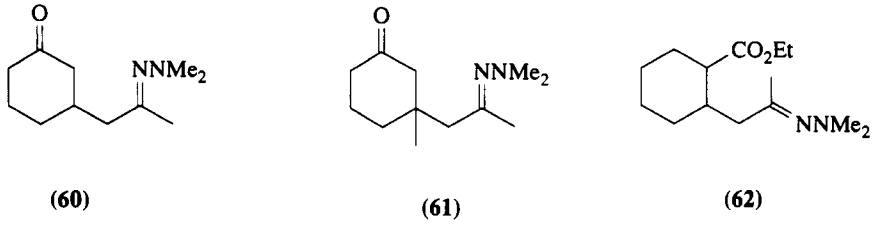
Conjugated ketene thioacetals have been successfully prepared starting with aldehyde dimethylhydrazones.[60] In these reactions, the first-formed azaallyllithium reagent was allowed to react with carbon disulfide to form an intermediate lithium 3-dimethylhydrazonoalkanedithiolate. A second deprotonation of this dithiolate with a second equivalent of LDA then generated a dianion that was successfully alkylated with two equivalents of methyl iodide to yield the ketene thioacetal (*e.g.* **55**; equation 25). This two step sequence avoided competing formation of a methyl dithiocarbamate by addition of LDA to carbon disulfide.

Examples of the reaction of carbon disulfide with lithium dimethylhydrazone anions derived from ketones were reported by Oliva and Delgado.[61] In these reactions, the initial lithium dimethylhydrazonoalkanedithioate (**56**) was not isolated but was instead alkylated to yield an alkyl dithiolate (**57**; equation 26). High yields of products were obtained using various alkyl iodides. Hydrolysis of the product hydrazone was not described.

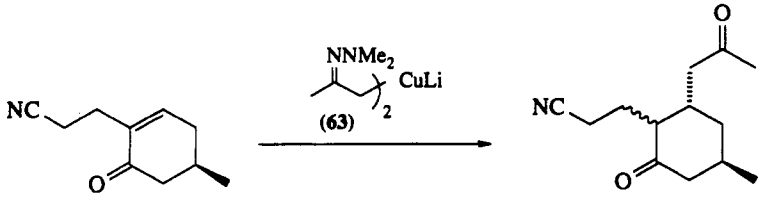
1.17.8 1,4-CONJUGATE ADDITIONS TO α,β-UNSATURATED CARBONYL DERIVATIVES

Addition of lithium dimethylhydrazone anions in a Michael fashion to α,β-unsaturated carbonyl compounds can be used in a variety of ways in synthesis. In their original paper describing 1,2-carbonyl additions of azaallyllithium reagents derived from *N,N*-dimethylhydrazones, Corey and Enders described the use of organocopper derivatives of dimethylhydrazones for conjugate additions.[21] In this chemistry, an azaallyllithium reagent derived from the dimethylhydrazone of 2-methylcyclohexanone was transmetalated with 0.5 equiv. of copper iodide/isopropyl sulfide at –78 °C for 1 h and then allowed to react with methyl vinyl ketone at –30 °C with gradual warming to 0 °C over 12 h to yield a Michael adduct. Oxidative hydrolysis to cleave the dimethylhydrazone yielded the octalone precursor (**59**) in 90–95% yield (equation 27). In a like manner, the 1,5-dicarbonyl compounds (**60**)–(**62**) were prepared from azaallylcopper reagents prepared from hydrazones *via* azaallyllithium reagents.





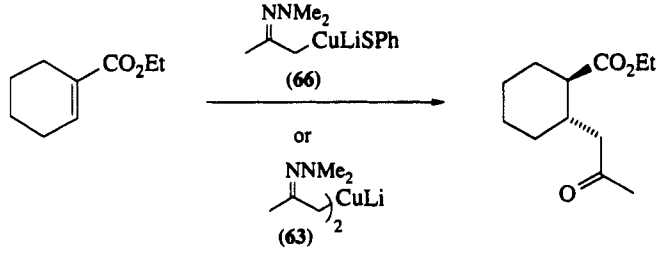
Homocuprates like (**58**) were used by Heathcock in the course of a total synthesis of lycopodine.[62] In this case, the cuprate derived from acetone dimethylhydrazone (**63**) was added to the cyano enone (**64**). In this example, the hydrazone-derived azaallylcuprate was about as effective as lithium dimethylallylcuprate addition followed by ozonolysis, and gave a lower overall yield than the Sakurai method using methallyltrimethylsilane and titanium tetrachloride. The product (**65**) was formed as a mixture of isomers (equation 28).



(28)

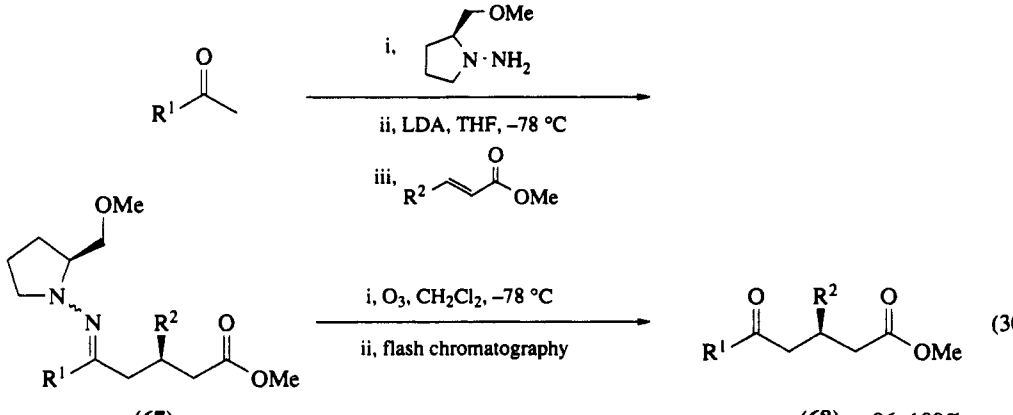
(**64**) (**65**)

Mixed cuprates derived from deprotonation and transmetalation of ketone dimethylhydrazones, using copper(I) thiophenoxide as the copper(I) source, are effective as enolate equivalents in 1,4-conjugate additions to α,β-unsaturated esters.[63] The mixed phenylthio cuprate was found to exhibit approximately the same selectivity and reactivity in these reactions as a similar homocuprate (**63**) prepared from the azaallyllithium reagents and copper(I) iodide (equation 29).



(29)

Regiospecific alkylation of dimethylhydrazone anions with the masked acrolein equivalent, 3-bromopropionaldehyde dimethyl acetal, has been used as an alternative to a conventional Michael reaction in Corey's total synthesis of picrotoxinin (*cf.* equation 13).[35] Azaallyllithium reagents derived from aldehyde and ketone hydrazones, unlike enolates, yield monoalkylation products with control of both regiochemistry and stereochemistry. In appropriate cases, alkylation followed by deprotection to form a dicarbonyl product can be a very effective synthetic strategy.



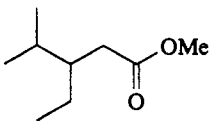
(30)

(**67**) (**68**) 96–100% *ee*
45–62% yield

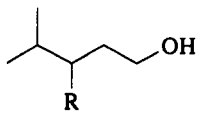
R^1 = Me, Et, Pr^n, Pr^i, n-C_5H_{11}, Ph; R^2 = Me, Ph

Asymmetric 1,4-conjugate additions can be carried out with SAMP and RAMP hydrazones without the need for added copper. This three-step reaction (equation 30) sequence yielded δ-keto esters in very high enantiomeric excesses ranging from 96 to 100%. Chemical yields ranged from 45 to 62%.[64]

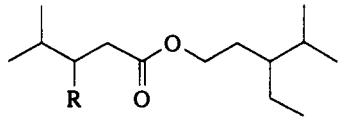
Enders has used these asymmetric Michael additions as the key steps in the enantioselective synthesis of various esters and alcohols (**69–73**) which are chiral volatile ant pheromones. In these syntheses, asymmetric Michael additions of the lithio salt of the SAMP hydrazone of propanal to methyl 2-butenoate and methyl 2-pentenoate were used to establish the chiral centers. Subsequent hydrolysis and reduction of the aldehyde or carboxylic acid ester by conventional procedures afforded the pheromones.[65]



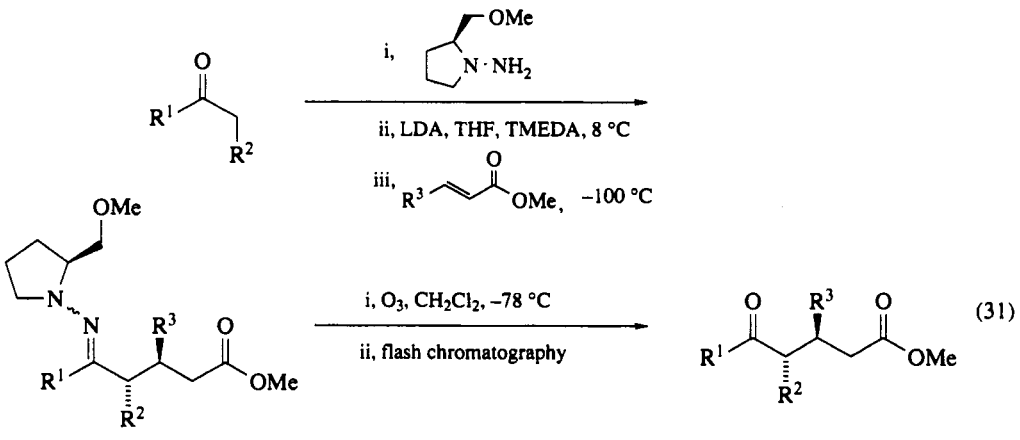
(69)



(70) R = Me
(71) R = Et



(72) R = Me
(73) R = Et

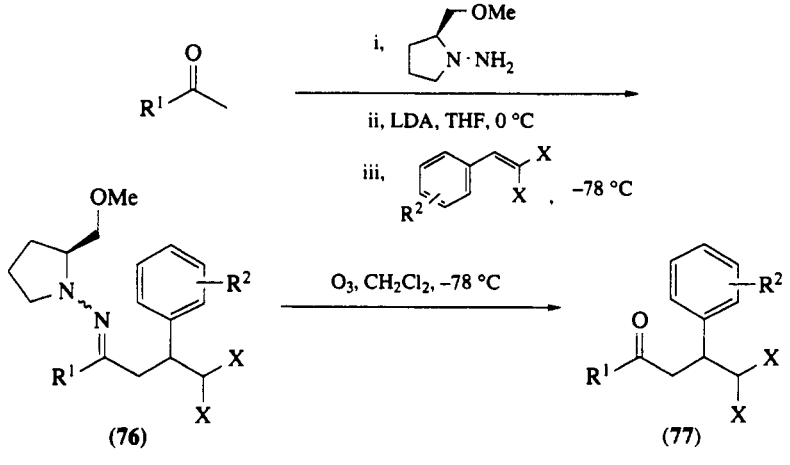


(74)

(75) 92–100% *ee*
90–100% *de*

(31)

R^1 = H, Et, Bu^n, Ph; R^2 = Me, Et, $PhCH_2$, Pr^n; R^3 = Me, Et, Ph



(76)

(77)

(32)

R^1 = Me, Et, Ph; R^2 = H, 3-OMe, 4-OCH_2Ph, 4-OMe; X = CO_2Me, CN

Extensions of the 1,4-conjugate addition methodology shown in equation (30) were recently described by Enders.[66] In this work, azaallyl metal reagents derived from aldehyde and ketone SAMP hydrazones were added to 2-alkenoates. Unlike the reactions leading to (**69**)–(**73**) in which the aldehyde carbonyl group was chemically reduced to form a methyl group, the aldehyde or ketone group was kept to yield chiral 3,4-disubstituted-5-oxoalkanoates. Both the diastereomeric excess and enantiomeric excess in these reactions were very high, with typical stereoselectivity exceeding 96% *de* and 96% *ee*. The overall chemical yields were also good and generally between 40 and 60%. The (*S,S*)-stereochemistry of the product shown in equation (31) was determined by X-ray analysis of the intermediate hydrazone (**74**; R^1 = Ph, R^2 = Me, R^3 = Me; equation 31). Substitution of RAMP for SAMP in this synthesis produced the (*R,R*)-enantiomer.

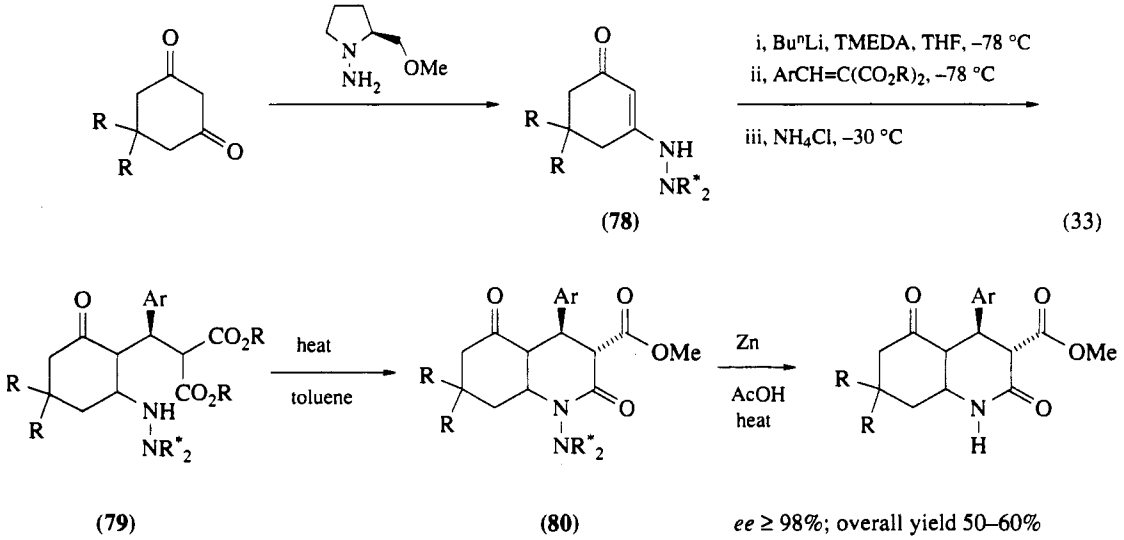
By coupling the asymmetric Michael additions of a SAMP or RAMP acetaldehyde hydrazone like those shown in equation (30) with hydrolysis and reduction of the chiral β-substituted δ-oxopentanoates, Enders was able to prepare chiral δ-lactones with control of stereochemistry at C-3 of the lactone ring.[67] As would be expected based on the results shown above, the enantioselectivity in this overall process was high (90–96%) and good chemical yields were obtained.

Recently Enders has shown that the asymmetric 1,4-conjugate addition methodology illustrated above will also work in enantioselective 1,4-additions of azaallyllithium derivatives of SAMP and RAMP methyl ketones to Knoevenagel acceptors like dimethyl benzylidenemalonates and benzylidenemalonitriles.[68] Oxidative cleavage of the SAMP (or RAMP) group leads to 2-aryl-4-oxo diesters and 2-aryl-4-oxodinitriles in overall yields of 50–82% with enantioselectivity exceeding 95%. The absolute stereochemistry of the products was shown to be (*R*) based on chemical correlation of (**77**) with methyl (*R*)-5-oxo-3-phenylhexanoate (equation 32).

1.17.9 HETEROCYCLE SYNTHESES *VIA* 1,2- AND 1,4-ADDITIONS OF HYDRAZONE ANIONS TO CARBONYL COMPOUNDS AND α,β-UNSATURATED CARBONYL COMPOUNDS

Extensions of the chemistry described in equation (32) have led to an enantioselective method for annulation of cyclic 1,3-diketones leading to tetrahydro-2,5(1*H*,3*H*)-quinolinediones.[69] As was true for the other 1,4-conjugate additions described above, these reactions proceed with exceptionally good enantioselectivity (>98%) and good chemical yields (50–60% overall). The absolute configuration of the products is as shown, and was confirmed by X-ray crystallographic analysis of (**80**; R* = SAMP, R = Me and Ar = Ph; equation 33).

By substituting (*S*)-(–)-1-amino-2-(dimethylmethoxymethyl)pyrrolidine (*S*)-(**83**) for (*S*)-(**4**), Enders has developed an efficient and enantioselective Hantzsch synthesis (Scheme 4). In this synthesis, the more-hindered hydrazone formed from (**83**) was condensed with an acetoacetic acid ester. Deprotonation of the hydrazone so-formed (the major tautomer present was an enehydrazine) followed by addition of an arylidene malonate derivative yielded (**85**), which could be closed with mild acid to yield optically active

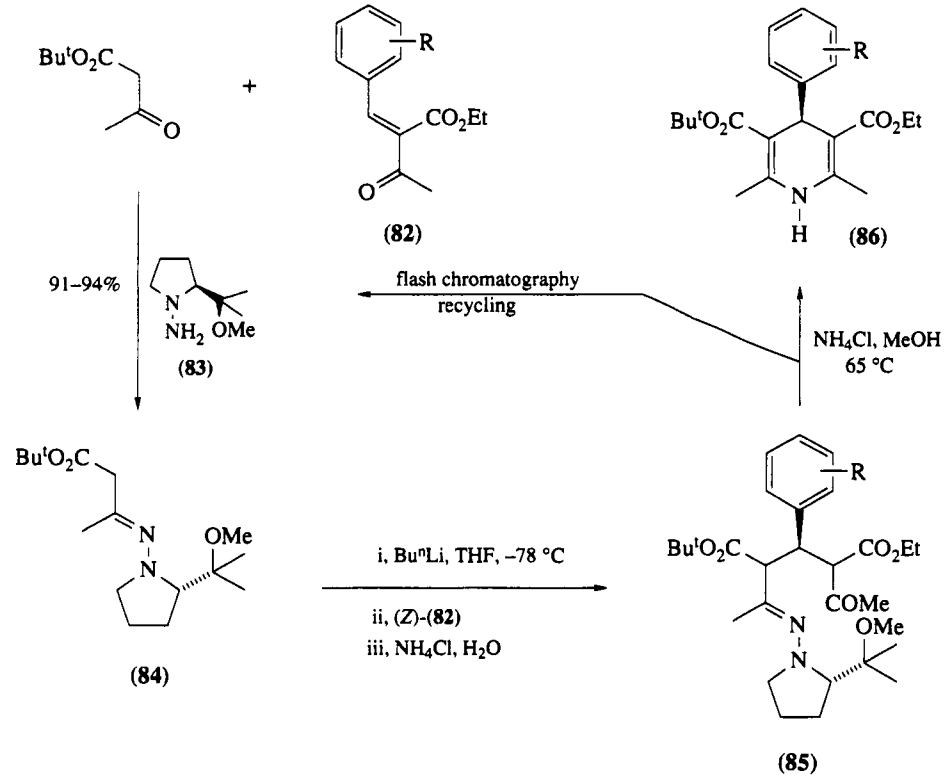


(**78**) (33)

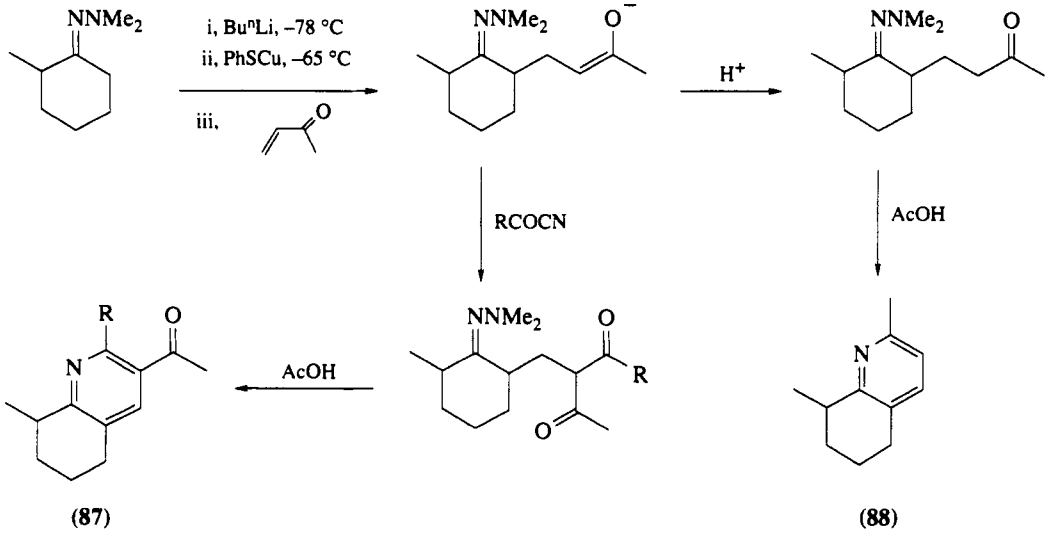
(**79**) (**80**) *ee* ≥ 98%; overall yield 50–60%

dihydropyridines. In the ring closure step, the pyrrolidine precursor to the chiral auxiliary (**83**) was regenerated and recoverable. Overall yields in this synthesis were very good and ranged from 64 to 72%. Enantioselectivities ranged from 84 to >96% with most reactions proceeding with >90% *ee*. Substituents on the aryl ring could be varied and examples with pyridyl, methyl and alkoxy groups were described.[70]

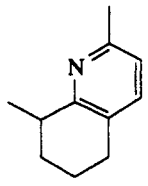
An earlier application of 1,4-conjugate additions employing azaallyllithium reagents formed from ketone dimethylhydrazones is Kelly's hydrazone version of the classical Knoevenagel route to substituted pyridine derivatives.[71] In this chemistry, a mixed cuprate derived from a dimethylhydrazone lithio anion and copper thiophenoxide was first allowed to react with an α,β-unsaturated ketone. The product enolate can then be acylated or protonated to yield either a diketo hydrazone or a keto hydrazone. Addition of



Scheme 4



Scheme 5



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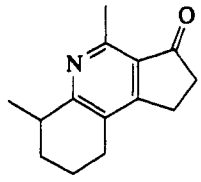

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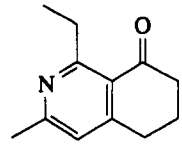

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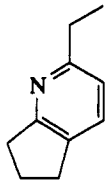

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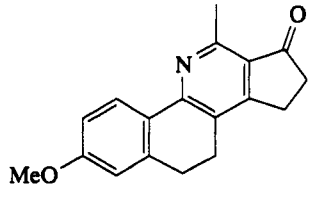
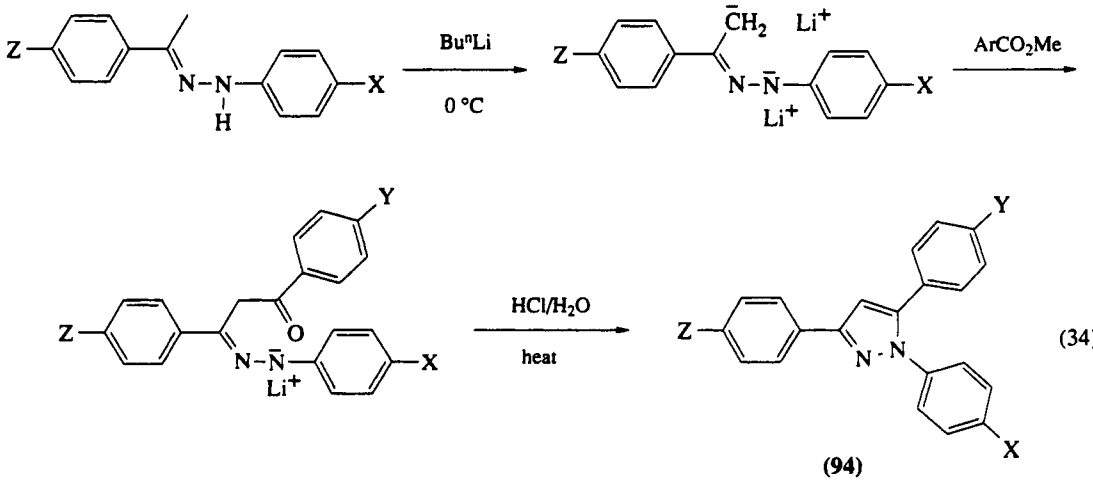


(93)

acetic acid then leads to cyclization. Unlike some other examples, hydrazone hydrolysis is not required in this synthesis. Instead, the hydrazone nitrogen is used for heterocycle formation. Overall, this one-pot sequence (Scheme 5) represents a very efficient and direct route to substituted pyridines like (**87**)–(**93**).

The 1,2-addition of hydrazone anions to carbonyl compounds has also been used to advantage in other heterocycle syntheses. The synthesis of heterocyclic compounds including pyrazoles and pyridazones using hydrazone anions are examples of this chemistry. Foote, Beam and Hauser first described application of this reaction for the synthesis of 1,3,5-trisubstituted aryl pyrazoles as shown in equation (34).[72] In this initial report, they found that various *p*-chloro and *p*-methoxy phenyl groups could be placed in predetermined and unambiguous positions on the product pyrazole ring. These reactions proceed by initial formation of a dianion from a starting *N*-arylhydrazone. In such cases, a strong base like Bu^{n}Li is used to deprotonate both the N—H and the α-Me of the starting ketone *N*-arylhydrazone. After addition of the ester, a transient β-keto *N*-phenylhydrazone anion is formed. Condensation of the anionic nitrogen with the new ketone carbon then closes the heterocycle. Loss of water at this point or during work-up then yields the product pyrazole. This pyrazole synthesis has the advantage of forming unambiguously a single isomeric triarylpyrazole in yields typically exceeding 80%.

The pyrazole synthesis described in equation (34) has been extended in a number of ways by Beam's group. Starting with unsubstituted hydrazones of various acetophenone and propiophenone derivatives, deprotonation with 3 equiv. of Bu^{n}Li leads to trianions that can be condensed with an ester and subsequently cyclized with acid to yield pyrazoles containing N—H groups (as opposed to N—Ar groups in



(34)

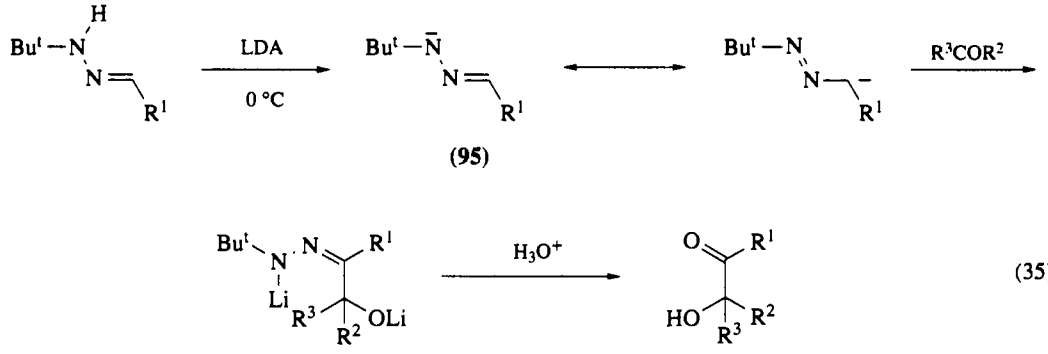
(**94**)

X,Y and Z = H, Cl, OMe

equation 34).[73] Substitution of an aroyl chloride for the aryl ester in equation (34) yields 4-acylpyrazoles.[74] More recently Beam's group has shown that *N*-phenylhydrazones of acetophenone can be doubly deprotonated with LDA to yield dianions which react with diethyl carbonate. The intermediate formed in this reaction is in effect the same as that prepared from a β-keto ester and phenylhydrazine, and can likewise cyclize to 2-pyrazolin-5-one derivatives.

1.17.10 HYDRAZONE ANIONS AS ACYL ANION EQUIVALENTS

Lithium salts of *t*-butylhydrazones of aldehydes have been shown to be useful acyl anion equivalents.[75] Treatment of an aldehyde *t*-butylhydrazone with an alkyllithium reagent or LDA gives the ambident nucleophile (**95**), which reacts with both aldehydes and ketones to give carbon-substituted products as shown in equation (35). The condensation works best with nonenolizable carbonyl derivatives. Extension of this chemistry to the reaction of (**95**) with α,β-unsaturated carbonyl compounds met with mixed success. While good yields of Michael products were seen in the addition of (**95**) to methyl crotonate, other α,β-unsaturated electrophiles such as methyl acrylate, acrylonitrile and methyl β,β-dimethylacrylate gave negligible yields of carbon-substituted products.



(95)

(35)

1.17.11 CLEAVAGE OF HYDRAZONES TO REGENERATE CARBONYL GROUPS

In cases other than the aforementioned heterocycle syntheses (see Section 1.17.9), the final step of a synthetic sequence employing azaallyl metal reagents derived from hydrazones is removal of the hydrazone group. This can be accomplished by several methods listed in Table 1 without affecting other functional groups in the molecule. The potential effects of oxidation, strong acid and racemization at any

Table 1 Reagents for Regeneration of Carbonyl Compounds from Ketone and Aldehyde Hydrazones

Reagents/Comments	*Ref.*
Aqueous $NaIO_4$ 2.2 equiv., pH 7, 20–25 °C suitable for ketone hydrazones, β-hydroxy groups are not affected	79
H_5IO_6 1 equiv., pH 4.5 buffer, 1:1 THF/H_2O, 20–25 °C, 2–3 h specific for aliphatic aldehydes	79
$BF_3{\cdot}Et_2O$ does not attack enol acetate groups	13
N-Bromosuccinimide in acetone/water not compatible with carbon–carbon double bonds	85
Nitronium or nitrosonium tetrafluoroborate	86
Clay-supported iron(III) nitrate	87
Molybdenyl chloride ($MoOCl_3$) in THF/H_2O	88
Molybdenum(VI) fluoride (MoF_6) in Freon 113	88
Tungsten(VI) fluoride (WF_6) in water	89
Cobalt(III) trifluoride in $CHCl_3$ with heat	90
Silica	91
Cerium(IV) ammonium nitrate in methanol/water	84
Tin(II) fluoride, pH 7 buffer, methanol/water	84

newly formed stereocenters are commonly subjects of concern in this regard. Three methods seem to be most generally useful: oxidative cleavage by ozonolysis at low temperature; *N*-methylation of the hydrazone using methyl iodide followed by hydrolysis in a biphasic HCl–pentane system; and copper-catalyzed hydrolysis.

The classical method is hydrolysis of a hydrazone using 1–6 M HCl.[2,76] However, this method is generally too harsh. In some cases, milder acids such as acetic acid and oxalic acid have successfully been used in place of HCl.[77,78]

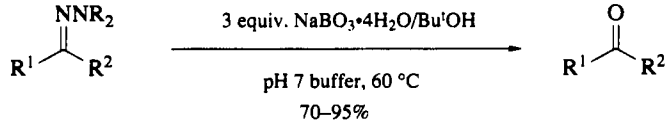
Regeneration by ozonolysis is most commonly used by Enders and coworkers for SAMP/RAMP hydrazones primarily because it allows almost complete recycling of the chiral auxiliary.[50] The method gives almost quantitative chemical yields with only a small degree of racemization in a few cases. Other advantages of this method are the neutral conditions, short reaction times (15–30 min) and the ease in detecting the endpoint *via* the development of a green color due to the presence of yellow nitrosamine and blue ozone.[50] However, the method cannot be used if there are other ozone-sensitive groups such as alkenes in the molecule.

Earlier, it was noted by Levisalles[79] that conversion of *N,N*-dimethylhydrazones to the corresponding trimethylhydrazonium iodides facilitated hydrolysis even under mild conditions. The reaction was carried out in quantitative yield by reacting the hydrazone with excess methyl iodide at 60 °C. Hydrolysis may be achieved using refluxing 95% ethanol, mineral acid or dilute sodium bicarbonate solution. In cases where aqueous sodium bicarbonate is used to hydrolyze aldehyde trimethylhydrazonium iodides, nitrile formation is also observed. However, keeping the pH below 2 by using mineral acid eliminates this problem.[80] A subsequent modification of this method by Enders[81] utilized a biphasic *n*-pentane/3–4 M HCl system to effect hydrolysis in good chemical yields and short reaction times (15–60 min). Yields seemed to be lower than those for ozonolytic cleavage. No racemization was observed with this biphasic method, presumably because the carbonyl compounds were rapidly transferred to the pentane phase by stirring. A partial recycling of the chiral auxiliary was also achieved.[50]

Still another powerful method for the regeneration of carbonyl compounds from dialkylhydrazones is copper-catalyzed hydrolysis. The reagents that have been tested for this purpose are 2% aqueous copper(II) acetate solution at pH 4,[53] copper(II) chloride in 0.05M phosphate buffer and 75% tetrahydrofuran/water,[53] and copper(II) sulfate pentahydrate[82,83]. Under the conditions of the hydrolysis, no reaction is observed in the absence of the copper(II) ion. Typical yields are 85–100%. Other functional groups like α-dicarbonyl, α-tricarbonyl, acetal and aldehydic formyl groups were not affected by this hydrolysis procedure. Nitrile formation in the case of aldehyde dimethylhydrazones was not a significant side reaction. However, reaction times ranged from 1 to 15 h. The reaction is believed to be nonoxidative in nature; rather, the copper is believed to activate the C=N bond and catalyze hydrolysis. The dimethylhydrazine produced during hydrolysis also complexes irreversibly with the copper(II) ion to drive the reaction to completion.

A new method for cleavage was recently reported by Enders.[84] Treatment of the hydrazone with three equivalents of sodium perborate regenerated the carbonyl compound in 70–95% yield according to equation (36). This oxidative cleavage was chemoselective and left carbon–carbon double bonds intact. This chemoselectivity plus the neutral hydrolytic conditions and the low cost of the oxidant make this method quite attractive. The main disadvantage of this method is the relatively long reaction time required, ranging from 4–24 h for aliphatic ketone hydrazones to 2–3 d for aromatic ketone hydrazones.

Many other reagents have been used to cleave hydrazones and to regenerate carbonyl groups. Table 1 lists some of these other examples of procedures to regenerate carbonyl compounds from their *N,N*-dialkylhydrazones.



(36)

$NR_2 = NMe_2$, SAMP/RAMP

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2.1
The Prins and Carbonyl Ene Reactions

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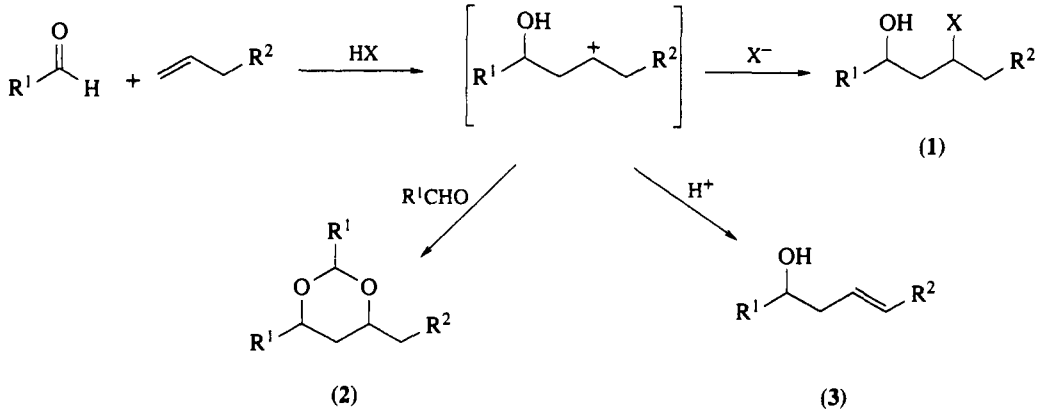
2.1.1 INTRODUCTION

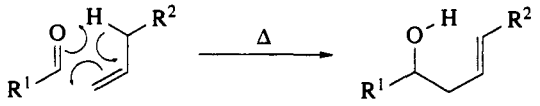
The addition of aldehydes and ketones to alkenes in the presence of Brønsted acids is usually called the Prins reaction.[1,2] Addition of the protonated carbonyl compound to the alkene gives a β-hydroxy carbocation which reacts with a nucleophile such as chloride, water or acetate to give (**1**), adds to a second molecule of aldehyde to give (**2**) or loses a proton to give homoallylic alcohol (**3**; Scheme 1). Formaldehyde and electron-deficient carbonyl compounds undergo concerted thermal ene reactions with alkenes at temperatures ranging from 100 to 200 °C to give homoallylic alcohols (equation 1; R^1 = H, CCl_3, or CO_2R).[3–7] A wide variety of carbonyl compounds undergo Lewis acid catalyzed reactions with alkenes to give homoallylic alcohol ene adducts in excellent yield with high selectivity, although in some cases γ-chloro alcohols are formed as by-products.[8,9] Recent investigations suggest that at least some of these

Lewis acid catalyzed ene reactions are stepwise, rather than concerted, but that the intermediate bears more resemblance to a π-complex than to the open carbocation intermediate in the Prins reaction.[10–13]



(1) (2) (3)

Scheme 1



(1)

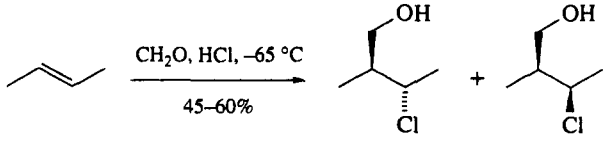
The ene and Prins reactions are not mechanistically distinct. Coverage will therefore be organized by the nature of the carbonyl compound, with intermolecular reactions presented first, followed by intramolecular reactions. The emphasis will be on material published since the field has been reviewed[1–9] and on examples demonstrating the stereo-, regio- and chemo-selectivity of these reactions. Coverage is restricted to the addition of carbonyl and thiocarbonyl compounds to simple alkenes. Addition of carbonyl compounds to vinylsilanes, allylsilanes and enol ethers is covered in the following chapters. Addition of imines and iminium compounds to alkenes is presented in Part 4 of this volume. Ene reactions with alkenes and alkynes as enophiles are covered in Volume 5, Chapter 1.1. Use of aldehydes and acetals as initiators for polyene cyclizations is covered in Volume 3, Chapter 1.6.

2.1.2 INTERMOLECULAR REACTIONS

2.1.2.1 Formaldehyde

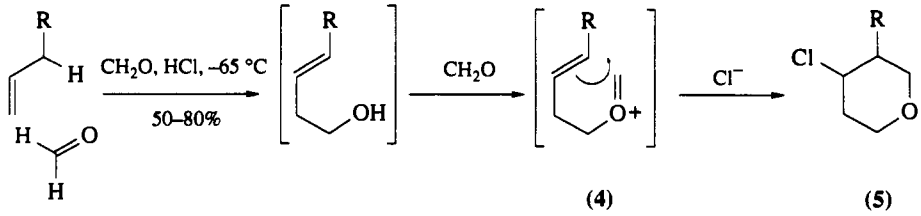
2.1.2.1.1 Prins reactions

The reaction of formaldehyde with alkenes is of industrial interest and has been extensively studied.[1,2] Reaction of excess formaldehyde as formalin with an alkene and aqueous acid gives 1,3-dioxanes (**2**) in 40–90% yield. Reaction of 2-butenes with paraformaldehyde and hydrogen chloride at –65 °C gives a mixture of diastereomeric γ-chloro alcohols rich in the isomer formed by *trans* addition to the alkenyl double bond.[14] For example *trans*-2-butene gives an 85:15 mixture of *erythro*- and *threo*-3-chloro-2-methyl-1-butanol (equation 2). Reaction of 1-alkenes under similar conditions gives 3-alkyl-4-chlorotetrahydropyrans (**5**) in 50–80% yield (Scheme 2).[15] Initial reaction occurs *via* addition of formaldehyde to the terminal carbon of the double bond, followed by loss of a proton to give the 3-alken-1-ol. Reaction of



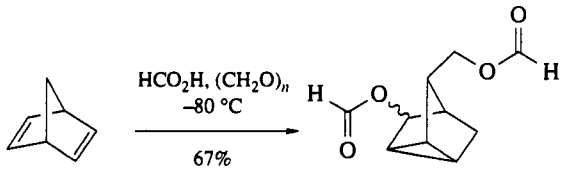
80–90% 10–20%

(2)

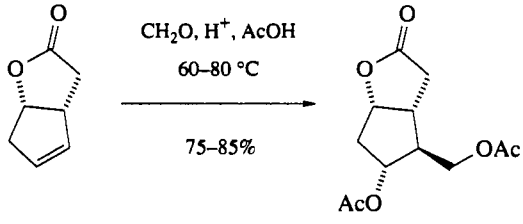


(4) (5)

Scheme 2



(6) (3)



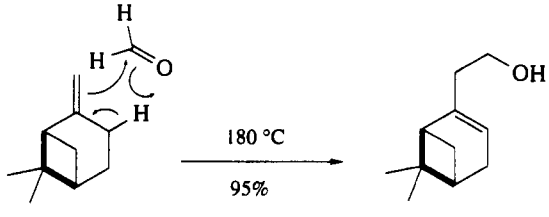
(7) (8) (4)

the 3-alken-1-ol with formaldehyde followed by loss of water gives (**4**), which undergoes an intramolecular Prins reaction followed by chloride attack on the cation to give (**5**).

Prins reactions with formaldehyde have been used to prepare prostaglandin intermediates. Reaction of norbornadiene with paraformaldehyde and formic acid at –80 °C gives (**6**) in 67% yield (equation 3).[16] Reaction of unsaturated lactone (**7**) with formaldehyde in acetic acid at 60–80 °C gives prostaglandin intermediate (**8**) in 75–85% yield (equation 4).[17] Addition of protonated formaldehyde occurs from the less-hindered face of the double bond followed by *trans* addition of acetate to the carbocation.

2.1.2.1.2 Thermal ene reactions

Formaldehyde undergoes thermal ene reactions with reactive 1,1-disubstituted and trisubstituted alkenes at 180–220 °C. β-Pinene, a particularly reactive ene component, reacts with formaldehyde at 180 °C to give nopol in 95% yield (equation 5).[18] Methylenecyclohexane reacts similarly.[19] Blomquist extended the scope of these reactions by using acetic acid–acetic anhydride as solvent at 180–190 °C.[20]

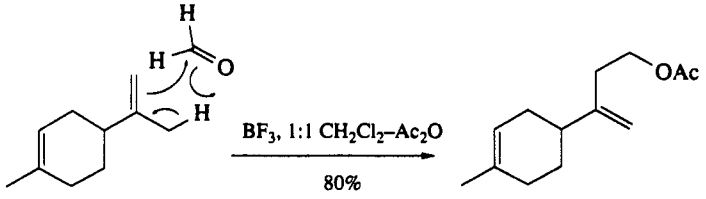


(5)

2.1.2.1.3 Lewis acid catalyzed ene reactions

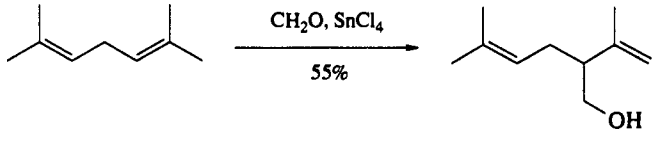
Excellent yields of ene adducts can be obtained from $BF_3{\cdot}Et_2O$- or $SnCl_4$- catalyzed addition of formaldehyde to alkenes that can give a tertiary carbocation.[21] Limonene reacts selectively at the 1,1-disubstituted double bond to give ene adduct (**9**) in 80% yield (equation 6). $SnCl_4$- catalyzed addition of formaldehyde to 2,6-dimethyl-2,5-heptadiene gives lavandulol (**10**) in 55% yield (equation 7).[22] $BF_3{\cdot}Et_2O$-catalyzed ene reaction of formaldehyde with (**11**) occurs exclusively from the less-hindered α-face to give ene adduct (**12**) with the correct stereochemistry at C-20 and functionality suitable for construction of the vitamin D side chain (equation 8).[23]

A problem with Lewis acid catalyzed ene reactions of aldehydes is that the alcohol–Lewis acid complex produced in the reaction is susceptible to solvolysis and is a strong protic acid capable of protonating the double bond of the ene adduct or alkene starting material. Me_2AlCl in equivalent or greater



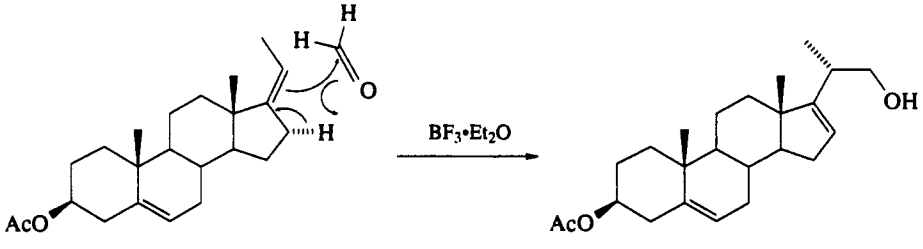
(6)

(9)



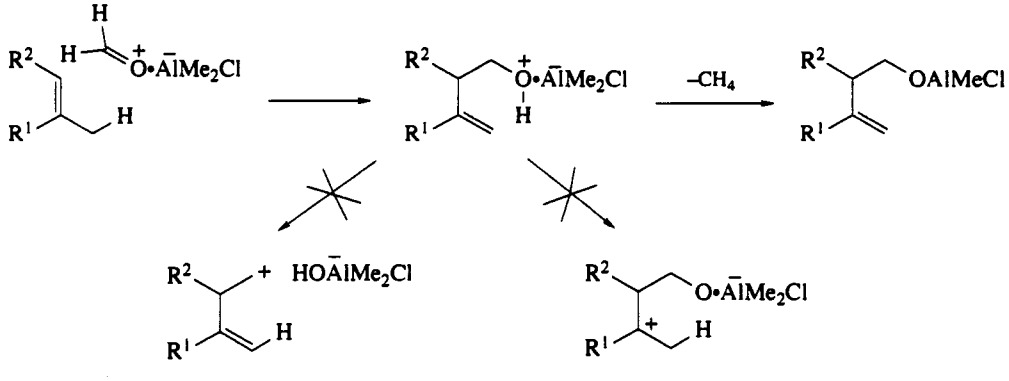
(7)

(10)



(8)

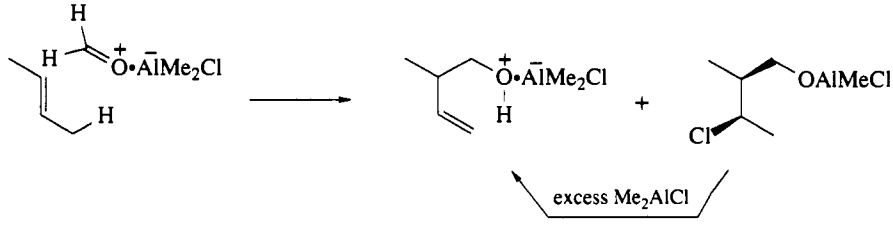
(11) (12)



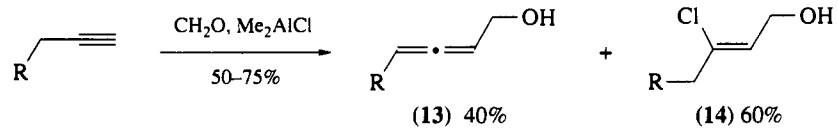
Scheme 3

amounts is a useful catalyst for these reactions.[24] The alcohol–Me_2AlCl complex formed in the reaction decomposes rapidly to give methane and a nonbasic aluminum alkoxide which does not undergo these side reactions (Scheme 3). With this Lewis acid, ene adducts are obtained in good yield from formaldehyde and mono- and 1,2-disubstituted alkenes as well as those that can give a tertiary carbocation.

These reactions involve a zwitterionic intermediate or π-complex that selectively undergoes a [1,5] proton shift to give the ene adduct–Me_2AlCl complex, which loses methane. With 1 equiv. of Me_2AlCl, a γ-chloro alcohol is formed as a by-product when the carbocation is secondary. With 1.5–2 equiv. of Me_2AlCl, γ-chloro alcohols are formed as transient intermediates. Those derived from acyclic alkenes give ene adducts. Those derived from cyclohexene and cyclopentene give complex mixtures of products. The chloro alcohols formed from 1,2-disubstituted alkenes result from the stereospecifically *cis* addition of the hydroxymethyl group and the chloride to the double bond (Scheme 4). Formaldehyde undergoes Me_2AlCl-induced reactions with terminal alkynes to give a 2:3 mixture of the ene adduct (**13**) and the (*Z*)-chloro alcohol (**14**) in 50–75% yield (equation 9).[25]

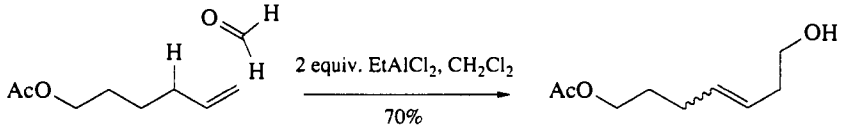


Scheme 4



(**13**) 40% (**14**) 60% (9)

These Me_2AlCl-catalyzed reactions of formaldehyde are successful because the Lewis acid is a Brønsted base as well as a strong Lewis acid.[26] Unfortunately, the methyl group of Me_2AlCl can also act as a nucleophile. Formaldehyde undergoes Me_2AlCl-induced reactions with all simple alkenes. However, many functionalized alkenes are not nucleophilic enough to react with the formaldehyde–Me_2AlCl complex. Reaction of 5-hexenyl acetate with formaldehyde and Me_2AlCl gives only ethanol from addition of a methyl group to the aldehyde. The acetate group is more basic than formaldehyde so Me_2AlCl preferentially complexes to it. Furthermore, the acetate–Lewis acid complex is electron withdrawing and decreases the nucleophilicity of the double bond relative to that of the methyl group of Me_2AlCl. Therefore, no ene reaction occurs even if a second equivalent of Me_2AlCl is used. Fortunately, use of 2 equiv. of $EtAlCl_2$, a stronger Lewis acid with a less nucleophilic alkyl group, gives (**15**) as a 3:1 (*E*):(*Z*) mixture in 70% yield (equation 10).[27]

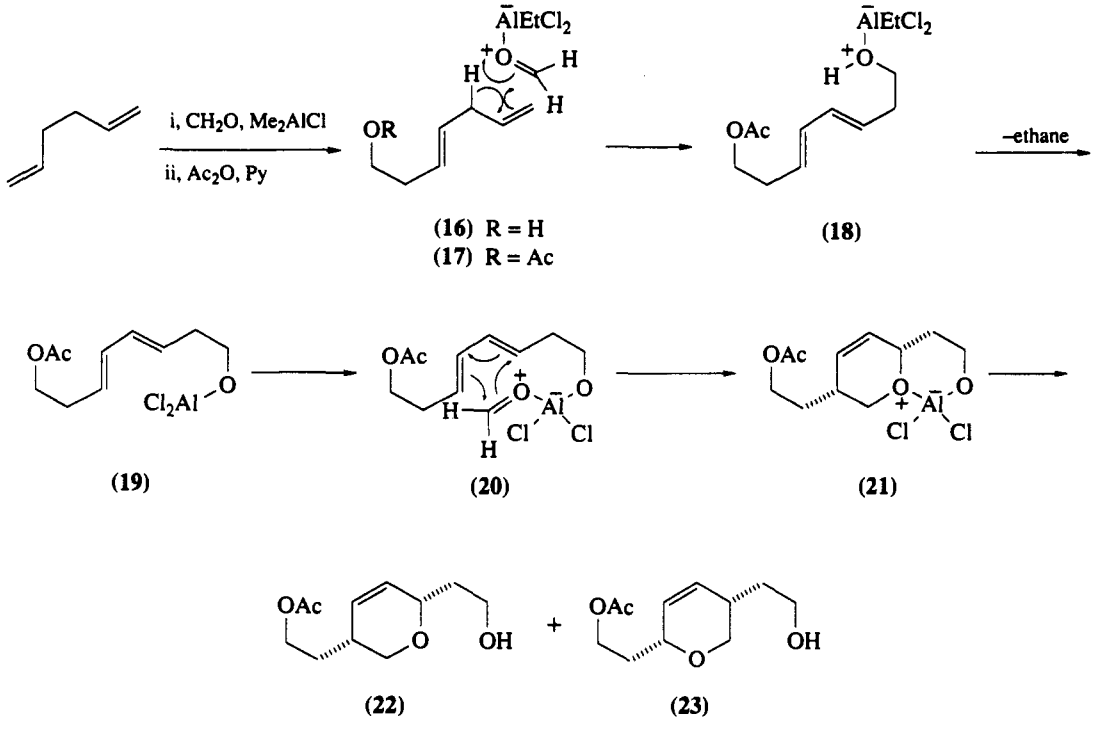


(**15**) (10)

A formal synthesis of pseudomonic acids A and C has been carried out using two ene reactions and a Diels–Alder reaction starting with 1,5-hexadiene and three molecules of formaldehyde to give the key intermediate (**22**) in only three steps (Scheme 5).[28] Me_2AlCl-catalyzed reaction of formaldehyde with 1,5-hexadiene gives (**16**) as an 8:1 mixture of (*E*)- and (*Z*)-isomers in 81% yield. Only traces of 2:1 adducts are obtained in the ene reaction, even when excess formaldehyde and Me_2AlCl are used, since the aluminum alkoxide inductively deactivates the double bond of (**16**). Treatment of acetate (**17**) with 3 equiv. of paraformaldehyde and 4.5 equiv. of $EtAlCl_2$ in 1:1 CH_2Cl_2:nitromethane for 12 h at 25 °C gives a 16:1 mixture of (**22**) and (**23**) in 37% yield. The acetate of (**17**) is more basic than formaldehyde and complexes to $EtAlCl_2$. This complex reacts selectively with formaldehyde·$EtAlCl_2$ at the less deactivated terminal double bond to give ene adduct (**18**), which loses ethane to give (**19**). Complexation of (**19**) with

formaldehyde gives (**20**), which undergoes a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction to give (**21**). Aqueous work-up gives (**22**). The regiochemistry of the Diels–Alder reaction is controlled by the Lewis acid, which is bound to the diene and complexed to the dienophile, giving rise to a quasi-intramolecular Diels–Alder reaction.

In most cases the ene adduct formed from Lewis acid induced addition of formaldehyde to an alkene does not react with a second equivalent of aldehyde due to the inductive effects of the aluminum alkox-

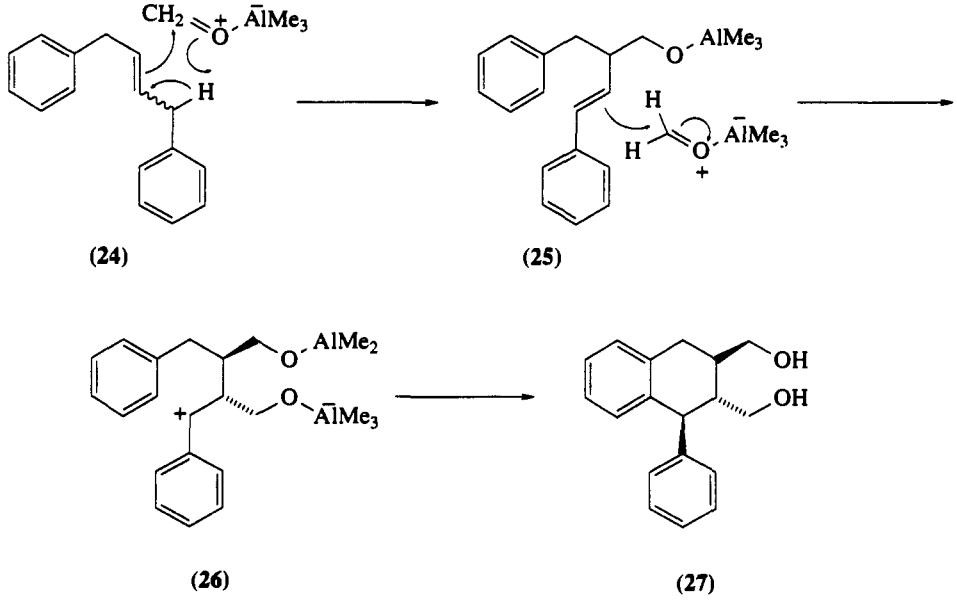


(**16**) R = H
(**17**) R = Ac

(**18**) (**19**) (**20**) (**21**)

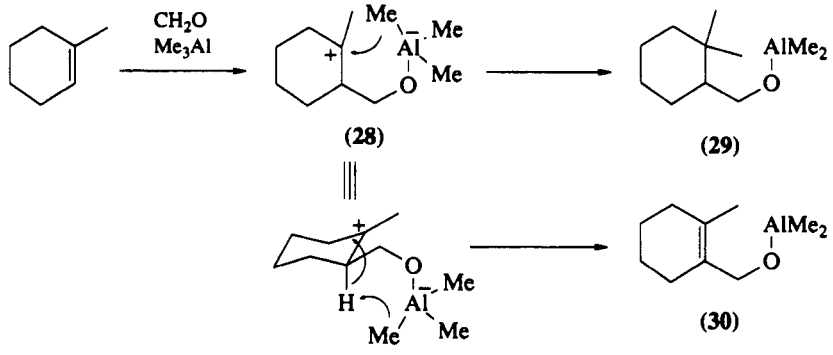
(**22**) (**23**)

Scheme 5



(**24**) (**25**) (**26**) (**27**)

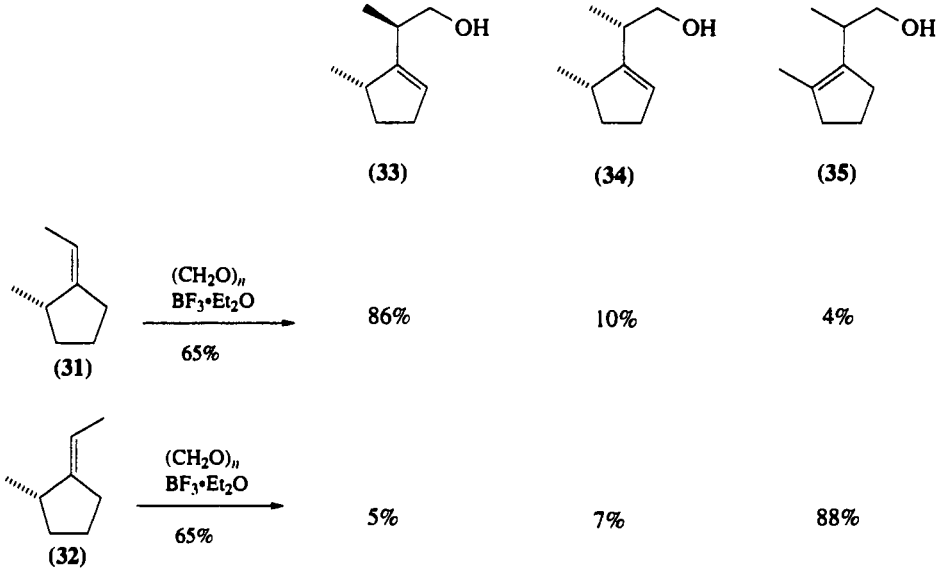
Scheme 6



Scheme 7

ide, which deactivates the double bond of the homoallylic alcohol ene adduct. In special cases, the double bond of the product is more nucleophilic than the starting alkene so that 2:1 adducts are formed. As shown in Scheme 6, a one-pot synthesis of the aryltetralin lignan skeleton was carried out by reaction of (*E*)- or (*Z*)-(**24**) with 6 equiv. of paraformaldehdye and methylaluminum sesquichloride to give a 40–50% yield of (**27**) as the only characterizable product.[29] Ene reaction occurs as expected to give the ene adduct (**25**). The styrene double bond of (**25**) is much more nucleophilic than the 1,2-disubstituted double bond of (**24**), so (**25**) reacts with formaldehyde to give benzylic cation (**26**), which undergoes a Friedel–Crafts reaction to give (**27**) as the *trans,trans* isomer.

The reaction of formaldehyde and Me_3Al with 1-methylcyclohexene gives only 5% of the expected ene adducts, the exclusive products from formaldehyde and Me_2AlCl.[24] The major products are the alcohol derived from (**29**), resulting from *cis* addition of the hydroxymethyl and methyl groups to the double bond and the allylic alcohol derived from (**30**; Scheme 7).[30] The enhanced basicity and nucleophilicity of the methyl groups of intermediate (**28**), as compared to the intermediate obtained with Me_2AlCl, are apparently responsible for the difference between these reactions. The yields in these reactions are acceptable only with 1,1-di- and tri-substituted alkenes, since competing addition of a methyl group to formaldehyde is a significant side reaction with these substrates and the only reaction with less nucleophilic alkenes.



Scheme 8

2.1.2.1.4 Regioselectivity of Lewis acid catalyzed ene reactions

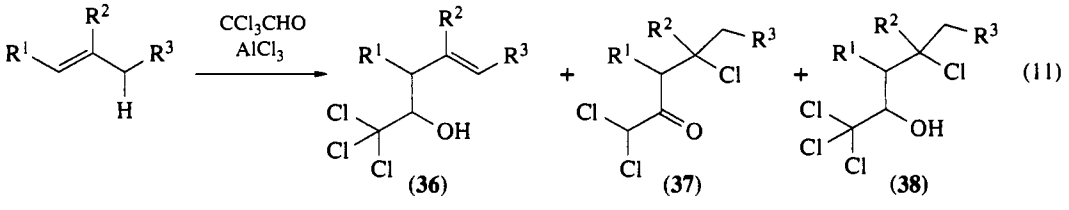
After correction for statistical factors a methylene hydrogen is twice as reactive as a methyl or methine hydrogen.[25] 1,2-Disubstituted double bonds are formed ≈90% (*E*) with Me_2AlCl and ≈75% (*E*) with $EtAlCl_2$. Trisubstituted double bonds are formed ≈70% (*E*). In the ene reactions of formaldehyde with trisubstituted double bonds, there is a preference for transfer of a hydrogen from the alkyl group *syn* to the vinylic hydrogen. In most cases this selectivity is modest,[25] although one highly selective example has been reported (Scheme 8).[31] The major product (**33**), obtained from (**31**), was converted to Prelog–Djerassi lactone. The regioselectivity is most likely due to steric interaction between the formaldehyde–BF_3 complex and the alkenyl methyl group in the transition state for proton abstraction from the carbon *anti* to the vinylic hydrogen. Reaction occurs with high facial selectivity from the less hindered β-face of (**31**) to give an 86:10 mixture of (**33**):(**34**). Reaction with (**32**) shows little facial selectivity.

2.1.2.2 Electron-deficient Aldehydes

The thermal and Lewis acid catalyzed reactions of electron-deficient aldehydes such as chloral, glyoxylate esters and phenylglyoxal have been extensively studied. The reactions with glyoxylate esters are particularly intriguing, since use of a chiral ester group has permitted these reactions to be carried out with excellent asymmetric induction.

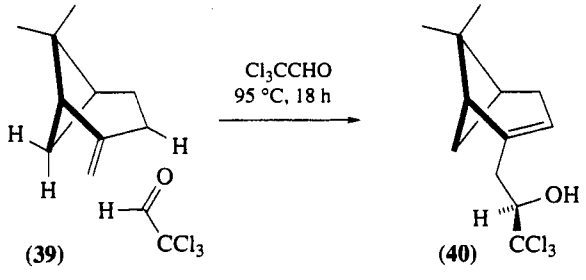
2.1.2.2.1 Chloral

Pioneering studies on the $AlCl_3$- and $SnCl_4$-catalyzed addition of chloral to alkenes were carried out by Colonge and Perrot, and Klimova and Arbuzov.[32] Recent studies by Gill and coworkers have provided a more complete understanding of this reaction.[33–36] The general trend in reactivity with alkenes is as follows: 1,1-di- > tri- > mono- > *cis*-1,2- > alkynes > *trans*-1,2-disubstituted.[33] Thermal reactions can be carried out at 90–130 °C with 1,1-di- and tri-substituted alkenes. Lewis acid catalyzed reactions are best carried out with 2% $AlCl_3$ in CH_2Cl_2 or CCl_4 for reactive alkenes and 6–20% $AlCl_3$ for less reactive alkenes. All products result from addition of the carbonyl group to the less-substituted end of the double bond. The ene adduct (**36**) is usually the major product (equation 11). Chloro ketones (**37**) are formed in significant amounts from mono- and 1,2-disubstituted alkenes. Prins type products (**38**) are occasionally isolated, particularly with less reactive alkenes. Bromal is less reactive than chloral in these reactions.



(11)

The *endo*/*exo* and regioselectivity of these reactions was carefully examined.[34] *Endo*/*exo* selectivity appears to be determined largely by steric interactions rather than electronic effects. Thermal reaction of β-pinene with chloral at 95 °C gives an 83:17 mixture of (**40**; equation 12) and (**42**; equation 13). The major product is formed *via* transition state (**39**) with the trichloromethyl group *endo* (under the π-system) to avoid steric interactions with the one-carbon bridge. Lewis acid catalyzed reactions of chloral with β-pinene provide mixtures rich in (**42**). Optimal results were obtained with $TiCl_4$, which gives exclusively (**42**). The Lewis acid complexes to the lone pair of the carbonyl group *trans* to the trichloromethyl group. Reaction occurs selectively from transition state (**41**) with the trichloromethyl group *exo* and the $TiCl_4$ *endo*, which minimizes steric interactions of the bulky Lewis acid with β-pinene.



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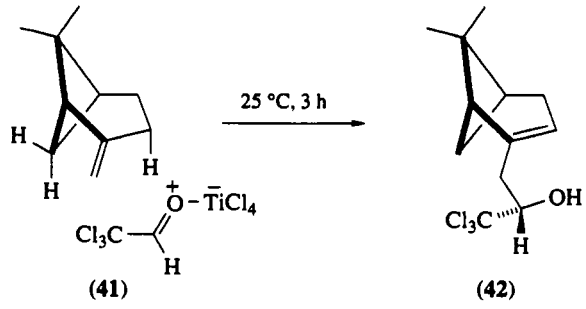
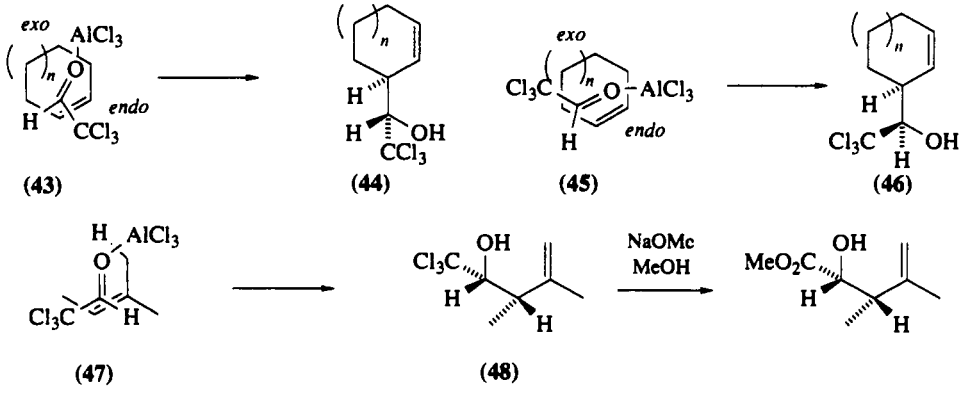


(41) (42) (13)

$AlCl_3$-catalyzed reaction of C-5 through C-8 cycloalkenes affords ≈90:10 mixtures of diastereomers. The major isomers were shown to be (**44**), formed from transition state (**43**) with the trichloromethyl group *endo* and the Lewis acid *exo*. Formation of the minor isomers (**46**) proceeds through transition state (**45**), with severe steric interactions between the *exo* trichloromethyl group and the ring carbons. Reactions with trisubstituted alkenes are more complex since the hydrogen can be transferred from two different sites. Reaction occurs with some preference for the alkyl group *anti* to the vinylic hydrogen. 2-Methyl-2-butene gives an 85:15 mixture of isomers with the major isomer (**48**) apparently formed *via* transition state (**47**; Scheme 9).[34]



Scheme 9

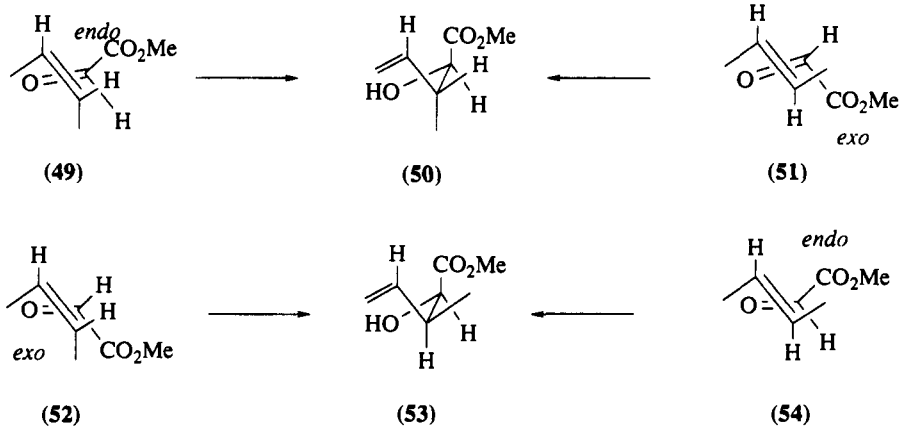
The synthetic utility of the chloral ene adducts has been extensively explored.[35] Reaction with NaOR in ROH gives the α-alkoxy ester with inversion of configuration.[37] Reaction of the corresponding tosylate with sodium ethoxide in ethanol affords ethyl alka-2,4-dienoates (Scheme 9).

2.1.2.2.2 Glyoxylate esters

Klimova and Arbuzov demonstrated that $SnCl_4$- and $AlCl_3$-catalyzed ene reactions of glyoxylate esters with cyclohexene, 1-alkenes, β-pinene and isobutene occur at 25–45 °C and that thermal ene reactions with this enophile occur at 150 °C.[38] Snider and van Straten determined the *endo*/*exo* stereochemistry of the thermal and $FeCl_3$-catalyzed ene reactions of methyl glyoxylate with *cis*- and *trans*-2-butene, cyclohexene, 2-methyl-2-butene and 1-methylcyclohexene.[39] Reaction of *cis*-2-butene with methyl glyoxylate for 60 h at 200 °C gives a 7.4:1 mixture of (**50**) and (**53**) in 54% yield. Similar reaction of *trans*-2-butene gives a 0.57:1 mixture of (**50**) and (**53**) in 20% yield. In both cases the *endo* transition states (**49**) and (**54**) are preferred due to minimized steric interactions between the ester and methyl groups (Scheme 10). Better selectivity and yields are obtained with *cis*-2-butene. Lewis acid catalyzed reactions show little selectivity and give chloro alcohols from a Prins reaction as significant by-product. $FeCl_3$-catalyzed ene reaction of methyl glyoxylate with cyclohexene affords a 4.4:1 mixture of ene adducts favoring the *endo* isomer.

Achmatowicz examined asymmetric induction in the ene reactions of (–)-menthyl glyoxylate with 1-pentene and found modest asymmetric induction of 5–30%.[40] The configuration of the new center in the adducts was (*S*) with $SnCl_4$, BF_3 and $TiCl_4$ and (*R*) with $AlCl_3$. In marked contrast to these results,

Whitesell found that excellent asymmetric induction is obtained with 8-phenylmenthyl and *trans*-2-phenylcyclohexyl glyoxylate esters.[41–48]

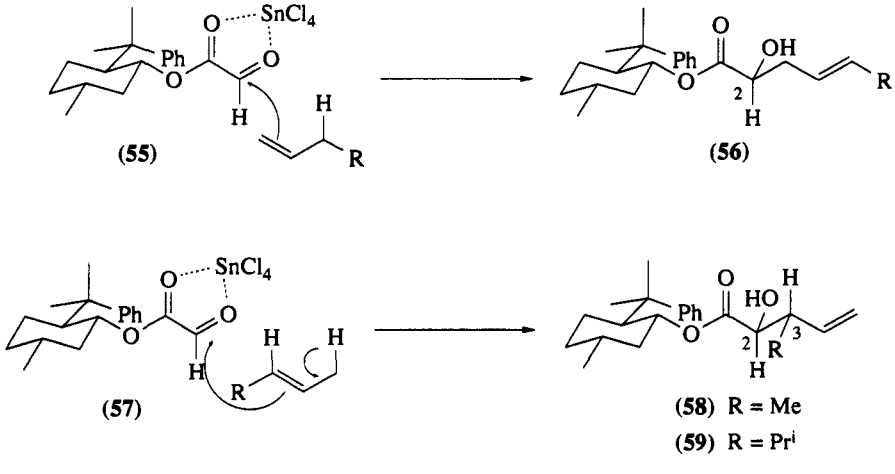


Scheme 10

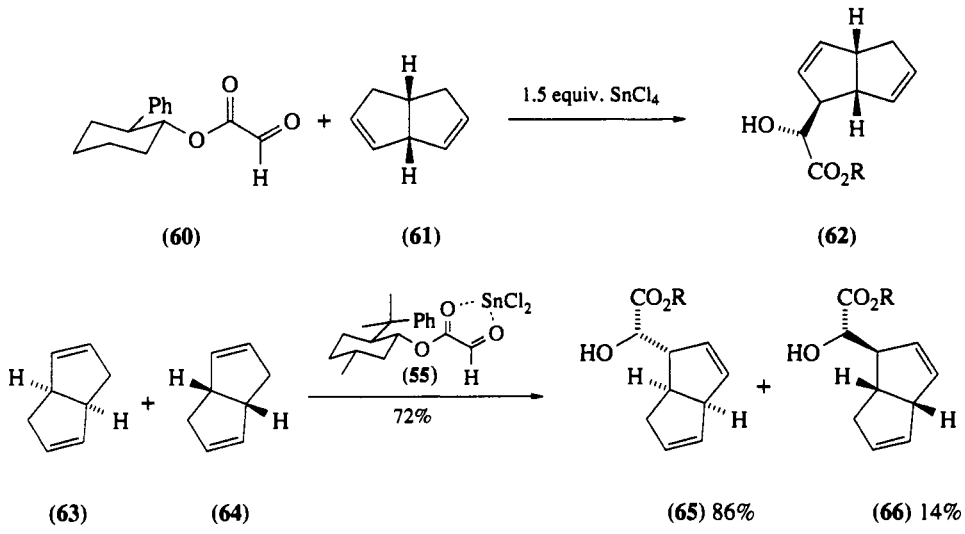
Ene reaction of 8-phenylmenthyl glyoxylate (**55**) with 1-alkenes occurs rapidly at –78 °C in CH_2Cl_2 with 1 equiv. of $SnCl_4$ to give (**56**) in ≈90% yield with >97% enantiomeric excess.[41,44] The phenyl group, which clearly plays a major role in asymmetric induction, may form a π-complex with the aldehyde–Lewis acid complex forcing addition to occur from the other face. The newly formed double bond is 94% *trans*. Similar facial selectivity occurs in the ene reactions of (**55**) with methylenecyclohexane. Excellent asymmetric induction has also been obtained in $SnCl_4$-catalyzed ene reactions of the glyoxylate ester of 2-*epi*,*ent*-8-phenylmenthol, obtained as an impurity in the preparation of 8-phenylmenthol.[46] A detailed study of the effect of auxiliary structure on asymmetric induction in the ene reaction of chiral glyoxylates with 1-hexene demonstrated that an aromatic group is necessary.[47]

Reaction of (**55**) with *trans*-2-butene also proceeds with excellent asymmetric induction to give a 15:1 mixture of (**58**) and the diastereomer at C-3 in 85% yield. The stereochemistry at C-2 is the same in both isomers. Mixtures of isomers are produced since *endo* and *exo* transition states give different products with an internal alkene. The major isomer (**58**) is formed *via* the less-hindered *exo* transition state (**57**). These reactions are stepwise, rather than concerted, since *cis*-2-butene is isomerized to *trans*-2-butene under the reaction conditions. $SnCl_4$-catalyzed addition of (**55**) to *cis*-4-methyl-2-pentene results in isomerization of the alkene to the *trans* isomer, which reacts exclusively at C-3 giving (**59**) in 86% yield (Scheme 11).

$SnCl_4$-catalyzed ene reactions of *trans*-2-phenylcyclohexyl glyoxylate (**60**) also proceed with very high asymmetric induction.[43] Since both enantiomers of *trans*-2-phenylcyclohexanol are readily available, this chiral auxiliary has practical advantages. $SnCl_4$-catalyzed reaction of (**60**) with diene (**61**) gives



Scheme 11



Scheme 12

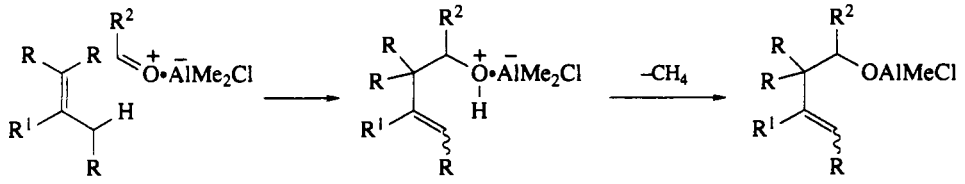
(**62**) in 81% yield.[42,48] Reaction occurs exclusively from the less-hindered β-face of diene (**61**) and only at the double bond that can react through the less-hindered *endo* transition state. For reasons which are not clear, the stereochemistry at C-2 of (**62**) is opposite to that obtained from diene (**61**) and glyoxylate (**55**) with the same three-dimensional orientation of groups. Ene adduct (**62**) has been converted to (–)-specionin.[48]

$SnCl_4$-catalyzed reaction of (**55**) with an excess of a mixture of racemates (**63**) and (**64**) gives a 72% yield of an 8:1 mixture of (**65**) and (**66**).[45] Reaction occurs exclusively from the less-hindered face of the diene and the face of the glyoxylate opposite the phenyl group. The double bonds of (**63**) and (**64**) are symmetrical; identical products are obtained from reaction at either site. Reaction with either double bond of (**63**) occurs through an unhindered *endo* transition state to give (**65**). Reaction with either double bond of (**64**) must occur through a hindered *exo* transition state to give (**66**). Reaction therefore occurs selectively with (**63**), giving (**65**), resulting in a kinetic resolution (Scheme 12). Adduct (**65**) has been converted to the secoiridoid (–)-xylomollin.[45]

Lewis acid catalyzed ene reactions of ethyl glyoxylate with allylglycine derivatives have been described as a route to highly functionalized unsaturated amino acids.[49] $SnCl_4$-catalyzed ene reactions of phenylglyoxal with alkenes occur in 40–78% yield. Treatment of the adducts obtained from monosubstituted alkenes with periodate gives 3-alkenals in 50–70% yield.[50]

2.1.2.3 Aliphatic and Aromatic Aldehydes

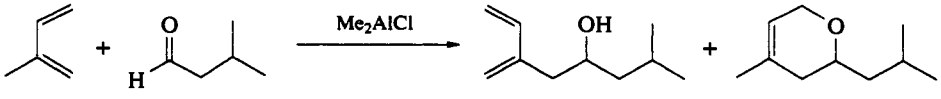
Normal aliphatic and aromatic aldehydes, *e.g.* acetaldehyde and benzaldehyde, are much less reactive than formaldehyde and electron-deficient aldehydes in ene and Prins reactions. Prins reactions of these aldehydes lead to even more complex mixtures of products than Prins reactions of formaldehyde, due to the additional stereocenter introduced in the reaction. Thermal ene reactions of these aldehydes cannot be carried out successfully. Snider and coworkers have found that moderate to good yields of adducts can be obtained from Me_2AlCl-catalyzed ene reactions of these aldehydes and 1,1-di-, tri- and tetra-substituted alkenes (equation 14).[24] Use of a stoichiometric amount of Me_2AlCl is necessary since the



(14)

R = H, alkyl; R^1 = alkyl; R^2 = alkyl or aryl

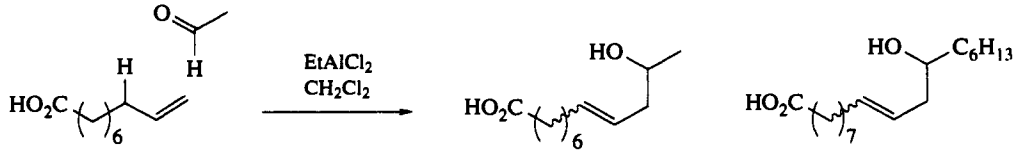
adduct–Me_2AlCl complex loses methane, preventing Brønsted acid catalyzed isomerization of the ene adduct or starting alkene (Scheme 3). Addition of a methyl group to the aldehyde is a significant side reaction in all cases and is more severe with sterically hindered aldehydes and alkenes. Mono- and 1,2-disubstituted alkenes are not nucleophilic enough to react with these aldehyde–Me_2AlCl complexes. Reaction with limonene occurs selectively on the 1,1-disubstituted double bond. Reaction of isovaleraldehyde with isoprene gives ene adduct ipsenol (**67**) in 16% yield and Diels–Alder adduct (**68**) in 60% yield (Scheme 13). Reaction of a series of aldehydes with (*E*)- and (*Z*)-3-methyl-2-pentene gives a complex mixture of *erythro* and *threo* isomers and double bond position isomers.[51] Ene reaction of 2-phenylpropionaldehyde with methylenecyclohexane affords a 1.5:1 mixture of diastereomers.



(**67**) (**68**)

Scheme 13

$EtAlCl_2$, a stronger Lewis acid than Me_2AlCl, with a less nucleophilic alkyl group, successfully catalyzes the ene reactions of aliphatic aldehydes with terminal alkenes. Reaction of an aliphatic aldehyde with a terminal alkene and $EtAlCl_2$ in CH_2Cl_2 for a few minutes at 0 °C gives the ene adduct as a 4:1 (*E*):(*Z*) mixture in 50–60% yield. Reaction of 9-decenoic acid with 1 equiv. of acetaldehyde and 2.2 equiv. of $EtAlCl_2$ affords (**69**) as a 4:1 (*E*):(*Z*) mixture in 66% yield.[27] Lactonization of the (*E*)-isomer provides recifeiolide. Reaction of 10-undecenoic acid with 1 equiv. of heptanal and 2.2 equiv. of $EtAlCl_2$ provides a 4:1 mixture of ricinelaidic acid (*E*)-(**70**) and ricinoleic acid (*Z*)-(**70**) in 41% yield (Scheme 14).[27]



(**69**) (**70**)

Scheme 14

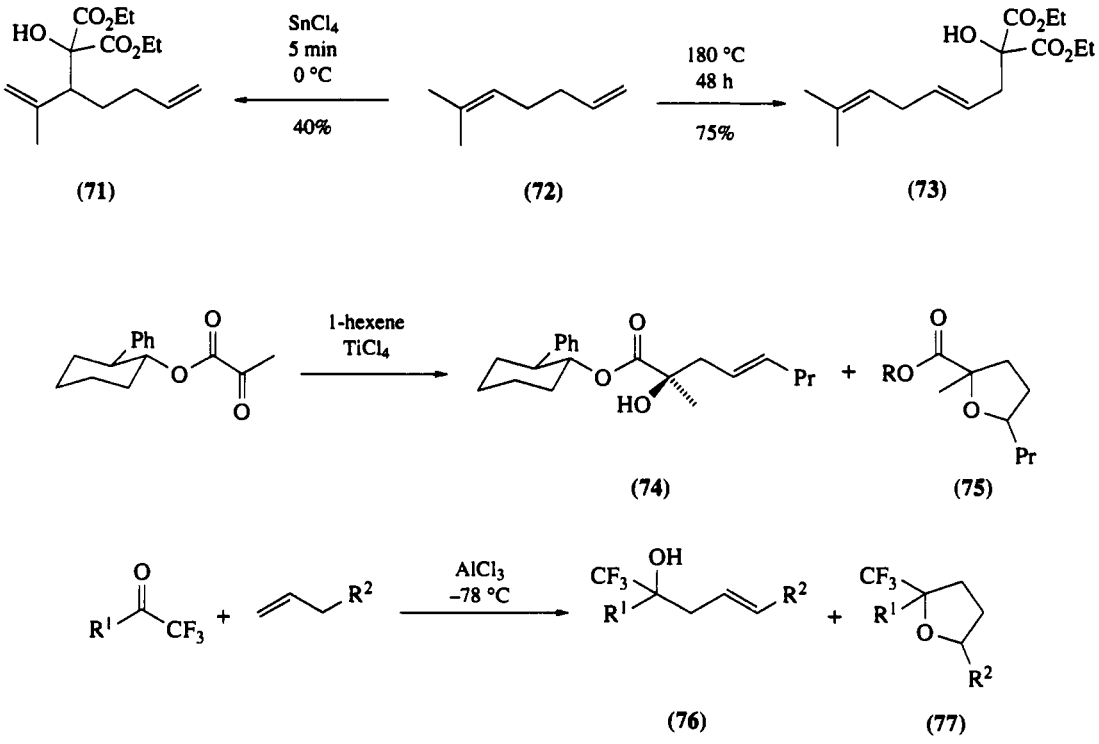
2.1.2.4 Ketones

Ketones are less electrophilic than aldehydes and the ene adducts are tertiary alcohols that are much less acid stable than the secondary alcohols produced from aldehydes. Ene adducts can be isolated from the $EtAlCl_2$-catalyzed reactions of cycloalkanones and reactive ene components, *i.e.* 1,1-disubstituted alkenes with one end of the double bond sterically accessible and the other end capable of stabilizing a positive charge in an intermediate.[52] The yields are moderate at best (6–55%), but the reaction does provide an extremely simple route to homoallylic tertiary alcohols.

2.1.2.4.1 Electron-deficient ketones

Thermal and Lewis acid catalyzed ene reactions of electron-deficient ketones proceed in good yield. Dialkyl oxomalonate esters[53–57] and pyruvate esters[58–60] have been most extensively studied. 1,2,3-Triketones,[61] methyl phenylglyoxylate,[62] carbonyl sulfide,[63] carbonyl cyanide,[64] hexafluoroacetone,[65,66] hexafluorocyclobutanone[67] and 1,1,1-trifluoromethyl ketones[68] have also been developed as enophiles.

Thermal and $SnCl_4$-catalyzed ene reactions of diethyl dioxomalonate have been extensively explored by Salomon.[56] The use of clay as a catalyst for this reaction has also been reported.[57] Mono-, 1,1-di-, 1,2-di- and tri-substituted alkenes afford ene adducts upon heating with 1 equiv. of diethyl oxomalonate at 80–185 °C for 1–340 h. Ene adducts can also be obtained in comparable yield with $SnCl_4$ at 0 °C. The enophile approaches the alkene from the less-hindered face. *Endo*/*exo* stereoisomerism is not possible



Scheme 15

with this symmetrical enophile. The regio- and stereo-chemistry of the double bond produced in the ene adduct was determined in several cases.[56]

Mechanistic differences between the thermal and Lewis acid catalyzed reactions were carefully examined. Thermal ene reaction with a series of 1-arylcyclopentenes show only a small rate enhancement with electron-donating substituents ($\rho = -1.2$). $SnCl_4$-catalyzed ene reactions show a strong rate enhancement with electron-donating substituents ($\rho = -3.9$). $SnCl_4$-catalyzed ene reaction with diene (**72**) occurs only at the more nucleophilic trisubstituted double bond to give (**71**) in 40% yield. Thermal ene reaction with (**72**) occurs mainly at the less-hindered terminal double bond to give an 11:1 ratio of (**73**) to (**71**) in 75% yield (Scheme 15).

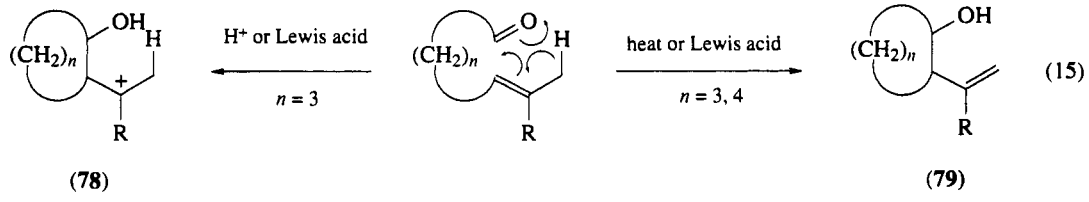
Oxidation of the hydroxymalonic acid ene adducts with cerium(IV) ammonium nitrate in aqueous acetonitrile or sodium periodate results in oxidative didecarboxylation to give an allylcarboxylic acid.[55] The two step process ene reaction with diethyl oxomalonate and oxidative didecarboxylation provides a general procedure for the conversion of alkenes to allylcarboxylic acids.

Thermal ene reaction of β-pinene with methyl pyruvate provides a 1:1 mixture of *endo* and *exo* ene adducts.[58] This reaction can also be carried out in quantitative yield at 40 kbar for 17 h at 25 °C.[59] Contrary to a published report 8-phenylmenthyl pyruvate does not undergo a Lewis acid catalyzed ene reaction with 1-hexene.[60] However, reaction of *trans*-2-phenylcyclohexyl pyruvate with 1-hexene and 2 equiv. of $TiCl_4$ for 15 min at 0 °C affords a 15:1 mixture in 85% yield of ene adduct (**74**) in 86% diastereomeric excess and tetrahydrofuran (**75**) derived from (**74**) by protonation of the double bond and cyclization.

Thermal ene reaction of 1,2,3-indanetrione with β-pinene, 1-hexene and cyclohexene occurs in quantitative yield on heating at 80 °C for 0.3–58 h. The ene adducts can be converted to allylcarboxylic acids by oxidative didecarboxylation with periodate.[61] Heating β-pinene with methyl phenylglyoxylate for 120 h at 165 °C gives the ene adduct resulting from hydrogen abstraction from the less-hindered α-face.[62] Ene reaction of hexafluoroacetone and hexafluorocyclobutanone occurs readily with most classes of alkenes under very mild conditions.[65–67] 1,1,1-Trifluoromethyl ketones undergo $AlCl_3$-catalyzed ene reactions with terminal alkenes at –78 °C to give ene adducts (**76**) in good yield and small quantities of tetrahydrofurans (**77**) derived from (**76**) by protonation of the double bond and cyclization (Scheme 15).[68]

2.1.3 INTRAMOLECULAR REACTIONS

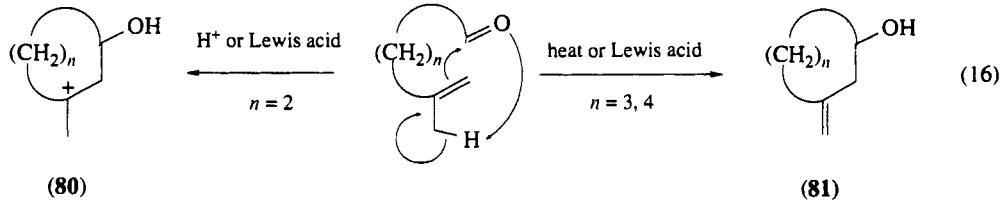
Intramolecular ene and Prins reactions have been divided into three classes depending on the connectivity pattern of the carbonyl and alkene.[5] In type I reactions the carbonyl group forms a bond to the internal carbon of the double bond. Concerted or stepwise ene reaction occurs to give (**79**). Prins reactions give products derived from cation (**78**), which may include ene type adducts (equation 15). Type I ene reactions are restricted to the formation of five- and six-membered rings. In type II reactions the carbonyl group forms a bond to the terminal carbon of the double bond. Concerted or stepwise ene reaction occurs to give (**81**). Prins reaction occurs to give products derived from (**80**; equation 16). Type II ene reactions are restricted to the formation of six- and seven-membered rings. Type II Prins reactions can form five-membered rings. In type III reactions the alkene-bearing side chain is attached to the carbonyl oxygen (**82**). These reactions are Prins reactions which give rise to cyclic ethers derived from cations (**83**) or (**84**; equation 17).



(15)

(**78**) (**79**)

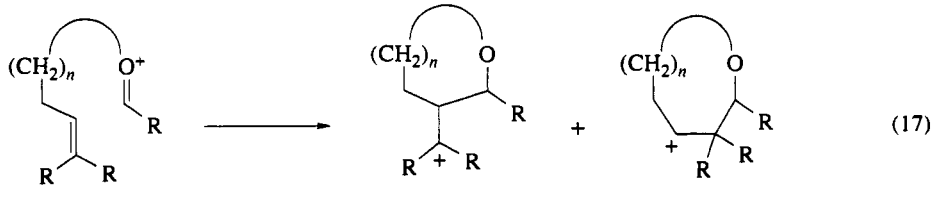
Type I



(16)

(**80**) (**81**)

Type II



(17)

(**82**) (**83**) (**84**)

Type III

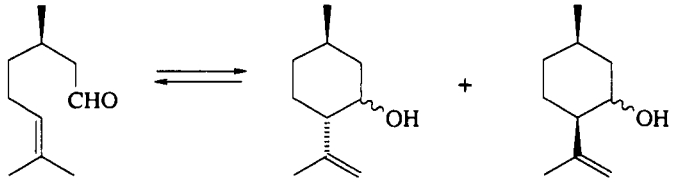
2.1.3.1 Type I Reactions

2.1.3.1.1 Formation of cyclohexanols

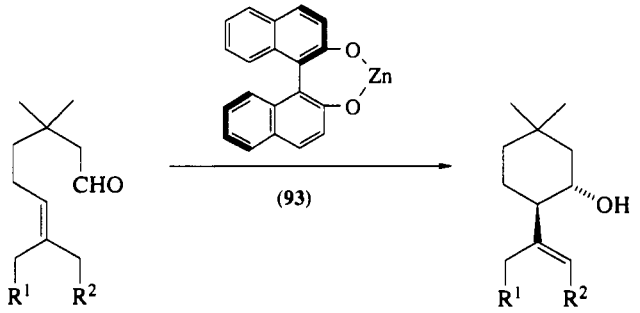
Thermal cyclization of citronellal (**85**) to give mixtures of the four ene adducts (**86**)–(**89**) is the prototypical type I ene reaction. The thermal cyclization at 180 °C gives a 49:16:4:12 mixture of adducts.[69] Zinc bromide was shown to be an optimal Lewis acid catalyst giving a 66:4:0:0 mixture of adducts.[70] Use of Wilkinson's catalyst gives a 14:41:0:0 mixture of products, although the reasons for this stereocontrol are not understood.[71] Oxidation of citronellol with PCC gives (**85**), which undergoes an acid or Lewis acid catalyzed cyclization to (**86**)–(**89**). Further oxidation by PCC and conjugation of the double bond gives pulegone.[72] The scope and limitations of this oxidative cyclization have been determined.[72] Thermal ene reactions of citral have been investigated.[73]

Yamamoto has shown that the zinc phenoxide (**93**; 6 equiv.) catalyzes the ene reaction of (**90**) to give (**94**) in 91% yield in 90% enantiomeric excess.[74] The ene reaction of (**85**) is also catalyzed by (**93**) to give exclusively (**86**). However, the absolute stereochemistry of the adduct (**86**) is controlled by the methyl group of (**85**) rather than the stereochemistry of the catalyst (**93**). Zinc phenoxide (**93**) catalyzes the ene reaction of 7-methyl-6-octenal, lacking a methyl group at C-3, to provide racemic adduct in only 31% yield. These results indicate that the *gem* dimethyl group of (**90**) is necessary for asymmetric induction and that the buttressing effect of the methyl groups facilitates the cycloaddition.

Yamamoto has also shown that the hydrogen is selectively removed from the *trans* alkyl group.[74] Ene reaction of (**91**) catalyzed by (**93**) gives (**95**) in 89% yield in 91% enantiomeric excess. Similar cyclization of (**92**) gives (**96**) in 83% yield in 32% enantiomeric excess. The ene reactions of (**85**), (**90**), (**91**) and (**92**) indicate that *trans*-2-alkenylcyclohexanols are produced selectively in type I reactions (Scheme 16).



(**85**) (**86**) β-OH (**87**) α-OH (**88**) β-OH (**89**) α-OH



(**93**)

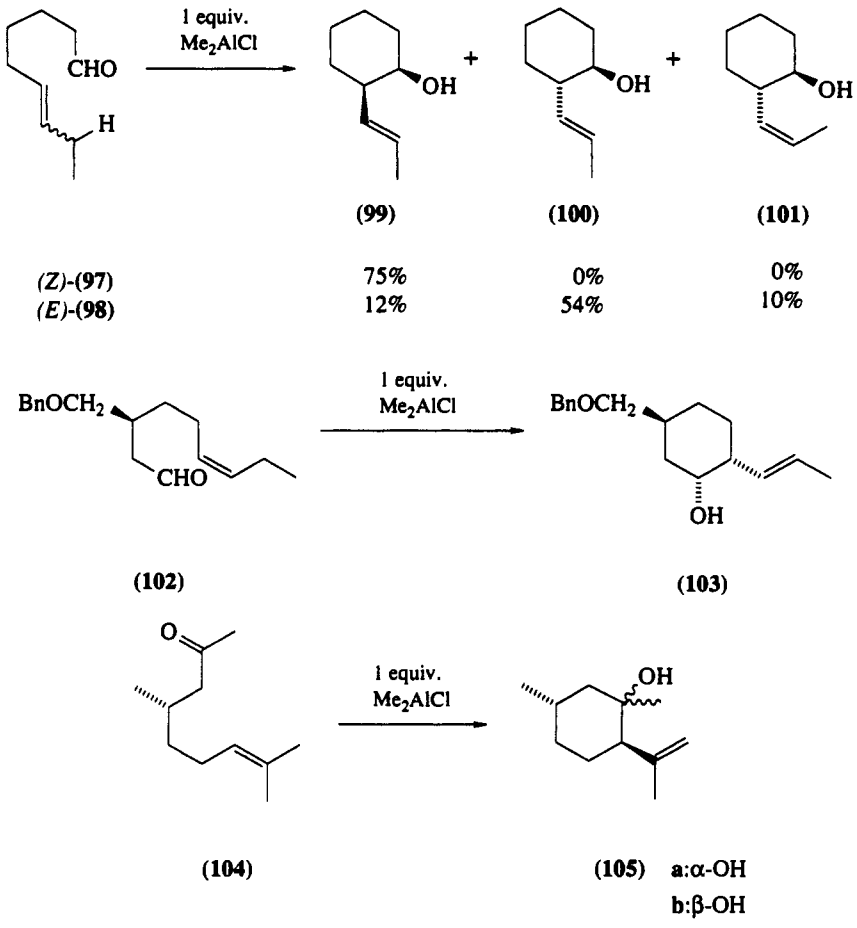
(**90**) $R^1 = R^2 = H$
(**91**) R^1 = prenyl; $R^2 = H$
(**92**) $R^1 = H$; R^2 = prenyl

(**94**) $R^1 = R^2 = H$
(**95**) R^1 = prenyl; $R^2 = H$
(**96**) $R^1 = H$; R^2 = prenyl

Scheme 16

Type I ene reactions with less nucleophilic 1,2-disubstituted double bonds have been more problematic.[75] Ene reaction has been achieved using 1 equiv. of Me_2AlCl as catalyst at 0 °C.[76] Cyclization of the (*Z*)-aldehyde (**97**) gives exclusively the *cis* cyclohexanol (**99**), due to geometrical constraints on the transition state which preclude the formation of (**100**) and (**101**). Cyclization of the (*E*)-aldehyde (**98**) gives mainly the *trans* cyclohexanols (**100**) and (**101**). Smith has used this reaction as a key step in the synthesis of phyllanthoside.[77] Me_2AlCl-catalyzed reaction of (**102**) gives (**103**) in 83% yield along with 5% of several stereoisomers. Not only are the hydroxy and alkenyl groups *cis* as expected from the cyclization of a (*Z*)-alkene, but they are introduced on the face opposite the benzyloxymethyl group. Me_2AlCl also catalyzes the ene reaction of ketone (**104**) giving a 4.5:1 mixture of tertiary alcohols (**105a**) and (**105b**) in 58% yield (Scheme 17).[76]

Type I ene reactions have been applied with good success to form polycyclic intermediates in total synthesis. $SnCl_4$-catalyzed cyclization of aldehyde (**106**) affords (**107**) as a mixture of isomers, one of which was converted to junenol.[78] Similar mixtures were obtained in the *cis* series. Cyclization of (**108**) with 0.002 M HCl in $CHCl_3$ provides (**109**), apparently as the *cis* isomer.[79] Cyclization of (**110**) with zinc iodide in CH_2Cl_2 gives a quantitative yield of a 1:3 mixture of (**111**) and (**112**).[80] It is possible that (**112**) is not a primary product since it can be formed by the acid-catalyzed isomerization of (**111**). Oxi-



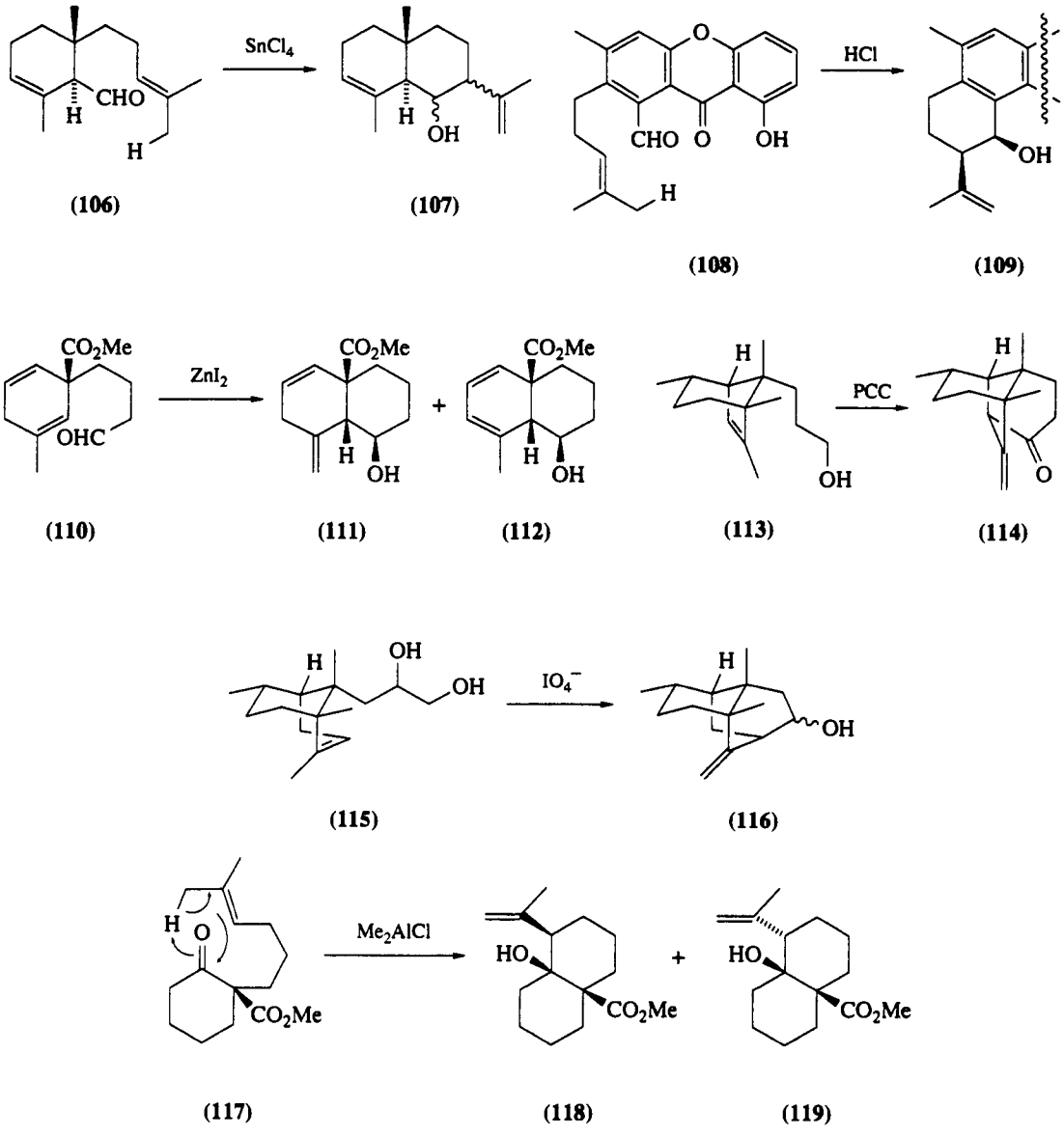
Scheme 17

dative Prins cyclization[72] of alcohol (**113**) with PCC gives (**114**) in 67% yield, which was converted to seychellene, isocycloseychellene and isoseychellene.[81] Periodate oxidation of diol (**115**) generated the aldehyde, which spontaneously cyclized to give (**116**) as a 3:1 mixture of diastereomers in 77% yield, which were converted to seychellene and cycloseychellene.[82] Treatment of β-keto ester (**117**) with Me_2AlCl gives (**118**) in 33% yield and (**119**) in 19% yield.[52] No ene adducts can be isolated from treatment of the corresponding cycloalkanone lacking the carboethoxy group (Scheme 18).

Excellent yields of ene adducts have been obtained in Lewis acid catalyzed intramolecular ene reactions of homoallylic glyoxylates. Treatment of (**120**) with $SnCl_4$ in nitromethane provides (**121**) in 85% yield.[83] Similar treatment of (**122**) gives (**123**) in 50–60% yield, which was converted to actinobolin.[84] Allylic glyoxylates decompose in the presence of Lewis acids but give modest yields of ene adducts in thermal reactions (Scheme 19).[40]

2.1.3.1.2 Formation of cyclopentanols

Intramolecular ene reactions of 1,6-dienes to give vinylcyclopentanes are much faster than intramolecular ene reactions of 1,7-dienes to give vinylcyclohexanes due to the less negative $\Delta S^{\ddagger}$ for formation of five-membered rings (see Volume 5, Section 1). Both reactions are thermodynamically favored even at elevated temperatures. Intramolecular ene reactions of unsaturated aldehydes are much faster than those of dienes due to the polarity of the carbonyl double bond. However, the ene reactions of carbonyl compounds are less exothermic than those of all carbon systems due to the greater bond strength of the carbonyl double bond. In type I intramolecular ene reactions, formation of cyclohexanols is both faster and more exothermic than formation of cyclopentanols due to the greater ring strain of cyclopentanols. Type I ene reactions to give cyclopentanols are reversible in unconstrained systems, which permits Lewis acid catalyzed stepwise reactions to compete effectively.



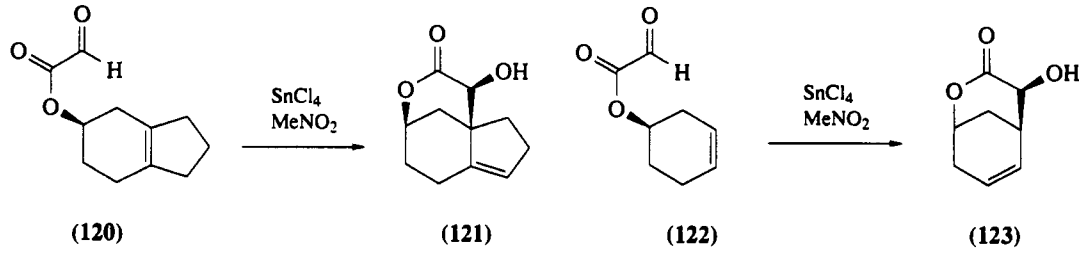
(106) (107) (108) (109)

(110) (111) (112) (113) (114)

(115) (116)

(117) (118) (119)

Scheme 18

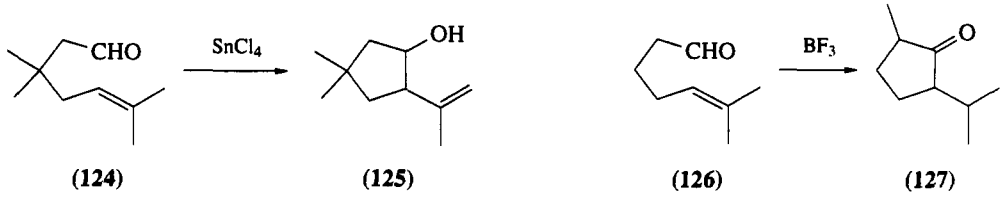


(120) (121) (122) (123)

Scheme 19

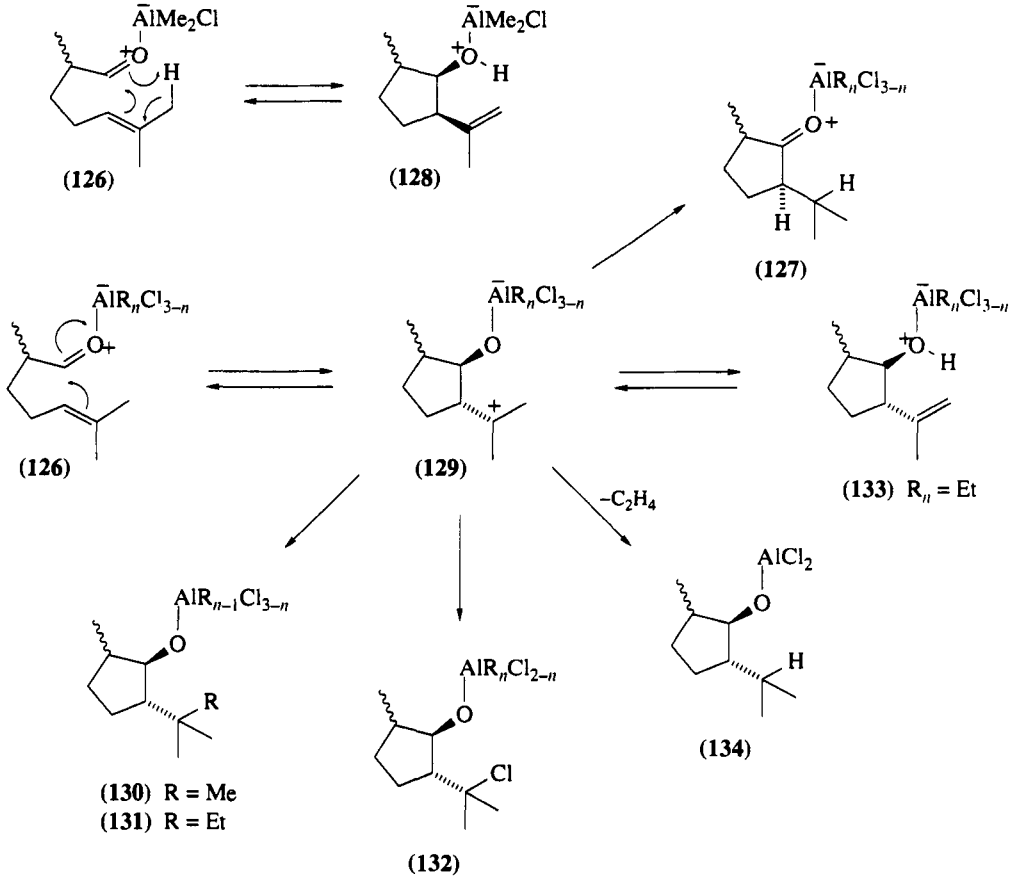
Treatment of (**124**) with 0.1 equiv. of $SnCl_4$ for <15 min at 0 °C gives ene adduct (**125**) in 85% yield as an 80:20 *cis:trans* mixture.[85] On the other hand, treatment of (**126**) with 2.9 equiv. of $BF_3{\cdot}Et_2O$ for 1 h at 25 °C gives cyclopentanone (**127**; Scheme 20).[86] Examination of the reactions of (**126**) with various alkylaluminum halides indicates that the nature of the reaction can be controlled by variation of the strength and amount of Lewis acid.[76] Treatment of (**126**) with 1 equiv. of Me_2AlCl at –78 °C gives primarily (**128**) as a 4:1 mixture of α-methyl and β-methyl isomers. (In the text (**126**)–(**134**) refer to the alcohol or carbonyl compound obtained after workup). Alcohol (**128**) is probably formed by a concerted ene reaction or a π-complex rather than a zwitterionic intermediate, since concerted thermal ene reactions of 1,6-dienes give mainly *cis*-substituted cyclopentanes.[5]

Treatment of (**126**) with 2 equiv. of Me_2AlCl gives the more electrophilic aldehyde–$(Me_2AlCl)_2$ complex or a species stoichiometrically equivalent to it. This complex reacts rapidly at –78 °C to give zwitterion (**129**). At –78 °C an irreversible [1,5] chloride shift to give chloro alkoxide (**132**) is the major process. At 0 °C, the [1,5] chloride shift is apparently reversible, so the products obtained from (**129**) by three competing processes are obtained. A [1,5] methyl shift gives (**130**) in 30% yield, a reversible [1,5]



(**124**) (**125**) (**126**) (**127**)

Scheme 20



(**126**) (**128**) (**127**) (**126**) (**129**) (**133**) R_n = Et

(**130**) R = Me
(**131**) R = Et

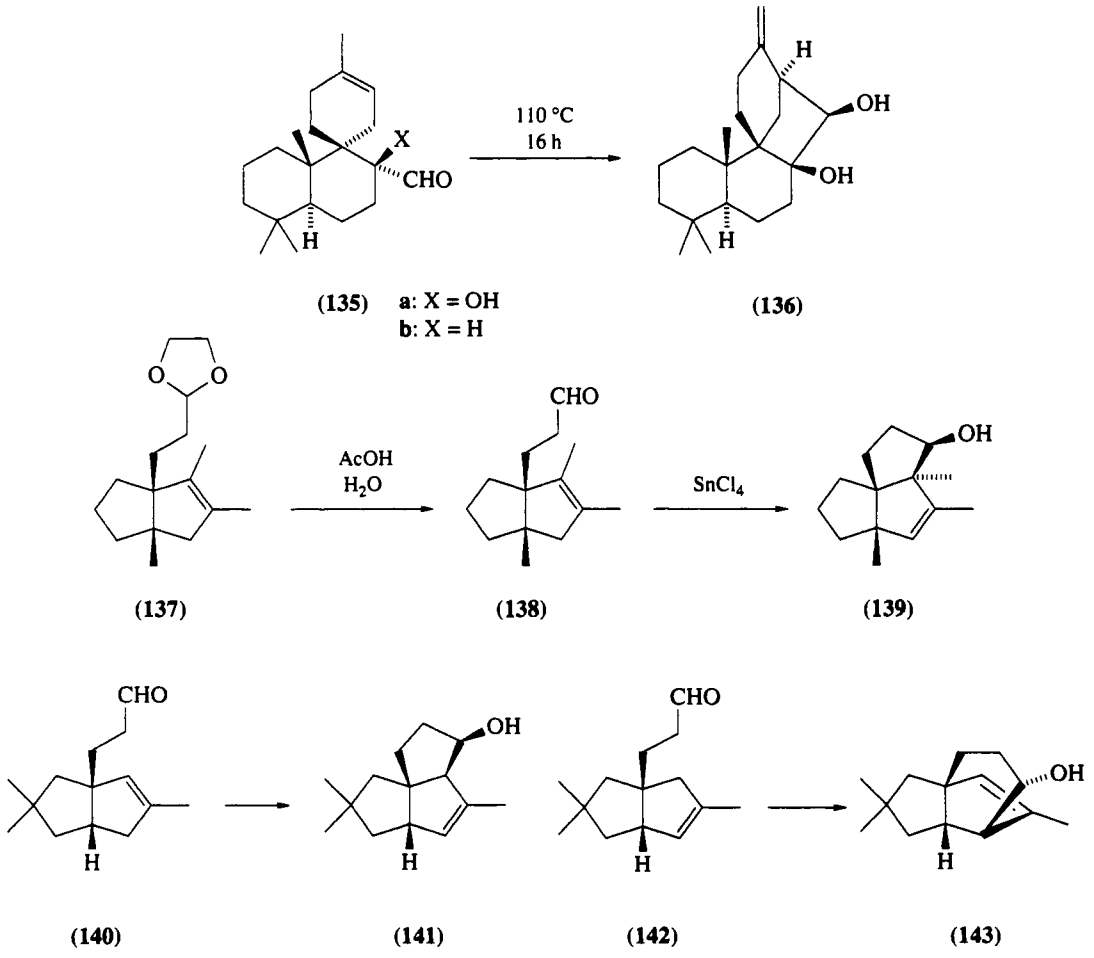
(**132**) (**134**)

Scheme 21

proton shift followed by an irreversible loss of methane gives (**133**) in 45% yield and two [1,2] hydride shifts give (**127**) in 22% yield (Scheme 21). The formation of *trans* ene adduct (**133**) by a stepwise ene reaction confirms that the *cis* adduct (**128**) is not formed from an open zwitterion intermediate. The reactions of (**126**)–$(Me_2AlCl)_2$ are consistent with the general observation that enhancing the electrophilicity of a carbonyl compound accelerates stepwise reactions more than concerted reactions.

Treatment of (**126**) with 2 equiv. of $MeAlCl_2$ at –78 °C gives mainly (**127**). The greater Lewis acidity of $MeAlCl_2$ leads to a faster cyclization, makes (**132**) unstable, even at –78 °C, and makes the oxygen of (**129**) less basic, decreasing the rate of [1,5] proton shift, which gives (**133**). The methyl group of $MeAlCl_2$ is less basic than those of Me_2AlCl so the [1,5] methyl shift to give (**130**) is slower. Addition of 2 equiv. of $EtAlCl_2$ to (**126**) at –78 °C gives mainly the reductive cyclization product (**134**; Scheme 21). The vastly different reactions with $EtAlCl_2$ and $MeAlCl_2$ were not anticipated. However, ethylaluminum compounds are much more nucleophilic than methylaluminum compounds and β-hydride delivery to the electrophilic site can be the major reaction of ethylaluminum compounds.[26]

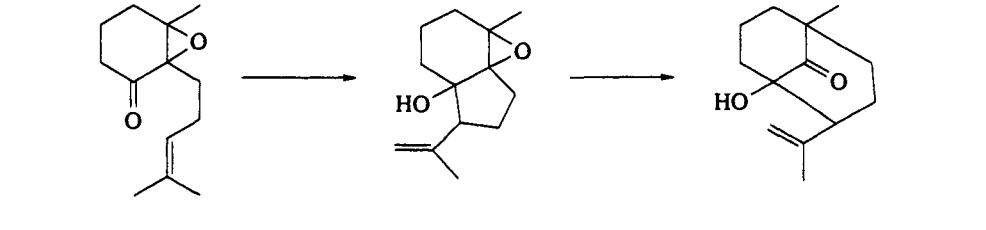
Excellent yields of cyclopentanols are obtained in type I intramolecular ene reactions if the aldehyde and alkene are held in close proximity by a cyclic system. This not only accelerates the cyclization by decreasing $\Delta S^{\ddagger}$ for the ene reaction, but also stabilizes the product relative to the starting material by removing repulsive steric interactions in the starting material. Thermolysis of (**135a**) for 16 h in toluene at reflux yields 94% of ene adduct (**136**), which was converted to 2-deoxystemodione.[87] A mixture of products was obtained from (**135a**) in Lewis acid catalyzed reactions. The presence of the hydroxy group is significant, since no ene adduct could be obtained from (**135b**) under thermal or Lewis acid catalyzed conditions. Hydrolysis of the acetal of (**137**) with aqueous acetic acid gives aldehyde (**138**) in 62% yield



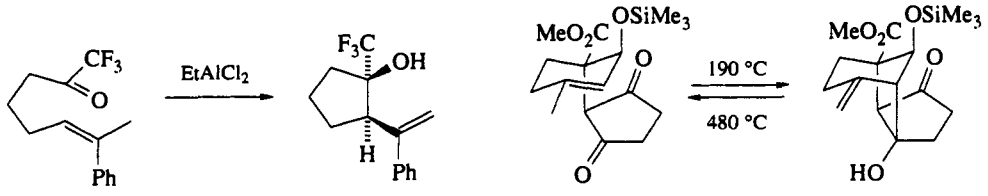
Scheme 22

and ene adduct (**139**) derived from it in 19% yield.[88] Cyclization of (**138**) with $SnCl_4$ in benzene at 5 °C gives (**139**) in 95% yield, an intermediate in the synthesis of isocomene. Cyclization of aldehydes (**140**) and (**142**) with $SnCl_4$ in benzene gives ene adducts (**141**) and (**143**), which are intermediates in the synthesis of pentalenene, in excellent yield (Scheme 22).[89]

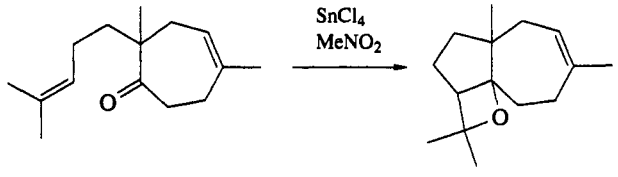
Ketones cannot be used as enophiles in simple systems since products analogous to (**127**) are formed.[76] Success has been achieved in special cases. Treatment of keto epoxide (**144**) with $SnCl_4$ in CH_2Cl_2 at –78 °C gives ketol (**146**) in 96% yield *via* the intermediacy of ene adduct (**145**).[90] $EtAlCl_2$-catalyzed intramolecular ene reaction of the electron-deficient trifluoromethyl ketone (**147**) gives (**148**) in quantitative yield.[91] Diels–Alder adduct (**149**) undergoes a remarkable ene reaction with a ketone eno-



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

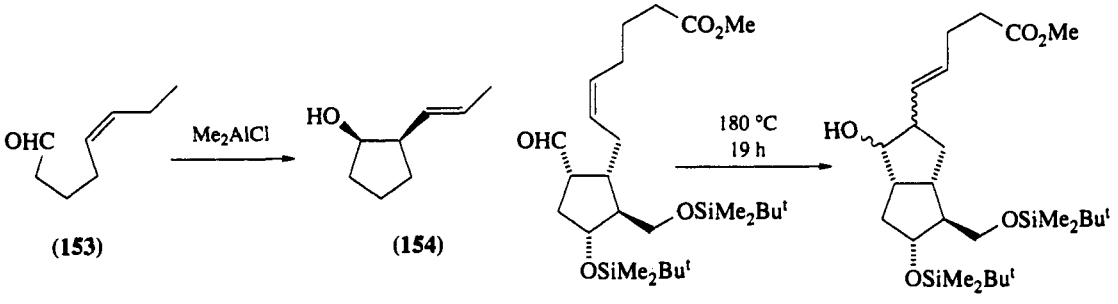


(**147**) (**148**) (**149**) (**150**)



(**151**) (**152**)

Scheme 23

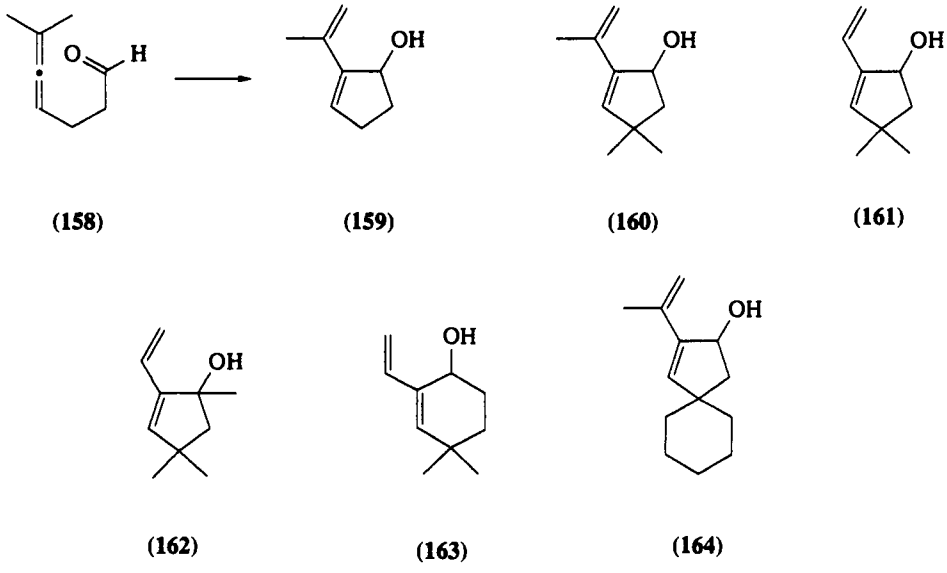


(**153**) (**154**) (**155**)

(**156**) β-OH, β-CH=CHR

(**157**) α-OH, α-CH=CHR

Scheme 24



(158) (159) (160) (161) (162) (163) (164)

Scheme 25

phile to give ene adduct (**150**), which was converted to verrucarol.[92] Treatment of (**151**) with $SnCl_4$ in nitromethane affords oxetane (**152**) in 58% yield.[93] Geometric constraints in (**151**) apparently preclude an ene reaction (Scheme 23).

Type I ene reactions of aldehydes with less nucleophilic 1,2-disubstituted double bonds have not been extensively explored. Treatment of (**153**) with 0.9 equiv. of Me_2AlCl at 25 °C at high dilution gives (**154**) in 66% yield.[76] Pyrolysis of (**155**) in toluene for 19 h at 180 °C affords a 5:3 mixture of (**156**) and (**157**) in 87% yield.[94] The exclusive formation of *cis*-2-alkenylcyclopentanols in both of these cases is noteworthy (Scheme 24).

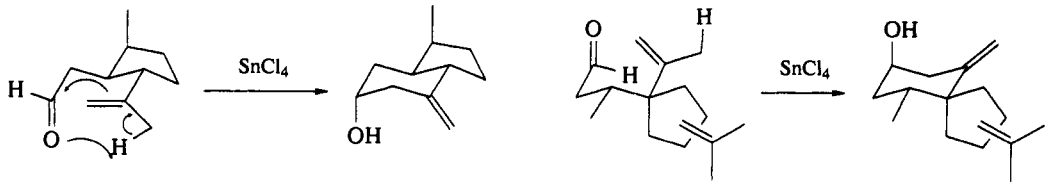
French workers have extensively explored type I intramolecular ene reactions of allenic aldehydes which give dienols.[95] Thermolysis of aldehydes and ketones such as (**158**) affords ene adducts (**159**; 42%, 150 °C, 30 min), (**160**; 75%, 150 °C, 60 min), (**161**; 70%, 200 °C, 15 min), (**162**; 52%, 200 °C, 60 min), (**163**; 65%, 230 °C, 60 min) and (**164**). Lewis acid catalysis was investigated with limited success (Scheme 25). Comparison of yields and reaction times indicates that buttressing *gem* methyl groups and trisubstituted allenes facilitate the reaction, while use of ketones and formation of six- rather than five-membered rings retard it.

2.1.3.2 Type II Reactions

Type II intramolecular ene reactions of unsaturated aldehydes and ketones have been extensively investigated. Ene reactions occur thermally or with Lewis acid catalysis to give 3-methylenecyclohexanols[52,96–109] or 3-methylenecycloheptanols.[110–114] 3-Methylenecyclopentanols cannot be formed in type II reactions. However, Lewis or Brønsted acid induced cyclization of γ,δ-unsaturated aldehydes and ketones gives zwitterionic intermediates that lose a proton to give unsaturated cyclopentanols[85,122] or rearrange to cyclopentanones.[115–121]

2.1.3.2.1 Formation of cyclohexanols

Treatment of (**165**) with $SnCl_4$ gives exclusively (**166**).[96] The selective formation of an axial alcohol and exocyclic double bond, a general characteristic of type II ene reactions, is required by either a concerted reaction or a stepwise reaction with an intramolecular proton transfer. Similar treatment of (**167**), as a mixture of isomers, gives the less stable isomer (**168**) with an axial alcohol and an equatorial methyl group, since the alcohol must be formed axial and the methyl group prefers to be equatorial in the transition state (Scheme 26).[97]

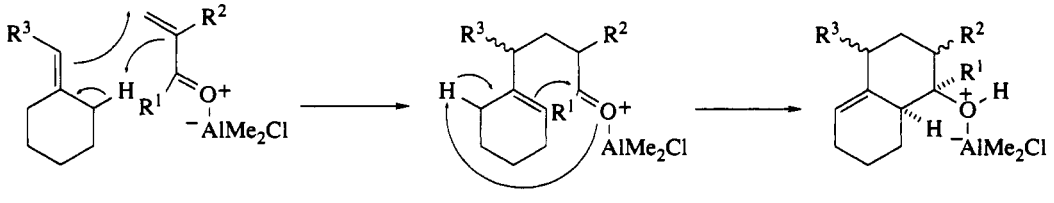


(165) (166) (167) (168)

Scheme 26

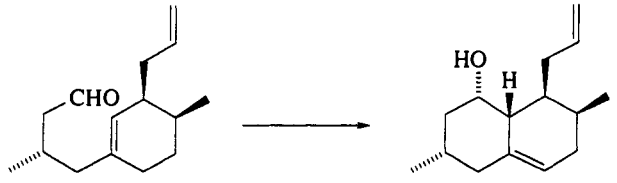
Reaction of alkylidenecyclohexanes with acrolein derivatives and Me_2AlCl generates unsaturated aldehydes (**169**; R^1 = H), which cannot be isolated but undergo type II intramolecular ene reactions to give (**170**). Reaction of alkylidenecyclohexanes with methyl vinyl ketone derivatives gives (**169**; R^1 = Me), which can be isolated if the reaction is carried out at –20 °C but cyclize at 25 °C to give (**170**; Scheme 27).[88,99] The alcohol group is formed exclusively in the axial orientation. Alkyl substituents at R^3 and R^2 are formed preferentially equatorial. On the other hand, a bromo substituent at R^2 is formed preferentially axial. Similar results have been obtained with alkylidenecyclopentanes[98] and 2- and 3-substituted methylenecycloalkanes.[99] Wovkulich, Uskokovic and coworkers have used an ene reaction as a key step in the total synthesis of mevinolin and an angular methyl regioisomer of compactin (equation 18).[100] The aldehyde approaches from the less hindered α-face of the cyclohexene despite the fact that this forces the methyl and hydroxy groups into a 1,3-diaxial relationship.

Aldehydes can also serve to initiate cation–alkene cyclizations (Scheme 28).[101] Cyclization of aldehyde (**171**) with $SnCl_4$ in CH_2Cl_2/ethylene carbonate for 3 min at 0 °C gives alcohol (**172**) in 68% yield.[102] Similar cyclization of (**173**) for 20 s at –30 °C affords a 4:1 mixture of tetracycle (**175**) and tri-

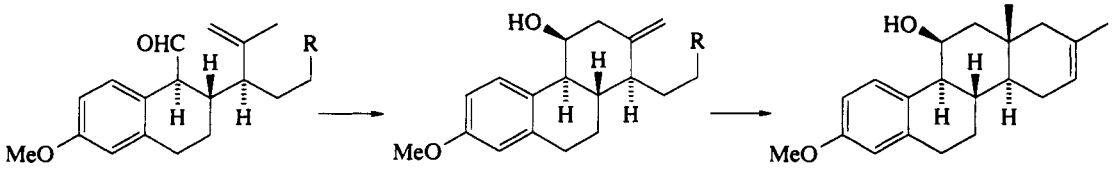


(169) (170)

Scheme 27



(18)



(171) R = C≡CMe
(173) R = C(CH$_2$)Me

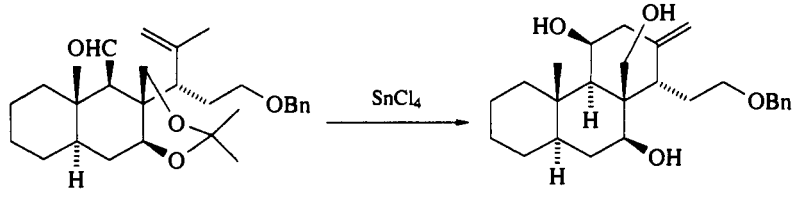
(172) R = C≡CMe
(174) R = C(CH$_2$)Me

(175)

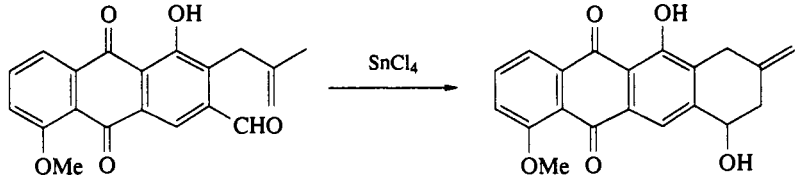
Scheme 28

cycle (**174**), which cyclized to (**175**) on further treatment with $SnCl_4$. This suggests that ene reaction of (**173**) to give (**174**) is the first step in the cation–alkene cyclization that gives (**175**; Scheme 28).

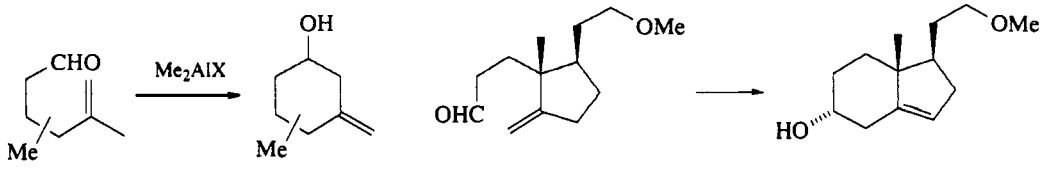
Treatment of (**176**) with $SnCl_4$ in CH_2Cl_2 for 3 min at 0 °C results in cyclization and cleavage of the ketal to give axial alcohol (**177**) in 70% yield as the sole product.[103] The alcohol is exclusively axial as required by the ene reaction despite severe steric interactions with adjacent axial substituents. Cyclization of (**178**) with $SnCl_4 \cdot 5H_2O$ in CH_2Cl_2 gives (**179**) in 93% yield, which was converted to citromycinone.[104] Lewis acid induced cyclization of (**180**), with a methyl group on carbon 2, 3 or 4, gives



(**176**) (**177**)

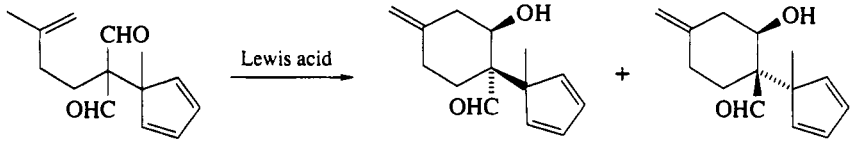


(**178**) (**179**)

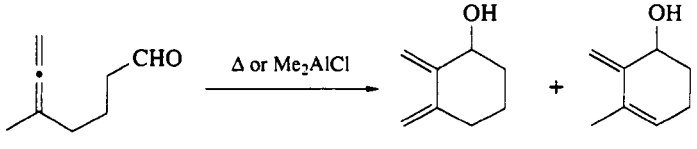


(**180**) (**181**) (**182**) (**183**)

Scheme 29



(**184**) (**185**) (**186**)



(19)

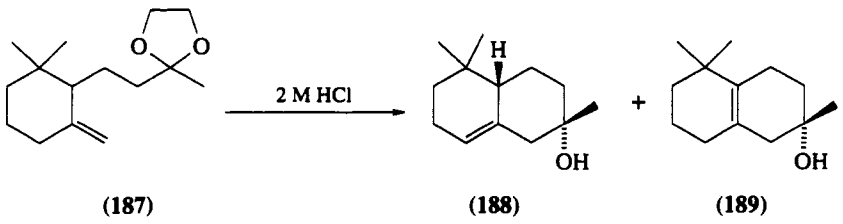
Scheme 30

selectively *cis*-6-methyl-3-methylenecyclohexanol, *trans*-5-methyl-3-methylenecyclohexanol and *cis*-4-methyl-3-methylenecyclohexanol (**181**) resulting from the methyl group adopting an equatorial conformation in the transition state.[105] Intramolecular ene reaction of (**182**) gives (**183**), which will be used for an enantiospecific route to the CD-ring system of steroids (Scheme 29).[106]

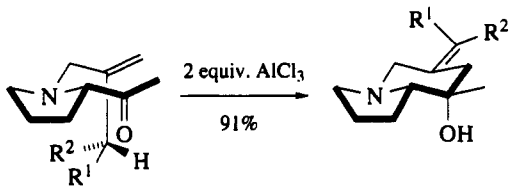
Intramolecular type II ene reaction of prochiral aldehyde (**184**) can give four adducts: both enantiomers of (**185**) and (**186**).[107] Cyclization on silica gel gives a 1:1 mixture. Cyclization with purified $Eu(fod)_3$ as Lewis acid catalyst for one week in CH_2Cl_2 gives an 8:1 mixture of (**185**), a potential intermediate for the synthesis of anguidine and (**186**). Use of $Eu(hfc)_3$, (+)-$Eu(DPPM)_3$ or (*S*)-1,1′-bi-2-naphthol/$TiCl_2$ as Lewis acid catalyst affords (**185**), with 20–38% enantiomeric excess.

Thermal or Lewis acid catalyzed type II ene reactions of allenic aldehydes give mixtures of dienols (equation 19; Scheme 30).[105]

Tertiary cyclohexanols such as (**170**; R^1 = Me) are formed in the ene reaction of ketones.[98] Treatment of acetal (**187**) with 2 M HCl in THF for 24 h at 25 °C gives the ketone, which cyclizes to α-ambrinol (**188**; 77%) and β-ambrinol (**189**; 6%). The selective formation of (**188**) with an axial alcohol suggests that this may be an ene rather than a Prins reaction.[108] Cyclization of unsaturated ketone (**190**) with 2 equiv. of $AlCl_3$ for 1.5 h at 25 °C gives a 3:1 mixture of (**191**) and (**192**) in 91% yield.[109] This cyclization, which leads to analogs of pumilotoxin A, is noteworthy for several reasons. The presence of the amine in (**193**) is remarkable. Two equivalents of catalyst are used; the first equivalent complexes with the amine, the second catalyzes the reaction. This is also the first example in which exocyclic trisubstituted double bonds were produced in a type II ene reaction. In simpler systems the opposite double bond stereoisomer predominates. An 88:12 mixture of (*E*)- and (*Z*)-3-ethylidenecyclohexanol (**194**) and (**195**) are produced in the cyclization of (**193**).[105] In both cases the major isomer results from the alkyl group adopting the less-hindered position in the transition state (Scheme 31).



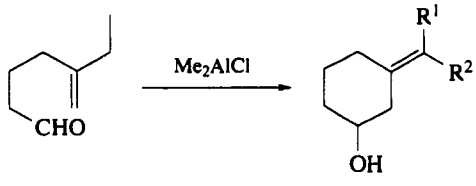
(**187**) (**188**) (**189**)



(**190**)

(**191**) R^1 = H; R^2 = Bu

(**192**) R^1 = Bu; R^2 = H



(**193**)

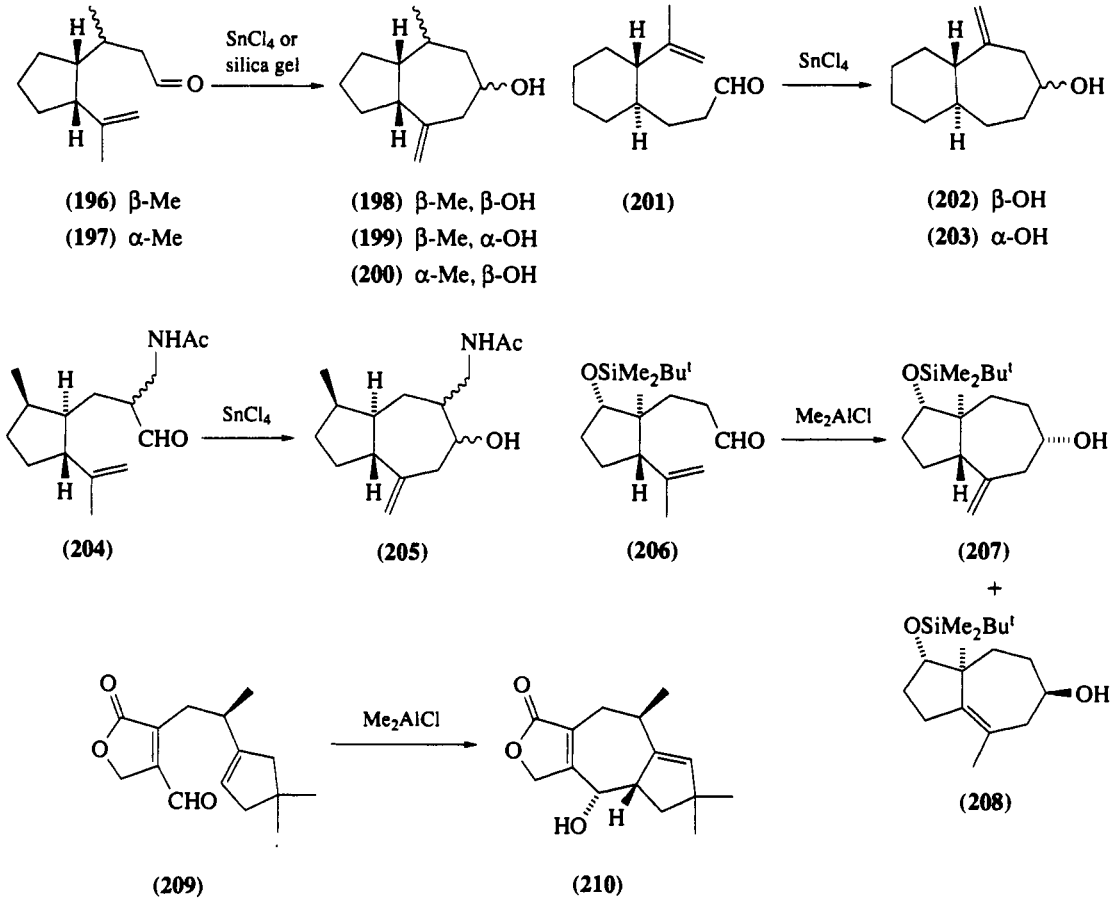
(**194**) R^1 = Me; R^2 = H

(**195**) R^1 = H; R^2 = Me

Scheme 31

2.1.3.2.2 Formation of cycloheptanols

The first examples of type II cyclizations of unsaturated aldehydes are due to Marshall, who showed that these reactions are well suited to hydroazulene synthesis.[96,110,111] Treatment of (**196**) with $SnCl_4$ in benzene gives an 88:12 mixture of (**198**) and (**199**) in 94% yield.[110] Cyclization of (**197**) on silica gel provides (**200**) with a trace of the regioisomer. Cyclization of (**201**) with $SnCl_4$ in CH_2Cl_2 gives a 26:1 ratio of (**202**) and (**203**).[111] Cyclization of acetals or acylals derived from (**201**) is less selective, giving significant amounts of (**203**).[96] $SnCl_4$-catalyzed cyclization of (**204**) gives (**205**) as a mixture of isomers, which were used for the synthesis of kessanol.[112] Cyclization of (**206**) with Me_2AlCl gives a 1.7:1 mixture of (**207**) and (**208**) in 62% yield, which were both converted to (+)-confertin.[113] Similar cyclization of aldehyde (**209**) gives (**210**) in 35% yield.[114] The stereochemistry of the methyl group controls the stereochemistry of the two new centers. The aldehyde adds to the double bond from the less hindered α-face; intramolecular proton transfer can only occur with an α-hydroxy group. These results indicate that the synthesis of cycloheptanols is general. Mixtures of isomers at the alcohol carbon are often obtained (Scheme 32).



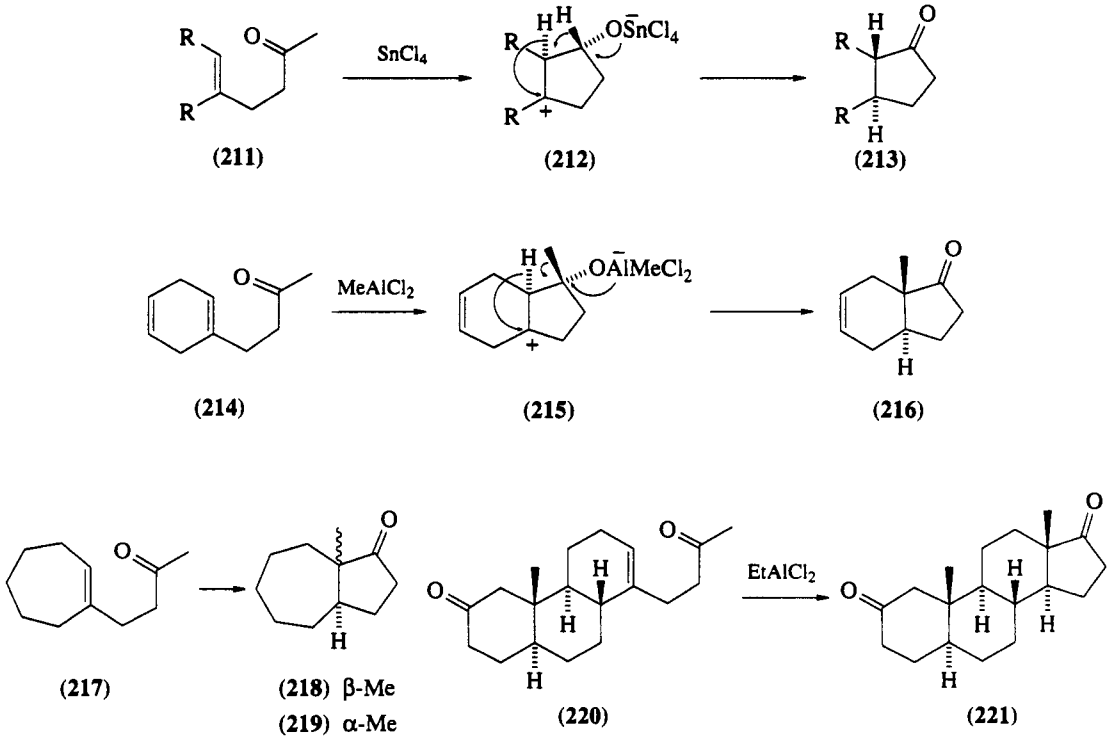
Scheme 32

2.1.3.2.3 Formation of cyclopentanols and cyclopentanones

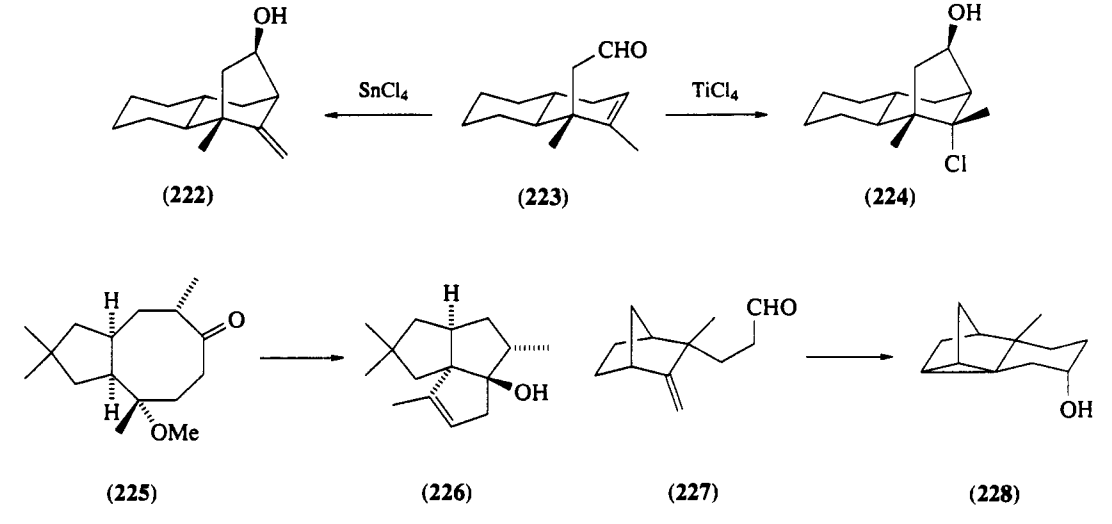
3-Methylenecyclopentanols cannot be formed by intramolecular ene reactions of γ,δ-unsaturated aldehydes, since the two-carbon tether makes the transition state for an ene reaction too strained. Cyclization to a zwitterionic intermediate does occur readily. Cyclization of (**211**) gives zwitterion (**212**), which undergoes two [1,2] hydride shifts to give cyclopentanone (**213**).[115–117] Using $MeAlCl_2$ as a catalyst, this process can be extended to methyl ketones.[118–121] Treatment of (**214**) with 1.1 equiv. of $MeAlCl_2$ in CH_2Cl_2 in a sealed tube at 90 °C for 2 h gives steroid intermediate (**216**) in 50% yield.[119] Similar cycliza-

tion of (**217**) provides a 9:1 mixture of *trans*- and *cis*-fused hydroazulenones (**218**) and (**219**) in 85% yield.[120] Cyclization of (**220**) gives androstane-2,17-dione (**221**) in 31% yield (Scheme 33).[121]

Cyclopentanol ene type products have been obtained in stepwise reactions. Treatment of (**223**) with $SnCl_4$ gives (**222**) in 42% yield. Cyclization with $TiCl_4$ affords chloro alcohol (**224**) in 80–90% yield.[85] Treatment of (**225**) with formic acid at 45 °C results in loss of methanol to give the unsaturated ketone, followed by transannular Prins reaction and loss of a proton to give, after hydrolysis of formate esters,



Scheme 33

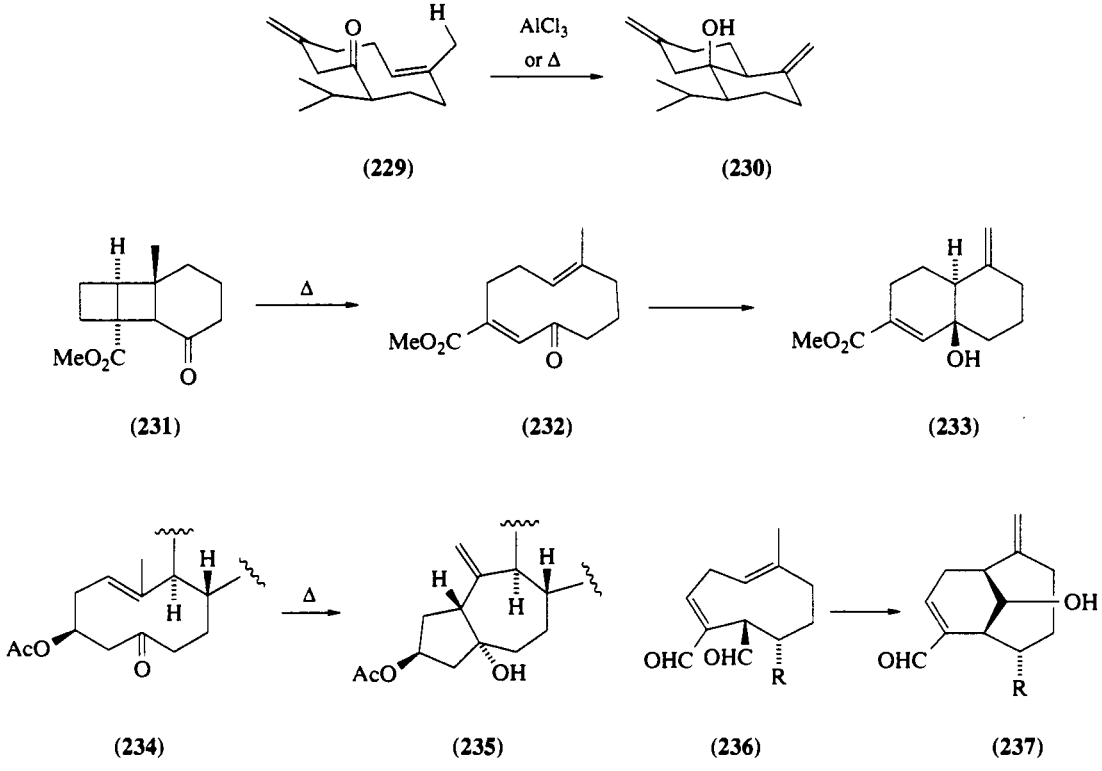


Scheme 34

(**226**) in 67% yield, an intermediate in the synthesis of pentalenolactones E and F.[122] $BF_3{\cdot}Et_2O$-induced cyclization of aldehyde (**227**), which cannot undergo an ene reaction, gives cyclopropane carbinol (**228**) in 67% yield (Scheme 34).[123]

2.1.3.3 Transannular Ene Reactions

Transannular ene reactions provide an effective route to bicyclic systems from medium-sized rings. Cyclization of preisocalamendiol (**229**) with $AlCl_3$ in ether for 10 min at 0 °C gives dienol (**230**) in 54% yield *via* a transannular ene reaction. A thermal ene reaction at 180 °C for 90 min gives (**230**) in 86% yield. Photolysis of cyclohexenones and methyl 1-cyclobutenecarboxylate gives tricyclo[6.2.0.$0^{2,7}$]decanes such as (**231**). Pyrolysis of (**231**) at 180–200 °C results in ring cleavage to give cyclodecadienone (**232**), which undergoes a transannular ene reaction to give decalin (**233**) in 92% yield.[124–127] This reaction has been used in the synthesis of calameon[125] and isocalamendiol.[126] Hydroazulenes can be obtained from transannular ene reactions of 5-cyclodecenones, if the substitution pattern of the double bond is different. Thermolysis of (**234**) in toluene for 16 h provides ene adduct (**235**) in 45% yield.[128] Treatment of dictyodial (**236**) with silica gel as catalyst in CH_2Cl_2 for 12 h at 25 °C gives sanadaol (**237**; Scheme 35).[129]



Scheme 35

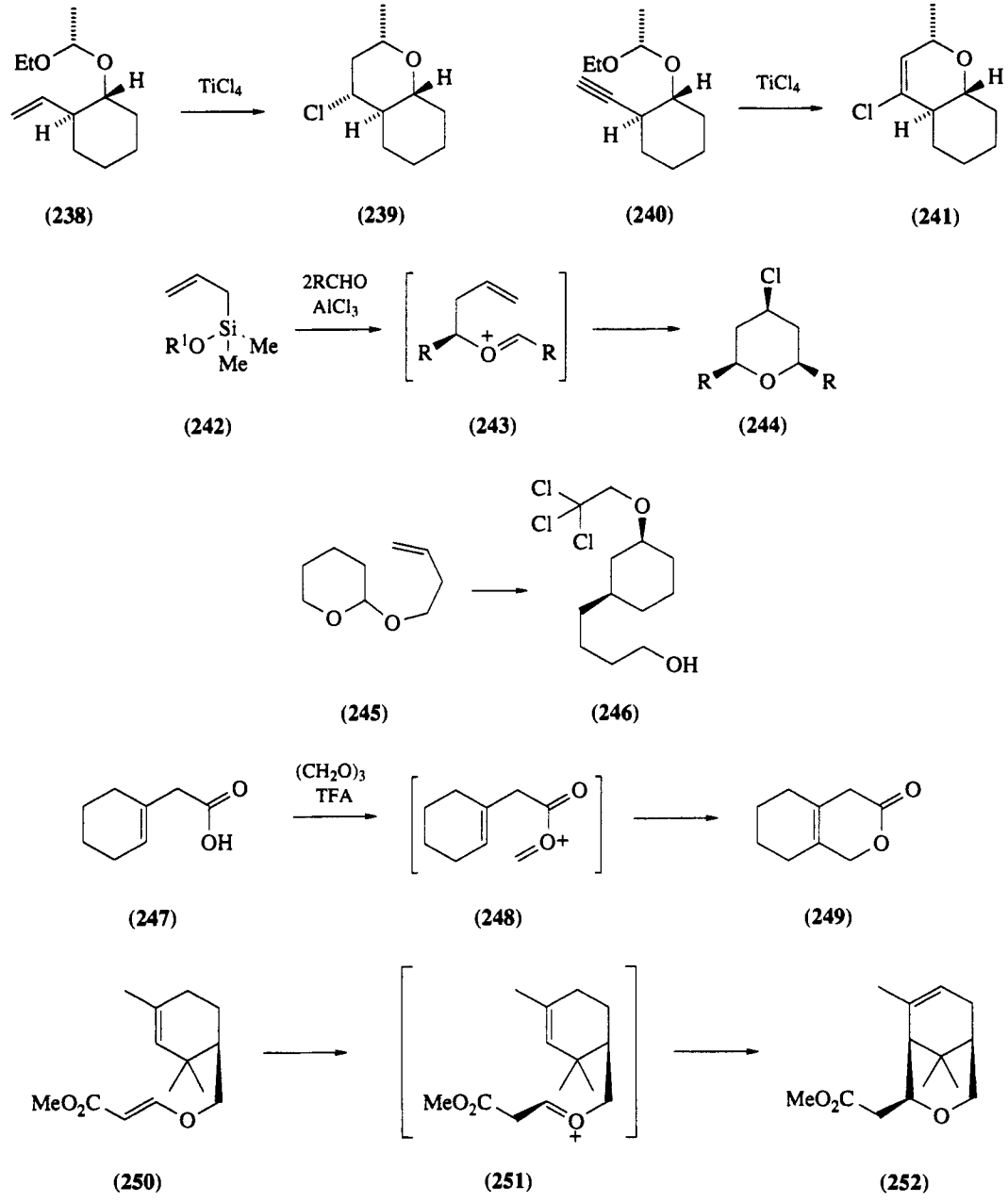
2.1.3.4 Type III Reactions and other Reactions of Acetals

In type III reactions an acetal, hemiacetal or enol ether is converted to a cation (**82**), which cyclizes to (**83**) or (**84**) depending on the substitution pattern of the double bond (equation 17). If the internal end of the double bond is more highly substituted, cyclization occurs in an endocyclic mode to give (**84**). This reaction has been extensively explored for the formation of 4-chlorotetrahydropyrans (**5**; Scheme 2).[1,2,15,130–132] Cyclization of acetal (**238**) with $TiCl_4$ at –45 °C gives (**239**) in 95% yield as a single isomer in which both new ring substituents are equatorial.[131] Similar cyclization of the homopropargyl acetal (**240**) gives (**241**) in 70% yield as a single isomer. Reaction of alkoxyallylsilanes (**242**) with alde-

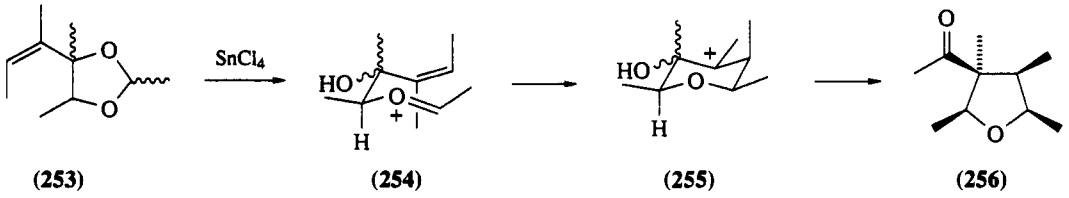
hydes and $AlCl_3$, $SnCl_4$ or $TiCl_4$ gives all *cis*-2,6-dialkyl-4-chlorotetrahydropyrans (**244**). The last step is probably the cyclization of (**243**), followed by trapping with chloride.[132]

Cyclization of tetrahydropyranyl ether (**245**) with $BF_3{\cdot}Et_2O$ in trichloroethanol gives (**246**) in 61% yield.[130] Similar cyclizations can be carried out on acylal derivatives.[133] Acid-catalyzed cyclization of 1-cyclohexeneacetic acid (**247**) with formaldehyde gives (**249**) *via* the presumed intermediacy of (**248**). If the terminal end of the double bond is more highly substituted, cyclization occurs in an exocyclic mode to give (**83**). Treatment of (**250**) with methanesulfonic acid gives (**251**), which cyclizes to give (**252**) after loss of a proton (Scheme 36).[134]

Overman has shown that treatment of cyclic acetals such as (**253**) with $SnCl_4$ results in cleavage to give (**254**), which undergoes an intramolecular Prins addition to give (**255**), which undergoes a pinacol rearrangement, providing (**256**; Scheme 37).[135] The stereochemistry of the methyl group results from a preference for equatorial substituents in a chair transition state for the Prins cyclization.

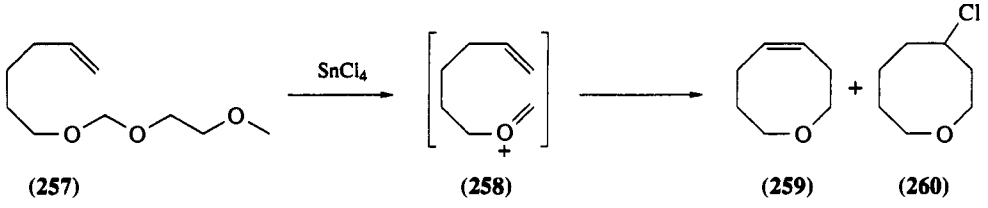


Scheme 36

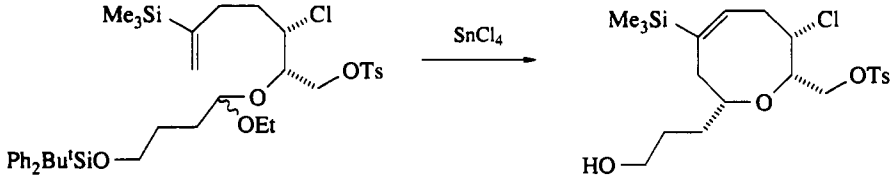


(253) (254) (255) (256)

Scheme 37



(257) (258) (259) (260)



(261) (262)

Scheme 38

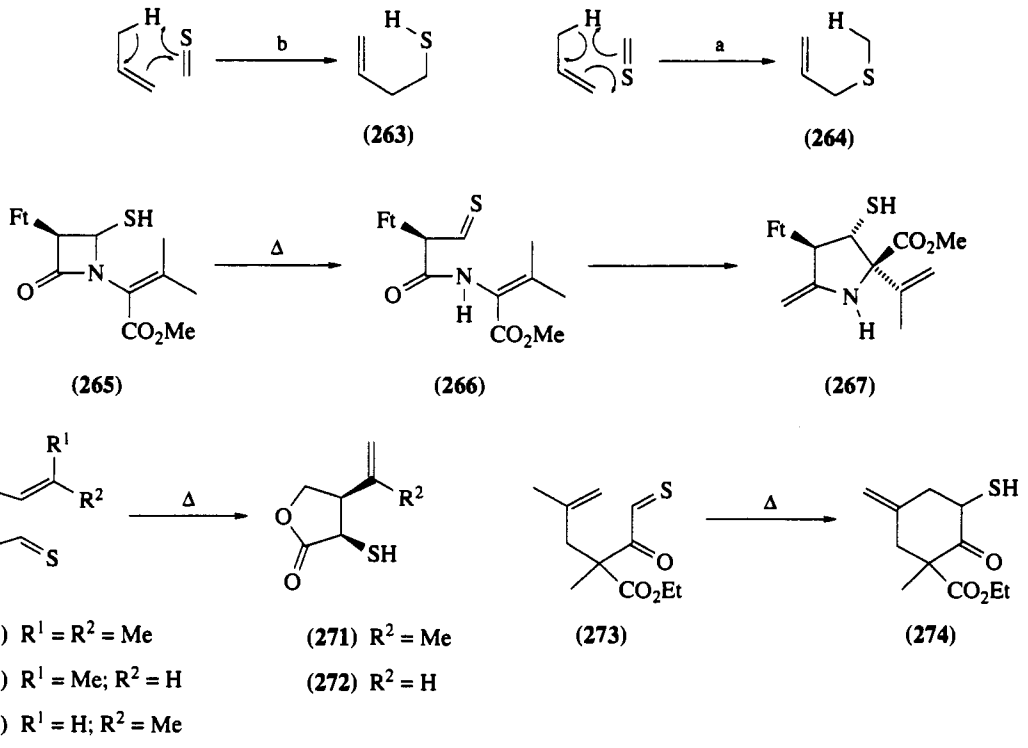
Overman has also shown that eight- and nine-membered cyclic ethers can be prepared by type III cyclizations.[136] Treatment of (**257**) with 2 equiv. of $SnCl_4$ for 13 h at –20 °C gives (**258**), which cyclizes to give a 2:1 mixture of (**259**) and (**260**) in 83% yield.[137] Cleaner reaction mixtures have been obtained using vinylsilanes, as in the synthesis of laurenyne.[138] $SnCl_4$-mediated cyclization of acetal (**261**) in CH_2Cl_2 at 0 °C, followed by *O*-desilylation produces oxocene (**262**) in 37% yield as the sole cyclic ether (Scheme 38).

Aside from the type III cyclizations described above, acetals have seen limited use in intermolecular Prins reactions[138–141] and extensive use as initiators for cation–alkene cyclizations.[142,143] Only limited success has been achieved in Lewis acid catalyzed addition of acetals to alkenes.[138,139] Better success has been achieved in the synthesis of *C*-glycosides by Lewis acid catalyzed addition of glycosyl acetates[140] or glycals to alkenes.[141] Johnson has extensively developed the use of acetals as initiators for cation–alkene cyclizations.[142] Recent studies have shown that excellent asymmetric induction can be obtained using chiral acetals derived from optically active 2,3-butanediol or 2,4-pentanediol.[143]

2.1.4 THIOCARBONYL COMPOUNDS

Electron-deficient thiocarbonyl compounds such as hexafluorothioacetone,[144] methyl cyanodithioformate[145] and thioglyoxylate esters[146] are particularly reactive enophiles. Since these compounds react primarily or exclusively by pathway (b) to give allylic sulfides (**264**), rather than by pathway (a) to give homoallylic thiols (**263**), they are outside the scope of this chapter (Scheme 39). Thiobenzaldehyde, generated *in situ*, reacts with β-pinene to give thiol in 38% yield and sulfide in 19% yield.[147]

Intramolecular type I ene reactions of thiocarbonyl compounds do give homoallylic thiols. Pyrolysis of (**265**) for 10 min at 176 °C generates the thioaldehyde (**266**), which undergoes an ene reaction to give (**267**) in 60% yield.[148] Thioaldehyde (**268**), generated *in situ* by a retro Diels–Alder reaction of the anthracene adduct of the thiocarbonyl group in toluene at reflux, gives (**271**) and (**269**) gives (**272**). The (*E*)-isomer (**270**) does not give any ene adduct.[149] The selective abstraction of a proton from the allylic site *cis* to the thioaldehyde and the formation of cyclopentanes with *cis* thiol and alkenyl groups suggests that these are concerted ene reactions. Preparation of (**273**) by a retro Diels–alder reaction from the cy-



Scheme 39

(20)

clopentadiene adduct at 140 °C leads to the type II intramolecular ene adduct (**274**) as mixture of stereoisomers in 62% yield (Scheme 39).[150]

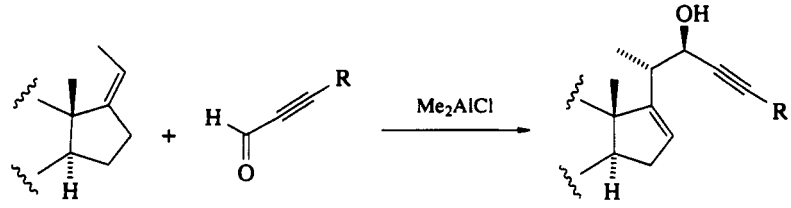
Alkylated thioaldehydes, generated by Pummerer rearrangements or treatment of α-chloro sulfides with $SnCl_4$, undergo ene type reactions with terminal alkenes to give homoallylic sulfides in 50–70% yield (equation 20).[151–153]

2.1.5 ADDENDUM

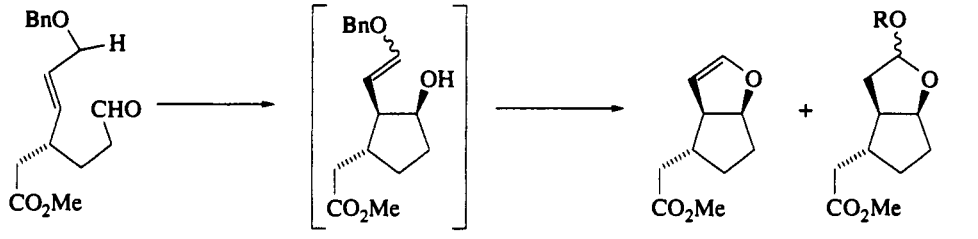
Lewis Acid Catalyzed Ene Reactions. Johnson and coworkers have used the $BF_3{\cdot}Et_2O$ catalyzed ene reaction of formaldehyde shown in equation (8) to prepare the Inhoffen–Lythgoe diol.[154]

Chloral. Yamamoto has found that the organoaluminum reagent prepared from Me_3Al and (*R*)-(+)-3,3′-bis(triphenylsilyl)binaphthol catalyzes the ene reaction of chloral and pentafluorobenzaldehyde with 1,1-disubstituted alkenes at –78 °C, giving the expected ene adducts in 40–90% yield and 60–90% enantiomeric excess.[155] Use of the sterically hindered chiral auxiliary is necessary. Low yields of racemic products are obtained with 3,3′-diphenylbinaphthol.

Glyoxylate Esters. Nakai and coworkers found that the reagent prepared from optically pure binaphthol and $(Pr^iO)_2TiX_2$ in the presence of molecular sieves catalyzes the ene reaction of methyl glyoxylate with 1,1-disubstituted alkenes at –30 °C to give ene adducts in 70–90% yield and 50–98% enantiomeric excess.[156] Nakai and coworkers found that the stereochemistry of ene reactions of glyoxylate esters with 2-butene could be controlled by choice of Lewis acid.[157] $SnCl_4$-catalyzed reaction of methyl glyoxylate with either (*E*)- or (*Z*)-2-butene at –78 °C gives a 4:1 mixture of *threo* adduct (**50**) and *erythro* adduct (**53**) in quantitative yield. Similar reactions catalyzed by Me_2AlOTf give mixtures rich in the *erythro* adduct (**53**) in 30–60% yield. Very low yields are obtained with Me_2AlCl.



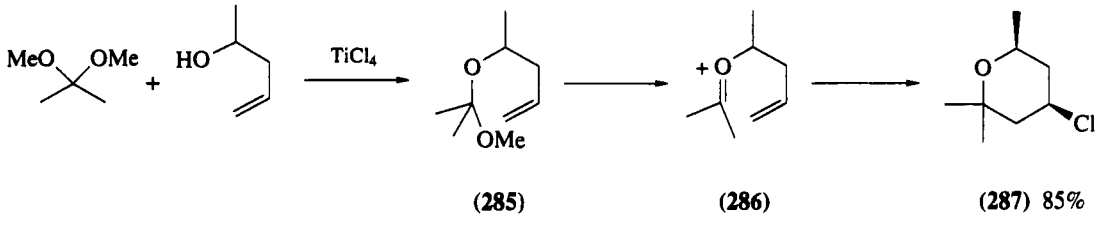
(275) (276) (277)



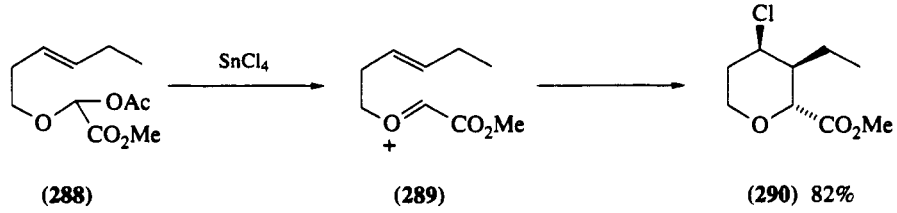
(278) (279) (280) (281) R = Bn
(282) R = H

(283) (284)

Scheme 40



(285) (286) (287) 85%



(288) (289) (290) 82%

Scheme 41

Aliphatic and Aromatic Aldehydes. Reaction of (*Z*)-$\Delta^{17,20}$-steroidal alkene (**275**) with alkynic aldehydes (**276**; R = Me, $SiMe_3$ or = Pr^i; R ≠ H) in the presence of Me_2AlCl produces a 9:1 mixture of the (20*S*,22*R*)-alcohol (**277**) and the (20*S*,22*S*)-alcohol.[158]

Formation of Cyclopentanols. Pyrolysis of unsaturated aldehyde (**278**) at 220 °C leads to ene adduct (**279**), which reacts further to give a mixture of enol ether (**280**) and acetal (**281**).[159] Hydrolysis of the mixture with hydrochloric acid gives hemiacetal (**282**) in 44% yield from (**278**).

Formation of Cyclohexanols. Tomioka and Koga used a type II ene reaction as a key step in the synthesis of the sesquiterpene (+)-ivalin.[160] Ene reaction and concomitant deprotection of the ketal occur on treatment of aldehyde (**283**) with $SnCl_4$ in CH_2Cl_2 at −10 to 25 °C to give 65% of adduct (**284**) with an axial hydroxy group.

Type III Reactions and Other Reactions of Acetals. Treatment of symmetric acetals with alkenols or alkynols in the presence of $TiCl_4$ results in transacetalization to give mixed acetals such as (**285**) which react further *via* cation (**286**) to give cyclic products such as (**287**) in 50–99% yield.[161] In this one-pot procedure the alkenic acetal need not be isolated. Acetoxyalkoxyacetic esters, such as (**288**), prepared in two steps from methyl glyoxylate and unsaturated alcohols, cyclize under the influence of $SnCl_4$ in CH_2Cl_2 to give oxacyclic carboxylic esters such as (**290**).[162] These reactions proceed through the intermediacy of methoxycarbonylcarbonium ion (**289**).

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2.2
Allylsilanes, Allylstannanes and Related Systems

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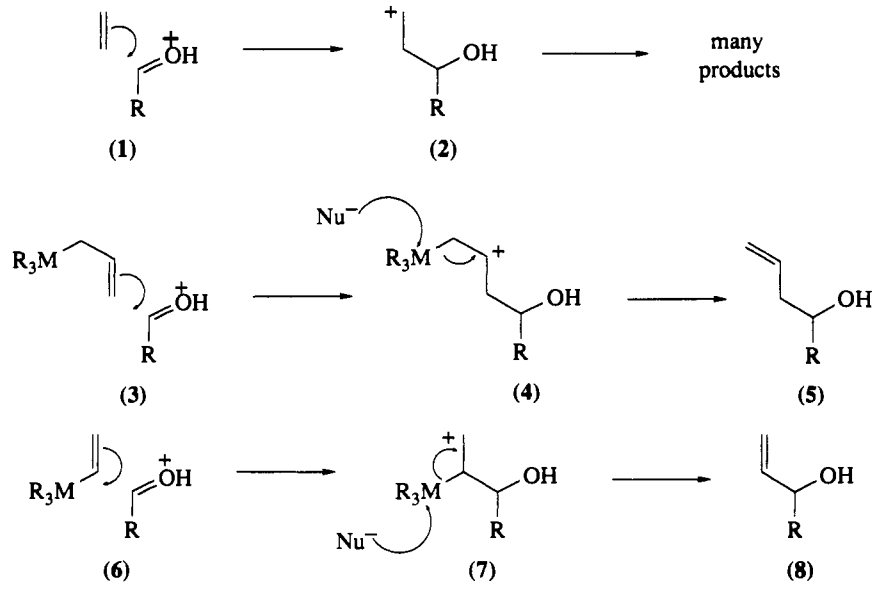
2.2.1 INTRODUCTION

The carbon–carbon bond forming step of the Prins reaction, the reaction of an alkene with a carbonyl group (**1**) → (**2**), is, in one sense, the most fundamental reaction of synthetic organic chemistry: at one extreme it is the base-catalyzed aldol reaction, where the alkene component is an enolate ion and the carbonyl group is unprotonated, and at the other extreme it is the Friedel–Crafts reaction. It is a paradigm for a fast organic reaction: both bonds involved in the key step are π-bonds, which are simultaneously more reactive than σ-bonds and more susceptible to modification in reactivity by the presence or absence of substituents on either or both components. It is no wonder that, in one form or another, it is the most frequently used of all carbon–carbon bond forming reactions.

The problem with the Prins reaction itself, and the reason that it plays such an inconspicuous part in organic synthesis, is the difficulty in controlling the outcome: the cation (**2**) can, and usually does, suffer



several different fates. Recently, cationic reactions of this type have been controlled by incorporating a silyl[1] or stannyl[2] group into the nucleophilic component of the reaction. Silyl or stannyl groups placed in the allylic (**3**) or the vinyl (**6**) position encourage the formation specifically of the cations (**4**) and (**7**), respectively, because these cations are *thermodynamically* stabilized by hyperconjugation of the adjacent carbon–metal bond. Furthermore, cations like these are *kinetically* unstable with respect to the loss of the metal group giving specifically the homoallylic alcohol (**5**) and the allylic alcohol (**8**). There is, of course, a continuity of behavior between that invoked here for silicon and tin and that of the more electropositive metals like lithium and magnesium, but it is necessary in the organization of books like this to make somewhat artificial separations of one group of reactions from another.

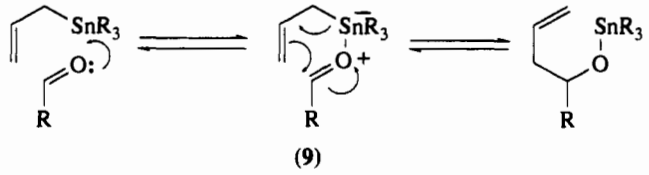
In this chapter, the carbon nucleophiles discussed will include allyl, vinyl, ethynyl, propargyl and allenyl silicon and tin systems, with most emphasis on the allyl, and the carbon electrophiles will be those at the oxidation level of aldehydes and ketones, including acetals, alkoxyalkyl halides and the corresponding sulfur derivatives. However, it does not include iminium ions, since these are covered in Chapter 4.3.

There is an extensive review of the electrophilic substitution reactions of allylsilanes and vinylsilanes in *Organic Reactions*[3] and the reactions of allylstannanes have been reviewed briefly.[4] The major books on synthetic organosilicon[5] and organotin chemistry[6] also cover the types of reaction discussed here.

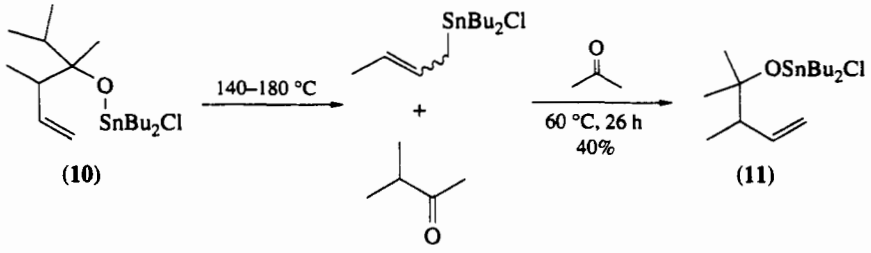
2.2.2 MECHANISM

The very general picture of the mechanism given in the introduction needs to be modified somewhat. It is fairly clear that allylsilanes react in the manner illustrated as (**3**) → (**5**), except that the acid catalyst is almost invariably a Lewis acid not a proton. Protic acid is apt to induce protodesilylation in competition with carbon–carbon bond formation, but Lewis acids are less likely to attack the carbon–carbon double bond. The intervention of a cationic intermediate (**4**) has not been proved for this type of reaction, but there is good circumstantial evidence that cations are involved: by analogy with protodesilylation,[7] from the occasional formation of oxepins, without loss of the silyl group,[8] and from the stereochemistry of the reaction.

With allylstannanes, however, the mechanistic picture is less clear: some Lewis acids, especially tin(IV) chloride, react very fast with allylstannanes, inducing an exchange of the trialkyltin group for the metal of the Lewis acid. The actual carbon nucleophile taking part in the carbon–carbon bond forming step, therefore, may not always be the original allylstannane.[9] Furthermore, tin is more electropositive and more powerful as a Lewis acid than silicon, so that it is possible, with a cyclic intermediate (**9**), for allylstannanes to react with aldehydes in the absence of any external acid catalysis. All that is needed to induce this behavior is heat,[2] pressure,[10] or electron-withdrawing ligands on the tin to increase its Lewis acidity.[11] These reactions are potentially, and sometimes actually, reversible, as in the conversion of the homoallylic alcohol derivative (**10**) into the homoallylic alcohol derivative (**11**).[12] Finally, some



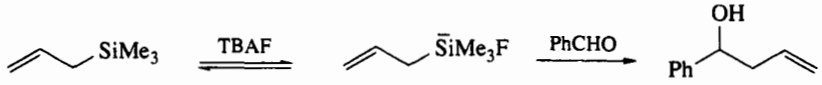
(9)



(10) (11)

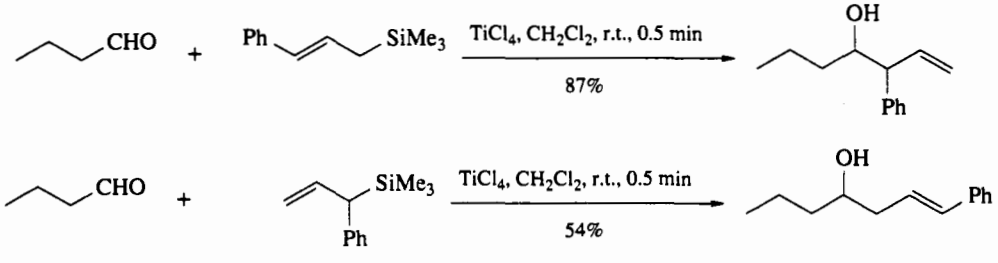
allylstannane reactions may take place in the tin(*II*) oxidation state, where the allylstannane is generated *in situ*.[13]

A different set of mechanistic possibilities comes into play when nucleophilic catalysis is used in place of the electrophilic catalysis induced by Lewis acids. The most common form of this reaction is fluoride ion catalysis of allylsilane reactions, where the carbon nucleophile is probably a hypervalent allylsilane (**12**), with the fluoride ion coordinated to the silicon, making the allylsilane unit nucleophilic enough to react with aldehydes without acid catalysis.[14]

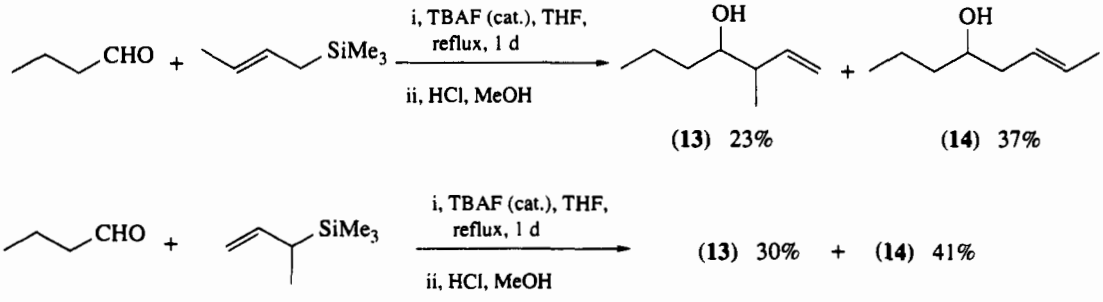


(12)

Allylsilanes are very stable thermally with respect to allylic shift of the silyl group[15] and regioisomeric allylsilanes are therefore very reliable in the regiospecificity of their Lewis acid catalyzed reactions (Scheme 1), the electrophile always bonding to the terminus of the allyl unit remote from the silyl group.[16] In contrast, fluoride-catalyzed reactions are not regiospecific (Scheme 2),[14] probably because

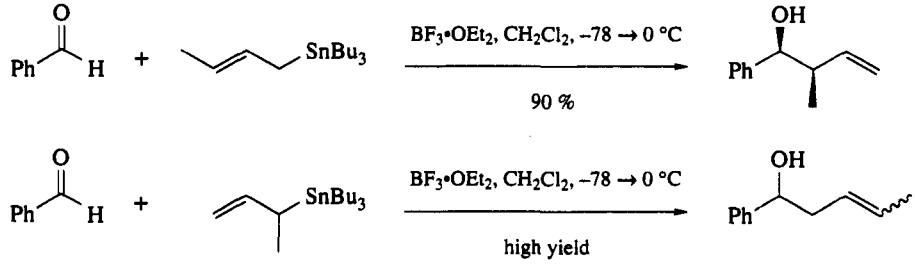


Scheme 1

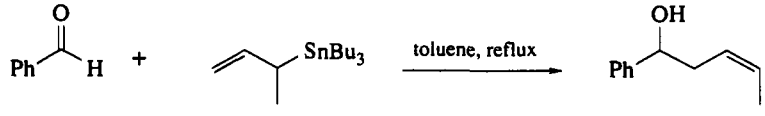


Scheme 2

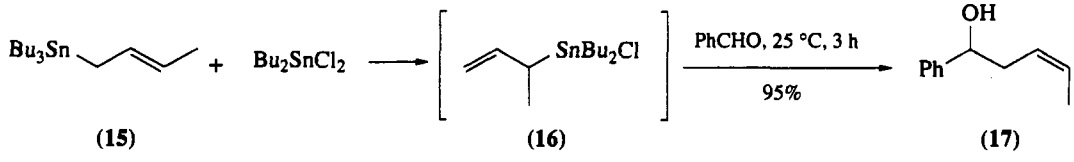
the hypervalent intermediate is no longer stable with respect to [1,3] sigmatropic shift of the silyl group.[17] Allylstannanes are less stable than allylsilanes in this respect, but they can react regiospecifically both in Lewis acid catalyzed reactions (Scheme 3)[18] and in thermal reactions (Scheme 4).[19] However, allylstannane reactions are not reliably regiospecific in this sense when other Lewis acids are used. They can even be regioselective in the opposite sense (Scheme 5).[20] The tributylstannyl group in the crotylstannane (**15**) is replaced by the chlorostannyl group from the Lewis acid, as already mentioned; the new allyl–metal species (**16**), which can be detected as an intermediate, is regioisomeric with that of the original allylstannane, and reacts in the normal way, with a second allylic transposition, to give the homoallylic alcohol (**17**), regioisomeric with that expected from the normal reaction. However, since the halogenated allylstannane is allylically unstable, this type of selectivity is rarely reliable. Furthermore, allyltrialkylstannanes themselves are allylically stable only in nonpolar solvents, and there is a risk of allylic interconversion even before the electrophile is introduced.



Scheme 3



Scheme 4



Scheme 5

The mechanism of the reactions of the other types of silanes and stannanes to be discussed in this chapter has hardly been studied, but the general outline given in the introduction is likely to be an adequate framework for thinking about these reactions. Fluoride-catalyzed reactions of vinylsilanes only work when there are anion-stabilizing groups present, which implies that there is substantial anionic character on carbon in the intermediate nucleophile, but this does not identify it as a carbanion; it could still be a hypervalent silyl species.

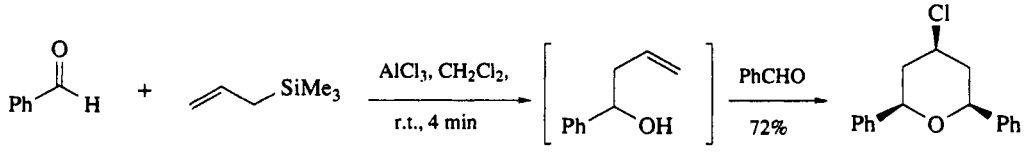
In general, the unreacting substituents on the silyl and stannyl groups make comparatively little difference. In the silicon series the trimethylsilyl group is much the most common, with phenyldimethylsilyl the next, because of the ease with which it can be introduced using the silyl–cuprate reagent. These two groups can usually be regarded as imparting similar reactivity, with the former perhaps about five times more reactive.[21] If larger groups are placed on the silicon, reactivity increases a little, but there is a serious risk that the silyl group is no longer capable of controlling the outcome: a proton may be lost in competition with the loss of the silyl group. In the tin series, tributylstannyl groups are the most common, for economic reasons, but trimethylstannyl occasionally shows some advantage, and halostannyl groups do significantly increase the reactivity by providing a built-in Lewis acid. Attempts to transfer chiral information from chiral substituents on the silyl[22] and stannyl[23] groups show some promise.

2.2.3 ALDEHYDES AND KETONES

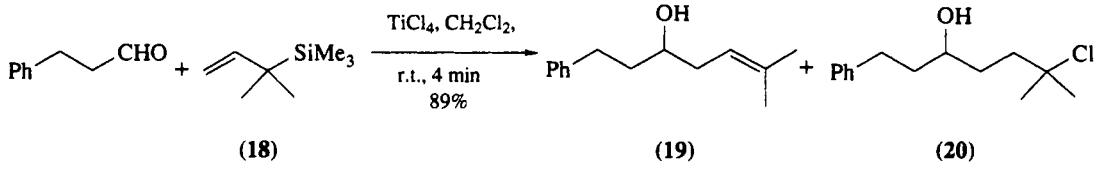
2.2.3.1 Allylsilanes

In the absence of Lewis acids, allylsilanes react only with very electrophilic ketones like hexafluoroacetone, when they undergo 'ene' reactions rather than electrophilic replacement of the silyl group.[24] In the presence of Lewis acids, allylsilanes react with aldehydes and ketones with clean allylic transposition (Scheme 1) and the formation of homoallylic alcohols. The range of Lewis acids used is wide, but titanium tetrachloride and boron trifluoride etherate are the most common. Typically, reaction takes place somewhere between –78 °C and 0 °C in dichloromethane solution, and a molar proportion of Lewis acid is used.

Sometimes, the reaction does not stop at the homoallylic alcohol. Thus ketones are more troublesome than aldehydes, since the product alcohols are tertiary and apt to react further.[25] Another problem arises when the alkene group of the product reacts with the electrophile (Scheme 6),[26] but further reaction is usually avoidable, because the double bond of the allylsilane, activated to a significant extent by the silyl group, is usually more nucleophilic than the double bond in the first-formed product. Occasionally, the product may be unavoidably more reactive than the allylsilane. This is chiefly a problem when the allylsilane has the silyl group at the more substituted end of the allyl group (Scheme 7),[27] in which the first-formed product (**19**) is a trisubstituted alkene, more nucleophilic than the monosubstituted double bond of the allylsilane (**18**), and consequently it reacts further, giving substantial amounts of the chloride (**20**). This sort of problem is less evident when acetals are used in place of aldehydes (Scheme 37). Another kind of reaction in which the first-formed product reacts further is less troublesome: a suitably placed ester group may lactonize onto the hydroxy group of the homoallylic alcohol (Scheme 8), where again the corresponding acetal reacts without this complication.[28]



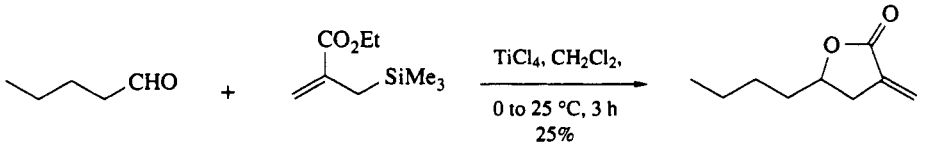
Scheme 6



(18) **(19)** **(20)**

(19):**(20)** 15:85

Scheme 7

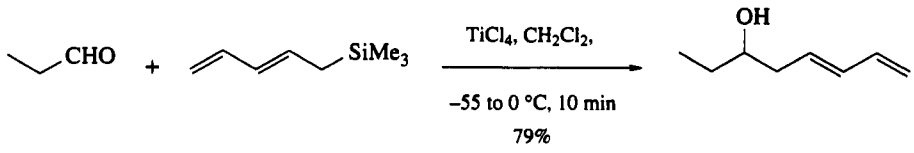


Scheme 8

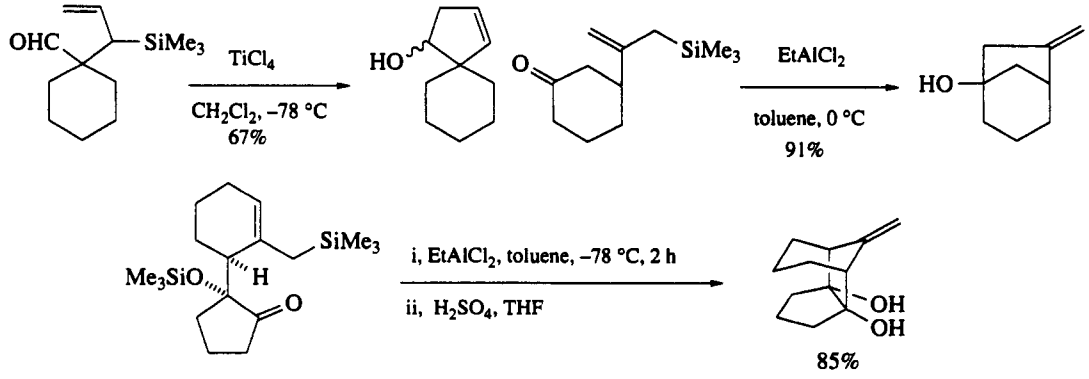
When the allylsilane has an extra double bond extending the conjugation, reaction takes place at the terminus of the diene system remote from the silyl group (Scheme 9).[29]

Intramolecular reactions work well (Scheme 10) giving bicyclic, spirocyclic and tricyclic homoallylic alcohols in these examples.[30]

Allylsilanes, monosubstituted at C-3, react with aldehydes to give more of the *syn* (= *erythro*) product than the *anti* (Scheme 11); the (*E*)-allylsilane (**21**) is very clean in this respect, especially with the more heavily substituted aldehydes, but the (*Z*)-allylsilane (**22**) is not very selective.[31] Antiperiplanar transition

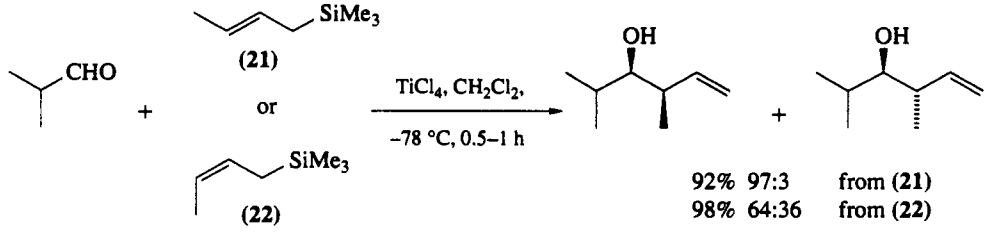


Scheme 9

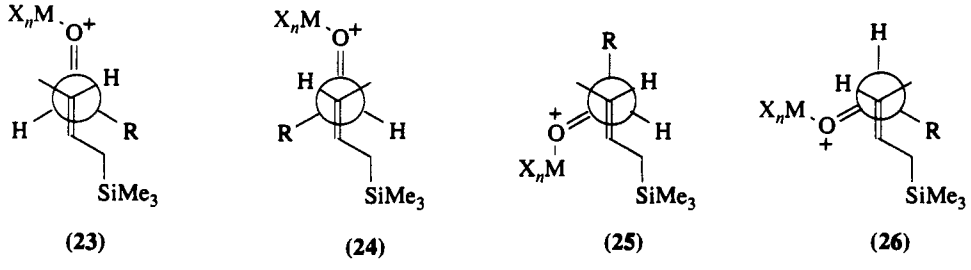


Scheme 10

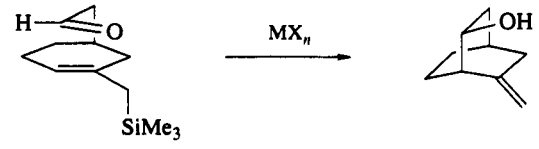
states (**23**) and (**24**) have been invoked to explain the preference for the formation of the *syn* products, the alternative arrangements placing the methyl group unfavorably between the R group of the aldehyde and the carbonyl oxygen. However, synclinal transition states, such as (**25**) and (**26**), in which the size of the Lewis acid attached to the oxygen atom helps to determine the most favorable transition state geometry, have also been suggested. In the only test designed to probe this point (Scheme 12), the Lewis acid was found to influence the proportion of reaction taking place from the synclinal (**27**) and antiperiplanar (**29**) arrangements, with the former in general the more important.[32]



Scheme 11

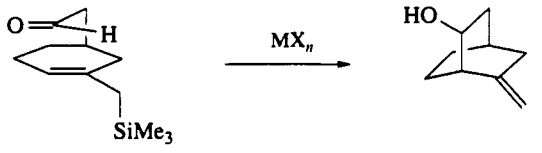


Chiral allylsilanes react antarafacially; the incoming electrophile attacks the double bond on the surface opposite to the silyl group (Scheme 13) and the major products are *syn*, in this case even from the (*Z*)-allylsilane.[33] The overall *anti* stereospecific reaction (*anti* to the extent of 90:10) in favor of product (**32**) having the substituents on the carbon chain *syn* to the extent of about 80:20 is still found with the (*Z,E*)-silane (**31**) in an S_E2'' reaction (Scheme 14), even though the new stereocenters are five and six



(27) (28)

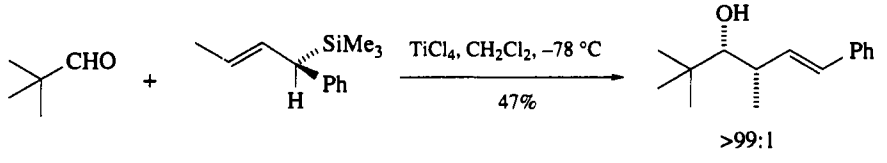
MX_n	(28):(30)
BF_3•OEt_2	80:20
$FeCl_3$	70:30
Et_2AlCl	66:34
$SnCl_4$	49:51

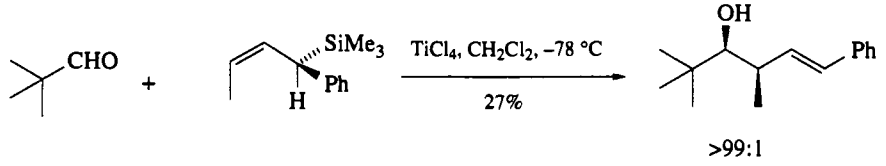


(29) (30)

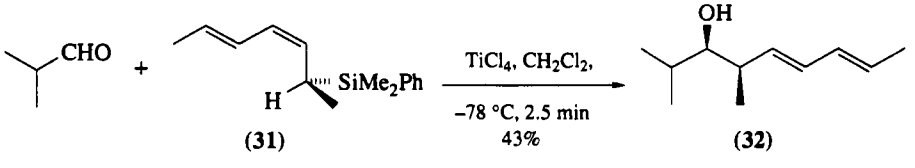
Scheme 12

atoms from the original stereocenter.[34] In the intramolecular reaction in Scheme 15, both the (*R*,*E*)-allylsilane (**33**) and the (*S*,*Z*)-allylsilane (**34**) react antarafacially to the silyl group, the former with a synclinal transition state and the latter with an antiperiplanar transition state, to give the same diastereoisomer and enantiomer (**35**).[35]





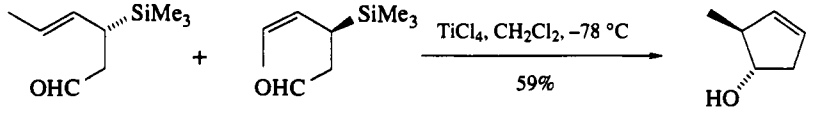
Scheme 13



(31) (32)

(+)-enantiomer 90:10

Scheme 14

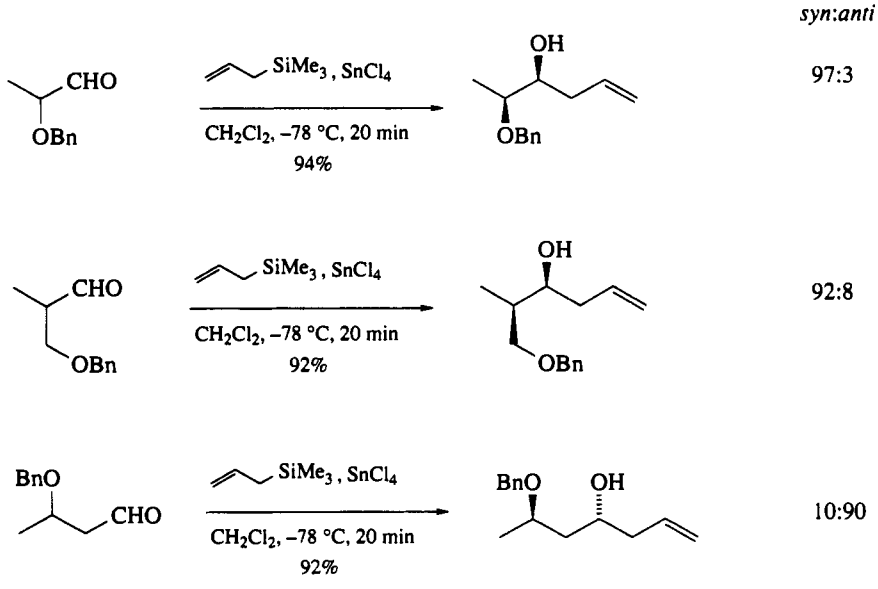


(33) (34) (35)

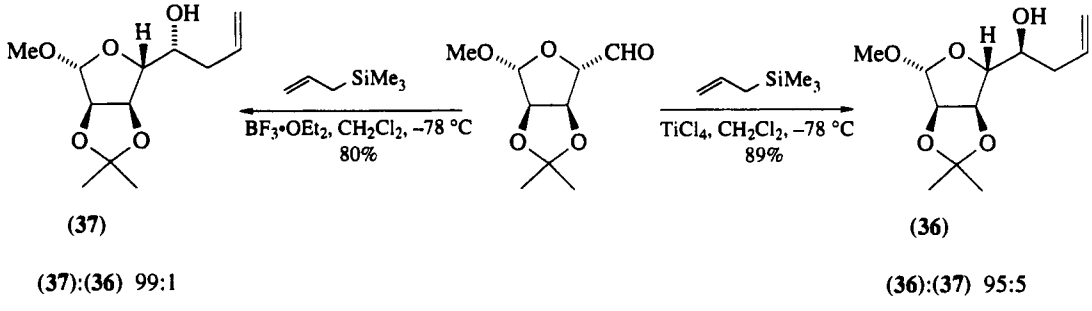
>98% *ee*

Scheme 15

When the aldehyde or ketone contains a stereocenter, diastereofacial selectivity on the carbonyl group is possible. 2-Phenylpropionaldehyde is moderately Cram-selective to an extent (up to 76% *de*) common with several other carbon nucleophiles.[36] However, when the stereocenter has an ether group α or β to the carbonyl group, very high diastereoselectivity is observed (Scheme 16), consistent with attack by the allylsilane from the less hindered side of a ring made up by chelation of the Lewis acid between the ether oxygen and the carbonyl oxygen.[36,37] Lewis acids like boron trifluoride, with only one coordination site, have different and usually rather lower diastereoselectivities. The choice of Lewis acid can invert the selectivity in favorable cases (Scheme 17), with titanium tetrachloride giving the product (**36**) of chelation control and boron trifluoride the product (**37**) in the normal Cram sense.[38]



Scheme 16

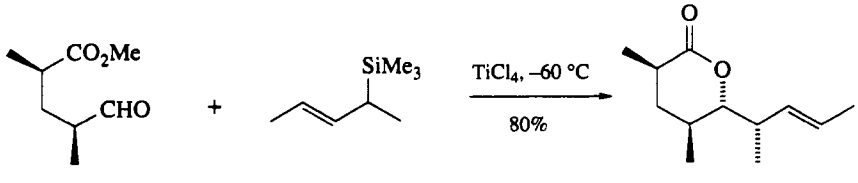


(37) **(36)**

(37):**(36)** 99:1 **(36)**:**(37)** 95:5

Scheme 17

When both the allylsilane and the aldehyde are chiral, double stereodifferentiation becomes possible. This has not yet been used in synthesis, probably because enantiomerically pure allylsilanes have only recently become available, but it appears likely to lead to very high levels of stereoselection: the racemic aldehyde (**38**) and the racemic allylsilane (**39**) combine (Scheme 18) to give largely (>90:10) one dia-

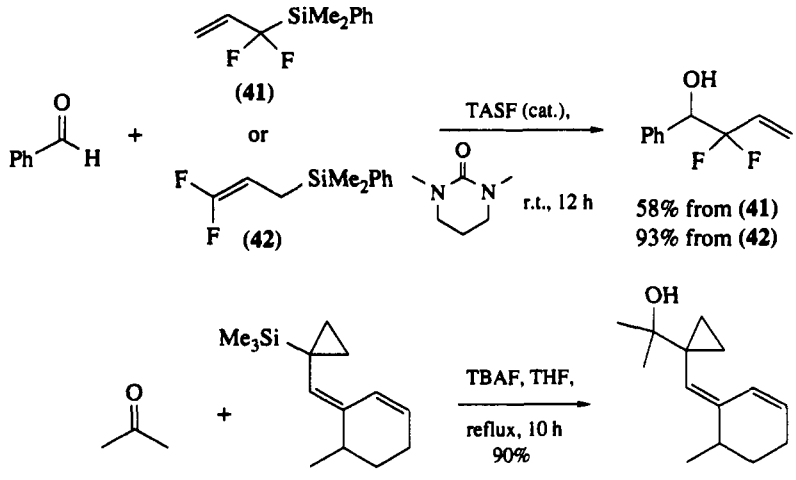


(38) **(39)** **(40)**

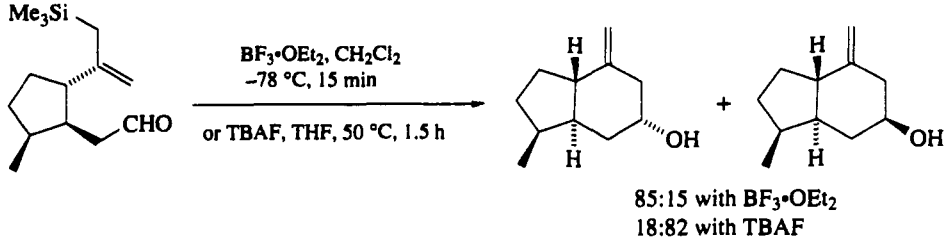
Scheme 18

stereoisomer, namely the racemic lactone (**40**), which implies that each enantiomer of the two reagents is finding its partner with considerable selectivity and reacting in the *anti*-Cram sense as a result of chelation to the ester group.[39]

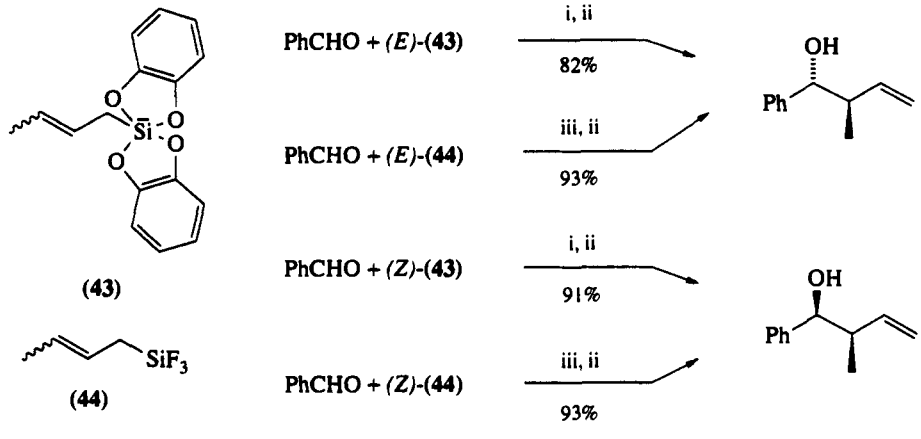
In fluoride ion catalyzed reactions of allylsilanes, aldehydes are the only carbon electrophiles that work well; protodesilylation is unavoidable with most other electrophiles, even in the most rigorously dried media. The most commonly used fluoride ion source, which only needs to be present in catalytic amounts, is TBAF in THF at room temperature or under reflux, benzyltrimethylammonium fluoride may be better, and cesium fluoride in DMF, potassium fluoride with 18-crown-6 in THF, and TASF in polar



Scheme 19



Scheme 20



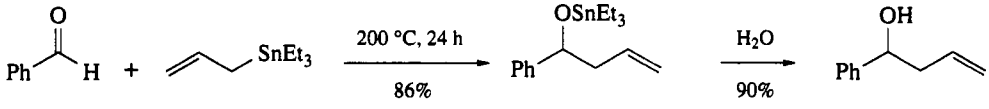
i, THF, reflux, 90 h; ii, HCl, H_2O; iii, CsF, THF, r.t., 16 h

Scheme 21

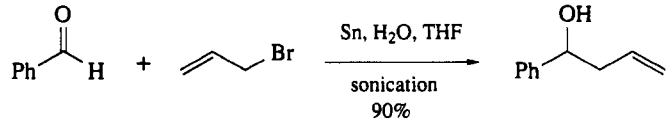
aprotic solvents have all been used. The first-formed product is the silyl ether, which is usually hydrolyzed in the workup. The reaction may not be regiospecific (Scheme 2), but it can be regioselective (Scheme 19), depending upon the ambident character of the intermediate anion.[40,41] The stereoselectivity can be different from the corresponding Lewis acid catalyzed reactions (Scheme 20).[42] The nucleophile does not have to be fluoride, nor do the substituents on the silicon need to be alkyl groups: hypervalent silyl systems like (**43**) and (**44**) in the presence of fluoride ion are nucleophilic enough to react directly with aldehydes.[43] The stereochemistry observed (Scheme 21), namely *anti* with respect to the disposition of the substituents on the carbon chain,[44] and *syn* with respect to the electrophilic substitution process,[45] is that expected for a cyclic transition state, implying that the aldehyde oxygen becomes one of the ligands on the silicon in the transition state.

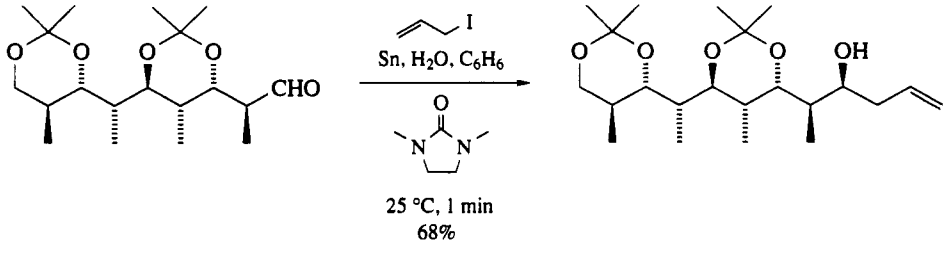
2.2.3.2 Allylstannanes

Unlike allylsilanes, allylstannanes react directly with aldehydes on heating, transferring the stannyl group to oxygen (Scheme 22).[2] Haloallylstannanes, where a Lewis acid is built into the reagent, are generally more reactive. They show little basic character, reacting in water, for example, where they can be generated *in situ* (Scheme 23).[13,46] They also react easily with ketones (Scheme 24).[47,48]

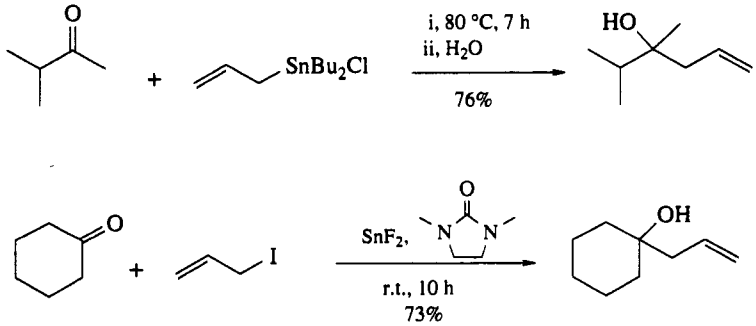


Scheme 22



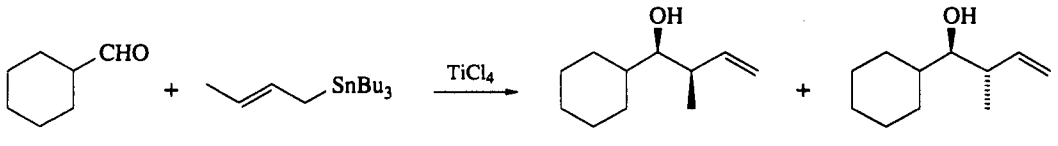


Scheme 23



Scheme 24

Boron trifluoride etherate is much the most commonly used Lewis acid in allyltrialkylstannane reactions. The preference for synclinal transition states is more marked with the stannane equivalent of the system illustrated in Scheme 12 than with the silyl system: the preference for the transition state (**27**) over (**29**) is 87:13 with boron trifluoride as the Lewis acid and a tributylstannyl group in place of the trimethylsilyl, and 99:1 using a proton.[49] As with allylsilanes, there is a preference, in the Lewis acid catalyzed reactions, for the formation of the product with the substituents *syn* on the carbon chain (Scheme 3), but with allylstannanes the (*Z*)-isomer is as effective as the (*E*).[18] However, the preference for the *syn* arrangement on the carbon chain is not always observed, even with Lewis acids like boron trifluoride: with a phenyl group on the double bond in place of the methyl, the product has the *anti* arrangement of the phenyl and hydroxy groups.[50] In reactions involving cyclic transition states, the *anti* arrangement of the substituents on the carbon chain is that expected from (*E*)-allylstannanes, and the *syn* is that expected from (*Z*)-allylstannanes.[51,52] For this reason, the order of mixing of an allylstannane and the Lewis acid can be important, because it affects the extent to which the Lewis acid replaces the stannyl group before reaction with the aldehyde takes place (Scheme 25).[53] Presumably an allyltitanium intermediate uses a cyclic transition state (**47**) and hence gives rise to the *anti* product.

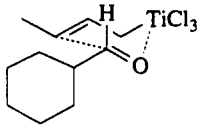


(**45**) (**46**)

Conditions: i, 93:7
Conditions: ii, 5:95

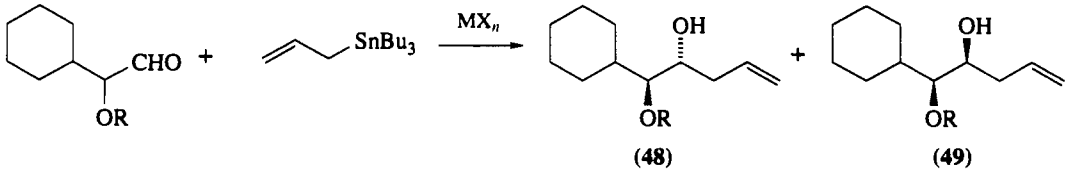
i, add (**46**) to a mixture of (**45**) and $TiCl_4$; ii, add (**45**) to a mixture of 2 equiv. of $TiCl_4$ and (**46**)

Scheme 25



(**47**)

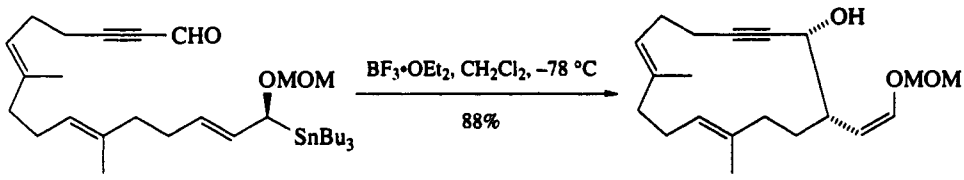
Chelation and Cram selectivity can also be controlled by taking advantage of the differing abilities of Lewis acids to accept chelation (Scheme 26). The *anti* product (**48**) is that expected from an open-chain transition state and Felkin–Anh effects, and the *syn* product (**49**) is that from chelation control. The former is the major product with boron trifluoride, especially when the oxygen function is protected with a TBDMS group, and the latter with titanium tetrachloride or magnesium bromide.[54] Normally, allylstannanes give higher levels of Cram control than other carbon nucleophiles,[55] but high *anti*-Cram selectivity is observed in a synthesis of the Prelog–Djerassi lactone[55] resembling the allylsilane reaction in Scheme 18. Chelation by the ester group to the Lewis acid, even though the Lewis acid is boron trifluoride, appears to be involved.[56]



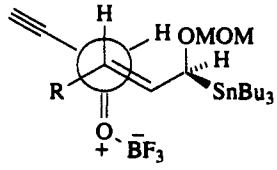
(**48**) (**49**)

R	MX_n		
Bu^tMe_2Si	$BF_3{\cdot}OEt_2$	83%	95:5
Bn	$MgBr_2$	85%	1:>250

Scheme 26



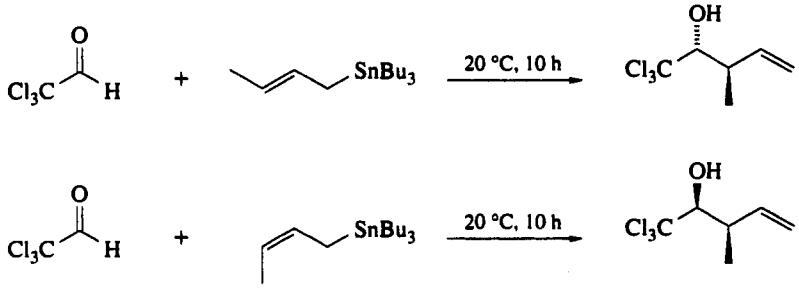
Scheme 27



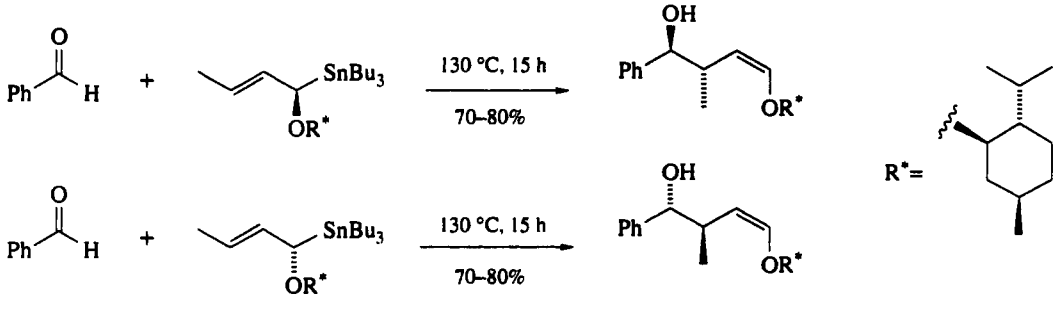
(50)

The overall electrophilic substitution reaction in the Lewis acid catalyzed reaction is *anti* (Scheme 27), with reaction probably taking place in the synclinal transition state (**50**).[57]

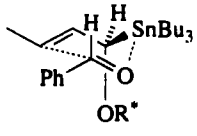
In the absence of Lewis acids, stereoselectivity is strongly dependent upon the geometry of the double bond in the allylstannane, both in simple thermal reactions (Scheme 28)[58] and in pressure-induced reactions,[18] as expected for a cyclic transition state. As well as being selective for the formation of the *anti* arrangement of substituents on the carbon chain, the overall electrophilic substitution in the thermal reaction of an (*E*)-allylstannane, is stereospecifically *syn* (Scheme 29),[59] with a cyclic transition state (**51**),



Scheme 28



Scheme 29



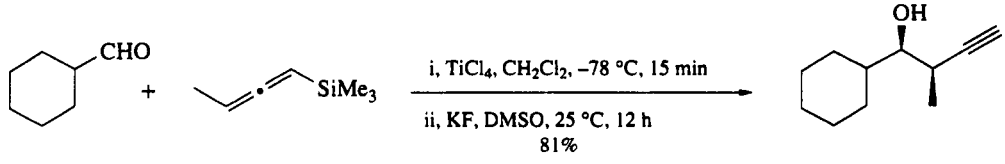
(51)

in contrast to the Lewis acid catalyzed reaction with the open chain transition state (**50**). In both cases it is the oxygen substituent that eclipses (or partly eclipses) the double bond in the allylstannane, causing the double bond in the product to have the (Z)-geometry, just as it has when the substituent on the stereocenter is methyl (Scheme 4).[19,51]

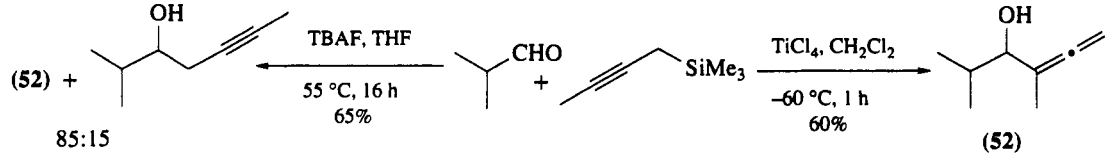
Dienylmethylstannanes react with aldehydes in the presence of Lewis acids equally at the γ and the ε position,[50] in contrast to the allylsilane reactions in Schemes 9 and 14.

2.2.3.3 Allenyl-, Propargyl-, Vinyl- and Ethynyl-silanes and -stannanes

Allenylsilanes react with aldehydes in the presence of Lewis acids (Scheme 30).[60] This reaction is also capable of being subverted: a [3 + 2] annulation takes place, forming a 3-silyldihydrofuran, when the silyl group is the TBDMS group, which is more reluctant to leave than the trimethylsilyl.[61] Propargylsilanes also react regiospecifically in the presence of Lewis acids, complementing the behavior of the corresponding allenylsilanes, but they react with loss of regiocontrol in the presence of fluoride ion (Scheme 31).[62]

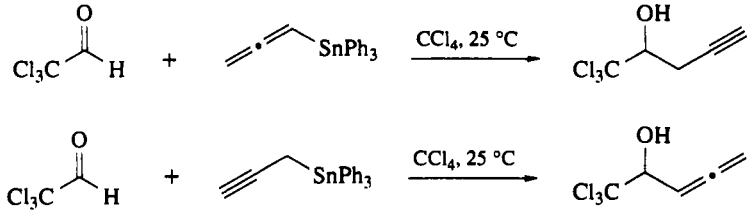


Scheme 30



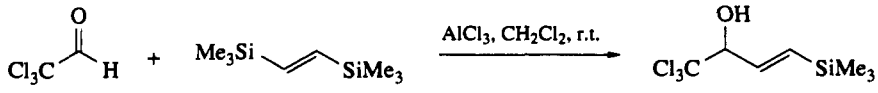
Scheme 31

Allenylsilanes and propargylsilanes are interconvertible only at high temperatures,[15] but allenylstannanes and propargylstannanes interconvert fast enough that product mixtures are sometimes seen when either reacts with an aldehyde or ketone,[63] just as with regioisomeric allylstannanes. Thus, when the reagent is generated *in situ* from tin and a propargyl iodide in dipolar aprotic solvents, the major product is the allene, but in diglyme the major product is the alkyne.[64] Simple thermal reactions appear to be more straightforward (Scheme 32), where the propargylstannane is 6.5 times more reactive than the allenylstannane.[63]

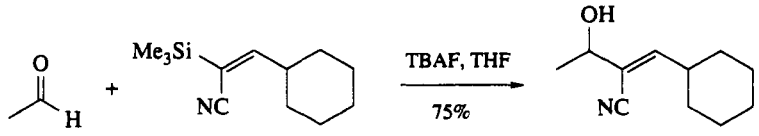


Scheme 32

Vinylsilanes react with chloral in the presence of Lewis acids (Scheme 33),[65] but this type of reaction is little used, probably because the products are allylic alcohols, which are apt to undergo ionization in the presence of Lewis acids to give allyl cations, and hence further reaction. Reactions employing nucleophilic catalysis, although free of this problem, are also limited, only anion-stabilized systems undergoing reaction (Scheme 34).[66,67] On the other hand, there is less of a problem with β-elimination of a halide ion, as there would be with most metals β to a halogen.[40]



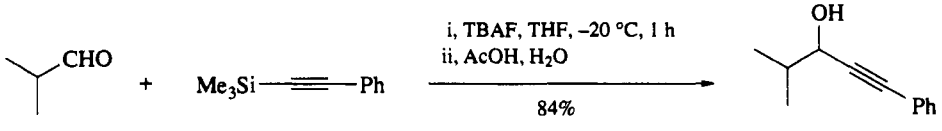
Scheme 33



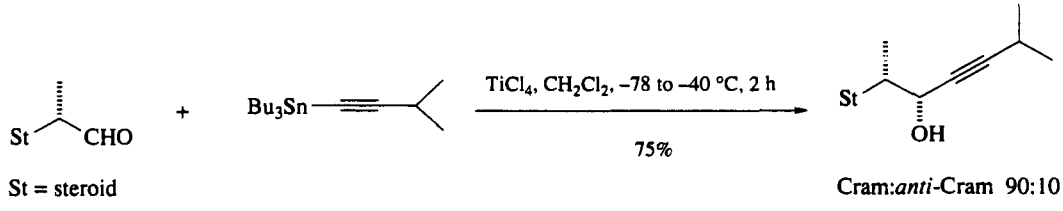
Scheme 34

Vinylstannanes might reasonably be expected to react with aldehydes and ketones. In practice this is not done: instead the stannyl group is replaced by lithium, using butyllithium, before any reaction with the aldehyde or ketone. Vinylstannanes are also effective carbon nucleophiles in a number of transition metal mediated reactions outside the scope of this chapter.[68]

Ethynylsilanes react with aldehydes and ketones in the presence of Lewis acids[65] or fluoride ion (Scheme 35).[69] Ethynylstannanes react in the presence of Lewis acids (Scheme 36),[2,70] showing higher Cram selectivity than other ethynyl nucleophiles.



Scheme 35



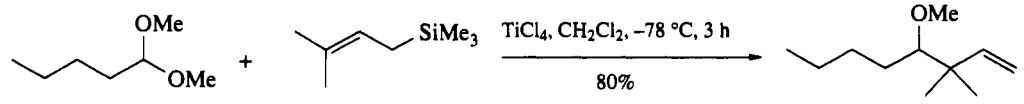
Scheme 36

2.2.4 ACETALS AND KETALS

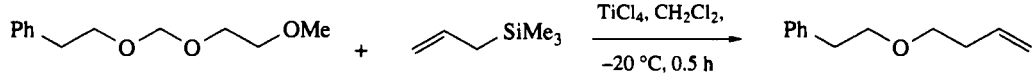
2.2.4.1 Allylsilanes

Acetals and ketals are exceptionally good electrophiles for allylsilanes,[71] often giving better yields than the corresponding aldehyde or ketone, because the products are less prone to further reaction. Typically the reactions are catalyzed by stoichiometric amounts of titanium tetrachloride in dichloromethane at –78 °C, and the regiospecific reaction is complete in a few minutes (Scheme 37).[27,72] Other Lewis acids used are boron trifluoride etherate, tin(IV) chloride and, in catalytic amounts, trimethylsilyl triflate,[73] trityl perchlorate[74] and montmorillonite clays.[75] With the unsymmetrical acetal (**53**), the methoxyethoxy group departs selectively (Scheme 38), presumably because it chelates the Lewis acid.[76]

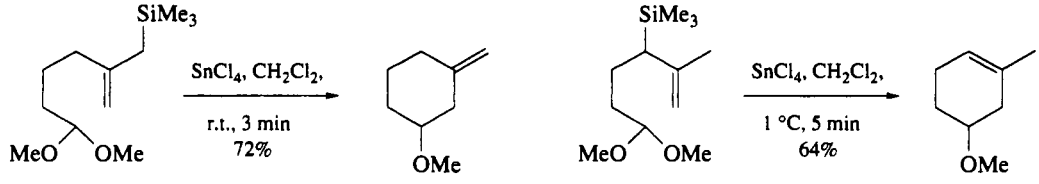
As in the reactions with aldehydes and ketones, intramolecular reactions are easy (Scheme 39),[77,78] and the reaction is selective for the formation of the product with the substituents *syn* on the carbon chain, whatever the geometry of the double bond in the allylsilane (Scheme 40).[79] However, this clean stereoselectivity is not seen with the acetals of aromatic aldehydes, where the choice of Lewis acid and the nature of *para* substituents affect the proportion of the diastereoisomers.



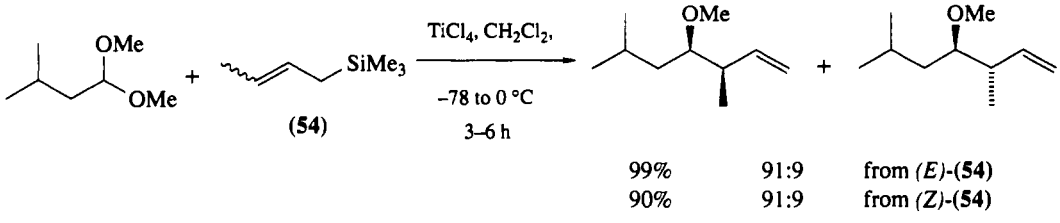
Scheme 37



Scheme 38

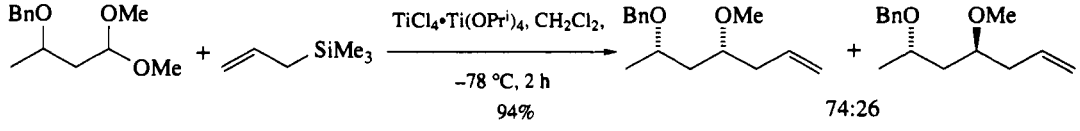


Scheme 39

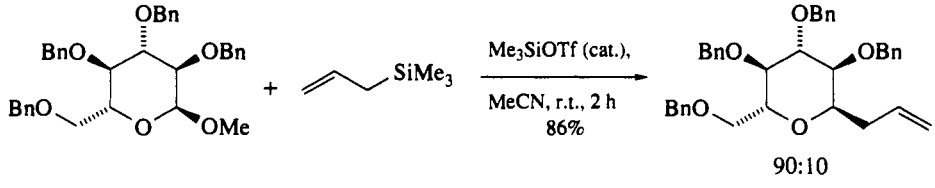


Scheme 40

Allylsilanes attack cyclohexanone ketals axially (93:7)[73] and attack 2-phenylpropionaldehyde acetal with a degree of Cram selectivity that is influenced by the choice of Lewis acid, tin(IV) chloride giving the highest ratio (3.5:1).[80] With β-alkoxyacetals, chelation control is not possible as it is with the corresponding aldehydes; stereoselectivity is not high, it is in the opposite sense (Scheme 41, compare Scheme 16), and it depends upon the choice of Lewis acid.[80]

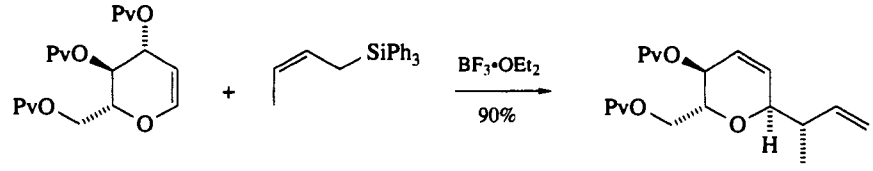


Scheme 41



Scheme 42

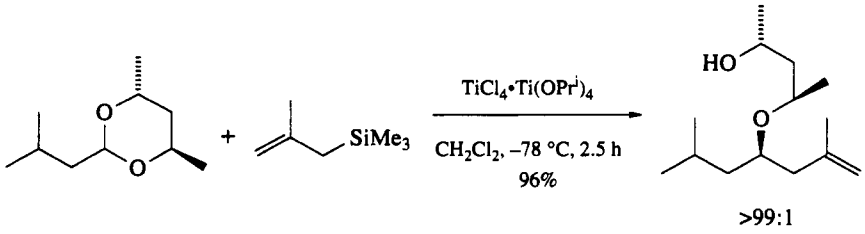
Sugar acetals and acetates react with α-axial attack on the ring (Scheme 42),[81] but the corresponding halides react somewhat faster and need less catalyst. It appears that the better the leaving group, the more polar the solvent and the more powerful the Lewis acid, the better the stereoselectivity, the combination of *p*-nitrobenzoate and boron trifluoride etherate being notably effective. A closely similar reaction takes place with vinylogous acetals,[82,83] where the example (Scheme 43) from Danishefsky's synthesis of avermectin A-1a is further notable in that the stereochemistry at the methyl-bearing carbon was determined by the geometry of the double bond in the allylsilane,[84] in contrast to the results in Scheme 40.



Pv = pivaloyl

Scheme 43

The acetals of optically active 1,2- and 1,3-glycols show striking stereoselectivity, giving homoallylic ethers in high diastereoisomeric excess, especially when titanium tetrachloride–titanium tetraisopropoxide mixtures are used as the Lewis acid (Scheme 44).[85] Even non-cyclic acetals made from aldehydes and enantiomerically pure 1-phenylethanol give homoallylic ethers with high diastereoselectivity.[86]

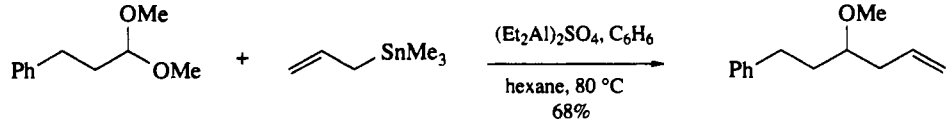


>99:1

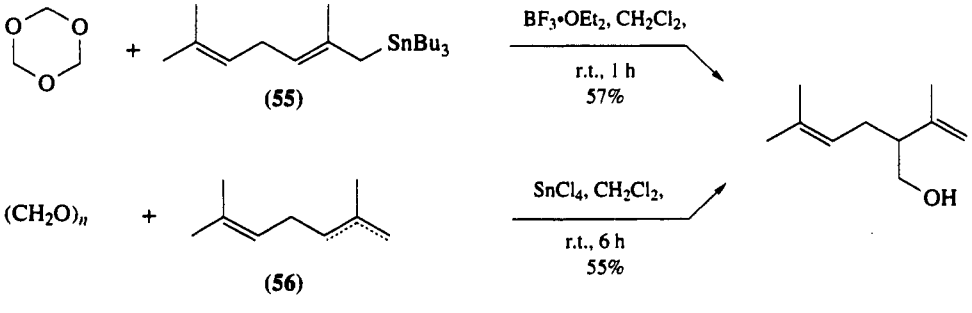
Scheme 44

2.2.4.2 Allylstannanes

Allylstannanes react with acetals in the presence of bis(diethylaluminum) sulfate (Scheme 45)[87] and the reaction has been used in a synthesis of lavandulol (Scheme 46). However, the allylstannane (**55**) was not necessary in this reaction, for the mixture of dienes (**56**) worked just as well in the presence of tin(IV) chloride. It is conceivable that in the latter reaction the tin(IV) chloride combines with the diene to make an allylstannane *in situ*.[88]

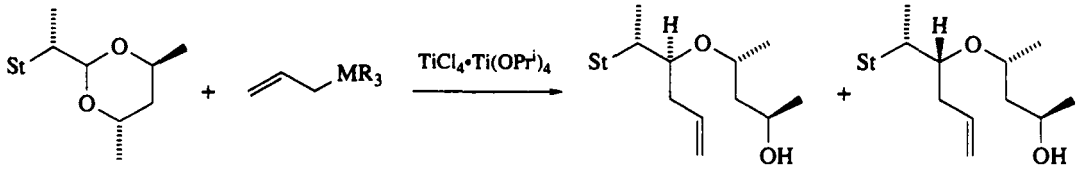


Scheme 45



Scheme 46

In the reaction in Scheme 47, the allylstannane gave the isomer (**58**) as the major product, whereas the corresponding allylsilane gave the isomer (**57**). The product (**57**) is that expected from Cram's rule and (**58**) is that expected by analogy with the reaction in Scheme 44. The explanation suggested is that the allylstannane, as the more nucleophilic species, has an early transition state, and the allylsilane a late transition state.[89] Of course, when the chiral centers in the acetal ring are inverted, the two influences support each other and very high diastereocontrol for the formation of the steroidal C-22 configuration of (**57**) is possible with both allyl–metal reagents. The controlling influence of an acetal of this type is similarly overridden by what appears to be a chelation effect to an oxygen substituent in a 1,3-relationship to the acetal oxygens.[90]



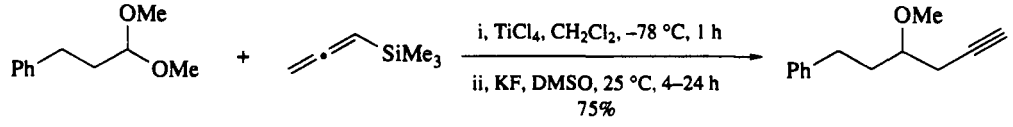
(**57**) (**58**)

St = steroid	$MR_3 = SiMe_3$	93%	90:10
	$MR_3 = SnBu_3$	84%	30:70

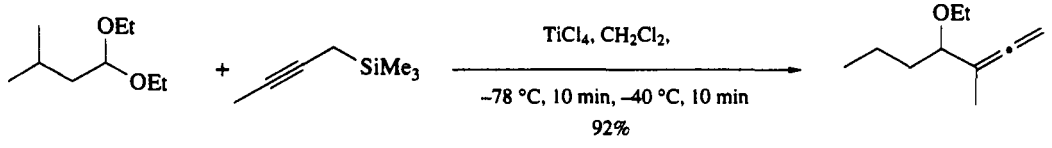
Scheme 47

2.2.4.3 Allenyl-, Propargyl-, Vinyl- and Ethynyl-silanes

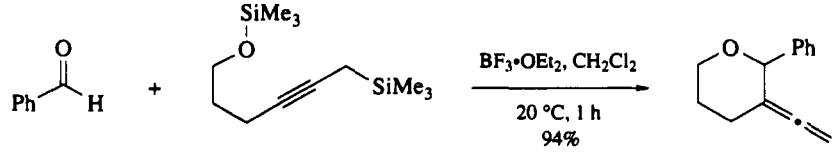
Allenylsilanes react with acetals, as they do with aldehydes, by addition, but a simple elimination step completes the substitution reaction (Scheme 48).[91] Propargylsilanes likewise react with acetals in the presence of Lewis acids (Scheme 49).[92] The reaction has been used intramolecularly (Scheme 50),[93] where the first step is likely to be acetal or hemiacetal formation followed by ring closure, and in reactions at the anomeric position of sugars with high levels of axial attack giving allenes.[94]



Scheme 48



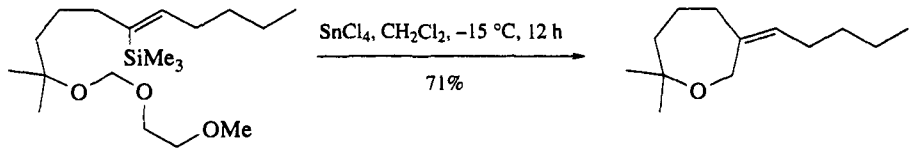
Scheme 49



Scheme 50

Vinylsilanes react with acetals in the presence of Lewis acids to give allylic ethers, which go on to react further.[95] Intramolecular reactions are less susceptible to this difficulty[78] and provide an opportunity for controlling the configuration of exocyclic double bonds (Scheme 51). As usual with vinylsilanes, the

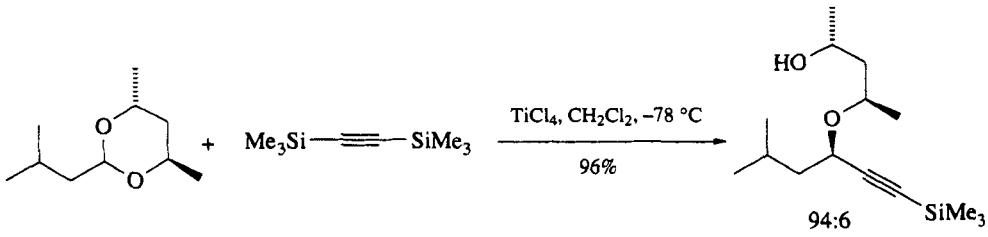
vinylsilane (**59**) reacts stereospecifically with retention of configuration; the (*E*)-stereoisomer of (**59**) gives the (*E*)-product corresponding to (**60**).[96]



(**59**) (**60**)

Scheme 51

Ethynylsilanes react with the chiral acetal in Scheme 52 with good diastereoselection,[97] providing a route to enantiomerically enriched alcohols to rival the Midland method.

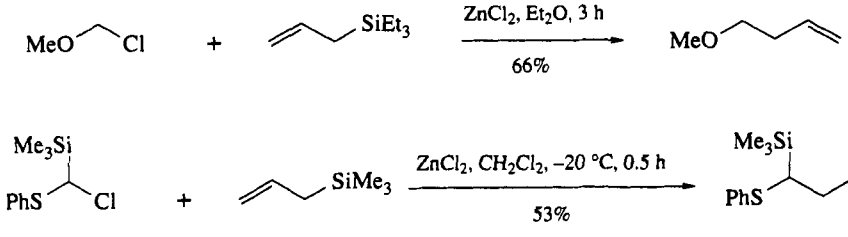


Scheme 52

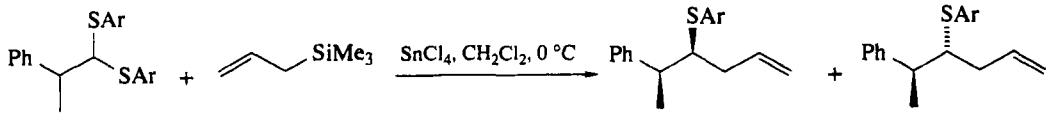
2.2.5 OTHER SUBSTRATES AT THE OXIDATION LEVEL OF ALDEHYDES AND KETONES

2.2.5.1 Allylsilanes and Allylstannanes

Allylsilanes react with alkoxymethyl and phenylthiomethyl chlorides in the presence of Lewis acids (Scheme 53),[98,99] and dithioacetals, similarly, where substantial stereoselection can be achieved with large aryl groups on the sulfur atoms (Scheme 54).[100] Monothioacetals react selectively with cleavage of the carbon–sulfur bond when tin(IV) chloride is used as the Lewis acid (Scheme 55).[101]

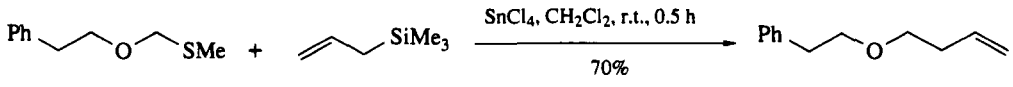


Scheme 53



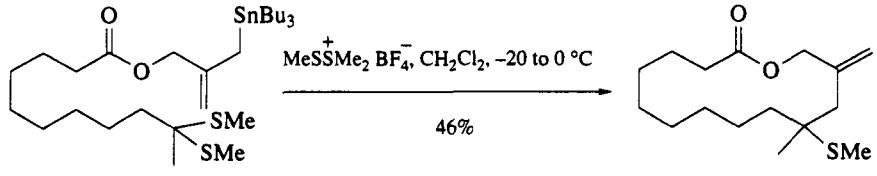
Ar = Ph	56%	75:25
Ar = 2,4,6-trimethylphenyl	74%	>97:3

Scheme 54

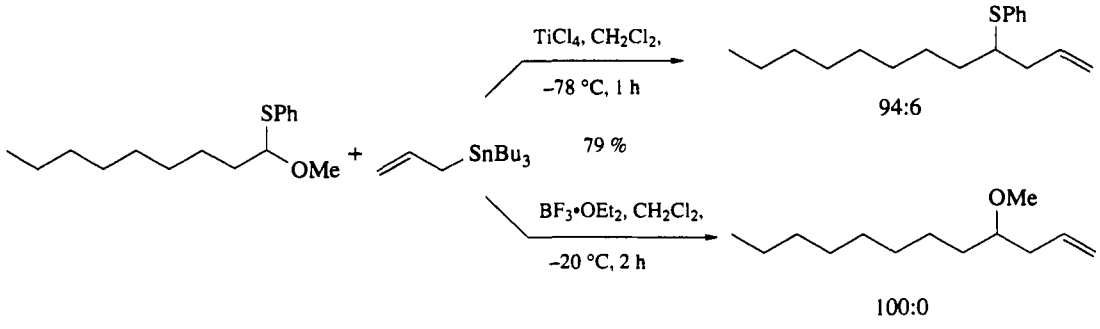


Scheme 55

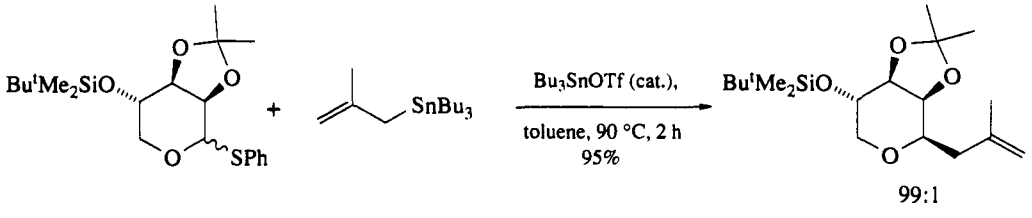
Allylstannanes are much better nucleophiles for dithioacetals than allylsilanes, and dimethyl(methylthio)sulfonium fluoroborate is a particularly good catalyst in this reaction. The reaction has been used tellingly in a macrocyclization (Scheme 56).[102] Monothioacetals also react with allylstannanes, with cleavage of either the carbon–oxygen or the carbon–sulfur bond, depending upon the choice of Lewis acid (Scheme 57).[103] Sugar thioacetals react in the same way (Scheme 58), but with the opposite anomeric stereoselectivity from that of the corresponding radical chain substitution.[104]



Scheme 56



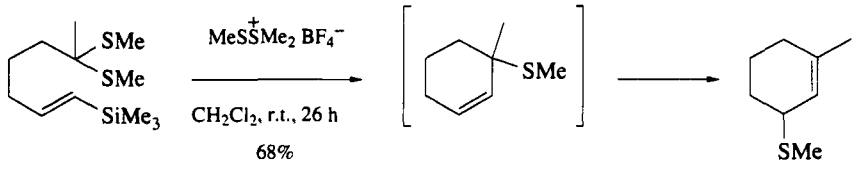
Scheme 57



Scheme 58

2.2.5.2 Vinylsilanes and Ethynylstannanes

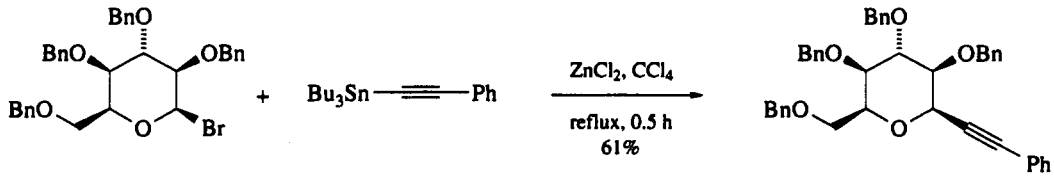
Vinylsilanes react with methoxymethyl chloride,[98] and with monothioacetals, cleaving the carbon–oxygen bond when molybdenum chloride is used as the catalyst.[105] Vinylsilanes also react intramolecu-



Scheme 59

larly with dithioacetals uniquely using dimethyl(methylthio)sulfonium fluoroborate as the Lewis acid, although the first-formed product suffers an allylic shift of the sulfur group (Scheme 59).[106]

Ethynylstannanes react with anomeric sugar bromides, and similar alkoxymethyl and alkylthiomethyl halides, to give propargyl ethers (Scheme 60).[107]



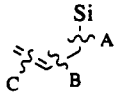
Scheme 60

2.2.6 SYNTHESES OF THE SILANES AND STANNANES

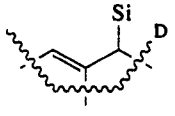
The methods described in this section are far from being a complete list. The growing importance of silylated and stannylated synthons in organic chemistry has led to the development of a great many syntheses, both controlled and uncontrolled, of which only a selection can be presented here to illustrate the range and the problems involved.

2.2.6.1 Allylsilanes

The methods to be summarized here can be divided into four main classes depending upon which bond (A–D) in the general structures (**61**) and (**62**) is made in the key step.



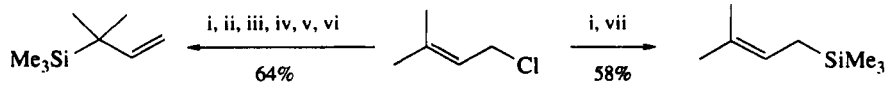
(**61**)



(**62**)

2.2.6.1.1 Syntheses based on disconnection A

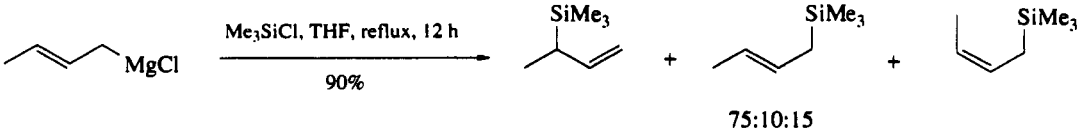
The most simple and direct route is the silylation of an allyl–metal reagent such as a Grignard or lithium reagent, a method that is also amenable to being carried out in the manner of a Wurtz reaction by treating an allyl halide and trimethylsilyl chloride with sodium.[77] The problem with this approach is that regiocontrol is not always possible. Thus the prenylsilanes (**63**) and (**64**) can be prepared selectively (Scheme 61),[27,108] but when the difference in the degree of substitution at the ends of the allyl system is less extreme, mixtures of regioisomers are usually produced (Scheme 62).[15,109]



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

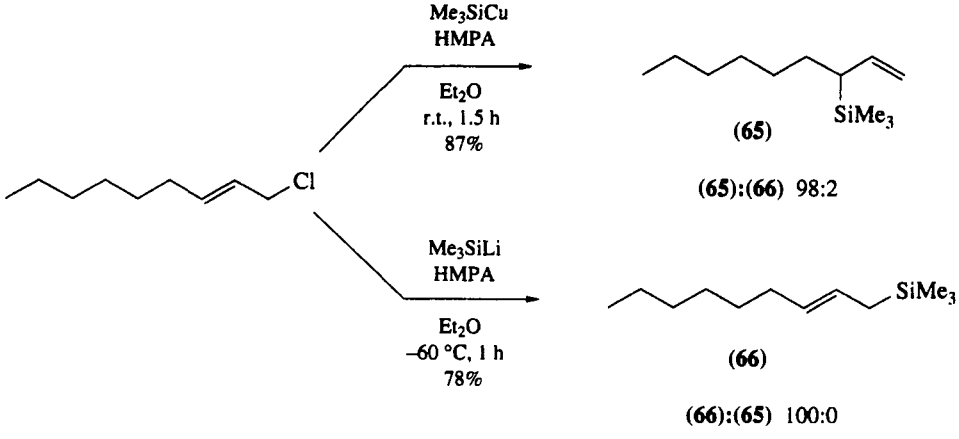
i, Mg; ii, $HSiCl_3$; iii, MeMgBr; iv, EtOH, H_2PtCl_6; v, HBF_4; vi, MeLi; vii, Me_3SiCl

Scheme 61

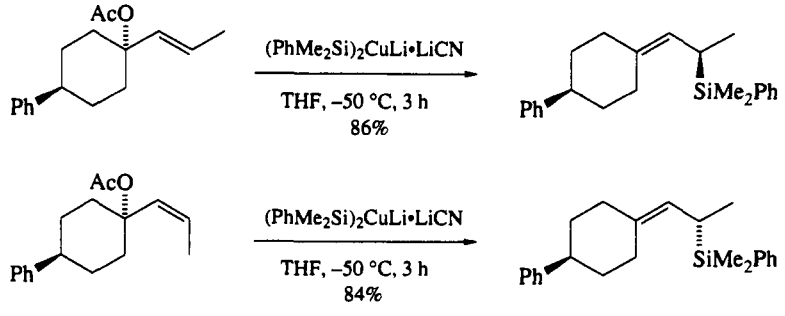


Scheme 62

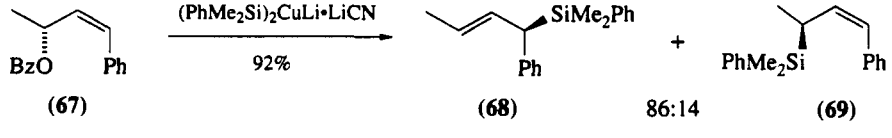
The umpolung version of this disconnection gives more regiocontrol, together with high levels of stereocontrol and a greater degree of compatibility with other functional groups that may be present. Allyl chlorides react with silyl–metal reagents with good regiocontrol when the allyl system is at the end of a chain (Scheme 63) to place the silyl group either at the more- (**65**) or at the less-substituted end (**66**) of the allyl system.[110,111] Silyl–cuprate reagents react with tertiary allylic acetates (Scheme 64) with complete regioselectivity to place the silyl group at the less-substituted terminus of the allyl system and with complete *anti* stereospecificity.[112] When the allyl ester is secondary at both ends (Scheme 65), the reaction (**67**) → (**68**) + (**69**) is still stereospecifically *anti*, and regioselectivity is moderately good when the double bond is *cis*, as it is in (**67**).[113] However, the regioselectivity is improved, and the stereospecificity changed to *syn* (**70**) → (**71**), when the corresponding urethane is used. Substituted allenes also react with the silyl cuprate reagent to give allylsilanes (Scheme 66).[114] When stereocontrol is not important and the silyl group is wanted at the less-substituted end of the allyl system, a simple method uses the allylic alcohol as its lithium alkoxide and hexamethyldisilane as the source of the nucleophilic silyl group (Scheme 67).[115]

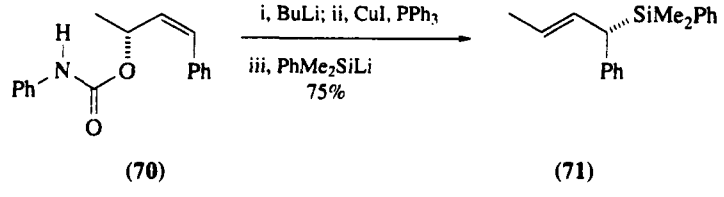


Scheme 63

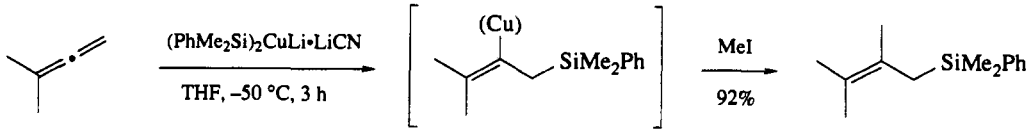


Scheme 64

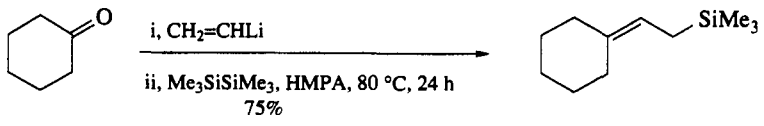




Scheme 65

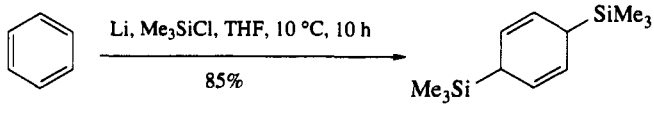


Scheme 66

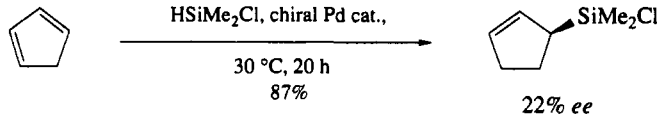


Scheme 67

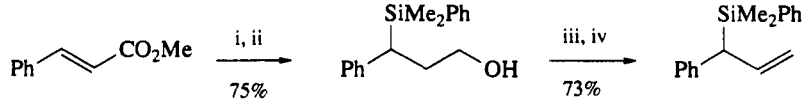
Other versions of disconnection A are (i) the sila-Birch reduction of aromatic rings and dienes (Scheme 68);[116] (ii) an impractical but intriguing [2,3] sigmatropic rearrangement following the interaction of a silylene with an allylic ether;[117] (iii) the hydrosilylation of dienes, a reaction that can be made enantiocontrolled using a chiral, enantiomerically enriched catalyst (Scheme 69);[118] and (iv) the reduction and dehydration of β-silyl esters, in a sequence that guarantees that the silyl group is placed at the more-substituted end of the allyl system (Scheme 70).[119]



Scheme 68



Scheme 69



i, $(PhMe_2Si)_2CuLi•LiCN$; ii, $LiAlH_4$; iii, $o\text{-}O_2NC_6H_4SeCN$, Bu_3P; iv, H_2O_2

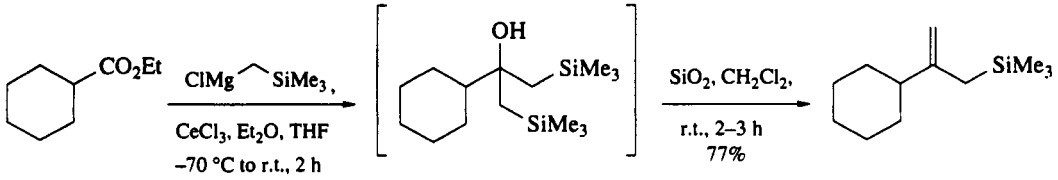
Scheme 70

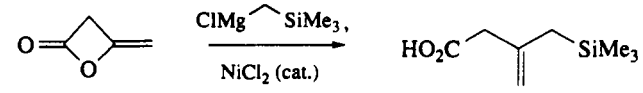
2.2.6.1.2 Syntheses based on disconnection B

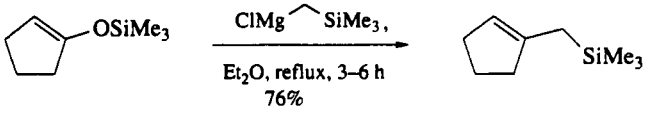
The most common version of this approach is the catalyzed reaction between the trimethylsilylmethyl Grignard reagent and various substrates, such as esters, enol derivatives, or vinyl halides (Scheme 71).[120–123] The same approach can be used to prepare enantiomerically pure allylsilanes using an appropriate catalyst (Scheme 72).[124] Trimethylsilylmethyl cuprate reagents react with alkynes by *syn* carbocupration and the products can be treated further with electrophiles (Scheme 73).[125] A quite different approach starting with an alkyne is to use a rearrangement set off by hydroalumination (Scheme 74).[126]

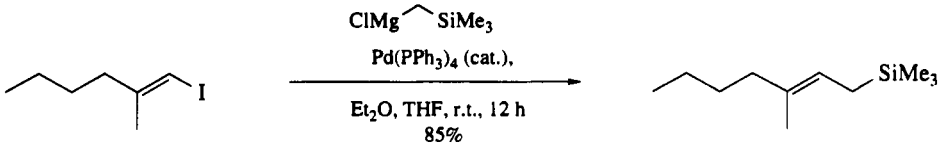
2.2.6.1.3 Syntheses based on disconnection C

The most simple of this category of syntheses is that based on the Wittig reaction (Scheme 75).[127] This method is limited by the difficulty of synthesizing phosphoranes substituted on the silicon-bearing carbon, by the low yields obtained when the phosphorus-bearing carbon is substituted, by the low yields ob-

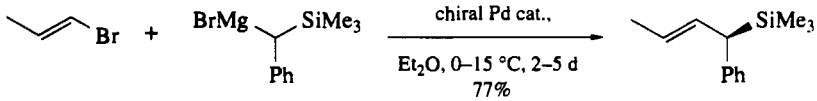




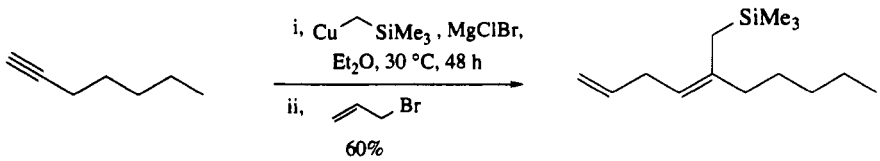




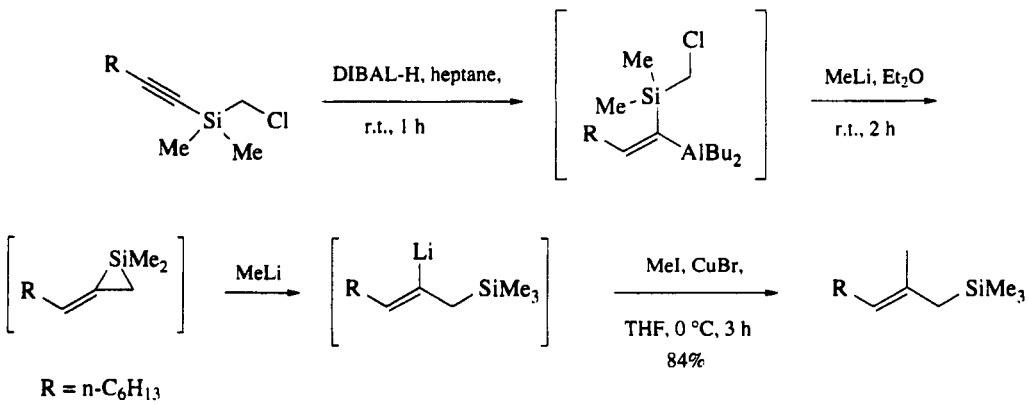
Scheme 71



Scheme 72



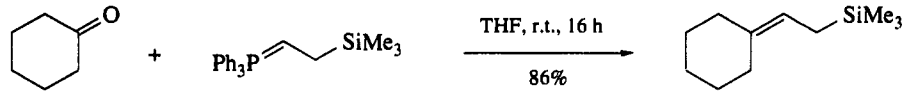
Scheme 73



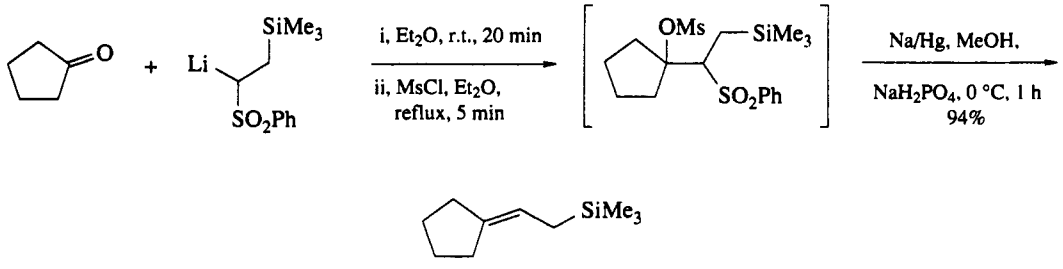
Scheme 74

tained with certain ketones such as cyclopentanones, and by an alternative reaction taking place in some cases to give the silyl ether of an allylic alcohol.[128] The reaction with aldehydes however can be very useful and it is possible to make it highly selective for the (*Z*)-allylsilane.[129]

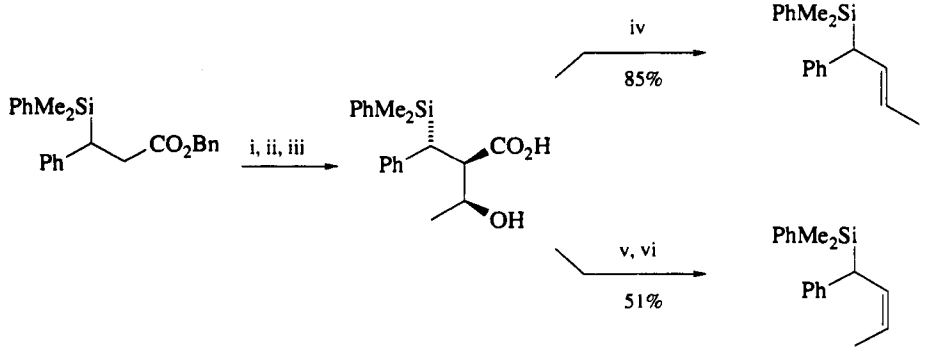
Methods for overcoming these difficulties include the reaction in Scheme 64 and the corresponding Julia (Scheme 76)[130] or Krief–Reich[131] alkene syntheses, which are all selective for the synthesis of (*E*)-allylsilanes. These methods use phosphorus, sulfur or selenium as the electrofugal group; another possibility is to use electrofugal carbon in a decarboxylative elimination, which can be carried out stereospecifically either *anti* or *syn* (Scheme 77).[132]



Scheme 75



Scheme 76

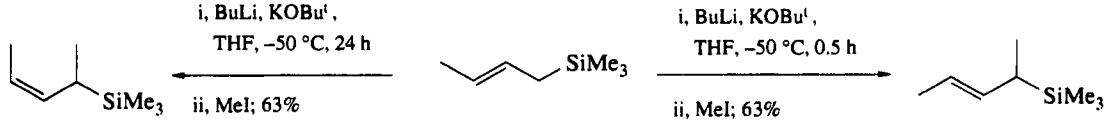


i, LDA, THF; ii, MeCHO; iii, H_2, Pd; iv, $Me_2NCH(OMe)_2$, reflux; v, $PhSO_2Cl$, Py; vi, collidine, reflux

Scheme 77

2.2.6.1.4 Syntheses based on disconnection D

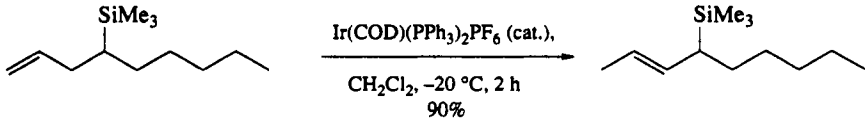
A different approach is to add substituents to or manipulate substituents on an existing allyl- or propargyl-silane system. Thus propargyltrimethylsilane itself can be alkylated at the terminus and the triple bond reduced with Brown's nickel catalyst[133] or by hydroalumination–protonation,[134] both of which give the (*Z*)-allylsilane. Alternatively, zirconium-catalyzed carboalumination of propargylsilanes introduces more substituents onto the allyl framework.[123] Allylsilane anions show some selectivity for alkylation α to the silyl group, and the geometry of the double bond can be controlled by using either the kinetic or the thermodynamic allyllithium intermediate (Scheme 78).[135]



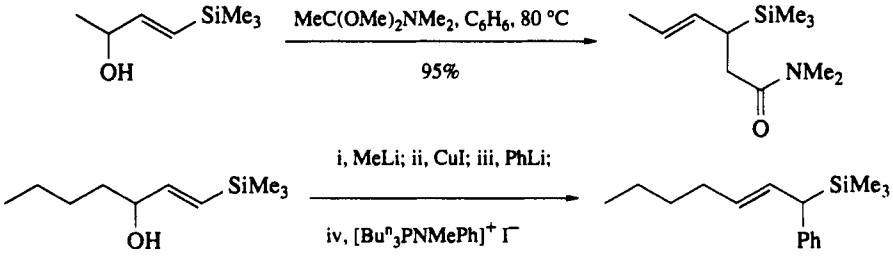
(Z):(E) 90:10

Scheme 78

Another approach is to move the double bond into the allylic position from somewhere else in the molecule. Thus, transition metal catalyzed isomerization of alkenes containing a remote silyl group brings a double bond into the allylic position and largely causes it to stop there (Scheme 79).[136] Presumably retrohydrometallation is slow when the hydrogen is adjacent to the silyl group, causing the allylsilane to accumulate. Diels–Alder reactions on butadienylsilanes give 3-silylcyclohexenes,[137] and allylic rearrangements convert some silicon-containing allylic alcohols into (*E*)-allylsilanes (Scheme 80).[138,139]



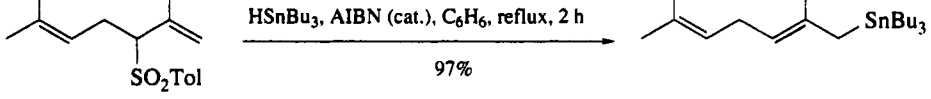
Scheme 79



Scheme 80

2.2.6.2 Allylstannanes

Allylstannanes are made by very similar methods to those used for allylsilanes, where the same problems arise when unsymmetrical allyl nucleophiles are treated with tin halides.[24,110] To solve this problem, there are tin equivalents of the reactions in Schemes 63, 65,[110,140] 69,[141] 70,[142] 75[143] and 77.[144] Specific to allylstannanes is a radical-chain sequence (Scheme 81).[88]

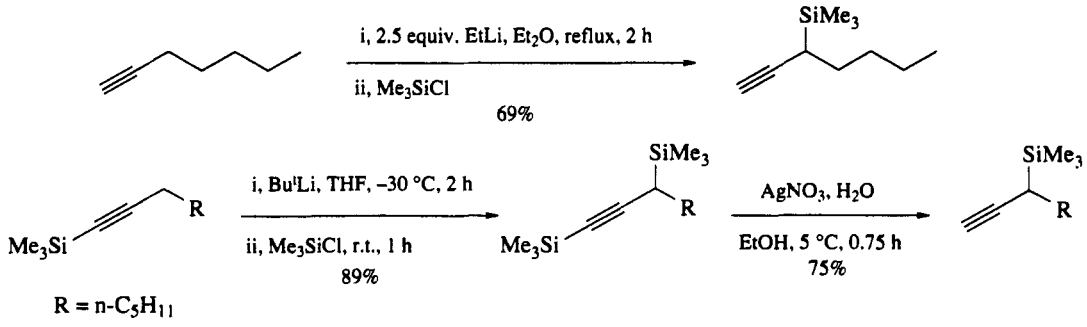


Scheme 81

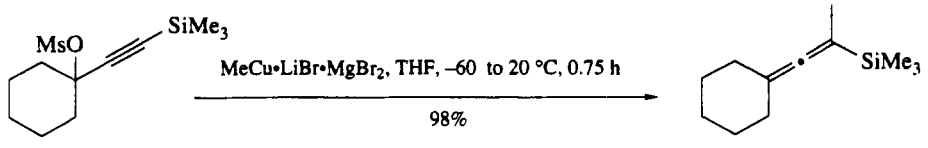
2.2.6.3 Allenyl- and Propargyl-silanes and -stannanes

The synthesis of allenyl- and propargyl-silanes and -stannanes is generally carried out by silylation or stannylation of the appropriate lithium or Grignard reagent. This method naturally runs into the same problem as in the regiocontrolled synthesis of allylsilanes, namely the control of which end of the conjugated system the silyl or stannyl group attaches itself to. In this case one regioisomer is the allenyl system and the other the propargyl. For terminal propargylsilanes, one simple solution to this problem is to use the commercially available parent propargyltrimethylsilane and to join it on to the rest of the molecule.[133] For propargylsilanes substituted on the silicon-bearing carbon, the starting material can be prepared by regioselective silylation of a terminal alkyne (Scheme 82), in which very little allenylsilane is formed, followed by desilylation.[145] For allenylsilanes, the standard synthesis is to start from a silylated propargyl alcohol and to introduce a second carbon group using cuprate chemistry (Scheme 83).[146] Allenylstannanes can be prepared using a similar reaction (Scheme 84)[147] and there are also syntheses based on silyl- and stannyl-cuprate reagents reacting with propargyl alcohol derivatives.[112,148] For terminal allenylsilanes, there is a good route from silylated ethynyl ketones (Scheme 85).[91]

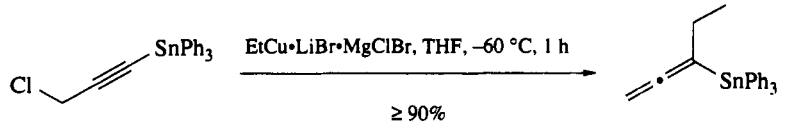
A radical chain reaction is again available in the tin series but not in the silyl, and it has been used in the synthesis of the parent allenylstannane (Scheme 86).[149]



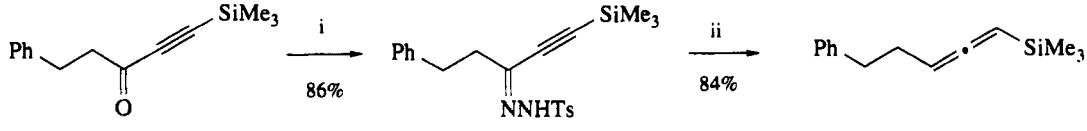
Scheme 82



Scheme 83

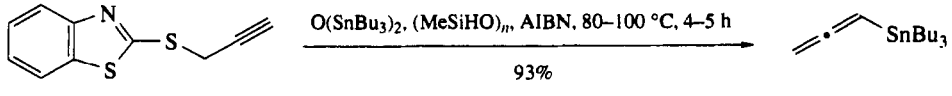


Scheme 84



i, $TsNHNH_2$; ii, 8 equiv. $NaBH_3CN$, DMF, cyclohexane, pH 1–2, 40–90 °C

Scheme 85

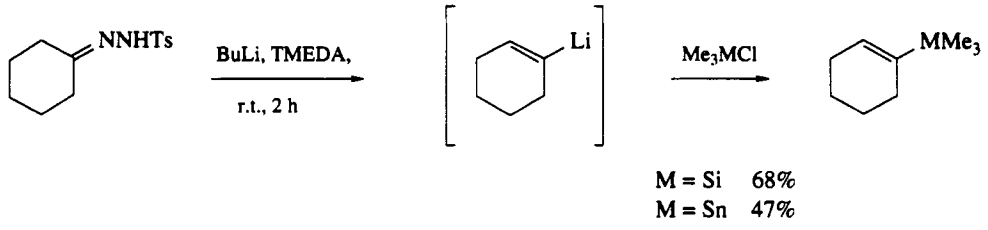


Scheme 86

2.2.6.4 Vinyl-silanes and -stannanes

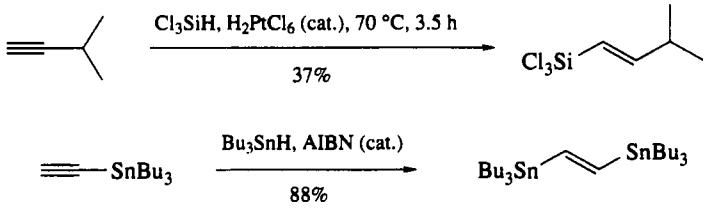
Vinyl-silanes and -stannanes can most easily be made from the corresponding vinyllithium or vinyl Grignard reagents by treating them with a silyl or tin(IV) chloride, but there is usually little point in exchanging the strongly electropositive metals, lithium or magnesium, for the much less electropositive metals, silicon or tin, when aldehydes or ketones are the electrophiles. However, this method is useful when it provides an opportunity for purification, as when the vinyllithium species are made by a Shapiro reaction (Scheme 87).[150] An umpolung version of this route to vinylstannanes is the combination of the enol triflate of the ketone reacting with a trimethyltin–magnesium reagent.[151]

Entirely different in concept are several useful methods based on alkynes. Hydrosilylation of alkynes, generally catalyzed by chloroplatinic acid and hydrostannation, generally in a radical chain process, give vinylsilanes and vinylstannanes (Scheme 88).[152] Catalyzed hydrosilylation is stereoselectively *syn*, but radical chain hydrostannylation is stereoselectively *anti* only when under kinetic control. Under thermodynamic control, as when there is a small excess of tin hydride present, the reaction is often stereoselectively *syn*. Alternatively, the silyl or stannyl groups can be introduced using the corresponding cuprate

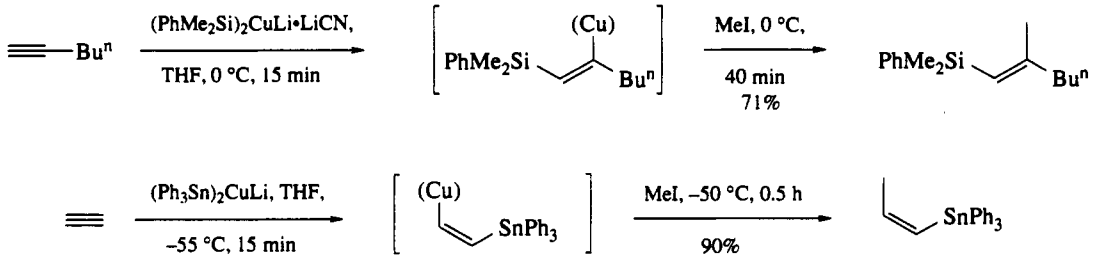


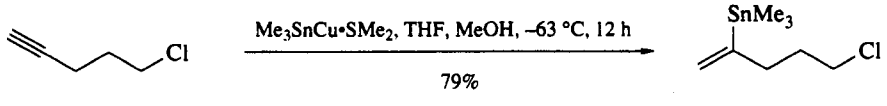
Scheme 87

reagents in reactions that are usually stereoselectively *syn* (Scheme 89).[153] Similar reactions, both for silicon[154] and tin,[151] can be carried out using catalytic quantities of transition metals in place of the stoichiometric use of copper(I). A silyl group can be attached to a terminal alkyne and the other groups added to the triple bond using such methods as hydroalumination (Scheme 90)[155] or hydroboration.[156] The alkyl group can be attached by rearranging it from boron in an alkynylborate, either with the silyl group already in the molecule (**72**)[157] or with a silyl halide as the electrophile initiating the rearrangement (**74**) → (**75**) (Scheme 91),[158] the two methods being stereochemically complementary. The boron atom in the vinylboranes (**73**) and (**75**) can be replaced by a proton or by other groups.

