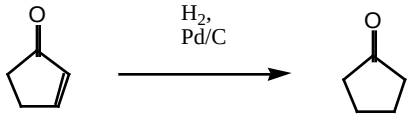
SELECTIVITY

Science **1983**, *219*, 245

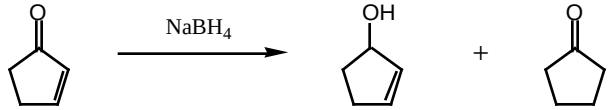
Chemoselectivity

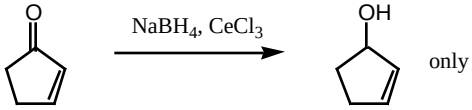
preferential reactivity of one functional group (FG) over another

- Chemoselective reduction of C=C over C=O:



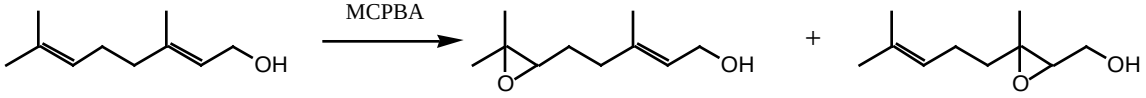
- Chemoselective reduction of C=O over C=C:





only

- Epoxidation:

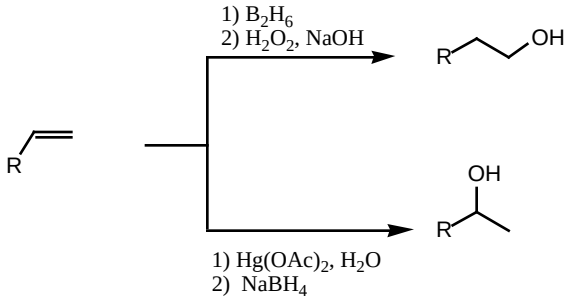


(2 : 1)

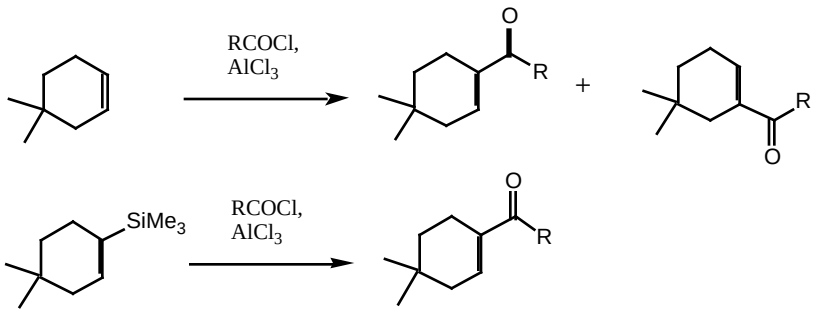
exclusively

Regioselectivity

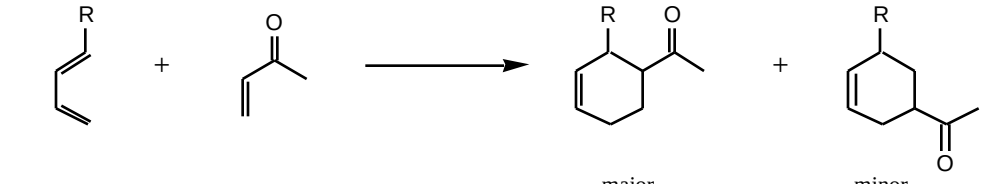
- Hydration of C=C:

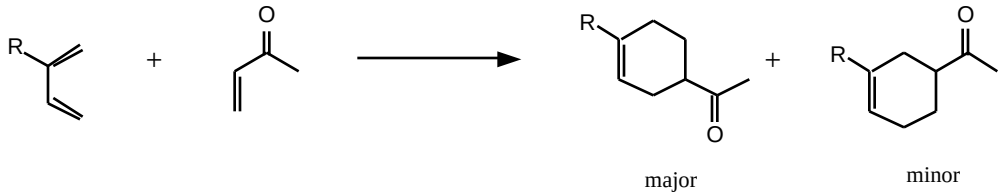


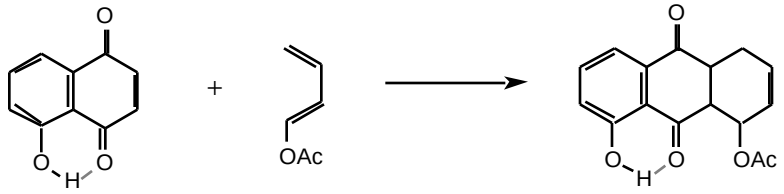
- Friedel-Crafts Reaction:

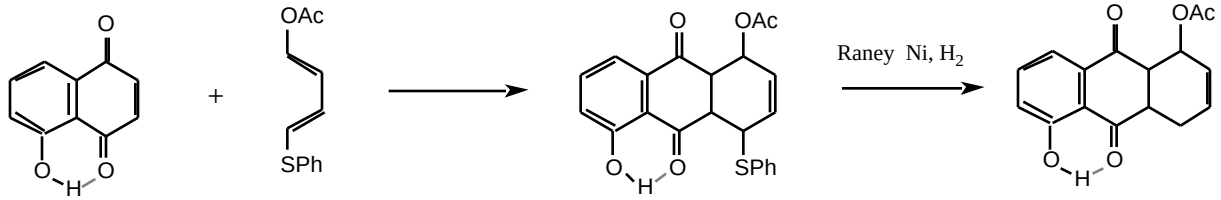


- Diels-Alder Reaction:

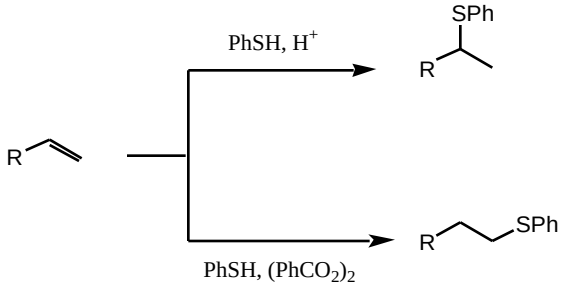






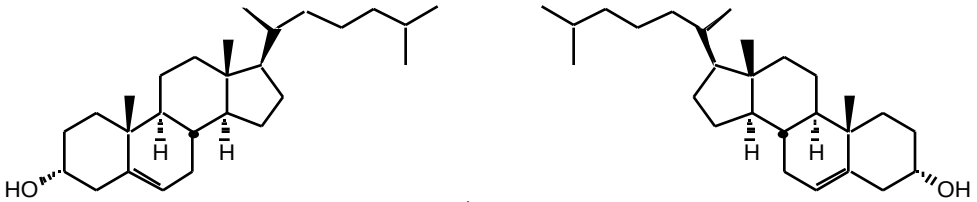


Change in mechanism:



Stereochemistry:

Relative stereochemistry: Stereochemical relationship between two or more stereogenic centers within a molecule



cholesterol

enantiomers
same relative stereochemistry

syn: on the same side (cis)
anti: on the opposite side (trans)

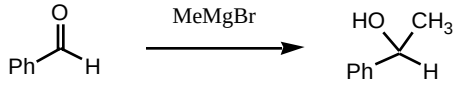
- differences in relative stereochemistry lead to diastereomers.

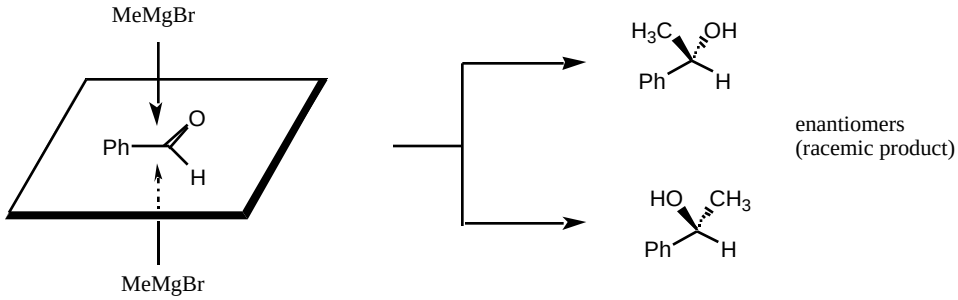
Diastereomers= stereoisomers which are not mirror images; usually have different physical properties

Absolute Stereochemistry: Absolute stereochemical assignment of each stereocenter (R vs S)
Cahn-Ingold-Prelog Convention (sequence rules)

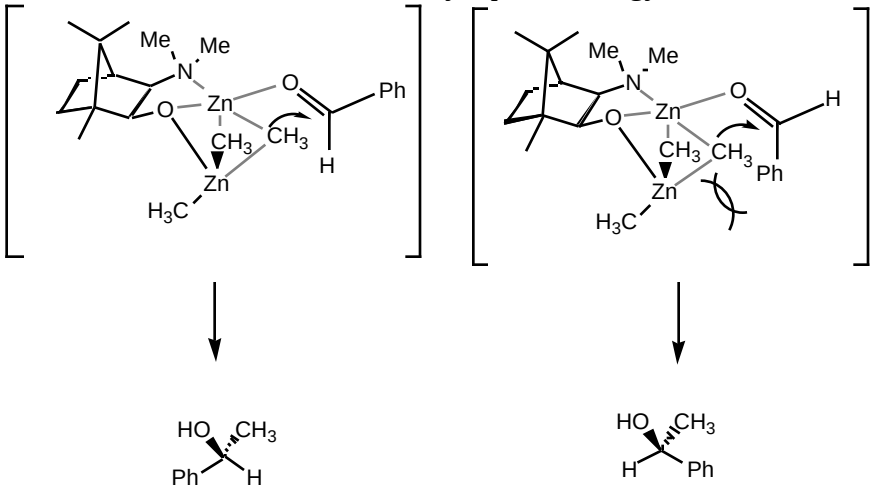
- differences in absolute stereochemistry (of all stereocenters within the molecule) leads to enantiomers.

- Reactions can "create" stereocenters

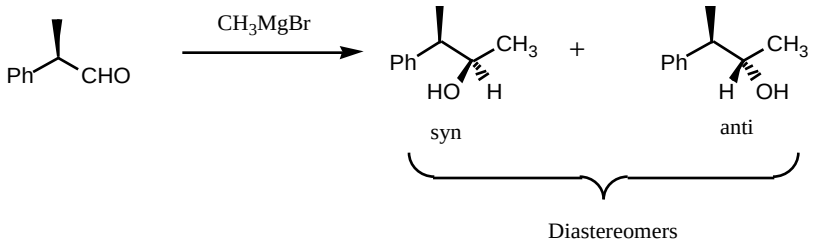




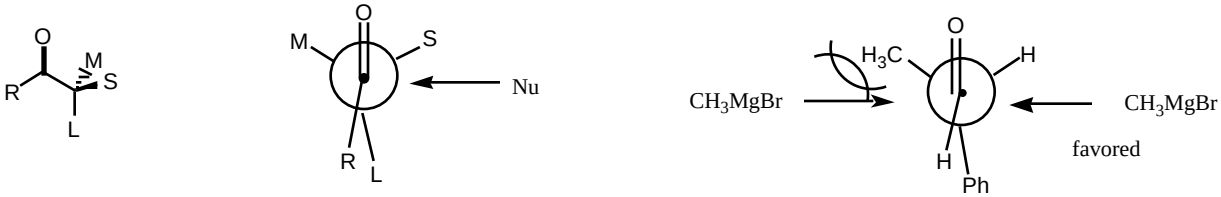
Diastereomeric transition states- not necessarily equal in energy



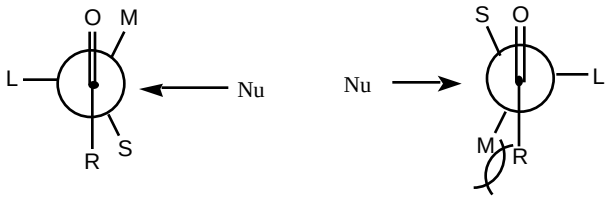
Diastereoselectivity



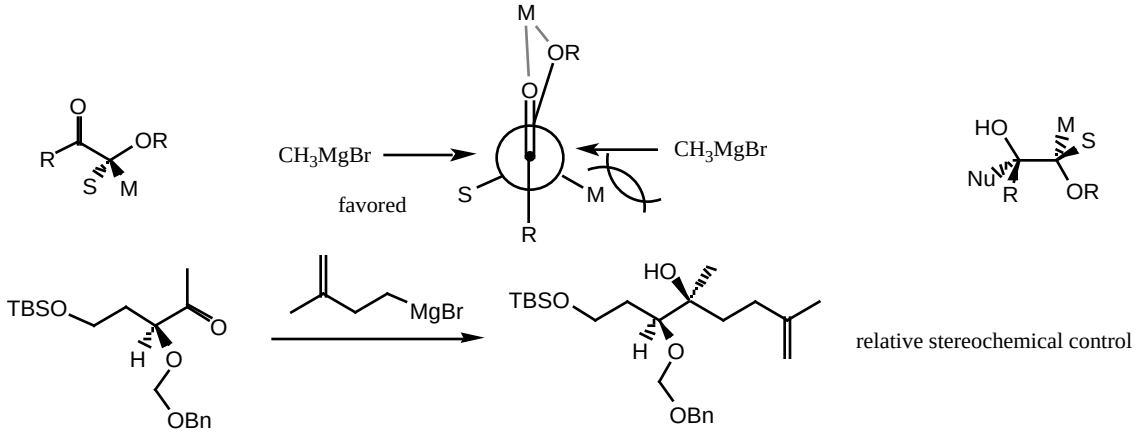
Cram Model (Cram's Rule): empirical



Felkin-Ahn Model

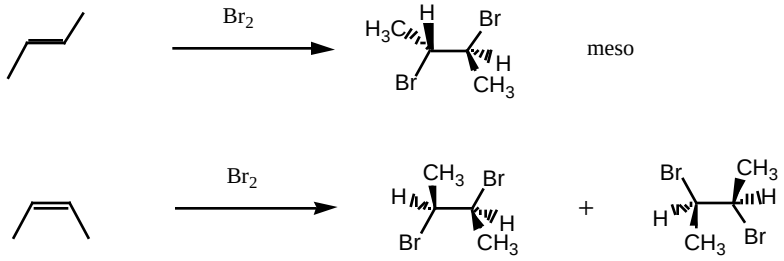


Chelation Control Mode



Stereospecific

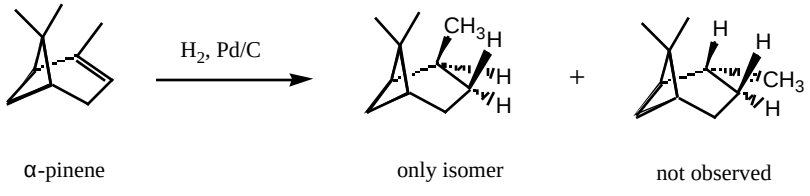
Stereochemictry of the product is related to the reactant in a mechanistically defined manner; no other stereochemical outcome is mechanistically possible.
i.e.; SN2 reaction- inversion of configuration is required



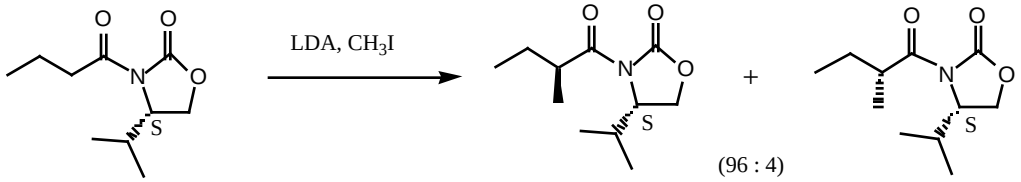
enantiomers (racemic)

Stereoselective

When more than one stereochemical outcome is possible, but one is formed in excess (even if that excess is 100:0).



α-pinene only isomer not observed



(96 : 4)

Diastereomers

Diastereoselective
Enantiospecific

Oxidations

Carey & Sundberg: Chapter 12 problems: 1a,c,e,g,n,o,q; 2a,b,c,f,g,j,k; 5; 9 a,c,d,e,f,l,m,n; 13
Smith: Chapter 3 March: Chapter 19

I. Metal Based Reagents
   1. Chromium Reagents
   2. Manganese Rgts.
   3. Silver
   4. Ruthenium
   5. other metals

II Non-Metal Based Reagents
   1. Activated DMSO
   2. Peroxides and Peracids
   3. Oxygen / ozone
   4. others

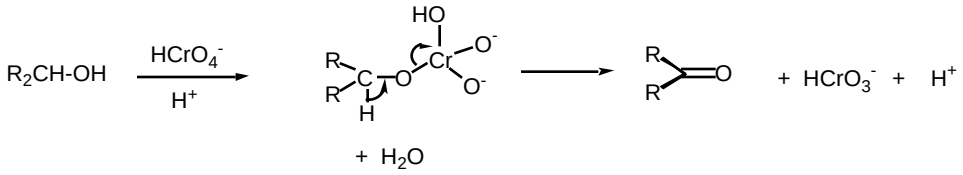
III. Epoxidations

Metal Based Reagents

Chromium Reagents

- Cr(VI) based
- exact stucture depends on solvent and pH
- Mechanism: formation of chromate ester intermediate

Westheimer et al. *Chem Rev*. **1949**, *45*, 419 *JACS* **1951**, *73*, 65.

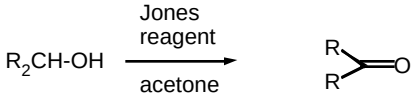


Jones Reagent (H_2CrO_4, $H_2Cr_2O_7$, $K_2Cr_2O_7$)

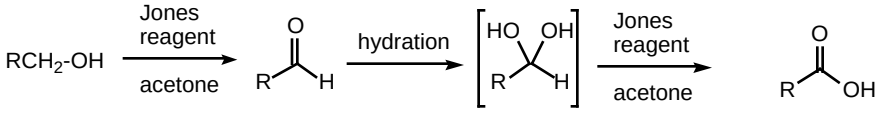
J. Chem. Soc. **1946** 39
Org. Syn. Col. Vol. V, **1973**, 310.

- $CrO_3 + H_2O \rightarrow H_2CrO_4$ (aqueous solution)
  $K_2Cr_2O_7 + K_2SO_4$
- Cr(VI) → Cr(III)
  (black) (green)

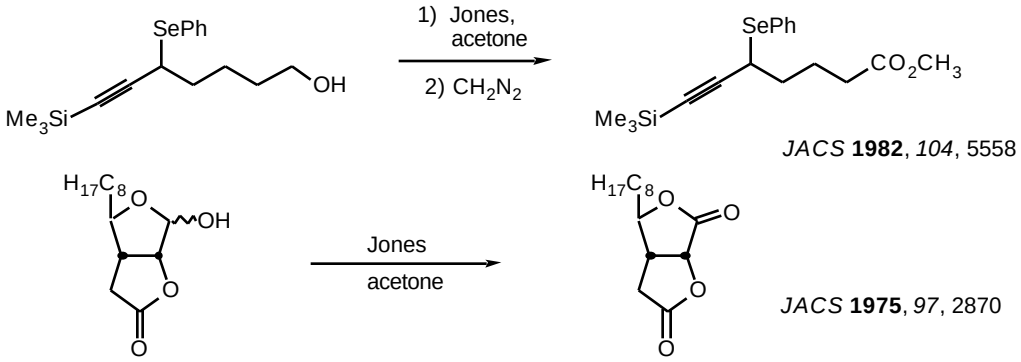
- 2°- alcohols are oxidized to ketones



- saturated 1° alcohols are oxidized to carboxylic acids.



- Acidic media!! Not a good method for H^+ sensitive groups and compounds



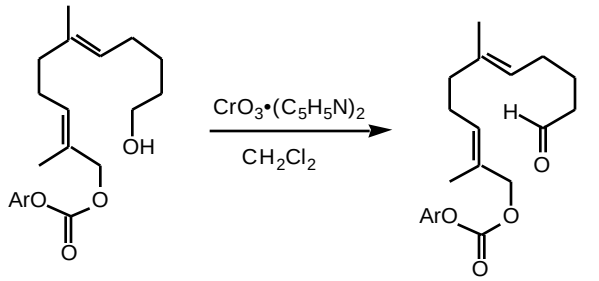
JACS **1982**, *104*, 5558

JACS **1975**, *97*, 2870

Collins Oxidation (CrO_3•2pyridine)

TL **1969**, 3363

- CrO_3 (anhydrous) + pyridine (anhydrous) → CrO_3•2pyridine↓
- 1° and 2° alcohols are oxidized to aldehydes and ketones in non-aqueous solution (CH_2Cl_2) without over-oxidation
- Collins reagent can be prepared and isolated or generated *in situ*. Isolation of the reagent often leads to improved yields.
- Useful for the oxidation of H^+ sensitive cmpds.
- not particularly basic or acidic
- must use a large excess of the rgt.



JACS **1969**, *91*, 44318.

CrO_3 catalyzed (1-2 mol % oxidation with $NaIO_6$ (2.5 equiv) as the reozidant in wet aceteonitrile. oxidized primary alcohols to carboxylic acids.

Tetrahedron Lett. **1998**, *39*, 5323.

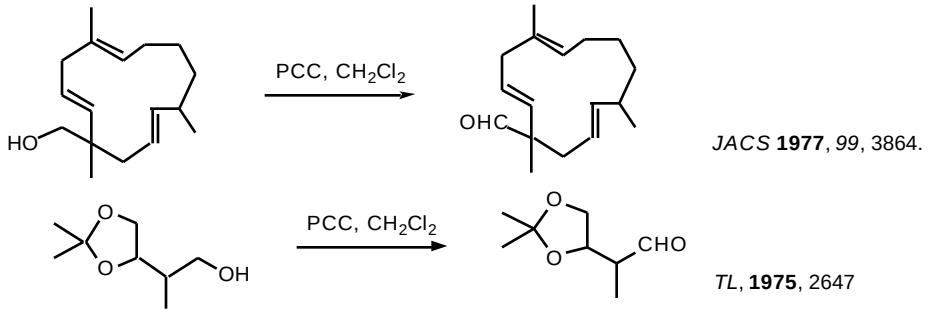
Pyridinium Chlorochromate (PCC, Corey-Suggs Oxidation)

TL **1975** 2647

Synthesis **1982**, 245 (review)

CrO3 + 6M HCl + pyridine → pyH^+CrO_3 Cl^- ↓

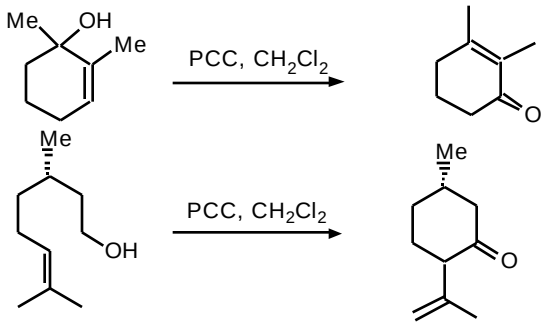
- Reagent can be used in close to stoichiometric amounts w / substrate
- PCC is slighly acidic but can be buffered w / NaOAc



JACS **1977**, *99*, 3864.

TL, **1975**, 2647

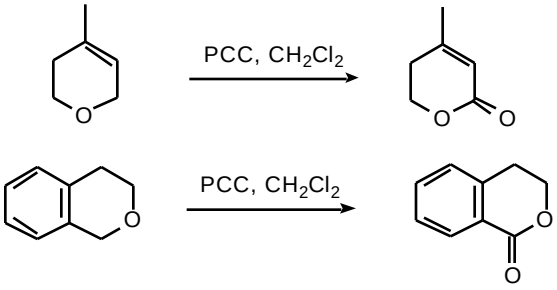
- Oxidative Rearrangements



JOC **1977**, *42*, 682

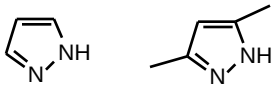
JOC **1976**, *41*, 380

- Oxidation of Active Methylene Groups

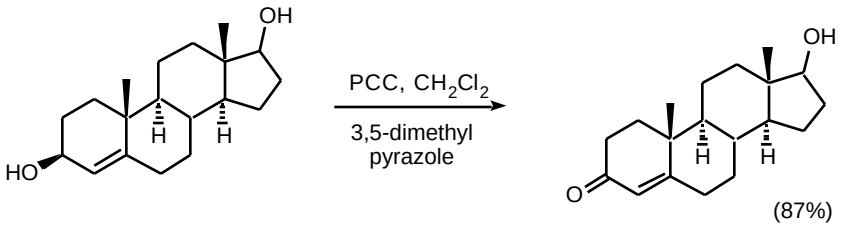


JOC **1984**, *49*, 1647

- PCC / Pyrazole PCC / 3,5-Dimethylpyrazole
JOC **1984**, *49*, 550.



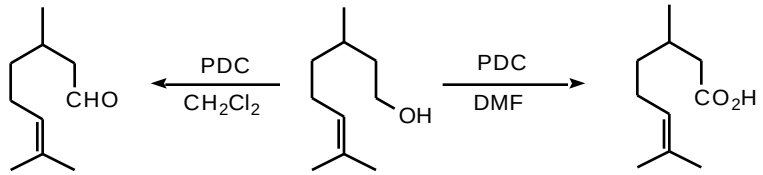
- selective oxidation of allylic alcohols



(87%)

Pyridinium Dichromate (PDC, Corey-Schmidt Oxidation)
TL **1979**, 399

- $Na_2Cr_2O_7 \cdot 2H_2O$ + HCl + pyridine → $(C_5H_5N)_2CrO_7$ ↓



1° alcohol

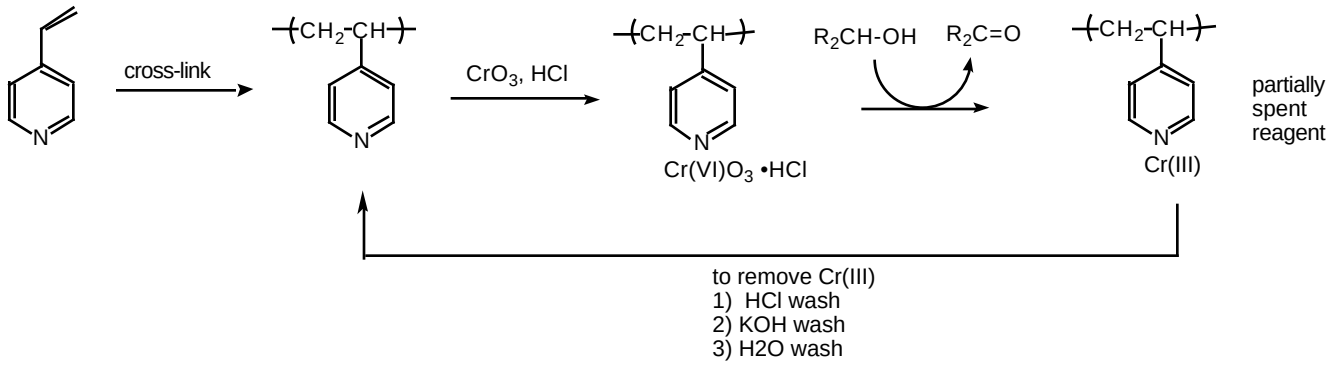
-allylic alcohols are oxidized to α,β-unsaturated aldehydes

- Supported Reagents *Comprehensive Organic Synthesis* **1991**, *7*, 839.

PCC on alumina : *Synthesis* **1980**, 223.

- improved yields due to simplified work-up.

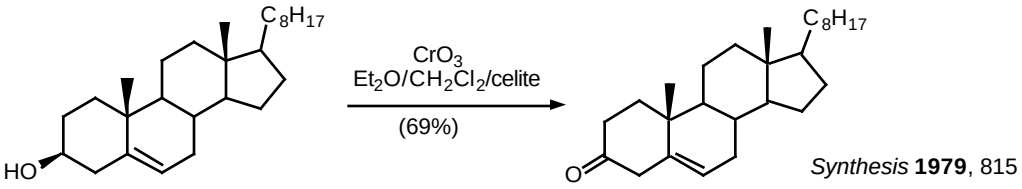
PCC on polyvinylpyridine : *JOC*, **1978**, *43*, 2618.



$CrO_3/Et_2O/CH_2Cl_2$/Celite

Synthesis **1979**, 815.

- CrO_3 in non-aqueous media does not oxidized alcohols
- CrO_3 in 1:3 Et_2O / CH_2Cl_2 / celite will oxidized alcohols to ketone and aldehydes



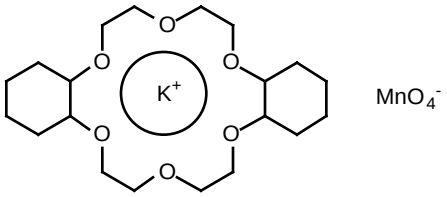
H_2CrO_7 on Silica

- 10% CrO_3 to SiO_2
- 2-3g H_2CrO_3 / SiO_2 to mole of R-OH
- ether is the solvent of choice

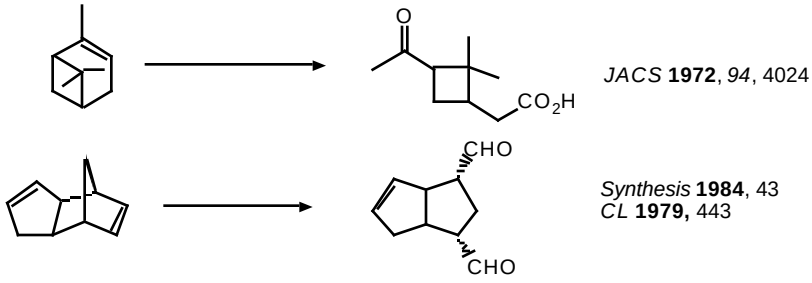
Manganese Reagents

Potassium Permanganate $KMnO_4$ / 18-Crown-6 (purple benzene)

JACS **1972** *94*, 4024.



- 1° alcohols and aldehydes are oxidized to carboxylic acids
- 1:1 dicyclohexyl-18-C-6 and $KMnO_4$ in benzene at 25°C gives a clear purple solution as high as 0.06M in $KMnO_4$.



Sodium Permanganate

TL **1981**, 1655

- heterogeneous reaction in benzene
- 1° alcohols are oxidized to acids
- 2° alcohols are oxidized to ketones
- multiple bonds are not oxidized

Barium Permanganate ($BaMnO_4$)

TL **1978**, 839.

- Oxidation if 1° and 2° alcohols to aldehydes and ketones- No over oxidation
- Multiple bonds are not oxidized
- similar in reactivity to MnO_2

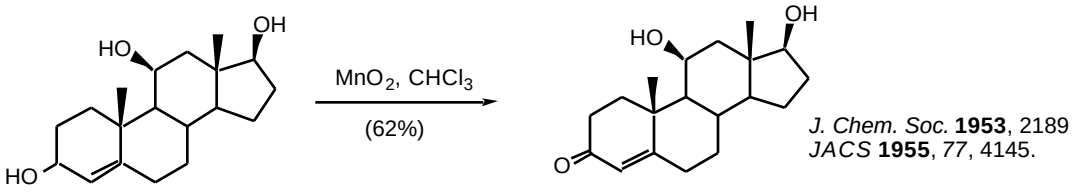
Barium Manganate

BCSJ **1983**, *56*, 914

Manganese Dioxide

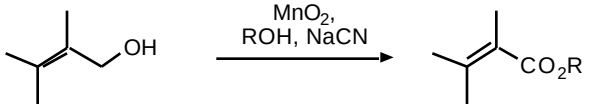
Review: *Synthesis* **1976**, 65, 133

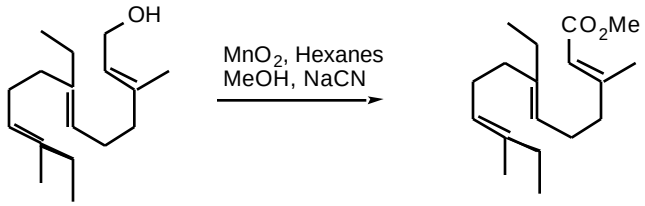
- Selective oxidation of α,β-unsatutrated (allylic, benzylic, acetylenic) alcohols.
- Activity of MnO_2 depends on method of preparation and choice of solvent
- cis & trans allylic alcohols are oxidized at the same rate without isomerization of the double bond.



J. Chem. Soc. **1953**, 2189
JACS **1955**, *77*, 4145.

- oxidation of 1° allylic alcohols to α,β-unsaturated esters

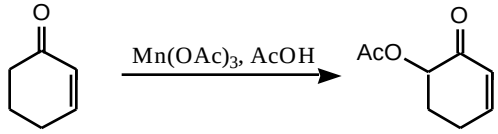




*JACS***1968**, *90*, 5616. 5618

Manganese (III) Acetate α-hydroxylation of enones

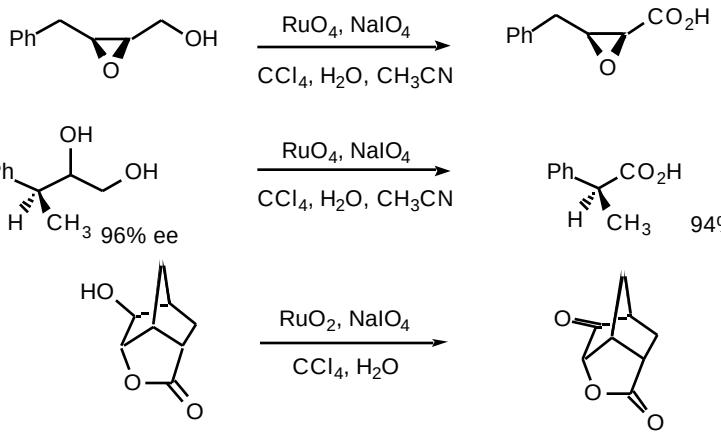
Synthesis **1990**, 1119 *TL* **1984** *25*, 5839



Ruthenium Reagents

Ruthenium Tetroxide

- effective for the conversion of 1° alcohols to RCO_2H and 2° alcohols to ketones
- oxidizes multiple bonds and 1,2-diols.

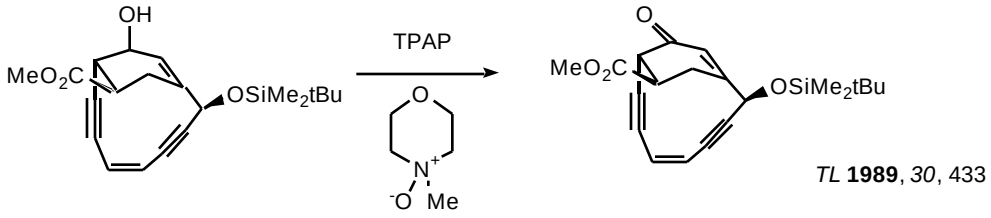


Tetra-n-propylammonium Perruthenate (TPAP, $nPr_4N^+ RuO_4^-$)

Aldrichimica Acta **1990**, *23*, 13.

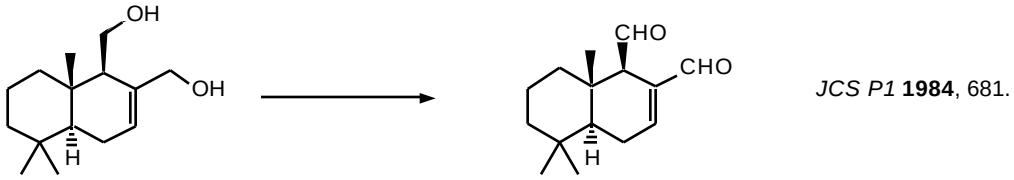
Synthesis **1994**, 639

- mild oxidation of alcohols to ketones and aldehydes <u>without</u> over oxidation



$(Ph_3P)_4RuO_2Cl_3$ *$RuO_2(bipy)Cl_2$*

- oxidizes a wide range of 1°- and 2°-alcohols to aldehydes and ketones without oxidation of multiple bonds.



$Ba[Ru(OH)_2O_3]$

-oxidizes only the most reactive alcohols (benzylic and allylic)

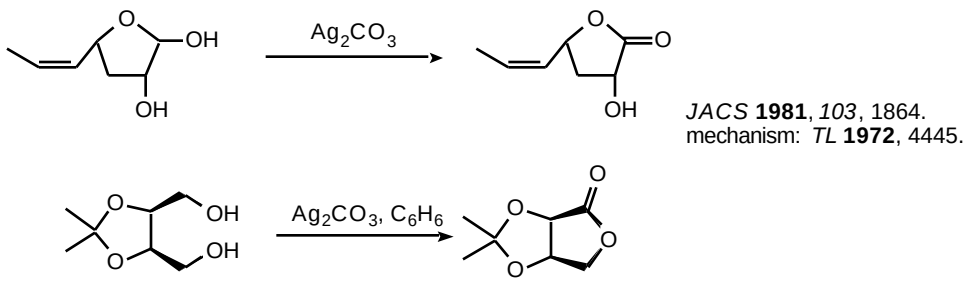
$(Ph_3P)_3RuCl_2$ + Me_3SiO-$OSiMe_3$

- oxidation of benzylic and allylic alcohols *TL* **1983**, *24*, 2185.

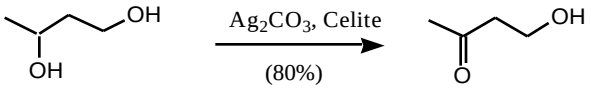
Silver Reagents

Ag_2CO_3 (Fetizon Oxidation) also Ag_2CO_3/celite *Synthesis* **1979**, 401

- oxidation of only the most reactive hydroxyl



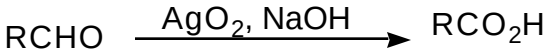
- Oxidation of 2° alcohol over a 1° alcohol

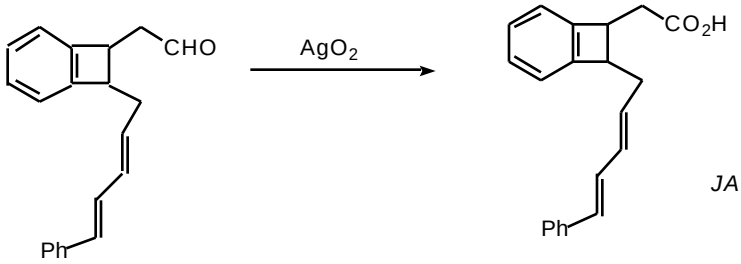


JCS,CC **1969**, 1102

Silver Oxide (AgO_2)

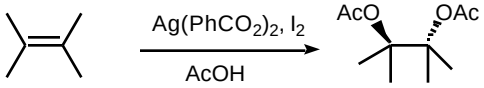
- mild oxidation of aldehyde to carboxylic acids

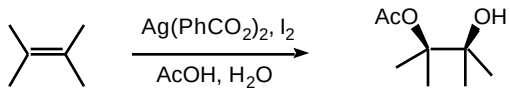




JACS **1982**, *104*, 5557

Prevost Reaction $Ag(PhCO_2)_2$, I_2





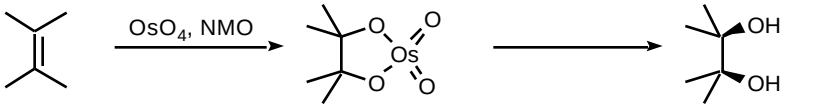
Other Metal Based Oxidations

Osmium Tetroxide OsO_4

review: *Chem. Rev.* **1980**, *80*, 187.

-cis hydroxylation of olefins

old mechanism:

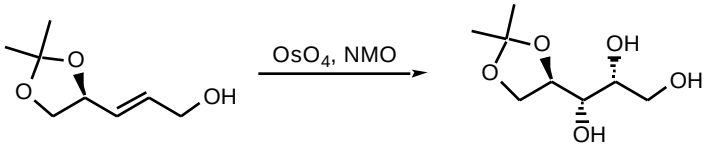


osmate ester intermediate

cis stereochemistry

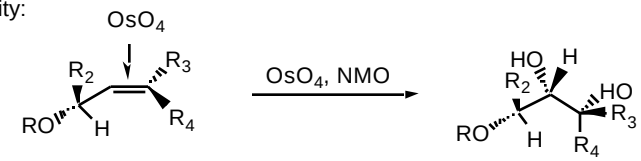
- use of R_3N-O as a reoxidant

TL **1976**, 1973.

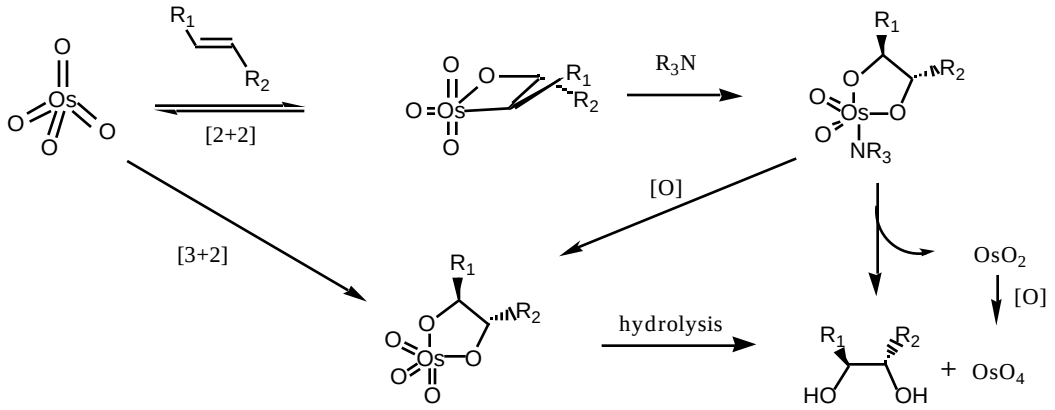


TL **1983**, *24*, 2943, 3947

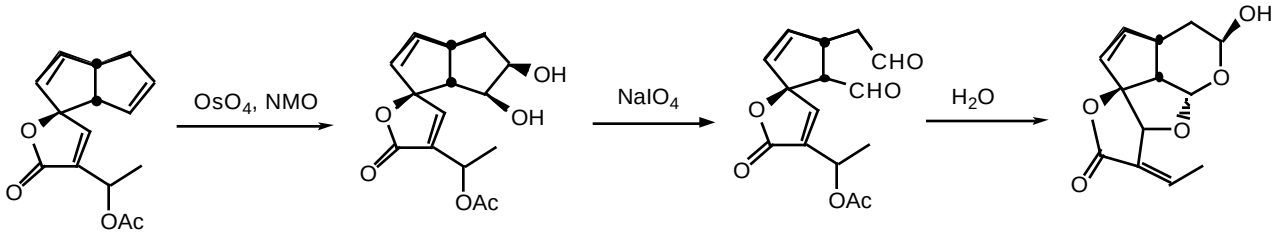
Stereoselectivity:



- new mechanism: reaction is accelerated in the presences of an 3° amine



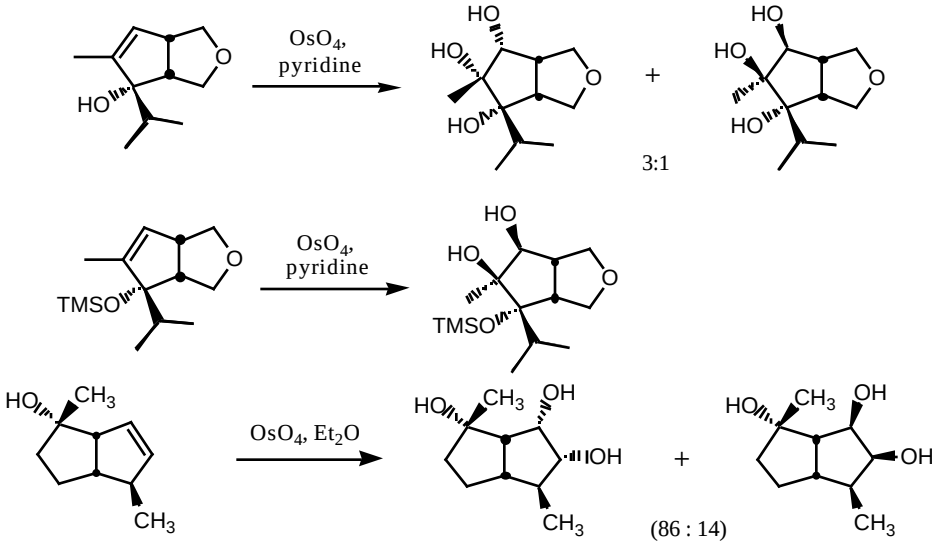
- Oxidative cleavage of olefins to carboxylic acids.
  JOC **1956**, *21*, 478.
- Oxidative cleavage of olefins to ketones & aldehydes.



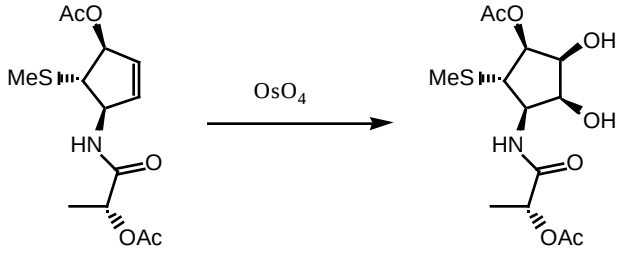
JACS **1984**, *105*, 6755.

Substrate directed hydroxylations: *Chem. Rev.* **1993**, *93*, 1307

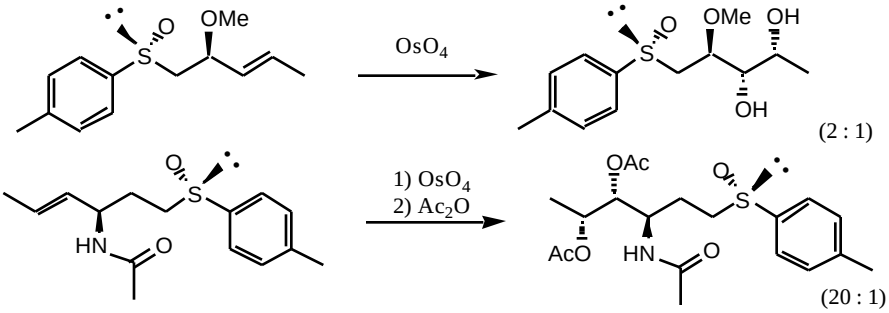
-by hydroxyl groups



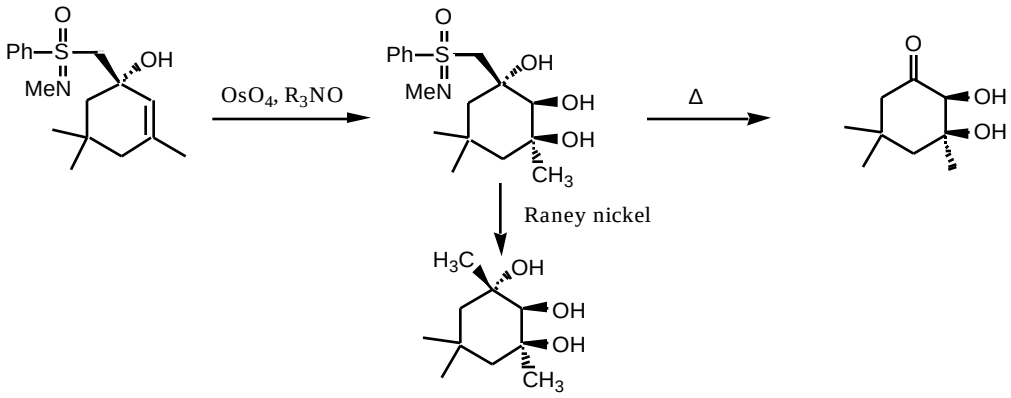
- by amides



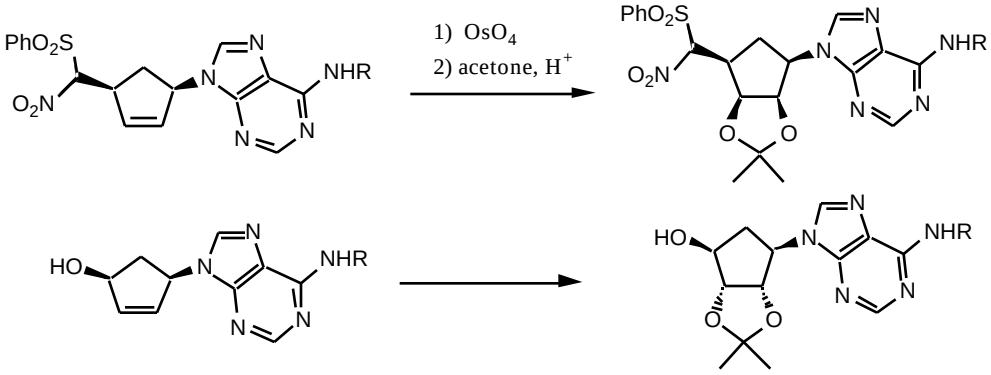
- by sulfoxides



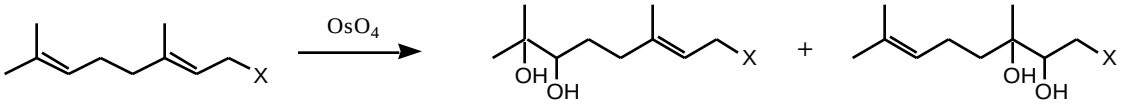
- by sulfoximines



- By nitro groups

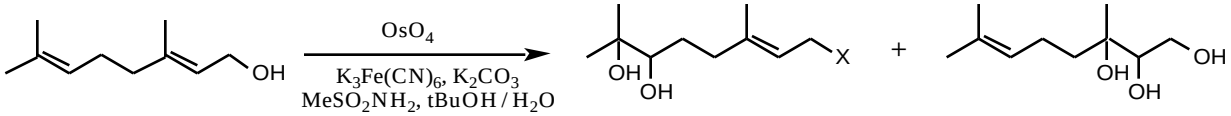


- OsO_4 bis-hydroxylation favors electon rich C=C.



X= OH	80 : 20	(directing effect ?)
= OMe	98 : 2	
= OAc	99 : 1	
= $NHSO_2R$	60 : 40	(directing effect ?)

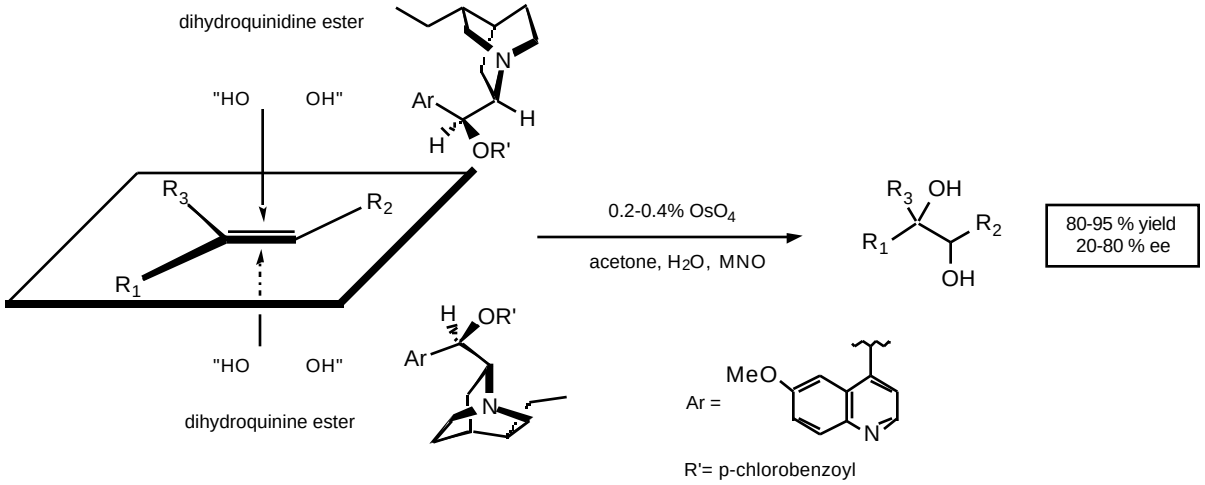
- Ligand effect:



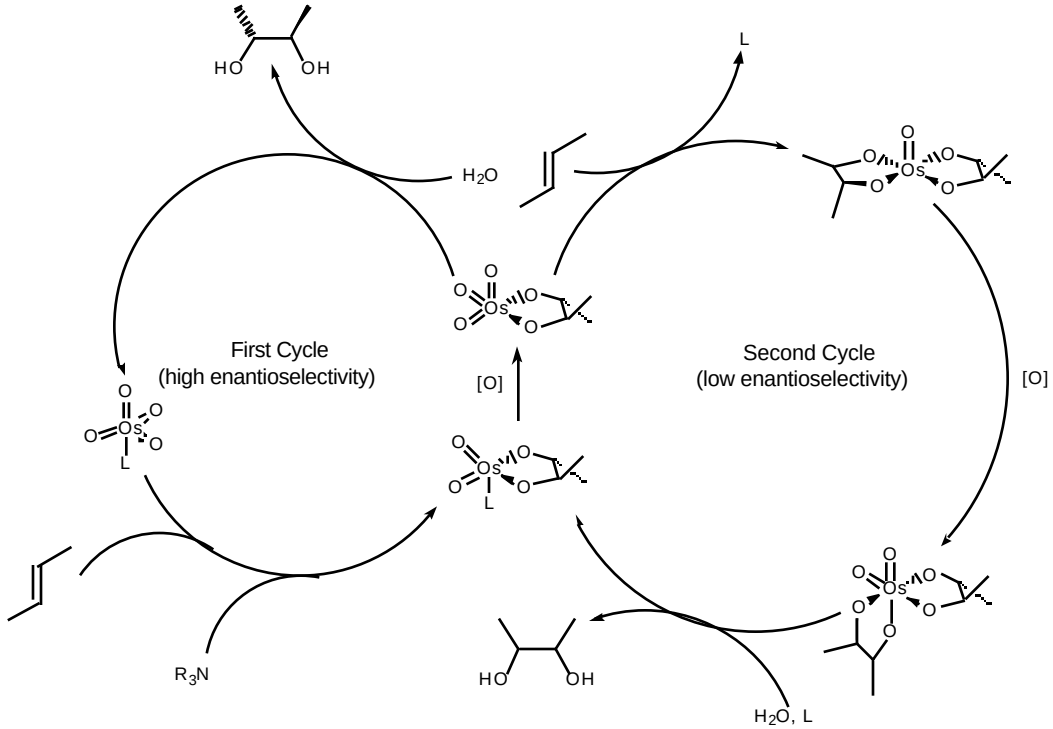
OsO_4 (no ligand)	4 : 1
Quinuclidine	9 : 1
DHQD-PHAL	> 49 : 1

Sharpless Asymmetric Dihydroxylation (AD) *Chem. Rev.* **1994**, *94*, 2483.

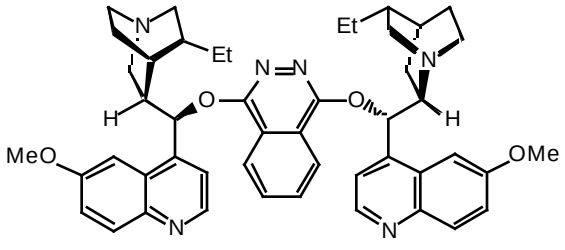
- Ligand pair are really diastereomers!!



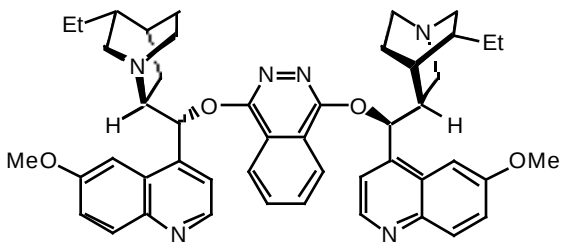
Mechanism of AD:



- $K_3Fe(CN)_6$ as a reoxidant gives higher ee's- eliminates second cycle
  TL **1990**, *31*, 2999.
- Sulfonamide effect: addition of $MeSO_2NH_2$ enhances hydrolysis of Os(VI) glycolate (accelerates reaction)
- New phthalazine (PHAL) ligand's give higher ee's



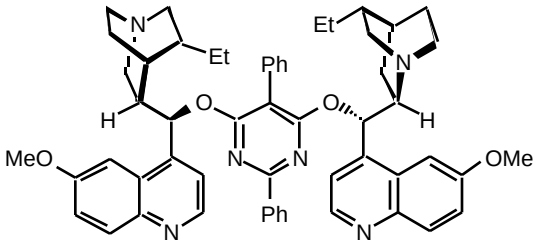
$(DHQD)_2$-PHAL



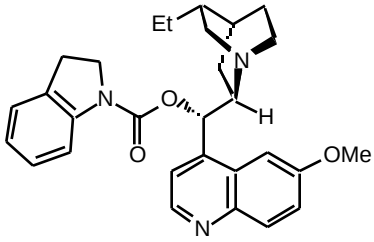
$(DHQ)_2$-PHAL

JOC **1992**, *57*, 2768.

- Other second generation ligands

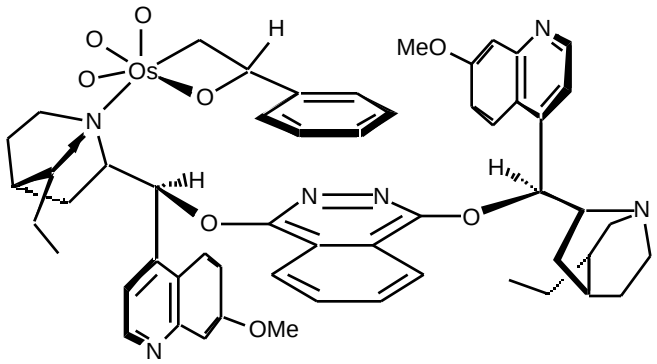


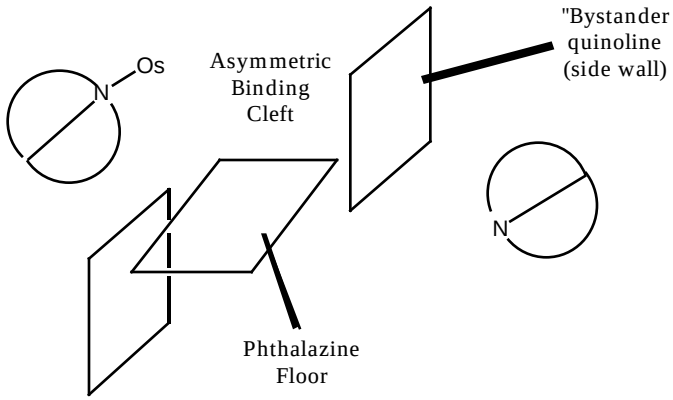
PYR



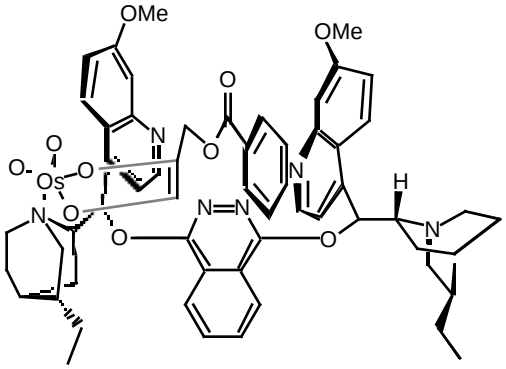
IND

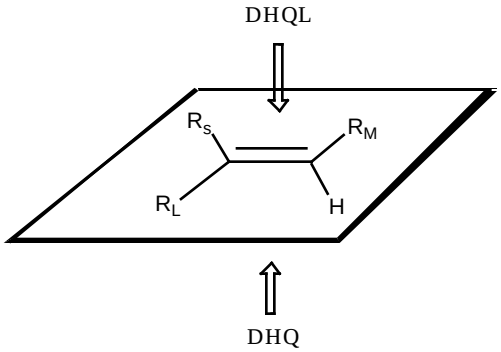
Proposed catalyst structure:



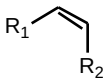
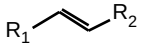
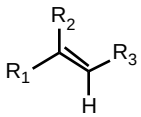
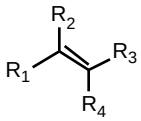


Corey Model: *JACS* **1996**, *118*, 319
Enzyme like binding pocket;
[3+2] addition of OsO_4 to olefin.





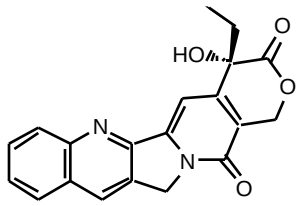
R_L large and flat,
i.e Aromatics work particularly well

Olefin	Preferred Ligand	ee's
	PYR, PHAL	30 - 97 %
	PHAL	70 - 97 %
	IND	20 - 80 %
	PHAL	90 - 99.8 %
	PHAL	90 - 99 %
	PHAL, PYR + $MeSO_2NH_2$	20 - 97 %

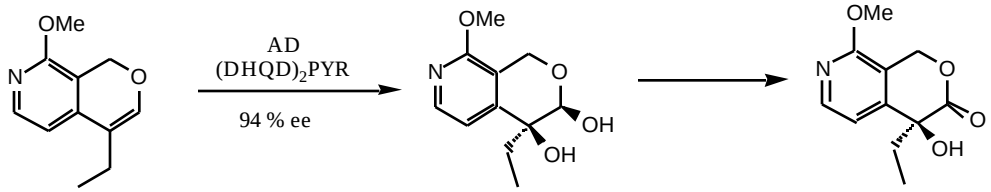
"AD-mixes" commercially available pre-mix solutions of Os, ligand and reoxidant

AD-mix α $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, K_2OsO_4 (0.4 MOL % Os to C=C)

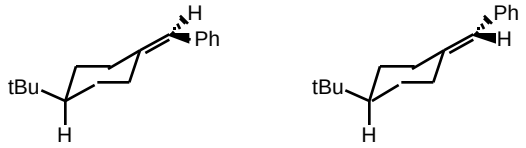
AD-mix β $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, K_2OsO_4



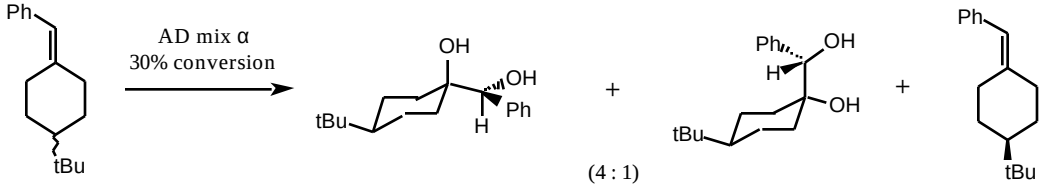
Campthothecin



- Kinetic resolution (not as good as Sharpless asymmetric epoxidation)



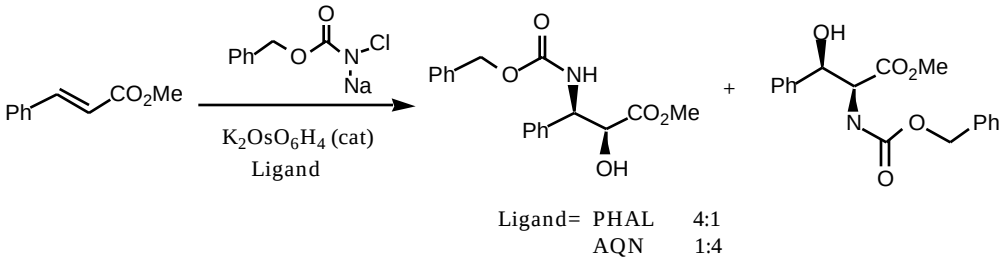
olefins with axial dissymmetry



enriched

Asymmetric Aminohydroxylation *TL* **1998**, *39*, 2507; *ACIEE* **1996**, *25*, 2818, 2813,

preparation of α-aminoalcohols from olefin. Syn addition as with the dihydroxylation regiochemistry can be a problem



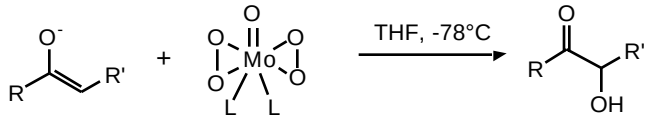
Ligand= PHAL 4:1
AQN 1:4

Molybdenum Reagents

MoOPH [MoO_5•pyridine (HMPA)]

JOC **1978**, *43*, 188.

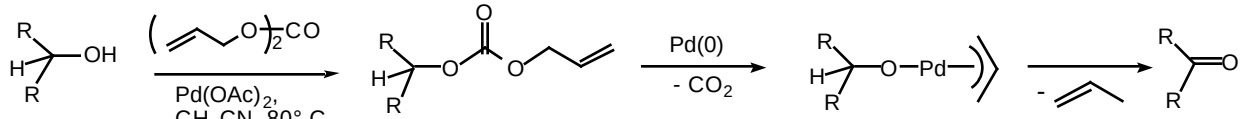
- α-hydroxylation of ketone, ester and lactone enolates.



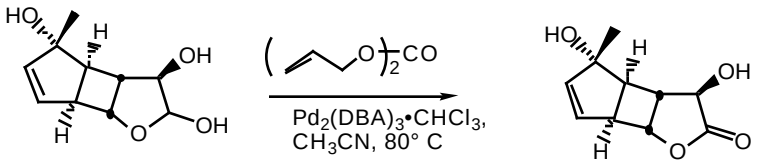
Palladium Reagents

Pd(0) catalyzed Dehydrogenation (oxidation) of Allyl Carbonates (Tsuji Oxidation)

Tetrahedron **1986**, *42*, 4361

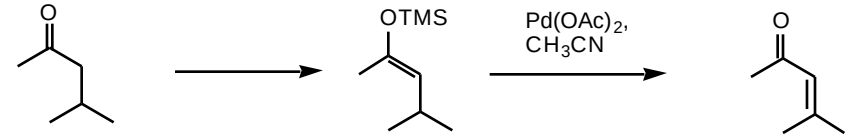


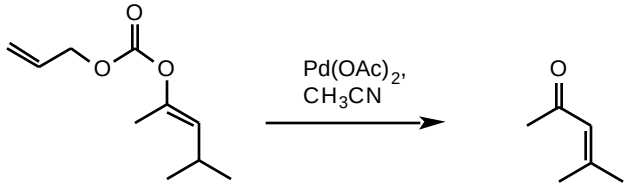
TL **1984**, *25*, 2791
Tetrahedron **1987**, *43*, 3903

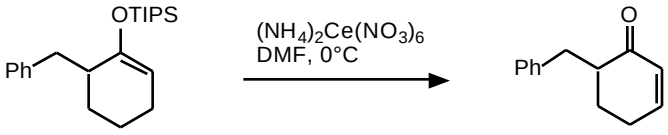


JACS **1989**, *111*, 8039.

Oxidation of silylenol ethers and enol carbonates to enones

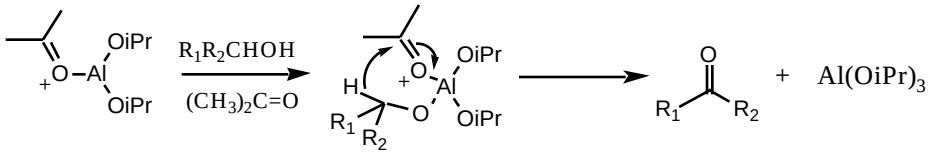






TL **1995**, *36*, 3985

Oppenauer Oxidation *Synthesis* **1994**, 1007 *Organic reactions* **1951**, *6*, 207



Nickel Peroxide

Chem Rev. **1975**, *75*, 491

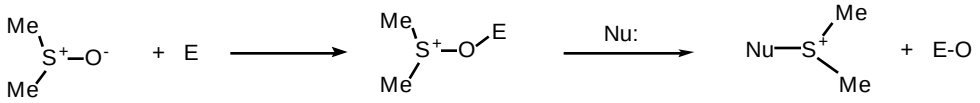
Thallium Nitrate (TNN, $Tl(NO_3)_3 \cdot 3H_2O$

Pure Appl. Chem. **1875**, *43*, 463.

Lead Tetraacetrate $Pb(OAc)_4$ *Oxidations in Organic Chemistry (D)*, **1982**, pp 1-145.

Non-Metal Based Reagents

Activated DMSO Review: *Synthesis* **1981**, 165; **1990**, 857. *Organic Reactions* **1990**, *39*, 297

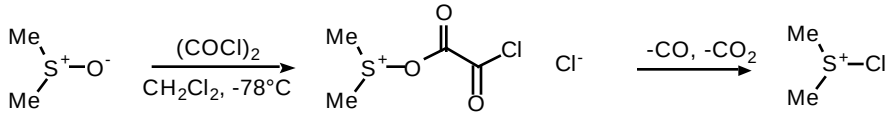


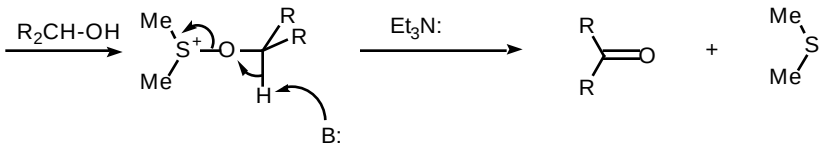
E= $(CF_3CO)_2O$, $SOCl_2$, $(COCl)_2$, Cl_2, $(CH_3CO)_2O$, TsCl, MeCl, SO_3/pyridine, F_3CSO_2H, PO_5, H_3PO_4, Br_2

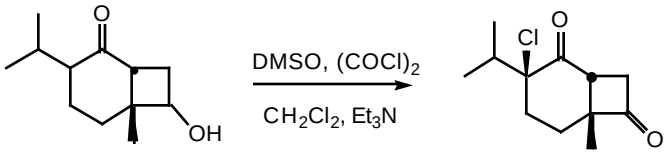
Nu:= R-OH, Ph-OH, R-NH_2, RC=NOH, enols

Swern Oxidation

- trifluoroacetic anhydride can be used as the activating agent for DMSO

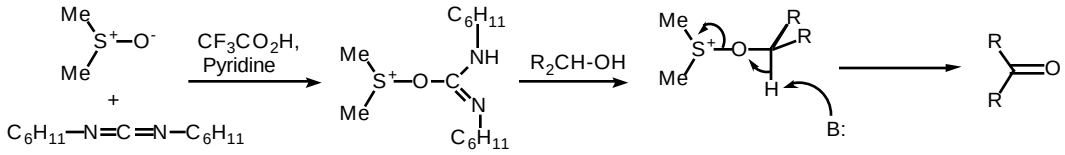


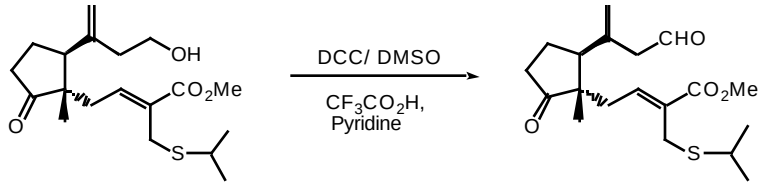




TL **1988**, *29*, 49.

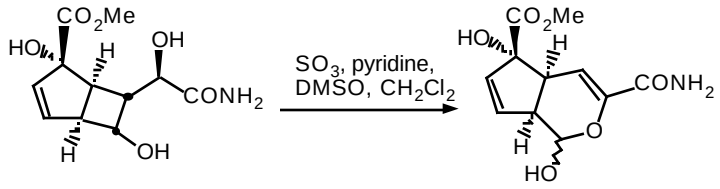
Moffatt Oxidation (DMSO / DCC) *JACS* **1965**, *87*, 5661, 5670.





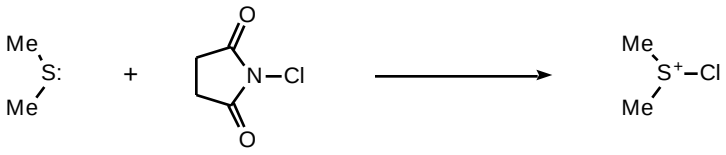
JACS **1978**, *100*, 5565

SO_3/Pyridine *JACS* **1967**, *89*, 5505.



JACS **1989**, *111*, 8039.

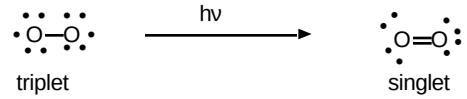
Corey-Kim Oxidation (DMS / NCS) *JACS* **1972**, *94*, 7586.

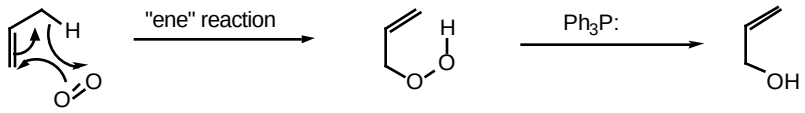


N-Chlorosuccinimide (NCS)

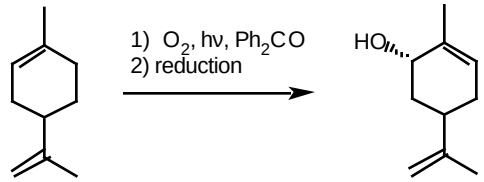
Oxygen & Ozone

Singlet Oxygen *Acc. Chem. Res.* **1980**, *13*, 419 *Tetrahedron* **1981**, *37*, 1825

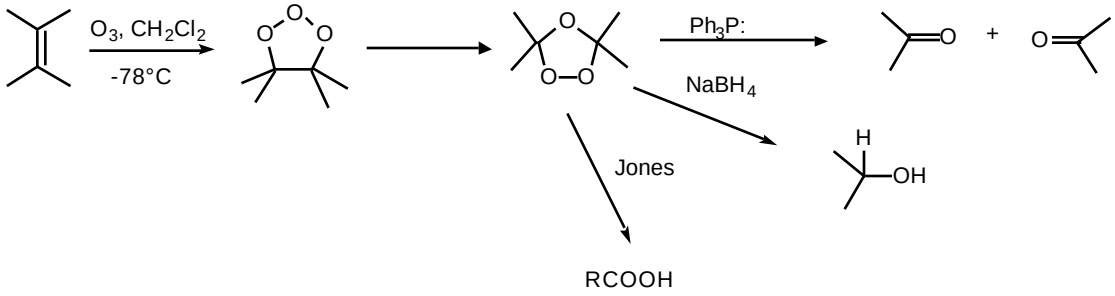




Tetrahedron **1981**, 1825

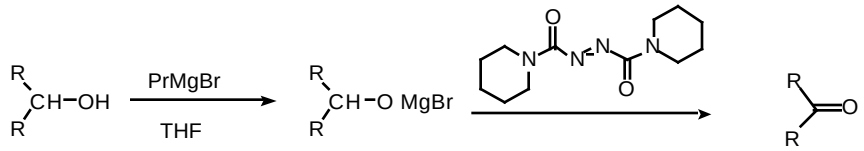


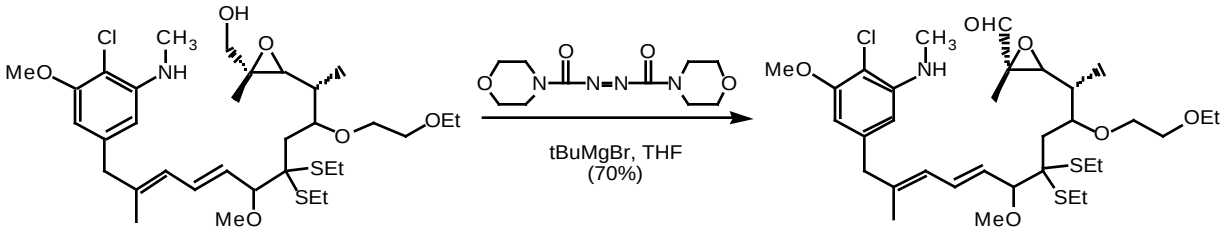
Ozone *Comprehensive Organic Synthesis* **1991**, *7*, 541



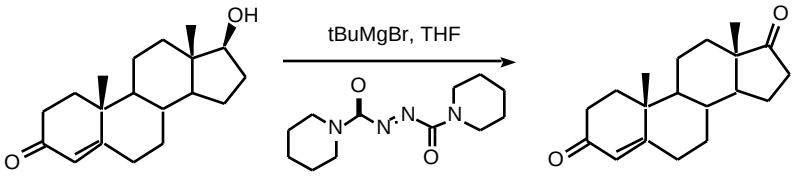
Other Oxidations

Mukaiyama Oxidation *BCSJ* **1977**, *50*, 2773



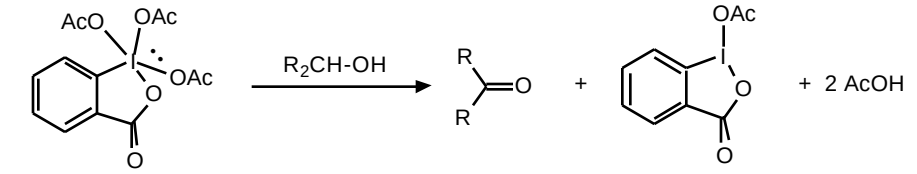


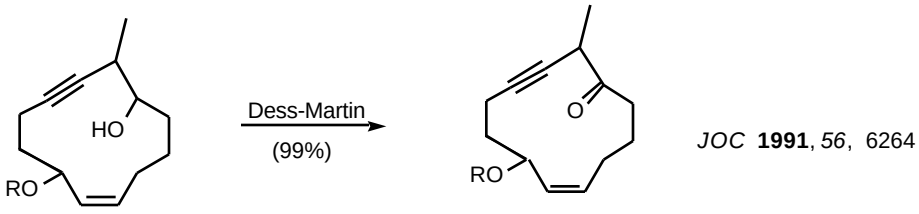
JACS **1979**, *101*, 7104



Dess-Martin Periodinane *JOC* **1983**, *48*, 4155. *JACS* **1992**, *113*, 7277.

- oxidation conducted in $CHCl_3$, CH_3CN or CH_2Cl_2
- excellent reagent for hindered alcohols
- very mild



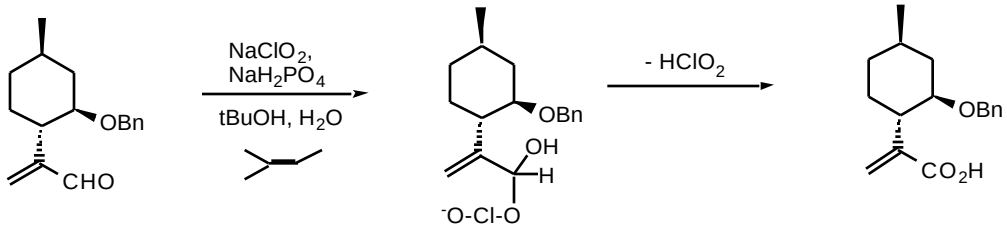


JOC **1991**, *56*, 6264

Chlorite Ion

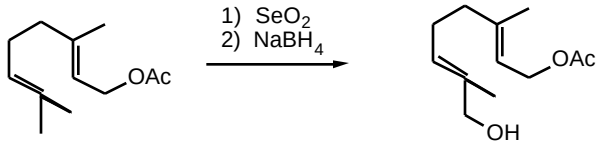
-oxidation of α,β-unsaturated aldehydes to α,β−unsaturated acids.

Tetrahedron **1981**, *37*, 2091

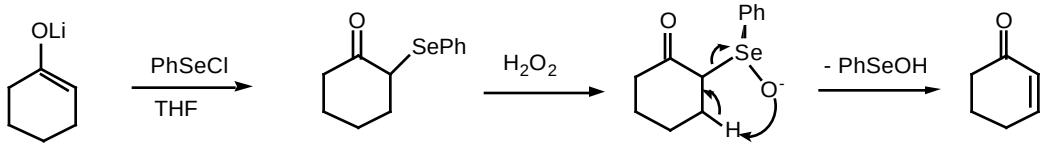


Selenium Dioxide

- Similar to singlet oxygen (allylic oxidation)



Phenyl Selenium Chloride



- PhS-SPh will do similar chemistry however a sulfoxide elimination is less facile than a selenoxide elinimation.

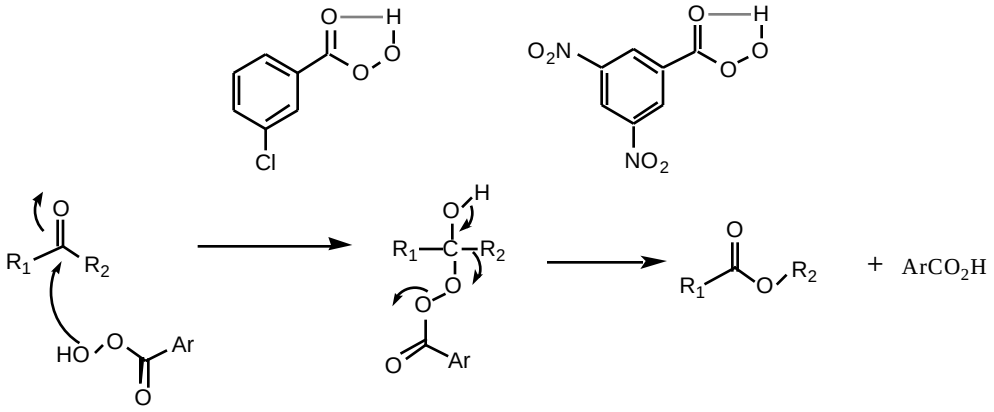
Peroxides & Peracids

- $R_3N: \rightarrow R_3N\text{-}O$
- sulfides → sulfoxides → sulfones

-Baeyer-Villiger Oxidation- oxidation of ketones to esters and lactones via oxygen insertion

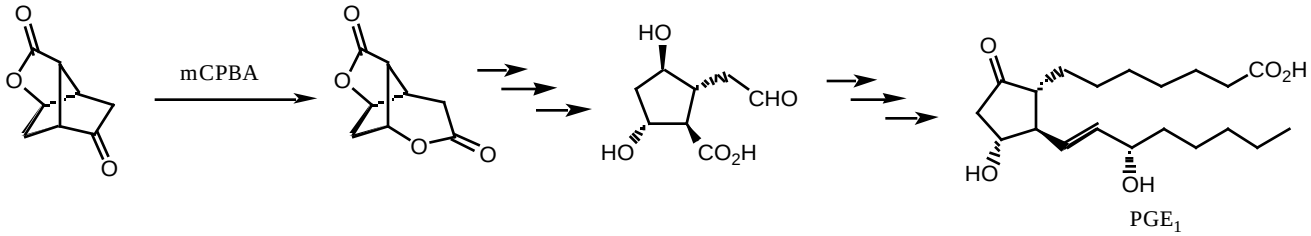
Organic Reactions **1993**, *43*, 251 *Comprehensive Organic Synthesis* **1991**, vol 7, 671.

m-Chloroperbenzoic Acid, Peracetic Acid, Hydrogen peroxide

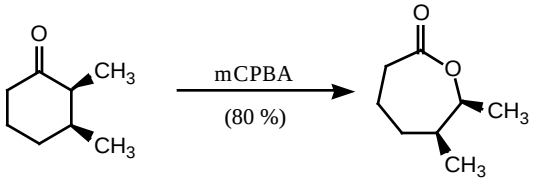


- Concerted R-migration and O-O bond breaking. No loss of stereochemistry
- Migratory aptitude roughly follows the ability of the group to stabilize positive charge:
  3° > 2° > benzyl = phenyl > 1° >> methyl

JACS **1971**, *93*, 1491

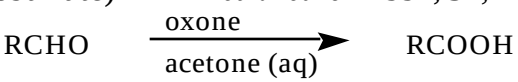


PGE$_1$



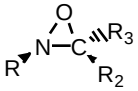
Tetrahedron Lett. **1977**, 2173
Tetrahedron Lett. **1978**, 1385

Oxone (postassium peroxymonosulfate) *Tetrahedron* **1997**, *54*, 401

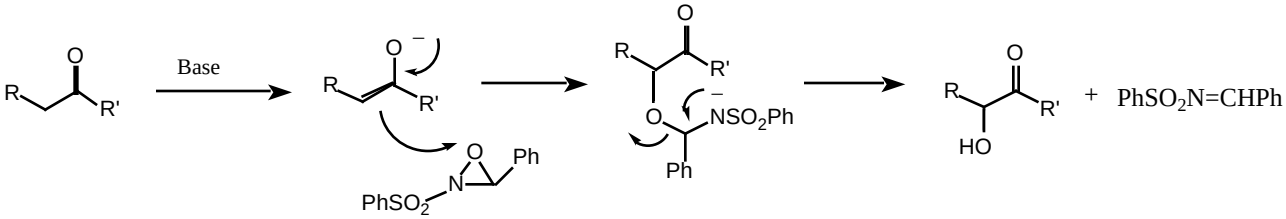


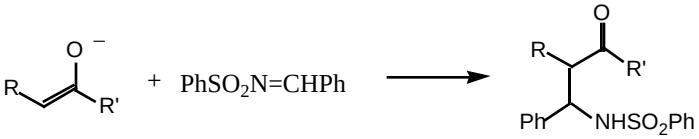
Oxaziridines

reviews: *Tetrahedron* **1989**, *45*, 5703; *Chem. Rev*. **1992**, *92*, 919



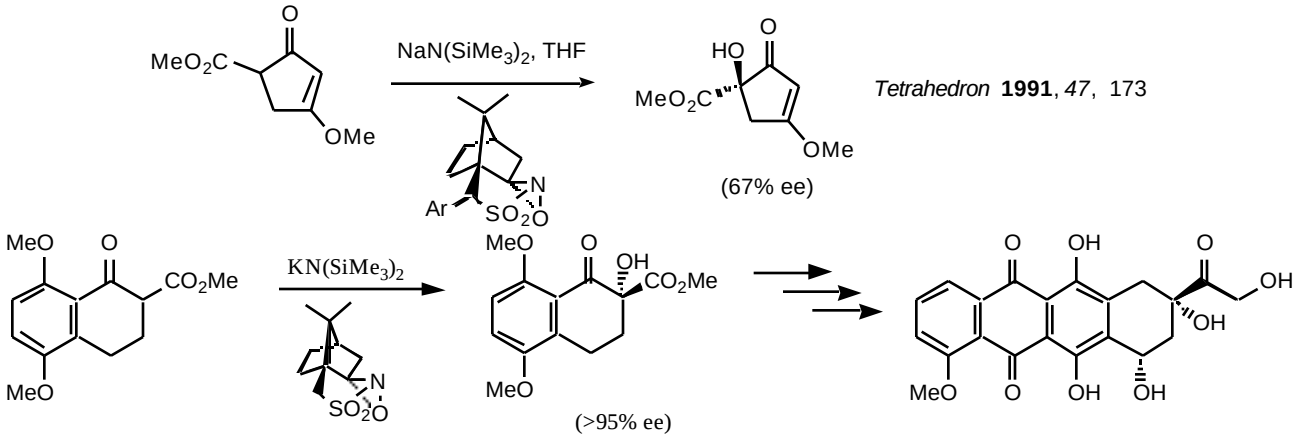
- hydroxylation of enolates





By-product supresed by using bulkier oxaziradine such as camphor oxaziradine

Asymmetric hydroxylations



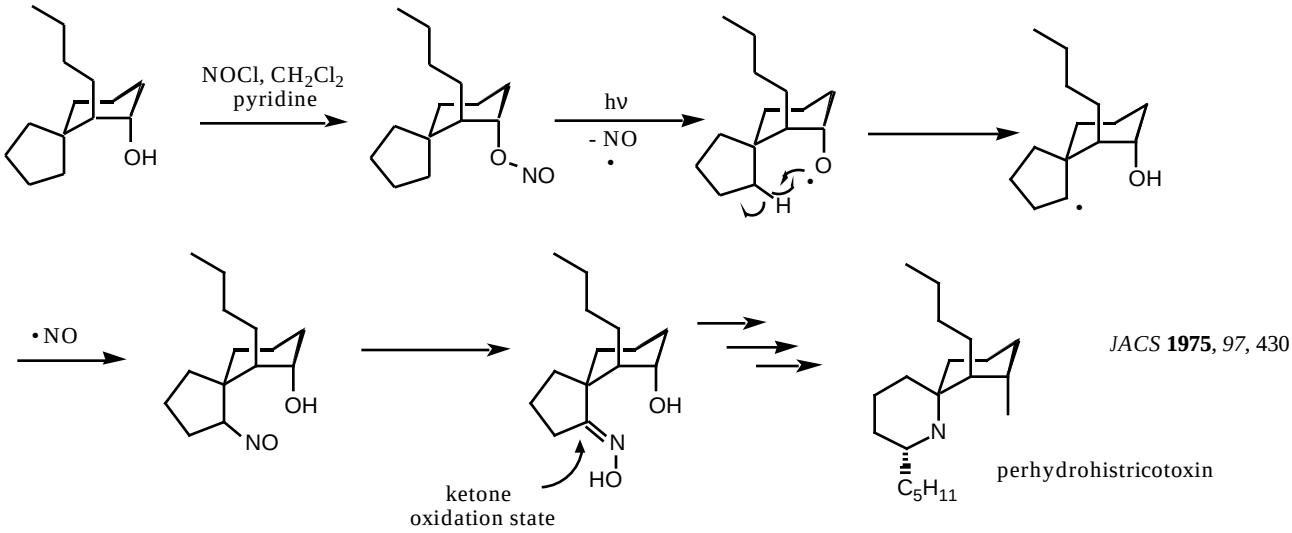
- hydroxylation of organometallics

R-Li or R-Mg → R-OH *JACS* **1979**, *101*, 1044

- Asymmetric oxidation of sulfides to chiral sulfoxides.

