

Advanced Organic Reactions

(Lecture notes)

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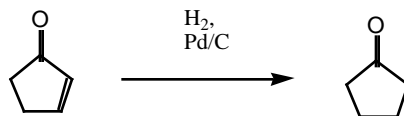
Source:

<http://www.vanderbilt.edu/AnS/Chemistry/Rizzo/chem223/chem223.htm>

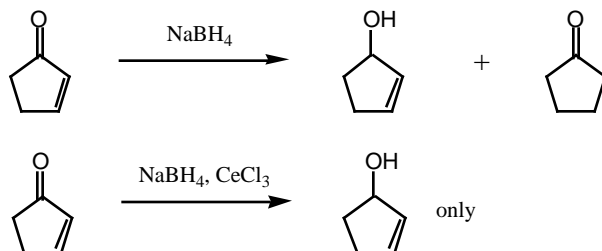
SELECTIVITY*Science* **1983**, 219, 245**Chemoselectivity**

preferential reactivity of one functional group (FG) over another

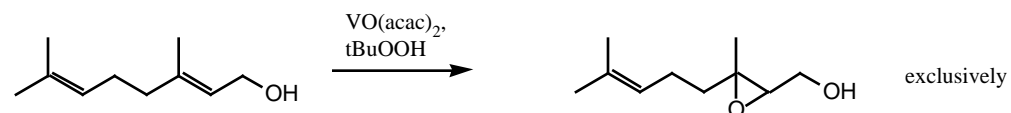
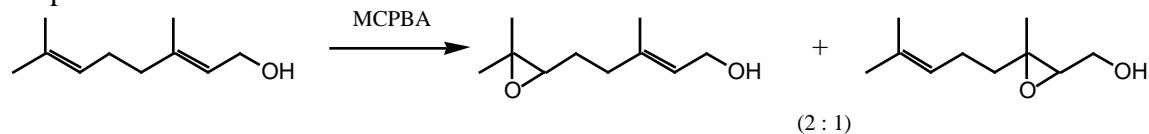
- Chemoselective reduction of C=C over C=O:



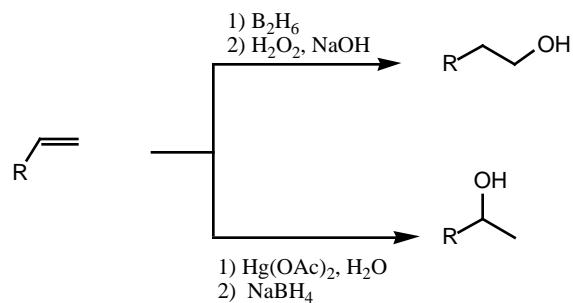
- Chemoselective reduction of C=O over C=C:



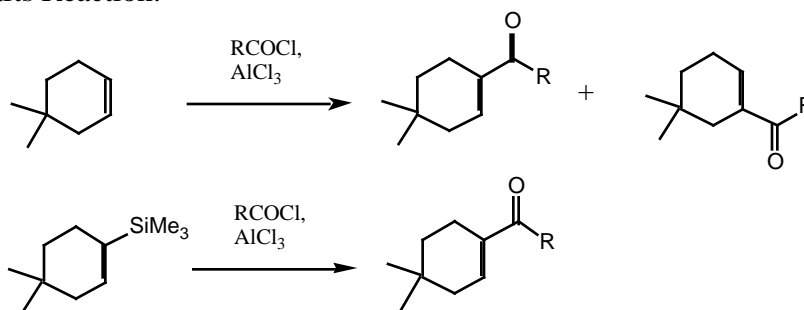
- Epoxidation:

**Regioselectivity**

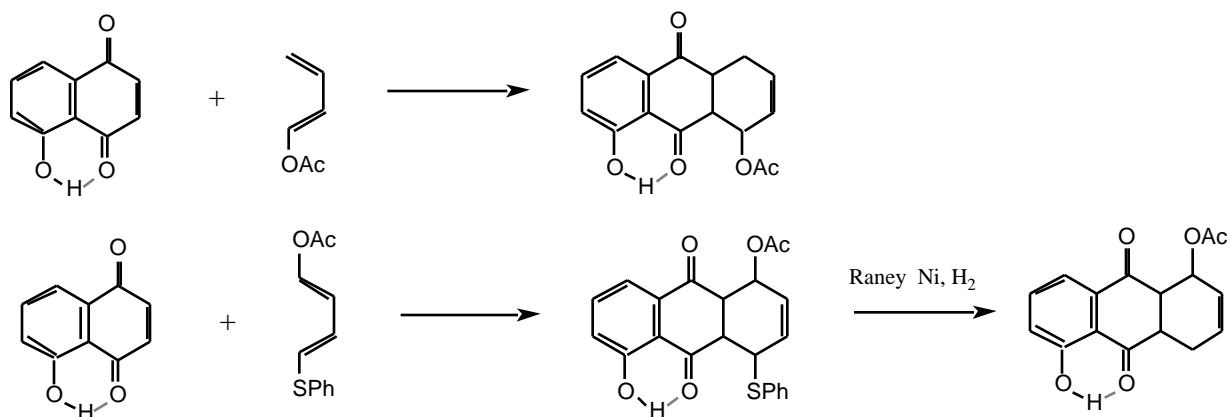
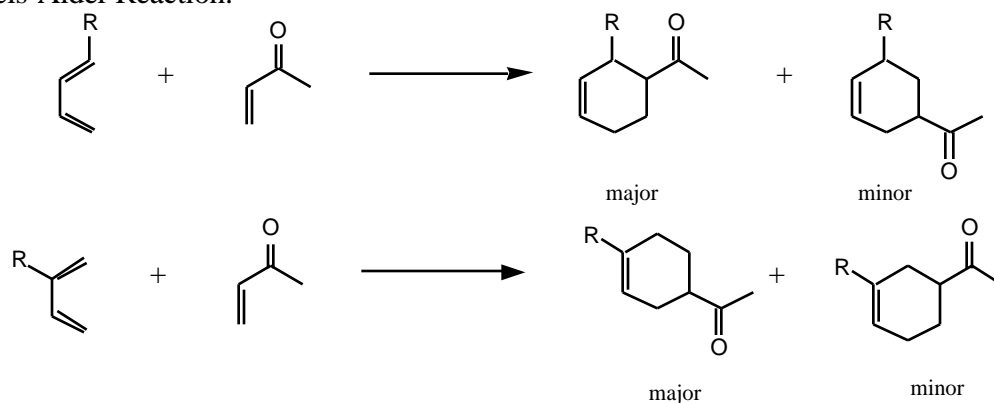
- Hydration of C=C:



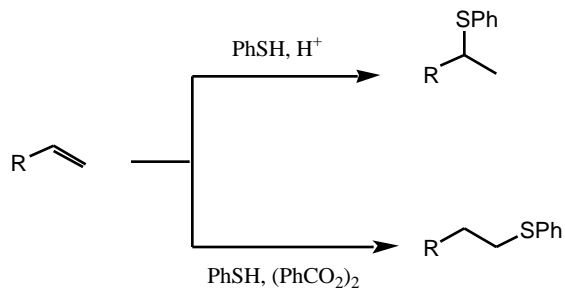
- Friedel-Crafts Reaction:



- Diels-Alder Reaction:

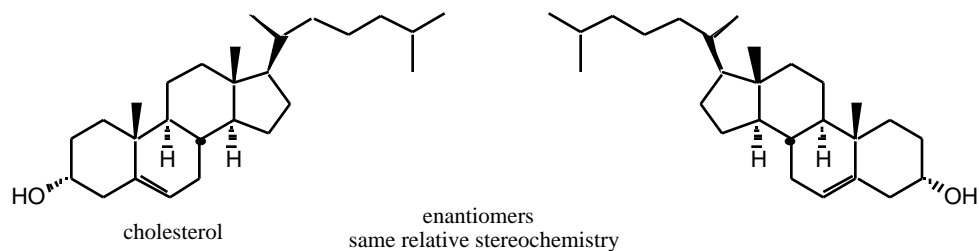


Change in mechanism:



Stereochemistry:

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



syn: on the same side (cis)

anti: on the opposite side (trans)

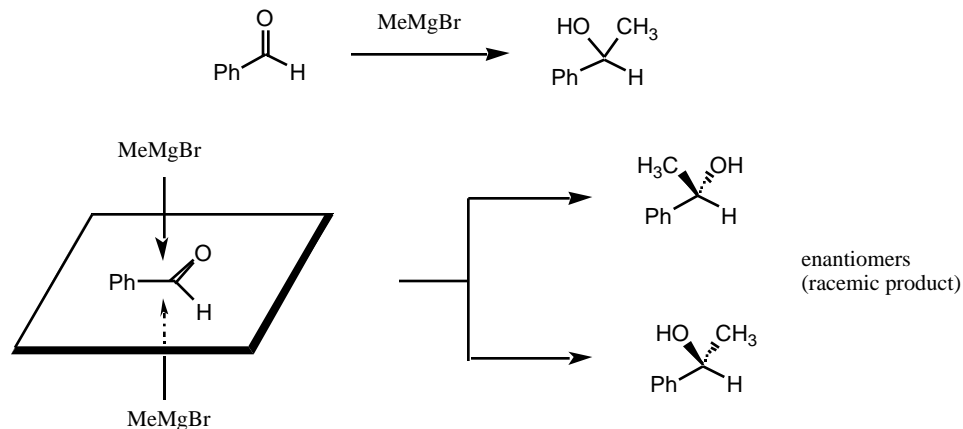
- differences in relative stereochemistry lead to diastereomers.

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

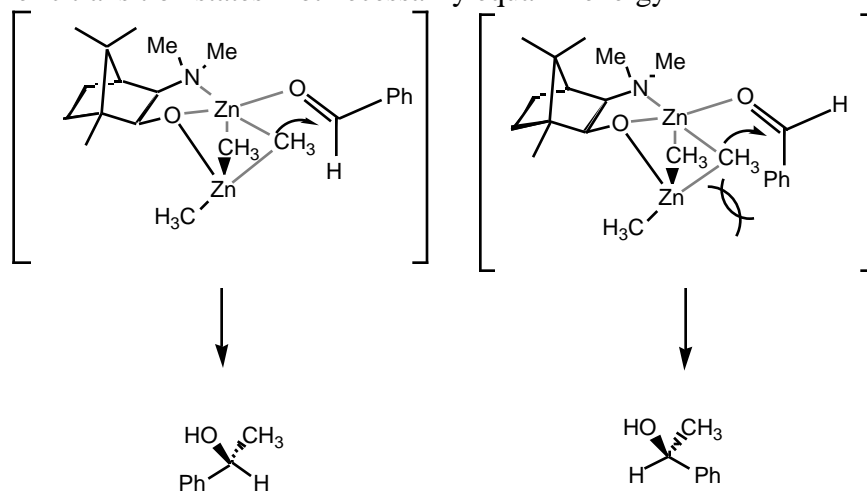
Absolute Stereochemistry: Absolute stereochemical assignment of each stereocenter (R vs S)
Cahn-Ingold-Prelog Convention (sequence rules)

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

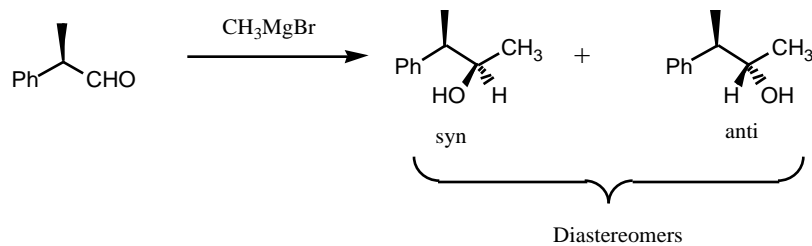
- Reactions can "create" stereocenters



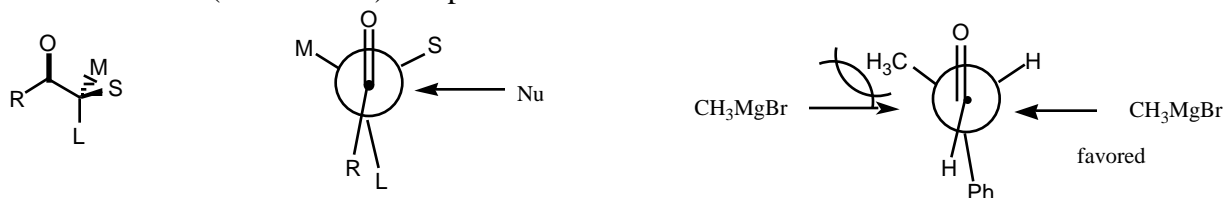
Diastereomeric transition states- not necessarily equal in energy



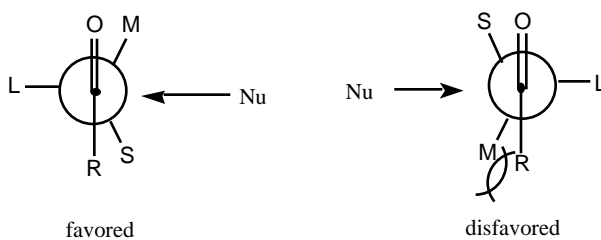
Diastereoselectivity



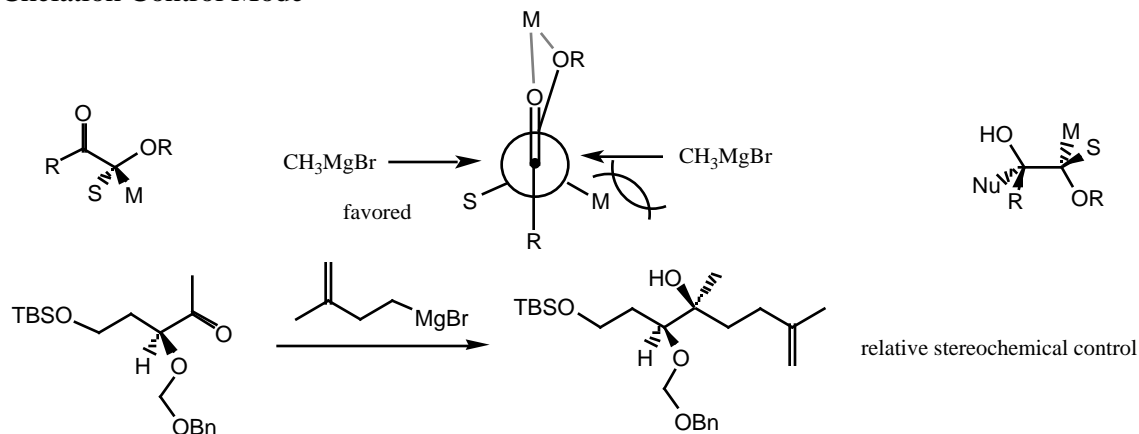
Cram Model (Cram's Rule): empirical



Felkin-Ahn Model

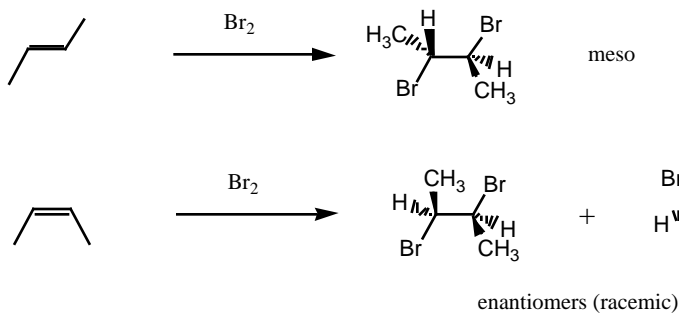


Chelation Control Mode



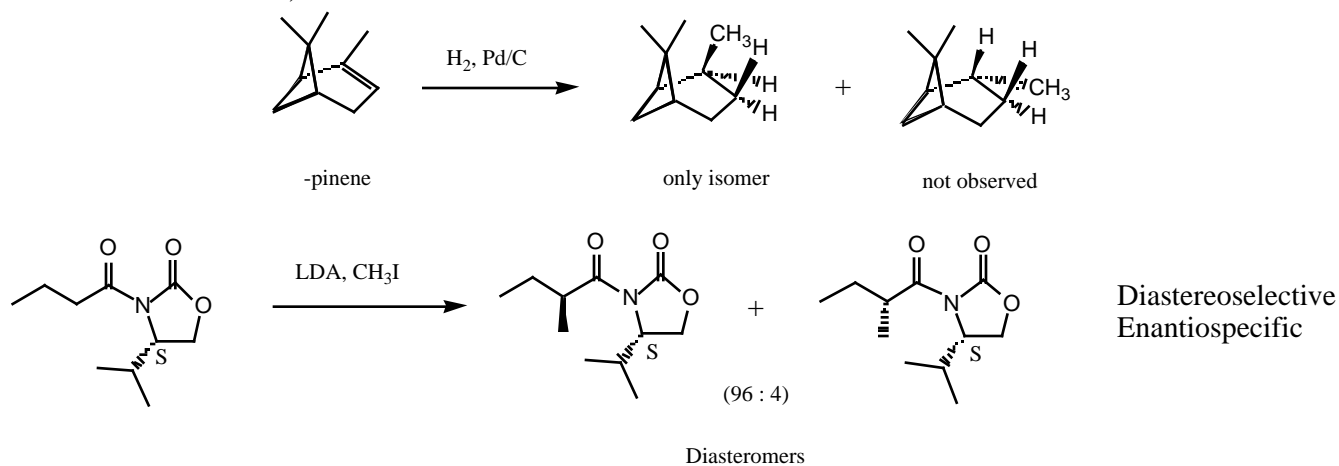
Stereospecific

Stereochemistry 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



Stereoselective

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



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

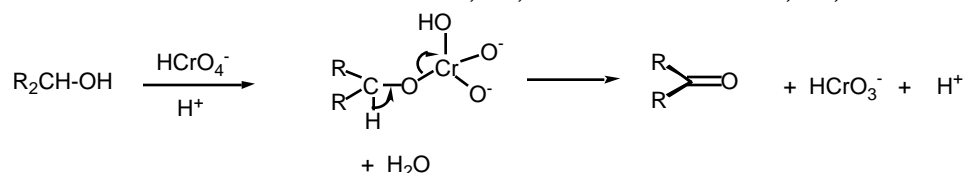
II Non-Metal Based Reagents

1. Activated DMSO
2. Peroxides and Peracids
3. Oxygen/ ozone
4. others

III. Epoxidations**Metal Based Reagents****Chromium Reagents**

- Cr(VI) based
- exact structure 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 , $\text{H}_2\text{Cr}_2\text{O}_7$, $\text{K}_2\text{Cr}_2\text{O}_7$)

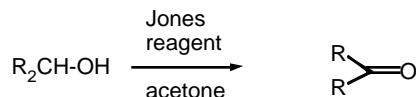
J. Chem. Soc. **1946** 39

Org. Syn. Col. Vol. V, **1973**, 310.

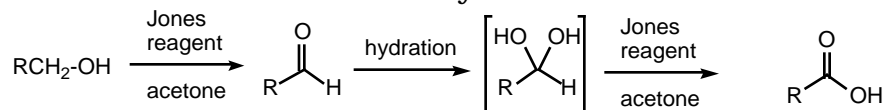
- $\text{CrO}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CrO}_4$ (aqueous solution)
- $\text{K}_2\text{Cr}_2\text{O}_7 + \text{K}_2\text{SO}_4$

- Cr(VI) Cr(III)
- (black) (green)

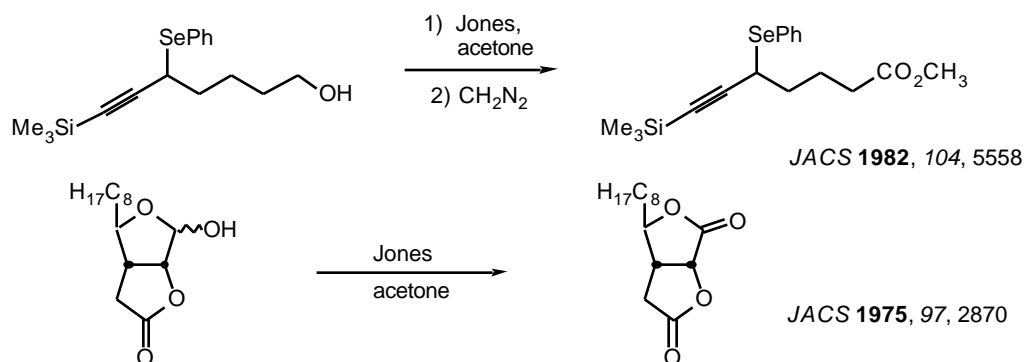
- 2°- alcohols are oxidized to ketones



- saturated 1° alcohols are oxidized to carboxylic acids.



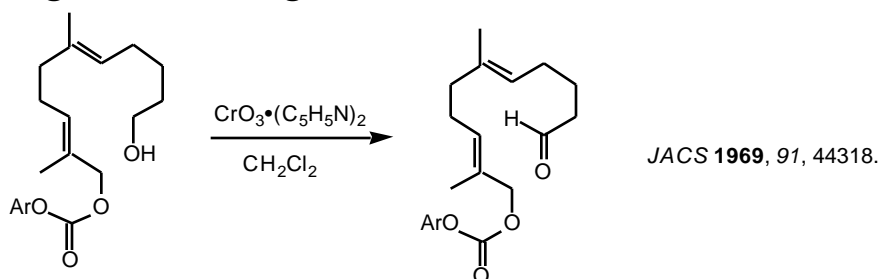
- Acidic media!! Not a good method for H^+ sensitive groups and compounds



Collins Oxidation (CrO₃•2pyridine)

TL 1969, 3363

- CrO₃ (anhydrous) + pyridine (anhydrous) CrO₃•2pyridine
- 1° and 2° alcohols are oxidized to aldehydes and ketones in non-aqueous solution (CH₂Cl₂) 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.



CrO₃ catalyzed (1-2 mol % oxidation with NaIO₆ (2.5 equiv) as the reoxidant in wet acetonitrile. oxidized primary alcohols to carboxylic acids.

Tetrahedron Lett. 1998, 39, 5323.

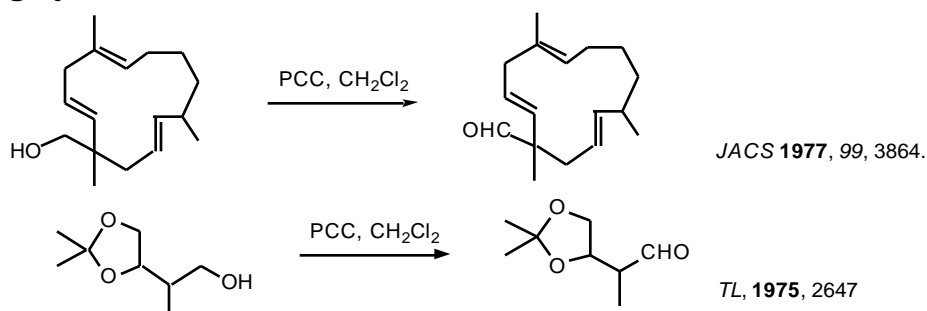
Pyridinium Chlorochromate (PCC, Corey-Suggs Oxidation)

TL 1975 2647

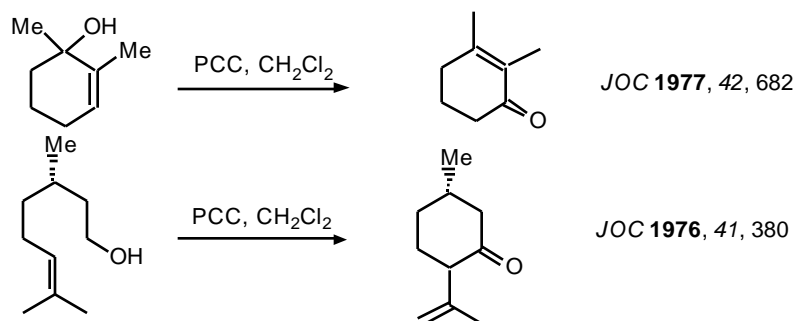
Synthesis 1982, 245 (review)

CrO₃ + 6M HCl + pyridine pyH⁺CrO₃ Cl⁻

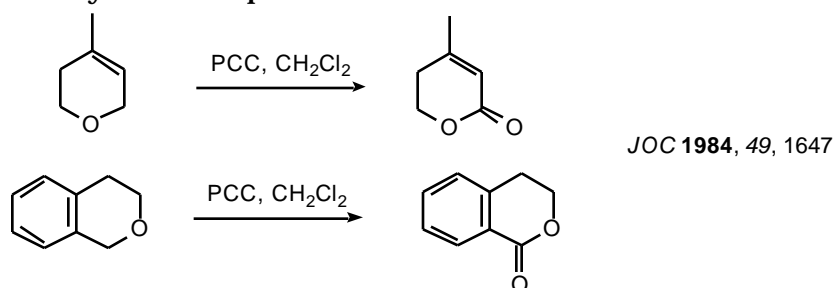
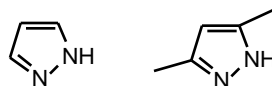
- Reagent can be used in close to stoichiometric amounts w/ substrate
- PCC is slightly acidic but can be buffered w/ NaOAc



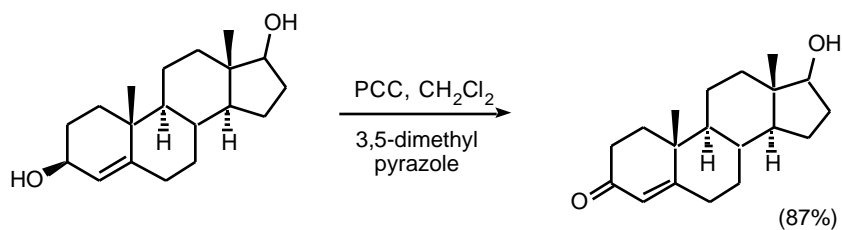
- Oxidative Rearrangements



- Oxidation of Active Methylene Groups

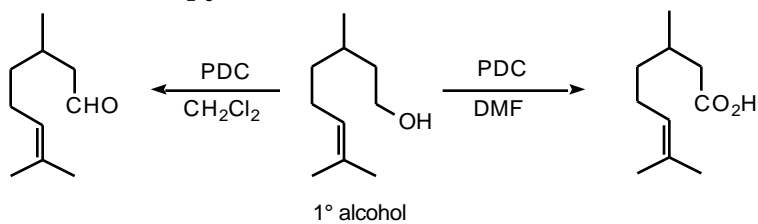

 - PCC/Pyrazole PCC/ 3,5-Dimethylpyrazole
JOC 1984, 49, 550.


- selective oxidation of allylic alcohols



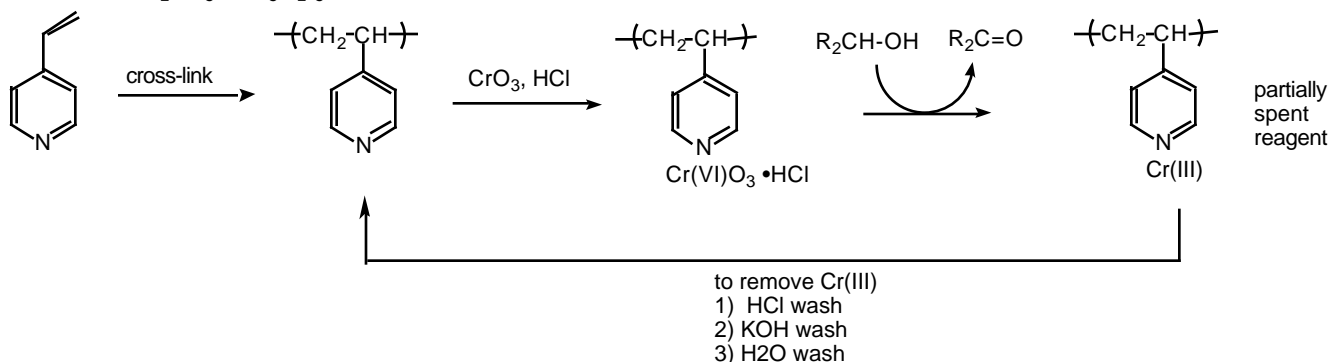
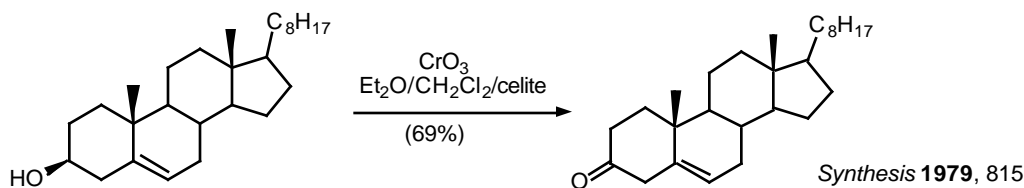
Pyridinium Dichromate (PDC, Corey-Schmidt Oxidation)

TL 1979, 399

 - $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O} + \text{HCl} + \text{pyridine}$ $(\text{C}_5\text{H}_5\text{N})_2\text{CrO}_7$

 -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. $\text{CrO}_3/\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{Celite}$ *Synthesis* **1979**, 815.- CrO_3 in non-aqueous media does not oxidized alcohols- CrO_3 in 1:3 $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{celite}$ will oxidized alcohols to ketone and aldehydes H_2CrO_7 on Silica- 10% CrO_3 to SiO_2 - 2-3g $\text{H}_2\text{CrO}_3/\text{SiO}_2$ to mole of R-OH

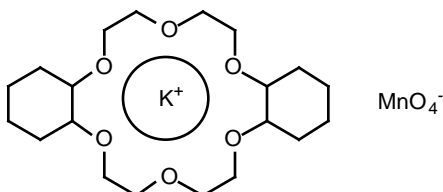
- ether is the solvent of choice

Manganese Reagents

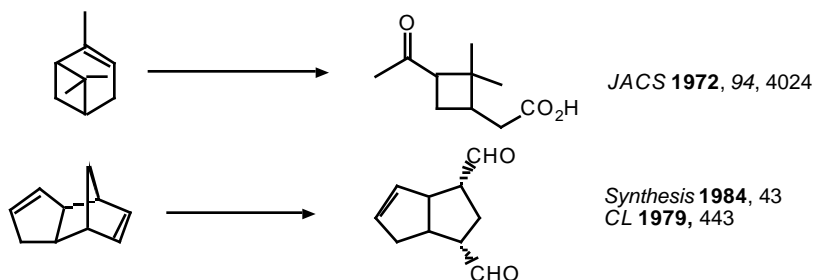
Potassium Permanganate

 $\text{KMnO}_4/18\text{-Crown-6}$

(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 PermanganateTL **1981**, 1655

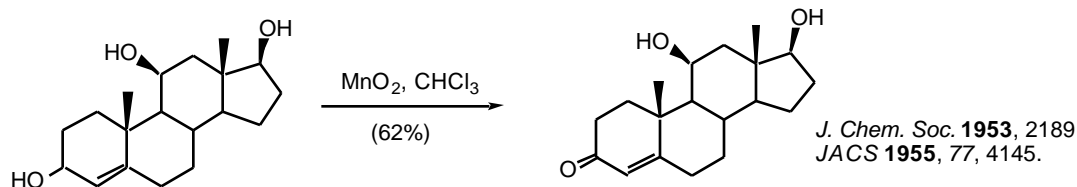
- heterogeneous reaction in benzene
- 1° alcohols are oxidized to acids
- 2° alcohols are oxidized to ketones
- multiple bonds are not oxidized

Barium Permanganate (BaMnO₄)TL **1978**, 839.

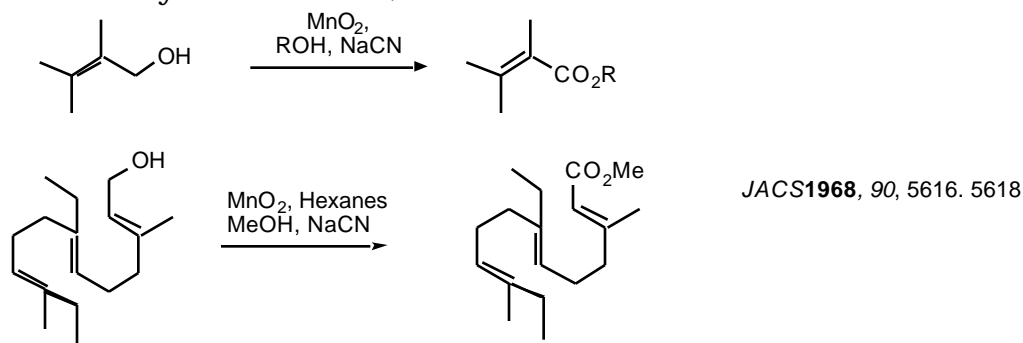
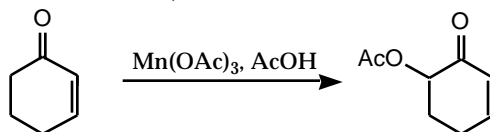
- Oxidation of 1° and 2° alcohols to aldehydes and ketones- No over oxidation
- Multiple bonds are not oxidized
- similar in reactivity to MnO₂

Barium ManganateBCSJ **1983**, 56, 914**Manganese Dioxide**Review: *Synthesis* **1976**, 65, 133

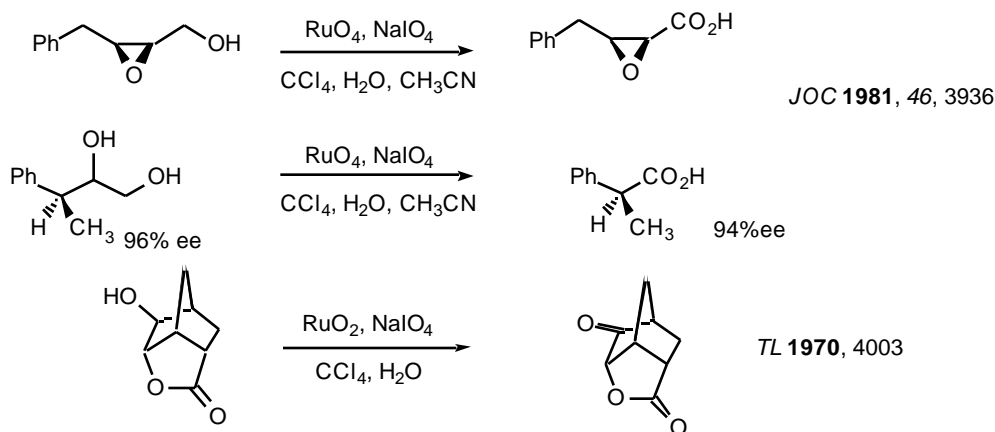
- Selective oxidation of , -unsaturated (allylic, benzylic, acetylenic) alcohols.
- Activity of MnO₂ depends on method of preparation and choice of solvent
- cis & trans allylic alcohols are oxidized at the same rate without isomerization of the double bond.



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

**Manganese (III) Acetate***Synthesis* **1990**, 1119**-hydroxylation of enones**TL **1984** 25, 5839**Ruthenium Reagents****Ruthenium Tetroxide**

- effective for the conversion of 1° alcohols to RCO₂H and 2° alcohols to ketones
- oxidizes multiple bonds and 1,2-diols.

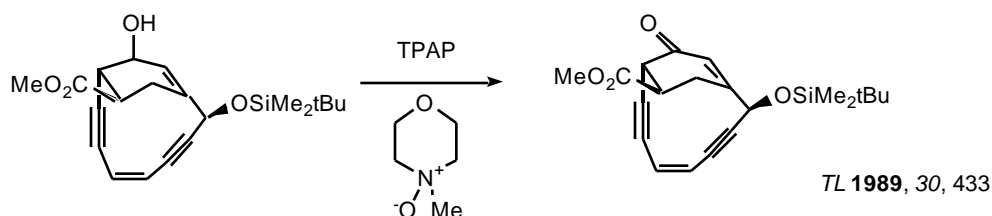


Tetra-*n*-propylammonium Perruthenate (TPAP, $\text{nPr}_4\text{N}^+ \text{RuO}_4^-$)

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

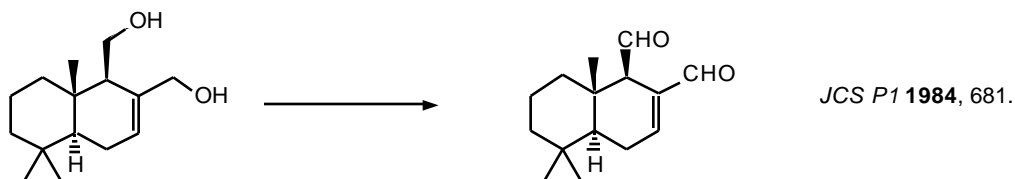
Synthesis **1994**, 639

- mild oxidation of alcohols to ketones and aldehydes without over oxidation



$(\text{Ph}_3\text{P})_4\text{RuO}_2\text{Cl}_3$ $\text{RuO}_2(\text{bipy})\text{Cl}_2$

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



$\text{Ba}[\text{Ru}(\text{OH})_2\text{O}_3]$

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

$(\text{Ph}_3\text{P})_3\text{RuCl}_2 + \text{Me}_3\text{SiO-OSiMe}_3$

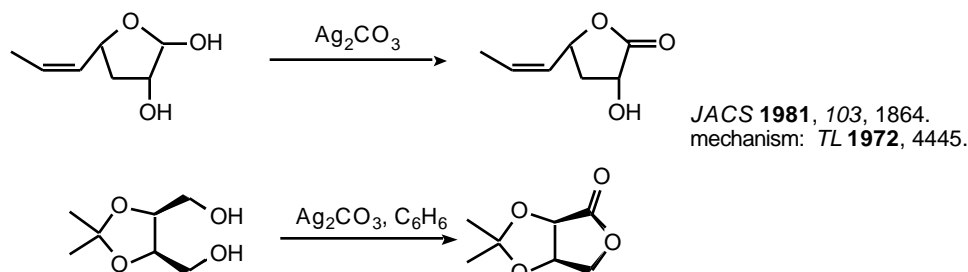
- oxidation of benzylic and allylic alcohols *TL* **1983**, 24, 2185.

Silver Reagents

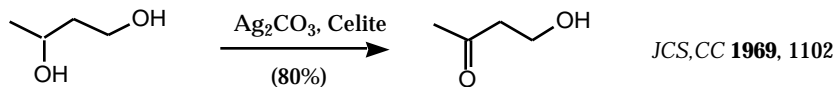
Ag_2CO_3 (Fetizon Oxidation) also $\text{Ag}_2\text{CO}_3/\text{celite}$

Synthesis **1979**, 401

- oxidation of only the most reactive hydroxyl

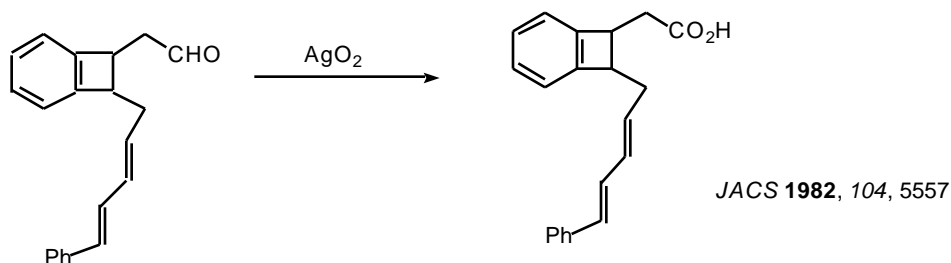
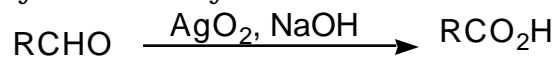


- Oxidation of 2° alcohol over a 1° alcohol

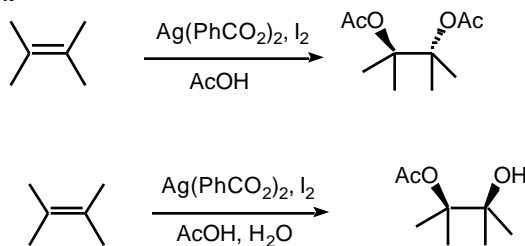


Silver Oxide (AgO_2)

- mild oxidation of aldehyde to carboxylic acids



Prevost Reaction $\text{Ag}(\text{PhCO}_2)_2, \text{I}_2$



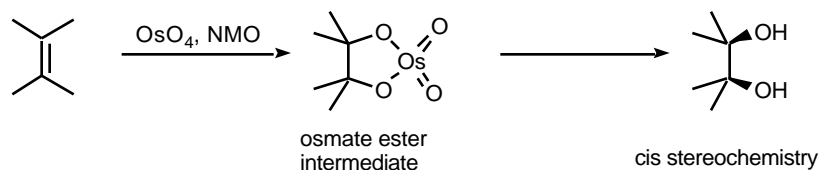
Other Metal Based Oxidations

Osmium Tetroxide OsO_4

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

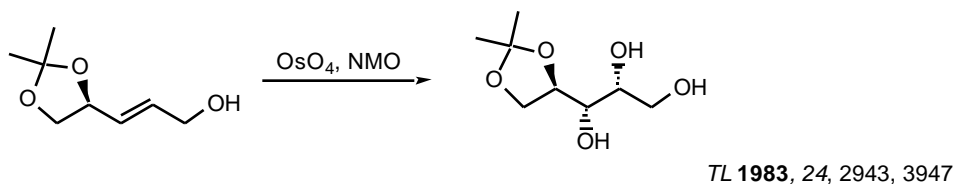
-cis hydroxylation of olefins

old mechanism:

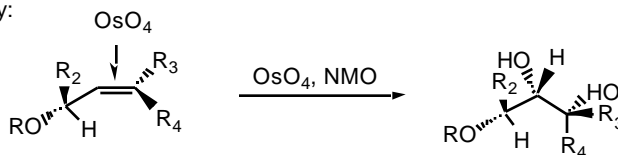


- use of $\text{R}_3\text{N-O}$ as a reoxidant

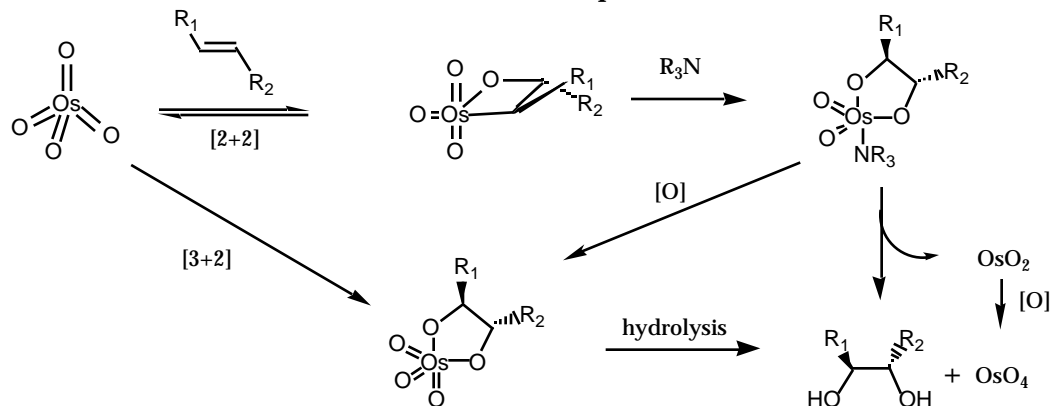
TL **1976**, 1973.



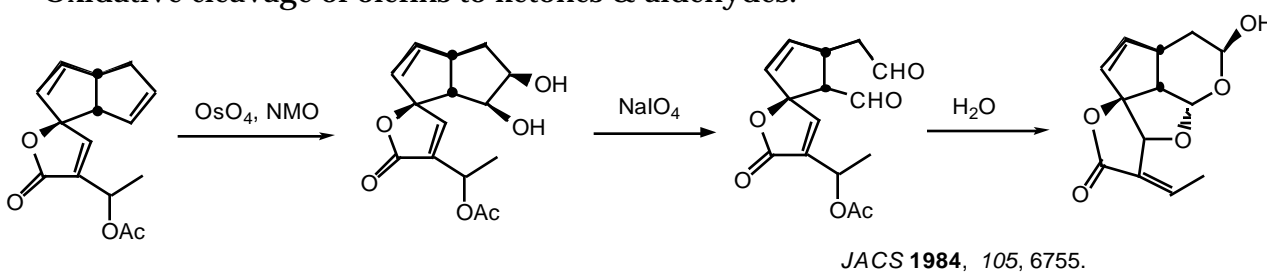
Stereoselectivity:



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

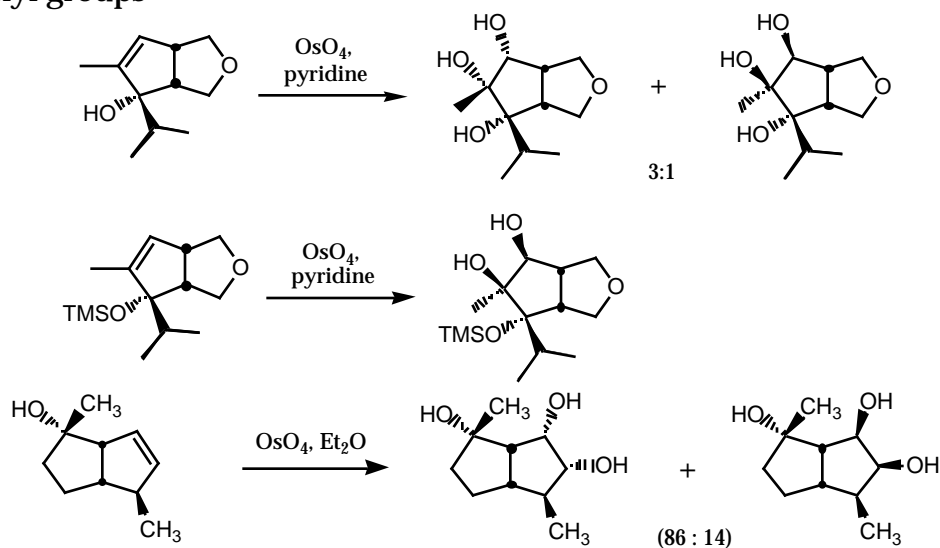


- Oxidative cleavage of olefins to carboxylic acids.
JOC **1956**, 21, 478.
- Oxidative cleavage of olefins to ketones & aldehydes.

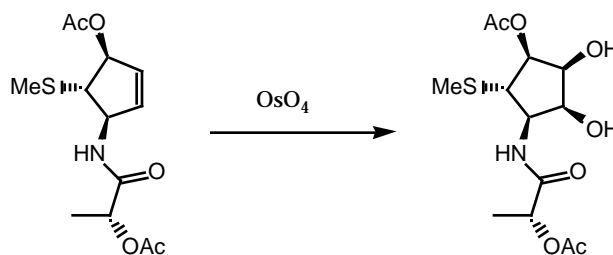


Substrate directed hydroxylations:
-by hydroxyl groups

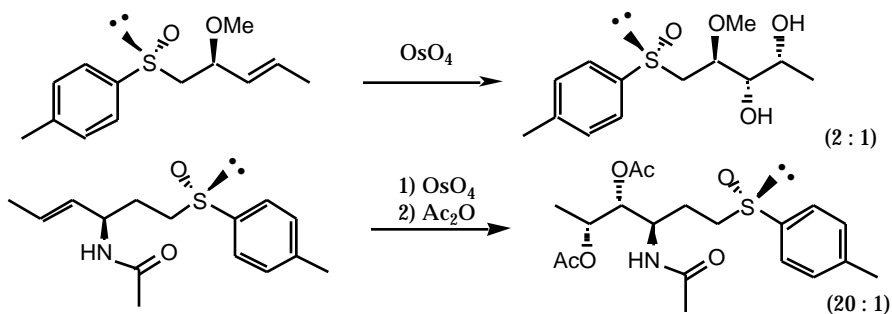
Chem. Rev. **1993**, 93, 1307



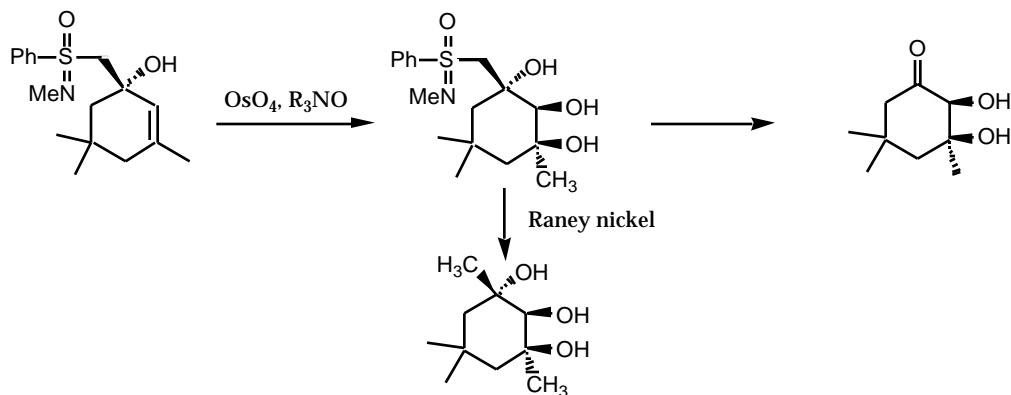
- by amides



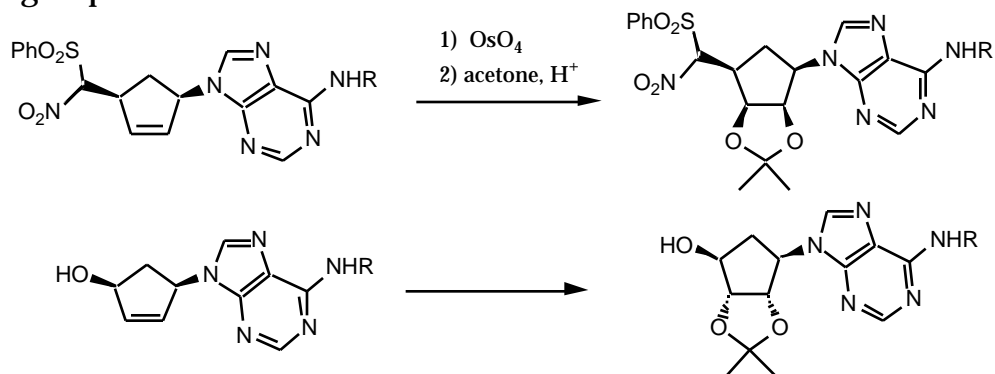
- by sulfoxides



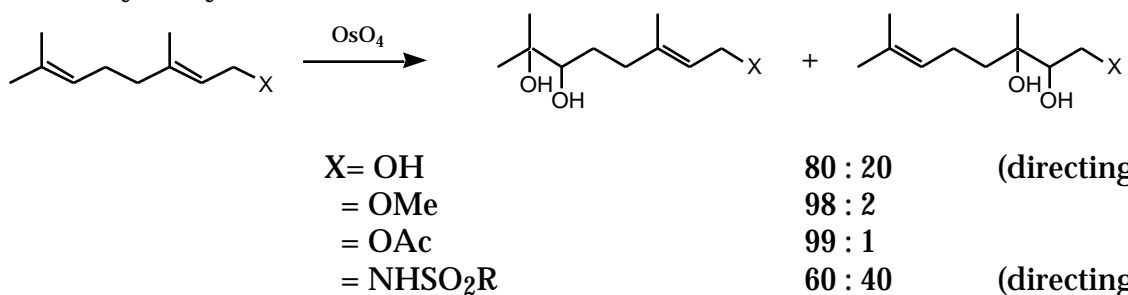
- by sulfoximines



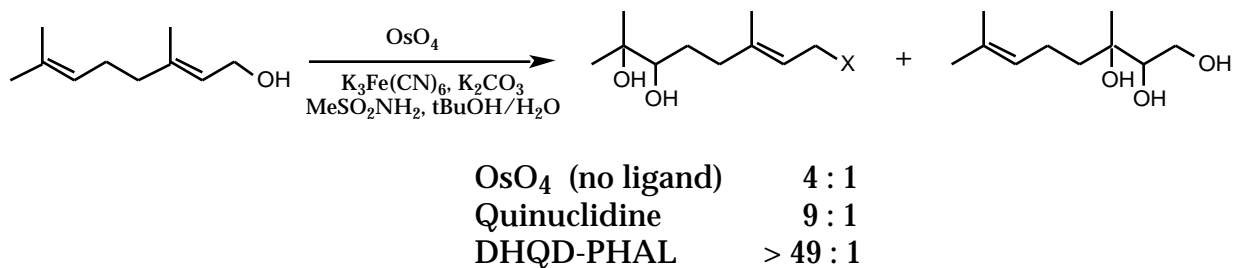
- By nitro groups



- OsO₄ bis-hydroxylation favors electron rich C=C.

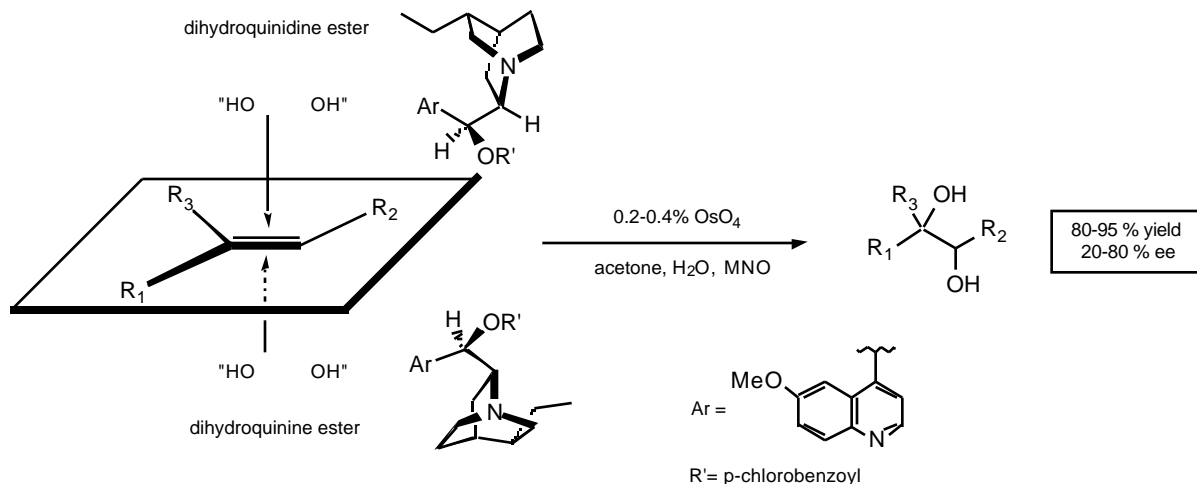
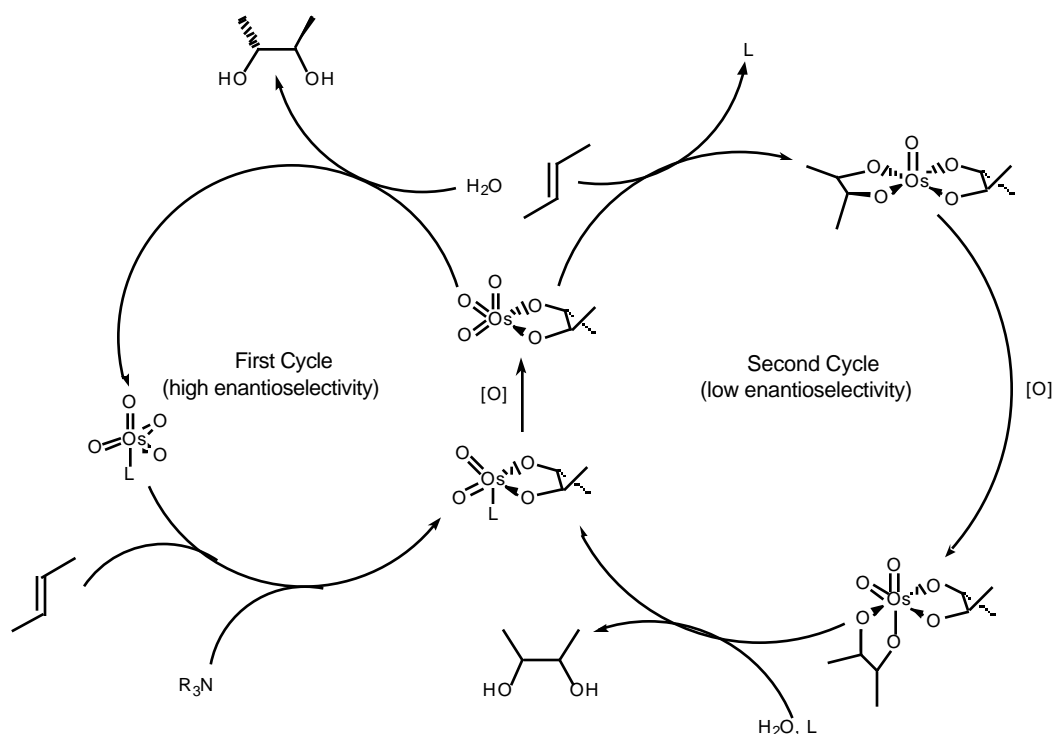


- Ligand effect:



Sharpless Asymmetric Dihydroxylation (AD)

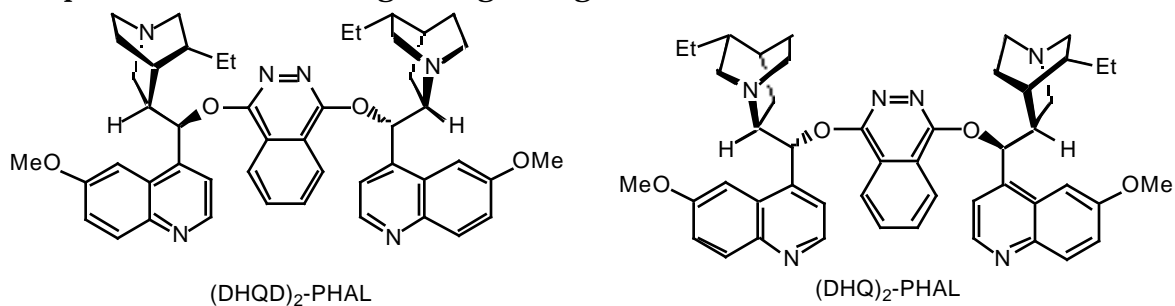
- Ligand pair are really diastereomers!!

Chem. Rev. **1994**, *94*, 2483.

Mechanism of AD:

 - K₃Fe(CN)₆ as a reoxidant gives higher ee's- eliminates second cycle

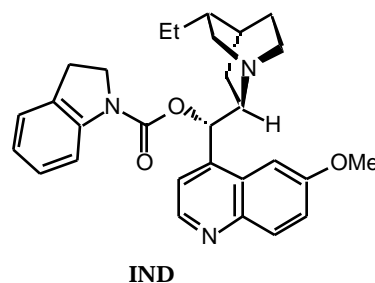
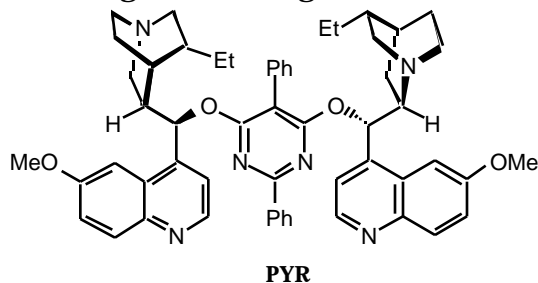
TL **1990**, *31*, 2999.

 - Sulfonamide effect: addition of MeSO₂NH₂ enhances hydrolysis of Os(VI) glycolate (accelerates reaction)

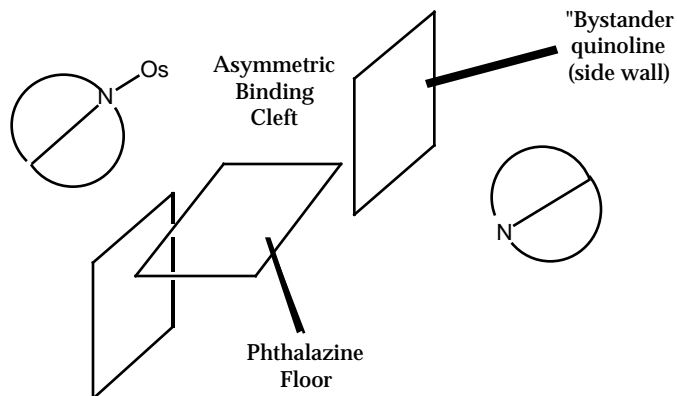
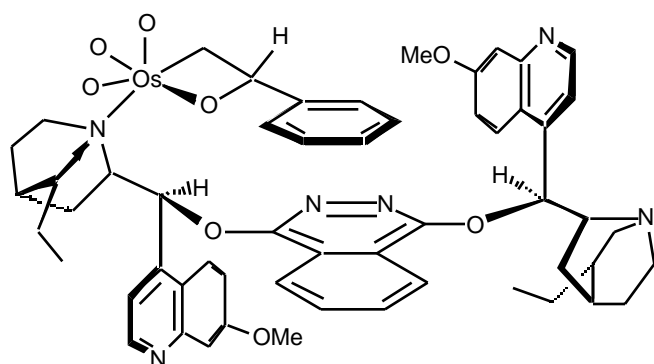
- New phthalazine (PHAL) ligand's give higher ee's


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

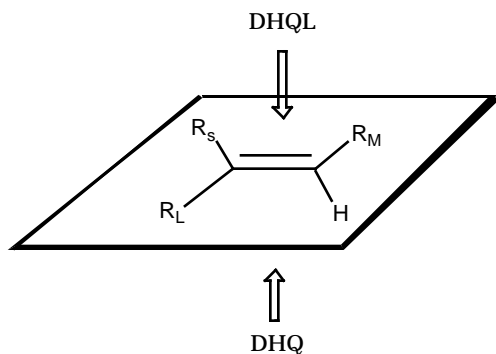
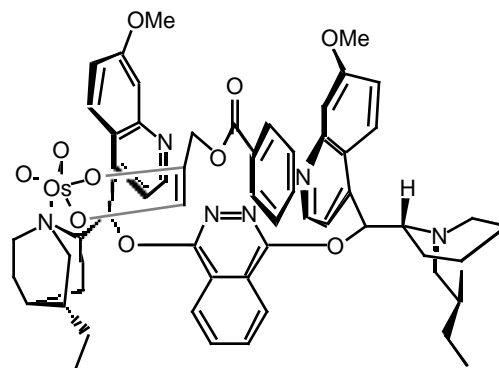
- Other second generation ligands





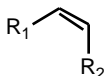
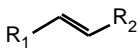
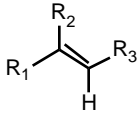
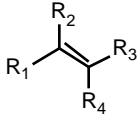
Proposed catalyst structure:



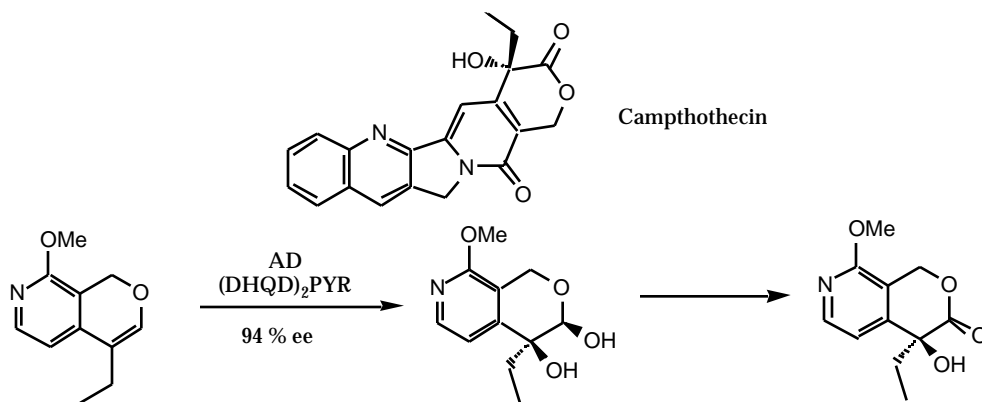
Corey Model: *JACS* **1996**, 118, 319
 Enzyme like binding pocket;
 [3+2] addition of OsO₄ to olefin.



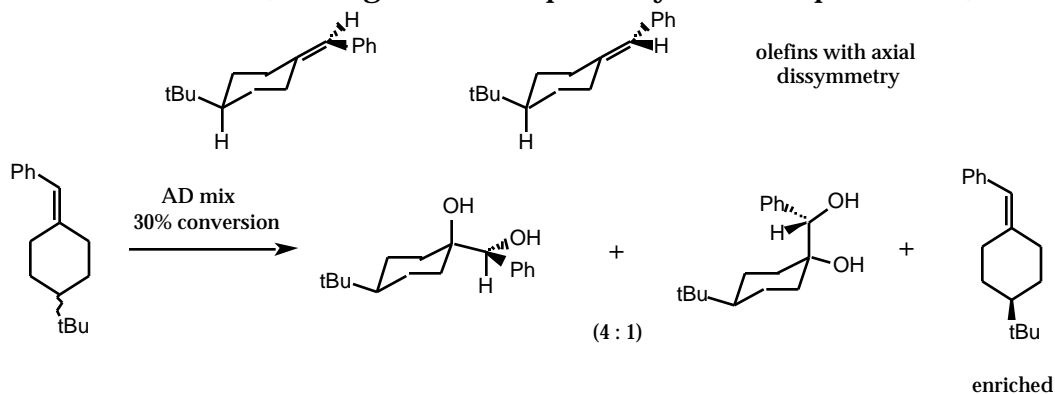
R_L large and flat,
 i.e Aromatics work particularly well

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 ₂ NH ₂	20 - 97 %

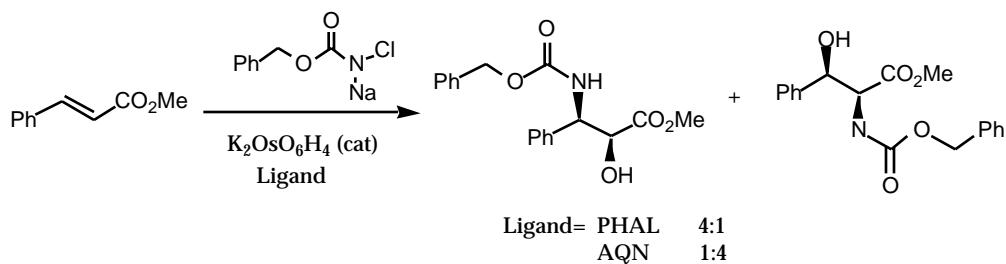
"AD-mixes" commercially available pre-mix solutions of Os, ligand and reoxidant
 AD-mix (DHQ)₂PHAL, K₃Fe(CN)₆, K₂CO₃, K₂OsO₄ (0.4 MOL % Os to C=C)
 AD-mix (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, K₂OsO₄



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



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

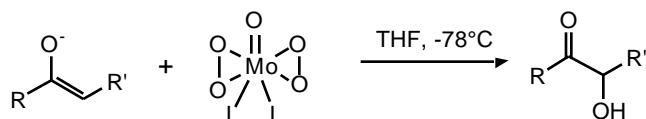


Molybdenum Reagents

MoOPH [MoO₅•pyridine (HMPA)]

JOC **1978**, 43, 188.