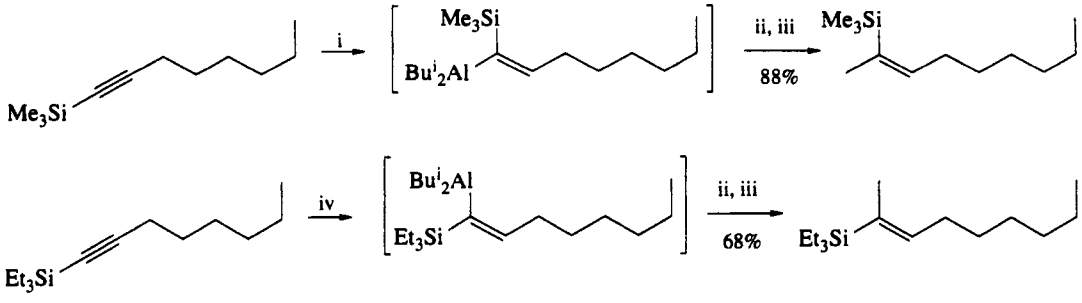


Scheme 88





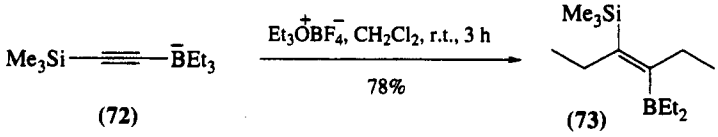
Scheme 89



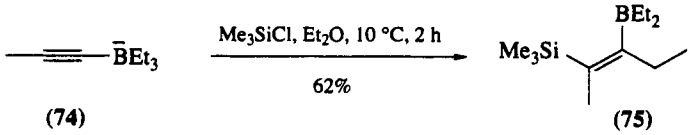
i, DIBAL-H, heptane, ether, r.t., 17 h; ii, MeLi; iii, MeI, r.t., 20 h; iv, DIBAL-H, heptane, r.t., 20 h

Scheme 90

Another pair of stereochemically complementary routes to mid-chain vinylsilanes starts from the allylic alcohol (**76**) made by combining the α-trimethylsilylvinyllithium reagent with the appropriate aldehyde. Cuprate chemistry allows the other chain to be attached with either stereochemical outcome (Scheme 92) and the route is also amenable to the synthesis of tetrasubstituted vinylsilanes, simply by starting with a ketone in place of the aldehyde.[159]

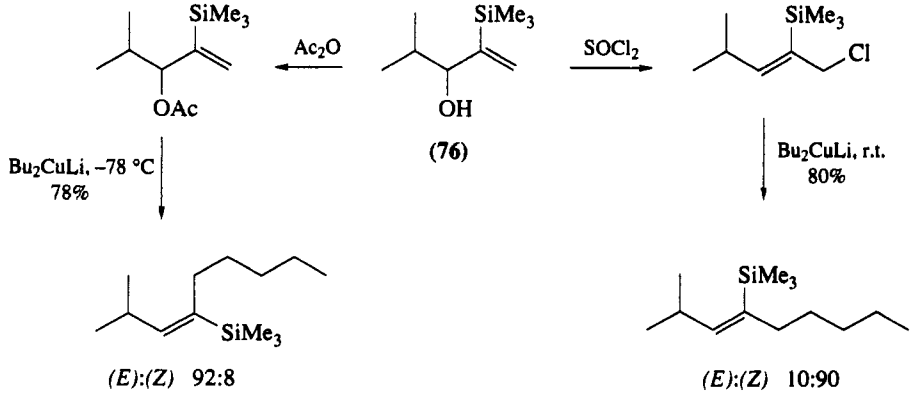


(72) (73)



(74) (75)

Scheme 91



(76)

(E):(Z) 92:8 *(E):(Z)* 10:90

Scheme 92

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2.3
Formation and Addition Reactions of Enol Ethers

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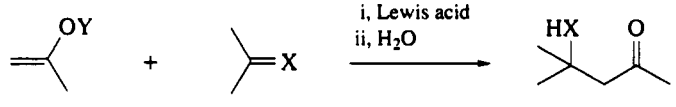
2.3.1 INTRODUCTION

This chapter is concerned with the reactions of enol ethers with carbonyl compounds as illustrated in Scheme 1. The enol ethers considered include alkyl, silyl, germyl and stannyl ethers, and to a small extent enol esters. The carbonyl compounds encompass aldehydes, ketones, esters and their functional equivalents. Overall, the reaction depicted in Scheme 1 is similar to the classical aldol and related condensations discussed in Part 1 of this volume. However, in contrast to the basic conditions inherent in



Y = alkyl, acyl, silyl, germyl or stannyl; X = O or equivalent

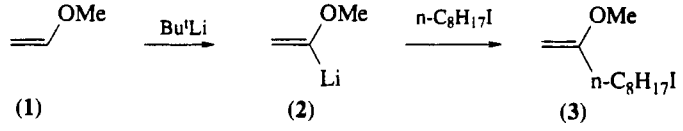
Scheme 1

enolate anion chemistry, the reactions of enol ethers with carbonyl compounds are usually carried out under neutral or acidic conditions. Their chemistry, and consequently their synthetic utilities, often complement each other.

2.3.2 PREPARATION OF ENOL ETHERS

2.3.2.1 Formation of Alkyl Enol Ethers and Enol Esters

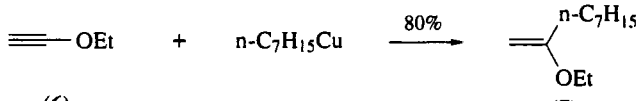
Alkyl enol ethers can be conveniently prepared by the alkylation of α-methoxyvinyllithium and related metallated enol ethers.[1] In a typical example, methyl vinyl ether (**1**) is converted by *t*-butyllithium to give α-methoxyvinyllithium (**2**). Reaction of (**2**) with octyl iodide gives the enol ether (**3**). Metallation of methyl propenyl ether (**4**) and methyl allenyl ether (**5**) can be similarly executed.[2]



(**1**) (**2**) (**3**)

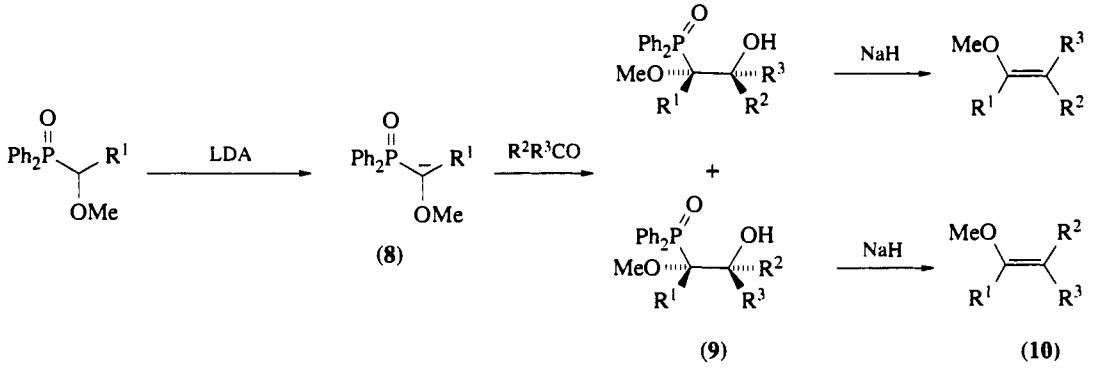
(**4**) (**5**)

Carbometallation of alkynic ethers with organocopper reagents can also give enol ethers.[3] Even though the triple bond in (**6**) is unsymmetrically substituted, carbometallation occurs regioselectively to give compound (**7**), presumably due to the directing effect of the ethoxy group. Regioselection is lost when the other carbon of the alkyne bears an alkyl group.



(**6**) (**7**)

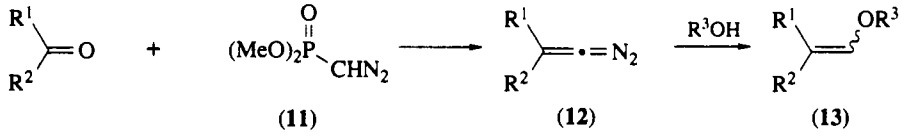
Alkenation of carbonyl compounds can be used as a general method for the synthesis of enol ethers. The Horner–Wittig reaction of the phosphorus-stabilized carbanion (**8**) with aldehydes or ketones gives the adducts (**9**), which on heating eliminate to give the enol ethers (**10**) as a mixture of (*E*)- and (*Z*)-isomers. Since the two diastereomeric adducts (**9**) can be separated and the elimination reaction is stereospecific, this method can be used to prepare the individual geometrical isomers[4] of (**10**) according to Scheme 2.



(**8**) (**9**) (**10**)

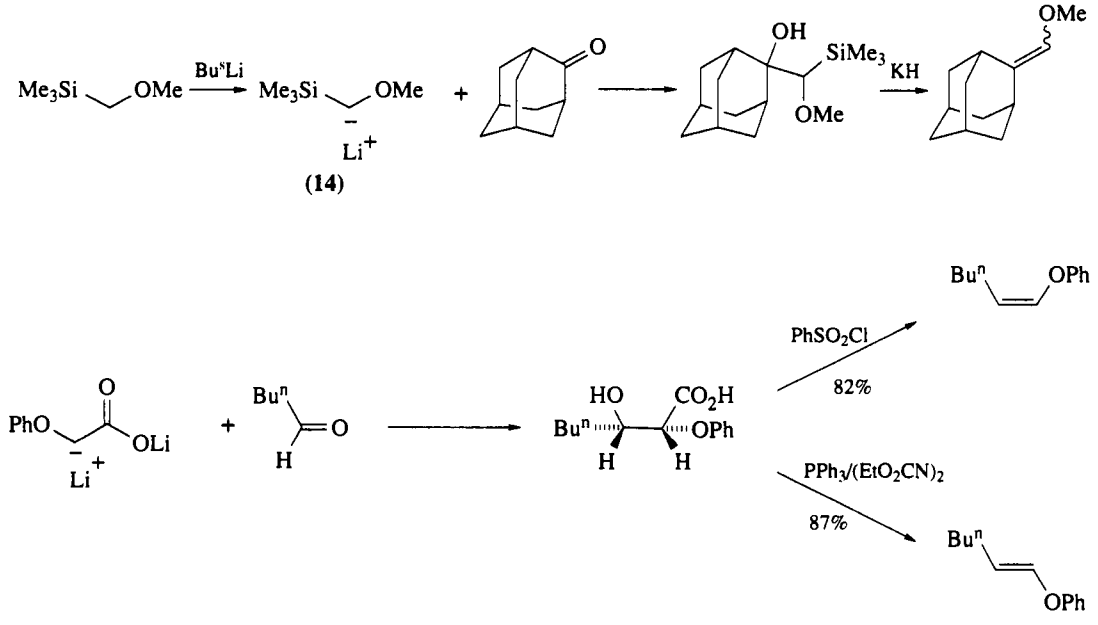
Scheme 2

Alternatively, Horner–Wittig reaction of diazomethylphosphonate (**11**) with carbonyl compounds gives, presumably, the diazoalkenes (**12**). Replacement of the diazo group *in situ* by an alkoxy group gives the enol ethers (**13**; Scheme 3).[5]



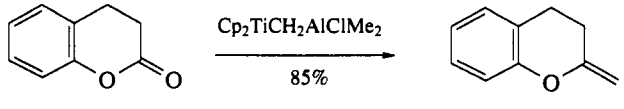
Scheme 3

Peterson alkenation of carbonyl compounds with trimethylsilylmethoxymethyl carbanion (**14**) can also give enol ethers.[6,7] An example is the reaction of (**14**) with adamantanone. Another method of alkene synthesis is the elimination of CO_2 and H_2O from a β-hydroxycarboxylic acid. If the carboxylic acid is substituted by an α-alkoxy group, the reaction can be used for the synthesis of enol ethers, as illustrated in Scheme 4.[8]



Scheme 4

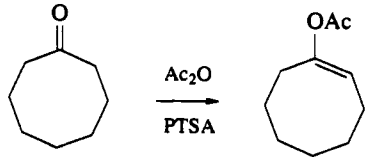
The carbonyl group of an ester function can be converted to the corresponding methylene compound using Tebbe's reagent. The reaction can thus be considered as a general method of enol ether synthesis.[9] An example of this reaction is given in Scheme 5.[96] The same conversion can be achieved by reagents prepared from the reduction of 1,1-dibromoalkanes with zinc and $TiCl_4$ in the presence of TMEDA.[10]



Scheme 5

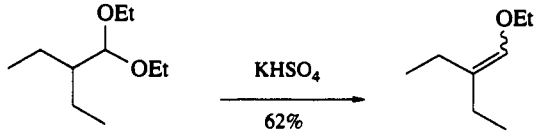
Alkylation of enolate anions usually gives *C*-alkylation and is therefore not suitable for the preparation of enol ethers. The exception is when triethyloxonium tetrafluoroborate is used as the alkylating agent in a dipolar aprotic solvent.[11] *O*-Alkylation can be regioselectively achieved if the enolate anion is derived from acetoacetate or a similar compound. On the other hand, *O*-acylation of enols or enolate anions is quite common. Enol esters can therefore be prepared readily from the parent carbonyl compounds. For

example, cyclooctanone (**15**) is converted by heating with acetic anhydride and *p*-toluenesulfonic acid to cyclooctenyl acetate (**16**).[12]

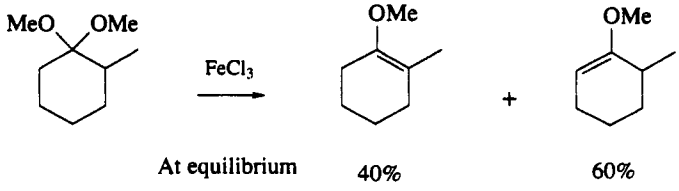


(**15**) (**16**)

Conversion of aldehydes and ketones to the corresponding acetals followed by elimination of an alcohol moiety is a general method to prepare enol ethers.[13] The elimination is usually conducted under mildly acid-catalyzed conditions as in the preparation of (**18**) from (**17**). When the ketone is unsymmetrically substituted, good regiocontrol of the enol ether formed is difficult to achieve (Scheme 6).[14]

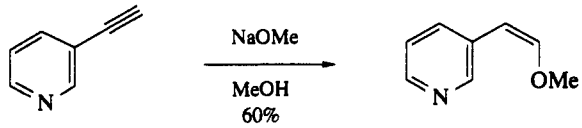


(**17**) (**18**)



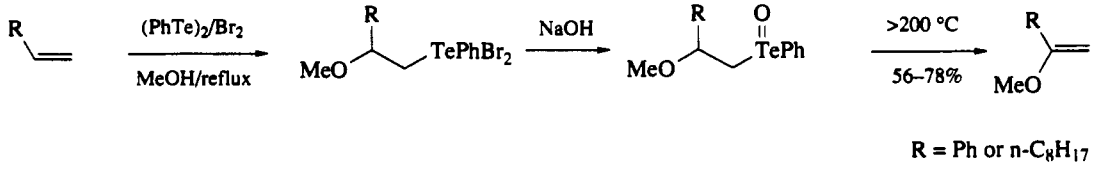
Scheme 6

Addition of an alcohol to a triple bond is another way to obtain an enol ether. An example is the conversion of *m*-ethynylpyridine (**19**) to β-methoxyvinylpyridine (**20**). Addition, in this particular case, is stereoselective to give the (*Z*)-isomer.[15]



(**19**) (**20**)

Oxytelluration of terminal alkenes followed by elimination of the tellurium moiety gives enol ethers as shown in Scheme 7.[16]



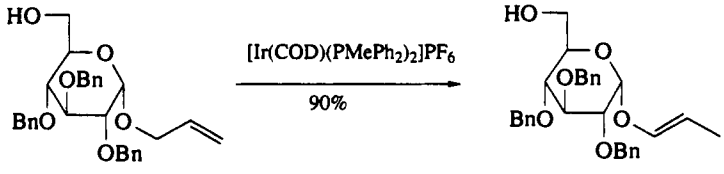
R = Ph or n-C_8H_{17}

Scheme 7

A very useful method to prepare carbocyclic enol ethers is the Birch reduction of aryl ethers.[17] In the simplest example, metal ammonia reduction of methoxybenzene gives methoxycyclohexadiene (**21**). The reaction has been applied to numerous aryl ethers of complex structures.

(21)

The isomerization of allyl ethers with a transition metal catalyst, though normally used as a method of deprotection of the allyl group,[18,19] can be considered as a convenient method of enol ether synthesis. The conversion of (22) to the propenyl ether (23) serves as an example.[20]



(22) (23)

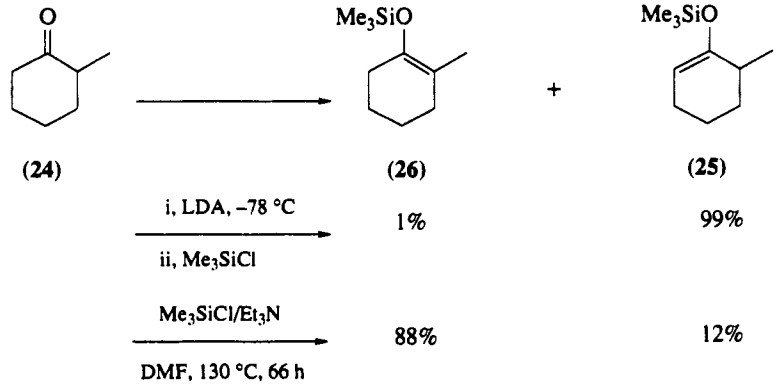
2.3.2.2 Formation of Enol Silyl Ethers and Silyl Ketene Acetals

Enol silyl ethers and silyl ketene acetals have become important synthetic reagents in organic synthesis. Their chemistry has been the subject of a number of recent reviews.[21]

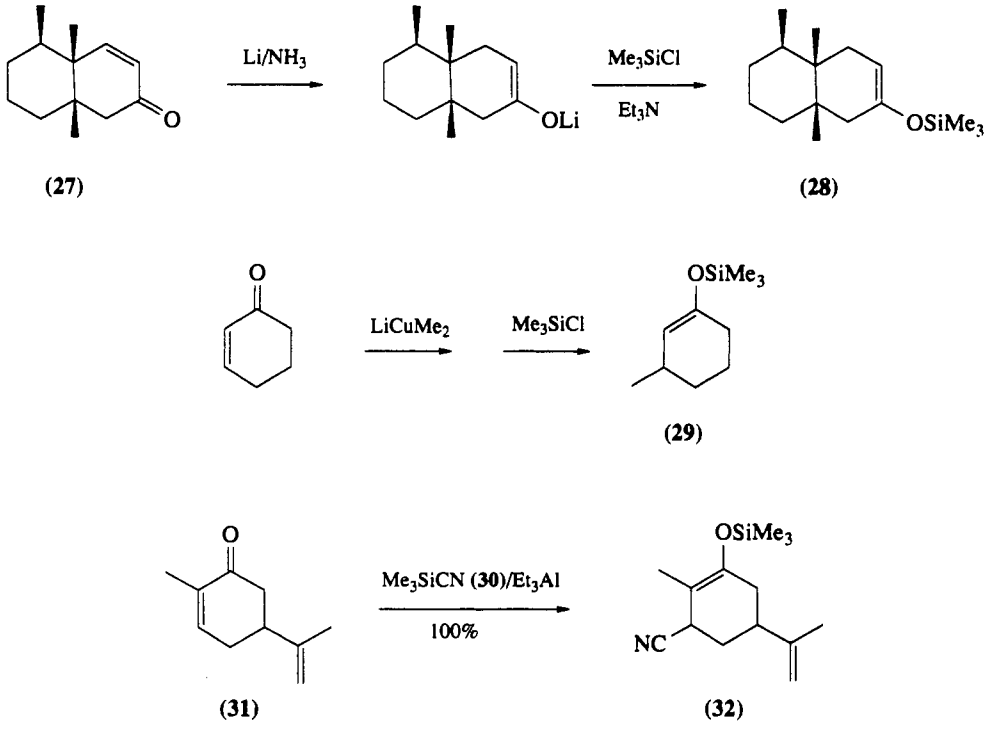
2.3.2.2.1 Enol silyl ethers of aldehydes and ketones

Enol silyl ethers can be prepared readily from the parent carbonyl compounds by silylation of the corresponding enolate anions.[22] Particularly useful is the observation[23] that with unsymmetrical ketones it is often possible to generate the less-substituted enol silyl ether under conditions of kinetic control, and the more-substituted enol silyl ether by equilibration, giving thermodynamic control. Using 2-methylcyclohexanone (24) as an example, generation of the enolate anion with LDA followed by quenching with trimethylchlorosilane gives the kinetic enol silyl ether (25), whereas treatment of (24) with triethylamine/trimethylchlorosilane in DMF at 130 °C for 66 h gives the more stable enol silyl ether (26; Scheme 8).

Regiospecific synthesis of enol silyl ethers can also be achieved from enones either by reductive silylation or by 1,4-addition of the conjugated system. Thus, Li/NH_3 reduction of the decalone (27) and silylation give the enol silyl ether (28).[24] Similarly, addition of lithium dimethylcuprate to cyclohexenone[25] followed by silylation gives the enol silyl ether (29). Trimethylsilyl cyanide (30) normally adds 1,2 to conjugated ketones (*e.g.* carvone, 31). However, in the presence of trialkylaluminum, 1,4-addition takes place to give the enol silyl ether (32; Scheme 9). The same overall transformation can be accomplished by diethylaluminum cyanide and trimethylchlorosilane.[26]

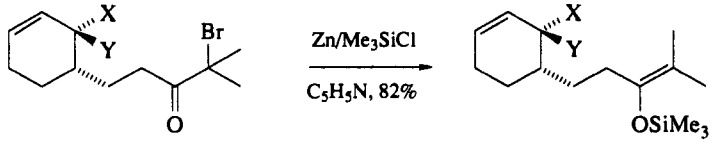


Scheme 8



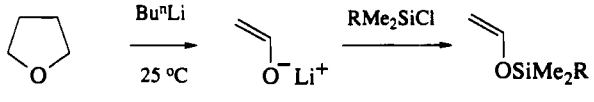
Scheme 9

Reductive silylation of α-halo ketones is synthetically useful if the halo ketone can be obtained regiochemically pure to begin with. An example is the zinc/TMS-Cl reaction with (**33**).[27]



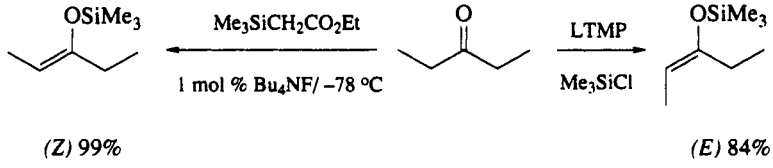
(**33**) X = H; Y = OAc
X = OAc; Y = H

Conversion of aldehydes into the corresponding enol silyl ethers can be accomplished with a number of enolization–silylation reagents: KH/DME–TMS-Cl/Et_3N,[28] TMS triflate with amines[29] or bis(trimethylsilyl)acetamide[30] among them. In the specific case of siloxyethylene, it has been prepared by the fragmentation of tetrahydrofuran with butyllithium and silylation of the resulting enolate anion (Scheme 10).[31]

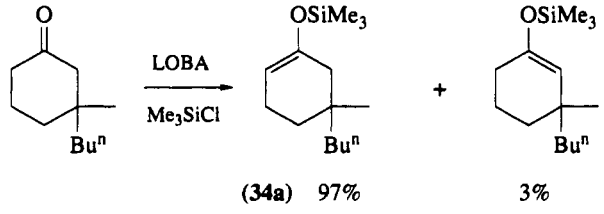


Scheme 10

Generation of enol silyl ethers from acyclic ketone precursors can be accomplished using the same kind of reagents. Depending on the reaction conditions, stereoselective formation of either the (*E*)- or the (*Z*)-isomer of the enol silyl ethers has been reported (Scheme 11).[32] An *in situ* method of generating the enolate anion with lithium dialkylamides in the presence of trimethylchlorosilane leads to enhanced selection for the kinetically preferred enol silyl ether (*e.g.* **34a**).[33] Lithium *t*-octyl-*t*-butylamide (LOBA) is

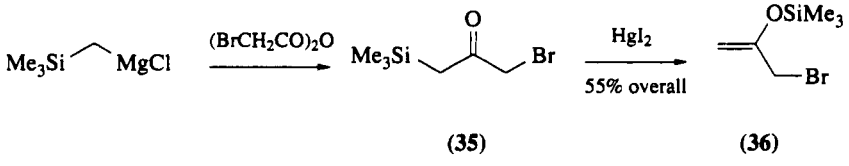


Scheme 11



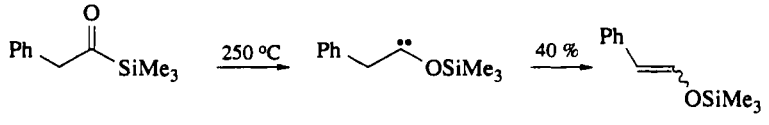
shown to be superior to LDA in the regioselective generation of enolates and in the stereoselective formation of (*E*)-enolates in this *in situ* method.

Rearrangement of the α-silyl ketone (**35**) has been used to prepare the halo-substituted enol silyl ether (**36**; Scheme 12).[34] Normal enolization of α-halo ketones would have given the other regioisomers.

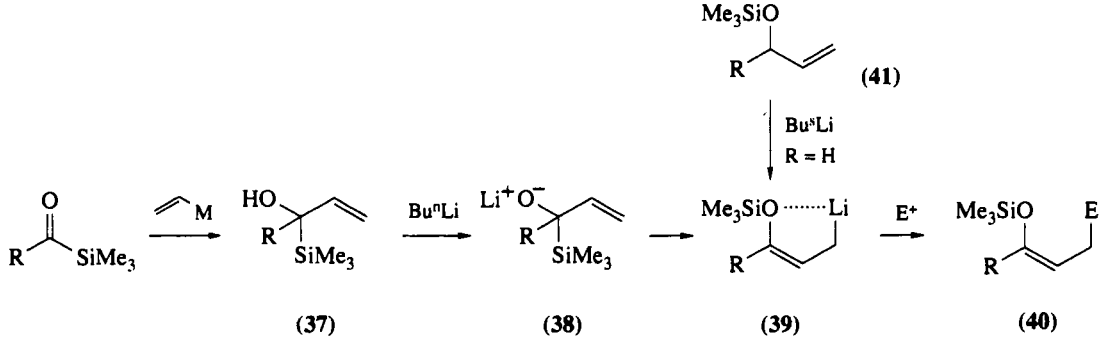


Scheme 12

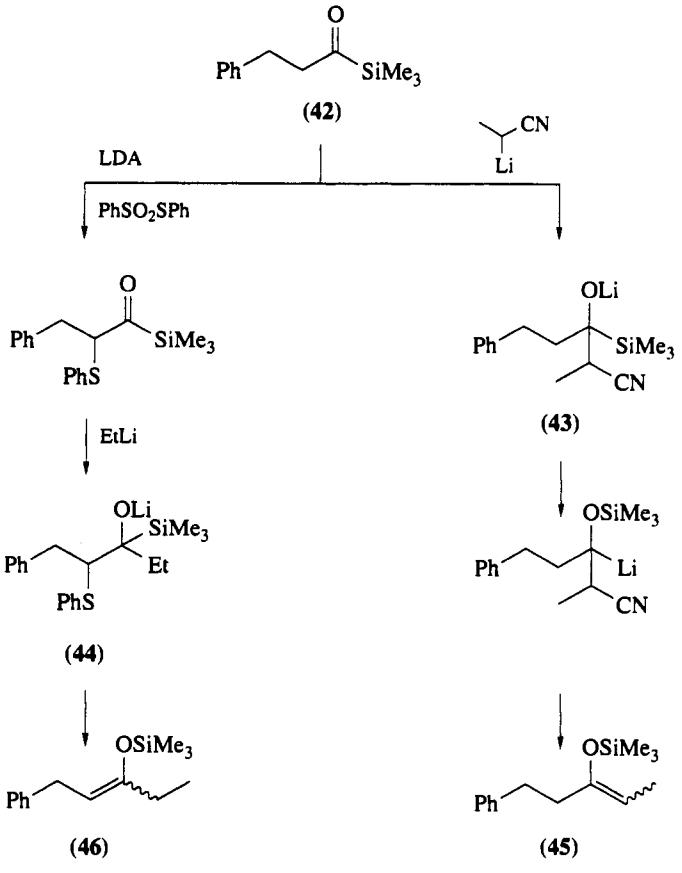
Rearrangement of acylsilanes under pyrolytic or photolytic conditions can give enol silyl ethers, presumably *via* α-siloxycarbenes (Scheme 13).[35] Reactions of acylsilanes with vinyl or alkynyl carbanions give the adduct α-silylcarbinols (**37**). Treatment of (**37**) with Bu^{n}Li gives the oxyanions (**38**), which can undergo the Brook rearrangement to give the siloxycarbanions (**39**). Quenching of (**39**) with electrophiles leads eventually to the enol silyl ethers (**40**; Scheme 14).[36] The same siloxycarbanions (**39**) can be generated from allyloxysilanes (**41**).[37] The enol silyl ethers (**40**) formed have the (*Z*)-stereochemistry be-



Scheme 13



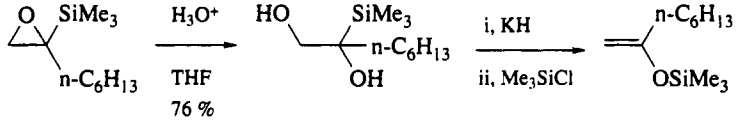
Scheme 14



Scheme 15

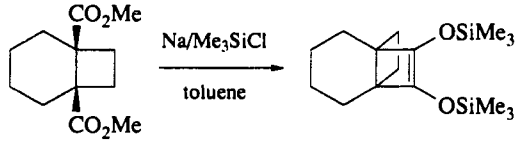
cause of the internal chelation present in (**39**). Alternatively, acylsilane (**42**) can be converted to the silyloxyanions (**43**) and (**44**). Similar rearrangement followed by elimination reaction gives regioselectively the enol silyl ethers (**45**) and (**46**) respectively as illustrated in Scheme 15. In these cases, the stereochemistry of the double bond is not controlled and a mixture of geometric isomers is formed.[38]

Epoxysilanes, which can be obtained by epoxidation of vinylsilanes or other methods, can rearrange to enol silyl ethers as shown in Scheme 16.[39]



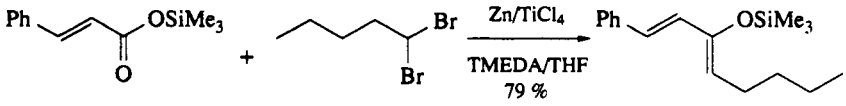
Scheme 16

Acyloin condensations of esters conducted with TMS-Cl and sodium in toluene give 1,2-bis(trimethylsilyloxy)alkenes.[40] In general, the silylacyloin reaction provides higher yields than the conventional acyloin reaction and is particularly useful for the preparation of cyclic enol silyl ethers.[41] The synthesis of compound (**47**) serves as an illustration.



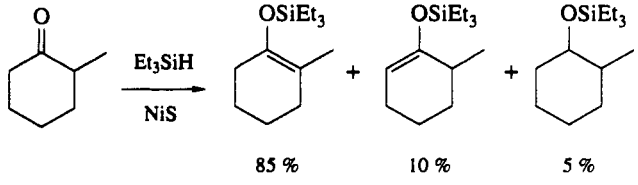
(**47**)

Alkylidenation of the carbonyl group of silyl esters with a reagent derived from the reduction of 1,1-dibromoalkanes with zinc/$TiCl_4$ gives (*Z*)-silyl enol ethers in good yield (*e.g.* **48**).[42]

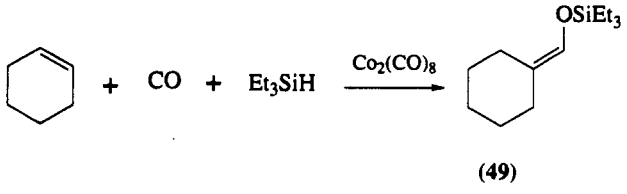


(48)

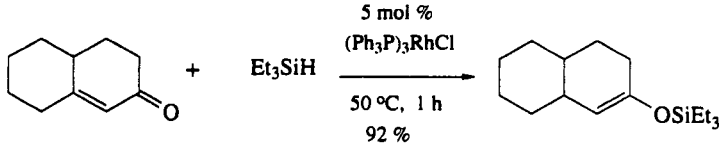
Silanes normally reduce aldehydes or ketones under catalytic conditions to the silyl ethers. However, with certain catalysts such as nickel sulfide,[43] $Co_2(CO)_8$,[44] or $(Ph_3P)_3RhCl$,[45] carbonyl compounds react with silanes to yield an equilibrium mixture of enol silyl ethers (Scheme 17). In a similar vein, the silyl–hydroformylation reaction of cycloalkenes with CO and silanes may be a practical way to prepare enol silyl ethers.[46] An example is the preparation of compound (**49**). Catalytic 1,4-hydrosilation of α,β-unsaturated ketones or aldehydes gives the corresponding enol silyl ethers. The reaction is similar to the reductive silylation referred to previously, but the reaction conditions are neutral and milder. The formation of the enol silyl ether (**50**) is outlined below.[47]



Scheme 17

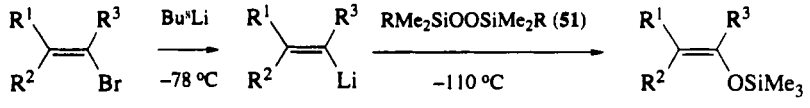


(49)



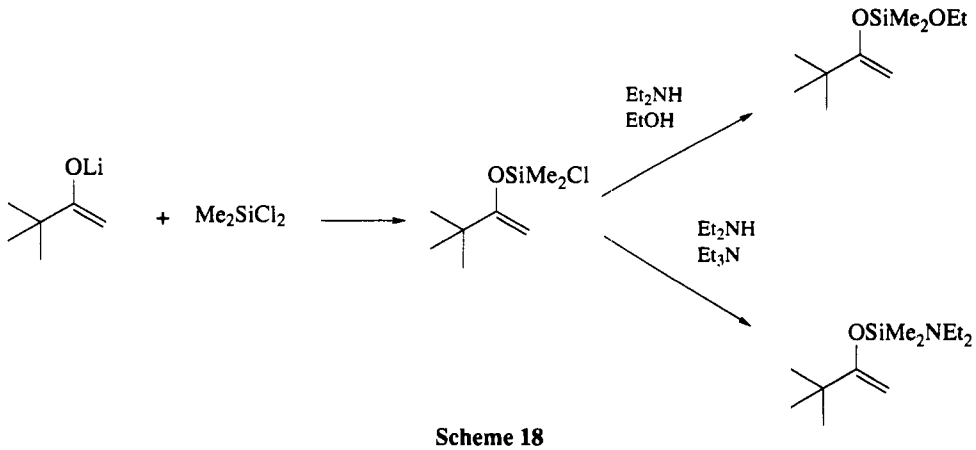
(50)

Oxidation of (*E*)- or (*Z*)-vinyllithium with silyl peroxide (**51**) at −110 °C affords enol silyl ethers in modest to good yield.[48] The reaction proceeds with retention of stereochemistry at the double bond.



R = Me or Bu^t

Recently, enol silyl ethers that bear chloro, alkoxy or amino groups on the silicon have been prepared (Scheme 18).[49]

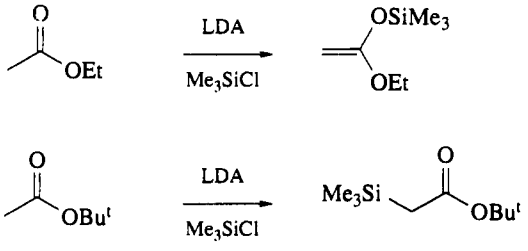


Scheme 18

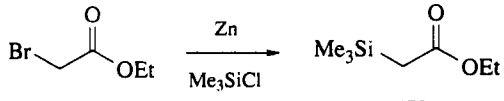
2.3.2.2.2 Silyl ketene acetals and related compounds

In principle, silyl ketene acetals can be prepared from the parent ester compounds using the same reagents as discussed above for the synthesis of enol silyl ethers. An important difference is the fact that *C*-silylation can be an effective competition in the silylation of the ester enolate anion (Scheme 19). The extent of *O- versus C*-silylation depends on the nature of the ester R group, the substitutent in the α-carbon, the structure of the silylating agent and the reaction conditions.[50] With TMS-Cl, silylation of the lithium ester enolates of methyl or ethyl acetate gives predominantly *O*-silylation. Ethyl esters of higher acids give almost exclusively *O*-silylation as well. *t*-Butyl esters, on the other hand, give better yields of the *C*-silylated products. For example, *t*-butyl acetate gives only *C*-silylation and *t*-butyl butanoate gives 60% *C*- and 40% *O*-silylation. It seems that substitution in the alcohol part favors *C*-silylation and substitution at the α-carbon favors *O*-silylation.[51] The extent of *O*-silylation depends also on the nature of the counterion. Zinc enolates are to be avoided since a Reformatsky-type reaction[52] of ethyl bromoacetate and TMS-Cl with zinc gives the *C*-silylated product (**52**). On the other hand, quenching of the Reformatsky reagent iododifluoroacetate–Zn with TMS-Cl is reported to give the corresponding silyl ketene acetal.[53] Another variable is the nature of the silylating agent. For example, reaction of methyl acetate with lithium cyclohexylisopropylamide followed by TMS-Cl yields methyl trimethylsilyl ketene acetal (65%) and methyl trimethylsilylacetate (35%). Higher selectivity for *O*-silylation can be achieved by the use of *t*-butyldimethylchlorosilane.[51] The polarity of the solvent can also play a significant role. The reaction of methyldiphenylchlorosilane with lithium ester enolate gives *C*-silylation in THF and *O*-silylation in THF–HMPA.[54]

Geometric isomers of silyl ketene acetals can be prepared from the acyclic ester precursors, depending on the solvent used.[55] Treatment of ethyl propanoate with LDA in THF, followed by reaction with TMS-

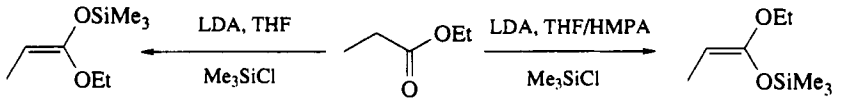


Scheme 19



(52)

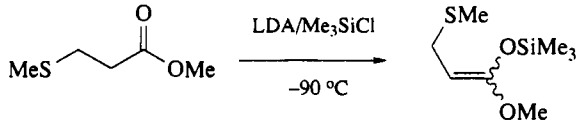
Cl, gives predominantly the (*E*)-isomer of (**53**), but addition of HMPA causes exclusive formation of the (*Z*)-isomer (Scheme 20).[56]



(**53**) (*E*):(*Z*) = 85:15 (**53**) (*E*):(*Z*) = 0:100

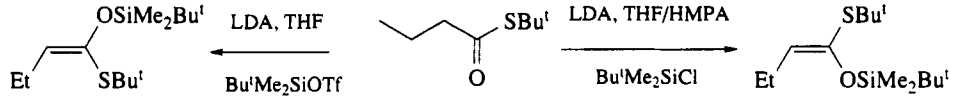
Scheme 20

In the case of compound (**54**) where there is an SMe group at the β-position, the usual reaction with LDA leads to β-elimination. The silyl ketene acetal (**55**) is prepared by the *in situ* method[33] of adding (**54**) to a solution of LDA and TMS-Cl at –90 °C.[57]

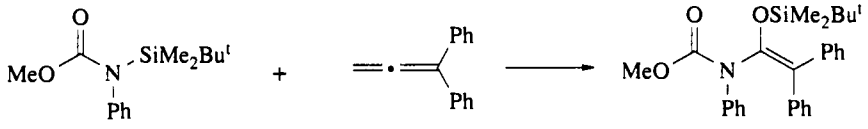


(**54**) (**55**)

Thiol esters can be converted to the corresponding *O*-silyl ketene thioacetals.[58] The thiol ester (**56**), under different silylating conditions, can be converted stereoselectively into either the (*E*)- or the (*Z*)-isomers of (**57**).[59]



(**57**) (*Z*):(*E*) > 95:5 (**56**) (**57**) (*E*):(*Z*) > 95:5



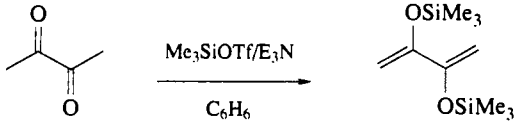
Scheme 21

Tertiary amides can also be silylated by LDA/TMS-Cl, but a mixture of *C*- and *O*-silylated products results.[60] An alternative approach may be through the reaction of ketenes with silylamines as illustrated in Scheme 21.[61]

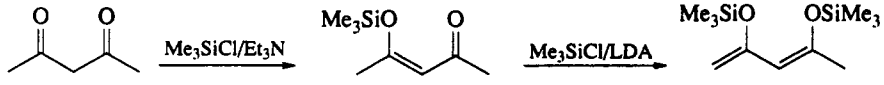
Lactones can be converted to the corresponding silyl ketene acetals in an unexceptional manner.[62]

2.3.2.2.3 Di- and poly-silyl enol ethers and ketene acetals

In contrast to metal enolates, enol silyl ethers are covalent compounds. It is easier to accommodate two or more enol silyl ether structures within the same molecule, whereas it would be more difficult to generate the corresponding enolate structures because of their strongly basic and reactive characters. 2,3-Butanedione has been converted to 2,3-bis(trimethylsiloxy)butadiene by a number of methods; the best appears to be TMS triflate and Et_3N in benzene.[63] Likewise, 1,3-diketones have been converted to the

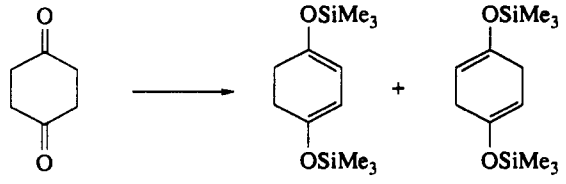


corresponding 1,3-bis(trimethylsiloxy)butadienes (*e.g.* **58**; Scheme 22).[64] With 1,4-diketones, two regioisomers of the dienol silyl ethers are usually formed, the proportions depending on the reagents used (Scheme 23).[65]



(58)

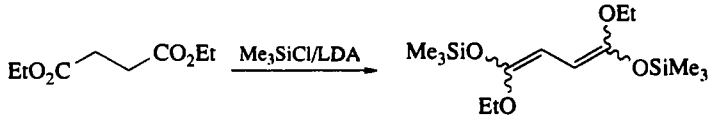
Scheme 22



Me_3SiOTf/C_6H_6	31%	51%
$Me_3SiCl/Et_3N/ZnCl_2/C_6H_6$	80%	20%

Scheme 23

The question of regiochemistry does not arise in the case of diesters. Diethyl succinate has been converted to the disilyl ketene acetal (**59**) in good yield.[66] A number of glutarate esters (**60**) have been similarly transformed to (**61**).[67]

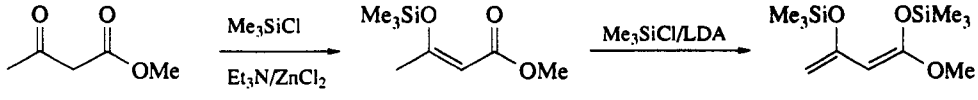


(59)

(60) **a**: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
c: $R^1 = R^2 = Me$; $R^3 = R^4 = H$
d: $R^1 = R^2 = R^4 = H$; $R^3 = Me$
e: $R^1 = R^2 = H$; $R^3 = R^4 = Me$

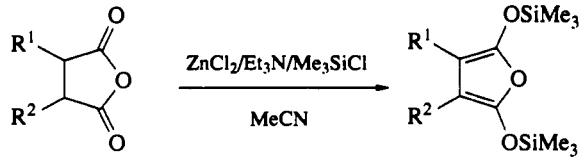
(61)

Mixed enol silyl ethers and silyl ketene acetals can be derived from keto esters. Methyl acetoacetate is first converted to a monoenol silyl ether (**62**), which is further silylated by LDA/TMS-Cl to the dienol silyl ether (**63**; Scheme 24).[68,69]

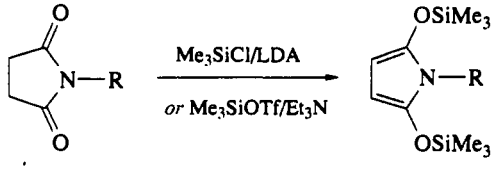


(62) **(63)**

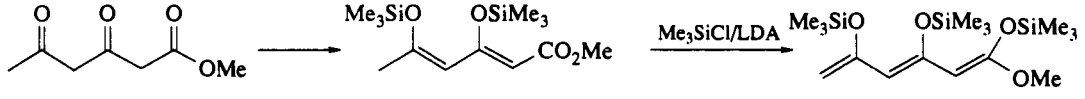
Scheme 24



(64) a: $R^1 = R^2 = H$ (65)
b: $R^1 = H$; $R^2 = Me$
c: $R^1 = R^2 = Me$
d: $R^1, R^2 = (CH_2)$
e: $R^1, R^2 = CH_2CH{=}CHCH_2$



(66) a: R = Me (67)
b: R = $PhCH_2$



(68) (69) (70)

Treating succinic anhydrides (**64**) with triethylamine, zinc chloride and trimethylchlorosilane in acetonitrile gives 2,5-bis(trimethylsiloxy)furans (**65**).[70] The relative ease of silylation in these cases demonstrates one of the differences between enol silyl ether chemistry and classical enolate anion chemistry. It would have been quite difficult to generate the dianion of succinic anhydride.

Succinimides (**66**) have been similarly converted to the corresponding 2,5-bis(trimethylsiloxy)pyrroles (**67**).[71,72]

Methyl 3,5-dioxohexanoate (**68**) has been converted first to the dienol silyl ether (**69**) and then to the trisilyl ether (**70**). Compound (**70**) can be considered as the equivalent of the trianion of (**68**).[73]

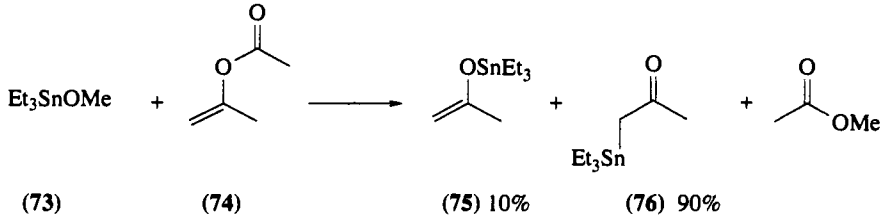
2.3.2.3 Formation of Enol Stannyl Ethers

Enol stannyl ethers have recently been used as synthetic equivalents of enolate anions.[74] However, organotin enol ethers usually exist as mixtures of *C*- and *O*-metallated species, irrespective of the methods of preparation.[75,76] Nevertheless, the two tautomers (**71**) and (**72**) often show similar reactivity and can be considered collectively as 'tin enolates'.

(71) (72)

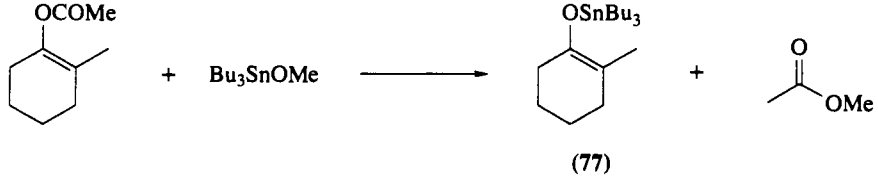
2.3.2.3.1 Organotin(IV) enol ethers

These compounds have been synthesized by several methods. A convenient method is by the interaction of trialkylmethoxytin compounds with enol acetates.[77] For example, reaction of triethylmethoxytin (**73**) with isopropenyl acetate (**74**) gives the tin(IV) enolates as a mixture of *O*- and *C*-isomers (**75**) and (**76**) (Scheme 25).[75] The exchange reaction appears to maintain the regiochemistry of the starting enol ester. Thus, reaction of 2-methyl-1-acetoxycyclohexene with tributylmethoxytin[77] gives compound (**77**). On the other hand, the regioisomer (**78**) has been generated *in situ* by treatment of the precursor lithium enolate with tri-*n*-butylstannyl chloride (Scheme 26).[78]



(**73**) (**74**) (**75**) 10% (**76**) 90%

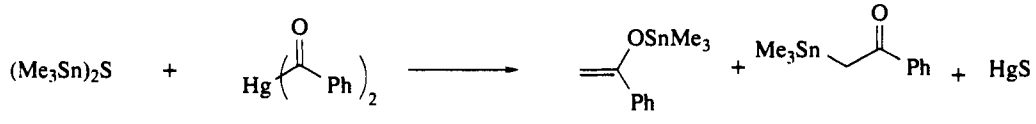
Scheme 25



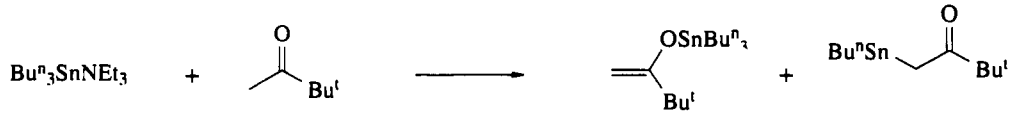
(**77**)

(**78**)

Scheme 26

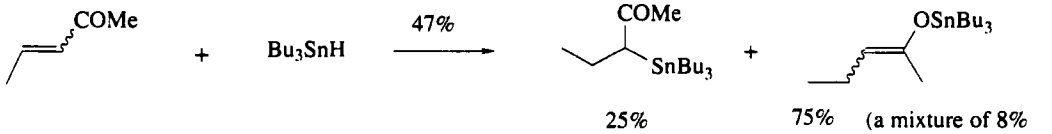


(**79**) (**80**) (**81**) 22% 78%



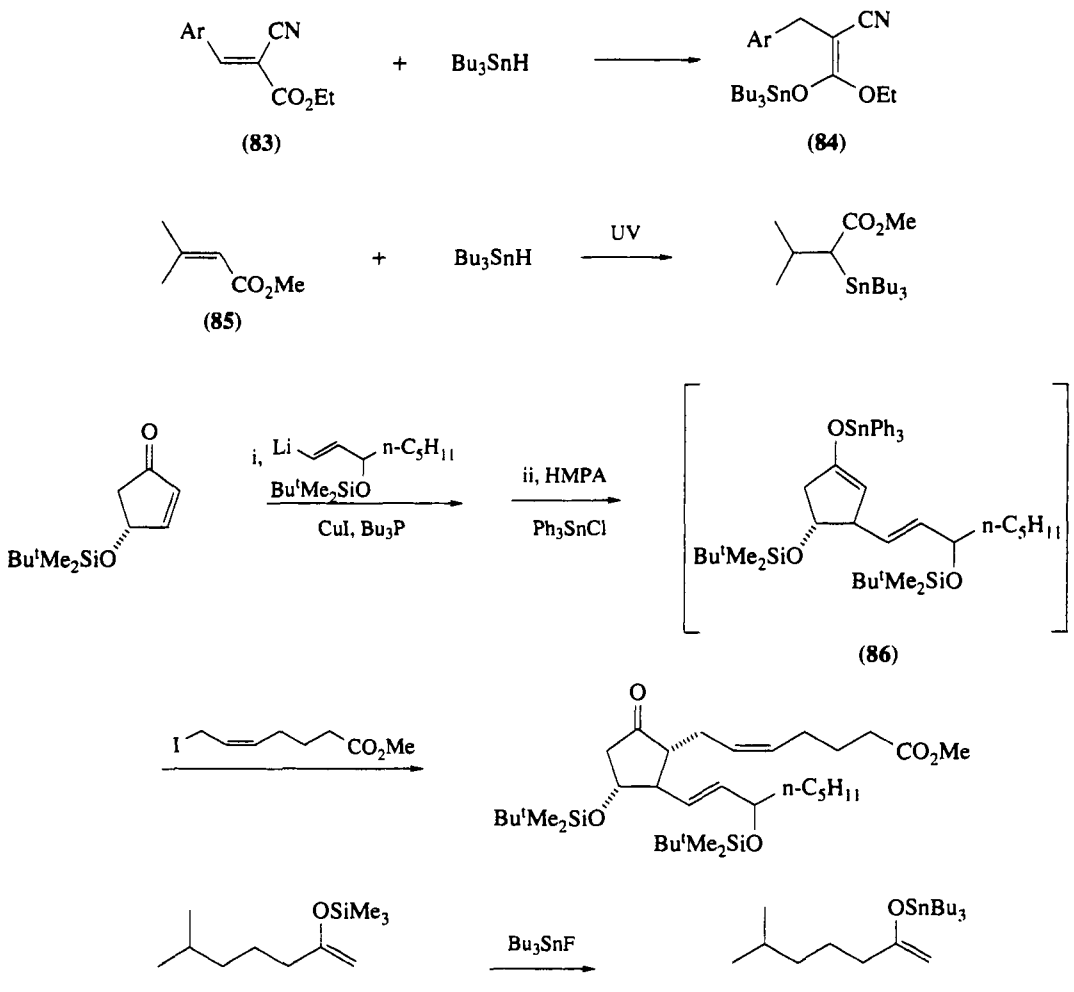
(**82**) 33% 66%

Scheme 27



25% 75% (a mixture of 8% *cis* and 67% *trans*)

Scheme 28



Scheme 29

Exchange reaction can also be carried out by treating bis(trimethylstannyl) sulfide (**79**) with the α-mercurated ketone (**80**) to yield the enol stannyl ether (**81**) and its *C*-isomer.[76,79] Direct reaction of carbonyl compounds with trialkylstannylamines can also give enol stannyl ethers. An example is the preparation of compound (**82**; Scheme 27).[80]

1,4-Addition of tin hydride to α,β-unsaturated carbonyl compounds is a general method of obtaining enol stannyl ethers. With triphenyltin hydride, the resulting tin enolate cannot be isolated and the reaction leads to the saturated carbonyl compounds.[81] With tributyltin hydride, a mixture of *O*- and *C*-stannylated adducts is obtained (Scheme 28).

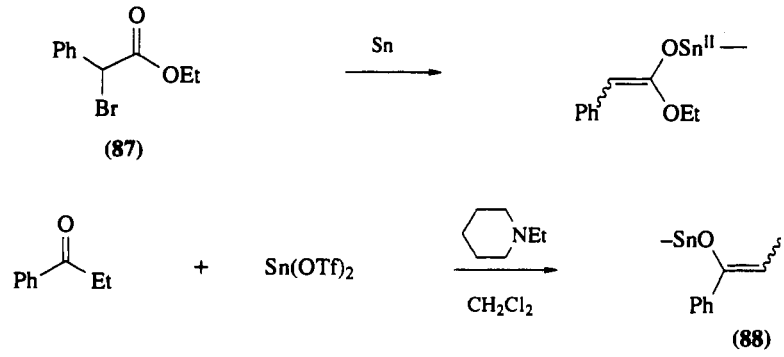
With the substrate (**83**), the *O*-stannyl ketene acetal (**84**) can be made by 1,4-hydrostannation.[82] Normally, addition of tin hydride to alkenic esters gives the *C*-stannylated compounds. An example is the reaction of (**85**) with tri-*n*-butyltin hydride.[83]

The enol stannyl ether (**86**), formed by conjugate addition to the precursor cyclopentenone and then stannylation, is implicated as an intermediate in a short and efficient synthesis of prostaglandins.[84]

Finally, a method of generating enol stannyl ethers *in situ* is to start from enol silyl ethers by an exchange reaction with tributyltin fluoride.[85] An example is given in Scheme 29.[86] It has been reported that this process occurs preferentially at the less-substituted enol silyl ether site if several are available.[87]

2.3.2.3.2 Tin(II) enol ethers

Strictly speaking, tin(II) enol ethers should be considered more as metal enolates. However, their chemistry resembles that of tin(IV) enol ethers in reactions with C—X π-bonds.

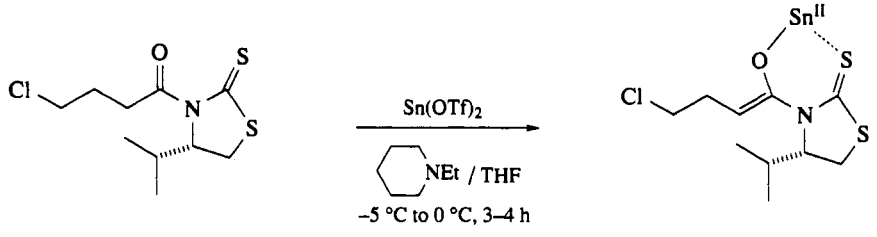


Tin(II) enolates can be generated from the reactions of α-bromo ketones with tin(0).[88] The activated metallic tin is typically prepared by the reduction of tin(II) chloride with lithium aluminum hydride.

A tin(II) ester enolate is also the presumed intermediate in the reaction of α-halo ester (**87**) with metallic tin in a Reformatsky-type reaction.[89]

More conveniently, tin(II) enolates can be generated by reaction of ketones and $Sn(OTf)_2$ in the presence of a tertiary amine. The choice of the amine is critical. For example, pyridine and DBU fail to promote the reaction, whereas *N*-ethylpiperidine gives excellent results.[90,91] Thus, the divalent tin enolate (**88**) of propiophenone has been generated by treating propiophenone with tin(II) triflate and *N*-ethylpiperidine in dichloromethane.[92]

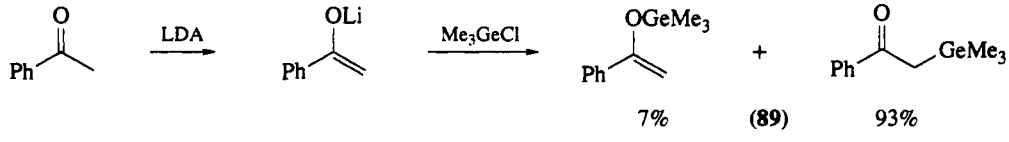
Under similar reaction conditions, tin(II) ester enolates derived from 3-acyl-1,3-thiazolidine-2-thiones have been prepared.[93,94] An example is given in Scheme 30.[95]



Scheme 30

2.3.2.4 Other Enol Ethers

Enol germyl ethers are known to equilibrate slowly with the *C*-isomers at room temperature.[96] They can be prepared by the reaction of lithium enolates of ketones with chlorotrimethylgermane as a mixture of the *O*- and *C*-germyl isomers (*e.g.* **89**).[97]



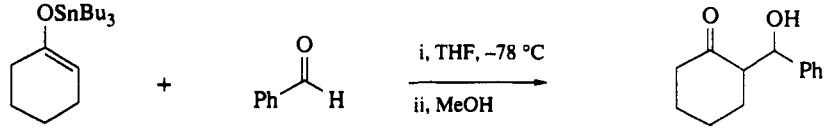
Enol phosphates have been suggested as enol equivalents.[98] Their use in synthesis seems to have been supplanted by enol silyl ethers.

Various enol boron derivatives have found extensive applications in synthesis. They form the subject matter of discussion elsewhere in Part 1 of this volume.

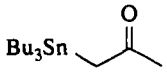
2.3.3 REACTIONS WITH C—X π-BONDS AND EQUIVALENTS

2.3.3.1 Uncatalyzed Aldol and Related Condensations

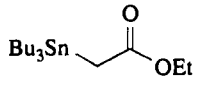
In the direct reaction of various enol ethers with carbonyl compounds in the absence of any catalyst to give the aldol condensation products according to Scheme 1, the reaction depends critically on the nature of the enol ethers. Enol stannyl ethers, being most similar to metal enolates, react readily. For example, 1-cyclohexenyloxytributyltin reacts with benzaldehyde at –78 °C in the absence of catalyst to give high yield of the aldol condensation product (**90**).[99] The reactivity of the organotin(IV) reagents is sensitive to the particular structure. Thus, although acetonyltributyltin (**91**) reacts spontaneously with aldehydes at –78 °C, the reaction of ethyl tributylstannylacetate (**92**) with benzaldehyde proceeds only at 80 °C.[99]



(**90**)

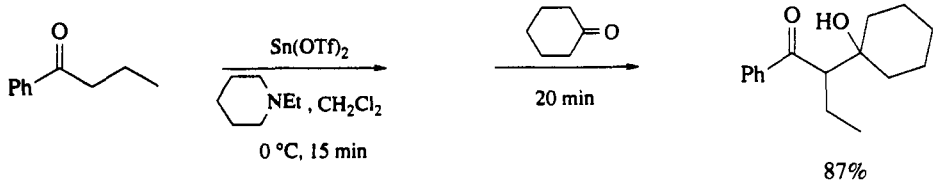


(**91**)



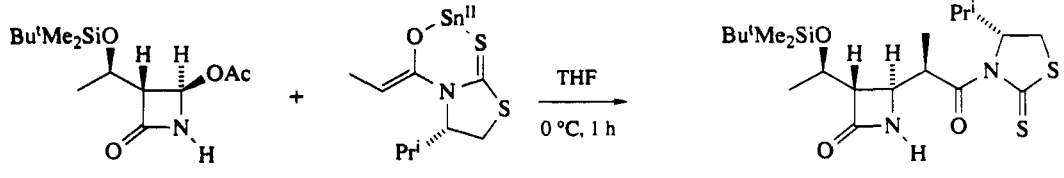
(**92**)

The crossed aldol reaction between two different ketones is a difficult reaction under the classical metal enolate conditions.[100] By employing divalent tin enol ethers, directed aldol reaction between ketones is easily achievable.[92] An example is given in Scheme 31.



Scheme 31

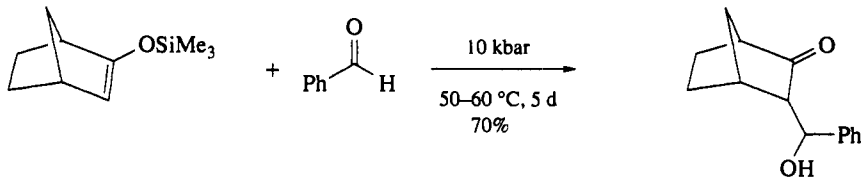
The aldol-type condensation can be extended to carbonyl equivalents such as the 4-acetoxy-2-azetidinone (**93**)[94] or similar α-acetoxylactams.[95] The condensation of (**93**) with the chiral tin(II) enol ether (**94**) has been used in a highly diastereoselective synthesis of chiral carbapenems.



(**93**) (**94**)

The condensation of an enol silyl ether with an aldehyde or ketone usually requires Lewis acid catalyzed conditions (*vide infra*). However, under high pressure, the reaction can be induced to proceed in the absence of catalyst (Scheme 32).[101] Silyl ketene acetals, on the other hand, can react with aldehydes to give the aldol products by heating in the absence of Lewis acid.[102]

Enol ethers are insufficiently nucleophilic to react with C—X π-bonds under uncatalyzed conditions.



Scheme 32

2.3.3.2 Catalyzed Addition to C—X π-Bonds and Equivalents

The catalyzed reaction of enol ethers with carbonyl compounds (Scheme 1) has become an important reaction in synthesis. Compared to the metal enolate reactions (Part 1, Volume 2), the catalyzed enol ether reactions offer the following distinct differences. Enol ethers are often isolable, stable covalent compounds, whereas the metal enolates are usually generated and used *in situ*. Under Lewis acid catalyzed conditions, a number of functional equivalents such as acetals, orthoesters, thioacetals, α-halo ethers and sulfides can participate as the electrophilic components, whereas many of them are normally unreactive towards metal enolates. In synthesis, enol ether reactions now rival and complement the enolate reactions in usefulness. Enol silyl ethers are particularly useful because of their ease of preparation, their reasonable reactivity and the mildness of the desilylation process.

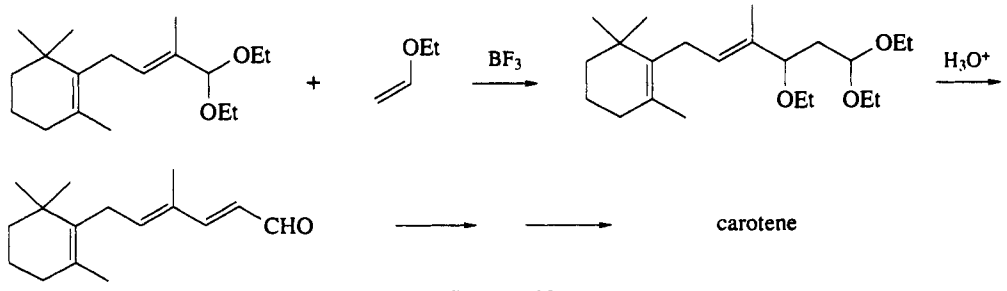
2.3.3.2.1 Reactions of enol ethers

Enol ethers react with acetals or ketals, promoted by Lewis acids, to give aldol-type adducts.[103,104] It has been used, for example, in a synthesis of carotene (Scheme 33).[105]

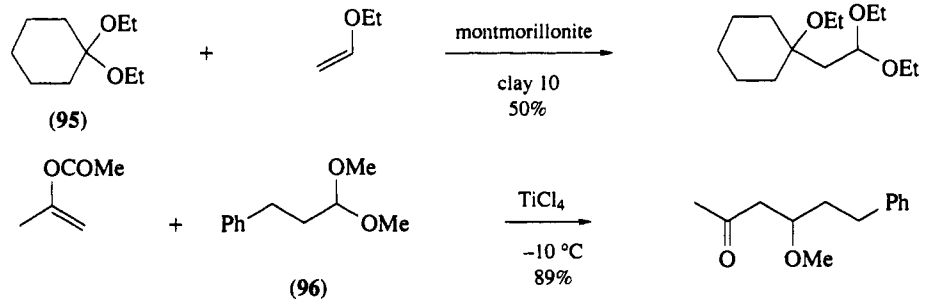
In the condensation of the ketal (**95**) with ethyl vinyl ether, montmorillonite clay 10 was found to be an effective catalyst and superior to the previously reported Lewis acid.[106] In this reaction, the work-up is simplified to filtration of the catalyst.

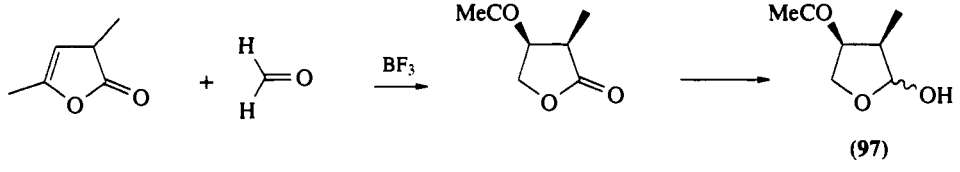
The relative reactivities of acetals and orthoesters in Lewis acid catalyzed reactions with enol ethers have been investigated. For $BF_3{\cdot}OEt_2$-catalyzed reactions with methyl vinyl ether, the following order has been found; saturated acetals < methyl orthoformate < benzaldehyde acetals < α,β-unsaturated acetals.[107]

Enol esters, like enol ethers, can also react with various acetals and aldehydes in the presence of Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_4$, $ZnCl_2$, and $BF_3{\cdot}OEt_2$ to afford the corresponding aldol-type addition products.[108] A typical example is the reaction of isopropenyl acetate and γ-phenylpropionaldehyde acetal

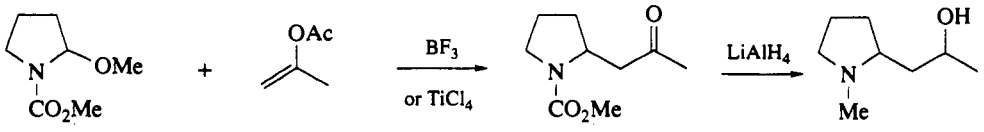


Scheme 33





(97)



(98)

(**96**).[109] The reaction has been used in a convenient synthesis of the antibiotic and antileukemic agent botryodiplodin (**97**).[110]

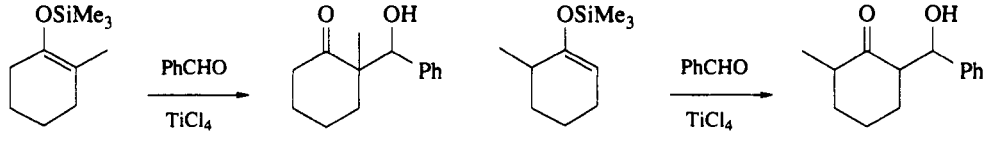
Aminohemiacetals (*e.g.* **98**) can also condense with enol ethers or enol esters to give the cross-aldol products.[111] A number of piperidine and pyrrolidine alkaloids have been synthesized by this approach.

The disadvantage of the acid-catalyzed reaction of enol ethers or esters is that there are often undesirable side reactions. On the other hand, the reaction may be a useful industrial process because of the relatively inexpensive nature of the starting materials.

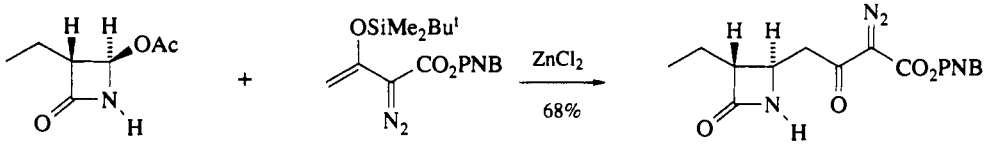
2.3.3.2.2 Reactions of enol silyl ethers

In 1974, Mukaiyama and his coworkers reported on the Lewis acid promoted condensation of enol silyl ethers with carbonyl compounds to give the cross-aldol products.[112] The reaction usually proceeds with retention of the regiochemical integrity of the starting enol silyl ethers as shown by those illustrated in Scheme 34. However, occasional examples of loss of regiointegrity of the starting enol silyl ethers have been noted in the literature.[113]

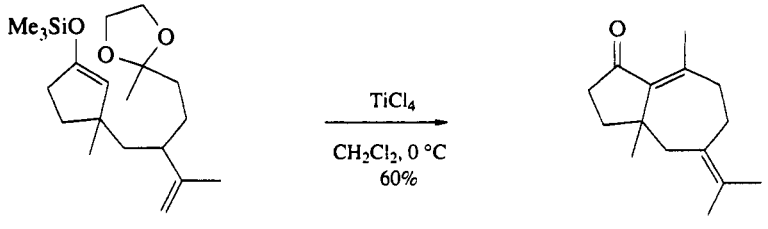
In addition to aldehydes and ketones, acetals, ketals, orthoesters,[112] α-halo ethers, α-halo sulfides, amino acetals[114] and their equivalents also react with enol silyl ethers in the presence of Lewis acid to af-



Scheme 34



Scheme 35

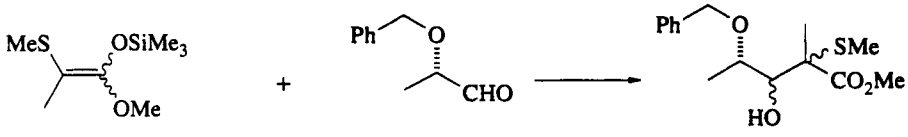


(**99**)

ford the corresponding condensation products in high yields.[115] An example is given in Scheme 35. Intramolecular reactions of this type can be used to synthesize cyclic compounds, for example in the construction of the pseudoquaiane system (**99**).[116]

(i) Choice of catalyst

A variety of Lewis acids have been used for the catalyzed reaction of enol silyl ethers with carbonyl compounds. Very often, these Lewis acids have to be used in stoichiometric amounts to promote the reaction. However, excess Lewis acid can sometimes lead to further transformations.[117] There have been no systematic studies on comparing the efficacy of the various catalysts. In general, for simple aldehydes and ketones, Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnCl_2$ and so on have been used. Among these acids, $TiCl_4$ is most commonly used and is usually superior to the other Lewis acids with respect to yields.[112] Occasionally, $TiCl_2(OR)_2$, generated by mixing equivalent amounts of $TiCl_4$ and $Ti(OR)_4$, is found to be better than $TiCl_4$ in promoting the reaction.[112] On the other hand, in the reaction of (*S*)-*O*-benzyllactaldehyde with the silyl ketene acetal (**100**), the best results come from $SnCl_4$ or $MgBr_2$. $TiCl_4$ fails to promote the reaction (Scheme 36).[57]

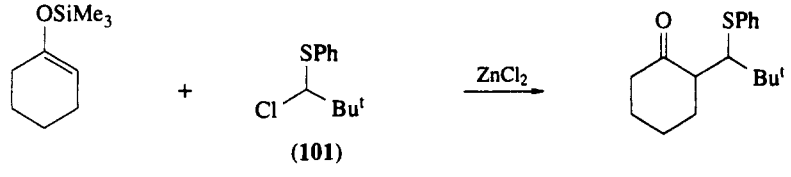


(**100**)

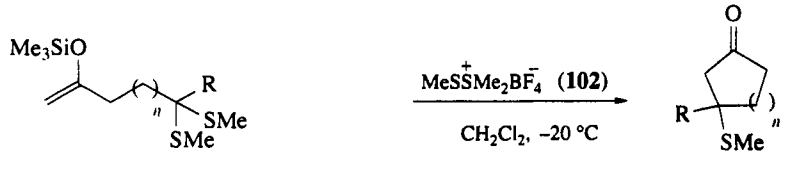
Lewis acid	*Temp* (°C)	*Yield* (%)
$TiCl_4$	−78 to 0	0
$SnCl_4$	−78	65
$ZnCl_2$	−40	45
$MgBr_2$	−40	60

Scheme 36

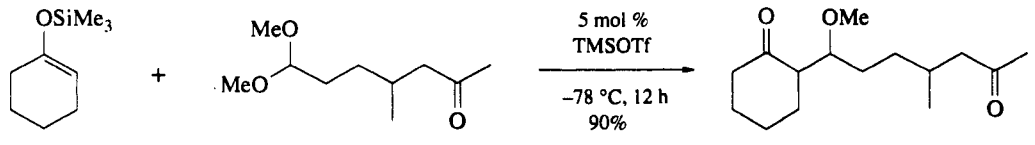
In the reaction of enol silyl ethers with α-chloro sulfides (*e.g.* **101**), $TiCl_4$ or ZnX_2 appears to be the Lewis acid of choice.[118] When dithioacetals[119] are used as the electrophiles, $FeCl_3$ or dimethyl(methylthio)sulfonium fluoroborate (DMTSF; **102**) have been used successfully as the initiator for the condensations with enol silyl ethers. For example, the intramolecular reactions of (**103**) induced by 1 equiv. of DMTSF lead to good yields of the cyclization products.[120]



(**101**)



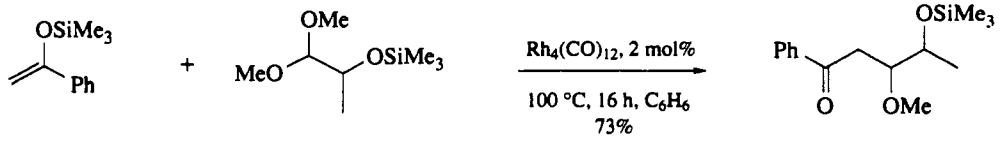
(**103**) n = 1, 2 or 3



Scheme 37

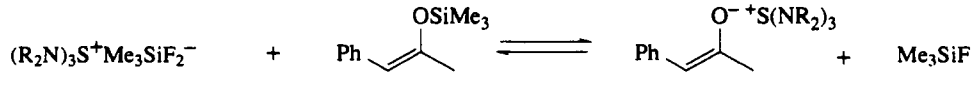
Aldol-type condensation of enol silyl ethers and acetals or orthoesters can be accomplished by the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[121] In these reactions, TMSOTf acts as a true catalyst and is required in 1–5 mol %. The reactions show interesting chemoselectivity in that acetals are highly reactive receptors of enol silyl ethers but the parent aldehydes and ketones do not react under these conditions (Scheme 37). Similarly, trityl perchlorate is found to be an efficient catalyst to promote the reaction between enol silyl ethers and acetals.[122,123]

Crossed aldol reactions of enol silyl ethers with aldehydes have been successfuly performed with the aid of catalytic amounts of the rhodium complex $[(COD)Rh(DPPB)]^+X^-$ (X = PF_6 or ClO_4) or $Rh_4(CO)_{12}$. Although the intermediacy of rhodium enolate has been suggested for these reactions,[124] the fact that the same rhodium catalysts can promote the condensations of acetals as well (Scheme 38) tends to indicate that the reactive species may not be a metal enolate.[125]



Scheme 38

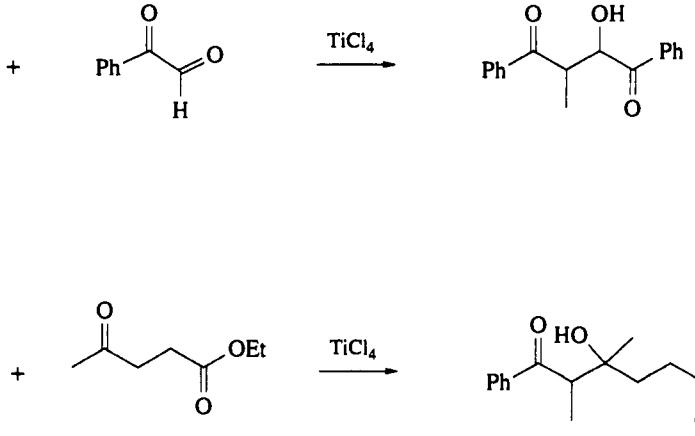
A number of organoaluminum reagents, especially Me_2AlCl, have been found to be effective catalysts for reactions of enol silyl ethers with aldehydes.[126] It is possible that in these reactions, aluminum enolates may be involved as the intermediates. Similarly, bismuth trichloride has been reported to be an efficient catalyst.[127] Since $BiCl_3$ is considered to be a weak Lewis acid, the involvement of a bismuth enolate is perhaps implicated. Enolate intermediates are definitely generated when tetraalkylammonium fluorides[128] or tris(dialkylamino)sulfonium (TAS) difluorotrimethylsiliconates (**104**)[129] are used as reagents to promote the reactions of enol silyl ethers. Their chemistry will therefore not be discussed in this chapter.



Heterogeneous catalysts such as cation-exchanged montmorillonite clay or Nafion also catalyze the aldol reaction of enol silyl ethers with aldehydes and acetals.[130]

(ii) Chemoselectivity

It is clear from the foregoing discussion that different kinds of carbonyl functions will react differently with enol silyl ethers depending on the choice of catalyst. Under the same reaction conditions, chemose-

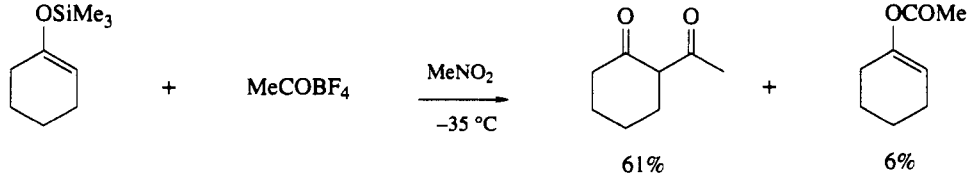


Scheme 39

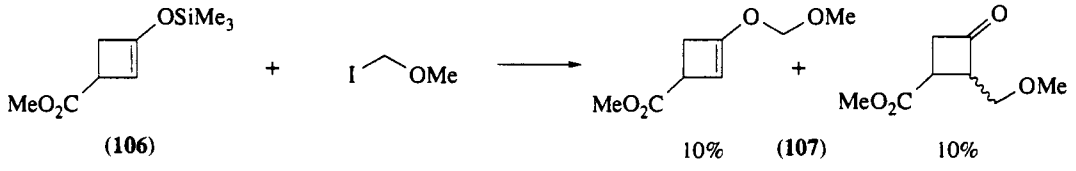
lectivity is observed with acceptors having two or more different kinds of carbonyl electrophilic sites in the same molecule. In general, with $TiCl_4$ as the Lewis acid, aldehydes are more reactive than ketones, which are in turn more reactive than esters. This is demonstrated in Scheme 39 where the enol silyl ether (**105**) is allowed to react with phenylglyoxal or with ethyl levulinate.[131] In another study, using the enol silyl ether (**63**) in a series of competitive experiments under $TiCl_4$ conditions, it is possible to establish qualitatively the following order of reactivity: aldehyde > conjugated position of β-oxy-α,β-unsaturated ketone ≈ isolated ketone > carbonyl position of β-oxy-α,β-unsaturated ketone > acetal or monothioacetal > conjugate position of β-oxy-α,β-unsaturated ester ≈ ester carbonyl.[132] The order may well be changed when other catalysts or enol silyl ethers are used.

(iii) Regioselectivity

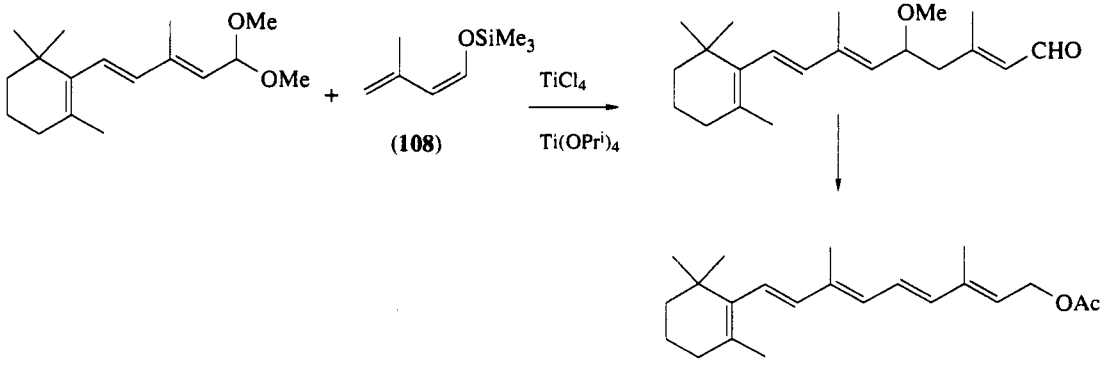
Although enol silyl ethers are ambident species capable of reacting either at carbon or at oxygen, nearly all the aldol-type condensations occur at carbon. The exception is in the reaction with acylating agents, where either the *O*- or the *C*-acylated products can be obtained depending on the reaction conditions (*e.g.* Scheme 40).[133,134] On the other hand, the more reactive silyl ketene acetals react with acid chlorides without a catalyst to give β-keto esters, the *C*-acylation products.[135,136] Another exception is the reaction of the enol silyl ether (**106**) with iodomethyl methyl ether. A mixture of *C*- and *O*-alkylation products (**107**) is obtained.[137] This has been attributed to the tendency of cyclobutanone to undergo *O*-alkylation.[138]



Scheme 40

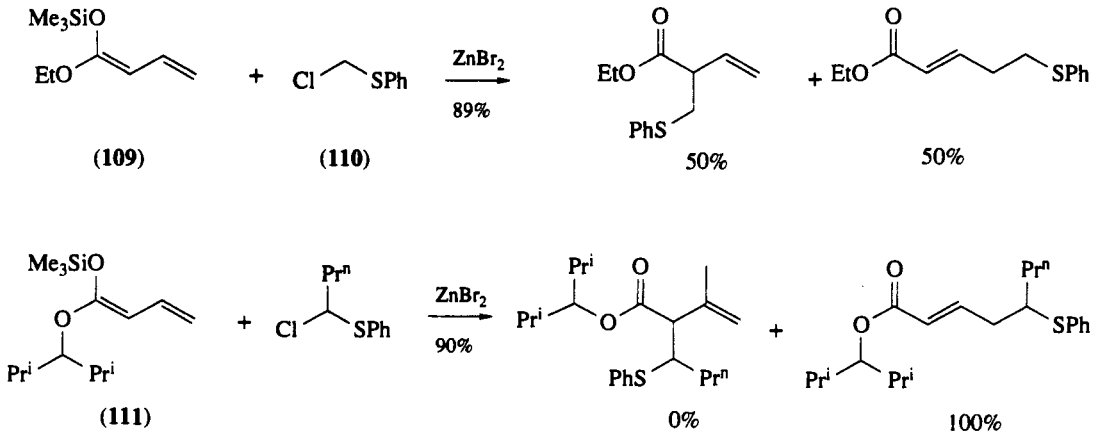


A question of regiochemistry arises with *O*-silylated dienolates derived from α,β-unsaturated aldehydes, ketones and esters. The silylated dienolates of crotonaldehyde and its 3-methyl derivative (**108**) react with acetals in Lewis acid catalyzed conditions at the γ-position. This high regioselectivity has been used in the synthesis of vitamin A acetate (Scheme 41).[139]

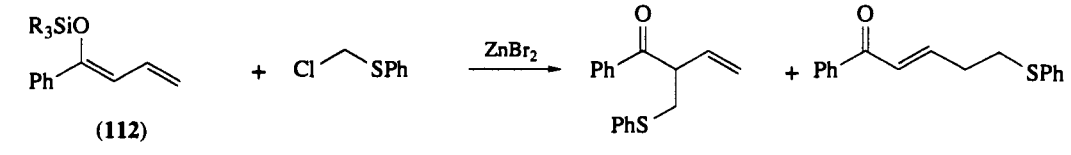


Scheme 41

The regioselectivity depends very much on the nature of the electrophile and on the structure of the siloxydiene.[140] For example, the silyl ketene acetal (**109**) reacts with chloromethyl phenyl sulfide (**110**) to give nearly equal amounts of the α- and γ-products, whereas the compound (**111**) is phenylthiobutylated with essentially complete γ-selectivity (Scheme 42).[141] Changing the substituents on the silyl group has the most dramatic effect. Using the reaction of the siloxydiene (**112**) with compound (**110**) as the standard reaction, it has been found that the *t*-butyldimethylsilyl group gives the highest proportion of the α-product (**113**), and the *m*-chlorophenyldiphenylsilyl group gives exclusively the γ-product (**114**).[142]

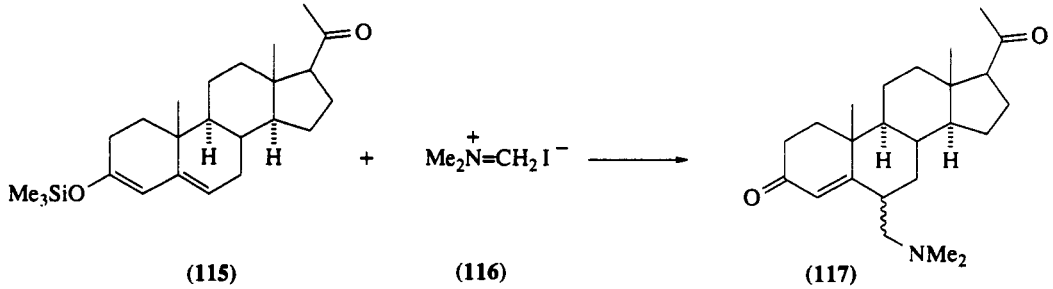


Scheme 42

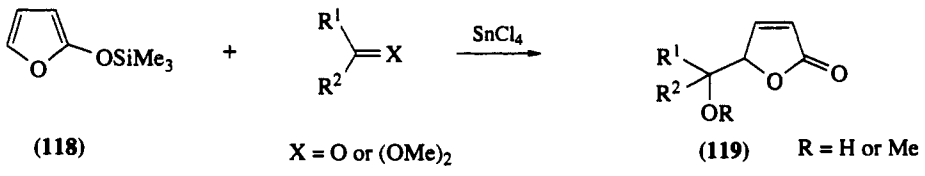


	Yield (%)	(**113**) (%)	(**114**) (%)
$R_3 = Me_2Bu^t$	62	77	23
$R_3 = Me_3$	58	55	45
$R_3 = Ph_3$	93	15	85
$R_3 = m\text{-}ClC_6H_4Ph_2$	58	0	100

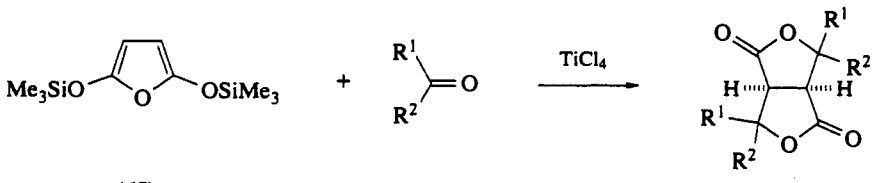
Similar γ-regioselectivity has been observed[143] in the reaction of the steroidal siloxydiene (**115**) with the Eschenmoser's salt (**116**) to give the Mannich adduct (**117**).



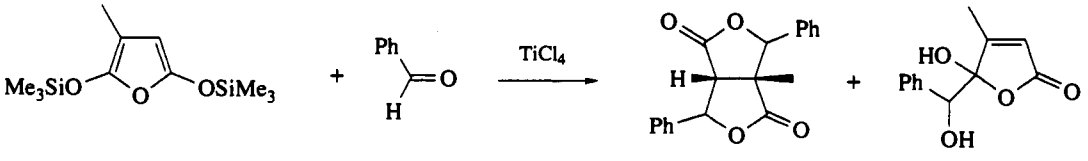
2-Trimethylsiloxyfuran (**118**) reacts with various aldehydes, ketones and acetals in the presence of tin(IV) chloride to give the corresponding γ-adducts (**119**).[144] On the other hand, 2,5-bis(trimethylsiloxy)furan (**65**) reacts with aldehydes and ketones under activation of titanium tetrachloride to give the 3,7-dioxabicyclo[3.3.0]octane system (**120**) by reaction at the α-positions.[145] However, with increasing



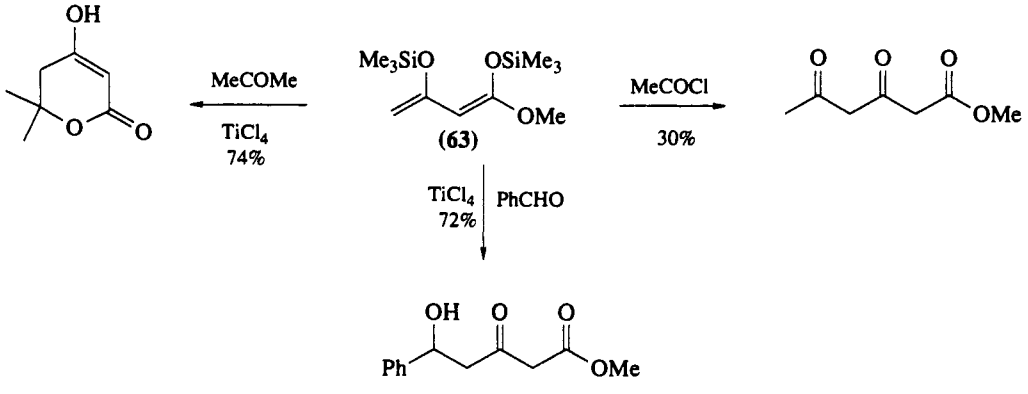
(118) (119)



(65) (120)

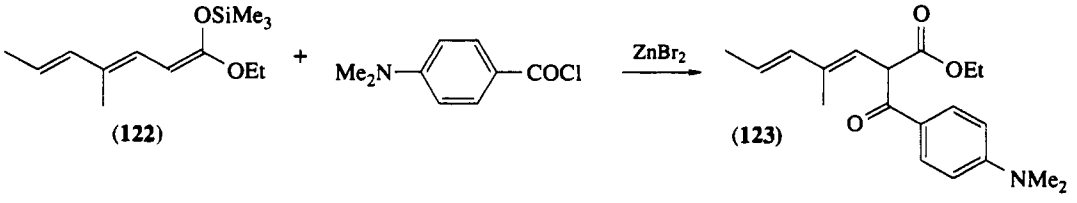


(121)

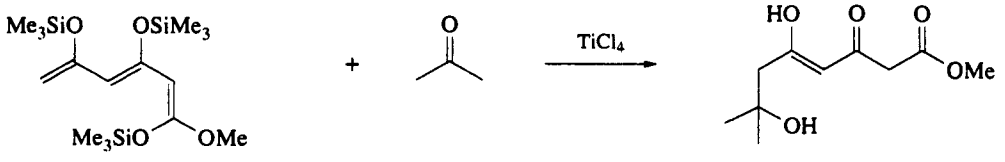


(63)

Scheme 43



(122) (123)



(70)

Scheme 44

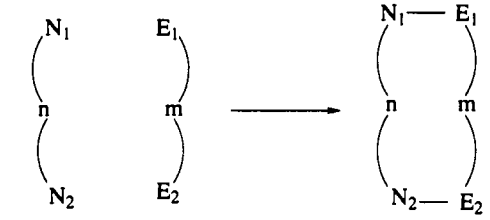
alkyl substitution in (**65**), addition of the carbonyl compound occurs at the γ-position to give the butenolides (**121**).[146]

In the dienol silyl ether (**63**), where the γ-selectivity of the siloxy diene is enhanced by the second siloxy substituent, reactions with electrophiles occur exclusively in the γ-position as illustrated in Scheme 43.[68,132] The same γ-selectivity is observed for the siloxydiene (**58**) derived from a 1,3-diketone.[64]

The trienol silyl ether (**70**) reacts with carbon electrophiles at the ε-position as illustrated in Scheme 44.[73,147] Unexpectedly, the trienyl silyl ketene acetal (**122**) reacts with *p*-dimethylaminobenzoyl chloride and zinc bromide at the α-position to give the ester (**123**) as the only isolable product.[134] It is not known at this time whether such α-selectivity is general for other aldol-type reactions of (**122**) or limited to acylations.[148]

(iv) Aldol condensation cascade as a general synthesis of cyclic compounds

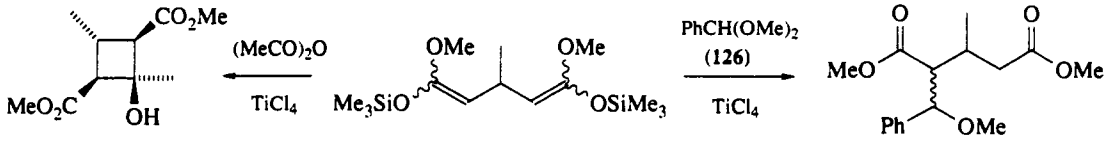
Aldol-type condensation of β-polyketides is an important pathway in nature to form cyclic compounds.[149] Based on these biogenetic considerations, the controlled aldol condensations of enolate anions have been extensively studied.[150] In view of the selective nature of the catalyzed condensation of enol silyl ethers with carbonyl compounds, the reaction has been used with some success for the synthesis of cyclic compounds. The general strategy is based on the condensation of two fragments: one fragment (**124**) containing two nucleophilic sites in the form of enol silyl ethers (represented as N), and the other fragment (**125**) containing two electrophilic sites in the form of carbonyl groups or their equivalents (represented as E). For compounds where the two enol silyl ethers are not of identical structure, their reactivities may be sufficiently different so that a reactivity order can be assigned (say, N_1 more reactive than N_2). Similarly, the two electrophilic sites may also have reactivity difference (say, E_1 more reactive than E_2) according to the order discussed in Section 2.3.3.2.2.ii. The regiochemistry of the cyclization reaction can then be controlled by the differential reactivities of these sites as shown in Scheme 45.



(**124**) (**125**)

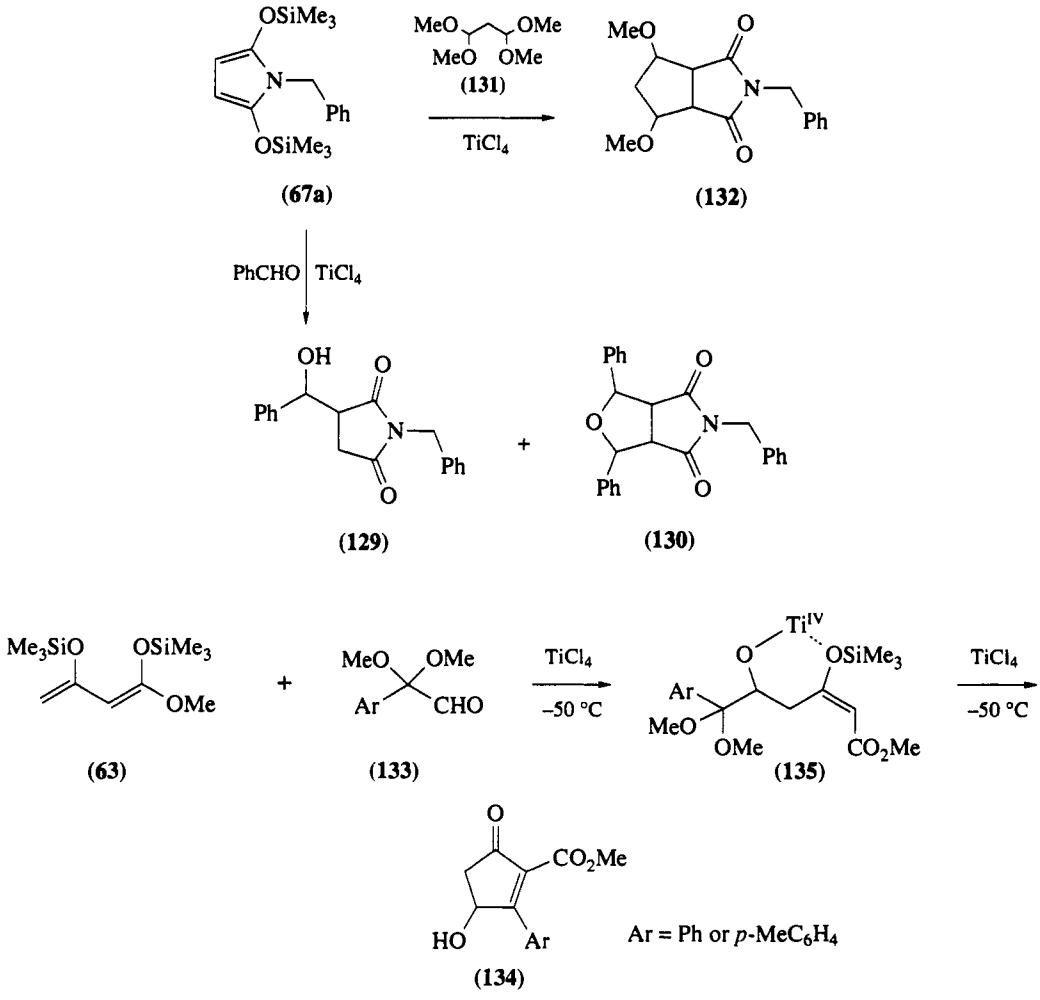
Scheme 45

(a) Formation of four-membered rings. The dienol silyl ketene acetals (**61a–e**) derived from dimethyl glutarates can be considered as 1,3-dinucleophiles. They react with carbon electrophiles preferentially at only one site. For example, (**61b**) on reaction with benzaldehyde dimethyl acetal (**126**) and $TiCl_4$ gives the methoxy diester (**127**) as the only product in the form of a mixture of diastereoisomers in 69% yield.[67] When acetic anhydride is used as the electrophile, the cyclobutane compound (**128**) is obtained (Scheme 46). The reaction is apparently highly stereoselective in that only one stereoisomer (**128**) is detected and isolated.



(**128**) (**61b**) (**127**)

Scheme 46

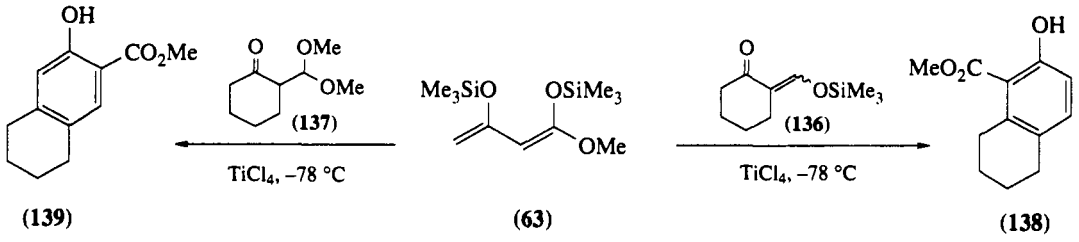


(b) Formation of five-membered rings. As mentioned previously, compound (**65**) behaves as a 1,2-dinucleophile in that it reacts with aldehydes and ketones under activation of $TiCl_4$ to give reactions at the α-positions, but the adducts rearrange to give dilactones (**120**). However, 2,5-bis(trimethylsiloxy)pyrrole (**67a**) reacts with aldehydes or ketones to give the substituted succinimides (**129**) and (**130**) without rearrangement. When a 1,3-dielectrophile such as (**131**) is used, condensation with (**67a**) gives the bicyclic compound (**132**).[72]

Alternatively, five-membered ring formation can be achieved by the condensation between a 1,3-dinucleophile and a 1,2-dielectrophile. This is demonstrated by the reaction of (**63**) with 2-aryl-2,2-dimethoxyethanal (**133**) to give the cyclopentenone product (**134**). The cyclization process is regioselective. INEPT ^{29}Si NMR has been used to follow the reaction,[151] which shows that the first condensation is between the more reactive nucleophilic site at C-4 of (**63**) with the more reactive electrophilic site at C-1 of (**133**) to give the intermediate (**135**).

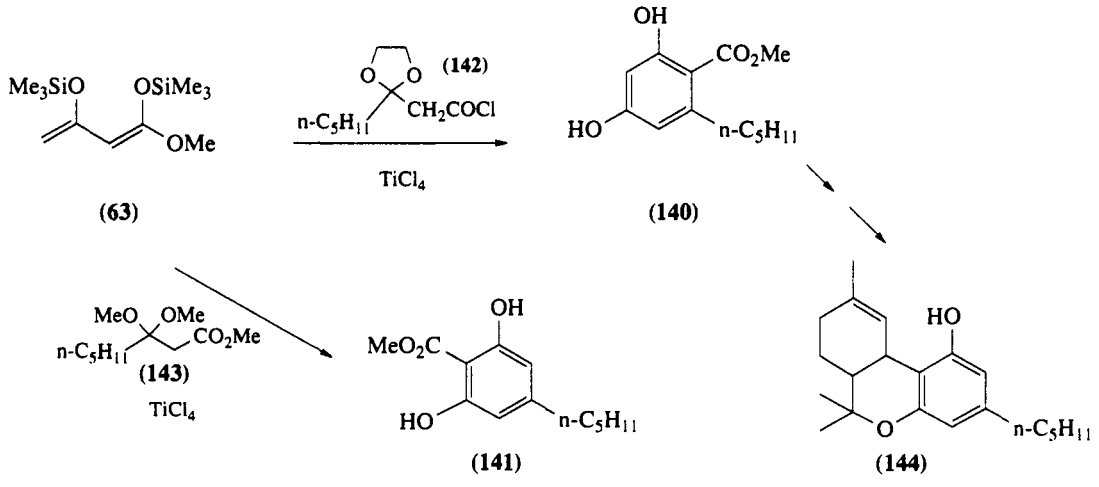
(c) Formation of six-membered rings. Using the enol silyl ether chemistry, sequential aldol-type condensation between a 1,3-dinucleophile and a 1,3-dielectrophile has been developed as a general method of synthesis for functionalized benzenoid compounds.[152]

The approach is illustrated by the reactions of (**63**) with the two 1,3-dielectrophiles (**136**) and (**137**) under identical reaction conditions to form regioselectively the two isomeric aromatic compounds (**138**) and (**139**) respectively (Scheme 47). The regiochemistry of the condensation is governed by the differential reactivity of the two sites in (**63**; C-4 > C-2) and in the electrophiles (conjugate position > ketone > acetal).



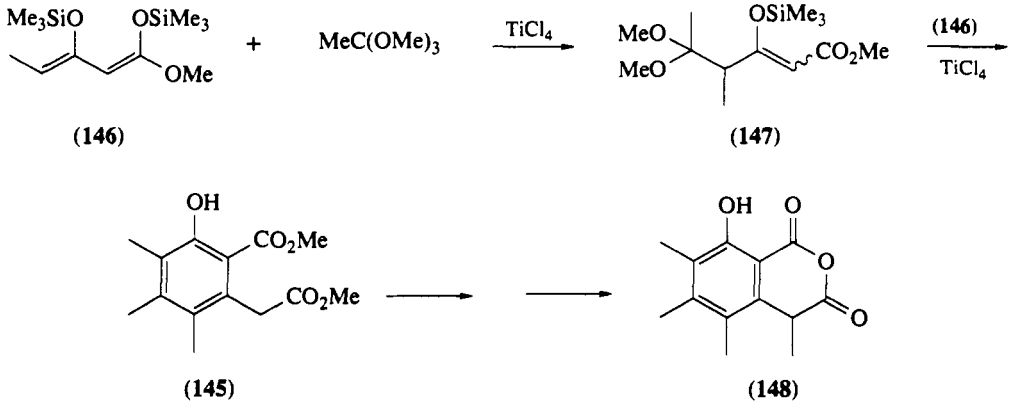
Scheme 47

Methyl olivetolate (**140**) and its regioisomer (**141**) have been prepared in a regiocontrolled manner by the condensation of (**63**) with the two 1,3-electrophiles (**142**) and (**143**) respectively (Scheme 48).[153] In these cases, the reactivity order in the electrophilic components is acid chloride > acetal > ester. This reaction has been used in a biomimetic synthesis of (–)-Δ^1-tetrahydrocannabinol (**144**).

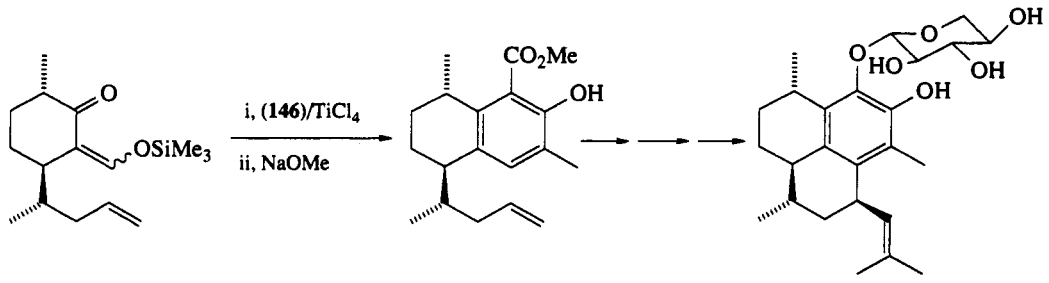


Scheme 48

The hexasubstituted benzenoid compound (**145**) is synthesized in one step by the condensation of 2 mol of the dienol silyl ether (**146**) with 1 mol of methyl orthoacetate and $TiCl_4$. The reaction is believed to proceed through the intermediate (**147**). Compound (**147**) can be considered as a potential 1,3,5-trielectrophile. The more reactive sites in (**147**) are at C-5 and at C-3 respectively. Condensation of (**147**) with a second mole of (**146**) gives therefore regioselectively the aromatic compound (**145**). By this method, the plant growth substance sclerin (**148**) can easily be prepared.[132,154]

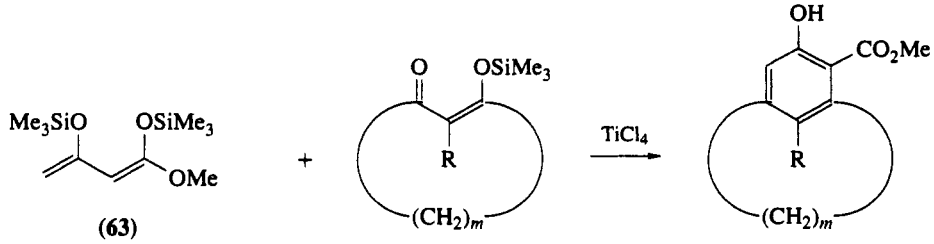


A similar cycloaromatization reaction has been used as a key step in the synthesis of (–)-pseudopterosin A (**149**), a marine natural product with analgesic activity.[155]



(149)

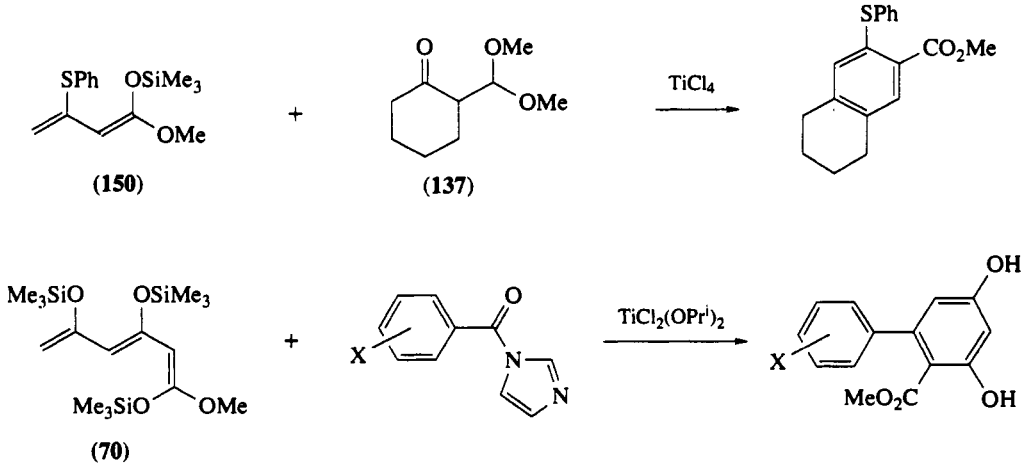
When the 1,3-dielectrophile is part of a macrocycle, the cycloaromatization reaction can be used as a synthesis of *m*-cyclophanes as illustrated in Scheme 49.[156]



(63)

m = 11 or 14
R = H, Me or $PhCH_2$

Scheme 49



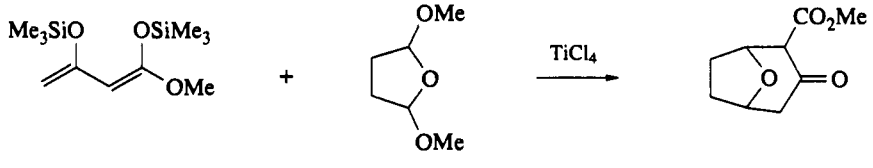
(150) **(137)** **(70)**

Scheme 50

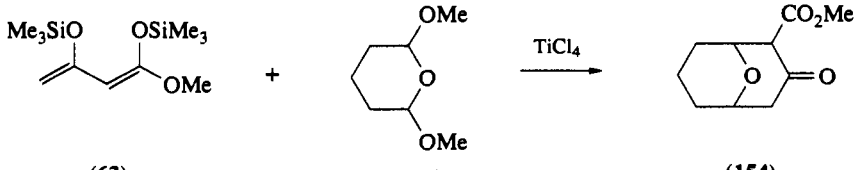
Aryl sulfides can be synthesized from acyclic precursors by the same cycloaromatization reaction starting from the thio-substituted compound (**150**). Compound (**150**) reacts with the 1,3-dielectrophile (**137**) selectively at the γ-position first, followed by an intramolecular condensation at the α-position and then aromatization (Scheme 50).[157] The regiochemistry of the condensation is governed by the same reactivity difference in (**137**) as the example in Scheme 47.

An alternative way to construct a six-membered ring is through the condensation of a five-carbon dinucleophilic unit and a one-carbon electrophilic unit, *i.e.* a [5 + 1] condensation.[73] This is demonstrated by the reaction of (**70**) with an acid chloride, an imidazolide or an orthoester in the presence of $TiCl_2(OPr^i)_2$. The reaction provides an easy route to unsymmetrical biphenyls (Scheme 50).[147]

(d) Formation of seven- and eight-membered rings. Reaction of (**63**) with 1,4-dielectrophiles such as the cyclic acetal (**151**) gives the 8-oxabicyclo[3.2.1]octyl system (**152**), which has been converted to the oxygen analog of cocaine.[158,159] 2,5-Hexanedione reacts in a similar fashion.



(**63**) (**151**) (**152**)

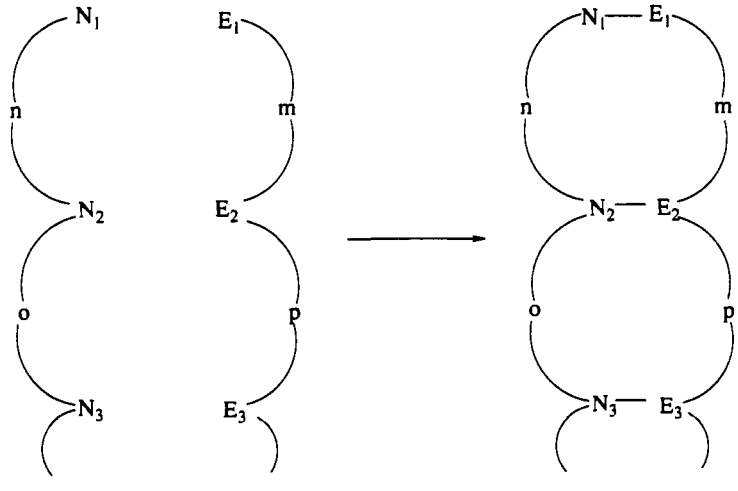


(**63**) (**153**) (**154**)

Using the acetal (**153**), the higher homolog 9-oxabicyclo[3.3.1]nonyl system (**154**) can be prepared by the same type of condensation.[158]

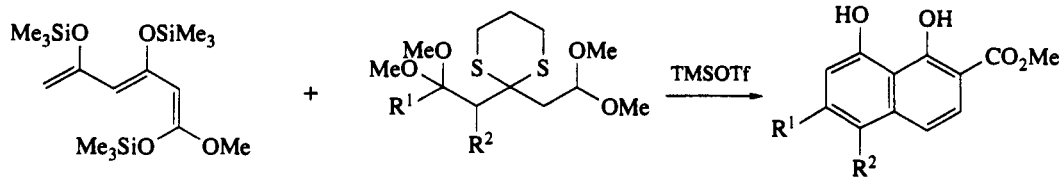
(e) Bicycloaromatization. Conceptually, the approach outlined in Scheme 45 for the construction of cyclic compounds can be extended into a general strategy for the formation of polycyclic compounds according to Scheme 51. It is not a trivial task to reduce the concept into practice experimentally. It requires the ability to assemble the appropriate precursors, (**155**) and (**156**), with the proper nucleophilic and electrophilic sites in the necessary order of reactivity.

Examples of a bicycloaromatization reaction have recently been demonstrated by the reactions of a 1,3,5-trinucleophile (**70**) with several 1,3,5-trielectrophiles (**157**) as illustrated in Scheme 52.[160] The regiochemistry of the reaction appears to be controlled by the first aldol condensation, which is initiated at the ε-position of (**70**) and the ketal position of (**157**).



(**155**) (**156**)

Scheme 51



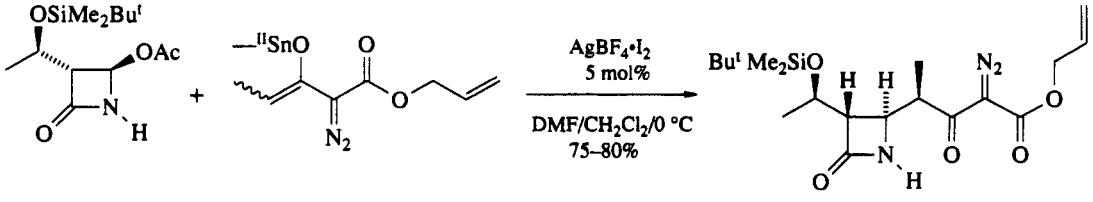
(70) (157) (158)

a : R^1 = Me, R^2 = H
b : R^1 = Et, R^2 = H
c : R^1 = Bu, R^2 = H
d : R^1 = Oct, R^2 = H
e : R^1 = R^2 = Me

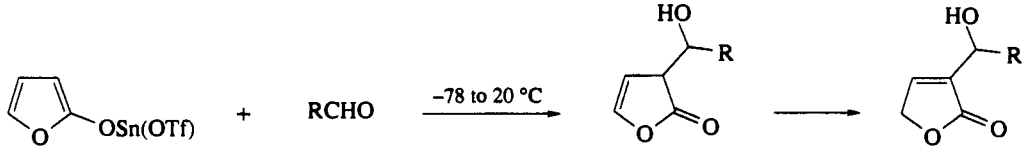
Scheme 52

2.3.3.2.3 Reactions of enol germyl and stannyl ethers

As discussed in Section 2.3.3.1, enol stannyl ethers react with carbonyl compounds readily without the need for catalysts. However, catalytic amounts of $AgBF_4$ and I_2 have been found[161] to improve considerably the yield of the condensation of the tin(II) enol ether (**159**) with the azetidinone (**93**). The use of a catalytic amount of $PdCl_2[P(o\text{-}MeC_6H_4)_3]_2$ improves the yield of the reactions between enol stannyl(IV) ethers and aldehydes.[86]

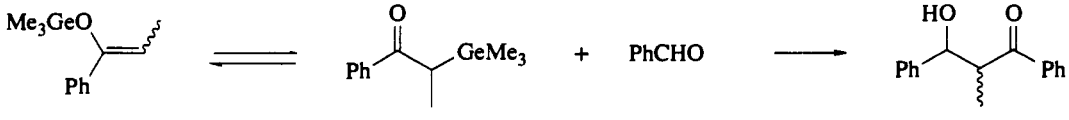


(93) (159) (160)



(161)

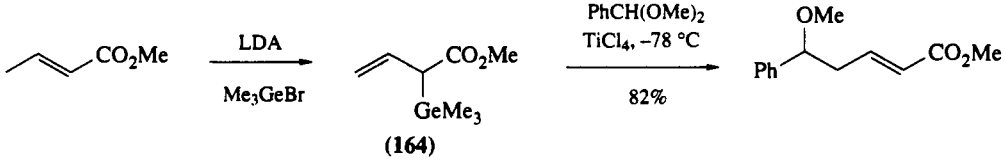
Scheme 53



(162) (163)

Additive	*Temp* (°C)	*Yield* (%)
none	–78 to –40	27
$BF_3 \cdot OEt_2$	–78	58
LiBr	–78 to –40	82

Scheme 54



(164)

Scheme 55

As mentioned previously, 1-trimethylsiloxyfuran (**118**) undergoes aldol reactions at the γ-position. The corresponding tin(II) furanolate (**161**) reacts with aldehydes regioselectively at the α-position to give the 2-substituted butenolides (Scheme 53).[162]

Enol germyl ethers are expected to be more stable than the corresponding enol stannyl ethers, but more reactive than the enol silyl ethers. A recent study[163] shows that enol germyl ethers derived from a number of ketones (*e.g.* **162**) condense with benzaldehyde at –78 to –40 °C without the need for a catalyst. However, the yield of the product (**163**) appears to be improved by the addition of $BF_3{\cdot}OEt_2$. Interestingly, the presence of lithium halide also affects the reaction (Scheme 54).

The α-germylated ester (**164**) reacts with a number of aldehydes and acetals in the presence of Lewis acid to give, regioselectively, the γ-products (Scheme 55).[164] In that sense the germanium-masked dienolate behaves like the siloxy dienes in their regioselection.

2.3.4 CONCLUSION

It is clear that the addition reactions of enol ethers to C—X π-bonds are useful transformations in organic synthesis. Selectivity can be exercised with a range of enol ethers, with the proper choice of catalysts, and with a range of carbon electrophiles. The question of stereoselectivity of these reactions will be discussed in the next chapter. In the future, we can expect more new developments in this area including a better understanding of the structural[61] and mechanistic details of these reactions.[165]

ACKNOWLEDGEMENT

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2.4
Asymmetric Synthesis with Enol Ethers

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2.4.1 INTRODUCTION

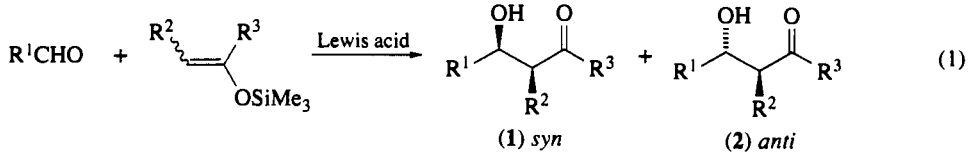
The Lewis acid mediated aldol-type reaction of nucleophilic alkenes (alkyl enol ethers, enol esters) has been investigated since 1939 and is well documented in the literature.[1] The first breakthrough in this field was in 1973–74 when Mukaiyama and coworkers found that silyl enol ethers are much more effective than alkyl enol ethers in Lewis acid mediated additions to carbonyl compounds.[2] This is related to the fact that silicon is markedly more electropositive than carbon (1.8 *versus* 2.5), resulting in a stronger polarization of Si—O bonds and in a stronger tendency for nucleophilic attack at silicon with consequent Si—O bond heterolysis.[3] Since then the 'Mukaiyama reaction' has become a useful chemo- and regio-selective synthetic method. During the 1980s several researchers made a second breakthrough by succeeding in making this reaction diastereo- and enantio-selective. These stereochemical aspects are the subject of the present review. The reader should be aware that progress in this area is still rapid and that some of the tentative conclusions drawn in this review are likely to change. Because of the mass of data that has

accrued in this field, this chapter is selective and critical rather than exhaustive. The reader is referred to earlier reviews for further discussion of individual points.[3,4]

2.4.2 PROCHIRAL NUCLEOPHILES AND ELECTROPHILES (SIMPLE STEREOSELECTION)

Although the mechanism of the 'Mukaiyama reaction' is not yet fully understood, several points have now been firmly established: (a) a Lewis acid enolate is not involved; (b) the Lewis acid activates the carbonyl group for the nucleophilic addition; and (c) the Si—O bond is cleaved by nucleophilic attack of the anionic species, generally halide, on silicon. Point (a) has been established by the use of INEPT–^{29}Si NMR spectroscopy.[5] Moreover, trichlorotitanium enolates have been synthesized, characterized and shown to give a completely different stereochemical outcome than the $TiCl_4$-mediated reactions of silyl enol ethers.[6] Complexes between Lewis acids and carbonyl compounds have been isolated and characterized by X-ray crystallography[7] and recently by NMR spectrometry.[8] On the basis of these observations 'closed' transition structures will not be considered here; 'open' transition structures with no intimate involvement between the silyl enol ether and the Lewis acid offer the best rationale for the 'after the fact' interpretation of the stereochemical results and the best model for stereochemical predictions.

If a prochiral silyl enol ether reacts with a prochiral C=X compound, a pair of racemic diastereoisomers results (equation 1). A reaction that gives an excess of one of these diastereoisomers is said to exhibit simple stereoselection.[4a] In this section we discuss the factors that govern the stereochemistry of this process. Diastereoisomers such as (**1**) and (**2**) will be called *syn* (**1**) and *anti* (**2**) in accord with the convention first proposed by Masamune *et al.*[9] Although only one enantiomer is depicted in each case, all structures in this section represent racemates.



(1)

2.4.2.1 Lewis Acid Mediated Additions to Aldehydes

Silyl enol ethers and silyl ketene acetals add to aldehydes in the presence of a stoichiometric amount of a Lewis acid (generally titanium tetrachloride, boron trifluoride etherate, tin(IV) chloride) with low levels or a complete lack of simple stereoselection. The *anti:syn* ratios usually range from 25:75 to 80:20, depending on the particular aldehyde, Lewis acid, enol ether and on the double bond stereochem-

Table 1 Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Enol Silanes with Aldehydes (equation 1)[a]

Entry	R^1	R^2	R^3	*(Z)/(E)*	*Lewis acid*	*(Anti)/(syn)*	*Yield (%)*	*Ref.*
1	Me_2CH	Me	OEt	15/85	$TiCl_4$	93/7	75	11
2	Ph	Me	OEt	25/75[b]	$TiCl_4$·PPh_3	91/9	79	19
3	Et(Me)CH	Me	Et	c	$TiCl_4$	98/2	92	20
4	Me_2CH	Me	Bu^t	100/0	BF_3·OEt_2	>95/5	84	10
5	Ph	Me	Bu^t	100/0	BF_3·OEt_2	>95/5	95	10
6	Ph	Me	$C(Me_2)OTMS$	100/0	$TiCl_4$	90/10	77	10
7	Ph	Me	SBu^t	<5/95[b,d]	BF_3·OEt_2	96/4	93	21
8	n-C_5H_{11}	Me	SBu^t	90/10[d]	BF_3·OEt_2	92/8	95	21
9	Me_2CH	Me	SBu^t	<5/95[b,d]	BF_3·OEt_2	91/9	93	21
10	C_6H_{11}	Me	SBu^t	90/10[d]	BF_3·OEt_2	91/9	95	21
11	PhCH=CH	Me	SBu^t	<5/95[b,d]	BF_3·OEt_2	93/7	85	21
12	Ph(Me)CH	Me	SBu^t	<5/95[b,d]	BF_3·OEt_2	93/7	75	21
13	Ph	Me	NMe_2[e]	100/0	$ZnBr_2$[f]	90/10	75	22
14	Ph	TMS	OMe	25/75	$TiCl_4$	<5/95	91	23
15	n-C_8H_{17}	TMS	OMe	95/5	$TiCl_4$	5/95	90	23
16	Ph	Bu^t	OEt	76/24	$TiCl_4$	<8/92	c	24
17	Ph	Bu^t	OEt	<5/95	$TiCl_4$	<8/92	c	24

[a] CH_2Cl_2 solvent. [b] $OSiMe_2Bu^t$ ether. [c] Not specified. [d] Note that silyl ketene acetals derived from thiol esters have opposite (*Z*)/(*E*) descriptors compared to esters due to change of sequence rule priority associated with the sulfur atom. [e] STMS ether. [f] Catalytic amount.

istry.[2,10–18] By judiciously choosing substrates and reaction conditions, preparatively useful ratios of the *anti* diastereoisomers (>90%) have been obtained in several cases (equation 1): significant results are summarized in Table 1.[10,11,19–24] When R^2 is small (Me), as in the case of ethyl ketones or propionate derivatives (Table 1; entries 1–13), the most general way to obtain good *anti* selectivities, independent of the double bond stereochemistry, is to have a bulky R^3 group, as with sterically demanding ketones (entries 4–6) and thiol esters (entries 7–12). Esters usually give poor stereoselectivity except for isolated cases (entries 1 and 2). Thiol esters, which are electronically more similar to ketones than esters because of the weak overlap of the C(2*p*) and S(3*p*) orbitals, can undergo a wide variety of further synthetic transformations and are therefore attractive reagents.[21]

The staggered transition structures for the Lewis acid mediated reaction of a (*Z*)-silyl enol ether with an aldehyde are summarized in Figure 1. It is assumed that the Lewis acid occupies a coordination site on the carbonyl oxygen that is *cis* to the aldehydic hydrogen.[7,10] We can immediately rule out A_2 (steric interaction between R^3 and the Lewis acid), A_3 (nonbonded interaction between R^1 and R^3 plus unfavorable dipole–dipole interaction of the two carbon–oxygen bonds) and S_2 (unfavorable dipole–dipole interaction of the two carbon–oxygen bonds). When R^3 is large (Bu^t, SBu^t) and R^2 is small (Me) both S_1 (nonbonded interaction between R^1 and R^3) and S_3 (nonbonded interaction between oxygen and R^3) are disfavored compared to A_1, destabilized only by the *gauche* interaction between R^1 and R^2, and the *anti*

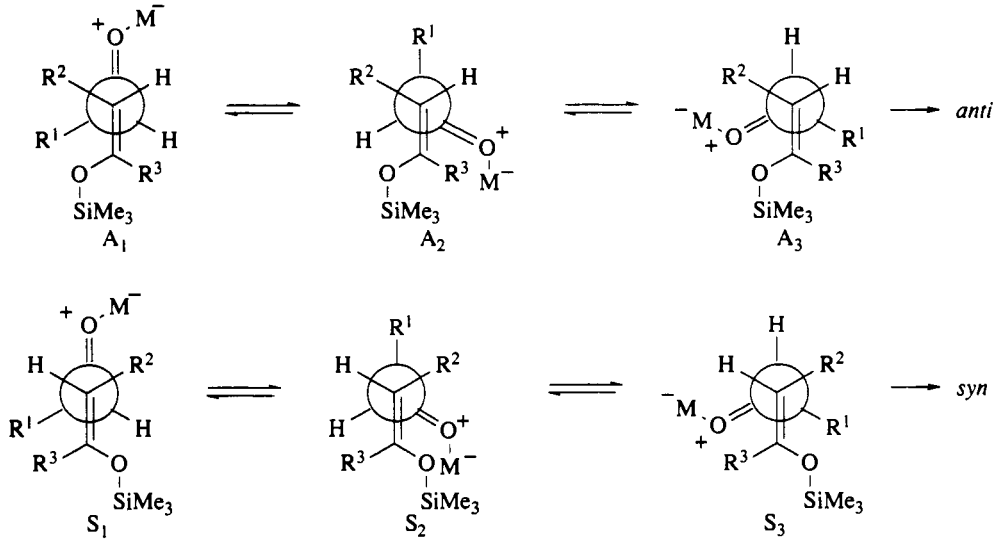


Figure 1

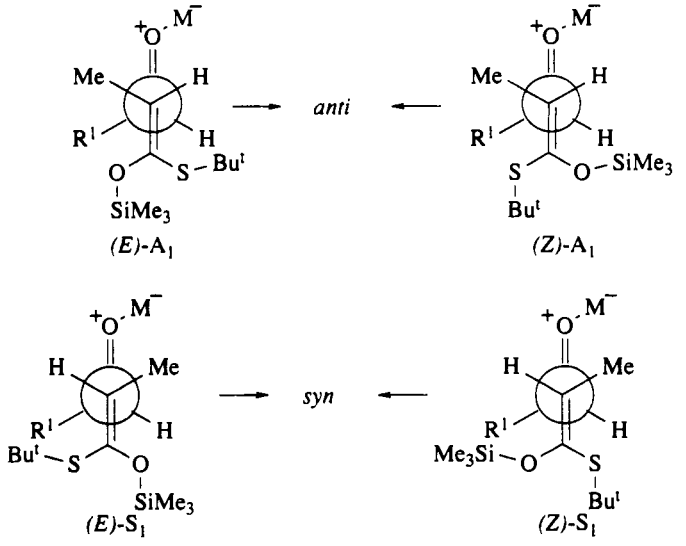
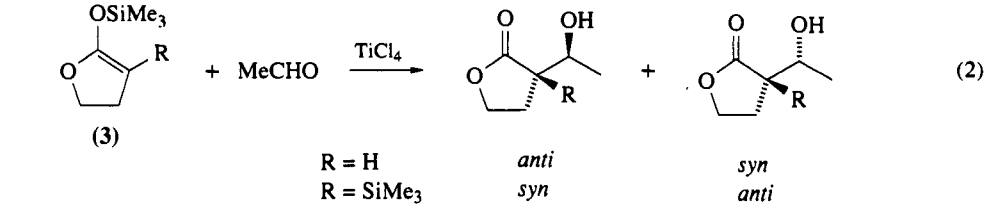


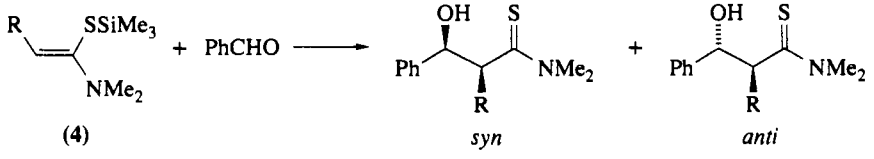
Figure 2

isomers are obtained. In the case of thiol esters the particular 'pinwheel' conformation[21] is probably responsible for the enhanced *anti* selectivity irrespective of the double bond geometry because of the greater effective transmission of the steric hindrance (Figure 2, (*E*) S_1 and (*Z*) S_1 destabilized by R^1/Bu^t and R^1/TMS interactions).

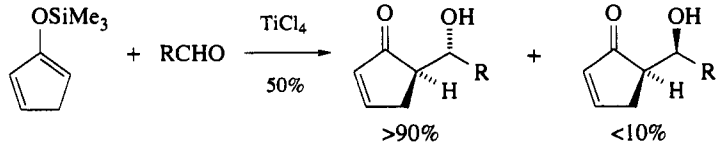
When R^3 is replaced by a smaller group, and R^2 is large (TMS, Bu^t), then both A_1 and S_3 (*gauche* interaction between R^1 and R^2) are disfavored compared to S_1, and the *syn* isomers are obtained (Table 1; entries 14–17). The same analysis applies to several other cases: ketene bis(trimethylsilyl) acetals (R^3 = OTMS) are *anti* selective when R^2 is Me (*anti* 86–89%) and *syn* selective when R^2 is Bu^t (*syn* 70–89%);[24] silyl ketene acetal (**3**) derived from butyrolactone is *anti* (*R*,R**) selective when R = H (*anti* 70%) and *syn* (*R*,S**) selective when R = TMS (single isomer, equation 2);[25a–c] *S*-trimethylsilyl *S,N*-acetals (**4**) are *anti* selective when R = Me (*anti* 60–87%) and *syn* selective when R = Pr^i (*syn* 60%, equation 3).[22] Cyclic enol silanes usually show poor selectivity,[2,10,26] apart from isolated cases where good *anti*:*syn* ratios were obtained by carefully choosing reagents and Lewis acids. Fair *anti* preferences were observed with the cyclopentenone-derived silyl enol ether and $TiCl_4$ (equation 4; R = Pr^i, Bn; *anti* (*R*,R**):*syn*(*R*,S**) >90:10)[27] and with 2-trimethylsilyloxyfuran (**5**; equation 5; *anti* (*R*,R**):*syn*(*R*,S**) 76–88:24–12).[17,27]



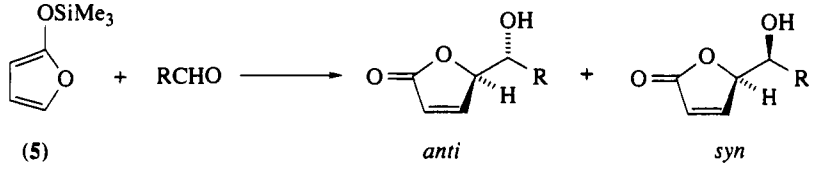
(2)



(3)



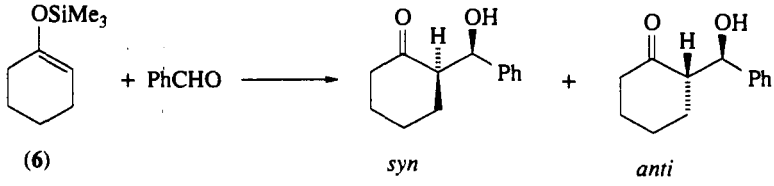
(4)



(5)

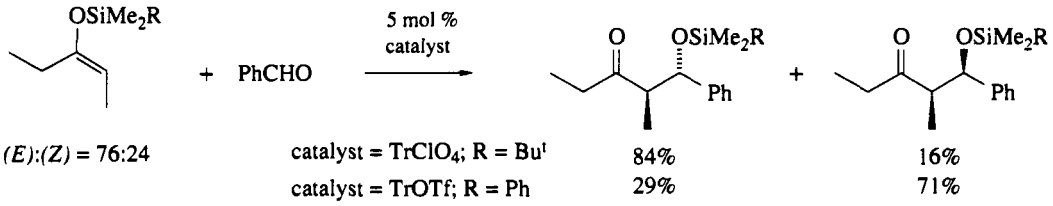
Similar to all the reactions with a negative activation volume $\Delta V^{\ddagger}$, the silyl enol ether aldol addition is accelerated by using high pressure (10 kbar)[28a] or the hydrophobic effect (water and sonication);[28b] under these conditions the reaction can be conducted without catalyst to give good yields of products with a stereoselectivity that is the reverse of that seen in the acid-catalyzed reaction. With $TiCl_4$ enol silane (**6**) gives the *anti* isomer predominantly (75:25), while under neutral conditions the *syn* isomer is preferred (75:25; equation 6). These studies show unambiguously that $\Delta V^{\ddagger}$ is smaller for the *syn* isomer transition structure, and that the Lewis acid not only acts as carbonyl group activator but also plays an important role for controlling the reaction stereoselectivity.

Recently Mukaiyama and coworkers introduced the use of trityl salts as efficient catalysts for the aldol reaction. Using a catalytic amount of trityl perchlorate (5 mol %) and *t*-butyldimethylsilyl enol ethers, the *anti* aldols were preferentially obtained (*anti* 73–84%) regardless of the double bond geometry.[29a] With trityl triflate (5 mol %) and dimethylphenylsilyl enol ethers, the *syn* isomers are produced predominantly (*syn* 63–79%; Scheme 1).[29b] Several variations of the catalyst system have been developed. Trityl

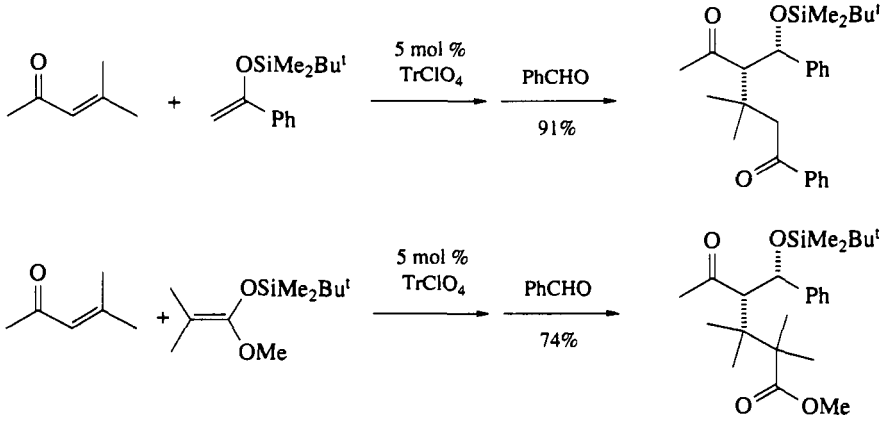


(6) *syn* *anti* (6)

perchlorate can be supported on a polymer.[30] The combined use of catalytic amounts of trityl chloride and tin(II) chloride (*anti* 69–82%)[31] or of trimethylsilyl chloride and tin(II) chloride[32] is a mild and effective procedure. Trityl perchlorate can also be used to catalyze the tandem Michael–aldol reaction with good yields and excellent stereoselectivity (Scheme 2).[33a] The aldol product is obtained as a single isomer (*syn*), in agreement with the foregoing discussion (Figure 1, transition structure S_I) when R^3 is small and R^2 is a large group. Analogously, a single aldol isomer (100% *syn*) is obtained in the Ph_3CSbCl_6-catalyzed tandem Michael–aldol reaction on cyclohexenone.[33b]



Scheme 1

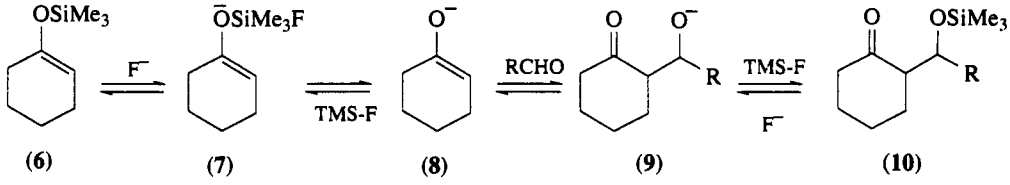


Scheme 2

2.4.2.2 Fluoride Ion Mediated Additions to Aldehydes

In 1976 Kuwajima, Nakamura and coworkers found that fluoride ion catalyzes the reaction of enol silanes with aldehydes.[34a] The efficacy of fluoride in such reactions reflects the high homolytic dissociation energy of the Si—F bond (807 kJ mol^{-1}).[3] The mechanism and stereoselectivity of this reaction have been examined by several groups, and the subject has been recently reviewed.[3,4a,6a] The aldol coupling is effected smoothly at low temperatures with about 0.1 equiv. of tetrabutylammonium fluoride (TBAF) in THF. The process appears to proceed through a catalytic cycle involving several reversible steps (Scheme 3). The principal features are the following: (a) TMSF is essential for trapping the unstable aldolate (**9**) and driving the reaction forward; (b) TMSF probably also acts as an activator of the carbonyl group; (c) the reactive species is probably the metal-free enolate anion (**8**) and not the anionic hypervalent silyl enol ether (**7**);[34b] and (d) the equilibration between enolate (**8**) and aldolate (**9**) is much more facile than the fluoride-mediated retrograde reaction of the aldol silyl ether (**10**). Usually the

kinetic products are the *syn* isomers; however, longer reaction times and higher temperatures lead to product mixtures approximating the thermodynamic ratio of *syn* and *anti* isomers. For example, the *syn:anti* diastereomeric ratio in the reaction of (**6**) with TBAF and benzaldehyde changed gradually from 65:35 (5 min) to final equilibrium of 54:46 (8 h).[35] With the (*Z*)-silyl enol ether derived from ethyl *t*-butyl ketone, TBAF and benzaldehyde, the *syn:anti* ratio varied from 100:0 (–70 °C, 1 h) to 20:80 (room temperature).[36] Added extra TMSF proved advantageous for both stereoselectivity and yield: reaction of the cyclopentanone-derived trimethylsilyl enol ether with isobutyraldehyde gave, in the presence of catalytic TBAF and 2 equiv. of TMSF, the *syn* isomer exclusively.[35] *Syn* selectivity was also obtained with ketene bis(trimethylsilyl) acetals (equation 7; Table 2, entries 1 and 2),[37] thiol ester silyl ketene acetals (entries 3 and 4),[21] 2-trimethylsilyloxyfuran (**5**), catalytic TBAF and various aldehydes (equation 5; *syn* 78–92%),[17] *S*-trimethylsilyl *S,N*-acetals (**4**; R = Me, Pr^i), catalytic TBAF and benzaldehyde (equation 3; *syn* 81–96%).[22] Preparatively useful ratios of the *syn* isomers, regardless of silyl enol ether geometry, are obtained using catalytic amounts of tris(dimethylamino)sulfonium (TAS) difluorotrimethylsiliconate as fluoride ion source.[38] For example the silyl enol ethers derived from both cyclopentanone and cyclohexanone give with isobutyraldehyde the *syn* isomers exclusively. The reaction has also been studied with several acyclic enol silanes (equation 7): *syn* selectivity ranged from moderate, when R^3 is a small alkyl group (Table 2, entries 5–7), to good when R^3 is aryl (entries 8 and 9).



Scheme 3

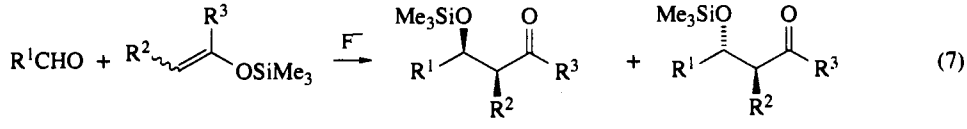


Table 2 Ratio of Diastereoisomers in the Fluoride Ion Catalyzed Reactions of Enol Silanes with Aldehydes (equation 7)

Entry	R^1	R^2	R^3	*(Z)/(E)*	*Catalyst*	*(Syn)/(anti)*	*Yield (%)*	*Ref.*
1	Ph	Me	OTMS	—	TBAF	79/21	75	37
2	Ph	Et	OTMS	—	CsF	78/22	78	37
3	Ph	Me	SBu^t	7/93[a]	TBAF	95/5	91	21
4	Ph	Me	SBu^t	90/10[a]	TBAF	57/43	42	21
5	Ph	Me	Et	100/0	$TASTMSF_2$	86/14	89	38
6	Ph	Me	Et	30/70	$TASTMSF_2$	63/37	84	38
7	Ph	Et	Pr^n	100/0	$TASTMSF_2$	86/14	65	38
8	Ph	Me	Ph	99/1	$TASTMSF_2$	95/5	75	38
9	Ph	Me	Ph	9/91	$TASTMSF_2$	94/6	78	38

[a] See footnote d of Table 1.

Nakamura, Kuwajima and coworkers have recently shown that TBAF and TAS difluorotrimethylsiliconate-catalyzed reactions give identical sense and degree of stereoselection.[34b] As the stereoselectivity of the fluoride-catalyzed aldol reaction is independent of the countercation and of the type of silyl group,[34b] the 'open' transition structures **A** (extended) and **B** (skew) have been proposed to account for the observed dependence of the *syn:anti* ratios on the steric hindrance of R^1, R^2 and R^3 (Figure 3).[34b,38]

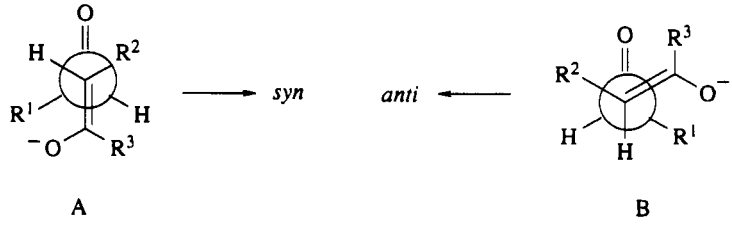
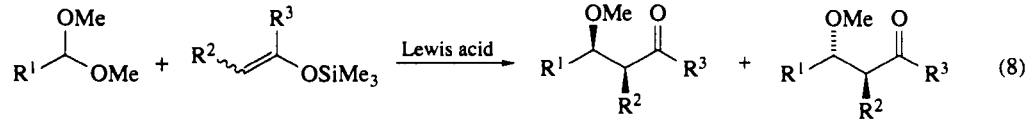


Figure 3

2.4.2.3 Lewis Acid Mediated Additions to Acetals

The $TiCl_4$-mediated reaction of enol silanes with acetals (equation 8) was reported by Mukaiyama and coworkers in 1974.[1] More recently various catalysts (1–10 mol %), *i.e.* trimethylsilyl trifluoromethanesulfonate (TMSOTf),[39,40] trityl perchlorate ($TrClO_4$),[41,42] polymer-supported trityl perchlorate,[30] clay montmorillonite,[14] trimethylsilyl iodide (TMSI)[43] and rhodium complexes,[44] have been used to promote the addition to give good yields of the aldol products. The reaction is usually *syn* stereoselective; significant results are reported in Table 3. Moderate to good *syn*:*anti* ratios were obtained with silyl enol ethers derived from cyclic ketones (entries 1–5), acyclic ketones when R^3 is aryl or a bulky alkyl group regardless of the enol ether geometry (entries 6–8), and thiol esters (entry 9). When R^3 is OMe or Et the selectivity is lost (entries 10 and 11). The mechanism of the TMSOTf-catalyzed reaction was recently studied in detail by ^1H and ^{13}C NMR spectroscopy and shown to proceed through carboxonium triflate ion pairs.[39c] 'Open' extended transition structures, similar to the ones proposed for the fluoride-catalyzed reactions (Figure 3, structure A) have been used to rationalize the *syn* selectivity irrespective of the double bond geometry.[39c]



(8)

Table 3 Ratio of Diastereoisomers in the Lewis Acid Catalyzed Reactions of Enol Silanes with Dimethyl Acetals (equation 8)

Entry	R^1	R^2	R^3	*(Z)/(E)*	*Catalyst*	*(Syn)/(anti)*	*Yield (%)*	*Ref.*
1	Ph	—$(CH_2)_4$—		0/100	TMSI	95/5	89	43
2	Pr^n	—$(CH_2)_4$—		0/100	TMSOTf	89/11	91	39
3	Pr^i	—$(CH_2)_4$—		0/100	$TrClO_4$	80/20	90	41
4	Ph	—$(CH_2)_3$—		0/100	TMSI	99/1	87	43
5	PhCH=CH	—$(CH_2)_3$—		0/100	TMSI	80/20	82	43
6	Ph	Me	Ph	0/100	TMSOTf	71/29	83	39
7	Ph	Me	Ph	100/0	TMSOTf	84/16	97	39
8	Ph	Me	Bu^t	100/0	TMSOTf	95/5[a]	94	39
9	Ph	Me	SBu^t	0/100	TMSOTf	78/22	92	39
10	Ph	Me	OMe	0/100[b]	TMSOTf	50/50	74	39
11	Ph	Me	Et	79/21	TMSI	57/43	84	43

[a] This stereochemical assignment was questioned (ref. 4a).[b] *(Z)/(E)* = 100/0 gave *(syn)/(anti)* = 55/45 (ref. 39c).

2.4.2.4 Lewis Acid Mediated Additions to Imines

The $TiCl_4$-mediated reaction of enol silanes with imines was first introduced by Ojima and coworkers in 1977.[45] The reaction was then extended to several similar substrates, *i.e.* nitrones,[46] α-methoxycarbamates,[47] aminals,[48] 4-acetoxyazetidin-2-one,[49,50] and to different Lewis acids, *i.e.* $SnCl_4$,[51] $TiCl_2(OPr^i)_2$,[51] catalytic ZnX_2,[49,51] catalytic TMSOTf,[50] to give good yields of the addition products with low levels (≤80:20) or a complete lack of simple stereoselection. Moderate to good *anti* selectivities were reported in the addition of silyl ketene acetals to imines under particular reaction conditions (equation 9); significant results are summarized in Table 4.

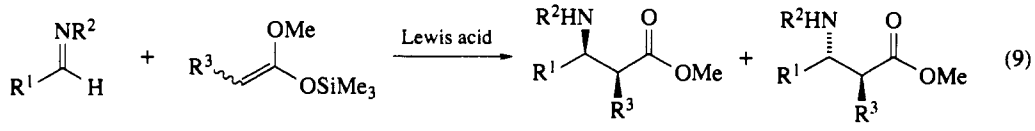


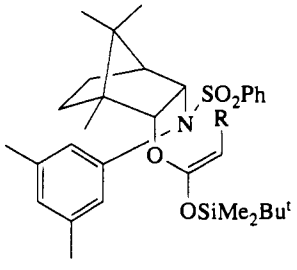
Table 4 Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Silyl Ketene Acetals with Imines (equation 9)

Entry	R^1	R^2	R^3	*(Z)/(E)*	*Lewis acid*	*(Anti)/(syn)*	*Yield (%)*	*Ref.*
1	Ph	TMS	Et	0/100	ZnI_2	90/10	61	52
2	TMSC≡C	TMS	Ph	0/100	ZnI_2	92/8	53	52
3	Ph	Ph	Ph	64/36	TMSOTf[a]	86/14	85	53
4	PhCH=CH	*p*-$MeOC_6H_4$	Ph	64/36	TMSOTf[a]	85/15	78	53
5	Ph	Ph	Me	25/75	TMSOTf[a]	100/0	85	53

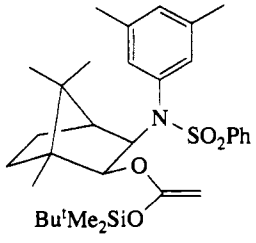
[a] Catalytic amount (10 mol %).

2.4.3 CHIRAL NUCLEOPHILES

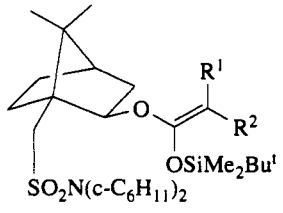
Chiral silyl ketene acetals (**11**)–(**20**) were recently introduced for diastereoselective aldol-type additions. Camphor derivatives (**11**)–(**16**) are conformationally rigid with one diastereotopic face of the enol silane sterically shielded.[54,55] *N*-Methylephedrine derivatives (**17**)–(**20**) are likely to bind to $TiCl_4$ through the NMe_2 group with consequent dramatic conformational constraint.[19,56,57] As a result the Lewis acid mediated additions to C=X occur in a highly stereoselective way. The chiral auxiliaries can then be removed (and recycled) by reduction, saponification or displacement with various nucleophiles to give useful synthetic intermediates.



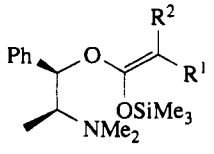
(**11**) R = H
(**12**) R = Me



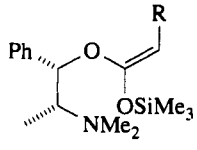
(**13**)



(**14**) $R^1 = R^2 = H$
(**15**) R^1 = Me; R^2 = H
(**16**) R^1 = H; R^2 = Me



(**17**) R^1 = H; R^2 = Me
(**18**) R^1 = Me; R^2 = H



(**19**) R = Me
(**20**) R = Et

2.4.3.1 Diastereoselective Aldol Additions of Chiral Silyl Ketene Acetals and Chiral Silyl Enol Ethers

Acetate-derived silyl ketene acetals (**11**, **13** and **14**) react with aldehydes with good stereoselectivity (equation 10); significant results are reported in Table 5. Removal of the auxiliary, with methanolic KOH, gave the corresponding β-hydroxy acids in good enantiomeric excess (*ee*). The asymmetric variants of the Mukaiyama reaction also helped to solve the long-standing problem of an efficient *anti* selec-

tive chiral propionate equivalent (equation 11);[4a] significant results are reported in Table 6. It is interesting to observe that with the camphor derivatives changing the double bond geometry gives rise to reversal of stereochemistry in the product aldol (entries 7 and 8), whereas with the *N*-methylephedrine derivatives the results are more or less the same (entries 8 and 10). It is therefore probable that these reactions, although appearing similar, have different mechanisms; transition structure hypotheses[54,55,57] are also likely to be *ad hoc* rather than general. The adducts (**23**) and (**24**) were reduced (using $LiAlH_4$) to diols,[54,55] saponified to hydroxy acids (LiOH; NaOH),[55–57] or converted to hydroxamates ($RONH_2 \cdot HCl$, Et_3Al) for β-lactam synthesis,[58] without detectable epimerization. It is worth noting that with the *N*-methylephedrine derivatives both the major *anti* (**23**) and the major *syn* (not shown) stereoisomers have the same absolute configuration (*S*) at C-2. This shows that, while the aldehyde π-facial selectivity is only moderate, the silyl ketene acetal π-facial selectivity is very high. Indeed, using trimethyl orthoformate (**25**) as electrophile, adduct (**26**) was obtained in 65% yield with good selectivity (≥95.5:4.5; Scheme 4). By simple functional group modifications (**26**) was converted in high yield to aldehyde (**27**; 91% *ee*).[59]

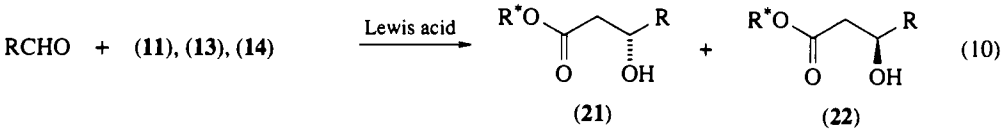


Table 5 Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Chiral Silyl Ketene Acetals with Aldehydes (equation 10)

Entry	*Reagent*	*R*	*Lewis acid*	*(21)/(22)*	*Yield (%)*	*Ref.*
1	(**11**)	Et	$TiCl_4$	93/7	67	54
2	(**11**)	n-C_7H_{15}	$TiCl_4$	93/7	59	54
3	(**11**)	Pr^i	$TiCl_4$	97/3	51	54
4	(**13**)	Pr^i	$TiCl_4$	5/95	62	54
5	(**13**)	Ph	$TiCl_4$	6/94	69	54
6	(**14**)	Ph	$TiCl_4$	92/8	56	55
7	(**14**)	Pr^i	$TiCl_4$	99/1	47	55
8	(**14**)	Pr^n	$TiCl_4$	92/8	48	55
9	(**14**)	n-C_8H_{17}	$TiCl_4$	92/8	51	55
10	(**14**)	Ph	$BF_3 \cdot OEt_2$	92/8	30	55
11	(**14**)	Pr^i	$BF_3 \cdot OEt_2$	95/5	44	55

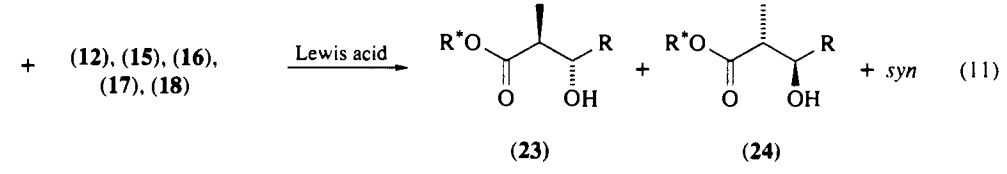
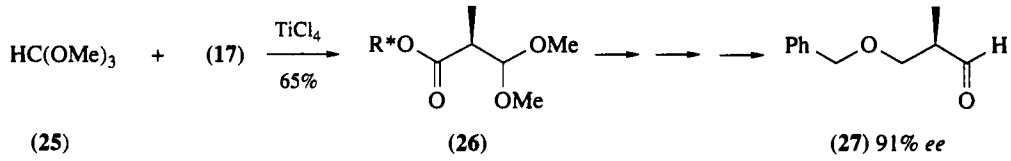


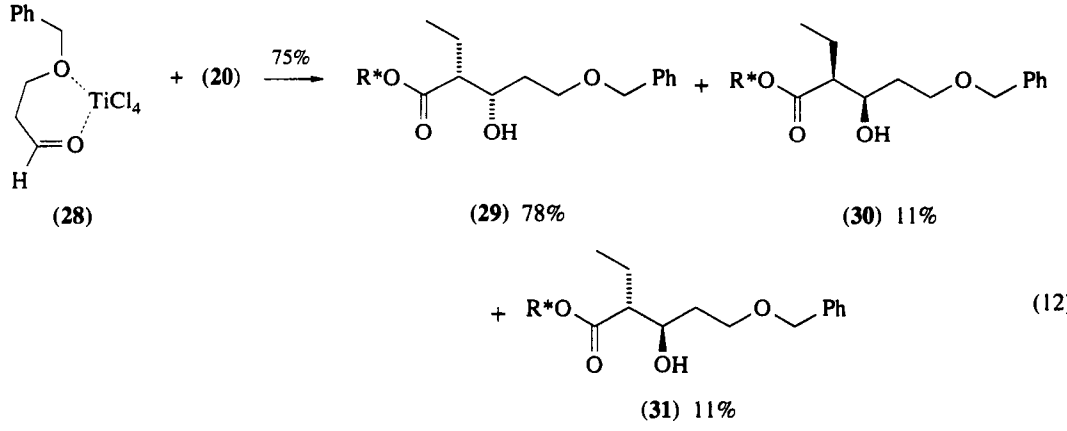
Table 6 Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Chiral Silyl Ketene Acetals with Aldehydes (equation 11)

Entry	*Reagent*	*R*	*Lewis acid*	*(Anti)/(syn)*	*(23)/(24)*	*Yield (%)*	*Ref.*
1	(**12**)	Pr^i	$TiCl_4$	93.5/6.5	2/98	66	54
2	(**15**)	Ph	$TiCl_4$	81/19	5/95	44	55
3	(**15**)	Et	$TiCl_4$	100/0	16/84	30	55
4	(**15**)	Pr^n	$TiCl_4$	94/6	7/93	50	55
5	(**15**)	Pr^i	$TiCl_4$	98.2/1.8	7.5/92.5	60	55
6	(**15**)	Pr^i	$BF_3 \cdot OEt_2$	73/27	3/97	58	55
7	(**16**)	Pr^i	$BF_3 \cdot OEt_2$	93.5/6.5	93.5/6.5	57	55
8	(**17**)	Ph	$TiCl_4$	85/15	97/3	80	56
9	(**17**)	Ph	$TiCl_4 \cdot PPh_3$	97/3	97/3	90	19
10	(**18**)	Ph	$TiCl_4$	80/20	95.5/4.5	65	56, 57
11	(**17**)	(*E*)-PhCH=CH	$TiCl_4$	85/15	95.5/4.5	60	56
12	(**17**)	(*E*)-PhCH=CH	$TiCl_4 \cdot PPh_3$	93.7/6.3	93/7	50	19
13	(**17**)	(*E*)-MeCH=CH	$TiCl_4$	80/20	95.5/4.5	78	56
14	(**17**)	Pr^n	$TiCl_4$	80/20	95.5/4.5	88	56
15	(**17**)	n-C_5H_{11}	$TiCl_4$	75/25	96.5/3.5	60	56



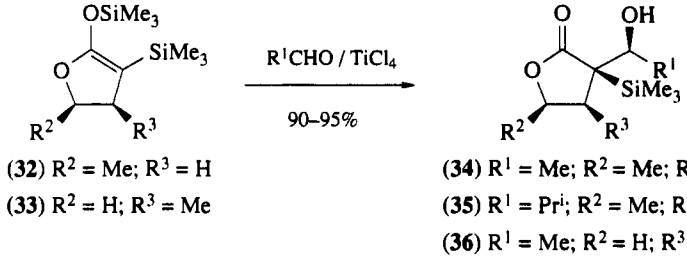
Scheme 4

Equation (12) illustrates the following general principle: 'electrophiles able to form a chelated complex with the Lewis acid (*e.g.* **28**) control (usually invert) the simple stereoselection of the reaction'. The major isomer (**29**) is, in fact, *syn*. Adducts (**29**) and (**30**) were then transformed, by simple functional group chemistry, into (+)-PS-5, a carbapenem antibiotic.[60] Transition structure models for this process are discussed in detail in Section 2.4.4.1.

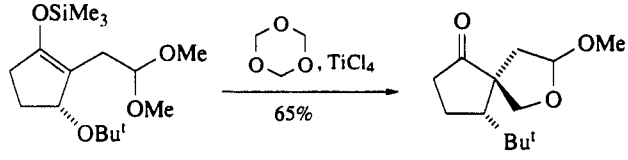


(12)

Chiral butyrolactone derivatives (**32**) and (**33**) react with aldehydes to give the condensation products (**34**)–(**36**) as single stereoisomers in high yield (equation 13);[25b,c] both simple stereoselection (TMS and OH *syn*, see Section 2.4.2.1) and diastereofacial selection are 100%. Another example where a substituent on a cyclic silyl enol ether causes 100% diastereofacial selection is shown in equation (14).[61]



(13)

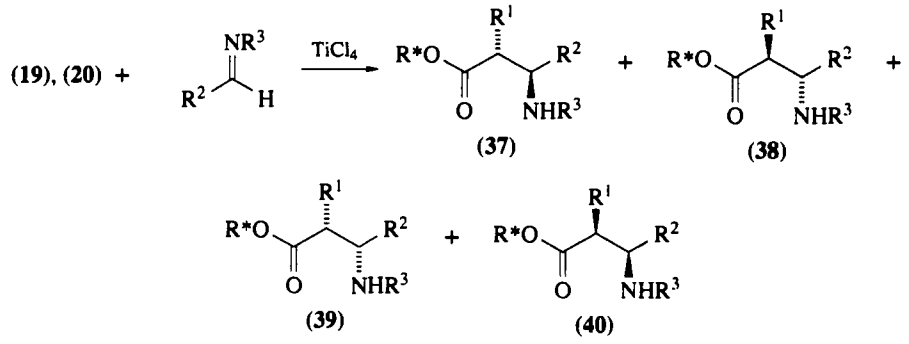


(14)

2.4.3.2 Diastereoselective Additions of Chiral Silyl Ketene Acetals to Imines

N-Methylephedrine-derived silyl ketene acetals react with imines in the presence of 2 mol equiv. of $TiCl_4$ to give β-amino esters (equation 15); significant results are summarized in Table 7. With benzylideneaniline the reaction is *anti* selective (entry 1), while with imino esters that chelate $TiCl_4$ to give complexes such as (**41**), the reaction is *syn* selective (entries 2 and 3), in agreement with the general prin-

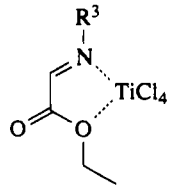
ciple described in the preceding section. Adducts (**37**)–(**40**) have been transformed into optically active *trans* and *cis* β-lactams.[58,62]



(15)

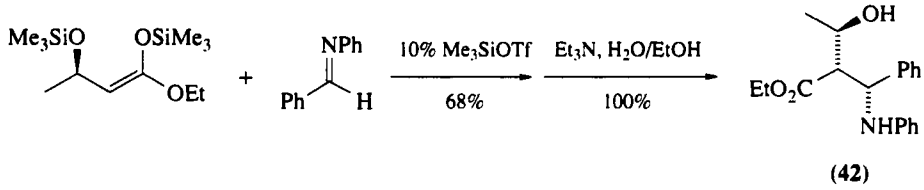
Table 7 Ratio of Diastereoisomers in the $TiCl_4$-mediated Reactions of Chiral Silyl Ketene Acetals with Imines (equation 15)

Entry	*Reagent*	R^1	R^2	R^3	(**37**) + (**38**)/(**39**) + (**40**)	(**37**)/(**38**)	(**39**)/(**40**)	*Yield* (%)	*Ref.*
1	(**19**)	Me	Ph	Ph	91.5/8.5	97.5/2.5	—	75	58, 62
2	(**20**)	Et	CO_2Et	CH_2Ph	11.1/88.9	—	75/25	53	58
3	(**20**)	Et	CO_2Et	*p*-$MeOC_6H_4$	12.5/87.5	—	87.5/12.5	70	58



(**41**)

Another case where simple stereoselection is reversed by the use of particular reagents is shown in Scheme 5; (**42**) was obtained as a single isomer (*syn*),[63] in contrast with the *anti* selectivity shown by achiral silyl ketene acetals with the same catalyst (Table 4, entries 3–5).



(**42**)

Scheme 5

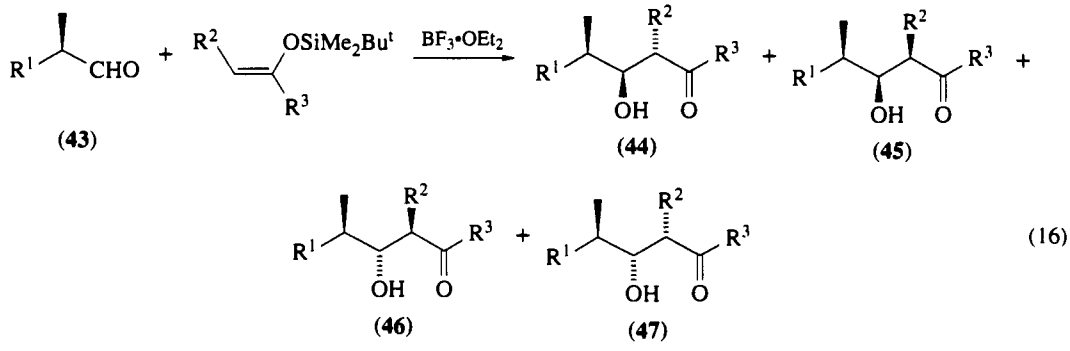
2.4.4 CHIRAL ELECTROPHILES

When the electrophile is chiral, besides simple stereoselection a second type of diastereoselectivity, termed 'diastereofacial selectivity', is possible. This sort of diastereofacial preference, qualitatively predictable by Cram's rule for asymmetric induction or one of its more modern descendants,[4a] is typical for additions to chiral aldehydes.

2.4.4.1 Diastereoselective Additions to Chiral Carbonyl Compounds

Chiral α-methyl aldehydes (**43**) show exceptional diastereofacial preferences in their Lewis acid mediated reactions with enol silanes (equation 16);[21,25c,26–64] selected data are reported in Table 8. The reason for this selectivity may be due to an approach trajectory of the nucleophile closer to the stereocenter when the carbonyl group is bound to the Lewis acid.[64] Additions to chiral α-alkoxy aldehyde (**48**) were studied with both nonstereogenic (equation 17; Table 9) and stereogenic enol silanes (equation 18; Table 10). (Stereogenic and nonstereogenic are defined according to Mislow and Siegel.)[170]

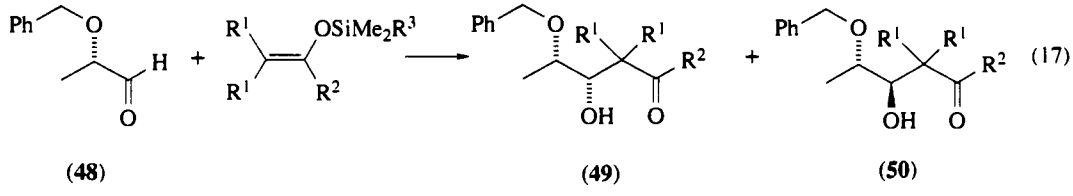
With nonstereogenic enol silanes (Table 9) usually (not always, see entry 2) a single isomer was obtained using tin(IV) chloride or titanium chloride as a promoter (entries 3, 5, 7 and 9). This high facial



(16)

Table 8 Ratio of Diastereoisomers in the $BF_3{\cdot}OEt_2$-mediated Reactions of Enol Silanes with Chiral α-Methyl Aldehydes (equation 16)

Entry	R^1	R^2	R^3	*Yield (%)*	*(44)*	*(45)*	*(46)*	*(47)*	*Ref.*
1	Ph	H	Me	75	91	—	9	—	64
2	Ph	H	But	74	96	—	4	—	64
3	Ph	H	OMe	81	94	—	6	—	64
4	Ph	H	OBut	81	97	—	3	—	64
5	Ph	Me	SBut	75	91	7	2	0	21
6	$PhCH_2$	H	OBut	88	72	—	28	—	64
7	$Me_2C{=}CH$	H	OBut	68	96	—	4	—	64
8	c-C_6H_{11}	H	OBut	77	94	—	6	—	64



(17)

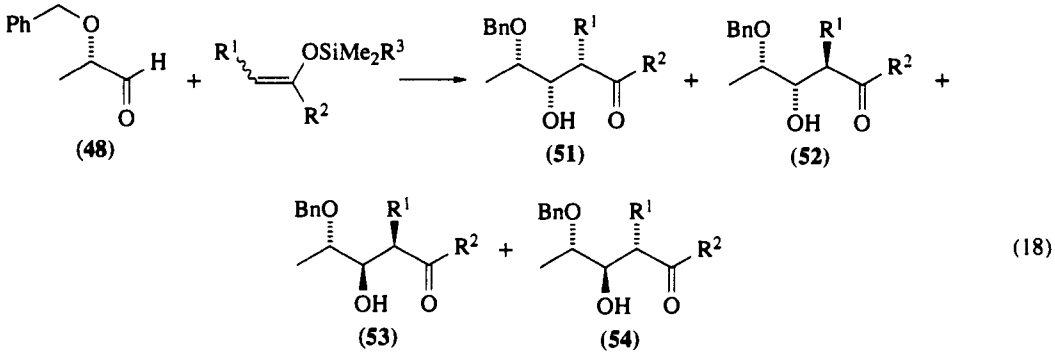
Table 9 Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Aldehyde (**48**; equation 17)

Entry	R^1	R^2	R^3	*Promoter*	*Yield (%)*	*(49)*	*(50)*	*Ref.*
1	H	OMe	But	$BF_3{\cdot}OEt_2$	48	60	40	10
2	H	OBut	But	$SnCl_4$	65	65	35	10
3	H	SBut	But	$SnCl_4$	50	>98	<2	80
4	H	But	Me	BF_3(gas)	85	10	90	65a
5	H	But	Me	$SnCl_4$ or $TiCl_4$	86	>99	<1	10, 66
6	H	But	Me	$BF_3{\cdot}OEt_2$	a	50	50	67
7	H	Ph	Me	$SnCl_4$ or $TiCl_4$	70	>99	<1	10, 68
8	H	Ph	Me	$BF_3{\cdot}OEt_2$	a	35	65	68
9	Me	OMe	Me	$SnCl_4$ or $TiCl_4$	85	>97	<3	66
10	Me	OMe	Me	$BF_3{\cdot}OEt_2$	85	35	65	66
11	Me	OMe	Me	BF_3(gas)	85	16	84	65a

[a] Not reported.

selectivity is due to the formation of a chelated complex between the aldehyde and the Lewis acid (*e.g.* **55**) and addition of the nucleophile to the less-encumbered face of the complex (to give **49**). A further remarkable example of this chelation control, taken from the synthesis of pestalotin, is shown in equation (19).[72]

The lack of facial selectivity in $BF_3{\cdot}OEt_2$-mediated reactions (entries 1, 6, 8 and 10) is not surprising as this Lewis acid is incapable of bis-ligation. Using an excess of gaseous BF_3 a conformationally rigid

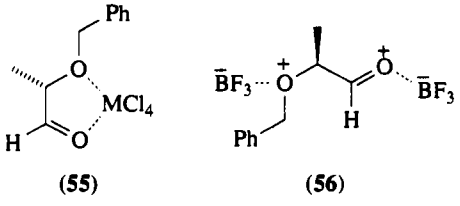


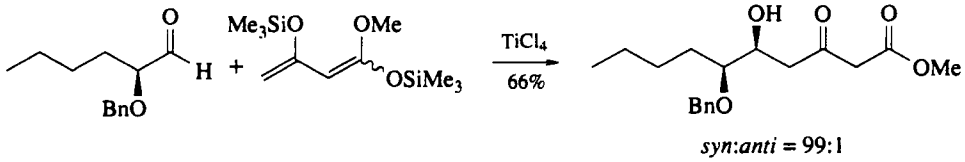
(18)

Table 10 Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Aldehyde (**48**; equation 18)

Entry	R^1	R^2	R^3	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(51)*	*(52)*	*(53)*	*(54)*	*Ref.*
1	Me	Et	Me	0/100	$TiCl_4$	a	18	82	0	0	69a
2	Me	Et	Me	34/66	$TiCl_4$	a	44	56	0	0	69a
3	Me	Pr^i	Me	0/100	$TiCl_4$	75	50	50	0	0	10
4	Me	Pr^i	Me	100/0	$TiCl_4$	73	88	12	0	0	10
5	Me	Bu^t	Me	0/100	$SnCl_4$	66	59	41	0	0	10, 70
6	Me	Bu^t	Bu^t	0/100	$TiCl_4$	80	39	61	0	0	70
7	Me	Ph	Me	0/100	$SnCl_4$ or $TiCl_4$	80	95	5	0	0	10, 68
8	Me	Ph	Me	100/0	$TiCl_4$	73	85	15	0	0	10, 70
9	Me	Ph	Me	0/100	TBAF	60	18	0	82	0	65a
10	Me	C(Me$_2$)OTMS	Me	0/100	$SnCl_4$	65	100	0	0	0	70
11	Me	OMe	Me	83/17	$TiCl_4$	75	77	23	0	0	69, 70
12	Me	OMe	Me	83/17	$SnCl_4$	75	80	20	0	0	69, 70
13	Me	OBu^t	Me	0/100	$TiCl_4$ or $SnCl_4$	a	58	31	7	4	69a
14	Me	SBu^t	Me	93/7[b]	$SnCl_4$	90	95	5	0	0	21, 71
15	Me	SBu^t	Me	10/90[b]	$SnCl_4$	87	85	15	0	0	21, 71
16	Me	SBu^t	Bu^t	>95/5[b]	$SnCl_4$	89	97	3	0	0	21, 71
17	Me	SBu^t	Bu^t	<5/95[b]	$SnCl_4$	90	76	24	0	0	21, 71
18	Me	SBu^t	Me	93/7[b]	$TiCl_4$	85	94	6	0	0	21
19	Me	SBu^t	Me	10/90[b]	$TiCl_4$	82	83	17	0	0	21
20	Me	SBu^t	Me	93/7[b]	TBAF	72	16	3	73	8	21, 71
21	Me	SBu^t	Me	10/90[b]	TBAF	68	13	3	72	12	21, 71
22	Me	SBu^t	Me	93/7[b]	$BF_3{\cdot}OEt_2$	57	6	22	12	60	21

[a] Not reported. [b] See footnote d of Table 1.





(19)

syn:*anti* = 99:1

complex such as (**56**) is likely to form due to electrostatic repulsion.[65a] Addition of the nucleophile to the less encumbered face of complex (**56**) gives the opposite stereoisomer (**50**; entries 4 and 11). With stereogenic enol silanes (Table 10) usually two (**51** and **52**) of the four possible diastereoisomers were obtained using tin(IV) chloride or titanium chloride. In particular cases [propiophenone silyl enol ethers (entries 7 and 8), Heathcock's reagent (entry 10), thiol ester silyl ketene acetals (entries 14–19)] mainly one (**51**) of the four possible isomers was obtained. The predominant isomer (**51**) is the result of *syn* simple stereoselection (at C-2, C-3), in agreement with the general principle that chelation controls (usually inverts) simple stereoselection (the same enol silanes are *anti* selective in their reactions with aldehydes incapable of chelation, see Table 1, entries 6–12). To rationalize these results the four staggered transition structures shown in Figure 4 were proposed.[10,21,71] The other eight possible staggered transition structures (not shown) were discarded because of steric interactions between the ligands of the chelated metal and R^1, Me or OTMS. For (*E*)-isomers the size of the R^1 group should not affect stereochemistry since R^1 interacts only with the aldehydic hydrogen in both S_I and A_I. S_I is favored over A_I because of the unfavorable dipole–dipole interactions between the two C—O bonds. As a result, the (*E*)-isomers are C-2,C-3 *syn* selective and in about the same degree (Table 10, entries 4, 8, 15, 17 and 19). For the (*Z*)-isomers the R^1 group interacts with C-2 in transition structure S_I and with the metal ligands in transition structure A_I. As a result the C-2,C-3 *syn*:*anti* ratios are related in some manner to the steric demand of R^1 (entries 1, 3 and 5) and are excellent only in particular cases (entries 7, 10, 14, 16 and 18). Fluoride ion catalyzed reactions (Table 10, entries 9, 20 and 21) gave (**53**) as the major stereoisomer, as a result of *syn* simple stereoselection (see Table 2), and diastereofacial selection predicted by the Felkin–Anh model.[4a] Note that silyl ketene acetals derived from thiol esters have opposite (*E*)/(*Z*) descriptors compared to esters and ketones due to change of sequence rule priority associated with the sulfur atom.

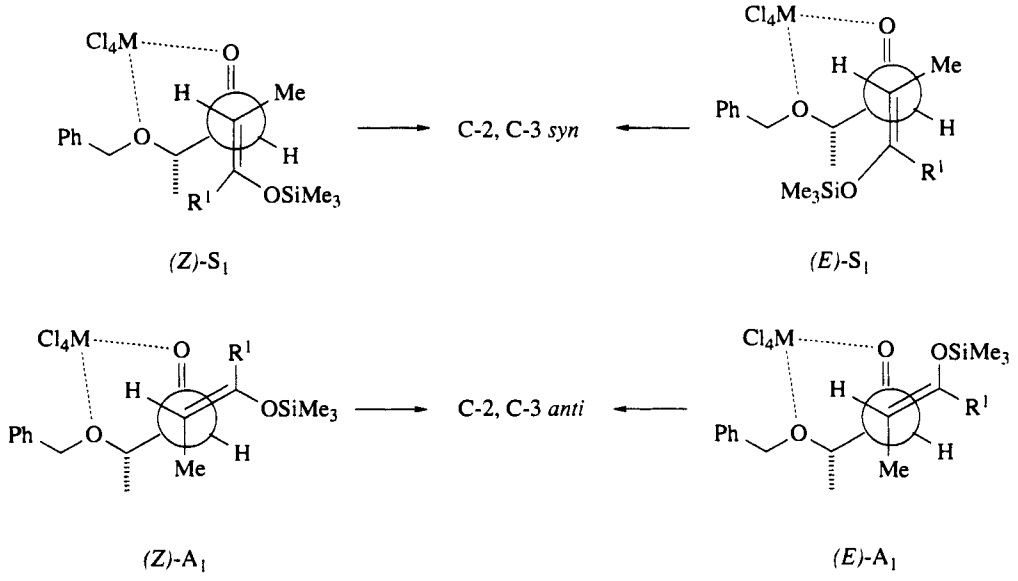
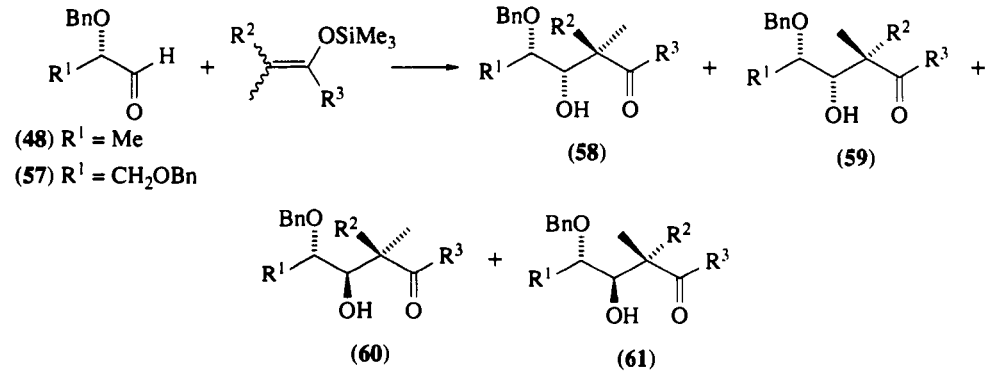


Figure 4

Additions of heteroatom-substituted enol silanes to aldehyde (**48**) were studied by several groups (equations 18 and 20);[73–78] significant results are reported in Tables 11 and 12. High facial selectivity (chelation control) was obtained in most cases using magnesium bromide as Lewis acid, whereas tin or titanium tetrachloride generally gave worse results. Simple stereoselection was found to be dependent on the Lewis acid (Table 12; entries 3–5) and on the type of heteroatom (Table 12; entries 6, 7 and 9). It is clear that the heteroatom can interfere with the formation of the aldehyde–Lewis acid chelated complex (**55**) causing different stereochemical outcomes when the metal in such a complex is coordinatively saturated (Sn, Ti) or unsaturated (Mg, Zn). Complete ratios are not available for the methylthio derivatives as the adducts were desulfurized by reduction (Raney Ni)[76] or elimination ($NaIO_4$; heat)[73,74] to give acetate or acrylate derivatives.

Additions to α,β-dialkoxy aldehydes (protected glyceraldehydes) are complicated by the possibility of chelation involving either the α or β alkoxy group. With 2,3-*O*-isopropylideneglyceraldehyde (**62**; equations 21 and 22) and ZnI_2 as catalyst, a preponderance of the β-chelated complex (**63**) was obtained with consequent formation of the C-3,C-4 *anti* compounds as major isomers (Table 13, entries 1–3; Table 14,



(48) R^1 = Me
(57) R^1 = CH_2OBn

(58) (59) (60) (61) (20)

Table 11 Ratio of Diastereoisomers in the Reactions of Heteroatom-substituted Enol Silanes with Chiral α-Alkoxy Aldehydes (equation 20)

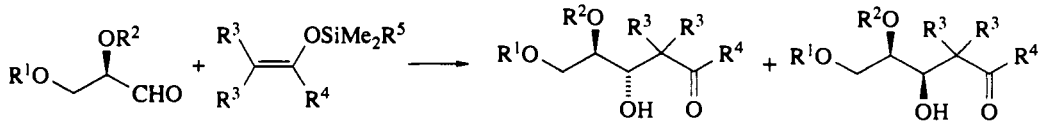
Entry	R^1	R^2	R^3	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(58)*	*(59)*	*(60)*	*(61)*	*Ref.*
1	Me	SMe	OMe	a	$MgBr_2$	50	(95)	5	(5)	0	73, 74
2	Me	OMe	OTMS	—	$SnCl_4$	a	95	5	0		75
3	CH_2OCH_2Ph	SMe	OMe	a	$MgBr_2$	45	(95)		(5)		73, 74
4	CH_2OCH_2Ph	SMe	OMe	a	$SnCl_4$	50	(25)		(75)		74

[a] Not reported.

Table 12 Ratio of Diastereoisomers in the Reactions of Heteroatom-substituted Enol Silanes with Aldehyde (**48**; equation 18)

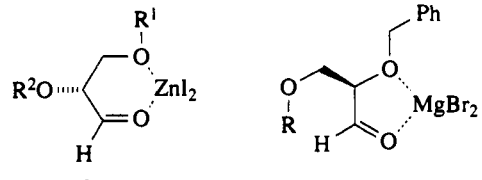
Entry	R^1	R^2	R^3	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(51)*	*(52)*	*(53)*	*(54)*	*Ref.*
1	SMe	Me	Me	80/20	$MgBr_2$	70	(99)		(1)		76
2	SMe	OBu^t	Me	a	$MgBr_2$	55	(96)		(4)		76
3	OCH_2Ph	OTMS	Me	—	$MgBr_2$	28	80	19	1	0	77
4	OCH_2Ph	OTMS	Me	—	$ZnCl_2$	54	39	61	0	0	77
5	OCH_2Ph	OTMS	Me	—	$Eu(fod)_3$	53	9	80	11	0	77
6	$N(CH_2Ph)_2$	OBu^t	Me	a	$MgBr_2$	40	1.5	97	0	1.5	78
7	$N(CH_2Ph)_2$	OBu^t	Me	a	$SnCl_4$	50	16	82.5	0	1.5	78
8	CH_2SMe	OMe	Me	a	$MgBr_2$	78	(99)		(1)		73
9	CH_2OCH_2Ph	OMe	Me	a	$MgBr_2$	81	75	25	0	0	73

[a] Not reported.



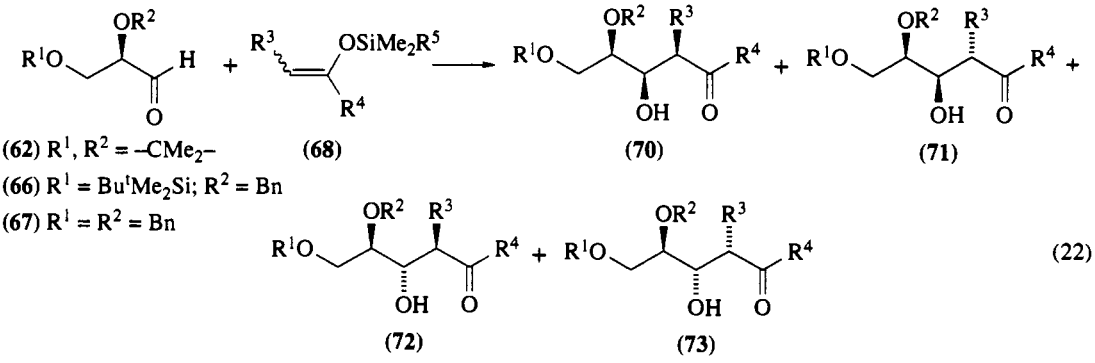
(62) R^1, R^2 = $-CMe_2-$
(66) R^1 = Bu^tMe_2Si; R^2 = Bn

(64) (65) (21)



(63) R^1,R^2 = $-CMe_2-$ (69)

entries 1–4).[79] With protected glyceraldehydes (**57**, **66** and **67**; equations 20–22) the α-chelated complex (**69**) can effectively compete, with consequent formation of the C-3,C-4 *syn* compounds as major isomers (Table 11, entry 3; Table 13, entry 4; Table 14, entries 5–7). Additions of nonstereogenic enol silanes to α-methyl-β-alkoxy aldehyde (**74**; equation 23) are reported in Table 15. High selectivity (che-



(62) R^1, R^2 = $-CMe_2-$ (68) (70) (71)

(66) R^1 = Bu^tMe_2Si; R^2 = Bn

(67) R^1 = R^2 = Bn

(72) (73) (22)

Table 13 Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Chiral α,β-Dialkoxy Aldehydes (equation 21)

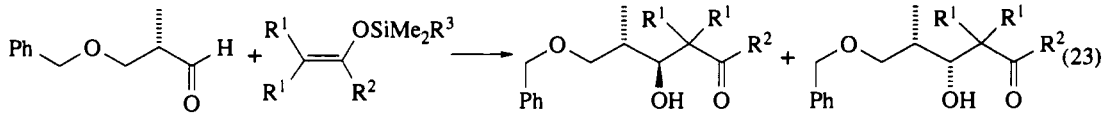
Entry	R^1	R^2	R^3	R^4	R^5	*Promoter*	*Yield (%)*	*(64)*	*(65)*	*Ref.*
1	—CMe_2—		H	OMe	Bu^t	ZnI_2[a]	67	96	4	79a
2	—CMe_2—		Me	OMe	Me	ZnI_2[a]	70	91	9	79a
3	—CMe_2—		F	OMe	Bu^t	ZnI_2	66	94.5	5.5	79b
4	TBDMS	Bn	H	OMe	Me	$SnCl_4$	90	<2	>98	65b, 69b

[a] Catalytic amount.

Table 14 Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Chiral α,β-Dialkoxy Aldehydes (equation 22)

Entry	R^1	R^2	R^3	R^4	R^5	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(70)*	*(71)*	*(72)*	*(73)*	*Ref.*
1	—CMe_2—		Me	OMe	Me	100/0	ZnI_2[a]	50	(12)		64	24	79a
2	—CMe_2—		Me	OMe	Bu^t	0/100	ZnI_2[a]	65	(10)		76	14	79a
3	—CMe_2—		Et	OMe	Bu^t	0/100	ZnI_2[a]	45	(6)		84	10	79a
4	—CMe_2—		Et	OMe	Bu^t	100/0	ZnI_2[a]	57	(8)		83	9	79a
5	TBDMS	CH_2Ph	Me	Ph	Me	0/100	$SnCl_4$	90	94	0	0	6	65b
6	CH_2Ph	CH_2Ph	Me	SBu^t	Bu^t	>95/5	$SnCl_4$	75	>95	<5	0	0	21
7	CH_2Ph	CH_2Ph	CH_2SMe	OMe	Me	b	$MgBr_2$	67	(98)		(2)		73

[a] Catalytic amount, [b] Not reported.



(74) (75) (76) (23)

Table 15 Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Aldehyde (**74**; equation 23)

Entry	R^1	R^2	R^3	*Promoter*	*Yield (%)*	*(75)*	*(76)*	*Ref.*
1	H	Bu^t	Me	$TiCl_4$	a	95	5	65a, 69a
2	Me	OMe	Me	$TiCl_4$	a	>97	<3	65a, 69a, 69b
3	H	SBu^t	Bu^t	$TiCl_4$	80	≥97	≤3	80
4	H	OBu^t	Bu^t	$TiCl_4$	45	50	50	80
5	H	Bu^t	Me	BF_3(gas)	a	12	88	65a, 69a
6	Me	OMe	Me	BF_3(gas)	a	55	45	65a
7	H	Bu^t	Me	$BF_3{\cdot}OEt_2$	a	23	77	65a

[a] Not reported.

lation control) was obtained with $TiCl_4$ (entries 1–3) due to the formation of the 1:1 complex (**77**), which was shown to be quite rigid and essentially conformationally locked.[8a,b] The other stereoisomer was obtained with BF_3 *via* the 1:2 complex (**79**; entries 5–7). Additions of stereogenic enol silanes to aldehyde (**74**; equation 24) are reported in Table 16. Excellent ratios were obtained with thiol ester silyl ketene

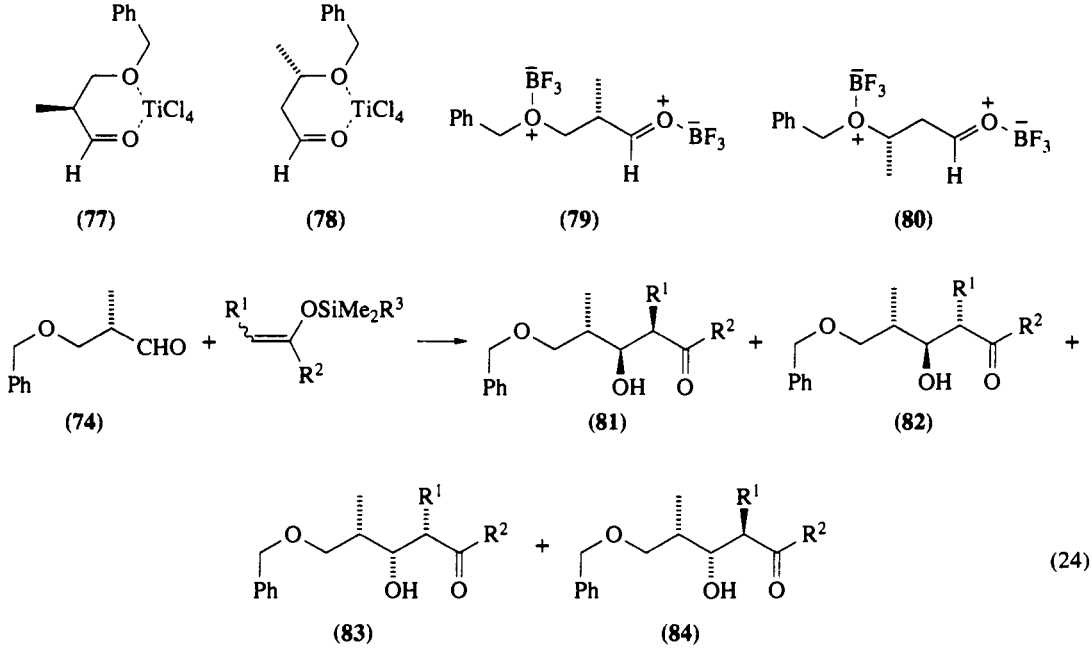
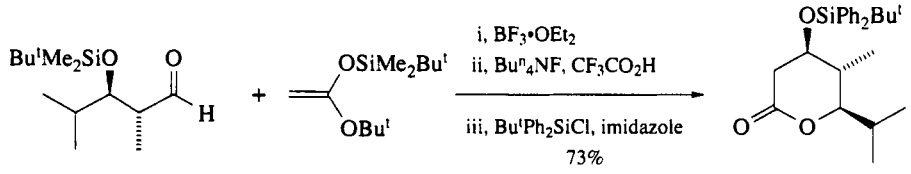


Table 16 Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Aldehyde (**74**; equation 24)

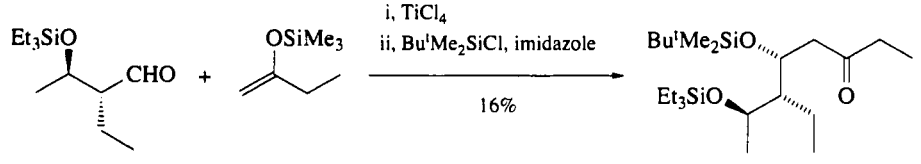
Entry	R^1	R^2	R^3	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(81)*	*(82)*	*(83)*	*(84)*	*Ref.*
1	Me	Ph	Me	0/100	$TiCl_4$	>90	91	9	0	0	69a
2	Me	Et	Me	0/100	$TiCl_4$	a	50	50	0	0	69a
3	Me	SBu^t	Bu^t	>95/5[b]	$TiCl_4$	67	>99	<1	0	0	21, 59
4	Me	SBu^t	Bu^t	<5/95[b]	$TiCl_4$	65	>99	<1	0	0	21, 59
5	Me	SBu^t	Me	93/7[b]	$SnCl_4$	65	97	3	0	0	21
6	Me	SBu^t	Me	10/90[b]	$SnCl_4$	69	46	3	0	51	21
7	Me	SBu^t	Bu^t	>95/5[b]	$BF_3{\cdot}OEt_2$[c]	75	0	9	14	77	21, 59
8	Me	SBu^t	Bu^t	<5/95[b]	$BF_3{\cdot}OEt_2$[c]	71	0	7	16	77	21, 59
9	Et	SBu^t	Bu^t	<5/95[b]	$TiCl_4$	75	96	(	4	)	60
10	Et	SBu^t	Bu^t	>95/5[b]	$TiCl_4$	80	99	(	1	)	60

[a] Not reported. [b] See footnote d of Table 1. [c] 2 mol. equiv.

acetals and $TiCl_4$ (entries 3, 4, 9 and 10) as a result of chelation control (C-3,C-4 *anti*) and *syn* simple stereoselection (C-2,C-3 *syn*). Staggered transition structures, analogous to the ones reported in Figure 4 for α-alkoxy aldehydes, were suggested in order to rationalize the high selectivity irrespective of the double bond geometry.[21,59] It is possible to obtain complete nonchelation control by changing the protecting group of the β-alkoxy aldehyde from benzyl to Et_3Si or Me_2Bu^tSi;[8b] two examples taken from total syntheses of natural products are shown in Scheme 6[81] and Scheme 7.[82]



Scheme 6



Scheme 7

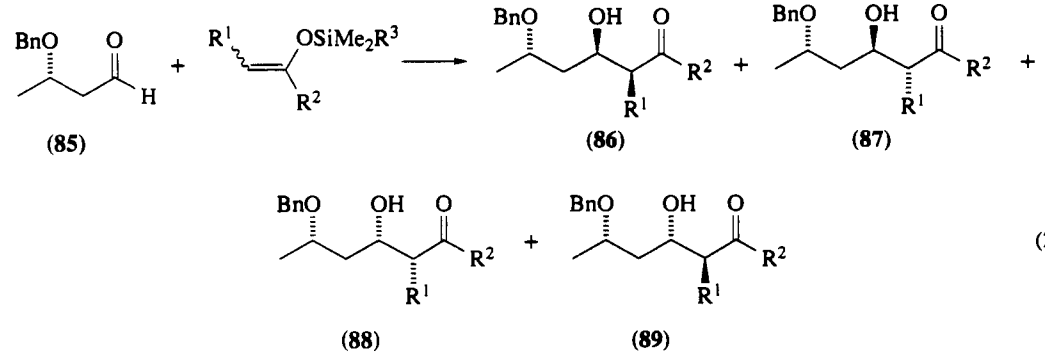
Additions of enol silanes to β-alkoxy aldehyde (**85**; equation 25) are reported in Table 17. High selectivity (chelation control) was obtained with $TiCl_4$ *via* complex (**78**; entries 1, 2).[8a,b] The same preference for isomers (**86**) and (**87**) was obtained with BF_3 *via* complex (**80**), which simulates chelation.[65a,66] The influence of chelation on simple stereoselection is also evident in the reactions of achiral aldehydes (**90**) and (**92**) with silyl enol ethers (*Z*)-(**91**) and (*E*)-(**93**), which are usually moderately *anti* selective in their reactions with aldehydes incapable of chelation;[10] high *syn* selectivity was obtained irrespective of the enol ether geometry (equations 26 and 27).[69,70]

$TiCl_4$-mediated addition of silyl enol ether (**95**) to chiral α-amino aldehyde (**94**) was reported to proceed with good chelation control, albeit in poor yield (equation 28).[84] Effective chelation control was also reported in the $TiCl_4$-mediated reactions of chiral α-alkoxy and β-alkoxy acyl cyanides (**96**) and (**97**) with silyl enol ether (**95**; equations 29 and 30).[69b,85] Reaction of acyl cyanide (**97**) with the (*E*)-silyl enol ether (**93**) gave a single stereoisomer as a result of complete chelation control and *syn* simple stereoselection (equation 31).[85] Additions of silyl enol ethers and silyl ketene acetals to (–)-menthyl phenylglyoxylate and pyruvate were reported to proceed with moderate facial selectivity; the best result (84:16) is shown in equation (32).[86]

Table 17 Ratio of Diastereoisomers in the Reactions of Enol Silanes with Aldehyde (**85**; equation 25)

Entry	R^1	R^2	R^3	*(E)/(Z)*	*Promoter*	*Yield (%)*	*(86)*	*(87)*	*(88)*	*(89)*	*Ref.*
1	H	Ph	Me	—	$TiCl_4$	95	92	—	8	—	69b, 83
2	Me	Ph	Me	0/100	$TiCl_4$	95	92	(	8	)	70, 83
3	H	Ph	Me	—	BF_3(gas)	82	85	—	15	—	66
4	Me	Ph	Me	0/100	BF_3(gas)	a	55	27	12	6	66

[a] Not reported.



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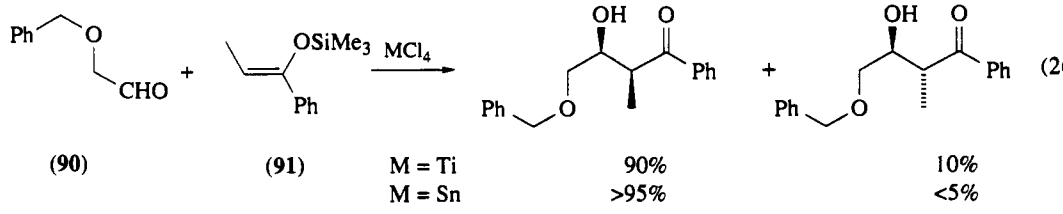

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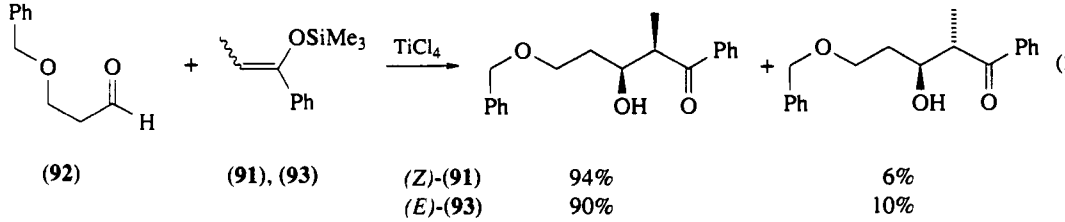

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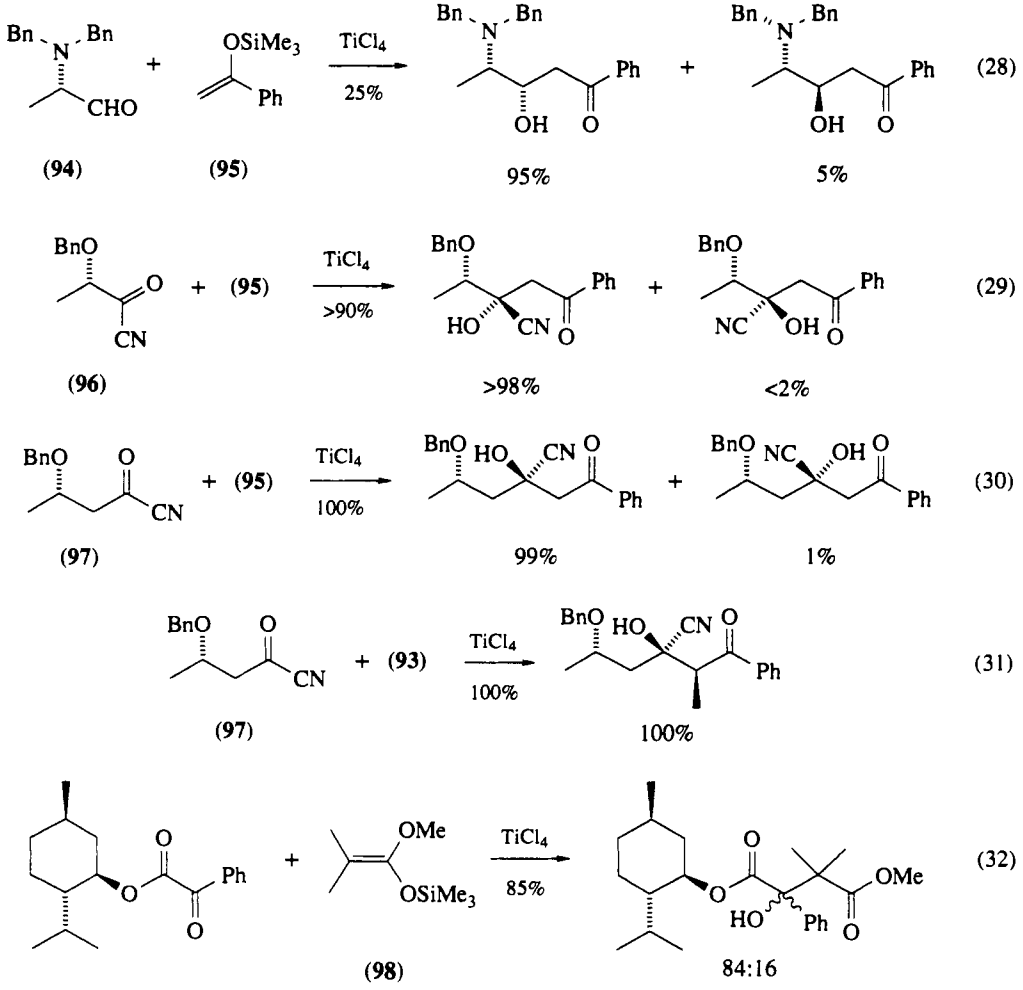
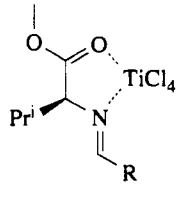
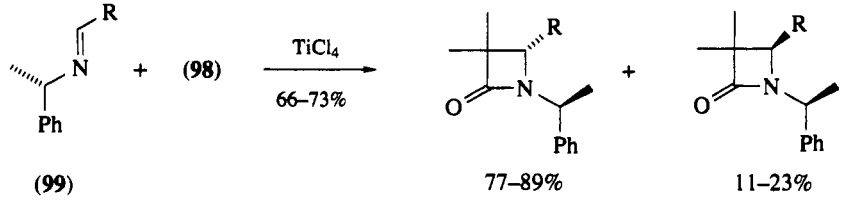


2.4.4.2 Diastereoselective Addition to Chiral Imines, Nitrones and 4-Acetoxyazetidin-2-ones

$TiCl_4$-mediated additions of silyl ketene acetal (**98**) to chiral imines (**99**) and (**100**) (R = Et, Pr^n, Bu^n, Bu^i) are described in equations (33) and (34); good diastereoisomeric ratios were obtained using imines (**100**), derived from (*S*)-valine methyl ester, which form with $TiCl_4$ the chelated complex (**101**).[87] ZnI_2-catalyzed additions of acetate-derived silyl ketene acetals to chiral α,β-dialkoxy nitrones (**102**; R^1 = H) were reported to proceed with good yield (86–100%) and high diastereofacial selectivity (*ca.* 90:10) in favor of the *anti* isomer (**103**; R^1 = H, R^2 = $CHPh_2$, R^3 = Bu^t) or of the *syn* isomer (**104**; R^1 = H, R^2 = CH_2Ph, R^3 = Me) depending on the steric hindrance of R^2 and R^3 (Scheme 8).[88a] Addition to nitrone (**102**; R^1 = Me) gave the *anti* isomer (**103**; R^1 = Me, R^2 = CHMePh, R^3 = Me) in quantitative yield and 100% diastereofacial selectivity. This material was further elaborated to *N*-benzoyl-L-daunosamine (Scheme 8).[88b]



(**101**)



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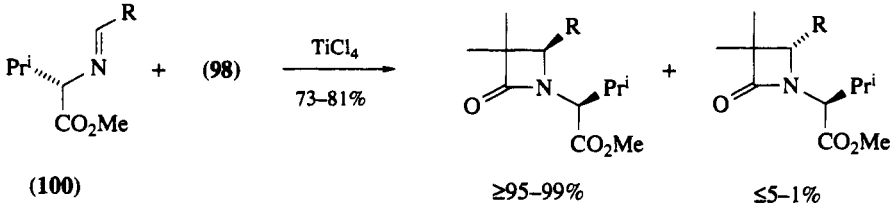

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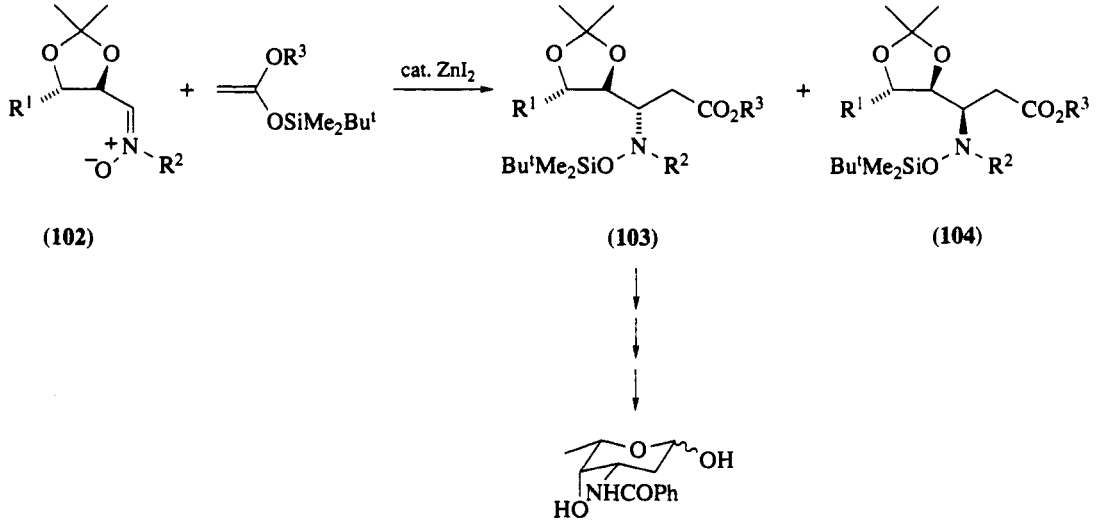
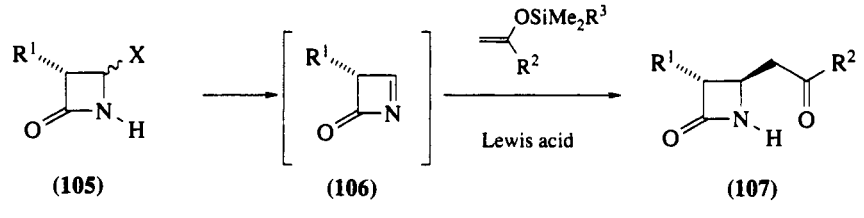


Scheme 8

Lewis acid mediated additions to chiral 4-acetoxyazetidin-2-ones (**105**) have been shown to proceed through azetinones (**106**) by trapping this reactive intermediate with silyloxydienes.[89,90] Enol silane additions to (**105**) were reported to give good yields of 100% *trans*-azetidinones (**107**; equation 35); results relevant for the synthesis of carbapenem antibiotics (PS-5, thienamycin and analogs) are shown in Table 18 (entries 1–8).[91–97a] Reactions with stereogenic enol silanes (equation 36) gave mixtures of the β-isomer (**108**) and the undesired α-isomer (**109**; Table 19, entries 1–5).[96,97c,98]

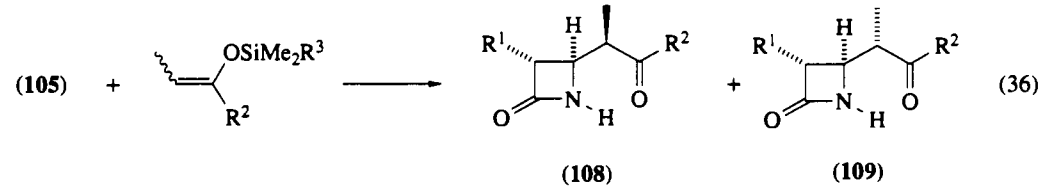


(35)

Table 18 Lewis Acid Mediated Reactions of Enol Silanes with Chiral Azetinones (**106**) and (**111**) (equations 35 and 37)

Entry	*X*	*R*	R^1	R^2	R^3	*Lewis acid*	*Yield (%)*	*Ref.*
1	OAc	—	(*R*)-MeCH(OH)	$C(N_2)CO_2Bn$	Me	ZnI_2	81	91
2	OAc	—	(*R*)-MeCH(OTBDMS)	$C(N_2)CO_2Bn$	Bu^t	$ZnCl_2$	84	92
3	OAc	—	(*S*)-MeCH(OTBDMS)	$C(N_2)CO_2Bn$	Bu^t	$ZnCl_2$	83	93
4	OAc	—	Et	$C(N_2)CO_2Bn$	Bu^t	$ZnCl_2$	63–83	94, 95
5	OAc	—	Et	$C(N_2)CO_2Bn$	Me	TMSOTf[a]	55	96
6	OAc	—	(*R*)-MeCH(OBz)	OEt	Me	ZnI_2	60	96
7	Cl	—	(*R*)-MeCH(OTBDMS)	$C(N_2)CO_2Bn$	Bu^t	$AgBF_4$	64	97a
8	OAc	—	(*R*)-MeCH(OTBDMS)	CH=CHPh	Bu^t	$ZnCl_2$	72	89
9	OAc	TMS	(*S*)-MeO_2CCH(OTBDMS)	$C(N_2)CO_2Bn$	Me	TMSOTf[a]	64	99
10	OAc	TMS	(*R*)-MeCH(OCO_2Bn)	SPh	Me	TMSOTf[a]	93	100
11	OAc	TMS	(*R*)-MeCH(OTBDMS)	OBn	Me	TMSOTf[a]	91	100
12	OAc	TMS	(*R*)-MeCH(OBz)	$C(N_2)CO_2Bn$	Me	TMSOTf[a]	90	96
13	Cl	TBDMS	(*R*)-MeCH(OTBDMS)	$C(N_2)CO_2Bn$	Me	$AgBF_4$	70	97b
14	OAc	TMS	(*R*)-MeCH(OTBDMS)	SPh	Me	TMSOTf[a]	83	100, 101
15	OAc	CH_2TMS	PhthN	Tol	Me	TMSOTf[a]	70	102

[a] Catalytic amount.



(108) (109) (36)

Table 19 Lewis Acid Mediated Reactions of Stereogenic Enol Silanes with Chiral Azetinones (**106**) and (**111**) (equations 36 and 37)

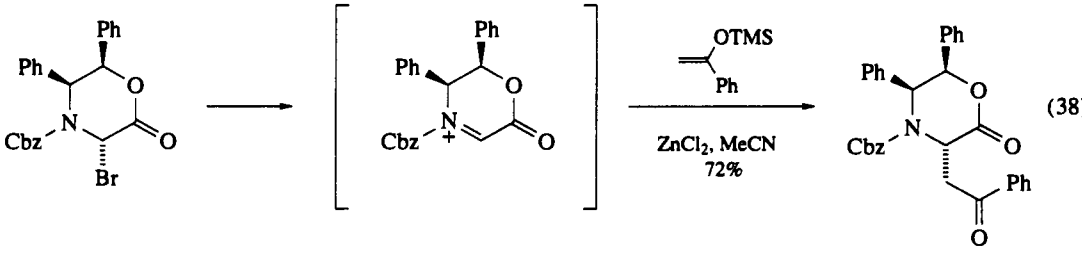
Entry	*X*	*R*	R^1	R^2	R^3	*Promoter*	(**108**)/(**109**)	*Yield (%)*	*Ref.*
1	OAc	—	(*R*)-MeCH(OTBDMS)	$C(N_2)CO_2Bn$	Bu^t	TMSOTf[a]	33/67	85	98
2	OAc	—	(*R*)-MeCH(OTBDMS)	OMe	Me	TMSOTf[a]	48/52	75	98
3	OAc	—	(*R*)-MeCH(OTBDMS)	SPh	Me	TMSOTf[a]	5/95	87	98
4	OAc	—	(*R*)-MeCH(OTBDMS)	OMe	Me	ZnI_2	50/50	b	96
5	OAc	—	(*R*)-MeCH(OTBDMS)	CH_2CO_2Me	Me	$SnCl_2$	69/31	70	97c
6	OAc	TMS	(*R*)-MeCH(OTBDMS)	OMe	Me	TMSOTf[a]	28/72	94	103
7	OAc	TMS	(*R*)-MeCH(OTBDMS)	SPh	Me	TMSOTf[a]	62/38	81	103

[a] Catalytic amount. [b] Not reported.

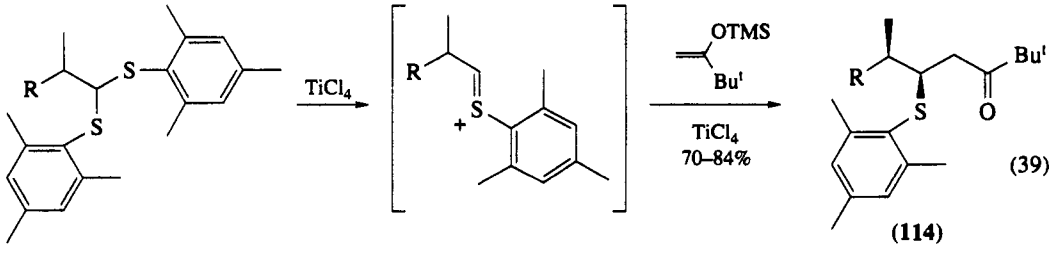
2.4.4.3 Diastereoselective Additions to Chiral Iminium, Oxonium and Thionium Ions

When the nitrogen of 4-acetoxyazetidin-2-ones is protected (**110**; R = TMS, TBDMS, CH_2TMS), the Lewis acid catalyzed condensation occurs through the corresponding iminium salt (**111**; equation 37); illustrative examples of this process yielding 100% *trans*-azetidinones are reported in Table 18 (entries 9–15) and Table 19 (entries 6 and 7). Iminium ions have also been invoked as intermediates in enol silane additions to chiral bromides (**112**; equation 38); predominant attack from the less encumbered α-face gives the *anti* adduct (**113**) as the major stereoisomer (93.5:6.5).[104] Additions to thionium ions[105] have been shown to proceed with excellent diastereofacial selectivity (equation 39); the product predicted by the Felkin–Anh model (**114**) was obtained as the major isomer not only when R is Ph or cyclohexyl (>98:2) but also when it is benzyl (97:3) or Et (83:17).[106] This behavior is consistent with an approach trajectory of the nucleophile very close to the stereocenter, in analogy with the Lewis acid mediated additions to chiral α-methyl aldehydes (see Section 2.4.4.1 and Table 8).[64,106] Highest selectivity required the use of bulky mesitylthio derivatives, while with phenyl-substituted thionium ions ratios were lower (80:20). The addition of a silyl enol ether to an α-chiral phenyl-substituted thionium ion was applied ($ZnBr_2$ as catalyst) in a macrolide total synthesis and reported to proceed with 100% facial selectivity in favor of the 'Felkin–Anh stereoisomer';[107] the very high facial selectivity in this reaction is probably due to use of a more-substituted silyl enol ether combined with a more sterically biased substrate.

(110) (111) (107) or (108)/(109) (37)

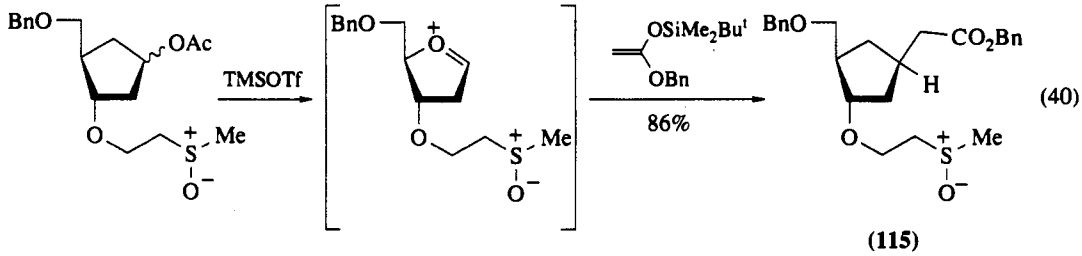


(112) (113) (38)



(114) (39)

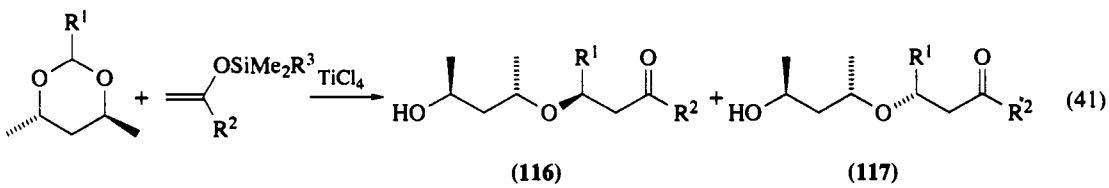
Enol silane additions to chiral oxonium ions have been shown to proceed with good stereoselectivity.[39c,d] In the field of *C*-glycoside synthesis, selective β-glycosylation was realized *via* neighboring group participation of a 2α-acyl group.[108] In the case of 2-deoxy sugars the neighboring participation of a group at the 3α-position was exploited for selective formation of the β-anomer (**115**; β:α = 91:9; equation 40).[109]



(115) (40)

2.4.4.4 Diastereoselective Additions to Chiral Acetals

Six-membered chiral acetals, derived from aliphatic aldehydes, undergo aldol-type coupling reactions with α-silyl ketones, silyl enol ethers,[110] and with silyl ketene acetals[111] in the presence of titanium tetrachloride with high diastereoselectivities (equation 41); significant results are reported in Table 20. This procedure, in combination with oxidative destructive elimination of the chiral auxiliary, has been applied



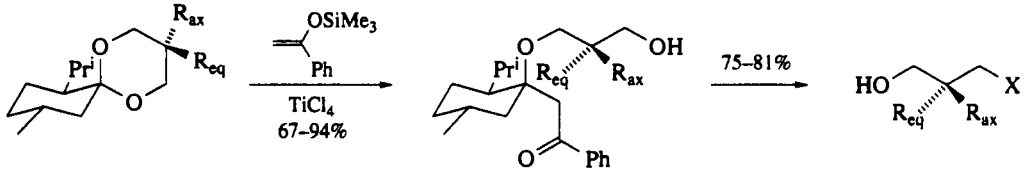
(116) (117) (41)

Table 20 Ratio of Diastereoisomers in the $TiCl_4$-mediated reactions of Enol Silanes with Chiral Acetals (equation 41)

Entry	R^1	R^2	R^3	*(116)/(117)*	*Yield (%)*	*Ref.*
1	$(CH_2)_2CH{=}CH_2$	Me	Me	97/3	89	110
2	Pr^i	Et	Me	96/4	84	110
3	n-C_8H_{17}	Et	Me	97/3	95	110
4	n-C_8H_{17}	Bu^t	Me	96/4	96	110
5	c-C_6H_{11}	OBu^t	Bu^t	97/3	98	111a
6	n-C_8H_{17}	OBu^t	Bu^t	98/2	98	111a
7	$(CH_2)_4CO_2Pr^i$	OBu^t	Bu^t	98/2	93	111a

to the preparation of (*R*)-(+)-α-lipoic acid,[111a] of mevinolin analogs,[111b] and of a key intermediate for the synthesis of nonactic acid.[110]

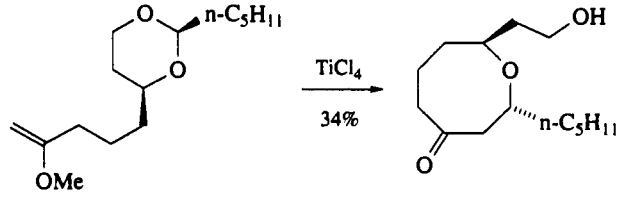
Lewis acid catalyzed aldol coupling of silyl enol ethers with substituted cyclohexanone acetals showed an excellent preference for equatorial attack (95–100%).[112] In accord with this general rule, additions of a silyl enol ether to equatorially or axially substituted chiral spiroketals derived from -menthone gave 100% equatorial attack and formation of a single one of the four possible diastereoisomers (Scheme 9).[113,114] This methodology, followed by protection of the hydroxy group (X = OTHP, $OCPh_3$) and alkaline removal of the chiral auxiliary was used for the synthesis of several natural products.[114]



Scheme 9

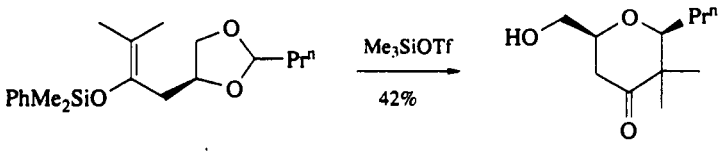
2.4.4.5 Intramolecular Diasteroselective Aldol-type Additions

Lewis acid mediated cleavage of an acetal to a trigonal oxonium ion followed by intramolecular capture of the oxonium ion by a trigonal enol silane proved a useful process for the stereoselective synthesis of five-,[115] six-,[116–119] seven-,[118–121] eight-[118,119] and eleven-membered rings.[122] The rapid formation of eight-membered rings by direct aldol reaction without the need for high dilution conditions is noteworthy since eight-membered rings are usually difficult to construct by any method of ring closure (equation 42). Compound (**118**) was obtained as a single diastereoisomer (*trans*), along with polymeric by-products.[119] In the six-membered ring case (equation 43) only the *cis*-tetrahydropyran-4-one (**119**) was obtained starting from either *cis*- or *trans*-dioxolanes.[118,119] Stereoselective cyclopentane annulations were realized (equation 44) using a TMSOTf-catalyzed addition to trimethyl orthoesters; compounds (**120**) were obtained as single stereoisomers with *cis* ring fusion and the phenylsulfonyl substituent *exo*.[115a]



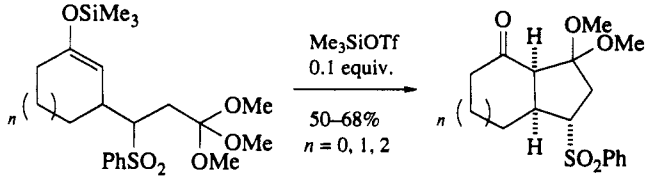
(42)

(**118**)



(43)

(**119**)



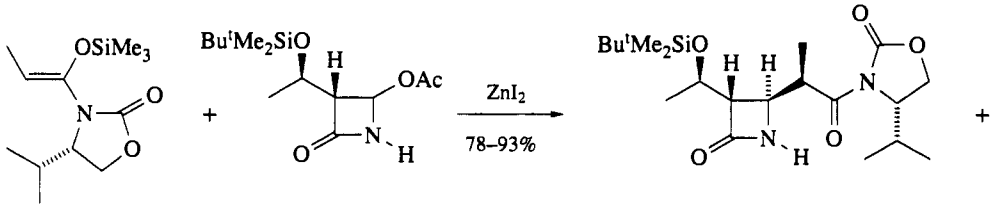
(44)

(120)

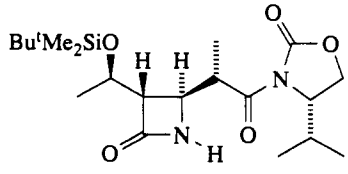
Highly stereoselective intramolecular reactions of a silyl enol ether ($BF_3{\cdot}OEt_2$)[123a] and a vinyl sulfide ($HgCl_2$, CSA)[123b] with *N*-acyliminium ions have recently been accomplished.

2.4.5 CHIRAL NUCLEOPHILES AND ELECTROPHILES

When both the enol silane and the electrophile are chiral, the inherent diastereofacial preferences of the two reactants may reinforce one another (matched pair) or oppose one another (mismatched pair).[4a,124] If the chiral enol silane shows sufficiently high diastereoface preference, it can completely override the modest diastereoface preference of particular electrophiles, and the sense of chirality of the new stereocenters is determined almost solely by the sense of chirality of the enol silane (reagent control).[4a,124] Reagent (**121**), for example, is able to override the preference of the chiral 4-acetoxyazetidin-2-one (**122**) for formation of the α-isomer with achiral enol silanes (see Section 2.4.4.2 and Table 19), although the net β-preference is still only moderate (equation 45).[125]



(121) (122) 75%



25%

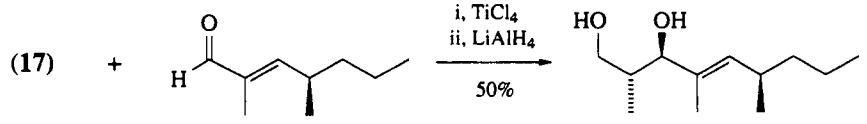
(45)

2.4.5.1 Diastereoselective Additions of Chiral Silyl Ketene Acetals to Chiral Aldehydes

In the total synthesis of zincophorin, *N*-methylephedrine-derived silyl ketene acetal (**17**) gave with chiral aldehyde (**123**) the desired adduct (**124**) as the major stereoisomer (*anti*:*syn* = 89:11; facial selectivity > 95:5) in the presence of a (likely) modest diastereofacial guidance from the remote stereocenter at C-4 (Scheme 10).[126] In the synthesis of tetrahydrolipstatin, *N*-methylephedrine-derived silyl ketene acetal (**125**) gave with chiral aldehyde (**126**) the desired adduct (**127**) as the major stereoisomer (C-2,C-3 *anti*:C-2,C-3 *syn* = 75:25; facial selectivity > 95:5; equation 46).[127] This result is particularly noteworthy as the reagent is able to override the strong preference of β-alkoxy aldehydes (*e.g.* **85**, equation 25 and Table 17) for chelation control and C-2,C-3 *syn* simple stereoselection. In the synthesis of the carbapenem antibiotic 1-β-methyl-PS-5, *N*-methylephedrine-derived silyl ketene acetal (**20**) gave with aldehyde (*S*)-(**128**), prepared in 91% *ee* according to Scheme 4,[59] the aldol addition product (**129**) in 70% yield as a single isomer out of the eight possible isomers (Scheme 11).[60] The explanation for this excellent selectivity is the following; both the (1*S*,2*R*)-*N*-methylephedrine-derived silyl ketene acetal (**20**) and (*S*)-(**128**) have an intrinsic preference for establishing a (2*R*,3*S*) absolute configuration at C-2,C-3, as is evident from the reaction of (**20**) with the achiral aldehyde (**28**) (see Section 2.4.3.1, equation 12) and from the

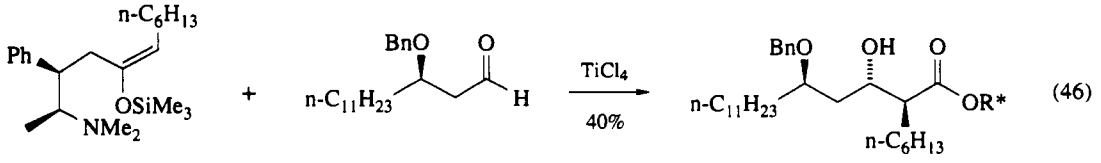
reaction of (*S*)-(**128**) with the achiral thiol ester derived silyl ketene acetals (see Section 2.4.4.1, equation 24, Table 16 entries 3, 4, 9, and 10). As (**20**) and the (*S*)-aldehyde form a matched pair (they cooperate to realize the same stereochemical result), while (**20**) and the (*R*)-aldehyde form a mismatched pair, only the (*S*)-enantiomer of the starting 95.5/4.5 = (*S*)/(*R*) mixture of aldehyde (**128**) reacts with (**20**), and the reaction occurs with concomitant kinetic resolution. The relative configuration of the three contiguous stereocenters is a result of chelation control (C-3,C-4 *anti*) and *syn* simple stereoselection (C-2,C-3 *syn*) in agreement with the transition structure model (Figure 5A).[57,60] An analogous matched pair condensation between enantiomerically pure aldehyde (*S*)-(**128**) and silyl ketene acetal (*R*)-(**130**) was reported to give the aldol product (**131**), in ≥ 97% diastereoisomeric purity, which was further elaborated to 1-β-methylthienamycin (Scheme 12).[128]

An example of the mismatched pair is shown in Scheme 13;[57] here the (1*R*,2*S*)-*N*-methylephedrine-derived silyl ketene acetal (**17**) reacts with (*S*)-(**128**) (91% *ee*) to give a mixture of adducts (**132**) and (**133**) in poor yield. Compound (**132**) was obtained in 100% *ee* through transition structure (Figure 5**B**), which is against the aldehyde preference (Me inside the titanium-containing ring), while (**133**) was obtained in 65% *ee* through transition structure (Figure 5C), which is against the silyl ketene acetal preference. It is also interesting to observe that, while (**132**) is enantiomerically pure, the *ee* of (**133**) is only 65%. This means that, as the starting aldehyde is a 95.5/4.5 (*S*)/(*R*) mixture, almost all the minor (*R*)-en-

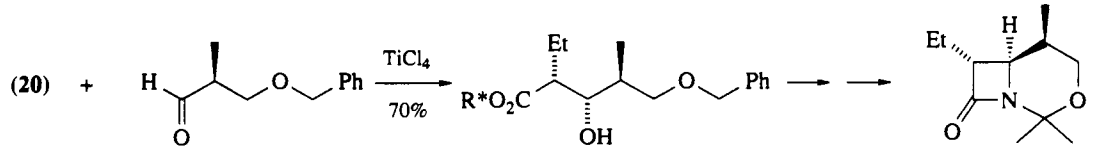


(**123**) (**124**)

Scheme 10

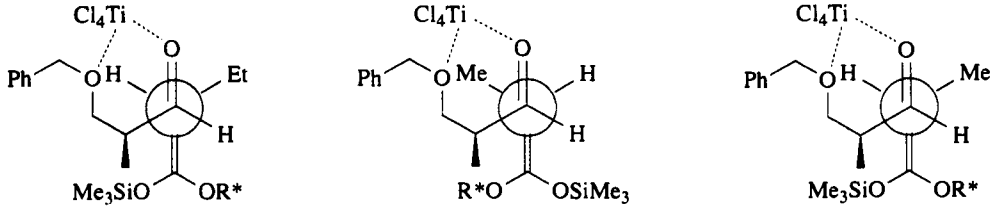


(**125**) (**126**) (**127**)



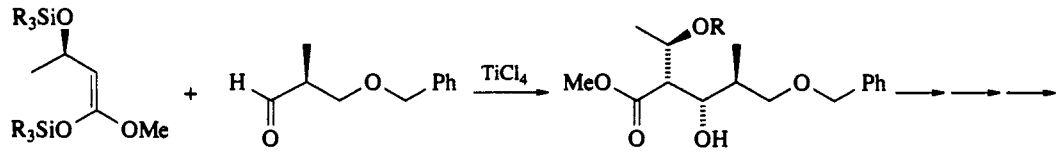
(**128**) (**129**)

Scheme 11

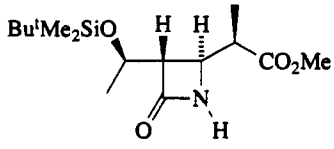


A B C

Figure 5

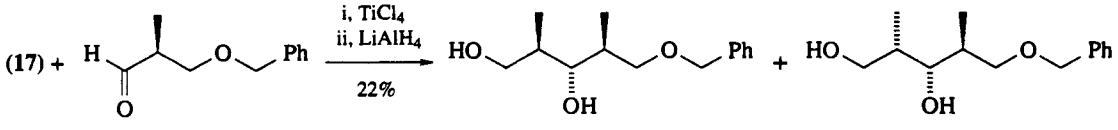


(130) (128) (131)



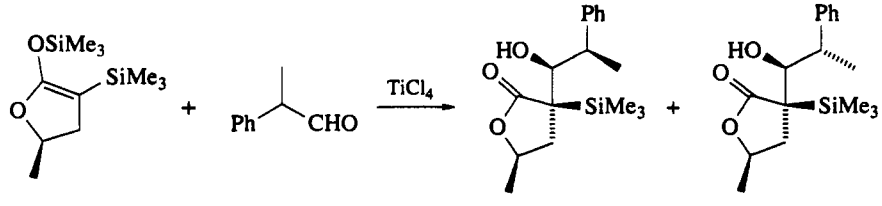
Scheme 12

antiomer was consumed to produce the enantiomer of (**133**), through a process of kinetic resolution opposite to the one described above. A process of mutual kinetic resolution is shown in equation (47); chiral enol silane (**32**) gave with 2-phenylpropanal (**134**) the aldol product as a 99:1 mixture of stereoisomers (**135**) and (**136**).[25c] As (**3**; R = TMS), the achiral analog of (**32**), gives with aldehyde (**134**) a 90:10 mixture, it is evident that the inherent diastereoselectivity of (**134**) was enhanced by a factor of 10 by advantageous face matching.[25c]



(128) (132) 44% (133) 56%

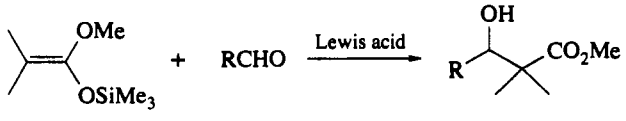
Scheme 13



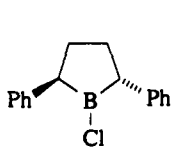
(32) (134) (135) 99% (136) 1% (47)

2.4.6 CHIRAL LEWIS ACIDS

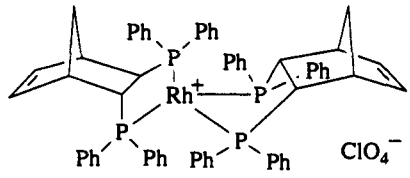
The use of chiral Lewis acids for enantioselective Diels–Alder and hetero Diels–Alder reactions and for other processes of C—C bond formation has recently received great attention. Reetz and coworkers reported that a stoichiometric amount of the chiral Lewis acid (**137**) effectively promotes the reaction of silyl ketene acetal (**98**) to give the aldol product in 57% yield and 90% *ee* (equation 48, R = Me_2CHCH_2—).[129] When a catalytic amount (5 mol %) of the chiral rhodium perchlorate (**138**) is used, the aldol product is obtained in >75% yield and 12% *ee* (equation 48; R = Ph).[130] Both reactions probably proceed through the corresponding metal enolates.[129,130] The development of new efficient chiral catalysts for the Mukaiyama reaction is certainly one of the challenges of the 1990s.



(98) (48)



(137)



(138)

ACKNOWLEDGEMENTS

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2.4.7 ADDENDUM

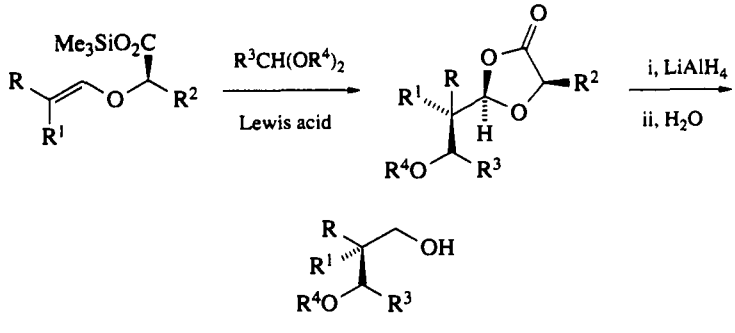
Since the submission of this chapter, a number of important contributions to this field have appeared in the literature.

Section 2.4.2

The 'pinwheel' shape of a *t*-butyl propionate derived silylketene acetal (see Section 2.4.2.1) was revealed by a single-crystal X-ray diffraction analysis.[131] Several different catalysts were reported to promote the aldol-type condensation of alkyl enol ethers[132,133,134a] and silyl enol ethers[134b–144] with aldehydes, acetals and various other electrophiles. In some cases the reaction proceeded with high simple stereoselection.[133–136] The mechanism of the Lewis acid mediated additions to acetals (see Section 2.4.2.3) was investigated in detail,[145] as well as the uncatalyzed aldol reaction of silyl enol ethers with aldehydes promoted by the hydrophobic effect[146] (see Section 2.4.2.1).

Section 2.4.3

In the field of chiral silyl enol ethers, the enolsilane derived from camphor was reported to give highly *exo* selective additions to iminium ions[147] and acetals;[148] the stereoselectivity at the acetal stereocenter was found to be strongly dependent on the acetal structure.[148] The optically active (*E*) enol ethers shown in Scheme 14 were reported to undergo highly diastereoselective reactions with a variety of aliphatic and aromatic acetals.[149] *Syn–anti* ratios ranged from 90:10 to 99:1 and enantiomeric excesses of the major *syn* isomer from 60 to 94%, depending on the various substituents. It is interesting to note that the reaction with benzaldehyde gave a 7:93 *syn–anti* ratio, in analogy with the reversal of stereoselectivity observed in the reaction of silyl enol ethers with acetals (*cf.* Section 2.4.2.3) and aldehydes (*cf.* Section 2.4.2.1).

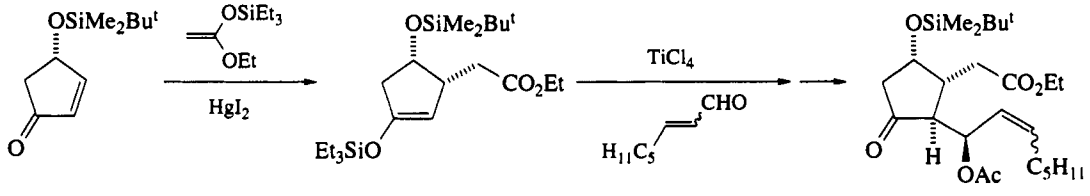


% *ee* = 60–94

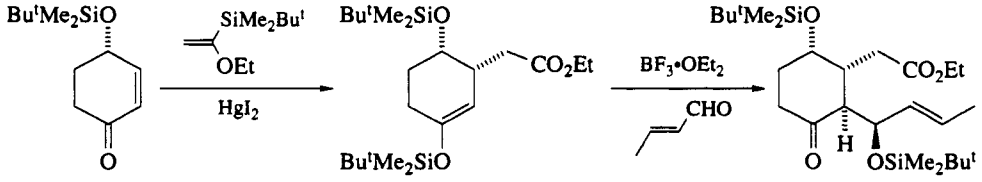
Scheme 14

The addition of a sugar-derived enol ether (glycal) to a dimethyl acetal was reported to proceed with good stereoselectivity.[134a] Danishefsky and coworkers reported the highly stereoselective additions of

chiral silyl enol ethers to aldehydes in the total synthesis of prostaglandins[150] and compactin[151] (Schemes 15 and 16). In both cases the aldol product shown was obtained as the only diastereoisomer.



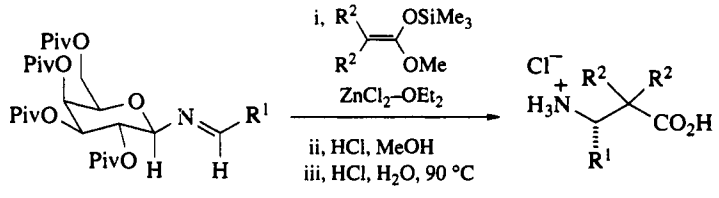
Scheme 15



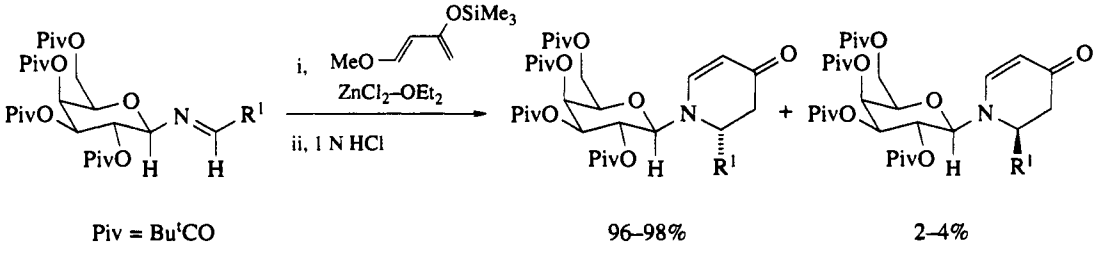
Scheme 16

Section 2.4.4

In the field of chiral electrophiles, diastereoselective additions of enolsilanes to chiral α-fluoro-α-methyl-β-alkoxy aldehydes,[152] α-methyl aldehydes,[137] α-alkoxy aldehydes,[137] α,β-dialkoxy aldehydes[138] and α-methyl-β-alkoxy aldehydes[153] were reported to proceed with good stereocontrol following Felkin–Anh or chelation models (*cf.* Section 2.4.4.1). Very good selectivities were reported in the addition of enolsilanes to chiral imines,[154–156] particularly those derived from carbohydrates (Scheme 17 and 18).[155,156]



Scheme 17



Scheme 18

In the addition to chiral 4-acetoxyazetidin-2-ones[157–159] (*cf.* Section 2.4.4.2) it is noteworthy that the desired β-isomer (**108**; equation 36) could now be obtained as a single diastereoisomer (>98%) in 85–90% yield by the use of $ZnCl_2$ and the silylketene acetal derived from 2-picolyl thiopropionate[158,159] (*cf.* Table 19, entries 1–5). *N*-Acyliminium ions (see Section 2.4.4.3) with chiral *N*-acyl substituents were re-

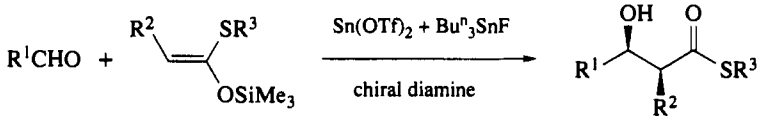
ported to undergo $TiCl_4$-mediated addition of silyl enol ethers with diastereomeric ratios up to 95:5.[160] $TiCl_4$-mediated addition of a silyl enol ether to a sugar-derived sulfonium ion (see Section 2.4.4.3) was reported to proceed with 70% yield and 4:1 diastereomeric ratio.[138] In the field of *C*-glycosides synthesis (see Section 2.4.4.3), selective α-[161a,b] or β-[161b] glycosylation was realized, depending on substrate and Lewis acid, by enolsilane addition to chiral oxonium ions (*cf.* equation 40). Oxonium ions are also probably involved in the diastereoselective $AlCl_3$-mediated additions of enolsilanes to chiral 2-benzenesulfonyl cyclic ethers.[162] In the diastereoselective additions to chiral acetals[163,164] (see Section 2.4.4.4), an extension of the methodology shown in Scheme 9 to the enantio differentiation of *meso* 1,2- and 1,4-diols was reported.[164] An intramolecular Mukaiyama acetal–aldol reaction (see Section 2.4.4.5) was reported as the key step to construct the 11-membered ring of hydroxyjatrophone A and B.[165]

Section 2.4.5

In the diastereoselective additions of chiral silylketene acetals to chiral aldehydes (see Section 2.4.5.1), details on the chemistry involved in Scheme 12 were published.[166]

Section 2.4.6

Spectacular results were reported by Mukaiyama and coworkers[167,168] in the field of chiral Lewis acids. Reaction of thiol ester derived silylketene acetals with aldehydes promoted by the combined use of a chiral diamine coordinated with tin(II) triflate and tributyltin fluoride gave excellent yields of aldol products in very high enantiomeric excess (Scheme 19).



R^2 = H; % *ee* = 78–95

R^2 = Me; % *ee* >98

Scheme 19

An interesting result (17–35% *ee*) was reported in the TMSOTf-catalyzed condensation of benzaldehyde dimethyl acetal with a cyclohexanone silyl enol ether bearing an optically pure binaphthylic derivative at silicon.[169]

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2.5
Reactions of Activated Dienes with Aldehydes

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2.5.1 INTRODUCTION

The reaction of activated dienes with aldehydes is emerging as a powerful tool in the synthesis of natural products.[1–4] This chapter reviews the major contributions that have led to the discovery and use of this reaction in organic synthesis. The first part of the chapter discusses the mechanism of the reaction, the second part describes the use of chiral aldehydes, chiral dienes and chiral catalysts in controlling stereochemistry, and the last section outlines applications in the synthesis of natural products.

2.5.1.1 Activated Dienes and Their Use in the Diels–Alder Reaction

Dienes that contain electron-donating groups (activated dienes) are more reactive in Diels–Alder reactions than unsubstituted or electron-deficient dienes.[5–8] In molecular orbital formalism, the substituents on the diene perturb the π-electron density to cause an increase in the energy of the highest occupied molecular orbital (HOMO; Figure 1).[9] In a normal-demand Diels–Alder reaction this results in an increase in the interaction between the HOMO of the diene and the LUMO (lowest unoccupied molecular orbital) of the dienophile. This interaction, in turn, lowers the transition state energy of the reaction.[10] Similar arguments have also been used to explain the increased reactivity of activated dienes towards heterodienophiles such as aldehydes.[10]

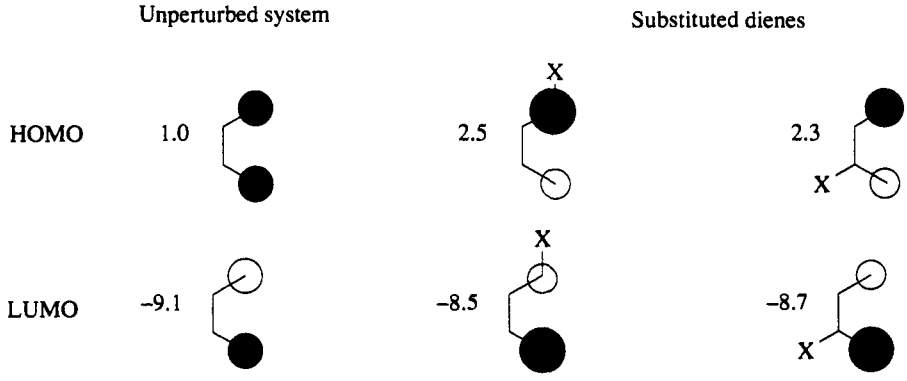


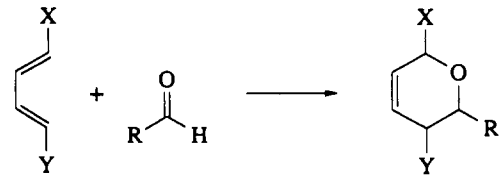
Figure 1 Orbital energies in eV are given for substituted and unsubstituted dienes. The size of the circles give relative indication of orbital coefficients. X = electron-donating substituents (*e.g.* OMe, NR_2)[9]

Activated dienes are also highly regioselective. This is due to the unsymmetrical polarization of the HOMO that is caused by the placement of substituents on the diene. The use of activated dienes is well documented in classical Diels–Alder reactions. They provide for high reactivity, good regioselectivity and introduce useful functionality into the cycloadducts.[11]

2.5.1.2 Aldehydes as Dienophiles

In 1951 Gresham and Steadman reported that formaldehyde can be used as a dienophile in Diels–Alder reactions (hetero Diels–Alder reaction).[12] This report led to the investigation of several dienes and aldehydes under thermal reaction conditions.[13–20] These studies revealed that the reaction is restricted to the use of formaldehyde or aldehydes that contain strong electron-withdrawing groups (such as glyoxaldehyde) as dienophiles (Scheme 1).

In an effort to cause unreactive aldehydes to react in the hetero Diels–Alder reaction Kubler introduced the use of the activated, electron-rich 1-alkoxy-1,3-butadiene.[21] This diene shows increased reactivity and high regioselectivity but only with activated aldehydes. In 1971 Scheeren showed that the potent diene 1,1-dimethoxy-3-silyloxy-1,3-butadiene also reacts with aldehydes.[22] The high reactivity of



(1) (2) (3)

R = H or an electron-withdrawing group (*e.g.* CO_2Me)
X and Y are electron-withdrawing groups

Scheme 1

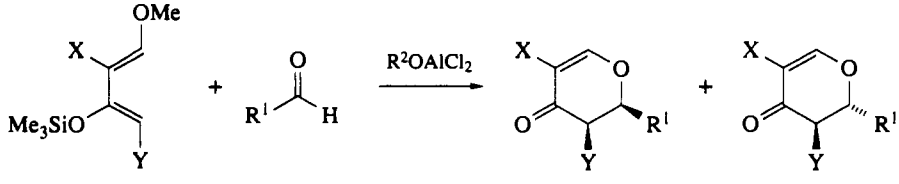
this diene allows the use of heterodienophiles at lower temperatures but the diene does not react with unactivated aldehydes. More recently, Jankowski and coworkers reported on the thermal cycloaddition reaction of trimethylsilyloxy dienes with mesoxylate [$(RO_2C)_2CO$].[20] This symmetrical dienophile shows only moderate regioselectivity and did not allow for the critical evaluation of the stereoselectivity; despite limitations and problems with *endo* to *exo* specificity David and coworkers applied this methodology to the synthesis of the human trisaccharide blood group antigens (this synthesis is discussed in more detail in Section 2.5.4.1).[23]

An important development in the hetero Diels–Alder reaction came when Jurczak used high pressure to help improve the reactivity of dienes with aldehydes. 1-Methoxybutadiene, for example, was shown to react at 15–25 kbar (1 bar = 100 kPa) with a variety of unactivated aldehydes.[24,25] These reactions give predominantly *endo* adducts and allow for the use of simple alkyl and aromatic aldehydes as dienophiles. Jurczak also realized the importance of this reaction in the synthesis of carbohydrates and applied it to the construction of simple monosaccharide derivatives (see Section 2.5.2.1).[26–28]

2.5.1.3 Lewis Acid Catalysis

Lewis acid catalysts increase the reactivity of dienophiles in Diels–Alder reactions by complexing to basic sites on the dienophile.[10] The Lewis acid lowers the LUMO of the adjacent π-system, which strengthens the overlap between the LUMO of the dienophile and the HOMO of the diene. In 1979 Scheeren reported that $ZnCl_2$ catalyzes the cyclocondensation reaction of unactivated aldehydes with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene.[22] Experimental details of this reaction, however, were not fully documented. In 1982 Scheeren also reported the use of aluminum alkoxydichlorides as catalysts

Table 1



(4) (5) (6) *syn* (7) *anti*

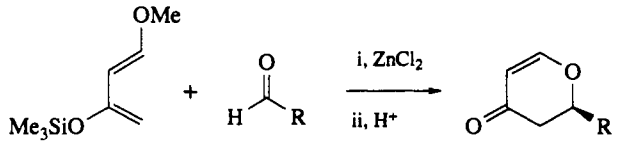
Diene	*X*	*Y*	*Aldehyde*	*R*[1]	*Adduct*	*Yield* (%)
(**4a**)	H	H	(**5a**)	H	(**6a**)	50
(**4a**)	H	H	(**5b**)	Pr^i	(**6b**)	65
(**4a**)	H	H	(**5c**)	$CH_2{=}CH$	(**6c**)	60
(**4a**)	H	H	(**5d**)	$MeCH{=}CH$	(**6d**)	60
(**4a**)	H	H	(**5e**)	Ph	(**6e**)	70
(**4b**)	H	Et	(**5b**)	Pr^i	(**6f:7f**)	35 (**6f:7f**; 3:1)
(**4c**)	Et	H	(**5e**)	Ph	(**6g**)	60
(**4d**)	H	OEt	(**5b**)	Pr^i	(**6h:7h**)	45 (**6h:7h**; not reported)
(**4e**)	OEt	H	(**5e**)	Ph	(**6i**)	45

R^2 = bornyl, propyl, isopropyl.

using diene (**4**) and unactivated aldehydes (**5**; Table 1).[29] The reaction using the aluminum catalyst was thought to be general but no critical investigation into the mechanism and stereochemistry was reported.