JACS **1987**, *109*, 3370.
Synlett, **1990**, 643.

Remote Oxidation (functionalization) *Comprehensive Organic Synthesis* **1991**, *7*, 39.
Barton Reaction

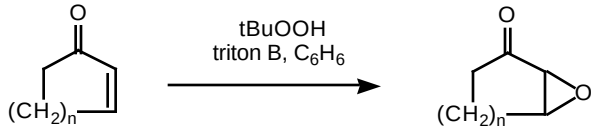


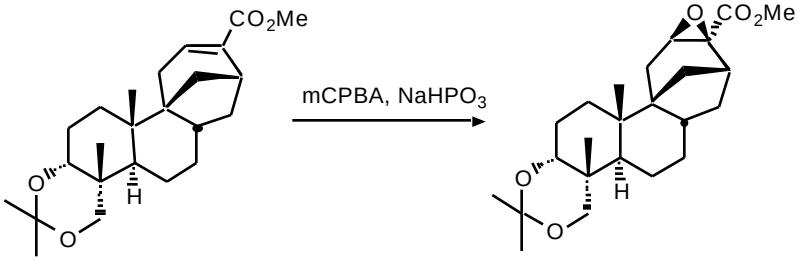
Epoxidations

Peroxides & Peracids

- olefins → epoxides *Tetrahedron* **1976**, *32*, 2855

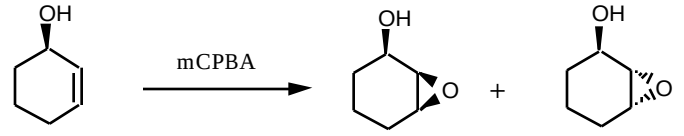
- α,β-unsaturated ketones, aldehydes and ester → α,β-epoxy- ketones, aldehydes and esters (under basic conditions).



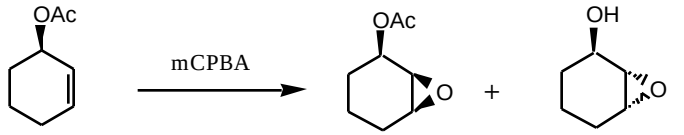


TL **1988**, *23*, 2793

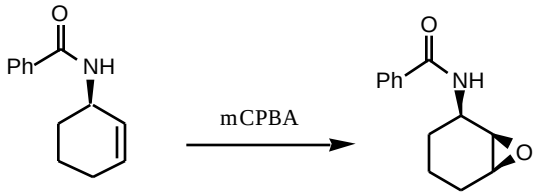
Henbest Epoxidation- epoxidation directed by a polar group



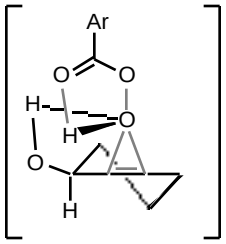
10:1 diastereoselection



1:4 diastereoselection



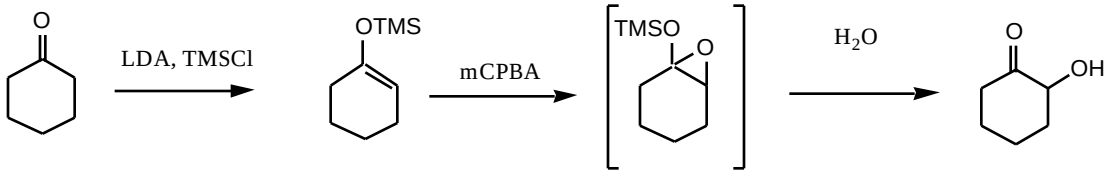
"highly selective"



proposed transition state:
-OH directs the epoxidation

- for acyclic systems, the Henbest epoxidation is often less selective

Rubottom Oxidation: *JOC* **1978**, *43*, 1588

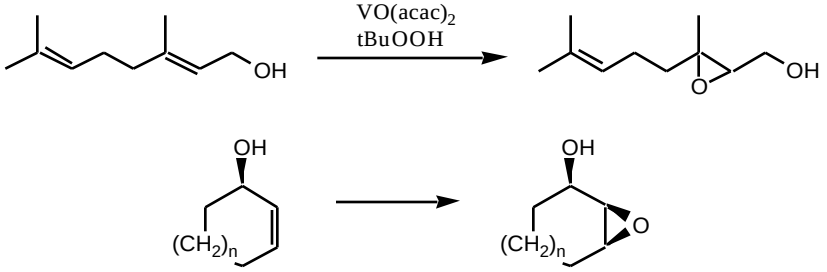


Sharpless Epoxidation tBuOOH w / $VO(acac)_2$, $Mo(CO)_6$ or $Ti(OR)_4$

Reviews: *Comprehensive Organic Synthesis* **1991**, vol 7, 389-438
Asymmetric Synthesis **1985**, *vol. 15*, 247-308
Synthesis, **1986**, 89. *Org. React.* **1996**, *48*, 1-299.
Aldrichimica Acta **1979**, *12*, 63
review on transition mediated epoxidations: *Chem. Rev.* **1989**, *89*, 431.

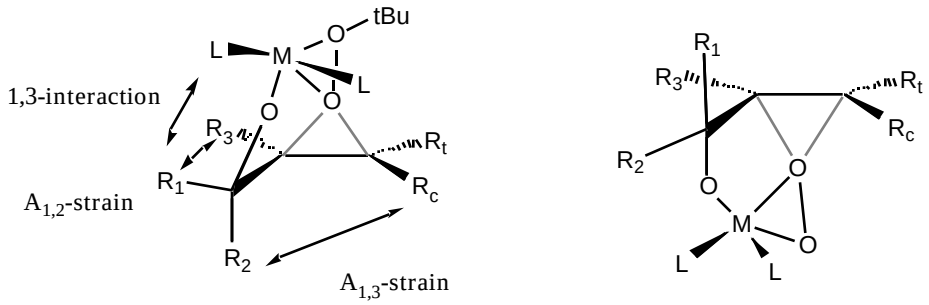
- Regioselective epoxidation of allylic and homo-allylic alcohols
- will <u>not</u> epoxidize isolated double bonds
- epoxidation occurs stereoselectively w / respect to the alcohol.

- Catalysts: $VO(acac)_2$; $Mo(CO)_6$; $Ti(OiPr)_4$
- Oxidant: tBuOOH; $PhC(CH_3)_2OOH$



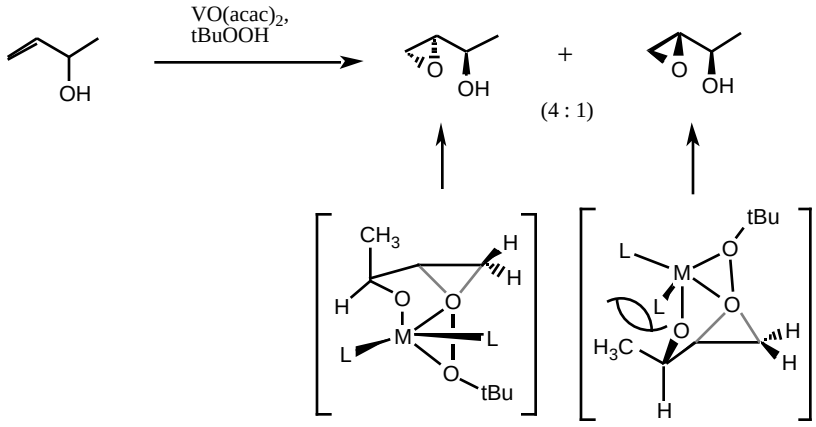
ring size	$VO(acac)_2$	$MoO_2(acac)_2$	mCPBA
5	>99%	--	84
6	>99	98	95
7	>99	95	61
8	97	42	<1
9	91	3	<1

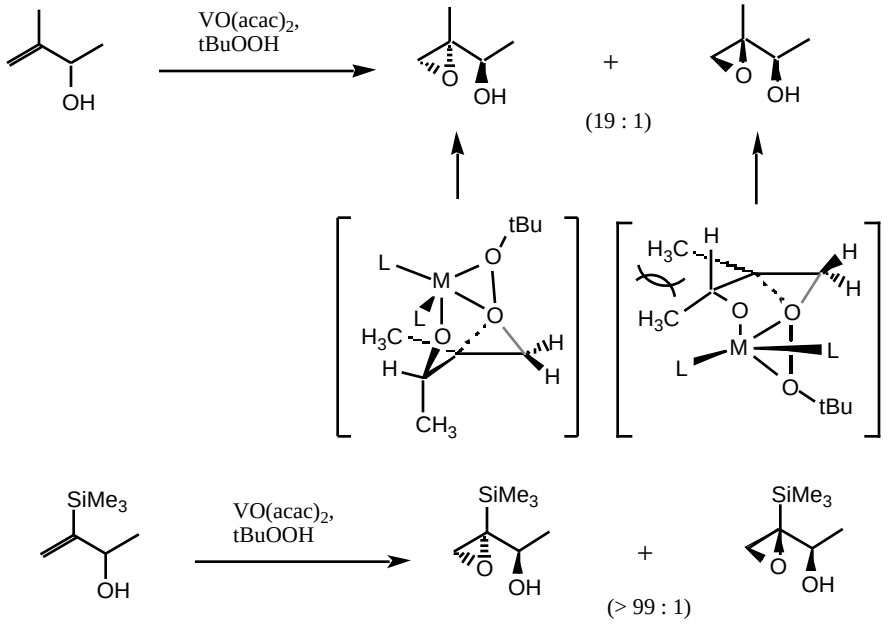
Acyclic Systems:



Major influences:

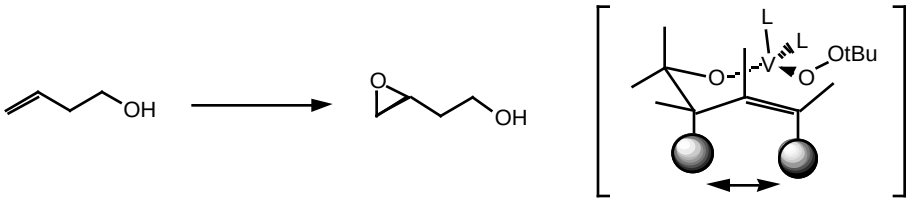
$A_{1,2}$-Strain between R_g and R_1	(R_g and R_2)
$A_{1,3}$-strain between R_2 and R_c	(R_1 and R_c)
1,3-interactions between L and R_1	(L and R_2)





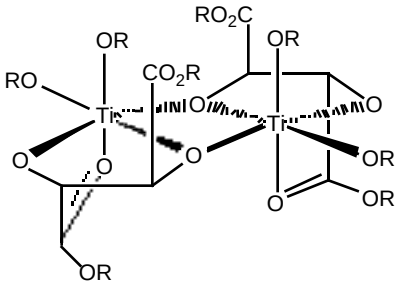
- Careful conformational analysis of acyclic systems is needed.

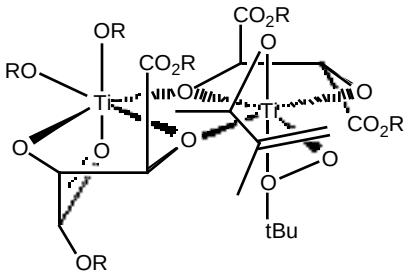
Homoallylic Systems



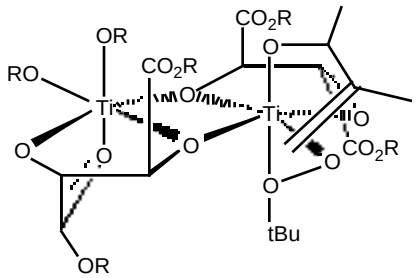
dominent stereocontrol element

Titanium Catalyst structure:





Disfavored

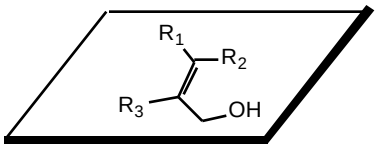


Favored

Asymmetric Epoxidation

tBuOOH, Ti(OiPr), (+) or (-) Diethyl Tartrate, 3Å molecular sieves

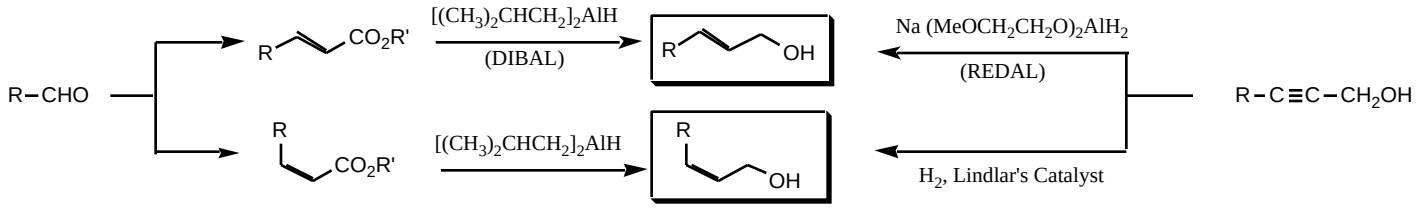
Empirical Rule



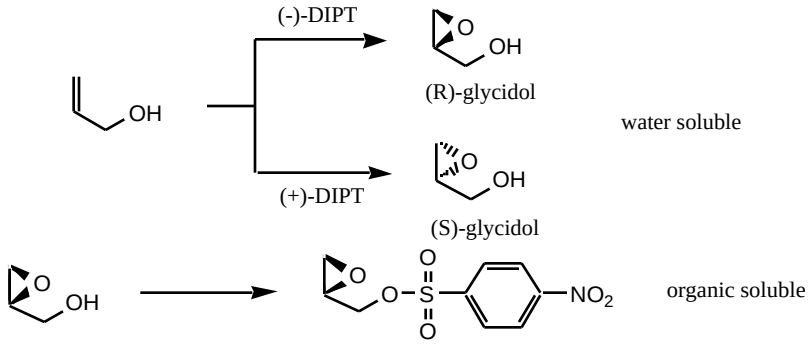
(+)- DET epoxidation from the bottom
(-)- DET epoxidation from the top

Catalytic system: addition of molecular sieves to "soak" up any water with 3A sieves, 5-10 mol % catalyst is used.

Preparation of Allylic Alcohols:

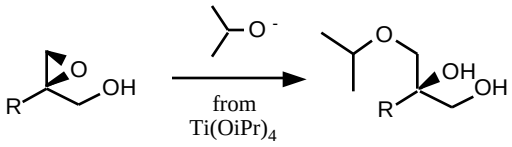


"In situ" derivatization of water soluble epoxy-alcohol

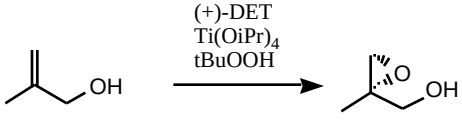


Alkoxide opening of epoxy-alcohol product

reduced by use of $Ti(OtBu)_4$ and catalytic conditions



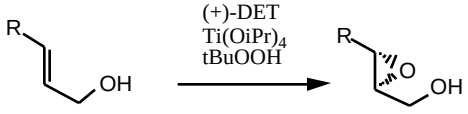
Stoicheometric vs Catalytic epoxidation:



stoicheometric: 85% ee

catalytic (6-7 mol %) 47% yield >95% ee

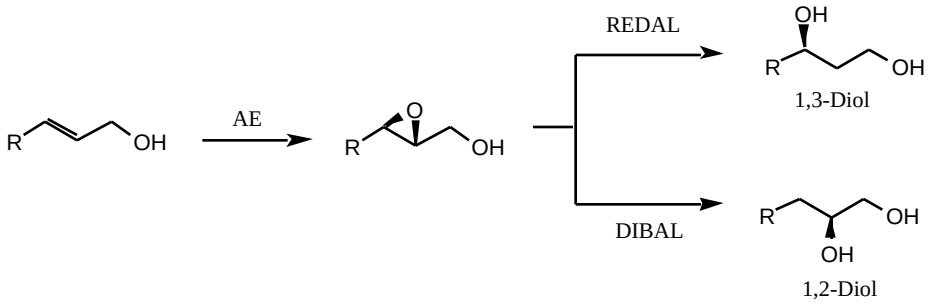
in situ deriv. with PNB 78% yield 92 % ee >98 %ee after 1 recrystallization



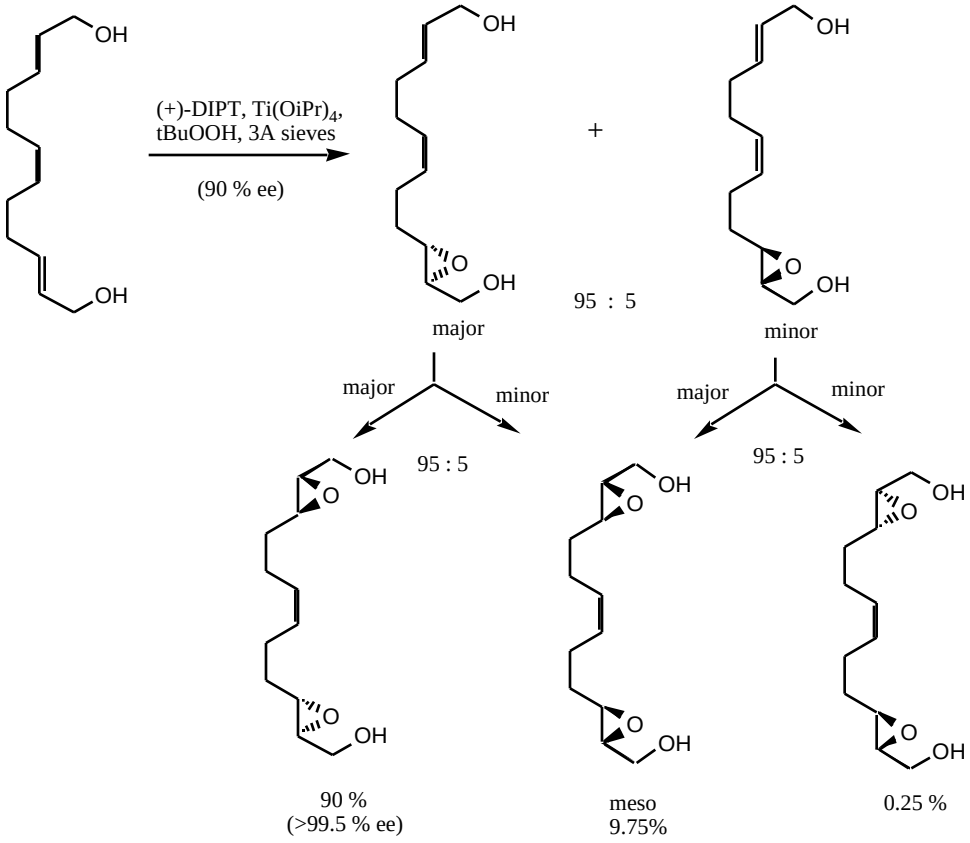
yields: 50 - 100 %

ee: > 95%

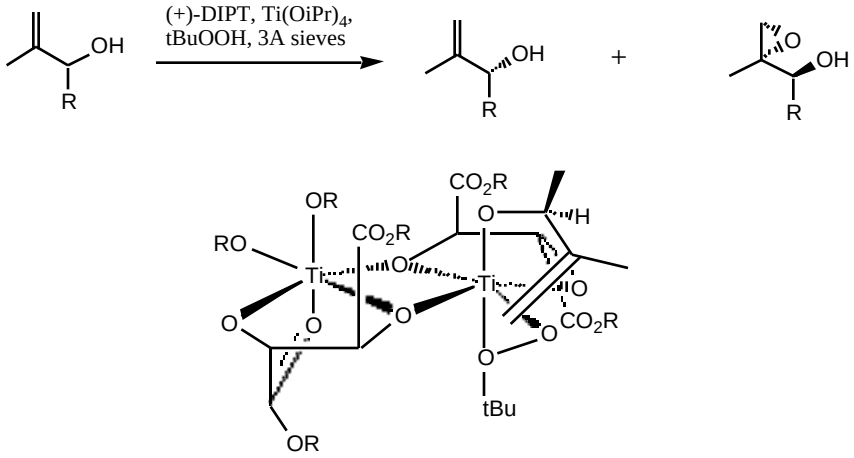
Ring Opening of Epoxy-Alcohols

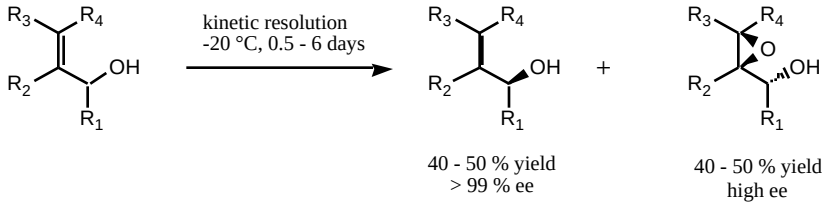


Two dimensional amplification

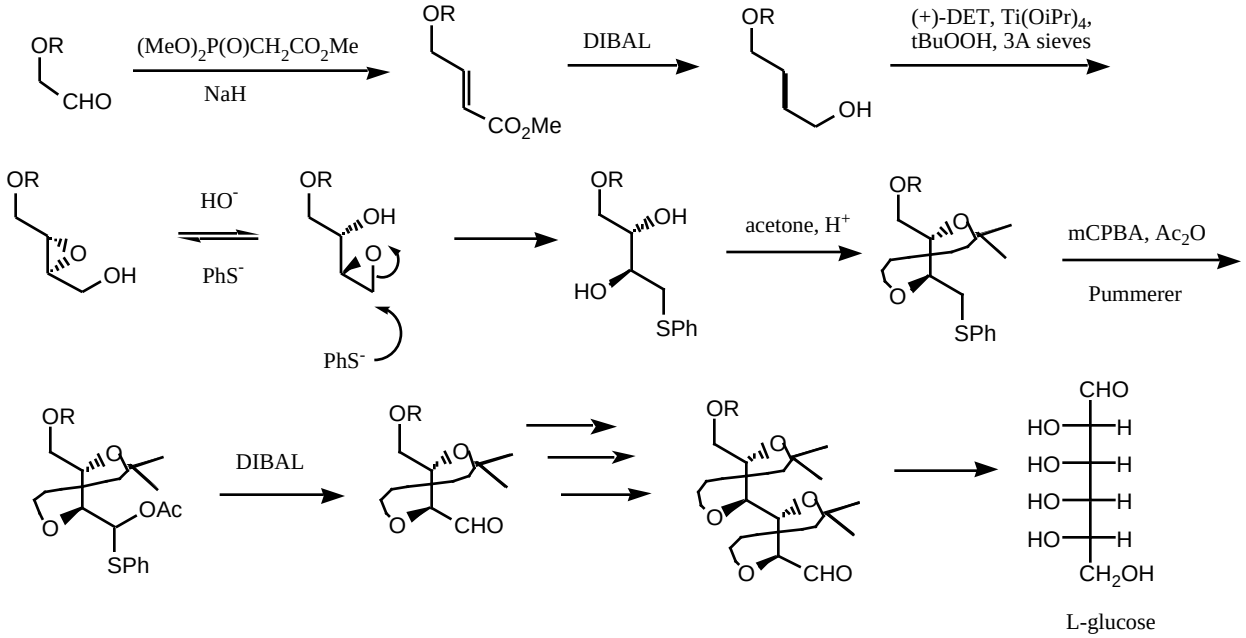


Kinetic Resolution of Allylic Alcohols





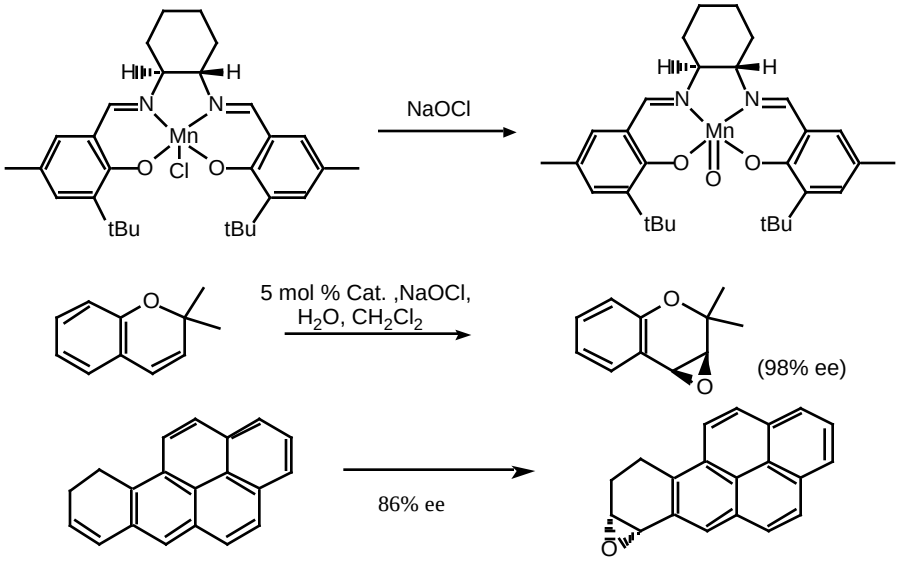
Reiterative Approach to the Synthesis of Carbohydrate



Jacobsen Aysmmetric Epoxidation

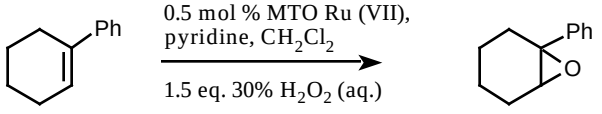
JACS **1990**, *112*, 2801; *JACS* **1991**, *113*, 7063; *JOC* **1991**, *56*, 2296.

- Reaction works best for cis C=C conjugated to an aromatic ring



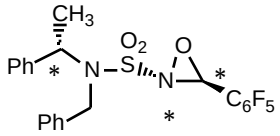
Methyltrioxoruthenium (MTO) Ru(VII)

Sharpless et al. *JACS* **1997**, *117*, 7863, 11536.

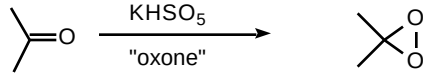


Oxaziridines

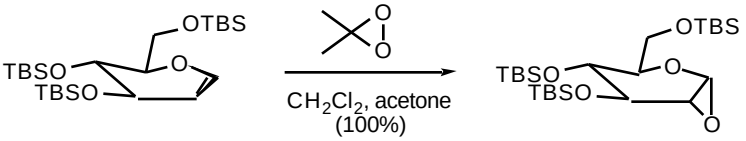
- Asymmetric epoxidation of olefins *Tetrahedron* ***1989*** *45* 5703



Dioxiranes (Murray's Reagent) Reviews: *Chem. Rev.* **1989**, *89*, 1187; *ACR* **1989**, *27*, 205
Org. Syn. **1996**, *74*, 91

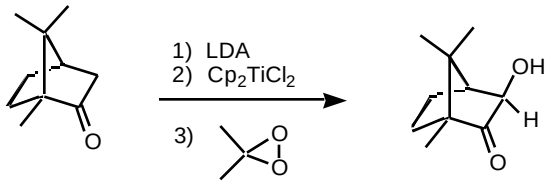


- epoxidation of olefins



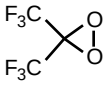
JOC **1990**, *55*, 2411

- Asymmetric epoxidation *JACS* **1996**, *118*, 491.
- oxidation of sulfides to sulfoxides and sulfones
- oxidation of amines to amine-N-oxides
- oxidation of aldehydes to carboxylic acids
- hydroxylation of enolates



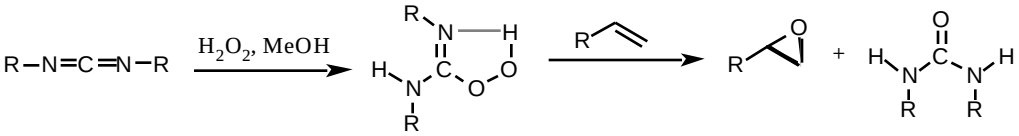
JOC **1994**, *59*, 2358

- bis-trifluoromethyldioxirane, much more reactive
JACS **1991**, *113*, 2205.



- oxidation of alcohols to carbonyl compounds. 1° alcohols give a mixture of aldehydes and carboxylic acids.
- Insertion into 3° C-H bonds to give R_3C-OH

DCC-H_2O_2 *JOC* **1998**, *63*, 2564



Carey & Sundberg Chapter 5 problems: 1a,b,c,d,f,h,j; 2; 3a-g, n,o; 4b,j,k,l; 9; 11;
Smith: Chapter 4 March: Chapter 19

Reductions

1. Hydrogenation
2. Boron Reagents
3. Aluminium Reagents
4. Tin Hydrides
5. Silanes
6. Dissolving Metal Reductions

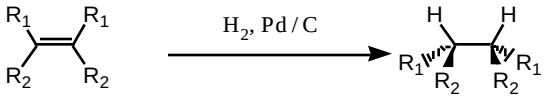
Hydrogenations

Heterogeneous Catalytic Hydrogenation

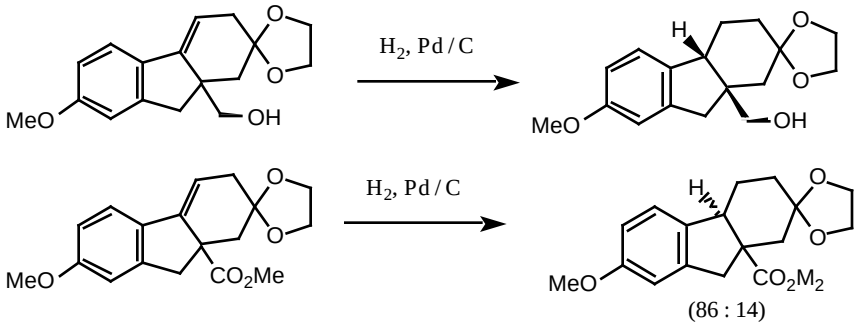
Transition metals absorbed onto a solid support

metal: Pd, Pt, Ni, Rh
support: Carbon, alumina, silica
solvent: EtOH, EtOAc, Et_2O, hexanes, etc.

- Reduction of olefins & acetylenes to saturated hydrocarbons.
- Sensitive to steric effects and choice of solvent
- Polar functional groups, i.e. hydroxyls, can sometimes direct the delivery of H_2.
- Cis addition of H_2.



- Catalyst can be "poisoned"
- Directed heterogeneous hydrogenation

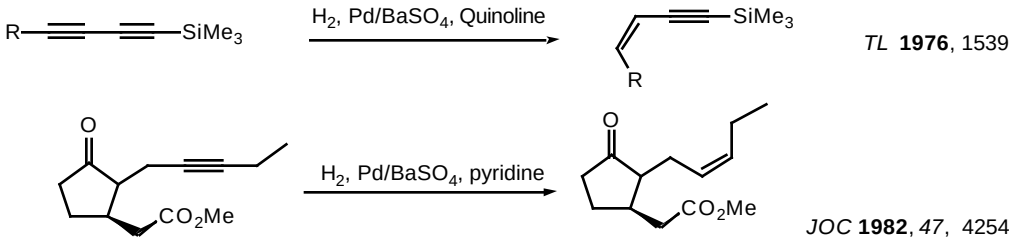


(86 : 14)

Lindlar Catalyst (Pd/ $BaSO_4$/ quinoline)- partially poisoned to reduce activity; will only reduce the most reactive functional groups.

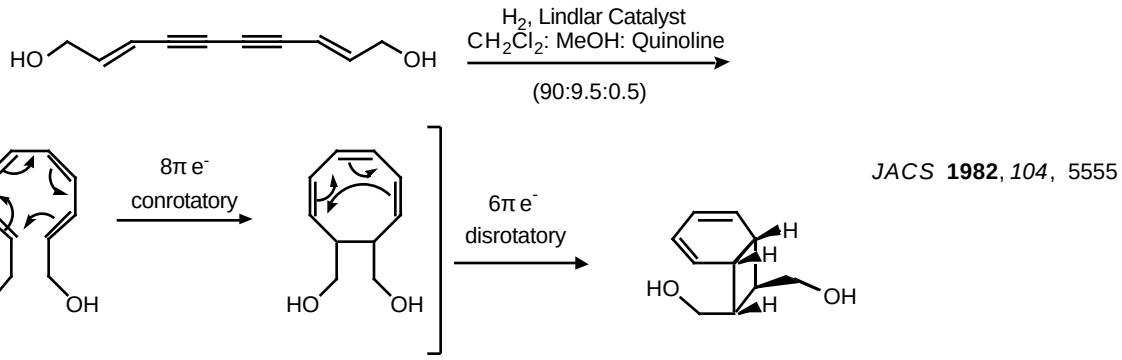
acetylenes + H_2, Pd/$BaSO_4$/ quinoline → cis olefins (Lindlar Reduction)

Acid Chlorides + H_2, Pd/$BaSO_4$ → Aldehydes (Rosemund Reduction)
Org. Rxn. **1948**, *4*, 362



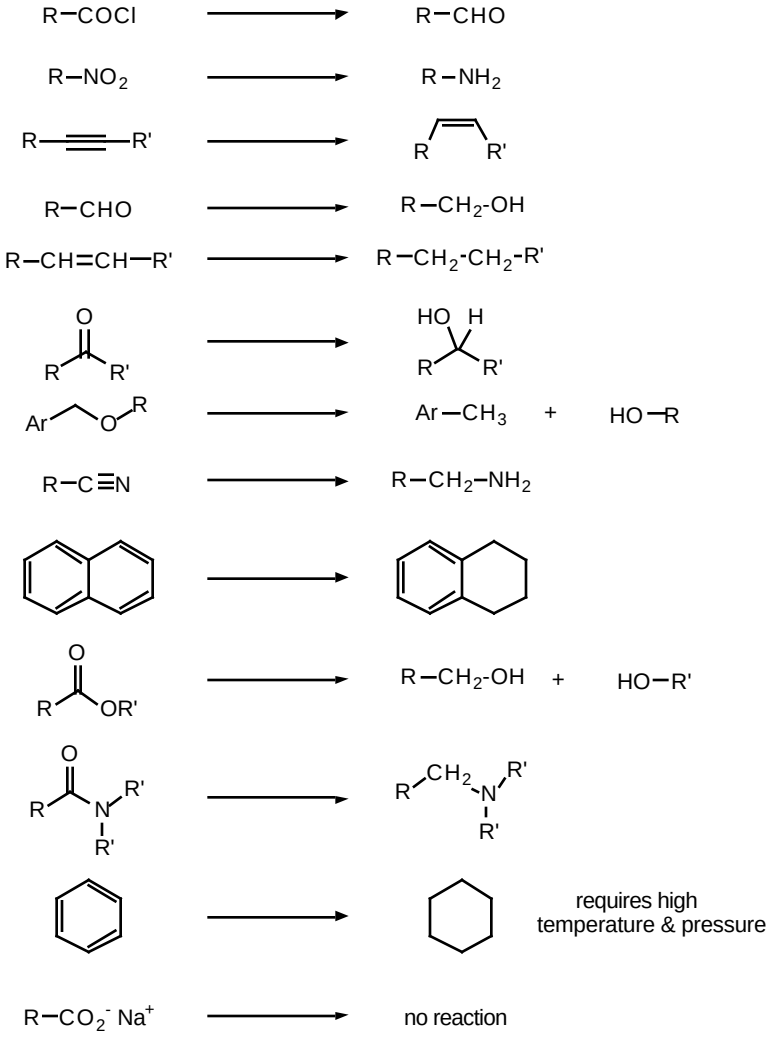
TL **1976**, 1539

JOC **1982**, *47*, 4254



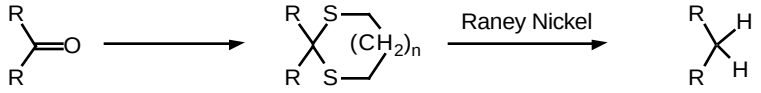
JACS **1982**, *104*, 5555

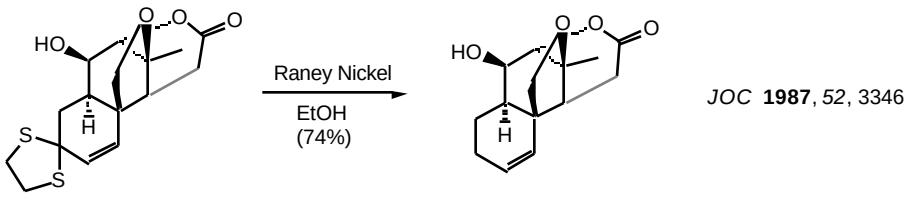
Ease of Reduction: (taken from H.O. House Modern Synthetic Reactions, 2nd edition)



Raney Nickel Desulfuriztion ,

Reviews: *Org. Rxn.* **1962**, *12*, 356; *Chem. Rev.* **1962**, *62*, 347.

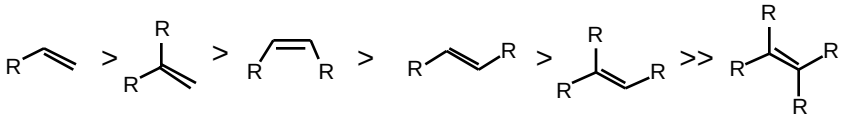




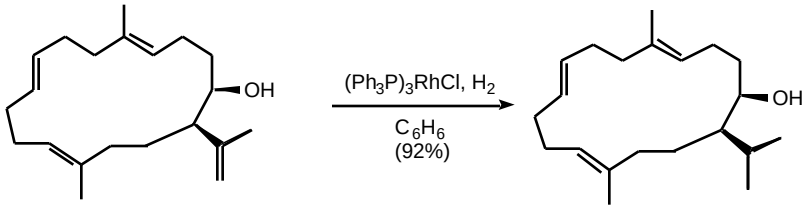
JOC **1987**, *52*, 3346

Homogeneous Catalytic Hydrogenation

- catalyst is soluble in the reaction medium
- catalyst <u>not</u> "poisoned" by sulfur
- very sensitive to steric effects
- terminal olefins faster than internal; cis olefins faster than trans



- $(Ph_3P)_3RhCl$ (Wilkinson's Catalyst); $[R_3P\ Ir(COD)py]^+\ PF_6^-$ (Crabtree's Catalyst)

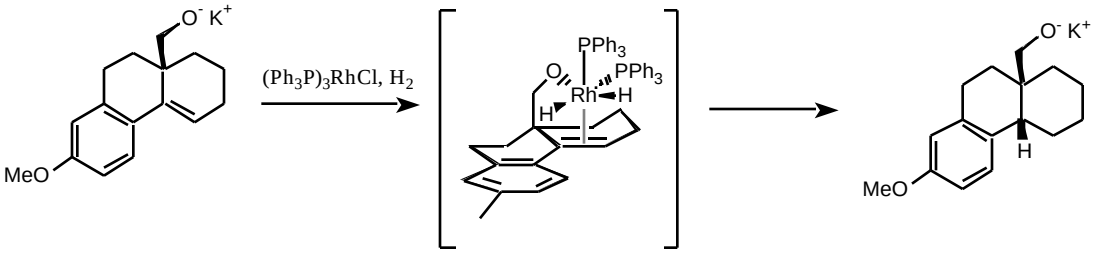


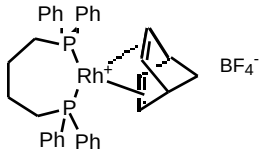
JOC **1992**, *57*, 2767

Directed Hydrogenation

Review: *Angew. Chem. Int. Ed. Engl.* **1987**, *26* , 190

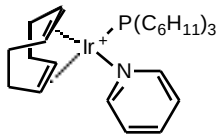
- Diasterocontrolled hydrogenation of allylic alcohols directed by the -OH group





BF_4^-

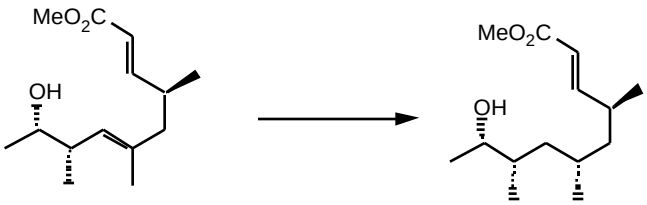
Brown's Catalyst



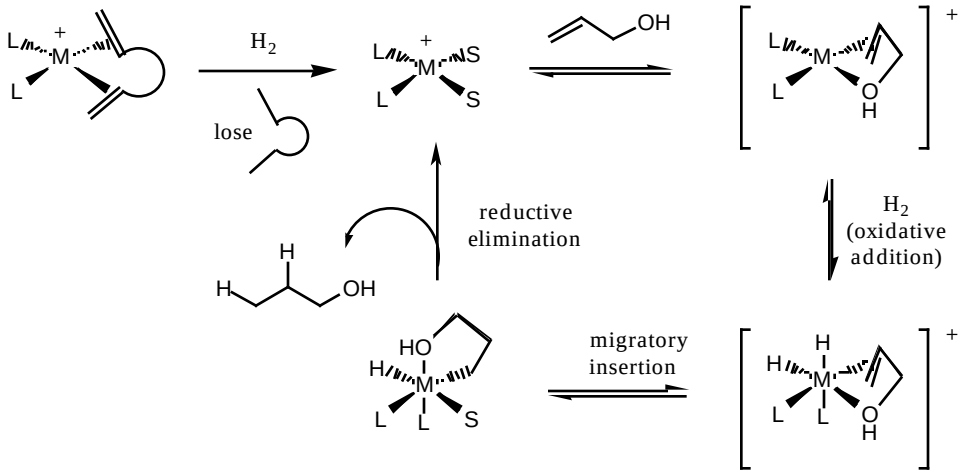
PF_6^-

(Crabtree's Ctalyst)
JACS **1983**, *105* , 1072

Regioselective Hydrogenation- allylic and homoallylic alcohols are hydrogenated faster than isolated double bonds



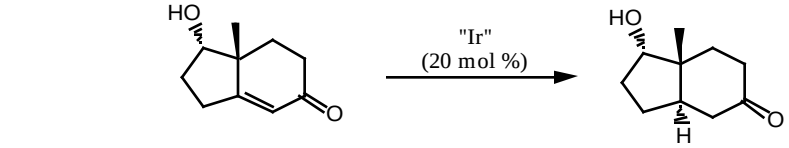
mechanism:



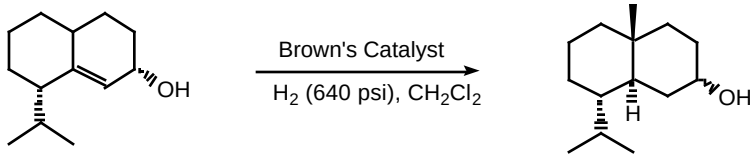
Diastereoselective Hydrogenation: since -OH directs the H2, there is a possibility for control of stereochemistry

- sensitive to: H_2 pressure
  catalyst conc.
  substrate conc.
  solvent.

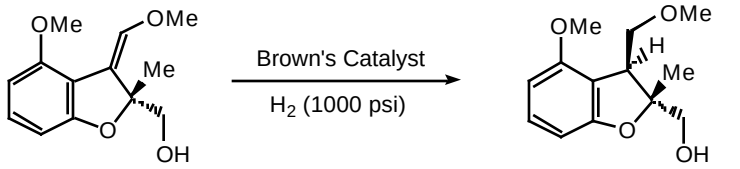
Regioselective Hydrogenation- allylic and homoallylic alcohols are hydrogenated faster than isolated double bonds



(24 : 1)

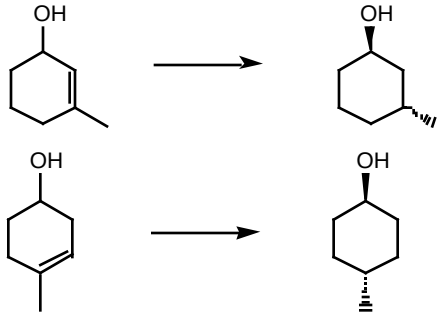


JACS **1984**, *106*, 3866



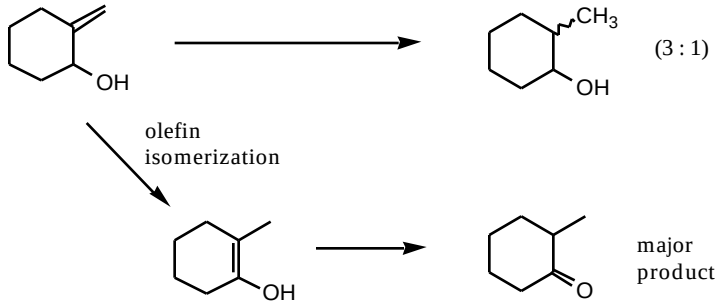
TL **1987**, *28* , 3659

Selectivity is often higher with lower catalyst concentration:



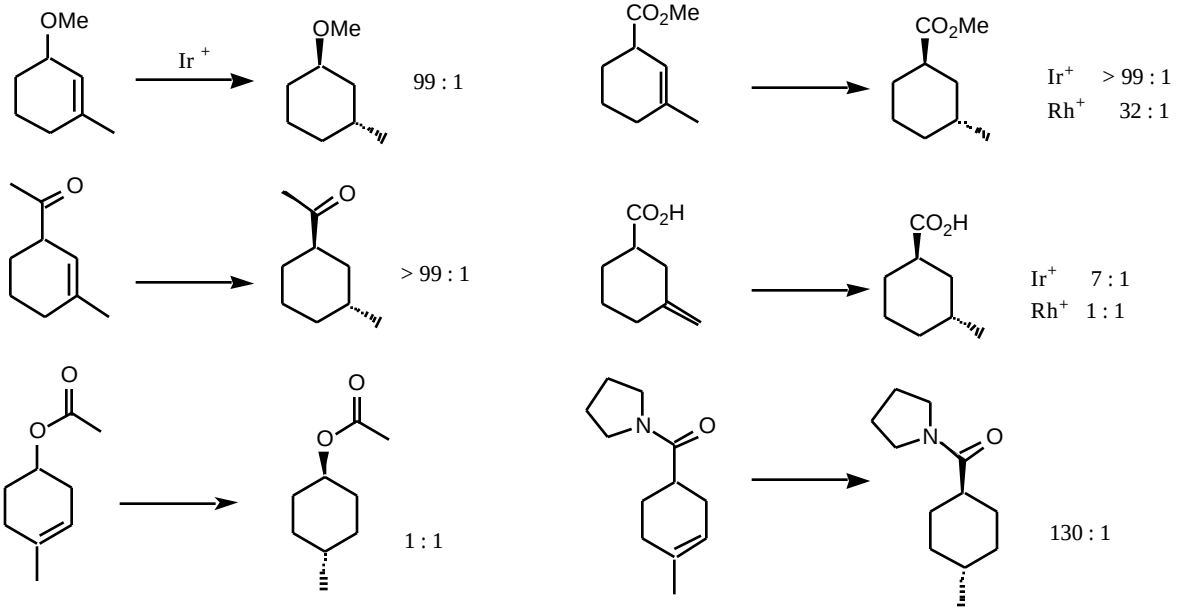
	20 mol % Catalyst	2.5 mol % Catalyst
	50 : 1	150 : 1
	33 : 1	52 : 1

Olefin Isomerization:

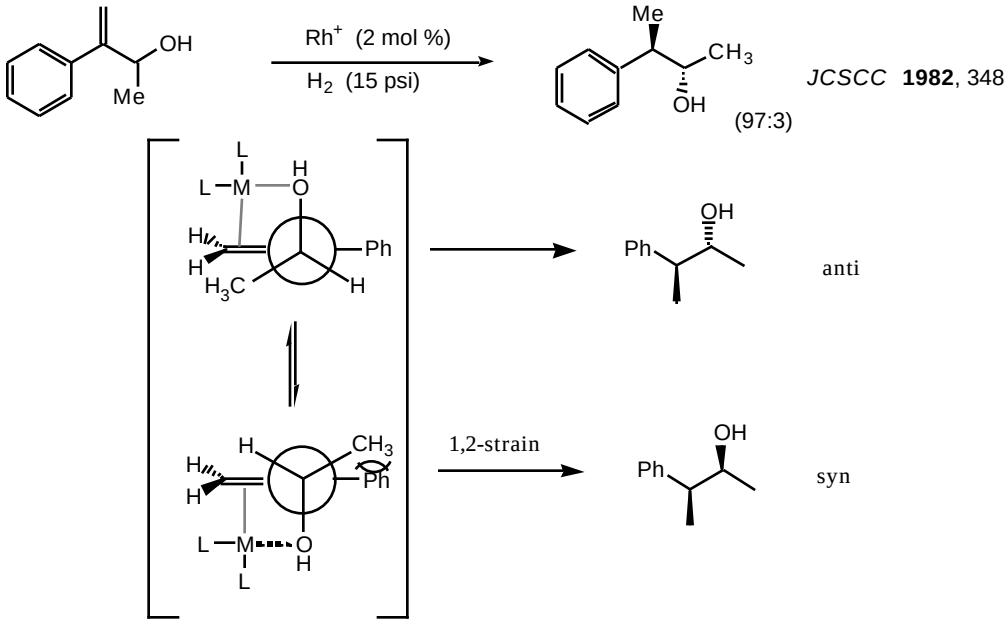


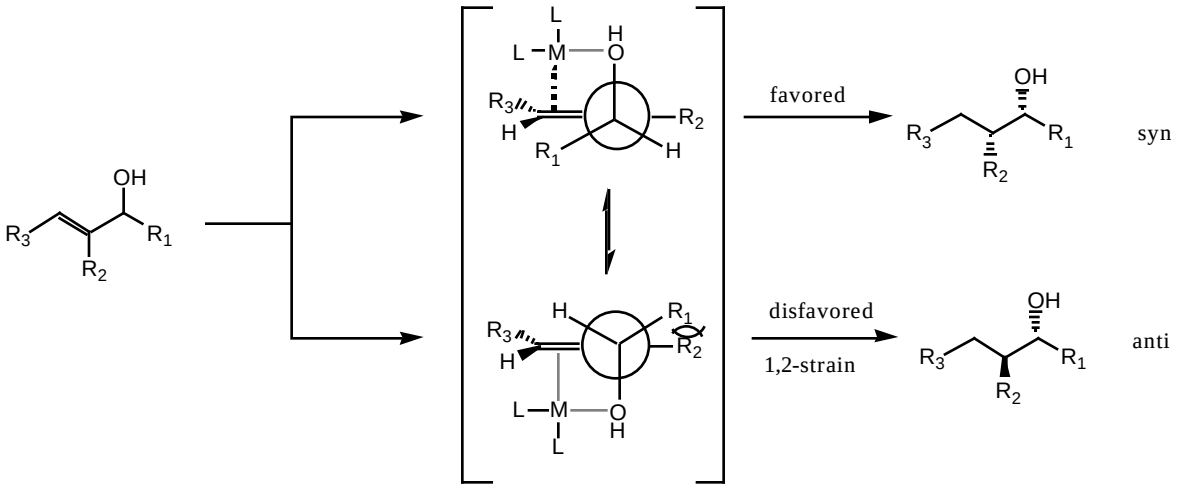
- Conducting the hydrogenation at high H_2 pressures supresses olefin isomerization and often gives higher diastereoselectivity.

Other Lewis basic groups can direct the hydrogenation. (Ir seems to be superior to Rh for these cases)

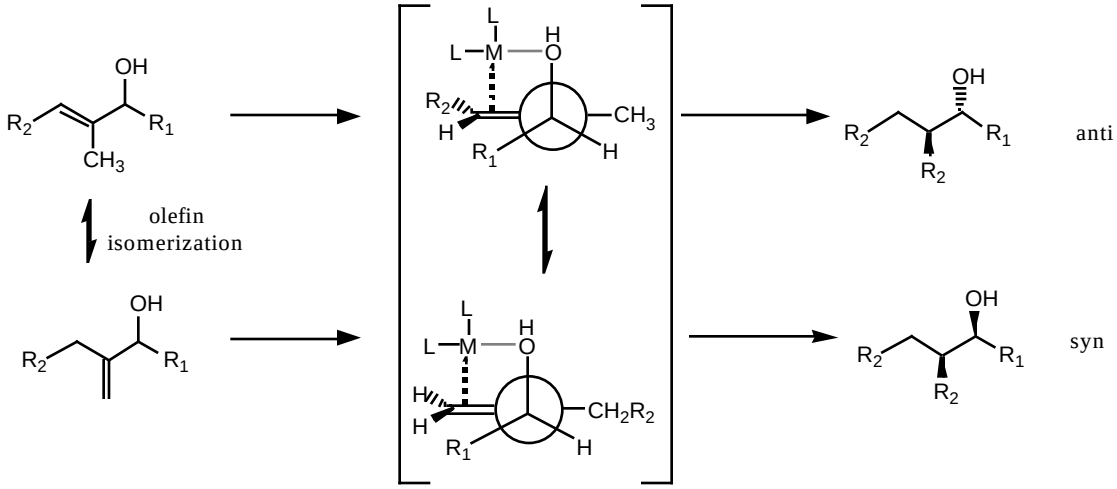


Acyclic Examples



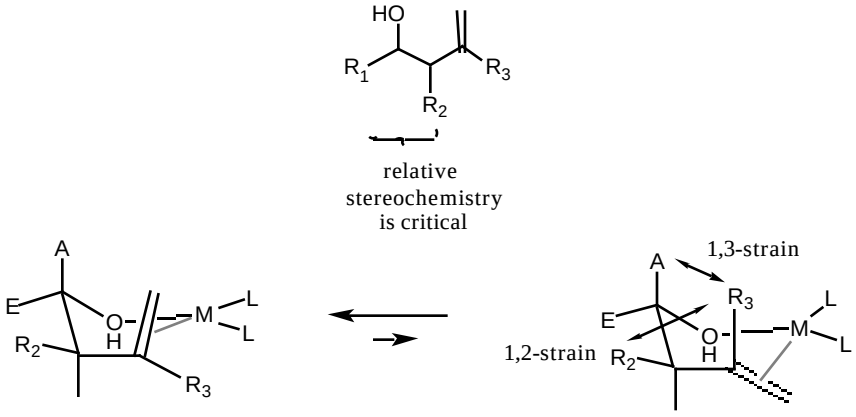


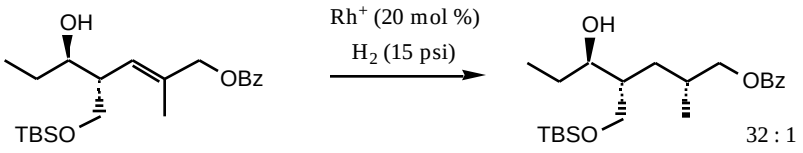
- Supression of olefin isomerization is critical for acyclic stereocontrol !



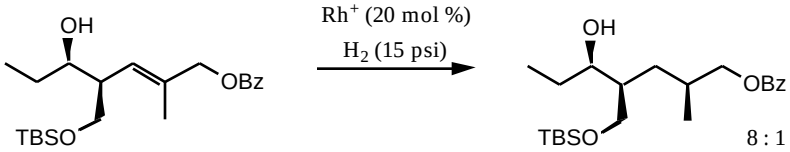
- Rh^+ catalyst is more selective than Ir^+ for acyclic stereoselection.

Acyclic homoallylic systems:



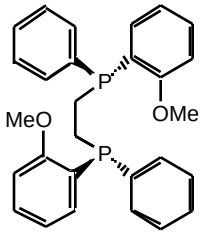


Tetrahedron Lett. **1985**, *26*, 6005

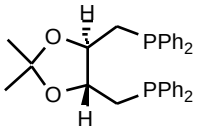


Asymmetric Homogeneous Hydrogenation

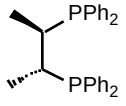
- Chiral ligands for homogeneous hydrogenation of olefins and ketones



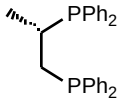
DIPAMP



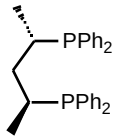
DIOP



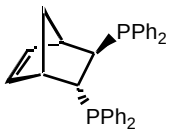
CHIRAPHOS



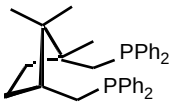
R= -CH_3 PROPHOS
= -Ph PHENPHOS
= -C_6H_{11} CYCPHOS



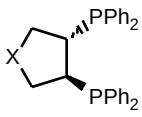
DBPP



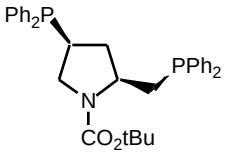
NORPHOS



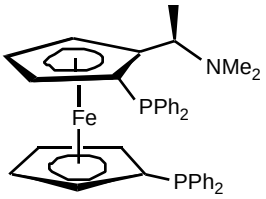
CAMPHOS



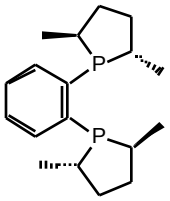
X= CH_2 DPCP
X= N-R PYRPHOS



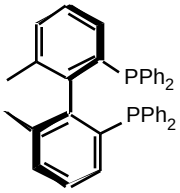
BPPM



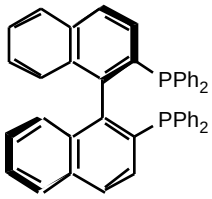
PPPFA



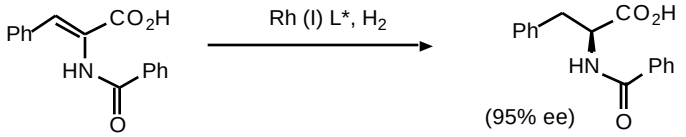
DUPHOS



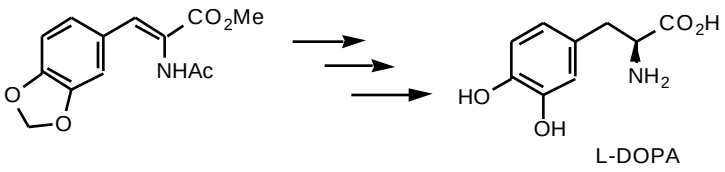
DIPHEMP



BINAP



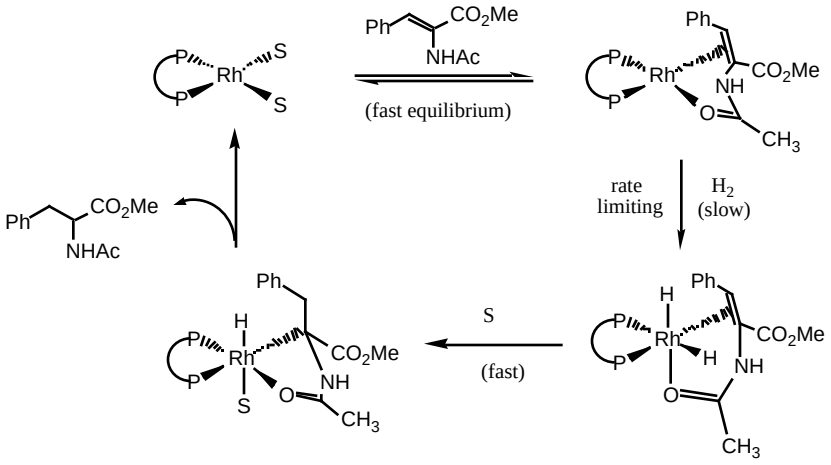
ACR **1983**, *16*, 106.



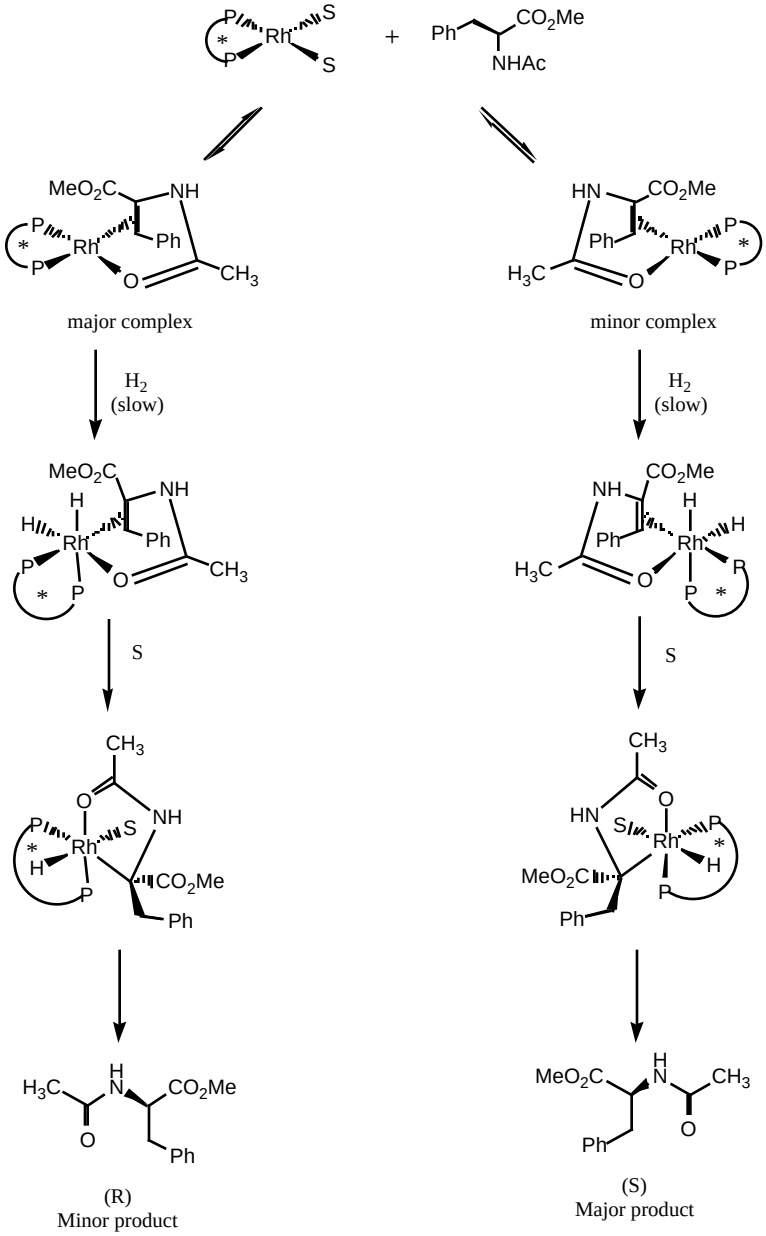
L-DOPA

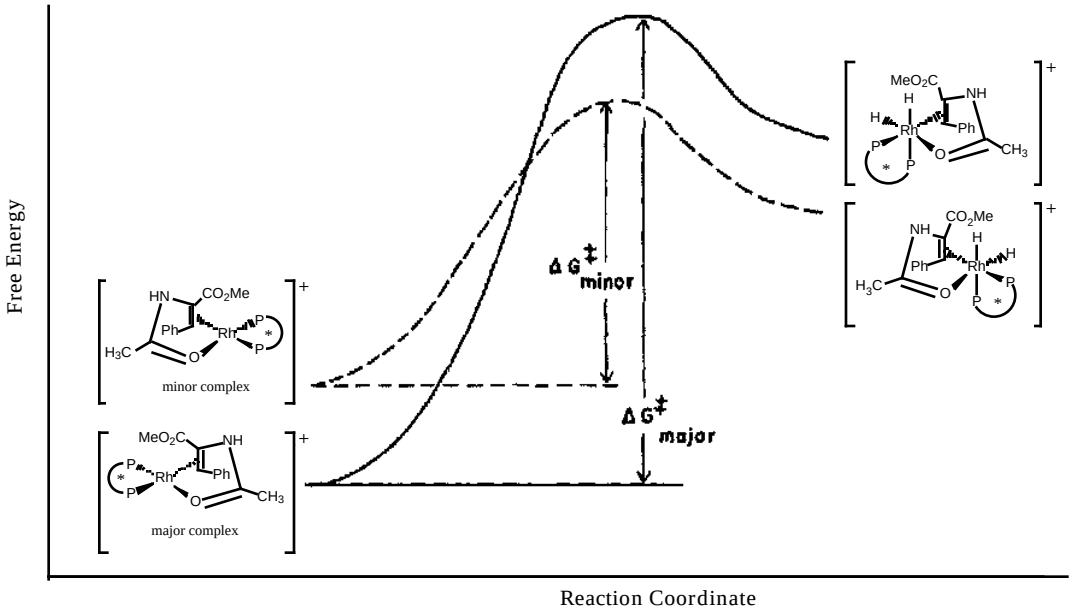
DIOP	85% ee
DIPAMP	96% ee
PPPFA	93% ee
BINAP	100% ee
NORPHOS	95% ee
BPPM	91% ee

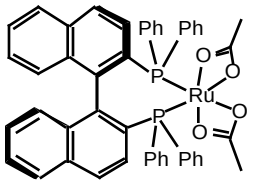
General Mechanism: J. Halpern *Science* **1982**, *217*, 401 *Asymmetric Synthesis* **1985**, vol 5, 41.



Detailed Mechanism:

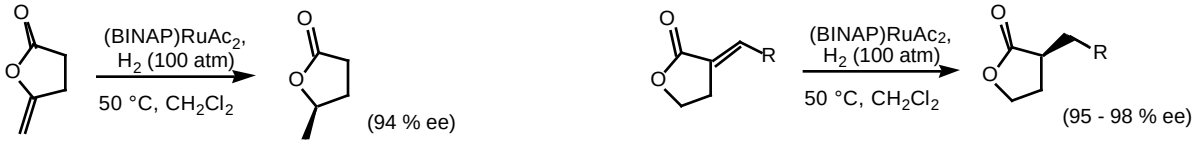


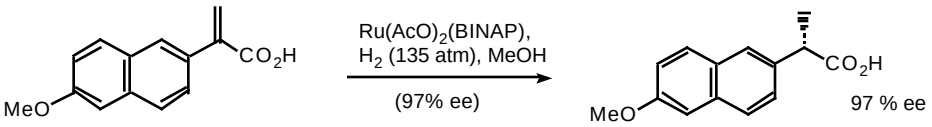




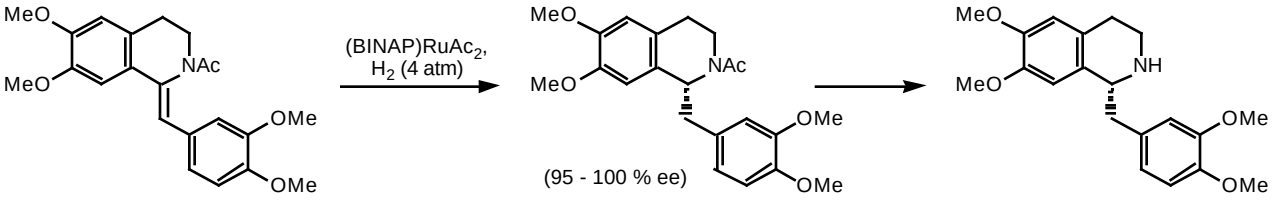
BINAP

ACR **1990**, *23*, 345.



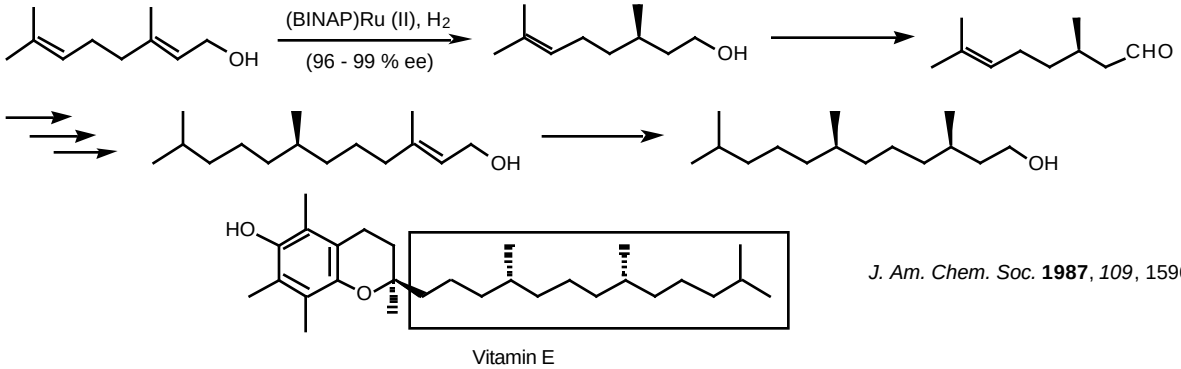


(S)-naproxen



Tetrahydropapaverine

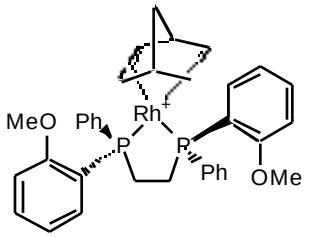
Directed Asymmetric Hydrogenation



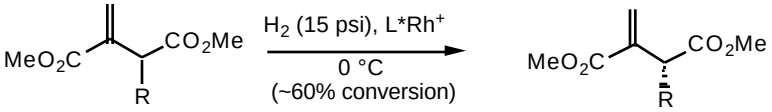
J. Am. Chem. Soc. **1987**, *109*, 1596

Vitamin E

Kinetic Resolution by Directed Hydrogenation



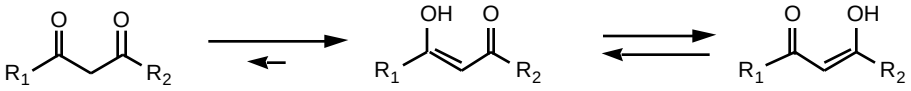
$CF_3SO_3^-$

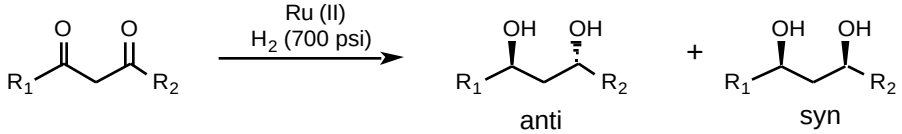


R =	Et	> 96 % ee
	Ph	82 %
	OMe	93 %

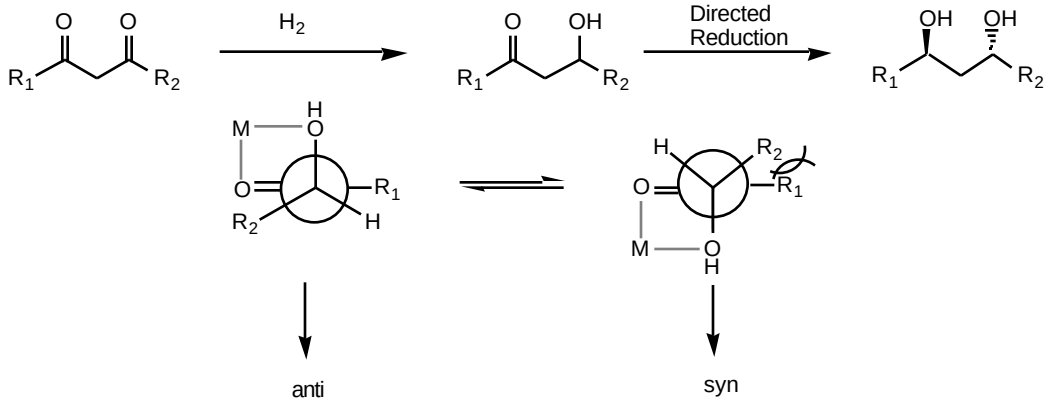
Hydrogenation of Carbonyls

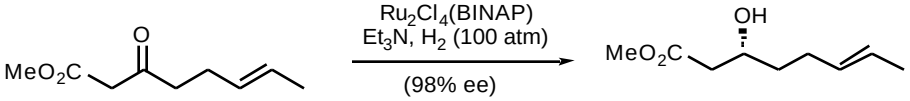
1,3-diketones:





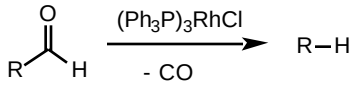
R_1=	R_2=	anti : syn=	
$-CH_3$	$-CH_3$	99 : 1	
$-CH_3$	$-CH_2CH_3$	16 : 1	(90 % ee)
$-CH_2CH_3$	-iPr	32 : 1	
$-CH_2CH_3$	$-CH_2CH_3$	49 : 1	

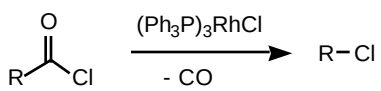


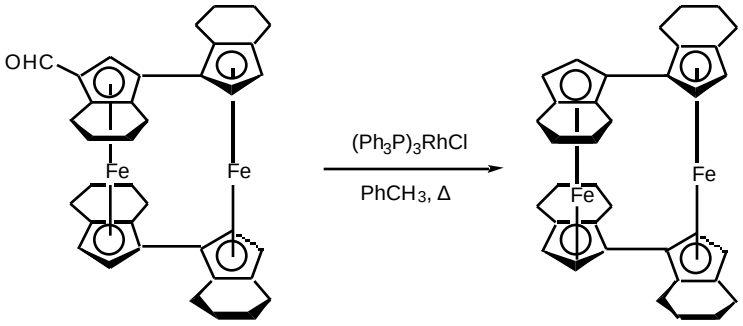


JACS **1988**, *110* , 6210

Decarbonylations







JOC **1990**, *55*, 3688

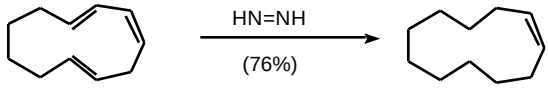
Diimide HN=NH

Review: *Organic Reactions* **1991**, *40J. Chem. Ed.* **1965**, 254

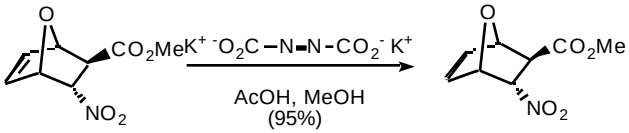
- Only reduces double bonds
- Syn addition of H_2
- will selectivley reduce the more strained double bond
- Unstable reagent which is generated *in situ*

$K^+O_2C\text{-}N{=}N\text{-}CO_2K^+ + AcOH \rightarrow H\text{-}N{=}N\text{-}H$

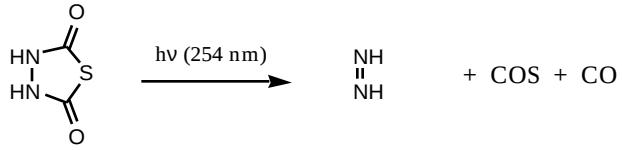
$H_2N\text{-}NH_2 + Cu^{2+} + H_2O_2 \rightarrow H\text{-}N{=}N\text{-}H$

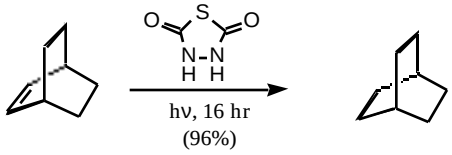


ACIEE **1965**, 271



JACS **1986**, *108* , 5908





TL **1993**, *34*, 4137

Metal Hydrides

Review on Metal Hydride Selectivity: *Chem Soc Rev*. **1976**, *5* , 23
Comprehensive Organic Synthesis **1991**, vol 8, 1.

Boron Hydrides Review: *Chem. Rev*. **1986**, *86* , 763.

$NaBH_4$	reduces ketones and aldehydes
$LiBH_4$	reduces ketones, aldehydes, esters and epoxides. THF soluble
$LiBH_4$/TMSCl	stronger reducing agent. *ACIEE* **1989**, *28*, 218.
$Zn(BH_4)_2$	reduces ketones and aldehydes
$R_4N\ BH_4$	organic soluble (CH2Cl2) borohydrides. *Synth Commun.* **1990**, *20*, 907
$LiEt_3BH$	reduces ketones, aldehydes, esters, epoxides and R-X
Li s-Bu_3BH	reduces ketones, aldehydes, esters and epoxides (hindered borohydride)
$Na(CN)NH_3$	reduces iminium ions, ketones and aldehydes
$Na(AcO)_3BH$	reduces ketones and aldehydes (less reactive)
$NaBH_2S_3$	reduces ketones and aldehydes

Sodium Borohydride $NaBH_4$

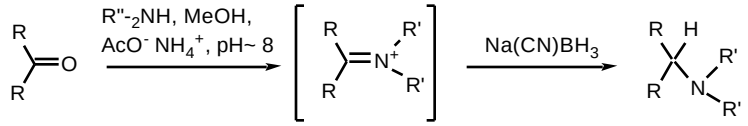
- reduces aldehydes and ketones to alcohols
- does not react with acids, esters, lactones, epoxides or nitriles.
- Additives can increase reactivity.

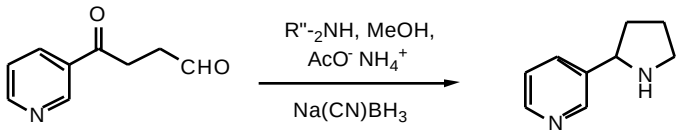
Sodium Cyanoborohydride $Na(CN)BH_3$

Reviews: *Synthesis* **1975**, 136; *OPPI* **1979**, *11* , 201

- less reactive than $NaBH_4$
- used in reductive aminations (Borch Reduction)

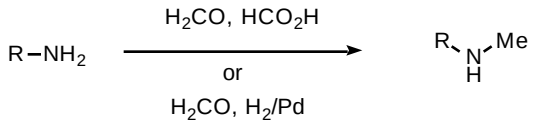
$Na(CN)BH_3$ reduces iminium ions much more quickly than ketones or aldehydes



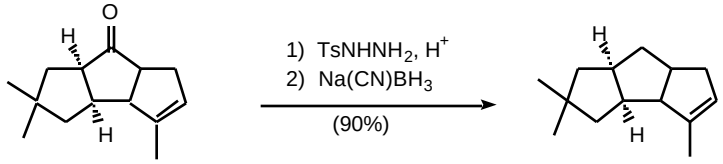


JACS **1971**, *93* , 2897

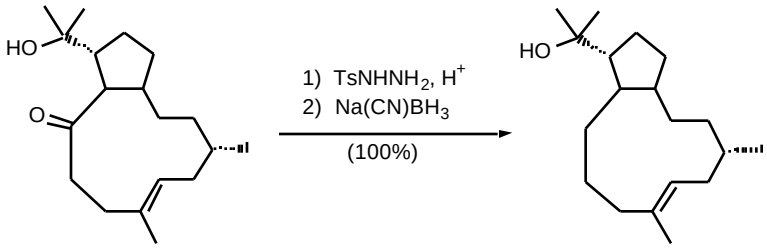
- Related to Eschweiler-Clark Reaction



- Reduction of tosylhydrazones gives saturated hydrocarbon

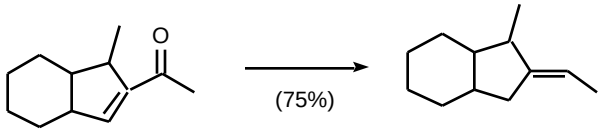


TL **1978**, 1991



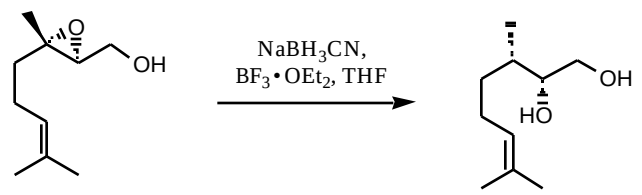
JOC **1977**, *42* , 3157

- migration of the olefin occurs w / α,β-unsaturated ketones



JACS **1978**, *100* , 7352

- Epoxide opening



JOC **1994**, *59*, 4004

$NaBH_2S_3$ Lalancette Reduction *Synthesis* **1972**, 526 *Can. J. Chem.* **1970**, *48* , 735.

$NaBH_4$/ $NiCl_2$ *Chem. Pharm. Bull.* **1981**, *29* , 1159; *Chem. Ber.* **1984**, *117* , 856.

$Ar\text{-}NO_2 \rightarrow Ar\text{-}NH_2$

$Ar\text{-}NO \rightarrow Ar\text{-}NH_2$

$R_2C{=}N\text{-}OH \rightarrow R_2CH\text{-}NH_2$

$NaBH_4$ / $TiCl_4$

Synthesis **1980**, 695.

$R\text{-}COOH \rightarrow R\text{-}CH_2\text{-}OH$

$R\text{-}COOR' \rightarrow R\text{-}CH_2\text{-}OH$

$R\text{-}CN \rightarrow R\text{-}CH_2\text{-}NH_2$

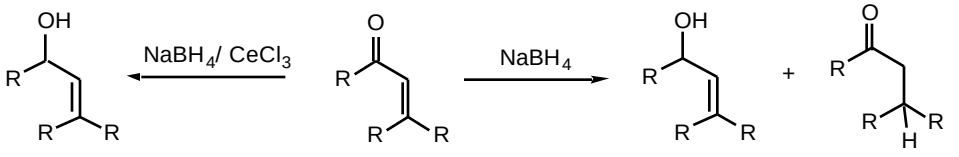
$R\text{-}CONH2 \rightarrow R\text{-}CH_2\text{-}NH_2$

$R_2C{=}N\text{-}OH \rightarrow R_2CH\text{-}NH_2$

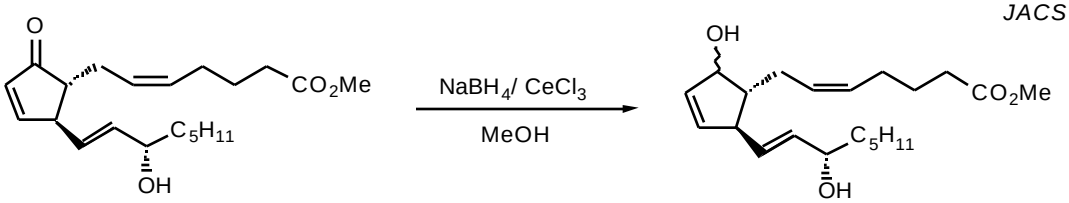
$R\text{-}SO2\text{-}R' \rightarrow R\text{-}S\text{-}R'$

$NaBH_4$ / $CeCl_3$ Luche Reduction

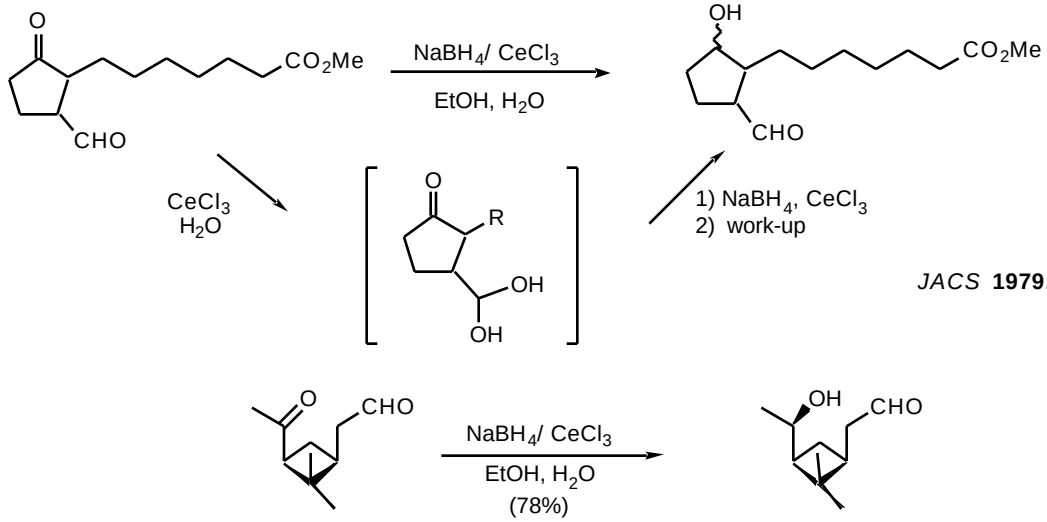
reduced α,β-unsaturated ketones in a 1,2-fashion



JCSCC **1978**, 601
JACS **1978**, *100* , 2226



- selective reduction of ketones in the presence of aldehydes.