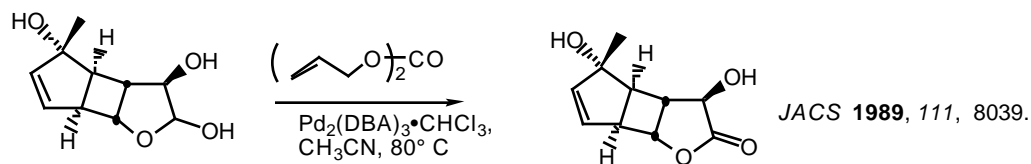
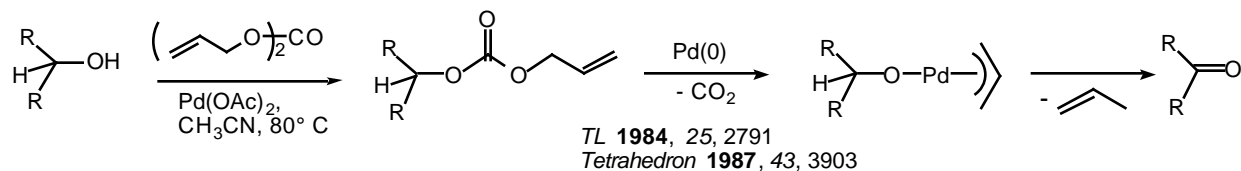
- α -hydroxylation of ketone, ester and lactone enolates.



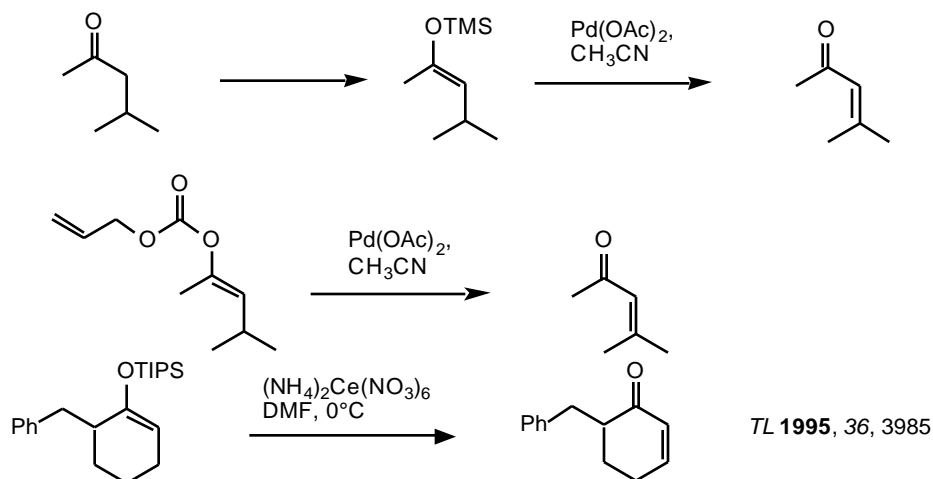
Palladium Reagents

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

Tetrahedron **1986**, 42, 4361

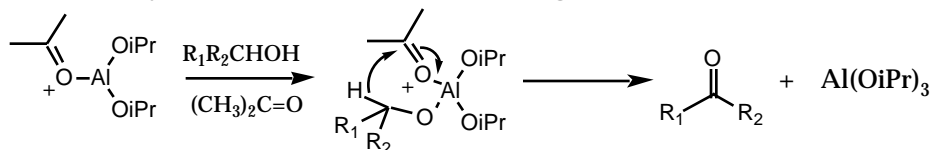


Oxidation of silylenol ethers and enol carbonates to enones



Oppenauer Oxidation

 Synthesis **1994**, 1007

 Organic reactions **1951**, 6, 207


Nickel Peroxide

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

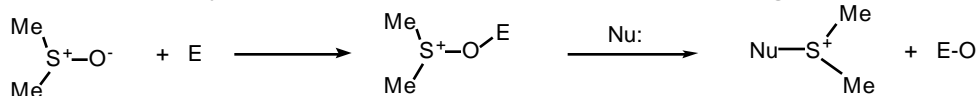
 Thallium Nitrate (TNN, Tl(NO₃)₃•3H₂O)

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

 Lead Tetraacetate Pb(OAc)₄ Oxidations in Organic Chemistry (D), **1982**, pp 1-145.

Non-Metal Based Reagents

Activated DMSO Review: Synthesis **1981**, 165; **1990**, 857.

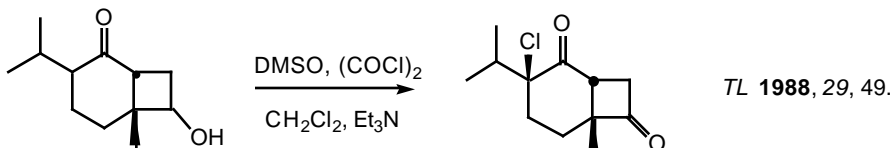
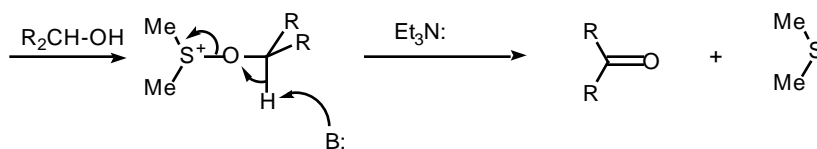
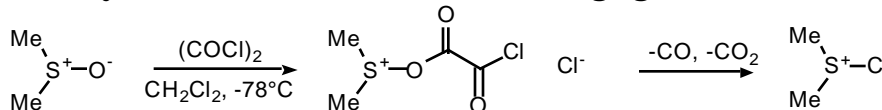
 Organic Reactions **1990**, 39, 297


E = (CF₃CO)₂O, SOCl₂, (COCl)₂, Cl₂, (CH₃CO)₂O, TsCl, MeCl, SO₃/pyridine, F₃CSO₂H, PO₅, H₃PO₄, Br₂

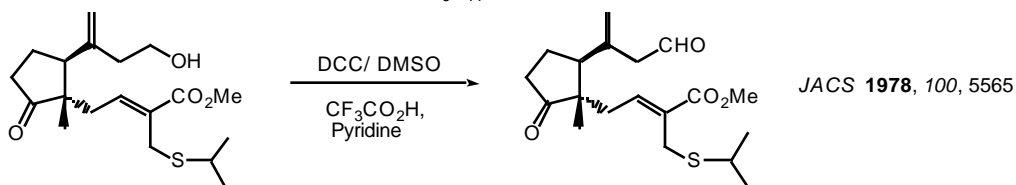
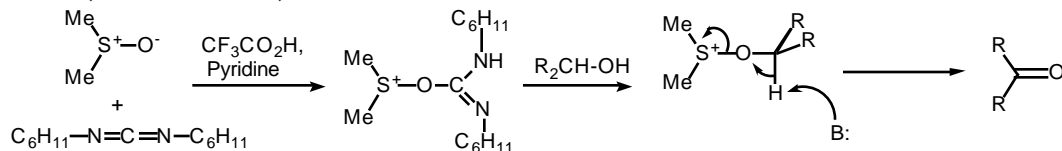
Nu := R-OH, Ph-OH, R-NH₂, RC=NOH, enols

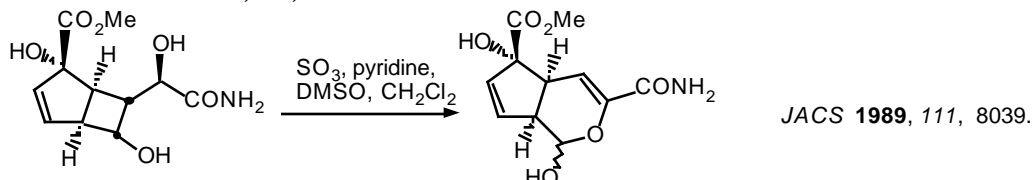
Swern Oxidation

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

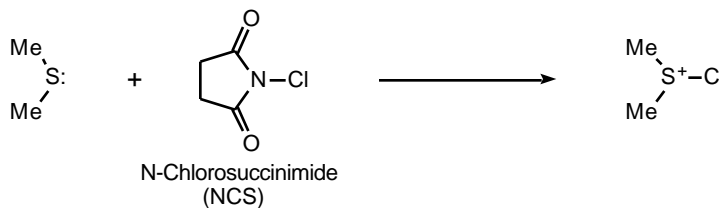


Moffatt Oxidation (DMSO/DCC)

 JACS **1965**, 87, 5661, 5670.

 SO₃/Pyridine

 JACS **1967**, 89, 5505.


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

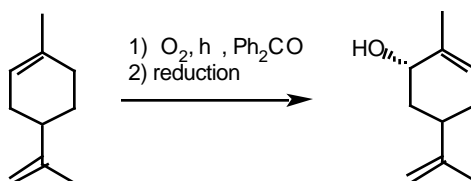
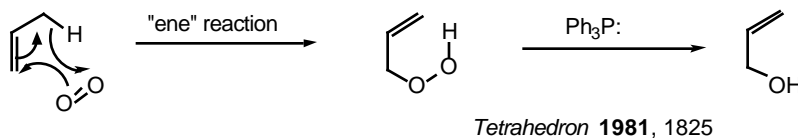
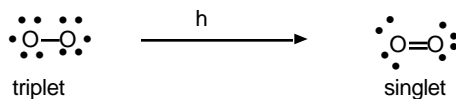


Oxygen & Ozone

Singlet Oxygen

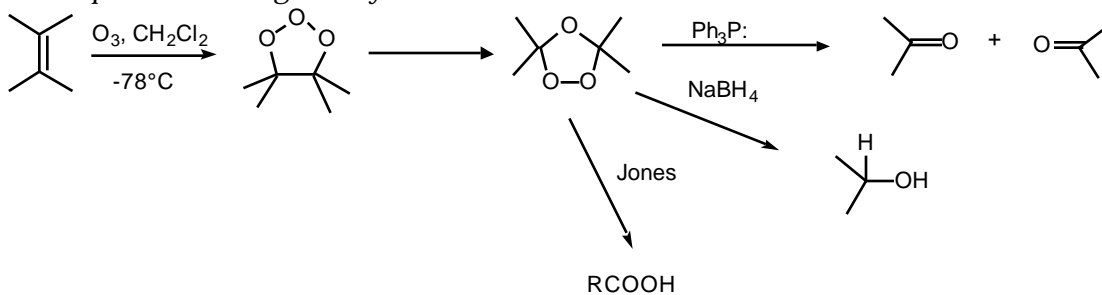
Acc. Chem. Res. **1980**, 13, 419

Tetrahedron **1981**, 37, 1825



Ozone

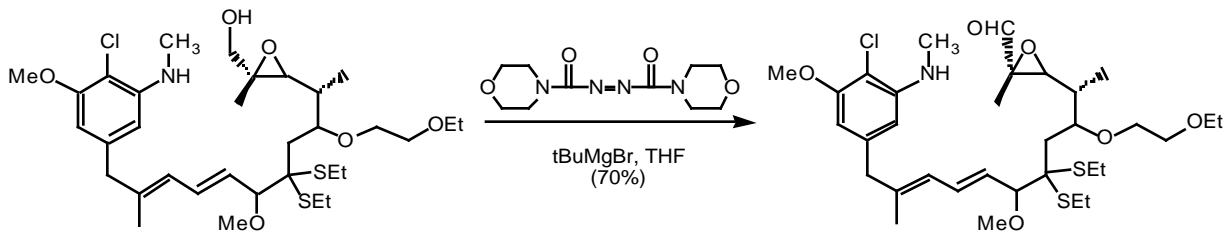
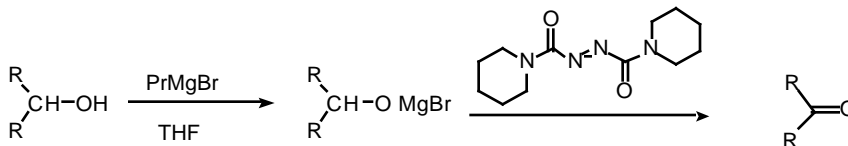
Comprehensive Organic Synthesis **1991**, 7, 541



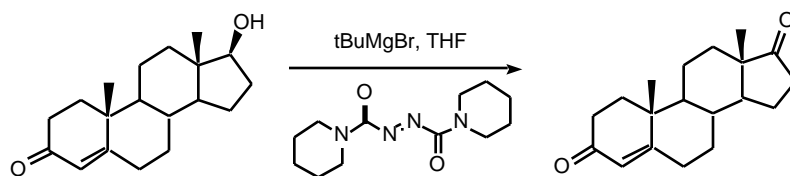
Other Oxidations

Mukaiyama Oxidation

BCSJ **1977**, 50, 2773



JACS **1979**, 101, 7104

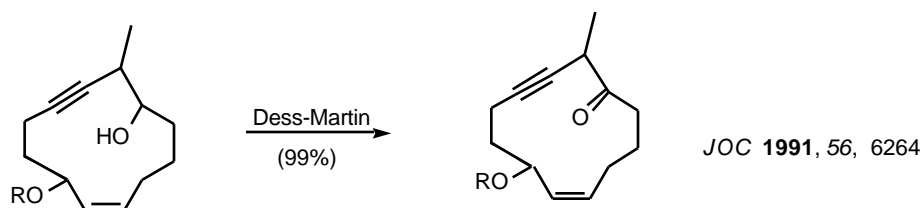
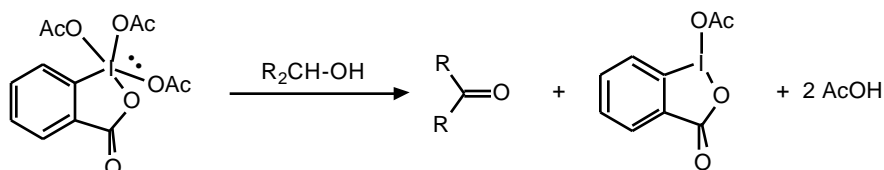


Dess-Martin Periodinane

JOC **1983**, 48, 4155.

JACS **1992**, 113, 7277.

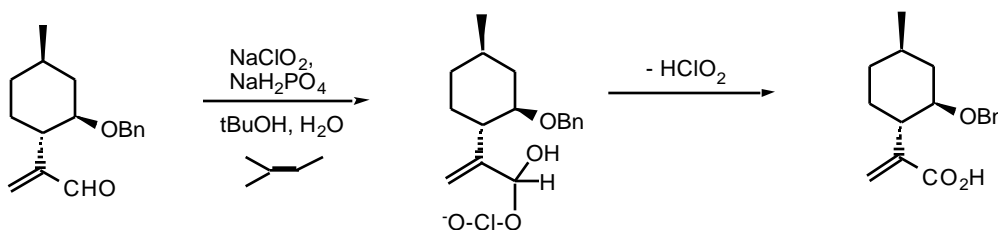
- oxidation conducted in CHCl_3 , CH_3CN or CH_2Cl_2
- excellent reagent for hindered alcohols
- very mild



Chlorite Ion

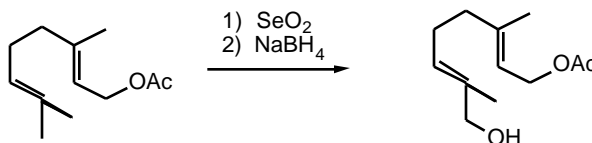
- oxidation of α,β -unsaturated aldehydes to α,β -unsaturated acids.

Tetrahedron **1981**, 37, 2091

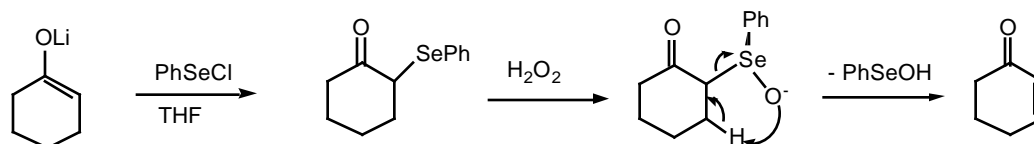


Selenium Dioxide

- Similar to singlet oxygen (allylic oxidation)



Phenyl Selenium Chloride

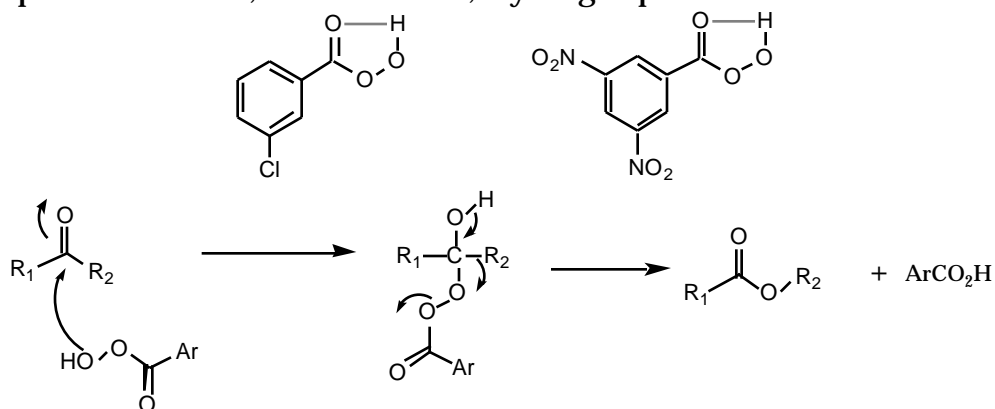


- PhS-SPH will do similar chemistry however a sulfoxide elimination is less facile than a selenoxide elimination.

Peroxides & Peracids

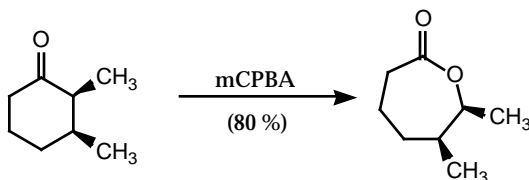
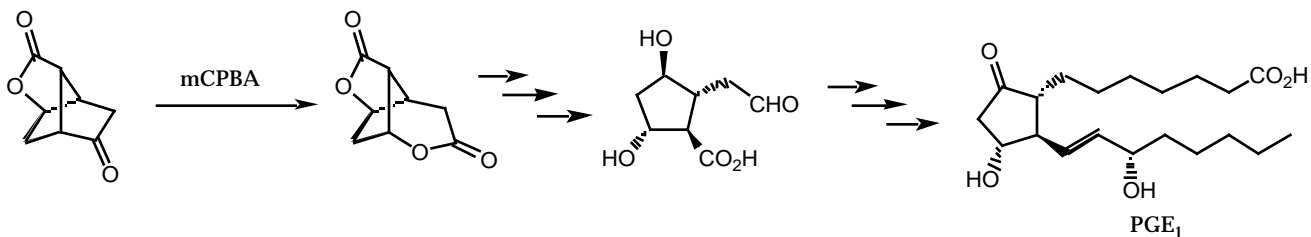
- $\text{R}_3\text{N-O}$
 - sulfides sulfoxides sulfones
 - Baeyer-Villiger Oxidation- oxidation of ketones to esters and lactones via oxygen insertion
- Organic Reactions **1993**, 43, 251 Comprehensive Organic Synthesis **1991**, vol 7, 671.

m-Chloroperbenzoic Acid, Peracetic Acid, Hydrogen peroxide



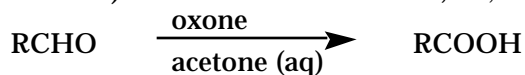
- Concerted R-migration and O-O bond breaking. No loss of stereochemistry
- Migratory aptitude roughly follows the ability of the group to stabilize positive charge:
 $3^\circ > 2^\circ > \text{benzyl} = \text{phenyl} > 1^\circ \gg \text{methyl}$

JACS 1971, 93, 1491



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

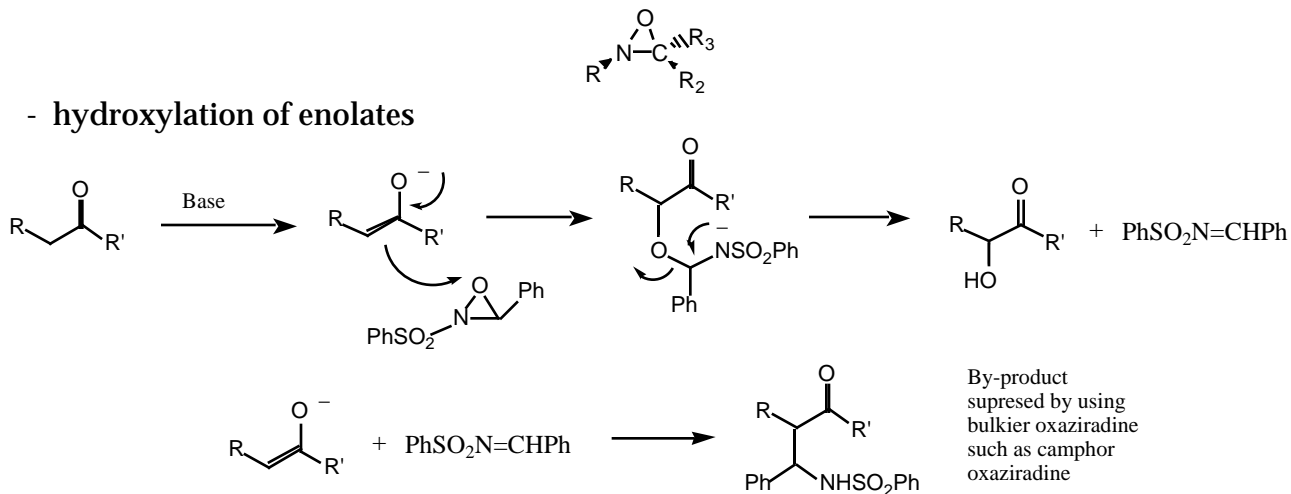
Oxone (postassium peroxydisulfate) *Tetrahedron* 1997, 54, 401

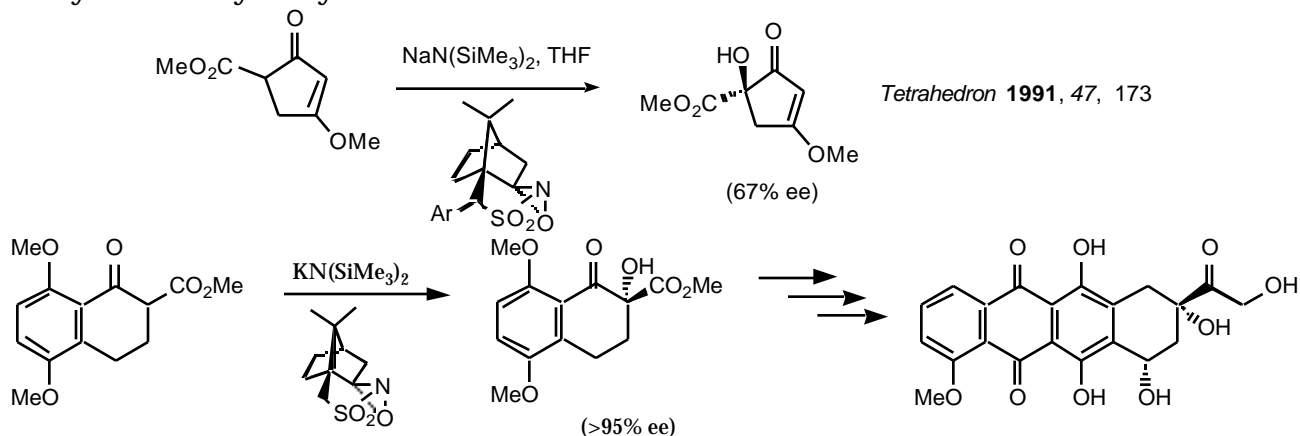


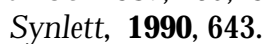
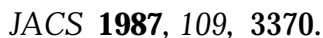
Oxaziridines

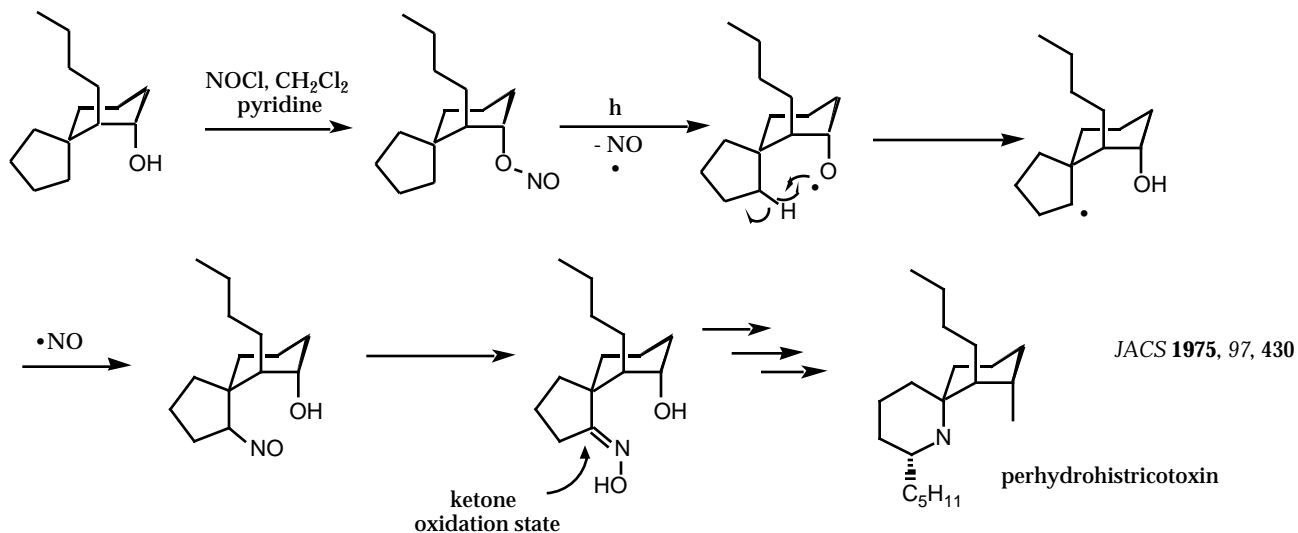
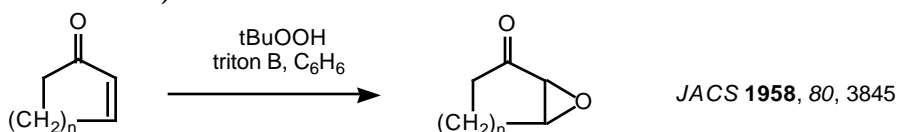
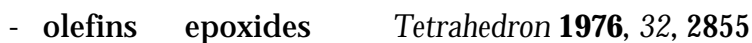
reviews: *Tetrahedron* 1989, 45, 5703; *Chem. Rev.* 1992, 92, 919

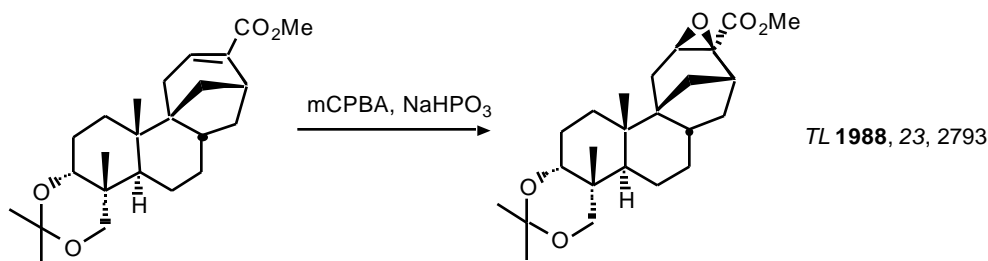
- hydroxylation of enolates



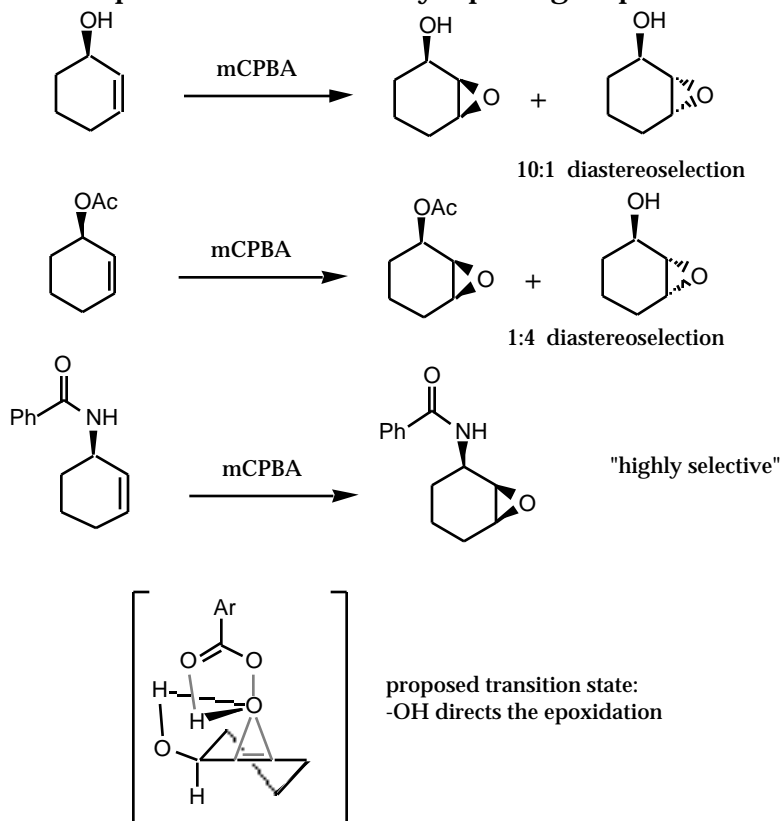
Asymmetric hydroxylations

- hydroxylation of organometallics

- Asymmetric oxidation of sulfides to chiral sulfoxides.

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

Barton Reaction

Epoxidations
Peroxides & Peracids


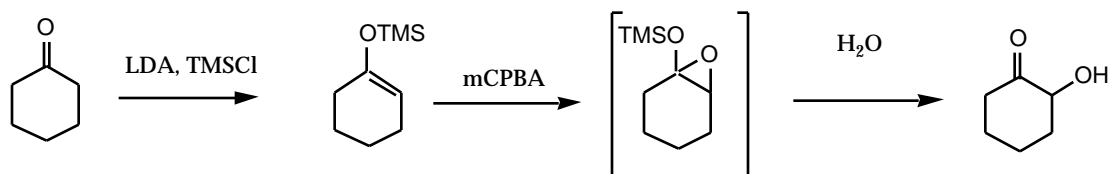


Henbest Epoxidation- epoxidation directed by a polar group



- 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

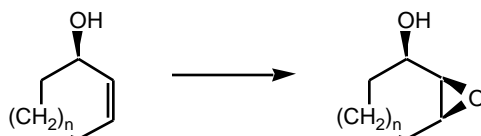
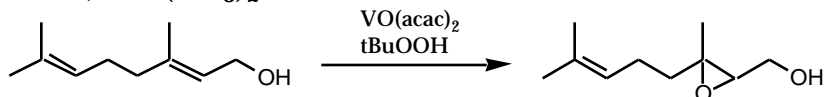
Synthesis, **1986**, 89. *Org. React.* **1996**, 48, 1-299.

Aldrichimica Acta **1979**, 12, 63

review on transition mediated epoxidations: *Chem. Rev.* **1989**, 89, 431.

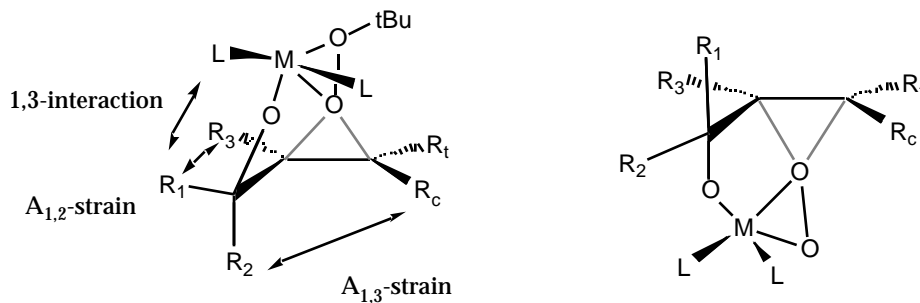
- Regioselective epoxidation of allylic and homo-allylic alcohols
- will not epoxidize isolated double bonds
- epoxidation occurs stereoselectively w/ respect to the alcohol.

- Catalysts: VO(acac)₂; Mo(CO)₆; Ti(OiPr)₄
- Oxidant: tBuOOH; PhC(CH₃)₂OOH



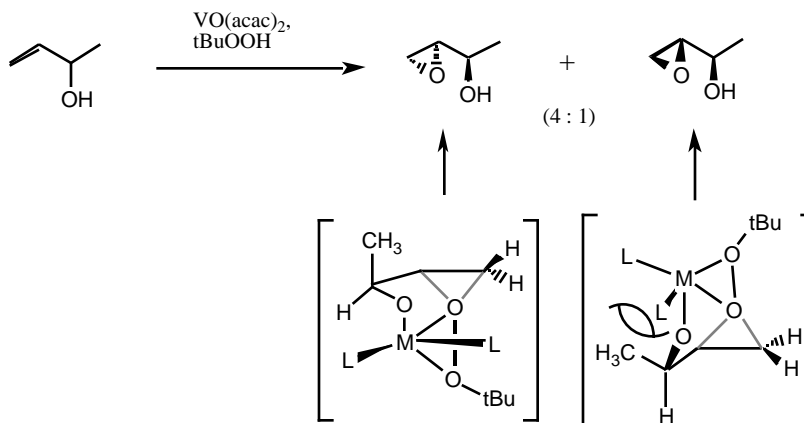
ring size	VO(acac) ₂	MoO ₂ (acac) ₂	mCPBA
5	>99%	--	84
6	>99	98	95
7	>99	95	61
8	97	42	<1
9	91	3	<1

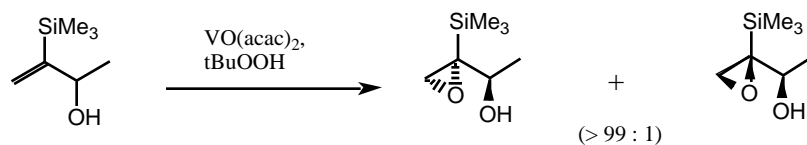
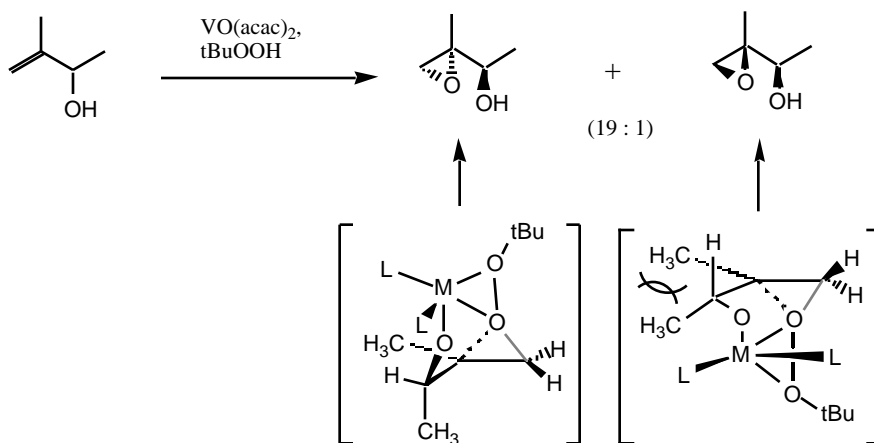
Acyclic Systems:



Major influences:

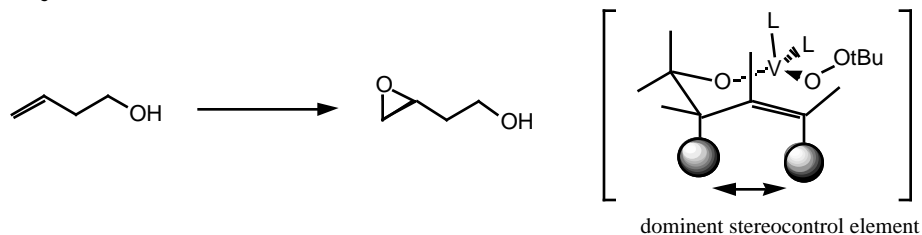
- A_{1,2}-Strain between R_g and R₁ (R_g and R₂)
- A_{1,3}-strain between R₂ and R_c (R₁ and R_c)
- 1,3-interactions between L and R₁ (L and R₂)



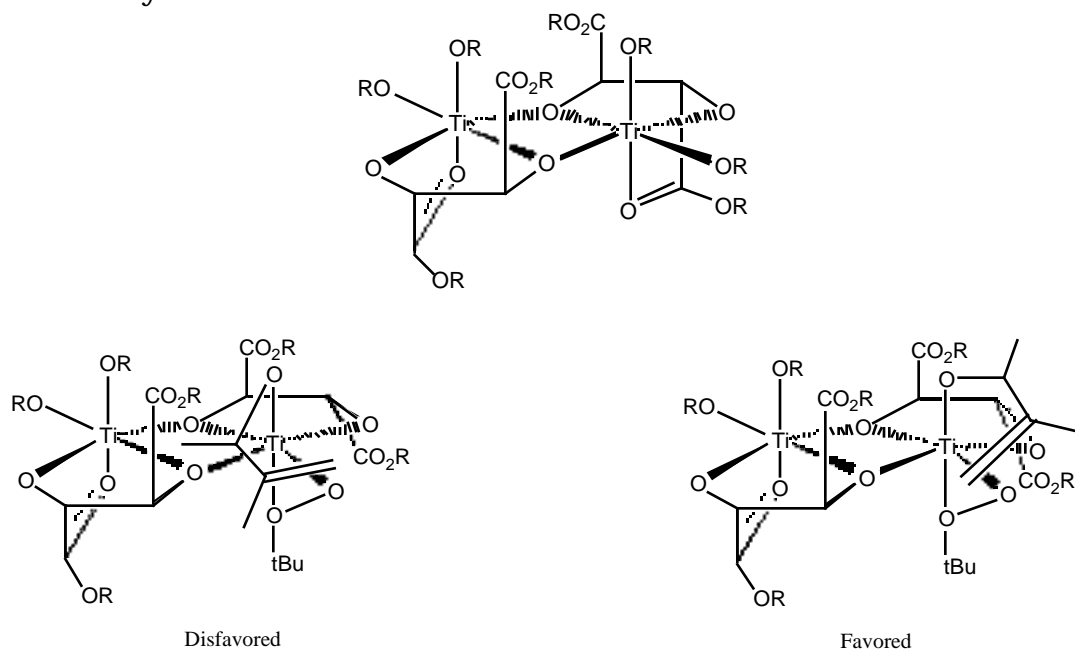


- Careful conformational analysis of acyclic systems is needed.

Homoallylic Systems

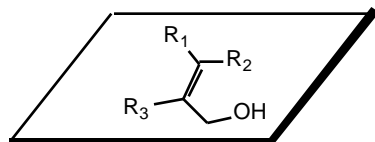


Titanium Catalyst structure:

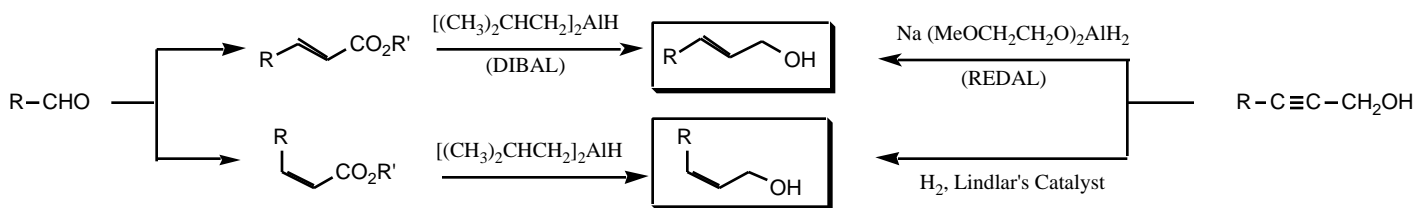
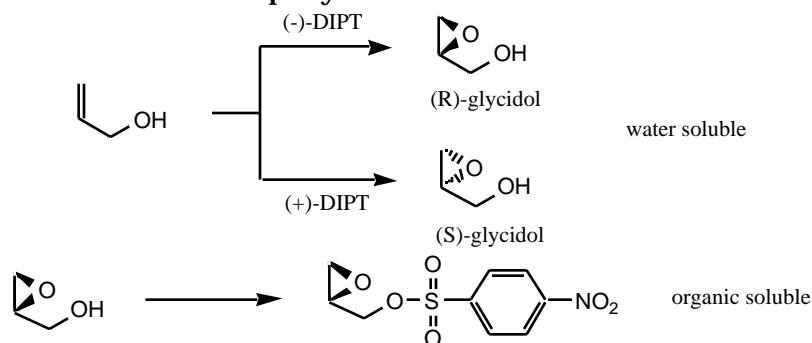


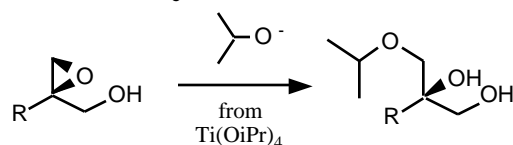
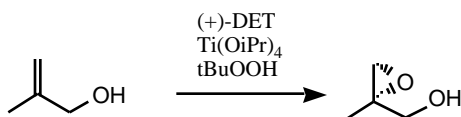
Asymmetric Epoxidation

 tBuOOH, Ti(OiPr)₄, (+) 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

Stoichiometric vs Catalytic epoxidation:


stoichiometric:

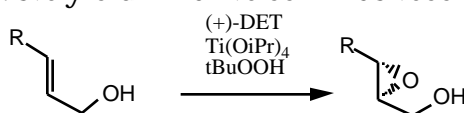
catalytic (6-7 mol %)

in situ deriv. with PNB

85% ee

47% yield >95% ee

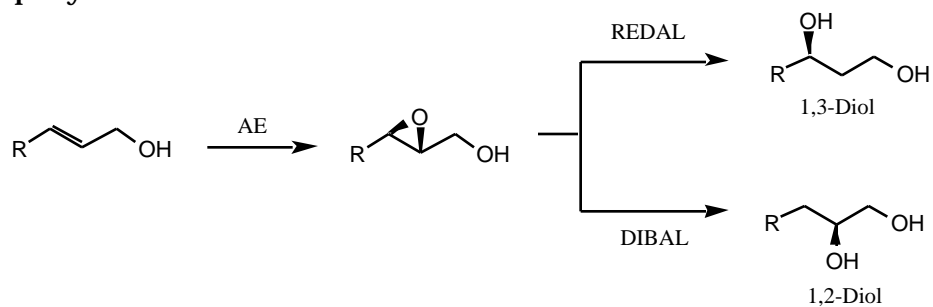
78% yield 92% ee >98% ee after 1 recrystallization



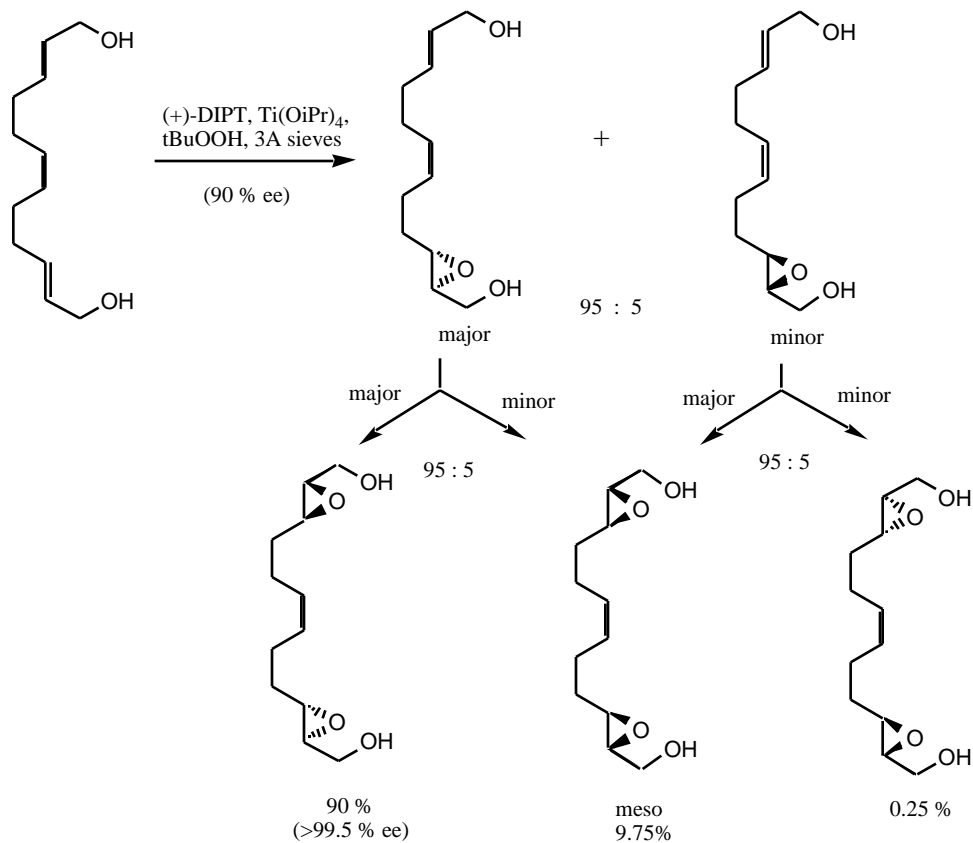
yields: 50 - 100 %

ee: > 95%

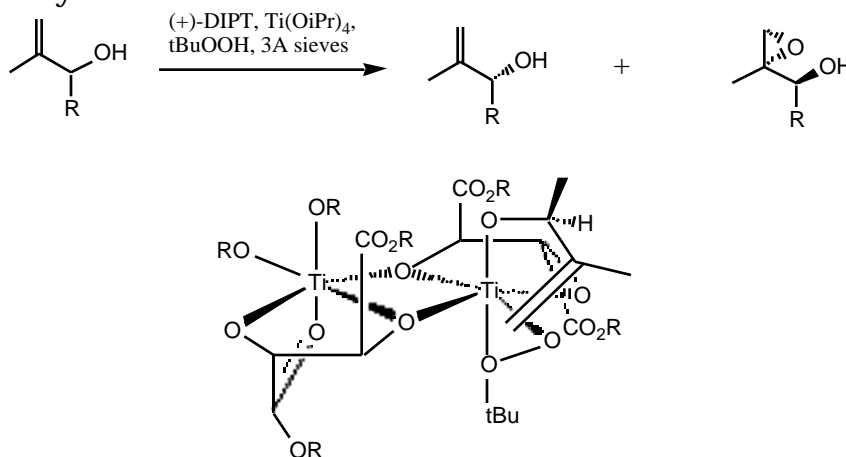
Ring Opening of Epoxy-Alcohols

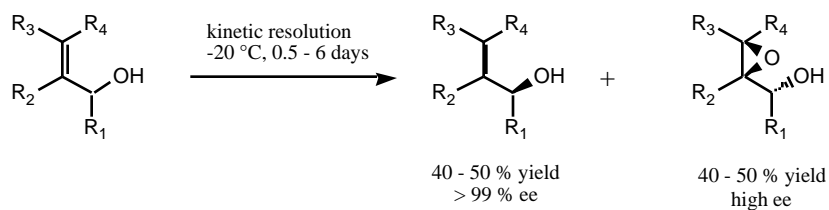


Two dimensional amplification

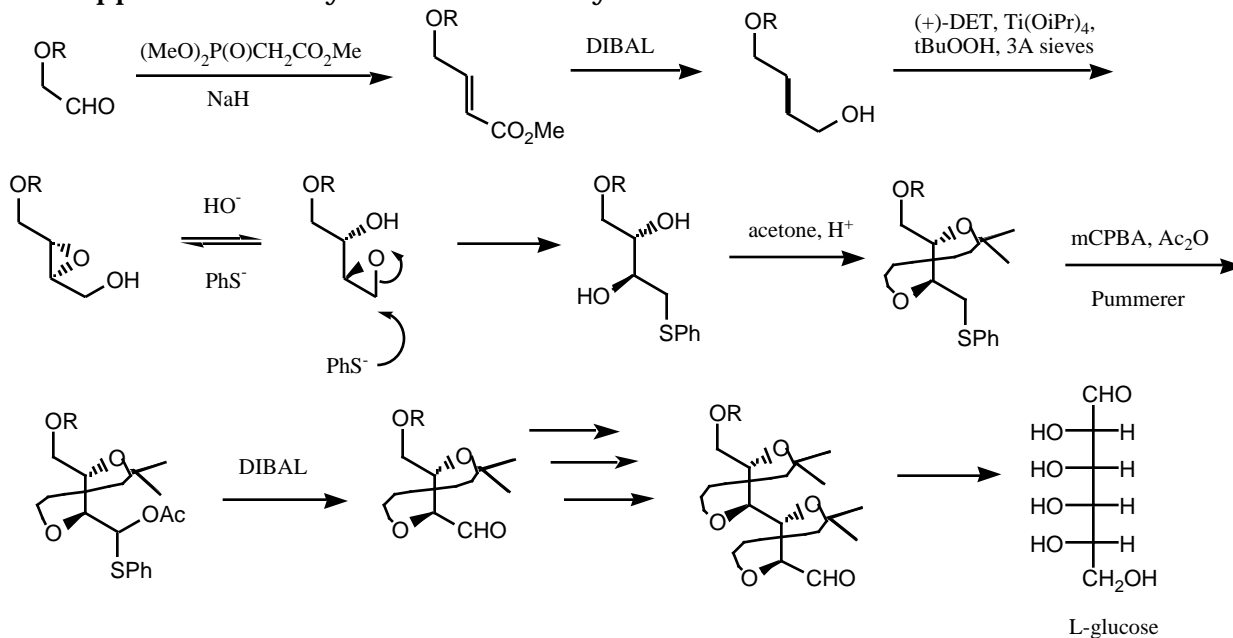


Kinetic Resolution of Allylic Alcohols





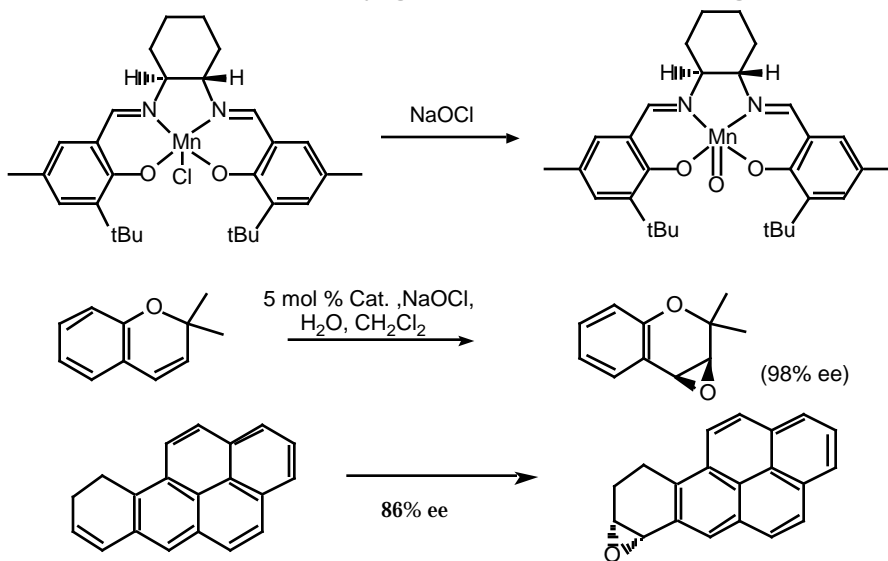
Reiterative Approach to the Synthesis of Carbohydrate



Jacobsen Asymmetric Epoxidation

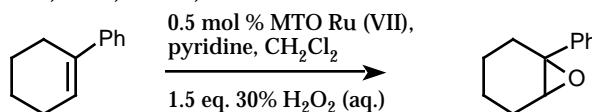
JACS **1990**, *112*, 2801; *JACS* **1991**, *113*, 7063; *JOC* **1991**, *56*, 2296.

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



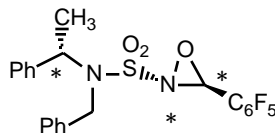
Methyltrioxoruthenium (MTO) Ru(VII)

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



Oxaziridines

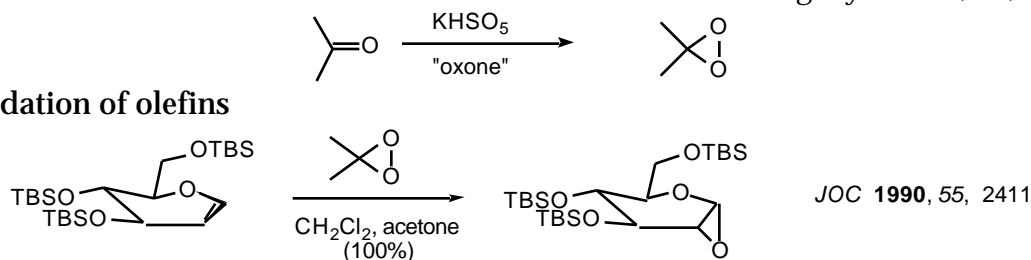
- Asymmetric epoxidation of olefins *Tetrahedron* **1989** 45 5703



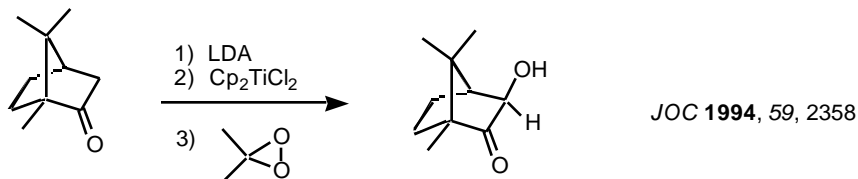
Dioxiranes (Murray's Reagent)

Reviews: *Chem. Rev.* **1989**, 89, 1187; *ACR* **1989**, 27, 205
Org. Syn. **1996**, 74, 91

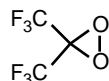
- epoxidation of olefins



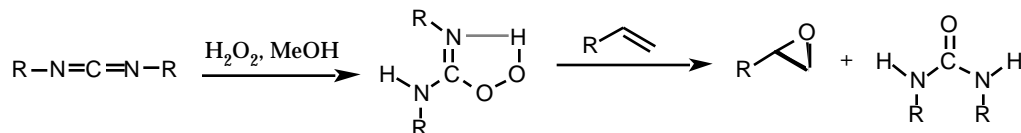
- Asymmetric epoxidation *JACS* **1996**, 118, 491.
- oxidation of sulfides to sulfoxides and sulfones
- oxidation of amines to amine-N-oxides
- oxidation of aldehydes to carboxylic acids
- hydroxylation of enolates



- 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 R₃C-OH

DCC-H₂O₂ *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

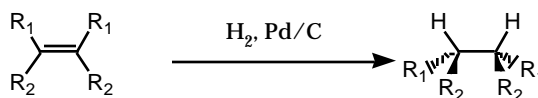
Transition metals absorbed onto a solid support

metal: Pd, Pt, Ni, Rh

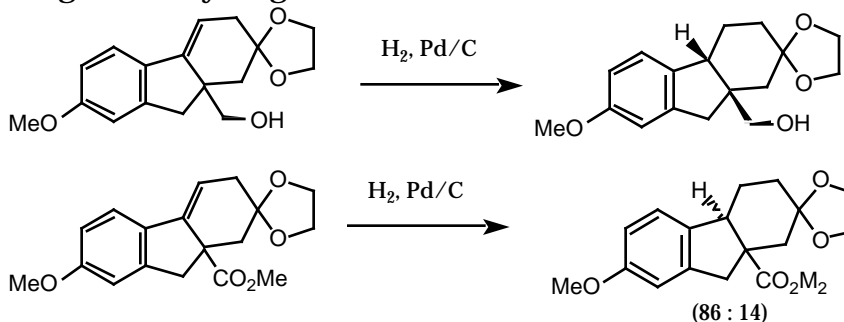
support: Carbon, alumina, silica

solvent: EtOH, EtOAc, Et₂O, 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 H₂.
- Cis addition of H₂.

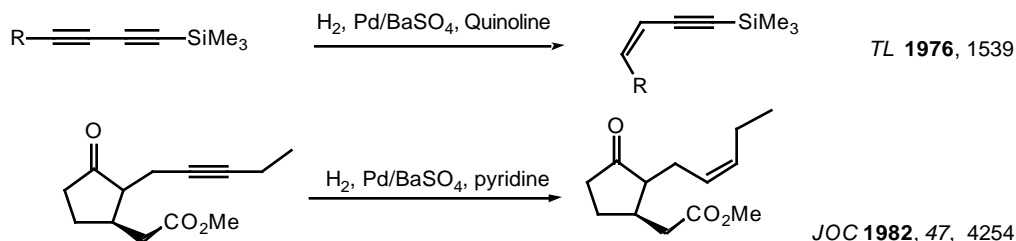


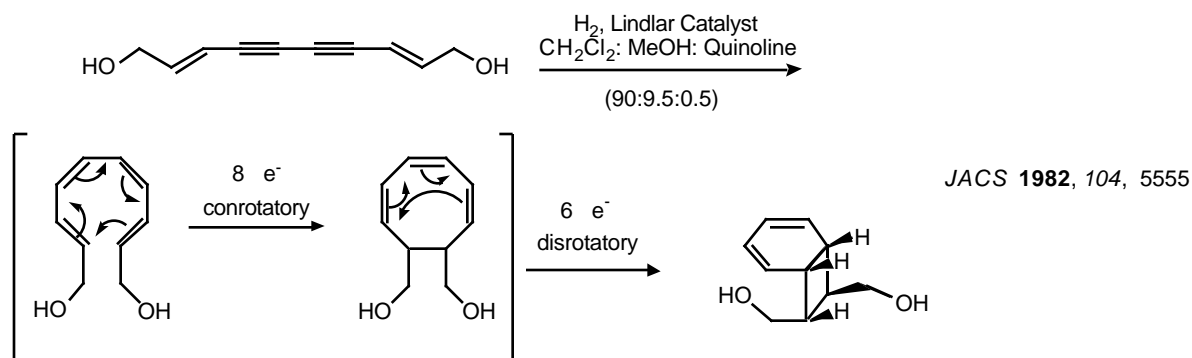
- Catalyst can be "poisoned"
- Directed heterogeneous hydrogenation



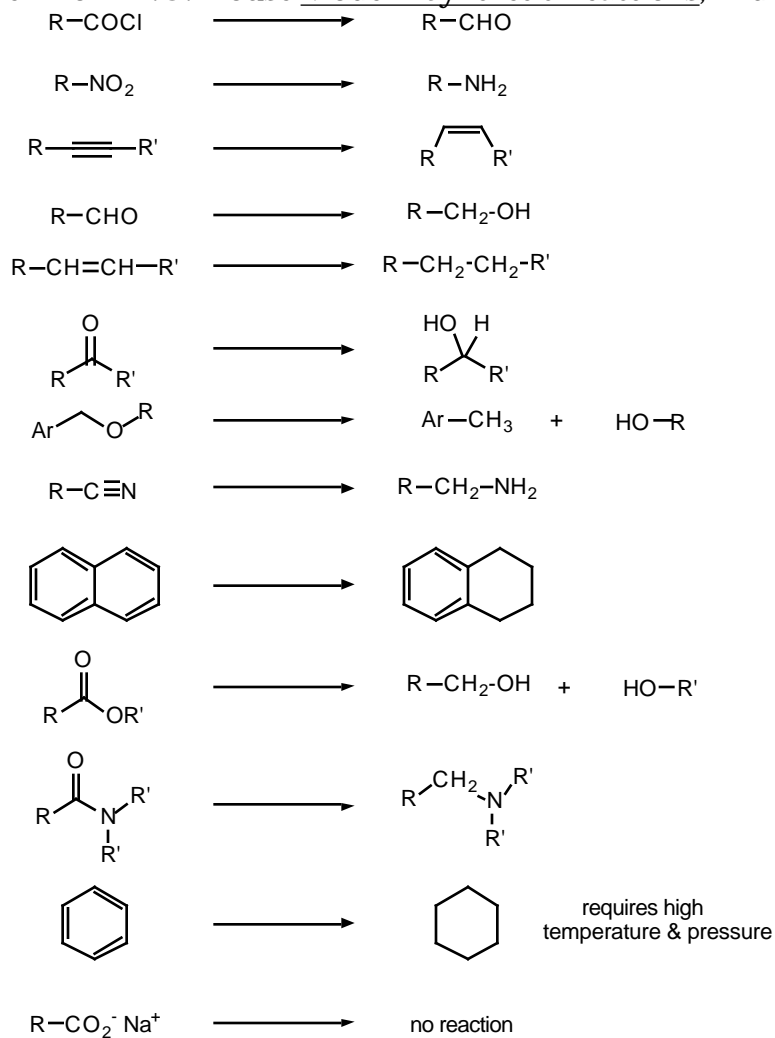
Lindlar Catalyst (Pd/ BaSO₄/ quinoline)- partially poisoned to reduce activity; will only reduce the most reactive functional groups.

acetylenes + H₂, Pd/BaSO₄/ quinoline cis olefins (Lindlar Reduction)
 Acid Chlorides + H₂, Pd/BaSO₄ Aldehydes (Rosemund Reduction)
Org. Rxn. **1948**, 4, 362



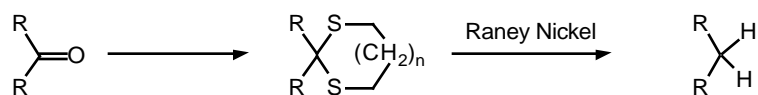


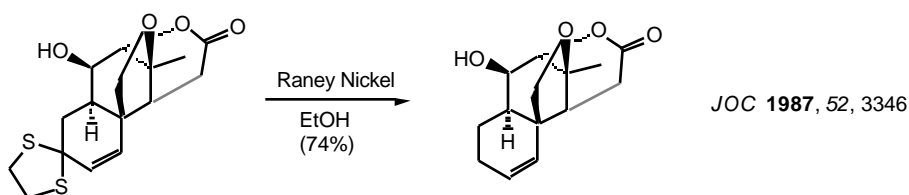
Ease of Reduction: (taken from H.O. House Modern Synthetic Reactions, 2nd edition)



Raney Nickel Desulfurization,

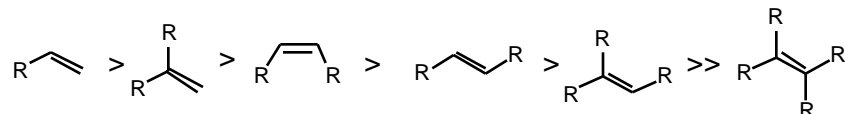
Reviews: *Org. Rxn.* **1962**, 12, 356; *Chem. Rev.* **1962**, 62, 347.