The major development in the Lewis acid catalyzed reaction came in 1981 when Danishefsky and co-workers reported that $ZnCl_2$ and $BF_3{\cdot}OEt_2$ catalyze the cyclocondensation of silyloxy dienes with unactivated aldehydes.[30] The use of these Lewis acid catalysts permits a variety of simple aldehydes to be used in the reaction (Table 2). Danishefsky also critically evaluated the mechanism and stereochemistry of the cyclocondensation reaction with a series of dienes, aldehydes and catalysts. These studies resulted in conditions to control the relative and absolute stereochemistry of the reaction and allowed the use of this chemistry in natural product synthesis.

Table 2



(**8**) (**9**) (**10**)

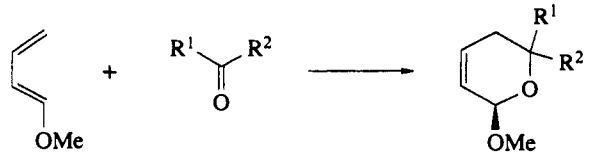
Aldehyde	*R*	*Adduct*	*Yield (%)*
(**9a**)	CH_2OCH_2Ph	(**10a**)	87
(**9b**)	CH_2SPh	(**10b**)	70
(**9c**)	CHNHCbz	(**10c**)	80
(**5e**)	Ph	(**10d**)	65
(**9d**)	*p*-$NO_2C_6H_4$	(**10e**)	58
(**9e**)	*o*-$OMeC_6H_4$	(**10f**)	58
(**9f**)	Me	(**10g**)	17
(**9g**)	Et	(**10h**)	48
(**5b**)	Pr^i	(**10i**)	43
(**9h**)	Bu^i	(**10j**)	37

2.5.2 MECHANISM

2.5.2.1 Thermal and High-pressure Reactions

Initial investigations focused on the use of thermal and high-pressure conditions to perform reactions between aldehydes and dienes.[13–28] Under these conditions the only products observed are those which

Table 3



(**11**) (**12**) (**13**)

Aldehyde	R^1	R^2	*Adduct*	*Pressure* (kbar)	*Temperature* (°C)	*Yield* (%)	*Isomer ratio endo (R^2 cis to OMe):exo (R^2 trans to OMe)*
(**12a**)	Me	$CO_2C_{10}H_{21}$	(**13a**)	25.0	20	79	79:21
(**12b**)	Me	CO_2Me	(**13b**)	20.0	50	85	70:30
(**12c**)	Me	Ph	(**13c**)	19.5	20	81	64:36
(**5e**)	H	Ph	(**13d**)	19.5	50	80	75:25
(**12d**)	H	2-Furyl	(**13e**)	19.5	50	73	73:27
(**9f**)	H	Me	(**13f**)	20.0	65	62	70:30
(**12e**)	H	n-C_5H_{11}	(**13g**)	23.5	20	16	78:22

seem to be derived from a classical Diels–Alder reaction. The high-pressure reactions reported by Jurczak give, for example, product ratios and rate accelerations which are similar to those observed for carbon–carbon bond-forming cycloaddition reactions.[25] The *endo* to *exo* ratios also reflect those expected for a Diels–Alder process (Table 3).

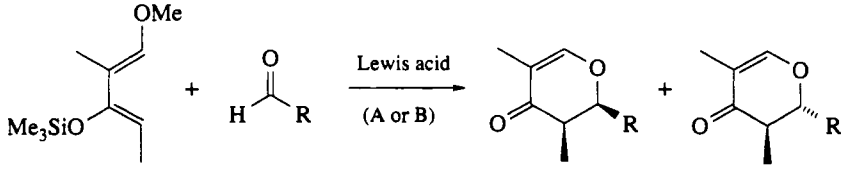
2.5.2.2 Lewis Acid Catalyzed Reactions

2.5.2.2.1 Zinc chloride and boron trifluoride etherate

The Lewis acid catalyzed reaction has two distinct mechanistic pathways. The first set of rigorous mechanistic investigations was performed by Danishefsky and coworkers. As previously mentioned only highly activated aldehydes bearing electron-withdrawing groups α to the carbonyl group participate in the thermal cycloaddition reaction. In 1982 Danishefsky, Kerwin and Kobayashi reported an important improvement that allows oxygenated dienes to react with simple aldehydes by using zinc chloride ($ZnCl_2$) as a catalyst.[30]

In further studies by Larson and Danishefsky it was shown that boron trifluoride etherate ($BF_3{\cdot}OEt_2$) also catalyzes the reaction but with a dramatically different stereochemical outcome.[31] When $ZnCl_2$ is used as a catalyst the reaction between benzaldehyde and diene (**14**) gives predominately the *cis* dihydropyrone (**16**). Under $BF_3{\cdot}OEt_2$ catalysis, however, the *trans* dihydropyrone (**17**) is the major product (Table 4).

Table 4 Comparison of the Ratio of *Cis* to *Trans* Products in the $ZnCl_2$- and BF_3-catalyzed Cyclocondensation Reactions



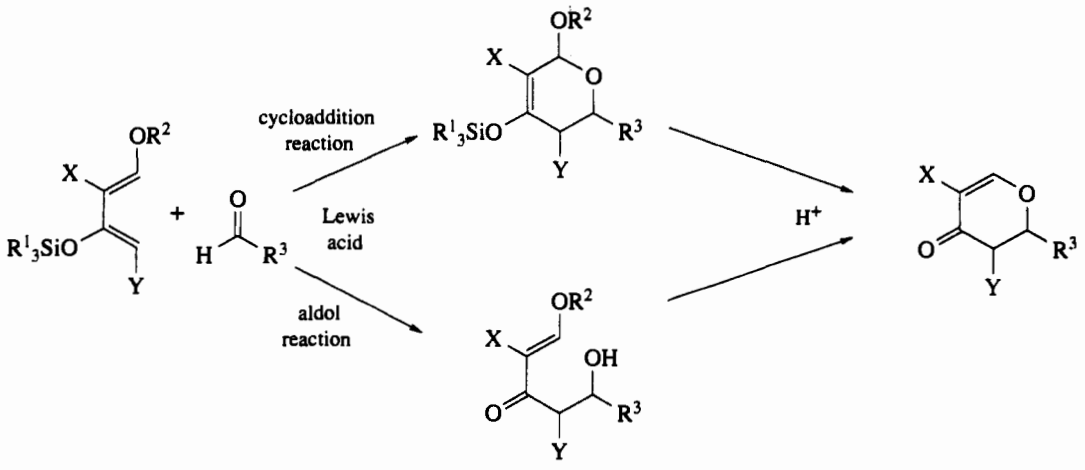
(**14**) (**15**) (**16**) *cis* (**17**) *trans*

Aldehyde	*R*	*Method*	(**16**) *Yield* (%)	(**17**) *Yield* (%)
(**12e**)	C_5H_{11}	A (BF_3–CH_2Cl_2, –78 °C; TFA)	21	69
		B ($ZnCl_2$–THF, 25 °C; $NaHCO_3$; TFA)	91	2
(**5e**)	Ph	A	23	68
		B	78	2
(**15a**)	$PH(CH_2)_3$	A	17	64
		B	83	2
(**9a**)	$BnOCH_2$	A	17	68
		B	66	24

The $ZnCl_2$ reaction seems to pass through a pericylic mechanistic pathway while the $BF_3{\cdot}OEt_2$-catalyzed reaction resembles a Mukaiyama aldol reaction.[32] Danishefsky described the process in which an activated diene is condensed with an aldehyde as a cyclocondensation reaction, thus avoiding the implication of a concerted reaction pathway in cases where aldol products are unambiguously isolated (Scheme 2).

To account for the stereoselectivity in the pericylic manifold it was proposed that the Lewis acid binds to the aldehyde so that it is *syn* to the hydrogen. If the steric demand of the catalyst solvent array exceeds that of the side chain on the aldehyde, *endo* selectivity is observed, yielding the *cis* cycloadduct (Scheme 3). The primary cycloadduct is either decomposed by the catalyst, or by the addition of acid, into dihydropyrones (**16**) and (**17**).

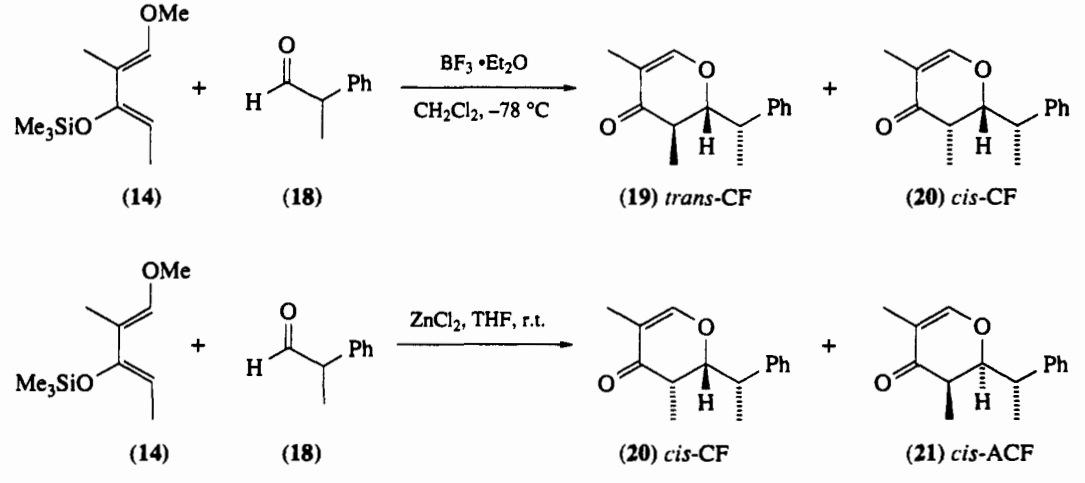
The $BF_3{\cdot}OEt_2$-catalyzed reaction, on the other hand, is characterized by the isolation of the β-hydroxy- or β-silyloxy-methoxy enones. These compounds upon treatment with acid cyclize into dihydropyrones (**16**) and (**17**). The mechanistic nature of the aldol process allows for high *anti (trans)* stereoselectivity on the dihydropyrone, but is dependent on the diene employed in the reaction.[33]



Scheme 2

Scheme 3

Initial investigations of chiral aldehydes by Danishefsky[34,35] demonstrated that both $ZnCl_2$ and $BF_3{\cdot}OEt_2$ exhibited high Cram,[36] Felkin–Ahn (CF)[37,38] stereoselectivity.[39] The cyclocondensation reaction of diene (**14**) with aldehyde (**18**) (2-phenylpropanal) under $BF_3{\cdot}OEt_2$ catalysis was found to give a 4.3:1 mixture of the *trans*-CF dihydropyrone (**19**) and the *cis*-CF dihydropyrone (**20**). Only traces of anti Cram–Felkin (ACF) products are isolated. Under $ZnCl_2$ catalysis, however, an 8:1 mixture of the *cis*-CF product (**20**) and the *cis*-ACF product (**21**) is obtained (Scheme 4). A detailed analysis of these stereochemical issues is given later in Section 2.5.3.1.



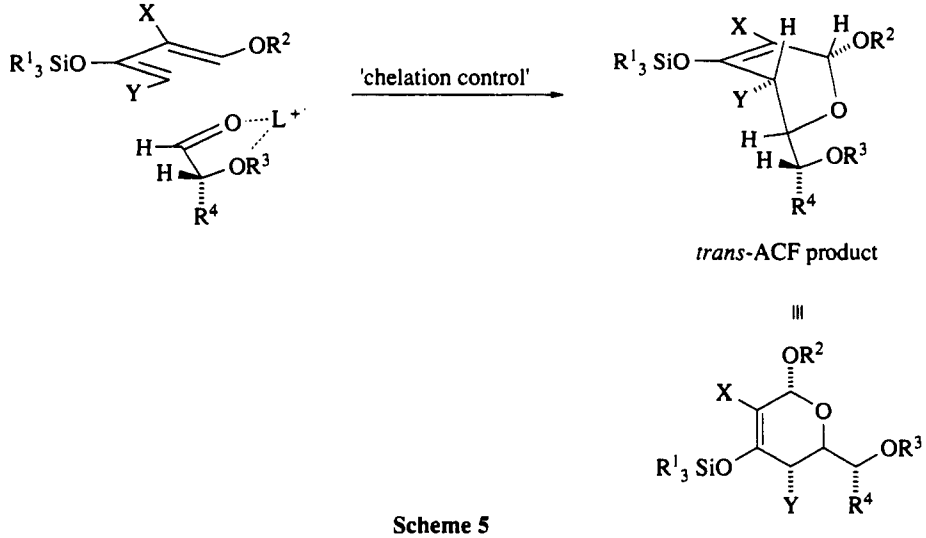
(**14**) (**18**) (**19**) *trans*-CF (**20**) *cis*-CF

(**14**) (**18**) (**20**) *cis*-CF (**21**) *cis*-ACF

Scheme 4

2.5.2.2.2 Magnesium bromide and titanium tetrachloride

Since the investigations which used $ZnCl_2$ and $BF_3{\cdot}OEt_2$ as catalysts, other Lewis acids have been shown to catalyze the cyclocondensation reaction. $MgBr_2$, for example, was used by Pearson and Danishefsky[40] to add the power of chelation control to the reaction. When chiral α-alkoxy aldehydes are condensed with dienes under the influence of $MgBr_2$, products derived from an ACF transition state predominate. The chelation of the metal by the α-alkoxy group of the aldehyde forces the aldehyde side chain to occupy the same side of the aldehyde as the metal. The diene, therefore, can attack the aldehyde from the least hindered *exo* face giving rise to the *trans*-ACF product (Scheme 5). When an aldehyde is used that cannot form a chelate to the metal (such as benzaldehyde) *syn* (*endo*) selectivity is observed.



Scheme 5

Other strongly chelating Lewis acids were investigated by Danishefsky, Pearson and Harvey.[41,42] When α-alkoxy aldehydes are used under $TiCl_4$ catalysis, *cis*-ACF products such as compound (**22**) are the major products (Scheme 6). The *cis* dihydropyrone stereochemistry is opposite to that obtained in the $MgBr_2$-mediated reaction. When using nonchelating aldehydes, however, the *trans* dihydropyrone (**23**) is the major product of the reaction. The $TiCl_4$-catalyzed reaction is thought to proceed through an aldol mechanism and the observed stereochemistry is consistent with studies by Mukaiyama and Reetz.[43,44] The stereochemistry with the $TiCl_4$ catalyst is, therefore, highly dependent on the aldehyde and diene employed in the reaction. We address the mechanistic details of this and other catalytic systems in Section 2.5.2.3. A summary of initial investigations of these catalysts is given in Table 5.

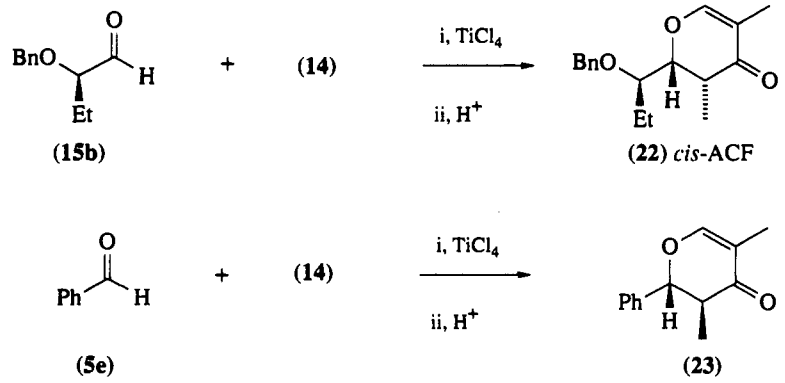
Table 5 General Consequences of some Commonly Used Catalysts in the Diene–Aldehyde Cyclocondensation Reaction

Catalyst/solvent	*Topology and stereochemistry*
$ZnCl_2$/THF[a]	Pericyclic/nonchelating with α-alkoxy aldehydes: *cis* Cram products with both chelatable and nonchelatable aldehydes
$MgBr_2$/THF[a]	Pericyclic/chelating with α-alkoxy aldehydes: *trans* anti-Cram products with chelatable aldehydes, *cis* Cram products with nonchelatable aldehydes
$BF_3{\cdot}Et_2O/Et_2O$[b]	Aldol/nonchelating with α-alkoxy aldehydes: *trans* Cram products with both chelatable and nonchelatable aldehydes
$TlCl_4$/THF[b]	Aldol/chelating with α- and β-alkoxy aldehydes: *cis* anti-Cram products with chelatable aldehydes, *trans* Cram products with nonchelatable aldehydes

[a] Nonpolar solvents (*e.g.* benzene) have also led to aldol products. [b] Topology and stereochemistry can be a function of aldehyde and diene used in the reaction (*vide infra*).

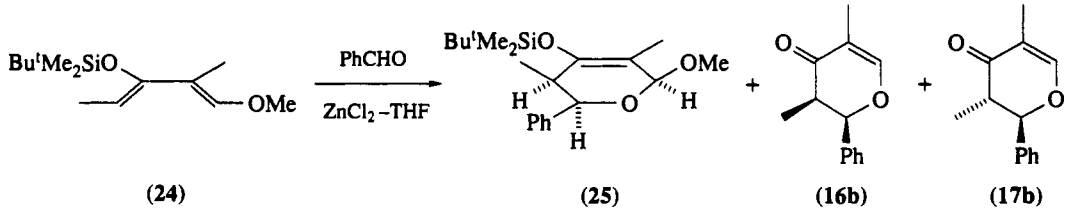
2.5.2.2.3 Lanthanide catalysts

Despite the effort put forth in developing catalytic systems, no general method existed for the production and preservation of the sensitive, highly functionalized primary cycloadducts. The only case in



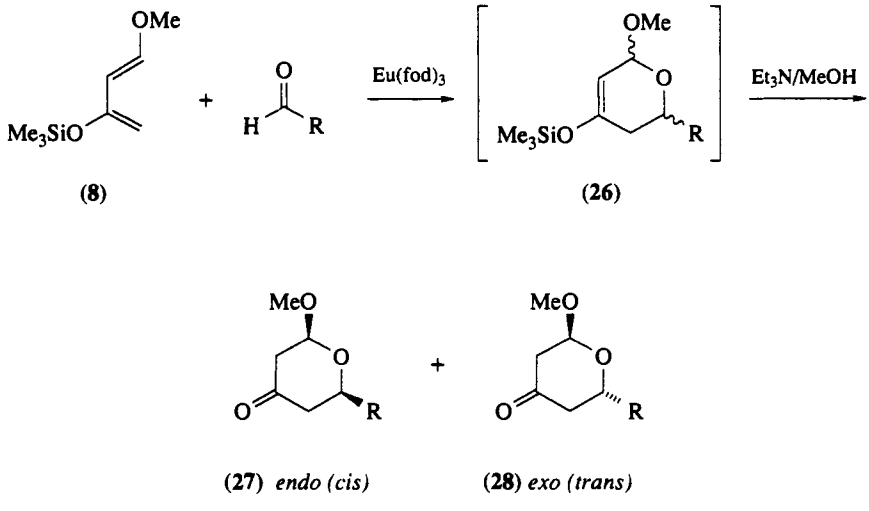
Scheme 6

which one of these intermediates had previously been isolated and fully characterized was in the reaction of benzaldehyde with diene (**24**) under $ZnCl_2$ catalysis (Scheme 7). Even in this case, however, the yield of (**25**) was low (40%) and the reaction mixture also contained significant amounts of pyrones (**16b**) and (**17b**).[31,32]



Scheme 7

Table 6 The Lanthanide-catalyzed Hetero Diels–Alder Reaction using $Eu(fod)_3$

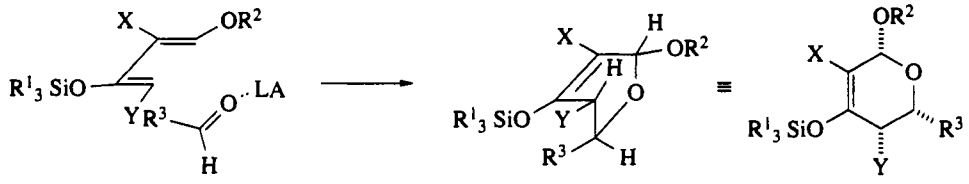


Aldehyde	*R*	*(27)*	:	*(28)*
(**5e**)	Ph	12		1
(**12d**)	2-Furyl	6		1
(**15c**)	*trans*-Styryl	8		1
(**9f**)	Me	2.8		1
(**12e**)	n-C_5H_{11}	1.2		1
(**5b**)	Pr^i	1.5		1

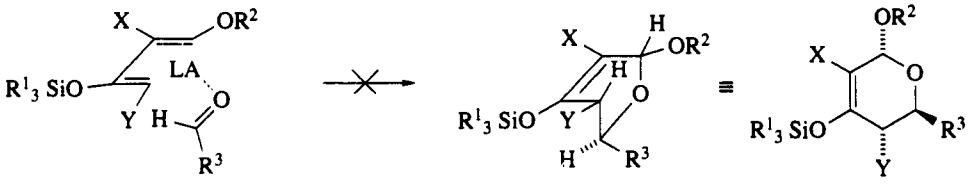
In 1984 Danishefsky and Bednarski demonstrated that lanthanide(III) complexes catalyze the cycloaddition of activated dienes with aldehydes.[45] The stereoselectivity increases dramatically when using these catalysts. When diene (**8**), for example, reacts with a variety of aldehydes with $Eu(fod)_3$ as catalyst virtually complete *cis (endo)* selectivity is observed (Table 6). The aldehydes that function as dienophiles can be aliphatic (acetaldehyde and hexanal) or aromatic (benzaldehyde and furfural).

The predominance of *cis* products is consistent with the model previously described for *endo* addition: the Lewis acid complexes to the lone pair of the aldehyde *anti* to the R group, driving the R group *endo* in the transition state. In the case of lanthanide catalysts, however, the large steric bulk of the lanthanide metal–ligand complex causes the *cis* selectivity to increase (Scheme 8).

LA = lanthanide(III) ion, $ZnCl_2$ or $MgBr_2$, where R cannot chelate to the metal



R^3 < LA–aldehyde complex gives *cis (endo)* addition products



Steric interactions between the lanthanide metal and the diene disfavor the *exo* transition state.

R^3 > LA–aldehyde complex gives *trans (exo)* addition products

Scheme 8

The high *endo* selectivity of aromatic aldehydes is also a result of their capability to participate in secondary orbital interactions.[10] The mixing of the LUMO of benzaldehyde with the HOMO of the diene can form secondary orbital overlap which lowers the energy of the *endo* transition state. The electron-withdrawing effect of the catalyst [*e.g.* $Eu(fod)_3$] on the aldehyde further enhances secondary orbital overlap with aromatic aldehydes by an additional reduction of the LUMO energy (Figure 2). Similar arguments have been made to rationalize the increase in *endo* selectivity of homo Diels–Alder reactions when Lewis acids are used as catalysts.[10] Secondary orbital interactions are, however, absent when the dienophile is an aliphatic aldehyde; in such reactions the *cis (endo)* stereoselectivity is based solely on steric interactions.

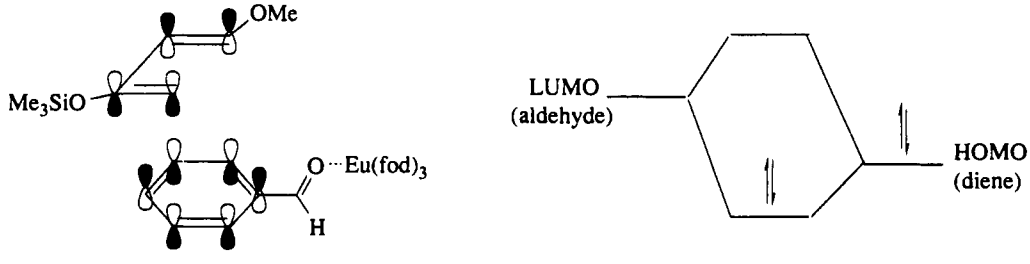
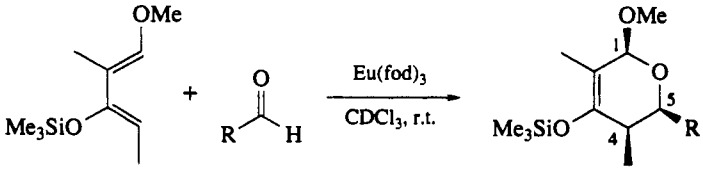


Figure 2

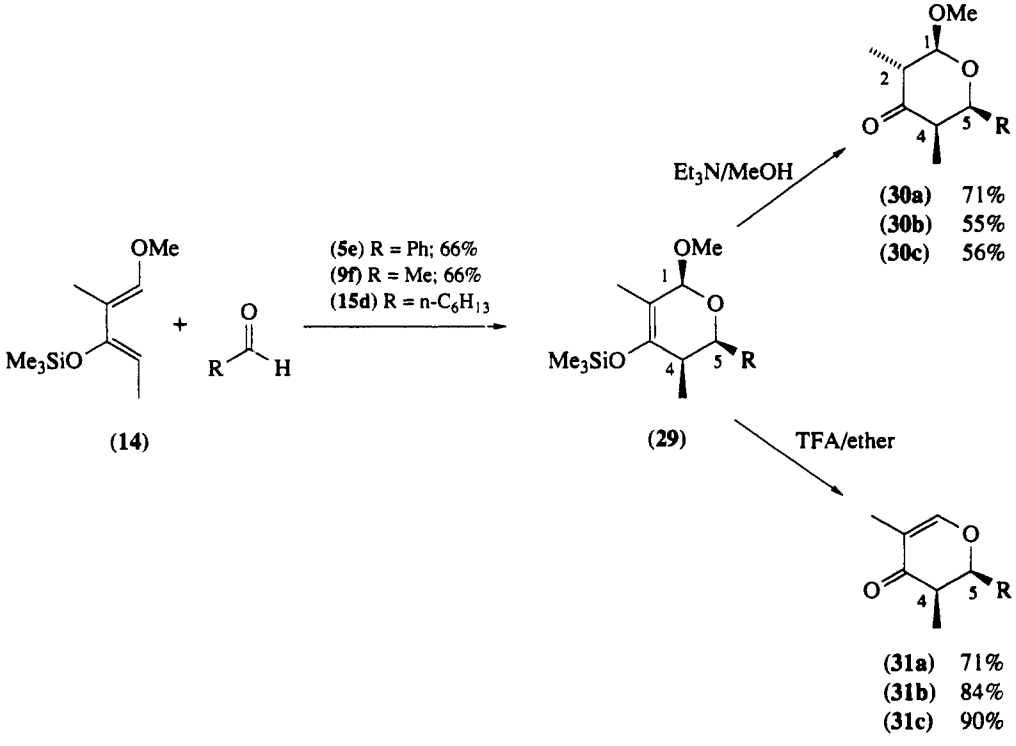
Virtually complete *endo* selectivity is maintained in the reaction of substituted dienes with both aromatic and aliphatic aldehydes. The 2,4-dimethyl diene (**14**), for example, reacts with benzaldehyde, acet-

aldehyde, or heptanal to give only the *syn* (*endo*) stereoisomers (**29a–c**; Scheme 9). Three stereocenters are established in this suprafacial *endo* cycloaddition process and a fourth stereocenter can be introduced by axial protonation of the silyl enol ether, giving methoxy ketones (**30a–c**). Alternatively, treatment of enol ethers (**30a–c**) with trifluroacetic acid (TFA) yields the *cis* dihydropyrones (**31a–c**; Scheme 10).[45]



(**14**) (**5e**) R = Ph; 66%
(**9f**) R = Me; 66%
(**15d**) R = n-C_6H_{13}; 40%
(**29a–c**)

Scheme 9

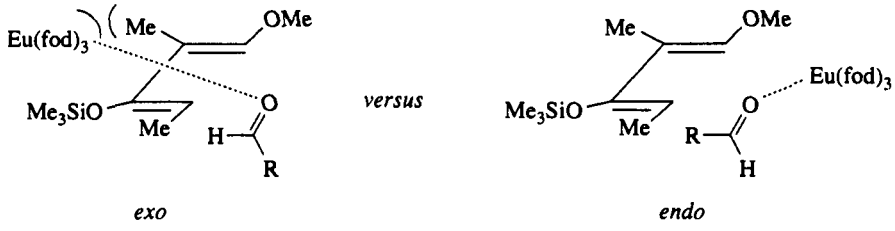


(**14**) (**29**)

Scheme 10

The high degree of *endo* topography observed for the substituted diene (**14**) may be due to the inherent increase in steric demands of 1,3-disubstituted dienes. The proposed *endo* and *exo* transition states between an aldehyde and the 2,4-dimethyl diene (**14**) are shown in Figure 3. Strong steric interactions can develop between the methyl group of the diene and the lanthanide–aldehyde complex in the *exo* transition state. This interaction, which is not present in the *endo* transition state, strongly disfavors the *exo* mode of addition. It will be shown later that other substitution patterns on the diene are a sufficient perturbation to cause high *endo* selectivity, leading to *syn* products.[46]

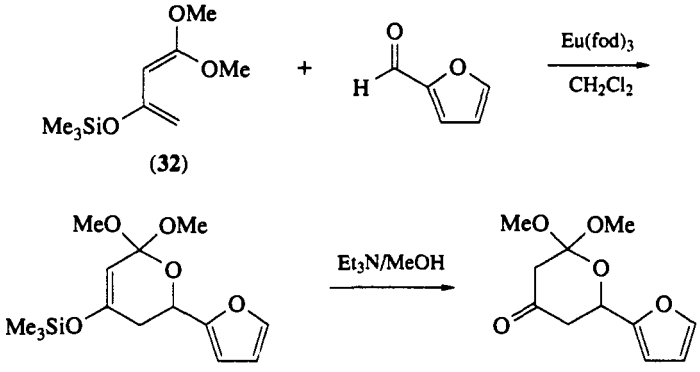
The use of the lanthanide catalyst was also investigated with sensitive highly oxygenated dienes.[47] The cycloaddition of furfural with diene (**32**) occurs at room temperature using 0.5 mol % $Eu(fod)_3$ as catalyst (Scheme 11). Treatment of the crude cycloadducts (**33**) with triethylamine and methanol, cleaves the silyl enol ether, while maintaining the sensitive dimethoxyketene acetal to yield compound (**34a**). Reduction of compound (**34a**) with L-selectride gives a 6:1 mixture of axial and equatorial alcohols, which



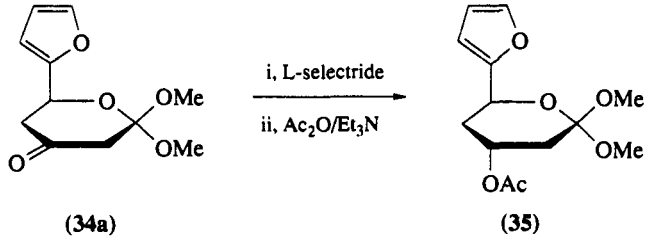
exo *endo*

Figure 3

were protected and characterized as the acetate (**35**; Scheme 12). These acetals serve as useful intermediates in synthesis.



Scheme 11



Scheme 12

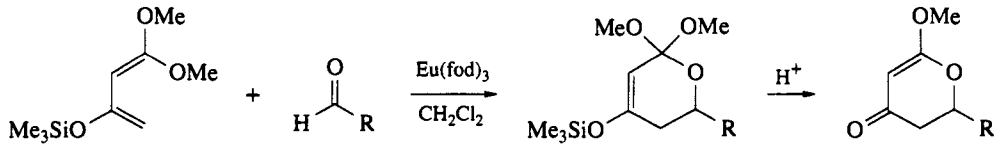
Castellino and Sims have also used $Eu(fod)_3$ to catalyze the hetero Diels–Alder reaction between a variety of aldehydes and the highly nucleophilic dienes such as (**32**).[49] The resulting dihydropyrones (**36a–d**) are also useful building blocks for natural product synthesis (Table 7).

Observations first made by Danishefsky and later confirmed by Sims and coworkers[48] showed that nucleophilic dienes such as (**32**) react with α,β-unsaturated aldehydes exclusively at the aldehyde functional group. Sims and coworkers have exploited this observation by condensing cinnamaldehyde (**15d**) with diene (**32**) to produce (**37**), an α-pyrone isolated from the kava plant (Scheme 13).[50]

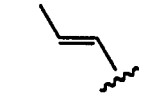
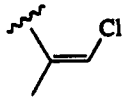
Danishefsky has also reported investigations on the cycloadditions of highly oxygenated dienes such as (**32**) and (**38**) under lanthanide catalysis.[48] This methodology has proven to be a rapid and general route to various dihydropyrone derivatives, including *C*-glycoside units (**39a, b**). These results are summarized in Scheme 14.

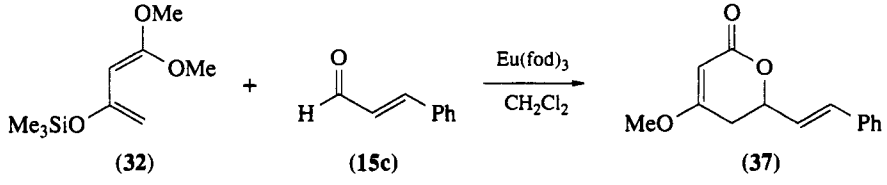
Jurczak has reported that $Eu(fod)_3$ can be used to improve conditions for the hetero Diels–Alder reaction of 1-methoxy-1,3-butadiene (**11**) with aldehydes under pressure; yields for this process range from 10 to 80% (Scheme 15). The attempted use of other Lewis acids such as $ZnCl_2$ or $BF_3{\cdot}OEt_2$ failed to give any products and led primarily to polymerization of the diene.[51]

Table 7 Lanthanide-catalyzed Hetero Diels–Alder Reaction of Highly Activated Dienes with Unactivated and α,β-Unsaturated Aldehydes

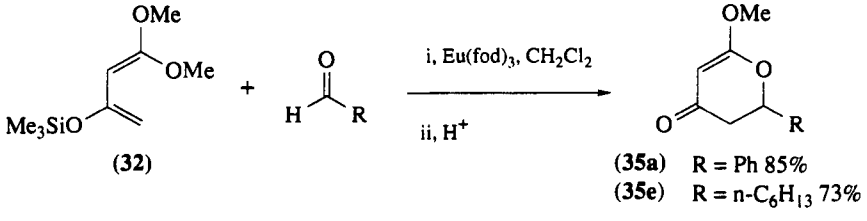


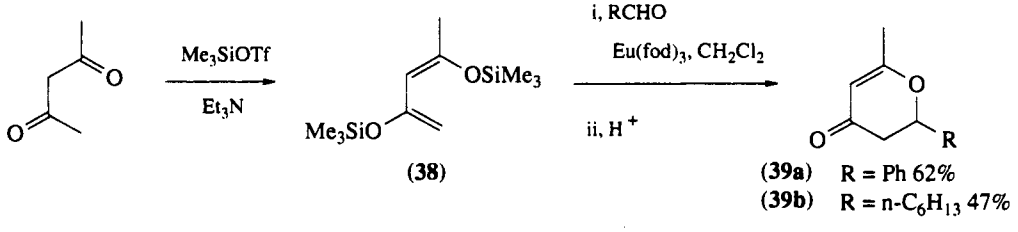
(32) **(36a–d)**

Aldehyde	*R*	*Yield (%)*
(5e)	Ph	85
(5b)	Pr^i	69
(5d)		70
(15e)		87
(15f)	CO_2Me	73

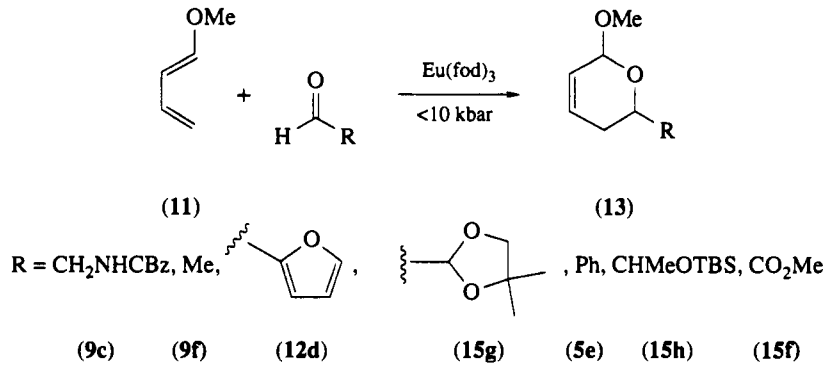


Scheme 13





Scheme 14



(11) (13)

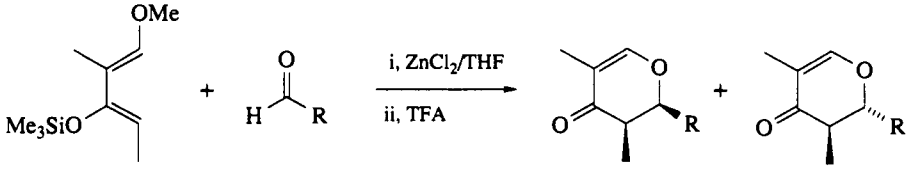
(9c) (9f) (12d) (15g) (5e) (15h) (15f)

Scheme 15

2.5.2.3 Comparison of Lewis Acid Catalysis: Analysis of Reaction Conditions

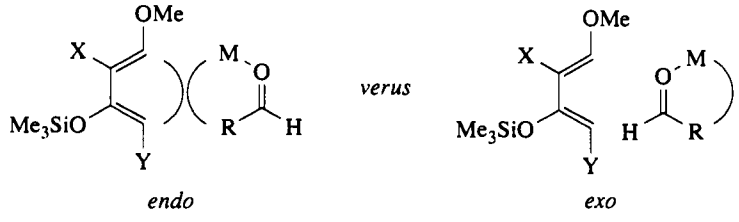
Further investigations of the use of Lewis acids with different dienes and under various solvent conditions and temperature expanded the control of stereochemistry in the cyclocondensation reaction. A summary of the results for $ZnCl_2$ in THF is given in Table 8. In general, high *endo* selectivity is observed with this catalyst–solvent system.[33] The modest *endo* selectivity observed for (**9a**) in Table 8, can be explained by a competing β-chelation complex. The benzyloxy group on the aldehyde can complex to the metal, thus restraining the R group to be *syn* to the Lewis acid and forcing an *exo* mode of addition for the diene. There exists, therefore, a competition between chelated and nonchelated dienophiles in cycloadditions of α-alkoxy aldehydes, resulting in decreased *endo* selectivity (Figure 4).[32,33]

Table 8 Summary of the Stereochemical Results using $ZnCl_2$ in THF as a Catalytic System



(14) (40) *endo* (41) *exo*

Aldehyde	*R*	*Yield (40) (%)*	*Yield (41) (%)*
(**12e**)	n-C_5H_{11}	91	2
(**5e**)	Ph	78	<2
(**18**)	PhCHMe	91	<2
(**15a**)	$Ph(CH_2)_3$	83	<2
(**9a**)	$PhCH_2OCH_2$	66	24



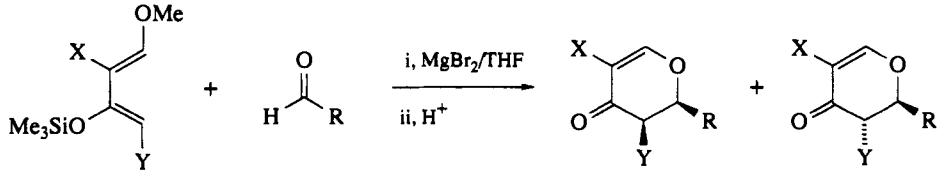
endo *exo*

Figure 4 Steric interactions between metal, aldehyde and the diene disfavor the *endo* transition state. Chelation control should prefer the *exo* transition state in the Diels–Alder cycloaddition pathway

When $MgBr_2$ in THF is used as the Lewis acid catalyst both dienes (**8**) and (**14**) show a high *endo* preference with benzaldehyde (Table 9).[40] As in the case of Eu(fod)3 catalysis, the dimethyl diene (**14**) exhibited a much higher *endo* selectivity than did the unsubstituted diene (**8**). In the case of aldehydes

(**19a**) and (**42**) the *exo (trans)* product is observed. As mentioned previously, magnesium is believed to form chelates with α-alkoxy aldehydes which, in turn, give products derived from *exo* transition states.[40–42]

Table 9 The Stereoselectivity of $MgBr_2$-catalyzed Cyclocondensation Reaction

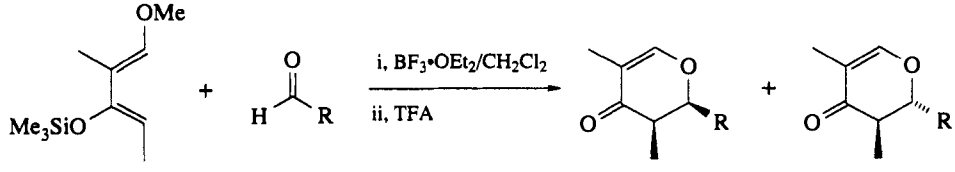


(**8**) or (**14**) *endo (cis)* *exo (trans)*

Diene	*X*	*Y*	*Aldehyde*	*R*	*Endo (cis)*		*Exo (trans)*
(**8**)	H	H	(**5e**)	Ph	3.6	:	1
(**14**)	Me	Me	(**5e**)	Ph	38	:	1
(**14**)	Me	Me	(**9a**)	$BnOCH_2$	<1	:	>99
(**14**)	Me	Me	(**42**)	BnOCHMe	<1	:	>99

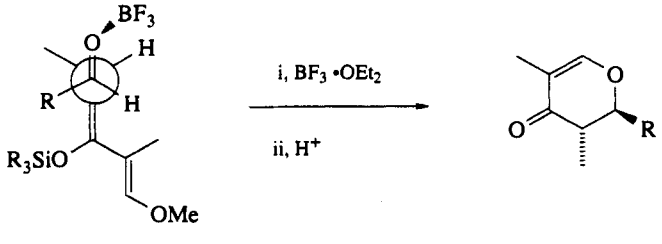
Diene (**14**) reacted with a series of aldehydes under $BF_3{\cdot}OEt_2$ catalysis in CH_2Cl_2 to give predominantly *trans* products (Table 10).[31,32] Aldol-type products, such as β-hydroxy enones, are isolated (along with dihydropyrones) from the reaction mixtures. Using TFA as a catalyst, the β-hydroxy enones are, as previously described, converted into dihydropyrones. The stereoselectivity of these reactions is consistent with a Mukaiyama–aldol reaction rather than a Diels–Alder cycloaddition. The stereochemistry of the β-hydroxy enones is also consistent with the observation that the (*Z*)-alkoxysilane reacts with the aldehyde in an extended transition state to give *anti (threo)* aldol products (Scheme 16). In the cases using $ZnCl_2$ or lanthanide ions as catalysts aldol products have not been detected.

Table 10 Stereochemistry of $BF_3{\cdot}OEt_2$-catalyzed Aldol Reactions with 2,4-Dimethyl-substituted Diene (**14**)



(**14**) (**43**) *endo (cis)* (**44**) *exo (trans)*

Aldehyde	*R*	*Yield (43) (%)*	*Yield (44) (%)*
(**12e**)	$n\text{-}C_5H_{11}$	21	69
(**5e**)	Ph	23	68
(**18**)	PhCHMe	17	73
(**15a**)	$Ph(CH_2)_3$	17	64
(**9a**)	$PhCH_2OCH_2$	17	68



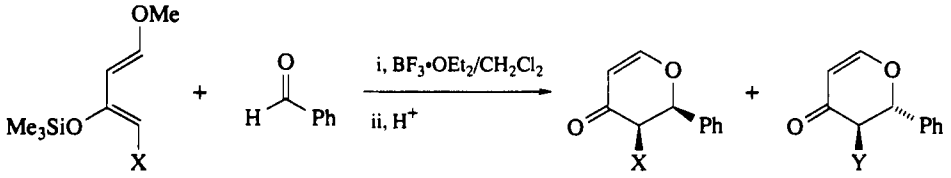
Scheme 16

When the monomethylated diene (**45a**) or the benzyloxy diene (**45b**) react under $BF_3{\cdot}OEt_2$ catalysis with benzaldehyde (**5e**) the *cis* pyrones (**46**) are the major products (Table 11).[33,35] This change in diastereoselectivity is consistent with a cycloaddition-type mechanism and not with the previously described aldol pathway.[35] A possible explanation for this change in stereochemistry is that the *s-cis* conformation of the diene that is necessary for a pericyclic reaction is more easily accessible in dienes (**45a**) and (**45b**) than in diene (**14**). An additional substituent (X) at C-2 of the diene causes severe steric interactions with the silyl group when the diene is in an *s-cis* conformation, raising the transition state energy for the cycloaddition pathway for 2,4-disubstituted dienes (Scheme 17). The aldol reaction, on the other hand, operates through an *s-trans* conformation, and this is now the lower energy path. The sense of the topographical diastereoselectivity in the $BF_3{\cdot}OEt_2$-catalyzed reaction is also dependent upon the solvent. When toluene is substituted for CH_2Cl_2 a dramatic reversal in diastereoselectivity is observed.[52] It has been suggested that in toluene the Diels–Alder reaction becomes a competitive (and even the dominant) reaction pathway, compared to the aldol process (Table 12). Interestingly, the magnitude of the diastereoselectivity is also dependent upon the silyloxy ligands.[52] The trimethylsilyl protecting group (compared to the *t*-butyldimethylsilyl group) would cause less steric hindrance to occur in the *s-cis* configuration (Table 13). This, in turn, could cause the reaction to proceed through the cycloaddition pathway as previously discussed.

When $TiCl_4$ is used as a catalyst with substituted dienes such as (**14**), a predominant route is the Mukaiyama aldol process.[40–42] When diene (**14**) reacts with benzaldehyde the *trans (anti)* product is observed. When compound (**42**) is used as the aldehyde, one observes exclusive formation of the *(erythro)* aldol products (Table 14). These stereochemical results can be rationalized by using a Zimmerman–Traxler transition state (Scheme 18).[53] Chelation by the metal of the aldehyde α-alkoxy group causes it to be placed in a pseudo axial position in the transition state structure. This results in a stereochemical relationship that gives *syn* aldol products.[54]

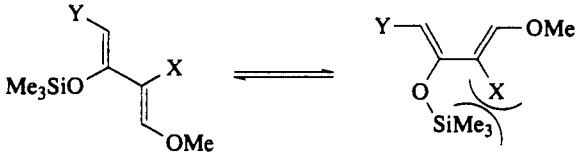
In summary, $ZnCl_2$ and the lanthanide catalysts give products derived from a classical [4 + 2] cycloaddition reaction. The side chain on the aldehyde occupies an *endo* position in the transition state, leading to *cis (endo)* products. This is probably due to the large steric bulk of the solvated metal complex, which binds *anti* to the aldehyde side chain. In addition, vinylogous ortho ester products, which are the expected products for a cycloaddition process, can be isolated when using these catalysts. $MgBr_2$ also

Table 11 The Stereochemistry of the BF_3-catalyzed Cyclocondensation Reaction with the C(4)-substituted Diene (**45**)



(**45**) (**5e**) (**46**) *cis* (**47**) *trans*

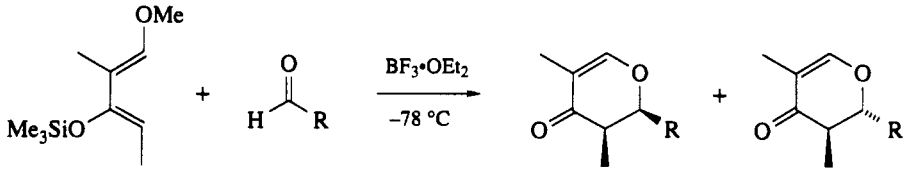
Diene	*X*	*(46)*	:	*(47)*
(**45a**)	Me	8.5		1
(**45b**)	OBz	11		1



The *s-trans* conformation is favored when X = Me. When X = H however the diene can adopt the *s-cis* conformation. The population of this conformation may be responsible for the change in stereoselectivity in these dienes

Scheme 17

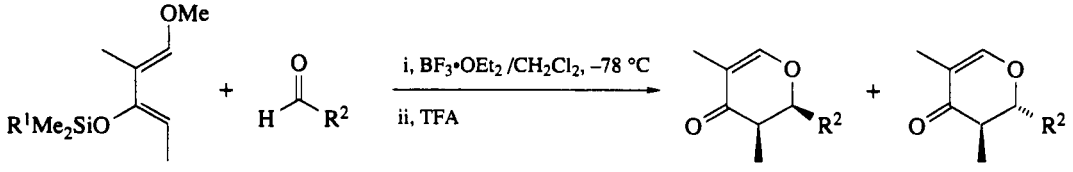
Table 12 Solvent Dependence in the Cyclocondensation Reaction using BF_3 as a Catalyst



(14) **(48)** **(49)** **(50)**

Aldehyde	*R*	*Solvent*	*(49)*	:	*(50)*
(48a)	Ph	CH_2Cl_2	1		2.3
		Toluene	7		1
(48b)	PhCHMe	CH_2Cl_2	1		2.0
		Toluene	10		1
(48c)	$BnOCH_2$	CH_2Cl_2	1		4.5
		Toluene	1		1.7

Table 13 The Dependency of the Silyl Protecting Group on the Stereoselectivity of the Cyclocondensation Reaction using BF_3 as a Catalyst



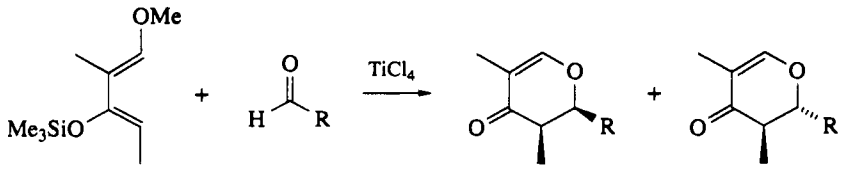
(14) or **(24)** **(51)** **(53)** **(54)**

Diene	*Aldehyde*	*Solvent*	*(53)*	:	*(54)*
(14) R^1 = Me	**(51a)** R = Ph	CH_2Cl_2	1		2.3
(24) R^1 = Bu^t	**(51a)**	CH_2Cl_2	1		4.6
(14)	**(51b)** R = PhCHMe	CH_2Cl_2	1		2.0
(24)	**(51b)**	CH_2Cl_2	1		6.5
(14)	**(51a)**	Toluene	7		1
(24)	**(51a)**	Toluene	2.2		1
(14)	**(51b)**	Toluene	10		1
(24)	**(51b)**	Toluene	3.7		1

seems to operate through the cycloaddition pathway. The advantage of this catalyst is its capability to form chelates with α-alkoxy aldehydes, resulting in an *exo* transition state that gives *trans (anti)* products. In general, BF_3·OEt_2 operates through an aldol mechanism. *Syn* pyrones predominate with dienes that have substitution only at C-4. When the diene is substituted at both C-2 and C-4, the *trans* pyrone is the major product. The BF_3·OEt_2 catalytic system is also very sensitive to solvent conditions. When toluene is substituted for CH_2Cl_2 the *syn* pyrone dominates even when using disubstituted dienes such as **(14)**. This is probably due to a change in mechanism from the aldol process to the Diels–Alder pathway.

$TiCl_4$ also operates through an aldol reaction mechanism. Unlike BF_3·OEt_2, however, $TiCl_4$ can form an ordered Zimmerman–Traxler transition state and is also able to chelate α-alkoxy aldehydes. This forces the production of *syn* pyrones from the reaction with aldehydes that contain groups that are able to chelate to the metal; aldehydes that cannot coordinate give *trans* aldol products. Primary [4 + 2] cycloaddition products (*i.e.* vinylogous ortho esters) have not been isolated in the $TiCl_4$-catalyzed reactions.

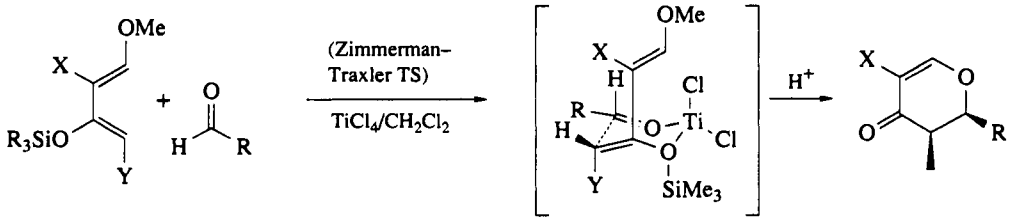
Table 14 The Stereochemistry of the Cyclocondensation Reaction using $TiCl_4$ as a Catalyst



(14) *cis (syn)* *trans (anti)*

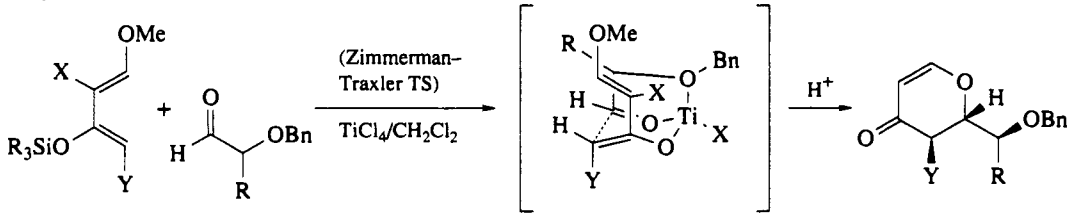
Aldehyde	*R*	*Cis (syn)/trans (anti)*		*Cis (syn)/trans (anti)*
(5e)	Ph	1	:	8
(42)	CH(Me)OBn	>99	:	<1

Non chelation model



(48)

Chelation model



(49)

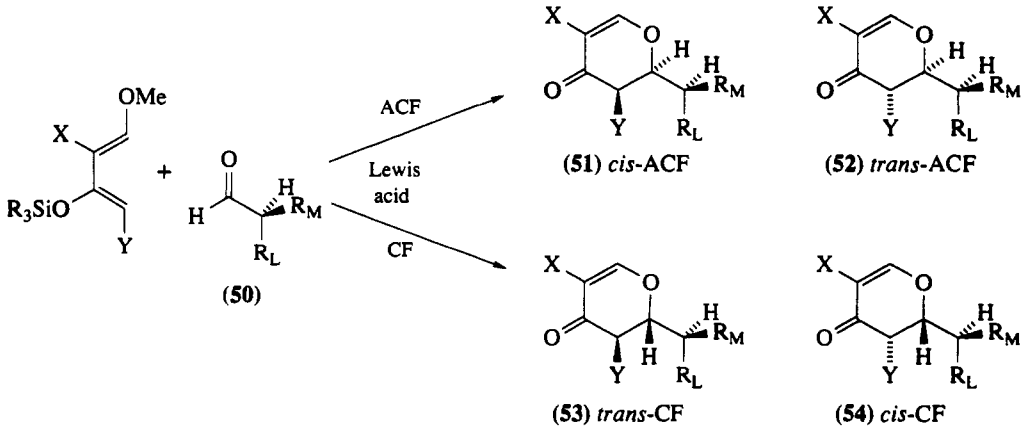
Scheme 18

2.5.3 DIASTEREOFACIAL SELECTIVITY

2.5.3.1 Cram–Felkin and Anti Cram–Felkin Stereochemical Control

Another major contribution put forth by the Danishefsky group was the realization and exploitation of the stereochemical control available through the use of chiral aldehydes in the cyclocondensation reaction. Scheme 19 shows the possible products that can be produced when a chiral aldehyde is condensed with a substituted diene. R_L represents a group that is the most sterically demanding or has the most electron-withdrawing characteristics; R_M represents a medium-sized group which, in most cases, will be a methyl substituent; X is a group that can chelate to a metal such as a benzyloxy substituent. A chiral aldehyde has two possible faces of attack, which we will denote as Cram–Felkin (CF) or anti Cram–Felkin (ACF) following the nomenclature adopted in the literature for this type of diastereofacial selectivity.[36–38,55] In addition, the pyranose ring can have a *cis (syn)* orientation (*i.e.* products derived from an *endo* pericylic reaction or *syn* aldol) or *trans (anti)* orientation (*i.e.* products derived from an *exo* pericylic reaction or *anti* aldol), which represents the stereochemistry of the aldehyde side chain relative to the substituent on the diene. The simple diastereofacial selectivity for the cyclocondensation reaction (*i.e. endo versus exo* products) was described in the previous section. The terms *cis* and *trans* will be

used synonymously with *syn* and *anti* as descriptors of the dihydropyrone stereochemistry because this nomenclature can be used to directly relate the stereochemistry of the products obtained from the cyclocondensation reaction with products derived from the aldol reaction.[55] In the past several years methods have been developed to control the relative stereochemistry (*syn versus anti* and CF *versus* ACF) and the absolute stereochemistry of products obtained from the reaction of activated dienes with aldehydes. These methods are discussed in the following sections.

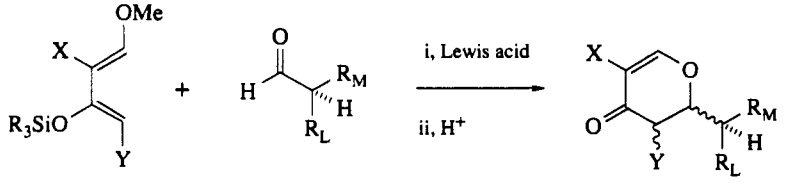


Scheme 19

2.5.3.2 The Effect of Lewis Acids on Diastereofacial Selectivity

As previously discussed two modes of addition (*endo* and *exo*) are possible for the orientation of the diene with respect to the aldehyde. In addition to these orientations are preferences for a particular diastereofacial selectivity (CF, ACF) for reactions with chiral aldehydes. A summary of these relationships and how the diastereofacial selectivity can be controlled by use of different Lewis acid catalysts is given in Table 15 and Scheme 19.

Table 15 The Topography and Diastereoselectivity of Different Lewis Acids with Chiral Aldehydes that *cannot* Chelate to the Metal

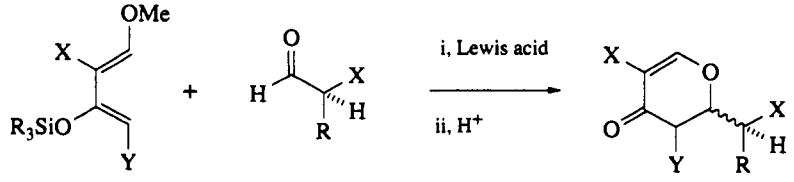


Catalyst	Topography: Cis/syn (endo)	Topography: Trans/anti (exo)	Diastereofacial selectivity: CF	Diastereofacial selectivity: ACF	Product
$ZnCl_2$	+	0	+	0	(54)
$BF_3{\cdot}OEt_2$ (X = H; Y = Me or OBz)	+	0	+	0	(54)
$BF_3{\cdot}OEt_2$ (X = Y = Me)	0	+	+	0	(53)
$Eu(fod)_3$ or $Eu(hfc)_3$	+	0	+	0	(54)
$MgBr_2$	+	0	NA	NA	NA
$TiCl_4$	+	0	NA	NA	NA

Table 15 shows the stereochemistry of the cyclocondensation products with chiral aldehydes that contain side chains that do not chelate to the catalyst. Table 16 summarizes the results for chiral aldehydes that are able to chelate the metal. The '+' implies that, in general, compounds from that particular transition state can be expected to be the major product of the reaction. The '0' implies that compounds aris-

ing from this transition state are usually minor products. 'NA' indicates the information on this reaction is not available. These catalysts are discussed individually below.

Table 16 The Topography and Diastereofacial Selectivity of Different Lewis Acids with Chiral Aldehydes that *can* Chelate to the Metal



Catalyst	*Topography* *Cis/syn (endo)*	*Trans/anti (exo)*	*Diastereofacial selectivity* *CF*	*ACF*
$ZnCl_2$	+	0	+	0
$BF_3{\cdot}OEt_2$ (X = H; Y = Me or OBz)	+	0	+	0
$BF_3{\cdot}OEt_2$ (X = Y = Me)	0	+	+	0
$Eu(fod)_3$ or $Eu(hfc)_3$[a]	+	NA	+	+
$MgBr_2$	0	+	0	+
$TiCl_4$	+	0	0	+

[a] One case of chelation controlled has been reported by Midland.

2.5.3.2.1 Zinc chloride and lanthanide complexes

The use of $ZnCl_2$ and β-diketonate complexes of lanthanide metals give predominately *endo*-type addition products and CF diastereofacial selectivity. The CF stereoselectivity seems to prevail in cases using $ZnCl_2$ as a catalyst and chiral aldehydes that contain groups that do not chelate to the metal. The selectivity clearly decreases when aldehydes that can form chelates are used. The lanthanide catalysts also exhibit strong CF-type selectivity with nonchelating chiral aldehydes. This trend seems to hold with most chelating aldehydes; however, ACF products have been reported when α-alkoxy aldehydes are used in the reaction.[56] The stereochemical consequences of using lanthanide catalysts with α-alkoxy aldehydes are therefore not predictable.

2.5.3.2.2 Boron trifluoride

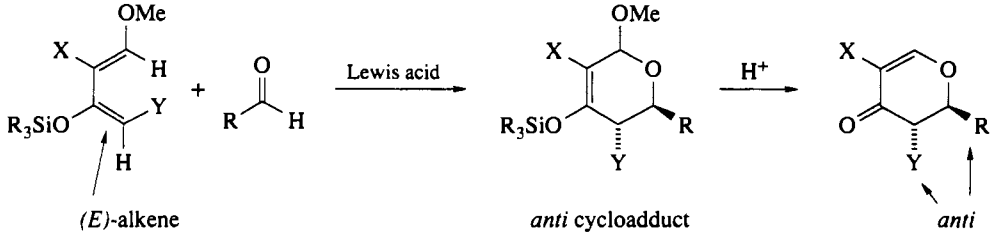
$BF_3{\cdot}OEt_2$ also shows strong CF selectivity, but the topography of the reaction depends on the substitution pattern of the diene. *Endo* products are observed when the diene is substituted at C-4 with a methyl or benzoyloxy group (*e.g.* dienes **45a** and **45b**). *Exo* products, however, dominate when C-2 and C-4 of the diene are substituted with methyl groups (*e.g.* diene **14**). This change in topography of the reaction could be due to a change in mechanism. In the case of dienes (**45a**) and (**45b**) a [4 + 2] cycloaddition process might dominate over the aldol reaction, as previously discussed.

2.5.3.2.3 Magnesium bromide and titanium tetrachloride

$MgBr_2$ and $TiCl_4$ give ACF products with chiral aldehydes that contain groups that can chelate with the metal. The use of $MgBr_2$ results in an almost exclusive preference for *exo* products, resulting from chelation control in the cycloaddition mechanism; *endo* products are observed for aldehydes that do not form chelates. However, $TiCl_4$ leads to products derived from *endo* topography while retaining the ACF diastereofacial selectivity. This change in diastereofacial selectivity is believed to represent a change in mechanism in which $TiCl_4$ causes an aldol-type reaction to give acyclic products that subsequently cyclize to dihydropyrones. Chelation models using a Zimmerman–Traxler transition state can be used to account for the change in topography while retaining the ACF stereoselectivity.

2.5.3.2.4 Summary

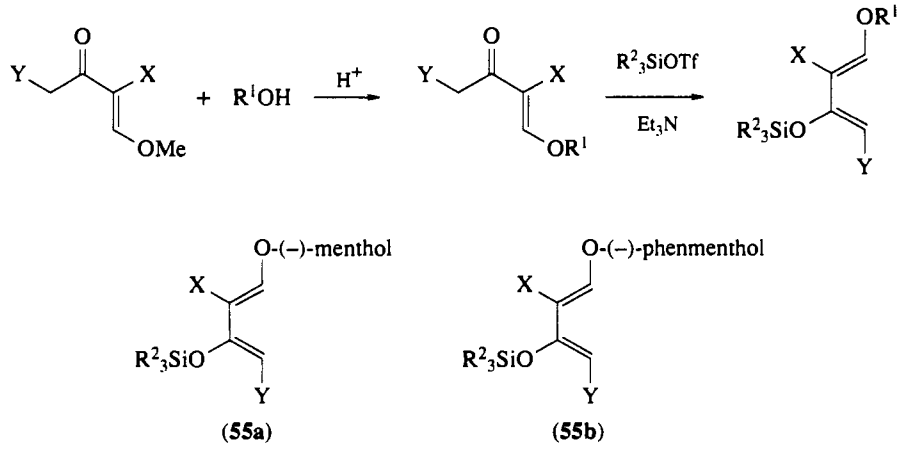
In summary, ACF products are available only through the use of chiral aldehydes with groups that are able to strongly chelate $MgBr_2$ or $TiCl_4$. The *endo* and *exo* topography is tunable by changing the metal: $MgBr_2$ gives *exo (trans* or *anti)* products while $TiCl_4$ gives *endo (cis* or *syn)* products. This allows the construction of both *syn*-ACF and *anti*-ACF products with chiral aldehydes that can form a chelate to the catalyst. Lanthanide catalysts such as $Eu(fod)_3$ and $ZnCl_2$ give *syn*-CF products with chiral aldehydes that do not have groups available for chelation. The stereochemistry when using aldehydes that can form chelates is not predictable for either $ZnCl_2$ or lanthanide catalysts. *Syn*-CF products can, therefore, be obtained with a variety of chiral aldehydes containing nonchelatable groups. To obtain *anti*-CF products the stereochemistry of the diene must be altered. This can be accomplished by synthesizing the (*E*)-alkene (*trans* alkene) on the diene, which, in conjunction with the *endo* topography, can give the *anti* relationship on the resulting dihydropyrone (Scheme 20). Despite the difficulty in obtaining these dienes the ability to obtain the *anti*-CF stereochemistry justifies the effort in many cases (*e.g.* Scheme 53). In summary, by choosing the appropriate catalyst, aldehyde and diene all possible combinations of stereochemistry (*syn*-CF, *anti*-CF, *syn*-ACF and *anti*-ACF) are available.



Scheme 20

2.5.4 METHODS TO CONTROL ABSOLUTE STEREOCHEMISTRY

Methods to control the absolute stereochemistry of the products obtained from the cyclocondensation reaction have also been developed. The use of both chiral auxiliary based methods and chiral catalysts have been investigated. The first and most straightforward method of controlling absolute stereochemistry is the use of a chiral and optically pure aldehyde. All of the methodology developed for the control of relative stereochemistry can then be directly applied to give optically pure cyclocondensation products. In many cases, however, the synthesis of optically pure aldehydes is difficult (if not impossible) due to their tendency to undergo racemization under the reaction conditions. This method also suffers from the fact that only chiral aldehydes can be used in the cyclocondensation reaction to get optically pure products; simple and readily available achiral aldehydes can not be used.



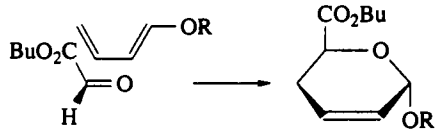
Scheme 21

2.5.4.1 Chiral Auxiliary Based Methods

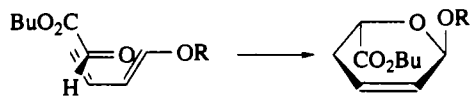
The first approach to this problem was to attach the chiral auxiliary to the diene by a vinylogous transesterification reaction of chiral alcohols with the β-alkoxy enones (Scheme 21).[57] This reaction was used to construct a variety of chiral dienes including the menthol and phenmenthol dienes (**55a**) and (**55b**) by transesterification followed by enol silylation using the Simchen procedure (R_3SiOTf/Et_3N).[58] However, these dienes exhibit poor diastereofacial selectivity despite the precedent for high stereochemical control in homo Diels–Alder reactions by the use of similar auxiliaries on α,β-unsaturated enones.[59–61]

High diastereofacial selectivities, but poor *endo:exo* preferences were observed in the use of chiral dienes (**60**)–(**63**) under thermal reaction conditions with activated aldehydes (Table 17).[62] Despite the low stereoselectivity David used this methodology to synthesize the ABX blood antigen oligosaccharides.

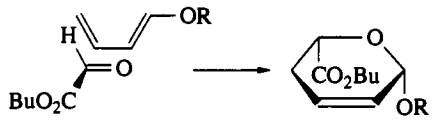
Table 17 The Topography and Diastereoselectivity of the Hetero Diels–Alder Reaction of Chiral Dienes with Activated Aldehydes



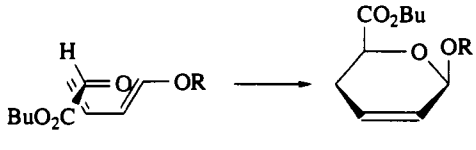
(**56**) α-D-sugar



exo (**57**) α-L-sugar

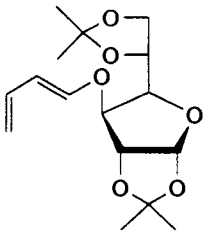


(**58**) β-L-sugar

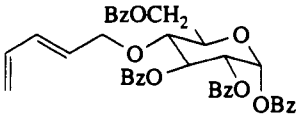


endo (**59**) β-D-sugar

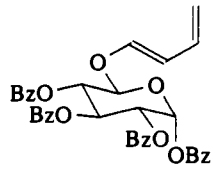
Diene	*(56) α-D (%)*	*(59) β-D (%)*	*(57) α-L (%)*	*(58) β-L (%)*
(**60**)	13	18	9	60
(**61**)	44	4	0	52
(**62**)	48	18	0	34
(**63**)	1	50	47	2



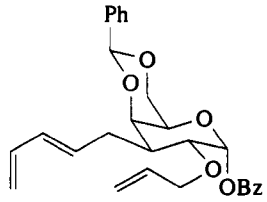
(**60**)



(**61**)



(**62**)

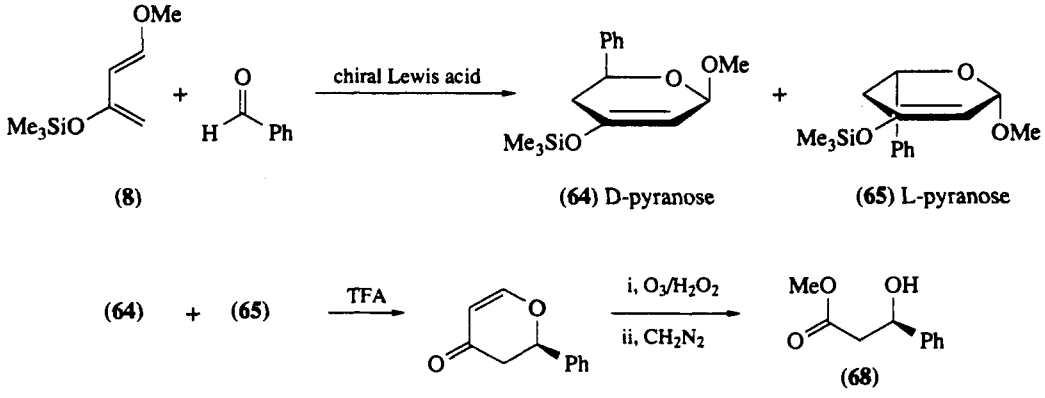


(**63**)

2.5.4.2 Chiral Catalysts

With the achievement of high stereochemical control resulting from nearly exclusive *endo* topography in the Lewis acid catalyzed reactions interest next turned to the effect of chiral Lewis acid complexes on the enantiofacial selectivity of the cyclocondensation reaction. For example, consider the cycloaddition of benzaldehyde to diene (**8**) under the influence of a chiral catalyst. Assuming a pericyclic reaction mode and high *endo* selectivity, a mixture of two possible products can result. Compound (**64**) is desig-

nated as a D-pyranose and compound (**65**) as an L-pyranose, based on carbohydrate nomenclature (compounds **64** and **65** are, of course, enantiomers). A simple and practical method to synthesize compounds such as (**64**) and (**65**) in either enantiomeric form and in high optical purity is of synthetic value (Scheme 22).

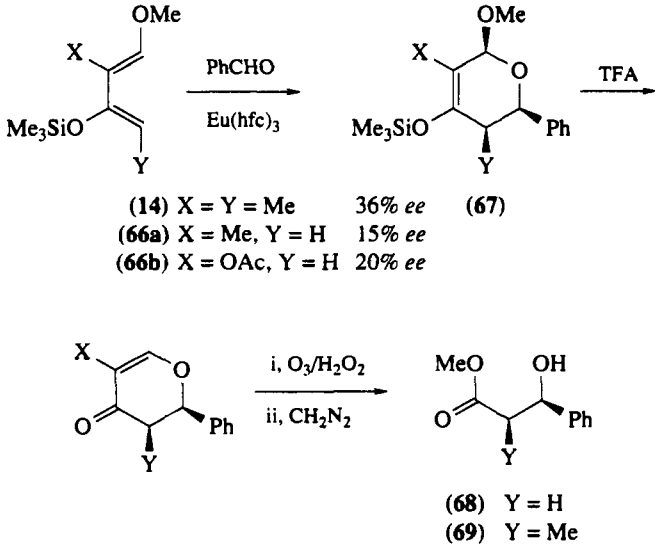


Scheme 22

2.5.4.2.1 Optical induction in the Eu(hfc)$_3$-catalyzed reaction

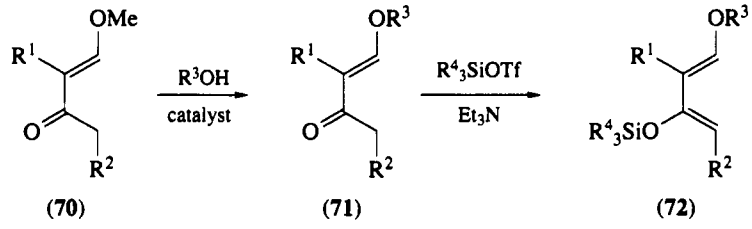
The first catalyst to be evaluated was the commercially available chiral lanthanide β-diketonate complex Eu(hfc)$_3$.[63] The reaction of benzaldehyde with diene (**8**) was chosen as the system to screen various catalysts for their enantiofacial selectivity. A simple method to assess the extent and sense of the optical induction was also developed.[63,64] This was accomplished by optical and NMR measurements on compound (**68**), obtained from (**64**) and (**65**) by a previously described protocol (Scheme 22).[30–33] The enantioselectivity with diene (**8**) and benzaldehyde is 18%.[64]

Attempts to improve the asymmetric induction by varying the substituents on the diene was explored (Scheme 23). Substitution at either C-2 or C-4 of the diene seemed to increase the optical induction. By using the 2,4-dimethyl diene (**14**), for example, the *ee* is increased to 36%.[64] Interestingly, both the 2-methyl diene (**66a**) and 2-acetoxy diene (**66b**) show no significant improvement in facial selectivity over the parent diene (**8**).



Scheme 23

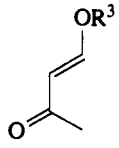
To help improve the optical induction in the chiral lanthanide catalyzed reaction the C-1 alkoxy group on the diene was also varied systematically. The previously described transesterification reaction provides an easy method to install different alkoxy groups at the C-1 position of the diene by conducting an exchange reaction of various enones (**70**) with alcohols (R^3OH) in refluxing benzene (Scheme 24). Pyridinium *p*-toluenesulfonate (PPTS) is an effective acid catalyst for this reaction, since it is sufficiently mild to allow survival of sensitive functionality in both the alcohol and enone components. With inexpensive volatile alcohols such as Bu^tOH, R^3OH is used in excess. When the alcohol is less readily available, nearly equivalent molar ratios can be employed. In some instances, a 3:1 excess of enone was helpful in driving the exchange reaction to completion. In this fashion, readily available β-methoxy enones (**73a**), (**74a**) and (**74d**) have been converted in the indicated yields to enones (**73b–f**) and (**74b, c, e–g**), respectively (Table 18). The resulting exchanged enones can be converted to dienes by the previous described enolsilylation procedure.[58]



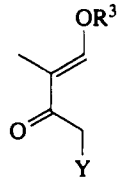
(**70**) (**71**) (**72**)

Scheme 24

Table 18 β-Alkoxy Enones Available Through the Vinylogous Transesterification Reaction



(**73**)



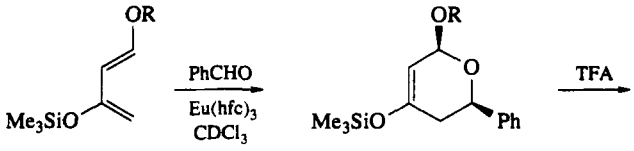
(**74**)

Enone	R^3	*Yield (%)*	*Enone*	R^3	*Y*
(**73a**)	Me		(**74a**)	Me	H
(**73b**)	Bu^t	55	(**74b**)	Bu^t	H
(**73c**)	(+)- or (−)-menthyl	80	(**74c**)	(−)-Menthyl	H
(**73d**)	(−)-8-Phenmenthyl	94	(**74d**)	Me	Me
(**73e**)	(+)- or (−)-Phenethyl	72	(**74e**)	(−)-Menthyl	Me
(**73f**)	3-Cholestanyl	92	(**74f**)	(−)-Phenmenthyl	Me
			(**74g**)	(+)- or (−)-Phenethyl	Me

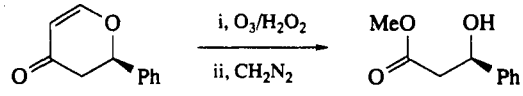
With the ability to change the C-1 functionality of the diene, investigations focused on the effects these changes had on the optical induction in the chiral lanthanide catalyzed cycloaddition reaction. The presence of large achiral alkoxy groups at C-1 of the diene results in a significant increase in facial selectivity (**75a,b**; Scheme 25).[64] In the case of the 2-methyl diene (**66a**) and the 2,4-dimethyl diene (**14**), changing the C-1 methoxy to a *t*-butoxy group increases the *ee* from 15% to 39% in the former and from 36% to 42% in the latter (Scheme 26). When using the 2-acetoxy diene (**77a**) and the corresponding 2-siloxy diene (**77b**), substantial increases in *ee* from 29% and 18% to 33% and 42%, respectively, occurred by replacing the methoxy group with the *t*-butoxy group (Scheme 27).

Finally, with two of the dienes the induction was maximized by modifying the experimental conditions. By conducting the reactions of dienes (**76a**) and (**76b**) in the absence of solvent and at reduced temperatures up to 55% and 58% *ee*, respectively, could be obtained.[64]

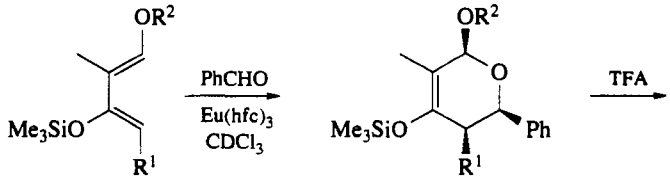
While the exact causes of the induction are not clearly understood, there seem to be some important general conclusions to be drawn from these experiments. First, chiral lanthanide complexes that are the most effective NMR shift reagents [*e.g.* Eu(hfc)$_3$] seem to give the best optical induction. Interestingly, Eu(hfc)$_3$ is also known to be one of the most acidic shift reagents since it carries the greatest number of



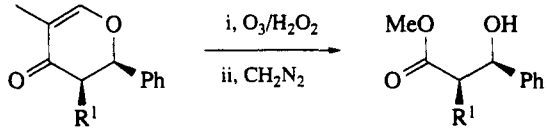
(8) R = Me 18% *ee*
(75a) R = Pr^i 28% *ee*
(75b) R = Bu^t 38% *ee*



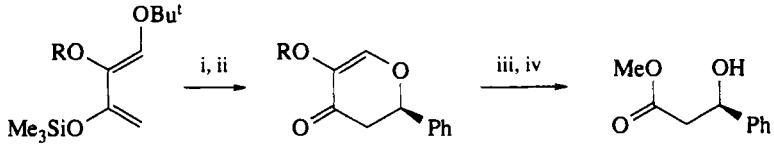
Scheme 25



(66a) R^1 = H; R^2 = Me 15% *ee*
(76a) R^1 = H; R^2 = Bu^t 39% *ee*
(14) R^1 = R^2 = Me 36% *ee*
(76b) R^1 = Me; R^2 = Bu^t 42% *ee*



Scheme 26



(77a) R = Ac 33% *ee* **(78a)** R = Ac
(77b) R = Me_3Si 42% *ee* **(78b)** R = Me_3Si

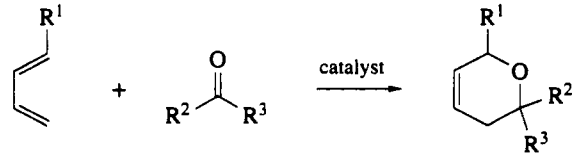
i, PhCHO, $Eu(hfc)_3$, $CDCl_3$, r.t.; ii, TFA; iii, O_3/H_2O_2; iv, CH_2N_2

Scheme 27

electron-withdrawing fluorine atoms on its ligands.[65] Secondly, conducting the reactions in nonpolar aprotic solvents or in the absence of any solvent and at reduced temperatures also helps increase the extent of optical induction. Finally, and most importantly, changing the substituents on the diene can dramatically affect the facial selectivity. Especially important in this respect is the C-1 position. It will be shown later that with the correct choice of alkoxy group a stereofacial selectivity of greater than 90% can be obtained (*e.g.* Table 25).

Major progress has recently been made in developing chiral catalysts for the cyclocondensation reaction. Initial investigations using chiral lanthanide complex $Eu(hfc)_3$ showed promising results. A study by Jankowski and coworkers has recently surveyed the use of a variety of chiral catalysts in the cyclocondensation reaction of chiral dienes with aldehydes.[66] A summary of these results is given in Table 19. The lanthanide catalyst $Eu(hfc)_3$ gave the highest (albeit modest) enantiofacial selectivity at 64% *ee*.

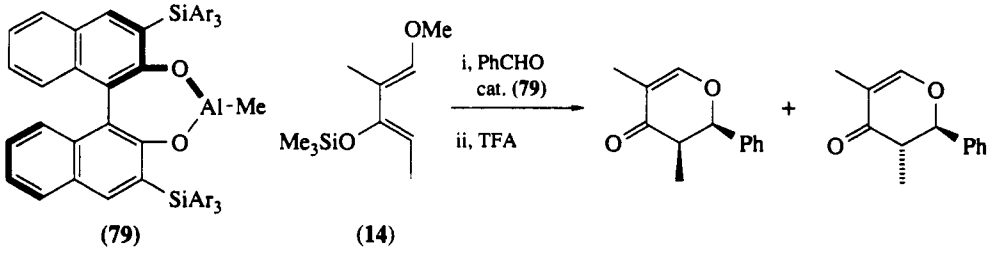
Table 19 Asymmetric Diels–Alder Reactions using Chiral Catalysts: Comparison of $Eu(hfc)_3$ with Menthol Aluminum Dichloride (Men^*OAlCl_2)



Diene	*Dieneophile*	*Catalyst*	*Yield (%)*	*ee (%)*
$R^1 = OMe$	$R^2 = R^3 = CO_2Et$	Men^*OAlCl_2	30	9
		$Eu(hfc)_3$	100	15
$R^1 = Me$	$R^2 = R^3 = CO_2Et$	Men^*OAlCl_2	15	4
		$Eu(hfc)_3$	>1	—
$R^1 = OMe$	$R^2 = H_2$; $R^3 = CO_2Bu$	Men^*OAlCl_2	*cis* : 17	16
			trans : 9	3
		$Eu(hfc)_3$	*cis* : 19	64
			trans : 79	39
$R^1 = Me$	$R^2 = H_2$; $R^3 = CO_2Bu$	Men^*OAlCl_2	*trans* : 25	<1
			cis : 6	5
		$Eu(hfc)_3$	*trans* : 6	5
			cis : trace	

2.5.4.2.2 Optical induction using a chiral aluminum catalyst

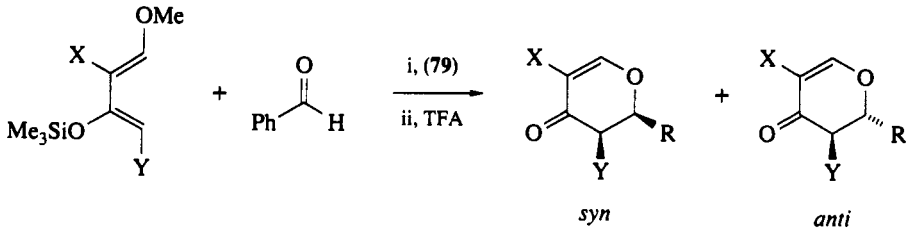
Yamamoto and coworkers have recently found a chiral aluminum catalyst (**79**) that catalyzes the hetero cyclocondensation reaction (Scheme 28).[67] In the reaction of benzaldehyde with diene (**14**) an enantiofacial selectivity of up to 95% *ee* was observed. A summary of substituted aldehydes and dienes used in this study is given in Table 20. As with the $Eu(hfc)_3$ catalyst, the more substituted dienes give higher enantiofacial selectivity. Aromatic aldehydes are the best substrates and xylyl groups give the most efficient catalysts. The aluminum catalyst has also been extended to other simple aldehydes (Table 21) and has recently been used for the resolution of racemic dienophiles.[67]



(**79**) (**14**)

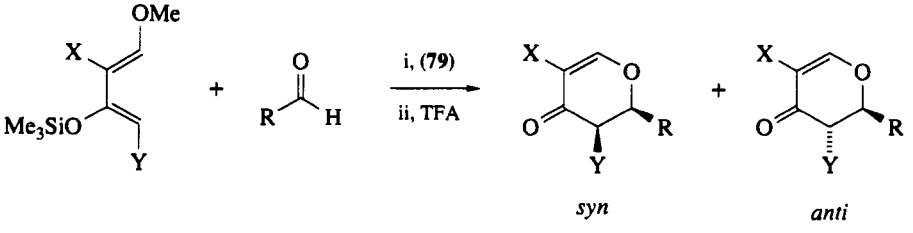
Scheme 28

Table 20 The Enantiofacial Selectivity of Various Chiral Aluminum Catalysts with Benzaldehyde



Diene	*Catalyst (79)*	*Temperature (°C)*	*Yields syn:anti*	*ee (%)*
X = Y = Me	Ar = Ph	0	89:7	92 (2*R*,3*R*)
X = Y = Me	Ar = Ph	–20	77:7	95 (2*R*,3*R*)
X = Y = Me	Ar = Ph	–78	75:7	95 (2*R*,3*R*)
X = Y = Me	Ar = 3,5-Xylyl	0	90:3	97 (2*R*,3*R*)
X = Y = H	Ar = Ph	–20	71	67 (*R*)
X = Y = H	Ar = 3,5-Xylyl	–20	81	81 (*R*)
X = Y = H	Ar = 3,5-Xylyl	–78	88	85 (*R*)
X = H; Y = Me	Ar = Ph	–20	91:5	95 (2*R*,3*R*)
X = OAc; Y = H	Ar = 3,5-Xylyl	–20	83	90 (2*S*,3*R*)

Table 21 The Enantiofacial Selectivity of Various Aldehydes with Chiral Aluminum Catalysts



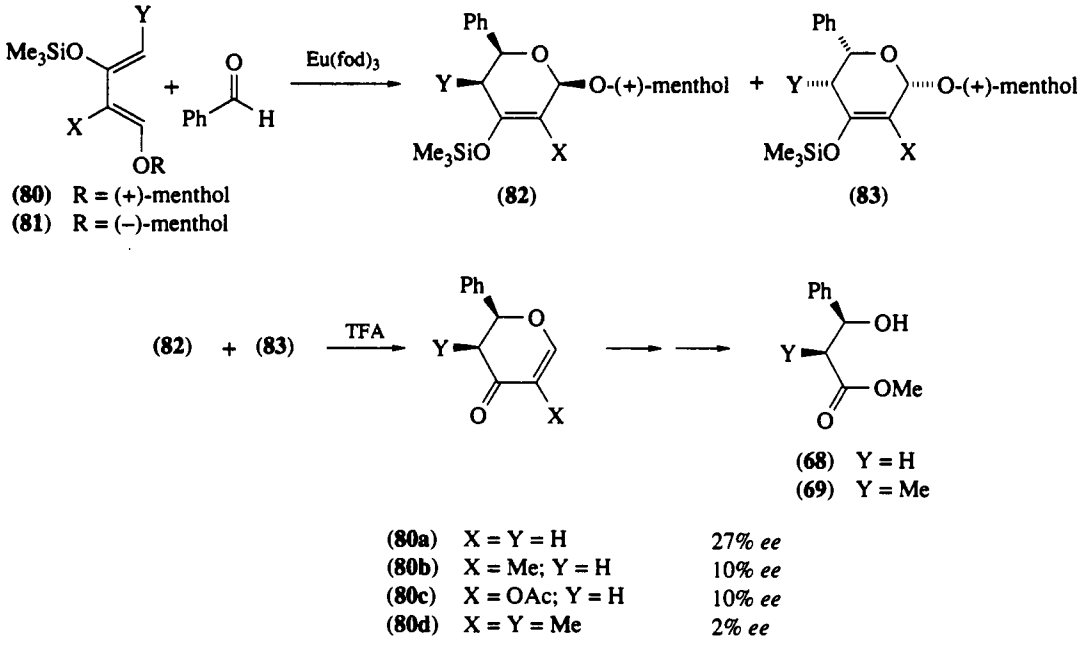
Diene	*Aldehyde*	*Catalyst*	*Temperature (°C)*	*Yields syn:anti*	*ee (%)*
X = Y = Me	R = PhCH=CH (*E*)	Ar= Ph	-20	89:10	90(*S*,3*R*)
X = Y = Me	R = PhCHCH (E)	Ar = 3,5-Xyly	0	93:2	96 (2*S*,3*R*)
X = Y = Me	R = C_6H_{11}	Ar = Ph	–20	65	91 (2*S*,3*R*)
X = H; Y = Me	R = C_6H_{11}	Ar = Ph	–20	76:9	93 (2*S*,3*R*)
X = Y = Me	R = Bu^n	Ar = Ph	–20	62:18	86 (2*S*,3*R*)

2.5.4.2.3 Double diastereofacial selectivity

To achieve high stereoselectivity applicable to any aldehyde in the cyclocondensation reaction the use of double diastereofacial selectivity has been investigated. These studies revealed an interesting relationship between the chiral catalyst used in the reaction and the chiral auxiliary. Contrary to the notion that the selectivity of a chiral diene and chiral dienophile are enhanced only in a matched pair,[68] the interactivity of a chiral catalyst with a chiral diene where the two individual components have an opposite facial preference seems to give a high degree of asymmetric induction in the cyclocondensation reaction.[63]

Dienes (**80**) and (**81**) were synthesized by previously described methods. The inherent facial selectivities of these dienes in their reactions with benzaldehyde under achiral [Eu(fod)$_3$] catalysis were determined (Scheme 29). In line with previous precedents, these reactions are highly *endo* specific, thus giving rise to a two-component mixture of (**82**) and (**83**). The extent and sense of the facial inductions were ascertained by conversion of this mixture to (**68**) and (**69**). The optical purities of compounds (**68**) and (**69**) were determined by NMR methods using chiral shift reagents.[63,64] The data shown in Scheme

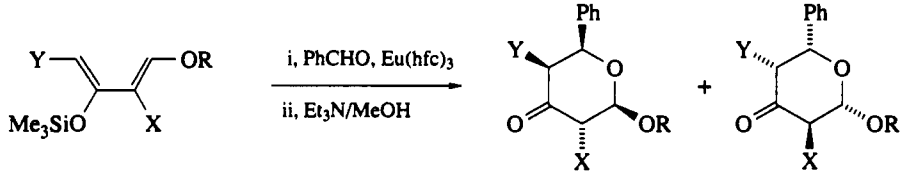
29 for the reactions starting with the (+)-menthyloxy dienes reveals a modest bias in favor of the 'D-pyranose' products (**82**), over their L-facial isomers (**83**).[63]



Scheme 29

The cyclocondensation reactions of these chiral dienes with benzaldehyde, under the influence of the chiral catalyst Eu(hfc)$_3$ were then examined.[71] The data are provided in Table 22. The inherent facial selectivity data for the Eu(fod)$_3$ reactions of the same dienes with benzaldehyde are given in parentheses.

Table 22 The Results of Mixing Matched and Mismatched Pairs of (+)- and (−)-Menthyloxy Dienes with Eu(hfc)$_3$



Diene	*X*	*Y*	*(84)* (%)	*(85)* (%)	*Diene*	*X*	*Y*	*(86)* (%)	*(87)* (%)
(80a)	H	H	37 (37)	63 (63)	**(81a)**	H	H	25 (63)	75 (37)
(80b)	Me	H	41 (45)	59 (55)	**(81b)**	Me	H	8 (55)	92 (45)
(80c)	OAc	H	41 (45)	59 (55)	**(81c)**	OAc	H	7 (55)	93 (45)
(80d)	Me	Me	49 (49)	51 (51)	**(81d)**	Me	Me	13 (51)	87 (49)
(80e)[a]	H	Me	34 (37)	66 (63)	**(81e)**[a]	H	Me	14 (63)	86 (37)

[a]TBDMSO diene used instead of the TMSO diene.

Recall that the intrinsic enantiotopic preference of the Eu(hfc)$_3$ catalyst with achiral alkoxy groups and benzaldehyde as the heterodienophile is in the 'L-pyranose' direction. Comparison of the Eu(hfc)$_3$ and Eu(fod)$_3$ diastereoselectivities in the case of (+)-menthyloxy diene (**80**) reveals essentially no cooperativity of the chiral elements. The situation is strikingly different in the case of the Eu(hfc)$_3$-catalyzed re-

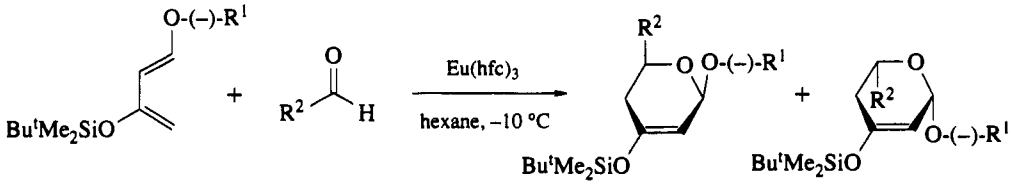
actions of the (–)-menthyloxy diene (**81**). These reactions, upon similar work-up, afford facial isomers (**86**) and (**87**), which are processed in the same way as (**84**) and (**85**).

The highest degree of diastereoselectivity is between the mismatched pairs. The normal low diastereoselectivity of the (–)-menthyloxy diene is completely reversed and enhanced by using the chiral catalyst with opposite enantiofacial selectivity. Since the primary cycloadducts also contain the chiral auxiliary, the major stereoisomers can be purified and subsequently eliminated to give optically pure dihydropyrones. This method can, therefore, be used as a general method for synthesis of a variety of optically pure dihydropyrones.

The (–)-phenmenthol parent diene (**88**) and (+)-Eu(hfc)$_3$ combination can also be used with a variety of aldehydes to produce optically pure cycloadducts (**90a–d**) with high diastereofacial selectivity (Table 23).[69] Separation of minor isomers can be easily accomplished by flash chromatography or crystallization at the stage of the cycloadducts. Treatment of the optically pure cycloadducts with TFA gives good yields of the L-pyranosides (**90a–d**). In many cases the less elaborate (–)-menthol diene can be used in place of the (–)-phenmenthol diene, as shown in Table 24 for benzaldehyde and furfural. Despite the lower diastereofacial selectivity the convenience of the menthol auxiliary can, in many cases, outweigh this disadvantage. As with the phenmenthol dienes, the cycloadducts can be obtained in optically pure form by chromatography or crystallization. A summary of the highest diastereofacial selective reactions using a combination of a chiral diene and catalyst is given in Table 25.

A variety of methods are now available to control the relative and absolute stereochemistry of the cyclocondensation reaction of activated dienes with aldehydes. Chiral aldehydes that posses a high degree of diastereofacial selectivity with a variety of dienes can be used and the stereoselectivity controlled by the choice of diene, aldehyde and catalyst. Chiral dienes in combination with chiral catalysts can also be used in an unusual process of double diastereofacial selectivity. The resulting adducts can be purified and eliminated to give optically pure dihydropyrones. The chiral auxiliary can be isolated and reused if

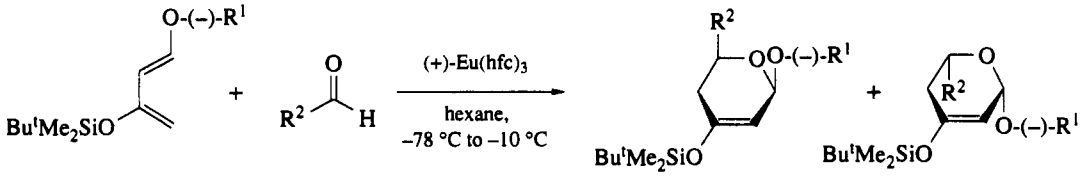
Table 23 The Use of the (–)-Phenmenthol Diene and Eu(hfc)$_3$ Catalyst in the Process of Double Asymmetric Induction



(**88**) R^1 = phenmenthol (**89**) D-pyranoside (**90**) L-pyranoside

Aldehyde	*R²*	*(89)*	*(90)*
(**5e**)	Ph	1	25
(**5d**)	MeCH=CH (*E*)	1	6.4
(**12d**)	2-Furyl	1	22
(**9f**)	Me	1	5.6

Table 24 The Practical Use of the (–)-Menthol Diene in the Process of Double Asymmetric Induction

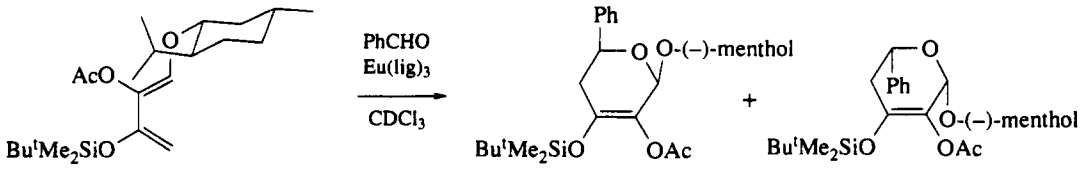


(**91**) R^1 = menthol (**92**) D-pyranoside (**93**) L-pyranoside

Aldehyde	*R²*	*(92)*	*(93)*
(**5e**)	Ph	1	7.2
(**12d**)	2-Furyl	1	5.8

Table 25 A Comparison of Chiral Dienes in the Process of Double Asymmetric Induction

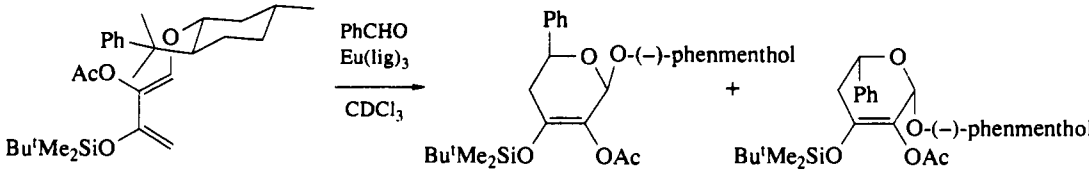
Chiral interactivity: (–)-menthol



(94) **(95)** D-sugar **(96)** L-sugar

Diene (94)	*Catalyst*	*Eu(lig)$_3$*	*(95)*	*(96)*
D-Selective	Achiral	Eu(fod)$_3$	1.22	1
D-Selective	D-Selective	(–)-Eu(hfc)$_3$	1.44	1
D-Selective	L-Selective	(+)-Eu(hfc)$_3$	1	13.3

Chiral interactivity: (–)-phenmenthol



(97) **(98)** D-sugar **(99)** L-sugar

Diene (97)	*Catalyst*	*Eu(lig)$_3$*	*(98)*	*(99)*
D-Selective	Achiral	Eu(fod)$_3$	1.50	1
D-Selective	D-Selective	(–)-Eu(hfc)$_3$	2.07	1
D-Selective	L-Selective	(+)-Eu(hfc)$_3$	1	25

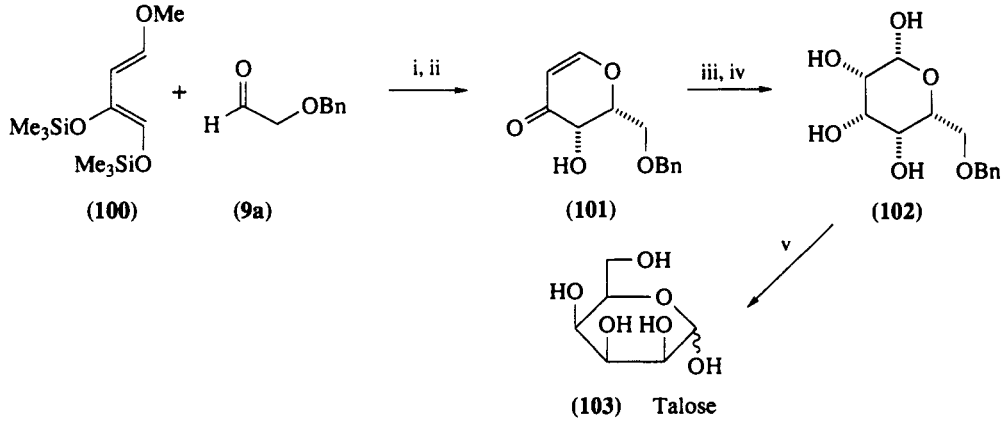
necessary. Finally, chiral catalysts such as the aluminum–binaphthalene complexes are available which give high enantiofacial selectivity.

2.5.5 APPLICATIONS IN ORGANIC SYNTHESIS

2.5.5.1 Simple Monosaccharides

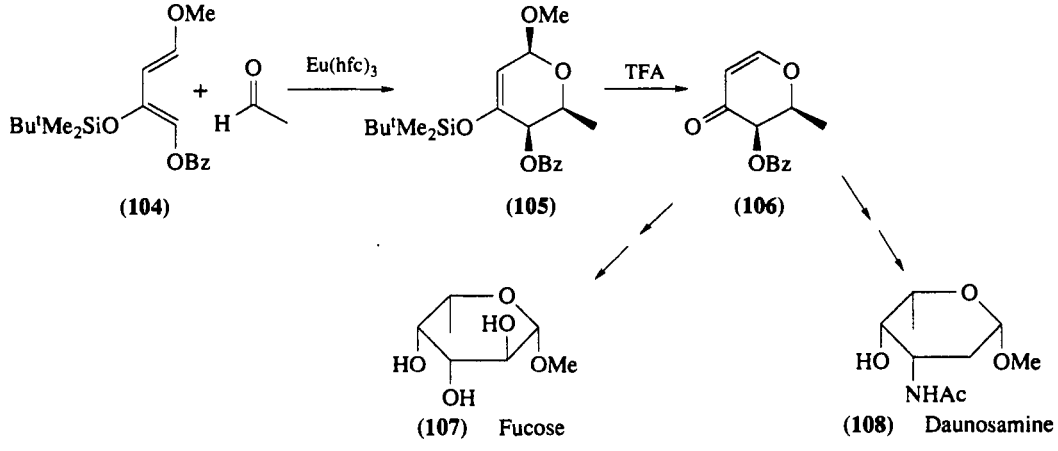
The most straightforward application of the cyclocondensation reactions of aldehydes with activated dienes is in the synthesis of simple monosaccharides.[30] Condensation of diene (**100**) with benzyloxyacetaldehyde (**9a**) using $BF_3{\cdot}EtO_2$ as a catalyst, followed by treatment with TFA, gives the dihydropyrone (**102**). Reduction of (**102**) using DIBAL-H followed by hydroxylation of the glycal gives, after deprotection, talose (**103**; Scheme 30).

More complex monosaccharides such as daunosamine and fucose are assembled using a similar strategy (Scheme 31).[33] Cyclocondensation of diene (**104**) with acetaldehyde (**9f**) using the lanthanide catalyst Eu(hfc)$_3$ gives the *syn* cycloadduct (**105**). Treatment of (**105**) with TFA followed by oxymercuration [$Hg(OAc)_2$–$NaCNBH_4$] and reductive amination of the oxime acetate (derived from the ketone) gives daunosamine (**108**). Fucose (**107**) is prepared from compound (**106**) by reduction of the ketone and treatment of the glycal with MCPBA in methanol.



i, BF_3•OEt_2; ii, TFA; iii, DIBAL; iv, hydroxylation; v, deprotection

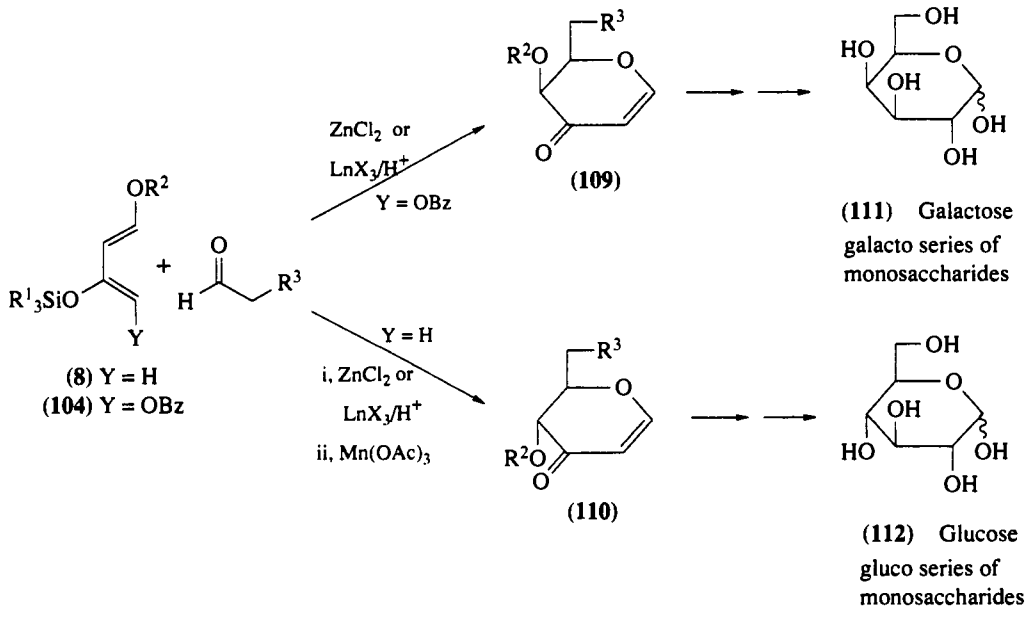
Scheme 30



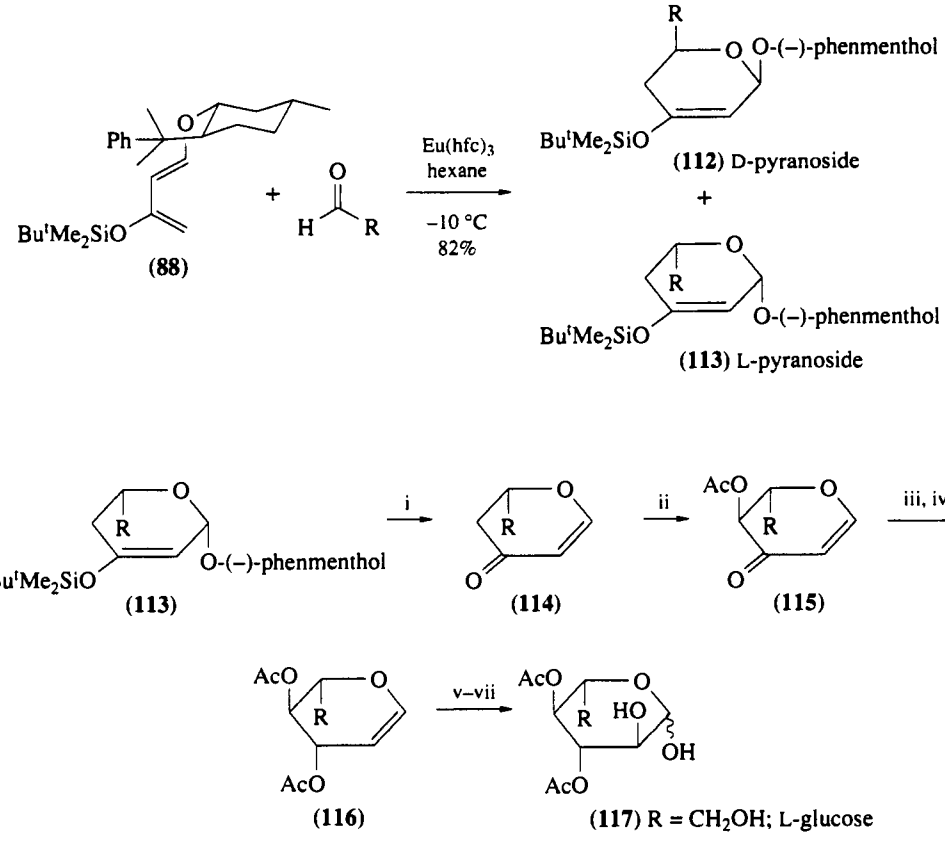
Scheme 31

The cyclocondensation reaction was expanded by Danishefsky and coworkers to synthesize any simple monosaccharide.[1,2] The key to this approach is a method to construct both the *syn* pyrone (**109**) and the *anti* pyrone (**110**; Scheme 32). From compounds (**109**) and (**110**) all possible sugars could be synthesized by controlling the stereochemistry of the reduction (axial and equatorial hydride delivery) and oxidation of the glycals (*syn* and *anti* to the C-3 hydroxy group). This strategy was demonstrated by the synthesis of glucose (**112**) and galactose (**111**) from their corresponding pyrones. The use of chiral catalysts in conjunction with chiral dienes were used to construct L-glucose in optically pure form to demonstrate the use of this chemistry to construct optically pure monosaccharides.

The synthesis of L-glucose (and a variety of L-glucal derivatives) begins with the hetero Diels–Alder reaction of the phenmenthol diene in hexane at -10 °C under (+)-Eu(hfc)$_3$ catalysis (Scheme 33). This reaction is *endo* specific and gives high diastereofacial selectivity resulting in a 25:1 mixture of the L-pyranoside (**113b**) to the D-pyranoside (**113a**). Chromatography and crystallization gives L-pyranoside (**113b**) in 78% yield. Treatment of (**113b**) with TFA unravels the enol ether to give the optically pure dihydropyrone (**114**) in 86% yield. Compound (**114**) is converted into L-glucose (and various L-glucose derivatives) by first introducing the acetoxy group at C-4 using manganese triacetate, $Mn(OAc)_3$,[70] followed by reduction of the ketone, osmylation of the glucal, oxidation of the aromatic group and reduction of glucuronic acid.[71] This chemistry has been demonstrated for a variety of side chains as shown in Table 26.



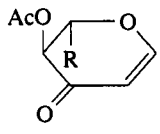
Scheme 32



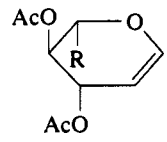
i, TFA; ii, $Mn(OAc)_3$; iii, $NaBH_4/CeCl_3$; iv, Ac_2O/Et_3N; v, $OsO_4/AcOH$; vi, O_3/H_2O_2; vii, $B_2H_6/NaOMe$

Scheme 33

Table 26 Acetoxylation of Chiral Glycals



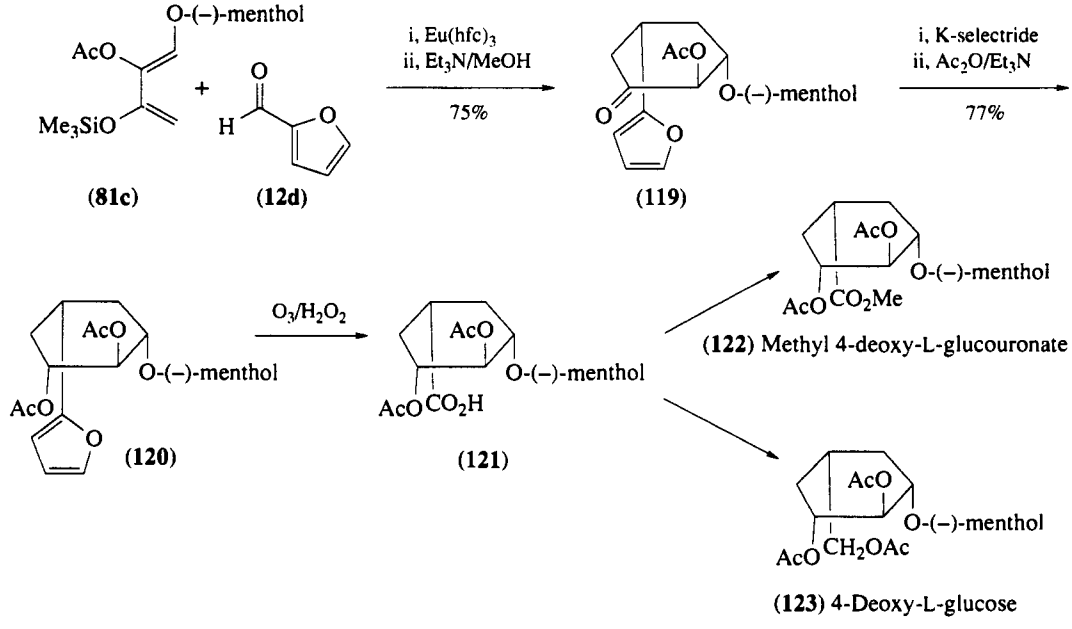
(115)



(116)

Dihydropyrone	*R*	*Yield (115)* (%)	*Yield (116)* (%)
(114a)	Ph	64	89
(114b)	Furyl	53	78
(114c)	Crotyl	51	83
(114d)	Me	44	78

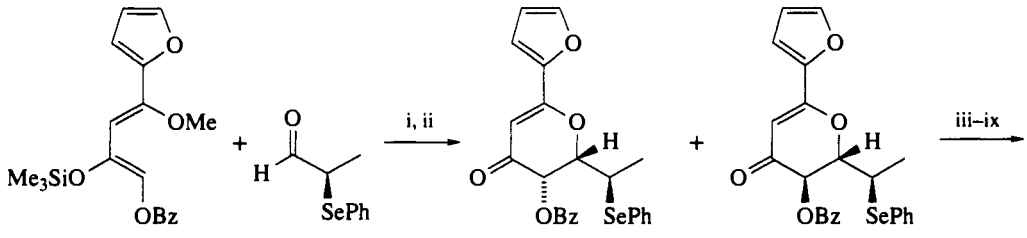
Various L-monosaccharide derivatives, including glycolipids, can be synthesized by simply varying the aldehyde, diene or catalyst used in the cycloaddition reaction. For example, 4-deoxy-L-glucose derivatives are synthesized by using the 2-acetoxy diene (**118**; Scheme 34). Cyclocondensation of (**118**) with furfural under (+)-Eu(hfc)$_3$ catalysis gives a cycloadduct which is worked up with Et$_3$N/MeOH (axial protonation) to give the optically pure ketone (**119**).[69] Reduction of this ketone with K-selectride followed by acetylation provides diacetate (**120**). Ozonolysis of the furan ring in (**120**) affords the 4-deoxyglucuronic acid derivative (**121**), characterized as its methyl ester (**122**). Reduction of (**121**) with borane–THF followed by acetylation affords the β-4-deoxy-L-glycoside of (–)-menthol (**123**), formally a glycolipid.



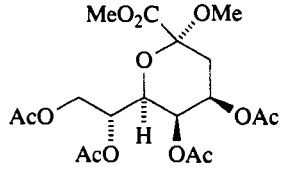
Scheme 34

2.5.5.2 3-Deoxy-D-manno-2-octulopyranosate (KDO)

The synthesis of more complex monosaccharides requires the construction of more complex and highly functionalized dienes and aldehydes. Furyl diene (**124**) serves as an important starting material in syntheses of KDO and NeuAc. This diene is easily synthesized from the condensation of benzoyloxy acetyl chloride with acetylfuran, followed by treatment with diazomethane.[72] Cyclocondensation of diene (**124**) with chiral aldehyde (**125a**) using $BF_3{\cdot}OEt_2$ as a catalyst gives the CF-type products (**126**) in a 5:1 ratio of *syn* and *anti* isomers (**126a** and **126b**). Aldehyde (**125**) is also available in optically pure form from



(124) **(125a)** **(126a)** *syn*-CF 5:1 **(126b)** *anti*-CF

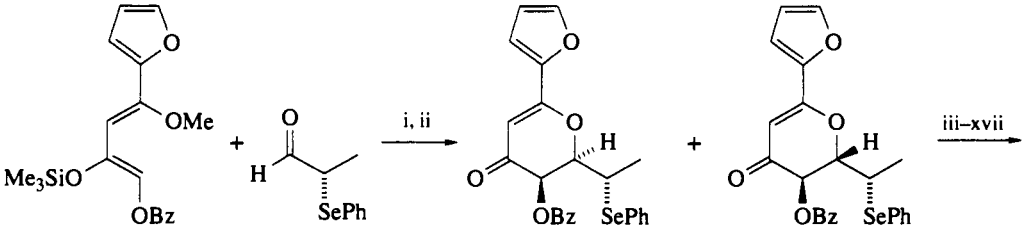


(128) KDO

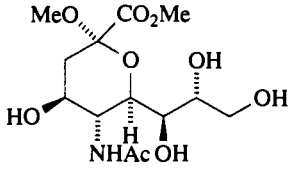
i, BF_3•OEt_2; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, TMSOTf, 2,6-lutidine, CH_2Cl_2; v, K_2CO_3/MeOH; vi, DMAP, Ac_2O, Py; vii, H_2O_2, H_2O; viii, OsO_4/NMO; ix, Ac_2O, Py, DMAP; x, RuO_2•$H_2O/NaIO_4$; xi, CH_2N_2; xii, H_2, Pd/C, EtOH; xiii, Ac_2O, Py, DMAP

Scheme 35

methyl lactate, which allows chiral synthesis of (**126**).[73] The *cis* isomer is transformed into KDO (**128**) by the standard transformations outlined in Scheme 35.



(124) **(125b)** **(127a)** *cis*-CF 5:1 **(127b)** *trans*-CF



(129) NeuAc

i, BF_3•OEt_2; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, CSA/MeOH; v, Bu^tMe_2SiOTf, 2,6-lutidine; vi, H_2O_2/Py; OsO_4/NMO; viii, $Pb(OAc)_4$; ix, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$/ KHMDS/18-crown-6; x, OsO_4; xi, $LiEt_3BH$; xii, BzCl/DMAP; xiii, RuO_2•$H_2O/NaIO_4$, CH_2N_2; xiv, HF/MeOH; xv, $Bu_4N^+N_3^-$; xvi, $Pd/CaCO_3$ (Lindlar), Ac_2O/DMAP; xvii, 4:1 THF/1M NaOH, H^+, CH_2N_2

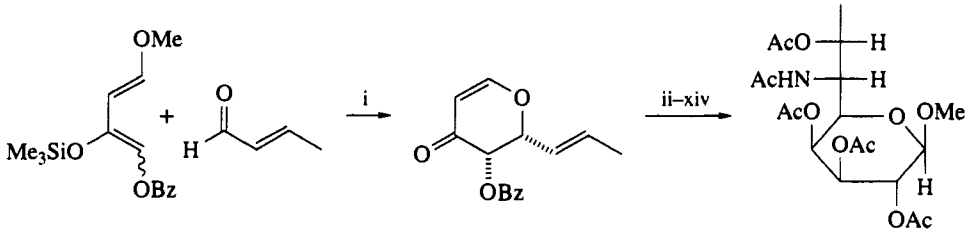
Scheme 36

2.5.5.3 *N*-Acetylneuraminic Acid (NeuAc)

Using a similar strategy diene (**124**) has also been used to synthesize *N*-acetylneuraminic acid (**129**) *via* cycloadduct (**126**; Scheme 36).[74] In contrast to the scheme used for KDO, the alkene resulting from the selenoxide elimination is oxidized to the aldehyde and the NeuAc side chain is installed by a modification of the Horner–Emmons reaction. Osmylation and reduction of the side chain followed by deprotection provides NeuAc (**129**).

2.5.5.4 Lincosamine

The synthesis of lincosamine employs a slightly different strategy than that used for NeuAc and KDO.[75] By using aldehyde (**130**) a precursor to the sugar side chain was installed directly in the cyclocondensation reaction (Scheme 37). Reduction of the carbonyl group of pyrone (**131**) under Luche conditions, epoxidation of the glycal, and a series of manipulations on the alkene side chain to install the amino alcohol portion gives lincosamine (**132**).



(**130**) (**131**) *syn*; 67% (**132**) Lincosamine

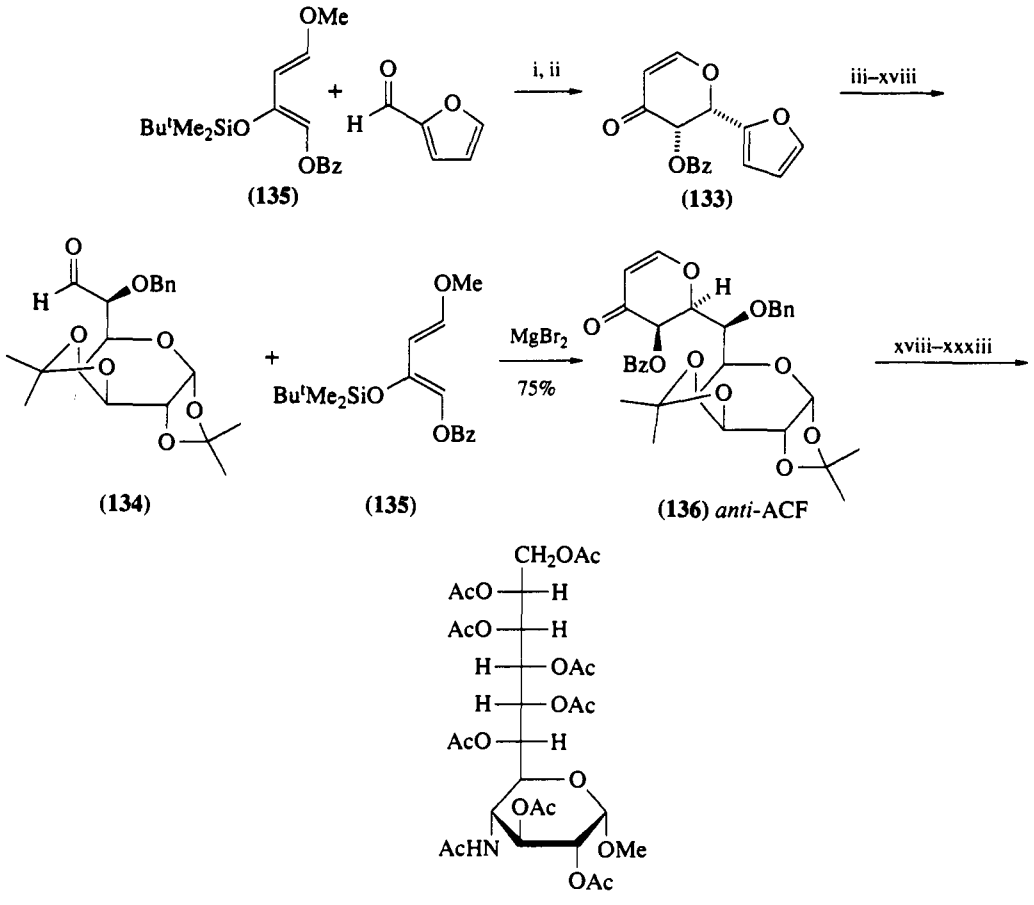
i, $BF_3{\cdot}OEt_2$; ii, $NaBH_4/CeCl_3{\cdot}7H_2O$/MeOH, DMAP, Et_3N, BzCl; iii, MCPBA/MeOH, BzCl/DMAP/Et_3N; iv, NBS/AcOH/H_2O; v, DBN; vi, $Bu^n{}_4N^+N_3^-/Me_3SiN_3$; vii, TFA/MeOH; viii, $Et_3N/MeSO_2Cl$; ix, $P(OMe)_3$, NaH; x, K_2CO_3/MeOH; xi, CDI; xii, AcOH; xiii, K_2CO_3/MeOH; xiv, Py/Ac_2O

Scheme 37

2.5.5.5 Hikosamine

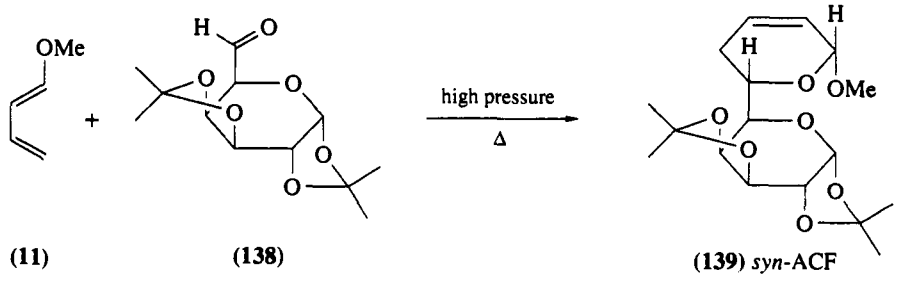
The synthesis of more complex carbohydrates employs a strategy of pyrone annulation that involves the cyclocondensation of activated dienes with the C-5 and C-6 aldehydes of simple carbohydrates. These aldehydes function as excellent heterodienophiles in the cyclocondensation reaction. The synthesis of hikosamine begins with the lanthanide-catalyzed condensation of furfural and benzoxyloxy diene (**135**; Scheme 38).[76] The Diels–Alder reaction using the lanthanide catalyst gives exclusively the *syn (endo)* cycloadduct which is cleaved to compound (**133**) using TFA. Conversion of (**133**) into a galactose derivative, followed by homolgation of the side chain provides aldehyde (**134**). Cycloaddition of (**134**) with diene (**135**) using $MgBr_2$ as a catalyst affords (**136**). The stereochemistry of this reaction can be described as an *anti*-ACF (*trans*-ACF) addition, which is expected for a chelation-controlled process using $MgBr_2$ as a catalyst. Luche reduction followed by a Henbest epoxidation (introduction of the amine) and acetylation gives hikosamine (**137**) in its peracetylated form.

Jurczak and coworkers have also used this strategy in the synthesis of annulated pyranosides.[77] The C-6 aldehyde of galactose (**138**) reacts with diene (**11**) under high pressure to give predominately *syn*-ACF product (**139**; Scheme 39). It is interesting to note the unusual stereochemistry of the high-pressure reaction compared to the Lewis acid catalyzed process; *syn*-ACF products are only available through the use of $TiCl_4$. Nevertheless, these products could represent an important class of starting materials for the synthesis of more complex carbohydrates.



i, $Eu(fod)_3$; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, BzCl/Py; v, OsO_4, NMO; vi, Me_2CO, H_2SO_4; vii, K_2CO_3/MeOH; viii, Me_2CO, H_2SO_4; ix, O_3/CH_2Cl_2/MeOH, –78 °C; x, BH_3•THF; xi, [O]; xii, BF_3•OEt_2, acylation; xiii, BnBr/NaH/DMF; xiv, O_3/CH_2Cl_2, –78 °C; xv, Zn, AcOH; xvi, Ac_2O/Et_3N, DMAP/CH_2Cl_2; xvii, O_3/CH_2Cl_2, –78 °C; xviii, Zn, AcOH; xix, $NaBH_4/CeCl_3$; xx, Henbest epoxidation; xxi, K_2CO_3/MeOH; xxii, $LiBH_4$/THF, reflux; xxiii, BnBr, NaH/DMF; xxiv, HCl/MeOH; xxv, BzCl/Py; xxvi, MsCl/Py; xxvii, $Bu^n{}_4N^+N_3^-$; xxviii, K_2CO_3/MeOH; xxix, acetylation; xxx; PPh_3; xxxi, acetylation of amino group; xxxii, $H_2/Pd(OH)_2$; xxxiii, Ac_2O

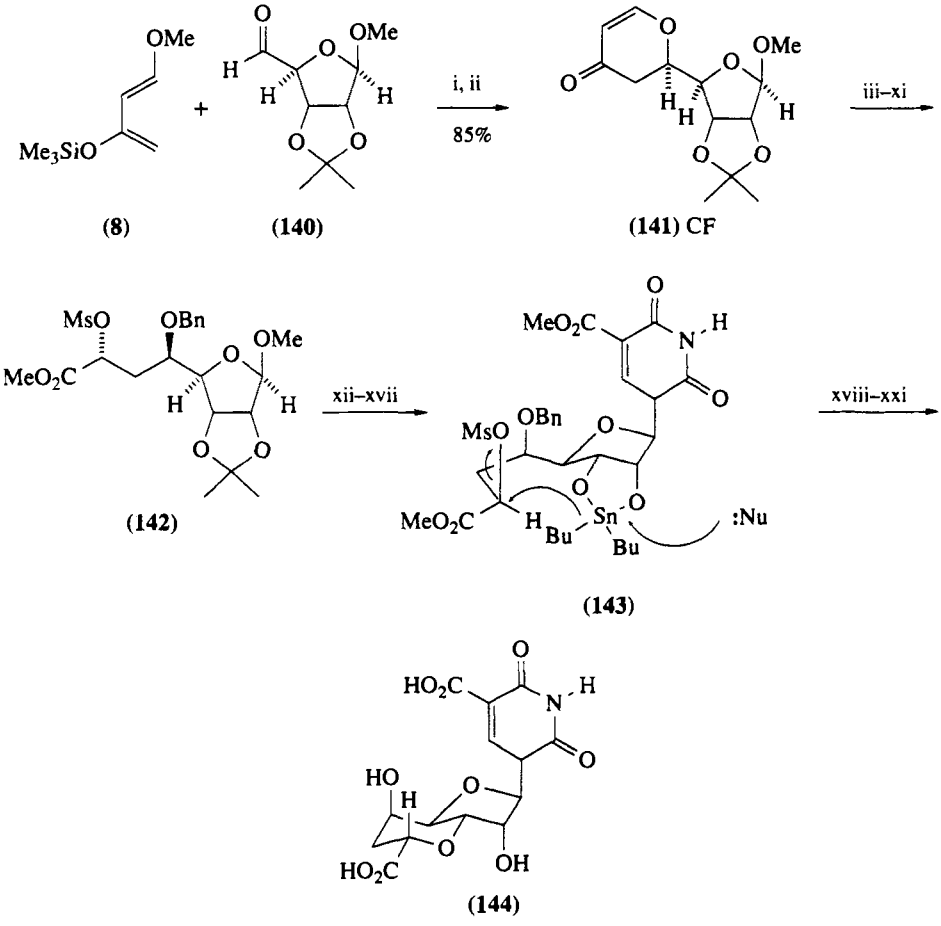
Scheme 38



Scheme 39

2.5.5.6 Octosyl Acid A

Danishefsky and coworkers have used a similar sequence of reactions to synthesize octosyl acid A (**144**; Scheme 40).[78] Aldehyde (**140**)[79] readily undergoes a hetero cyclocondensation reaction with diene (**8**), catalyzed by $ZnCl_2$, to give the CF pyrone (**141**). Reduction of the ketone followed by osmylation, oxidation and introduction of the mesylate gives compound (**142**). Introduction of the pyrimidine glycoside, followed by an intramolecular displacement of the mesylate through the tin complex (**143**), gives an intermediate that is converted to octosyl acid A (**144**) by a series of standard manipulations.



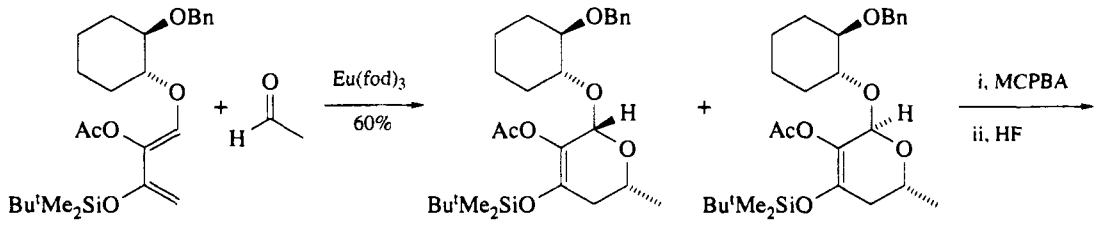
i, $ZnCl_2$/THF; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, NaH, *p*-methoxybenzyl chloride; v, OsO_4, $NaIO_4$; vi, K_2CO_3/MeOH; vii, Ag_2CO_3/Celite/xylene, Δ; viii, LiOH•H_2O/THF; ix, NaH/BnBr/DMF; x, CH_2N_2, DDQ; xi, MsCl/Et_3N/CH_2Cl_2; xii, HCl/MeOH; xiii, acetylation; xiv, Ac_2O/AcOH, CH_2Cl_2/H_2SO_4; xv, 2,4-bis(trimethylsilyloxy)-5-carbomethoxypyrimidine/Me_3SiOTf; xvi, NaOMe/MeOH, xvii, Bu_2SnO/MeOH; xviii, CsF/DMF/60 °C; xix, $Pd(OH)_2$; xx, LiOH•H_2O/H_2O/THF; xxi, H^+

Scheme 40

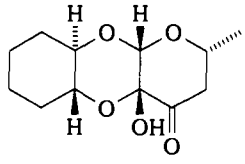
2.5.5.7 Spectinomycin Analogs

In the synthesis of analogs of the antibiotic spectinomycin, Danishefsky and coworkers used the hetero Diels–Alder reaction to construct a precursor to install the stereochemistry on the tricyclic ring system.[80] Trimethylsilyl diene (**145**) reacts with acetaldehyde and a catalytic amount of $Eu(fod)_3$ to give a 5.7:1

ratio of *cis (syn)* cycloadduct (**146**) and the *trans (anti)* epimer (**147**; Scheme 41). These compounds can be separated and treated sequentially with MCPBA and HF to yield the ring-closed products, of which (**148**) is the major product.



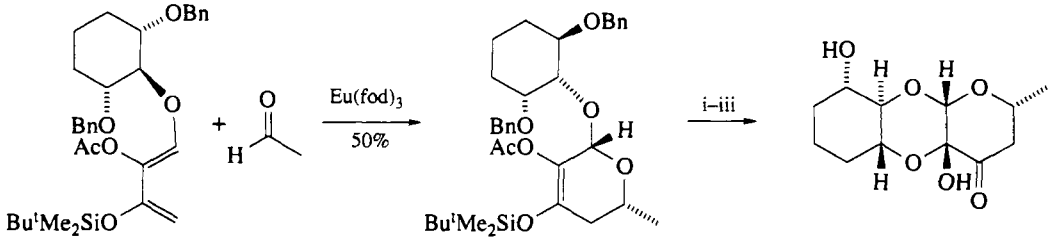
(**145**) (**146**) *cis* (**147**) *trans*



(**148**)

Scheme 41

Diene (**149**) reacts with acetaldehyde in the presence of 10% Eu(fod)$_3$ to give cycloadduct (**150**); only minor amounts of the *trans* compound are observed. Treatment of (**150**) with MCPBA, Pd(OH)$_2$ and HF gives (**151**), an analog of spectinomycin (Scheme 42).



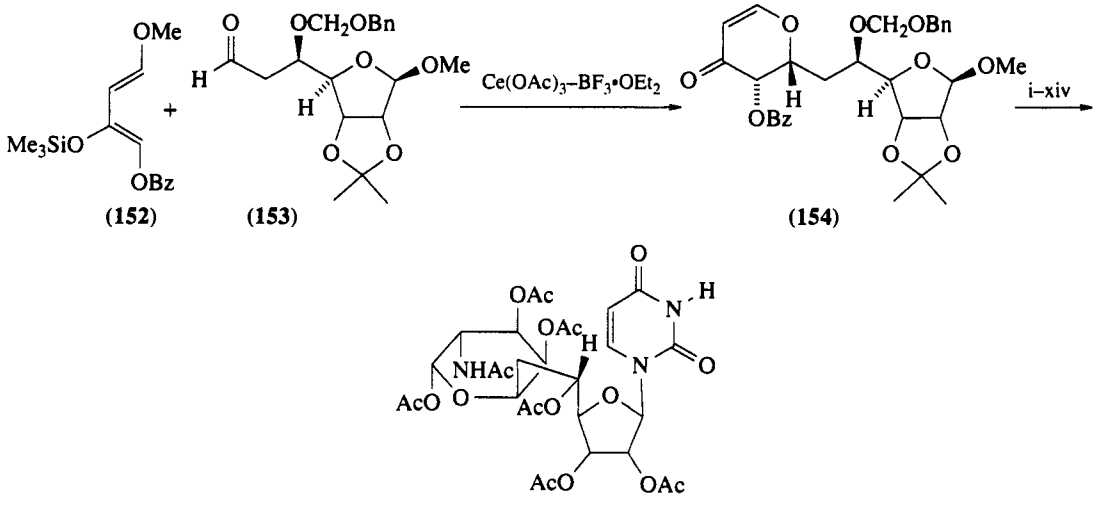
(**149**) (**150**) *syn* (**151**)

i, MCPBA; ii, Pd(OH)$_2$/H$_2$/EtOAc; iii, HF

Scheme 42

2.5.5.8 Tunicaminyluracil

In 1985 Danishefsky and Barbachyn reported the total synthesis of the glycosidase inhibitor tunicaminyluracil (Scheme 43).[81] The crucial parts of this synthesis involve a cyclocondensation reaction between diene (**152**) and chiral aldehyde (**153**). Using Ce(OAc)$_3$–BF_3·OEt$_2$ as a catalyst in toluene a 45% yield of a single dihydropyrone (**154**; the *syn*-ACF stereoisomer) was obtained. No explanation was offered for the high diastereofacial selectivity observed with this aldehyde. In similar systems other catalysts gave two (of the four possible) dihydropyrones in varying ratios. Compound (**154**) is transformed into tunicaminyluracil (**155**) by a series of reactions outlined in Scheme 43.

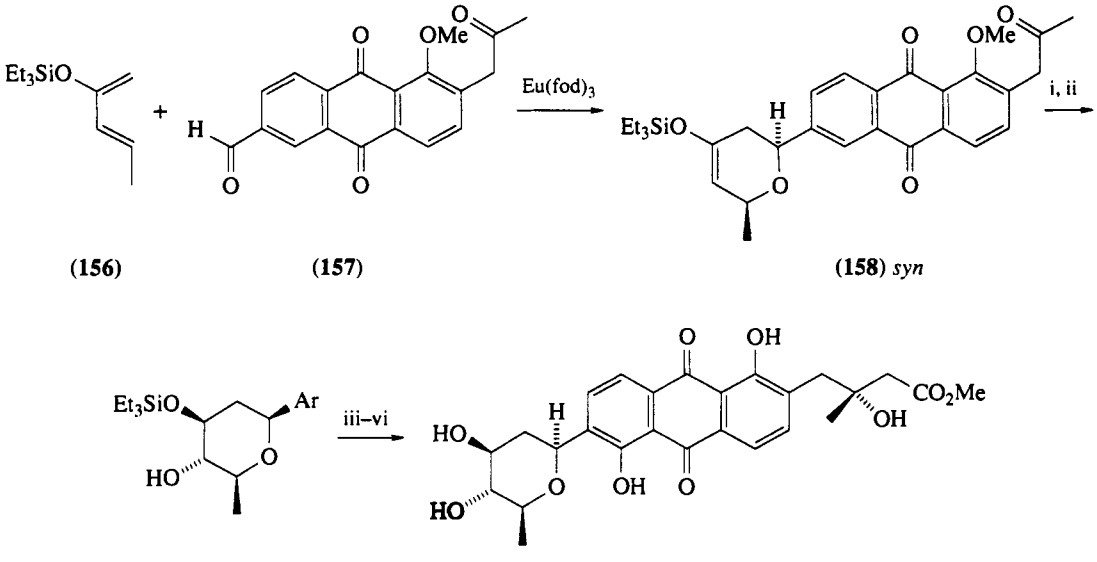


i, $NaBH_4/CeCl_3$; ii, benzoylation; iii, azidonitration; iv, LiBr/MeCN; v, AgOTf, $(Me_2N)_2CO$, THF; vi, PPh_3/THF; vii, Ac_2O, Py; viii, H_2, $Pd(OH)_2/C$, MeOH; ix, K_2CO_3/MeOH; x, Ac_2O/Et_3N/DMAP; xi, MeOH/HCl; xii, acetylation; xiii, $AcOH/Ac_2O/H_2SO_4/CH_2Cl_2$; xiv, 2,4-bis[(trimethylsilyl)oxy]pyrimidine/Me_3SiOTf/MeCN

Scheme 43

2.5.5.9 Vineomycinone B_2

The total synthesis of the methyl ester of the anthracycline antibiotic vineomycinone B_2 is summarized in Scheme 44.[82] The key step of this synthesis is introduction of the pyranose side chain by means of a



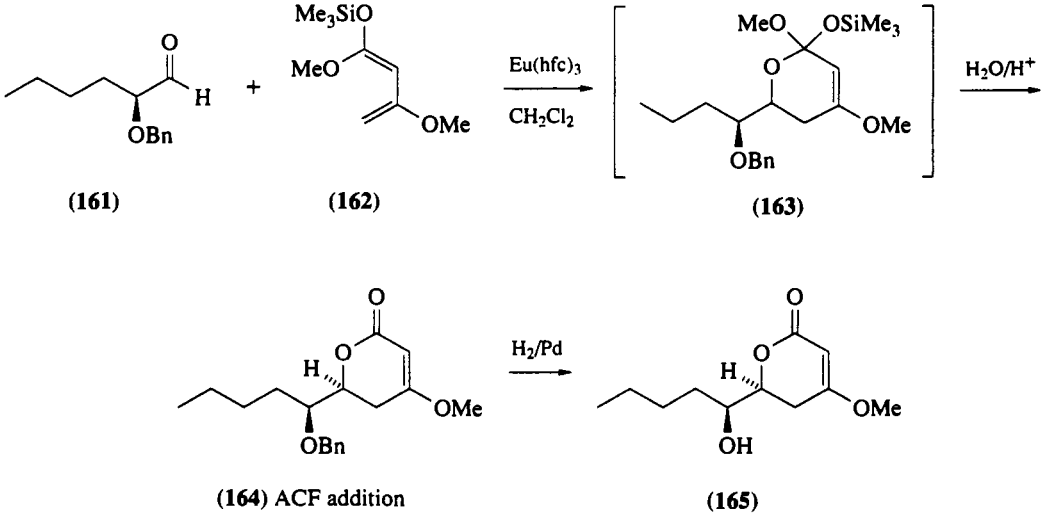
i, BH_3•DMS; ii, H_2O_2; iii, BH_3•DMS/H_2O_2; iv, BBr_3/CH_2Cl_2/–78 °C; v, $BrMgCH_2C$Omenthyl; vi, K_2CO_3/MeOH (resolved via (–)-menthoxy esters)

Scheme 44

hetero Diels–Alder reaction between triethylsilyloxy diene (**156**) and keto aldehyde (**157**). The reaction is catalyzed by 5% $Eu(fod)_3$ in $CHCl_3$ giving a 95% yield of the *endo (syn)* product (**158**); no *anti (exo)* product is produced. The silyl enol ether (**158**) is hydroborated and oxidized to give the monosilyl-protected *trans* diol (**159**). The sense of the hydroboration is exclusively *trans* to the methyl group and aromatic side chain on the pyranose ring. After demethylation with BBr_3, reaction of the methyl ketone with the reagent derived from magnesium and (–)-menthyl bromoacetate results in a diastereomeric mixture. The diastereomers are separated by HPLC and deprotected to give optically active (**160**). This approach demonstrates the usefulness of the cyclocondensation reaction in the construction of *C*-glycosides.

2.5.5.10 Pstelotin

Midland has used the cyclocondensation reaction with activated dienes to synthesize pstelotin A (**165**; Scheme 45)[56]. The key step in the Midland synthesis is the ACF addition of diene (**162**) with aldehyde (**161**) to give (**164**), using $Eu(hfc)_3$ as catalyst. Deprotection of the benzyl group gave the target molecule (**165**).



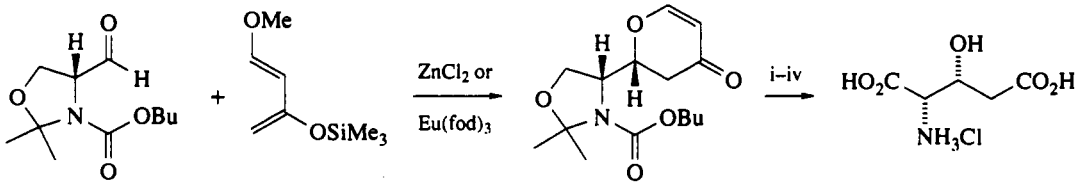
(**161**) (**162**) (**163**)

(**164**) ACF addition (**165**)

Scheme 45

2.5.5.11 Lantin

Garner has used the cyclocondensation reaction of chiral α-alkoxy aldehydes with $ZnCl_2$ and $Eu(fod)_3$ as catalysts (Scheme 46).[83] In this case, however, the CF product (**166**) dominated the reaction. A variety of catalysts were surveyed; the lanthanide complex and $ZnCl_2$ gave similar results. Compound (**166**) was converted into lantin (**167**) by standard manipulations.



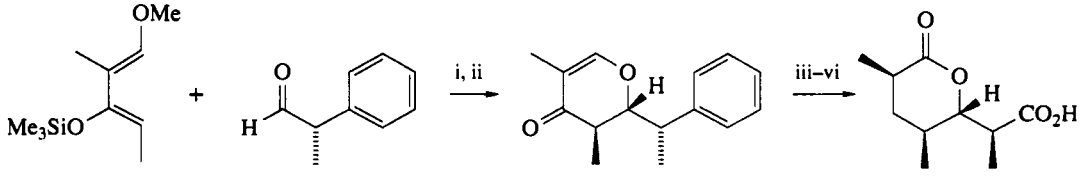
(**166**) (**167**) *threo*-β-Hydroxy-L-glutamic acid

i, $NaIO_4$, RuO_2, CH_2N_2; ii, Et_2NSiMe_3; iii, MeOH/TsOH; iv, $KMnO_4$

Scheme 46

2.5.5.12 Prelog–Djerassi Lactone

Application of the diene–aldehyde cyclocondensation reaction to polypropionate synthesis has also been investigated. The 2,4-dimethyl diene (**14**) plays a major role in this chemistry. Danishefsky and co-workers have carried out an efficient synthesis of the Prelog–Djerassi lactone using this diene (Scheme 47).[34,35] The cyclocondensation reaction between trimethylsilyloxy diene (**14**) and chiral aldehyde (**168**), catalyzed by $BF_3{\cdot}OEt_2$ in CH_2Cl_2 gives the *anti*-CF pyrone (**169**) in an overall yield of 95% with a 4.3:1 ratio (*anti* to *syn*). Each pyrone is derived from a CF-type addition of the diene to the chiral aldehyde. The *anti* pyrone is purified and treated with DIBAL-H in toluene to give a mixture of epimeric alcohols, which is subjected to a Ferrier-type rearrangement with Pr^iOH in the presence of *p*-toluenesulfonic acid (*p*TsOH), followed by reduction of the glycal and ozonolysis to give the Prelog–Djerassi lactone (**170**).



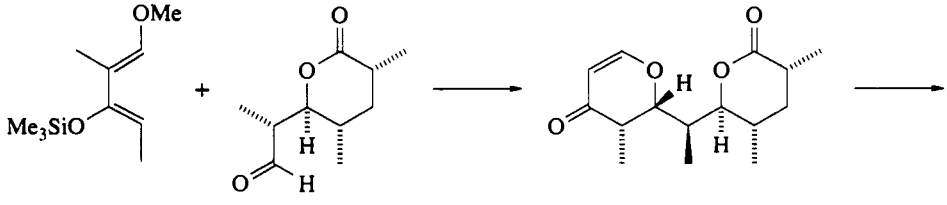
(14) **(168)** **(169)** 4.3:1 *anti*-CF:*syn*-CF **(170)**

i, BF_3; ii, TFA; iii, DIBAL; iv, Pr^iOH/*p*-TsOH; v, H_2/Pd–alumina/EtOAc; vi, O_3/AcOH/H_2O/TFA; H_2O_2/AcOH/H_2O

Scheme 47

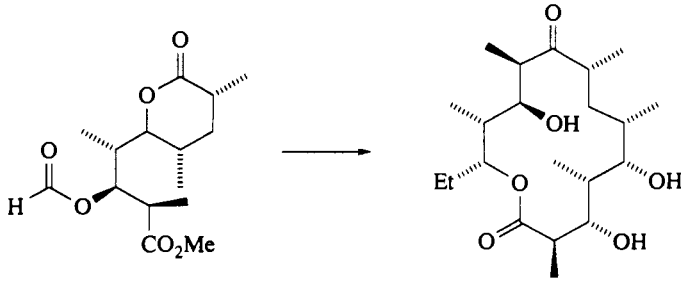
2.5.5.13 6-Deoxyerythronolide B

Lactone (**170**) is reduced to aldehyde (**171**) and used as a heterodieneophile in a Diels–Alder reaction with diene (**14**), with $ZnCl_2$ in THF as a catalyst, to give (**172**; Scheme 48).[34,35] The major product of this cycloaddition is the *syn* pyrone derived from a Cram–Felkin attack (*syn*-CF); 27% of the *syn*-ACF product is also produced. The *syn*-CF pyrone (**172**) is ozonized and subjected to an oxidative work-up fol-



(14) **(171)** **(172)** *syn*-CF

1.6:1 *syn*-CF: *anti*-CF



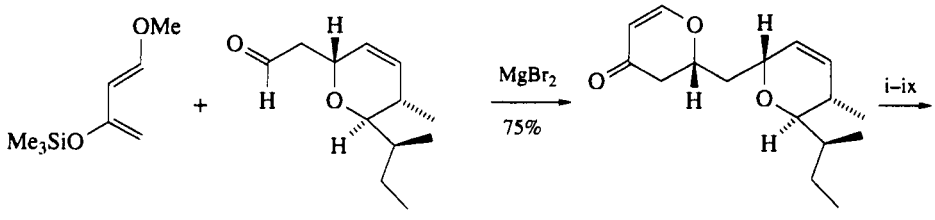
(173) **(174)**

Scheme 48

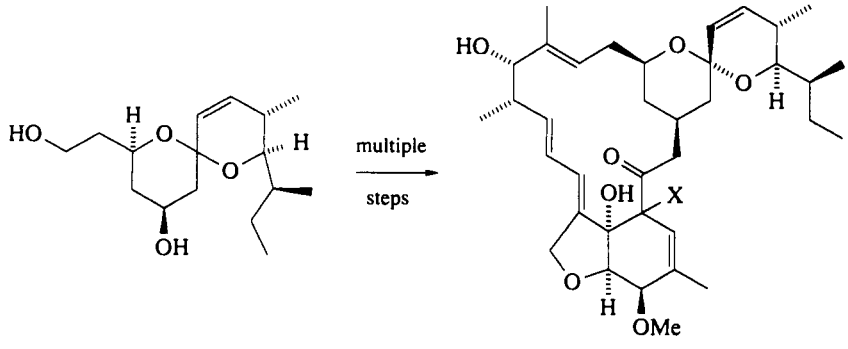
lowed by methylation of the resulting acid with diazomethane to give intermediate (**173**). Compound (**173**) has been used by Masamune to synthesize 6-deoxyerythronolide B (**174**).

2.5.5.14 Avermectin

Danishefsky and coworkers have synthesized the algylcon of avermectin based on a hetero Diels–Alder reaction between trimethylsilyloxy diene (**8**) and chiral aldehyde (**175**; Scheme 49).[84] The pyrone must come from an anti Cram–Felkin addition, so $MgBr_2$ is used as the catalyst in this reaction. The cycloaddition reaction gives the expected product (**176**) and the CF diastereomer in a ratio of 3:1. The target compound (**178**) is obtained after a series of reactions outlined in Scheme 49.[85]



(**8**) (**175**) (**176**) ACF
5:1 ACF:CF



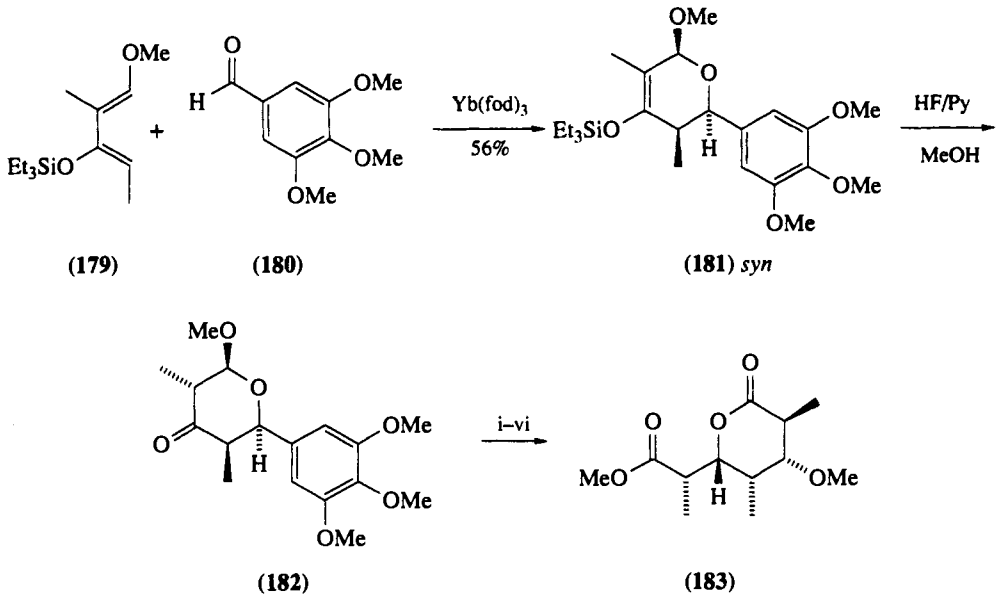
(**177**) (**178**)

i, $NaBH_4$–$CeCl_3$; ii, TBSOTf; iii, NBS•H_2O/THF; iv, Bu_3SnH, PhMe, AIBN; v, $LiBH_4$, THF; vi, pivaloyl chloride/Py, DMAP/CH_2Cl_2; vii, HF/MeCN; viii, HgO–I_2, CCl_4; ix, LiOH/MeOH/THF/H_2O

Scheme 49

2.5.5.15 Monensin Lactone

A total synthesis of the monensin lactone is summarized in Scheme 50.[86] The crucial point of this synthesis is the hetero Diels–Alder reaction of triethylsilyloxy diene (**179**) with aldehyde (**180**), carried out with 10 mol % of Yb(fod)$_3$ to give the *syn* Diels–Alder cycloadduct (**181**) as the only isomer. Compound (**181**) is treated with HF in pyridine and MeOH to obtain ketone (**182**), which is converted into the monensin lactone (**183**).



(179) (180) (181) *syn*

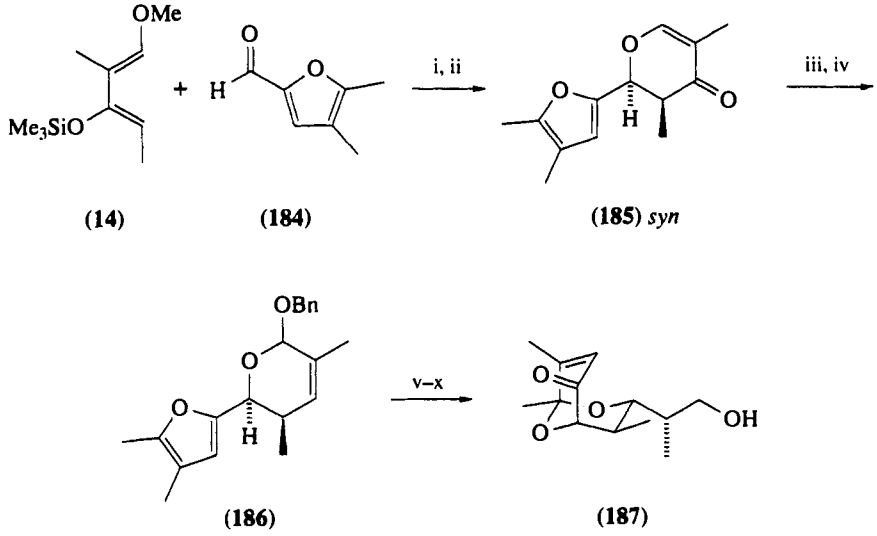
(182) (183)

i, HF/pyridine/MeOH; ii, $NaBH_4$–MeOH/THF; iii, NaH (MeI/DMF); iv, HCl–THF, v, RuO_2–$NaIO_4$; vi, CH_2N_2/ether

Scheme 50

2.5.5.16 Tirandamycin

Danishefsky and Harvey have reported the synthesis of an important subunit in the construction of tirandamycin (Scheme 51).[86] Trimethylsilyl diene (**14**) reacts with 4,5-dimethylfuran-2-carbaldehyde (**184**) followed by a brief treatment with TFA to give exclusively the *syn* pyrone (**185**). Pyrone (**185**) is reduced using LAH and subjected to a Ferrier-like rearrangement using benzyl alcohol in the presence of



(14) (184) (185) *syn*

(186) (187)

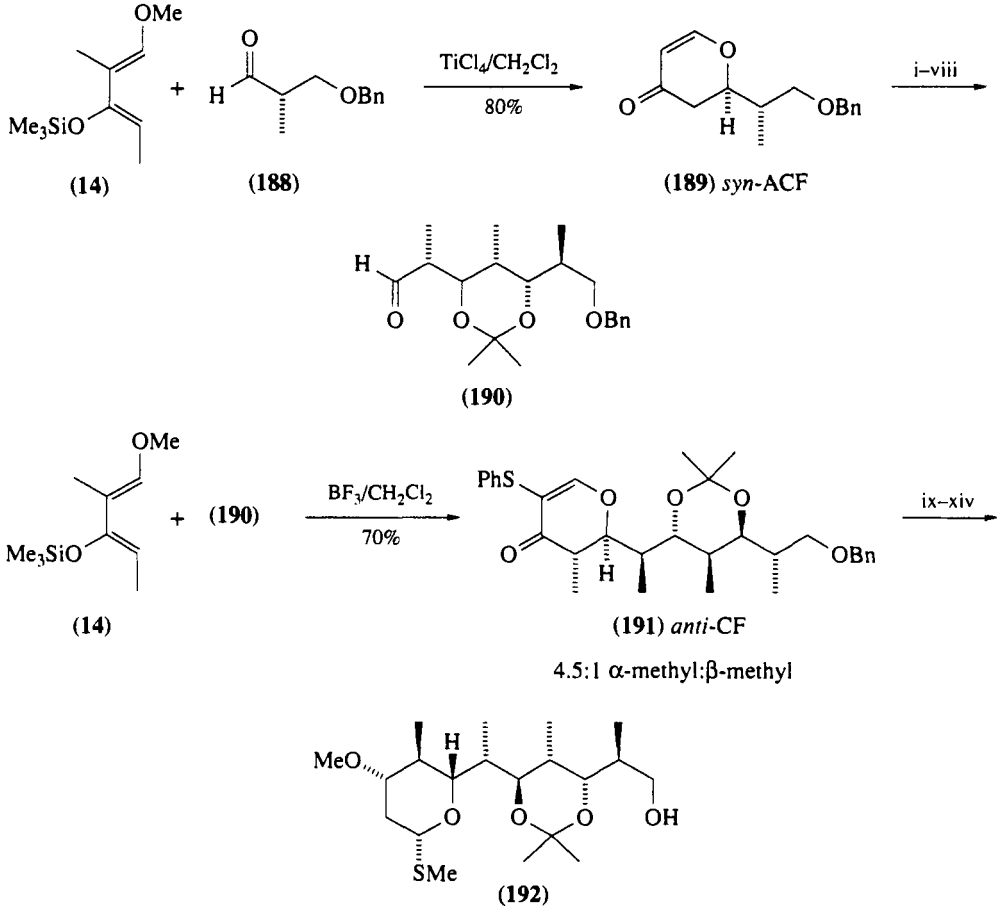
i, $Yb(fod)_3$, $CHCl_3$; ii, TFA; iii, $LiAlH_4$; iv, BnOH/TsOH; v, B_2H_6–THF, H_2O_2/OH^-; vi, Swern oxidation; vii, $NaBH_4$; viii, TBDMSOTf/Et_3N; ix, Na, NH_3, Et_2O, –33 °C, 1 h; x, MCPBA, HF–MeCN

Scheme 51

p-toluenesulfonic acid to give (**186**). Hydroboration followed by a Swern oxidation and reduction with sodium borohydride establishes the proper stereochemistry at C-3. The alcohol is then protected as its *t*-butyldimethylsilyl ether and the pyrone ring is opened and reduced. Treatment with MCPBA followed by HF in acetonitrile provides (**187**), a subunit of triandamycin.

2.5.5.17 Rifamycin S

Danishefsky and coworkers employed two hetero Diels–Alder reactions in a total synthesis of the ansa bridge of rifamycin S (Scheme 52)[87] The first cyclocondensation reaction uses the trimethylsilyloxy diene (**14**) and a preincubated solution of 3-(benzoyloxy)-2-methyl-1-propanal (**188**) with an excess of $TiCl_4$ in $CHCl_2$. The product is exclusively the *syn*-ACF pyrone (**189**). Through a Ferrier rearrangement and a sequence of oxidation–reduction steps followed by functional group manipulations aldehyde (**190**) is obtained.



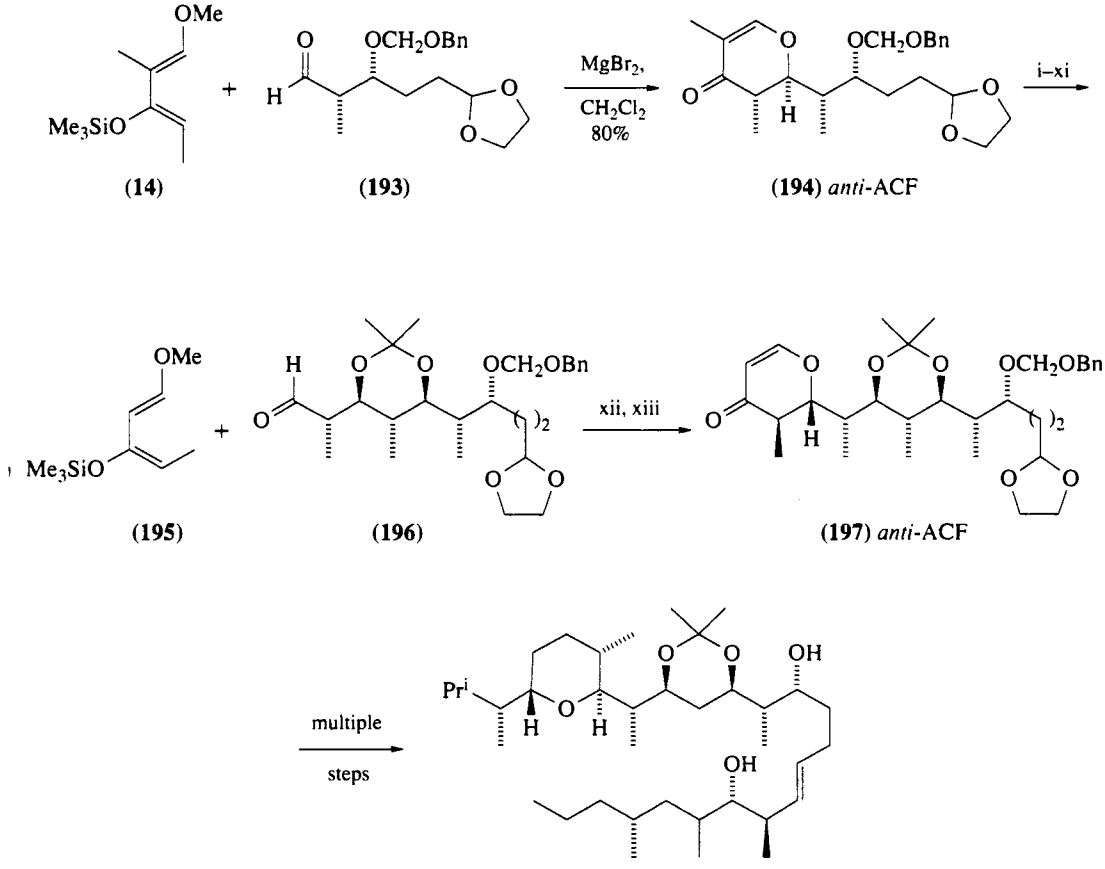
i, $LiAlH_4$; ii, Ferrier, MeOH, TsOH; iii, BH_3•THF, OH^-, H_2O_2; iv, Swern (oxalyl chloride/DMSO); v, $NaBH_4$/MeOH; vi, 1,3-propanedithiol/BF_3•OEt_2; vii, 2,2-dimethoxypropane/ CSA; viii, NBS/acetone, H_2O; ix, L-selectride; x, MCPBA, Δ; xi, MeSH/$Bu^n{}_4N^+$ F^-/THF; xii, $NaBH_4$, MeOH; xiii, NaH, MeI; xiv, Na, NH_3

Scheme 52

In the second hetero Diels–Alder reaction an *anti* pyrone derived from Cram–Felkin addition was needed, so trimethylsilyloxy diene (**14**) was allowed to react with aldehyde (**190**) in CH_2Cl_2 using BF_3·OEt_2 as the catalyst. Under these conditions, *anti*-CF pyrone (**191**) is obtained in 57% yield, accompanied by 13% of the *syn*-CF pyrone. Through further manipulations compound (**192**), a key intermediate in the Kishi synthesis of the ansa bridge of rifamycin S, was obtained.

2.5.5.18 Zincophorin

In the synthesis of zincophorin,[88] two cyclocondensation reactions are also used. In the first cyclocondensation reaction, trimethylsilyloxy diene (**14**) reacts with aldehyde (**193**) using anhydrous $MgBr_2$ as the catalyst to give the *anti*-ACF pyrone (**194**) in 80% yield (Scheme 53). The *syn:anti* ratio in this reaction is 7:1. After a series of standard manipulations aldehyde (**196**) is obtained. In the second cyclocondensation reaction, *anti*-CF pyrone (**197**) results from reaction of the (4*E*)-*t*-butyldimethylsilyloxy diene (**195**) with aldehyde (**196**) under $BF_3{\cdot}OEt_2$ catalysis; (**197**) and its *syn*-CF isomers are obtained in a ratio of 4:1 and overall yield of 68%. The *anti*-CF aldol product is purified and cyclized to *anti*-CF pyrone (**197**) in benzene using pyridinium *p*-toluenesulfonate as a catalyst. Pyrone (**197**) converted into zincophorin (**198**) by a sequence of steps shown in Scheme 52.



i, $NaBH_4$–$CeCl_3$; ii, Ferrier rearrangement (3,4-dimethoxybenzyl alcohol), *p*-TsOH, benzene; iii, BH_3–DMS, H_2O_2–NaOH; iv, Swern; v, L-selectride; vi, DDQ; vii, $LiBH_4$; viii, Bu^tPh_2SiCl/DMF/imidazole; ix, dimethoxypropane, PPTS; x, $Bu^n{}_4NF$; xi, Swern; xii, $BF_3{\cdot}Et_2O$; xiii, PPTS, benzene

Scheme 53

In summary, the condensation of activated dienes with aldehydes is a versatile tool in organic synthesis. The reaction is applicable to both complex and simple aldehydes and dienes; a list of the dienes which were used in cyclocondensation reactions is given in Figure 5. The high degree of stereoselectivity also makes the cyclocondensation of activated dienes with aldehydes a useful synthetic tool.

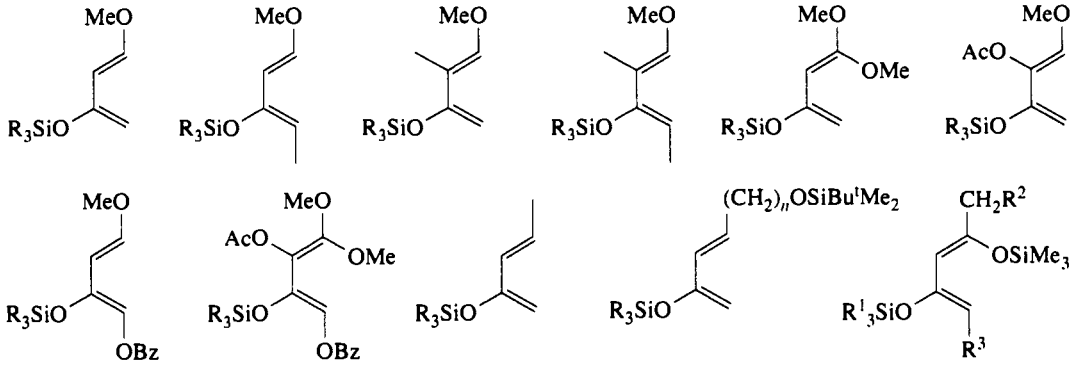


Figure 5

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3.1
The Aliphatic Friedel–Crafts Reaction

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3.1.1 INTRODUCTION

The Friedel–Crafts acylation reaction is one of the oldest reactions for the preparation of ketones by carbon–carbon bond formation, and is one of the major methods used for the preparation of aromatic ketones.[1] However, acylation by an acid chloride in the presence of a Lewis acid is also applicable to nonaromatic substrates. Whilst it has been known for almost as long as its better-known relative, the

aliphatic Friedel–Crafts reaction has not been used as often. Nevertheless, two reviews of early aliphatic Friedel–Crafts acylations do summarize the reaction's history and a considerable body of information.[2,3]

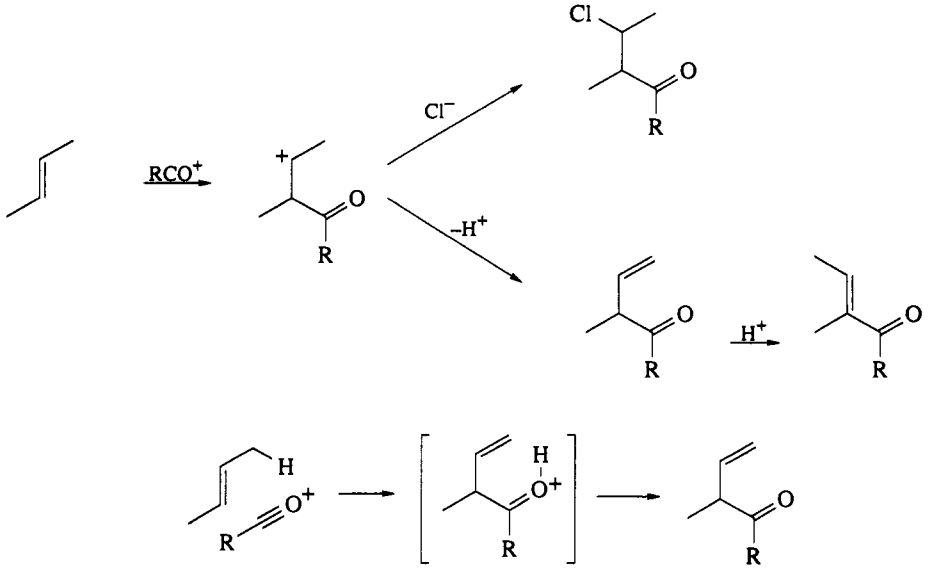
By comparison with the reactions with aromatic substrates, the absence of the driving force of rearomatization by proton loss in electrophilic acylations of alkenes leads to competition between alternative pathways for the carbocation intermediate. In particular, capture of halide to form β-halo ketones can become dominant. Hence, the aliphatic Friedel–Crafts acylation reaction need not necessarily result in substitution of an acyl residue for a hydrogen atom in an alkene, nor in the formation of unsaturated ketones. Indeed, within this broader scope, acylations of alkynes and some classes of alkanes can be synthetically useful.

Recently, considerable progress has been made in extending the acylation to new substrates, particularly silanes, providing a far greater degree of chemo- and regio-selectivity.

3.1.2 GENERAL ASPECTS OF ALIPHATIC FRIEDEL–CRAFTS ACYLATIONS

3.1.2.1 Mechanistic Aspects

The course of the Friedel–Crafts reaction of alkenes is commonly considered to proceed by reaction of the alkene with the reactive acylating agent to form the β-ketocarbenium ion, which can then either react with a nucleophile (usually halide) to give overall addition to the double bond, or eliminate a proton, forming unsaturated products (Scheme 1).



Scheme 1

A number of factors influence the nature of the unsaturated products formed. Under nonequilibrating workup conditions, β,γ-unsaturated ketones tend to predominate, an observation attributed to [1,5] hydrogen shifts in the intermediate β-ketocarbenium ion. Equilibration readily leads to the more thermodynamically stable conjugated enone, particularly under the influence of the released acid. The intermediacy of the β-ketocarbenium ion opens further pathways for rearrangements *via* hydride migration and carbon–carbon bond cleavage depending on substrate structure.[3] However, the lack of rearrangement observed in acylations by preformed acylium ions and the clean formation of β,γ-unsaturated ketones suggest that reactions can occur mechanistically *via* an ene reaction (Scheme 1).[4] Reactions with acylium salts give highest conversions to β,γ-unsaturated ketones when the reaction is performed in the presence of a base to neutralize and hence prevent the build up of released acid. Non-nucleophilic bases such as ethyldiisopropylamine or dicyclohexylethylamine are most effective, but even weak bases such as tetramethylurea can suppress the formation of the conjugated enone.

Ene reactions of electron-deficient nitriles and trisubstituted alkenes in the presence of boron trichloride offer related routes to β,γ-unsaturated ketones.[5]

3.1.2.2 Catalysts

Aluminum chloride is the most frequently used Lewis acid in aliphatic Friedel–Crafts acylations, and is one of the strongest. Its complexes with acyl halides are strong, producing very active acylating species. Titanium and tin tetrachlorides also find use as catalysts, and are powerful enough to induce reaction at low temperatures.

With anhydrides, aluminum chloride reacts to form the acid chloride complex. Zinc chloride is more commonly used with acid anhydrides, although this is restricted practically to acetic and other simple anhydrides that can be used as the reaction solvent. This nevertheless remains a useful reagent for acylations, giving predominantly nonconjugated products.[6] Active zinc compounds prepared from a zinc–copper couple and alkyl halides also promote the acylation of alkenes by acyl chlorides at room temperature.[7]

Ethylaluminum dichloride has been described as a catalyst for acylation of alkenes by acyl chlorides, giving nonconjugated enones together with the chloroketone.[8] This is interpreted as a result of the deprotonation by $EtAlCl_3^-$ rendering the [1,5] proton shift irreversible. This catalyst has not been utilized to any great extent at present, but should offer advantages in that acylium salts do not need to be prepared.

The use of protic acids is discussed in Section 3.1.3.3.

3.1.2.3 Reaction Temperatures

The ease with which alkenes undergo electrophilic addition is demonstrated by the ready reaction with acylating reagents at low temperatures. Indeed, the propensity for alkenes to polymerize under the influence of acid catalysts means that temperatures should be kept as low as possible. In addition, the stability of acyl chlorides in the presence of Lewis acids in general, and aluminum chloride in particular, supports the use of low temperatures. Decarbonylation can occur readily if the resulting carbenium ion is tertiary, and elimination of proton from acylium ions leads to ketenes, which can themselves be acylated in a Friedel–Crafts reaction. The high reactivity of both acylating agent and substrate combine to give reaction times that are short, and reaction temperatures that are low.

3.1.2.4 Stability of Acylating Reagents

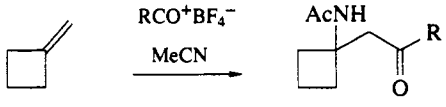
Acyl halides bearing α-hydrogen atoms, and acetyl chloride in particular, have limited stability in the presence of strong Lewis acids. Elimination of proton from the acylium ion leads to the ketene. This intermediate undergoes ready Friedel–Crafts acylation, acetyl chloride eventually forming the diacetylacetylium ion,[9,10] which is a poor acylating agent. For this reason, excessive reaction temperatures and times should be avoided in Friedel–Crafts acetylations.

3.1.3 ACYLATIONS OF ALKENES

3.1.3.1 Intermolecular Acylations

The regioselectivity of Friedel–Crafts acylations of unsymmetrical alkenes can often be predicted simply by consideration of the alternative carbenium ions formed in an initial electrophilic attack. Pathways *via* tertiary carbocations are generally preferred over those involving secondary ions. It is the subsequent fate of the initially generated ion that determines the products formed. As has been indicated already, elimination of a proton completes a substitution, although there is a predominance of nonconjugated unsaturated ketone formed, and treatment with base is required to form the conjugated product.[11]

Capture of a nucleophile, usually halide, represents a second major pathway, leading to overall addition to the alkene double bond. Acylations of ethylene (conveniently by automatic gasimetric techniques)[12] and simple alkenes often give mainly the chloroethyl ketones.[13,14] Nucleophile capture has been used to advantage in the preparation of β-amido ketones by using nitriles as the reaction solvent (equation 1).[15]

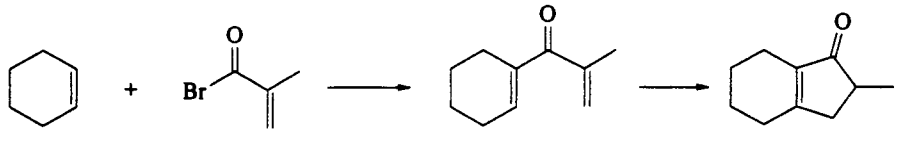


(1)

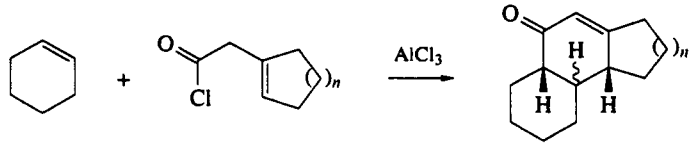
Further pathways that may be followed include hydride transfer, leading to the possibility of more remote functionalization of the carbon skeleton, and carbon migration, leading to a rearranged skeleton. This is more common when there is a quaternary center next to the carbenium carbon,[16] or in polycyclic systems, as observed in the acetylation of cedrene.[17]

The rich chemistry of carbenium ions that may be accessed by the Friedel–Crafts acylation means that careful consideration must be given to any particular reaction planned, especially with regard to competing pathways.[3] Nevertheless, the method remains an important, if relatively infrequently used, route to aliphatic ketones.

Acylations by α,β-unsaturated acyl halides provide routes to α,β,α′,β′-unsaturated ketones.[18] Care must be taken in choice of reaction conditions, since Lewis acids are excellent catalysts for Nazarov cyclizations[19] to cyclopentenones (Scheme 2). Indeed, this can be exploited as a synthesis of the five-membered ketones without isolation of the intermediate divinylic ketones.[20] Cyclizations are also observed after acylations of cyclohexenes with vinylacetyl chloride derivatives (equation 2).[21,22] The acylation–cycloalkylation sequence provides a complement for the Robinson annelation, since the carbonyl function is located adjacent to the bridgehead position. This potential has been realized in natural product syntheses.[23]



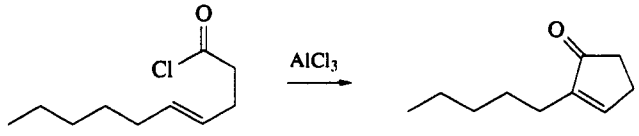
Scheme 2



(2)

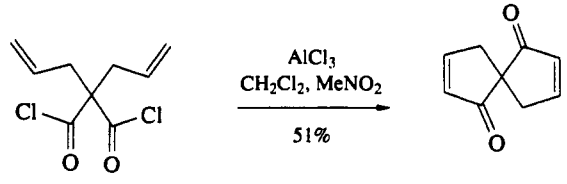
3.1.3.2 The Formation of Cyclic Ketones

Intramolecular Friedel–Crafts acylation provides a useful synthetic approach to cyclic ketones.[2] The cyclization is well-suited to the preparation of six- and particularly five-membered rings, as used in key steps in routes to methyl dihydrojasmonate (equation 3),[24] and precursors to some marine sesquiterpenes (equation 4)[25] and the theoretically interesting spiro[4.4]nonatetraene (equation 5).[26] Extension to cycloheptanones has been achieved,[27,28] but tars were formed on attempting to prepare cyclooctanones.[27]

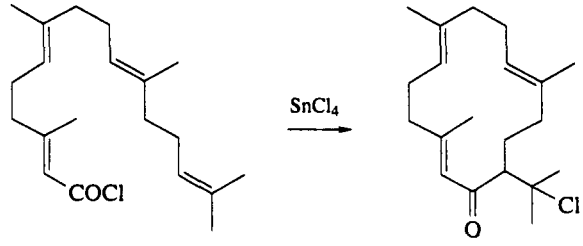


(3)

(4)



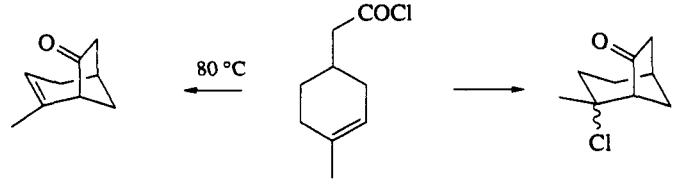
(5)



(6)

However, high dilution techniques were successful for the cyclization of geranylgeranic acid chloride to the cembrene skeleton (equation 6).[29]

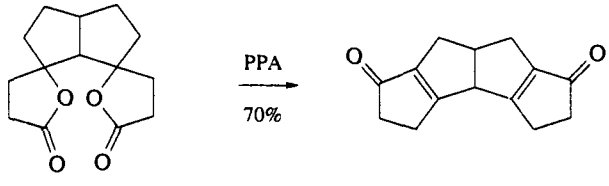
Intramolecular cyclizations offer a versatile method for the preparation of bicyclic and polycyclic ketones. Indeed, in favorable cases, reaction can ensue on simply heating the acyl halide[30] as well as on treatment with a Lewis acid,[31] offering control of the product isolated (Scheme 3). However, the structural constraints imposed in detailed examination of specific ring systems in which the stereochemistry of cyclization can be determined[31–34] may well preclude the deduction of more general conclusions about stereochemical control.



Scheme 3

3.1.3.3 The Use of Protic Acid

Protic acids can be used in acylations of alkenes by carboxylic acids and their derivatives. Polyphosphoric acid is the protic acid most frequently used, but suffers from several well-known disadvantages, particularly on scale-up. Its extreme viscosity requires that reactions be carried out at elevated temperatures to permit stirring, and it is a poor solvent for organic substrates. Hydrolysis during work-up is often tedious. Phosphorus pentoxide in methanesulfonic acid is a more convenient reagent for dehydrative cyclization of lactones and unsaturated carboxylic acids, being a mobile liquid with good solvent properties. In comparison with polyphosphoric acid, yields were also higher with the methanesulfonic acid derived reagent.[35] The reagent, which was superior to that based on trifluoromethanesulfonic acid, was developed for cyclizations of dilactones (equation 7),[36] and has found application for the cyclopentannelation of six- to twelve-membered rings.[37] Ester groups do not interfere with such cyclizations.[38]



(7)

Acylations with carboxylic acids and anhydrides have been carried out with sulfuric acid as both solvent and catalyst, the reactive acylating agents from acyl halides probably being haloacyloxonium ions. Trifluoroacetic anhydride offers a rather milder reagent for reactions of carboxylic acids, with mixed anhydrides being likely intermediates. However, polyphosphoric acid remains the most widely used dehydrating agent for acylations by carboxylic acids.

Such reactions are particularly well suited to intramolecular dehydrative acylations for the formation of cyclic ketones.[2] One advantage of this procedure is the fact that acid chloride need not be preformed, a process that often causes problems with unsaturated acids. Polyphosphoric acid is again the most commonly used reagent for the necessary dehydration and cyclization.

Substrate structure plays a greater role than double bond location, in determining the ring size of the cyclization product, since under the strongly acidic reaction conditions migration of the site of unsaturation can occur prior to ring closure. In simple cases, five-membered rings are preferred, but substitution patterns can control the site of reaction, by stabilization of the intermediate carbonium ion.[39]

The reaction can be extended to substrates that can form unsaturated acids under the acidic reaction conditions, the most important being lactones, as cited previously (*e.g.* equation 7).

3.1.3.4 Di- and Poly-acylation

The acylation of alkenes gives rise to unsaturated ketones, which themselves may be further acylated under the same reaction conditions. This is particularly the case with the nonconjugated products that often are formed preferentially. The diacyl derivatives readily cyclize to form pyrylium salts when this can be accommodated, and the sequence represents one of the best strategies for the formation of pyrylium salts symmetrically substituted at the 2- and 6-positions. Friedel–Crafts acylation as a route to pyrylium salts has been reviewed, and compared with other synthetic strategies.[40]

In diacylations of alkenes, the Perrier procedure, where the alkene is added to the complex of the Lewis acid and acyl halide, has been used most frequently. Precursors of alkenes, for example *t*-butyl chloride or the alcohol, can also be used, relying on the presence of the Lewis acid, usually aluminum chloride, to form the acylation substrate, in these cases isobutene.

Yields of pyrylium salts are often higher in diacylations of alkenes than in the acylation of an equilibrium mixture of unsaturated ketones. This may be attributed to the preferential formation of the nonconjugated isomer in the first acylation, whereas isomerization of the (usually) thermodynamically more stable isomer is required before an α,β-unsaturated ketone may acylate.

Di- and poly-acylated products are often water soluble, and so require care in isolation. Low recoveries of desired products from aliphatic Friedel–Crafts monoacylations may suggest that over reaction is leading to water-soluble products that have not been recognized, and therefore lost during work up.

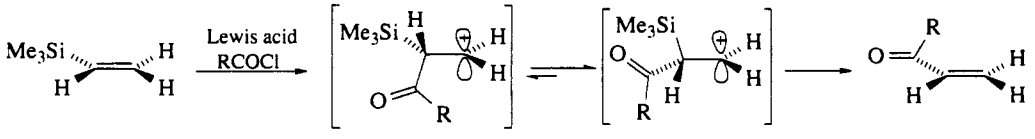
3.1.4 ACYLATIONS OF SILANES

3.1.4.1 Introduction

The well-established stabilization of a positive charge on carbon β to silicon[41,42] has been utilized in very versatile methods for the control of aliphatic Friedel–Crafts reactions. The specificity of this stabilization lies behind the utility of both alkenyl- and allyl-silanes as substrates for electrophilic substitutions, and acylations in particular. These classes offer complementary regiospecificities in controlling both the site of acylation and the location of the double bond. This promotion of simple substitution is one of the most significant advances in aliphatic Friedel–Crafts acylations of recent times, and has recently been the subject of an exhaustive review.[43]

3.1.4.2 Alkenylsilanes

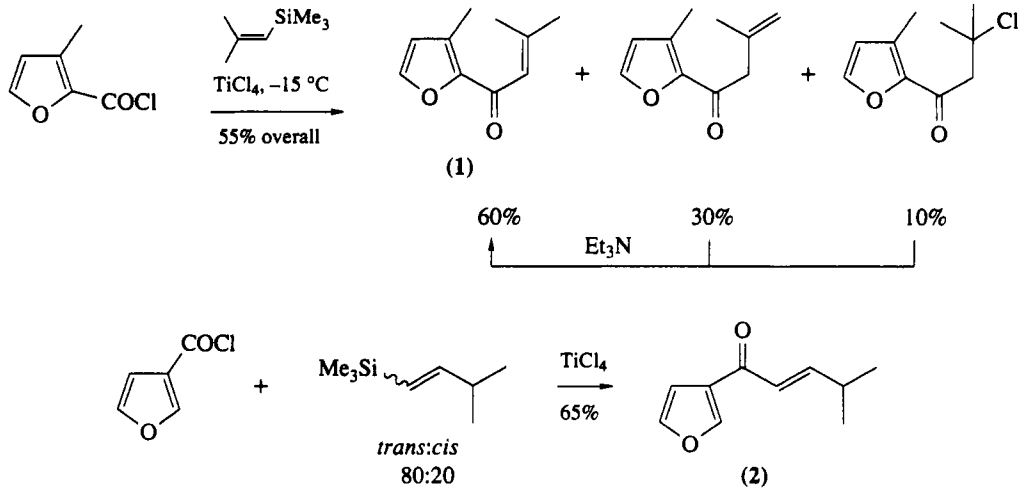
The β-effect of silicon tends to direct the site of electrophilic attack on alkenylsilanes to the carbon bearing the silicon atom (Scheme 4). In comparison with a proton, the greater ease with which the trimethylsilyl group is displaced from carbon leads more often to the formation of substitution products rather than those of addition. Thus vinyltrimethylsilane (b.p. 55 °C) is a convenient equivalent for ethylene in Friedel–Crafts acylations. The alkenyl ketone is formed directly, in contrast to the β-chloroethyl ketone formed in the acylation of ethylene.



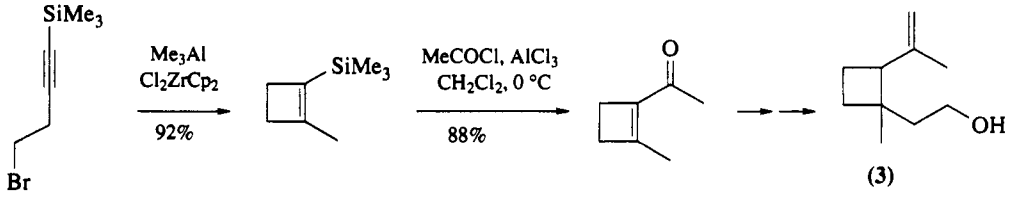
Scheme 4

Alkenylsilane acylation has been employed for the synthesis of two furano monoterpenes, dehydroelsholzione (**1**) and isoegomaketone (**2**; Scheme 5).[44] Acylation of isobutene with 3-methyl-2-furoyl chloride gave dehydroelsholzione in poor yield with a variety of Lewis acid catalysts ($SnCl_4$, $AlCl_3$, $TiCl_4$), but using the equivalent silane substrate, the ketone was obtained in 55% overall yield. Probably as a result of work-up conditions, the initial reaction gave a mixture of three products, the conjugated and deconjugated ketones, together with the chloro ketone addition product. Isomerization and dehydrochlorination were effected with a tertiary amine base to maximize the yield of the desired product.

Friedel–Crafts acetylation of a cyclobutenylsilane has been used in a short synthesis of grandisol (**3**; Scheme 6).[45]



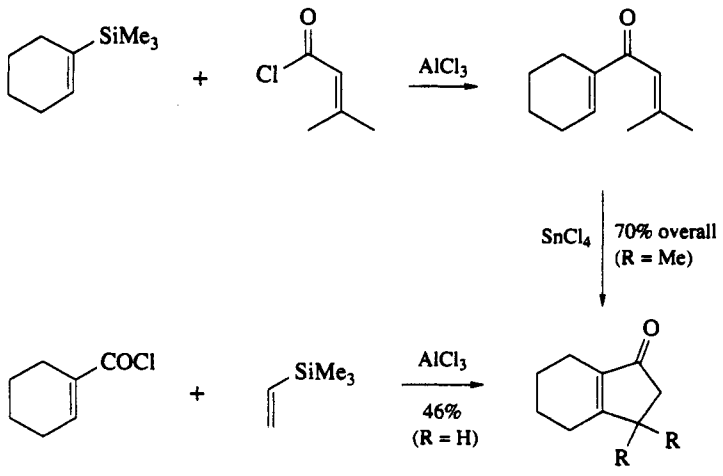
Scheme 5



Scheme 6

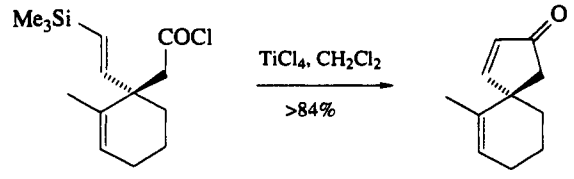
Acylations of alkenylsilanes with α,β-unsaturated acid chlorides lead to dienones in good yield. These may undergo Nazarov-type cyclization to the cyclopentenone, synthetically useful yields in particular being realized when fused ring systems are formed. This leads to two strategies for cyclopentenone annulation. Dienones may be synthesized from either a cyclic α,β-unsaturated acid chloride and a simple alkenylsilane,[46] or from an acrylic acid derivative and a cyclic alkenylsilane (Scheme 7).[47] The regiospecificity of acylation of the silane results in regiocontrol in the annulation.[47] In the former strategy, tin(IV) chloride has been used for both the Friedel–Crafts acylation at *ca.* −30 °C and the cyclization at room temperature in a one-pot reaction. In the second, the two steps were carried out separately, using aluminum chloride at low temperature for the acylation, with tin(IV) chloride or boron trifluoride for the cyclization. In the acylation of vinyltrimethylsilane with acyclic α,β-unsaturated acyl chlorides using aluminum chloride as the catalyst at *ca.* −10 °C, the use of 1,2-dichloroethylene as cosolvent with the usual chlorinated hydrocarbons in some instances reduced the addition of hydrogen chloride to the product.[48] Cyclization to the simple cyclopentenone was observed at higher temperatures with this catalyst. It is therefore apparent that solvent, catalyst and reaction temperature, as well as mode of addition and work-up conditions, are all factors of importance in maximizing yields in these acylation reactions.

The β-stabilization of positive charge by silicon requires that the carbon–silicon bond be in the same plane as the *p*-orbital carrying the positive charge. As the electrophile approaches, the principle of least motion generates a further characteristic of the initial reaction with acylating agents. The substitution usually takes place with retention of geometrical configuration of the alkene.[49] However, under the conditions of both reaction and work-up, isomerization to any thermodynamically more stable enone may occur.

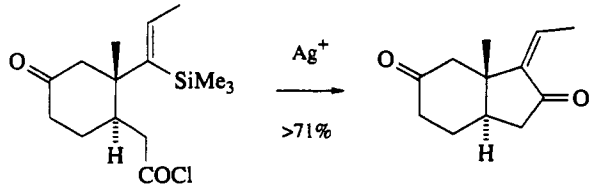


Scheme 7

Intramolecular acylations proceed with greater success for alkenylsilanes than the simple alkenyl substrates. In several cases, (*E*)-silyl substrates have been cyclized to enones, ring size constraints precluding reaction with retention of alkene geometry (equation 8).[50,51] The cyclization approach can be used to prepare enones where the double bond lies exocylic to the ring.[52] In the example shown, retention of configuration is also evident, although the product was easily isomerized under acidic conditions (equation 9).

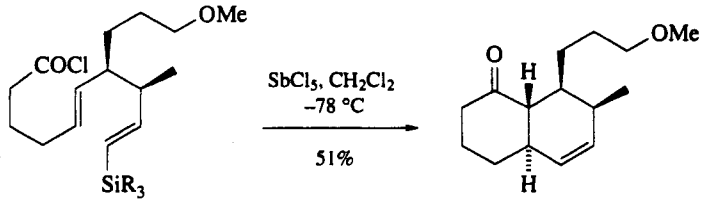


(8)



(9)

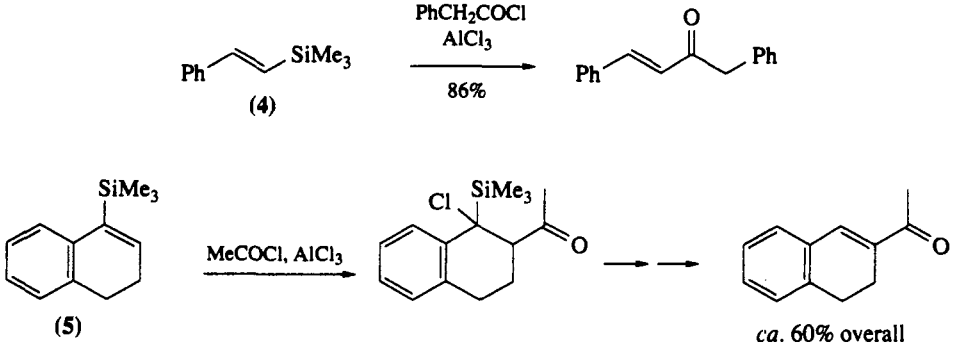
Initiation of polyalkene cyclization by an acid chloride and termination by an alkenylsilane have been combined in a synthesis of an octahydronaphthalene as part of studies towards the synthesis of dihydrocompactin, where the silane can be viewed as controlling the Friedel–Crafts acylation of the disubstituted double bond (equation 10).[53] In this case, antimony pentachloride gave superior yields compared to a wide variety of commonly used Lewis acid catalysts.



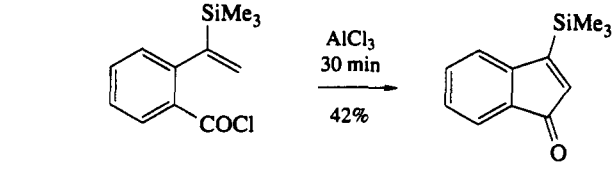
(10)

Although the silyl group confers a site selectivity on the acylation reaction, other structural factors may be sufficient to override the β-effect. This is demonstrated by comparison of acylations of the alkenylsilanes (**4**) and (**5**) (Scheme 8).[54] In the former, both the aromatic and silyl substituents direct the electrophile to the same carbon site, and acylation proceeds in high yield. However, in the latter substrate, where the substituents are in opposition, the aromatic group dominates the site of acylation, and the

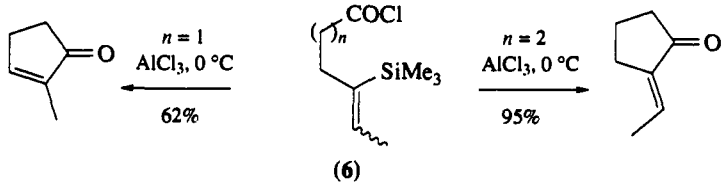
initial product retains the silicon substituent. Nevertheless, elimination of hydrogen halide followed by protodesilylation gives the substitution product in a higher overall yield than in the 'direct' acylation of the nonsilylated dihydronaphthalene. Similarly, cyclizations to form indenones are preferred, not only for electronic reasons, but also from ring strain considerations (equation 11).[55] A β-acylation is also the major pathway for the $AlCl_3$-induced cyclization of (**6**; $n = 1$), with the 'normal' α-acylation less favored as a result of the increased strain in forming the four-membered ring. In addition, cyclization reactions have demonstrated the limits of the β-effect's control of the regioselectivity of acylation.[56] Whilst the substrate (**6**; $n = 2$) cyclizes in very high yield to the methylenecyclopentanone anticipated from consideration of the β-effect, the isomeric silane (**7**) gives the cyclohexenone from β-acylation and rearrangement (Scheme 9). In order to rationalize such reactions, consideration must be given to the relative stability of the incipient potential cations. In the cyclization of (**7**), the tertiary α-silyl cation predominates over the primary β-silyl intermediate.

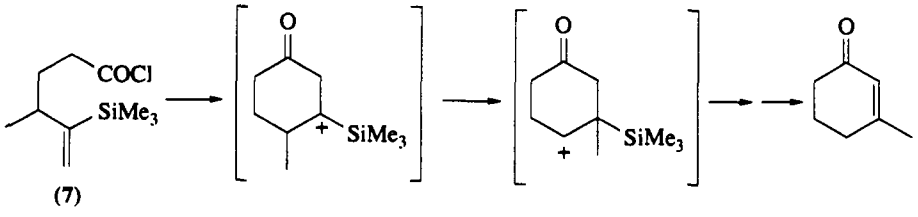


Scheme 8



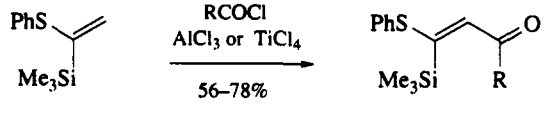
(11)



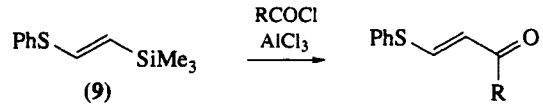


Scheme 9

Other substituents on the alkene are tolerated, but may influence the regiochemical outcome. The silyl group is replaced in the acylation of 1-halo-2-trimethylsilylethylenes, although Lewis acids catalyzed the



(12)



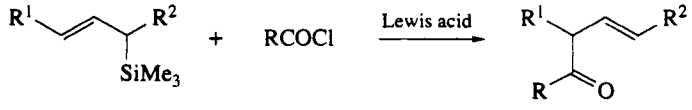
(9) (13)

isomerization of *cis* products to the more stable *trans* isomers.[57] Sulfur substituents on a double bond dominate over silicon,[58,59] as shown by comparison of the alkenes (**8**; equation 12) and (**9**; equation 13).

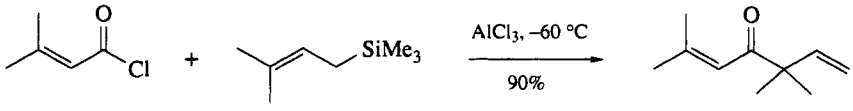
3.1.4.3 Allylsilanes

The silyl group in allylsilanes exerts a strong influence on the regioselectivity of reactions with a variety of electrophiles, and acylating agents in particular.

The stabilization of intermediates and transition states with β-carbenium character by silicon may be explained as a σ–π-conjugative interaction between the silicon–carbon bond and the π-system. This requires an overlap that can occur far earlier along the reaction coordinate for allylsilanes than with alkenylsilanes, where the orbitals are initially orthogonal. This earlier stabilization accounts for the observations that acylations of allylic silanes are regiochemically reliable. In common with reactions with other electrophiles, acylation reaction occurs with allylic rearrangement to give β,γ-unsaturated ketones (equation 14). Even γ,γ-disubstituted allylsilanes readily react at the more-hindered site with acyl chlorides in the presence of a Lewis acid at low temperature to give tertiary alkyl ketones,[60] a reaction used in a short high-yielding synthesis of the monoterpene artemesia ketone (equation 15).[61] Allylsilanes are therefore efficient precursors for the construction of quaternary carbon centers.



(14)

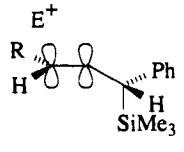


(15)

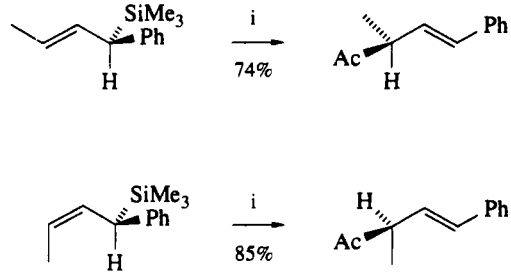
β,γ-Unsaturated ketones derived from α-substituted allylsilanes have disubstituted double bonds with predominantly (*E*)-configuration, and reactions of optically active examples have shown a high *anti* selectivity with the product ketone retaining a stereochemical relation to the precursor.[62] This is consistent with a reaction geometry of the form shown in (**10**), where the electrophile approaches the double bond selectively *anti* to the leaving trimethylsilyl group, and the product stereochemistry reflects the configuration of the disubstituted double bond in the substrate (Scheme 10). Stereochemical transfer is also pronounced in the high-yielding acylations of fluorodimethylsilyl derivatives, but in reactions of trifluorosilyl substrates yields appear low, and products racemic.[63]

Unusual circumstances in allyl substrates can lead to unusual acylation products. Extremely hindered allylsilanes have been noted to react without allylic rearrangement (equation 16),[64] and steric arguments may account for acylations that take place with apparent overall *syn* addition (equation 17).[65]

Lewis acids used for acylation of allylsilanes with acid chlorides include titanium and tin tetrachlorides, aluminum, gallium and indium trichlorides and zinc dichloride, and boron trifluoride for reactions with acid anhydrides. Although gallium and indium chlorides have been used successfully in catalytic (*ca.* 2 mol %) amounts,[66] most frequently aluminum chloride has been used as catalyst, with titanium tetrachloride also commonly employed, both in molar quantities. With these catalysts, acylations can often be carried out at low temperatures, and with short reaction times.

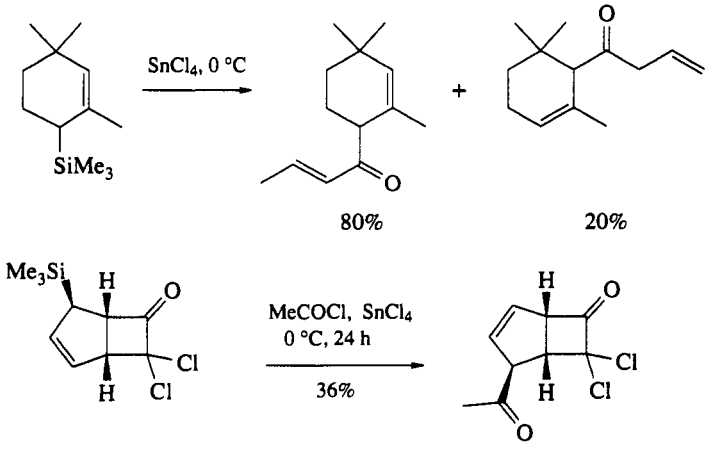


(10)

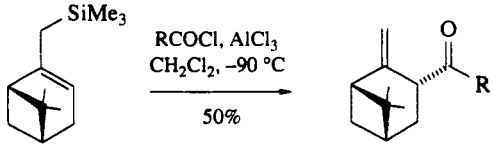


i, AcCl, $AlCl_3$, CH_2Cl_2, –78 °C, 5 min

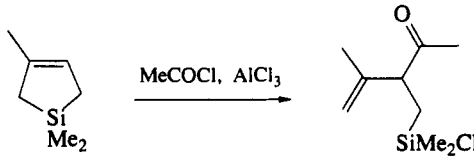
Scheme 10



The regiochemical reliability of the Friedel–Crafts acylation of allylsilanes extends to a wide variety of substrates, including cycloalkenylsilanes,[67] and 1-trimethylsilylmethylcyclohexenes.[68] The mild conditions necessary for acylation are demonstrated in the reactions of 7-trimethylsilyl-α-pinene, where the acid sensitive pinene carbon skeleton survives without rearrangement (equation 18). The formation of methylenecyclohexanes from silylmethylcyclohexenes should be contrasted with Friedel–Crafts acylations of the simple methyl derivatives, which lead to cyclohexenyl products.

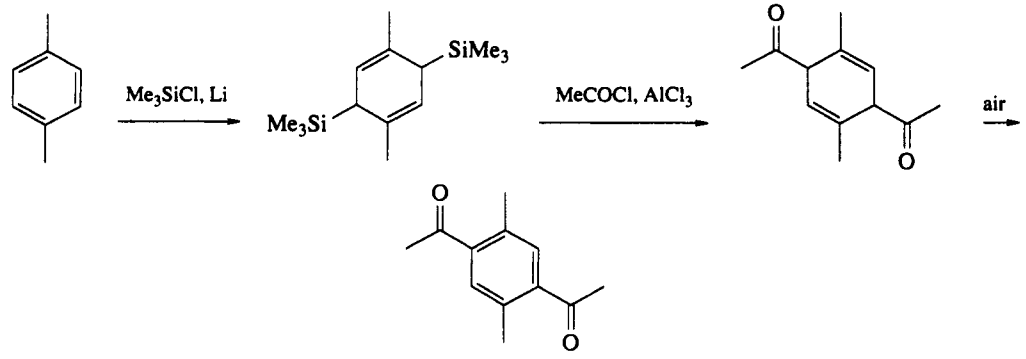


Thus the double bond may be either cyclic or exocyclic to a ring, and the silyl group on a ring substituent or on a ring. Silacyclopentene derivatives also may be acetylated, either with acetyl chloride/aluminum chloride or acetic anhydride/boron trifluoride, with retention of the silyl group (equation 19).[69]



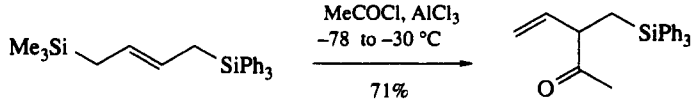
1,4-Disilylcyclohexa-2,5-dienes, obtained by reductive silylation of benzene derivatives, undergo regiospecific diacylation giving, after aerial oxidation, *p*-diacylated arenes.[70] The aliphatic Friedel–Crafts

reaction can thus be used to prepare benzenoid compounds difficult to obtain by classical aromatic chemistry (Scheme 11).



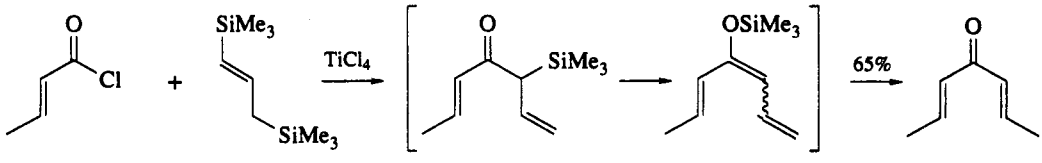
Scheme 11

Unsymmetrically substituted 1,4-disilyl-2-butenes undergo selective acylation, with the trimethylsilyl group being replaced in preference to triphenylsilyl (equation 20).[71]



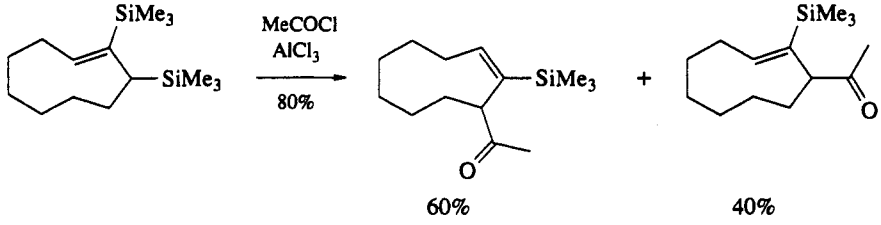
(20)

1,1-Disilylalkenes provide an access to acylated (*E*)-vinylsilanes. 1,3-Disilylpropenes tend to behave as 3-silylpropenes towards acylation, because of the lability of the α-silyl ketone formed initially.[72] Divinyl ketones are isolated from reactions with unsaturated acid chlorides.[73] Since these are cyclized under the reaction conditions, they are presumably formed during work up, possibly from silyl dienolate intermediates (Scheme 12).



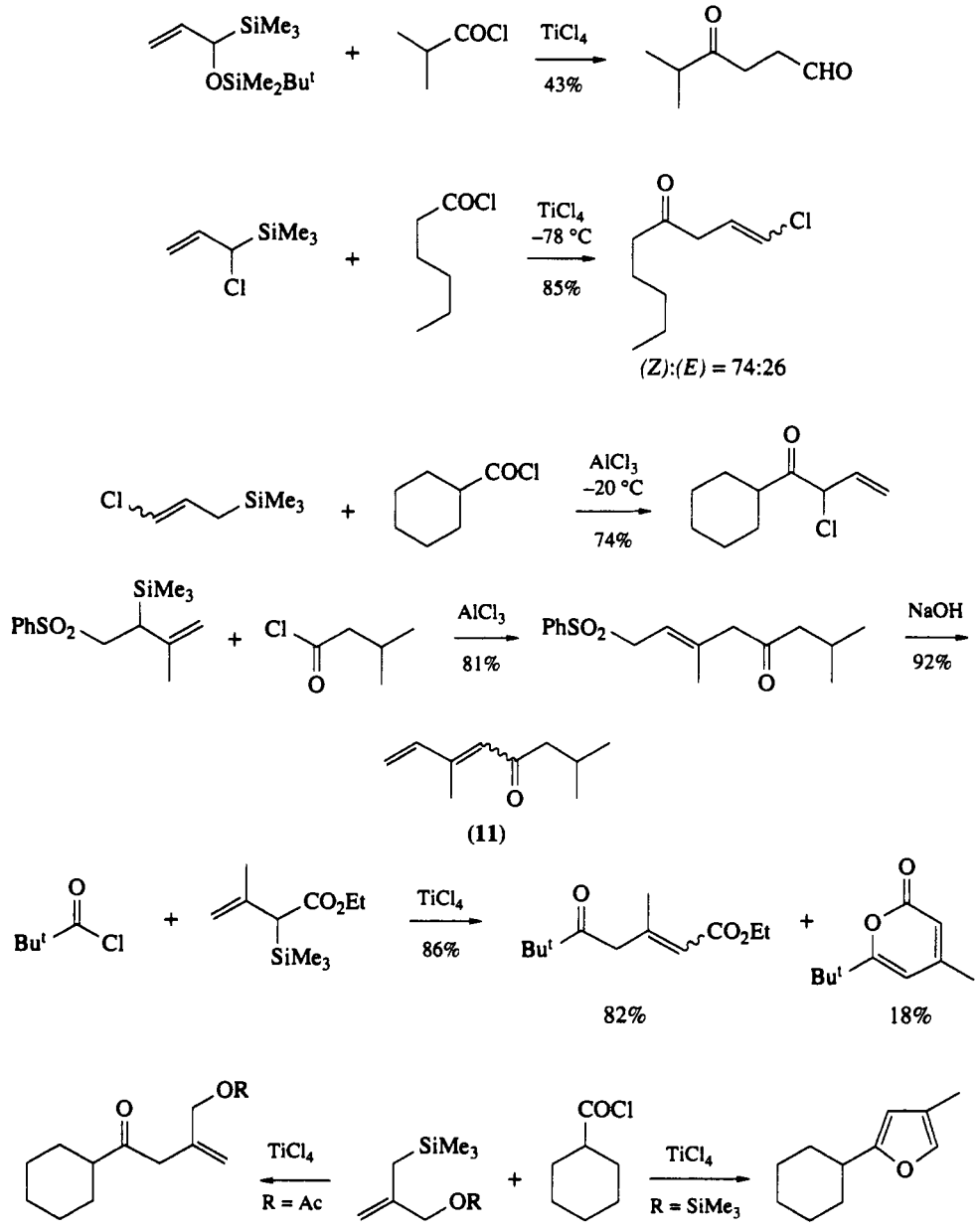
Scheme 12

The greater reactivity of allyl- compared to vinyl-silanes is shown in the acylation of 2,3-disilylalkenes, giving rearranged alkenylsilanes.[74] Interestingly, this acylation offers a route to the *trans*-cyclononene skeleton (equation 21).[75]



(21)

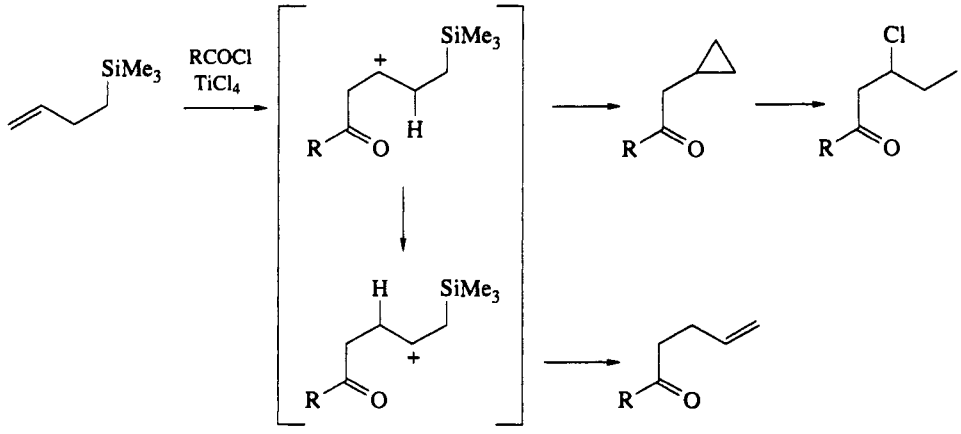
Many functional groups are tolerated during the Friedel–Crafts acylation of allylsilanes, giving rise to a wide variety of functionalized ketones, some of which are shown in Scheme 13.[76–81] The stability of a sulfone group under conditions required for acylation has potential for the formation of dienones, as demonstrated in the synthesis of (*E*)- and (*Z*)-tagetones (**11**) shown in Scheme 13.[79]



Scheme 13

3.1.4.4 Acylations of Other Unsaturated Silanes

Three types of products have been observed in intermolecular acylations of homoallylic silanes, the major one being cyclopropylmethyl ketones, along with minor amounts of 3-butenyl ketones and β-chloro ketones.[82] It is likely that all derive from the carbenium ion formed by acylation of the double bond, which then undergoes cyclodesilylation or hydride transfer followed by β-elimination (Scheme 14). The former leads to the cyclopropane, which can ring open to give the chloro products. The latter pathway gives the butenyl ketone, and is supported by location of substituent positions on methylated substrates. However, the direct acylation of the carbon–silicon bond should not necessarily be excluded in consideration of more general cases. Titanium tetrachloride seems the preferred catalyst in these cyclodesilylations, and low temperatures minimize the formation of the chloro by-products. Intramolecular versions



Scheme 14

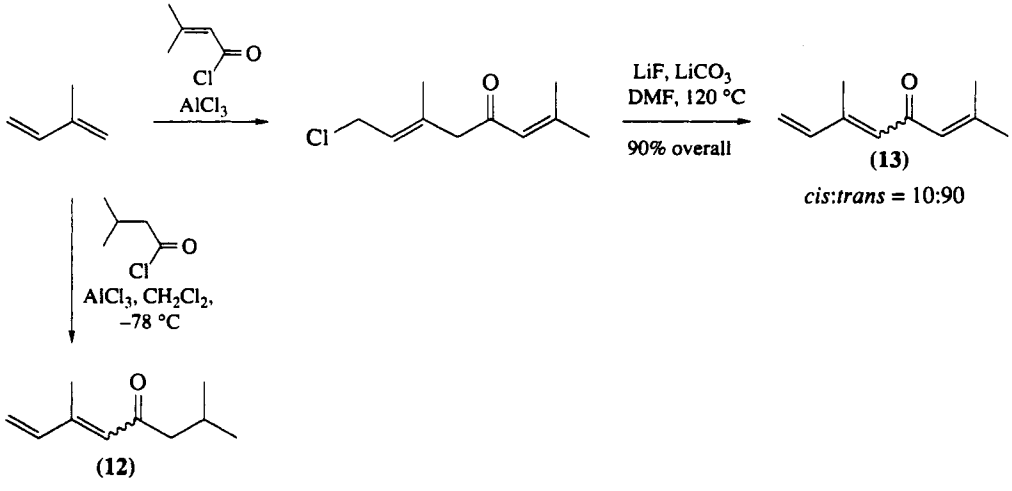
of the reaction are also successful, leading to 2-cyclopropylcycloalkanones, particularly when forming five-, six- and seven-membered ring ketones.[52,83] Moving the silyl group further from the double bond removes its influence, and simple cyclic ketones retaining the silicon are formed.

3.1.5 ACYLATIONS OF CONJUGATED DIENES

3.1.5.1 Simple Dienes

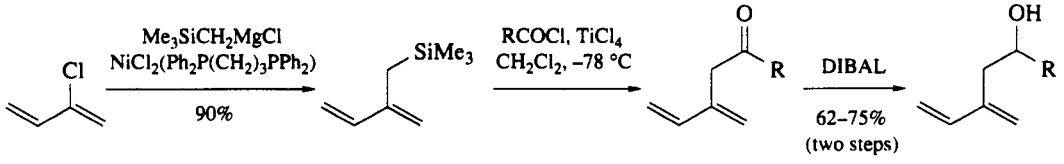
Early reviews indicate that few conjugated dienes had been successfully acylated under Friedel–Crafts conditions. This probably results from the sensitivity of such substrates to the strongly acidic reaction conditions, leading to polymerization. However, provided reaction temperatures are low enough, synthetically useful yields of acylated products can be obtained. Butadiene itself is acylated at the terminal position in the presence of aluminum chloride at dry ice temperatures to give the *trans*-dienone.[84] In the presence of the more mild Lewis acid tin(IV) chloride, propionylation occurred at slightly higher temperatures (*ca.* –40 °C), although the yield of 42% quoted was after prolonged treatment with calcium carbonate, presumably to effect dehydrochlorination.[85]

Chloro ketones have been observed in tin(IV) chloride catalyzed acylations of isoprene as part of high-yielding synthetic approaches to tagetones (**12**) and ocimenones (**13**; Scheme 15).[86] Typically, it was not necessary to isolate these, dehydrohalogenation to mixtures of *cis*- and *trans*-dienones being accomplished using lithium fluoride and lithium carbonate in DMF.



Scheme 15

Silicon has also been used to control the acylation of 1,3-dienes in a manner analogous to the situation with alkenes. Isoprenylation with 2-trimethylsilylmethylbuta-1,3-diene follows the course expected of acylation of the allylic silane. In these very rapid reactions, titanium tetrachloride seems to be one of the more efficient catalysts, as is aluminum chloride. The method was used in synthetic approaches to the terpenes ipsenol (**14**) and ipsdienol (**15**; Scheme 16).[87] Of particular interest is the comparison of this isoprenylating agent with isoprene itself. The examples of Friedel–Crafts acylations cited show the regiocontrol that can be achieved by suitable choice of substrate.

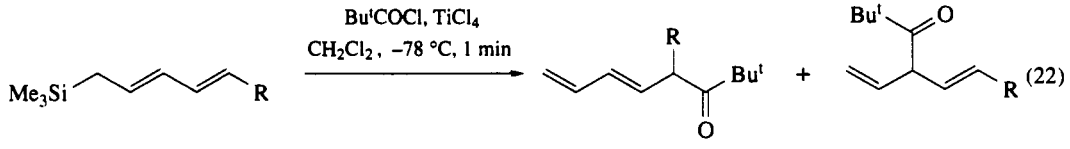


(14) R = Bu^t

(15) R = CH=CMe$_2$

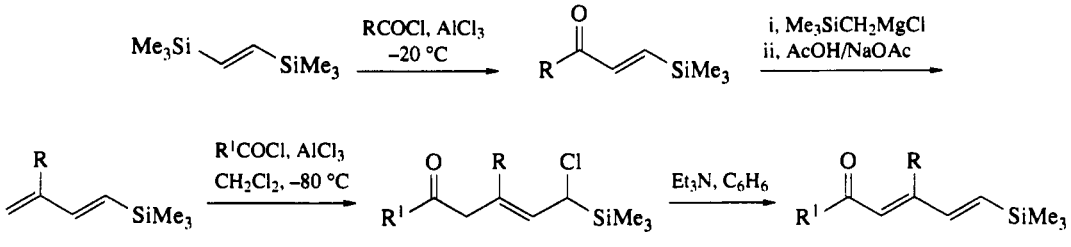
Scheme 16

(Pentadienyl)trimethylsilane, in its reaction with pivaloyl chloride in the presence of titanium tetrachloride, acylates to give a mixture of products, chiefly derived from reaction at the ε-carbon, with γ-acylation also observed (equation 22).[88] The latter mode of reaction is more prevalent if the ε-carbon is further substituted, presumably because of steric hindrance. This electrophile showed lower selectivity for the ε-carbon than other electrophiles, including aldehydes and acetals.



R = H	59%	58%	:	42%
R = Me	55%	22%	:	78%

Relatively little work has been reported on the acylation of 1-trialkylsilyl-1,3-butadienes. As is observed with vinylic substrates, the regioselectivity of reaction can be controlled by substituents other than the silyl group. For example, acylations of 3-alkyl derivatives are controlled by the relative stability of the tertiary carbenium ion following attack of the electrophile at the C-4 terminus (Scheme 17). Silicon is retained in both the immediate chloride addition product, and the diene formed by subsequent base-catalyzed eliminations.[89]

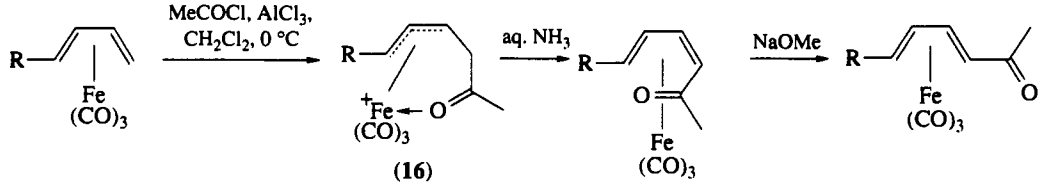


Scheme 17

3.1.5.2 Diene Complexes

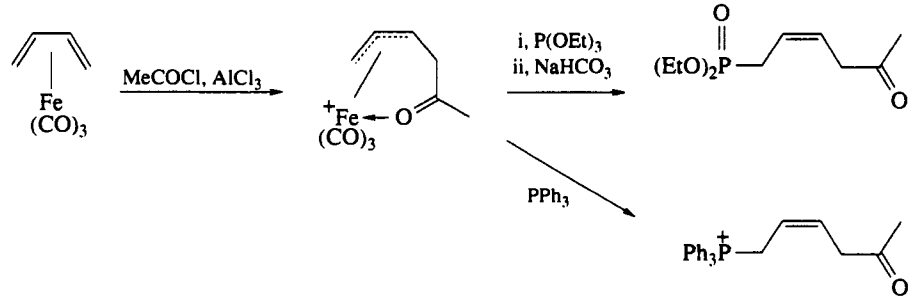
Although few examples of acylations of 1,3-butadienes have been described, Friedel–Crafts acylations of diene complexes, in particular iron tricarbonyl derivatives, can give synthetically useful yields. In acylations of iron tricarbonyl complexes with the Perrier reagent from acetyl chloride and aluminum chloride, acylation occurs only at unsubstituted terminal carbons (Scheme 18).[90] The primary product is

the *cis*-dienone complex, although the intermediate σ-complex (**16**) has on occasion been isolated,[91] X-ray structure determination showing that under Friedel–Crafts conditions the complex undergoes stereospecific *endo* attack.[92] In order to isolate the primary *cis* product, the reaction should be quenched with cold aqueous ammonia.[93] Isomerization to the more stable *trans*-dienone complex takes place under more strongly acidic or basic conditions. Methanolic sodium methoxide is recommended for preparative isomerization.[94]

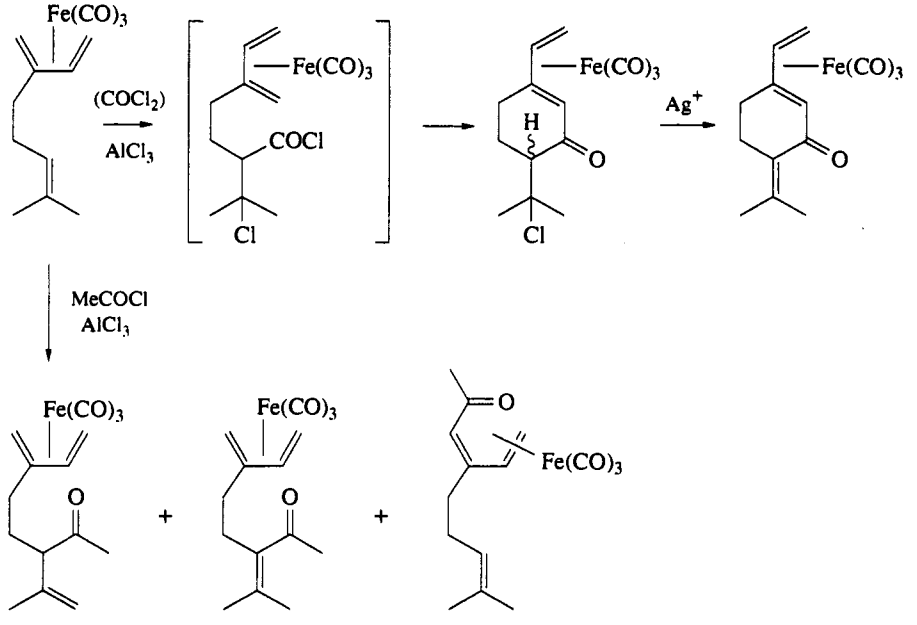


Scheme 18

The value of the metal complexation results from control of the reaction, rather than any activation, Lewis acids being excellent catalysts for diene polymerization. Friedel–Crafts acylations of diene complexes have been used for the preparation of dienes, with decomplexation following carbonyl reduction.[95] Decomplexation to afford dienones has been less explored. The intermediate cationic σ-complex on treatment with triethyl phosphite or triphenylphosphine affords metal-free β,γ-unsaturated phosphonates or phosphonium salts (Scheme 19).[96] The initial *s-cis* conformation of the diene fragment of the



Scheme 19



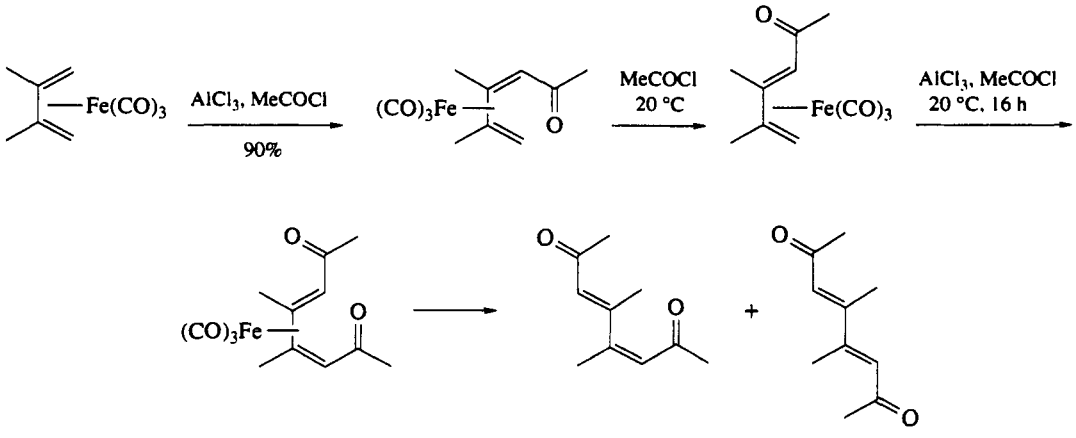
Scheme 20

complex is retained, and leads stereospecifically to functionalized (*Z*)-alkenes with considerable synthetic potential.

2-Trialkylsilylated butadienyliron tricarbonyl complexes acylate to give solely terminal *cis*-dienone complexes, reacting preferentially at the 4-position.[97]

The iron tricarbonyl unit has been described as a protecting group for a 1,3-diene, as in the acetylation of the complex of myrcene at low temperature (Scheme 20). The usual combinations of α,β- and β,γ-unsaturated ketones were formed. At higher temperatures, some acylation at the terminus of the diene complex was also observed. In an interesting extension, reaction of the complex with oxalyl chloride resulted in cyclization of the acid chloride initially formed by reaction at the alkene.[98]

A terminal acyl group is not totally deactivating towards further acylation of dienone–iron complexes derived from isoprene and 2,3-dimethylbutadiene,[99] and 2-trialkylsilylbutadienes,[97] provided the acyl group lies in the *exo* configuration (Scheme 21). The required isomerization may be carried out using acetyl chloride. With excess acetylating agent, *trans*-dienone complexes acylate slowly to give the *cis–trans*-dienedione complexes. Partial isomerization to the *trans–trans* isomers was noted. These interesting dienediones could be released (although with further isomerization) from their complexes by cleavage with hydrogen peroxide in methanolic sodium hydroxide. Other cleavage methods proved unsuitable.[99]

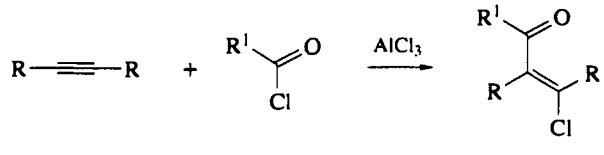


Scheme 21

3.1.6 ACYLATION OF ALKYNES

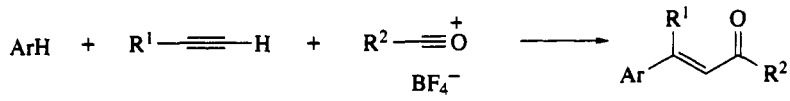
3.1.6.1 Simple Alkynes

The Friedel–Crafts acylation of alkynes is an extremely rapid reaction, and usually leads to the formation of the *trans*-β-chlorovinyl ketone (equation 23). Reaction temperatures can be as low as –70 °C. The reaction proceeds *via* reaction of the acyl halide–Lewis acid complex with the alkyne, and whilst the implied vinyl cation has not been observed directly, the reaction products can be understood in terms of reaction of such an intermediate with nucleophiles, usually halide ion. Whilst the *trans*-chlorovinyl ketone has been described as the sole product of the reaction by some workers, others have reported the formation of mixtures of the *cis* and *trans* forms, under conditions that did not appear to lead to isomerization.[100]



(23)

Other nucleophilic species can be present in the reaction medium to trap the cationic 'intermediate'. The rate of acylation of an alkyne is indicated by reaction in the presence of an aromatic compound, leading to arylated products (equation 24).[101] This reaction can take place at low temperatures where the



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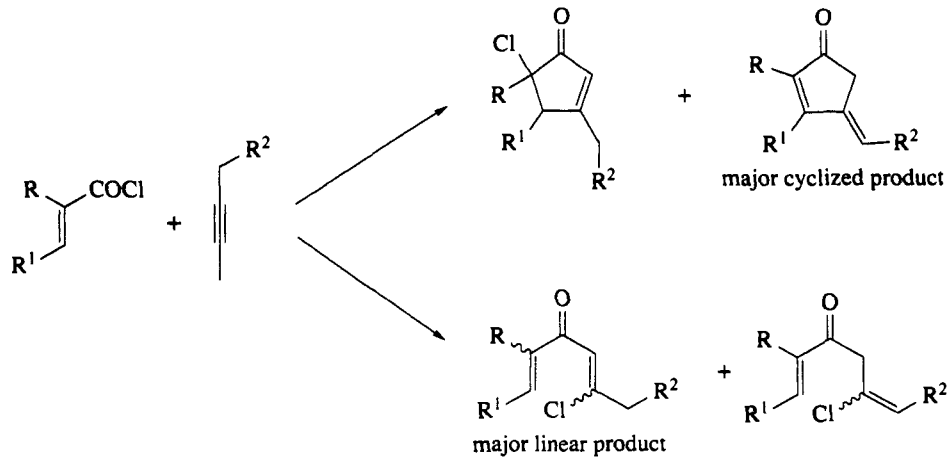
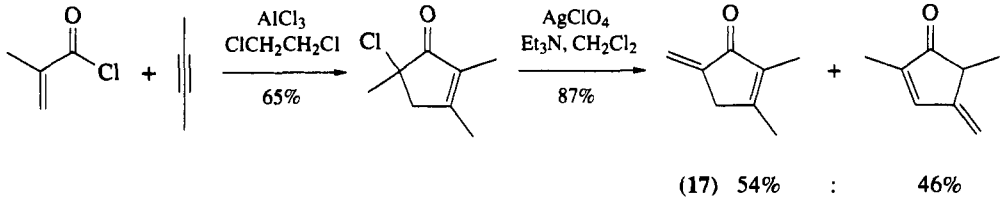
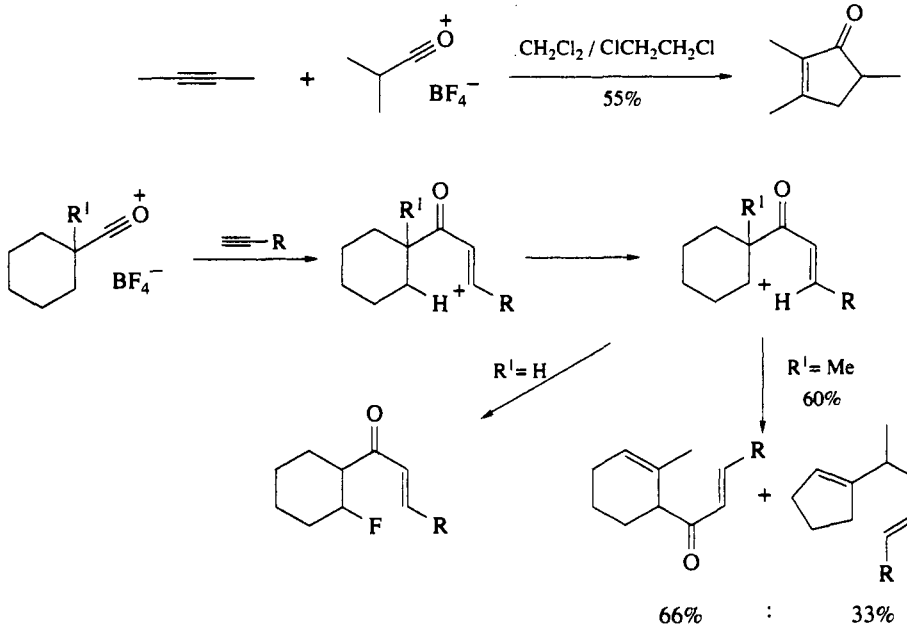


Scheme 22



Scheme 23



Scheme 24

rate of arene acylation is essentially zero, although a limiting factor to this reaction is probably the reactivity of the arene used. Halogenated and alkylated arenes have been used successfully.

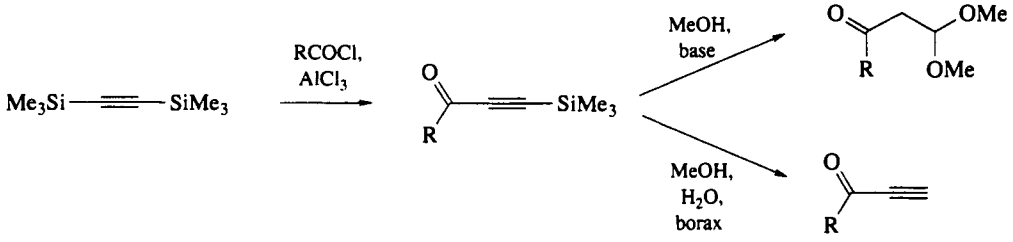
Unsaturated acyl chlorides react with substituted alkynes to give mixtures of linear and cyclopentenyl products, the latter being formed in greater yield at higher temperatures (Scheme 22).[102] This offers a convenient access to a variety of 5-chlorocyclopentenones bearing substituents at the 4- and 5-positions, with control over the location of the double bond.[103–105] Application of this method includes a short synthesis of the antibiotic methylenomycin B (**17**; Scheme 23).[106]

Hydride transfers are implicated in several acylations of alkynes by saturated acyl chlorides leading to cyclopentenes.[107] Intramolecular [1,5] hydride shifts have been shown to be a common feature in silver-assisted reactions of cyclohexanylcarbonyl chloride with alkynes.[108,109] The nature of the final product depends on the structure of the resulting cation. Capture of fluoride ion, ring contraction and acyl or alkyl migrations of axial substituents have been observed (Scheme 24).

In a related transformation, acylation of terminal alkynes catalyzed by copper(I) iodide and bis(triphenylphosphine)dichloropalladium(II) leads directly to alkynic ketones.[110]

3.1.6.2 Alkynylsilanes

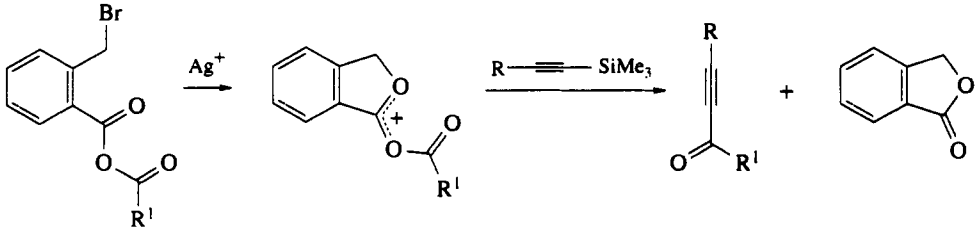
Only rarely is proton loss observed from the 'intermediate' cation derived from acylation of a terminal alkyne. In contrast, acylation of alkynylsilanes provides an excellent strategy for the synthesis of alkynyl ketones.[111] Here, it is apparent that elimination of the silyl substituent competes very effectively with capture of a nucleophile. Acylation of bis(trimethylsilyl)ethyne[111] provides a convenient route to terminal alkynic ketones, particularly since desilylation can be carried out using bases as weak as dilute aqueous borax, conditions mild enough to prevent the ready hydration of the triple bond (Scheme 25).[112] Silylated diynes are also excellent substrates for Friedel–Crafts acylation.[112–114]



Scheme 25

Acylations have generally been carried out using aluminum chloride as catalyst, although on occasions no catalyst was required.[115] Titanium tetrachloride proved superior to aluminum, tin(IV) and zinc chlorides in reactions of 4-substituted-1-trimethylsilylbuta-1,3-diynes and the derived (*Z*)-enynes.[114] The most frequently used solvents are chlorinated hydrocarbons,[116,117] in preference to carbon disulfide and nitrobenzene.[111]

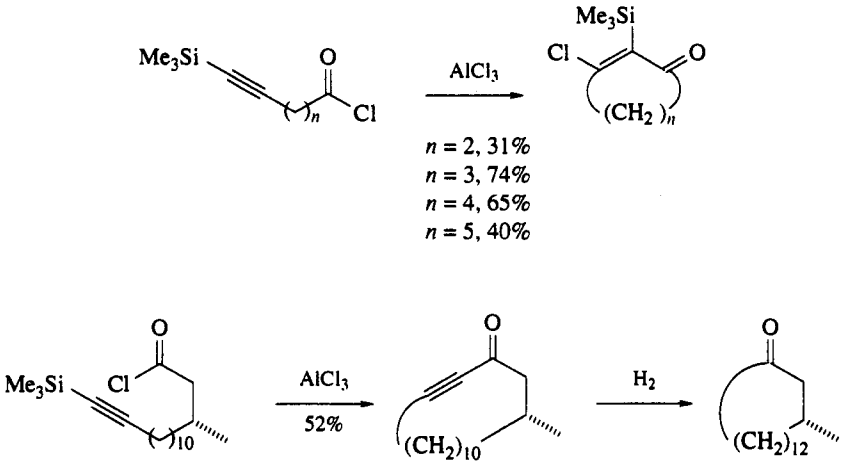
Both acid chlorides, including ethylsuccinyl chloride,[118] and acid anhydrides[111,119] have been used as acylating agents, as have carbamoyl chlorides.[120] Silver-assisted reactions of anhydrides of α-bromotoluic acid also lead to alkynic ketones, probably *via* an intermediate acyloxyalkyloxycarbenium salt (Scheme 26).[121]



Scheme 26

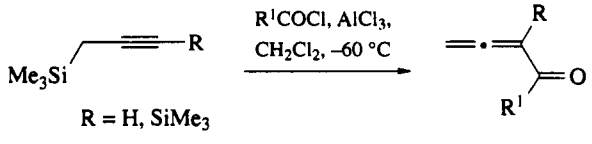
With chloroacetyl chloride and aluminum chloride,[111] addition of chloride gave the β-chloro-α-silyl enone in addition to the alkynic ketone. Addition of halide has also been observed in alkynations of 2-alkoxy-1-trimethylsilylethynes.[122]

ω-Trimethylsilylethynylalkanoyl chlorides cyclize under high dilution conditions to form large (11–15-membered) ring ynones, exemplified by syntheses of (±)- and (*R*)-muscone (Scheme 27).[123] Extension of the cycloacylation to smaller ring systems provides products of chloride addition to the intermediate vinyl cation, rather than desilylation to form strained alkynes.



Scheme 27

Propargylsilanes react with acyl halides to afford α-allenic ketones by rearrangement (equation 25).[124]



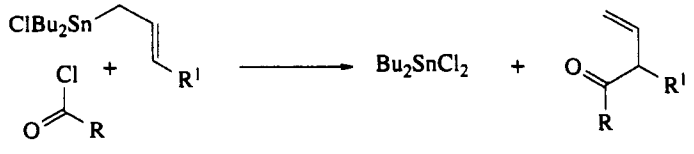
(25)

3.1.7 ACYLATION OF TIN SUBSTRATES

3.1.7.1 Lewis Acid Catalyzed Acylations of Stannanes

The similarities between organic tin and silicon compounds, particularly their abilities to stabilize positive charge on a β-carbon atom,[125] suggest that vinylic and allylic tin compounds should be useful substrates for Friedel–Crafts acylation reactions. However, very few examples of the acylation of stannanes under the action of Lewis acids have been reported, and this remains a field of Friedel–Crafts reactions not yet fully exploited. The acylation of 1,2-bis(tri-*n*-butylstannyl)ethylene in the presence of aluminum chloride offers a moderately yielding route to tributylstannyl-substituted enones, useful as precursors to 4,5-dialkylcyclopent-2-enones.[126]

Allylchlorostannanes react with acyl chlorides in the absence of any added catalyst, the chlorostannane having sufficient Lewis acid character to promote acylation with allylic rearrangement (equation 26).[127] Similarly, no added catalyst appears necessary for acylations of alkynylstannanes, although the trialkylchlorostannane formed in the thermal acylation may exert a catalytic influence on the reaction.



(26)

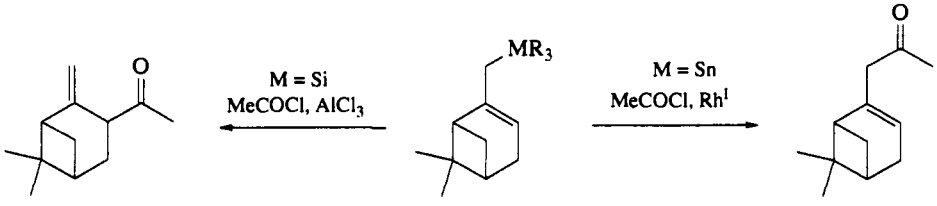
3.1.7.2 Alternatives to Lewis Acids for the Acylation of Stannanes

Despite the lack of examples of Friedel–Crafts acylations catalyzed by Lewis acids,[128] reactions of stannanes with acyl halides catalyzed by palladium species have found considerable use for the preparation of ketones.[129] Since alkyl groups are only transferred slowly from tin, more rapid transfer to the acyl chloride is observed for alkynyl, alkenyl and allyl, as well as aryl and benzyl, groups. This leads to a versatile synthesis of ketones.[130] Acylations of alkenylstannanes are both regio- and stereo-specific.

This alternative to the Friedel–Crafts reaction, extensively developed by Stille and coworkers, is particularly important, since the reaction conditions are essentially neutral, and so provides a method for acylation of compounds containing an acid-sensitive functionality which would preclude the use of the Friedel–Crafts reaction. Reaction temperatures are often below 100 °C, and high (1000-fold) turnovers of the catalyst have been achieved. Solvents employed include chloroform, toluene, and, on occasions, HMPA. Some reactions have been carried out under an atmosphere of carbon monoxide to prevent excessive decarbonylation of the acyl palladium intermediate. Indeed, carbonylative coupling of alkenylstannanes with allyl halides in the presence of carbon monoxide (*ca.* 3 atm or greater; 1 atm = 101 kPa) offers an alternative to the Friedel–Crafts acylation, ketones being formed by the reaction of the stannane with the acyl species formed by carbon monoxide insertion into the allyl palladium intermediate.[131]

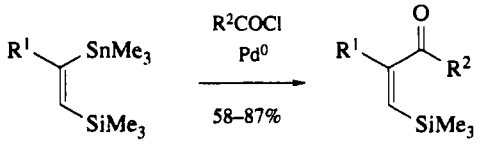
Aromatic, aliphatic and heterocyclic acid chlorides all give high yields of ketones, [1,4] addition not being observed with α,β-unsaturated acid chlorides. This leads to a potentially very useful synthesis of divinyl ketones since, in contrast to Lewis acid catalyzed acylations of alkenes, under the neutral reaction conditions for the acylation of alkenylstannanes, cyclizations to cyclopentenones do not occur.[132]

Rhodium has also been found to catalyze regioselective acylations of allylic tin derivatives, with chlorotris(triphenylphosphine)rhodium(I) being particularly efficient in the terpenoid field.[133] Again, the use of nonacidic conditions for stannanes offers advantages over classical conditions both in the elimination of skeletal rearrangement and in the observance of altered regioselectivity by comparison with acylations of silyl substrates (Scheme 28). However, it has not yet been firmly established that rhodium-catalyzed acylations always proceed without rearrangement.



Scheme 28

Palladium-catalyzed acylations offer a useful chemoselectivity. Since alkenylsilanes do not react, this allows the formation of silyl-substituted ketones which could not readily be made by classical aliphatic Friedel–Crafts acylations (equation 27).[134]



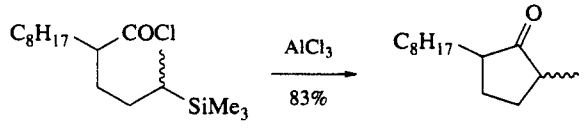
(27)

3.1.8 ACYLATIONS OF ALKANES

The acylation of alkanes has also been known for a long time,[2] but for synthetic purposes is limited to simple substrates. The initial step is hydride abstraction by an acylium ion, a process well established in the presence of a powerful Lewis acid, most commonly an aluminum halide, or strong protic acid.[135] The carbocation so formed can then undergo elimination, possibly after hydride or alkyl migration, to give an alkene which is then acylated. In the presence of excess alkane, saturated ketones are formed by a further intermolecular hydride transfer, whereas with an excess of acyl halide, the product is the (conjugated) unsaturated ketone.[136] The synthetic potential is obviously likely to be limited to simple substrates,

which undergo specific initial hydride transfer. One such example is the preparation of 1-acetyl-2-methylcyclopentene by acetylation of cyclohexane.[137]

Whilst acylation of alkanes requires initial hydride abstraction, and has limited application, the weakly polarized carbon–silicon bond in tetraalkylsilanes can be cleaved by electrophilic attack. Since silanes are generally relatively stable, strong Lewis acids are required to induce reaction. In the limited studies to date, aluminum chloride is the only reagent described as effective in acylation of silanes. This acylation offers potential for conversion of acid halides to simple (methyl, ethyl) ketones, primarily because of the availability of the necessary tetraalkylsilanes, and the fact that only one alkyl group is transferred.[138] Unsymmetrical silanes have not been studied, except for intramolecular reactions leading to cylcopentanones.[139] Here the selectivity for cyclization is high, with no methyl ketones observed. Even *s*-alkyltrimethylsilanes cyclize in good yield (equation 28). However it is unlikely that this selectivity will apply to intermolecular acylations. Of greater potential is the use of cyclopropylsilanes, which acylate readily to form cyclopropyl ketones,[140] provided there are no further substituents on the three-membered ring. Acylations of 1-trimethylsilyl-2-methylcyclopropanes are both regio- and stereo-specific, the *trans* isomer giving the (*Z*)-β,γ-unsaturated ketone and the *cis*-cyclopropane the (*E*)-isomer (equation 29).[141]



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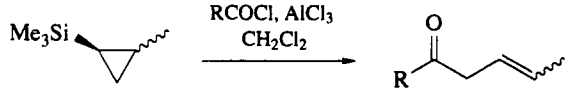


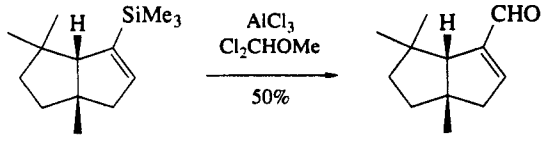
(29)

cis or *trans* (*E*) or (*Z*) respectively

3.1.9 ALIPHATIC FORMYLATION

Direct formylation of alkenes has rarely proved a satisfactory route to unsaturated aldehydes. The classical Gatterman–Koch formylation with carbon monoxide, hydrogen chloride and aluminum chloride gives ketonic and acidic products, whilst formylation under Gatterman conditions using hydrogen cyanide in place of carbon monoxide generally leads to *N*-formylamino compounds by addition to the double bond.[142] Although outside the scope of reactions related to aliphatic Friedel–Crafts acylations, hydroformylation reactions of alkenes do provide well-established routes to (saturated) aldehydes.

More-controlled formylation can be achieved by the use of silylated substrates. The familiar use of the titanium tetrachloride catalyzed formylation of aromatic substrates by dichloromethyl methyl ether can be extended to the formylation of alkenylsilanes.[49,143] As with the aromatic case, the reaction proceeds by initial chloromethoxylation, followed by hydrolysis to the aldehyde. The formylation is also applicable to 1-silyl-1,3-dienes, leading to 2,4-dienals.[144] The anticipated regioselectivity is observed, with substitution of the silyl group to give the α,β-unsaturated aldehyde, but unlike the acylation of alkenylsilanes where substitution occurs with retention of geometry about the double bond, the (*E*)-configuration is observed in the product irrespective of the configuration of the starting alkene.[145] This is likely to be a result of isomerization of the allylic chloride intermediate in the presence of the Lewis acid. The formylating species shows lower steric requirements than acylating agents, since formylation has been observed of substrates which failed to acetylate (equation 30).[146]



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3.2
The Bimolecular Aromatic Friedel–Crafts Reaction

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3.2.1 INTRODUCTION

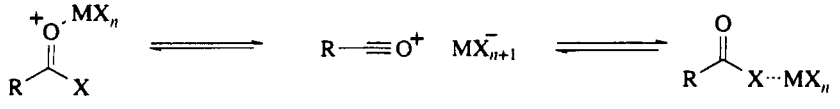
This chapter is concerned with intermolecular reactions that lead, either directly or indirectly, to the acylation of an aromatic system. A series of books is available[1] and Friedel–Crafts chemistry has also been updated in a single volume that covers the literature to mid-1972.[2] By comparison with the acylation of amino and hydroxy groups, the acylation of aromatic carbon requires, in the majority of cases, a considerable increase in the electrophilicity of the reagent. An electrophilic catalyst is thus normally required in addition to the aromatic substrate and the acylating reagent. Although acyl halides and carboxylic anhydrides are the most frequently used sources of the acyl group, we will consider a number of others. For many benzenoid derivatives a strongly electrophilic Lewis acid such as aluminum chloride is used, while for nucleophilic heterocycles such as furan, a milder reagent such as zinc chloride may well suffice. Many acylation reactions of very nucleophilic heterocycles such as pyrrole can be carried out in the absence of a catalyst. We will also discuss the use of a number of acyl cation equivalents but we will exclude certain formylation procedures that are the subjects of other chapters. There are a number of rea-

sons why this method of carbon–carbon bond formation is widely investigated. The importance of the introduction of an acyl residue into an aromatic system relates to a number of important transformations that can be easily carried out, as well as to the inherent importance of aromatic ketones themselves. The conversion of acetophenone derivatives into amines *via* the Beckmann rearrangement[3] and into phenols *via* the Baeyer–Villiger rearrangement is well known.[4] An acyl group can also be converted, using a number of reductive methods, in dihydro-deoxo-disubstitution reactions, into the related hydrocarbon residue.[5]

The acylation of an aromatic system can therefore serve as a valuable alternative to direct alkylation even though extra steps are required. Acylating agents are generally more reactive than alkylating agents in Friedel–Crafts reactions. The lower energy of alkyl cation equivalents makes them more accessible and results in alkylation occurring in preference to acylation, for example when using lactones as Friedel–Crafts precursors. The alkyl-substituted aromatic compounds are more nucleophilic than their precursors and so over-alkylation is often a problem. In addition, where alkylation proceeds by way of a carbocation, rearrangement of the alkyl residue is not unusual. On the other hand, the aromatic ketones are less nucleophilic than their precursors. It is usually difficult to introduce more than one acyl group into an aromatic ring and over-acylation is not normally a major problem. Mesitylene is an exception; diacetylmesitylene is formed easily, presumably because the methyl groups prevent the first-formed ketone complex from being coplanar with the ring. In addition no rearrangement of the carbon chain of the acylating agent is observed. The only problem that is observed occurs when the product of the reaction is soluble in the reaction medium. Under those conditions deprotonation of the ketone–Lewis acid complex can lead to side chain acylation, and hence to the formation of β-diketones *via* an enol complex.

3.2.2 MECHANISMS

We will consider the mechanisms that may operate in Friedel–Crafts acylations; the mechanisms of other reaction types that are included in this chapter will be considered in the appropriate subsections along with their chemistry. One can, in principle, envisage two extreme mechanistic pathways for acylation reactions. The interaction of an acyl halide with a Lewis acid can give rise to two donor–acceptor complexes that can be in equilibrium with an acylium ion, as shown in equation (1). Which species is the acylating agent will depend on the structure of the acyl halide, the Lewis acid and the solvent. The interaction of the aromatic substrate with a donor–acceptor complex can lead to a product *via* a transition state that resembles that of an S_N1 reaction of an alkyl halide. Reaction involving an acylium ion may be compared with an S_N1 reaction involving a carbenium ion. It is possible that in between the two extremes reactions proceed that involve tight ion pairs. The effect of an electron-releasing substituent will normally lead, in a benzene derivative, to substitution *ortho* and/or *para* to the group. It is clear that the former transition state will be more sterically demanding than the latter transition state and so differing regioselectivities may be expected to arise from the two mechanistic extremes. A donor–acceptor complex will be expected to afford mainly, and in some cases exclusively, the *para* derivative in reactions of aromatic compounds that contain electron-releasing substituents. There are a small number of exceptional cases where mixtures of *meta* and *para* isomers are obtained. The acetylation of ethyl phenylacetate with acetyl chloride and aluminum chloride in carbon disulfide is one such case.[6]



(1)

A considerable amount of research has been concerned with the nature of the electrophiles that are involved in Friedel–Crafts acylation reactions. We will summarize the main points. Acyl halides and carboxylic acid anhydrides have been known, for many years, to form stable complexes with a variety of acid catalysts. A well-defined product is formed between acetyl fluoride and boron trifluoride at low temperatures. Analytical and conductivity data characterized the material as acetylium tetrafluoroborate,[7] and this was further confirmed by IR measurements.[8] In the system acetyl chloride–aluminum chloride the acetylium ion can be differentiated from the donor–acceptor complex involving the carbonyl group by means of their IR carbonyl stetching frequencies.[9] A number of other acyl fluorides have been shown to form well-defined acylium salts by interaction with a number of metal fluorides. Acylium salts can also be prepared from acyl chlorides by means of metathetical reactions involving anhydrous salts such as silver hexafluoroantimonate. As well as characterization by means of IR spectroscopy, acylium salts have been studied in non-nucleophilic solvents by NMR spectroscopy. The ^{13}C NMR data for the ben-

zoylium ion[10] show why that ion is relatively stable. Considerable delocalization of the positive charge to the *ortho* and *para* positions and away from the *ipso* position, which has some ketene-like character, is indicated by the chemical shifts (δ_C = 87.7 (C-1), 141.3 (C-2), 132.9 (C-3), 149.9 (C-4), and 154.8 (C=O) p.p.m.).

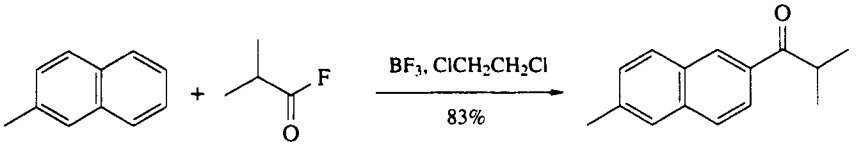
Kinetic studies of acylation reactions are somewhat limited by the insolubility of the acyl halide–Lewis acid complexes in many of the solvent systems that are used. However, useful results have been obtained and, as far as we are concerned, relative rates of reactions are of greater importance than absolute values. In any case it is not possible to distinguish between the two mechanistic extremes on the basis of the observed kinetics.[11] Friedel–Crafts acylations are generally characterized by high substrate selectivity and frequently by high positional selectivity. Relative rate data show, as expected, that toluene is more reactive than benzene and that *m*-xylene is the most reactive of the dimethylbenzenes. Values, relative to benzene, for benzoylation catalyzed by aluminum chloride were: *t*-butylbenzene (72), toluene (1.1×10^2), *p*-xylene (1.4×10^2), *o*-xylene (1.12×10^3), and *m*-xylene (3.94×10^3). Competition data for the trifluoroacetylation of a number of heterocycles using trifluoroacetic anhydride at 75 °C gave the relative rates: thiophene (1.0), furan (1.4×10^2), 2-methylfuran (1.2×10^5) and pyrrole (5.3×10^7).[12]

3.2.3 REAGENT SYSTEMS

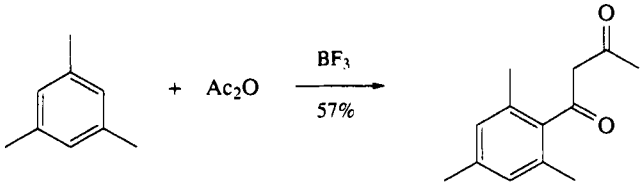
3.2.3.1 Catalysts

It is normally assumed that anhydrous conditions are required in order to carry out Friedel–Crafts reactions. However, it is very difficult to obtain a Lewis acid in a completely anhydrous state. In fact, traces of moisture are found to accelerate the reactions that are catalyzed by some Lewis acids, such as aluminum chloride. Water functions as a cocatalyst. The effectiveness of a catalyst depends on its purity and it is not unusual for what is apparently the same catalyst to give different yields of products when the catalyst is purchased from different suppliers. It is impossible to establish a scale for the effectiveness of Lewis acids for all Friedel–Crafts acylation reactions. An indication of the range and relative reactivity of some Lewis acids is given by the relative efficiency of the following metal chlorides in catalyzing the reaction between acetyl chloride and toluene: $ZnCl_2 < BiCl_3 < TeCl_4 < TiCl_4 < SnCl_4 < TeCl_2 < FeCl_3 < SbCl_5 < AlCl_3$.[13] In spite of the foregoing reservations about establishing a generally applicable sequence, aluminum chloride and aluminum bromide are the most effective catalysts. We will exemplify the use of aluminum halides when we consider the acylating reagent in more detail.