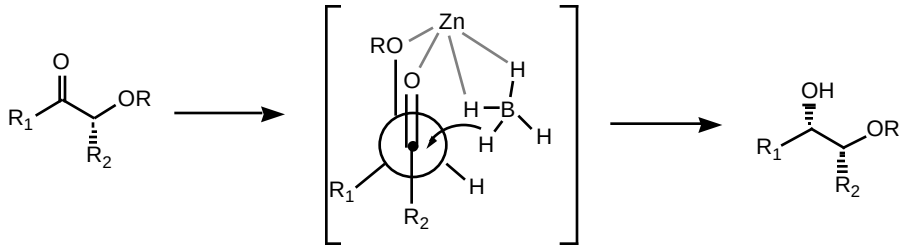


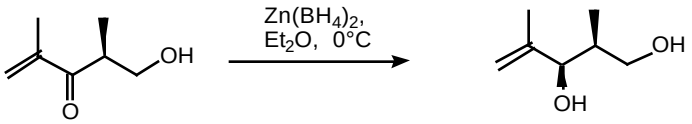
JACS **1979**, *101* , 5848

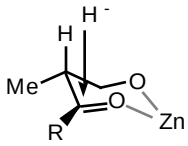
Zinc Borohydride $Zn(BH_4)_2$ *Synlett* **1993**, 885.

$ZnCl_{2\,(ether)} + NaBH_4 \rightarrow Zn(BH_4)_2$

- Ether solution of $Zn(BH_4)_2$ is neutral- good for base sensitive compounds
- Chelation contol model





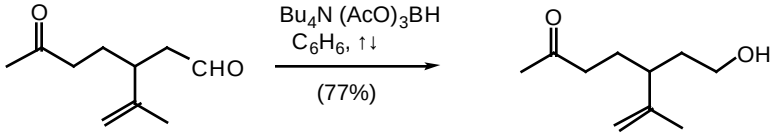


TL **1983**, *24* , 2653, 2657, 2661

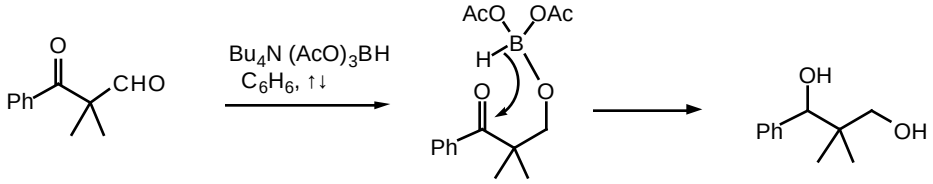
$Na^+ (AcO)_3BH$, $Me_4N^+ (AcO)_3BH$

Review: *OPPI* **1985**, *17* , 317

- used in Borch reductive amination *TL* **1990**, *31* , 5595; *Synlett* **1990**, 537
- selective reduction of aldehydes in the presence of ketones

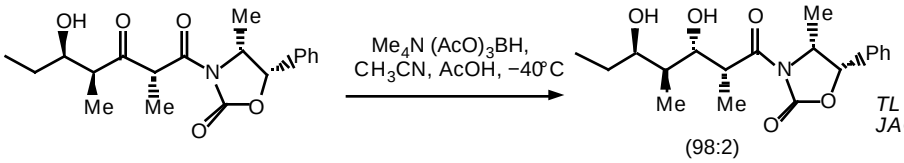


TL **1983**, *24* , 4287



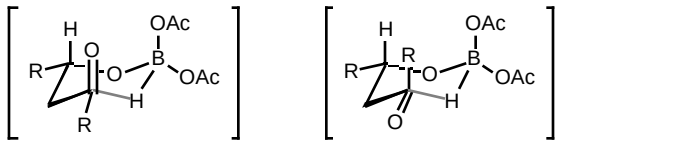
-hydroxyl-directed reduction of ketones

TL **1983**, *24* , 273; *TL* **1984**, *25* , 5449

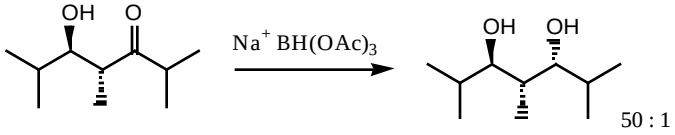


(98:2)

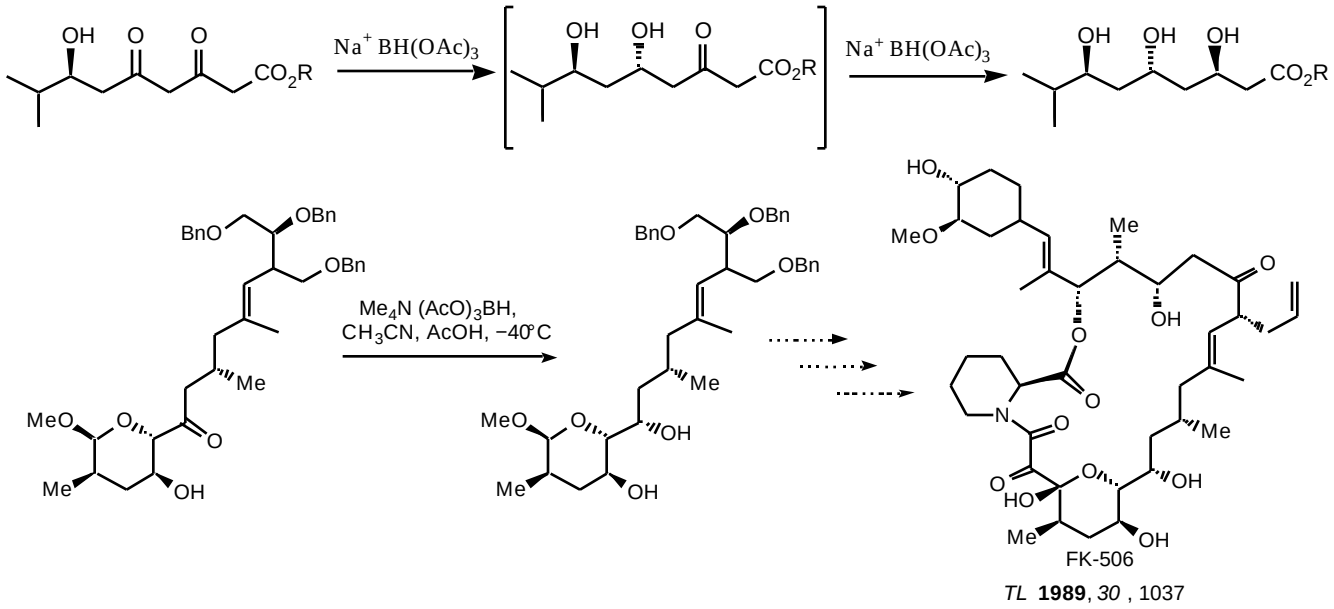
TL **1986**, *27* , 5939
JACS **1988**, *110* , 3560



major minor



50 : 1



TL **1989**, *30* , 1037

$(Ph_3P)_2Cu\ BH_4$

reduction of acid chlorides to aldehydes *JOC* **1989**, *45*, 3449
reduction of alkyl and aryl azides to amines *J. Chem. Res. (S)* **1981**, 17

$R_4N\ BH_4$ organic soluble borohydride (CH_2Cl_2)

R_4N= $BnEt_3N$ or Bu_4N Heterocylces **1980**, *14*, 1437, 1441
reduction of amides to amines
reduction of nitriles to amines

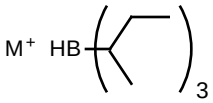
$BnEt_3N\ BH_4$ / Me_3SiCl

reduction of carbolxylic acids to alcohols *Synth. Commun.* **1990**, *20*, 907

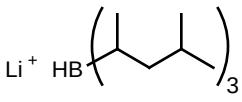
$LiBH_4$/ Me_3SiCl *ACIEE* **1989**, *28*, 218.

<u>*Alkyl Borohydrides*</u>

Selectrides

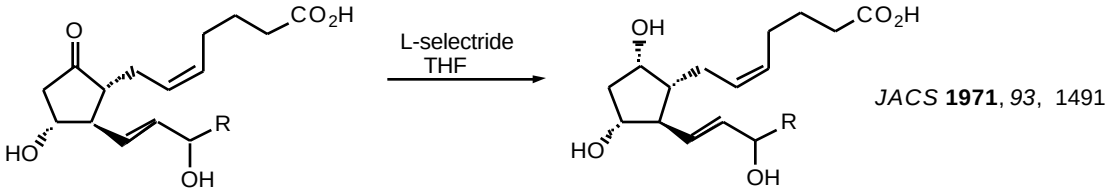


M^+ = Li (L-selectride)
K (K-selectride)



LS-selectride

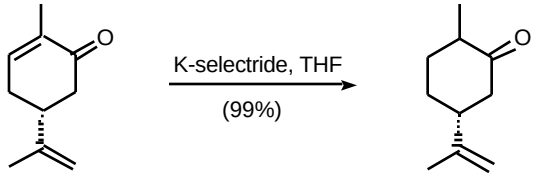
- hindered reducing agent
increased selectivity based on steric considerations



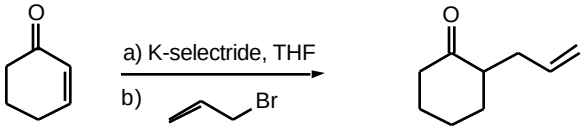
JACS **1971**, *93*, 1491

- selective 1,4-reductions of α,β-unsaturated carbonyl cmpds.

JOC **1975**, *40* , 146; *JOC* **1976**, *41* , 2194



- 1,4-reduction generates an enolate which can be subsequently alkylated.



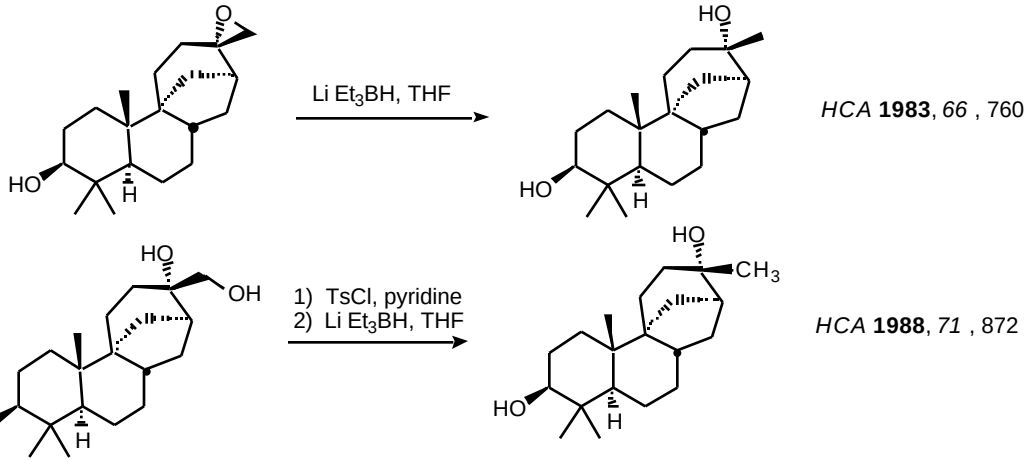
$K^+ HBPh_3$

Syn. Comm. ***1988****, 18* , 89.

- even greater 1,4-selectivity

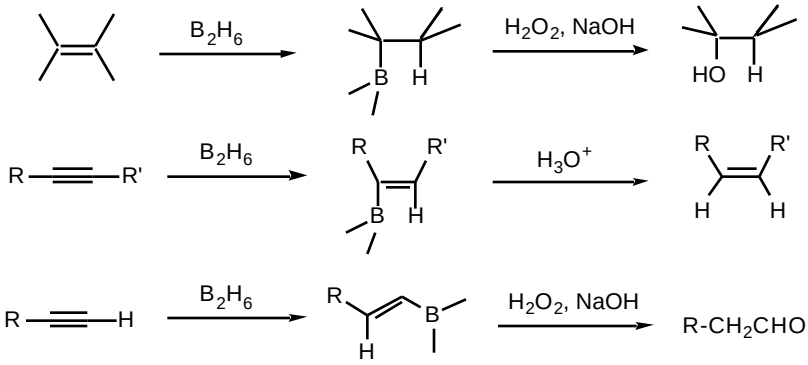
$Li^+ HBEt_3$ (Super Hydride)

- very reactive hydride source
- reduces ketones, aldehydes, esters, epoxides and C-X (alkyl halides and sulfonates)

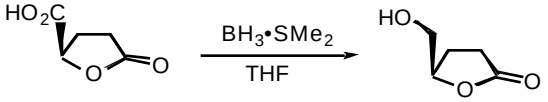


Boranes

Hydroboration

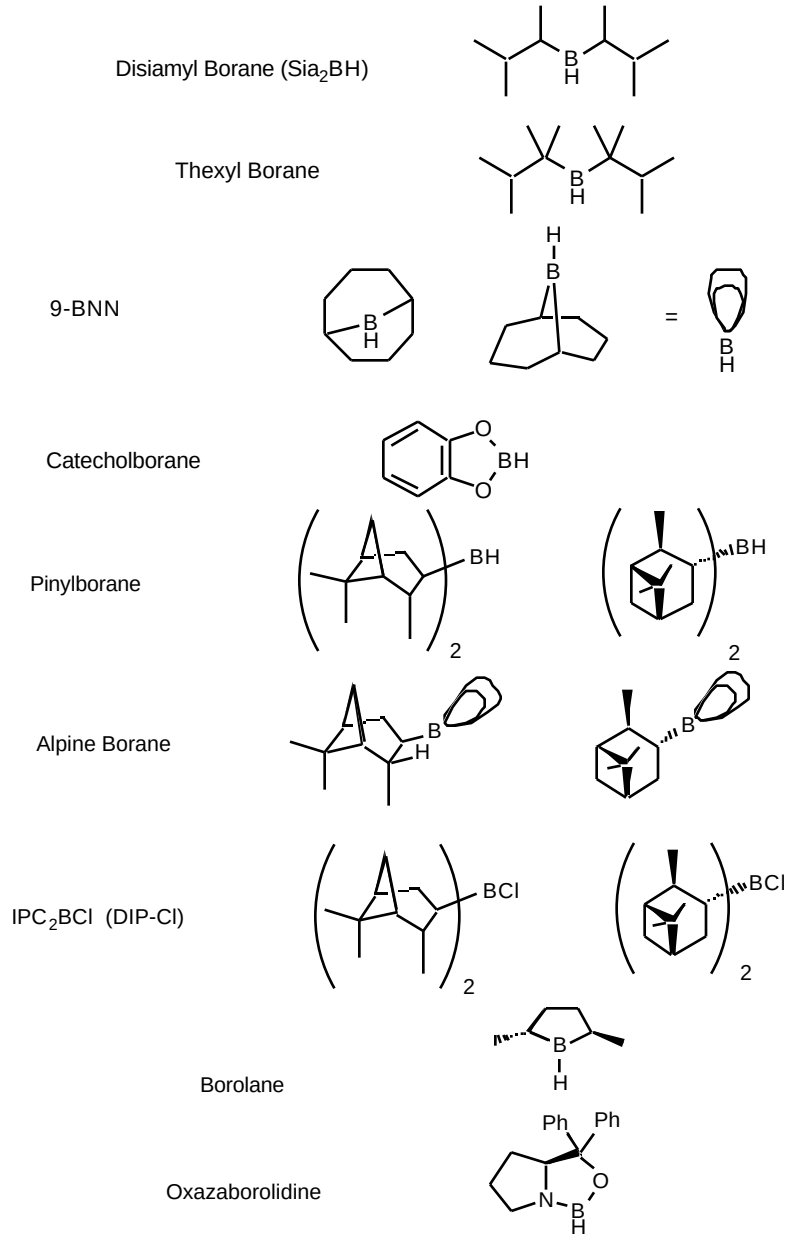


- BH_3 reduces carboxylic acids to 1° alcohols in the presence of esters, nitro and cyano groups.
- BH_3 reduces amides to amines



- Boranes also reduce ketones and aldehydes to the corresponding alcohols.

Hindered Boranes



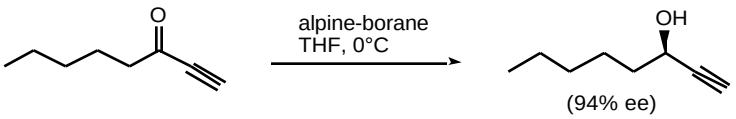
Asymmetric Reduction of Unsymmetrical Ketones Using Chiral Boron Reagents

Review: *Synthesis* **1992**, 605.

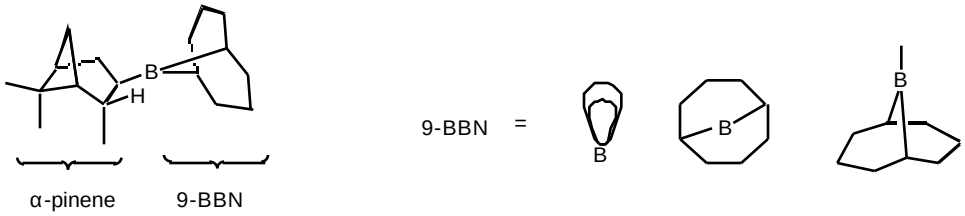
Alpine Borane Midland Reduction

JACS **1979**, *111* , 2352; *JACS* **1980**, *112* , 867

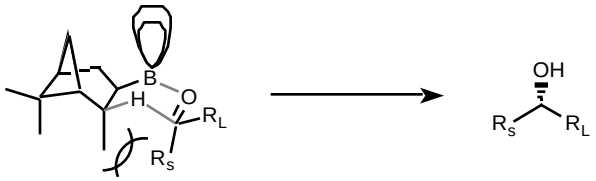
review: *Chem. Rev.* **1989**, *89* , 1553.



Tetrahedron **1984**, *40* , 1371



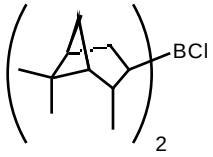
Mechanism:



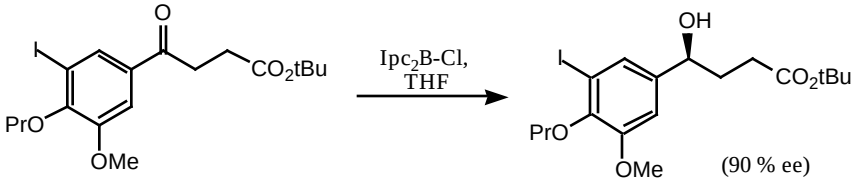
- works best for aryl- and acetylenic ketones
- because of steric hindrance, alpine-borane is fairly unreactive

Chloro Diisopinylcamphenylborane (DIP-Cl, Ipc_2BCl) H.C. Brown

Review: *ACR* **1992**, *25* , 16. *Aldrichimica Acta* **1994**, *27 (2)*, 43



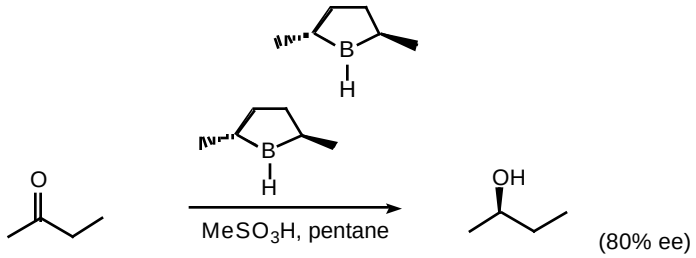
- Cl increases the Lewis acidity of boron making it a more reactive reagent
- saturated ketones are reduced to chiral alcohols with varying degrees of ee.



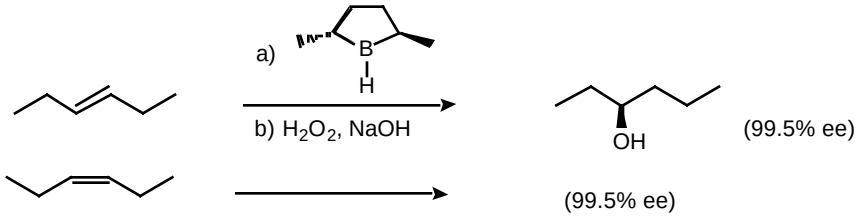
JOC **1992**, *57*, 7044

Borolane (Masamune's Reagent)

JACS **1986**, *108* , 7404; *JACS* **1985**, *107*, 4549

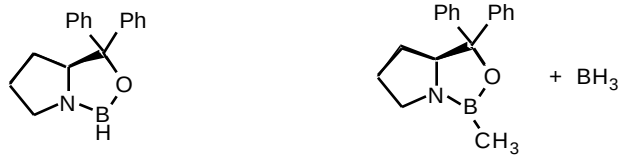


Asymmetric Hydroboration:

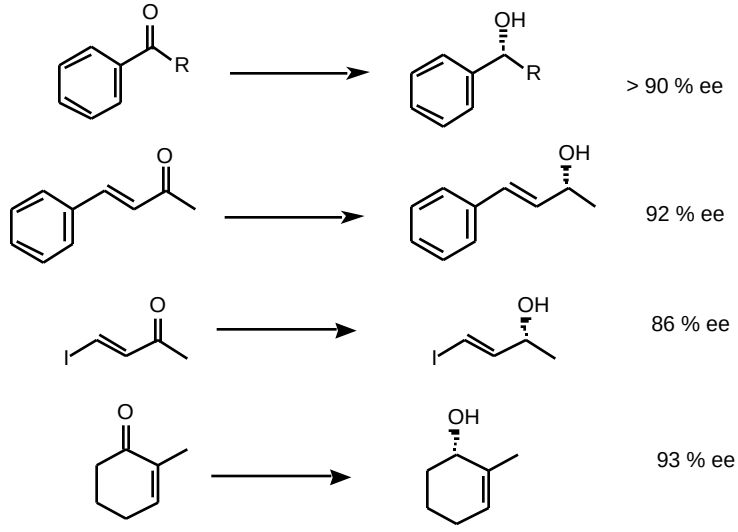


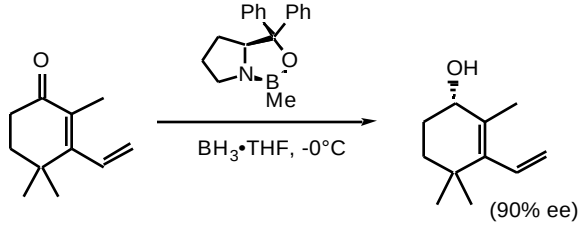
Oxazaborolidine (Corey)

JACS **1987**, *109* , 7925; *TL* **1990**, *31*, 611l ; *TL* **1992**, *33* , 4141

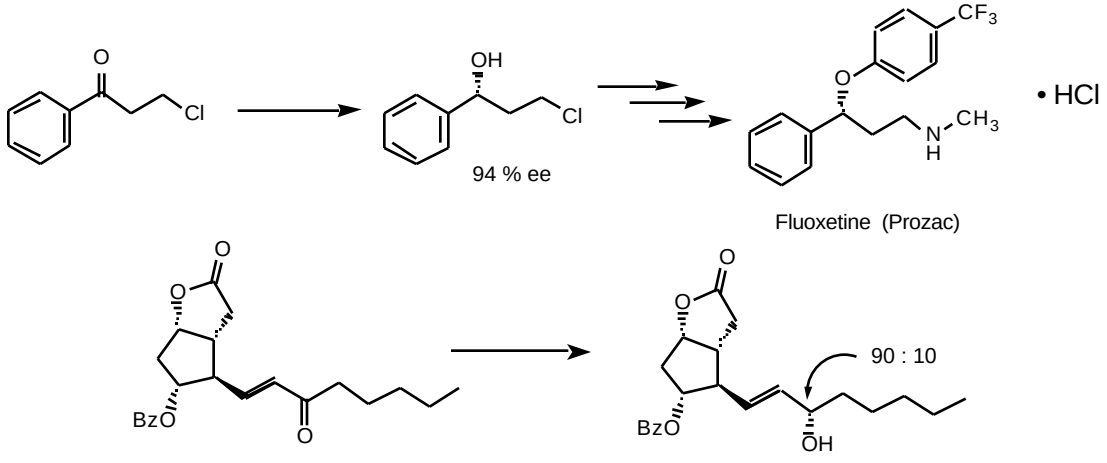


Catalytic





TL **1988**, *29* , 6409

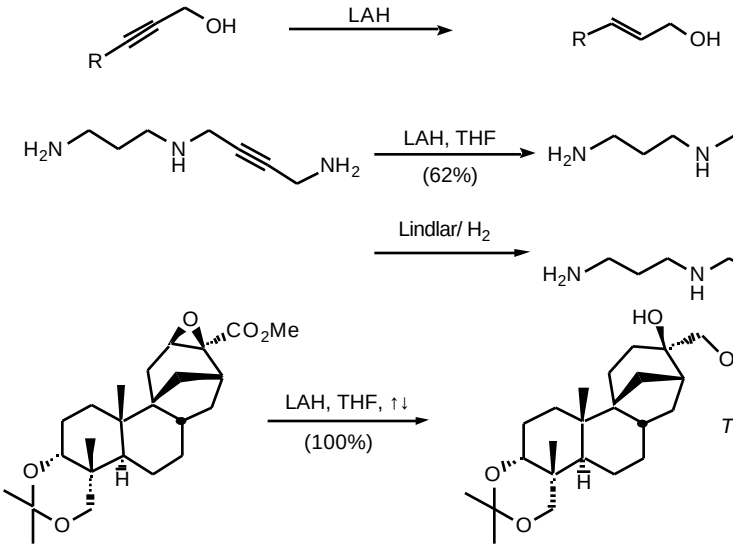


Aluminium Hydrides

1. $LiAlH_4$
2. AlH_3
3. Li $(tBuO)_3AlH$
4. $(iBu)_2AlH$ DIBAL-H
5. Na $(MeOCH_2CH_2O)_2AlH_2$ REDAL

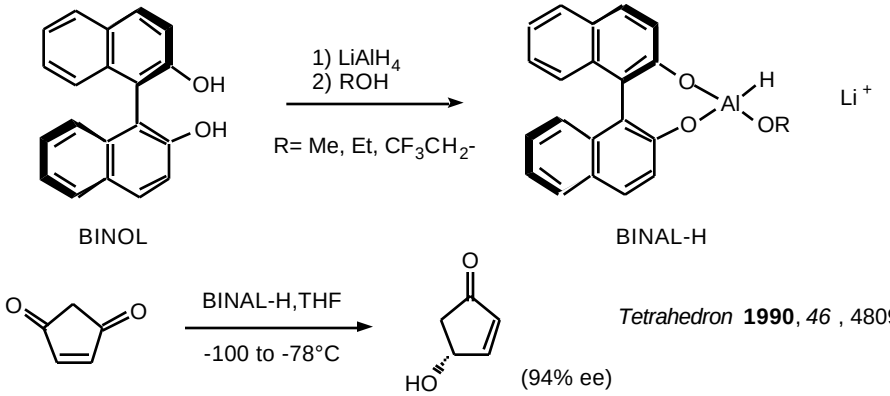
Lithium Aluminium Hydride $LiAlH_4$ (LAH) *Chem. Rev.* **1986**, *86*, 763 *Org. Rxn.* **1951**, *6*, 469.

- very powerful reducing agent
- used as a suspension in ether or THF
- Reduces carbonyl, carboxylic acids and esters to alcohols
- Reduces nitrile, amides and aryl nitro groups to amines
- opens epoxides
- reduces C-X bonds to C-H
- reduces acetylenic alcohols trans-allylic alcohols

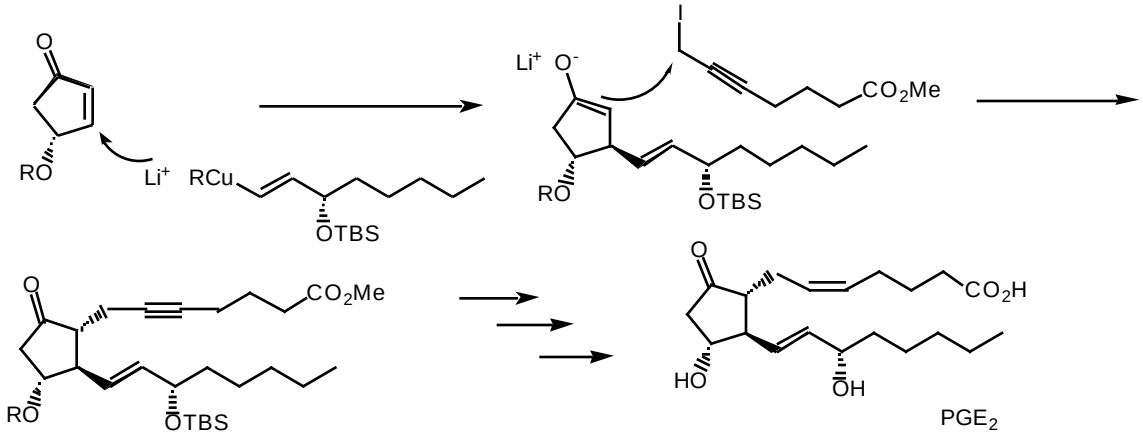


BINAL-H (Noyori)

- Chiral aluminium hydride for the asymmetric reduction of prochiral ketones



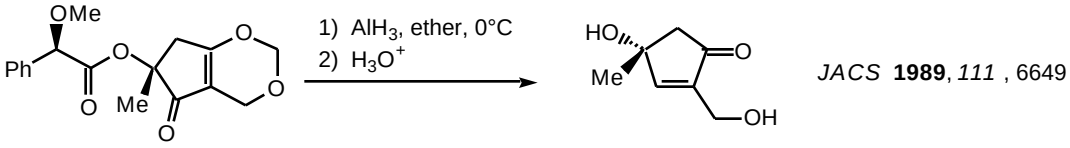
Intermediate for 3-Component Coupling Strategy to Prostaglandins



Alane AlH_3

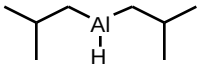
$LiAlH_4 + AlCl_3 \rightarrow AlH_3$

- superior to LAH for the 1,2-reduction of α,β-unsaturated carbonyls to allylic alcohols

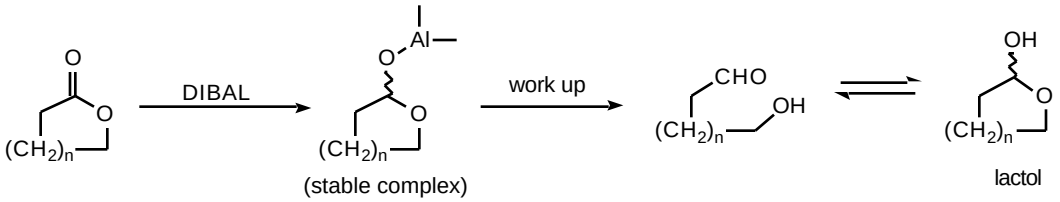


JACS **1989**, *111* , 6649

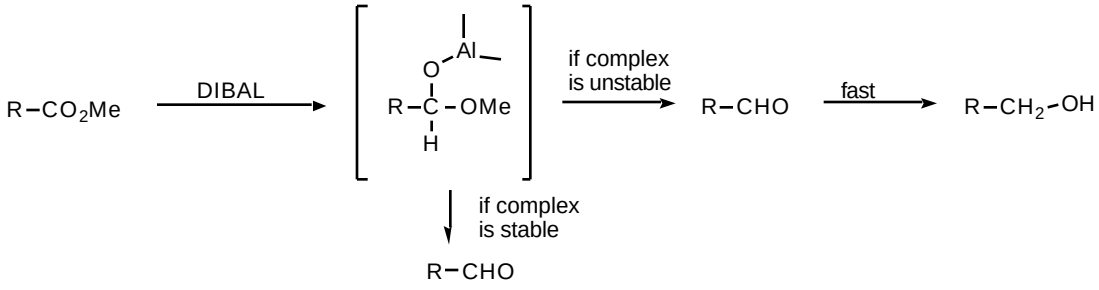
Diisobutyl Aluminium Hydride DIBAL or DIBAL-H

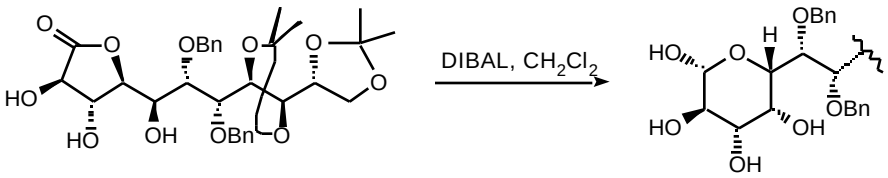


- Reduces ketones and aldehydes to alcohols
- reduces lactones to hemi-acetals

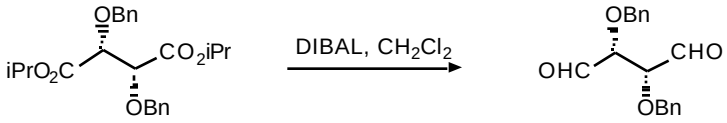


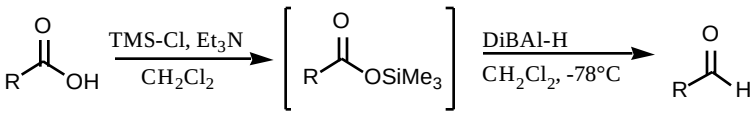
- reduces esters to alcohols
- under carefully controlled reactions conditions, will partially reduce an ester to an aldehyde





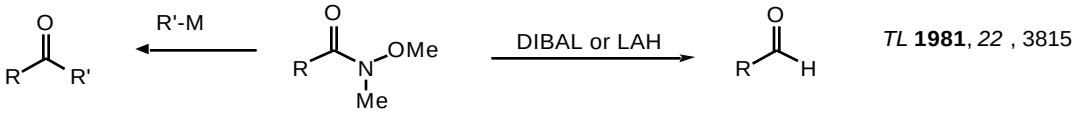
JACS **1990**, *112* , 9648





TL **1998**, *39*, 909

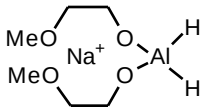
Reduction of O-Methyl hydroxamic acids



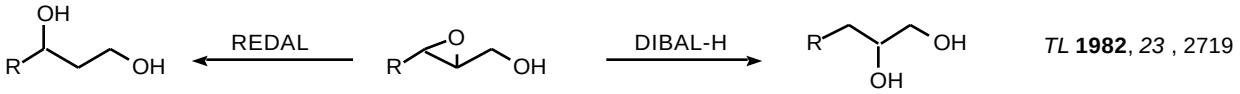
TL **1981**, *22* , 3815

Sodium Bis(2-Methoxyethoxy)Aluminium Hydride REDAL

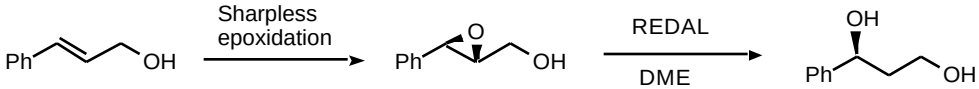
Organic Reactions **1988,** *36,* 249 *Organic Reactions* **1985**, *36,* 1.



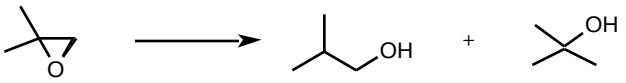
- "Chelation" directed opening fo allylic epoxides



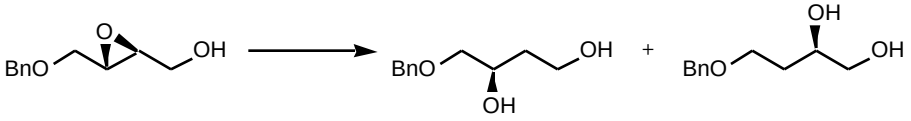
TL **1982**, *23* , 2719



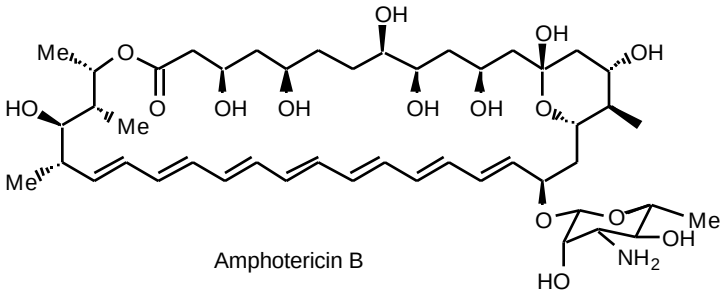
JOC **1988**, *53* , 4081



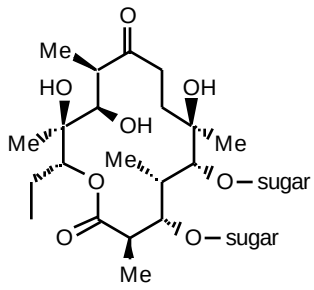
$LiAlH_4$	2 : 98
AlH_3	95 : 5



REDAL	150 : 1
DIBAL	1 : 13



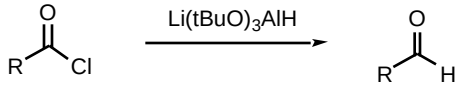
Amphotericin B

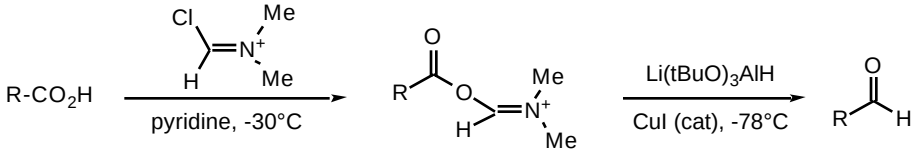


Erythromycin A

Lithium Tri(t-Butoxy)aluminium Hydride $Li^+ (tBuO)_3AlH$

- hindered aluminium hydride, will only react with the most reactive FG's

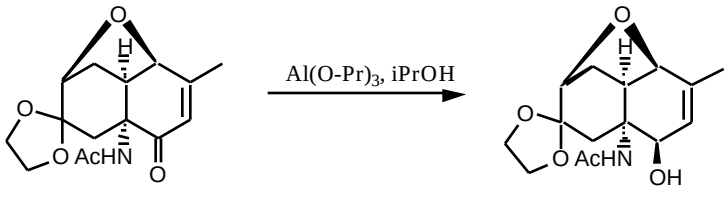




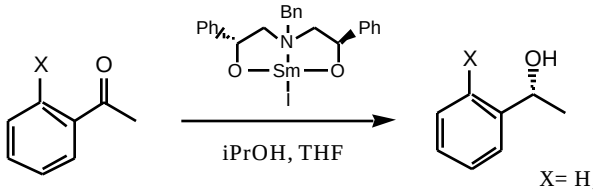
TL **1983**, *24* , 1543

Meerwein-Ponndorf-Verley Reduction: opposite of Oppenauer oxidation

Synthesis **1994**, 1007 *Organic Reactions* **1944**, *2*, 178



Asymmetric M-P-V Reduction



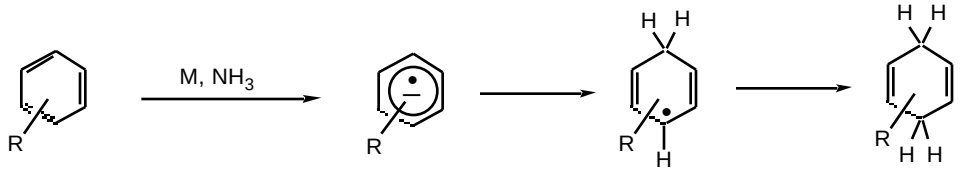
JACS **1993**, *115*, 9800

X= H, Cl, OMe
yield: 83-100 %
96% ee

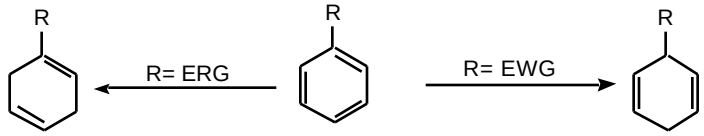
Dissolving Metal Reductions

Birch Reductions reduction of aromatic rings *Organic Reactions* **1976**, *23*, 1.
Tetrahedron **1986**, *42*, 6354. *Comprehensice Organic Synthesis* **1991**, *vol. 8, 107.*

- Li, Na or K metal in liquid ammonia

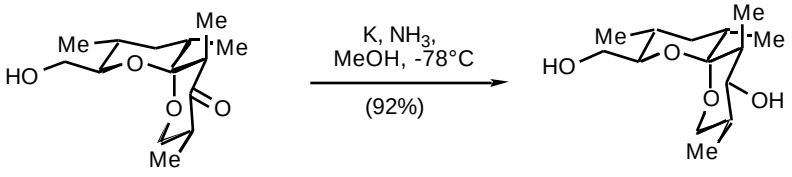


- position of the double bond in the final product is dependent of the nature of the substituent

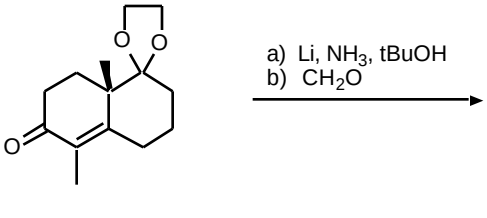


- ketones and nitro groups are also reduced but esters and nitrile are not.

- α,β-unsaturated carbonyl cmpds are reduced in a 1,4-fashion to give an enolate which can be subsequently used to trap electrophiles



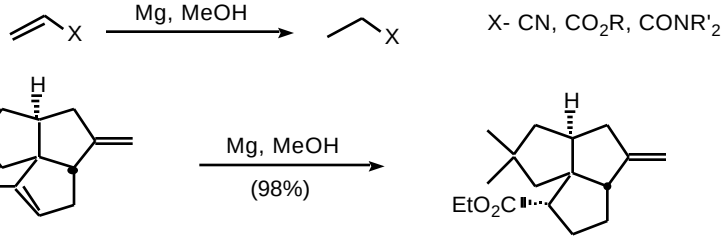
JOC **1991**, *56* , 6255



JOC **1984**, *59* , 3685

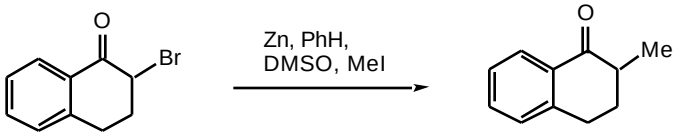
Other Metals

- Mg



TL **1987**, *28* , 5287

- Zn reduction of α-halocarbonyls

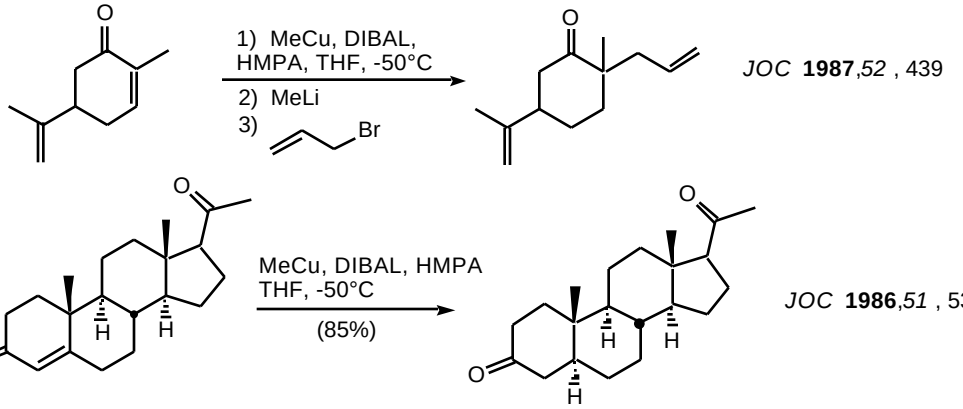


JACS **1967**, *89*, 5727

"Copper Hydrides"

LAH or DIBAL-H + MeCu → "CuH"

- selective 1,4-reduction of α,β-unsaturated ketones (even hindered enones)



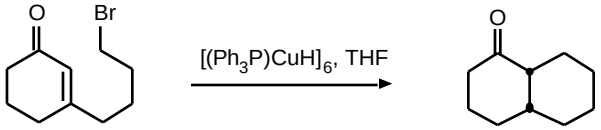
JOC **1987**,*52* , 439

JOC **1986**,*51* , 537

$[(Ph_3P)CuH]_6$ Stryker Reagent

JACS **1988**, *110* , 291 ; *TL* **1988**, *29* , 3749

- 1,4-reduction of α,β-unsaturated ketones and esters; saturated ketones are not reduced
- halides and sulfonates are not reduced
- 1,4-reduction gives an intermediate enolate which can be trapped with electrophiles.



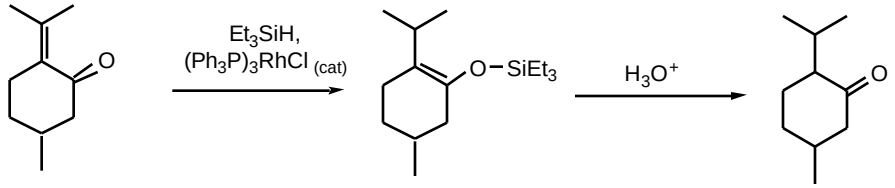
TL **1990**, *31* , 3237

Silyl Hydrides

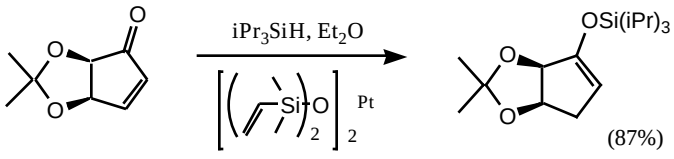
- Hydrosilylation

Et_3SiH + $(Ph_3P)_3RhCl$ (cat)

- selective 1,4-reduction of enones, 1,2-reduction of saturated ketones to alchohols.



TL **1972**, 5085
J. Organomet. Chem. **1975**, *94* , 449



JOC **1994**, *59*, 2287

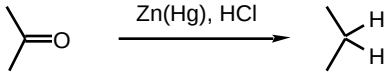
- Buchwald Reduction

JACS **1991**, *113* , 5093

- catalytic reagent prepared from Cp_2TiCl_2 + nBuLi and stoichometric $(Et)_3SiH$ in THF will reduce ester, ketones and aldehydes to alcohols under very mild conditions.
- α,b– unsaturated esters are reduced to allylic alcohols
- free hydroxyl groups, aliphatic halides and epoxides are not reduced

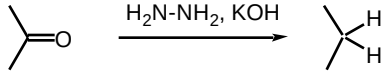
Clemmensen Reduction *Organic Reactions* **1975**, *22*, 401
Comprehensive Organic Synthesis **1991**, vol 8, 307.

- reduction of ketones to saturated hydrocarbons



Wolff-Kishner Reduction *Organic Reactions* **1948**, *4*, 378
Comprehensive Organic Synthesis **1991**, vol. 8, 327.

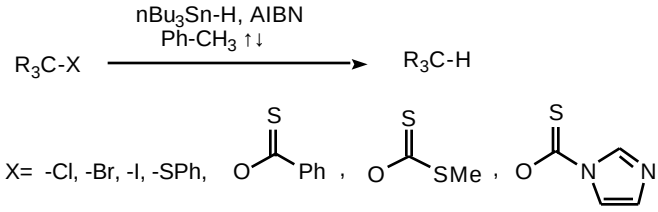
- reduction of ketones to saturated hydrocarbons

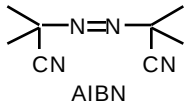


Radical Deoxygenation

Review: *Tetrahedron* **1983**, *39* , 2609 *Chem. Rev.* **1989**, *89*, 1413.
Comprehensive Organic Synthesis **1991**, vol. 8, 811
Tetrahedron **1992**, *48*, 2529
W. B. Motherwell, D. Crich *Free Radical Chain Reactions in Organic Synthesis* (Academic Press: 1992)

- free radical reduction of halide, thio ethers, xanthates, thionocarbanates by a radical chain mechanism.

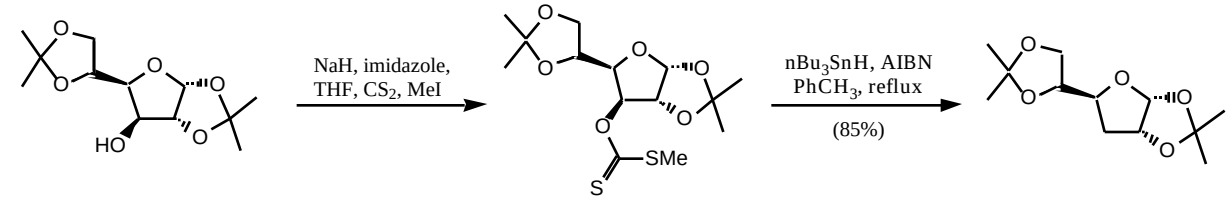




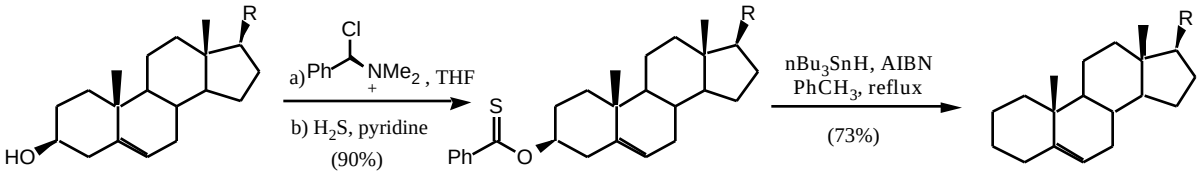
Barton-McCombie Reduction

JCS P1 **1975**, 1574

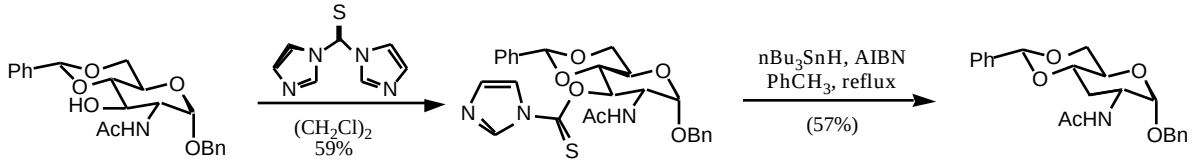
$R_3C\text{-}X \rightarrow R_3C\text{-}H$ X= -OC(=S)-SMe, -OC(=S)-Im, -OC(=S)Ph



Xanthate

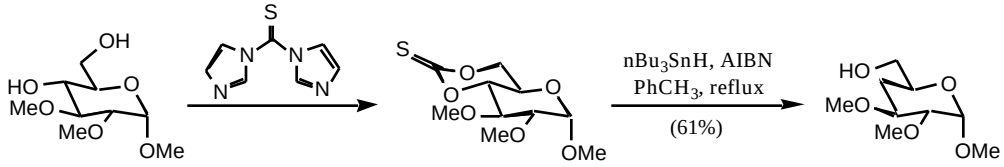


Thionobenzoates



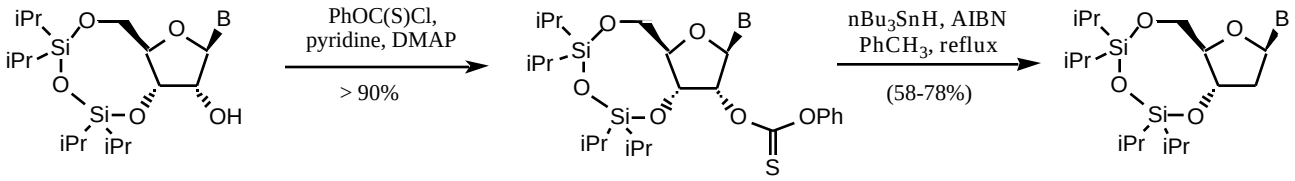
Thiocarbonyl Imidazolides

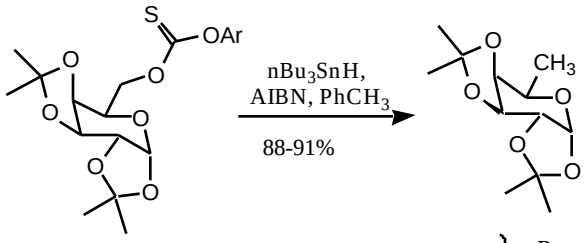
- Cyclic Thionocarbonates: deoxygenation of 1,2- and 1,3-diols to alcohols



JCS P1 **1977**, 1718

- Thionocarbonate Modification (Robbins)
JACS **1981**, *103* , 932; *JACS* **1983**, *105* , 4059.

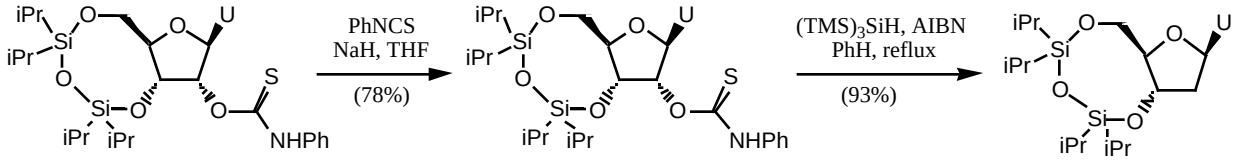




Tetrahedron **1991**, *47, 8969*

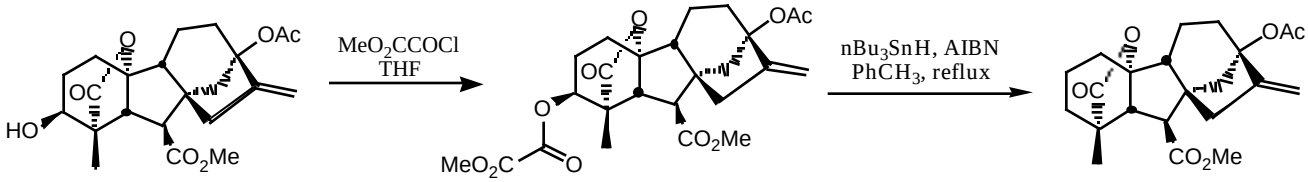
Ar= 2,4,6-trichlorophenyl, 4-fluorophenyl } Best method for deoxygenation of primary alcohols

- N-Phenyl Thionocarbamates *Tetrahedron* **1994**, *34*, 10193.



Thiocarbamates

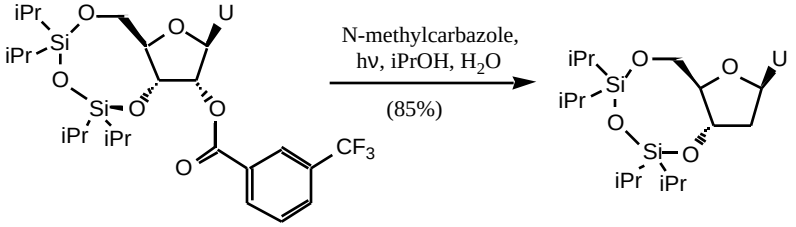
- Methyl oxylates



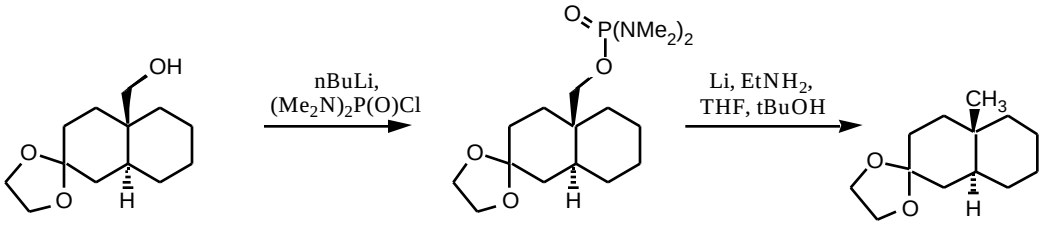
Methyl Oxylate Esters

- Water Soluble Tin Hydride: $[MeO(CH_2)_2O(CH_2)_3]_3SnH$ / 4,4'-Azo(bis-4-cyanovaleric acid)
TL **1990**, *31* , 2957
- Silyl Hydride Radical Reducing Agents
- replacement for nBu_3SnH
$(Me_3Si)_3SiH$ *Chem Rev*. **1995**, *95*, 1229.
JOC **1991**, *56* , 678; *JOC* **1988**, *53* , 3641; *JACS* **1987**, *109* , 5267
Ph_2SiH_2 / Et_3B / Air
TL **1990**, *31* , 4681; *TL* **1991**, *32* , 2569
- hypophosphorous acid as radical chain carrier
JOC **1993**, *58*, 6838

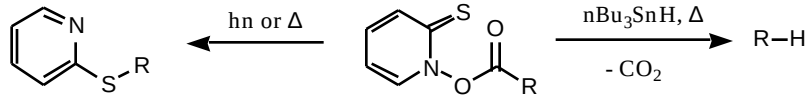
- Photosensitized electron transfer deoxygenation of m-trifluoromethylbenzoates
JACS **1986**, *108*, 3115, *JOC* **1996**, *61*, 6092, *JOC* **1997**, *62*, 8257



Dissolving Metal : *JACS* **1972**, *94*, 5098

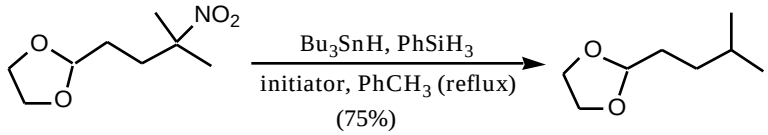


Radical Decarboxylation: Barton esters
Aldrichimica Acta **1987**, *20 (2)*, 35



Radical Deamination
Comprehensive Organic Synthesis **1991**, vol. 8, 811

Reduction of Nitroalkanes *JOC* **1998**, *63*, 5296



Carey & Sundberg Chapter 13.1 problems # 1; 2; 3a, b, c ;
Smith: Chapter 7

Protecting Groups

T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd edition) J. Wiley & Sons, 1991.
P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994

1. Hydroxyl groups
2 Ketones and aldehydes
3. Amines
4. Carboxylic Acids

- Protect functional groups which may be incompatible with a set of reaction conditions
- 2 step process- must be efficient
- Selectivity a. selective protection
  b. selective deprotection

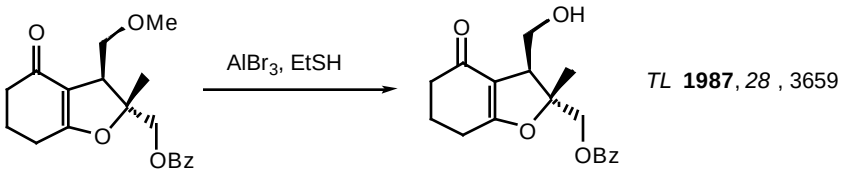
Hydroxyl Protecting Groups

Ethers

Methyl ethers

R-OH → R-OMe difficult to remove except for on phenols

Formation: - CH_2N_2, silica or HBF_4
- NaH, MeI, THF
Cleavage: - $AlBr_3$, EtSH
- $PhSe^-$
- Ph_2P^-
- Me_3SiI



TL **1987**, *28* , 3659

Methoxymethyl ether MOM

R-OH → R-OCH_2OMe stable to base and mild acid

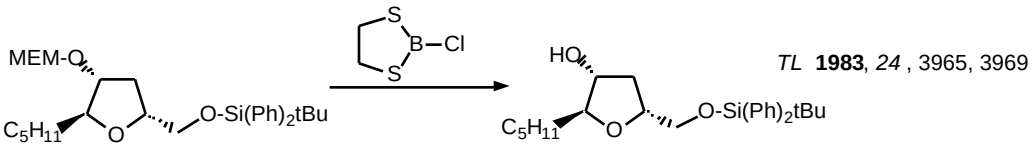
Formation: - $MeOCH_2Cl$, NaH, THF
- $MeOCH_2Cl$, CH_2Cl_2, iPr_2EtN
Cleavage - Me_2BBr_2 *TL* **1983**, *24* , 3969

Methoxyethoxymethyl ethers (MEM)

R-OH → R-$OCH_2OCH_2CH_2OMe$ stable to base and mild acid

Formation: - $MeOCH_2CH_2OCH_2Cl$, NaH, THF
- $MeOCH_2CH_2OCH_2Cl$, CH_2Cl_2, iPr_2EtN *TL* **1976**, 809

Cleavage - Lewis acids such as $ZnBr_2$, $TiCl_4$, Me_2BBr_2



TL **1983**, *24* , 3965, 3969

- can also be cleaved in the presence of THP ethers

Methyl Thiomethyl Ethers (MTM)

R-OH → R-OCH_2SMe Stable to base and mild acid

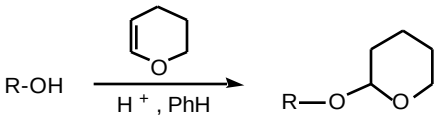
Formation: - $MeSCH_2Cl$, NaH, THF
Cleavage: - $HgCl_2$, CH_3CN / H_2O
- $AgNO_3$, THF, H_2O, base

Benzyloxymethyl Ethers (BOM)

R-OH → R-OCH_2OCH_2Ph Stable to acid and base

Formation: - $PhOCH_2CH_2Cl$, CH_2Cl_2, iPr_2EtN
Cleavage: - H_2 / PtO_2
- Na / NH_3, EtOH

Tetrahydropyranyl Ether (THP)

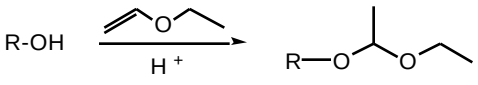


Stable to base, acid labile

Formation - DHP (dihydropyran), pTSA, PhH
Cleavage: - AcOH, THF, H_2O
- Amberlyst H-15, MeOH

Ethoxyethyl ethers (EE)

JACS **1979**, *101* , 7104; *JACS* **1974**, *96* , 4745.



(R-OEE) base stable, acid labile

Benzyl Ethers (R-OBn)

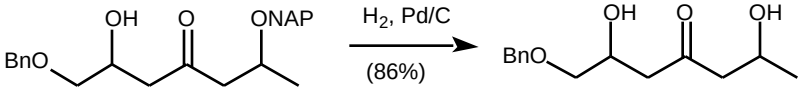
R-OH → R-OCH_2Ph stable to acid and base

Formation: - KH, THF, $PhCH_2Cl$
- $PhCH_2OC(=NH)CCl_3$, F_3CSO_3H *JCS P1* **1985**, 2247
Cleavage: - H_2 / PtO_2
- Li / NH_3

2-Napthylmethyl Ethers (NAP) *JOC* **1998**, *63*, 4172

formation: 2-chloromethylnapthalene, KH

cleavage: hydrogenolysis



p- Methoxybenzyl Ethers (PMB)

Formation: - KH, THF, p-MeOPhCH$_2$Cl

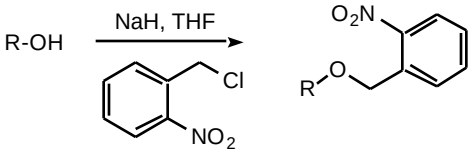
- p-MeOPhCH$_2$OC(=NH)CCl$_3$, F$_3$CSO$_3$H *TL* **1988**, *29* , 4139

Cleavage: - H_2 / PtO_2

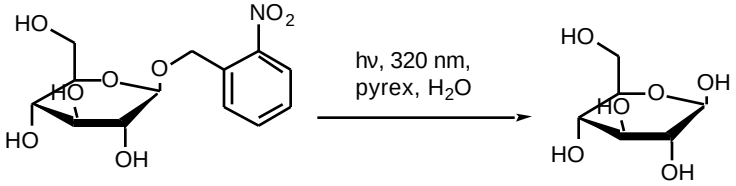
- Li / NH_3
- DDQ
- $Ce(NH_4)_2(NO_3)_6$ (CAN)
- e^-

o-Nitrobenzyl ethers

Review: *Synthesis* **1980**, 1; Organic Photochemistry, **1987**, *9* , 225



Cleavage: - photolysis at 320 nm



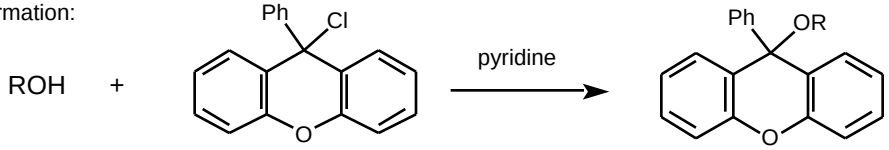
JOC **1972**, *37* , 2281, 2282.

p-Nitrobenzyl Ether *TL* **1990**, *31* , *389*

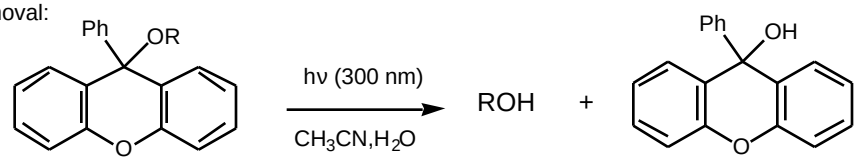
-selective removal with DDQ, hydrogenolysis or elctrochemically

9-Phenylxanthyl- (pixyl, px) *TL* **1998**, *39*, 1653

Formation:



Removal:



Trityl Ethers -CPh_3 = Tr

R-OH → R-OCPh_3 - selective for 1° alcohols

- removed with mild acid; base stable

formation: - Ph_3C-Cl, pyridine, DMAP

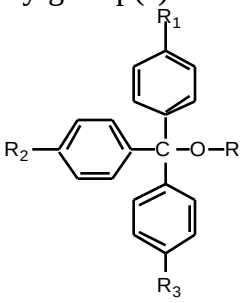
- Ph_3C^+ BF_4^-

Cleavage: - mild acid

Methoxytrityl Ethers

JACS **1962**, *84* , 430

- methoxy group(s) make it easier to remove

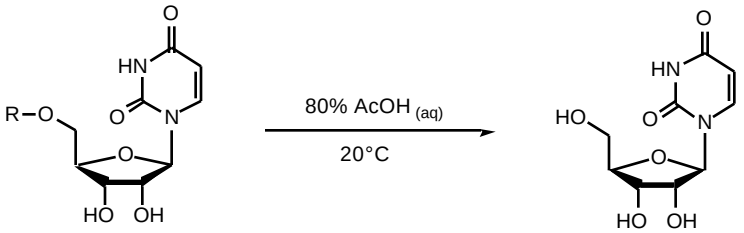


(p-Methoxyphenyl)diphenylmethyl ether
4'-methoxytrityl MMTr-OR

Di-(p-methoxyphenyl)phenylmethyl ether
4',4'-dimethoxytrityl DMTr-OR

Tri-(p-methoxyphenyl)methyl ether
4',4',4'-trimethoxytrityl TMTr-OR

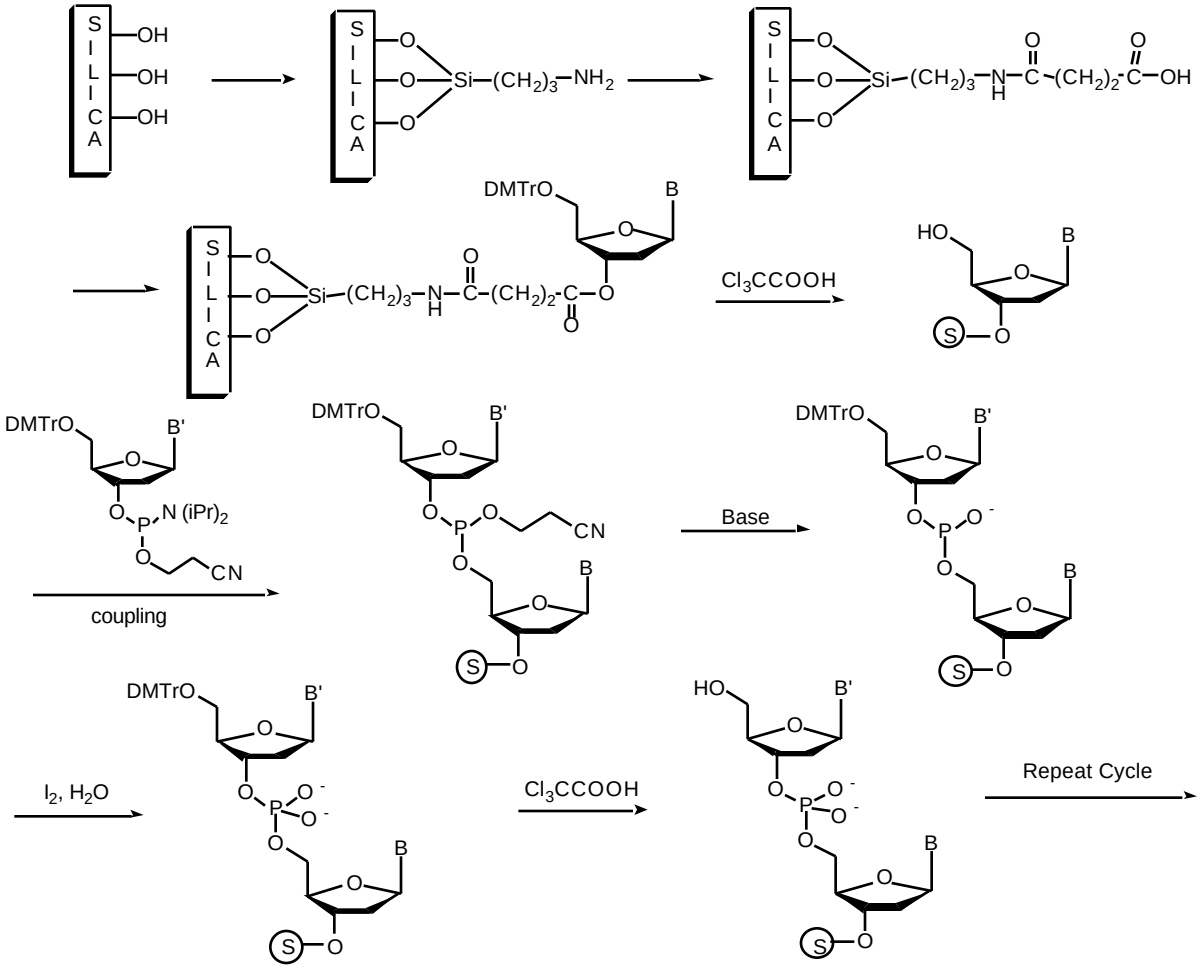
Tr-OR < MMTr-OR < DMTr-OR << TMTr-OR



R = Tr 48 hr.
R= MMTr 2 hr.
R= DMTr 15 min.
R= TMTr 1 min. (too labile to be useful)

Oligonucleotide Synthesis (phosphoramidite method - Lessinger)

Review: *Tetrahedron* **1992**, *48* , 2223



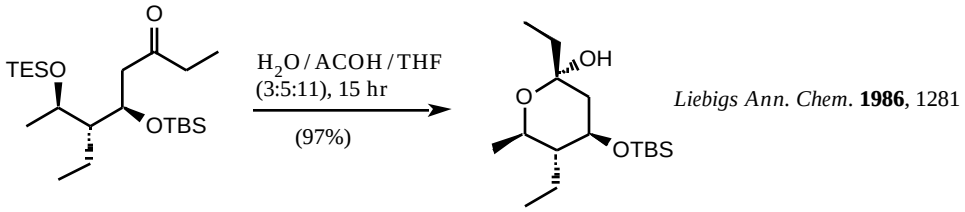
Silyl Ethers *Synthesis* **1985**, 817 *Synthesis* **1993**, 11 *Synthesis* **1996**, 1031

R-OH → R-O-SiR_3

formation: - R_3Si-Cl, pyridine, DMAP
- R_3Si-Cl, CH_2Cl_2 (DMF, CH_3CN), imidazole, DMAP
- R_3Si-OTf, iPr_2EtN, CH_2Cl_2

Trimethylsilyl ethers Me_3Si-OR TMS-OR
- very acid and water labile
- useful for transiant protection

Triethylsilyl ethers Et_3Si-OR TES-OR
- considerably more stable that TMS
- can be selectively removed in the presence of more robust silyl ethers with with F^- or mild acid



Liebigs Ann. Chem. **1986**, 1281

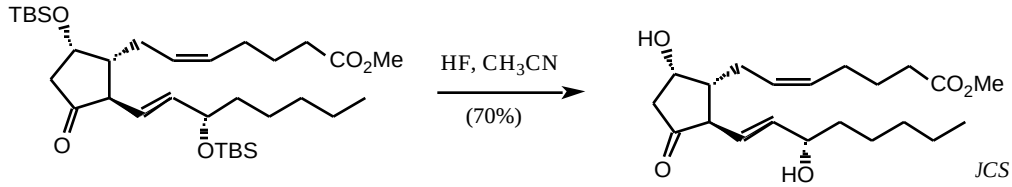
Triisopropylsilyl ethers iPr_3Si-OR TIPS-OR
- more stabile to hydrolysis than TMS

Phenyldimethylsilyl ethers
J. Org. Chem. **1987**, *52* , 165

t-Butyldimethylsilyl Ether $tBuMe_2Si$-OR TBS-OR TBDMS-OR
JACS **1972**, *94* , 6190
- Stable to base and mild acid
- under controlled condition is selective for 1° alcohols

t-butyldimethylsilyl triflate $tBuMe_2Si$-OTf *TL* **1981**, *22* , 3455
- very reactive silylating reagent, will silylate 2° alcohols

cleavage:
- acid
- F^- (HF, nBu_4NF, CsF, KF)

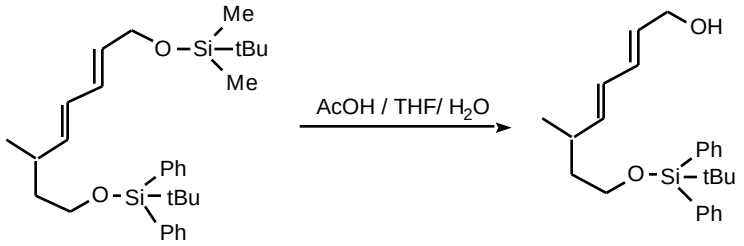


JCS Perkin Trans. 1 **1981**, 2055

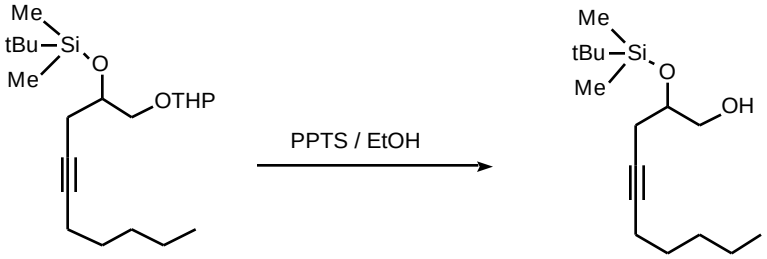
t-Butyldiphenylsilyl Ether $tBuPh_2Si$-OR TBDPS-OR ∑-OR
- stable to acid and base
- selective for 1° alcohols
- Me_3Si- and iPr_3Si groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.
TL **1989**, *30* , 19

cleavage - F^-

- Fluoride sources: - nBu_4NF (basic reagent)
  - HF / H_2O / CH_3CN *TL* **1979**, 3981.
  - HF • pyridine *Synthesis* **1986**, 453
  - SiF_4. CH_2Cl_2 *TL* **1992**, *33* , 2289



JOC **1981**, *46* ,1506
TL **1989**, *30* , 19.



JACS **1984**, *106* , 3748

Esters

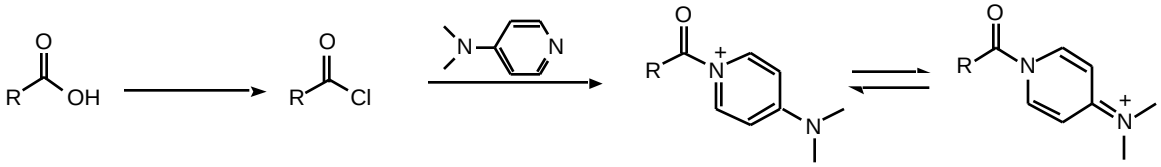
R-OH → R-O_2CR'

Formation: - "activated acid", base, solvent, (DMAP)

Activated Acids *Chem. Soc. Rev.* **1983**, *12*, 129 A*ngew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

RCO_2H → "activated acid" → carboxylic acid derivative (ester, amide, etc.)

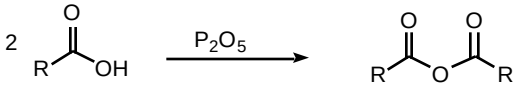
Acid Chlorides



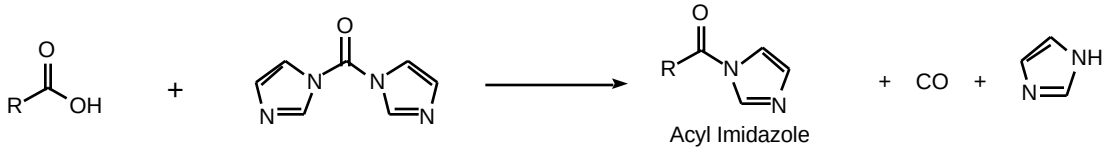
acyl pyridinium ion
(more reactive)

1. $SOCl_2$
2. PCl_5
3. $(COCl)_2$

Anhydrides

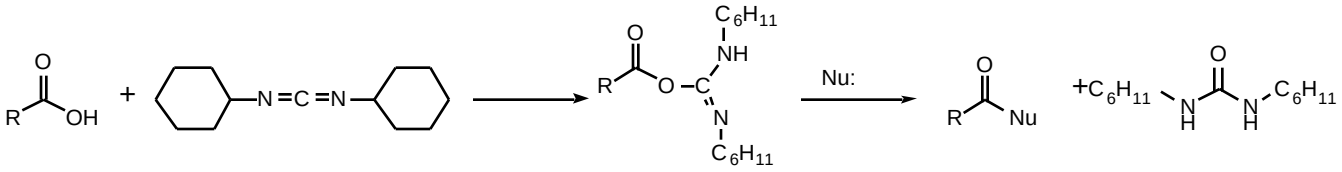


Activating Agents:
Carbonyl Diimidazole

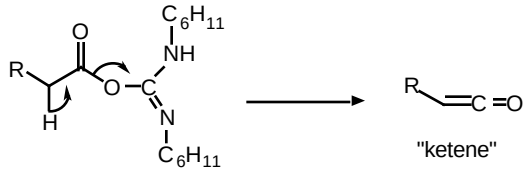


Acyl Imidazole

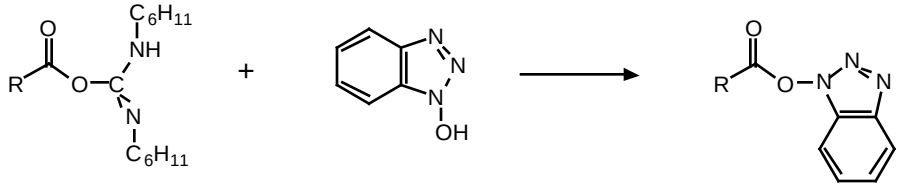
Dicyclohexylcarbodiimide



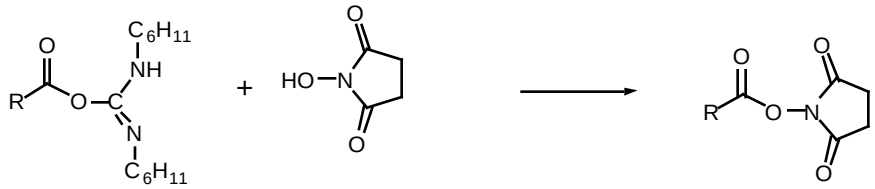
Ketene formation is a common side reaction- scambling of chiral centers



Hydroxybenzotriazole (HOBT) - reduces ketene formation

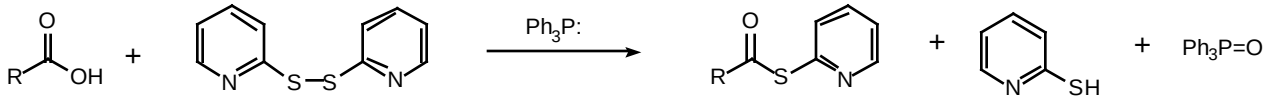


N-Hydroxysuccinimide (NHS)



2,2'-Dipyridyl Disulfide (Aldrithiol, Corey Reagent)

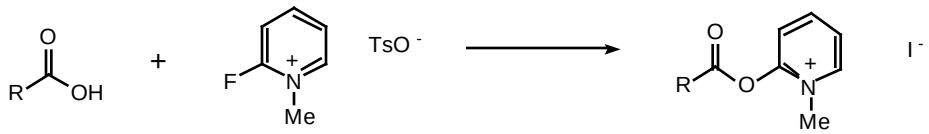
Aldrichimica Acta **1971**, *4* , 33



Mukaiyama's Reagent (2-Chloro-1-methyl pyridinium Iodide or 2-Fluoro-1-methyl pyridinium p-toulenesulfonate)

Aldrichimica Acta **1987**, *20* , 54

Chem. Lett. **1975**, 1045; 1159; **1976**, 49; **1977**, 575



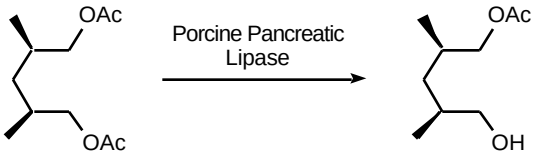
Acetates

R-OH → $R\text{-}O_2CCH_3$

- stable to acid and mild base
- not compatable with strong base or strong nucleophiles such as organometallic reagents

Formation: - acetic anhydride, pyridine
- acetyl chloride, pyridine

Cleavage: - K_2CO_3, MeOH, reflux
- KCN, EtOH, reflux
- NH_3, MeOH
- LiOH, THF, H_2O
- enzymatic hydrolysis (Lipase) *Org. Rxns.* **1989**, *37*, 1.

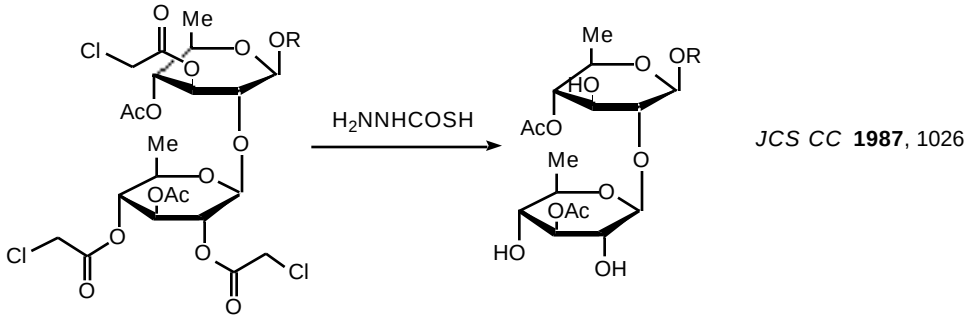


TL **1988**, *30* , 6189

(96% ee)

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



JCS CC **1987**, 1026

Trifluoroacetates

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride
Cleavage: - K_2CO_3, MeOH

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

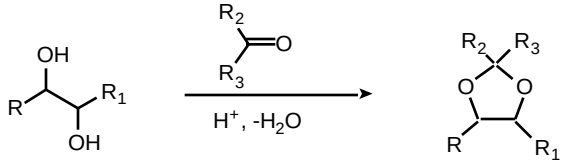
Formation: - tbutylacetyl chloride or t-butylacetic anhydride
Cleavage: - removed with mild base

Benzoate (Bz)

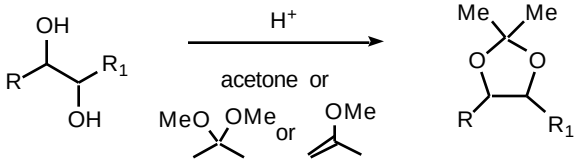
- more stable to hydrolysis than acetates.

Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (*TL* **1971**, 185) , benzoyl tetrazole (*TL* **1997**, *38*, 8811)
Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- Diols *Synthesis* **1981**, 501 *Chem. Rev.* **1974**, *74*, 581



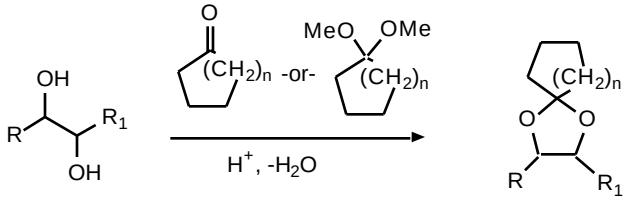
Isopropylidenes (acetonides)



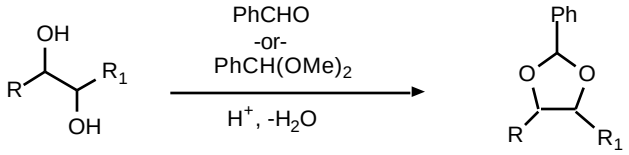
- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

- Cyclopentylidene are slightly easier to cleave than acetonides
- Cyclohexylidenes are slightly harder to cleave than acetonides



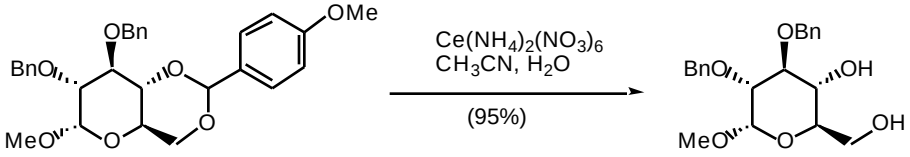
Benzylidene Acetals



- in competition between 1,2- and 1,3-diols, 1,3-benzylidene formation for is usually favored
- benzylidenes can be removed by acid hydrolysis or hydrogenolysis
- benzylidene are usually hydrogenolyzed more slowly than benzyl ethers or olefins.