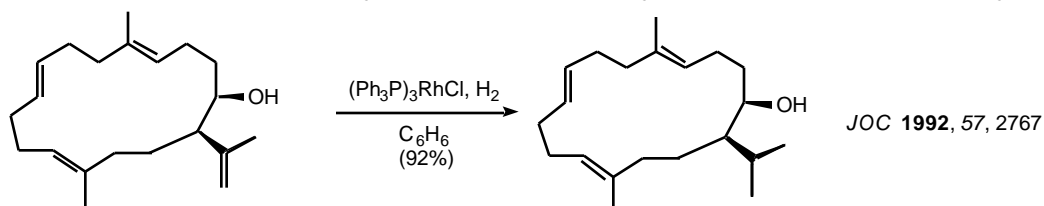


Homogeneous Catalytic Hydrogenation

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



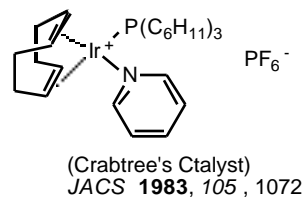
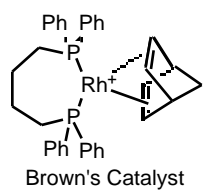
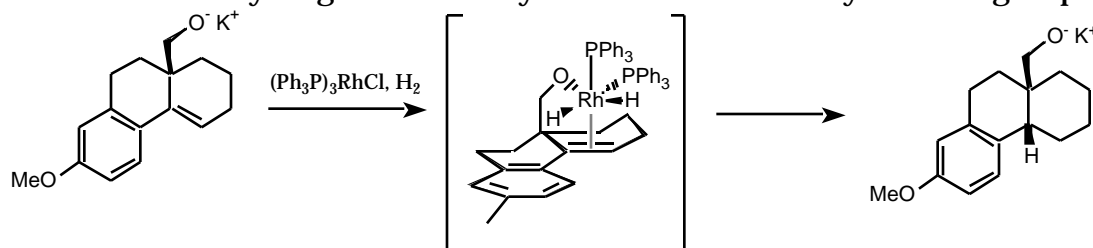
- $(Ph_3P)_3RhCl$ (Wilkinson's Catalyst); $[R_3P Ir(COD)py]^+ PF_6^-$ (Crabtree's Catalyst)



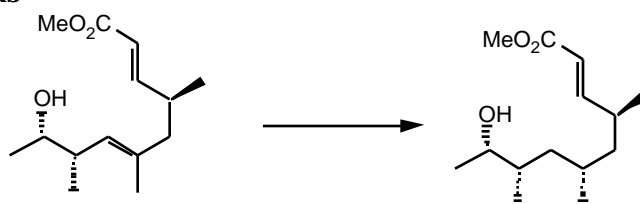
Directed Hydrogenation

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

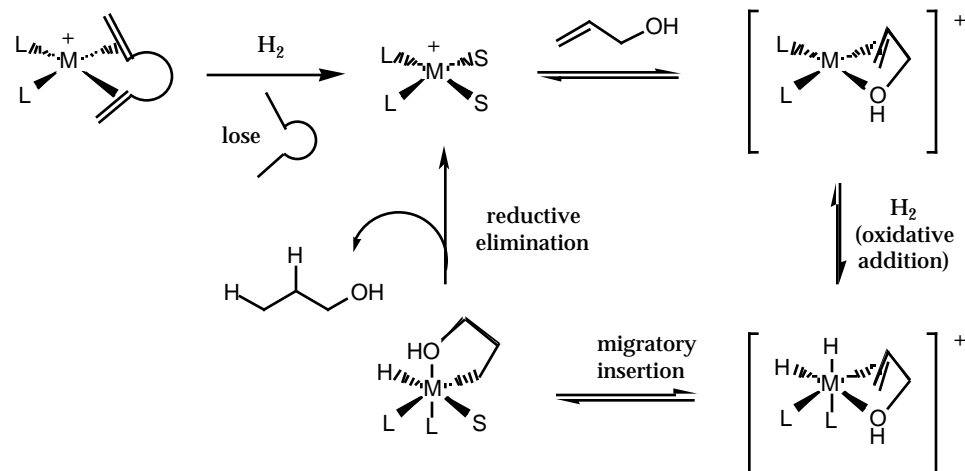
- Diastereocontrolled hydrogenation of allylic alcohols directed by the -OH group



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



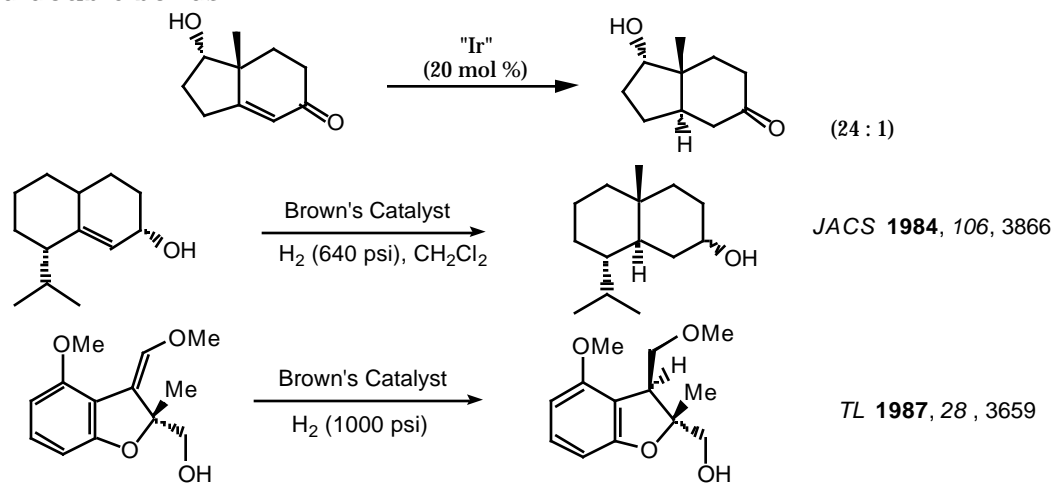
mechanism:



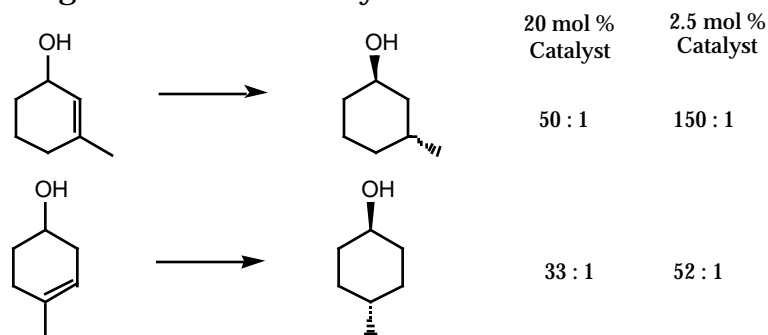
Diastereoselective Hydrogenation: since -OH directs the H_2 , there is a possibility for control of stereochemistry

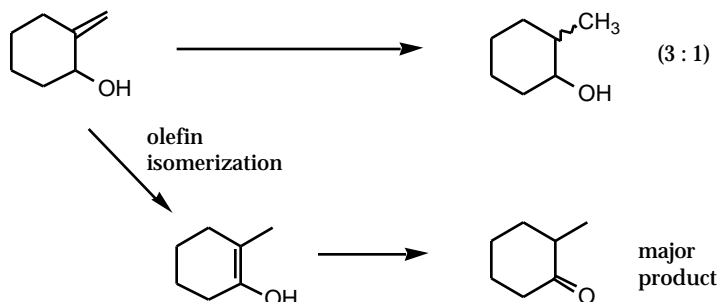
- sensitive to: H_2 pressure
- catalyst conc.
- substrate conc.
- solvent.

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



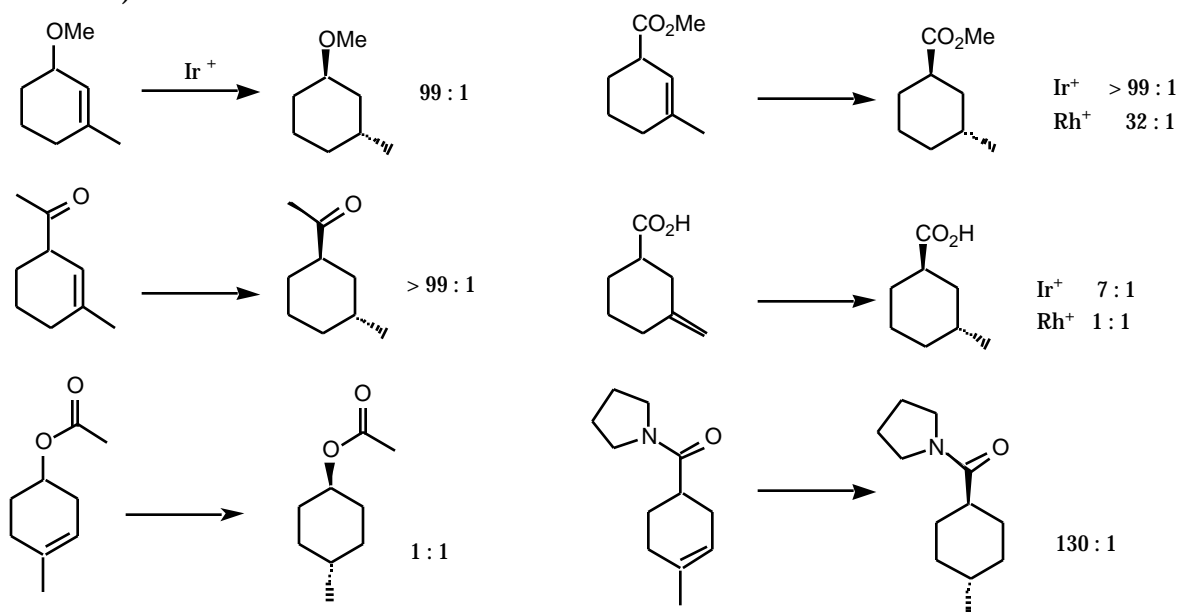
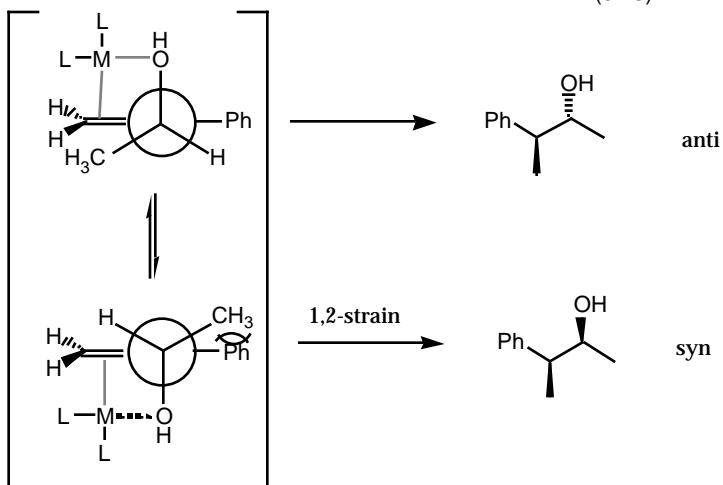
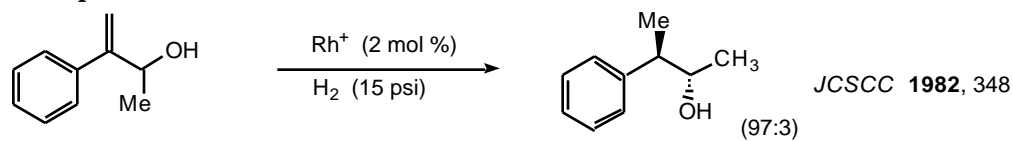
Selectivity is often higher with lower catalyst concentration:

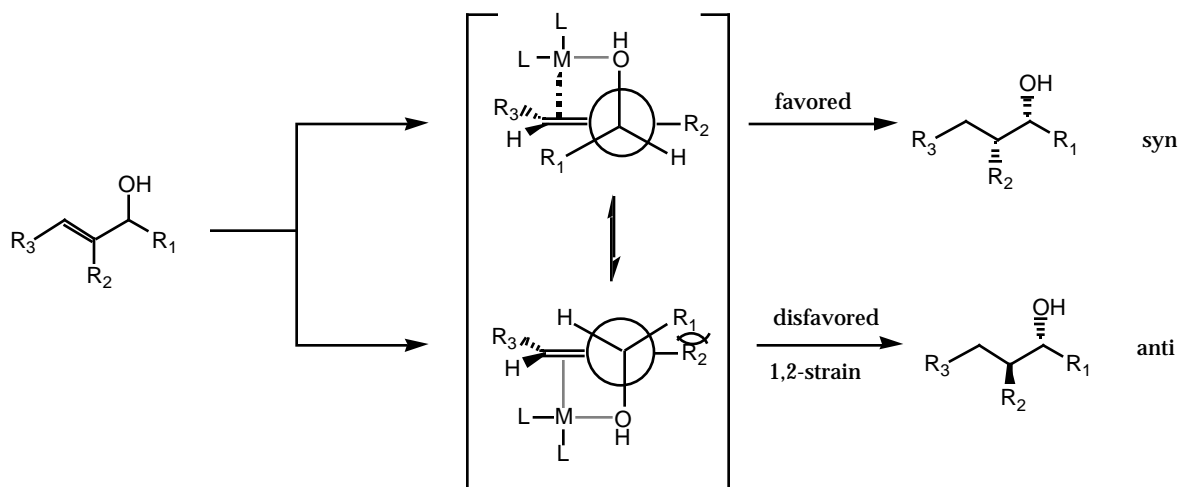


Olefin Isomerization:


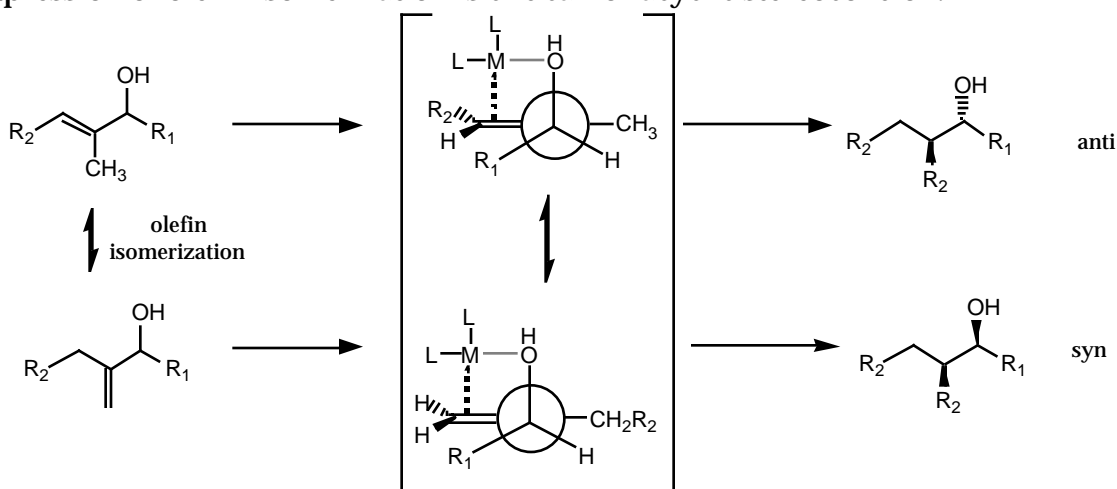
- Conducting the hydrogenation at high H₂ pressures suppresses olefin isomerization and often gives higher diastereoselectivity.

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


Acyclic Examples


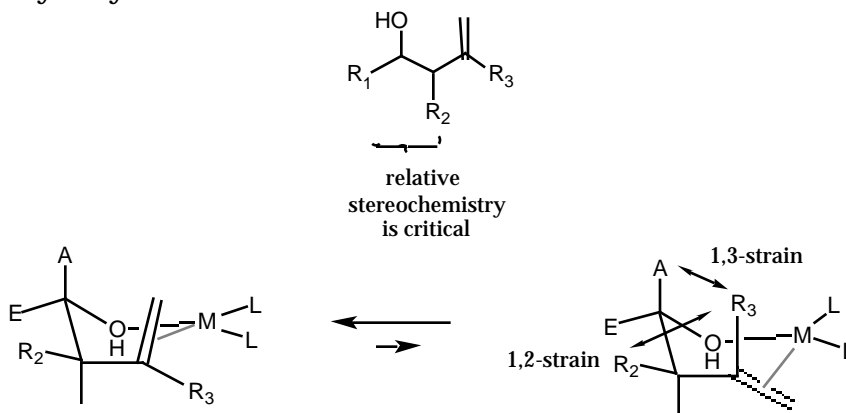


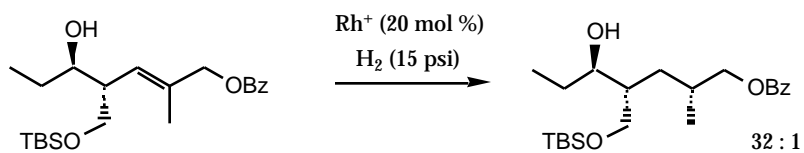
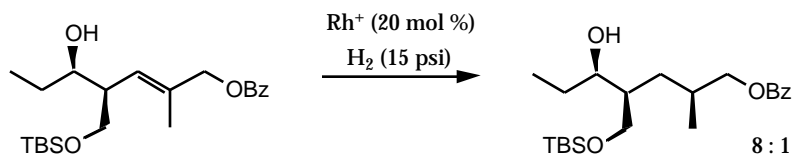
- Suppression of olefin isomerization is critical for acyclic stereocontrol !



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

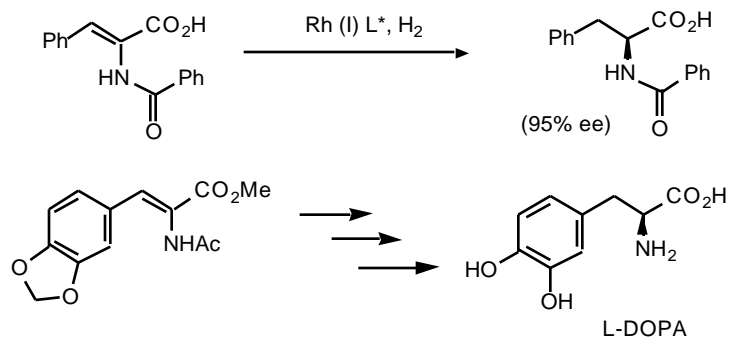
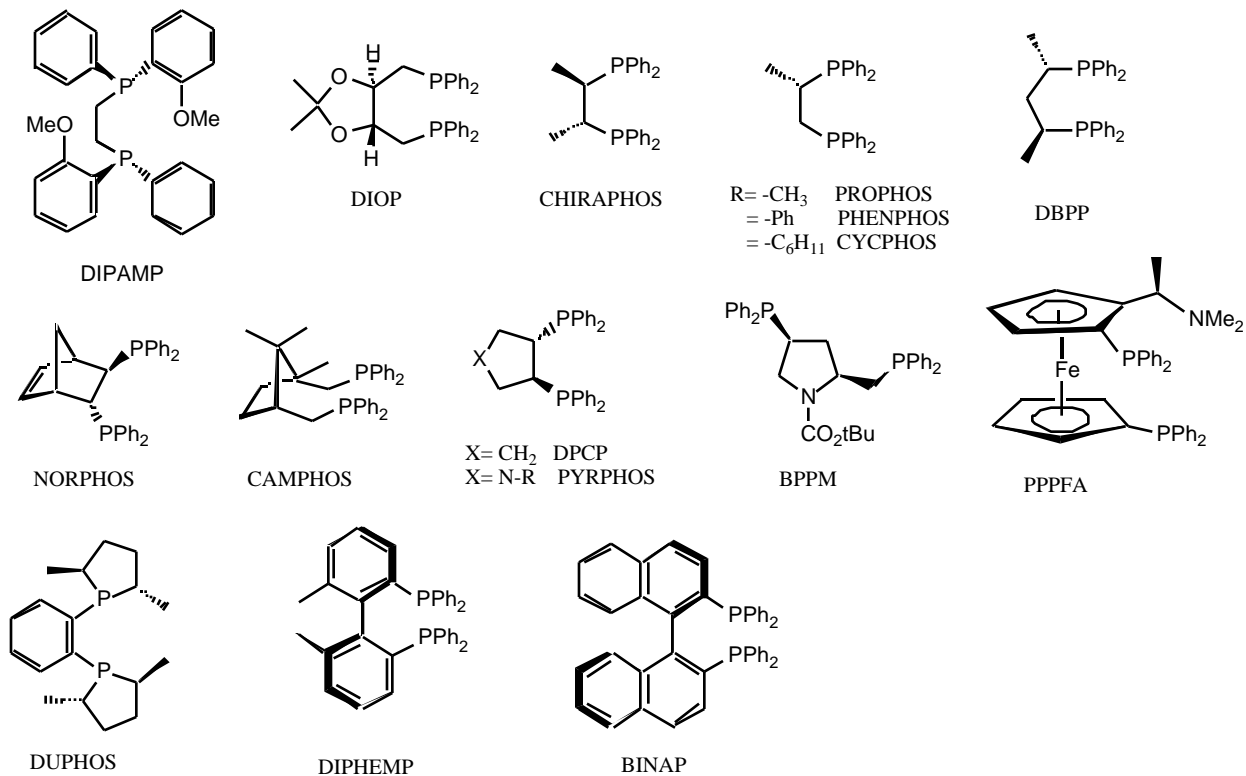
Acyclic homoallylic systems:




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


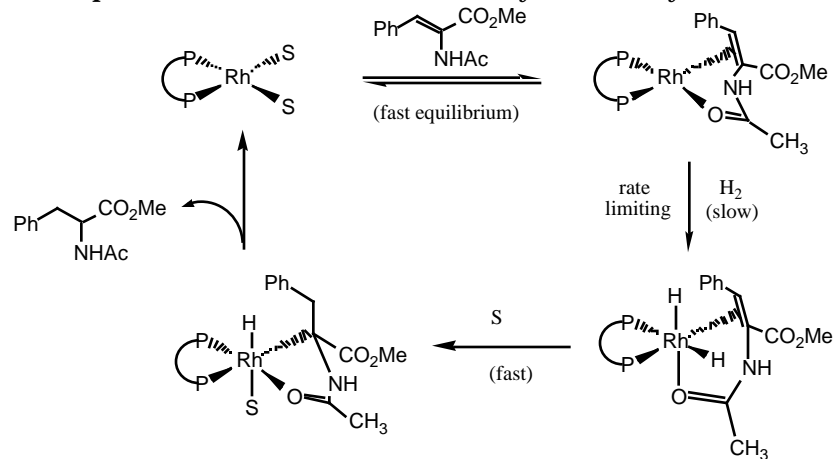
Asymmetric Homogeneous Hydrogenation

- Chiral ligands for homogeneous hydrogenation of olefins and ketones

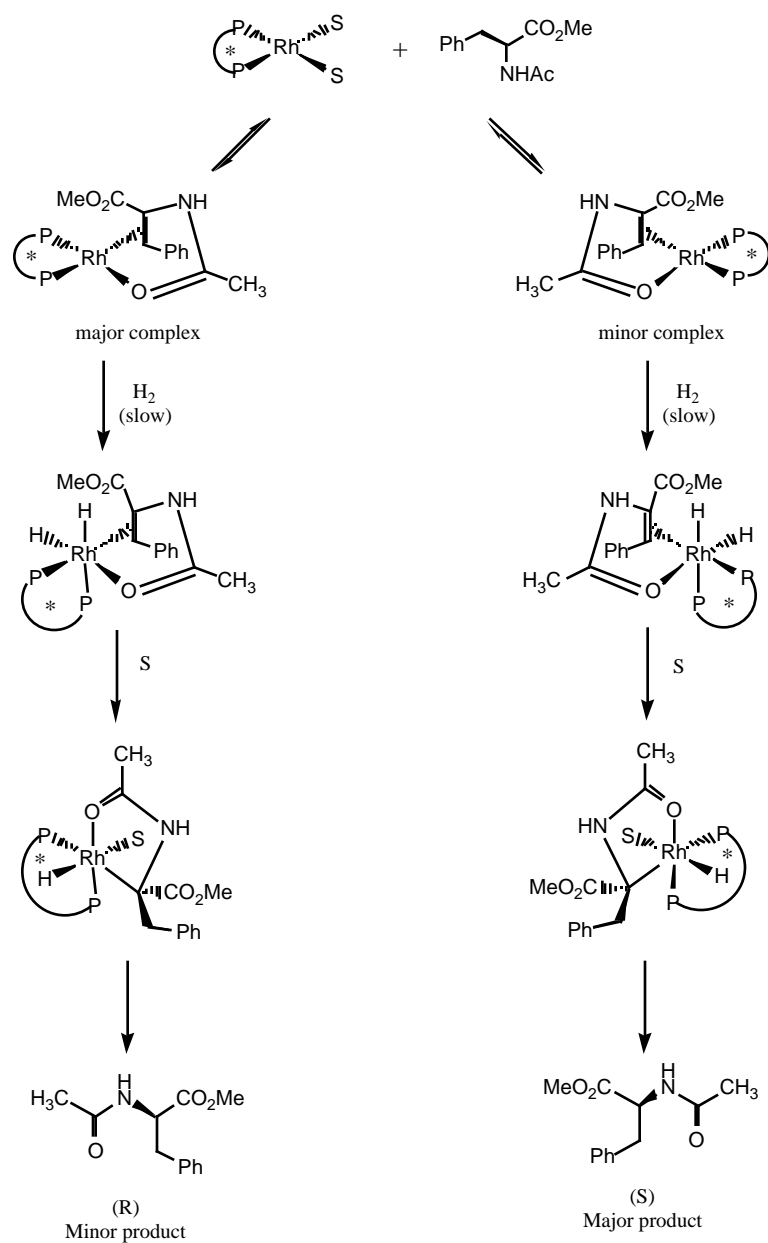

 ACR **1983**, 16, 106.

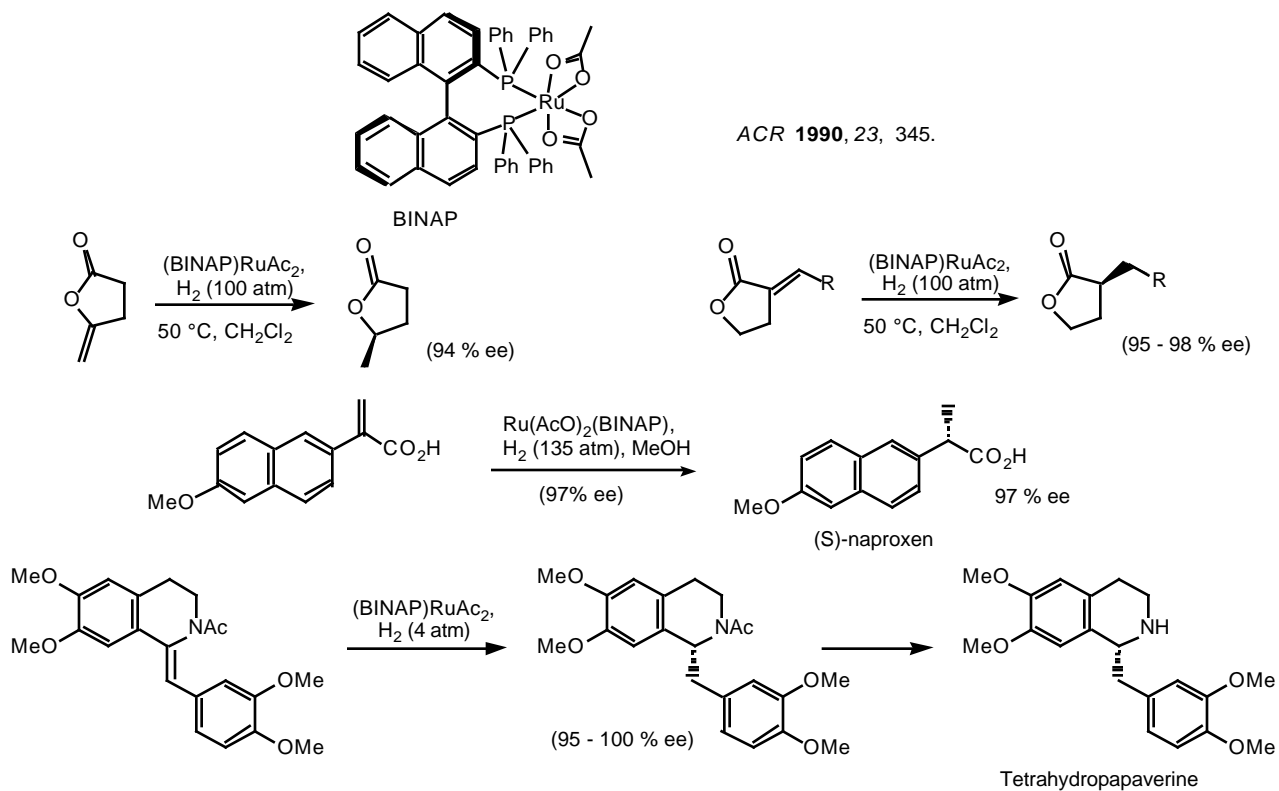
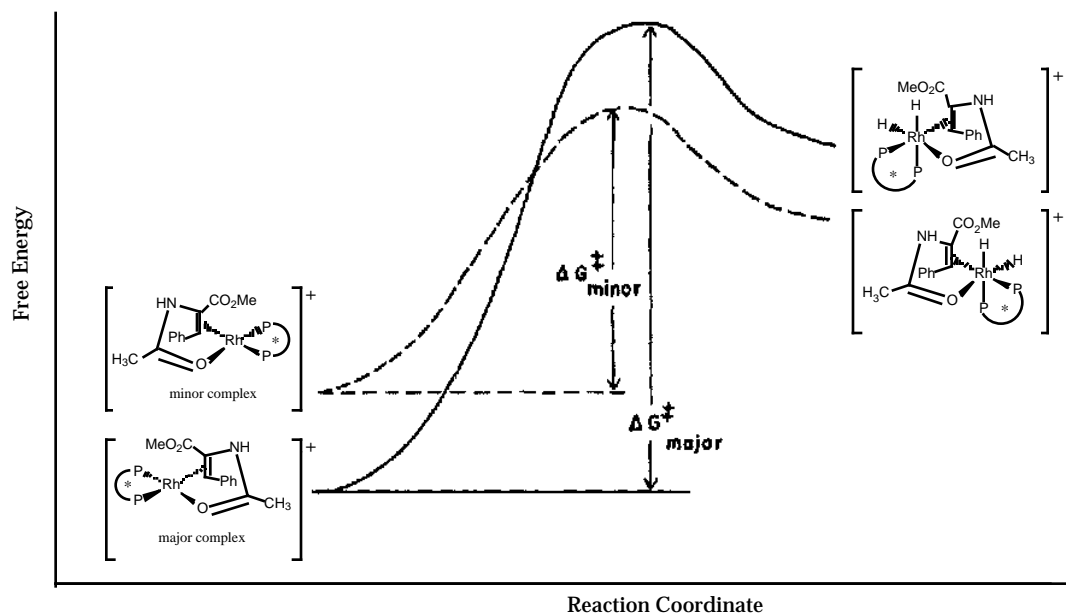
DIOP	85% ee
DIPAMP	96% ee
PPPFA	93% ee
BINAP	100% ee
NORPHOS	95% ee
BPPM	91% ee

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

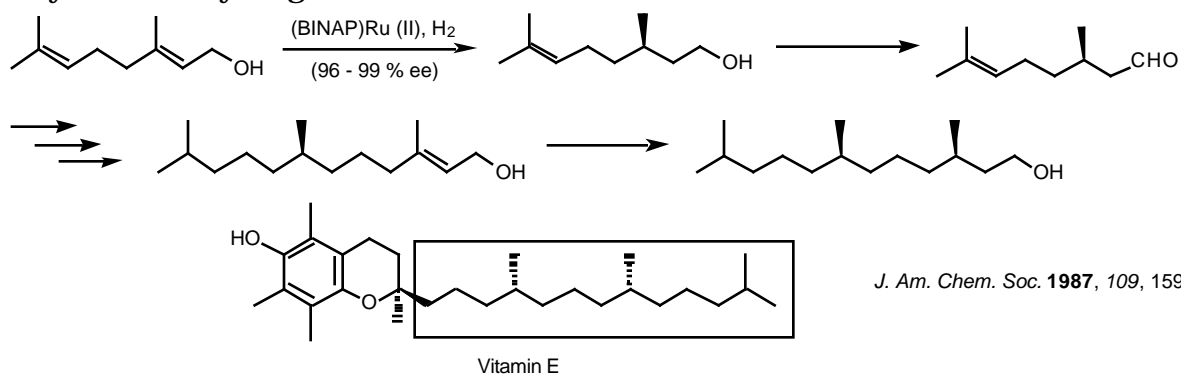


Detailed Mechanism:

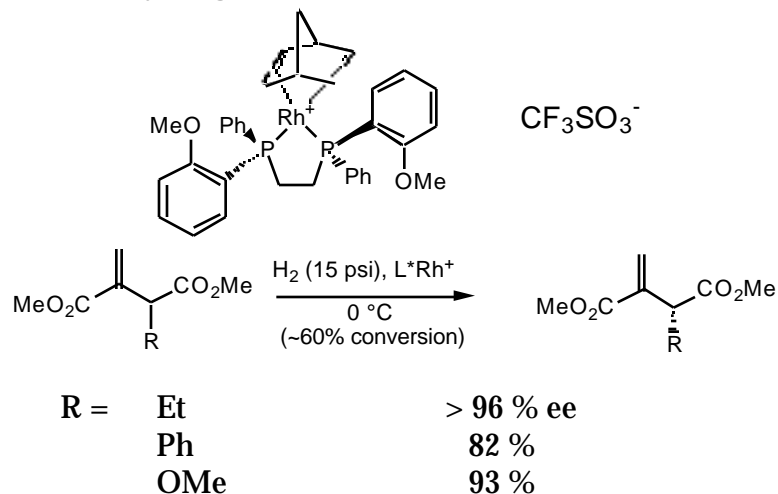
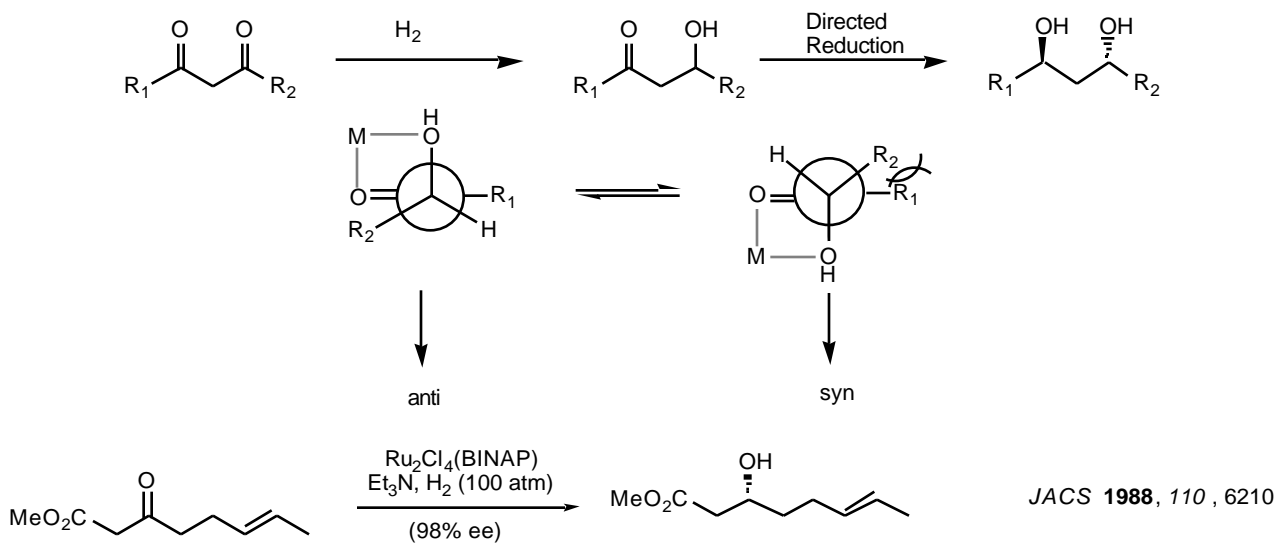
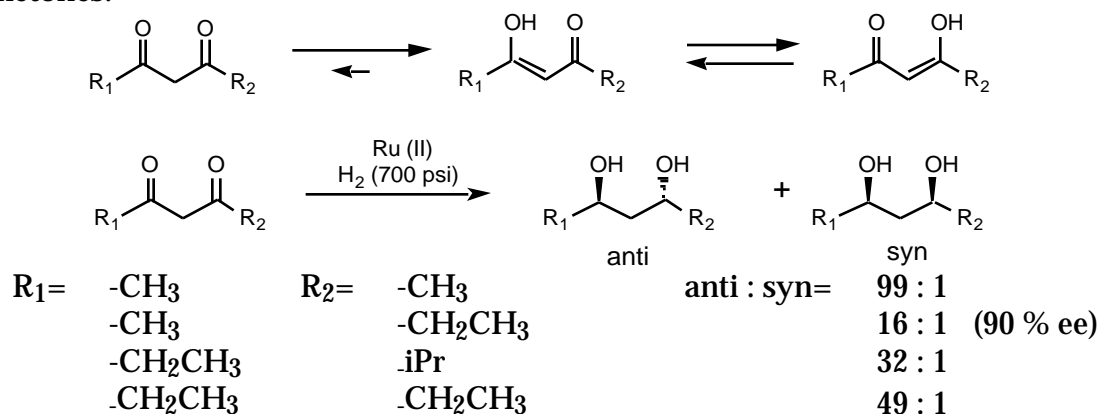




Directed Asymmetric Hydrogenation

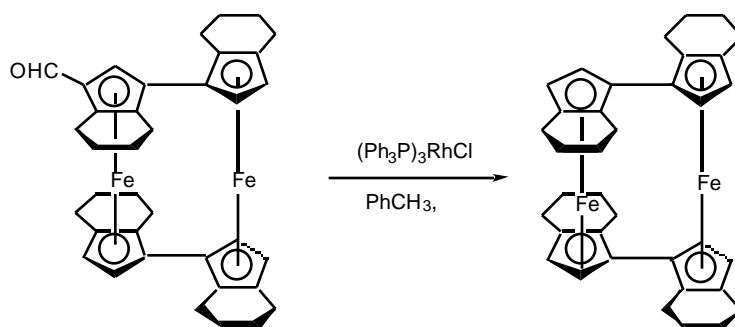


Kinetic Resolution by Directed Hydrogenation


 Hydrogenation of Carbonyls
 1,3-diketones:


Decarbonylations

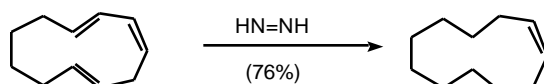
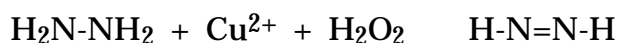
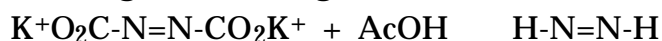




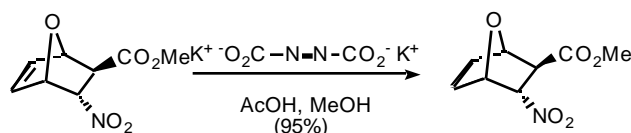
JOC 1990, 55, 3688

Diimide $\text{HN}=\text{NH}$ Review: *Organic Reactions* **1991**, 40J. *Chem. Ed.* **1965**, 254

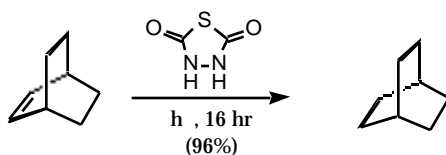
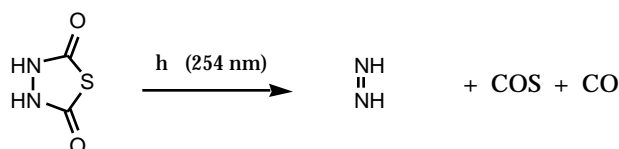
- Only reduces double bonds
- Syn addition of H_2
- will selectively reduce the more strained double bond
- Unstable reagent which is generated *in situ*



ACIEE 1965, 271



JACS 1986, 108, 5908



TL 1993, 34, 4137

Metal HydridesReview 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
- $\text{LiBH}_4/\text{TMSCl}$ stronger reducing agent. *ACIEE* **1989**, 28, 218.
- $\text{Zn}(\text{BH}_4)_2$ reduces ketones and aldehydes
- $\text{R}_4\text{N} \text{BH}_4$ organic soluble (CH_2Cl_2) borohydrides. *Synth Commun.* **1990**, 20, 907
- LiEt_3BH reduces ketones, aldehydes, esters, epoxides and R-X
- $\text{Li s-Bu}_3\text{BH}$ reduces ketones, aldehydes, esters and epoxides (hindered borohydride)
- $\text{Na}(\text{CN})\text{NH}_3$ reduces iminium ions, ketones and aldehydes
- $\text{Na}(\text{AcO})_3\text{BH}$ reduces ketones and aldehydes (less reactive)
- NaBH_2S_3 reduces ketones and aldehydes

Sodium Borohydride NaBH₄

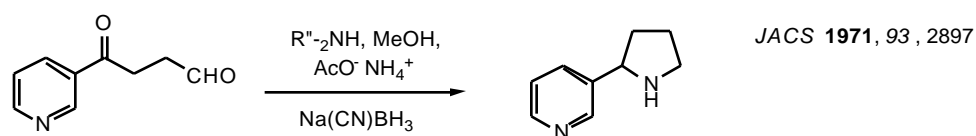
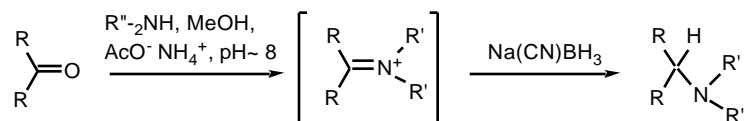
- reduces aldehydes and ketones to alcohols
- does not react with acids, esters, lactones, epoxides or nitriles.
- Additives can increase reactivity.

Sodium Cyanoborohydride Na(CN)BH₃

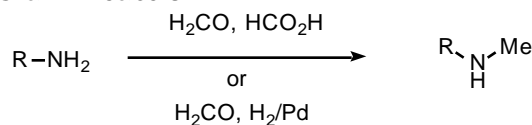
Reviews: *Synthesis* **1975**, 136; *OPPI* **1979**, 11, 201

- less reactive than NaBH₄
- used in reductive aminations (Borch Reduction)

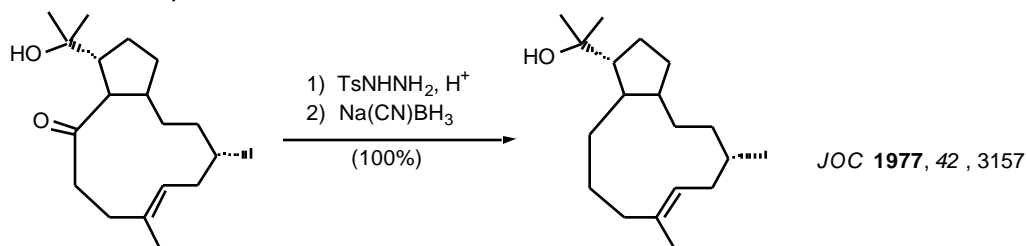
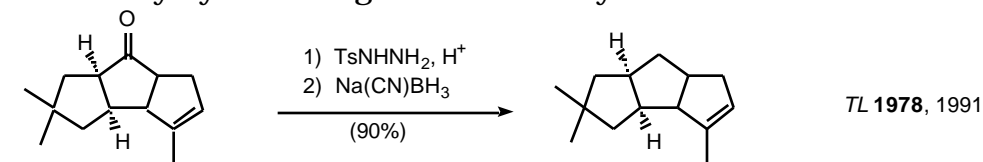
Na(CN)BH₃ reduces iminium ions much more quickly than ketones or aldehydes



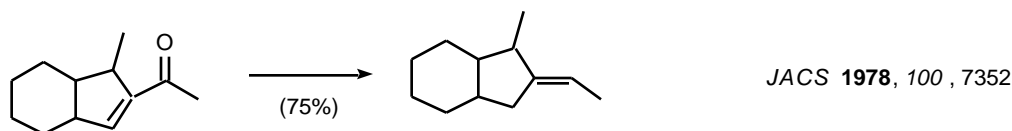
- Related to Eschweiler-Clark Reaction



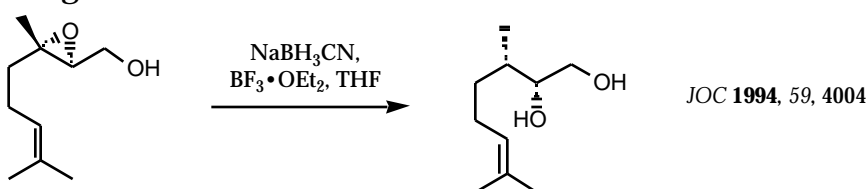
- Reduction of tosylhydrazones gives saturated hydrocarbon



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



- Epoxide opening



NaBH_2S_3 Lalancette Reduction

Synthesis **1972**, 526 *Can. J. Chem.* **1970**, 48, 735.

$\text{NaBH}_4/\text{NiCl}_2$ *Chem. Pharm. Bull.* **1981**, 29, 1159; *Chem. Ber.* **1984**, 117, 856.

Ar-NO₂ Ar-NH₂

Ar-NO Ar-NH₂

R₂C=N-OH R₂CH-NH₂

$\text{NaBH}_4/\text{TiCl}_4$

Synthesis **1980**, 695.

R-COOH R-CH₂-OH

R-COOR' R-CH₂-OH

R-CN R-CH₂-NH₂

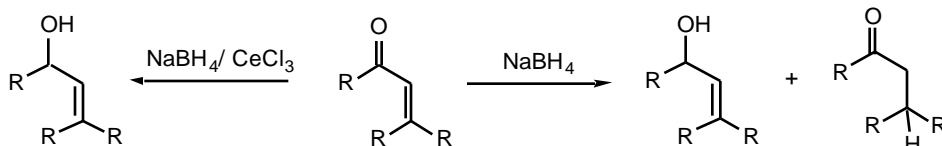
R-CONH₂ R-CH₂-NH₂

R₂C=N-OH R₂CH-NH₂

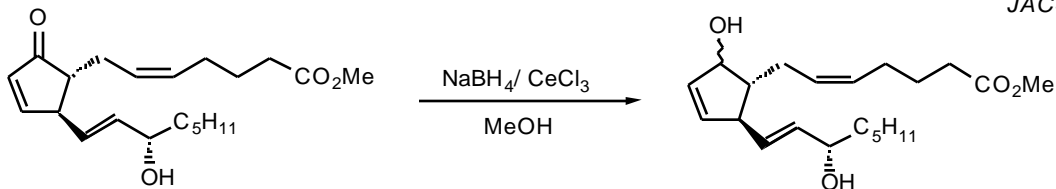
R-SO₂-R' R-S-R'

$\text{NaBH}_4/\text{CeCl}_3$ Luche Reduction

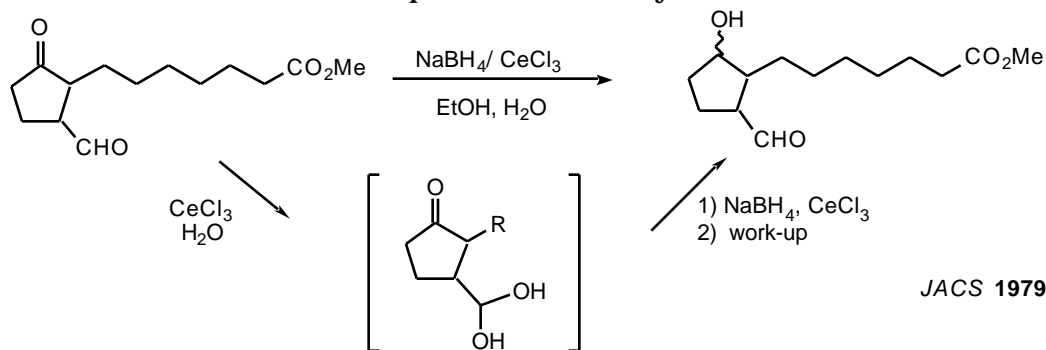
reduced, -unsaturated ketones in a 1,2-fashion



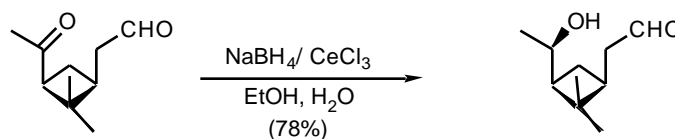
JCS **1978**, 601
JACS **1978**, 100, 2226



- selective reduction of ketones in the presence of aldehydes.

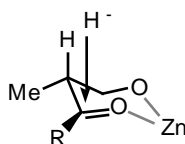
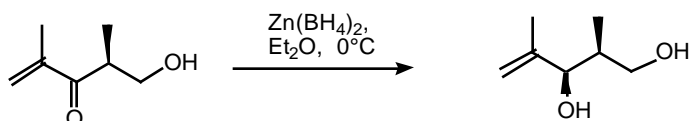
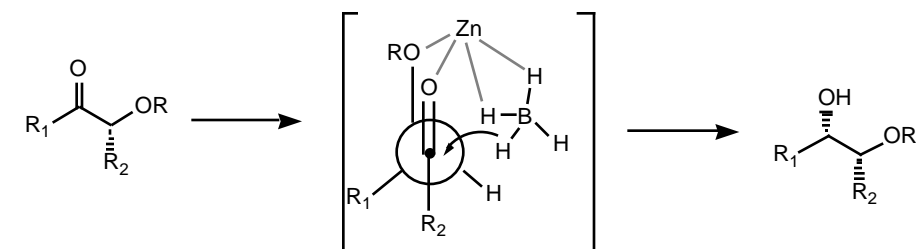


JACS **1979**, 101, 5848

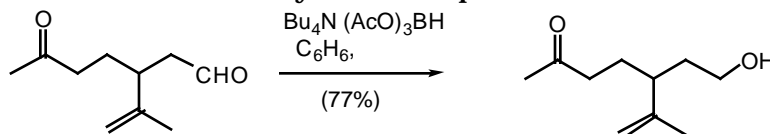
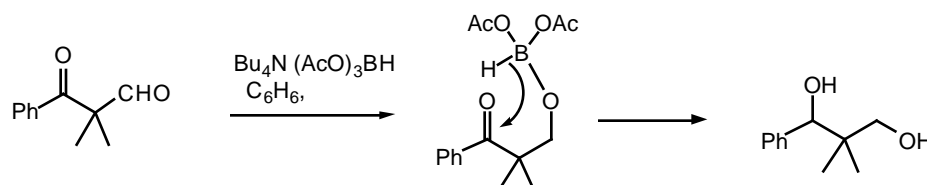


Zinc Borohydride $\text{Zn}(\text{BH}_4)_2$ Synlett **1993**, 885. ZnCl_2 (ether) + NaBH_4 $\text{Zn}(\text{BH}_4)_2$ - Ether solution of $\text{Zn}(\text{BH}_4)_2$ is neutral- good for base sensitive compounds

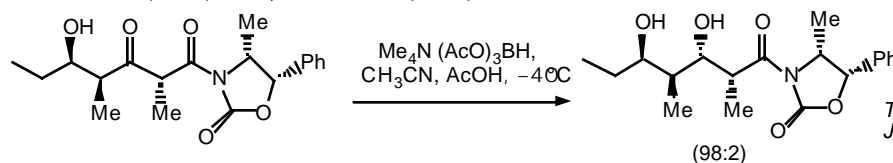
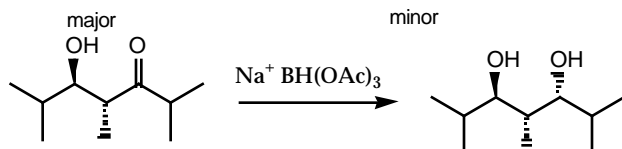
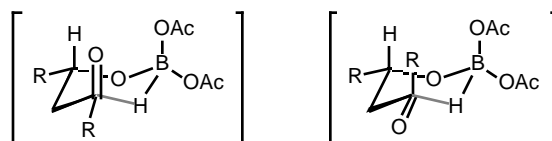
- Chelation control model

TL **1983**, 24, 2653, 2657, 2661 $\text{Na}^+ (\text{AcO})_3\text{BH}$, $\text{Me}_4\text{N}^+ (\text{AcO})_3\text{BH}$ Review: OPPI **1985**, 17, 317- used in Borch reductive amination TL **1990**, 31, 5595; Synlett **1990**, 537

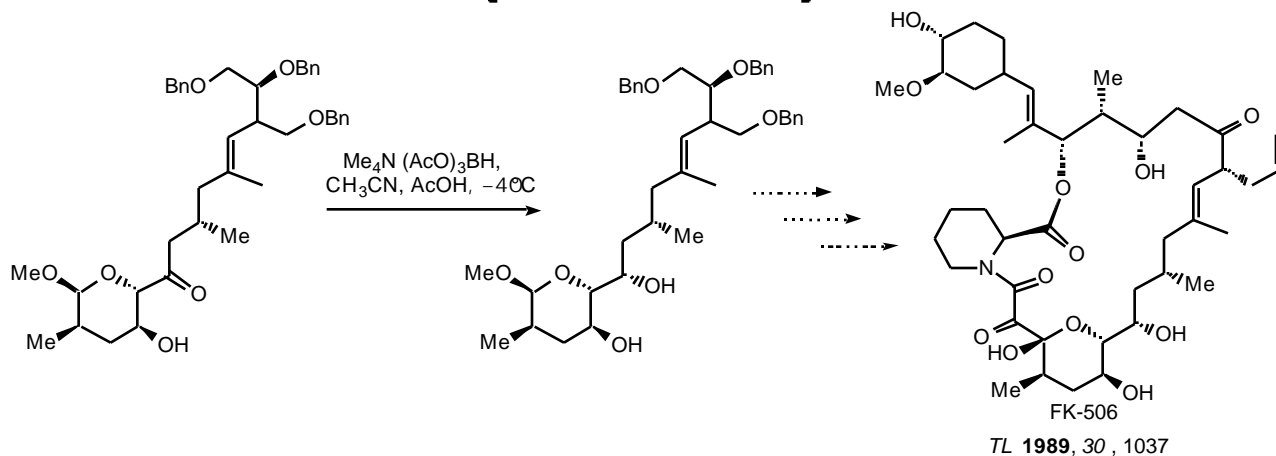
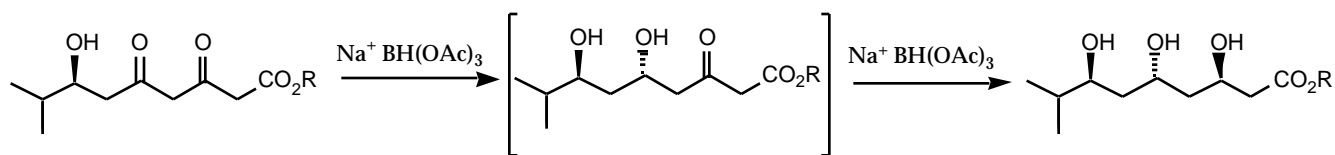
- selective reduction of aldehydes in the presence of ketones

TL **1983**, 24, 4287

-hydroxyl-directed reduction of ketones

TL **1983**, 24, 273; TL **1984**, 25, 5449TL **1986**, 27, 5939
JACS **1988**, 110, 3560

50:1



$(Ph_3P)_2Cu BH_4$

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 Heterocycles 1980, 14, 1437, 1441

reduction of amides to amines

reduction of nitriles to amines

$BnEt_3N BH_4 / Me_3SiCl$

reduction of carboxylic acids to alcohols

Synth. Commun. 1990, 20, 907

$LiBH_4 / Me_3SiCl$

ACIEE 1989, 28, 218.

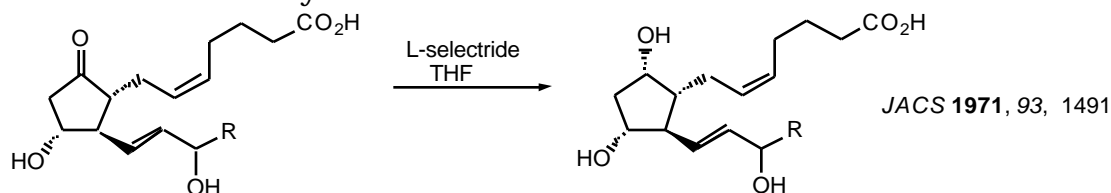
Alkyl Borohydrides

Selectrides

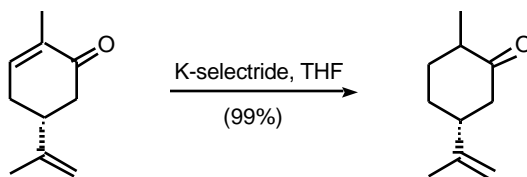


- hindered reducing agent

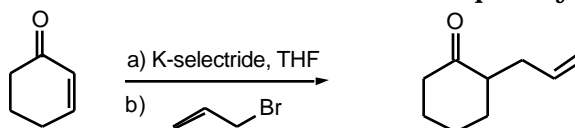
increased selectivity based on steric considerations



- selective 1,4-reductions of α,β -unsaturated carbonyl compounds.
JOC **1975**, 40, 146; *JOC* **1976**, 41, 2194



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



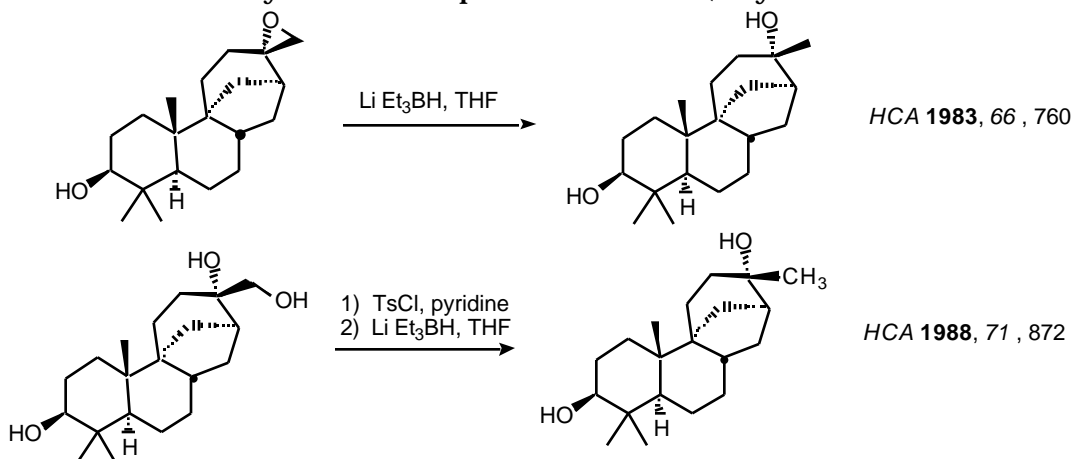
$\text{K}^+ \text{HBPh}_3$

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

- even greater 1,4-selectivity

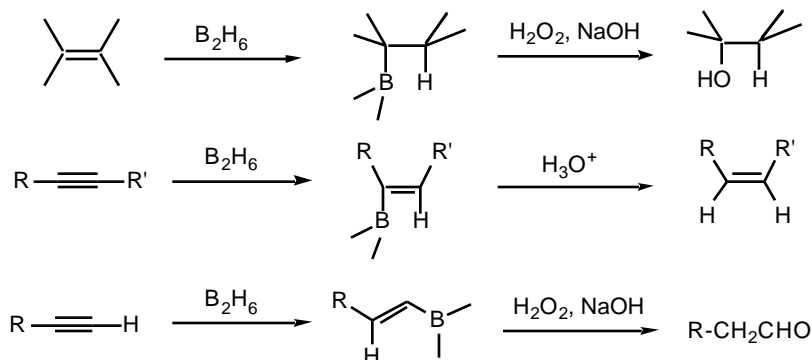
$\text{Li}^+ \text{HBtEt}_3$ (Super Hydride)

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

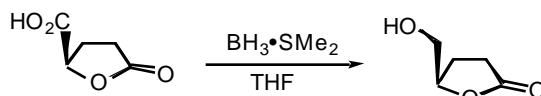


Boranes

Hydroboration

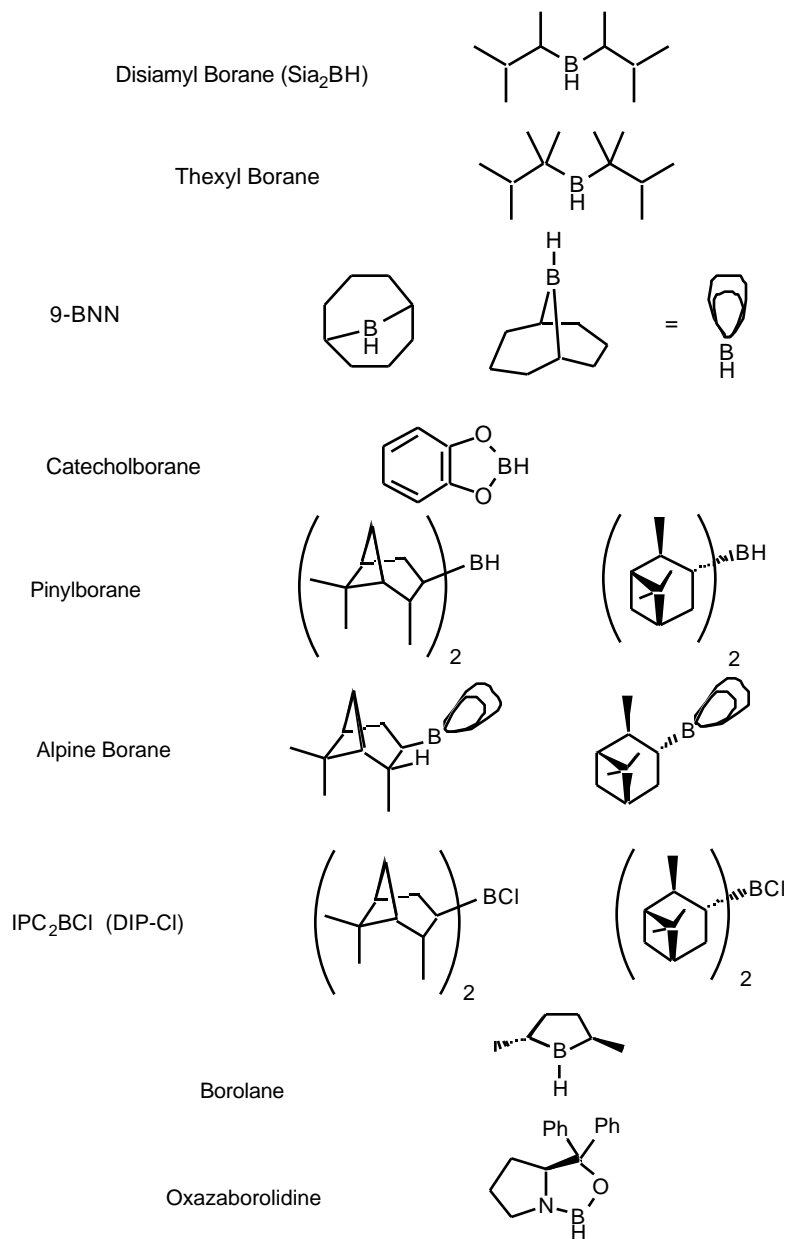


- BH_3 reduces carboxylic acids to 1° alcohols in the presence of esters, nitro and cyano groups.
- BH_3 reduces amides to amines



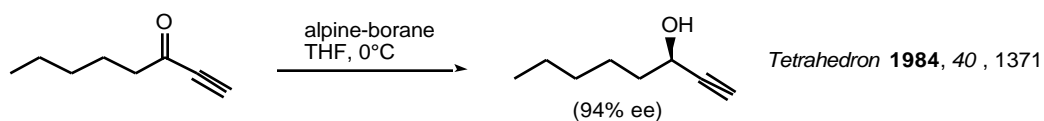
- Boranes also reduce ketones and aldehydes to the corresponding alcohols.

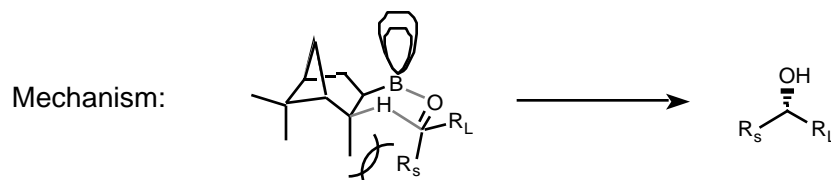
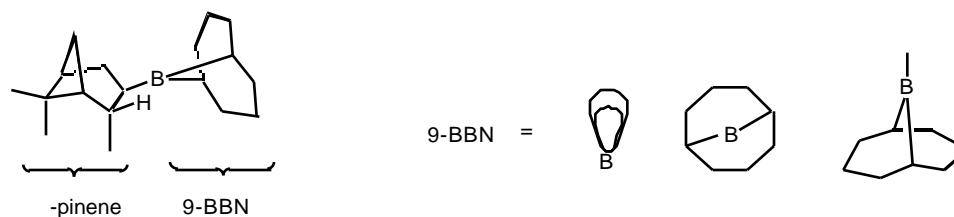
Hindered Boranes

Asymmetric Reduction of Unsymmetrical Ketones Using Chiral Boron ReagentsReview: *Synthesis* **1992**, 605.

Alpine Borane

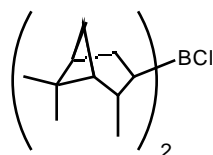
Midland Reduction

JACS **1979**, 111, 2352; *JACS* **1980**, 112, 867review: *Chem. Rev.* **1989**, 89, 1553.