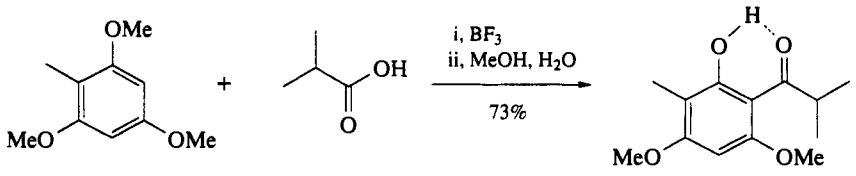
We have mentioned the use of boron trifluoride as a reagent together with an acyl fluoride. Good regioselectivity has been reported for a number of reactions that give mixtures of products when using aluminum chloride as the catalyst. The reaction of isobutyryl fluoride with 2-methylnaphthalene gives an 83% yield of the product shown in equation (2).[14] Boron trichloride has also been used as a catalyst in the benzoylation of *m*-methoxyphenol in high yield *ortho* to the hydroxy group.[15] This type of catalyst can, however, give rise to problems associated with side chain acylation as exemplified by the reaction of mesitylene with acetic anhydride in the presence of boron trifluoride (equation 3).[16] Carboxylic acids have also been used in reactions of phenols[17] and aryl ethers[18] (equation 4) together with boron trifluoride. Dealkylation of an ether residue *ortho* to the introduced acyl group is commonly observed. Advantage was taken of this method in the synthesis of the naturally occurring phenol aurentiacin as shown in equation (5).[19]



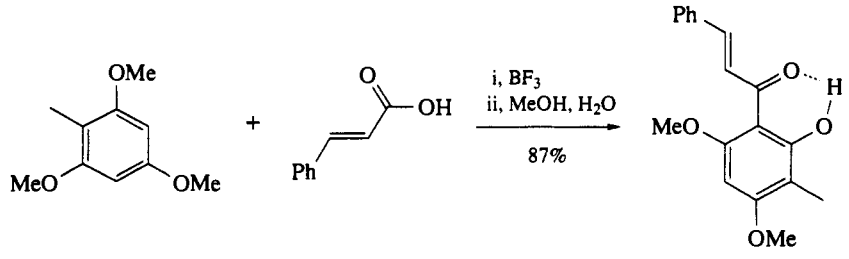
(2)



(3)

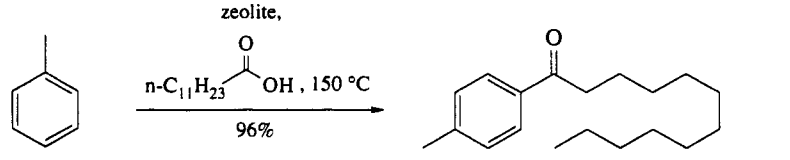


(4)

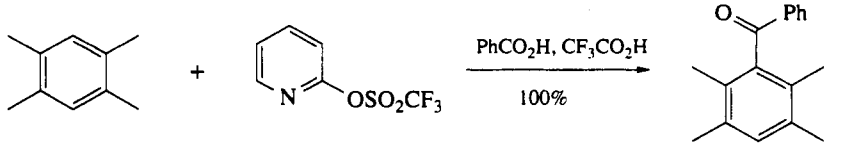


(5)

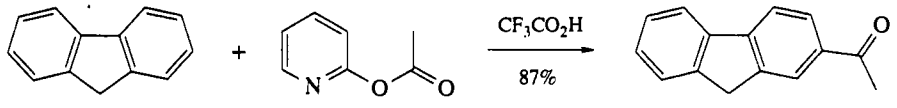
A number of protic acids have been used to catalyze acylation reactions. It is assumed that the reactions involve the generation of acylium ions. Polymeric reagents such as Nafion-H have been used; for example 2-fluorobenzoyl chloride and toluene give the benzophenone derivatives with an *ortho:para* ratio of 4:81.[20] A zeolite-catalyzed acylation (equation 6) has been reported to afford 4-dodecenoyltoluene in 96% yield but the yields are low with short chain carboxylic acids.[21] Early examples of the use of trifluoroacetic[22] and perchloric[23] acids reported good yields of products. Some more recent examples are shown in equations (7) to (9). Phosphoric[27] and polyphosphoric acids[28] have been used together with carboxylic acids (equation 10),[29] anhydrides and acylureas (equation 11).[30]



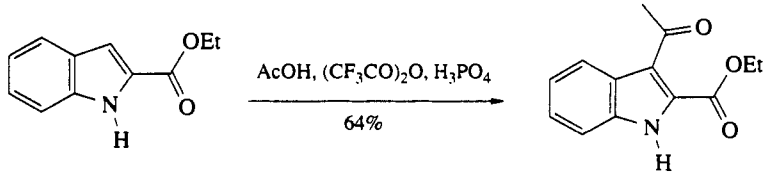
(6)



(7)[24]



(8)[25]



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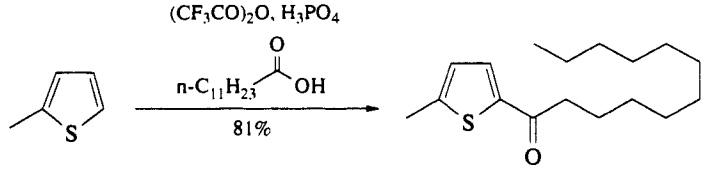

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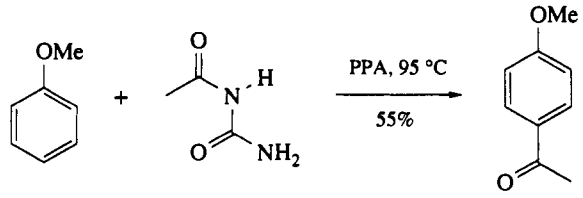
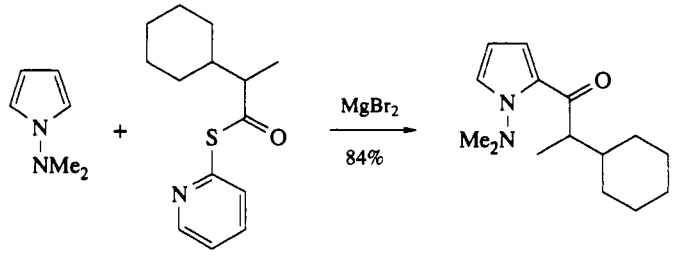


(11)

Other metallic salts and metalloidal compounds have been recommended and in many cases excellent yields are indicated. Thiophene, when heated under reflux with acetic anhydride in the presence of magnesium perchlorate, was reported to give 2-acetylthiophene in 90% yield.[31] 1-Dimethylaminopyrrole is acylated in the 2-position as shown in equation (12) using a thiol ester and magnesium bromide.[32] Veratrole is acylated in the 4-position in high yield by *o*-chlorobenzoyl chloride[33] and 2-benzoylthiophene is obtained in a 90% yield[34] using iodine as the catalyst. Included among the transition metal species that have been used are the chromium(III) chloride–DMSO complex,[35] molybdenum pentachloride[36] and a zirconium catalyst.[37] One of the most interesting recent developments involves the use of selenol esters in reactions catalyzed by copper(I) triflate (equations 13 and 14).[38] 2-Substituted-1,3-benzoxathiolium salts react with electron-rich aromatic species to afford very high yields of ketones in a two-step process.[39] It is interesting to compare the acylations of 1-methylindole shown in equations (13) and (15). *O*-Acetyldiethyloxonium hexachloroantimonate acetylates anisole as shown in equation (16).[40]



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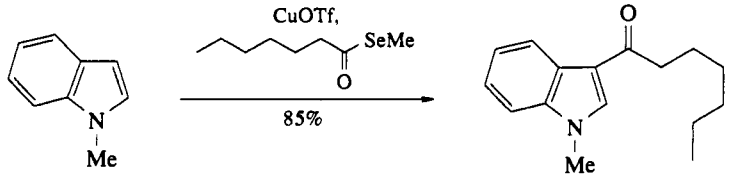

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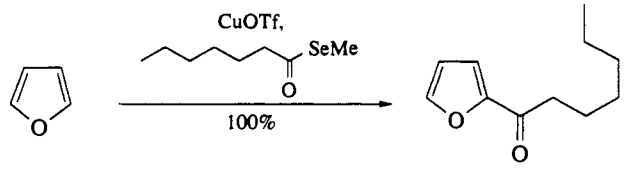

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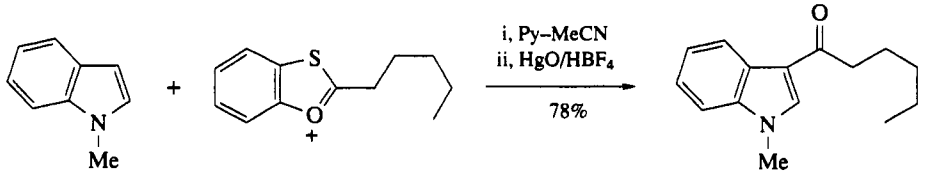

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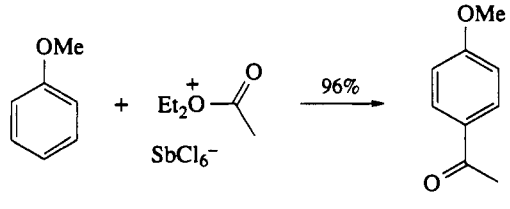
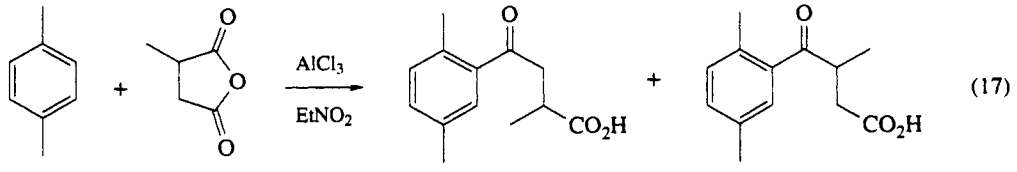


(16)

3.2.3.2 Solvents

The choice of solvent for a Friedel–Crafts acylation reaction is very important. When the substance to be acylated is a cheap liquid, it is frequently convenient to carry out the reaction in an excess of the substrate. This is the case, for example, in the preparation of acetophenone or β-benzoylpropionic acid from benzene. Hydrocarbons are poor solvents for many Lewis acid catalysts and so only act as diluents in two-phase reactions. The possibility of Lewis acid catalyzed protodealkylation or rearrangement of alkyl-substituted benzenes may render them unsuitable for use both as substrate and solvent. The acetylation of *p*-xylene at high temperatures in the absence of another solvent leads to the formation of 2,4-dimethylacetophenone. It is also sensible not to leave reaction mixtures in solution for prolonged periods before the product is isolated. For example, if a reaction mixture containing 2,4-diisopropylacetophenone and aluminum chloride in carbon disulfide is kept at room temperature for several hours, rearrangement and disproportionation reactions take place. Carbon disulfide is one of the best solvents even though reaction rates may be lower than in some other solvents. Other solvents that are frequently used include dichloromethane and 1,2-dichloroethane, although for slow reactions they may themselves function as alkylating agents. Although aluminum chloride is essentially insoluble in these chlorinated hydrocarbons, they do dissolve many of the complexes that are formed between acyl halides and aluminum chloride.

Nitrobenzene and nitroalkanes are good solvents for Friedel–Crafts acylation reactions. As well as being good solvents they also form addition complexes with Lewis acids such as aluminum chloride. The formation of the complex appears to reduce disproportionation and rearrangement reactions and thus allow acylation to be achieved under mild conditions. The acetylation of toluene in nitrobenzene affords more 4-methylacetophenone than when the reaction is conducted in carbon disulfide. These results evidently reflect a lower steric demand in the reaction carried out in carbon disulfide. The reaction shown in equation (17) when carried out in nitrobenzene leads to the formation of the products (**1**) and (**2**) in good yield. However, when the solvent was changed to nitroethane, an improved yield (82%) was obtained and the ratio of (**1**):(**2**) changed from 44:1 to 61:1.[41]



(17)

(1) (2)

3.2.3.3 The Sequence of Addition of the Reagents

In spite of the impression that may have been gained from the earlier part of this chapter, reactions involving the use of aluminum halides, and especially aluminum chloride, constitute the majority of Friedel–Crafts acylation reactions. The interaction of the three components, *i.e.* the acyl halide, the aromatic substrate and the aluminum halide, results in the formation of hydrogen halide and a complex of the aromatic ketone with aluminum halide from which the ketone is liberated after hydrolysis. There are a number of sequences in which the three components can be mixed.

The least satisfactory method involves the addition of an acyl halide to a mixture of the aluminum halide and the aromatic compound (the Bouveault procedure). The problem with this sequence relates to the presence of hydrogen halide, which may be present as a result of the reaction of moisture with the aluminum halide or which will be present in increasing amounts as the reaction proceeds. The hydrogen halide can result in isomerization or disproportionation of, for example, alkylbenzenes.

The most widely used sequence is that developed by Elbs. It is a modification of the method used by Friedel and Crafts in which the catalyst is added as the last reactant.

The prior formation of the reactive species, for example by mixing an acyl halide with aluminum halide, which is then allowed to react with the aromatic substrate, is known as the Perrier procedure. It is normally carried out in a solvent, such as carbon disulfide or dichloromethane, that allows the 1:1 complex to be separated from excess aluminum halide. The main advantage of this method is the solubility of the addition complex in the solvent, but it is frequently observed that the complex of the acylation product and catalyst is insoluble in carbon disulfide and may be separated from soluble by-products. The prior formation of acylium salts mentioned earlier[7–10,42] and their use in the preparation of aromatic ketones can be regarded as a modification of the Perrier procedure.

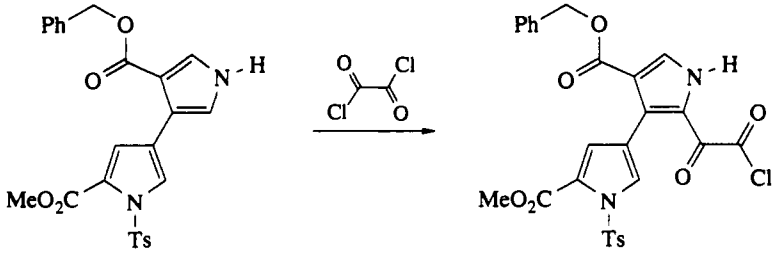
3.2.3.4 Stoichiometry and the Catalyst

The alkylation of aromatic compounds using alkyl halides and a Lewis acid only requires a small amount of catalyst. Because Lewis acids form complexes with carbonyl compounds, the Lewis acids are effectively removed from the reagent system to the extent that product is formed. Although an equilibrium exists between the product complex and free Lewis acid, there is an apparent inhibition of formation of the acylating species. The net effect is that the amount of the ketone that is formed is normally proportional to the molar quantity of catalyst added. In reactions using acyl halides, completion occurs when slightly more than 1 mol of catalyst is used. When using a carboxylic anhydride, an excess over 2 mol of catalyst will usually be required because the other product, a carboxylic acid, will also complex with the Lewis acid.

3.2.4 ACYLATION REACTIONS

3.2.4.1 Reactions Carried Out in the Absence of Catalysts

Very electron-rich aromatic systems interact with acid chlorides and anhydrides in the absence of a catalyst to afford good yields of ketones. Reactions of pyrrole[43a] and substituted pyrroles[43b] exemplify these reactions. The oxalylation shown in equation (18)[44] was part of the synthesis of a complex, highly functionalized antitumor agent. Use of the triisopropylsilyl group to direct reaction to the 3-position (equation 19) is noteworthy.[45]



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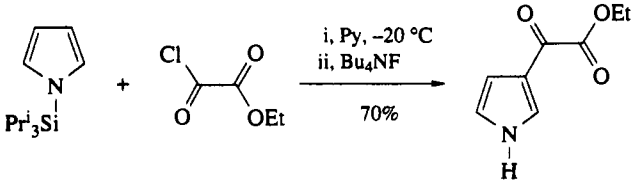
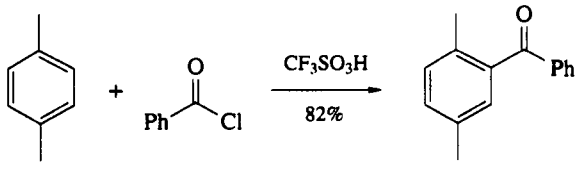


(19)

The use of heptafluorobutanoyl chloride[46] in a reaction with *N,N*-diethylaniline pointed the way towards the development of mixed anhydrides that have a very good leaving group. The formation of 2-acetylthiophene in 69% yield using acetylmethanesulfonic anhydride[47] and of 2-acetylfuran in 96% yield using acetyltoluene-*p*-sulfonic anhydride[48] exemplify this principle. The addition of 1% trifluoromethanesulfonic acid (triflic acid) to solutions of acyl chlorides in a number of benzene derivatives led to the formation of ketones in good yields.[49] For example, *p*-xylene and benzoyl chloride gave 2,5-dimethylbenzophenone in 82% yield (equation 20). Similar results have been obtained using nonafluorobutanesulfonic acid.[50] The mixed anhydrides formed between carboxylic acids and triflic acid have also been shown to be very powerful acylating agents (equation 21)[51] and the triflic acid can be recovered almost quantitatively as the barium salt. Kinetic studies of reactions of carboxylic acids in triflic acid suggest



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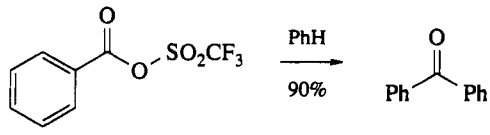

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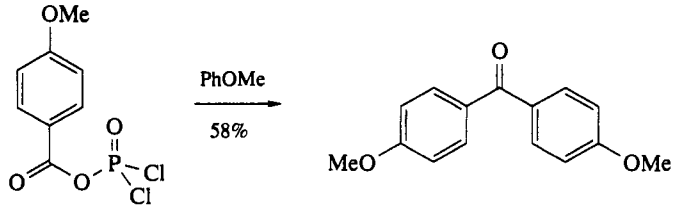

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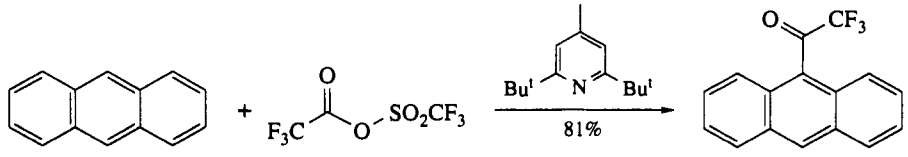


(23)

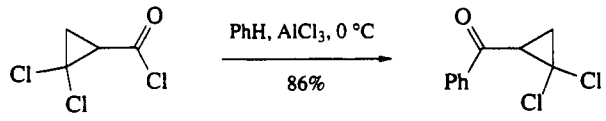
that protonated mixed anhydrides are the probable precursors to the electrophiles involved in the acylation reactions.[52] Aryl ketones may also be prepared from alkyl and aryl carboxylic dichlorophosphoric anhydrides in reactions with electron-rich compounds such as anisole (equation 22).[53] Trifluoroacetyl trifluoromethanesulfonate is capable of the uncatalyzed trifluoroacetylation of a variety of aromatic rings (equation 23).[54]

3.2.4.2 Reactions Using Lewis Acid Catalysts

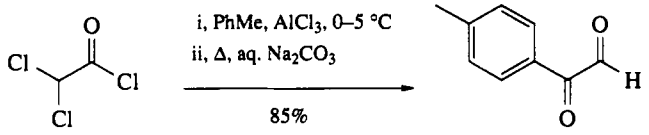
3.2.4.2.1 Reactions using acyl halides

The use of an acyl chloride in the presence of aluminum chloride constitutes the most frequently used type of Friedel–Crafts ketone synthesis. Many examples from the earlier literature are reported in the reviews mentioned at the beginning of this chapter.[1,2] The reactivity of acyl halides in reactions of acyl halides with aluminum halides decreases in the order I > Br > Cl > F, but a different order was reported for reactions catalyzed by boron halides. In the latter case the order was acyl fluoride > acyl bromide > acyl chloride. We shall concentrate our attention on recently reported examples.

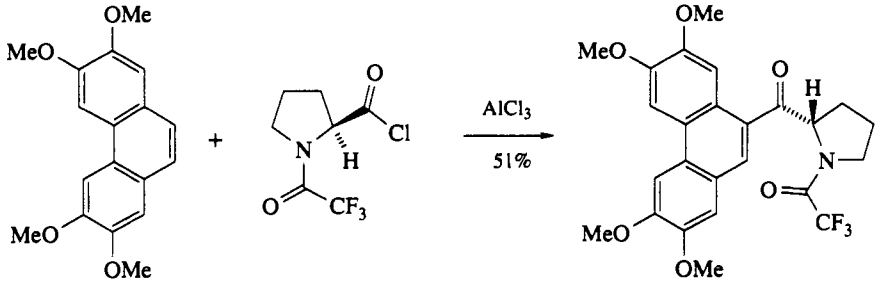
A very wide range of acyl chlorides interact with aluminum chloride to afford good to excellent yields with both carbocyclic and heterocyclic aromatic compounds. The use of aluminum chloride is implied in the examples quoted in this section. Acetophenone was formed in 97% yield in a reaction of benzene with acetyl chloride carried out at 15–20 °C in which air was passed through the reaction mixture to remove hydrogen chloride.[55] Propionyl chloride reacts with 2-bromonaphthalene and results in substitution at the 6-position[56] and veratrole affords 3,4-dimethoxyacetophenone.[57] Isobutyryl chloride[58] reacts with 4-bromoanisole at the 2-position and pivaloyl chloride reacts *para* to the methyl group with *o*-cresol methyl ether.[59] It is not unusual for decarbonylation to occur with the latter acyl chloride and *t*-butylation of the aromatic substrate is then a problem. Likewise protio-de-*t*-butylation does sometimes occur. For example, the benzoylation of 4-*t*-butylanisole results in the formation of 2-hydroxybenzophenone.[60] The presence of halogens in the alkyl residue of the acyl halide[61] may cause no significant problem and may prove useful as shown in equations (24) and (25). Other types of functionality can be tolerated in both the aromatic compound (for example tyrosine)[62] and in the acylating agent. The use of *N*-(trifluoroacetyl)-α-amino acid chlorides has been reported in the preparation of α-arylalkylamines,[63a] and in a synthesis of (*S*)-(+)-tylophorine the reaction of (*S*)-*N*-(trifluoroacetyl)prolyl chloride to yield the ketone shown in equation (26) is the key step.[63b] Protection of the amino function with the trifluoroacetyl group gives much better results than those obtained with other acyl and sulfonyl groups that have been investigated. Decarbonylation occurs rapidly at room temperature with a number of tertiary amino acid chlorides and *N*-sulfonylated acid chlorides in the presence of Lewis acids.



(24) [61c]

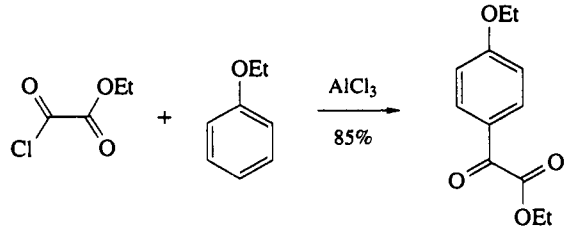


(25) [61d]



(26)

The acylation of aryl ethers and sulfides is widely used. The acylation of phenyl methyl sulfide[64] using 100 mol % of aluminum chloride gives the maximum yield and *para* selectivity.[64b] It has also been shown that acylation of a number of aryl alkyl ethers proceeds rapidly and in high yield with 100 mol % of catalyst but that reaction is arrested with a large excess of catalyst.[65] The reactions were studied using aluminum bromide because that catalyst allowed a more precise control of the stoichiometry than would be the case with aluminum chloride. The reactions using acetyl chloride in *o*-dichlorobenzene were almost quantitative using 100 mol % aluminum bromide, but the inhibiting effect of an excess of the catalyst was so great that the solvent then became the reactant. In a competition reaction an equimolar mixture of benzene and veratrole was allowed to react at room temperature with 200 mol % of acetyl chloride and 400 mol % of aluminum bromide in *o*-dichlorobenzene. After 1 h more than 95% of the benzene had been consumed and acetophenone was the only product detected by gas chromatography. Methylenedioxybenzene and benzene gave similar results. The ketal formed between catechol and 2,4-dimethylpentan-3-one is acylated particularly easily and does not suffer the inhibition effect. The inhibition is evidently due to coordination of the Lewis acid with the methyl ether and methylenedioxy functions. Acylation with some half-ester half-acid chlorides and some diacid chlorides proceeds satisfactorily. Ethyl oxalyl chloride gives a good yield of the expected product using phenetole (equation 27),[66] and adipoyl chloride gave a reasonable yield using catechol (equation 28).[67] It is not unusual to



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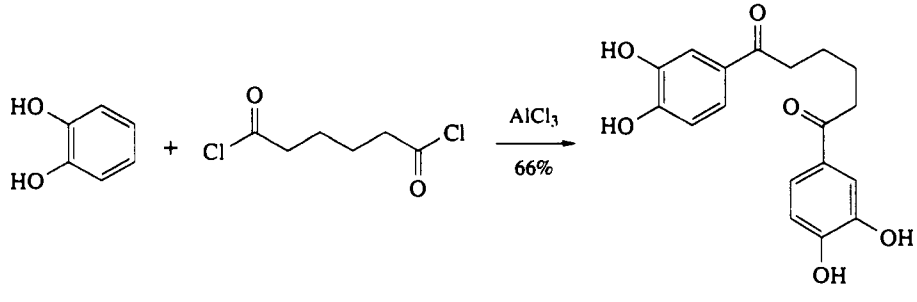

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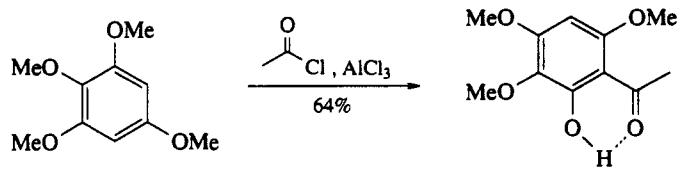

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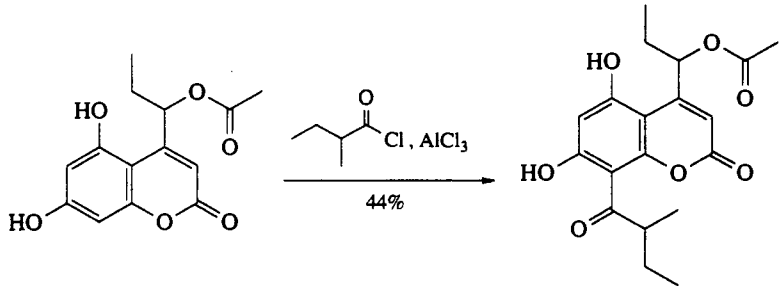

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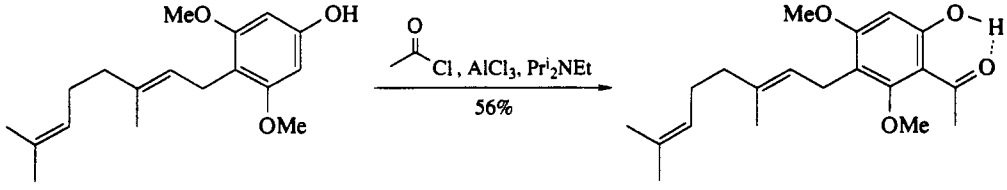
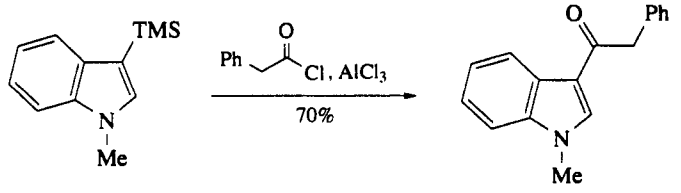


(31)

find that dealkylation of an ether function occurs when an *o*-acyl group is introduced. This effect is exemplified in equation (29).[68] Difficulties are sometimes experienced with highly functionalized compounds. The product shown in equation (30) was obtained in 44% yield,[69] and a 56% yield of the product shown in equation (31) was obtained after sonication.[70]

Problems have been observed when attempting to carry out reactions with either diacid chlorides or half-ester half-acid chlorides when the two carbonyl functions are separated by either two or three carbon atoms. Rearrangement reactions occur with those compounds and so Friedel–Crafts acylation reactions may yield mixtures of products.[71] Optically active methyl 3-methylglutarate was shown to racemize easily.[72] Suggested explanations of these effects include the involvement of alkyl diacyloxonium and acyloxy–alkoxycarbenium ions. ^{13}C NMR studies have shown that the half methyl ester–half acid chloride from phthalic acid forms the acyloxy–alkoxycarbenium ion very easily,[73] and that the related ions derived from succinic and glutaric acids can also be generated under stable ion conditions.[74]

The Friedel–Crafts acylation reactions of simple indoles and pyrroles leads to the formation of 3- and 2-substituted products, respectively. Ketones can be prepared from sodium salts of carboxylic acids in a 'one pot' process. Sodium pyridine-3-carboxylate reacts with phosphoryl chloride/DMF and then with aluminum chloride at low temperature in the presence of 2-isopropylindole to afford the 3-substituted indolyl ketone in 81% yield.[75] A particularly mild method for the introduction of a 3-acyl residue into *N*-methylindole involves electrophilic desilylation as shown in equation (32).[76] The *ipso* replacement of a silyl group is particularly useful for controlling the position of entry when using strong electrophiles. 1-Acetyl-4-trimethylsilylindole reacts with 3-chloropropanoyl chloride as shown in equation (33).[77] The replacement of the silyl residue is finely balanced *versus* attack at the 3-position. Deactivation of the heterocyclic ring is necessary if *ipso* replacement is required. It is also of interest to compare the reactivity of an acylating agent with that of a Mannich reagent (Volume 2, Chapter 4.2). The replacement of the silyl residue would not occur in a Mannich reaction. It is worth noting at this point that the replacement



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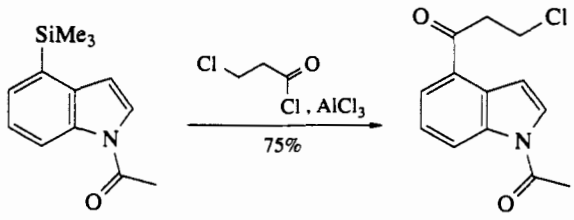

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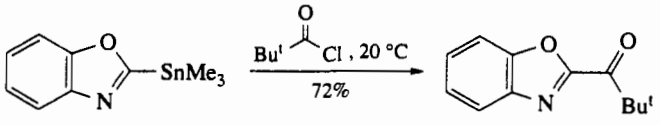
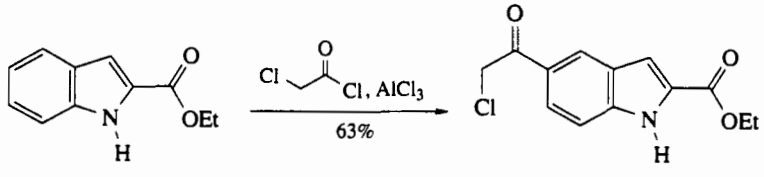


(34)

of a stannyl residue can be effected even more easily.[78] 2-Trimethylstannyl-pyridine and -quinoline and 1-trimethylstannylisoquinoline react with acyl chlorides in the absence of a catalyst,[79] and the benzoxazole shown in equation (34) reacts with pivaloyl chloride to give the expected ketone in 72% yield.[80]

Although reactions of indoles with electrophiles normally take place at the 3-position, the use of a strong electrophile and the presence of an electron-withdrawing group in the heterocyclic ring can lead to substitution at the 5-position. This effect is demonstrated as shown in equations (35) and (36).



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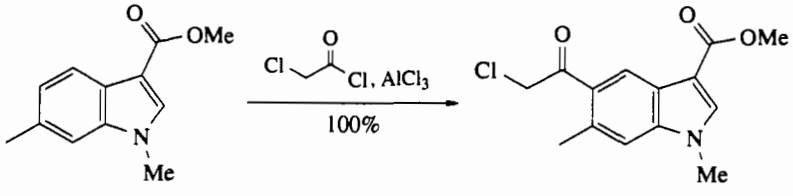
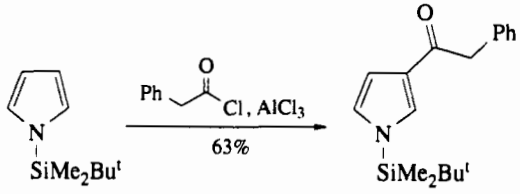


(36)[82]

The introduction of substituents at the 3-position in pyrrole is a desirable objective that has been addressed recently. The method that is mostly used depends on a steric effect being caused by *N*-substitution. The reaction of *N*-methylpyrrole with pivaloyl chloride and tin(IV) chloride rather surprisingly was reported to give 3-*N*-methylpyrryl *t*-butyl ketone in 33% yield.[83] 1-Benzenesulfonylpyrrole is deactivated towards electrophilic attack as well as being to some extent sterically hindered; eneamine-like reactivity may be anticipated. In a reaction with benzoyl chloride and aluminum chloride no 2-acylation was observed.[84] In the reaction of 1-TBDMS-pyrrole (equation 37)[85] with phenylacetyl chloride the effect is presumably exclusively steric in origin. In the case of heavily substituted pyrroles, ester functions (equation 38) do not reduce the reactivity enough to prevent reaction at the 3-position.[86] In the case of pyrroles that are substituted with an electron-withdrawing group at the 2-position, further substitution will be directed to the 4-position which, after removal of the directing group, then effectively becomes the 3-position, as shown in equation (39).[87]



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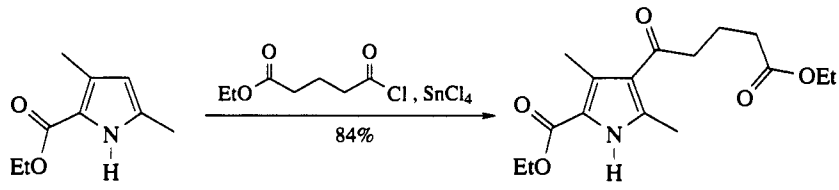

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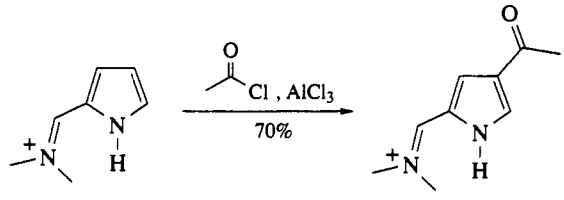


(39)

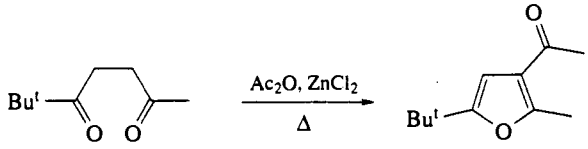
Other derivatives of carboxylic acids and some unusual catalyst systems have found favor. Diarylboryl hexachloroantimonates activate acyl chlorides, carboxylic anhydrides and acyl enolates.[88] A number of metal oxides have been successfully employed.[89] It is worth noting at this point that the chloroacetylium and bromoacetylium ions, which can be prepared in either Freon 113 or sulfur dioxide, are more stable than the acetylium ion and have been shown to give high yields of ketones at low temperatures.[90]

3.2.4.2.2 Reactions using other derivatives of carboxylic acids

We have already considered the use of mixed anhydrides and so in this section we shall be concerned with homocarboxylic anhydrides. The use of anhydrides constitutes the most frequently reported method after the use of an acyl chloride and aluminum chloride. Anhydrides from monocarboxylic acids yield ketones, and cyclic anhydrides derived from dicarboxylic acids afford keto acids. Very nucleophilic aromatic compounds react with trifluoroacetic anhydride in the absence of a catalyst. The confirmation of aromatic character invariably involves establishing reactivity towards a range of electrophiles. Trifluoroacetic anhydride reacts with homoazulene in the presence of an excess of triethylamine to afford 1-trifluoroacetylhomoazulene in 91–95% yield.[91] The preparations of 3-aroylpropanoic acids from succinic anhydride and 4-aroylbutanoic acids from glutaric anhydride have been known for many years.[92] Maleic anhydride can be used in a similar way to prepare 3-aroylacrylic acids. We will now concentrate our attention on more recent examples.

Acetic anhydride and aluminum chloride in carbon disulfide gives a high yield of the *para*-acylated product with thioanisole,[93] and in dichloromethane the same reagents give an almost quantitative yield of 3-acetyl-1-benzenesulfonylindole.[94] Acylation of more nucleophilic heterocycles can be achieved using milder catalysts, such as zinc chloride. It has been known for some time that furan can be acylated very efficiently using acetic anhydride and zinc chloride. The Paal–Knorr furan synthesis (1,4-diketone, acetic anhydride and zinc chloride) can sometimes result in acylation as well as cyclization (equation 40).[95] Equations (41) and (42) further exemplify the acylation of furan derivatives that have been used in the synthesis of cytotoxic furanonaphthoquinones.

1-Acetylpyrazole has been used in high-boiling petrol together with aluminum chloride in the *C*-acetylation of phenol[98] and the use of oxazolones (equation 43) results in the formation of acylamino ketones.[99] Enol lactones have been used in the preparation of 1,4-diketones.[100]



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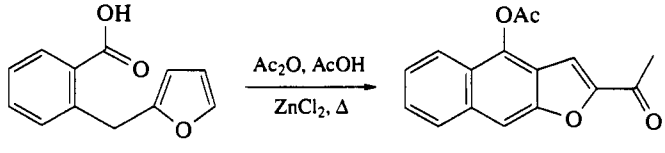
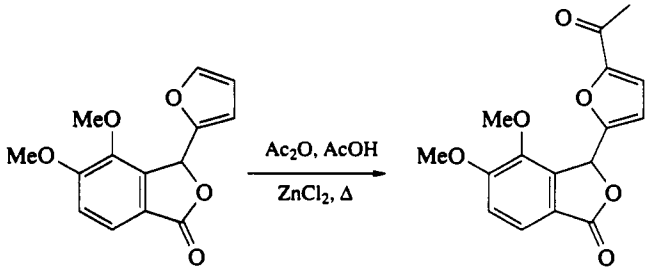
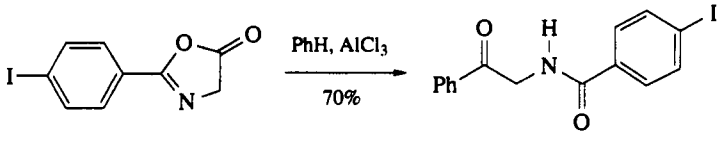


(41)[96]



(42)[97]



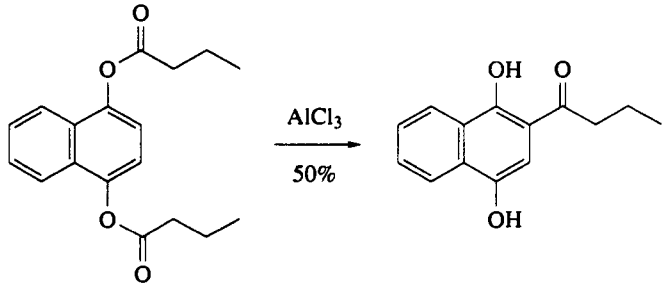
(43)[99]

3.2.4.2.3 Rearrangement and transacylation reactions

We have mentioned previously the possibility of rearrangement of the substrate; for example, the rearrangement of 2,4,6-trimethylacetophenone to afford the 2,4,5 and 3,4,5 isomers. There is also the possibility, especially with highly substituted compounds, that the acylation reaction may be reversible. The reaction of acetyldurene with aluminum chloride that results in the formation of diacetyldurene and durene was the first reported example.[101] Protiodeacylation–reacylation is evidently involved. A number of hindered ketones interact with a variety of Lewis acids in transacylation reactions. Acetyldurene and mesitylene undergo transacylation in the presence of 2 mol equiv. of aluminum chloride[102] and 2,3,5,6-tetramethylacetophenone interacts with aluminum chloride and anisole to give 4-methoxyacetophenone and durene.[103] Examples are also known in which heterocyclic ketones rearrange. For example, 2-acetyl-1-methylpyrrole gives the 3-isomer in 80% yield on treatment with trifluoroacetic acid, and 2-(4′-chlorobenzoyl)-1,3,5-trimethylpyrrole rearranges slowly in trifluoroacetic acid to 3-(4′-chlorobenzoyl)-1,2,4-trimethylpyrrole.[104] Protiodeacetylation has been studied using Nafion-H but no acetyl transfer was observed.[105] The method may prove to be useful as a method of temporarily protecting a specific position in an aromatic compound that has a number of electron-releasing substituents. The kinetics of acetyl exchange in acetylmesitylene and deuterium labeling has shown that *ipso* acetyl exchange is important.[106]

3.2.5 FRIES REACTIONS

Acid-catalyzed reactions of the phenol esters resulting in the formation of phenolic ketones are known as Fries rearrangements. Aluminum chloride was the first catalyst used but other Lewis acids are also effective. Examples from the recent literature are shown in equations (44) to (48). A nitrogen analog, that is the rearrangement of an acyl derivative of an arylamine, is shown in equation (49). Photo–Fries rearrangement reactions have also been studied in detail and are exemplified in equations (50) to (55).



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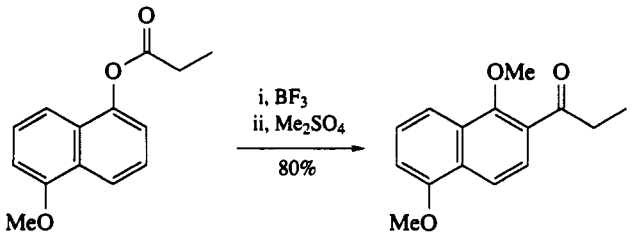

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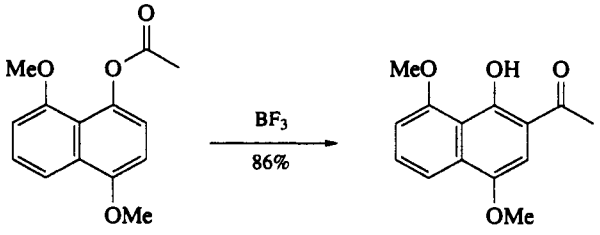

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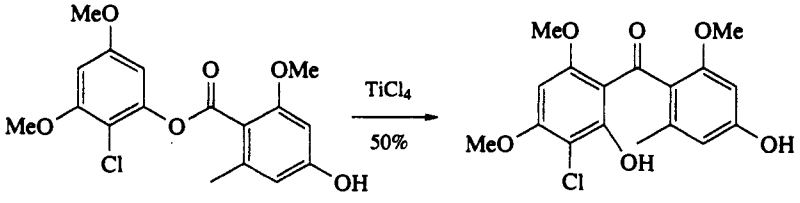

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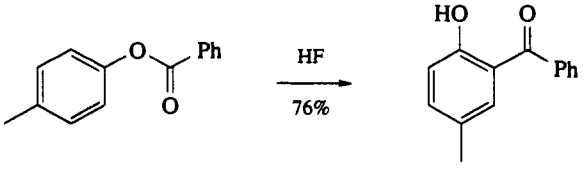

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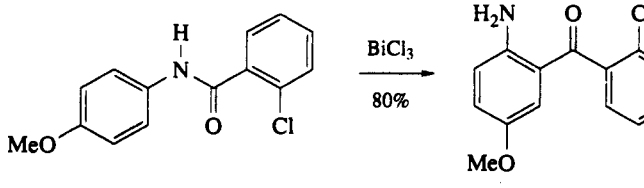

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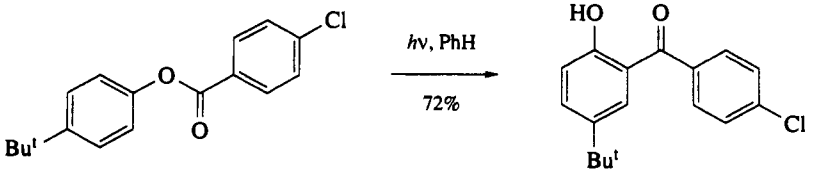

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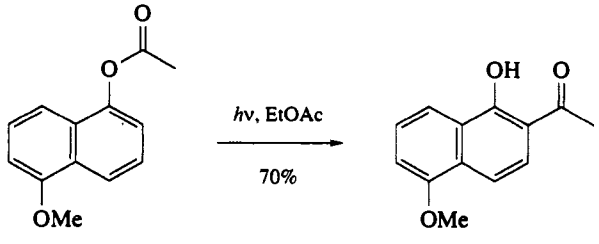

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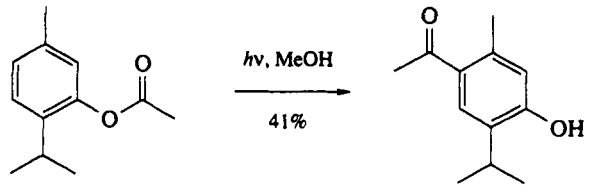
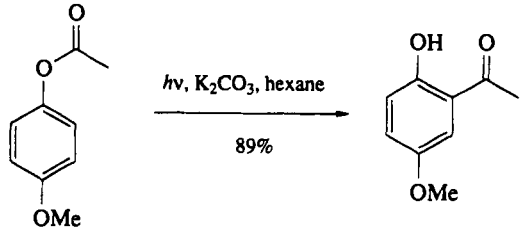


(52)[115]



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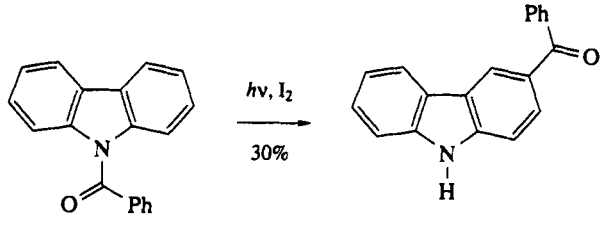

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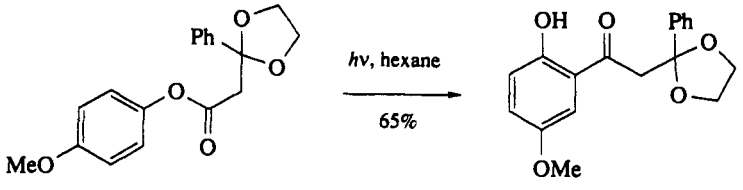
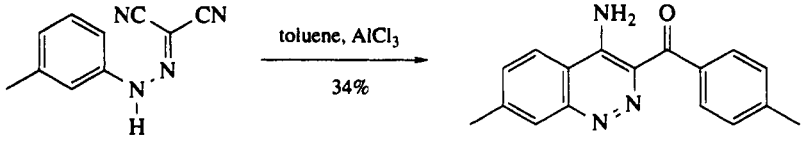


(55)[118]

3.2.6 REACTIONS USING NITRILES — THE HOUBEN–HOESCH SYNTHESIS

The acylation of aromatic compounds can be achieved by a modification of the Gattermann reaction in which an alkyl or an aryl cyanide replaces hydrogen cyanide.[119] Although zinc chloride was originally the most frequently used catalyst, boron trichloride has often been used in recent studies. The initially formed ketiminium salt is hydrolyzed to give the ketone. In reactions of benzenoid derivatives that lack strong electron-releasing substituents the nitrile must contain an electron-attracting group that increases the electrophilicity of the reactive species. The catalyst is presumed to coordinate with the nitrile function to generate the electrophile. Benzene, for example, reacts with dichloroacetonitrile and aluminum chloride to afford ω,ω-dichloroacetophenone. An interesting intramolecular Houben–Hoesch reaction



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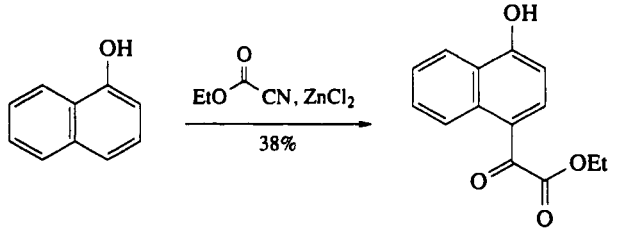
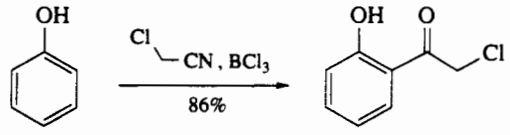
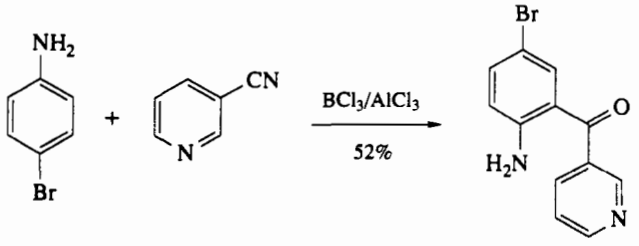


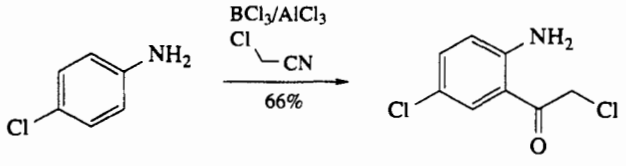
(57)[121]



(58)[122]



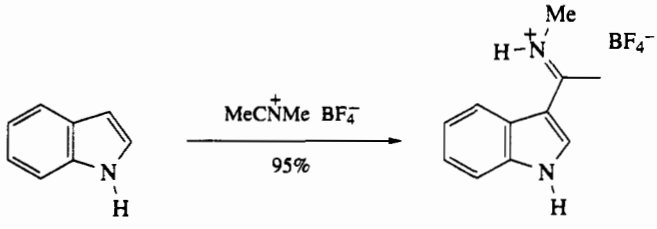
(59)[123]



(60)

followed by an intermolecular version is shown in equation (56).[120] The method works well with phenols and arylamines as shown in equations (57) to (59), and has been developed into a new indole synthesis by modification of the type of product shown in equation (60).[124]

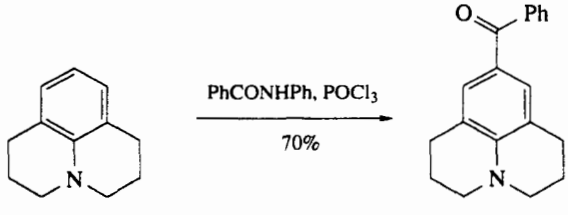
The possibility of using *N*-alkylnitrilium salts as acyl cation equivalents has been investigated by allowing nitriles to react with methyl triflate and a nucleophilic aromatic derivative such as 1,3-dimethoxybenzene.[125] *N*-Methylnitrilium salts have also been made by warming nitriles with trimethyloxonium fluoroborate. Subsequent reactions with pyrroles and indoles gave the expected iminium salts in excellent yields, as shown in equation (61).[126]



(61)

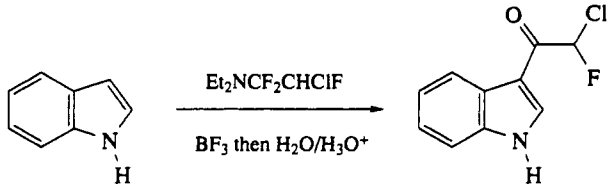
3.2.7 VILSMEIER AND RELATED KETONE SYNTHESES

The relationship between the formylation reactions carried out with formamide derivatives and the formation of ketones when using amides of other carboxylic acids has been pointed out.[127] The method has not been as widely exploited as one might have expected. *N*-Methylacetamide and *N,N*-dimethylacetamide both give substituted acetophenones when they are allowed to interact with phosphoryl chloride in the presence of nucleophilic benzene derivatives. The initial product has to be hydrolyzed. Similarly, benzamide derivatives give substituted benzophenones as exemplified in equation (62).[128]



(62)

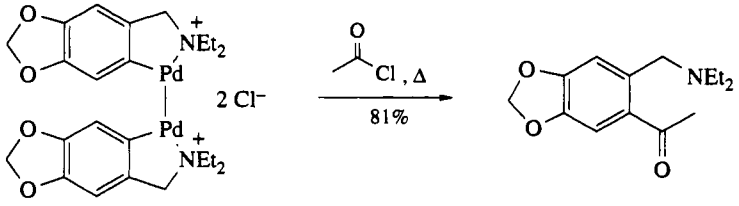
1,1-Dihaloalkylamines are dehalogenated by Lewis acids and react in a manner that is reminiscent of the Vilsmeier reaction. We show an example in equation (63).[129] The Lewis acid catalyzed dihaloalkylation reactions of, for example, phenyltrichloromethane can be regarded as a further extension.[130]



(63)

3.2.8 PALLADIUM-MEDIATED KETONE SYNTHESES

A number of *ortho*-palladated *N,N*-dialkylbenzylamines have been shown to react with acetyl or benzoyl chloride to form *o*-dialkylaminomethylaryl ketones.[131] The yields reported were in the range 60–90%. The example shown in equation (64) is representative. Other examples have extended the scope of the reaction.[132]



(64)

Acid chlorides couple with arylstannanes to form ketones in HMPA solution in the presence of chlorobis(triphenylphosphinebenzyl)palladium.[133] The same methodology has been used as part of a very efficient synthesis of manoalide and its *seco* derivative.[134] The coupling of aroyl chlorides with benzylzinc bromides also produces arylbenzyl ketones under palladium catalysis.[135] The benzylzinc bromides are formed '*in situ*'.

3.2.9 GATTERMANN AND RELATED FORMYLATION REACTIONS

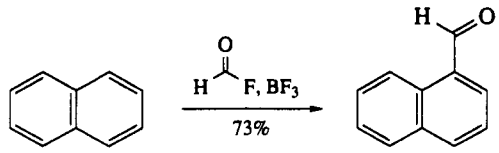
We include in this section formylation reactions involving carbon monoxide, hydrogen cyanide, formyl fluoride and dichloromethyl alkyl ethers.[119] The Vilsmeier and Reimer–Tiemann formylation reactions are the subjects of other chapters (Volume 2, Chapters 3.4 and 3.5).

Formylation of benzene and simple alkylbenzenes can be achieved in good yields using carbon monoxide, hydrogen chloride and aluminum chloride at high pressures ($1–2.5 \times 10^7$ Pa). The reactions can be carried out at atmospheric pressure in the presence of copper(I) chloride, which apparently provides a high local concentration of carbon monoxide by coordination. This is known as the Gattermann–Koch reaction. The reaction functions as if formyl chloride ionizes to give the formylium ion and this is the presumed electrophile. However, the high yields of 4-formylalkylbenzenes suggests that a bulkier electrophile is involved. The reagent mixture is conveniently generated by the action of chlorosulfuric acid on formic acid. Formyl chloride is known to be very unstable; it may be generated from *N*-formylimidazole by reaction with hydrogen chloride in dichloromethane at –65 °C.

Benzene and toluene afford benzaldehyde and *p*-tolualdehyde in 90% and 85% yield respectively using the atmospheric pressure methods, and biphenyl has been converted into 4-formylbiphenyl in yields as high as 73%. With some alkylbenzenes there is, however, a tendency for dealkylation or transalkylation reactions to occur during the course of the reactions. Thus *p*-xylene gives 2,4-dimethylbenzaldehyde and triisopropylbenzene gives only diisopropylbenzaldehydes. Naphthalene appears not to give a naphthaldehyde.

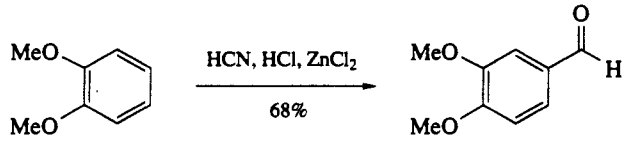
A useful modification of this reaction involves the use of formyl fluoride, which is prepared by the reaction of the mixed anhydride of formic and acetic acids with anhydrous hydrogen fluoride. The formyl fluoride is continuously removed (b.p. –29 °C) as it is formed. Formyl fluoride and boron trifluoride do react with naphthalene to give 1-naphthaldehyde in 73% yield (equation 65).[136]

Formylation using zinc(II) cyanide and hydrogen chloride is known as the Gattermann reaction. Whereas the Gattermann–Koch method fails with phenols and aryl ethers, this method does give good



(65)

yields. The original method used hydrogen cyanide, hydrogen chloride and a Lewis acid such as zinc(II) chloride. The reaction shown in equation (66) is typical. The mechanism of the Gattermann reaction is obscure but aldiminium salts are the initial products and are then hydrolyzed to give the aldehydes. The electrophile may be a formimidium complex with the Lewis acid catalyst.



(66)

Arenes such as benzene, biphenyl and naphthalene are formylated using dichloromethyl alkyl ethers in the presence of a Lewis acid. The dichloromethyl alkyl ethers are easily prepared by the reaction of phosphorus pentachloride with alkyl formates. The most frequently used Lewis acids are titanium(IV) chloride and tin(IV) chloride. It is presumed that the electrophiles involved are alkoxychlorocarbenium ions.

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3.3
The Intramolecular Aromatic Friedel–Crafts Reaction

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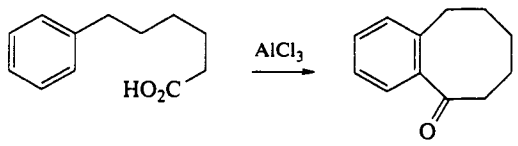
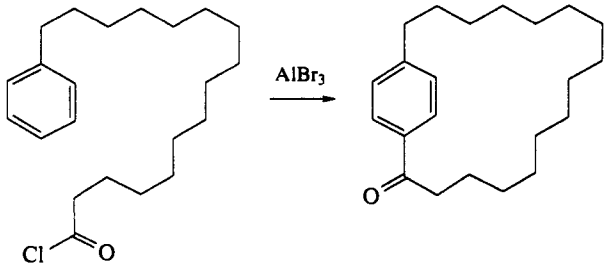
3.3.1 INTRODUCTION

Most of the general features of the intermolecular Friedel–Crafts acylations that are the subject of Volume 2, Chapter 3.2 also apply to the intramolecular versions. The present chapter should be regarded as an extension to the earlier one. The intramolecular Friedel–Crafts reaction has been reviewed previously,[1] including reactions specifically involving the use of polyphosphoric acid.[1c] We will concentrate our attention on more recent examples in order to exemplify the general principles that were also described in those reviews. There is no reason to suppose that the mechanistic considerations that we considered in the earlier chapter do not also apply in the present case. The thermodynamic problems associated with intermolecular reactions result in some important changes to those general features when we consider the intramolecular versions. The enthalpy effect relates to any ring or steric strain that may be present in the transition state leading to cyclization and the entropy effect relates to the ease or difficulty of making the two ends of the reacting system meet. As is the case with the majority of nonradical cyclization reactions, six-membered rings are formed most easily, followed by five- and seven-membered systems. Medium-sized rings are not easily obtained[2] and large-sized rings are only obtained in reasonable yields using high dilution techniques. Thus the conversion of 6-phenylhexanoic acid into the acid chloride and cyclization using aluminum chloride in dichloromethane gave the benzocyclooctenone in only 38% yield (equation 1).[2b] Other reactions leading to the formation of, for example, an eight-membered heterocyclic ring (a benzazocinone),[2c] have also been reported using a procedure[2d] that involves the use of 3 equiv. of aluminum chloride. A reaction of 16-phenylhexadecanoyl chloride with aluminum bromide gave the 20-membered ring product shown in equation (2) in 70% yield using a high dilution procedure.[3] In analogous reactions leading to the formation of 18-, 15- and 13-membered rings the products were obtained in 57%, 30% and 5% yields respectively. Rather surprisingly the cyclization of *o*-β-phenethylphenylacetic acid using polyphosphoric acid gave 2,3,6,7-dibenzocyclooctanone in 93% yield.[4] Presumably this results from the presence of the four sp^3 carbon atoms, which impart significant

rigidity to the molecule and hence increase the chance that the two ends of the reacting system will meet. We will classify the remaining parts of this chapter according to the size of ring produced.



(1)



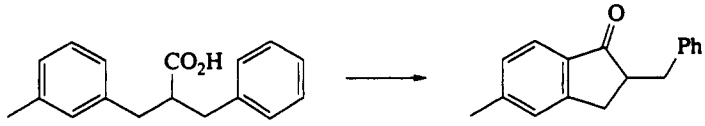
(2)

The most striking difference, by comparison with bimolecular Friedel–Crafts acylation reactions, is that the presence of an acyl group does not necessarily completely inactivate the substrate. Additionally, milder catalysts than were required in the intermolecular reactions may well be more appropriate. The generation of an acylium ion from a carboxylic acid, if it is to be observed at all, normally requires a very strong protic acid. In many intramolecular Friedel–Crafts reactions polyphosphoric or sulfuric acid can be used. The known involvement of mixed anhydrides in intermolecular acylation reactions suggests that a number of the well-known procedures probably also involve the intermediacy of mixed anhydrides. The use of, for example, mixtures of zinc chloride, acetic anhydride and acetic acid represents one such system. Another system that has been investigated involves the use of trifluoroacetic anhydride.[5] The mixed anhydrides that are effective in intermolecular Friedel–Crafts acylation reactions suggest that anhydrides involving other strong acids, such as trifluoromethanesulfonic acid and dichlorophosphoric acid, may well provide additional methodology. It is useful to consider the preparation of the starting materials that are required for intramolecular Friedel–Crafts acylation reactions. Intermolecular acylation using a cyclic anhydride will afford a product that can be cyclized, sometimes after reduction of the ketone function. We will observe, however, that in the case of products obtained from phthalic anhydride and its derivatives, the direct conversion into anthraquinones can be achieved. As was seen in Volume 2, Chapter 3.2, there may be examples when products are obtained that indicate that rearrangement of a reactant or a product has occurred. Examples which are particularly important involve the use of acid chlorides derived from dicarboxylic acids. Thus, phthaloyl chloride reacts with aluminum chloride to afford *pseudo*-phthaloyl chloride and so does not afford a derivative of benzophenone on reaction with benzene. The use of a combination of alkylation followed by intramolecular acylation is a particularly useful strategy that can be effected using lactones as the initial coreactant. The well-known Haworth method for the synthesis of polycyclic hydrocarbons involves succinoylation, reduction of the ketone function and an intramolecular acylation followed by aromatization. We will return to this synthesis in the concluding section. Attention was drawn in the earlier reviews to the variation in yields obtained and their dependence on the purity of the starting materials and the control of the amount of water in the reaction. It is worth reminding ourselves of these factors.

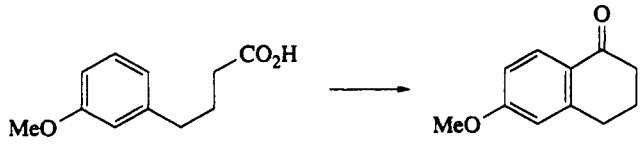
3.3.2 ELECTRON DENSITY CONSIDERATIONS

Electron-releasing substituents have their normal effects on intramolecular acylation reactions. Where cyclization could occur to afford a mixture of products, the one that is formed involves reaction with the more electron-rich ring. The indan-1-one shown in equation (3) was formed in 75% yield, and was the only ketone detected. The strongly electron-releasing methoxy group normally directs substitution to the *para* position as indicated in equation (4). There are, however, examples where coordination of a Lewis acid with methoxy groups results in deactivation of an aryl residue towards intramolecular Friedel–Crafts acylation reactions as was mentioned in Volume 2, Chapter 3.2. Except when using polyphosphoric acid, there is no firm evidence that intramolecular acylation reactions can be reversible and so the cyclization reactions of 2-naphthyl-3′-propanoic and -4′-butanoic acids, as illustrated in equation (5), lead to angu-

larly substituted products by way of the anticipated lower energy transition states. We will return to the question of reversibility in the concluding section.



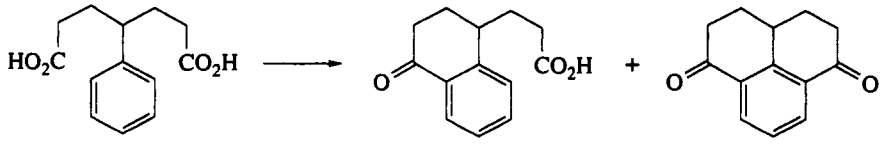
(3)



(4)

(5)

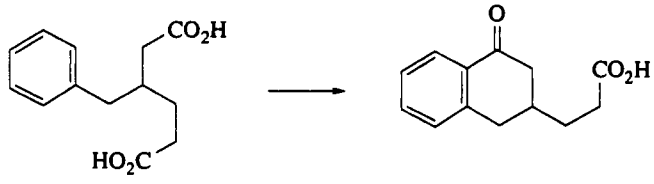
The presence of strongly electron-withdrawing substituents, such as the nitro group, inhibits cyclization when positioned *ortho* or *para*, but, remarkably, the presence of a carbonyl group has less influence and double cyclizations of dicarboxylic acids are not uncommon, as exemplified in equation (6).



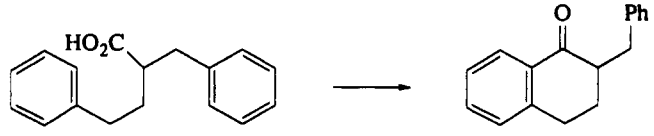
(6)

3.3.3 THE SIZE OF THE RING

Qualitative indications concerning the ease of formation of various ring sizes have been indicated in the Introduction. Early studies using substrates that could give mixtures of products with various ring sizes showed that six-membered ring formation is always preferred over the formation of five- and seven-membered rings (equations 7–9). The examples shown in equations (10) and (11) indicate that indan-1-ones are formed more easily than benzosuberones.



(7)



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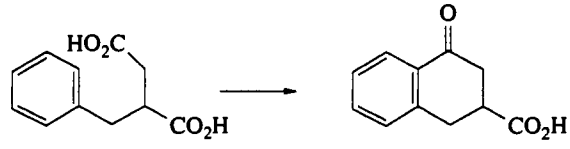
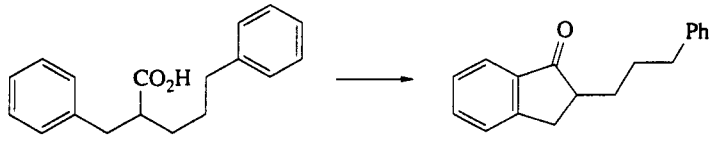


(9)

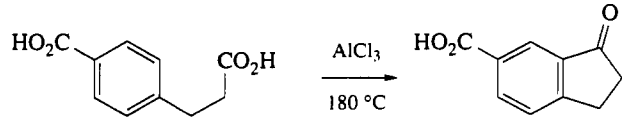
(10)



(11)

3.3.3.1 Reactions Leading to the Formation of Five-membered Rings

A wide variety of cyclopentanone derivatives have been reported and we will restrict ourselves to a general overview. One of the more important earlier papers[6] reported the cyclization of β-phenylpropanoic acid derivatives that contain electron-withdrawing substituents, using a mixture of aluminum chloride and sodium chloride at relatively high temperatures. The catalyst, which may be regarded as sodium tetrachloroaluminate, is more potent than aluminum chloride alone. In the example shown in equation (12), 4-carboxy-β-phenylpropanoic acid was heated at 180 °C with sodium chloride–aluminum chloride and gave indan-1-one-6-carboxylic acid. A detailed study[7] of a number of procedures for the formation of indanones from β-phenylpropanoyl chlorides concluded that the best method involved the portionwise addition of the acid chloride and aluminum chloride to a large volume of dichloromethane. The amount of aluminum chloride was specified precisely. Other procedures, for example using benzene as the solvent, resulted in attack on the solvent. Intermolecular acylation, including the formation of a cyclic tetramer, was also observed. It was concluded that coordination of excess aluminum chloride with the methoxy function deactivates the ring to intramolecular reaction. This effect is also mentioned in Volume 2, Chapter 3.2. Even when using the optimized conditions, 2-methoxy-β-phenylpropanoyl chloride only gave polymeric material. On the other hand, 4-methoxy-β-phenylpropanoyl chloride gave 6-methoxyindan-1-one in 77.5% yield.[7b] The product shown in equation (13) was obtained in 94% yield.[7a] Cyclization reactions of *N*-methoxycarbonyl-protected phenylalanine derivatives have been studied (an example is shown in equation 14), and enantiomeric excesses better than 96% can be achieved.[8] The retention of chirality was found to be dependent on the use of the *N*-methoxycarbonyl protecting group. Attempts to use *N*-benzyloxycarbonyl protection were unsuccessful, presumably due to the ease of formation of a benzyl cation under the reaction conditions. The synthesis of α-amino ketones *via* azlactones works well for the formation of five-, six- or seven-membered rings. However, their known rapid racemization due to the high acidity of the hydrogen at C-5 invalidates their use in the synthesis of enantiomerically pure α-amino ketones. Mention was made in the Introduction of the use of an alkylation–acylation sequence for building rings. In an interesting variation to the use of lactones, ethyl cyclopropanecarboxylate has



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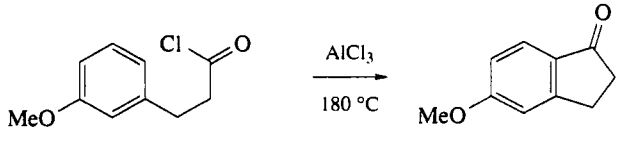

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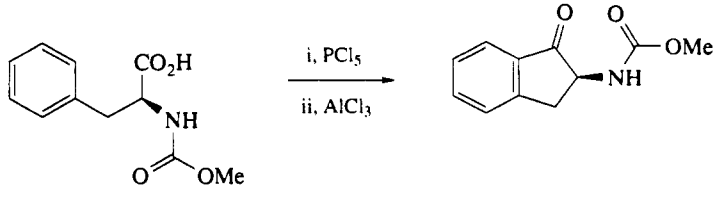

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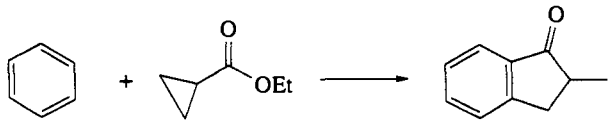

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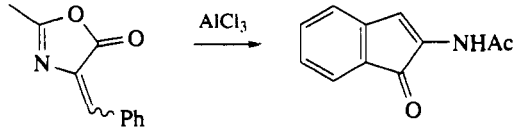
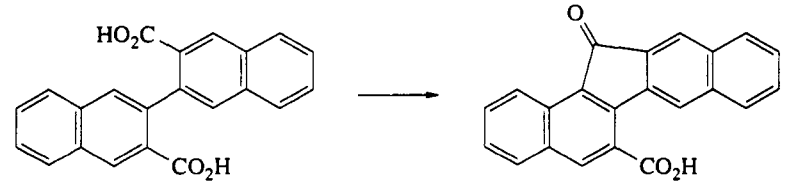


(16)

been shown (equation 15) to give 2-methylindan-1-one in 93% yield.[9] The reaction is assumed to proceed in the normal manner, that is that alkylation precedes acylation. In support of this suggested mechanism, toluene reacts to afford 2,6-dimethylindan-1-one in 67% yield.

The cyclization of what are effectively *cis*-cinnamic acid derivatives to yield indenones can be carried out using azlactones, which are themselves readily available from arylcarbaldehydes and an *N*-acylglycine. The product obtained from *N*-acetylglycine and benzaldehyde gave 2-acetylaminoinden-1-one (equation 16) in 73% yield.[10] The preparation of fluorenones and their benzo analogs by the cyclization of biaryl-2-carboxylic acid derivatives has been studied over a long period of time. Fluorenone-4-carboxylic acid was obtained in quantitative yield when diphenic anhydride was heated with tin(IV) chloride for 7 h at 130 °C.[11] Sulfuric acid has also been used.[12] In a more recent study[13] the cyclizations of biphenyl-2-carboxylic acid using polyphosphoric acid and sodium tetrachloroaluminate have been compared. In the case of the latter reagent, fused sodium tetrachloroaluminate was used both as reagent and solvent and a quantitative yield of fluorenone was obtained when the reagents were heated together for 20 min. The cyclization of 2,2′-binaphthyl-3,3′-dicarboxylic acid occurs readily in sulfuric acid by attack at one of the α-positions (equation 17).[14] Similarly, the cyclization of 2,4-dimethoxy-6,2′-naphthylbenzoic acid proceeds to give the expected product (equation 18) in quantitative yield using trifluoroacetic anhydride in chloroform at room temperature.[15] Other cyclizations, for example using 1-phenanthrylacetyl chloride[16] and 5,6,7,8-tetrahydro-2-phenanthryl-3′-butanoic acid,[17] have been carried out to give acceptable yields of the anticipated polycyclic ketones. In the former case attempted cyclization reactions of the acid failed, using a number of different reagents. The cleavage of benzo[*c*]fluorenone by heating with potassium hydroxide in toluene affords *o*-(2-naphthyl)benzoic acid. This acid was reclosed using polyphosphoric acid to afford the isomeric benzofluorenone in 70% yield.[18] A number of cyclization reactions of half-oxalyl esters to afford coumaran-2,3-diones have been reported. Esterification of 2,5-di-*t*-butylphenol with oxalyl chloride gave the half-ester half-acid chloride and the resulting crude acid chloride gave 4,7-di-*t*-butylcoumaran-2,3-dione in 90% yield on treatment with aluminum chloride in 1,2-dichloroethane.[19]



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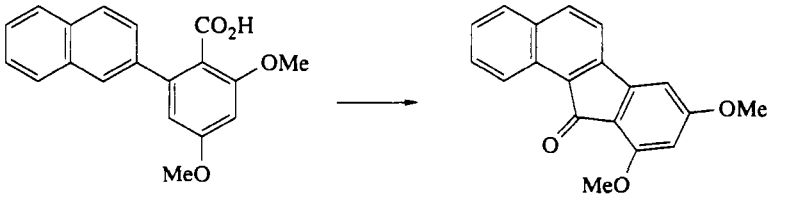
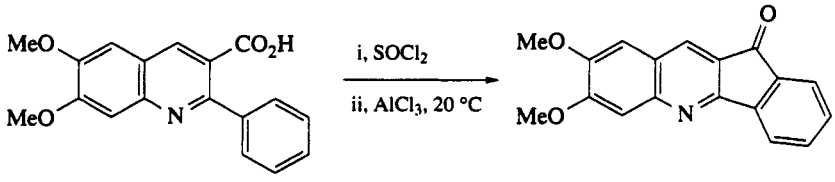


(18)

The reactions of acids and acid chlorides derived from a number of different heterocyclic systems have been studied. Cyclizations either onto a benzene ring or onto a π-excessive heterocycle have been reported. Reactions of 2-phenylquinoline-3-carbonyl chlorides give good yields of the expected products.[20] The product shown in equation (19) was obtained in 90% yield. It was found that the cyclization of pyrrole 1-aspartates proceeds more efficiently using phosphoric anhydride (equation 20) than was the

case using polyphosphoric acid.[21] A number of derivatives of indeno[2,1-*b*]thiophen-8-one have been prepared by cyclizations using the trifluoroacetic anhydride–sulfuric acid[22a] and aluminum chloride[22b] methods. Reactions of 2-[23a] and 3-substituted[23b] thienyl-β-propanoyl chlorides give cyclic thienyl ketones as exemplified in equation (21).



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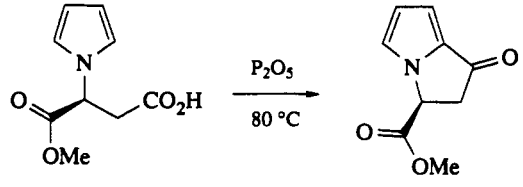

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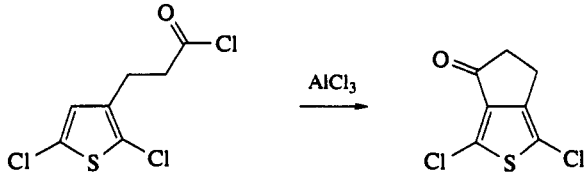

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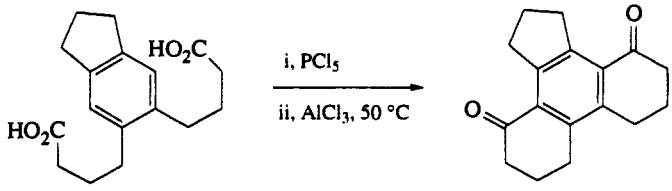
3.3.3.2 Reactions Leading to the Formation of Six-membered Rings

As is expected, the majority of the work carried out on intramolecular Friedel–Crafts acylation reactions has been concerned with the formation of six-membered rings. Examples where double cyclizations have been effected in a single operation include that shown in equation (22).[24] As well as the use of the reactions in carbocyclic ring formation there are cases where cyclization results in the formation of a heterocyclic ring. For example chromanones are obtained from 3-aryloxyacryloyl chlorides and xanthones from 2-aryloxybenzoyl chlorides. The intramolecular version of the Houben–Hoesch synthesis has also been studied. Equation (23), in which the nitrile group functions as a precursor to an acyl cation equivalent, shows one of the steps in a synthesis of the schistosomicidal agent hycanthone.[25] The intermediate imine was hydrolyzed to the product shown without isolation. The aluminum chloride catalyzed cyclization of the phenyl hydrazone derived from ethyl cyanoacetate gives the expected 3-cyanocinnolone. In other examples lacking the ester function, cyclization involving attack at the nitrile group results in aromatization of the intermediate imine to afford a 4-aminocinnoline rather than hydrolysis, as exemplified in equation (24).[26]



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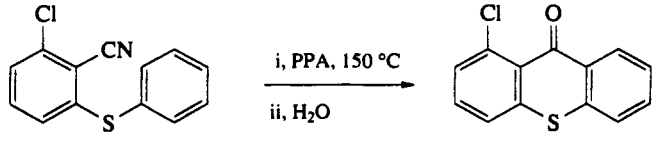

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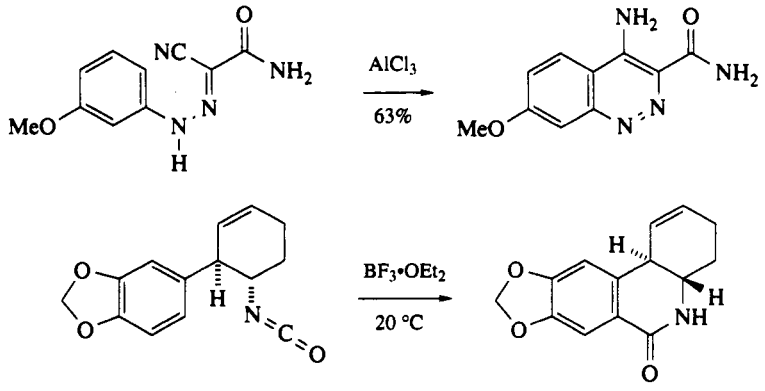

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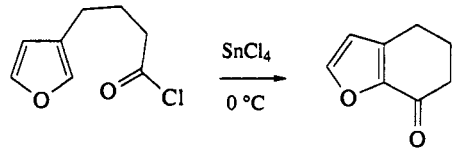
Isocyanates[27] and isothiocyanates[28] have been used as precursors to formamidyl and thioformamidyl cation equivalents. The reaction shown in equation (25), catalyzed by boron trifluoride etherate, was used in a synthesis of the alkaloid lycoricidine, and proceeded in 89% yield.[27] This type of reaction also works efficiently using other β-phenethyl isocyanates.

The ring-closure reactions of derivatives of γ-arylbutanoic acids proceed in high yields under very mild conditions when the aryl residue is electron rich. This is particularly the case when the aryl residue is a π-excessive heterocycle. Both 2- and 3-furyl-γ-butanoyl chlorides (equation 26) afford the 3,4-dihydro-1(2*H*)-ones in good yields at 0 °C using tin(IV) chloride as the catalyst, though, as expected, the yield is better when the cyclization proceeds by attack at the 2-position on the furan ring.[29] Reactions that have been investigated in the thiophene series include those shown in equations (27)[30] and (28).[31] A number of isomers of the product shown in equation (28) were also prepared. It is of interest to note that the cyclization of the acid chloride derived from 3,3′-dithienylmethane-2-carboxylic acid when reacted with tin(IV) chloride in the presence of acetic anhydride gave the enol acetate in 77% yield. Attempts to form seven-membered rings under conditions similar to those shown in equation (27) were not successful.



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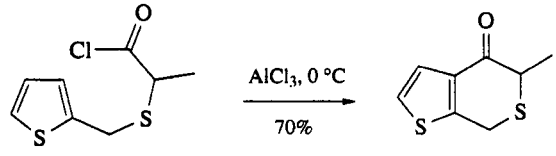

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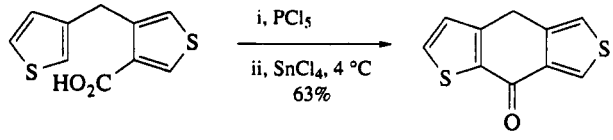
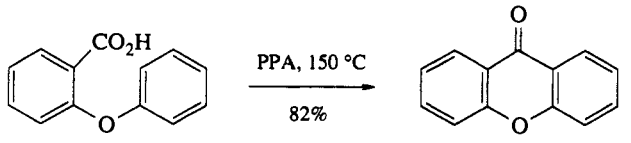


(28)

Many examples of intramolecular Friedel–Crafts acylation reactions that lead to the formation of benzo six-membered heterocyclic systems have been reported over a long period of time. Early examples involved the formation of thiochromanones.[32] The cyclization of 2-phenoxybenzoic acid using sodium tetrachloroaluminate gave chromanone in 99% yield.[13] The synthesis of 1-pyrido[3,2,1-*kl*]phenothiazine[33] *via* the organocadmium compound proceeds in 69% yield, whereas the more conventional treatment of the acid chloride with tin(IV) chloride gave the product in a reduced yield. Other syntheses include acridonecarboxylic acids from *N*-arylaminoisophthalic acids[34a] and diphenylamine-2,2′-dicarboxylic acids,[34b] dibenzochroman-4-ones[35] and thio analogs (equations 29 and 30),[36] and azaanthranols.[37] *N*-(3-Trifluoromethylphenyl)anthranilic acid gave the acridone in 95% yield using polyphosphoric acid as the reagent.[35] The cyclization of *N*-4-quinolylmethylglycine derivatives has been

reported using polyphosphoric acid or sulfuric acid.[38] Reactions using sulfuric acid were more successful at lower temperatures than those employing the former reagent system. When reactions were carried out using phosphoryl chloride, the initial product was converted into a chloro derivative, as illustrated in equation (31). The use of an excess of oxalyl chloride in the synthesis of dihydro-*O*-methylsterigmatocystin as shown in equation (32)[39] is interesting and may involve the cyclization of a mixed anhydride type reagent where the driving force for the cyclization is derived from the loss of carbon dioxide and carbon monoxide as chloride ion departs.



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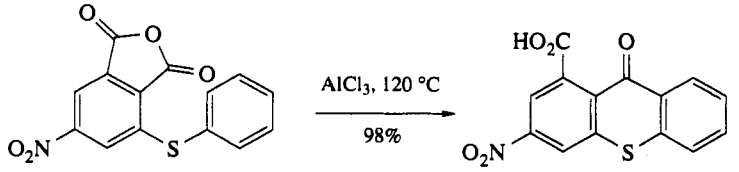

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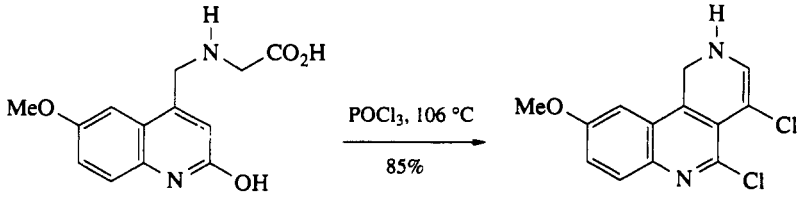

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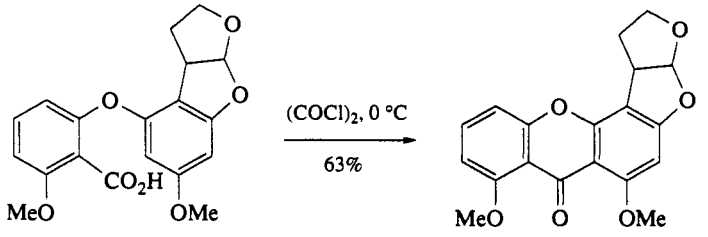
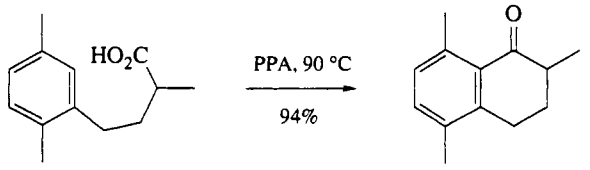


(32)

As is expected, the majority of the papers published on cyclization reactions that result in the formation of six-membered rings involve the synthesis of fully carbocyclic systems. We discussed the use of sodium tetrachloroaluminate in connection with the formation of indanones that have electron-withdrawing groups on the benzene ring.[6] 7-Acetyl-3,4-dihydronaphthalen-1(2*H*)-one was obtained from *p*-acetyl-4-phenylbutanoic acid in 70% yield by that procedure. In the modified Haworth naphthalene synthesis using γ-valerolactone and *p*-xylene, the acid [4-(2,5-dimethylphenyl)pentanoic acid] was cyclized in high yield using polyphosphoric acid. Wide variations have been reported in both the cyclization conditions and in the reagents used. Polyphosphoric acid is widely recommended for the cyclization of γ-arylbutanoic acid derivatives. In the example shown in equation (33)[40] it was found that the use of polyphosphoric acid was preferable to the use of aluminum chloride. Phosphoric acid[41] has been used with acid chlorides and sulfuric acid (equation 34) with some activated substrates.[42] The use of pyridinium fluoride in the reaction shown in equation (35) results in cyclization with a reduced tendency to *O*-demethylation.[43] In the synthesis of aurentiacin,[44] which was mentioned in Volume 2, Chapter 3.2, advantage was taken of the fact that Lewis acids frequently cause *O*-demethylation *ortho* to an introduced acyl group. The cyclohexannelation of polycyclic aromatic hydrocarbons can frequently be achieved using mild Lewis acids such as tin(IV) chloride. An example is shown in equation (36).[45] The cyclization of a number of 3-arylidenelevulinic acid derivatives using acetic anhydride has been shown to proceed reasonably efficiently (equation 37) even when electron-withdrawing groups are present.[46] The resulting cyclohexadienone undergoes the expected dienone–phenol rearrangement to the α-naphthol under the reaction conditions. A number of *o*-aroylbenzoic acid derivatives have been subjected to reductive cyclization using hydriodic acid[47] as shown in equation (38), or hydriodic acid–red phosphorus. In the case of reactions carried out using hydriodic acid–red phosphorus, cyclization and reduction

proceeded eventually to the 9,14-dihydro derivative. The reductive cyclization of a number of *o*-benzoylbenzoic acid derivatives to 9,10-dihydroanthracenes proceed in very high yields.[48]



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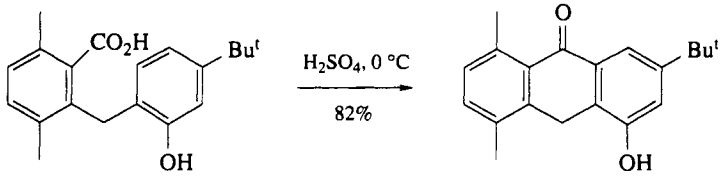

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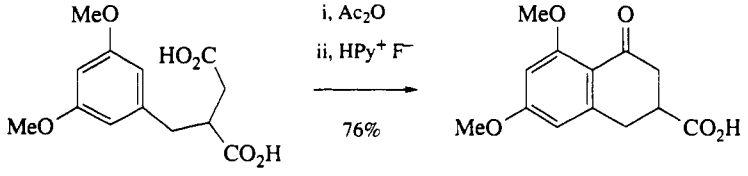

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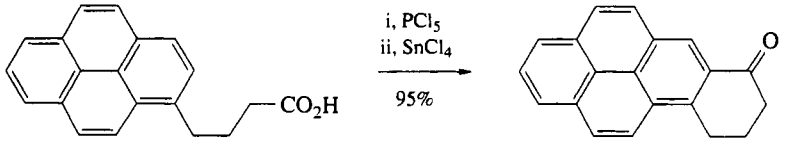

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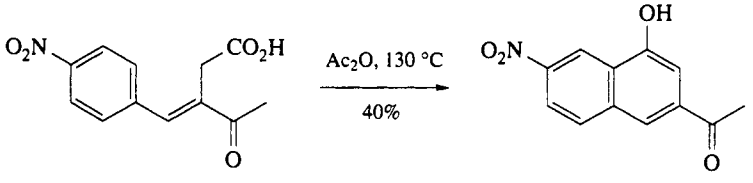

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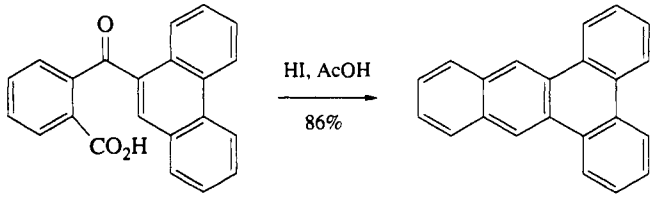
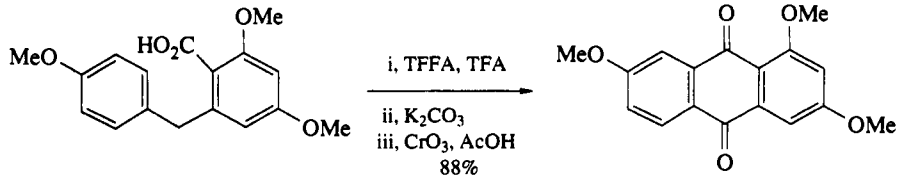


(38)

Ring-closure reactions of alkyl-substituted *o*-benzoylbenzoic acids that are carried out using aluminum chloride are often accompanied by rearrangement of alkyl groups to give the thermodynamically most favoured orientation. 2,5-Diethylbenzoylbenzoic acid gives the anthraquinone that is expected to be formed by the cyclization of the 2,4-diethyl isomer. Once again this mirrors effects that were noted in bimolecular Friedel–Crafts acylation reactions. The cyclization of *o*-benzylbenzoic acids can lead to the formation of anthrones which in some cases are unstable and then afford anthraquinones after oxidation. The example shown in equation (39) is such a case where the 4,6-dimethoxy-2-(4′-methoxybenzyl)benzoic acid does afford an unstable anthrone.[49] The possibility of using masked *o*-benzoylbenzoic acids in connection with anthracycline synthesis is exemplified in equation (40). An overall yield of 75% was obtained in the sequence which included the demethylation steps shown.[50]

The most important applications are involved in the synthesis of polycyclic systems. The cyclization reactions of suitably substituted 2-naphthylcyclopentylacetic acids have been investigated in connection with syntheses of A,B aromatic ring steroids but the traditional Friedel–Crafts procedures proved disappointing.[51] On the other hand, the cyclization shown in equation (41), which used hydrofluoric acid as

the electrophile, gave a significant improvement in the yield.[52] It was observed that attempted cyclization of the related but unprotected ketone gave a very poor yield of the expected product. Polyphosphoric acid and polyphosphoric acid containing phosphoryl chloride sometimes give improved yields. It may be in the latter case that, as well as reducing the viscosity of the polyphosphoric acid, the phosphoryl chloride converts the acid into the acyl chloride.



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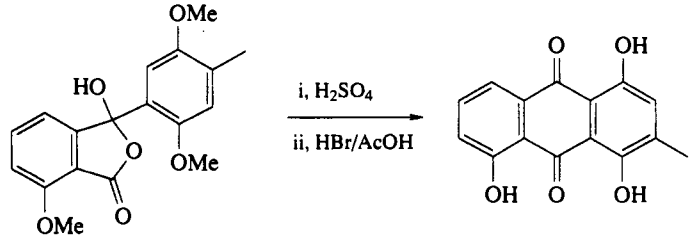

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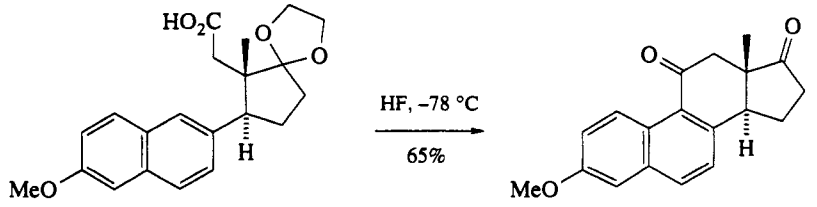
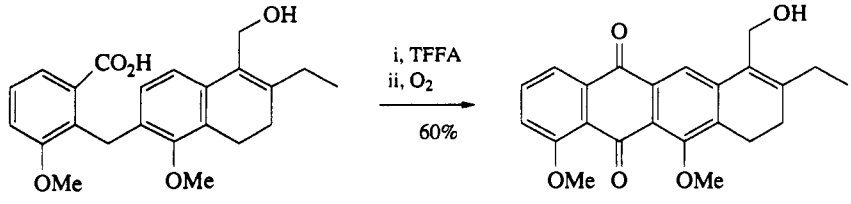


(41)

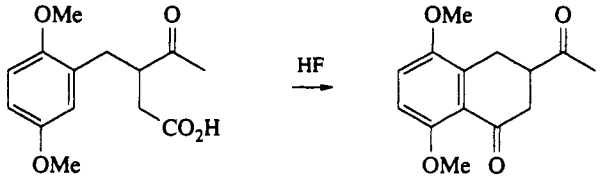
Many of the more recent applications of intramolecular Friedel–Crafts acylation reactions have involved the synthesis of biologically active tetracycline derivatives. In the synthesis of aclacinomycin[53] the acid shown in equation (42) was cyclized efficiently to the anthrone using trifluoroacetic anhydride in dichloromethane and then converted immediately into the anthraquinone shown.



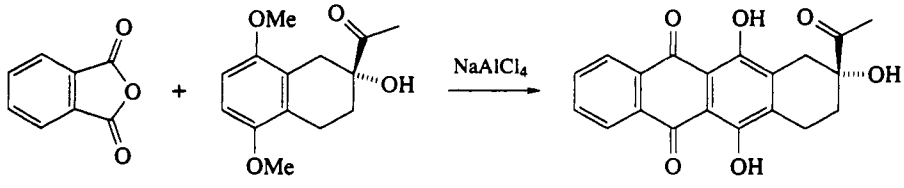
(42)

Considerable attention has been given to the synthesis of the aglycone portions of the antitumor anthracyclines.[54] In one of the seminal procedures[55] the construction of rings A and B (using the Brockmann nomenclature) and the joining together of the two remaining rings were both achieved using Friedel–Crafts methodology. The cyclization of the 2,5-dimethoxyphenylbutanoic acid derivative containing the acetyl group, suitably placed so that it would eventually appear at the 9-position, was achieved using hydrofluoric acid as shown in equation (43). It is of interest to note that similar attempted cyclizations of a 1,4-dihydroxy-5-methoxy-9,10-anthraquinone failed using a variety of acids. An unsaturated lactone (a 2,5-dihydrofuranone) was the major product.[56] On the other hand the cyclization of phthalic anhydride with 2-methyl-1,4-dihydroxybenzene to the anthraquinone was achieved in 79% yield using the sodium tetrachloroaluminate procedure.[56] In a related series of investigations[57] the fusion of the (*R*)-(–)-5,8-dimethoxytetralin derivative (equation 44) gave the (–)-enantiomer of the tetracyclinone shown. The earlier synthesis[55] was continued as shown in equation (45) in which the mixture of methyl hydrogenphthalate and the 5,8-dimethoxytetralin was treated sequentially with trifluoroacetic anhydride and then hydrogen fluoride. We mentioned previously the instability of a trimethoxyanthrone.[49] On the other hand, there have been a number of reports[58] of the successful cyclization reactions involving the

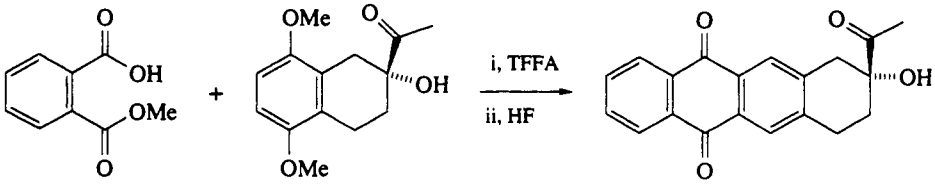
formation and isolation of anthrone derivatives in high yields as exemplified in equation (46). The construction of a suitably substituted 5,8-dimethoxy-3,4-dihydronaphthalen-1-(2*H*)one, shown in equation (47), was achieved by using tin(IV) chloride as the catalyst.[59] The acid can be cyclized directly in high yield using polyphosphoric acid to give mainly the 8-hydroxy derivative. In a rather different approach to the synthesis of the tetracyclinone ring system, illustrated in equation (48), the intramolecular Friedel–Crafts acylation was carried out with trifluoroacetic anhydride.[60] The protective group that was required was, of course, removed during the cyclization reaction and had to be reintroduced.



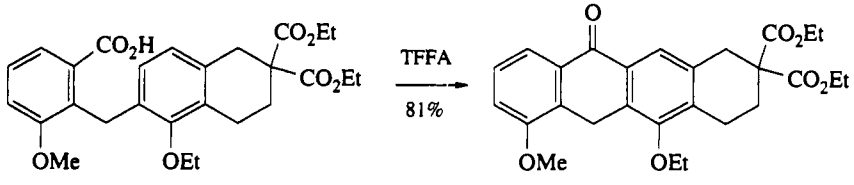
(43)



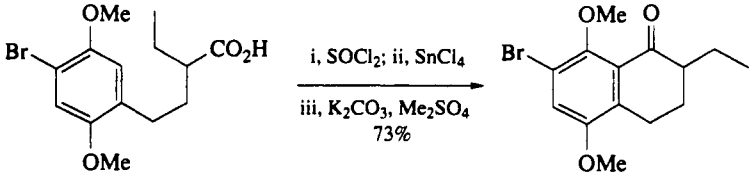
(44)



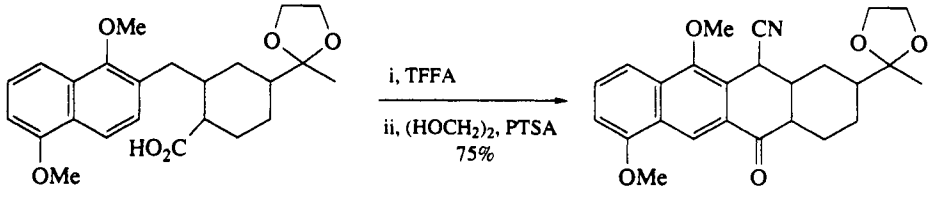
(45)



(46)



(47)

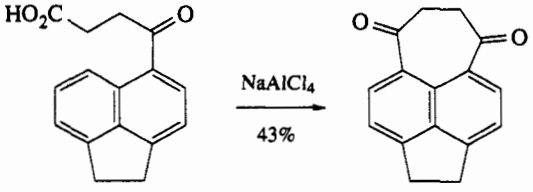


(48)

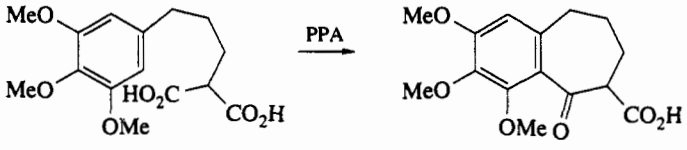
3.3.3.3 Reactions Leading to the Formation of Seven-membered Rings

One of the early examples of the use of sodium tetrachloroaluminate in intramolecular Friedel–Crafts acylation reactions involved the reaction shown in equation (49), in which β-(3-acenaphthoyl)propanoic acid was converted into perisuccinoylacenaphthene.[61] The formation of the benzosuberanone ring system is particularly easy when electron-releasing substituents are present on the benzene ring. Under those cir-

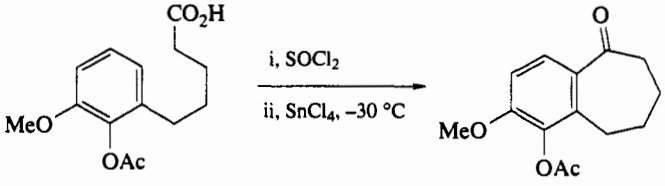
cumstances mild reaction conditions may be used. In reactions that are carried out using polyphosphoric acid it is normal to use an unspecified excess of the acid.[62] However, in the example shown in equation (50) the yield of the benzosuberone was found to vary with the amount of acid used. The yield changed from 50% to 79% on doubling the amount of polyphosphoric acid used.[63] The cyclization of 5-(2,3-dimethoxyphenyl)valeric acid proceeds to give the expected product in 78% yield when it is stirred in polyphosphoric acid at 40 °C for 40 h.[64] The same authors reported that 5-(2-acetoxy-3-methoxyphenyl)valeryl chloride was reacted with tin(IV) chloride and gave the product shown in equation (51) in 85% yield. It is noteworthy that the relatively labile acetoxy group survives those reaction conditions. Efficient cyclization reactions of arylalkanoic acids have been carried out using hydrofluoric acid in polythene apparatus.[65] 5-(4-Isopropylphenyl)valeric acid was converted into the expected benzosuberanone in virtually quantitative yield and was isolated in 85% yield after purification. Pyridine hydrochloride has been used with some malonic acid derivatives.[66] The reaction apparently only succeeds with malonic acid derivatives that have a suitably positioned aryl residue, specifically having a *meta* methoxy group and a free *para* position. Demethylation was also observed in this last reaction.



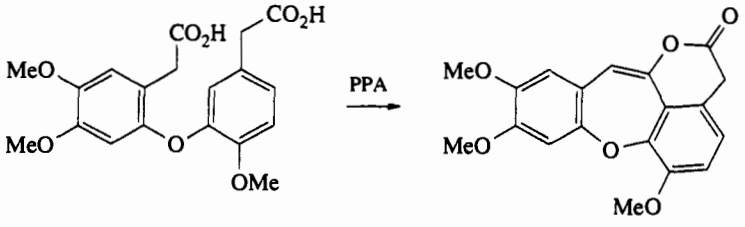
(49)



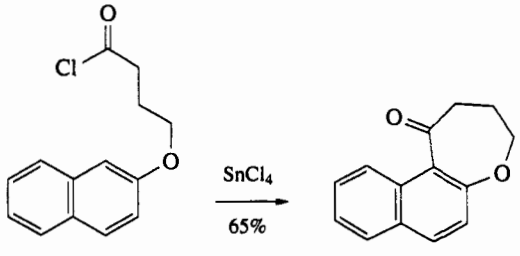
(50)



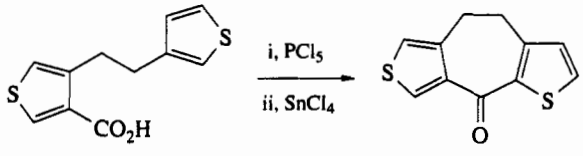
(51)



(52)



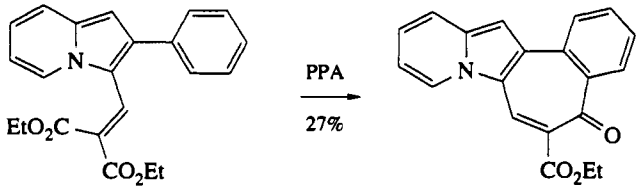
(53)



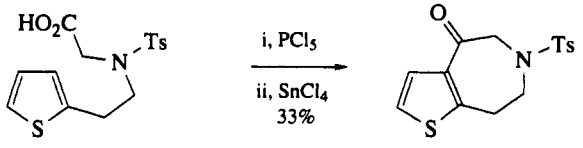
(54)

The construction of the pyranooxepin system shown in equation (52) proceeds by way of a dibenzoxepinone acetic acid, followed by intramolecular enol ester formation.[67] The regioselective cyclization of 4-(2-naphthyloxy)butanoyl chloride proceeds as expected (equation 53) using tin(IV) chloride as the catalyst, but a mixture of products was obtained when the related carboxylic acid was treated with polyphosphoric acid.[68] The preparation of a thieno[*b*]suberanone in 40% yield has been achieved by the interaction of tin(IV) chloride with 5-(2-thienyl)valeryl chloride.[69] Once again, the expected increase in yield is obtained when cyclization occurs to the 2-position in thiophene. The product shown in equation (54) was isolated in 81% yield.[70] Other intramolecular reactions involving thiophenes have been reported.[71]

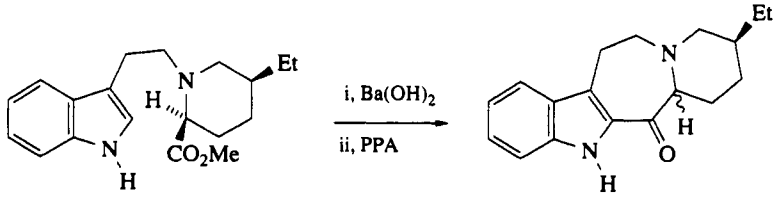
Cyclization reactions resulting in the formation of indolo- and indolizino-suberenones are exemplified by equation (55)[72] and a range of benzo-[73] and thieno-[*b*]azepinones[74] have been prepared from glycine derivatives. The example shown in equation (56) showed platelet antiaggregating activity. The cyclization of a 5-(1-indolyl)valeric acid[75] and 3-(3,4-dimethoxyphenyl)propyl isothiocyanate[76] using polyphosphoric acid led to an indoloazepinone and a benzoazepinethione respectively. In the case of the isothiocyanate it appears that the electrophile involved is not very reactive. The yield of the cyclized product dropped to 30% in the absence of the methoxy groups. In the example shown in equation (57) a 1:1 mixture of diastereoisomers was obtained from which the *cis* isomer was isolated by fractional crystallization.[77]



(55)

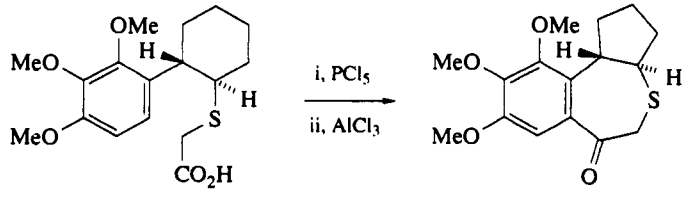


(56)

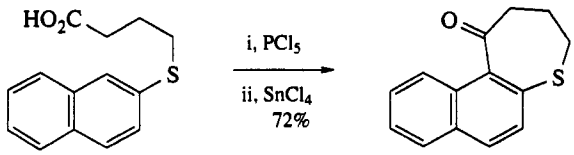


(57)

A wide range of benzo- and dibenzo-thiepinones has been prepared by cyclizing both the free carboxylic acids using polyphosphoric acid,[78] and by using Lewis acids after conversion into the acyl chlorides.[79] In the example shown in equation (58) the *trans* product was obtained in 50% yield while the *cis* isomer gave a slightly improved yield of the *cis* product.[80] Cyclization reactions of 4-(2-thionaphthoxy)butanoyl chloride using aluminum chloride[81] and tin(IV) chloride[82] proceed as expected by reaction at the 1-position in the naphthalene ring. The latter reaction, shown in equation (59), gives the better yield. When the 4-(2-thionaphthoxy)butanoic acid was reacted in polyphosphoric acid, both possible regioisomeric naphthothiepinones were obtained as a 1:1 mixture. This result is similar to the result that was obtained using the naphthoxybutanoic acid.[68]



(58)

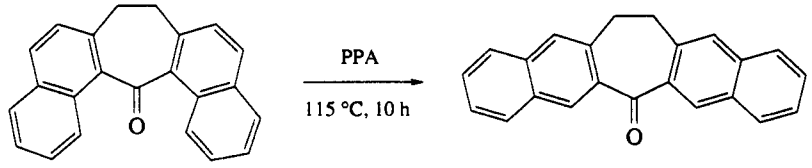


(59)

3.3.4 CONCLUSION

We have seen that the intramolecular version of the Friedel–Crafts acylation reaction is wide-ranging and that reaction conditions can normally be devised to allow the synthesis of a large number of different ring sizes. Cyclizations can also be carried out when the aryl residues have widely differing electron densities. The reaction is subject to fewer anomalies than is the case with the intermolecular version. There have been examples reported where unexpected products have been obtained, but a careful choice of reaction conditions will normally allow these problems to be avoided. To quote just one example, cinnamoyl chloride (the *trans* isomer) would not be expected to give a cyclized product, and a reaction with toluene using aluminum chloride as the catalyst leads to the expected intermolecular reaction product. A reaction carried out in benzene solution, however, gave rise to a mixture of 3-phenylindan-1-one and 1,3,3-triphenylpropanone.

It was assumed for many years that the Haworth polycyclic aromatic hydrocarbon synthesis only allowed access to angularly annelated systems. The realization[83] that the benzoylation of naphthalene using benzoic acid in polyphosphoric acid was reversible led to an investigation of potential rearrangements in intramolecular acylation reactions. Although the intramolecular acylation of a 2-substituted naphthalene proceeds under kinetic control to afford the angularly annelated product, heating that compound in polyphosphoric acid has been shown to result in rearrangement to the linearly annelated ketone.[84] In the example shown in equation (60) the linearly annelated ketone is obtained as the predominant product, isolated in a ratio of 4:1, when the angularly annelated ketone is heated in polyphosphoric acid at 115 °C for 10 h. Interestingly, the other possible isomer was shown to be present in only trace amounts. The rearrangement of 3,4-dihydrophenanthren-1-(2*H*)one to 3,4-dihydroanthracen-1-(2*H*)one also proceeds efficiently under thermodynamic reaction conditions.[85]



(60)

The origin of the thermodynamic difference is presumably that the ketone is protonated in polyphosphoric acid and interaction with a *peri*-hydrogen causes tilting of the protonated carbonyl group out of the plane of the aromatic system.[86] This effect would reduce the conjugation of the carbonyl group with the aromatic residue. The destabilizing effect is greater for an angular (kinetic) product than for the linearly annelated ketone because a *peri*-hydrogen is closer in the former case. Under thermodynamic reaction conditions of higher temperatures, the rearrangement to the linear ketone is favored.

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3.4
The Reimer–Tiemann Reaction

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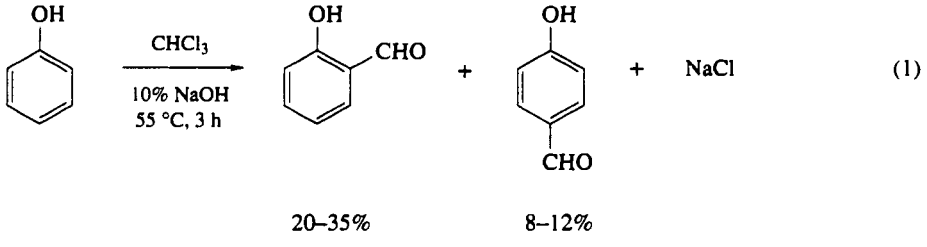
3.4.1 INTRODUCTION

The Reimer–Tiemann reaction, an aromatic substitution reaction that occurs under basic conditions, is in many respects a unique reaction. It is one of the few organic reactions whose industrial importance seems to increase yearly, notwithstanding the environmental hazards associated with the use of chloroform, while academic interest remains considerable. In addition to the fact that the 'normal' reaction continues to intrigue chemists, the so-called 'abnormal' Reimer–Tiemann reaction that furnishes substituted cyclohexadienes remains of considerable interest. Several previous surveys of the Reimer–Tiemann reaction have been published.[1] Consequently, we focus here on recent developments.

3.4.2 THE NORMAL REACTION

It is convenient to discuss the Reimer–Tiemann reaction in terms of its normal and abnormal versions. The normal reaction, discovered in 1876[2] by Reimer, consists of the treatment of a phenol or naphthol with chloroform in the presence of an alkali metal hydroxide solution (see equations 1 and 2), and results

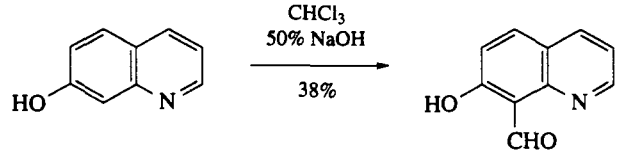


(2)

in the formation of phenolic aldehydes. Depending on the substituents, the products may be mixtures of *o*- and *p*-hydroxy aldehydes[1–5] or pure hydroxy aldehydes.[6–8]

In a recent paper, Rocke and Ihde[9] question the attribution of the name Reimer, citing evidence that the wrong Reimer has been credited with the reaction.

In addition to mono- and poly-hydric phenols and naphthols, several heterocyclic compounds also yield aldehydes upon treatment with chloroform and aqueous base. Thus, we find that hydroxypyridines, hydroxyquinolines and hydroxypyrimidines can be formylated. Even the nonhydroxylated pyrrole yields pyrrole-2-carbaldehyde in fair yield (see equations 3 and 4).[1,7,10]



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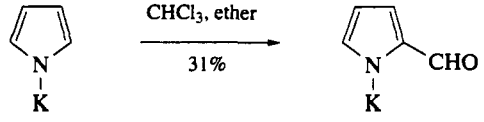

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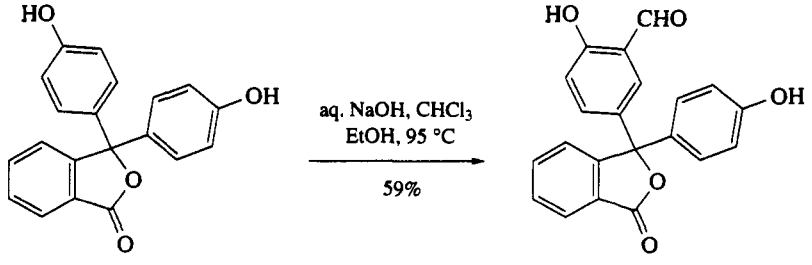
3.4.3 SCOPE AND LIMITATIONS

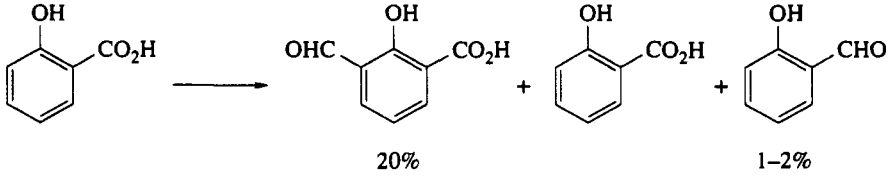
In addition to phenols, naphthols, their alkyl derivatives and the heterocyclic compounds mentioned above, a large variety of substituted monocyclic as well as condensed phenols have been subjected to the Reimer–Tiemann reaction. Although with a few exceptions the yields are only moderate, the facile reaction conditions, at least on a laboratory scale, have assured the reaction a permanent place among the variety of methods by which an aldehyde group can be attached to an aromatic nucleus. For example, phenolphthalein (**1**) has been formylated under standard Reimer–Tiemann conditions by van Kampen to yield the *o*-hydroxy aldehyde in 59% yield (equation 5).[11]



(5)

(**1**)

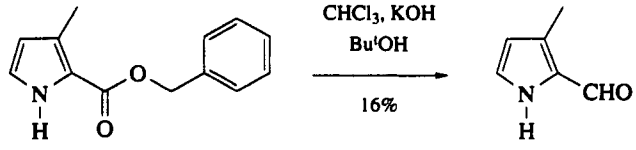
In addition to phenolphthalein, other carboxy-substituted phenols have been subjected to the Reimer–Tiemann reaction. Mixtures of compounds, some lacking the carboxyl group, result (equation 6).[1] Even though the nature of the reaction (*i.e.* the attack by the electrophilic dichlorocarbene on the nucleophilic



(6)

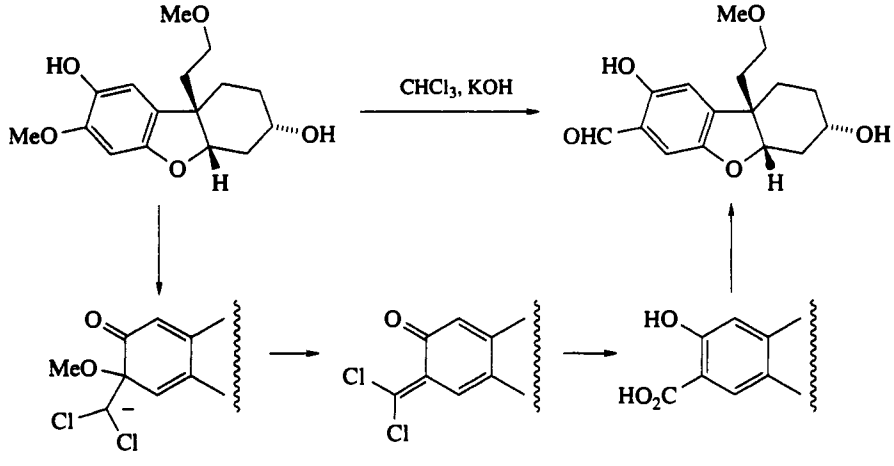
phenolate carbanion) would seem to preclude successful substitution on phenols carrying such negative substituents as carboxyl and sulfonic acid groups, reports of such substitution can be found, albeit mostly in the patent literature.[1]

A recent careful examination of the substitution pattern of a series of pyrrole-2-carboxylates established that loss of the carboxyl group occurs with simultaneous entry of the formyl group (equation 7).[10]



(7)

Another unusual observation concerns the replacement of a methoxy group by a formyl group under Reimer–Tiemann reaction conditions. The mechanism proposed by the authors (Scheme 1) seems reasonable[12] and supposes two consecutive replacements. First, the methoxy substitutent is replaced by the dichlorocarbene to give an *o*-quinone methide. The latter is hydrolyzed to a carboxyl group by a mechanism involving conjugate addition of hydroxide. A second replacement occurs, the carboxyl group being displaced by the formyl (*via* the carbene) group. All-in-all, this is a strange, unsubstantiated, but not unreasonable sequence of events.



Scheme 1

3.4.4 RECENT DEVELOPMENTS

Since several recent reviews of the Reimer–Tiemann reaction are readily available, the last one dating from 1982,[1] it is perhaps most useful to summarize recent developments.

3.4.4.1 Regioselectivity

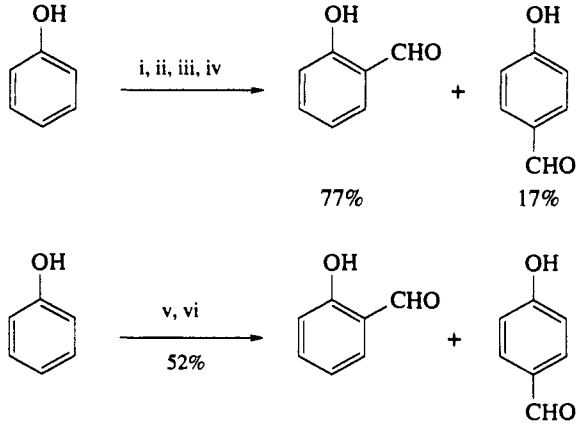
Since the Reimer–Tiemann reaction always yields a mixture of *ortho*- and *para*-substituted phenols whenever the two positions are unsubstituted (and sometimes even when the positions are substituted, see carboxy-substituted phenols), it is not surprising that attempts have been made to increase the regioselectivity. Earlier attempts (for details, see reviews) emphasized the nature of the cation, the solvent, or used phase-transfer catalysis. Recent studies have concentrated on the use of cyclodextrins as base-stable host compounds, permitting exclusive *para* substitution. Attaching the cyclodextrins to a solid support has also been attempted, a natural step in view of the high cost of the cyclodextrins and the need for cheap product (*i.e.* *p*-hydroxybenzaldehyde). *p*-Hydroxybenzaldehyde has been prepared in 59–65% yield using β-cyclodextrin that has been immobilized with epichlorohydrin.[13] The catalyst is easily recovered and can be reused without appreciable loss of activity.

Increased selectivity has also been obtained using polyethylene glycol as complexing agent.[14] Using toluene as solvent, the authors report a 1:10 *para:ortho* ratio in the formylation of phenol.

Greater *ortho* selectivity has also been observed under conditions that the authors call a photo Reimer–Tiemann reaction. Since the original paper[15] was not available for perusal, no judgment can be made about the validity of the interesting report. It is worthwhile to recall that the acidity of the phenol changes several orders of magnitude in the excited state. If substitution indeed takes place while phenol is in the excited state, a change in the substitution pattern might well occur.

3.4.4.2 Industrial Applications

Even though chloroform as industrial solvent or reagent does not seem to have a bright future, emphasis on the industrially viable Reimer–Tiemann processes continue to appear in the literature, especially from countries such as India and China.[16] This author is familiar with some of the conditions prevailing in these countries from personal experience. It is evident that processes, long ago abandoned by western countries because of environmental hazards or uneconomical procedures, are still finding their way into the industries of developing countries, an interesting but disturbing phenomenon. However, even western companies appear to find the Reimer–Tiemann reaction still of sufficient importance to spend money on research and patents. Thus, a Dow Chemical Company patent[17] describes the use of high pressure and temperatures to accelerate the reaction, with yields reported as high as 52% (Scheme 2).



i, 9.4 g phenol, 20 g NaOH; ii, 100 mL $CHCl_3$, 3.6 mL H_2O; iii, 58 °C, 1 h; iv, 12 g NaOH, 2 h; v, 27 g phenol, 25 g NaOH, 100 g H_2O, 11 g $CHCl_3$; vi, 80–88 °C, 100 atm, 12 min

Scheme 2

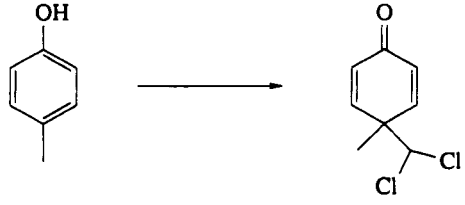
Intriguing but confusing information is available in two *Chemical Abstracts* references to Chinese publications. A 1988 abstract[18] reports the behavior of phenol under Reimer–Tiemann reaction conditions with the addition of tertiary amines. The authors claim that the *para:ortho* ratio is reversed from that normally observed and 60% yield of *p*-hydroxybenzaldehyde, 7% yield of *o*-hydroxybenzaldehyde and only 1% tars are obtained when phenol is subjected to the new conditions. One year later[19] a report appeared in which it is claimed that the use of tertiary amines under phase-transfer conditions increases the yield of *ortho* product. The authors report a yield of 79% of salicylaldehyde from phenol using 0.37% catalyst (the nature of the catalyst is not mentioned in the abstract and the Chinese publication is not available to this author), and 35% sodium hydroxide at 55–60 °C for 90 min. Surely, these results (or the translation) warrant checking.

Greater reliance can be placed on a recent report of the effect of ultrasonic irradiation on the Reimer–Tiemann reaction.[20] The authors report 'significant improvement in Reimer–Tiemann yields through ultrasonic irradiation of the reaction system. The effects of ultrasonic intensity and reactor design are discussed.'

3.4.5 THE 'ABNORMAL' REIMER–TIEMANN REACTION

It is interesting to compare early experimental work with the facilities available in a modern laboratory. Von Auwers was the first to separate the chloro ketones from the normal phenolic aldehydes of the Reimer–Tiemann reaction.[21] Identification and structure proof by chemical means followed. It is a tribute to von Auwers' skill and insight that his identification procedures have withstood the onslaught of modern spectroscopic means. Although the chloro ketones (equations 8–10) have been called the abnormal products of the reaction, in cases where the *ortho* and *para* positions are occupied (see equation 10) only ketonic material is obtained.[1,22] In fact, the presence of the dichloro ketones provides one of the better arguments for the intermediacy of dichlorocarbene in the reaction mechanism.[23]

(8)



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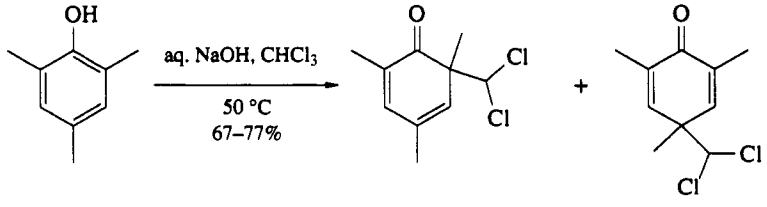
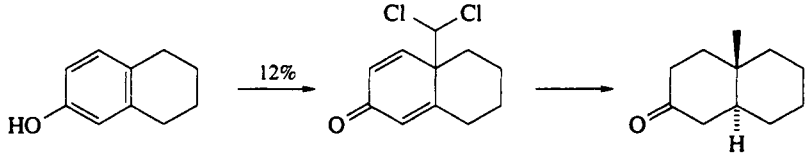


(10)

Although at first these ketonic by-products were mere curiosities, their potential value was noted by Woodward, who used the abnormal Reimer–Tiemann reaction for a synthesis of *trans*-10-methyldecalone from β-(*ar*)-tetralol (equation 11).[24] This author applied this principle for the preparation of a 9-methyldecalone from an α-(*ar*)-tertralol (equation 12).[25]



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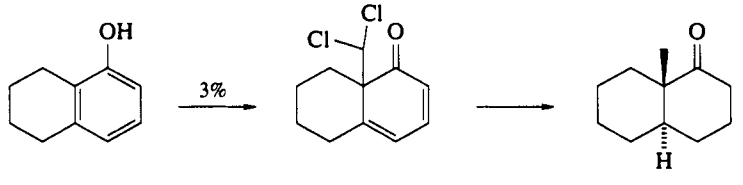
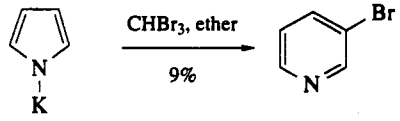


(12)

As is the case with the normal reaction, the abnormal reaction can also be influenced by the use of β-cyclodextrin to give higher selectivity for the *para* position. Australian chemists have carried out a careful product analysis of the normal, abnormal and ring-expansion products resulting from the Reimer–Tiemann reaction with a series of 4-alkylguaiacols.[26]

Ring expansion during Reimer–Tiemann reaction conditions on pyrroles and indoles to furnish pyridines and quinolines was observed by Ciamician in 1881 (equations 13 and 14).[27] Although a preparative reaction of little use due to the low yield, this transformation stimulated others to carry out ring expansion attempts on nonphenolic substrates with considerable success.[28]



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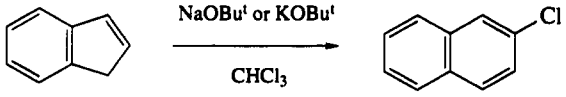
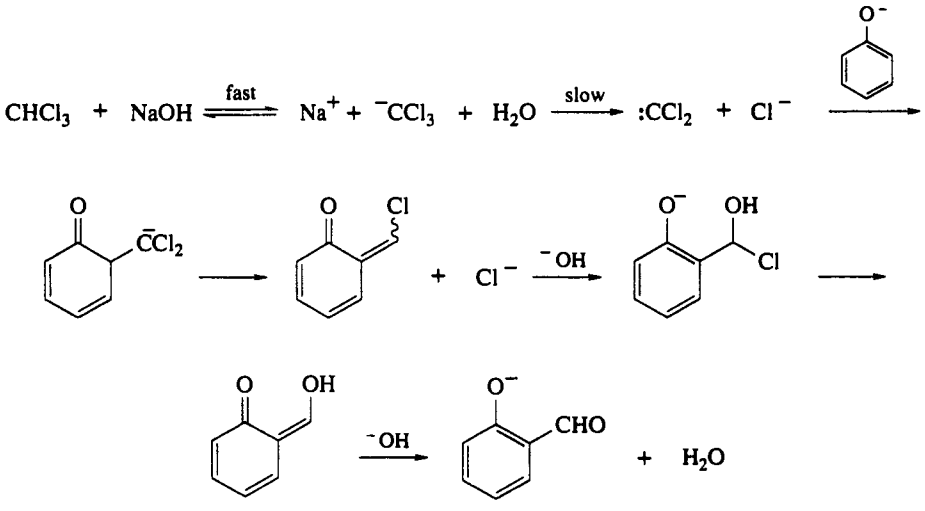


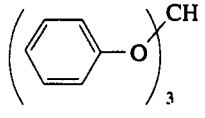
(14)

3.4.6 THE MECHANISM OF THE REACTION

The formation of all of the reaction products, phenolic aldehydes, dichloro ketones and ring-expansion products, can be explained satisfactorily by postulating the carbene intermediate originally proposed by Hine (Scheme 3).[23] The only products that might be thought of as resulting from direct nucleophilic displacement of phenolate anion on chloroform are the orthoformic esters (*e.g.* **2**) formed in low yields in most Reimer–Tiemann reactions (and rarely isolated or identified). However, even these can result from a version of the Hine mechanism.

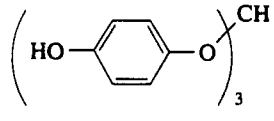


Scheme 3



(2)

Even less structural information is available on the 'leucarins' or triphenylmethane type dyes, which are a natural result of the condensation of aldehydes with phenols. It is clear that the products of the Reimer–Tiemann reaction can react further with themselves as well as with the starting phenol to yield a delightful variety of colored materials, erroneously called 'tars' by some (*e.g.* **3**).



(3)

Finally, it should be mentioned that hot alkaline solutions in the presence of air cause oxidation of the sensitive phenols and phenolic aldehydes. Thus, the isolation of traces of acids is not unexpected.

3.4.7 CONCLUSIONS

Since 1876, approximately 240 publications have appeared in which the Reimer–Tiemann reaction plays a prominent role. Two publications per year does not seem to be an overwhelming number of publications or interest in a carbon–carbon bond-forming reaction. But quantity may not be the best criterion for explaining the continued interest in this reaction. Certainly, the products of the normal reaction, the hydroxybenzaldehydes, are not only among the most important intermediates in the synthesis of aromatic compounds, their occurrence in nature, naturally not in the free form, but as obvious parts of complex structures (see, for example the vast variety of flavones), also attests to their importance. Undoubtedly, it would be rather extreme to presume that a biochemical/biosynthetic equivalent to the Reimer–Tiemann reaction exists in nature. After all, another certainly more important carbon–carbon bond-forming reaction such as the Michael reaction (with approximately 10 times as many references in the literature as the Reimer–Tiemann reaction) does not seem to have a biochemical equivalent either. Nevertheless, in the absence of strong evidence to the contrary, it can be argued that carbene formation under physiological conditions is eminently feasible, since chloroform is readily identified in (Dutch) waters, and mildly basic conditions would certainly lead to the formation of carbene. Phenols, oxidative degradation products of aromatics, are also obvious organic compounds in our environment, setting the stage for the Reimer–Tiemann reaction under biological circumstances.

An improved synthesis of salicylaldehyde, using solid sodium hydroxide and little water, has recently been reported.[29]

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3.5
The Vilsmeier–Haack Reaction

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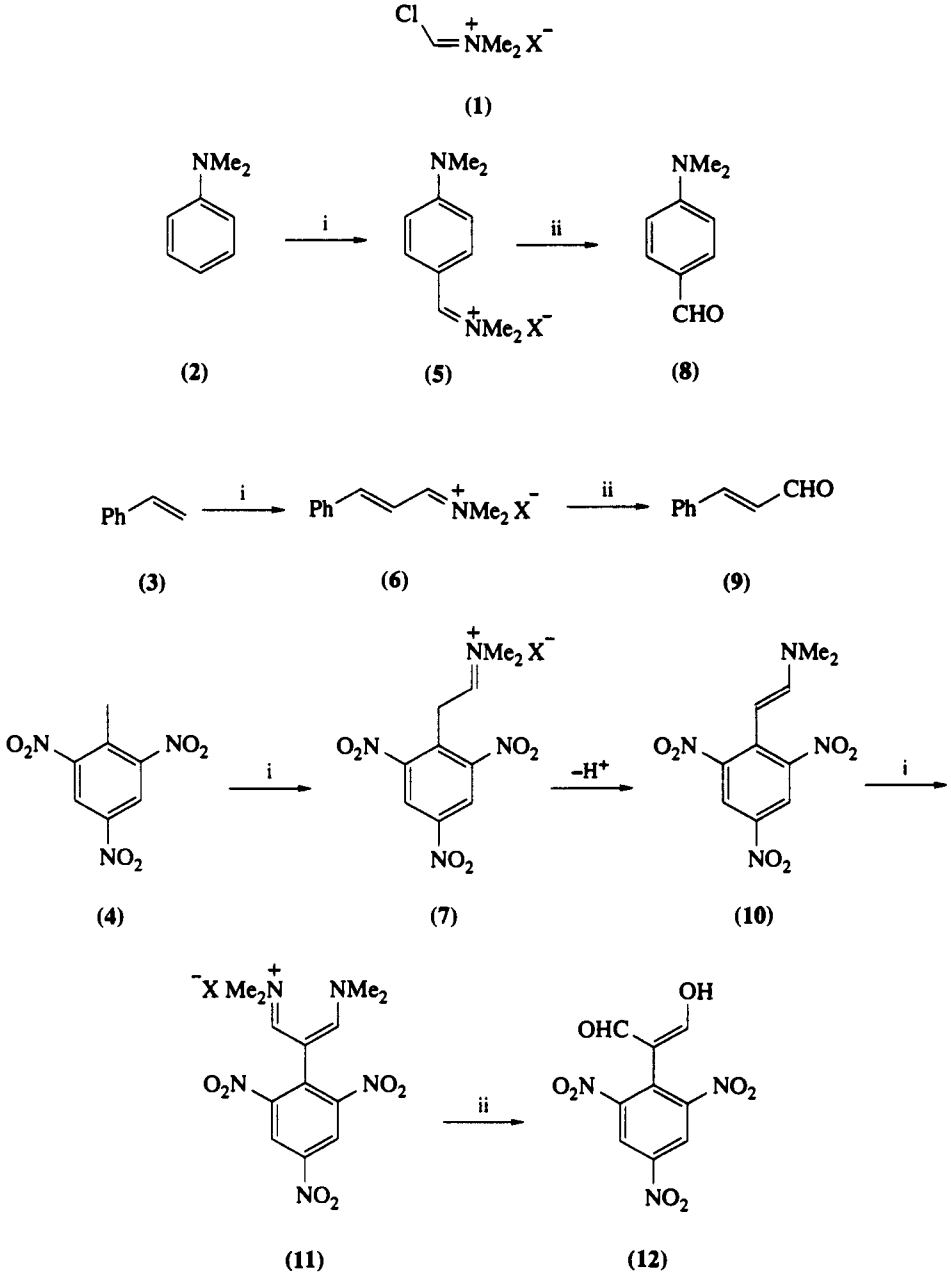
3.5.1 INTRODUCTION

The classical Vilsmeier–Haack reaction[1,2] involves electrophilic substitution of a suitable carbon nucleophile with a chloromethyleneiminium salt, for example salt (**1**). Suitable carbon nucleophiles are generally electron-rich aromatic compounds such as *N,N*-dimethylaniline (**2**), alkene derivatives such as styrene (**3**) or activated methyl or methylene compounds such as 2,4,6-trinitrotoluene (**4**; Scheme 1). These compounds (**2**–**4**) react with salt (**1**) giving, after loss of hydrogen chloride, the corresponding iminium salts (**5**–**7**). Hydrolysis of iminium salt (**5**) affords aldehyde derivative (**8**) and this transformation (Ar—H → Ar—CHO) is the well-known Vilsmeier–Haack formylation reaction. Hydrolysis of iminium

salt (**6**) similarly yields the formylated product (**9**). Compounds that possess activated methyl or methylene groups such as 2,4,6-trinitrotoluene (**4**) react with salt (**1**) giving iminium salts like (**7**). Proton loss from iminium salt (**7**) affords the enamine derivative (**10**), which can participate in a further electrophilic substitution reaction with salt (**1**) giving vinylamidinium salt (**11**). Hydrolysis of this salt (**11**) yields the malondialdehyde derivative (**12**).



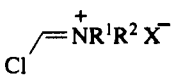
i, salt (**1**); ii, hydrolysis

Scheme 1

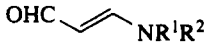
The Vilsmeier–Haack reaction, as depicted in Scheme 1, is an important method for synthesizing aldehyde derivatives. Numerous other transformations of iminium salts into products other than aldehydes have been achieved, and these additional transformations add considerable scope and versatility to the Vilsmeier–Haack reaction. The Vilsmeier–Haack reaction is not restricted to carbon nucleophiles: oxygen and nitrogen nucleophiles also react with chloromethyleneiminium salts.

3.5.2 FORMATION OF CHLOROMETHYLENEIMINIUM SALTS

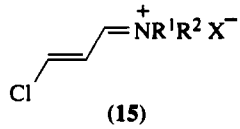
Chloromethyleneiminium salt (**1**) is formed by treating dimethylformamide (DMF) with an acid chloride.[1] A large number of other chloromethyleneiminium salts (**13**) are available from formamide derivatives $HCONR^1R^2$, but DMF is used most frequently. Formamide derivatives $HCONR^1R^2$ that have been employed in the Vilsmeier–Haack reaction include *N*-methylformanilide, *N*-formylpiperidine and *N*-formylmorpholine. Vilsmeier and Haack originally discovered[3] that *N*-methylformanilide formylated aniline derivatives in the presence of $POCl_3$. The chloromethyleneiminium salt (**13**; R^1 = Me, R^2 = Ph) was the electrophile in this reaction. Vinylogous formamide derivatives (**14**) give the corresponding vinylogous chloromethyleneiminium salts (**15**), which also participate in the Vilsmeier–Haack reaction.[1,4]



(**13**)

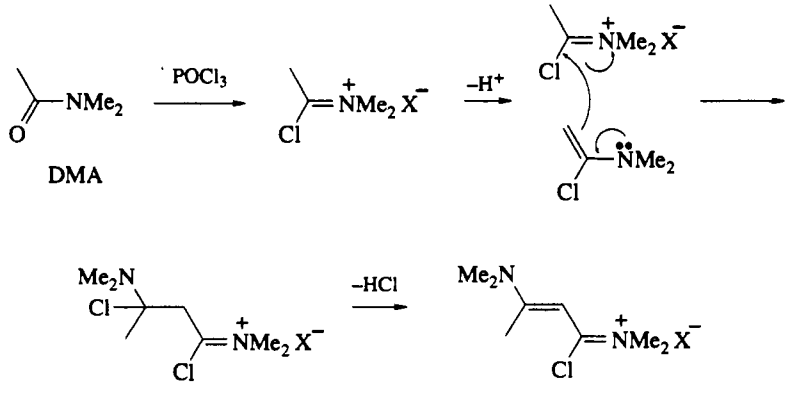


(**14**)



(**15**)

Formamide derivatives can sometimes be replaced with other amides, and examples include *N*,*N*-dimethylacetamide (DMA), *N*-methylpyrrolidone and *N*,*N*-dimethylbenzamide. The resulting chloromethyleneiminium salts react with suitable nucleophiles yielding iminium salts, but self-condensation reactions are frequently encountered when proton loss from the iminium salt can occur. This is illustrated in Scheme 2 for DMA.



Scheme 2

A large number of acid chlorides have been used to convert formamide derivatives into their corresponding chloromethyleneiminium salts (**13**). These include $POCl_3$ (the most popular), $SOCl_2$, phosgene, oxalyl chloride and many others.

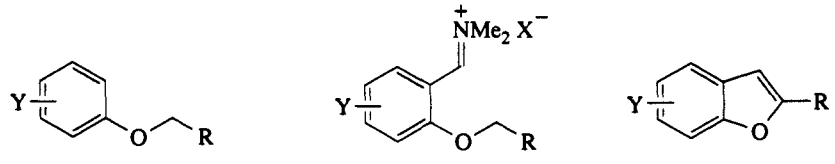
Solvents for the Vilsmeier–Haack reaction include DMF (the most common), $POCl_3$ and chlorinated alkanes such as dichloromethane, chloroform and tetrachloromethane. The choice of solvent and conditions is often an important consideration in Vilsmeier–Haack reactions when both mono- and di-substituted products can be formed.

3.5.3 REACTIONS OF AROMATIC COMPOUNDS WITH CHLOROMETHYLENIMINIUM SALTS

3.5.3.1 Carbocyclic Compounds

The Vilsmeier–Haack reaction of electron-rich carbocyclic aromatic compounds (Ar—H) with chloromethyleneiminium salt (**1**) gives aldehyde derivatives (Ar—CHO), generally in good yield.[1] The intermediate iminium salt (*cf.* salt **5**; Scheme 1) can be treated with hydroxylamine to obtain nitrile derivatives (Ar—CN).[5] Benzene and naphthalene are not sufficiently electron rich to participate in the Vilsmeier–Haack reaction, but polycyclic hydrocarbons, such as anthracene, do react. Benzene and naphthalene derivatives that possess an electron-releasing substituent (—OMe,—SMe,—NMe_2, *etc.*) af-

ford aldehyde derivatives. Electrophilic substitution is sometimes followed by intramolecular cyclization. This is exemplified by the synthesis of several 2-substituted benzo[*b*]furan derivatives that were prepared by treating compound (**16**; Y = one or more electron-releasing substituents; R = acetal group, CN, COPh) with salt (**1**).[6] In this reaction the intermediate iminium salt (**17**) cyclizes, and, after loss of dimethylamine, compounds (**18**; R = CHO, CN, COPh; 3–78%) are isolated. Ring-formylated products are also produced in these reactions.



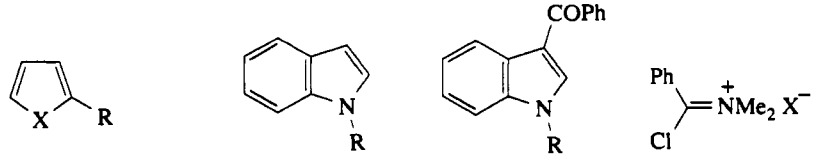
(**16**) (**17**) (**18**)

Y = electron-releasing group

Nonbenzenoid carbocyclic compounds also participate in the Vilsmeier–Haack reaction yielding aldehyde derivatives. Examples include azulene[7] and the cyclopentadienyl anion.[8]

3.5.3.2 Heterocyclic Compounds

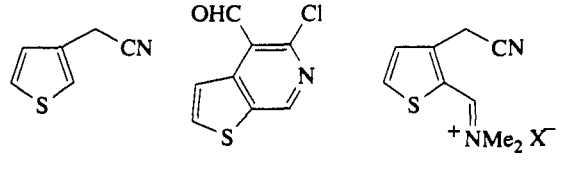
Pyrrole,[4,9] furan, thiophene and selenophene derivatives (**19**) yield aldehyde derivatives (**20**) in the Vilsmeier–Haack reaction with salt (**1**).[1] Yields are generally good. Substitution usually occurs at positions 2 or 5 unless there are suitably located blocking groups or electron-releasing groups that direct substitution to other positions. These heterocycles (**19**) are so reactive towards electrophilic substitution that deactivating groups (*e.g.* halogen, ester) do not preclude substitution. Benzo derivatives of heterocycles (**19**) also participate in the Vilsmeier–Haack reaction.[1,10] Pyrrole derivatives (**19**)[11] and indole derivatives (**21**)[12] afford ketones (**22**) and (**23**) respectively, when allowed to react with appropriate chloromethyleneiminium salts, for example salt (**24**). Numerous other electron-rich heterocycles give aldehyde derivatives under Vilsmeier–Haack conditions, and examples include 1-substituted pyrazoles and indolizines.



(**19**) R = H; X = NH, O, S, Se
(**20**) R = CHO; X = NH, O, S, Se
(**22**) R = COPh; X = NH, O, S, Se

(**21**) (**23**) (**24**)

Electrophilic substitution is often followed by intramolecular cyclization,[2] as exemplified by the reaction of 3-cyanomethylthiophene (**25**) with (**1**) yielding the thienopyridine derivative (**26**) *via* the intermediate iminium salt (**27**).[13]



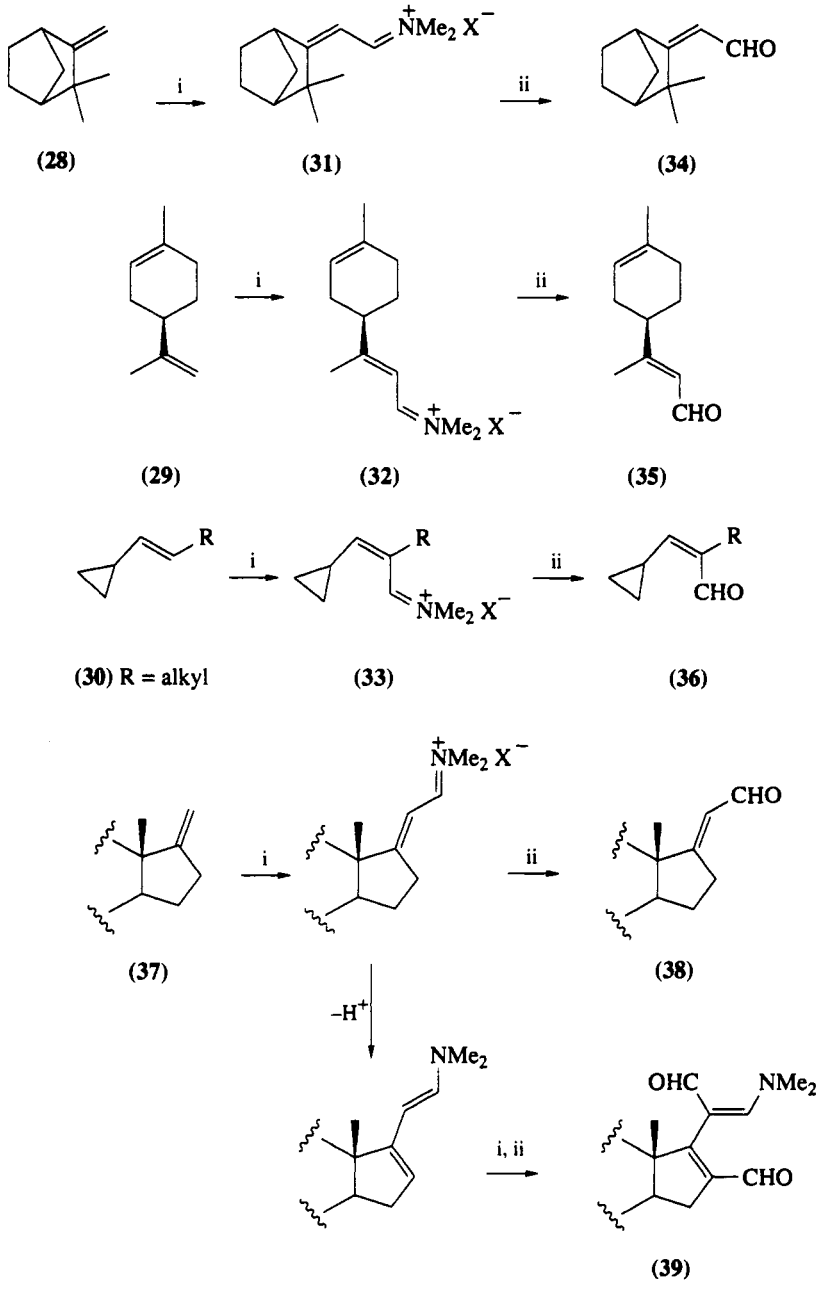
(**25**) (**26**) (**27**)

Several porphyrin derivatives participate in the Vilsmeier–Haack reaction giving products of substitution in either the pyrrole ring or at the methylene bridge position.[14]

3.5.4 REACTIONS OF ALKENE DERIVATIVES WITH CHLOROMETHYLENEIMINIUM SALTS

3.5.4.1 Alkene Derivatives without Electron-releasing Substituents

The reactions of alkene derivatives that do not possess electron-releasing substituents with chloromethyleneiminium salt (**1**) are illustrated for some representative examples in Scheme 3.[1] Electrophilic

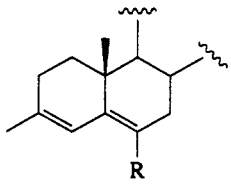


i, salt (**1**); ii, hydrolysis

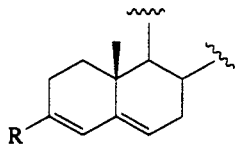
Scheme 3

substitution of camphene (**28**),[15] limonene (**29**)[16] and vinylcyclopropane derivatives (**30**)[17] by salt (**1**) affords, after loss of hydrogen chloride, the corresponding vinyliminium salts (**31–33**) which can be hydrolyzed giving the α,β-unsaturated aldehydes (**34**; 81%), (**35**; 40%) and (**36**; good yield), respectively. When proton abstraction from a vinyliminium salt can occur giving an enamine, further reaction with salt (**1**) usually occurs, eventually yielding products of polysubstitution. One illustrative example (Scheme 3) is the reaction of steroid derivative (**37**), which affords the monosubstituted product (**38**; 40%) under mild conditions (DMF:$POCl_3$, 1:1.5; 1 d) and product (**39**; 50%) of polysubstitution under forcing conditions (DMF:$POCl_3$, 1:15; 15 d).[18]

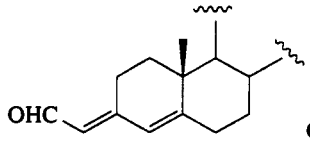
1,3-Dienes participate in the Vilsmeier–Haack reaction as illustrated by formation of aldehydes (**40**) and (**41**) from steroid derivatives (**42**) and (**43**) respectively.[19] Carbon–carbon bond migration also occurs in these two reactions and the corresponding aldehydes (**44**) and (**45**) are produced as by-products. 1,3,5-Trienes also yield aldehyde derivatives in the Vilsmeier–Haack reaction.[20,21]



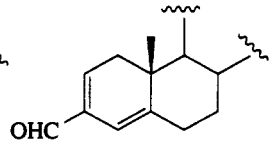
(**40**) R = CHO
(**42**) R = H



(**41**) R = CHO
(**43**) R = H



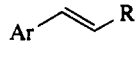
(**44**)



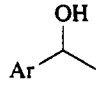
(**45**)

Numerous styrene derivatives (**46**),[22] including 1,2-dihydronaphthalene[23] and chromene[24] derivatives, react with salt (**1**) giving iminium salts (**47**) after loss of hydrogen chloride. Hydrolysis of iminium salts (**47**) gives cinnamaldehyde derivatives (**48**) and treatment with hydroxylamine affords nitriles (**49**),[25] generally in good yield. Iminium salts (**47**) can be conveniently prepared from alcohols (**50**) and related compounds if an excess of salt (**1**) is employed to promote initial dehydration of the alcohols (**50**) to the styrenes (**46**). If the aryl group in styrene derivatives (**46**) possesses a sufficient number of electron-releasing substituents then intramolecular electrophilic substitution of the iminium salt (**47**) can occur under forcing conditions, resulting in the formation of 1-dimethylaminoindene derivatives (**51**; 10–29%). Under mild conditions the corresponding cinnamaldehyde derivatives (**48**; 46–56%) are isolated.[26]

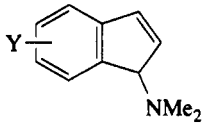
The formylation of styrene derivatives has been extended to several related alkene derivatives: indene (**52**) gives 2-formylindene (**53**; 20%),[27] polyenes (**54**)[28] and (**55**)[29] afford aldehydes (**56**; 92%) and (**57**; 29–65%), and fulvene derivative (**58**)[30] yields (**59**). In several cases, the products of monosubstitution described above are accompanied by products of polysubstitution, particularly under forcing conditions. For example, 2-phenylpropene reacts with salt (**1**) to give 4-phenylpyridine-3-carbaldehyde (**60**) after treatment with aqueous ammonium chloride solution.[31] A useful synthesis of biphenyls (**61**; 30–98%) from alcohol derivatives (**62**) and salt (**1**) has recently been reported.[32]



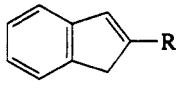
(**46**) R = H
(**47**) R = $CH{=}\overset{+}{N}Me_2\ X^-$
(**48**) R = CHO
(**49**) R = CN



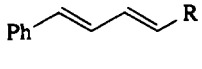
(**50**)



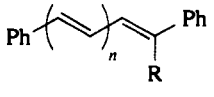
(**51**) Y = electron-releasing group



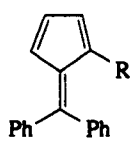
(**52**) R = H
(**53**) R = CHO



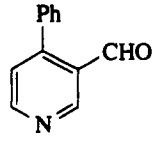
(**54**) R = H
(**56**) R = CHO



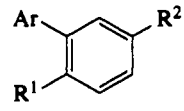
n = 1, 2, 3 (**55**) R = H
(**57**) R = CHO



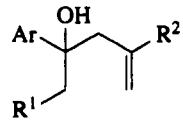
(58) R = H
(59) R = CHO



(60)



(61)



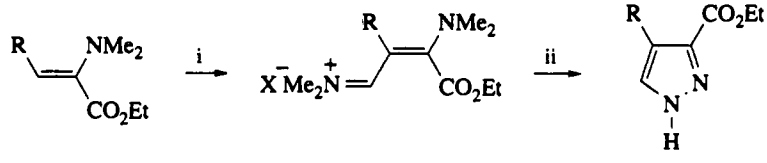
(62)

3.5.4.2 Alkene Derivatives with Electron-releasing Substituents and their Equivalents

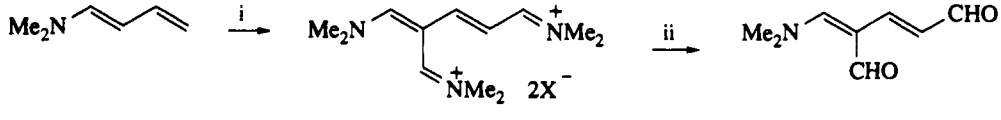
Numerous alkene derivatives that possess one electron-releasing substituent have been found to react with salt (**1**).[1] These include enamines, enamides, enecarbamates, enol ethers and enol acetates. Electrophilic substitution of these alkene derivatives occurs readily, yielding iminium salts that have found substantial use in synthesis.

Enamine derivatives (**63**) give salts (**64**) when treated with salt (**1**) and these salts (**64**) form pyrazole derivatives (**65**; 18–64%) when treated with hydrazine (Scheme 4).[33]

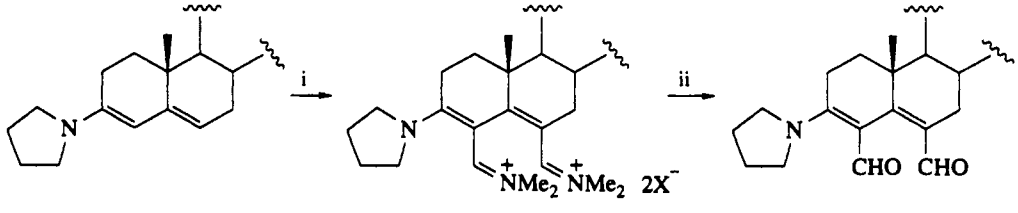
The dienamines (**66**)[34] and (**67**)[35] afford the corresponding iminium salts (**68**) and (**69**) resulting from disubstitution. Hydrolysis of these salts gives the dialdehyde derivatives (**70**; 35%) and (**71**; 36%) respectively. Salt (**68**) forms pyridine-3-carbaldehyde (97%) when treated with aqueous ammonium chloride solution.



(63) (64) (65)



(66) (68) (70)

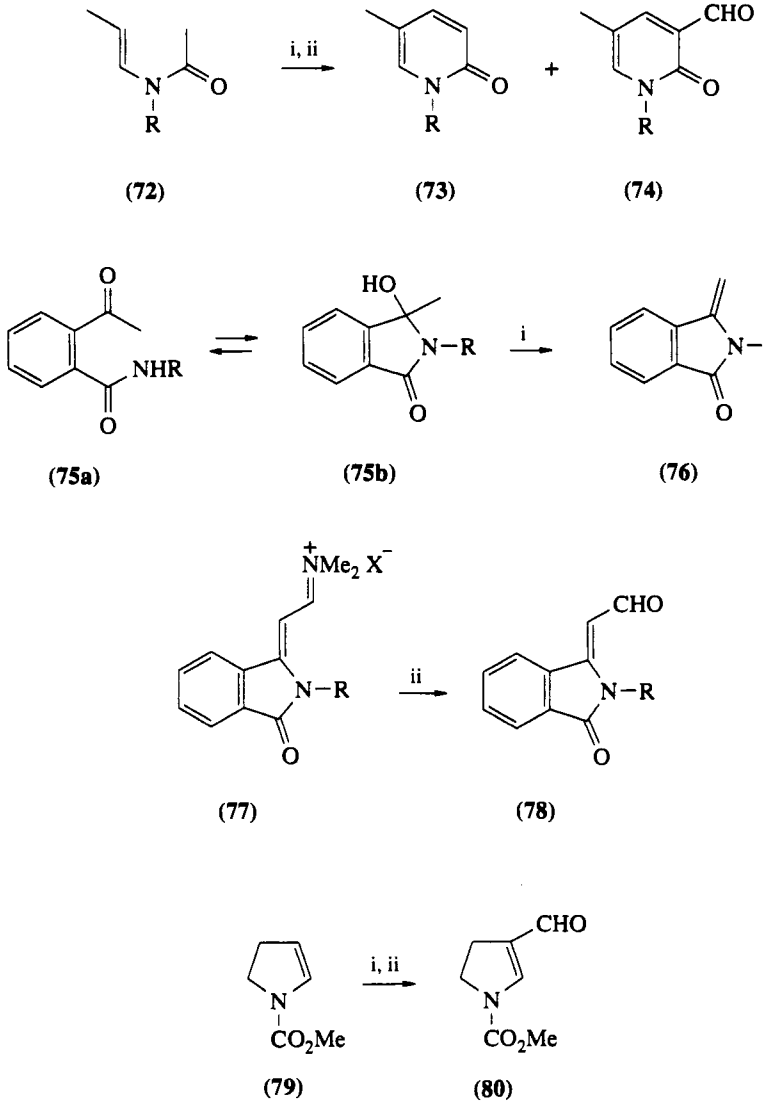


(67) (69) (71)

i, salt (**1**); ii, hydrolysis

Scheme 4

Several enamides, for example compound (**72**; Scheme 5), have been used as precursors to 1-substituted-2-pyridone derivatives (**73**) and pyridine-3-carbaldehyde derivatives (**74**; 14–69%).[36] Salt (**1**) promotes dehydration of tautomers (**75b**) of 2-acetylbenzamide derivatives (**75a**) to give enamides (**76**), which are converted by further reaction with salt (**1**) into iminium salts (**77**). Hydrolysis of these salts yields aldehydes (**78**; 81–99%; Scheme 5).[37] Enecarbamates, such as (**79**), give formylation products (**80**; 26–94%) in the Vilsmeier–Haack reaction (Scheme 5).[38]

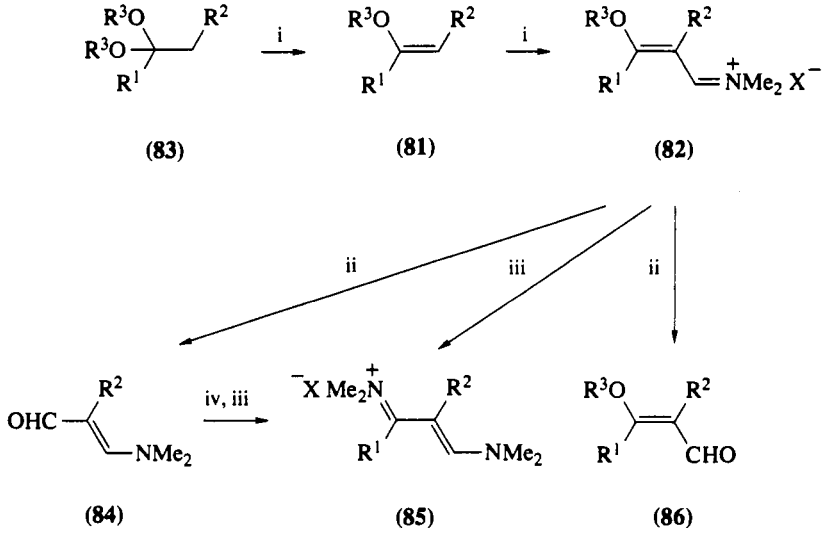


i, salt (**1**); ii, hydrolysis

Scheme 5

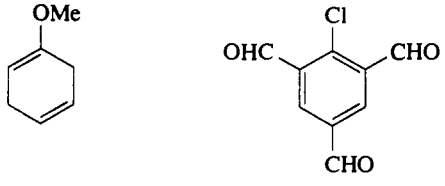
Enol ethers represented by the general structure (**81**; Scheme 6) and their vinylogs react with salt (**1**) to give iminium salts (**82**).[39a] Enol ethers (**81**) are often prepared *in situ* by treating acetals or ketals (**83**) with salt (**1**). Acetals (**83**) react with an excess of chloromethyleniminium salt (**1**) to provide iminium salts (**82**; R^1 = H, R^2 = alkyl or phenyl) that are hydrolyzed under basic conditions to afford β-dimethylaminoacrolein derivatives (**84**; 48–89%).[39b] Synthetically useful vinylamidinium salts (**85**; R^1 = H)[40] can be prepared by *O*-methylation of compounds (**84**) followed by treatment with dimethylamine. Ketals (**83**; R^3 = Et) similarly yield iminium salts (**82**; R^3 = Et, R^1 = alkyl or phenyl, R^2 = alkyl) from which either β-ethoxyacrolein derivatives (**86**; R^3 = Et; 59–92%) are isolated after basic hydrolysis or vinylamidinium

salts (**85**; 49–56%) are produced after treatment with dimethylamine.[39c] An interesting reaction of 1-methoxycyclohexa-3,6-diene (**87**) and derivatives has recently been reported: this compound gives chlorobenzene-2,4,6-tricarbaldehyde (**88**; 44%) in the Vilsmeier–Haack reaction.[41]



i, salt (**1**); ii, hydrolysis; iii, Me_2NH; iv, *O*-methylation

Scheme 6



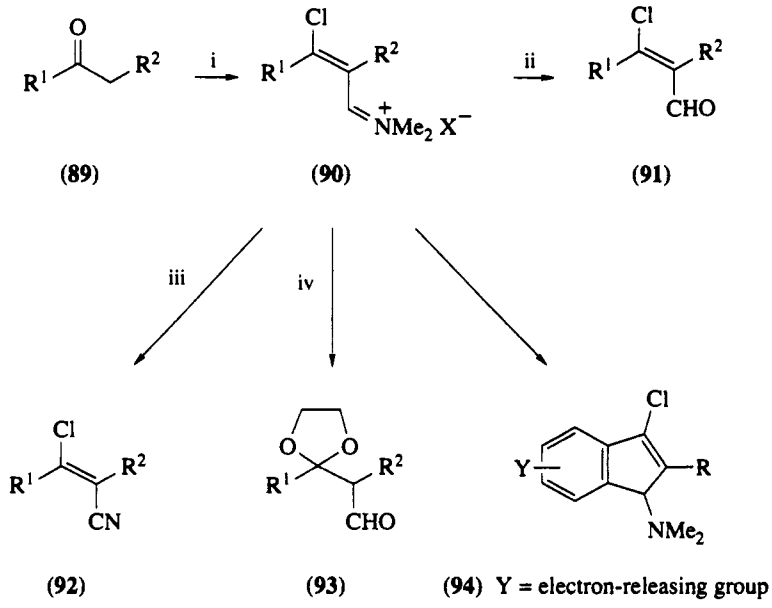
3.5.5 REACTIONS OF ACTIVATED METHYL AND METHYLENE GROUPS WITH CHLOROMETHYLENEIMINIUM SALTS

3.5.5.1 Aldehydes and Ketones

The reaction of ketone derivatives (**89**) with chloromethyleneiminium salt (**1**) gives iminium salts (**90**) which yield, after hydrolysis, β-chloroacrolein derivatives (**91**; Scheme 7).[42] Numerous β-chloroacrolein derivatives have been prepared by this method and yields are generally moderate to good. β-Chloroacrylonitrile derivatives (**92**) are also available in good yield from iminium salts (**90**; R^2 = H) by treatment with hydroxylamine.[43] Ketals (**93**) can be prepared from iminium salts (**90**) by treatment with the monosodium salt of ethylene glycol followed by hydrolysis under basic conditions (32–69%).[44] If the group R^1 in ketone (**89**) is aromatic and electron rich, then intramolecular electrophilic substitution of iminium salt (**90**) can occur giving a 1-dimethylamino-3-chloroindene derivative (**94**). The general reaction (**89**) → (**91**) depicted in Scheme 7 has been extended to vinylogs of aldehydes and ketones (**89**).[45]

Ketones that possess active methyl or methylene groups at both α-positions can undergo polysubstitution reactions as exemplified by the Vilsmeier–Haack reaction of dibenzyl ketone (**95**), which affords 3,5-diphenylpyrone (**96**; 35%).[46] Products of polysubstitution are also observed in the Vilsmeier–Haack

reaction of 1,3-diketones: a useful synthesis of 2,4-dichlorobenzaldehyde derivatives from 1,3-diketones has recently been reported.[47] Cyclohexenone derivatives similarly yield products of polysubstitution.[48]

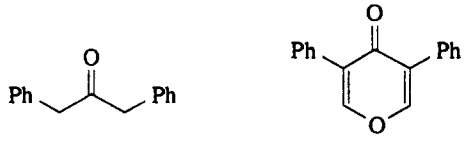


(89) (90) (91)

(92) (93) (94) Y = electron-releasing group

i, salt (**1**); ii, hydrolysis; iii, NH_2OH; iv, $NaOCH_2CH_2OH$

Scheme 7



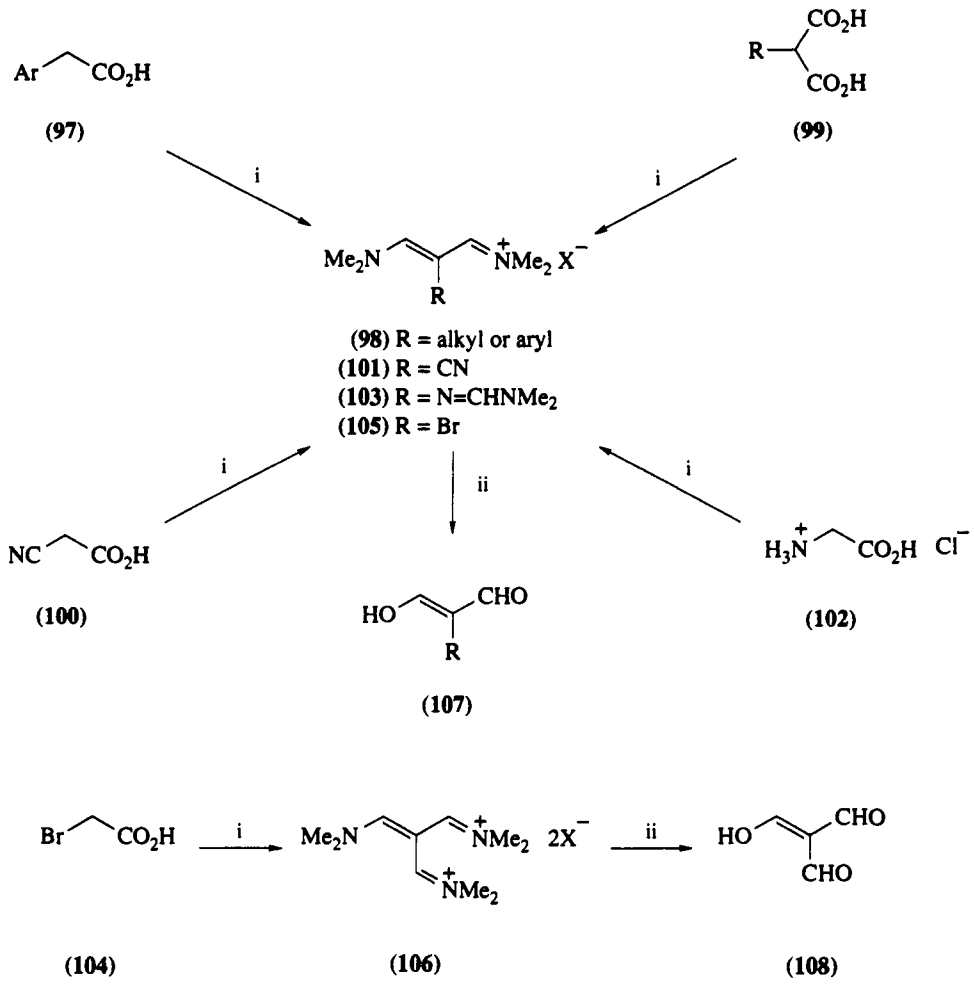
(95) (96)

3.5.5.2 Carboxylic Acids

Arylacetic acid derivatives (**97**) react with salt (**1**) to give vinylamidinium salts (**98**; R = Ar; Scheme 8). Carbon dioxide is evolved during this reaction. The corresponding vinylamidinium salts (**98**; R = alkyl) are not available from acetic acid derivatives, but can be readily obtained by treating malonic acid derivatives (**99**; R = alkyl) with salt (**1**). Cyanoacetic acid (**100**) affords vinylamidinium salt (**101**) and glycine hydrochloride (**102**) gives salt (**103**) with salt (**1**). In the latter reaction, *N*-substitution also occurs (see Section 3.5.6.2). Bromoacetic acid (**104**) does not give amidinium salt (**105**) but instead yields salt (**106**; Scheme 8), which can also be prepared from malonic acid and salt (**1**). The vinylamidinium salts (**98**), (**101**) and (**103**) are useful precursors of malondialdehyde derivatives (**107**; R = alkyl or aryl, R = CN, R = $NH_3^+Cl^-$) and salt (**106**) is a precursor of triformylmethane (**108**).[1] The acid chloride of cyclohexa-2,6-dienecarboxylic acid yields 1,3,5-triformylbenzene (62%) when treated with salt (**1**).[49]

3.5.5.3 Amides, Lactams and Lactones

Amides, for example *N,N*-dimethylcarboxamides, represented by the general formula (**109**), react with salt (**1**) to yield chloroiminium salts (**110**; Scheme 9). Hydrolysis of these salts affords 2-dimethylaminomethylene amide derivatives (**111**). If group R in salt (**110**) is hydrogen, further reaction with salt (**1**) is possible, giving chloroiminium salts (**112**). Hydrolysis of these salts (**112**) affords aldehydes (**113**).

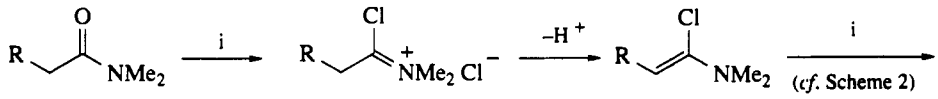


i, salt (**1**); ii, hydrolysis

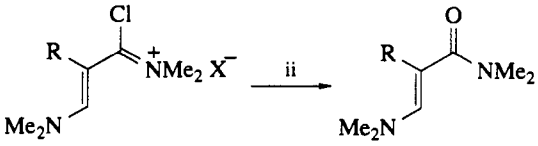
Scheme 8

An excellent method for preparing quinolines from acetanilide derivatives (**114**) and salt (**1**) has been reported.[50] Acetanilide derivatives (**114**) are generally disubstituted (*cf.* Scheme 9) yielding the corresponding chloroiminium salts (**115**). These salts (**115**) undergo an intramolecular electrophilic substitution giving, after loss of dimethylamine, iminium salts (**116**). Hydrolysis of salts (**116**) gives aldehydes (**117**; 0–78%). Propionanilides give 3-substituted-2-chloroquinoline derivatives (28–95%) in an analogous reaction. Acetyl derivatives of aminothiophenes and aminopyrazoles similarly yield thienopyridine and pyrazolopyridine derivatives, respectively. 2-Quinolone derivatives (**118**) are available from *N*-substituted acetanilides (**119**) and related compounds.[51]

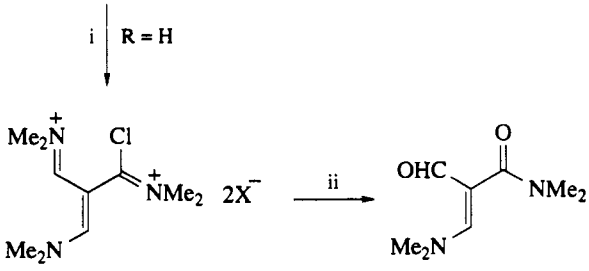
Lactams represented by the general formula (**120**), including 2-oxyindole derivatives, yield 2-dimethylaminomethylene derivatives (**121**; *cf.* Scheme 9) or chloroaldehyde derivatives (**122**; *cf.* Scheme 7) when treated with salt (**1**).[52] Lactams (**120**; R = H) react with formamide/$POCl_3$ complex to give pyrimidine derivatives (**123**). Δ^3-Pyrrolidin-2-ones (**124**) behave as vinylogous amides and react with salt (**1**) or DMF/$POBr_3$ to provide iminium salts (**125**; Y = Cl, Br), which yield pyrrole-2-carbaldehydes (**126**; Y = Cl, Br) after hydrolysis. Lactone derivatives (**127**) generally behave analogously to lactam derivatives: products (**128**) and/or (**129**) are formed.[1,53]



(109)



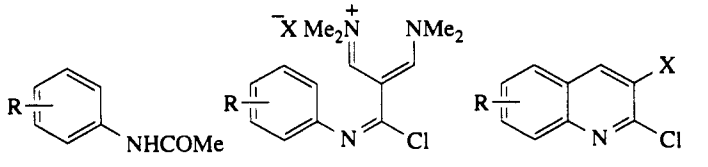
(110) **(111)**



(112) **(113)**

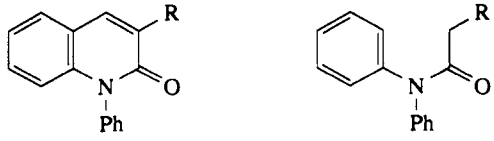
i, salt (**1**); ii, hydrolysis

Scheme 9

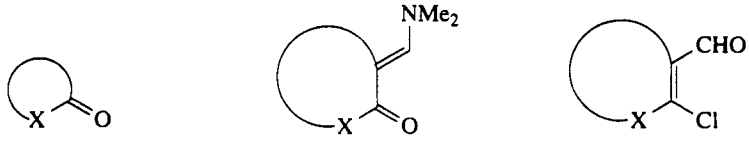


(114) **(115)** **(116)** X = $CH{=}\overset{+}{N}Me_2$ X^-

(117) X = CHO



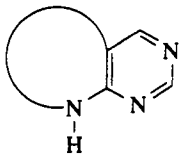
(118) **(119)**



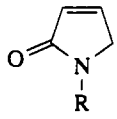
(120) X = NR
(127) X = O

(121) X = NR
(128) X = O

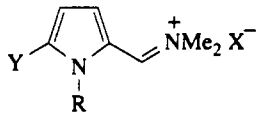
(122) X = NR
(129) X = O



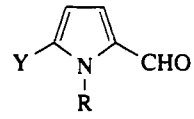
(123)



(124)



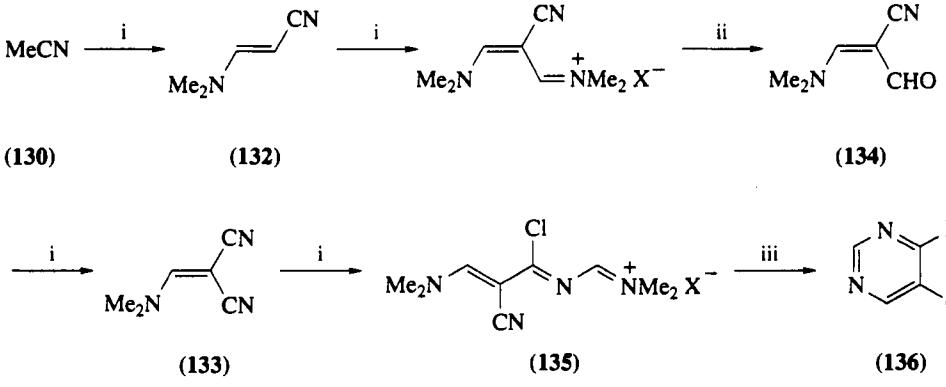
(125) Y = Cl, Br



(126) Y = Cl, Br

3.5.5.4 Nitriles

Acetonitrile (**130**) and malononitrile (**131**) both react with salt (**1**) to yield products of disubstitution (Scheme 10). The monosubstituted intermediates (**132**) and (**133**) react at carbon and nitrogen, giving, after hydrolysis, products (**134**) and (**135**), respectively. Salt (**135**) affords the heterocycle (**136**) when treated with ammonia.[1,54]

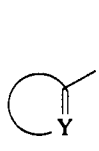


i, salt (**1**); ii, hydrolysis; iii, NH_3

Scheme 10

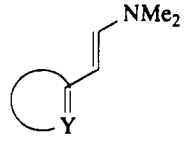
3.5.5.5 Benzylic Methyl and Methylene Groups

Benzylic methyl groups in nitrogen-containing aromatic compounds represented by general formula (**137**) and salt (**1**) afford products of monosubstitution (**138**) or products of disubstitution (**139**; *cf.* Scheme 1). Hydrolysis of salt (**139**) affords malondialdehyde derivatives (**140**) and this represents an important method of synthesizing these aldehyde derivatives (**140**).[1,55] Benzylic methylene groups behave similarly, yielding the corresponding products of monosubstitution.[1,56] Representative heterocycles that participate in this reaction include 4-methylpyridine and 6-methylpyrimidine. Several nitrogen-containing heterocycles that posses appositely located methyl and amine groups, for example pyrazine derivative (**141**), react with salt (**1**) giving, after loss of hydrogen chloride, amidinium salts like (**142**). After reaction of a second molecule of salt (**1**) at the methyl group in salt (**142**), giving salt (**143**), cyclization and loss of dimethylamine occur, yielding iminium salt (**144**). Hydrolysis of this salt gives aldehyde (**145**). Heterocyclic iminium salts (**146**) react with salt (**1**) giving, after loss of hydrogen chloride, monosubstituted (**147**) or disubstituted (**148**) products. Oxonium salts react similarly.[1] 2,4,6-Trinitrotoluene (**4**) and related compounds react with salt (**1**) to give iminium salts (**11**), which can be converted into aldehyde derivatives (**12**) by hydrolysis (Scheme 1).[1]



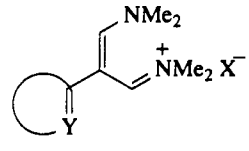
(137) Y = N

(146) Y = $\overset{+}{N}$R



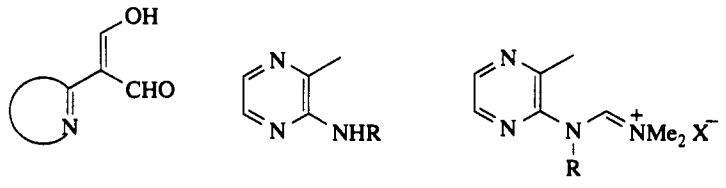
(138) Y = N

(147) Y = $\overset{+}{N}$R

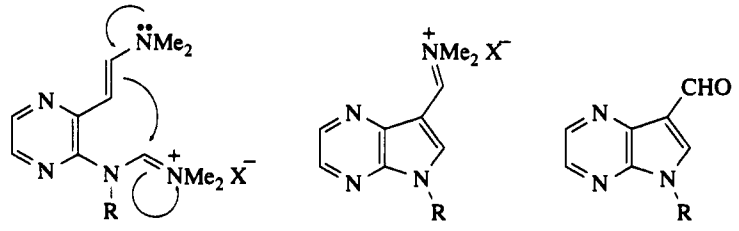


(139) Y = N

(148) Y = $\overset{+}{N}$R



(140) (141) (142)



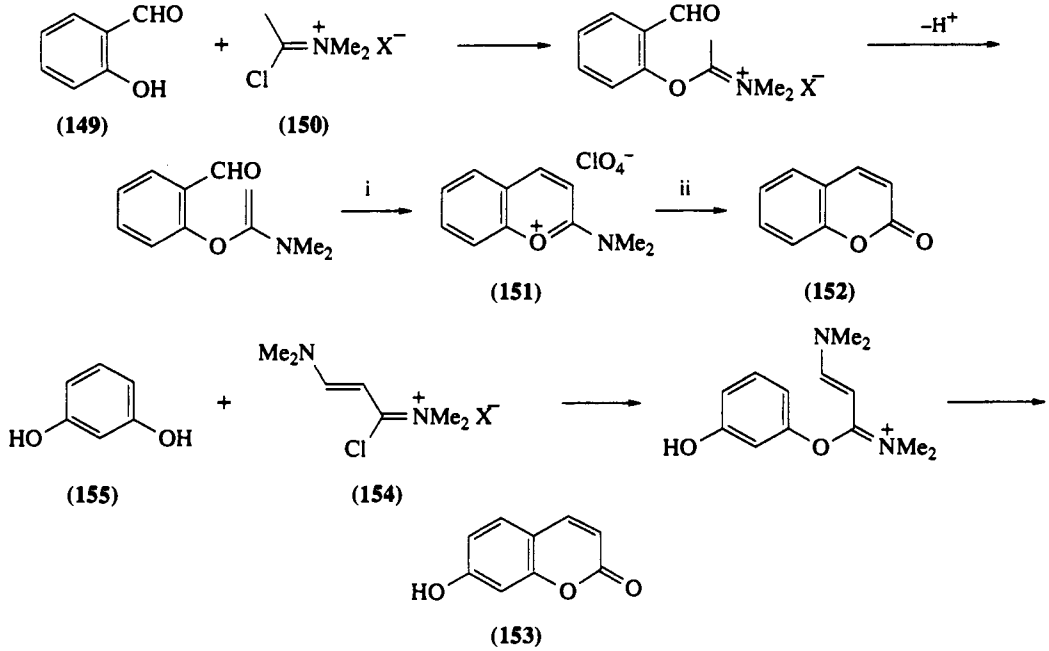
(143) (144) (145)

3.5.6 REACTIONS OF NONCARBON NUCLEOPHILES WITH CHLOROMETHYLENE IMINIUM SALTS

3.5.6.1 Oxygen Nucleophiles

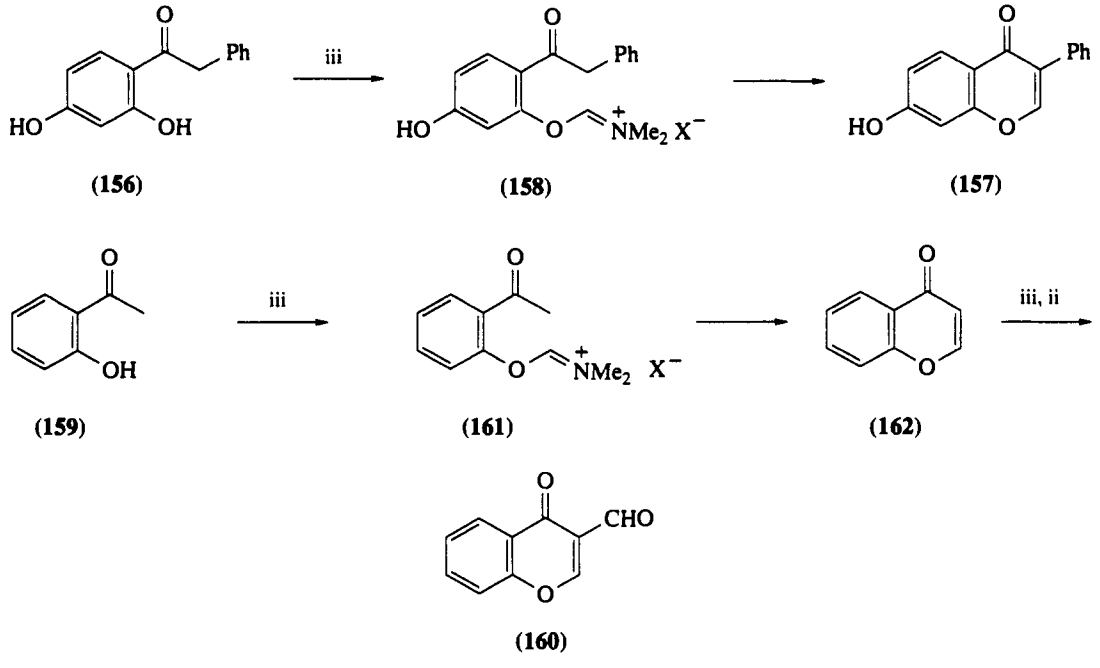
Formates have been prepared by the reaction of chloromethyleneiminium salts with derivatives of alcohols and phenols. Yields are generally good.[57]

The synthesis of several oxygen-containing heterocycles from phenolic precursors using the Vilsmeier–Haack reaction has been achieved (Schemes 11 and 12). Salicylaldehyde (**149**) and chloromethyleneiminium salt (**150**) afford, after treatment with perchloric acid, the benzopyrylium salt (**151**) which yields coumarin (**152**) when treated with aqueous base.[58] Umbelliferone (**153**) has been prepared (62%) by treating DMF with DMA in the presence of $POCl_3$ and condensing the resulting iminium salt (**154**) with resorcinol (**155**).[59] 2,4-Dihydroxydeoxybenzoin (**156**) and chloromethyleneiminium salt (**1**) give isoflavone (**157**), presumably by cyclization of the intermediate (**158**) and loss of dimethylamine. 2-Hydroxyacetophenone (**159**) and related compounds afford aldehyde derivatives (**160**) in the Vilsmeier–



Scheme 11

Haack reaction in good yield. In this reaction, the intermediate salt (**161**) cyclizes with loss of dimethylamine giving chromenone (**162**), which then undergoes formylation, yielding product (**160**).



(**156**) (**158**) (**157**)

(**159**) (**161**) (**162**)

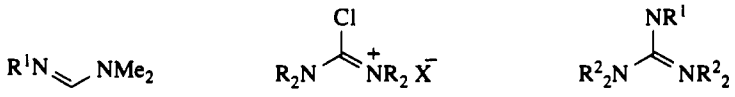
(**160**)

i, $HClO_4$; ii, hydrolysis; iii, salt (**1**)

Scheme 12

3.5.6.2 Nitrogen Nucleophiles

Primary amines (R^1NH_2) react with salt (**1**) to give, after loss of hydrogen chloride, amidine derivatives (**163**).[1] Salts (**164**) derived from urea derivatives react similarly, giving guanidines (**165**).[60]



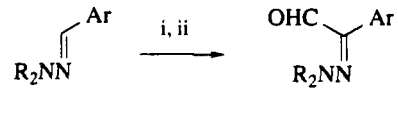
(**163**) (**164**) (**165**)

Lactams represented by the general structure (**120**; R = H) are *N*-formylated to give products (**120**; R = CHO) in the Vilsmeier–Haack reaction unless the amide has an available α-hydrogen atom in which case products (**121**) and (**122**) are formed (see Section 3.5.5.3).[1]

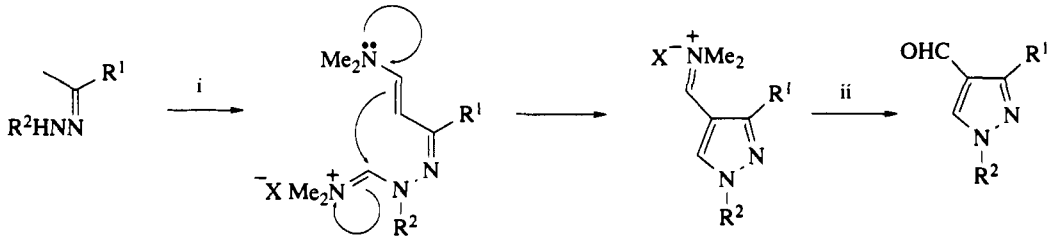
3.5.7 MISCELLANEOUS REACTIONS OF CHLOROMETHYLENEIMINIUM SALTS

3.5.7.1 Hydrazones and Semicarbazones

Hydrazones (**166**) react with chloromethyleneiminium salt (**1**) giving, after hydrolysis, aldehydes (**167**; Scheme 12). In this transformation the hydrazones (**166**) are clearly behaving as aza–enamines.[1,61] Hydrazones (**168**) and (**169**) react with chloromethyleneiminium salt (**1**) at both the methyl group and at nitrogen to yield the corresponding iminium salts (**170**) and (**171**), which cyclize with loss of dimethylamine to provide iminium salts (**172**) and (**173**), respectively. Hydrolysis of these salts (**172**) and (**173**) affords pyrazole-4-carbaldehyde derivatives (**174**) and (**175**; 72–96%; Scheme 13).[1] Product (**174**) can also be prepared from semicarbazone (**176**).



(166) (167)



(168) R^2 = H (170) R^2 = H (172) R^2 = H (174) R^2 = H
(169) R^2 = Ph (171) R^2 = Ph (173) R^2 = Ph (175) R^2 = Ph
(176) R^2 = $NHCONH_2$

i, salt (**1**); ii, hydrolysis

Scheme 13

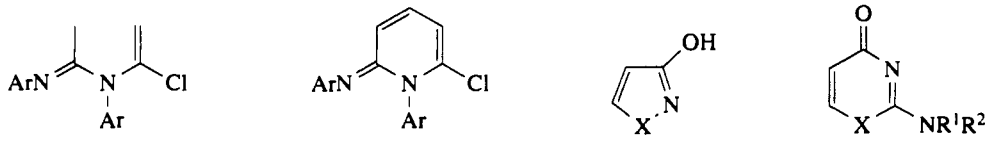
3.5.7.2 Enamidines

Enamidine derivatives (**177**) afford pyridinimines (**178**; 31–75%) in the Vilsmeier–Haack Reaction.[62]

3.5.7.3 Other Groups

Other groups[1] that react with chloromethyleneiminium salts include hydroxylamines,[63] hydrazines,[64] oximes,[65] imines, azines, anhydrides,[66] imides[67] and ketene *O*-alkyl-*O'*-silyl acetal derivatives;[68] however, reactions with these compounds have been relatively infrequent.

Heterocycles represented by the general structure (**179**) afford ring-expanded products (**180**) in the Vilsmeier–Haack reaction[53,69] with chloromethyleneiminium salt (**13**).



(177) (178) (179) X = O, S (180) X = O, S

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3.6
Acylation of Esters, Ketones and Nitriles

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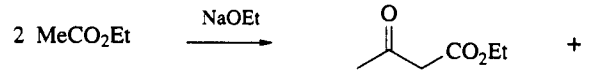
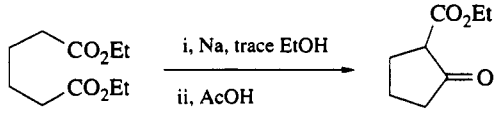
3.6.1 INTRODUCTION

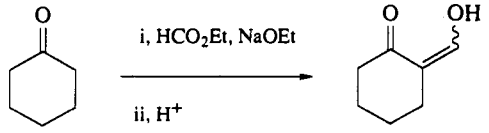
In 1887, Claisen and Lowman[1] reported that the condensation of 2 mol of an ester, such as ethyl acetate, in the presence of base gave the β-keto ester, ethyl acetoacetate (ethyl 3-oxobutanoate; equation 1). The intramolecular equivalent was recognized by Dieckmann in 1894.[2] He found that heating an adipic acid ester with sodium and a trace of alcohol led to cyclization, with the formation of a cyclopentanone (equation 2). The reaction was, at an early stage, extended to the acylation of ketones. Claisen himself reported the base-catalyzed reaction of acetophenone and ethyl benzoate to give dibenzoylmethane in 1887.[3] This reaction, too, has an intramolecular parallel. The acylation of ketones with esters and other acid derivatives is sometimes called a Claisen condensation, although this usage is criticized by some writers and avoided by others. A widely used example of ketone acylation is the synthesis of α-formyl (hydroxymethylene) ketones (equation 3). Intramolecular variants of this reaction include the classical synthesis of dimedone (Scheme 1).



(1)



(2)



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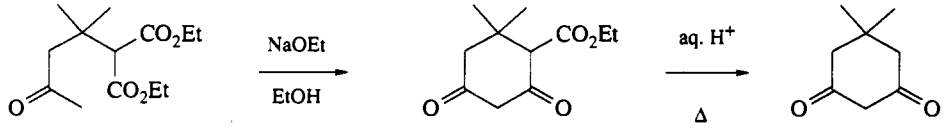
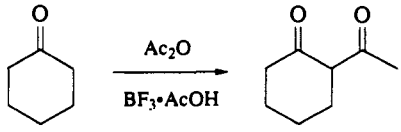
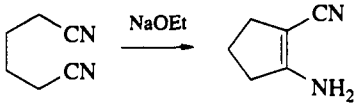


Scheme 1

Ketones can be acylated in the presence of acid catalysts such as boron trifluoride, polyphosphoric acid and other proton acids; acid anhydrides are typically used as acylating agents (equation 4). Other anion-stabilizing groups, such as nitrile, have been used in the carbon–carbon bond-forming step. These reactions are also described after their discoverers as the Thorpe and Thorpe–Ziegler reactions (equation 5).



(4)



(5)

Modern synthetic practice frequently requires the use of methods more specific than those outlined above. Much attention has been focused on the 'mixed' Claisen or Dieckmann reaction, *i.e.* the acylation of one ester by another, or its intramolecular equivalent, the regioselective cyclization of an unsymmetrical diester. A similar problem arises with the acylation of unsymmetrical ketones. This chapter thus describes the inter- and intra-molecular carbon–carbon bond-forming reactions in which a delocalized enolate anion (or close equivalent) reacts at an sp^2 carbon atom in an addition–elimination sequence, as well as the acid-catalyzed equivalent employing an enol. In Table 1 we list the potential nucleophiles and the electrophiles that have been employed in these reactions, although not every possible combination has been reduced to synthetic practice. Table 2 gives details of acid-catalyzed acylations (see Section 3.6.4.3).

Table 1 Reactions Involving an Enolate Anion or Equivalent

Potential nucleophiles	*Electrophiles*
Esters	Esters
Carboxylic acids	Nitriles
Nitriles	Acyl chlorides
Ketones	Acid anhydrides
Amides	Acyl cyanides
	Carbon dioxide
	Alkyl dialkoxyphosphinyl formate
	Acyl imidazoles
	Thiol esters
	Thio esters

Table 2 Acid-catalyzed Acylations

Nucleophiles	*Electrophiles*
Ketones	Acid anhydrides
	Acyl chlorides
	Carboxylic acids

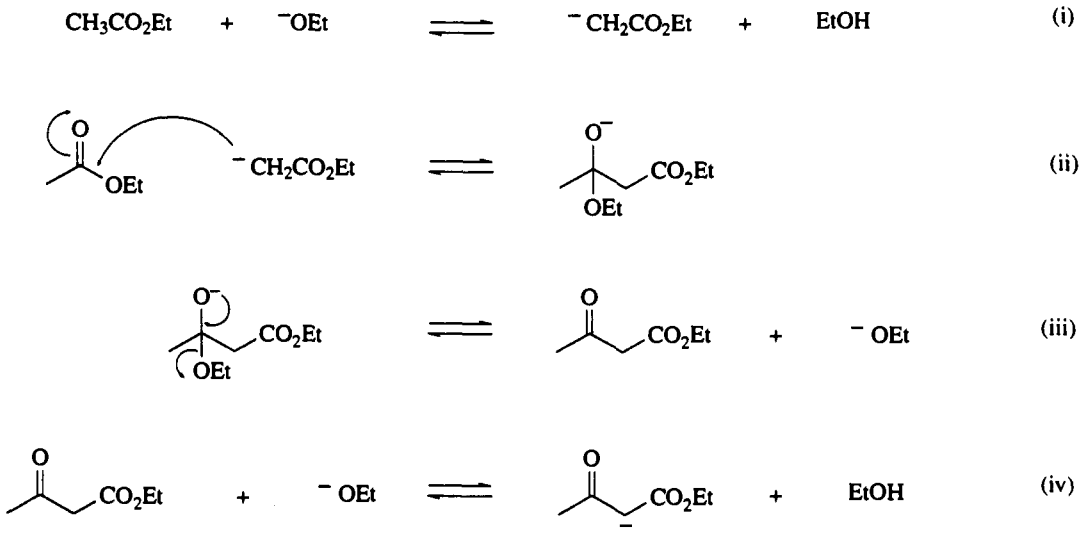
The reactions have been comprehensively reviewed in *Organic Reactions*; the acylation of esters in Volume 1 (1942),[4] the acylation of ketones in Volume 8 (1954)[5] and the Dieckmann and Thorpe–Ziegler reactions in Volume 15 (1967).[6] More recent reviews are provided by House[7] and in a book on carbon–carbon bond-forming reactions.[8] Specific examples of many of these reactions are given in '*Organic Syntheses*'.

3.6.2 MECHANISM

The condensation of one ester with another under basic conditions is generally thought to proceed by an ionic mechanism involving anionic species and the transfer of electron pairs.[4] Substantial evidence supports this view, but recent work does indicate the possibility of a single electron transfer (SET) process in some cases.

For an ester with two hydrogens on the α-carbon atom, the accepted mechanism, using sodium ethoxide as catalyst, is shown in Scheme 2. With bases such as sodium ethoxide, with $pK_a \approx 18$, each of the

steps leading to the conjugate base of the keto ester is reversible and the initial equilibrium with the ester ($pK_a \approx 25$) is not favored. However, the overall process is driven towards the product by the formation of the anion of the β-keto ester ($pK_a \approx 11$) in the final step. For typical aliphatic esters, the equilibrium constant for the overall reaction shown in equation (6) is approximately 1. Thus, the equilibrium can be moved to the right by the use of excess ester or by the removal of ethanol.



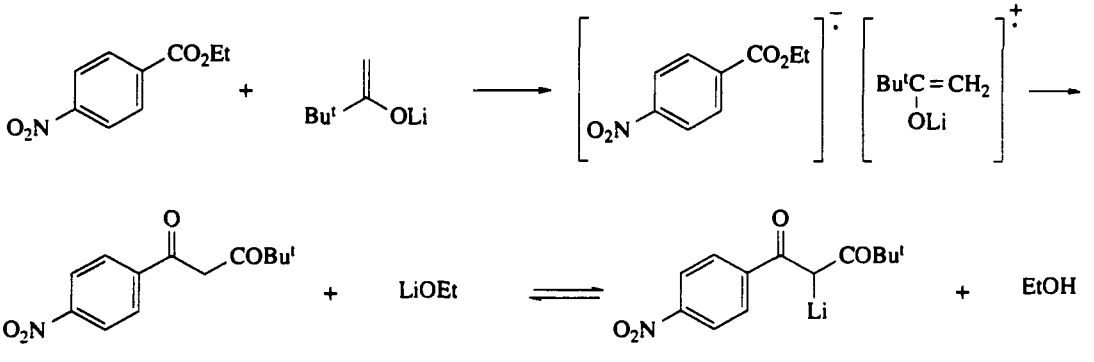
Scheme 2

2 ester + EtO^- ⇌ keto ester anion + EtOH (6)

In cases where the starting ester contains only one α-hydrogen, *e.g.* ethyl 2-methylpropanoate, the procedure leads to a β-keto ester disubstituted on the α-carbon atom, $Me_2CHCOCMe_2CO_2Et$. Such reactions are not effected by the use of ethoxide ion, which is not a strong enough base to form the conjugate base of the keto ester product. Strong bases, such as sodium hydride, are sufficient to deprotonate the starting ester, the β-keto ester product and ethanol. In the overall equilibrium, the latter two reactions favor products, while the first favors reactants. On balance, the equilibrium favors products and good yields are obtained. A discussion of the equilibria involved is contained in ref. 9.

Processes occurring in the acid-catalyzed acylation of ketones are discussed in Section 3.6.4.

Work by Ashby *et al.* has established the intermediacy of radicals in a variety of processes previously thought to be purely ionic. The Claisen condensation of ethyl *p*-nitrobenzoate with the lithium enolate of pinacolone gave an EPR-active species whose rate of formation and decay indicated that it was on the pathway to the product.[10] The postulated mechanism is shown in Scheme 3. However, this was the only example of SET observed by this group for this reaction and the intermediacy of the radical anion of the ester in this case is plausible but not proved.[11]



Scheme 3

3.6.3 THE ACYLATION OF ESTERS

3.6.3.1 Introduction

The classic acetoacetic ester condensation, named after Claisen but modeled closely on the conditions reported by Geuther in 1863,[12] employed sodium ethoxide as a base in the self-condensation of ethyl acetate. Yields may be increased by removal of the ethanol formed in the reaction and also by the use of stronger bases, including sodium, sodium amide, bromomagnesium diisopropylamide, sodium hydride or potassium hydride, dimsyl sodium in dimethyl sulfoxide, or various lithium dialkylamide bases (for leading references see ref. 13). Sodium hydride may be used with a catalytic amount of ethanol; the alkoxide is continuously replenished as the reaction proceeds and effects the condensation. The reaction has been performed in a variety of aprotic solvents, such as toluene or THF. α,α-Disubstituted esters do not undergo efficient Claisen condensation using sodium ethoxide, as described above. Very similar procedures are used for the intramolecular variant of the reaction, the Dieckmann cyclization, particularly in the formation of five- and six-membered rings.

3.6.3.2 Mixed Esters and Unsymmetrical Diesters

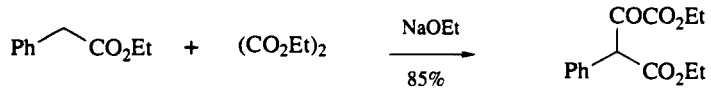
As a reaction of synthetic utility the simple Claisen condensation is limited to the self-condensation of esters possessing one or, more usually, two hydrogen atoms α to the ester carbonyl group. Likewise the original Dieckmann reaction is of most use with symmetrical diesters. However, on many occasions a more complex or less symmetrical β-keto ester is required and the literature continues to provide examples of the synthetic art, where the problem of mixed esters is overcome. A simple condensation of two esters, $R^1CH_2CO_2Et$ and $R^2CH_2CO_2Et$ with base may provide a mixture of four β-keto esters. These are not all formed in the same yield, as the product of reaction between the least hindered carbanion and the least hindered carbonyl group is likely to predominate. However, the reaction is of little synthetic utility today and a number of modifications to the original procedure have allowed considerable scope in developing the synthesis of specific β-keto esters.

3.6.3.2.1 One ester has no α-hydrogen

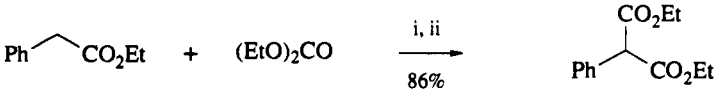
One effective technique for selective reaction is to employ one ester which possesses no α-hydrogen atoms. Simple aliphatic esters such as ethyl formate, diethyl oxalate and diethyl carbonate are commonly used while, among the aromatic esters, benzoic, substituted benzoic and furoic esters are commonly employed. Self-condensation of the ester providing the carbanion is not a major problem. Examples of this reaction are given in Scheme 4; further examples are listed in the reviews. Diethyl oxalate and ethyl formate react readily in this way, although forcing conditions are often necessary with diethyl carbonate and aromatic esters.

3.6.3.2.2 Preformed enolates

In the reactions as originally described, the enolate anion of one ester is generated in the presence of another ester and, with weaker bases such as sodium ethoxide, is not generated quantitatively, leading to the possibility of mixed products. The opportunity exists, therefore, that a preformed enolate, widely used in aldol chemistry, might be employed in the condensation of two different esters, both possessing α-hydrogen atoms. Rathke and Deitch[18] formed the lithium enolates of ethyl acetate, hexanoate and isobutyrate, using LICA. Treatment of these enolates with a variety of acid chlorides gave the corresponding β-keto ester in isolated yields from 51 to 81%. To prevent attack of the enolate on the ketone function of the product, a second mole of base was used to convert the product into its enolate anion. In a similar manner, Logue[19] reacted *t*-butyl α-lithioisobutyrate with a number of substituted benzoyl chlorides; yields of the derived β-keto esters were generally in the range 55–88%. The *t*-butyl group could be removed readily by brief treatment with trifluoroacetic acid at room temperature; decarboxylation occurred at reflux temperatures. Couffignal and Moreau[20] acylated a number of saturated and unsaturated esters with a carboxylic carbonic anhydride (RCO_2CO_2Et) to obtain yields of β-keto ester in the range 40–70%. This synthesis was also applied to ketone enolates, producing β-diketones. Cowan



(ref. 14)

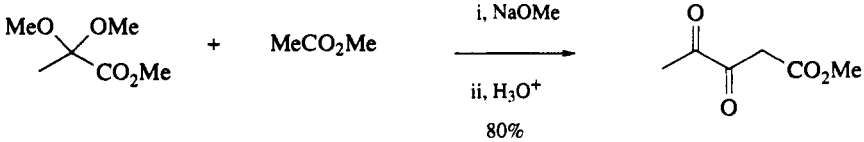


(ref. 15)

i, NaOEt, continuous removal of EtOH; ii, H_3O^+

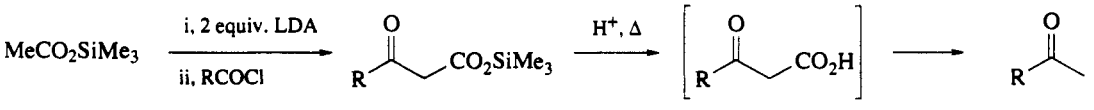
(ref. 16)

i, 1 equiv. LDA, THF, –78 °C; ii, $Bu^tC{\equiv}CCO_2Ph$



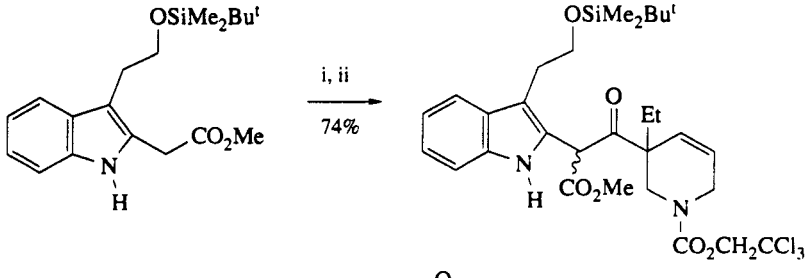
(ref. 17)

Scheme 4



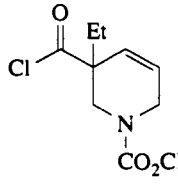
R = Ph, *o*-Tol, Bu^t, Pr^i, Pr^n

Scheme 5



(7)

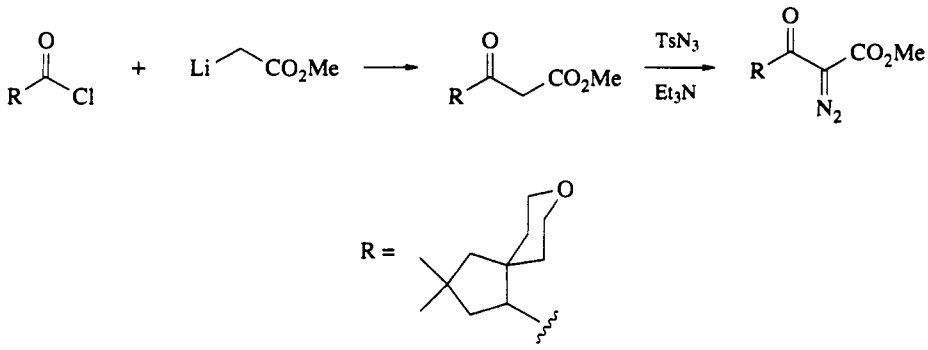
i, 2 equiv. LDA; ii,



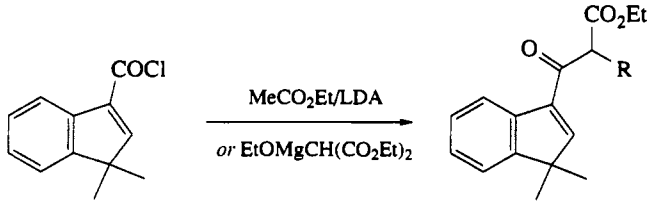
and Rathke[21] utilized the acylation of the lithium enolate of trimethylsilyl acetate as a route to β-keto acids and thus methyl ketones (Scheme 5).[21] Preformed enolates were chosen to synthesize some long chain β-hydroxy acids related to mycolic acid. Acylation with a suitable acid chloride gave the desired β-keto ester in high yield.[22]

The use of preformed enolates continues to provide a valuable route for performing mixed Claisen condensations. Reaction of a 2-indolylacetic ester with 2 mol of LDA and treatment of the product with an α-trisubstituted acid chloride gave the corresponding keto ester as a diastereomeric mixture in 74% yield (equation 7).[23]

In another example, 2 mol of base were used in the production of the enolate; the resulting enolate product was then trapped as the diazo ketone (Scheme 6).[24] A comparative study was provided by the work of Kurihara *et al.* in their approaches to the total synthesis of lysergic acid (equation 8).[25]



Scheme 6

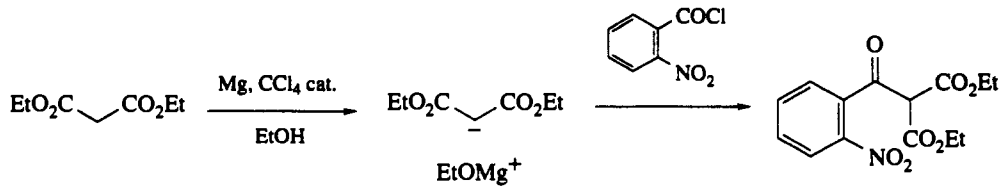


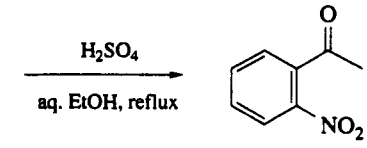
(8)

R = H; 86%
R = CO_2Et; 89%

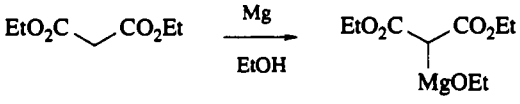
3.6.3.2.3 One ester is more acidic

In a mixed Claisen ester condensation, employing two simple monoesters, the acidity of the two sets of α-hydrogen atoms is unlikely to differ greatly and can lead to mixed products. The chemoselectivity can be greatly improved by employing one ester whose α-hydrogen atoms are considerably more acidic, *e.g.* a malonic ester derivative or a β-keto ester.[26] In practice, an anion from diethyl malonate is most often acylated with an acid chloride or acid anhydride. Magnesium enolates have found particular use here, as illustrated in Scheme 7. Acyl cyanides[29] and 1-acyl imidazoles[30] have also been used in this way (Scheme 8). Masamune and coworkers[31] showed that the neutral magnesium salt of a malonic or methyl malonic half ester or half thiol ester reacted with an acylimidazolide to give β-keto esters in excellent yield (equation 9). The reaction appeared to be a substantial improvement on the use of the basic magnesium enolate and has been used by other workers. Useful applications of Masamune's work are illustrated in Scheme 9. A variant allows the direct *C*-acylation of malonic acid derivatives with carboxylic acids themselves, using diethyl phosphorocyanidate and triethylamine (equation 10).[34] Yields varied from good to quantitative, using a number of simple carboxylic acids. Other workers have acylated the dianion of monoethyl malonate to give β-keto esters in over 90% yield,[35] while β-keto acids have been obtained by acylation and hydrolysis of the lithium anion of bis(trimethylsilyl)malonate.[36] With these reactions may be classed the acylation of Meldrum's acid with acyl chlorides.[37] Various β-keto esters were obtained in good yield under mild conditions (Scheme 10).

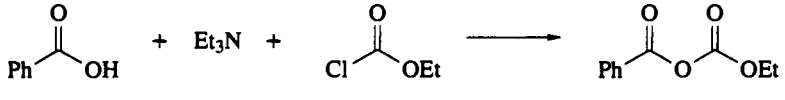




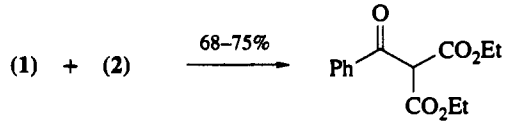
(ref. 27)



(1)

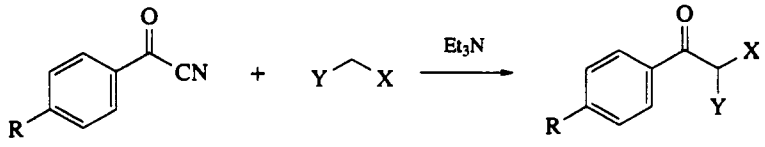


(2)

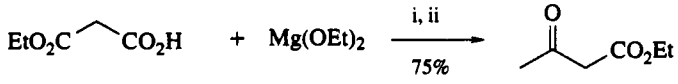


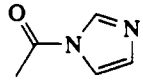
(ref. 28)

Scheme 7



R = H, NMe_2, Cl, NO_2; X, Y = CN, Ph, CO_2Et, PhCO



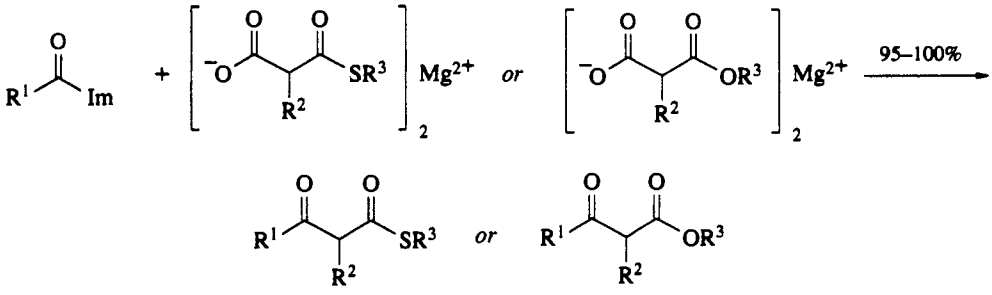
i, 

, THF; ii, aq. HCl

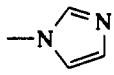
Scheme 8

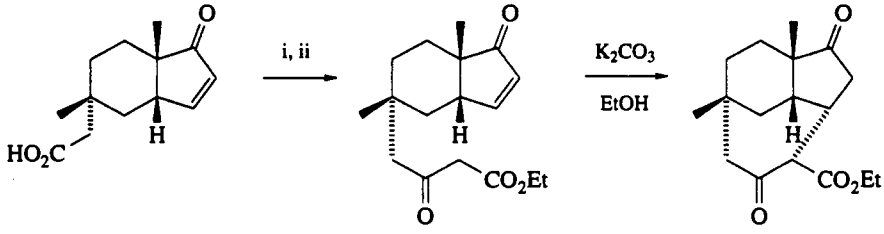
3.6.3.2.4 Coordination by titanium(IV) bistriflate

A potentially valuable example of a crossed Claisen condensation was described by Tanabe and Mukaiyama in 1986.[38] It arose from their earlier work on titanium(IV) ditriflate [dichlorobis(trifluoromethanesulfonato)titanium(IV)] and triethylamine as a catalytic promoter of the simple Claisen reaction. The reaction was run in the presence of benzaldehyde, added to observe the aldol reaction, but the propionate anion added to the carbonyl group of another ester molecule in preference (equation 11). The same result was observed in a Dieckmann reaction; dimethyl adipate, $TiCl_2(OTf)_2$ (1.5 equiv.) and triethylamine



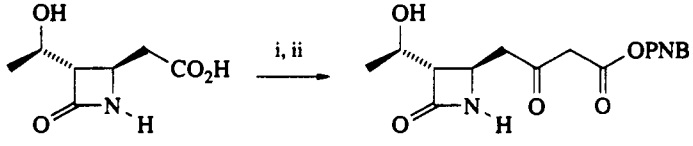
(9)

Im =  ; R^2 = H or Me; R^3 = Et or Bu^t



(ref. 32)

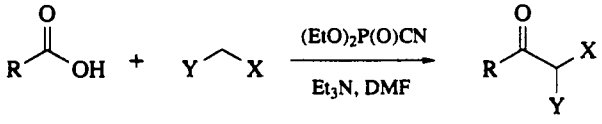
i, carbonyl diimidazole, ii, $(EtO_2CCH_2CO_2)_2Mg$



i, carbonyl diimidazole, MeCN, DMF; ii, 1.2 equiv. $Mg(O_2CCH_2CO_2PNB)_2$, r.t., 16 h

PNB = *p*-$O_2NC_6H_4$ (ref. 33)

Scheme 9



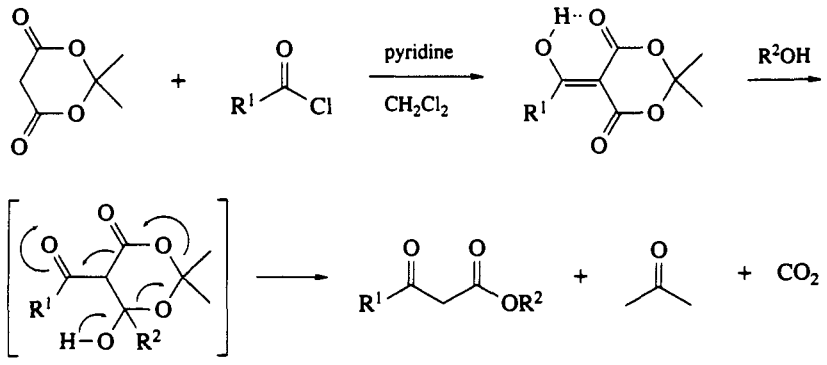
(10)

X, Y = EWG; R = Ph, $Ph(CH_2)_2$, n-C_5H_{11}, $MeCO(CH_2)_2$

gave, in the presence of molecular sieves, an 80% yield of the cyclic keto ester. This led on to a successful crossed Claisen ester condensation between a methyl ester and a methoxymethyl ester (equation 12). The titanium ditriflate coordinates strongly with the methoxymethyl ester allowing the tertiary amine base to remove the α-proton from that ester and permit it to undergo acylation by the methyl ester. An intramolecular version was equally successful; methoxymethyl methyl adipate gave, almost exclusively, the cyclic methoxymethyl ester (equation 13).

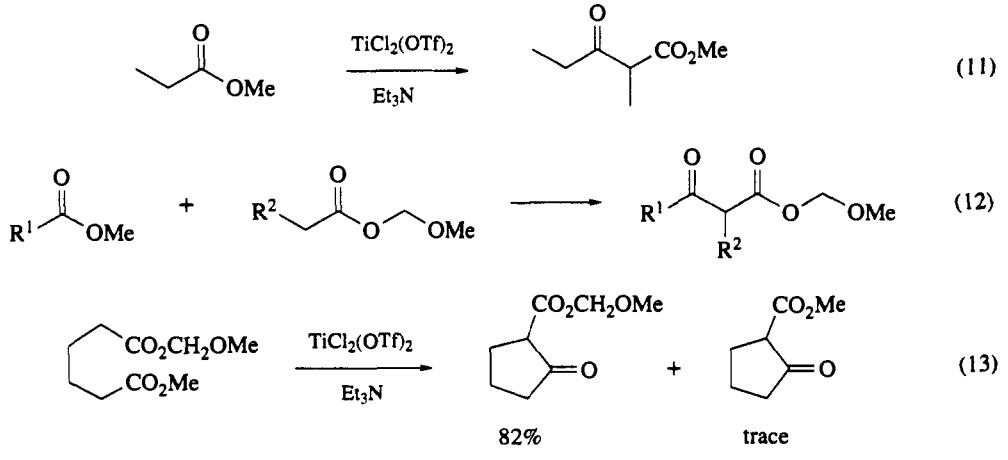
3.6.3.2.5 Silyl ketene acetals

Silyl alkyl ketene acetals, as ester enolate equivalents, are capable of regioselective acylation by acid chlorides. Rathke and Sullivan[39] showed that a variety of acid chlorides reacted with the acetal (**3**) to give protected β-keto esters (Scheme 11). Acid hydrolysis of the silylated products gave the free β-keto ester. The reaction was successful with a variety of acyl chlorides, including acetic, butanoic, (2*E*)-buten-

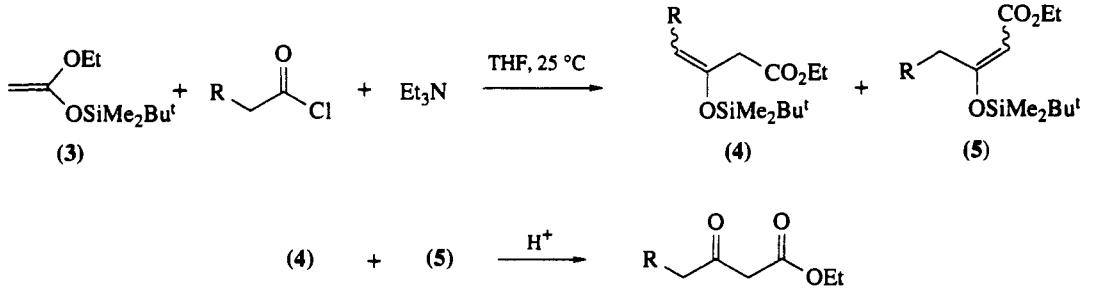


R^1 = Et, Pr^i, Bu, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, CH_2=$CH(CH_2)_8$, $PhCH_2$, $MeCOCH_2CH_2$ $EtOCH_2CH_2$; R^2 = Me, Et, $PhCH_2$, Bu^t

Scheme 10



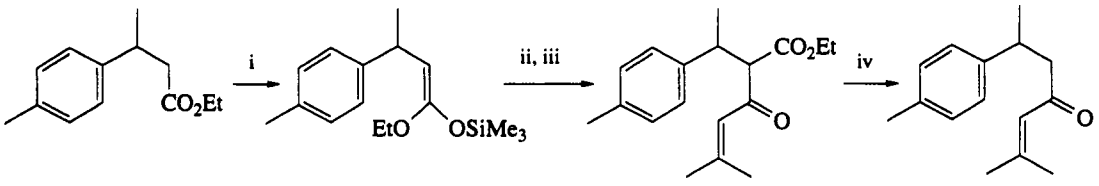
oic, pivalic and benzoic. In those acids possessing an α-hydrogen atom, the reaction is thought to proceed through a ketene intermediate. Similar results were reported by a Russian group.[40]



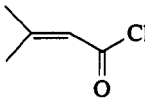
Scheme 11

More recently, Rousseau and Blanco[41] reacted 3-methylbut-2-enoyl chloride with a number of silyl ketene acetals to produce γ,δ-ethylenic β-keto esters, with yields in the range 62–80%; neither but-2-enoyl chloride nor propenoyl chloride reacted under these conditions. They employed this reaction in a new synthesis of (±)-turmerone (**6**; Scheme 12).

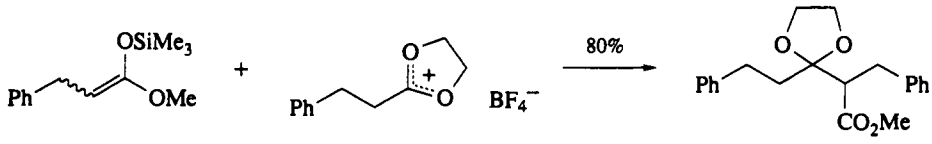
1,3-Dioxolan-2-ylium cations (**7**), derived from aldehyde ethylene acetals by hydride abstraction, react with silyl ketene acetals to give β-keto esters, selectively monoprotected at the ketone carbonyl (equation 14).[42]



(6)

i, LDA, Me_3SiCl, THF; ii,  , MeCN, 1 equiv. Et_3N; iii, aq. HCl, THF; iv, aq. HCl, Δ

Scheme 12

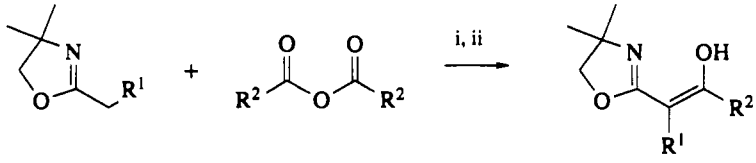


(7)

(14)

3.6.3.2.6 Acylation of oxazolines

Tohda *et al.*[43] reported on the use of 2-primary alkyl 4,4-dimethyl-2-oxazolines in a crossed Claisen condensation (equation 15). The 2-primary alkyl oxazoline was treated with an acid anhydride in the presence of aluminum chloride and triethylamine in acetonitrile to give moderate yields (typically 50–65%) of the oxazoline derivative of a β-keto acid. The product can be monoalkylated selectively on the carbon adjacent to the heterocyclic ring, while the 2-oxazoline group can be converted into a variety of functional groups.

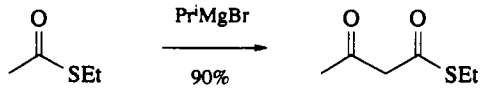


(15)

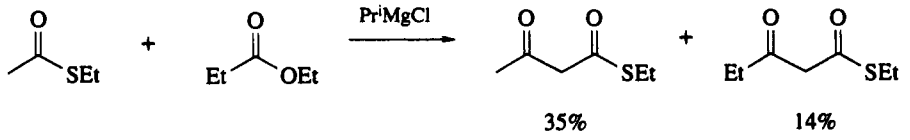
i, $AlCl_3$–Et_3N, MeCN; ii, KOH, r.t., MeOH

3.6.3.2.7 Thiol esters

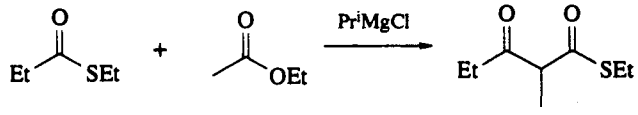
Thiol esters readily undergo both Claisen (equation 16) and Dieckmann condensations. The sulfur atom renders the α-protons more acidic and makes the thioalkoxide a better leaving group than alkoxide, properties recognized in the biosynthesis of fatty acids. In mixed Claisen condensations with oxy esters, the thiol ester acts both as nucleophile and electrophile. Reaction of a mixture of thioethyl acetate and ethyl propanoate with isopropylmagnesium chloride gave thioethyl 3-oxobutanoate as the main product (equation 17). When the same catalyst was used with a mixture of thioethyl propanoate and ethyl acetate, the sole product detected was thioethyl 2-methyl-3-oxopentanoate (equation 18).[44] Another group reporting on the value of thiol esters as acylating agents reacted *t*-butyl lithioacetate with various thiomethyl α-hydroxy esters to give β-keto esters in good yield (equation 19).[45]



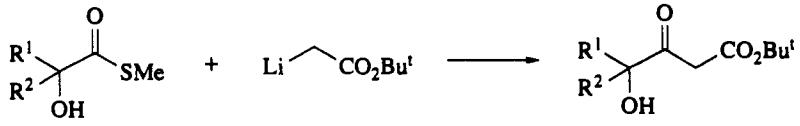
(16)



(17)



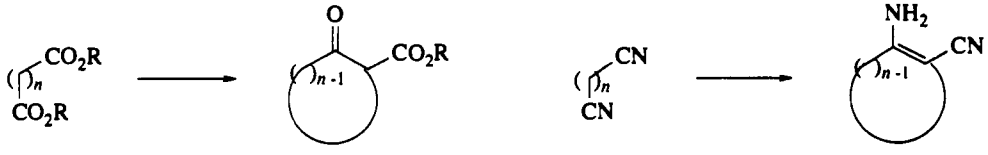
(18)



(19)

3.6.3.3 The Dieckmann Reaction

The Dieckmann, Thorpe and Thorpe–Ziegler reactions all involve intramolecular cyclization of a stabilized anion to form a cyclic ketone. The Dieckmann reaction is the intramolecular equivalent of the Claisen condensation and yields cyclic 2-alkoxycarbonyl ketones as primary products, whereas the primary products of the Thorpe reaction are 2-cyanoenamines (Scheme 13). Subsequent hydrolysis affords cyclic ketones but the primary products, particularly those from the Dieckmann reaction, have a useful synthetic role (see Section 3.6.3.5.1).

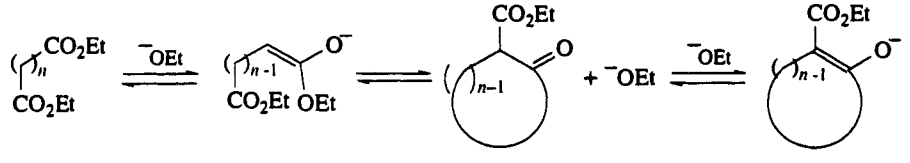


Scheme 13

The Dieckmann reaction is of major importance for the synthesis of five- and six-membered ring compounds. The present account will review the earlier work where necessary, but will concentrate on important developments since the review in *Organic Reactions*.[6]

3.6.3.3.1 Mechanism of the reaction

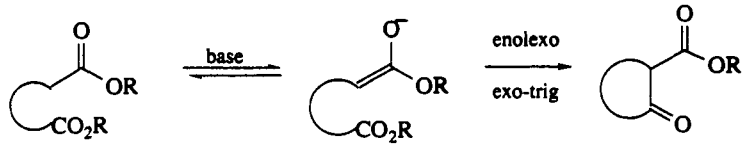
The classical Dieckmann reaction occurs under equilibrium conditions, the initial step involving the base-catalyzed formation of the ester enolate anion. The rate-determining step is ring closure, the subsequent loss of the alkoxide being rapid (Scheme 14).[6]



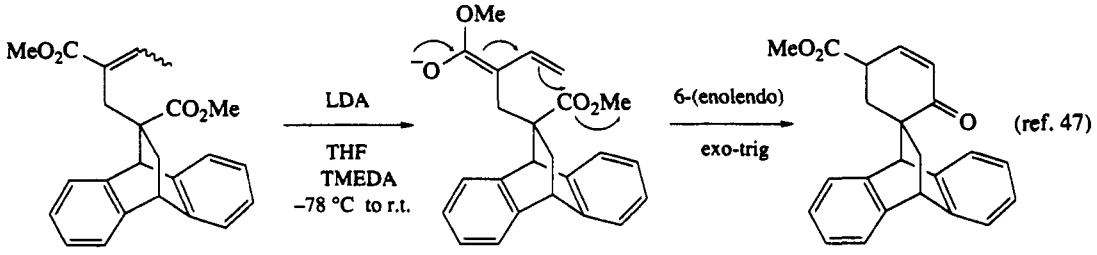
Scheme 14

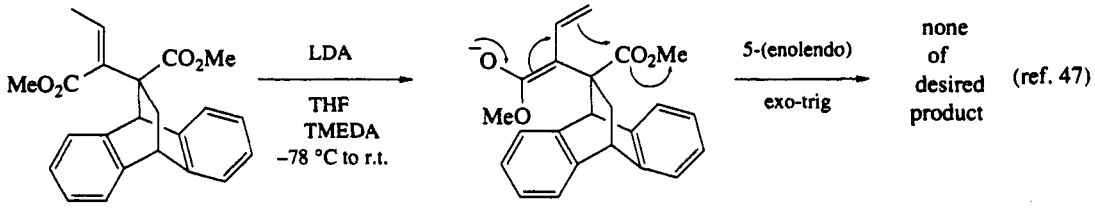
The reversibility of the process means that cyclic 2-alkoxycarbonyl ketones can be cleaved by alkoxide in the retro-Dieckmann reaction, a process of synthetic significance (see Section 3.6.9.1). More recently, nonequilibrium conditions have been employed in the reaction and this may lead to a change in regioselectivity (see Section 3.6.3.3.3).

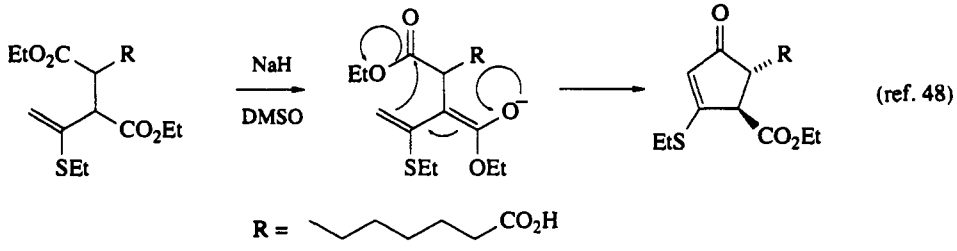
The Dieckmann reaction is an *n*-(enolexo)-exo-trig cyclization in Baldwin's terminology,[46] and is a favored reaction (Scheme 15). Kodpinid and Thebtaranonth[47] have extended this to the vinylogous reaction, and have shown (for the substrates chosen) that the 4-(enolendo)-exo-trig mode is disfavored and does not occur to give the desired 4-alkoxycarbonylcyclo-3-pentenones, whereas the 6-(enolendo)-exo-trig mode is favored and does give the desired 4-alkoxycarbonylcyclo-3-hexenones (Scheme 16). However, other workers[48] have reported a successful 5-(enolendo)-exo-trig cyclization. The difference in behavior is probably due both to the presence of the ethanethiol group and the greater flexibility of the cyclizing molecule.



Scheme 15





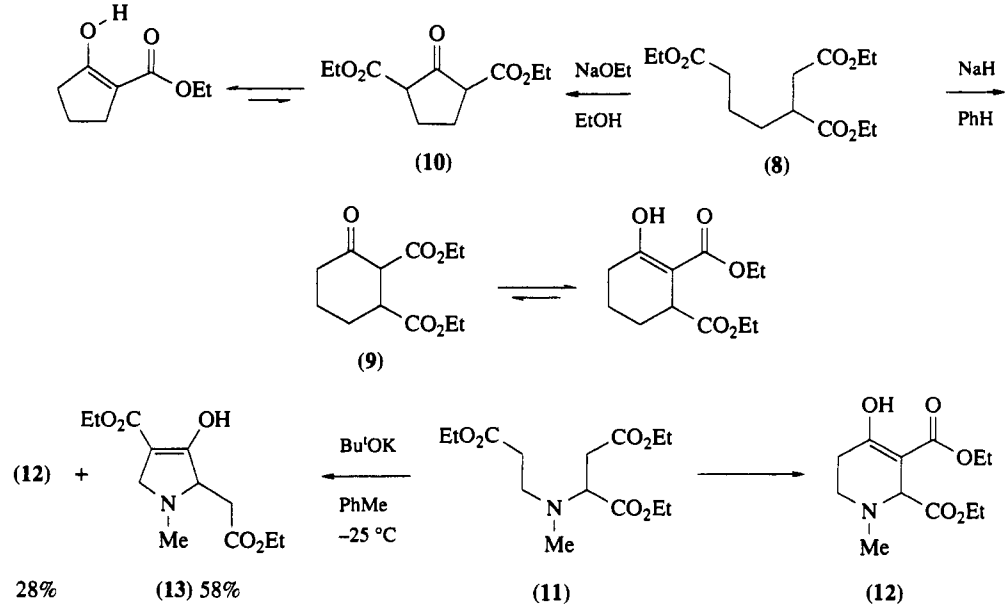


Scheme 16

The mechanism in solution and in the gas phase appears to be the same,[49] except that an alkyl substituent stabilizes the anion in the gas phase and destabilizes it in solution. The mass spectral decomposition of diethyl 2-methylheptanedioate under negative chemical ionization (NCI) conditions shows formation of the methyl-substituted enolate, ring closure and then loss of ethyl methyl ether.

3.6.3.3.2 Ring size

The Dieckmann reaction is usually used to prepare five- or six-membered rings. A variety of substituents can be tolerated on the intervening atoms, although these may influence the regioselectivity of the reaction (see Section 3.6.3.3.3), and some of the intervening atoms need not be carbon. In competition between five- or six-membered ring formation, ambiguous results have been obtained depending on the substrate and conditions. Thus diethyl 3-ethoxycarbonylheptanedioate (**8**) gives the six-membered ring product (**9**) with sodium hydride in benzene and the five-membered ring product (**10**) with sodium ethoxide in ethanol (Scheme 17). This appears to be an example of kinetic *versus* equilibrium control, but other experiments suggest that the five-membered product is formed first and equilibrates to the six-membered. The corresponding 5-methyl-5-aza derivative (**11**) gives the six-membered ring derivative (**12**) with sodium hydride in benzene and mainly the five-membered derivative (**13**) with Bu^{t}OK in toluene at –25 °C.[50]



Scheme 17

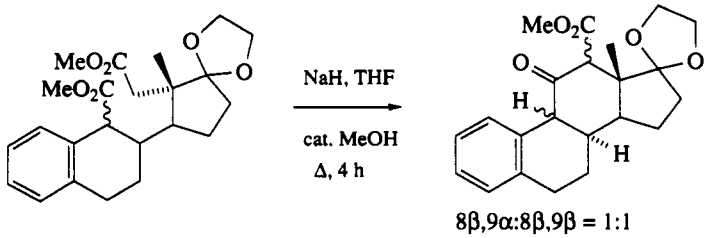
Examples of five- and six-membered ring formation are illustrated by the following reactions (Scheme 18).

Seven-membered and larger rings can be prepared by this method and the yields can often be satisfactory. Carefully controlled nonequilibrium conditions and high dilution techniques are often required. Medium rings (9–12) are either not formed, or formed in low yield, a combination of a Claisen condensation followed by a Dieckmann reaction giving macrocyclic diketones.[6] The conformational energies of the linear precursor influences ring closure.[69] Examples are illustrated in Scheme 19.

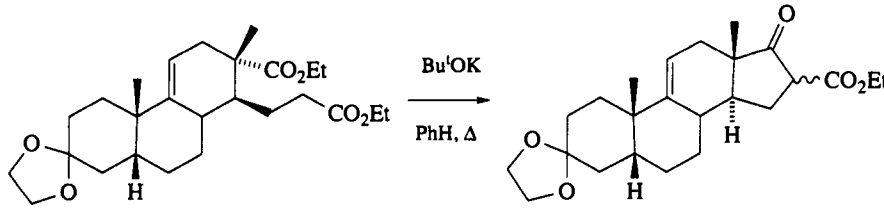
The reaction does not work well for three- or four-membered rings. A small number of examples of four-membered ring formation have been reported but in very low yield (usually <1%).[6]

3.6.3.3.3 Regioselectivity

If the two ester groups are not equivalent then, providing both ester groups have α-carbon atoms bearing protons, two products can result from the ring closure. The two resultant cyclic β-keto esters can often be decarboxylated to the same cyclic ketone and if this is the desired product then nonregioselective ring closure is acceptable. If the β-keto ester is the desired product, or if the two products of ring closure cannot be converted to a common substance, then methods of controlling the regioselectivity must be employed.



(ref. 51)



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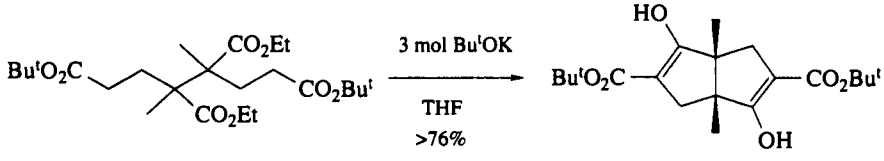

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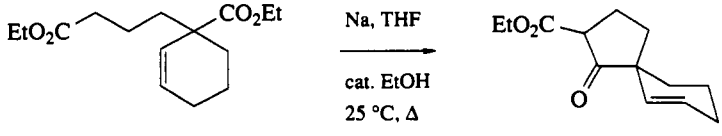

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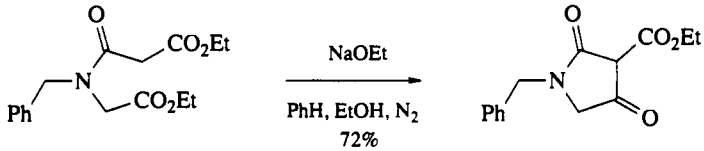

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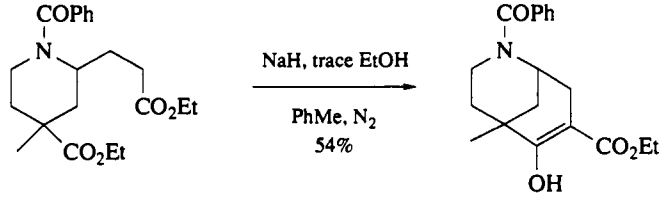
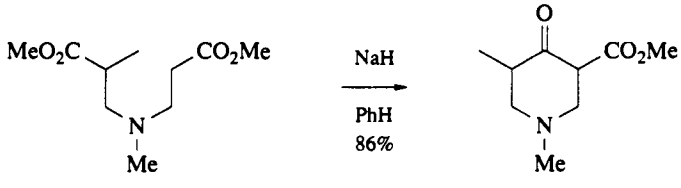


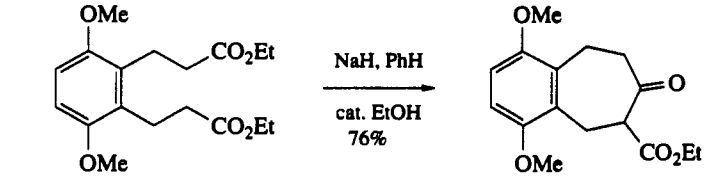
(ref. 56)

(ref. 57)



(ref. 58)

Scheme 18



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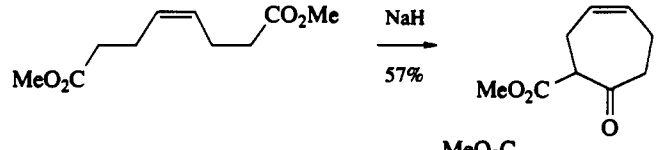

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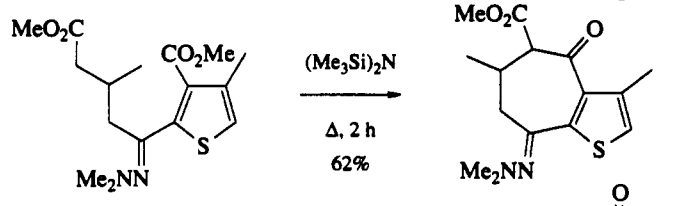

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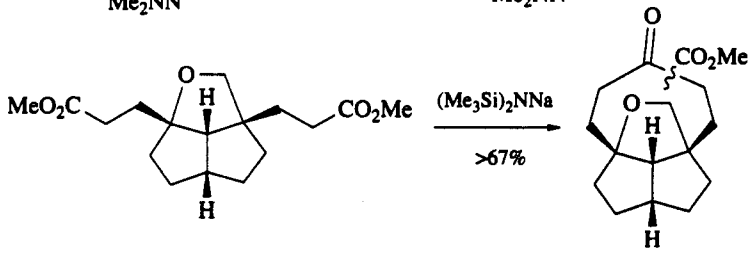
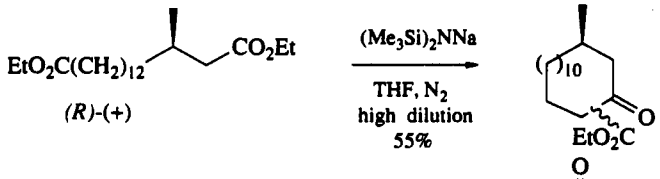
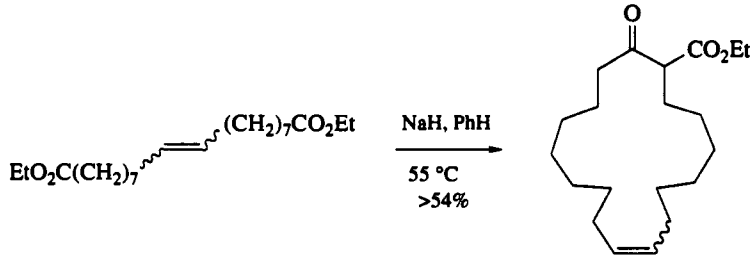


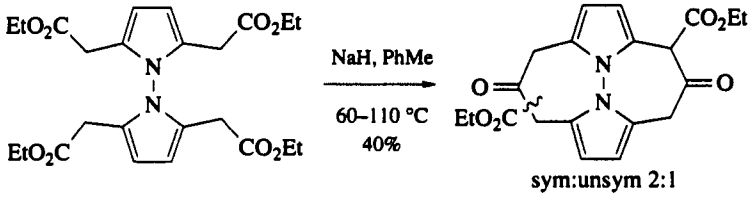
(ref. 62)



(ref. 63)

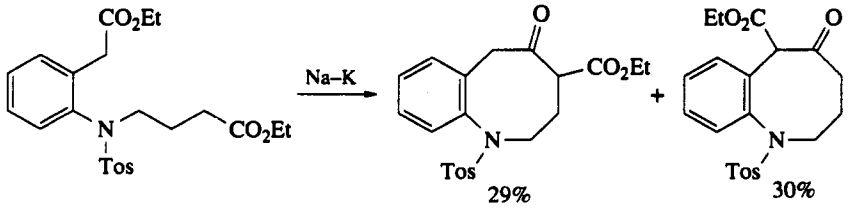


(ref. 64)



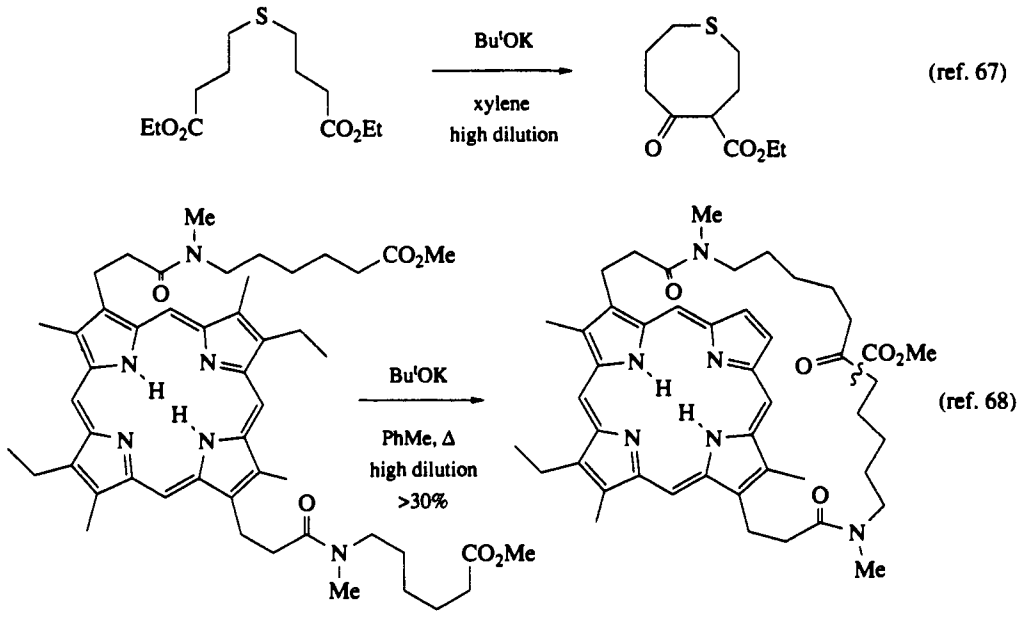
sym:unsym 2:1

(ref. 65)



(ref. 66)

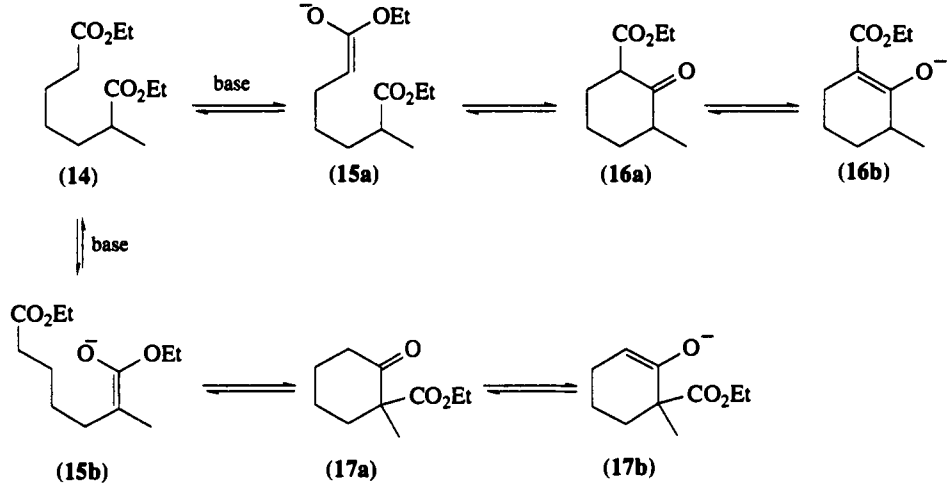
Scheme 19



Scheme 19 ***(continued)***

(i) Substituents at the α-carbon atom

The stability of the initially formed enolates has a crucial bearing on the direction of ring closure. α-Alkyl substituents destabilize the enolate in solution and the nonsubstituted enolate is favored. Diethyl 2-methylheptanedioate (**14**) cyclizes preferentially through the unsubstituted enolate (**15a**) rather than the substituted enolate (**15b**) to give (**16**) rather than (**17**).[70] This is also the thermodynamic preference since the enolate (**16b**) is more stable than the enolate (**17b**) (Scheme 20).

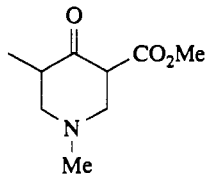


Scheme 20

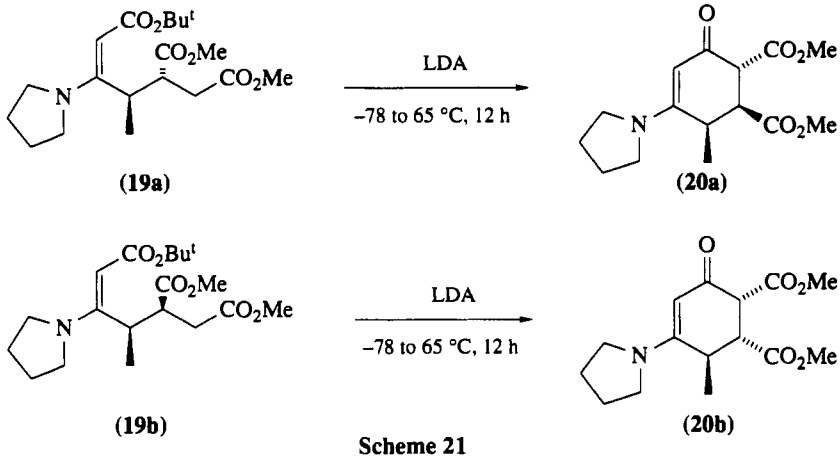
Similarly, dimethyl 2,4-dimethyl-4-azaheptanedioate gives *N*-methyl-3-methoxycarbonyl-5-methyl-4-oxopiperidine (**18**).[58]

It also follows that primary ester enolates should cyclize preferentially to secondary ester enolates, as is illustrated in the reaction of (**19**).[71] The conformational requirement of the ring closure gives a single diastereomer (**20a** and **20b**) from each diastereomeric ester (**19a** and **19b**; Scheme 21).

If the substituent is electron withdrawing then the enolate is stabilized and the direction of cyclization reversed. Under equilibrium conditions, however, the enolate of the unsymmetrically disubstituted ke-



(18)



(19a) (20a)

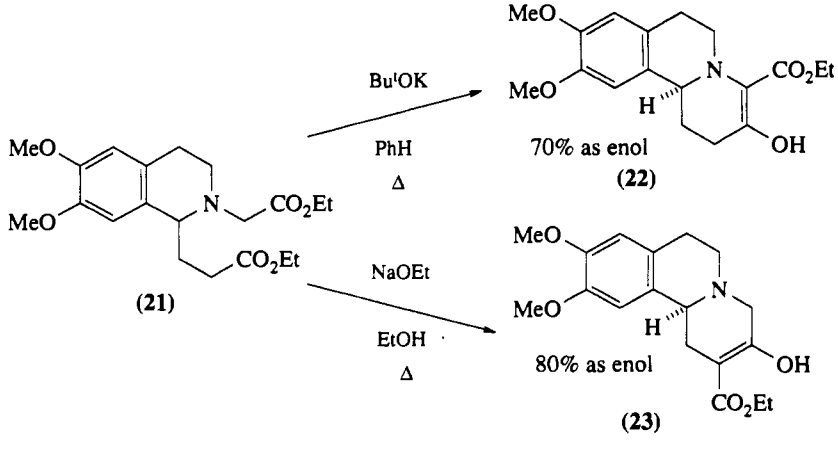
(19b) (20b)

Scheme 21

tone may be less stable than that of the symmetrically substituted ketone and the final product then results from addition of the unsubstituted enolate.

(ii) β-Heteroatoms

The presence of a heteroatom at a β-position to one of the ester groups stabilizes that enolate. Under nonequilibrating conditions, ring closure should be regioselective. Thus the ester (**21**) undergoes cyclization under nonequilibrium conditions to give (**22**), whereas under equilibrium conditions (**23**) is formed, presumably because of the greater stability of the enolate of the cyclized product (Scheme 22).[72]

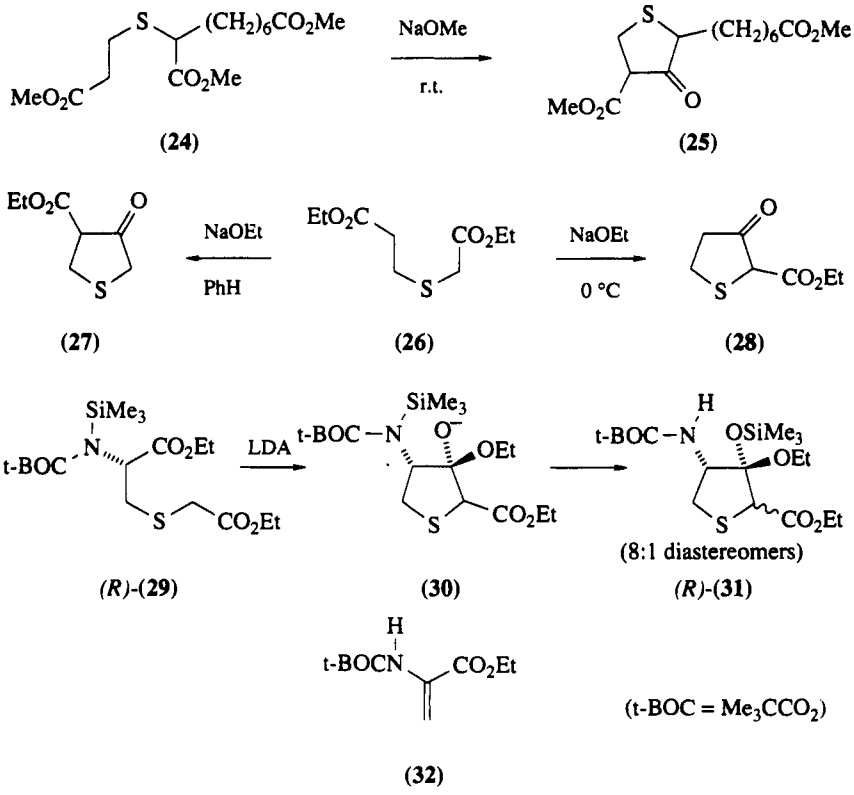


(21) (22) (23)

Scheme 22

Cyclization of (**24**) regioselectivity gives (**25**).[73] The conditions are nonequilibrating, which suggests that the destabilizing effect of the alkyl group is greater than the stabilizing effect of the sulfur atom on the enolate. However, the enolate of (**25**) is also more stable than that of the alternative cyclized product. The combination of substituent effects with equilibrium or nonequilibrium conditions has been examined for diethyl 3-thiohexanedioate (**26**) and derivatives.[74] Under nonequilibrium conditions (**26**) gives (**27**), whereas with sodium ethoxide at 0 °C it gives (**28**). Alkylation at C-5 gives products of type (**27**), while

substitution at C-4 can lead to both products, the one obtained depending on the reaction conditions. Under nonequilibrium conditions with LDA, the (*R*)-amino ester (**29**) forms the enolate of the secondary α-C, sulfur-stabilized ester, which ring-closes to (**30**) and transfers Me_3Si to give (*R*)-(**31**) as an 8:1 mixture of diastereomers.[75] Some of the substituted ethyl acrylate (**32**) is also formed from the *N*-substituted enolate by elimination of the α-thio ester (Scheme 23).

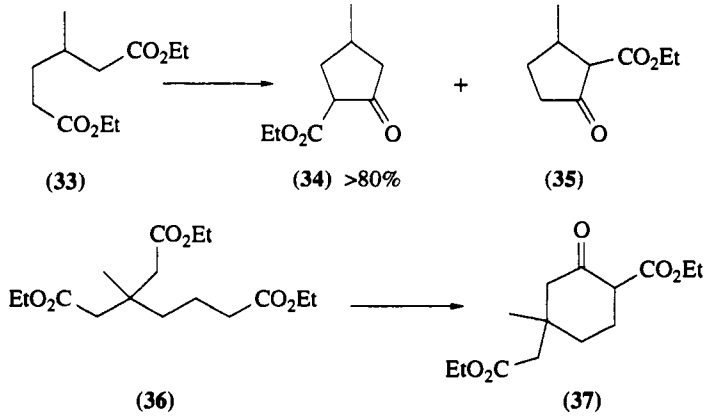


(**24**) (**25**) (**27**) (**26**) (**28**) (*R*)-(**29**) (**30**) (*R*)-(**31**) (**32**)

Scheme 23

(iii) Substitution at the β-carbon atom

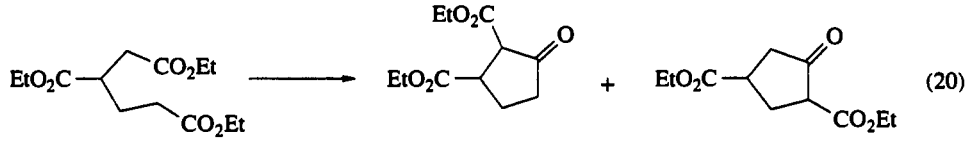
With a β-alkyl substituent, cyclization occurs through the least hindered enolate to give the least hindered ketone. Diethyl 3-methylhexanedioate (**33**) cyclizes to give mainly (**34**; >80%), not (**35**), and the triester (**36**) cyclizes to the substituted cyclohexanone (**37**; Scheme 24).[6,70]



(**33**) (**34**) >80% (**35**) (**36**) (**37**)

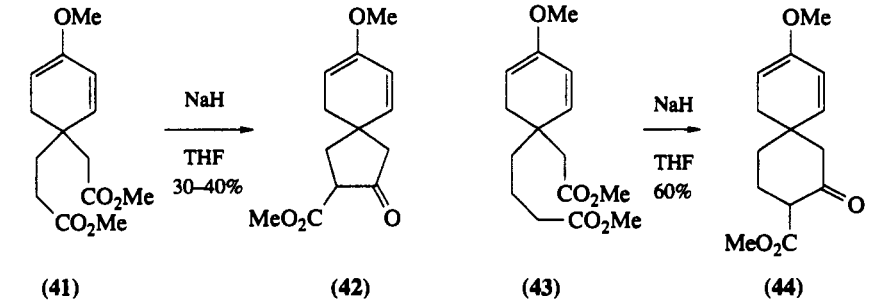
Scheme 24

Where the β-substituent is an ester, cyclization occurs at the hindered, but electronically stabilized, enolate. The triester (**38**) thus gives (**39**) as the major product with lesser amounts of (**40**), the actual proportions depending on the reaction conditions (equation 20).[6,70]

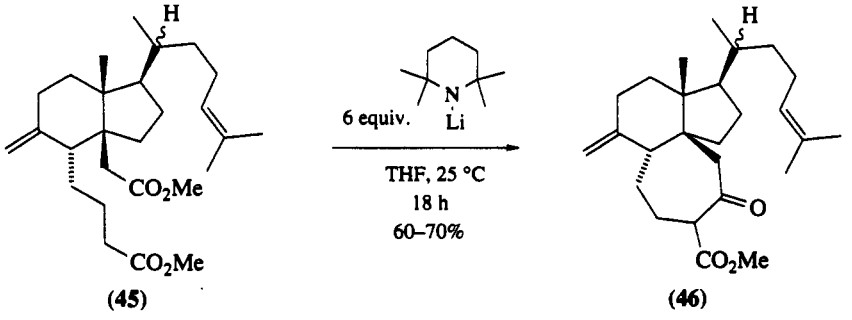


(**38**) (**39**) major (**40**) minor (20)

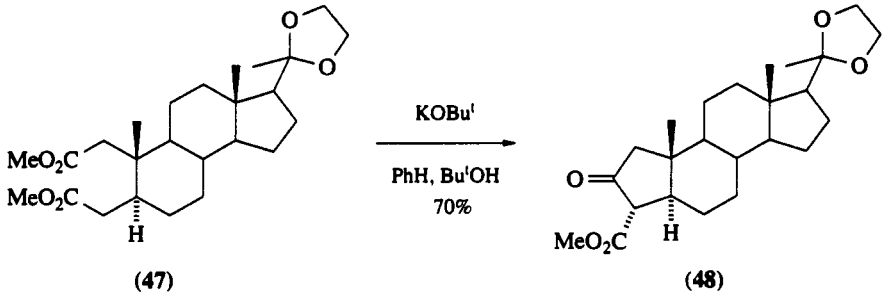
With both alkyl and ester β-substituents, cyclization occurs on the least hindered side, steric effects or the stability of the product enolates being product determining. Steric effects also dominate the cyclization of the substituted cyclohexadienes (**41**) and (**43**) to the spiroketones (**42**) and (**44**),[76] the cyclization of (**45**) to (**46**) *en route* to gascardic acid,[77] and the cyclization of (**47**) to the norsteroid (**48**; Scheme 25).[78]



(**41**) (**42**) (**43**) (**44**)



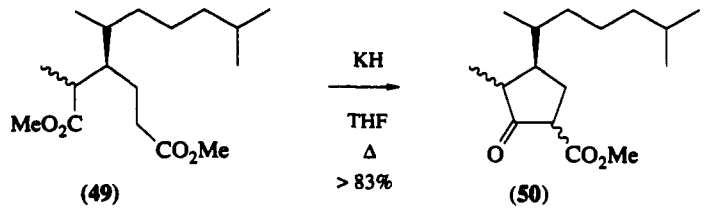
(**45**) (**46**)



(**47**) (**48**)

Scheme 25

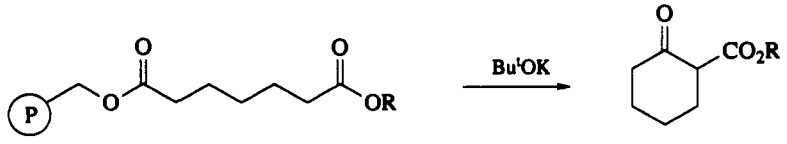
A β-vinyl substituent appears to give a balance between the steric and electronic effect, almost equal amounts of the two products being obtained.[79,80] A reinforcing combination of α- and β-substituents directs ring closure exclusively in one direction, as in the conversion of (**49**) to (**50**) with retention of the stereochemistry at C-3 (equation 21).[81]



(49) (50) (21)

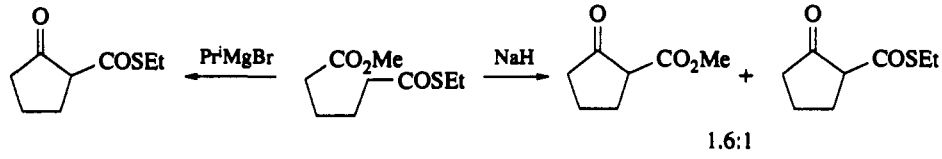
(iv) Variation of the ester group

Crowley and Rapoport[82] have made a detailed investigation, including labeling studies, of the reaction, both with one carboxylic function attached to a resin, and in solution with the carboxylic functions esterified by different alcohols. Cyclization of the resin-attached methyl (**51**; R = Me) or *t*-butyl ester (**51**; R = Bu^t) with Bu^{t}OK gave the methyl (**52**; R = Me) or *t*-butyl 2-oxocarboxylates (**52**; R = Bu^t) as the exclusive autocleaved product. Similar results were obtained with the half-benzyl esters in solution but the products were less readily isolated (equation 22).