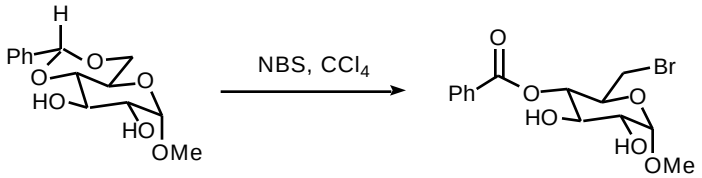
p-Methoxybenzylidenes

- hydrolyzed about 10X faster than regular benzylidenes
- Can be oxidatively removed with $Ce(NH_4)_2(NO_3)_6$ (CAN)



Other Reactions of Benzylidenes

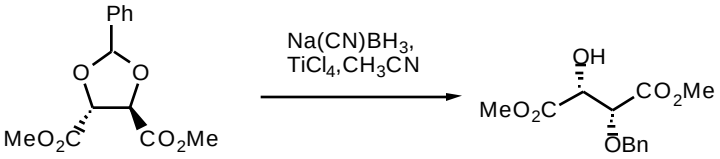
- Reaction with NBS (Hanessian Reaction)



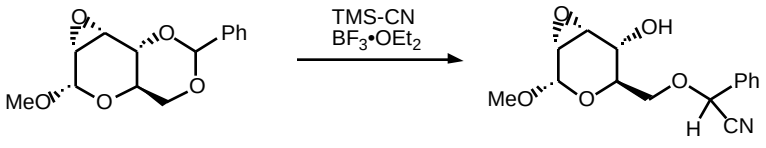
Org. Syn. **1987**, *65*, 243

- if benzylidene of a 1° alcohol, then 1° bromide

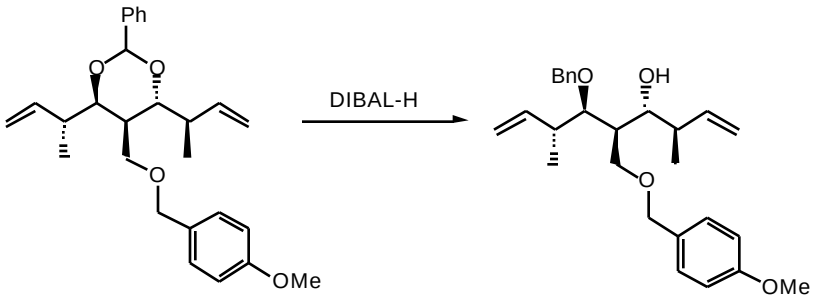
- Reductive Cleavage



Synthesis **1988**, 373.

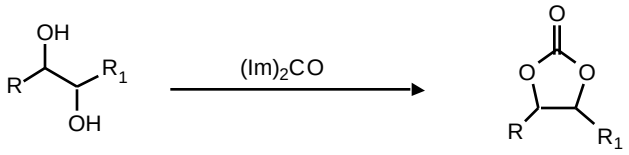


Tetrahedron **1985**, *41*, *3867*



TL **1988**, *29* , 4085

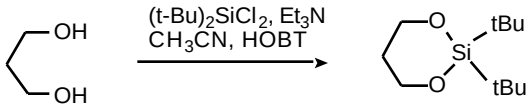
Carbonates



- stable to acid; removed with base
- more difficult to hydrolyze than esters

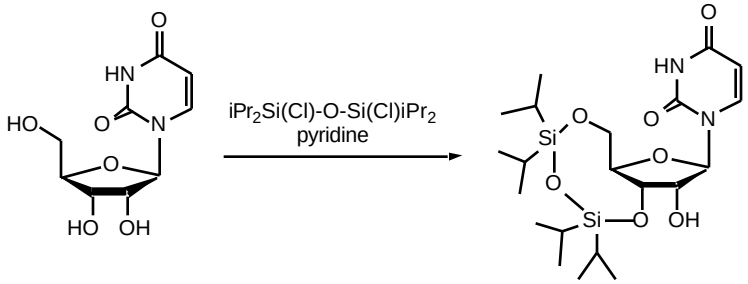
Di-t-Butylsilylene (DTBS) *TL* **1981**, *22* , 4999

- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH_3CN -or- Bu_4NF -or- HF•pyridine)
- will not fuctionalize a 3°-alcohol



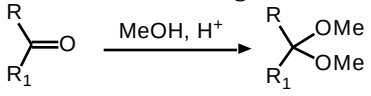
1,3-(1,1,3,3)-tetraisopropyldisiloxanylidene (TIPDS) *TL* **1988**, *29* , 1561

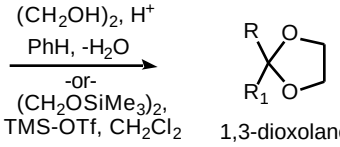
- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I



Ketones and Aldehydes

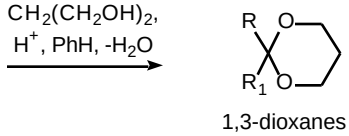
- ketones and aldehydes are protected as cyclic and acyclic ketals and acetals
- Stable to base; removed with H_3O^+





1,3-dioxolanes

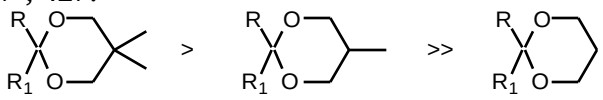
TL **1980**, *21* , 1357



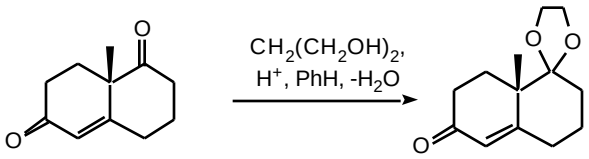
1,3-dioxanes

Cleavage rate of substituted 1,3-dioxanes:

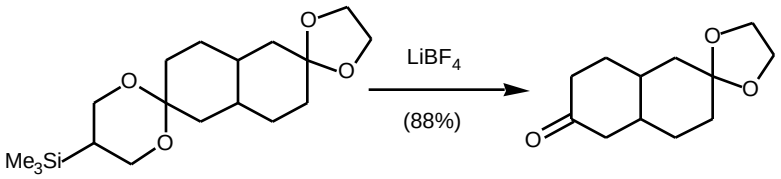
Chem. Rev. **1967**, *67* , 427.



- Ketal formation of α,β-unsaturated carbonyls are usually slower than for the saturated case.

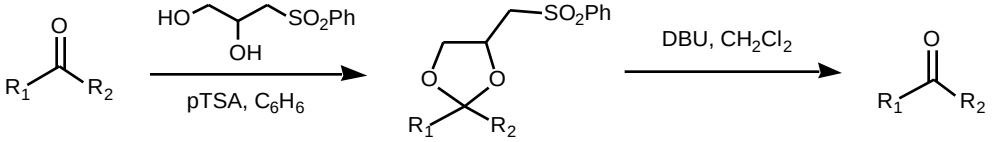


Fluoride cleavable ketal:



TL **1997**, *38*, 1873

Base cleavable ketal:



TL **1998**, *39*, 2401

Carboxylic Acids *Tetrahedron* **1980**, *36*, 2409. *Tetrahedron* **1993**, *49*, 3691

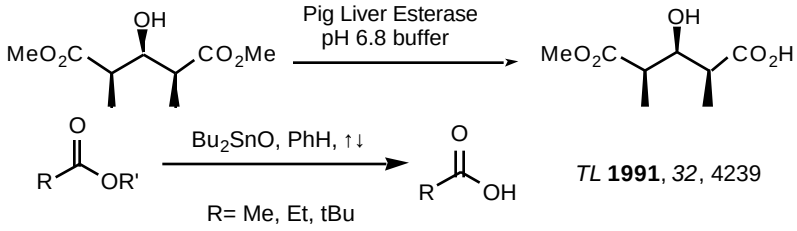
Nucelophilic Ester Cleavage: *Organic Reactions* **1976**, *24*, 187.

<u>*Esters*</u>

Alkyl Esters

formation:
- Fisher esterification (RCOOH +R'OH + H^+)
- Acid Chloride + R-OH, pyridine
- t-butyl esters: isobutylene and acid
- methyl esters: diazomethane

Cleavage:
- LiOH, THF, H_2O
- enzymatic hydrolysis *Org. Rxns.* **1989**, *37*, 1.
- t-butyl esters are cleaved with aqueous acid
- Bu_2SnO, PhH, reflux (TL **1991**, *32*, 4239)

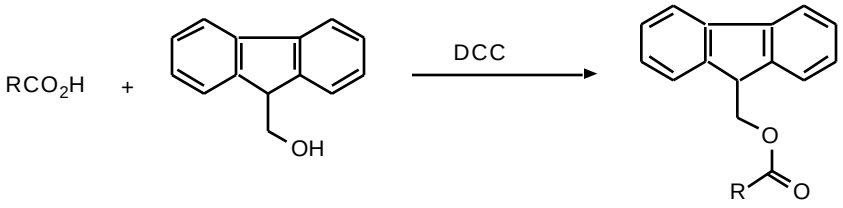


TL **1991**, *32*, 4239

9-Fluorenylmethyl Esters (Fm)

TL **1983**, *24* , 281

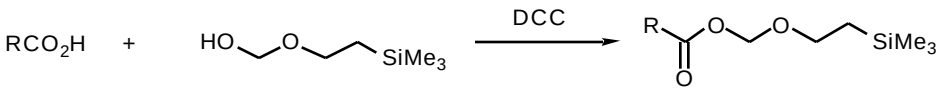
- cleaved with mild base (Et_2NH, piperidine)



2-Trimethylsilyl)ethoxymethyl Ester (SEM)

HCA **1977**, *60* , 2711.

- Cleaved with Bu_4NF in DMF

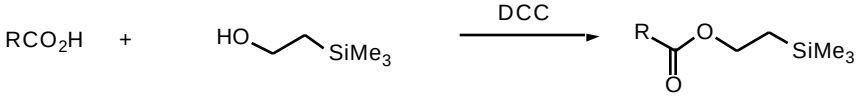


- Cleaved with MgBr2•OEt2 *TL* **1991**, *32*, 3099.

2-(Trimethylsilyl)ethyl Esters

JACS **1984**, *106* , 3030

- cleaved with Fluoride ion



Haloesters

- cleaved with Zn(0) dust or electrochemically

Benzyl Esters

$RCO_2H + PhCH_2OH \rightarrow RCO_2Bn$

Formation: - DCC
- Acid chloride and benzyl alcohol

Cleavage: - Hydrogenolysis
- Na, NH_3

Diphenylmethyl Esters

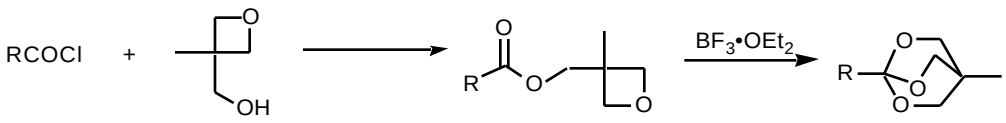
Cleavage: - mild H_3O^+
- H_2, Pd/C
- $BF_3 \bullet OEt_2$

o-Nitrobenzyl Esters

- selective removed by photolysis

Orthoesters *Synthesis* **1974**, 153 *Chem. Soc. Rev.* **1987**, 75

TL **1983**, *24* , 5571



- Stable to base; cleaved with mild acid

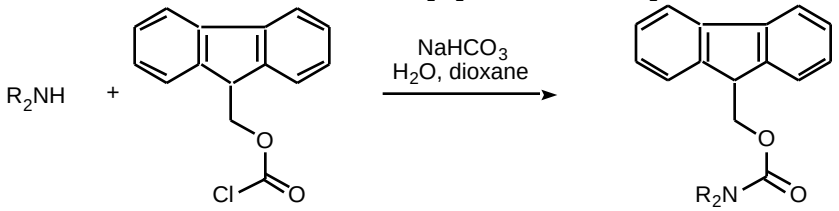
Amines

Carbamates

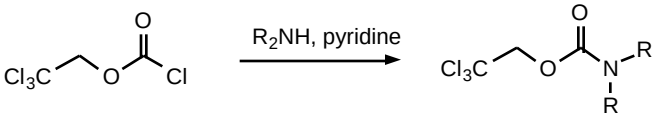
9-Fluorenylmethyl Carbamate (Fmoc)

Acc. Chem. Res. **1987**, *20* , 401

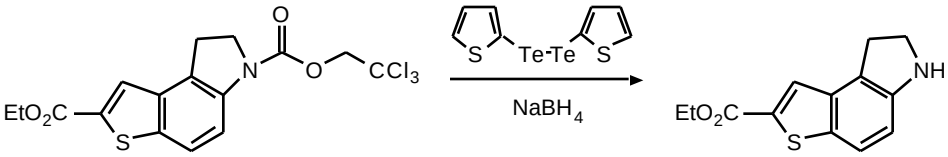
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



2,2,2-Trichloroethyl Carbamate



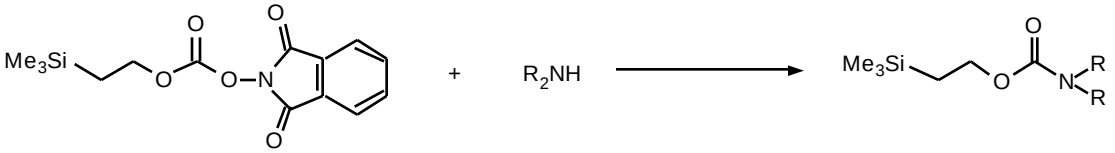
- Cleaved with zinc dust or electrochemically.

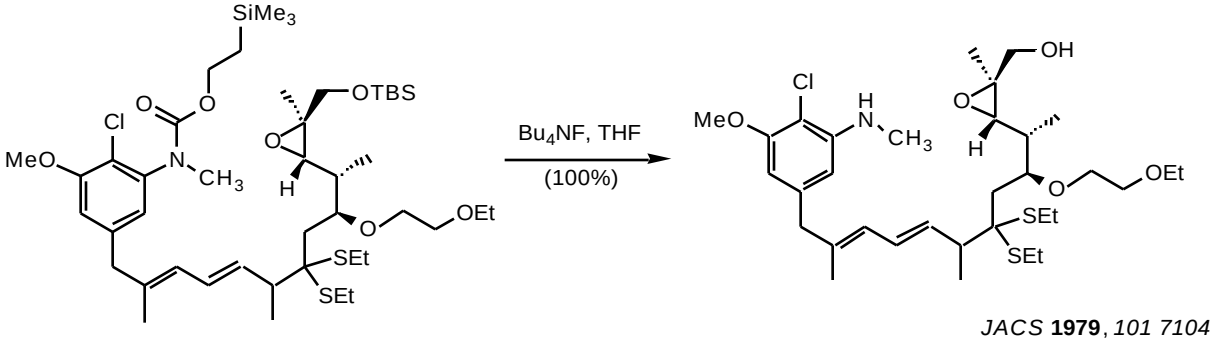


TL **1986**, *27* , 4687

2-Trimethylsilylethyl Carbamate (Teoc)

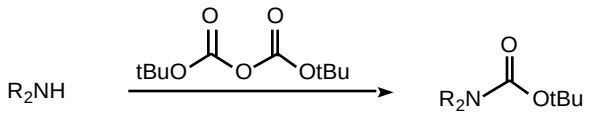
- cleaved with fluoride ion.





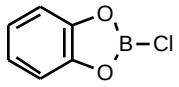
JACS **1979**, *101 7104*

t-Butyl Carbamate (BOC)



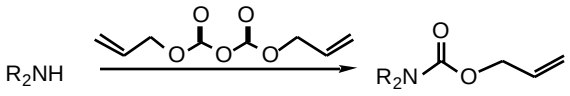
Cleavage: - with strong protic acid (3M HCl, CF_3COOH)

- TMS-I

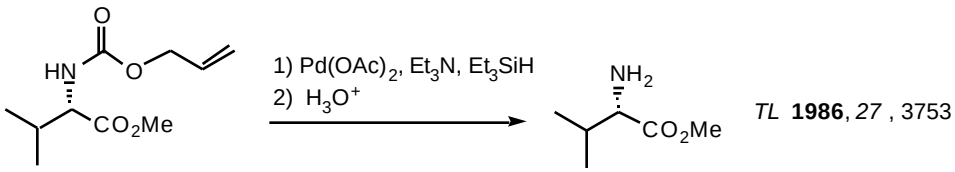
- 

TL **1985**, *26* , 1411

Allyl Carbamate (Alloc) *TL* **1986**, *27* , 3753

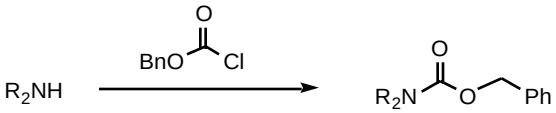


- removed with Pd(0) and a reducing agent (Bu_3SnH, Et_3SiH, HCO_2H)



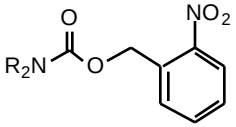
TL **1986**, *27* , 3753

Benzyl Carbanate (Cbz)



Cleavage:
- Hydrogenolysis
- $PdCl_2$, Et_3SiH
- TMS-I
- BBr_3
- hν (254 nm)
- Na / NH_3

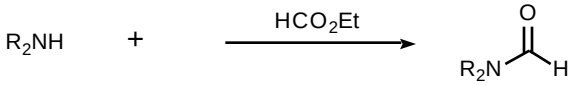
m-Nitrophenyl Carbamate
JOC **1974**, *39* , 192



- removed by photolysis

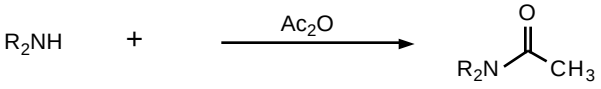
Amides
Formamides

- removed with strong acid

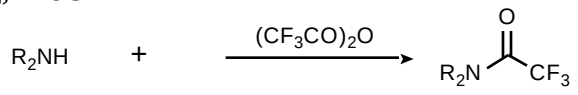


Acetamides

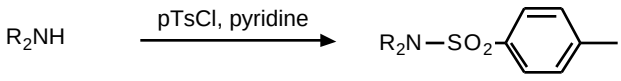
- removed with strong acid



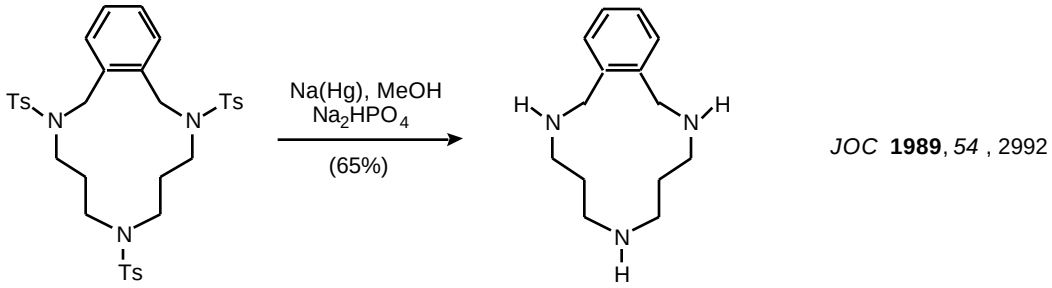
Trifluoroacetamides
Cleavage:
- base (K_2CO_3, MeOH, reflux)
- NH_3, MeOH



Sulfonamides
p-Toluenesulfonyl (Ts)

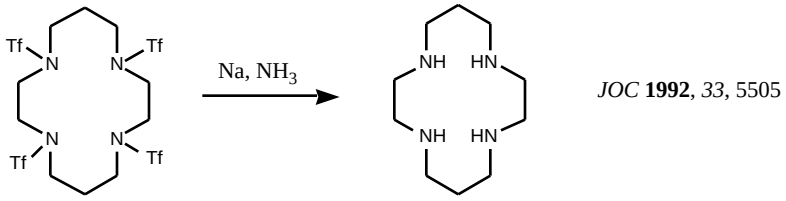


Cleavage: - Strong acid
- sodium Naphthalide
- Na(Hg)



JOC **1989**, *54* , 2992

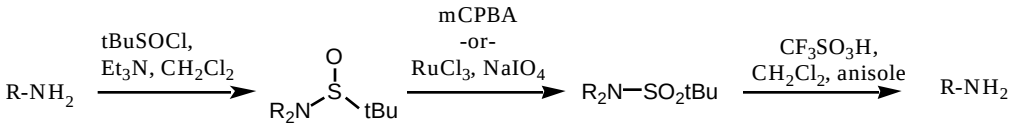
Trifluoromethanesulfonyl



JOC **1992**, *33*, 5505

Trimethylsilylethanesulfonamide (SES)
TL **1986**, *54* , 2990; *JOC* **1988**, *53*, 4143
- removed with CsF, DMF, 95°C

tert-Butylsulfonyl (Bus) *JOC* **1997**, *62*, 8604

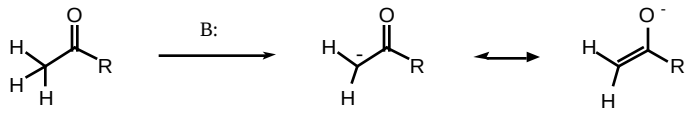


Carbon- Carbon Bond Formation

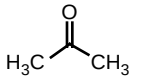
1. Alkylation of enolates, enamines and hydrazones
   C&S: Chapt. 1, 2.1, 2.2 problems Ch 1: 1; 2; 3, 7; 8a-d; 9; 14 Ch. 2: 1; 2; 4)
   Smith: Chapt. 9
2. Alkylation of heteroatom stabilized anions C&S :Chapt. 2.4 - 2.6)
3. Umpolung Smith: Chapt. 8.6
4. Organometallic Reagents
   C&S: Chapt. 7, 8, 9 problems ch 7: 1; 2; 3, 6; 13 Ch. 8: 1; 2
   Smith: Chapt. 8
5. Sigmatropic Rearrangements . C&S Chapt. 6.5, 6.6, 6.7 # 1e,f,h,op
   Smith Chapt. 11.12, 11.13

Enolates *Comprehensive Organic Synthesis* **1991**, vol. 2, 99.

- α-deprotonation of a ketone, aldehyde or ester by treatment with a strong non-nucleophillic base.
- carbonyl group stabilizes the resulting negative charge.

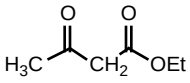


- Base is chosen so as to favor enolate formation. Acidity of C-H bond must be greater (lower pK_a value) than that of the conjugate acid of the base (C&S table 1.1, pg 3)


$pK_a = 20$

MeO^- $pK_a = 15$
$tBuO^-$ $pK_a = 19$

unfavorable enolate concentration

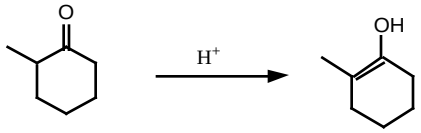

$pK_a = 10$

more favorable enolate concentration

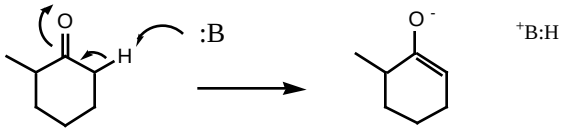
- Common bases: NaH, EtONa, tBuOK, $NaNH_2$, $LiNiPr_2$, M $N(SiMe_3)_2$, Na $CH_2S(O)CH_3$

Enolate Formation:

- H^+ Catalyzed (thermodynamic)

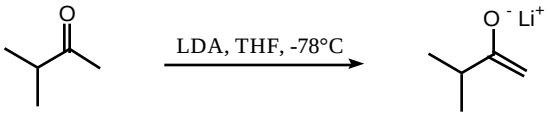


- Base induced (thermodynamic or kinetic)



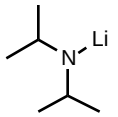
Regioselective Enolate Formation *Tetrahedron* **1976**, *32*, 2979.

- Kinetic enolate- deprotonation of the most accessable proton (relative rates of deprotonation). Reaction done under essentially irreversible conditions.

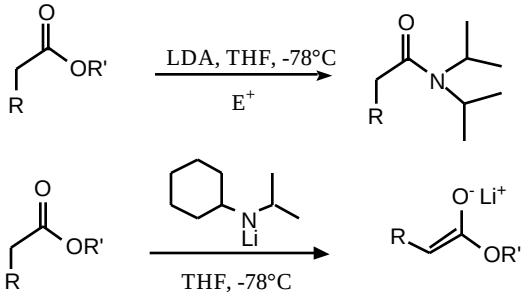


typical conditions: strong hindered (non-nucleophilic) base such as LDA

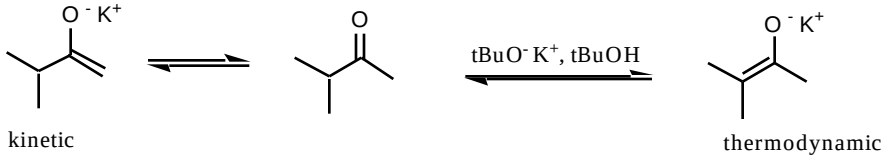
R_2NH pKa= ~30



Ester Enolates- Esters are susceptible to substitution by the base, even LDA can be problematic. Use very hindered non-nucleophillic base (Li isopropylcyclohexyl amide)

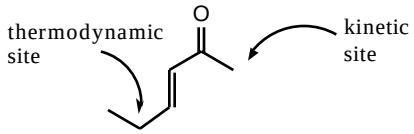


- Thermodynamic Enolate- Reversible deprotonation to give the most stable enolate: more highly substituted C=C of the enol form



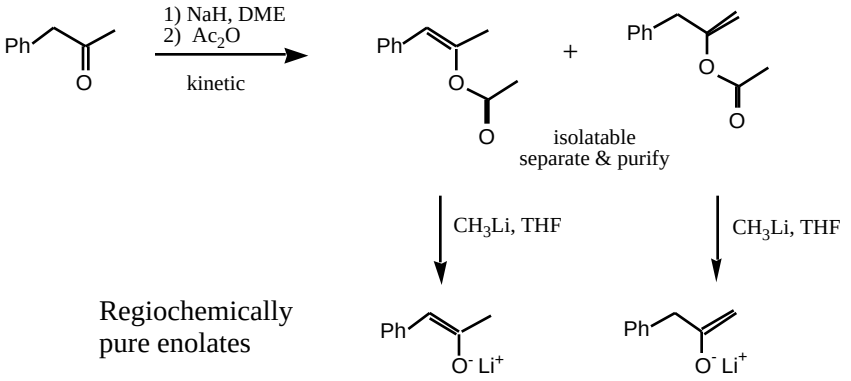
typical conditions: $RO^- M^+$ in ROH , protic solvent allows reversible enolate formation. Enolate in small concentration (pKa of ROH= 15-18 range)

- note: the kinetic and thermodynamic enolate in some cases may be the same
- for α,β-unsaturated ketones

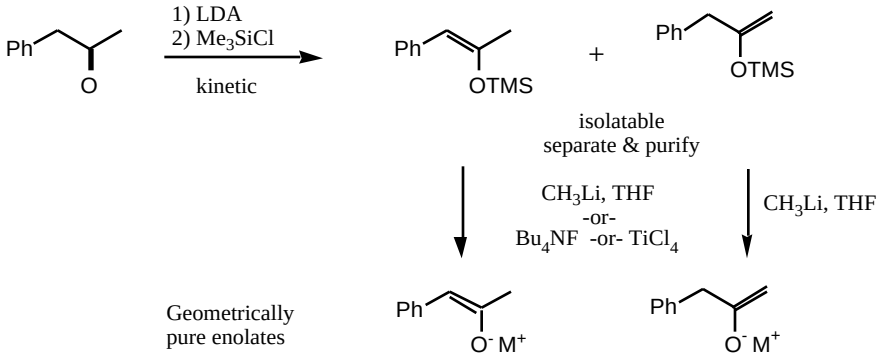


Trapping of Kinetic Enolates

- enol acetates

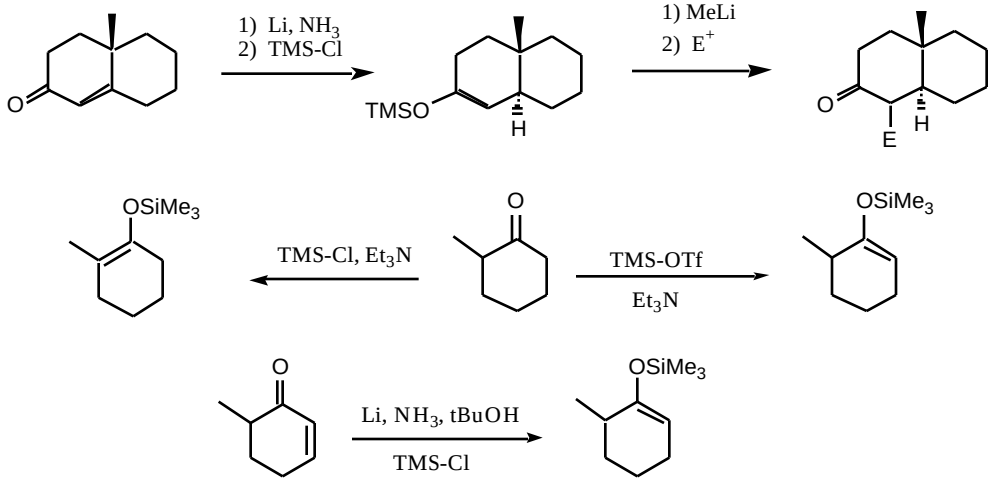


- silyl enolethers *Synthesis* **1977**, 91. *Acc. Chem. Res.* **1985**, *18*, 181.

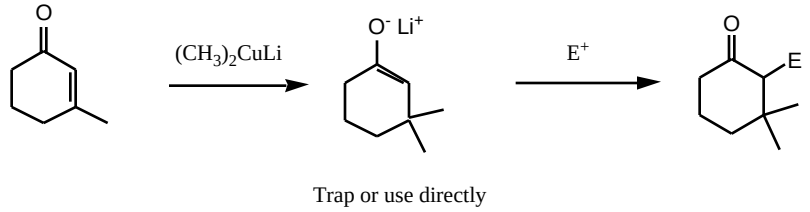


- tetraalkylammonium enolates- "naked" enolates
- TMS silyl enol ethers are labile: can also use Et_3Si-, iPr_3Si- etc.
- Silyl enol ether formation with R_3SiCl+ Et_3N gives thermodyanamic silyl enol ether

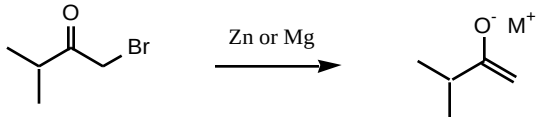
- From Enones



- From conjugate (1,4-) additions

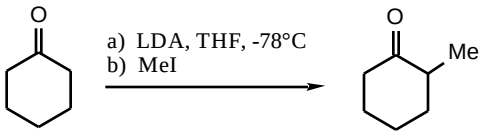


- From reduction of α-halo carbonyls

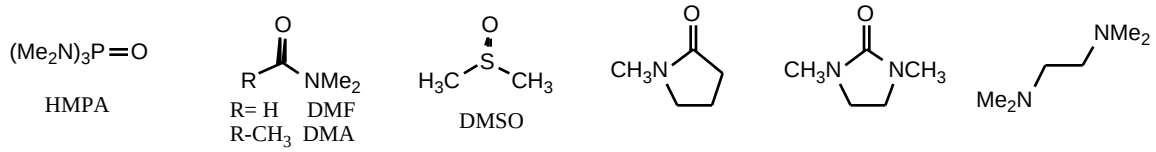


Alkylation of Enolates (condensation of enolates with alkyl halides and epoxides)
Comprehensive Organic Synthesis **1991**, vol. 3, 1.

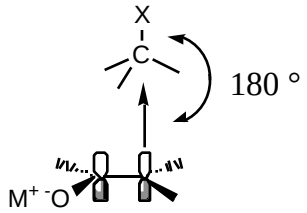
1° alkyl halides, allylic and benzylic halides work well
2° alkyl halides can be troublesome
3° alkyl halides don't work



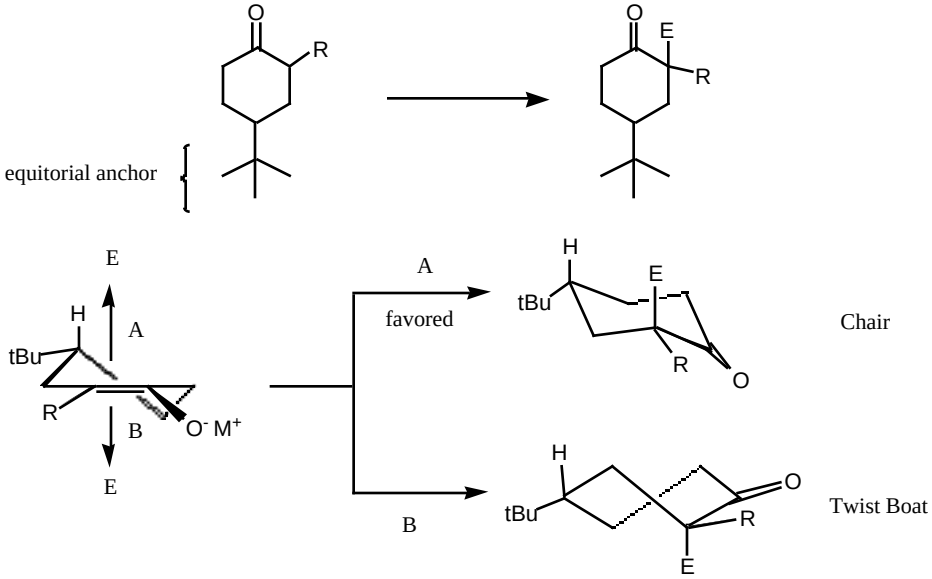
- Rate of alkylation is increased in more polar solvents (or addition of additive)



Mechanism of Enolate Alkylation: SN2 reaction, inversion of electrophile stereochemistry

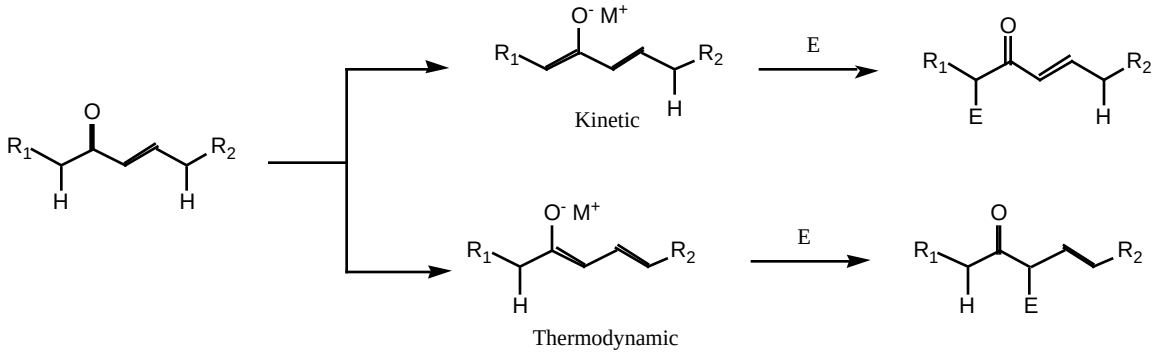


Alkylation of 4-t-butylcyclohexanone:



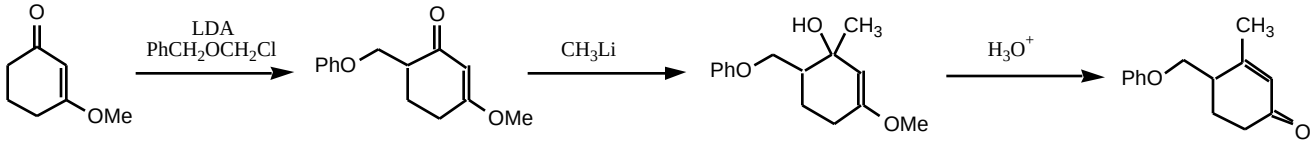
on cyclohexanone enolates, the electrophile approaches from an "axial" trajectory. This approach leads directly into a chair-like product. "Equitorial apprach leads to a higher energy twist-boat conformation.

Alkylation of α,β-unsaturated carbonyls



Stork-Danheiser Enone Transposition:

- overall γ-alkylation of an α,β-unsaturated ketone

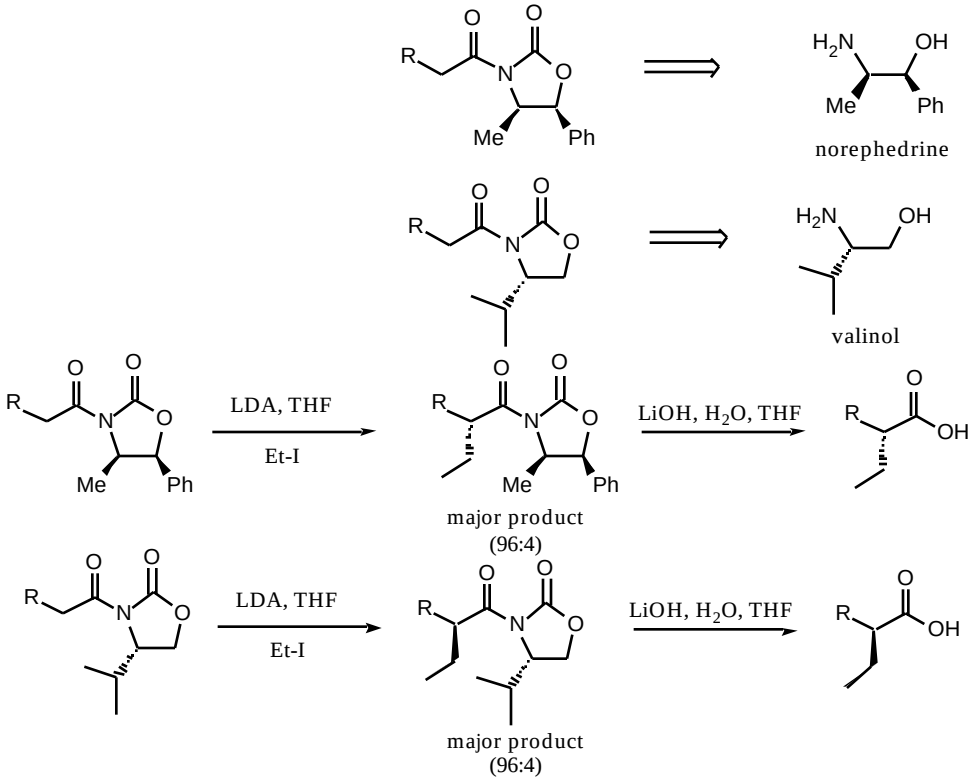


J. Org. Chem. **1995**, *60*, 7837.

Chiral enolates- Chiral auxilaries.

D.A. Evans *JACS* **1982**, *104* , 1737; *Aldrichimica Acta* **1982**,*15* , 23.
Asymmetric Synthesis **1984**, *3*, 1.

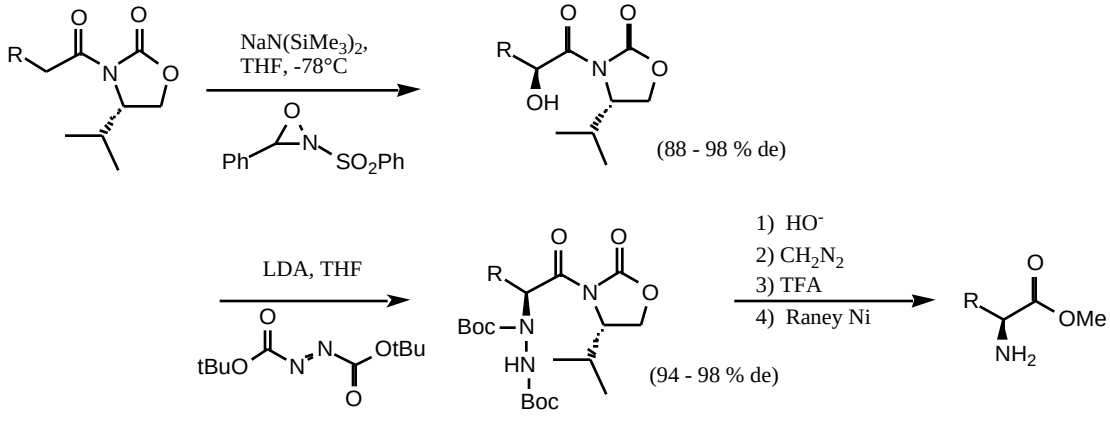
- N-Acyl oxazolidinones

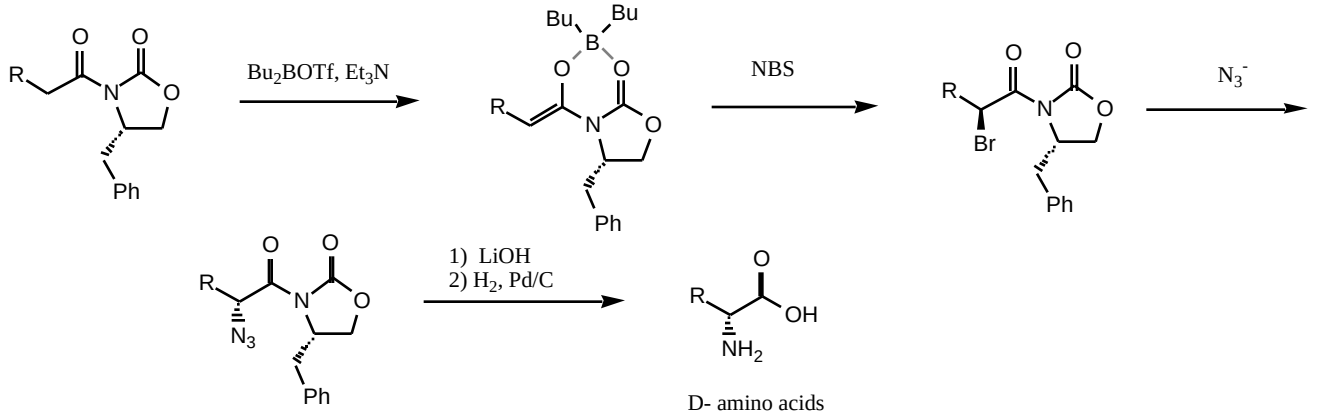


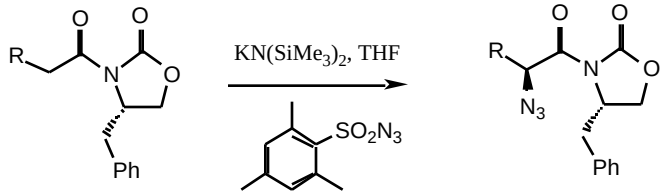
Complimentary Methods
for enantiospecific alkylations

Diastereoselectivity: 92 - 98 %
for most alkyl halides

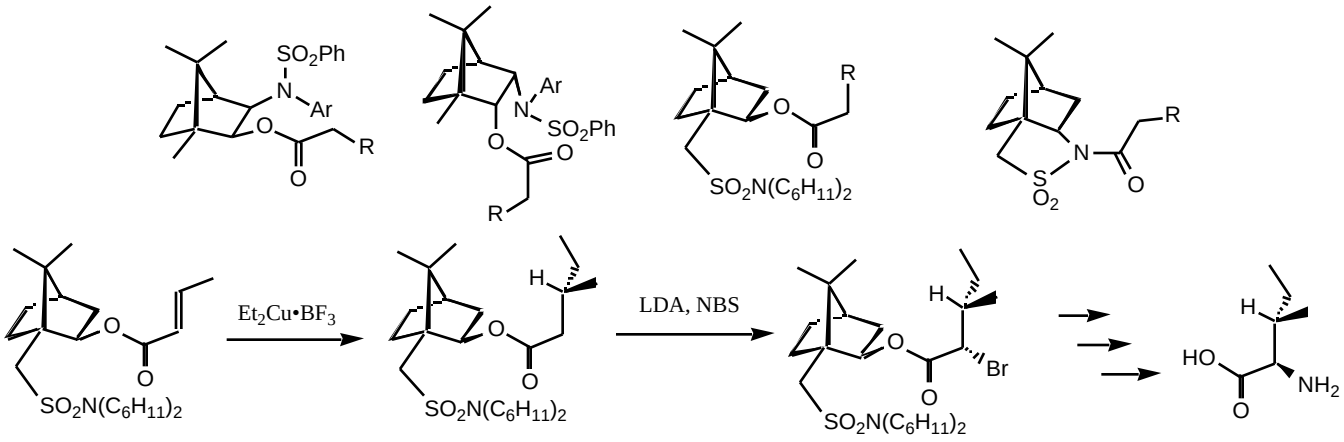
Enolate Oxidation *Chem. Rev.* **1992**, *92*, 919.



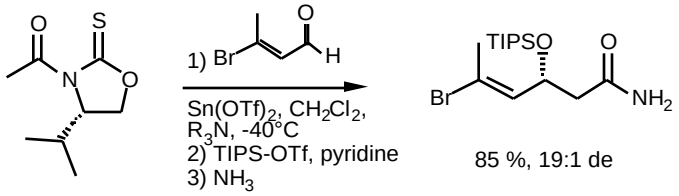




Oppolzer Camphor based auxillaries *Tetrahedron*, **1987**, *43*, 1969.
diastereoselectivities on the order of 50 : 1

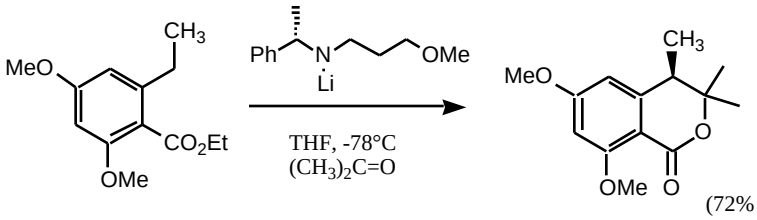


Asymmetric Acetate Aldol

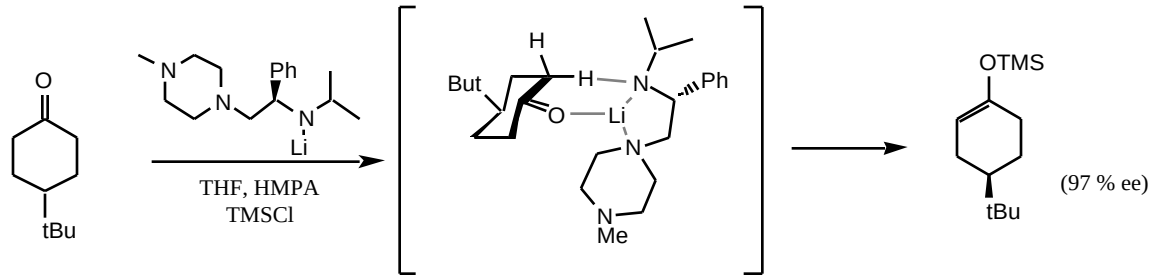


J. Am. Chem. Soc. **1998**, *120*, 591
J. Org. Chem. **1986**, *51*, 2391

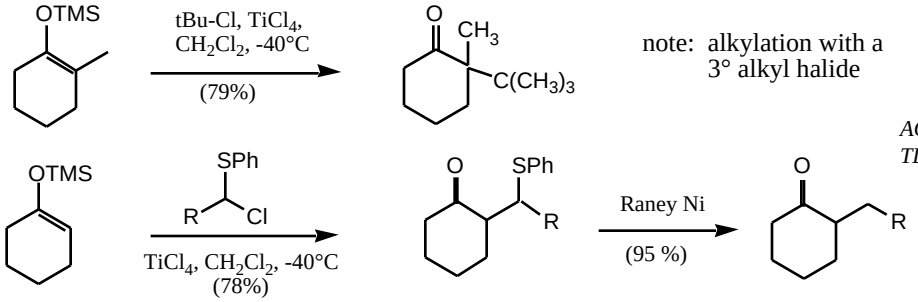
Chiral lithium amide basess



(72% ee)

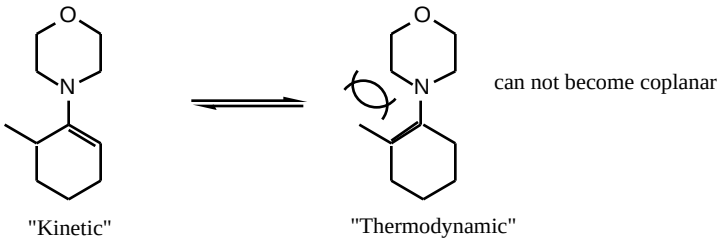


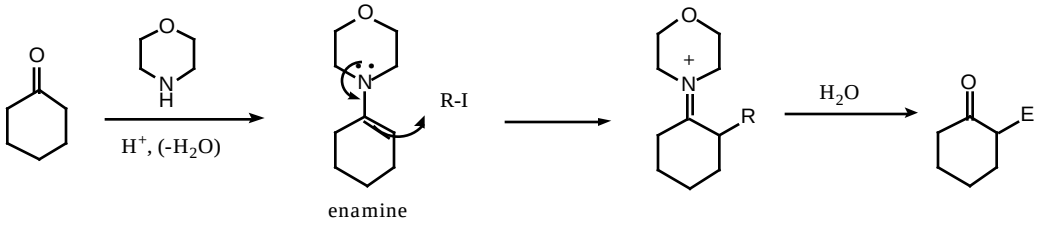
Lewis Acid Mediated Alkylation of Silyl Enolethers- SN1 like alkylations



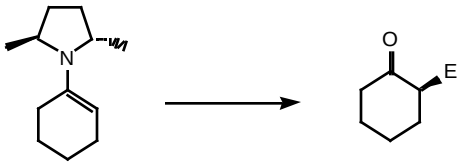
Enamines Gilbert Stork *Tetrahedron* **1982**, *38*, 1975, 3363.

- Advantages: mono-alkylation, usually gives product from kinetic enolization

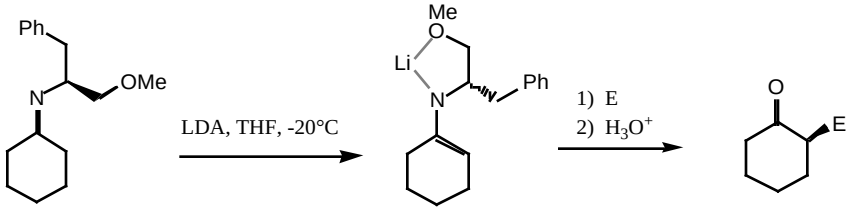




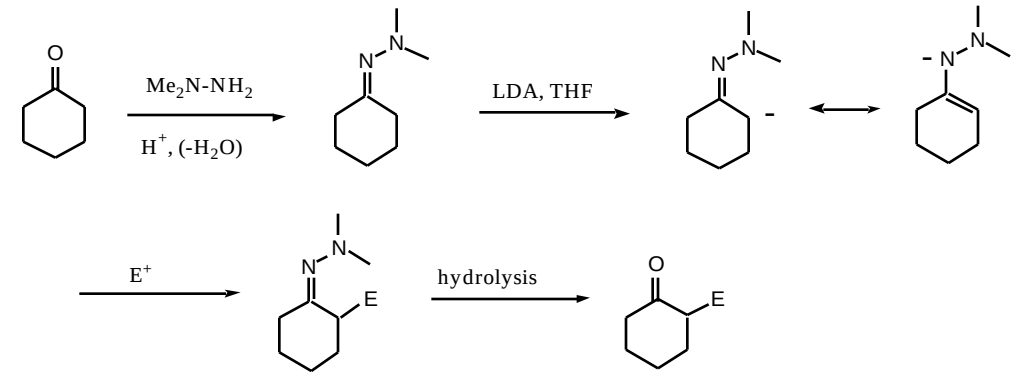
-Chiral enamines



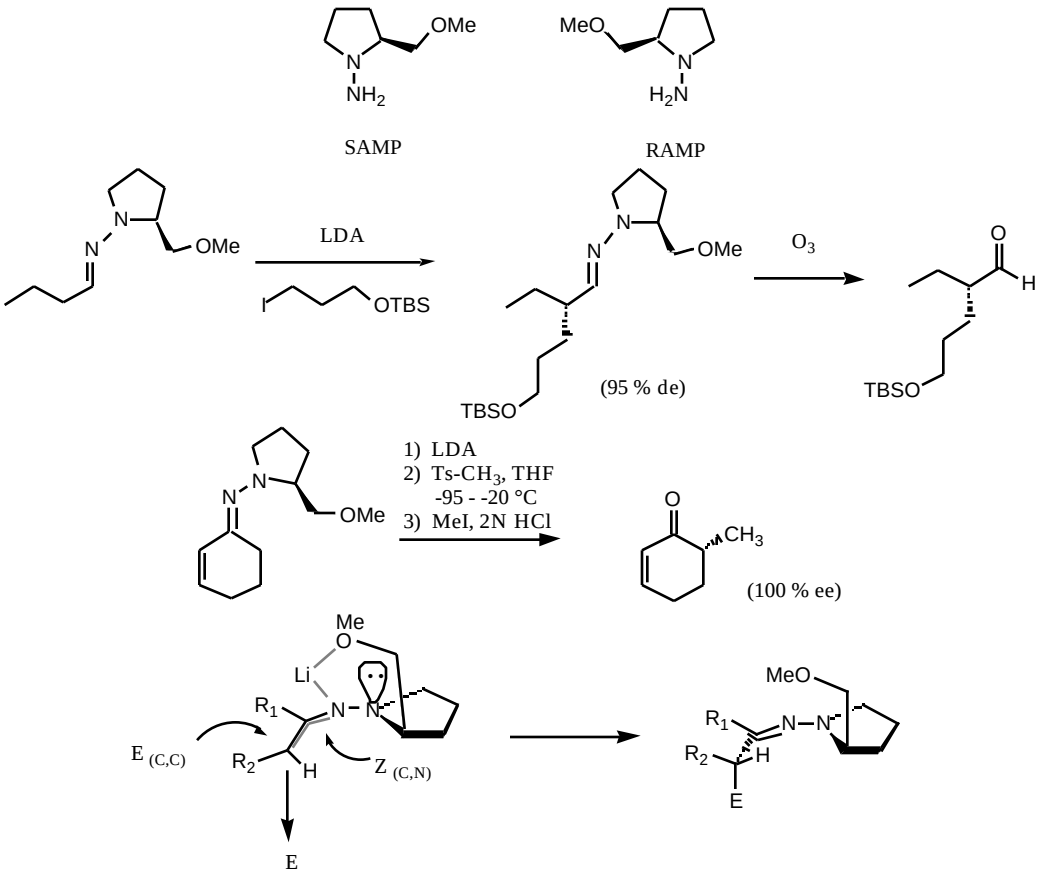
Imines Isoelectronic with ketones



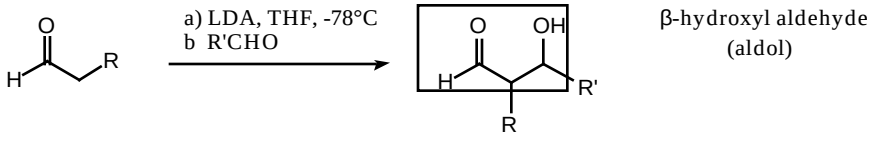
Hydrazones isoelectronic with ketones *Comprehensive Organic Synthesis* **1991**, *2*, 503



- Hydrazone anions are more reactive than the corresponding ketone or aldehyde enolate.
- Drawback: can be difficult to hydrolyze.
- Chiral hydrazones for asymmetric alkylations (RAMP/SAMP hydrazones- D. Enders "Asymmetric Synthesis" vol 3, chapt 4, Academic Press; **1983**)

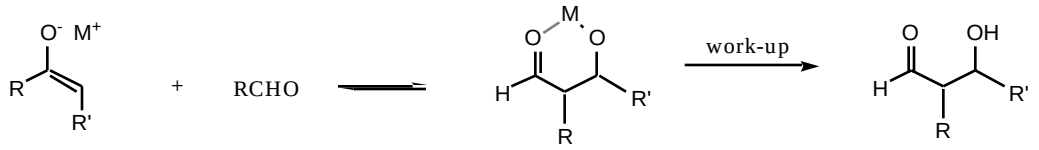


Aldol Condensation *Comprehensive Organic Synthesis* **1991**, *2*, 133, 181.

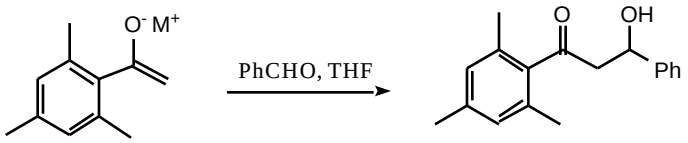


- The effects of the counterion on the reactivity of the enolates can be important
  Reactivity $Li^+ < Na^+ < K^+ < R_4N^+$ addition of crown ethers

- The aldol reaction is an equilibrium which can be "driven" to completion.

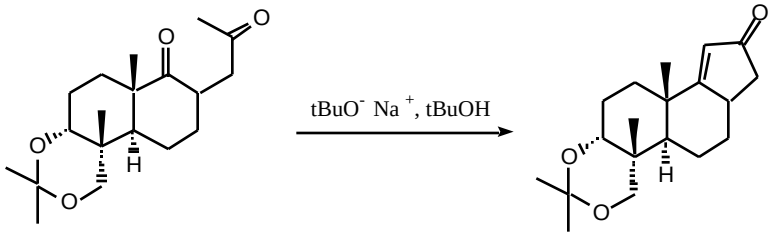


In the case of hindered enolates, the equillibrium favors reactants. Mg^{2+} and Zn^{2+} counterions will stabilize the intermediate β-alkoxycarbonyl and push the equillibrium towards products. (*JACS* **1973**, *95*, 3310)



M= Li 16% yield
M= MgBr 93% yield

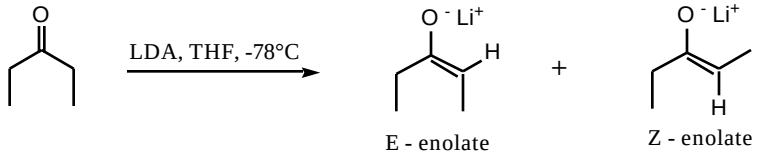
- Dehydration of the intermediate β-alkoxy- or β-hydroxy ketone can also serve to drive the reaction to the right.



JACS **1979**, *101* , 1330

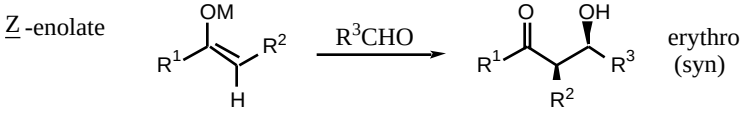
Enolate Geometry

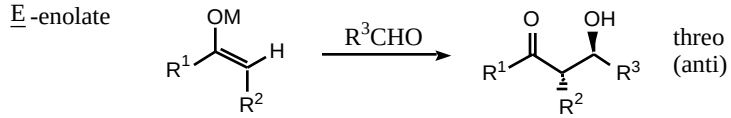
- two possible enolate geometries



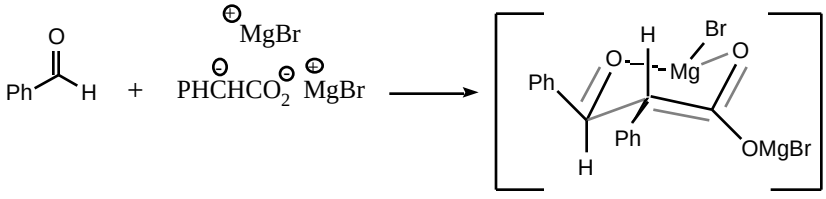
E - enolate Z - enolate

- enolate geometry plays a major role in stereoselection.



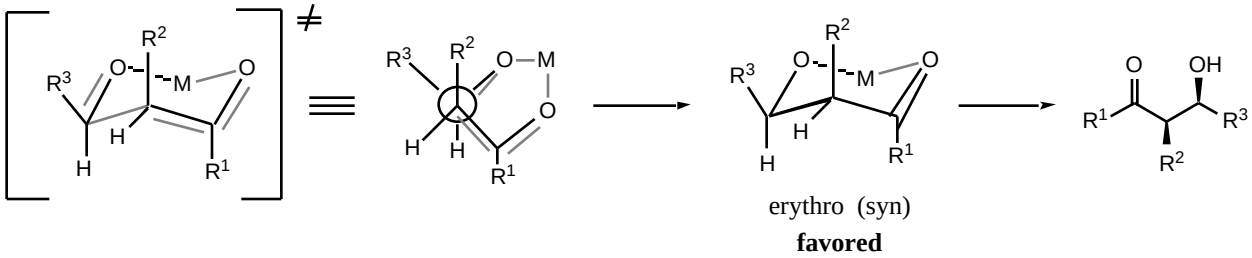


- Zimmerman-Traxler Transition State : Ivanov condensation
  JACS **1957**, *79* , 1920.

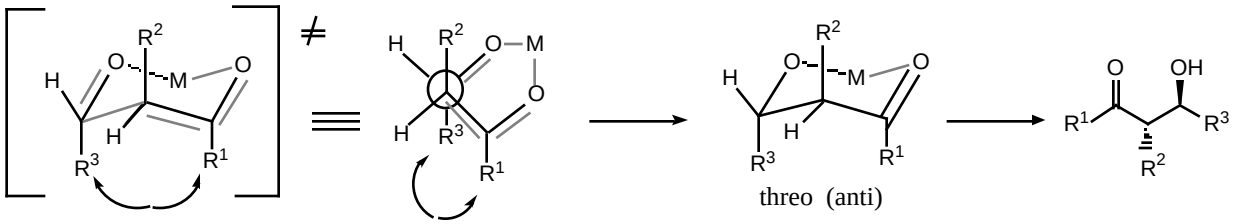


"pericyclic" T.S.

Analysis of Z-enolate stereoselectivity

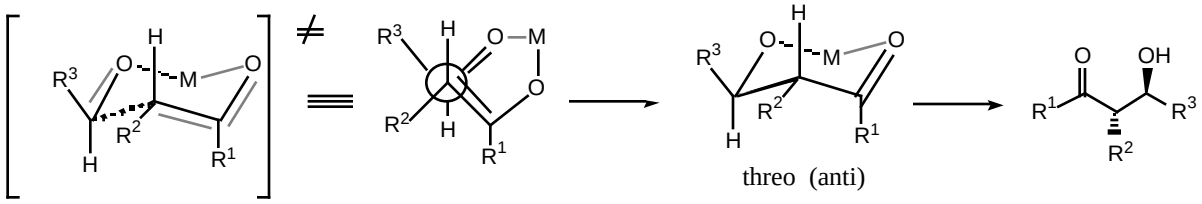


erythro (syn)
favored

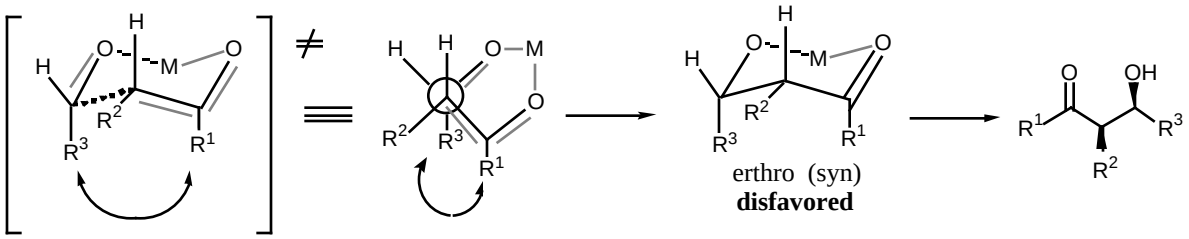


threo (anti)
disfavored

Analysis of E-enolate stereoselectivity

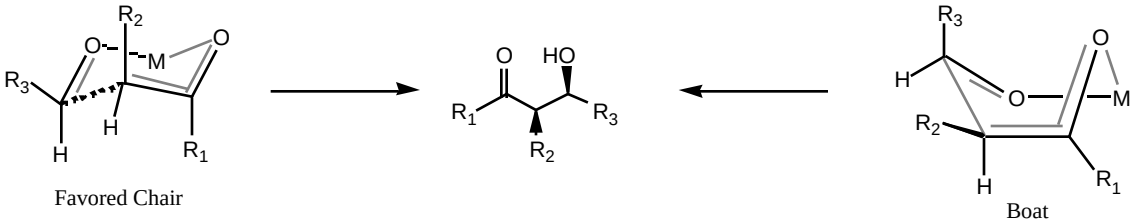


threo (anti)
favored



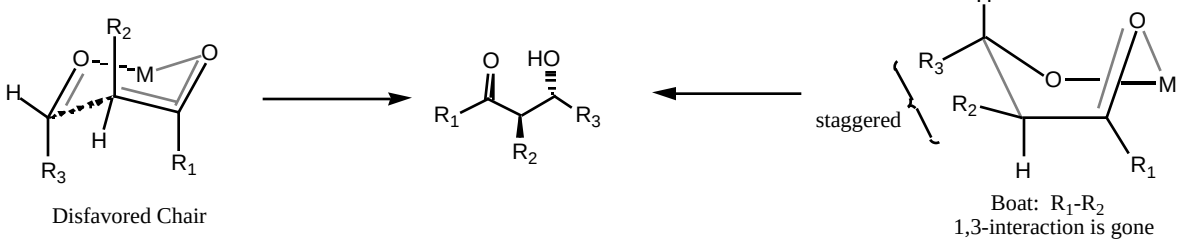
erthro (syn)
disfavored

Analysis of Boat Transition State for Z-Enolates



Favored Chair

Boat

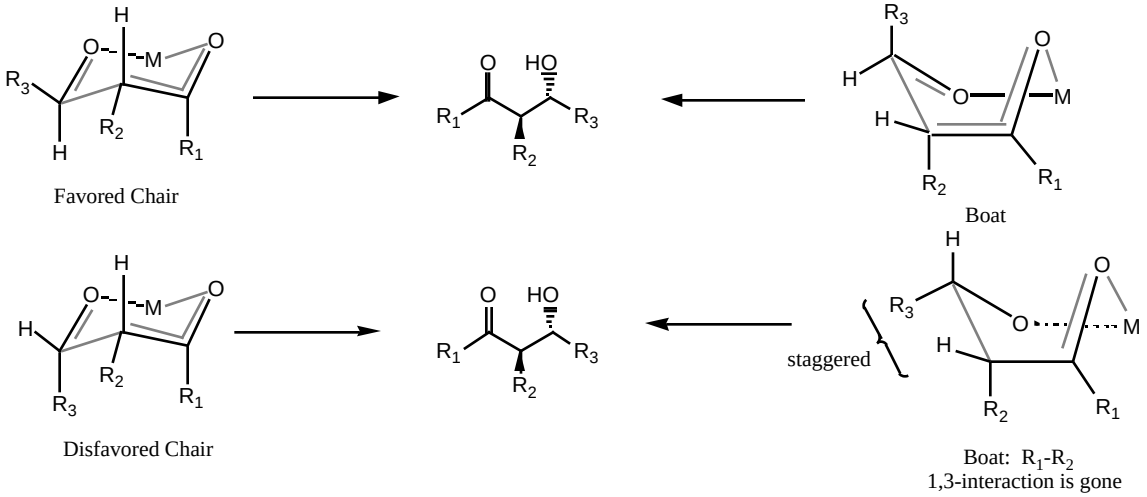


Disfavored Chair

staggered

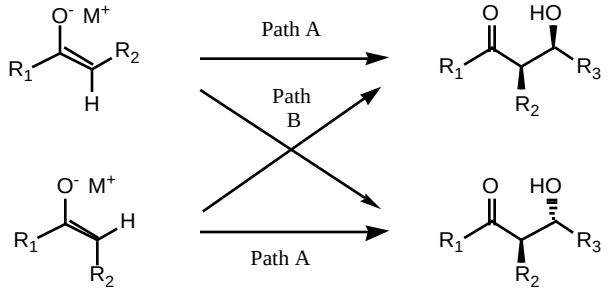
Boat: R_1-R_2
1,3-interaction is gone

Analysis of Boat Transition State for E-Enolates



Summary of Aldol Transition State Analysis:

1. Enolate geometry (E- or Z-) is an important stereochemical aspect. Z-Enolates usually give a higher degree of stereoselection than E-enolates.
2. Li^{+}, Mg^{2+}, Al^{3+}= enolates give comparable levels of diastereoselection for kinetic aldol reactions.
3. Steric influences of enolate substituents (R_1 & R_2) play a dominent role in kinetic diastereoselection.



When R_1 is the dominent steric influence, then path A proceeds. If R_2 is the dominent steric influence then path B proceeds.

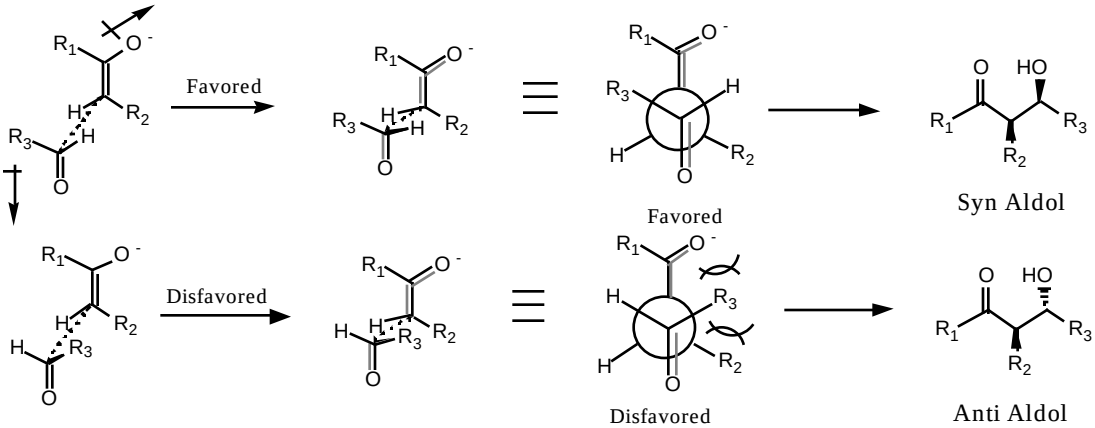
4. The Zimmerman-Traxler like transition state model can involve either a chair or boat geometry.

Noyori "Open" Transition State for non-Chelation Control Aldols

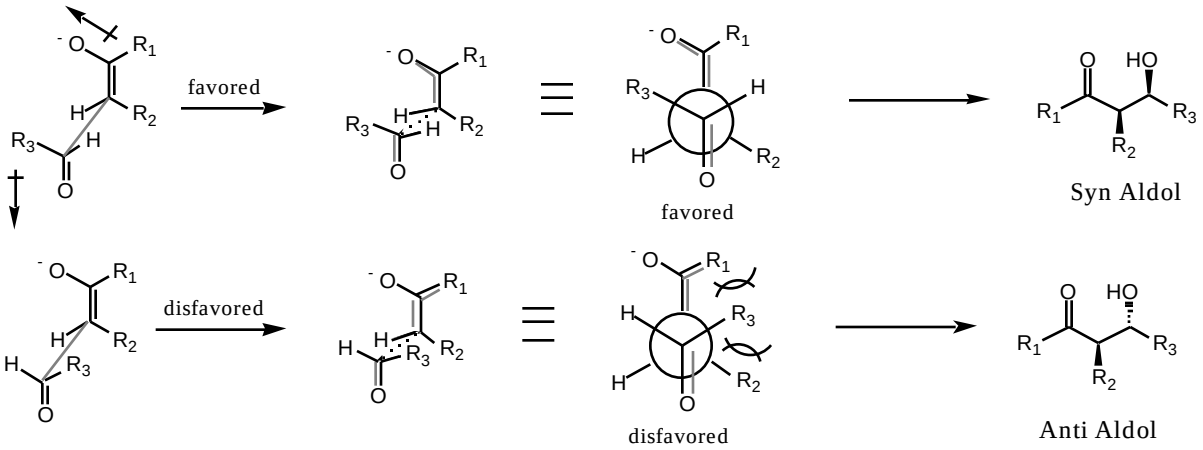
Absence of a binding counterion. Typical counter ions: R_4N^{+}, K^{+} / 18-C-6, Cp_2Zr^{2+}

- Non-chelation aldol reactions proceed via an "open" transition state to give syn aldols regardless of enolate geometry.

Z- Enolates:

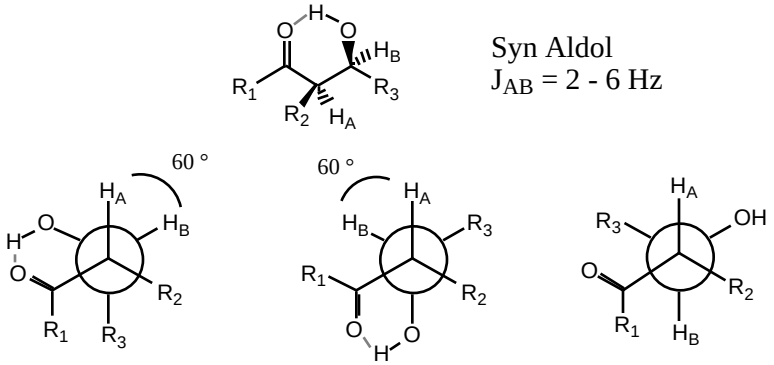


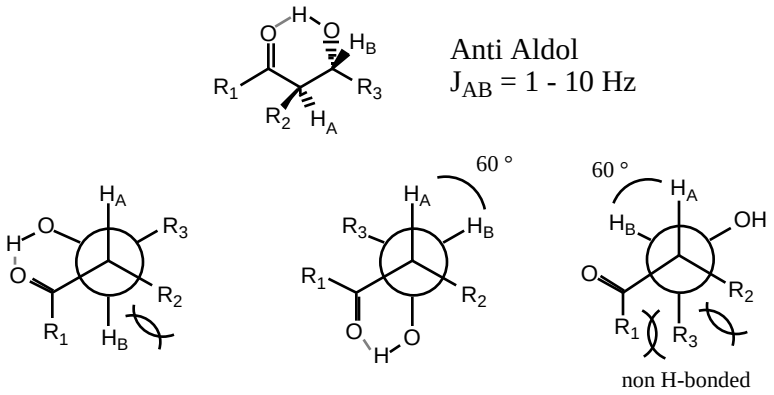
E- Enolate:



NMR Stereochemical Assignment.

Coupling constants (J) are a weighted average of various conformations.

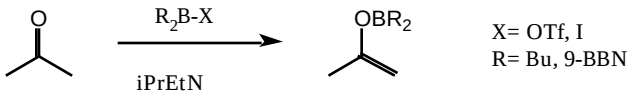


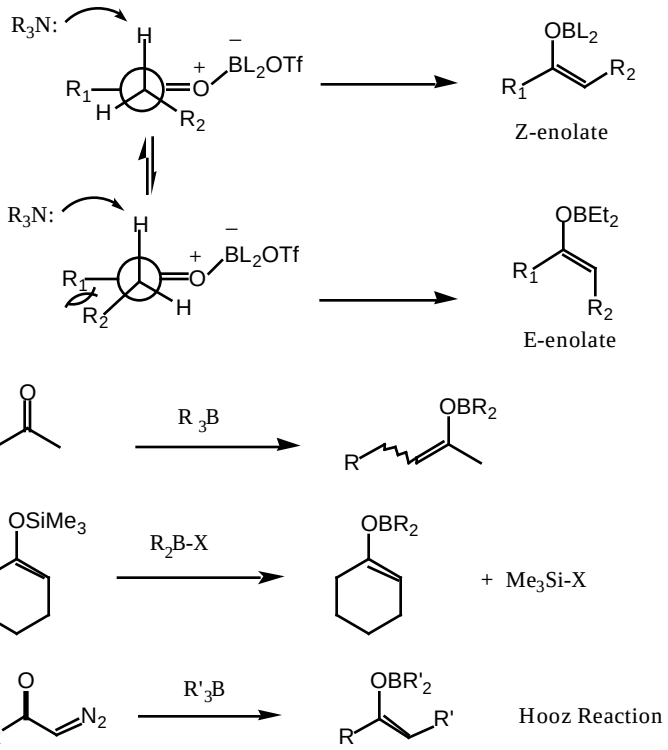


Boron Enolates: *Comprehensive Organic Synthesis* **1991**, *2*, 239. *Organic Reactions* **1995**, *46*, 1; *Organic Reactions* **1997**, *51*, 1. *OPPI* **1994**, *26*, 3.

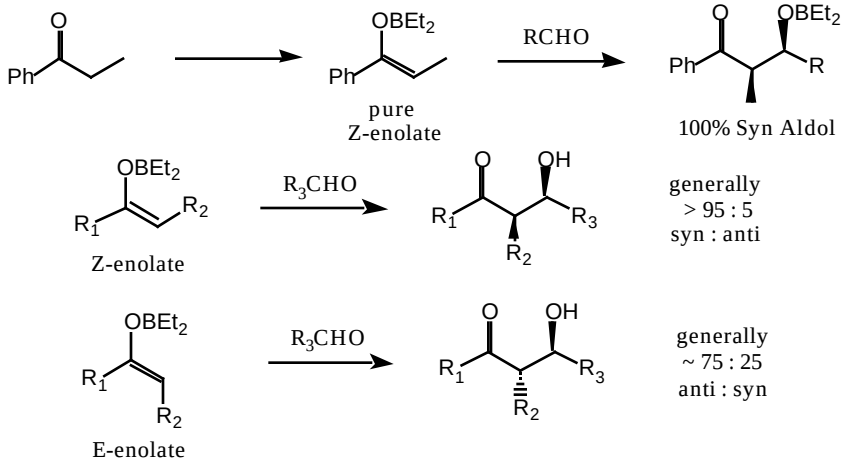
- Alkali & alkaline earth metal enolates tend to be aggregates- complicates stereoselection models.
- Boron enolates are monomeric and homogeneous
- B-O and B-C bonds are shorter and stronger than the corresponding Li-O abd Li-C bonds (more covalent character)- therefore tighter more organized transition state.

Generation of Boron Enolates:





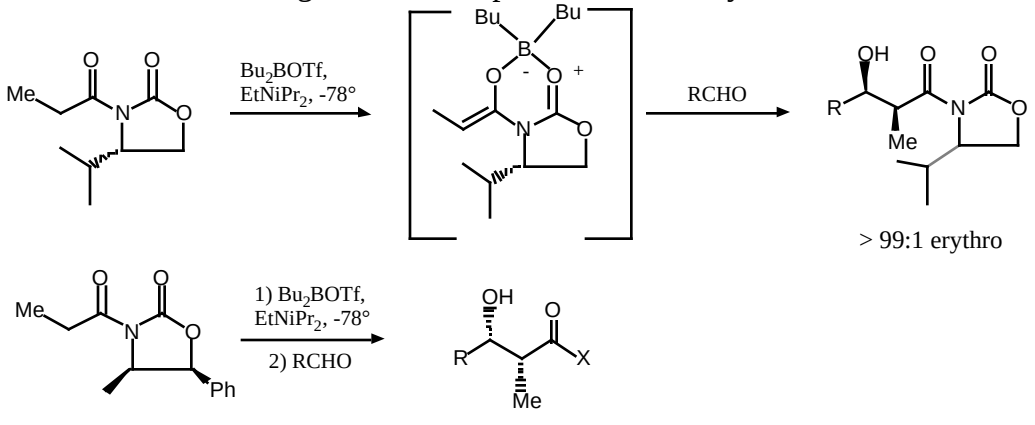
Diastereoselective Aldol Condensation with Boron Enolates

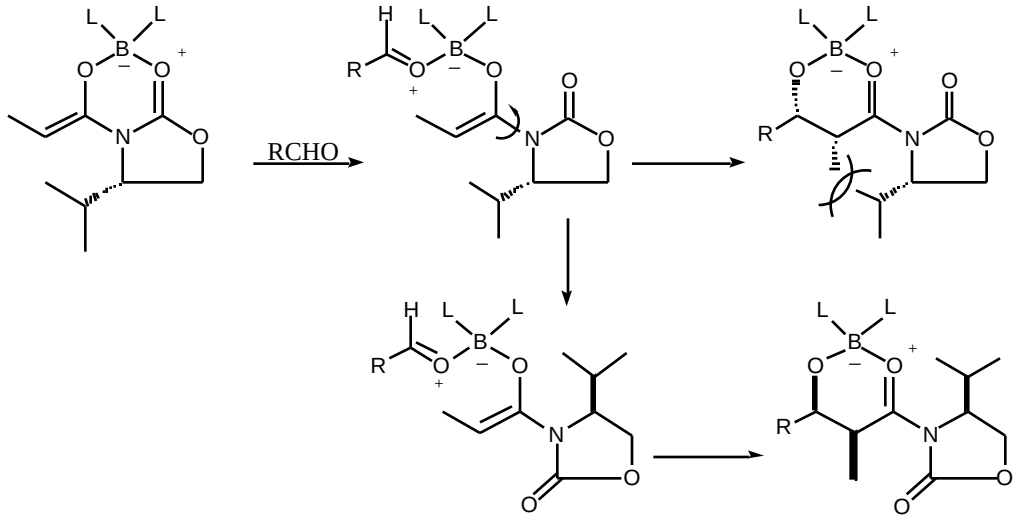


Asymmetric Aldol Condansations with Chiral Auxilaries-

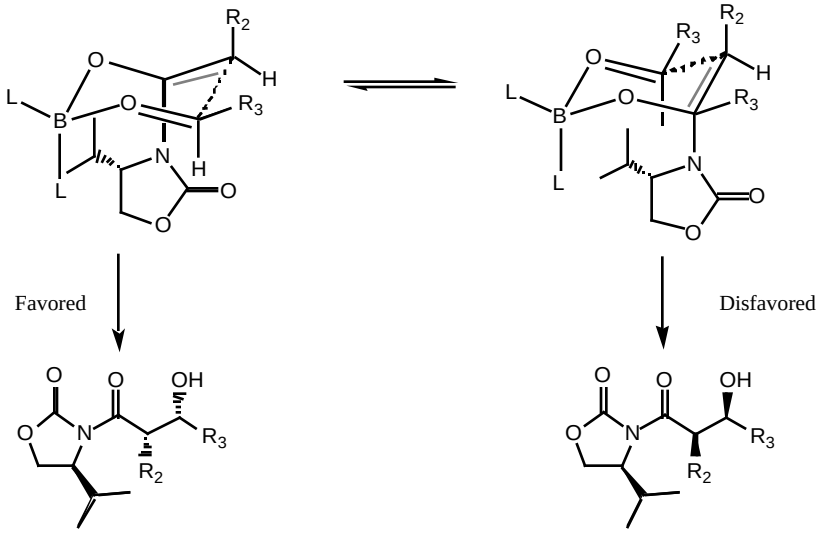
D.A. Evans et al. *Topics in Stereochemistry*, **1982**, *13* , 1-115.

- Li^+ enolates give poor selectivity (1:1)
- Boron and tin enolates give much improved selectivity

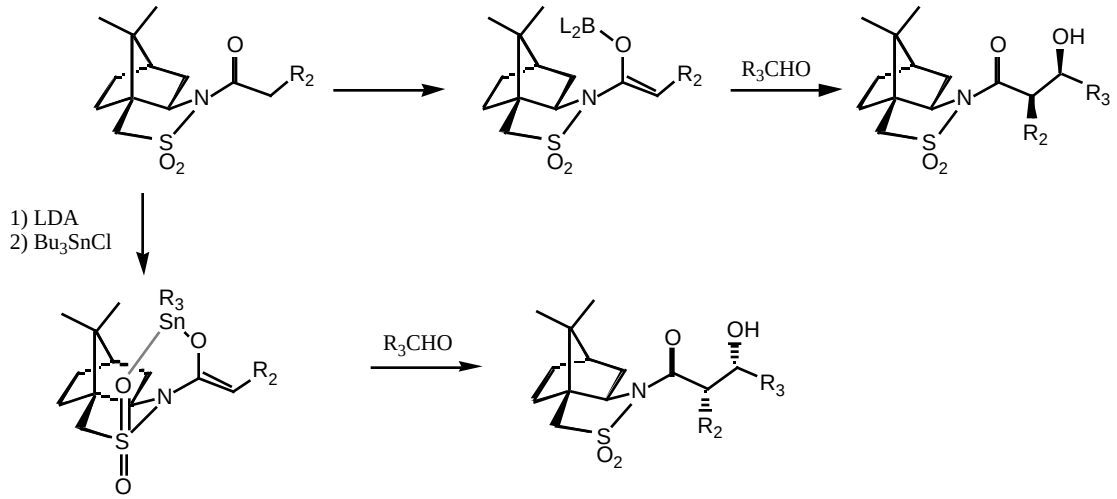




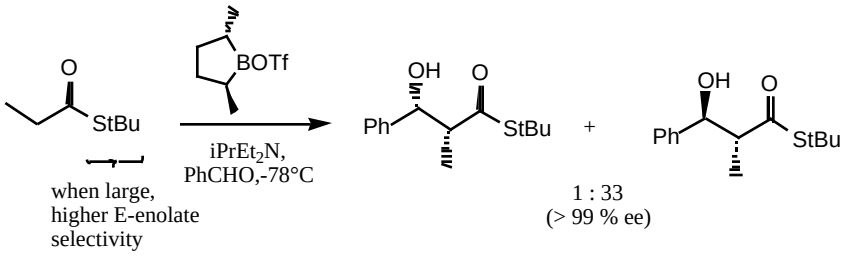
preferred conformation

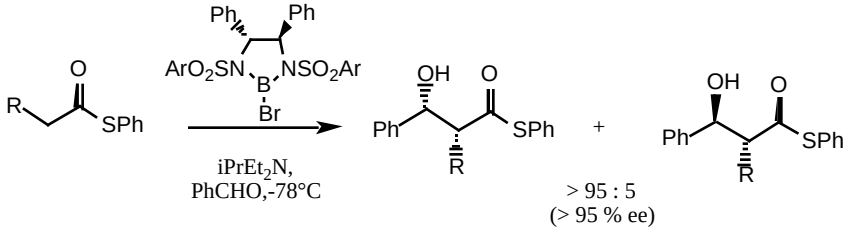


Oppolzer Sultam



Chiral Boron

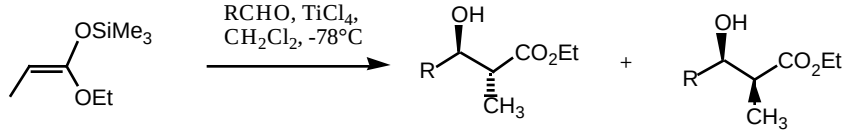




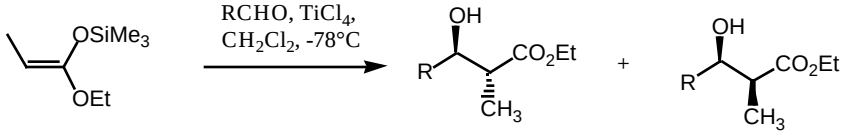
• In general, syn aldol products are achievable with high selectivity, anti aldols are more difficult

Mukaiyama-Aldol- Silyl Enol Ethers as an enolate precursors.