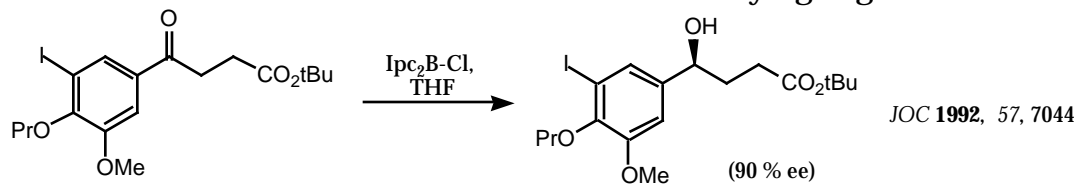


- works best for aryl- and acetylenic ketones
- because of steric hindrance, alpine-borane is fairly unreactive

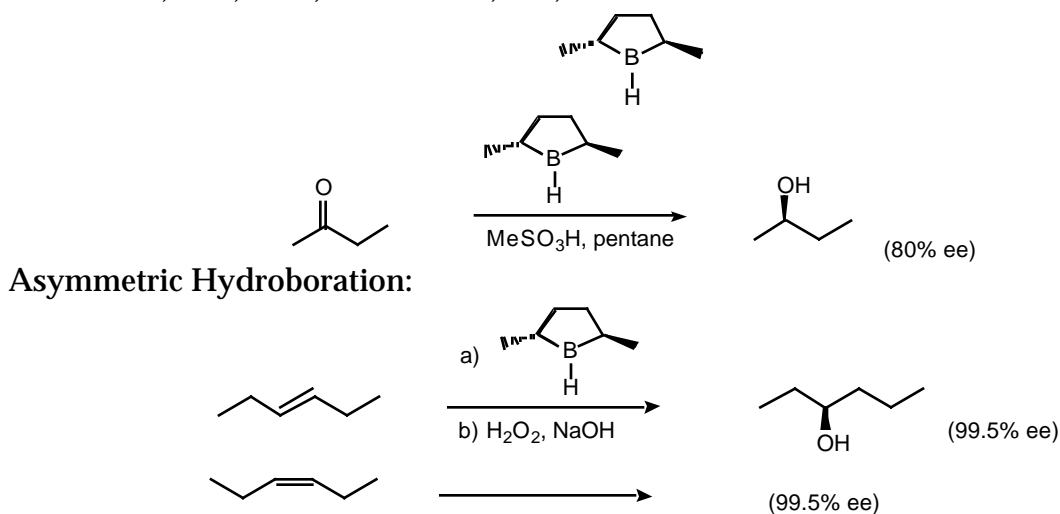
Chloro Diisopinylcamphenylborane (DIP-Cl, Ipc_2BCl) **H.C. Brown**
 Review: *ACR* **1992**, 25, 16. *Aldrichimica Acta* **1994**, 27 (2), 43



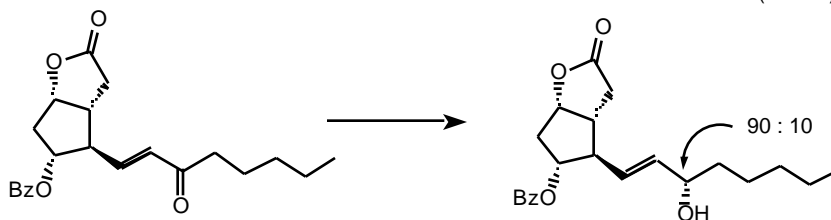
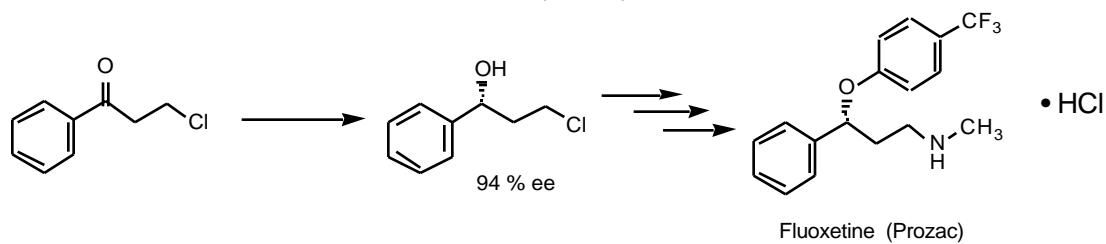
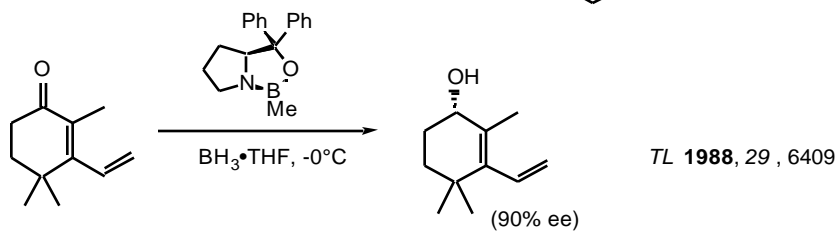
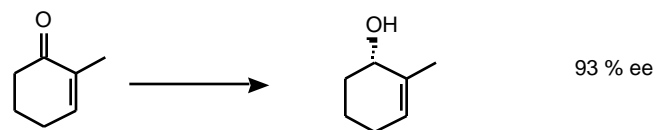
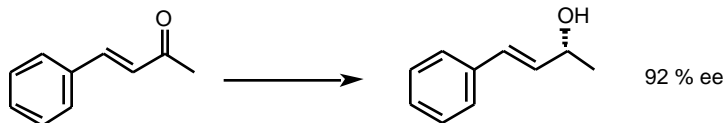
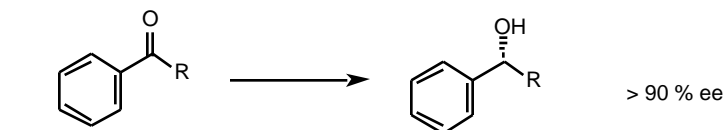
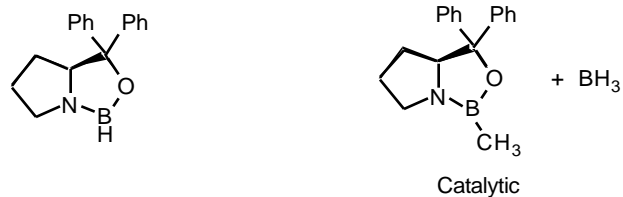
- Cl increases the Lewis acidity of boron making it a more reactive reagent
- saturated ketones are reduced to chiral alcohols with varying degrees of ee.



Borolane (Masamune's Reagent)
JACS **1986**, 108, 7404; *JACS* **1985**, 107, 4549



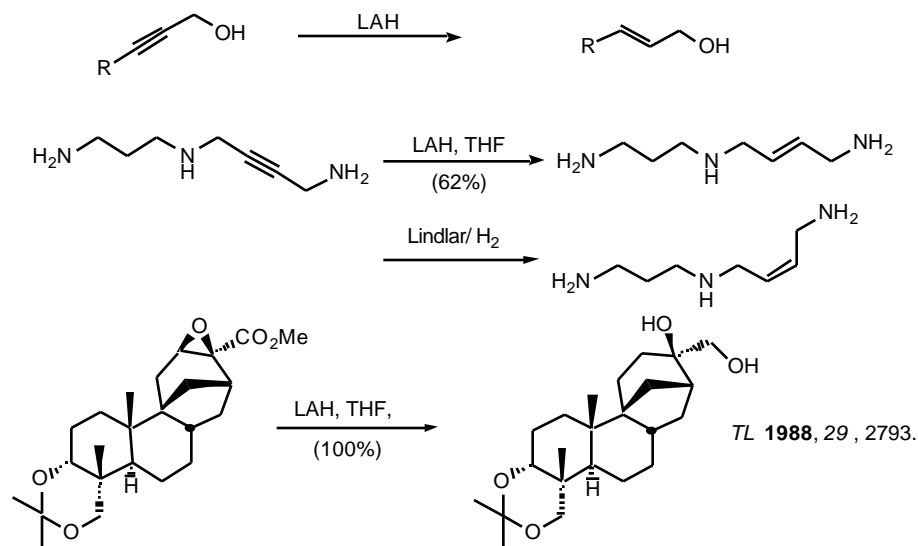
Oxazaborolidine (Corey)

 JACS **1987**, 109, 7925; TL **1990**, 31, 6111; TL **1992**, 33, 4141

Aluminium Hydrides

1. LiAlH_4
2. AlH_3
3. $\text{Li}(\text{tBuO})_3\text{AlH}$
4. $(\text{iBu})_2\text{AlH}$ DIBAL-H
5. $\text{Na}(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{AlH}_2$ REDAL

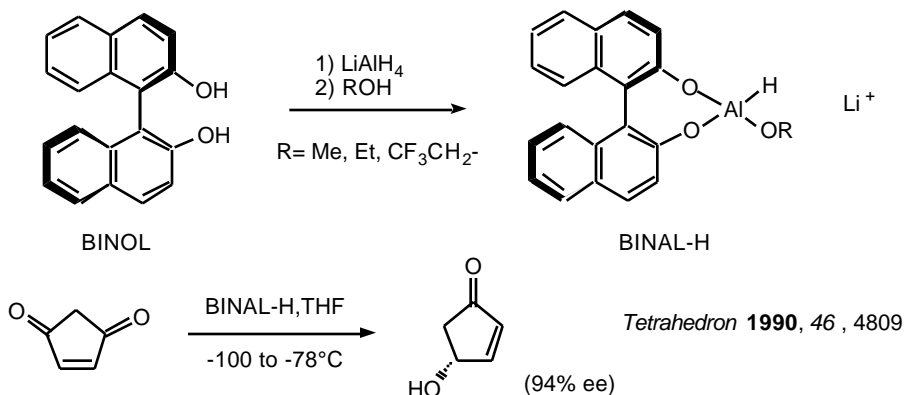
Lithium Aluminium Hydride LiAlH_4 (LAH) *Chem. Rev.* **1986**, 86, 763 *Org. Rxn.* **1951**, 6, 469.

- 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

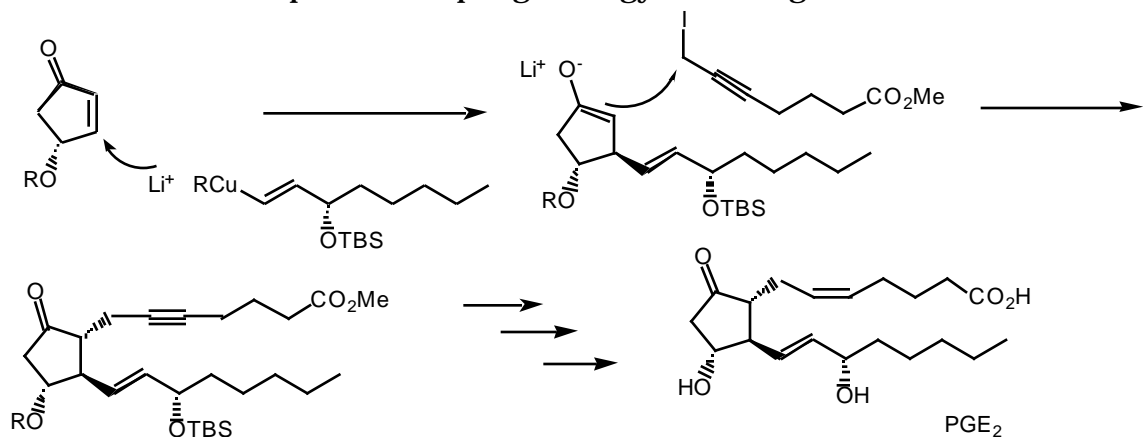


BINAL-H (Noyori)

- Chiral aluminium hydride for the asymmetric reduction of prochiral ketones



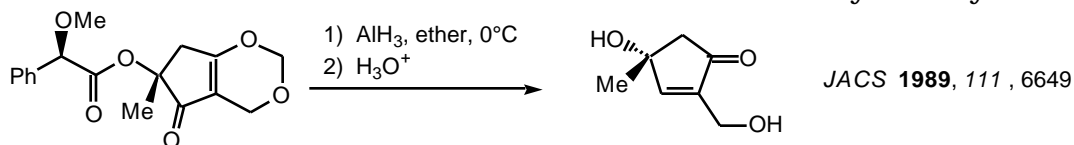
Intermediate for 3-Component Coupling Strategy to Prostaglandins



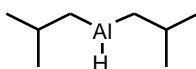
Alane AlH_3

$\text{LiAlH}_4 + \text{AlCl}_3$ AlH_3

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

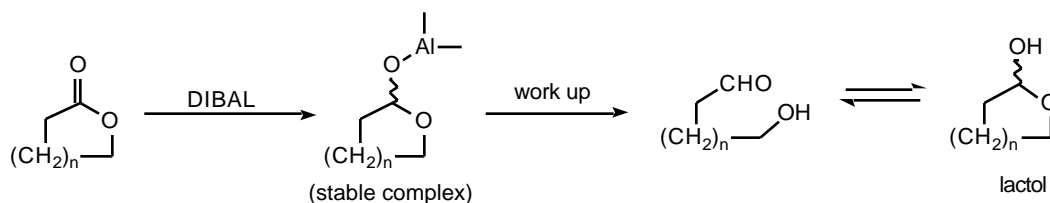


Diisobutyl Aluminium Hydride **DIBAL or DIBAL-H**



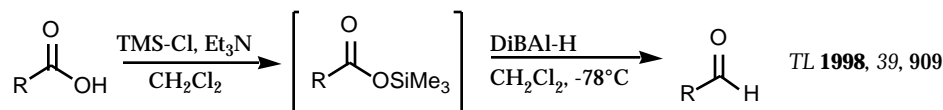
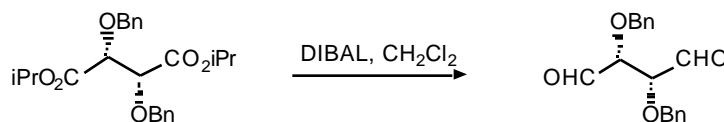
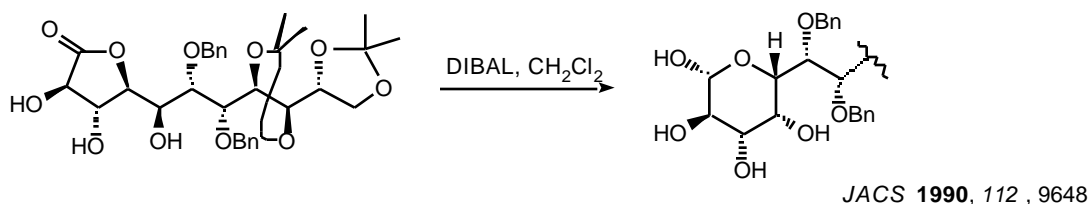
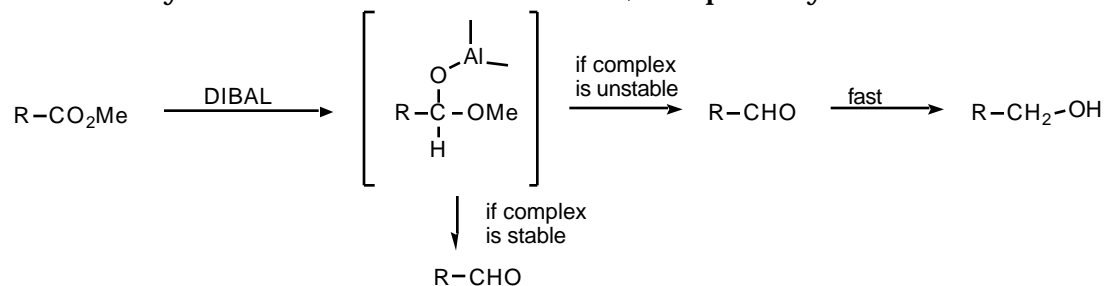
- Reduces ketones and aldehydes to alcohols

- reduces lactones to hemi-acetals



- reduces esters to alcohols

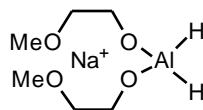
- under carefully controlled reactions conditions, will partially reduce an ester to an aldehyde



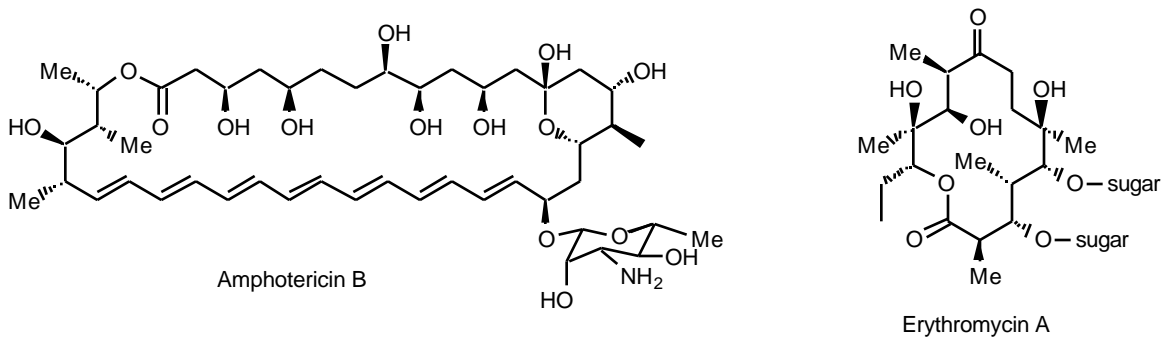
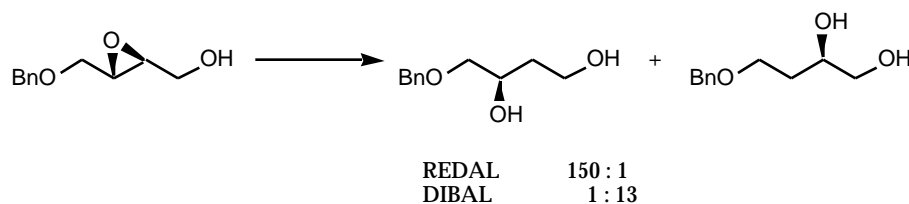
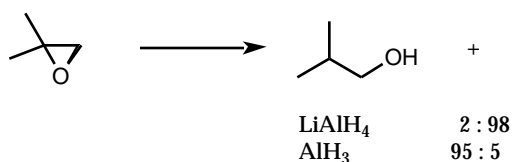
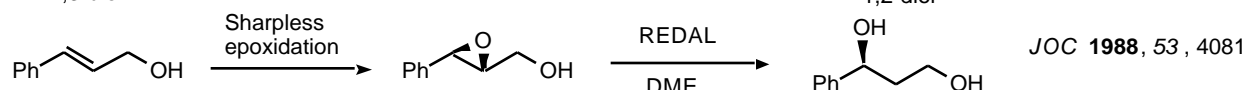
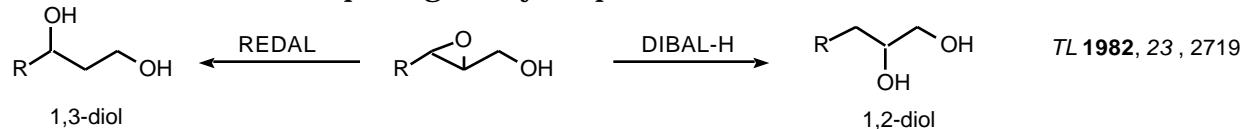
Reduction of O-Methyl hydroxamic acids



Sodium Bis(2-Methoxyethoxy)Aluminium Hydride **REDAL**
Organic Reactions **1988**, 36, 249 *Organic Reactions* **1985**, 36, 1.



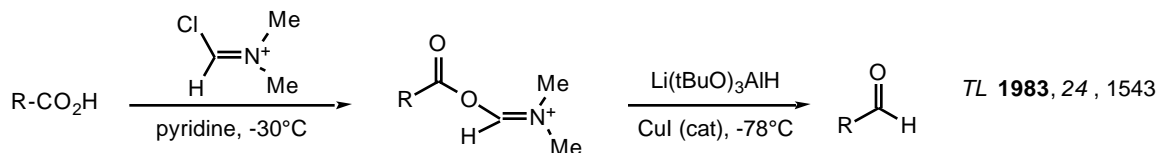
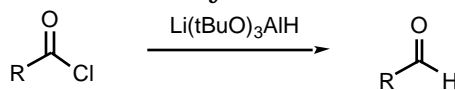
- "Chelation" directed opening fo allylic epoxides



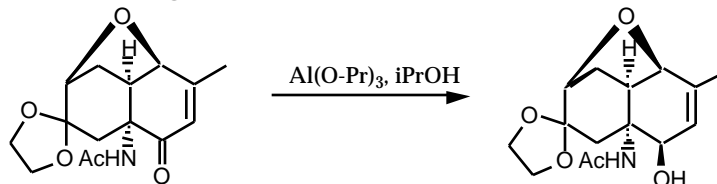
Lithium Tri(*t*-Butoxy)aluminium Hydride

$\text{Li}^+ (\text{tBuO})_3\text{AlH}$

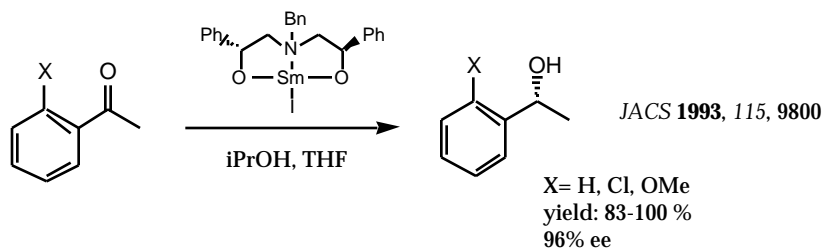
- hindered aluminium hydride, will only react with the most reactive FG's



Meerwein-Ponndorf-Verley Reduction: **opposite of Oppenauer oxidation**
Synthesis **1994**, 1007 *Organic Reactions* **1944**, 2, 178



Asymmetric M-P-V Reduction

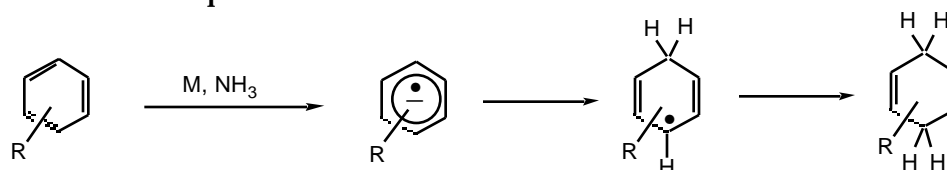


Dissolving Metal Reductions

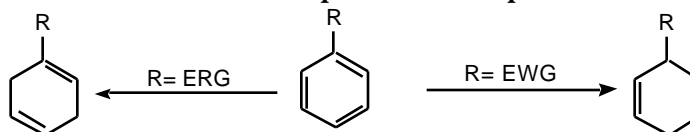
 Birch Reductions reduction of aromatic rings *Organic Reactions* **1976**, 23, 1.

Tetrahedron **1986**, 42, 6354. *Comprehensive Organic Synthesis* **1991**, vol. 8, 107.

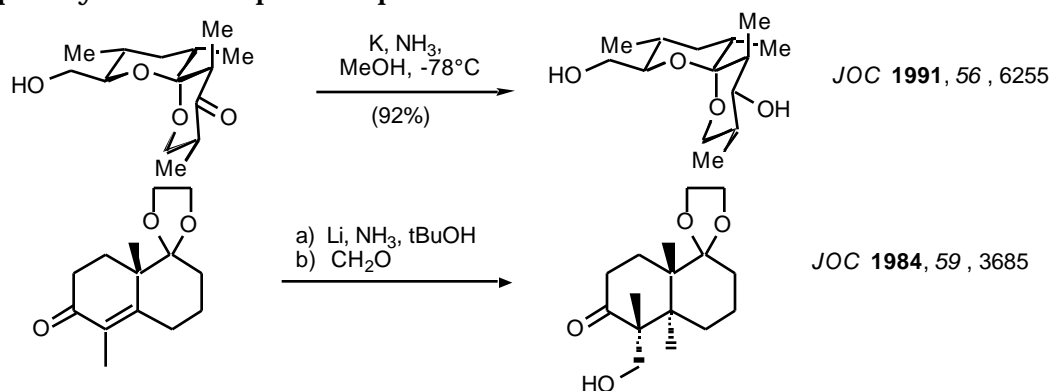
- Li, Na or K metal in liquid ammonia



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

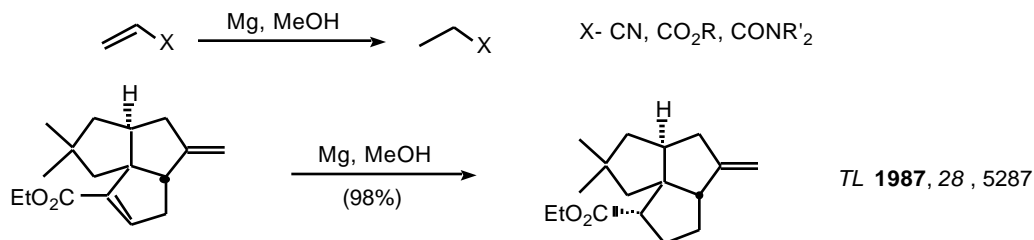
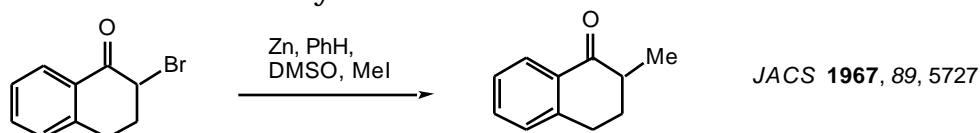


- ketones and nitro groups are also reduced but esters and nitrile are not.

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


Other Metals

- Mg

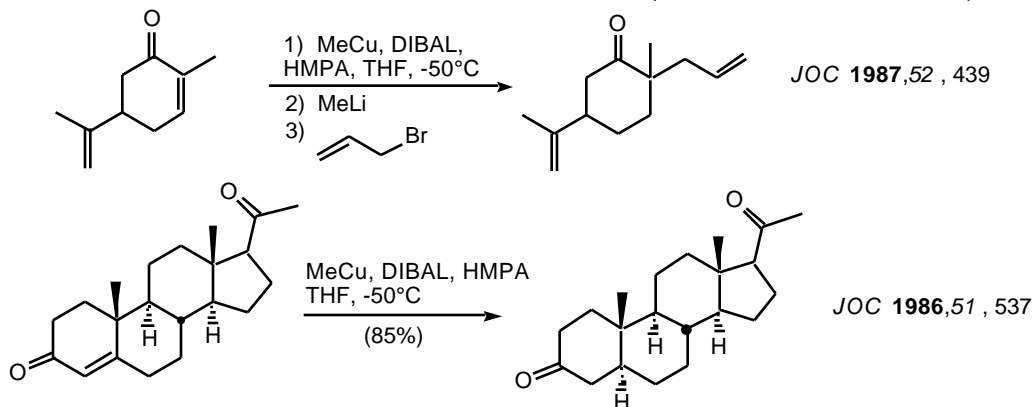

 - Zn reduction of α -halocarbonyls




"Copper Hydrides"

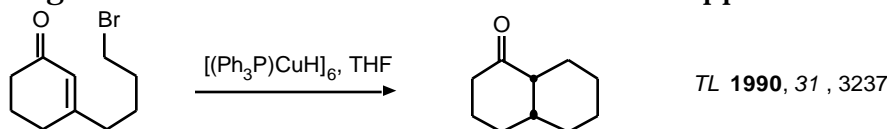
LAH or DIBAL-H + MeCu "CuH"

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



$[(\text{Ph}_3\text{P})\text{CuH}]_6$ 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.

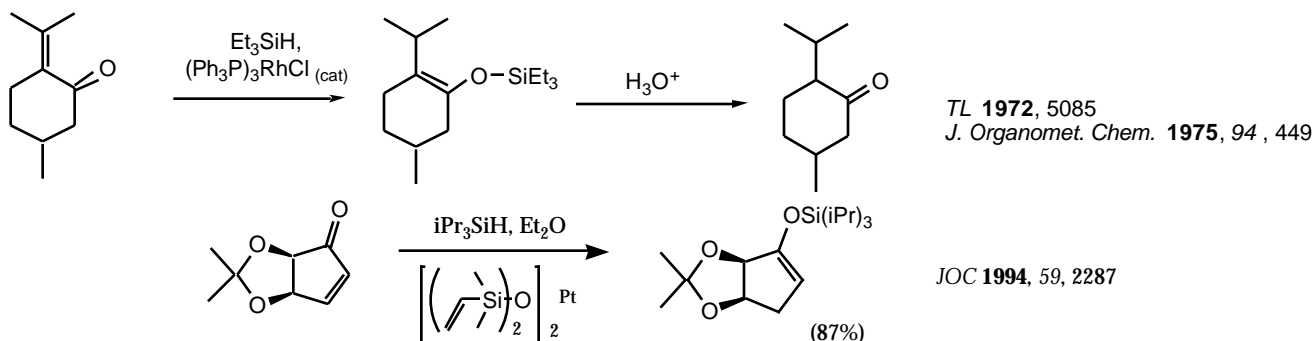


Silyl Hydrides

- Hydrosilylation

Et₃SiH + (Ph₃P)₃RhCl (cat)

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



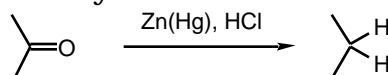
- Buchwald Reduction

JACS 1991, 113, 5093

- catalytic reagent prepared from Cp₂TiCl₂ + nBuLi and stoichiometric (Et)₃SiH in THF will reduce ester, ketones and aldehydes to alcohols under very mild conditions.
- α,β -unsaturated esters are reduced to allylic alcohols
- free hydroxyl groups, aliphatic halides and epoxides are not reduced

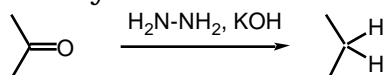
Clemmensen Reduction *Organic Reactions* **1975**, 22, 401
Comprehensive Organic Synthesis **1991**, vol 8, 307.

- 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

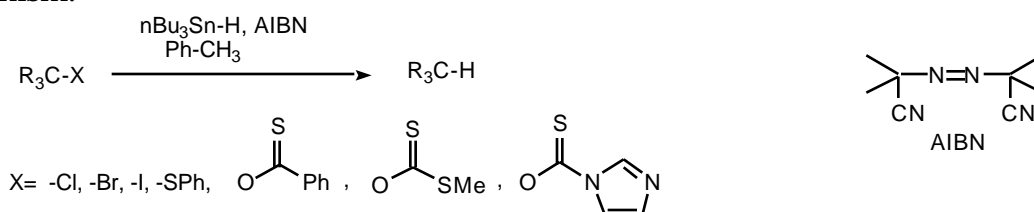
Review: *Tetrahedron* **1983**, 39, 2609 *Chem. Rev.* **1989**, 89, 1413.

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

Tetrahedron **1992**, 48, 2529

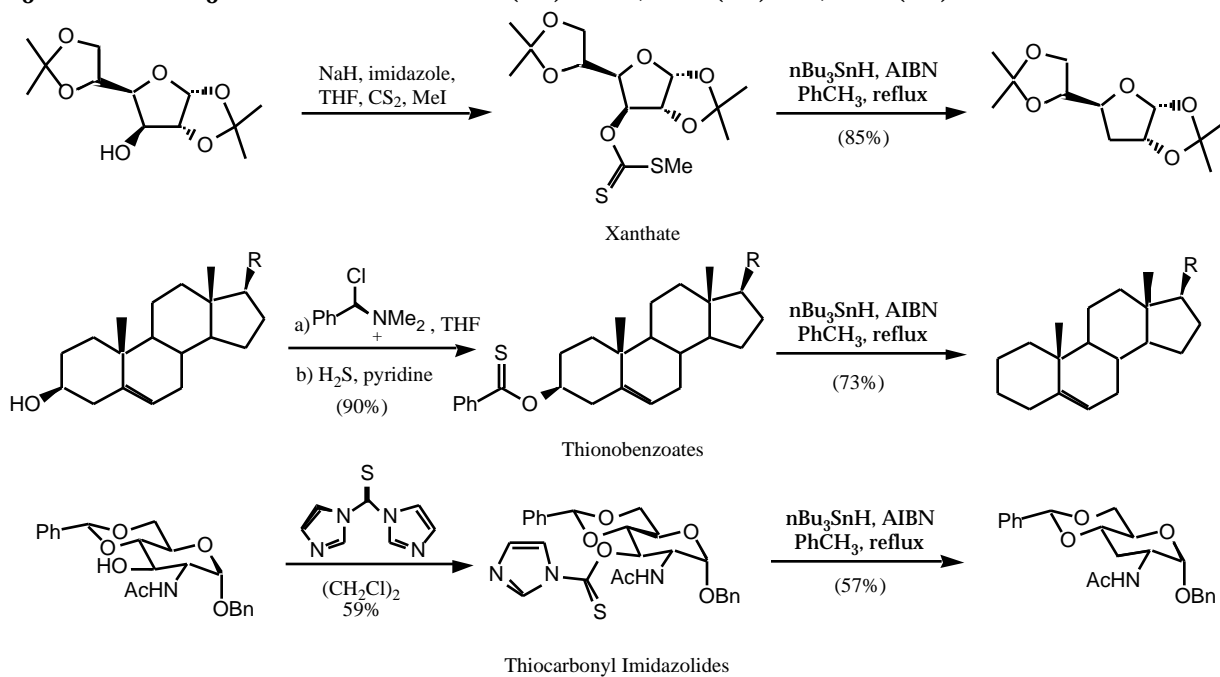
W. B. Motherwell, D. Crich *Free Radical Chain Reactions in Organic Synthesis*
 (Academic Press: 1992)

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

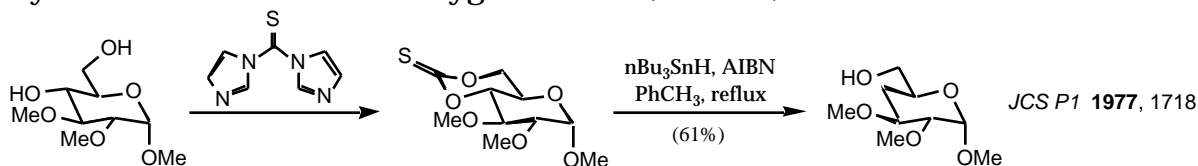


Barton-McCombie Reduction
JCS P1 **1975**, 1574

$\text{R}_3\text{C-X} \quad \text{R}_3\text{C-H} \quad \text{X} = \text{-OC(=S)-SMe, -OC(=S)-Im, -OC(=S)Ph}$

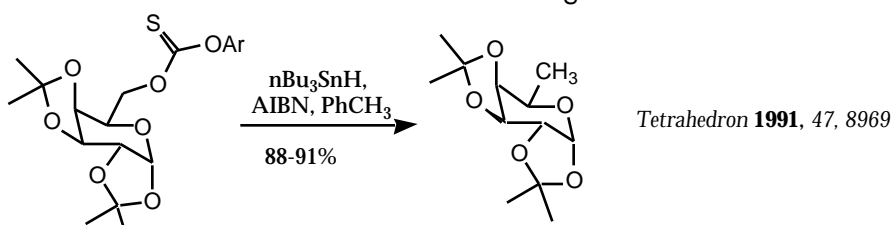
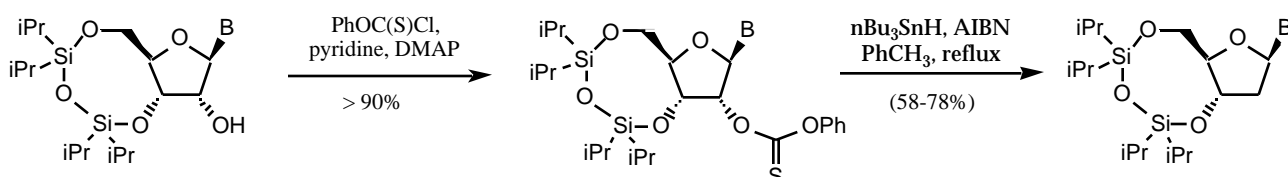


- Cyclic Thionocarbonates: deoxygenation of 1,2- and 1,3-diols to alcohols



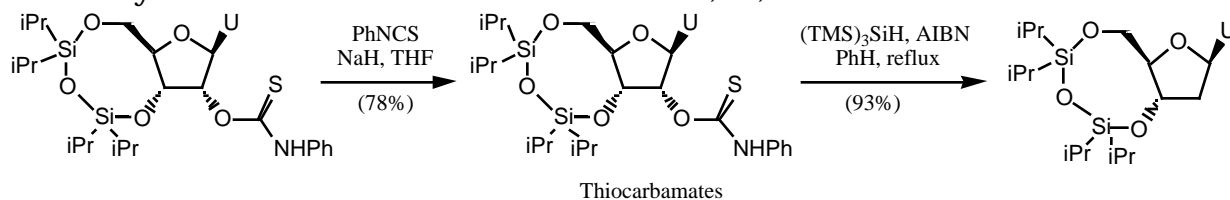
- Thionocarbonate Modification (Robbins)

JACS **1981**, 103, 932; *JACS* **1983**, 105, 4059.



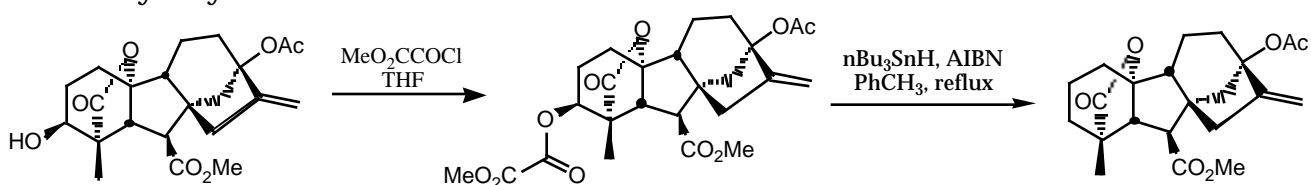
Ar = 2,4,6-trichlorophenyl, 4-fluorophenyl } Best method for deoxygenation of primary alcohols

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



Thiocarbonates

- Methyl oxylates



Methyl Oxylate Esters

- Water Soluble Tin Hydride: $[\text{MeO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3]_3\text{SnH}$ / 4,4'-Azo(bis-4-cyanovaleic acid)
TL **1990**, 31, 2957

- Silyl Hydride Radical Reducing Agents

- replacement for $n\text{Bu}_3\text{SnH}$

$(\text{Me}_3\text{Si})_3\text{SiH}$ *Chem Rev.* **1995**, 95, 1229.

JOC **1991**, 56, 678; *JOC* **1988**, 53, 3641; *JACS* **1987**, 109, 5267

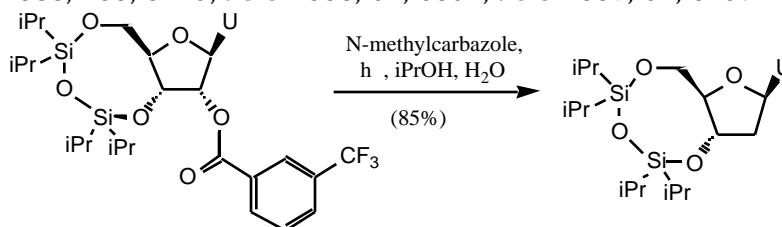
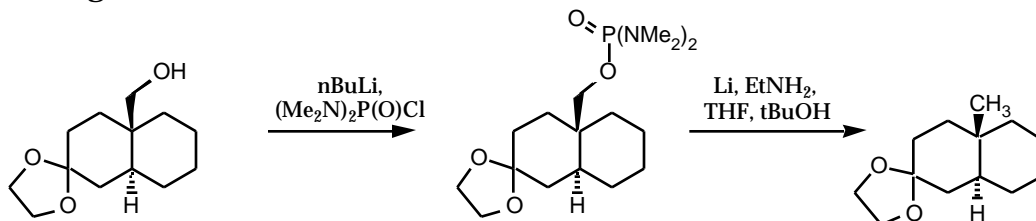
Ph_2SiH_2 / Et_3B / Air

TL **1990**, 31, 4681; *TL* **1991**, 32, 2569

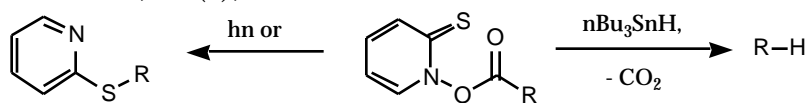
- hypophosphorous acid as radical chain carrier

JOC **1993**, 58, 6838

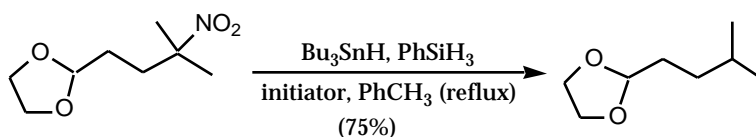
- Photosensitized electron transfer deoxygenation of m-trifluoromethylbenzoates

JACS **1986**, 108, 3115, JOC **1996**, 61, 6092, JOC **1997**, 62, 8257Dissolving Metal: JACS **1972**, 94, 5098

Radical Decarboxylation: Barton esters

Aldrichimica Acta **1987**, 20 (2), 35

Radical Deamination

Comprehensive Organic Synthesis **1991**, vol. 8, 811Reduction 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

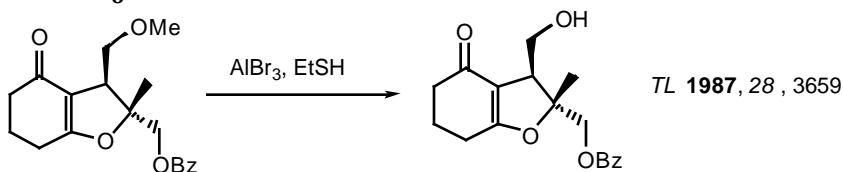
Ethers

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



Methoxymethyl ether MOM

R-OH R-OCH₂OMe stable to base and mild acid

Formation: - MeOCH_2Cl , NaH, THF
- MeOCH_2Cl , CH_2Cl_2 , iPr_2EtN

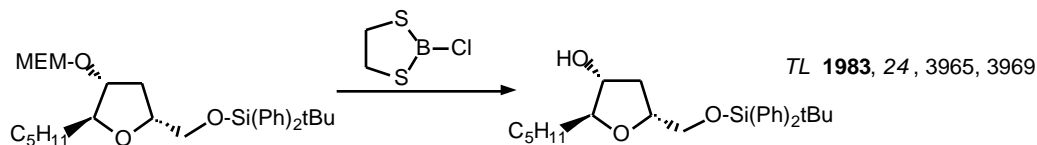
Cleavage - Me_2BBr_2 TL 1983, 24, 3969

Methoxyethoxymethyl ethers (MEM)

R-OH R-OCH₂OCH₂CH₂OMe stable to base and mild acid

Formation: - MeOCH₂CH₂OCH₂Cl, NaH, THF
 - MeOCH₂CH₂OCH₂Cl, CH₂Cl₂, iPr₂EtN TL 1976, 809

Cleavage - Lewis acids such as ZnBr₂, TiCl₄, Me₂BBr₂



- can also be cleaved in the presence of THP ethers

Methyl Thiomethyl Ethers (MTM)

R-OH R-OCH₂SMe Stable to base and mild acid

Formation: - MeSCH₂Cl, NaH, THF

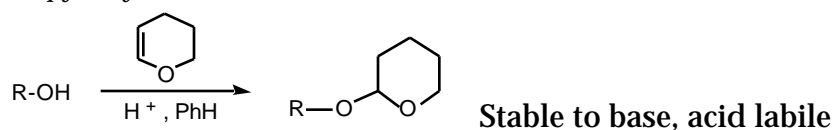
Cleavage: - HgCl₂, CH₃CN/H₂O
 - AgNO₃, THF, H₂O, base

Benzyloxymethyl Ethers (BOM)

R-OH R-OCH₂OCH₂Ph Stable to acid and base

Formation: - PhOCH₂CH₂Cl, CH₂Cl₂, iPr₂EtN

Cleavage: - H₂/ PtO₂
 - Na/ NH₃, EtOH

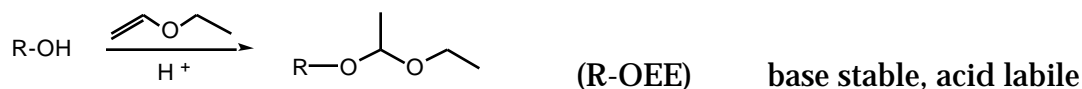
Tetrahydropyranyl Ether (THP)


Formation - DHP (dihydropyran), pTSA, PhH

Cleavage: - AcOH, THF, H₂O
 - Amberlyst H-15, MeOH

Ethoxyethyl ethers (EE)

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


Benzyl Ethers (R-OBn)

R-OH R-OCH₂Ph stable to acid and base

Formation: - KH, THF, PhCH₂Cl

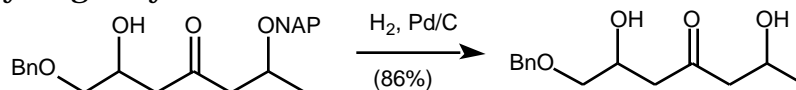
- PhCH₂OC(=NH)CCl₃, F₃CSO₃H JCS P1 1985, 2247

Cleavage: - H₂ / PtO₂
 - Li / NH₃

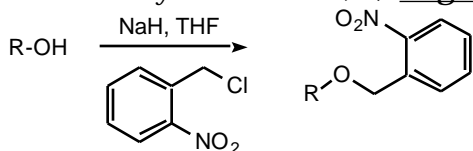
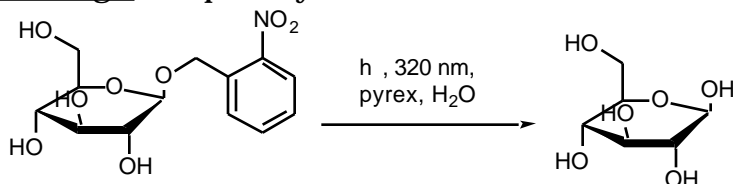
2-Naphthylmethyl Ethers (NAP) *JOC* **1998**, 63, 4172

formation: 2-chloromethylnaphthalene, KH

cleavage: hydrogenolysis


***p*-Methoxybenzyl Ethers (PMB)**
Formation: - KH, THF, *p*-MeOPhCH₂Cl

 - *p*-MeOPhCH₂OC(=NH)CCl₃, F₃CSO₃H *TL* **1988**, 29, 4139

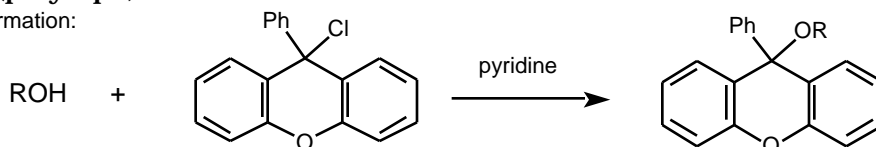
Cleavage: - H₂ / PtO₂
 - Li / NH₃
 - DDQ
 - Ce(NH₄)₂(NO₃)₆ (CAN)
 - e⁻
***o*-Nitrobenzyl ethers**
Review: *Synthesis* **1980**, 1; *Organic Photochemistry*, **1987**, 9, 225

Cleavage: - photolysis at 320 nm

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

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

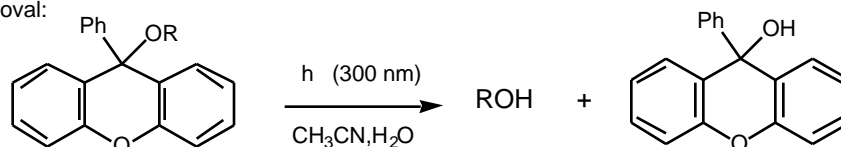
-selective removal with DDQ, hydrogenolysis or electrochemically

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

Formation:



Removal:


Triyl Ethers -CPh₃ = Tr

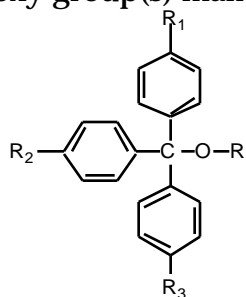
R-OH **R-OCPh₃** - selective for 1° alcohols
 - removed with mild acid; base stable

formation: - Ph₃C-Cl, pyridine, DMAP
 - Ph₃C⁺ BF₄⁻
Cleavage: - mild acid

Methoxytrityl Ethers

JACS 1962, 84, 430

- methoxy group(s) make it easier to remove

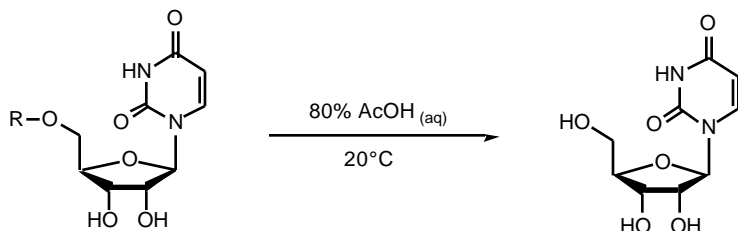


(p-Methoxyphenyl)diphenylmethyl ether
4'-methoxytrityl MMTr-OR

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

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

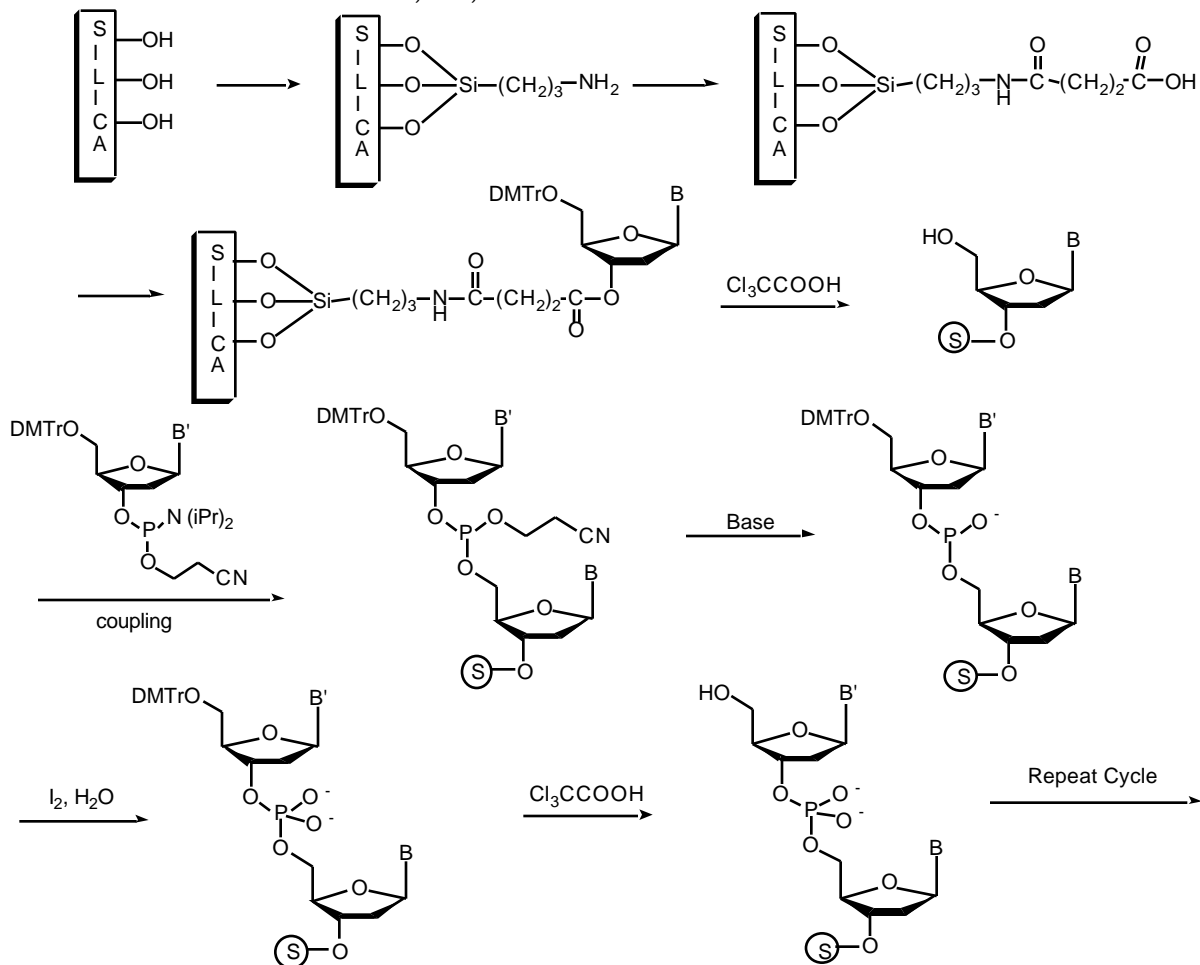
Tr-OR < MMTr-OR < DMTr-OR << TMTr-OR



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-SiR₃

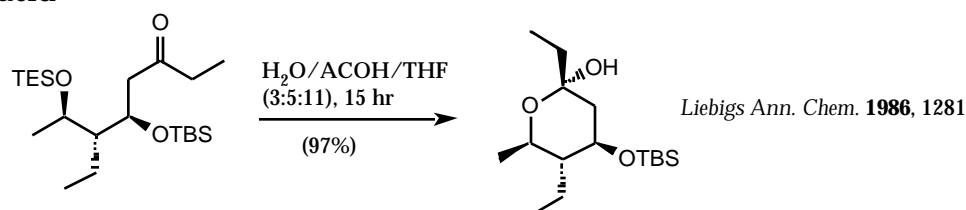
- formation:
- R₃Si-Cl, pyridine, DMAP
 - R₃Si-Cl, CH₂Cl₂ (DMF, CH₃CN), imidazole, DMAP
 - R₃Si-OTf, iPr₂EtN, CH₂Cl₂

Trimethylsilyl ethers Me₃Si-OR TMS-OR

- very acid and water labile
- useful for transient protection

Triethylsilyl ethers Et₃Si-OR TES-OR

- considerably more stable than TMS
- can be selectively removed in the presence of more robust silyl ethers with F⁻ or mild acid



Triisopropylsilyl ethers iPr₃Si-OR TIPS-OR

- more stable to hydrolysis than TMS

Phenyldimethylsilyl ethers

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

t-Butyldimethylsilyl Ether tBuMe₂Si-OR TBS-OR TBDMS-OR

JACS **1972**, 94, 6190

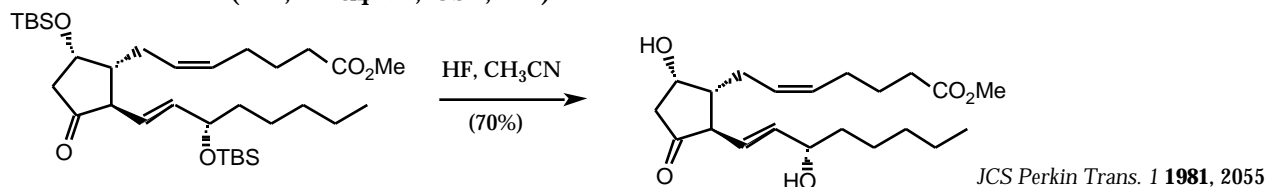
- Stable to base and mild acid
- under controlled condition is selective for 1° alcohols

t-butyldimethylsilyl triflate tBuMe₂Si-OTf *TL* **1981**, 22, 3455

- very reactive silylating reagent, will silylate 2° alcohols

cleavage:

- acid
- F⁻ (HF, nBu₄NF, CsF, KF)



t-Butyldiphenylsilyl Ether tBuPh₂Si-OR TBDPS-OR -OR

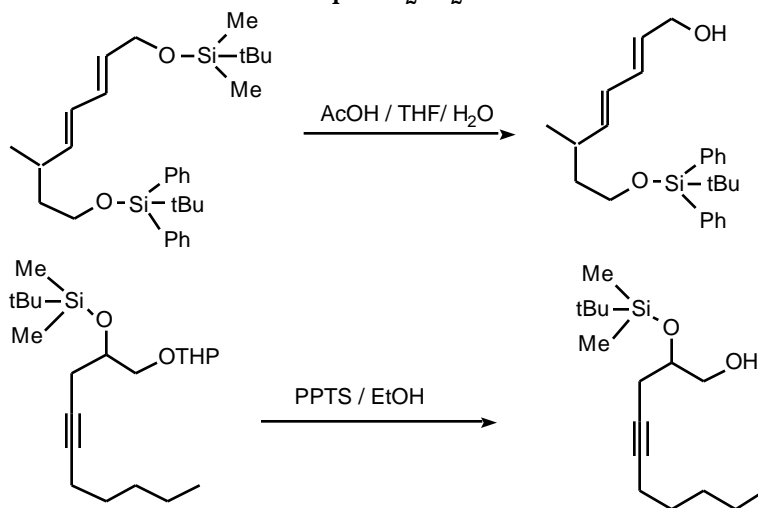
- stable to acid and base
- selective for 1° alcohols
- Me₃Si- and iPr₃Si groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.

TL **1989**, 30, 19

cleavage - F⁻

- Fluoride sources:
- nBu₄NF (basic reagent)
 - HF / H₂O / CH₃CN
 - HF • pyridine
 - SiF₄ • CH₂Cl₂

TL 1979, 3981.
 Synthesis 1986, 453
 TL 1992, 33, 2289



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

JACS 1984, 106, 3748

Esters

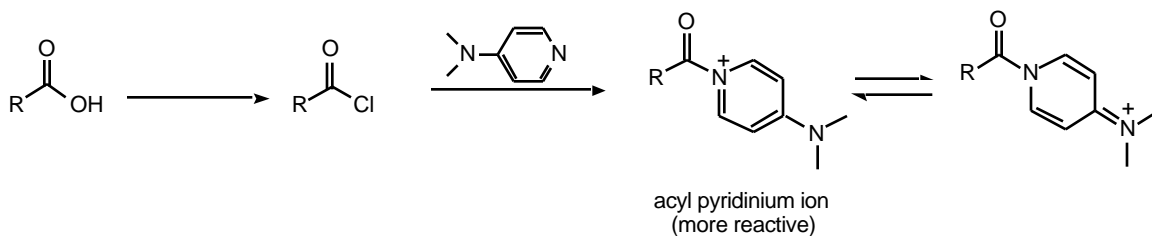


Formation: - "activated acid", base, solvent, (DMAP)

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

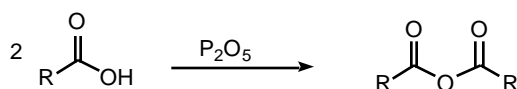
RCO₂H "activated acid" carboxylic acid derivative (ester, amide, etc.)

Acid Chlorides

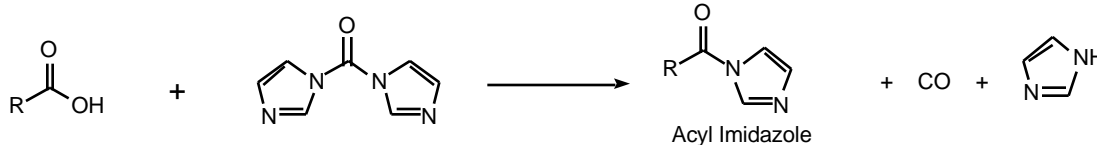


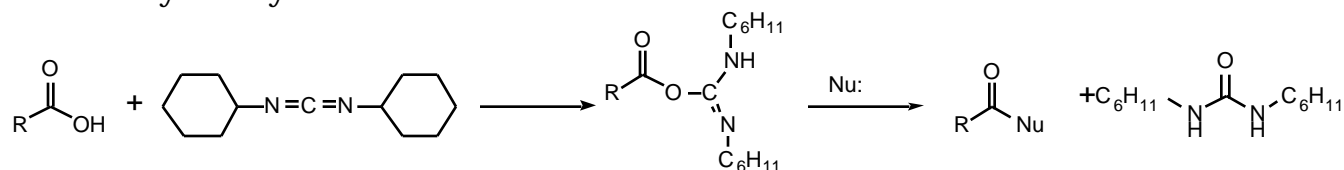
1. SOCl₂
2. PCl₅
3. (COCl)₂

Anhydrides

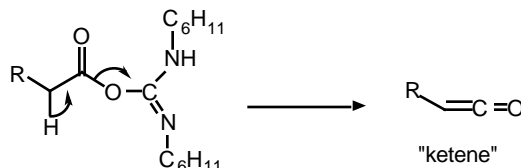


Activating Agents: Carbonyl Diimidazole

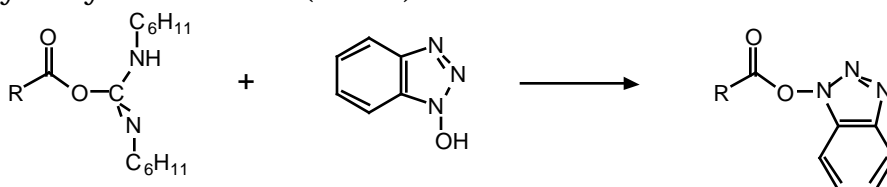


Dicyclohexylcarbodiimide


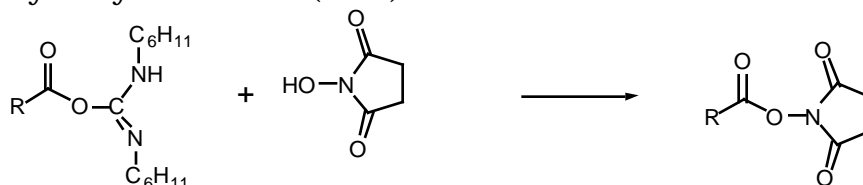
Ketene formation is a common side reaction- scrambling of chiral centers



Hydroxybenzotriazole (HOBT) - reduces ketene formation

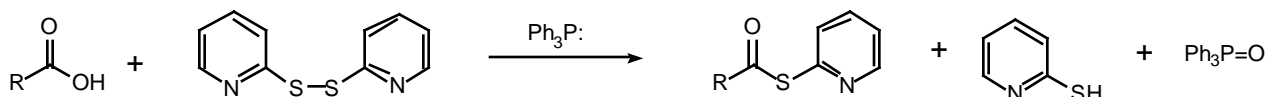


N-Hydroxysuccinimide (NHS)



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

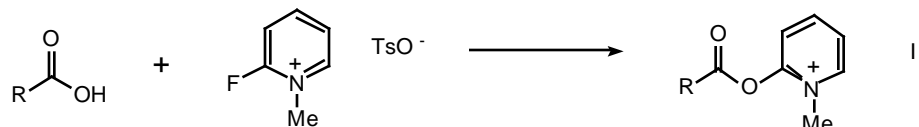
Aldrichimica Acta **1971**, 4, 33



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-O₂CCH₃

- stable to acid and mild base
- not compatible 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)

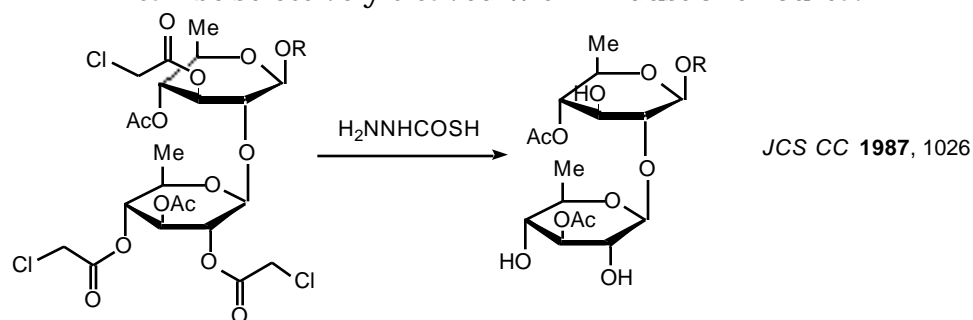
Org. Rxns. **1989**, 37, 1.



TL **1988**, 30, 6189

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



Trifluoroacetates

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride

Cleavage: - K_2CO_3 , MeOH

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

Formation: - t-butylacetyl chloride or t-butylacetic anhydride

Cleavage: - removed with mild base

Benzoate (Bz)

- more stable to hydrolysis than acetates.

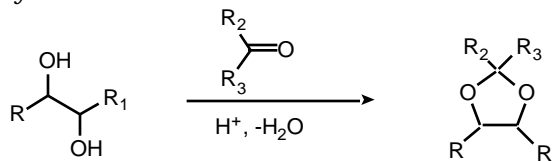
Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (TL **1971**, 185), benzoyl tetrazole (TL **1997**, 38, 8811)

Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- Diols

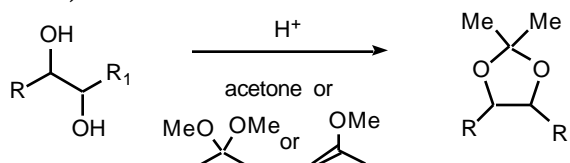
Synthesis **1981**, 501

Chem. Rev. **1974**, 74, 581



Isopropylidenes (acetonides)

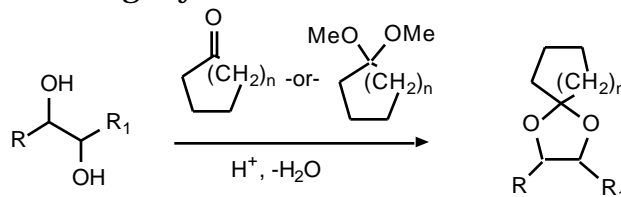
(acetonides)



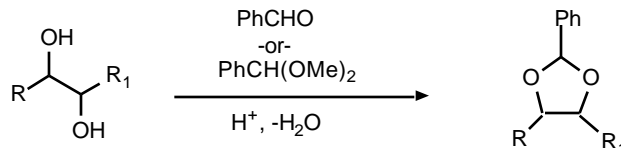
- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

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



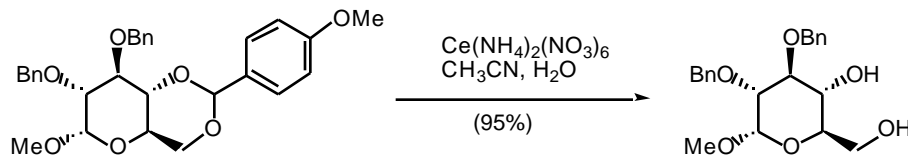
Benzylidene Acetals



- 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.