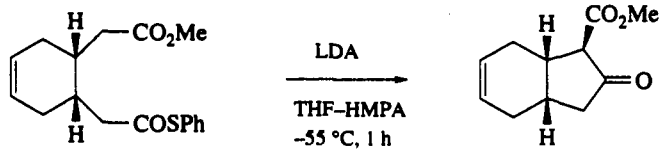
(51) (52) (22)

Another way of differentiating the cyclizing groups is to change one of the ester groups to another functional group, for example to a thiol ester (Scheme 26). The thiol ester acts as a good activating group for the Dieckmann reaction and five- and six-membered ring compounds can be prepared from dithiol esters.[44] Substrates with one thiol ester and one ester group can cyclize regioselectively, the direction of cyclization depending on the reaction conditions. Thus (**53**) with sodium hydride gives a 1.6:1 mixture of

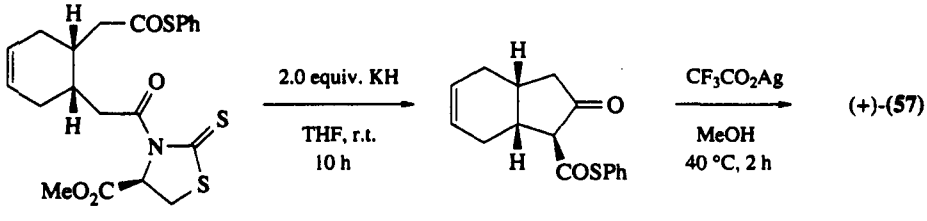


(55) (53) (54) (55)

Scheme 26



(56) (–)-(57)

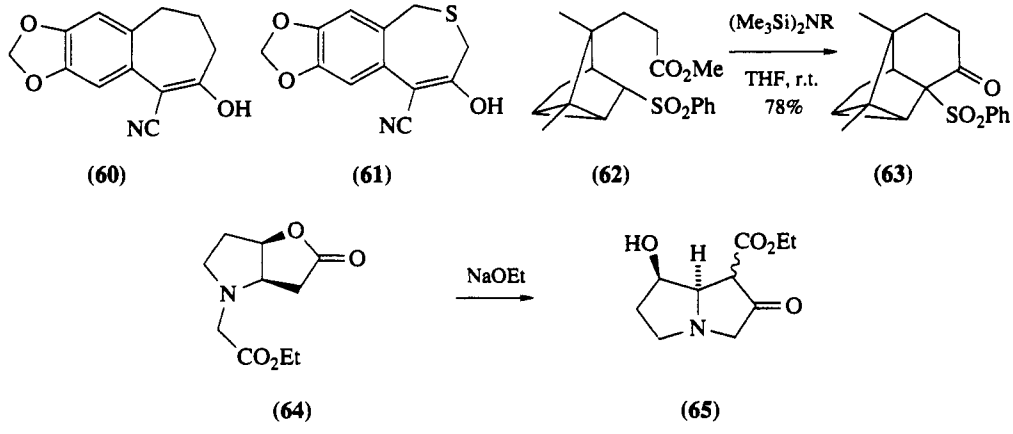


(58) (59)

Scheme 27

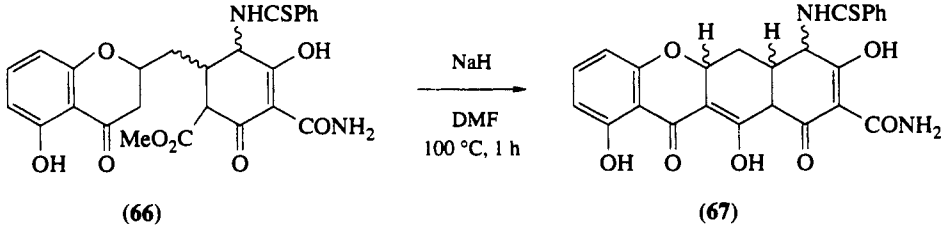
(**54**) and (**55**), whereas with 2-propylmagnesium bromide it gives only (**55**; Scheme 32). An elegant use of this method has been employed for the cyclization of the 4-cyclohexene (**56**).[83] Reaction of (**56**) with LDA in THF–HMPA at –55 °C gave the enantiomer (–)-(**57**) in 57% yield with >98% optical purity. Dimsyl sodium or dimsyl potassium gave mixtures of enantiomers. With (**58**) cyclization onto the thiol ester group occurs to give (**59**), displacement of the chiral amine group by PhS^- having subsequently occurred. Replacement of the thiophenol group by methoxide occurs when (**59**) is treated with silver trifluoroacetate in methanol and the other enantiomer (+)-(**57**) is obtained (Scheme 27).

Substitution of one of the ester groups for another functional group may also allow one mode of cyclization to occur. Where cyanide replaces one of the esters, cyclization occurs from the cyano-stabilized anion.[84,85] Seven-membered (*e.g.* **60**) and heterocyclic (*e.g.* **61**) rings[84,85] can be prepared regioselectively.[85] In competition between an ester and the $PhSO_2$-stabilized anion the latter cyclizes even where it is secondary and the ester is primary, (**62**) to (**63**), presumably in part a reflection on the electrophilicity of the two groups and the stabilities of the products.[86] The ester lactone (**64**) cyclizes to the keto ester (**65**) involving the enolate of the lactone, but cyclization in the opposite sense is sterically unlikely (Scheme 28).[87]

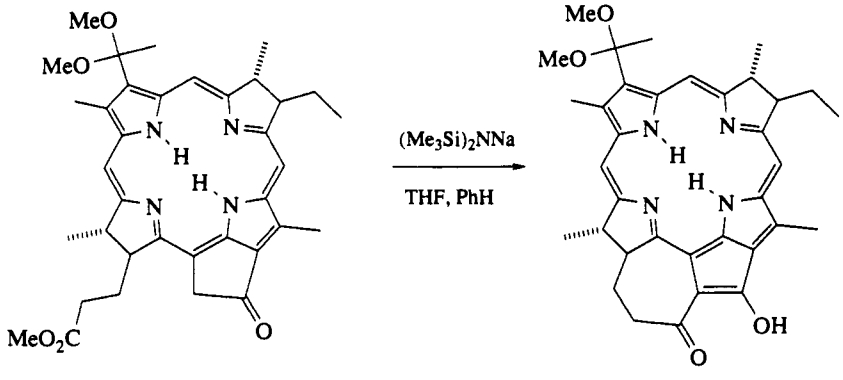


(**60**) (**61**) (**62**) (**63**) (**64**) (**65**)

Scheme 28



(**66**) (**67**)



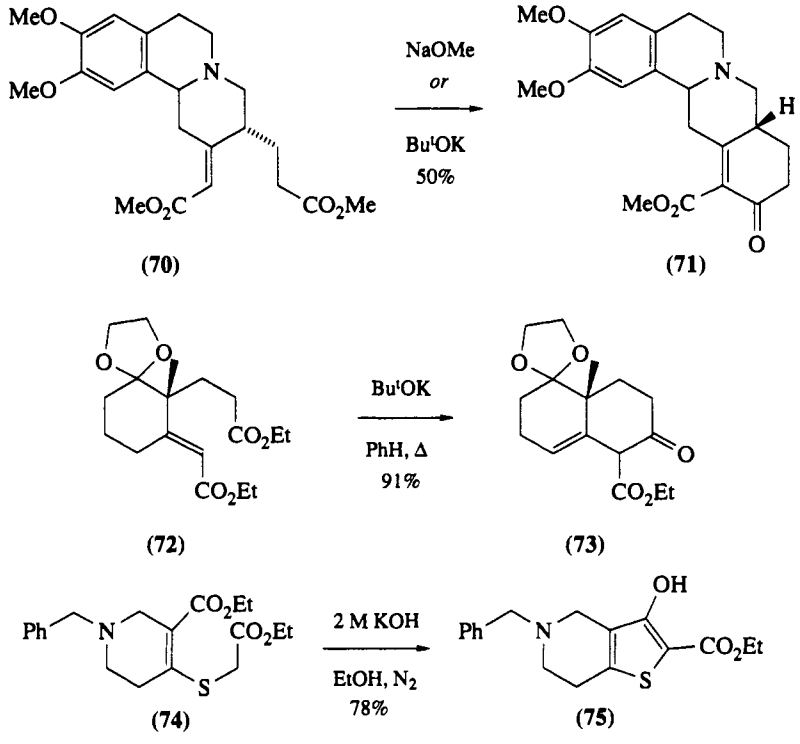
(**68**) (**69**)

Scheme 29

With the replacement of one ester grouping by a ketone, the ketone enolate acts as the nucleophile. Thus (**66**) cyclizes regioselectively to (**67**) and (**68**) cyclizes to (**69**; Scheme 29).[88,89] This reaction is described more fully in Section 3.6.4.

(v) α,β-Unsaturated esters

The enolate of an α,β-ester cyclizes preferentially to an alkyl ester enolate, ring closure occurring at the α-carbon. Treatment of (**70**) with either sodium methoxide or potassium *t*-butoxide gives (**71**), *via* the enolate of the α,β-unsaturated ester.[90] Similarly, (**72**) cyclizes to (**73**) with potassium *t*-butoxide.[91] Cyclization of (**74**) occurs, however, from the saturated rather than unsaturated enolate to give (**75**).[92] This may reflect the stabilizing effect of sulfur on the enolate or the greater stability of the enolate of (**75**) relative to that of the alternative product (Scheme 30).



(**70**) (**71**) (**72**) (**73**) (**74**) (**75**)

Scheme 30

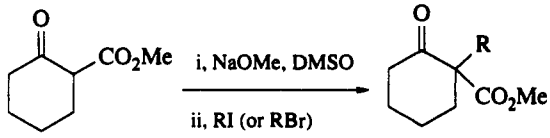
3.6.3.4 Application to Synthesis

3.6.3.4.1 β-Keto ester as a synthon

The β-keto esters formed in the Claisen and Dieckmann condensations can act as synthons for a variety of groups. If the α-carbon bears a proton then this is acidic and can be replaced by another electrophile. Alkylation and acylation are important synthetic reactions and can be carried out sequentially or, since the cyclizing reactions are basic, consecutively in one pot. Examples are illustrated in Scheme 31.

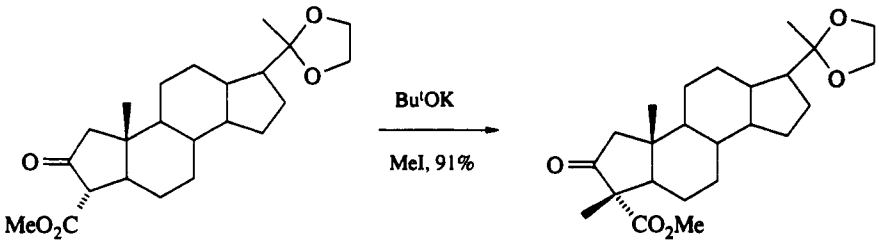
O-Alkylation of the enolate may compete with *C*-alkylation. The benzoselenophene (**76**) gives a 3:1 mixture of *C*-alkylation (**77**) and *O*-alkylation (**78**) with methyl iodide in methanol but a 1:3 mixture with dimethyl sulfate in water (equation 23).[95]

The most frequent operation carried out on the β-keto esters, particularly those resulting from intramolecular cyclization, is decarboxylation, since in many cases the two products resulting from the two different modes of cyclization give the same ketone. This means that the initial cyclization need not be regioselective and allows mixed products to be carried through the sequence and one-pot procedures to be used. Alkylation or acylation may precede decarboxylation, the ester group then controlling the nucleophilic site. As shown in Scheme 32, 2-ethyl-4-methoxycarbonylcyclohexanone (**82**) has been made

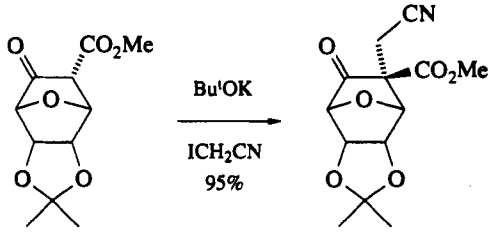


(ref. 93)

R = Me, Et, Pr

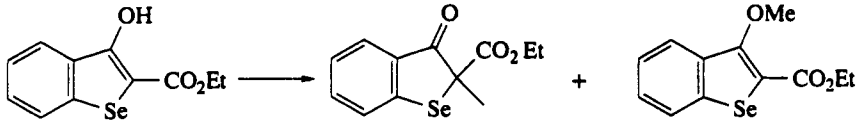


(ref. 78)



(ref. 94)

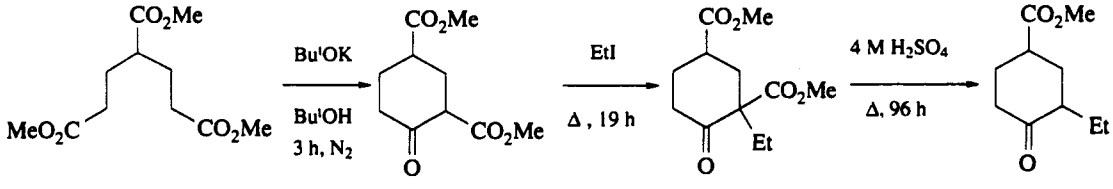
Scheme 31



(23)

(76)	(77)	(78)
MeI, MeOH	60%	20%
Me_2SO_4, H_2O	20%	60%

in a one-pot preparation by cyclization of dimethyl 4-methoxycarbonylheptanedioate (**79**), alkylation with iodoethane, hydrolysis and decarboxylation.[96]

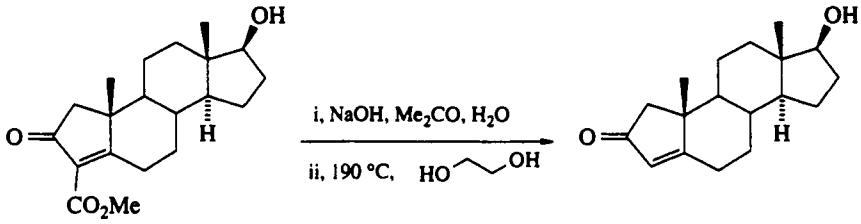


(79) (80) (81) (82) *trans*:*cis* 1:2

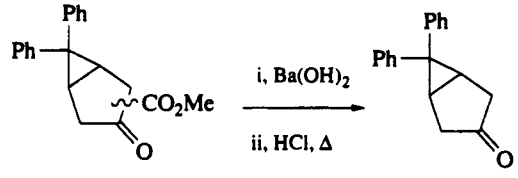
Scheme 32

Besides the classical method of ester hydrolysis followed by decarboxylation under acidic conditions, a variety of other methods can be carried out in basic or neutral media. The availability of these routes is important if the compound has acid-labile groups and also for hindered esters that are difficult to hydrolyze. A selection of methods is illustrated in Scheme 33.

Reduction or removal of the ketone function leads to β-hydroxy esters or to esters, respectively. If decarboxylation is carried out first, the alcohol or hydrocarbon results. The Merrell Dow group[75] desilyl-

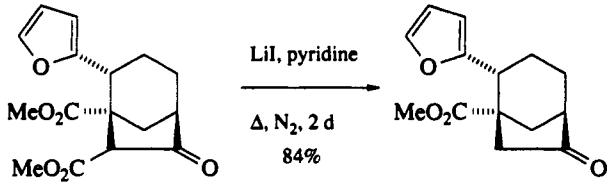


(ref. 97)

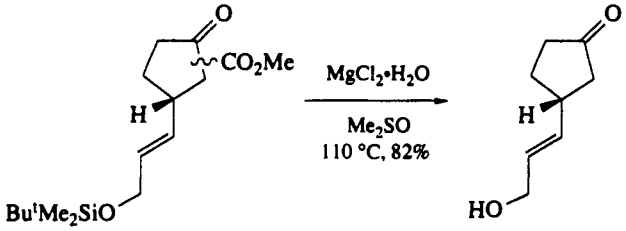


(ref. 98)

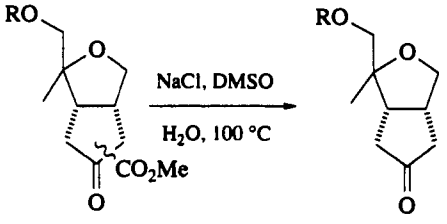
44% from diester



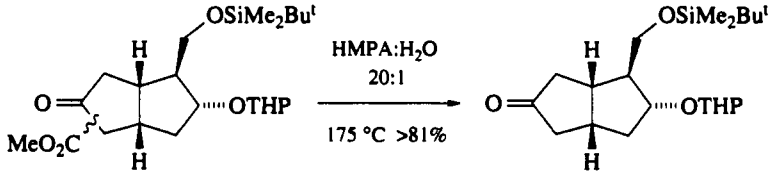
(ref. 99)



(ref. 100)



(ref. 101)



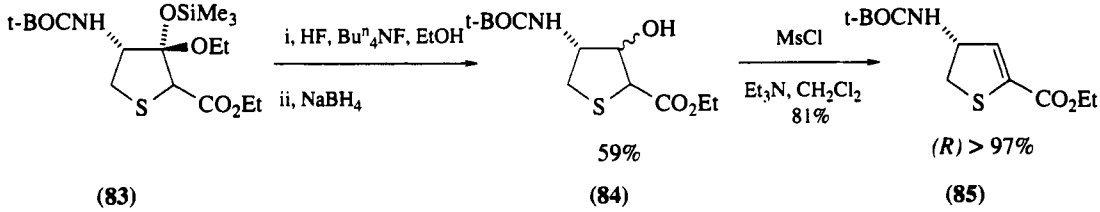
(ref. 102)

Scheme 33

ated the acetal (**83**) with Bu^n_4NF and HF and reduced the resulting ketone, without isolation, with sodium borohydride to (**84**). Elimination then gave (*R*)-(**85**), an inhibitor of GABA-T (Scheme 34).

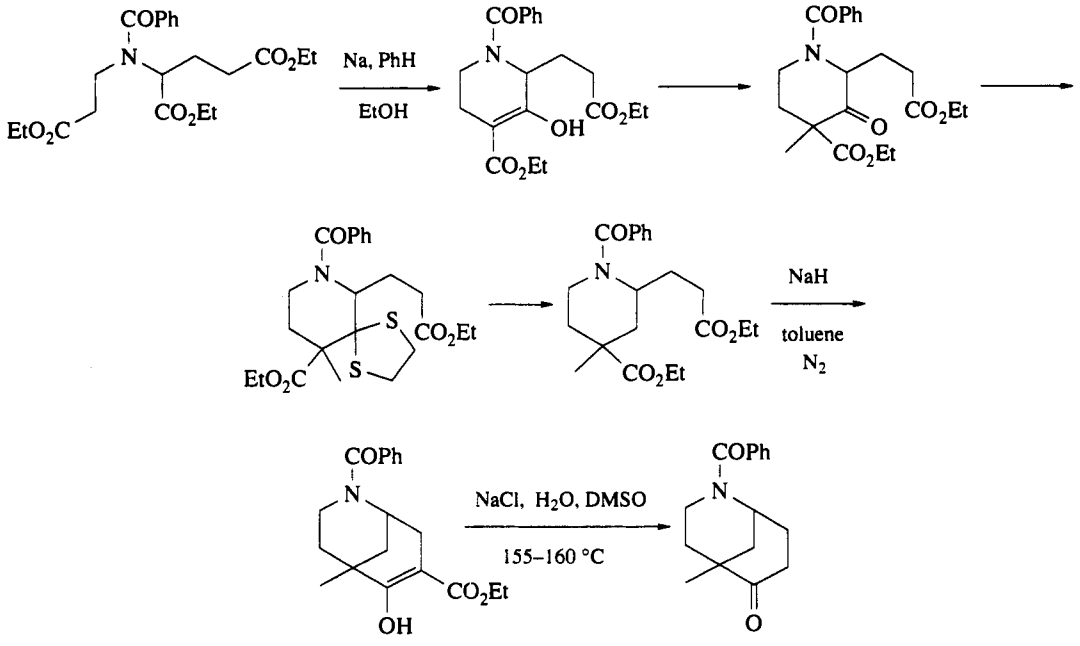
Bosch and Bonjoch[56] used a reaction combination of Dieckmann reaction, alkylation, ketone removal, a second Dieckmann reaction and finally decarboxylation to prepare functionalized 2-azabicyclo-[3.3.1]nonanes (Scheme 35).

Decarboxylation of the product from (**86**) followed by Wolff–Kishner reduction of the ketone gave (**87**; equation 24).[103]

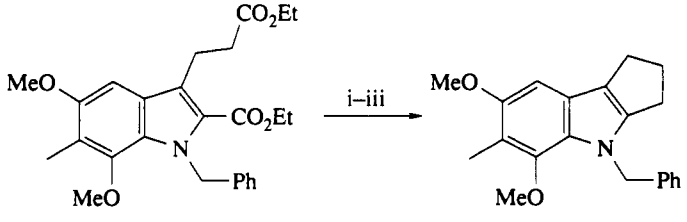


(83) (84) (85)

Scheme 34



Scheme 35



(24)

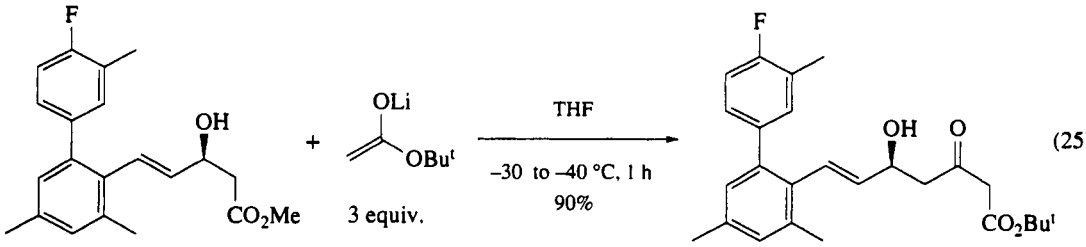
(86) (87)

i, NaH, PhH, Δ, 16 h; ii, 10% H_2SO_4, EtOH, Δ, 8 h; iii, NH_2NH_2, $HOCH_2CH_2OH$, KOH, 180–190 °C

3.6.3.4.2 Use of the Claisen condensation in synthesis

The Claisen condensation has been widely used as a means of C—C bond formation, the reaction having a biological counterpart in the formation of β-keto esters *via* acetylcoenzyme A. The value of the reaction is greatly enhanced if it can be made regioselective. This can be accomplished simply if one of the esters has no available α-hydrogen, otherwise the means must be found for distinguishing the nucleophilicity (and electrophilicity) of the reacting species. One possibility is to preform the enolate of one com-

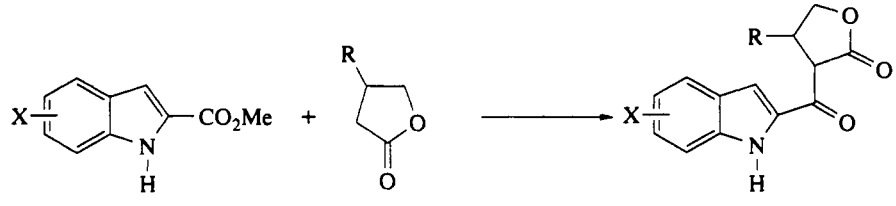
ponent. The lithium enolate of *t*-butyl acetate (**89**) reacts regioselectively with (**88**) to give the keto ester (**90**; equation 25).[104]



(25)

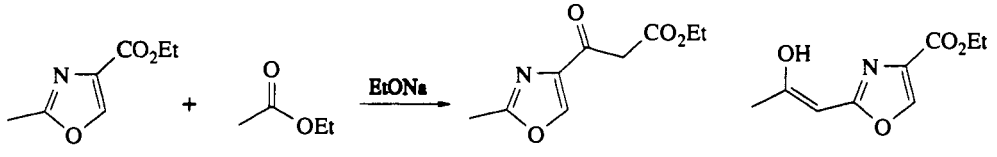
(**88**) (**89**) (**90**)

The indole esters (**91**) are not readily enolized and reaction with the lactones (**92**) regioselectively gives (**93**; equation 26).[105] Similarly, the ester function of the oxazole (**94**) acts as the electrophile with ethyl acetate giving (**95**)[106] rather than (**96**) as was originally thought (equation 27).



(26)

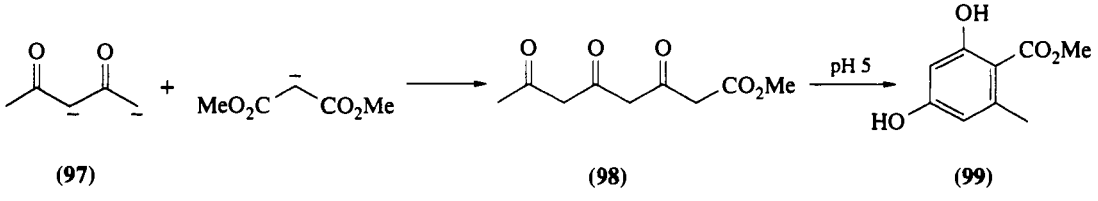
(**91**) (**92**) (**93**)



(27)

(**94**) (**95**) (**96**)

The dianion of pentane-2,4-dione (**97**) reacts as the nucleophile with the enolate of dimethyl malonate to give the labile (**98**), which cyclizes to methyl 2,4-dihydroxy-6-methylbenzoate (**99**) at pH 5 (Scheme 36).[107]

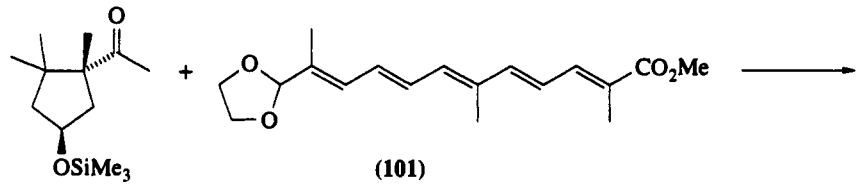


(**97**) (**98**) (**99**)

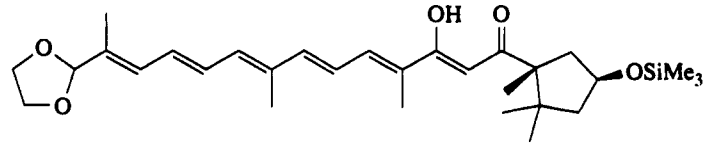
Scheme 36

Weedon and coworkers used the condensation of the methyl ketone (**100**) with polyene ester (**101**) to form the enolic β-diketone portion (**102**) of the carotenoids mytloxanthin and trikentriorhodin (equation 28).[108] A similar condensation was used to form the β-diketone (**105**) of all-(*E*)-wallemia C by reaction of (**103**) with the methyl ketone (**104**; equation 29).[109]

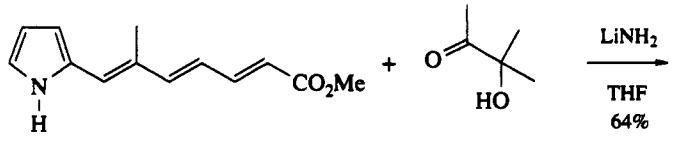
Self-condensation reactions, as in the original Claisen reaction, are still synthetically valuable. The ester (**106**) was self-condensed with isopropylmagnesium bromide as the base and this product used in spherand formation (equation 30).[110]



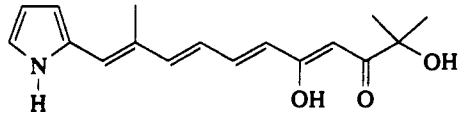
(100) (101)



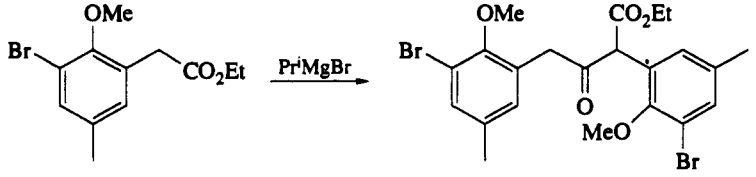
(102) (28)



(103) (104)

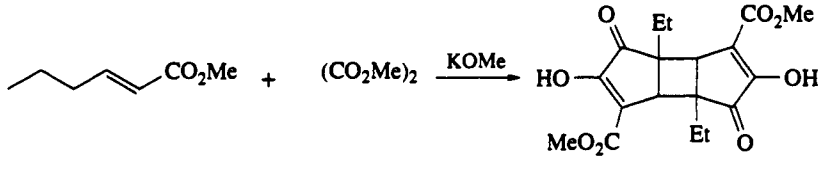


(105) (29)



(106) (30)

An interesting double vinylogous Claisen condensation was used in a total synthesis of (±)-secologanin aglycone.[111] Potassium methoxide-catalyzed condensation of methyl 2-hexenoate with dimethyl oxalate gave the tricyclic derivative (**107**; equation 31).



(107) (31)

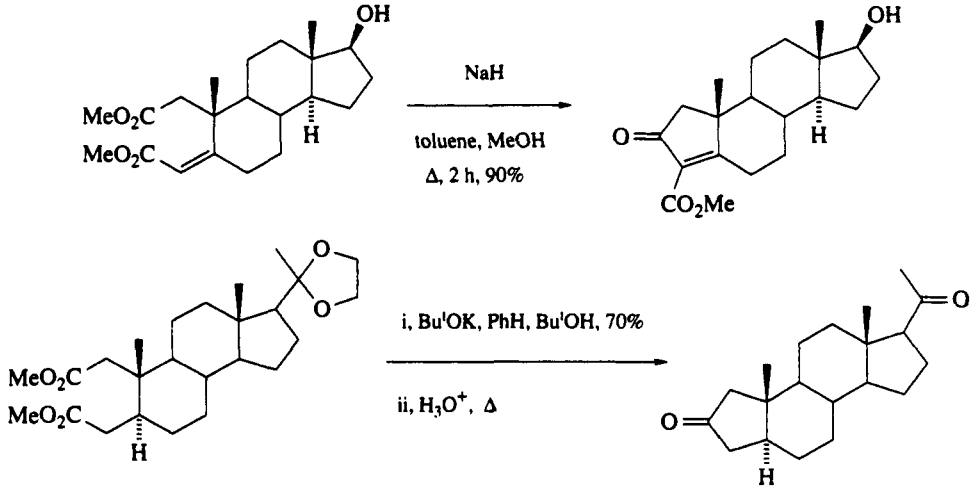
3.6.3.4.3 Use of the Dieckmann reaction in synthesis

The synthetic value of the Dieckmann reaction has been demonstrated in Section 3.6.3.3. It has been used as a major synthetic tool for the preparation of a great variety of natural and nonnatural products. A large measure of its value lies in the range of functional groups that can be tolerated and the variety of re-

action conditions that can be used to effect the cyclization. The reaction is more often used at an early stage in the synthetic route, but that is not necessarily always the case.

(i) Steroids

The reaction has been used to prepare both five- and six-membered steroidal rings (Scheme 37). Both the six-membered C-ring[51] and the five-membered D-ring[52,112] have been prepared from the corresponding diesters. Ring A norsteroids are readily prepared by oxidative cleavage of ring A and cyclization of the resulting diacid as the diester (**47**) to (**48**; Scheme 25).[78,97,113,114] The C-10 methyl group (steroid numbering) controls the direction of cyclization, further emphasized in the case of the α,β-unsaturated ester.[97] Subsequent alkylation and decarboxylation gave the 3-methyl-2-ketonorsteroid.[78]

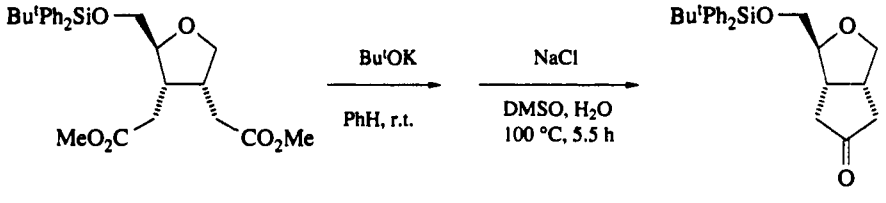


(**47**)

Scheme 37

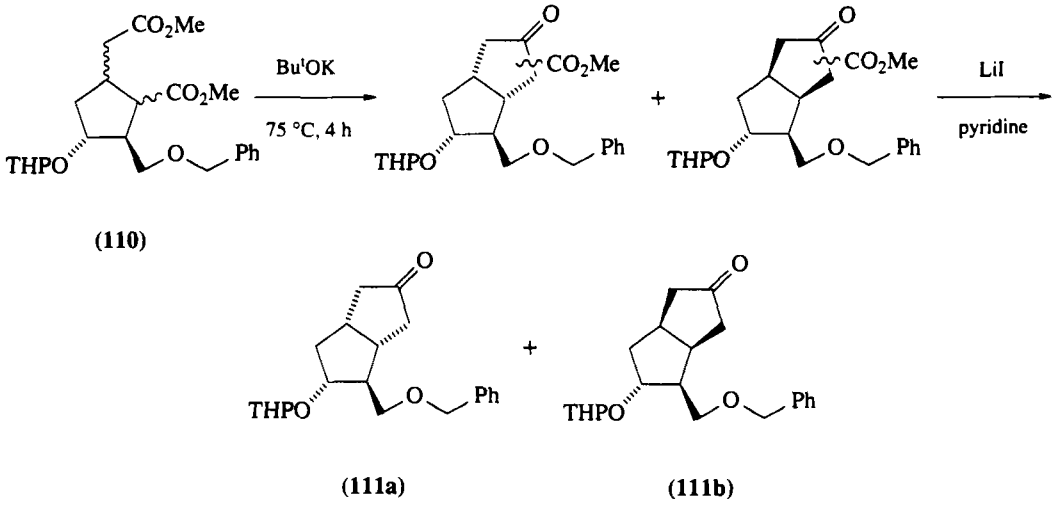
(ii) Prostaglandins

The diester enantiomer (**108**) derived from ribonolactone, has been cyclized and decarboxylated to the bicyclic ketone (**109**) in 83% overall yield for the two steps (Scheme 38).[115] Similarly, the cyclopentanol diester (**110**) has been cyclized and decarboxylated to (**111**), separation of the two diastereomers being effected on the deprotected alcohols (Scheme 39).[116] Cyclization of (**112**) occurs regioselectively as expected to give (**113**) in 81% yield (equation 32).[117] The 9-azaprostaglandin skeleton has been formed through a combination of Michael and Dieckmann reactions.[118]



(**108**) (**109**)

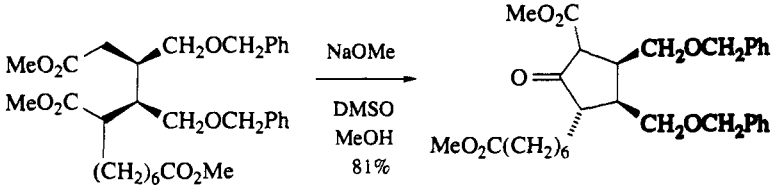
Scheme 38



(110)

(111a) (111b)

Scheme 39

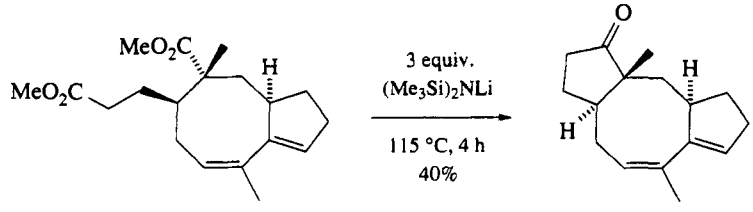


(32)

(112) (113)

(iii) Terpenoids

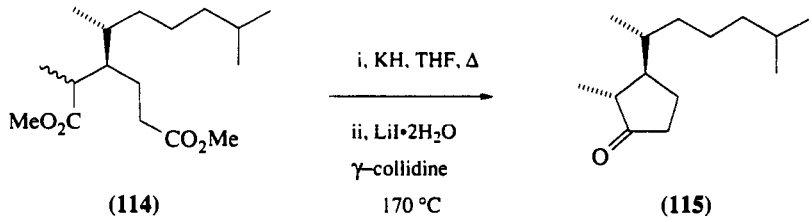
A variety of terpenoid syntheses have employed the Dieckmann condensation in ring formation. Corey *et al.*[54] constructed the five-membered ring of the 5,6-spiro system of (±)-perhydrohistrionicotoxin in this way and one of the five-membered rings of the sesterterpenes ceroplastol and ophiobolin was similarly formed (equation 33).[119] Cyclization and decarboxylation of the diester (**114**) gave the single enantiomer (**115**), equilibration of the methyl group into the favorable thermodynamic *trans* configuration having occurred under the reaction conditions.[81] The enantiomer (**117**) was prepared from (**116**) in a similar manner (Scheme 40).[100] The seven-membered rings of gascardic acid[71] and (±)-gnididone[61] and the 15-membered ring of optically active muscone[63] were formed in the same way, the salts of hindered bases being used to effect these condensations with high dilution conditions for the macrocyclic ring.



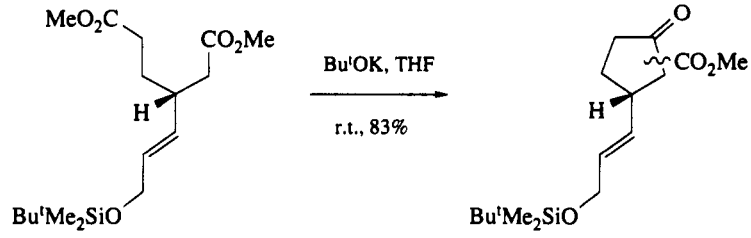
(33)

(iv) Anthracycline antibiotics

Regioselective cyclization of (**118**) *via* the ketone enolate occurs to give (**119**).[120] Zinc is necessary for a reasonable yield, and longer heating rearranges (**119**) to (**120**). Similarly, but under standard conditions, the 4-ketopyran (**121**) cyclizes regioselectively to (**122**)[88] and the anthraquinone (**123**) cyclizes to (**124**; Scheme 41).[121]

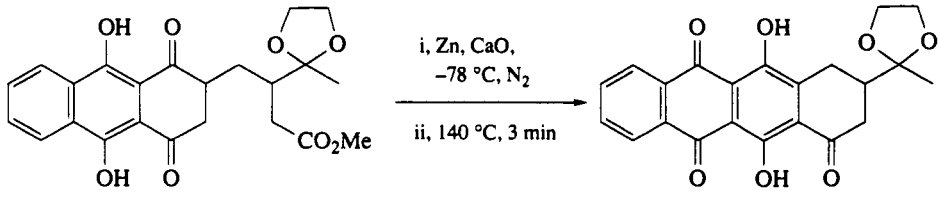


(114) (115)

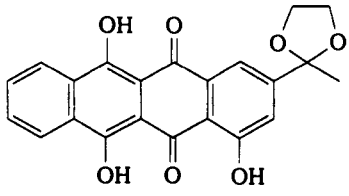


(116) (117)

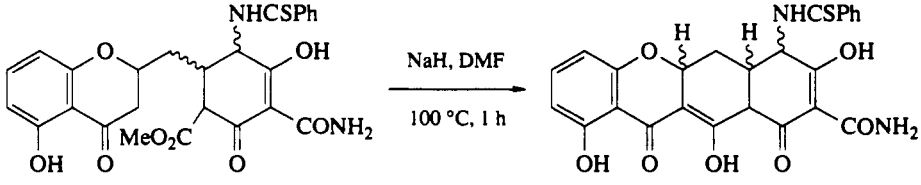
Scheme 40



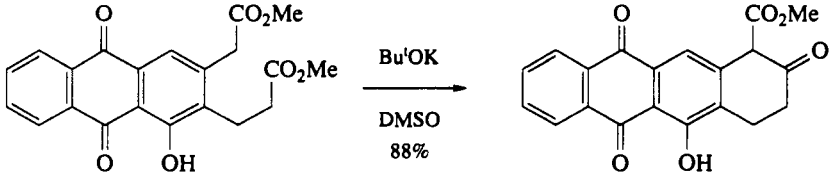
(118) (119)



(120)



(121) (122)

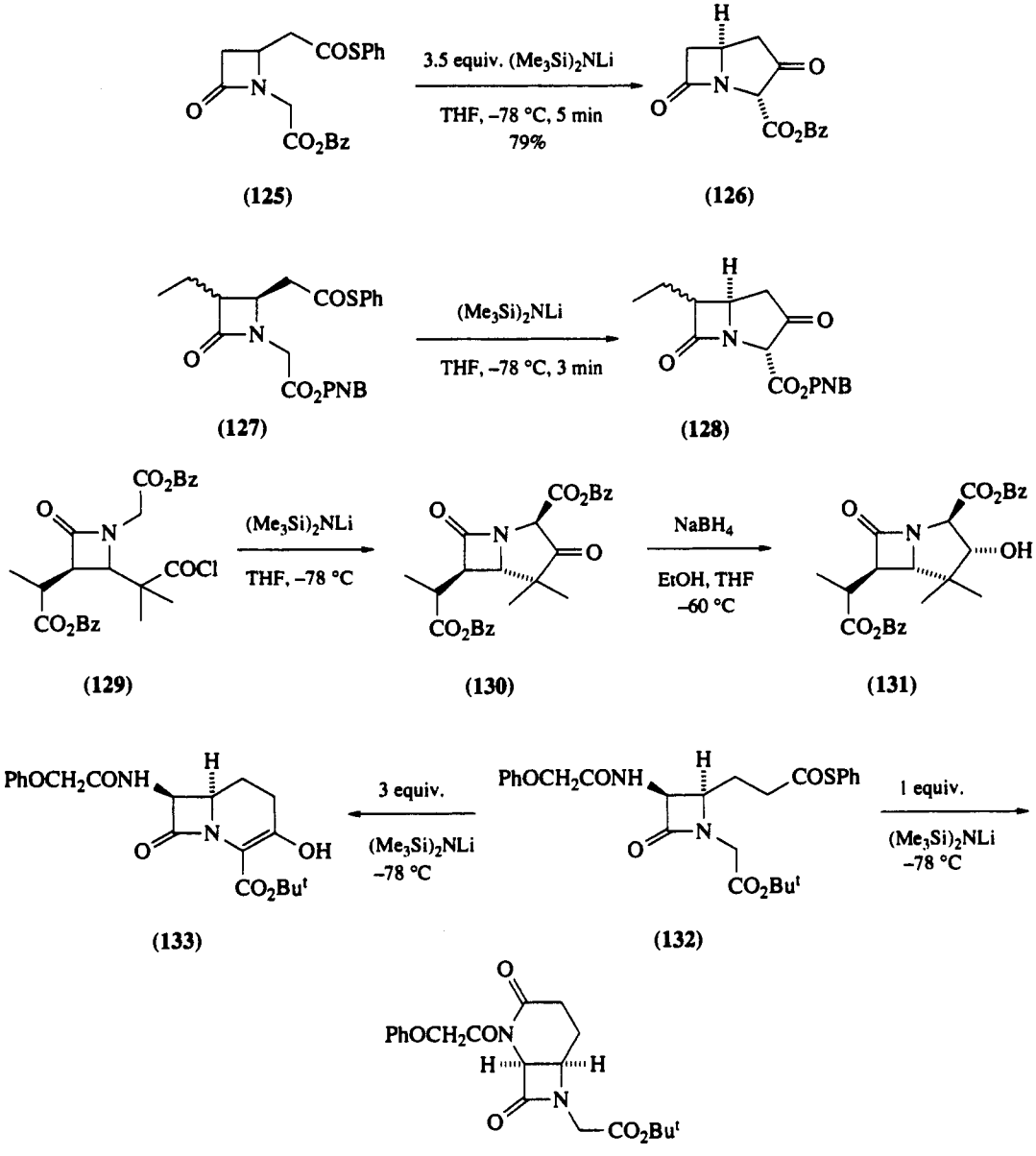


(123) (124)

Scheme 41

(v) Penicillin antibiotics

Remarkably, cyclization of a five- or six-membered ring onto the already strained β-lactam can be effected under mild conditions and in high yield (Scheme 42). Regioselective control has been effected by use of a thiol ester, as illustrated in the conversion of (**125**) into (**126**)[122] and of the two diastereomers of (**127**) into the diastereomers of (**128**).[123] In order to facilitate reaction under mild conditions, one of the groups can be made more electrophilic by conversion to an acid chloride. Reaction of (**129**) with lithium hexamethyldisilazane at –78 °C gave (**130**). The ketone group in (**130**) could be reduced selectively with $NaBH_4$ at –60 °C to give (**131**).[124]

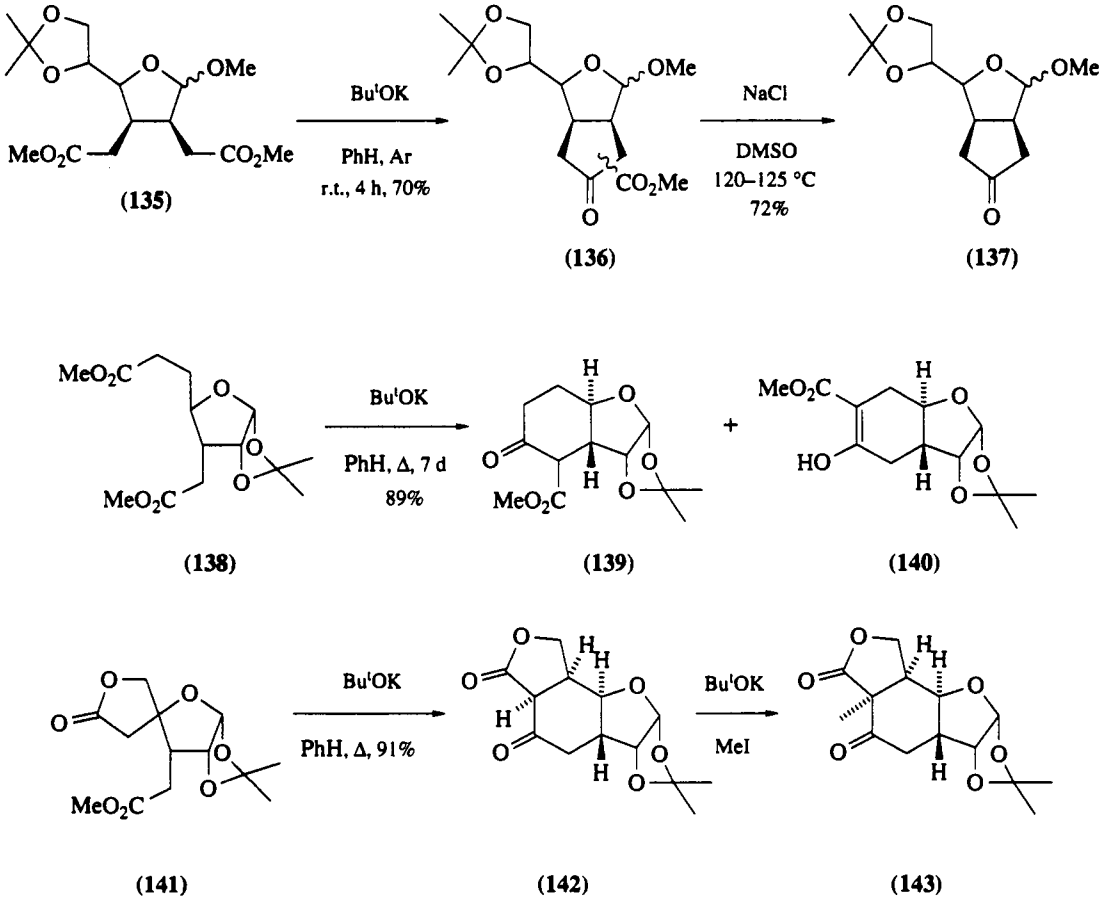


Scheme 42

In their synthesis of the 1-carbacephem derivatives, Hatanaka and Ishimaru observed that the β-lactam (**132**) cyclized to the desired carbacephem skeleton (**133**) with 3 equiv. of lithium hexamethyldisilazane (Scheme 42), but cyclized through the amine nitrogen to give (**134**) with 1 equiv.[125] Presumably deprotonation of the amine occurs with the first equivalent of base.

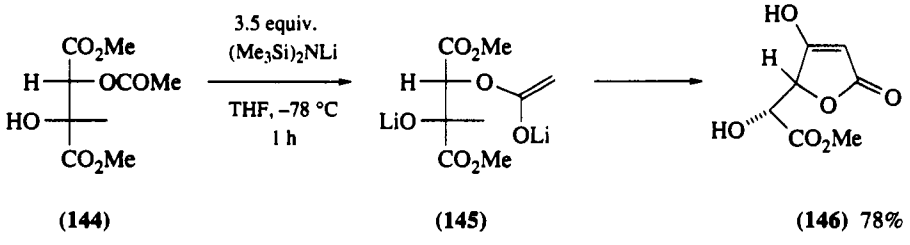
(vi) Carbohydrates

Carbohydrates, which have recently been used extensively as chiral components in syntheses, have been transformed into diesters that, on cyclization, lead to precursors of polycyclic natural products. The tetrahydrofuran diester (**135**) was cyclized with potassium *t*-butoxide to an isomeric mixture (**136**) that was decarboxylated to (**137**).[126] The related diester (**138**) was cyclized to a mixture (8:1) of (**139**) and (**140**), whereas the lactone (**141**) cyclized regioselectively to (**142**) and this was in turn methylated with iodomethane to the *trans-syn-cis* isomer (**143**; Scheme 43).[127]

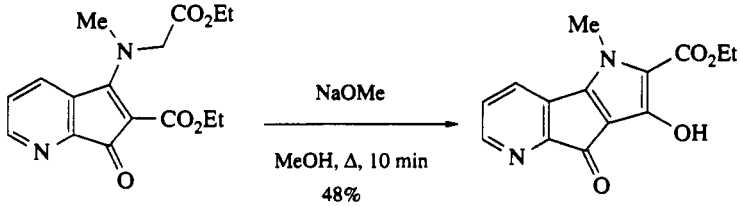


Scheme 43

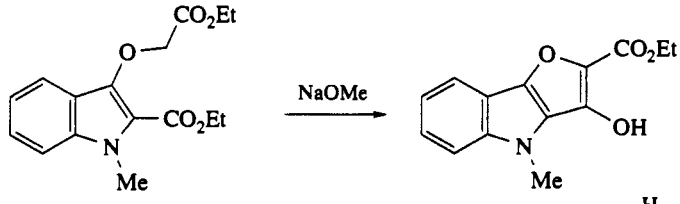
The dimethyl tartrate derivative (**144**) forms the dilithium salt (**145**) with excess lithium hexamethyldisilazane and this smoothly transforms into the butenolide (**146**), which is obtained crystalline in 78% yield.[128] Lithiation of the hydroxy group prevents 1,2-elimination (Scheme 44).



Scheme 44



(ref. 129)



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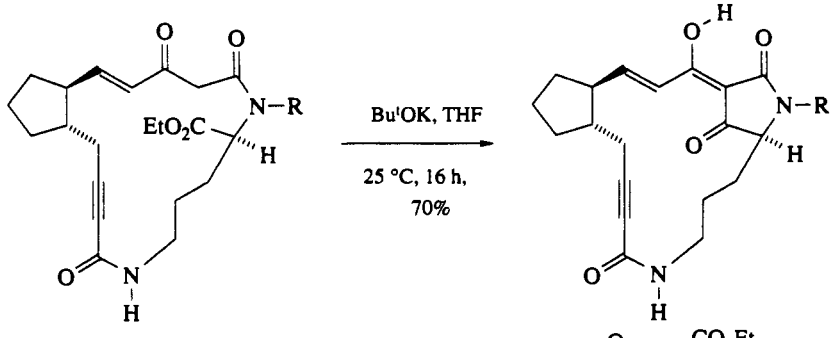
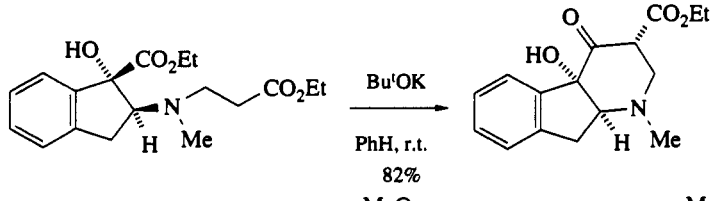
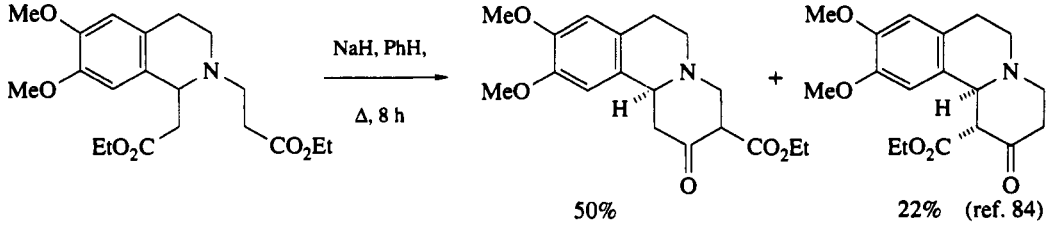


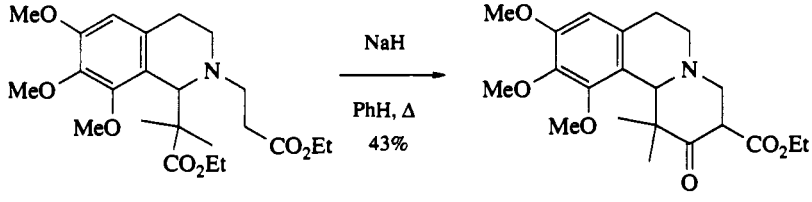
(ref. 131)



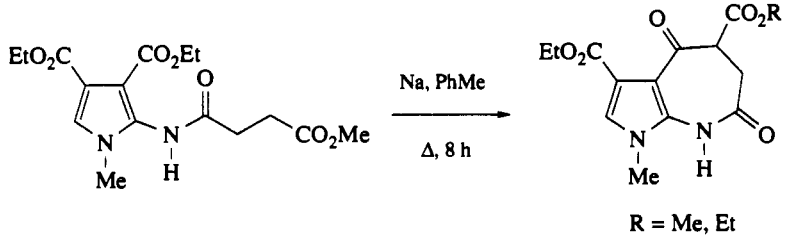
(ref. 132)



50% 22% (ref. 84)



(ref. 133)



(ref. 134)

R = Me, Et

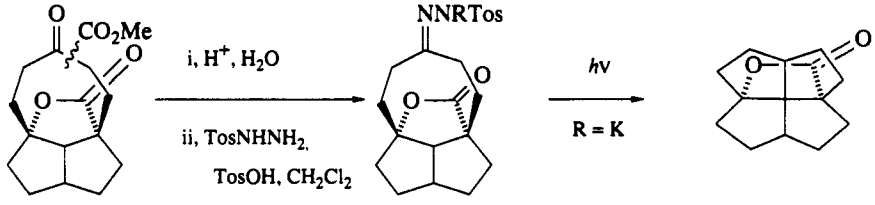
Scheme 45

(vii) Heterocycles and alkaloids

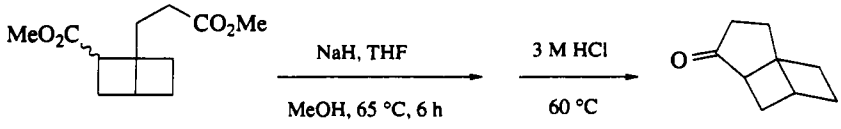
The ability of the Dieckmann reaction to tolerate heteroatoms in the ring-forming sequence of atoms has led to its extensive use in heterocyclic synthesis. Many complex systems containing heterocyclic rings have been prepared by routes that include this reaction, and both aromatic and alicyclic rings have been constructed. A variety of bases and solvents have been employed and representative examples are illustrated in Scheme 45.

(viii) Fenestranes

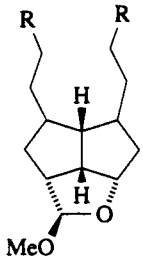
A number of routes to the fenestranes have involved Dieckmann reactions (Scheme 46). The ester (**147**)[62] was decarboxylated and the resulting ketone converted into the tosylhydrazone (**148**). Irradiation of the potassium salt gave the [5.5.5.5]fenestrane derivative (**149**) *via* carbene insertion. The bicyclo[2.2.0]hexane diester (**150**) was cyclized with sodium hydride in THF containing a little methanol and the product decarboxylated to give (**151**).[135] The diester (**152a**), however, underwent the Dieckmann reaction in >5% yield, whereas the corresponding dinitrile (**152b**) underwent a Thorpe–Ziegler cyclization in 59% yield.[136]



(**147**) (**148**) (**149**)



(**150**) (**151**) 74%



(**152a**) R = CO_2Me
(**152b**) R = CN

Scheme 46

3.6.4 ACYLATION OF KETONES BY ESTERS AND OTHER ACID DERIVATIVES

3.6.4.1 Introduction

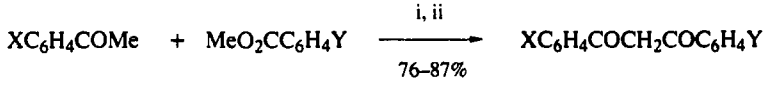
The acylation of ketones by esters and other acid derivatives is a well-established route to β-diketones and β-keto aldehydes. The reaction has been reviewed with extensive coverage to 1949 in *Organic Reactions*[5] and more recently by House[7] and by Caine.[8] The reaction may be effected either with basic or

acidic catalysts. With base, a four-step ionic mechanism, similar to that described for the acylation of esters, is involved. Side reactions, such as an aldol reaction of the ketone or a self-condensation of the ester, are also observed but may be minimized by suitable choice of substrate, base and conditions.

3.6.4.2 Generation and Use of Enolates and Enol Ethers

3.6.4.2.1 Enolate generation in situ

For acylations with reactive esters, such as formate or oxalate (see Section 3.6.4.5), sodium alkoxides are still the bases of choice, but sodium hydride, dimsyl sodium, sodium or potassium amide or sodium metal have all been used for the *in situ* generation of the enolate anion. A typical example is shown in Scheme 47.[137] Acylation by esters results in the production of 1 equiv. of the alkoxide ion, along with the β-dicarbonyl compound; proton transfer then results in the production of the conjugate base of the dicarbonyl compound. This process normally leads to the more stable anion in the acylation of an unsymmetrical ketone. The acyl group thus becomes attached to the less-substituted α-position of the ketone. The less stable *O*-acylated products are normally not observed in such reversible base-catalyzed reactions. Methyl alkyl ketones are normally acylated on the methyl group; where both α-carbons are substituted to the same extent, acylation occurs at the less-hindered site. Acylation is observed only rarely at a methine carbon as the more stable β-diketone enolate cannot be formed.



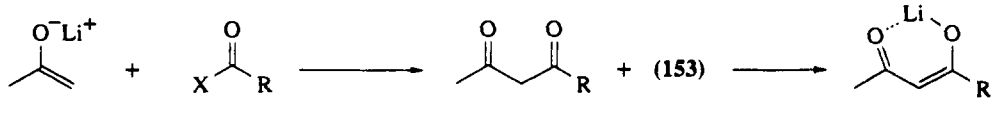
X = H, Y = H; X = *p*-MeO, Y = *p*-MeO; X = *p*-MeO, Y = H

i, NaH, DMSO, <15 °C; ii, H_3O^+, 0 °C

Scheme 47

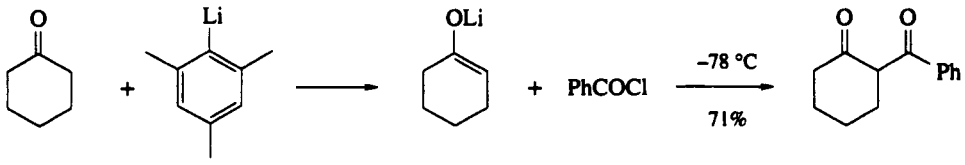
3.6.4.2.2 Preformed enolates and enol ethers

Preformed metal enolates and enol ethers, well-established intermediates in aldol chemistry and in the acylation of esters (see Section 3.6.3.2) have also been widely used in the acylation of ketones. The use of enamines for the acylation of ketones is covered elsewhere in this volume. A significant problem in the acylation of enolates is the reaction of the newly formed diketone with the enolate (Scheme 48). Addition of 1 equiv. of acid chloride to 2 equiv. of enolate gives fair to good yields of diketone, calculated from the acylating reagent, but with a theoretical yield of only 50% with respect to the enolate. Further, the diisopropylamine produced if LDA is used as the base may itself undergo acylation. A number of strategies have been developed to overcome this problem. Emphasis in the examples has been on establishing the methodology with simple systems; the extension to more complex systems is less common. The use of mesityllithium[138] avoided the presence of free diisopropylamine and employed a 1:1 ratio of ketone and acid chloride (Scheme 49). The use of dimethylhydrazones[139] avoided *O*-acylation, giving regiospecific *C*-acylation with a 1:1 ratio of reagents (Scheme 50). Acyl cyanides have again proved their value, either with lithium enolates[140] or trimethylsilyl enol ethers (Scheme 51).[141] The latter derivatives were also acylated using acid chlorides with Lewis acids catalysis (equation 34).[142] The less familiar boroxazine intermediates allowed for regioselective acylation in good yield (Scheme 52),[143] a result also achieved using α-chloroacyltrimethylsilanes followed by an intramolecular rearrangement (Scheme 53).[144] Dialkyl acylphosphonates have also been used to acylate a lithium enolate (equation 35).[145]

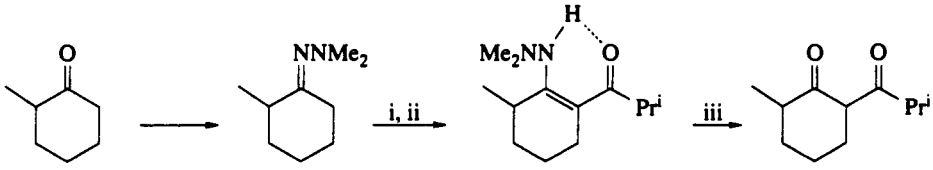


(153)

Scheme 48

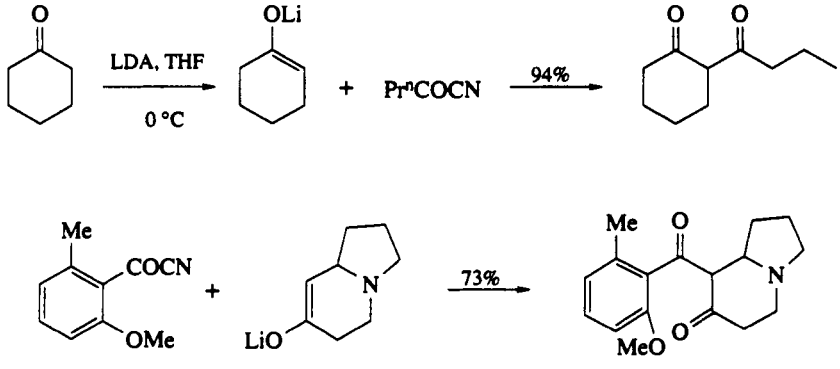


Scheme 49



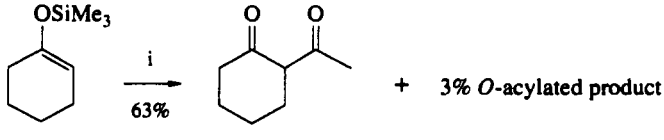
i, BuLi, THF, -78 °C *or* LDA, THF, 0 °C 67% overall; ii, Pr^iCOCl; iii, H_3O^+, MeOH

Scheme 50



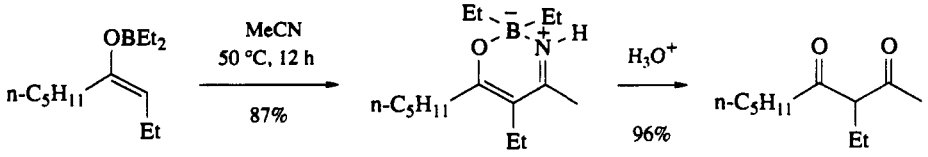
i, MeCOCN, $TiCl_4$, CH_2Cl_2, -78 °C; ii, cold aq. OH^-

Scheme 51

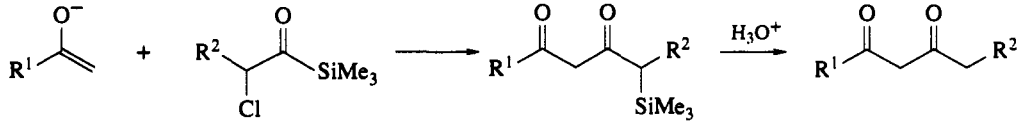


(34)

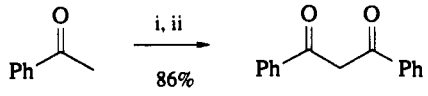
i, MeCOCl, $ZnCl_2$, CH_2Cl_2, 0 °C ($SbCl_3$ also used)



Scheme 52



Scheme 53



(35)

i, $LiN(SiMe_3)_2$; ii, $PhCOPO(OEt)_2$, -78 °C, 30 min

3.6.4.2.3 Trapped enolates, organocopper conjugate addition

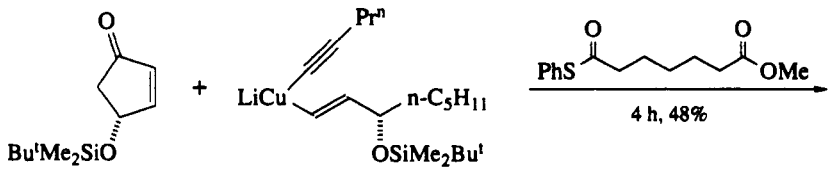
Enolates formed by organocopper conjugate addition may be acylated cleanly by acid chlorides to give β-diketones.[146] Although *O*- and *C*-acylation are both possible, the latter is favored by the use of acid chlorides rather than anhydrides and by the use of diethyl ether as solvent, rather than DME. Good yields of β-diketones have been obtained by acylation of the anions derived from both acyclic and cyclic unsaturated ketones with cuprates, or in copper-catalyzed Grignard reactions. Some synthetic applications are given in Scheme 54.

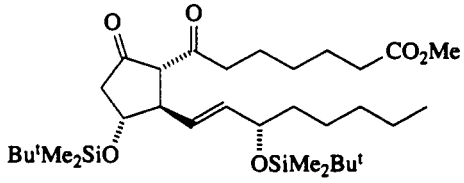
3.6.4.2.4 Dianions γ-acylation

Dianions of β-keto esters undergo γ-acylation when reacted with esters to produce diketo esters in fair yield (Scheme 55). As the monoanion of the product has a more acidic proton than the monoanion of the starting β-keto ester, proton transfer from the monoanion of the diketo ester to the dianion of the starting material should occur and the maximum conversion of β-keto ester to product would be 50% in this reaction. The problem has been overcome, as shown in Scheme 55, by adding 0.5 equiv. of the ester to the dianion and regenerating the quenched dianion by the addition of more base before adding further ester; in this way yields of about 70% were obtained.[151] The reaction has been put to good use in the synthesis of poly-β-diketones which, on cyclization with base, produce polyketides in a biomimetic synthesis. Yamaguchi *et al.*[152] reacted a number of substituted glutarate esters with the dianion of methyl acetoacetate (Scheme 56), while another group[153] reacted the dianion of pentane-2,4-dione with the ethylene ketal of diethyl 3-oxoglutarate to produce, eventually, the anthraquinone emodin (Scheme 57).

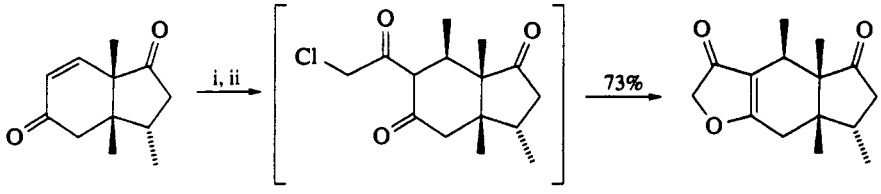
3.6.4.3 Ketones as Enols: Acid Catalysis of Acylation

Complementary to the acylation of enolate anions is the acid-catalyzed acylation of the corresponding enols, where the regiochemistry of acylation can vary from that observed in base-catalyzed reactions. Although the reaction has been studied extensively in simple systems, it has not been widely used in the synthesis of complex molecules. The catalysts most frequently employed are boron trifluoride, aluminum chloride and some proton acids, and acid anhydrides are the most frequently used acylating agents. Reaction is thought to involve electrophilic attack on the enol of the ketone by a Lewis acid complex of the anhydride (Scheme 58). In the presence of a proton acid, the enol ester is probably the reactive nucleophile. In either case, the first formed 1,3-dicarbonyl compound is converted into its borofluoride complex, which may be decomposed to give the β-diketone, sometimes isolated as its copper complex.[154]



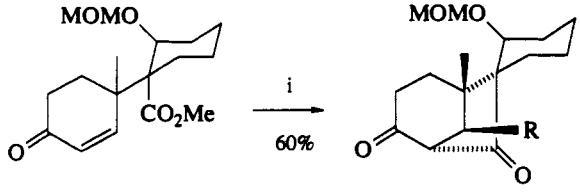


(ref. 147)



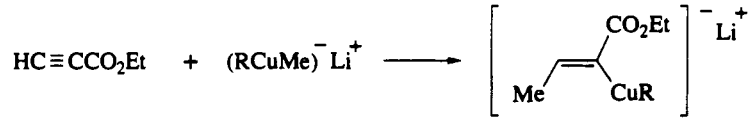
(ref. 148)

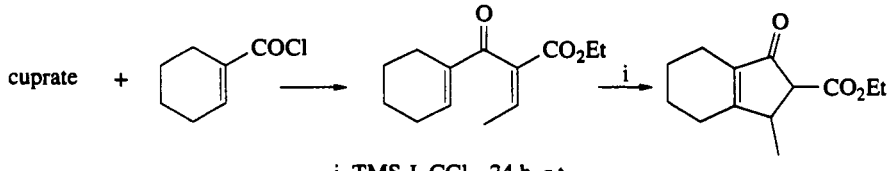
i, Me_2CuLi; ii, $ClCH_2COCl$



(ref. 149)

i, RMgBr, CuBr (0.25 equiv.), THF, -20 to -23 °C; R = CH_2=$CHCH_2CH_2$–

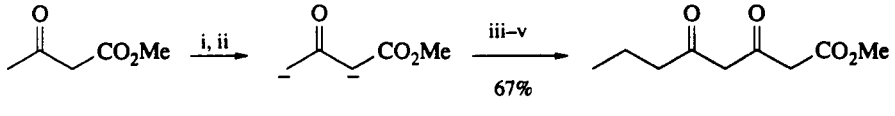




(ref. 150)

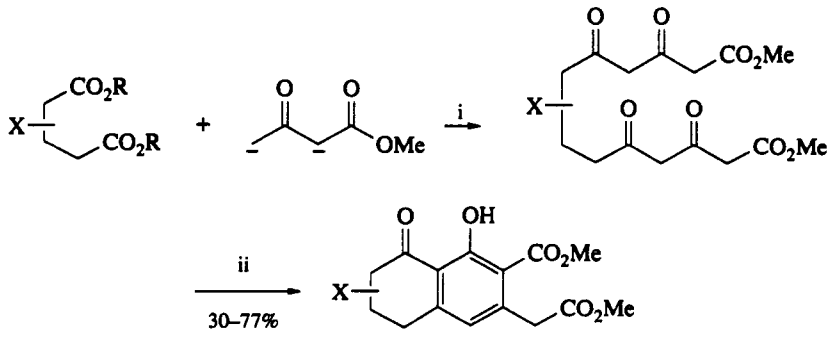
i, TMS-I, CCl_4, 24 h, r.t.

Scheme 54



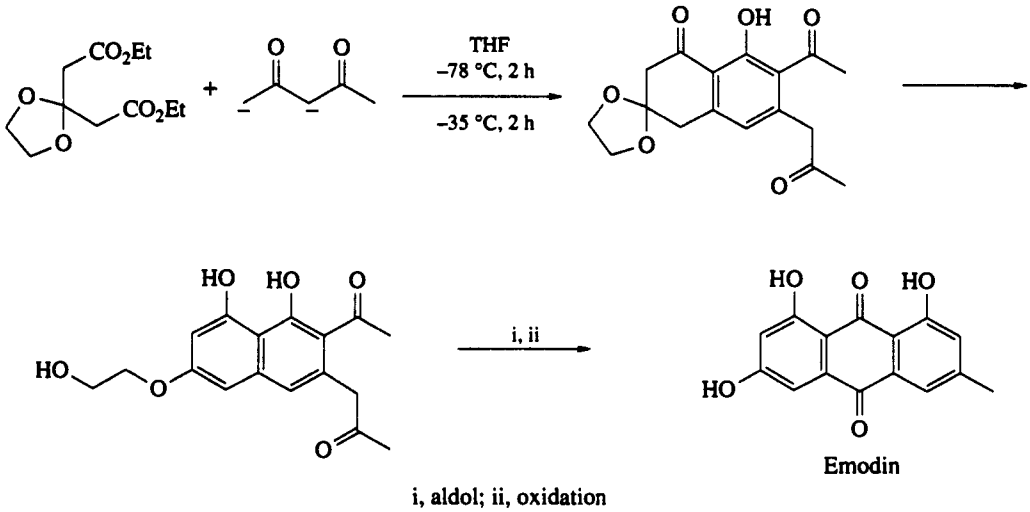
i, NaH, 1 equiv.; ii, Bu^nLi, 1 equiv.; iii, methyl butanoate, 0.5 equiv.; iv, Bu^nLi, 1 equiv.; v, methyl butanoate, 0.5 equiv.

Scheme 55



i, THF, r.t., 2 h; ii, $Ca(OAc)_2$, MeOH, reflux, 2 h

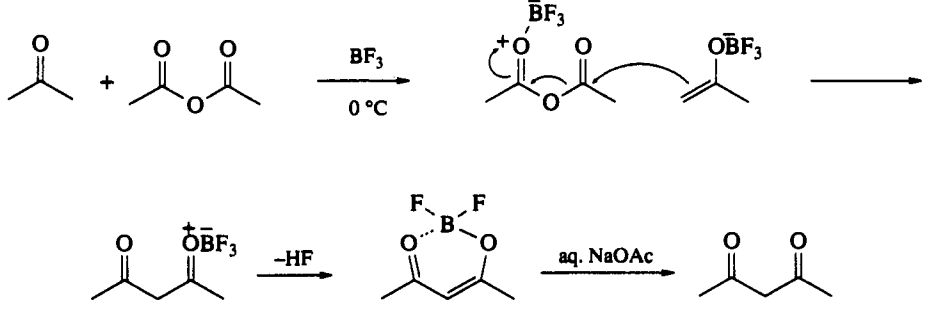
Scheme 56



i, aldol; ii, oxidation

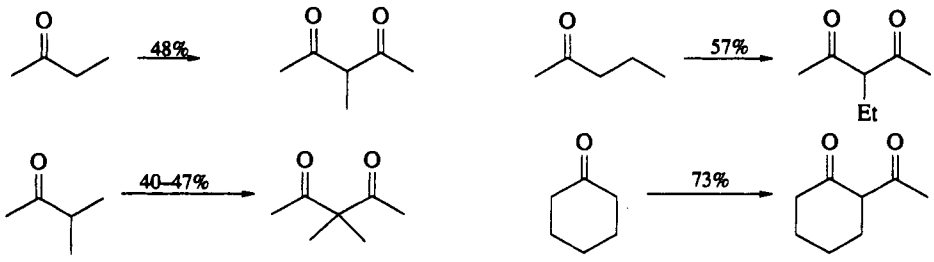
Scheme 57

Boron trifluoride has been used in gaseous form, or as its complex with acetic acid or diethyl ether. Unsymmetrical ketones may be acylated to produce either of the two possible diketones. In general, the use of gaseous boron trifluoride, in the absence of a proton acid, favors acylation of the kinetic enol and thus leads to substitution at the less highly substituted α-carbon. By contrast, if the reaction is performed in the presence of a proton acid, using one of the boron trifluoride acid complexes, the thermodynamically more stable enol is formed, thus leading to reaction at the more highly substituted carbon atom. A number of simple acyclic and cyclic ketones were acylated in the presence of the boron trifluoride–acetic acid complex to produce diketones in good yield (Scheme 59).[155] The acetylation of 3-methyl-2-buta-

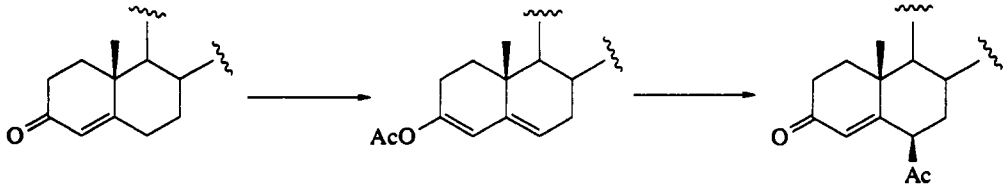


Scheme 58

none to give only 3,3-dimethylpentane-2,4-dione (40–47%) indicates that nonenolizable diketones may be synthesized by this method. α,β-Unsaturated ketones may be acylated on the γ-carbon *via* the dienol acetate (Scheme 60);[156] this reaction has been extended to the acylation of cyclohexane-1,3-dione enol ethers.[157]



Scheme 59 Acetylation with acetic anhydride and boron trifluoride–acetic acid complex

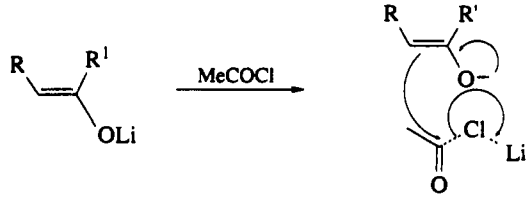


Scheme 60

3.6.4.4 Regiochemistry of Acylation

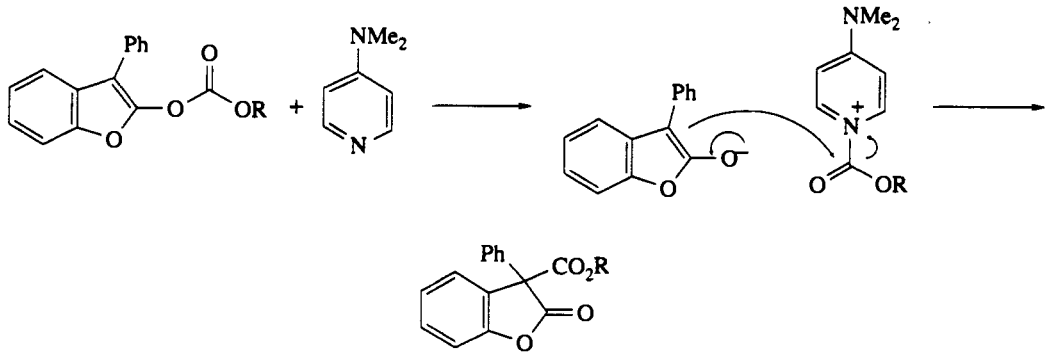
3.6.4.4.1 O- versus C-*acylation*

The regiochemistry of acylation of enolate anions, enols and enol ethers has been extensively studied and reviewed.[7,8] In the base-catalyzed acylation of ketones by esters 1 equiv. of alkoxide ion is produced, along with the β-dicarbonyl compound. The reactions are thus reversible and usually proceed to the more stable anion. Although *O*-acyl products may be formed initially, they are not isolated in the final product. However, when ketone enolates are reacted with other acid derivatives in an irreversible reaction, the regiochemistry of acylation becomes critical. *C*-Acylation is favored by tight ion-pairs, rather than solvent-separated ions; this condition is favored by less polar solvents such as diethyl ether or THF, rather than DME, and by cations such as $Mg^{2+}/2$ or $MgBr^{+}$ rather than the alkali metal ions, Li^{+}, Na^{+} and K^{+}, and by some divalent ions such as Zn^{2+}. *C*-Acylation is also favored by using acyl chlorides or acyl cyanides, rather than acid anhydrides, and by low temperatures. Inverse addition, which ensures the presence of the acylating agent in high concentration, also favors *C*-acylation. In geometrically isomeric enolates, *C*-acylation is favored when the larger β-substituent is *trans* to the alkoxide ion. The evidence points to an intramolecular electrophilic catalysis favoring *C*-acylation (equation 36).[158] When the cation is more firmly bound to the oxygen, such intramolecular catalysis is more readily effected; also the formation of metal chlorides or cyanides should be more favorable than the formation of the metal acetate. The correlation of a high covalent character for the enolate with *C*-acylation is supported by the fact that silyl enol ethers undergo almost exclusive *C*-acylation. In a recent paper[159] 4-(dimethylamino)pyridine has been shown to be an effective catalyst in promoting exclusive *C*-acylation in a benzofuranone. The



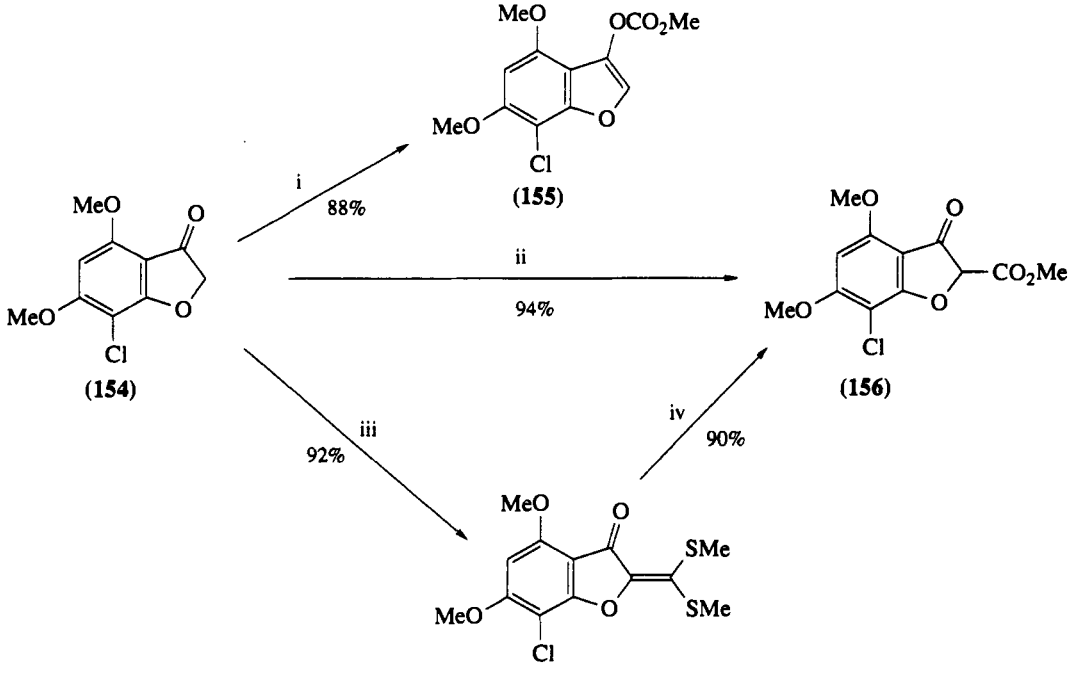
(36)

kinetically favored *O*-acyl compound is converted into the thermodynamically more stable *C*-acyl derivative, as shown in Scheme 61.



Scheme 61

Another route to *C*-acylation is illustrated in Scheme 62.[160] The benzofuranone (**154**) on reaction with methyl chloroformate in the presence of LDA gave the *O*-acylated product (**155**) in 88% yield. With methyl cyanoformate, the *C*-acylated product (**156**) was obtained in 94% yield. However, the larger scale use of this reagent was unsatisfactory, so an alternative strategy was devised. The ketone (**154**) was treated with carbon disulfide, dimethyl sulfate and base in DMSO to give the bis(methylthio) ketene acetal. Aqueous base yielded the *C*-acylated product (**156**) in 83% overall yield.



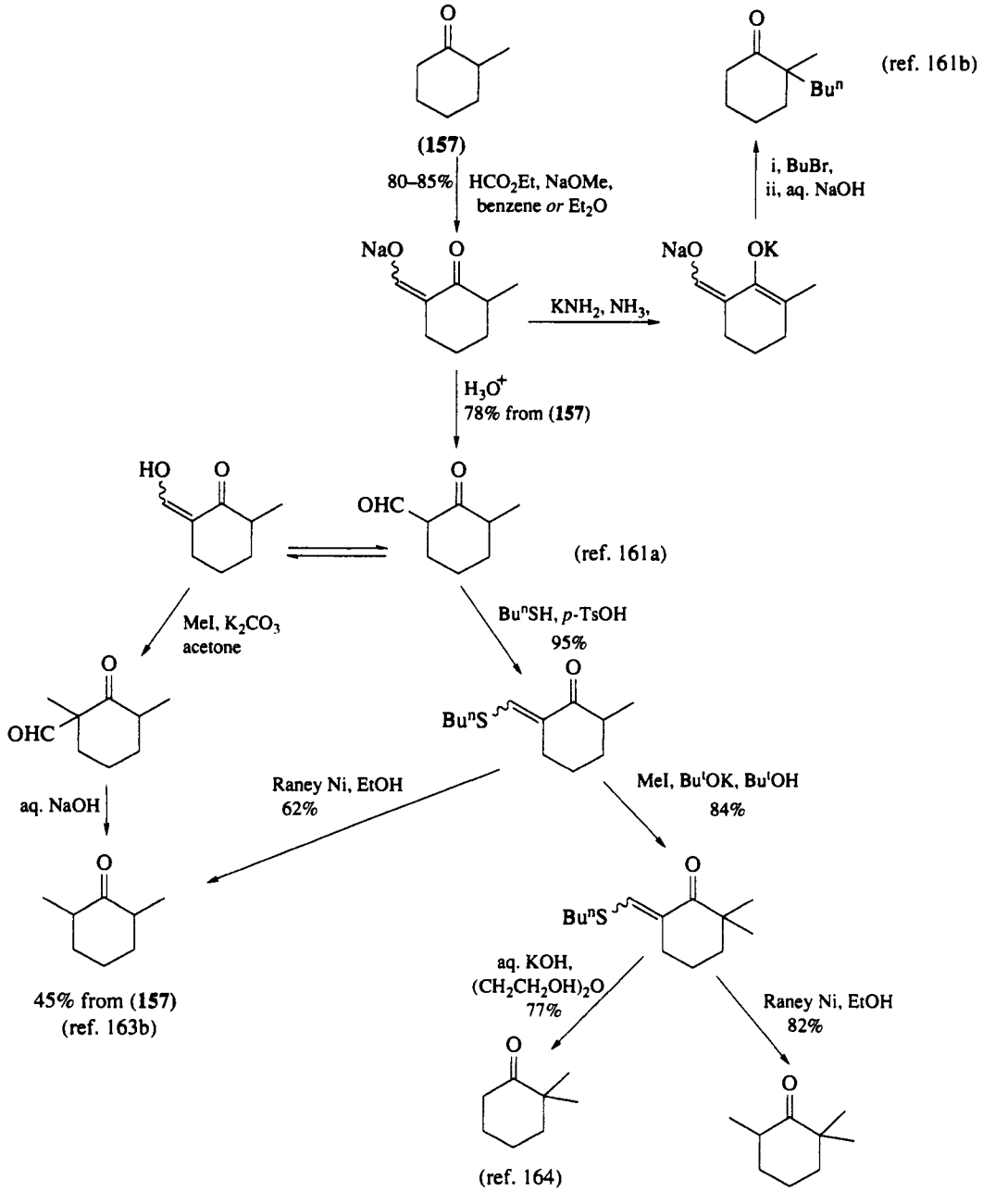
i, $ClCO_2Me$, LDA, THF, –78 °C; ii, $NCCO_2Me$, LDA, THF, –78 °C; iii, CS_2, Me_2SO_4, NaOH, DMSO, 5 °C; iv, MeOH, NaOH, THF, 50 °C

Scheme 62

3.6.4.5 Synthetic Applications of Intermolecular Acylation of Ketones

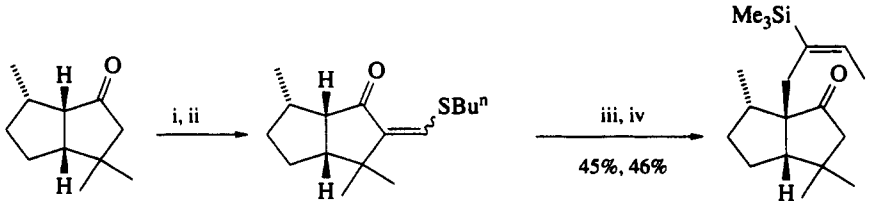
3.6.4.5.1 Formylation

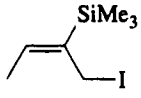
One of the reactions used most extensively to acylate ketones employs formate esters to produce α-formyl or hydroxymethylene ketones. Earlier work has been reviewed;[5,7] this section summarizes the important reactions of these products, particularly in alicyclic chemistry. As an illustration, the conversion of 2-methylcyclohexanone (**157**) into its 6-hydroxymethylene derivative and the subsequent chemistry of that compound are shown in Scheme 63. Such ketones normally undergo formylation at the less



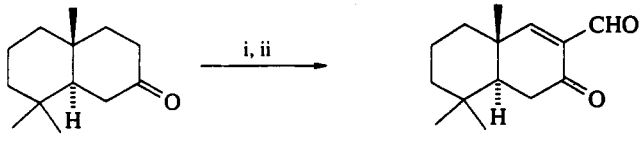
Scheme 63

substituted carbon atom, with the product existing mainly in the enolic form.[161] Acyclic methyl *n*-alkyl ketones give mixtures of acylated products, but reaction at the methyl group is generally favored.[162] The hydroxymethylene group may serve to activate to alkylation the carbon atom to which it is attached.[163] The formyl group can be readily removed by the use of aqueous base. The same function also serves as a precursor of the *n*-butylthiomethylene group,[164] the most widely used removable blocking group for ketone alkylation. The corresponding enamine[165] or enol ether[166] are now rarely used. The extensive chemistry of β-alkylthio-α,β-unsaturated enones has been reviewed.[167] Some examples of its use as a blocking group are described;[168] a recent and testing example of its blocking function is given in Scheme 64.[169] Hydroxymethylene ketones may serve as intermediates to α-formyl α,β-unsaturated ketones (equation 37),[170] to α-methylene ketones in a crossed Cannizzarro reaction followed by dehydration (equation 38),[171] and may be reduced to hydroxymethyl ketones by a variety of reagents (Scheme 65).



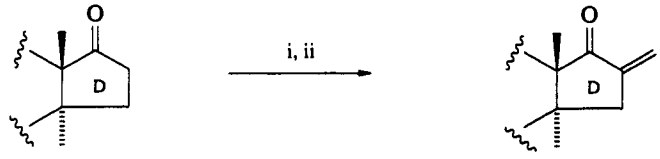
i, HCO_2Et, NaOEt; ii, Bu^nSH, *p*-TsOH; iii, LDA,  ; iv, 25% KOH, $(CH_2CH_2OH)_2O$, Δ

Scheme 64



(37)

i, NaH, HCO_2Et; ii, PhSeCl, Py, H_2O_2



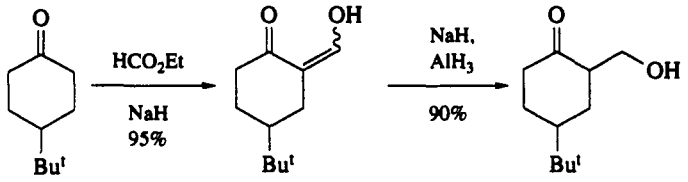
Various steriods

(38)

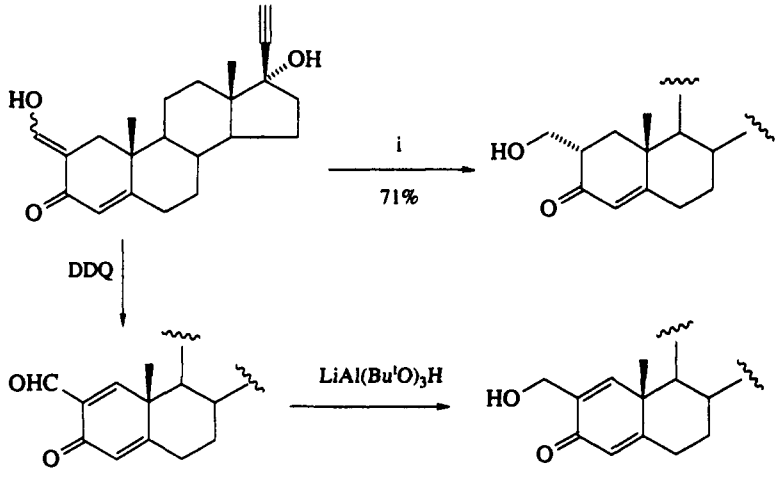
i, HCO_2Et, NaOMe, PhH, 70–96%; ii, HCHO, EtOH, K_2CO_3, 68–80%

3.6.4.5.2 Oxalylation

The reaction of diethyl oxalate with ketones in the presence of sodium ethoxide, or other bases, has been used extensively; examples are given in Scheme 66. Reaction may occur with ester:ketone ratios of 1:1, 2:1, or 1:2, but only the 1:1 case finds substantial use in modern synthetic practice. Frequently the α-oxalyl ketone is thermally decarbonylated to give the β-keto ester.[174] An early example of this was provided by Bachmann's synthesis of equilenin.[175] The mechanism of this reaction has been examined;[176] labeling studies showed that it was the ester carbonyl that was eliminated. The intact oxalyl group has been used as a directing group in steroid methylation[177] while, more recently, 2-oxalylcyclohexanone has provided a route to (*R*)-(–)-hexahydromandelic acid (Scheme 67).[178] The products of acylation of suitable acyclic ketones can cyclize to form (enolic) cyclopentane-1,2,4-triones (equation 39).[179]



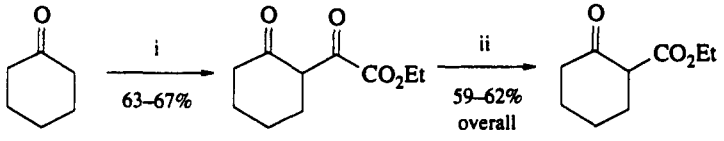
(ref. 172)



(ref. 173)

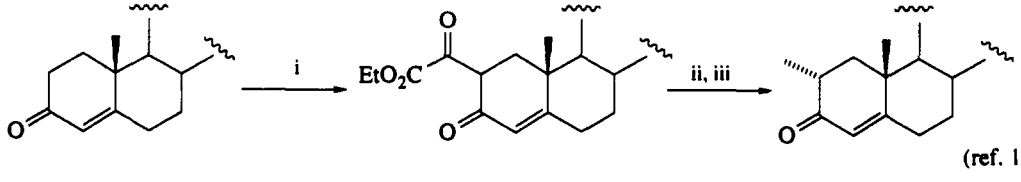
i, *Streptomyces roseochromogenus*

Scheme 65



(ref. 174)

i, $(CO_2Et)_2$, NaOEt; ii, powdered glass, 165–170 °C



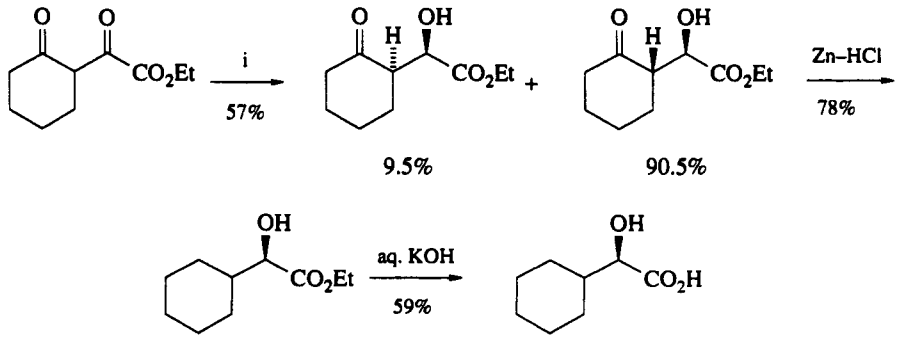
(ref. 177)

i, $(CO_2Et)_2$, NaH; ii, MeI, K_2CO_3, Me_2CO; iii, NaOEt

Scheme 66

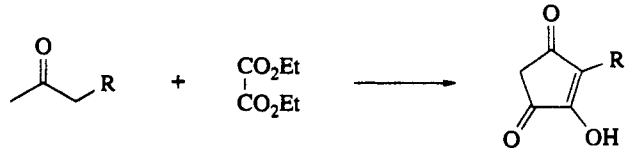
3.6.4.5.3 Alkoxycarbonylation

A variety of reagents will effect the conversion $COCH_2 \rightarrow COCHCO_2R$; the decarbonylation of glyoxalate esters was described above. The most recently described reagent, methyl cyanoformate, reported by Mander and Sethi in 1983,[180] allows the conversion of a preformed lithium enolate to the β-keto ester in high yield (Scheme 68). Diethyl dicarbonate with potassium hydride in benzene effects the same reaction with symmetrical ketones, and with lithium dicyclohexylamide in ether introduces the ethoxycarbonyl group into the α′-position of α,β-unsaturated ketones (Scheme 69).[181] Diethyl carbon-



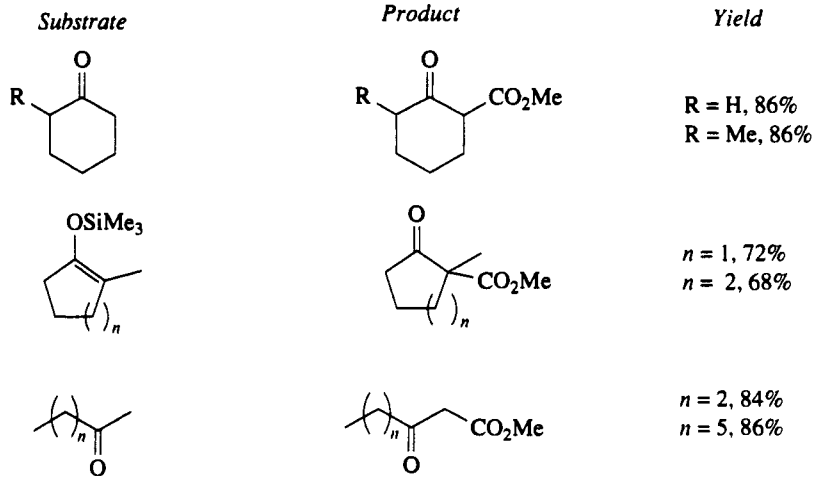
i, Baker's yeast

Scheme 67

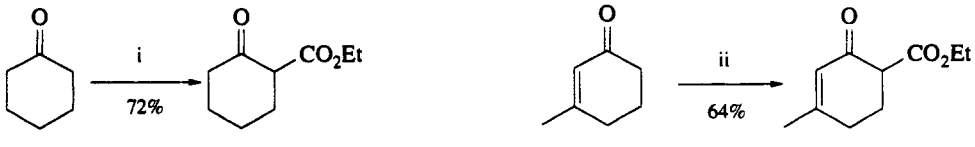


(39)

ate[182] and $EtOCOPO(OEt)_2$ (Scheme 70)[183] also introduce the ethoxycarbonyl group, while thioesters were prepared by reaction of ketones with *O,O*-diethyl trithiodicarbonate, using sodium hydride as base (Scheme 71). Ultrasonication of the reaction mixture gave the thioester in 93% yield based on the ester used.[184] In general, these reactions do not give control of regiochemistry. Thus the examples cited[181–184]

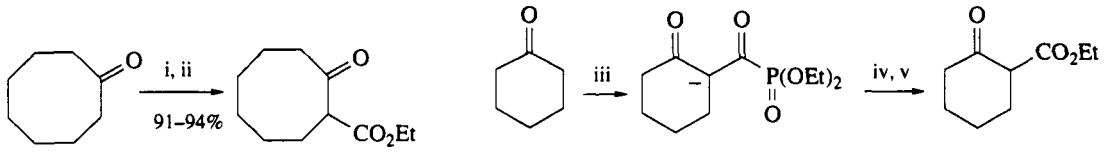


Scheme 68



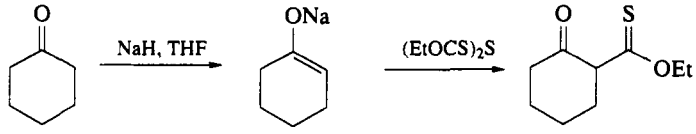
i, KH, $EtOCO_2CO_2Et$, PhH, 80 °C; ii, $EtOCO_2CO_2Et$, $LiN(c\text{-}C_6H_{11})_2$

Scheme 69



i, $(EtO)_2CO$, NaH, PhH; ii, AcOH, H_2O; iii, $EtOCOPO(OEt)_2$, NaH, Bu^n_2O, 30–60 °C; iv, EtOH, H_2SO_4, 50–55 °C; v, H_2O

Scheme 70

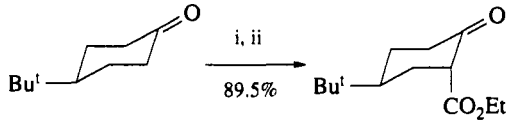


Scheme 71

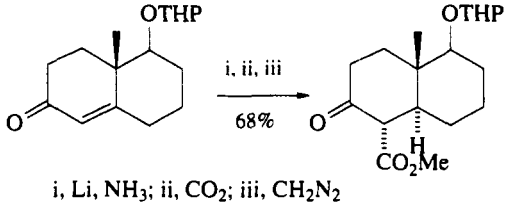
include only symmetrical ketones or methyl *n*-alkyl ketones, where the ethoxycarbonyl group is introduced on the methyl group. The use of methyl magnesium carbonate (Stiles' reagent), where the isolated product is often a β-keto ester, is described in the next section.

3.6.4.5.4 Carboxylation

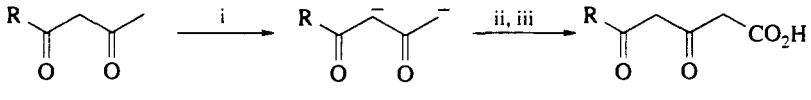
Ketones may be converted into the corresponding β-keto acid, sometimes isolated as its ester, by direct carbonation of the enolate anion or by the use of methylmagnesium carbonate (Stiles' reagent, MMC). Three examples of the former process are shown in Scheme 72; the first[185] involves the generation of the enolate with base while in the second[186] it is formed by reduction of an α,β-unsaturated ketone. In the third example,[187] the dianion of a β-diketone was, as expected, carboxylated on the most basic carbon atom. The more widely used processes for carboxylation employ Stiles' reagent,[188] formed by bubbling carbon dioxide into magnesium methoxide in dimethyl formamide. The reaction mixture is heated to 120 °C and methanol removed by distillation. The pertinent equilibria are shown in Scheme 73. The reagent as normally employed is probably represented by (**158a**), although some of the species (**158b**) may also be present. Typical examples of its use are shown in Scheme 74, which also illustrates the regiochemistry of the reaction; the 2-tetralone gave the 3-carboxylic acid while 4-oxopentanoic acid was carboxylated exclusively on the methyl group. Bis-carboxylation is illustrated in the fourth example.



i, Ph_3CK, Et_2O; ii, CO_2



i, Li, NH_3; ii, CO_2; iii, CH_2N_2



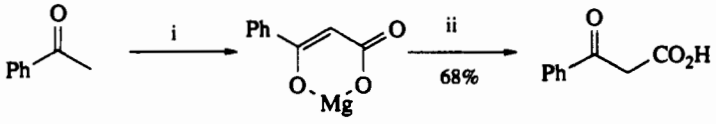
i, $NaNH_2$, NH_3; ii, CO_2, Et_2O; iii, H_3O^+

Scheme 72

$$Mg(OMe)_2 + CO_2 \rightleftharpoons MeOMgOCO_2Me{\cdot}xCO_2 \rightleftharpoons (MeOCO_2)_2Mg$$

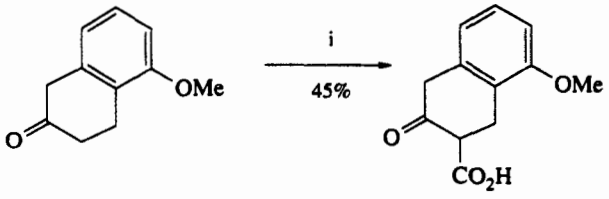
(158a) **(158b)**

Scheme 73



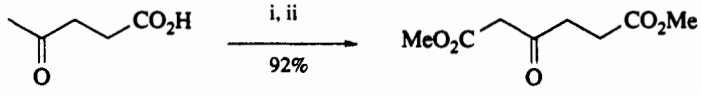
(ref. 188)

i, MMC, DMF, 110–120 °C; ii, H_3O^+



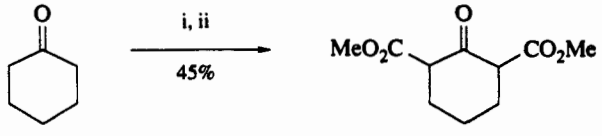
(ref. 189)

i, MMC, DMF, 130 °C, 4 h



(ref. 190)

i, MMC, DMF; ii, MeOH, HCl

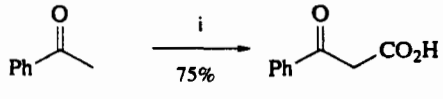


(ref. 191)

i, MMC, DMF; ii, MeOH, HCl

Scheme 74

More recently Rathke and coworkers[192] have described a procedure involving the carboxylation of a ketone in the presence of magnesium halide and triethylamine in acetonitrile with an optimal ratio of amine:halide:ketone of 4:2:1. Advantages included a lower reaction temperature and a solvent more readily removed (equation 40). The reaction showed little regioselectivity, as 2-butanone was carboxylated on the methyl and methylene groups in a ratio of 55:45. The same group reacted a magnesium enolate with butenone in the initial Michael step of a Robinson annelation.[193]

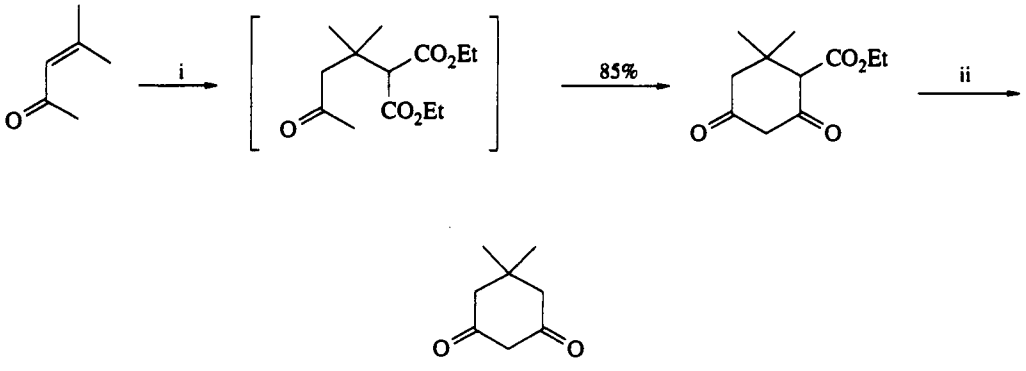


(40)

i, Et_3N, CO_2, MeCN, 'MgI_2' ($MgCl_2$ + 2NaI)

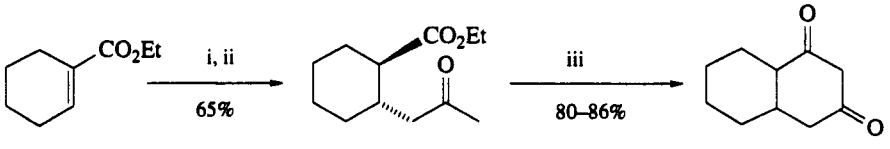
3.6.4.6 Intramolecular Acylation of Ketones

The synthesis of alicyclic 1,3-diketones from γ- or δ-keto esters is a well-established reaction. Over 50 examples are tabulated in the 1954 chapter in *Organic Reactions*,[5] and a similar number are tabulated as involving a Michael addition of a diester or keto ester to an unsaturated ketone followed by a Claisen condensation. These latter reactions involve such well-known syntheses as that of dimedone (5,5-dimethylcyclohexane-1,3-dione; Scheme 75).

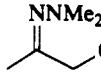


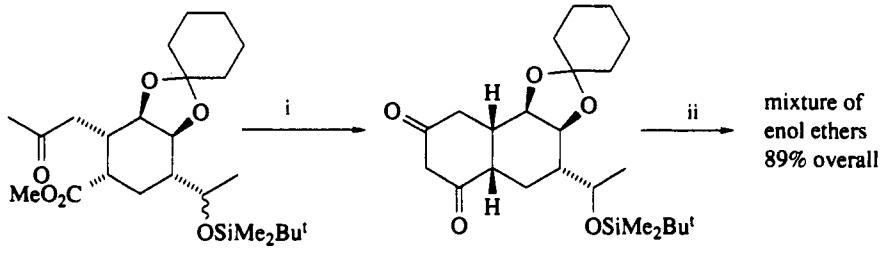
i, $CH_2(CO_2Et)_2$, NaOEt; ii, aq. HCl, Δ

Scheme 75



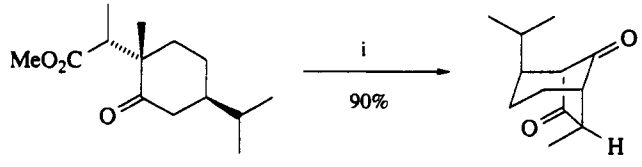
(ref. 194)

i,  ; ii, $CuCl_2$, pH 7, THF, H_2O; iii, NaH (2–2.2 equiv.), PhH, trace MeOH



(ref. 195)

i, $KOBu^t$ (3.3 equiv.), PhH, 25 °C, 20 min; ii, CH_2N_2, Et_2O, 0 °C, 10 min

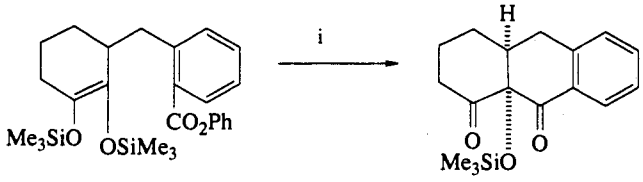


(ref. 196)

i, $(Me_3Si)_2NNa$, DME

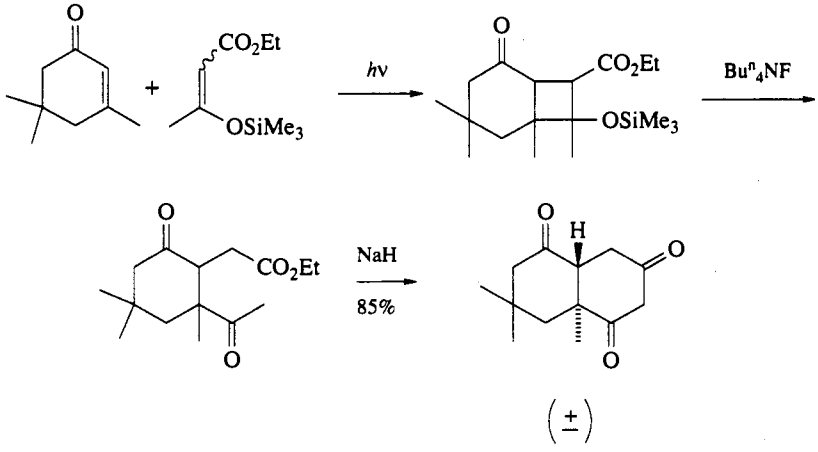
Scheme 76

Such reactions are normally base catalyzed, Scheme 76 illustrates the use of this reaction to provide both fused and bridged rings. Other techniques for synthesizing the keto ester from trimethylsilyl ethers are shown in Scheme 77. The diketones shown were usually isolated as a mixture of enols or enol ethers. Acid-catalyzed acylation also provides a route to diketones not readily obtained by other routes (Scheme 78). The acid catalysts included polyphosphoric acid and naphthalene-2-sulfonic acid. In the latter example continuous removal of water facilitated the reaction. A related reaction involved treatment of an acid chloride with silver perchlorate in nitromethane (equation 41), although the yield of diketone was low.[201]



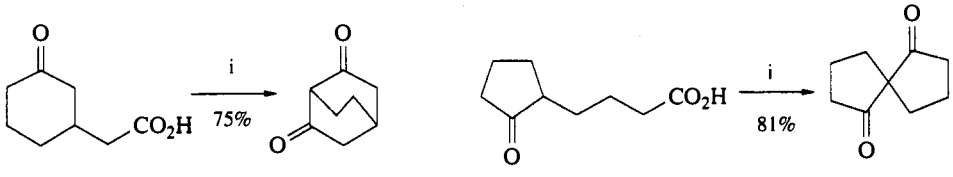
(ref. 197)

i, Bu^n_4NF, THF, –78 °C



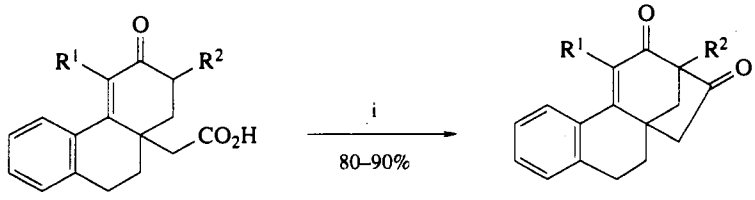
(ref. 198)

Scheme 77



(ref. 199)

i, PPA, AcOH

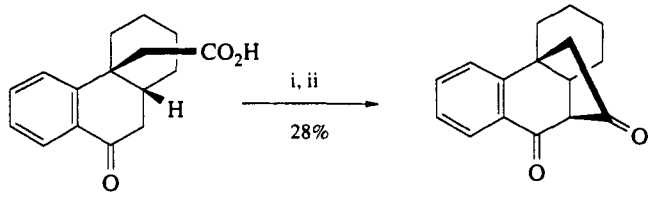


(ref. 200)

$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^1 = Me$, $R^2 = H$

i, naphthalene-2-sulfonic acid, toluene, water removal

Scheme 78

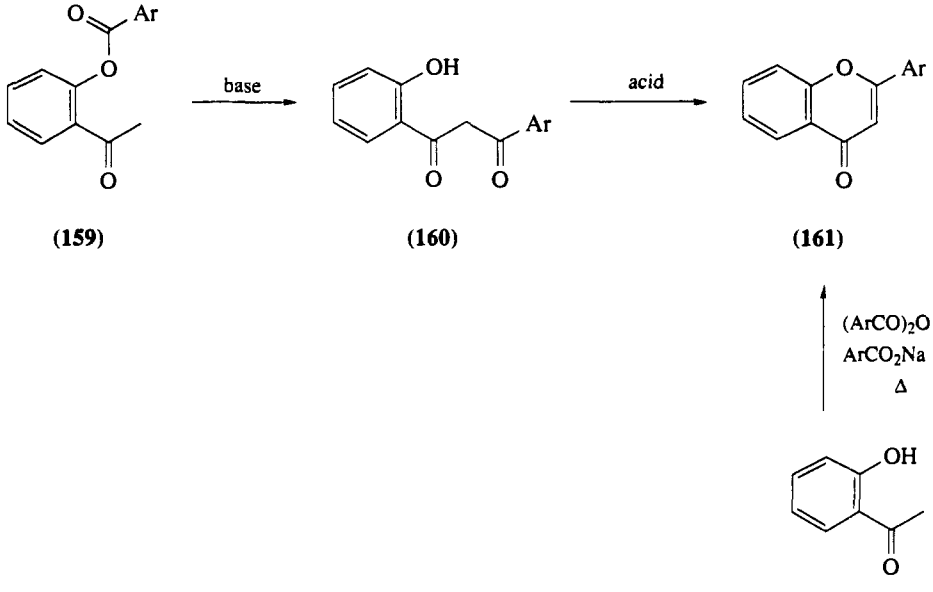


(41)

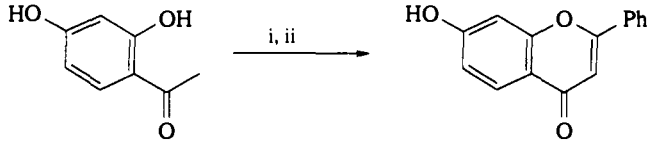
i, $(COCl)_2$; ii, $AgClO_4$, $MeNO_2$

3.6.4.7 Intramolecular Acyl Transfer

Aromatic *o*-acyloxy ketones of general formula (**159**) undergo an intramolecular acyl transfer in the presence of base to give *o*-hydroxyaryl β-diketones (**160**; Scheme 79).[5] In one variant, the 'Baker–Venkataraman' synthesis, the rearrangement is effected with bases such as NaH or KOH in pyridine. Acid catalysis facilitates transformation into a flavone (**161**). In the closely related 'Kostanecki' reaction, the *o*-hydroxyacetophenone is heated with an acid anhydride in the presence of the sodium or potassium salt of the corresponding acid to give the flavone directly (equation 42). The reactions have, for the most part, involved the transfer of an aromatic or heteroaromatic group and the reactions have been widely employed in flavone chemistry. More recently, examples of the transfer of aliphatic acyl groups have

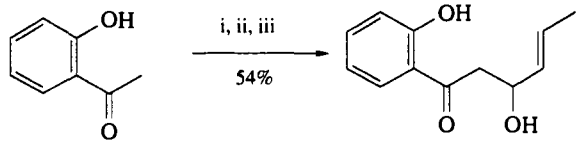


Scheme 79



(42)

i, $(PhCO)_2O$, $PhCO_2Na$, 185 °C, 4 h; ii, KOH, EtOH, reflux 30 min



(43)

i, NaH; ii, MeCH=CHCOCl; iii, $KOBu^t$, Bu^tOH

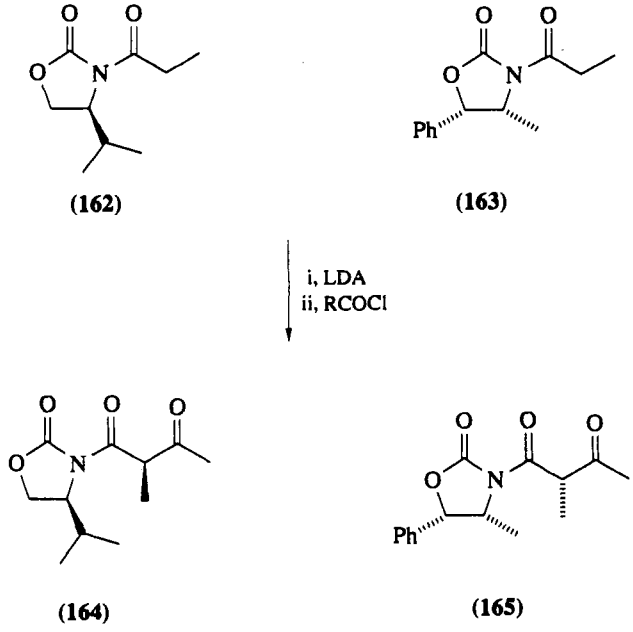
been reported (equation 43).[202] Satisfactory yields were obtained with crotonyl and related esters, but transfer of an acetyl group was effected in only 28% yield.

3.6.5 STEREOCHEMISTRY

3.6.5.1 Chiral β-Dicarbonyl Synthons

A new stereocenter is established in the Claisen condensation whenever the carbanionic carbon center that is undergoing acylation bears two different groups. Normally, however, the basic conditions of the reaction result in the formation of the enolate of the β-dicarbonyl system and the loss of stereochemical integrity. Two groups have now reported the asymmetric acylation of optically active imide enolates.

Evans *et al.*[203] acylated the oxazolidine imides (**162**) and (**163**) with a number of acid chlorides to produce the β-dicarbonyl systems (**164**) and (**165**) in high chemical yield and diastereoselection at the 95% level (Scheme 80). Purification of the reaction products readily afforded material that was diastereomerically pure (≥99%). The surprisingly low kinetic acidity of the β-keto imide system was ascribed to the fact that the bond to the acidic proton is nearly orthogonal to the π-system of the adjacent carbonyl functions. Movement to align the two systems would result in increased $A^{1,3}$ strain. The difficulty in removing a proton in a similar situation was noted, in alkylation studies, by a Japanese group,[204] who also provided the second example of an asymmetric acylation.[205] They showed (Scheme 81) that *C*-acylation of the propionamide derivatives of *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine with a number of acid chlorides produced good to excellent yields of β-keto amides with a *de* of around 98%. The ketonic products were reduced with $Zn(BH_4)_2$ to give the *syn* aldol compound.

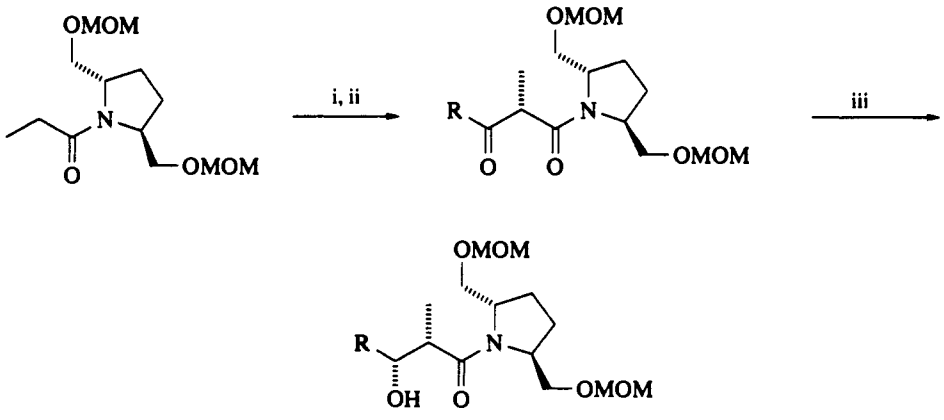


Scheme 80

The availability of these chiral β-dicarbonyl synthons has been put to good use by Evans and Di Mare[206] in an asymmetric synthesis of premonensin (**166**) and by a Japanese group[207] in the synthesis of (+)-pederin (**167**).

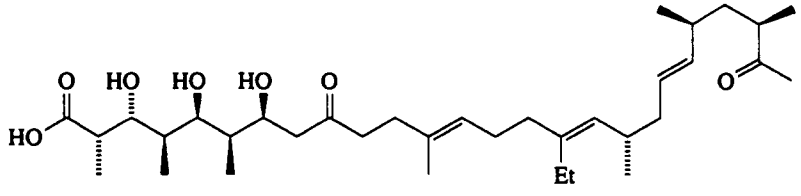
When a quaternary carbon atom is produced in the acylation process, racemization is not possible and the stereochemical outcome can be affected by the presence of an adjacent stereocenter. Treatment of the chiral lactone (**168**) with LDA and acetyl cyanide gave the diastereomeric products (**169**) and (**170**) in the ratio 60:1 (equation 44).[208]

Studies pertinent to the acylation of chiral ketones were reported by Seebach and Ehrig (Scheme 82).[209] Acylation of the enolate (**172**) of the optically active (but not optically pure) ketone (**171**) gave

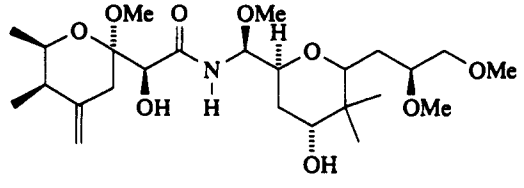


i, BuLi; ii, RCOCl; iii, $Zn(BH_4)_2$

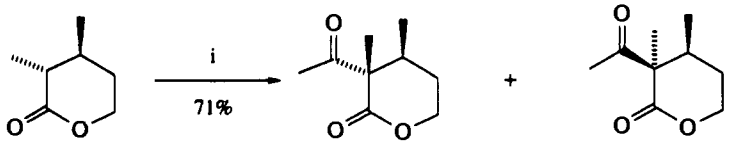
Scheme 81



(166)



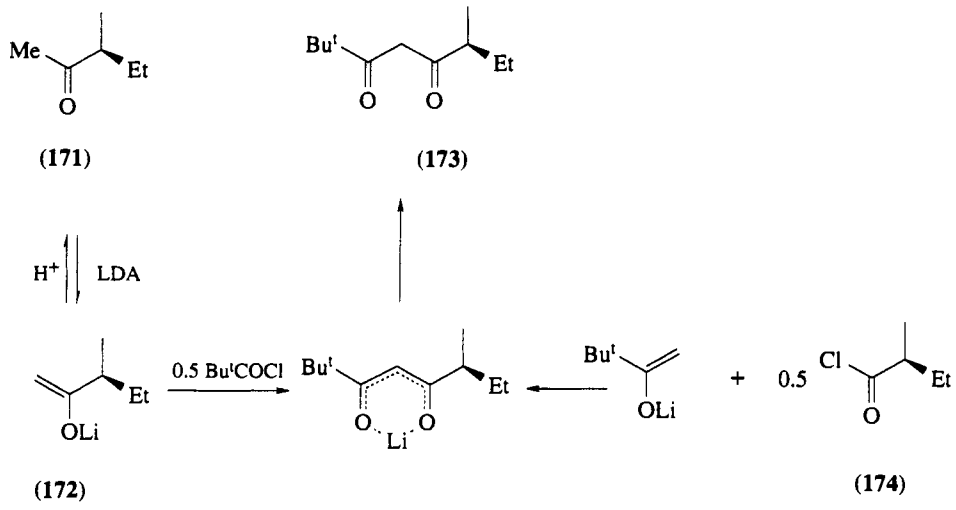
(167)



(168) **(169)** **(170)** (44)

i, LDA–THF, MeCOCN, –78 °C

the diketone (**173**) with minimal racemization. A similar result was obtained when the acid chloride (**174**) was reacted with the lithium enolate of pinacolone to give the same diketone.



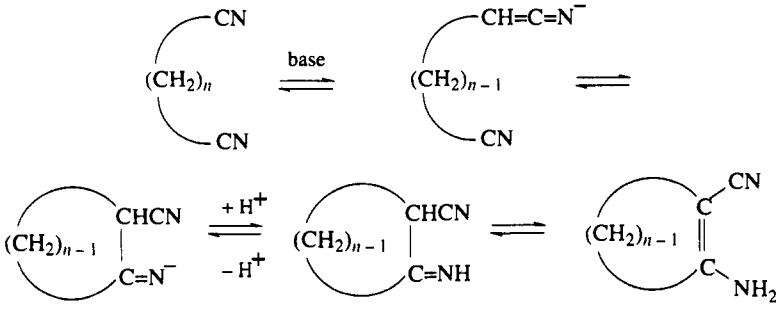
Scheme 82

3.6.6 THORPE AND THORPE–ZIEGLER REACTIONS

Thorpe originally investigated the condensation of alkyl cyanides to give 3-iminoalkyl cyanides by analogy with the Claisen and aldol reactions.[6,210] Moore and Thorpe then applied this reaction to a bis-nitrile and showed that the intramolecular version of the reaction proceeded to give the cyclic product.[211] The use of Thorpe as a named reaction has usually indicated the cyclic version, the simple condensation not having found great use because of problems with its application to crossed reactions, but it should strictly apply to either. The Ziegler modification of the Thorpe reaction allowed it to be used for the preparation of macrocyclic ring systems, but the term Thorpe–Ziegler reaction is quite often used for intramolecular reactions to form standard rings in which neither of Ziegler's modifications, a soluble base and high dilution conditions, are used. We will not distinguish between the Thorpe and Thorpe–Ziegler reactions and will also include the few examples of the intermolecular condensation in our discussion. A number of intramolecular reactions in systems containing an ester and a nitrile have been considered under the Dieckmann reaction; others will be considered here. The separation is somewhat arbitrary and the reactions have been described in the literature by both names.

3.6.6.1 Mechanism

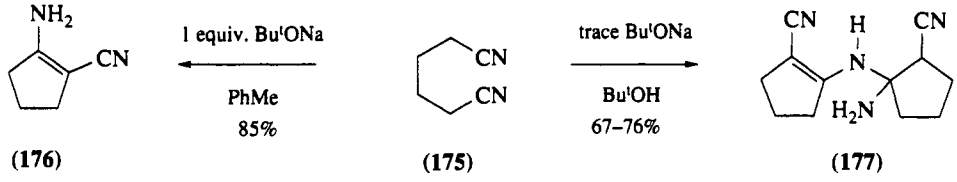
The mechanism of this reaction is closely similar to that described for the Claisen and Dieckmann reactions. The α-protons are acidic, the resulting anion being stabilized by conjugation to the cyanide, and the anion can then act as a nucleophile towards a second molecule of the cyanide. The resulting imine can then rearrange to the enamine and this results in the reaction being driven towards completion (Scheme 83).



Scheme 83

3.6.6.2 Reaction Conditions

The original Thorpe conditions involved a catalytic amount of base, as the mechanism would imply. Later workers[6] found that in certain reactions equivalent amounts of base were required or that catalytic and equivalent amounts of base gave different products. As shown in Scheme 84, the Michael dimer (**177**) is the major product when adiponitrile (**175**) is cyclized with a trace of sodium *t*-butoxide in *t*-butyl alcohol, whereas an equivalent of this base in toluene gave the monomer (**176**).



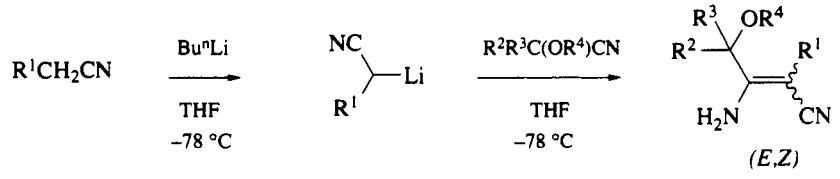
(**176**) (**175**) (**177**)

Scheme 84

Ziegler and his coworkers modified the reaction conditions by conducting the reaction under high dilution conditions and using a soluble base in ether as the solvent. Sodium methylanilide was reported to be the best base[6] but an example has been reported in which this gave unexpected products.[212] A variety of other bases have been used more recently and a comparison of LDA, $LiNEt_2$ and $NaN(SiMe_3)_2$ has been made.[213]

3.6.6.3 Scope of the Reaction

The reaction has found much less general use than the Dieckmann reaction for a variety of reasons. Dinitriles are less readily available than diesters and the resulting cyanoenamines are both more difficult to hydrolyze and less versatile in their transformation into other groups. Virtually no use has been made of the acyclic reaction but the recent description of a method for cross-coupling may stimulate interest. If the anion of one component of the intermolecular crossed reaction is pregenerated good yields of the desired product can be obtained when the reaction is run at –78 °C in THF.[214] Acetonitrile has usually acted as the nucleophile, being lithiated with butyllithium, and a range of cyanides have acted as the electrophile (Scheme 85). In most cases a mixture of (*Z,E*)-cyanoenamines was obtained but in some cases only the (*Z*)-isomer was isolated, presumably because of steric effects.



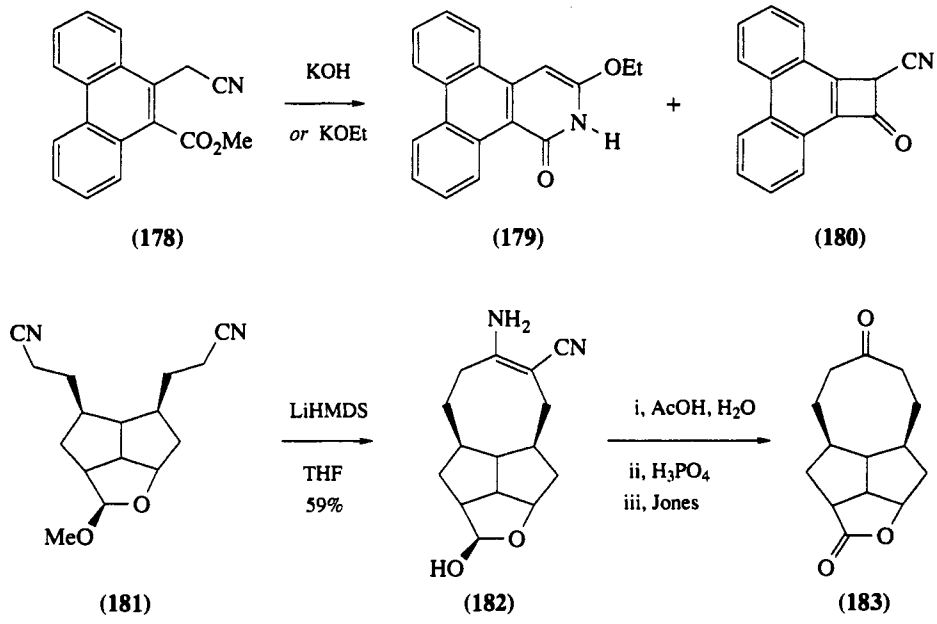
R^1	R^2	R^3	R^4	*Yield* (%)
H	H	Me	Et	83
H	H	Me	1-EE[a]	**87**
H	Me	Me	1-EE	78
Et	H	Me	1-EE	51

[a] 1-EE = 1-ethoxyethyl

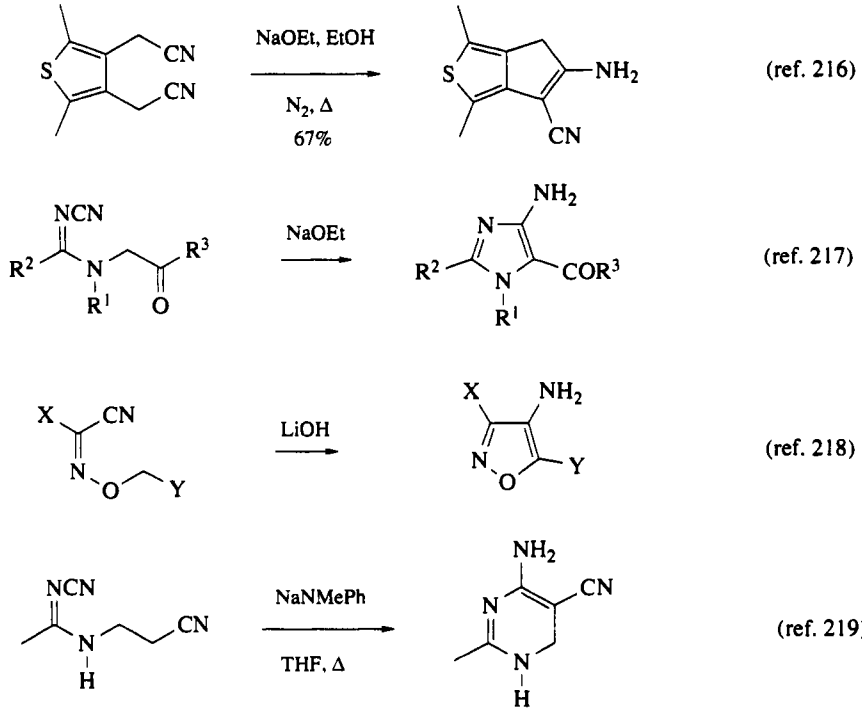
Scheme 85

The intramolecular reaction has led to cyclic compounds with both standard and macrocyclic rings, but small rings are not readily prepared. An attempt to cyclize (**178**), containing a nitrile and an ester function, gave the cyclic amide (**179**) rather than the desired cyanocyclobutenone (**180**).[215] One disadvantage of the reaction is that if the cyclic ketone is the desired product then the cyanoenamine is often hydrolyzed much less readily than the β-keto esters generated from the Dieckmann reaction. In certain cases, however, the Dieckmann reaction does not occur, whereas the Thorpe–Ziegler does, and hydrolysis and oxidation give the ketone.[216] Cyclization of (**181**) with LiHMDS in THF at reflux gave the

cyanoenamine (**182**) in 59% yield, whereas the Dieckmann reaction gave <5% of the equivalent β-keto ester.[216] Hydrolysis, decarboxylation and oxidation of (**182**) gave the cyclooctanone (**183**; Scheme 86). Like the Dieckmann reaction, the Thorpe–Ziegler reaction can readily accommodate heteroatoms and unsaturation in the cyclizing chain and a variety of heterocycles have been prepared. Many of these involve cyano esters and cyano ketones, and examples are given in Scheme 87.



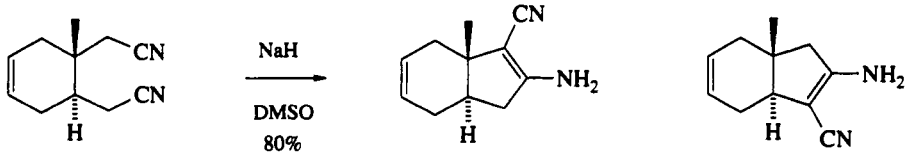
Scheme 86



Scheme 87

3.6.6.4 Regioselectivity

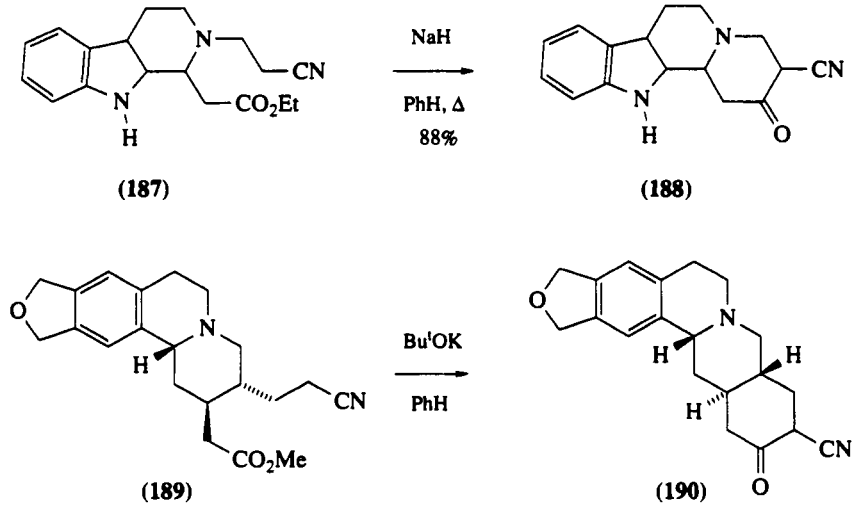
The Thorpe–Ziegler reaction has been little studied with regard to its regioselectivity. As mentioned in Section 3.6.3.3.3.iv, cyclization of mixed cyano esters occur with the ester as electrophile and the cyano-stabilized anion as nucleophile. In many of the known examples cyclization occurs on the cyanide because this is at a tertiary center. One would expect that the control of regioselectivity in the reactions of dicyanides would closely parallel the effects observed in the Dieckmann reaction. Treatment of the dicyanide (**184**) with sodium hydride in DMSO gives, however, the cyclized product (**185**) resulting from the more hindered anion,[220] a finding at variance with that usually observed in the Dieckmann reaction (Section 3.6.3.3.3.iii). It appears that the enamine with the double bond adjacent to the bridgehead methyl is more stable than the alternative isomer (**186**) and it is this that controls the product formation. This may also apply to the final enolate in the cyclization of the equivalent diester, although this would lead to the less stable β-keto ester. A related diester has been cyclized but only the ketone was isolated after decarboxylation, while a steroidal diester analog cyclizes as expected with the ester at the hindered position as electrophile (equation 45).[221]



(184) (185) (186) (45)

3.6.6.5 Application to Synthesis

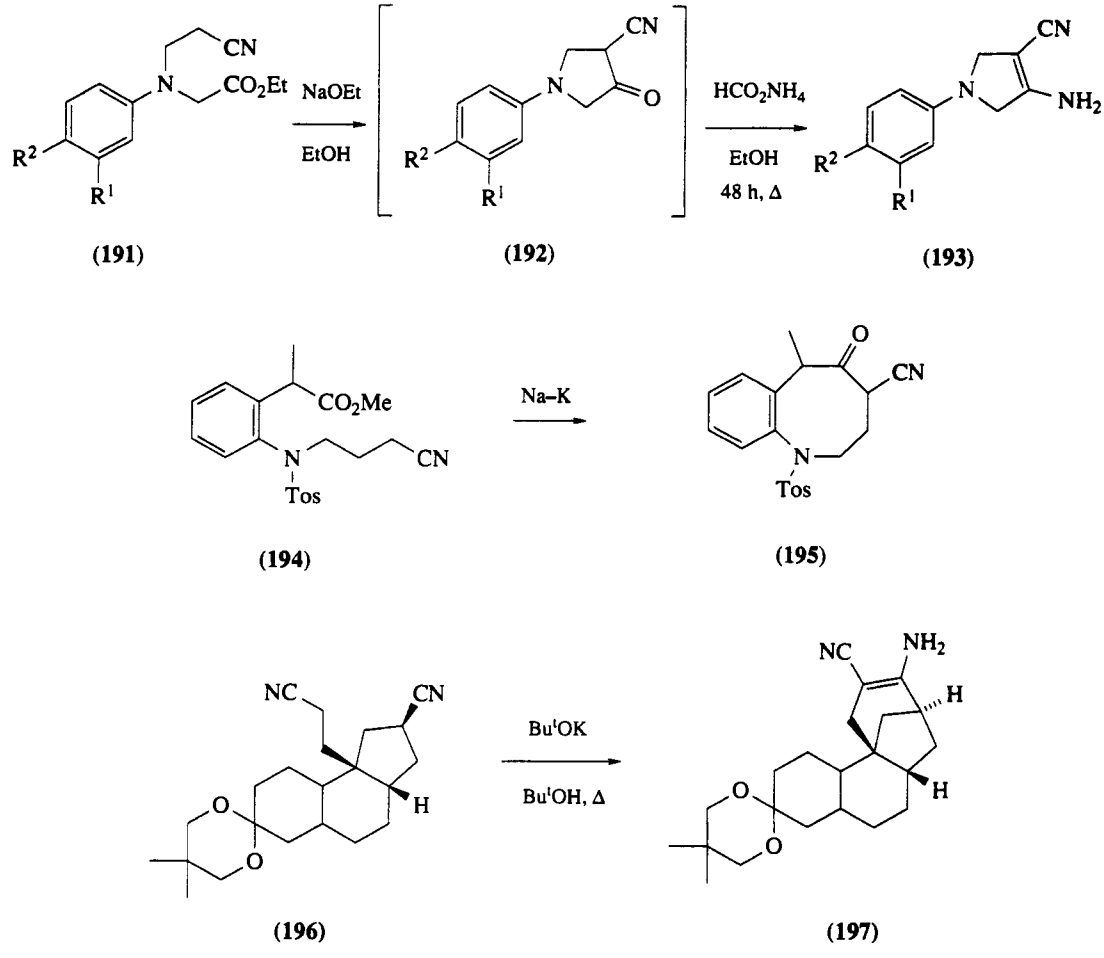
In contrast to the Dieckmann reaction, very few examples of dicyanides being used in synthetic schemes have been reported. Rather, more examples of cyano esters or cyano ketones are known, often taking advantage of the lesser electrophilicity of the cyano group; some examples are shown in Scheme 88. Kametani *et al.* employed the cyclization of the cyano ester (**187**) to (**188**) with sodium hydride in a total synthesis of (±)-yohimbine.[222] A similar advantage was taken in the cyclization of the cyano ester (**189**) to the cyano ketone (**190**) with potassium *t*-butoxide in benzene,[223] and of the regioselectivity of closure of the cyano ester (**191**) to give the cyano ketone (**192**), which was not isolated but converted to the cyanoenamine (**193**) with ammonium formate.[224] The dihydropyrroles were converted to 2,4-diaminopyrrolpyrimidines by condensation with guanidine. Another example is the cyclization of the cyano ester (**194**) to the azocinone (**195**) in 46% yield, cyclization of the corresponding diester going in higher yield but with low regioselectivity.[66] The dicyanide (**196**) cyclizes with the primary cyanide as the electrophile to give (**197**) in 90% yield. This material was hydrolyzed with a phosphoric acid/acetic acid mixture to give the desired ketone in 80% yield.[225]



(187) (188)

(189) (190)

Scheme 88



Scheme 88 *(continued)*

3.6.7 TANDEM REACTIONS

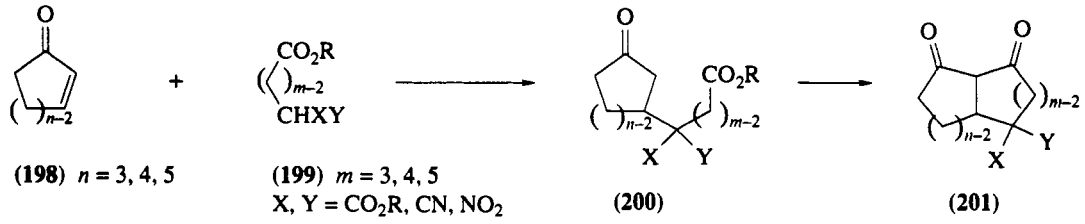
The cyclization reactions described in this chapter and, occasionally, even the acyclic condensation reactions, can often be prefaced by a different type of process such as a Michael reaction. We shall term such a sequence a tandem reaction and a number of these have already been described. Others will be collected here to illustrate the types of processes that have been observed. The cycloenones (**198**), when treated with a nucleophile (**199**) under basic conditions, react in a Michael fashion to give the intermediates (**200**), which then undergo the Dieckmann reaction to give the bicyclic dione (**201**).[226] Similarly, methyl cinnamate (**202**) reacts with the nucleophile (**203**) in the same tandem sequence to give the cyclopentanone (**204**) as a diastereomeric mixture (Scheme 89).[227]

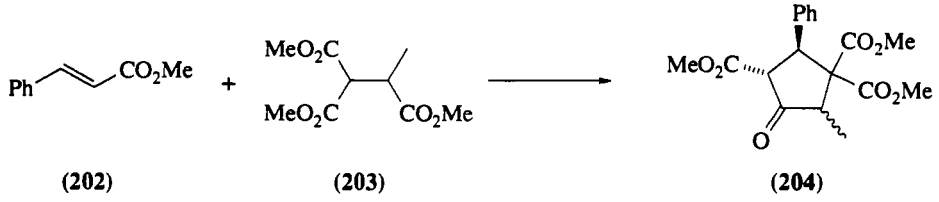
Other examples of this tandem sequence are illustrated by the reactions shown in Scheme 90.

Dimethyl oxalate (**205**) reacts with (**206**)[233] and with α,ω-diesters (**207**)[234] in a Claisen–Dieckmann tandem reaction to give cyclopentadienes (**208**) and (**209**), the former spontaneously dimerizing to give (**210**; Scheme 91).

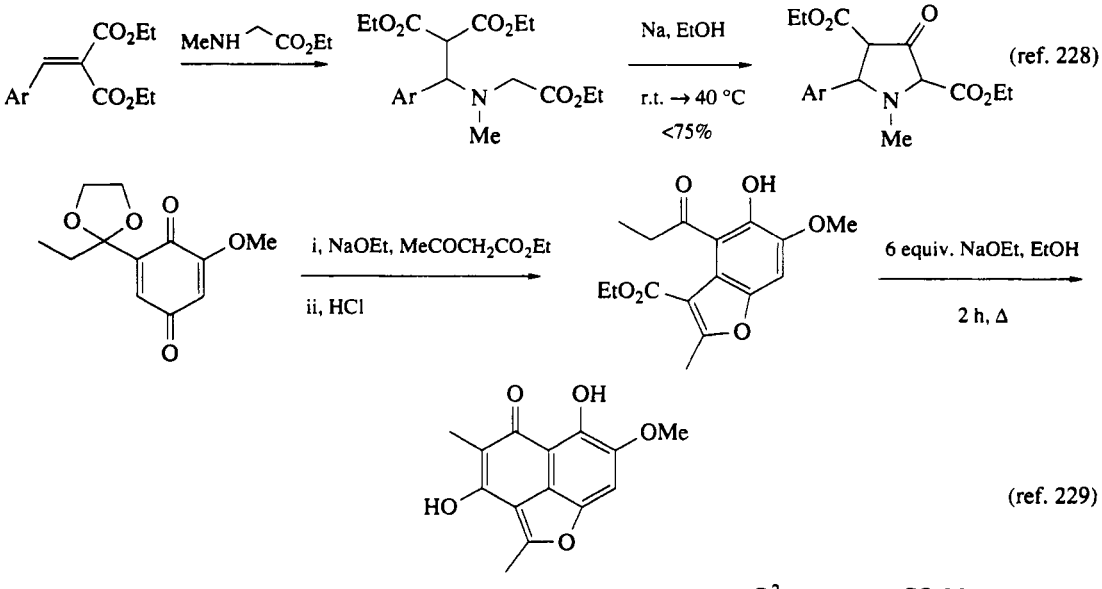
An aldol–Claisen tandem sequence is illustrated by the reaction of the cinnamaldehyde (**211**) with the chiral acetate (**212**) to give (**88**) followed by treatment with the lithium enolate (**89**) to give (**90**; equation 46; see equation 25, Section 3.6.3.4.2).[104]

There are a number of examples of Michael–Thorpe tandem reactions, closely related to the Michael–Dieckmann described above. Some of these are illustrated in Scheme 92.

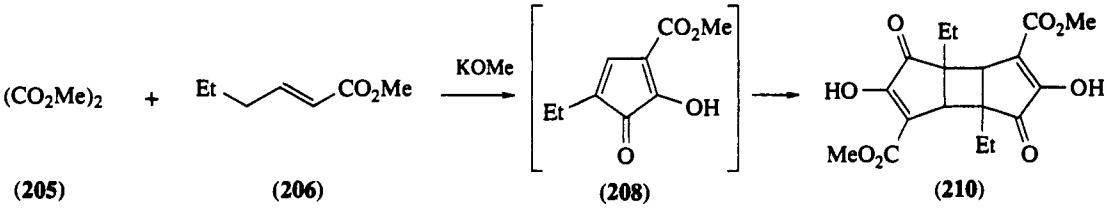




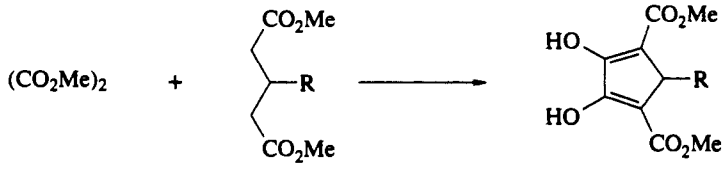
Scheme 89



Scheme 90

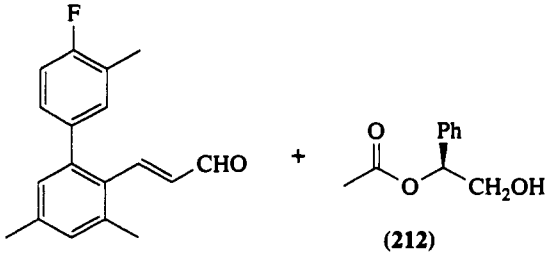


(205) (206) (208) (210)



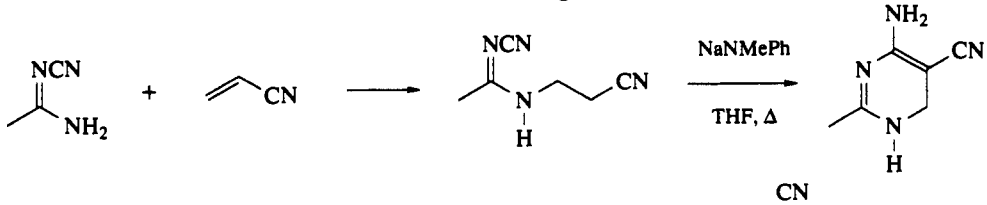
(205) (207) R = $(CH_2)_7Me$ (209)

Scheme 91

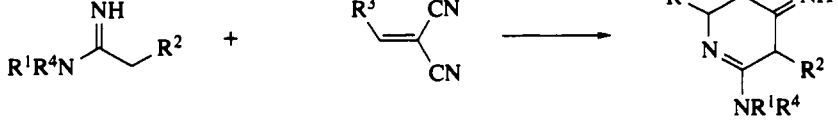


(211) (212) (88) (46)

i, LDA; ii, MgBr; iii, NaOMe

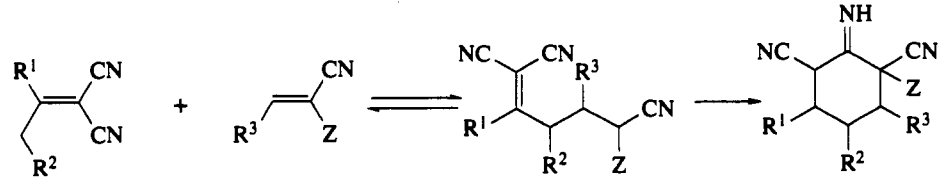


(ref. 219)



(ref. 235)

R^1	R^2	R^3	R^4	*Yield* (%)
Ph	Ph	Ph	Et	63
Ph	Ph	Ph	Me	68
2-MeC_6H_4	Ph	2-EtC_6H_4	Et	77



(ref. 236)

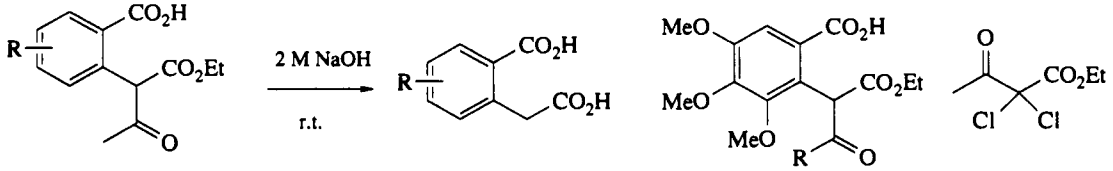
Scheme 92

3.6.8 RETRO-REACTIONS

The equilibrium character of the reactions described in this chapter means that the reverse processes also occur. The retro-Claisen, retro-Dieckmann and retro-Thorpe–Ziegler reactions are all known and can be synthetically useful. In some cases the substrate may have been formed by the same or similar forward reaction, whereas in others the substrate has to be formed by another process since the equilibrium lies completely on the side of the retro-reaction product. As in the case of the forward reaction, tandem reaction sequences can be constructed, often with the same types of preceding reaction as were described for the forward sequence.

3.6.8.1 Cleavage of β-Keto Esters

Both simple retro-reactions and complex sequences involving retro-reactions of this type are known. Treatment of (**213**) with NaOH at room temperature for a few minutes gives (**214**), both a retro-Claisen and saponification having occurred.[237] The reaction was not successful with more complex derivatives such as (**215**). Treatment of (**216**) with sodium acetate in EtOH gave ethyl acetate and ethyl dichloroacetate, the facile cleavage resulting from further stabilization of the leaving anion by the chlorines (Scheme 93).[238]



R = H, 4-Me, 4-NO_2, 5-OMe

(**213**)

(**214**)

R = Me, OEt

(**215**)

(**216**)

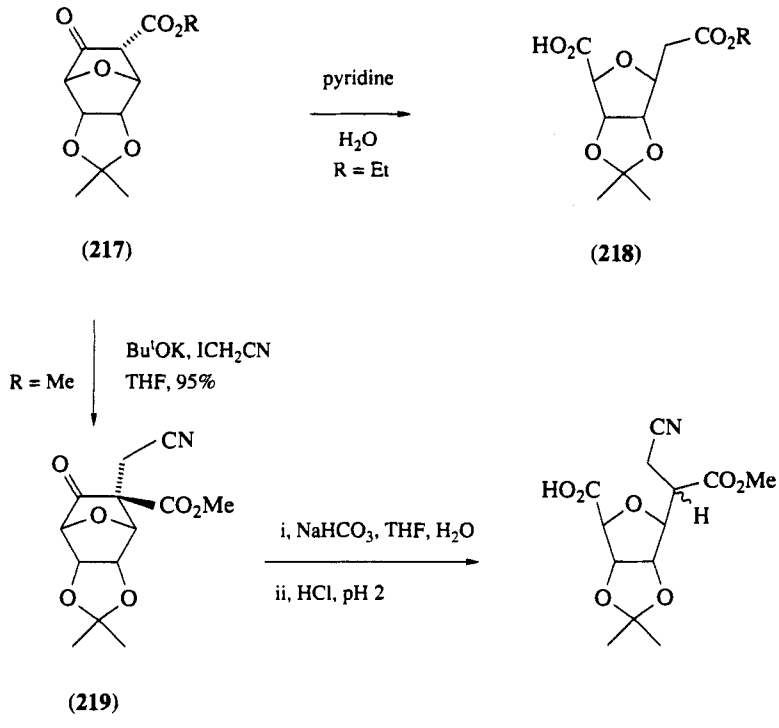
Scheme 93

The bicyclic β-keto ester (**217**) undergoes cleavage to (**218**) with pyridine and water.[239] This reaction was used in a more complex sequence leading to the *C*-nucleoside (±)-showdomycin, compound (**217**) first being alkylated with iodoacetonitrile and the product (**219**) being cleaved with $NaHCO_3$ in THF (Scheme 94). The diterpene derivative (**220**) underwent a similarly facile retro-Dieckmann reaction to (**221**) with potassium carbonate in 80% methanol at room temperature over 3 d.[240] The 2-alkyl-2-methoxycarbonylcyclohexanones (**223**), derived by alkylation of (**222**), undergo ready retro-Dieckmann cleavage followed by reclosure to give the 6-alkyl derivative (**224**; Scheme 95).[93] Lithium methylcuprate addition to 5-methylcyclohex-2-enone (**225**) occurs stereospecifically to give *trans*-3,5-dimethylcyclohexanone (**226**) in 54% yield. This material can then be methoxycarbonylated to (**227**; Scheme 96).[241] Treatment of (**227**) with sodium methoxide in methanol followed by saponification with KOH gives (±)-3,5-dimethylpimelic acid (**228**), in which the relative stereochemistry of the two stereocenters is retained. 3-Oxocarbapenam esters can be readily cleaved to the corresponding β-lactam diester derivatives (equation 47).[242]

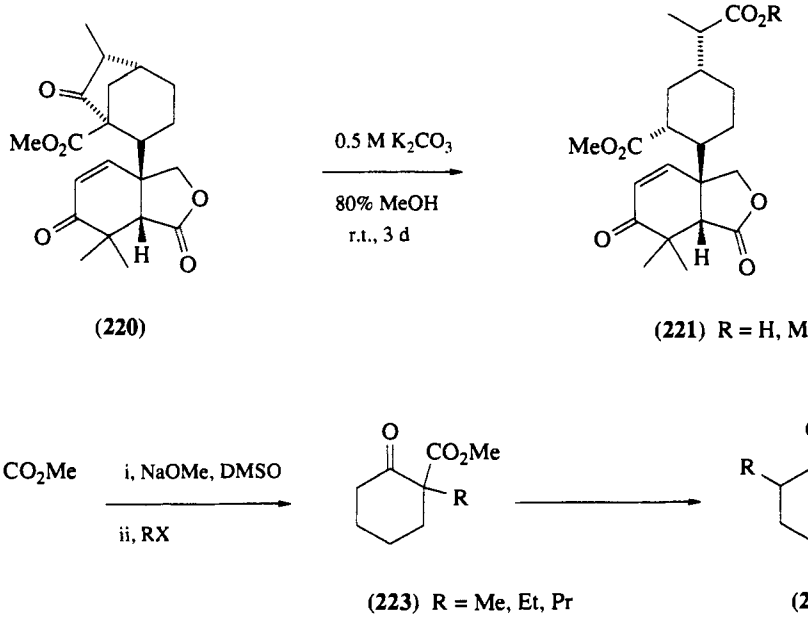
Alkylation of 2-methoxycarbonylcyclopentanone followed by treatment with sodium methoxide in methanol led to the ring-opened product, which was then cyclized to the 5-alkyl derivative (Scheme 97).[243] The retro-Claisen competes with transesterification in the reaction of the β-keto ester (**229**) with alkoxide (Scheme 98).[244]

3.6.8.2 Cleavage of β-Diketones

This is the reverse of the addition of ketone to an ester and has again found considerable synthetic application. Mahajan[245] found that 1,3-cyclohexanediones substituted at the 2-position with a group with an alcohol function at the terminal position (**230**) when treated with sodium hydride in benzene gave the macrocyclic lactones (**231**). The reaction may occur by nucleophilic addition to give the intermediate (**232**) followed by ring cleavage, the alkoxide acting as the intramolecular nucleophile, or the ketene (**233**) may be formed by proton abstraction and nucleophilic addition then follows. Mahajan has extensively explored this method[246,247] and has described a modification[248] in which the hemiacetal (**234**) is

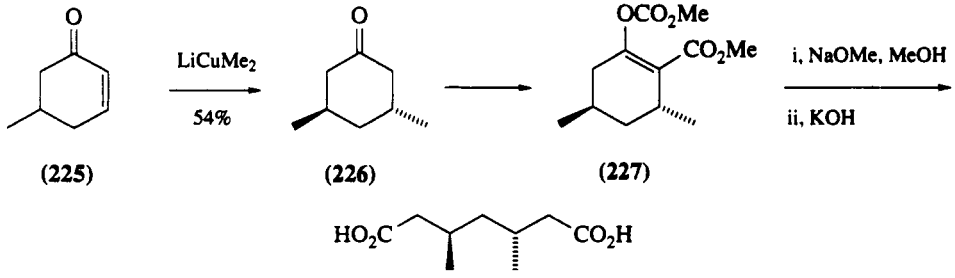


Scheme 94



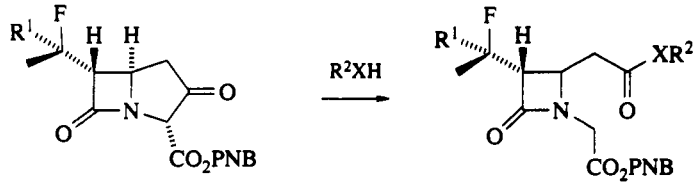
Scheme 95

ring opened in a fragmentation reaction. Others[250] have changed the solvent to THF and obtained good yields of macrocyclic lactones (**235**) together with some dimer (**236**), the formation of the latter supporting the ketene mechanism (Scheme 99).[248]



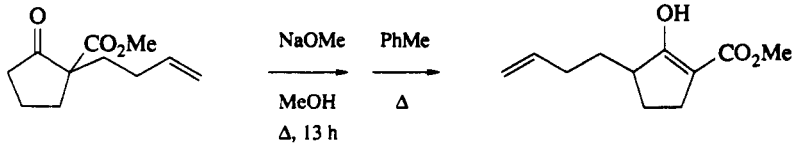
(225) (226) (227) (228)

Scheme 96

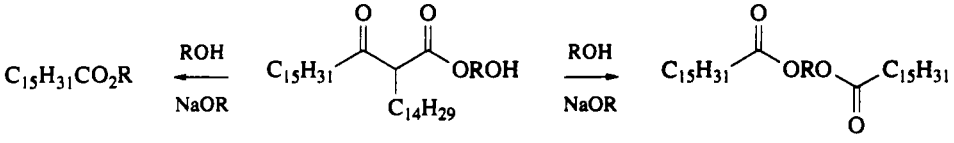


(47)

R^1 = Me, XR^2 = $HNCH_2Ph$; R^1 = H, XR^2 = $HNCH_2Ph$; R^1 = H, XR^2 = CH_2NO_2



Scheme 97



(229)

Scheme 98

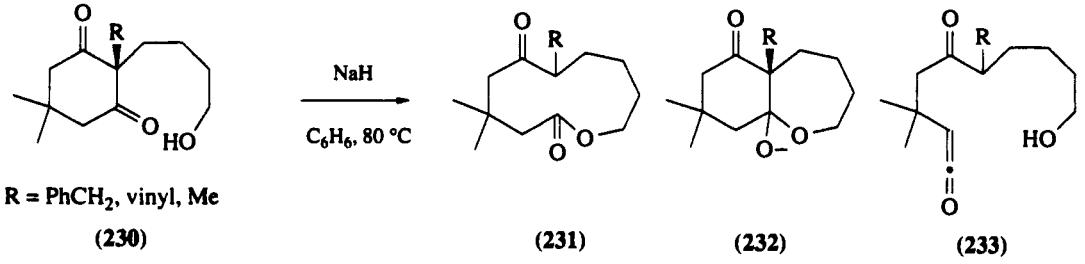
An acid-catalyzed retro-Dieckmann reaction converts the β-keto ketal (**237**) into (**238a**), which can be transesterified to the methyl ester (**238b**).[250] No racemization occurs at the noncleaving ring junction, both enantiomers of (**237**) proceeding with retention of configuration (Scheme 100).

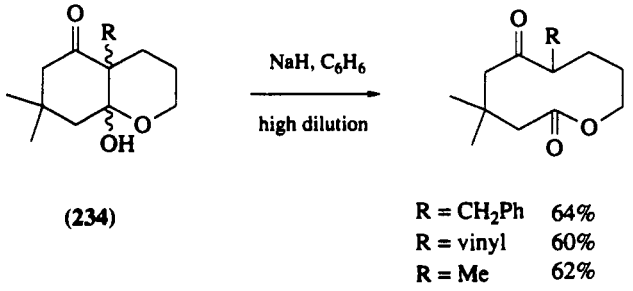
3.6.8.3 Cleavage of 2-Cyanoenamines

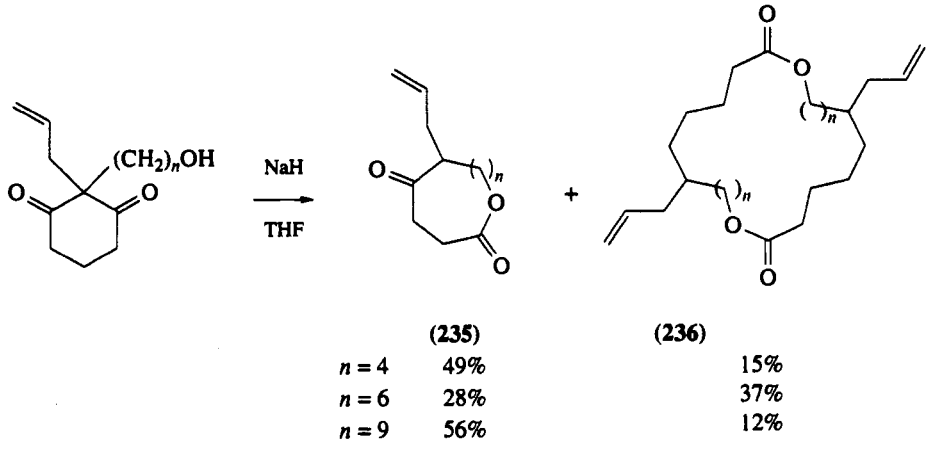
As with the forward reaction, the retro-Thorpe–Ziegler reaction has found much less use than the retro-Dieckmann reaction. A Thorpe–Ziegler, retro-Thorpe–Ziegler sequence has been used to α-tetramethylate the bisnitrile (**239**; Scheme 101).[251]

3.6.9 CONCLUSIONS

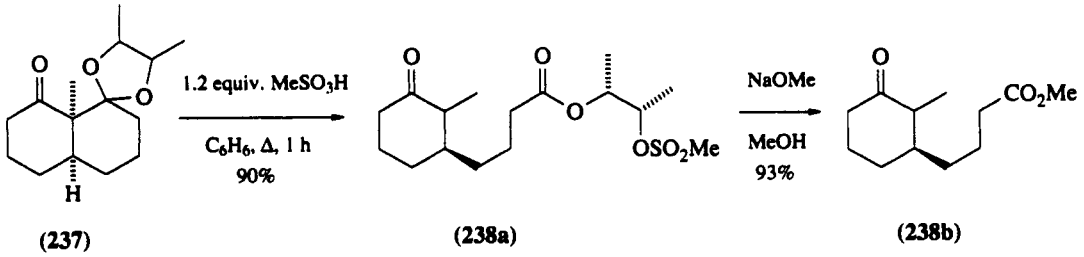
The Claisen and Dieckmann reactions and their modifications are major synthetic methods for the formation of acyclic and cyclic systems. The resulting β-keto esters, or analogous systems, can undergo a variety of synthetic modifications allowing entry into a range of derivatives. The reactions can be con-



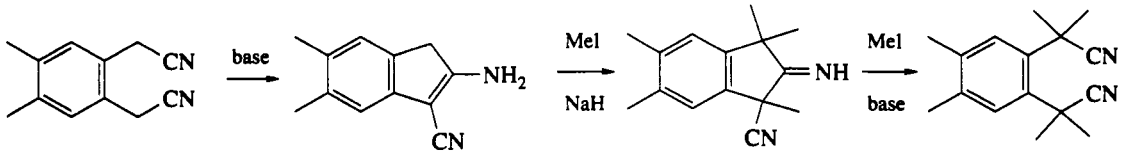




Scheme 99



Scheme 100



(239)

Scheme 101

trolled in a number of ways to give regioselective products but, in the case of the Dieckmann reaction, regioselectivity is not important if the cyclic ketone, derived by decarboxylation, is required. Examples of highly enantioselective Claisen acylations and Dieckmann reactions have recently been described.[252] The reactions are generally successful and tolerate a wide range of other functional groups, and non-carbon atoms in the chain are generally acceptable. Occasionally the Thorpe–Ziegler reaction gives better yields than the Dieckmann reaction and there is at least one reported case of an exhaustive examination of the latter reaction which did not give any product.[253] The Dieckmann is an excellent method for the preparation of five- and six-membered rings and has been applied successfully to the preparation of larger systems. The Thorpe–Ziegler reaction has also been used for the preparation of five- and six-membered rings, particularly heterocycles, and it was a method, in Ziegler's high-dilution procedure, for the synthesis of large rings, although it does not appear to have a great current use in this way.

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3.7
The Eschenmoser Coupling Reaction

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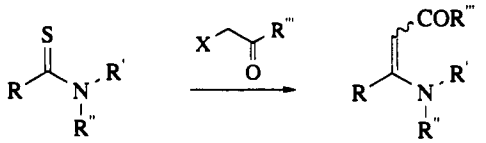
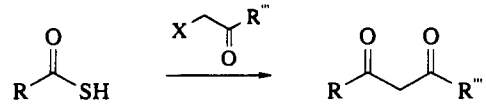
3.7.1 INTRODUCTION

The Eschenmoser coupling reaction represents a versatile and efficient method to prepare vinylogous amides and urethanes by alkylation of a secondary or tertiary thioamide with an appropriate electrophilic component followed by elimination of sulfur (equation 1). This coupling, which in essence condenses an enolizable carbon with an amide carbonyl, can be formally considered a variant of the Claisen condensation. An extension of this process through alkylation of thiocarboxylic acids leads to direct synthesis of 1,3-dicarbonyl compounds (equation 2). Vinylogous amides and carbamates along with their hydrolysis products, the 1,3-dicarbonyl compounds, are important synthetic intermediates; their value is attested by the numerous methods available for their synthesis.[1,2] The Eschenmoser reaction provides an alternative approach to prepare these compounds that offers several distinct advantages. The unambiguous formation of a particular vinylogous amide or carbamate or a substituted 1,3-dicarbonyl compound can be achieved. Since the reaction conditions are sufficiently mild, incorporation of various functional groups and preservation of base-sensitive stereocenters are possible. The reacting centers also are relatively insensitive to the steric environment. In addition, the range of applications now available to the reaction has been broadened significantly through modifications and extensions on the original studies.

The coupling reaction is referred to commonly as the 'sulfide-contraction' or 'sulfur-extrusion' reaction. However, this reaction is distinct from other sulfur-eliminating, carbon–carbon bond-forming



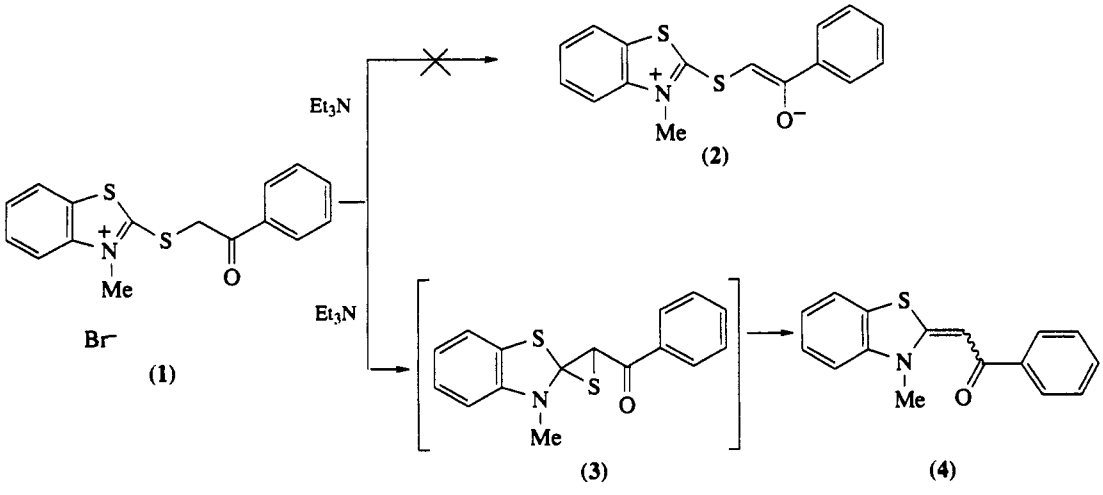
(1)



(2)

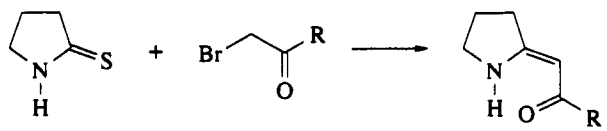
processes that also are designated as 'sulfur-extrusion' reactions. Several examples of these alternative contractions *via* extrusion methods include the thermal elimination of elemental sulfur in prearomatic systems[3] and the photolytic expulsion of sulfur to form carbon–carbon bonds.[4,5]

The novel method of effecting carbon–carbon bond formation *via* alkylative coupling followed by sulfide contraction was first described by Knott[6] during an investigation of various sulfur-containing chromophores. Knott observed that attempts to enolize the benzothiazolium salt (**1**) with triethylamine did not yield the anticipated salt (**2**; Scheme 1). Rather, a compound was isolated for which compositional data indicated loss of a sulfur atom. Further studies eventually identified the product as the conjugated ketone (**4**). A mechanism proceeding through an episulfide intermediate (**3**) followed by expulsion of sulfur was proposed to explain these observations.



Scheme 1

These findings lay dormant in the literature for a number of years until Eschenmoser developed the general synthetic utility of this sulfide-contraction process.[7] This development stemmed from investigation of a related method that was critical in constructing the corrinoid structure involved in the synthesis of vitamin B_{12}.[8,9] Eschenmoser demonstrated the versatility and efficiency of this novel reaction by condensing thiopyrrolidinone with bromo ketones and esters to produce vinylogous amides and urethanes (**6**), respectively (equation 3; Table 1). The reagents and reaction conditions necessary to conduct the condensation were determined as well. Similar studies were performed on a set of thiocarboxylic acids, allowing preparation of the complementary β-dicarbonyl compounds. Based on this initial investigation, along with modifications and extensions that have since evolved, the Eschenmoser coupling reaction has proved to be a useful synthetic method that has found wide applications in numerous synthetic endeavors.



(3)

(5) (6)

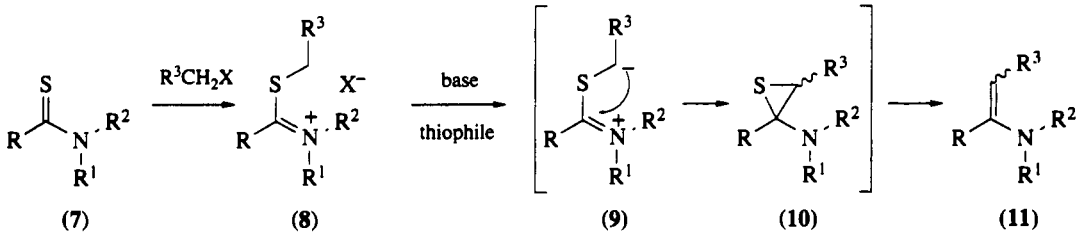
Table 1 Preparation of Vinylogous Amides and Urethanes *via* Sulfide-contraction (equation 3)[7]

R	*Yield* (%)	*R*	*Yield* (%)
4-BrC_6H_4	90[a]	$C(Me)_2CH_2CO_2Me$	56[c]
Me	70[b]	*O*-Bu^t	75[d]
$CH_2CH_2CO_2Me$	85[c]		

[a]i, Diisopropylaminomethyl–polystyrene; ii, Ph_3P, 60 °C. [b]i, $KHCO_3$, CH_2Cl_2; ii, Ph_3P, Bu^{t}OK, benzene (reflux). [c]Ph_3P, $CHCl_3$, 60 °C. [d]i, $KHCO_3$, CH_2Cl_2; ii, Ph_3P, Bu^{t}OK, xylene (reflux).

3.7.2 MECHANISM

The Eschenmoser coupling reaction is composed of two distinct steps. First, a thioamide (**7**) is alkylated selectively on the sulfur with an electrophile to form an intermediate α-thioiminium salt (**8**; Scheme 2). In the second step, addition of a base and a sulfur scavenger (thiophile) promotes the extrusion of sulfur with concomitant formation of an alkenic bond. According to the accepted mechanism through which the second step of the reaction is believed to proceed, the base abstracts an α-proton in the appended side chain of the α-thioiminium salt (**8**). The anion (**9**) thus generated is then captured by the iminium species (or an imine, depending on the nature of the thioamide) to form a proposed episulfide (**10**). This intermediate then collapses with, or in some cases without, the assistance of a thiophile through elimination of sulfur to produce the unsaturated product (**11**). Although this mechanistic pathway is widely accepted, actual isolation and characterization of the proposed episulfide intermediate (**10**) have not been achieved. In most applications, the intermediate α-thioiminium salt (**8**) is not isolated but is subjected directly to the reagents that promote the second step of the reaction. In doing so, the entire coupling process can be conducted as a one-pot procedure.



Scheme 2

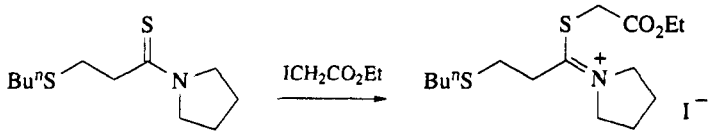
3.7.2.1 α-Thioiminium Salt Formation

The Eschenmoser coupling reaction is initiated by the selective *S*-alkylation of a thioamide with a suitable electrophile. Thioamides can be prepared conveniently from the corresponding amides by using either phosphorus(V) sulfide[10,11] (P_4S_{10}; also known as phosphorus pentasulfide) or Lawesson's reagent[12] (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide). Both reagents are able to convert amides into thioamides, selectively and efficiently, under mild, neutral conditions in the presence of other functional groups, including esters. However, the more reactive Lawesson's reagent will convert ester carbonyls into the thio analogs under more drastic conditions.[13] In some instances, addition of sodium bicarbonate or triethylamine to the phosphorus(V) sulfide improved yields of the thiation.[14,15] Alternative methods to prepare thioamides are available,[16] although these routes have not been employed as extensively. These alternatives include treatment of dithioesters with an amine to produce thioamides[17] and conversion of amides into imidates followed by reaction with hydrogen sulfide.[18]

A variety of thioamides possessing either mono- or di-alkyl substitution on the nitrogen can undergo the Eschenmoser coupling reaction. Primary thioamides are not acceptable substrates because of their ready conversion to nitriles under the condensation conditions. Although alkylation proceeds more readily on secondary rather than tertiary thioamides,[19] use of the latter allows subsequent sulfur extrusion to

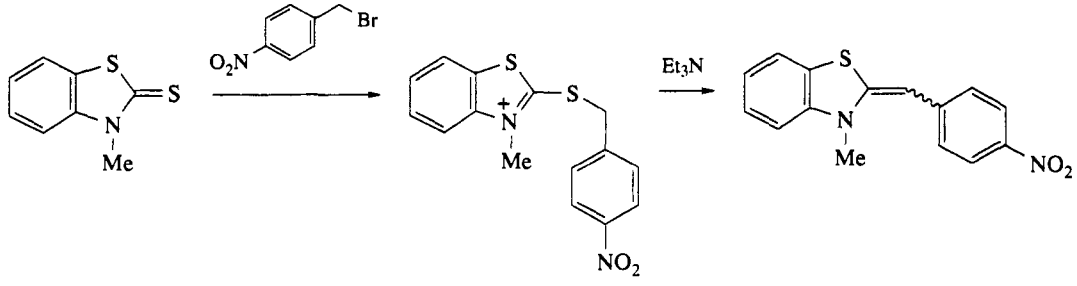
proceed under milder conditions and with higher yields. The reasons for this difference will be discussed in the following section.

The thioamide can accommodate a number of functional groups since alkylation proceeds under mild conditions, *i.e.* neutral solutions at room temperature. For example, the presence of a sulfide did not interfere with alkylation on the thioamide (equation 4).[20] The range of functional groups compatible with this reaction will become evident in the discussion of its applications in total synthesis (Section 3.7.4).



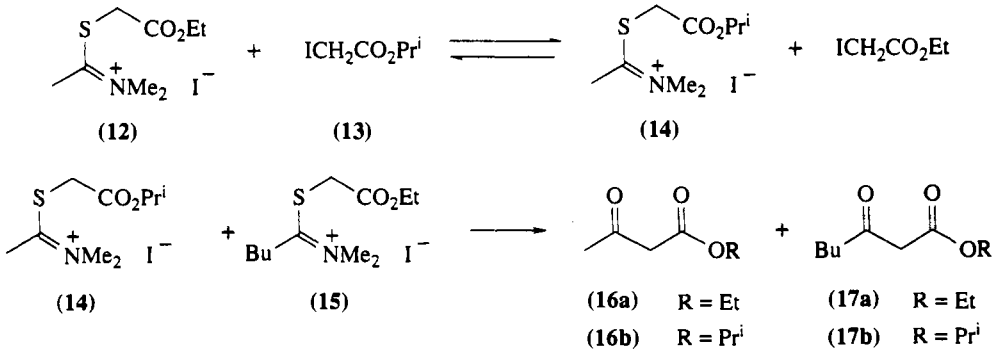
(4)

The electrophile used in thioamide alkylation must possess a sufficiently acidic α-proton for abstraction in the following step to initiate sulfur extrusion. Common electrophiles include α-activated carbonyl compounds such as esters, ketones, malonates and nitriles. However, alkylation with 4-nitrobenzyl bromide (Scheme 3) provided an intermediate iminium species containing a sufficiently acidic benzylic proton to promote subsequent sulfide contraction.[6]



Scheme 3

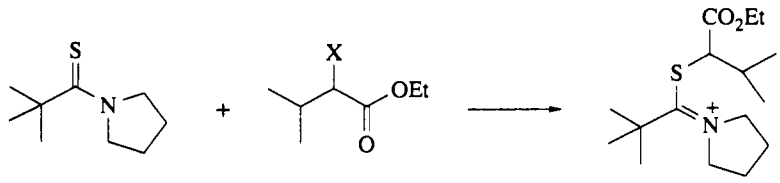
The alkylation of a thioamide is a reversible process when the electrophile bears a nucleophilic leaving group. The reversibility was demonstrated[20] by combining a preformed α-thioiminium salt (**12**) with a second, distinguishable electrophile (**13**; Scheme 4). Upon standing in solution, exchange of the alkyl appendage to form a second α-thioiminium salt (**14**) was observed. As further support, the preformed α-thioiminium salts (**14**) and (**15**) were combined and allowed to equilibrate under the alkylation conditions. The mixture then was subjected to the sulfur-extrusion process, followed by hydrolysis, to produce the β-keto esters (**16a**), (**16b**), (**17a**) and (**17b**). The resulting mixture of products, yielding four rather than two β-keto esters, demonstrated that a scrambling of the side chains through reversible alkylation had occurred.



Scheme 4

In certain applications, the reversibility has led to problems. For example, alkylation of pivaloylthioamide (**18**) with ethyl 2-bromoisovalerate (**19a**) would not proceed to completion despite the use

of forcing conditions (equation 5).[21] This difficulty was attributed to formation of a highly congested α-thioiminium intermediate (**20a**) in which the steric strain could be alleviated by reversion back to starting materials, thereby establishing an unfavorable equilibrium. To eliminate this reversal, alkylation was conducted with an electrophile bearing a non-nucleophilic leaving group. In particular, employing the trifluoromethanesulfonyl reagent (**19b**) enabled complete conversion of thioamide (**18**) to α-thioiminium salt (**20b**). This key finding has expanded significantly the scope of the Eschenmoser reaction to include the preparation of various α-substituted vinylogous products.

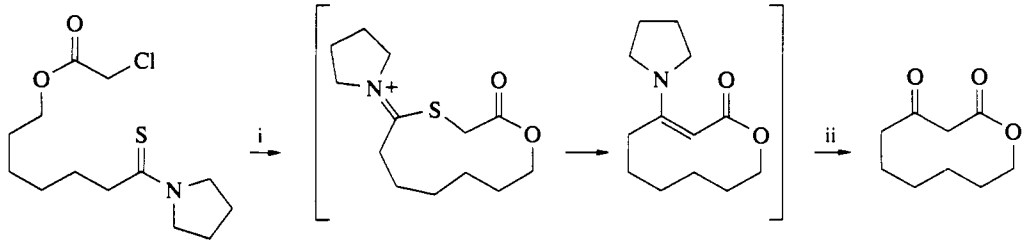


(5)

(**18**) (**19a**) X = Br (**20a**) X = Br

(**19b**) X = OSO_2CF_3 (**20b**) X = OSO_2CF_3

An alternative strategy was devised to overcome similar difficulties encountered while attempting an intramolecular Eschenmoser-based closure of chloro ester (**21**).[20] By immediately routing the intermediate α-thioiminium salt (**22**) as it was being formed through the sulfur-extrusion step, the ring-closed product was obtained in moderate to good yield (Scheme 5). Carefully controlled reaction conditions were developed in which the chloro ester (**21**) was added to a solution containing sodium iodide, base and thiophile at elevated temperature under high dilution.



(**21**) (**22**)

i, NaI, Pr^i_2NEt, $P(OEt)_3$; ii, H^+, H_2O

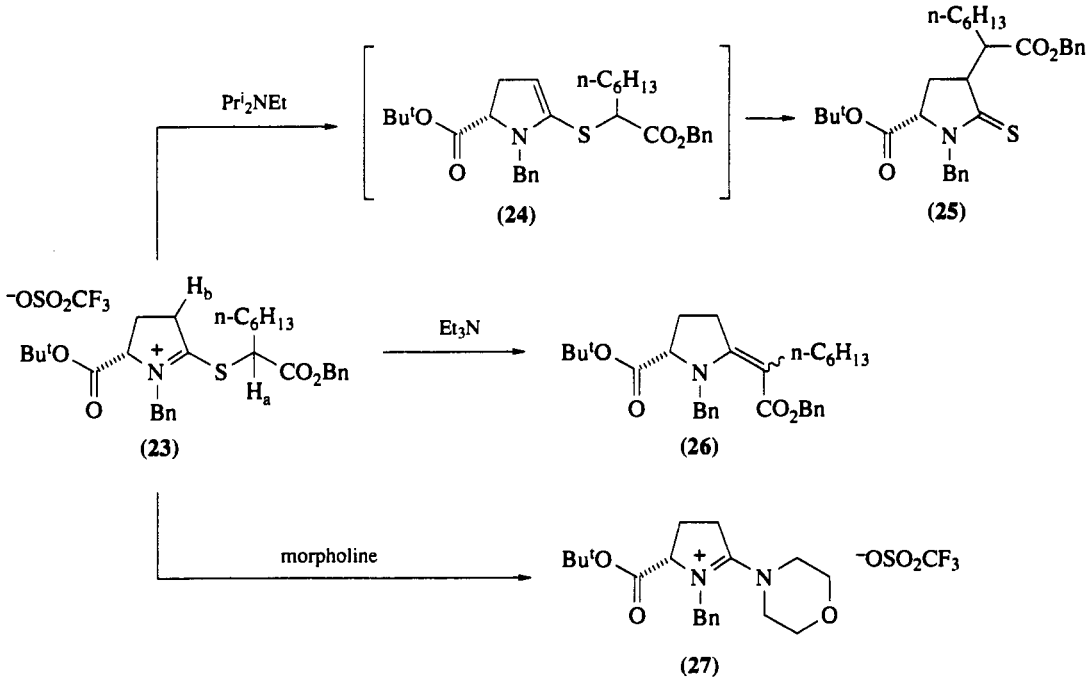
Scheme 5

3.7.2.2 Sulfide Contraction and Carbon–Carbon Bond Formation

The second step of the Eschenmoser coupling reaction requires the presence of a base to generate an anion in the α-thioiminium intermediate that leads to episulfide formation. Inorganic bases such as bicarbonate, hydroxide, alkoxides and hydrides have been employed successfully, as have various organic bases such as triethylamine, *N*-methylmorpholine and diisopropylethylamine. Since a mild organic base is sufficient for deprotonation in most examples, the reaction is compatible with numerous functional groups and base-sensitive asymmetric centers. For compounds that are highly base sensitive, the base strength can be titrated to levels that permit deprotonation yet preserve stereochemical integrity. Significant improvement in enantiomeric purity can be achieved by conducting the reaction at lower temperatures.[22]

In addition to its basicity, the structural nature of the base can affect the course of the reaction. For example, a sterically imposing base such as diisopropylethylamine was prevented from abstracting proton (H_a) residing in a congested environment of the α-thioiminium salt (**23**; Scheme 6).[22] Instead, a less-hindered hydrogen (H_b) was abstracted, leading to formation of a proposed S,N-ketene acetal (**24**), which underwent rearrangement to yield the α-alkylated thioamide (**25**) as the major product. A less

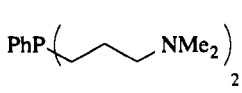
bulky base, such as triethylamine under the same reaction conditions, abstracted the desired proton (H_a) to produce the expected product (**26**) in good yield. The use of a secondary amine gave yet a different result. The addition of morpholine to the same intermediate α-thioiminium salt (**23**) led exclusively to formation of the stable amidinium salt (**27**). These findings emphasize the importance of proper base selection to prevent undesired results in the sulfide contraction.



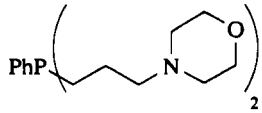
Scheme 6

The role of the thiophile is to assist extrusion of the sulfur atom from the episulfide intermediate to produce the unsaturated product. Studies have established that the presence of a thiophile affects the rate as well as the yield of the sulfur-extrusion reaction.[19] This participation was observed by measuring the difference in reaction rates and yields upon inverting the order of addition of the base and thiophile to a given α-thioiminium salt. Better results were obtained when the thiophile was allowed to stand in the presence of the α-thioiminium salt prior to addition of base. Presumably a sulfur–phosphine complex is established that enhances the acidity of the α-proton slated for abstraction and results in shorter reaction times and better yields.

A number of compounds can serve as an acceptable thiophile, including triphenylphosphine, trialkylphosphines and trialkyl phosphites. Eschenmoser developed a dual reagent, bis(*N*,*N*-dimethyl-3-aminopropyl)phenylphosphine (**28**), which contains both base and thiophile.[7] The main advantage of this dual reagent is its efficient removal from the product through aqueous washings, thereby simplifying purification. A derivative of the dual reagent was developed[21] by substituting a less basic morpholine for the trialkylamine to produce a new base–thiophile reagent (**29**) for use with base-sensitive compounds.



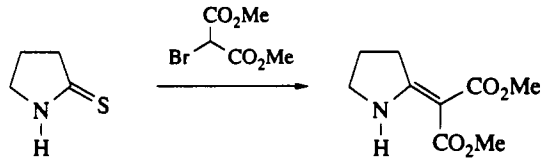
(**28**)



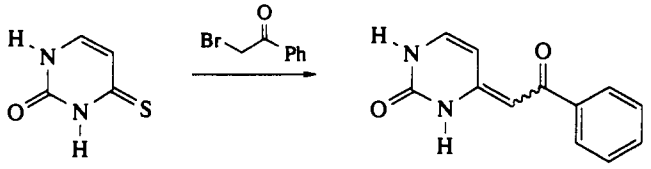
(**29**)

For most examples, addition of both a base and a thiophile is necessary for sulfide contraction to occur. However, the process can proceed in the absence of either reagent when a thioamide is alkylated with an active methylene species such as an α-halo malonate (equation 6)[7] or another 1,3-dicarbonyl compound that exists primarily in the enolized form. In some cases, heat was needed to initiate sulfide contraction; alkylation of monothiouracil (equation 7) with bromoacetophenone yielded an intermediate

that extruded sulfur upon heating.[23] Sulfur extrusion also occurred on secondary thioamides alkylated with bromo ketones when heated in the presence of a thiophile.[7]



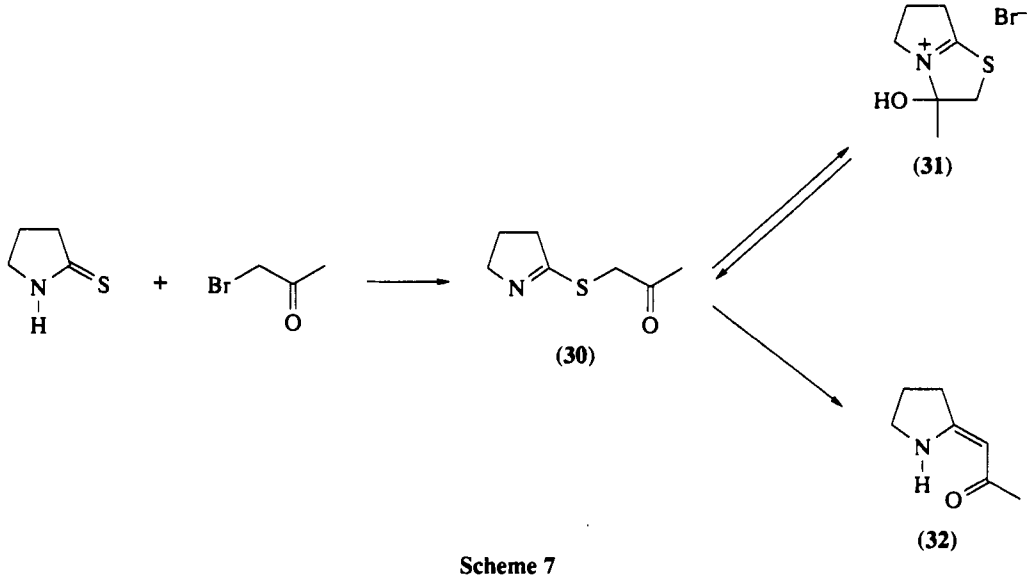
(6)



(7)

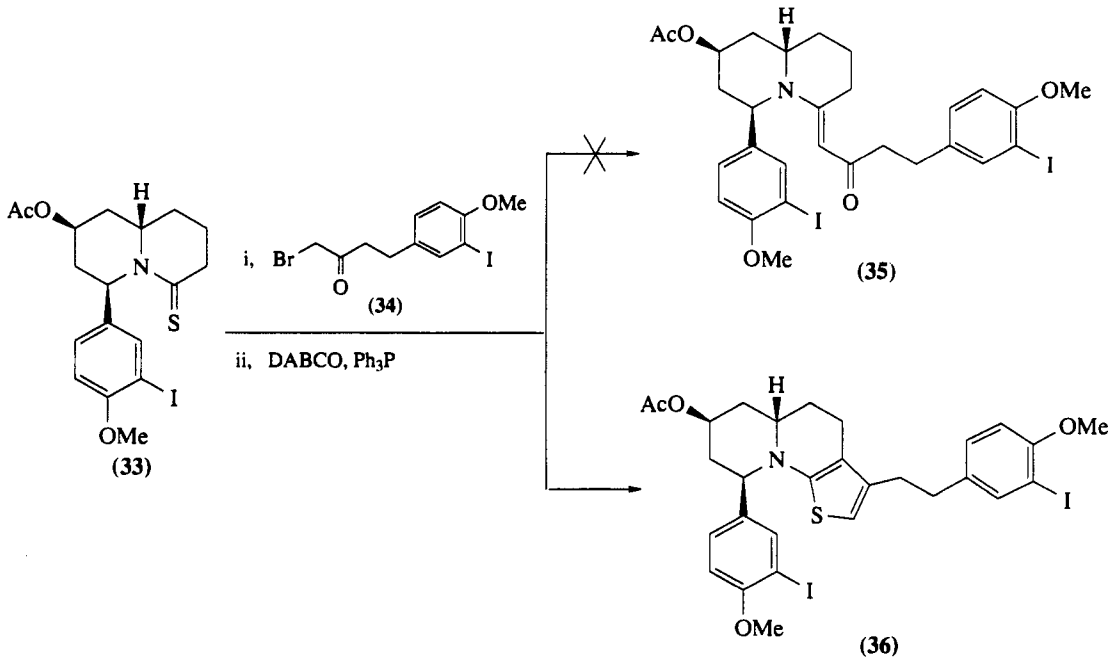
The degree of alkyl substitution on the thioamide nitrogen has an effect on both the reaction rate and the overall yield of the sulfide-contraction process. Tertiary thioamides produce higher yields of product with shorter reaction times than secondary thioamides under similar reaction conditions. This enhancement in both rate and yield is attributed to generation of a quaternary nitrogen in the α-thioiminium species derived from a tertiary thioamide. In contrast, alkylation of a secondary thioamide yields a tertiary iminium nitrogen that is converted to an imine upon addition of the first equivalent of base. The acidity of the side-chain α-proton in the charged, quaternary iminium species is expected to be greater than in the neutral imine intermediate, thereby facilitating deprotonation and resulting in better yields and shorter reaction times.[20] In addition, charge neutralization upon episulfide formation by the quaternary iminium species helps drive the reaction. An example of a secondary thioamide that would not undergo sulfide contraction until its tertiary derivative was prepared has been reported.[19]

Although the sulfide-contraction reaction is compatible with a wide range of steric and functional groups existing within either the thioamide or the electrophile, some precautions and limitations of the reaction need to be considered. The use of an α-halo ketone as the electrophile can result in an alkylated intermediate in which the thioamide nitrogen can undergo further addition to the keto group of the side chain to form a cyclized species. For example, a solvent-dependent equilibrium was established between the imine (**30**) and thiazolium salt (**31**) (Scheme 7).[7] In ethanol, the cyclized intermediate (**31**) was favored and could be isolated in good yield. Nonpolar solvents such as methylene chloride and chloroform appeared to suppress this side reaction and permitted formation of the desired vinylogous amide (**32**) upon treatment of the intermediate with a base and a thiophile.



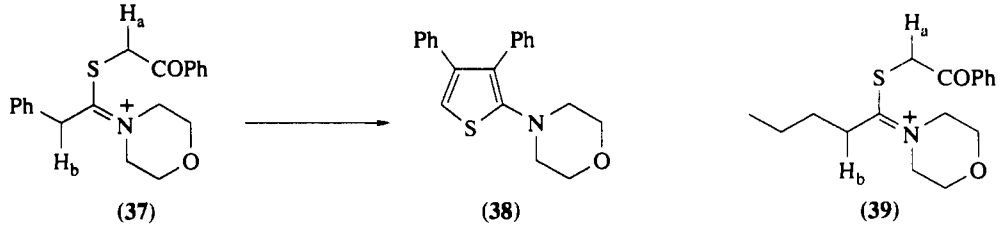
Scheme 7

In another example, α-bromo ketone (**34**) was used to alkylate the thioamide (**33**) in hopes of obtaining directly the vinylogous amide (**35**; Scheme 8).[24] However, abstraction of an undesired proton in the α-thioiminium salt formed the S,N-ketene acetal as in a previously described example. This proposed intermediate then rearranged and dehydrated to produce the thiophene (**36**) as the major product.



Scheme 8

In a similar case, the benzylic proton (H_b) in the α-thioiminium species (**37**) was abstracted instead of the α-keto proton (H_a) (Scheme 9). The resulting S,N-ketene acetal reacted with the ketonic carbonyl group to produce a similar 2-aminothiophene product (**38**). In contrast, the aliphatic iminium species (**39**) having a less acidic proton (H_b) gave the desired sulfide-contraction product.[20]



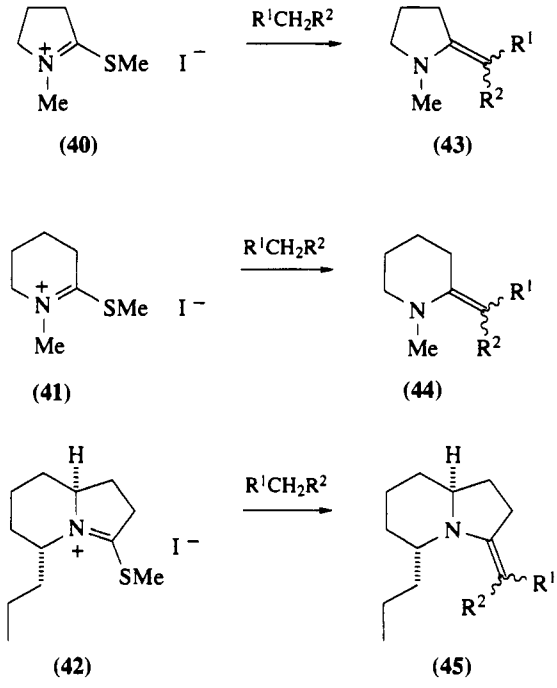
Scheme 9

A pair of geometric isomers about the alkene can result from the condensation process. Eschenmoser demonstrated that sulfide contraction on the secondary thiolactam produced exclusively the (*Z*)-isomer (equation 3).[7] Other studies have indicated sole formation of the (*E*)-isomer using tertiary thiolactams and bromoacetates or a mixture of isomers when α-substituted electrophiles were employed (*vide infra*). However, most synthetic applications of the Eschenmoser reaction have not stringently identified the geometry about the resulting alkene since the double bond is later reduced or equilibrated in the final product. A systematic investigation to identify factors that may influence the stereochemical outcome has not been reported.

3.7.3 MODIFICATIONS AND EXTENSIONS

3.7.3.1 Knoevenagel-based Modification

Several modifications of the sulfide-contraction reaction have appeared since the original report by Eschenmoser, offering complementary methods of conducting the condensation and broadening the scope of its applications. One adaptation, developed by Hart and coworkers,[25] utilized preformed α-thioiminium salts (**40**)–(**42**), generated from alkylation of the corresponding thiolactams with methyl iodide, as substrates for a Knoevenagel-based condensation. The preformed salts (**40**)–(**42**) were condensed with an active methylene compound in the presence of base to produce the corresponding vinylogous products (**43**)–(**45**) (Scheme 10; Table 2). Deacylated side products, *e.g.* (**46a**), (**46b**) and (**48**), were observed when the condensation was conducted with either β-keto esters or 1,3-diketones. However, deacylation could be minimized by proper choice of conditions. Condensation of the α-thioiminium salts (**40**)–(**42**) with the dibasic magnesium salt of ethyl hydrogen malonate followed by decarboxylation was the method of choice to prepare α-unsubstituted vinylogous urethanes (**46a**), (**47**) and (**48**). The advantages of this modification are the excellent handling and storage properties of the iminium salts and the ability to conduct the reaction with mild bases in the absence of a thiophile. This procedure was employed in the preparation of various carboxyl-modified amino acids and peptides.[26]

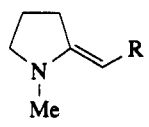


Scheme 10

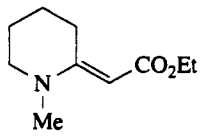
Table 2 Reactions of α-Thioiminium Salts with Active Methylene Compounds (Scheme 10)[25]

Salt	R^1	R^2	*Product*	*Yield (%)*
(**40**)	H	NO_2	(**43a**)	53[a]
(**40**)	CO_2Me	CO_2Me	(**43b**)	85[a]
(**40**)	CO_2Et	CN	(**43c**)	80[a]
(**40**)	CO_2Et	COMe	(**43d**)	84[b,c]
(**40**)	COMe	COMe	(**43e**)	53[a,d]
(**41**)	CO_2Me	CO_2Me	(**44**)	71[a]
(**42**)	CO_2Et	COMe	(**45**)	57[a,e]

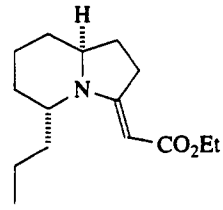
[a]K_2CO_3 (2.0 equiv.), DMF, 25 °C. [b]Et_3N (2.0 equiv.), CH_2Cl_2, 25 °C. [c]Contains 2% of the deacylated product (**46a**). [d]Contains 23% of the deacylated product (**46b**). [e]Contains 32% of the deacylated product (**48**).



(46a) R = CO_2Et
(46b) R = COMe



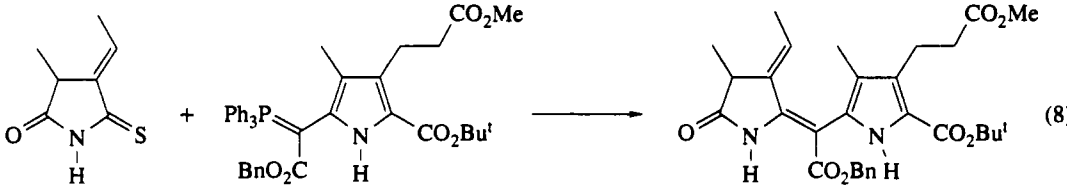
(47)



(48)

3.7.3.2 Thio-Wittig Modification

The thiocarbonyl alkenation procedure developed by Gossauer and coworkers enables the condensation of *N*-acylthioamides with resonance-stabilized phosphorus ylides and can be considered a modification of the Eschenmoser process. The two reactions are formally equivalent and both are believed to proceed through a common episulfide intermediate. This methodology was developed by Gossauer to couple highly functionalized pyrrole-based fragments in the synthesis of bile pigments (equation 8).[27] In contrast to the Eschenmoser method, the thiocarbonyl alkenation procedure is restricted to substrates containing an *N*-acylthioamide. For example, various monothioimides (**49**) were reacted with methyl (triphenylphosphoranylidene)acetate to yield the homologated products (**50**) (equation 9; Table 3). Dithioimides (**51**) were homologated, either singly or doubly, *via* this method (Scheme 11; Table 4).[28] In



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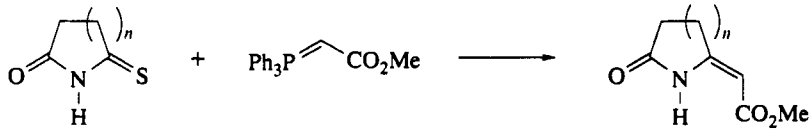


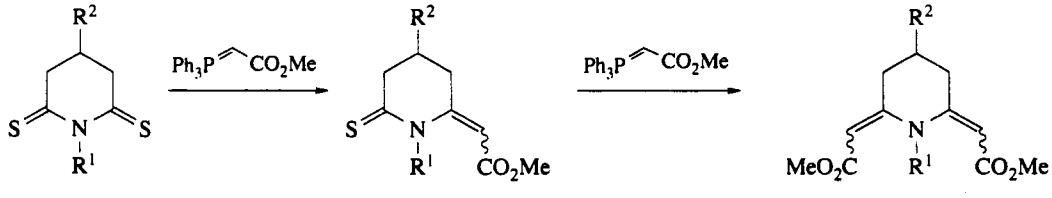
(9)

(49) (50)

Table 3 Preparation of Homologated Imides (equation 9)[27]

n	*Yield* (%)[a]
1	66
2	45
3	51

[a]In boiling toluene for 20 h.



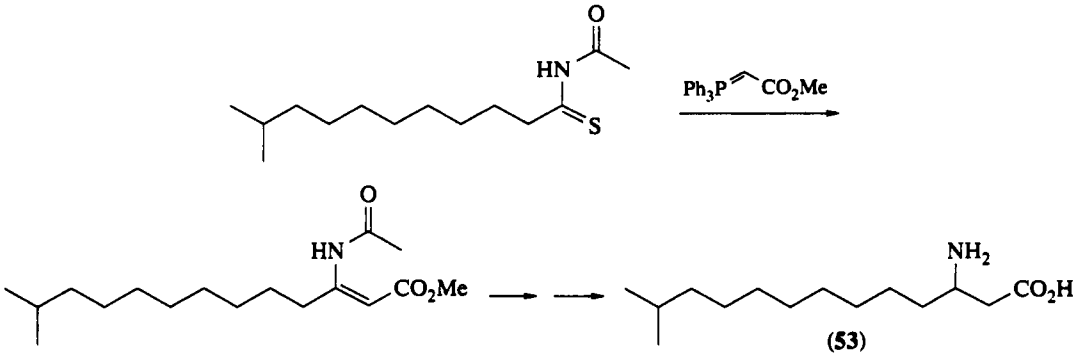
(51) (52)

Scheme 11

Table 4 Preparation of Homologated Thioimides (**52**; Scheme 11)[28]

R^1	R^2	*Yield* (%)[a]
H	H	95
Me	H	94
H	Me	61

[a]Refluxing toluene.

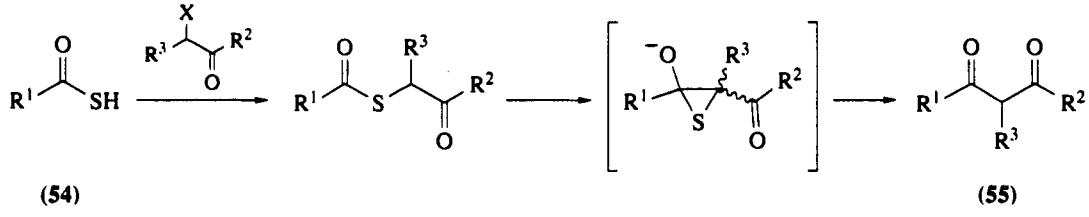


Scheme 12

addition, the thio-Wittig procedure has been conducted on acyclic *N*-acylthioamides and applied in the racemic synthesis of a β-amino acid, iturinic acid (**53**; Scheme 12).[29]

3.7.3.3 Preparation of β-Dicarbonyl Compounds

Although most of the synthetic developments and applications of the Eschenmoser reaction have employed thioamides as substrates, the two-step condensation process is applicable to the extension of thiocarboxylic acids (**54**).[30] A parallel mechanism to that described for the thioamide-based process is operating here and affords a direct synthesis of β-dicarbonyl compounds (**55**; Scheme 13). Eschenmoser demonstrated this application in his original report by alkylating various thiocarboxylic acids (**54**) with bromo ketones and esters in the presence of a base such as triethylamine.[7] The *S*-alkylated intermediate then was subjected to the sulfide-contraction process. In contrast to the α-thioiminium species generated from thioamides, the use of a thiophile and an organic base such as triethylamine did not promote sulfur extrusion from the thiol ester intermediate. A stronger base such as potassium neopentyl oxide was required for deprotonation to produce the desired 1,3-dicarbonyl product. For certain examples, an alternative to these strongly basic conditions was developed. The addition of lithium perchlorate or lithium bromide to those intermediates alkylated with α-halo ketones provided sufficient assistance through complexation to allow formation of the β-diketone products using tertiary amines rather than alkoxides. These conditions were not effective in preparing β-keto esters. This application of the Eschenmoser reaction has allowed the preparation of various substituted β-dicarbonyl compounds, in particular those



Scheme 13

which possess a single α-substitution (Table 5). A complementary route, *via* hydrolysis of the vinylogous product resulting from sulfide-contraction on a thiamide, has provided an efficient method for the synthesis of β-keto esters, ketones and nitriles.[20,21]

Table 5 Preparation of β-Dicarbonyl Compounds *via* Sulfide-contraction (Scheme 13)[7]

R^1	R^2	R^3	*Yield* (%)
$EtCH_2$	Et	H	85[a]
$EtCH_2$	Me	Me	80[a]
$EtCH_2$	4-BrC_6H_4	H	80[b]
$EtCH_2$	OEt	H	69[c]
$EtCH_2$	OEt	Me	79[c]

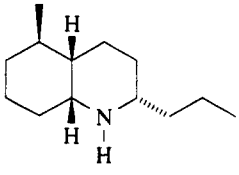
[a] i, Et_3N, $R^2C(O)CHR^3Br$; ii, bis(*N,N*-dimethyl-3-aminopropyl)phenylphosphine, LiBr, MeCN, 70 °C. [b] i, Et_3N, $R^2C(O)CHR^3Br$; ii, $LiClO_4$, Et_3N, Ph_3P, 20 °C. [c] i, Et_3N, $R^2C(O)CHR^3Br$; ii, potassium neopentyl oxide, Ph_3P, 50 °C.

3.7.4 APPLICATIONS IN TOTAL SYNTHESIS

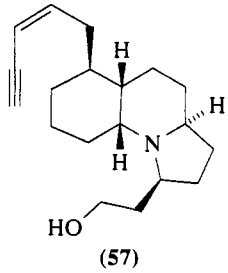
The Eschenmoser coupling reaction has found numerous applications in the preparation of a wide-ranging, structurally diverse set of biologically and synthetically intriguing compounds. Since the reaction enables generation of carbon-based extensions from amide carbonyls, it has proven valuable in the synthesis of alkaloids and heterocycles containing various α-substituted amino fragments as structural elements. However, by recognizing the 1,3-dicarbonyl entity masked within the resultant enaminone of the sulfide-contraction process, the application of this reaction has been extended to include the preparation of non-nitrogen containing compounds as well.

3.7.4.1 Dendrobatid and Other Neurotoxic Alkaloids

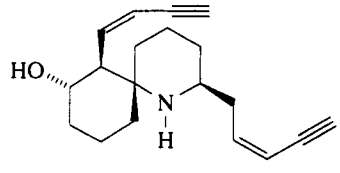
Several synthetic approaches toward the poison-dart frog alkaloids, including pumiliotoxin C (**56**), gephyrotoxin (**57**) and histrionicotoxin (**58**), have utilized the Eschenmoser reaction in a variety of distinct applications. These structurally related alkaloids are isolated from skin extracts of various Central and South American frogs in the *Dendrobates* genus and possess neurotoxic properties. Since their initial isolation and characterization, these toxins have attracted considerable attention for both their synthetic challenge and their interesting biological properties.[32]



(**56**)

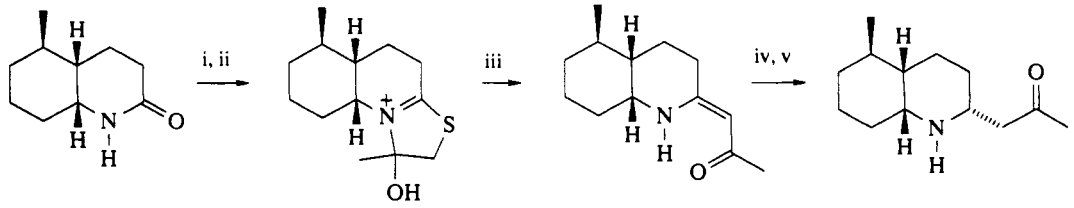


(**57**)



(**58**)

Pumiliotoxin C (**56**) is the prototypic member of a family of related alkaloids isolated from the skin of the poison-dart frog *Dendrobates pumilio* and *D. auratus*.[33] Several synthetic studies of pumiliotoxin C have been reported, including a racemic synthesis[34] in which the Eschenmoser reaction introduced the *n*-propyl side chain onto the decahydroisoquinoline nucleus. An advanced intermediate in the synthesis, the bicyclic lactam (**59**), was converted to the thiolactam with P_4S_{10} (Scheme 14). Alkylation with bromoacetone provided the isolable thiazole intermediate (**60**), which was treated with triphenylphosphine and potassium *t*-butoxide to produce the vinylogous amide (**61**) in 71% yield from the starting thioamide. Catalytic reduction of the vinylogous amide (**61**), followed by oxidation, yielded a single amino ketone (**62**) possessing the desired stereochemistry about the piperidine nucleus. Deoxygenation of the amino ketone provided racemic pumiliotoxin C (**56**). Thus, the Eschenmoser reaction was able to introduce the three-carbon segment directly onto the bicyclic lactam and provide an intermediate on which the new stereocenter was established with excellent selectivity.



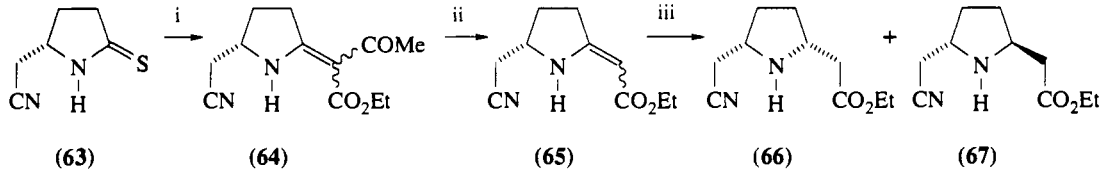
(59) (60) (61) (62)

i, P_4S_{10}; ii, bromoacetone; iii, $NaHCO_3$, then PPh_3, $KOBu^t$; iv, H_2, PtO_2; v, Jones' reagent

Scheme 14

Gephyrotoxin (**57**) is isolated from the frog *Dendrobates histrionicus* and possesses similar neurotoxic properties. Numerous chemical approaches have been developed to synthesize the parent compound and its hydrogenated analogs. Several of these approaches have incorporated the Eschenmoser reaction, each in a different application.

The first synthesis of optically pure gephyrotoxin[35] utilized the Eschenmoser reaction to generate a key disubstituted pyrrolidine intermediate. Thiolactam (**63**), derived from L-pyroglutamic acid to provide an optical center of known configuration at the start of the synthesis, was alkylated with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to yield the α-acyl vinylogous carbamate (**64**; Scheme 15). Deacylation was conducted in the presence of hydroxide and the resulting vinylogous carbamate (**65**) was reduced over Pt–C to yield a 2.3:1 mixture of the *cis* (**66**) and *trans* (**67**) disubstituted pyrrolidines. The optically pure, *cis*-2,5-disubstituted pyrrolidine (**66**) possessing the differentiated side chains served as the starting substrate from which the synthesis of optically pure gephyrotoxin (**57**) was accomplished *via* a previously established route.[36]



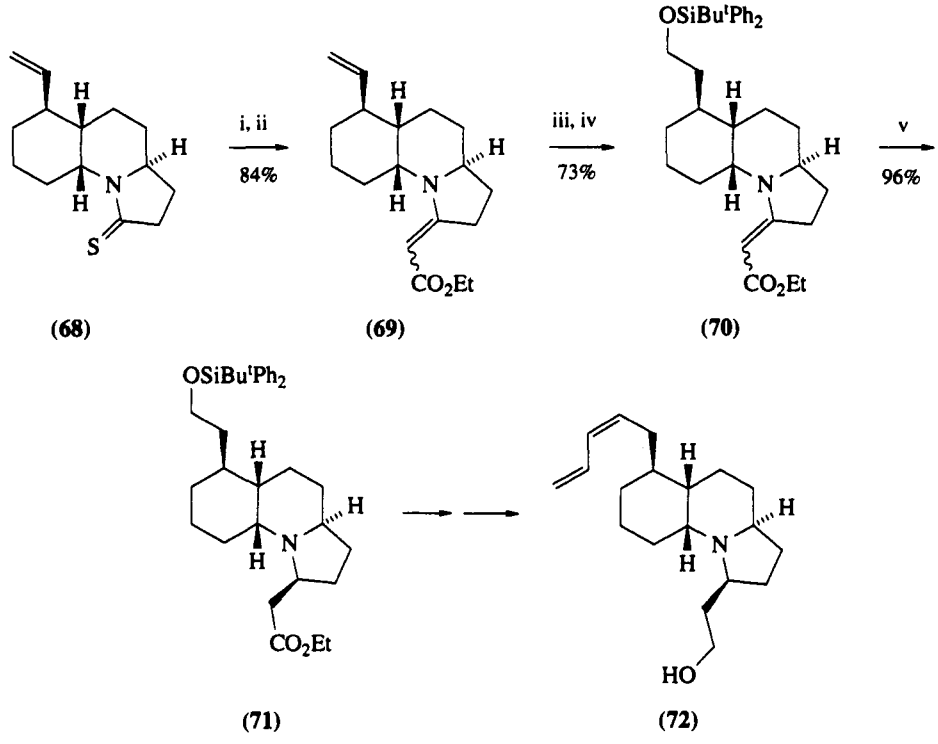
(63) (64) (65) (66) (67)

i, $MeCOCH(Br)CO_2Et$, $NaHCO_3$; ii, 0.1 N KOH, EtOH; iii, H_2, Pt–C, $HClO_4$, MeOH

Scheme 15

An alternative synthesis[37] of racemic gephyrotoxin (**57**) and one of its dihydro analogs (**72**) employed the Eschenmoser reaction to introduce a three-carbon segment that would eventually become the pendent hydroxyethyl side chain in the final compound. Alkylation of the tricyclic thiolactam (**68**) with ethyl bromoacetate, followed by treatment of the resulting α-thioiminium salt with triphenylphosphine and triethylamine, afforded the desired vinylogous carbamate (**69**) in good yield (Scheme 16). Reduction of the carbamate (**69**) under a variety of conditions did not proceed with a sufficient degree of selectivity. However, significant improvement in reduction selectivity was accomplished by employing remote functionality to control the stereochemical outcome. To this end, the pendent vinyl group was hydroxylated and protected as the silyl ether (**70**), at which stage reduction of the vinylogous carbamate again was attempted. The bulky silyl group directed preferential approach of the catalyst from the less-hindered side of the vinylogous carbamate to provide a 96:4 ratio in favor of the desired isomer (**71**). The two differentiated side chains extending from the major isomer (**71**) were ultimately elaborated to achieve racemic gephyrotoxin (**57**) and the dihydro derivative (**72**).

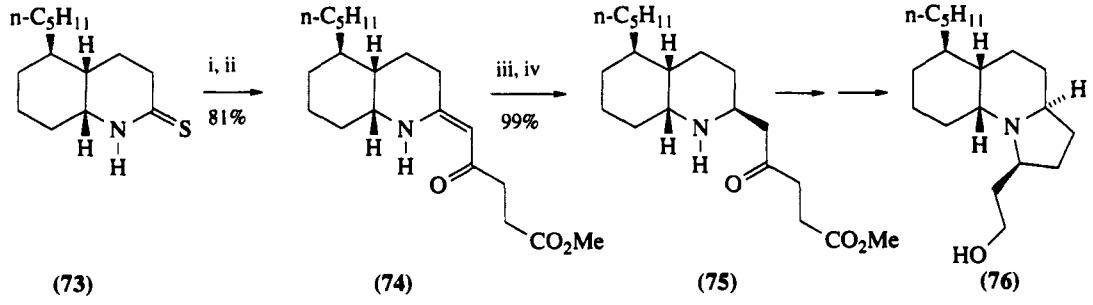
A third application of the Eschenmoser reaction in the synthesis of racemic perhydrogephyrotoxin (**76**) is based on an extension of the chemistry developed during the pumiliotoxin C synthesis.[38,39] Beginning with the bicyclic thiolactam (**73**), the sulfide-contraction reaction was used to append to the decahydroisoquinoline a functionalized five-carbon side chain that would later be cyclized and become the α-hydroxyethylpyrrolidine portion of the molecule. Alkylation of the thiolactam (**73**) with methyl 5-bromolevulinate followed by treatment with the Eschenmoser dual base–thiophile reagent (**28**) produced the vinylogous carbamate (**74**) in 81% yield from the starting thiolactam (**73**; Scheme 17). Reduction of the vinylogous amide (**74**), followed by equilibration of the amino ketones in the presence of



i, $BrCH_2CO_2Et$; ii, Et_3N, Ph_3P; iii, disiamylborane, 30% H_2O_2; iv, Bu^tPh_2SiCl, imidazole; v, H_2, Pt/Al_2O_3

Scheme 16

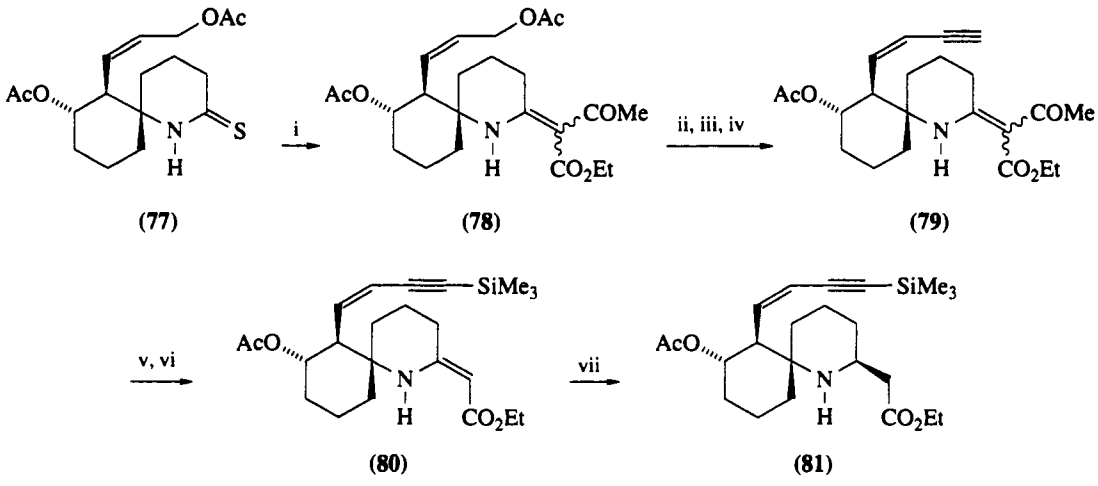
triethylamine, provided a satisfactory ratio favoring the desired isomer (**75**), which was converted to perhydrogephyrotoxin (**76**).



i, $BrCH_2COCH_2CH_2CO_2Me$; ii, $PhP(CH_2CH_2CH_2NMe_2)_2$; iii, $NaCNBH_3$, pH 4.0; iv, Et_3N

Scheme 17

The first total synthesis[40] of racemic histrionicotoxin (**58**), the parent structure in a family of related spirocyclic alkaloids isolated from the skins of *Dendrobates histrionicus*, utilized the Eschenmoser reaction to generate the anchor of what would become the enyne group extending from the α-position of the piperidine nucleus. The spirothiolactam intermediate (**77**) was condensed with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to produce (**78**) in good yield (Scheme 18). Prior to further reaction on the vinylogous carbamate, the pendent allylic acetate was elaborated to the enyne (**79**). Subsequent deacylation and enyne protection yielded spirobicycle (**80**), which gave a 1:1 mixture of isomers upon reduction. The desired diastereomer (**81**) was isolated and subsequently converted to racemic histrionicotoxin (**58**).

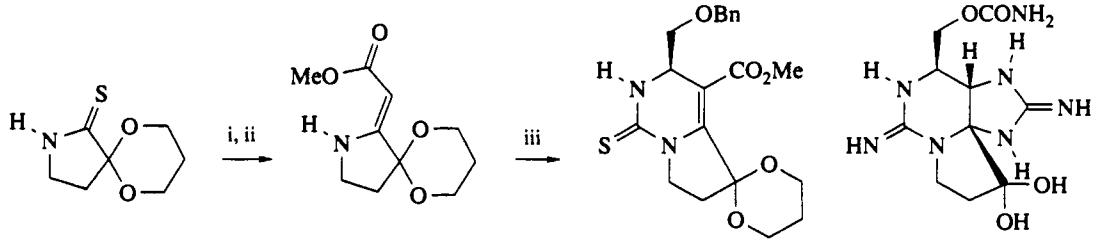


(77) (78) (79) (80) (81)

i, $MeCOCHBrCO_2Et$, $NaHCO_3$; ii, NaOH; iii, PCC; iv, $(Ph)_3\overset{+}{P}CH_2Cl\ Cl^-$, Bu^nLi; v, NaOEt; vi, MeLi, TMSCl; vii, $NaCNBH_3$

Scheme 18

The Eschenmoser coupling reaction has been extensively employed to prepare other compounds of biological and chemical interest. Saxitoxin (**85**),[41] one of the most toxic nonproteinaceous neurotoxins known, is isolated from the paralytic shellfish poison associated with episodes of algae-related 'red-tides'. The first total synthesis[42] of racemic saxitoxin employed the Eschenmoser reaction to incorporate a key functional handle from which the piperazine ring was later constructed. The spirothiolactam (**82**) was condensed with methyl 2-bromoacetoacetate in the presence of sodium bicarbonate followed by basic hydrolysis of the α-acetyl group to provide the vinylogous carbamate (**83**; Scheme 19). This key intermediate was condensed with benzyloxyacetaldehyde and silicon tetraisothiocyanate to yield directly the bicyclic thiourea ester (**84**), which was converted into saxitoxin (**85**).



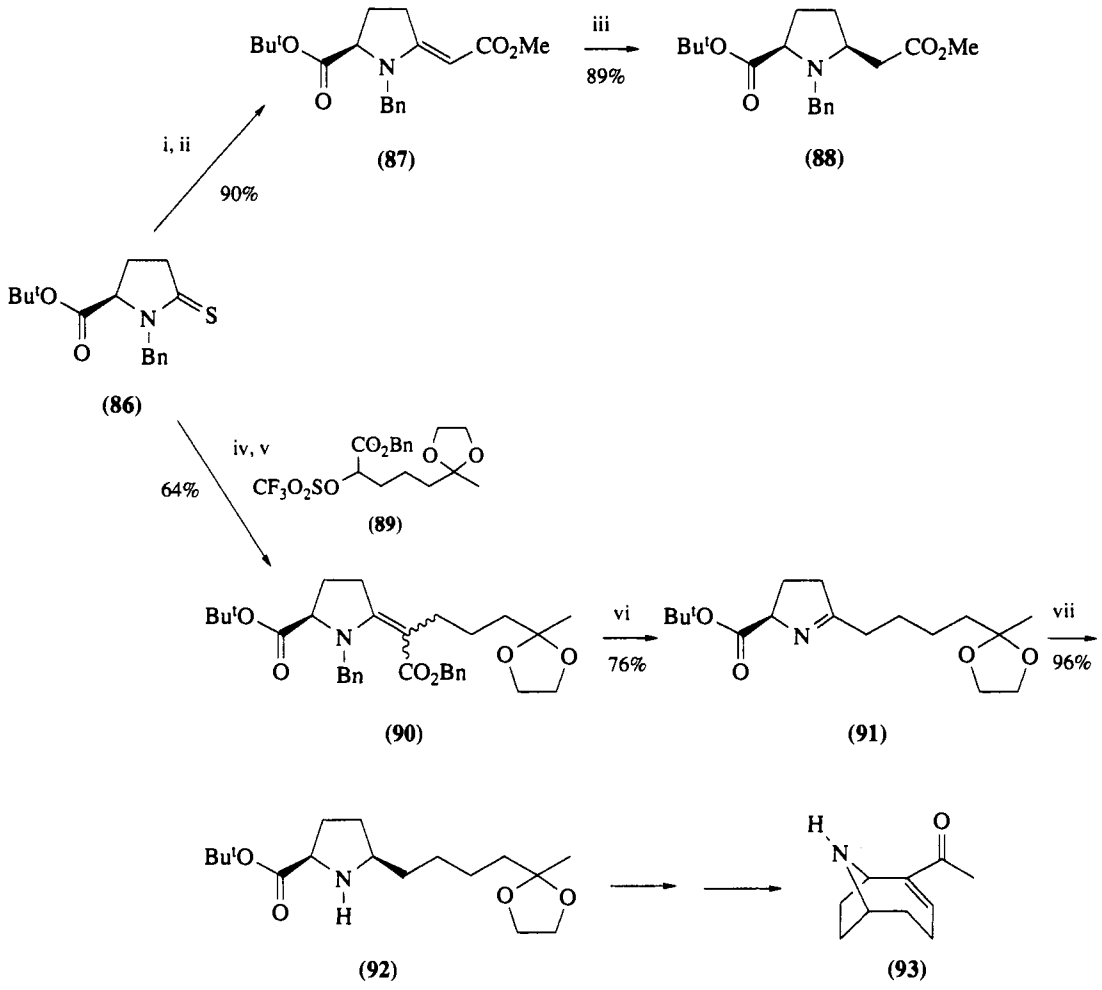
(82) (83) (84) (85)

i, $MeCOCHBrCO_2Me$, $NaHCO_3$; ii, KOH, MeOH; iii, $BnOCH_2CHO$, $(SCN)_4Si$

Scheme 19

The first synthesis[19] of optically pure anatoxin a (**93**), a potent nerve-depolarizing agent isolated from fresh-water blue-green algae, employed the Eschenmoser reaction to construct a functionalized side chain onto the pyroglutamate derivative (**86**) in a stereoselective manner. This side chain would be cyclized later into an iminium species, generated through decarbonylation of the α-amino acid, to form the bicyclic homotropane structure. Two strategies were investigated to build the side chain: a step-wise construction and a direct introduction of the entire side chain at once. Both approaches utilized the sulfide-contraction reaction to accomplish the key condensation onto the pyrrolidine ring. Optically pure thiopyroglutamate (**86**) was alkylated with methyl bromoacetate and the resulting thioiminium salt treated with triphenylphosphine and triethylamine to obtain the desired vinylogous carbamate (**87**; Scheme 20). Catalytic reduction of (**87**) proceeded with excellent transfer of chirality to produce a 98:2 ratio in favor of the *cis* amino diester (**88**). In contrast, reduction of (**87**) with $NaCNBH_3$ (pH 2) afforded

a 3:1 mixture of the *cis* and *trans* amino diesters. Studies conducted on the amino diester (**88**) established that the optical purity of the α-center was maintained throughout the course of the sulfide-contraction process. The acetate side chain in the pure *cis* isomer (**88**) was extended to the requisite segment that enabled cyclization to the bicyclic structure of anatoxin a (**93**).



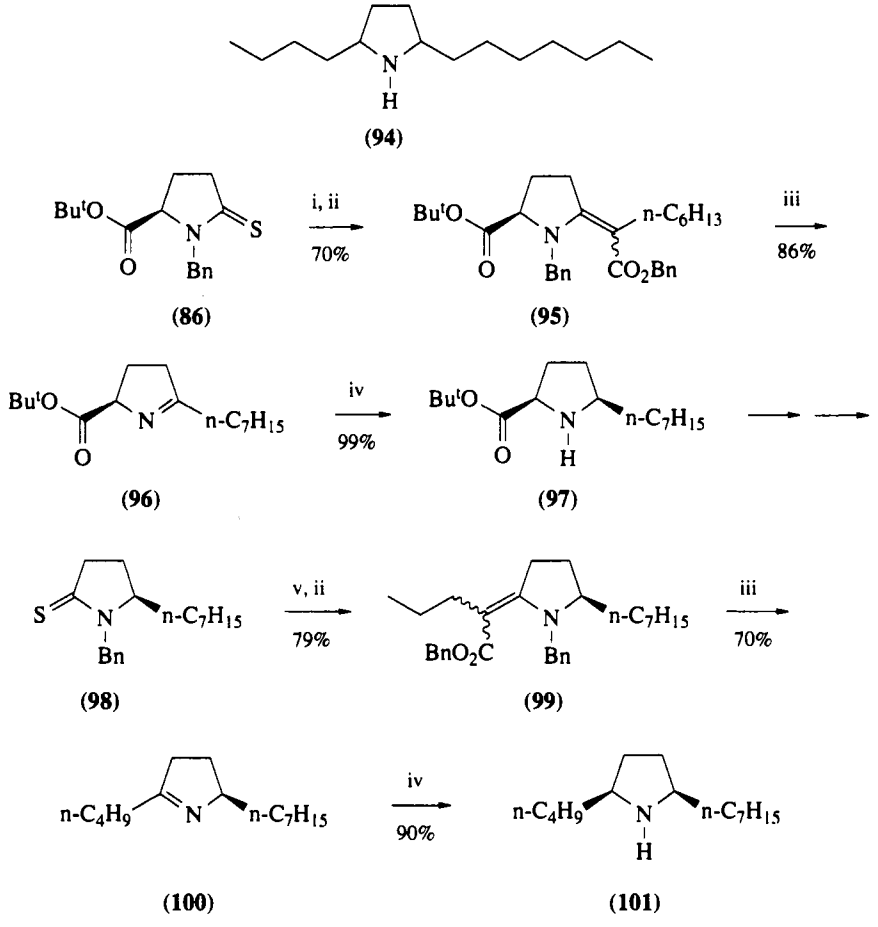
i, $BrCH_2CO_2Me$; ii, Ph_3P, Et_3N; iii, 5% Pt/C; iv, (**89**); v, Ph_3P, Et_3N; vi, 5% Pd/C, 1,4-cyclohexadiene; vii, H_2, PtO_2

Scheme 20

To complement the step-wise construction, the Eschenmoser reaction was adapted in a more convergent manner to introduce the entire side chain at once. This required alkylation of the thiopyroglutamate (**86**) with an α-substituted electrophile of the desired chain length and having the correct functionality. As previously noted,[21] this alkylation requires a triflate as the electrophile. Thus the thiopyroglutamate (**86**) was alkylated with (**89**) followed by reaction with triphenylphosphine and triethylamine to yield the anticipated vinylogous carbamate (**90**) as a mixture of geometric isomers. Treatment of the isomeric mixture with palladium using transfer hydrogenolysis conditions removed both benzyl groups; the resulting acid underwent decarboxylation and the enamine isomerized to the disubstituted pyrroline (**91**). Catalytic reduction of the pyrroline proceeded with efficient transfer of chirality to yield a 98:2 ratio favoring the *cis*-disubstituted pyrrolidine (**92**).

3.7.4.2 Pyrrolidine Alkaloids

The synthesis of all four possible stereoisomers of 5-butyl-2-heptylpyrrolidine (**94**), components of the trail pheromone of an ant in the genus *Solenopsis*, was conducted in a similar manner through extension of the same pyroglutamate derivative (**86**) *via* the Eschenmoser reaction.[22] Alkylation of the thiolactam (**86**) using an alkyl triflate reagent introduced the entire *n*-heptyl side chain in one step (Scheme 21). The resulting iminium salt intermediate was allowed to undergo sulfide contraction to yield a mixture of the vinylogous carbamates (**95**). The mixture was subjected to the transfer hydrogenolysis conditions and underwent debenzylation, decarboxylation and tautomerization to produce the pyrroline (**96**). Catalytic reduction of the pyrroline (**96**) proceeded with excellent selectivity to produce, in greater than 99:1 ratio, the *cis*-2,5-disubstituted pyrrolidine (**97**).



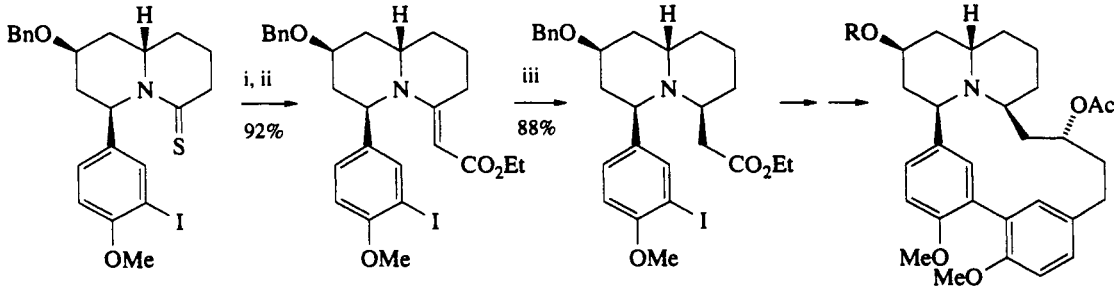
i, $Me(CH_2)_5CH(OSO_2CF_3)CO_2Bn$; ii, Ph_3P, *N*-methylmorpholine; iii, 5% Pd/C, 1,4-cyclohexadiene; iv, Pt_2O, H_2; v, $Me(CH_2)_2CH(OSO_2CF_3)CO_2Bn$

Scheme 21

The Eschenmoser reaction was applied a second time as one of the methods to introduce the *n*-butyl appendage. The alkylated α-amino ester (**97**) was oxidized to the monosubstituted thiolactam (**98**), and introduction of the butyl side chain, *via* sulfide contraction as described above, yielded a mixture of vinylogous carbamates (**99**). Treatment of the carbamates (**99**) under transfer hydrogenolysis conditions yielded the optically pure dialkylpyrroline (**100**), another component of the ant trail pheromone. Subsequent reduction of the pyrroline with platinum afforded the optically pure *cis*-2,5-dialkyl-substituted pyrrolidine (**101**). Other pyrrolidine-containing alkaloids have been prepared by similar approaches involving the Eschenmoser reaction.[43]

3.7.4.3 Quinolizidine, Pyrrolizidine and Related Alkaloids

The preparation[24,44] of several quinolizidine metacyclophane alkaloids, lythrancepine II (**105**) and III (**106**), employed the sulfide-contraction process to introduce a key segment onto an aryl bicyclic thiolactam (**102**), prepared from the corresponding lactam developed during the synthesis of vertaline alkaloids.[45] As described earlier, attempts to extend directly the thiolactam with the entire side chain containing the substituted phenyl group *via* the sulfide-contraction process did not produce the desired unsaturated ketone (**35**) but yielded the thiophene (**36**) instead. In the light of this finding, a step-wise approach was adopted in which alkylation of thiolactam (**102**) with ethyl iodoacetate, followed by treatment of the intermediate salt with DABCO and triphenylphosphine in refluxing chloroform, produced the desired vinylogous carbamate (**103**) in good yield (Scheme 22). Subsequent reduction of the alkene using sodium cyanoborohydride under acidic conditions yielded the desired amino ester (**104**) and its diastereomer in a ratio of 8.8:1. The acetate was elaborated into the requisite side chain and cyclized to the lythrancepines.



(**102**) (**103**) (**104**) (**105**) R = H; Lythrancepine II

(**106**) R = Ac; Lythrancepine III

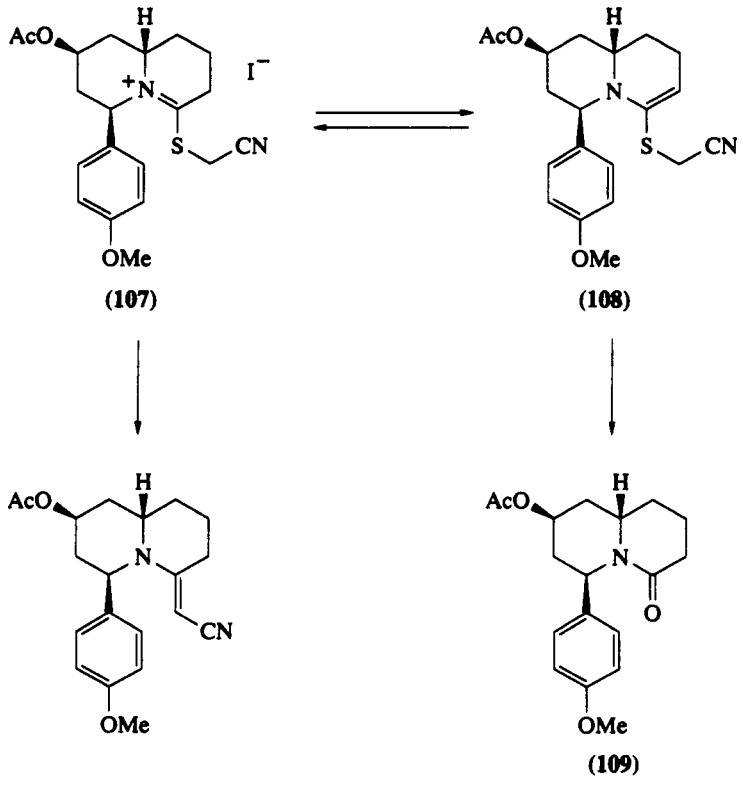
i, ICH_2CO_2Et; ii, DABCO, Ph_3P, $CHCl_3$ (reflux); iii, $NaCNBH_3$

Scheme 22

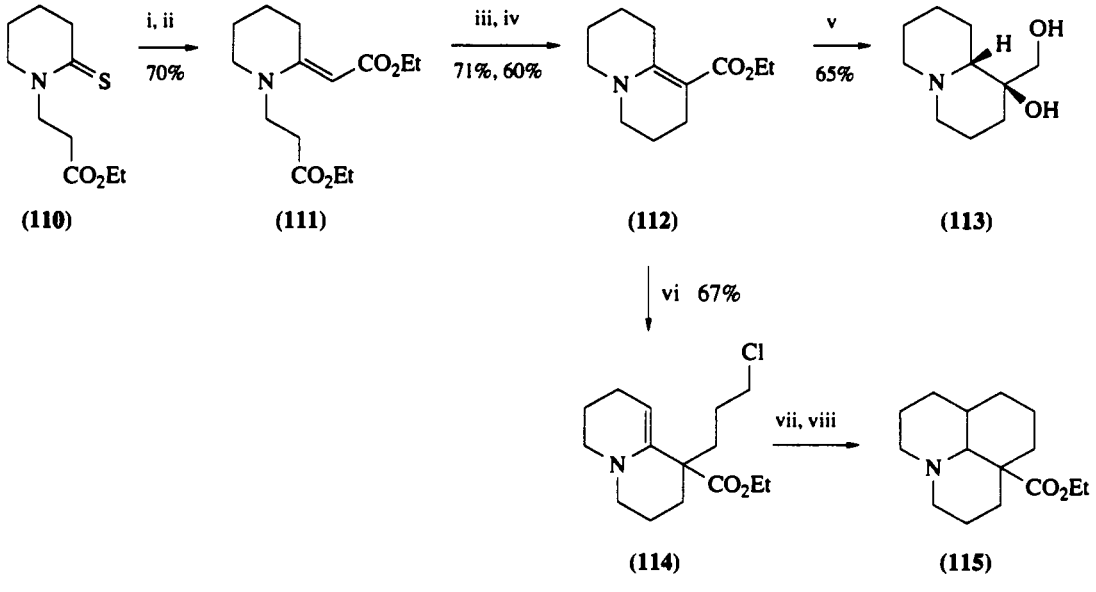
Warming the above α-thioiminium salt in the presence of the thiophile and base was critical in order to accomplish the sulfide-contraction process. At ambient temperature, work-up of the same reaction mixture produced the oxolactam analog of (**102**) as the major product (74%) along with a small amount (12%) of vinylogous carbamate (**103**). In order to better understand the underlying mechanism that prevailed under ambient *versus* elevated temperatures, NMR studies were conducted on the α-thioiminium salt (**107**). This intermediate, when dissolved in deuterated chloroform at ambient temperature in the presence of DBU, was converted immediately to a proposed S,N-ketene acetal (**108**; Scheme 23). Triphenylphosphine had no effect on the iminium salt. Aqueous work-up yielded the lactam (**109**), which is consistent with formation of the S,N-ketene acetal. However, warming the intermediate (**107**) in the presence of the base and thiophile allowed the reaction to eventually proceed *via* the sulfur-extrusion pathway, due to the reversibility of the S,N-ketene acetal formation.

The Eschenmoser reaction was employed in a general method[46] for preparing other functionalized quinolizidines. The *N*-alkylated thiocaprolactam (**110**) was alkylated with ethyl bromoacetate followed by the standard sulfide-contraction procedure using triphenylphosphine and triethylamine to afford the desired vinylogous carbamate (**111**) in good yield (Scheme 24). The ester in the saturated propionate side chain was selectively reduced to the alcohol, converted to a leaving group and cyclized directly into the vinylogous carbamate (**112**). Step-wise reduction of this intermediate yielded a naturally occurring alkaloid, lupinine (**113**). In addition, a second alkylation on the bicyclic vinylogous carbamate (**112**) produced the α-alkylated derivative (**114**) as the major product along with a minor amount of the γ-substituted isomer. Cyclization of the α-alkylated compound produced the tricyclic structural framework (**115**) that comprises the nucleus of the julolidine alkaloids.

A similar strategy[47] generated two of the simplest members in the pyrrolizidine family of alkaloids, isoretronecanol (**120**) and trachelanthamidine (**121**). The enamino ester (**117**) was prepared *via* the Eschenmoser reaction by the condensation of thiolactam (**116**) and ethyl bromoacetate (Scheme 25). A second alkylation with bromoacetate on the resulting vinylogous carbamate (**117**) yielded the amino diester (**118**). Cyclization of the diester in the presence of potassium hydride generated the bicyclic lactam (**119**), which served as the common intermediate for preparation of both pyrrolizidine alkaloids.

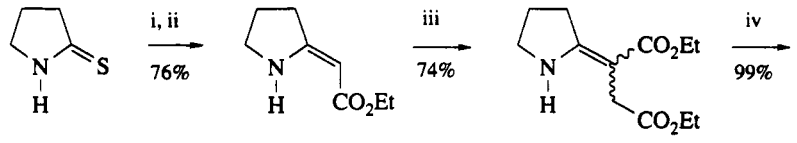


Scheme 23

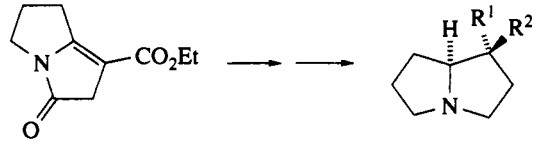


i, $BrCH_2CO_2Et$; ii, Et_3N, Ph_3P; iii, $LiAlH_3OEt$; iv, NaH, TsCl; v, $NaBH_4$ then $LiAlH_4$; vi, Bu^nLi, $BrCH_2CH_2CH_2Cl$; vii, NaI; viii, PtO_2

Scheme 24



(116) (117) (118)



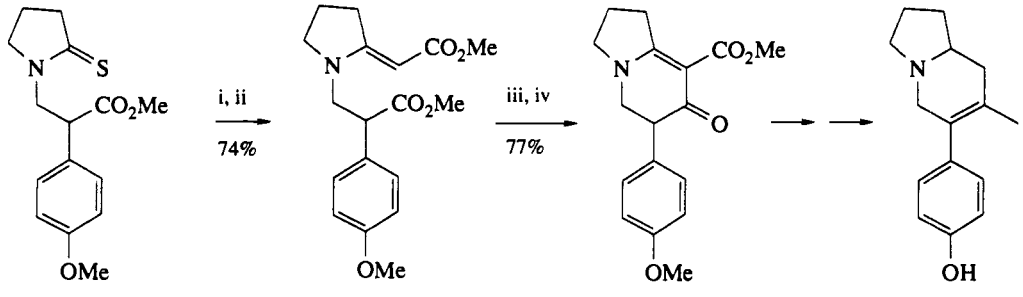
(119)

(120) $R^1 = H$; $R^2 = CH_2OH$; Isoretronecanol

(121) $R^1 = CH_2OH$; $R^2 = H$; Trachelanthamidine

i, $BrCH_2CO_2Et$; ii, Ph_3P, $KOBu^t$ iii, LDA, $BrCH_2CO_2Et$; iv, KH

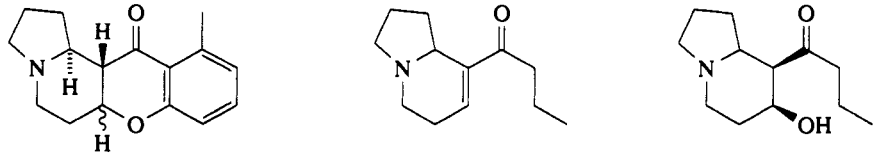
Scheme 25



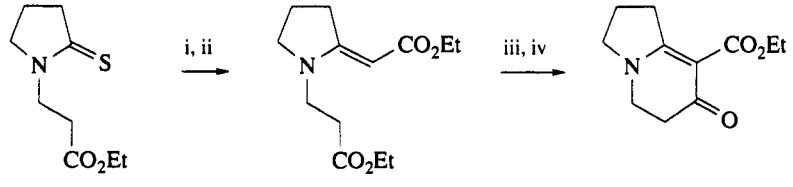
(122) (123) (124) (125)

i, $BrCH_2CO_2Me$; ii, Et_3N, Ph_3P; iii, NaOH, H_2O; iv, Bu_4NI, $ClCO_2Me$

Scheme 26



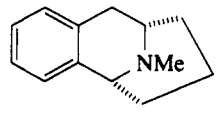
(126) (127) (128)



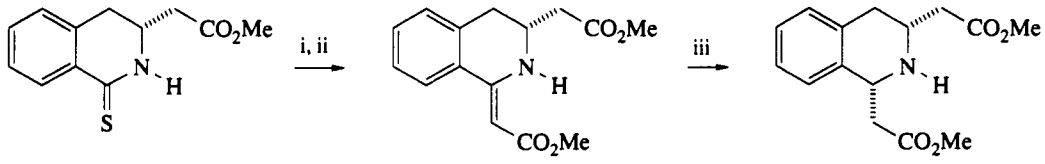
i, $BrCH_2CO_2Et$; ii, Et_3N, Ph_3P; iii, NaOH, H_2O; iv, Ac_2O

Scheme 27

The synthesis of ipalbidine (**125**),[48] the aglycon of ipalbine, was based on a related approach. The vinylogous carbamate (**123**) was prepared from the *N*-alkylated thiobutyrolactam (**122**) *via* an analogous sulfide-contraction process as described above (Scheme 26). The bicyclic intermediate (**124**) was generated by selective hydrolysis of the saturated ester followed by immediate treatment with methyl chloroformate in the presence of catalytic tetrabutylammonium iodide. The bicyclic compound (**124**) was further elaborated to racemic ipalbidine (**125**). Parallel applications of this strategy were employed to prepare a series of *Elaeocarpus* alkaloids (**126**), (**127**) and (**128**) (Scheme 27)[49] as well a benzomorphan analog (**129**; Scheme 28).[50]



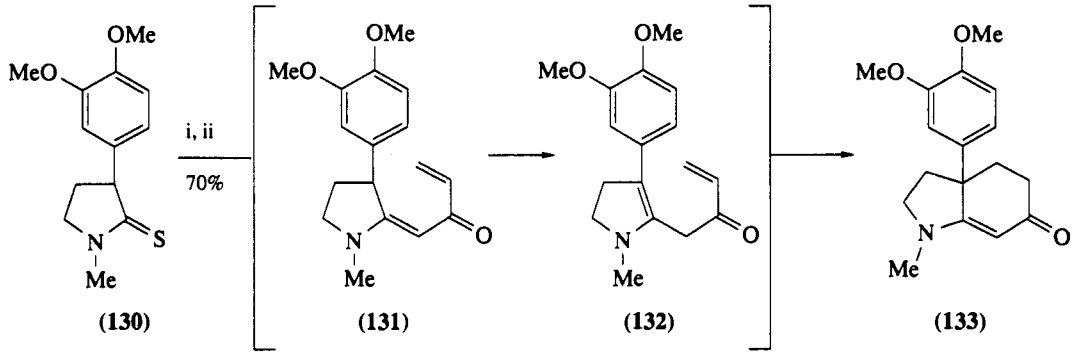
(**129**)



i, $BrCH_2CO_2Me$; ii, Ph_3P, $KOBu^t$; iii, Pt_2O

Scheme 28

A tandem sulfide-contraction and Robinson annelation reaction[51] was used for the synthesis of a mesembrine analog, Δ^7-mesembrenone (**133**). The aryl-substituted thiobutyrolactam (**130**) was treated with chloromethyl vinyl ketone followed by diisopropylethylamine to afford Δ^7-mesembrenone (**133**) in good yield (Scheme 29). The reaction probably proceeds through initial sulfide contraction to the intermediate vinyl enaminone (**131**), which tautomerized to the enamine (**132**) and underwent intramolecular Michael closure to produce (**133**).



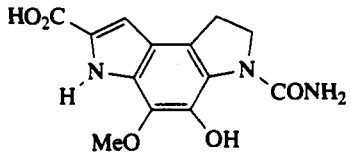
i, chloromethyl vinyl ketone; ii, Pr^i_2NEt

Scheme 29

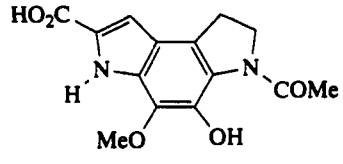
3.7.4.4 Phosphodiesterase Inhibitor Analogs

The synthesis of several analogs of the phosphodiesterase inhibitors PDE-I (**134**) and PDE-II (**135**)[52] adapted the Eschenmoser reaction to perform a key cyclization that demonstrated its utility in constructing highly functionalized heterocycles. These tricyclic compounds are of additional interest because of their presence in the potent antitumor antibiotic CC-1065 (**136**). Cyclization of the pyrrolylthiopyrrolidinone (**137**) to the tricyclic structure was achieved either by the Eschenmoser reaction or by the Knoeven-

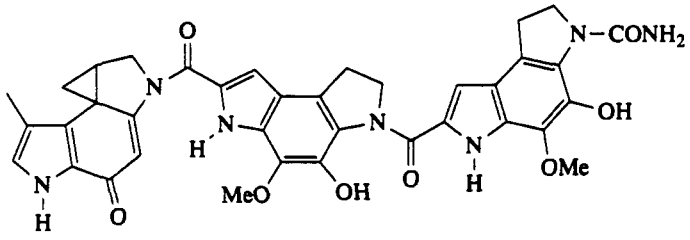
agel-based modification. To effect ring closure by the former route, the β-diketone was converted to the α-bromo derivative (**138**) through conversion to the diazo intermediate, deacylation and displacement with bromide (Scheme 30). Cyclization afforded the thiepinone (**139**) in quantitative yield after neutralization of the reaction mixture. Treatment of the diazo ketone with boron trifluoride etherate also provided the identical cyclized product. Thiepinone (**139**) underwent an oxidative sulfide contraction with liberation of hydrogen sulfide upon heating to yield the benzodipyrrole, isolated as the acetate (**140**). In the presence of tributylphosphine, equal amounts of the oxidized benzodipyrrole (**140**) and the expected compound (**141**) from the Eschenmoser reaction were isolated as their acetates.



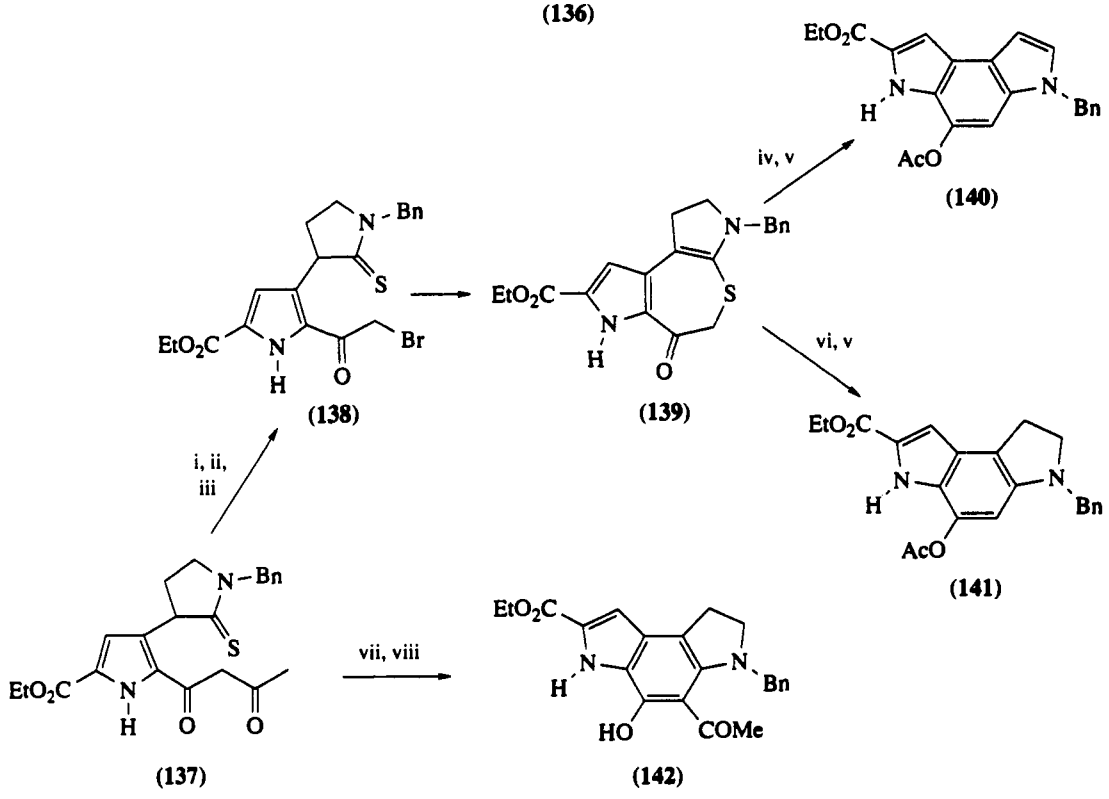
(**134**) PDE I



(**135**) PDE II



(**136**)



(**137**) (**138**) (**139**) (**140**) (**141**) (**142**)

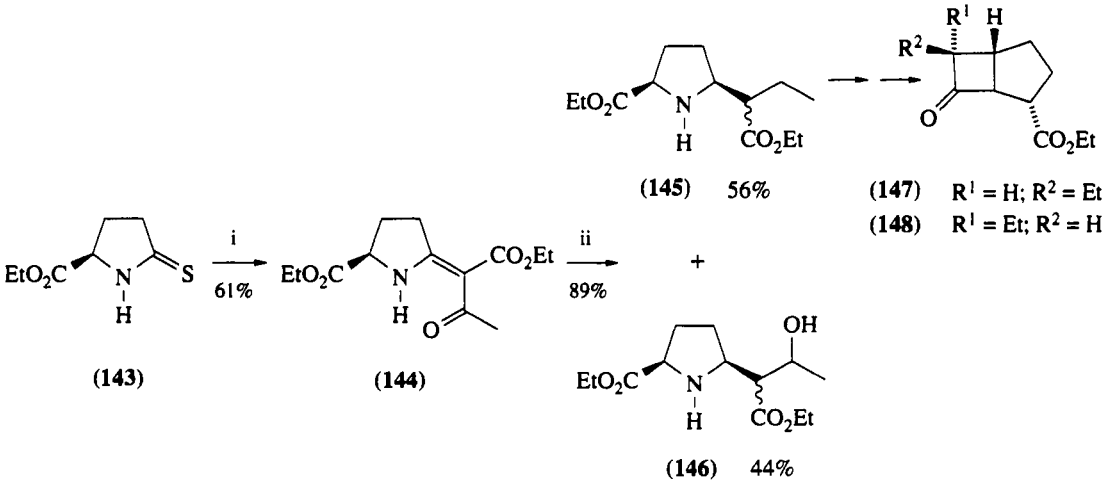
i, *p*-$NO_2C_6H_4SO_2N_3$; ii, pyrrolidine; iii, HBr or $BF_3{\cdot}Et_2O$; iv, MeCN (reflux); v, Ac_2O; vi, Bu_3P; vii, MeI or Br_2; viii, $NaHCO_3$

Scheme 30

To implement the Knoevenagel-based modification, the β-diketone derivative (**137**) was treated with methyl iodide to yield a white solid, presumed to be the α-thioiminium salt. Upon treatment of the salt with base, the expected cyclized product (**142**) was isolated in excellent yield. Likewise, the diketone (**137**) was treated with an equivalent of bromine to produce the same product. The bromine-based cyclization is believed to occur by formation of the α-bromo β-diketone and closure *via* the Eschenmoser-based mechanism. A mechanism involving bromination at the sulfur atom also would be consistent with the results.