Lewis acid promoted condensation of silyl ketene acetals (ester enolate equiv.) with aldehydes: proceeds via "open" transition state to give anti aldols starting from either E- or Z- enolates.

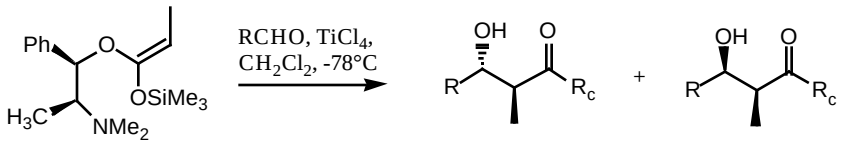


R= iPr (anti : syn) = 100 : 0
C_6H_{11} 94 : 6
Ph 75 : 25



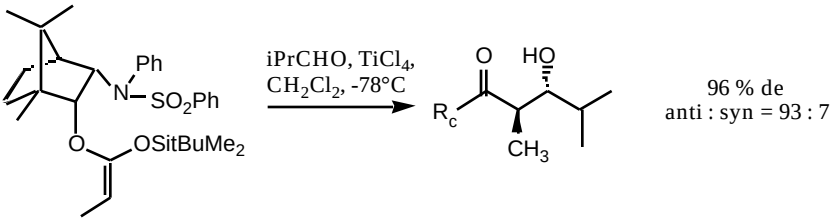
R= iPr (anti : syn) = 52 : 48
C_6H_{11} 63 : 37
Ph 67 : 33

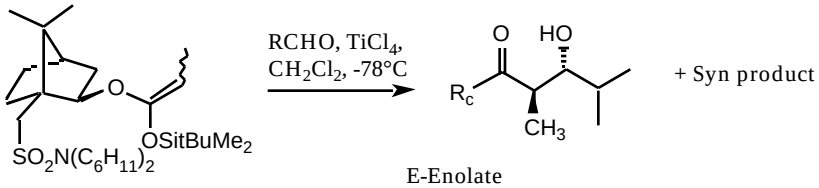
Asymmetric Mukiayama Aldol:



(90-94% de)

syn : anti = 85 : 15
selectivity insenstivie to enolate geometry





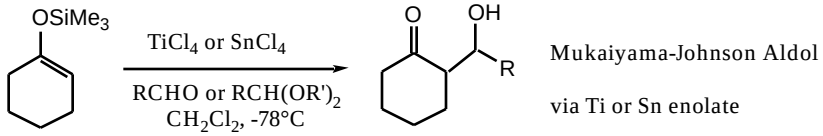
E-Enolate

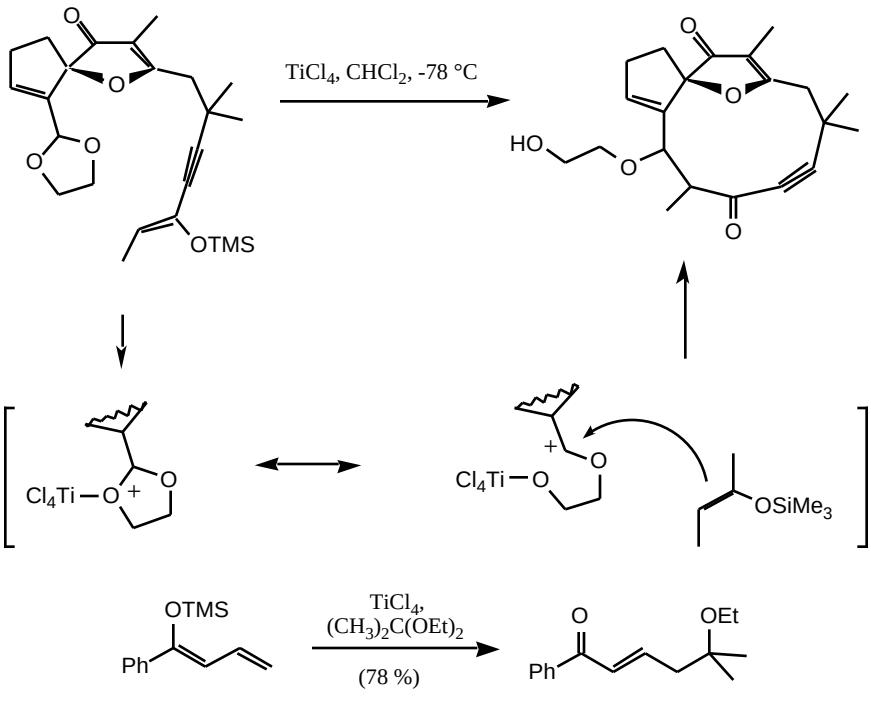
R= Ph	% de= 90	anti : syn = 91 : 19	
nPr	85	94 : 6	
iPr	85	98 : 2	

Z-Enolate

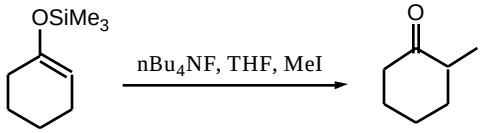
R= iPr	% de= 87	anti : syn = 97 : 7

Mukaiyama-Johnson Aldol- Lewis acid promoted condensation of silyl enol ethers with acetals:

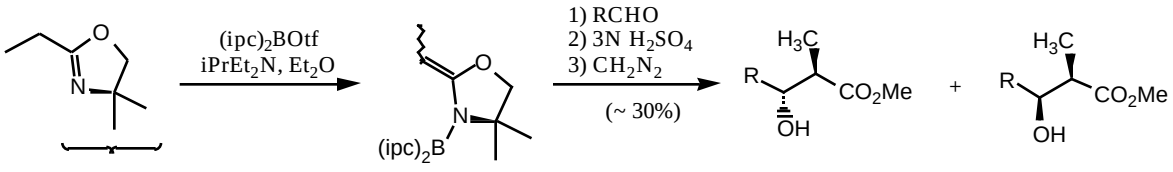




Fluoride promoted alkylation of silyl enol ethers *Acc. Chem. Res.* **1985**, *18*, 181

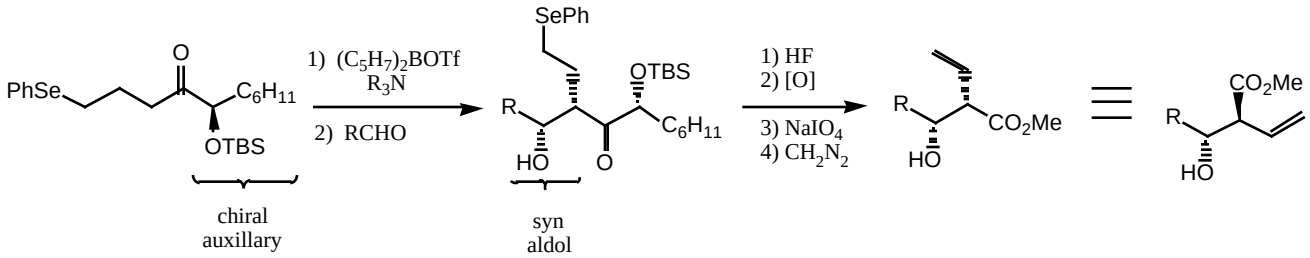


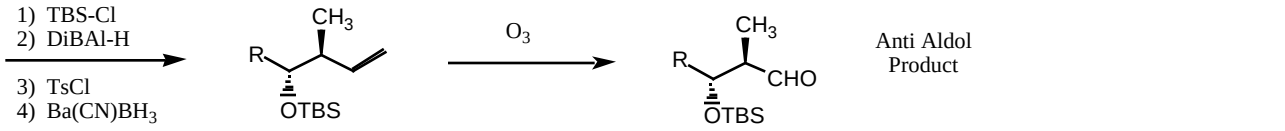
Meyer's Oxazolines:

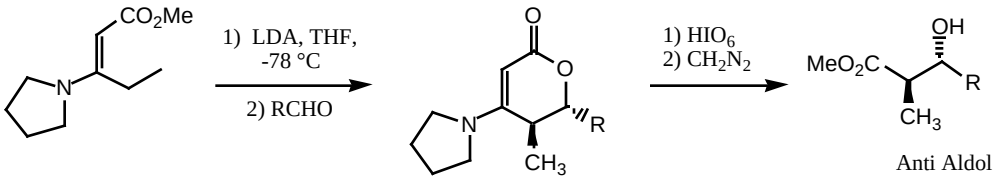


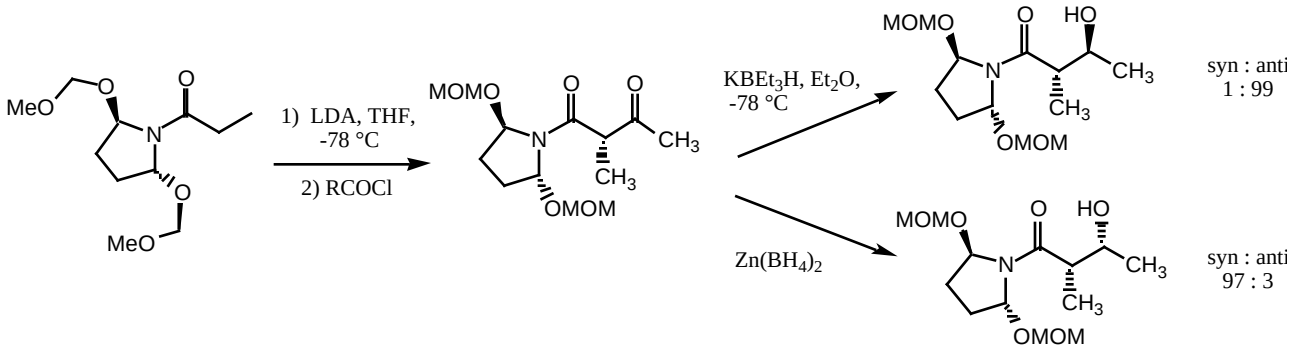
R= nPr	%ee (anti) = 77	anti : syn = 91 : 9
C_6H_{11}	84	95 : 5
tBu	79	94 : 6

Anti-Aldols by Indirect Methods:

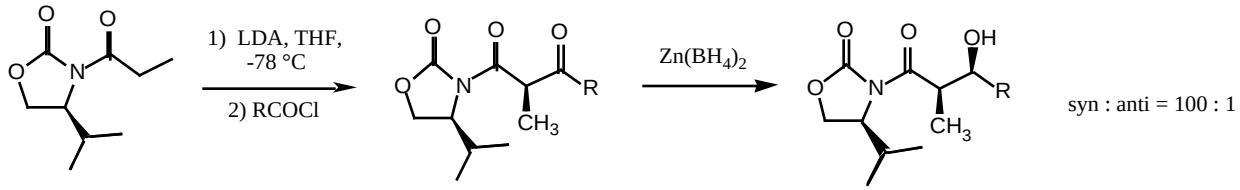




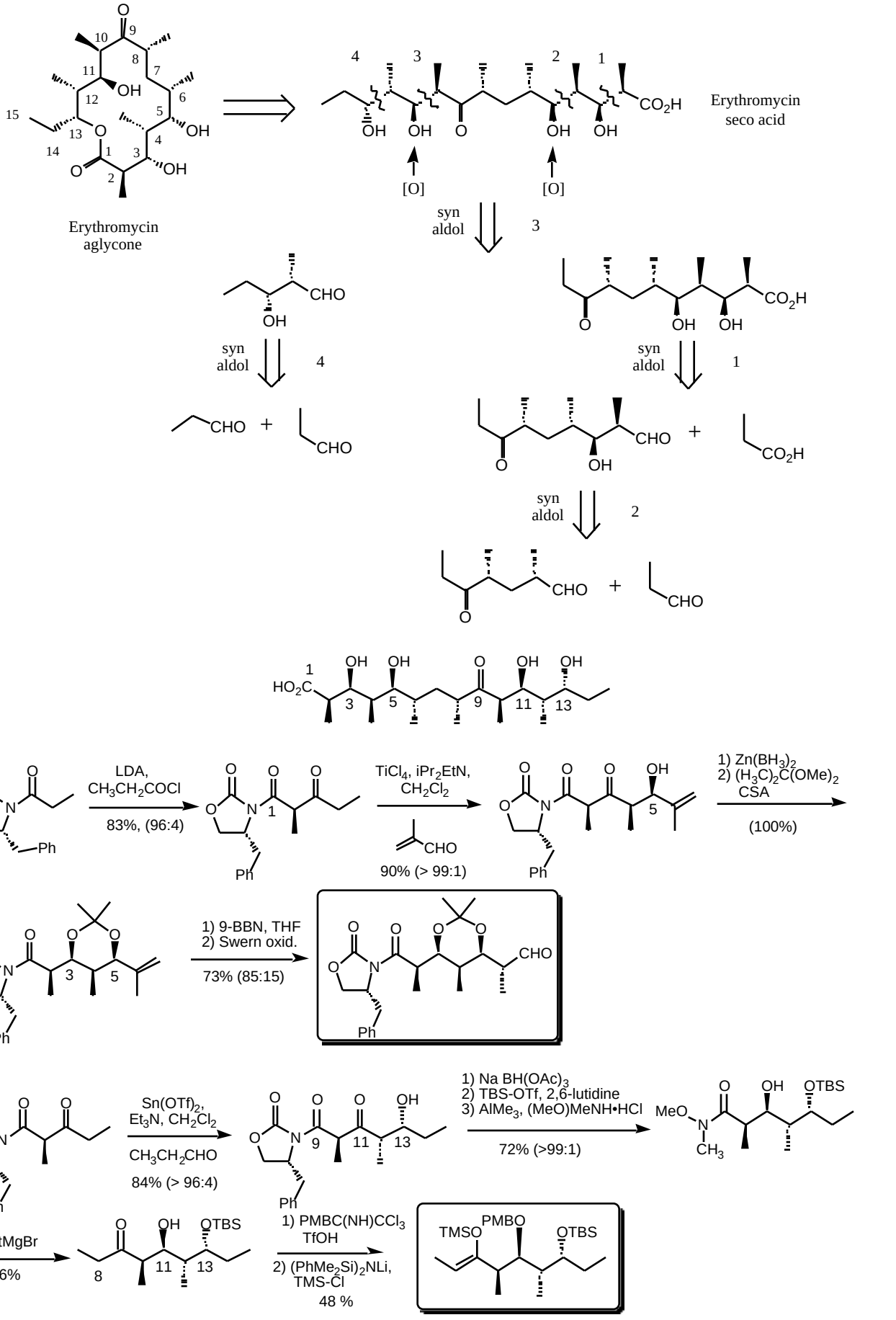


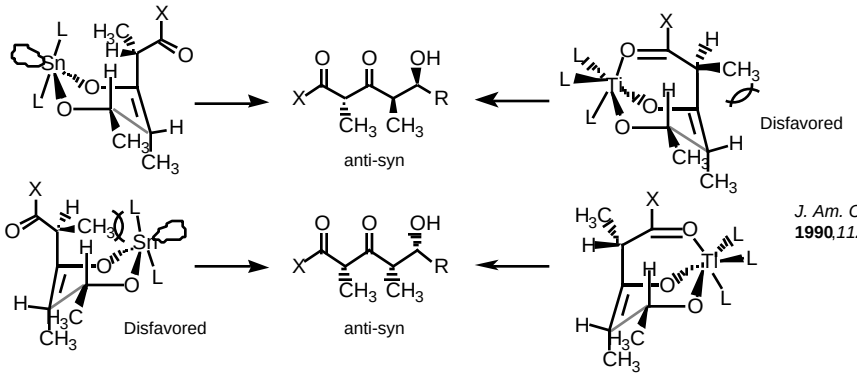


Syn Aldols by Indirect Methods:

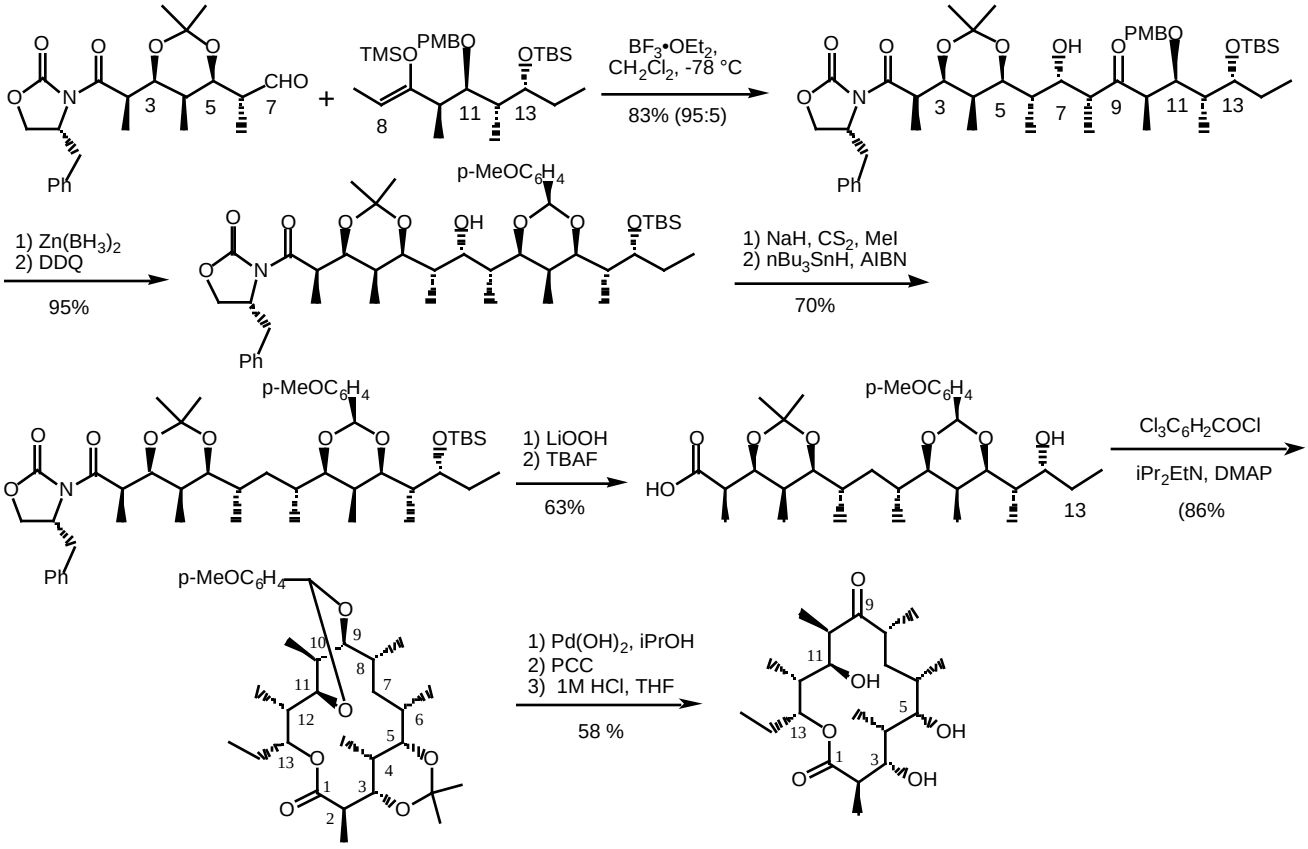


Aldol Strategy to Erythromycin:



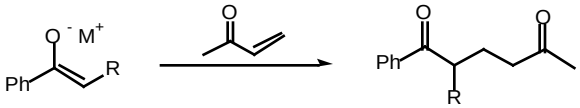


J. Am. Chem. Soc. **1990**,*112*, 866



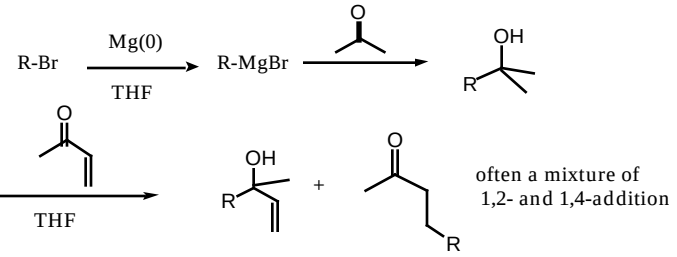
Michael Addition

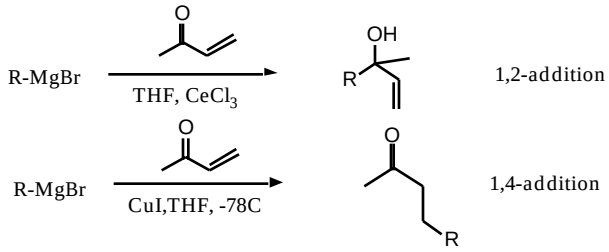
- 1,4-addition of an enolate to an α,β-unsaturated carbonyl to give 1,5-dicarbonyl compounds



Organometallic Reagents

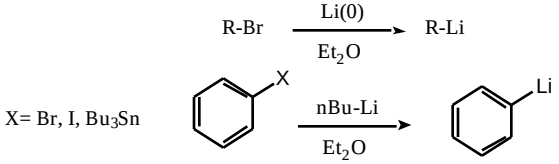
Grignard reagents:





Organolithium reagents

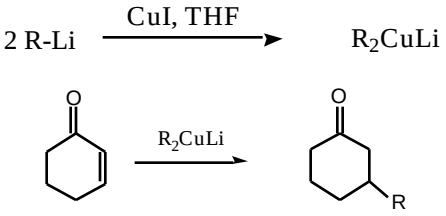
- usually gives 1,2-addition products
- alkyllithium are prepared from lithium metal and the corresponding alkyl halide
- vinyl or aryl- lithium are prepared by metal-halogen exchange from the corresponding vinyl or aryl- haidide or trialkyl tin with n-butyl, sec-butyl or t-butyllithium.



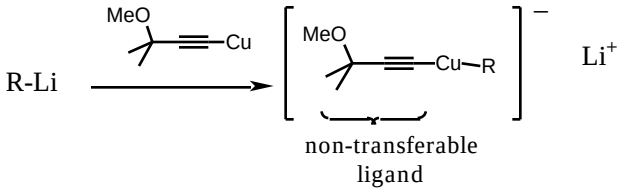
Organocuprates

Reviews: *Synthesis* **1972**, 63; *Tetrahedron* **1984**, *40* , 641; *Organic Reactions* **1972**, *19* , 1.

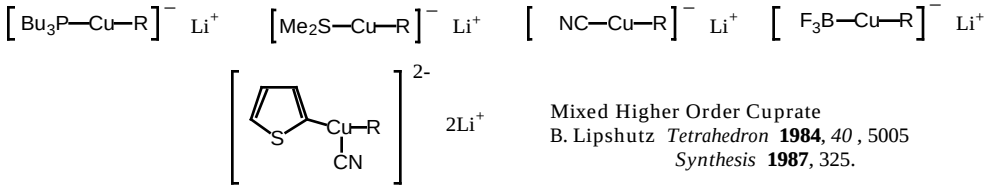
- selective 1,4-addition to α,β-unsaturated carbonyls



- curprate "wastes" one R group- use non transferable ligand

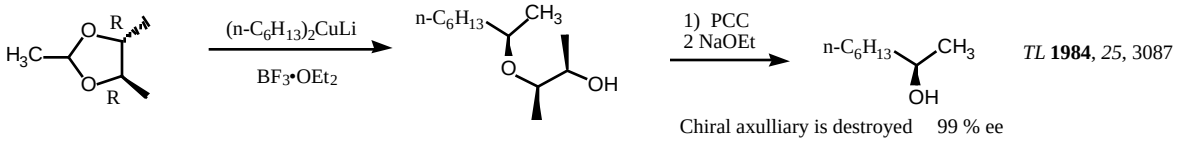


Other non transferable ligands



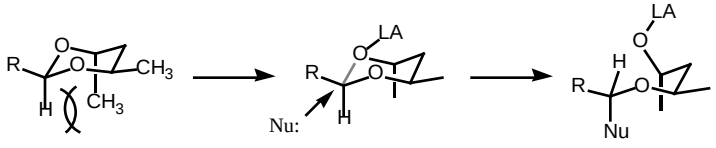
Mixed Higher Order Cuprate
B. Lipshutz *Tetrahedron* **1984**, *40* , 5005
Synthesis **1987**, 325.

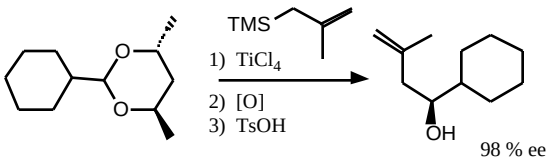
Addition to Acetals *Tetrahedron Asymmtetry* **1990**, *1*, 477.



TL **1984**, *25*, 3087

Chiral axulliary is destroyed 99 % ee



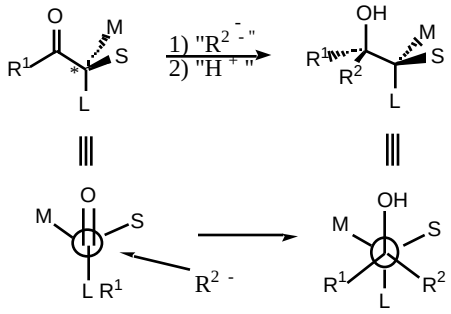


JACS **1984**, *106*, 7588

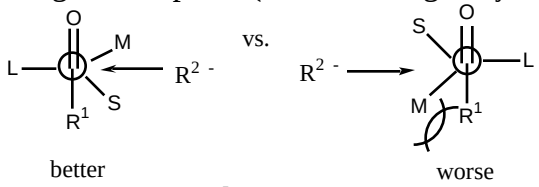
Stereoselective Addition to Aldehydes

- Aldehydes are "prochiral", thus addition of an organometallic reagent to an aldehydes may be stereoselective.

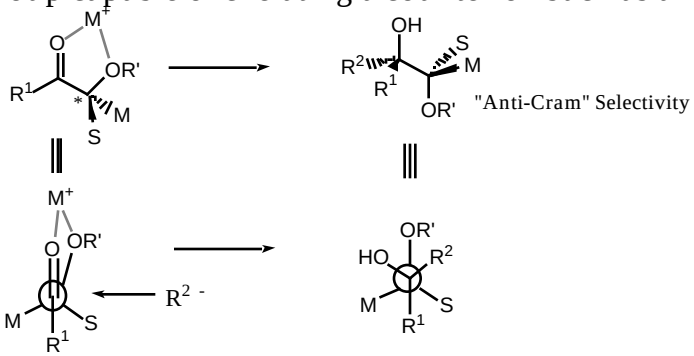
- Cram's Rule *JACS* **1952**, *74* , 2748; *JACS* **1959**, *84* , 5828.
  empirical rule



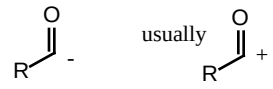
- Felkin-Ahn *TL* **1968**, 2199; *Nouv. J. Chim.* **1977**, *1* , 61.
  based on *ab initio* calculations of preferred geometry of aldehyde which considers the trajectory of the in coming nucleophile (Dunitz-Burgi trajectory).



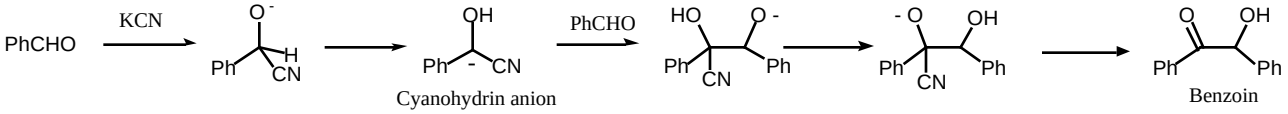
- Chelation Control Model- "Anti-Cram" selectivity
  - When L is a group capable of chelating a counterion such as alkoxide groups



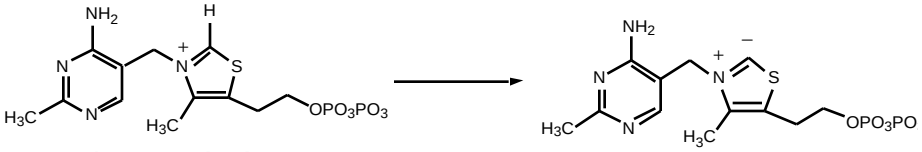
Umpolung - reversal of polarity *Aldrichimica Acta* **1981**, *14*, 73; *ACIIE* **1979**, *18*, 239.
i.e: acyl anion equivalents are carbonyl nucleophiles (carbonyls are usually electophillic)



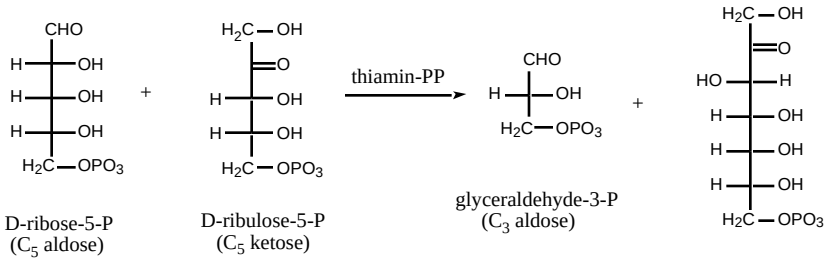
Benzoin Condensation *Comprehensive Organic Synthesis* **1991**, *1*, 541.



Thiamin pyrophosphate- natures acyl anion equivalent for trans ketolization reactions



Thiamin pyrophosphate



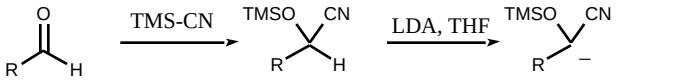
D-ribose-5-P (C_5 aldose)

D-ribulose-5-P (C_5 ketose)

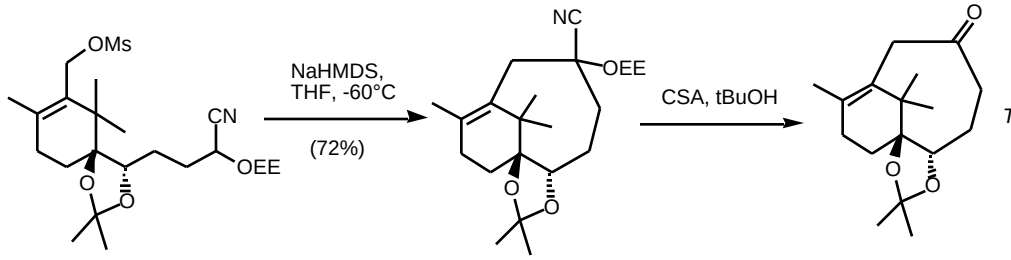
glyceraldehyde-3-P (C_3 aldose)

sedohepulose-7-P (C_7 ketose)

Trimethylsilycyanohydrins

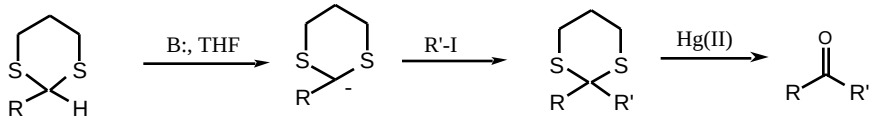


acyl anion equivalent

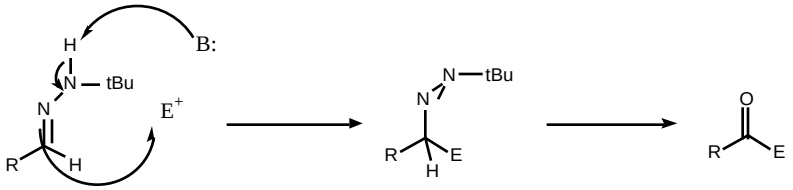


Tetrahedron Lett. **1997**, *38*, 7471

Dithianes

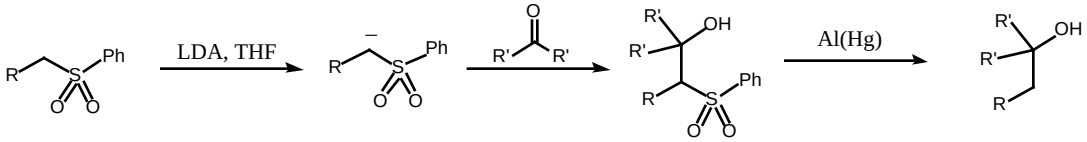


Aldehyde Hydrazones

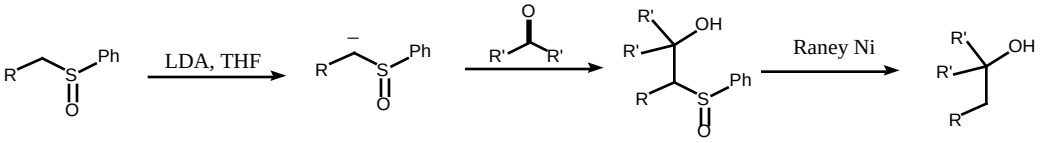


Heteroatom Stabilized Anions (Dithiane anion is an example)

Sulfones

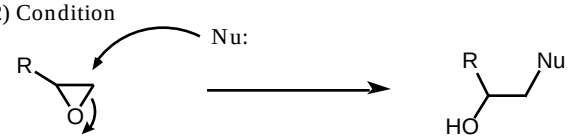


Sulfoxides



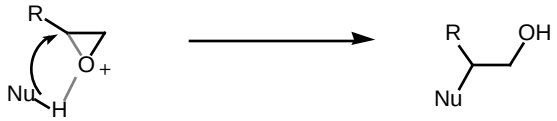
Epoxide Opening *Asymmetric Synthesis* **1984**, *5*, 216.

Basic (SN2) Condition

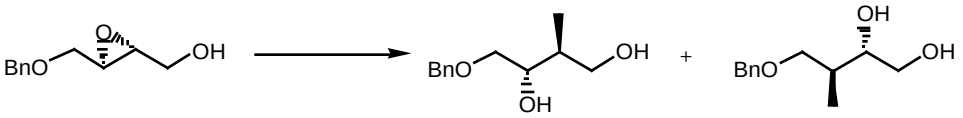


Steric Approach Control

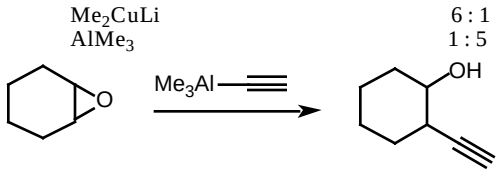
Acid (SN1-like) Condition



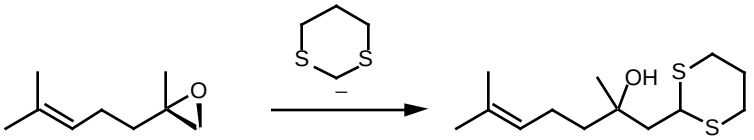
Nu: attachs site that best stabilizes a carbocation



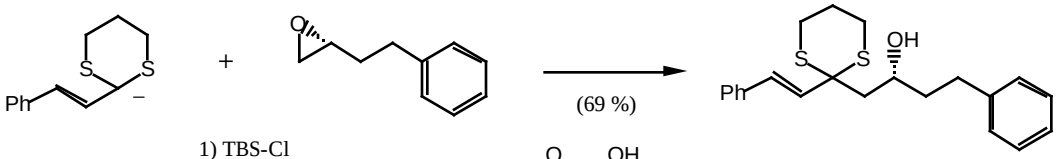
TL **1983**, *24*, 1377

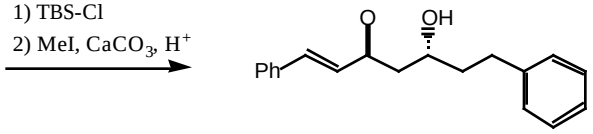


JACS **1981**, *103*, 7520



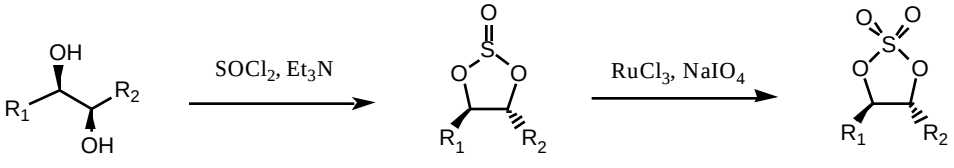
JOC **1974**, 3645





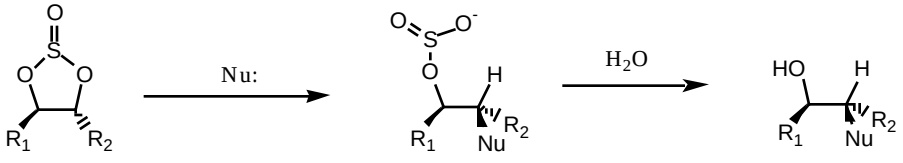
Tetrahedron Lett. **1992**, *33*, 931

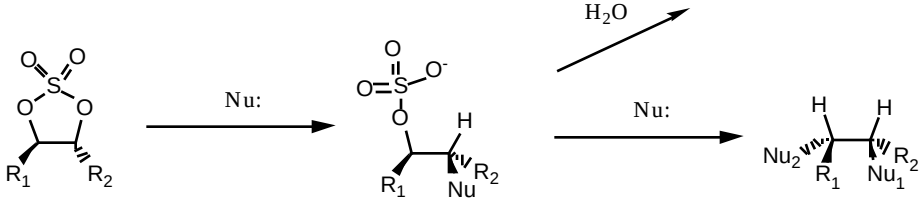
Cyclic Sulfites and Sulfates (epoxide equivalents) *Synthesis* **1992**, 1035.

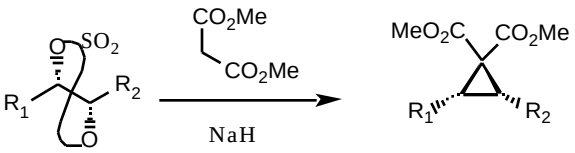


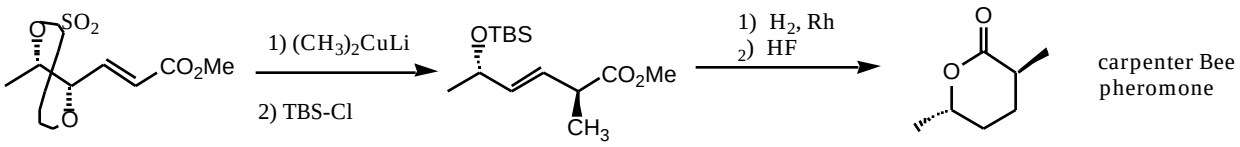
sulfite

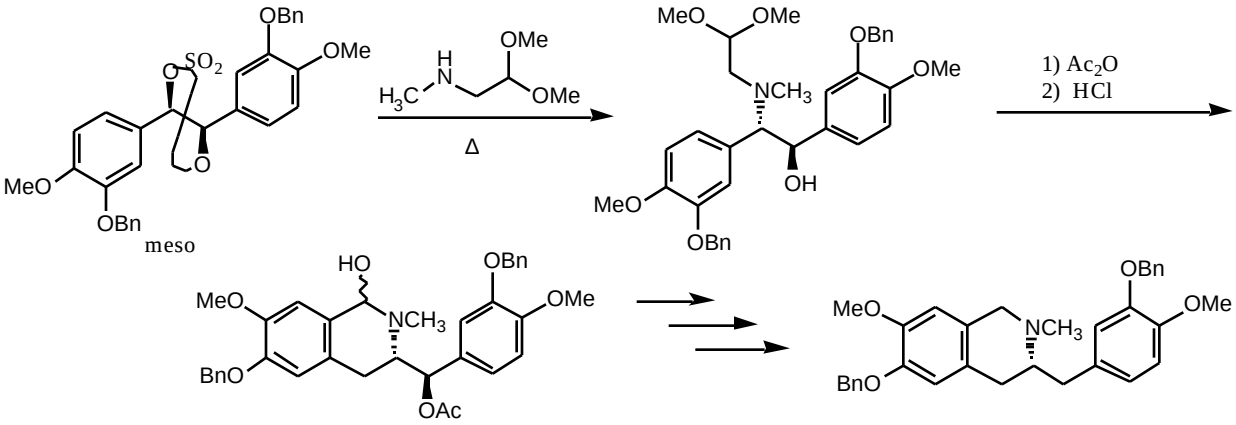
sulfate



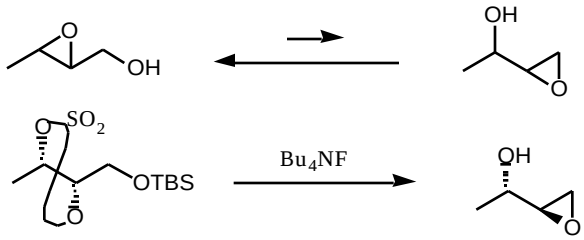








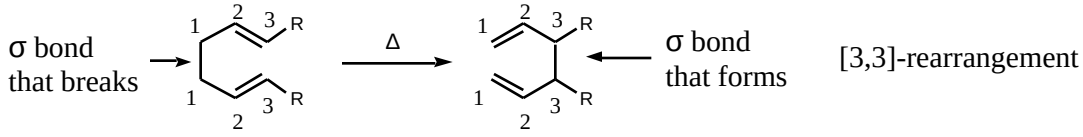
Irreversible Payne Rearrangement

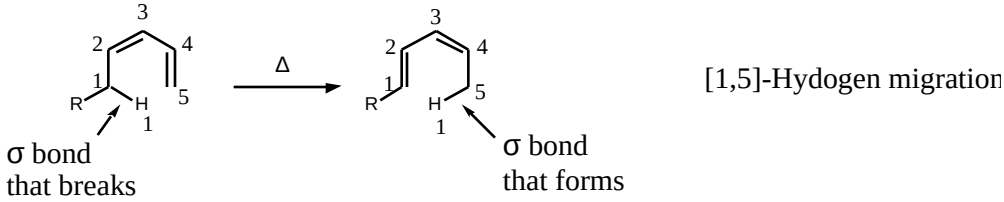


Payne Rearrangement of 2,3-epoxyalcohols *Aldrichimica Acta* **1983**, *16*, 60

Sigmatropic Rearrangements *Asymmetric Synthesis* **1984**, *3*, 503.

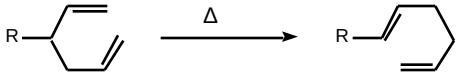
Nomenclature:



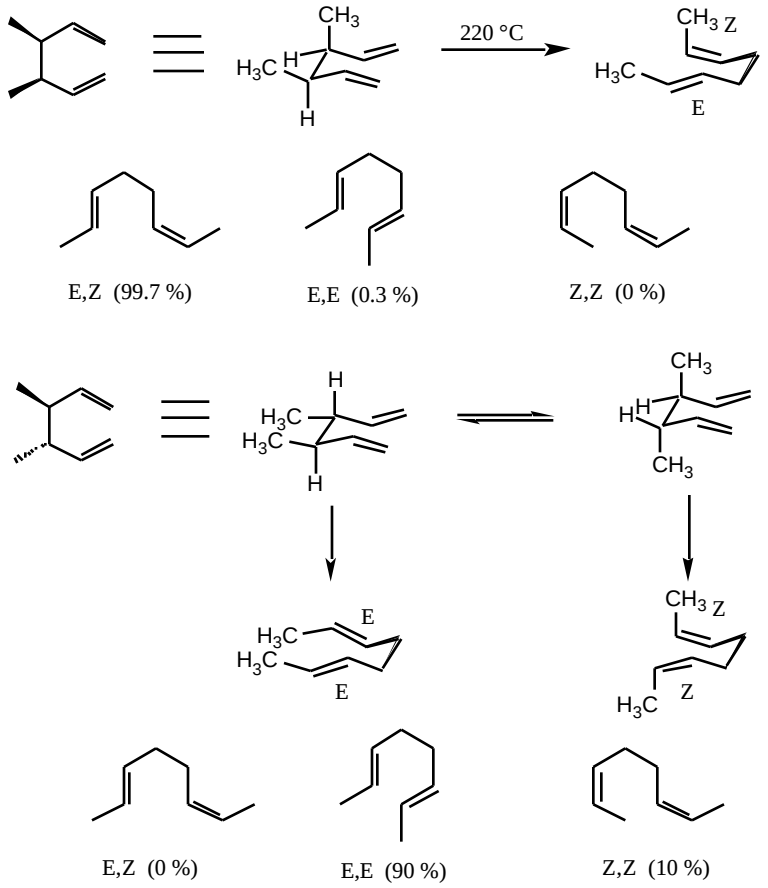


3,3-sigmatropic Rearrangements

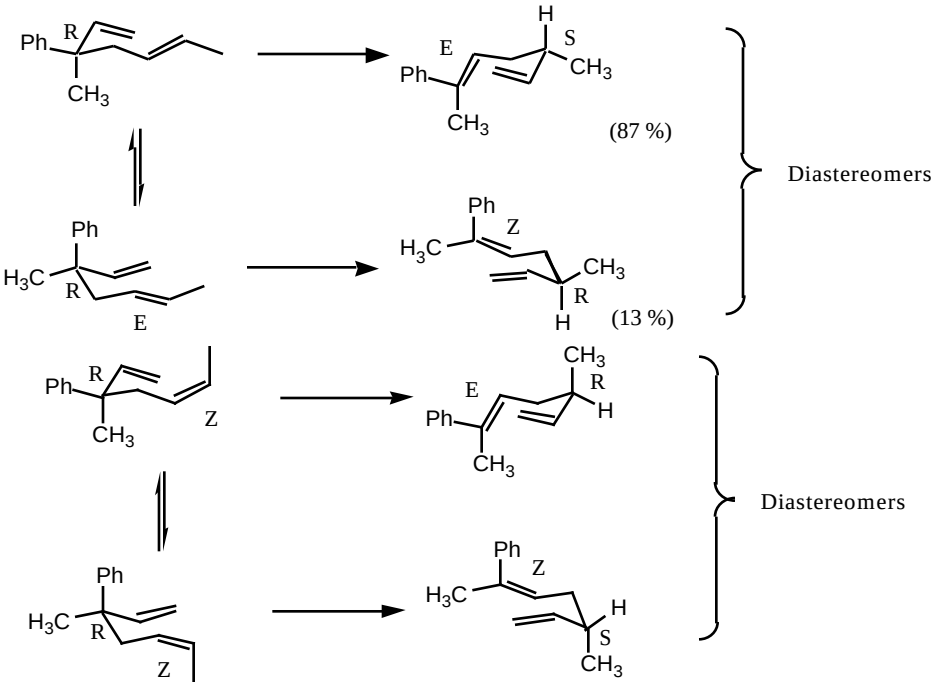
Cope Rearrangemets- requires high temperatures *Organic Reaction* **1975**, *22*, 1



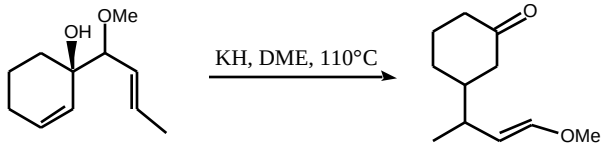
Chair transition state:

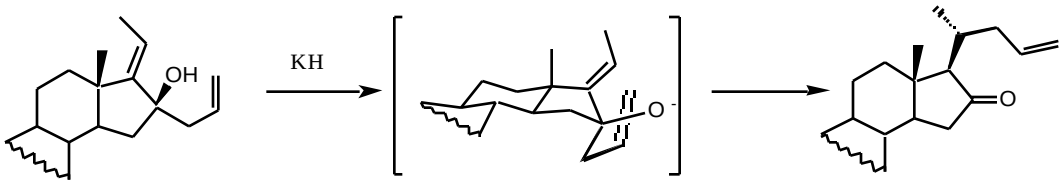


"Chirality Transfer"

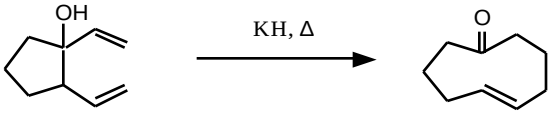


- anion accelerated (oxy-) Cope- proceeds under much milder conditions (lower temperature) *JACS* **1980**, *102* , 774; *Tetrahedron* **1978**, *34*, 1877; *Organic Reactions* **1993**, *43*, 93; *Comprehensive Organic Synthesis* **1991**, *5*, 795. *Tetrahedron* **1997**, *53*, 13971.



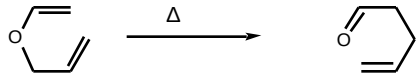


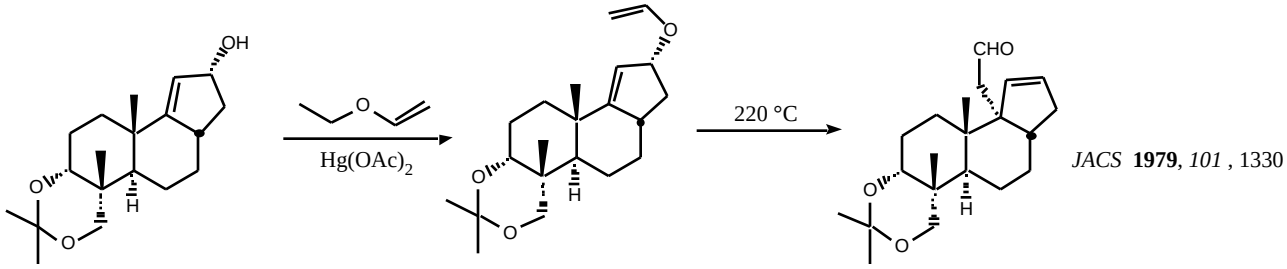
Ring expansion to medium sized rings



Claisen Rearrangements - allyl vinyl ether to an γ,δ-unsaturated carbonyl

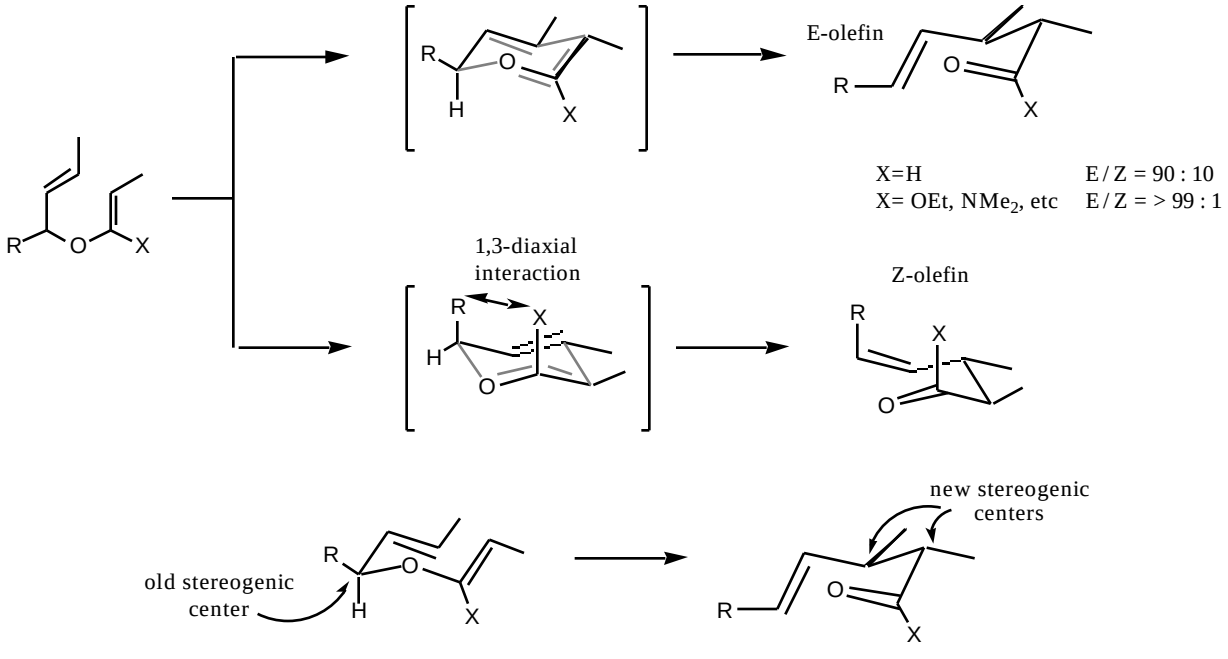
Chem. Rev. **1988**, *88*, 1081.; *Organic Reactions* **1944**, *2*, 1.; *Comprehnsive Organic Synthesis* **1991**, *5*, 827.



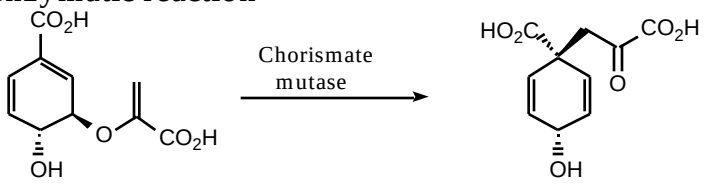


JACS **1979**, *101* , 1330

Chair Transition State for Claisen

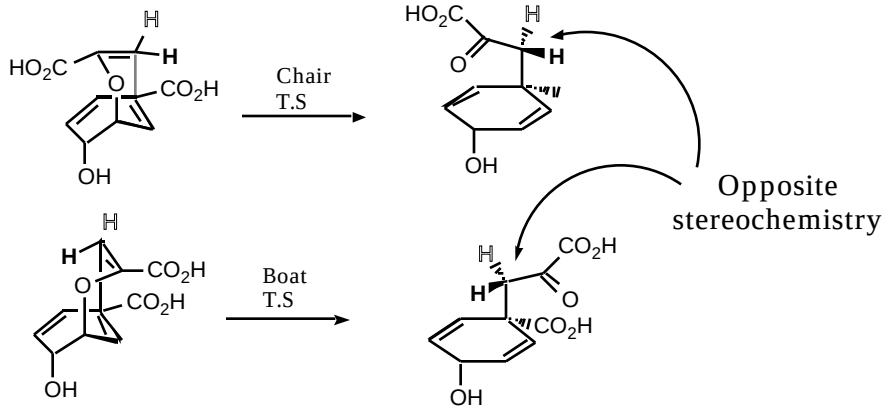


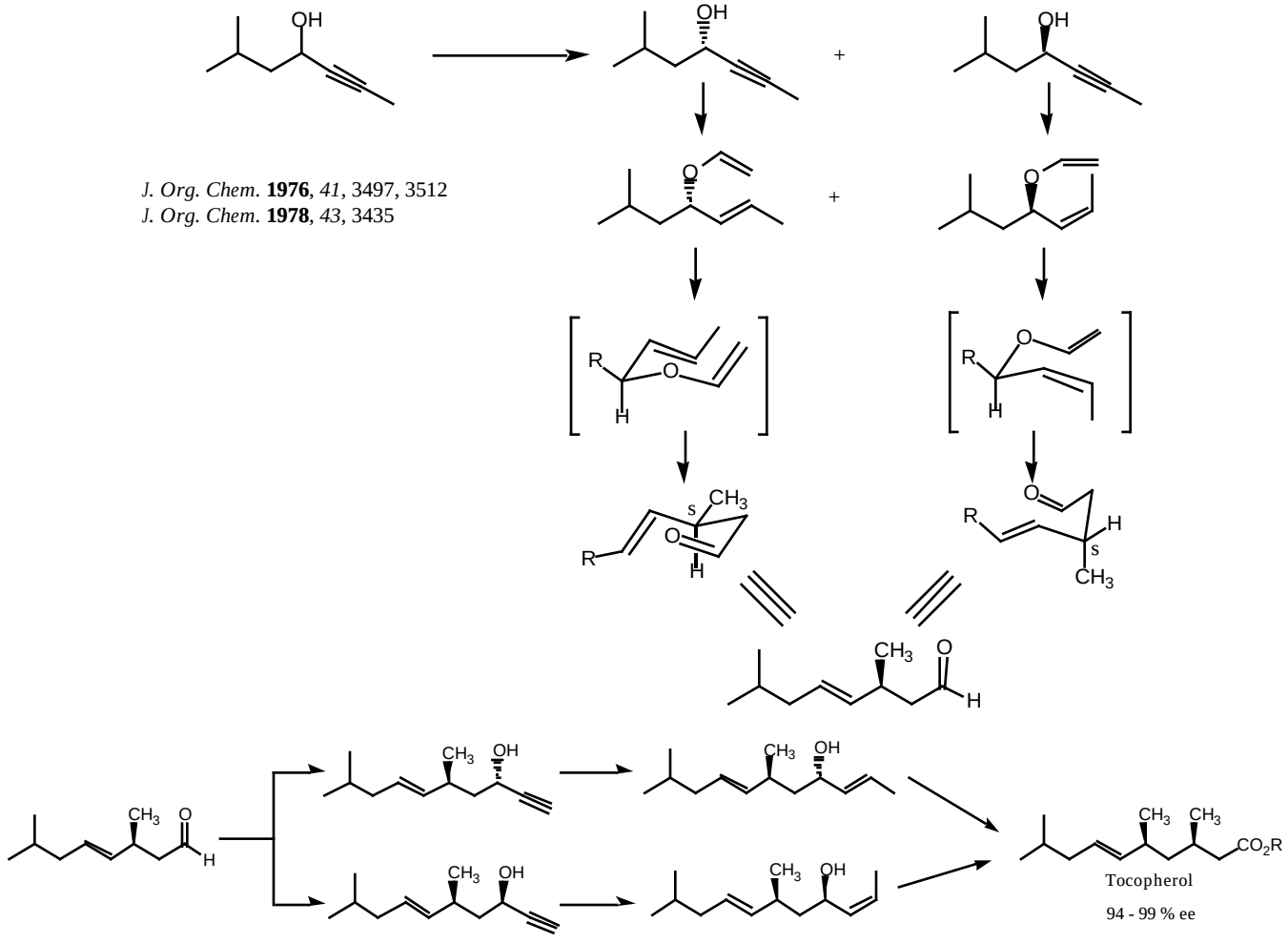
- Chorismate Mutase catalyzed Claisen Rearrangement- 10^5 rate enhancement over non-enzymatic reaction



J. Knowles
JACS **1987**, *109*, 5008, 5013

- Claisen rearrangement usually proceed by a chair-like T.S.

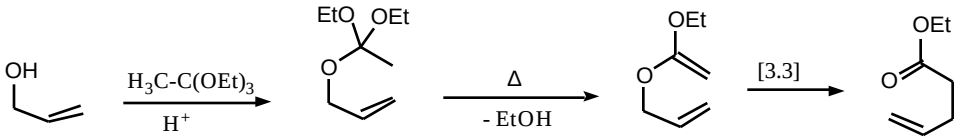




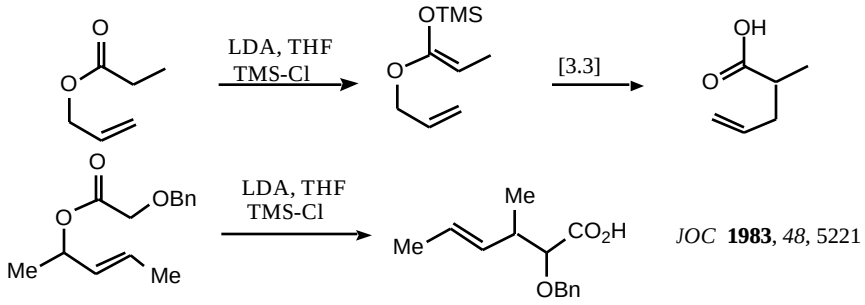
J. Org. Chem. **1976**, *41*, 3497, 3512
J. Org. Chem. **1978**, *43*, 3435

hydrophobically accelerated Claisen - *JOC* **1989**, *54*, 5849

Johnson ortho-ester Claisen:

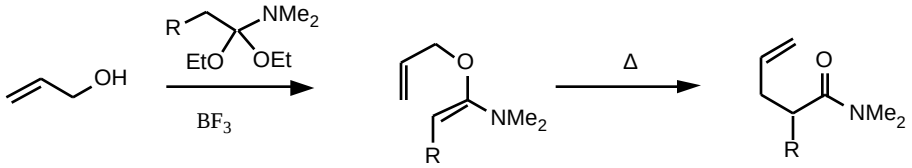


Ireland ester-enolate Claisen. *Aldrichimica Acta* **1993**, *26*, 17.

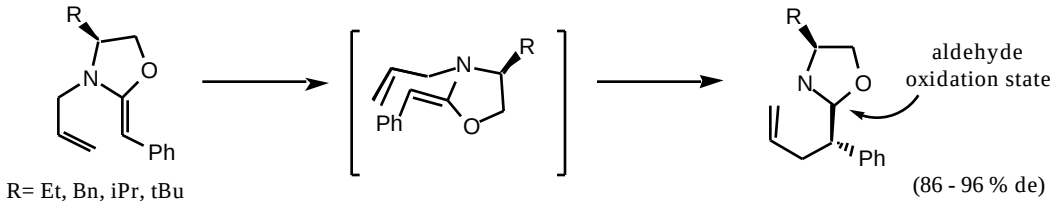


JOC **1983**, *48*, 5221

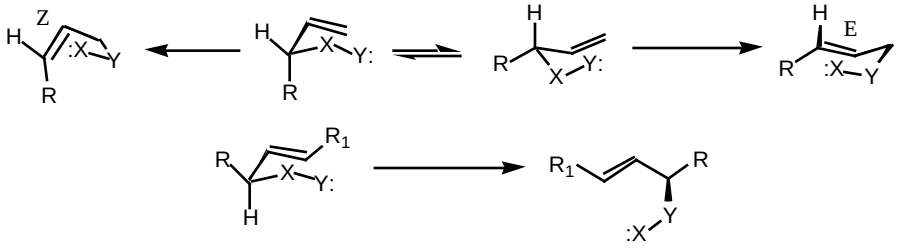
Eschenmoser



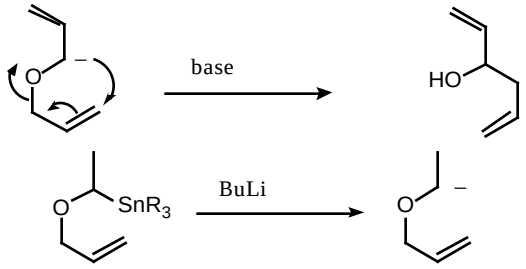
"Chirality Transfer"

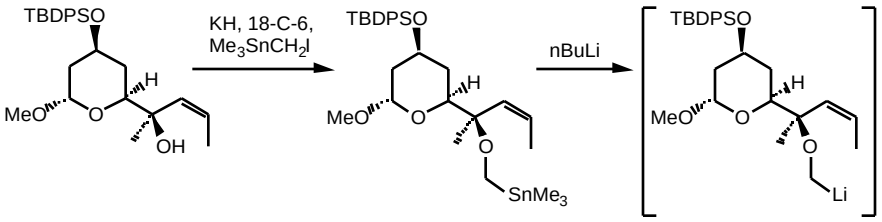


[2,3]-Sigmatropic Rearrangement *Comprehensive Organic Synthesis* **1991**, *6*, 873.

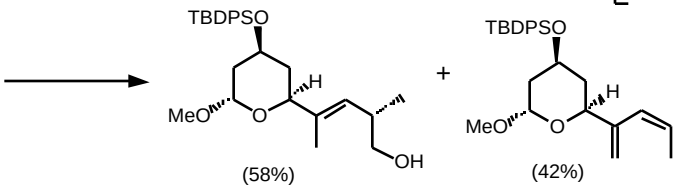


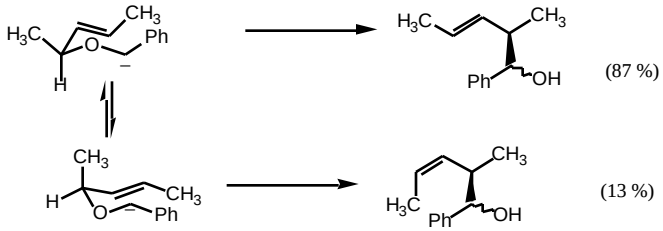
-Wittig Rearrangement *Organic Reactions* **1995**, *46*, 105 *Synthesis* **1991**, 594.



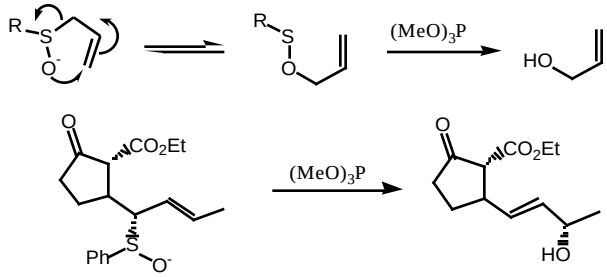


J. Am. Chem. Soc. **1997**, *119*, 10935

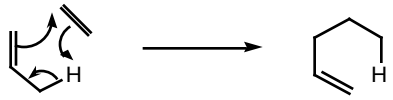




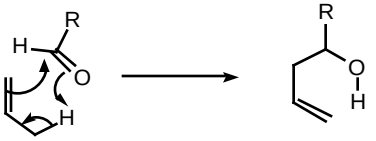
Sulfoxide Rearrangement

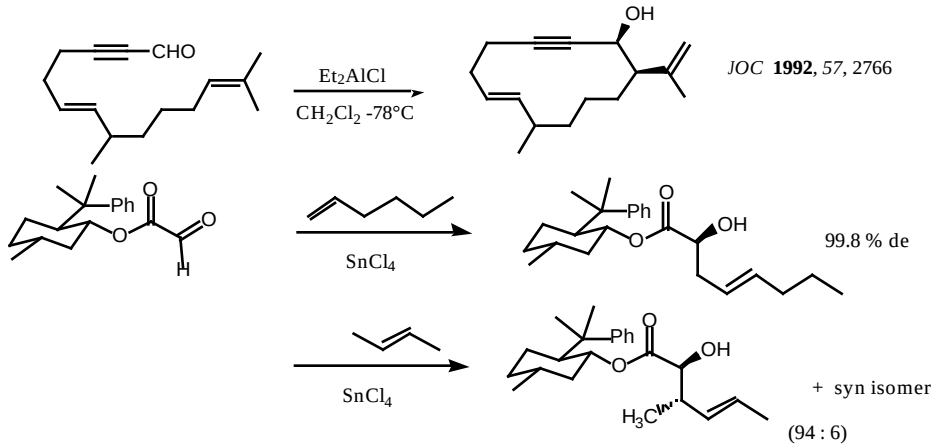


Ene Reaction Comprehensive Organic Synthesis **1991**, *5*, 1; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876; ; *Chem. Rev.* **1992**, *28*, 1021.

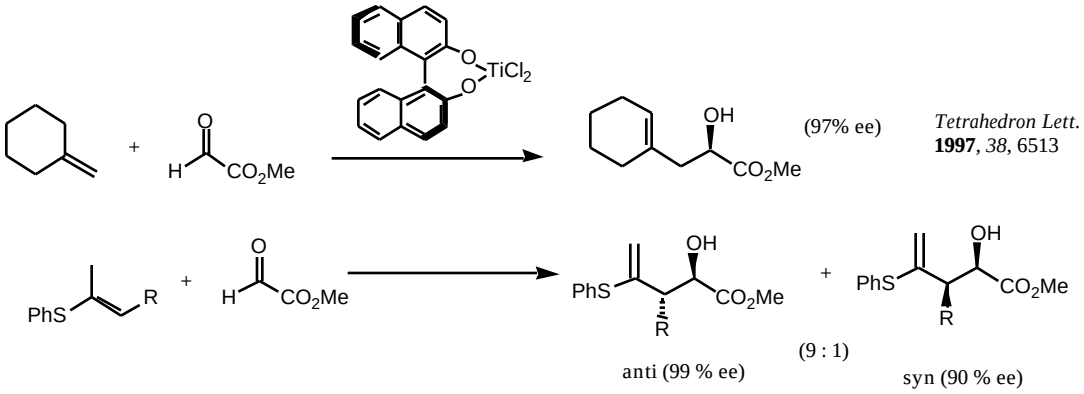


- Ene reaction with aldehydes is catalyzed by Lewis Acids (Et_2AlCl)

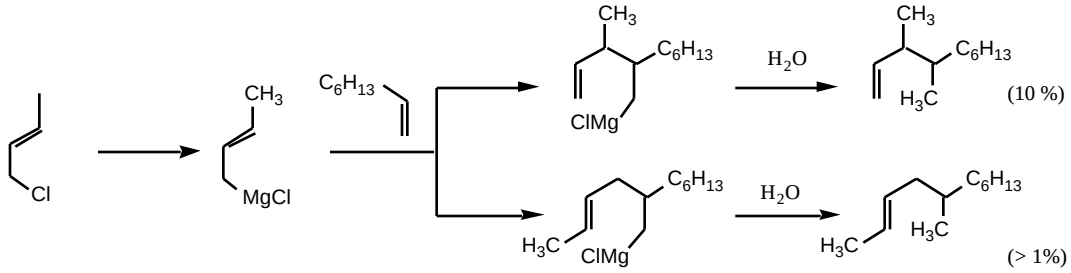




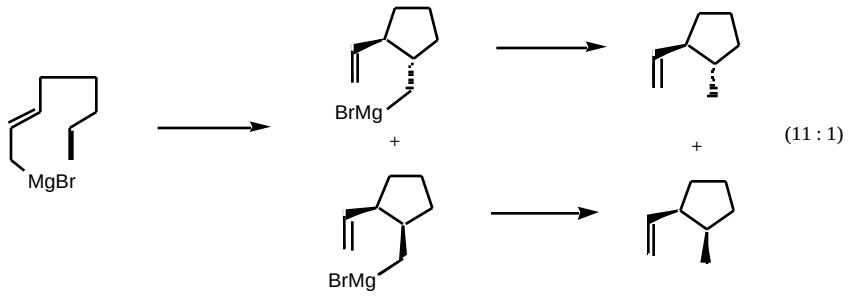
JOC **1992**, *57*, 2766

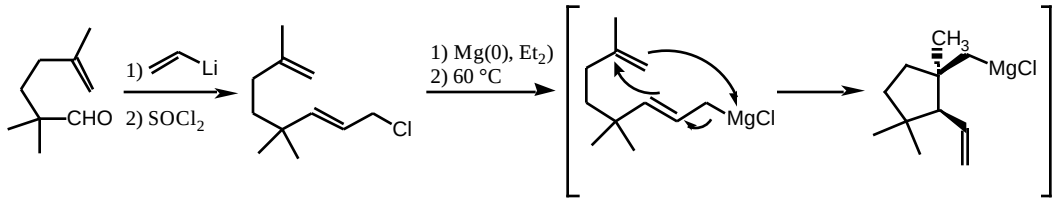


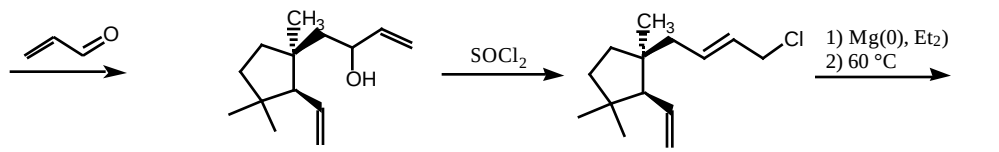
- Metallo-ene Reaction *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38

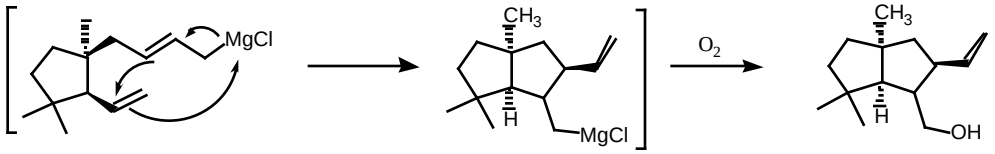


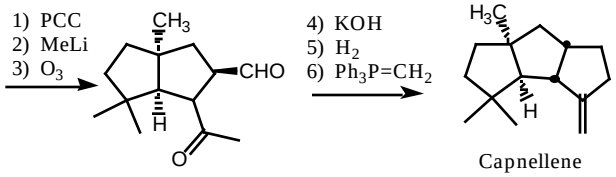
intramolecular





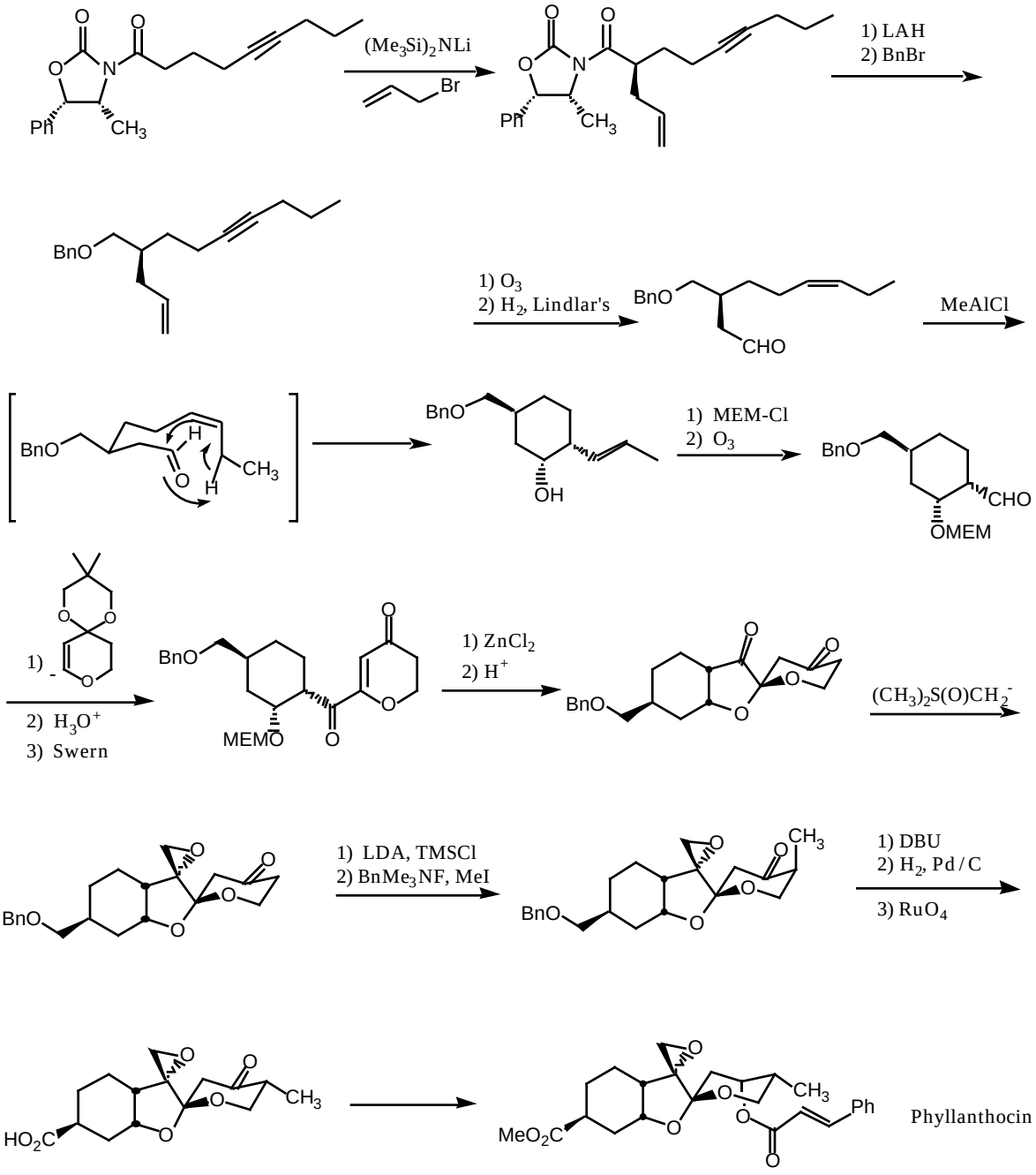






Capnellene

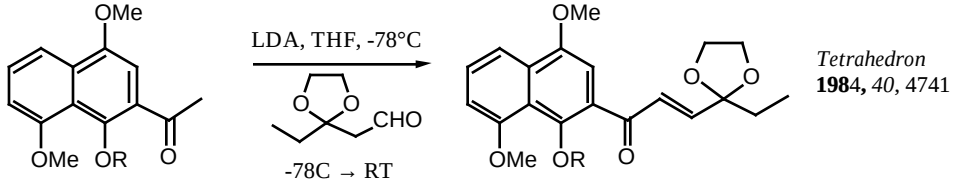
Synthesis of Phyllanthocin A. B. Smith et al. *J. Am. Chem. Soc.* **1987**, *109*, 1269.



C=C Bond Formation C&S Chapt. 2 # 5,6,8,9,12

1. Aldol Condensation
2. Wittig Reaction (Smith, Ch. 8.8.A)
3. Peterson Olefination
4. Julia-Lythgoe Olefination
5. Carbonyl Coupling Reactions (McMurry Reaction) (Smith Ch. 13.7.F)
6. Tebbe Reagent
7. Shapiro and Related Reaction
8. β–Elimination and Dehydration
9. From Diols and Epoxides
10 From Acetylenes
11. From Other Alkenes-Transition Metal Catalyzed Cross-Coupling and Olefin Metathesis

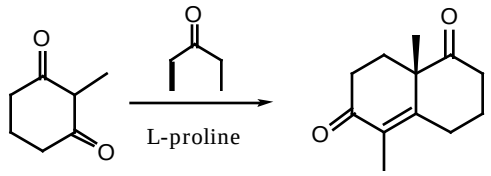
Aldol Condensation -Aldol condensation initially give β-hydroxy ketones which under certain conditions readily eliminated to give α,β-unsaturated carbonyls.



Tetrahedron **1984,** *40*, 4741

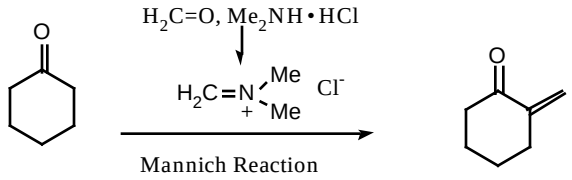
Robinson Annulation : Sequential Michael addition / aldol condensation between a ketone enolate and an alkyl vinyl ketone (i.e. MVK) to give a cyclohex-2-en-1-one

JOC **1984**, *49* , 3685 *Synthesis* **1976**, 777.

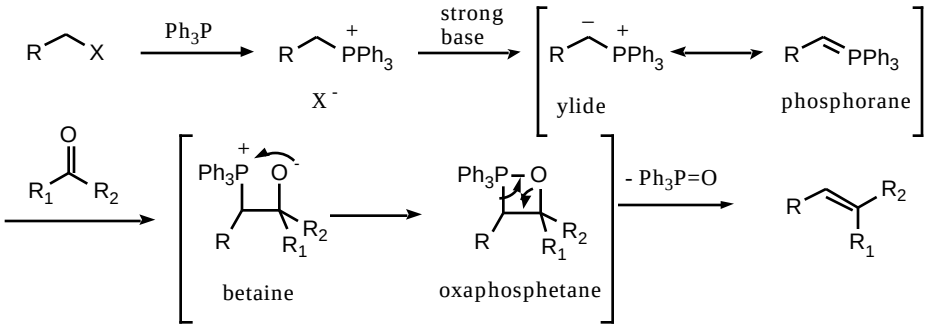


Weiland-Mischeler Ketone
(chiral starting material)

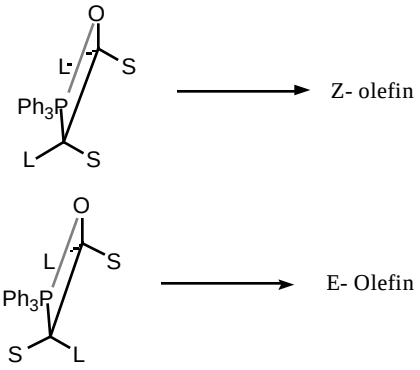
Mannich Reaction - α,β-unsaturated carbonyls (α-methylene carbonyls)



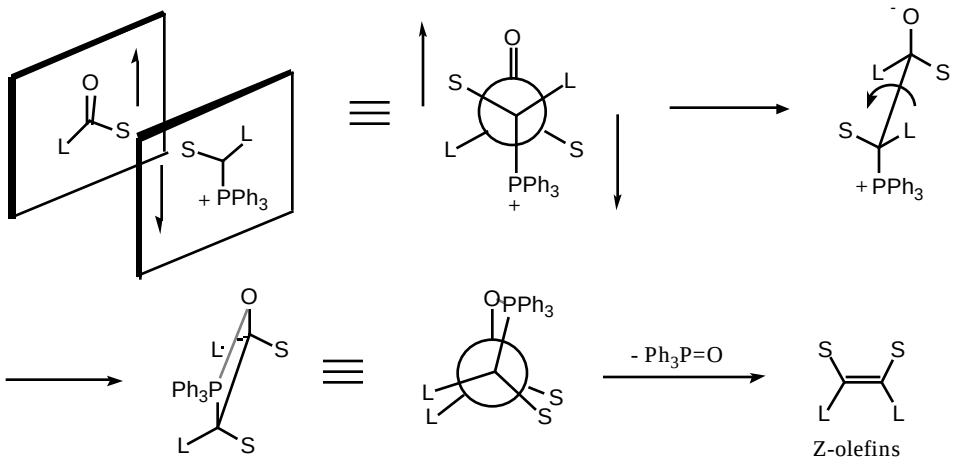
Wittig Reaction review: *Chem. Rev.* **1989**, *89*, 863.
mechanism and stereochemistry: *Topic in Stereochemistry* **1994**, *21*, 1
- reaction of phosphonium ylide with aldehydes, ketones and lactols to give olefins



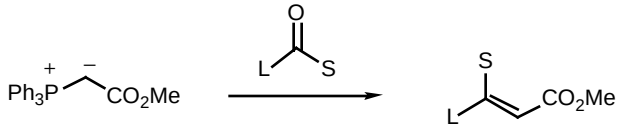
- Olefin Geometry



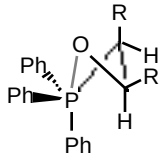
- With "non-stabilized" ylides the Wittig Reaction gives predominantly Z-olefins. Seebach et al *JACS*



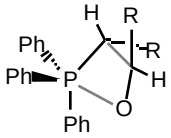
- "Stabilized ylides" give predominantly E-olefins



- Betaine formation is reversible and the reaction becomes under thermodynamic control to give the most stable product.
- There is NO evidence for a betaine intermediate.
- Vedejs Model:

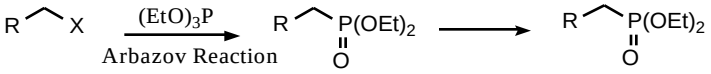


Cis — Pukered (cis) oxaphosphetane (kinetically favored)



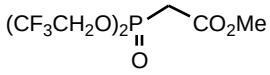
Trans — Planar (trans) oxaphosphetane (thermodynamically favored)

Phosphonate Modification (Horner-Wadsworth-Emmons)

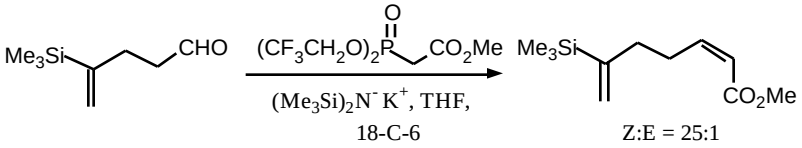


- R is usually restricted to EWG such as CO_2H, CO_2Me, CN, SO_2Ph etc. and the olefin geometry is usually E.

- Still Modification *TL* **1983**, *24*, 4405.

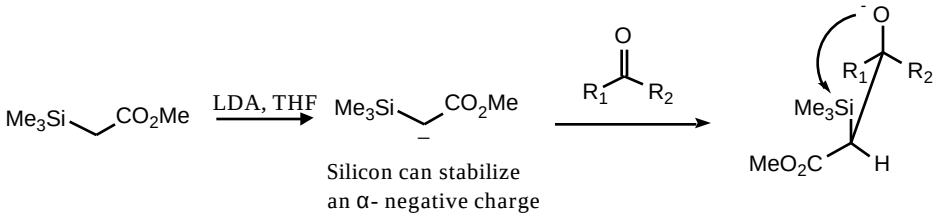


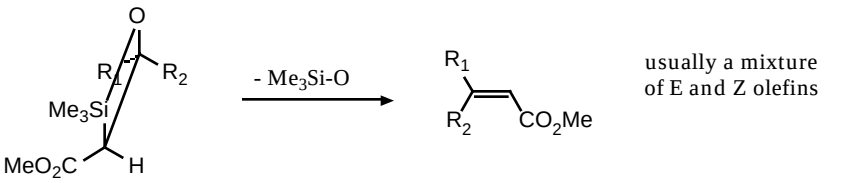
- CF_3CH_2O- groups make the betaine less stable, giving more Z-olefin.