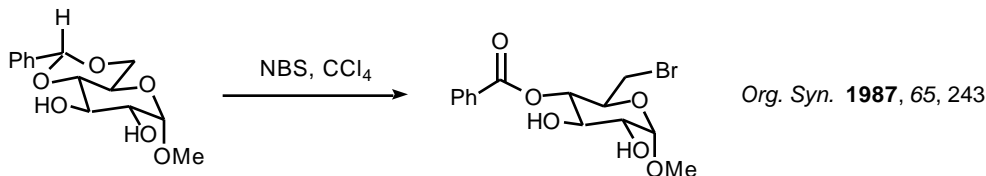
p-Methoxybenzylidenes

- hydrolyzed about 10X faster than regular benzylidenes
- Can be oxidatively removed with $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ (CAN)



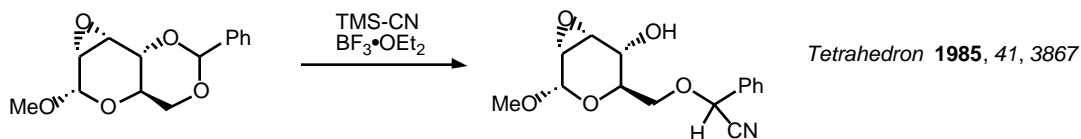
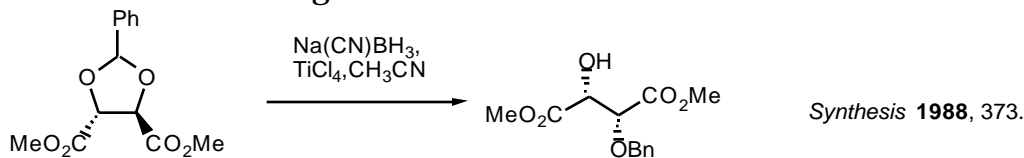
Other Reactions of Benzylidenes

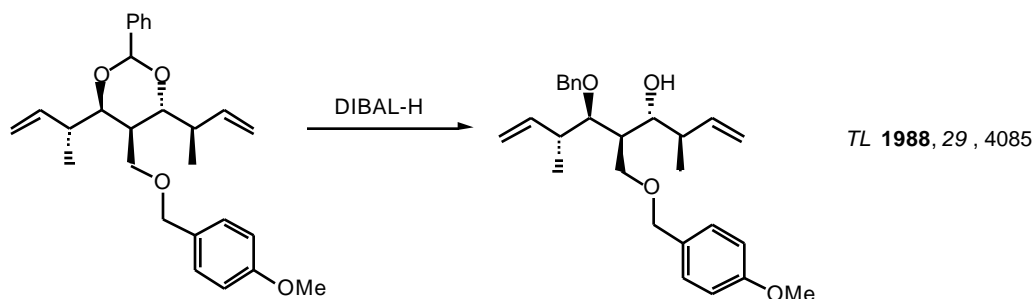
- Reaction with NBS (Hanesian Reaction)



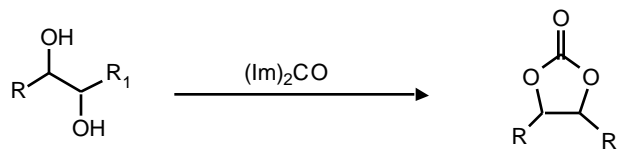
- if benzylidene of a 1° alcohol, then 1° bromide

- Reductive Cleavage





Carbonates

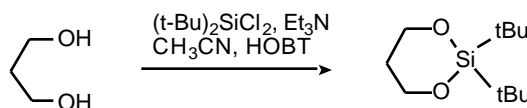


- stable to acid; removed with base
- more difficult to hydrolyze than esters

Di-*t*-Butylsilylene (DTBS)

TL 1981, 22, 4999

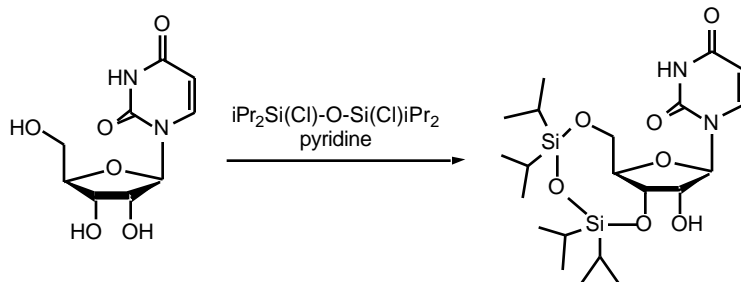
- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH₃CN -or- Bu₄NF -or- HF•pyridine)
- will not functionalize a 3°-alcohol



1,3-(1,1,3,3)-tetraisopropylidisiloxanylidene (TIPDS)

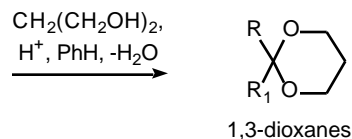
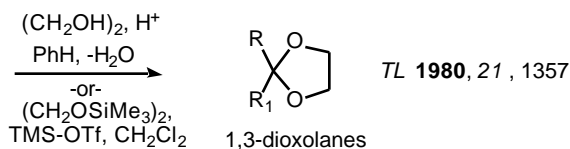
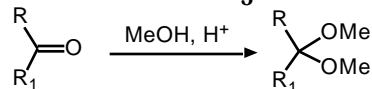
TL 1988, 29, 1561

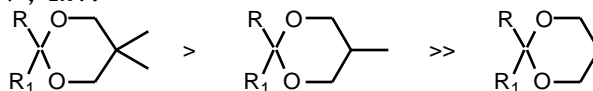
- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I



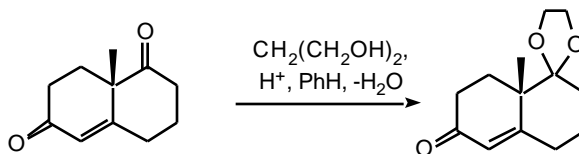
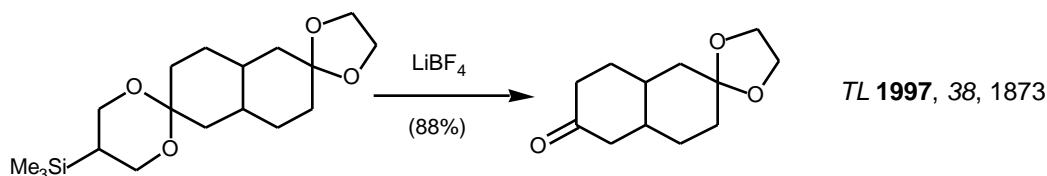
Ketones and Aldehydes

- ketones and aldehydes are protected as cyclic and acyclic ketals and acetals
- Stable to base; removed with H₃O⁺



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.

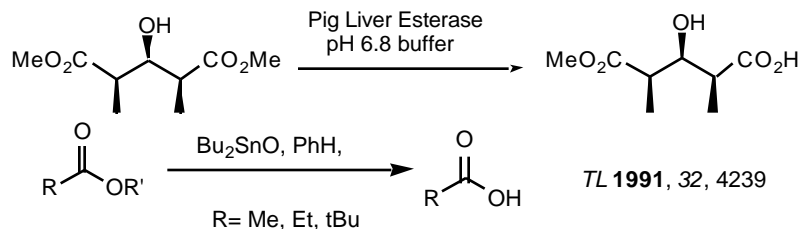

Fluoride cleavable ketal:

Base cleavable ketal:

Carboxylic Acids *Tetrahedron* **1980**, 36, 2409. *Tetrahedron* **1993**, 49, 3691
Nucleophilic Ester Cleavage: *Organic Reactions* **1976**, 24, 187.

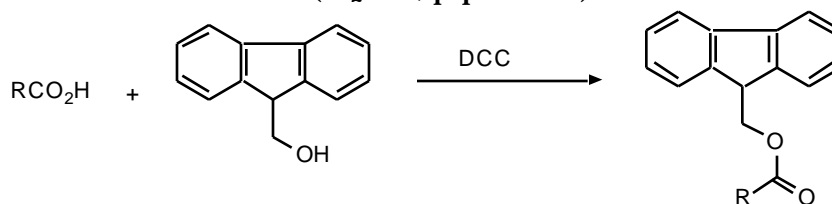
Esters
Alkyl Esters

formation: - Fisher esterification ($\text{RCOOH} + \text{R}'\text{OH} + \text{H}^+$)
 - 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)


9-Fluorenylmethyl Esters (Fm)
TL **1983**, 24, 281

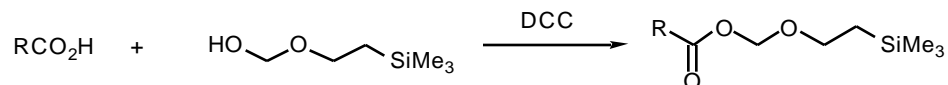
- cleaved with mild base (Et_2NH , piperidine)



2-(Trimethylsilyl)ethoxymethyl Ester (SEM)

 HCA **1977**, 60, 2711.

- Cleaved with Bu_4NF in DMF

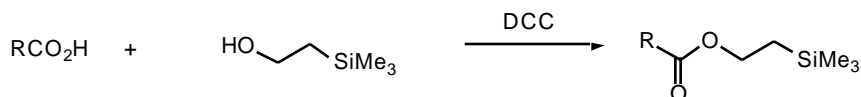


- Cleaved with $\text{MgBr}_2 \cdot \text{OEt}_2$ TL **1991**, 32, 3099.

2-(Trimethylsilyl)ethyl Esters

 JACS **1984**, 106, 3030

- cleaved with Fluoride ion



Haloesters

- cleaved with $\text{Zn}(0)$ dust or electrochemically



Benzyl Esters

 $\text{RCO}_2\text{H} + \text{PhCH}_2\text{OH} \rightarrow \text{RCO}_2\text{Bn}$
Formation: - DCC

- Acid chloride and benzyl alcohol

Cleavage: - Hydrogenolysis

- Na, NH_3

Diphenylmethyl Esters


Cleavage: - mild H_3O^+

- H_2 , Pd/C

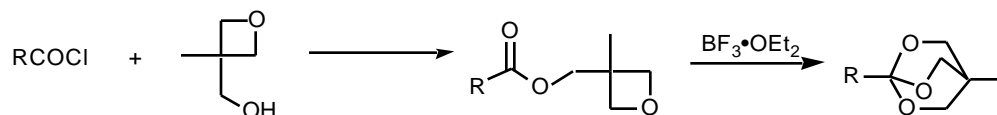
- $\text{BF}_3 \cdot \text{OEt}_2$

o-Nitrobenzyl Esters

- selective removed by photolysis

 Orthoesters Synthesis **1974**, 153

 Chem. Soc. Rev. **1987**, 75

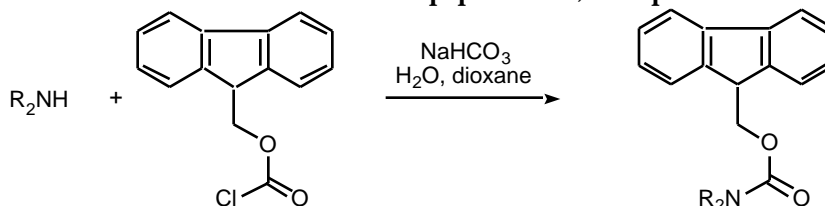
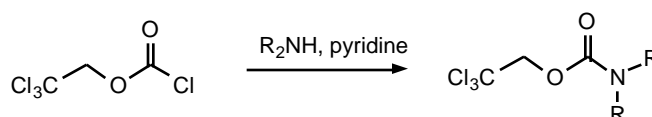
 TL **1983**, 24, 5571


- Stable to base; cleaved with mild acid

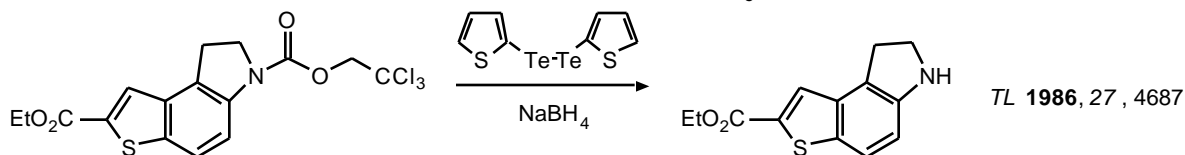
Amines
Carbamates
9-Fluorenylmethyl Carbamate (Fmoc)

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

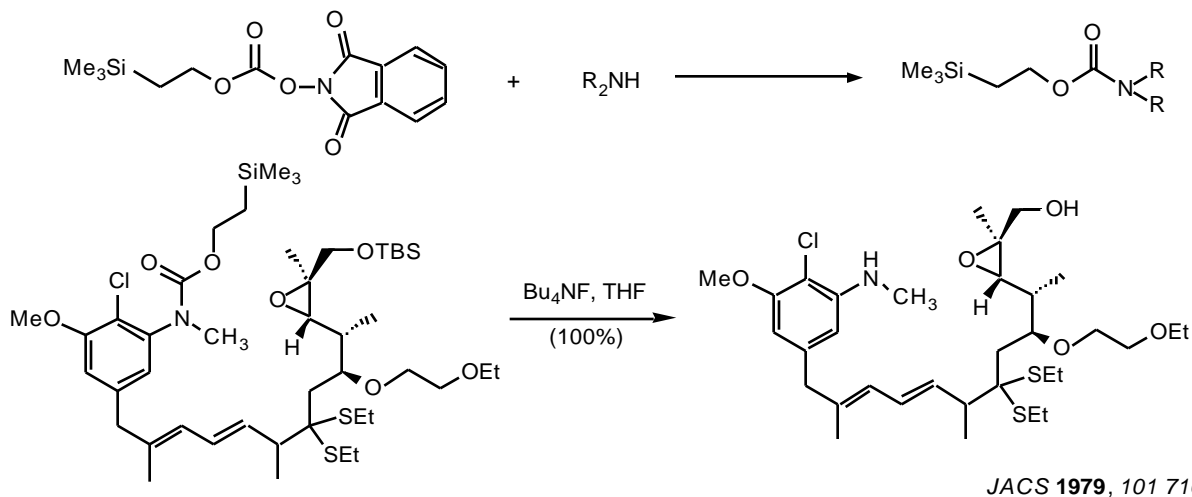
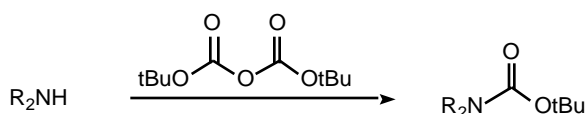
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine


2,2,2-Trichloroethyl Carbamate


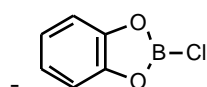
- Cleaved with zinc dust or electrochemically.


2-Trimethylsilylethyl Carbamate (Teoc)

- cleaved with fluoride ion.

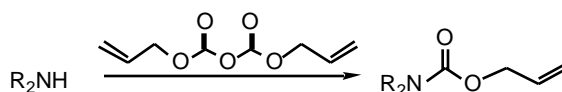

t-Butyl Carbamate (BOC)

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

- TMS-I

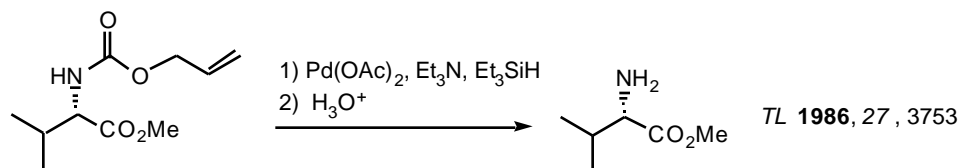

 TL **1985**, 26, 1411

Allyl Carbamate (Alloc)

 TL **1986**, 27, 3753



- removed with Pd(0) and a reducing agent (Bu₃SnH, Et₃SiH, HCO₂H)



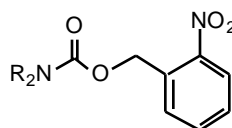
Benzyl Carbamate (Cbz)



Cleavage:

- Hydrogenolysis
- PdCl₂, Et₃SiH
- TMS-I
- BBr₃
- hν (254 nm)
- Na/ NH₃

m-Nitrophenyl Carbamate
JOC 1974, 39, 192

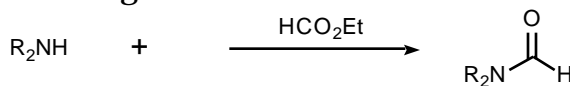


- removed by photolysis

Amides

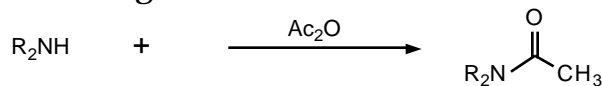
Formamides

- removed with strong acid



Acetamides

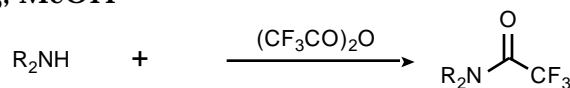
- removed with strong acid



Trifluoroacetamides

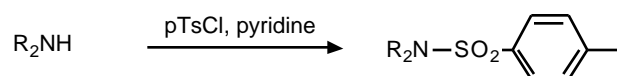
Cleavage:

- base (K₂CO₃, MeOH, reflux)
- NH₃, MeOH

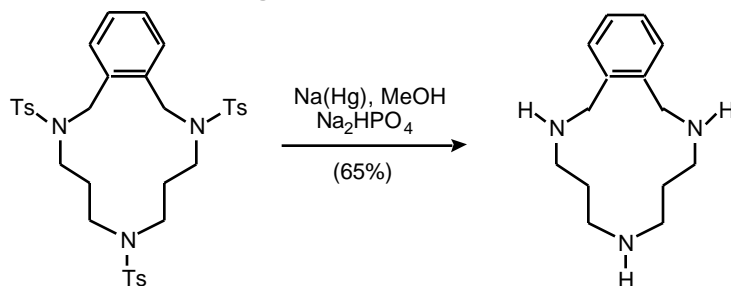


Sulfonamides

p-Toluenesulfonyl (Ts)

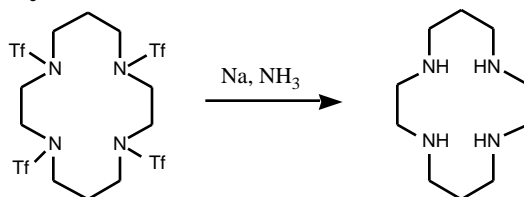


Cleavage: - Strong acid
 - sodium Naphthalide
 - Na(Hg)



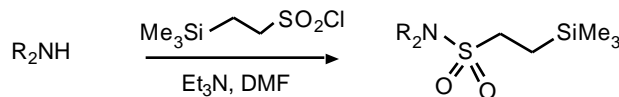
JOC 1989, 54, 2992

Trifluoromethanesulfonyl

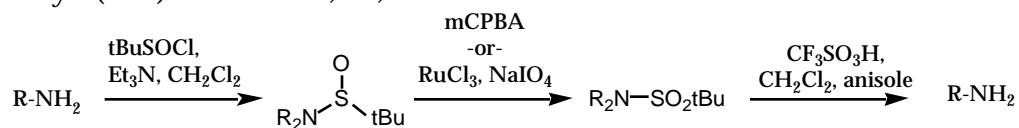


JOC 1992, 33, 5505

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



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

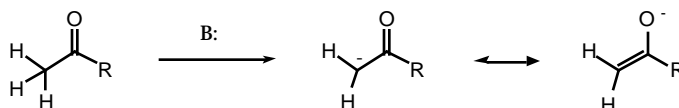


Carbon- Carbon Bond Formation

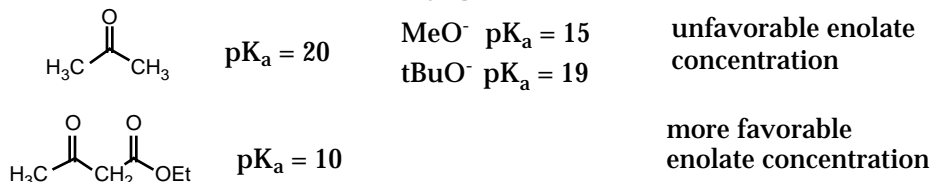
- Alkylation of enolates, enamines and hydrazones
C&S: Chapt. 1, 2.1, 2.2 problems Ch 1: 1; 2; 3, 7; 8a-d; 9; 14 Ch. 2: 1; 2; 4)
Smith: Chapt. 9
- Alkylation of heteroatom stabilized anions C&S :Chapt. 2.4 - 2.6)
- Umpolung Smith: Chapt. 8.6
- Organometallic Reagents
C&S: Chapt. 7, 8, 9 problems ch 7: 1; 2; 3, 6; 13 Ch. 8: 1; 2
Smith: Chapt. 8
- 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.

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



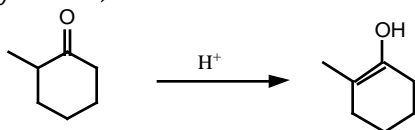
- Base is chosen so as to favor enolate formation. Acidity of C-H bond must be greater (lower pK_a value) than that of the conjugate acid of the base (C&S table 1.1, pg 3)



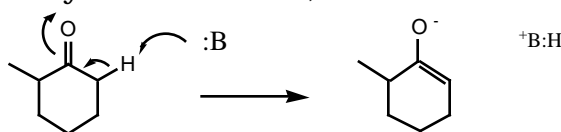
- Common bases: NaH, EtONa, tBuOK, NaNH₂, LiNiPr₂, M N(SiMe₃)₂, Na CH₂S(O)CH₃

Enolate Formation:

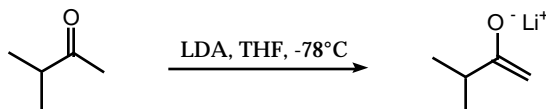
- H⁺ Catalyzed (thermodynamic)



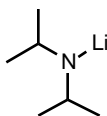
- Base induced (thermodynamic or kinetic)

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

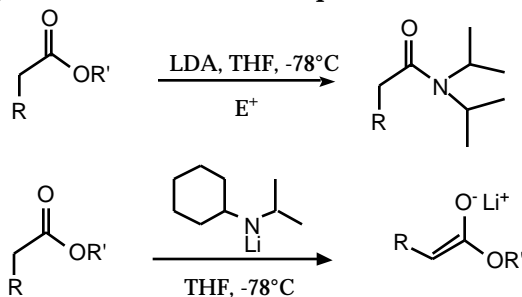
- Kinetic enolate- deprotonation of the most accessible proton (relative rates of deprotonation). Reaction done under essentially irreversible conditions.



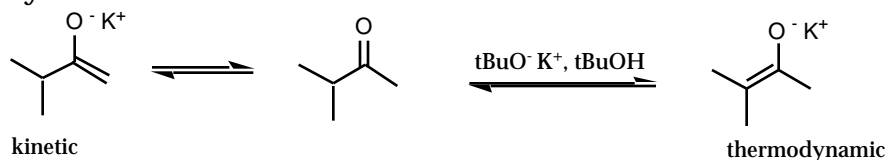
typical conditions: strong hindered (non-nucleophilic) base such as LDA
 R_2NH $pK_a = \sim 30$



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

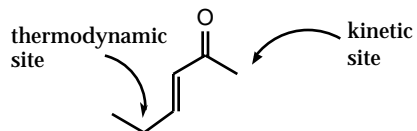


- Thermodynamic Enolate- Reversible deprotonation to give the most stable enolate: more highly substituted C=C of the enol form



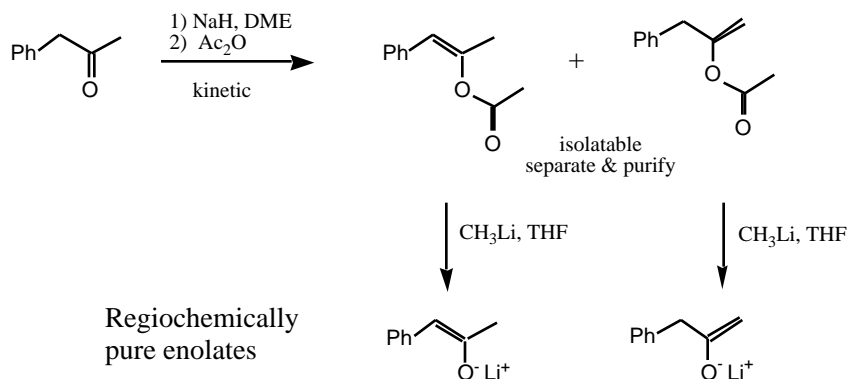
typical conditions: $RO^- M^+$ in ROH, protic solvent allows reversible enolate formation. Enolate in small concentration (pK_a of ROH = 15-18 range)

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

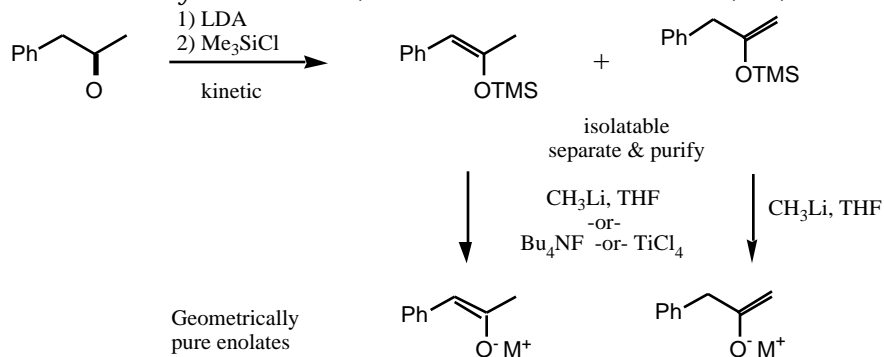


Trapping of Kinetic Enolates

- enol acetates

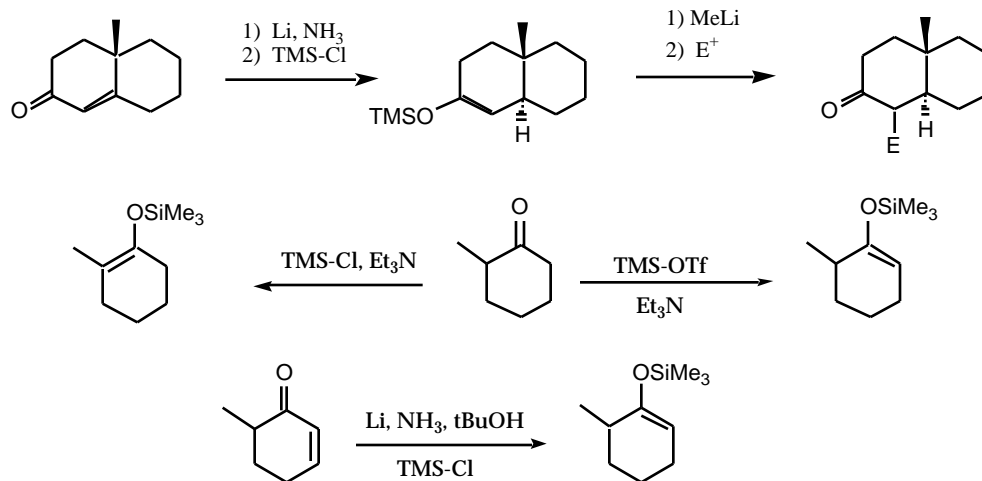


- silyl enolethers *Synthesis* **1977**, **91**. *Acc. Chem. Res.* **1985**, **18**, **181**.

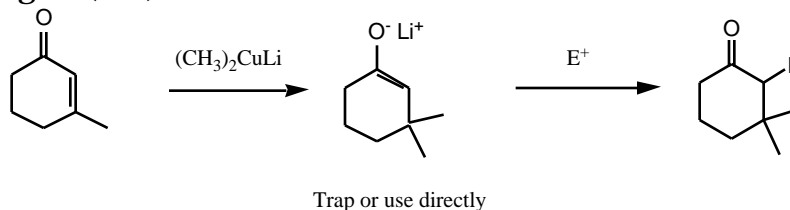


- tetraalkylammonium enolates- "naked" enolates
- TMS silyl enol ethers are labile: can also use Et_3Si -, iPr_3Si - etc.
- Silyl enol ether formation with $\text{R}_3\text{SiCl} + \text{Et}_3\text{N}$ gives thermodynamic silyl enol ether

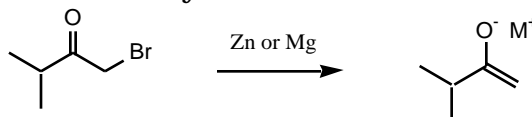
- From Enones



- From conjugate (1,4-) additions



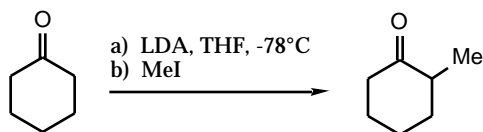
- From reduction of -halo carbonyls



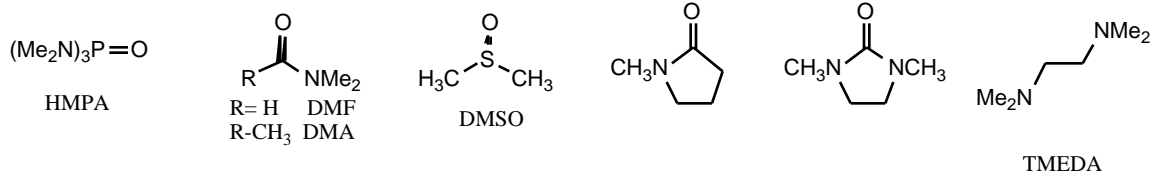
Alkylation of Enolates (condensation of enolates with alkyl halides and epoxides)

Comprehensive Organic Synthesis **1991**, vol. **3**, **1**.

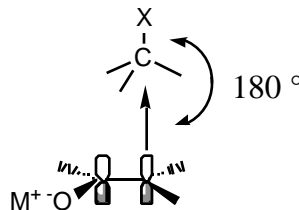
- 1° alkyl halides, allylic and benzylic halides work well
- 2° alkyl halides can be troublesome
- 3° alkyl halides don't work



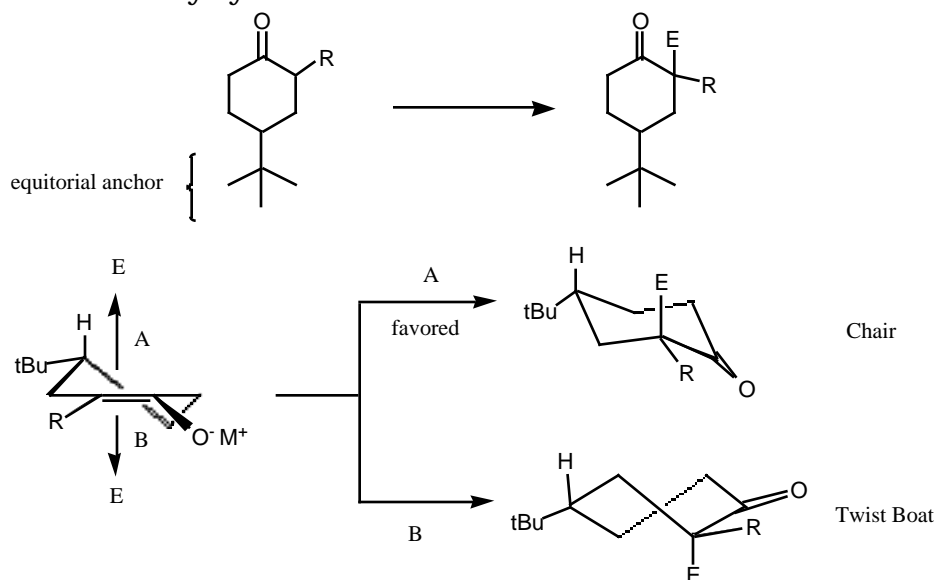
- Rate of alkylation is increased in more polar solvents (or addition of additive)



Mechanism of Enolate Alkylation: S_N2 reaction, inversion of electrophile stereochemistry

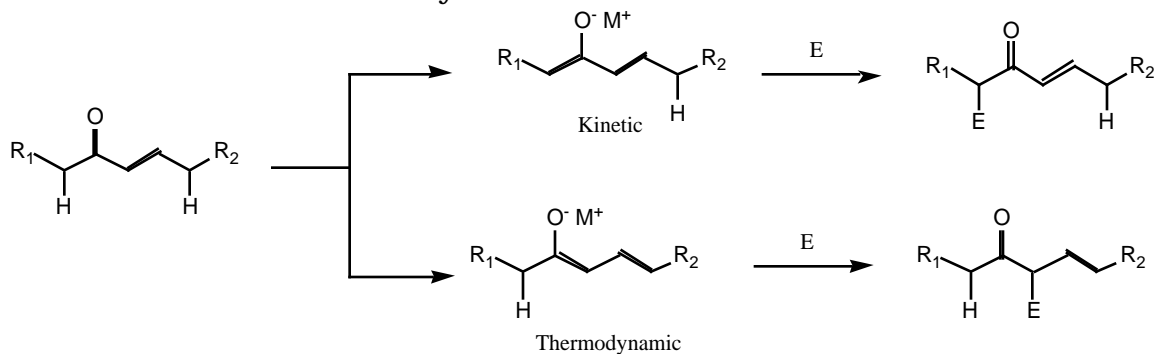


Alkylation of 4-t-butylcyclohexanone:

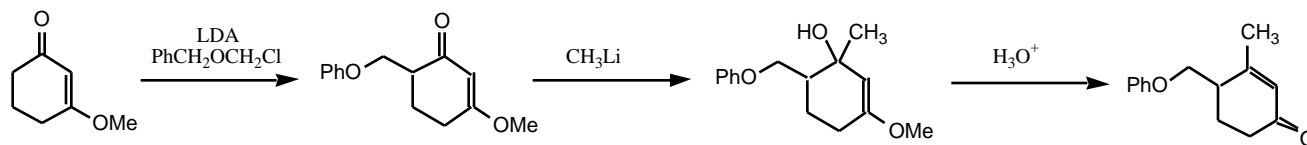


on cyclohexanone enolates, the electrophile approaches from an "axial" trajectory. This approach leads directly into a chair-like product. "Equatorial approach leads to a higher energy twist-boat conformation.

Alkylation of α,β -unsaturated carbonyls



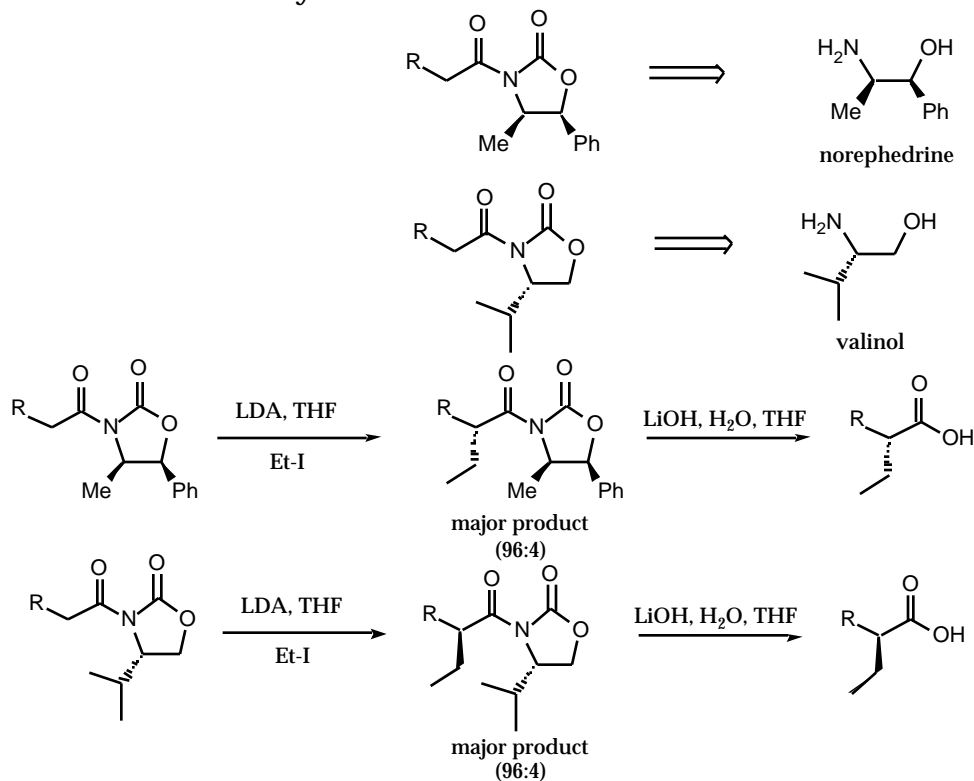
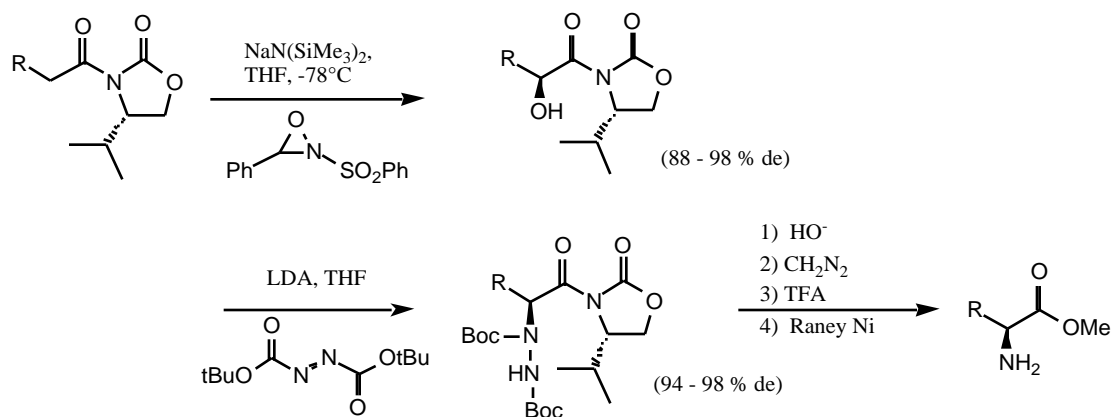
Stork-Danheiser Enone Transposition:

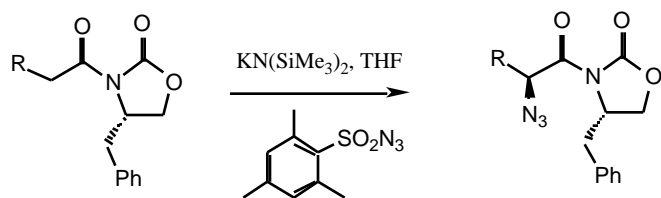
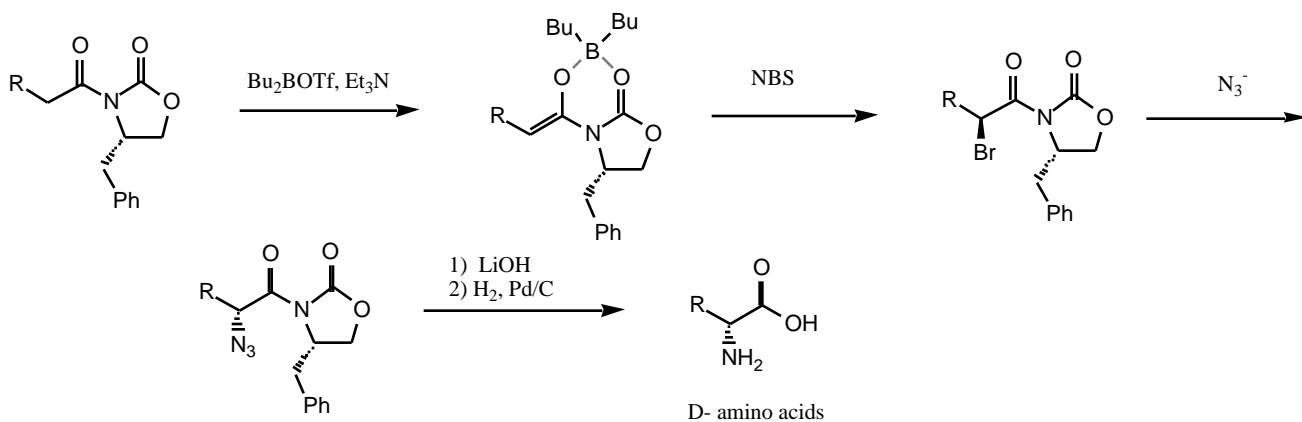
- overall α -alkylation of an α,β -unsaturated ketone*J. Org. Chem.* **1995**, *60*, 7837.

Chiral enolates- Chiral auxiliaries.

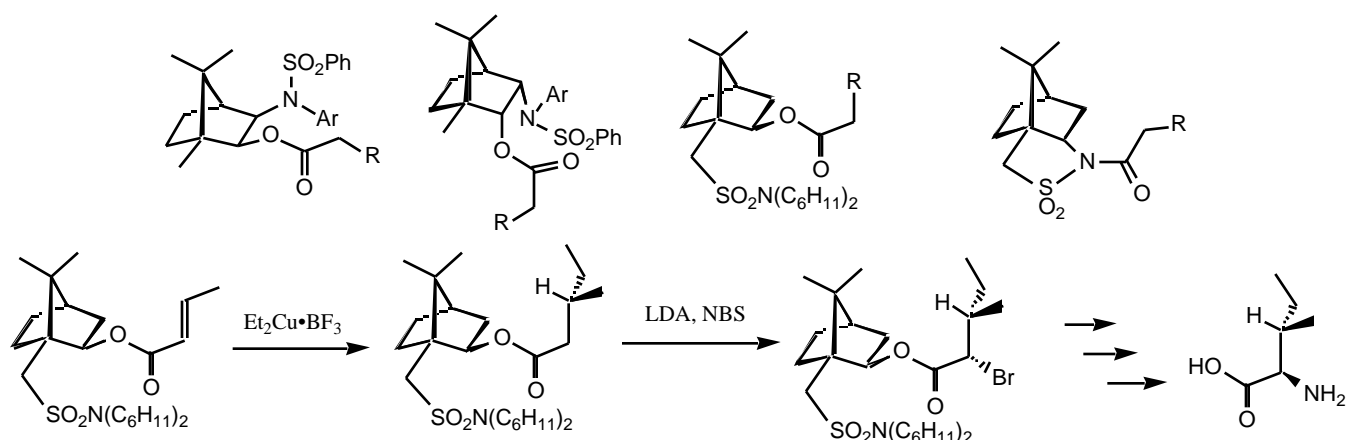
D.A. Evans *JACS* **1982**, *104*, 1737; *Aldrichimica Acta* **1982**, *15*, 23.*Asymmetric Synthesis* **1984**, *3*, 1.

- N-Acyl oxazolidinones

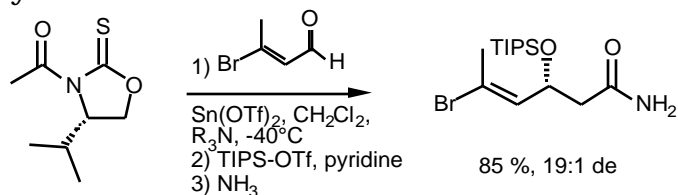
Complimentary Methods
for enantiospecific alkylationsDiastereoselectivity: 92 - 98 %
for most alkyl halidesEnolate Oxidation *Chem. Rev.* **1992**, *92*, 919.



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

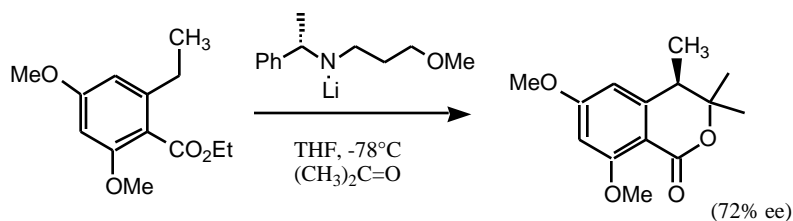


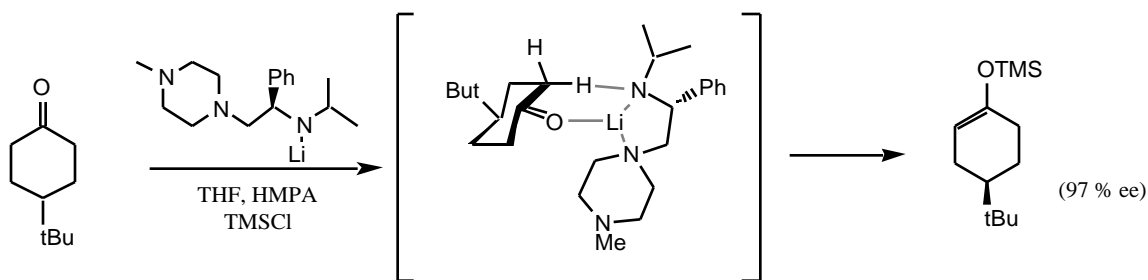
Asymmetric Acetate Aldol



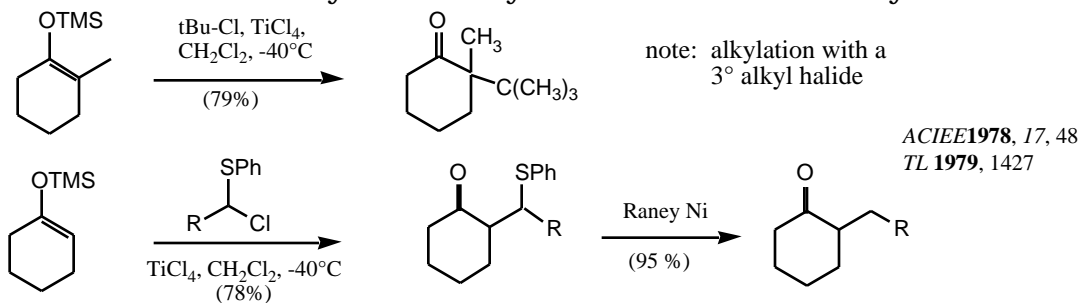
J. Am. Chem. Soc. **1998**, 120, 591
J. Org. Chem. **1986**, 51, 2391

Chiral lithium amide bases





Lewis Acid Mediated Alkylation of Silyl Enolethers- SN1 like alkylations

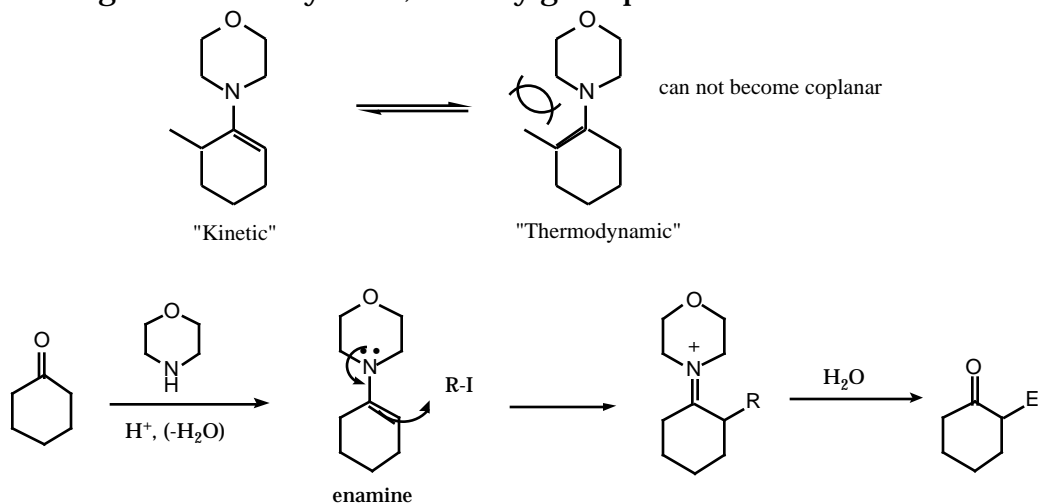


Enamines

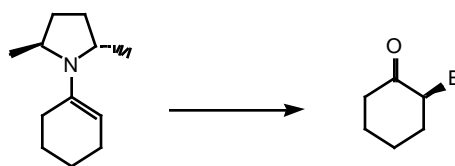
Gilbert Stork

Tetrahedron **1982**, 38, 1975, 3363.

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

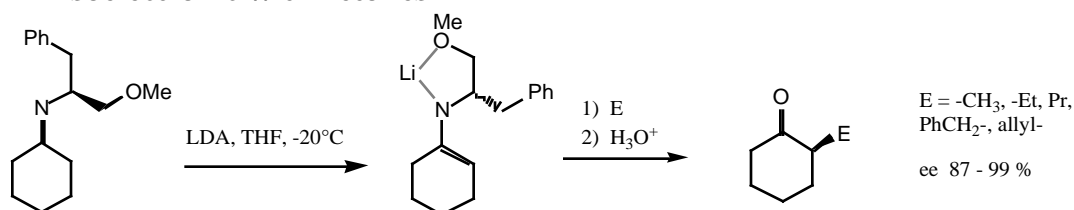


-Chiral enamines

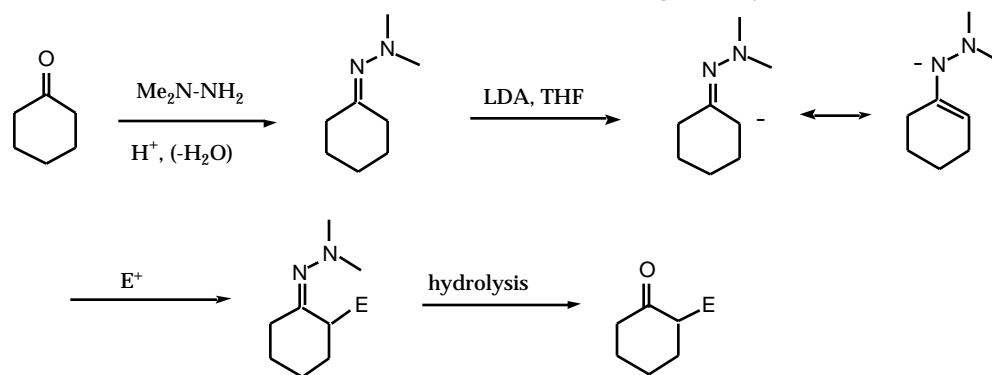


Imines

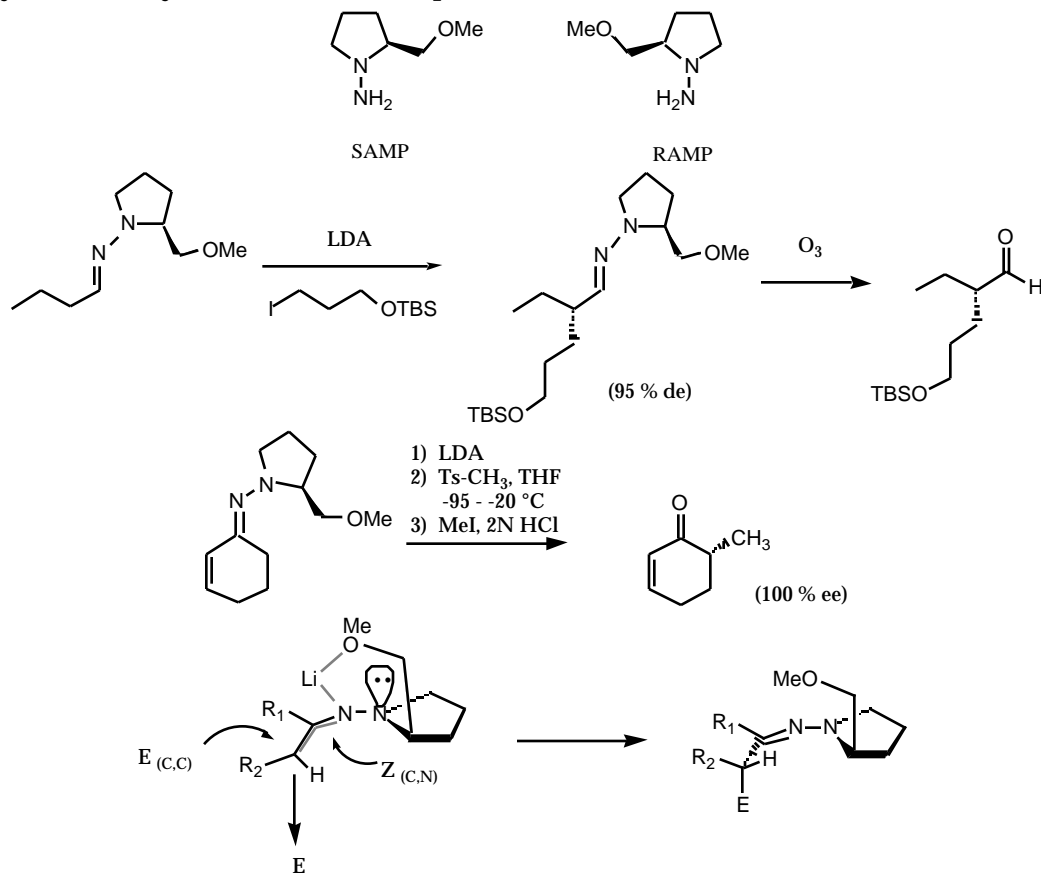
Isoelectronic with ketones



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

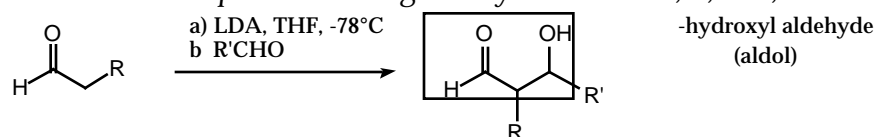


- Hydrazone anions are more reactive than the corresponding ketone or aldehyde enolate.
- Drawback: can be difficult to hydrolyze.
- Chiral hydrazones for asymmetric alkylations (RAMP/SAMP hydrazones- D. Enders "Asymmetric Synthesis" vol 3, chapt 4, Academic Press; **1983**)



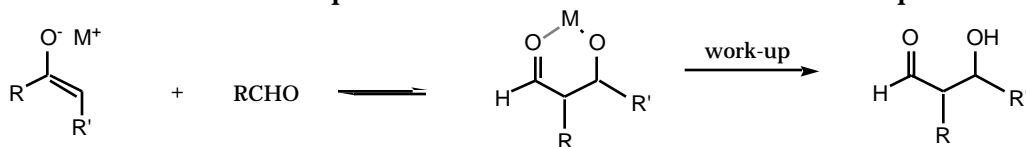
Aldol Condensation

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

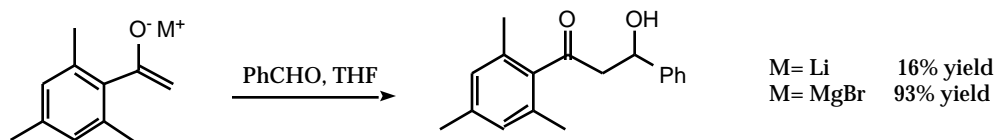


- The effects of the counterion on the reactivity of the enolates can be important
 Reactivity $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < \text{R}_4\text{N}^+$ addition of crown ethers

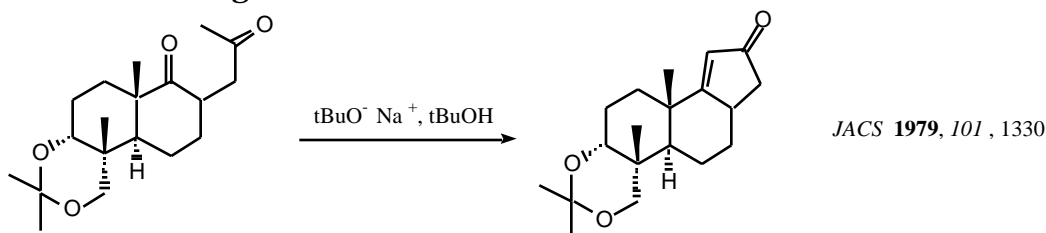
- The aldol reaction is an equilibrium which can be "driven" to completion.



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

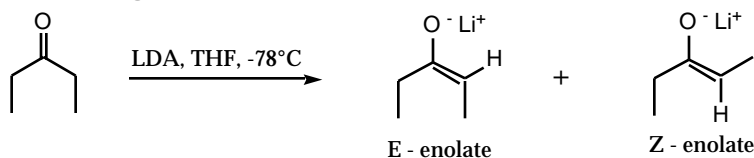


- Dehydration of the intermediate α -alkoxy- or α -hydroxy ketone can also serve to drive the reaction to the right.

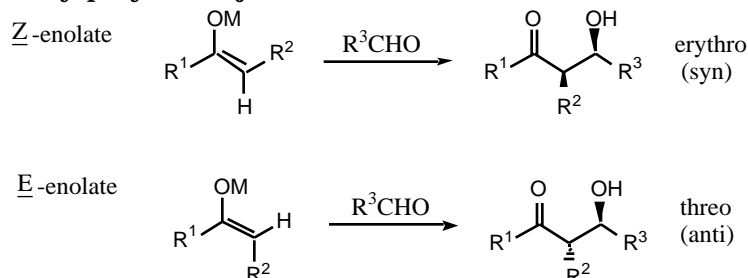


Enolate Geometry

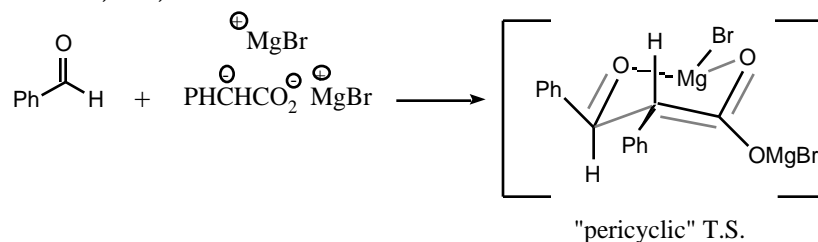
- two possible enolate geometries



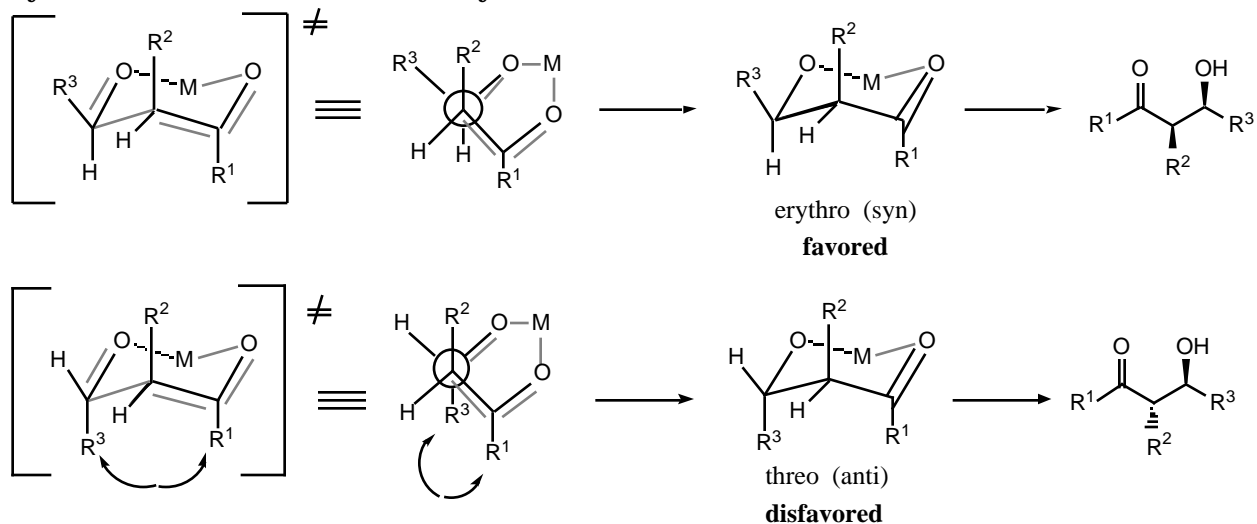
- enolate geometry plays a major role in stereoselection.



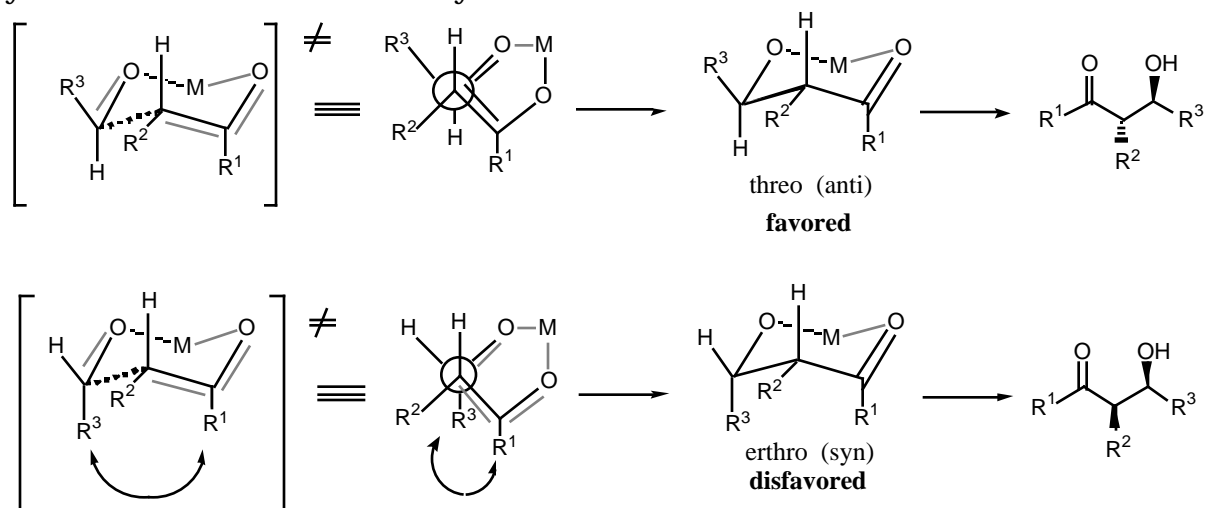
- Zimmerman-Traxler Transition State : Ivanov condensation
JACS **1957**, 79, 1920.



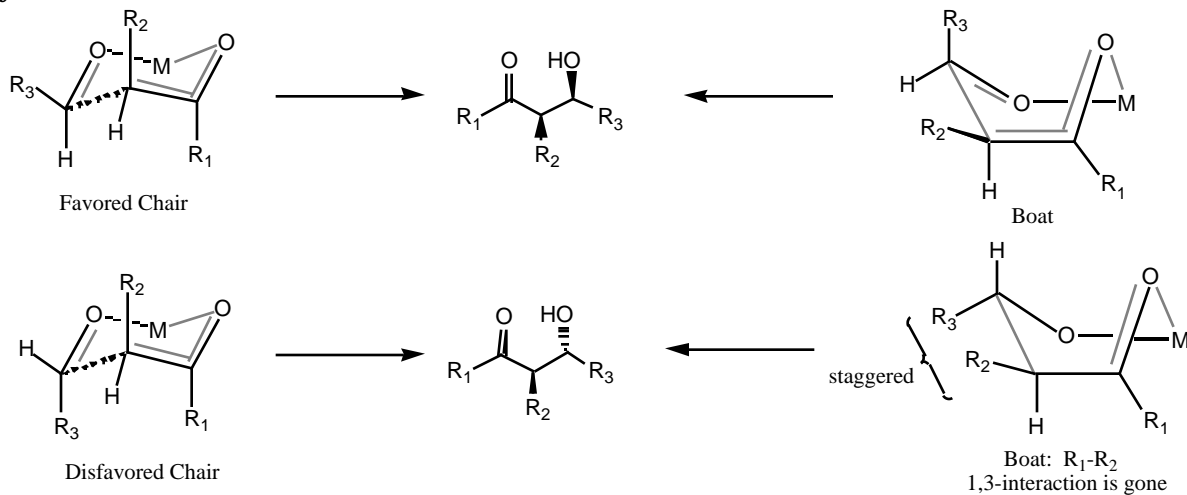
Analysis of Z-enolate stereoselectivity



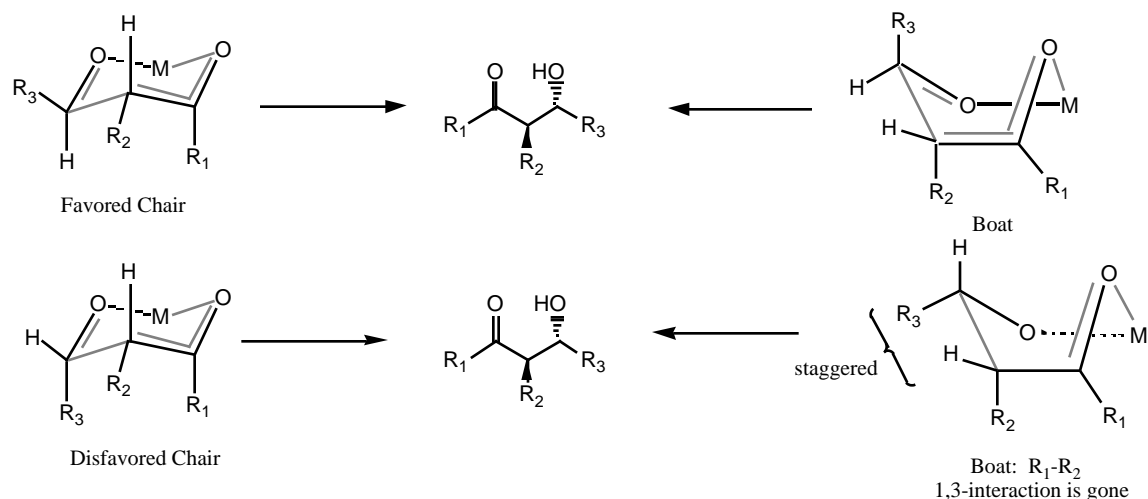
Analysis of E-enolate stereoselectivity



Analysis of Boat Transition State for Z-Enolates

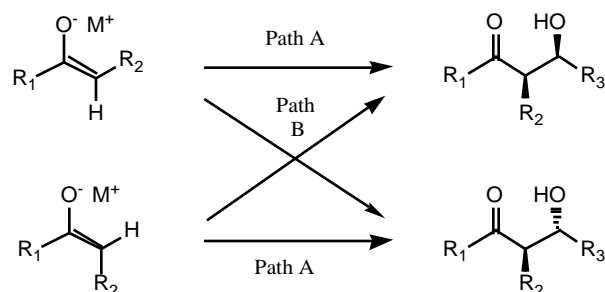


Analysis of Boat Transition State for E-Enolates



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 dominant role in kinetic diastereoselection.



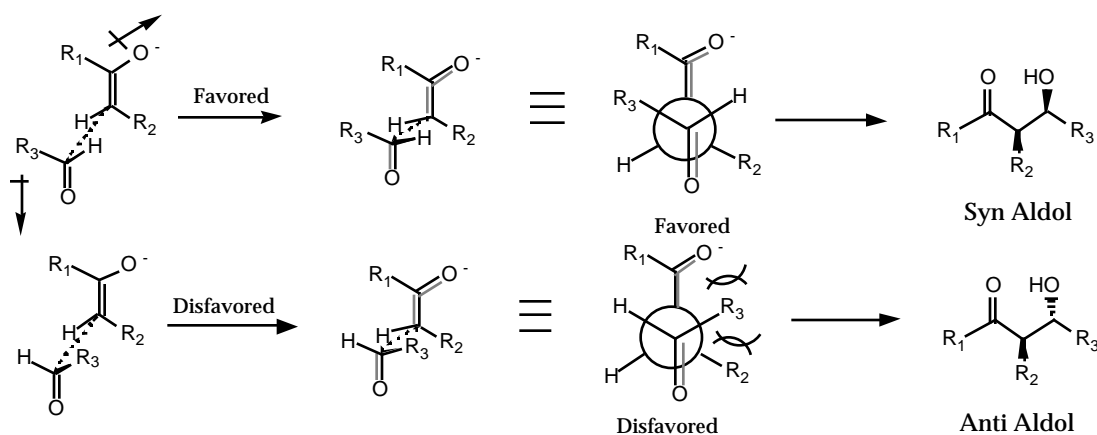
When R_1 is the dominant steric influence, then path A proceeds. If R_2 is the dominant steric influence then path B proceeds.