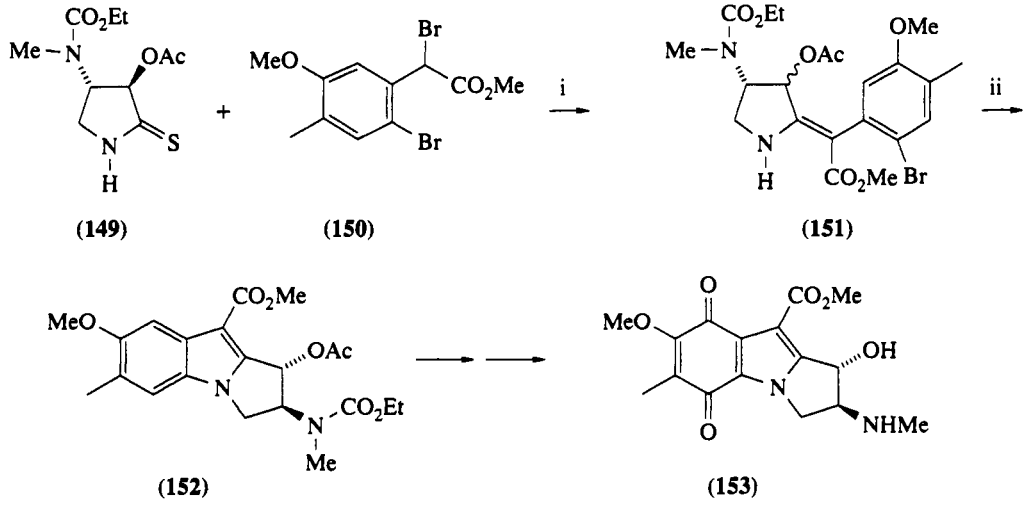
3.7.4.5 Antibiotics

A series of carbapenams have been generated using the sulfide-contraction reaction to construct the constituent β-amino acid segment.[53] The thiopyroglutamate derivative (**143**) was condensed with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to afford the α-acyl vinylogous carbamate (**144**; Scheme 31). The use of sodium bicarbonate in the sulfide contraction was critical in this particular



i, $MeCOCHBrCO_2Et$, $NaHCO_3$; ii, PtO_2, 20% TFA/$MeCO_2H$

Scheme 31

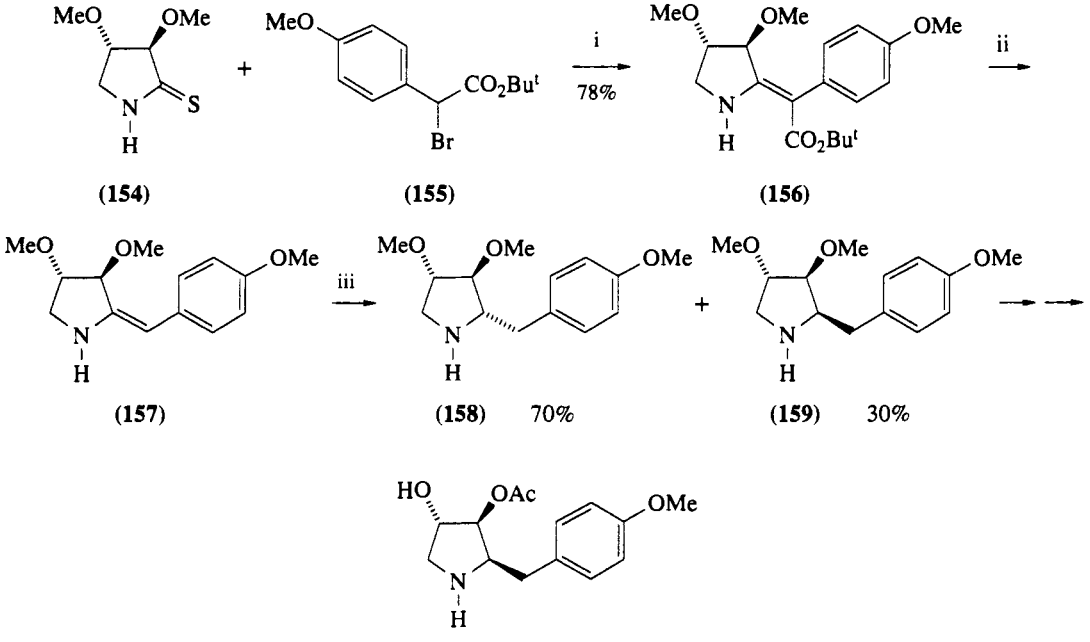


i, DBU; ii, NaH, CuBr

Scheme 32

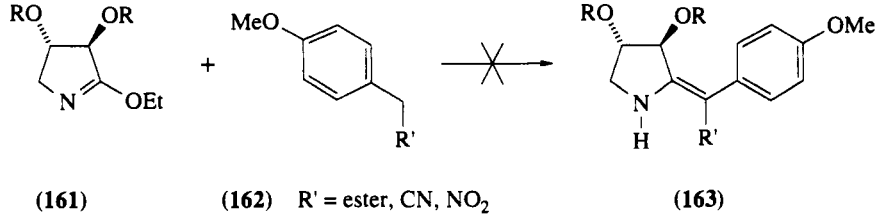
example; stronger bases such as triethylamine, sodium carbonate, sodium hydride and sodium methoxide gave significantly lower yields of the vinylogous carbamate (**144**). The tetrasubstituted, cross-conjugated double bond was quite resistant to standard reducing conditions, although reduction was finally achieved using platinum in 20% TFA/acetic acid. The reduction effectively established the *cis* stereochemistry about the pyrrolidine nucleus but produced a mixture of the desired epimeric saturated ethyl isomers (**145**) along with the hydroxyethyl compounds (**146**). The mixture of fully reduced isomers (**145**) was cyclized to the carbapenams (**147**) and (**148**).

The mitomycins are a class of antitumor antibiotics that has been the target of numerous synthetic efforts. The Eschenmoser reaction was a key coupling step in the synthesis of a mitomycin intermediate, apomitomycin (**153**).[54] Thiopyrrolidinone (**149**) was alkylated with the aryl bromoacetate (**150**), and the intermediate α-thioiminium salt was heated with DBU (Scheme 32). The desired condensation product (**151**) was obtained in excellent yield, although epimerization about the pyrrolidine ring had occurred to produce a 1:1 mixture of the *cis* and *trans* substituted diastereomers. Note that, in contrast to α-alkyl-substituted electrophiles, which require conversion to triflates for complete thioamide alkylation, the more reactive benzylic bromide in (**150**) gave efficient alkylation. The key intermediate (**151**) was cyclized in the presence of sodium hydride and copper(I) bromide to yield a single product (**152**) in nearly quantitative yield. Epimerization to the more stable *trans* isomer occurred under the cyclization conditions. This intermediate was readily converted to the final product (**153**).



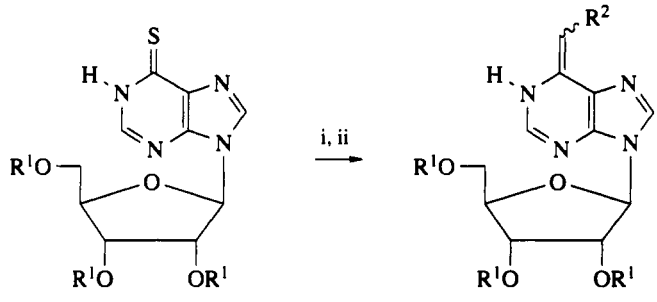
i, $(MeO)_3P$, $KOBu^t$; ii, TFA; iii, H_2, PtO_2

Scheme 33



Scheme 34

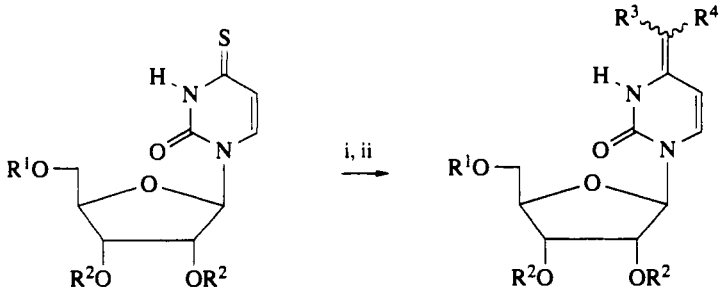
The synthesis of the antibiotic anisomycin (**160**)[55] provides another example of the efficient alkylation of a thioamide with an α-bromoarylacetate. Thiolactam (**154**) was alkylated with α-bromo ester (**155**) followed by sulfide contraction to generate the vinylogous carbamate (**156**) in good yield (Scheme 33). In contrast, initial attempts to condense the imidate of the dimethoxylactam (**161**) with various aryl components (**162**) met with failure that was attributed to the steric hindrance created by the alkoxy groups (Scheme 34). The vinylogous carbamate (**156**) was converted to the acid, which decarboxylated to the enamine (**157**). Reduction yielded a 70:30 mixture of pyrrolidines (**158**) and (**159**) and the latter was converted to anisomycin.



(164) (165) (10)

Table 6 Preparation of Substituted Purines (equation 10)[56]

R^1	*i*	*ii*	R^2	*Yield* (%)
Ac	$BrCH_2COPh$	Bu^tOK, Ph_3P	COPh	77
Ac	$BrCH_2CO_2Bu^t$	LDA, Ph_3P	CO_2Bu^t	88
Ac	$BrCH_2C_6H_4$-4-NO_2	LDA, Ph3P	4-$NO_2C_6H_4$	78



(166) (167) (11)

Table 7 Preparation of Substituted Thiopyrimidines (equation 11)[57]

R^1	R^2	*i*	*ii*	R^3	R^4
H	H	$BrCH_2COPh$	Ph_3P, Bu^tOK or pyridine (reflux)	COPh	H
H	H	$BrCH_2COMe$	Ph_3P, Bu^tOK	COMe	H
H	Acetonide	$BrCH(CO_2Et)_2$	$NaHCO_3$, CO_2	CO_2Et	CO_2H
Ac	Acetonide	$BrCH_2CO_2Et$	NaH, Ph_3P	CO_2Et	H

3.7.4.6 Nucleoside Analogs

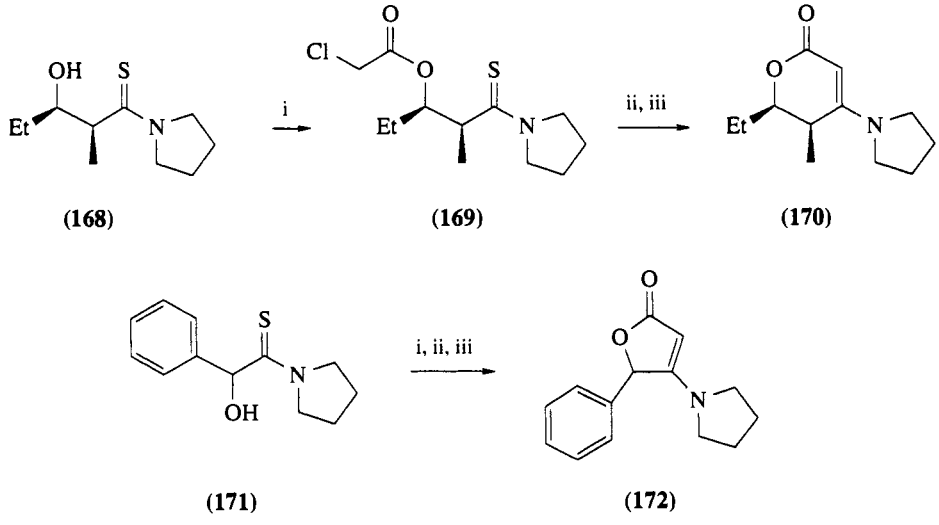
The sulfide-contraction process is ideally suited to introduce carbon substituents at various positions of purines and pyrimidines in nucleosides.[56,57,58] Typically, a thio-purine or -pyrimidine was *S*-alkylated with electrophiles such as phenacyl bromide, ethyl bromoacetate or diethyl bromomalonate and then

treated with base and a thiophile (not always required) to produce the corresponding carbon-extended nucleoside (equations 10 and 11). Several representative examples of this application are listed in Tables 6 and 7.

3.7.4.7 Macrocycles

The Eschenmoser coupling reaction has demonstrated its utility repeatedly in the preparation of various nitrogen-containing compounds of interest. However, its application in synthesizing wholly carbon-based targets has been accomplished as well. A masked β-keto ester resides within the vinylogous carbamate, the product of the sulfide-coupling reaction, which can be unveiled upon mild hydrolysis. This aspect of vinylogous carbamates was applied toward the synthesis of a macrocyclic lactone, diplodialide A, by performing the key macrocyclic ring closure *via* an intramolecular Eschenmoser coupling reaction.[20] A separate study also exploited this feature of vinylogous carbamates and culminated in the development of a general method for preparing substituted β-keto esters and nitriles.[21]

The preparation of substituted five- and six-membered lactones served as a model system to examine the feasibility of this novel ring-forming strategy. A hydroxythioamide (**168**) was allowed to react with chloroacetyl chloride, and the resulting α-chloro ester (**169**) was treated with sodium iodide and the Eschenmoser dual base–thiophile reagent (**28**) to afford the cyclic enamino lactone (**170**) in high yield (Scheme 35). No epimerization of the lactone was observed. Likewise, the five-membered enamino lactone (**172**) resulted from reaction of the hydroxythioamide (**171**) with chloroacetyl chloride followed by sulfide contraction.

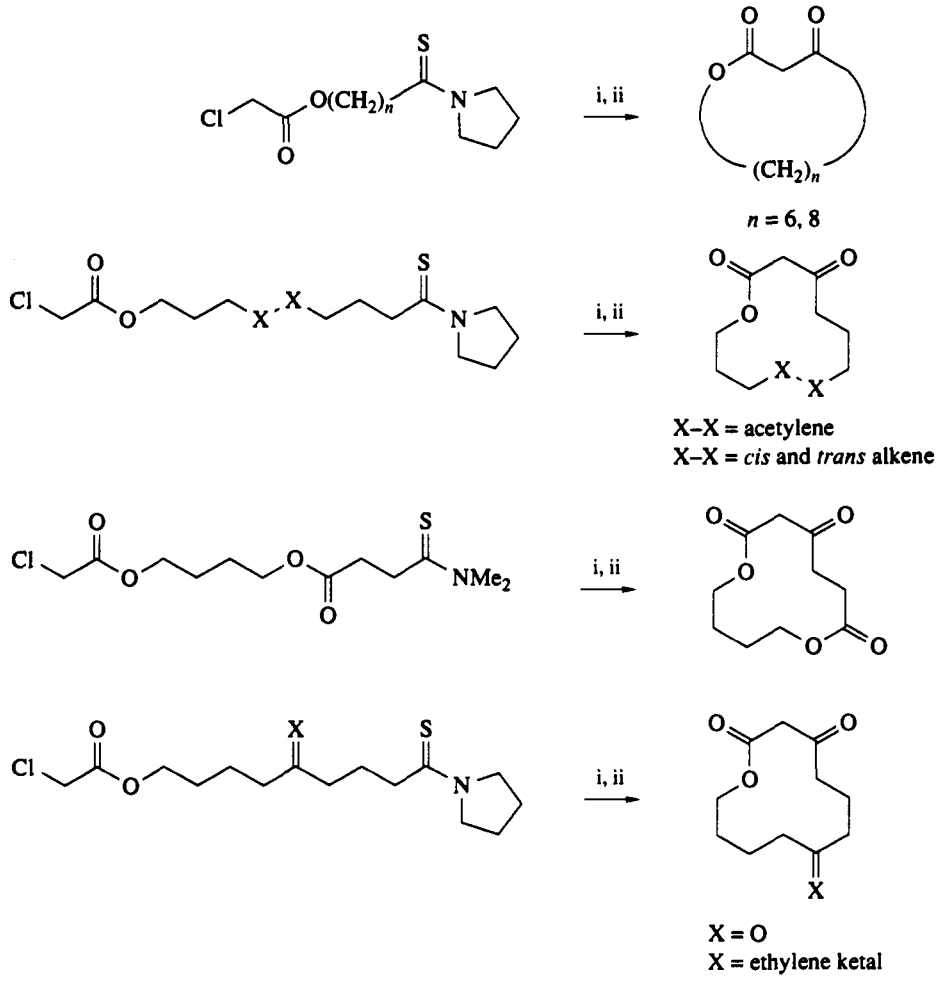


i, $ClCH_2COCl$; ii, NaI; iii, $PhP[(CH_2)_3NMe_2]_2$

Scheme 35

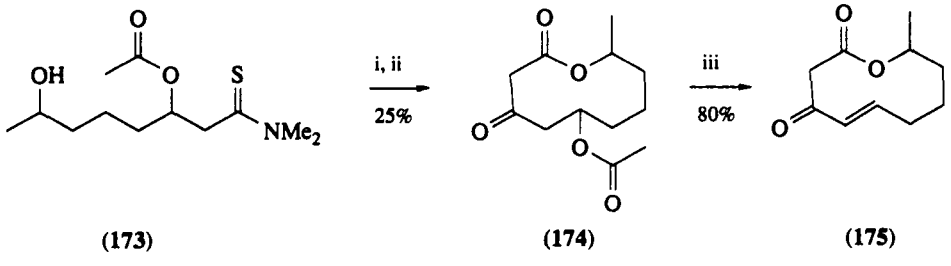
Unfortunately, the synthesis of larger ring systems could not be achieved under the above conditions. A modification was therefore developed, previously described in Section 3.7.2.1, that exposed the cyclic α-thioiminium salt as it was being formed to the sulfur-extruding reagents. The preformed α-chloro ester was added to a refluxing solution of sodium iodide, diisopropylethylamine and triethyl phosphite in acetonitrile. Aqueous work-up unveiled the β-keto ester to produce the 10- and 12-membered macrolides in moderate yields (Scheme 36). These conditions were compatible with incorporation of alkynic, alkenic and other functional groups within the macrocycle. A limitation of this method is the inability to construct seven-membered ring systems.

The foregoing conditions were applied successfully in the synthesis of diplodialide A (**175**; Scheme 37). Since earlier studies had demonstrated that the sulfide-contraction conditions were not compatible with α,β-unsaturated thioamides, the β-acetoxy precursor (**173**) was used instead. The intramolecular sulfide-contraction reaction successfully accomplished the cyclization to generate the β-keto lactone (**174**) in modest yields. Elimination of the acetoxy group yielded diplodialide A (**175**).



i, NaI, $P(OEt)_3$, Pr^i_2NEt, MeCN (reflux); ii, H^+, H_2O

Scheme 36



(173) **(174)** **(175)**

i, $ClCH_2COCl$, pyridine; ii, NaI, $P(OEt)_3$, Pr^i_2NEt, MeCN (reflux); iii, Pr^i_2NEt, MeCN (reflux)

Scheme 37

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4.1
The Bimolecular Aliphatic Mannich and Related Reactions

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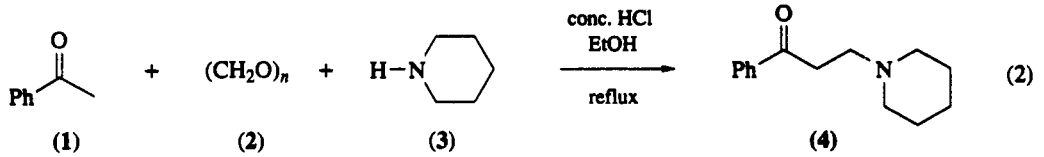
4.1.1 BACKGROUND — THE CLASSICAL MANNICH REACTION

4.1.1.1 Introduction

The Mannich reaction is the prototype of carbon–carbon bond forming reactions that involve the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines. In its original and most widely recognized form, the Mannich reaction consists of three components: (i) ammonia, a primary amine, or a secondary amine; (ii) a nonenolizable aldehyde, usually formaldehyde; and (iii) an active

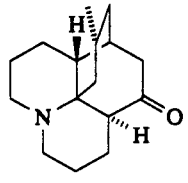
methylene compound. These components condense with concomitant release of water to produce a new base, known as a 'Mannich base', in which the active hydrogen is replaced by an aminomethyl group (equation 1). A typical example is the reaction of acetophenone (**1**), paraformaldehyde (**2**) and piperidine (**3**) to produce phenyl β-piperidinoethyl ketone (**4**; equation 2). The formation of both a carbon–carbon and a carbon–nitrogen bond in this aminomethylation process makes the Mannich reaction an extremely useful synthetic transformation. In addition, Mannich bases have important synthetic applications as intermediates for other compounds. They also occur in natural products such as the alkaloids lycopodine (**5**), cocaine (**6**) and elaeocarpine (**7**).

(1)



(2)

(1) (2) (3) (4)



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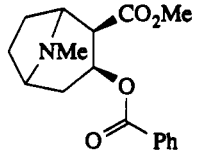

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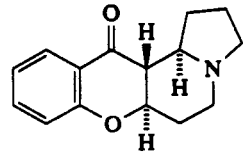


(7)

4.1.1.2 Earlier Reviews and Scope of this Chapter

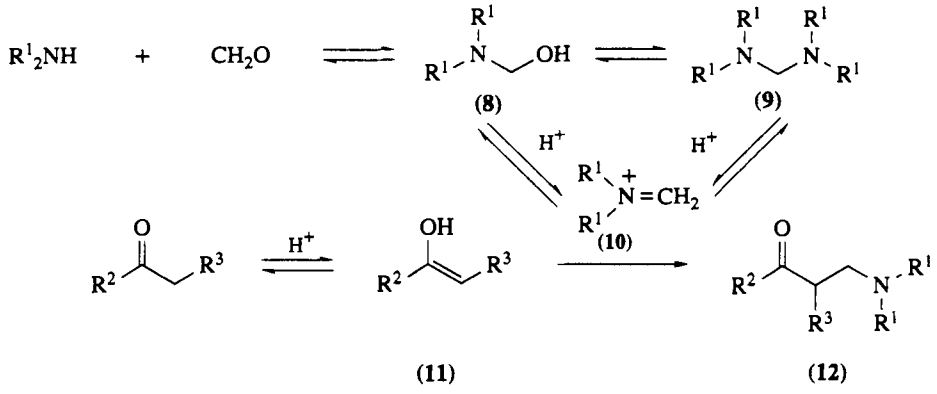
The Mannich reaction has been reviewed comprehensively by Blicke (1942),[1] Reichert (1959),[2] Hellmann and Opitz (1960),[3] and Tramontini (1973).[4] These reviews also include synthetic applications of Mannich bases. Mechanistic studies of the Mannich reaction have been reviewed by Thompson (1968).[5] Some variants of the Mannich reaction have been covered as subtopics in other reviews; for example, Layer (1963)[6] and Harada (1970)[7] have reviewed general additions of stabilized carbanions to imines, while Böhme and Haake (1976)[8] have reviewed similar additions to methyleneiminium salts. In more specific reviews, Pai and coworkers (1984)[9] have summarized stabilized carbanion additions to 3,4-dihydroisoquinolines and 3,4-dihydroisoquinolinium salts in connection with the total synthesis of protoberberines and phthalide isoquinolines, and Evans *et al.* (1982)[10] have analyzed the stereochemical aspects of ester enolate and silyl ketene acetal additions to imines.

Since 1973, when the last comprehensive review of the Mannich reaction appeared,[4] there has been an explosive growth in the variant of this reaction that employs preformed iminium salts and imines for the synthesis of Mannich bases. The use of preformed iminium salts and imines, some examples of which date back to the turn of the century, has had a renaissance in recent years primarily because of the advent of modern enolate chemistry, *e.g.* formation of enolates under kinetic control and the use of enol silanes with Lewis acid catalysis. As a result, there have been two major advances in the synthesis of Mannich bases: (i) the development of extremely mild conditions, enabling the use of highly functionalized substrates; and (ii) increasing control of regiochemistry and stereochemistry, two aspects of the Mannich reaction that had been virtually ignored prior to the 1970s. Because of the recent impact which preformed iminium salts and imines have had on the Mannich reaction, this review focuses almost entirely on their applications, which comprise the next two sections. Each of the subsections is arranged according to the type of N-substitution because of the important role N-substituents play in the reactivity of the iminium salt or imine and in the elaboration of the Mannich base. Cyclic preformed iminium salts and imines and *in situ* methods for the formation of imines are also included as subsections. Additional divisions of subsections are used where the literature is more extensive, especially in Sections 4.1.2.2 and 4.1.3.2, and

are arranged according to the nature of the active methylene compound. Every attempt has been made to cite review articles covering prior work with the intent of providing the reader with both a direct and an indirect avenue to all of the literature pertaining to the bimolecular Mannich reaction. Due to the number of excellent review articles of the classical tricomponent Mannich reaction and to the lack of significant new methodology (see, however, Section 4.1.1.5), only a brief overview is given. This overview includes a discussion of the scope and limitations of the classical Mannich reaction as a prelude to the more recent methodology. The reader should note that Mannich reactions involving aromatic hydrogen donors are covered in Chapter 4.2.

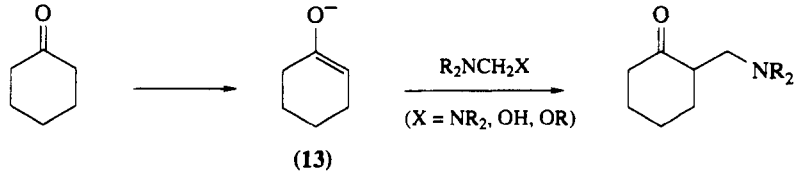
4.1.1.3 Mechanism

A detailed account of the mechanism of the Mannich reaction and factors that affect the selection of conditions has been written by Thompson.[5] Only the salient features of the mechanism are given here. For the conditions under which the Mannich reaction is most commonly performed, *i.e.* protic solvents and acid catalysis (usually by employing the amine component as its hydrochloride salt), the mechanism is thought to involve the intermediacy of a highly reactive, positively charged iminium ion (**10**), which reacts with the active methylene component in its enol form (**11**) to produce the Mannich base (**12**; Scheme 1). This step has an obvious parallel to the aldol condensation. Formation of (**10**) occurs by decomposition of a methylenediamine (**9**) or, to a lesser extent, a hydroxymethylamine (**8**), both of which are generated reversibly by condensation of the aldehyde and amine components. Acid catalysis not only promotes the decomposition of (**8**) and (**9**) to the iminium salt (**10**), but also the enolization of the active methylene component. Protic solvents, by virtue of their high dielectric constant, also support the formation of the charged iminium species. Elevated temperatures are often necessary for generation of sufficient concentrations of iminium ions.



Scheme 1

In Mannich reactions performed in basic media, the active aminomethylating species is less well defined. It may be a methylenediamine (**9**), a hydroxymethylamine (**8**), or an alkoxymethylamine ($ROCH_2NR_2'$) (in alcoholic solvents). Aminomethylation in base-catalyzed Mannich reactions, as shown for cyclohexanone, is believed to occur by an S_N2 mechanism in which the enolate (**13**) displaces either NR_2^-, OH^-, or OR^- from one of the intermediates above (Scheme 2).



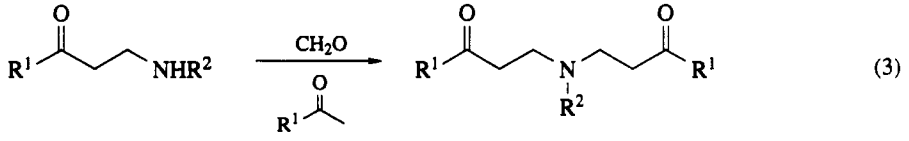
Scheme 2

Depending upon the nature of the substrates involved, the Mannich reaction may be reversible. In cases where isomeric products are possible, product ratios may therefore reflect thermodynamic factors.

4.1.1.4 Scope and Limitations

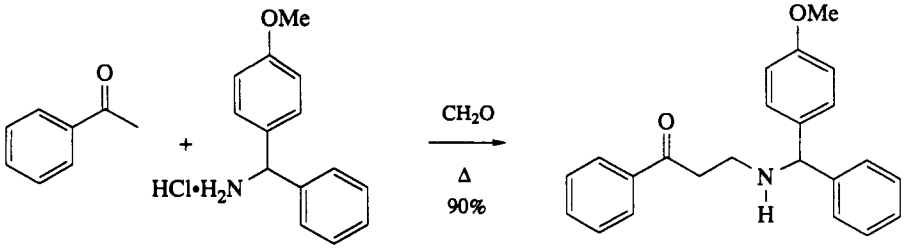
Active methylene compounds ranging in acidity from β-keto esters, malonates and nitroalkanes (pK_a = 9–13) to ketones (pK_a = 16–20) can be used in the Mannich reaction. The lack of examples using simple unactivated esters (pK_a = 25) appears to be due to their weaker acidity or to transamination and/or hydrolysis side reactions. Enolizable aldehydes have also been used in certain instances; however, side products arising from subsequent aldol condensation of the resulting β-amino aldehyde often occur. Best results are achieved with α-branched aldehydes, which produce Mannich bases without enolizable protons.

Of the amine components that may be used, secondary amines react the most predictably and in the highest yields, giving tertiary Mannich bases. Here steric factors are important since reactions employing dimethylamine and cyclic amines tend to be more successful than those employing bulkier secondary amines. With primary amines, yields are more unpredictable because the initially formed secondary Mannich base (**14**) can further react to give a tertiary amine (**15**; equation 3). Bulky primary amines[11] and, interestingly, use of amine oxalate salts[12] instead of hydrochloride salts tend to suppress these cross-condensation reactions. The use of ammonia for the synthesis of primary Mannich bases is more complicated because of the greater likelihood of obtaining products derived from multiple substitution. The synthesis of primary Mannich bases can be achieved indirectly, however, by condensing a bulky primary amine containing a cleavable alkyl group. As shown in Scheme 3, benzhydrylamine (**16**) condenses cleanly with acetophenone (**1**) to give a secondary Mannich base (**17**), which upon deprotection affords primary Mannich base (**18**; Scheme 3).[11]

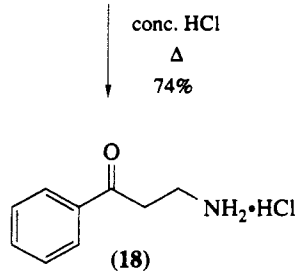


(3)

(14) (15)



(1) (16) (17)

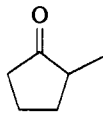
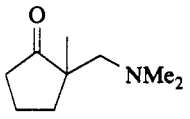
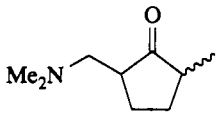
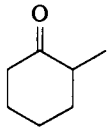
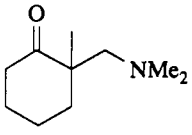
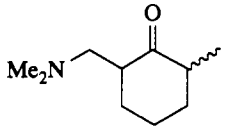
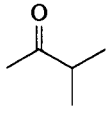
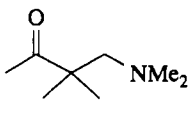
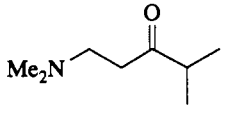


(18)

Scheme 3

In cases involving unsymmetrical ketones, mixtures of regioisomeric Mannich bases are usually obtained. As shown in Table 1, aminomethylation occurs predominantly at the site containing the fewest α-hydrogens, reflecting the thermodynamic stability of the corresponding enols.[13]

Table 1 Mannich Reactions of Unsymmetrical Ketones

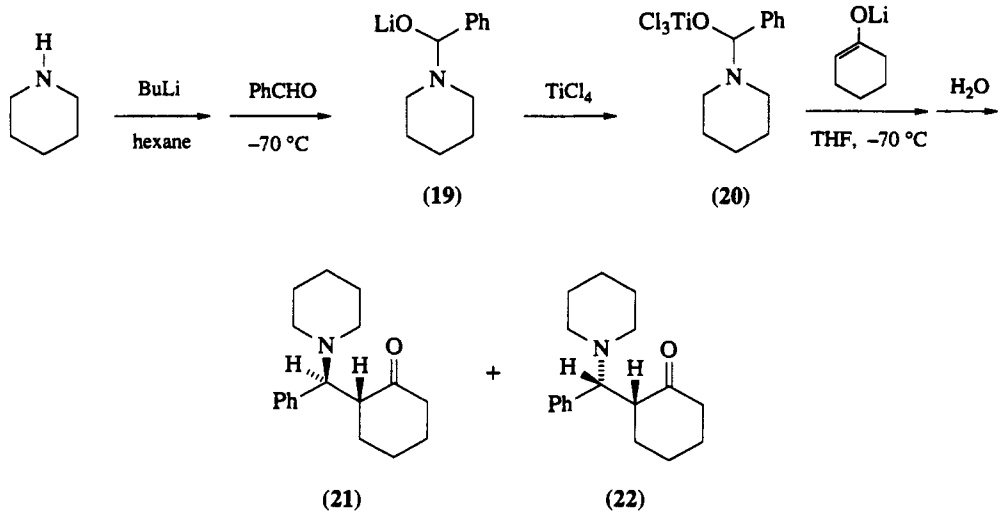
Ketone	*Products*		*Ratio*	*Ref.*
			>4:1	13
			7:3	13
			3.5:1	14

In addition to the side reactions mentioned above, deamination of Mannich bases can occur, especially at elevated temperature, to give α,β-unsaturated derivatives. This route of decomposition of Mannich bases has been exploited as a means of *in situ* generation of α,β-unsaturated ketones in the Michael reaction[15] and for the direct synthesis of α,β-unsaturated ketones; several reviews of the Mannich reaction have discussed aspects of these applications.[1–4] Recently, a direct 'one-pot' synthesis of α-methylene ketones has been reported involving condensation of ketones with formaldehyde and *N*-methylaniline trifluoroacetate in aprotic solvents.[16] Also, a less direct method has been described in which Mannich bases prepared from β-keto esters, formaldehyde and dimethylamine are subjected to quaternarization and thermal fragmentation to yield α-methylene ketones.[17] This method is particularly useful for the regiospecific synthesis of α-methylene ketones because the aminomethylation reaction always takes place at the most activated position flanked by the ketone and ester groups.

Bisaminomethylation, occurring when the active methylene compound contains more than one acidic hydrogen, is another possible side reaction. Reported cases of bisaminomethylation are rather infrequent, however, suggesting that the protonated β-ammonium group slows down the rate of enolization of the Mannich base relative to the unreacted active methylene compound. Thermodynamic factors reflected in the steric congestion of the bisaminomethylated product may also be important.

4.1.1.5 New Modifications

An interesting $TiCl_4$-mediated modification of the classical tricomponent Mannich reaction using aprotic solvents and low temperatures has recently been reported by Seebach *et al.*[18,19] The reaction is carried out as illustrated in Scheme 4 for the condensation of cyclohexanone, piperidine and benzaldehyde. Piperidine is first deprotonated with *n*-butyllithium and then condensed with benzaldehyde to give a lithium alkoxide (**19**), which is converted to a titanium alkoxide (**20**) by treatment with $TiCl_4$. Condensation of (**20**) at −70 °C with the preformed enolate of cyclohexanone then yields diastereomeric Mannich bases (**21**) and (**22**) (4:1 mixture). The preference for *lk*-addition,[20] favoring diastereomer (**21**), appears to be common to these reactions. The reaction is general for other enolates, including those of acetone, acetophenone and *t*-butyl acetate. Besides benzaldehyde, enolizable aldehydes such as *n*-pentanal can also be used as aldehyde components. Yields are generally good (60–80%) except in cases involving bulky, acyclic amines. Although this reaction is more tedious to perform than the classical Mannich reaction, it has the advantage of requiring milder conditions and permitting the use of enolizable aldehydes and less acidic active methylene compounds such as esters. The mechanism of the reaction needs further clarification, as it is not known whether titanium alkoxides or iminium salts are the reactive aminomethylating species.



78%; (**21**):(**22**) = 4:1

Scheme 4

4.1.2 USE OF PREFORMED IMINIUM SALTS

4.1.2.1 Introduction

A vast improvement in the scope and efficiency of the Mannich reaction has been achieved using preformed iminium salts. In this variant of the classical Mannich reaction the iminium salt, rather than being generated under equilibrium conditions, is preformed separately and is condensed with the active methylene component in a second step. Higher concentrations of iminium salts than those generated under the reversible conditions of the classical Mannich reaction are achieved; consequently, reactions with preformed iminium salts are faster and can be run under far milder conditions. Another advantage is that reactions employing preformed iminium salts can be carried out in aprotic solvents, permitting regiospecifically generated enolates and enol silanes to be used as active methylene components. From a practical standpoint, preformed iminium salts can be conveniently stored and weighed in stoichiometric amounts, although some tend to be hygroscopic and must be stored in a dry atmosphere to preserve their reactivity.

4.1.2.2 Acyclic *N,N*-Dialkyliminium Salts

4.1.2.2.1 General

Pioneering investigations by Böhme *et al.* into the synthesis, properties and reactions of preformed iminium salts have provided much of the basis for their recent applications in organic synthesis. These and related investigations are described in his extensive review on 'Methyleneiminium Salts',[8] covering work up to the early 1970s.

Of the numerous methods reported by Böhme *et al.* for the synthesis of preformed iminium salts, the most general and convenient involves cleavage of methylenediamines (**23**) by acyl halides (**24**) or alkyl chlorocarbonates (**25**), providing preformed iminium salts (**26**) in quantitative yield and in near analytical purity (equation 4).[21] The by-product of these reactions, a dialkylamide (**27**) or a dialkylurethane (**28**), is easily removed since it remains in solution during precipitation of the iminium salt. The ionic nature of iminium salts produced by this method is well established, although an equilibrium between the

ionic and covalent forms cannot be ruled out (Figure 1). The term 'α-haloamine', which is sometimes used synonymously with iminium salts, can be misleading.

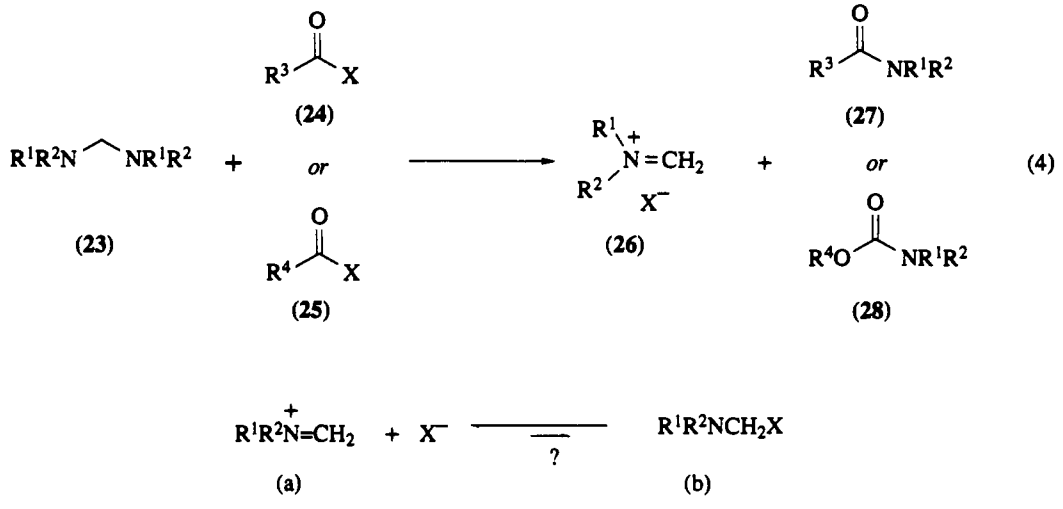


Figure 1 (a) Ionic and (b) covalent forms of iminium salts

Once isolated, the iminium salt can undergo addition reactions with a variety of carbon nucleophiles. Most of the early examples of these reactions were confined to the use of highly acidic active methylene compounds (pK_a = 9–13), and some representative examples are shown in Table 2. It should be noted that less acidic ketone and ester substrates have been used more extensively in reactions with *N,N*-dimethyl(methylene)iminium salts; these reactions will be discussed separately in the next section. With malonates, cyano esters, β-diketones, triesters, nitroalkanes and β-disulfones (entries 1–7), the reaction is normally performed using the sodium enolate in MeCN or DMF and at elevated temperature. With the more reactive dithiane anion (entry 8), the reaction occurs at much lower temperature (–30 °C). Some examples have also been reported using iminium salts bearing α-carboxamide and α-carboethoxy groups. These more electrophilic iminium salts react with aryl ketones directly in refluxing CH_2Cl_2 without catalysis (entry 9); less acidic alkyl ketones (entry 10) and aldehydes, on the other hand, must be activated as enamine derivatives. It should be noted that the preformed iminium salts used in these examples are limited to those that do not bear α-hydrogens. 'Enolizable' iminium salts (**29**) (*i.e.* those with α-hydrogens) fail in these reactions due to deprotonation to give the enamine (Figure 2).[25]

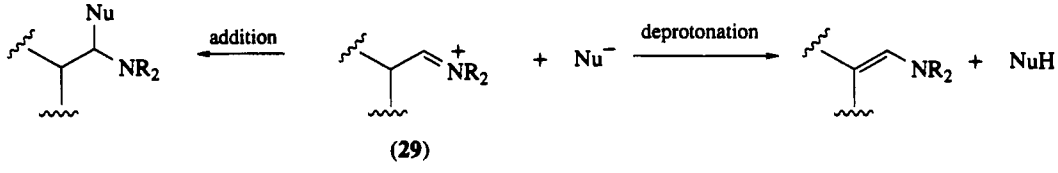


Figure 2 Competitive deprotonation in the reactions of enolizable iminium salts

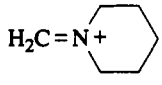
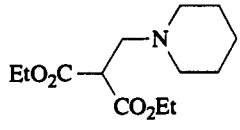
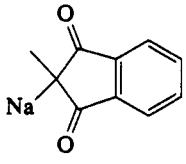
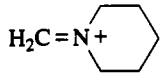
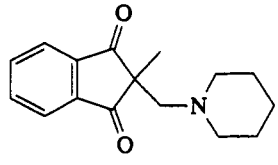
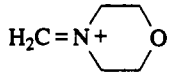
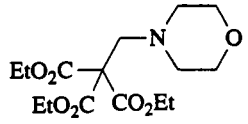
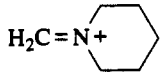
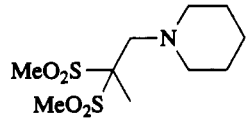
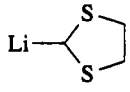
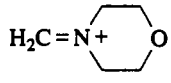
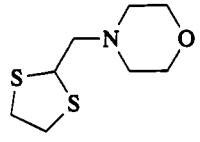
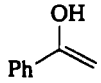
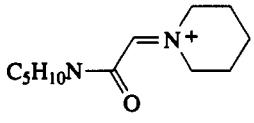
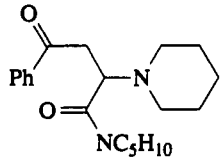
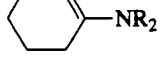
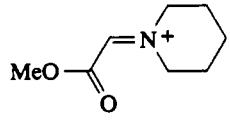
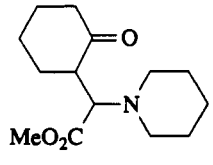
4.1.2.2.2 N,N-*Dimethyl(methylene)iminium salts*

(i) Preparation and in situ *methods*

N,N-Dimethyl(methylene)iminium salts have been the most widely used class of preformed iminium salts, mainly due to their applications in the synthesis of α,β-unsaturated carbonyl compounds, normally accomplished by subjecting the *N,N*-dimethyl Mannich base to quaternarization followed by base-induced elimination. Table 3 outlines various counterion forms of *N,N*-dimethyl(methylene)iminium salts that have been used in Mannich reactions as well as their synthetic precursors. The crystalline iodide (**30**), known also as 'Eschenmoser's salt', has seen the most widespread use and is prepared by thermal fragmentation of (iodomethyl)trimethylammonium iodide[27] or, more conveniently, by a variant of the

Böhme procedure involving cleavage of *N,N,N',N'*-tetramethyl(methylene)diamine (**34**) with TMS-I.[28] Cleavage of (**34**) with acetyl chloride in analogy to the Böhme procedure furnishes the crystalline chloride (**31**),[29] as does cleavage of methyl dimethylaminomethyl ether with methyltrichlorosilane.[30] The trifluoroacetate (**32**), unlike the iodide or chloride, is a liquid and is prepared by Polonovski reaction of

Table 2 Addition Reactions of Carbon Nucleophiles to Preformed Iminium Salts

Entry	*Nucleophile*	*Iminium salt*	*Product*	*Yield*	*Ref.*
1	$NaC(Me)(CO_2Et)_2$	$H_2C{=}N^+Et_2\ Cl^-$	$(EtO_2C)_2C(Me)CH_2NEt_2$	70	22
2	$NaCH(CO_2Et)_2$			a	22
3	$NaC(Me)(CN)CO_2Et$	$H_2C{=}N^+Et_2\ Cl^-$	$EtO_2CC(CN)(Me)CH_2NEt_2$	a	22
4				a	22
5	$NaC(CO_2Et)_3$			40	23
6	$NaCH_2NO_2$	$H_2C{=}N^+Et_2\ Cl^-$	$NO_2CH_2CH_2NEt_2$	49	22
7	$NaC(Me)(SO_2Me)_2$			57	24
8				54	25
9				93	26
10				65	26

[a] No yield given.

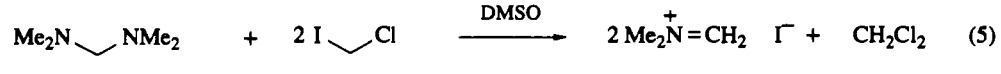
trimethylamine oxide with TFAA.[31,32] The triflate (**33**), prepared by treating chloride (**31**) with TMS-OTf, has been recently introduced for use in reactions with 2-silyloxycyclopropanecarboxylates.[33,34]

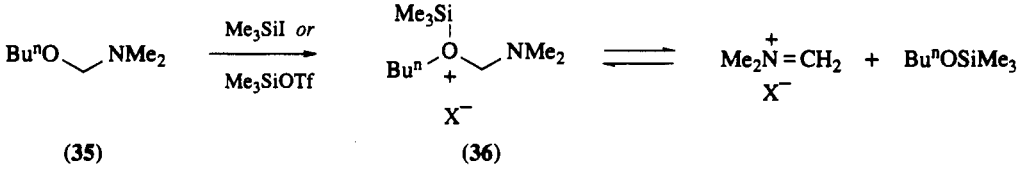
Table 3 Preformed Dimethyl(methylene)iminium Salts and Their Preparation

Iminium salt	*Precursor*	*Conditions*	*Ref.*
$[Me_2N{=}CH_2]^+I^-$ (**30**)	$[Me_3NCH_2I]^+I^-$ $Me_2NCH_2NMe_2$ (**34**)	Thermolysis (150 °C) TMS-I, ether, 0 °C	27 28
$[Me_2N{=}CH_2]^+Cl^-$ (**31**)	(**34**) $MeOCH_2NMe_2$	MeCOCl, CH_2Cl_2, 0 °C $MeSiCl_3$, MeCN, 25 °C	29 30
$[Me_2N{=}CH_2]^+[TFA]^-$ (**32**)	Me_3NO	TFAA, CH_2Cl_2, 0 °C	31, 32
$[Me_2N{=}CH_2]^+[OTf]^-$ (**33**)	(**31**)	TMS-OTf, CH_2Cl_2, 0 °C	33, 34

In a comparison study involving Mannich reactions of enol silanes, Holy *et al.* report that iminium salts (**30**)–(**32**) react at similar rates in DMF, where they are soluble, but in less polar solvents reduced solubility slows the rate and adversely affects the yield.[35] For this reason the more soluble trifluoroacetate (**32**) should be used in place of the iodide (**30**) or chloride (**31**) when conducting reactions in less polar solvents such as CH_2Cl_2. Iminium salts (**30**)–(**32**) must be stored in the absence of moisture, while the iodide (**30**) should be kept from light. The trifluoroacetate (**32**) is a liquid and must be distilled to remove traces of TFA, which will adversely affect reactions with enol silanes and enolates.

Two *in situ* methods for the generation of *N,N*-dimethyl(methylene)iminium salts, which are limited to reactions with enol silanes, are also available and avoid the need to handle these moisture-sensitive reagents. In the first method, iodide (**30**) is prepared *in situ* by treating *N,N,N',N'*-tetramethyl(methylene)diamine (**34**) with chloroiodomethane (equation 5);[36,37] DMSO must be used as solvent to achieve maximum yields. Cleavage of *n*-butyl dimethylaminomethyl ether (**35**) with TMS-I or TMS-OTf in MeCN comprises the second method (Scheme 5).[38] A silyloxonium ion (**36**) was originally proposed as the reactive aminomethylating species, but a recent ^{13}C NMR study of the reactions of aminol ethers with halosilanes in CD_3CN–SO_2 did detect the presence of iminium salts.[39] Use of these methods in reactions with enol silanes is discussed in Section 4.1.2.2.2.iii.



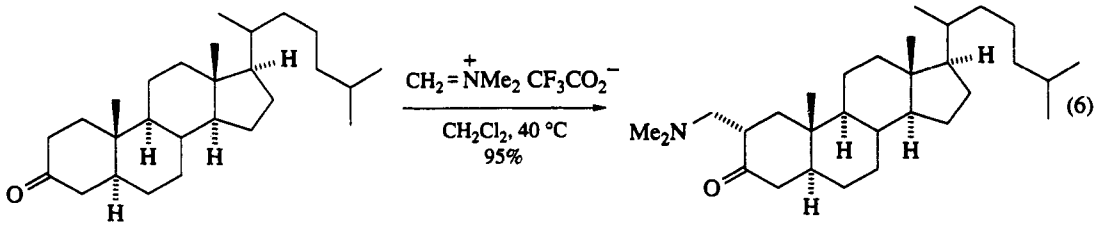


Scheme 5

(ii) Reactions with carbonyl compounds directly

Certain carbonyl compounds will react directly with *N,N*-dimethyl(methylene)iminium salts without added catalysts or special activation. It is not known to what extent the highly electrophilic iminium salt may itself act as a catalyst to promote enolization. The mechanism of enolization is an aspect of these reactions that needs further study. Temperatures required to effect aminomethylation range from 0 °C to reflux and depend on the acidity of the carbonyl compound. Early work by Potier[31,32] using steroidal ketone substrates stimulated much of the early interest in these reactions as an alternative to the classical Mannich reaction. An example is shown in equation (6), in which 5α-cholestan-3-one (**37**) reacts with iminium salt (**32**) to give the 3α-*N,N*-dimethylaminomethyl derivative (**38**) in high yield. Similar reactions of 3α-5-cyclo-5α-androstan-6-one and 3β,20α-diacetoxy-5α-pregnan-6-one also occur in high yield to give a single equatorially substituted product. The latter case is noteworthy since it is unlikely that the diacetoxy protecting groups would survive under the conditions of the classical Mannich

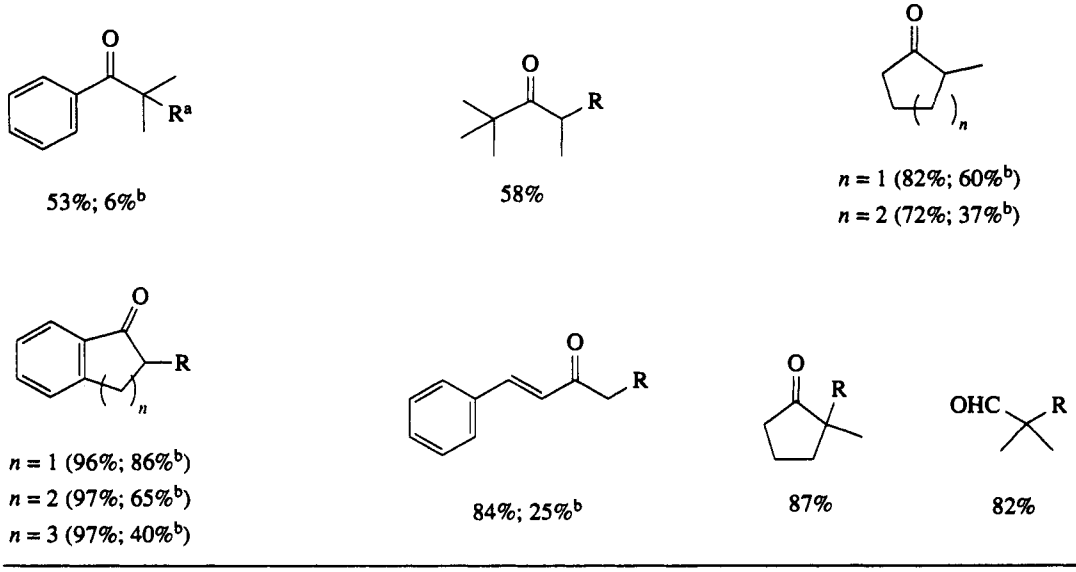
reaction. *N,N*-Dimethylaminomethylation of 8α-estrone using iminium salt (**31**) has also been reported by Neef and coworkers.[40]



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

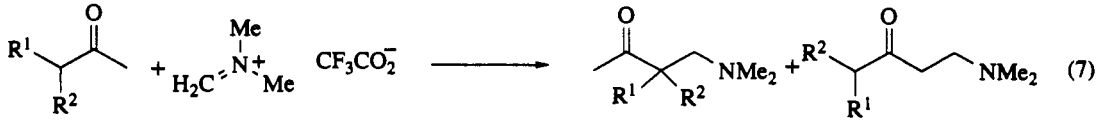
A study by Kinast and Tietze[29] has compared the yields of β-amino ketones obtained using iminium salt (**31**) in refluxing MeCN with those reported using the classical method. The ketone and aldehyde substrates used in this study and yields of the corresponding Mannich bases are shown in Table 4. The superiority of the new method is clearly demonstrated in the case of sterically crowded ketones such as α-methylpropiophenone and the enone 4-phenyl-3-buten-2-one where yields of the corresponding Mannich bases synthesized under the classical conditions are only 6%[41] and 25%,[42] respectively. Higher yields are also observed with two seven-membered ring ketone substrates, cycloheptanone and 1-benzosuberone (yields using the classical method are 37%[43] and 40%,[44] respectively). In one example involving an unsymmetrical ketone substrate, 2-methylcyclopentanone, *N,N*-dimethylaminomethylation occurs almost exclusively at the more-substituted position as in the classical Mannich reaction.[13] Other types of ketone substrates reported to react with preformed iminium salts in a superior manner to the classical method include chromanones and thiochromanones[45] and 1*H*-pyrido[3,2,1-*kl*]phenothiazines.[46]

Table 4 Yields of Mannich Reactions of Ketones and Aldehydes Using *N,N*-Dimethyl(methylene)iminium Chloride[29]



[a] R designates the site of aminomethylation. [b] Yield using the classical reaction.

In a regiochemical investigation of the reaction of iminium salt (**32**) with a series of unsymmetrical methyl ketones, Jasor *et al.* have observed that the site of aminomethylation is solvent dependent (equation 7, Table 5).[47] It is found that in MeCN, reaction occurs exclusively at the least-substituted position, while in TFA it occurs mainly at the most-substituted position. Yields are good (70–90%) in TFA but are somewhat reduced in MeCN due to dialkylation, which can be overcome if the more bulky *N,N*-diisopropyliminium salt is used. How the solvent influences the two possible rate-determining steps, enolization *versus* aminomethylation, and the extent of reversibility of the reaction need further investigation in order to determine the basis for the observed dichotomy in regiochemistry.

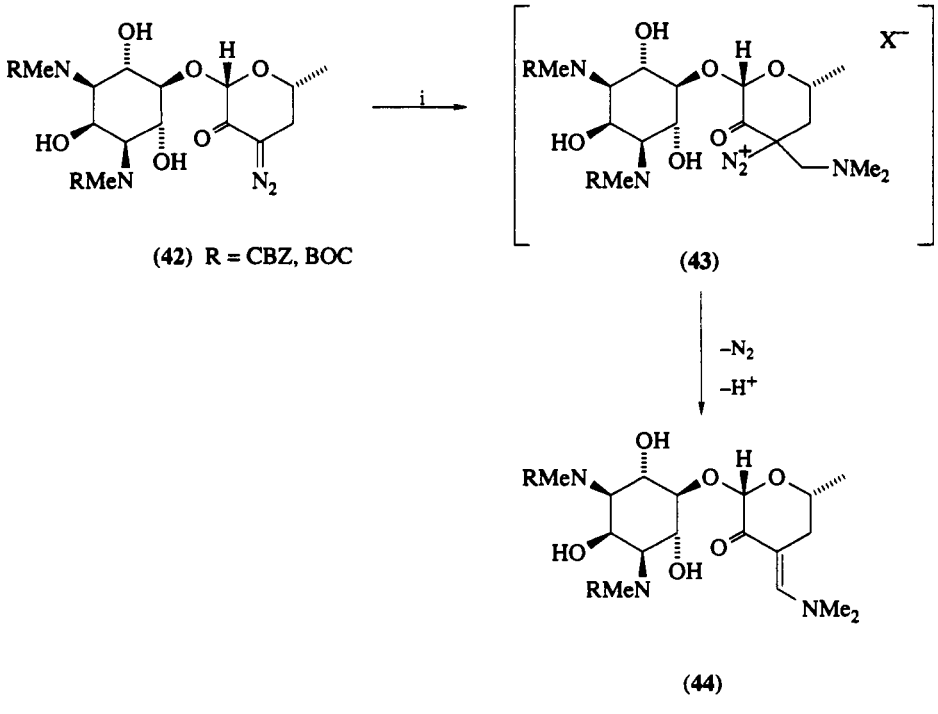


(39) (32) (40) (41) (7)

Table 5 Regioselective Mannich Reactions of Methyl Ketones (**39**) Using *N,N*-Dimethyl(methylene)iminium Trifluoroacetate (**32**) in Trifluoroacetic Acid *versus* Acetonitrile[47]

(39) *Methyl ketone*			(40)	*Mannich base* (41)
R^1	R^2	*Solvent*	*Ratio*	
—$(CH_2)_4$—		TFA	95	5
		MeCN	0	100
—$(CH_2)_5$—		TFA	69	31
		MeCN	0	100
Me	Me	TFA	85	15
		MeCN	0	100

As reported by Thomas and Fritzen, α-diazo ketones react with preformed iminium salts with loss of N_2 to afford vinylogous amides.[48] An example is shown in Scheme 6 involving an α-diazo ketone derivative (**42**) of spectinomycin, which upon treatment with salt (**31**) affords enamide (**44**) *via* the diazonium adduct (**43**). Triethylamine must be present in the reaction to prevent hydrolysis of the enamide. If the iodide salt (**30**) is used instead of the chloride salt (**31**), multiple products are obtained due to the higher reactivity of the counterion. This example elegantly portrays the degree of complex functionality which can be tolerated in Mannich reactions using preformed iminium salts.



(42) R = CBZ, BOC

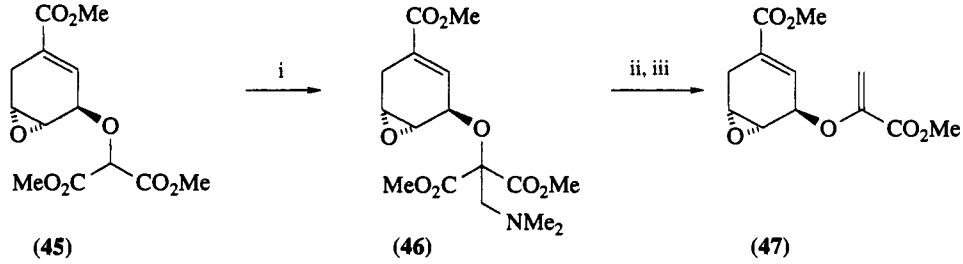
(43)

(44)

i, $CH_2{=}\overset{+}{N}Me_2\ Cl^-$, Et_3N, MeCN, 25 °C (60% for R = CBZ)

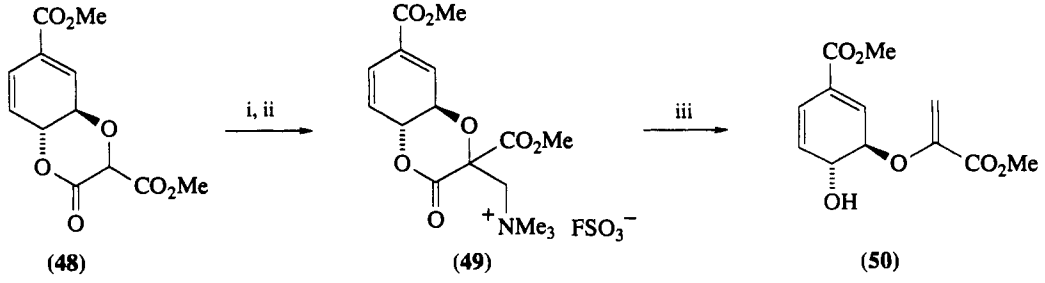
Scheme 6

Esters, which are less acidic than ketones by about 5 pK_a units, do not react directly with preformed iminium salts unless they contain activating groups to boost the acidity of the α-protons. In connection with the total synthesis of shikimate/chorismate biosynthetic metabolites, Mannich bases prepared from α-alkoxymalonates and preformed iminium salts have been employed by Berchtold and coworkers,[49a–d] Chouinard and Bartlett,[50] and Ganem and coworkers[51a–c] as synthons for the sensitive enol pyruvate moiety present in these natural products. For example, α-alkoxymalonate (**45**) is reacted with iminium salt (**30**) to provide Mannich base (**46**), which upon quaternarization and thermal fragmentation yields enol pyruvate (**47**; Scheme 7).[49c] It is noteworthy that during this transformation the epoxycyclohexene ring remains intact, a tribute to the mild conditions of these types of Mannich reactions. In a synthesis of (±)-dimethyl chorismate (**50**) using the more sensitive cyclohexadiene substrate (**48**), Ganem *et al.* have found it necessary to employ the less nucleophilic TFA salt (**32**) instead of the iodide salt (**30**) due to aromatization, probably induced by attack of iodide on the ring (Scheme 8).[51a] The resulting Mannich base is quaternarized to give (**49**), which is converted directly to (±)-dimethyl chorismate (**50**) upon base-induced fragmentation. A similar transformation involving an α-carboxylactone has been used by Landsbury and Mojica in the total synthesis of (±)-arteannuin B to introduce an α-methylenelactone moiety.[52] As demonstrated by Tarzia *et al.*, *N,N*-diphenylmethyleneglycinate esters (**51**) are another class of activated esters which add directly to *N,N*-dimethyl(methylene)iminium salts (Scheme 9).[53] The resulting Mannich base (**52**) is a convenient synthon for the α-aminoacrylate derivative (**53**), obtained by elimination of the *N,N*-dimethylamino group.



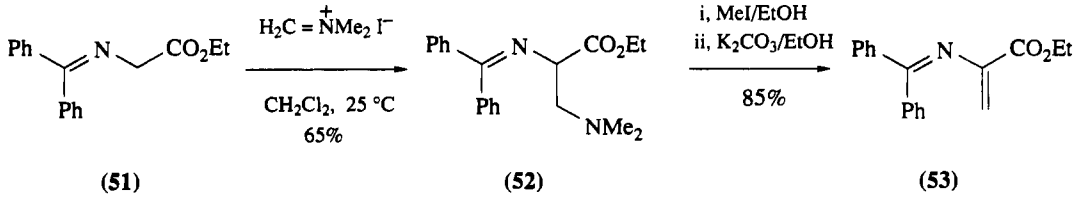
i, $CH_2{=}\overset{+}{N}Me_2\ I^-$, Et_3N, CH_2Cl_2, 25 °C; ii, MeI, CH_2Cl_2, 25 °C; iii, DMSO, 80 °C (25% overall)

Scheme 7



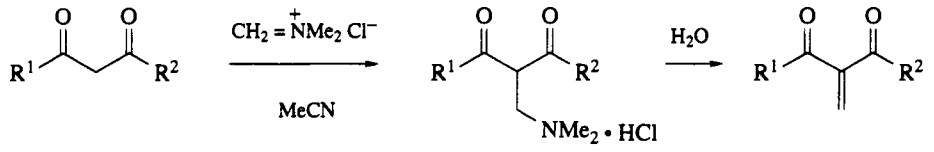
i, $CH_2{=}\overset{+}{N}Me_2\ TFA^-$; ii, $MeOSO_2F$ (37%); iii, NaOH, H_2O, 0 °C (25%)

Scheme 8



Scheme 9

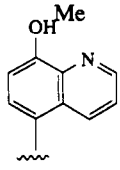
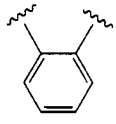
In addition to activated esters, Möhrle and Schaltenbrand have shown that β-diketones (**54**) add readily to preformed iminium salts (Scheme 10; Table 6).[54] The HCl salt (**55**) of the resulting Mannich base can be isolated under anhydrous conditions but in water it spontaneously eliminates to give an α-methylene β-diketone (**56**).



(**54**) (**55**) (**56**)

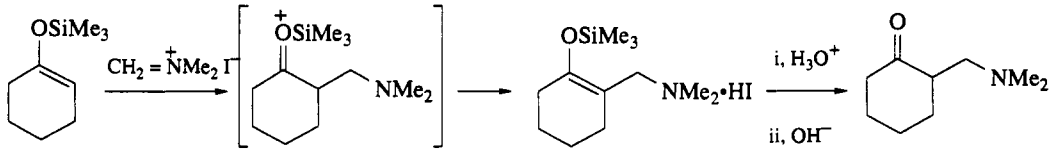
Scheme 10

Table 6 Reactions of β-Diketones (**54**) with Iminium Salt (**31**)[54]

Entry	*β-Diketone (54)* R^1	R^2	*Products* (**55**) *Yield (%)*	(**56**) *Yield (%)*
1	Ph	Ph		90
2	Me	Me		50
3		Ph		40
4	—$CH_2C(Me)_2CH_2$—		87	
5			27	

(iii) Reactions with enol silanes

Reactions of enol silanes with *N,N*-dimethyl(methylene)iminium salts occur under milder conditions than those of simple ketones because an initial enolization step is not required. The reaction is normally performed at room temperature, and aprotic solvents must be used to prevent hydrolysis of the enol silane. Danishefsky and coworkers,[55] in their pioneering investigations of this reaction using TMS enol silanes and iminium iodide (**30**), have suggested the intermediacy of a silyloxonium salt (**57**), which loses a proton to give a 2-substituted enol silane (**58**) as its HI salt (Scheme 11). Subsequent hydrolysis of the enol silane during acid–base work-up affords the Mannich base (**59**).

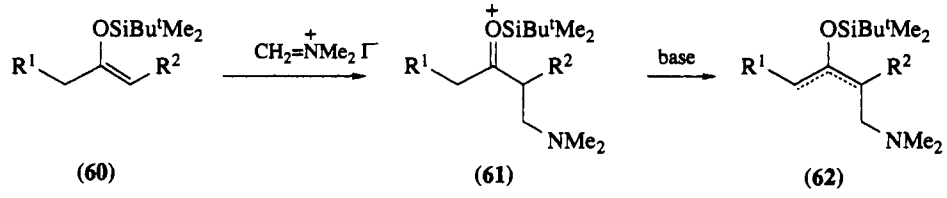


(**57**) (**58**) (**59**)

Scheme 11

In the corresponding reactions of TBDMS enol silanes (**60**), Akiba and coworkers have shown that the more stable TBDMS group is able to survive the work-up, affording Mannich bases as their TBDMS enol silane derivatives (**62**; Scheme 12).[56] Interestingly, acyclic TBDMS enol silanes react with migra-

tion of the position of the enol silane double bond (Table 7, entries 1–4). The authors propose that deprotonation of the silyloxy intermediate (**61**) occurs intramolecularly by the neighboring amino group, as illustrated in the transition state depicted in Figure 3. In cyclic cases, such a transition state is disfavored because the amino group must be axial and the more-substituted, thermodynamically favored product is obtained (Table 7, entries 5–6).



Scheme 12

Figure 3 Proposed intramolecular proton abstraction occurring in Mannich reactions of TBDMS enol silanes

Table 7 Reactions of *t*-Butyldimethyl Enol Silanes with Iminium Iodide (**30**)[56]

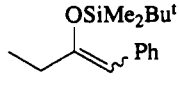
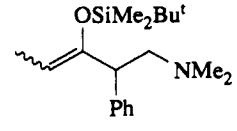
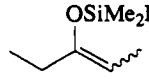
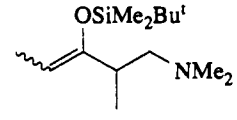
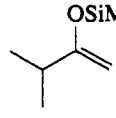
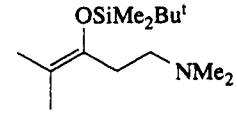
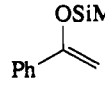
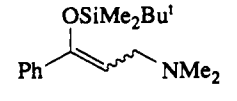
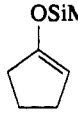
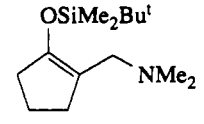
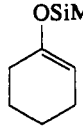
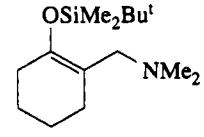
Entry	*Enol silane*	*Conditions*	*Product*	*Yield (%)*
1		r.t., 18 h		89
2		r.t., 24 h		76
3		r.t., 16 h		58
4		r.t., 5 h		92
5		r.t., 20 h		71
6		r.t., 20 h		76

Table 8 highlights some versatile applications of the Mannich reaction of enol silanes, providing Mannich bases that in some cases are very difficult, if not impossible, to obtain using the classical method. Regiocontrol is observed in the preparation of the two Mannich bases of 2-methylcyclohexanone from the corresponding regioisomeric enol silane derivatives (entries 1 and 2).[57] Aminomethylation of the enol

Table 8 Mannich Reactions of Enol Silanes Using *N,N*-Dimethyl(methylene)iminium Salts

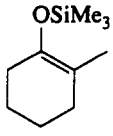
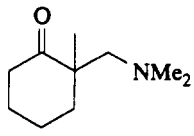
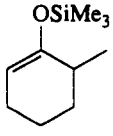
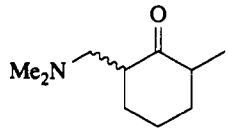
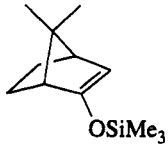
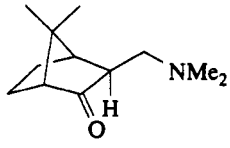
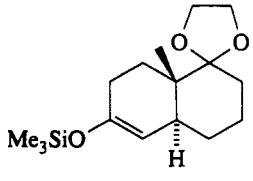
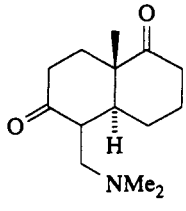
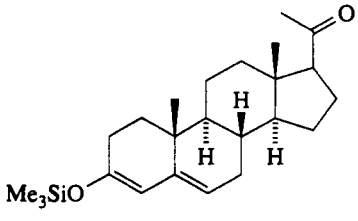
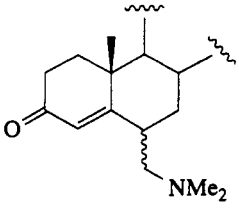
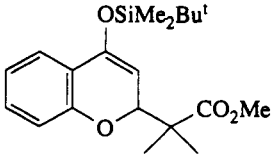
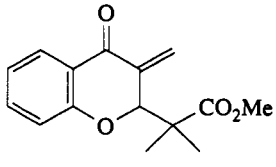
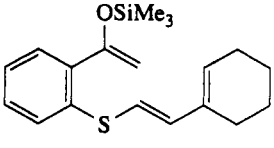
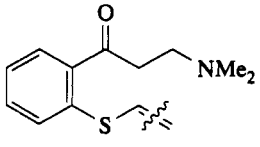
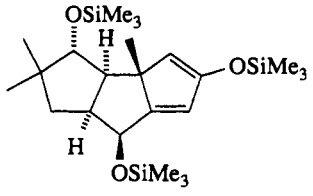
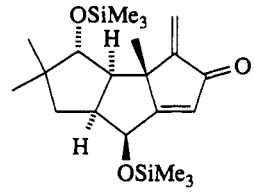
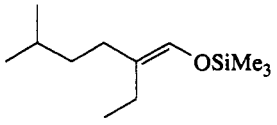
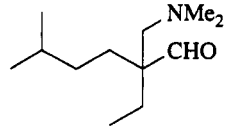
Entry	*Enol silane*	*Product*	*Iminium salt*	*Yield* (%)	*Ref.*
1			(30)	65	57
2			(30)	79[a]	57
3			(30)	86	58
4			(30)	95[b]	55
5			(30)	58[c]	57
6			(31)	66	59
7			(31)	92	60

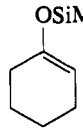
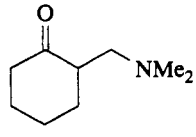
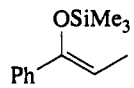
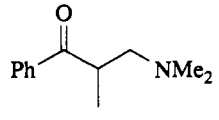
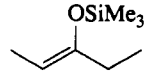
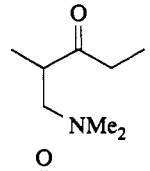
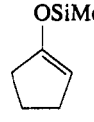
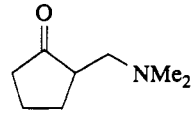
Table 8 *(continued)*

Entry	*Enol silane*	*Product*	*Iminium salt*	*Yield (%)*	*Ref.*
8			(30)	46	61
9			(32)	55	35

[a] Contaminated with *ca.* 4% of the 2,2-disubstituted ketone. [b] The ketal is lost during work-up; yield is based on conversion to the methiodide salt. [c] Yield is based on conversion to the dienone.

silane derivative of (+)-camphor (entry 3) occurs under kinetic control to give the *exo* isomer contaminated with less than 3% of the *endo* isomer (the equilibrium mixture is 1:4 *exo:endo*).[58] This example is noteworthy since (+)-camphor fails to react under the classical conditions. Functional groups including ketals (entry 4), ketones (entry 5), esters (entry 6), vinyl sulfides (entry 7), and silyl ethers (entry 8) are

Table 9 Comparison of the Mannich Reactions of Enol Silanes with *N,N*-Dimethyl(methylene)iminium Salts Using *In Situ* and Non *In Situ* Methods

Entry	*Enol silane*	*Product*	*Iminium salt*	*Yield (%)*	*Ref.*
1			(30)[a] (30)	67 87	36, 37 55
2			(30)[a] (31) (32)	71 41 60	36, 37 35 35
3	$C_5H_{11}CH{=}CHOSiMe_3$	$C_5H_{11}CH(CHO)CH_2NMe_2$	(30)[a] (32)	18 70	36, 37 35
4			b (32)	83 60	38 35
5			b	68	38

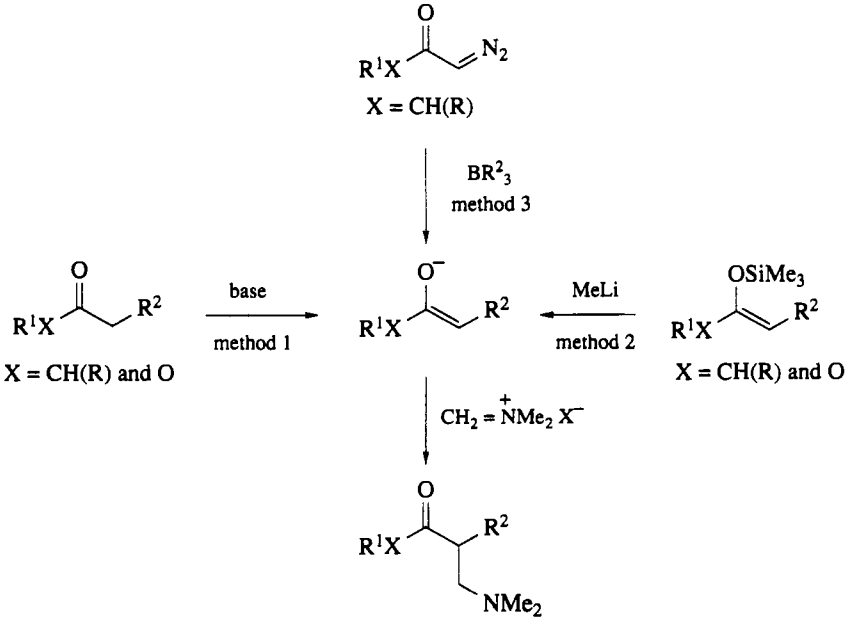
[a] Prepared *in situ* from chloroiodomethane and *N,N',N,N'*-tetramethyldiaminomethane. [b] Prepared *in situ* from n-butyl dimethylaminomethyl ether and a catalytic amount of Me_3SiI or Me_3SiOTf; the exact structure of the aminomethylating agent is unknown.

compatible with the reaction. Conjugated (entry 5) and cross-conjugated enol silanes (entry 8) and aldehyde enol silanes (entry 9) also react successfully. For further examples, see the mini-review by Holy.[35]

Some comparisons between the yields of the Mannich reaction of enol silanes using *in situ* methods for preparation of the iminium salt and non *in situ* methods are shown in Table 9. Higher yields (20–30%) of β-amino ketones using *in situ* methods are seen in entries 2 and 4 but not in entry 1. Although a clear advantage of the *in situ* methods is not evident in these limited examples, *in situ* methods may be preferred from the standpoint of convenience. With aldehyde enol silanes (entry 3), the *in situ* method of Miyano *et al.*[36,37] is less practical due to elimination of the amino group, presumably caused by the strongly basic *N,N,N′,N′*-tetramethyl(methylene)diamine present in solution.

(iv) Reactions with enolates

Enolates, because of their greater nucleophilicity, add to *N,N*-dimethyl(methylene)iminium salts under milder conditions than do enol silanes. Reactions of nonstabilized enolates (*i.e.* those without α-activating groups) are typically performed by adding the iminium salt to the enolate at –78 °C, followed by slow warming to room temperature. With less reactive enolates such as boron enolates and stabilized ester enolates, the reaction is carried out at room temperature. Three methods of enolate generation have been used in these types of Mannich reactions: (1) deprotonation of the active methylene compound with strong base; (2) cleavage of enol silanes and silyl ketene acetals with MeLi; and (3) decomposition of α-diazoketones with trialkylboranes to give boron enolates. These are summarized schematically in Scheme 13. In method 1, which has the advantage of being a one-pot procedure starting with the active methylene compound, LDA has been the most widely used base. The presence of diisopropylamine, however, can lead to reduced yields because of its ability to combine with the iminium salt to form a methylenediamine adduct.[35] In the case of ketone enolates, this complication can be avoided by using Poulter's procedure employing KH as base.[62] Method 2 is useful for the regiospecific synthesis of β-amino ketones if the corresponding regioisomerically pure enol silanes can be prepared. This method is complementary to the enol silane method but is carried out at lower temperatures. Equilibration between regioisomeric enolates generated by this method does not occur during the Mannich reaction.[63,35] One potential limitation, however, is the use of MeLi, which may be incompatible with other functional groups. Method 3 is extremely useful for the regiospecific synthesis of β-amino ketones.[64] It is more advantageous than method 2 because of the ease with which the regioisomeric enolates can be prepared; however, the availability of the starting diazoketones and trialkylboranes may limit its use.



Scheme 13

As illustrated in Table 10, a wide variety of enolates undergo Mannich reactions with *N,N*-dimethyl(methylene)iminium salts. They include ester (entries 1), lactone (entries 2–4), α-ethoxycarbonyllactone (entry 5), acyliron (entry 6), aldehyde (entry 7), carboxylic acid (entry 8), and ketone (entries 9–12) enolates. Yields are generally comparable to the direct enol silane method except in the case of aldehydes

Table 10 Enolate-mediated Mannich Reactions Using Preformed *N,N*-Dimethyl(methylene)iminium Salts

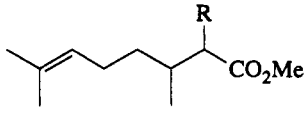
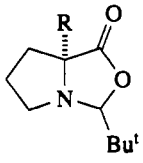
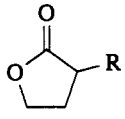
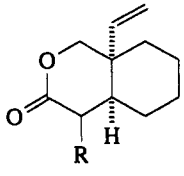
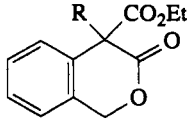
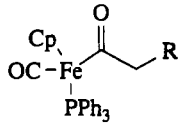
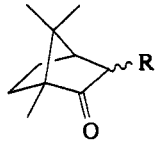
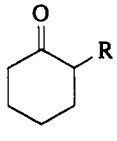
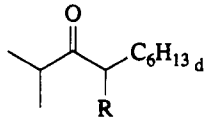
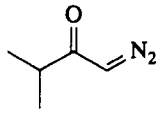
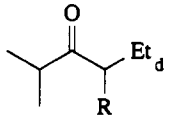
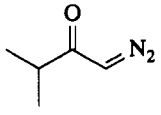
Entry	*Starting material (R = H) Mannich base (R = CH_2NMe_2)*	*Enolate formation*	*Iminium salt*	*Yield (%)*	*Ref.*
1		LDA	(30)	66	65
2		LDA	(31)	56	66
3		Enol silane, MeLi	(32)	60	63
4		LDA	(30)	53[a]	55
5		NaH	(30)	80[b]	28
6		BuLi	(30)		67
7	$C_5H_{11}CH(R)CHO$	Enol silane, MeLi	(32)	30	63
8	$C_{16}H_{23}CH(R)CO_2H$	Disilyl ketene acetal, MeLi	(32)	45	63
9		KH	(32)	60[c]	35
10		KH	(30)	90	62

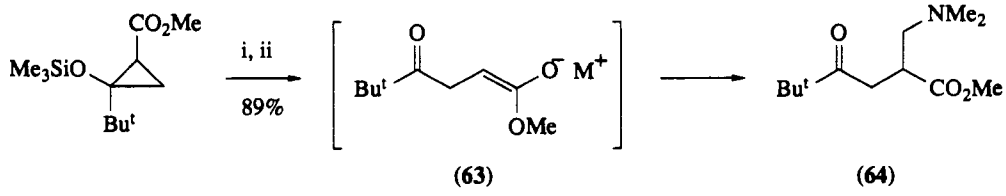
Table 10 *(Continued)*

Entry	*Starting material (R = H) Mannich Base (R = CH_2NMe_2)*	*Enolate formation*	*Iminium salt*	*Yield (%)*	*Ref.*
11		 $(C_6H_{13})_3B$	(30)	84	64
12		 Et_3B	(30)	94	64

[a] Yield is based on conversion to the α-methylene lactone. [b] Yield is based on conversion to the methiodide. [c] A 1:4 ratio of *exo*:*endo* products was determined independently by Mosher *et al.*[38] but using the iminium salt (**30**) instead of (**32**). [d] The starting materials are shown to the right.

(entry 7), where diminished yields can result due to instability of the enolate or to proton abstraction of the product. For the regiospecific synthesis of simple acyclic β-amino ketones, the method of Hooz (entries 11 and 12) provides regioisomerically pure products in excellent yield. For other, related examples of enolates that have been used in these Mannich reactions, see the references listed in Table 10.

2-Silyloxycyclopropanecarboxylates are masked homoenolate equivalents which can also add to *N,N*-dimethyl(methylene)iminium salts. In one of several examples reported by Reissig and Lorey, methyl 2-*t*-butyl-2-(trimethylsilyloxy)cyclopropanecarboxylate and triflate salt (**33**) react to produce α-*N,N*-dimethylaminomethyl-γ-oxo ester (**64**; Scheme 14).[33] The reactive intermediate has not been precisely determined but is most likely a ring-opened enolate (**63**) or its silyl ketene acetal derivative. The reaction can also be performed using the chloride iminium salt (**31**) in the presence of $TiCl_4$, but the reproducibility is poor due to reduced solubility. The products of these reactions are convenient precursors to α-methylene-δ-lactones and acrylic acid derivatives.



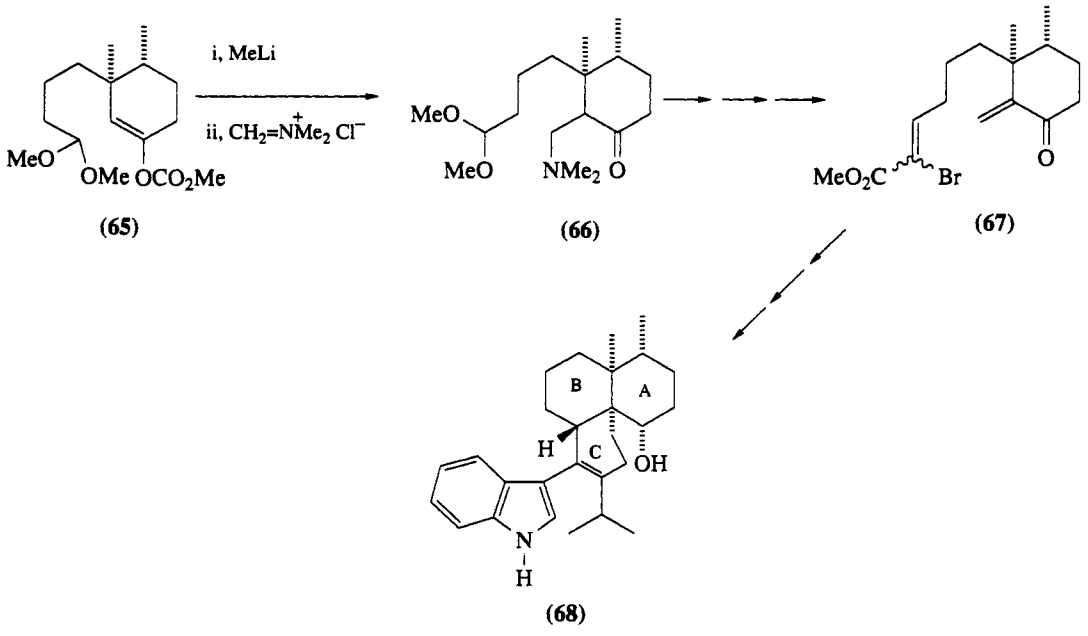
(**63**) (**64**)

i, $CH_2{=}\overset{+}{N}Me_2$ Cl^-, Me_3SiOTf, CH_2Cl_2, 0 °C; ii, add cyclopropyl ester, 0 to 20 °C

Scheme 14

Enolate-mediated Mannich reactions using preformed *N,N*-dimethyl(methylene)iminium salts have been widely used in the total synthesis of sesquiterpene α-methylene lactones and other natural products for the introduction of α-methylene units by subsequent quaterization and elimination of the tertiary amine. Examples include the sesquiterpene α-methylene lactones vernolepin[55,68] and dehydrocostus lactone,[69] and a carbohydrate analog.[70] In an interesting application used in the synthesis of 3-demethylaflavinine (**68**), Danishefsky *et al.* have prepared β-amino ketone (**66**) regiospecifically by cleavage of enol carbonate (**65**) and subsequent addition to iminium salt (**31**; Scheme 15).[71a] Mannich base (**66**) is used as a synthon for enone (**67**), which serves as a double Michael acceptor for construction of the B- and C-rings of 3-demethylaflavinine (**68**). It should be noted that in an earlier study by these workers, reaction of iminium salt (**31**) with a related 3,3-disubstituted enol silane derivative of (**65**) led, unexpectedly, to the 6-substituted Mannich base.[71b] The reversal of regiocontrol using the enol silane instead of the free

enolate is most likely a result of the steric interaction between the adjacent quaternary center at C-3 and the incoming electrophile.



Scheme 15

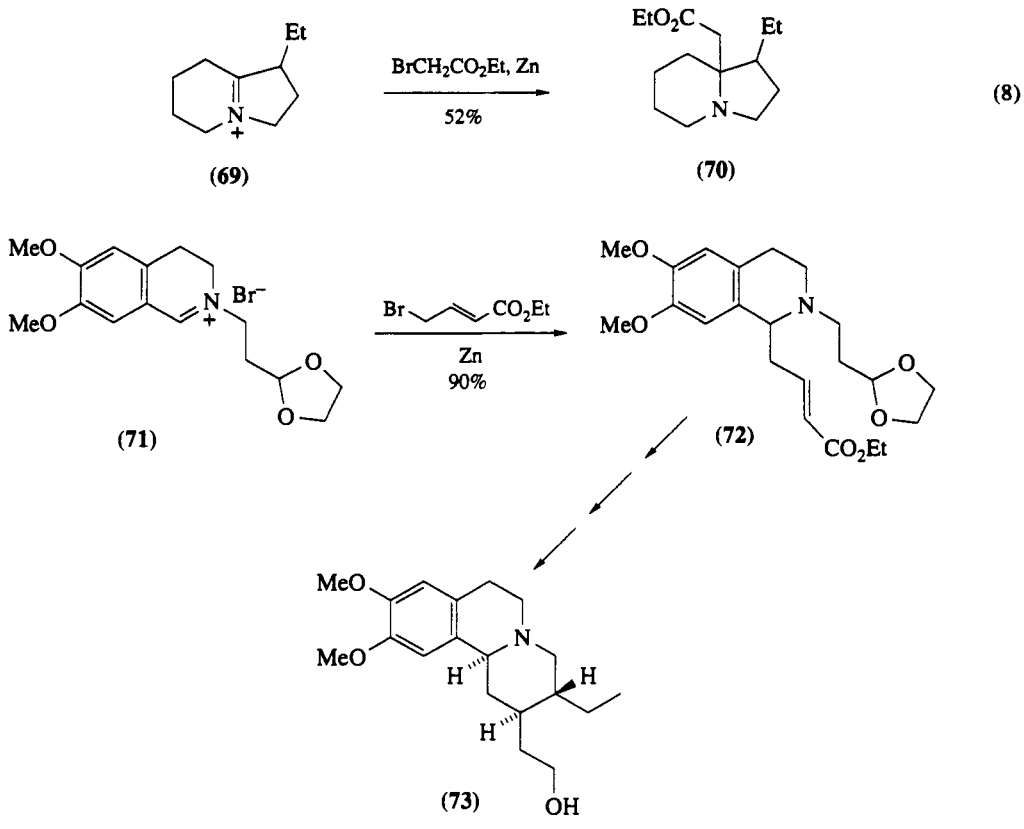
(v) Summary

The use of preformed *N,N*-dimethyl(methylene)iminium salts has a number of advantages over the classical method for the synthesis of Mannich bases and corresponding α-methylene compounds. These include (i) mild conditions and toleration of other functional groups; (ii) the ability to regiospecifically synthesize β-amino ketones; and (iii) a broadened scope, including simple, non-α-activated carboxylic acid derivatives as active methylene components. Sterically crowded substrates also react more successfully. Different counterion forms (I^-, Cl^-, TFA^-, OTf^-) of the iminium salt may be used for improved solubility and to reduce side reactions. *In situ* methods of iminium salt generation are also available in reactions of enol silanes. The active methylene component can be used directly as in the classical method or preactivated *via* its enol silane or enolate derivative, allowing the reaction to proceed at lower temperatures. For the regiospecific aminomethylation of ketones, regiospecifically generated enol silanes or enolates must be used since regiocontrol is unpredictable when the ketone is employed directly. For the regiospecific synthesis of simple acyclic β-amino ketones, the enol borinate method of Hooz is the method of choice because of the ease with which the enolate can be prepared regiospecifically. The classical method, which is more adaptable to large scale, may be preferred, however, for the synthesis of simple, unfunctionalized Mannich bases.

4.1.2.3 Cyclic Iminium Salts

Preformed cyclic *N,N*-dialkyliminium salts (*i.e.* where a ring joins the α-carbon and positively charged nitrogen) have been used in enolate condensation reactions. The number of examples, however, is rather limited, probably because of complications arising through abstraction of enolizable protons. Δ^4-Dehydroindolizidinium salt (**69**) represents one of the few examples of an enolizable, cyclic *N,N*-dialkyliminium salt known to react with an enolate (equation 8).[72] The use of a soft zinc enolate in this reaction may be crucial. The relative stereochemistry of the resulting β-amino ester (**70**) is undefined. *N*-Alkyl-3,4-dihydroisoquinolinium salts (*e.g.* **71**), a class of nonenolizable, cyclic iminium salts, have had extensive applications in the total synthesis of protoberberine and phthalide isoquinoline alkaloids. A review by Pai and coworkers[9] has covered much of this work. In a more recent application by Yamazaki and co-

workers, a dihomoenolate is added to isoquinolinium salt (**71**) to give tetrahydroisoquinoline (**72**), which is converted to (±)-protoemetinol (**73**) in several steps (Scheme 16).[73]



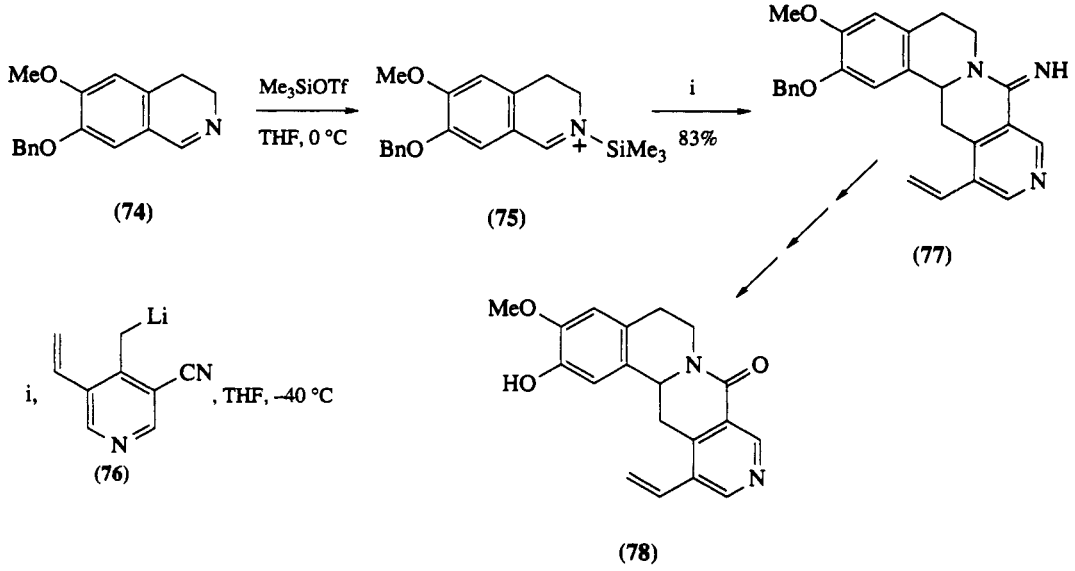
Scheme 16

4.1.2.4 *N*-Silyl- and *N,N*-Disilyl-iminium Salts

An inherent limitation in the use of *N,N*-dialkyliminium salts in the Mannich reaction is that the product derived is a tertiary amine, which restricts elaboration of the nitrogen. As a means of overcoming this limitation, MacLean and coworkers[74] have introduced *N*-silyliminium salts, prepared *in situ* from the corresponding imine using TMS-OTf; facile cleavage of the silyl group following the Mannich reaction liberates a free site on the amine. An example is shown in Scheme 17 involving the reaction of *N*-silyliminium salt (**75**) with the lithium salt of 3-cyano-4-methyl-5-vinylpyridine (**76**). The initial adduct cyclizes directly to form a tetracyclic amidine (**77**), an intermediate in the synthesis of (±)-alangimaridine (**78**). It is proposed that the mechanism of amidine formation most likely involves transfer of the silyl group to the exocyclic amidine nitrogen; the silyl group is then lost upon work-up. The *N*-silyl group also has a special role in activating the imine since the parent imine (**74**) fails to react with anion (**76**). *N*-Silyliminium salts of other 3,4-dihydroisoquinolines have been used in the total synthesis of alamaridine[75] and the pentacyclic alkaloids nauclefine, angustidine, angustine and 13b,14-dihydroangustine.[76]

In reactions with silyl ketene acetals (**79**), Sekiya and coworkers have reported two *in situ* methods for the generation of *N*-silyliminium salts. The first method generates *N,N*-disilyliminium salts by TMS-OTf-catalyzed cleavage of *N,N*-bis(trimethylsilyl)methoxymethylamine (**80**); the *N,N*-disilyliminium salt then reacts with silyl ketene acetals (**79**) to afford *N,N*-bis(trimethylsilyl)-β-amino esters (**81**) in high yield (equation 9; Table 11).[77] Desilylation of (**81**) can be easily accomplished by methanolysis to afford the corresponding primary β-amino esters. The overall process introduces a primary aminomethyl group (NH_2CH_2), a transformation difficult to perform using the classical method. The compatibility of this method with a-amino substitution in the silyl ketene acetal (entry 6) may render it particularly useful for the synthesis of monobactam antibiotics.[78] An *N,N*-bis(trimethylsilyl)methyleneiminium triflate species [$(TMS)_2N^+{=}CH_2$ OTf^-; **83**] is implicated in this reaction, based on the observation that methoxytri-

methylsilane (**82**) is released when aminol ether (**80**) and TMS-OTf are reacted in the absence of silyl ketene acetal. The second method involves TfOH-catalyzed cleavage of 1,3,5-trialkylhexahydro-1,3,5-triazines (**84**),[79] prepared by the method of Reynolds and Cossar.[80] The putative iminium species [TMS(R^3)N$^+$=CH$_2$ OTf$^-$; **86**] condenses with silyl ketene acetals (**79**) to afford secondary β-amino esters (**85**) after aqueous work-up (equation 10; Table 12). Yields are generally good, even in sterically crowded cases (entries 1 and 8). The method also allows for easy variation of the amino substituent (R^3).



Scheme 17

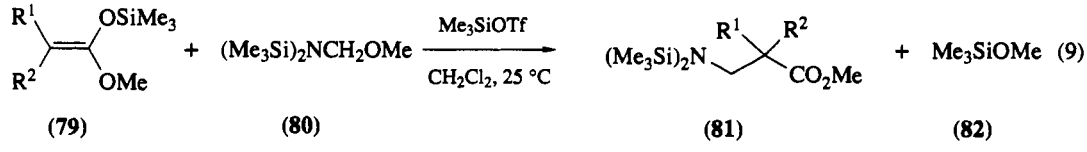
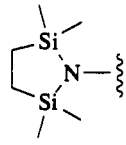


Table 11 Reactions of Silyl Ketene Acetals (**79**) with *N,N*-Bis(trimethylsilyl)methoxymethylamine (**80**) Catalyzed by TMS-OTf[77]

Entry	*Silyl ketene acetal (79)* R^1		R^2	*Product (81) Yield (%)*
1	Me		Me	84
2	Me		H	85
3	Ph		H	95
4		—(CH$_2$)$_4$—		78
5		—(CH$_2$)$_5$—		85
6			H	93

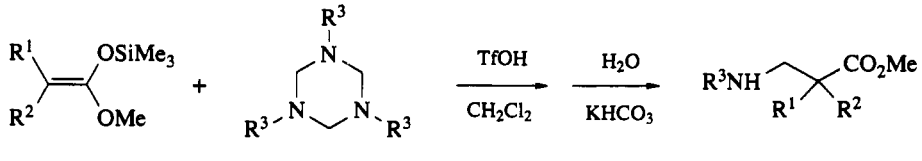


Table 12 Reactions of Silyl Ketene Acetals (**79**) with 1,3,5-Trialkylhexahydro-1,3,5-triazines (**84**) Catalyzed by TfOH[79]

Entry	*Silyl ketene acetal (79)* R^1	R^2	*Triazine (84)* R^3	*β-Amino ester (85) Yield (%)*
1	Me	Me	Pr^i	83
2	Me	H	Pr^i	87
3	H	H	Pr^i	41
4	Me	Me	Bn	83
5	Me	Me	Et	58
6	Me	Me	Allyl	76
7	Me	Me	Ph	67
8	Me	Me	Ph(CO_2Me)CH	69

4.1.3 USE OF IMINES

4.1.3.1 Introduction

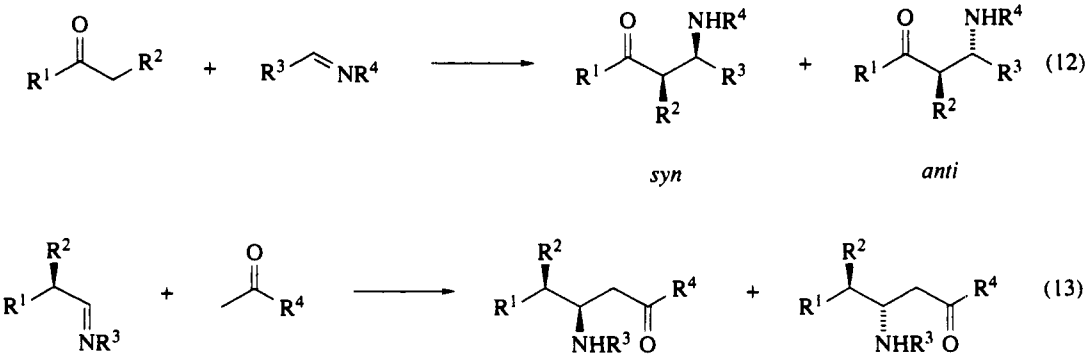
Imines are more versatile than preformed iminium salts in reactions with active methylene compounds because the product, a secondary Mannich base, has an additional site on the nitrogen for further elaboration (equation 11). Imine condensation reactions are also superior to the classical method for the synthesis of secondary Mannich bases because cross-condensation reactions do not occur, due to the absence of free aldehyde in solution. The major side reactions occurring in imine condensation reactions are abstraction of enolizable α-protons and self-condensation reactions of enolizable imines at elevated temperature.

(11)

Imines, being neutral species, are less reactive than iminium salts. Consequently, active methylene compounds with pK_a values greater than ~15–16 must be preactivated as an enolate or enol silane derivative. Lewis acids are sometimes used in reactions with enolates to improve reactivity and stereoselectivity, but in contrast to the reactions of preformed iminium salts, Lewis acids are required in reactions with enol silanes. Additional activation of the active methylene compound or catalysis is not usually required in reactions with more acidic active methylene compounds (pK_a values below ~15–16). In these reactions, higher acidity not only gives higher enol concentrations but also serves to catalyze the reaction through protonation of the imine.

Of the various imines known to condense with active methylene compounds, α-arylimines have been the most widely used, especially in earlier work, because of their stability, ease of preparation and the absence of enolizable protons. Aliphatic imines containing enolizable protons have broader synthetic applications but their use is more restricted because they are prone to deprotonation and self aldol type condensations. As will be discussed, new methods utilizing Lewis acids and the less basic boron enolates have been devised to overcome the problem of deprotonation. Other innovations that have extended the scope of imine condensations include *in situ* methods for the preparation of elusive formaldehyde imines (CH_2=NR_2) and the utilization of *N*-heterosubstituted imines (N = Si, O and S) for the synthesis of primary Mannich bases and *N*-unsubstituted β-lactams, available *via* hydrolysis or reduction of the N—X bond.

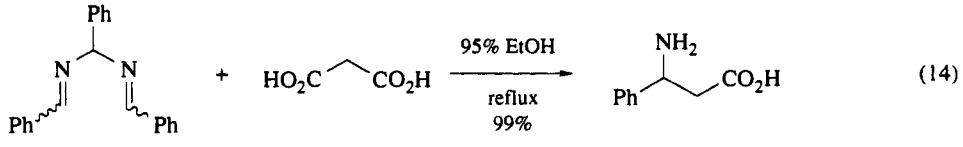
Largely stimulated by the synthesis of β-lactam antibiotics,[78] there have been widespread investigations into the stereochemical aspects of imine condensations, mainly involving reactions of enolates of carboxylic acid derivatives or silyl ketene acetals. In analogy to the aldol condensation, stereoselectivity of imine condensations will be discussed in terms of two types in this chapter: (i) simple diastereoselectivity or *syn–anti* selectivity, when the two reactants are each prochiral (equation 12); and (ii) diastereofacial selectivity, when a new chiral center is formed in the presence of a pre-existing chiral center in one of the reactants (*e.g.* equation 13). The term 'asymmetric induction' may be used synonymously with 'diastereofacial selectivity' when one of the chiral reactants is optically active. For a more explicit explanation of these terms, see Heathcock's review on the aldol condensation.[81]



4.1.3.2 Acyclic *N*-Aryl- and *N*-Alkyl-imines

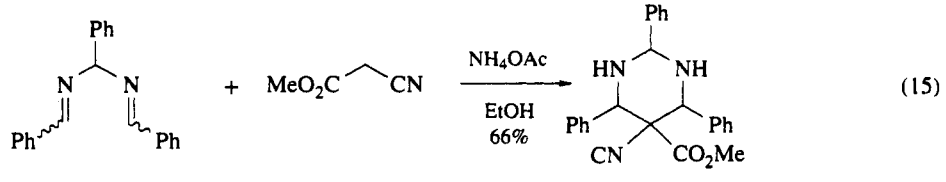
4.1.3.2.1 Reactions with highly acidic active methylene compounds

Reactions using highly acidic active methylene compounds (pK_a = 9–13) comprise nearly all the early examples of imine condensation reactions, some of which date back to the turn of the century. Reviews by Layer[6] and Harada[7] have summarized many of these reactions and include examples using diethyl malonate, ethyl cyanoacetate, ethyl malonamide, acetoacetic acid, benzoylacetic esters and nitroalkanes. Conditions of these reactions vary; they have been performed both in protic and aprotic solvents, neat, and with and without catalysts. Elevated temperatures are generally required. Reactions with malonates have useful applications for the synthesis of β-amino acids. For example, hydrobenzamide (**87**), a trimeric form of the benzaldehyde–ammonia Schiff base, and malonic acid condense with concomitant decarboxylation to produce β-phenylalanine (**88**) in high yield (equation 14).[82] This is one of the few examples of a Mannich reaction in which a primary Mannich base is produced in a direct manner but is apparently limited to aromatic imines.



(**87**) (**88**)

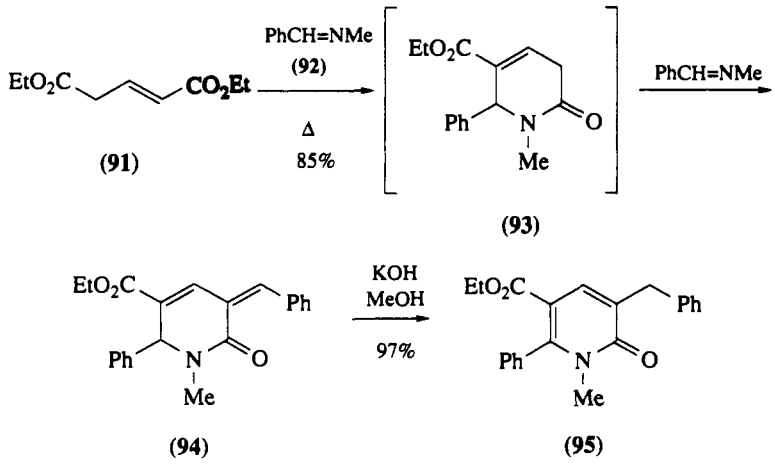
In more recent applications, Takajo and Kambe[83] have reported a new synthesis of perhydropyrimidines (**90**) by a double Mannich reaction (one step is intramolecular) using hydrobenzamide (**87**) and methyl cyanoacetate (**89**; equation 15). The reaction is general for other highly acidic methylene compounds including malononitrile, dimethyl malonate and nitroethane. In some cases, the intramolecular Mannich step is slow and side products arising from decomposition of the initial adduct are formed. This phenomenon is temperature dependent, indicating that intermediates in the reaction are formed reversibly.



(**87**) (**89**) (**90**)

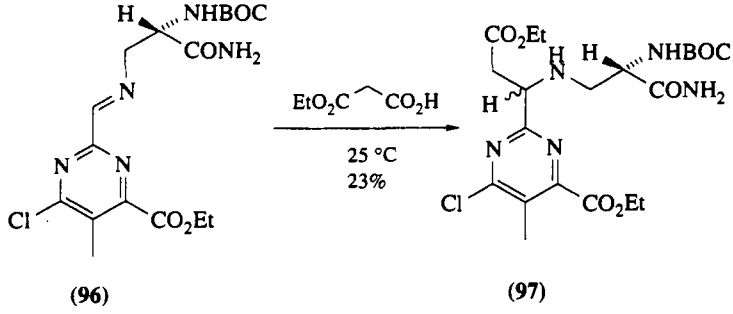
In another example of heterocyclic synthesis, Shamma *et al.* have prepared 2-pyridone (**95**) by condensing diethyl glutaconate (**91**) with imine (**92**; Scheme 18).[84] The initial adduct (**93**) cannot be isolated, as

it reacts with a second equivalent of (**92**) to give an α-benzylidine derivative (**94**), which can be easily isomerized to (**95**) with base.



Scheme 18

In their synthesis of the pyrimidine segment of the potent antitumor antibiotic bleomycin, Umezawa, Ohno and coworkers have described the reaction of highly functionalized imine (**96**) with malonic acid monoethyl ester to afford β-amino ester (**97**; equation 16).[85] The low yield of (**97**) is largely due to elimination of the amino side chain, giving the corresponding acrylate derivative. A subsequent modification[86] of this reaction using a boron enolate overcomes this problem and will be discussed in Section 4.1.3.2.2.ii.



(16)

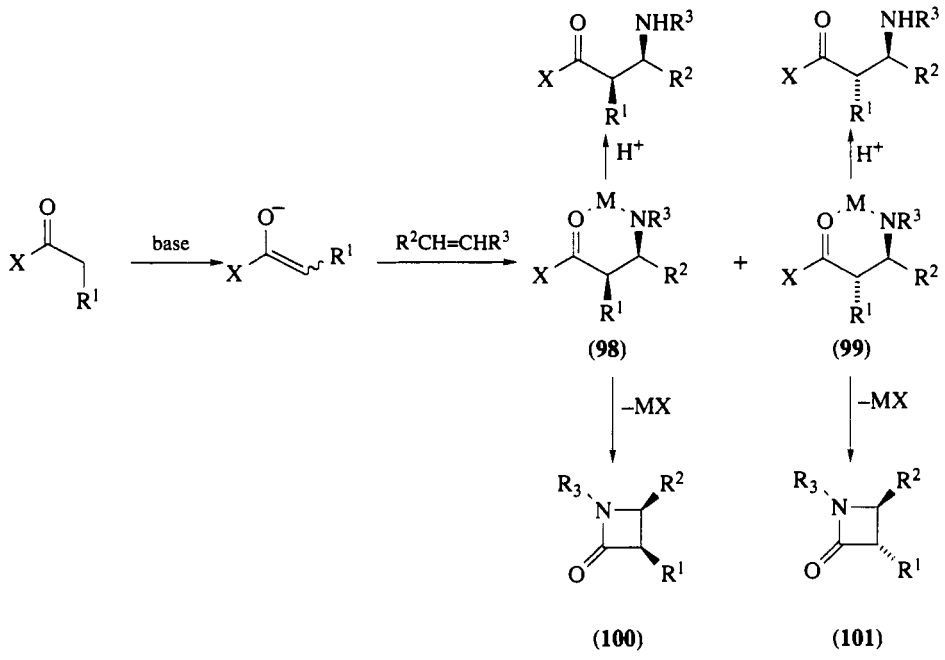
4.1.3.2.2 Reactions with carboxylic acid derivatives

(i) Introduction

Condensation reactions of simple carboxylic acids with imines are of intense interest because of their applications to β-lactam synthesis. Activation of the carboxylic acid derivative is accomplished by preforming the enolate *in situ* or by using a silyl ketene acetal derivative with Lewis acid catalysis. The first example of an enolate–imine condensation of this type can be attributed to Gillman and Speeter, who in 1943 reported the synthesis of β-lactams from Reformatsky reagents and Schiff bases.[87] Subsequently, other workers have investigated the mechanism and *syn–anti* selectivity of this reaction. A review of these studies by Evans *et al.* covering work through 1980 has appeared in their review, 'Stereoselective Aldol Condensations'.[10]

The mechanism of β-lactam formation in enolate–imine condensations proceeds by the stepwise pathway depicted in Scheme 19, in which diastereomeric β-lactams (**100**) and (**101**) are formed by cyclization of intermediate, metalated amine adducts (**98**) and (**99**), respectively. The possibility of a less likely [2 + 2] cycloaddition mechanism has been discussed.[88,89] Equilibration between β-lactams (**100**) and (**101**) *via* epimerization at C-3 does not normally occur.[88] The stepwise mechanism is supported by the fact that *trans* β-lactam (**101**; R^1 = Pr; R^2 = R^3 = Ph) is formed from (**99**; M = MgBr) without loss of

stereochemistry when it is generated from the corresponding *anti* β-amino ester.[90] Under certain conditions, especially at elevated temperatures, formation of the metalated amine adducts (**98**) and (**99**) can be reversible. Consequently, product ratios of diastereomeric β-lactams (**100**) and (**101**) will reflect this equilibrium, not the kinetic formation of adducts (**98**) and (**99**).[91] Due consideration of this phenomenon should therefore be given when interpreting stereochemical results. It should be noted that cyclization of (**98**) and (**99**) to β-lactams does not always occur and the corresponding β-aminocarboxylic acid derivatives are often isolated upon work-up. The nature of the leaving group X is an important factor in determining whether the metalated amine intermediates cyclize or not. Esters (X = OR), provided they are unhindered, generally give β-lactams, whereas amides (X = NR_2), carboxylic acids (X = OH), and thioesters (X = SR) give acyclic products. Bulky substituents at the amine nitrogen (R^3) also tend to suppress cyclization to β-lactams.



Scheme 19

Evans *et al.*[10] have analyzed *syn–anti* stereoselectivity in enolate–imine condensations using the four postulated pericyclic transition states shown in Figure 4. The indicated three-letter descriptors designate the overall geometry of transition state, chair (*C*) or boat (*B*), and the geometries of the enolate and imine, (*E*) or (*Z*), in that order. In this treatment *syn* products are formed *via* $C(E,E)^‡$ and $B(Z,E)^‡$ transition states and *anti* products are formed *via* $B(E,E)^‡$ and $C(Z,E)^‡$ transition states. These transition states are based on the more stable (*E*)-imine geometry, while for cyclic imines a complementary set of transition states can be derived based on the (*Z*)-imine geometry. In their review, Evans *et al.*[10] have concluded that the dichotomy between the *syn* selectivity of ester enolates and the *anti* selectivity of amide enolates, based on studies from the laboratories of Kagan and Gaudemar (pioneering French workers who first investigated the stereochemical aspects of enolate–imine condensations using Reformatsky reagents, zinc enolates), is a consequence of differing enolate geometries. Thus, ester enolates, which prefer the (*E*)-geometry, react *via* a $C(E,E)^‡$ transition state to give mainly *syn* products, whereas amide enolates, preferring the (*Z*)-geometry, give mostly *anti* products *via* a $C(Z,E)^‡$ transition state. As will be discussed, these trends are upheld in subsequent work using different types of enolates. The reader should note that throughout this chapter, enolate geometry, (*E*) or (*Z*), is assigned based on giving the negatively charged oxygen highest priority.

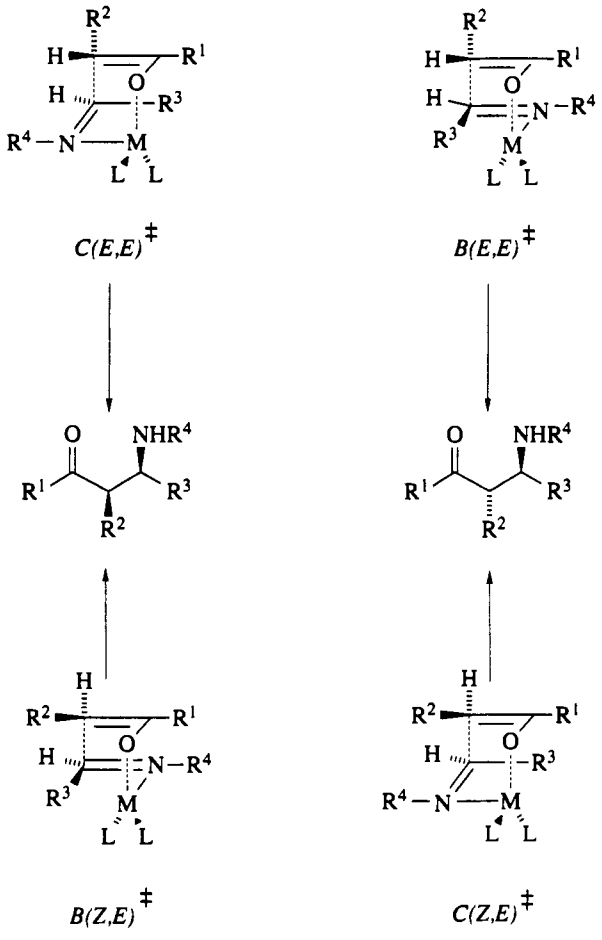
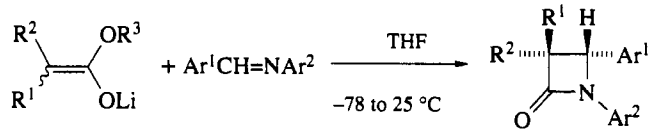


Figure 4 Postulated pericyclic transition states involved in enolate–imine condensations[10]

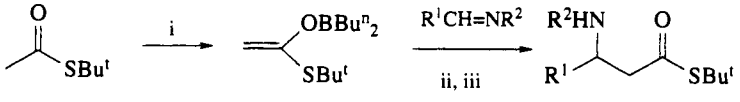
(ii) Reactions with enolates

Following the early studies of enolate–imine condensations using Reformatsky reagents, the advent of kinetic deprotonation for the generation of enolates has led to new applications involving other types of enolates. Bergbeiter, Newcomb and coworkers have demonstrated the viability of using lithium enolates of esters (**102**),[89] easily prepared by deprotonation of the ester with LDA. These enolates react with Schiff bases (**103**) under milder conditions (–78 → 25 °C) than do Reformatsky reagents, affording β-lactams (**104**) in 70–90% yield when the α-position of the ester is disubstituted (equation 17). Lower yields (35–45%) are found in cases where R^1 and/or R^2 is hydrogen, most likely due to the greater susceptibility of the less hindered, monosubstituted enolates to undergo self-condensation reactions in the neighborhood of 0 °C, the temperature at which the imine addition occurs. A further limitation of this method is the restriction to nonenolizable imines, not surprising in view of the strong basicity of lithium enolates. *Trans* β-lactams (**104**) are formed almost exclusively in cases when R^1 = Ar, R^2 = Me or OLi, and R^3 = Et. The basis for the observed *anti* selectivity is not clear. The authors suggest that the carbon–carbon bond-forming step is reversible, and product ratios therefore reflect the thermodynamic stability of the *anti* aldolate. That the disubstituted enolates are probably formed stereorandomly also supports the notion that kinetic factors are not involved. Asymmetric induction can also be achieved using optically active esters. For example, β-lactam (**104**; R^1 = Ph; R^2 = Me; Ar^1 = Ar^2 = Ph) is prepared in 60% *ee* from the corresponding (–)-menthyl ester enolate (**102**; R^3 = (–)-menthyl). Since asymmetric induction is found with a 3:2 mixture of diastereomeric enolates (demonstrated by trapping experiments), a reversible first step seems likely. Similar applications of the reactions of lithium enolates to the synthesis of monocyclic cephamycin analogs (**104**; R^1 = NHCOAr; R^2 = OMe) have been reported by Manhas and coworkers.[92]



(102) (103) (104) (17)

Using the boron enolate (or vinyloxyborane) of *t*-butyl thioacetate (**105**), Ohno and coworkers have prepared β-amino thioesters (**107**) *via* reactions with various imines (Scheme 20; Table 13).[86] The products can subsequently be converted to β-lactams[93] if desired, or to other carboxylic acid derivatives. Formation of the boron enolate (**106**) is accomplished using di-*n*-butylboryl triflate and diisopropylethylamine in ether at 0 °C, and the imine addition is performed at 0–25 °C. A hydrogen peroxide work-up is necessary to break up a boron chelation complex of the product. Ether is superior to other solvents in the condensation reaction. Advantages of this method over those using Reformatsky reagents and lithium enolates are (i) compatibility with enolizable imines (Table 13; entries 5–6); and (ii) greater flexibility in terms of elaboration of the product. Also, the combination of mild conditions and weak enolate basicity is compatible with additional ester functionality (entries 3 and 4). Application of this method to the transformation depicted above in equation (16) for the synthesis of bleomycin provides the β-amino thioester derivative of (**97**) in nearly double the yield of the process using malonic half-ester.



(105) (106) (107)

i, Bu^n_2BOTf, Pr^i_2NEt, ether, 0 °C; ii, 0 °C to r.t., 1.5 h; iii, 20% H_2O_2

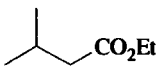
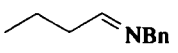
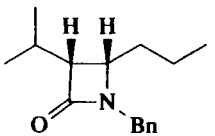
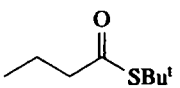
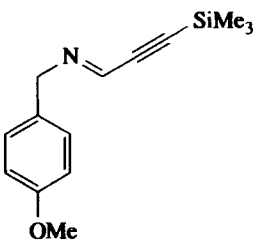
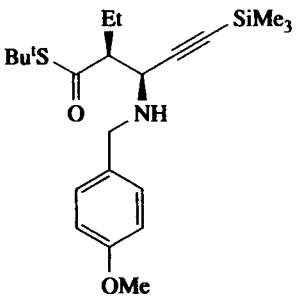
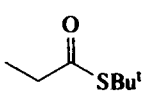
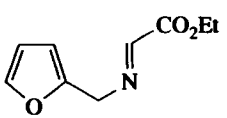
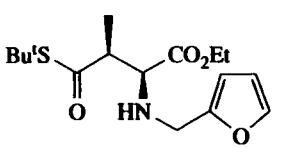
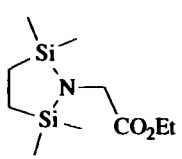
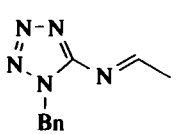
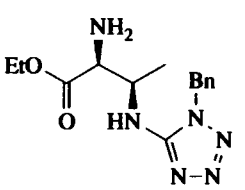
Scheme 20

Table 13 Reactions of Boron Enolate (**106**) with Imines[86]

Entry	*Imine* $R^1CH{=}NR^2$ R^1	R^2	*β-Amino thioester* (**107**) *Yield (%)*
1	Ph	$PhCH_2$	80
2	$PhCH{=}CH_2$	$PhCH_2$	63
3	Ph	MeO_2CCH_2	52
4	Ph	$MeO_2C(CH_2)_2$	86
5	Et	$PhCH_2$	43
6	Pr^i	$PhCH_2$	45

Representative examples of *syn* selective enolate–imine condensations using different types of enolates are shown in Table 14 (entries 1–3). The nonlithium enolates (entries 1–3) are prepared by treating the lithium enolate with different Lewis acids; exchange between the Lewis acid and lithium cation takes place to form a new enolate. All of the lithium enolates are generated using LDA at −78 °C and are treated with the Lewis acid before the addition of the imine. Addition of thioester enolates (entries 2 and 3) employing $CpZrCl_2$[93] and $SnCl_2$[94] additives is conducted at −78 °C to give acyclic products. In the case of the ethyl ester enolate employing Me_2AlCl as additive (entry 1), warming to 25 °C is apparently necessary to induce cyclization to the β-lactam.[95] *Syn* selectivity of these reactions is general for a variety of α-alkyl substituents in the examples of entries 1–3; the reader should consult the individual papers for further examples. It is noteworthy that enolizable imines successfully condense using Me_2AlCl (entry 1), whereas lithium enolates do not. The reaction of the lithium enolate of ethyl glycinate protected as its tetramethyldisilylazacyclopentane (STABASE)[96] adduct has been used in the synthesis of *N*-tetrazol-5-yl substituted β-lactams (entry 4).[97] It is interesting that this reaction is successful despite other claims that lithium enolates do not react with enolizable imines in the absence of a Lewis acid additive.[89] This anomaly may be a result of unusual coordination of the lithium with the glycine nitrogen or with the nitrogens of the tetrazole group of the imine. If (*E*)-enolates are involved in these reactions, *syn* selectivity can be explained by a $C(E,E)^‡$ transition state. In the case of thioester enolates, it is known that the lithium enolate of *t*-butyl thiopropionate[98] and the zirconium enolate of *t*-butyl thiobutyrate[93] are indeed predominately (*E*) (>95:5). It should be noted, however, that the *syn–anti* selectivity of thioester enolates

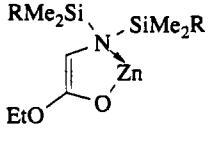
Table 14 *Syn* Selective Enolate–Imine Condensations[a]

Entry	*Ester*	*Imine*	*Lewis acid*	*Product*	*Yield (%) (syn:anti)*	*Ref.*
1			Me_2AlCl		58 (9:1)	95
2			Cp_2ZrCl_2		57 (5:1)	93
3			$SnCl_2$		82 (95:5)	94
4			—		44[b] (3:1)	97

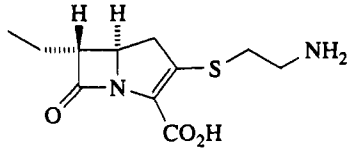
[a] Enolates are generated using LDA. [b] The disilyl protecting group is lost during work-up.

can vary considerably if Lewis acids other than those mentioned above are used.[94] Different enolate geometries could be involved in these cases.

Complementary reactions displaying *anti* selectivity are shown in Table 15. Enolates of STABASE-protected glycinate esters add to enolizable imines in the presence of $ZnCl_2$, giving *trans* β-lactams in high yield (entry 1).[99] This reaction is also general for *N,N*-dialkyl glycinate esters and α-aryl-imines.[99,100] The *anti* selectivity can be explained by a $C(Z,E)^‡$ transition state in which the zinc enolate has a (*Z*)-chelated structure (**108**). This model is supported by the tendency of simple α-alkyl zinc enolates (*i.e.* Reformatsky reagents) without an additional coordination site for the zinc cation to give predominantly *cis* β-lactams (see Section 4.1.2.2.i). Apparently, the zinc cation is critical to the formation of a chelate (**108**) since the opposite (*syn*) selectivity is found in the analogous reaction previously described employing the corresponding lithium STABASE-protected glycine enolate (Table 14; entry 4). In entry 2, *anti* selectivity is observed unexpectedly using a similarly protected lithium glycinate enolate, but is most likely due to epimerization induced by the electronegative trifluoromethyl group at the C-4 position of the β-lactam product.[101] As represented in entry 3, tin(II) thioester enolates, formed *in situ* from tin(II) *t*-butylthiolate and ketenes, are *anti* selective in the presence of $Sn(OTf)_2$, affording β-amino thioesters.[102] This example, used in the synthesis of β-lactam antibiotic PS-5 (**109**), demonstrates the compatibility of enolizable imines with these reactions. In other reported examples employing nonenolizable aryl- and styryl-imines, decreased yields are observed with less bulky substituents on the imine nitrogen, perhaps due to oligomerization of the imine.[102] It is interesting to note that the *anti* selectivity of tin(II) thioester enolates generated in this manner and condensed with α-alkyl- and α-aryl-imines in the presence of $Sn(OTf)_2$ contrasts with the *syn* selectivity observed when tin(II) thioester enolates are generated from the corresponding lithium enolates using $SnCl_2$ in reactions with α-carboethoxyimines (Table 12; entry 3).[94] This dichotomy may be a consequence of differing enolate geometries or, perhaps, be attributable to a special role of the α-carboethoxy group in the latter case, involving chelation with the tin(II) cation. *Anti* selectivity is also found in the reactions of aluminum enolates of straight chain thioesters (entry 4).[93] Interestingly, this result stands in contrast to the *syn* selectivity observed in similar reactions of aluminum enolates of ethyl esters (Table 14; entry 1). It is perplexing, moreover, that reversal of *anti* selectivity to *syn* selectivity is reported when the thioester is β-branched (*e.g. S-t*-butyl isobutylthioate).[93] Clearly, a more detailed study of the geometries of the aluminum enolates is needed before these results can be rationalized.

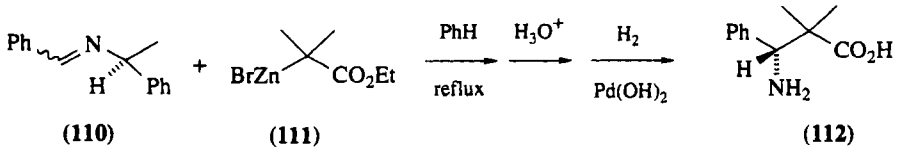


(**108**)



(**109**)

Reactions exhibiting diastereofacial selectivity, which occur when the imine or the enolate contains an endogenous stereocenter or a chiral auxiliary, have important applications for the synthesis of optically active β-lactams and β-amino carboxylic acid derivatives. Early work by Furukawa *et al.* has demonstrated the viability of preparing optically active β-amino acids from chiral imines.[103] For example, the Schiff base derived from (*S*)-α-methylbenzylamine (**110**) reacts with Reformatsky reagent (**111**) to give, after hydrolysis and removal of the chiral auxiliary, 3-amino-2,2-dimethyl-3-phenylpropionic acid (**112**) in 33% *ee* (Scheme 21). Similar Reformatsky reactions have been performed using (–)-menthyl esters but the enantiomeric excess values are lower.[104]

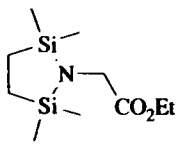
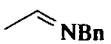
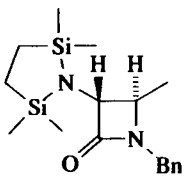
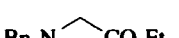
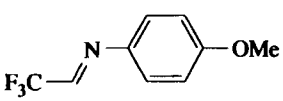
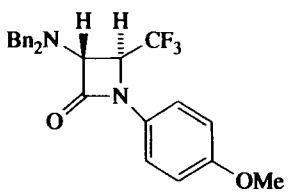
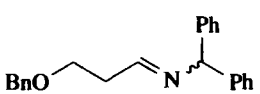
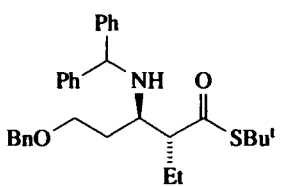
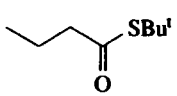
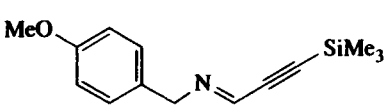
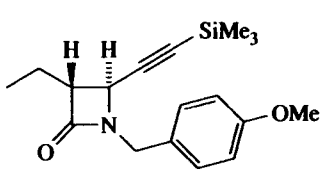


(**110**) (**111**) (**112**)

Scheme 21

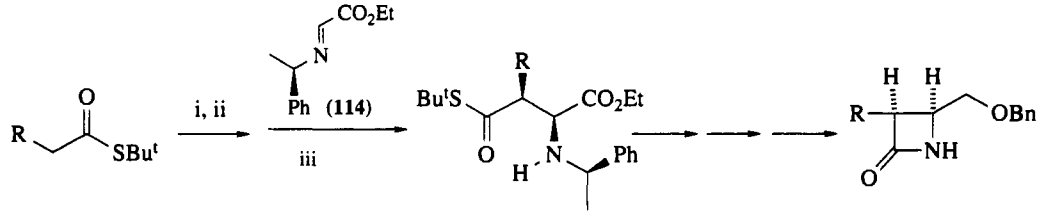
Mukaiyama and coworkers have applied their thioester tin enolate methodology, previously described in Table 14 (entry 3), to reactions with chiral imines.[105] As shown in Scheme 22 and Table 16, tin(II) enolates of thioesters (**113**), generated by treating the lithium enolates with $SnCl_2$, add to optically active

Table 15 *Anti* Selective Enolate–Imine Condensations[a]

Entry	*Ester or equivalent*	*Enolate generation*	*Imine*	*Product*	*Yield (%) (anti:syn)*	*Ref.*
1		i, LDA; ii, $ZnCl_2$			98 (100:0)	99
2		LDA			63 (100:0)	101
3		$Sn(SBu^t)_2$, $Sn(OTf)_2$			60 (88:12)	102
4		i, LDA; ii, Et_2AlCl			80 (3:1)	93

[a] Enolates are generated using LDA.

imine (**114**), affording predominantly *syn* adducts (**115**) with the indicated absolute stereochemistry in good yield. The authors rationalize the *syn* selective process (*syn:anti* > 9:1) by a *C(E,E)*‡ type of transition state. The diastereofacial selectivity, determined by converting β-amino esters (**115**) to β-lactams (**116**) and measuring their optically purity, is good (≈70% *ee*).



(**113**) (**115**) (**116**)

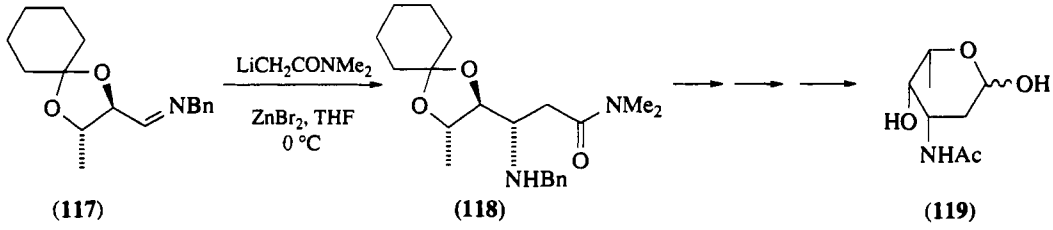
i, LDA, ether, –70 °C; ii, $SnCl_2$, –78 °C; iii, –70 °C, 3 h

Scheme 22

Table 16 *Syn–Anti* and Diastereofacial Selectivities in the Reactions of Tin(II) Enolates of Thioester (**113**) with Imine (**114**)[105]

Entry	*Thioester* (**113**) *R*	*Yield (%)*	(**115**) *Products* *Syn:anti*	(**116**) *ee (%)*
1	Me	78	91:9	70
2	Et	78	95:5	72
3	Pr^i	79	95:5	71

In another example by Mukaiyama and coworkers related to the synthesis of L-daunosamine (**119**), high diastereofacial selectivity is seen in the addition of the zinc enolate of *N,N*-dimethylacetamide to the chiral imine (**117**) derived from 2,3-*O*-cyclohexylidine-4-deoxy-L-threose, providing almost pure β-aminoamide (**118**) in good yield (Scheme 23).[106] This is one of the few examples of a stereoselective enolate–imine addition involving chirality attached to the imine α-carbon chain. A mechanistic rationale has not been proposed for the high level of diastereofacial selectivity, although the zinc cation must play an important role since the corresponding lithium enolate reacts to produce a 1:2 mixture of diastereomers enriched in the opposite C-3 *lyxo* configuration.

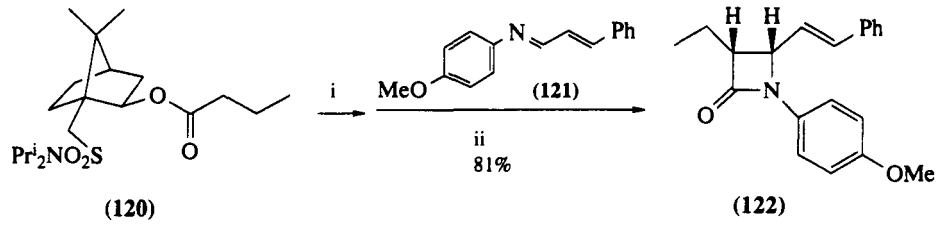


(**117**) (**118**) (**119**)

Scheme 23

Hart and coworkers[107] have prepared optically active β-lactams with extremely high *ee* values using lithium enolates of the 10-diisopropylsulfonamide isobornyl esters (**120**) developed by Oppolzer and coworkers for use in chiral Diels–Alder reactions and chiral alkylations.[108a,b] An example is shown in Scheme 24 involving the reaction of butyrate ester (**120**) with cinnamaldimine (**121**) to produce predominantly the *cis* β-lactam (**122**) in 91% *ee* (*cis:trans*, 10:1). Similar results are obtained using the corresponding isovalerate ester, with *cis* β-lactams predominating by an even greater ratio (>20:1). The absolute stereochemistry of β-lactam (**122**) is proven by its subsequent conversion to antibiotic (+)-PS-5 (**109**). Similar lithium enolate condensations have also been described by Bergbeiter, Newcomb and coworkers using (–)-menthyl esters; the *ee* values in those cases however are lower (4–60%).[89] Although no mechanistic rationale is proposed to account for the observed asymmetric induction, it is interesting to

note that the *syn* selectivity inherent in condensations of enolates of simple alkyl esters is preserved despite the presence of the chiral auxiliary.

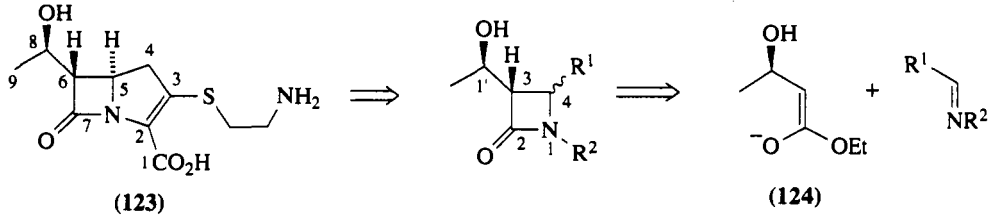


(120) (122)

i, LDA, THF, –78 °C; ii, –78 °C to r.t.

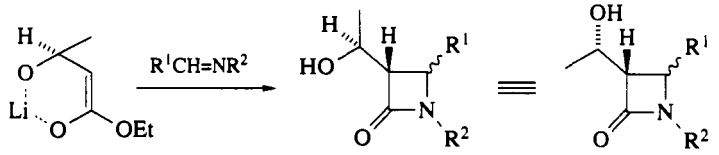
Scheme 24

Widespread interest in the synthesis of the potent antibiotic thienamycin (**123**)[78] has led to numerous applications of enolate–imine condensations involving enolates of 3-hydroxybutyrates (**124**). These enolates, which constitute the C(7)–C(6)–C(8)–C(9) backbone of thienamycin according to the widely adopted retrosynthetic analysis in Scheme 25, are attractive intermediates because the corresponding 3-hydroxybutyrate esters are readily available in optically active form. Critical in this approach is good relative diastereofacial control between C-3 and the C-1′ hydroxy group of the β-lactam. The configuration at C-4 is less crucial because it can be easily readjusted later in the synthesis. The lithium dianion of 3-hydroxybutyrate (**125**), which is known to alkylate in a highly diastereoselective (>95:5) *anti* fashion due to the chelated form of the enolate,[109] has been used extensively in reactions with imines and *N*-silylimines since it is expected to produce β-lactam (**126**) with predictable relative stereocontrol between C-3 and C-1′ (Scheme 26). Use of dianion (**125**), however, requires inversion of stereochemistry at the C-1′ hydroxy group of β-lactam (**126**) to establish the correct thienamycin stereochemistry.



(123) (124)

Scheme 25

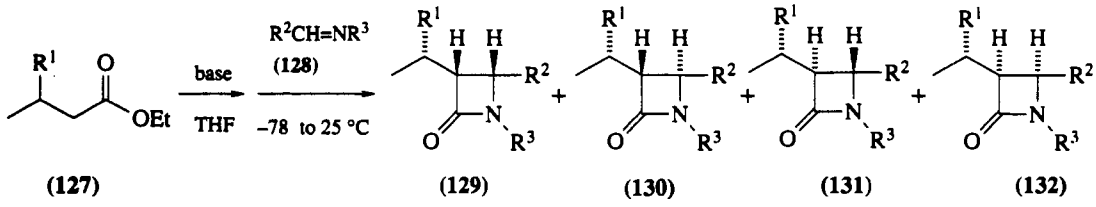


(125) (126)

Scheme 26

Condensation reactions between the lithium dianion of (*S*)-ethyl 3-hydroxybutyrate (**127**; R^1 = OH) and cinnamaldimine (**128**), in connection with the synthesis of thienamycin, have been reported independently by three groups: Georg *et al.*,[110] Cainelli *et al.*[111] and Hart and Ha.[112] Their results are summarized in Scheme 27 and Table 17 (entries 1–3); analogous reactions of dianion (**127**) with *N*-silylimines are discussed in Section 4.1.3.3.1. Of the four possible diastereomeric β-lactams (**129**)–(**132**) that can be produced in this reaction, the two that prevail, (**129**) and (**130**), contain the predicted relative stereochemistry at C-3 and C-1′. Subsequent inversion of the hydroxy groups of (**129**) and (**130**) led to intermediates which constituted formal total syntheses of thienamycin.[111,113] In addition to β-lactams (**129**) and (**130**), *trans* β-lactam (**131**) is sometimes isolated but *cis* β-lactam (**132**) is never observed. The product distributions are not uniform and may reflect the different bases used or the rate at

which the reaction mixture is allowed to warm to room temperature. There is only weak *syn–anti* selectivity in these reactions even though the enolate is of known (*Z*)-geometry, which should favor *trans* β-lactam (**130**) *via* a (*Z,E*)‡ transition state. Although competing transition states may be involved, it is nevertheless interesting to note that the high level of *syn* selectivity usually observed for the reactions of lithium ester enolates is eroded due to, presumably, the abnormal (*Z*)-geometry of the enolate. When HMPA is used different product distributions are found,[111,114] which has been explained by reversibility in the carbon–carbon bond forming step (see Scheme 19). Possible epimerization of the product has been ruled out in control experiments. In a related reaction using the enolate of (*R,S*)-ethyl 3-(dimethylphenylsilyl)butyrate (entry 4) in which the silyl group serves as a synthon for the hydroxy group, there is an even more random product distribution. It is unclear what effect the bulky silyl group has on the enolate geometry or on the transition state.[115]



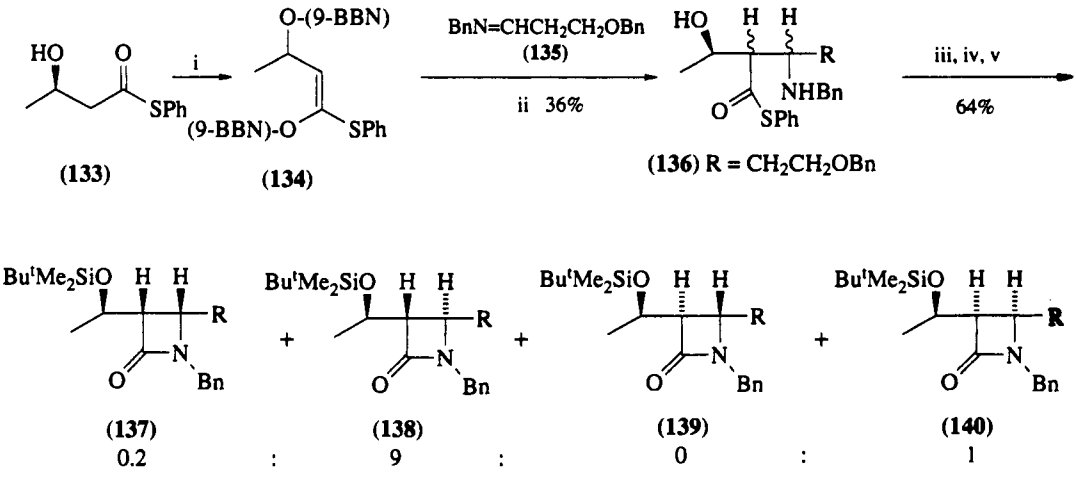
(**127**) (**129**) (**130**) (**131**) (**132**)

Scheme 27

Table 17 Formation of β-Lactams in the Reactions of the Enolates of 3-Substituted Ethyl Butyrates (**127**) with Imines (**128**)

	Reactants				*Products*				
	(**127**)	(**128**)			(**129**)	(**130**)	(**131**)	(**132**)	
Entry	R^1 *(Chirality)*	R^2	R^3	*Base*	*Yield (%)*				*Ref.*
1	OH *(S)*	Ph	OMe	2 LICA	45	45	—	—	110
2	OH *(S)*	Ph	OMe	2 LHMDS	35	54	9	—	111
3	OH *(S)*	Ph	OMe	2 LDA	25	27	6	—	112
4	$SiMe_2Ph$ *(S,R)*	Ph	OMe	LDA	35	5	15	11	115

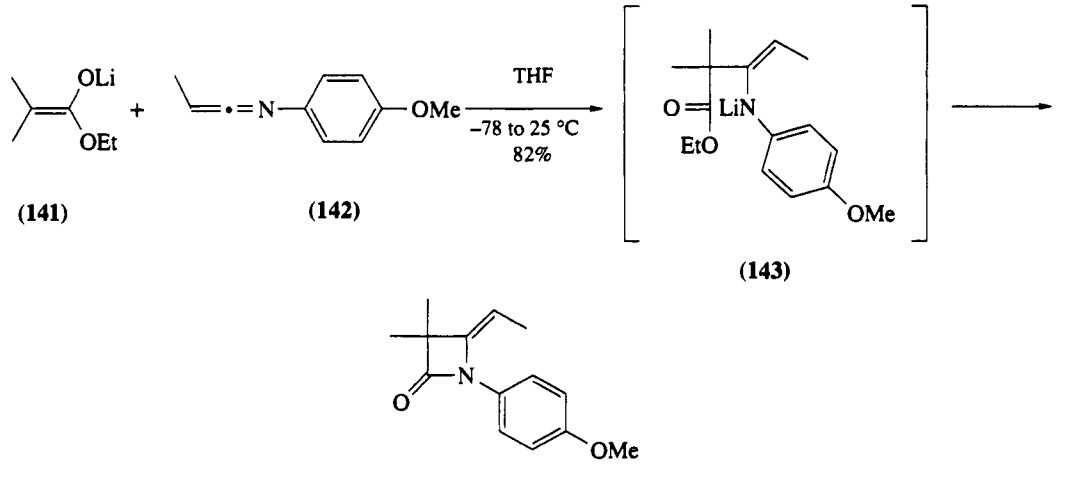
The limitation associated with inversion of the C-1′ hydroxy group using the 3-hydroxybutyrate dianion method for the synthesis of thienamycin has been overcome by Shibasaki and Iimori by using the *S*-phenyl thioester derivative of 3-(*R*)-hydroxybutyric acid (**133**; Scheme 28).[116] In this method, thioester (**133**) is converted to its boron enolate (**134**) using 9-BBN-OTf and Hunig's base with simultaneous protection of the 3(*R*)-hydroxy as a 9-BBN ether. Enolate (**134**) is then reacted with enolizable imine (**135**) corresponding to C(3)–C(5) of thienamycin to produce a mixture of β-amino thioesters (**136**). The stereochemical outcome of the condensation is revealed upon conversion of (**136**) to the mixture of O-TBDMS-protected β-lactams (**137**)–(**140**), in which β-lactam (**138**), with the correct stereochemistry for thienamycin, predominates by ~9:1. The possibility that epimerization occurs during the conversion of (**136**) to (**137**)–(**140**) has been ruled out. Based on the presumed (*Z*)-geometry of enolate (**134**),[117] the authors attribute the high level of *anti* selectivity (9:1) to a *C(Z,E)*‡ type transition state.[118] The *anti* selectivity of enolate (**134**) is also general for reactions with nonenolizable, alkynic and cinnamyl imines.[118,119] The authors discuss in a separate paper possible explanations for the high level of diastereofacial control between C-3 and C-1′.[118]



i, (9-BBN)OTf, Pr^i_2NEt, –70 to 35 °C; ii, –35 to 25 °C; iii, KOH, H_2O, THF; iv, 2,2'-dipyridyl disulfide–Ph_3P; v, Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2

Scheme 28

Ketenimines, as demonstrated by Battaglia *et al.*,[120] display remarkable diastereofacial selectivity in enolate–imine condensations. In the example illustrated in Scheme 29, enolate (**141**) and ketenimine (**142**) condense to give (*Z*)-4-ethylidene-β-lactam (**144**). The reaction is general for several mono- and di-substituted enolates and is completely stereospecific for the (*Z*)-alkylidene product. The carbon–carbon bond forming step occurs at –78 °C to produce an intermediate metalloenamine (**143**) that cyclizes upon warming to room temperature. When the reaction is quenched at –78 °C, hydrolysis of intermediate (**143**) occurs and the corresponding β-keto ester is isolated. Yields of β-lactams range from 30 to 82% and are highest using α,α-disubstituted enolates; apparently enolization of ketenimine (**142**) is not a serious problem. The stereospecificity of the reaction is attributed to favored attack of the enolate on the diastereotopic face of the ketenimine opposite the α-substituent (Figure 5).[120]



Scheme 29

Phthalide enolates (**145**), which can be viewed as dihomoenolates, add to Schiff bases to produce intermediate adducts (**146**) that cyclize to mixtures of *cis* and *trans* 3-aryl-4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolones (**147**) and (**148**) (Scheme 30). As originally described by Dodsworth, Sammes and

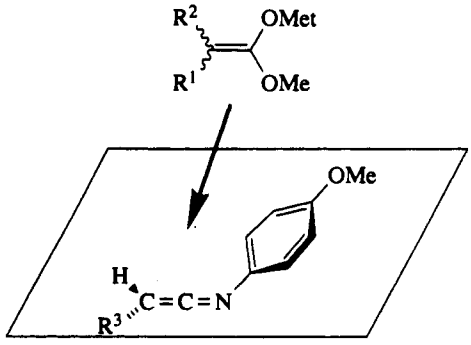
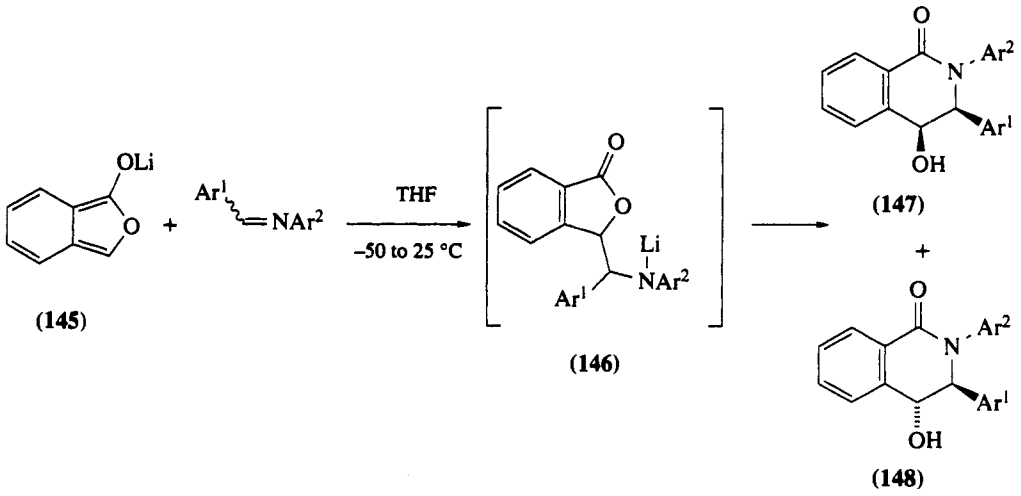


Figure 5 Addition of enolates to ketenimines occurs on the diastereotopic face opposite the α-substituent (R^3)

coworkers,[121,122] *cis* products predominate consistently by ~2:1 over a series of nonenolizable arylimines; yields range from 40 to 70%. The preference for the *cis* isomer has been explained by a cyclic transition state in which the steric interactions of the α-substituent of the imine are minimized by placing it *gauche* to the lactone oxygen instead of to the more bulky aromatic portion of the phthalide (Figure 6). As will be discussed in Section 4.1.3.5, the opposite stereochemical outcome occurs in analogous reactions of cyclic imines (*i.e.* 3,4-dihydroisoquinolines).



Scheme 30

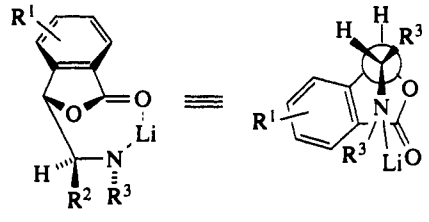
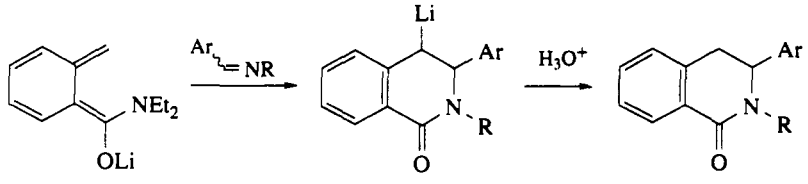


Figure 6 Proposed transition state involved in the addition of phthalide enolates to imines[122]

Analogous condensations using lithium enolates of *N,N*-diethyl-*o*-toluamide (**149**) have been described by Clark and Jahangir for the synthesis of 3,4-dihydro-1(2*H*)-isoquinolones[123,124] (**151**; Scheme 31). It is fortunate that the enolate–imine addition–cyclization process occurs at low temperature, since warming the reaction mixture to room temperature, a common practice in many enolate–imine additions, leads to side reactions due to the instability of the 4-lithiated derivative (**150**) formed by release of lithium diethylamide. The authors have exploited the *in situ* formation of (**150**) for the synthesis of 4-substituted isoquinolones by trapping it with electrophiles. A cycloaddition mechanism *via* an

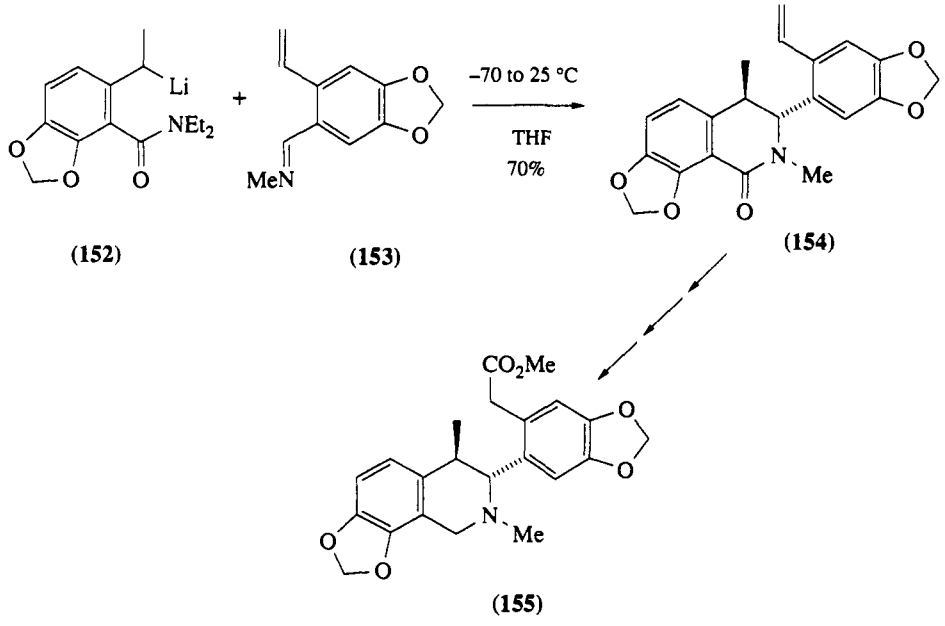
o-quinodimethane (a vinyl ketene) formed by possible loss of lithium diethylamide from (**149**) does not seem to be involved. Yields of 3,4-dihydro-1(2*H*)-isoquinolones (**151**) are moderate (30–50%) for the 'one-pot' process. Besides arylimines, certain bulky enolizable imines such as those derived from cyclohexanone and cyclohexanecarbaldehyde also react. Analogous reactions using dilithiated *N*-methyl-*o*-toluamide have also been reported; the adducts, however, do not cyclize *in situ*.



(**149**) (**150**) (**151**)

Scheme 31

Clark and Jahangir have elegantly applied the above methodology to the total synthesis of (±)-corydalic acid methyl ester (**155**), an alkaloid isolated with protoberberine and benzo[*c*]phenanthridine from *Corydalis incisa* (Scheme 32).[125] The *o*-toluamide enolate (**152**), which in this case is substituted at the methyl group, adds stereospecifically to imine (**153**), affording *trans*-isoquinolone (**154**). The overall yield of (**154**) is based on the isolation of some uncyclized aminoamide (28%), which is cleanly cyclized to (**154**) by treatment with *t*-butyllithium. Because the uncyclized aminoamide contains the same relative stereochemistry as the cyclized material, it is likely that the overall stereospecificity of the reaction is reflected in the carbon–carbon bond forming step and not *via* epimerization at C-4. Conversion of isoquinolone (**154**) to (±)-corydalic acid (**155**) is accomplished by elaboration of the vinyl group and reduction of the lactam.



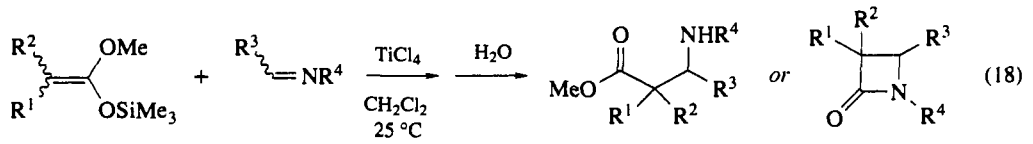
(**152**) (**153**) (**154**) (**155**)

Scheme 32

(iii) Reactions with silyl ketene acetals

The condensation of silyl ketene acetals (**156**) with imines in the presence of Lewis acids, usually $TiCl_4$, to afford β-lactams or β-amino esters (equation 18) was first reported by Ojima *et al.*[126] The mechanism of β-lactam formation is similar to the one previously outlined in Scheme 19 for enolate–

imine additions, involving metalated amine intermediates (**98**) and (**99**) (M = $TiCl_3$), which undergo cyclization. Aspects of the initial carbon–carbon bond-forming step, however, are less clear. Ojima *et al.* postulate that titanium enolates generated by cleavage of the silyl ketene acetal by $TiCl_4$ add to imines *via* pericyclic transition states.[126,127] On the other hand, recent stereochemical evidence supports an open transition state. Both mechanisms will be discussed in light of the current investigations.

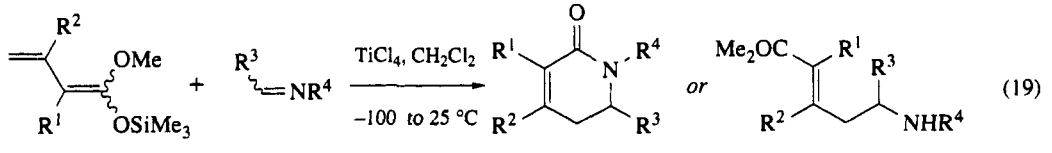


(18)

(**156**) (**157**) (**158**) (**159**)

The review by Evans *et al.*[10] has covered the early investigations of Ojima *et al.*[126–128] and only some brief generalizations are presented here. Yields using nonenolizable imines (**157**; R^3 = Ph) are good to excellent (70–95%) based on a twofold excess of imine. Enolizable imines (**157**; R^3 = Et, Pr^i) also react but in lower yield (40–50%). Formation of β-lactams (**159**) occurs readily with *N*-alkylimines (**157**; R^4 = Bn, Me, Ph(Me)CH) but not with *N*-arylimines (**157**; R^4 = Ph), in which case β-amino esters (**158**) are isolated. That β-lactam formation occurs with *N*-arylimines in condensation reactions with lithium and zinc enolates indicates that the corresponding titanium amide intermediates (**98**) and (**99**) (R^3 = Ph; M = $TiCl_3$; Scheme 19) are less nucleophilic. High levels of diastereofacial selectivity are also observed using chiral imines derived from (*S*)-(1-arylethyl)amines[127] and (*S*)-valine methyl ester.[128] The *ee* values of these β-lactam-forming reactions are 40–70% and 90–98%, respectively. In the latter case, formation of a titanium template between the imine lone pair and the carbomethoxy group is proposed to account for the high level of asymmetric induction.

In an extension of their earlier work, Ojima and coworkers have described analogous reactions using vinyl silyl ketene acetals (**160**; equation 19).[129] The carbon–carbon bond forming step in these reactions occurs exclusively at the terminal carbon of the vinyl silyl ketene acetal (**160**) to give cyclized 5,6-dihydro-2-pyridones (**162**), methyl 5-amino-2-pentenoates (**163**), or mixtures. Steric and electronic factors play an important role in the formation of cyclized products, which are favored by the lack of an α-substituent (R^1) and the presence of an *N*-alkyl group on the imine (R^4). Formation of (**162**) and (**163**) proceeds by a common metalated intermediate, since in reactions that form cyclized products (**162**), quenching at –50 °C leads to acyclic products. Yields are good to excellent when corrected for recovered imine (**161**), but a *100%* excess of vinyl silyl ketene acetal (**160**) must be employed. It is curious to note that these reactions require much lower initial temperatures (–100 °C) than those of silyl ketene acetals.

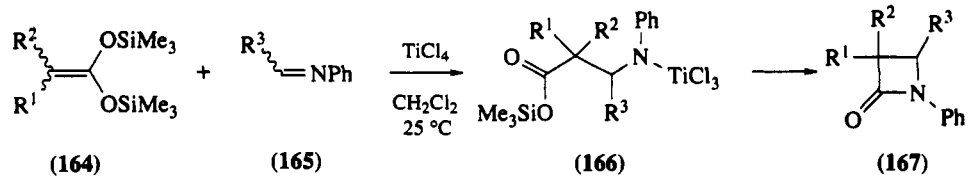


(19)

(**160**) (**161**) (**162**) (**163**)

As noted above, β-lactam formation in reactions of silyl ketene acetals with imines is dependent on the N-substituent of the imine. In a new variation using ketene bis(trimethylsilyl) acetals (**164**), Dubois and Axiotis have reported that β-lactams (**167**) can be obtained exclusively in $TiCl_4$-catalyzed reactions with nonenolizable (R^3 = Ph) and hindered enolizable imines (**165**; R^3 = Pr^i; Scheme 33; Table 18).[130] In contrast to the reactions of silyl ketene acetals which produce acyclic adducts using *N*-arylimines, the exclusive formation of β-lactams in the reactions of ketene bis(trimethylsilyl) acetals (**164**) with *N*-arylimines is attributed to the superior leaving group ability of the trimethylsilyloxy group in the metalated amine intermediate (**166**). Yields of β-lactams (**167**) are good (65–75%) and are based on stoichiometric amounts of reagents. No relative stereochemistry is reported in the cases involving unsymmetrical ketene bis(trimethylsilyl)acetals (entries 4 and 5).

Chiral silyl ketene acetals derived from (1*S*,2*R*)-*N*-methylephedrine (**168**), known to exhibit high levels of *syn–anti* and diastereofacial selectivities in the aldol condensation,[131] have been used by Gennari *et al.* in $TiCl_4$-mediated imine condensations for the asymmetric synthesis of β-lactams (Scheme 34).[132,133] β-Amino esters (**169**) are produced in these reactions, and are characterized by their sub-



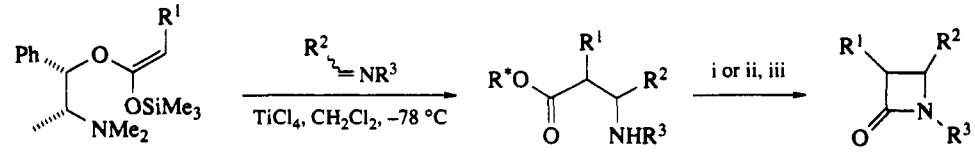
(164) (165) (166) (167)

Scheme 33

Table 18 Formation of β-Lactams (**167**) *via* $TiCl_4$-catalyzed Condensations of Ketene Bis(trimethylsilyl) Acetals (**164**) with Imines (**165**)[130]

Entry	*Ketene bis(trimethylsilyl) acetal (164)* R^1	R^2	*Imine (165)* R^3	*β-Lactam (167) Yield (%)*
1	Me	Me	Ph	75
2	Me	Me	Pr^i	66
3	—$(CH_2)_5$—		Ph	60
4	Ph	H	Ph	69
5	Ph	H	Pr	65

sequent conversion to the corresponding β-lactam derivatives (**170**). In the examples shown in Table 19, it is interesting to note that *anti* selectivity is observed in the reaction of an (*E*)-silyl ketene acetal with benzylideneaniline (entry 1), since the opposite *syn* selectivity is normally found in the corresponding reactions of (*E*)-enolates, presumably *via* a *C*(*E*,*E*)‡ transition state. This dichotomy between the *syn–anti* selectivity of enolates and silyl ketene acetals possessing like geometry strongly suggests that the mechanisms of the two reactions are different. Thus, addition of silyl ketene acetals to imines may not involve free enolates as originally proposed,[126] but rather direct addition to the activated imine *via* an open transition state to form an oxonium ion intermediate (**171**), followed by cleavage of the silyl group (Scheme 35). Heathcock and coworkers have proposed similar open transition states for related Lewis acid mediated reactions of enol silanes with aldehydes.[134] It is also curious that the opposite *syn* selectivity is observed with α-carboethoxyimines (entries 2 and 3), even when the silyl ketene acetals are 1:1 mixtures of (*E*)- and (*Z*)-isomers. The authors propose that the different stereochemical outcome of reactions of arylimines and α-carboethoxyimines is due to the formation of a five-membered ring titanium chelate complex in the case of the α-carboethoxyimine. Clearly, a more systematic study of the *syn–anti* selectivity of these reactions and its relationship to the geometry of the silyl ketene acetal is needed. The high diastereofacial selectivities of these reactions are also noteworthy, especially in the case involving a single silyl ketene acetal geometry which gives the corresponding β-lactam in >95% *ee* (entry 1). In the analogous $TiCl_4$-mediated aldol condensation of silyl ketene acetals (**168**), which gives similar high levels of asymmetric induction, a six-coordinate intermediate titanium complex with binding to the ephedrine dimethylamine and aldehyde carbonyl groups has been suggested.[131]



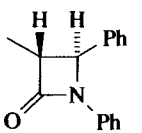
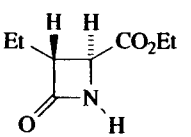
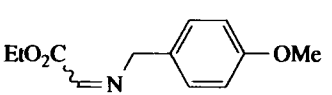
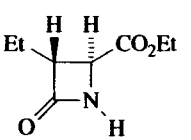
(168) (169) (170)

i, LHMDS, THF, –10 °C; ii, HCO_2H, MeOH, Pd–C; iii, 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN

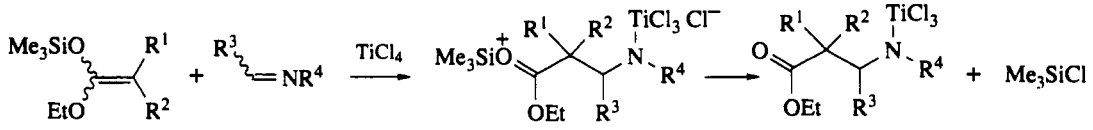
Scheme 34

Guanti and coworkers have reported that catalytic amounts (0.1 equiv.) of TMS-OTf can be used in place of stoichiometric amounts of $TiCl_4$ in silyl ketene acetal–imine additions.[135] When conducted at the optimal temperature of –65 °C, β-amino esters enriched in the *anti* diastereomer are obtained in 45–85% yields. Use so far has been limited to nonenolizable imines. Interestingly, the observed *anti* stereoselectivity is independent of the geometry of the silyl ketene acetal, further evidence that a nonpericyclic mechanism is involved in the Lewis acid catalyzed addition of silyl ketene acetals to imines. An applica-

Table 19 Condensations of Silyl Ketene Acetal (**168**) with Imines Mediated by $TiCl_4$

Entry	R^1	*Silyl ketene acetal (168) Geometry*	*Imine*	*Conversion to (170)*[a]	*Major product (170)*	*ee (%)*	*Syn:anti selectivity*	*Ref.*
1	Me	*(E)*	PhCH=NPh	i	 59%	>95	<1:10	132
2	Et	*(E)*:*(Z)* 1:1	EtO_2CCH=NBn	ii, iii	 46%	50	8:1	133
3	Et	*(E)*:*(Z)* 1:1		ii, iii	 46%	75	7:1	133

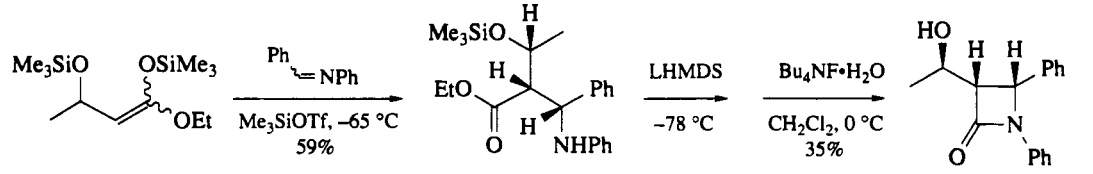
[a] See Scheme 34.



(171)

Scheme 35

tion of this method to the synthesis of thienamycin using the hydroxysilylated silyl ketene acetal derived from racemic 3-hydroxybutyrate (**172**) (unspecified enolate geometry) is shown in Scheme 36.[136] The condensation of (**172**) with benzylideneaniline in the presence of TMS-OTf is amazingly stereospecific, giving a single β-amino ester (**173**). The relative stereochemistry of β-amino ester (**173**) was determined upon subsequent conversion to β-lactam (**174**) and was found to be correct for thienamycin at C-3 and C-1′. It is interesting to note that the β-silyloxy group changes the selectivity of these reactions from *anti* to *syn*; the silyl ketene acetal derived from methyl propionate condenses with benzylideneaniline to give exclusively the *anti* β-amino ester.[135]



(172) (173) (174)

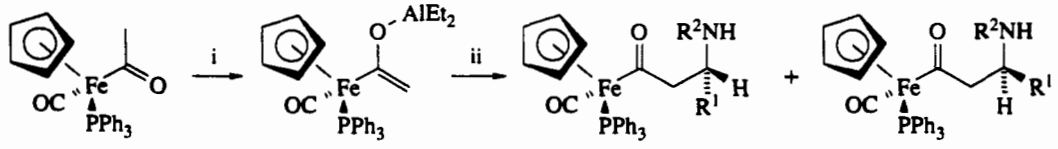
Scheme 36

4.1.3.2.3 Reactions with ketones

Reactions of free ketones with imines are far more restricted than those with preformed iminium salts. Examples of ketone–imine condensations are included in several reviews[3,4,6,7] and are limited to the use of arylimines, mainly benzylideneaniline. Blatt and Gross have noted that the reproducibility of uncatalyzed additions of ketones to Schiff bases is poor but can be improved by the addition of small amounts of hydrochloric acid.[137] The highest yields of β-amino ketones are obtained using 10 mol % of concentrated hydrochloric acid and 95% ethanol as solvent, and by performing the reaction at room temperature. The reaction, however, is of limited applicability, as it is restricted to methyl ketones and cycloalkanones. Deamination leading to unsaturated ketones is a major side reaction. In addition to hydrochloric acid, boron trifluoride etherate has been used as a catalyst in reactions of aromatic imines with methyl ketones, cyclic ketones[138] and an epoxy ketone.[139]

Examples of ketone–imine additions involving kinetically formed enolates or enol silanes are surprisingly few in comparison to those of carboxylic acid derivatives and silyl ketene acetals. An interesting example, nevertheless, has been reported independently by Broadly and Davies[140] and Liebeskind *et al.*[141] involving the use of the chiral–racemic, acyliron complex [η⁵-CpFe(PPh₃)(CO)COMe] (**175**), treated here as a ketone. Enolates of (**175**) condense with nonenolizable imines with impressive levels of 1,4-diastereofacial selectivity to form predominately diastereomer (**177**; Scheme 37). For example, the diethylaluminum enolate (**176**) reacts with benzylidenepropylamine to afford a >20:1 ratio of (**177**):(**178**) (R^1 = Ph; R^2 = Pr^n).[141] Lithium enolates also exhibit high levels of diastereofacial selectivity but are less successful in reactions with *N*-alkylimines. Yields are also good (80–90%) if corrected for recovered ketone (**175**). Liebeskind and coworkers rationalize the diastereofacial selectivity of the reaction by invoking two possible chair-like transition states (**179a**) and (**179b**) (Figure 7). It is argued that the imine prefers to condense in such a way as to minimize the steric interaction between R^1 and the bulky PPh_3 ligand of the iron enolate; thus attack at the accessible diastereotopic face of the enolate in transition state (**179a**) is favored, leading to diastereomer (**177**). An alternative model suggested by Broadly and Davies proposes that imine addition occurs opposite to the PPh_3 group in rotomer (**180**).[140] A detailed discussion

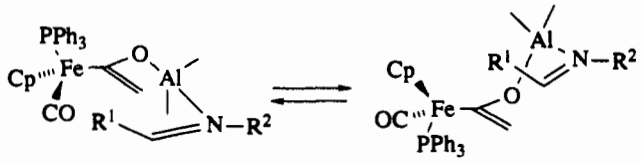
of the two mechanisms is presented in a full paper by Liebeskind *et al.*[142] The use of enolates of (**175**) in optically active form should have important applications to the asymmetric synthesis of β-lactams, since β-amino iron acyls can be converted to β-lactams by oxidative insertion.[143]



(**175**) (**176**) (**177**) (**178**)

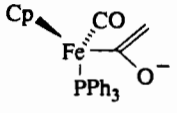
i, LDA, THF, –42 °C, Et_2AlCl; ii, $R^1CH{=}NR^2$, –42 °C

Scheme 37



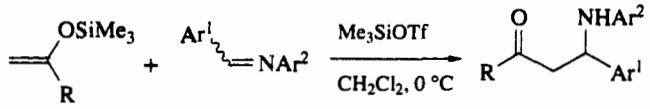
(**179a**) (**179b**)

Figure 7 Proposed transition states involved in the addition of the enolate of acyliron complex (**175**) to imines[141]



(**180**)

Enol silanes (**181**), as reported by Pilli and Russowsky, add to arylimines (**182**) in the presence of catalytic amounts of TMS-OTf to afford *N*-aryl-β-amino ketones (**183**; equation 20).[144] The reaction is carried out by adding the enol silane to the imine in the presence of 15 mol % of TMS-OTf at 0 °C in CH_2Cl_2, followed by aqueous work-up. Yields range from 50% to 98% in a series of benzylideneaniline derivatives using the enol silanes derived from acetophenone and *t*-butyl methyl ketone. The extent to which the reaction may be limited to nonenolizable imines, as in the analogous TMS-OTf-promoted reactions of silyl ketene acetals (see Section 4.1.3.2.2.iii),[135,136] is not reported. The authors describe some spectral characteristics of an insoluble material formed by treating benzylideneaniline with TMS-OTf in $CHCl_3$. The data are consistent with the derived *N*-silyliminium salt of (**182**), the putative reactive intermediate.



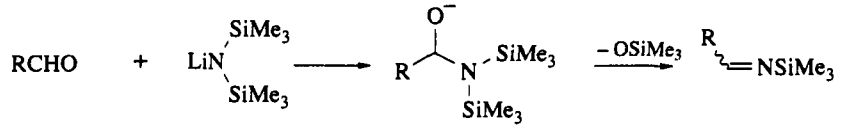
(**181**) R = Ph, Bu^t (**182**) (**183**) (20)

4.1.3.3 N-Heterosubstituted Imines

4.1.3.3.1 N-*Silylimines*

N-Silylimines display similar reactivity and stereoselectivity to *N*-arylimines in reactions with enolates and silyl ketene acetals; their advantage is that they provide easy access to *N*-unsubstituted β-lactams by

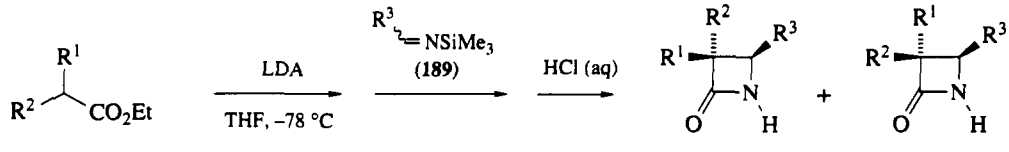
protodesilylation during work-up. Like acyclic imines, they exist in one geometrical form, presumably (*E*). *N*-Silylimines (**187**) are usually prepared *in situ* by condensing lithium hexamethyldisilazide (LHMDS; **185**) with an aldehyde (**184**) to form an initial alkoxide adduct (**186**), which spontaneously loses trimethylsilyl oxide in analogy to the Peterson alkenation (Scheme 38). If desired, *N*-silylimines can be isolated by distillation, providing they are nonenolizable. A more detailed discussion of the preparation of N-TMS and N-TBDMS imines, their mechanism of formation and their structure, is presented in an article by Colvin *et al.* related to condensations of silyl ketene acetals with *N*-silylimines.[145]



(184) **(185)** **(186)** **(187)**

Scheme 38

Pioneering investigations by Hart and coworkers have provided much of the insight into the scope and stereoselectivity of enolate–*N*-silylimine condensations. In the original paper, the viability of these reactions was demonstrated using mainly α,α-disubstituted esters (**188**), which add *via* their lithium enolates to nonenolizable *N*-silylimines (**189**) to afford mixtures of diastereomeric *N*-unsubstituted β-lactams (**190**) and (**191**) following aqueous acidic work-up (Scheme 39; Table 20; entries 1–6).[146] *N*-Silylimines derived from cinnamaldehyde and 3-(trimethylsilyl)propargylaldehyde (entries 4–6) can be used to facilitate further elaboration of C-4 of the β-lactam. The mechanism of β-lactam formation is postulated to be stepwise, based on the analogy to the reactions of *N*-aryl- and *N*-alkyl-imines (see Scheme 19) and the known ability of β-trimethylsilyl(amino) esters to undergo cyclization to β-lactams.[145,147] Further studies by Hart and coworkers have shown that β-lactams can be prepared using lithium enolates of mono-α-substituted esters (entries 8–14).[148] The reported failure of these enolates to produce β-lactams in good yields in reactions with *N*-arylimines[89] implies that the carbon–carbon bond forming step in reactions of *N*-silylimines occurs at lower temperatures than those of *N*-arylimines, and decomposition of the enolate is therefore less likely. However, in the case of the unsubstituted enolate (entry 7), which is more prone to decomposition, the β-lactam is obtained in poor yield. Under the conditions of enolate generation (THF, –78 °C) that produce predominantly (*E*)-enolates, stereocontrol in favor of *cis* β-lactams (**190**) is excellent (entries 8, 10 and 12). These results are consistent with a $C(E,E)^{\ddagger}$ transition state and parallel the earlier investigations of Luche and Kagan where *syn* selectivity is observed in analogous reactions using Reformatsky reagents.[91,149] Not surprisingly, erosion in stereoselectivity occurs using (*Z*)-enolates, prepared according to the Ireland procedure using HMPA,[150] resulting in nearly 50:50 mixtures of *cis* and *trans* β-lactams (entries 9, 11 and 13). Control experiments demonstrate that HMPA affects only the enolate geometry and does not promote epimerization of the β-lactam. It is worth noting that *N*-aryl-β-lactams epimerize in the presence of LDA/HMPA as demonstrated by the conversion of the *cis* *N*-phenyl derivative of β-lactam (**190**) of entry 12 to the *trans* *N*-phenyl derivative of β-lactam (**191**).[148] Thus, in β-lactam-forming reactions that require coordinating solvents, *N*-silylimines should react with more predictable stereocontrol than *N*-arylimines.

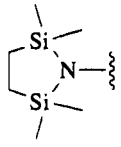
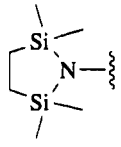
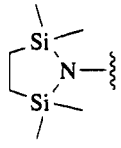


(188) **(190)** **(191)**

Scheme 39

Although formation of enolizable *N*-silylimines is usually accompanied by isomerization to the enamine and by deprotonation of the aldehyde precursor,[145] *N*-silylimines derived from enolizable aldehydes have nevertheless been reported by Cainelli, Panunzio and coworkers to condense with enolates (Table 20; entries 15–17).[151] The temperature at which the *N*-silylimine is generated, –30 °C, may be critical since nonenonolizable *N*-silylimines are normally generated at -70 °C. Condensations with enolizable *N*-silylimines, like those with nonenolizable *N*-silylimines, are stereoselective and produce mainly *cis* β-lactams. The yields (30–40%), however, are lower.

Table 20 β-Lactam-forming Reactions of *N*-Silylimines (**189**) and Lithium

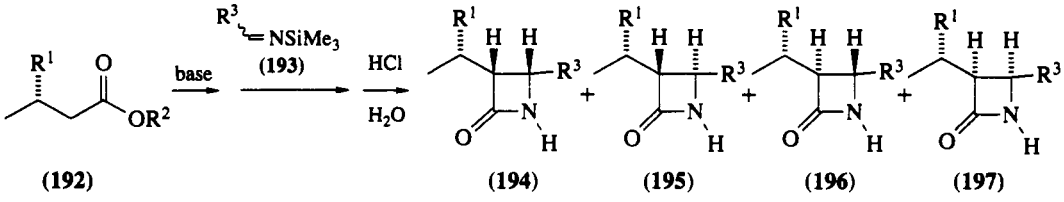
Entry	Ester (**188**) R^1	R^2	*N*-Silylimine (**189**) R^3	Yield (%)	β-Lactams (**190**):(**191**) Ratio	Ref.
1	Me	Me	Ph	72		146
2	Me	SPh	Ph	58	2.4:1	146
3	H	SPh	Ph	53	9.6:1	146
4	Me	Me	PhCH=CH	69		146
5	Me	Me	TMSC≡C	79		146
6	Me	SPh	TMSC≡C	74	2.7:1	146
7	H	H	Ph	14		148
8	Me	H	Ph	44	93:7	148
9	Me	H	Ph	44	43:57[a]	148
10	Et	H	Ph	72	100:0	148
11	Et	H	Ph	66	42:58[a]	148
12	Pr^i	H	Ph	81	99:1	148
13	Pr^i	H	Ph	86	50:50[a]	148
14	Bu^t	H	Ph	40	100:0	148
15	Me	H	Me	38	86:14	151
16	Et	H	C_9H_{19}	44	92:8	151
17		H	Me	40	90:1[b]	151
18		H	TMSC≡C	80	7:93[c]	99
19		H	Ph	90	30:70[c]	99
20	TMS_2N	H	Ph	70	11:89[c]	99

[a]HMPA is used as a cosolvent in the generation of the enolate. [b]The product is isolated as its *N*-CBZ derivative. [c]$ZnCl_2$ is added to the lithium enolate in ether prior to addition of the *N*-silylimine.

(*Z*)-Zinc enolates of *N,N*-bissilylglycine esters, according to van Koten and coworkers, condense with *N*-silylimines with high *anti* selectivity (Table 20; entries 18–20).[99,100] These results parallel those previously described in Section 4.1.3.2.2.i using *N*-aryl- and *N*-alkyl-imines and are consistent with a *C(Z,E)*‡ transition state. Reactions of *N*-silylimines are slightly less *anti* selective, however, than those of *N*-aryl- and *N*-alkyl-imines. Retroaldolization prior to cyclization has been cited as a possible cause for the erosion in stereoselectivity based on the slow rates of cyclization found in the reactions of entries 19 and 20.

Condensations of enolates of 3-substituted butyrates (**192**) with *N*-silylimines (Scheme 40), like those with *N*-arylimines (see Section 4.1.3.2.2.ii), have been used widely in the synthesis of thienamycin. Examples are shown in Table 21, where it should be noted that entries 2, 3 and 5 have a direct parallel with entries 3, 2 and 4, respectively, in Table 17, describing related *N*-arylimine condensations. The product distributions of diastereomeric β-lactams (**194**)–(**197**) in *N*-silylimine condensations are similar to those found in *N*-arylimine condensations, which is not surprising in view of their similar *syn–anti* selectivities. *N*-Silylimines exhibit somewhat higher stereoselectivity, however, as evidenced by the minimal formation of β-lactams (**196**) and (**197**). Even the reaction of ethyl 3-(dimethylphenylsilyl)butyrate (entry 5) is considerably more stereoselective than its *N*-aryl counterpart (Table 15; entry 4), providing almost exclusively a single β-lactam (**194**). Nakai and coworkers have noted that in the reactions of the propargyl-*N*-silylimine (entry 4), higher yields are obtained using (*S,R*)-methyl 3-hydroxybutyrate in-

stead of the corresponding ethyl ester and LHMDS instead of LDA as base.[152] In an alternative approach to the synthesis of thienamycin, these workers have also prepared the β-lactams of entry 4 in the enantiomeric series using (*R*)-methyl 3-hydroxybutyrate.[153–155]



(192) (194) (195) (196) (197)

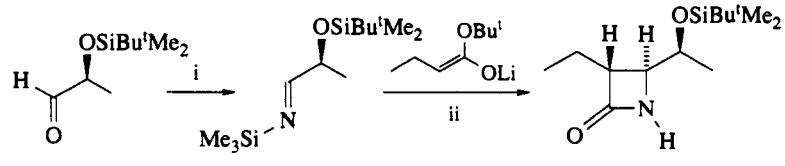
Scheme 40

Table 21 β-Lactam-forming Reactions of *N*-Silylimines (**193**) and Enolates of 3-Substituted Ethyl and Methyl Butyrates (**192**)

Entry	Ester (192) R^1 (Chirality)	R^2	*N*-Silylimine (193) R^3	Base	β-Lactams (194)	(195)	(196)	(197)	Yield (%)	Ref.
1	OH (*S,R*)	Et	PhSCH=CH	2LDA	31	8	2	—		148
2	OH (*S*)	Et	PhCH=CH	2 LDA	27[a]	16[a]	—	—		112
3	OH (*S*)	Et	PhCH=CH	2 LHMDS	35	15	—	—		156
4	OH (*S,R*)	Me	TMSC≡C	2 LHMDS	56	19	—	—		152
5	Me_2PhSi (*S,R*)	Et	Ph	LDA	63	—	b	—		115

[a]Products are characterized as *O*-TBDMS derivatives. [b]Trace.

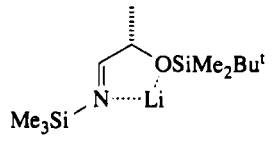
Cainelli, Martelli and coworkers have reported an interesting case of combined *syn–anti* and diastereofacial selectivity using chiral *N*-silylimine (**199**), prepared *in situ* from (*S*)-O-TBDMS-lactic aldehyde (**198**).[157] As shown in Scheme 41, condensation of the lithium enolate of *t*-butyl butyrate with *N*-silylimine (**199**) affords essentially a single β-lactam (**200**), contaminated with only 4% of the corresponding other *trans* diastereomeric β-lactam. The authors propose that the high level of diastereofacial selectivity (14:1) is due to the formation of lithium chelate (**201**), which undergoes attack by the enolate from the least hindered π-face of the imine. The authors do not discuss the unusual *anti* selectivity of this reaction.



(198) (199) (200)

i, LHMDS, THF, –40 °C; ii, THF, –78 °C to r.t.

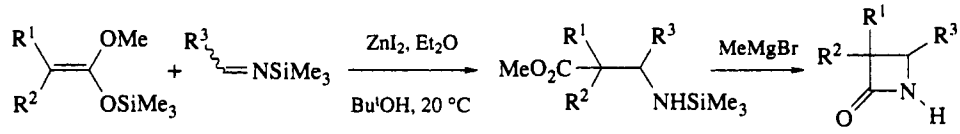
Scheme 41



(201)

Condensations of *N*-silylimines with silyl ketene acetals have been reported by Colvin and coworkers using ZnI_2 as catalyst (Scheme 42; Table 22).[145,158] Interestingly, titanium tetrachloride, the catalyst of

choice in the corresponding reactions of silyl ketene acetals with *N*-aryl- and *N*-alkyl-imines, is not effective in these reactions. When an equivalent of Bu^{t}OH is present in the reaction, the products are β-(trimethylsilyl)amino esters (**204**), which can be easily cyclized to β-lactams (**205**) by *in situ* addition of MeMgBr. Without the presence of Bu^{t}OH to protonate the initial adduct, cross-condensation side reactions occur between the adduct and unreacted *N*-silylimine. Yields of β-lactams, 50–80%, are generally comparable to those obtained using enolates. Figure 8 depicts two proposed synclinal transition states, (**206**) and (**207**), leading to *trans* and *cis* adducts, respectively, used by Colvin and coworkers to explain the *anti* selectivity of these reactions.[145] Transition state (**206**) is preferred, based on the more stable *anti* relationship between the silyl ketene acetal and the R group of the *N*-silylimine, whereas in transition state (**207**) they are in a less favored *gauche* relationship. This model is also consistent with the fact that the *syn–anti* selectivity of these reactions is independent of the silyl ketene acetal geometry. These results parallel those found in the reactions of *N*-aryl- and *N*-alkyl-imines and further support a mechanism that does not involve free enolates.



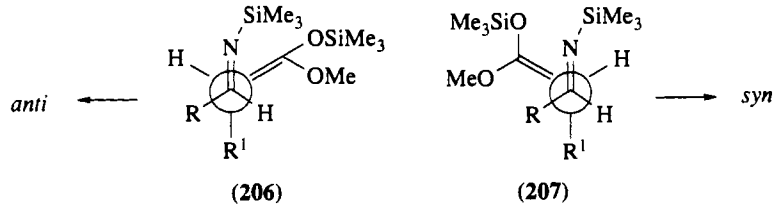
(**202**) (**203**) (**204**) (**205**)

Scheme 42

Table 22 Reactions of Silyl Ketene Acetals (**202**) with *N*-Silylimines (**203**) Catalyzed by ZnI_2[145,158]

	Silyl ketene acetal (**202**)		*N-Silylimine* (**203**)	*β-Lactam*[a] (**205**)	
Entry	R^1	R^2	R^3	*Yield (%)*	*Trans:cis ratio*
1	Me	Me	Ph	75	
2	Me	Me	2-Furyl	76	
3	Me	Me	PhC≡C	78	
4	Me	Me	TMSCH=CH	75	
5	PhO	H	2-Furyl	58	0.77:1
6	Et	H	Ph	61	9:1
7	Me	H	PhC≡C	82	3:1
8	Me	H	TMSC≡C	62	1.5:1
9	Ph	H	TMSC≡C	53	12:1

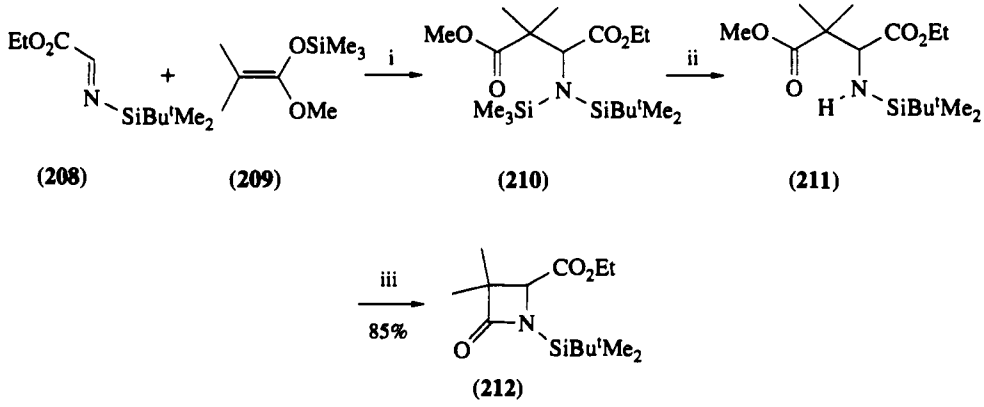
[a]Formed by treating the corresponding β-(trimethylsilyl)amino esters (**204**) with MeMgBr *in situ*.



(**206**) (**207**)

Figure 8 Proposed open transition states involved in silyl ketene acetal–*N*-silylimine additions[145]

Similar reactions of silyl ketene acetals with *N*-(*t*-butyldimethylsilyl)imines have also been described by Colvin *et al.*[145] An example is shown in Scheme 43 involving the condensation of the *N*-TBDMS-imine derived from ethyl glycinate (**208**) and the silyl ketene acetal of methyl isobutyrate (**209**). Catalysis by TMS-OTf is preferred over ZnI_2 in these reactions, and it is thus unnecessary to use Bu^{t}OH as a proton source because the silyl group of the silyl ketene acetal is transferred to the imine nitrogen, thereby protecting the initial adduct (**210**) from condensation with unreacted *N*-silylimine. Following aqueous work-up, the more stable TBDMS group survives, affording *N*-TBDMS-β-amino ester (**211**), which can be cyclized to *N*-TBDMS-β-lactam (**212**) using MeMgBr. The use of *N*-(*t*-butyldimethylsilyl)imines may be preferred over *N*-trimethylsilylimines if further elaboration of the β-lactam requires protection of the nitrogen.



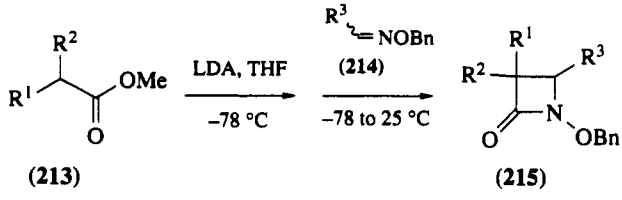
(208) (209) (210) (211) (212)

i, Me_3SiOTf, 0 to 25 °C; ii, Na_2HPO_4, H_2O; iii, MeMgBr

Scheme 43

4.1.3.3.2 Oxime ethers

Oxime ethers are alternatives to *N*-silylimines for the synthesis of *N*-unsubstituted β-lactams, uncovered by reductive cleavage of the N—OR bond. They also serve, unlike other classes of imines, as primary aminomethylating reagents CH_2NH_2, since the formaldehyde adducts for the introduction of CH_2NH_2 (CH_2=NOR) are resistant to polymerization. Some examples reported by Sekiya and coworkers of the reactions of *O*-benzyl oxime ethers (**214**) with lithium enolates of methyl esters to produce *N*-benzyloxy-β-lactams (**215**) are shown in Scheme 44 and Table 23.[159] Yields range from 40 to 80% and tend to be higher with the methyleneamino oxime derivatives (entries 1–4) than those containing enolizable protons (entries 5 and 6).



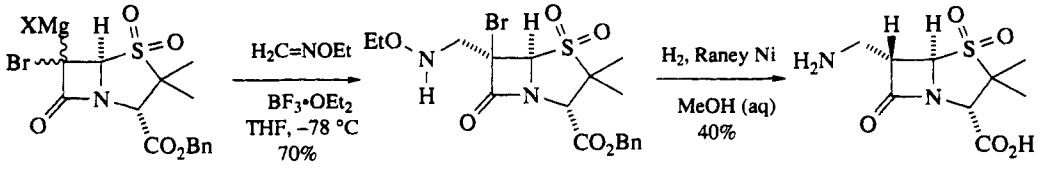
(213) (215)

Scheme 44

Table 23 β-Lactam-forming Reactions of *O*-Benzyl Oxime Ethers (**214**) and Enolates of Ester (**213**)[159]

Entry	*Ester (213)* R^1		R^2	*Oxime (214)* R^3	*β-Lactam (215) Yield (%)*
1	Me		Me	H	67
2	Ph		Et	H	82
3		—$(CH_2)_6$—		H	65
4		—$(CH_2)_5$—		H	49
5	Me		Me	Me	48
6	Me		Me	Et	40

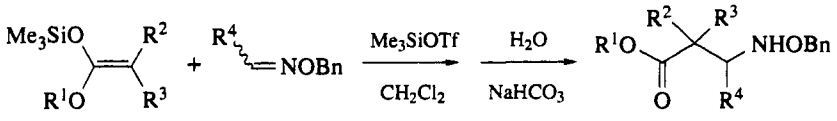
A useful application of an enolate–oxime ether condensation, described by Weeks, Volkmann and coworkers, is found in the synthesis of 6-aminomethylpenicillin derivative (**218**), a potent β-lactamase inhibitor.[160] As shown in Scheme 45, the sensitive penicillin Grignard (**216**) is condensed with ethyl formaldoxime at –80 °C in the presence of BF_3·OEt_2 to afford adduct (**217**). The use of BF_3·OEt_2 is critical because it allows the reaction to proceed at the low temperature required for the stability of enolate (**216**). Hydrogenolysis of (**217**) simultaneously results in removal of the ethoxy, bromo and benzyl groups, affording (**218**).



(216) (217) (218)

Scheme 45

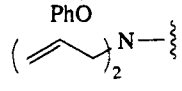
Sekiya and coworkers have demonstrated that silyl ketene acetals (**219**) add to *O*-benzyl oxime ethers (**220**) in the presence of catalytic amounts of TMS-OTf to afford β-benzyloxyamino esters (**221**; Scheme 46; Table 24).[161] As in the analogous TMS-OTf-catalyzed reactions of silyl enol ethers with *N*-aryl-[135,136,144] and *N*-silyl-imines,[145] β-lactam formation does not occur because the silyl group is transferred to the amine nitrogen *in situ*, thereby blocking cyclization. Yields are generally good (80–90%) but are reduced when unsubstituted silyl ketene acetal (entry 3) and enolizable oxime ethers (entries 8 and 9) are used. No systematic study of the *syn–anti* selectivity of oxime ether additions to enolates or silyl ketene acetals has been reported. It would be interesting to see if the direction of *syn–anti* selectivity relative to other imine derivatives is changed because of the additional metal coordination site on the oxime ether oxygen.



(219) (220) (221)

Scheme 46

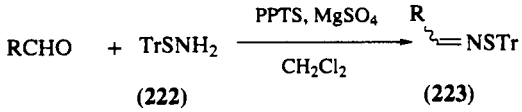
Table 24 Condensation Reactions of Silyl Ketene Acetals (**219**) and *O*-Benzyl Oxime Ethers (**220**) Catalyzed by TMS-OTf[161]

	Silyl ketene acetal (**219**)			*Oxime ether* (**220**)	*β-Benzyloxyamino ester* (**221**)
Entry	R^1	R^2	R^3	R^4	*Yield (%)*
1	Me	Me	Me	H	89
2	Me	Me	H	H	76
3	Bn	H	H	H	42
4	Me	—(CH$_2$)$_6$—		H	95
5	Me	Ph	H	H	93
6	Me	PhO	Me	H	88
7	Me		H	H	52
8	Me	Me	Me	Me	52
9	Bn	H	H	Me	61

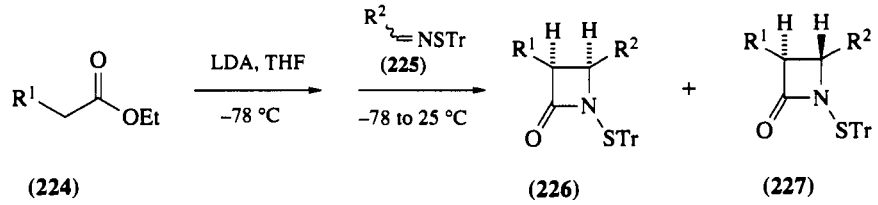
4.1.3.3.3 Sulfenimines

Sulfenimines, as demonstrated by Hart and coworkers, behave similarly to *N*-arylimines and *N*-silylimines in enolate condensations with respect to yield and stereoselectivity. Like oxime ethers they are useful for the synthesis of *N*-unsubstituted β-lactams by reductive cleavage.[162] It is important that the alkyl group attached to the sulfur of the sulfenimine is bulky in order to block attack of the enolate on the electropositive sulfur. *S*-Tritylsulfenimines (**223**), prepared according to the method of Branchaud by condensing aldehydes with tritylsulfenamide (**222**) in the presence of $MgSO_4$ and PPTS (equation 21),[163] are well suited for this purpose and condense with lithium ester enolates to afford diastereomeric mixtures of β-lactams (**226**) and (**227**) in good yield (Scheme 47; Table 25). The reaction is also compatible with enolizable sulfenimines (entries 2 and 3). *Syn* selectivity predominates, paralleling the reactions of lithium enolates with other types of imines. Several reagents including tri-*n*-butylphosphine, Raney

nickel, TMSI, and lithium–ammonia can be used to convert *N*-tritylsulfenyl β-lactams (**226**) and (**227**) to their corresponding *N*-unsubstituted β-lactams.



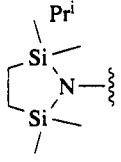
(21)



(224) (226) (227)

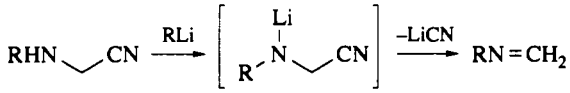
Scheme 47

Table 25 β-Lactam-forming Reactions of Sulfenimines with Ester Enolates[162]

Entry	*Ester (224) R^1*	*Imine (225) R^2*	*Products (226)–(227) Yield (%)*	*Cis:trans ratio*
1	Pr^i	Ph	70	82:18
2	Pr^i	Me	71	97:3
3		Me	78	83:17

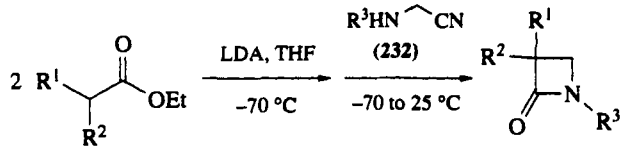
4.1.3.4 *In Situ* Methods

An *in situ* method for the preparation of *N*-methyleneamines has been devised by Overman and Osawa for use in condensation reactions with enolates[164] and organometallic reagents.[165] These species, with the exception of very hindered *N*-methyleneamines, cannot be isolated in the condensed phase because they rapidly trimerize to hexahydro-1,3,5-triazines. In this *in situ* method, *N*-methyleneamines (**230**) are generated from *N*-(cyanomethyl)amines (**228**) by deprotonation with an equivalent of enolate to give an intermediate amide (**229**) which loses LiCN (equation 22). When two equivalents of enolate are present, addition to the *N*-methyleneamine occurs and β-lactams (**233**) are obtained in 60–70% yield upon warming the reaction mixture to 25 °C (Scheme 48; Table 26). Uncyclized β-amino esters can be isolated if the reaction is quenched at lower temperature; a possible cycloaddition mechanism is thus ruled out. It is not clear to what extent, if any, the reaction is limited to α,α-disubstituted enolates. *N*-Methyleneamines, like oxime ethers, are useful for the synthesis of 4-unsubstituted β-lactams and should also have important applications in the synthesis of monobactam antibiotics.



(228) (229) (230) (22)

In an application to asymmetric monobactam synthesis, Overman and Osawa observe a high level of 1,4-diastereofacial selectivity in the reaction of (*S*)-cyanoamine (**235**) with the enolate of STABASE-protected glycine ester (**234**), affording diastereomeric 3-amino-2-azetidinones (**236**) and (**237**) in a 10:1 ratio, respectively, and in 65% yield (Scheme 49).[164] Based on the (*E*)-enolate geometry of glycine ester (**234**), determined in trapping experiments with TMSCl, the authors postulate a chelated, chair-like transition state (**238**) that is consistent with the observed stereoselectivity.

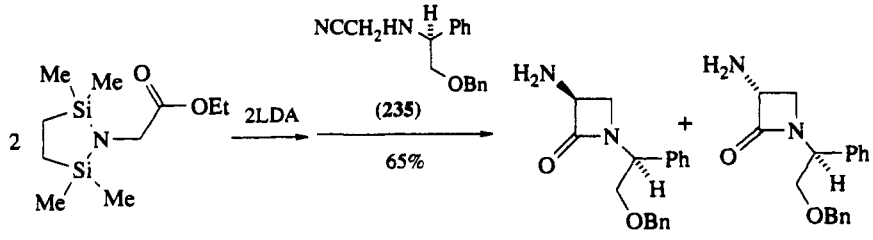


(231) (233)

Scheme 48

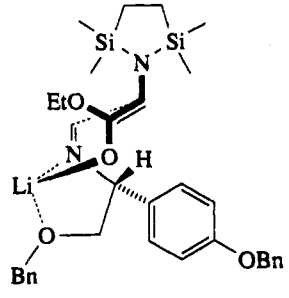
Table 26 β-Lactam-forming Reactions of Enolates of Ester (**231**) and *N*-Methyleneamines Prepared *In Situ* from *N*-(Cyanomethyl)amines (**232**)[164]

Entry	*Ester (231)* R^1	R^2	*N-(Cyanomethyl)amine (232)* R^3	*β-Lactam (233) Yield (%)*
1	Me	Me	Bn	66
2	Me	Me	Ph	77
3	Me	Me	C_6H_{11}	66
4	—(CH$_2$)$_5$—		Bn	65
5	Me	SPh	Bn	62



(234) (236) 10:1 (237)

Scheme 49

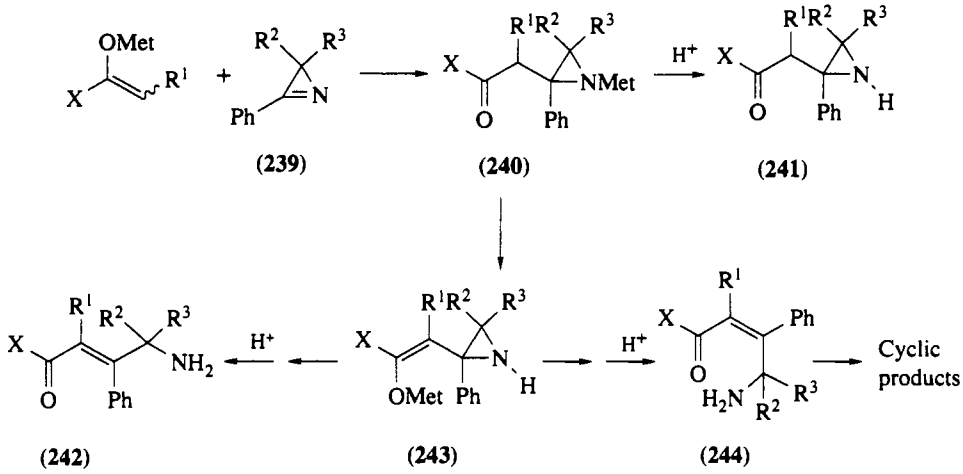


(238)

4.1.3.5 Cyclic Imines

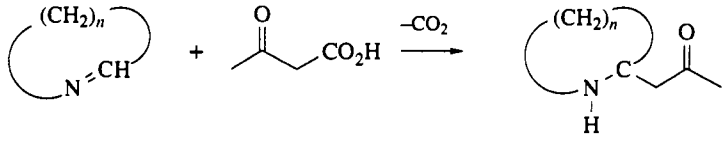
Condensations of 2-phenyl-2*H*-azirines (**239**) with enolates have been described by Blagoev and Novkova[166] and Laurent *et al.*[167] As shown in Scheme 50, these reactions are often accompanied by fragmentation of the aziridine ring. This occurs by an internal proton transfer in the initial 1,2-adduct (**240**) to generate an enolate (**243**), which suffers a retro-Michael-type reaction leading to *trans*-γ-amino-α,β-unsaturated compounds (**242**) and to products arising from cyclization of the corresponding *cis* isomer (**244**). When enolate (**243**) is not generated, the normal products of 1,2-addition, *i.e.* 2-substituted aziridines (**241**), are isolated upon work-up. Some examples of these reactions are shown in Table 27. Entries 1 and 2 demonstrate an interesting effect of the enolate counterion where the 1,2-addition product is obtained using the magnesium enolate of phenylacetic acid, while fragmentation products are obtained using the corresponding sodium enolate. This dichotomy in reaction pathways can be rationalized by the

different basicities of the two amide anions (**240**; Met = Na *vs.* Mg), where internal proton transfer occurs with the more basic sodium anion. The reaction depicted in entry 1 leading to 2-aziridine acetic acids is also general for magnesium dianions of other arylacetic acids (yields = 50–60%). Reactions of sodium ketone enolates (entries 3 and 4), like those of sodium dianions of phenylacetic acid, result in fragmentation of the aziridine ring. Depending upon the degree of substitution of the 2*H*-azirine at position 3, pyrroles (entry 3) or 2*H*-pyrroles (entry 4) are obtained in good yield. The authors conclude that the failure to detect appreciable amounts of *trans*-α,β-unsaturated ketones (**242**; X = Et; R^1 = Me; R^2 = Me; R^3 = Me or H) in these reactions is due to reversible fragmentation of enolate (**243**), where the equilibrium is driven by cyclization of the *cis* fragmentation product.[167]



Scheme 50

In the Schopf reaction, five- and six-membered ring imines 3,4-dihydro-2*H*-pyrrole (**245**) and 2,3,4,5-tetrahydropyridine (**246**) condense with β-keto acids to afford β-amino ketones (equation 23). Imine (**246**), for example, condenses with acetoacetic acid to give 2-acetonylpiperidine (**247**) (n = 4), an alkaloid known as pelletierine (or isopelletierine).[168] More recent applications of these reactions are shown in Table 28. Imines (**245**) and (**246**) are most conveniently prepared by dehydrohalogenation of *N*-chloropiperidine[169] and *N*-chloropyrrolidine,[170] respectively, but are difficult to isolate due to self-condensation reactions occurring below pH 11.5.[168] To avoid this problem, Rapoport and coworkers have used ether–ethanol solutions of imine (**246**), prepared *in situ* by dehydrohalogenation, in reactions with the sodium salt of oxalylacetate esters (entry 1).[171] The Rapoport modification has also been used by Quick and Oterson in a more efficient synthesis of pelletierine (entry 2).[172] Grisar and coworkers have recently introduced another modification of the Schopf reaction that avoids handling the elusive monomeric forms of imines (**245**) and (**246**).[173] Here, internally chelated magnesium enolates of β-keto acids, prepared from the corresponding methyl ketone derivatives using magnesium methyl carbonate, react with solid α-trimeric forms of imines (**245**) and (**246**) to afford 2-piperidylmethyl and 2-pyrrolidinylmethyl ketones (entries 3–6). 3,4-Dihydroisoquinoline also reacts with these enolates (entry 7). Presumably under the reaction conditions (DMF, 25 °C, CO_2 atmosphere), there is slow decomposition of the α-trimers to provide sufficient concentrations of free imines. The use of magnesium salts overcomes also the solubility limitations of other β-keto acid salts. This method, however, is mainly limited to magnesium keto acid enolates derived from aryl and styryl methyl ketones.



(**245**) n = 3
(**246**) n = 4

(**247**)

(23)

Table 27 Condensation Reactions of 2*H*-Azirines with Enolates

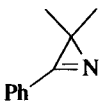
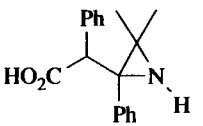
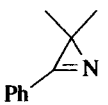
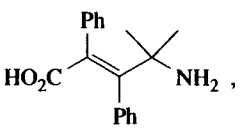
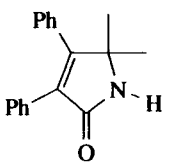
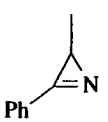
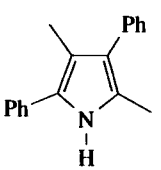
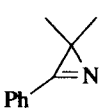
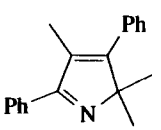
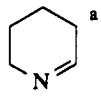
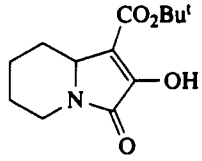
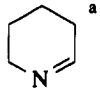
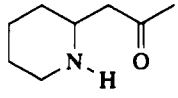
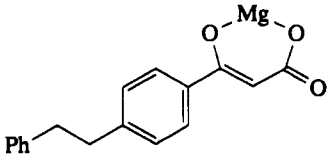
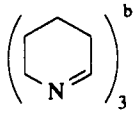
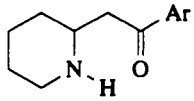
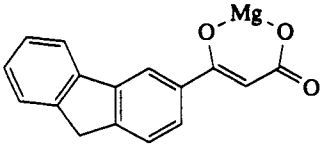
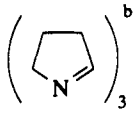
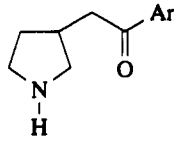
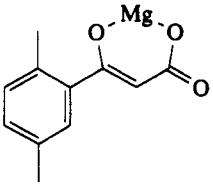
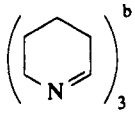
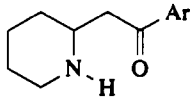
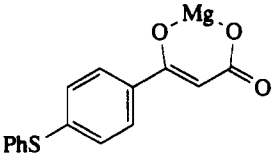
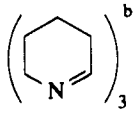
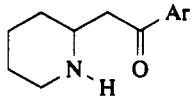
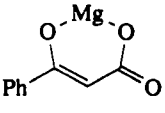
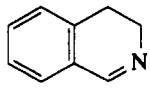
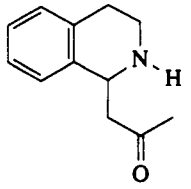
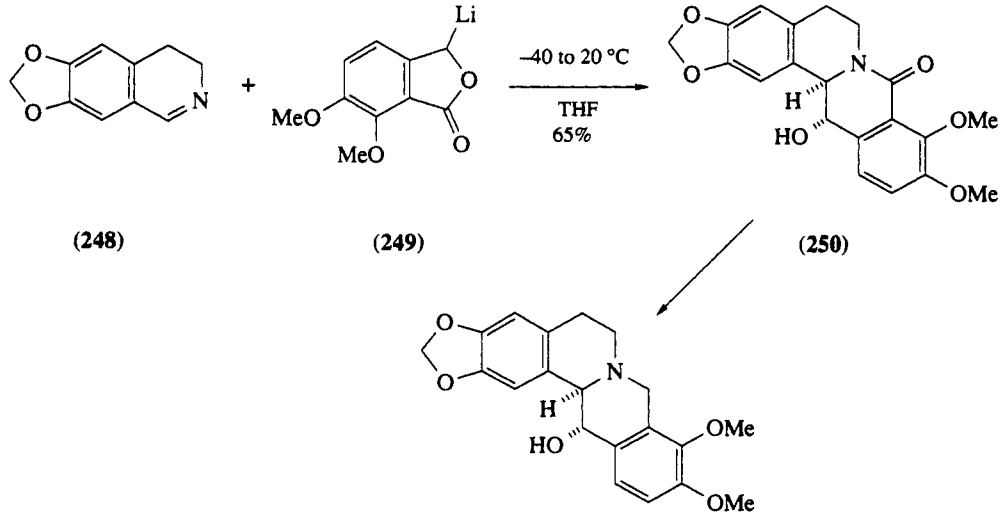
Entry	*Carbonyl Compound*	*Azirine*	*Conditions*	*Products*	*Yield (%)*	*Ref.*
1	$PhCH_2CO_2H$		Pr^iMgCl, DME, reflux		65	166
2	$PhCH_2CO_2H$		Na naphthalide, THF, 50°C	 , 	25, 41	166
3	PhCOEt		NaH, DMSO		90	167
4	PhCOEt		NaH, DMSO		72	167

Table 28 Condensation Reactions of 3,4-Dihydro-2*H*-pyrrole and 2,3,4,5-Tetrahydropyridine with β-Keto Acid Derivatives

Entry	*Carbonyl compound*	*Imine*	*Product*	*Ref.*
1	$EtO_2CCOCH(Na)CO_2Bu^t$	 [a]	 60%	171
2	$MeCOCH_2CO_2Na$	 [a]	 42%	172
3		 [b]	 63%	173
4		 [b]	 65%	173
5		 [b]	 75%	173
6		 [b]	 50%	173
7			 60%	173

[a] Formed *in situ* according to the procedure of Rapoport, see ref. 171. [b] For details of preparation, see ref. 173.

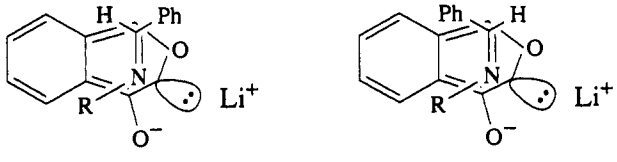
In connection with the synthesis of protoberberine alkaloids, Marsden and MacLean have investigated the addition of phthalide enolates to 3,4-dihydroisoquinolines.[174,175] These reactions are an extension of the previously described work of Dodsworth *et al.*[121,122] involving phthalide additions to acyclic imines (Section 4.1.3.2.2.ii). An example involving the condensation of 3,4-dihydroisoquinoline (**248**) with phthalide (**249**) to yield *trans* tetracyclic lactam (**250**) is shown in Scheme 51. Reduction of (**250**) gives (±)-epiophinocarpine (**251**). In contrast to the modest *cis* stereoselectivity (~2:1) seen in reactions of acyclic imines, reactions of cyclic imines are completely stereospecific and give *trans* adducts exclusively. To explain the difference in stereochemical outcome between reactions of cyclic *vs.* acyclic imines, the authors have revised the model of Dodsworth *et al.* (see Figure 6) by proposing a coordination complex involving the imine lone pair, the two oxygens of the phthalide ring and the lithium cation (Figure 9). The stereochemical outcome of the addition is therefore determined by the geometry of the imine.



(248) (249) (250)

(251)

Scheme 51

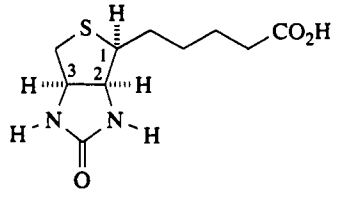


(a) Acyclic, *(E)*-imine (b) Acyclic or cyclic, *(Z)*-imine

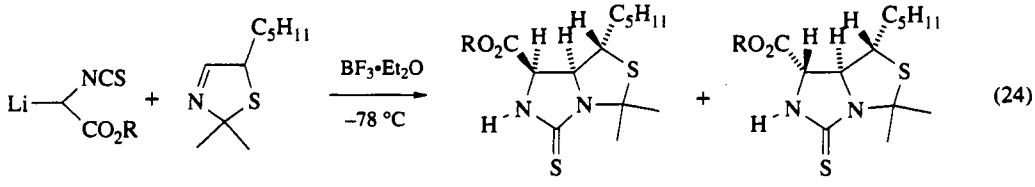
Figure 9 Proposed orientation of reactants in phthalide enolate–imine additions leading to (a) *cis* or (b) *trans* adducts[175]

In studies directed towards the synthesis of (+)-biotin (**252**), Volkmann and coworkers have studied additions of isothiocyanatoacetate enolates (**253**) to 3-thiazolines (**254**), yielding diastereomeric thiazolidines (**255**) and (**256**; equation 24; Table 29).[176,177] Boron trifluoride etherate is a necessary additive to enhance the reactivity of the sterically congested 3-thiazoline ring, which is otherwise inert to nucleophilic attack. The diastereofacial selectivity of these reactions is controlled by attack of the enolate on the face of the imine opposite to the 5-pentyl group and correctly establishes the relative stereochemistry at C-1 and C-2 of biotin. The *syn–anti* selectivity, corresponding to the C-2,C-3 relative configuration of biotin, is not as stereoselective but does favor the desired *anti*-thiazolidine (**255**) (note that (**255**) has the *anti* relative configuration even though the ring is *cis*). Enhancement of *anti* selectivity can be achieved by using more bulky alkyl (entries 1–4) or phenoxy (entries 5–7) esters. It is interesting to note that the BHT ester (entry 7), the most *anti* selective ester known in the aldol condensation,[81] is also the most *anti* selective ester in these reactions. Assuming that (*E*)-enolates are involved, these results can be rationalized by invoking $C(E,Z)^{\ddagger}$ and $B(E,Z)^{\ddagger}$ transition states for the formation of diastereomeric 3-thiazolines

(**255**) and (**256**), respectively; thus, bulky esters favor 3-thiazoline (**255**) by destabilization of the $B(E,Z)^{\ddagger}$ transition state *via* the steric interaction between OR of the enolate and the quaternary carbon of the 3-thiazoline (see Figure 4).

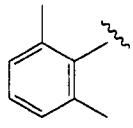
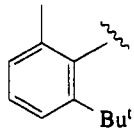
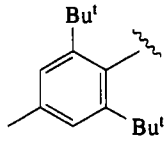


(**252**)

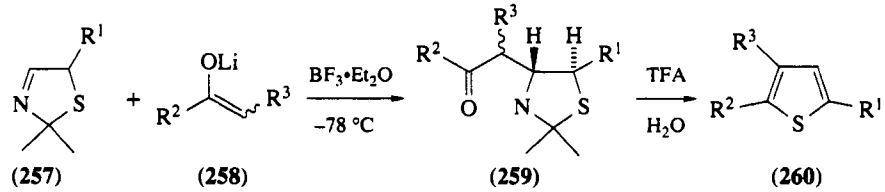


(**253**) (**254**) (**255**) (**256**) (24)

Table 29 Stereoselective Condensations of Isothiocyanoacetate Enolates With 3-Thiazoline (**254**)[177]

Entry	*Enolate (253) R*	*Products (255):(256) Ratio*	*Entry*	*Enolate (253) R*	*Products (255):(256) Ratio*
1	Me	1.4	5		1
2	$MeOCH_2$	2	6		3
3	Et	3	7		>5
4	Pr^i	3			

In addition to ester enolates, ketone enolates and nitronates also add to 3-thiazolines in the presence of $BF_3{\cdot}Et_2O$.[178] Reactions of ketone enolates have been cleverly exploited in the synthesis of 2,3,5-trisubstituted thiophenes (**260**) by hydrolysis of adducts (**259**) and spontaneous cyclization to liberate water and ammonia (Scheme 52; Table 30).[178] The 5-substituent of the thiophene is derived from the 5-substi-



(**257**) (**258**) (**259**) (**260**)

Scheme 52

tuent of the 3-thiazoline (**257**), while the 2,3-substituents of the thiophene are derived from the enolate. Overall yields of thiophenes are generally good.

Table 30 Formation of 2,3,5-Trisubstituted Thiophenes (**260**) from Ketone Enolates and 3-Thiazolines (**257**)[178]

Entry	*3-Thiazoline (257)* R^1	*Ketone enolate (258)* R^2	R^3	*Thiophene (260) Yield (%)*
1	n-C_5H_{11}	Ph	H	80
2	n-C_5H_{11}	Bu^t	Me	89
3	n-C_5H_{11}	—$(CH_2)_4$—		87
4	n-C_5H_{11}	1-Adamantyl	H	70
5	$(CH_2)_4CO_2Et$	—$CH_2CH_2SCH_2$—		50

4.1.4 ADDENDUM

A comprehensive review article on β-lactam formation *via* the ester enolate–imine condensation has been written by Hart and Ha.[179] Achiwa and coworkers have published a full paper detailing their work on the synthesis of *N*-benzyloxy-β-lactams utilizing the reaction of *N*-benzyloxyimines with silylketene acetals in the presence of TMS-OTf, or with lithium ester enolates.[180]

Enolizable *N*-trimethylsilylaldimines can be generated *in situ* by the addition of organolithium reagents to bis(trimethylsilyl)formamide.[181] These undergo addition reactions with enolates to form β-lactams. Phosphonium salts used in catalytic amounts promote the reaction between aryl aldimines and silylketene acetals to form β-amino esters.[182] Mannich bases with *N*-2-hydroxyethyl-*N*-methyl substitution are prepared by the reaction of the iminium salt synthon, 3-methyl-1,3-oxazolidine, with enol silanes in the presence of chloromethylsilanes.[183]

Tramontini has updated his earlier review on the Mannich reaction.[184]

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4.2
The Bimolecular Aromatic Mannich Reaction

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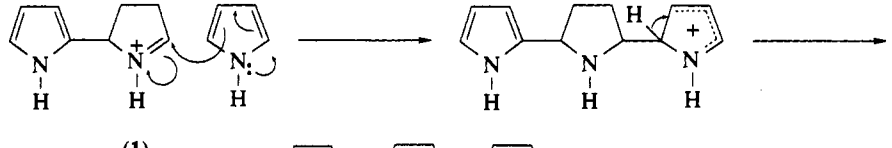
4.2.1 INTRODUCTION

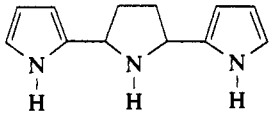
The importance of α-aminoalkylation as a method of carbon–carbon bond formation has been recognized for many years, especially among those organic chemists interested in biologically active molecules. The earliest papers were published towards the end of the last century but Mannich was the first to recognize the generality of the reaction and his first paper appeared over 75 years ago. A number of reviews[1] and two books[2] record data up to 1973. The importance of the Mannich reaction relates in part to the fact that the protonated bases are normally water soluble and also to the ease with which the amino function may be converted into a variety of other groups. New examples continue to be published. For example, the nuclear *ortho* methylation of phenols has been reported *via* the reduction of Mannich bases and their quaternary methiodides and *N*-oxides using tributyltin hydride;[3a] sodium cyanoborohydride has also been used.[3b] Chapter 4.1 is concerned with aliphatic bimolecular Mannich reactions, while this chapter deals with intermolecular reactions of Mannich reagents with aromatic substrates. This chapter concentrates on recent advances in synthetic methodology.

The two components that are required in addition to the aromatic substrate are an amine and an aldehyde. Only electron-rich aromatic compounds interact successfully with the relatively weak electrophiles that function as Mannich reagents. In many cases failures may be due to low electrophilicity of the intermediates, resulting from heteroatom stabilization. The reaction is quite general. The least nucleophilic aromatic substrates that have been shown to react are thiophene, *m*-dimethoxybenzene and phenyltrialkylstannanes. Very electron-rich heterocycles, such as indole(s), and carbocyclic compounds, such as phenol(s), react under a wide variety of very mild conditions. It is not possible to formulate a set of general reaction conditions and reagents. The most frequently used classical procedure involves the mixing of all three components simultaneously. There are, however, many examples in which the amine and aldehyde are condensed first, sometimes with the isolation of the initial product. Very few examples are recorded of reactions involving secondary amines other than with formaldehyde (aminomethylation). Some aminoalkylation reactions are successful using 2-naphthol when other aromatic substrates fail. It is clear that 2-naphthol is a good substrate on which to evaluate new reagents or reaction types. In the few cases in which successful reactions with other aldehydes have been reported, yields have usually been extremely poor. For example, pyrrole, acetaldehyde and dimethylamine afford the expected Mannich base in less than 5% yield.[4] The reasons for this are obscure because a range of mechanistic pathways are thought to operate. Many Mannich reactions may proceed by what is essentially an S_N2 process and hence are subject to steric hindrance. It is also possible that earlier failures result from the ease of deprotonation of iminium salts to enamines.

Reactions involving primary amines have been successfully carried out *via* Schiff's bases derived from a number of aldehydes. Thus, the reaction of pyrrole with the protonated enamine (**1**), which results in the formation of the pyrrole trimer (**2**; equation 1), constitutes a good example of a Mannich reaction involving an aldehyde other than formaldehyde.[5]



(1)



(2)

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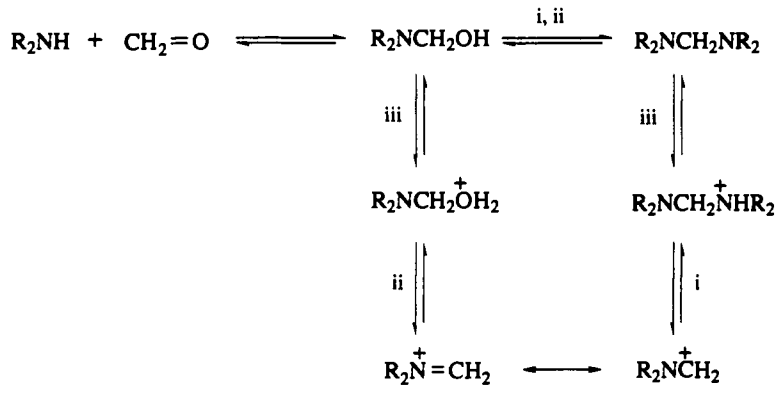
4.2.2 MECHANISMS

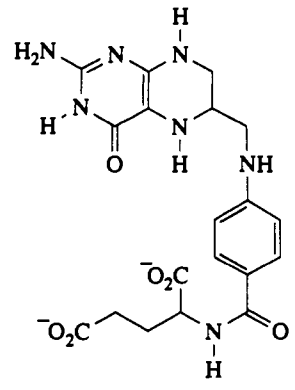
An understanding of the mechanism or mechanisms that operate allows one to predict how a synthesis should be planned and so a brief discussion is appropriate. As with Friedel–Crafts alkylation reactions, a number of mechanisms appear to operate. At one end of the spectrum iminium salts are involved in S_N1-type reactions and at the other end S_N2-like transition states may well be involved. The majority of the work published on mechanistic aspects of the Mannich reaction concerns reactions carried out in aqueous or other protic solvents.[1d,6] There is little evidence for the conversion of hydroxymethyl derivatives into Mannich bases, so the initial steps must involve the interaction of formaldehyde with the amine to give a carbinolamine that is in equilibrium with the reactants. Where the equilibrium lies depends on the pH. At high pH and in the presence of an excess of secondary amine a carbinolamine is converted to a bis(dialkylamino)methane, which itself may be hydrolyzed back to the amine and carbinolamine. A carbinolamine and a bis(dialkylamino)methane can give rise to an iminium salt at low pH. The first suggestion that iminium ions are involved in Mannich reactions appeared in a paper in 1949.[7] Different mechanisms were proposed at an early stage for reactions carried out in acidic or basic media.[8] Although a number of kinetic and a polarographic studies purport to show the involvement of iminium salts at pH values well above 7, it is clear that a carbinolamine would be the predominant species present if an iminium ion were produced in the presence of hydroxide ions. The possibility that the protonated carbinolamine, the required precursor to an iminium ion in acidic media, could function as a Mannich reagent does not appear to have been suggested previously. An S_N2 displacement of water from such a cation is at least as likely at intermediate pH values as the displacement of the poorer leaving group (hydroxide) from a carbinolamine in reactions carried out at high pH. These equilibria are summarized in Scheme 1. It has also been argued that reactions carried out in alcoholic solutions may well proceed by way of alkoxydialkylaminomethanes (aminol ethers).



i, R_2NH; ii, $-H_2O$; iii, H^+

Scheme 1

One of the most interesting diaminomethanes that has been investigated is a model for the coenzyme tetrahydrofolate (**3**), a biological one-carbon transfer agent. The mechanism of its conversion into the imidazolidine derivative N^5,N^{10}-methylenetetrahydrofolate (**4**) has been studied.[9] The pH rate profile apparently results from a change in the rate-determining step with changing acidity. Secondary amines such as morpholine and imidazole catalyze the reaction between tetrahydrofolic acid and formaldehyde *via* a



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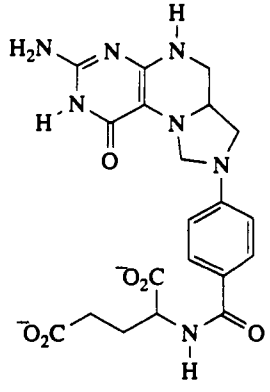

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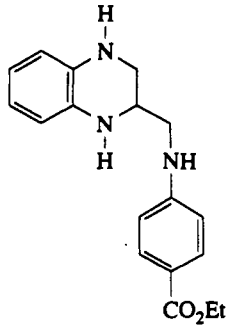

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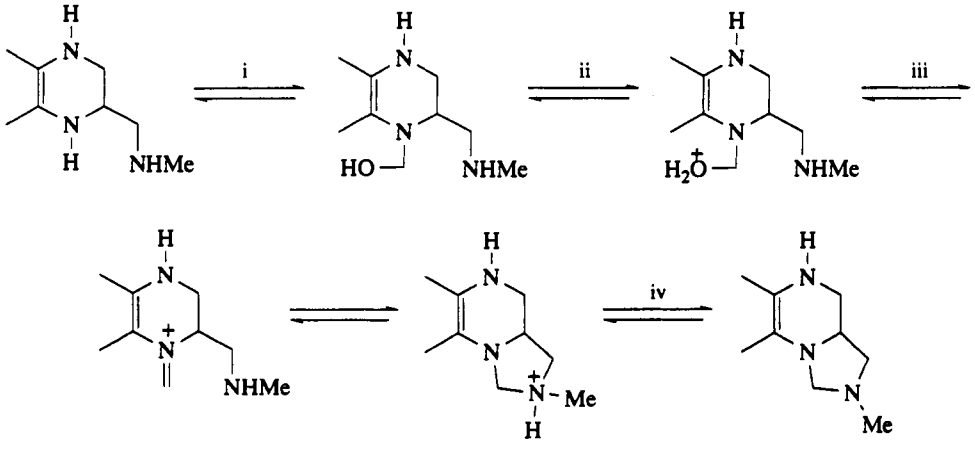


i, CH_2O; ii, H^+; iii, $-H_2O$; iv, $-H^+$

Scheme 2

pathway involving an iminium ion. The model tetrahydroquinoxaline derivative (**5**) has been studied[10] over a broad pH range and an aminol, an iminium ion and a protonated amine detected in equilibrium, as shown in Scheme 2.

In recent years reactions have been carried out in aprotic solvents with preformed iminium salts. Another recent modification is the use of bis(dialkylamino)methanes (aminals) and alkoxydialkylaminomethanes (aminol ethers) in aprotic solvents in the presence of nonprotic acids. A number of aromatic substrates that do not give Mannich bases under the classical aqueous reaction conditions do react under these aprotic conditions.

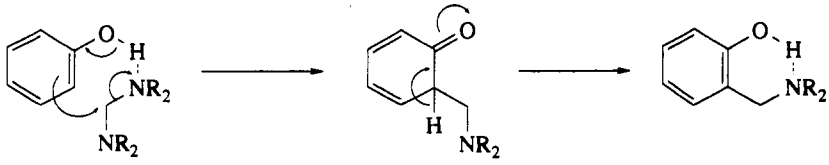
4.2.3 REACTIONS USING SECONDARY AMINES

4.2.3.1 Aminoalkylation Reactions of Phenols

4.2.3.1.1 Reactions using protic solvents

(i) Reactions using formaldehyde

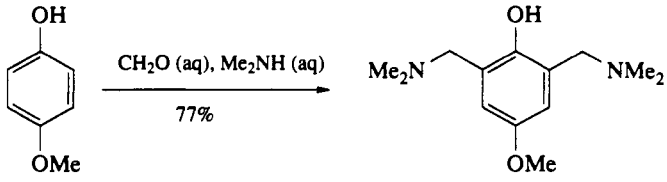
A wide range of phenols take part in Mannich reactions under classical conditions. The precise reaction conditions required depend on the nucleophilicity of the phenol. The two extremes are exemplified by 2-naphthol and 4-nitrophenol. In the case of a reactive phenol such as 2-naphthol, aqueous formaldehyde and the amine, sometimes in ethanolic solution, are either allowed to stand at room temperature for a lengthy period of time or heated for a brief period. When more than one activated position is available it is not usual to obtain one exclusive product. It may even be that polysubstitution is the norm, since the introduction of an aminomethyl group increases the electron density in the ring. This effect is reminiscent of Friedel–Crafts alkylation. Phenol, for example, when heated at *ca.* 60 °C for 2 h with aqueous dimethylamine and formaldehyde affords the 2,4,6-trisubstitution product in 86% yield.[11] In the cases where reactions have been studied over a period of time it is normal for the first substitution to occur at the 2-position. In a recent careful study[12] it was observed that the reaction rate for the interaction of phenol with aqueous formaldehyde and di-*n*-propylamine is increased tenfold when the amount of water is increased from 8.6 to 65.7%. In reactions of 3-pentadecylphenol with formaldehyde and a number of secondary amines three dialkylaminomethyl groups are introduced, with the order being C-6, C-4 and C-2. The observed preference for attack *ortho* to the hydroxy group has resulted in the suggestion that the mechanism of the reaction involves hydrogen bonding of a bis(dialkylamino)methane with the phenolic hydroxy group, as shown in equation (2).[13] The failure of 2,4-dimethyl-6-hydroxymethylphenol to react with morpholine eliminated a possible reaction sequence. We will return to the question of mechanism when we discuss reactions involving preformed intermediates (Section 4.2.3.1.2).



(2)

Yields appear to depend not only on the nucleophilicity of the phenol, but also on the amine. Diethylamine is more sterically demanding than dimethylamine and strongly hindered secondary amines such as diisopropylamine and dicyclohexylamine usually do not take part in Mannich reactions.[14] Dicyclopentylamine is reported to give an exotherm when mixed with formaldehyde, but no bis(dialkylamino)methane has been isolated. In equations (3)–(12) it is seen that reaction almost invariably occurs *ortho* to a hydroxy group; irrespective of the presence of other functional groups. It is worth drawing attention to specific examples. Sarcosine (*N*-methylglycine) gives products (equation 6) that can be transformed, because of the extra functionality, into heterocyclic systems such as benzoxazepinones and dihydroisoquinolones.[18] 4-Hydroxyacetophenone reacts at the enolized ketone function under acidic reaction conditions; reaction at the benzenoid ring (equation 8) only occurs in a mildly basic medium. On the other hand, 3,5-dihydroxyacetophenone affords the ring-substitution product in a reaction using

morpholine hydrochloride (equation 9). Reactions of 2,5-dimethylphenol result in substitution at the 4-position, presumably because the normal reagent is too sterically demanding.



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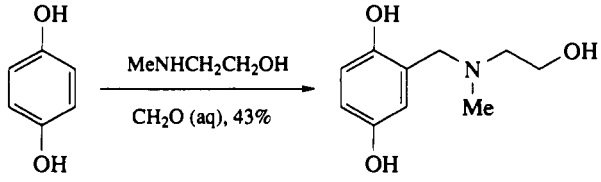

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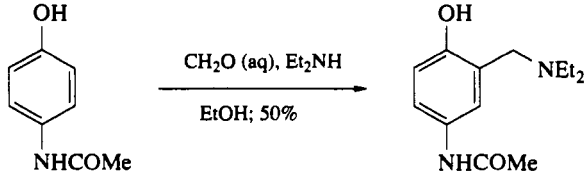

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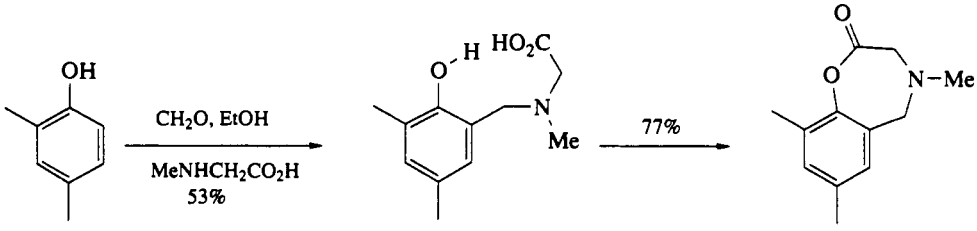

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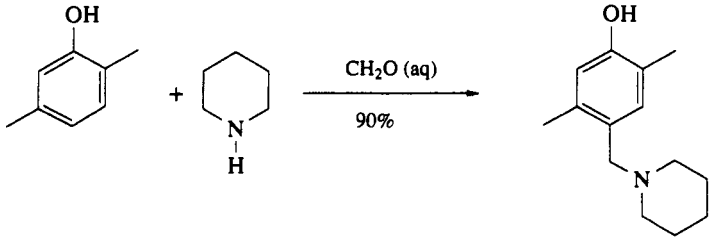

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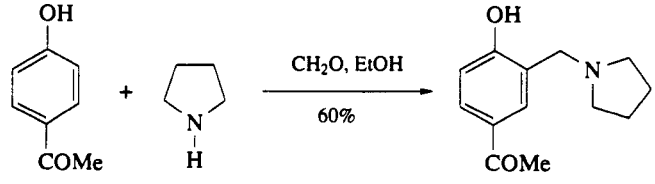

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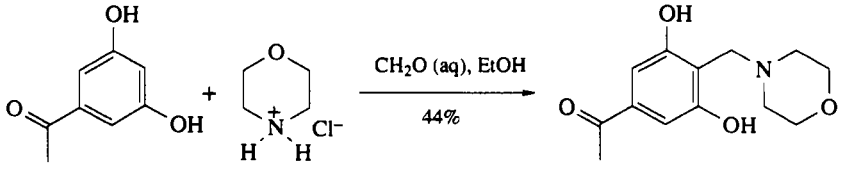

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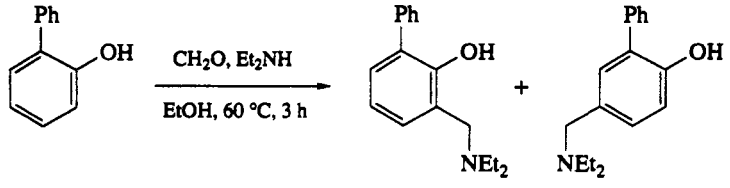

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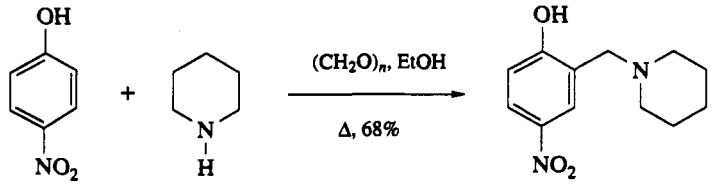

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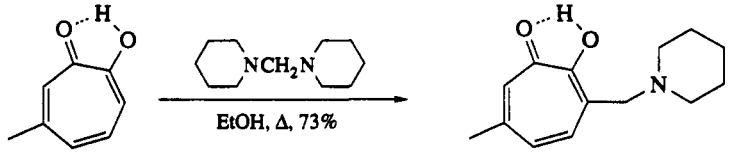
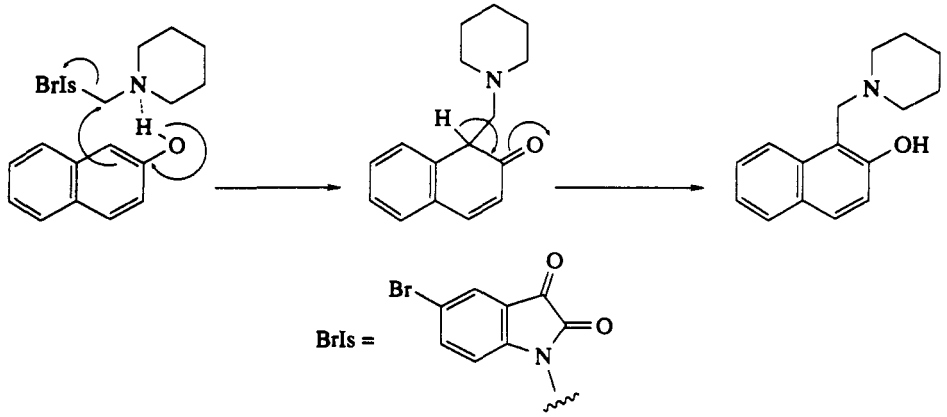


(12)

(ii) Reactions involving bis(dialkylamino)methanes (aminals) or alkoxydialkylaminomethanes (aminol ethers)

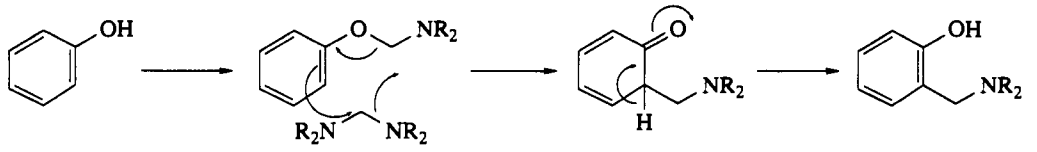
The rate of the reaction of 2,4-dimethylphenol with formaldehyde and morpholine depends on the concentration of morpholine if it is present at less than twice the formaldehyde concentration, but if the formaldehyde concentration is less than half that of morpholine then the rate depends on the concentration of formaldehyde. These data suggest that di-*N*-morpholinylmethane is an intermediate in the reaction. Di-*N*-morpholinylmethane was shown to give essentially the same kinetics.[13,24] A kinetic study of the reaction of 3-pentadecylphenol with formaldehyde and di-*n*-propylamine led to a similar conclusion.[25] These results suggest that aminals and aminol ethers should take part in Mannich reactions since both can be formed reversibly in the aqueous or alcoholic media used under the more traditional reaction conditions.

1-Naphthol gives the 2-substitution product in 77% yield when heated in ethanolic solution with dipiperidylmethane; 2-naphthol gives the 1-substitution product in 97% yield under similar conditions.[26] The reaction of 4-methyltropolone with dipiperidylmethane affords the 7-substitution product (equation 12).[27] That 5-bromo-1-piperidylmethylisatin reacts with 2-naphthol and results in the exclusive incorporation of the piperidylmethyl residue into the product led to the suggestion that the Mannich reactions with aminals involve the prior hydrogen bonding of the phenolic hydroxy group *via* the more basic nitrogen, as shown in equation (13).[6b] The interesting comment is made[6b] that the *ortho* substitution of the phenol may be comparable to the Claisen rearrangement of allyl ethers, rather than a normal electrophilic



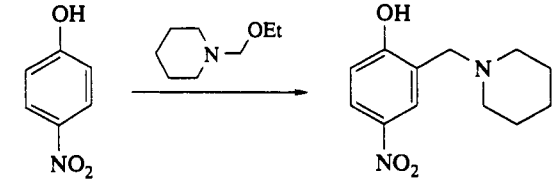
(13)

substitution reaction. It could be that the reactions are more complex than has previously been thought and that *O*-aminoalkylation precedes a concerted intermolecular rearrangement (equation 14). A similar mechanism would account for the rapid formation of products when ketones interact with iminium salts (see Chapter 4.1). Some of the successful reactions shown in the equations have used aminol ethers and it is possible, therefore, that classical reactions using ethanol as a solvent involve the intermediacy of an aminol ether rather than an aminal. It has recently been shown that the yields of the expected products are increased significantly if the reactions of aminals that are carried out in acetonitrile are activated by means of sulfur dioxide. We return to this topic in the next section.



(14)

A number of studies report the use of aminol ethers in reactions with phenols; representative examples are given in equations (15)–(17).



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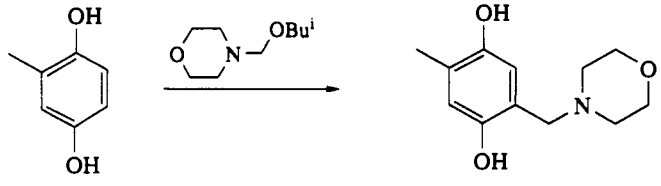

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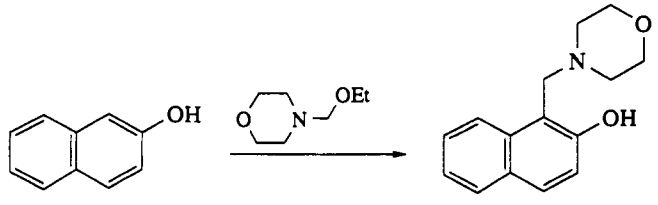

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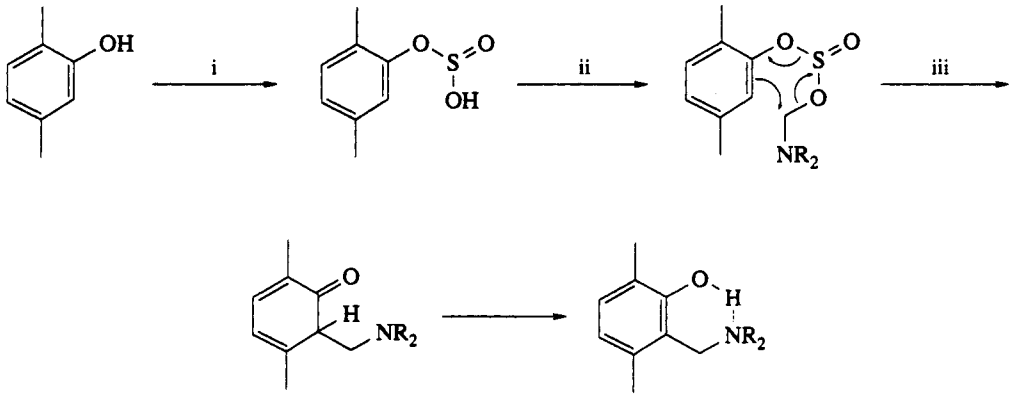
4.2.3.1.2 Reactions using nonprotic solvents

(i) Reactions involving aminals and aminol ethers

Until very recently the only reported example of a reaction being carried out in a nonprotic solvent was that involving the interaction of 2-naphthol with ethoxy-*N*-morpholinylmethane in dioxane (equation 17).[30] A number of other reactions using less-reactive phenols have also been investigated in acetonitrile. The yields of products are normally improved when sulfur dioxide is added to activate the aminal and some improvement also accrues using aminol ethers. We indicated earlier that 2,5-dimethylphenol takes part in the classical Mannich reaction to afford the 4-substitution product (for example equation 7). The reaction of 2,5-dimethylphenol with sulfur dioxide and then with a variety of aminol ethers results in a change in the regioselectivity. The effect is most marked when a low molar ratio of sulfur dioxide to reagent is employed. It has been suggested that a half-sulfite ester interacts with aminol ethers as shown in Scheme 3 and affords the *ortho* substitution product after the elimination of sulfur dioxide.[31] This device may prove to be generally useful in controlling the regiochemistry.



i, SO_2; ii, R_2NCH_2OEt or $(R_2N)_2CH_2$; iii, $-SO_2$

Scheme 3

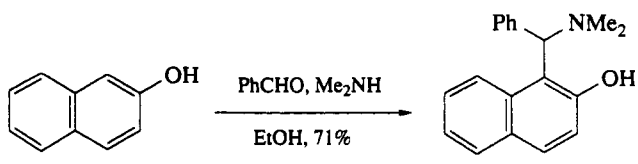
(ii) Reactions using preformed iminium salts

Although *N,N*-dialkylmethyleneiminium salts have been widely used in reactions with ketones and a number of heterocyclic systems, phenols have not been investigated in great detail. The regioselective formation of *ortho* substitution products has been reported under what are described as 'solid–liquid phase-transfer conditions'.[32] Excellent yields of *ortho* substitution products were reported under these conditions for electron-rich phenols such as *o*-cresol, 2-*t*-butylphenol and phenol. It was suggested that reactions carried out in the presence of potassium carbonate resulted in gegenion exchange to give the iminium phenoxide ion pair, which collapses to product. However, under the same reaction conditions, 2,5-dimethylphenol gives mixtures of products.[31] A difference has been observed with 2-methyl-1-naphthol between the results of a classical reaction and one involving a preformed iminium salt.[33] Whereas a reaction using *N*-piperidinylmethyleneiminium chloride affords the expected Mannich base hydrochloride, the classical reaction conditions using formaldehyde and piperidine yields the related diarylmethane.

4.2.3.1.3 Reactions involving aldehydes other than formaldehyde

As was indicated in the introduction, few successful studies have been reported with aldehydes other than formaldehyde. For this reason this section is not subdivided. Once again two general points emerge. First, 2-naphthol is the best phenol with which to evaluate new systems, and second, reactions involving diethylamine generally give low yields, presumably for steric reasons.

2-Naphthol reacts with benzaldehyde and secondary amines (equation 18) in ethanolic solution to afford the corresponding Mannich bases in yields ranging from 21% with diethylamine to 72% with piperidine.[34] The aminal derived from benzaldehyde and piperidine is also effective. Aminals and aminol ethers derived from glyoxylic acid and the related iminium salts react efficiently with a number of substrates, including 2-naphthol (equation 19).[35] Although not strictly within the purview of this section, it is worth noting the reactions of 2-hydroxy-1,4-naphthoquinone with acetaldehyde and secondary amines. Once again piperidine gives a significantly higher yield (30%) than diethylamine (5%).[36]



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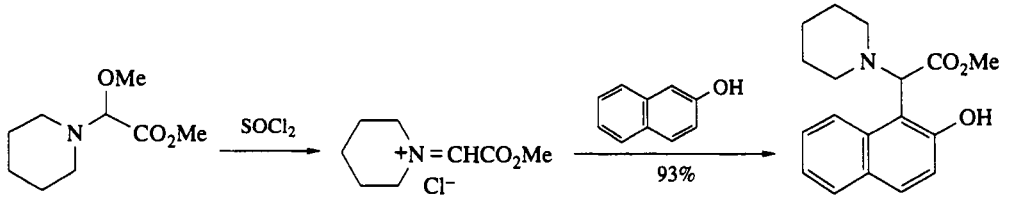

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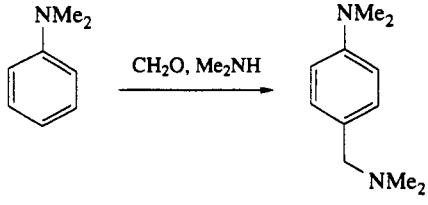
4.2.3.2 Aminoalkylation Reactions of Arylamines

The Mannich reactions of arylamines have not been studied in as much detail as those of phenols. Nevertheless, interesting features have been established and further developments can be envisaged.

N,N-Dialkylarylamines react under classical conditions at C-4 if that position is unsubstituted. For example, *N,N*-dimethylaniline reacts with formaldehyde and dimethylamine to afford 4-*N',N'*-dimethylamino-*N,N*-dimethylbenzylamine in 82% yield (equation 20).[37] Under acidic conditions fragmentation of the initial product can occur, leading to the formation of diarylmethanes. In the reaction of *N,N*-dimethylaniline with formaldehyde and pyrrolidine the best yield of the Mannich base (44%) is obtained in the presence of 1.5 mol equiv. of acetic acid; with 4.0 mol equiv. the yield is only 7%.[38] The reaction of *N*-methylenemorpholinium chloride with 4-*N'*-morpholinylmethyl-*N,N*-dimethylaniline results in the introduction of a second *N*-morpholinylmethyl residue at the 2-position, but with other iminium chlorides quaternary salts are formed by reaction with the nitrogen of the 4-dialkylaminomethyl group.[39] There is also a brief report of the use of the mixed *N,N*-dialkylmethyleneiminium salt, *N*-*t*-butyl-*N*-methylmethyleneiminium perchlorate, with *N,N*-dimethylaniline.[40]



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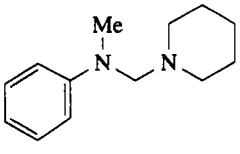
Secondary arylamines give products of attack at nitrogen as well as ring-substitution products. Thus, *N*-methylaniline reacts with formaldehyde and piperidine in the absence of acids to afford the aminal (**6**). In the presence of 0.5 mol equiv. of acetic acid the ring-substitution product (**7**) is obtained in 40% yield.[41] Another type of aminal has also been obtained in reactions of secondary arylamines; *N*-ethyl-*p*-toluidine gives the important by-product (**8**) in a reaction with piperidine and formaldehyde.[42]



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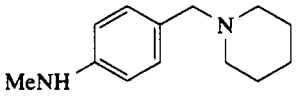

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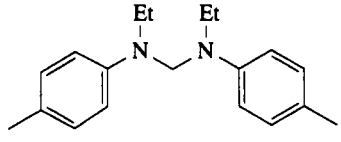

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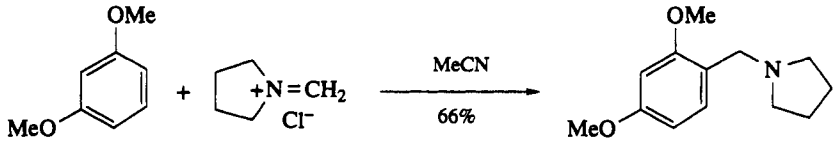
4.2.3.3 Aminoalkylation Reactions of other Carbocyclic Compounds

Because the Mannich reaction involves relatively weak electrophiles there are few other substituted benzenes that are sufficiently nucleophilic to react. Thus, anisole is not nucleophilic enough but 1,3-dimethoxybenzene is. Even with the latter compound the classical aqueous reaction conditions cannot be used. The reactions of 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene with preformed methyleneiminium chlorides in aprotic solvents were the first examples that used this procedure, which has subsequently been shown to be one of the most important recent advances in Mannich technology.[43]

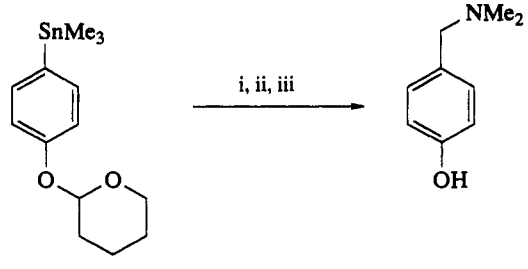
1,3-Dimethoxybenzene reacts with *N*-methylenemorpholinium chloride in acetonitrile to afford the Mannich product, characterized as the hydrobromide, in 66% yield. The analogous reaction using the pyrrolidinium salt is shown in equation (21). Ferrocene gives low yields of products, for example with

bis(dimethylamino)methane in the presence of protic acids, and as with a number of other electrophiles a substituent is introduced into each of the rings.[44]



(21)

An alternative strategy for introduction of an aminomethyl residue involves *ipso*-aminoalkylation–destannylation reactions. This type of reaction takes advantage of the relatively high electron density at the carbon *ipso* to tin, and thereby is particularly useful for the formation of products with unusual regiochemistry.[45] We have indicated in Section 4.2.3.1 that Mannich reactions of phenols normally result in the introduction of an *ortho*-aminoalkyl residue. The reaction of 4-tetrahydropyranyloxyphenyltrimethylstannane with *N,N*-dimethylmethyleneiminium chloride in acetonitrile results in the formation, after aqueous acidic work-up, of the abnormal regioisomer as shown in equation (22). It is worth noting that aryltrialkylsilanes do not, in general, confer enough nucleophilicity to allow reaction with the weakly electrophilic iminium salts.



(22)

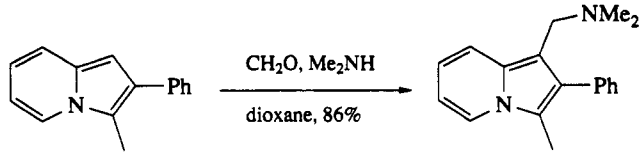
i, $Me_2\overset{+}{N}=CH_2$ Cl^-; ii, H_2O/H_3O^+; iii, OH^-

Because a wide range of aryltrialkylstannanes are available from the corresponding aryl bromides this reaction can be used to introduce one or more dialkylaminomethyl groups into a variety of aromatic substrates. The reaction of *N,N*-dimethylmethyleneiminium chloride with 1,4-bis(trimethylstannyl)benzene gives *N,N,N′,N′*-tetramethyl-1,4-diaminobenzene in 58% yield.[45]

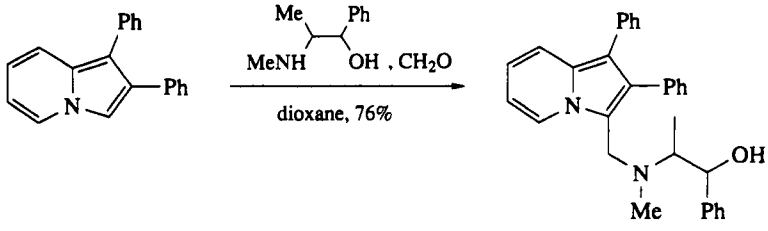
4.2.3.4 Reactions with Electron-rich Heterocyclic Systems

Because of the wide variation in nucleophilicity of five-membered aromatic heterocycles, this group of compounds has been extensively studied. The different experimental procedures that may be used reflect the π-electron densities in this family of compounds. The most nucleophilic heterocycles, for example pyrrole, react using aqueous solutions of formaldehyde and a secondary amine, whereas relatively unreactive compounds such as thiophene only react successfully with preformed iminium salts. Reactions of certain heterocyclic ring systems have been investigated primarily because of the potential for biological activity of the products. For example, indolizines undergo high-yield *C*-aminoalkylation in the five-membered ring under the classical conditions.[46] Some examples are shown in equations (23) and (24), including the use of (1*S*,2*R*)-ephedrine.[47] The iminium salt derived from methyl 1-morpholino-1-methoxyacetate[35] reacts with 8-acetoxy-3-acetylindolizine in acetonitrile at room temperature to afford the Mannich base hydrochloride (**9**) in quantitative yield.[48] So far, it has not been possible to isolate pure samples of a number of diaminomethanes derived from bulky secondary amines.[14] Nevertheless, successful reactions have been reported, for example that of 1,2-diphenylindolizine with formaldehyde and dicyclohexylamine.[49] The reaction of the 2,3-dihydro-5(1*H*)-indolizinone (**10**) with *N,N*-dimethylmethyleneiminium chloride gives compound (**11**); once again, it is noteworthy that the trimethylsilyl group is not involved in the substitution reaction.[50]

Functionalizations of some rather unusual systems have been reported. For example, a Mannich reaction of a 4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine at the free position in the triazole ring occurs on heating with *N,N*-dimethylmethyleneiminium chloride in degassed DMF.[51] Although no successful reactions of thiazole have been reported, 2-acetylamino-4-methylthiazole reacts with formaldehyde and



(23)



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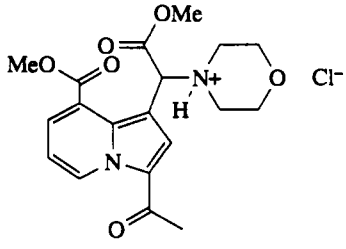

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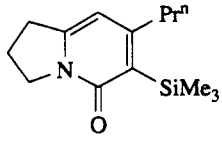

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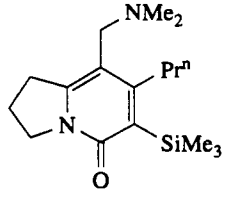
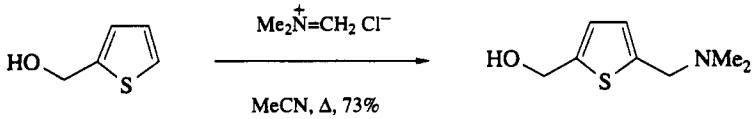


(11)

dimethylamine in acetic acid to afford the 3-*N*,*N*-dimethylaminomethyl derivative in 92% yield.[52] Imidazole reacts at nitrogen at low pH but in basic media *C*-aminoalkylation occurs.[53] We will subdivide the remainder of this section according to the parent ring system.

4.2.3.4.1 Reactions of thiophenes

It has been known for some time that thiophenes that are activated by electron-releasing substituents undergo the Mannich reaction with formaldehyde and secondary amines.[54] Reactions of 2- or 3-methoxythiophene with formaldehyde and dimethylamine, piperidine or morpholine give Mannich bases in 69–89% yield. 3,4-Dimethyoxythiophene is apparently less reactive than the monomethoxy compounds but it also gives the 2-*N*,*N*-dimethylaminomethyl derivative in 66% yield. A modification of the classical procedure, in which gaseous formaldehyde is passed into a hot solution of 2-hydroxymethylthiophene and dimethylamine hydrochloride, gives the expected Mannich base in 25% yield. However, a better yield is obtained (equation 25) by heating the thiophene derivative under reflux with *N*,*N*-dimethylmethyleneiminium chloride in acetonitrile.[55] Thiophene itself gives the Mannich base in 55% yield using the latter reagent and reaction conditions. In all of the examples reported[55] substitution occurs at the 2-position. If a reaction is carried out at room temperature with 3-thienyltrimethylstannane (equation 26) the C-3 isomer is obtained in good yield. In this last experiment no evidence was found for the presence



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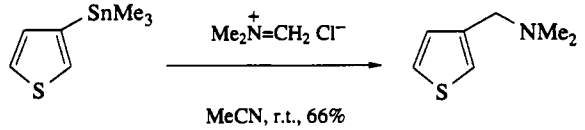
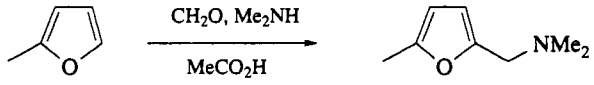


(26)

of the 2-substitution product,[45] once again showing the value of using an arylstannane in an *ipso* electrophilic demetallation reaction when control over unusual regiochemistry is desired.

4.2.3.4.2 Reactions of furans

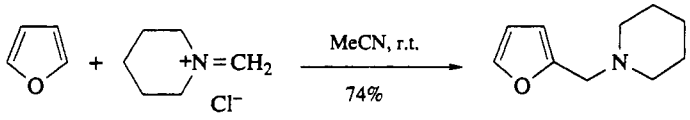
Reactions of 2-methylfuran with aqueous formaldehyde and secondary amines have been reported using a variety of procedures.[56] Thus, 2-methylfuran, formaldehyde and dimethylamine react in aqueous acetic acid at 100 °C to give the expected product (equation 27) in 69–76% yield.[56c] Remarkably, it is reported[56b] that attempted Mannich reactions with furan itself yields no liquid amine. It has been suggested[57] that this type of reaction can only be carried out with alkyl-substituted furans, because of the marked activating effect of methyl substitution on electrophilic substitution reactions.



(27)

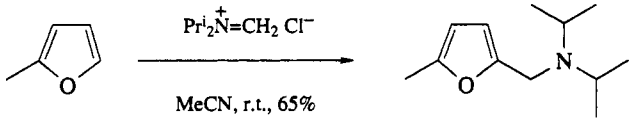
Competition data for the trifluoroacetylation of a number of heterocycles using trifluoroacetic anhydride at 75 °C give the relative rates: thiophene (1.0), furan (1.4×10^2), 2-methylfuran (1.2×10^5) and pyrrole (5.3×10^7).[58] Similar values, thiophene (1.0), furan (3.0×10^3) and pyrrole (5.0×10^5); are obtained for reactions with $[C_6H_7Fe(CO)_3]^+$.[59] We have already discussed the fact that thiophene does undergo the Mannich reaction using preformed methyleneiminium salts and therefore it is not surprising that furan also affords the aminomethyl derivatives in reactions with iminium salts.

The yields of the Mannich bases obtained when a number of methyleneiminium salts were allowed to interact with furan in acetonitrile at room temperature ranged from 66 to 74%.[60] A representative example is shown in equation (28). The reasons for the earlier failures remain obscure but the amine would not have been lost under the aqueous reaction conditions.



(28)

Preformed methyleneiminium salts react with 2-methylfuran to give the expected products in 65–94% yield.[60] It is even possible to carry out a reaction with *N,N*-diisopropylmethyleneiminium chloride (equation 29), the latter reagent being prepared in excellent yield by the interaction of ethoxy-*N,N*-diisopropylaminomethane with trichloromethylsilane.