JACS **1988**, *110*, 2248

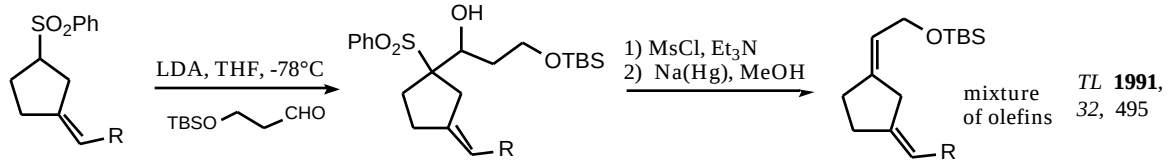
Peterson Olefination review: *Synthesis* **1984**, 384 *Organic Reactions* **1990**, *38* 1.





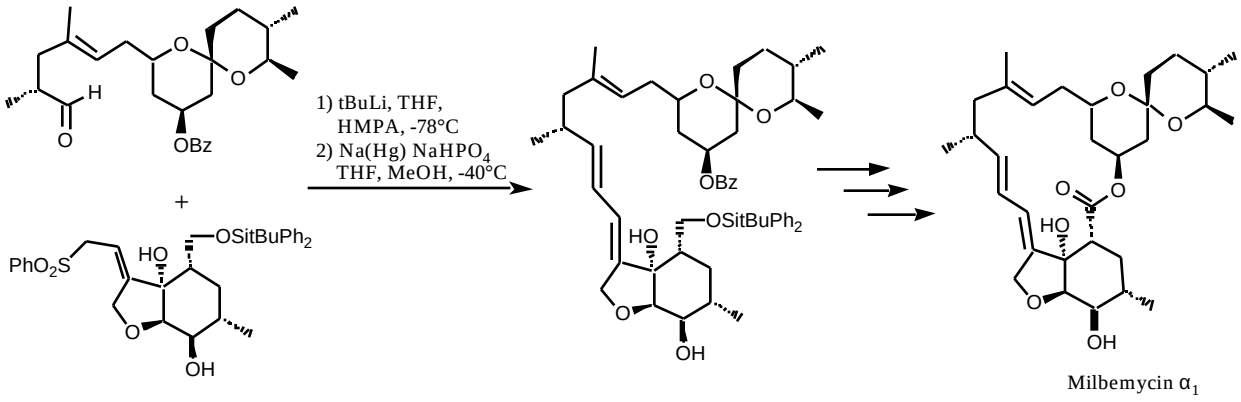
usually a mixture of E and Z olefins

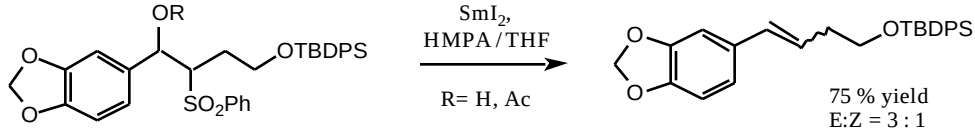
Julia-Lythgoe Olefination *TL* **1973**, 4833 *Tetrahedron* **1987**, *43*, 1027



TL **1991**, *32*, 495

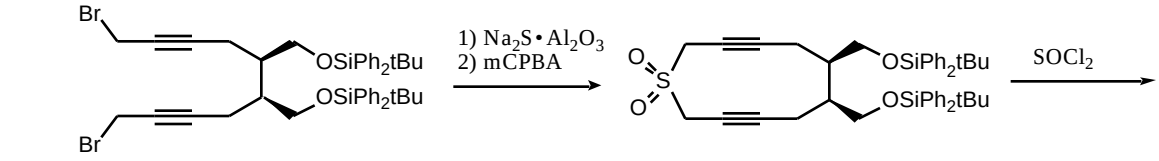
Tetrahedron Lett. **1993**, *34*, 7479

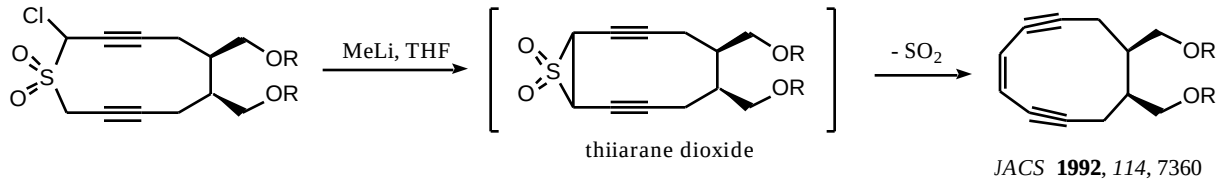




Synlett **1994**, 859

Ramberg-Backlund Rearrangement



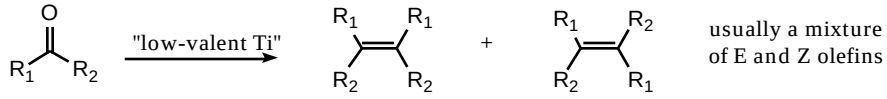


JACS **1992**, *114*, 7360

Carbonyl Coupling Reactions (McMurry Reaction)

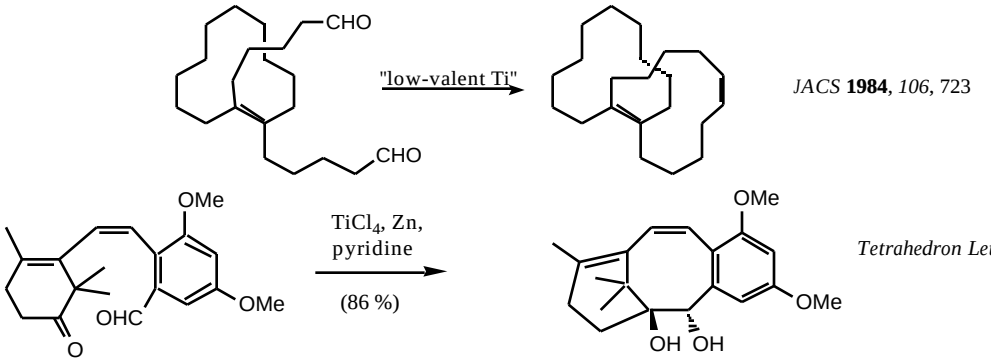
Reviews: *Chem. Rev.* **1989**, *89*, 1513.

- reductive coupling of carbonyls with low valent transition metals, Ti(0) or Ti(II), to give olefins



excellent method for the preparation of strained (highly substituted) olefins

- Intramolecular coupling gives cyclic olefins

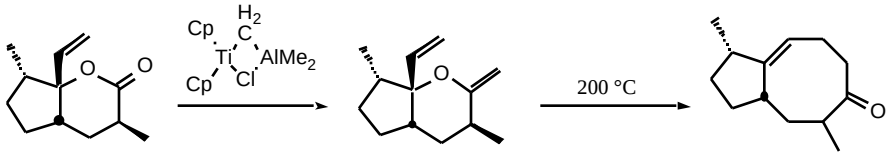


JACS **1984**, *106*, 723

Tetrahedron Lett. **1993**, *34*, 7005

Tebbe Reagent $Cp_2Ti(CH_2)ClAlMe_2$

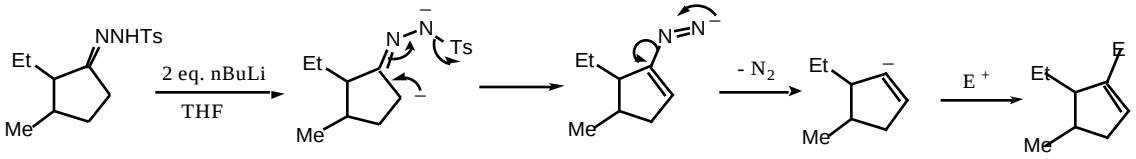
- methylenation of ketones and lactones. The later gives cyclic enol ethers.



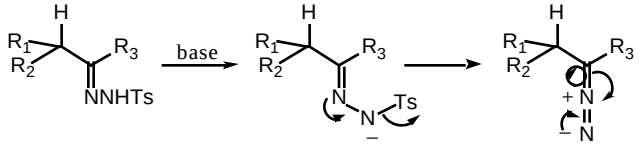
- Cp_2TiMe_2 will also do the methylenation chemistry
  JACS **1990**, *112*, 6393.

Shapiro and Related Reactions *Organic Reactions* **1990**, *39*, 1 : **1976**, *23*, 405

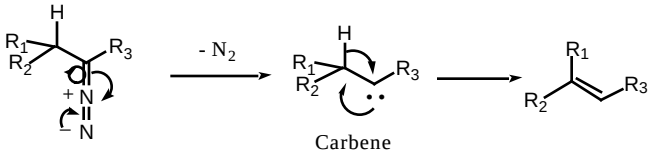
- Reaction of a tosylhydrazone with a strong base to give an olefin.



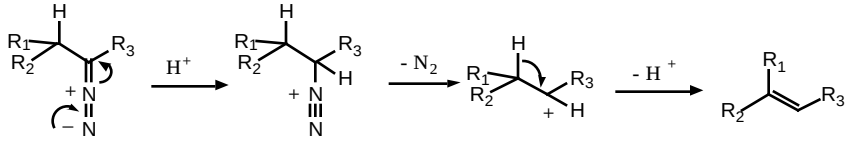
Bamford-Stevens Reaction- initial conversion of a tosylhydrazone to a diazo intermediate



a: aprotic- decomposition of the diazo intermediate under aprotic conditions gives and olefin through a carbene intermediate.



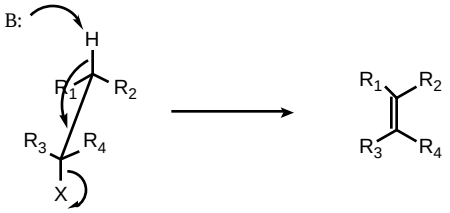
b. protic- decomposition of the diazo intermediate under protic conditions an olefin through a carbonium ion intermediate.



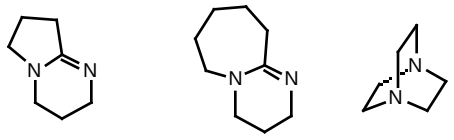
β- *Eliminations*

Anti Eliminations

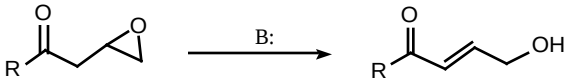
- elimination of HX from vicinal saturated carbon centers to give a olefin, usually base promoted.
- base promoted E_2- type elimination proceeds through an anti-periplanar transition state.

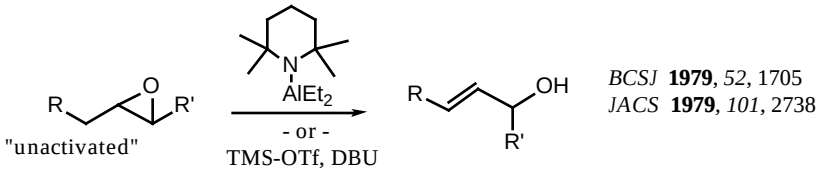


- typical bases: NaOMe, tBuOK, DBU, DBN, DABCO, etc.



- X: -Br, -I, -Cl, -OR, epoxides

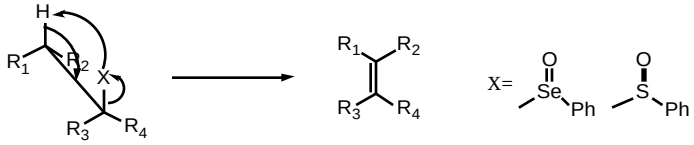




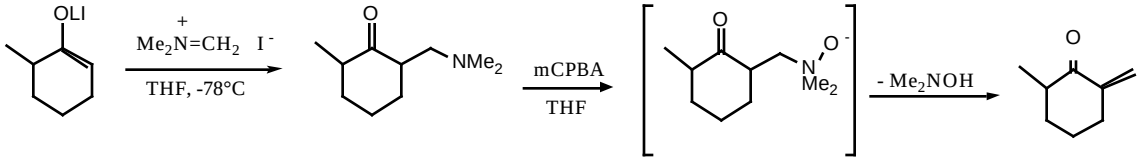
BCSJ **1979**, *52*, 1705
JACS **1979**, *101*, 2738

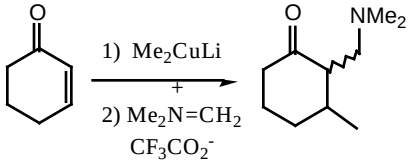
Syn Elimination

- often an intramolecular process



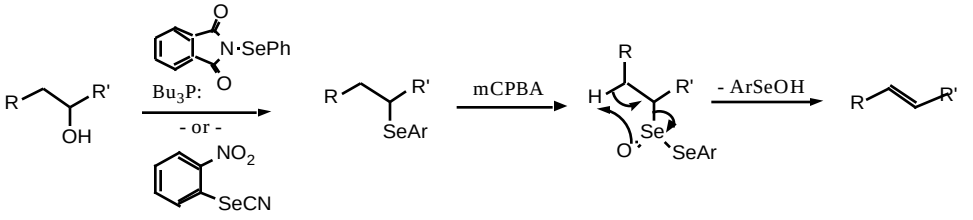
Cope Elimination- elimination of R_2NOH from an amine oxide



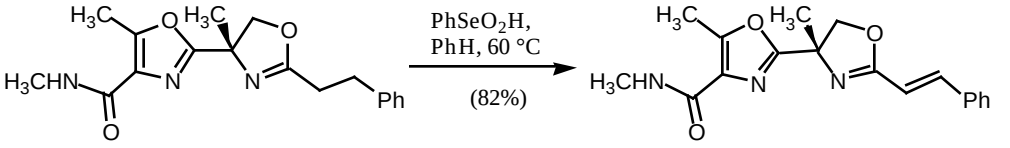


JACS **1977**, *99* , 944
Tetrahedron **1977**, *35* , 613

Selenoxide Elimination *Organic Reactions* **1993**, *44*, 1.



JACS **1979**, *101*, 3704

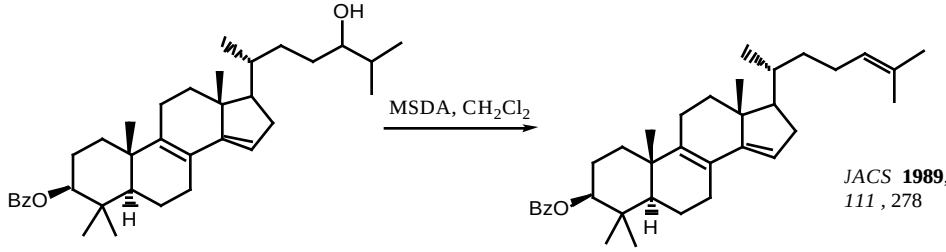


JOC **1995**, *60*, 7224
JCS P1 **1985**, 1865

Dehydration of Alcohols

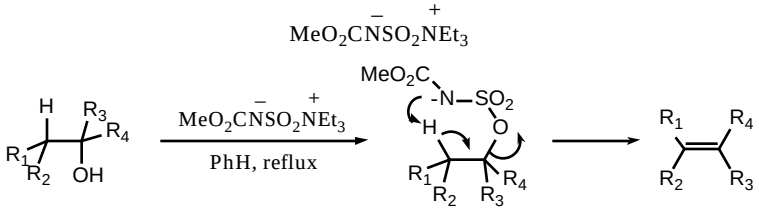
- alcohols can be dehydrated with protic acid to give olefins via an E_1 mechanism.
- other reactions dehydrate alcohols under milder conditions by first converting them into a better leaving group, i.e. $POCl_3$ / pyridine, P_2O_5

Martin sulfurane; $Ph_2S[OCPh(CF_3)_2]_2$ *JACS*, **1972**, *94*, 4997 dehydration occurs under very mild, neutral conditions, usually gives the most stable olefin



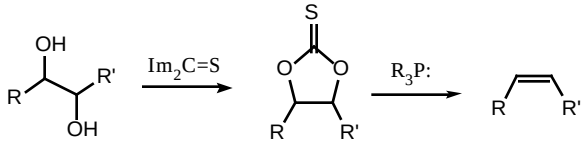
JACS **1989**, *111* , 278

Burgess Reagent (inner salt) *JOC*, **1973**, *38*, 26 occurs vis a syn elimination



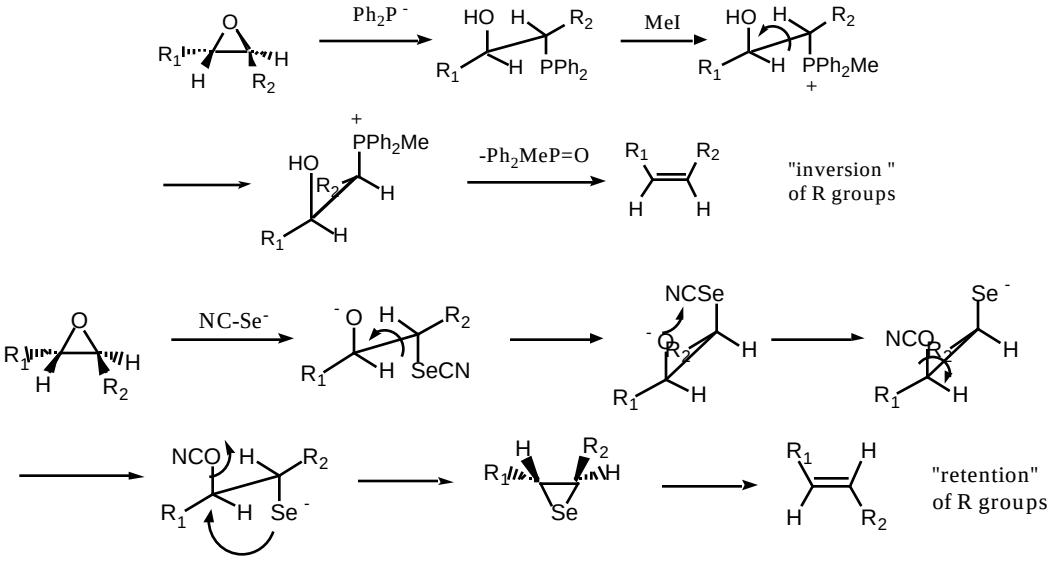
Olefins from Vicinal Diols

Corey-Winter Reaction *JACS* **1963**, *85*, 2677; *TL* **1982**, 1979; *TL* **1978**, 737



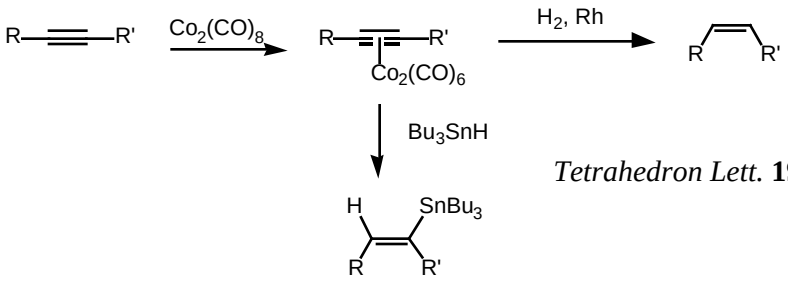
- vic-diols can be converted to olefins with K_2WCl_6 *JCSCC* **1972**, 370; *JACS* **1972**, *94*, 6538
- This reaction worked best with more highly substituted diols and give predominantly syn elimination.
- Low valent titanium; McMurry carbonyl coupling is believed to go through the vic-diol. vic-diols are smoothly converted to the corresponding olefins under these conditions. *JOC* **1976**, *41* , 896

Olefins from Epoxides



From Acetylenes

- Hydrogenation with Lindlar's catalyst gives cis-olefins



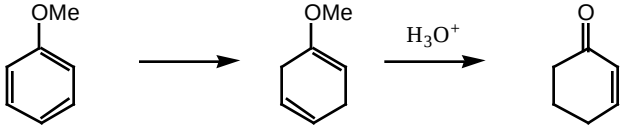
Tetrahedron Lett. **1998**, *39*, 2609

From Other Olefins

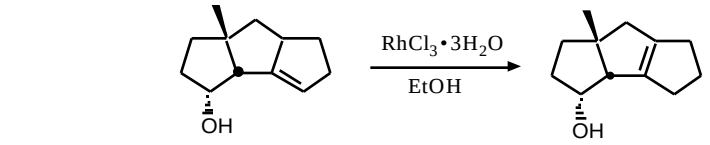
Sigmatropic Rearrangements

- transposition of double bonds

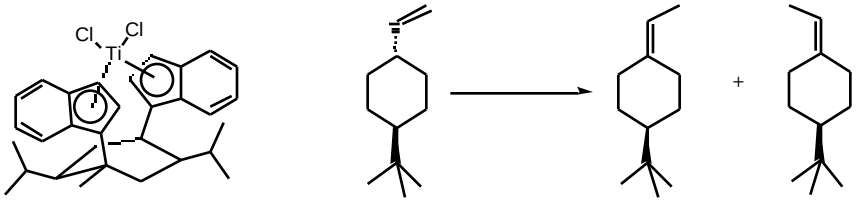
Birch Reduction *Tetrahedron* **1989**, *45*, 1579



Olefin Isomerization- a variety of transition metal ($RhCl_3 \cdot H_2O$) catalyst will isomerize doubles bonds to more thermodynamically favorable configurations (i.e. more substituted, trans, conjugated)



JOC **1987**, 52 , *2875*

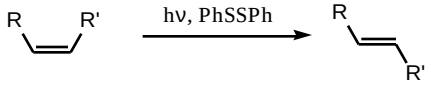


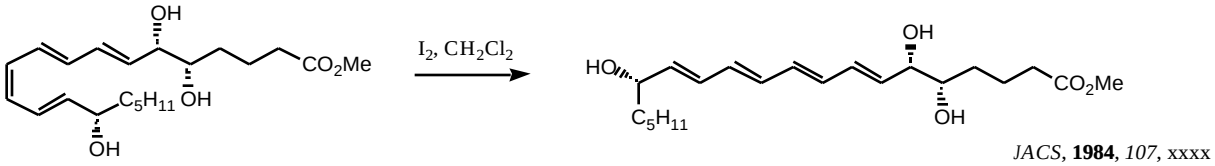
JACS **1992** *114* , 2276

up to 80% ee

Olefin Inversion *Tetrahedron* **1980**, 557

- Conversion of cis to trans olefins
- Conversion of trans to cis- olefins



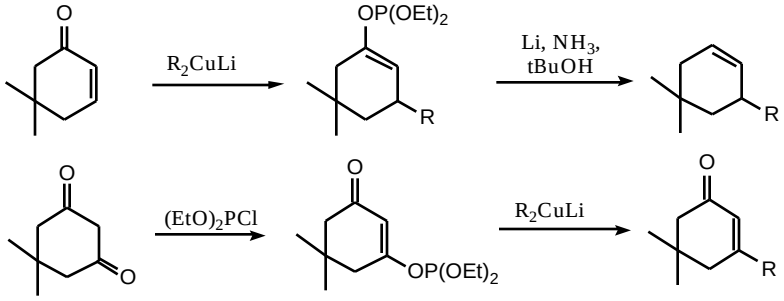


JACS, **1984**, *107*, xxxx

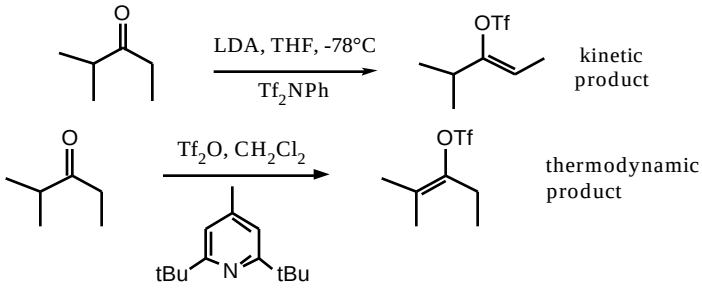
Transition Metal Catralyzed Cross-Coupling Reactions

Coupling of Vinyl Phosphonates and Triflates to Organometallic Reagents

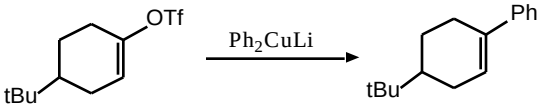
- vinyl phosphates review: *Synthesis* **1992**, 333.



- preparation of enol triflates *Synthesis* **1997**, 735



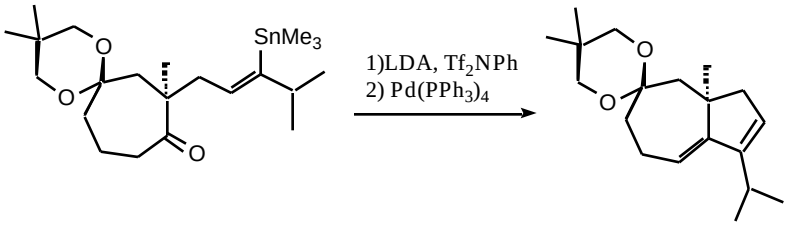
- reaction with cuprates. *Acc. Chem. Res.* **1988**, *25*, 47



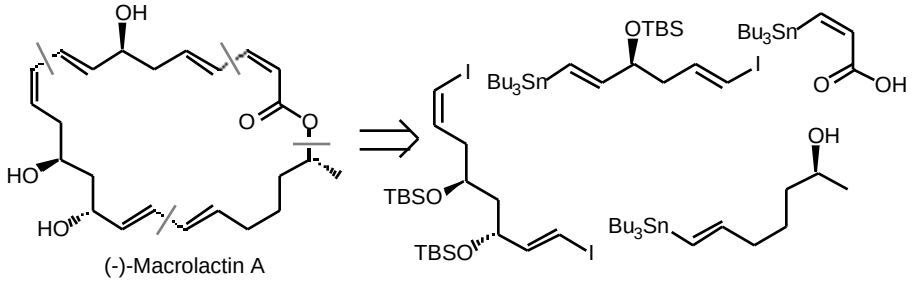
TL **1980**, *21* , 4313

- palladium (0) catlyzed cross-coupling of vinyl or aryl halides or triflates with organostannanes (Stille Reaction)

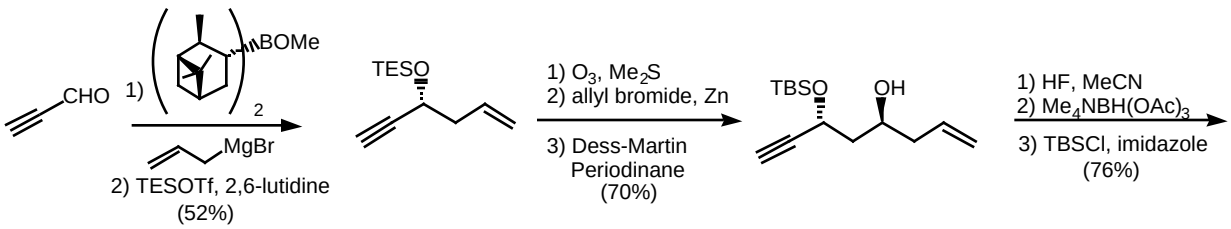
Angew. Chem. Int. Ed. Engl. **1986**, *25*, 508.; Organic Reactions **1997**, *50*, 1-652

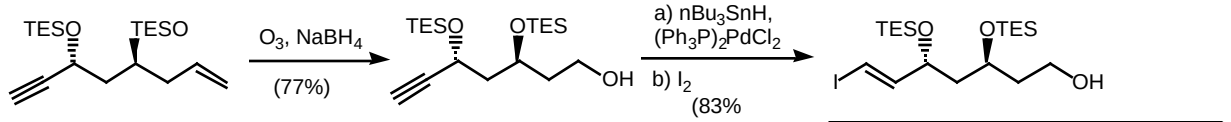


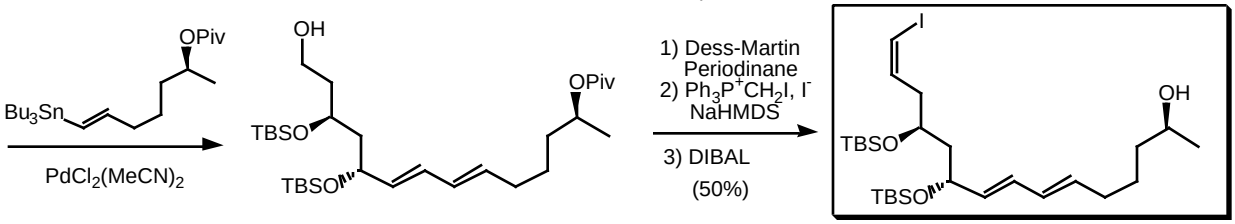
JOC **1986**, *51* , 3405

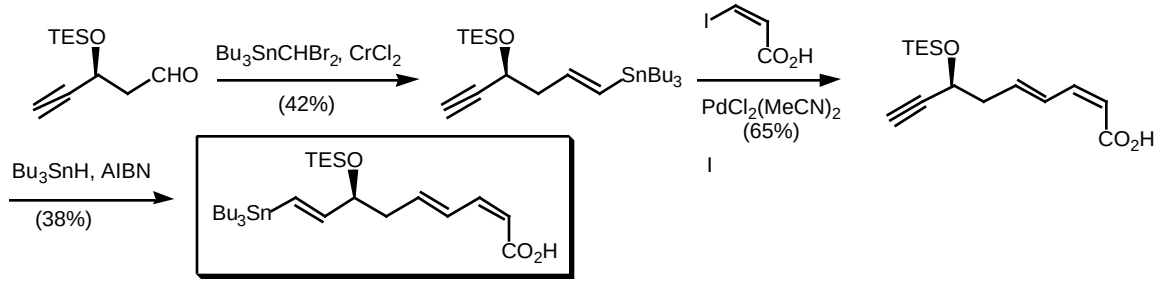


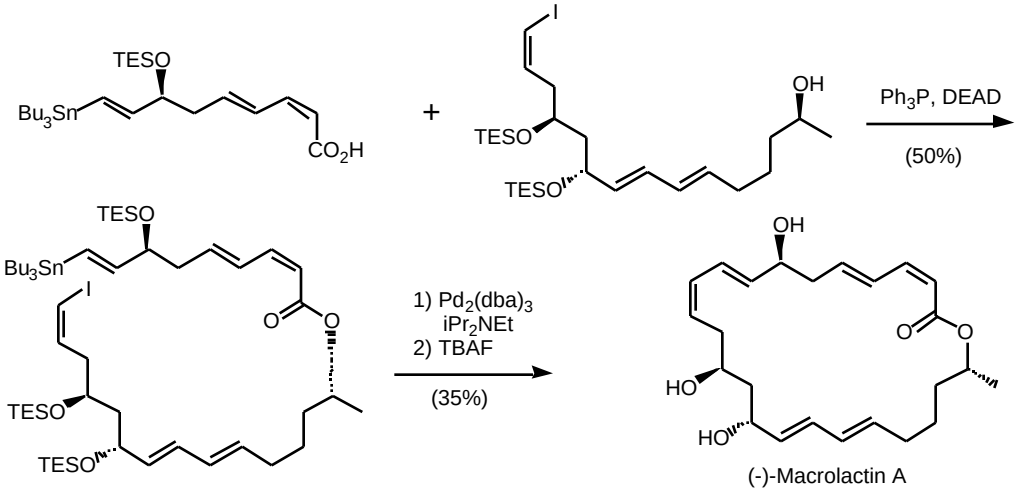
J. Am. Chem. Soc. **1998**, *120*, 3935



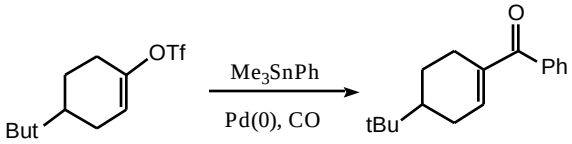






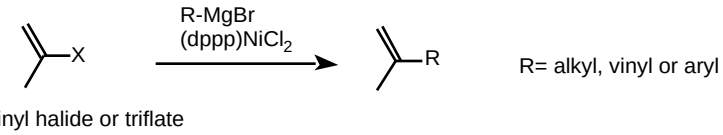


palladium (0) catalyzed carbonylations- coupling of a vinyl triflate with a organostanane to give α,b-unsaturated ketones.

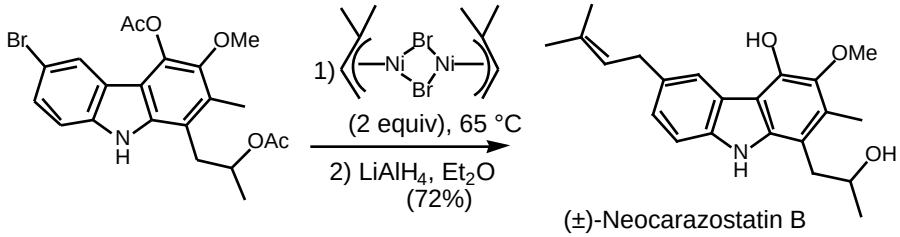


JACS **1994**, *106* , 7500

Nickel (II) Catalyzed Cross-Coupling with Grignard Reagents (Kumada Reaction): *Pure Appl. Chem.* **1980**, *52*, 669 *Bull Chem. Soc. Jpn.* **1976**, *49*, 1958

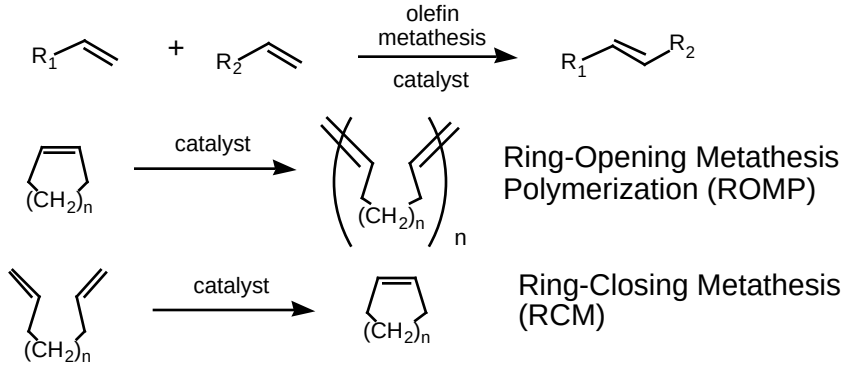


Aryl or vinyl halide or triflate

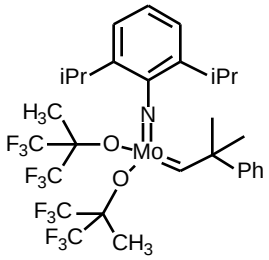


Tetrahedron Lett. **1998**, *39*, 2537, 2947,

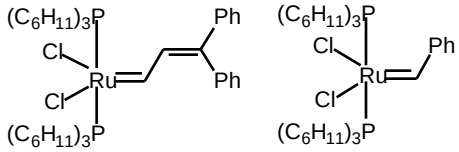
Olefin Metathesis *Tetrahedron* **1998**, *54*, 4413, *Acc. Chem. Res.* **1995**, *25*, 446.



Metathesis Catalysts:

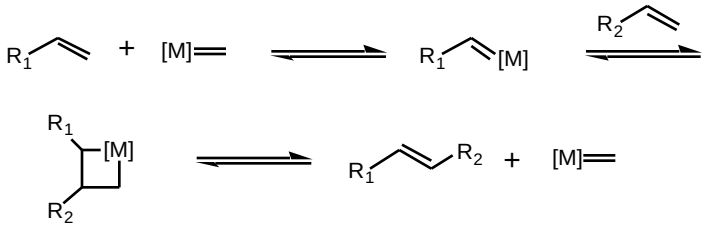


Schrock' s Catalyst



Grubbs' Catalyst

Mechanism:

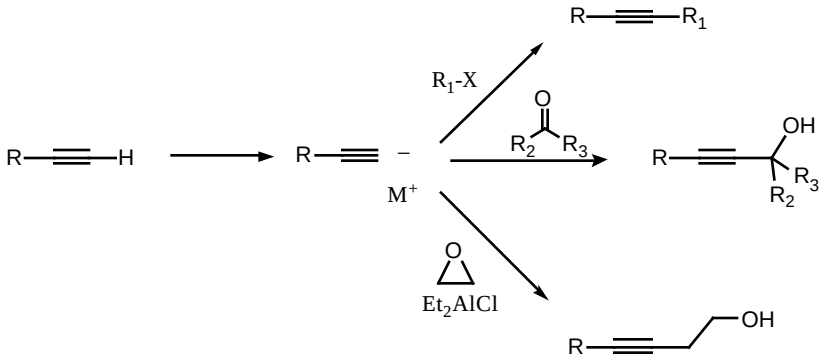


C≡C Bond Formation

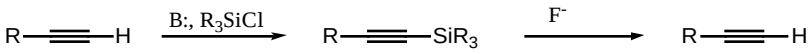
1. From other acetylenes
2. From carbonyls
3. From olefins
4. From Strained Rings
5. Eschenmosher Fragmentation
6. Allenes

From Other Acetylenes

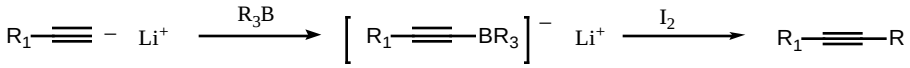
- The proton of terminal acetylenes is acidic (pK_a= 25), thus they can be deprotonated to give acetylide anions which can undergo substitution reactions with alkyl halides, carbonyls, epoxides, etc. to give other acetylenes.



- Since the acetylenic proton is acidic, it often needs to be protected as a trialkylsilyl derivative. It is conveniently deprotected with fluoride ion.

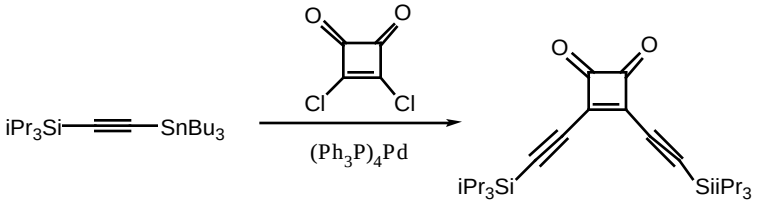


Acetylide anions and organoboranes

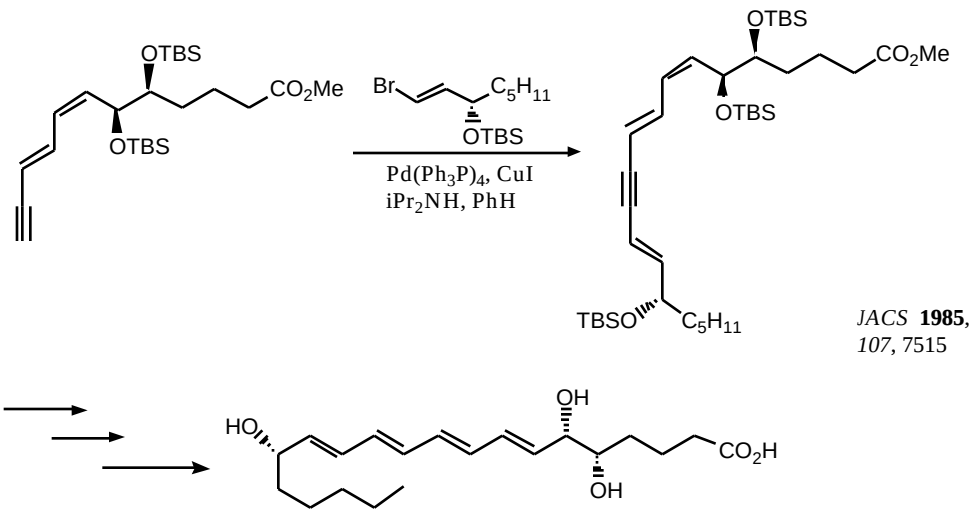


JOC **1974**, *39* , 731
JACS, **1973**, *95* , 3080

Palladium Coupling Reactions:

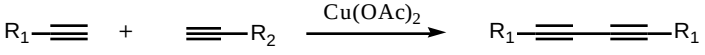


JACS **1990**, *112*, 1607



JACS **1985**, *107*, 7515

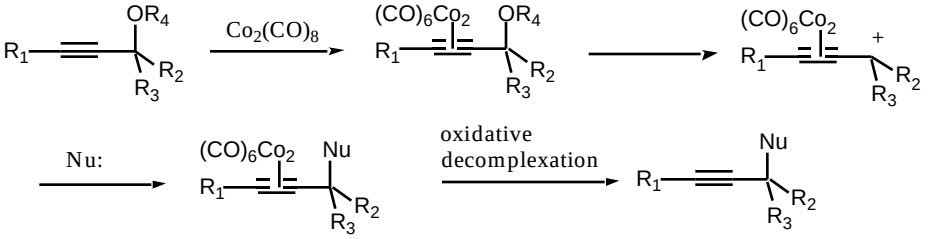
Copper Coupling- 1,3-diynes

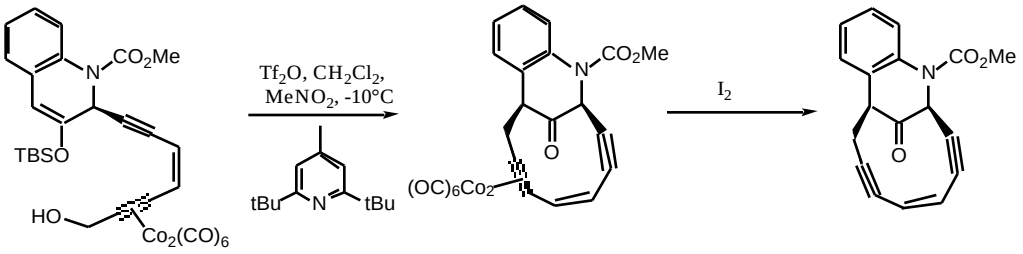


Adv. Org. Chem. **1963**,*4* , 63

Nicholas Reaction

- acetylenes as their $Co_2(CO)_8$ complex can stabilize an α-positive charge, which can subsequently be trapped with nucleophiles.

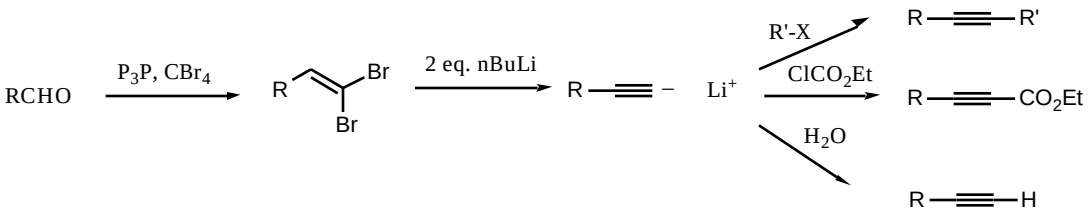


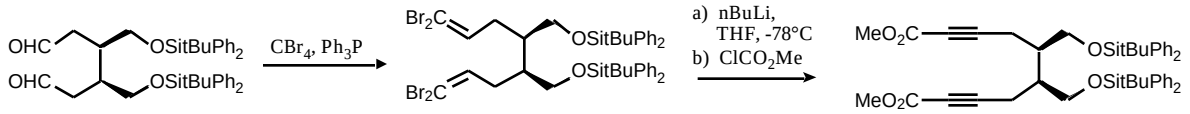


JCSCC **1991**, 544

$Co_2(CO)_6$-acetylene deocomplexation: *JOC* **1997**, *62*, 9380

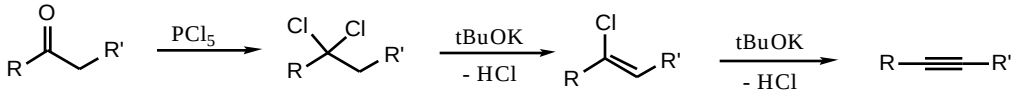
From Aldehydes and Ketones



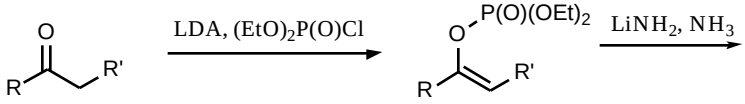


JACS **1992**, *114* , 7360

- by conversion of ketones to gem-dihalides followed by elimination

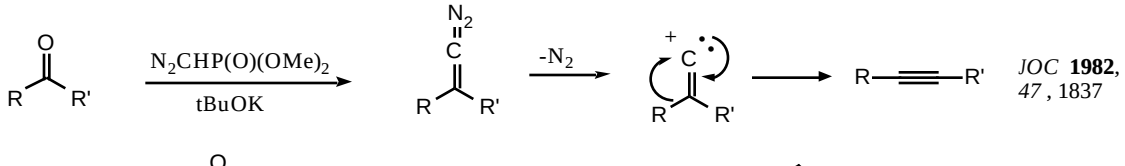


- by conversion of ketones to enol phosphates followed by elimination

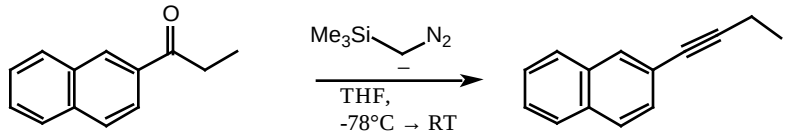


JOC **1987**, *52* , 4885

- Insertion reaction of a vinyl carbene (terminal acetylenes)



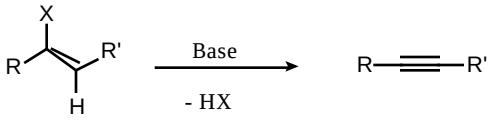
JOC **1982**, *47* , 1837



Synlett **1994**, 107

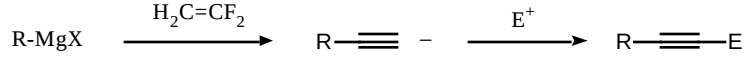
Via Elimination Reactions of Vinyl Halides

- Treatment of vinyl halides with strong base gives acetylenes.



X= Cl, Br, I, OTf, O_3SR, $OP(O)R_2$ Base= LDA; tBuOK; $NaNH_2$, DBU

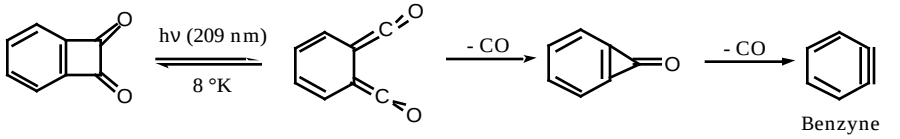
- Addition of Grignard reagents to 1,1-difluoroethylene yields an acetylide anion which can be subsequently trapped with electrophiles.



TL **1982**, *23* , 4325
JOC **1976**, *41* , 1487

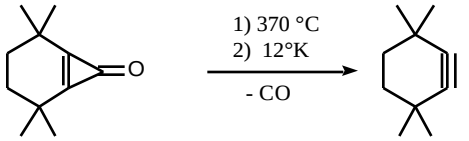
Strained Rings *Topics in Current Chemistry* **1983**, *109*, 189.

- Cyclopropenones and cyclobutendiones can be photolyzed or thermolyzed (FVP) to give acetylenes.

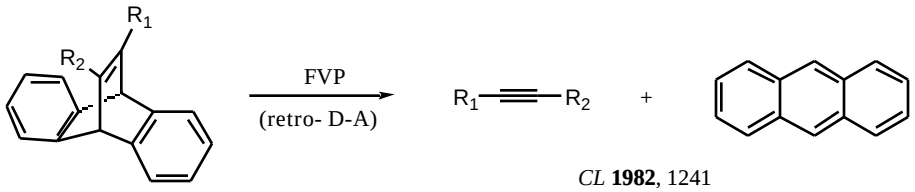


JACS **1973**, *95* , 6134

Benzyne

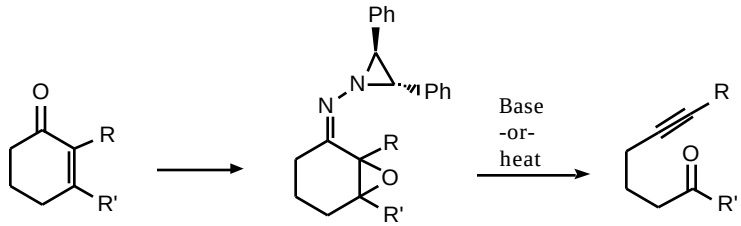


ACIEE **1988**,*27* , 398
JACS **1991**, *113* , 6943

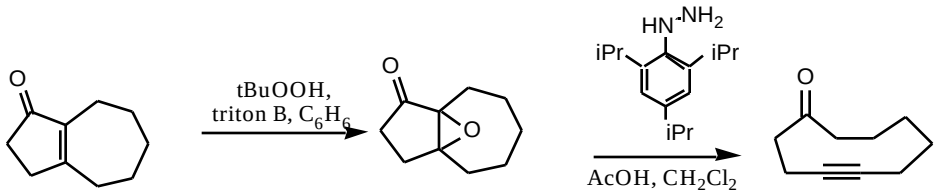


CL **1982**, 1241

Eschenmoser Fragmentation



HCA **1972**, *55* , 1276

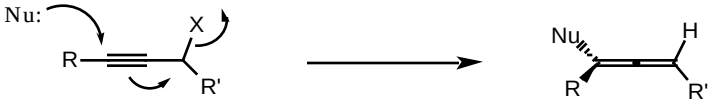


JOC **1992**, *57*, 7052

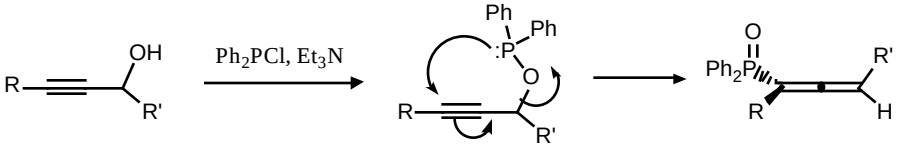
Allenes *Tetrahedron* **1984**, *40*, 2805

- from dihalocyclopropanes

- From SN2' Reactions



- from sigmatropic rearrangements from propargyl sulfoxides and phosphine oxides.



TL **1990**, *31* , 2907
JACS **1990**, *112* , 7825

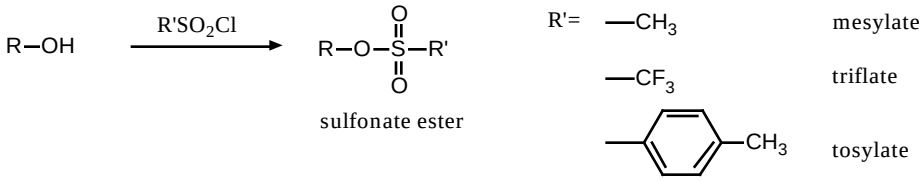
Functional Group Interconversions

C&S Chapter 3 #1; 2; 4a,b, e; 5a, b, d; 6a,b,c,d; 8

1 sulfonates
2 halides
3 nitriles
4 azides
5 amines
6 esters and lactones
7 amides and lactams

Sulfonate Esters

- reaction of an alcohols (1° or 2°) with a sulfonyl chloride

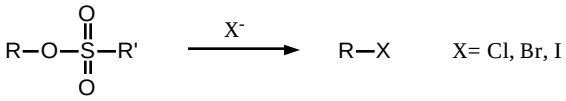


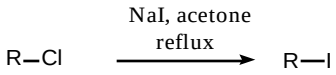
- sulfonate esters are very good leaving groups. Elimination is often a competing side reaction

Halides

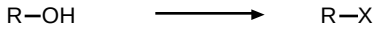
- halides are good leaving groups with the order of reactivity in S_N2 reactions being I>Br>Cl. Halides are less reactive than sulfonate esters, however elimination as a competing side reaction is also reduced.

- sulfonate esters can be converted to halides with the sodium halide in acetone at reflux. Chlorides are also converted to either bromides or iodides in the same fashion (Finkelstein Reaction).





- conversion of hydroxyl groups to halides: *Organic Reactions* **1983**, *29*, 1



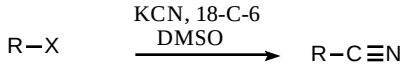
- R-OH to R-Cl
  - $SOCl_2$
  - Ph_3P, CCl_4
  - Ph_3P, Cl_2
  - Ph_3P, $Cl_3CCOCCl_3$

- R-OH to R-Br
  - PBr_3, pyridine
  - Ph_3P, CBr_4
  - Ph_3P, Br_2

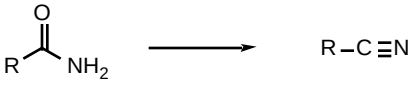
- R-OH to R-I
  - Ph_3P, DEAD, MeI

Nitriles

- displacement of halides or sulfonates with cyanide anion

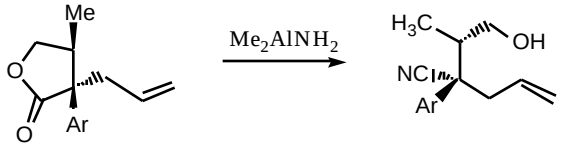


- dehydration of amides



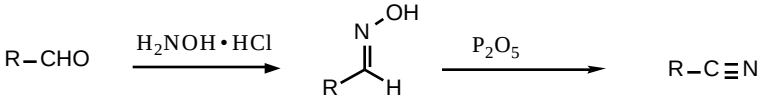
  - $POCl_3$, pyridine
  - TsCl, pyridine
  - P_2O_5
  - $SOCl_2$

- Reaction of esters and lactones with dimethylaluminium amide
  TL **1979**, 4907

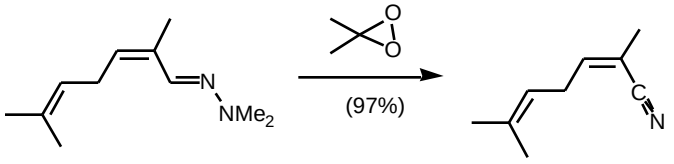


JOC **1987**, *52*, 1309

- Dehydration of oximes

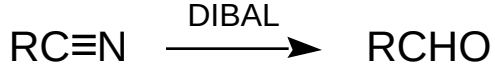


- Oxidation of hydrazones



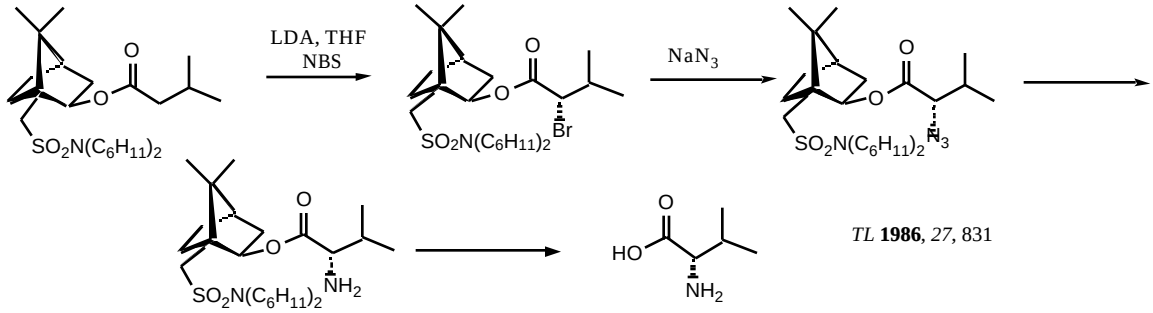
Tetrahedron Lett. **1998**, *39*, 2009

- Reduced to aldehydes with DIBAL.



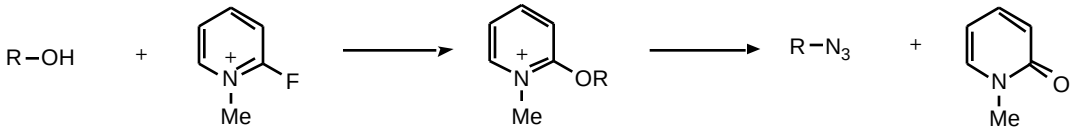
Azides

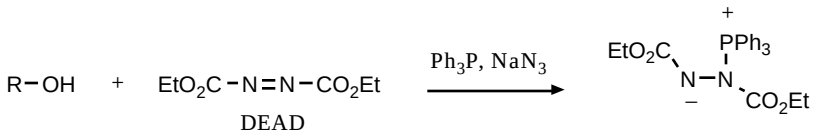
- displacement of halides and sulfonates with azide anion

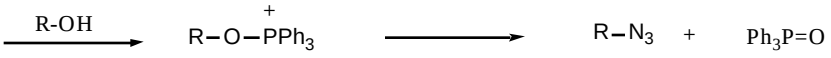


TL **1986**, *27*, 831

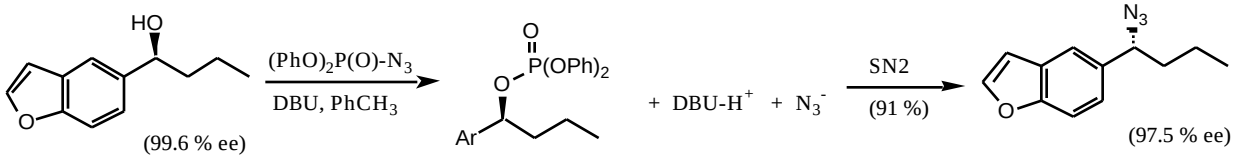
- activation of the alcohol







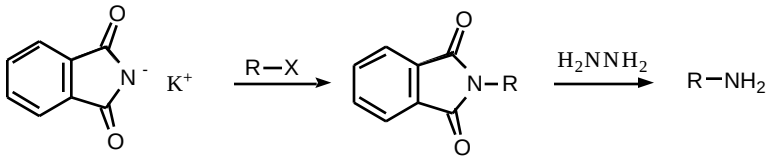
JOC **1993**, *58*, 5886



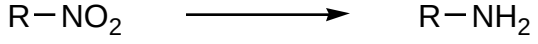
- Photolyzed to aldehydes

Amines

- Gabriel Synthesis

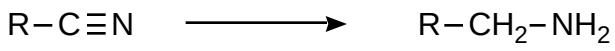


- reduction of nitro groups



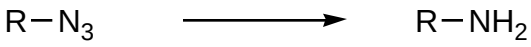
H_2, Pd / C
Al(Hg), H_2O
$NaBH_4$
$LiAlH_4$
Zn, Sn or Fe and HCl
H_2NNH_2
sodium dithionite

- reduction of nitriles



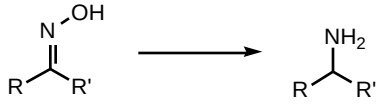
H_2, PtO_2 / C
B_2H_6
$NaBH_4$
$LiAlH_4$
AlH_3
Li, NH_3

- reduction of azides



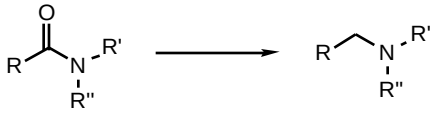
H_2, Pd / C
B_2H_6
$NaBH_4$
$LiAlH_4$
Zn, HCl
$(RO)_3P$
Ph_3P
thiols

- reduction of oximes (from aldehydes and ketones)



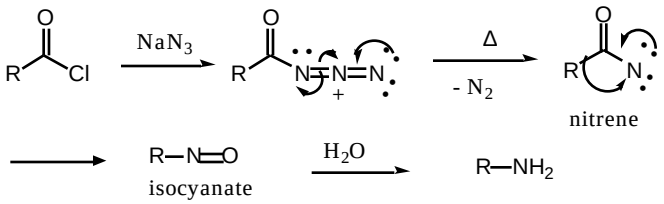
H_2, Pd / C
Raney nickel
$NaBH_4$, $TiCl_4$
$LiAlH_4$
Na(Hg), AcOH

- reduction of amides



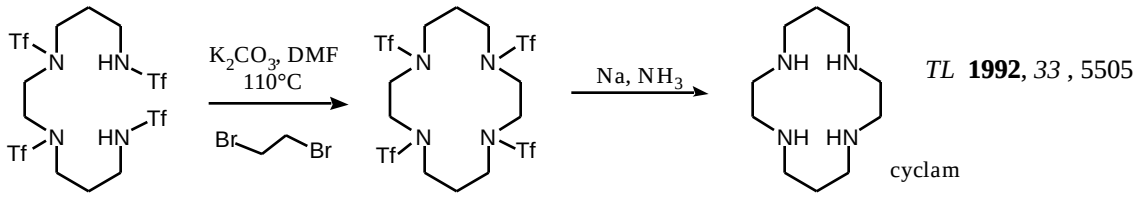
H_2, Pd / C
B_2H_6
$NaBH_4$, $TiCl_4$
$LiBH_4$
$LiAlH_4$
AlH_3

- Curtius rearrangement



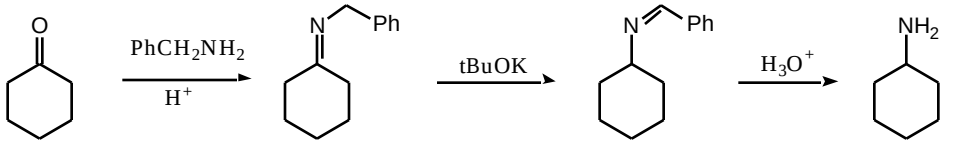
- reductive aminations of aldehydes and ketones
  - Borsch Reaction
  - Eschweiler-Clark Reaction

- alkylation of sulfonamides



TL **1992**, *33* , 5505

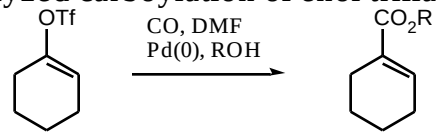
- transamination



Can. J. Chem. **1970**, *48*, 570

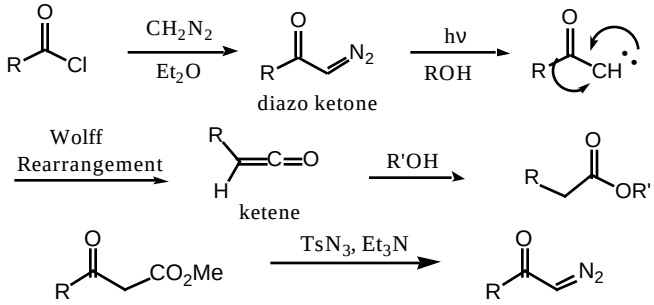
Esters and Lactones

- Reaction of alcohols with "activated acids"
- Baeyer-Villigar Reaction *Organic Reactions* **1993**, *43*, 251
- Pd(0) catalyzed carboylation of enol triflates

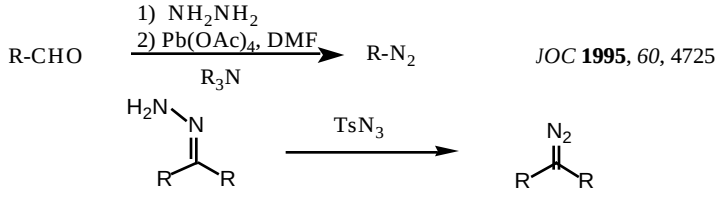


TL **1985**, *26* , 1109

- Arndt-Eistert Reaction *Angew. Chem. Int. Ed. Engl.* **1975**, *15*, 32.

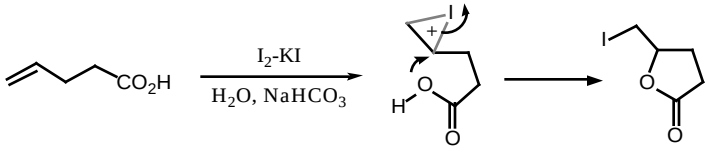


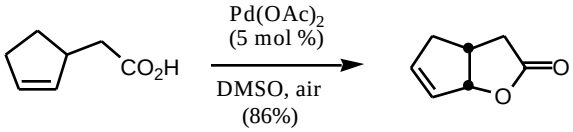
- Diazoalkanes: carbene precursors



JOC **1995**, *60*, 4725

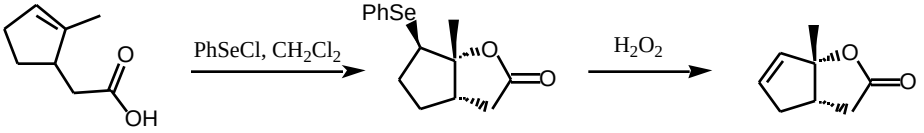
- Halo Lactonizations review: *Tetrahedron* **1990**, *46* , 3321





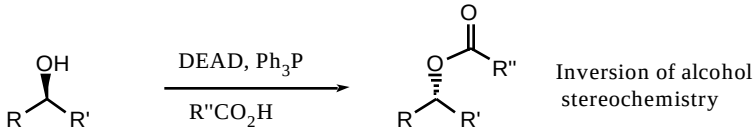
JOC **1993**, *58*, 5298

- Selenolactonization



JACS **1985**, *107* , 1148

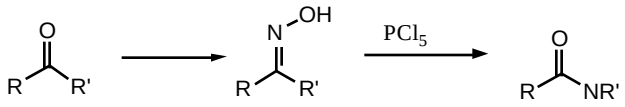
- Mitsunobu Reaction *Synthesis* **1981** , 1; *Organic Reactions*, **1991**, *42*, 335
  Mechanism: *JACS* **1988**, *110* , 6487



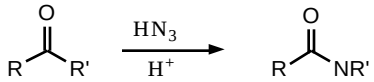
Inversion of alcohol stereochemistry

Amides and Lactams

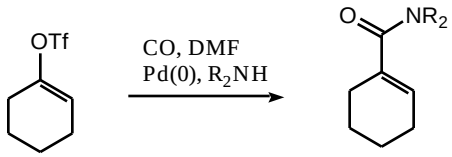
- reaction of an "activated acid" with amines
- Beckman Rearrangement *Organic Reactions* **1988**, *35*, 1



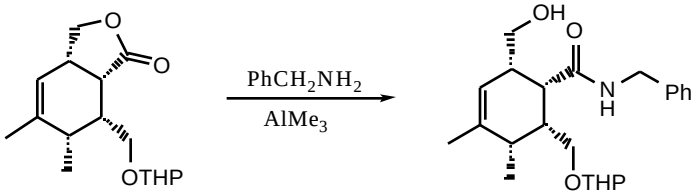
- Schmidt rearrangement



- others

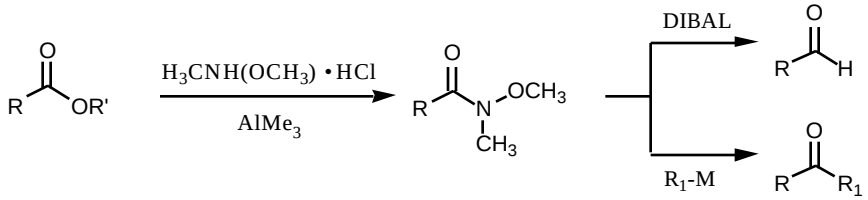


TL **1985**, *26* , 1109



TL **1977**, 4171

-Weinreb amide *Tetrahedron Lett.* **1981**, *22*, 3815



3 Membered Rings

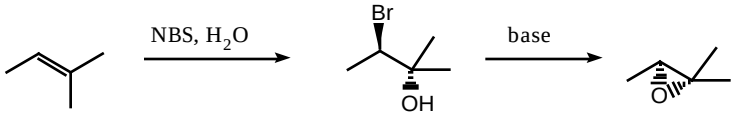
1. epoxides
    a. peracids, hydroperoxides and dioxiranes
    b. transition metal catalyzed epoxidations
    c. halohydrins
    d. Darzen's condensation
    e. sulfur ylides
2. cyclopropanes
    a. Simmons-Smith reactions
    b. diazo compounds
    c. sulfur ylides
    d. S_N2 displacements
3. aziridines
    a. nitrenes
    b. S_N2 displacements

Epoxides

- peracid, hydroperoxide and dioxirane oxidation of alkenes

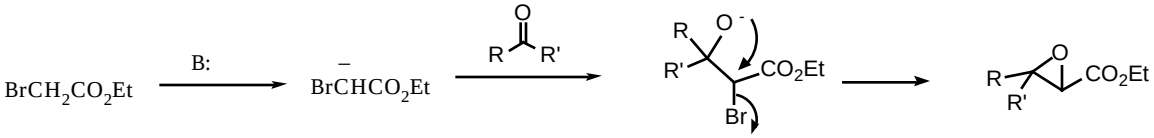
- transition metal catalyzed epoxidation of alkenes
    - Sharpless epoxidation
    - Metal oxo reagents (Jacobsen's reagent)

- from halohydrins

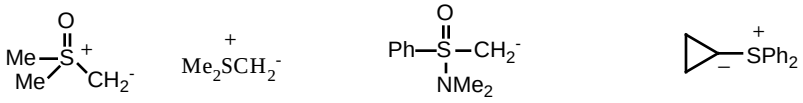


bromohydrin

- Darzen's Condensation



- sulfur ylides *Chem. Rev.* **1997**,*97*, 2421.

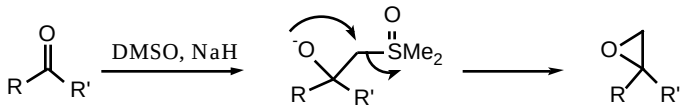


Corey

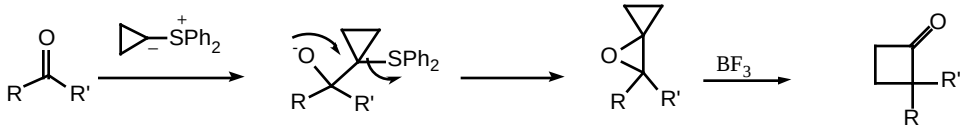
Johnson sulfoximine

Trost

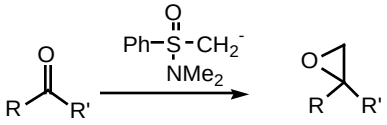
- dimethylsulfoxonium methylide and dimethylsulfonium methylide (Corey's reagent) review: *Tetrahedron* **1987**, *43* , 2609.



- cyclopropyldiphenylsulfonium ylide (Trost's reagent) *ACR* **1974**, *7*, 85.

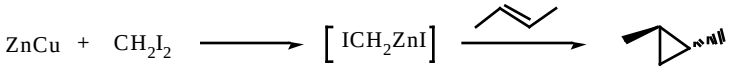


- sulfoximine ylides (Johnson's reagent) *ACR* **1973**, *6* , 341

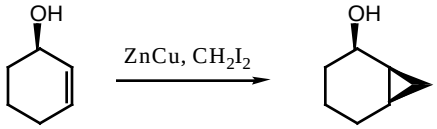


Cyclopropanes

- Simmons-Smith Reaction *Org. Reactions* **1973**, *20*, 1.

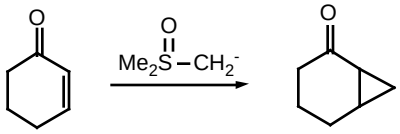


- polar groups (-OH, -NR_2- CO_2R) can direct the cyclopropanation

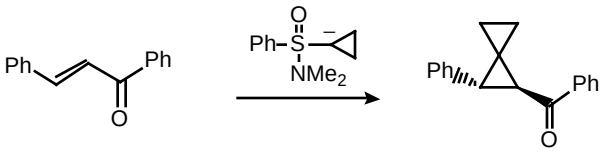


JACS **1979**, *101* , 2139

- sulfur ylides



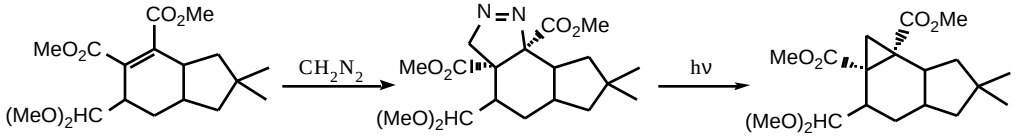
Tetrahedron **1987**, *43* , 2609



ACR **1973**, *6* , 341

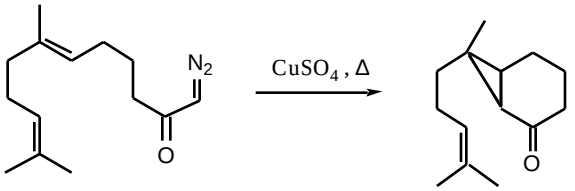
- diazo alkanes and diazo carbonyls *Synthesis* **1972**, 351; **1985**, 569

- cyclopropanation with diazoalkanes; olefin requires at least on electron withdrawing group.

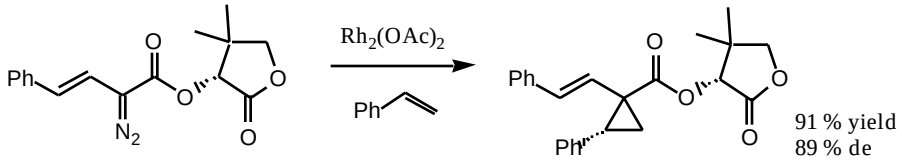


JACS **1975**, *97* , 6075

- diazoketones; photochemical or metal catalyzed decomposition of diazoketones to carbenes followed by cyclopropanation of olefins. *Org. Rxns.* **1979**, *26*, 361; *Tetrahedron* **1981**, *37*, 2407



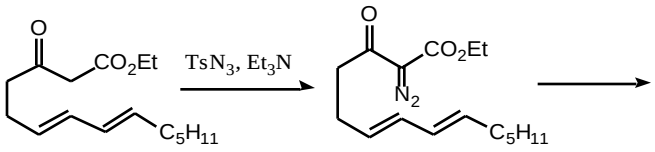
JACS **1970**, *92* , 3429
JACS **1969**, *91* , 4318

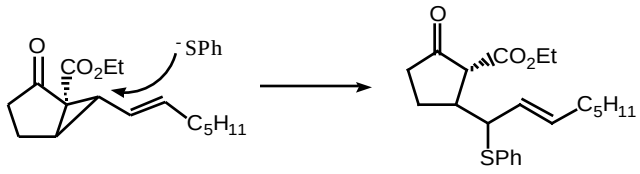


91 % yield
89 % de

JACS **1993**, *115*, 9468

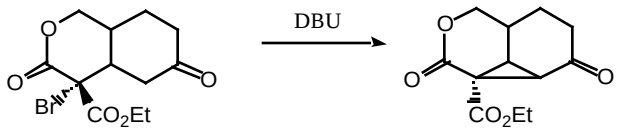
Asymmetric cyclopropanation: Doyle, *Chem Rev*. **1998**, *98*, 911
Aldrichimica Acta **1997**, *30*, 107





JACS **1977**, *99*, 1940

- S_N2 Reactions

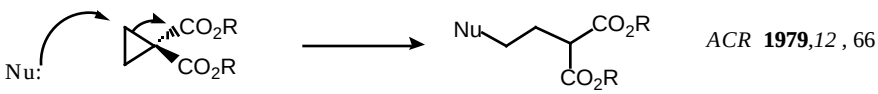


JACS **1978**, *99* , 1940

- Electrophillic Cyclopropanes review: *ACR* **1979**, *12* , 66

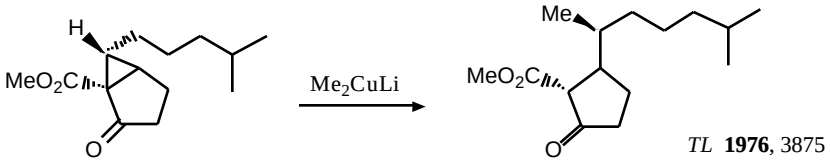
in many ways, cyclopropanes react silmilarly to double bonds

- homo-1,4-addition



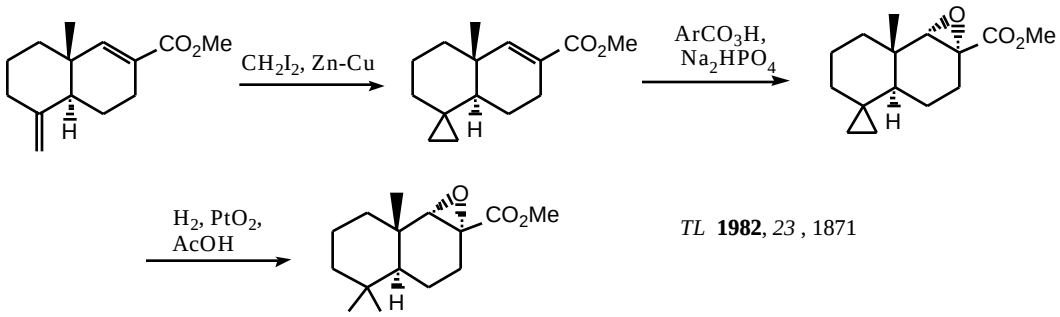
ACR **1979**,*12* , 66

Nu:= malonate anion, amines, thiolate anion, enamines, cuprates
(usually requires double activation of cyclopropane)



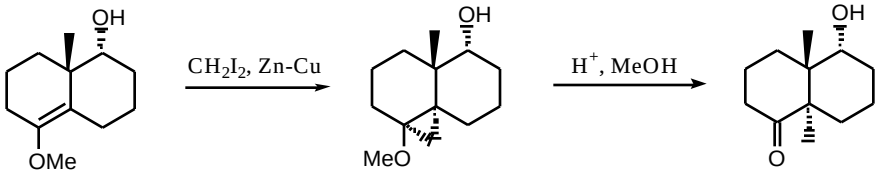
TL **1976**, 3875

- hydrogenation



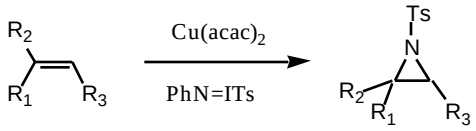
TL **1982**, *23* , 1871

- hydrolysis



JACS **1967**
89 , 2507

Aziridines



J. Org. Chem. .**1991**, *56*, 6744

4 Membered Rings

1. cyclobutanes & cyclobutenes
2. oxatanes

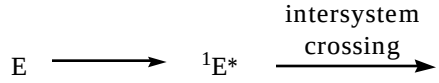
Cyclobutanes

- [2+2] cycloadditions

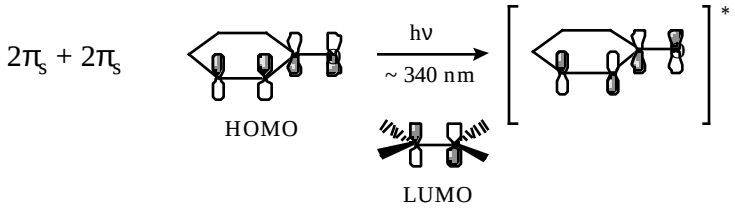
  - photochemical cycloadditions ($2\pi_s + 2\pi_s$)

  Acc. Chem. Res. **1968**, *1*, 50; *Synthesis* **1970**, 287; *Acc. Chem. Res.* **1971**, *4*, 41; *Organic Photochemistry* **1981**, *5*, 123; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 820; *Acc. Chem. Res.* **1982**, *15*, 135; *Organic Photochemistry* **1989**, *10*, 1 *Organic Reactions* **1993**, *44*, 297

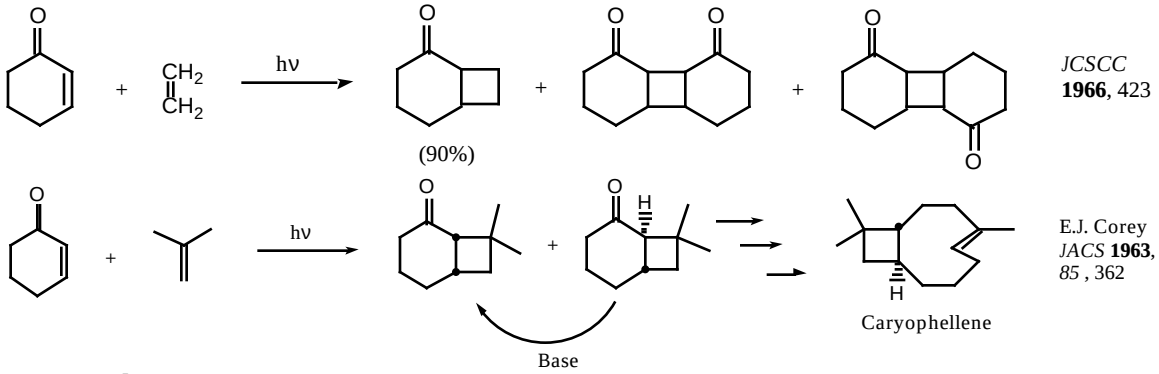
  - for synthetic purposes, cyclic α,β-unsaturated carbonyl are the most useful.



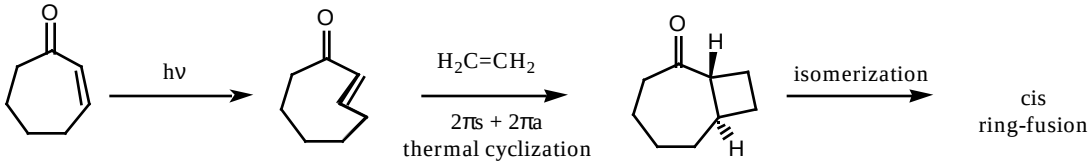
  - symmetry requirements

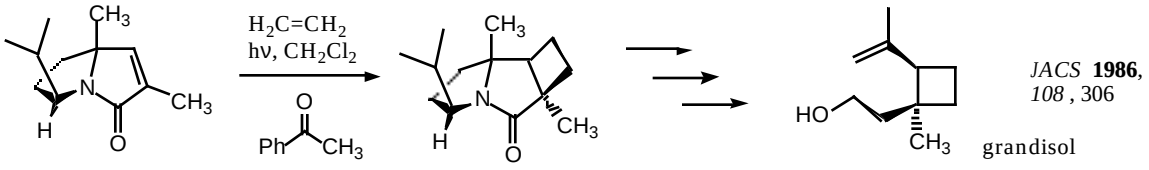


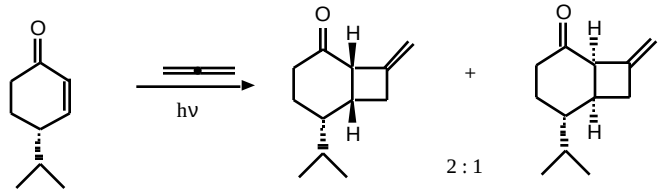
  - enones with olefins



Hot Ground State?

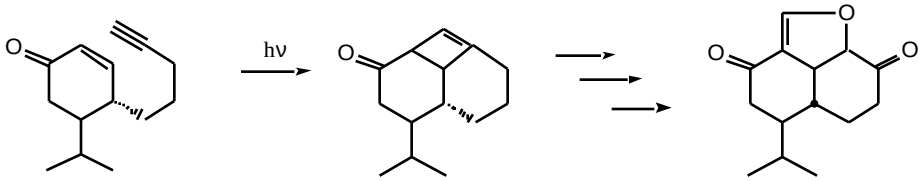






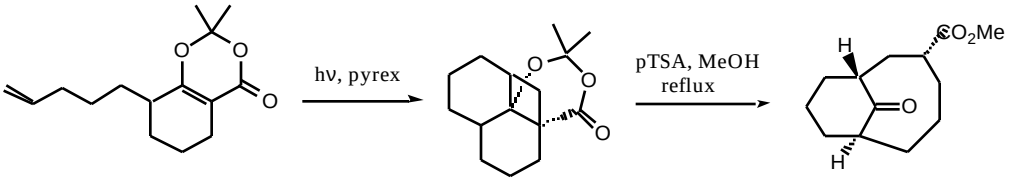
JACS **1984**
106 , 4038

- enones with acetylenes

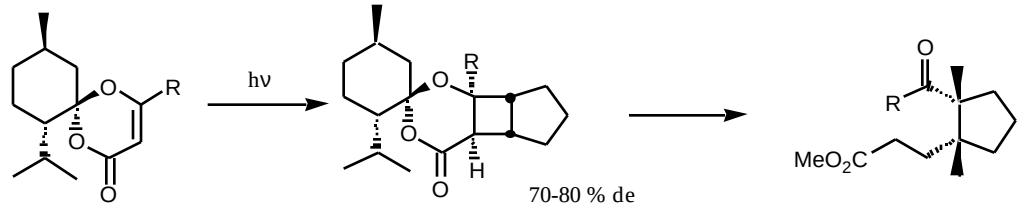


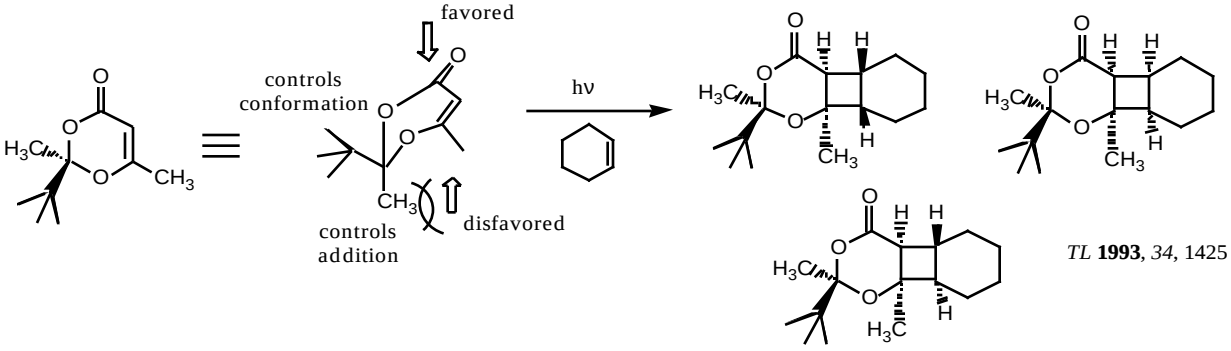
JACS **1982**
104, 5070

- DeMayo Reaction



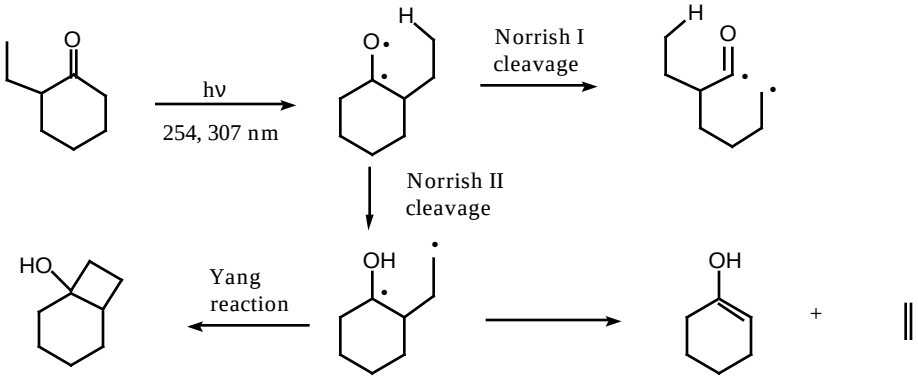
JACS **1986**,
108 , 6425





TL **1993**, *34*, 1425

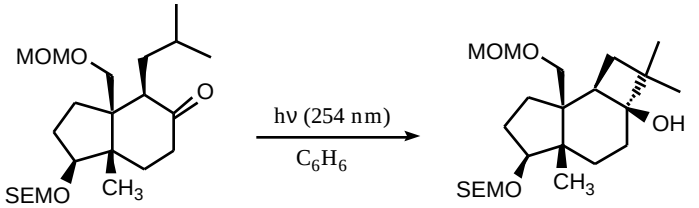
- Photochemistry of Ketones (Norrish Type I and II reactions)



- filtering photchemical reaction to prevent Norrish reactions

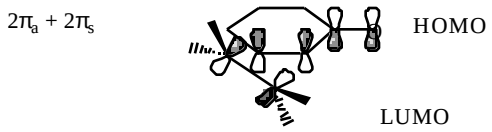
quartz	180 nm
Vycor	200 nm
Pyrex	280 nm
Uranium glass	320 nm

- Yang Reaction

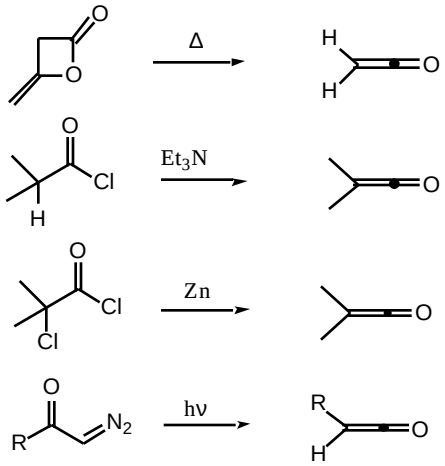


JACS **1987**, *109* , 3017

- thermal cycloadditons ($2\pi_a + 2\pi_s$)
  - symmetry requirements

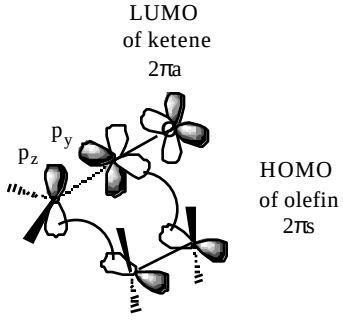


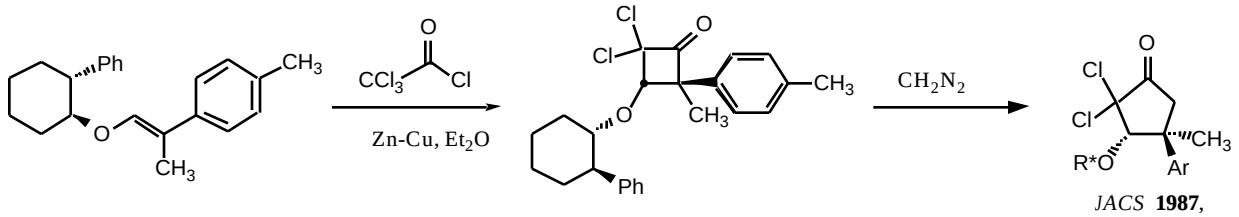
  - ketenes



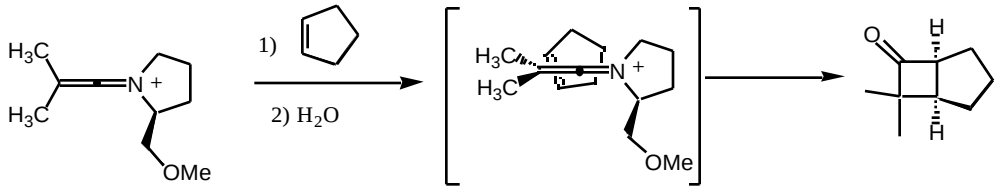
- thermal cyclization of ketene with olefins

Tetrahedron **1986**, *42*, 2587; **1981**, *37*, 2949; *Organic Reactions* **1994**, *45*, 159.