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

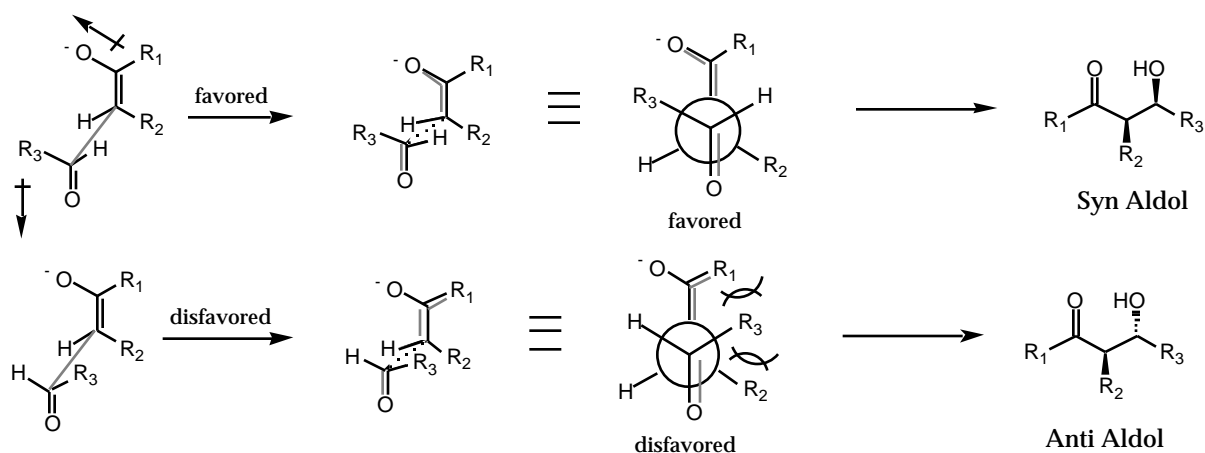
Noyori "Open" Transition State for non-Chelation Control Aldols

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:

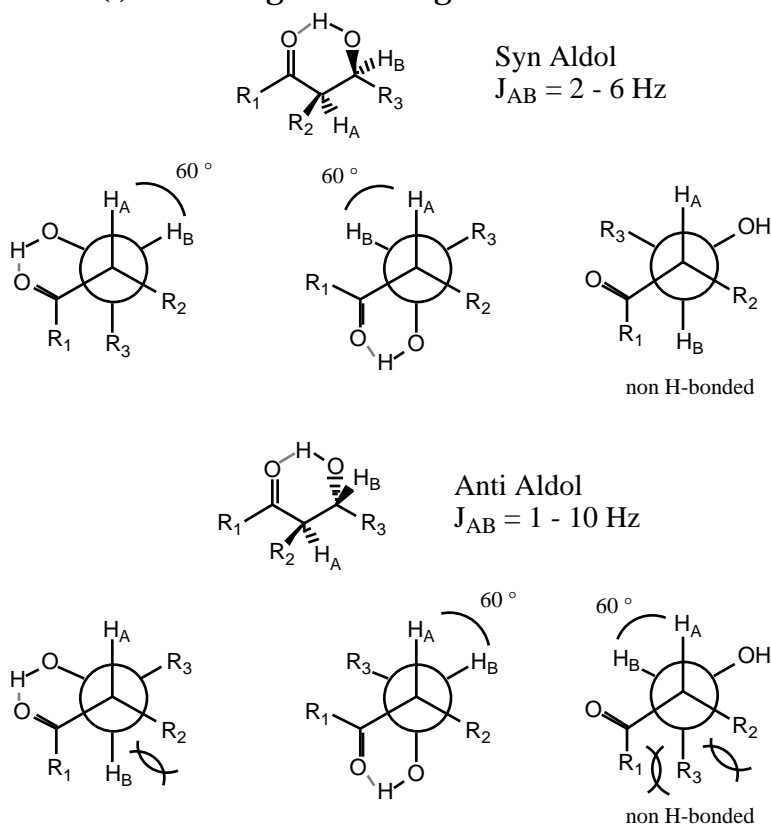


E- Enolate:



NMR Stereochemical Assignment.

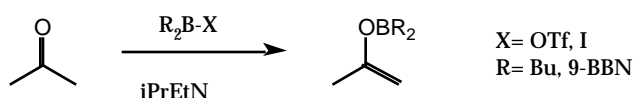
Coupling constants (J) are a weighted average of various conformations.

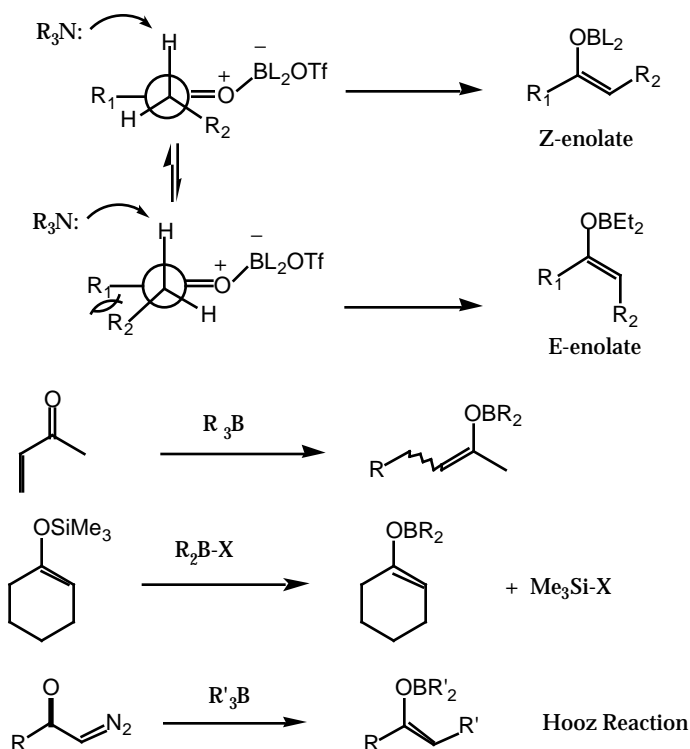


Boron Enolates: *Comprehensive Organic Synthesis* **1991**, 2, 239. *Organic Reactions* **1995**, 46, 1; *Organic Reactions* **1997**, 51, 1. *OPPI* **1994**, 26, 3.

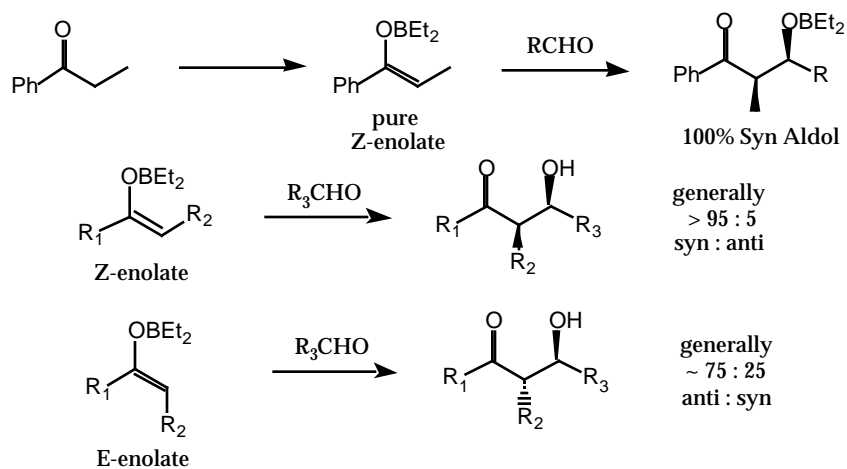
- Alkali & alkaline earth metal enolates tend to be aggregates- complicates stereoselection models.
- Boron enolates are monomeric and homogeneous
- B-O and B-C bonds are shorter and stronger than the corresponding Li-O and Li-C bonds (more covalent character)- therefore tighter more organized transition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

Generation of Boron Enolates:





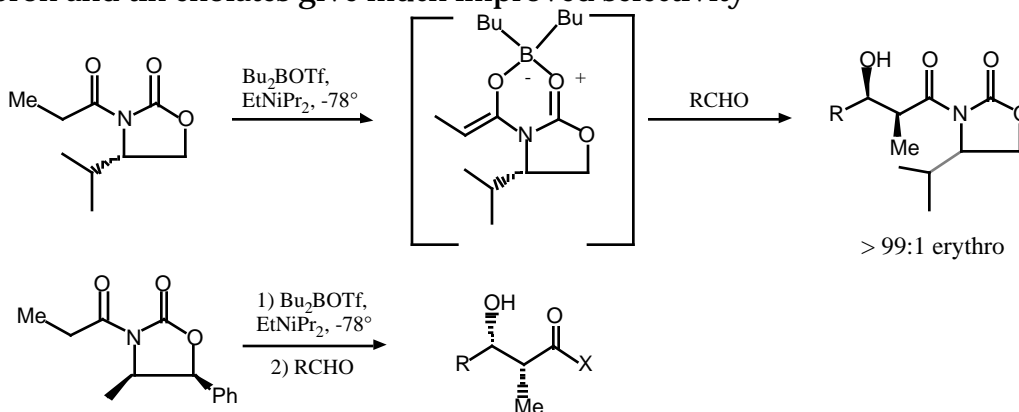
Diastereoselective Aldol Condensation with Boron Enolates

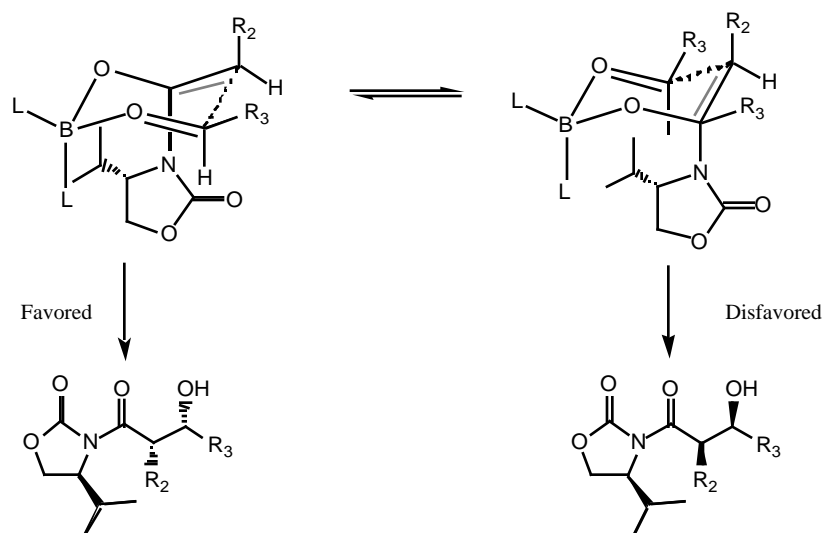
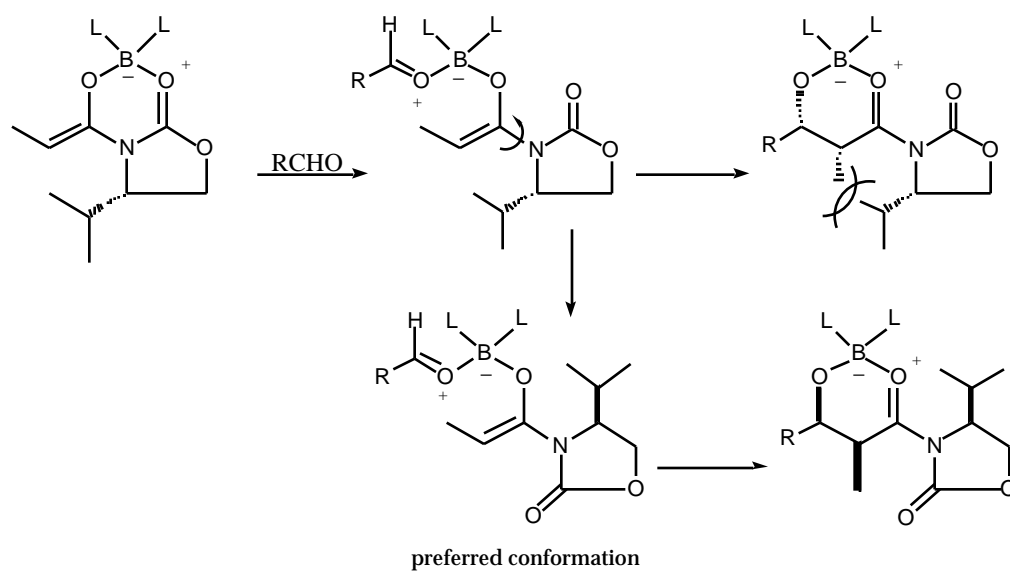


Asymmetric Aldol Condansations with Chiral Auxiliaries-

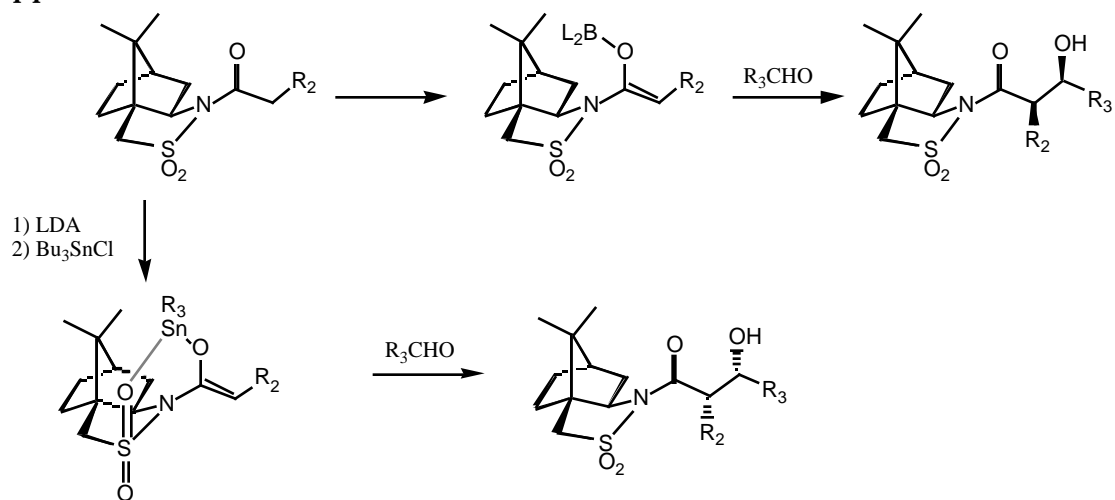
D.A. Evans et al. *Topics in Stereochemistry*, **1982**, 13, 1-115.

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

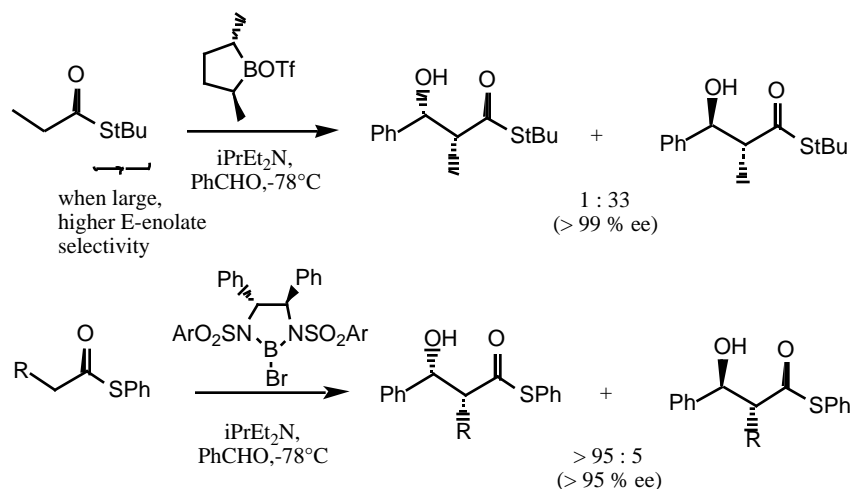




Oppolzer Sultam



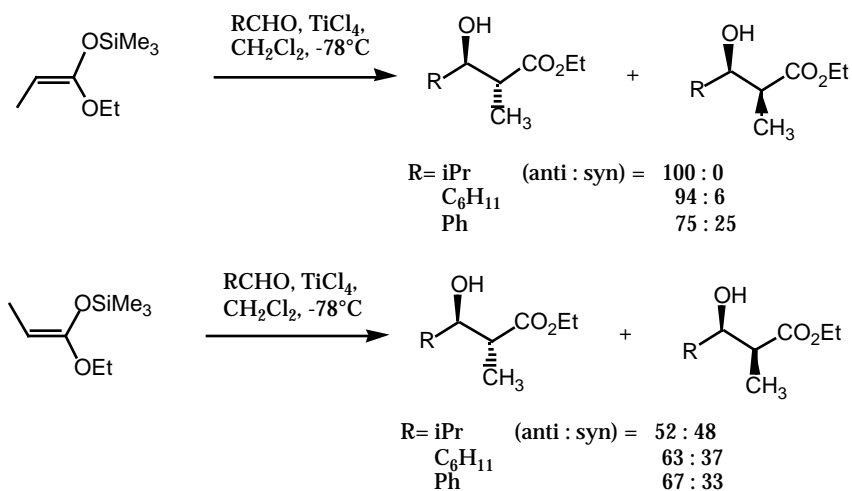
Chiral Boron



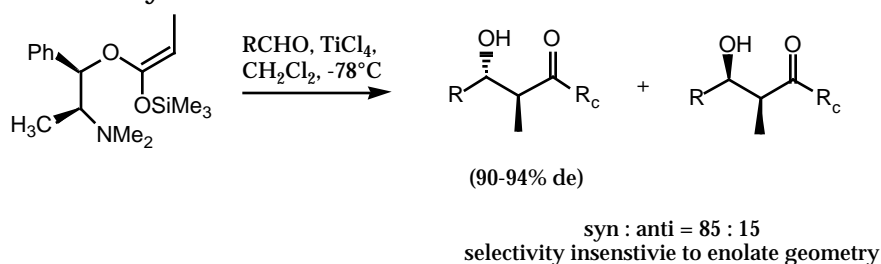
- In general, syn aldol products are achievable with high selectivity, anti aldols are more difficult

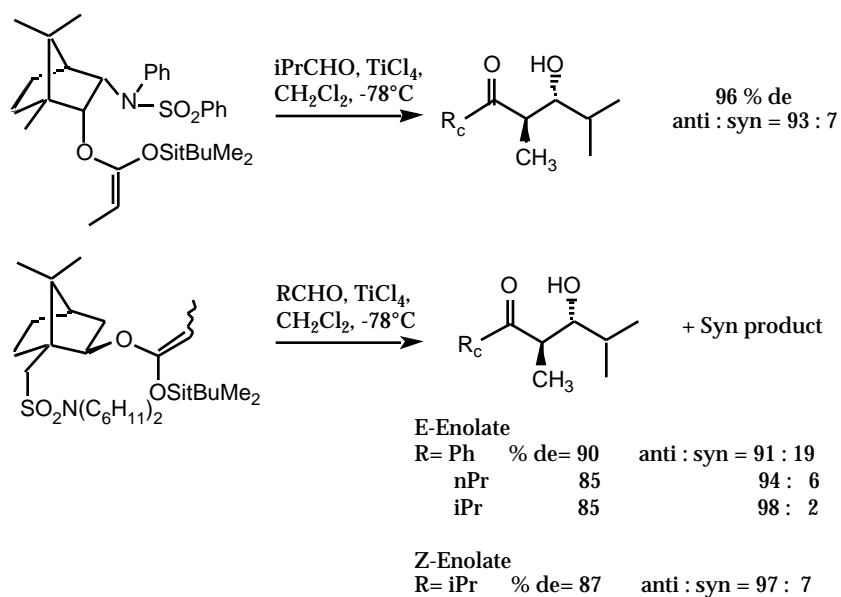
Mukaiyama-Aldol- Silyl Enol Ethers as an enolate precursors.

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.

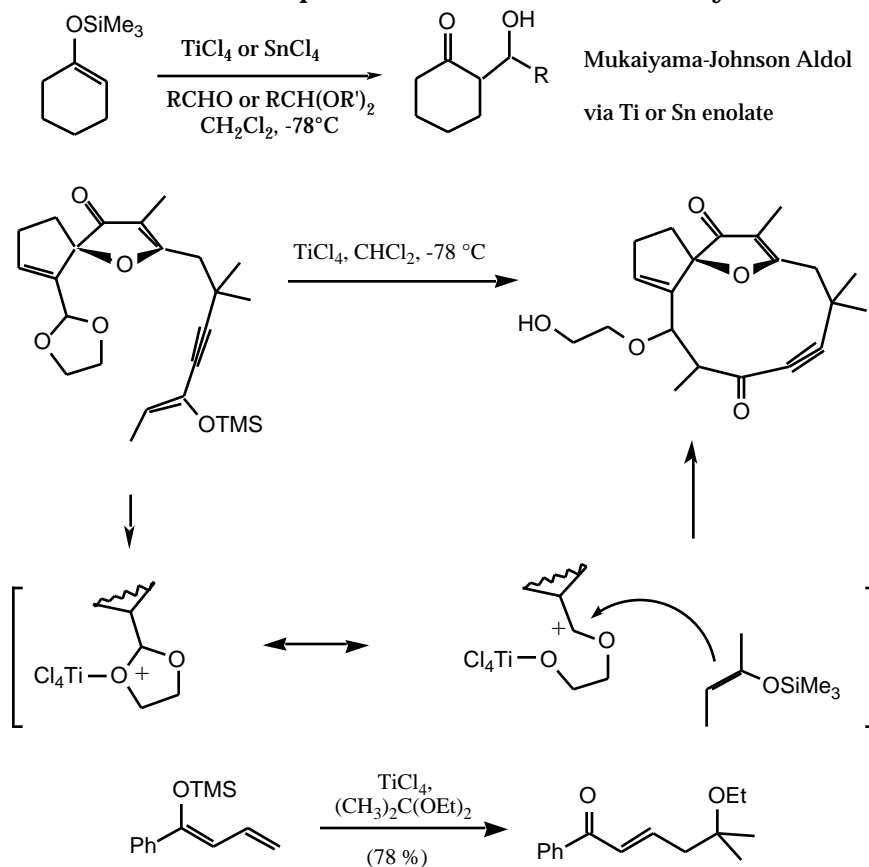


Asymmetric Mukiyama Aldol:



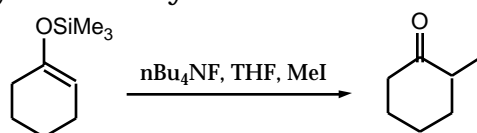


Mukaiyama-Johnson Aldol- Lewis acid promoted condensation of silyl enol ethers with acetals:

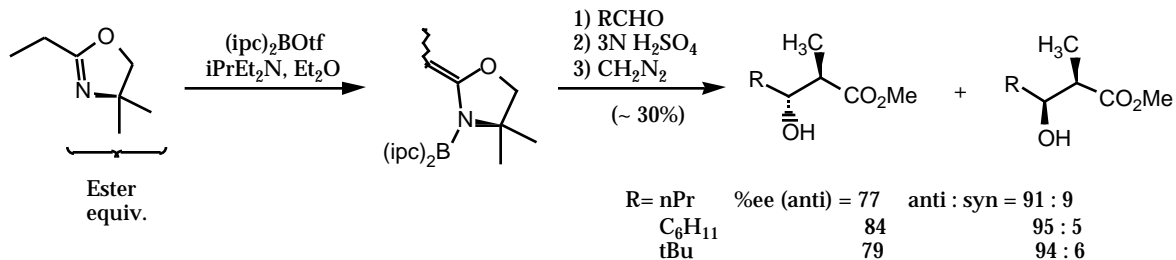


Fluoride promoted alkylation of silyl enol ethers

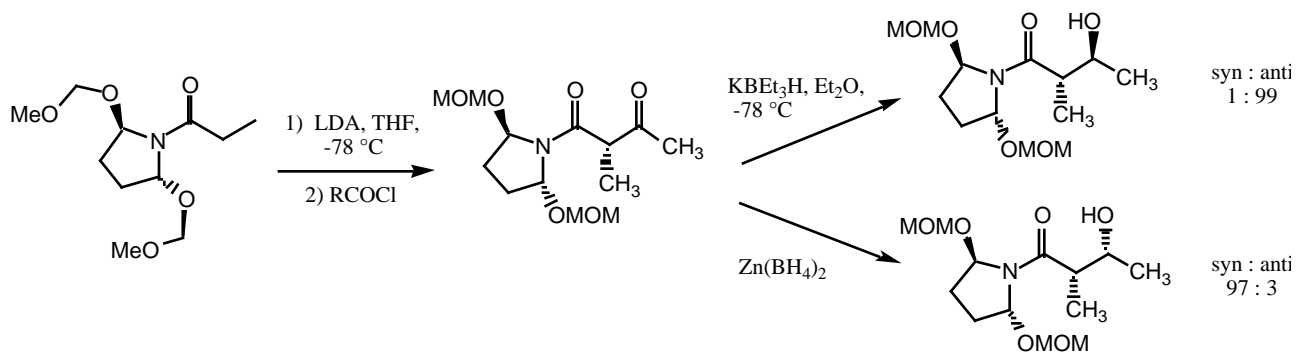
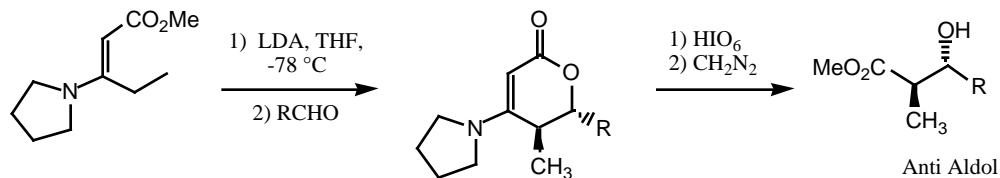
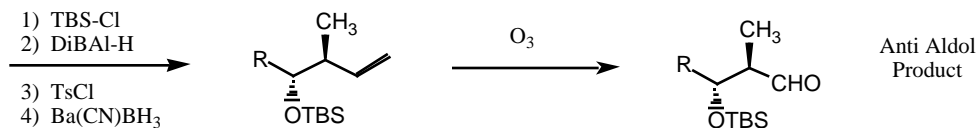
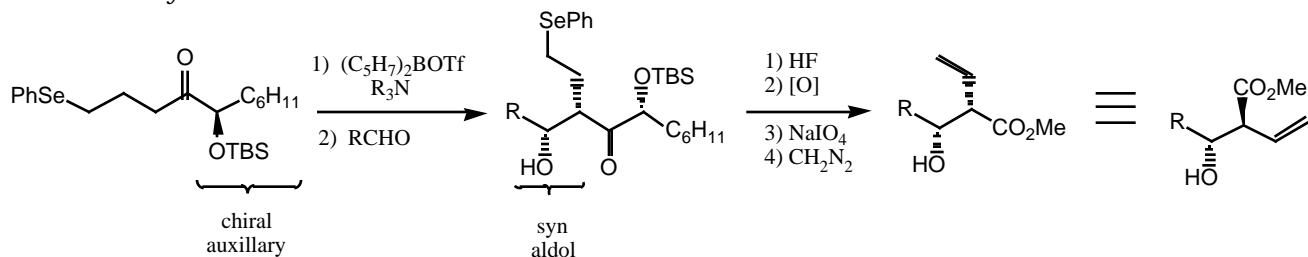
Acc. Chem. Res. **1985**, 18, 181



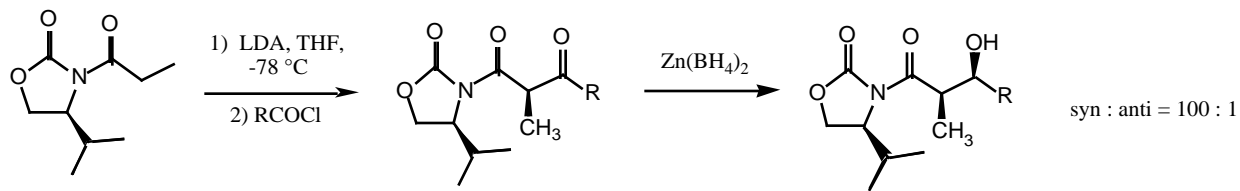
Meyer's Oxazolines:



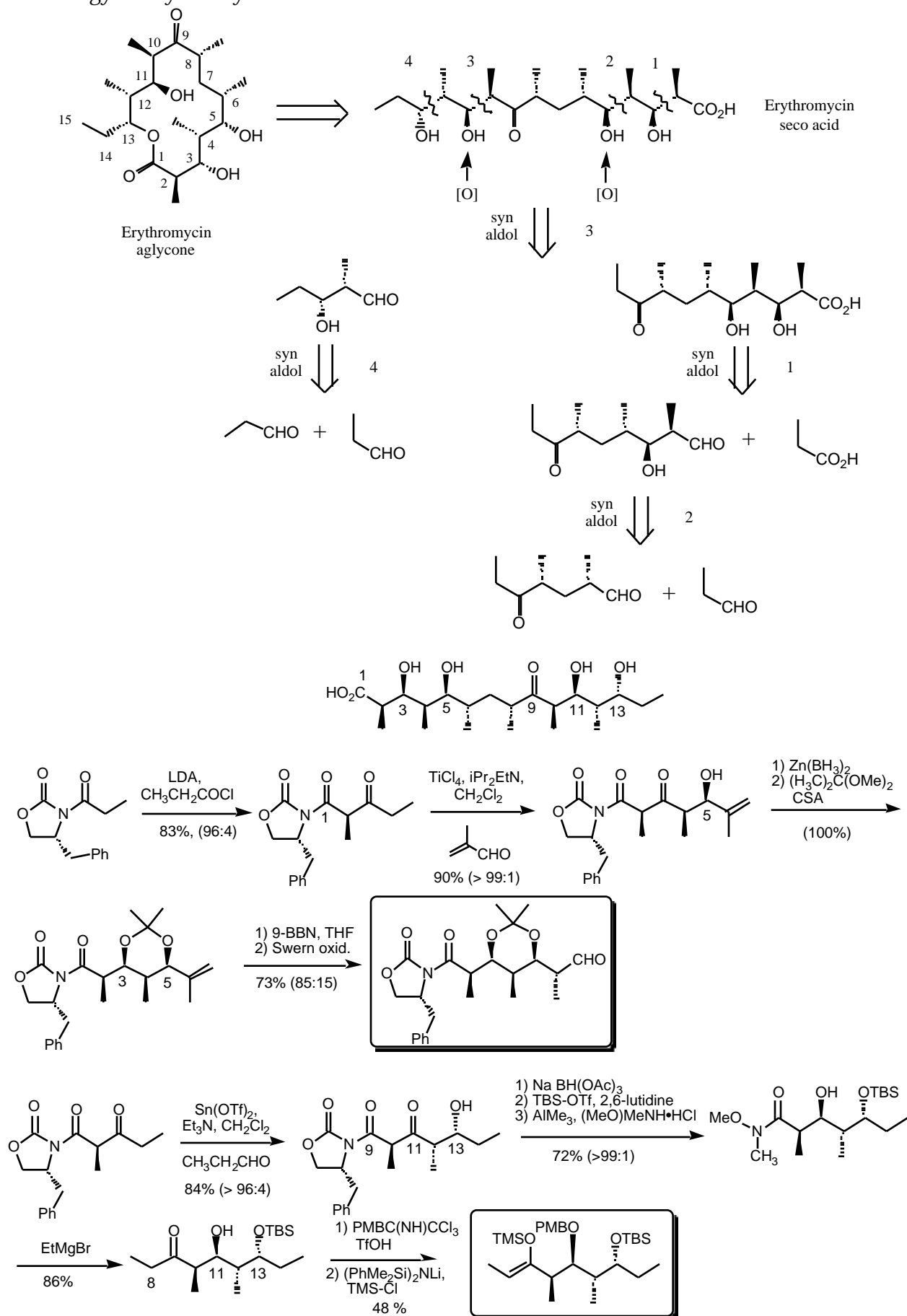
Anti-Aldols by Indirect Methods:

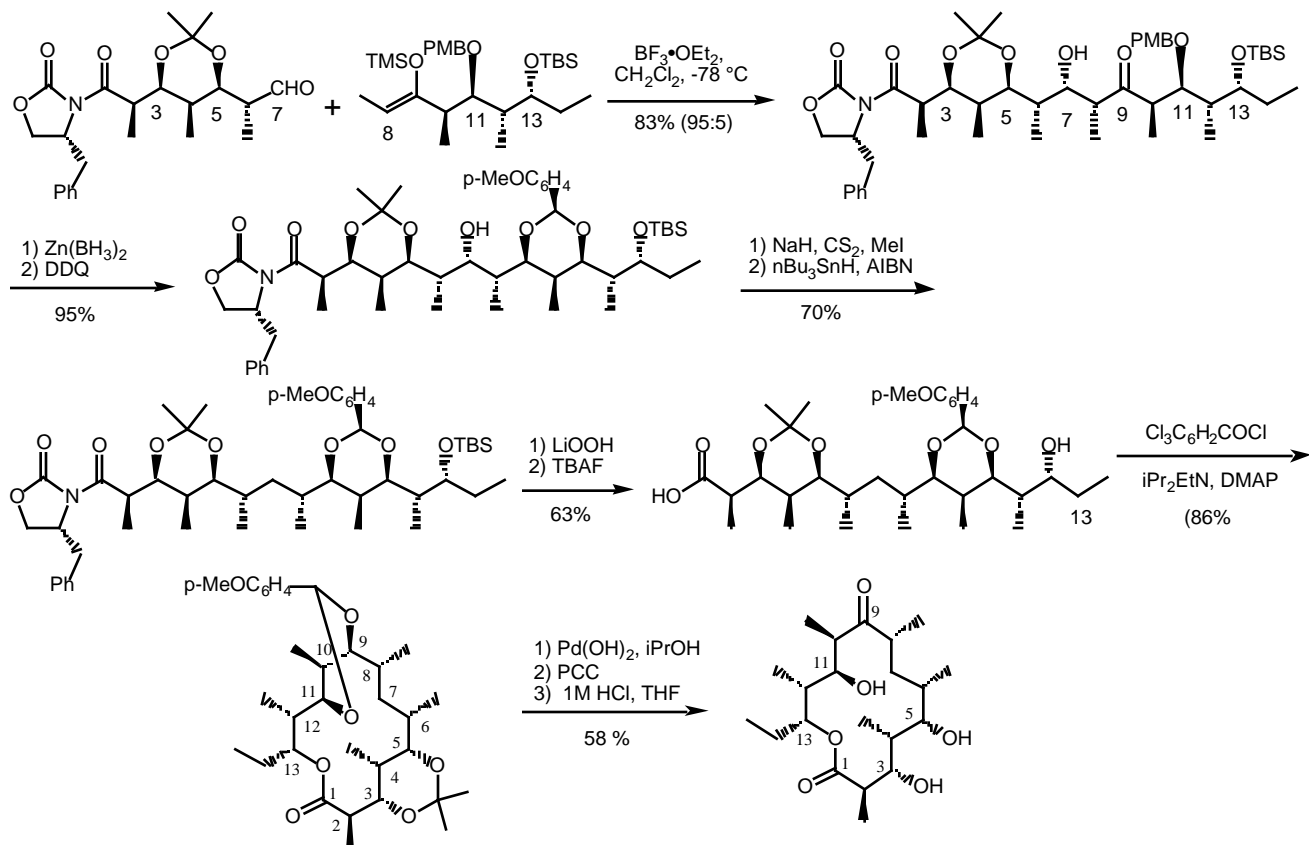
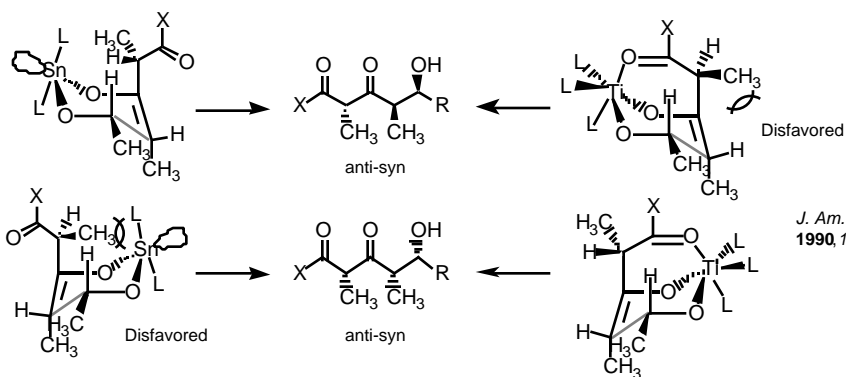


Syn Aldols by Indirect Methods:



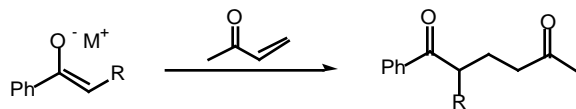
Aldol Strategy to Erythromycin:





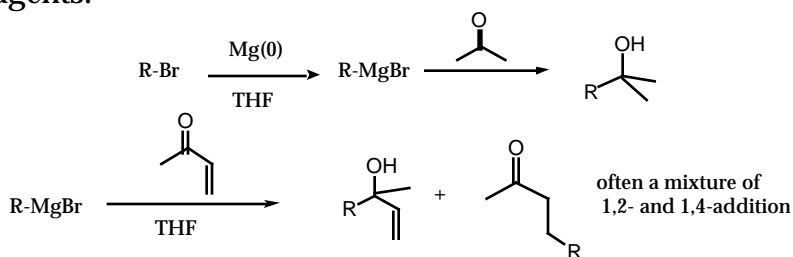
Michael Addition

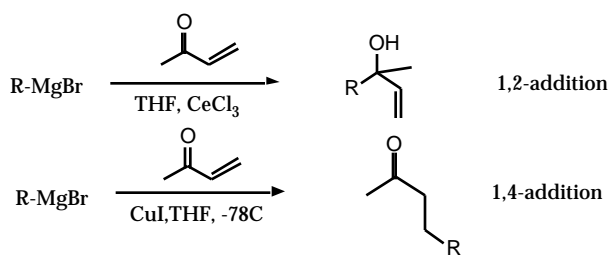
- 1,4-addition of an enolate to an α,β -unsaturated carbonyl to give 1,5-dicarbonyl compounds



Organometallic Reagents

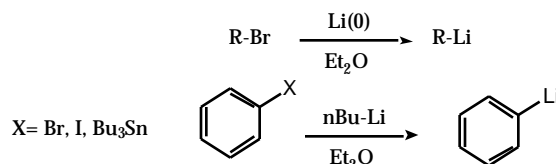
Grignard reagents:





Organolithium reagents

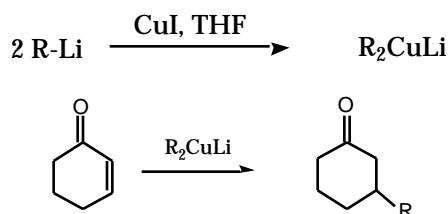
- usually gives 1,2-addition products
- alkyllithium are prepared from lithium metal and the corresponding alkyl halide
- vinyl or aryl- lithium are prepared by metal-halogen exchange from the corresponding vinyl or aryl- halide or trialkyl tin with n-butyl, sec-butyl or t-butyl lithium.



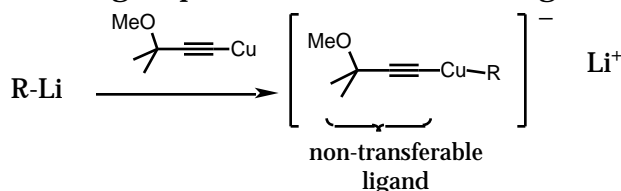
Organocuprates

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

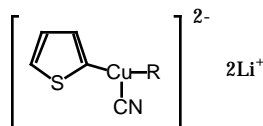
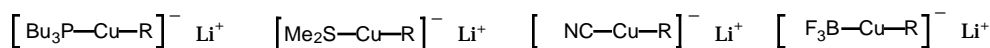
- selective 1,4-addition to α,β -unsaturated carbonyls



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



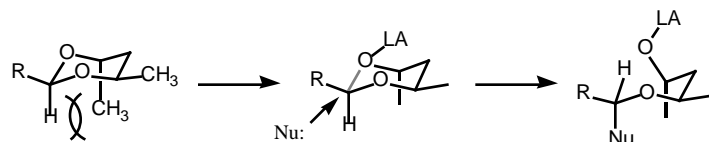
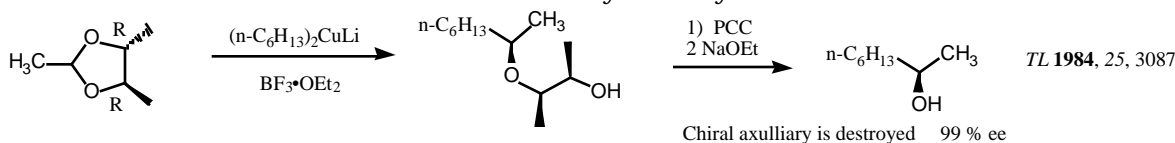
Other non transferable ligands

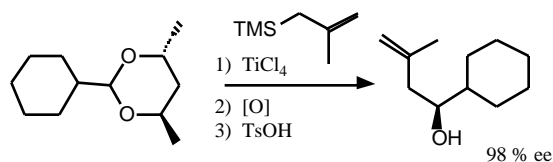


Mixed Higher Order Cuprate
B. Lipshutz *Tetrahedron* **1984**, 40, 5005
Synthesis **1987**, 325.

Addition to Acetals

Tetrahedron Asymmetry **1990**, 1, 477.

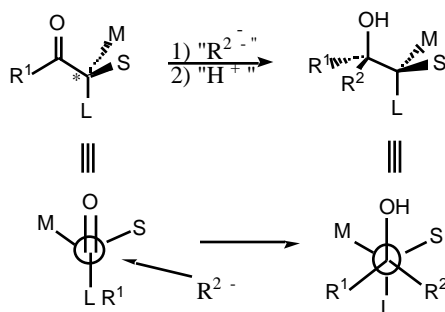




Stereoselective Addition to Aldehydes

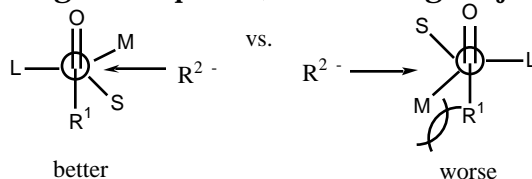
- Aldehydes are "prochiral", thus addition of an organometallic reagent to an aldehydes may be stereoselective.

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



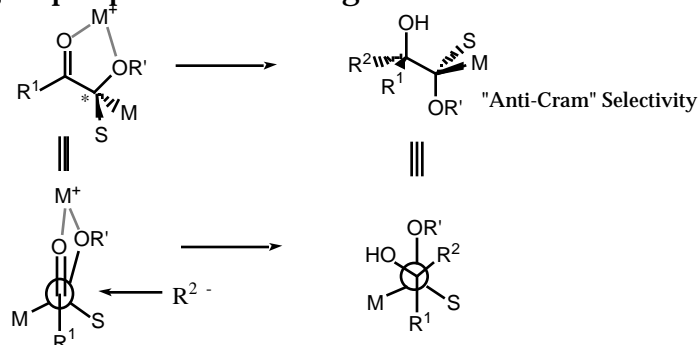
- Felkin-Ahn TL **1968**, 2199; *Nouv. J. Chim.* **1977**, *1*, 61.

based on *ab initio* calculations of preferred geometry of aldehyde which considers the trajectory of the incoming nucleophile (Dunitz-Burgi trajectory).



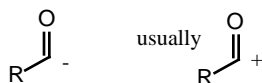
- Chelation Control Model- "Anti-Cram" selectivity

- When L is a group capable of chelating a counterion such as alkoxide groups



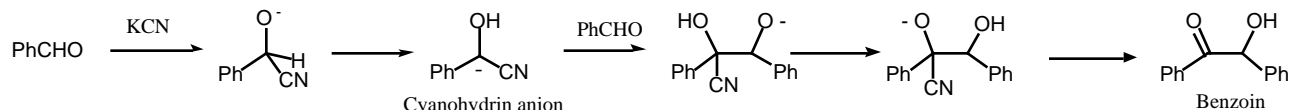
Umpolung - reversal of polarity Aldrichimica Acta **1981**, *14*, 73; ACIE **1979**, *18*, 239.

i.e: acyl anion equivalents are carbonyl nucleophiles (carbonyls are usually electrophilic)

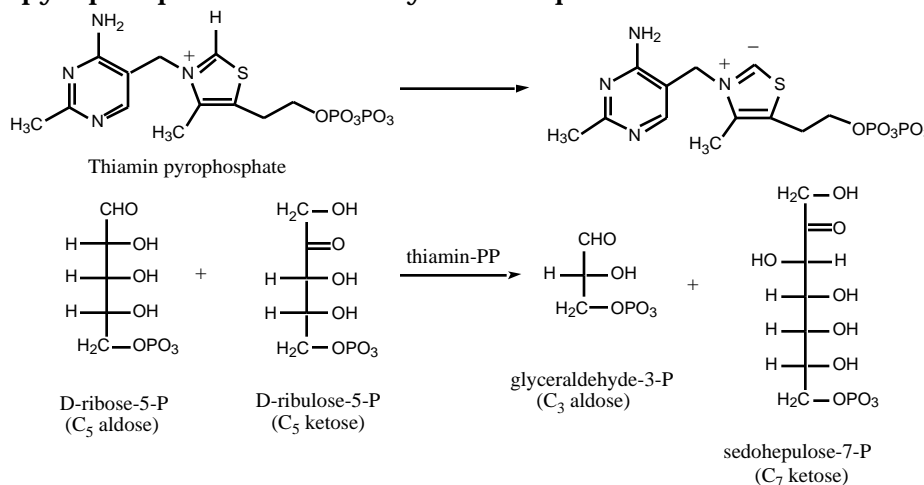


Benzoin Condensation

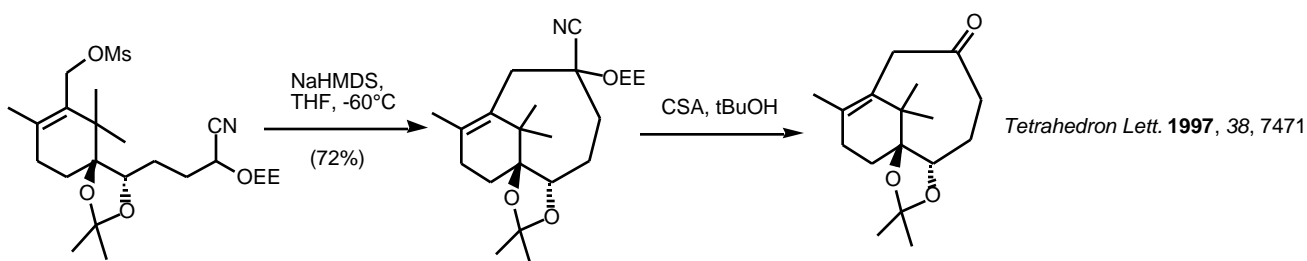
Comprehensive Organic Synthesis **1991**, *1*, 541.



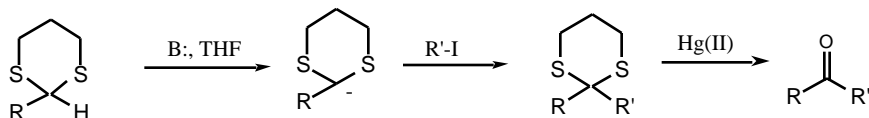
Thiamin pyrophosphate- nature's acyl anion equivalent for trans ketolization reactions



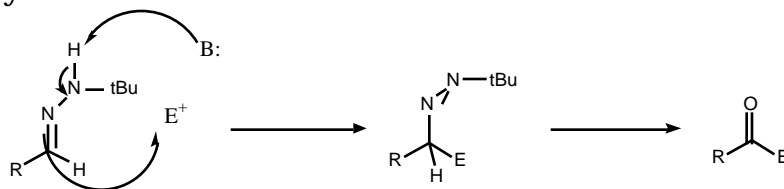
Trimethylsilylcyanohydrins



Dithianes



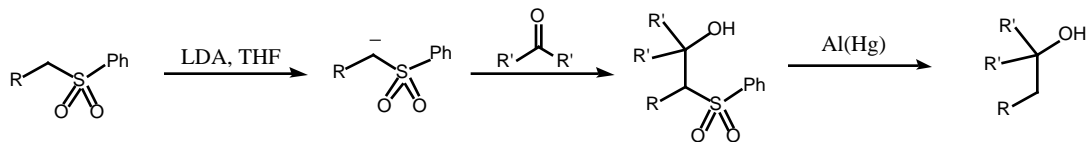
Aldehyde Hydrazones



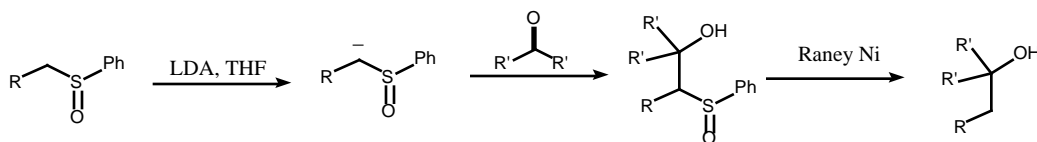
Heteroatom Stabilized Anions

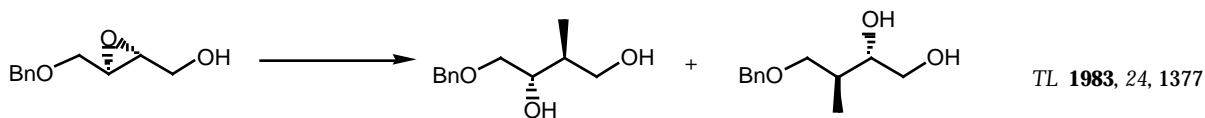
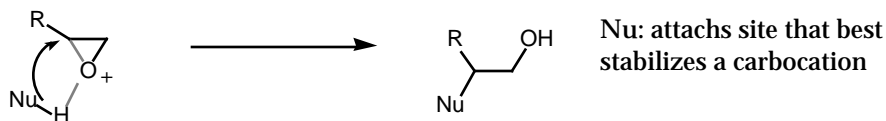
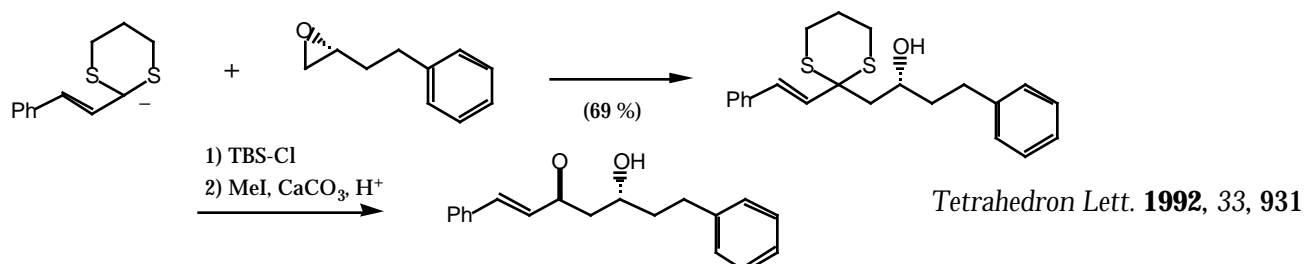
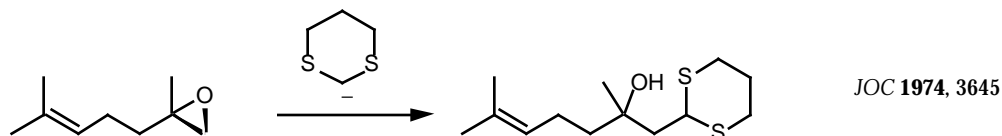
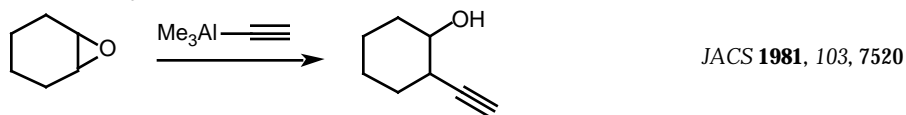
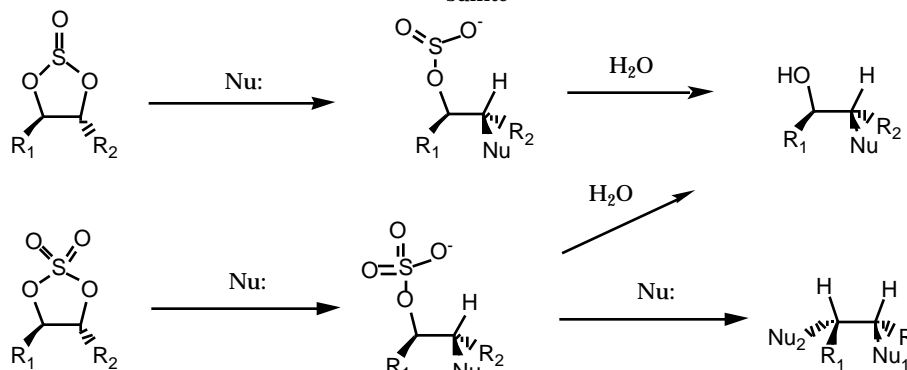
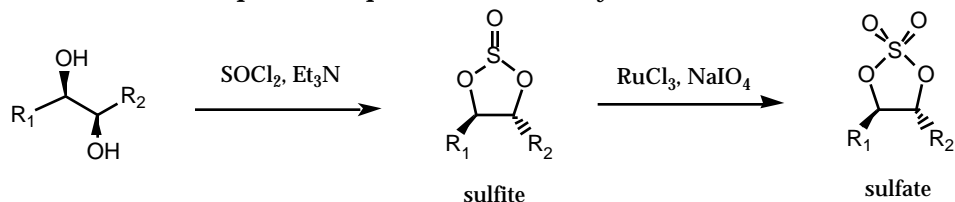
(Dithiane anion is an example)

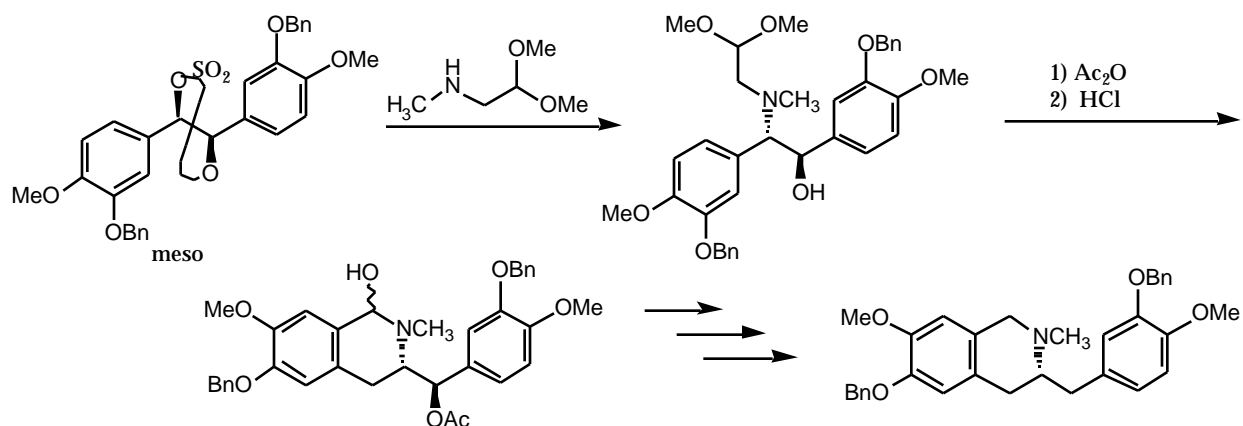
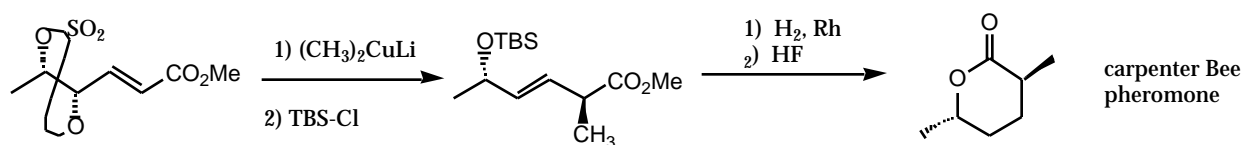
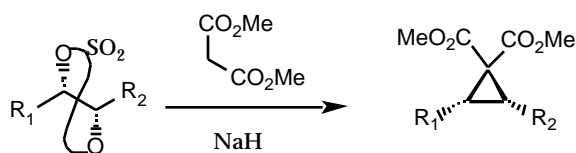
Sulfones



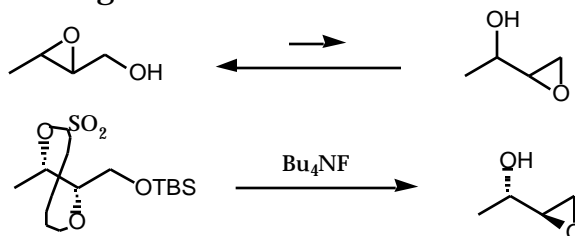
Sulfoxides



Epoxide Opening Asymmetric Synthesis **1984**, 5, 216.Basic (S_N2) ConditionAcid (S_N1-like) ConditionMe₂CuLi
AlMe₃Cyclic Sulfites and Sulfates (epoxide equivalents) Synthesis **1992**, 1035.



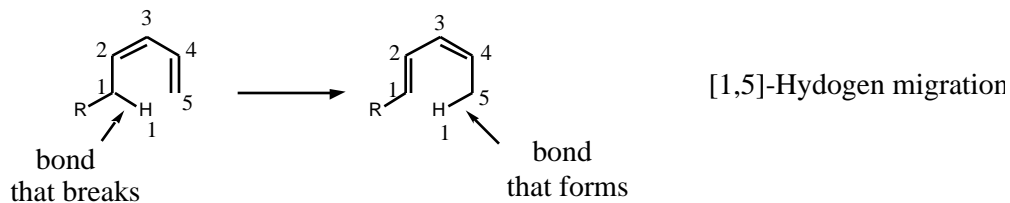
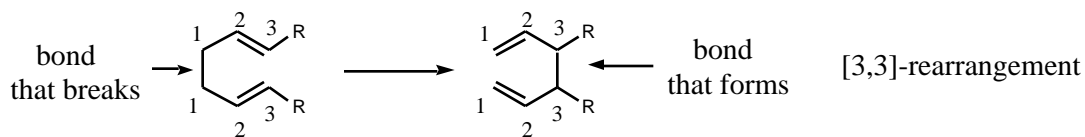
Irreversible Payne Rearrangement



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

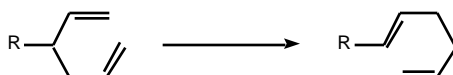
Sigmatropic Rearrangements Nomenclature:

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

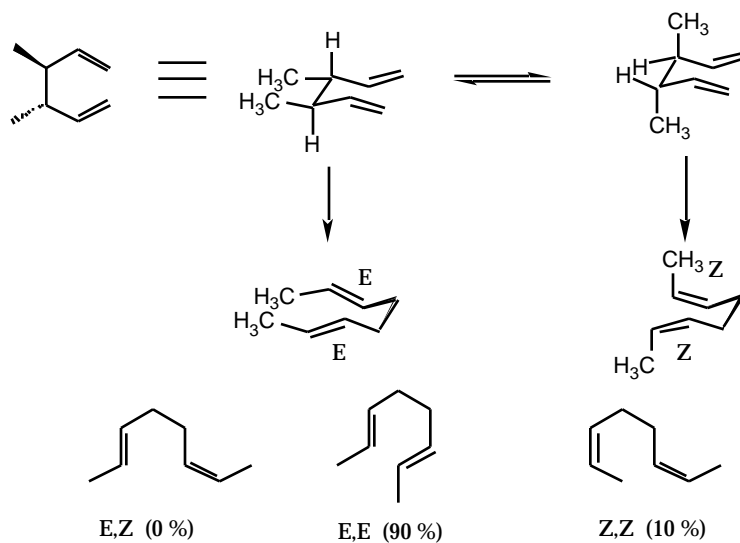
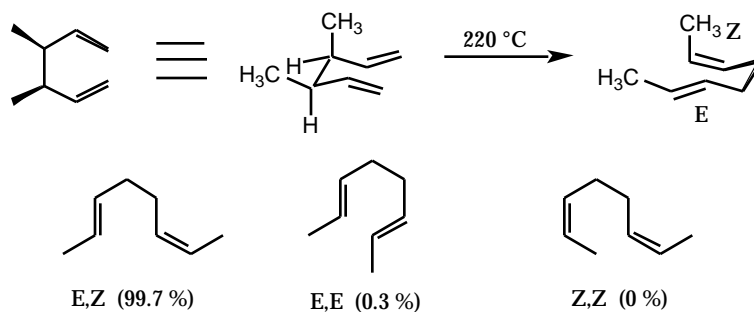


3,3-sigmatropic Rearrangements

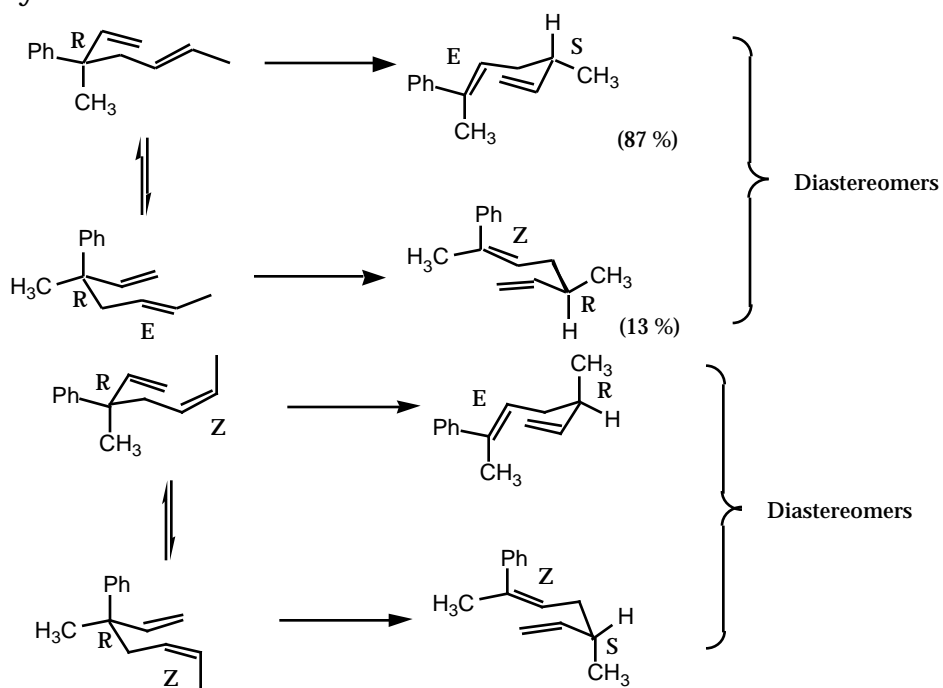
Cope Rearrangements- requires high temperatures *Organic Reaction* **1975**, 22, 1



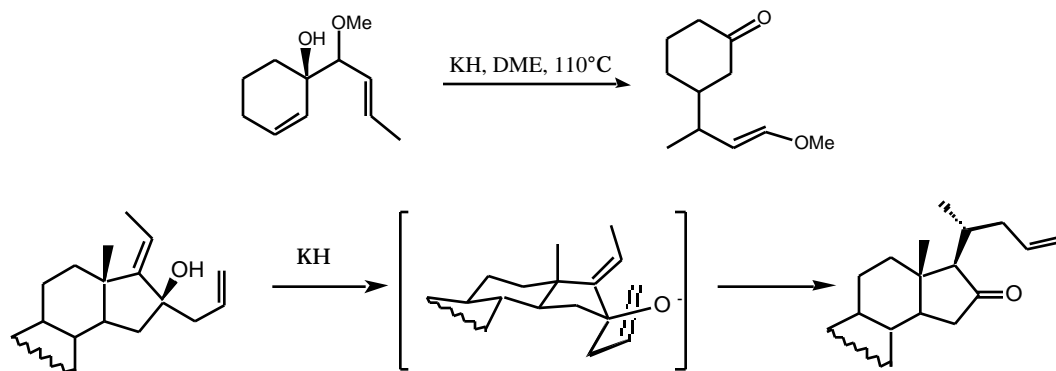
Chair transition state:



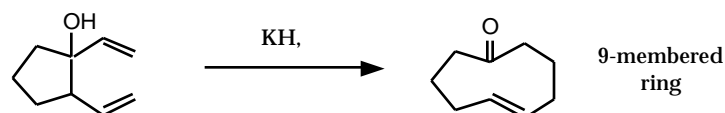
"Chirality Transfer"



- 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.

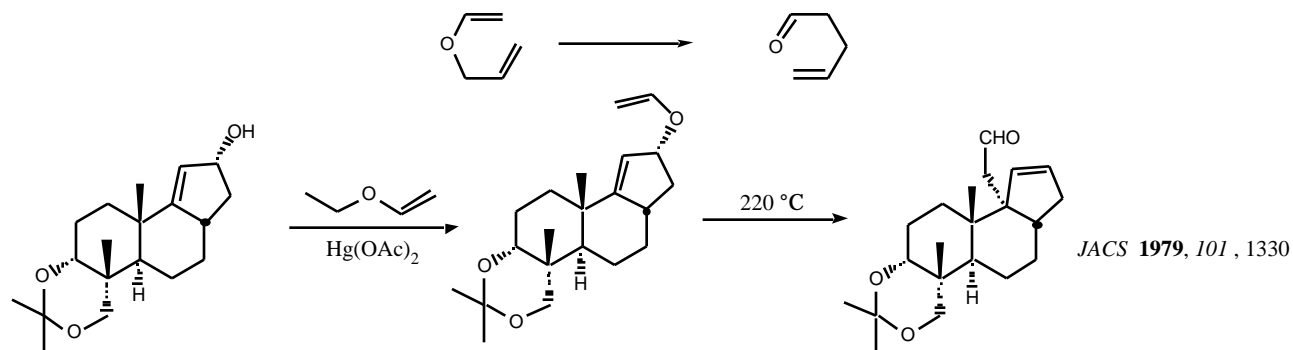


Ring expansion to medium sized rings

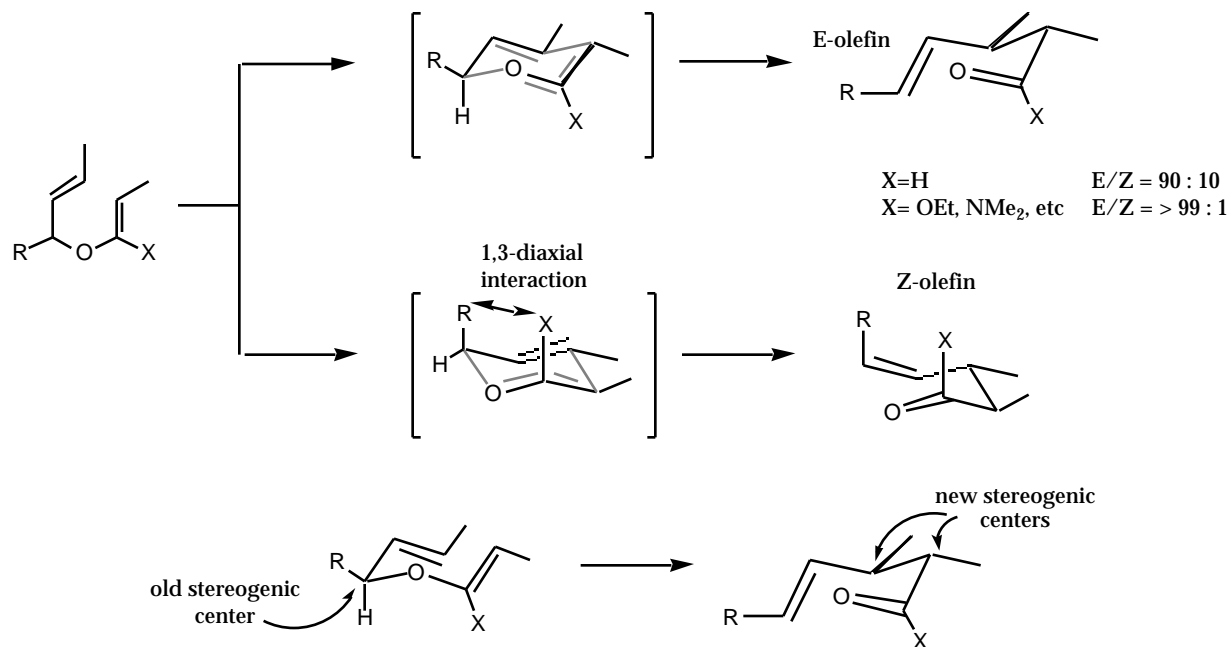


Claisen Rearrangements - allyl vinyl ether to an α,β -unsaturated carbonyl

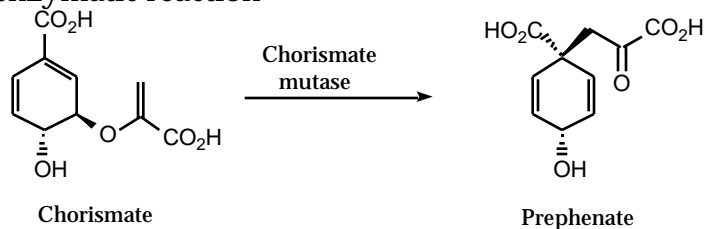
Chem. Rev. **1988**, 88, 1081.; *Organic Reactions* **1944**, 2, 1.; *Comprehensive Organic Synthesis* **1991**, 5, 827.