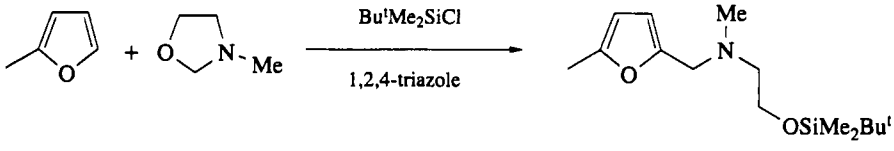


(29)

The possibility of carrying out reactions of furan and 2-methylfuran in nonprotic media without the isolation of reactive intermediates has also been investigated.[61] The results provide some help in understanding the mechanistic complexities involved in Mannich reactions and perhaps explain the failure of furan to afford a product using aqueous reaction conditions. A comparison of the strengths of the silicon–oxygen and silicon–nitrogen bonds also suggested the use of aminol ethers and aminals in *in situ* reactions, activated by derivatives of silicon tetrachloride. The formation of *N,N*-dialkylmethyleneiminium chlorides from ethoxy-*N,N*-dialkylaminomethanes had already been reported[62] using trichloromethylsilane. The ^{13}C NMR spectra of aminol ethers showed that iminium salts are also formed on treatment with dichlorodimethylsilane or chlorotrimethylsilane. On the other hand, iminium salts are not detected when aminals interact with chlorotrimethylsilane. Both furan and 2-methylfuran give good yields of Mannich bases when treated with, for example, ethoxypyrrolidinylmethane in the presence of chlorotrimethylsilane. In contrast, no Mannich base is formed when di-*N*-pyrrolidinylmethane is treated with chlorotrimethylsilane in the presence of 2-methylfuran. The conclusion may be drawn that, while both furan and 2-methylfuran are sufficiently nucleophilic to react with iminium salts, the intermediates formed when aminals interact with chlorotrimethylsilane are not electrophilic enough to participate in Mannich reactions with these substrates. We will consider these reagents further in the section concerned with

pyrroles (Section 4.2.3.4.3). It is likely, therefore, that the reactions of furan that were attempted in aqueous solution failed because the electrophilic intermediate that is generated in that system was too mild—it was not an iminium salt.

The possibility of carrying out Mannich reactions with cyclic aminol ethers has been alluded to earlier. It has also been shown that the *in situ* method using chlorosilanes can be applied to oxazolidines such as 3-methyl-1,3-oxazolidine.[63] The ring–chain tautomerism of 1,3-oxazolidines in the presence of protic acids has been studied[64] by NMR spectroscopy and the hydroxy Schiff base; oxazolidine tautomerism has been discussed in terms of the apparent violation of Baldwin's rules.[65] The idea that a Mannich reaction could be carried out while at the same time protecting the resulting alcoholic function was explored in a reaction of 2-methylfuran with 3-methyl-1,3-oxazolidine and *t*-butyldimethylchlorosilane. The yield in this reaction is only modest (33%) but catalysis with 1,2,4-triazole results in an improvement to 61% (equation 30). Good yields are obtained in reactions of 2-methylfuran with 3-methyl-1,3-oxazolidine and chlorotrimethylsilane (73%) or trichloromethylsilane (87%). Even the reaction of furan gives a good yield (75%) with trichloromethylsilane.



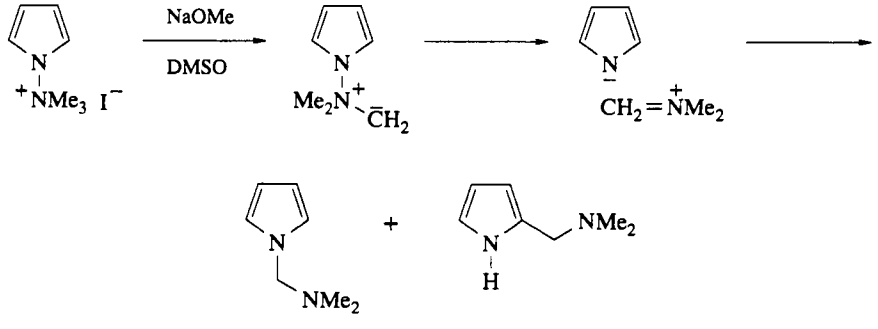
(30)

4.2.3.4.3 Reaction of pyrroles

Pyrroles are exceptionally nucleophilic heterocycles and undergo electrophilic substitution reactions with very weak electrophiles. The reactivity of pyrrole may be compared with that of *N,N*-dimethylaniline or phenol; all three compounds couple with the benzenediazonium ion. It is no surprise, therefore, that Mannich reactions of pyrrole and substituted pyrroles have been studied in considerable detail. We will concentrate our attention on recent studies.

Pyrrole reacts with aqueous formaldehyde and secondary amines in the presence of acetic acid to afford, in some cases, mixtures of products derived from attack at the 2- and 2,5-positions. The disubstitution products can be obtained in very high yields at about room temperature; for example, a 92% yield of 2,5-bis(piperidylmethyl)pyrrole is obtained using this method.[66] The same procedure apparently does not yield a Mannich base with 1-methylpyrrole, but the use of aqueous formaldehyde and dimethylamine hydrochloride at 60 °C results in the formation of the 2-substitution product in 73% yield.[67] Even highly substituted pyrroles react. Thus, ethyl 4,5-dimethylpyrrole-2-carboxylate and ethyl 2,5-dimethylpyrrole-3-carboxylate both undergo *C*-aminoalkylation at the unsubstituted position in 45 and 68% yields, respectively, with dimethylamine and formaldehyde in ethanolic solution.[68] A number of tri- and tetra-substituted 2-methylpyrroles have been investigated; with the exception of Knorr's pyrrole all gave side-chain substituted products with formaldehyde and a secondary amine in acetic acid.[69]

More modern technology has also produced some interesting results. Quaternization of 1-*N,N*-dimethylaminopyrrole and treatment of the product with sodium methoxide in DMSO leads to Stevens-type rearrangement products.[70] No CIDNP was observed in an NMR study of the rearrangement and it was concluded that the ylide fragments to an ion pair, which recombines as shown in Scheme 4.

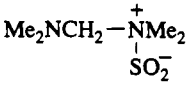


Scheme 4

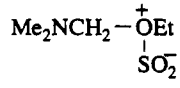
Reactions carried out in nonprotic solvents using *in situ* generation of reactive intermediates have also been studied with *N*-methylpyrrole as the substrate. Attempts to achieve good conversions using acetyl

chloride and an aminal were relatively unsuccessful but better yields were obtained using sulfur dioxide in reactions with both aminals and aminol ethers.[71]

Although reactions of di-*N*-morpholinylmethane with acetyl chloride in the presence of *N*-methylpyrrole give good yields of either the 2-substituted (54%) or 2,5-disubstituted (87%) products, reactions with bis-*N*,*N*-(dimethylamino)methane are poor. In the case of a reaction using 1 mol equiv. of aminal and acetyl chloride the yield was only 18% and an attempt to form 1-methyl-2,5-bis-*N*,*N*-(dimethylaminomethyl)pyrrole failed due to the formation of 1,1′-dimethyl-di-2,2′-pyrrylmethane. Reactions using sulfur dioxide as the anhydride-activating agent give high yields of the expected products with a range of aminals and aminol ethers. Iminium salts were not detected in NMR experiments and it was tentatively concluded that dipolar compounds such as (**12**) and (**13**) are the most likely reactive intermediates.

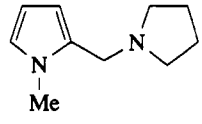


(**12**)

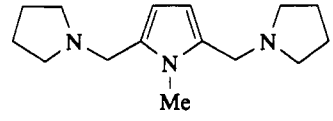


(**13**)

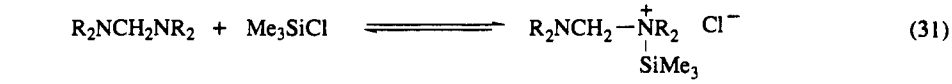
Reactions of *N*-methylpyrrole with aminol ethers and aminals in the presence of derivatives of silicon tetrachloride permit control of the number of aminoalkyl groups that are introduced.[61] The reactions of a number of aminol ethers with chlorotrimethylsilane and trichloromethylsilane give mixtures of 2- and 2,5-disubstitution products. The use of aminals, on the other hand, allows a good measure of control over the degree of substitution. Thus the reaction of di-*N*-pyrrolidinylmethane with *N*-methylpyrrole and trichloromethylsilane affords the monosubstitution product (**14**) in 75% yield, whereas with chlorotrimethylsilane the disubstitution product (**15**) is produced in 70% yield based on the aminal. It was concluded that the reaction leading to the formation of (**14**) is controlled by the formation of a salt of the Mannich base which is less nucleophilic than the starting material. The formation of (**15**) in the reaction involving chlorotrimethylsilane was interpreted as implicating the presence of the free Mannich base (**14**), which would be more nucleophilic than the starting material. This suggests that no accumulation of hydrogen chloride occurs in the reaction and led to the prediction that the reaction should be catalytic in chlorotrimethylsilane. Experiments have confirmed this prediction and in a reaction carried out under reflux with 5 mol % of chlorotrimethylsilane the compounds (**14**) and (**15**) were isolated in 17 and 61% yields respectively.[61] We mentioned in the section on furans (Section 4.2.3.4.2) the failure to detect iminium salts in NMR experiments using aminals and chlorotrimethylsilane. The formation of (**15**) was therefore explained in terms of equations (31)–(33).



(**14**)



(**15**)



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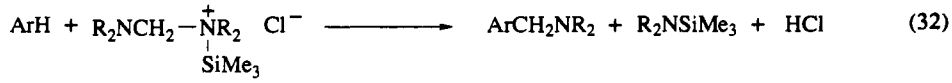

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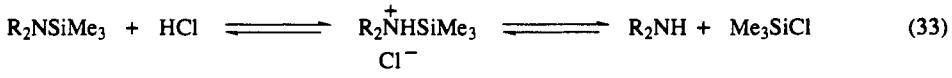
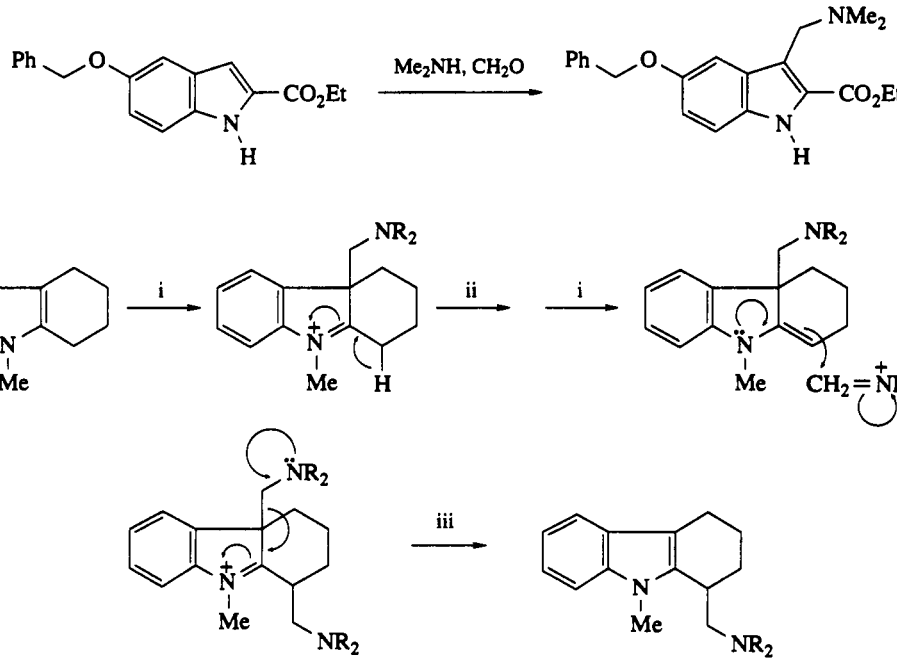


(33)

4.2.3.4.4 Reactions of indoles

Like pyrrole, indole is a highly nucleophilic aromatic heterocycle and takes part in Mannich reactions under a wide variety of reaction conditions, including the very mildest. We will only mention a few important examples from the very large number of reactions carried out under classical conditions.[2]

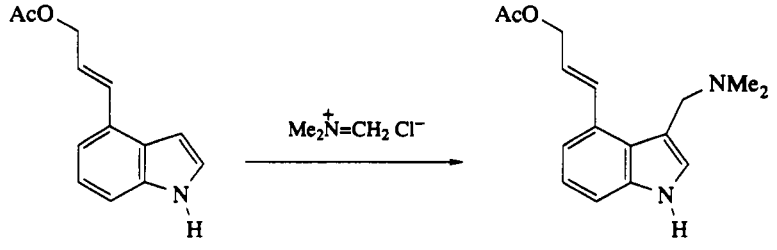
3-*N*,*N*-Dimethylaminomethylindole (gramine) can be obtained in 90–95% yield and the *N*-methyl analog in 77–80%. 2-Ethoxycarbonyl-5-hydroxyindole undergoes reaction at the 4-position, while the benzyl analog affords the 3-dimethylaminomethyl derivative (equation 34).[72] 1,2,3-Trialkylindoles like *N*-methyltetrahydrocarbazole undergo aminoalkylation on the carbon at the 2-position.[73] This reaction presumably proceeds by a mechanism (Scheme 5) that is similar to those operating when other electrophiles react with highly alkylated indoles. The quaternary salts derived from Mannich bases have been widely used in synthesis. Well-known examples include a tryptophan synthesis and preparations of the plant growth hormones 3-indolylacetonitrile and 3-indolylacetic acid.



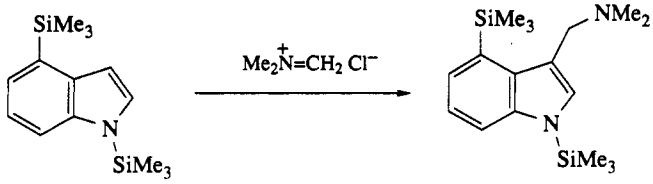
i, $R_2\overset{+}{N}{=}CH_2$; ii, $-H^+$; iii, $-R_2\overset{+}{N}{=}CH_2$

Scheme 5

Good yields of the expected Mannich bases are also obtained in reactions using recently described methodology, including *in situ* generation of reactive intermediates.[61,63,71,74] Functionalization of indoles at C-3 and C-4 has been widely studied in connection with syntheses of ergot alkaloids. Reactions with preformed *N*,*N*-dimethylmethyleneiminium chloride are especially useful in this context. A number of 4-substituted indoles give the 3-*N*,*N*-dimethylaminomethyl derivatives in yields ranging from 91 to 100%.[73] This type of reaction is exemplified by equation (35).[75] The synthesis of *cis*- and *trans*-clavicipitic acids from 4-cyanomethylindole also involves functionalization at C-3 by reaction with *N*,*N*-dimethylmethyleneiminium chloride.[76] Classical reaction conditions have also been used in a total synthesis of racemic 6,7-*seco*-agroclavine.[77]



A reversal of the reaction sequence, that is the introduction of the C-3 substituent first, is accomplished by starting with 1,4-bis(trimethylsilyl)indole. Reaction of this compound with the usual iminium salt gives the product shown in equation (36) in variable yields.[78] Once again, we observe that iminium salts are not electrophilic enough to effect *ipso* substitution of a silyl residue.



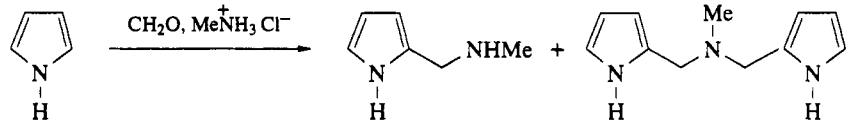
(36)

4.2.4 REACTIONS USING PRIMARY AMINES

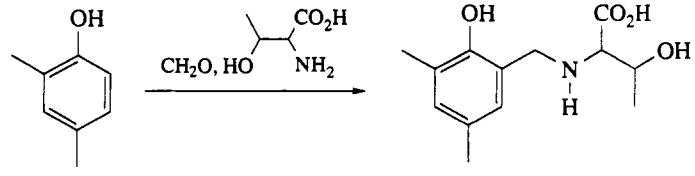
A number of different types of product can be formed when an aromatic substrate reacts with a primary amine and an aldehyde. The first-formed product will be a secondary amine and can therefore take part in a second Mannich reaction. A third possibility is that another suitable functional group may be correctly positioned to enable a cyclic product to be formed.

4.2.4.1 Reactions Leading to Acyclic Products

Mannich reactions of pyrroles with primary amine hydrochlorides give yields that were significantly lower than those obtained with secondary amine hydrochlorides.[67,79] For example, whereas formaldehyde and dimethylamine hydrochloride react with pyrrole to give the expected product in 77% yield, reaction with methylamine hydrochloride only gives a 15% yield of 2-*N*-methylaminomethylpyrrole. A by-product in the reaction is the di(2-pyrrylmethyl)amine derivative (equation 37).[80] Increasing the steric bulk of the group on the nitrogen of the primary amine gives a higher yield of the first-formed product; no di(2-pyrrylmethyl)amine derivative is formed in reactions of pyrrole with formaldehyde and isopropylamine or *t*-butylamine. As expected, increasing the amount of amine hydrochloride used also favors formation of secondary amine. The steric effect of large groups on nitrogen is also observed in products derived from amino acids. The reaction of threonine with formaldehyde and 2,4-dimethylphenol (equation 38) also gives the secondary amine.[81]



(37)

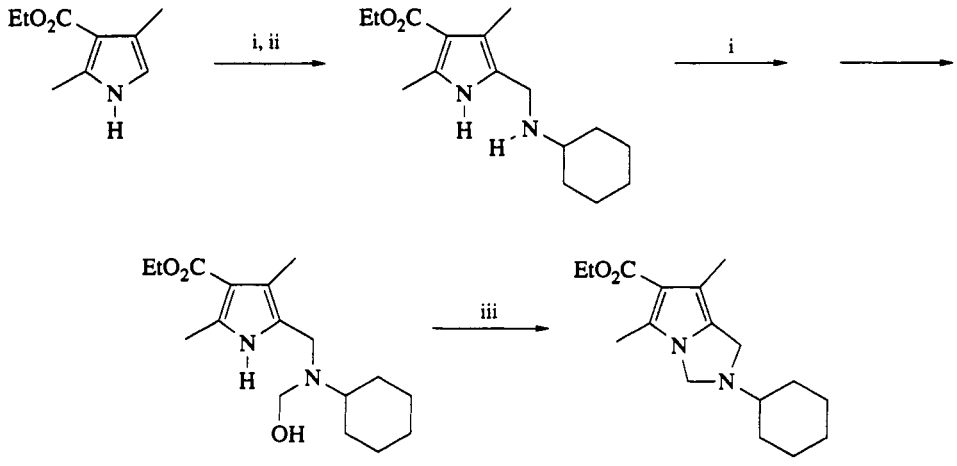


(38)

4.2.4.2 Reactions Leading to Cyclic Products and Their Reactions

The reactions of ethyl 2,4-dimethylpyrrole-3-carboxylate with a number of primary amines and an excess of formaldehyde lead to the formation of 2,3-dihydro-1*H*-imidazo[1,5-*a*]pyrroles. The reaction of cyclohexylamine, which, as indicated in the foregoing section, would not be expected to yield a product involving two pyrrole nuclei, does result in the formation of the dihydroimidazopyrrole in 70% yield as shown in Scheme 6.[82]

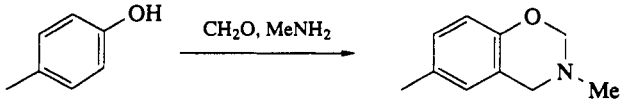
The main substrates that have been investigated as partners in cyclization reactions are phenols. As with reactions involving secondary amines, phenols react with aldehydes and primary amines principally *ortho* to the hydroxy group. A reaction of the first-formed secondary amine with a second molecule of aldehyde can therefore lead to the formation of a benzoxazine derivative. A wide range of phenols, includ-



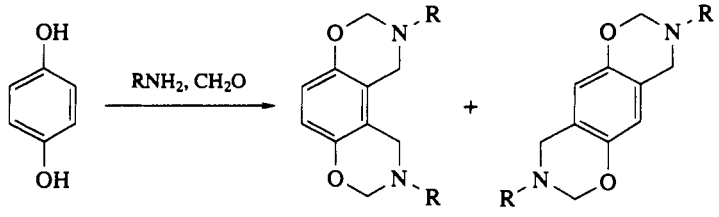
i, CH_2O; ii, $C_6H_{11}NH_2$; iii, $-H_2O$

Scheme 6

ing for example *p*-cresol (equation 39) and 2,4-dichlorophenol form benzoxazines in good yields using methylamine and formaldehyde.[83] It is interesting to note that of the two possible dioxazine derivatives that can be formed from hydroquinone, the compounds (**16**) (equation 40) are the major products.[84] The possibility of using a diaminol ether as a bisaminoalkylating agent has been investigated briefly in connection with the reaction of 2-methylhydroquinone as shown in equation (41).[29]

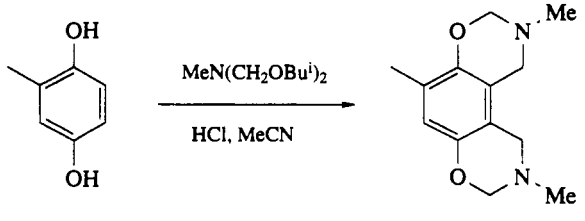


(39)



(40)

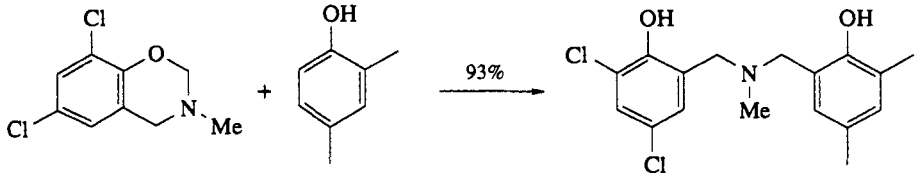
(**16**)



(41)

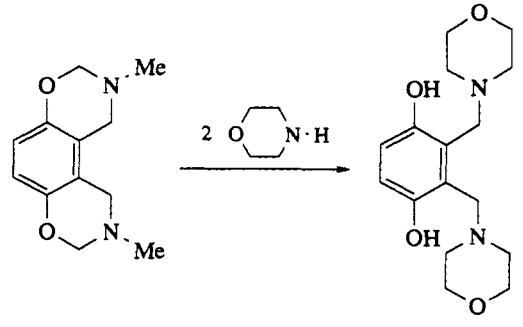
It was noted at an early stage[83a] that the heterocyclic ring in benzoxazines is easily cleaved, for example by ethanol. The ring–chain tautomerism of 2-aryl-1,3-benzoxazines has been investigated,[85] and it has been shown that the equilibration of benzoxazines in the presence of primary or secondary amines involves Mannich bases and ring-opened coupling products.[86] It is not surprising, therefore, that benzoxazines have been investigated as potential Mannich reagents in reactions with phenols.[83b] What is surprising is that the promised extension to other systems does not appear to have materialized so far. An example of the reaction with a phenol is shown in equation (42).[83b] Electronic effects both in the benz-

oxazine and also in the phenolic coreactant are, as expected, important. Thus the dichlorobenzoxazine shown in equation (42) is a very reactive species because of the enhanced electrophilicity of the amino-alkylating agent that results from the presence of the chlorine atoms. On the other hand, the most reactive phenolic coreactants are those with high electron density in the aromatic ring. 2-Naphthol is particularly reactive due to the low activation energy involved in reactions with electrophiles at the 1-position.



(42)

Amine exchange reactions have been reported in which, for example, a secondary amine replaces the primary amine. This type of reaction is exemplified in equation (43).[29] The use of newer technology, for example involving mild Lewis acids in nonprotic solvents, should allow additional reactions of benzoxazines to be carried out.

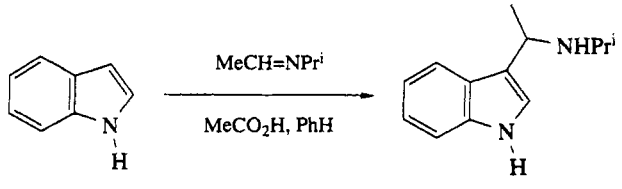


(43)

4.2.5 REACTIONS USING IMINES

We indicated in the introduction that the trimerization of pyrrole involves, in the reaction of the third molecule of pyrrole, the interaction with a protonated enamine. Such an intermediate could also be generated by protonation of an imine. Although few examples of intermolecular reactions have been reported, it is clear that this is another method that is capable of further exploitation. Acyclic and cyclic imines have been shown to interact successfully with nucleophilic aromatic substrates such as indole. In the case of the cyclic imines they may be generated *in situ* from relatively stable trimers.

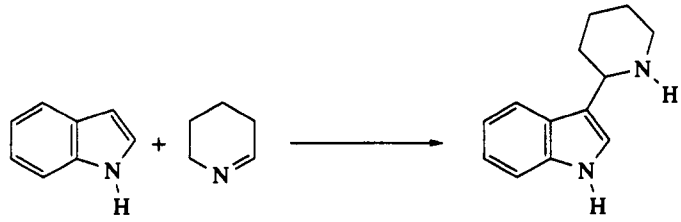
The reactions of indole with the imines derived from acetaldehyde and *t*-butylamine and isopropylamine have been reported using acetic acid as the proton source in benzene.[87] A poor yield (15%) is obtained with ethylidene-*t*-butylamine but a better yield (60%) results with the isopropylamine analog (equation 44). A 'one pot' reaction using indole, acetaldehyde and isopropylamine gives the same product in 40% yield. This type of reaction depends for its success on the stability of the aldimine under the acidic reaction conditions. However, while the more sterically demanding primary amines afford the most stable imines, it appears that this can lead to too great a steric demand in the transition state leading to reaction with, for example, indole, and hence the low yield reported in the *t*-butylamine reaction.



(44)

The trimer of 1-piperidine, best prepared by dehydrochlorination of *N*-chloropiperidine, has been known for some time.[88] 1-Pyrroline also appears to exist largely as the trimer.[89] Both undergo Mannich reactions with electron-rich heterocycles. Indole reacts with 1-piperidine in a citrate buffer to afford 3-(2-piperidyl)indole in 40–55% yield (equation 45).[90] The *N*-methylpiperidyl analog has also been

prepared, but only in very low yield. Once again, we note the remarkable variations in yields obtained in Mannich reactions involving primary and secondary amines and aldehydes other than formaldehyde. Although 1-pyrroline is only obtained from its trimer in very low yield,[89] its formation may be inferred by the fact that 2-(2-pyrrolidyl)pyrrole is produced in high yield when the trimer is heated with an excess of pyrrole.[89]

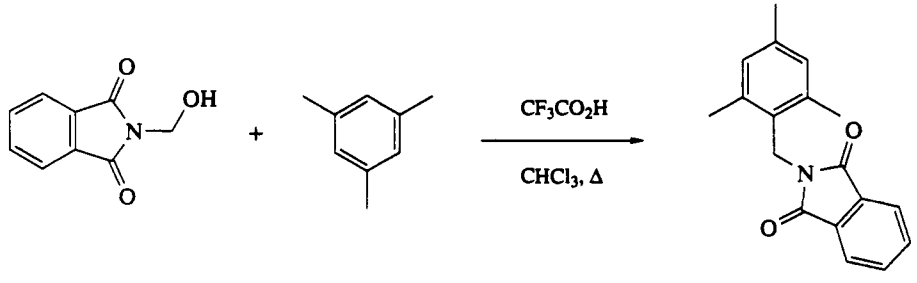


(45)

4.2.6 AMIDOALKYLATION REACTIONS

Acyliminium ions are the reactive intermediates in amidoalkylation reactions and are the subject of Chapter 4.5. This section is restricted to a brief coverage to allow comparisons to be made with the earlier sections in this chapter. The topic has been reviewed several times.[91]

The most important feature of the chemistry of amidoalkylating reagents is related to the increased electrophilicity of such reagents compared to those involved in aminoalkylation reactions. It is possible to vary the reactivity of the reagents by adjusting the electron-withdrawing acyl group. A frequently used amidomethylating agent is *N*-hydroxymethylchloroacetamide. This reagent combines the involvement of a reasonably electrophilic reagent with the presence of an easily hydrolyzed acyl residue. Thus, amidoalkylation of, for example, 2,4-dimethylanisole can be achieved.[92] Even more electrophilic is *N*-hydroxymethylphthalimide. Mesitylene gives, with the latter reagent, an 86% yield of product (equation 46).[93]



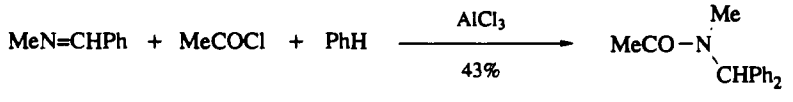
(46)

The reaction of furan with the acetaldehyde derivative (**17**) in the presence of toluene-*p*-sulfonic acid gives (**18**) in 67% yield (equation 47).[94]

(47)

(**17**) (**18**)

N-α-Chloroalkylamides are relatively unstable precursors and form acyliminium ions easily. They are frequently formed *in situ* as indicated in equation (48).[95]



(48)

The chemistry that has been reviewed in this chapter demonstrates that although the bimolecular Mannich reactions of aromatic compounds have now reached the venerable stage, they are still much used by synthetic organic chemists and that they are capable of further development.

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4.3
Reactions of Allyl and Propargyl/Allenic Organometallics with Imines and Iminium Ions

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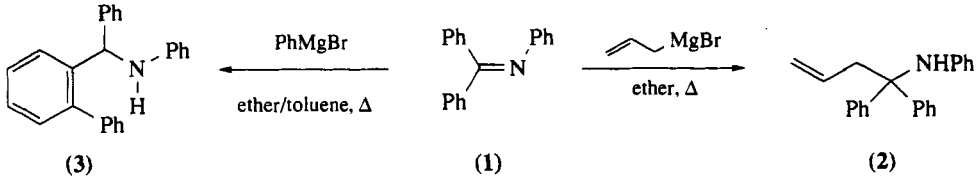
4.3.1 INTRODUCTION

4.3.1.1 Reactivity and Structure

Gilman and Eisch were the first to recognize that allyl organometallic reagents possess superior reactivity relative to ordinary, nonresonance-stabilized organometallic reagents in imine addition re-

actions.[1] In an investigation of the reactions of *N*-diphenylmethyleneaniline (**1**) with organometallic reagents, these workers observed that while imine (**1**) is inert to ordinary Grignard reagents in refluxing ether, it cleanly reacts with allylmagnesium bromide in a 1,2-manner, affording 1-allyl-1,1-diphenylmethylaniline (**2**; Scheme 1). Interestingly, under forcing conditions (refluxing ether–toluene), phenylmagnesium bromide adds in a 1,4-manner to one of the aromatic rings of (**1**) to give amine (**3**). These results, together with the observation that the more ionic, nonresonance-stabilized lithium, potassium, sodium, calcium, barium and strontium organometallics add to imine (**1**) in a 1,2-manner, led to the suggestion that resonance stabilization of the allyl anion in allyl organometallic reagents promotes greater ionization of the carbon–metal bond and, hence, greater reactivity (Figure 1). This conclusion should not be confused with the fact that allyl anions are less nucleophilic than nonresonance-stabilized anions, because it is assumed that the reactivity is not governed by the nucleophilicity of the naked anion but by the ease of heterolysis of the carbon–metal bond.



(3) (1) (2)

Scheme 1

Figure 1 Resonance stabilization of the allyl anion in allyl organometallic reagents results in greater ionization of the carbon–metal bond[1]

A general survey of the different types of allyl organometallic reagents reported to add in a 1,2-manner to imines, iminium salts and related compounds is shown in Table 1. The organometallic reagents are listed in order of increasing metal electronegativity, reflecting the increased covalent (less ionic) character of the carbon–metal bond. Allyl organometallics containing metals with electronegativities less than or equal to 1.65 add directly to imines while, except for allylboranes, less reactive reagents with electronegativities >1.65 require the use of Lewis acid additives to enhance the electrophilicity of the imine. The reactivity of allylboranes, which is greater than predicted based on the electronegativity of boron, may be attributed to the Lewis acidity of boron which enhances imine reactivity by coordination to the imine lone pair of electrons. Iminium salts, being more electrophilic than imines due to the positively charged nitrogen, are capable of reacting directly with less reactive reagents such as allylsilanes and allylstannanes.

Table 1 Survey of Allyl Organometallic Reagents Known to React with Imines, Iminium Salts and Related Derivatives

Metal	*Ligand(s)*	*Electro-negativity*[a]	*Imines*	*Oximes*	*Sulfenimines*	*Iminium salts*	*gem-Amino ether*
Lithium	—	0.98	x	x		x	x
Magnesium	Halogen	1.31	x	x	x	x	x
Titanium	Alkoxy	1.54	x				
Aluminum	Halogen	1.61	x			x	x
Zinc	Halogen	1.65	x	x	x	x	x
Tin	Alkyl	1.72	x[b]			x	
Silicon	Alkyl	1.90				x	
Boron	Alkyl	2.04	x				
Boron	Alkoxy		x	x[c]	x		
Lead	d	2.33	x[b]				

[a]Estimated by Pauling's method. [b]Lewis acid additive is necessary. [c]Reaction is performed at high pressure (4–9 kbar). [d]The allyllead reagent is formed *in situ*, the ligand is not known (see ref. 2).

Insight into the structure of several allyl/crotyl organometallic reagents has been obtained spectroscopically. Kramer and Brown have examined the NMR spectra of β-allyl-9-BBN and β-crotyl-9-BBN

and conclude that at temperatures above –60 °C, β-allyl-9-BBN exists in a dynamic equilibrium in which the boron exchanges rapidly between the 1- and 3-positions of the allylic system (Figure 2).[3] Since the process is concentration independent, the exchange process must be intramolecular. The Lewis acidity of boron appears to be a critical factor in the exchange process because allylic rearrangement is not observed when a Lewis base such as pyridine is added. In the case of β-crotyl-9-BBN, equilibrating *cis* and *trans* alkene isomers are observed above 0 °C, instead of products of allylic rearrangement. Isomerization is postulated to proceed *via* allylic rearrangement through the transient 1-methallyl isomer (Figure 3). In another study by Gross, *cis* and *trans* forms of crotyl-magnesium, -zinc and -aluminum reagents are indicated in their solution IR spectra in the 1600 cm^{-1} region; it is not clear, however, whether the isomers are in equilibrium.[4]

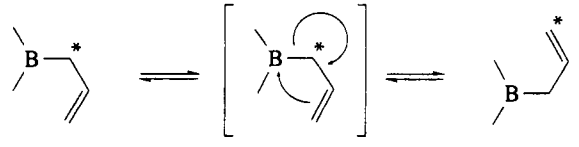


Figure 2 β-Allyl-9-BBN exists in a state of permanent allylic rearrangement[3]

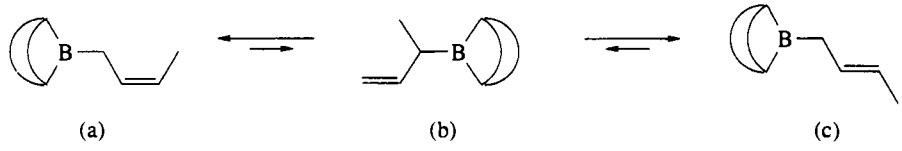


Figure 3 Equilibrium between *cis* (a) and *trans* (c) β-crotyl-9-BBN involving the intermediacy of the β-methallyl isomer (b)[3]

The isotopic perturbation technique[5] has been used by Schlosser and Stähle to distinguish between the σ- and π-bond structures of allyl- and crotyl-magnesium, -potassium and -lithium reagents.[6] The ^{13}C NMR spectra of the deuterated crotyl reagents demonstrate that: (i) crotylmagnesium reagents are σ-structures in which the metal is attached to the primary carbon (Figure 4a); and (ii) crotylpotassium and crotyllithium reagents are π-structures in which the metals are bonded to carbons 1 and 3 of the allylic system (Figures 4b and 4c). The data also suggest that the carbon–metal lengths in the crotylpotassium reagents are essentially equal, whereas those of the crotyllithium reagents are unequal. Similar conclusions can be drawn for the corresponding allyl organometallic reagents. As has been noted by Schlosser and Stähle,[6] energy differences between σ- and π-forms of allyl and crotyl organometallic reagents are not large; therefore, caution should be exercised in using structural knowledge for the interpretation of regio- and stereo-selective allyl and crotyl organometallic addition reactions since ground state organometallic structures are not necessarily involved in the rate determining step of the reaction.

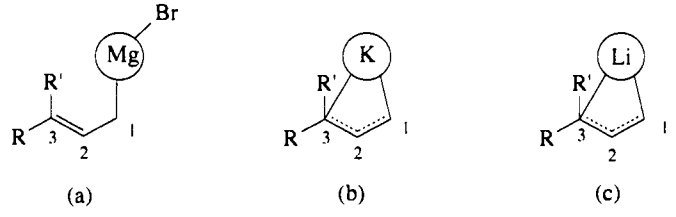
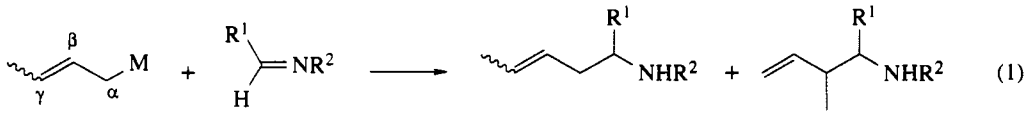


Figure 4 Structures of allyl- and crotyl-magnesium, -lithium and -potassium reagents as determined by isotopic perturbation studies.[6] The magnesium reagent (a) exists as a σ-structure and the potassium (b) and lithium (c) reagents exist as π-structures

In contrast with the more reactive crotyl reagents discussed above, crotyl-silanes,[7] -stannanes[8] and -boronates[9] can be prepared in isomerically pure *cis* and *trans* forms for use in imine and aldehyde addition reactions. However, isomerization of these reagents under certain reaction conditions, particularly those requiring the presence of Lewis acids, cannot be ruled out. Nonetheless, in connection with a study involving aldehyde additions, Yamamoto *et al.* have shown that *trans*-crotyltri-*n*-butylstannane is stable to $BF_3{\cdot}Et_2O$ at –78 °C.[8]

4.3.1.2 Regio- and Stereo-chemistry

Reactions of crotyl organometallics with aldimines can give linear (**4**) and/or branched (**5**) homoallylamines, a result of addition at the α- and γ-crotyl carbon atoms (equation 1). Although branched products usually dominate, the metal (M) and the imine substituents (R^1 and R^2) can strongly influence the regiochemical outcome of the reaction; similar effects are observed with crotyl in additions to iminium salts and *gem*-amino ethers.



(4) (5) (1)

Branched homoallylamines obtained in the reaction of crotyl organometallics contain two adjacent stereocenters and therefore can be produced in two diastereomeric forms, *syn* (**6**) and *anti* (**7**).[10] Cyclic and open transition state models have been used by Yamamoto *et al.* to explain *syn–anti* stereoselectivity in reactions of imines and are shown in Figures 5 and 6.[11] The cyclic models involve coordination between the metal and the imine lone pair and comprise two chair (C) and two boat (B) transition states. The substituents are placed axially or equatorially according to the geometry of the crotyl reagent and the preferred (*E*)-geometry of the imine. A complementary set of transition states leading to the opposite diastereoselectivity can be derived from the (*Z*)-imine geometry. The open transition states, drawn as Newman projections, are depicted as antiperiplanar (A) or synclinal (S)[12] and are differentiated by the geometry of the crotyl reagent. The synclinal transition states are divided into two types, S_g and S_a, depending upon whether the vinyl group and the imine α-substituent are *gauche* or *anti*, respectively. The open transition states shown are also based on (*E*)-imine geometry; those based on the (*Z*)-imine geometry, unlike the cyclic models, give the same diastereoselectivity. The three letter descriptors designating the overall geometry of the transition state, and the geometries of the crotyl reagent and imine, respectively, are used throughout this chapter.

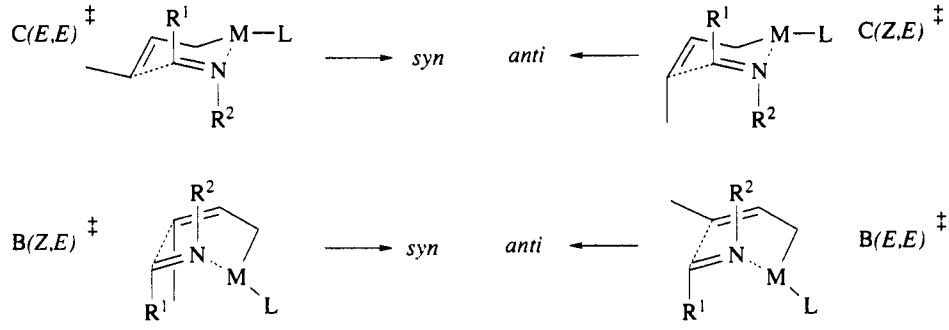


Figure 5 Postulated cyclic chair and boat transition states involved in the reactions of crotyl organometallics[11]

Diastereofacial selectivity in allyl organometallic additions to aldimines containing one or more stereogenic centers has been studied extensively in recent years. Chiral imines used in these investigations have been derived from: (i) chiral aldehydes and achiral amines, (ii) achiral aldehydes and chiral amines and, in a few cases, (iii) chiral aldehydes and chiral amines. A few examples involving the use of allyl organometallics bearing chiral ligands have also been recorded.

Models used to explain and predict diastereofacial selectivity in related carbonyl addition reactions (Figure 7) can be utilized to predict similar selectivity in allyl organometallic–aldimine condensations. As a consequence of the type of imine substitution, addition reactions can be divided into two types: (i)

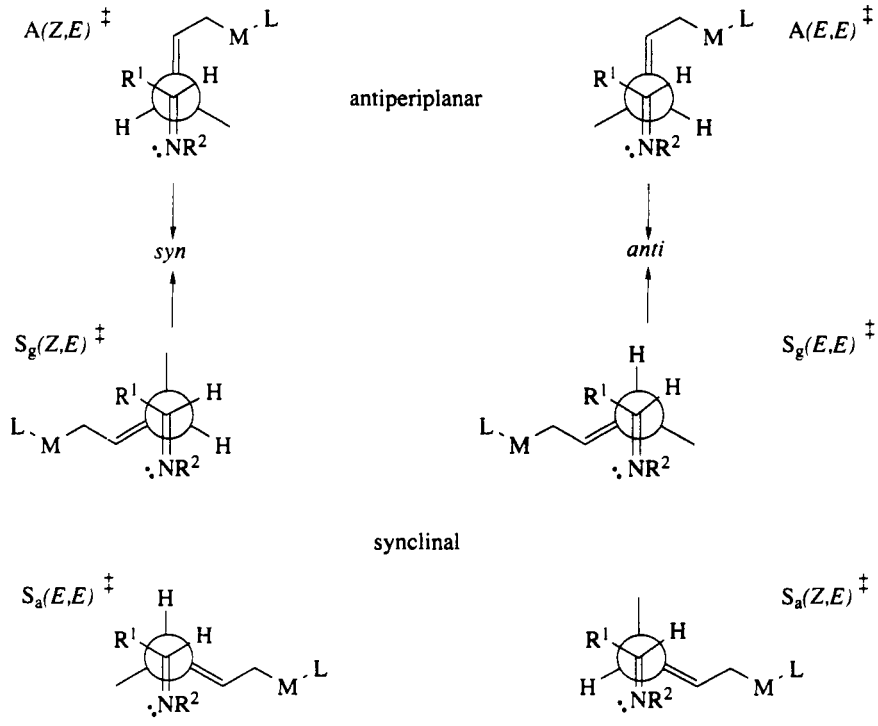


Figure 6 Postulated antiperiplanar and synclinal transition states involved in the reactions of crotyl organometallics with imines[11]

chelation control, in which the formation of metal chelates (A) reduces the degree of freedom of a molecule and renders a diastereotopic face of the imine more accessible for nucleophilic addition; and (ii) nonchelation control (Cram selectivity), in which the addition is governed by steric and/or electronic effects. In nonchelation control, the bias for addition from a diastereotopic face was first predicted by Cram (Cram's rule; B),[13] and is supported by the Felkin–Ahn (C) and Cornforth (D) models.[14] Normally, chelation and nonchelation (Cram) control lead to opposite diastereofacial selectivity. The reader should note that the term 'Cram selectivity' used throughout this chapter does not necessarily reflect a particular transition state but rather selectivity that is consistent with addition as shown in (B). Imines, by virtue of substitution on nitrogen, can contain chiral nitrogen auxiliaries that provide an option not available to aldehydes and ketones for influencing (controlling) diastereofacial selectivity. In these cases diastereofacial selectivity is governed by steric/electronic effects of the chiral nitrogen auxiliary, and a model (E) shown in Figure 7 has been suggested by Yamamoto *et al.*[15,16] Aldimines can also have stereogenic centers on both nitrogen and carbon. Changing the absolute configuration at either center can have a cooperative (matched) or antagonistic (unmatched) effect on reaction diastereofacial selectivity.[17]

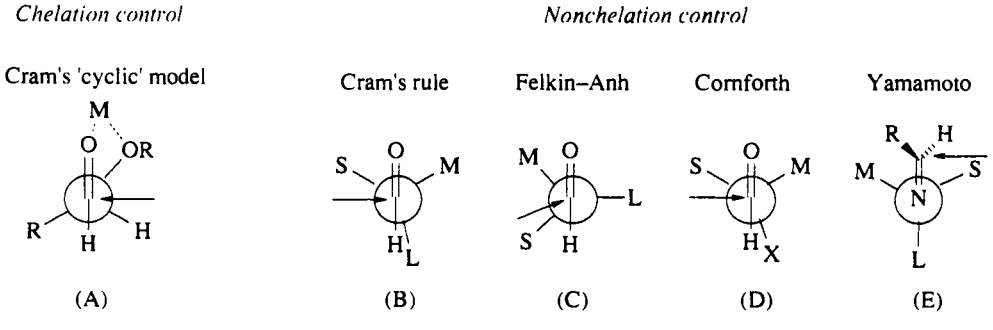


Figure 7 Models used to explain diastereofacial selectivity in the addition of nucleophiles to C=X

4.3.1.3 Reversibility

Reversibility in the reactions of crotyl-lithium, -magnesium and -zinc reagents with aldimines has been observed at room temperature by measuring changing linear:branched product ratios as a function of time.[18] Aspects of this phenomenon have been covered in a review by Courtois and Miginiac.[19] Branched products are favored kinetically and are converted to the more stable linear products as the reaction proceeds. Reversibility is more common with crotyl-lithium and -zinc reagents than with crotylmagnesium reagents, except when bulky imine substituents are employed. The phenomenon of reversibility in allyl organometallic–aldimine reactions must be fully taken into account when stereochemical results are interpreted by purely kinetic reasoning.

4.3.1.4 Earlier Reviews and Scope of this Chapter

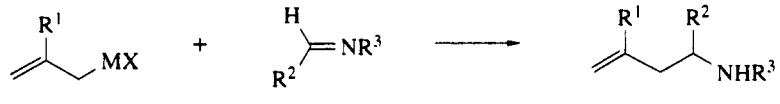
A review by Courtois and Miginiac published in 1974 entitled, 'The Reactivity of Allylic Organometallic Compounds of Lithium, Sodium, Magnesium, Zinc, Cadmium and Aluminum: Recent Advances', covers reactions of the title reagents with a wide range of electrophiles including imines and iminium salt equivalents such as *gem* amino ethers, *gem*-amino nitriles and *gem*-haloamines.[19] Surprisingly, no more recent reviews devoted exclusively to additions of allyl and crotyl reagents to imines, iminium salts and their equivalents have appeared despite the recent surge of interest in allyl organometallic additions. It is the intention of this chapter to fill this void. In addition to imines and iminium salts, reactions of *N*-heterosubstituted imines (oximes, sulfenimines, *etc.*) and *gem*-amino ethers (masked iminium salts) are described. Included also are reactions of propargyl/allenic organometallic reagents. Reactions of allyl, crotyl and propargyl/allenic reagents are discussed separately because each gives rise to different stereochemical issues. The term 'crotyl' is used loosely to describe any γ-substituted allyl reagent, not necessarily methyl. The reader should consult Volume 1, Chapter 1.12 for analogous reactions of nonresonance-stabilized carbanions.

4.3.2 REACTIONS WITH IMINES

4.3.2.1 Using Allyl Organometallic Reagents

4.3.2.1.1 Achiral imines

The reaction of allyl organometallics (**8**) with achiral aldimines (**9**) is the simplest combination of reactants, stereochemically, and affords (except in the case of formaldehyde imines) homoallylamines (**10**) containing one stereocenter (equation 2). These reactions, which typify the general scope of allyl organometallic–imine reactions are surveyed in Table 2. Reactions of allyl-borane, -titanium and -aluminum reagents are not shown in Table 2, only because they have been reported in reactions with chiral imines and are discussed in Sections 4.3.2.1.2 and 4.3.2.2.



(8) (9) (10) (2)

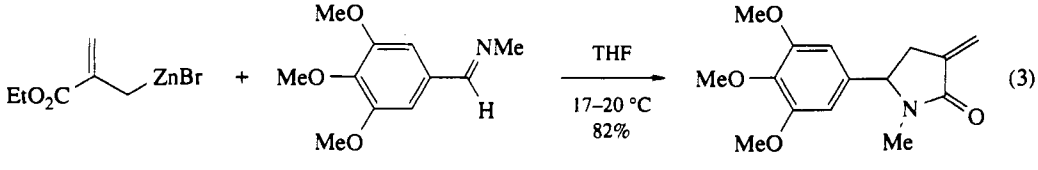
Examples involving the more reactive allyl-lithium, -magnesium and -zinc reagents are limited to imines that are nonenolizable or contain branched α-alkyl substituents. Presumably, reactions of linear α-alkylaldimines are complicated by α-deprotonation.[20] Higher yields are reported using the less basic magnesium and zinc reagents than the corresponding lithium reagents. Some specific examples deserve further comment. An unstable *N*-cyclohexylmethyleneamine (a formaldehyde imine) which must be prepared *in situ* condenses with allylmagnesium bromide (entry 4, Table 2).[21] The reaction is also general for ordinary, nonresonance-stabilized organometallics. Allyl reagents containing reactive groups (R^1) at the β-carbon (entries 5–7, Table 2) can have useful synthetic applications. For example, the Reformatsky reagent (**11**) derived from ethyl α-(bromomethyl)acrylate reacts with α-arylimine (**12**) to afford α-methylene-δ-lactam (**13**) as a result of spontaneous cyclization of the 1,2-adduct (equation 3).[22] In a

Table 2 Yields of Homoallylamines Formed in the Reactions of Allyl Organometallic Reagents with Achiral Imines (Equation 2)

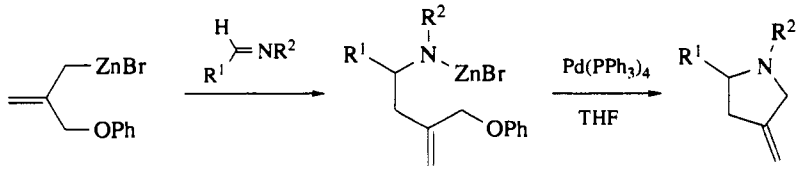
Entry	*Organometallic (8)* R^1	*Imine (9)* R^2	R^3	*Yield of products (10) (%)* metal *Li*	*MgBr*	*ZnBr*	$SnBu_3$[a]	$SnBu_3$[b]	$B(OMe)_2$	*Ph*[b,c]	*Ref.*
1	H	Pr^i	Pr^n	70							20
2	H	Pr^i	Pr^i	66							20
3	Me	Pr^i	Pr^i	42							20
4	H	H	c-C_6H_{11}		82						21
5	CO_2Et	Ar[d]	Me			82[e]					22
6	CH_2OPh	Pr^i	Bu^n			91					23
7	CH_2OPh	Ph	Me			90					23
8	H	c-C_6H_{11}	Bn				81	48			24
9	H	Bu^s	Bn				75	53			24
10	H	Ph	Bn				53	73			24
11	H	Furyl	Bn				88	61			24
12	CH_2OAc	Ph	Ph					81			25
13	CH_2OAc	Ph	Pr^n					88			25
14	CH_2OAc	Pr^i	Pr^n					70			25
15	CH_2OAc	3-Pyr	Me					64			25
16	H	Me	Bn						90		26
17	H	Pr^i	Bn						78		26
18	H	n-C_5H_{11}	Bn						70		26
19	H	Ph	Bn						65		26
20	H	Ph	Bn							84	2
21	H	*p*-Cl-Ph	Bn							94	2
22	H	*p*-Tol	Bn							64	2
23	H	2-Furyl	Bn							78	2
24	H	3-Heptyl	Bn							72	2
25	H	c-C_6H_{11}	Bn							90	2
26	H	$Me_2C{=}C$	Bn							53	2

[a]$TiCl_4$ additive is employed. [b]$BF_3{\cdot}Et_2O$ additive is employed. [c]The allyllead reagent is formed *in situ* according to ref. 2, its structure is not known. [d]Ar = 3,4,5-trimethoxyphenyl. [e]The product isolated is the α-methylene-γ-lactam.

useful annellation process reported by Klumpp and coworkers, adducts (**15**) obtained from 2-(phenoxymethyl)allylzinc bromide (**14**) and aldimines can be cyclized to 3-methylenepyrrolidines (**16**) by treatment with palladium(0) (Scheme 2).[23]



(11) (12) (13) (3)



(14) (15) (16)

Scheme 2

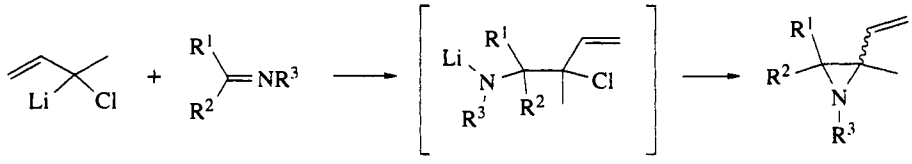
Allyltri-*n*-butylstannane reacts with aromatic and branched α-alkylimines in the presence of $TiCl_4$ and $BF_3{\cdot}Et_2O$ (entries 8–11, Table 2); yields using $TiCl_4$ tend to be higher. Keck and Enholm have demonstrated that the Lewis acid participates by activating the imine, not by exchanging with the metal of the organometallic reagent.[24] This is confirmed by the fact that no homoallylamines are formed when the

Lewis acid and allylstannane are mixed prior to the addition of the imine. The reaction is normally performed by adding the Lewis acid to the imine at –78 °C, warming the mixture to 23 °C, recooling to –78 °C and then adding the allylstannane. The initial warming period is necessary to insure complete complexation of the imine. As will be discussed in Section 4.3.2.2.2, conditions employed for imine complexation strongly influence the *syn–anti* selectivity of crotyl organometallic additions. Similar reactions using [2-(acetoxymethyl)-3-allyl]-tri-*n*-butylstannane and $BF_3{\cdot}Et_2O$ have also been reported by Trost and Bonk[25] (entries 12–15, Table 2). The survival of the acetate group suggests that the reaction may be compatible with other reactive functional groups. Adducts obtained in these reactions can be cyclized to 3-methylenepyrrolidines using palladium(0), as in the reactions of 2-(phenoxymethyl)allylzinc bromide. As in the reactions of the more reactive allyl reagents, examples of Lewis acid mediated allylstannane additions involve nonenolizable or branched α-alkylaldimines. It is not clear if the scope of this reaction extends to linear α-alkylaldimines.

Hoffmann *et al.*[26] have reported the addition of allyl(dimethoxy)borane to linear and branched α-arylaldimines (entries 16–19, Table 2). The absence of α-deprotonation may be explained by a delicate balance between the basicity and the reactivity of the allylboronate. Allyl(dimethoxy)borane should thus be considered the reagent of choice in reactions with enolizable aldimines. Reactions are conveniently carried out at 25 °C in CH_2Cl_2 and work-up is performed using triethanolamine to break up amine–boronate complexes. Allyl(dimethoxy)borane also adds to the cyclic imine, Δ^1-piperideine, in 90% yield. The reported yields for the addition of allyllithium and allylmagnesium chloride to Δ^1-piperideine are low.

An *in situ* method reported by Torii and coworkers for preparing a reactive allyllead reagent is attractive from the standpoint of convenience since it avoids the need to isolate the organometallic reagent.[2] The reagent, which is formed by treatment of allyl bromide with aluminum foil (1.0 equiv.) and a catalytic amount of lead(II) bromide (0.03–0.1 equiv.) in ether, adds to α-aryl- and branched α-alkyl-aldimines in the presence of $BF_3{\cdot}Et_2O$ (entries 20–26, Table 2). Details of the structure of the reactive allyllead species and its mechanism of formation are not clear. The reaction does not extend to enolizable ketimines.

As reported by Mauze, the reaction of *gem*-chloro(methyl)allyllithium (**17**) with aldimines and ketimines (**18**) is an efficient method for the synthesis of 2-vinylaziridines (**20**; Scheme 3).[27] The aziridine ring is formed by intramolecular S_N2 chloride displacement *via* the intermediate lithium amide (**19**). The products are formed as diastereomeric mixtures, as indicated by NMR, and ratios of diastereomers vary depending on the imine substitution. Yields tend to be higher with more accessible linear and branched



(**17**) (**18**) (**19**) (**20**)

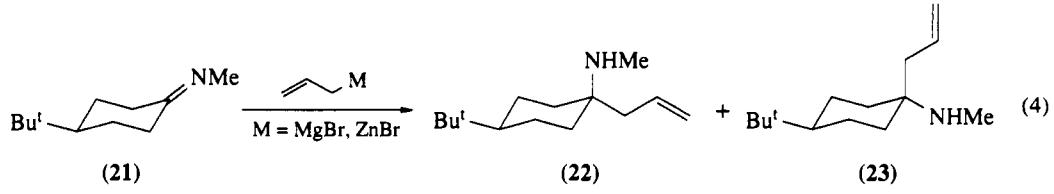
Scheme 3

Table 3 Formation of Vinylaziridines (**20**) in the Reaction of *gem*-Chloro(methyl)allyllithium (**17**) with Imines (**18**; Scheme 3)[27]

Entry	*Imine (18)* R^1	R^2	R^3	*Aziridine (20)* *Yield (%)*
1	n-C_6H_{13}	H	Me	56
2	n-C_6H_{13}	H	Pr^i	60
3	Pr^i	H	Me	28
4	Pr^i	H	Et	38
5	Pr^{n}MeCH	H	Me	48
6	Et_2CH	H	Me	43
7	Bu^{n}EtCH	H	Me	65
8	Bu^{n}EtCH	H	Et	60
9	Ph	H	Me	58
10	Ph	H	Et	68
11	Me	Me	Bu^n	30
12	Et	Me	Bu^n	35
13	Pr^n	Me	Bu^n	38
14	—$(CH_2)_5$—		Bu^n	57

aldimines (entries 1–10, Table 3) than with ketimines (entries 11–14, Table 3). Deprotonation apparently is not a serious problem in these additions, perhaps because of the inductive effect of the α-chlorine, which lowers the basicity of the allyl reagent. Interestingly, reaction at the γ-position of allyllithium is not observed. Very hindered aldimines (**18**; $R^1 = Bu^t$, $R^2 = H$, $R^3 = Me$; $R^1 = Ph$, $R^2 = H$, $R^3 = Bu^t$; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Pr^i$) fail to produce aziridines.

The stereochemistry of the addition of allylzinc and allylmagnesium bromide to *N*-methyl-4-*t*-butylcyclohexylimine (**21**) has been studied by Gaudemar and coworkers[28] (equation 4, Table 4). Both reagents favor axial attack in ether or in THF, giving mainly diastereomer (**23**; entries 1 and 2, Table 4). In THF/DMSO, allylzinc bromide gives predominantly diastereomer (**22**) *via* equatorial attack (entry 5, Table 4). The reactions are kinetically controlled as demonstrated by the fact the resubjection of a 34:66 mixture of (**22**):(**23**) under the reaction conditions (THF/DMSO) that normally gives an 85:15 mixture of (**22**):(**23**) does not result in equilibration. Also, product ratios do not change as a function of reaction time. No explanation of the kinetic factors involved in these reactions is given.



(**21**) (**22**) (**23**)

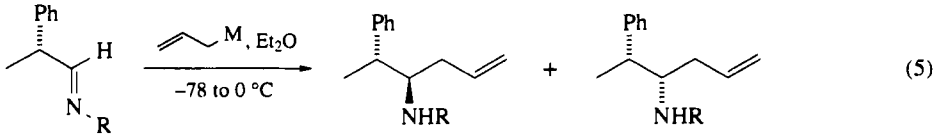
Table 4 Reaction of *N*-Methyl-4-*t*-butylcyclohexylimine (**21**) with Allylmagnesium Bromide and Allylzinc Bromide (Equation 4)[28]

Entry	*Metal*	*Solvent*	*Product ratio (**22**):(**23**)*	*Yield (%)*
1	MgBr	Ether	12:88	68
2	ZnBr	THF	34:66	57
3	ZnBr	THF + LiBr	37:63	67
4	ZnBr	THF + HMPA	40:60	66
5	ZnBr	THF + DMSO	85:15	67

4.3.2.1.2 Imines containing one stereocenter

(i) 1,2-Asymmetric induction

Yamamoto *et al.*[15,16] have examined organometallic additions to *N*-propylaldimines (**24**) derived from α-phenylpropionaldehyde to evaluate the influence of a nonchelating α-phenyl substituent on reaction diastereofacial selectivity (equation 5). The allyl organometallic reactions, summarized in Table 5, provide predominantly Cram products (**25**). The addition of allyl-9-BBN to aldimine (**24**; R = Pr^i) affords exclusively amine (**25**) in good yield (entry 2, Table 5). The diastereoselectivity is lower in the additions of allylstannanes ($TiCl_4$) and allyl Grignards (entries 3–7, Table 5). The imine nitrogen substituent appears to have a minimal impact on reaction stereoselectivity, although greater structural diversity is needed to better assess the scope of this Cram selectivity.



(**24**) (**25**) Cram (**26**) anti-Cram

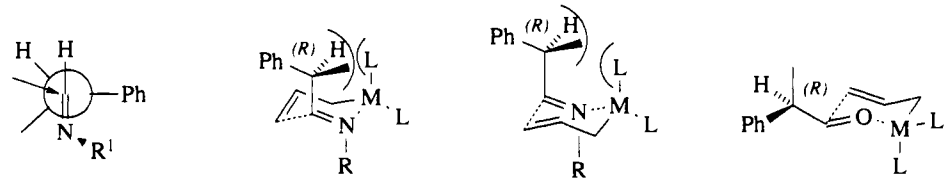
M = 9-BBN, MgX; 88–98%
M = $SnBu_3/TiCl_4$; 60–90%

The Cram selectivity is consistent with Felkin–Ahn addition, as shown in Figure 8a, with the large phenyl substituent controlling the organometallic approach. In addition, Yamamoto *et al.*[15,16] have proposed more detailed chair-like transition state models shown in Figures 8b and 8c to account for the un-

Table 5 Cram Selectivity in Allyl Organometallic Additions to α-Phenylaldimine (**24**; Equation 5)[15,16]

Entry	*Imine (24) R*	*Allyl organometallic M*	*Product ratio (25):(26)*	*α-Phenylpropionaldehyde additions Cram:anti-Cram*	*Ref.*
1	Pr^n	9-BBN	96:4	55:45	15,16
2	Pr^i	9-BBN	100:0	55:45	15,16
3	Pr^n	$SnBu_3/TiCl_4$	93:7	69:31	15
4	Pr^i	$SnBu_3/TiCl_4$	92:8	69:31	15
5	Pr^n	MgCl	84:16	60:40	15,16
6	Pr^i	MgCl	70:30	60:40	15,16
7	Pr^n	MgBr	68:32	60:40	15

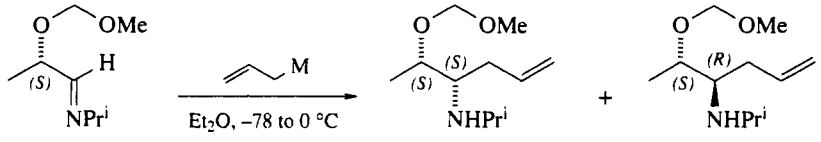
usually high diastereoselectivity. The authors suggest that the additional steric demands created by the axial metal ligands (L; *via* a 1,3-diaxial nonbonded interaction) are responsible for the difference in energy between the Cram (Figure 8b) and anti-Cram (Figure 8c) transition states. This hypothesis is supported, in part, by the poor diastereoselectivity (see Table 5) obtained in analogous organometallic additions to α-phenylpropionaldehyde.[15,16,29] In the aldehyde additions, the Lewis acidic metal can complex the aldehyde oxygen *cis* to the hydrogen; as a result the aldehyde carbon framework will occupy the equatorial position and avoid these severe nonbonded interactions (Figure 8d).



(a) (b) (c) (d)

Figure 8

If there is an alkoxy substituent adjacent to the aldimine there is the opportunity for chelation control. Yamamoto *et al.*[30] have examined the addition of allyl organometallic reagents to (*S*)-2-(methoxy)methoxypropanal-derived aldimines (**27**; equation 6, Table 6). Chelation control (Figure 9a) to generate predominantly *syn* homoallylamine (**28**) occurs with reagents capable of α-chelation (allyl-MgCl, -$AlEt_3MgCl$, and -ZnBr). While the level of chelation-controlled 1,2-asymmetric induction is not complete, it is nonetheless synthetically useful and is better than that of the parent α-alkoxyaldehyde itself[29] (see entries 1–3, Table 6). In contrast, the use of allylboronates or (allyl)$Ti(Pr^iO)_3$, which lack the requisite Lewis acidity for chelation, result, as expected, in good Cram selectivity (Figure 9b; entries 4 and 5, Table 6). Once again, allyl-9-BBN (entry 6, Table 6) provides excellent Cram diastereofacial control (>99:1) and is the method of choice for preparing the *anti* homoallylamine (**29**).

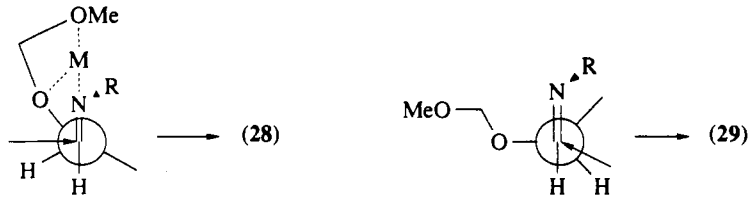


(6)

(**27**) (**28**) chelation (**29**) nonchelation (Cram)

Table 6 Chelation and Nonchelation Control in Allyl Organometallic Additions to α-Alkoxyaldimines (**27**; Equation 6)[30]

Entry	*Allyl organometallic M*	*Product ratio (28):(29)*	*(S)-2-(Methoxy)methoxypropanal additions chelation:nonchelation control*[29]
1	MgCl	79:21	53:47
2	$AlEt_3MgCl$	93:7	58:42
3	ZnBr	78:22	41:59
4	$Ti(Pr^iO)_3$	23:77	45:55
5	$B(OMe)_2$	7:93	—
6	9-BBN	—:>99	52:48

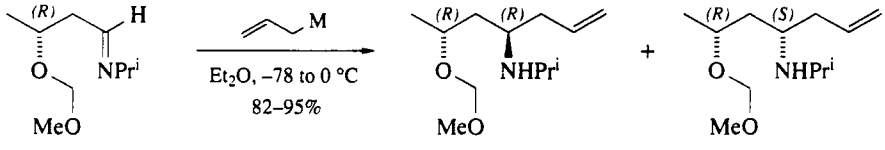


(a) Chelation (b) Felkin–Anh (nonchelation)

Figure 9

(ii) 1,3-Asymmetric induction

Allyl organometallic additions to chiral β-alkoxyaldimines (**30**) have been investigated for the preparation of amines (**31**) and (**32**; equation 7).[30] The results are summarized in Table 7 and illustrate the limitations of utilizing substituents β to the aldimine for controlling reaction diastereofacial selectivity. Modest chelation control [(**31**):(**32**) = 1.6–9.0:1], which is superior to that of the corresponding β-alkoxyaldehydes,[29] can be obtained using organometallics capable of β-chelation (allyl-MgCl, -AlEt$_3$MgCl, and -ZnBr; entries 1–3, Table 7). On the other hand, little or no diastereoselectivity is observed with reagents incapable of internal chelation such as 9-allyl-BBN or (allyl)Ti(Pr^{i}O)$_3$. These results suggest that the presence of a remote stereocenter does not alone provide synthetically useful Cram diastereofacial control in aldimine additions.

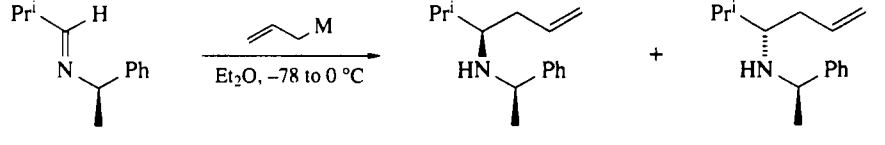


(**30**) (**31**) chelation (**32**) nonchelation (Cram) (7)

Table 7 1,3-Asymmetric Induction in Allyl Organometallic Additions to β-Alkoxyaldimines (**30**; Equation 7)[30]

Entry	*Allyl organometallic M*	*Product ratio (31):(32)*	*(R)-3-(Methoxy)methoxybutanal additions chelation:nonchelation control*[29]
1	MgCl	85:15	64:36
2	AlEt$_3$MgCl	90:10	42:58
3	ZnBr	62:38	68:32
4	Ti(Pr^{i}O)$_3$	30:70	47:53
5	9-BBN	46:54	51:49

The addition of organometallic reagents to aldimines derived from chiral amines provides another option (unique to imines) for controlling reaction diastereofacial selectivity. Yamamoto *et al.*[15,16] have examined the addition of allyl organometallics to aldimine (**33**) derived from 1-phenylethylamine (equation 8). Results are shown in Table 8 and indicate that modest selectivity ranging from 1.5:1 to 11:1 (**34:35**) can be obtained. Allyl-9-BBN once again provides the best diastereoselectivity (entry 1, Table 8). While the origin of the *re* facial selectivity is unknown, Yamamoto *et al.* have proposed organometallic addition to a low energy conformation of (**33**), shown in Figure 10a, in which the largest (phenyl) substituent is antiperiplanar to the imine, which would render the *re* face of (**33**) more accessible to addition. In the case of allyl organometallics that are capable of internal coordination with the imine, such as



(**33**) M = 9-BBN, MgX; 88–98% (**34**) (**35**) (8)
M = SnBu$_3$; 60–70%

allyl-9-BBN, cyclic chair versions of this model, shown in Figures 10b and 10c have also been proposed. Cyclic six-membered transition states may not, however, be crucial for 1,3-asymmetric induction since addition of allyltri-*n*-butylstannane in the presence of Lewis acids (entries 3 and 4, Table 8) is stereoselective.

Table 8 1,3-Asymmetric Induction in Allyl Organometallic Additions to Aldimine (**33**) Derived from 1-Phenylethylamine (Equation 8)[15,16]

Entry	*Chirality of imine (33)*	*Allyl organometallic M*	*Product ratio[a] (34):(35)*	*Ref.*
1	(*R*,*S*)	9-BBN	92:8	15,16
2	(*R*,*S*)	MgBr	80:20	15
3	(*R*,*S*)	$SnBu_3/TiCl_4$	82:18	15
4	(*R*,*S*)	$SnBu_3/BF_3$	67:33	15
5	(*R*)	$B(OMe)_2$	60:40	15
6	(*R*)	b	67:33	15
7	(*R*)	c	80:20	15
8	(*S*)	c	80:20	16

[a] Structures (**34**) and (**35**) reflect the relative (not the absolute) stereochemistry. [b]

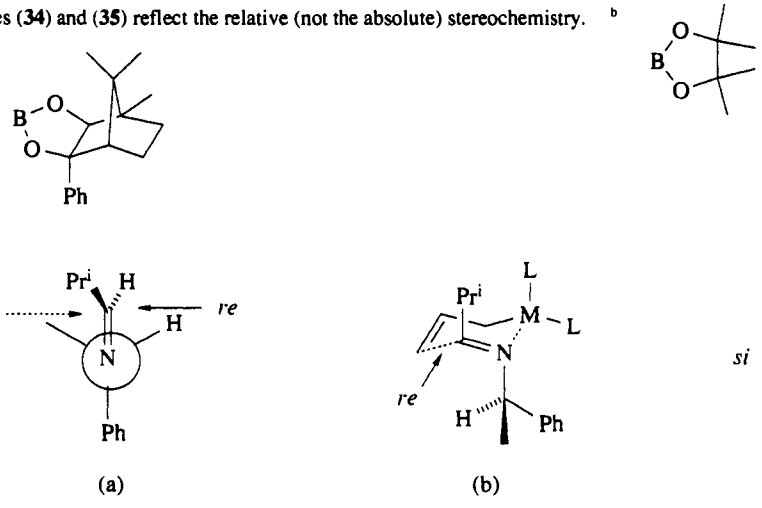
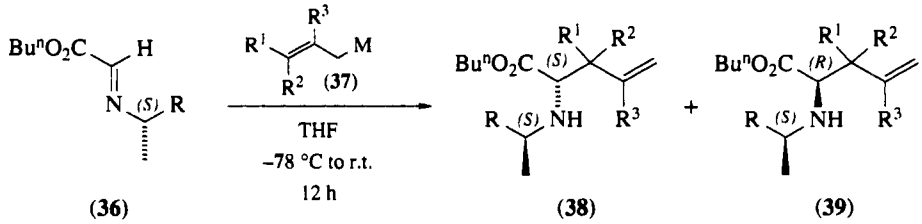


Figure 10

An enantioselective synthesis of amino acids has been examined using chiral nonracemic α-imino esters (**36**) derived from (*S*)-1-phenylethylamine and (–)-1-cyclohexylethylamine (equation 9, Table 9).[15,31] Allyl-magnesium, -copper and -titanium reagents react at both the imine and ester carbon atoms of (**36**), a result of the molecule's ambient electrophilicity. The addition of allyl-, methallyl- and prenyl-9-BBN and -ZnBr to α-imino ester (**36**), however, generates amines (**38**) and (**39**). While the absolute stereochemistry of (**38**) and (**39**; R = Ph) has been determined (entries 1–4, Table 9), that of the cyclohexylethylamine-derived products has not (entries 5–8, Table 9).

In all cases, allyl-9-BBN provides the best diastereoselectivity. The high 1,3-asymmetric induction (96:4) produced in allyl-9-BBN addition to (**36**; R = Ph; entry 1, Table 9) is consistent with a proposed cyclic chair transition state shown in Figure 11a. Diastereofacial selectivity is reversed in methallyl-9-BBN addition to (**36**; R = Ph; entry 3, Table 9). As a result of additional 1,3-diaxial interactions invol-

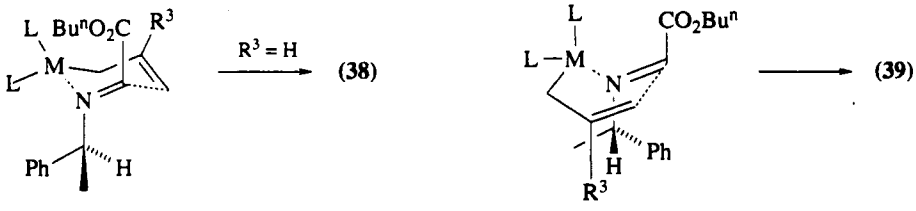


(9)

ving the methallyl methyl group in the chair transition state, shown in Figure 11a, a boat transition state shown in Figure 11b which would provide amine (**39**) has been proposed. Reaction yields and selectivity erodes in the addition of prenyl-9-BBN (**37**; $R^1 = R^2 = Me$; $R^3 = H$) to (**36**; entries 9 and 10, Table 9).

Table 9 1,3-Asymmetric Induction in the Addition of Allyl Organometallic Reagents (**37**) to Glyoxylate Aldimines (**36**) Derived from Chiral Amines (Equation 9)[15,31]

Entry	*Imine (36)* *R*	*Organometallic reagent (37)* R^1	R^2	R^3	*M*	*Product ratio (38):(39)*	*de* (%)	*Yield* (%)	*Ref.*
1	Ph	H	H	H	9-BBN	96:4	92	92	15,31
2	Ph	H	H	H	ZnBr	—	10	94	15,31
3	Ph	H	H	Me	9-BBN	5:95	90	80	15
4	Ph	H	H	Me	ZnBr	—	16	83	15
5	c-C_6H_{11}	H	H	H	9-BBN	—	96	94	15,31
6	c-C_6H_{11}	H	H	H	ZnBr	—	30	53	15,31
7	c-C_6H_{11}	H	H	Me	9-BBN	—	78	94	15
8	c-C_6H_{11}	H	H	Me	ZnBr	—	14	90	15
9	Ph	Me	Me	H	9-BBN	—	54	33	15,31
10	Ph	Me	Me	H	ZnBr	—	16	60	15,31

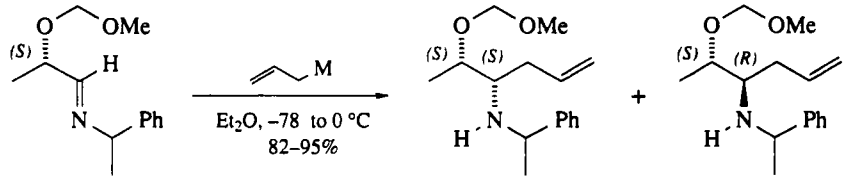


(a) (b)

Figure 11

4.3.2.1.3 Imines containing two stereocenters

Yamamoto *et al.*[30] have examined the addition of allyl organometallic reagents to α-alkoxyaldimines (**40**) derived from (*S*)-2-methoxy(methoxy)propionaldehyde and (*R*)- and (*S*)-1-phenylethylamine (equation 10). The results are summarized in Table 10. Chelation control with allyl-$AlEt_3MgCl$, -MgCl and -ZnBr (entries 1–3, Table 10) and nonchelation (Cram) control with allyl-$Ti(Pr^iO)_3$, $-B(OMe)_2$ and -9-BBN (entries 4–6, Table 10) parallels that observed in the allyl metal–α-alkoxyaldimine additions (involving aldimines that lack a chiral nitrogen substituent) shown in Table 6. The chirality of the α-alkoxy



(10)

(**40**) (**41**) chelation (**42**) nonchelation

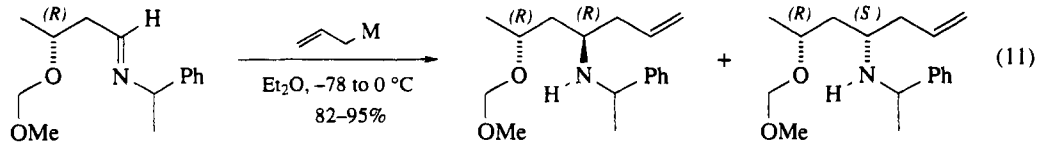
Table 10 Chelation and Nonchelation Control in Allyl Organometallic Additions to α-Alkoxyaldimines (**40**) Derived from (*R*)- and (*S*)-1-Phenylethylamine (Equation 10)[30]

Entry	*Allyl organometallic M*	*Product ratios (41):(42)*[a]	*(41):(42)*[b]
1	MgCl	70:30	86:14
2	$AlEt_3MgCl$	89:11	95:5
3	ZnBr	76:24	92:8
4	$Ti(Pr^iO)_3$	6:94	20:80
5	$B(OMe)_2$	10:90	10:90
6	9-BBN	3:97	—:>99

[a]*N*-Imine substituent has (*S*)-chirality. [b]*N*-Imine substituent has (*R*)-chirality.

center (1,2-asymmetric induction) and the type of allyl metal employed are the most important determinants of the stereochemical outcome of the reaction and essentially override the influence of the nitrogen chiral auxiliary (1,3-asymmetric induction).

In the addition of allyl-MgBr and -9-BBN to β-alkoxyaldimines (**43**) derived from (*R*)-3-methoxy(methoxy)butyraldehyde and (*R*)- and (*S*)-phenylethylamine, chelation and nonchelation products (**44**) and (**45**) are generated, respectively (equation 11, Table 11).[30] Of the two remote 1,3-centers of chirality, the chiral nitrogen auxiliary in this small sampling now plays the major role in controlling diastereoselectivity as the (*R*,*S*) combination with ether allyl organometallic reagent provides predominantly (**44**) while the (*R*,*R*) combination provides amine (**45**; entries 1 and 2, Table 11). While the concept of matched *versus* unmatched pairs for diastereofacial selectivity is demonstrated with aldimine (**43**), neither the direction nor the degree of this asymmetric induction is easily rationalized.



(**43**) (**44**) chelation (**45**) nonchelation

Table 11 1,3-Asymmetric Induction in Allyl Organometallic Additions to β-Alkoxyaldimines (**43**) Derived from (*R*)- and (*S*)-Phenylethylamine (Equation 11)[30]

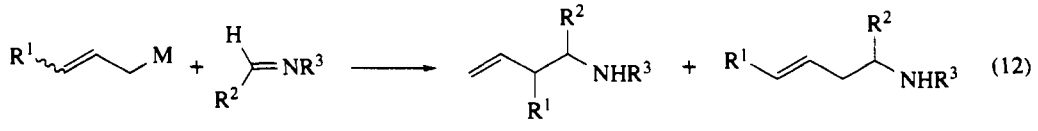
Entry	*Allyl organometallic M*	*Product ratios* (*44*):(*45*)[a]	(*44*):(*45*)[b]
1	MgCl	92:8	38:62
2	9-BBN	63:37	10:90

[a]*N*-Imine substituent has (*S*)-chirality. [b]*N*-Imine substituent has (*R*)-chirality.

4.3.2.2 Using Crotyl Organometallic Reagents

4.3.2.2.1 Regioselectivity

The regioselectivity of additions of crotyl-zinc, -magnesium, and -lithium reagents (**46**) to aldimines (**47**) has been studied by Miginiac and coworkers (equation 12).[32,33] Ratios of branched (**48**) and linear (**49**) homoallylamines and yields using ether as solvent are shown in Table 12; similar results are obtained using THF. Neither the *syn–anti* stereochemistry (branched products) nor the alkene geometry (linear products) were determined. Two trends are observed. First, metals favor branched products in the order MgBr > ZnBr > Li for a given imine. Second, linear products (**49**) predominate using α-alkylimines (entries 3–8, Table 12) while branched products (**48**) predominate using formaldehyde imines (entries 1 and 2, Table 12) and α-arylimines (entries 9 and 10, Table 12). Exceptions are found in the α-alkyl-*N*-arylimine series using magnesium and lithium reagents (entries 7 and 8, Table 12) where branched products (**48**) are favored, and in the case of benzylidenemethylamine using the lithium reagent (entry 9, Table 12) where the linear product (**49**) is favored. Also, the zinc cinnamyl reagent (entry 11, Table 12), unlike the aliphatic crotyl reagents, gives almost exclusively the linear product (**49**) in a reaction with an α-arylimine. Miginiac and coworkers note a relationship between the observed trends in regioselectivity and imine basicity, *i.e.* more basic imines with electron-donating α-alkyl groups give linear products while less basic imines lacking α-substituents or containing α-aryl substituents give branched products. If branched products are formed *via* a cyclic six-centered transition state, the reduced nucleophilicity of the imine lone pair is apparently not severe enough to retard coordination with the metal. The fact that the zinc reagent, unlike the magnesium and lithium reagents, gives linear products (**49**) in reactions with branched α-alkyl-*N*-arylimines (entries 7 and 8, Table 12), suggests that its cyclic transition state is more sensitive to the steric environment. Clearly, the influence of the electronic properties of the imine on reaction regioselectivity needs further study. Yields in most cases are good, even when the imine contains bulky substituents.



(46) (47) (48) (49) (12)

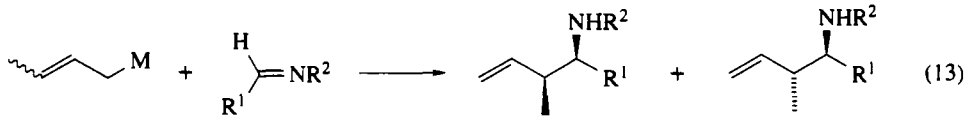
Table 12 Regioselectivity in the Reaction of Crotyl Organometallic Reagents (**46**) with Aldimines (**47**; Equation 12)

Entry	Organometallic (**46**) R^1	Imine (**47**) R^2	Imine (**47**) R^3	ZnBr Yield (%)	ZnBr (**48**):(**49**)	MgBr Yield (%)	MgBr (**48**):(**49**)	Li Yield (%)	Li (**48**):(**49**)	Ref.
1	Et	H	Ph[a]	67	100:0	94	100:0	92	84:16	33
2	Et	H[b]	Bu^t	60	75:25	18	99:1	55	36:64	33
3	Et	Me	Pr^n	57	1:99	56	10:90	29	0:100	33
4	Et	Pr^i	Me	84	0:100	74	3:97	84	1:99	33
5	Et	Pr^i	Pr^n	63	1:99	69	1:99	31	1:99	32
6	Et	Bu^t	Me	80	0:100	89	3:97	70	0:100	33
7	Et	Pr^i	Ph	95	8:92	85	92:8	88	88:12	33
8	Et	Bu^t	Ph	91	7:93	91	88:12	95	65:35	33
9	Et	Ph	Me	80	72:28	82	98:2	63	5:95	33
10	Et	Ph	Ph	82	84:16	88	98:2	83	76:24	33
11	Ph	Ph	Me	67	1:99					33

[a]Generated from $PhSCH_2NHPh$ *in situ*. [b]Imine reacted as the trimer.

4.3.2.2.2 Syn–Anti *selectivity*

Syn–anti selectivity in the reactions of crotyl organometallic reagents with aldimines (**50**) (equation 13) is surveyed in Table 13. Examples involving crotyl-magnesium, -zinc and -lithium reagents are limited to reactions with α-arylimines because, as noted above, α-alkylimines react to produce primarily linear products. This restriction could apply to crotylaluminum reagents since reported examples using crotylaluminum bromide are also limited to reactions with α-arylimines. In contrast, α-alkylimines react with crotyltri-*n*-butylstannane[24] and crotyl-9-BBN[11] to give branched products, allowing the *syn–anti* selectivity to be examined.



(50) (51) (52) (13)

The levels of *syn–anti* selectivity in the reactions of crotyl-magnesium, -zinc, -lithium and -aluminum reagents are not synthetically useful. Of these reagents, crotyllithium is the most selective, favoring *anti* products (**52**) in additions to *N*-alkyl-α-arylimines (entries 1–3 and 5, Table 13). *Syn:anti* ratios are about 1:4. With magnesium and zinc reagents, *syn:anti* ratios are very similar to each other and tend to favor *anti* products as the size of the *N*-alkyl substituent (R^2) increases. Gaudemar and coworkers have rigorously proven that these reactions are not reversible.[34] To evaluate the effect of the allylic double bond of the crotyl reagent on *syn–anti* selectivity, Moreau and Gaudemar have compared the *syn–anti* selectivity of *s*-butylmagnesium bromide to that of crotylmagnesium bromide in additions to the imines of entries 1–6 (Table 13).[35] Unfortunately, the levels of *syn–anti* selectivity of *s*-butylmagnesium bromide are too low to draw any definitive conclusions.

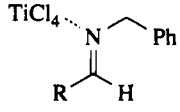
Reactions of crotyltri-*n*-butylstannane in the presence of $TiCl_4$ (entries 9, 14 and 15, Table 13) favor *syn* products (**51**).[24] Extremely high levels of *syn* selectivity (ratios >20:1) can be obtained if Lewis acid–imine complexation is carried out at –78 °C for 2.5 h prior to the addition of the organometallic reagent, otherwise *syn* selectivity diminishes to 4:1. Keck and Enholm have interpreted the stereoselectivity of this reaction to be a result of two $TiCl_4$–imine complexes, (**53**) and (**54**), formed kinetically and thermodynamically, respectively. Formation of the thermodynamic complex (**54**) at higher temperatures is driven, presumably, by the steric bulk of the $TiCl_4$ moiety. It is suggested that higher *syn* selectivity (>20:1) originates from the kinetic complex (**53**), which is formed slowly at –78 °C, while lower *syn* se-

Table 13 *Syn–Anti* Selectivity in the Reactions of Crotyl Organometallics with Imines (**50**; Equation 13)

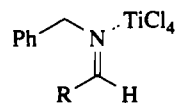
	Imine (50)		*Metal*												
			MgBr		*ZnBr*		*Li*		*Al$_{2/3}$Br*		*SnBu$_3$*[a]		*9-BBN*		
Entry	R^1	R^2	*Yield (%)*	*(51):(52)*	*Yield (%)*	*(51):(52)*	*Yield (%)*	*(51):(52)*	*Yield (%)*	*(51):(52)*	*Yield (%)*	*(51):(52)*	*Yield (%)*	*(51):(52)*	*Ref.*
1	Ph	Me	69	64:36	84	63:37	95	20:80	55	54:46					34
2	Ph	Et	66	41:59	85	35:65	91	21:79	65	54:46					34
3	Ph	Pr^i	66	38:62	60	50:50	88	31:69	48	50:50					34
4	Ph	Pr^i											79	65:35	11
5	Ph	Bu^i	65	28:72	78	26:74	74	15:85	38	63:37					34
6	Ph	Ph	48	47:53	85	45:55	86	46:54	30	34:66					34
7	Ph	Ph	95	74:26[b]			50	60:40					93	0:100	11
8	Ph	Pr^n	95	63:37									95	15:85	11
9	Furyl	Bn									84	30:1			24
10	Pr^n	Pr^n											90	75:25	11
11	Pr^n	Pr^i											97	100:0	11
12	Pr^i	Pr^n											95	34:66	11
13	Pr^i	Pr^i											60	30:70	11
14	Pr^i	Bn									60	20:1			24
15	c-C$_6$H$_{11}$	Bn									78	23:1			24

[a]$TiCl_4$ additive is used. [b]The crotyl MgCl reagent is used instead.

lectivity (4:1) results from the thermodynamic complex (**54**). Assuming that $TiCl_4$-promoted additions of allylstannanes to aldimines proceed *via* open transition states (Figure 6), the observed *syn* selectivity can be rationalized by a $S_a(E,E)^‡$ transition state for complex (**53**) and a $S_a(E,Z)^‡$ transition state for complex (**54**; note that the alkene geometry of the crotyl reagent is *E*). These transition states are also consistent with the fact that the direction of *syn*:*anti* selectivity is preserved despite the change in imine geometry.

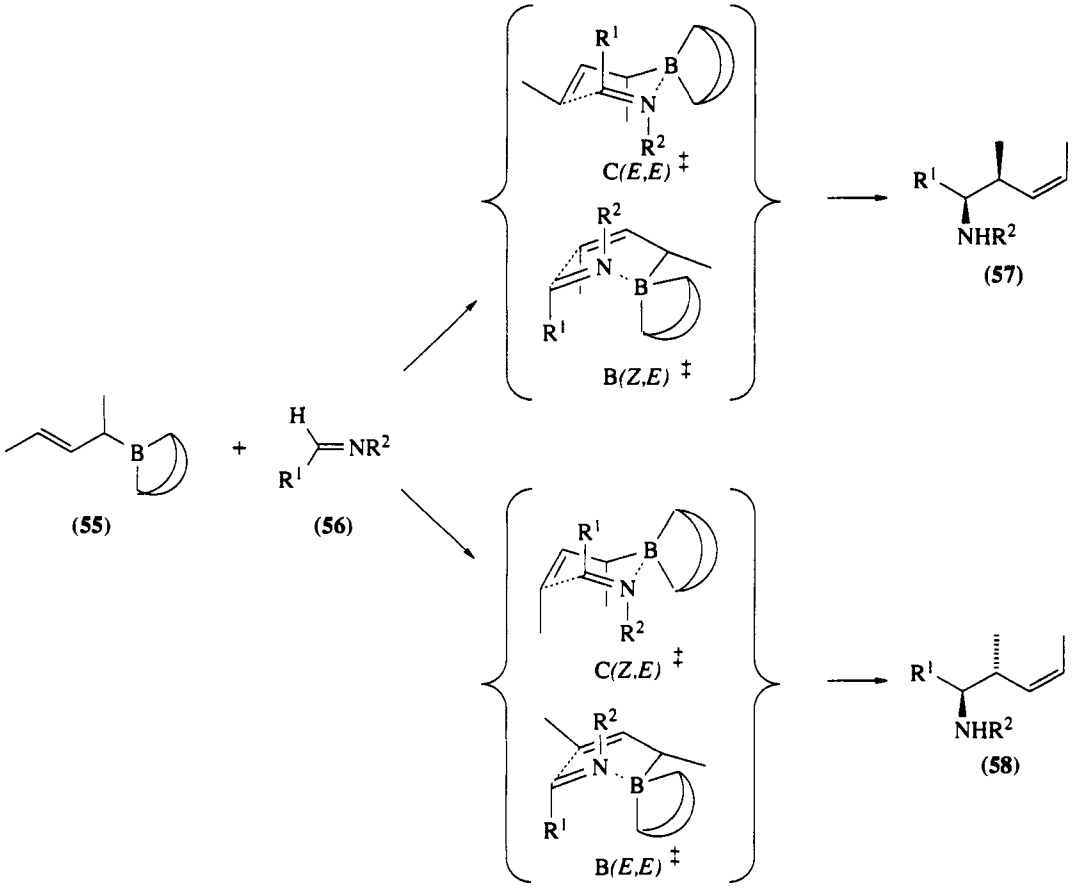


(**53**)



(**54**)

In the case of crotyl-9-BBN, *syn–anti* selectivity is very sensitive to the nature of the imine. For example, the *anti* product (**52**) is formed exclusively with benzylideneaniline (entry 7, Table 13), while the *syn* product (**51**) is formed exclusively with the aliphatic imine, *n*-butylideneisopropylamine (entry 11, Table 13). In these limited examples, α-alkylimines (entries 10 and 11, Table 13) exhibit *syn* selectivity when the α-alkyl group is linear, while α-arylimines (entries 7 and 8, Table 13) exhibit *anti* selectivity when the *N*-substituent is aryl or linear alkyl. In view of the similar carbon–boron, carbon–carbon bond lengths (*ca.* 1.5–1.6 Å), it is reasonable to assume that highly ordered cyclic transition states are involved. Yamamoto *et al.* view the formation of *syn* products as arising *via* a $C(E,E)^‡$ transition state (Figure 5).[11] The erosion in *syn* selectivity which occurs when the α-substituent is bulky (entries 12 and 13, Table 13) is attributed to destabilizing nonbonded 1,3-diaxial interactions between the aldimine R^1 substituent and the 9-BBN ring, and to 1,2-axial–equatorial interactions between R^1 and the crotyl methyl group. In these cases, the $B(E,E)^‡$ transition state (Figure 5) leading to *anti* products may dominate. The anomalous behavior of benzylideneaniline and other α-arylimines, however, has not been satisfactorily explained. In control experiments, the failure to detect (by NMR) isomerization of benzylideneaniline in



Scheme 4

the presence of Bu^n-9-BBN or BF_3·Et_2O at temperatures ranging from –78 °C to 25 °C suggests that α-arylimines do not react *via* the (*Z*)-isomer.[11]

To further evaluate their transition state hypotheses, Yamamoto *et al.* have examined the *syn–anti* selectivity of pent-3-en-2-yl-9-BBN (**55**), the α-methyl derivative of crotyl-9-BBN (Scheme 4).[11] As shown in Table 14, *syn* selectivity is more dominant in these reactions than with crotyl-9-BBN; even a small amount of *syn* product (**57**) is formed in the reaction of benzylideneaniline (entry 1, Table 14) which gives exclusively the *anti* product (**52**) using crotyl-9-BBN. Both *syn* and *anti* products (**57**) and (**58**) contain the *cis* alkene geometry. The results are consistent with a dominant C(*E*,*E*)‡ transition state (Scheme 4) in which the α-methyl group occupies the axial position, resulting in *cis* alkenic geometry. The increase in *syn* selectivity over the crotyl (des-α-methyl) series is explained by destabilizing interactions of the α-methyl group in the alternative cyclic transition states depicted in Scheme 4. For example, in the C(*Z*,*E*)‡ transition state, the α-methyl group produces an additional 1,3-diaxial interaction, while in both boat transition states there are 1,2-interactions between the α-methyl group and the 9-BBN group. It is interesting that *trans* alkenic products are not produced, since equatorial instead of axial placement of the α-methyl in the C(*E*,*E*)‡ transition state would seem more likely. Perhaps the resulting 1,2-equatorial interaction between the α-methyl and the 9-BBN group is more severe than other 1,3-diaxial interactions in the C(*E*,*E*)‡ transition state.

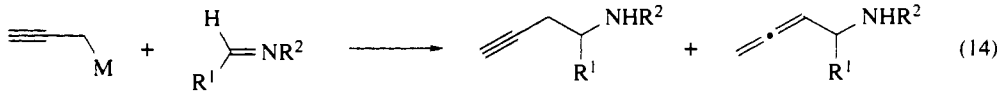
Table 14 *Syn–Anti* Selectivity in the Reactions of Pent-3-en-2-yl-9-BBN (**55**) with Imines (**56**; Scheme 4)[11]

	Imine (56)		*Products*	
Entry	R^1	R^2	*Yield (%)*	*(57):(58)*
1	Ph	Ph	90	8:92
2	Ph	Pr^n	84	100:0
3	Pr^n	Pr^i	75	100:0
4	Pr^i	Pr^n	78	85:15

Some examples of combined *syn–anti* and diastereofacial selectivity employing *N*-*n*-propyl- and *N*-isopropyl-aldimines, derived from α-phenylpropionaldehyde, and crotyl-9-BBN, -magnesium and -zirconium reagents have been reported by Yamamoto *et al.*[15] Cram selectivity, which is observed in the analogous reactions of these chiral imines with allyl organometallics (see Section 4.3.2.1.2i), is preserved as ratios of Cram:anti-Cram products are consistently about 8:1. *Anti* selectivity is also observed but the ratios do not exceed 7:3. The weak *anti* selectivity parallels that observed in reactions of crotyl-9-BBN with branched α-alkylaldimines. Since *syn–anti* selectivity is influenced more by the α-substituent than by the *N*-substituent of the aldimine, more synthetically useful levels of combined *syn–anti* and diastereofacial selectivity might be expected in other series of α-substituted aldimines.

4.3.2.3 Using Propargyl/Allenic Organometallics

Additions of propargyl/allenic aluminum, zinc and magnesium reagents (**59**) to aldimines (**60**) have been studied by Moreau and Gaudemar;[36] use of the lithium reagent is mentioned in an earlier study by Huet.[20] Alkynic (**61**) or allenic (**62**) products result from attack of the reagent (**59**) at the methylene or methine carbons, respectively (equation 14). Propargyl/allenic magnesium reagents do not give useful yields of (**61**) and (**62**) due to propargyl–alkynyl anion migration.[36]



(59) (60) (61) (62) (14)

As shown in Table 15, alkynic products (**61**) are obtained exclusively in the reactions of the aluminum reagent, while mixtures enriched mainly in the alkynic product are obtained in the reactions of the zinc and lithium reagents. Yields tend to be lower and more variable than those of allyl organometallics (see Table 2). If cyclic six-centered transition states are involved, the dominance of alkynic products (**61**) could be explained by preference of a transition state in which the metal is coordinated to the more accessible methine instead of methylene carbon.

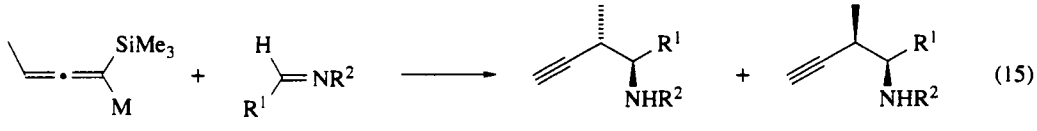
Syn–anti selectivity of the reactions of α-silylallenic organometallic reagents (**63**; M = Ti(Pr^{i}O)$_3$, $AlEt_3$ and Li) with imines (**64**) has been studied by Yamamoto *et al.* (equation 15).[37] The lithium reagent (**63**;

Table 15 Reaction of Propargyl/Allenyl Organometallic Reagents (**59**) with Imines (**60**; Equation 14)

	Imine (60)		*Metal*						
			AlR_2Br		$ZnBr$		Li		
Entry	R^1	R^2	*Yield (%)*	***(61):(62)***	*Yield (%)*	***(61):(62)***	*Yield (%)*	***(61):(62)***	*Ref.*
1	Me	Pr^i	50	99:t[a]	47	85:15			36
2	Me	Bu^n	34	99:t					36
3	Pr^i	Me	68	99:t					36
4	Pr^i	Bu^n			36	60:40			36
5	Pr^i	Pr^i					28	70:30	20
6	Pr^i	Ph	52	99:t	80	43:57			36
7	Bu^t	Me			40	75:25			36
8	Ph	Me	57	99:t	34	65:35			36
9	Ph	Ph	25	99:t					36

[a]t = trace.

M = Li), prepared by deprotonation of 1-trimethylsilyl-1-butyne with Bu^nLi, is treated with $ClTi(Pr^iO)_3$, and $AlEt_3$, respectively, to generate the corresponding titanium and aluminum (ate) reagents. The reactions are regiospecific, giving only alkynic products (**65**) and (**66**). The α-alkylimine reactions are stereospecific; the *anti* products (**65**) are formed exclusively (entries 1–5, Table 16). Selectivity erodes, however, in additions to α-arylimines (entries 6 and 7, Table 16). It is interesting that the aberrant behavior of α-arylimines witnessed in the reactions of crotyl organometallics[11] is also found in the reactions of these allenic reagents. Yields vary depending on the metal and are highest in reactions with unhindered imines, as hindered imines react sluggishly. A cyclic transition state in which the α-substituent of the imine and the methyl group of the allenic reagent are aligned in a less sterically congested *anti* relationship (Figure 12) has been proposed to rationalize the preference for *anti* selectivity.[37] The erosion in *anti* selectivity which occurs with α-arylimines, however, is not readily explained by this model.



(**63**) (**64**) (**65**) (**66**)

Table 16 *Syn–Anti* Selectivity in the Reactions of Allenic Organometallic Reagent (**63**) with Aldimines (**64**; Equation 15)[37]

	Imine (64)		*Metal*					
			$Ti(OPr^i)_3$		$AlEt_3$		Li	
Entry	R^1	R^2	*Yield (%)*	***(65):(66)***	*Yield (%)*	***(65):(66)***	*Yield (%)*	***(65):(66)***
1	Et	Bn	95	>99:1	28	>99:1	65	>99:1
2	Pr^n	Bn	95	>99:1				
3	Pr^n	Pr^i	57	>99:1	80	>99:1	46	>99:1
4	Pr^i	Pr^n	64	>99:1	90	>99:1		
5	Pr^i	Pr^i	37	>99:1				
6	Ph	Ph	97	54:46	67	50:50	94	65:35
7	Ph	Pr^n	95	81:19				

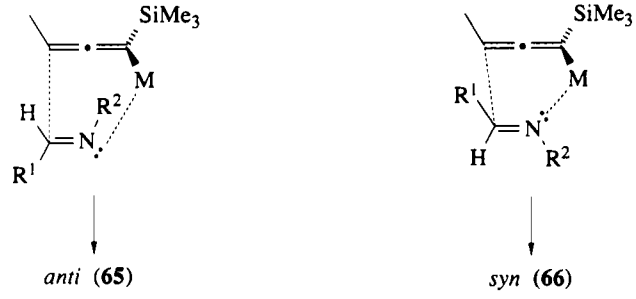
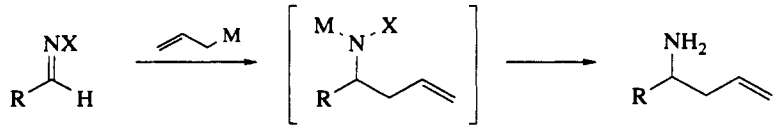


Figure 12 Proposed transition states for the formation of diastereomeric *syn* and *anti* alkynic amines in reactions of α-silylallenic reagent (**63**) with aldimines[37]

4.3.3 REACTIONS WITH *N*-HETEROSUBSTITUTED IMINES

4.3.3.1 Introduction

The reaction of *N*-unsubstituted aldimines (**67**; X = H) derived from ammonia with organometallic reagents to generate primary amines (**68**) is not practical because of the inherent instability of these imine substrates. For this reason, masked imines (**67**) with a labile N—X bond such as oximes (X = OH), sulfenimines (X = SAr), trimethylsilylimines (X = SiMe$_3$) and sulfonylimines (X = SO$_2$R) are commonly utilized (Scheme 5). Oximes, including oxime ethers and sulfenimines, have been examined in great detail and react with a variety of allyl (crotyl) organometallic reagents (entries 1 and 2, Table 17). Trimethylsilylimines and sulfonylimines (diarylidinesulfamides) have a more limited role and have been used only for the preparation of α-aryl-substituted homoallylamines (entries 3 and 4, Table 17).



(**67**) (**68**)

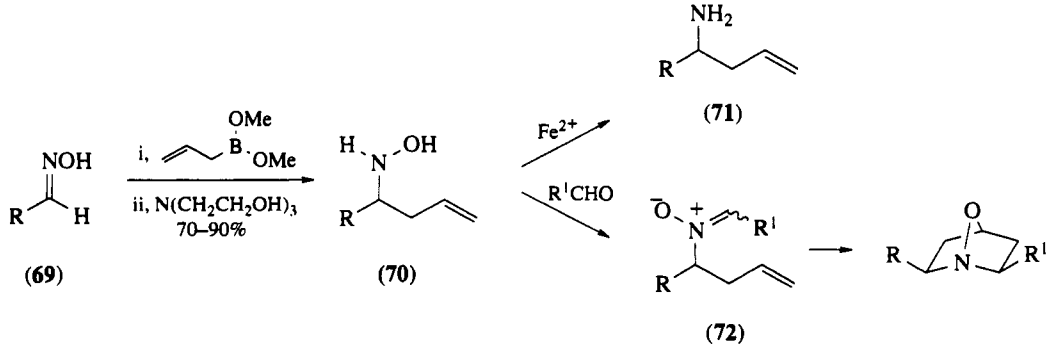
Scheme 5

Table 17 The Use of *N*-Heterosubstituted Aldimines (**67**) for the Preparation of Homoallylamines (**68**; Scheme 5)

Entry	*RCH=NX (67)*	*X*	*RCH=NX preparation*	*Substituent (R)* *Aryl*	*Alkyl*	*Conditions for NX cleavage*
1	Oximes (ethers)	OH(OR)	$NH_2OH(OR) + RCHO$	x	x	Reduction; iron(II) dihydrolipoate[9]
2	Sulfenimines	SAr	$(Me_3Si)_2NSAr + RCHO$[38]	x	x	Aqueous work-up
3	Trimethylsilylimines	$SiMe_3$	$LiN(SiMe_3)_2 + RCHO$[39]	x		Aqueous work-up
4	Sulfonylimines	1/2 SO_2	$NH_2SO_2NH_2 + RCHO$[40]	x		H_2O/pyridine; NaOH

4.3.3.2 Oximes and Oxime Ethers

Treatment of *syn*/*anti* mixtures of aldoximes (**69**) with allylboronates generates *N*-(homoallyl)hydroxylamines (**70**) in good yield (Scheme 6).[26,41] The *anti* oxime reacts faster than the *syn* isomer. *N*-(Homoallyl)hydroxylamines (**70**) have been converted to homoallylamines (**71**) (with iron(II) dihydrolipoate) and have been treated with aldehydes to generate highly functionalized nitrone intermediates (**72**) for use in 1,3-dipolar addition reactions.

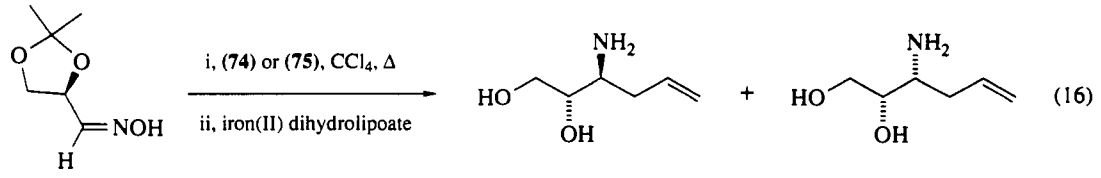


(**69**) (**70**) (**71**) (**72**)

R = Me, Pr^i, Pr^n and Ph

Scheme 6

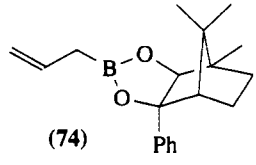
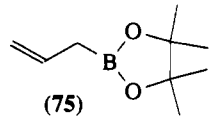
Hoffmann *et al.*[26] have also examined the addition of allylboronates (**74**) and (**75**) to 2,3-isopropylidene-D-glyceraldehyde oximes (**73**; *E*:*Z* = 3:7; equation 16 and Table 18). Cram selectivity is obtained. As is the case of the parent 2,3-isopropylidene-D-glyceraldehyde,[42,43] optically pure boronate (**74**; entry 1, Table 18) provides better diastereofacial selectivity than (**75**). The relationship, if any, between oxime geometry and Cram diastereoselectivity has not been established.



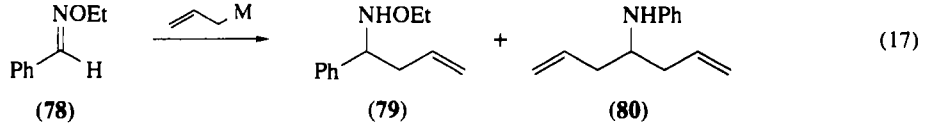
(16)

(**73**) (*E*):(*Z*) = 3:7 (**76**) Cram (**77**) anti-Cram

Table 18 Cram Selectivity in the Addition of Allylboronate Esters to 2,3-*O*-Isopropylidine-D-glyceraldehyde Oximes (**73**; Equation 16)[26]

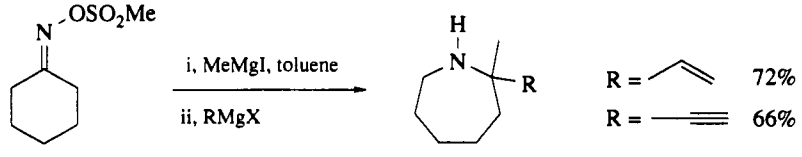
Entry	*Allyl boronate*	*Product ratio (76):(77)*	*2,3-O-Isopropylidine-D-glyceraldehyde addition (Cram:anti-Cram ratio)*[42,43]
1	 (**74**)	90:10	96:4
2	 (**75**)	70:30	80:20

The addition of allyl organometallic reagents to aldoxime ethers (**78**) has also been explored (equation 17).[44] The course of the reaction is reagent and solvent dependent, as allylzinc bromide affords predominantly *N*-(homoallyl)alkoxyamines (**79**; 60%; 1,2-addition) while allylmagnesium bromide provides amine (**80**; 96%), a Beckmann rearrangement product. Beckmann rearrangement products can also be selectively generated in the addition of organometallic reagents to ketoxime methanesulfonates. For example, treatment of (**81**) in toluene with alkyl Grignard reagents (1.5 equiv.), followed by allyl- or propargyl-magnesium bromide (2 or 4 equiv., respectively) provides the corresponding 2,2-disubstituted-azacycloheptanes (**82**) in *ca.* 70% yield (equation 18).[45]



(17)

(**78**) (**79**) (**80**)

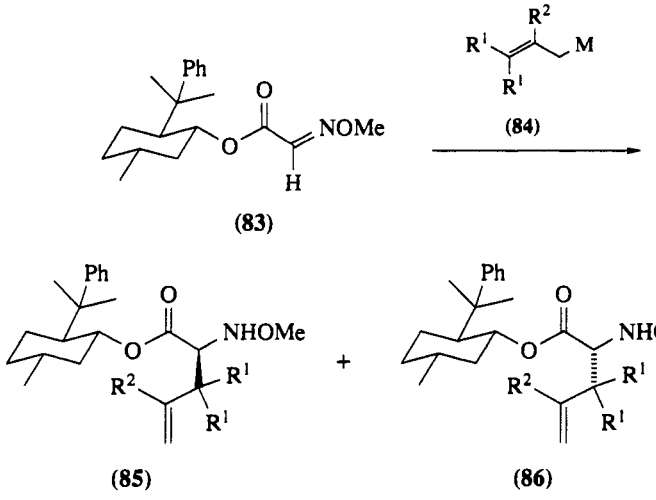


(18)

(**81**) (**82**)

The addition of allyl and prenyl organometallics (**84**) to 8-(–)-phenylmenthyl *N*-methoxyiminoacetate (**83**; equation 19) has been examined for the asymmetric synthesis of amino acids.[46] Treatment of (**83**) with allylboronates and allylzinc bromide affords *N*-alkoxyamines (**85**) and (**86**; Table 19). Both allyl-

and prenyl-zinc bromide (entries 1 and 3, Table 19) provide good stereocontrol. Predominant formation of (**85**; $R^1 = R^2 = H$) is consistent with a chelation-controlled allyl addition as shown in Figure 13, with attack occurring from the more accessible *si* face. Parallel results are obtained in the addition of organometallic reagents to *in situ* generated 8-(–)-phenylmenthyl N-acyliminoacetates.[47]



(19)

Table 19 Diastereoselectivity in the Addition of Allyl Organometallic Reagents (**84**) to 8-(–)-Phenylmenthyl-*N*-methoxyiminoacetate (**83**; Equation 19)[46]

Entry	*Organometallic (84)* R^1	R^2	*M*	*Product ratio (85):(86)*	*de*	*Yield (%)*
1	H	H	ZnBr	87:13	74	52
2	H	H	$B(OMe)_2$	53:47	6	29
3	Me	Me	ZnBr	—	>98	55

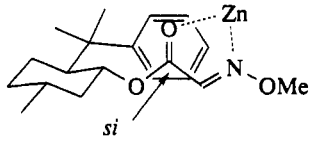
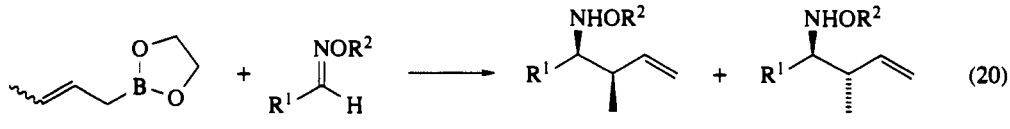


Figure 13

The *syn–anti* selectivity of oxime and oxime ether additions has been studied by Hoffmann and Endesfelder using separated (*E*)- and (*Z*)-crotylboronates (**87**) and (**88**; equation 20).[9] The reactions are carried out under high pressure (3.6–9 kbar) because of low oxime reactivity. As shown in Table 20, a good correlation exists between the direction of *syn–anti* selectivity and the geometry of the crotyl boronate, *i.e.* (*E*)-crotyl gives *anti* products (**91**), while (*Z*)-crotyl gives *syn* products (**90**). This trend, unlike the addition of crotyl-9-BBN to imines, is independent of whether the α-substituent on the imine is alkyl or aryl. Cyclic transition states do not satisfactorily explain these results because they are consistent with the boat rather than chair models. The possibility that alternative C(*E*,*Z*)‡ and C(*Z*,*Z*)‡ cyclic transition states are involved, assuming facile isomerization of the oxime, seems unlikely in view of the fact that no change in the direction of *syn–anti* selectivity is observed in the reactions of geometrically rigid (*E*)- and (*Z*)-benzaldoxime trimethylsilyl ethers (entries 7–10, Table 20). The *syn–anti* selectivity of oxime–crotylboronate additions is more satisfactorily rationalized using open transition state models (Figure 6), which are consistent with the fact that *syn–anti* selectivity is dependent on the geometry of crotyl reagent, and not on the geometry of the imine.

The addition of (*E*)-γ-(trimethylsilyl)allylboronate (**93**)[48] to racemic oxime (**92**) has been utilized by Wuts and Jung in connection with a total synthesis of cannabisativine (Scheme 7).[49] Paralleling the investigations of Hoffmann and Endesfelder using (*E*)-crotylboronate (**87**; see equation 20),[9] the reaction of (**93**) is *anti* selective and affords diastereomeric hydroxylamines (**94**) and (**95**). The diastereofacial se-



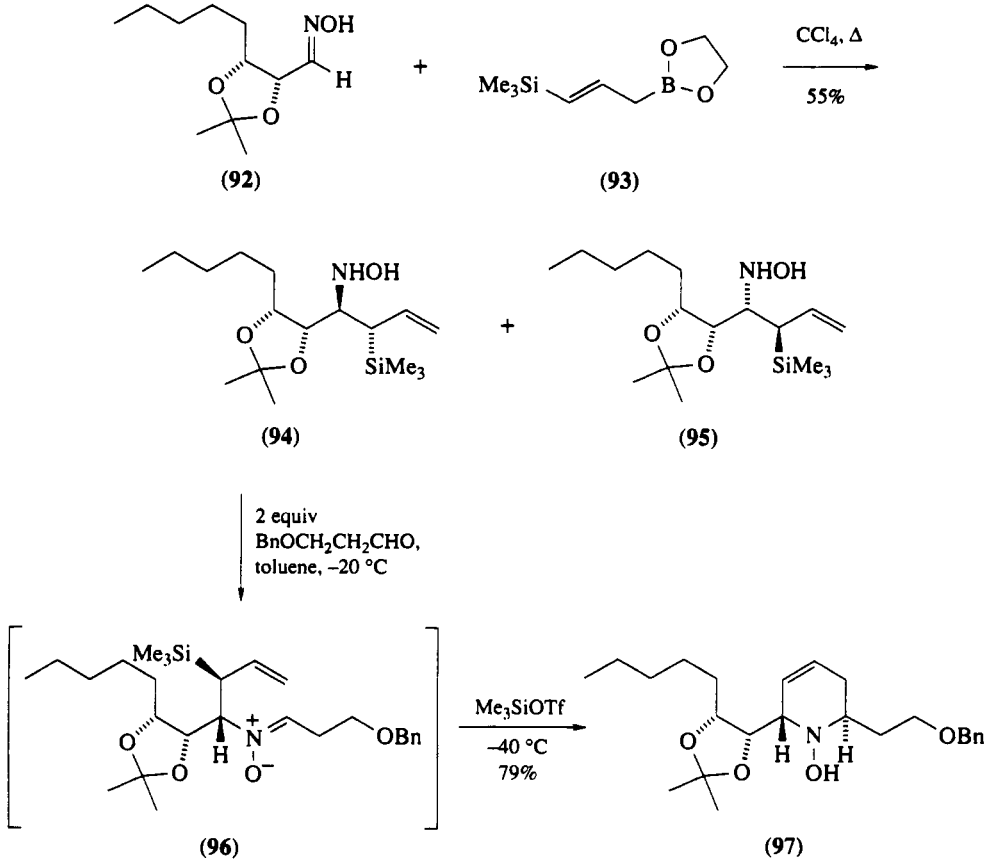
(87) (*E*)
(88) (*Z*)
(89)
(90)
(91)
(20)

Table 20 *Syn–Anti* Selectivity in the Reactions of Crotyl Boronates (**87**) and (**88**) with Oximes (**89**; Equation 20)[9]

Entry	*Crotylboronate geometry*	*Oxime (89)* R^1	R^2	*Geometry*	*Conditions*	*Yield (%)*	*Product ratio (90):(91)*
1	(*E*)	Ph	H	(*E*)	a	64	5:95
2	(*Z*)	Ph	H	(*E*)	a	38	88:12
3	(*E*)	Pr^i	H	(*E*)	a	81	19:81
4	(*Z*)	Pr^i	H	(*E*)	a	65	80:20
5	(*E*)	Bu^t	H	(*E*)	a	84	25:75
6	(*Z*)	Bu^t	H	(*E*)	a	60	70:30
7	(*E*)	Ph	TMS	(*E*)	b	40	5:95
8	(*E*)	Ph	TMS	(*Z*)	a	49	5:95
9	(*Z*)	Ph	TMS	(*E*)	a	24	87:13
10	(*Z*)	Ph	TMS	(*Z*)	a	25	85:15

[a]3.6–9 kbar, 28–88 °C, pet. ether. [b]9 kbar, 46 °C, CH_2Cl_2.

lectivity, however, is modest as the ratio of (**94**):(**95**) is 1.7:1. Diastereomer (**94**) is converted to tetrahydropyridine (**97**), a useful intermediate for the synthesis of cannabisativine, by TMS-OTf-promoted cyclization of the nitrone derivative (**96**).

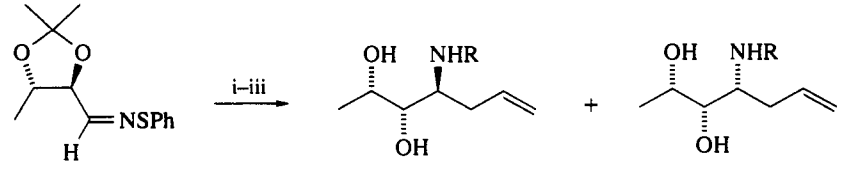


(92)
(93)
(94)
(95)
(96)
(97)

Scheme 7

4.3.3.3 Sulfenimines

The reaction of organometallic reagents with *S*-arylsulfenimines yields sulfenamides whose weak sulfur–nitrogen bond is readily cleaved upon aqueous work-up to generate primary amines. Fuganti *et al.*[50] have examined the addition of diallylzinc and allylmagnesium bromide to sulfenimine (**98**; equation 21) and isomeric sulfenimine (**101**; equation 22) to probe the influence of the α- and β-alkoxy substituents on reaction diastereoselectivity. The results are summarized in Tables 21 and 22. The reaction is performed by treatment of an ethereal solution (–78 °C) of (**98**) and (**101**) with the organometallic reagent (2 equiv.) followed by hydrolysis and benzoylation. Treatment of (**98**) with diallylzinc provides exclusively *N*-homoallylamide (**99**), the product of Cram addition in *ca.* 60% yield (entry 1, Table 21). Similarly, phenylsulfenimine (**101**) provides under identical conditions the Cram product, *N*-homoallylamide (**102**), as the sole product (entry 1, Table 22). The diastereofacial selectivity erodes with the addition of allylmagnesium bromide to (**98**; entry 2, Table 21) and is reversed with Grignard addition to (**101**; entry 2, Table 22).



(21)

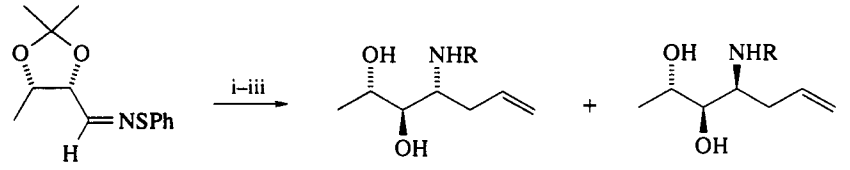
(**98**) (**99**) Cram (**100**) anti-Cram

R = COPh

i, , Et_2O, –78 °C; ii, H^+; iii, $NaHCO_3$, BzCl

Table 21 Cram Selectivity in the Addition of Allyl Organometallic Reagents to Sulfenimine (**98**; Equation 21)[50]

Entry	*Allyl organometallic M*	*Product ratio (99):(100)*	*Aldehyde addition (Cram:anti-Cram ratio)*[51]
1	1/2 Zn	>98:—	95:5
2	MgBr	55:45	*ca.* 65:35



(22)

(**101**) (**102**) Cram (**103**) anti-Cram

R = COPh

i, , Et_2O, –78 °C; ii, H^+; iii, $NaHCO_3$, BzCl

Table 22 Cram Selectivity in the Addition of Allyl Organometallic Reagents to Sulfenimine (**101**; Equation 22)[50]

Entry	*Allyl organometallic M*	*Product ratio (102):(103)*	*Aldehyde addition (Cram:anti-Cram ratio)*[51]
1	1/2 Zn	>98:—	95:5
2	MgBr	30:70	*ca.* 65:35

The diallylzinc-induced Cram diastereofacial selectivity closely parallels that of the corresponding aldehyde precursors[51] (Tables 21 and 22) and is consistent with Felkin–Ahn addition, as is shown in Figure 14. The high selectivity in the addition of diallylzinc to (**101**) is somewhat surprising given the added steric interactions with the incoming nucleophile and the (3*S*)-methyl group of (**101**) with Felkin–Ahn addition (Figure 14b) and that models other than Felkin–Ahn (*i.e.* Cornforth) might be more relevant. β-Chelation transition states involving a six-membered zinc chelate are possible and would have a syner-

gistic effect on diastereofacial selectivity. α-Chelation (five-membered zinc chelate), however, is not likely since it would favor the formation of (**100**) and (**103**). The erosion of diastereoselectivity in the addition of allylmagnesium bromide to sulfenimines (**98**) and (**101**) parallels that observed in the aldehyde additions.[51] The presence of a competing five-membered magnesium chelate involving the α-alkoxy group has been suggested.[50]

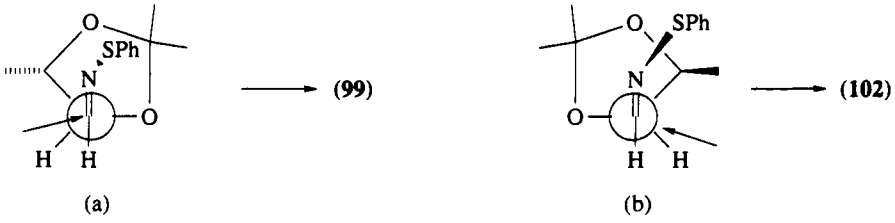
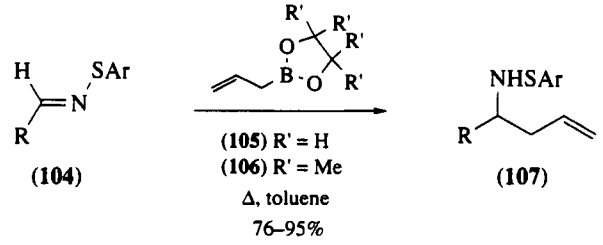


Figure 14

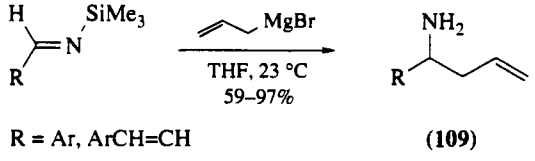
The addition of allylboronates (**105**) and (**106**) to aryl sulfenimines (**104**) to provide sulfenamides (**107**) has also been reported by Wuts and Jung (equation 23).[52] High yields of (**107**) are obtained even though the reaction is slow (4 h to 3 d, refluxing toluene). The reaction rate is a function of the size of the boronate ligand (**106** is slower than **105**). The authors attribute the reaction sluggishness to a cyclic boronate transition state.



(23)

4.3.3.4 *N*-Trimethylsilylimines

N-Trimethylsilylimines (**108**) can be conveniently generated *in situ* by treatment of nonenolizable aldehydes with lithium bis(trimethylsilyl)amide.[39] Treatment of a solution of (**108**) with allylmagnesium bromide affords after aqueous work-up homoallylamine (**109**) in good/excellent yield (equation 24).[39] Although the methodology works best with nonenolizable aldimines, it nonetheless provides a convenient method for preparing many primary homoallylamines.

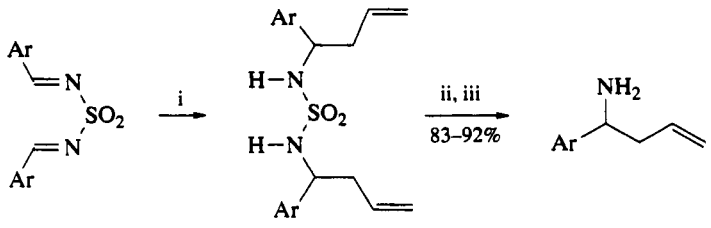


(**108**) R = Ar, ArCH=CH (**109**)

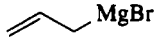
(24)

4.3.3.5 Sulfonylimines

Although *N*-sulfonylimines react with a variety of nucleophilic reagents, the products are not particularly useful since the sulfonyl protecting group is not easily removed. To overcome this problem, Davis *et al.*[40] have examined the addition of organometallic reagents including allylmagnesium bromide to diarylidenesulfamides (**110**) derived from nonenolizable aldehydes (equation 25). In this case the reaction products, diaryl sulfamides (**111**) can be hydrolyzed in refluxing aqueous pyridine to afford, after sodium hydroxide treatment, primary homoallylamines (**112**) in good yield.



(110) (111) (112) (25)

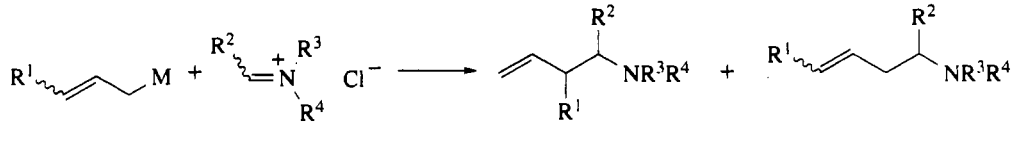
i, 

, Et_2O, Δ; ii, H_2O/pyridine; iii, ^-OH

4.3.4 REACTIONS WITH IMINIUM SALTS

4.3.4.1 Using Preformed Iminium Salts

Miginiac *et al.* have examined the reactions of crotyl-zinc, -magnesium, -aluminum and -lithium organometallics (**113**) with preformed iminium salts (**114**), for the synthesis of branched and linear tertiary amines (**115**) and (**116**), respectively (equation 26).[53] The iminium salts were prepared by treatment of the corresponding enamines with hydrogen chloride. Neither the (*E*):(*Z*) isomeric ratio of the linear products (**116**) nor the *syn*:*anti* ratio of branched products (**115**) were determined. α-Deprotonation is not a serious problem since yields are generally good even though the iminium salts are enolizable. The reactions are performed in THF/ether or in ether (with Grignard reagents) and at temperatures between 10 and 25 °C (the more reactive crotyllithium reagents, however, add more effectively at –60 °C). Results are shown in Table 23. The preference for branched homoallylamines (**115**), with the exception of the vinyl crotyl reagents, follows the trend $Al_{2/3}X > ZnX > MgX > Li$, paralleling the covalent character of the carbon–metal bond. Crotylaluminum reagents are noteworthy because they are entirely regiospecific, providing branched products (**115**) when R^1 = alkyl or aryl (entries 1–9, Table 23) and linear products (**116**) when the R^1 is vinyl (entries 10–12, Table 23). There is little similarity between the regiochemistry of these reactions and that observed in reactions of imines, the latter of which are strongly influenced by imine substitution (see Section 4.3.2.2.1). This is not unexpected because iminium salts do not contain an available lone pair of electrons, which is necessary for the involvement of cyclic transition states. The preference for products of allylic rearrangement in crotyl additions (*i.e.* branched products) could also apply to vinyl crotyl reagents, since linear product formation which dominates in these cases (entries 10–12, Table 23) can be explained by homoallylic transposition, *i.e.* attack at the ε-carbon atom.



(113) (114) (115) (116) (26)

Additions of propargyl/allenic reagents (**117**) to iminium salts (**118**) have also been studied by Miginiac *et al.* (equation 27).[54] Reaction conditions and yields are similar to those used in the analogous crotyl additions. Results are shown in Table 24. The regioselectivity, paralleling the reactions of imines with propargyl/allenic reagents, is influenced by the presence of a γ-substituent in the propargyl/allenic reagent; thus, the absence of γ-substitution favors alkynic products (**120**; entries 1–4, Table 24), while γ-substitution favors allenic products (**119**; entries 5–11, Table 24). As in crotyl organometallic additions to iminium salts, aluminum reagents are far more selective than zinc, magnesium or lithium reagents. The size of the γ-substituent of the organometallic reagent does not have a large effect on the regiochemical outcome, since replacement of the alkynic methyl group by an *n*-butyl group does not significantly increase the amount of alkynic product (**120**; entries 5 *versus* 9, Table 24). The type of alkylimine substituents (branched, linear or cyclic) also has little impact on regiochemistry.

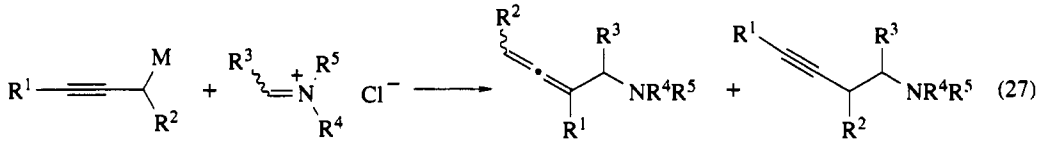
An interesting example of bis(dimethylamino)methylation has been reported by Reich *et al.* involving the reaction of 1,4-bis(trimethylstannyl)-2-butyne (**121**) with Eschenmoser's salt (**122**) to afford

Table 23 Reactions of Crotyl Organometallic Reagents (**113**) with Iminium Salts (**114**; Equation 26)[53]

	Organometallic (113)	*Iminium salt (114)*			*Metal*							
					ZnBr		*MgX*		*$Al_{2/3}X$*		*Li*	
Entry	R^1	R^2	R^3	R^4	*Yield (%)*	*(115):(116)*	*Yield (%)*	*(115):(116)*	*Yield (%)*	*(115):(116)*	*Yield (%)*	*(115):(116)*
1	Me	Pr^i	—$(CH_2)_4$—		82	90:10	76	86:14	75	100:0	77	32:68
2	Me	Pr^n	—$(CH_2)_4$—						53	100:0		
3	Me	Pr^i	Bu^n	Bu^n					74	100:0		
4	Bu^n	Pr^i	—$(CH_2)_4$—		80	90:10	68	75:25	65	100:0		
5	Bu^n	Pr^n	—$(CH_2)_4$—						55	100:0		
6	Bu^n	Pr^i	Bu^n	Bu^n					56	100:0		
7	Ph	Pr^i	—$(CH_2)_4$—		37	56:44	51	57:43	42	100:0	74	16:84
8	Ph	Pr^n	—$(CH_2)_4$—						39	100:0		
9	Ph	Pr^i	Bu^n	Bu^n					56	100:0		
10	CH_2=CH	Pr^i	—$(CH_2)_4$—		31	16:84	62	23:77	83	0:100	73	8:92
11	CH_2=CH	Pr^n	—$(CH_2)_4$—						64	0:100		
12	CH_2=CH	Pr^i	Bu^n	Bu^n					76	0:100		

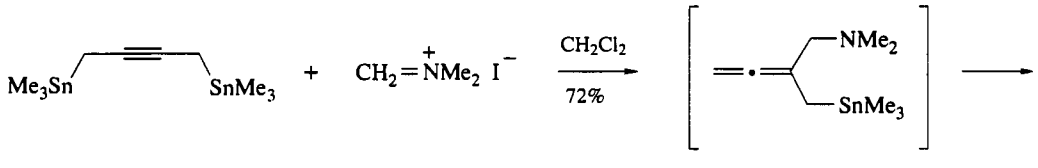
Table 24 Reactions of Propargyl/Allenic Organometallic Reagents (**117**) with Iminium Salts (**118**; Equation 27)[54]

	Organometallic (117)		*Iminium salt (118)*			*Metal*							
						ZnX		*MgX*		*$Al_{2/3}X$*		*Li*	
Entry	R^1	R^2	R^3	R^4	R^5	*Yield (%)*	*(119):(120)*	*Yield (%)*	*(119):(120)*	*Yield (%)*	*(119):(120)*	*Yield (%)*	*(119):(120)*
1	H	H	Pr^i	—$(CH_2)_4$—		32	53:47	70	2:98	66	2:98		
2	H	Me	Pr^i	—$(CH_2)_4$—		40	50:50	45	40:60	72	10:90		
3	H	H	Pr^n	—$(CH_2)_4$—						65	0:100		
4	H	H	Pr^i	Bu^n	Bu^n					86	0:100		
5	Me	H	Pr^i	—$(CH_2)_4$—		73	99:1	71	70:30	64	91:9	65	41:59
6	Me	H	Pr^n	—$(CH_2)_4$—						49	100:0		
7	Me	H	Pr^i	Bu^n	Bu^n					87	96:4		
8	Et	H	Pr^i	—$(CH_2)_4$—		68	90:10	70	61:39	69	92:8		
9	Bu^n	H	Pr^i	—$(CH_2)_4$—		71	70:30	65	57:43	70	92:8		
10	Bu^n	H	Pr^n	—$(CH_2)_4$—						51	95:5		
11	Bu^n	H	Pr^i	Bu^n	Bu^n					52	90:10		

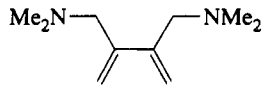


(117) (118) (119) (120)

2,3-bis(*N*,*N*-dimethylamino)methyl-1,3-butadiene (**124**) in good yield (Scheme 8).[55] The regiochemical outcome of the reaction suggests the intermediacy of an *N*,*N*-(dimethylamino)-methylated allenic species (**123**).



(121) (122) (123)

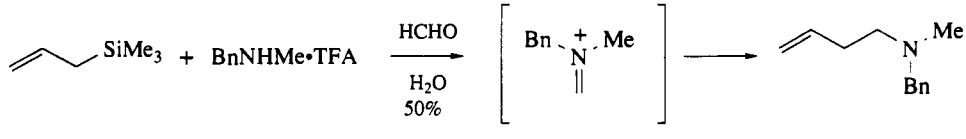


(124)

Scheme 8

4.3.4.2 Using Iminium Salts Generated *In Situ*

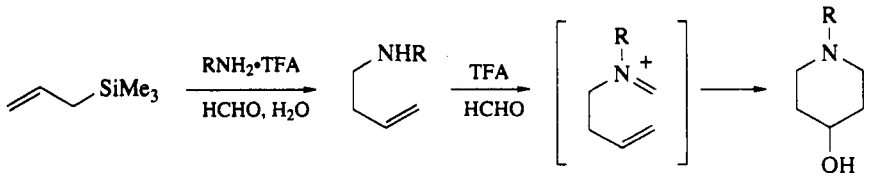
As reported by Grieco and coworkers,[56,57] additions of allyl- and crotyl-silanes and -stannanes to iminium salts can be performed in protic media in which the iminium salt is generated reversibly, as in the Mannich reaction. A typical example is the reaction of allyltrimethylsilane with *N*-benzyl-*N*-methylammonium trifluoroacetate (**125**) and formaldehyde to afford, *via* iminium salt (**126**), tertiary amine (**127**; Scheme 9). Reactions are normally carried out by stirring the allylsilane (1.1 equiv.) in a mixture of 3.0–3.5 M aqueous 37% formaldehyde solution (2.3 equiv.) and the amine trifluoroacetate salt (1.0 equiv.) at room temperature.[56] Slightly higher temperatures are required using secondary amines instead of primary amines. Protodesilylation, surprisingly, is not a serious problem even though the pH of the medium is slightly acidic. As shown in Scheme 10, secondary homoallylamine products (**128**) are difficult to isolate in reactions employing primary amines because *N*-homoallyliminium salts (**129**), formed by further condensation with formaldehyde, cyclize to form 4-hydroxypiperidines (**130**).[56] Overall yields of 4-hydroxypiperidines (**130**) starting with the primary amine salts are in the range of 50–100%. The reaction is also general for β-substituted allyl- and crotyl-silanes.



(125) (126) (127)

Scheme 9

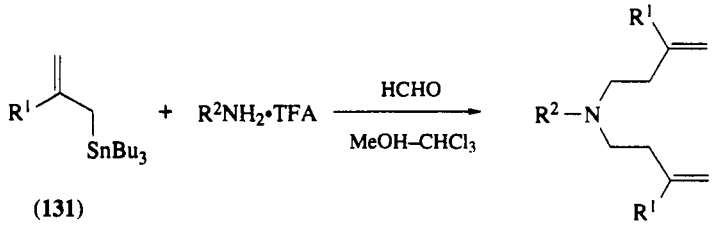
Analogous reactions of allylstannanes (**131**) with primary amines and aqueous formaldehyde yield bishomoallylamines (**132**; equation 28).[57] Reactions are conducted at ambient temperature in a 1:1 mixture of methanol and chloroform using 37% aqueous formaldehyde (2.1 equiv.), 2.0 equiv. of the allyltri-*n*-butylstannane and 1.1 equiv. of the amine trifluoroacetate. The failure to observe 4-hydroxy-



(128) (129) (130)

Scheme 10

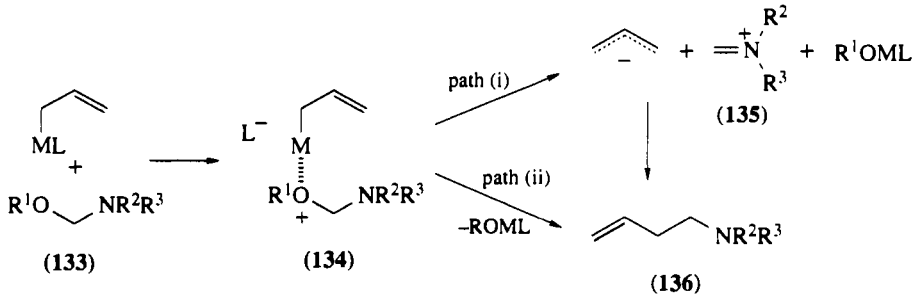
piperidines, as in the reactions of allylsilanes, is attributed to the higher reactivity of allylstannanes (**131**), which add to the derived homoallylamine salt (**129**) faster than the ensuing cyclization process (see Scheme 10). Because allylstannanes react considerably faster than allylsilanes in reactions with iminium salts derived from secondary amines, they are the reagents of choice for preparing tertiary homoallylamines from secondary amines. The reaction has been performed with methallyltributylstannanes (**131**; R^1 = Me) and with aromatic amines. Yields are excellent (75–100%).



(131) (132) (28)

4.3.5 REACTIONS WITH *GEM*-AMINO ETHERS

gem-Amino ethers (**133**) behave as masked iminium salts and react with allyl organometallics to afford *N,N*-disubstituted homoallylamines (**136**; Scheme 11). The use of *gem*-amino ethers is preferred over preformed iminium salts for the synthesis of (**136**) because they are more easily handled and can be purified by distillation. The mechanism of addition most likely involves an initial coordination complex (**134**) between the metal and the ether oxygen, which fragments by one of two general pathways: (i) an ionic S_N1-like process leading to an iminium salt intermediate (**135**) which captures the allyl anion; or (ii) a cyclic four- or six-centered internal S_N2-like process in which the alkoxide is displaced by attack at the α- or γ-carbon of the organometallic reagent, respectively. A third possibility exists in which complex (**134**) undergoes S_N2 displacement by another molecule of allyl reagent, regenerating the allyl reagent. Evidence so far has been unable to distinguish between these mechanisms.



(133) (134) (135) (136)

Scheme 11

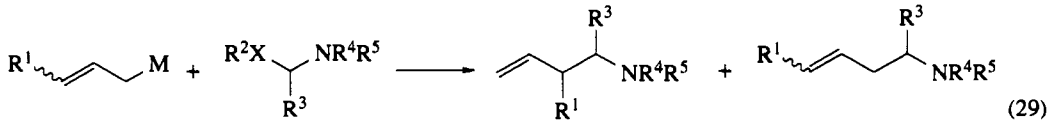
Most of the reported reactions of *gem*-amino ethers have been confined to the use of crotyl or propargyl/allenic reagents. A few examples involving allyl reagents are shown in Table 25 and involve mainly *N*-(trimethylsilyl)- and *N,N*-bis(trimethylsilyl)-*gem*-amino ethers (**133**; R^2 = TMS, R^3 = alkyl; $R^2 = R^3$ = TMS). These silylated reagents, which also react with nonresonance-stabilized reagents, provide access

Table 25 Reactions of Allyl Organometallic Reagents with *gem*-Amino Ethers (**133**; Scheme 11)

Entry	*gem-Amino ether (133)* R^1	R^2	R^3	*Yield of products (136) (%)* *MgBr*	*AlR_2Br*	*Ref.*
1	Me	TMS	TMS	70		58
2	Me	TMS	TMS	88		59
3	Me	TMS	TMS		40	60
4	Me	TMS	Bu^t		45	60
5	Ph	—$(CH_2)_2O(CH_2)_2$—		75		61

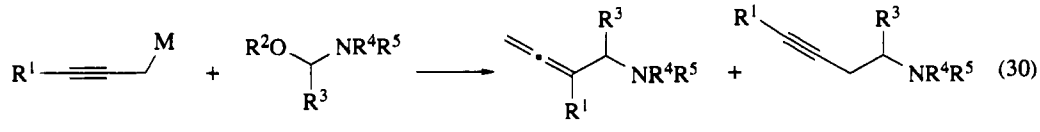
to *N*-unsubstituted homoallylamines upon protodesilylation during work-up. Although the examples are limited, allylmagnesium reagents appear to be superior to aluminum reagents.

Paralleling their investigations of the additions of crotyl organometallics to preformed iminium salts (see Table 23), Miginiac and coworkers have examined similar additions to *gem*-amino ethers and sulfides (**138**; equation 29 and Table 26).[60,62,63] Branched products (**139**) are favored over linear products (**140**) as in the reactions of preformed iminium salts. The reactions of *gem*-amino ethers (**138**) are somewhat more regioselective than those of preformed iminium salts, although no direct comparison between reactants with identical *N*- and α-substituents has been made. Little difference in regiochemistry is observed between the *gem*-amino ethers and *gem*-amino sulfides (entries 5 *versus* 7, Table 26). The erosion in branched product regioselectivity that occurs with more ionic crotyl reagents (*e.g.* crotyllithium) has been explained by Miginiac and Mauze[62] in terms of greater charge density at the imine carbon induced by the increased polarizability of the π-bond. It is tempting to conclude that iminium salts are involved in these reactions since a similar trend in regiochemistry is observed in the reactions of preformed iminium salts. Further insight into the mechanism could be obtained from the *syn–anti* ratios (in branched products); unfortunately, these were not reported.



(137) (138) X = O, S (139) (140) (29)

Reactions of propargyl/allenic organometallic reagents (**141**) with *gem*-amino ethers (**142**) (equation 30) have also been studied extensively by Miginiac and coworkers.[60,63] The results are shown in Table 27. Like crotyl reagents, propargyl/allenic reagents (**141**) display similar regiochemistry in their reactions with *gem*-amino ethers as they do with preformed iminium salts (see equation 27 and Table 24). Thus, allenic (branched) products (**143**) are favored with substituted propargyl/allenic reagents (R^1 = alkyl) and alkynic (linear) products (**144**) are favored with unsubstituted propargyl/allenic reagents (R^1 = H). Also, the more covalent organometallic reagents, aluminum and zinc, are more regioselective than the magnesium reagent. Regioselectivity diminishes, however, as the size of the amino substituents (R^4, R^5) in (**142**) increases (entries 11, 12 and 15, Table 27). Yields generally range between 40 and 60%.



(141) (142) (143) (144) (30)

Table 26 Reactions of Crotyl Organometallic Reagents (**137**) with *gem*-Amino Ethers (**138**; Equation 29)

	Crotyl reagent (137)	*gem-Amino ether (138)*					*Metal*								
							ZnX		*MgX*		*Li*		*$Al_{2/3}X$*		
Entry	*R^1*	*R^2*	*X*	*R^3*	*R^4*	*R^5*	*Yield (%)*	*(139):(140)*	*Yield (%)*	*(139):(140)*	*Yield (%)*	*(139):(140)*	*Yield (%)*	*(139):(140)*	*Ref.*
1	Et	Bu^n	O	H	Et	Et	70	100:0	77	100:0	53	72:28			62
2	Me	Bu^n	O	H	Et	Et	65	100:0	71	100:0	48	80:20	70	100:0	63
3	Et	Ph	S	H	Et	Et	60	99:t[a]	87	96:4	85	76:24			62
4	Ph	Bu^n	O	H	Et	Et	82	100:0							62
5	Et	Bu^n	O	Ph	Me	Me	75	100:0	90	87:13	14	20:80			62
6	Me	Bu^n	O	Ph	Me	Me	75	100:0	90	90:10			70	100:0	63
7	Et	Bu^n	S	Ph	Me	Me	83	99:t	67	85:15	15	11:89			62
8	Me	Me	O	H	Bu^t	TMS							45	95:5	60
9	Ph	Me	O	H	Bu^t	TMS							74	95:5	60
10	Bu^n	Me	O	H	Bu^t	TMS							75	95:5	60
11	Me	Me	O	H	TMS	TMS							47	100:0	60
12	Bu^n	Me	O	H	TMS	TMS							74	100:0	60
13	Me	Me	O	H	t-Oct[b]	TMS							65	92:8	60

[a]t = trace. [b] —$C(Me)_2CH_2Bu^t$.

Table 27 Reaction of Propargyl/Allenic Organometallics (**141**) with *gem*-Amino Ethers (**142**; Equation 30)

	Organometallic (141)	*gem-Amino ether (142)*				*ZnX*		*MgX*		*$Al_{2/3}X$*		
Entry	*R^1*	*R^2*	*R^3*	*R^4*	*R^5*	*Yield (%)*	*(143):(144)*	*Yield (%)*	*(143):(144)*	*Yield (%)*	*(143):(144)*	*Ref.*
1	H	Bu	H	Et	Et	60[b]	0:100	60[a]	0:100	60[b]	0:100	63
2	H	Me	H	TMS	TMS			50[c]	0:100			58
3	H	Bu	Ph	Me	Me	42[b]	10:90	80[a]	5:95	62[b]	2:98	63
4	Me	Bu	H	Et	Et	38[b]	90:10	80[a]	65:35	65[b]	93:7	63
5	Me	Bu	H	Et	Et					50[a]	99:1	63
6	Et	Bu	H	Et	Et					60[a]	97:3	63
7	Bu^n	Bu	H	Et	Et					60[a]	98:2	63
8	Me	Bu	Ph	Me	Me	49[b]	88:12	88[b]	70:30	52[a]	90:10	63
9	Et	Bu	Ph	Me	Me					65[a]	85:15	63
10	Bu^n	Bu	Ph	Me	Me					56[a]	88:12	63
11	Me	Me	H	TMS	Bu^t					40[a]	70:30	60
12	Bu	Me	H	TMS	Bu^t					60[a]	70:30	60
13	Me	Me	H	TMS	TMS					40[a]	85:15	60
14	Bu^n	Me	H	TMS	TMS					60[a]	90:10	60
15	Me	Me	H	TMS	Oct					50[a]	50:50	60

[a]Solvent is ether: [b]Solvent is THF.

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4.4
The Intramolecular Mannich and Related Reactions

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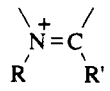
4.4.1 INTRODUCTION

Cyclization reactions of iminium ions, $R^1{}_2C{=}NR_2{}^+$, are a recurring theme in the assembly of cyclic nitrogenous compounds by both chemists and Nature.[1] The electron-deficient iminium ion is the nitrogen analog of an α-alkoxycarbenium (oxonium) ion or activated carbonyl group and as such is a fundamental electrophilic component of C—C bond formation. Although it is common practice in synthesis to modify the reactivity of simple iminium ions by introducing electron-withdrawing or electron-donating groups (Figure 1), only cyclization reactions of the parent species will be covered in this chapter. The important cyclization reactions of *N*-acyliminium ions are examined separately (see Volume 2, Chapter 4.5).

As this chapter is concerned with the intramolecular variants of iminium ion initiated condensations, a brief outline of possible cyclization modes is in order (Scheme 1). Examples (a) and (b) depict the generation of monocyclic compounds by way of exocyclic–trigonal and endocyclic–trigonal cyclizations, respectively.[2] Cases (c), (d) and (e) exemplify the construction of bicyclic compounds. Since rotational barriers for simple iminium ions are comparable to those of alkenes,[3] all of these cyclization modes

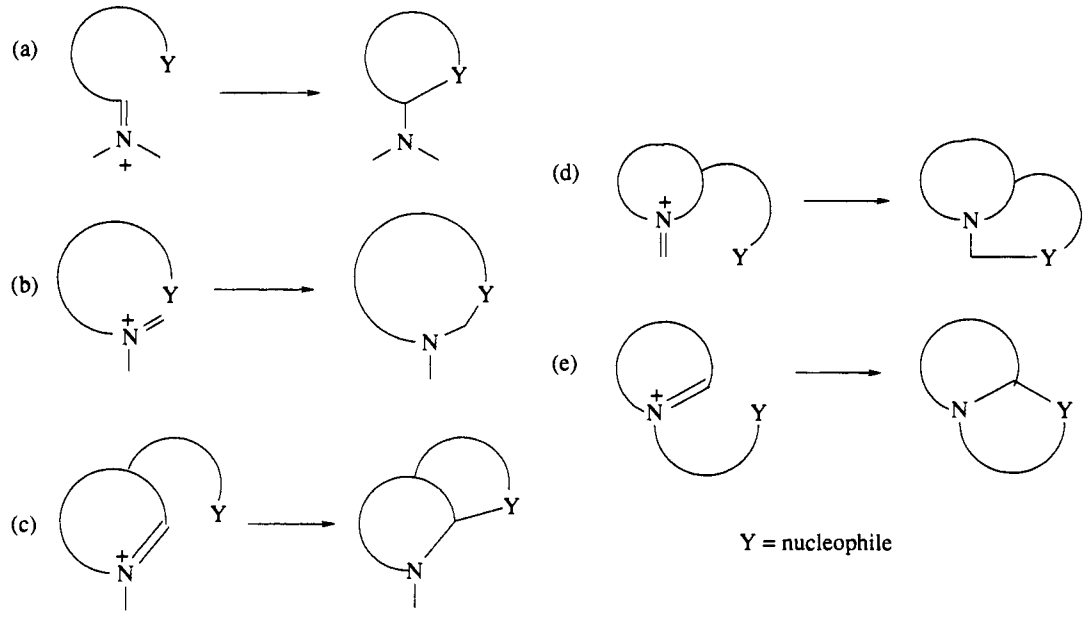


Stabilizing*	Destabilizing*
R = alkyl	R = acyl, aryl
R' = alkyl, alkenyl, aryl, alkynyl, SH, NH_2	R' = F, Cl, acyl

* relative to R = R' = H

Figure 1

should be subject to Baldwin's suggestions concerning orbital alignment and cyclization aptitude.[2] There is literature precedent for each of the generalized cyclization modes illustrated in Scheme 1.

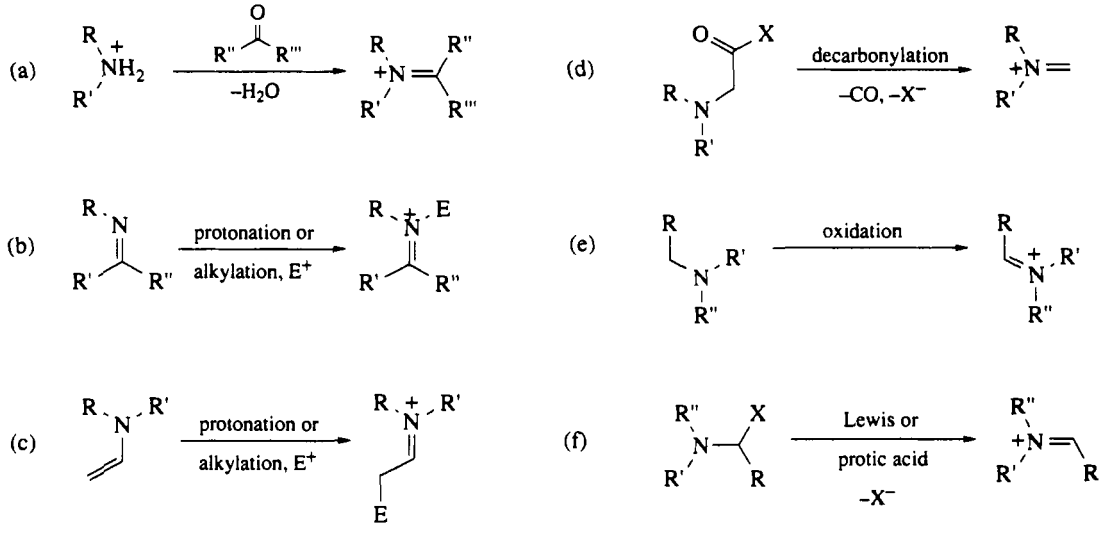


Scheme 1

While these various intramolecular cyclization modes make accessible a myriad of azacycles, the practitioner is faced with the delicate art of orchestrating an efficient cyclization. Cyclization conditions must be such that the reactivity of the nucleophile is preserved, while unleashing intramolecularly the electrophilicity of an iminium ion. A listing of the most important routes to iminium ions is found in Scheme 2.[4] It is important to note that many of the methods for iminium ion generation are not conducive to the preservation of certain nucleophiles. The judicious choice of reaction conditions is the key to an effective intramolecular Mannich or Mannich-related reaction.

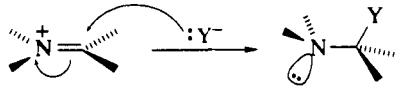
Since the conjugate base of an iminium ion (*i.e.* an enamine, see transformation c of Scheme 2) is a moderately strong base, iminium ions can be generated in stoichiometric quantities under essentially neutral conditions.[5] In contrast, *N*-acyliminium ions are accessible in stoichiometric quantities only under acidic conditions, since their conjugate bases (enamides) are only weakly basic. Thus, although *N*-acyliminium ions are more reactive cyclization initiators than iminium ions, and consequently react with a broader range of nucleophiles, azacycle synthesis strategies that employ simple iminium ions as the electrophilic components have more flexibility with regard to reaction medium.

Numerous studies over the past 30 years have highlighted the role that stereoelectronic effects can play in determining the success and stereochemical outcome of nucleophilic additions to iminium ions.[6] An antiperiplanar orientation of the forming nonbonded electron pair on nitrogen and the entering nucleophile is typically favored as illustrated in equation (1). Cyclization pathways that allow a nucleophile trajectory of this type and lead, upon rehybridization of the iminium ion carbon and nitrogen atoms, to an energetically nontaxing conformation of the cyclic product are highly favored. Numerous examples to

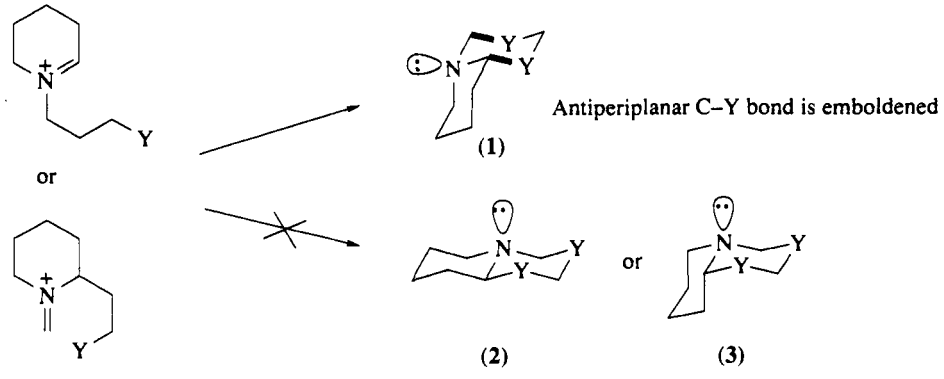


Scheme 2

support this conclusion are found in Section 4.4.2 of this chapter. A corollary of the *anti* preference depicted in equation (1) is that iminium ion cyclizations of modes (d) and (e) (Scheme 1) occur preferentially to afford initially only a single conformer of the azacyclic product.[7] This feature is illustrated in Scheme 3 for the specific case of cyclizations that form quinolizidines. Only the *cis*-quinolizidine conformer (**1**) has the favored antiperiplanar orientation of the nonbonded electron pair and the entering nucleophile. Thus, even though the *trans*-quinolizidine (**2**) or alternate *cis*-quinolizidine conformer (**3**) may be more stable, Mannich cyclization is expected preferentially to form (**1**) initially.



(1)



Scheme 3

4.4.2 CYCLIZATION WITH π-NUCLEOPHILES

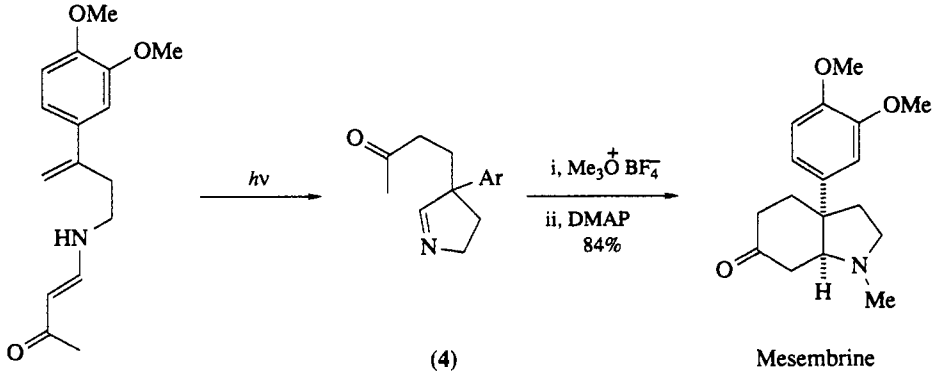
Carbon–carbon bond formation results from the electronic quenching of electrophilic iminium ions. This chapter will deal with cases where the nucleophilic electrons are supplied intramolecularly by a tethered sp^2- or *sp*-hybridized carbon center. The overall result of such a process is to transfer the electron-deficient center from a position α to nitrogen to another center in the molecule. The resulting

carbocations funnel into many of the classical manifolds that eventuate molecular electronic neutralization, *e.g.* carbenium ion additions, eliminations and rearrangements.

The following subsections are organized according to the nature of the π-nucleophile. Most classes of π-nucleophiles participate in iminium ion initiated cyclizations. The classes specifically covered in this chapter are: enols, enol ethers, arenes, alkenes, alkynes and organosilanes (vinyl, allyl and benzyl). Attention will be paid to the size of the resulting azacycle and any accompanying diastereoselection. Additional notice will be given to the method of iminium ion generation and its compatibility with each class of π-nucleophile.

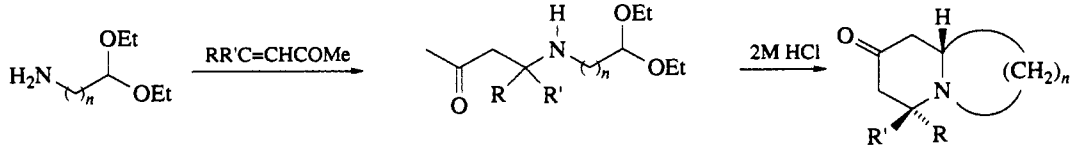
4.4.2.1 Carbonyl Compounds

The classical Mannich reaction, the condensation of an iminium ion and an enol, remains a powerful method for the chemical synthesis of naturally occurring alkaloids and related nitrogenous materials. Intramolecular condensations are frequently used to construct azapolycyclic ring systems. A recent example of using an intramolecular Mannich cyclization for constructing a linearly fused azacycle is provided in Scheme 4.[8] Imine (**4**) was secured by a novel [2 + 2] cyclization/retro-Mannich sequence. Subsequent iminium ion generation through alkylation of imine (**4**) with a Meerwein salt followed by treatment with 4-(dimethylamino)pyridine in refluxing acetonitrile afforded (±)-mesembrine in 84% yield. Note the exclusive formation of the kinetically favored *cis* stereochemistry.



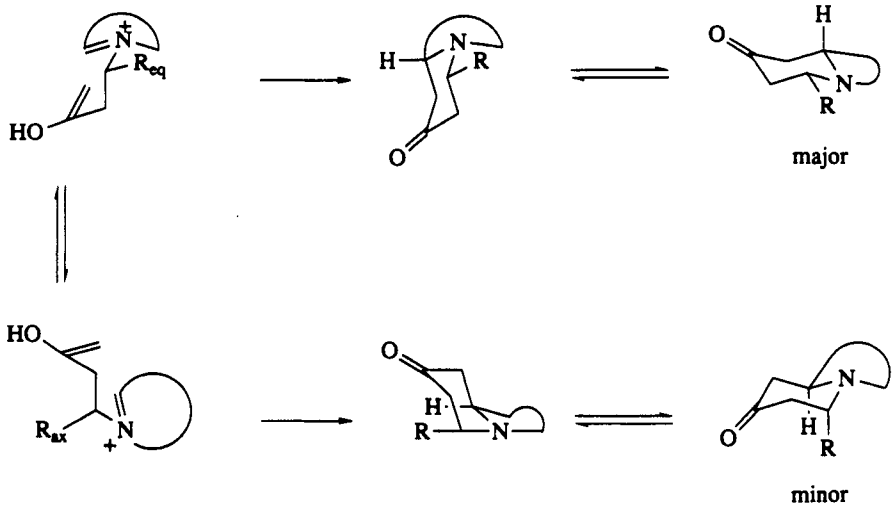
Scheme 4

A variety of quinolizidines and indolizidines may be accessed in good yields by the facile two-step process shown in Scheme 5.[9] Although not noted in this publication, the distribution of diastereomers (where possible) most likely reflects the relative energies of the diastereomeric transition state conformations depicted in Scheme 6. The transition state conformation that orients the larger substituent (R or R′) in the less sterically encumbered equatorial position gives rise to the major diastereomer in all of the per-



n	3	3	3	3	3	3	4	4	4
R	H	Me	H	Me	Pr^i	H	H	Me	H
R'	H	H	Me	Me	H	Pr^i	H	H	Me
Yield (%)	55	60	15	60	45	20	50	55	20

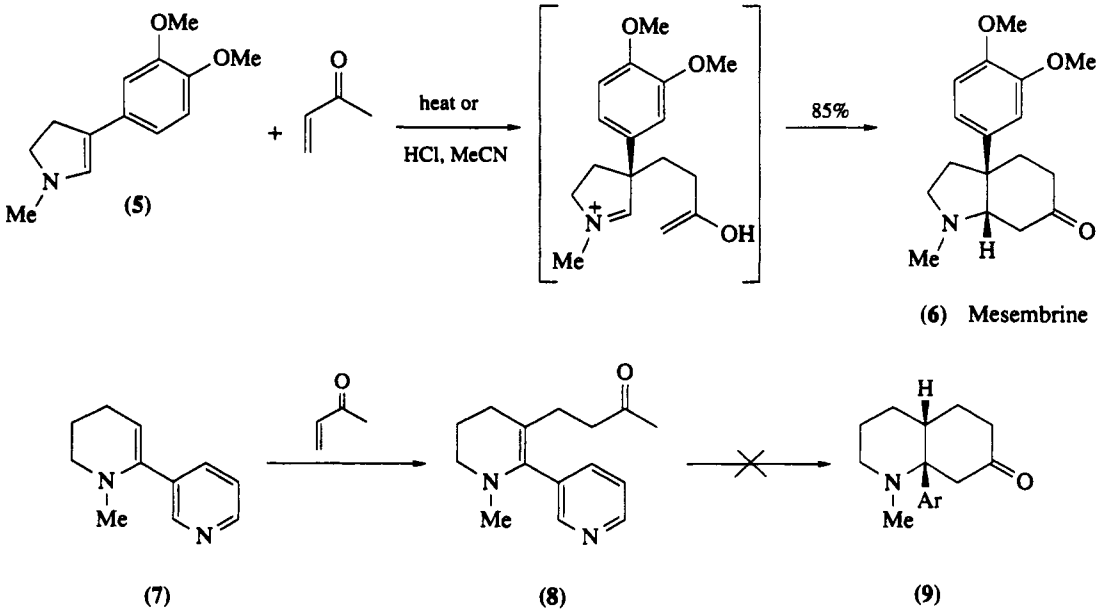
Scheme 5



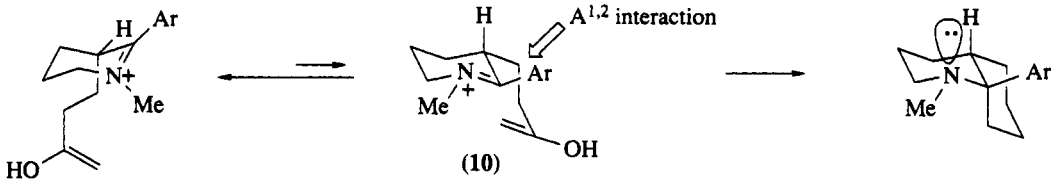
Scheme 6

tinent trials. Interestingly, although both *trans*-4-phenyl-3-buten-2-one and 2-cyclohexen-1-one formed the initial Michael adducts, these adducts failed to cyclize upon acidolysis. This result was attributed to retro-Michael reactions in these cases.

The reaction of endocyclic enamines with α,β-unsaturated ketones to afford *cis*-fused hydroindolones or hydroquinolones constitutes a complementary and highly useful annulation sequence developed extensively by Stevens and coworkers, see the reaction of (**5**) to give (**6**) in Scheme 7.[10] The importance of stereoelectronic effects is highlighted in the reaction of (**7**) with methyl vinyl ketone, which provided only the alkylated product (**8**) and none of the expected *cis*-hydroindolone (**9**).[11] The failure of intermediate (**8**) to cyclize in this case was attributed to nonbonded interactions between the aryl group and the side chain. This destabilizing allylic ($A^{1,2}$) interaction[12] disfavors formation of conformer (**10**), the intermediate required for antiperiplanar addition of the enol nucleophile (Scheme 8). Cyclization *via* the alternate conformation would require a double boat-like transition state.

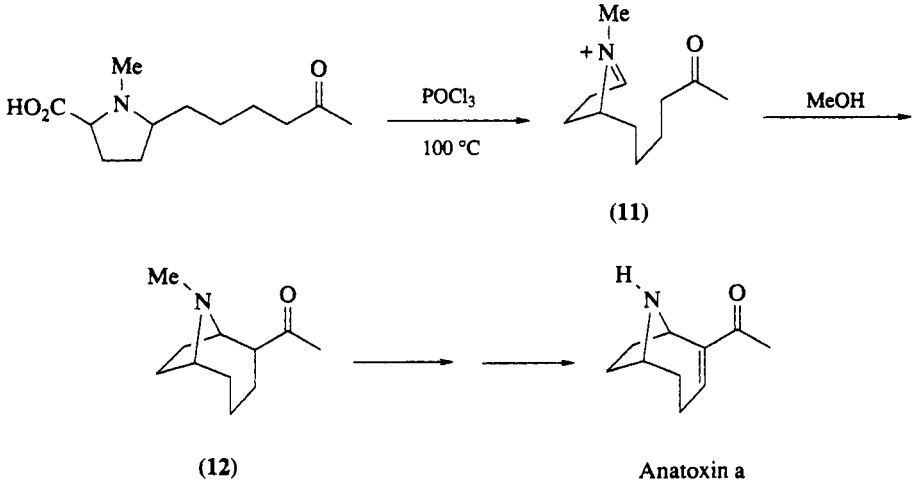


Scheme 7



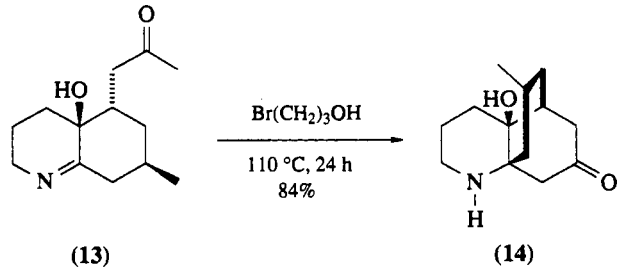
Scheme 8

The generation of bridged systems by intramolecular Mannich reactions has served as the cornerstone of several alkaloid constructs.[13–15] An excellent example is Rapoport and coworkers' synthesis of the neuromuscular toxin anatoxin a, a 9-azabicyclo[4.2.1]nonane. Initially, this group developed a high-yielding regiospecific route to iminium salts from α-tertiary amino acids by way of thermal decarbonylation of the corresponding acid chlorides.[16] In this way, iminium salt (**11**) was generated, then cyclized in 47% yield to (**12**) in refluxing acidified methanol (Scheme 9). The moderate yield is thought to result from the potentially reversible Mannich cyclization being followed by a nonreversible polymerization of iminium ion (**11**). A subsequent report details enantioselective syntheses of (+)- and (–)-anatoxin a using D- and L-glutamic acid, respectively, to generate the requisite optically active proline derivatives.[15]



Scheme 9

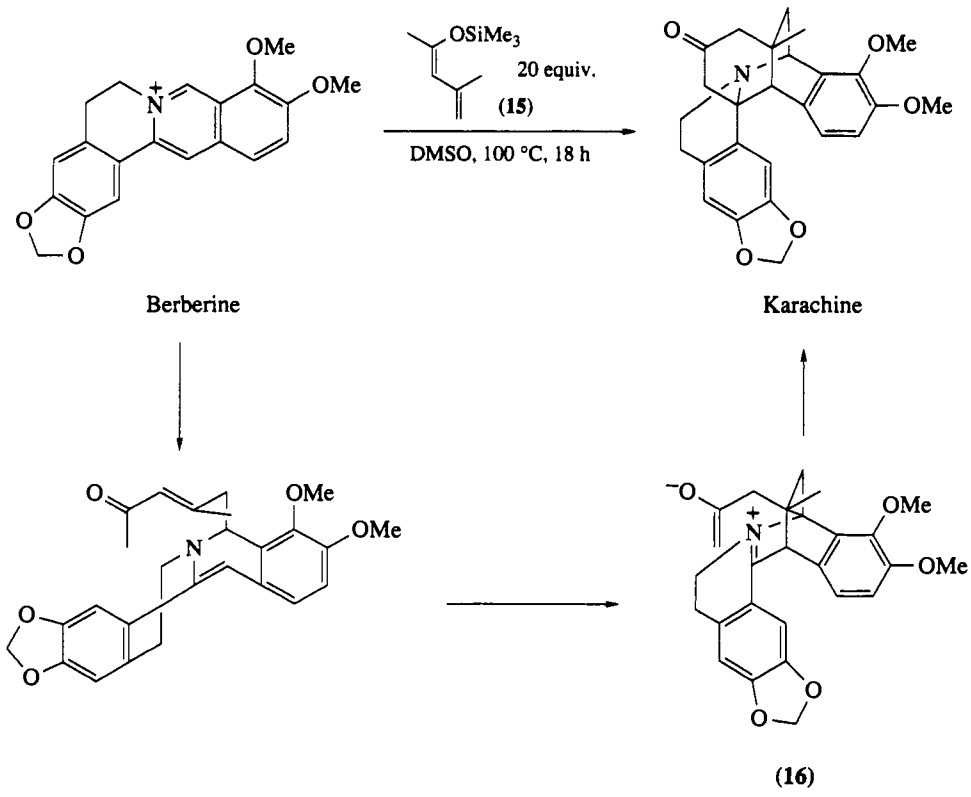
In Heathcock and coworkers' synthesis of the *Lycopodium* alkaloid (±)-lycodoline an interesting solution to the problem of inducing Mannich cyclization in acid-sensitive compounds was found.[17] Treatment of imine (**13**) with 3 M methanolic hydrochloric acid provided complex mixtures, while heating the preformed iminium bromide in refluxing toluene occasioned no cyclization (equation 2). However, when imine (**13**) is dissolved in a 5:1 mixture of toluene and 3-bromo-1-propanol and the resulting solution refluxed for 24 h, the crystalline ammonium salt of (**14**) precipitates from the solution. The authors suggest that formation of (**14**) may involve slow generation of hydrogen bromide by base-catalyzed polymeriza-



(13) (14) (2)

tion of the bromo alcohol. Under these low acid concentrations, enolization is thought to occur before iminium ion formation, thus obviating formation of the energetically unfavorable dication intermediate which would intervene under more acidic conditions.

Although careful consideration of the stereoelectronics of an iminium ion cyclization (antiperiplanar orientation of the nucleophile and developing nonbonded electron pair) may portend a successful ring closure, a synperiplanar addition is suggested as the key step of Stevens and Pruitt's synthesis of the *Protoberberine* alkaloid (±)-karachine.[18] Treatment of berberine with the silyloxydiene (**15**) gave a 66% yield (based on recovered berberine) of racemic karachine. Stevens proffers the pathway illustrated in Scheme 10 as a potential reaction course. The boat conformation that the tetrahydropyridinium salt is required to adopt in order to allow synperiplanar closure of zwitterion (**16**) is enforced by the geometric constraints of the bicyclooctane framework.

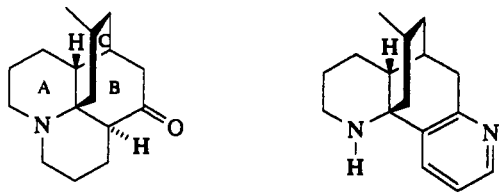


Scheme 10

4.4.2.2 Acetals and Enol Ethers

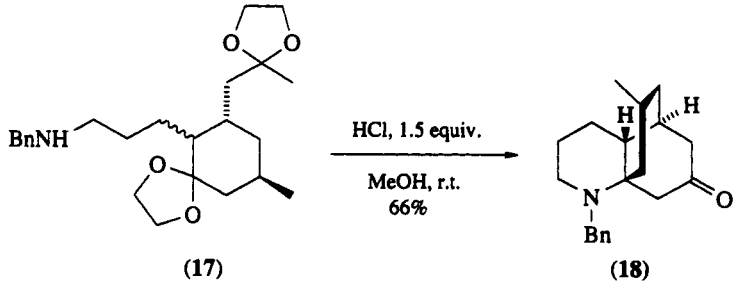
Mannich cyclizations are also successful when the carbonyl participant is masked as an acetal or enol ether. Considering the acetal, if the cyclization is conducted in aqueous acid, there is a good possibility that the cyclization terminator is actually the enol of the parent carbonyl (*i.e.* a classic Mannich cyclization). Under anhydrous acid conditions the reactive terminator is most likely the enol ether.

The successful use of acetal-protected carbonyl groups as iminium ion terminators for the construction of alkaloids is typified by Heathcock and coworkers' syntheses of *Lycopodium* alkaloids; to wit, lycopodine and lycodine (Figure 2).[17] A model cyclization that constructs the A-, B- and C-ring nuclei of the *Lycopodium* alkaloids is shown in equation (3). Treatment of diacetal (**17**) (a 1:1 diastereomeric mixture at C-2) with 1.5 equiv. of 3 M hydrochloric acid in methanol at room temperature for 2 d gave a single tricycle (**18**) in 66% yield. The authors advance that only one of the diastereomeric iminium ions will cyclize; however, enolization allows equilibration of these intermediates (Scheme 11). Thus, while diastereomer (**19**) can readily cyclize, (**20**) has no low energy cyclization pathway available, and must epimerize prior to cyclization. Corroborative support for this argument is found in the fact that the separated diastereomers of a related system cyclize to the same extent.[17]



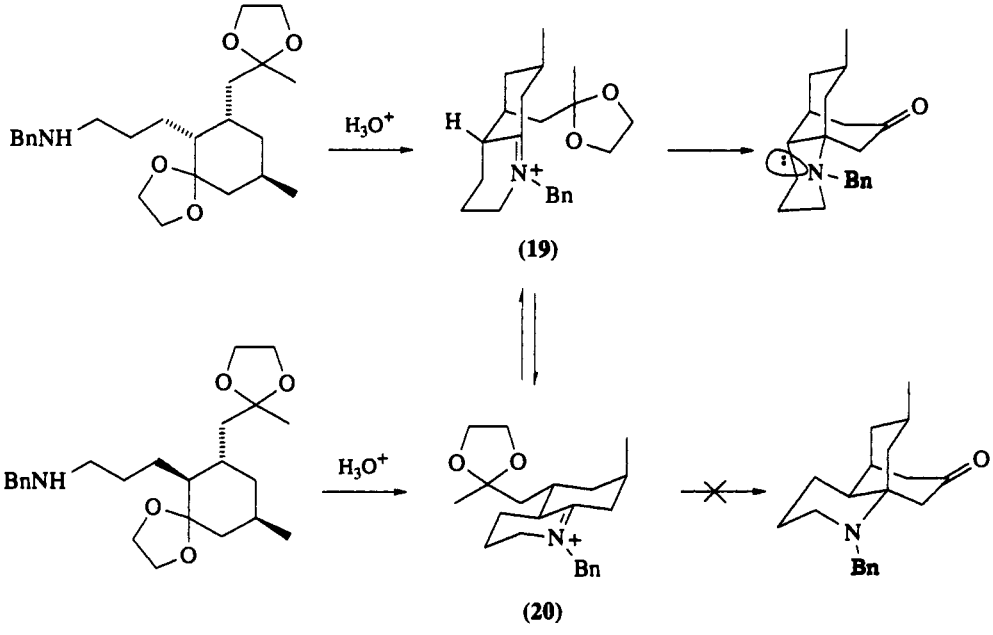
Lycopodine Lycodine

Figure 2



(17) (18)

(3)

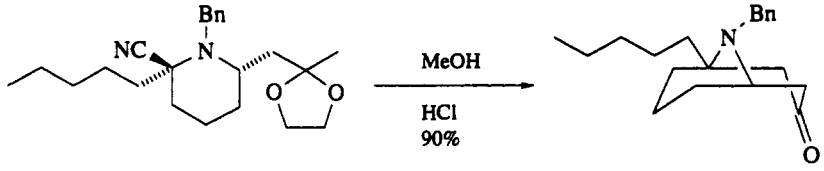


(19)

(20)

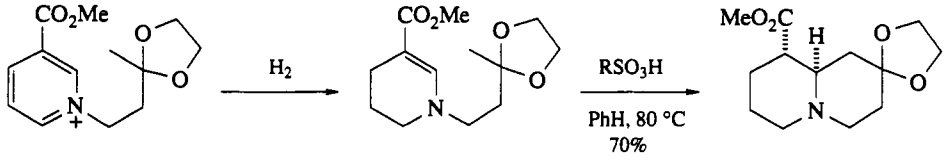
Scheme 11

Bridged bicyclic systems can be constructed with equal facility using acetal terminators under hydrolytic conditions. Husson and coworkers' construction of the lady bug alkaloid adaline is exemplary.[19] Aminonitrile (**21**) served as the iminium ion precursor. Refluxing a solution of (**21**) in methanol containing 10% hydrochloric acid for 48 h afforded the bicyclic adaline precursor (**22**) in 90% yield.



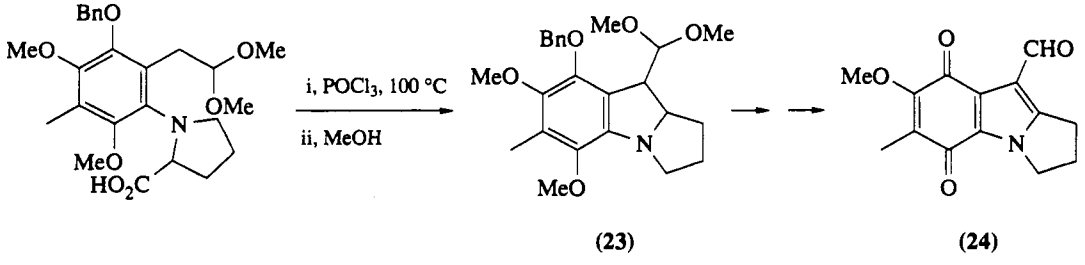
(21) (22)

As mentioned previously, there are many Mannich-type cyclizations of acetals that undoubtedly occur *via* enol ether intermediates and afford β-amino acetal products. A prototypical example is presented in Scheme 12. In this sequence, due to Wenkert, the iminium ion precursor is formed by semihydrogenation of a nicotinic ester salt.[20]



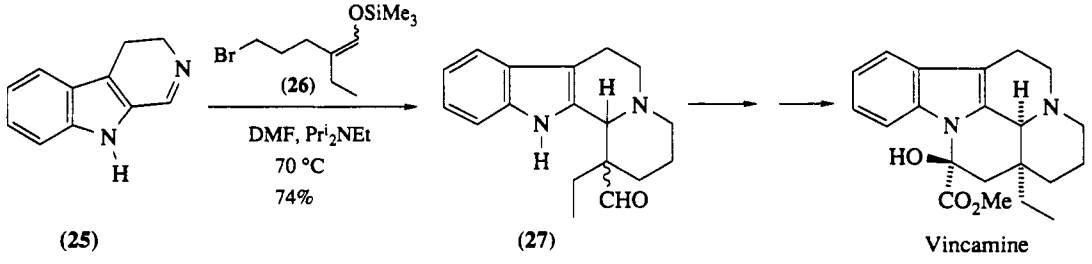
Scheme 12

A related example involving a more complex substrate is found in Rapoport and Luly's formal synthesis of the 7-methoxymitosene (**24**).[21] Again, decarbonylation of an α-tertiary amino acid chloride is employed to generate the iminium ion. The indoline acetal (**23**) produced in this way is essentially one diastereomer; however, its stereochemistry was not established (Scheme 13).



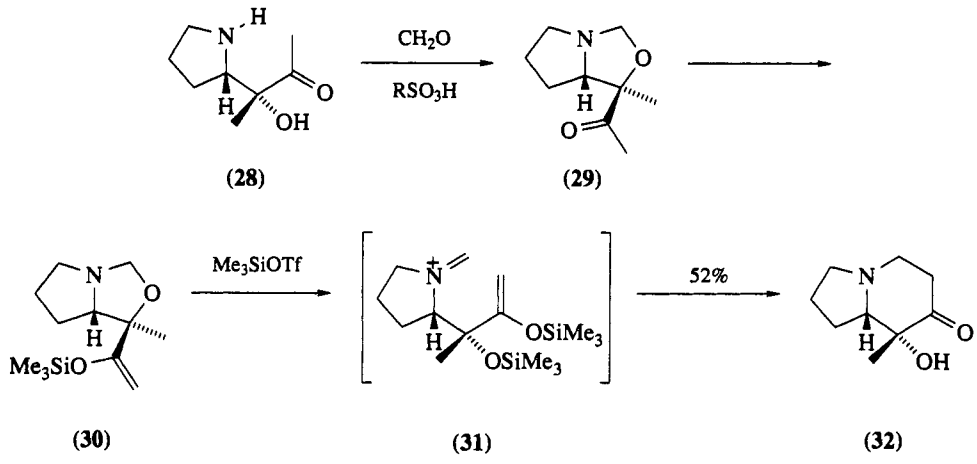
Scheme 13

Although enol ethers have received moderate notice as nucleophiles to quench intramolecular iminium ions, silyl enol ethers have been given scant attention. The first report of a silyl enol ether participating in an intramolecular Mannich reaction is found in Oppolzer and coworkers' synthesis of (±)-vincamine (Scheme 14).[22] Dihydro-β-carboline (**25**) and silyl enol ether (**26**) were mixed in DMF, then warmed to 70 °C for 64 h in the presence of diisopropylethylamine to provide a 1:1 mixture of *cis* and *trans* tetracyclic aldehydes (**27**) in 74% yield.



Scheme 14

An example that illustrates the advantages that an enol ether can offer *vis-à-vis* the parent carbonyl compound in iminium ion cyclization is found in Overman and Goldstein's construction of the allopumiliotoxin A alkaloid intermediate (**32**).[23] A variety of Mannich conditions failed to produce (**32**) from amino ketone (**28**), but yielded only cyclopentaoxazolidine (**29**). However, intramolecular Mannich cyclization was accomplished in 52% yield at low temperature by treatment of the bicyclic trimethylsilyl enol ether (**30**) with 1.1 equiv. of trimethylsilyl trifluoromethanesulfonate (Scheme 15). Remarkably, (**32**) produced in this manner was racemic, a result ascribed to facile [3,3] sigmatropic rearrangement of intermediate (**31**).

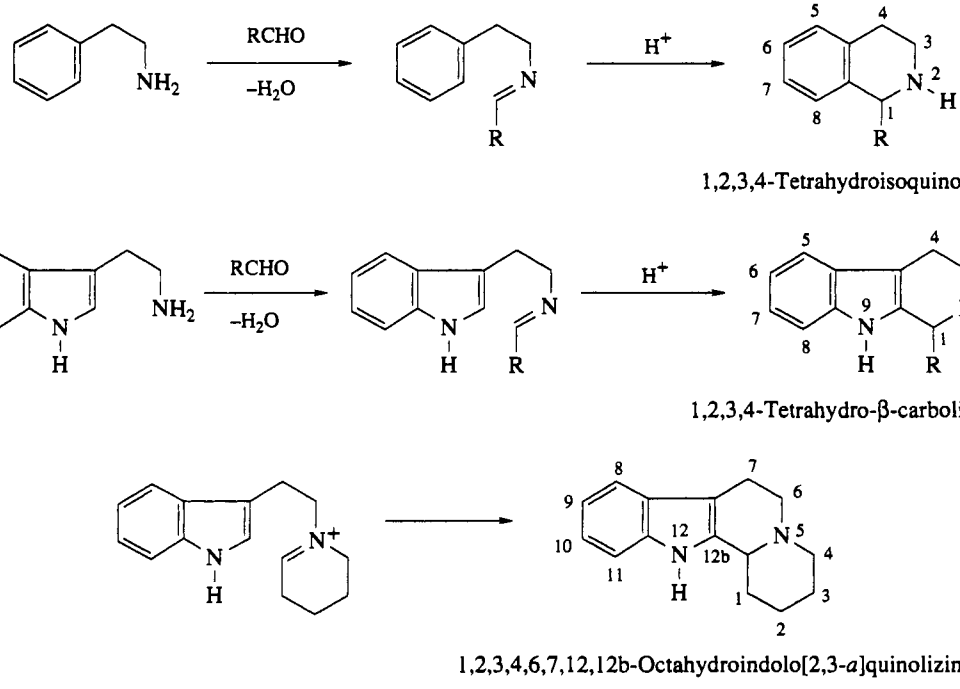


(28) (29) (30) (31) (32)

Scheme 15

4.4.2.3 Arenes

Since its discovery the Pictet–Spengler cyclization has formed the basis of numerous syntheses of alkaloids containing aromatic subunits. This high-yielding reaction involves, in its broadest sense, nucleophilic attack on an iminium ion by the π-electrons of a tethered aromatic moiety. In the classical reaction a substituted β-phenethylamine is condensed with an aldehyde under acidic conditions to produce a tetrahydroisoquinoline (Scheme 16).[24,25] A useful variant of the Pictet–Spengler reaction, which provides tetrahydro-β-carbolines and their derivatives,[26] involves the condensation of a tryptamine derivative and an aldehyde (Scheme 16). Whether nucleophilic attack on the resulting iminium ion occurs initially at the α- or β-indole carbon is a topic of current debate and, indeed, there is evidence to suggest that the mechanistic pathway could be substrate dependent.[27]



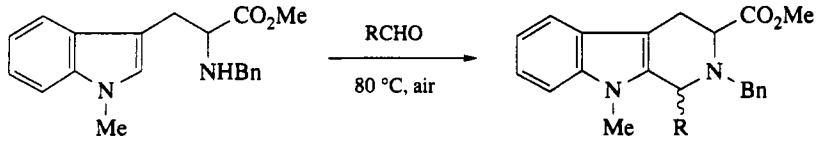
Scheme 16

Several reviews affirm the invaluable role played by the Pictet–Spengler cyclization in the assembly of almost every class of aromatic alkaloids.[28–30] In this section, we focus on recent examples and pay par-

ticular attention to the diastereoselection associated with intramolecular Mannich closures conducted as an integral part of alkaloid syntheses.

4.4.2.3.1 1,2,3,4-Tetrahydro-β-carbolines

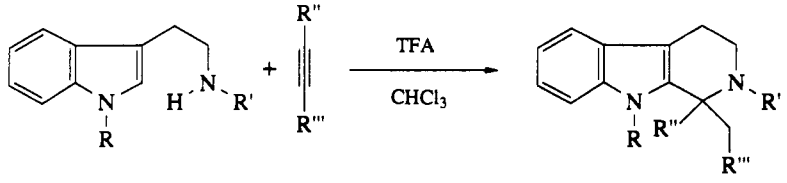
A brief look at some of the newer methods for generating these ring systems shall serve as our starting point. Prolonged heating of tryptophan methyl ester and an aldehyde in benzene (with Dean–Stark removal of water) provides excellent yields of 1-alkyl-3-carbomethoxy-1,2,3,4-tetrahydro-β-carbolines (Scheme 17).[31] There is some evidence to suggest that benzoic acid formed by air oxidation of benzaldehyde catalyzes this reaction.[32] These reaction conditions are, however, mild enough to accommodate the cyclization of acid-labile substrates like glyoxal diethyl acetal. In all of the cases reported, these 'aprotic' conditions afforded an increase in yield of the cyclization product when compared to the more classical protic solvent/acid catalyst conditions.



R	*Yield (%) 'aprotic'*	*Yield (%) 'aqueous'*
$HC(OEt)_2$	90	<20
CH_2CO_2Et	75	59
CH_2COEt	94	25

Scheme 17

Another newly introduced method generates the iminium ion intermediate by Michael addition of tryptamine to an activated alkyne in an acidic medium.[33] Yields of the resulting 1-alkyltetrahydro-β-carbolines range from good to excellent (Scheme 18).



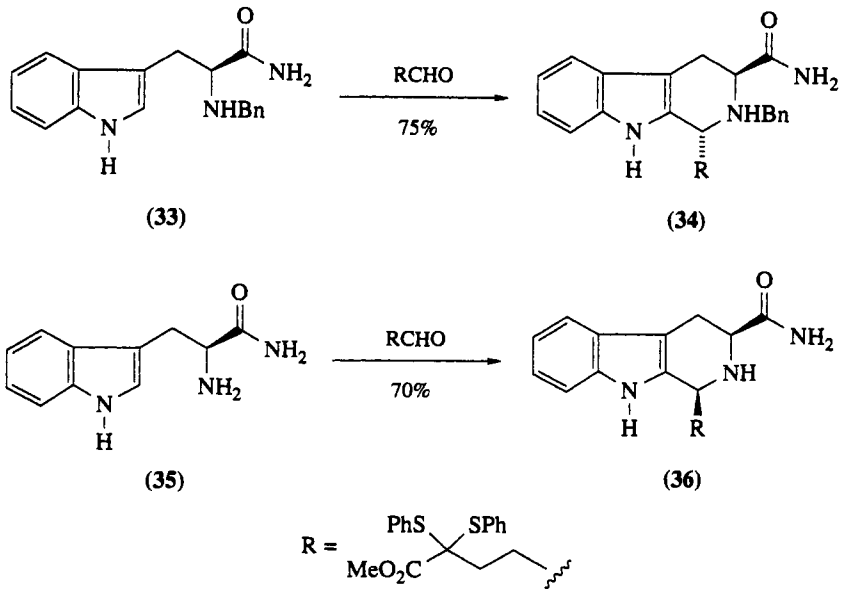
R	*R'*	*R''*	*R'''*	*Yield (%)*
H	H	CO_2Me	CO_2Me	83
Me	Bn	CO_2Me	CO_2Me	92
H	Bn	H	CO_2Me	85
H	Bn	H	COMe	76

Scheme 18

The factors that control diastereoselection in the construction of 1,3-disubstituted tetrahydro-β-carbolines are not, as yet, well understood. With many aldehydes a slight preference for forming the *trans* diastereomer is observed.[34] This preference is somewhat greater when the indole nitrogen (N_a) of the tryptamine is alkylated. Pictet–Spengler cyclizations of N_b-benzyltryptophan methyl ester under Cook's 'aprotic' conditions are reported to provide nearly exclusively the *trans*-N_b-benzyl-3-methoxycarbonyl-1-substituted-1,2,3,4-tetrahydro-β-carbolines.[35]

In 1983 an approach for forming either enantiomer of a 1-alkyl-1,2,3,4-tetrahydro-β-carboline from L-(−)-tryptophan was published.[36] Specifically, tryptophan was converted into derivatives (**33**) and (**35**) (Scheme 19). When the secondary amine (**33**) was condensed/cyclized with methyl 4-formyl-2,2-

bis(phenylthio)butyrate, ester (**34**) was generated in 75% yield as the only detectable diastereomer (^{13}C NMR). Perhaps more surprising, when the primary amine (**35**) was condensed/cyclized with the same aldehyde, a 70% yield of the *cis* diastereomer (**36**) was obtained (purportedly as the only detectable epimer). The authors also observed that cyclizations of tryptophan methyl esters were significantly less stereoselective than those of tryptophanamides, a trend corroborated by another investigation.[7] There are means which remove the diastereo-directing C-3 acyl functionality, thus providing for selective synthesis of either enantiomer of 1-alkyltetrahydro-β-carbolines.[37–40]



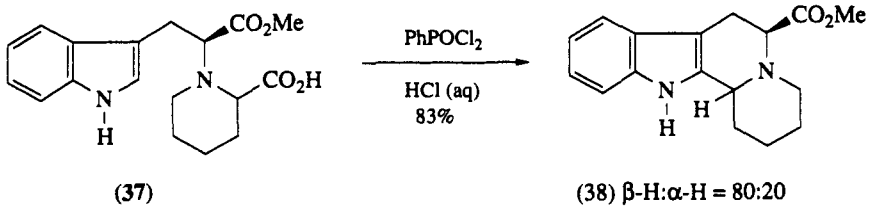
Scheme 19

4.4.2.3.2 Octahydroindolo[2,3-a]quinolizines

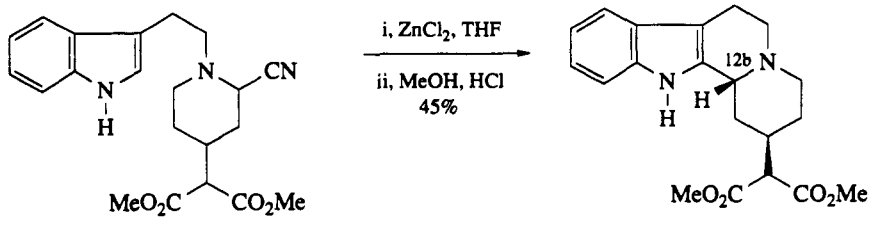
Numerous classes of biologically active alkaloids contain an indoloquinolizine (sub)nucleus (Scheme 16). The first consideration in the construction of an indoloquinolizine *via* the cyclization of a 1-[2-(3-indolyl)ethyl]-Δ^1-tetrahydropyridinium ion is the issue of iminium ion generation. The oxidation of tertiary amines (Polonovsky–Potier; $Hg(OAc)_2$; Pt, O_2) has been widely employed for this purpose; however, mixtures of regioisomeric iminium ions are typically produced.[41] Nevertheless, a number of extant methodologies serve well for regioselective iminium ion generation (Scheme 2).

The construction of indoloquinolizines through Pictet–Spengler cyclization produces a new stereogenic center. Thus, pre-existing stereocenters potentiate diastereomeric cyclization products. For example, cyclization of tryptophan derivative (**37**) affords a 4:1 mixture of stereoisomeric indoloquinolizines in 83% yield.[42] In concurrence with results obtained from tetrahydro-β-carboline studies,[35] the major diastereomer (**38**) possesses a *trans* stereorelationship of substituents on the newly formed ring. Numerous indoloquinolizidine alkaloids contain asymmetric centers in the D-ring and hence a considerable body of information exists concerning diastereoselection in Pictet–Spengler cyclizations of substituted Δ^1-tetrahydropyridinium ions. A few illustrative examples are summarized in Scheme 20.[42–44] The predominant formation of indoloquinolizidines (**40**) and (**41**) is readily rationalized by the stereoelectronic considerations advanced earlier. Thus, for the conversion of (**39**) to (**40**), stereoelectronically favored axial approach of the indole nucleophile to the Δ^1-tetrahydropyridinium ion conformer having the malonic ester side chain in an equatorial orientation would lead to (**40**; equation 4).

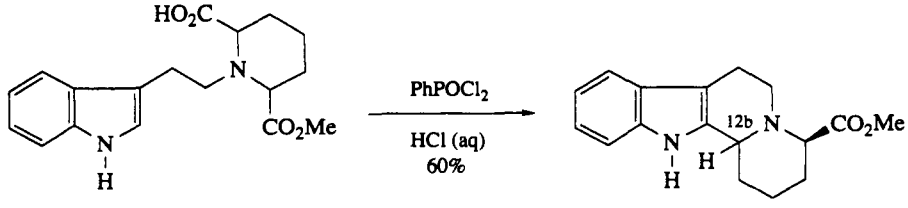
When the pre-existing stereocenter is adjacent to the iminium ion carbon atom, Pictet–Spengler cyclization most commonly occurs from the face opposite the substituent, as in the conversion of (**42**) to (**43**) (Scheme 20).[42] A related example is the cyclization of the disubstituted Δ^2-tetrahydropyridine (**44**), which was treated with hydrogen chloride gas in anhydrous methanol to produce three of the four possible diastereomeric products in the indicated abundances (Scheme 21).[45] The relative stereochemistry at C-1 is set by protonation of the enamine, while that at C-12b is determined in the cyclization step. The authors argue that protonation is kinetically controlled and occurs preferentially from the



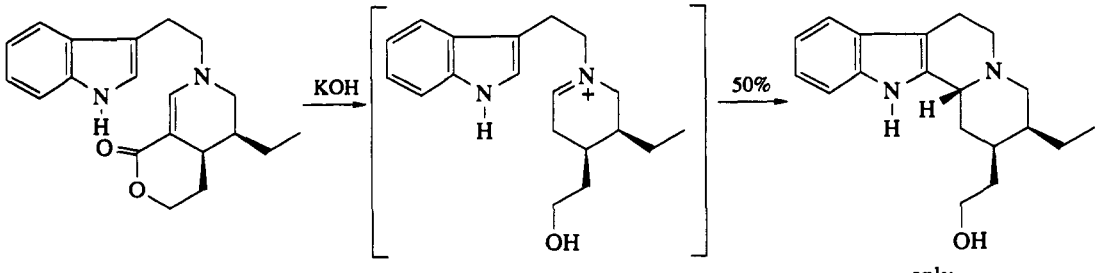
(37) (38) β-H:α-H = 80:20

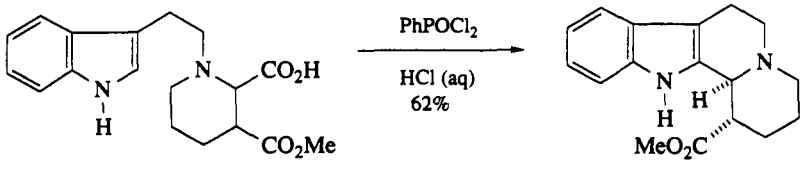


(39) (40) 12bβ-H major product
12bα-H trace only



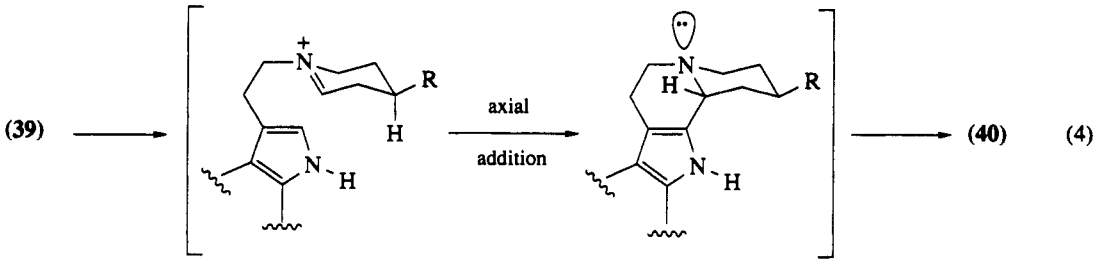
(41) 12bβ-H 75%
12bα-H 25%



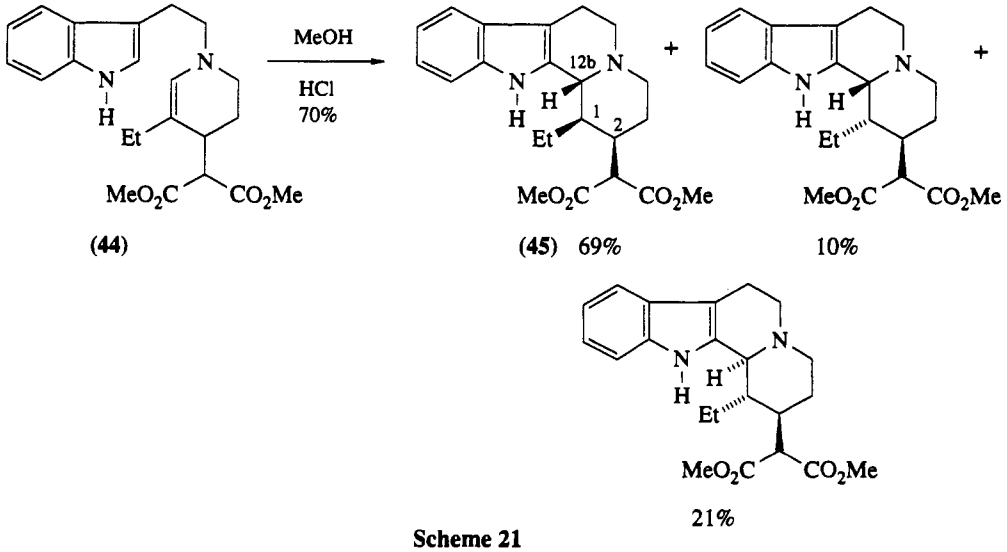


(42) (43) only diastereomer detected

Scheme 20

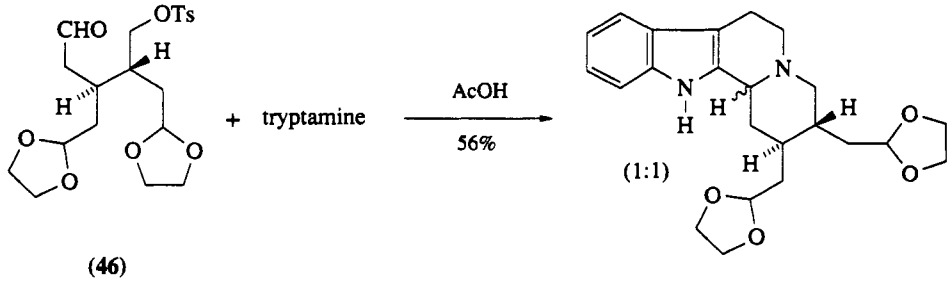


enamine face opposite to the C-2 malonyl substituent. Once set, the C-1 ethyl group relegates nucleophilic approach of the indole nucleus to a *trans* trajectory. This scenario nicely explains the C-12b/C-1/C-2 relative stereochemistry observed in the major product (**45**).



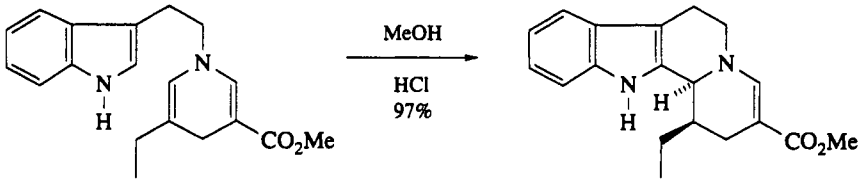
Scheme 21

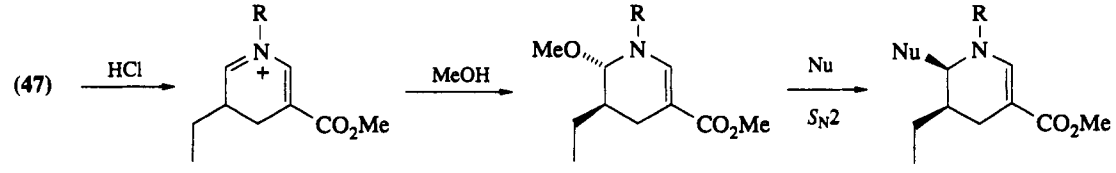
A stereorandom cyclization is reported to result from the reaction of tosyl aldehyde (**46**) with tryptamine.[46] This outcome would be expected if Pictet–Spengler cyclization occurred prior to displacement of the tosylate by the N_b nitrogen.



There is an increasing body of evidence which suggests that discrete iminium ions may not intervene in all Pictet–Spengler cyclizations. In particular, the exact nature of the reaction environment can markedly affect the outcome of Pictet–Spengler cyclizations. As an example, treating an anhydrous methanolic solution of dihydropyridine (**47**) with hydrogen chloride gas affords a 97% yield of indoloquinolizine (**48**) as a single diastereomer.[47] Note the exclusive formation of the *cis* C-12b/C-1 stereoisomer; none of the expected *trans* diastereomer was detected (equation 5). The authors explain these results in terms of an exocyclic cyclization, involving tetrahedral intermediate (**50**), in which a methoxy group (from the solvent) is oriented *trans* to the ethyl side chain. A cyclization with S_N2 character would then lead to the observed C-12b/C-1 *cis* relative stereochemistry. The low stability of the inter-

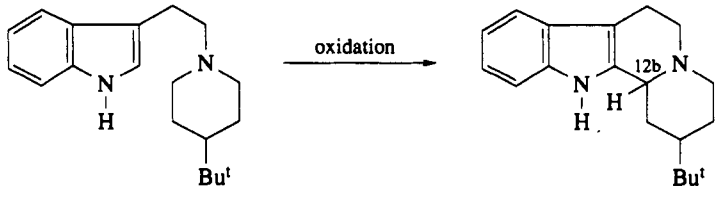
mediate iminium ion (**49**), by virtue of its vinylogous carbamate disposition, may contribute to these anomalous results (Scheme 22).





Scheme 22

In some cases the method of iminium ion generation may have a profound influence on the diastereoselectivity of the resulting cyclization. Cyclization of amine (**51**) by the Polonovsky–Potier method affords the expected C-12b/C-2 *trans*-indoloquinolizine (**52**).[48] In contrast, mercury(II) acetate oxidation of the same amine affords a 60:40 ratio of the *trans* (**52**) and *cis* (**53**) products respectively in 50% yield (Scheme 23). The authors suggest that this discrepancy may be reflective of the relative nucleophilicity of the two counterions. In the Polonovsky–Potier cyclization the relatively non-nucleophilic trifluoroacetate counterion allows the intermediacy of a discrete iminium ion and hence diastereoselection is governed by stereoelectronic determinants. However, mercury(II) acetate oxidation generates a more nucleophilic acetate counterion, which may add to the iminium ion, producing an α-acetoxyamine in equilibrium with the iminium ion. Cyclization of these different intermediate species may explain the formation of the C-12b/C-2 diastereomers. This variance in diastereoselection that is dependent upon the method of amine oxidation has been observed in other systems as well.[49,50]



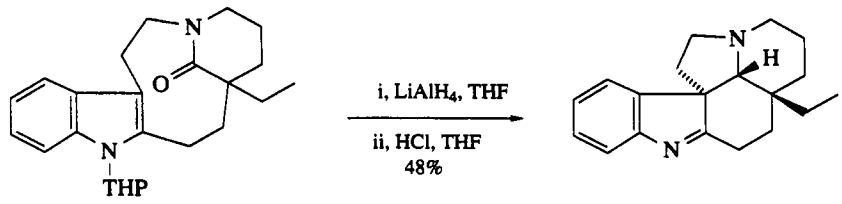
Oxidant	*Yield*
i, H_2O_2; ii, TFAA	30% (**52**)
$Hg(OAc)_2$	50% 60:40 (**52**):(**53**)

Scheme 23

4.4.2.3.3 Various indole alkaloids

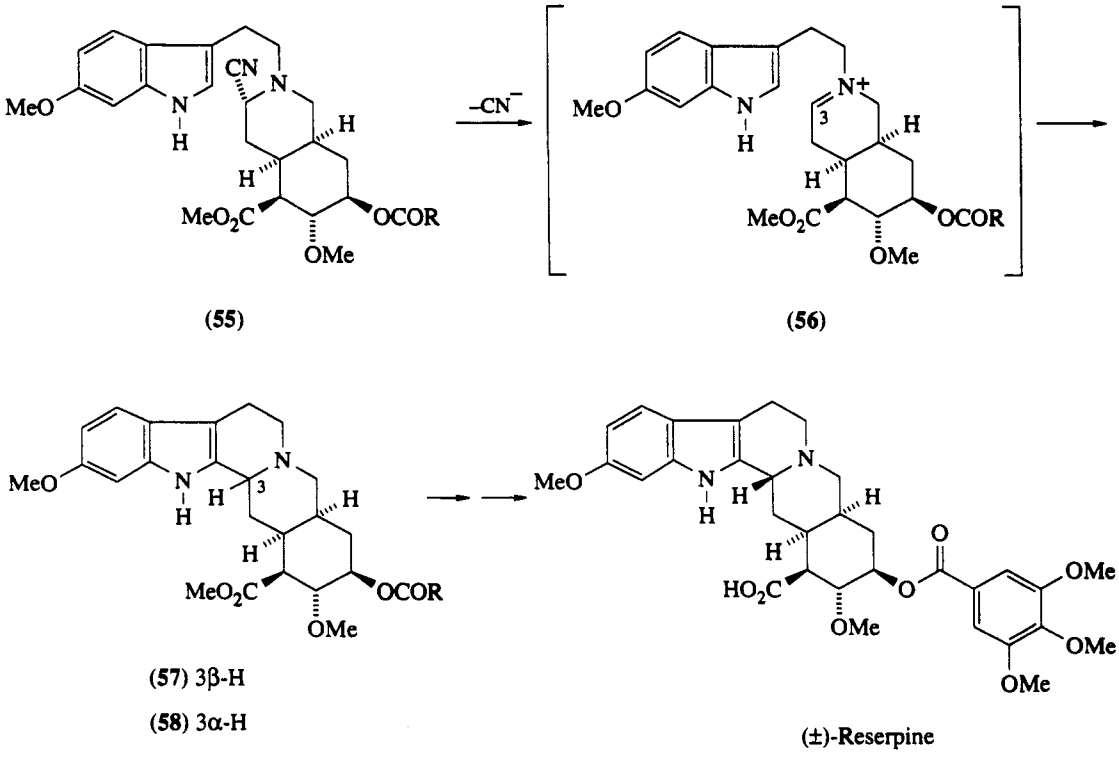
For years, iminium ion–arene cyclizations have punctuated the construction of members of many classes of indole alkaloids.[51] Cyclizations in these more complex cases often proceed with excellent effi-

ciency and with better levels of stereocontrol than similar conversions in simpler systems, presumably reflecting restricted conformational possibilities in the former cases. To illustrate, lithium aluminum hydride reduction of amide (**54**) provides an intermediate hemiaminal, which upon acid treatment dehydrates to the iminium ion and cyclizes to afford the *Aspidosperma* ring system (equation 6).[52]



(54) (6)

As a last example, the concluding stage of Stork and coworkers' recent total synthesis of (±)-reserpine is summarized in Scheme 24.[49] It was expected that the reserpine stereochemistry at C-3 would evolve directly from engagement of the methoxyindole nucleophile from the convex face of the *cis*-hydroisoquinolinium ion intermediate (**56**). Such a tactic would obviate having to invert this stereocenter as was required when the order of introducing the hydrogen and indole substituents at C-3 was reversed, as in Woodward's original total synthesis.[53] In accordance with this expectation, treatment of (**55**) with $AgBF_4$ in acetonitrile led stereoselectively to (**57**), a pentacycle readily converted to (±)-reserpine. In striking contrast, these workers report that direct cyclization of (**55**) in refluxing acetonitrile affords the epimeric product (**58**). This latter, unexpected stereochemical outcome is rationalized as resulting from backside attack of the indole moiety on an iminium cation–cyanide anion ion pair intermediate.



(55) (56)

(57) 3β-H

(58) 3α-H

(±)-Reserpine

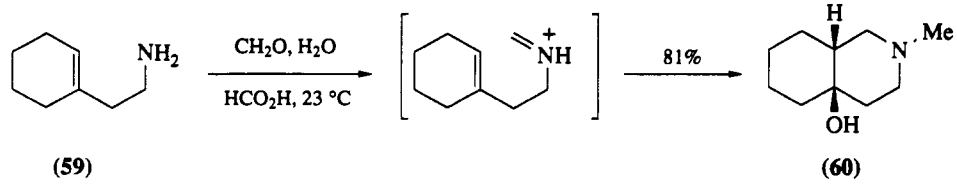
Scheme 24

4.4.2.4 Alkenes

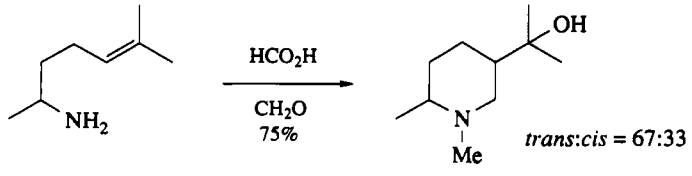
Most π-nucleophiles employed in iminium ion cyclizations have a predetermined postcyclization destiny. For example, aromatic terminators will rearomatize, organosilanes will eliminate silicon through anticipated pathways and acetals and enol ethers will produce carbonyl compounds. However, the cyclizations of simple alkenes have supplied products that are the formal results of eliminations, additions and Wagner–Meerwein rearrangements. Almost exclusively Mannich-type cyclizations of unsaturated amines have been employed to prepare piperidines.

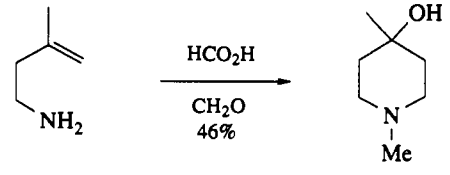
4.4.2.4.1 Monocyclizations

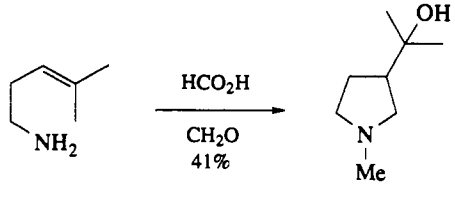
Early examples, due to Grewe, dealt with the formation of hydroisoquinolines from the reaction of aldehydes with cyclohexenylethylamine and its derivatives.[54] The *cis* stereochemistry of the 10-hydroxydecahydroisoquinoline (**60**) produced from treatment of (**59**) with formaldehyde and formic acid demonstrates that the alkene participant undergoes *trans* addition.[55,56]



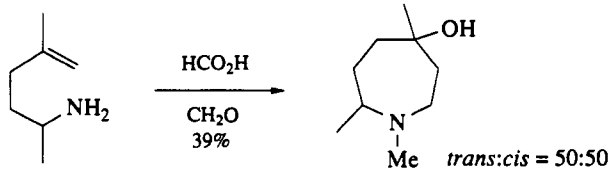
(**59**) (**60**)





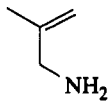


(**61**)

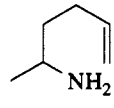


Scheme 25

Iminium ion–alkene cyclizations accomplished under standard Eschweiler–Clarke methylation conditions have been employed to prepare five-, six- and seven-membered azacycles (Scheme 25).[57,58] It is important to note that under identical conditions amines (**62**) and (**63**) did not cyclize but afforded the corresponding *N,N*-dimethylamines. With regard to the alkene participant these results are in full accord with Baldwin's rules for ring formation.[2] However, the formation of pyrrolidine (**61**) demonstrates that 5-*endo*-trig cyclizations[2] can take place with respect to the iminium ion π-participant. The observed regioselectivity and the failure of (**63**) to cyclize are in accord with obligatory formation of an intermediate with tertiary carbocation character.

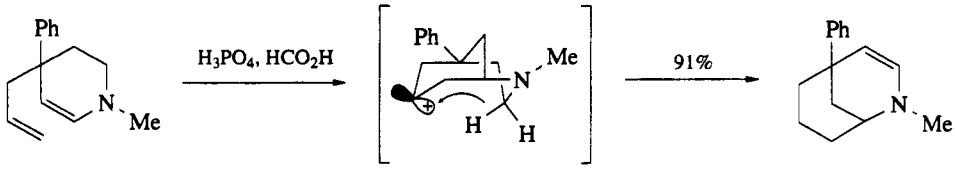


(**62**)

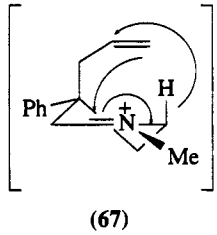


(**63**)

An iminium ion–alkene cyclization has been employed to assemble the phenylmorphan ring system (Scheme 26).[59] The conversion of enamine (**64**) to (**66**) was suggested to arise by 1,5-hydride migration of an initially formed bicyclic cation (**65**). Direct intramolecular ene cyclization of the iminium ion (**67**) produced by protonation of (**64**) provides an alternative rationale for the net *cis* addition to the terminal alkene that occurs in this transformation, and avoids postulating the intervention of a relatively unstable fully formed secondary carbocation.



(**64**) (**65**) (**66**)

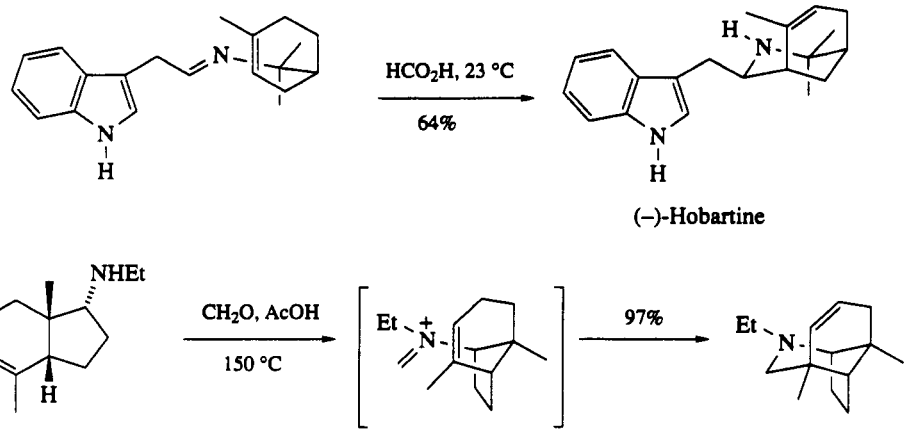


(**67**)

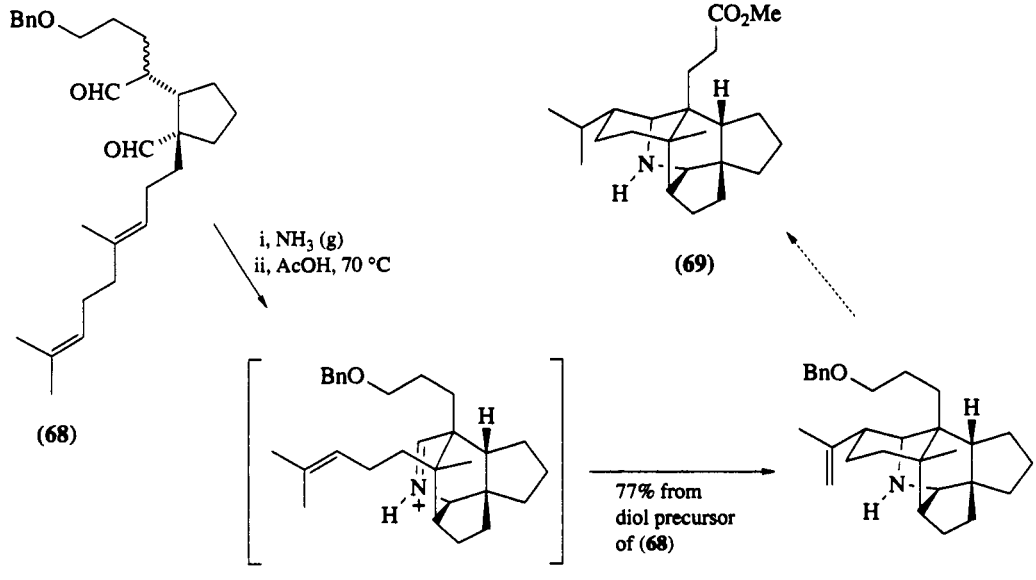
Scheme 26

A variety of polycyclic skeletons containing the azabicyclo[3.3.1]nonane ring system have been accessed by employing alkenic π-nucleophiles in iminium ion initiated cyclizations.[60–63] These reactions are conducted in relatively non-nucleophilic solvents and hence afford alkenic products in good yields (Scheme 27). A dramatic example is provided in Heathcock and coworkers' synthesis of (±)-methyl homosecodaphniphyllate (**69**).[63] The key cyclization reaction of dialdehyde (**68**) and ammonia forms four of the five rings of the *Daphniphyllum* alkaloid target in exceptional yield. The high yields and high regioselectivities for forming a single alkene product in cyclizations such as those illustrated in Schemes 27 and 28 have led some authors to suggest a pericyclic 'ene' mechanism for the cyclization step.[61,62] We note that the results of these cyclizations are explained equally well by stepwise cyclizations to form tertiary carbocation intermediates, followed by the tertiary amine thus produced—in the capacity of a general base—removing the most accessible hydrogen β to the carbocationic center.

On the other hand, the $SnCl_4$-promoted cyclization of imine (**70**) to provide the methylenecyclohexane (**71**) is well rationalized as proceeding in a concerted manner as illustrated in Scheme 29.[64] None of the thermodynamically more stable endocyclic double bond isomers were observed in the crude product—a result inconsistent with the formation of a fully developed tertiary carbocation intermediate. The alterna-

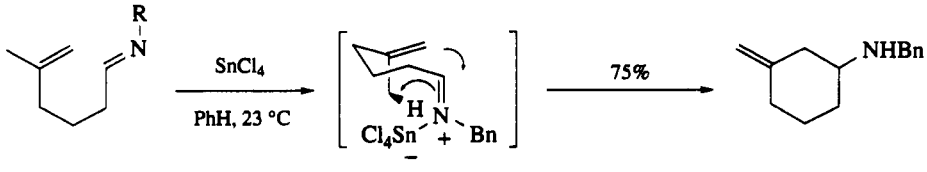


Scheme 27



Scheme 28

tive stepwise sequence, proceeding *via* a fully formed tertiary cation which then suffers intramolecular general base assisted deprotonation by the amine substituent, is not geometrically feasible in this case. The related cyclization of the chiral imine (**72**) proceeded with low diastereoselectivity.[65]

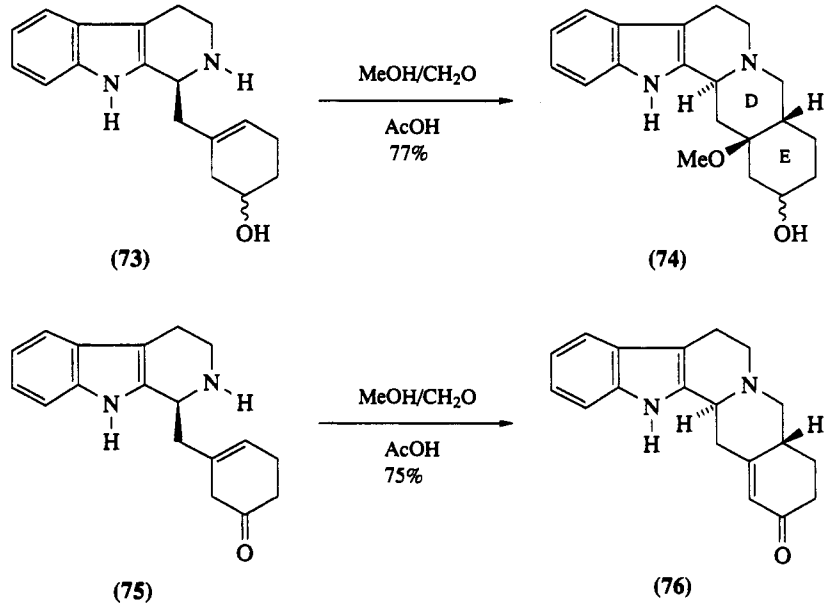


(**70**) R = Bn
(**72**) R = (*S*)-CHMePh

(**71**)

Scheme 29

In contrast, when the stereogenic center is contained within the tether connecting the reacting partners, high levels of stereoinduction can be realized. For example, reaction of optically active amines (**73**) with an acidic methanolic formaldehyde solution proceeded with high stereoselectivity to provide the epimeric pentacyclic alcohols (**74**; Scheme 30).[66] The *cis* D/E-ring junction would be expected, based on earlier work (*vide supra*).[56] It is of interest that cyclization of optically active amine (**75**) under similar conditions afforded racemic (**76**),[66,67] a result perhaps rationalized by enone (**76**) undergoing ready retro-Mannich unraveling.



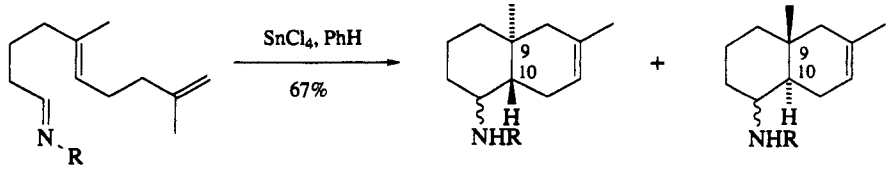
(**73**) (**74**) (**75**) (**76**)

Scheme 30

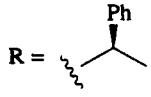
Related cyclizations of alkenes and electrophilic iminium ion intermediates such as *N*-tosyliminium[68,69] and iminomalonate salts,[70,71] although outside the scope of this chapter, have been employed for assembling a variety of azacyclic materials.

4.4.2.4.2 Polycyclizations

The feasibility of cyclizing polyenes with iminium ion initiators has received only scant attention.[64,72] Cyclization of imine (**77**) under aprotic conditions with $SnCl_4$ affords predominantly *trans*-decalins containing endocyclic unsaturation. This mixture was deduced by ^1H NMR analysis to contain diastereomers (**78**) to (**81**) in the indicated abundances as depicted in equation (7). The extent of asymmetric induction in forming the decalin ring system (9*S*,10*S*:9*R*,10*R* = 61:39) is significantly lower than that of related cyclizations of chiral acetal substrates.[73]



(7)

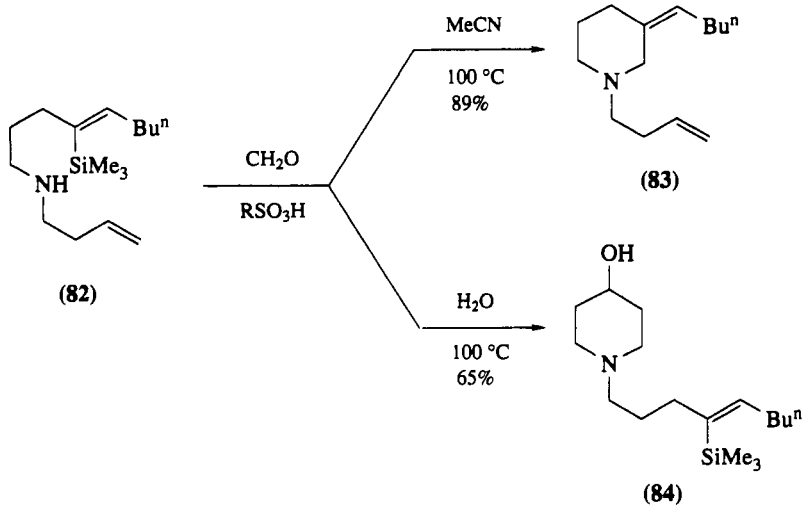
(**77**) R = 

(**78**) α-NHR 14% (**80**) α-NHR 10%

(**79**) β-NHR 47% (**81**) β-NHR 29%

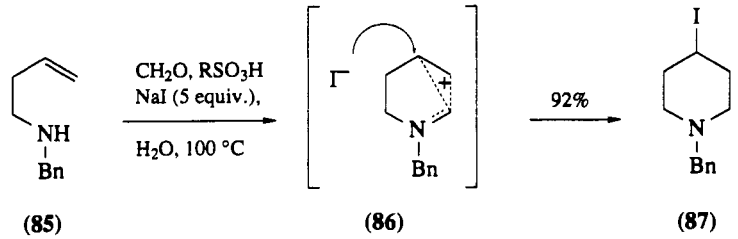
4.4.2.4.3 Importance of reaction medium

A recent report highlights the critical role that reaction medium (primarily counterion and solvent nucleophilicity) can play in determining the outcome of iminium ion initiated cyclizations.[74] In this study the cyclization of the formaldiminium ion derived from amine (**82**), containing disparate π-nucleophiles, was conducted in a variety of solvents (Scheme 31). In acetonitrile the reaction produced pentylidenepiperidine (**83**), resulting from participation of the vinylsilane terminator, as the sole product. Remarkably, relative terminator reactivity is completely reversed by a change of solvent. Thus, identical treatment of (**82**) in water resulted in cyclization with the butenyl group providing 4-hydroxypiperidine (**84**) as the predominant product. Cyclization of (**82**) in acetic or formic acid shows intermediate behavior, providing substantial amounts of products arising from participation of both nucleophilic terminators. It was thus concluded that the reaction of π-nucleophiles whose participation forms relatively unstable carbocationic intermediates will be favored by increases in solvent polarity and reaction medium nucleophilicity. On the other hand, less polar and less nucleophilic reaction conditions will favor participation of π-nucleophiles that afford more-stabilized carbocationic intermediates or intermediates that can dissipate charge in an intramolecular fashion. These studies and others attest that even weak π-nucleophiles, such as terminal vinyl groups, can effectively participate in iminium ion cyclizations provided that the reaction medium is sufficiently nucleophilic.[75,76]



Scheme 31

Halide anions have also been employed to facilitate the cyclization of weakly nucleophilic terminal vinyl π-nucleophiles. For example, the butenylamine (**85**) undergoes Mannich cyclization in the presence of excess NaI to provide the 4-iodopiperidine (**87**) in excellent yield.[74] The success of this cyclization should be contrasted with the failure of related amines to cyclize in formic acid with formaldehyde (Scheme 25). A detailed study[74] of the effect that nucleophile concentration has on the outcome of Mannich cyclizations provides definitive evidence that the cyclization of iminium ions with alkenes is not a concerted process, but rather proceeds *via* a cationic intermediate capable of partitioning between product formation and reversal to the starting iminium ion. A bridged cation or π-complex, *e.g.* (**86**) in equation (8), is a reasonable description of this intermediate.

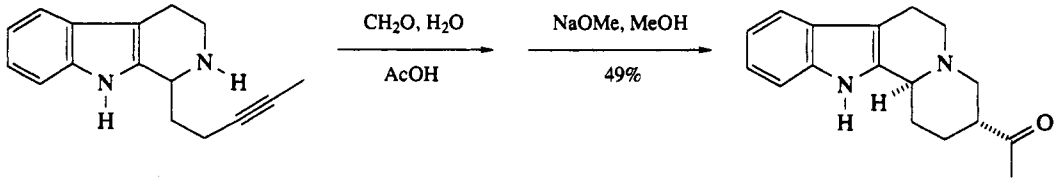


(8)

4.4.2.5 Alkynes

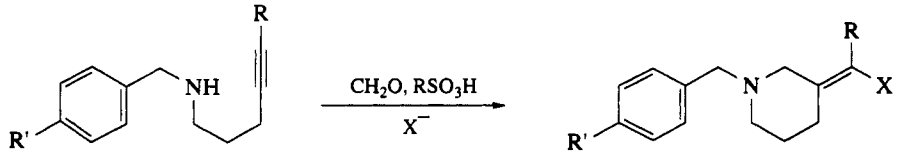
Successful cyclization reactions of alkynes with weakly electrophilic iminium ions requires the presence of strong external nucleophiles. The only study to date which addresses the nature of useful cyclization promoters indicates that nonbasic nucleophiles with nucleophilic constants η-MeI > 5.8 are required.[77]

The first example of a successful iminium ion–alkyne cyclization appeared in 1977.[67] The 4-alkynylamine (**88**) was cyclized in acidified aqueous formaldehyde to a mixture of indoloquinolizidine ketones which could be equilibrated in base to provide the more stable epimer (**89**) in 49% yield. Not surprisingly, the six-membered ring was formed exclusively.



(**88**) (**89**)

The formaldiminium ion formed from the reaction of 4-hexynylamine (**90**; R = R′ = Me) with paraformaldehyde and camphorsulfonic acid is reported not to cyclize when heated for 1 h at 100 °C in the weakly nucleophilic solvent acetonitrile. However, when nucleophilic salts are added the 3-alkylidenepiperidines (**91**) are formed in good yields (Scheme 32).[77] Attempted cyclizations of (**90**) in the presence of weaker nucleophiles such as benzenethiol or methanol were less effective, the former yielding <15% of the expected alkylidenepiperidine product, while the latter provided no products of cyclization. If the strong nucleophile iodide is employed, even a weakly nucleophilic terminal alkyne can be successfully cyclized. In all of these cyclizations of 4-alkynylamines only formation of a six-membered ring product was observed. The (*Z*)-stereochemistry of the alkylidene side chain evolves from antarafacial addition of the internal iminium cation and the external nucleophile to the alkyne.



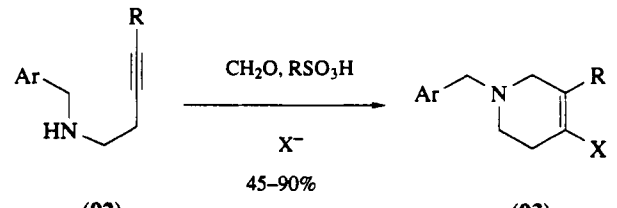
(**90**) (**91**)

R′	*R*	*X*	*Yield (%)*
OMe	Me	Br	89
OMe	Me	I	80
H	Me	N_3	72
H	Me	SCN	82
OMe	H	I	56
OMe	Me	SPh	<15

Scheme 32

A study of 3-alkynylamines (**92**) addressed the question of endocyclic *versus* exocyclic ring closure in nucleophile-assisted alkyne cyclizations (equation 9).[77] Cyclizations of the formaldiminium ion derived from (**92**) occurred only in the endocyclic sense affording tetrahydropyridines (**93**). Terminal as well as substituted alkynes were observed to react with endocyclic regioselectivity in the presence of a variety of nucleophiles.

The utility of stereospecific nucleophile-induced iminium ion–alkyne cyclizations that proceed in the exocyclic mode was recently demonstrated by Overman and coworkers in efficient enantioselective total syntheses of the *Dendrobatid* alkaloids (+)-pumiliotoxin A and (+)-allopumiliotoxin 323B′.[78,79] The piperidine ring and 6-alkylidene side chain of these alkaloids were stereospecifically generated in good



(9)

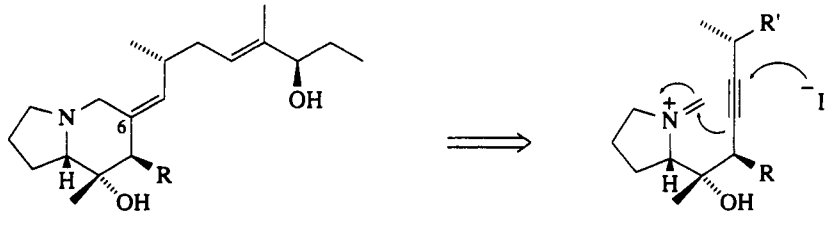
(92)

Ar = 4-methoxyphenyl

(93)

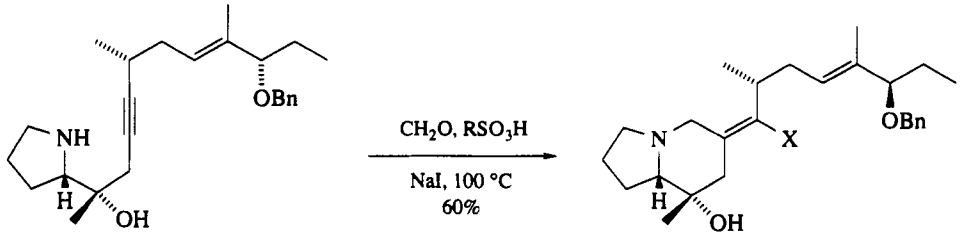
R	*X*
Me	I, Br, N_3
H	I
$SiMe_3$	I, Br

yield by the iodide-promoted cyclization of iminium ion intermediate (**94**), depicted in Scheme 33. The key cyclization step to form (+)-pumiliotoxin A was accomplished by treating alkynylamine (**95**) with formaldehyde, camphorsulfonic acid and excess NaI in H_2O at 100 °C to provide (**96**) in 60% yield (Scheme 33). Subsequent halogen/metal exchange with BuLi and protonolysis of the resulting lithium reagent afforded (**97**). Debenzylation of (**97**) then provided (+)-pumiliotoxin A in 10% overall yield from L-proline. The two-step conversion of (**95**) to (**97**) is the equivalent of a 'reductive' iminium ion–alkyne cyclization in which the iminium carbon and an external hydride are added in an *anti* fashion to the starting alkyne.



(+)-Pumiliotoxin A; R = H
(+)-Allopumiliotoxin 323B'; R = OH

(94)

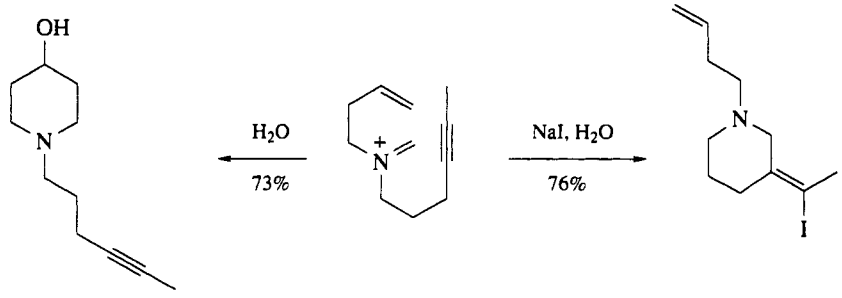


(95)

(96) X = I
(97) X = H

Scheme 33

The pronounced sensitivity of alkynes to cyclization in the presence of external nucleophiles is illustrated in studies of formaldiminium ion (**99**) in which an alkyne and alkene compete as intramolecular π-nucleophiles.[77] While cyclization of (**99**) in water afforded 4-hydroxypiperidine (**98**) in 73% yield, cyclization in the presence of 10 equiv. of NaI gave vinyl iodide (**100**) in 76% yield (Scheme 34). It has been suggested that the mechanism of these nucleophile-promoted iminium ion–alkyne cyclizations probably involves rate-determining attack of the nucleophile on a π-complex or bridged cation produced from reversible interaction of the iminium ion and alkyne groups.[77]



(98) (99) (100)

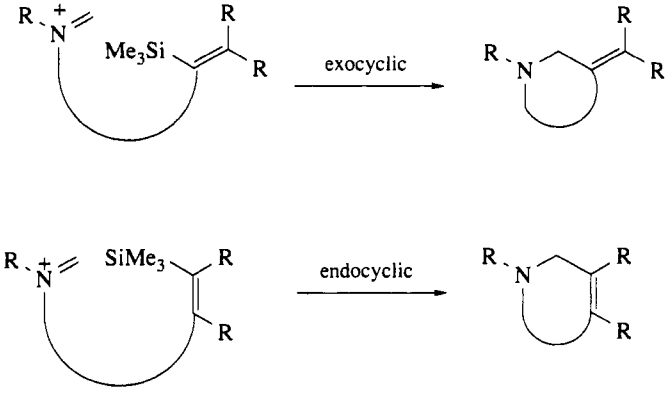
Scheme 34

4.4.2.6 Organosilanes

In less than 10 years, organosilanes have emerged as an unusually versatile class of nucleophiles for terminating Mannich-type cyclizations. Their utility derives from the ability of the silicon substituent to control the regioselectivity of bond formation and dictate the postcyclization destiny of the carbenium ion intermediate produced upon cyclization. The characteristics of silicon that are responsible for this exceptional control have been discussed in several recent reviews.[80–82]

4.4.2.6.1 Vinylsilanes

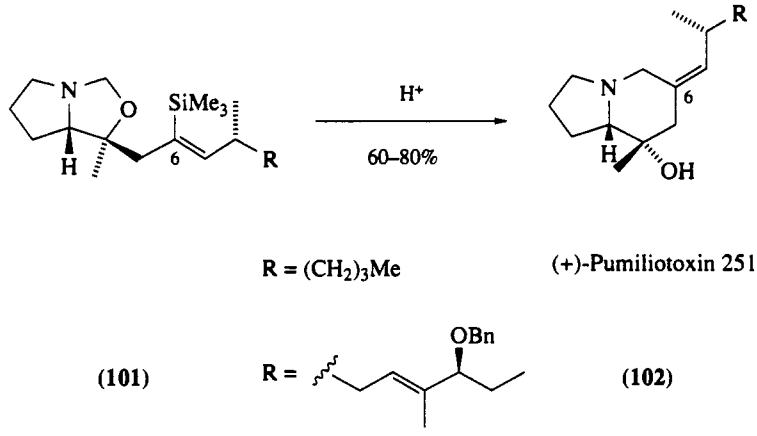
Towards electrophiles, the reactivity of vinylsilanes is similar to that of the corresponding alkene. However, incorporating a silicon substituent at the vinylic carbon of a π-nucleophile markedly affects the cyclization outcome. Specifically, iminium ion–vinylsilane cyclizations occur cleanly to substitute, preferentially with retention of double-bond configuration, the iminium ion carbon for the silyl substituent. Both endocyclic and exocyclic modes of intramolecular electrophilic substitution have been demonstrated (Scheme 35).



Scheme 35

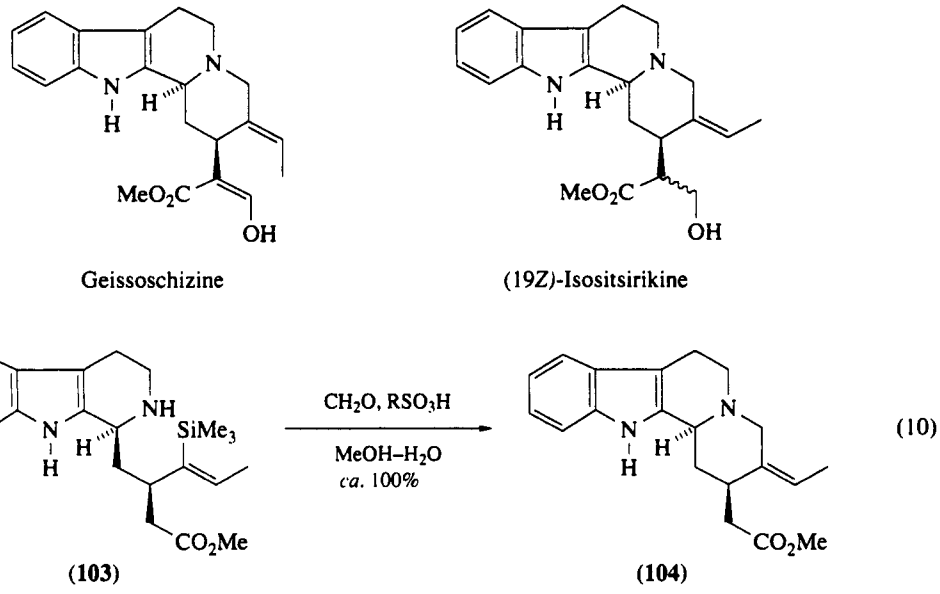
Mannich-type cyclizations of vinylsilanes have found considerable application in the area of alkaloid total synthesis.[81] Cyclizations that occur in the exocyclic mode with respect to the vinylsilane nucleophile have been widely employed to assemble 3-alkylidenepiperidine substructures with high stereocontrol. Overman and coworkers have made extensive use of the acid-promoted conversion of bicyclic oxazolidines to alkylideneindolizidines in their total syntheses of pumiliotoxin A alkaloids (Scheme 36).[83–85] An illustration of the mild nature of iminium ion–vinylsilane cyclizations is provided in the conversion of (**101**) to (**102**), the penultimate precursor of (+)-pumiliotoxin A. This conversion was accomplished in 71% yield by heating (**101**) at 80 °C in a methanolic pyridine–pyridinium tosylate buffer (pH ≈ 4.5). More strongly acidic conditions had to be avoided since they led to competitive solvolysis of the allylic benzyl ether functionality of the pumiliotoxin A side chain. To the limits of detection by high

field NMR and GC, the formation of (**102**) and pumiliotoxin 251D occurred with complete retention of configuration at C-6.

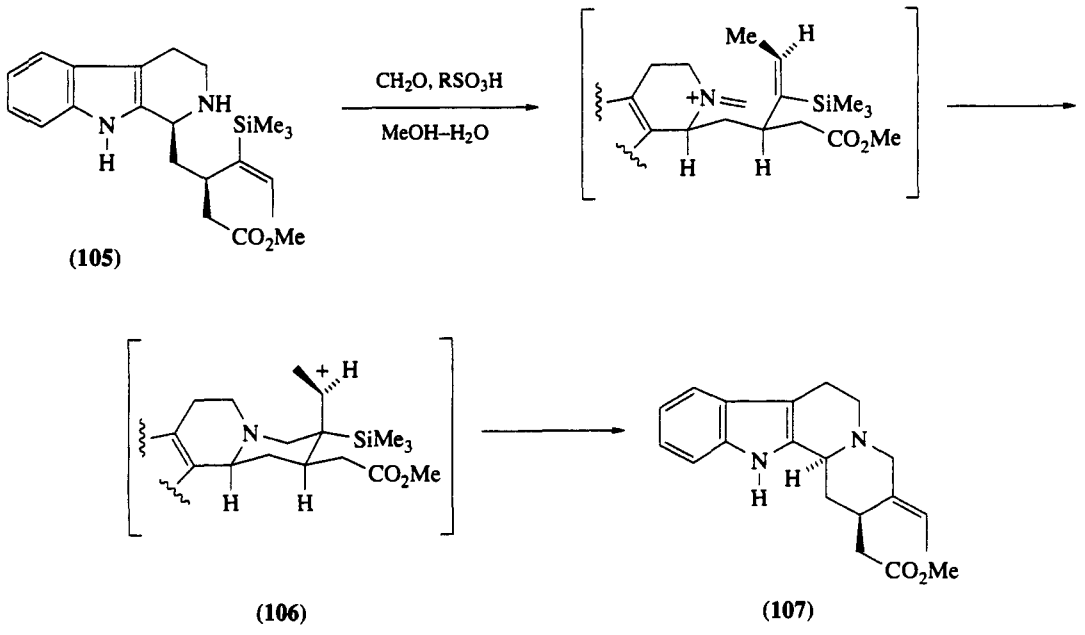


Scheme 36

The stereocontrolled formation of exocyclic double bonds by stereospecific iminium ion–vinylsilane cyclizations has also been employed by Overman and coworkers as the key step in total syntheses of *Corynanthe* alkaloids.[7,86] The crucial cyclization step in the synthesis of (±)-(19*Z*)-isositsirikine is shown in equation (10). The (*Z*)-vinylsilane (**103**) cyclizes in 1:1 methanol–water to provide, in essentially quantitative yield, the (*Z*)-ethylideneindoloquinolizidine (**104**).

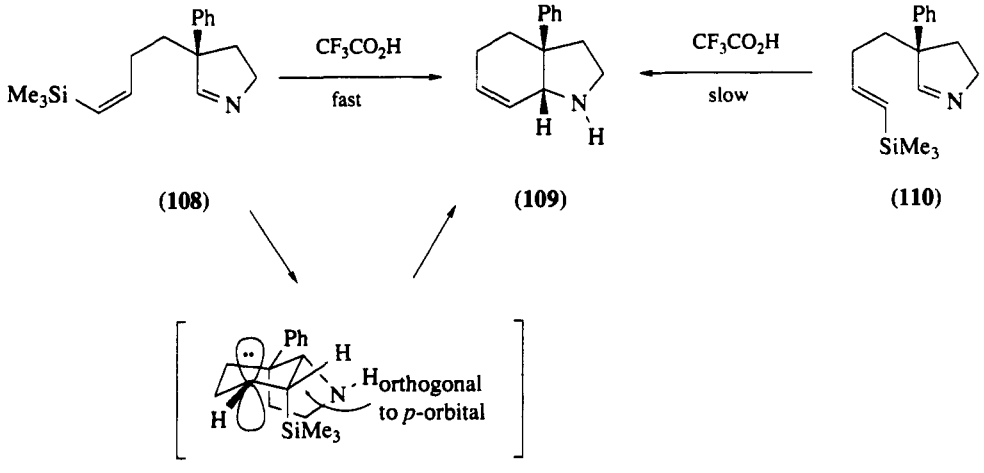


In contrast, the stereospecificity of the conversion of (*E*)-vinylsilane (**105**) to (**107**), the key step in the total synthesis of (+)-geissoschizine, was highly solvent dependent (Scheme 37). Stereospecificity was considerably higher when silylphilic solvents (MeOH, H_2O) or additives such as NaF were employed. Under optimum conditions the conversion of (**105**) to methyl geissoschizoate (**107**) occurred with 9:1 stereoselectivity and provided enantiomerically pure (**107**) in 80% yield.[7] The lower degree of sterospecificity observed in the cyclization of the (*E*)-stereoisomer was attributed to different lifetimes for the respective β-silyl cation intermediates. The serious steric interaction that would develop between the vinyl methyl group and the acetic acid side chain (an $A^{1,3}$ interaction)[12] if intermediate (**106**) transferred its $SiMe_3$ group to a nucleophile prior to ring inversion is believed to be responsible for the partial erosion of stereochemical integrity in the conversion of (**105**) to (**107**).[7]

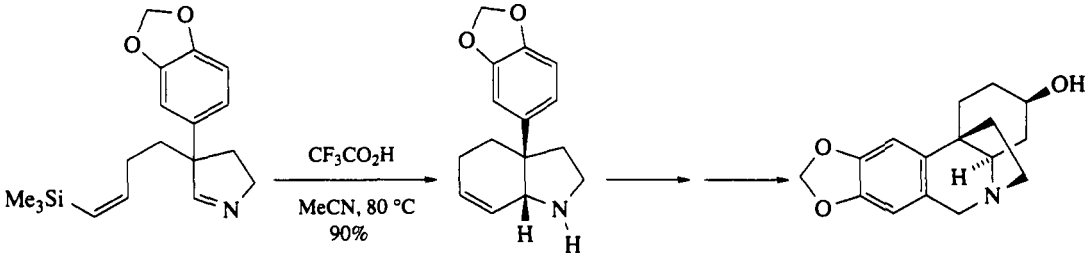


Scheme 37

Cyclizations that are endocyclic with respect to the vinylsilane nucleophile have been employed to prepare *Amaryllidaceae* alkaloids.[87] An important stereochemical consideration in the use of a vinylsilane nucleophile in an endocyclic cyclization is illustrated by the disparate behaviors of (**108**) and (**110**). It was found that (*Z*)-vinylsilane (**108**) cyclizes to *cis*-hexahydroindole (**109**), when treated with 1 equiv. of CF_3CO_2H, at a rate that is at least 7000 times greater than that of the (*E*)-stereoisomer (**110**). This rate difference is thought to reflect the importance of σ–π hyperconjugative stabilization in the cyclization transition state. Only the (*Z*)-isomer (**108**) can cyclize to initially form a cationic intermediate in which the β-C—Si σ-bond is oriented coplanar with — and thus able to stabilize maximally — the developing vacant *p*-orbital (Scheme 38). The utility of this type of cyclization was demonstrated in Overman and Burk's total synthesis of the *Amaryllidaceae* alkaloid (±)-epielwesine.[87] The exigent step in this construction is the iminium ion–vinylsilane cyclization of (*Z*)-vinylsilane imine (**111**), which proceeded in 90% yield. *cis*-Hexahydroindole (**112**) was hydrated then cyclized under Pictet–Spengler conditions affording the target alkaloid (Scheme 39).

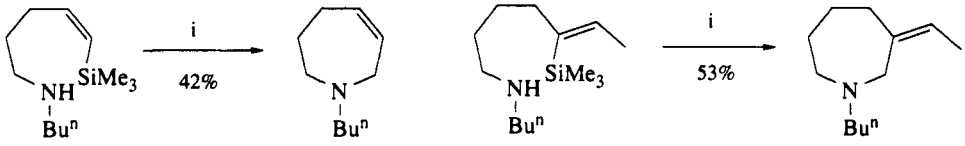


Scheme 38



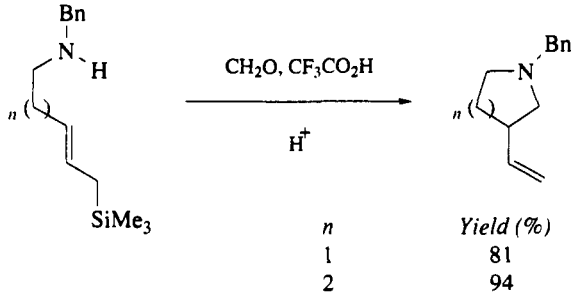
(111) **(112)** (±)-Epielwesine

Scheme 39

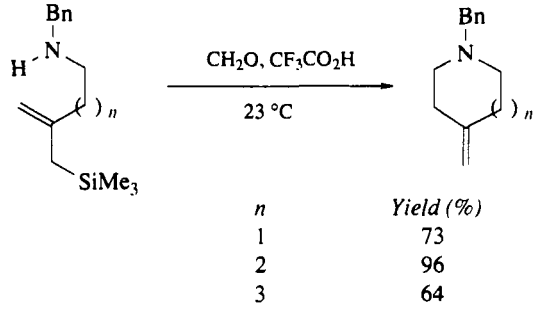


i, CH_2O (excess), camphorsulfonic acid (0.95 equiv.), MeCN, 80 °C

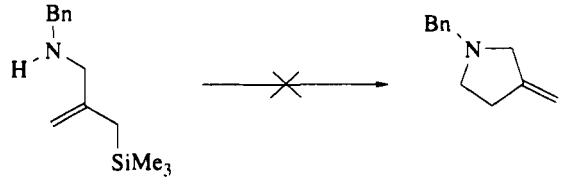
Scheme 40



n	*Yield (%)*
1	81
2	94



n	*Yield (%)*
1	73
2	96
3	64



(113)

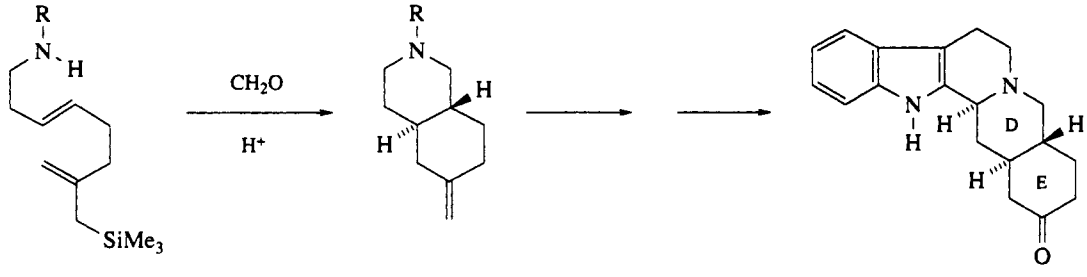
Scheme 41

The use of iminium ion–vinylsilane cyclizations for forming azacyclic rings other than six-membered has received little attention.[82,88] Examples of forming azepines containing either endocyclic or exocyclic unsaturation are shown in Scheme 40.

4.4.2.6.2 Allylsilanes

A number of Mannich-type cyclizations that proceed in an exocyclic mode with respect to the allylsilane terminator have been reported. In this way, five-, six-, seven- and eight-membered azacycles are accessed in good yields.[89] In keeping with Baldwin's suggestion concerning ring closure aptitudes,[2] the iminium ion derived from amine (**113**) could not be cyclized (Scheme 41).

The synthesis of (±)-yohimbone by Grieco and Fobare illustrates the use of an allylsilane to terminate an iminium ion initiated polyene cyclization.[90] The D/E-ring system of the target alkaloid was assembled by treating diene amines (**114**) with formaldehyde and CF_3CO_2H in aqueous THF to give (**115**) in good yield. Only the *trans*-hydroisoquinoline stereoisomer was produced (Scheme 42).

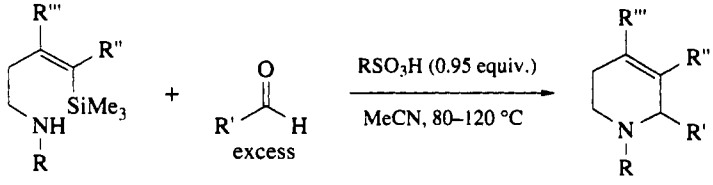


(**114**) (**115**) (±)-Yohimbone

R = Bn 80%
R = *N*-tosyltrytophyl 63%

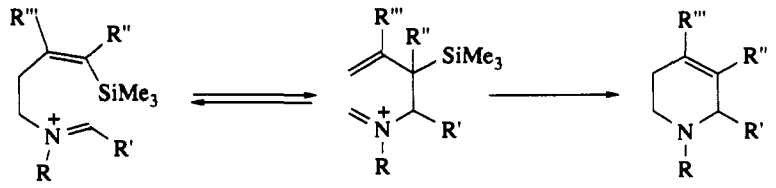
Scheme 42

A variety of tetrahydropyridines have been prepared with complete regiocontrol by the reaction of 4-(trimethylsilyl)-3-butenylamines with aldehydes and acid (Scheme 43).[88] This reaction, although ostensibly an iminium ion–vinylsilane cyclization, is believed to occur by the pathway illustrated in equation (11), in which ring formation ensues from the allylsilane sigmatropic isomer. Consistent with this mechanism pathway, either the (*E*)- or (*Z*)-vinylsilane amine stereoisomer can be employed.



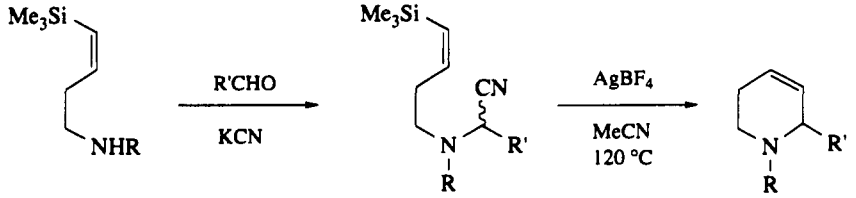
R	*R'*	*R''*	*R'''*	*Yield (%)*
4-Methoxybenzyl	H	H	H	95
4-Methoxyphenyl	H	H	H	85
4-Methoxybenzyl	n-C_6H_{13}	H	H	64
Ph	n-C_6H_{13}	H	H	68
Bu^i	H	H	Me	66
Bu^i	H	H	Ph	83
Pr^n	H	$SiMe_3$	H	82

Scheme 43



(11)

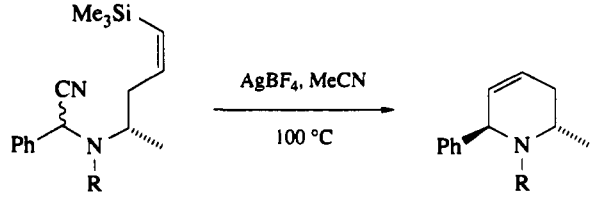
An alternative sequence in which an α-cyanoalkylamine is employed as an iminium ion precursor has also been described (Scheme 44). This two-step alternative is attractive if the aldehyde component is scarce since only one equivalent of the aldehyde is employed.[88]



R	*R'*	*Yield* (%)
Pr^n	CH_2CH_2Ph	73
4-Methoxybenzyl	CH_2CH_2Ph	76
Pr^n	2-Furyl	58
4-Methoxybenzyl	3-Pyridinyl	82

Scheme 44

There is one report of forming 2,6-disubstituted-1,2,5,6-tetrahydropyridines from 4-(trimethylsilyl)-3-butenylamines (equation 12).[91] The *trans* diastereomer is produced with high stereoselectivity only if the nitrogen substituent is an alkyl group. Optically active tetrahydropyridines cannot be prepared in this manner, however, since cyclization of nonracemic (**116**) (from L-alanine) yielded racemic (**117**). Racemization is suggested to derive from both 2-azonia[3,3] sigmatropic rearrangement (equation 11) and iminium ion stereomutation, these being more rapid than the final iminium ion–allylsilane cyclization.[91]



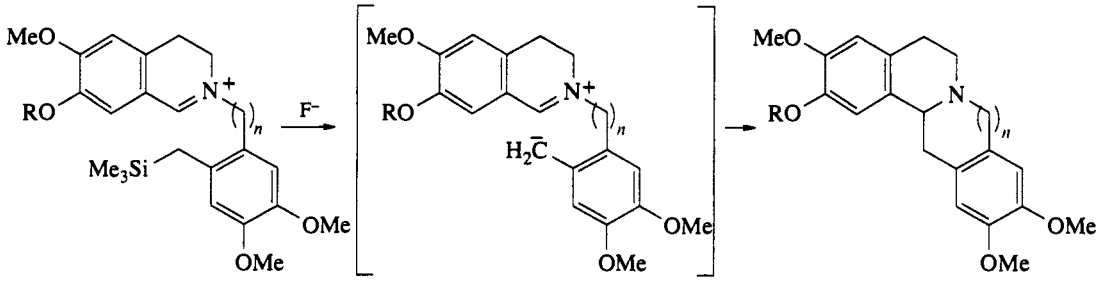
57% R = Bn
51% R = Me

(**116**) (**117**)

(12)

4.4.2.6.3 Benzylsilanes

Fluoride anion promoted cyclizations of benzylsilane dihydroisoquinolinium salts have been employed to form five- and six-membered azacyclic rings (Scheme 45). For example, CsF in either protic (EtOH–H_2O) or aprotic (MeCN) solvents has been used to form the isoquinoline alkaloid (±)-xylopinine (**121**) from (**118**). Yields for this conversion in the range 25–70% have been obtained.[92,93] The *N*-arylisoquinolinium salt (**119**) is reported to cyclize under aprotic conditions only (Bu^n_4NF in refluxing THF) to give (**122**) in 60% yield.[94] A betaine intermediate (**120**) has been proposed for these transformations. The conversion of this intermediate (R = Bn; $n = 0$) to (**122**), formally a 5-*endo*-trig cyclization, can then be formulated as a six-electron electrocyclization. Iminium ion–benzylsilane cyclizations have been accomplished, sometimes with greater efficiency, photochemically (see Section 4.4.3).