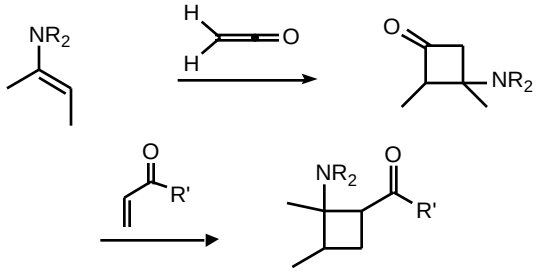


JACS **1987**, *109* , 4753

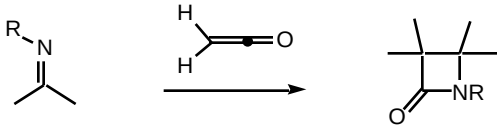


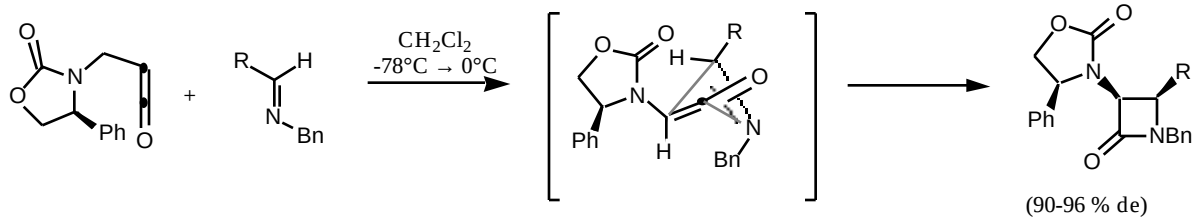
JACS **1982**, *104*, 2920

-reaction of ketene with enamines



- reaction of ketene with imines to give β-lactams (Staudinger Reaction)

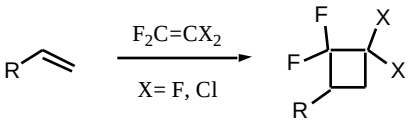




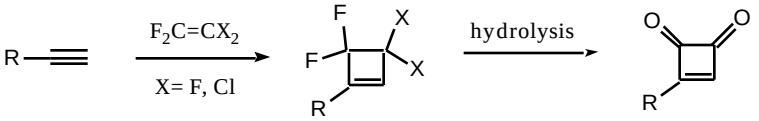
(90-96 % de)

- reaction of difluorodihaloethylene with olefins

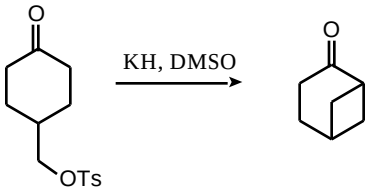
Organic Reactions **1962**, *12*, 1



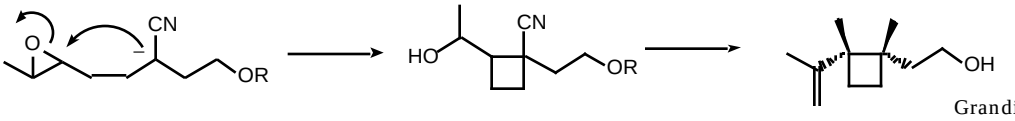
- reaction of difluorodihaloethylene with acetylenes- biradical mechanism



- S_N2 Reaction



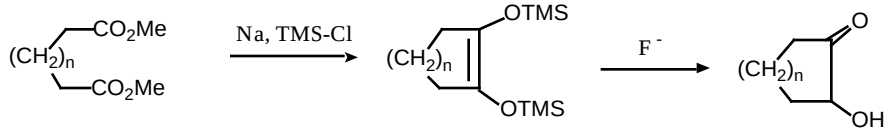
JACS **1980**, *102* , 1404

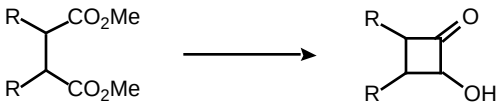


JACS **1974**, 96, 5268, 5272

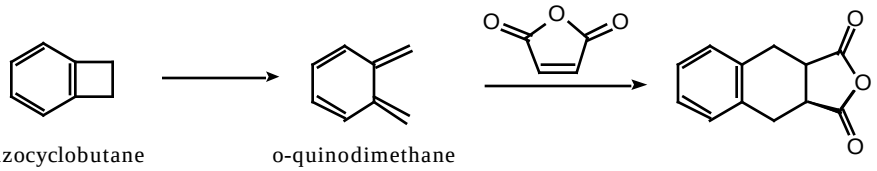
Grandisol

- acyloin reaction *Organic Reactions* **1976**, *23*, 259



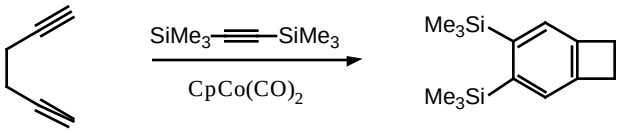


- benzocyclobutanes *ACIEE* **1984**, *23*, 539; *Synthesis* **1978**, 793

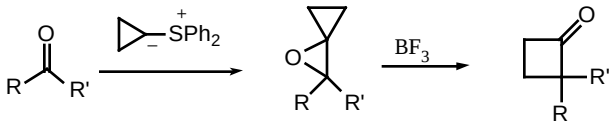


benzocyclobutane o-quinodimethane

- cyclotrimerization of 1,5-diyenes with an acetylenes

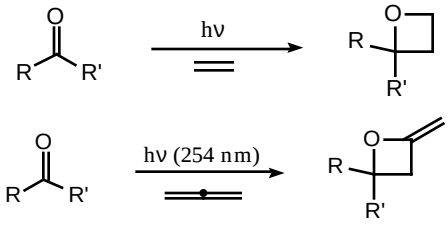


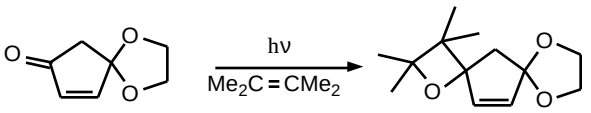
- sulfur ylides



Oxatanes *Organic Photochemistry* **1981**, *5*, 1

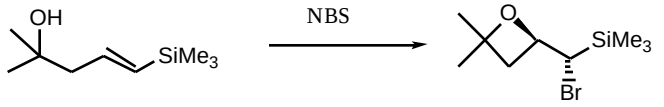
- [2+2] cycloaddition (Paterno-Buchi Reaction)



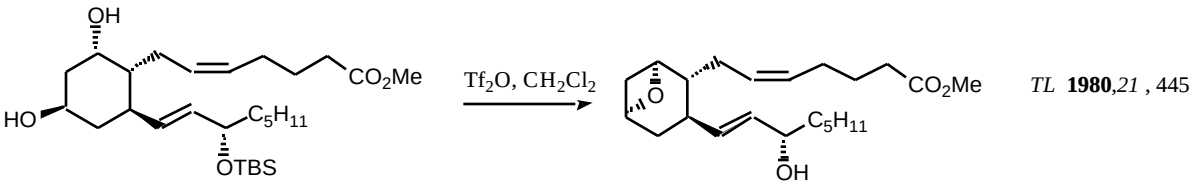


TL **1975** 1001

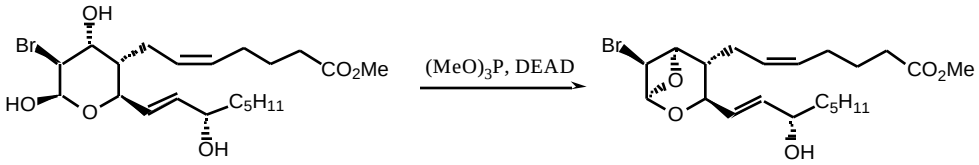
- S_N2 reaction



JCSCC **1979**, 421

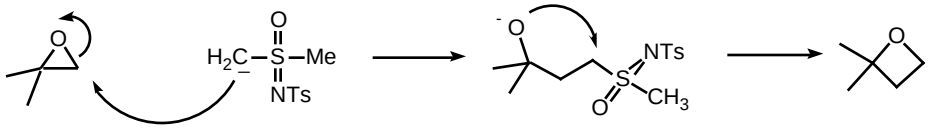


TL **1980**,*21* , 445



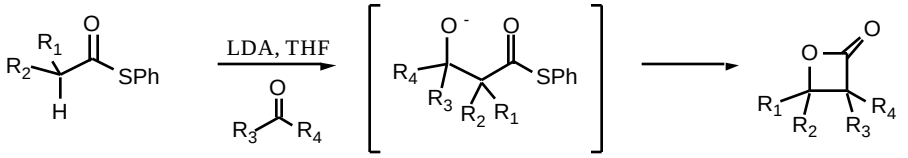
JACS **1984**, *107* , 6372

- sulfur ylides

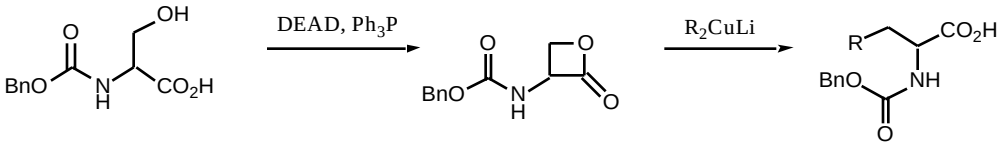


JACS **1979**, *101* , 6135

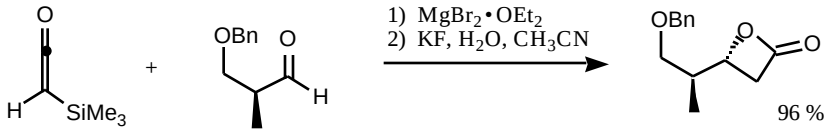
β-*Lactones*



JOC **1991**, *56* , 1176



JACS **1987**, *109* , 4649



TL **1995**, *36*, 4159

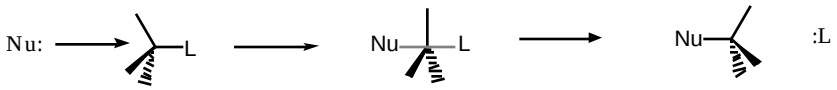
96 % de

Baldwin's Rules (Suggestions) for Ring Closure

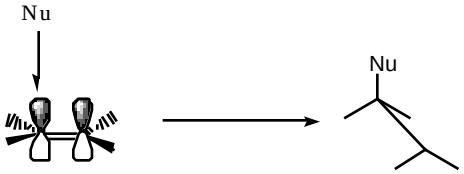
JOC **1977**, *42* , 3846
JCSCC **1976**, 734, 736, 738

Approach Vector Analysis

- for an S_N2 displacement at a tetrahedral center, the approach vector of the entering nucleophile is 180° from the departing leaving group



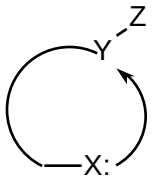
- for the addition of a nucleophile to an Sp2 center, the nucleophile approaches perpendicular to the π-system.



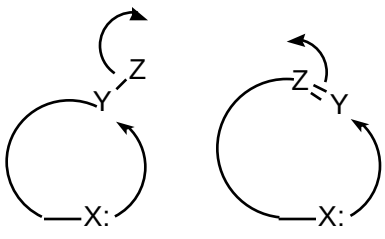
Nomenclature

1. indicate ring size being formed
   3 membered ring = **3**
   4 membered ring = **4**
   etc.

2. indicate geometry of electrophilic atom
   if Y= Sp3 center; then **Tet** (tetrahedral)
   if Y= Sp2 center; then **Trig** (trigonal)
   if Y= Sp center; then **Dig** (digonal)



3. indicate where displaced electrons end up
   - if the displaced electron pair ends up out side the ring being formed; then **Exo**
   - if the displaced electron pair ends up within the ring being formed; then **Endo**

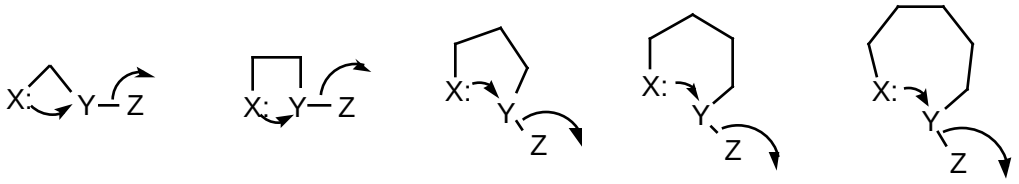


Exo Endo

4. Ring forming reaction is designated as **Favored** or **Disfavored**
disfavored does not imply the reaction can't or won't occur- it only means the reaction is more difficult than favored reactions.

Rules (Suggestions) for Ring Closure

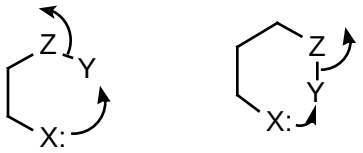
- All **Exo-Tet** reactions are *favored*



3- **4-** **5-** **6-** **7-**

----------Favored----------

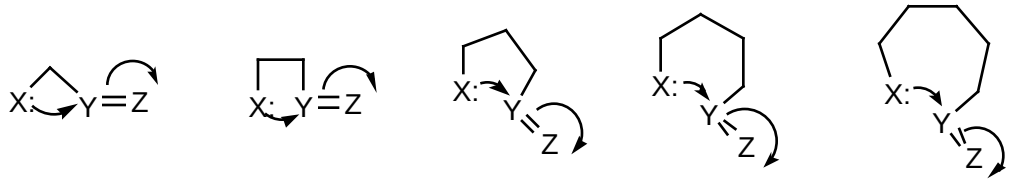
- **5-Endo-Tet** and **6-Endo-Tet** are *disfavored*



5- **6-**

-----Disfavored-----

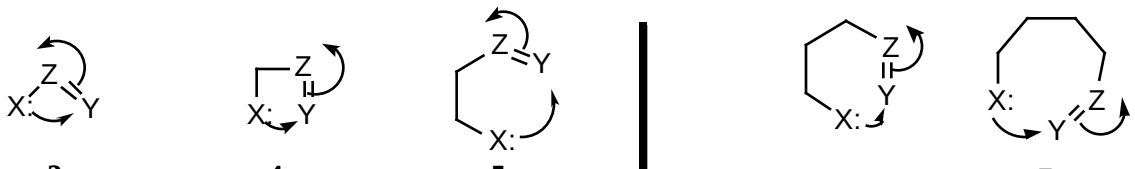
- All **Exo-Trig** reactions are *favored*



3- **4-** **5-** **6-** **7-**

----------Favored----------

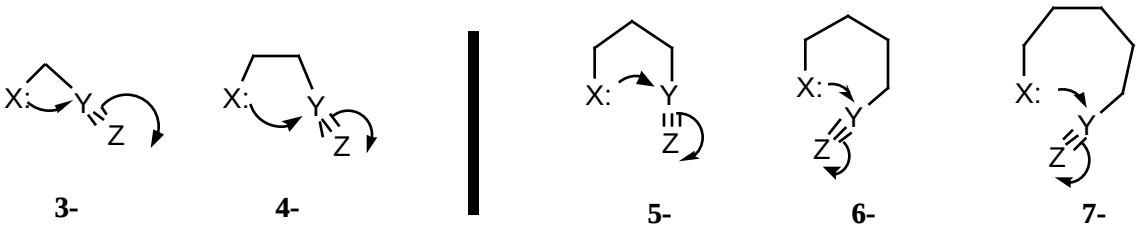
- **3-Endo-Trig**, **4-Endo-Trig** and **5-Endo-Trig** are *disfavored*; **6-Endo-Trig**, **7-Endo-Trig**, etc. are *favored*



3- **4-** **5-** **6-** **7-**

----------Disfavored---------- **------Favored------**

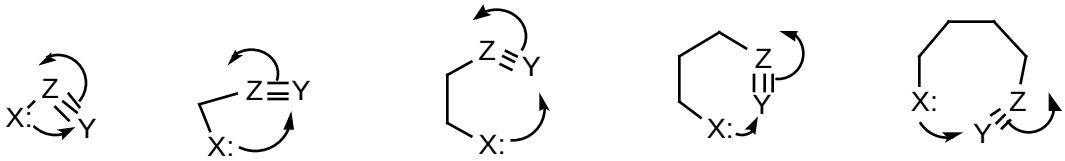
- **3-Exo-Dig** and **4-Exo-Dig** are *disfavored*; **5-Exo-Dig**, **6-Exo-Dig**, **7-Exo-Dig**, etc. are *favored*



3- **4-** **5-** **6-** **7-**

------Disfavored------ **----------Favored----------**

- All **Endo-Dig** are *favored*



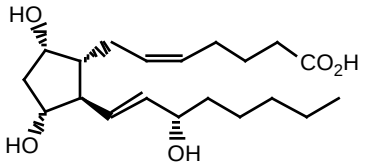
3- **4-** **5-** **6-** **7-**

----------Favored----------

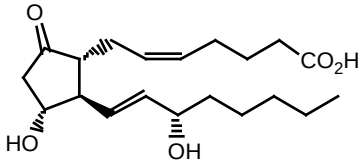
EXCEPTION:

There are many !!! (see March p 212-214)

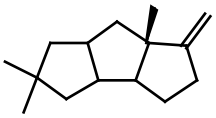
5 Membered Rings



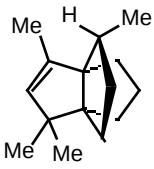
$PGF_{2\alpha}$



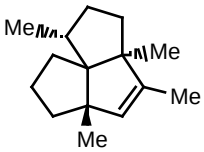
PGE_2



Hirsutene



Modhephane

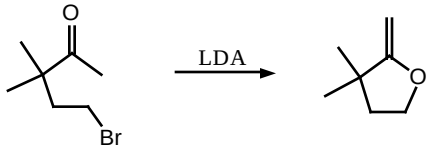


Isocumene

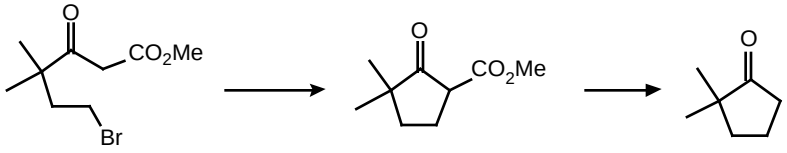
1. Intramolecular S_N2 Reactions
2. Intramolecular Aldol Condensation and Michael Addition
3. Intramolecular Wittig Olefination
4. Ring Expansion and Contraction Reactions
    a. 3 → 5
    b. 4 → 5
    c. 6 → 5
5. 1,3-Dipolar additions
6. Nazarov Cyclization
7. Arene-Olefin Photocyclization
8. Radical Cyclizations
9. Others

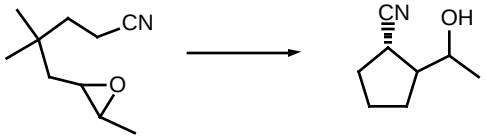
Synthesis **1973**, 397; *ACIEE* **1982**, *21* , 480;

Intramolecular S_N2 Reaction 5-exo-tet: favored

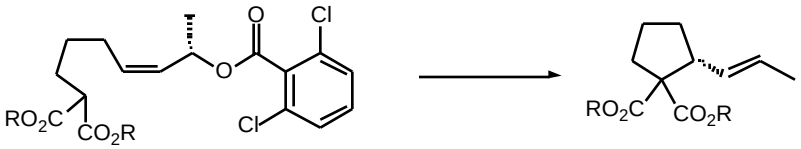


JCSCC **1973**, 233

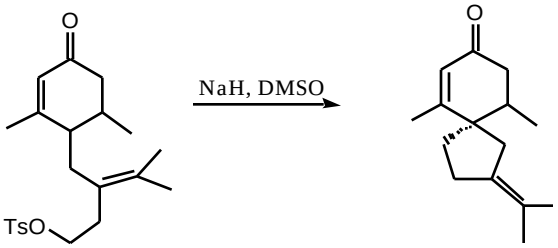




JACS **1974**, *96* , 5268

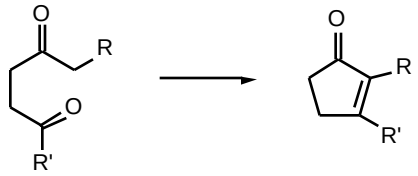


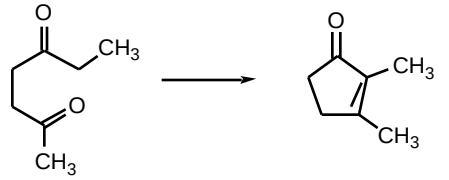
JACS **1979**, *101* , 5081



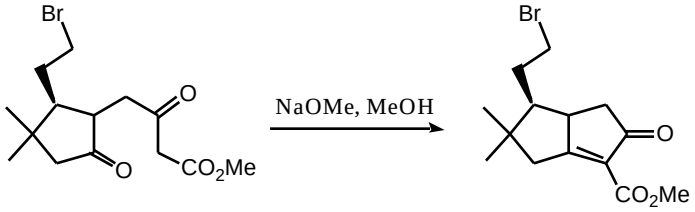
JCSCC **1979**, 817

Intramolecular Aldol Condensation 5-exo-trig: favored
intramolecular aldol condensation of 1,4-diketones

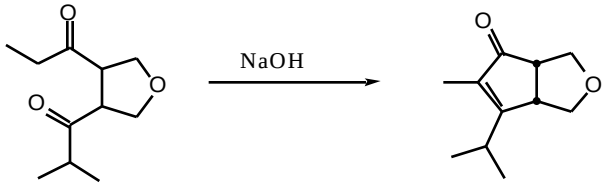




TL **1982**, *29*, 2237

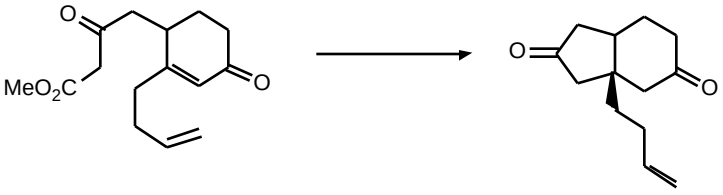


JACS **1980**, *102* , 4262



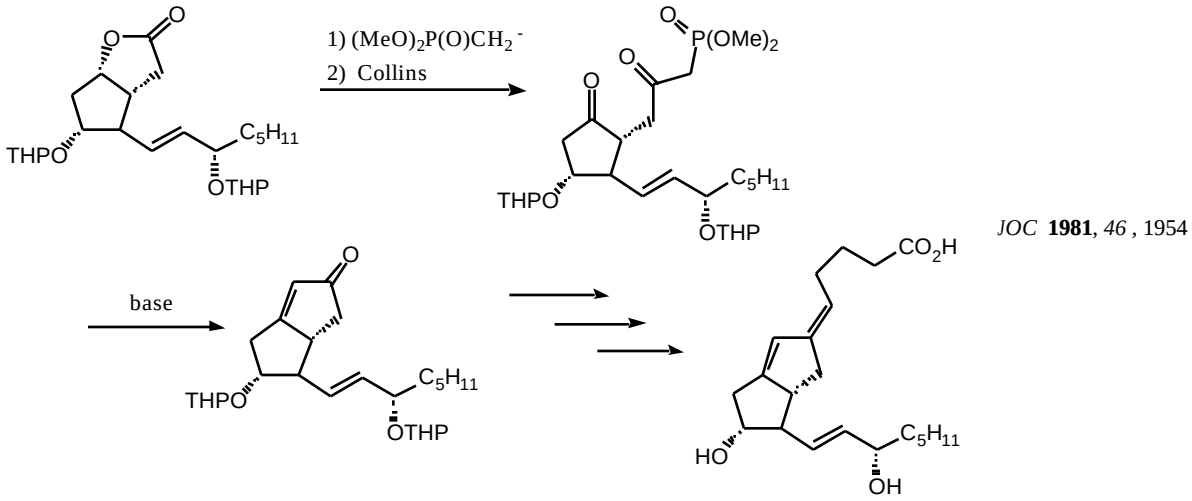
JOC **1983**, *48* , 1217

Intramolecular Michael Addition 5-exo-tet: favored
Organic Reactions **1995**, *47*, 315-552



JACS **1979**, *101* , 7107

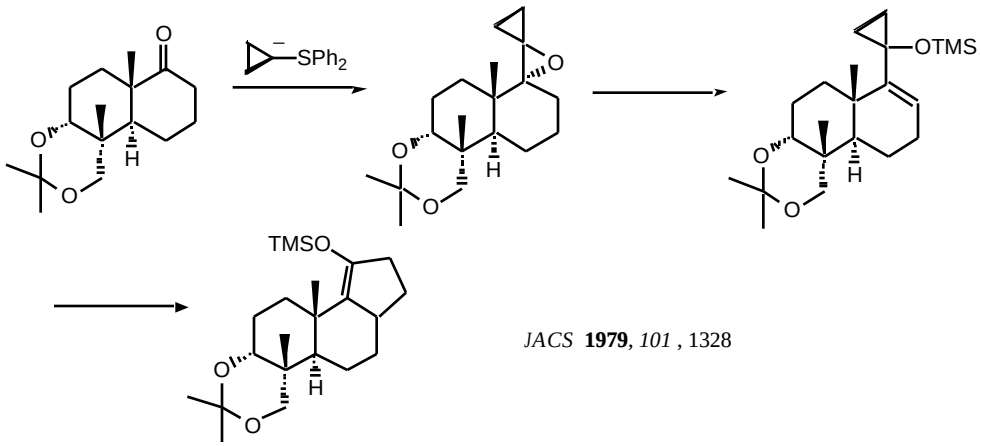
Intramolecular Wittig Olefination *Tetrahedron* **1980**, *36*, 1717



JOC **1981**, *46* , 1954

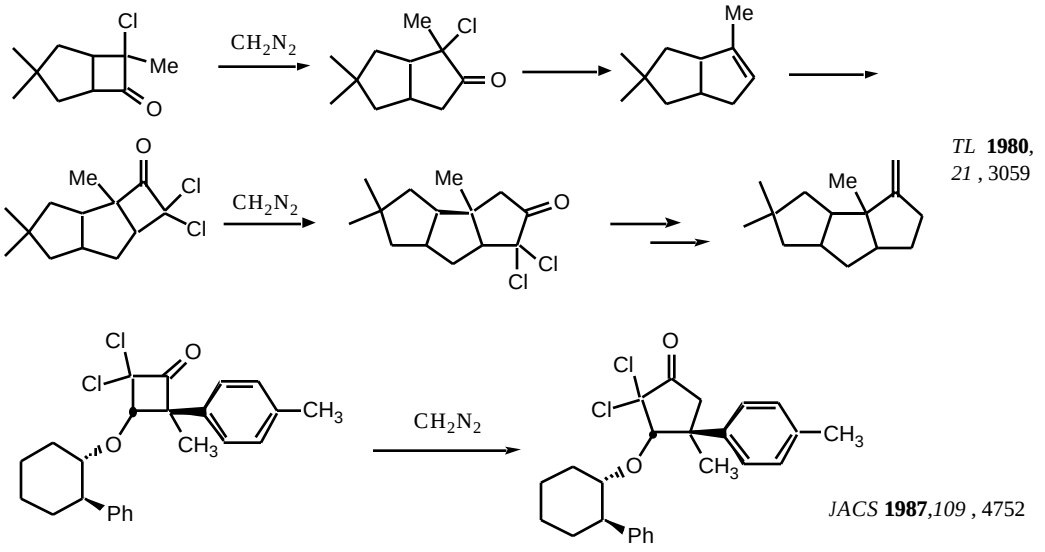
Ring Expansion Reactions

- 3 → 5: Vinyl Cyclopropane Rearrangement *Organic Reactions* **1985**, *33*, 247.



JACS **1979**, *101* , 1328

- 4 → 5: Reaction of cyclobutanones with Diazomethane

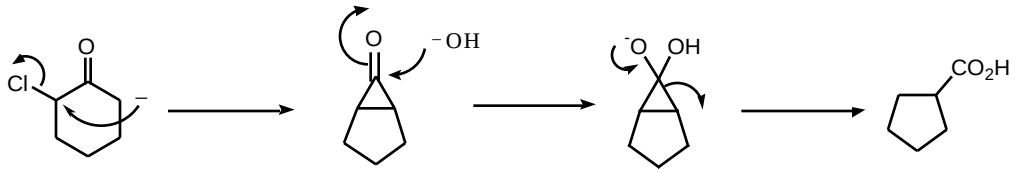


TL **1980**, *21* , 3059

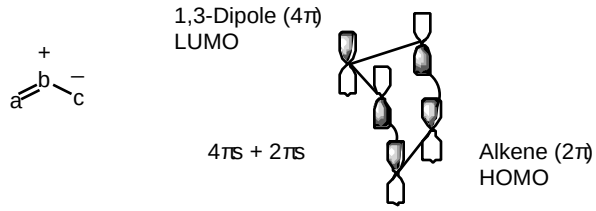
JACS **1987**,*109* , 4752

Ring Contraction Reactions

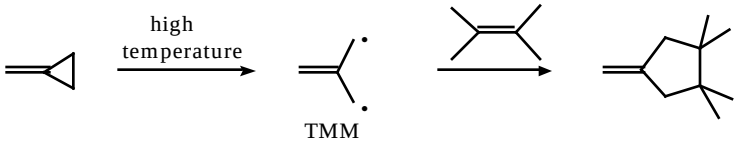
- 6 → 5: Favorskii Reaction *Organic Reactions* **1960**, *11* , 261

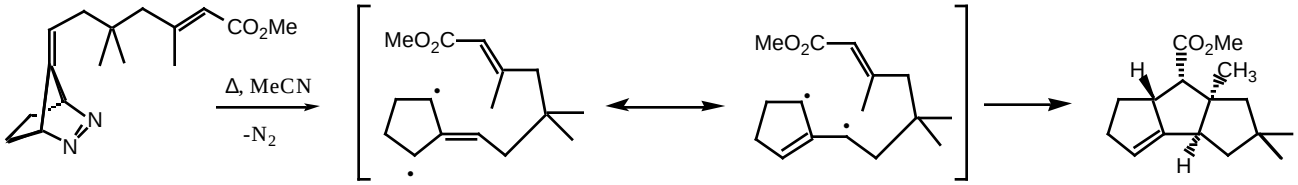


1,3-Dipolar Addition to Olefins *1,3-Dipolar Cycloaddition Chemistry , vol 1 & 2* (A. Padwa ed.) (Wiley, NY 1984); *ACIEE* **1977**, *16* , 10. *Chem Rev*. **1998**, *98*, 863.



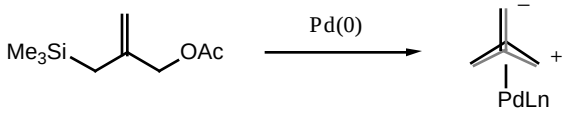
- trimethylenemethane (TMM) *ACIEE* **1986**, *25* , 1. *Synlett* **1992**, 107.

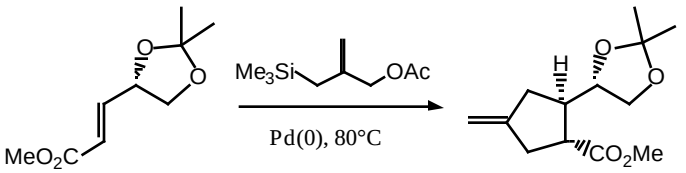




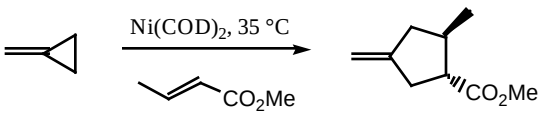
JACS **1981**, *103* , 2744

note: TMM usually reacts poorly w / electron defficient olefins



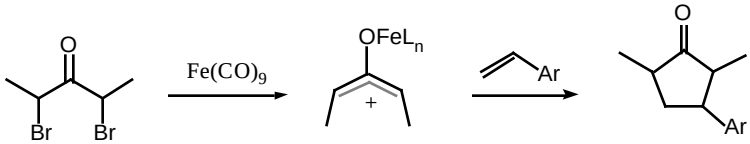


TL **1986**, *27* , 4137



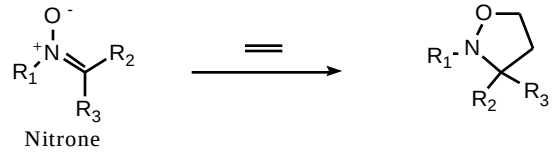
ACIEE **1985,** *24 , 316*
TL **1983**, *24* , 5847

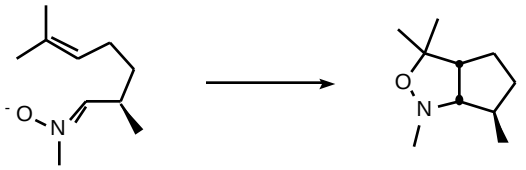
- α,α'-dihaloketones



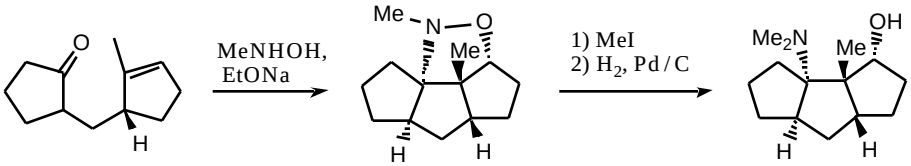
ACR **1979**, *12* , 61

- nitrones *ACR* **1979**, *12* , 396; *Organic Reactions*, **1988**, *36* , 1





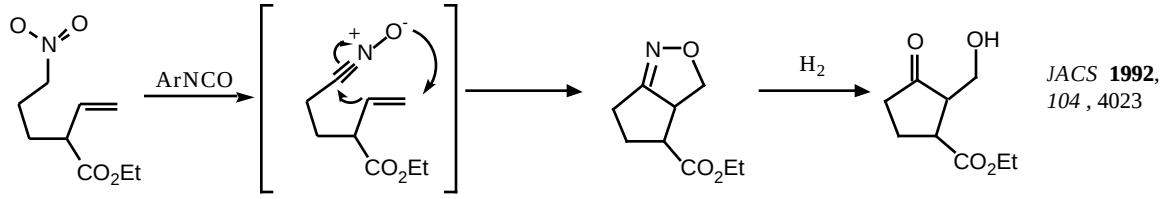
JACS **1964**, *86* , 3756



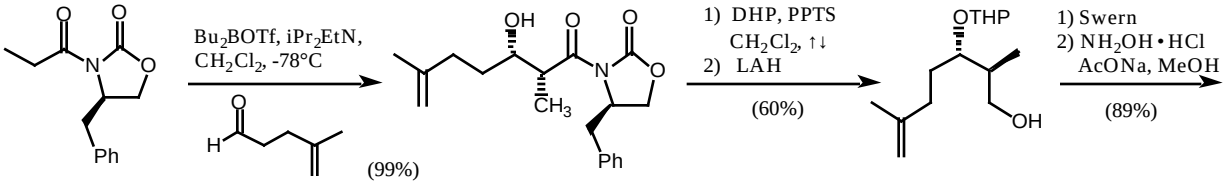
JOC **1984**, *49* , 5021

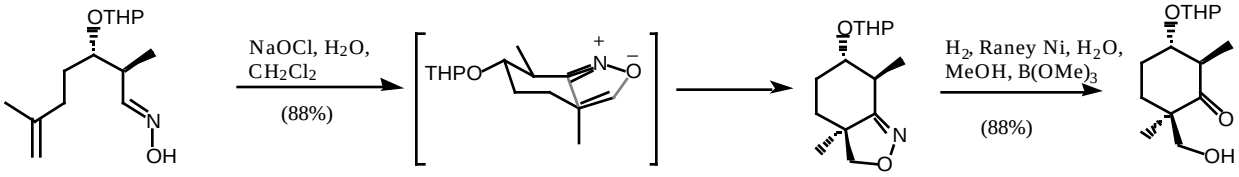
JACS **1983**, *104* , 6460

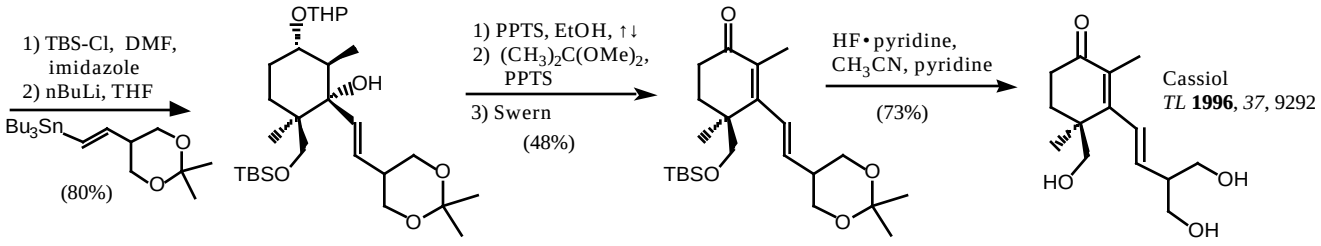
- nitrile oxides



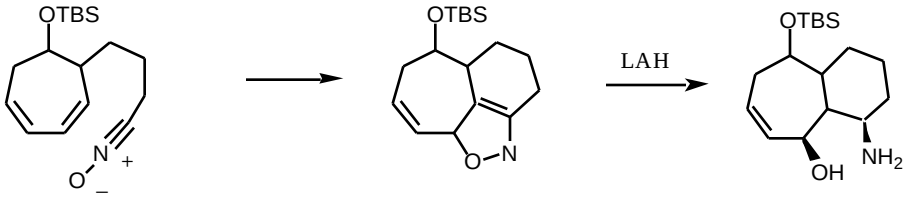
JACS **1992**, *104* , 4023







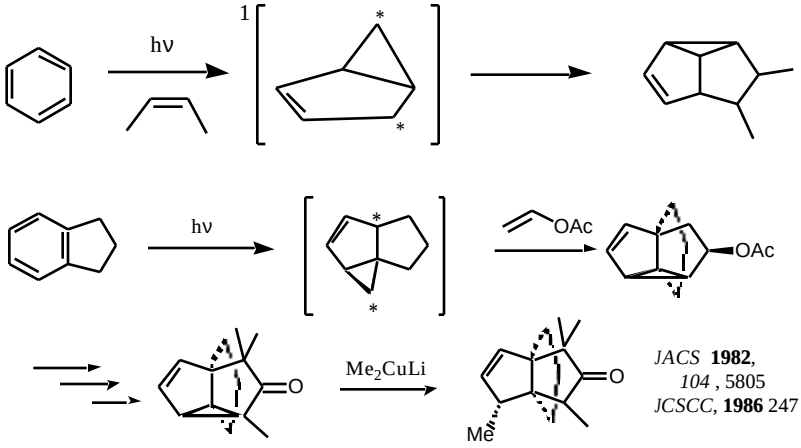
Cassiol *TL* **1996**, *37*, 9292



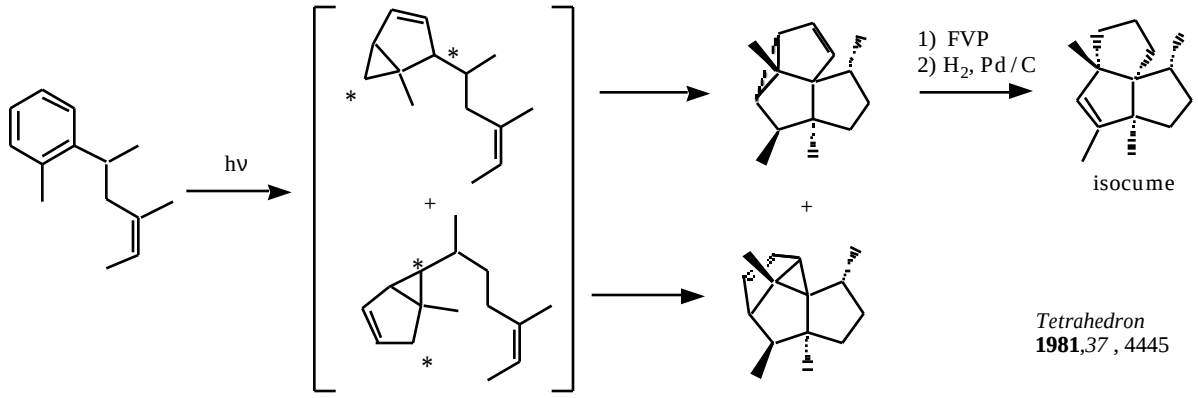
TL **1993**, *34*, 3017

Arene -Olefin Photocyclization *Organic Photochemistry* **1989**, *10* , 357

- the photochemistry of benzene is dominated by the singlet state

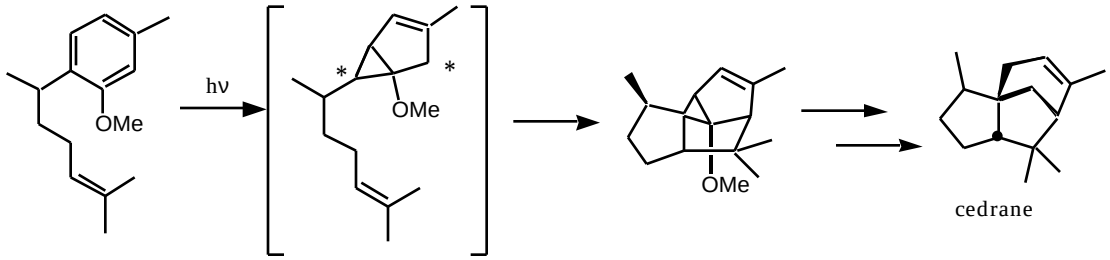


JACS **1982**, *104* , 5805
JCSCC, **1986** 247



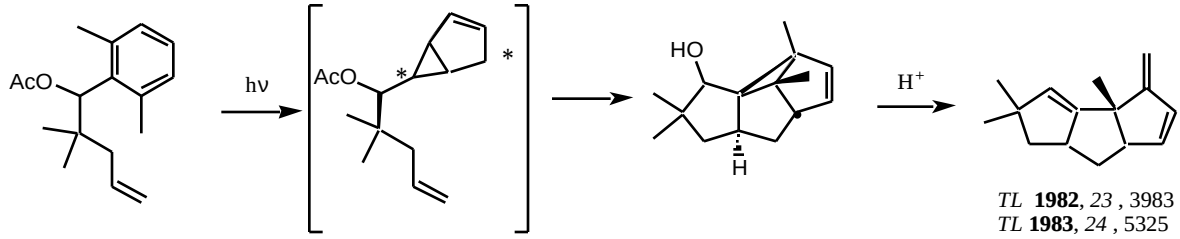
isocume

Tetrahedron **1981**,*37* , 4445



cedrane

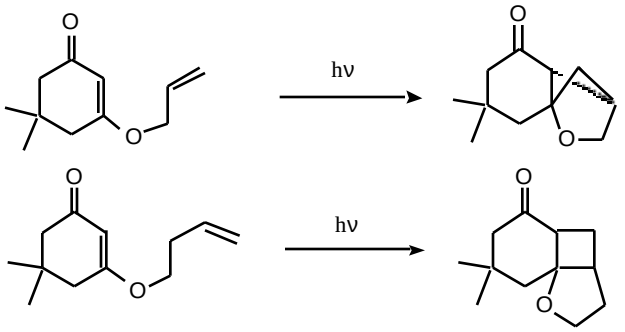
JACS **1981**, *103* , 688



TL **1982**, *23* , 3983
TL **1983**, *24* , 5325

Intramolecular Photochemical [2+2]

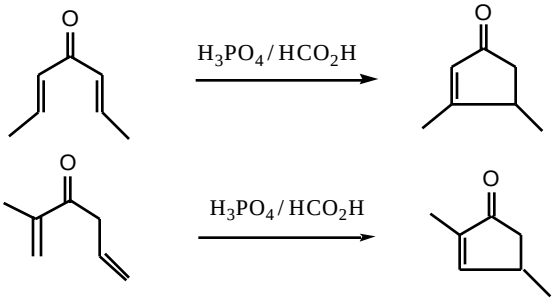
"Rule of Five"



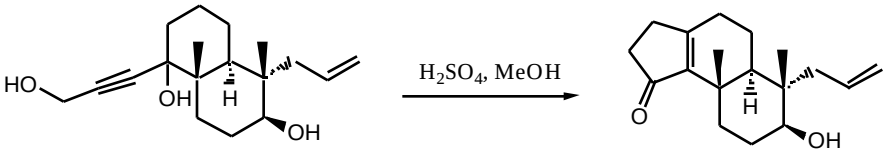
JOC **1975**, *40* , 2702
JOC **1979**, *44* , 1380

Nazarov Cyclization review: *Synthesis* **1983**, *429* *Organic Reaction* **1994**, *45*, 1

- cyclization of allyl vinyl or divinyl ketones

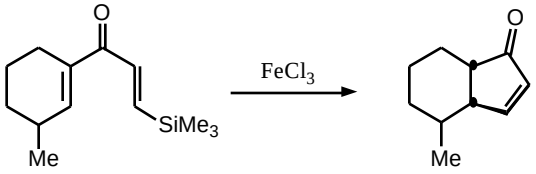


- 1,4-hydroxy-acetylenes



JOC **1989**, *54* , 3449

- Silicon-Directed Nazarov



Tetreahedron **1986**, *42* , 2821

- Tin -directed Nazarov *TL* **1986**, *27* , 5947

Radical Cyclization

B. Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds* (Pergamon Press; NY) **1986**; *Bull. Soc. Chim. Fr.* **1990**, *127* , 675; *Tetrahedron* **1981**, *37* , 3073; *Tetrahedron* **1987**, *43*, 3541; *Advances in Free Radical Chemistry* **1990**, *1*, 121. *Organic Reactions* **1996**, *48*, 301-856.

Radical Addition to multiple bonds:

1. Free radical addition is a two stage process involving an addition step followed by an atom transfer step.
2. In general, the preferred regioselectivity of the addition is in a manor to give the most stable radical (thermodynamic control)

Advantages of free radical reactions:

1. non-polar, little or no solvent effect
2. highly reactive- good for hindered or strained sysntems
3. insensitive to acidic protons in the substrates (i.e. hydroxyl groups do not necessarily need to be protected

Mechanism of radical chain reactions

1. initiation
2. propagation
3. termination (bad)

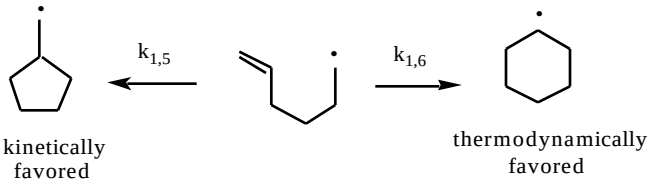
Formation of carbon centered radicals:

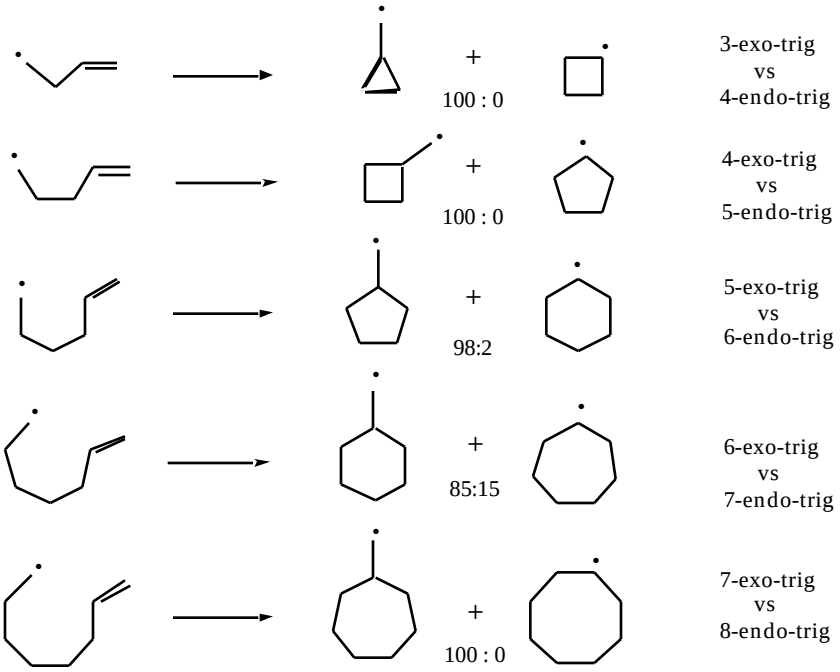
tin hydride reduction of
- alkyl, vinyl and aryl halides,
- alcohol derivatives:
  - xanthates, thionocarbonate, thiocarbonylimidazolides
- organosselenium & boron compounds
- carboxylic acid derivatives (Barton esters)

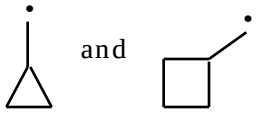
reduction of organomercurials
thermolysis of organolead compounds
thermolysis or photolysis of azoalkanes.

Radical Ring Closure

For irreversible ring closure reaction, the kinetic product will predominate. Both the 5-exo-trig and 6-endo trip are favored reactions, with the 6 exo-trig mode producing the most stable radical. However, the 5-exo-trig is about 50 time faster

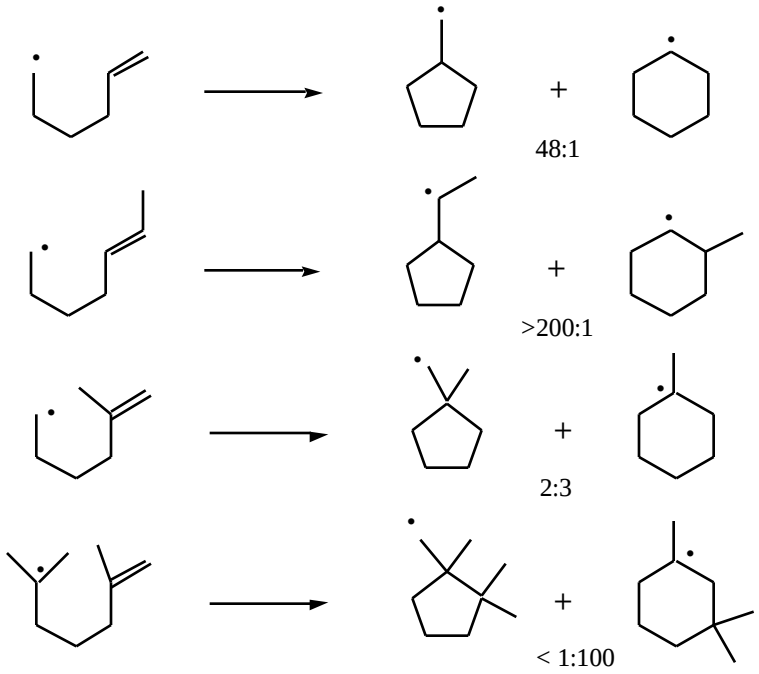





and

radicals open up fast and are not synthetically useful;
often used as probes for radical reaction

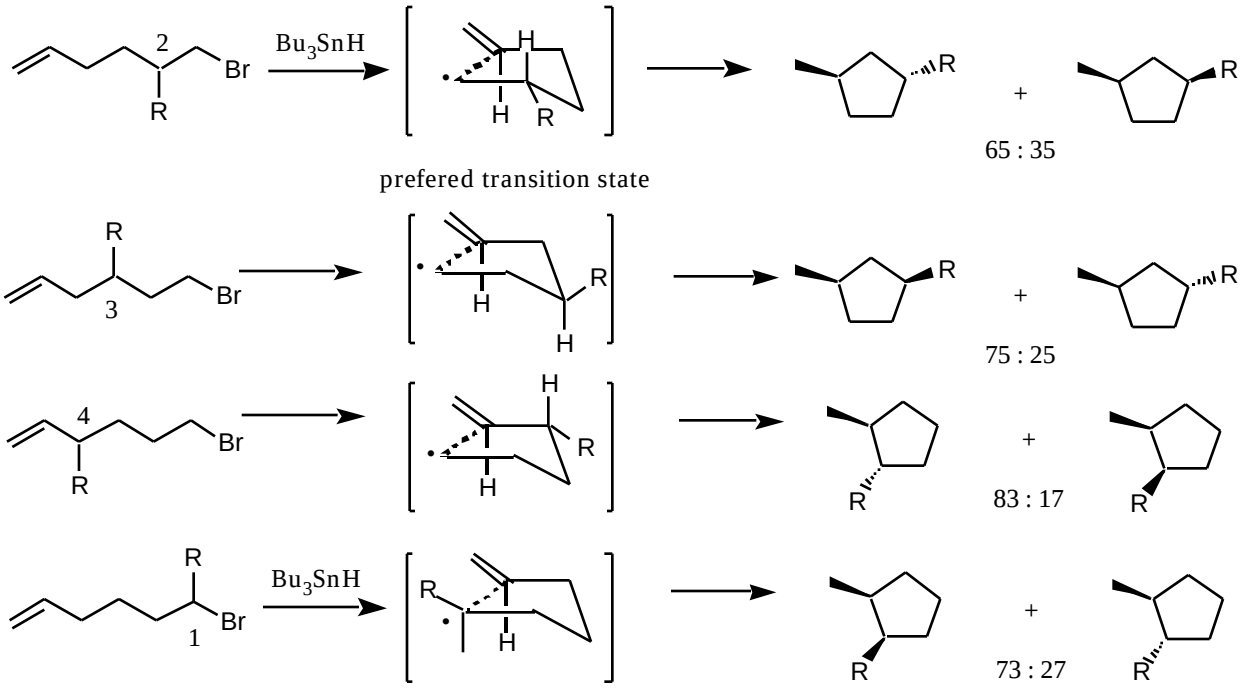
Effects of substituent on the regiochemistry of the 5-hexenyl radical cyclization

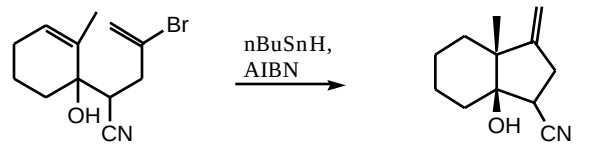


Stereochemistry of 5-hexenyl radical cyclization

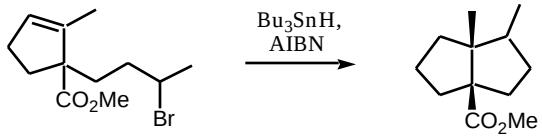
1-, or 3-substitued 5-hexenyl radicals give cis disubstituted cyclopentanes

2-, or 4-substituted 5-hexenyl radicals give trans disubstitued cyclopentanes

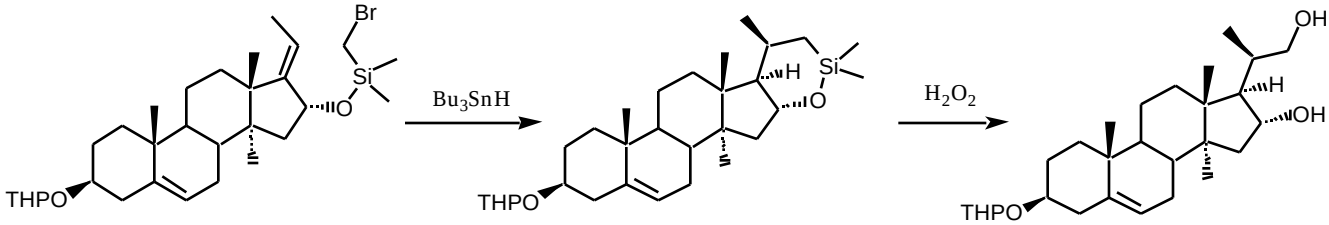




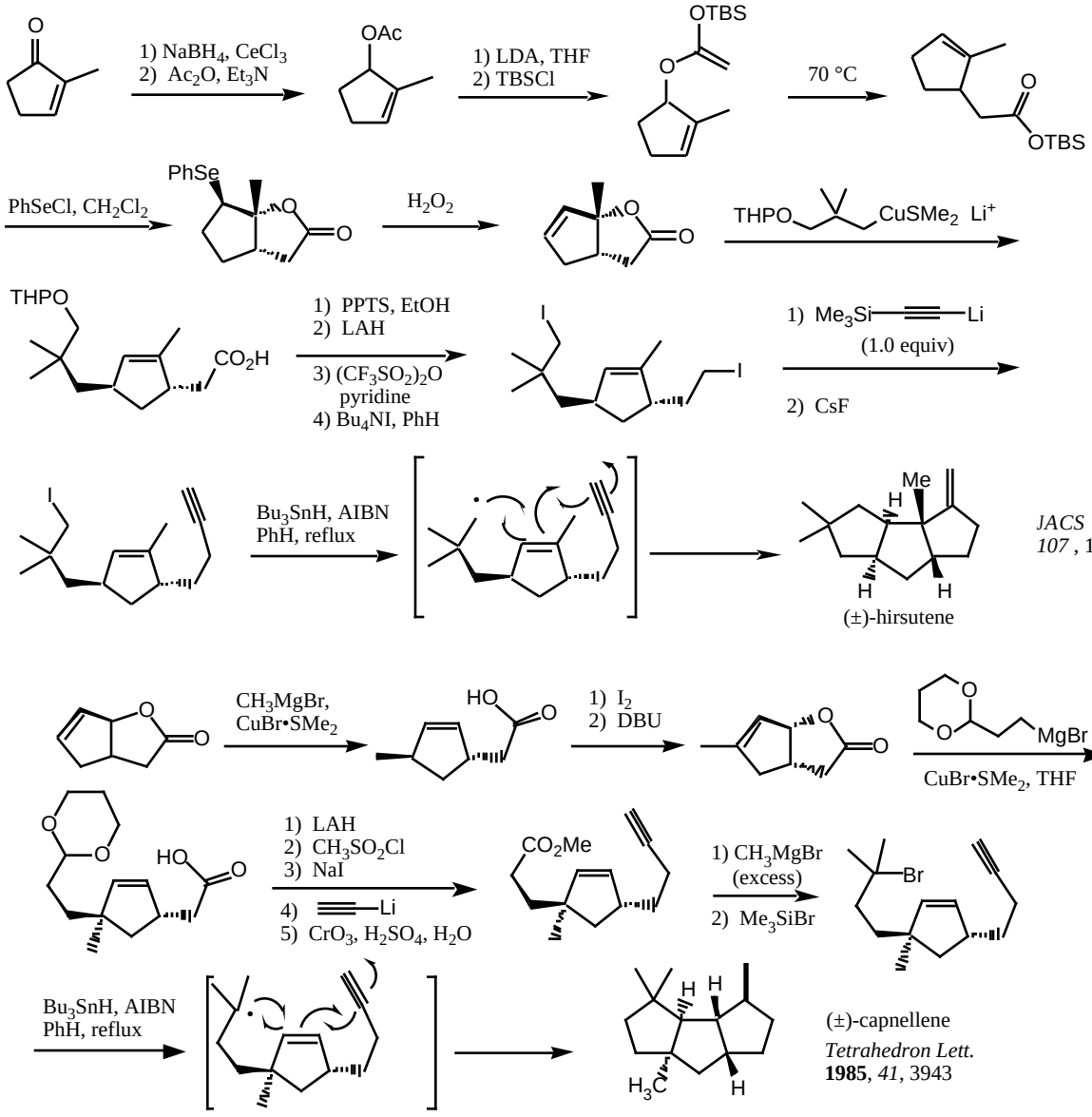
JACS **1983**, *105* , 3720



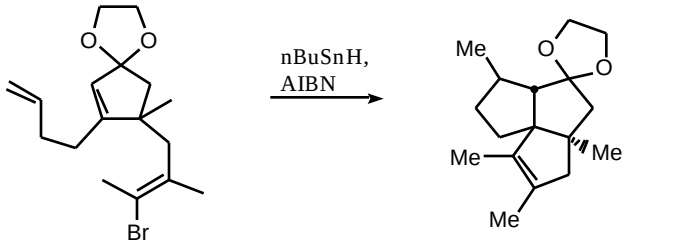
JACS **1990**, *112, 5601*



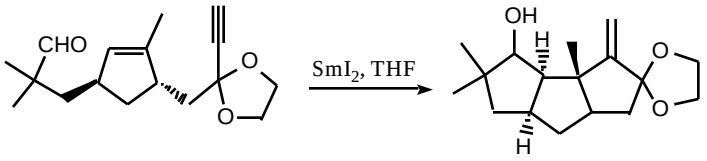
multiple cyclizations: D. Curran *Advances in Free Radical Chemistry* **1990**, *1*, 121.



(±)-capnellene
Tetrahedron Lett.
1985, *41*, 3943

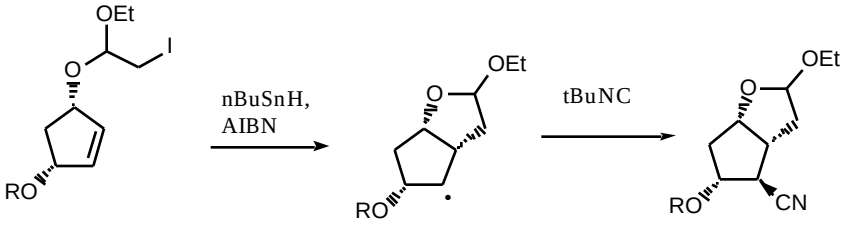


JACS **1986**, *108*, 1106



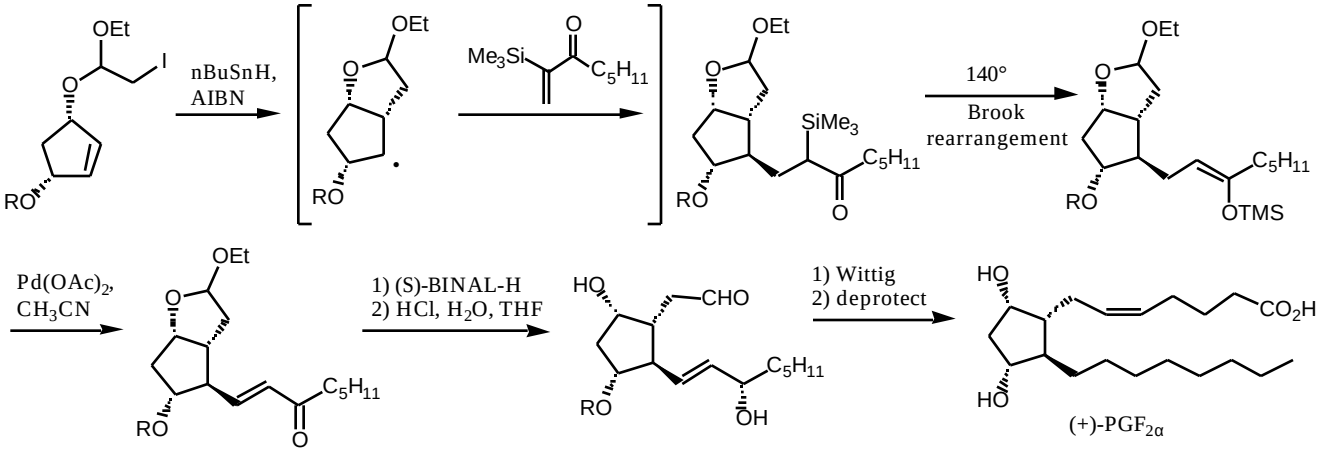
JACS **1988**, *110* , 5064

radical trapping

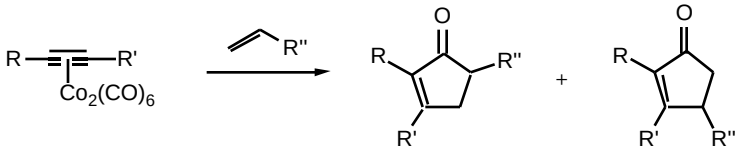


JACS **1986**, *108* , 6384

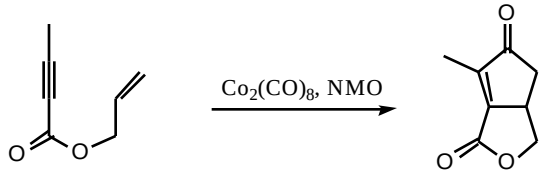
can also be trapped with acrylate esters or acrylonitrile.



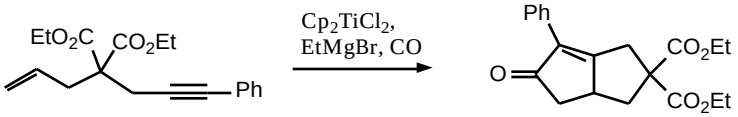
Paulson-Khand Reaction *Tetrahedron* **1985**, *41* , 5855; *Organic Reactions* **1991**, *40* , 1.



Organometallics **1982**, *1* , 1560

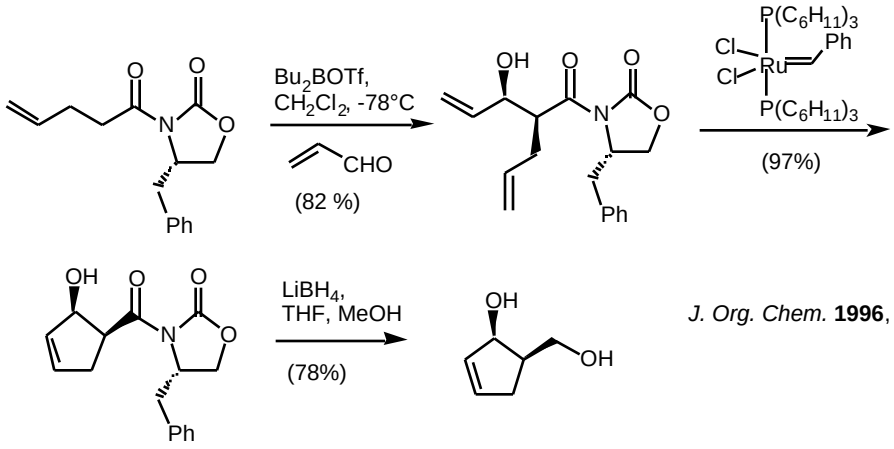


JOC **1992**, *57* , 5277



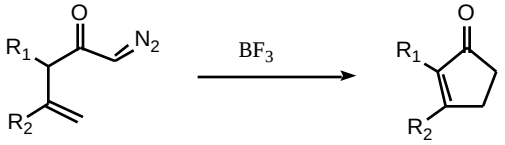
JOC **1992**, *57* , 5803

Ring-Closing Metathesis *Tetrahedron* **1998**, *54*, 4413, *Acc. Chem. Res.* **1995**, *25*, 446.



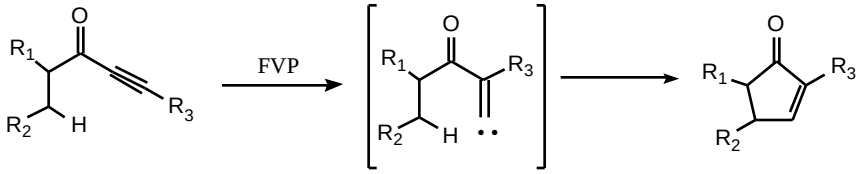
J. Org. Chem. **1996**, *61*, 4192

Diazoketones *Tetrahedron* **1981**, *37* , 2407; *Organic Reactions* **1979**, *26* , 361



TL **1975**, 4225

FVP of Acetylenic Ketones



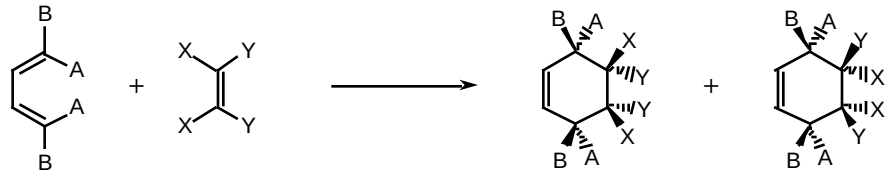
TL **1986**, *27* , 19

Six Membered Rings

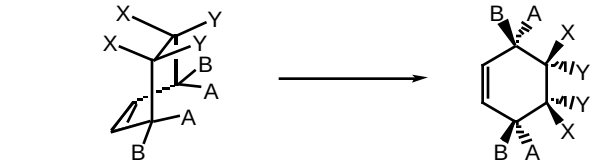
1. Diels-Alder Reaction
2. o-Quinodimethanes
3. Intramolecular ene reaction
4. Cation olefin cyclizations
5. Robinson annulation

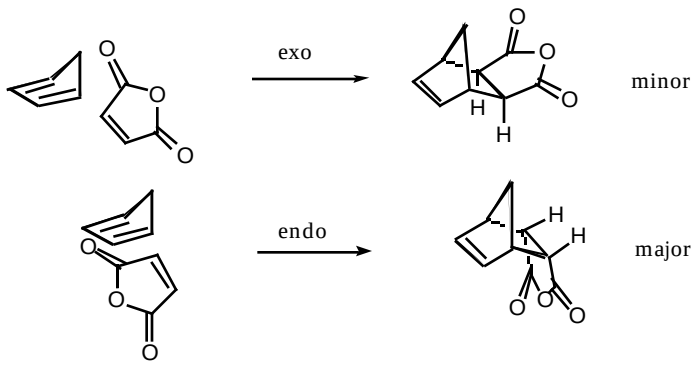
Diels-Alder Reaction
ACIEE **1984**, *23* , 876; *ACIEE* **1977**, *16* , 10; *Organic Reactions* **1984**, *32* , 1
W. Carruthers *Cycloadditions Reactions in Organic Synthesis* (Pergamon Press, Oxford) **1990**

- reaction of a 1,3-diene with an olefin to give a cyclohexene.
- thermal symmetry allowed pericyclic reaction
- diene must reaction is an s-cis conformation
- highly stereocontrolled process- geometry of starting material is preserved in the product
- possible control of 4 contiguous stereocenters in one step

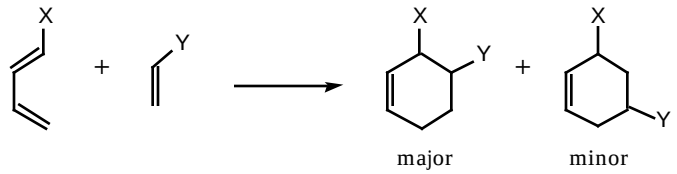


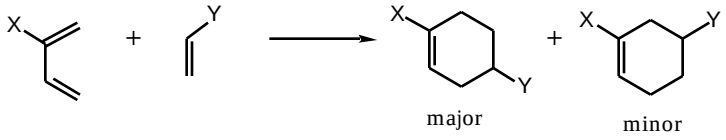
- Alder Endo Rule: In order to maximize secondary orbital interactions, the endo TS is favored in the D-A rxn. *Tetrahedron* **1983**, *39*, 2095



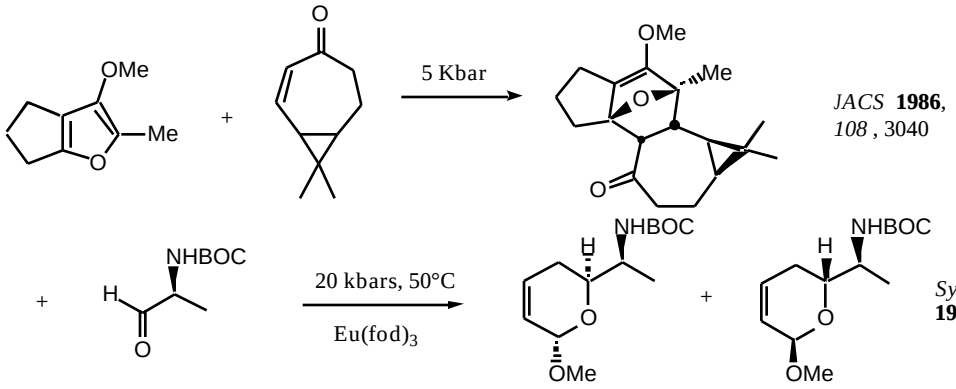


Orientation Rules

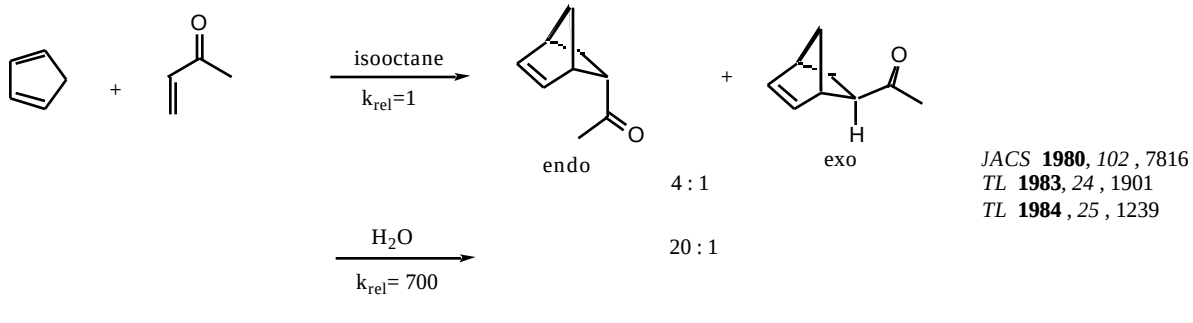


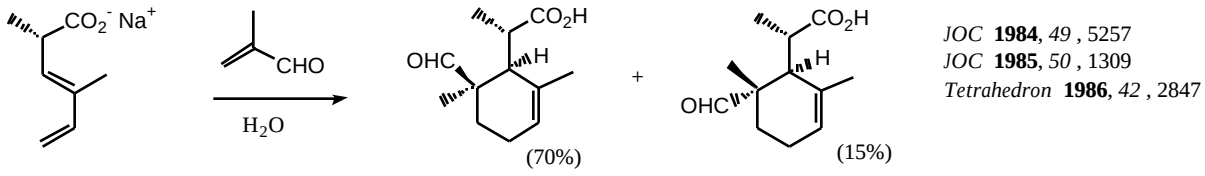


- when both the diene and dienophile are "unactivated" the D-A rxn is sluggish
- D-A rxns with electron rich dienes and electron defficient dienophiles work the best. Some electron deficient dienophiles are quinones, maleic ahydride, nitroalkenes, α,β-unsaturated ketones, esters and nitriles.
- D-A rxns with electron deficient dienes and electron rich dienophiles also work well. These are refered to as reverse demand D-A rxns.
- D-A rxns are sensitive to steric effects of the dienephiles, particularly at the 1- and 2-postions. Steric bulk at the 1-position may prevent approach of the dienophile while steric bulk at the 2-position may prevent the diene from adopting the s-cis conformation.
- The D-A rxn is promoted by Lewis acids ($TiCl_4$, BF_3 $AlCl_3$, $AlEt_2Cl$, $SnCl_4$,...)
- The D-A rxn is promoted by high pressure (1 kbar ~ 14200 psi) *Synthesis* **1985**, 1.

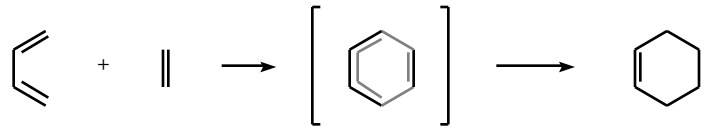


- The D-A rxn is usually insenstive to solvent effects, except for water. *ACR* **1991**, *24* , 159



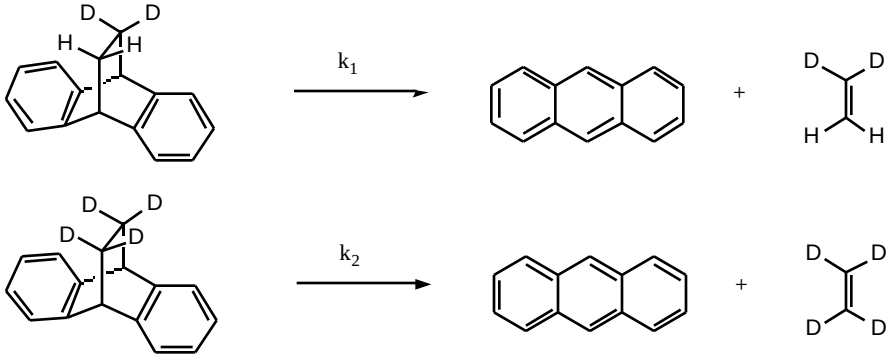


- The mechanism of the D-A rxn is believed to be a one-step, concerted, non-synchronous process.
- concerted- bond making and bond breaking processes take place in a single kinetic step (no dip in the transition state)
- synchronous- bond making and bond breaking take place at the same time and to the same extent.



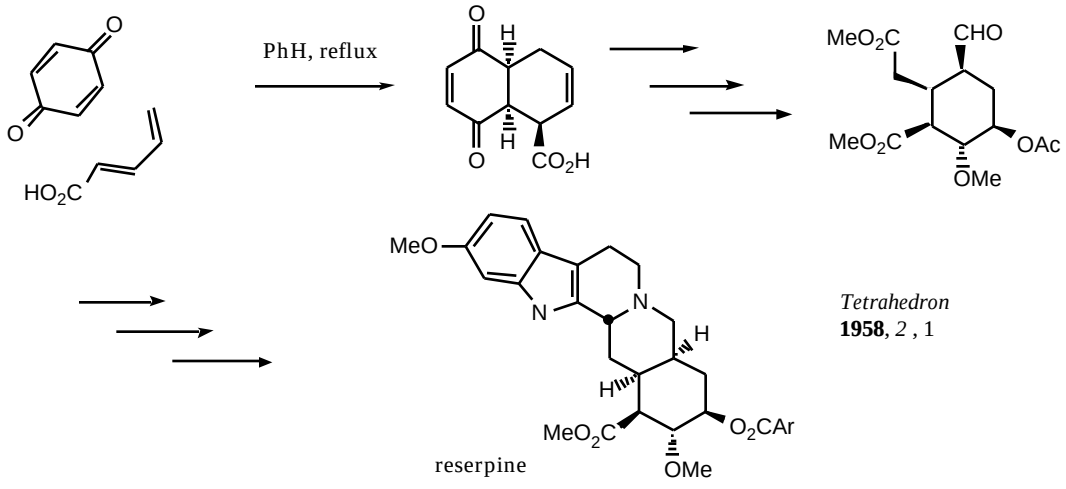
M.J.S. Dewar *JACS* **1984**, *104* , 203, 209.

- study of secondary D-isotope effects have indicated a highly symmetrical T.S.