Chair Transition State for Claisen

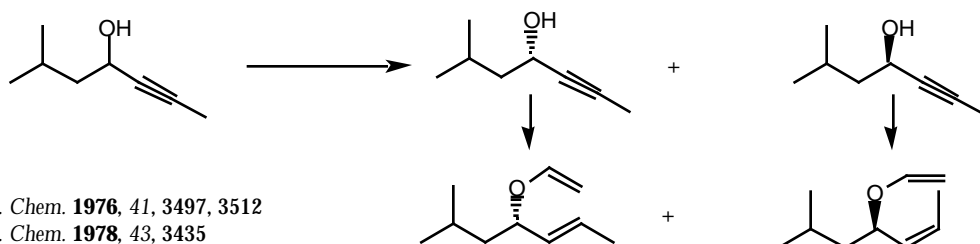
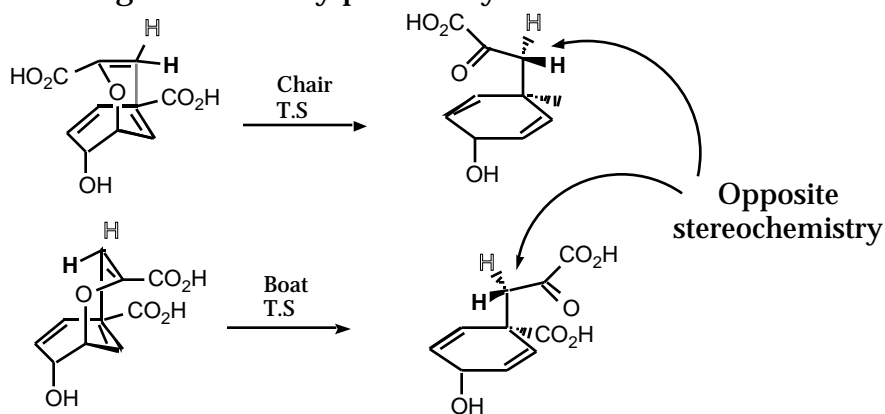


- Chorismate Mutase catalyzed Claisen Rearrangement- 10^5 rate enhancement over non-enzymatic reaction

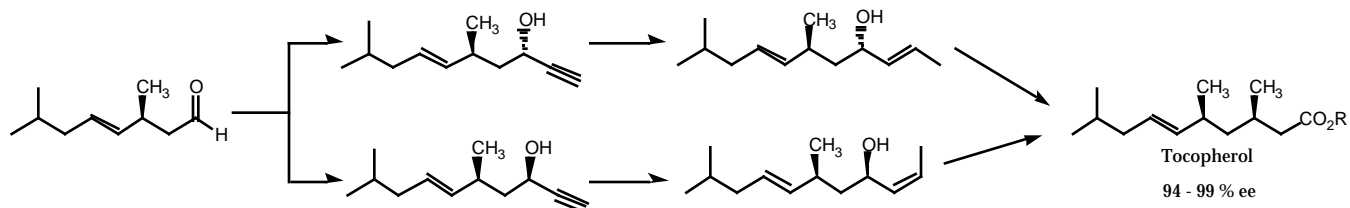
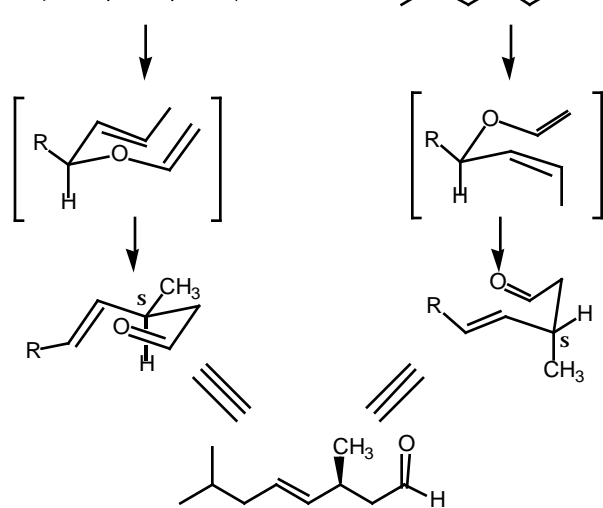


J. Knowles
JACS **1987**, 109, 5008, 5013

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

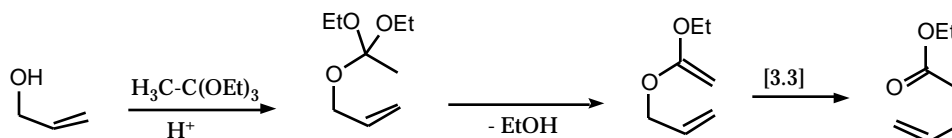


J. Org. Chem. **1976**, 41, 3497, 3512
J. Org. Chem. **1978**, 43, 3435

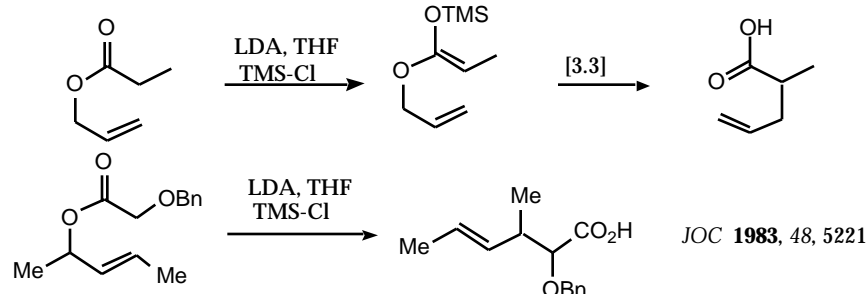


hydrophobically accelerated Claisen - JOC **1989**, 54, 5849

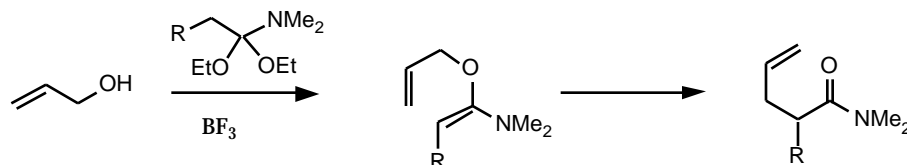
Johnson ortho-ester Claisen:



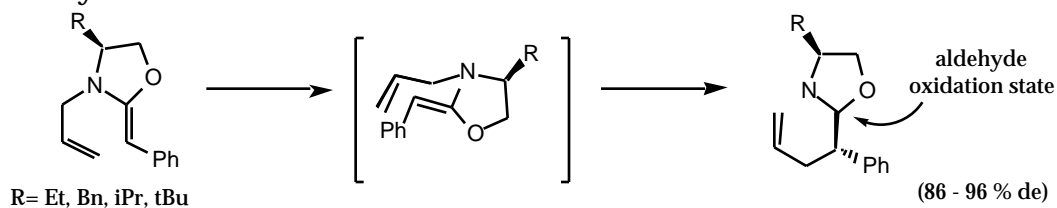
Ireland ester-enolate Claisen.

Aldrichimica Acta **1993**, 26, 17.

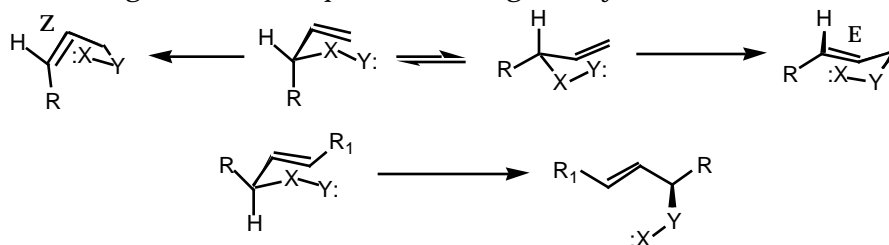
Eschenmoser



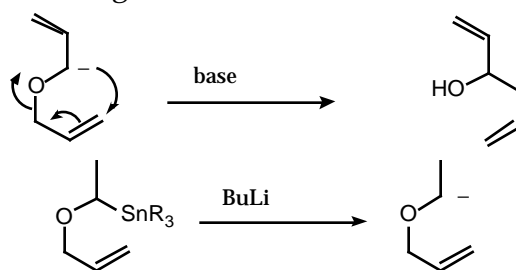
"Chirality Transfer"

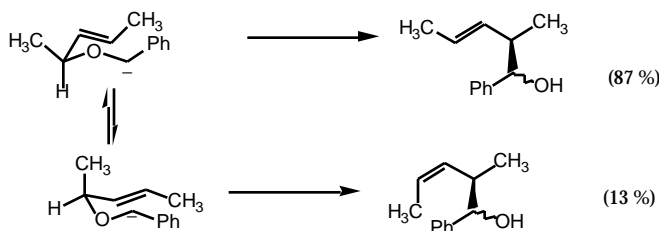
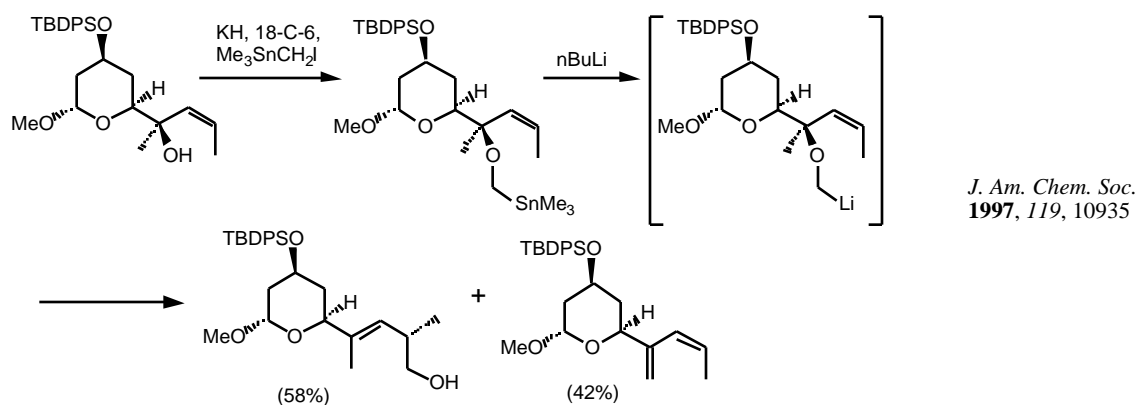


[2,3]-Sigmatropic Rearrangement

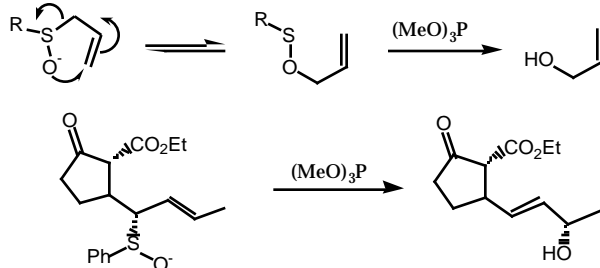
Comprehensive Organic Synthesis **1991**, 6, 873.

-Wittig Rearrangement

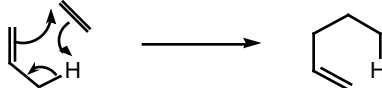
Organic Reactions **1995**, 46, 105Synthesis **1991**, 594.



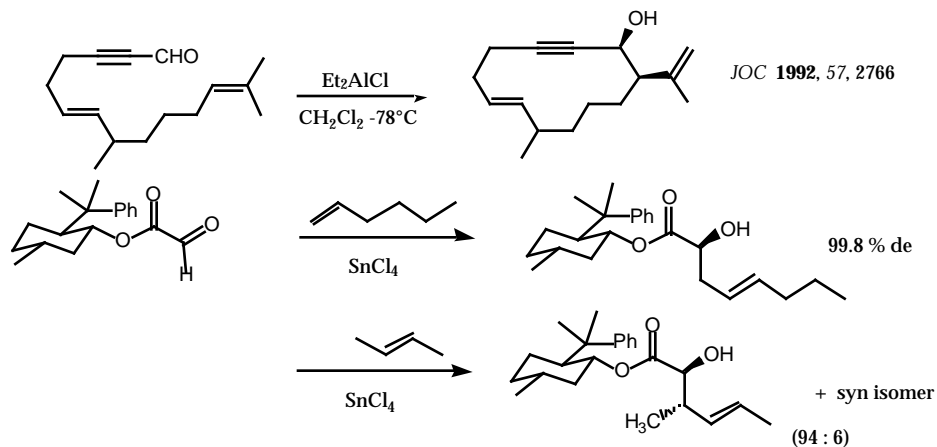
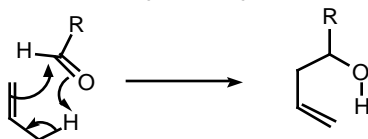
Sulfoxide Rearrangement

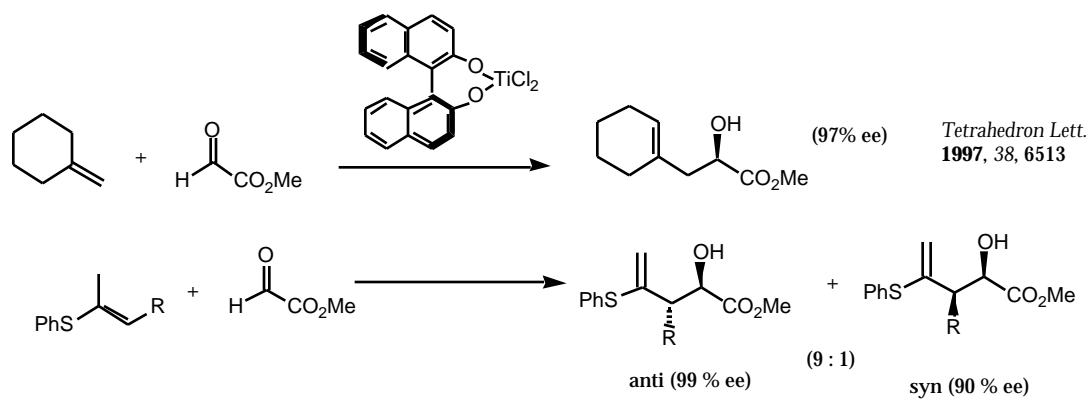


Ene Reaction *Comprehensive Organic Synthesis* **1991**, 5, 1; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 876; ; *Chem. Rev.* **1992**, 28, 1021.

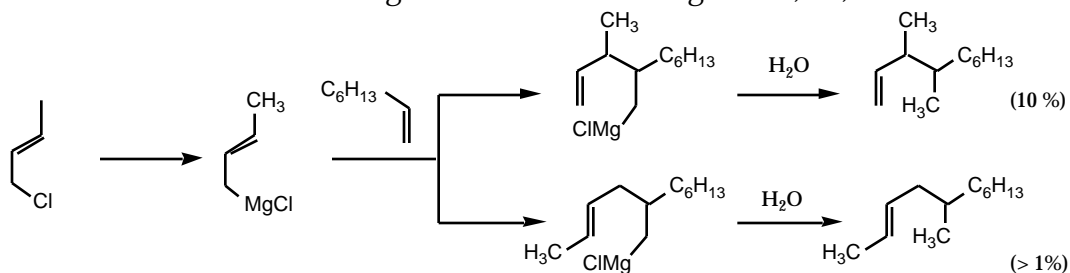


- Ene reaction with aldehydes is catalyzed by Lewis Acids (Et₂AlCl)

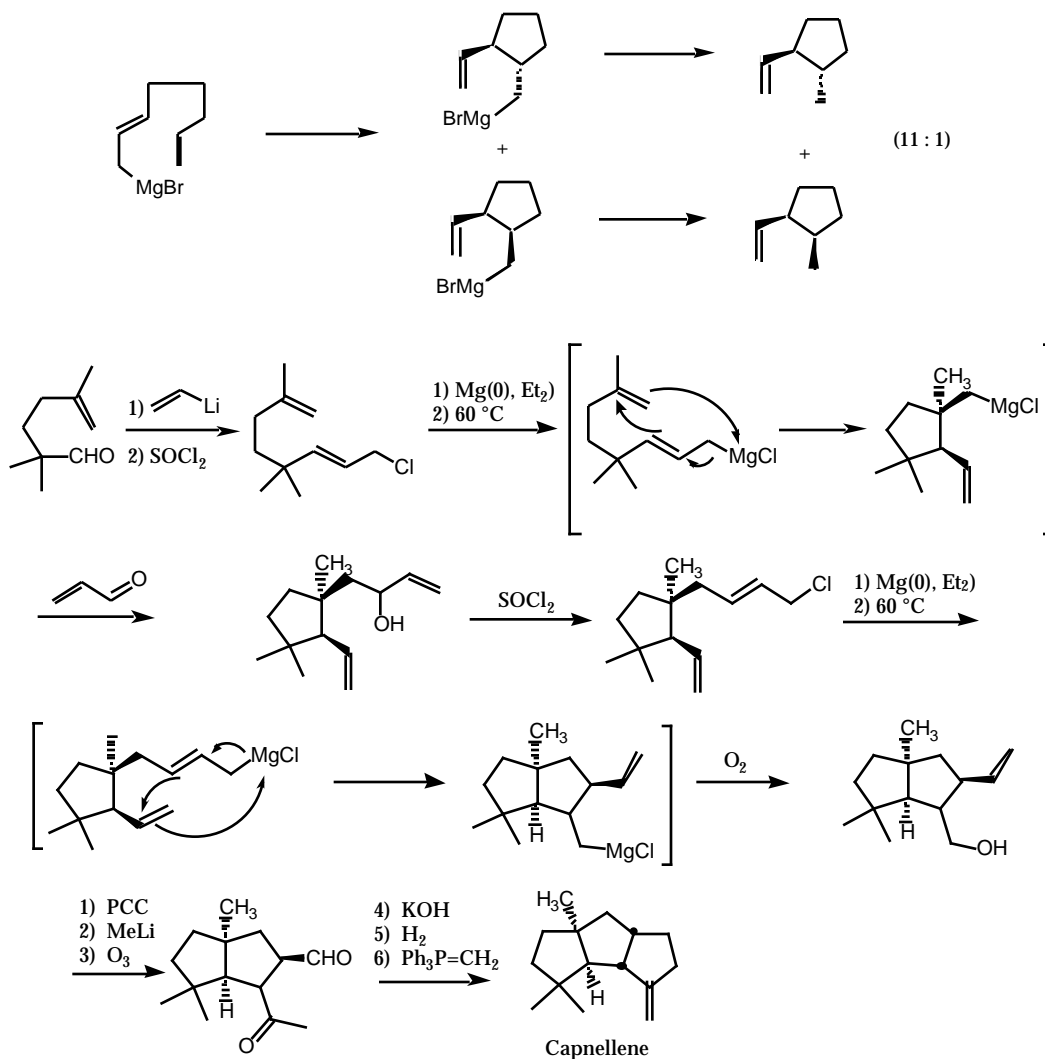




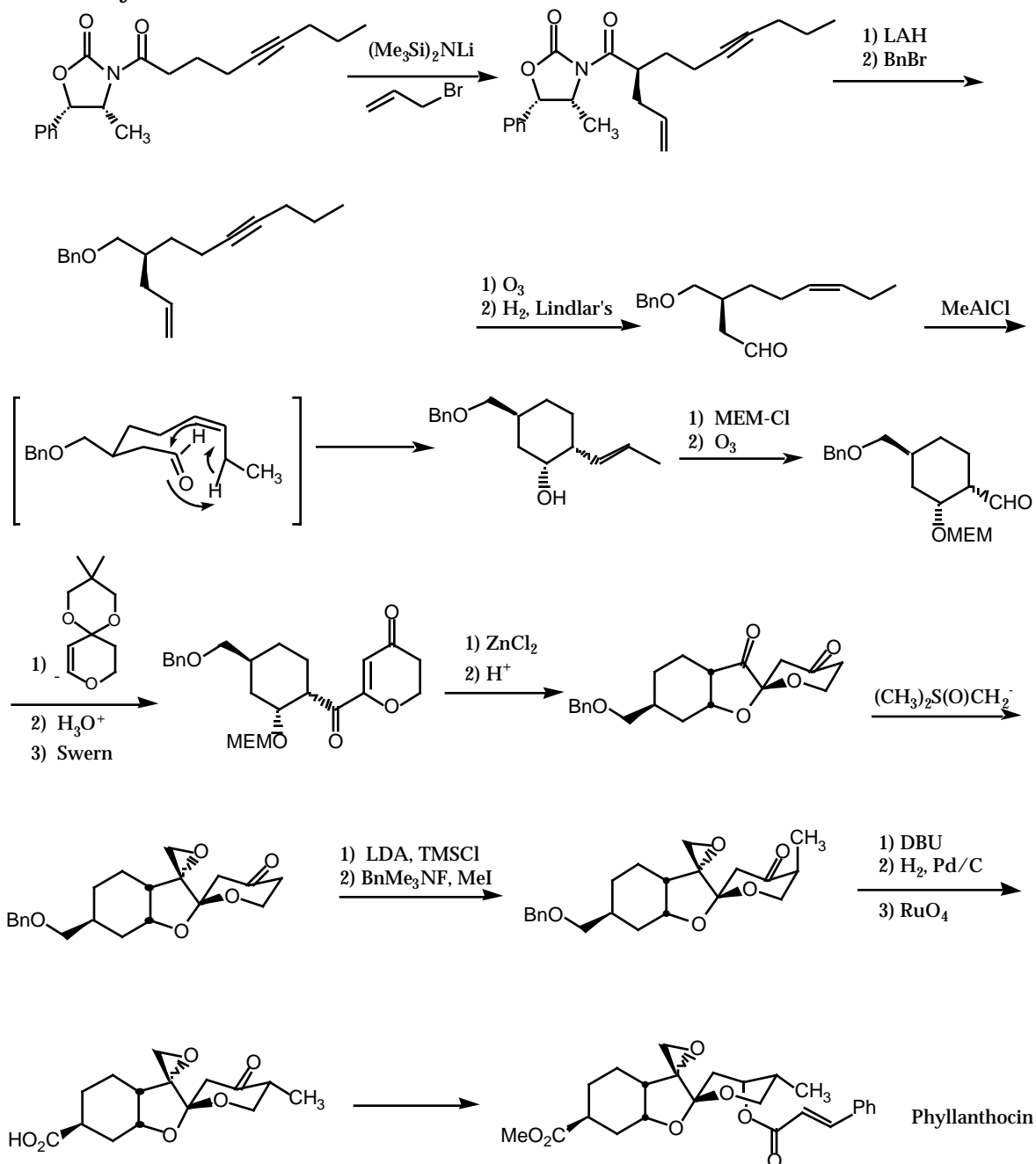
- Metallo-ene Reaction *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 38



intramolecular



Synthesis of Phyllanthocin

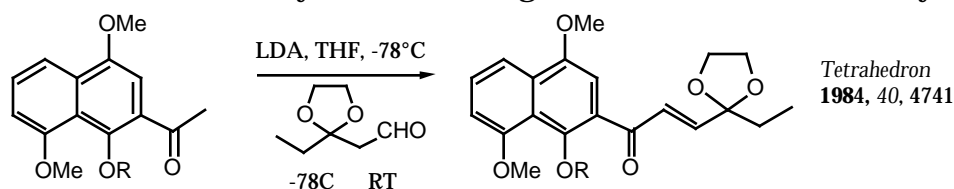
A. B. Smith et al. *J. Am. Chem. Soc.* **1987**, *109*, 1269.

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. – Elimination and Dehydration
9. From Diols and Epoxides
10. From Acetylenes
11. From Other Alkenes-Transition Metal Catalyzed Cross-Coupling and Olefin Metathesis

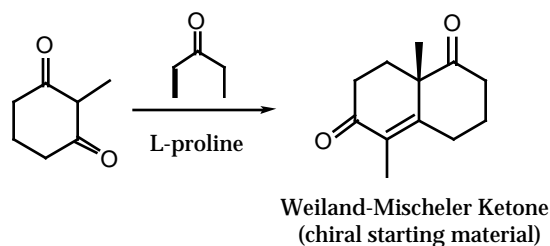
Aldol Condensation - Aldol condensation initially give β -hydroxy ketones which under certain conditions readily eliminated to give α,β -unsaturated carbonyls.



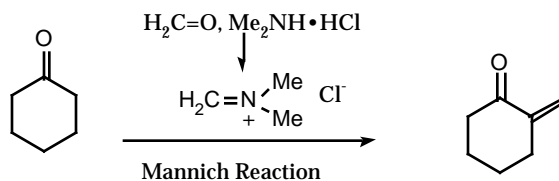
Robinson Annulation : Sequential Michael addition/aldol condensation between a ketone enolate and an alkyl vinyl ketone (i.e. MVK) to give a cyclohex-2-en-1-one

JOC **1984**, 49, 3685

Synthesis **1976**, 777.



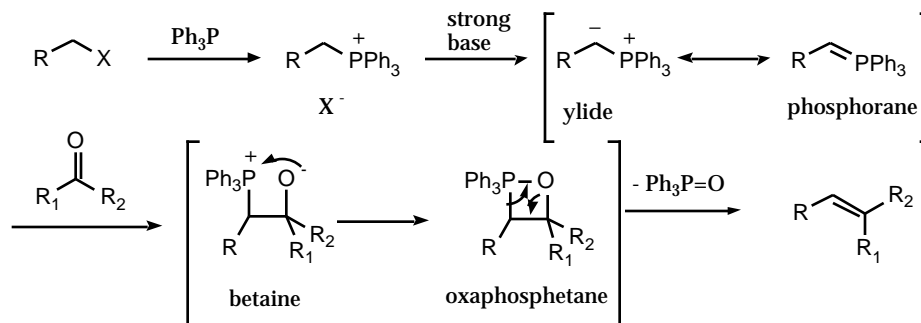
Mannich Reaction - α,β -unsaturated carbonyls (α -methylene carbonyls)



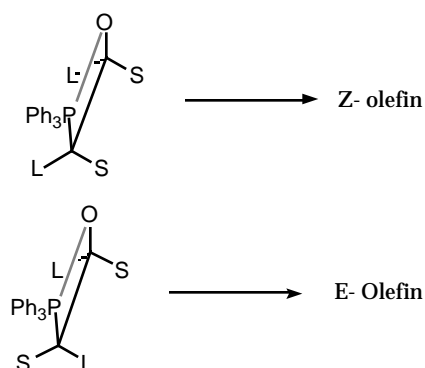
Wittig Reaction review: *Chem. Rev.* **1989**, 89, 863.

mechanism and stereochemistry: *Topic in Stereochemistry* **1994**, 21, 1

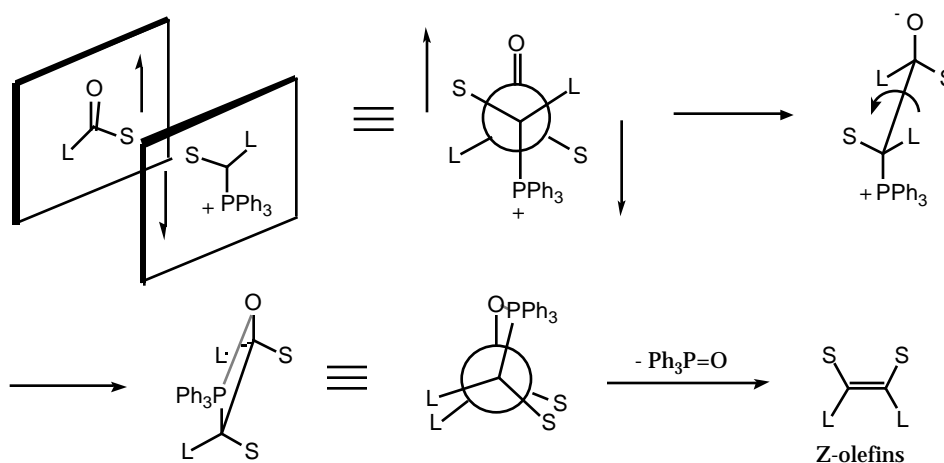
- reaction of phosphonium ylide with aldehydes, ketones and lactols to give olefins



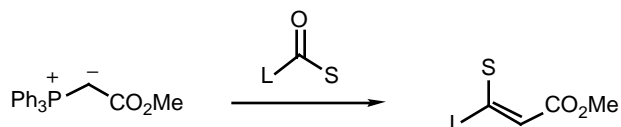
- Olefin Geometry



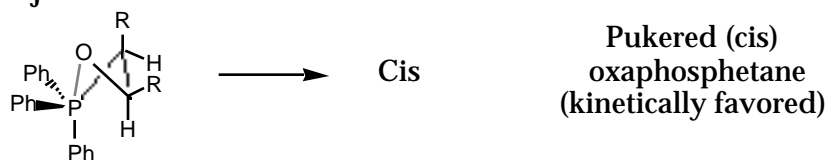
- With "non-stabilized" ylides the Wittig Reaction gives predominantly Z-olefins.
Seebach et al *JACS*



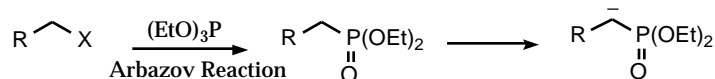
- "Stabilized ylides" give predominantly E-olefins



- 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:

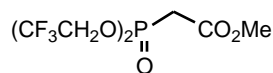


Phosphonate Modification (Horner-Wadsworth-Emmons)

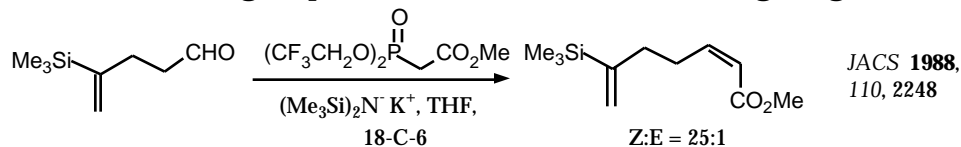


- R is usually restricted to EWG such as CO₂H, CO₂Me, CN, SO₂Ph etc. and the olefin geometry is usually E.

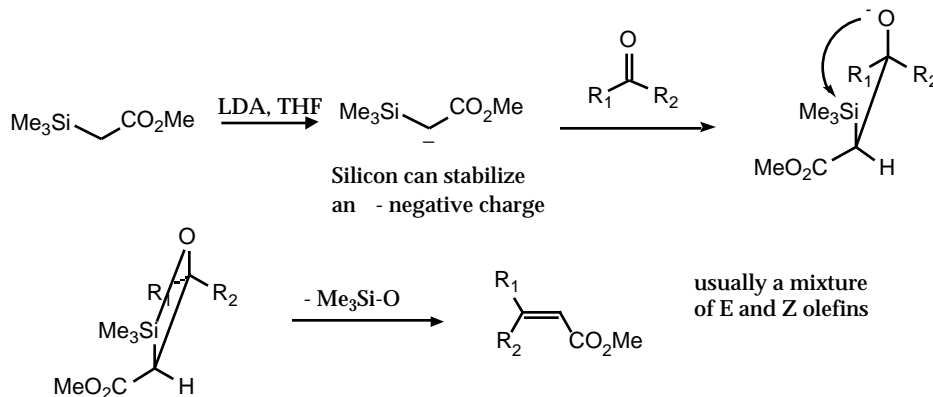
- Still Modification TL **1983**, 24, 4405.



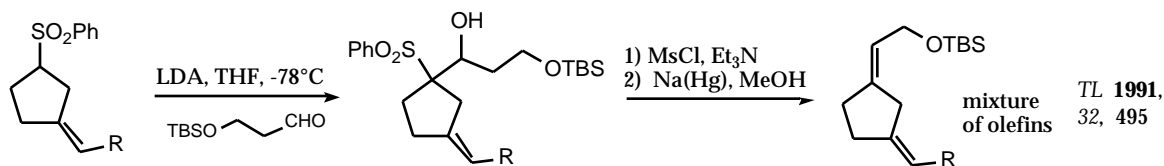
- CF₃CH₂O- groups make the betaine less stable, giving more Z-olefin.



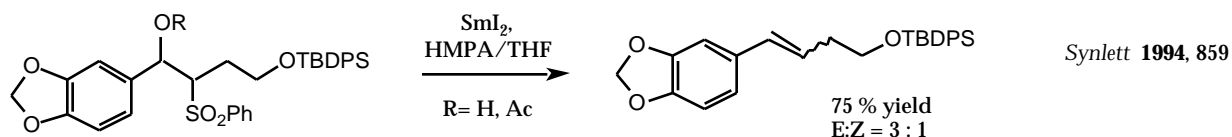
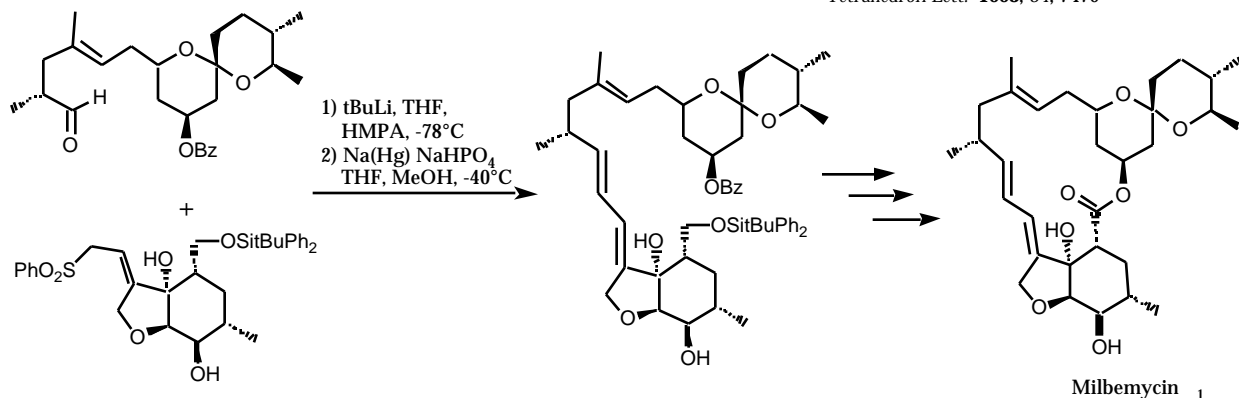
Peterson Olefination review: *Synthesis* **1984**, 384 *Organic Reactions* **1990**, 38 1.



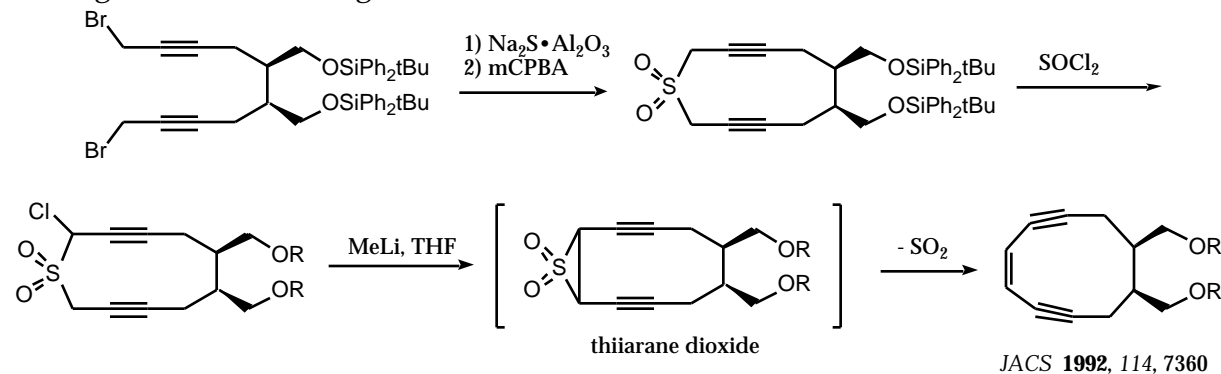
Julia-Lythgoe Olefination TL 1973, 4833 Tetrahedron 1987, 43, 1027



Tetrahedron Lett. 1993, 34, 7479



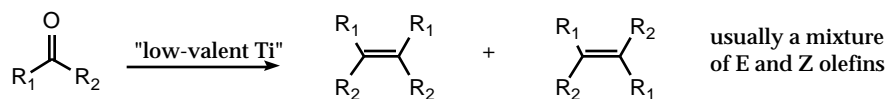
Ramberg-Bäcklund Rearrangement



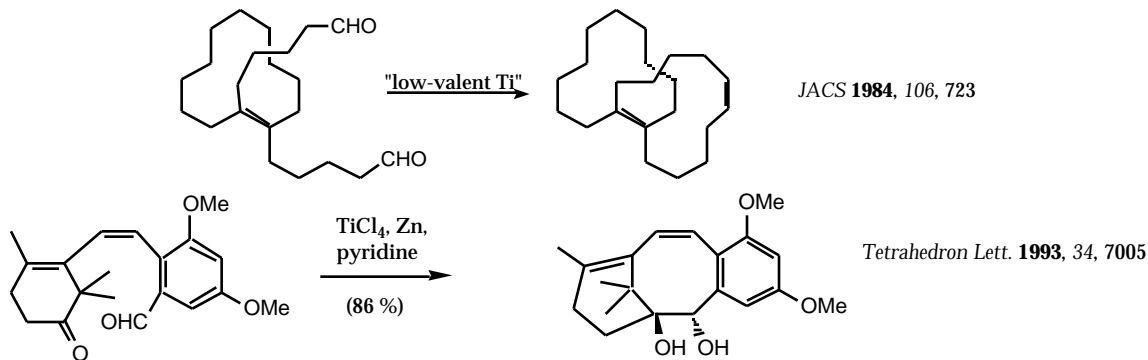
Carbonyl Coupling Reactions (McMurry Reaction)

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

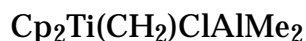
- reductive coupling of carbonyls with low valent transition metals, Ti(0) or Ti(II) , to give olefins



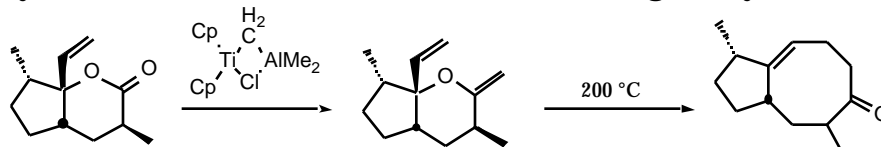
excellent method for the preparation of strained (highly substituted) olefins
- Intramolecular coupling gives cyclic olefins



Tebbe Reagent



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



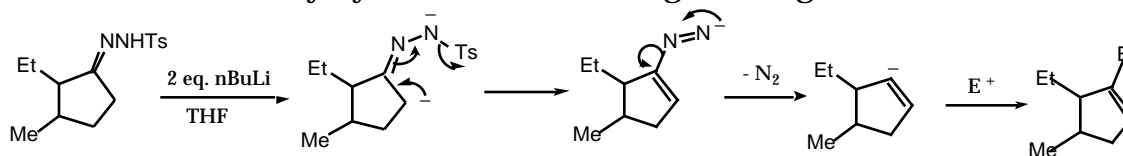
- Cp_2TiMe_2 will also do the methylenation chemistry

JACS **1990**, 112, 6393.

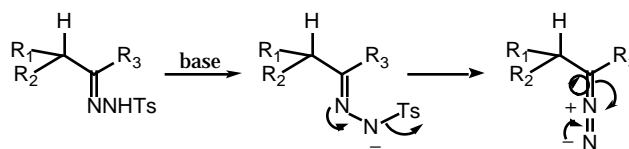
Shapiro and Related Reactions

Organic Reactions **1990**, 39, 1 : **1976**, 23, 405

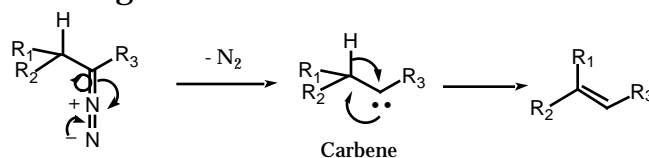
- Reaction of a tosylhydrazone with a strong base to give an olefin.



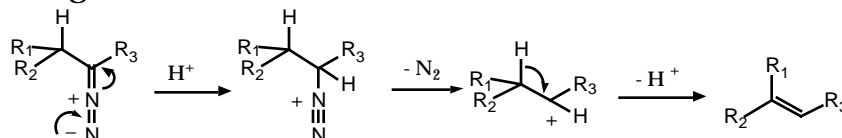
Bamford-Stevens Reaction- initial conversion of a tosylhydrazone to a diazo intermediate



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



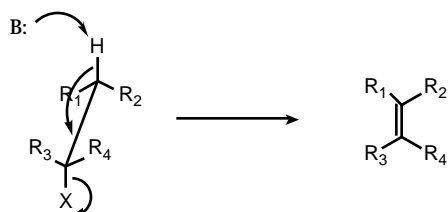
b. protic- decomposition of the diazo intermediate under protic conditions an olefin through a carbonium ion intermediate.



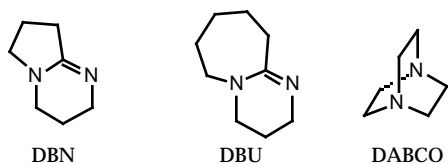
- Eliminations

Anti Eliminations

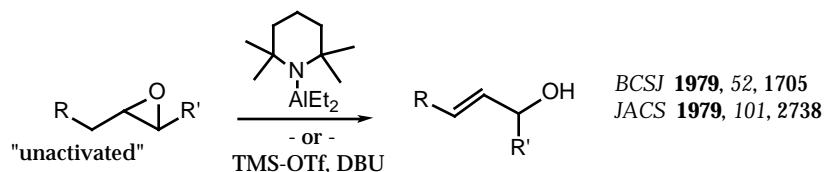
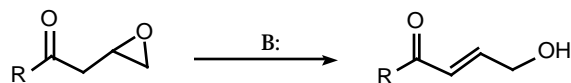
- elimination of HX from vicinal saturated carbon centers to give a olefin, usually base promoted.
- base promoted E₂- type elimination proceeds through an anti-periplanar transition state.



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

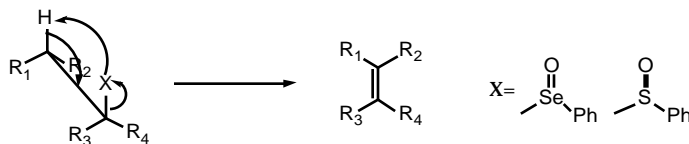
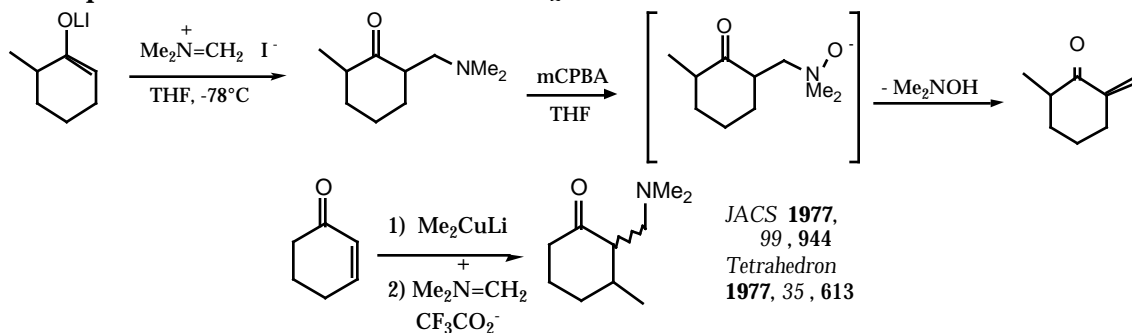


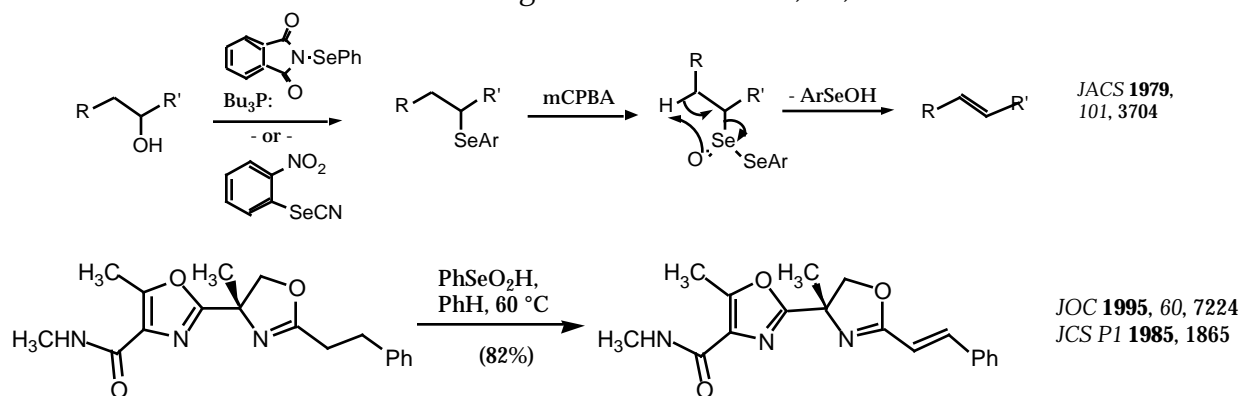
- X: -Br, -I, -Cl, -OR, epoxides



Syn Elimination

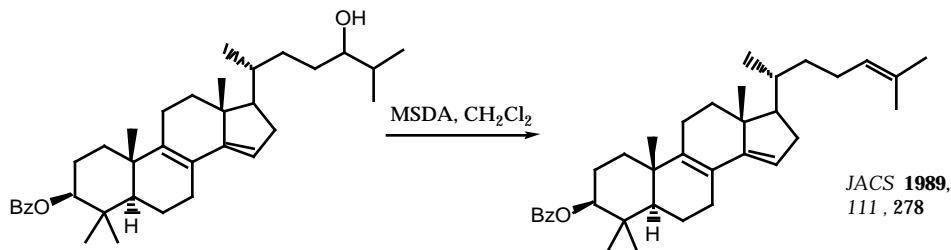
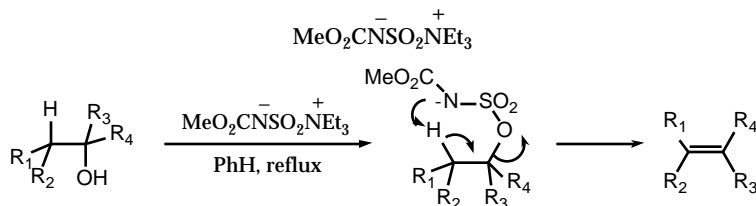
- often an intramolecular process

Cope Elimination- elimination of R₂NOH from an amine oxide

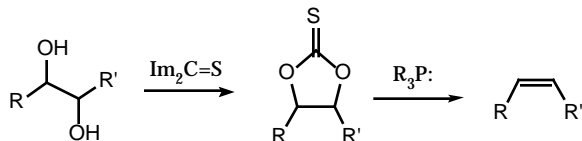
Selenoxide Elimination *Organic Reactions* **1993**, 44, 1.

Dehydration of Alcohols

- alcohols can be dehydrated with protic acid to give olefins via an E₁ mechanism.
 - other reactions dehydrate alcohols under milder conditions by first converting them into a better leaving group, i.e. POCl₃/ pyridine, P₂O₅
- Martin sulfurane; Ph₂S[OCPh(CF₃)₂]₂ *JACS*, **1972**, 94, 4997 dehydration occurs under very mild, neutral conditions, usually gives the most stable olefin

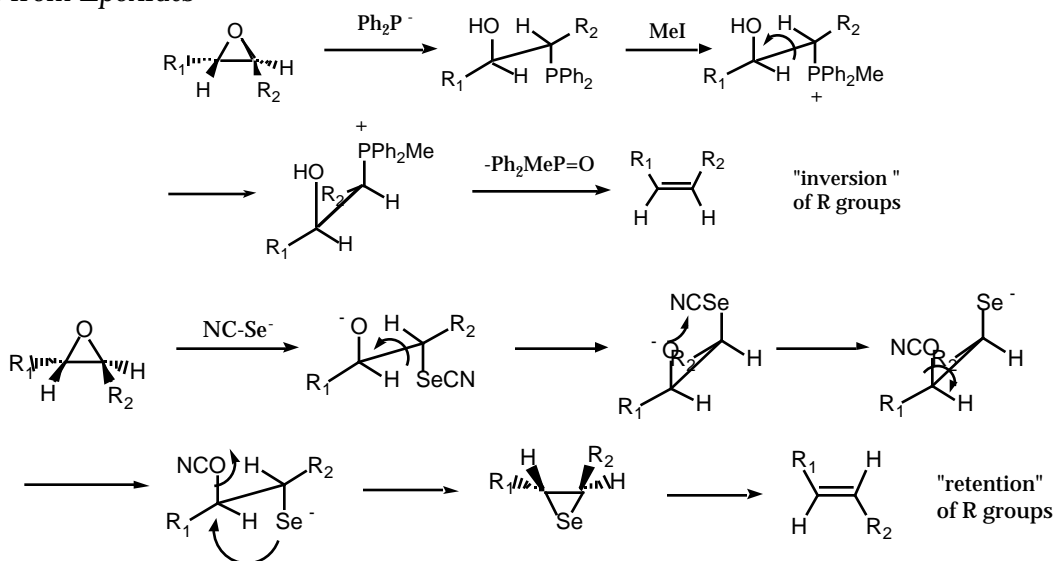
Burgess Reagent (inner salt) *JOC*, **1973**, 38, 26 occurs via a syn elimination

Olefins from Vicinal Diols

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

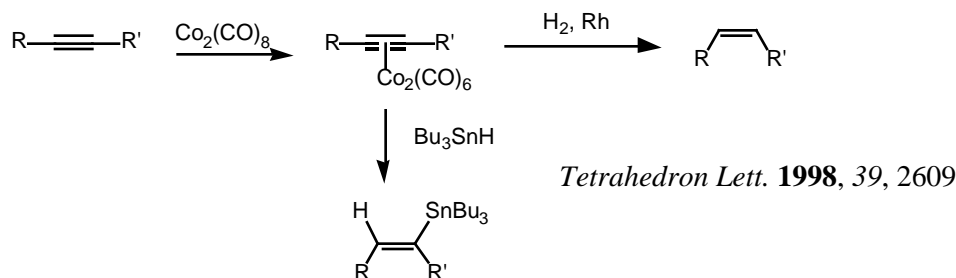
- vic-diols can be converted to olefins with K_2WCl_6 *JCS* **1972**, 370; *JACS* **1972**, 94, 6538
- This reaction worked best with more highly substituted diols and give predominantly syn elimination.
- Low valent titanium; McMurry carbonyl coupling is believed to go through the vic-diol. vic-diols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

Olefins from Epoxides



From Acetylenes

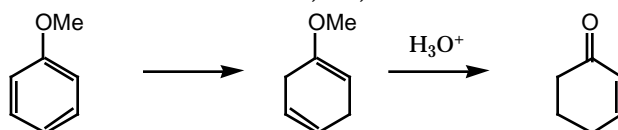
- Hydrogenation with Lindlar's catalyst gives cis-olefins



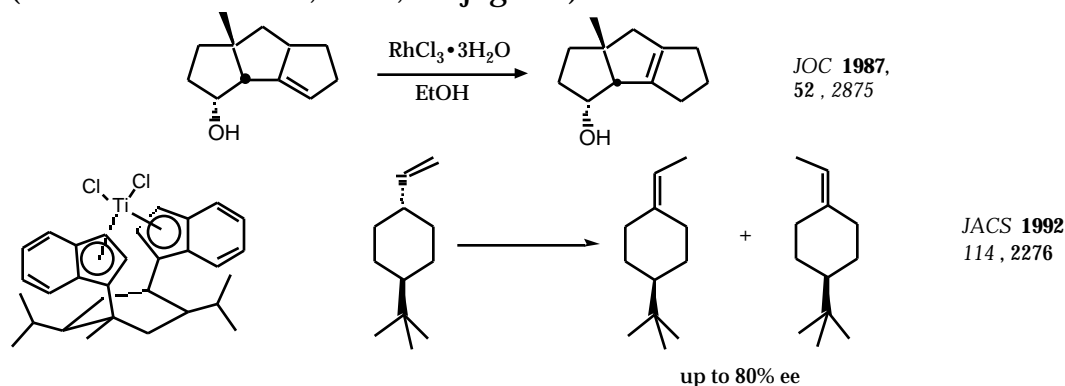
From Other Olefins

Sigmatropic Rearrangements

- transposition of double bonds

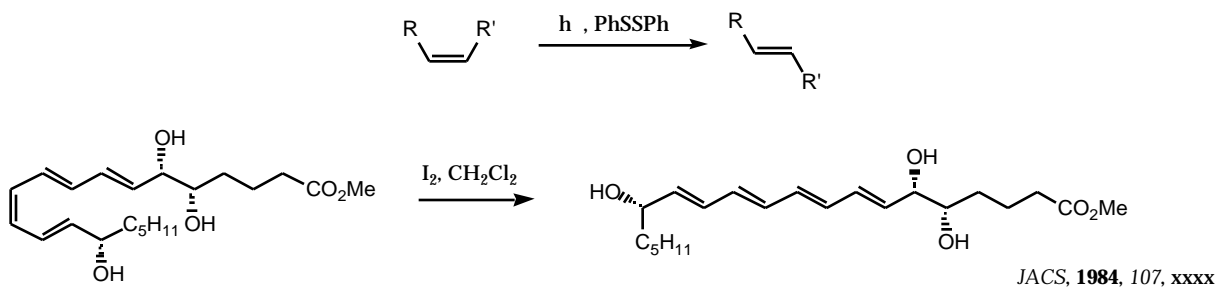
Birch Reduction *Tetrahedron* **1989**, 45, 1579

Olefin Isomerization- a variety of transition metal ($\text{RhCl}_3 \cdot \text{H}_2\text{O}$) catalyst will isomerize double bonds to more thermodynamically favorable configurations (i.e. more substituted, trans, conjugated)



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

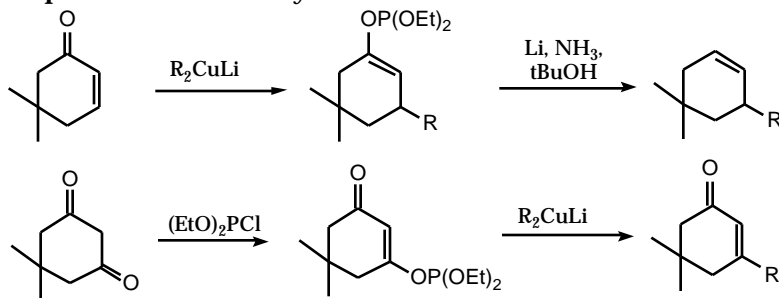
- Conversion of cis to trans olefins
- Conversion of trans to cis-olefins



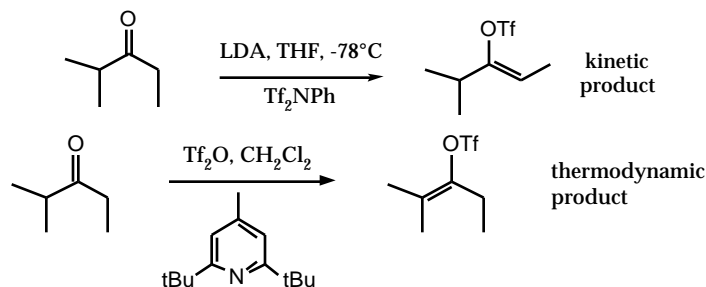
Transition Metal Catalyzed Cross-Coupling Reactions

Coupling of Vinyl Phosphonates and Triflates to Organometallic Reagents

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

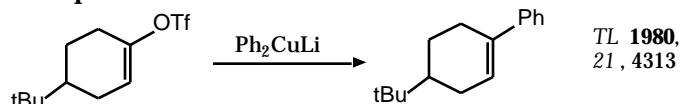


- preparation of enol triflates *Synthesis* **1997**, 735



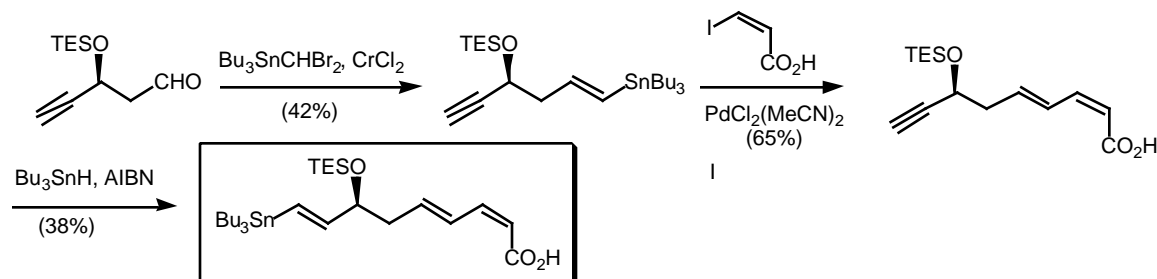
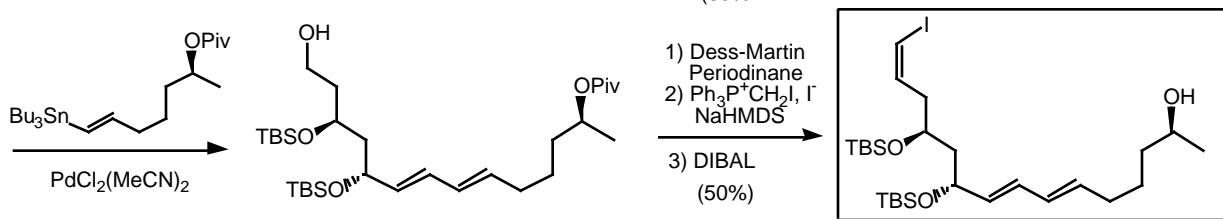
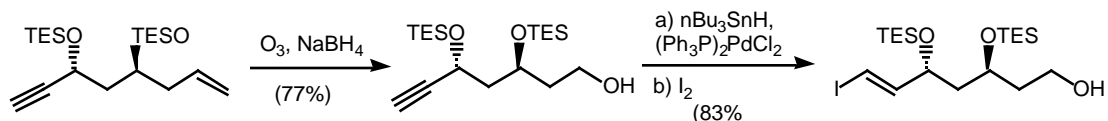
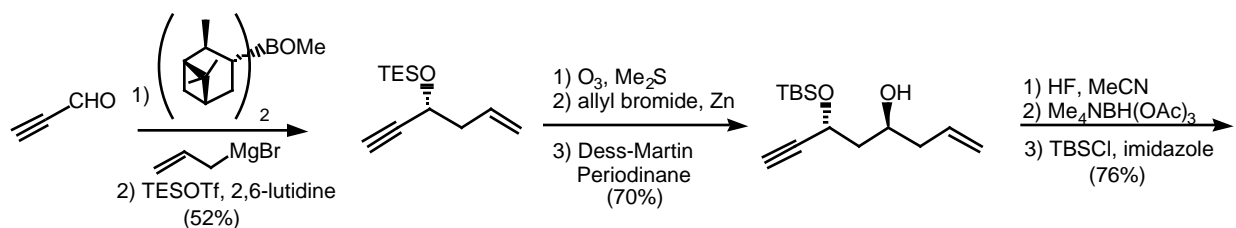
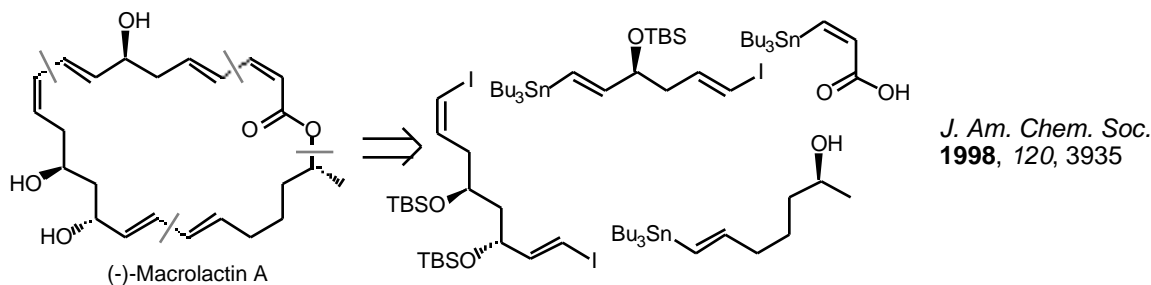
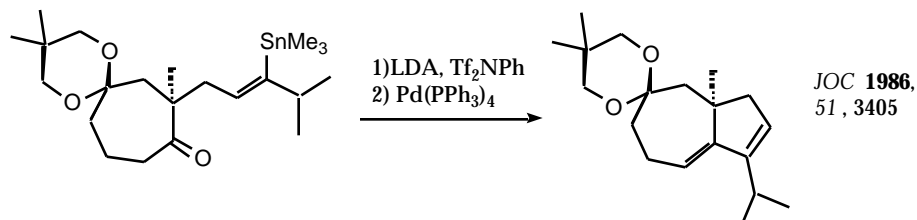
- reaction with cuprates.

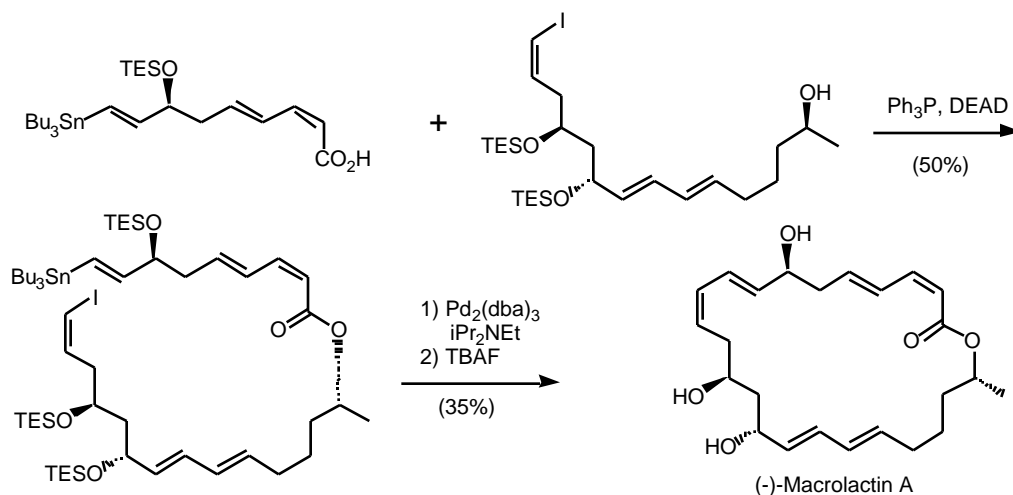
Acc. Chem. Res. **1988**, 25, 47



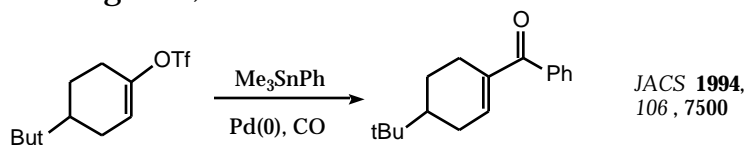
- palladium (0) catalyzed cross-coupling of vinyl or aryl halides or triflates with organostannanes (Stille Reaction)

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

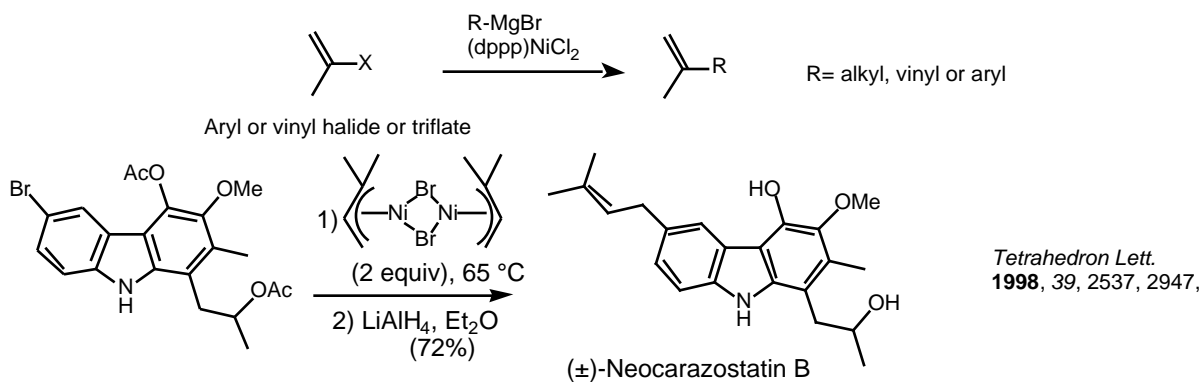




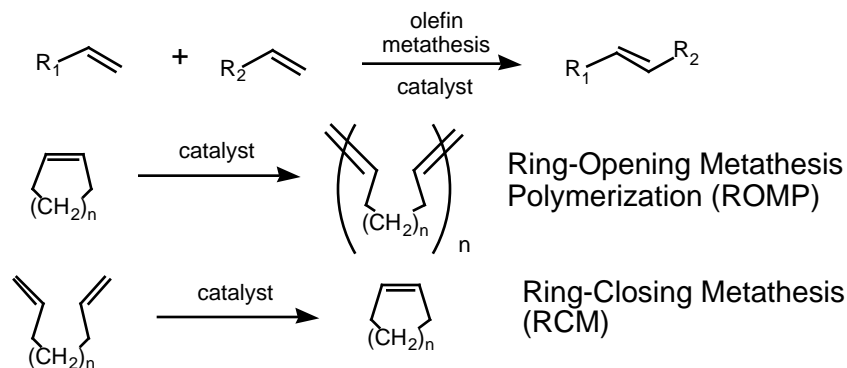
palladium (0) catalyzed carbonylations- coupling of a vinyl triflate with a organostanane to give α,β -unsaturated ketones.