(118) R = Me; n = 1
(119) R = Bn; n = 0

(120)

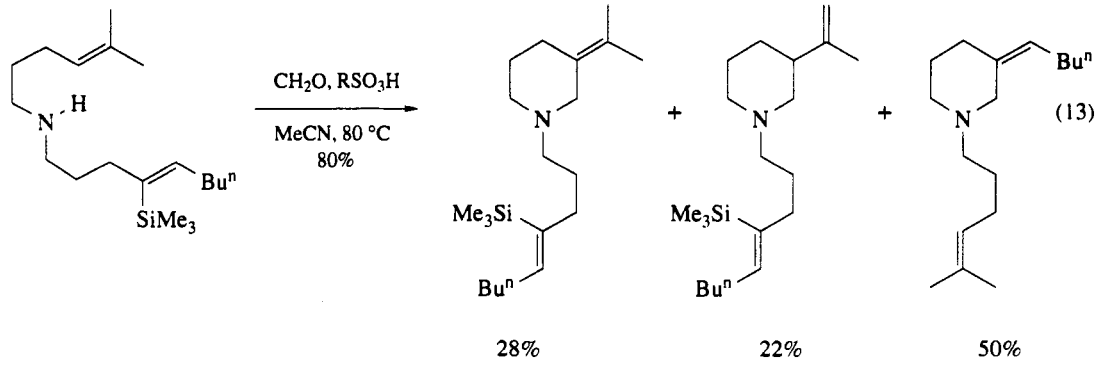
(121) Xylopinine; R = Me; n = 1
(122) R= Bn; n = 0

Scheme 45

4.4.2.7 Relative Reactivities of Intramolecular π-Nucleophiles

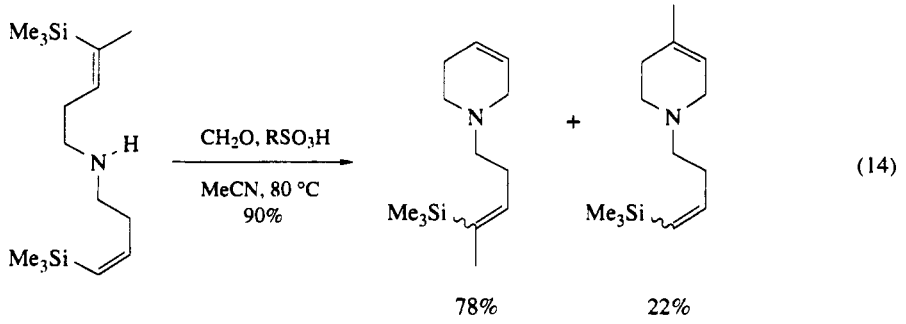
Two of the factors that determine the reactivity of tethered π-nucleophiles in Mannich-type cyclizations have been emphasized: stereoelectronic effects and reaction medium effects. The stereoelectronics of orbital overlaps between the π-nucleophile and the iminium electrophile are best evaluated by considerations such as antiperiplanar addition trajectories and Baldwin's rules for ring formation. The critical importance of the reaction medium has received serious attention only recently. However, it already appears clear that π-nucleophiles that would lead, upon cyclization, to relatively unstable carbocations can have their reactivity markedly increased by carrying out the cyclization in the presence of a nucleophilic solvent or additive which, by nucleophilic participation, can obviate the formation of high energy cyclic carbenium ion intermediates.

The third factor of obvious importance in determining the reactivities of π-nucleophiles is their structure. One recent study examined the relative reactivity of a number of π-nucleophiles in the non-nucleophilic solvent acetonitrile.[95] The approach taken was to order the reactivity of π-nucleophiles from the results of terminator competition experiments such as those shown in equations (13) and (14). The order of terminator reactivity that emerged from this study is summarized in Figure 3. In some cases quantitative comparisons could be made: 3-methyl-3-butenyl (**123**) is twice as reactive as the (*Z*)-4-(trimethyl-



28% 22% 50%

(13)



78% 22%

(14)

silyl)-3-butenyl (**124**); and the (*Z*)-vinylsilane (**125**) is twice as reactive as the (*E*)-stereoisomer (**126**). When they were competed against the (*Z*)-vinylsilane terminator (**125**), no products resulting from participation of the six terminators listed at the bottom of Figure 3 were observed. It should be stressed that this reactivity order pertains only to Mannich-type cyclizations conducted in a non-nucleophilic solvent such as acetonitrile.

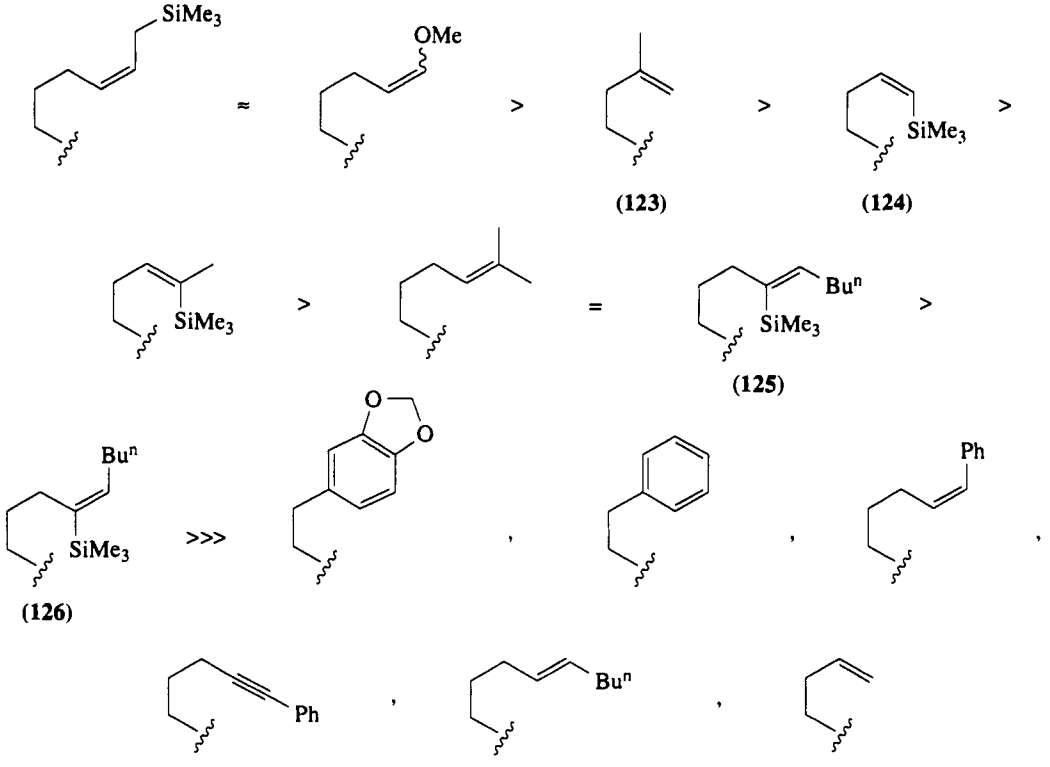


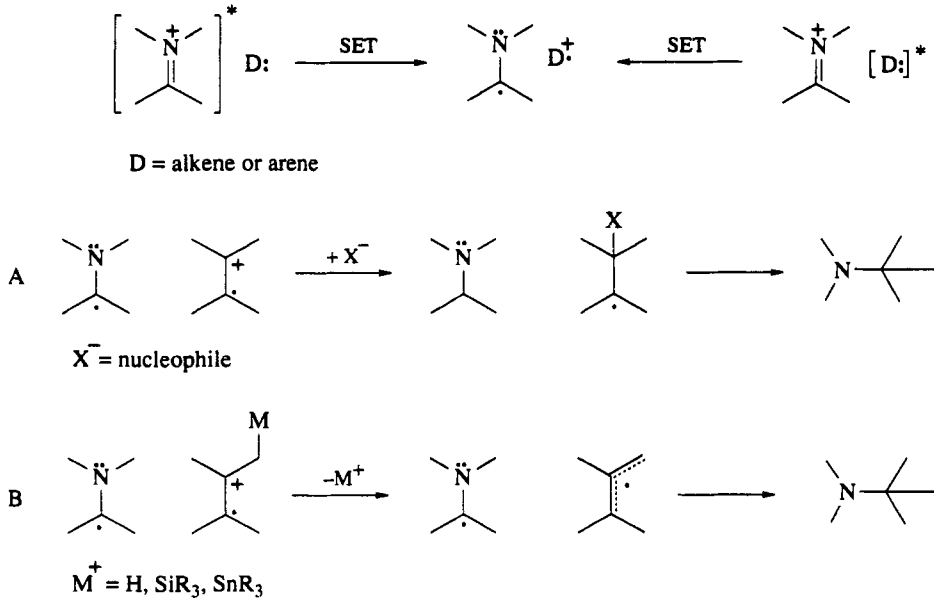
Figure 3 Relative terminator reactivities in acetonitrile

4.4.3 ELECTRON TRANSFER INDUCED PHOTOCYCLIZATIONS

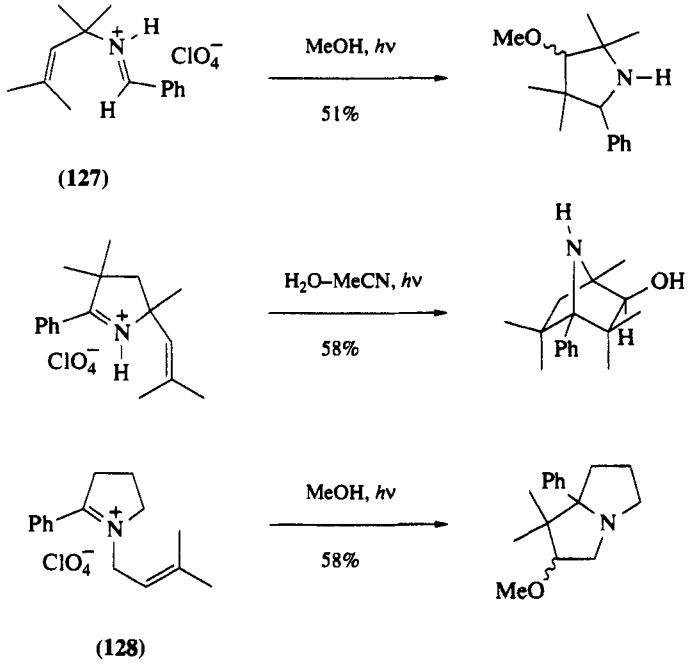
In several instances, Mannich-type cyclizations can be carried out expeditiously under photochemical conditions. The photochemistry of iminium ions is dominated by pathways in which the excited state iminium ion serves as a one-electron acceptor. The photophysical and photochemical ramifications of such single-electron transfer (SET) processes as applied to excited state iminium ions have been expertly reviewed.[96–98] In short, one-electron transfer to excited state iminium ions occurs rapidly from one of several electron donors: electron rich alkenes, aromatic hydrocarbons, alcohols and ethers. Alternatively, an excited state donor, usually aromatic, can transfer an electron to a ground state iminium ion to afford the same reactive intermediates. Scheme 46 adumbrates the two pathways that have found most application in intramolecular cyclizations. Simple alkenes and aromatic hydrocarbons will typically suffer addition processes (pathway A). However, alkenic and aromatic systems with allylic or benzylic groups more electrofugal than hydrogen (*e.g.* silicon, tin) commonly undergo elimination reactions (pathway B) to generate the reactive radical pair.

If the iminium ion and electron donor are tethered, these SET-induced addition reactions can be efficient to the point of synthetic practicality. For example, such photocyclizations have been used to secure reasonable yields of azacycles of monocyclic, bridged and linearly fused topographies (Scheme 47).[99,100] Note that the cyclizations of iminium ions (**127**) and (**128**) occur in an endocyclic mode with respect to both reacting partners. This mode of cyclization has not been observed in related ground state reactions (*vide supra*).

Typically the iminium ion is conjugated, although conjugation is not an absolute prerequisite for a successful cyclization. Perchlorate is selected as the counter anion because it does not offer the possibility of



Scheme 46

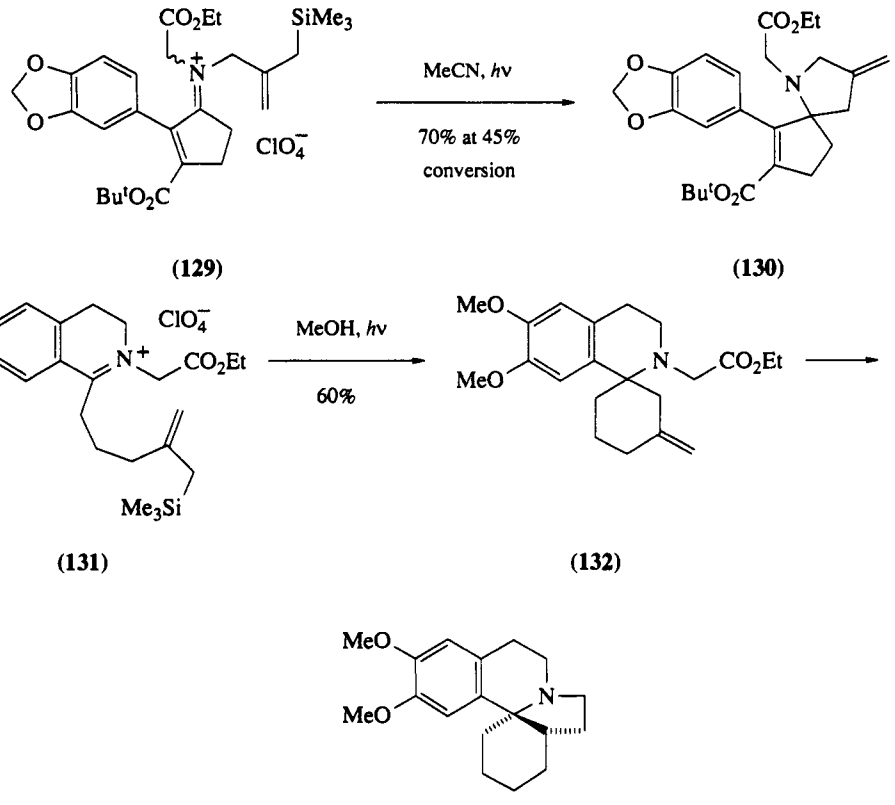


Scheme 47

SET from the counter anion to the excited state iminium salt. In addition, a successful one-electron alkenic donor must be electron rich, in most cases trialkyl substituted.

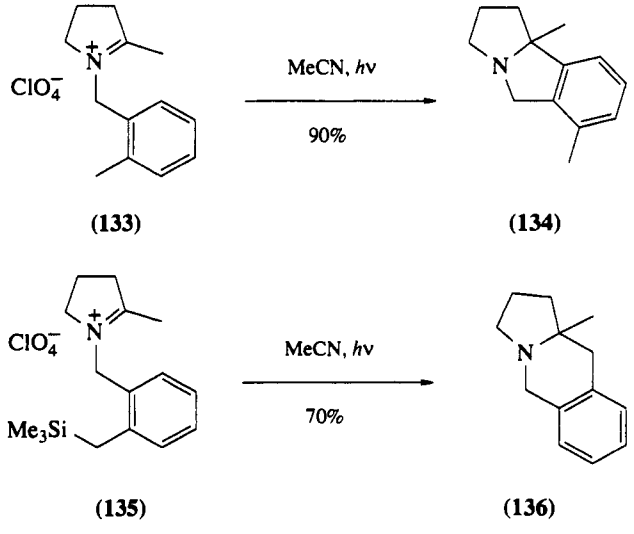
In studies directed toward the synthesis of members of the *Cephalotaxus* alkaloid family, irradiation of allylsilane iminium ion (**129**) provided a 70% yield (at 45% conversion) of spiroazacycle (**130**).[101] It should again be noted that this 5-*endo*-trig cyclization does not occur without photochemical activation (*cf.* Scheme 25).

A related cyclization was recently used by Mariano and coworkers as the key step in a construction of the skeleton of the *Erythrina* alkaloids. Photocyclization of 3,4-dihydroisoquinolinium perchlorate (**131**) afforded a 60% yield of tricycle (**132**; Scheme 48). This spiro tricycle was converted in eight additional steps to 15,16-dimethoxy-*cis*-erythrinan.[102,103]



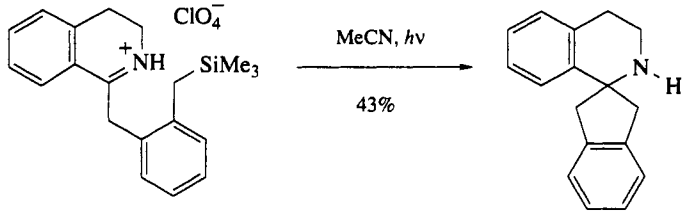
Scheme 48

The electrofugal benzylic trimethylsilyl group will also admirably direct photocyclizations. This directing effect is enunciated in the cyclizations of *N*-xylylpyrrolinium perchlorates (**133**) and (**135**). Upon irradiation in acetonitrile, salt (**133**) is converted to the dimethylbenzopyrrolizidine (**134**) in 90% yield. In comparison, silicon analog (**135**) cleanly photocyclizes at the benzylic site in acetonitrile to yield the benzoindolizidine (**136**; Scheme 49).[104]



Scheme 49

Photoinduced iminium ion–benzylsilane cyclizations have also been employed to construct the protoberberine and spiro benzylisoquinoline alkaloid skeletons. For example, the spiro benzylisoquinoline (**138**) can be accessed in 50% yield by the photocyclization of isoquinolinium salt (**137**).[105] Photocyclization of the electron rich isoquinolinium salt (**118**) gave a 70% yield of (±)-xylopinine (Scheme 45).[94] This photocyclization is claimed to proceed more cleanly and with higher efficiency than the corresponding fluoride-promoted ground state cyclization.

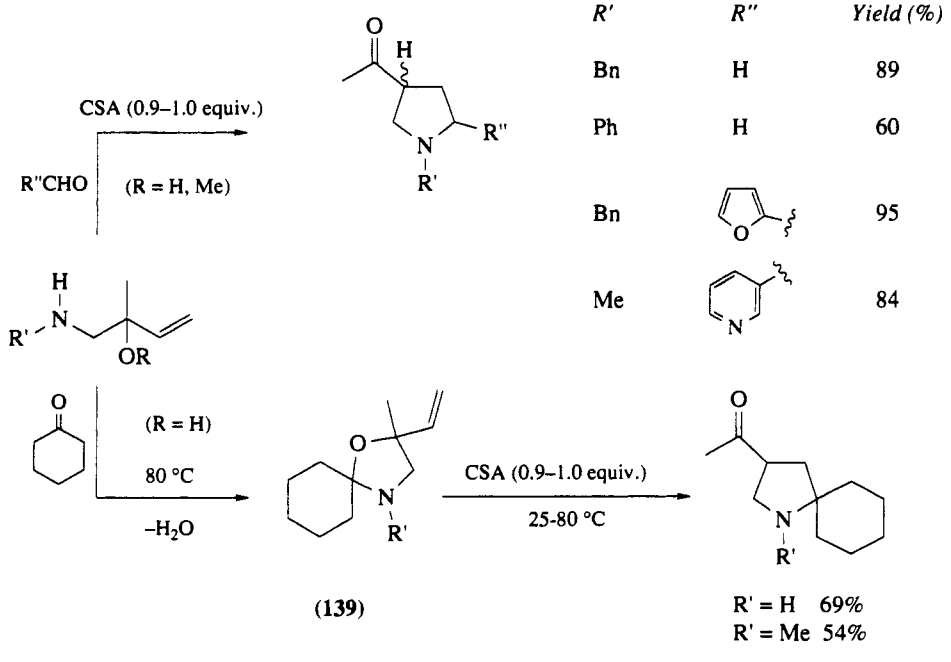


(**137**) (**138**)

Although only recently introduced, it is apparent that photoinduced SET cyclizations of iminium salts are a useful tool in azacycle synthesis. Of particular note is the ability to construct pyrrolidines by endocyclic cyclizations which, as a result of stereoelectronic constraints, cannot be realized with ground state intermediates.

4.4.4 MOLECULAR REARRANGEMENTS TERMINATED BY MANNICH CYCLIZATIONS

The intramolecular Mannich reaction has been combined with the facile [3,3] sigmatropic rearrangement of iminium cations to provide a versatile synthesis of 3-acylpyrrolidines and other more complex ring systems containing this subunit.[106] In the simplest case, a homoallylic amine with alkoxy or hydroxy substitution at the allylic site is allowed to react with an aldehyde in the presence of an equivalent or less of acid to yield substituted 3-acylpyrrolidine products (Scheme 50). The mild conditions of this transformation—which occurs at near ambient temperature and neutral pH—are apparent in the success of this sequence with labile aldehydes such as furfural. Ketones can be employed also: in this case a two-step

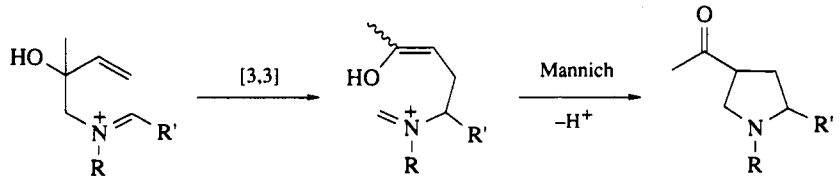


R'	*R''*	*Yield (%)*
Bn	H	89
Ph	H	60
Bn		95
Me		84

(**139**)

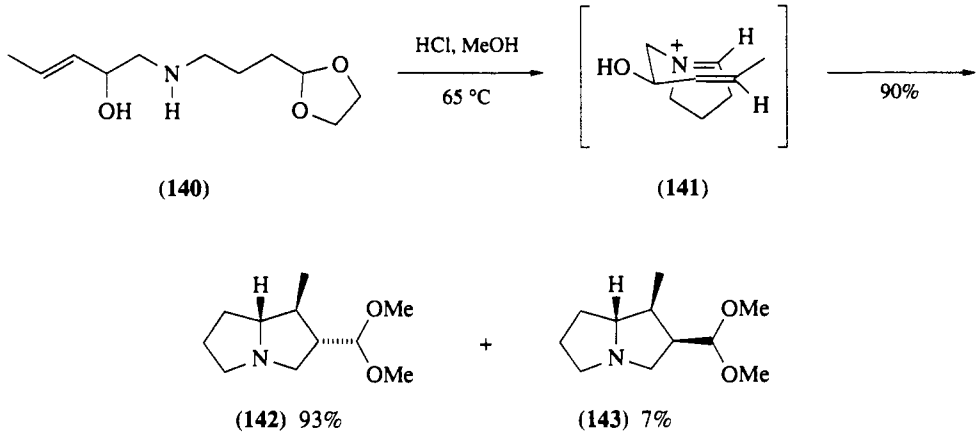
Scheme 50

procedure is utilized in which the ketone and a 2-hydroxy-3-butenylamine are condensed to form a 5-vinyloxazolidine (**139**), which is then rearranged in acid to afford the acylpyrrolidine product. A variety of evidence is consistent with these transformations occurring by a sequential cationic aza-Cope (2-azonia[3,3] sigmatropic) rearrangement–Mannich cyclization sequence as depicted in equation(15).[107]



(15)

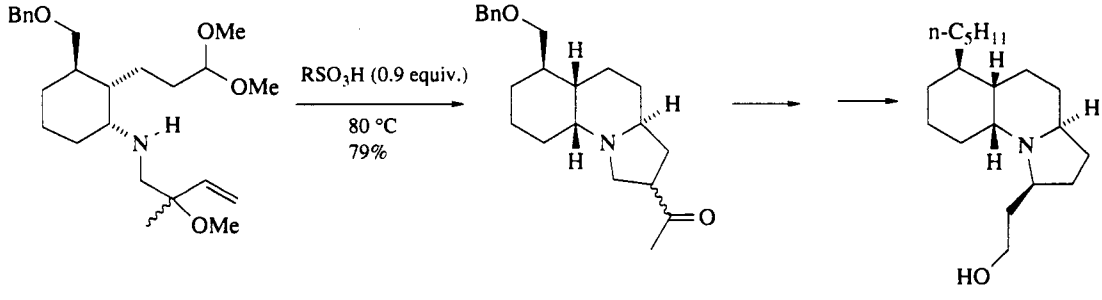
The above rearrangement has been utilized to assemble pyrrolizidine and indolizidine ring systems from acyclic precursors. The *cis* relationship between the bridgehead hydrogen and the vicinal methyl group in pyrrolizidines (**142**) and (**143**) demonstrates that the rearrangement of (**140**) occurs preferentially in a chair topography, *i.e.* (**141**) in Scheme 51.[108] The indolizidine annulation (**144**) to (**145**) was a key transformation in Overman and Fukaya's synthesis of (±)-perhydrogephyrotoxin (Scheme 52).[109]



(**140**) (**141**)

(**142**) 93% (**143**) 7%

Scheme 51

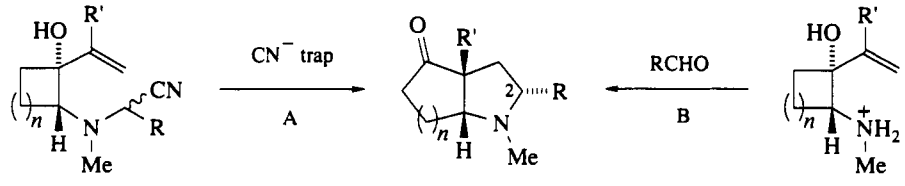


(**144**) (**145**) (±)-Perhydrogephyrotoxin

Scheme 52

If the starting amino alcohol is cyclic, the aza-Cope rearrangement–Mannich cyclization reaction provides a pyrrolidine-annulated product in which the initial ring is expanded by one carbon. This transformation has been utilized to prepare a wide variety of *cis*-fused hydroindoles, cyclopenta[*b*]pyrrolidines and cyclohepta[*b*]pyrrolidines (**147**), as shown in Scheme 53.[110-112] The *cis* stereochemistry of the ring fusion as well as the relative orientation of the C-2 substituent are suggested to arise directly from the chair topography of the aza-Cope rearrangement step, as illustrated in equation (16) for the formation of (**149**). The rearrangement can be initiated either by direct reaction of ammonium salt (**148**) with an alde-

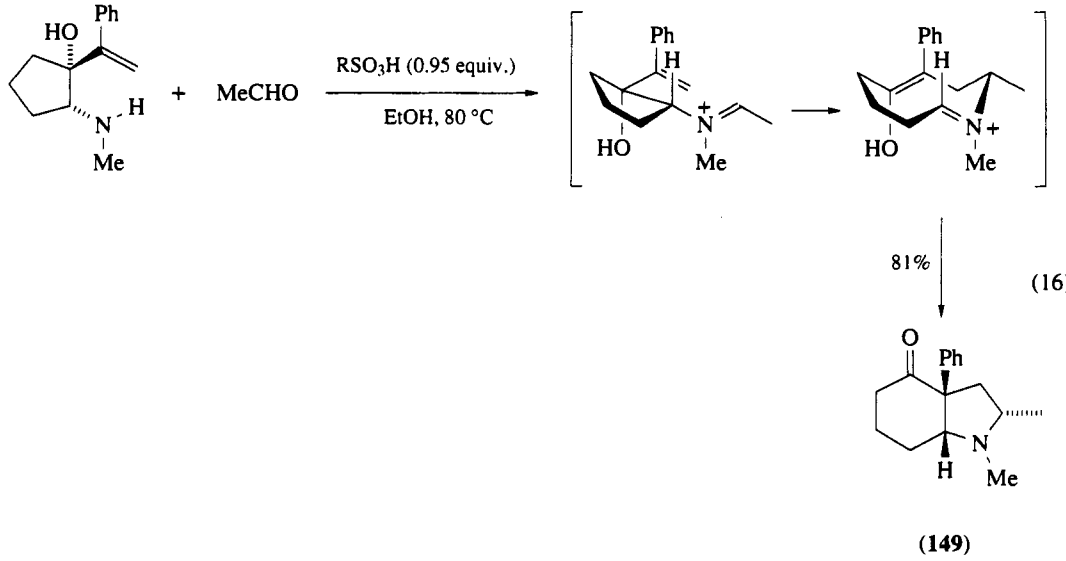
hyde or by cyanide ejection from α-cyanoalkylamine (**146**). This latter precursor is particularly attractive when R = H because (**146**) can be directly assembled from the reaction of a vinyllithium or vinyl Grignard reagent with the corresponding α-cyanomethylcycloalkanone.



(**146**) (**147**) (**148**)

Method	*n*	*R*	*R'*	*Yield* (%)
A (RSO_3H)	3	H	Ph	70
A [$Cu(OCOCF_3)_2$]	3	H	Ph	91
A ($AgNO_3$)	3	H	Ph	63
A ($AgNO_3$)	3	H	H	64
A ($AgNO_3$)	2	H	Ph	74
B	2	Me	Ph (**149**)	81
A ($AgNO_3$)	1	H	Ph	78
A ($AgNO_3$)	1	Me	Ph	66

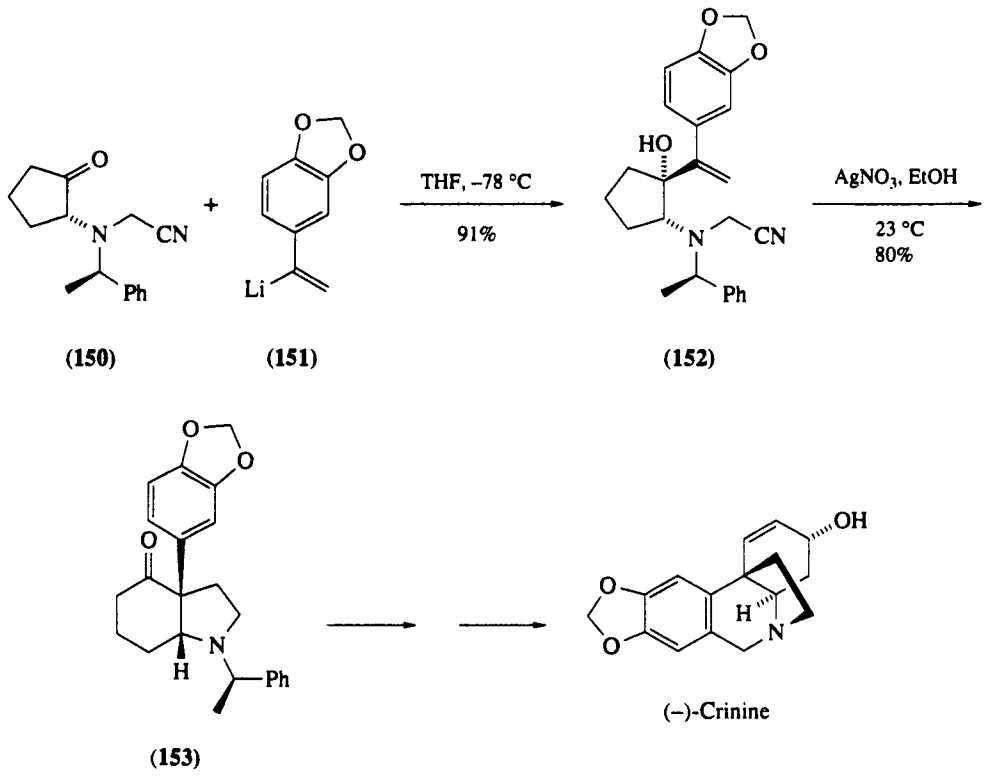
Scheme 53



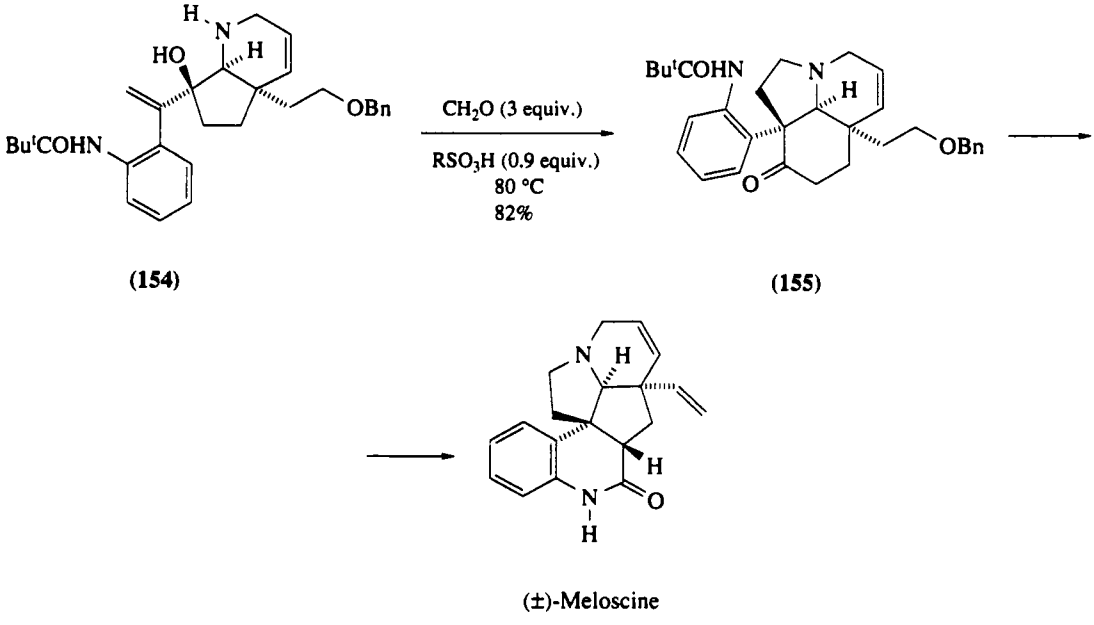
(**149**)

The ring-enlarging pyrrolidine annulation reaction has been employed by Overman and coworkers as the key step in syntheses of *Amaryllidaceae, Melodinus* and *Aspidosperma* alkaloids. In all cases a *cis*-3a-aryl-4-oxooctahydroindole subunit (**147**; R' = aryl; *n* = 2) is developed during the rearrangement step. Two key steps in the enantioselective synthesis of the *Amaryllidaceae* alkaloid (–)-crinine are summarized in Scheme 54.[113] Addition of lithium reagent (**151**) to the enantiomerically pure ketone (**150**) at –78 °C occurs exclusively from the ketone face opposite the amine substituent to provide (**152**) in 91% yield. Exposure of (**152**) to $AgNO_3$ in EtOH at room temperature proceeded in 80% yield to give the key hydroindolone intermediate (**153**). Debenzylation, Pictet–Spengler cyclization and adjustment of the C-ring functionality then provided (–)-crinine.

The formation of the tricyclic 9a-arylhydrololilidine ring system is exemplified in the conversion of (**154**) to (**155**).[114] Wolff ring contraction of the ketonic ring of (**155**) and further functional group modifications provided the *Melodinus* alkaloid (±)-meloscine. (Scheme 55).



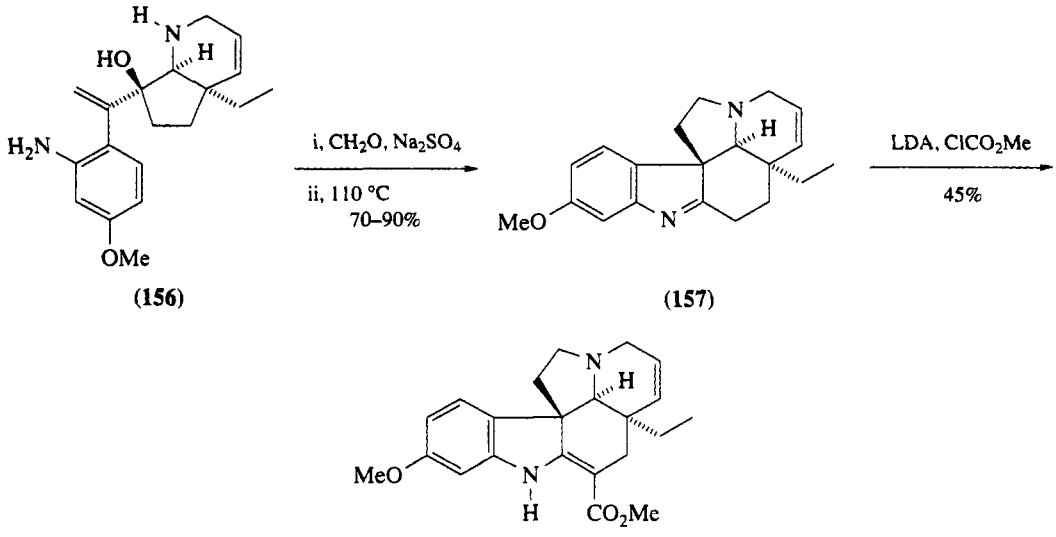
Scheme 54



Scheme 55

Perhaps the best illustration of the utility of tandem aza-Cope rearrangement–Mannich cyclization reactions for assembling complex molecular skeletons is found in the total synthesis of the *Aspidosperma* alkaloid (±)-16-methoxytabersonine (Scheme 56).[115] The crucial step in this synthesis was the high-yielding conversion of aniline (**156**) to 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (**157**), a trans-

formation that stereoselectively develops three of the five rings of the alkaloid target. This reorganization was accomplished by treating (**156**) with paraformaldehyde and anhydrous Na_2SO_4 at room temperature to form the corresponding oxazolidine, which was not isolated but directly transformed into (**157**) upon heating in toluene. The authors suggest that the small amount of formic acid present in the paraformaldehyde is sufficient in this case to catalyze the desired molecular rearrangement. Carbon acylation of the lithium derivative of (**157**) then provided (±)-16-methoxytabersonine.



(±)-Methoxytabersonine

Scheme 56

4.4.5 REFERENCES

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4.5
Additions to *N*-Acyliminium Ions

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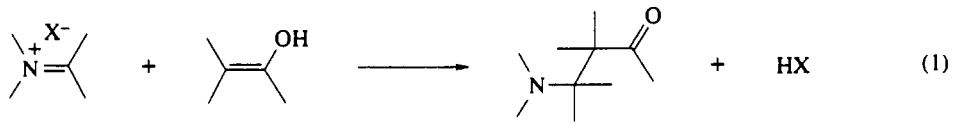
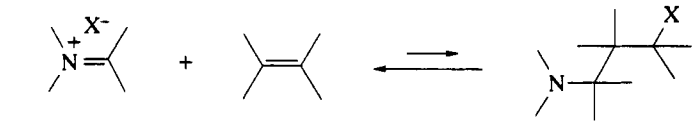
4.5.1 INTRODUCTION

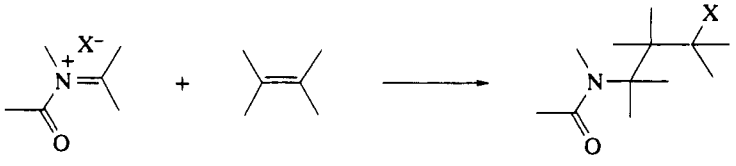
The addition of strongly polarized carbon–carbon double bonds (enols) to simple iminium ions, known as the Mannich reaction (equation 1), is a fundamentally important route to amines, especially in biosynthetic processes.[1,2] This reaction type is less synthetically useful if weakly polarized or unpolarized carbon–carbon π-bonds are used as nucleophiles (equation 2).[3] Because of the low electrophilic reactivity of the iminium moiety, the reverse reaction, known as the Grob fragmentation (equation 2), is often the more important process.[4] However, if the iminium moiety has a carbonyl substituent on nitrogen, its



(1)



(2)



(3)

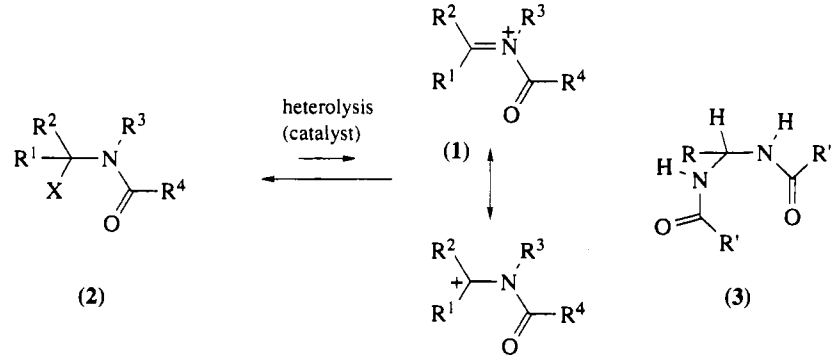
electrophilicity is strongly enhanced, and reactions with C=C bonds are irreversible and synthetically useful (equation 3).

A number of recent reviews exist about intermolecular[5] and intramolecular reactions[6] of the *N*-acyliminium intermediate. Moreover, detailed accounts of the application in alkaloid synthesis have recently appeared.[7,8] This chapter deals with reactions of species (**1**) with nucleophilic alkenes (and alkynes). Other synthetically useful nucleophiles like aromatic rings, active methylene compounds and organometallics will not be discussed here. In (**1**) R^1, R^2 and R^3 are hydrogen or carbon substituents, and R^4 may also be a hetero substituent, such as alkylamino or alkoxy. This chapter differs from previous reviews, as the material is ordered here on the basis of the structural features of the *N*-acyliminium intermediate. Major emphasis is placed on recent developments and stereochemical details.

4.5.2 GENERAL ASPECTS

4.5.2.1 Methods to Generate *N*-Acyliminium Ions

For synthetic applications the *N*-acyliminium species (**1**) is nearly always generated *in situ* because of its high reactivity. Heterolysis of an acetal-like structure of type (**2**) is a very popular method to effect *N*-acyliminium ion reactions. In most cases X is a hydroxy, alkoxy or acyloxy function and an acidic catalyst is used to generate (**1**). If X is methanesulfonyloxy, no catalyst is required, as thermal conditions suffice to produce the intermediate.[9] If X is methoxy or ethoxy, precursor (**2**) is usually a stable molecule, which allows the execution of diverse reactions under neutral or basic conditions elsewhere in the molecule before the *N*-acyliminium intermediate is employed.



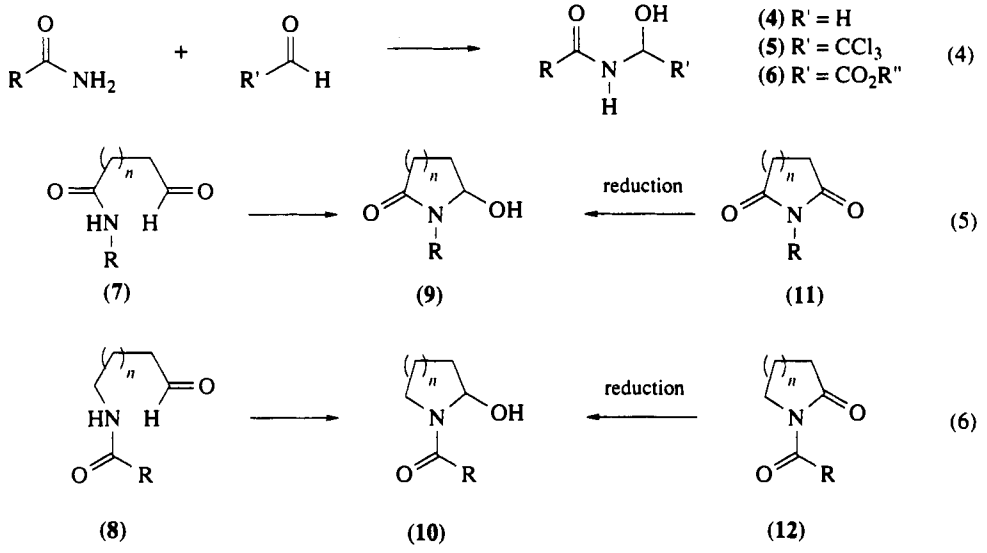
(2) (1) (3)

Other X groups in (**2**) that are occasionally used to produce the reactive intermediate (**1**) are chloride, sulfur and nitrogen substituents. Chloride is used for systems that lead to particularly reactive (electrophilic) *N*-acyliminium species, *e.g.* with R^1 and R^2 hydrogen or with R^1 (or R^2) a carboxyl function. The latter species can be characterized as glycine cation equivalents and are very useful for the synthesis of α-amino acids.[5] Standard Lewis acids such as $BF_3{\cdot}Et_2O$ and $SnCl_4$ can be used to ionize chloride precursors. The alkyl- or aryl-thio function can be activated as a leaving group in a quite different way to chloride and oxygen leaving groups, which may be beneficial with acid-sensitive substrates like β-lactams. Thus, mercury(II) acetate,[10] chloramine-T[11] and zinc reagents[12] have been used for this purpose, as

well as α-diazocarbonyl compounds in the so-called carbenoid displacement reaction.[13] *N*-Acyliminium ion precursors with a nitrogen substituent as leaving group are bisamides, biscarbamates and bisureas (**3**). They are easily prepared from aldehydes and are usually ionized by treatment with a Brønsted acid or $BF_3{\cdot}Et_2O$.[5]

The ease of formation of (**1**) from (**2**) depends, among other factors, on the nature of the leaving group. The only systematic study pertains to 4-substituted azetidinones, where the order of reactivity Cl > RCO_2 > RSO_2 > N_3 > RO > RS was found for substitution reactions under nonacidic conditions.[14] In an acidic medium this order will very likely be different.

Various methods are available for the preparation of the foregoing precursors to *N*-acyliminium ions. The most straightforward synthesis of *N*-(1-hydroxyalkyl)-amides or -carbamates (**2**; X = OH) involves the addition of primary or secondary amides (carbamates) to aldehydes or ketones. This reaction is an equilibrium process and usually disfavors the adduct except for two special cases. The first involves very reactive aldehydes like formaldehyde, chloral and glyoxylic acid and its esters (equation 4); compounds (**4**)–(**6**) are fairly stable compounds that are frequently used in amidoalkylation reactions.[5,15] The second special case is the intramolecular variant (ring–chain tautomerism), if it leads to five- or six-membered rings (equations 5 and 6). Thus, for $n = 1$ or 2, (**7**) and (**8**) cyclize to (**9**) and (**10**), respectively, although the nature of R has an influence on this process.[5–8,16]



(4)

(5)

(6)

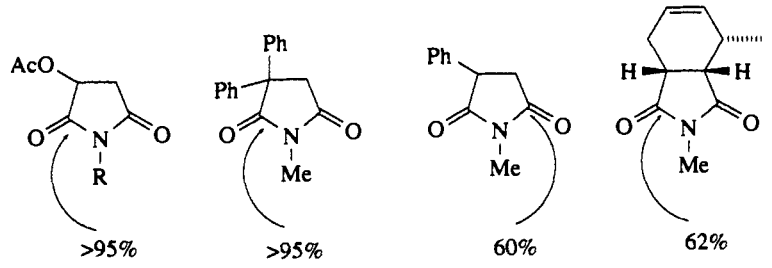
(**7**) (**9**) (**11**)

(**8**) (**10**) (**12**)

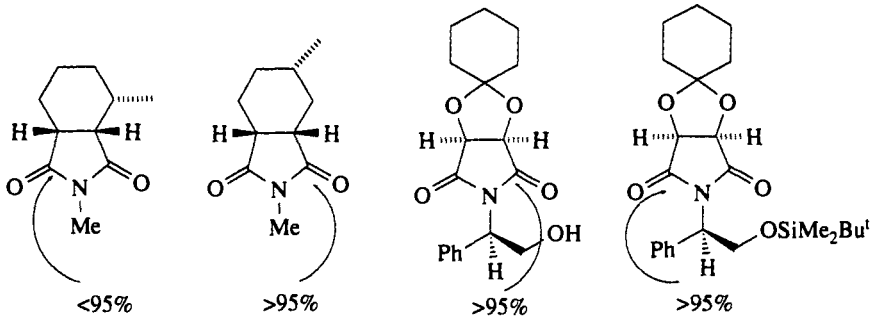
An alternative method for the preparation of cyclic *N*-(1-hydroxyalkyl)amides (or carbamates) is the partial reduction of cyclic imides (**11**) and (**12**) (equations 5 and 6). The usual reducing agents for this purpose are $NaBH_4$ and DIBAL-H.[17–19] When the $NaBH_4$ reduction is carried out in ethanol solution, addition of acid is usually necessary to obtain good yields.[17] Acid is not required if the reduction is performed in methanol solution with a large excess of $NaBH_4$.[9] Moreover, the reaction temperature for $NaBH_4$ reductions is quite important. Typical temperatures for reductions in ethanol solution are –20 °C for six- and 0 °C for five-membered rings. Higher temperatures give rise to (some) ring-opening, which is irreversible because of further reduction.[17]

Inherent to this reductive method is the problem of regioselectivity. Imide systems in which one carbonyl is part of a carbamate or a urea function (*e.g.* **12**; R = OR′ or NR'_2) usually show excellent selectivity for reduction of the other carbonyl group.[7,18] Chemically more symmetrical imides may still provide very high regioselectivity.[20–22] Imides (**13**)–(**18**) are typical examples (the arrows show the carbonyl groups, which are preponderantly or exclusively reduced). Of synthetic relevance is the fact that DIBAL-H and $NaBH_4$ may show opposite regioselectivity.[23] Very recently, the problem of diastereoselective reduction of *meso*-imides has been elegantly solved by using a chiral *N*-substituent. Thus, (**19a**) and (**19b**) are reduced with virtually complete, yet opposite selectivity with $Me_4NHB(OAc)_3$ and L-selectride, respectively.[24]

Addition of Grignard reagents to five- and six-membered systems (**11**) and (**12**) also leads to *N*-acyliminium ion precursors. The products, being tertiary alcohols, are rather susceptible, however, to ring-opening and dehydration, so that their isolation may be problematic. Nevertheless, this methodology has proven highly useful for the synthesis of the amphibian alkaloid histrionicotoxin.[25,26]

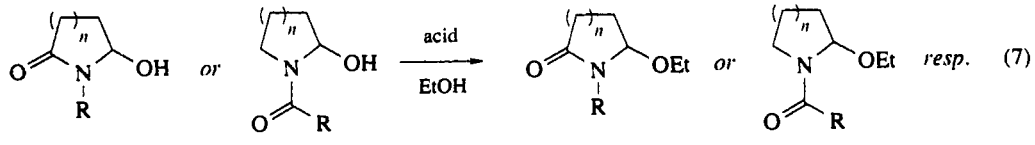


(13)[9,21] **(14)**[20] **(15)**[20] **(16)**[22]



(17)[22] **(18)**[22] **(19a)**[23] **(19b)**[23]

N-(1-Alkoxyalkyl)-amides or -carbamates (2; X = OR), most frequently used as stable precursors for *N*-acyliminium ions, are usually prepared by one of the following routes (equations 7–13). For five- or six-membered cyclic cases a simple acid-catalyzed solvolysis of the hydroxy compound provides the alkoxy derivative (equation 7).[17] A silicon-assisted approach involves the TMSOTf-catalyzed reaction of bis(trimethylsilyl)formamide with aldehydes (equation 8). *N*-(1-Trimethylsilyloxyalkyl)formamides are thus formed in good yields, which on TMSOTf-catalyzed solvolysis lead to the *N*-(1-alkoxyalkyl)formamides.[27] A third method is based on the $NaBH_4$ reduction of imidates (equation 9), and has proved useful for a total synthesis of the insect poison pederine.[28] Addition of reactive acid derivatives to imines constitutes another method (equations 10 and 11). Acylation with acid chlorides followed by treatment with ethanol in the presence of base leads to *N*-(1-alkoxyalkyl)amides.[29–31] A one-step protocol using diethyl dicarbonate provides the corresponding carbamates.[30–32]



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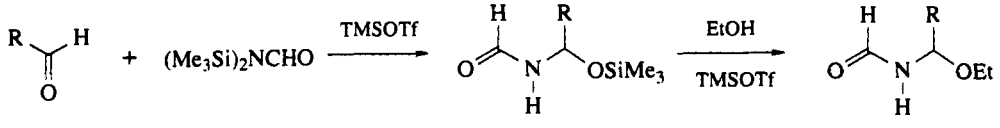

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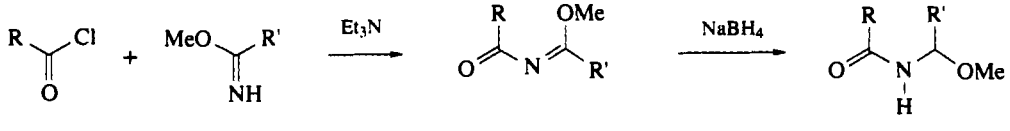

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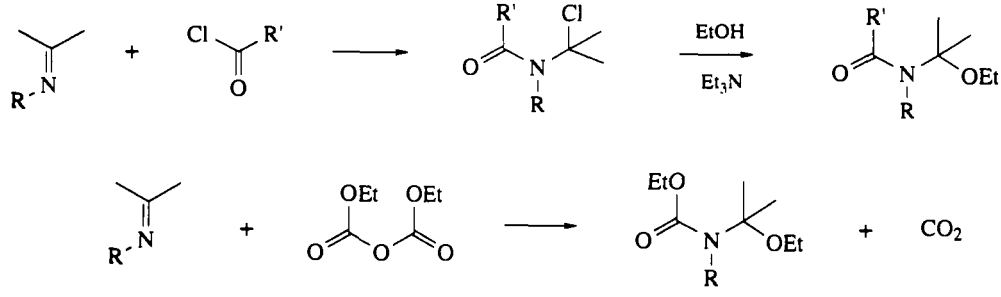
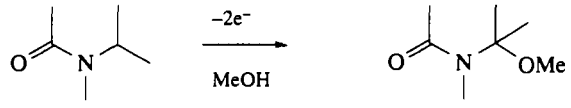


(10)

(11)

Two electrochemical methods (equations 12 and 13) deserve special attention.[33,34] The oxidation of amides and carbamates in methanol solution is a very general method (equation 12), applicable to acyclic as well as cyclic systems, varying from four-membered to large rings. Compounds (**20**)–(**26**) are typical products from this process, which is also regioselective in such a way that the least-substituted α-carbon is preferentially oxidized, exemplified with (**25**) and (**26**). *N*-Protected α-amino acid esters are also methoxylated *via* this method.[39] The Kolbe-type decarboxylative electrochemical oxidation of *N*-acylated α-amino acids (equation 13) constitutes a useful synthetic application of (naturally occurring) α-amino acids.[40] This methodology has found several interesting recent applications (equations 14–16).[41–43] Even the sensitive β-lactam ring can be manipulated in high yield to give a useful thienamycin precursor (equation 16).[43]



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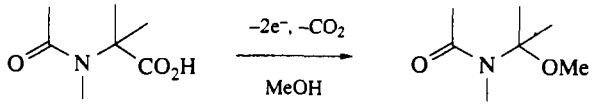

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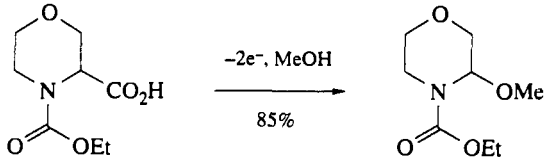

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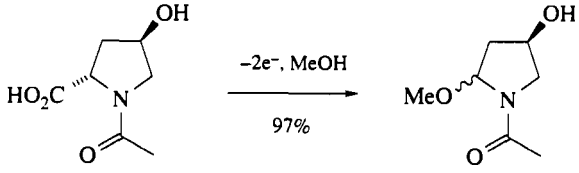

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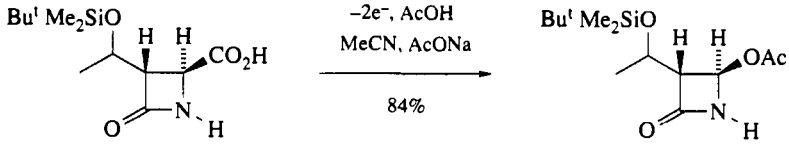
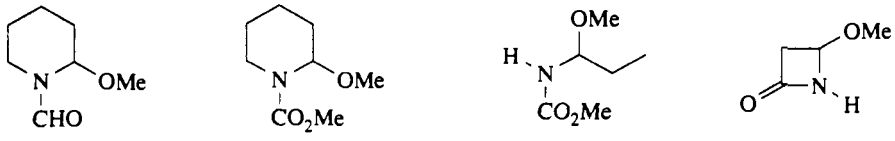
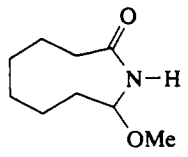


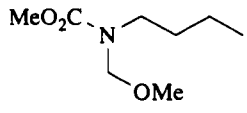
(16)



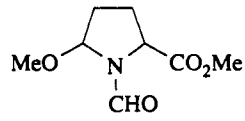
(20) 95%[35] **(21)** 65%[36] **(22)** 62%[36] **(23)** 51%[37]



(**24**) 57%[35]

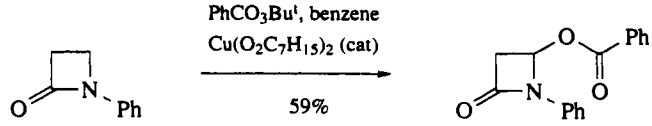


(**25**) 53%[36]

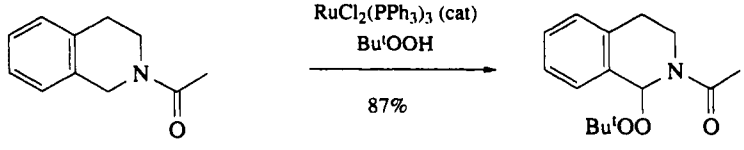


(**26**) 86%[38]

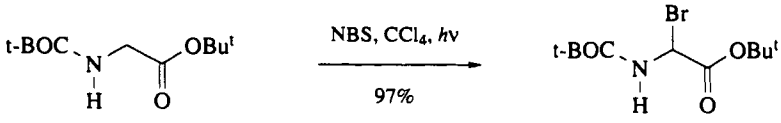
Various other, more specialized oxidative methods have been developed to synthesize relatively stable *N*-acyliminium ion precursors of type (**2**). To mention a few, free radical mediated oxidation of azetidinones provides 4-benzoyloxy-substituted derivatives (equation 17).[44] A transition metal catalyzed procedure has been described to give a precursor with a *t*-butylperoxy leaving group (equation 18).[45] Important for the synthesis of α-amino acids is the halogenation of glycine equivalents (equations 19–21). The products are precursors to the so-called glycine cation equivalent, which is in fact an *N*-acyliminium intermediate bearing an extra electron-withdrawing carbonyl substituent. These precursors are useful intermediates in the synthesis of both racemic (equation 19)[46] and nonracemic α-amino acids (equations 20 and 21).[47,48]



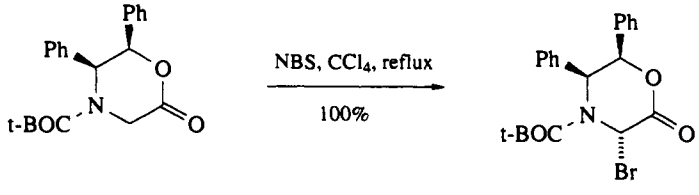
(17)



(18)



(19)



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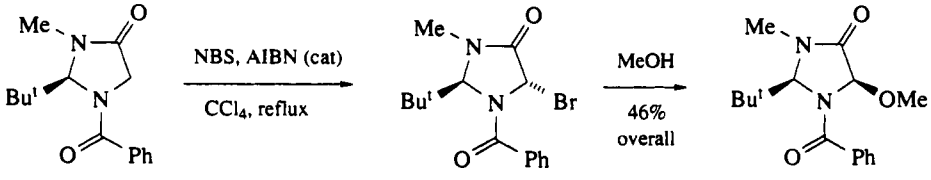
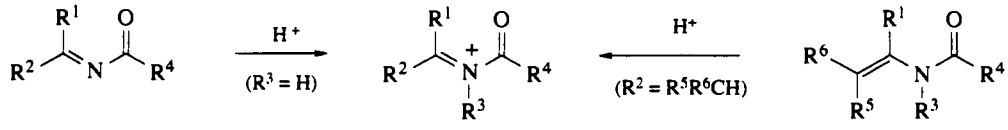


(21)

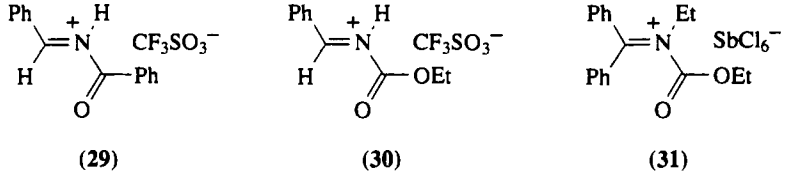
In addition to heterolysis of compounds of type (**2**), *N*-acyliminium intermediates (**1**) are also obtained by protonation of *N*-acylimines (**27**) and by protonation of enamides or enecarbamates (**28**). The former method is mainly of theoretical interest,[49] because *N*-acylimines (**27**) are rather unstable compounds. The latter technique is occasionally applied,[50] although compounds (**28**) are usually synthesized through elimination of HX from (**2**).[51] Other preparatively very useful methods for the *in situ* generation of the *N*-acyliminium ion are the acid-mediated coupling of an aldehyde (or ketone) with a primary (or secondary) amide or a nitrile, and the thermal reaction between an acid chloride and an imine.[5]



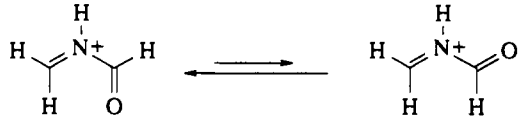
(27) (1) (28)

4.5.2.2 Structure *versus* Reactivity

Because of their high reactivity, *N*-acyliminium ions usually occur as transient intermediates in synthetic applications. However, in a few special cases stable *N*-acyliminium salts have been synthesized and characterized.[49,52] Thus, triflate salts (**29**) and (**30**) arise through *N*-protonation of the corresponding acylimines and salt (**31**) is formed as a crystalline colorless solid (m.p. 132–140 °C) through *N*-ethylation of the corresponding acylimine with triethyloxonium hexachloroantimonate. Particularly diagnostic for the structures (**29**) and (**30**) are the ^{1}H NMR chemical shifts (δ(NH) = 13.6, δ(CH) = 9.6 p.p.m.) and the coupling constant (J = 16 Hz) of the hydrogens attached to the iminium double bond.[49,52] *Ab initio* calculations on the simple *N*-protonated *N*-methyleneformamide ion indicate, that the *s-cis* form is about 3 kcal mol^{-1} (1 cal = 4.18 J) more stable than the *s-trans* isomer (equation 22).[53] This can be understood by considering the better compensation of the dipole moment vectors of the iminium and the carbonyl bond in the *s-cis* relative to the *s-trans* form. Of course, in highly substituted systems, steric factors may offset this preference for the *s-cis* form.[50]



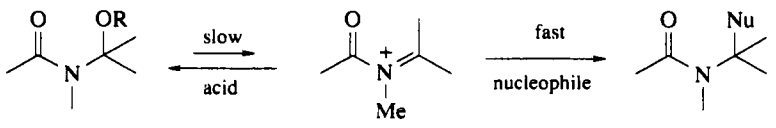
(29) (30) (31)



(22)

s-cis *s-trans*

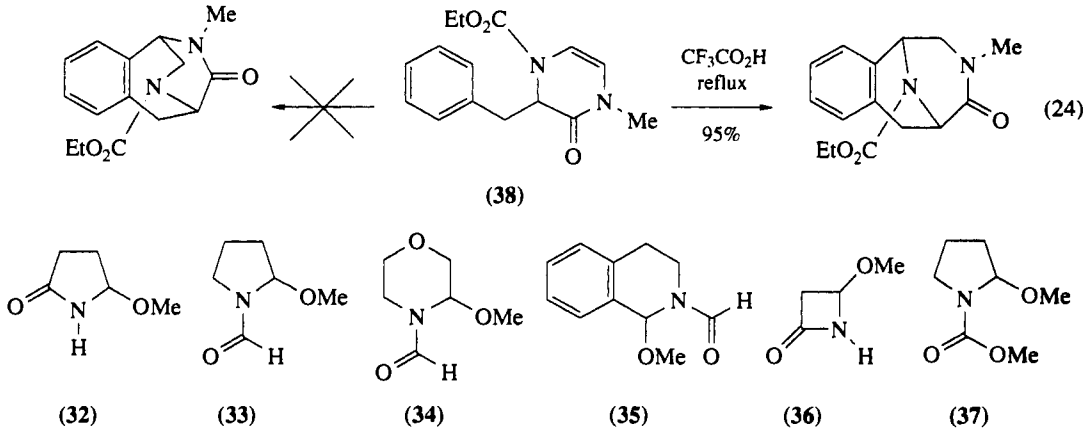
Elaborate synthetic applications of *N*-acyliminium chemistry usually require mild conditions, so that only a low equilibrium concentration of the reactive intermediate is present. Formation of the *N*-acyliminium ion is probably the rate-determining step in most cases (equation 23).[5,6] This implies that a greater stability of the iminium intermediate leads to a higher reaction rate. This supposition was borne out in one case by competition experiments to determine the relative reactivity of methoxyamides (**32**)–(**35**) towards arylation with 1,3,5-trimethoxybenzene, catalyzed by $AlCl_3$.[54] The order of reactivity (**32**:**33**:**34**:**35** = 30:4.5:1:200) is in good agreement with the expected stability order of the derived *N*-acyliminium ions. Although further data are lacking, one may expect that azetidinone (**36**) is less reactive than (**32**), because of the strain of an iminium double bond in a four-membered ring. Carbamate (**37**), on the other hand, is expected to be more reactive than formamide (**33**) because a carbamate nitrogen lone pair is more available for cation stabilization than an amide nitrogen. Experimental evidence for the latter reactivity difference follows from the cyclization of (**38**), which solely proceeds *via* the carbamate-stabilized cation (equation 24).[55]



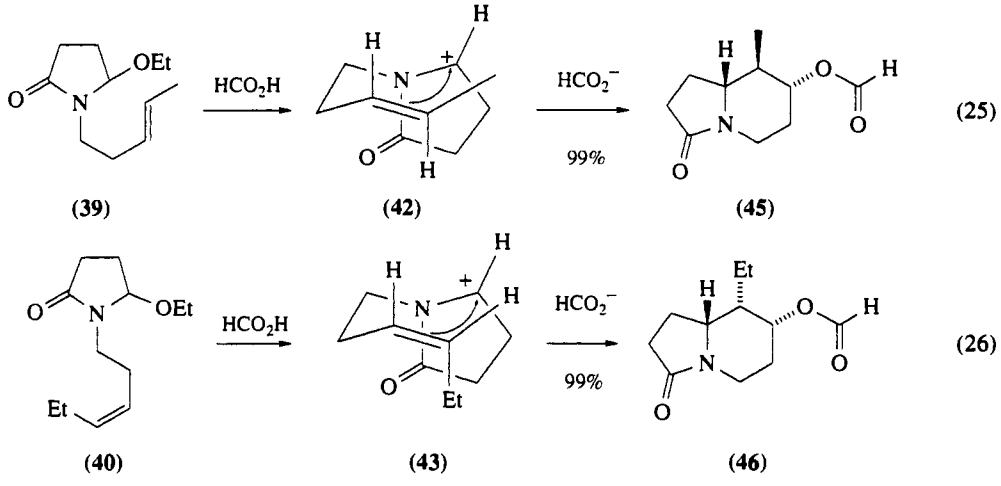
(23)

4.5.2.3 Reaction Behavior

For a discussion of the general mechanism of reactions of *N*-Acyliminium intermediates with alkenes (and alkynes) an important distinction has to be made between *N*-acyliminium ions locked in the *s-trans*

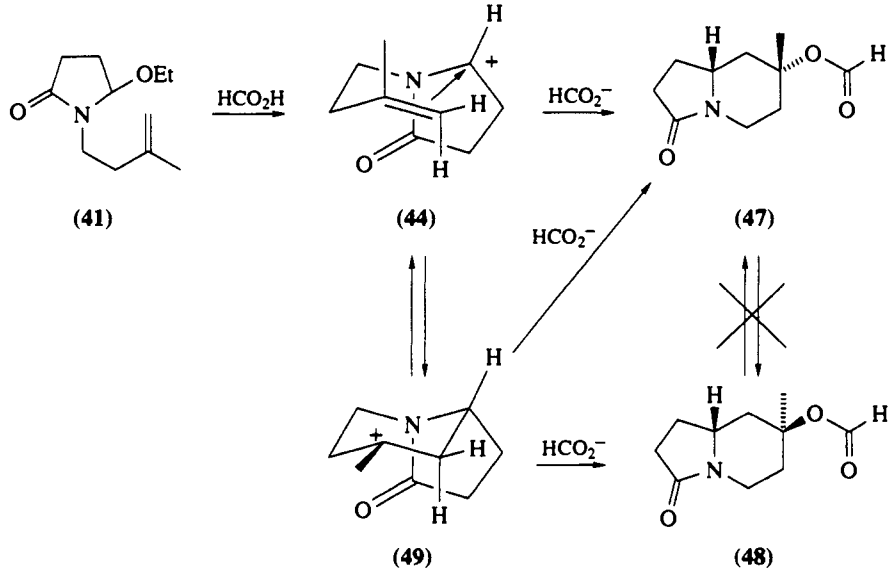


conformation, and those that (can) adopt the *s-cis* conformation. The former type, represented by cyclic species derived from (**39**)–(**41**), reacts as a (nitrogen-stabilized) carbocation with carbon–carbon multiple bonds. The π-complex theory gives a good description of the mechanistic details of this process.[56] Thus, the *N*-acyliminium ions derived from (**39**)–(**41**) form, in equilibrium processes, π-complexes (**42**)–(**44**), respectively, with chair-like six-membered rings (equations 25–27).[57] In these π-complexes the double bond geometry is retained. Subsequently, formate anion attacks these π-complexes in such a manner that only six-membered rings are formed. Clearly, the strain in the bicyclic π-complexes renders them unsymmetrical. The most positively charged carbon atom of the original alkene is then attacked by formate from behind, leading to high yields of single isomers (**45**) and (**46**). On the contrary, π-complex (**44**) leads to a *ca.* 60:40 mixture of formates (**47**) and (**48**). As the latter isomers do not interconvert under the reaction conditions, a reasonable explanation for the low stereoselectivity of cyclization of (**41**) is the involvement of (classical) tertiary carbocation (**49**).

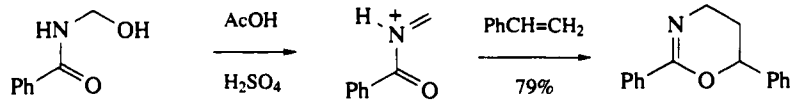


For *N*-acyliminium ions that (can) adopt the *s-cis* conformation, the mechanistic picture is quite different. Now the *N*-acyliminium intermediate reacts as a 4π-electron component in a Diels–Alder cycloaddition with inverse electron demand (equation 28).[58–60] This process also shows high regio- and stereo-selectivity in most cases. A nice illustration of high stereospecificity is found in recent work on the intramolecular Diels–Alder reaction of *N*-acyliminium species (equations 29 and 30).[61] The bisamides (**50**) and (**51**) serve as precursors to the reactive intermediates, which cycloadd to the alkenes with high selectivity to give *trans*-fused bicyclic 5,6-dihydro-1,3-oxazines.

In the case of *N*-acyliminium ions lacking a hydrogen on nitrogen, the Diels–Alder adducts lose their charge in a different way (equations 31 and 32). Thus, carbamate-derived intermediate (**52**) gives 1,3-oxazin-2-one (**53**) as a minor product and the acyclic carbamate (**54**) as the major product.[62] Reaction of the same starting material with the enol silane from acetophenone produces solely the acyclic product (**55**).[63] An interesting mechanistic question pertains to the origin of the acyclic products (**54**) and (**55**). Are these formed *via* a cycloaddition pathway (*via* (**52**) and (**56**), respectively), or do they directly arise from re-



(41) (44) (47) (49) (48) (27)



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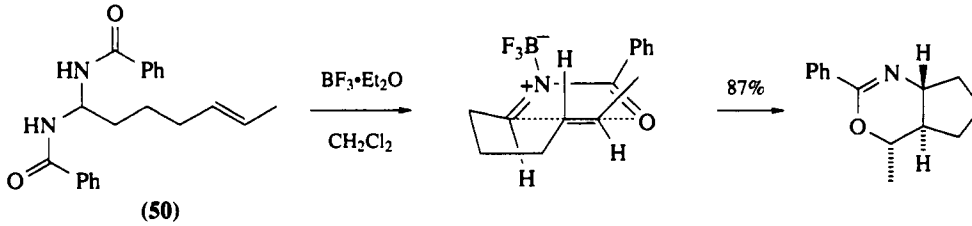
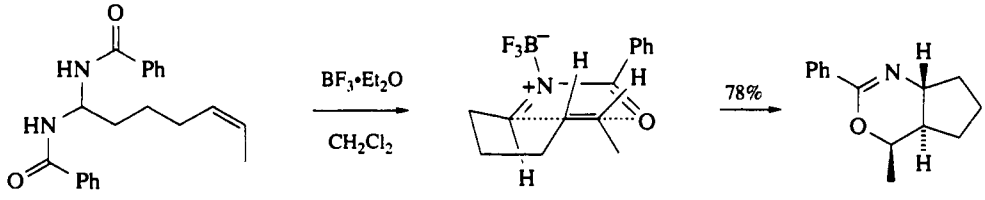
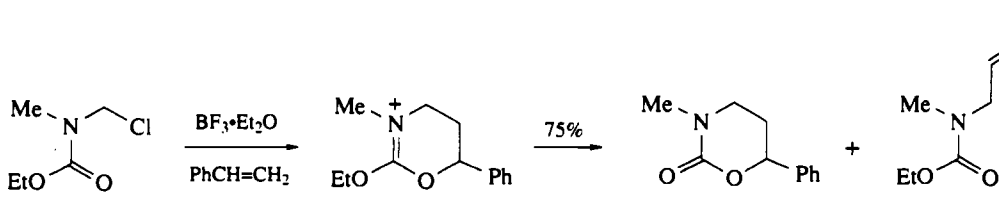


(50) (29)



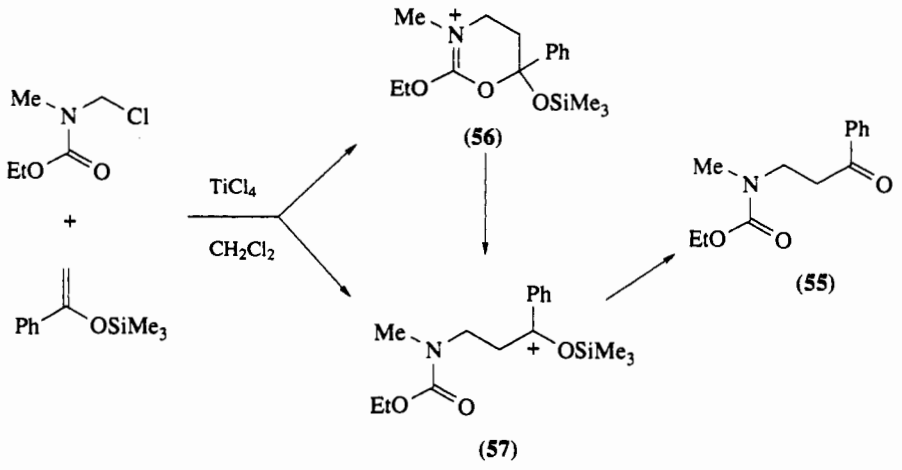
(51) (30)

action of the iminium cation with the carbon–carbon double bond, giving cation (**57**) without mediation of the carbamate carbonyl function? Most probably, the cycloaddition pathway is very general. It should be noted here again that calculations indicate that the *s-cis* form is considerably more stable than the *s-trans* geometry,[53] so that *N*-acyliminium ions usually have the correct geometry for Diels–Alder chemistry.



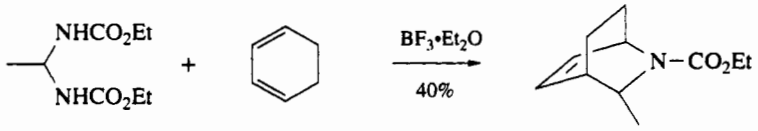
(52) (53) (54) 13:87 (31)

N-Acyliminium ions may behave as Diels–Alder dienophiles in reactions with conjugated dienes. Thus, biscarbamate (**58**) and cyclohexa-1,3-diene react in the presence of $BF_3{\cdot}Et_2O$ to give cycloadduct



(32)

(**59**) in moderate yield (equation 33).[64] This reaction type has been extensively reviewed and will receive only limited attention here.[65,66]

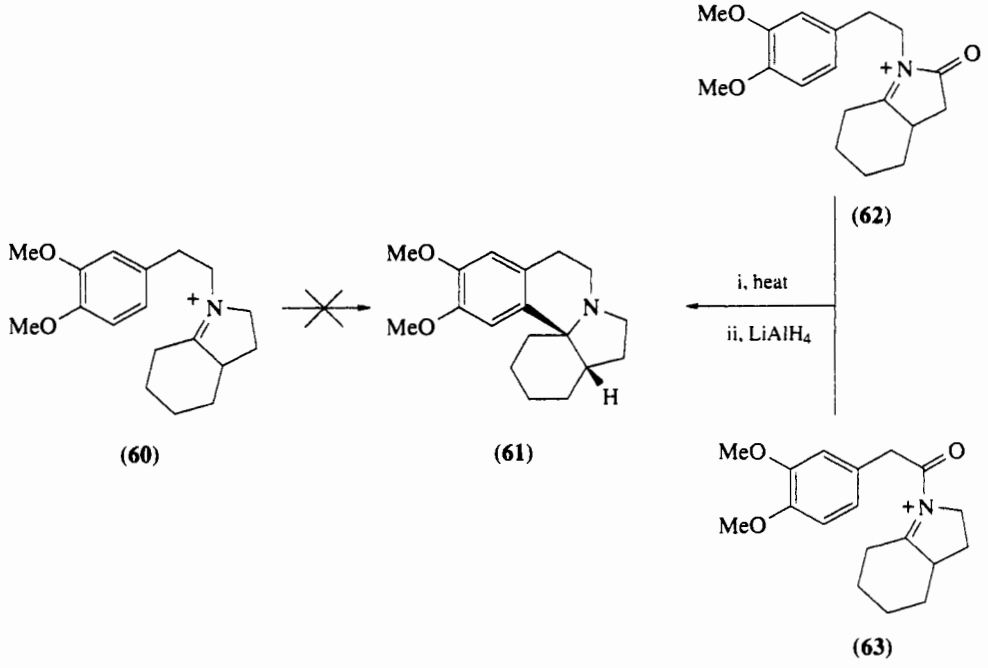


(33)

(**58**) (**59**)

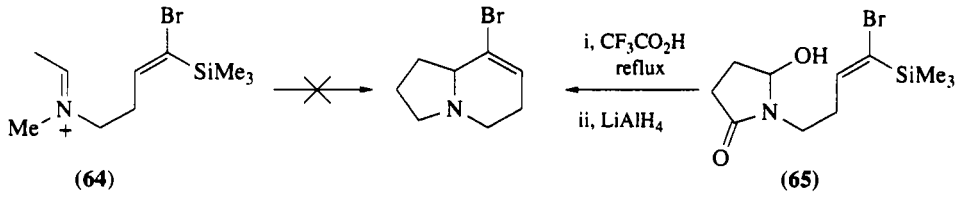
4.5.2.4 Reactivity Compared with Other Electrophilic Species

The greater electrophilicity of the *N*-acyliminium ion as compared with an ordinary iminium ion was nicely illustrated as early as 1957. In experiments directed at the total synthesis of erythrina alkaloids, cyclization of iminium ion (**60**) to the erythrinane skeleton (**61**) fails (equation 34). However, *N*-acyliminium ions (**62**) and (**63**) can both be converted into the desired skeleton in good yields.[67,68] A recent il-



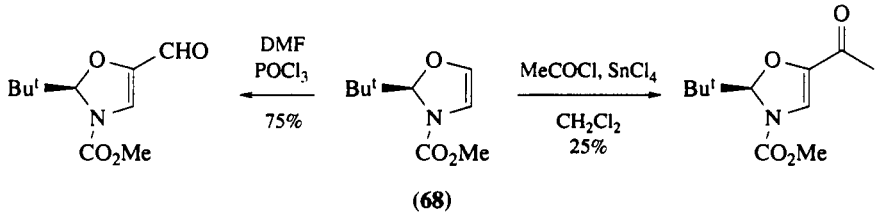
(34)

lustration of this reactivity difference can be found in studies on the use of vinylsilanes as π-nucleophiles (equation 35).[69] Whereas iminium ion (**64**) cannot be cyclized, the *N*-acyliminium species derived from (**65**) undergoes ring closure in refluxing TFA.



(35)

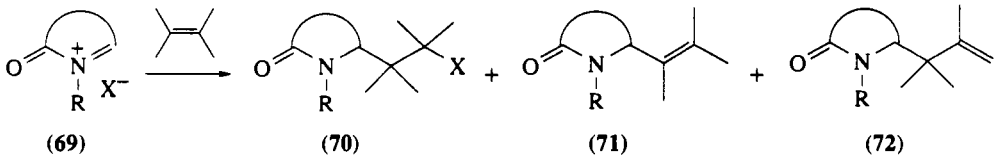
Very recently, the cation-stabilizing ability of a carbamate nitrogen and an oxygen atom were compared.[70] Calculations indicate that *N*-acyliminium ion (**66**) is *ca.* 11 kcal mol^{-1} more stable than oxonium ion (**67**). This difference is confirmed by experiments on oxazoline (**68**). Both Vilsmeier formylation and acid-induced reaction with acetal chloride occur at C-5 (equation 36), indicating a greater charge-donating ability of a carbamate nitrogen compared with an ether oxygen atom.



(36)

4.5.3 ENDOCYCLIC IMINIUM IONS WITH THE *N*-ACYL GROUP IN THE RING

This section deals with addition reactions to cyclic *N*-acyliminium ions of type (**69**), locked in the *s-trans* conformation. Being unable to participate as a 4π-system in a Diels–Alder type reaction, (**69**) simply reacts as a nitrogen-stabilized carbocation with carbon–carbon multiple bonds. The products can be either the result of addition (**70**) or substitution (**71** and **72**), mainly dependent on the substitution pattern of the nucleophilic multiple bond (equation 37).

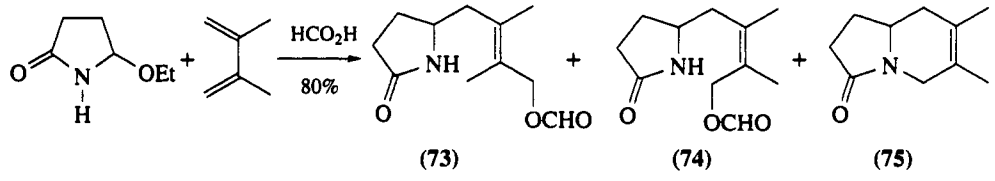


(37)

4.5.3.1 Intermolecular Reactions

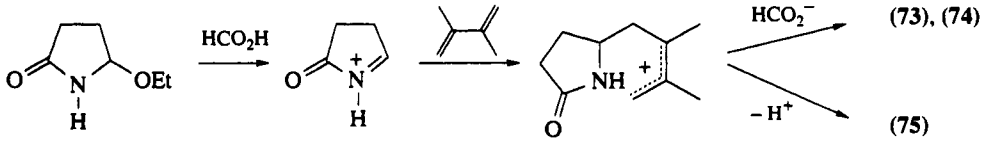
Intermolecular reactions of species (**69**) with simple alkenes have received little attention. Recently, a study of the reaction of 5-ethoxy-2-pyrrolidinone with several 1,3-dienes in the presence of acid was published.[71] When a mixture of ethoxylactam and 2,3-dimethylbutadiene is stirred in neat formic acid, the formates (**73**) and (**74**) are isolated as the main products in 43% yield. The bicyclic product (**75**) is obtained in only 16% (equation 38). If the reaction is carried out in benzene with *p*-toluenesulfonic acid as catalyst (**75**) is formed in 19% yield. Other dienes show similar behavior, producing bicyclic compounds as byproducts in low to moderate yields except for one or two cases, as illustrated with com-

pounds (**76**)–(**80**) with yields given for reactions in formic acid.[71] The mechanism of these reactions can best be viewed as a stepwise process with the *N*-acyliminium ion as the first intermediate (equation 39). It is rather unclear which factors determine the ratio of mono- and bi-cyclic products.



(38)

(**73**) (**74**) (**75**)



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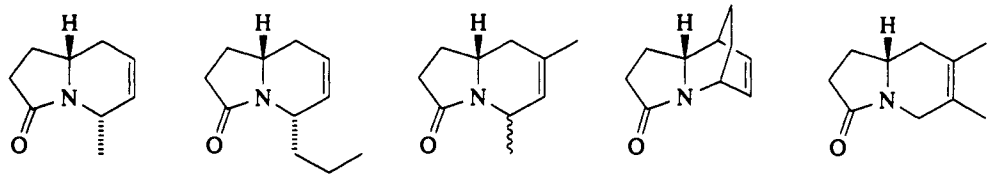
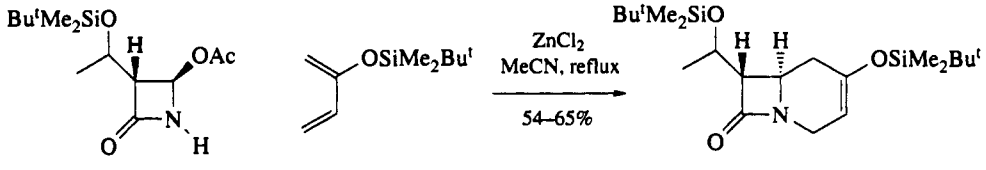


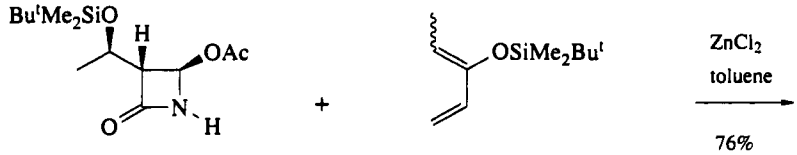
(**76**) 11% (**77**) 20% (**78**) 70% (**79**) 40% (**80**) 16%

The above reaction type was also applied to the acetoxyazetidinone (**81**).[72] Heating of (**81**) with diene (**82**) and $ZnCl_2$ in acetonitrile at reflux gives *ca.* 60% of (formal) cycloadduct (**83**) as a single *trans* stereoisomer (equation 40). From (**83**) the carbapenam skeleton was readily prepared in three steps. The reaction was repeated for silyloxydiene (**84**) in order to gain access to the more potent 1β-methyl analog of thienamycin.[73] In refluxing acetonitrile the monocycle (**86**) is formed as the major product (equation 41).

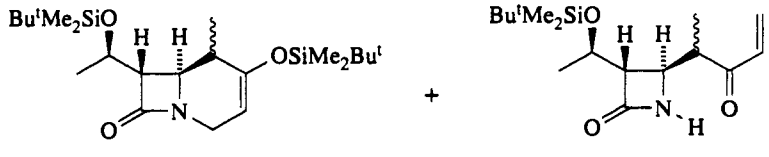


(40)

(**81**) (**82**) (**83**)



(**81**) (**84**)

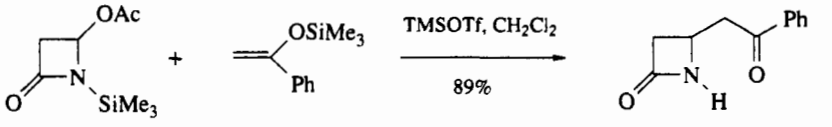


(41)

(**85**) (**86**)

It was finally found that simply changing the solvent to toluene produces bicyclic (**85**) in *ca.* 65% yield as a 70:30 mixture of β- to α-methyl isomers. This isomer ratio well reflects the isomer ratio of the diene, but the diene unfortunately isomerizes under the reaction conditions. The stereospecificity of the formation of (**85**) as well as the success in an apolar solvent points to a more or less concerted cycloaddition pathway.[65]

Lewis acid induced coupling of enolsilanes and ketene acetals with 4-acetoxyazetidinones is an excellent method to introduce a carbon substituent at the 4-position of the β-lactam ring. This reaction tolerates various different substituents on nitrogen (equations 42–44),[74,75] but electron-withdrawing groups lower the yield.[75] Intermediates for the synthesis of 1β-methylcarbapenems can be readily prepared *via* this method[76,77] with remarkably high stereoselectivity in some cases (equation 45[77]). Very high stereoselectivity is also attained by using tin(II) or boron enolates, derived from enantiomerically pure carboximides (equations 46 and 47). Apparently, the conformationally well defined enolates (**87**) and (**88**) highly favor one specific mode of approach of the *N*-acyliminium intermediate.[78–80] Further mechanistic evidence is obtained by starting from simple 4-acetoxyazetidinone[81] or 5-acetoxypyrrolidinone.[82] The prochiral *N*-acyliminium intermediate in (**89**) is functionalized α to nitrogen to give (**90**) with a selectivity of *ca.* 95% (equation 48). The attractive interaction between the imine nitrogen atom and Sn^{II} is important, as follows from the stereochemical result of a similar reaction with 1-methyl- 5-acetoxypyrrolidinone, which gives the opposite ring stereochemistry as compared to (**90**), albeit with somewhat lower selectivity.[83]



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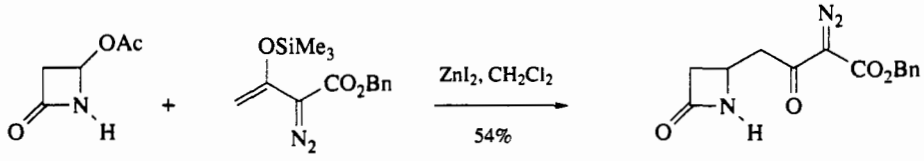

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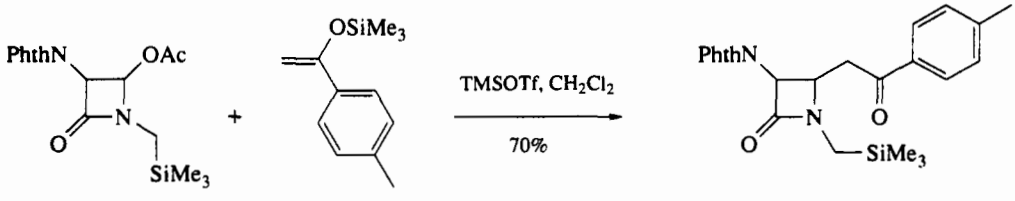

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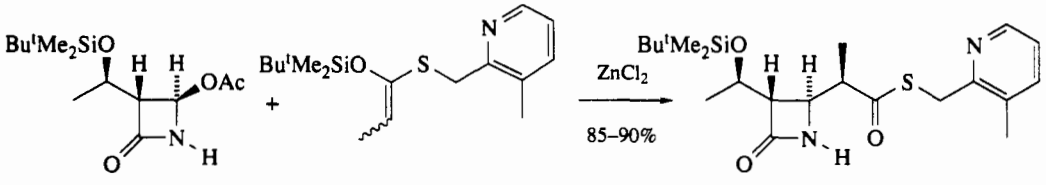

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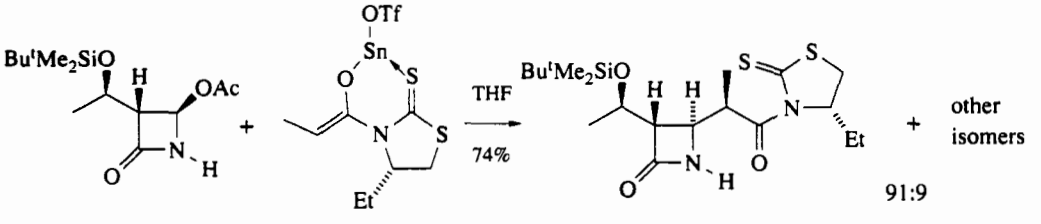
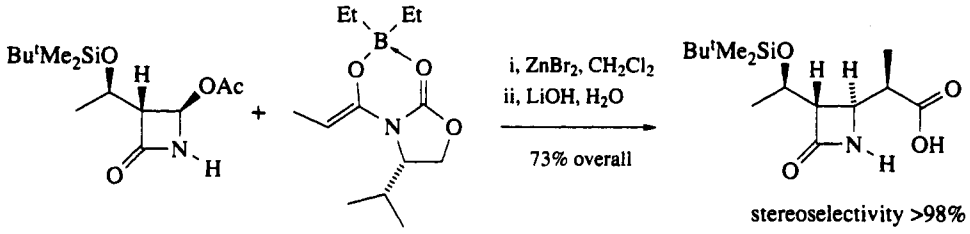


(46)

(**87**)



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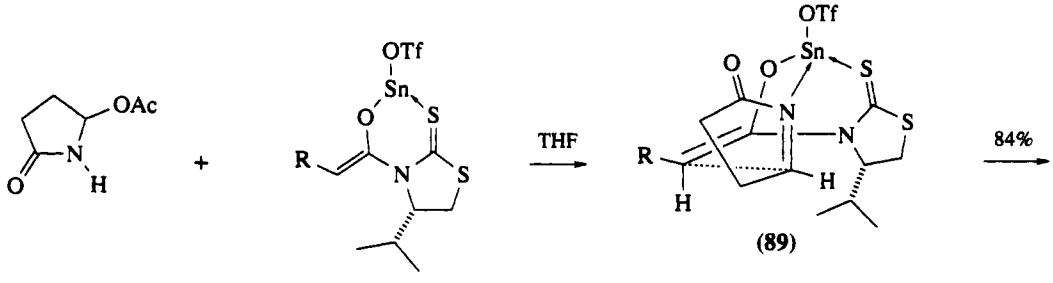
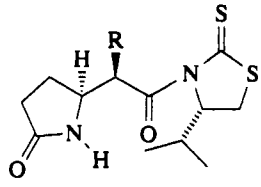
(47)



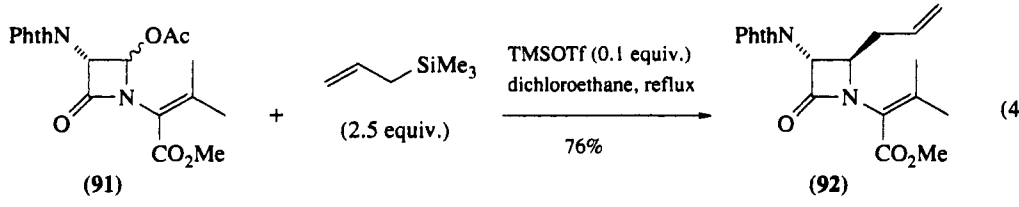
(89)



(90)

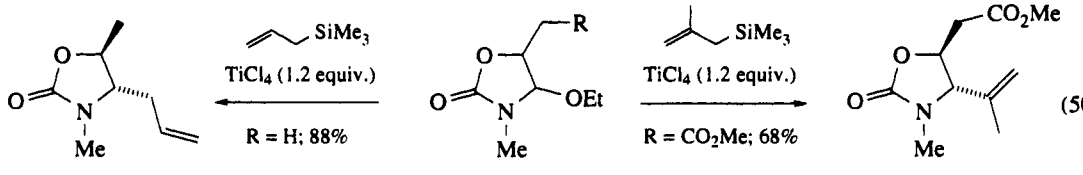
(48)

Acid-induced reactions of silicon-containing unsaturated compounds with *N*-acyliminium intermediates have proven particularly useful. Allylsilanes lead to the corresponding allyl-substituted products.[84,85] This reaction proceeds well even for β-lactams (equation 49).[85,86] The penicillin-derived 4-acetoxyazetidinone (**91**) reacts with excess allylsilane in refluxing dichloroethane, catalyzed by TMSOTf, to produce as the sole product *trans* compound (**92**).[86] *N*-Acyliminium ions generated from cyclic ureas[87] and carbamates (**93**)[88] likewise yield allylated products with virtually complete *trans* stereoselectivity (equation 50). Allylstannanes react under somewhat milder conditions than allylsilanes, requiring only a catalytic amount of $BF_3Z{\cdot}Et_2O$ at room temperature for a β-lactam system (equation 51).[89] This allylstannane procedure was applied to cyclic carbamate systems for the stereoselective synthesis of several isomers of statine.[90,91] Thus, ethoxycarbamate (**94**) reacts with methallyltributylstannane in excellent yield and diastereoselectivity (equation 52).[91]



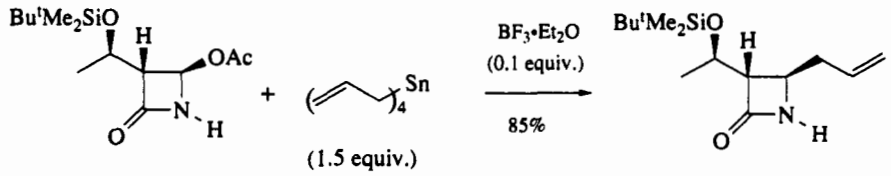
(91) (92)

(49)



(93)

(50)



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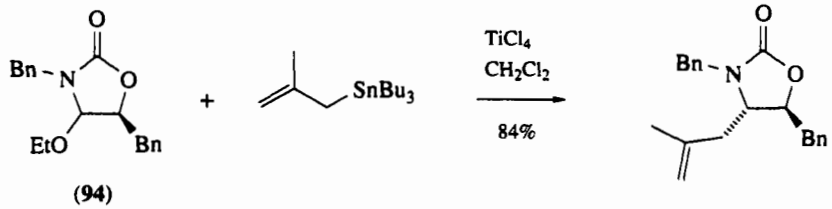
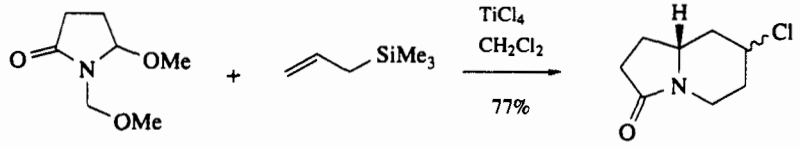


(94)

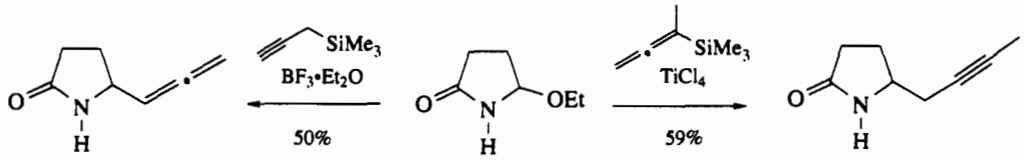
(52)

An intriguing tandem *N*-acyliminium process occurs when allylsilane reacts with *N,N*-bis(alkoxyalkyl)amides under the influence of $TiCl_4$ (equation 53).[92] The initially formed substitution product cyclizes after generation of a second *N*-acyliminium ion in an addition process with chloride acting as nucleophile.



(53)

Propargyltrimethylsilanes give allenyl derivatives on reaction with *N*-acyliminium precursors.[93,94] On the other hand, application of allenyl-silanes or -stannanes provides access to propargyl-substituted lactams.[95,96] All reactions proceed with high regio- and stereo-selectivity (equations 54 and 55). 4-Allenylazetidinones can be cyclized to Δ^1-carbapenem systems, mediated by Ag or Pd salts.[94,96] The reactions of ethoxylactams with allenylsilanes can be modified in such a way that bicyclic systems are obtained in one step (equation 56).[95]



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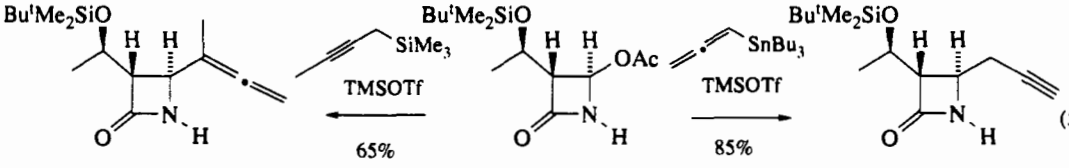

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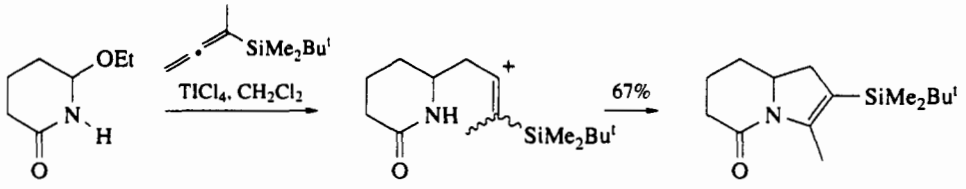
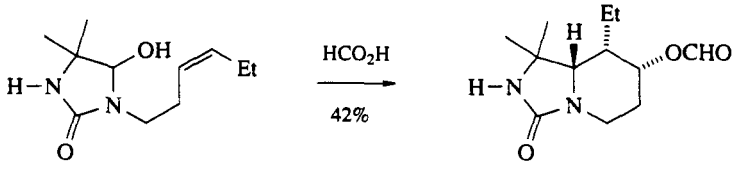


(56)

4.5.3.2 Intramolecular Reactions

4.5.3.2.1 Nucleophiles tethered to nitrogen

Intramolecular reactions of species (**69**) with simple alkenes have been of great importance in the field of *N*-acyliminium chemistry.[6] In Section 4.4.2.2, the mechanistic principles of *N*-acyliminium cyclizations using these π-nucleophiles have already been treated. If the carbon–carbon double bond tethered to the nitrogen atom does not have an electronic bias, a considerable preference exists for the formation of a six-membered ring by way of a chair-like transition state.[57] Some recent applications of this reaction type are the preparation of bicyclic imidazolidin-2-ones (equation 57)[97] and a cyclization reaction proceeding *via* a tertiary *N*-acyliminium intermediate generated by protonation of an enamide (equation 58).[98] A third example (equation 59) leads to a bicyclic system that apparently prefers proton loss instead of formation of a tertiary formate.[99]



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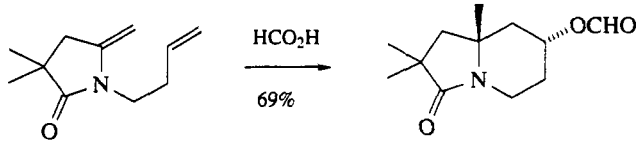

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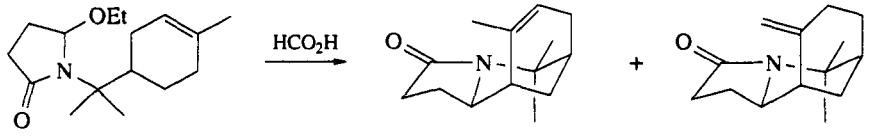
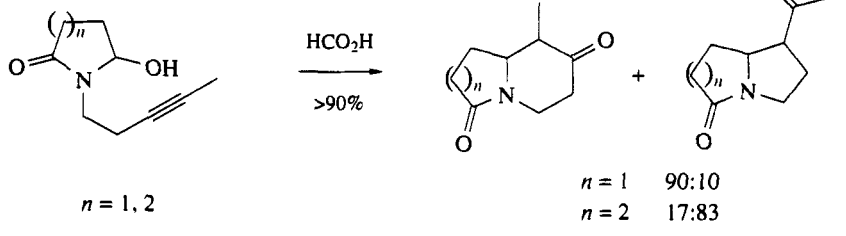
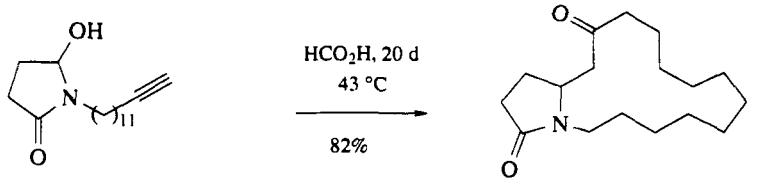


(59)

With alkynes the regiochemical outcome is subject to more subtle factors as is illustrated with the formic acid induced cyclization of two homologous hydroxylactams (equation 60). Starting from a pyrrolidinone, mainly six-membered ring formation occurs, whereas annulation onto a piperidinone ring leads mainly to the five-membered ring.[100] Important factors are the greater stability of linear *versus* bent vinyl cation character, which appears to be important for $n = 2$, and the lesser strain in a [4.3.0] compared to a [3.3.0] bicyclic system, which is dominant for $n = 1$. Terminal alkynes, biased for cyclization in the endo-dig mode, can be used for the preparation of macrocyclic rings (equation 61).[101]

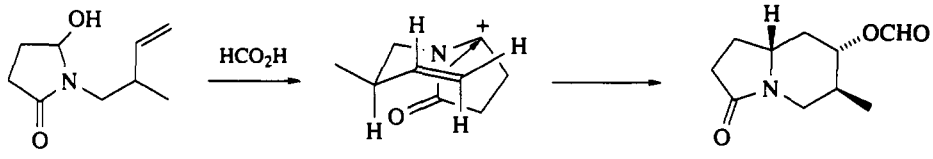


(60)

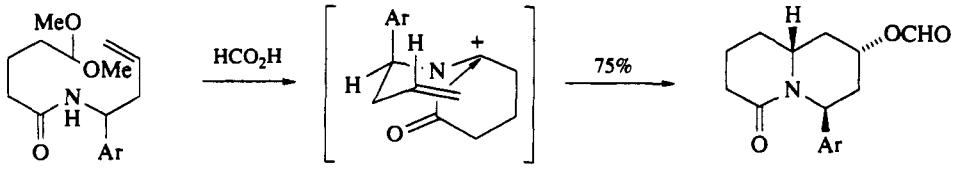


(61)

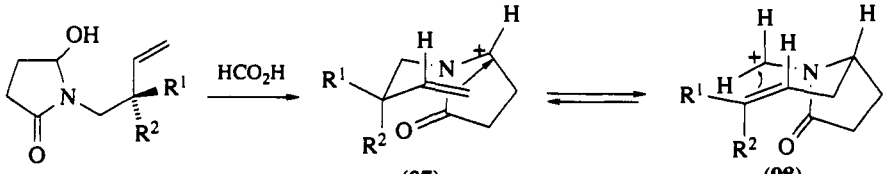
The effect of stereogenic centers along the chain connecting the π-nucleophile and the iminium moiety has been studied (equation 62 and 63). Hydroxylactam (**95**) cyclizes *via* a π-complex with the methyl group disposed equatorially in a chair geometry.[102] On the other hand, a substituent adjacent to nitrogen as in (**96**) prefers an axial orientation in order to avoid pseudo-allylic strain between the substituent and the lactam carbonyl group.[103] An interesting aspect becomes obvious when other substituents are present in the connecting chain (equation 64). The occurrence of a cationic aza-Cope equilibrium between (**97**) and (**98**) follows from the fact that with appropriate substituents R^1 and R^2 high yields of pyrrolizidines (**99**) instead of indolizidines (**100**) are obtained.[104,105] Pyrrolizidines are major products if both substituents are methyl groups, and if one is hydrogen and the other is aryl or methoxy. Such substituents clearly stabilize (**98**) relative to (**97**), so the equilibrium shifts to (**98**). Because the alkene is electronically biased with these substituents a five-membered ring (**99**) is preferentially formed. An elaborate application of this chemistry is the highly selective synthesis of (**101**) en route to a pyrrolizidine alkaloid (equation 65).[104] Alkynes also give rise to rearrangement (equation 66), which is obvious from the allenic product.[106] Apparently, the π-cyclization of both *N*-acyliminium ions is slower than hydrolysis of the rearranged species.



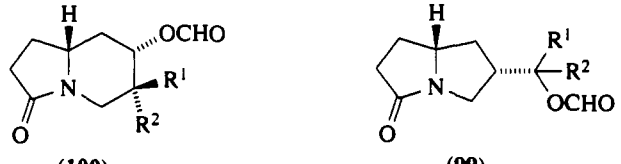
(95) (62)



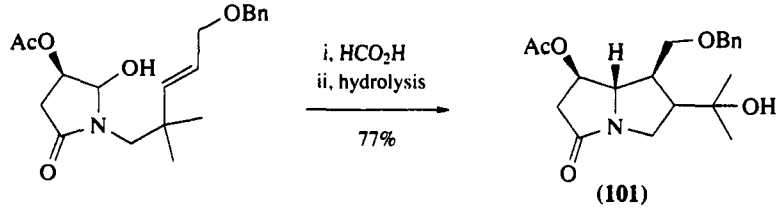
(96) (63)



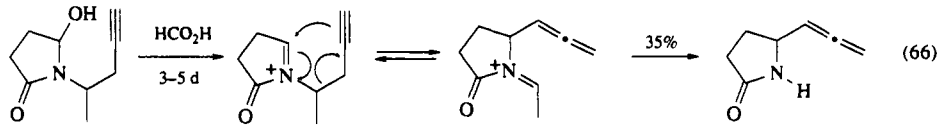
(97) (98)



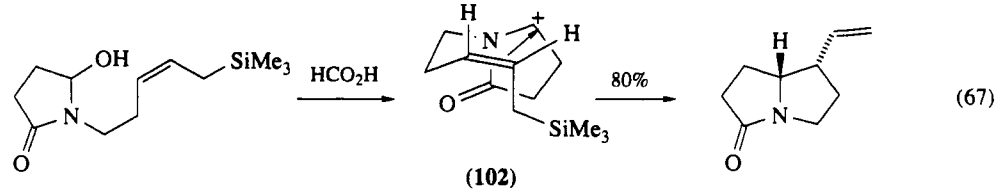
(100) (99) (64)



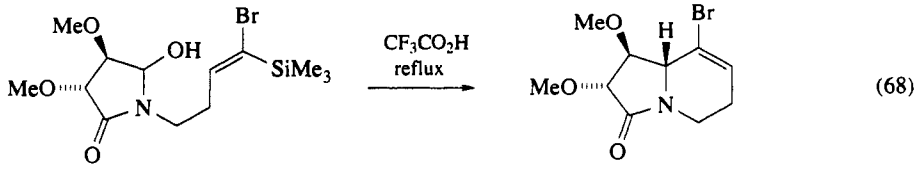
(101) (65)

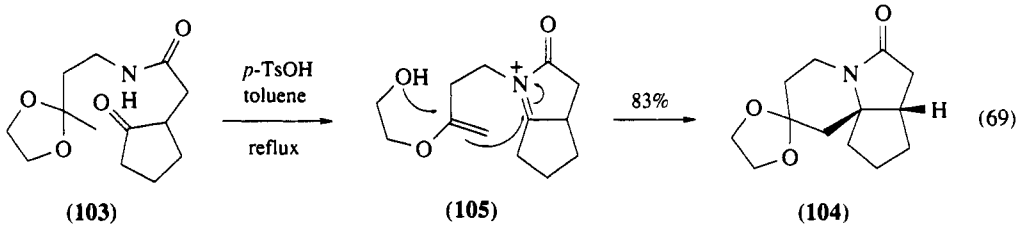


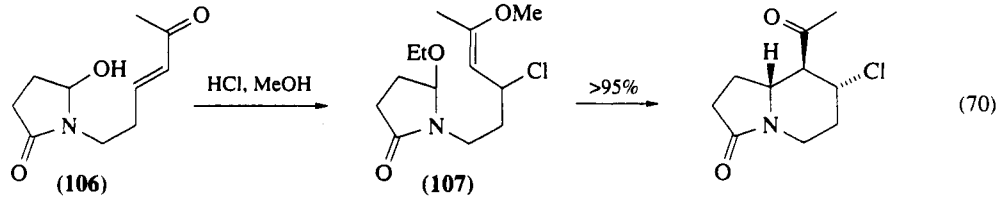
Special substituents have been introduced onto the alkene in order to direct the cyclization reaction to five-membered formation. Examples of electronically biased alkenes for this purpose are vinyl chlorides,[107] allylsilanes,[108] allylstannanes[109] and ketene thioacetals.[9] The cyclization of allyl-silanes and -stannanes to the pyrrolizidine system is highly stereoselective.[108,109] The chair geometry of π-complex (**102**) explains this selectivity (equation 67).



Vinylsilanes and enol ethers are also useful as π-nucleophiles. A vinylsilane cyclization is an important step in a synthesis of (+)-streptazoline from tartaric acid (equation 68).[110] This reaction also nicely illustrates the high *trans* stereoselectivity of cyclization with respect to the C-4 oxygen substituent.[9] The use of enol ethers is exemplified by two special cases (equations 69 and 70). The keto amide (**103**) is converted into tetracyclic (**104**) in a one-pot procedure involving (**105**) as a key intermediate.[111] A remarkable process is the quantitative cyclization of enone (**106**), despite the low nucleophilicity of an enone double bond (equation 70).[112] The most likely mechanism involves enol ether (**107**). It must be added that the conditions, saturated methanolic HCl, are crucial for the success of this reaction.



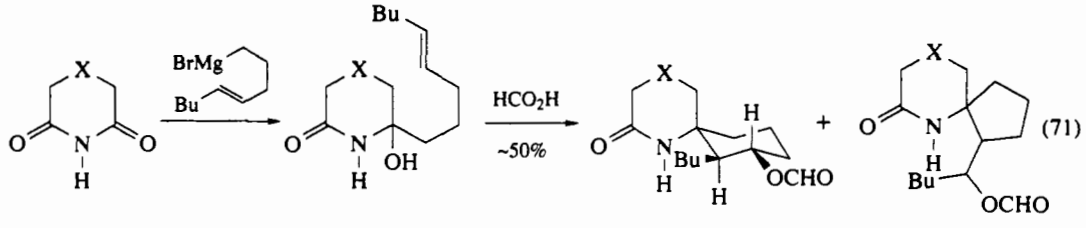




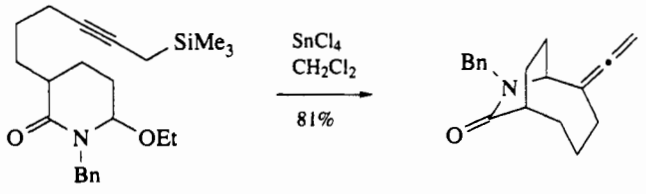
4.5.3.2.2 Nucleophiles tethered otherwise to the N*-acyliminium moiety*

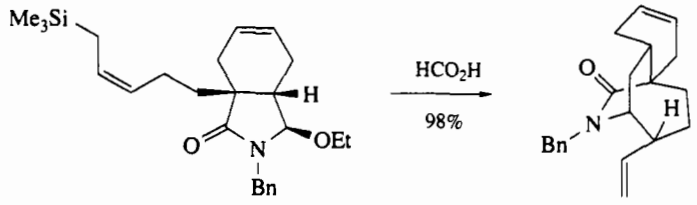
If the carbon chain containing the nucleophile is not attached to nitrogen, the preference for six-membered ring formation is less pronounced. This is apparent from the spirocyclizations utilized for the synthesis of perhydrohistrionicotoxin (equation 71).[25,26] The tertiary *N*-acyliminium ion derived from (**108**) cyclizes to a mixture of (**109**) and (**110**). Surprisingly, the amount of five-membered ring product (**110**)

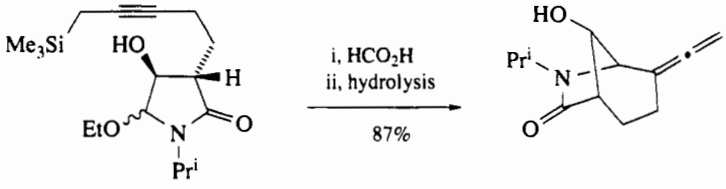
is much higher for X = O than for X = CH_2. Cyclizations of *N*-acyliminium precursors in which the nucleophile is connected to the carbon atom adjacent to the carbonyl function proceed very well, if the more reactive allyl- or propargyl-silanes are employed.[113,114] These reactions lead to bridged systems, containing a vinyl or an allenyl function, respectively (equations 72 and 73). The starting materials are readily synthesized through alkylation of the lithium enolate derived from a simple ethoxylactam. This methodology is used for the synthesis of (–)-peduncularine from (*S*)-malic acid (equation 74).[115] Another type of cyclization precursor, utilized for the total synthesis of mesembrine, bears the nucleophile-containing chain at the carbon adjacent to the iminium carbon atom (equation 75).[116] Ring closure in this case is effected through heterolysis of a mesylate. The final example forms part of a synthetic approach to gelsemine and involves the use of a triisopropylsilyl enol ether as nucleophile (equation 76).[117] A special aspect of this process is its high stereospecificity. The (*E*)-enol ether (**111**) produces aldehyde (**112**) in *ca.* 90% yield, whereas the (*Z*)-isomer yields (**113**) with similar selectivity.

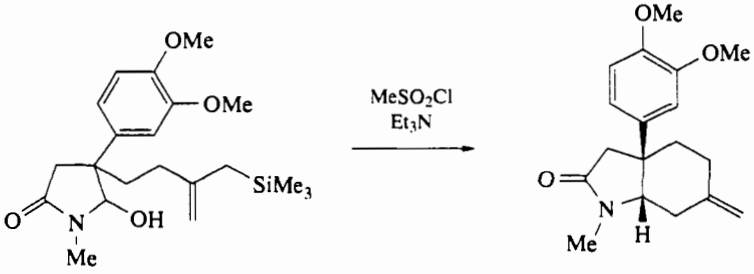


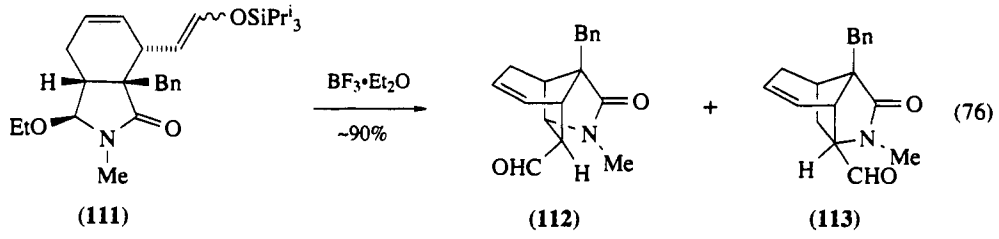
(**108**) (**109**) (**110**)











(111) (112) (113) (76)

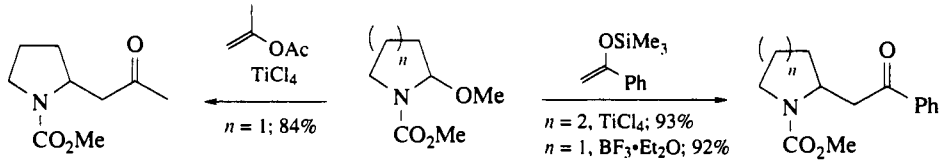
4.5.4 ENDOCYCLIC IMINIUM IONS WITH THE *N*-ACYL GROUP OUTSIDE THE RING

N-Acyliminium ions of this type can adopt the *s-cis* conformation (equation 77), so that Diels–Alder type cycloadducts might be expected on reaction with carbon–carbon multiple bonds. Although they may be intermediates, such cycloadducts have not been isolated thus far, mainly because of the type of π-nucleophile used in these reactions.

(77)

4.5.4.1 Intermolecular Reactions

Highly nucleophilic alkenes such as enol silanes and enol acetates react very well with this class of iminium ions (equation 78).[118] Slightly more than stoichiometric amounts of $TiCl_4$ or $BF_3{\cdot}Et_2O$ give the best results, and carbamates provide higher yields than amides.[118] The presence of an ester substituent at C-2 of the pyrrolidine system leads to a 70:30 mixture of products with the *cis* isomer in excess (equation 79).[119] Remarkably, a silyloxy substituent at C-4 gives rise to a highly stereoselective reaction with allylsilane, producing the *cis* product in greater than 97% selectivity (equation 80).[120] The origin of this large preference for formation of the *cis* product is unclear. The presence of an acetoxy function adjacent to the iminium carbon atom gives a surprisingly low selectivity in the allylation reaction (equations 81 and 82).[121] Similar reactions in the piperidine system are attended with high selectivity. Thus, an ester substituent at C-2 imparts high preference for *cis* attack in reactions at C-6 (equation 83).[119,122] This is in agreement with the expectation that the C-2 carbomethoxy function is axially disposed and addition at C-6 takes place from an axial direction. Less readily understood is the observation that a C-5 hydroxy func-



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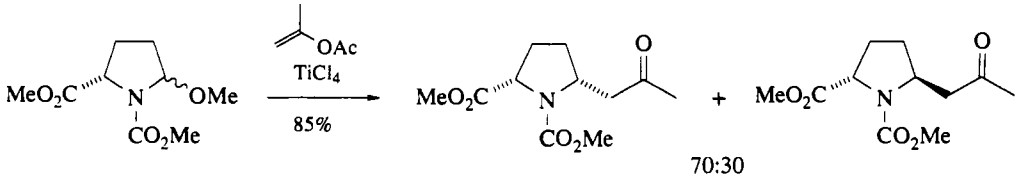

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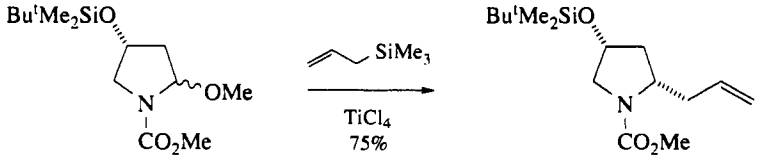
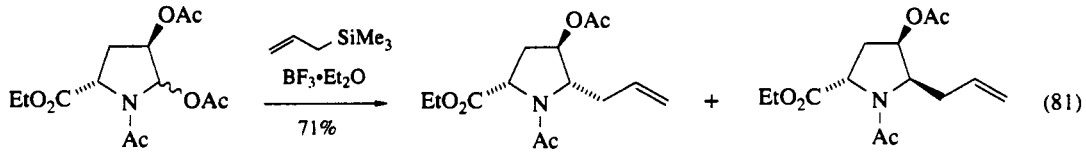
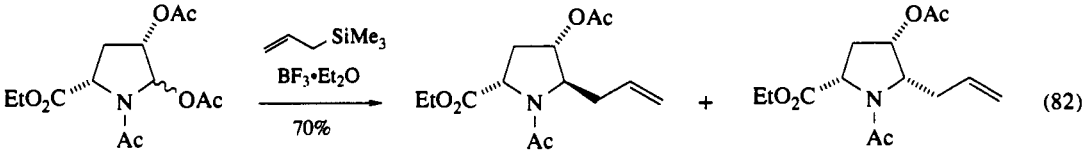
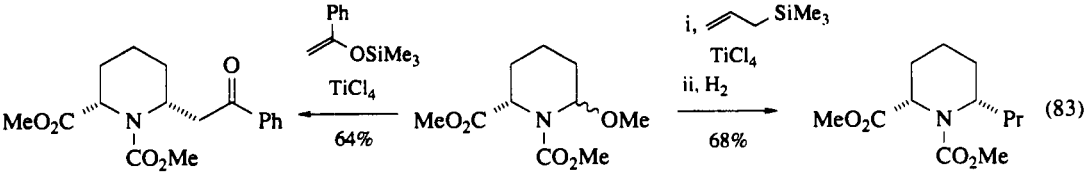


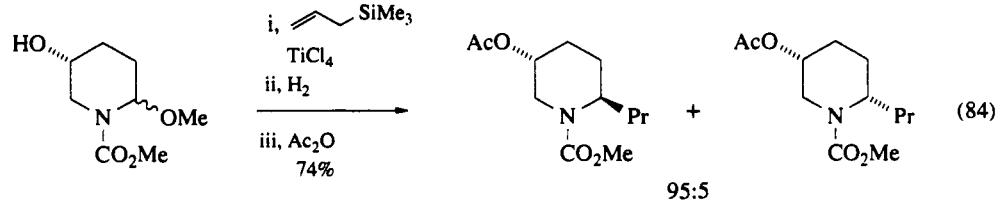
(80)

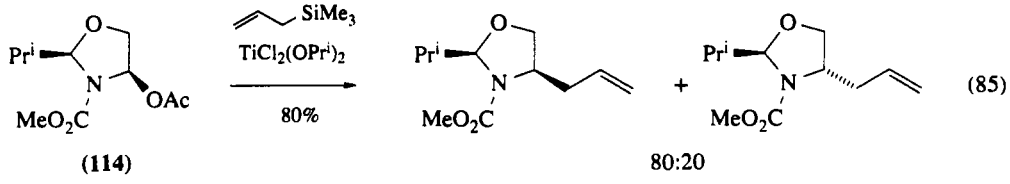
tion directs allylation at C-2 to occur in a *trans* fashion (equation 84).[123] The oxazolidine (**114**), readily derived from serine, leads mainly to the *cis* product on reaction with allylsilane (equation 85).[124]





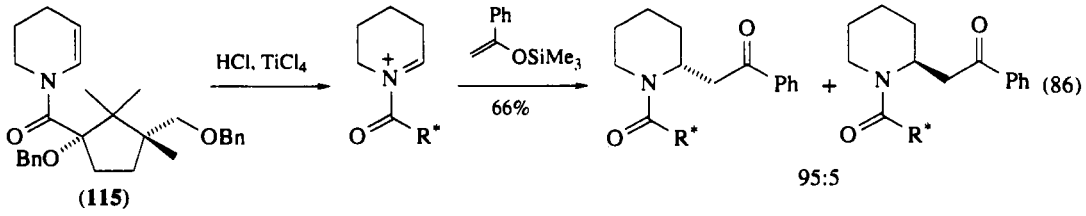


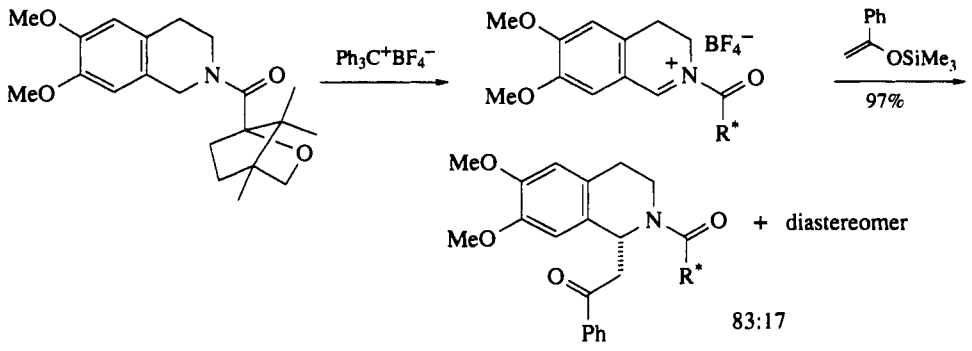




Chirality in the *N*-acyl substituent can also induce stereoselectivity in the iminium addition process (equation 86).[50] The chiral auxiliary in (**115**) appears to be one of the best chiral inductors and reacts with the silyl enol ether from acetophenone in 90% diastereoselectivity. It is argued that the *N*-acyliminium intermediate in this reaction adopts the *s-trans* conformation.[50] Similar methodology is used for the asymmetric synthesis of tetrahydroisoquinolines (equation 87).[125] The reactive intermediate is generated through hydride abstraction from the amide by using the triphenylmethane cation.

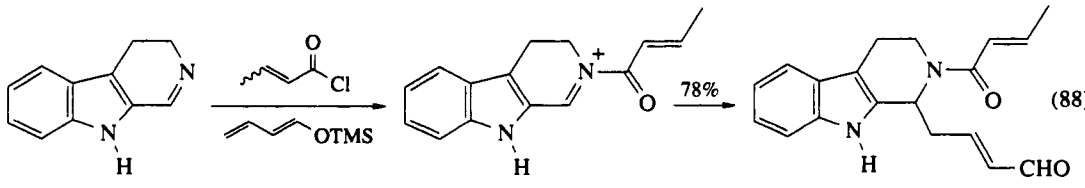
N-Acyliminium ions, generated from imines by acylation, are trapped in a one-pot reaction with reactive π-nucleophiles like allylstannanes[126] and enol silanes (equation 88).[127] Thus, β-dihydrocarboline





(87)

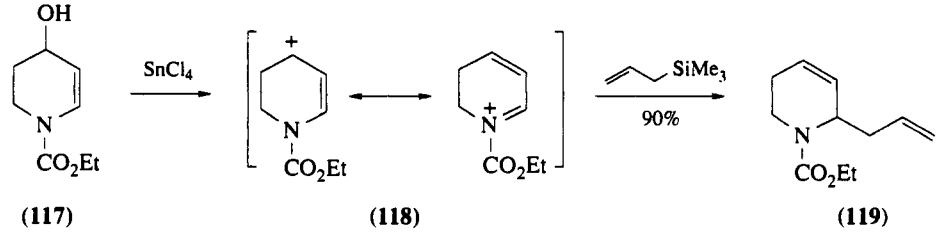
reacts with crotonyl chloride in the presence of a dienol silane to produce (**116**) in good yield.[127] This methodology is useful for the synthesis of alkaloids.



(88)

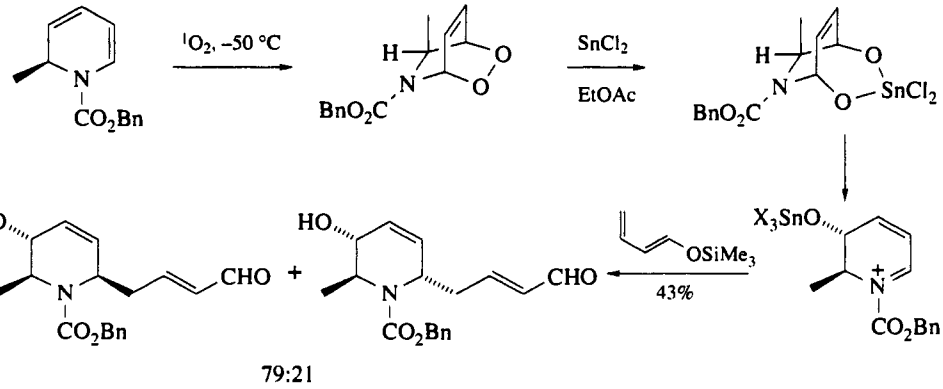
(**116**)

N-Acyliminium ions conjugated with an alkene have received particular attention in six-membered rings and are usually prepared from pyridines. Alcohol (**117**) gives on treatment with Lewis acid the delocalized species (**118**), which reacts with allylsilane to produce the 2-substituted product (**119**) as a single regioisomer (equation 89).[128] A different method to generate such reactive intermediates consists of the treatment of dihydropyridines with singlet oxygen, followed by tin(II) chloride (functioning both as reducing agent and Lewis acid) in the presence of a π-nucleophile (equation 90).[129] The reaction with oxygen is very stereoselective and the addition to the iminium species gives mainly the 2,6-*cis* product, exemplified by the reaction with 1-(trimethylsilyl)oxybuta-1,3-diene (equation 90).[130] Another example of this methodology (equation 91) features a simple silyl enol ether as nucleophile and a methyl group at C-5. The nucleophile again enters mainly *cis* with respect to the methyl substituent.[131]



(89)

(**117**) (**118**) (**119**)



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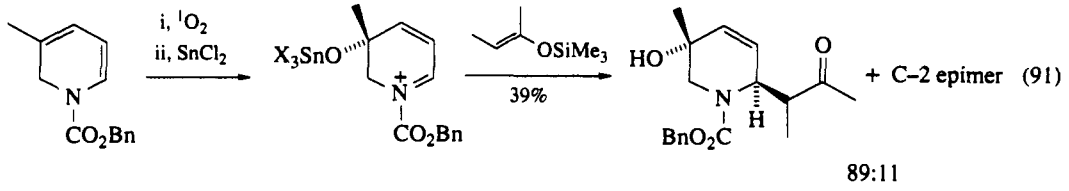
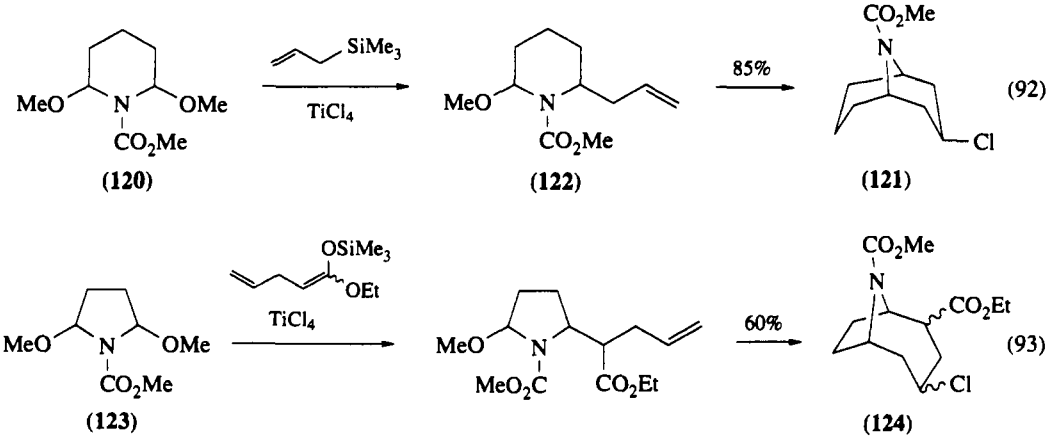
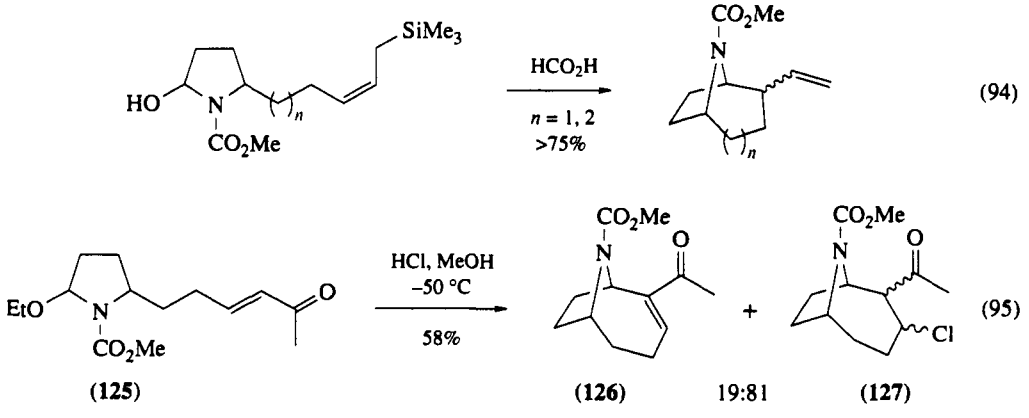


If the nitrogen atom in the *N*-acyliminium precursor is flanked by two methoxy groups, two consecutive carbon–carbon bond-forming reactions can occur (equations 92 and 93). Piperidine derivative (**120**) reacts with allylsilane under the influence of $TiCl_4$ to produce azabicycle (**121**) in one step, probably *via* intermediate (**122**).[92] Likewise, pyrrolidine (**123**) directly leads to bicycle (**124**), which is useful for the synthesis of anatoxin-a.[132]

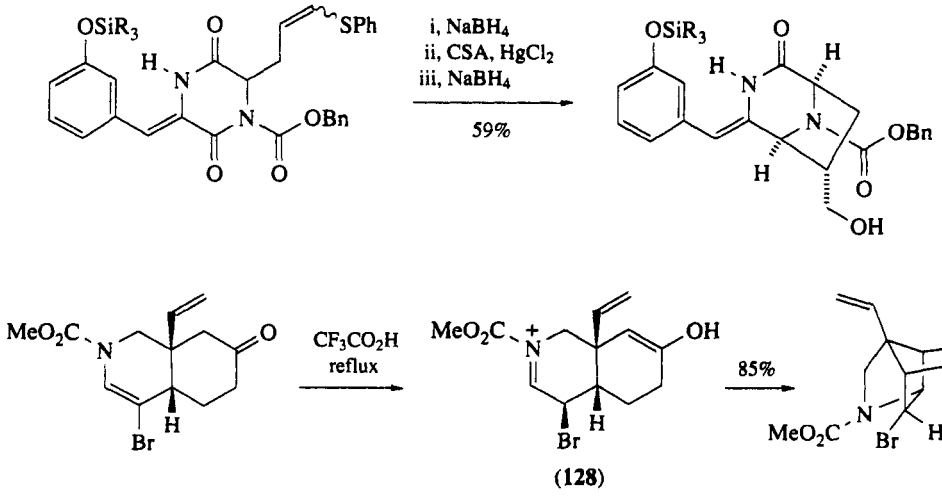


4.5.4.2 Intramolecular Reactions

This reaction type is useful for the synthesis of tropane-like azabicycles (equations 94 and 95). Allyl- and propargyl-silanes are excellent nucleophiles in this process.[133] Enone (**125**) is probably first transformed into an enol ether (*cf.* equation 70) before it cyclizes to the homotropane skeleton, which is eventually isolated as a mixture of enone (**126**) and chloride (**127**).[134]



Two more complex examples of this reaction type are used in work on the total synthesis of quinocarcin and gelsemine. A vinyl sulfide is employed as nucleophile in an *N*-acyliminium cyclization to produce the bridged substructure of quinocarcin (equation 96).[135] A genuine equivalent of the Mannich reaction is put to practice in a synthetic approach to gelsemine (equation 97).[136] The iminium intermediate, simply generated by protonation of the enecarbamate, apparently reacts only with the enol shown in (**128**).



(96)

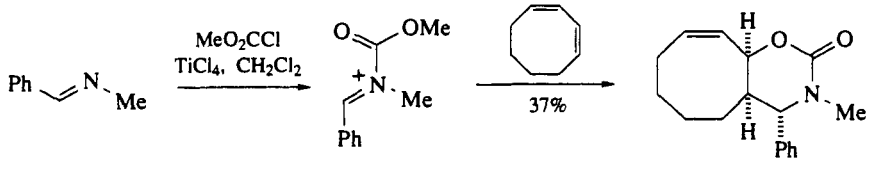
(97)

(128)

4.5.5 ACYCLIC *N*-ACYLIMINIUM IONS

4.5.5.1 Intermolecular Reactions

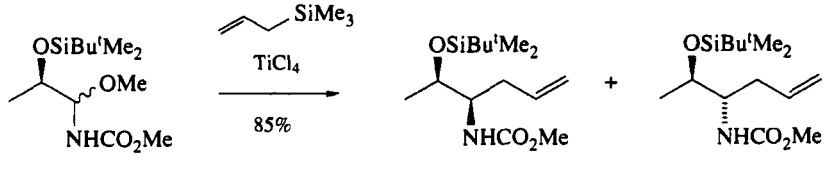
The majority of the presently known *N*-acyliminium reactions are of this type and have been reviewed extensively.[5,58,59] Depending on the substitution patterns of iminium species and π-nucleophile, either a cycloadduct is obtained as the product, or an acyclic product is isolated, often *via* the intermediacy of an unstable cycloadduct. When 1,3-dienes are used as nucleophiles they often behave as 4π-electron components in a Diels–Alder type reaction (equation 33).[64–66] Interestingly, cycloocta-1,3-diene, unsuited as a Diels–Alder diene, reacts as an isolated alkene with *N*-acyliminium species (**129**) to give cycloadduct (**130**) in moderate yield (equation 98).[137]



(98)

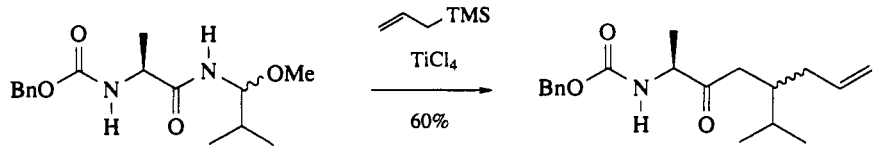
(129) (130)

The use of enol silanes[118] and allylsilanes[124,138] as π-nucleophiles usually leads to acyclic products. The enantiomerically pure *N*-acyliminium precursors (**131**) and (**132**) are prepared from α-amino acid derivatives.[124] Reaction with allylsilane under the influence of $TiCl_4$ proceeds with 60% stereoselectivity in the case of carbamate (**131**); however, the precursor (**132**) reacts indiscriminately under these circumstances (equations 99 and 100).[124] A more complex allylsilane (**133**) reacts with iminium precursor (**134**) in the presence of $EtAlCl_2$ to produce carbamate (**135**) as a single diastereomer in 48% yield (equation 101).[139]



(99)

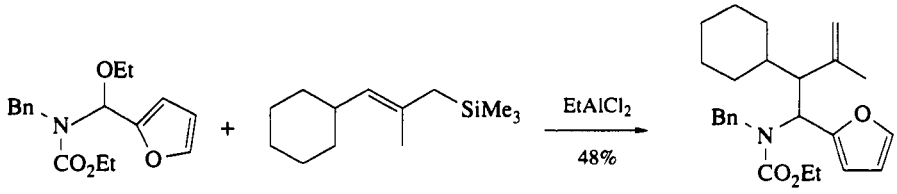
(131) 80:20



(100)

(132)

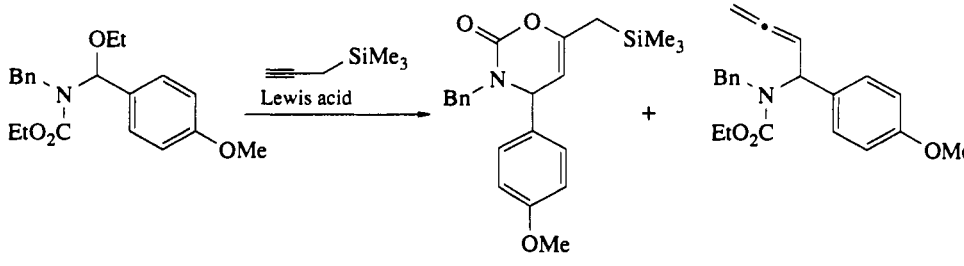
ca. 50:50 mixture



(101)

(134) (133) (135)

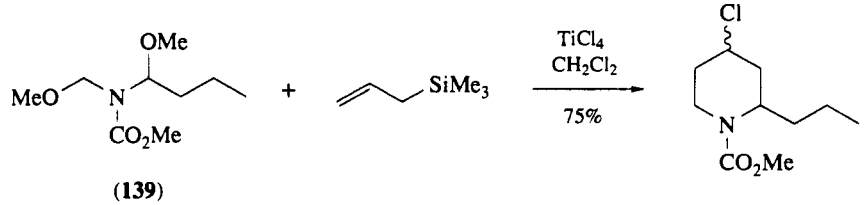
The use of propargyltrimethylsilane as π-nucleophile may lead to cyclic products.[138] Thus, reaction of ethoxycarbamate (**136**) in the presence of $SnCl_4$ gives oxazinone (**137**) as the sole product in 56% yield (equation 102). However, when $EtAlCl_2$ is used as Lewis acid, a 75:25 mixture of (**137**) and allene (**138**) is obtained in 63% total yield. Interesting further details are that 1-pentyne does not react with (**136**) under similar conditions and that allyltrimethylsilane produces the allyl analogue of (**138**) in almost quantitative yield. It remains unclear whether (**138**) arises *via* the intermediacy of a cycloadduct or is formed directly from (**136**) without involvement of the carbonyl function.



(102)

(136) (137) (138)

An interesting application of allylsilane as π-nucleophile is the tandem *N*-acyliminium coupling with dimethoxycarbamate (**139**). Piperidine derivative (**140**) is obtained as a mixture of diastereoisomers (equation 103).[92]



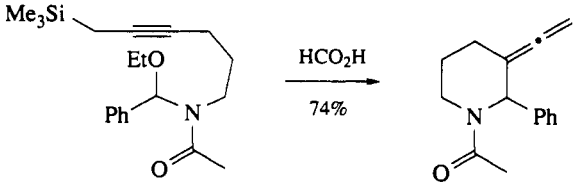
(103)

(139)

4.5.5.2 Intramolecular Reactions

If the π-nucleophile is geometrically well positioned with respect to the *N*-acyliminium moiety, an intramolecular cycloaddition takes place with high stereospecificity giving bicyclic 5,6-dihydro-1,3-oxazines (equations 29 and 30).[61] However, geometric or electronic reasons often prevent this cycloaddition, or render the cycloaddition product unstable, so that simple π-cyclization products are usually obtained. Very successful nucleophiles are again propargyl- and allyl-silanes. The former lead to

heterocyclic allenes (equation 104)[30] and the latter give rise to formation of vinyl-substituted products (equation 105).[31] Pyrrolidines are obtained as pure *trans* isomers, which is the result of the favorable chair-like conformation (**140**) of the intermediary π-complex with an (*E*)-iminium geometry (equation 105). Piperidines are formed less stereoselectively as a 2:1 mixture, with the *trans* product still as the major isomer.[31] An elegant application of this methodology can be found in a synthetic approach to gelsemine (equation 106).[140]



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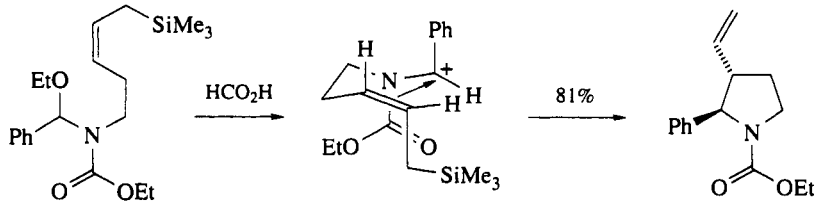
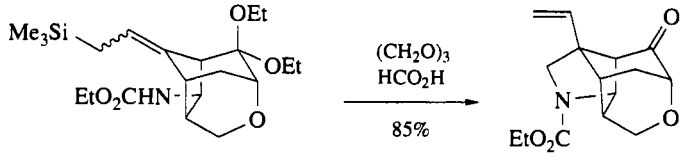


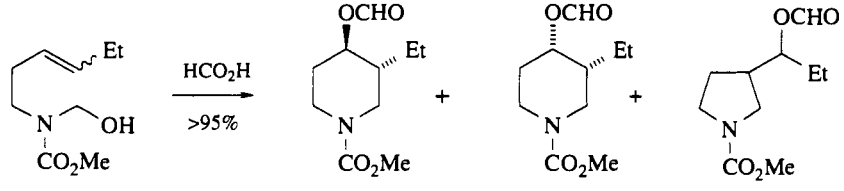
(105)

(**140**)



(106)

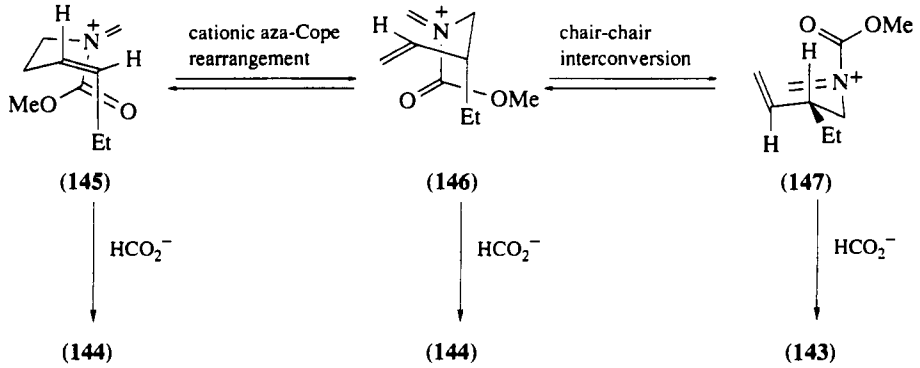
Recently, cyclizations of the isomeric unsaturated carbamates (**141**) and (**142**) have been investigated (equation 107).[139] These fundamental reactions are not as regio- and stereo-selective as similar cyclizations starting from cyclic *N*-acyliminium ions (equations 25 and 26).[57] The loss of stereoselectivity might have to do with the occurrence of cationic aza-Cope rearrangements in combination with chair–chair interconversions (equation 108). Normal cyclization of (**142**) occurs *via* conformation (**145**) and should lead to (**144**). If sigmatropic rearrangement competes with normal cyclization, (**146**) arises, but this conformation still leads to (**144**). Only after chair–chair interconversion to (**147**) and subsequent cyclization, (**143**) is formed. *Via* the same mechanism (**141**) can produce the abnormal product (**144**).



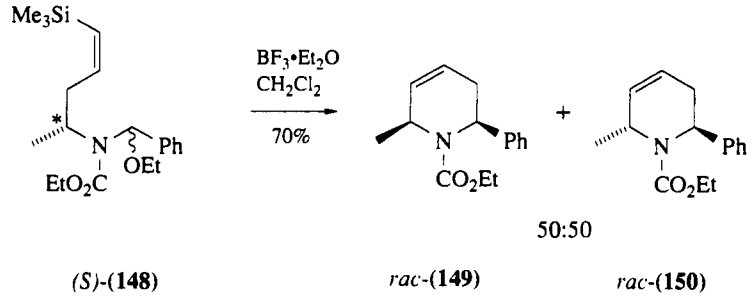
(107)

		(**143**)		(**144**)		
(**141**)	(*E*)	88	:	8	:	4
(**142**)	(*Z*)	18	:	73	:	9

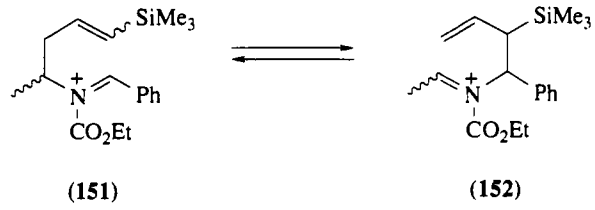
The occurrence of a fast cationic aza-Cope rearrangement has been proven in the case of vinylsilane cyclizations (equation 109).[32] Enantiomerically pure ethoxycarbamate (**148**) cyclizes under the influence of $BF_3{\cdot}Et_2O$ to a 1:1 mixture of racemic tetrahydropyridines (**149**) and (**150**). Thus, the equilibration of iminium ions (**151**) and (**152**), attended with racemization (equation 110), occurs much faster than π-cyclization. Because allylsilanes are more nucleophilic than vinylsilanes, π-cyclization probably takes place from (**152**). The fast rate of cyclization of allylsilanes is apparent from the cyclization *via* (**140**), where cationic aza-Cope rearrangement cannot compete (equation 105).



(108)

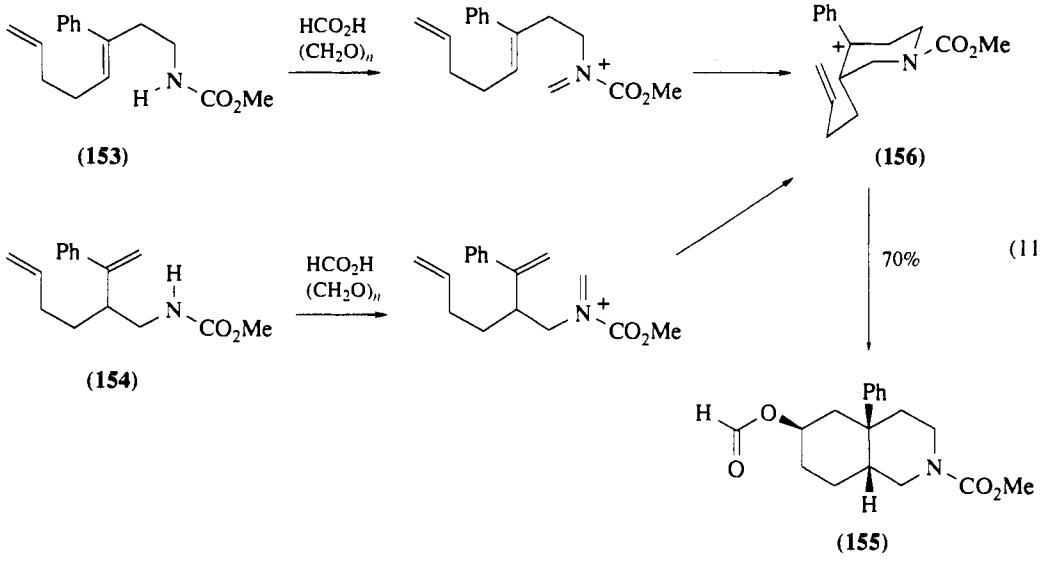


(109)



(110)

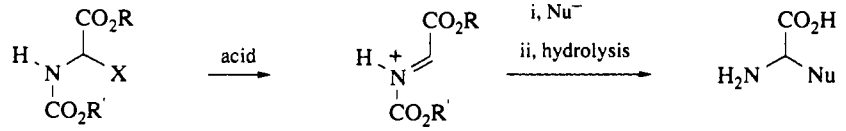
Two consecutive π-cyclizations take place when carbamates (**153**) and (**154**) are dissolved in formic acid containing paraformaldehyde (equation 111).[141,142] From both starting materials the same single *cis*-fused perhydroisoquinoline (**155**) is obtained. This means that carbocation (**156**) is a common intermediate, which cyclizes further in the conformation as depicted.



(111)

4.5.6 *C,N*-DIACYLIMINIUM IONS (GLYCINE CATION EQUIVALENTS)

N-Acyliminium intermediates (**157**), bearing a carbonyl function at the iminium carbon atom, are of great utility for the synthesis of α-amino acids (equation 112). The presence of the extra electron-withdrawing functionality renders the iminium species (**157**) more electrophilic, compared to the intermediates described heretofore. Therefore, better leaving groups X or stronger acids may be necessary to generate (**157**), which otherwise behaves as a normal *N*-acyliminium intermediate.



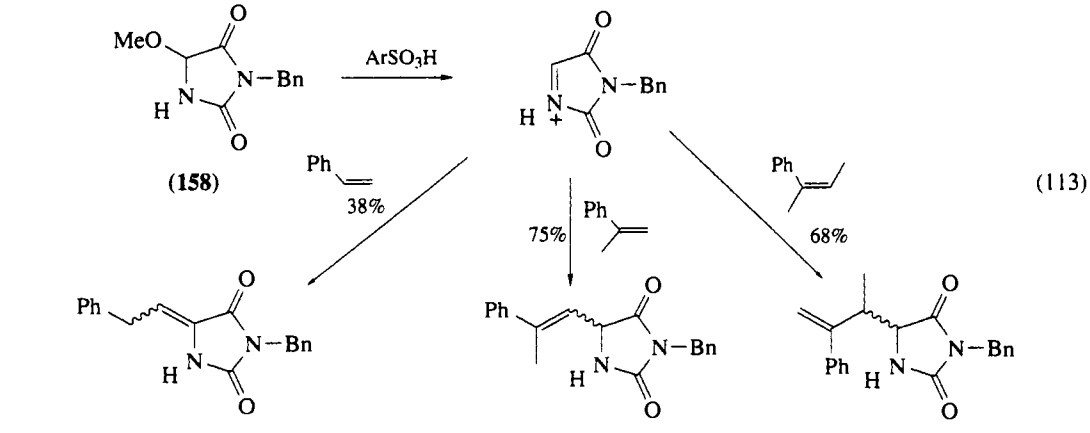
(112)

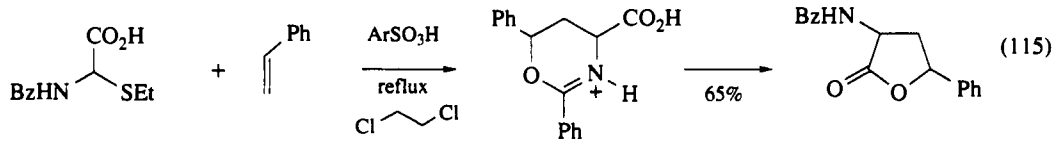
(**157**)

4.5.6.1 Intermolecular Reactions

The first studies of this reaction type were performed with 5-methoxyhydantoin (**158**).[143] Three different products can be formed on reaction with alkenes, dependent on the substitution pattern of the alkene (equation 113). The strongly acidic and non-nucleophilic conditions apparently disfavor formation of addition products. Such conditions lead to similar results in the case of acyclic iminium precursor (**159**),[144,145] although in the case of styrene the double bond ends up in a different position (*cf.* equations 113 and 114).[146] Interestingly, milder conditions (BF_3·Et_2O, 20 °C) lead to cycloadduct (**160**) in good yield. It is probable that protonated (**160**) is an intermediate in the sulfonic acid induced procedure (equation 114). When styrene is allowed to react with the free acid of (**159**) in the presence of sulfuric acid in ice-cold dioxane, the γ-lactone (**161**) is produced as the product, albeit in only 25% yield, presumably by way of rearrangement of intermediate (**162**).[146] A better yield of (**161**) is obtained when the ethylthio function is used as leaving group (equation 115).[147] With 1,3-dienes a similar course of the reaction is observed as the major process, giving, for example, vinyl-substituted γ-lactone (**163**) from 1,3-butadiene (equation 116).[148] A minor portion of the diene reacts as a 4π-electron component with the *N*-acyliminium moiety,[65,66] producing pipecolic acid derivatives, *e.g.* (**164**).

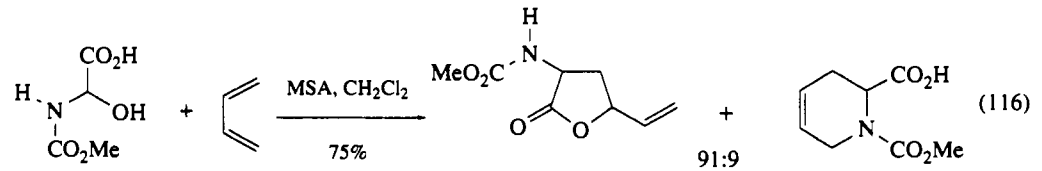
Reaction of glycine cation equivalents with vinylsilanes leads to β,γ-unsaturated α-amino acid derivatives with high regio- and stereo-selectivity.[149] Thus, chloroglycine derivative (**165**) reacts with (*E*)-β-tri-





(115)

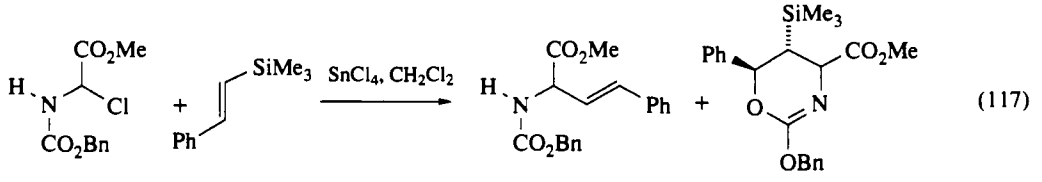
(162) (161)



(116)

(163) (164)

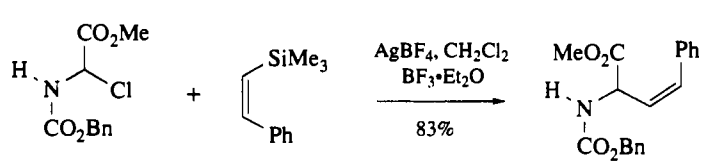
methylsilylstyrene to give substitution product (**166**) in >95% stereospecificity. The cycloaddition product (**167**) is isolated in negligible amount. The corresponding (*Z*)-silylstyrene does not react, however, under the same conditions, but requires a stoichiometric quantity of silver cation (equation 118). In this way the (*Z*)-β,γ-unsaturated α-amino acid derivative (**168**) is accessible in good yield.[149]



(117)

>75% <5%

(165) (166) (167)

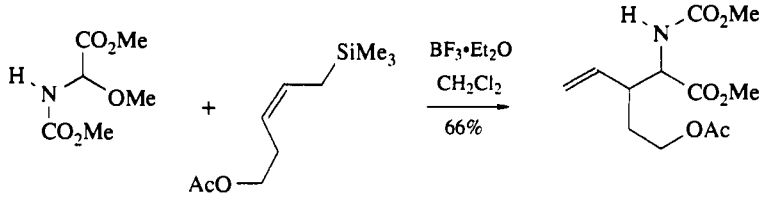


(118)

(165) (168)

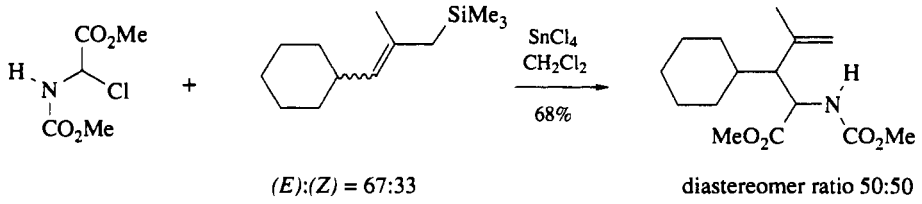
The use of allylsilanes as nucleophiles gives γ,δ-unsaturated α-amino acid derivatives.[150,151] These reactions proceed with high regioselectivity, governed by the silicon β-effect, but the stereoselectivity is low (equations 119 and 120).[151] Enol silanes provide a ready access to γ-oxo-α-amino acid derivatives (equation 121).[39,151] Interestingly, propargyltrimethylsilane does not give a linear product, but instead gives rise to formation of stable cycloadduct (**169**) in moderate yield (equation 122).[151] The different outcome of reactions of allyl- and propargyl-silanes bears analogy with earlier results.[138]

The enantiomerically pure cyclic *N*-acyliminium precursor (**170**) has proven useful for the synthesis of α-amino acids in enantiomerically pure form.[48] Both (**170**) and its enantiomer can be obtained from ben-



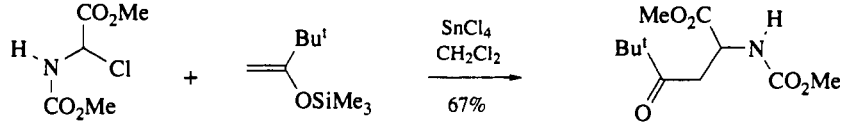
(119)

diastereomer ratio 63:37

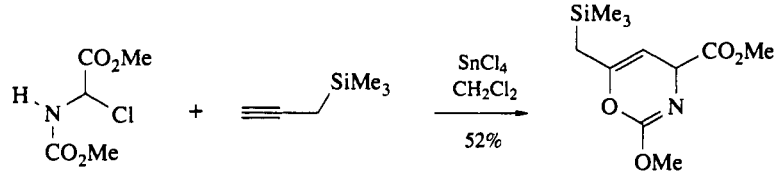


(120)

(*E*):(*Z*) = 67:33 diastereomer ratio 50:50



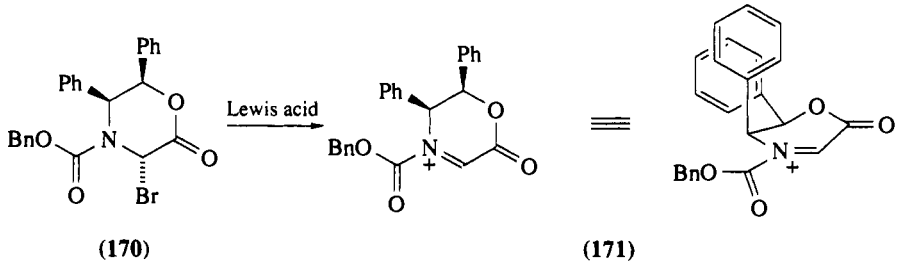
(121)



(122)

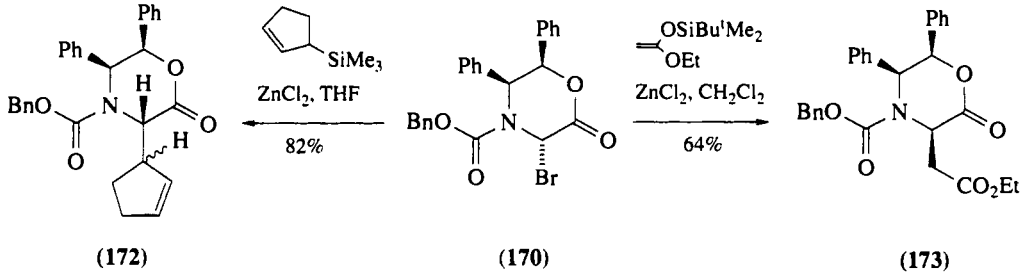
(169)

zoin in a few steps, including the resolution of racemic *erythro*-α,β-diphenyl-β-hydroxyethylamine by recrystallization of its L-glutamic acid salt. Lewis acidic treatment of (**170**) generates *N*-acyliminium species (**171**), which has a preferred conformation as depicted (equation 123). The 5-phenyl function adopts a pseudo-axial orientation, so that nucleophiles preferentially add to (**171**) in a trans fashion with respect to the phenyl substituents. Thus, allylsilanes give solely the trans products as exemplified (equation 124) with the preparation of (**172**), from which both cyclopentenyl- and cyclopentyl-glycine can be synthesized in one step. However, a strongly nucleophilic π-system like a silyl ketene acetal produces the cis product (**173**) almost exclusively (equation 124).[48,152] Apparently, the latter reaction follows a genuine S_N2 pathway. That both S_N1 and S_N2 mechanisms can be operative has been confirmed by using enol silanes as nucleophiles under various conditions, which give mixtures of cis and trans products. The trans/cis ratio increases by using a less nucleophilic enolsilane, a stronger Lewis acid, or a more polar solvent.



(123)

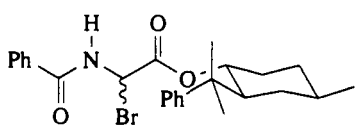
(170) **(171)**



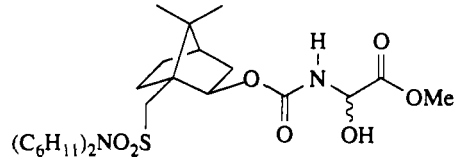
(124)

(172) **(170)** **(173)**

Other chiral glycine cation equivalents useful for the synthesis of enantiomerically pure α-amino acids are (**174**)[153,154] and (**175**).[155] However, acid-catalyzed reactions of these *N*-acyliminium precursors with alkenes or alkynes have not been reported yet. The $BF_3{\cdot}Et_2O$-mediated electrophilic aromatic substitution of (**175**) onto anisole in 98% diastereoselectivity deserves mention here.[155]



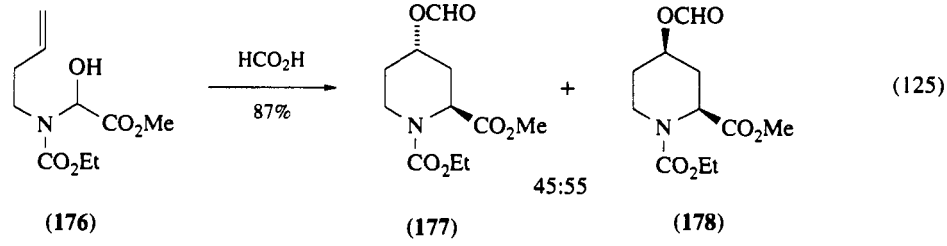
(**174**)



(**175**)

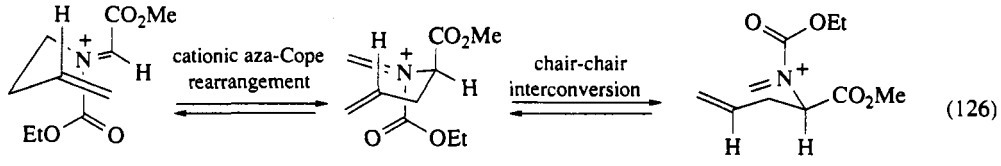
4.5.6.2 Intramolecular Reactions

Dissolution of glyoxylic ester adduct (**176**) in formic acid and stirring for 3 d gives rise to formation of two cyclization products (**177**) and (**178**) in good yield (equation 125).[139] If one assumes that cyclization only occurs *via* a chair-like transition state with an (*E*)-iminium geometry, the equilibria between species (**179**) to (**181**) well account for the products obtained (equation 126). In addition, one may expect that the cationic aza-Cope rearrangement between (**179**) and (**180**) lies at the side of the latter, because the electron-withdrawing ester function destabilizes species (**179**). Evidence for these assumptions has been obtained as follows. First, treatment of carbamate (**182**) with paraformaldehyde in formic acid also leads to a *ca.* 1:1 ratio of (**177**) and (**178**). Second, reduction of acetate (**183**) with triethylsilane in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gives carbamate (**184**) as the only isolable product. The cyclizations (equations 127



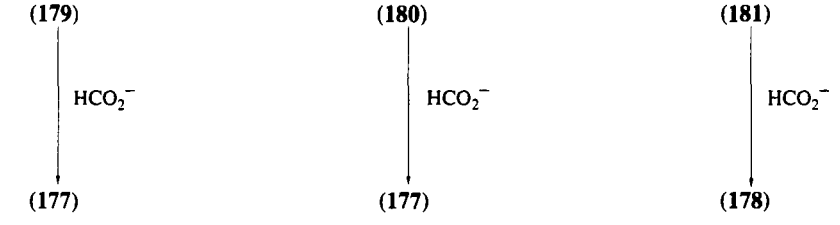
(125)

(**176**) (**177**) (**178**)



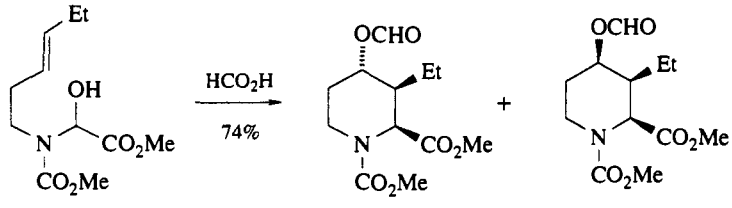
(126)

(**179**) (**180**) (**181**)



(**182**) (**183**) (**184**)

and 128) of the (*E*)- and (*Z*)-ethyl-substituted alkenes (**185**) and (**186**) proceed in a similar way as (**176**).[139] On the other hand, ring closure of allylsilane (**187**) does not show competition with a cationic aza-Cope rearrangement, because only proline derivatives are obtained (equation 129). Apparently, allylsilane cyclization is much faster than rearrangement followed by cyclization of the rearranged system. The major trans product arises from π-complex conformation (**188**). The origin of the minor cis product remains unclear. Thermal cyclization of the mesylate (**189**) gives a better yield and isomer ratio (equation 129). Pipecolic acid derivatives are formed by cyclization of the homolog of (**187**) to give an approximate 1:1 ratio of stereoisomers (equation 130).[15] The use of a propargylsilane moiety as nucleophile leads to an allenic product (equation 131).[15]



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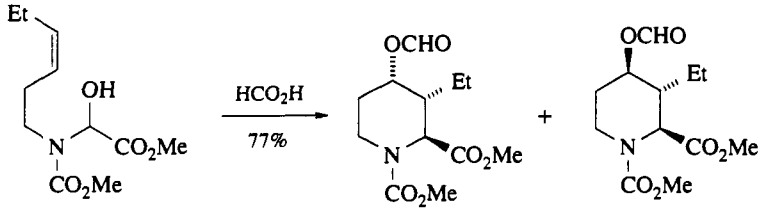

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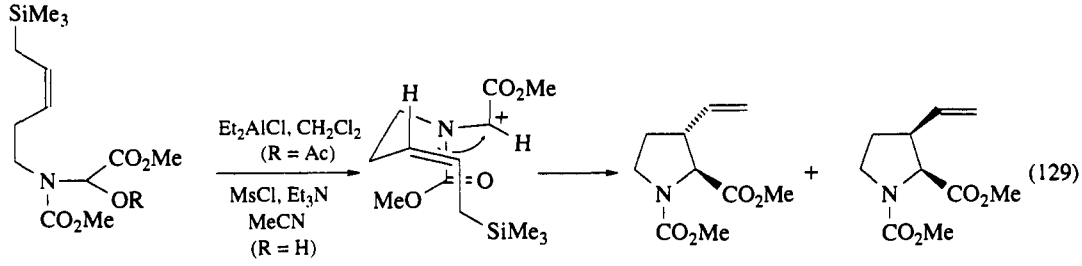

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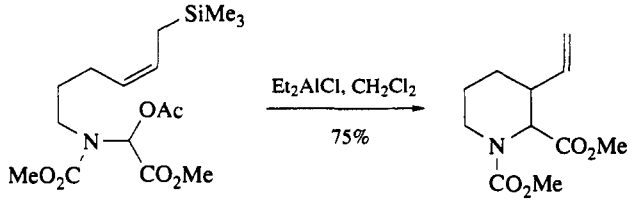

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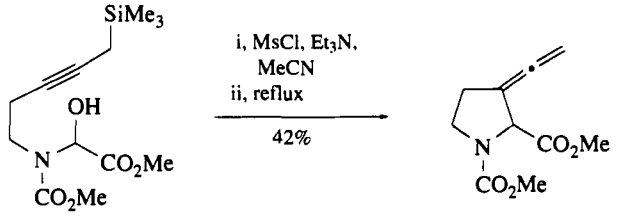
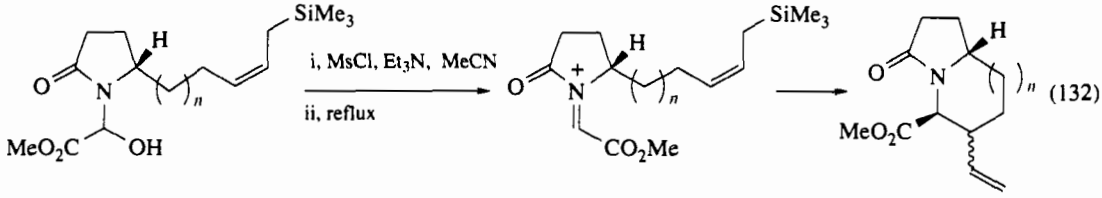


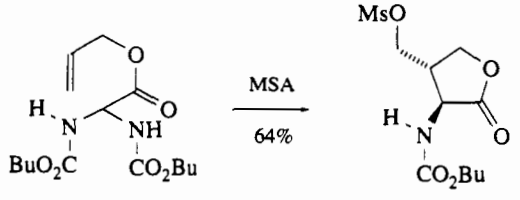
(131)

Addition of 5-substituted 2-pyrrolidinones to methyl glyoxylate produces useful precursors (**190**) to exocyclic *N*-acyliminium ions (equations 132).[156] The preferred iminium ion geometry is most probably (*E*) as depicted in (**191**) for steric reasons. This geometry explains the stereochemical relationship between the ring junction hydrogen atom and the ester function in the products (**192**) and (**193**). Best yields are achieved by using the thermal cyclization of intermediate mesylates, and the major products have the ester and vinyl function trans.[156]

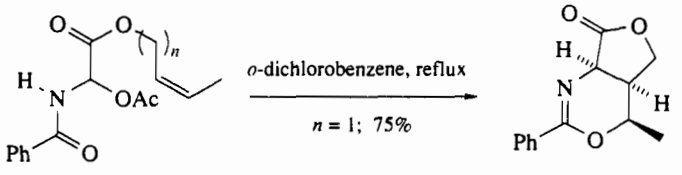


(**190**) (**191**) (**192**) n = 1; 57%
(**193**) n = 2; 97%

A remarkable observation is the cyclization of biscarbamate (**194**) to γ-lactone (**195**) mediated by methanesulfonic acid (equation 133).[157] No trace of the expected δ-lactone is formed, presumably because of the unfavorable ester geometry in the transition state required for six-membered ring formation. Such problems with δ-lactone formation have been observed also in Diels–Alder chemistry.[158,159] A nice example related to *N*-acyliminium chemistry is the thermal hetero Diels–Alder reaction of acylimine precursor (**196**) to bicyclic γ-lactone (**197**) in good yield. The corresponding intramolecular cycloaddition of (**198**) fails.[159] Finally, Lewis acid mediated cyclization of allylsilane (**199**) is unsuccessful, although lactonization of (**200**) proceeds very well (equation 135, *cf.* equation 119).[151]

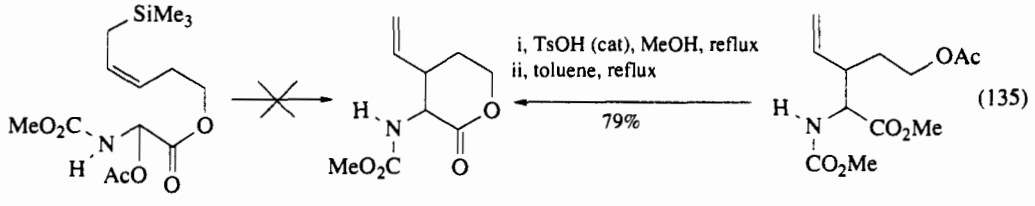


(**194**) (**195**)



(**196**) *n* = 1
(**198**) *n* = 2

(**197**)



(**199**) (**200**)

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4.6
The Passerini and Ugi Reactions

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4.6.1 INTRODUCTION AND BRIEF HISTORY OF ISOCYANIDE CHEMISTRY

Among the functional groups of organic chemistry the isocyanide group is not only unique because of its formally divalent carbon atom but also because of its unsurpassed versatility in chemical reactivity. Nevertheless, the chemistry of the isocyanides (**2**) developed quite sluggishly for a century.

The first isocyanide, allyl isocyanide, was prepared by Lieke in 1859[1,2a] from allyl iodide and silver cyanide; it 'tainted the air in the room for days' and provoked 'continuing complaints in the neighborhood about the vile odor'. At that time it was, however, not noticed that a new distinct class of chemical compounds had been discovered.

The realization that this was a new type of compound, isomeric to the nitriles,[3] and the elaboration of the classical methods for the preparation of isocyanides, the 'alkylation method' and the 'carbylamine method' by Gautier[2b,3] and Hofmann,[2c,4] initiated an active period of isocyanide chemistry that ended by the turn of the century with Nef's investigations on the reactions of the formally divalent carbon atom in the isocyanides.[2d,5] The discovery of the Passerini reaction in 1921[2e,6] led to a brief renaissance of isocyanide chemistry.

The reason why isocyanide chemistry did not attract more researchers in its first century was not the suspected toxicity,[2f] nor the vile smell of the volatile isocyanides, but rather it was the lack of accessi-

bility of pure isocyanides. In general, the aforementioned classical syntheses of isocyanides[2c,g-4] are not suitable for the preparation of any appreciable quantities of pure isocyanides.

The last step of the synthesis of the antibiotic xanthocillin by Hagedorn in 1956[7] is the first published synthesis of an isocyanide (**2**) by dehydration of an *N*-monosubstituted formamide (**1**).

(**1**) (**2**)

Since then most isocyanides have become readily available by the transformation (**1**) → (**2**), the method of choice for the preparation of isocyanides. The best dehydrating agents for (**1**) are phosgene and diphosgene in the presence of triethylamine, and phosphorus oxychloride in the presence of diisopropylamine.[8-10]

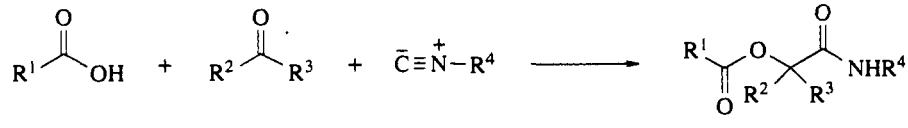
As a result of this convenient method of synthesizing isocyanides, their chemistry has flourished vigorously in the past 30 years. Isocyanides are no longer an exotic class of compounds; they are now routinely used as reagents by organic chemists. The preparative methods based on α-metallated isocyanides[11] and the Ugi reaction[12] are amongst the most important contributions of modern isocyanide chemistry to organic synthesis.

4.6.2 THE PASSERINI REACTION AND RELATED REACTIONS

The essentially nucleophilic isocyanides react with acid-activated aldehydes and ketones in combination with a nucleophile such as water, hydrazoic acid or carboxylic acids to yield α-hydroxycarboxamides or some of their derivatives. Such reactions are the topic of this section.

4.6.2.1 α-Acyloxycarboxamides

In 1921 Passerini[6a] reported the synthesis of the α-acyloxycarboxamides (**6a–e**) according to the scheme below. The formation of α-acyloxycarboxamides by a three-component reaction of carboxylic acids (**3**), carbonyl compounds (**4**) and isocyanides (**5**) is the proper Passerini reaction. The reactions described in Sections 4.6.2.2–4.6.2.4 are closely related to the Passerini reaction; we call them reactions of the Passerini type.[2e,6]



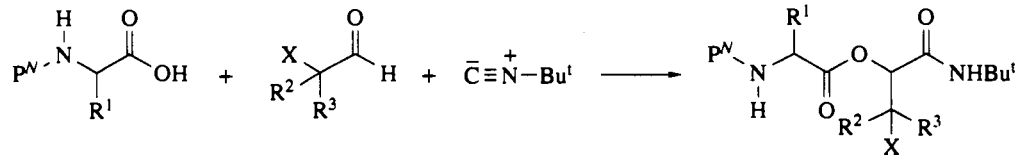
(**3**) (**4**) (**5**) (**6**)

(**6**) **a**: R^1 = Me; R^2 = Me; R^3 = Me; R^4 = Ph
b: R^1 = Me; R^2 = Me; R^3 = Me; R^4 = *p*-PhN=NC$_6$H$_4$
c: R^1 = Me; R^2 = Me; R^3 = EtO_2CCH_2; R^4 = Ph
d: R^1 = Ph; R^2 = H; R^3 = Ph; R^4 = Ph
e: R^1 = Ph; R^2 = H; R^3 = Ph; R^4 = *p*-PhN=NC$_6$H$_4$

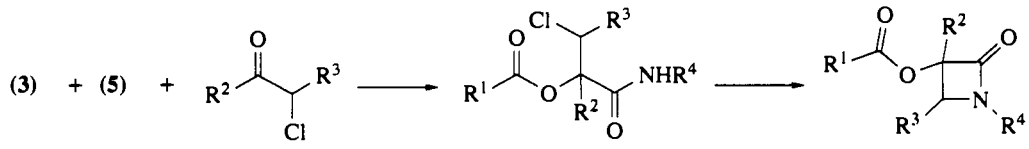
Concentrated solutions of the components (**3**)–(**5**) in inert organic solvents react at 0–20 °C to form (**6**); the reaction time varies with the nature of the components and the reaction conditions (1–100 h), as does the yield (18–95%). A wide variety of α-acyloxycarboxamides (**6**) have been prepared by the Passerini reaction,[2i,6] including some depsipeptide derivatives[17] and their phospho analogs.[18a]

The Passerini reaction of α-halogenated carbonyl compounds (**8**; X = Cl, Br) can be used for the protection of the C-terminal carboxyl groups of *N*-protected α-amino acid derivatives (**7**).[19]

The synthesis of 3-acyloxy-2-azetidinones (**13**) from the chloro ketones (**11**)[20] is another example that demonstrates the versatility of the Passerini reaction in syntheses.

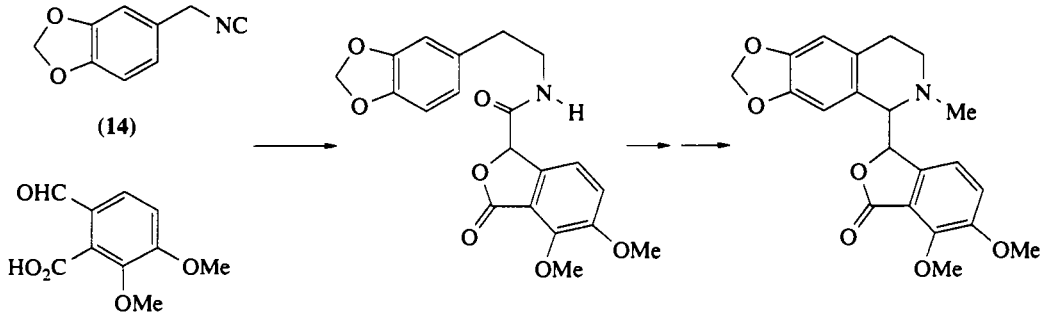


(7) (8) (9) (10)



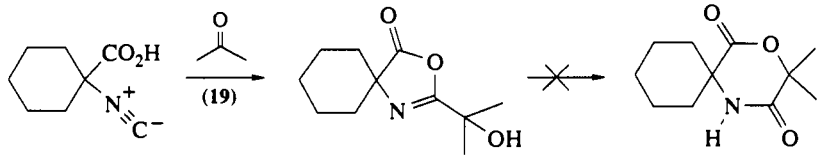
(11) (12) (13)

The synthesis of (±)-hydrastine (**17**) *via* (**16**) is an elegant use of the Passerini reaction in the field of alkaloids.[21]



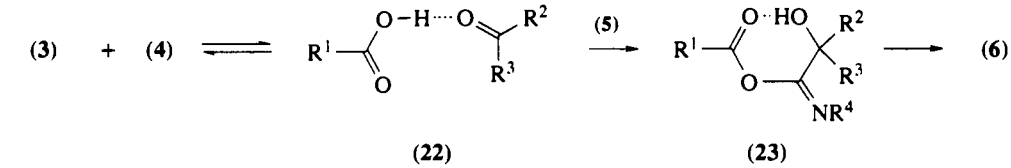
(14) (15) (16) (17)

The following experimental evidence is relevant to the mechanistic interpretation of the Passerini reaction:[2j] Baker and Stanonis[22] observed third-order kinetics for the reaction. Polar solvents with strong hydrogen bond affinity interfere with the Passerini reaction.[23] When (**18**) is reacted with acetone (**19**) the α-adduct (**20**) is formed instead of the expected product (**21**).[2k]



(18) (20) (21)

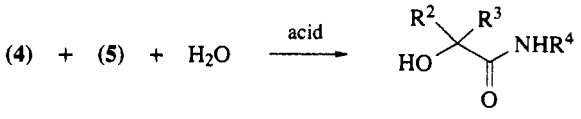
Based on this evidence, the reaction mechanism (**22**) + (**5**) → (**23**) → (**6**) is the most convincing of the many proposed reaction mechanisms for the Passerini reaction.[2j]



(22) (23)

4.6.2.2 α-Hydroxycarboxamides and α-Alkoxycarboxamides

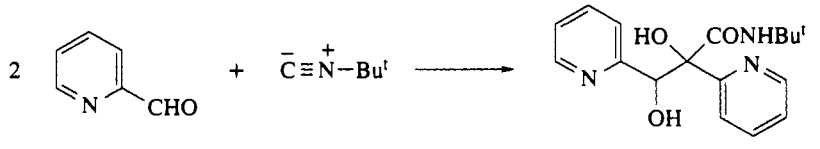
Aqueous inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid and, preferentially, sulfuric acid, as well as some Lewis acids, *e.g.* boron trifluoride etherate[24] and titanium tetrachloride, catalyze the α-addition of the isocyanides, yielding the α-hydroxycarboxamides (**24**) in 12–88% yield.[2m,6b,d,f,14,25–29] The catalysis of this reaction by acids is due to an enhancement of the electrophilic reactivity of the carbonyl compound (**4**).



(**24**)

A great variety of carbonyl compounds has been used in this reaction in order to produce the respective α-hydroxycarboxamides, but to the best of our knowledge, formaldehyde had never been reported in the literature as the carbonyl component in the synthesis of (**24**). We wondered whether or not formaldehyde displays any abnormal behavior in the preparation of (**24**), but we noticed that in dilute sulfuric acid paraformaldehyde reacted with isocyanides to form (**24**; R^2, R^3 = H; R^4 = Bu^t, Oct^t, c-Hex and *o*-ClC$_6$H$_4$) in yields of 45–60%,[29a] and in the presence of $TiCl_4$[28] even in yields of up to 95%.[29b]

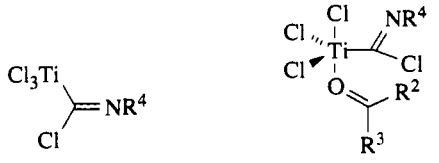
When Lumma[30] synthesized a series of α-hydroxycarboxamides (**6**) as intermediates for analogs of isoproterenol, he observed the formation of (**27**), an unusual reaction of 2-pyridinecarbaldehyde (**25**) with (**26**) in the presence of hydrochloric acid.



(**25**) (**26**) (**27**)

The $TiCl_4$-mediated synthesis of (**24**) from (**4**) and (**5**) by Seebach *et al.*[28] proceeds particularly well, as has been demonstrated by many examples; yields of up to 98% are encountered. This variant of the α-hydroxycarboxamide synthesis proceeds *via* an α-adduct (**28**) of $TiCl_4$ and presumably a species (**29**) with pentacoordinated Ti.

α-Alkoxynitriles (**32**) and α-alkoxycarboxamides (**33**) are obtained from acetals in the presence of $TiCl_4$.[31]

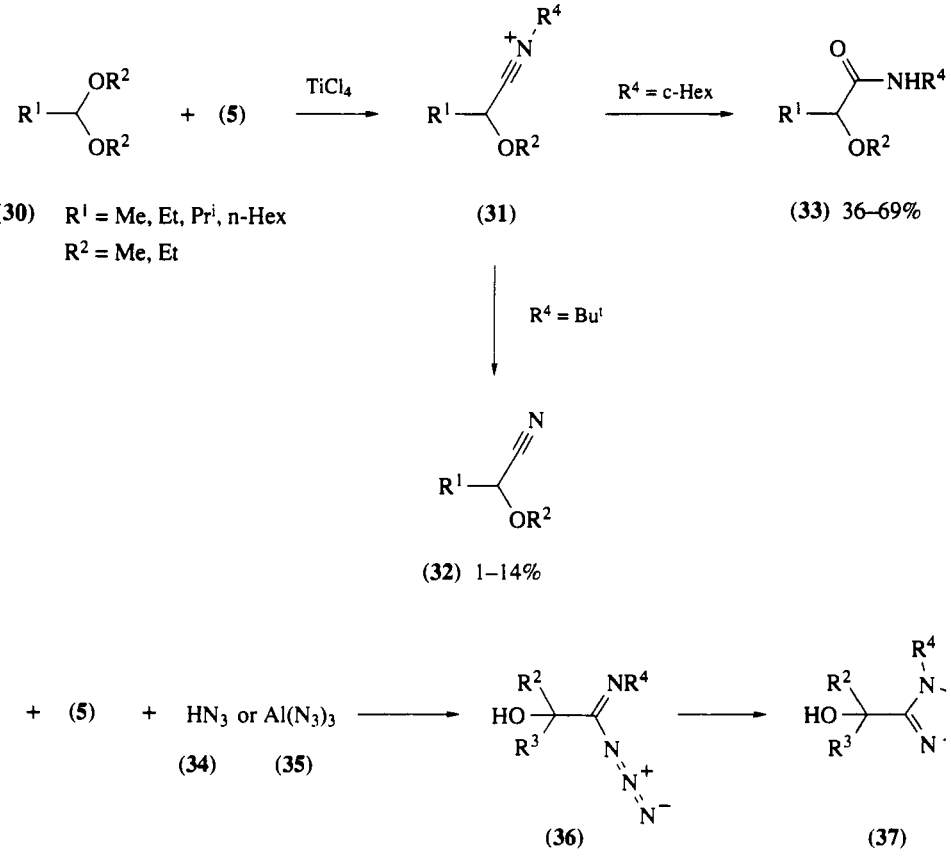


(**28**) (**29**)

4.6.2.3 α-Hydroxyalkyltetrazoles

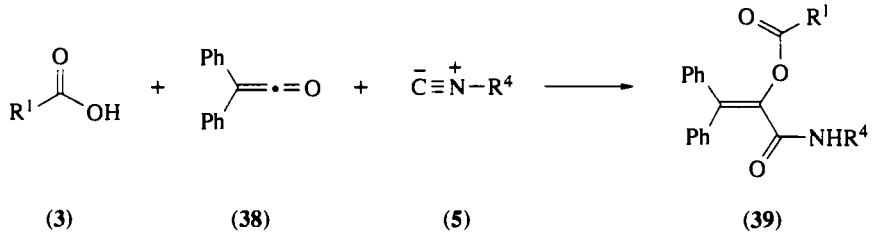
Besides water and the carboxylic acids (**3**), hydrazoic acid (**34**) is the only acid that can be combined with carbonyl compounds (**4**) and isocyanides (**5**) to form a tetrazole derivative (**37**), a three-component adduct, in 7–95% yield.[2k,32]

With sterically hindered aldehydes and ketones considerably higher yields of (**36**) (68–86% *vs.* 8–32%) are obtained by the use of aluminum azide (**35**) instead of (**34**).



4.6.2.4 α-Acyloxyacrylamides

Carboxylic acids (**3**), diphenylketene (**38**) and isocyanides (**5**) react in analogy to the Passerini reaction to form α-acyloxyacrylamides (**39**).[33–35]

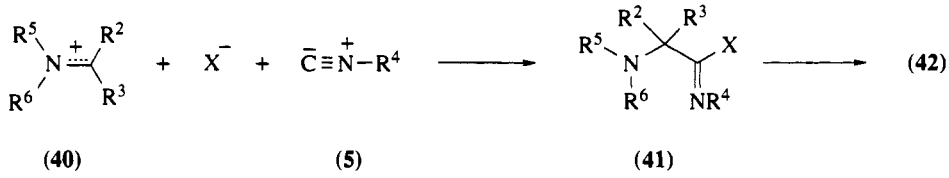


4.6.3 THE UGI REACTION

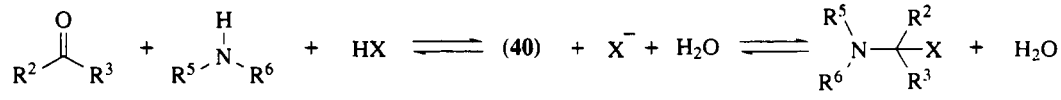
4.6.3.1 General Features, Scope and Limitations

The characteristic feature of the Ugi reaction[12] is the α-addition of an iminium ion (**40**) and the anion X^- of a suitable acid HX to an isocyanide, followed by a spontaneous rearrangement of the α-adduct (**41**) into a stable α-aminocarboxamide derivative (**42**).[2n,16,36,37]

Carbonyl compounds (**4**) and amines (**43**), or their condensation products, such as the imines, enamines and aminals, in combination with the acid HX are generally the source of the iminium ion (**40**) and the anion.



(40) (5) (41) (42)

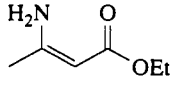


(4) (43) (44)

Thus the product (**42**) results from four distinct reactants, namely (**4**), (**5**), (**43**) and HX, through a condensation reaction. Therefore, such an Ugi reaction was initially called the four-component condensation (4CC).[2n]

Any compound with a sufficiently nucleophilic NH group may serve as the amine component (**43**) of the 4CC, *e.g.* ammonia, primary and secondary amines, hydrazine and its derivatives[38–41] including the diaziridines,[42] as well as hydroxylamine.[43] Diarylamines are not sufficiently nucleophilic to participate as (**43**) in the Ugi reaction.

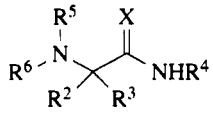
With the exception of diaryl ketones, all aldehydes and ketones undergo the 4CC as the carbonyl component (**4**). Note that the derivatives of the α-oxocarboxylic acids react very well as the carbonyl components (**4**),[29,44] whereas the derivatives of the β-oxocarboxylic acids may form the resonance-stabilized derivatives of β-aminoacrylic acid, such as ethyl β-aminocrotonate (**45**), which can even be used as the amine component (**43**) of the Ugi reaction.[45]



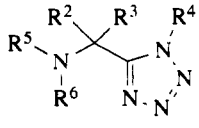
(45)

There are no restrictions with regard to the structure of the isocyanide (**5**), as long as it is a *C*-isocyanide.[2n] An acid HX is only suitable as the acid component of the 4CC if it is not irreversibly converted into an α-aminoalkylation product, as happens with the cyanide and the thiolate ions.[46] Furthermore, the acid component HX must yield an α-adduct (**41**) that is capable of rearranging into a stable product (**42**).

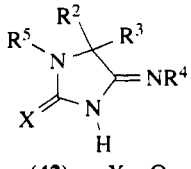
The nature of the secondary reaction (**41**) → (**42**) and of its product (**42**) is primarily determined by HX. As the acid component HX, water leads to the α-aminocarboxamides (**42a**),[14,27,42,47,48] thiosulfuric acid to the thioamides (**42b**),[37] hydrogen selenide to the selenoamides (**42c**),[37] hydrazoic acid to the tetrazoles (**42d**)[27,39,44,49–52] and hydroxylamines to the amidines (see also ref. 14) and *N*-hydroxyamidines.[43]



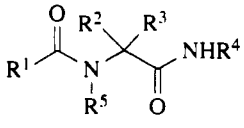
(**42**) **a**: X = O
b: X = S
c: X = Se



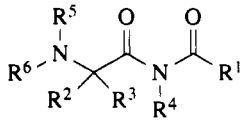
(**42d**)



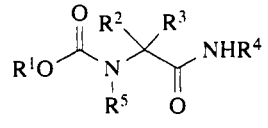
(**42**) **e**: X = O
f: X = S



(**42g**)



(**42h**)



(**42i**)

When primary amines (**43**; R^6 = H) are used as the amine component, hydantoinimides (**42e**) and thiohydantoinimides (**42f**) result from hydrogen cyanate and thiocyanate as the acid component HX.[53,54] The most important acid components are the carboxylic acids. With primary amines (**43**; R^6 = H) they yield α-acylaminocarboxamides (**42g**),[39,55–57] whereas with secondary amines (**42**; R^1, R^2 = organyl), the diacylimines (**42h**) are the products, provided that acylatable nucleophiles are absent.[55,58,59] The diacylimides (**42h**) are acylating reagents that transfer an R^1CO group, and so are their precursors, the α-adducts (**41**; X = R^1CO_2).[55]

In the presence of bases, carbon dioxide and alcohols such as methanol (**46**; R = Me) form alkyl carbonates.

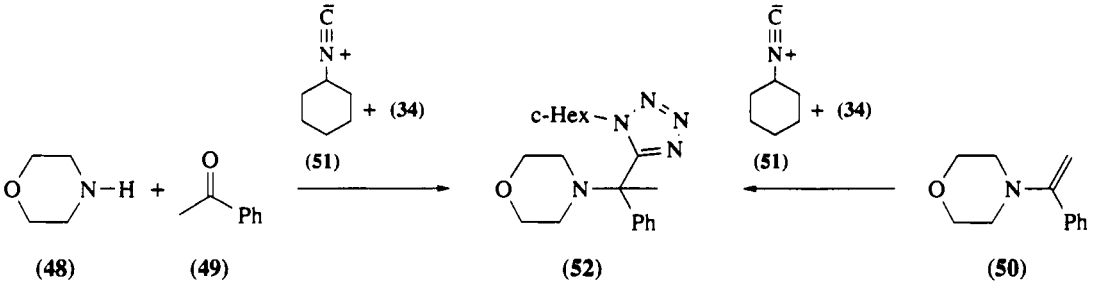
$$\underset{\textbf{(46)}}{ROH} + CO_2 + B: \rightleftharpoons \underset{\textbf{(47)}}{ROCO_2^-} + {}^+BH$$

When an alkyl carbonate anion participates in an Ugi reaction, a urethane (**42i**) is formed through a reaction between five distinct components.[48,55]

4.6.3.2 Reaction Conditions

The Ugi reaction is very easy to execute. Note, however, that it is strongly exothermic. With reactive combinations of amine and carbonyl components (**43**) and (**4**) it suffices to add the isocyanide to a stirring, well-cooled, concentrated methanol solution of the other three components at 0–20 °C. The available temperature range for the reaction is, however, –80 to +80 °C. In some cases the reaction proceeds to completion within a few minutes, but in some cases it takes weeks. It is advisable to exclude oxygen when a slow Ugi reaction is carried out on a small scale (see Section 4.6.3.6). Methanol is generally a suitable solvent, although any other organic solvents lacking interfering functional groups may be used. Often the product crystallizes when the reaction is over. Otherwise the solvent is evaporated and the unreacted components are removed by extraction with acid and base from a solution of the product in a water-immiscible solvent.

When less reactive amine and carbonyl components are used, it is advisable to precondense these components before the reaction with the acid component and the isocyanide. For example, 68% of (**52**) is obtained from (**48**) + (**49**) at 20–25 °C in three weeks, while 94% is produced when (**50**) is reacted for 15 min at 0–10 °C.[50]



(48) **(49)** **(52)** **(50)**

Under suitable conditions the yield is generally very good, in many cases close to quantitative. As a rule, some preliminary experiments are needed in order to determine the optimum reaction conditions for a given combination of components.

4.6.3.3 Preparative Advantages

The Ugi reaction is an easily performed one-pot reaction that is applicable to the synthesis of many distinct types (**42a–i**) of organic compounds, mostly in good to excellent yields. Some of the products (**42a–i**) represent important classes of synthetic targets, while others are useful as intermediates for the preparation of a variety of nitrogen compounds.

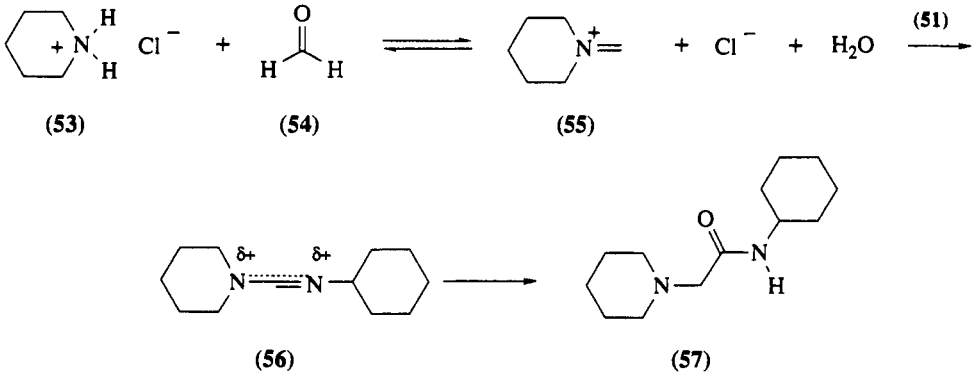
Thus, the Ugi reaction has a wide range of applications in the preparation of organic compounds. Relative to sequences of other reactions with equivalent results, it has definite advantages, whenever it

can be employed, because its use involves fewer steps and higher yields. Whenever the Ugi reaction can be incorporated in a synthesis, as a rule, it shows distinct preparative superiority over any alternative (see Section 4.6.4).

4.6.3.4 Grandparents, Parents and Godparents

For organic synthesis and biosynthesis the Mannich reaction[60–62] is the most important multicomponent reaction. The Mannich reaction is an α-aminoalkylation[46] (**4**) + (**43**) + HX ↔ (**40**) + X^- + H_2O → (**44**) + H_2O, where the anion X^- is a carbanion. Ugi was curious to find out whether or not a carbanion-like isocyanide is capable of undergoing a 'Mannich reaction', and the relevant experiments were conducted by his doctoral student Cornelius Steinbrückner.

Steinbrückner[36] reacted piperidine hydrochloride (**53**), aqueous formaldehyde (**54**) and cyclohexyl isocyanide in concentrated methanol solution without cooling, and he was surprised by the violent exothermic reaction. A more carefully executed repetition of the reaction at 0 °C yielded 78% of (**57**) as the product.



This result was interpreted in terms of the intermediate nitrilium ion (**56**) and its subsequent reaction with water, or a hydroxide ion, as the acid/anion component, to form (**57**). Subsequently a great number of acids/anions were tested in analogous experiments, and the complete set of the suitable acid/anion components 4CC was identified within three weeks.[36]

Accordingly, the Ugi reaction is closely related to the Mannich reaction and may be classified as an α-aminoalkylation. However, at the same time, a special type of Ugi reaction, the formation of α-acylaminocarboxamides (**42g**) by 4CC of carboxylic acids and primary amines with carbonyl compounds and isocyanides, resembles the Passerini reaction (see Section 4.6.2).

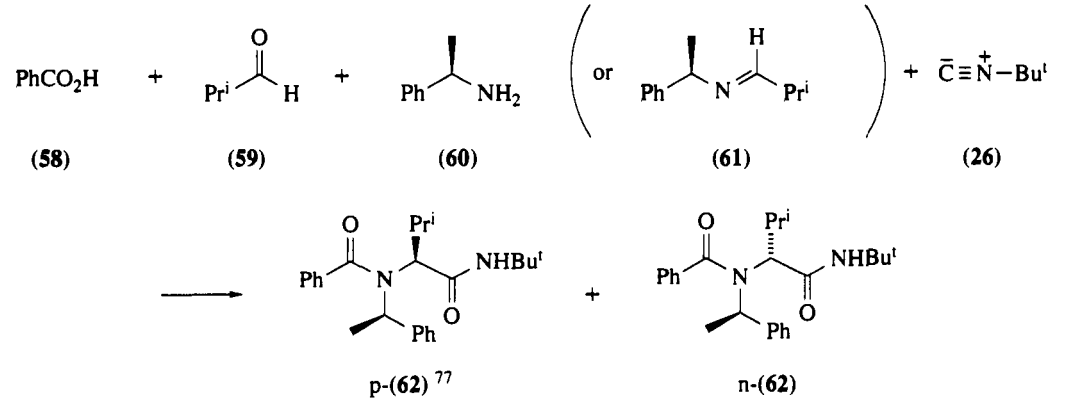
Mannich and Passerini, to whom we owe the two best-known three-component reactions, are the grandparents of the four-component condensation, the Ugi reaction. Its parents are Ugi and Steinbrückner, assisted by coworkers of that period.[36,55] The godparents[12] are Opitz and Merz,[13] McFarland[14] and Sjöberg.[15]

4.6.3.5 Stereochemical Course and Reaction Mechanism

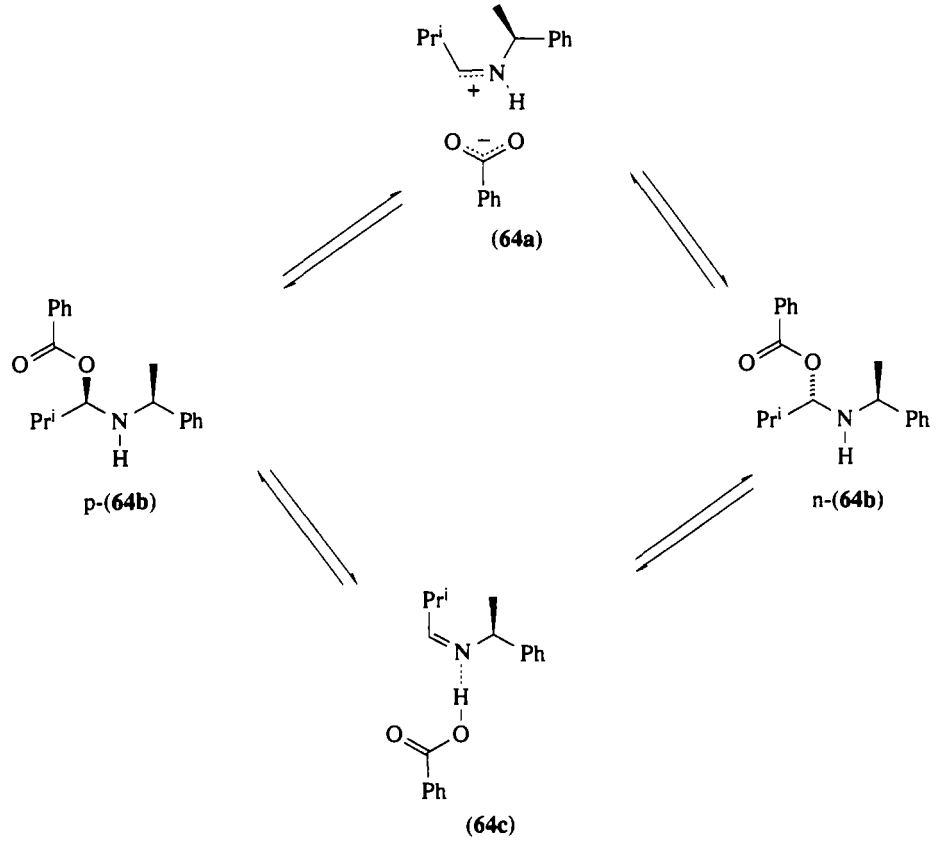
When unsymmetrical carbonyl compounds (**4**; $R^2 \neq R^3$) are subjected to the 4CC, a new stereocenter is generated, and two diastereomeric products (**42**) result. Since these are formed *via* pairs of corresponding reactions with diastereomeric transition states,[20,63–66] the products (**42**) are generally formed at different relative rates, *i.e.* stereoselectively.

Since 1963 stereoselective Ugi reactions have been under investigation.[67–73] It has been demonstrated that such asymmetrically induced[74,75] 4CC proceed only with an appreciable degree of stereoselectivity if a chiral amine component is used whose amino group is directly attached to an asymmetric carbon atom. The chiral α-sulfoxido aldehydes would also be promising asymmetrically inducing chiral templates, but they are not available in enantiomerically pure form.[73,76]

The 4CC of benzoic acid (**58**), isobutyraldehyde (**59**) and (*S*)-α-phenylethylamine (**60**), or their imine (**61**), with *t*-butyl isocyanide (**26**) has been studied quite extensively as a model reaction for stereoselective 4CC.[64,67–69]

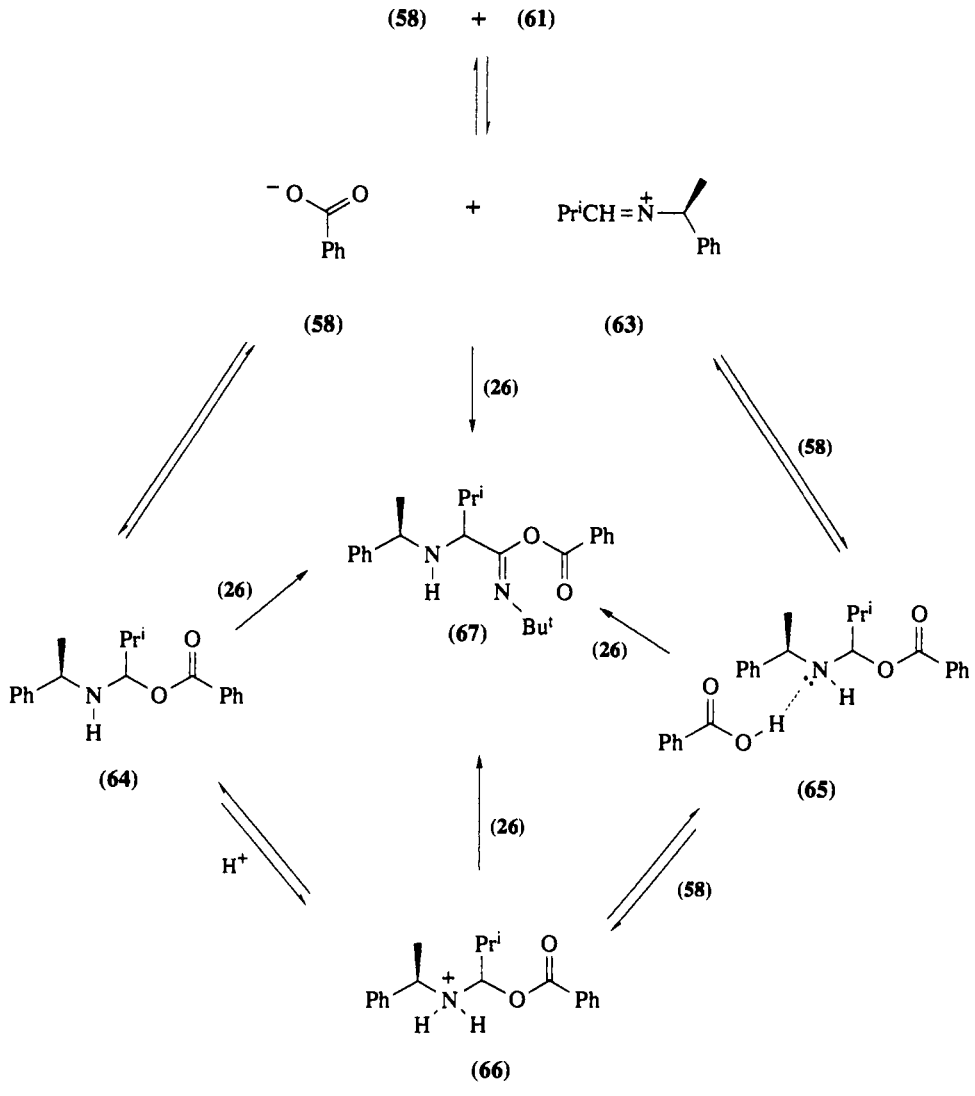


The ratio Q_{pn} of the relative amounts of the products p-(**62**) and n-(**62**) depends strongly on the reaction conditions.[69] Q_{pn} can range from $Q_{pn} << 1$ to $Q_{pn} >> 1$. A mathematical model for the mechanism of the Ugi reaction, a complex system of parallel and consecutive reactions, was established by a computer-assisted analysis of Q_{pn} as a function of the concentration of the reactants in methanol at 0 °C.[20,64,69] In a solution of (**58**)–(**60**), or (**58**) and (**61**), we have an equilibrium of the species (**63**)–(**66**). The formulas (**63**)–(**66**) describe primarily the stoichiometric composition of the species. The formula (**64**) represents, for instance, the equilibrium system (**64a**)–(**64c**), where (**64a**) is a tight ion pair, (**64b**) is a pair of diastereomers and (**64c**) is a hydrogen-bonded adduct.



When (**26**) is added sufficiently slowly to this equilibrium system, it is maintained while (**62**) is formed *via* the α-adduct (**67**). Each of the species, or pairs of diastereomers (**63**)–(**66**) belongs to a pair of corresponding reactions whose stereoselectivity is determined by a pair of diastereomeric transition states. Thus (**67**), and thereby also (**62**), is formed by four competing pairs of corresponding reactions. Each one of these has its own intrinsic stereoselectivity $Q_{pn,\nu}$ ($\nu = 63,\ldots,66$). The observed overall stere-

oselectivity is determined by these $Q_{pn,\nu}$ and the relative contributions of the respective pairs of corresponding reactions.[65]



The relative contributions of the individual pairs of corresponding reactions are determined by the equilibrium concentrations of (**63**)–(**66**) and the rates at which these react with (**26**).

The equilibrium concentrations of (**63**)–(**66**) depend on the initial concentrations of (**58**)–(**61**) and of added tetraethylammonium benzoate. Knowing the reaction mechanism, it is possible to influence the contributions of the individual pairs of corresponding reactions, and thereby the overall stereoselectivity, by the choice of the reaction conditions.

4.6.3.6 Side Reactions

The four components (**4**), (**5**), (**43**) and HX of the Ugi reaction react with each other in many reversible ways, but, in the ideal case, only the formation of the α-adduct (**41**) and its conversion into the final product are irreversible. Under such conditions a quantitative yield of (**42**) results, as actually happens in some favorable cases.

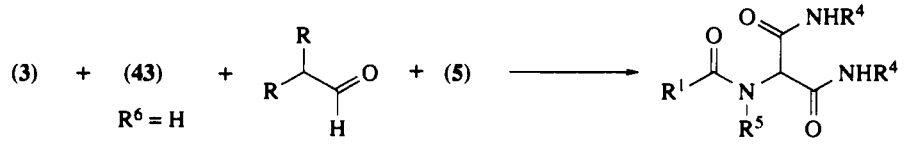
Generally, the Ugi reaction is, however, in competition with various irreversible side reactions[71] that consume some of the starting materials. Familiarity with the expected side reactions is a prerequisite for avoiding the formation of by-products.

For preparative purposes the Ugi reaction of the carboxylic acids (**3**) is the most important type of 4CC, and their side reactions have been investigated most thoroughly.[71]

The Passerini reaction and the formation of α-hydroxycarboxamides (**24**) may compete with the Ugi reaction.[14] When carboxylic acids (**3**) and carbonyl compounds (**4**) with electron-withdrawing groups are subjected to 4CC in nonpolar solvents such as dichloromethane, the Passerini reaction may compete strongly.[81] Also, with bulky components the Passerini reaction becomes a serious side reaction of the Ugi reaction.[71]

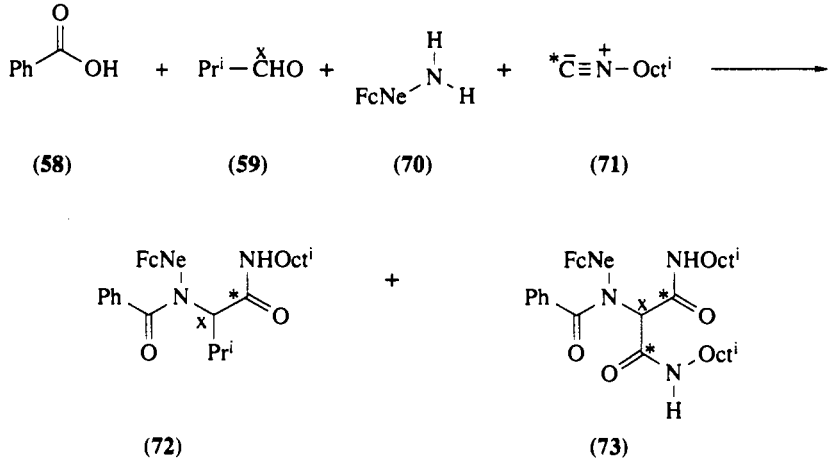
When α-ferrocenylalkylamines are used as (**43**), *N*-dealkylation of the product (**42g**) may occur.[71]

An intriguing and sometimes quite bothersome side reaction is the formation of the malonamide derivatives (**69**)[82,83] that are hard to remove as contaminants of the products (**42g**).



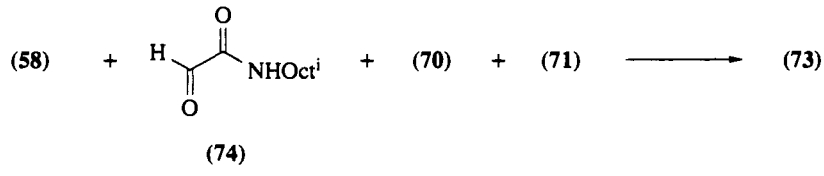
Until recently, none of the attempts to elucidate the nature of this side reaction had been successful. When Ugi was invited to contribute this chapter, we resumed the investigation of the side reaction that produces (**69**), in order to be able to discuss its mechanistic aspect. Since the formation of (**69**) is a minor side reaction of a main reaction that involves at least four distinct participating reactants, its reaction mechanism cannot be elucidated by the customary methods such as kinetic measurements.

For experimental reasons the condensation of (**58**), (**59**), (**70**) and (**71**) was chosen as a model reaction. It was studied by a combination of experimental and computer-assisted methods involving the computer program RAIN (Reaction And Intermediates Networks).[84] The results provide evidence for the intermediacy of (**74**) or a derivative of (**74**).[29b,85]

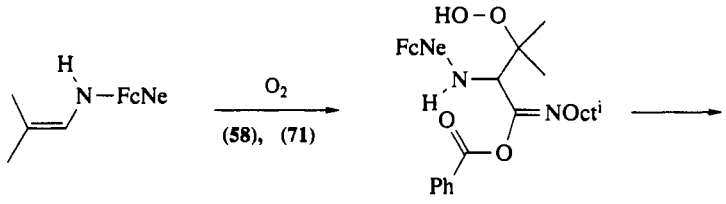


When ^{13}C-labeled (**71**; ^{13}C = *C) is employed, the ^{13}C appears, according to ^{13}C NMR data, only in the two *N*-isooctylcarboxamide groups of (**73**) with none in the central CH groups, whereas ^{13}C-labeled (**59**; ^{13}C = ^{x}C) leads to (**73**) with the ^{13}C label at the central CH group. Acetone (**19**) is a coproduct of (**73**). When oxygen is rigorously excluded, no (**73**) is formed. No malonamide derivative is obtained from aldehydes without an α-hydrogen. The 4CC of (**58**), *N*-isooctylglyoxylamide (**74**) with (**70**) and (**71**) proceeds smoothly and gives an almost quantitative yield of (**73**).[29b]

In view of the above experimental evidence, a route *via* (**75**), (**76**), (**77**) and (**78**) is the most plausible among the conceivable reaction pathways from (**58**), (**59**), (**70**), (**71**) and O_2 to (**73**) and its coproducts. Accordingly, we have the overall process (**58**) + (**59**) + 2(**70**) + (**71**) + O_2 → (**19**) + (**73**), *i.e.* a reaction with six participating molecules.



(58) + (74) + (70) + (71) → (73)



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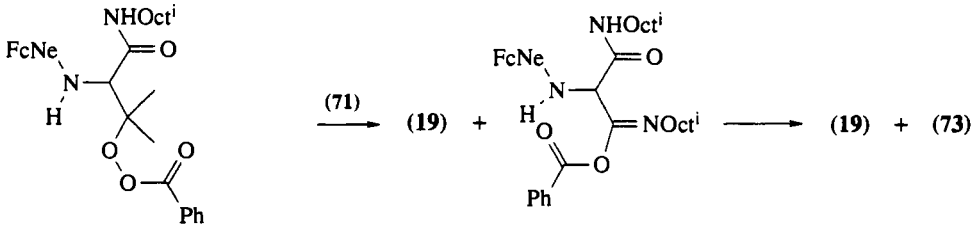
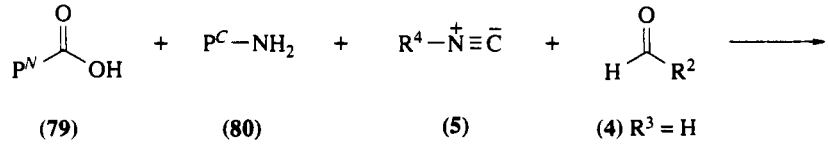


(77) (78)

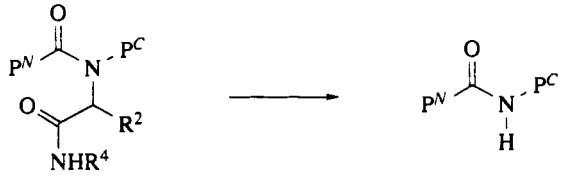
4.6.4 SYNTHESES WITH THE UGI REACTION

4.6.4.1 Peptide Coupling

Amino acid or peptide derivatives (**79**) and (**80**) with suitable protective groups at their terminal amino and carboxyl groups can be coupled by the Ugi reaction.

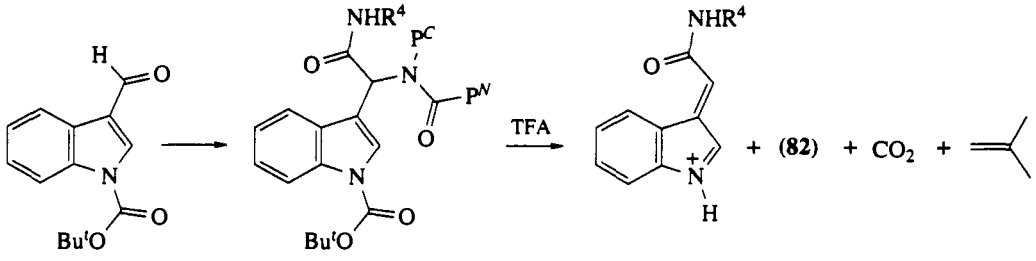


(79) (80) (5) (4) R^3 = H

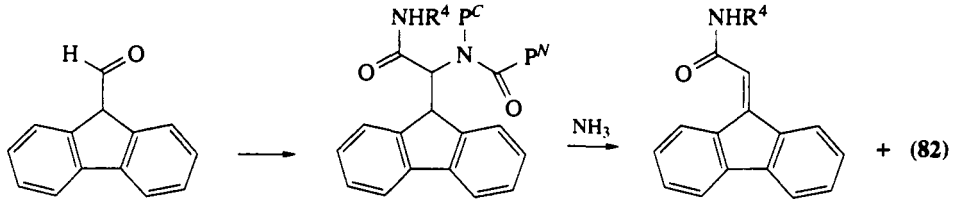


(81) (82)

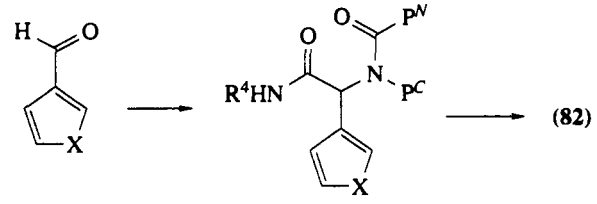
The aldehyde (**4**; R^3 = H) must carry a group R^2 that renders the 4CC product (**81**) cleavable in order to obtain the *N*-unsubstituted peptide derivative (**82**).[71,86–90] About 50 aldehydes have been tested as candidates for peptide coupling, but only a few (**4a–d**) undergo the required Ugi reaction (**4**; R^3 = H) + (**5**) + (**79**) + (**80**) → (**81**) in sufficient yield of a readily cleaved product (**81**), and with an acceptable degree of racemization.[88] The cleavage of (**81c, d**) requires treatment with HBr/AcOH.[91]



(4a)[89] (81a) (83)



(4b)[90] (81b) (84)



(4)[91] c: X = O
d: X = S

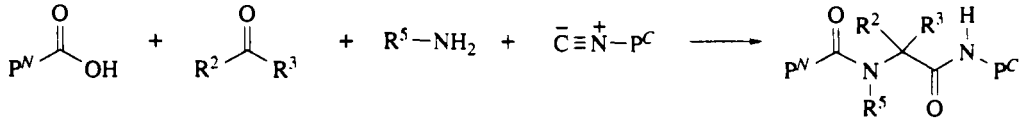
(81)

An elegant application of peptide coupling by 4CC is the synthesis of cyclopeptides by Failli, Immer and Götz.[92]

The main advantage of peptide coupling by the Ugi reaction is that the peptide derivatives (**81**) are generally much more soluble in organic solvents than the *N*-unsubstituted peptides (**82**). Some of the common difficulties in peptide synthesis that are due to insoluble intermediates can be overcome by this type of 4CC.

4.6.4.2 α-Amino Acid Derivatives from Achiral Amines

A new amino acid unit can be generated from a carbonyl compound (**4**), during the synthesis of an α-amino acid or peptide derivative (**86**) by the Ugi reaction.

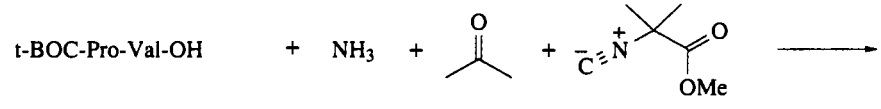


(79) (4) (43) $R^6 = H$ (85) (86)

The required α-isocyano derivatives (**85**) of α-amino acids are prepared from the corresponding α-formylamino acids. If (**85**) is a peptide derivative, no racemization is observed at the α-isocyanoacyl unit.[93] The preparation of chiral α-isocyanocarboxylate esters, however, is possible with phosgene[24] or

diphosgene[28] in the presence of *N*-methylmorpholine. The use of carbonyldiimidazole dimesylate[94] is inadvisable.[95]

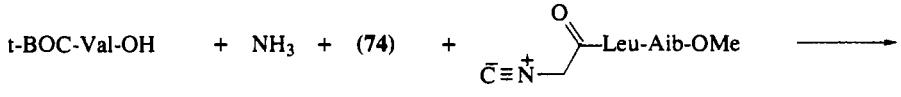
By conventional methods the peptides of α-aminoisobutyric acid (Aib) are difficult to synthesize, whereas their preparation by 4CC proceeds very well. The syntheses of the alamethicine segments (**89**) and (**92**)[71] serve as examples.



(**87**) (**19**) (**88**)

t-BOC-Pro-Val-Aib-Aib-OMe

(**89**) 74%

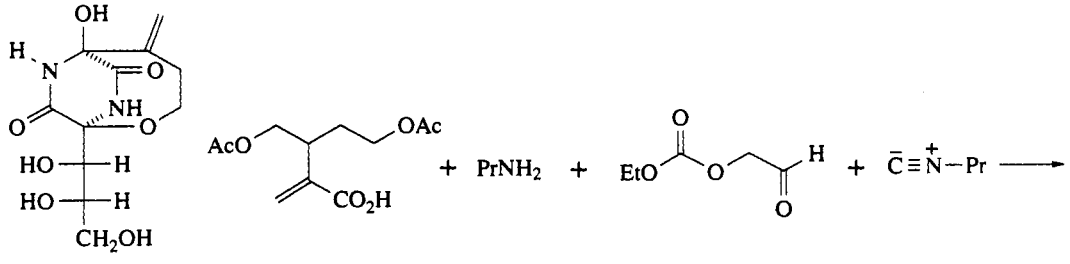


(**90**) (**91**)

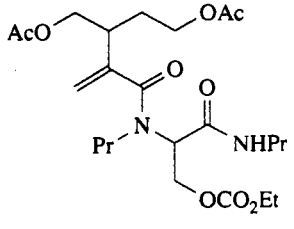
t-BOC-Val-Aib-Gly-Leu-Aib-OMe

(**92**) 93%

A 4CC synthesis of an α,α-di-*n*-propylglycine derivative has been reported by Hardy and Lingham.[96] The synthesis of bicyclomycin (**93**) by Fukuyama *et al.*[97] begins with an Ugi reaction of (**94**)–(**97**).



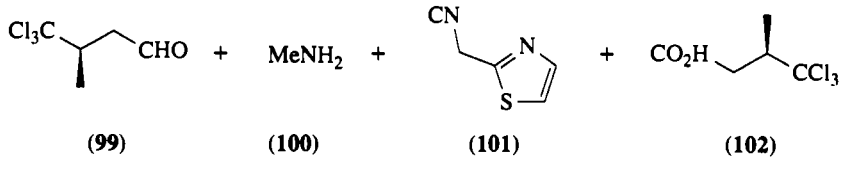
(**93**) (**94**) (**95**) (**96**) (**97**)



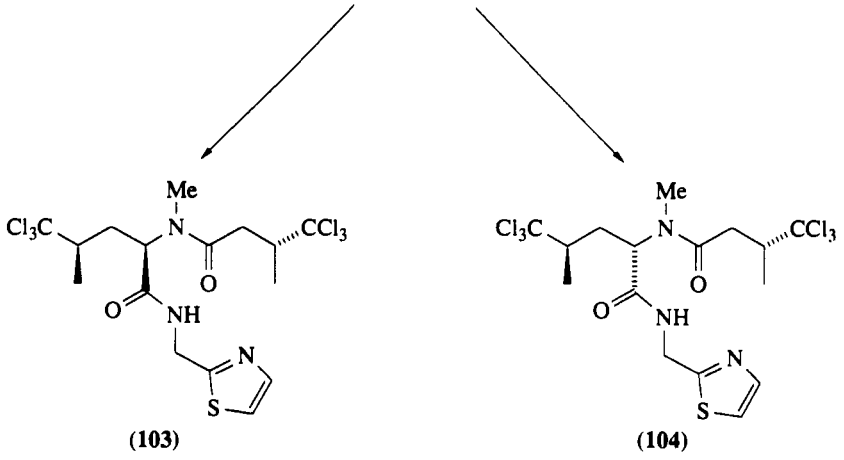
(**98**)

De Laszlo and Williard[98] obtained the marine natural products (+)-dimethyldysidenin (**103**) and (–)-dimethylisodysidenin (**104**) by 4CC.

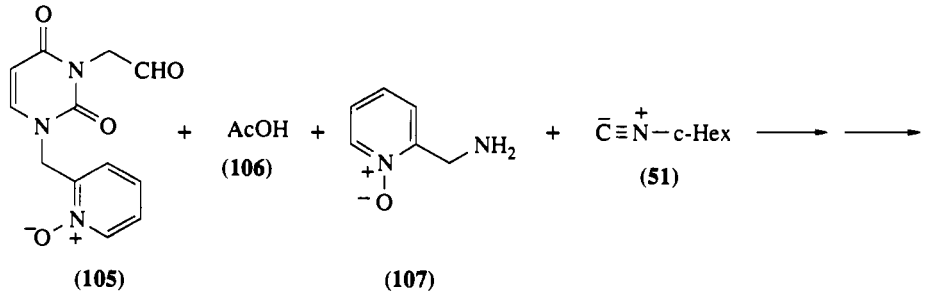
The syntheses of the nucleoside antibiotics willardiin (**108**) and the analog (**109**)[99] of nikkomycin and sinefugin are based on the Ugi reaction.



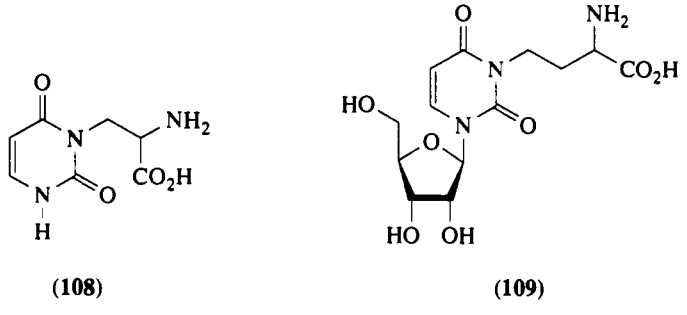
(99) (100) (101) (102)



(103) (104)



(105) (106) (107) (51)



(108) (109)

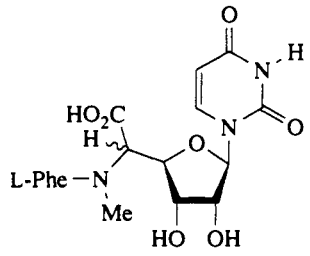
The Ugi reaction also played a key role in the syntheses of the di- and tri-peptide polyoxins (**110**) and (**111**).[100]

Joullié *et al.*[101] have developed a totally novel and very elegant approach to the synthesis of proline peptides that is based on the Ugi reaction of pyrroline derivatives.

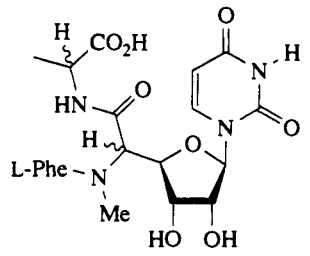
Some racemic phospho analogs of tri- and tetra-peptides have been obtained by 4CC of (**112**) in 68–93% yield, *e.g.* (**113**).[18b]

The key step in the syntheses of the antibiotics plumbemycin (**114a**) and (**114b**) by Natchev[102] is the Ugi reaction.

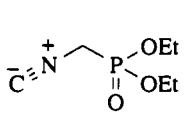
The Ugi reaction has also been used for the synthesis of numerous racemic *N*-amino analogs of eloidisine.[40]



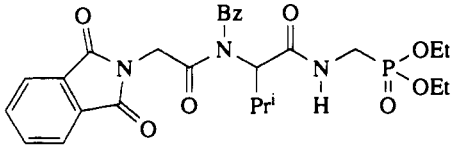
(110)



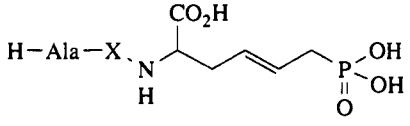
(111)



(112)



(113)



(114) **a**: X = Asn
b: X = Asp

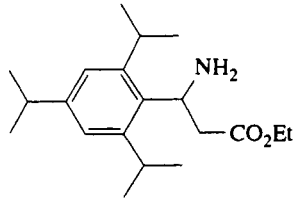
4.6.4.3 Asymmetric Syntheses of α-Amino Acid and Peptide Derivatives

The synthesis of α-amino acid and peptide derivatives (**86**) whose newly formed amino acid unit corresponds to a chiral α-amino acid requires an asymmetric 4CC with a high degree of stereoselectivity.

Under suitable conditions the amine component (**43**; R^6 = H) for peptide syntheses by a stereoselective Ugi reaction must be a good chiral template, *i.e.* it must have strong asymmetric inducing power, and it must be endowed with a group R^5 that is cleavable from the 4CC product (**86**) under mild conditions. The search for a suitable chiral amine component (**43**; R^6 = H) has been the most challenging subproblem in the development of peptide syntheses by stereoselective Ugi reactions.[2p,71]

First, the resonance-stabilized vinylamines, *e.g.* ethyl β-aminocrotonate (**45**), were tested as amine components, because their 4CC products are cleavable by mild acidolysis.[45] In amines of the type (**45**) any center of chirality could, at best, be placed three bonds from the newly formed center of chirality. Accordingly, such amines would not be effective as chiral templates.

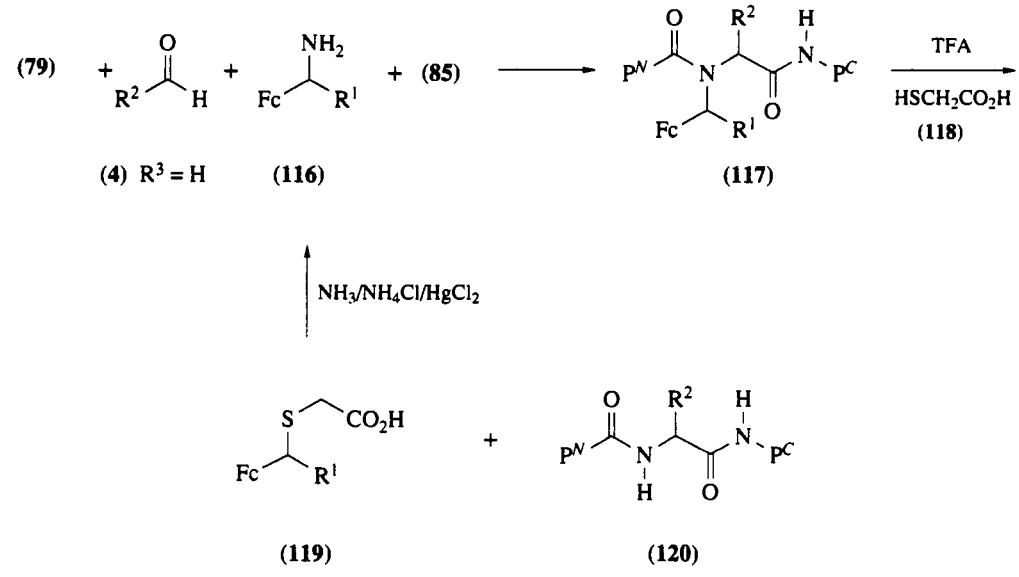
Next, β-alanine derivatives (**115**) were studied. They are fairly powerful as chiral templates in 4CC. Their 4CC products are, however, only cleavable by strong bases that damage peptide derivatives.



(115)

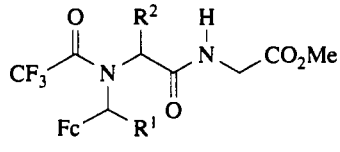
Until recently the most promising chiral amine components (**43**; R^6 = H) for peptide syntheses by stereoselective 4CC were the α-ferrocenylalkylamines (**116**).[71,103,104] The α-ferrocenylalkylamines (**116**) have a unique combination of desirable properties: they are easy to synthesize from the aldehydes;[104] any substitution at the α-carbon of alkylferrocenes proceeds with retention;[105] in the presence of (**118**) the

acidolytic cleavage of (**117**) yields, besides (**120**), its coproduct (**119**), which is reconvertible into (**116**) with full retention of its configuration;[106] furthermore, the cleavage of (**117**) can be conducted in a destructively stereoselective mode.[107]



In the early work with the α-ferrocenylalkylamines (**116**), the preferred amine component was (**116**; R = Pr^i).[103] At –40 to –80 °C in methanol this compound undergoes the above 4CC with very good stereoselectivity, but often the results are not reproducible,[108] because sometimes the reactants stay in supersaturated solution, and the reaction proceeds at the low temperature, whereas in other instances some of the reactants precipitate, and the condensation takes place upon warming. Therefore, amine components like (**116**; R = Me) with acceptable selectivity at higher temperatures ($T > 0$ °C) are preferred, due to a low estimated zero selectivity temperature.[66]

In the search for optimum amine components and reaction conditions for the synthesis of peptides by the stereoselective Ugi reaction, model 4CC reactions with TFA as the acid component are very convenient because the products (**121**) are easy to analyze by ^{19}F NMR.[109,110]



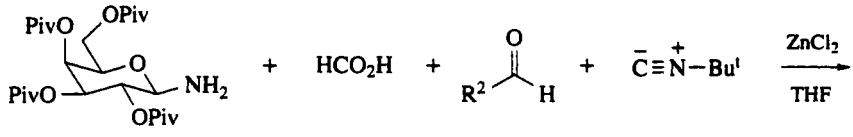
(**121**)

Recently important progress has been made by Kunz *et al.*[111] in the development of the syntheses of chiral amino acid and peptide derivatives by stereoselective 4CC. These authors demonstrated that *O*-acylated 1-aminocarbohydrates, *e.g.* 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**122**), undergo chelate-assisted highly stereoselective 4CC (diastereomer ratio 91:9 to 97:3) in THF in the presence of $ZnCl_2$ at –78 °C.

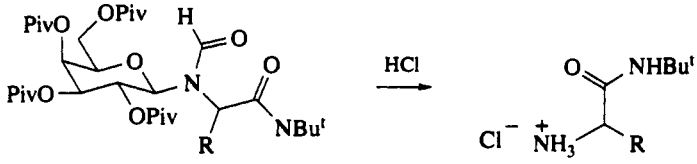
The acidolytic removal of the chiral auxiliary group from (**124**) is achieved by HCl in methanol. The drastic conditions of acidolysis may limit this method to the synthesis of amino acids.

These results stimulated us to synthesize tetra-*O*-methyl-β-D-glucopyranosylamine (**126**).[112a] The 4CC products of (**126**) undergo acidolytic N—C cleavage under milder conditions than (**124**).[112b] We are now studying the stereoselective model 4CC of (**126**), as well as of (**127**) and (**128**), in the presence of chelating catalysts like $ZnCl_2$ and Ti(OPr^i)$_4$. The latter enhances the stereoselectivity of 4CC with (**127**) considerably.[109b,113]

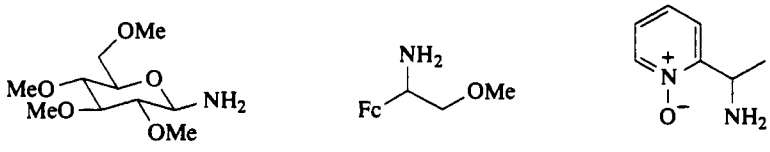
By analogy with Carlson's[114] optimization of syntheses by computer-assisted multivariate methods,[115] Fleck[116] is presently conducting a systematic search for an optimum set of conditions (including the chiral amine component and catalysts) for peptide syntheses by stereoselective 4CC.



(122) (123) (4) $R^3 = H$ (26)



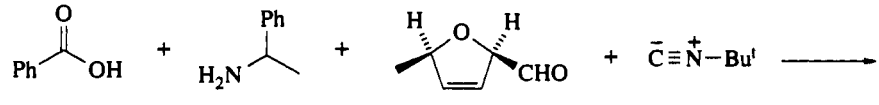
(124) (125)



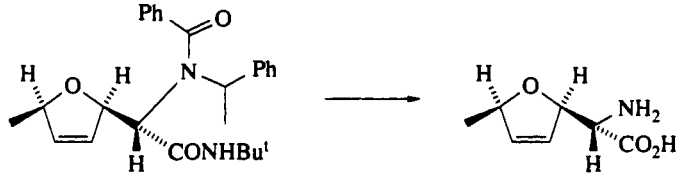
(126) (127) (128)

The potential advantage of amino acid and peptide syntheses by stereoselective 4CC *vs.* the traditional methods is not only the smaller number of steps needed, but also the fact that almost any chiral amino acid can be synthesized in both configurations from carbonyl compounds, also as a moiety of a peptide. *N*-Substituted peptide segments with improved solubility are available using the Ugi reaction.[71] These create new possibilities for the synthesis of large peptides.

Joullié *et al.*[70] have synthesized (+)-furanomycin (**131**) by an asymmetric Ugi reaction. This synthesis led to revision of the assumed structure.



(58) (60) (129) (26)

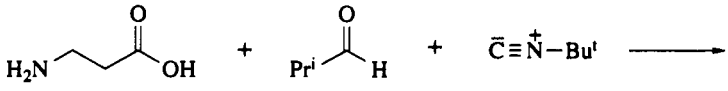


(130) (131)

4.6.4.4 β-Lactams

As a rule, the synthesis of β-lactams by cyclization of β-amino acids such as (**132**) is impeded by Bayer strain and adverse conformational effects.[117] By contrast, the conversion of β-amino acids into β-lactams by the Ugi reaction occurs with ease and in good yield.[55,118]

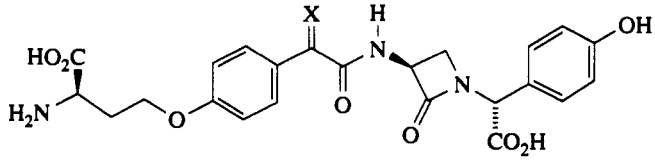
In such syntheses of β-lactams a seven-membered cyclic α-adduct (**133**) is formed; from (**133**) the β-lactam system (**134**) results by transannular acyl transfer. As a consequence, the Ugi reaction has been used in numerous syntheses of β-lactam antibiotics and related compounds.[118]



(**132**) (**59**) (**26**)

(**133**) (**134**)

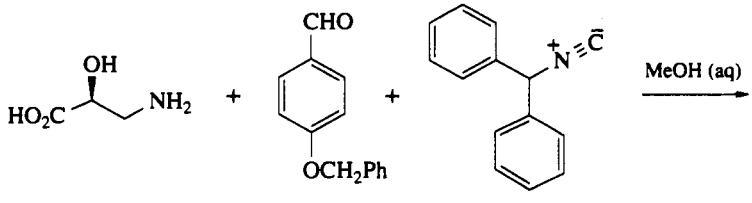
The nocardicins (**135**) are monocyclic β-lactam antibiotics. The essential step in the synthesis of the nocardicins by Isenring and Hofheinz[119] is the formation of (**139**) from (*S*)-isoserine (**136**) by 4CC. Their synthesis of isonocardicin A, a diastereomer of (**135a**) from (*S*)-homoserine follows the same pattern, as well as the preparation of numerous analogs of nocardicin.



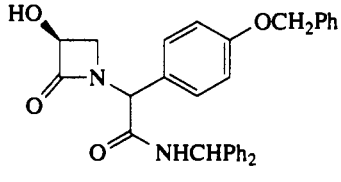
(**135**) **a**: X = N–OH

b: X = HO–N

c: X = O

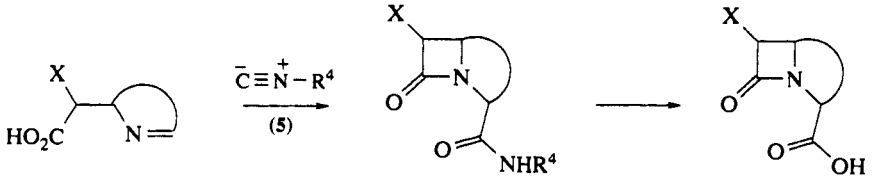


(**136**) (**137**) (**138**)



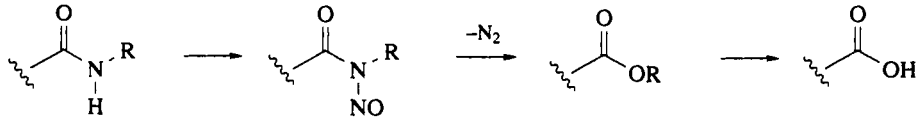
(**139**)

The synthesis of the β-lactam antibiotics and related compounds (**142**) by the Ugi reaction proceeds *via* the carboxamide derivatives (**141**).



(140) **(141)** **(142)**

The latter must be converted into the free carboxylic acids (**142**) in the presence of the relatively labile β-lactam moiety, a conversion that still poses a major problem; for the step (**141**) → (**142**) there is still no generally applicable and satisfactory method available.



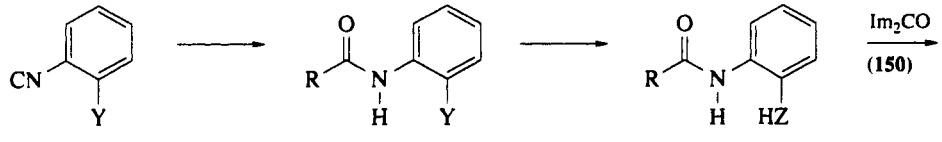
(143) **(144)** **(145)** **(146)**

The most promising approach to (**141**) → (**142**) is based on *N*-nitrosation[120] of the carboxamide group, and conversion of (**144**) into an ester (**145**) whose R group can be replaced by H under mild conditions.

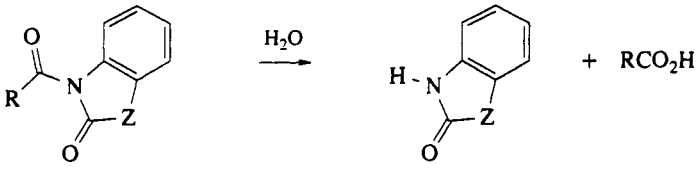
In the aforementioned syntheses of the nocardicins and their analogs the benzhydryl group (**145**; R = $CHPh_2$) was removed by hydrogenolysis, and so was the *p*-nitrobenzyl group (**145**; R = Pbn).[121b]

In a previous carbapenem synthesis of Hatanaka *et al.*[121a] *via* the methyl ester (R = Me), the latter was subjected to mild alkaline hydrolysis. As Achatz[122] has found, the *N*-ethoxycarbonylmethylcarboxamides (**143**; R = CH_2CO_2Et) undergo the conversion (**143**) → (**145**) particularly well, and the resulting esters are selectively hydrolyzable under mild conditions. The allyl group (R = All) has recently emerged as a most promising protecting group; it is cleavable by nucleophiles in the presence of $Pd(PPh_3)_4$.[123] In the context of (**143**) → (**146**) the allyl group has also performed very well.[73]

The *o*-aminophenyl- and *o*-hydroxyphenyl-carboxamides (**149**) undergo the sequence of reactions (**149**) → (**151**) → (**152**) smoothly.[124] This is the basis of a method for achieving (**141**) → (**142**). The somewhat cumbersome preparative access to the isocyanides (**147**), and the sometimes less than satisfactory yields (58–75%) of penam syntheses by the Ugi reaction (**140**) + (**147**) → (**149**), are the disadvantages of this method.[125,126]

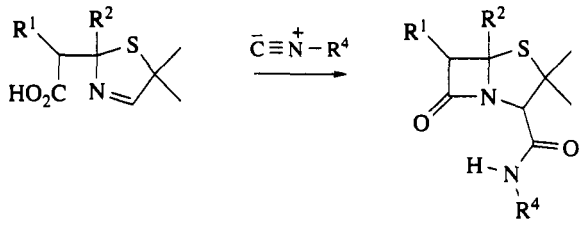


(147) Y = N_3, OBz,[124] $OSiMe_2Bu^t$[125] **(148)** **(149)** Z = NH, O



(151) **(152)**

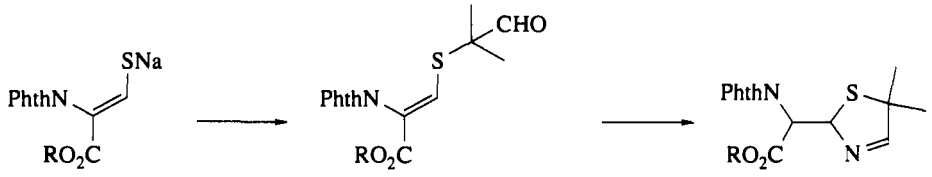
The first preliminary studies towards the synthesis of penam derivatives by the Ugi reaction were carried out roughly 30 years ago.[127] 3-Thiazoline derivatives (**153**) were allowed to react with isocyanides in the two-phase system water/petroleum ether to yield up to 95% of the penam derivatives (**154**).



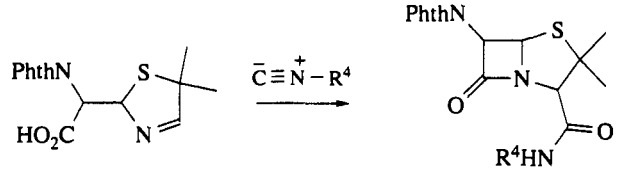
(**153**) $R^1 = R^2 = H$, Me (**154**) $R^4 = Bu^t$, c-Hex

We were surprised to find that despite the general lability of penam derivatives, the products (**154**) could be purified by sublimation *in vacuo*. Using a similar scheme, Sjöberg[128] synthesized the amide of a stereoisomer of penicillin G, but in very low overall yield, because formation of the required 3-thiazoline derivative by the Asinger condensation did not proceed satisfactorily.

Schutz and Ugi[129] developed the synthesis of penam derivatives (**155**; R = Me) → (**159**; $R^4 = Bu^t$). This penam synthesis was improved by the use of R = All and R^4 = All or CH_2CO_2Et.[122] In these recent β-lactam syntheses the Ugi reaction was executed in trifluoroethanol, a 'magic solvent' for such conversions.[73,125] In a recent carbacephem synthesis ethylene glycol/glycerol gave very good results as the solvent.[118b]



(**155**) (**156**) (**157**)

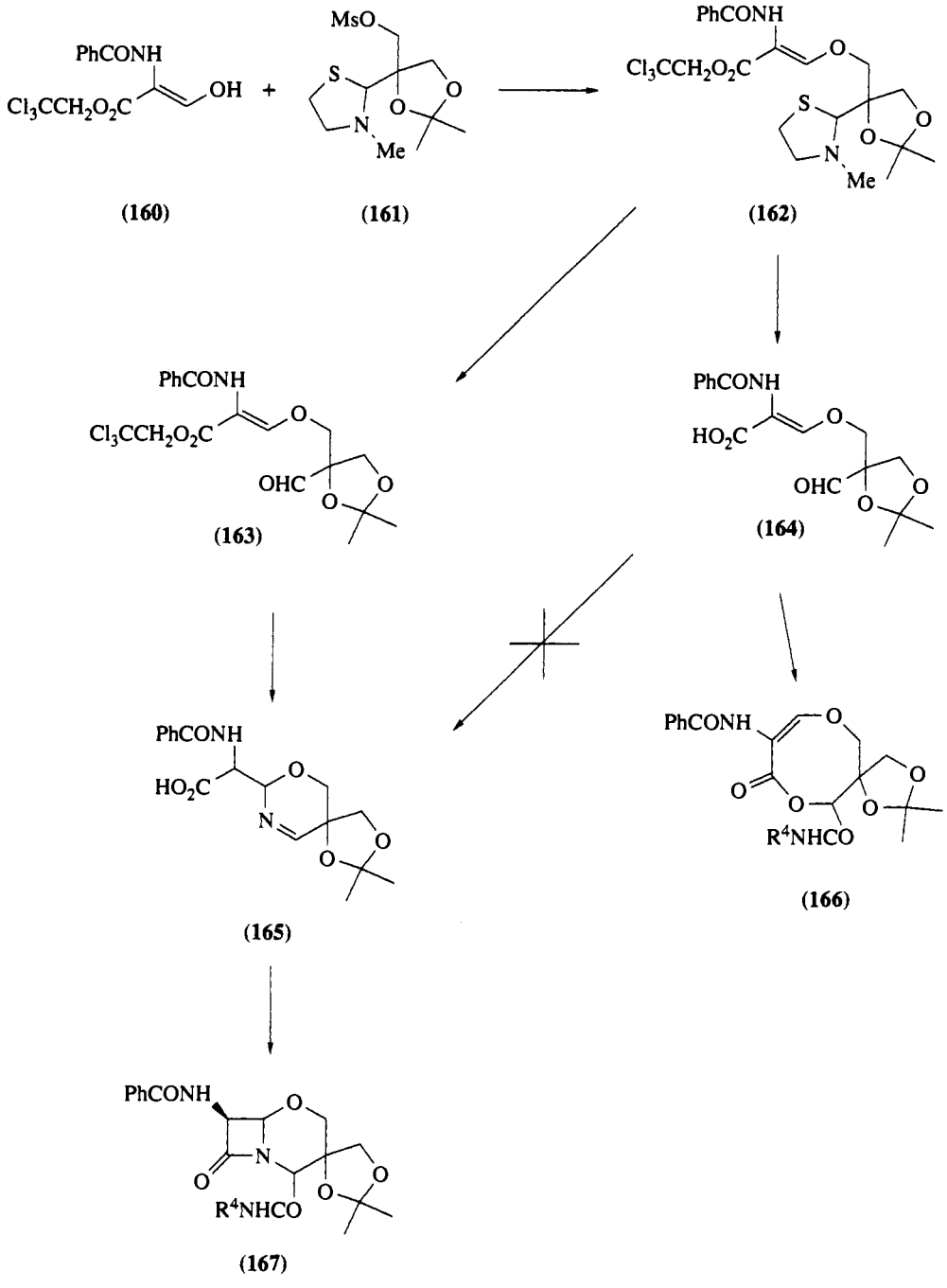


(**158**) (**159**)

Just *et al.*[130] attempted the synthesis of the oxacepham derivatives (**167**) as outlined below. This synthesis was planned as a model for analogous syntheses of cepham derivatives. Its design is ingenious, but it was not a complete success, because (**164**) did not react with NH_3 to form (**165**); it gave (**166**). The ring closure with NH_3 might have worked better with (**163**). Presumably discouraged by this result of their model study, these authors terminated their efforts in this field.

They demonstrated the effectiveness of the alkylation of enolates (**160**) + (**161**) → (**162**) for preparing precursors of penam and cepham derivatives. The penam synthesis by Schutz and Ugi, as well as the cepham synthesis[131] (**168**) → (**173**) profited from Just *et al.* immensely.[130]

In the field of the carbapenem syntheses Hatanaka *et al.*[121] have set new standards by their elegant syntheses of the carbapenem (**179**) and the synthesis of the carbapenem antibiotic PS-5 (**180**) and its 6-epi analog in remarkably few steps.[121]

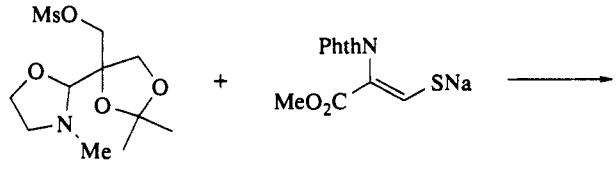


4.6.4.5 Macromolecules

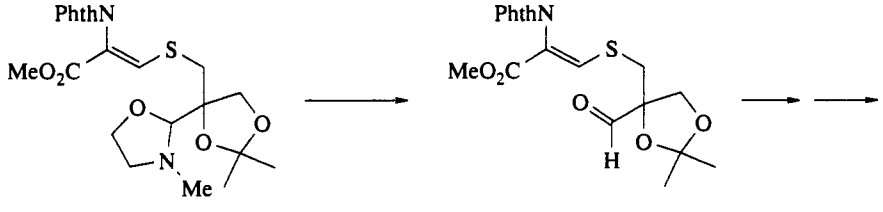
The usefulness of the Ugi reaction is not confined to the chemistry of small molecules, but also has applications in macromolecular chemistry.

The Ugi reaction is, for instance, used for the immobilization of enzymes,[132] and it is one of the best methods for attaching peptide and protein molecules to a solid support for sequence analysis by a modified Edman degradation.[133]

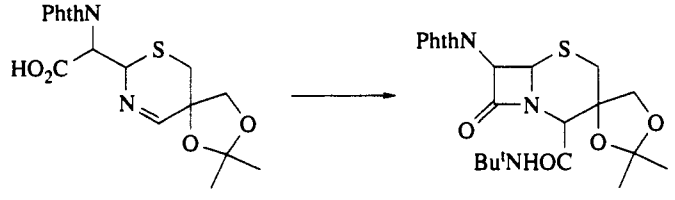
Enzymes can be immobilized by inclusion without significant loss of activity through a crosslinking 4CC of alginic acid, bis(*N*-3-aminopropyl)methylamine (**181a**), the corresponding isocyanide (**181b**) and formaldehyde in dilute aqueous solution of the enzyme.[134]



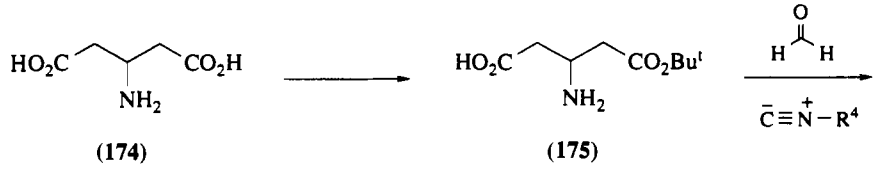
(168) (169)



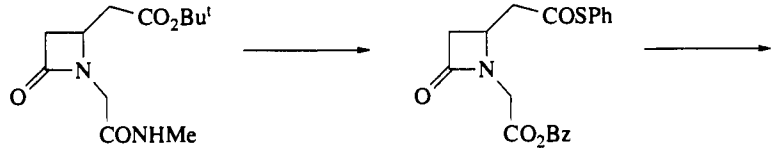
(170) (171)



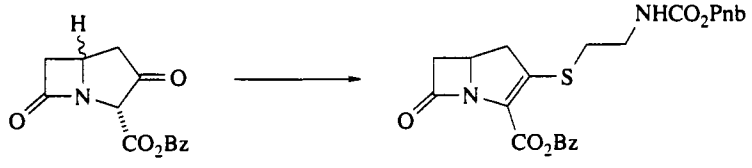
(172) (173)



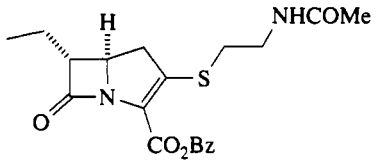
(174) (175)



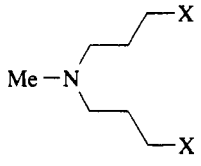
(176) (177)



(178) (179)



(180)



(181) **a**: X = NH_2

b: X = NC

4.6.5 ABBREVIATIONS

Ac = acetyl; All = allyl; Bu^t = *t*-butyl; Bz = benzyl; Fc = ferrocenyl; FcEt = 1-ferrocenylethyl; FcNe = 1-ferrocenyl-2,2-dimethylpropyl; c-Hex = cyclohexyl; Im = imidazoyl; Me = methyl; Oct^t = 2,4,4-trimethylpentyl; Ph = phenyl; PhEt(NH_2) = (*S*)-1-phenylethyl(amine); Piv = pivaloyl; Pnb = *p*-nitrobenzyl; Pr^i = isopropyl.

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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

Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

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

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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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