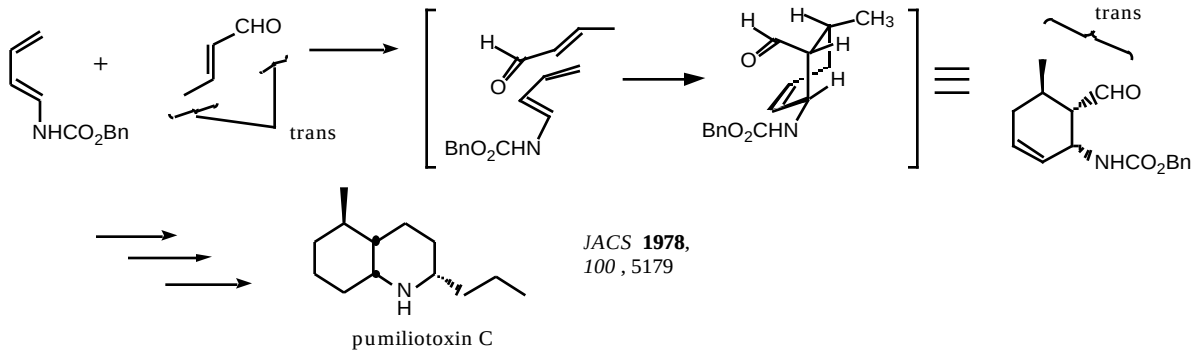


JACS **1972**, *94* , 1168

Diels Alder Reactions:

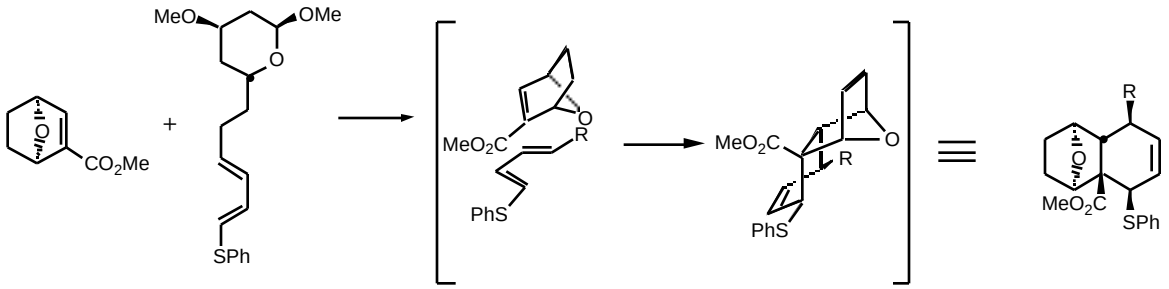


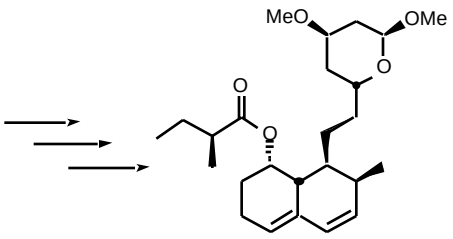
Tetrahedron **1958**, *2* , 1



JACS **1978**, *100* , 5179

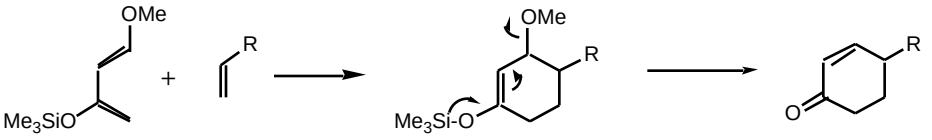
pumiliotoxin C





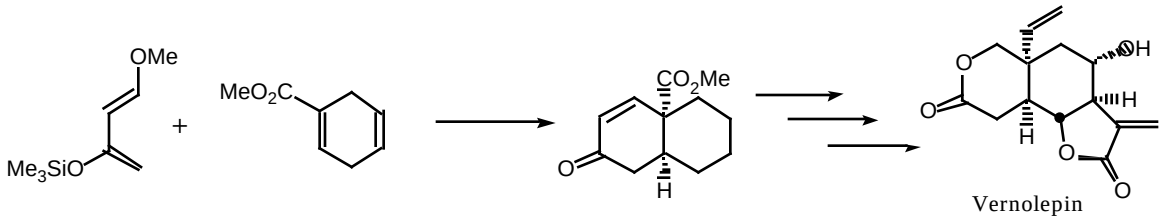
JACS **1986**, *108* , 5908

Compactin



ACR **1981**, *14* , 400

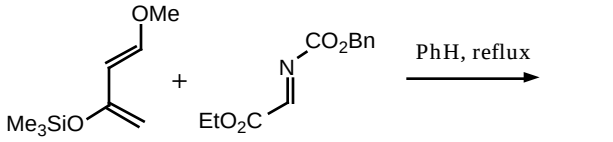
Danishefsky's Diene



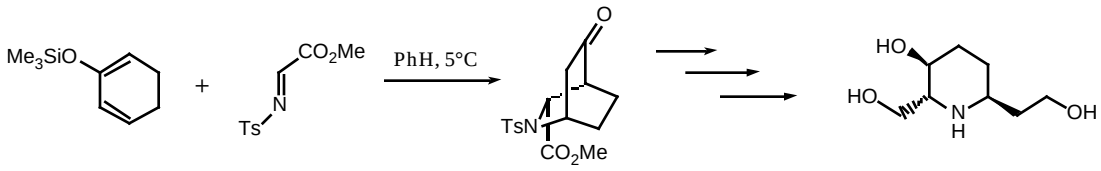
Vernolepin

Hetero Diels-Alder Reactions

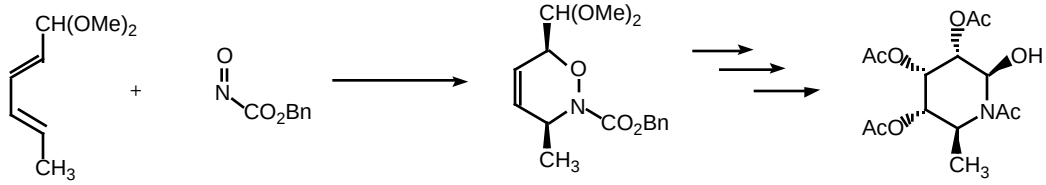
- Heterodienophiles



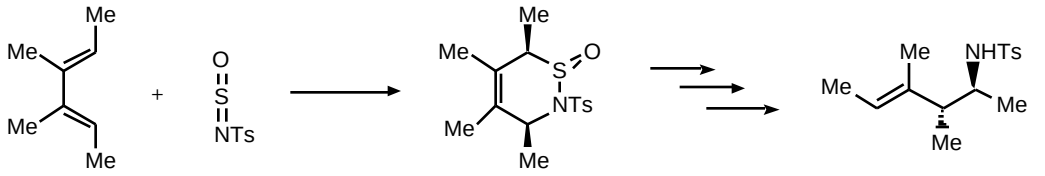
JACS **1982**, *102* , 1428



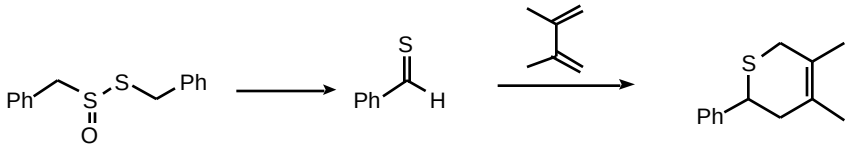
TL **1987**, *28* , 813



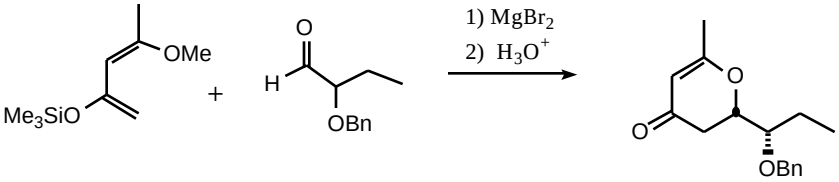
TL **1985** *27* , 4727



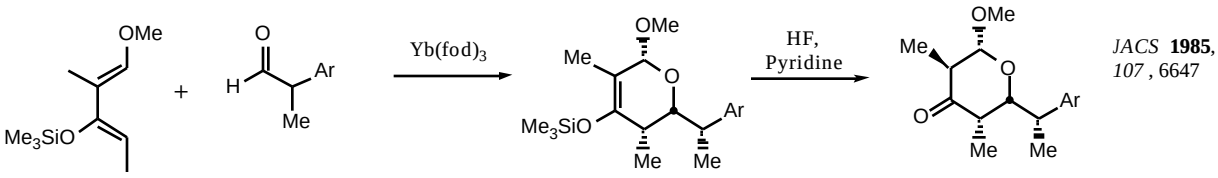
TL **1983**, *24* , 987



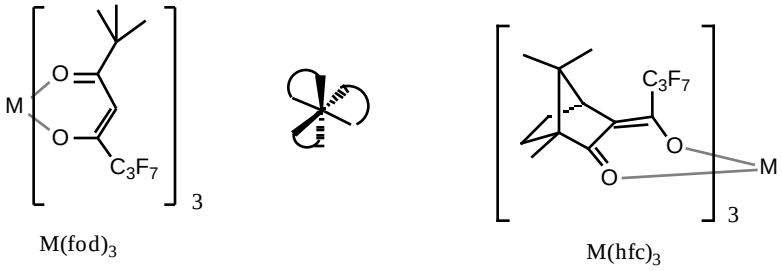
Tetrahedron, **1983**, *39* , 1487



JACS **1985**, *107* , 1256

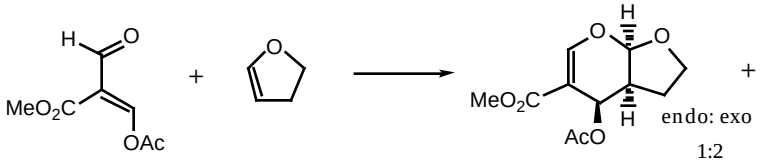


JACS **1985**, *107* , 6647

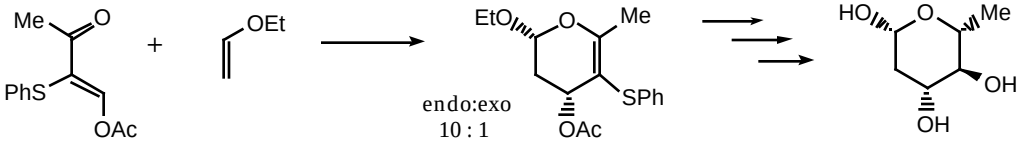


$M(fod)_3$ $M(hfc)_3$

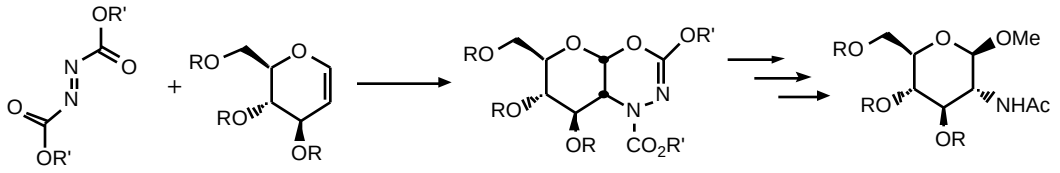
- Heterodienes



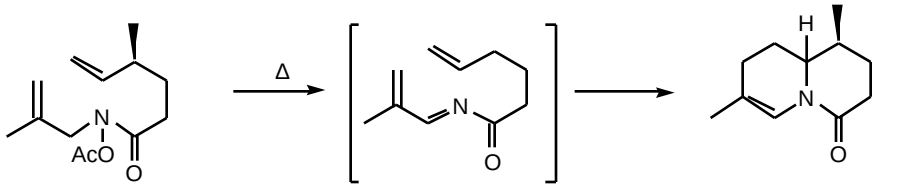
ACIEE **1983**, *22* , 887



ACR **1986**, *19* , 250



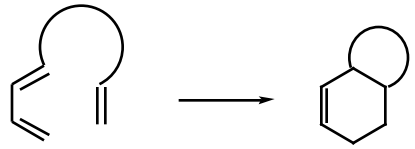
JACS **1987**, *109* , 285



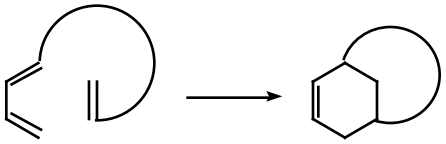
JOC **1985**, *50* , 2719

Intramolecular Diels-Alder Reactions (IDA)

- Type I IDA rxns



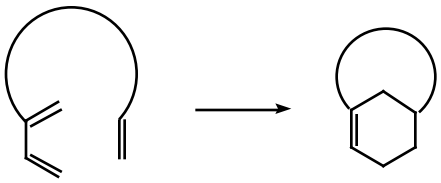
Fused bicyclc

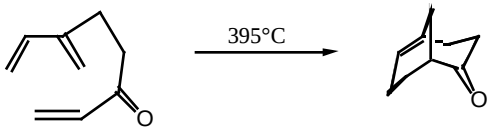


Bridged Bicyclic

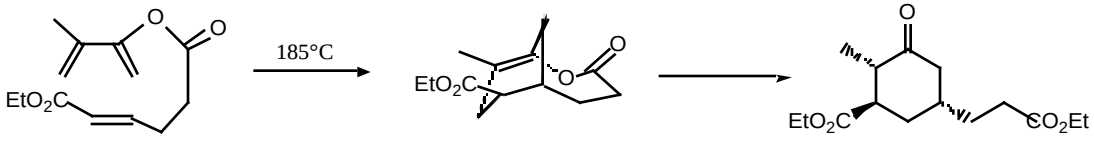
- Generally, for E-dienes, the fused product is observed unless the connecting chain is very long. For Z-dienes, either the fused or bicyclic products are possible.

- Type II IDA rxns: gives bridgehead olefin

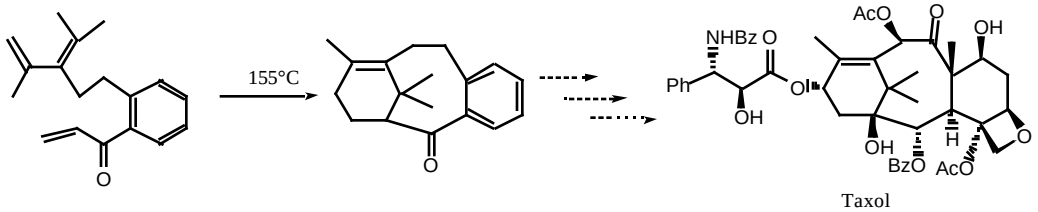




JACS **1982**, *104* , 5708, 5715



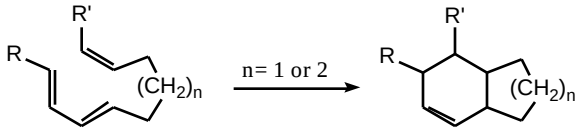
JACS **1987**, *109* , 447



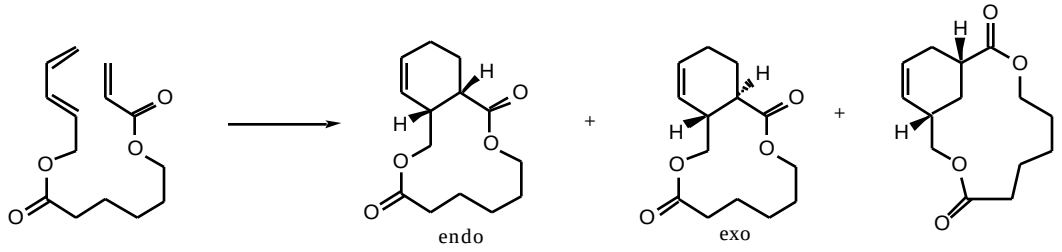
ACIEE **1983**, *24* , 419

Taxol

- IDA reactions to give fused 6•5 (hydroindene) and 6•6 (hydronaphthalene) ring systems are usually favorable reactions.



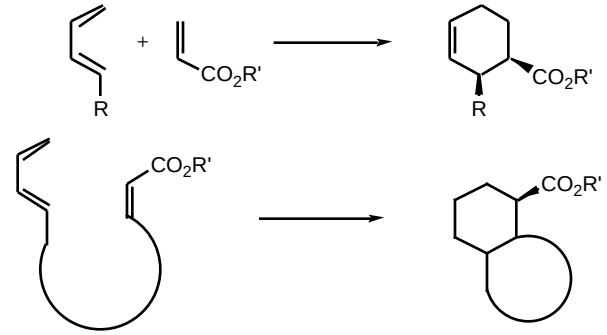
- Intramolecular D-A rxns that give medium sized rings (7,8,9, 10) are much less favorable.
- Intramolecular D-A rxn which form large rings are often favorable reactions with the diene and olefin portions act as if they were seperate molecules



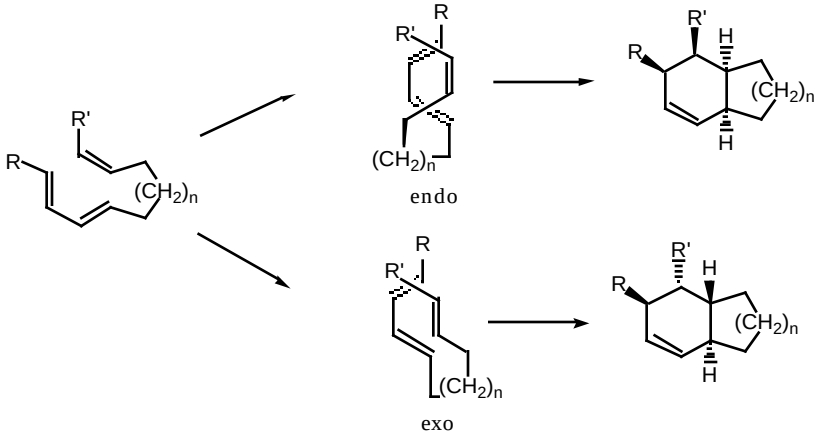
JACS **1980**, *102* , 1390

6.2 : 6.8 : 1 (77% combined yield)

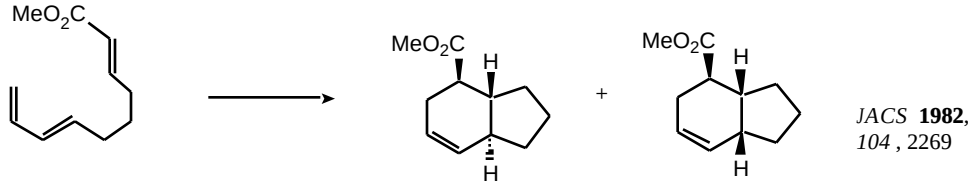
- Preference for endo or exo transition state depends on the substituition of the diene, dieneophile and connecting chain.
- For intramolecular D-A rxns, geometric constraints can now reverse the normal regiochemistry of the addition as compared to the intermolecular rxn.



- for intramolecular D-A reactions, we will use endo and exo to described the disposition of the connecting chain

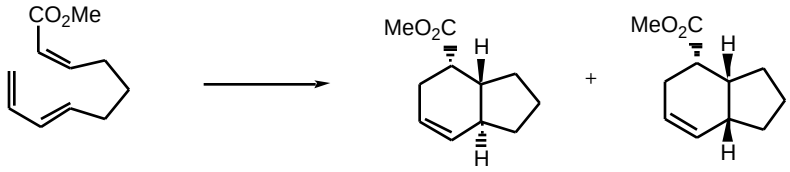


- Lewis acids can greatly effect the endo / exo ratio of IDA reactions especially when the olefin portion is E. The effects for Z-olefins is much more subtle



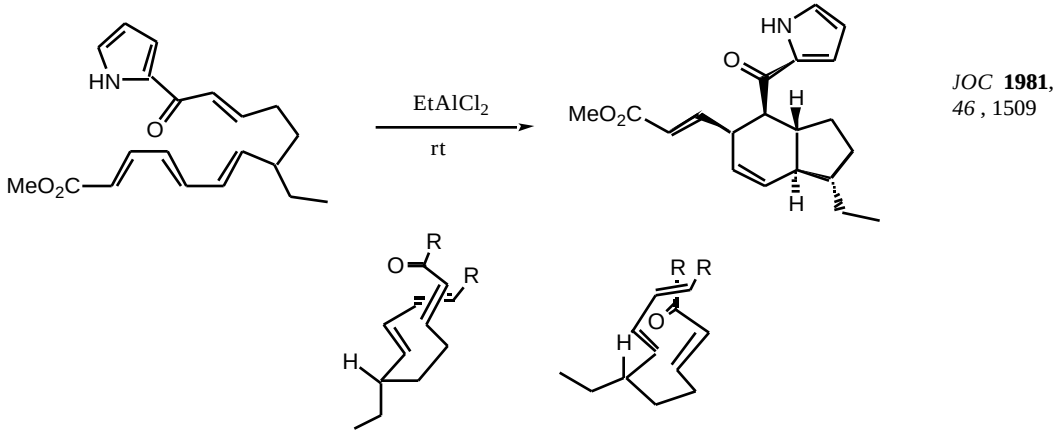
JACS **1982**, *104* , 2269

150°C	75 : 25	(75% combined yield)
$(RO)_2AlCl_2$, rt	100 : 0	(72% combined yield)



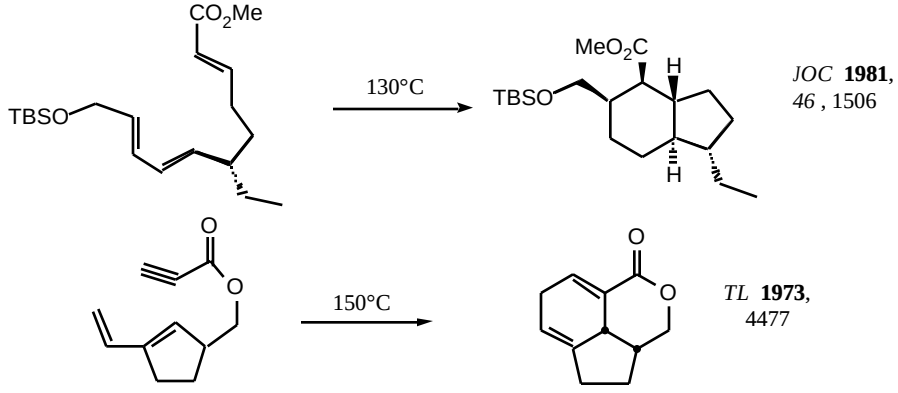
180°C	75 : 25	(74% combined yield)
$EtAlCl_2$, rt	63 : 37	(60% combined yield)

- the effect of substituents on the connectinng chain can influence the stereochemical course of the IDA reaction



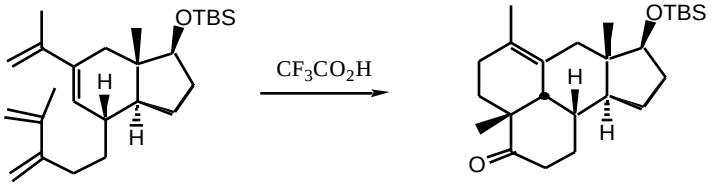
JOC **1981**, *46* , 1509

Intramolecular Diels-Alder Reactions:

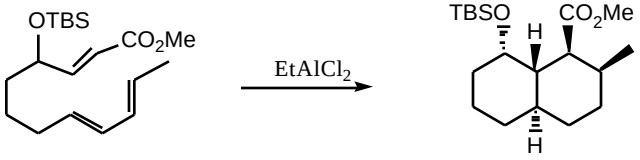


JOC **1981**, *46* , 1506

TL **1973**, 4477



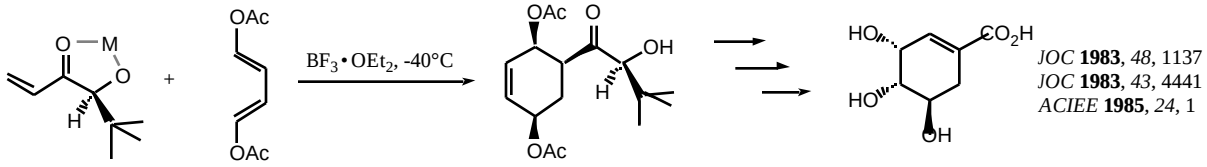
JACS **1981**, *103* , 4948



JOC **1982**, *47* , 180

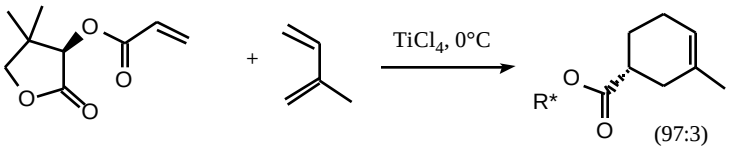
Asymmetric Diels-Alder Reactions

- Chiral Auxillaries *Chem. Rev*. **1992**, *92* , 953; *Tetrahedron* **1987**, *43* , 1969



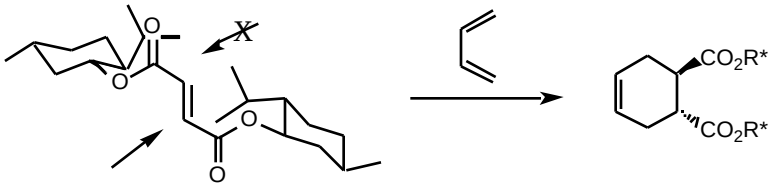
JOC **1983**, *48*, 1137
JOC **1983**, *43*, 4441
ACIEE **1985**, *24*, 1

>98% d.e. (-)- Shikimic Acid

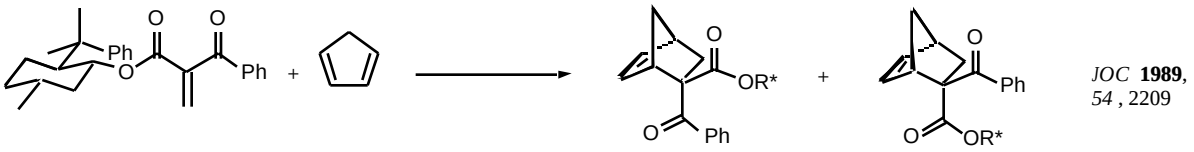


(97:3)

TL **1984**, *25* , 2191



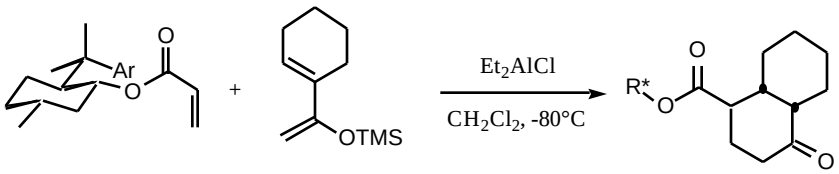
Δ = 4.5 %ee
$TiCl_4$= 78% ee
iBu_2AlCl= 90% ee



JOC **1989**, *54* , 2209

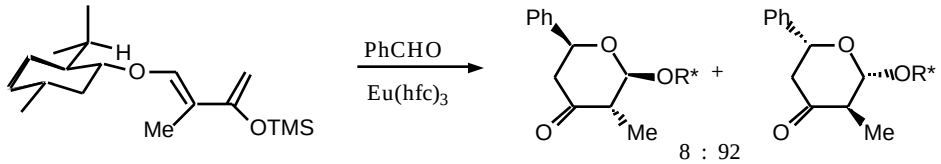
18 : 82
w / $BF_3 \cdot OEt_2$ 92 : 8

d.e > 95%



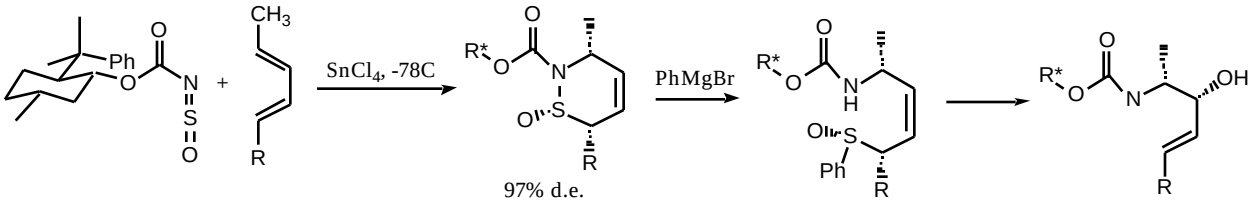
Chem Lett. **1989**, 2149

up to 70% d.e.

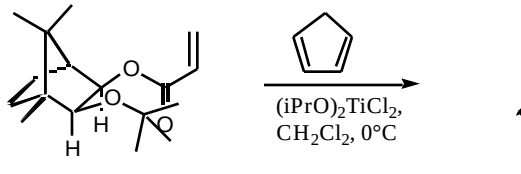


JACS **1986**, *108*, 7060

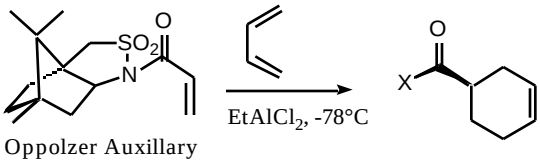
8 : 92



JCSCC , **1985** , 1449
TL 1986**, *27* , 1853**



Tetrahedron
1987, *43* , 1969

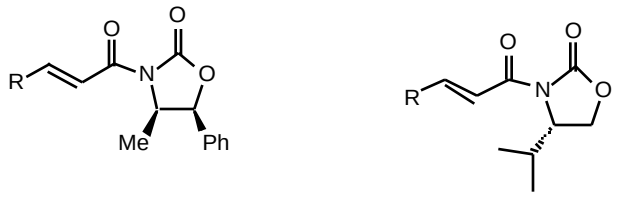


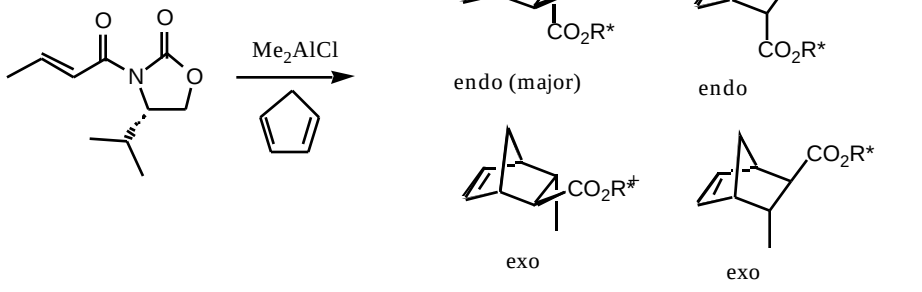
Oppolzer Auxillary

endo / exo= 86:4
98% de

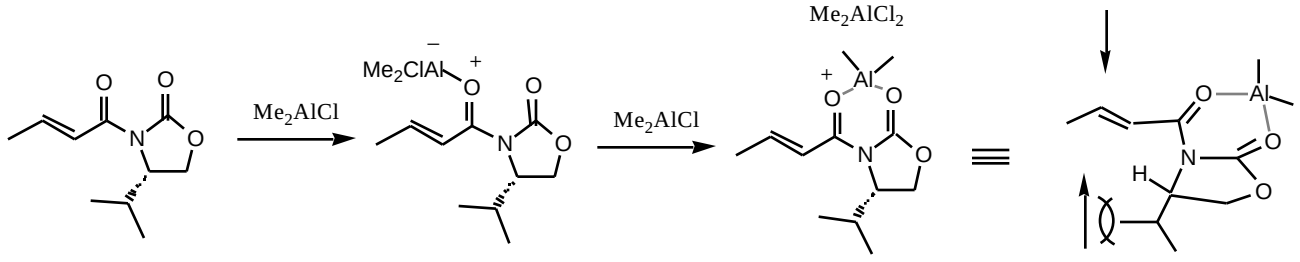
TL **1989**, *30* , 6963

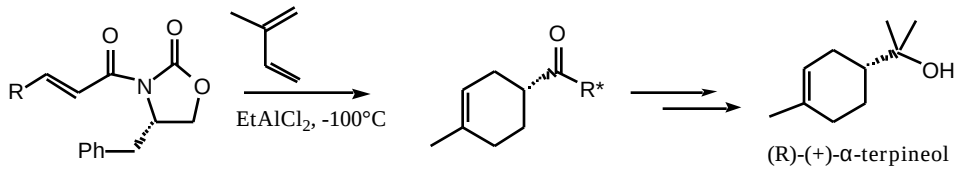
Evan's auxillaries



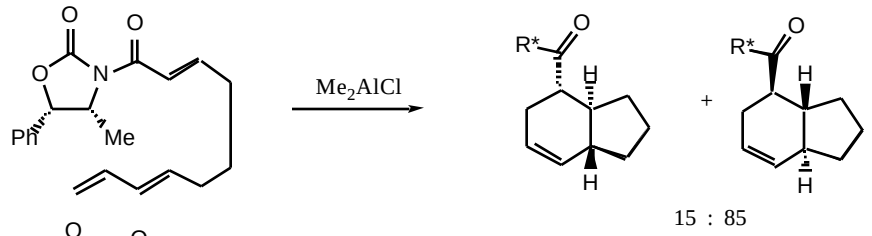


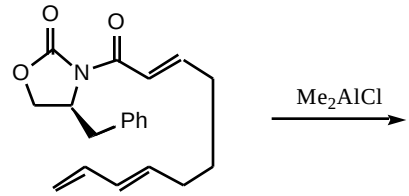
	1 equiv Me_2AlCl	2 equiv. Me_2AlCl
endo / exo	20:1	60:1
endo A / endoB	4:1	20:1
k(rel)	1	100





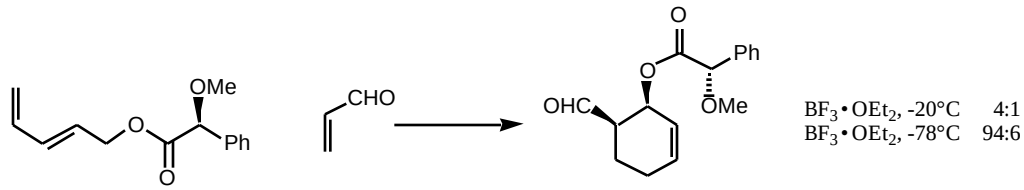
JACS **1984**, *106*, 4261
JACS **1988**, *110* , 1238

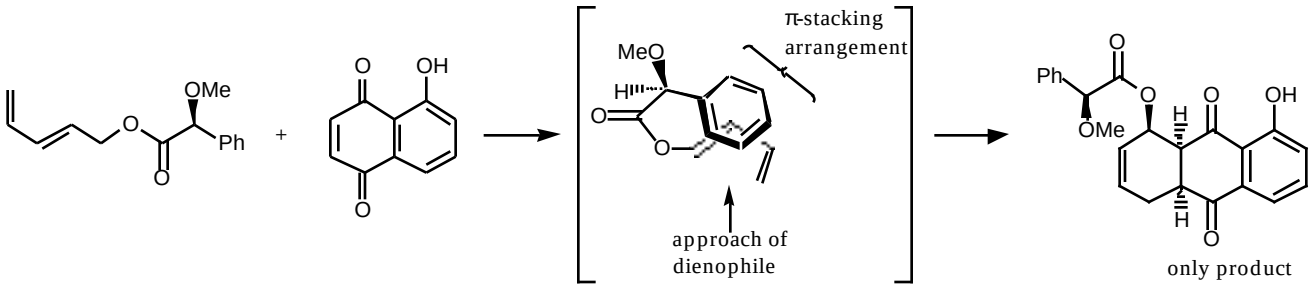




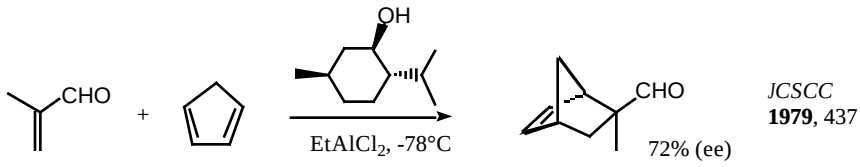
TL **1984** , *25* , 4071
JACS ***1988***, 110 , *1238*

- Chiral Dienes

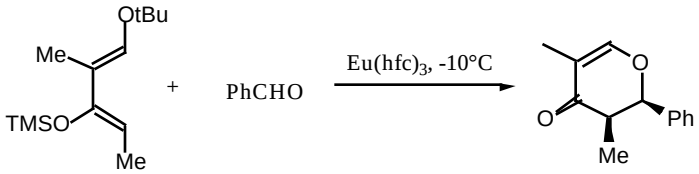




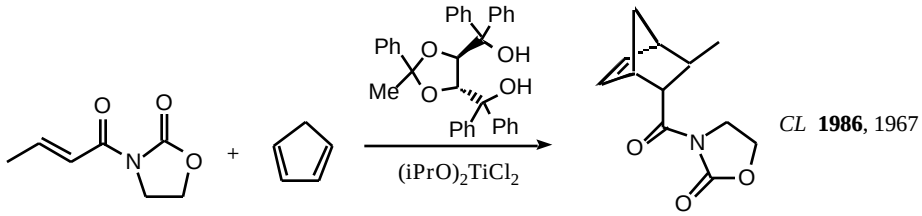
- Chiral Catalysts *Chem. Rev.* **1992**, *92* , 1007; *Synthesis* **1991**, 1; *OPPI* **1994**, *26*, 129-158



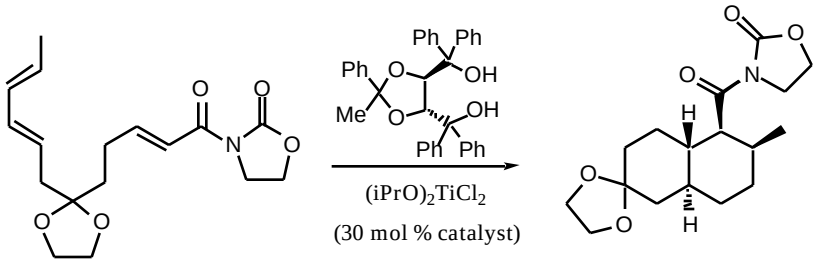
JCSCC **1979**, 437



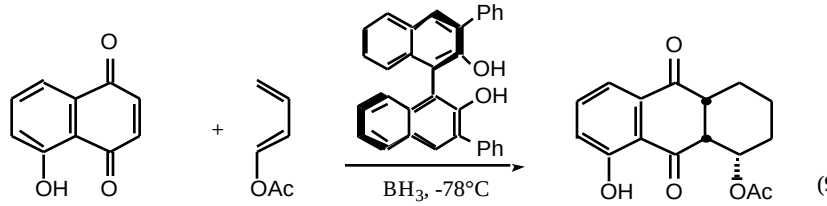
TL **1983**, *24* , 3451



CL **1986**, 1967

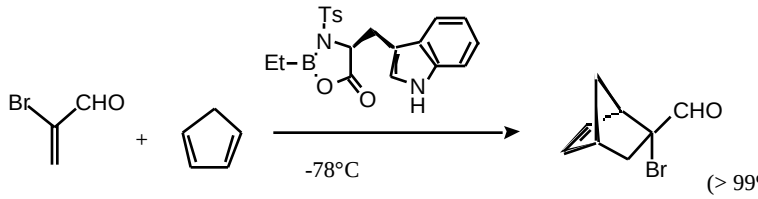


70% yield
95% ee



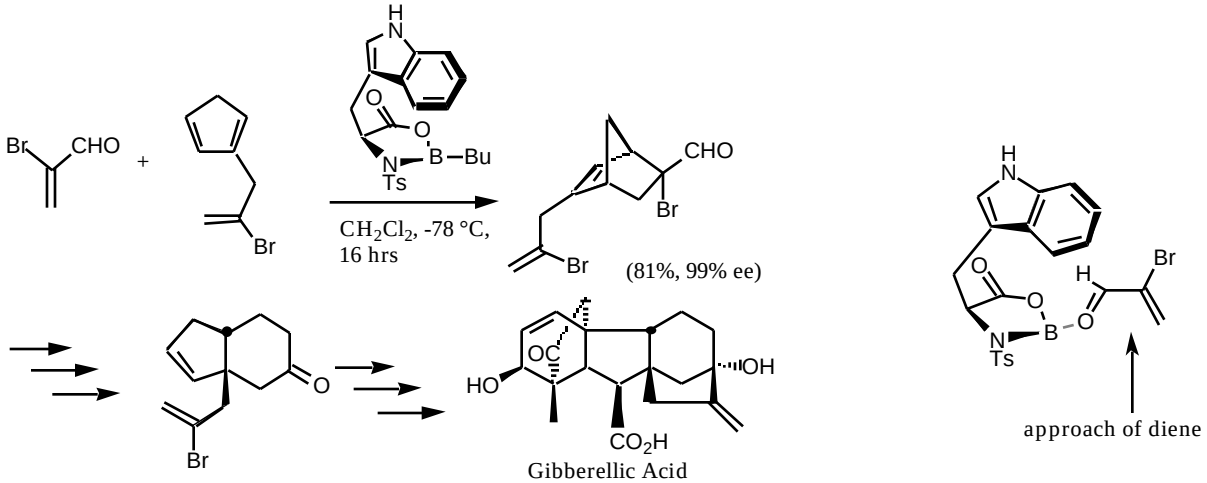
JACS **1986**, *108* , 3510

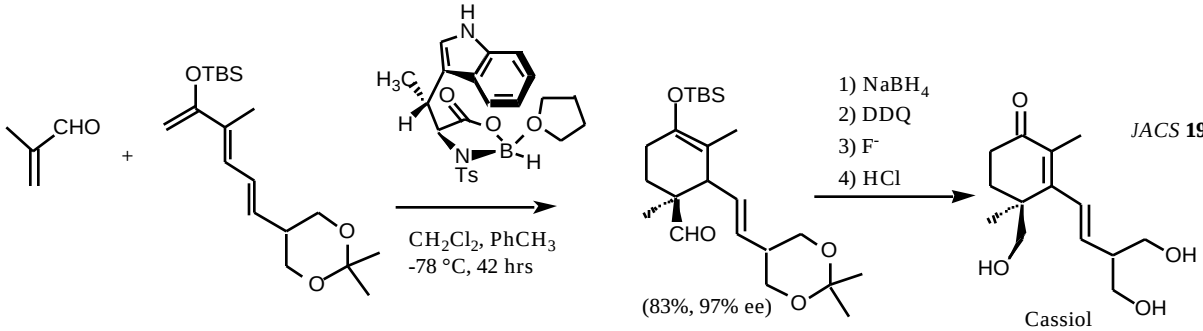
(98%)



JACS **1992**, *114* , 8290

(> 99% ee)

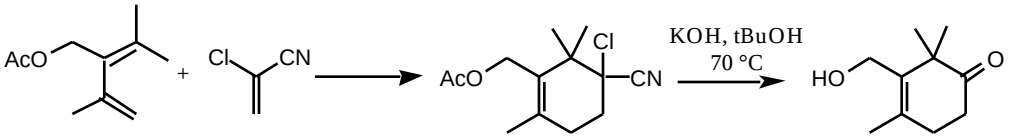




JACS **1994**, *116*, 3611

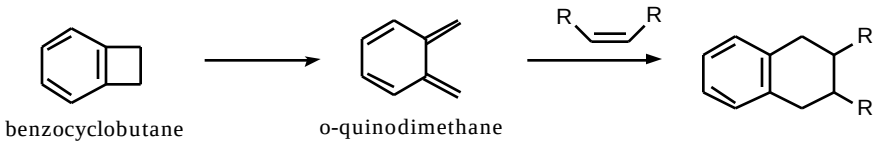
Ketene Equivalents in the D-A reaction

- ketenes undergo thermal [2+2] cycloaddition with dienes to give vinyl cyclobutanones.
- 2-chloroacrylonitrile as a ketene equiv. for D-A rxns.

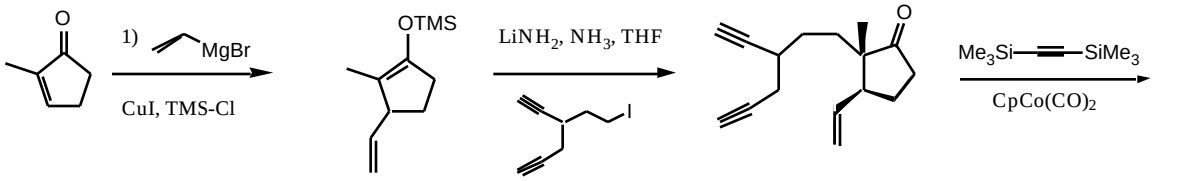


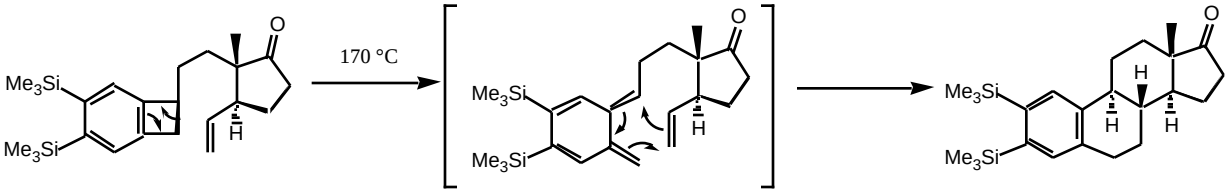
Nature (London) **1994**, *367*, 630
ACIEE **1995**, *34*, 2079

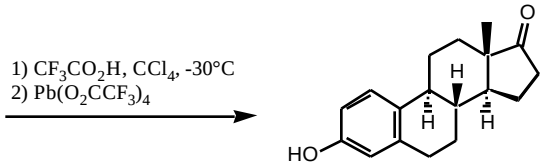
ortho-Quinodimathanes *Synthesis* **1978**, 793; *Tetrahedron* **1987**, *43* , 2873



benzocyclobutane o-quinodimethane

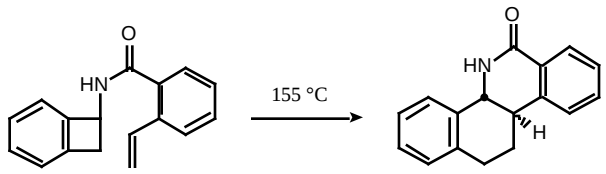




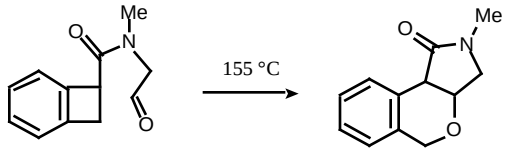


Estrone

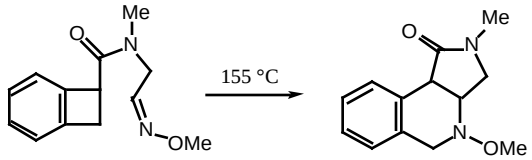
ACIEE **1984**, *23* , 539
JACS **1977**, *99* , 5483
JACS **1979**, *101* , 215
JACS **1980**, *102* , 241



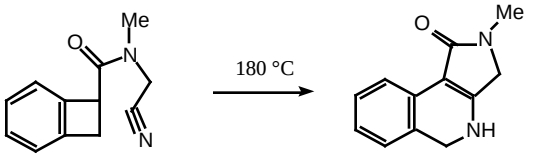
JACS **1971**, *93* , 3836



ACIEE **1971**, *11* , 1031

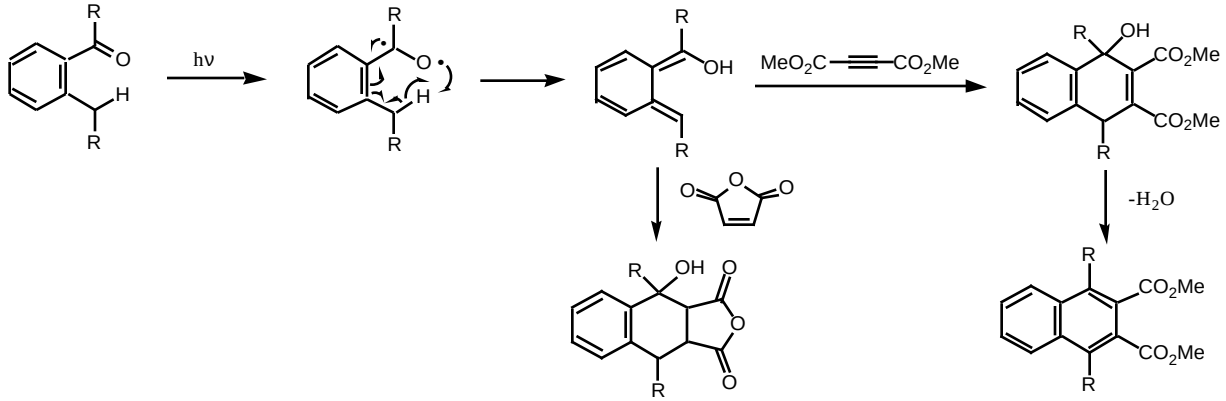


ACIEE **1971**, *11* , 1031

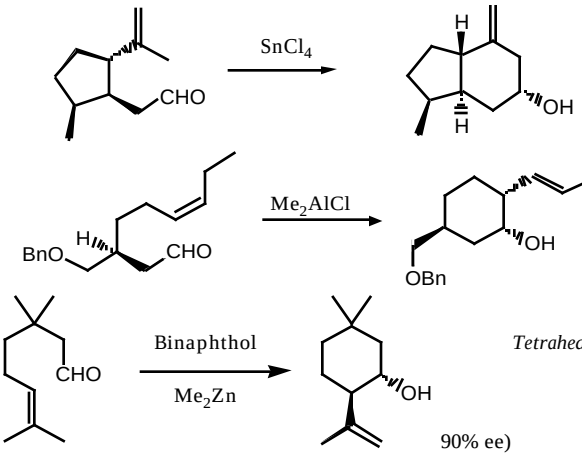


ACIEE **1971**, *11* , 1031

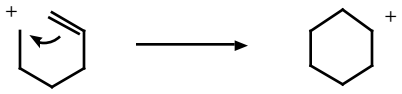
Photoenolization *Tetrahedron* **1976**, *22*, 405



Intramolecular Ene Reactions *ACIEE* **1984**, *23* , 876, *Synthesis* **1991**, 1



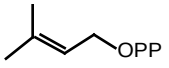
Polyene Cyclization



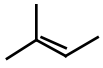
Terpene Biosynthesis

terpenes	C_{10}	geraniol
sesquiterpenes	C_{15}	farnesol
diterpenes	C_{20}	geranylgeraniol
steroids	C_{30}	squalene

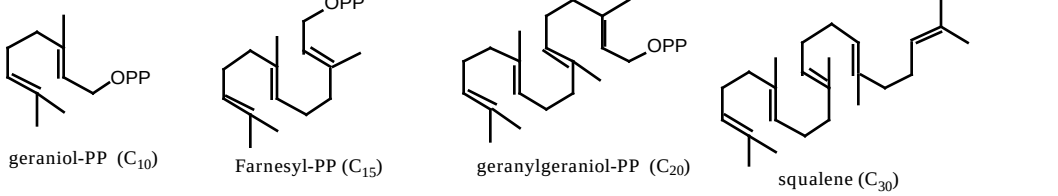
- isoprene- basic building block



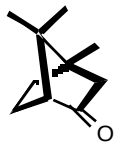
isopentyl-PP



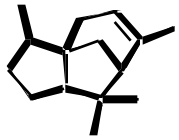
isoprene unit



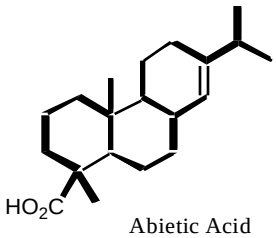
geraniol-PP (C_{10}) Farnesyl-PP (C_{15}) geranylgeraniol-PP (C_{20}) squalene (C_{30})



Camphor

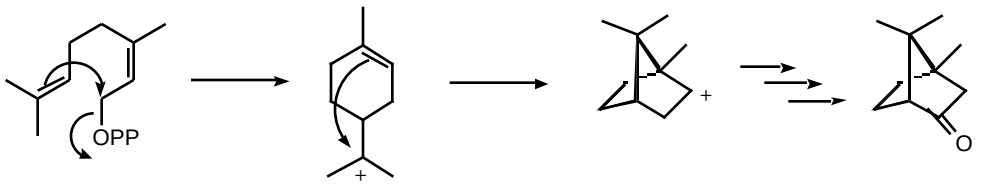


α-Cedrane

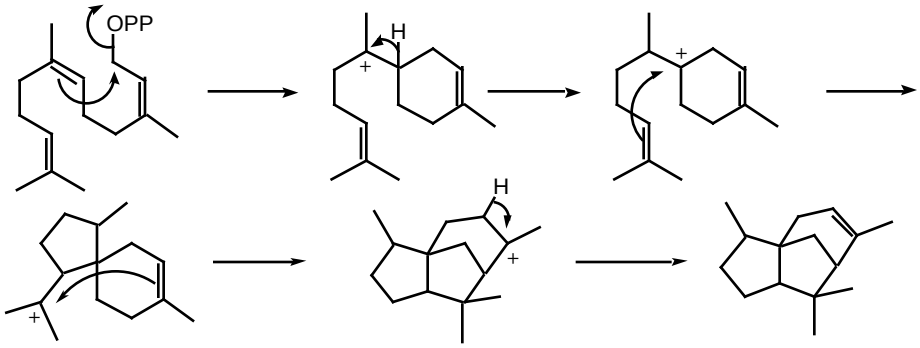


Abietic Acid

Biosynthesis of camphor:

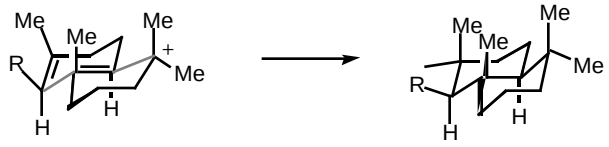


Biosynthesis of cedrane:

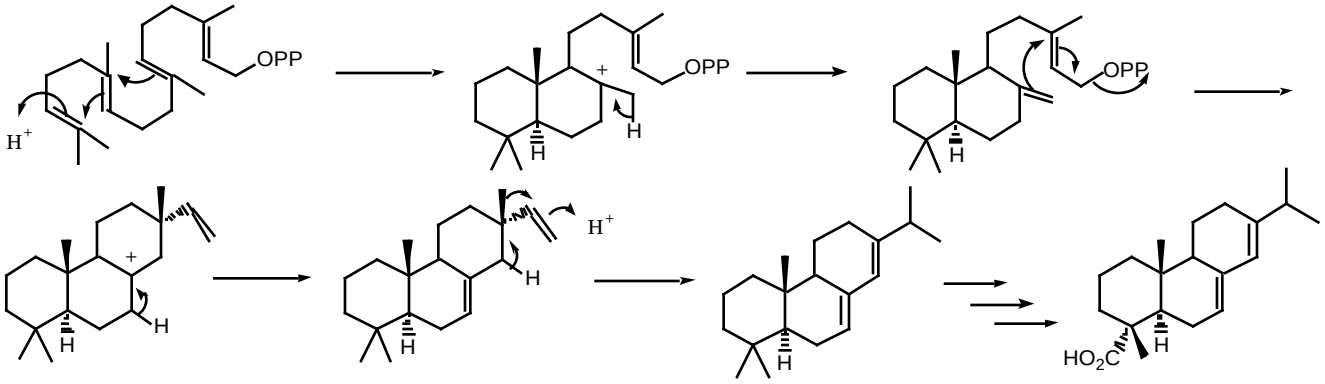


Stork-Eschenmoser Hypothesis- Olefin Geometry is preserved in the cyclization reaction, i.e. trans olefin leads to a trans fused ring jucntion

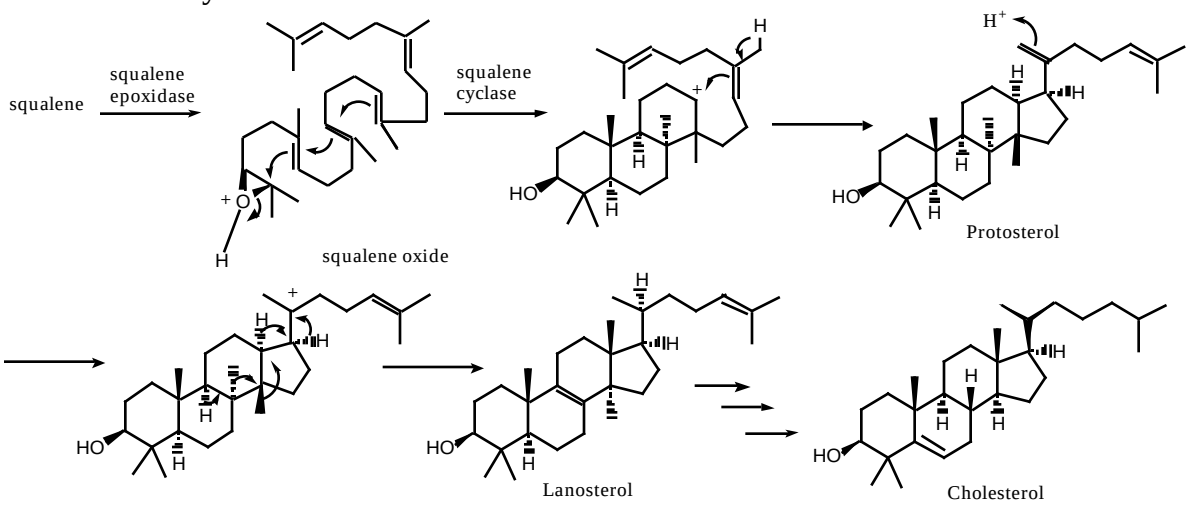
A. Eschenmoser *HCA* **1955**, *38*, 1890; G. Stork *JACS* **1955**, *77*, 5068



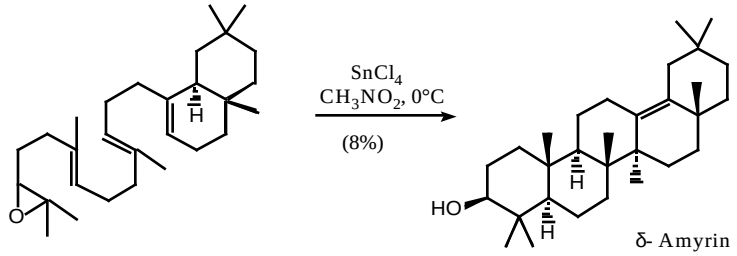
Biosynthesis of Abietic acid:



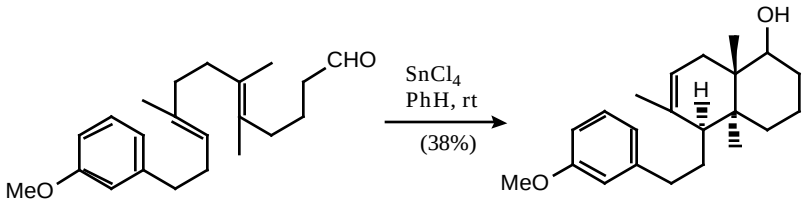
-Steroid Biosynthesis:



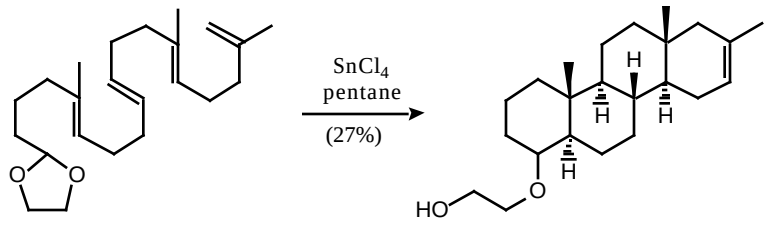
- Polyene cyclization in synthesis *ACR* **1968**, *1*, 1; *Bioorg. Chem.* **1976**, *5*, 51; *Asymmetric Synthesis* **1984**, *3*, 341-409; *ACIEE* **1976**, *15*, 9



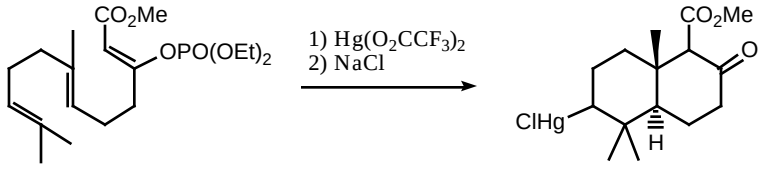
E.E. van Tamelen
JACS **1972**, *94* , 8229



JACS **1974**, *96* , 3333

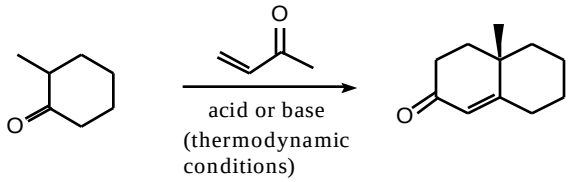


W.S. Johnson
JACS **1974**, *96*, 3979

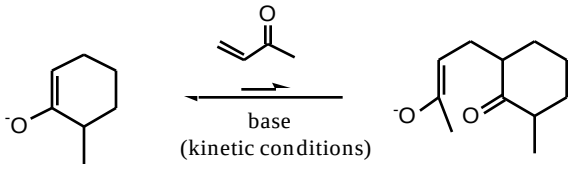


JACS **1980**, *102* , 7612

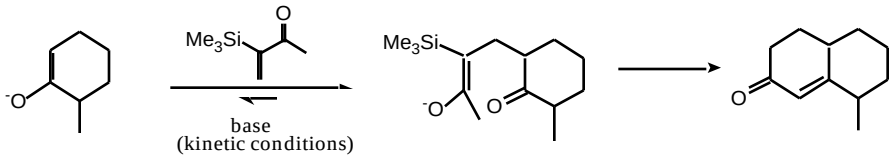
Robinson Annulation *Synthesis* **1976**, 777; *Tetrahedron* **1976**, *32*, 3.

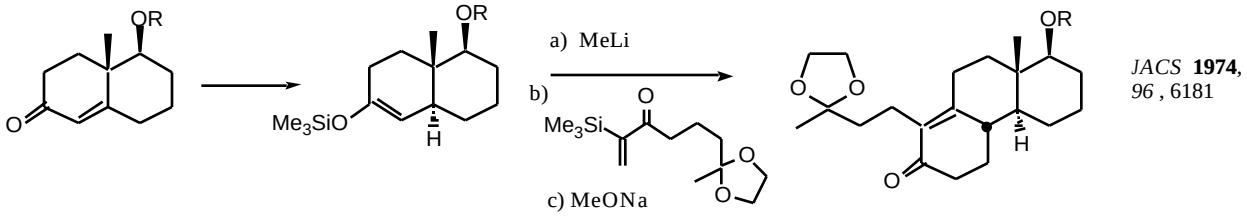


- unfavorable equillibium for the Michael addition under kinetic conditions



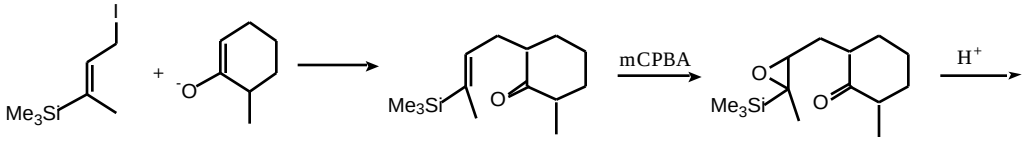
- stabilizing the resulting enolate of the Michael Addition product can shift the equilibrium as in the case of the vinyl silane shown below

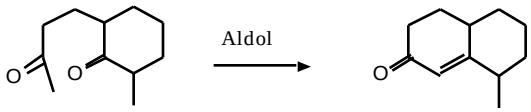




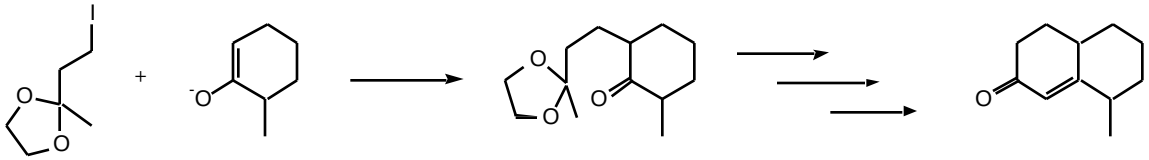
JACS **1974**, *96* , 6181

- Methyl Vinyl Ketone equivalents



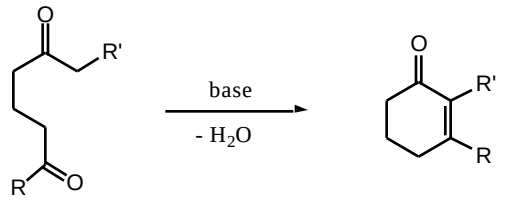


JACS **1974**, *96* , 3862

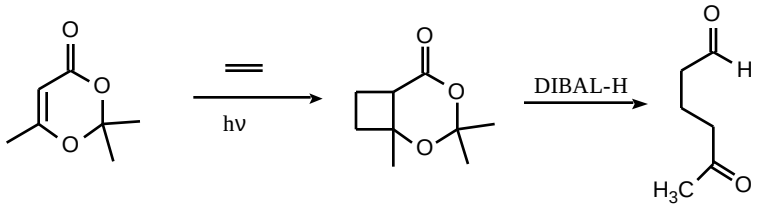


Intramolecular Aldol Condensation of 1,5-Diketones

6-exo-trig; favored process



- DeMayo reaction to 1,5-diketones



Intramolecular Alkylations (SN2 reaction)

Radical Cyclizations

Acyloin Reaction

Birch Reduction *Organic Reactions* **1992**, *42*, 1.

Aromatic Substitution (Carey & Sundberg, Chapter 11)

Intramolecular Wittig Reaction

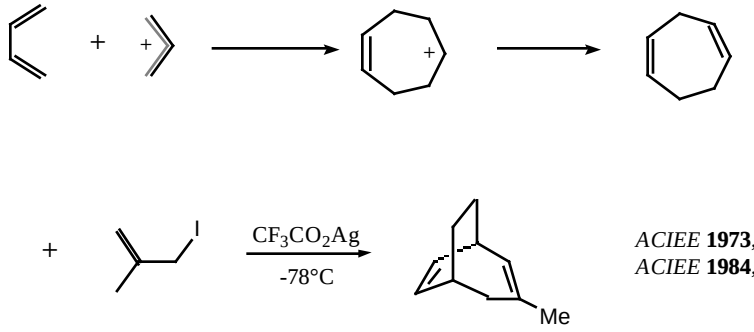
Sigmatropic Rearrangements

Medium Sized Rings

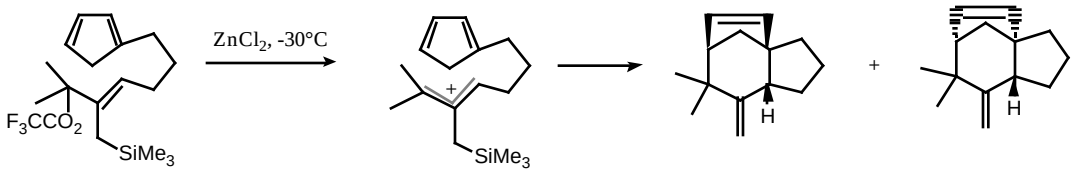
7-Membered Rings

[4+2] cycloadditions

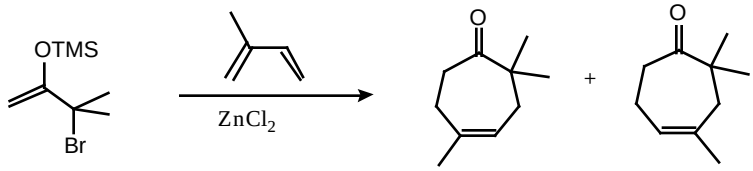
- [4+2] cycloadditions between dienes and allylcations leads to cycloheptadienes
  review: *ACIEE* **1984**, *23* , 1; *ACIEE* **1973**, *12* , 819



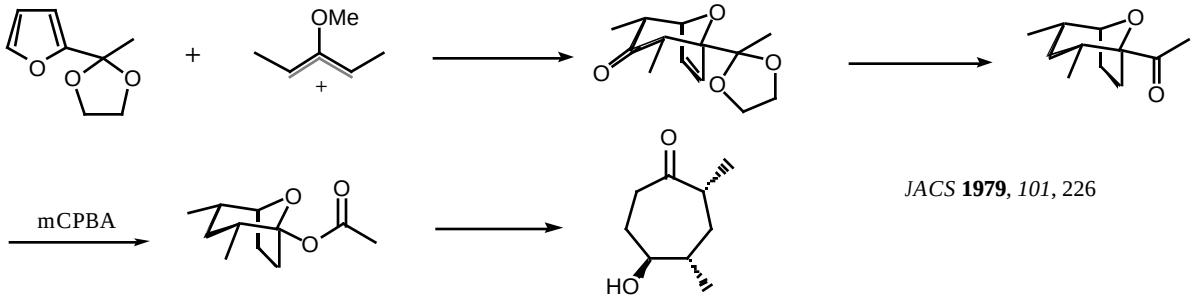
ACIEE **1973**, *12*, 819
ACIEE **1984**, *23*, 1



ACIEE **1982**, *21*, 442

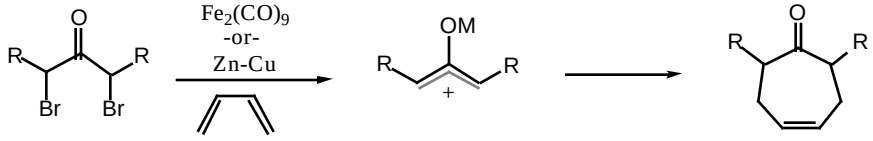


JACS **1982**, *104* , 1330

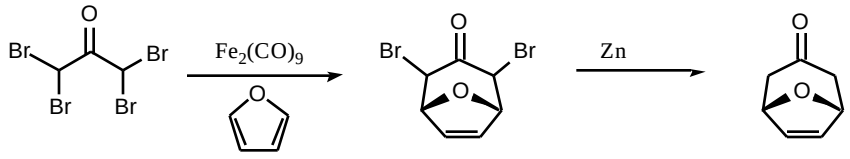


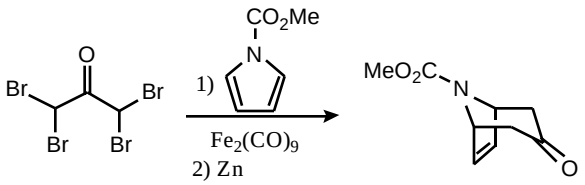
JACS **1979**, *101*, 226

- Noyori [4+2] cycloaddition of α,α'-dibromoketones and dienes
  review: *ACR* **1979**, *12* , 61

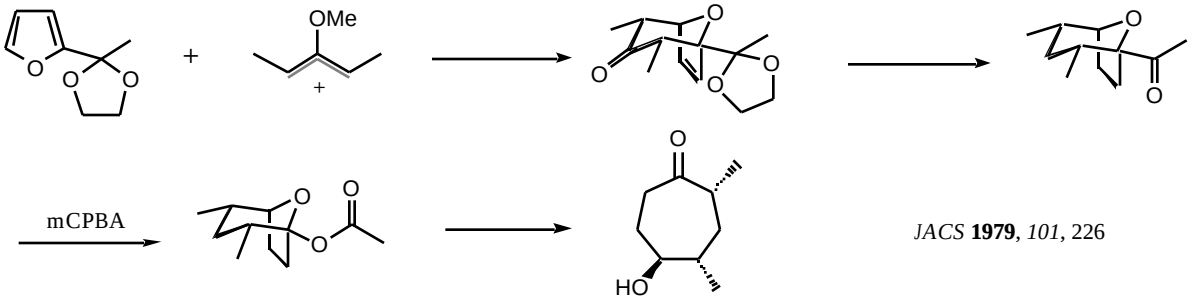


ACR **1979**, 61
Organic Reactions **1983**, *29*, 163

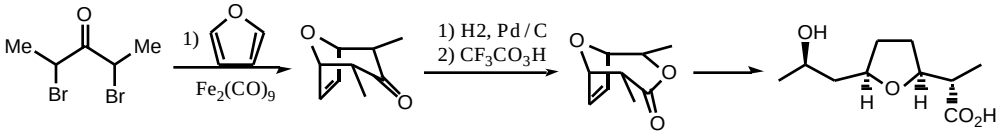




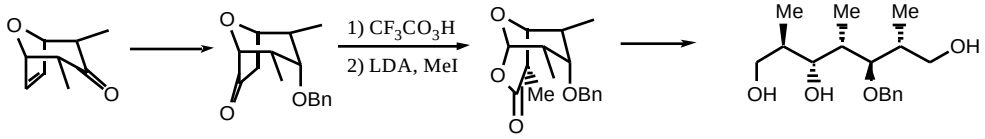
JACS **1978**, *100* , 1786
Tetrahedron **1985**, *41*, 5879



JACS **1979**, *101*, 226

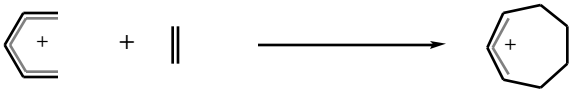


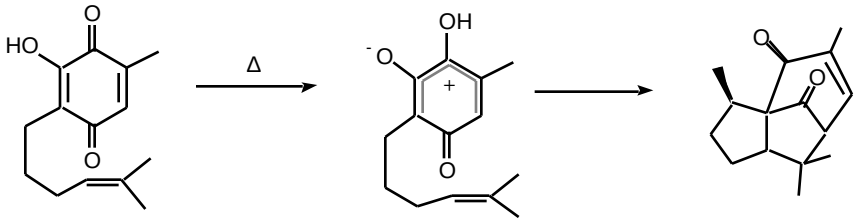
JACS **1972**, *94*, 3940
JOC **1976**, *41*, 2075



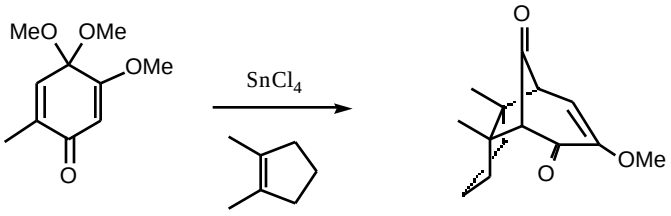
JCSCC **1985**, 55

- [4+2] cycloaddition between pentadienyl cations and olefins



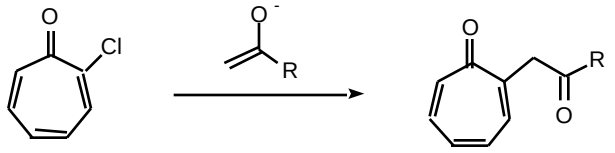


Tetrahedron **1966**, *22*, 2387
JOC **1987**, *52*, 759



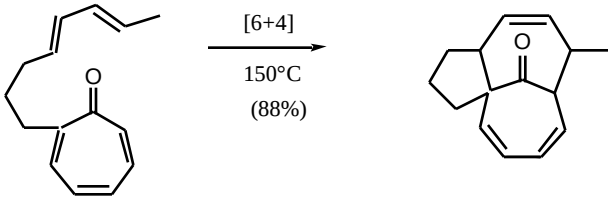
JACS **1977**, *99*, 8073
JACS **1979**, *101*, 6767
JACS **1981**, *103*, 2718

Seven-Membered Rings from Funnctionalization of Tropone
Organic Reactions **1997**, *49*, 331-425

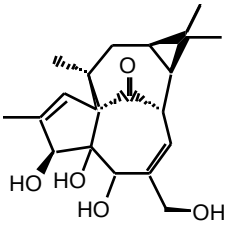


JOC **1988**, *53*, 4596
JACS **1987**, *109*, 3147

- [6+4] cycloadditions of tropones with dienes

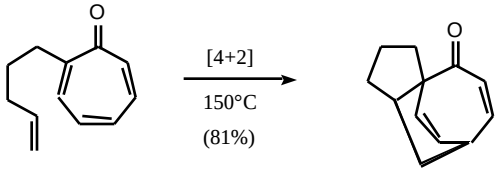


JACS **1986**, *108*, 4655
JOC **1986**, *51*, 2400



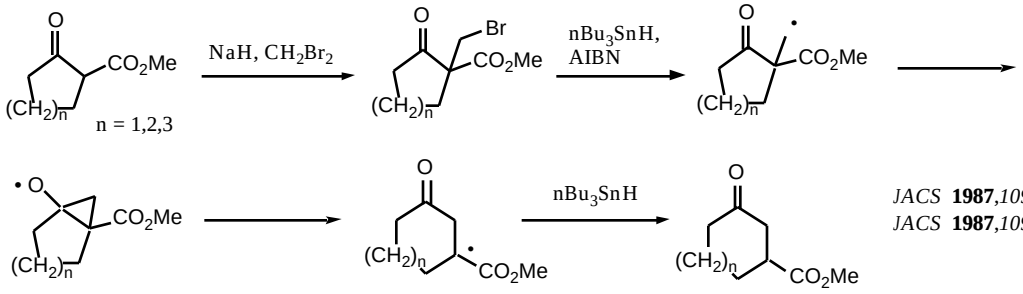
Ingenol

- [4+2] cycloaddition between tropone and olefins

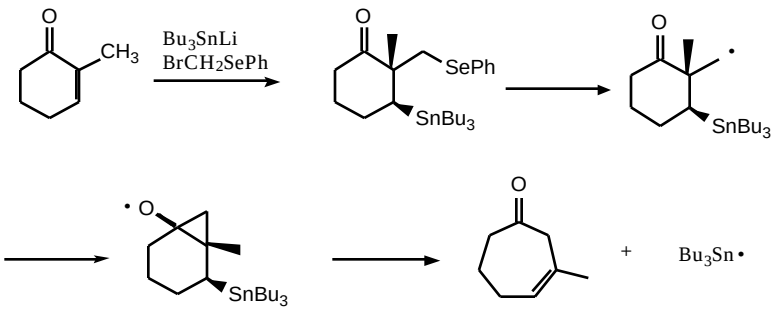


Radical Ring Expansion Reactions

- one carbon ring expansions

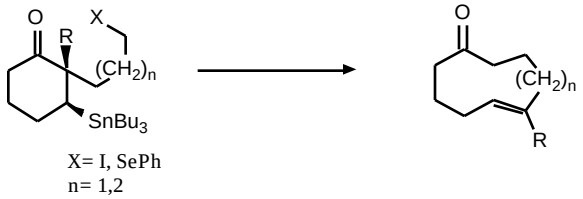


JACS **1987**,*109*, 3493
JACS **1987**,*109* , 6548



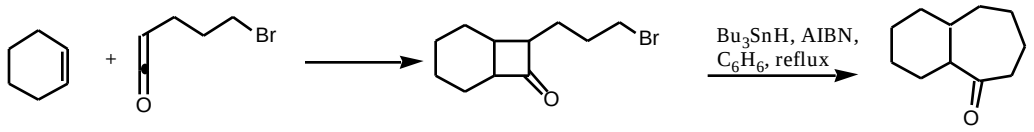
Tetrahedron **1989**, *45*, 909
Tetrahedron **1991**, *47*, *6795*

- more than one carbon expansion



X= I, SePh
n= 1,2

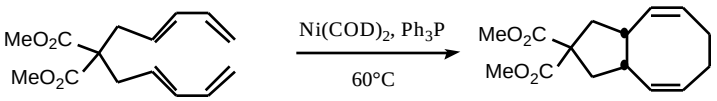
Tetrahedron **1989**, *45*, 909
Tetrahedron **1991**, *47*, *6795*



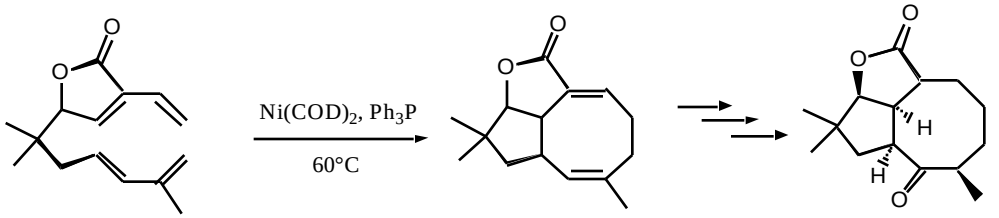
JOC **1992**, 57, *7163*

Eight-Membered Rings review:*Tetrahedron* **1992**, *48* , 5757.

[4+4] Cycloaddition of Dienes



JACS **1986**, *108* , 4678

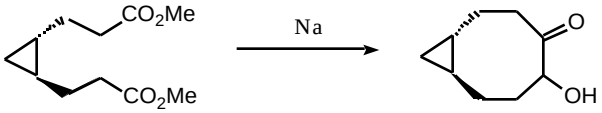


Asteriscanolide

JACS **1988**, *110* , 5904

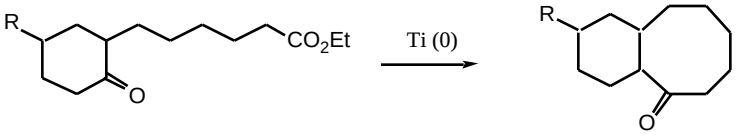
Carbonyl Coupling Reactions

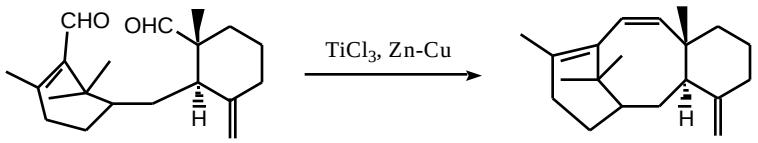
- Acyloin Reaction



JACS **1971**, *93* , 1673

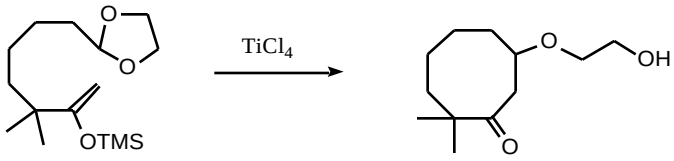
- McMurry Reaction



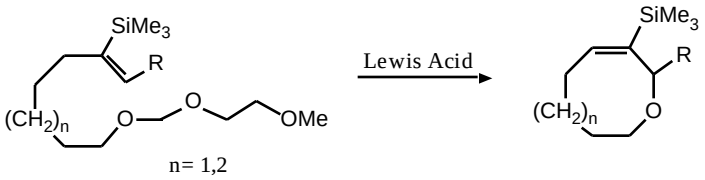


JACS **1986**, *108* , 3513

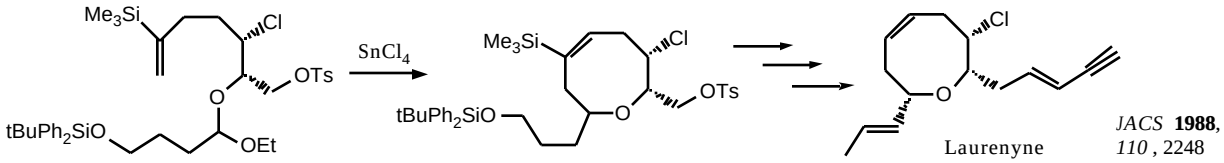
Aldol-like Condensations



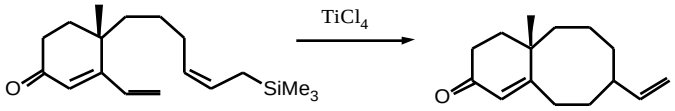
JCSCC **1983**, 703



JACS **1986**, *108* , 3516

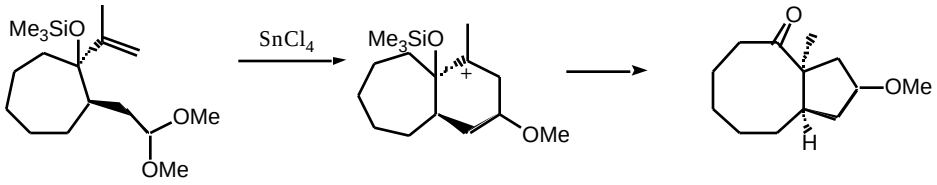


JACS **1988**, *110* , 2248



JOC **1988**, *53* , 50

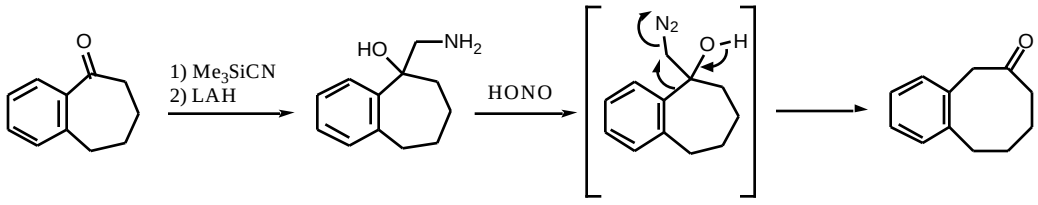
Pinocol Rearrangement



JACS **1989**, *111* , 1514

Tiffeneu-Demyanov Ring Expansion

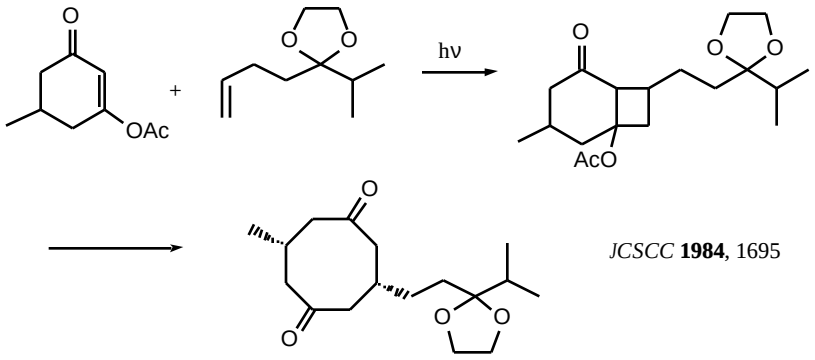
- one carbon ring expansion for virtually any size ring



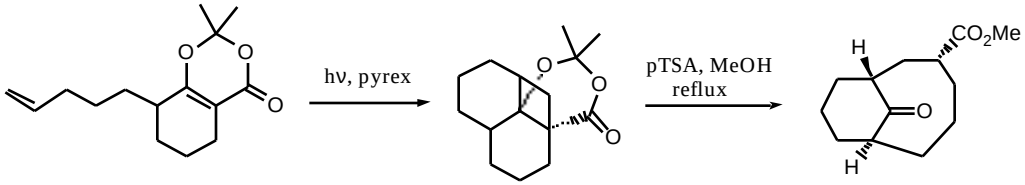
JOC **1980**, *45* , 185

- also see Beckman and Schmidt rearrangements as a one atom ring expansion for the conversion of cyclic ketones to lactams.

DeMayo Reaction



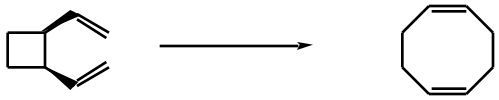
JCSCC **1984**, 1695

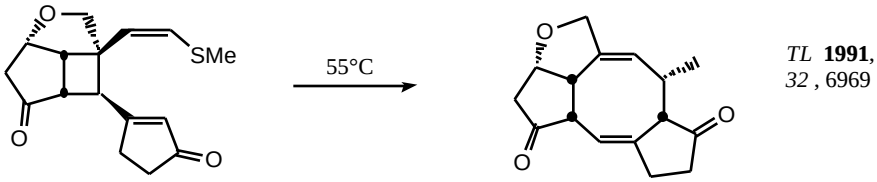


JACS **1986**, *108* , 6425

Ring Expansion/Contraction via Sigmatropic Rearrangements

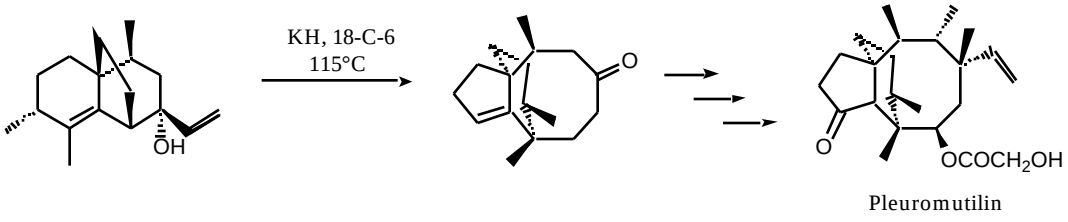
- Cope Rearrangement





TL **1991**, *32* , 6969

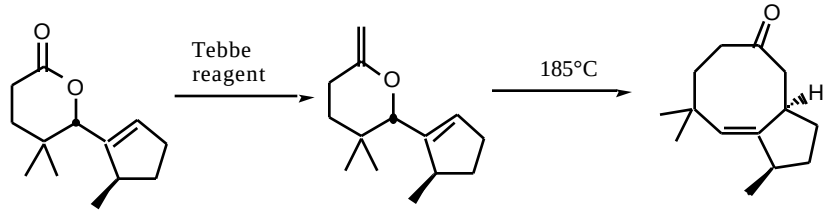
- Anion Accelerated Cope



JACS **1989**, *111*, 8284

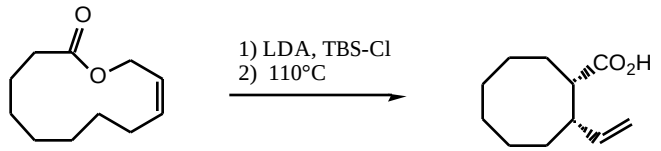
Pleuromutilin

- Claisen Rearrangement

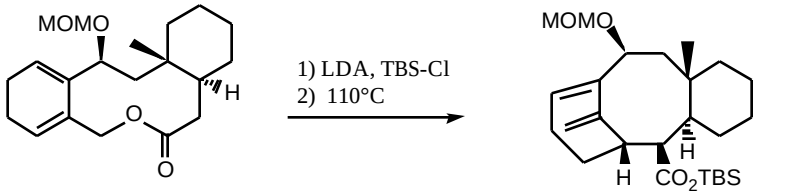


TL **1990**, *31* , 6799

- Ester Enolate Claisen- 4 carbon ring contractions



JACS **1982**, ***104*** , 4030
Tetrahedron **1986**, *42* , 2831



JOC **1988**, *53* , 4141