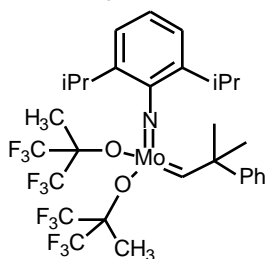
Nickel (II) Catalyzed Cross-Coupling with Grignard Reagents (Kumada Reaction): *Pure Appl. Chem.* **1980**, *52*, 669 *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958



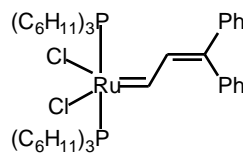
Olefin Metathesis *Tetrahedron* **1998**, *54*, 4413, *Acc. Chem. Res.* **1995**, *25*, 446.



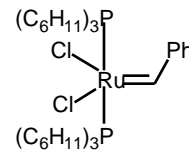
Metathesis Catalysts:



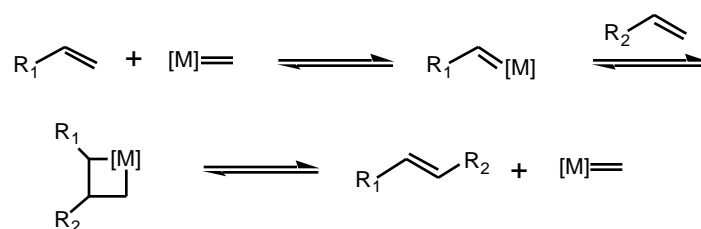
Schrock's Catalyst



Grubbs' Catalyst



Mechanism:

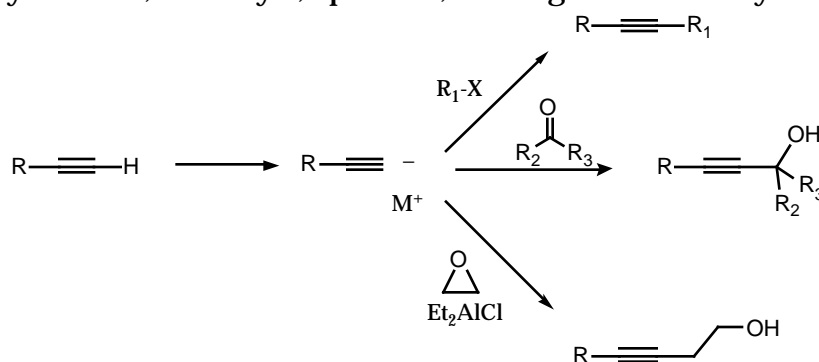


C C Bond Formation

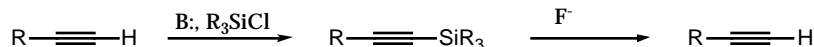
1. From other acetylenes
2. From carbonyls
3. From olefins
4. From Strained Rings
5. Eschenmosher Fragmentation
6. Allenes

From Other Acetylenes

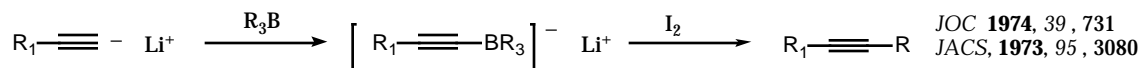
- The proton of terminal acetylenes is acidic ($pK_a = 25$), thus they can be deprotonated to give acetylide anions which can undergo substitution reactions with alkyl halides, carbonyls, epoxides, etc. to give other acetylenes.



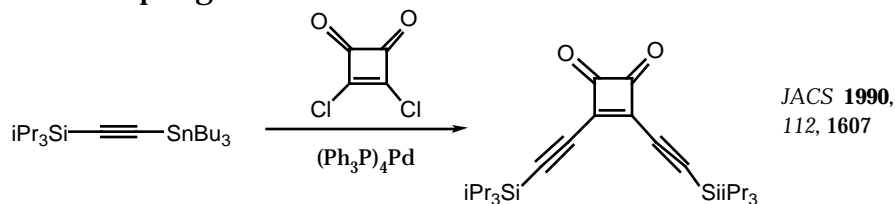
- Since the acetylenic proton is acidic, it often needs to be protected as a trialkylsilyl derivative. It is conveniently deprotected with fluoride ion.

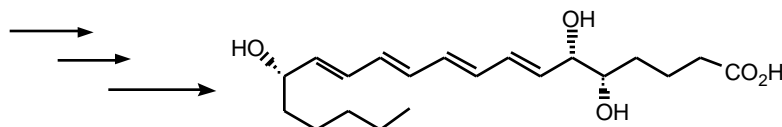
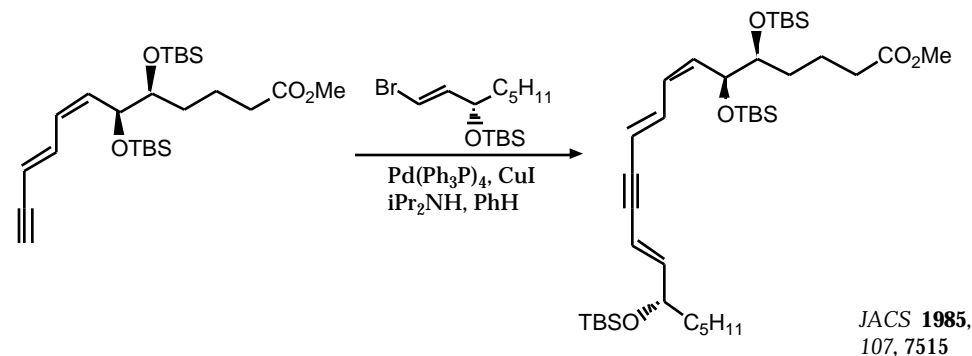


Acetylide anions and organoboranes

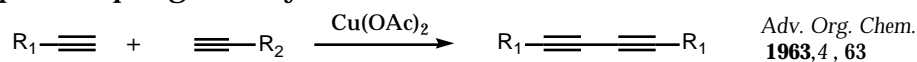


Palladium Coupling Reactions:



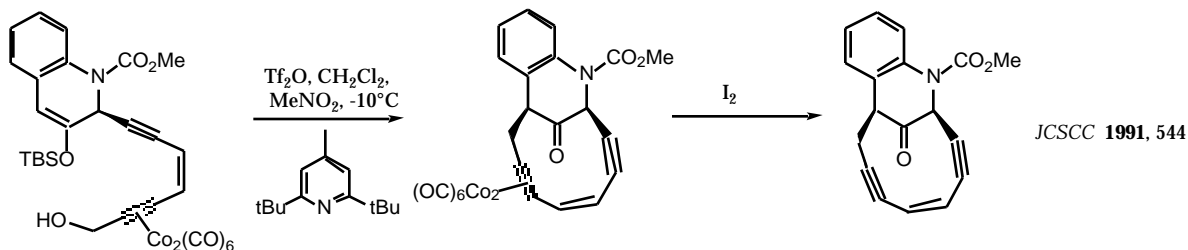
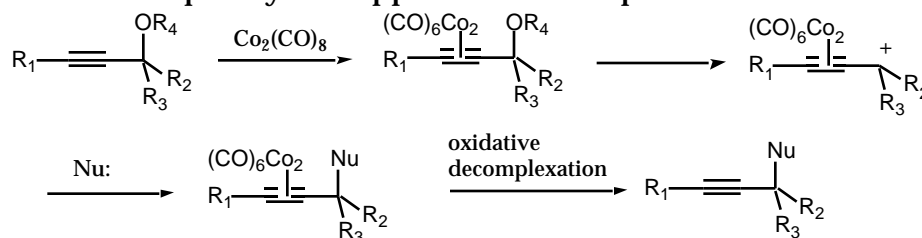


Copper Coupling- 1,3-diynes



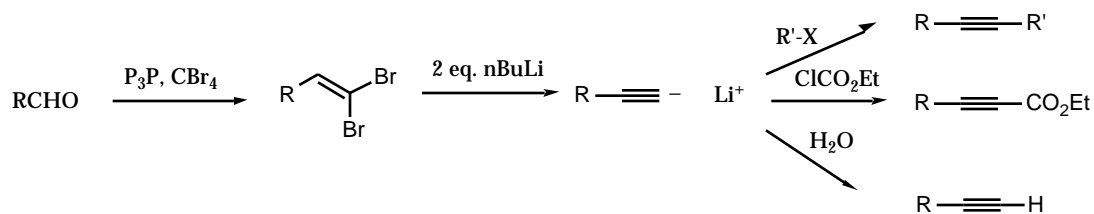
Nicholas Reaction

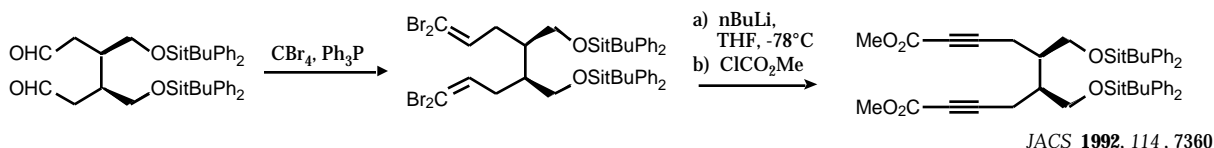
- acetylenes as their $Co_2(CO)_8$ complex can stabilize an η^5 -positive charge, which can subsequently be trapped with nucleophiles.



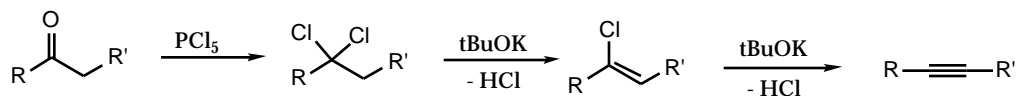
$Co_2(CO)_6$ -acetylene decomplexation: JOC **1997**, 62, 9380

From Aldehydes and Ketones

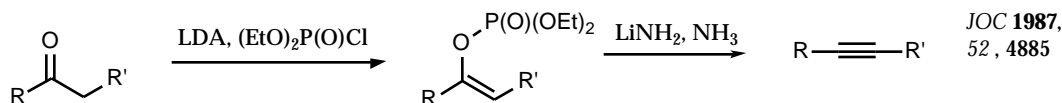




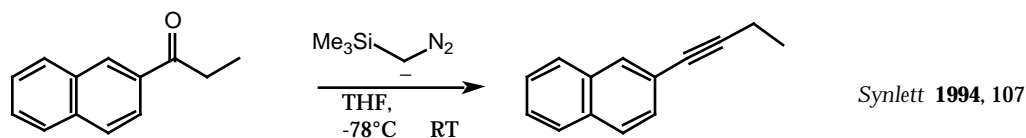
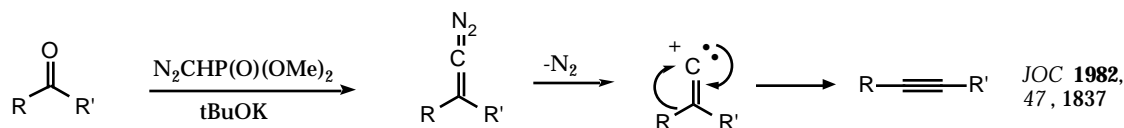
- by conversion of ketones to gem-dihalides followed by elimination



- by conversion of ketones to enol phosphates followed by elimination

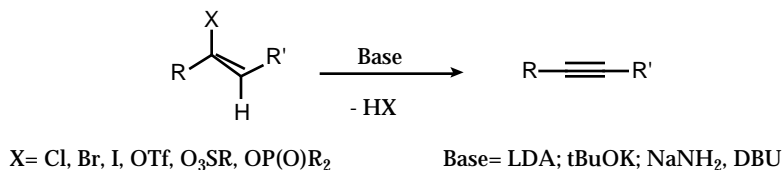


- Insertion reaction of a vinyl carbene (terminal acetylenes)

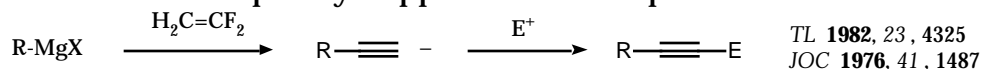


Via Elimination Reactions of Vinyl Halides

- Treatment of vinyl halides with strong base gives acetylenes.

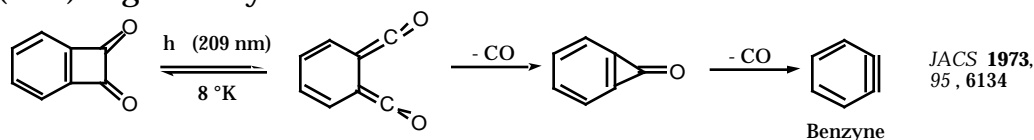


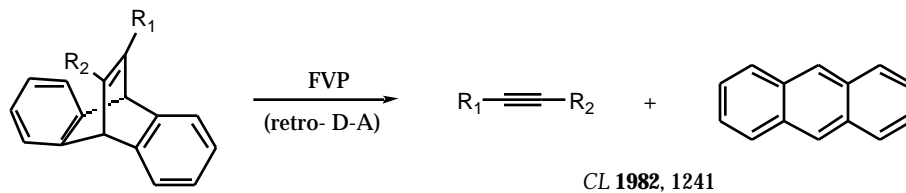
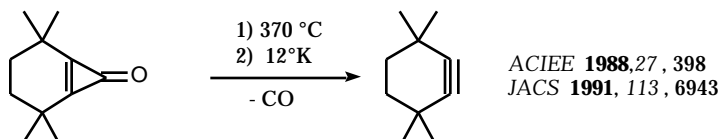
- Addition of Grignard reagents to 1,1-difluoroethylene yields an acetylide anion which can be subsequently trapped with electrophiles.



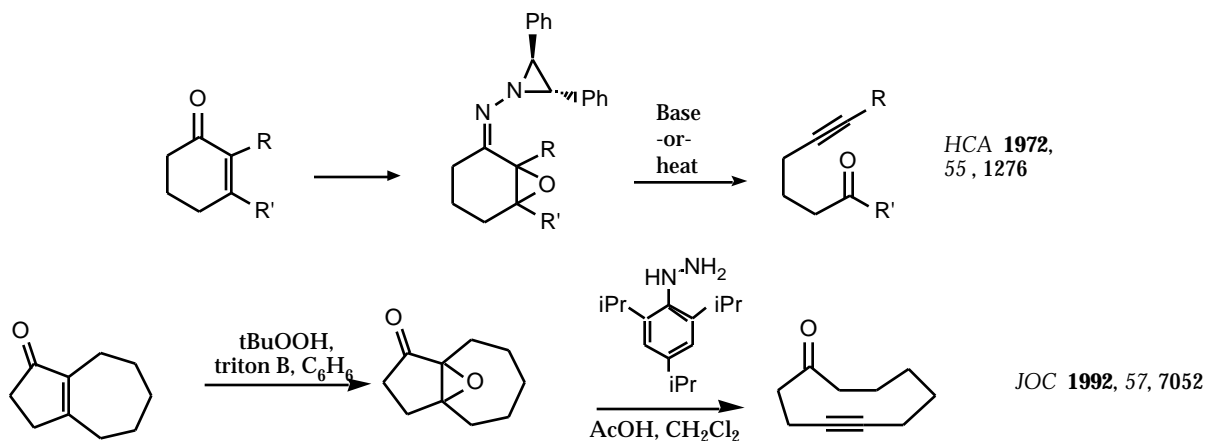
Strained Rings Topics in Current Chemistry **1983**, 109, 189.

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



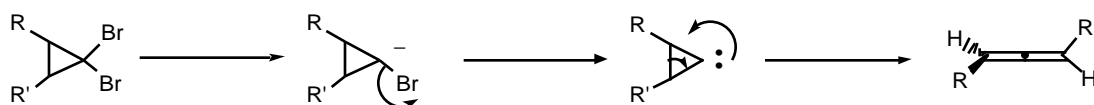


Eschenmoser Fragmentation

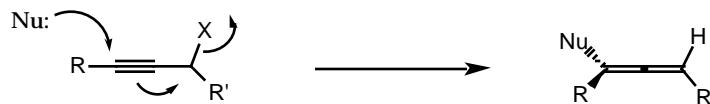


Allenes Tetrahedron **1984**, 40, 2805

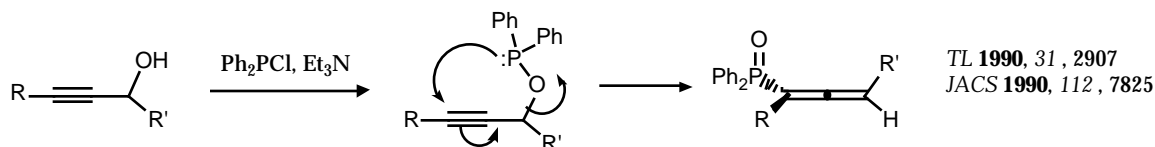
- from dihalocyclopropanes



- From SN2' Reactions



- from sigmatropic rearrangements from propargyl sulfoxides and phosphine oxides.



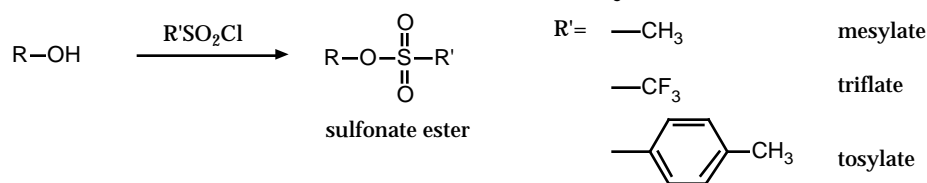
Functional Group Interconversions

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

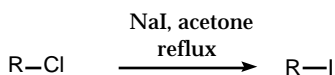
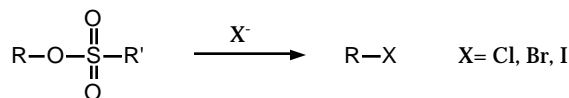


- sulfonate esters are very good leaving groups. Elimination is often a competing side reaction

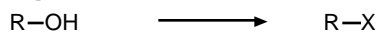
Halides

- halides are good leaving groups with the order of reactivity in $\text{S}_{\text{N}}2$ reactions being $\text{I} > \text{Br} > \text{Cl}$. 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

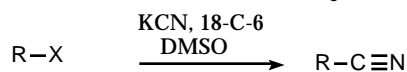


- R-OH to R-Cl
 - SOCl_2
 - $\text{Ph}_3\text{P, CCl}_4$
 - $\text{Ph}_3\text{P, Cl}_2$
 - $\text{Ph}_3\text{P, Cl}_3\text{CCOCCl}_3$

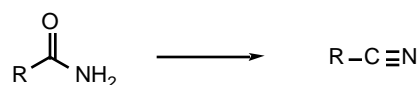
- R-OH to R-Br
 - PBr₃, pyridine
 - Ph₃P, CBr₄
 - Ph₃P, Br₂
- R-OH to R-I
 - Ph₃P, DEAD, MeI

Nitriles

- displacement of halides or sulfonates with cyanide anion



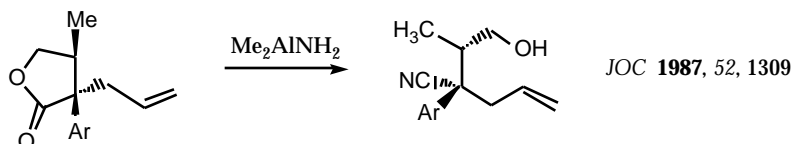
- dehydration of amides



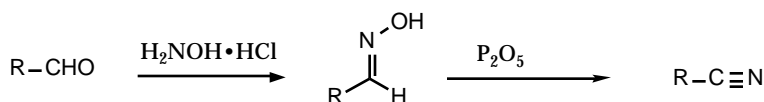
- POCl₃, pyridine
- TsCl, pyridine
- P₂O₅
- SOCl₂

- Reaction of esters and lactones with dimethylaluminium amide

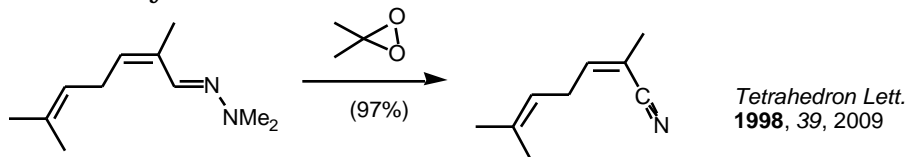
TL 1979, 4907



- Dehydration of oximes



- Oxidation of hydrazones

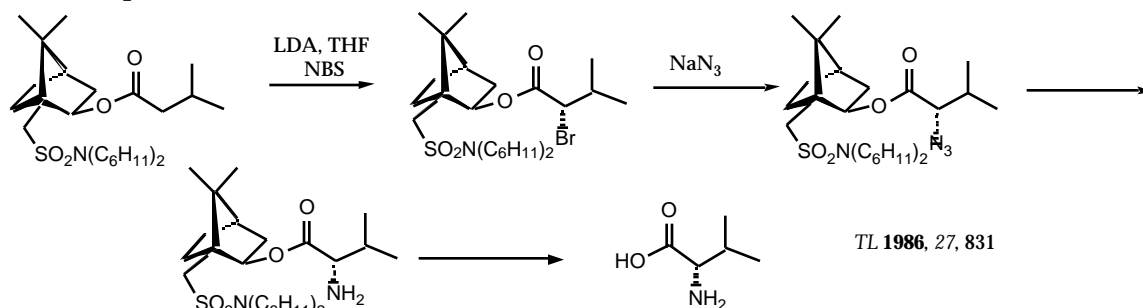


- Reduced to aldehydes with DIBAL.

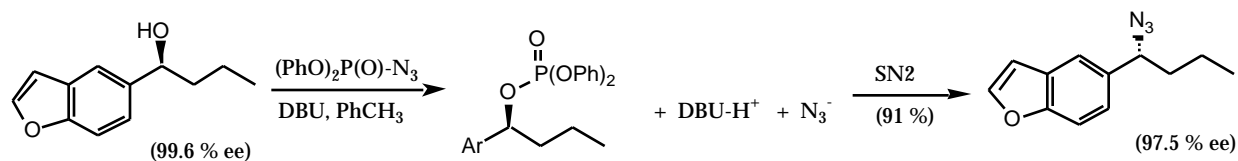
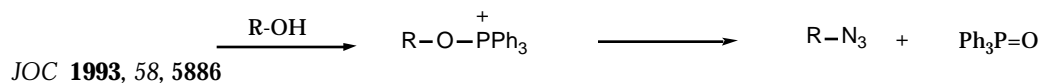
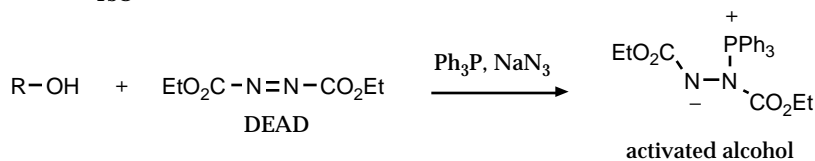
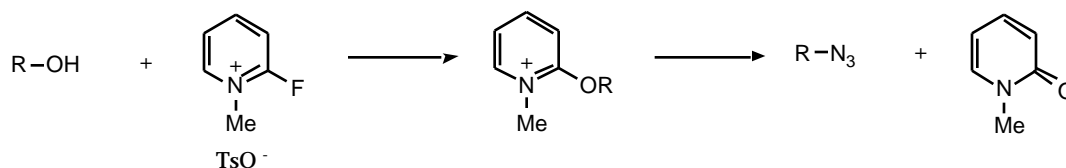


Azides

- displacement of halides and sulfonates with azide anion



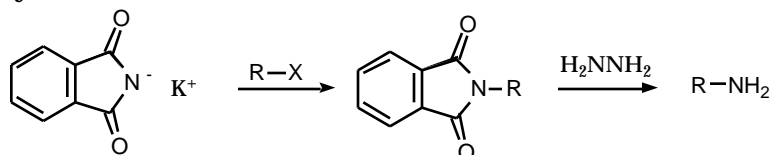
- activation of the alcohol



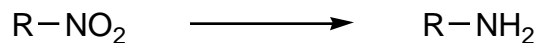
- Photolyzed to aldehydes

Amines

- Gabriel Synthesis

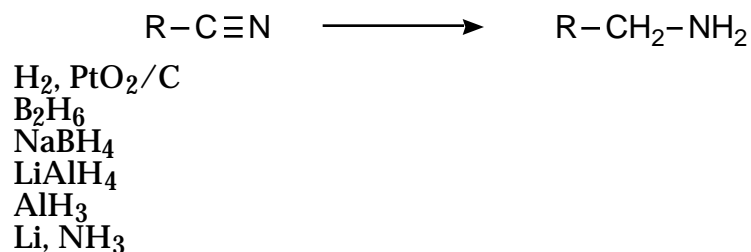


- reduction of nitro groups

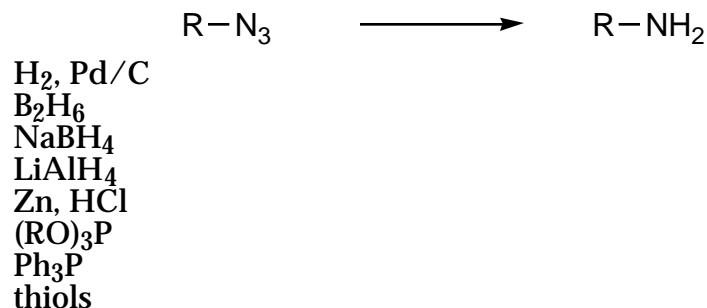


H₂, Pd/C
 Al(Hg), H₂O
 NaBH₄
 LiAlH₄
 Zn, Sn or Fe and HCl
 H₂NNH₂
 sodium dithionite

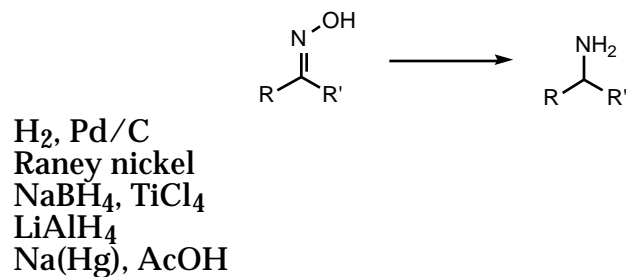
- reduction of nitriles



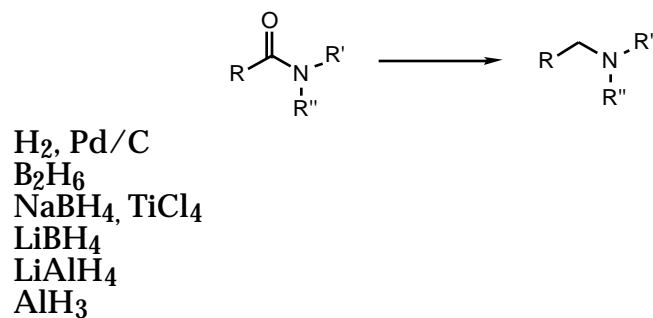
- reduction of azides



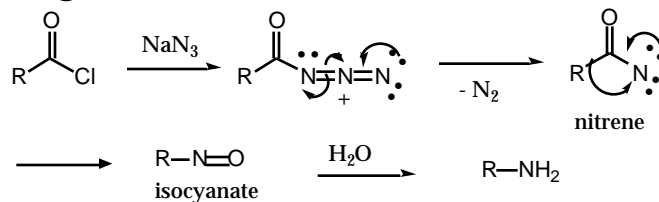
- reduction of oximes (from aldehydes and ketones)



- reduction of amides

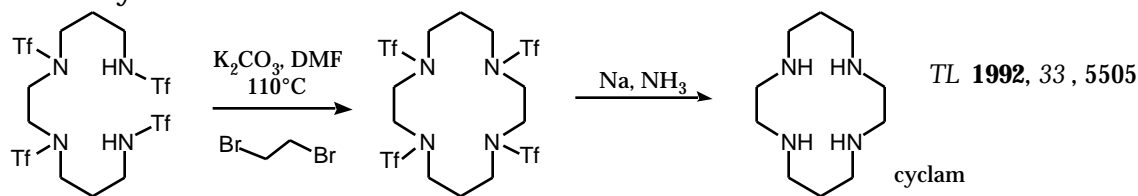


- Curtius rearrangement

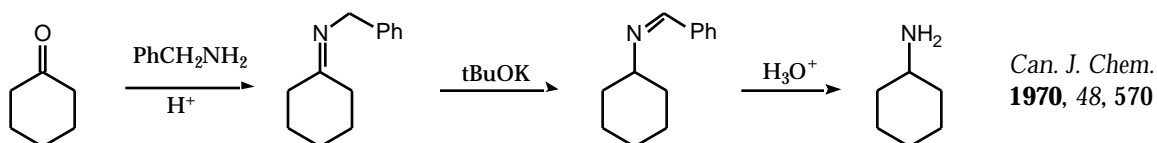


- reductive aminations of aldehydes and ketones
 - Borsch Reaction
 - Eschweiler-Clark Reaction

- alkylation of sulfonamides

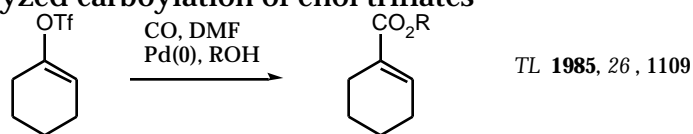


- transamination

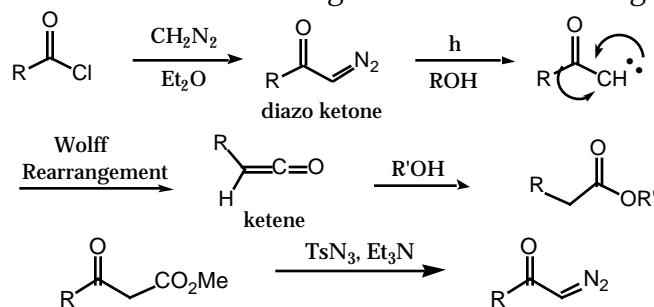


Esters and Lactones

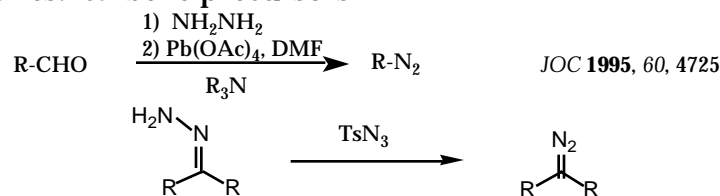
- Reaction of alcohols with "activated acids"
- Baeyer-Villiger Reaction *Organic Reactions* **1993**, 43, 251
- Pd(0) catalyzed carbonylation of enol triflates



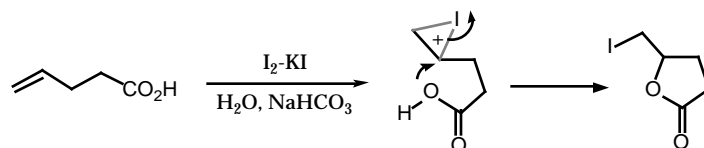
- Arndt-Eistert Reaction *Angew. Chem. Int. Ed. Engl.* **1975**, 15, 32.

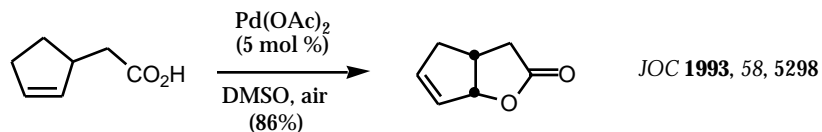


- Diazoalkanes: carbene precursors

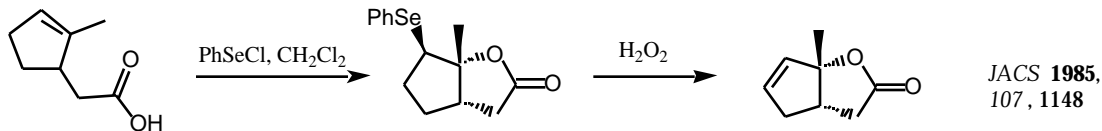


- Halo Lactonizations *review: Tetrahedron* **1990**, 46, 3321



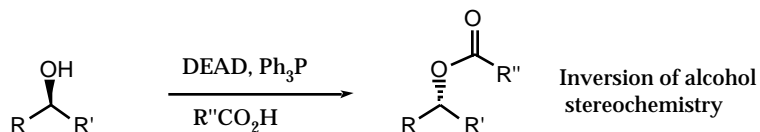


- Selenolactonization



- Mitsunobu Reaction

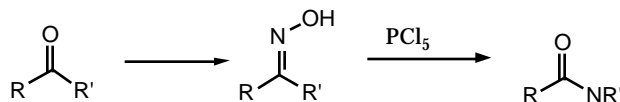
Synthesis **1981**, 1; Organic Reactions, **1991**, 42, 335
 Mechanism: JACS **1988**, 110, 6487



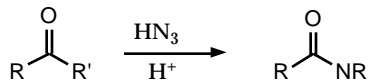
Amides and Lactams

- reaction of an "activated acid" with amines

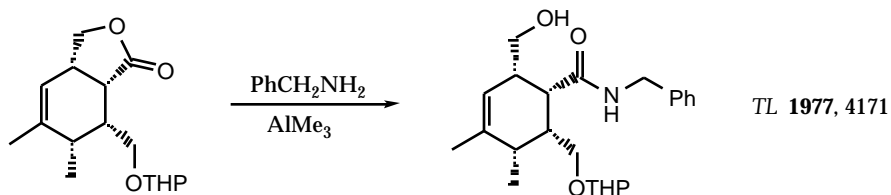
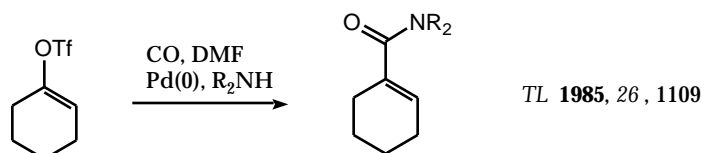
- Beckman Rearrangement Organic Reactions **1988**, 35, 1



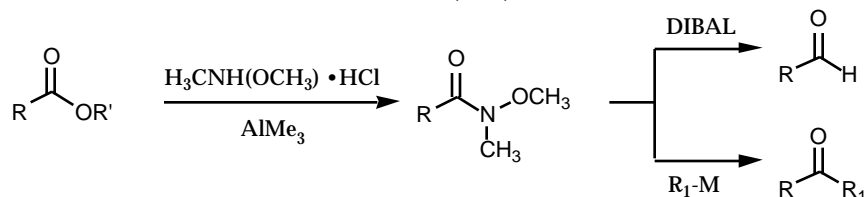
- Schmidt rearrangement



- others



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



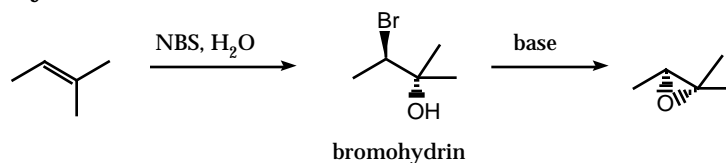
3 Membered Rings

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

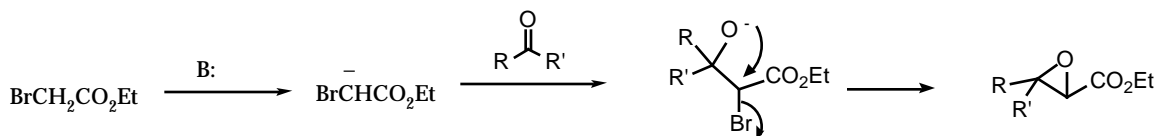
Epoxides

- peracid, hydroperoxide and dioxirane oxidation of alkenes
- transition metal catalyzed epoxidation of alkenes
 - Sharpless epoxidation
 - Metal oxo reagents (Jacobsen's reagent)

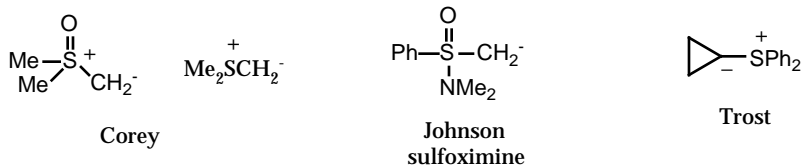
- from halohydrins



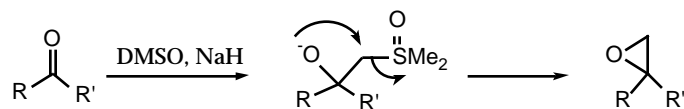
- Darzen's Condensation



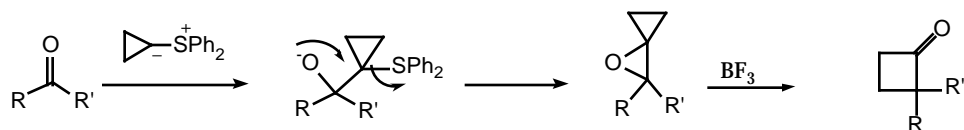
- sulfur ylides *Chem. Rev.* **1997**,97, 2421.



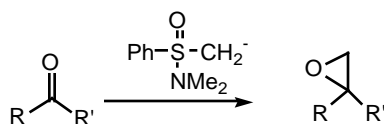
- dimethylsulfoxonium methylide and dimethylsulfonium methylide (Corey's reagent) review: *Tetrahedron* **1987**, 43, 2609.



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

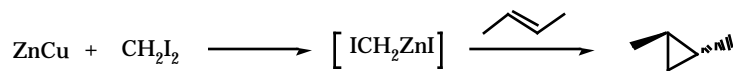


- sulfoximine ylides (Johnson's reagent) *ACR* **1973**, 6, 341

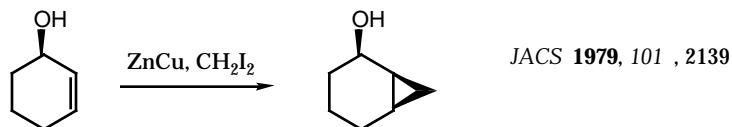


Cyclopropanes

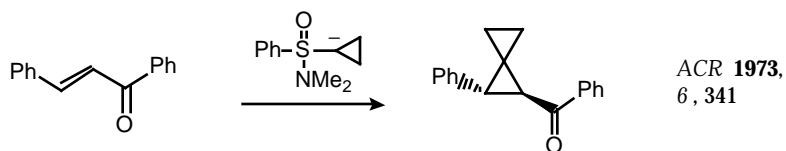
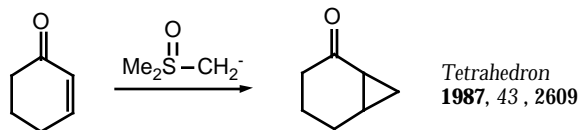
- Simmons-Smith Reaction *Org. Reactions* **1973**, 20, 1.



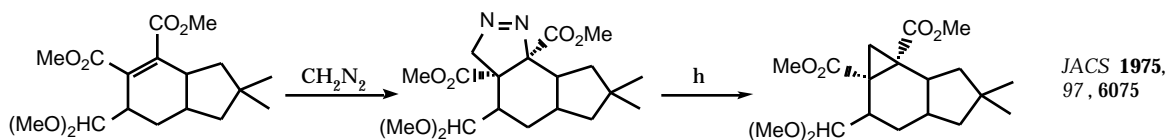
- polar groups (-OH, -NR₂, -CO₂R) can direct the cyclopropanation



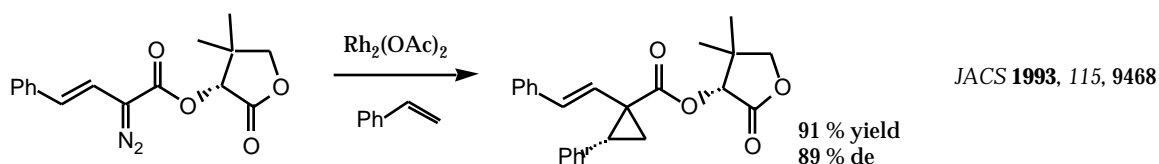
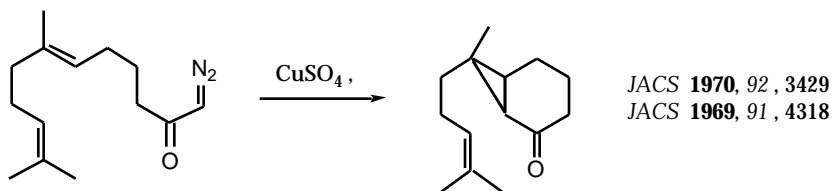
- sulfur ylides



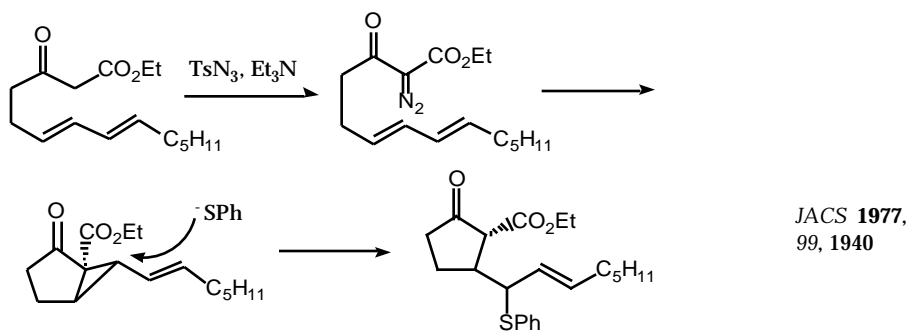
- diazo alkanes and diazo carbonyls *Synthesis* **1972**, 351; **1985**, 569
 - cyclopropanation with diazoalkanes; olefin requires at least one electron withdrawing group.



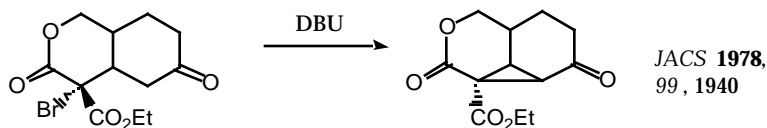
- diazoketones; photochemical or metal catalyzed decomposition of diazoketones to carbenes followed by cyclopropanation of olefins. *Org. Rxns.* **1979**, 26, 361; *Tetrahedron* **1981**, 37, 2407



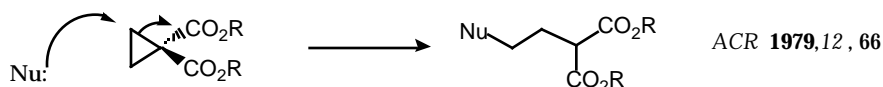
- Asymmetric cyclopropanation: Doyle, *Chem Rev.* **1998**, 98, 911
Aldrichimica Acta **1997**, 30, 107



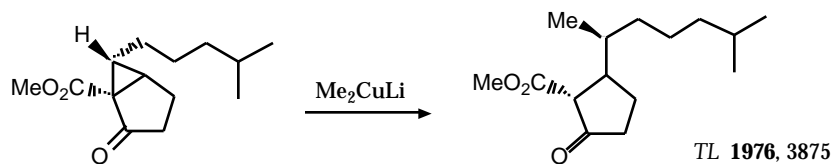
- $\text{S}_{\text{N}}2$ Reactions



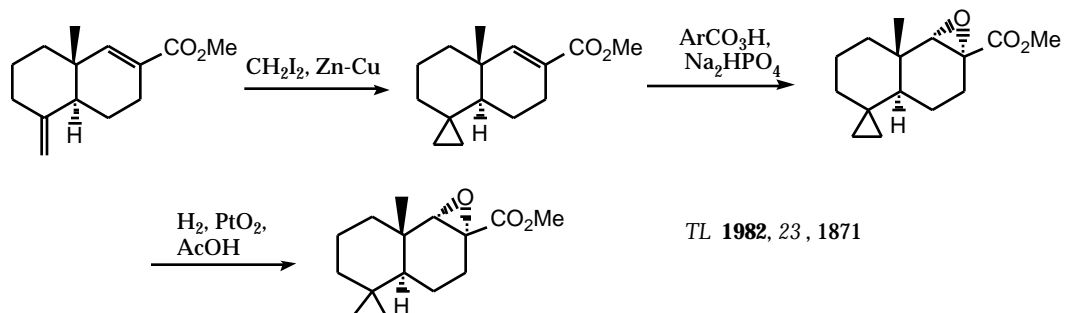
- Electrophilic Cyclopropanes review: *ACR* **1979**, 12, 66
 - in many ways, cyclopropanes react similarly to double bonds
 - homo-1,4-addition



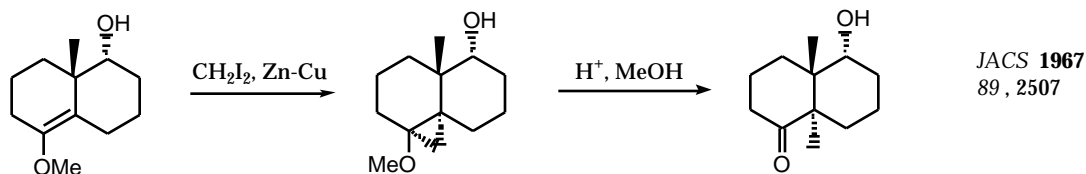
Nu: = malonate anion, amines, thiolate anion, enamines, cuprates
(usually requires double activation of cyclopropane)



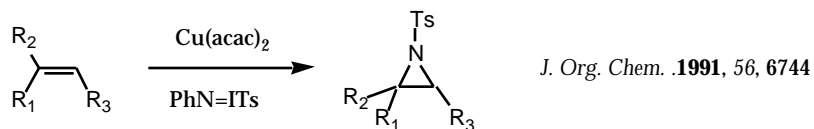
- hydrogenation



- hydrolysis



Aziridines



4 Membered Rings

1. cyclobutanes & cyclobutenes
2. oxatanes

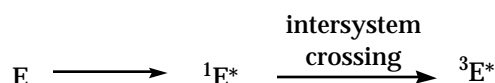
Cyclobutanes

- [2+2] cycloadditions

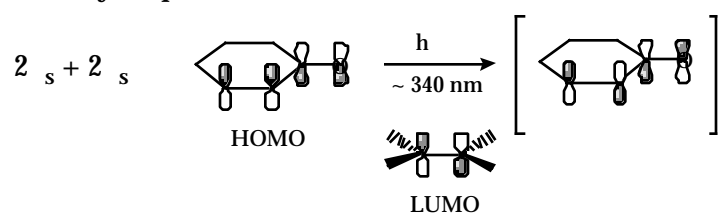
- photochemical cycloadditions ($2s + 2s$)

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

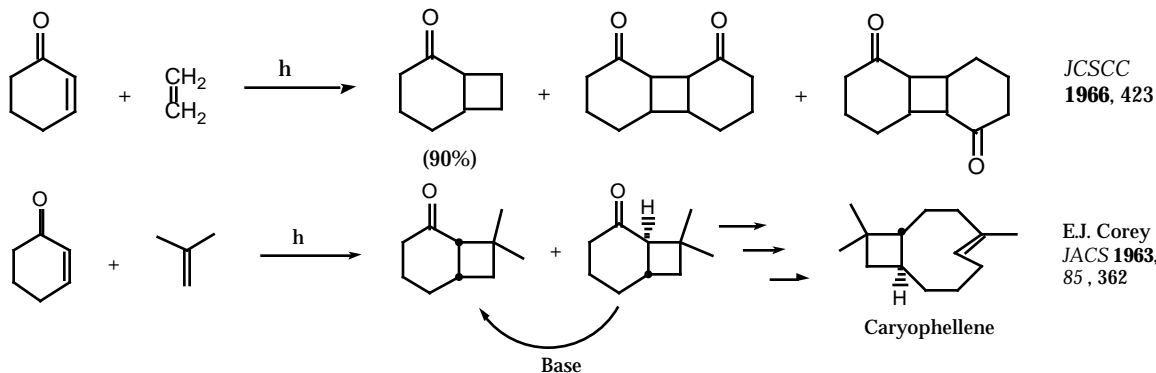
- for synthetic purposes, cyclic, α,β -unsaturated carbonyl are the most useful.



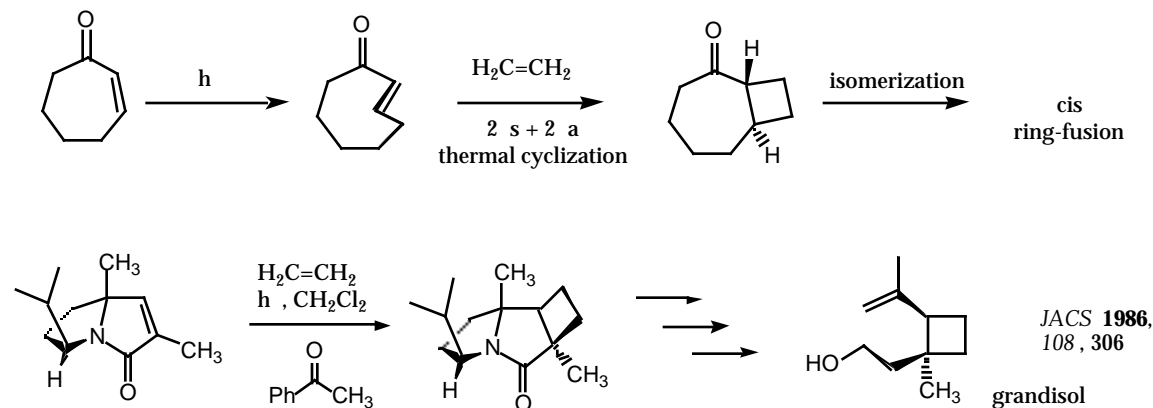
- symmetry requirements

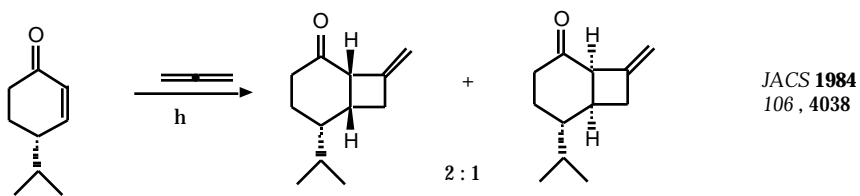


- enones with olefins

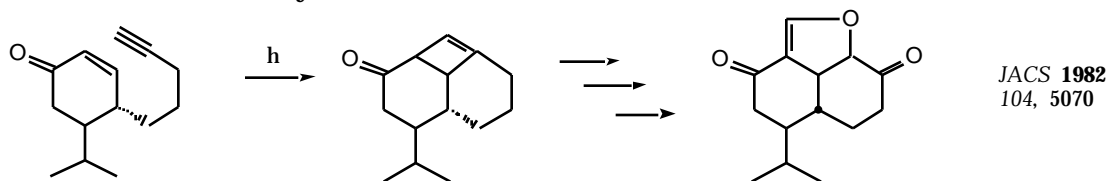


Hot Ground State?

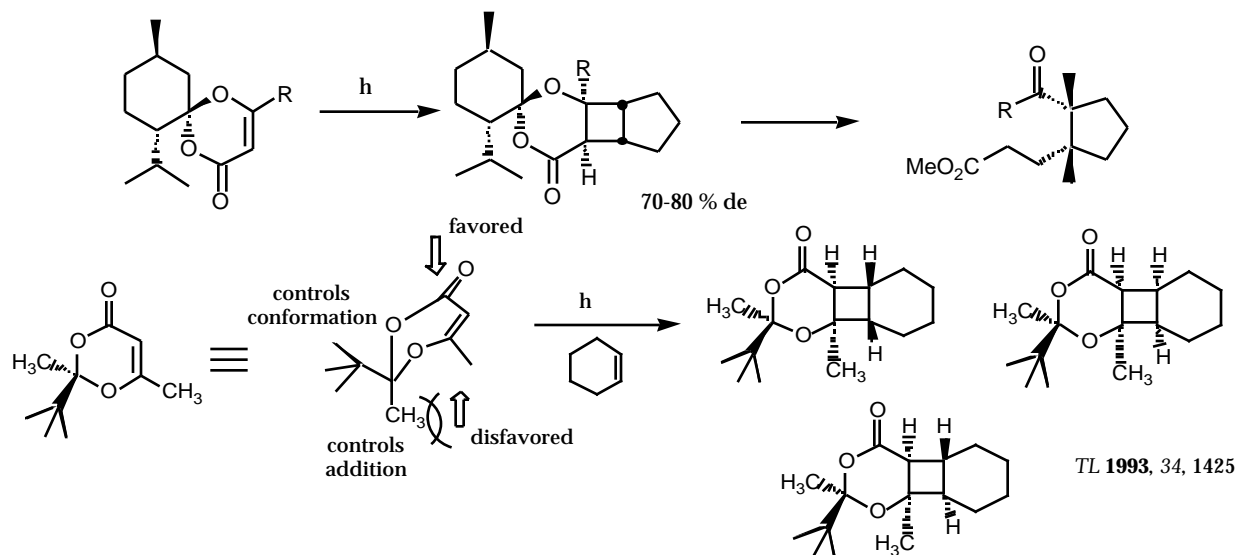
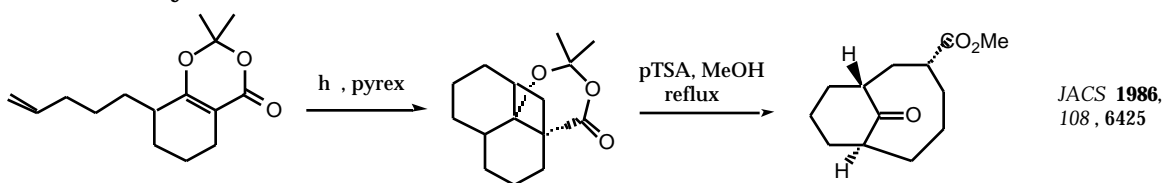




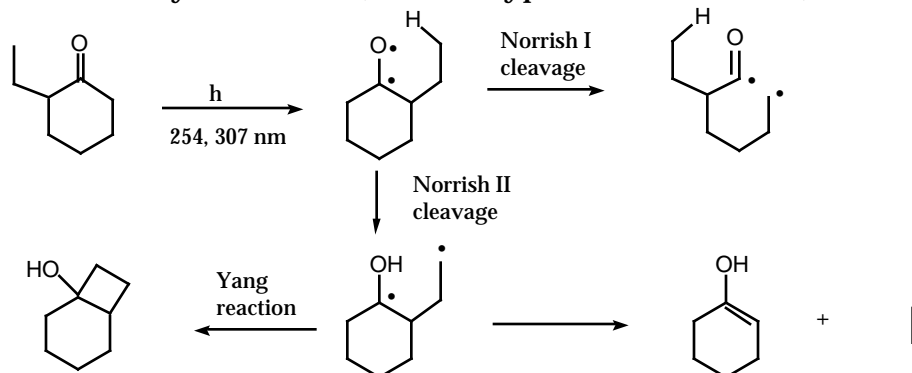
- enones with acetylenes



- DeMayo Reaction



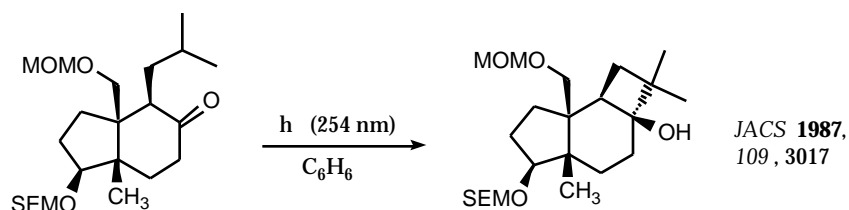
- Photochemistry of Ketones (Norrish Type I and II reactions)



- filtering photochemical reaction to prevent Norrish reactions

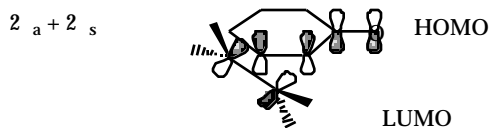
quartz	180 nm
Vycor	200 nm
Pyrex	280 nm
Uranium glass	320 nm

- Yang Reaction

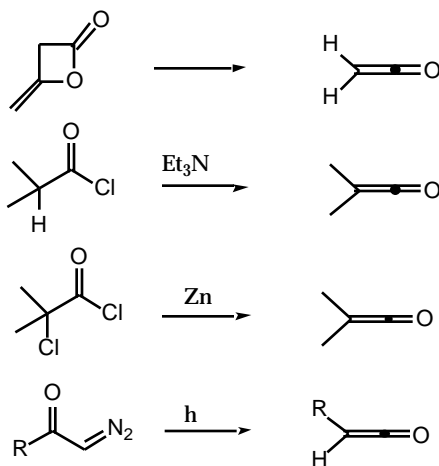


- thermal cycloadditions ($2_a + 2_s$)

- symmetry requirements

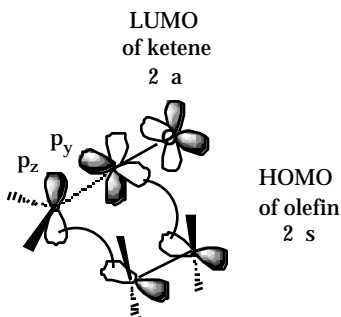


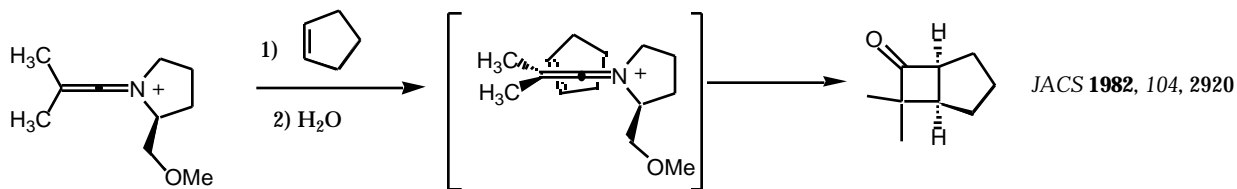
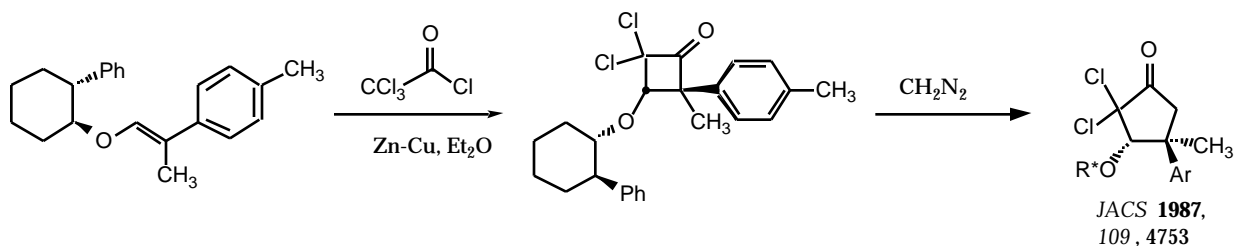
- ketenes



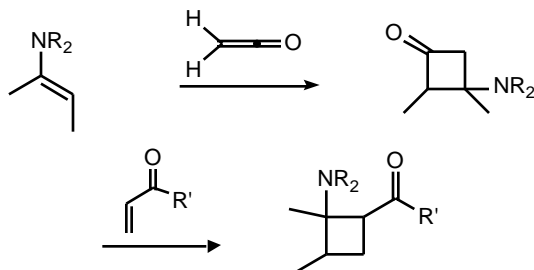
- thermal cyclization of ketene with olefins

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

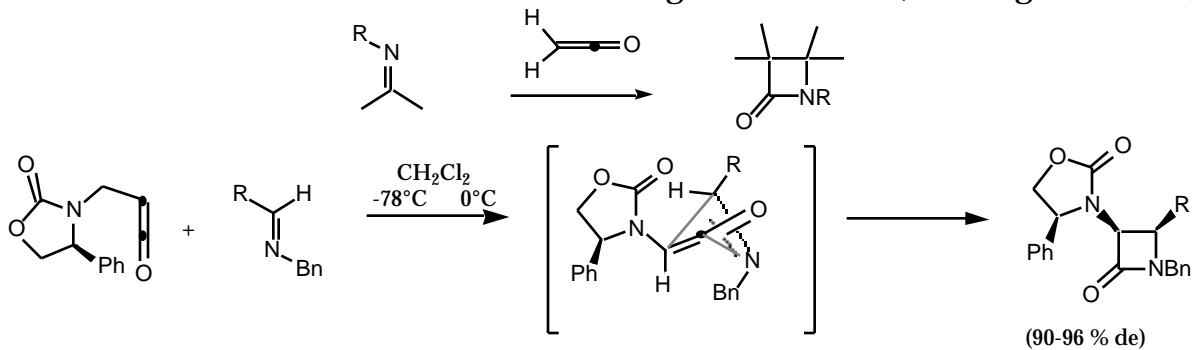




-reaction of ketene with enamines

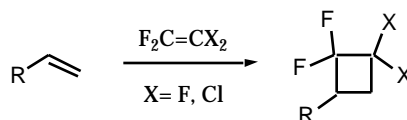


- reaction of ketene with imines to give β -lactams (Staudinger Reaction)

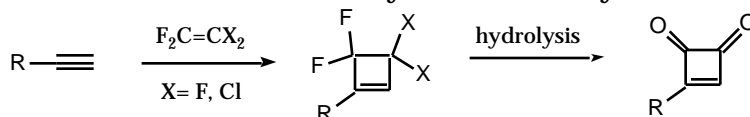


- reaction of difluorodihaloethylene with olefins

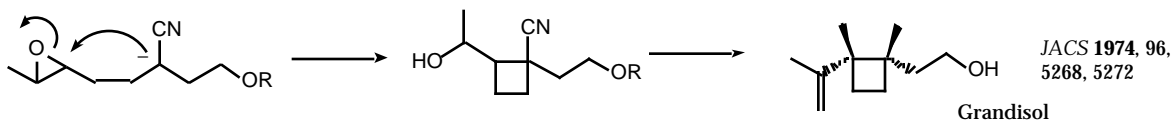
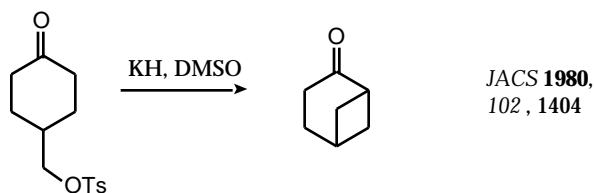
Organic Reactions **1962**, 12, 1



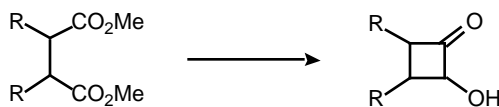
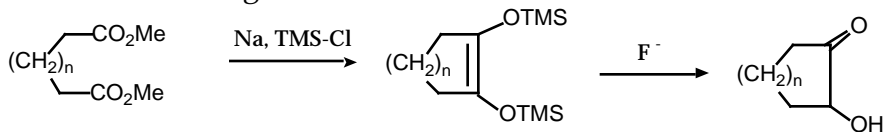
- reaction of difluorodihaloethylene with acetylenes- biradical mechanism



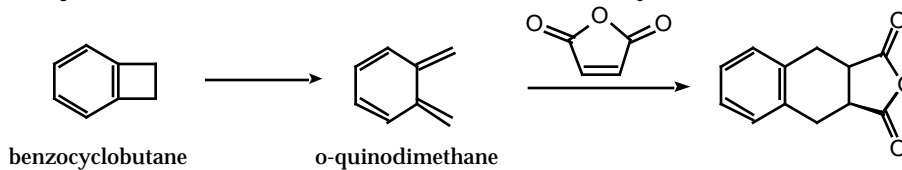
- S_N2 Reaction



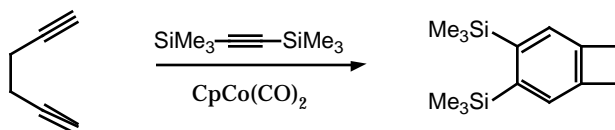
- acyloin reaction *Organic Reactions* **1976**, 23, 259



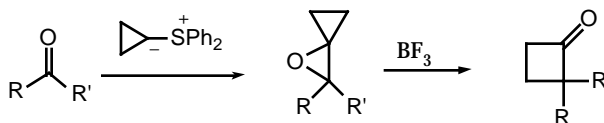
- benzocyclobutanes *ACIEE* **1984**, 23, 539; *Synthesis* **1978**, 793



- cyclotrimerization of 1,5-dienes with an acetylenes

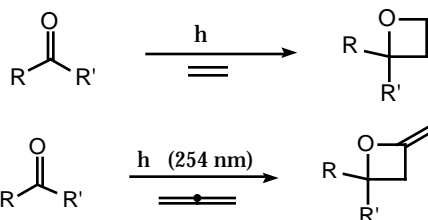


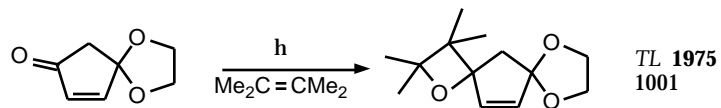
- sulfur ylides



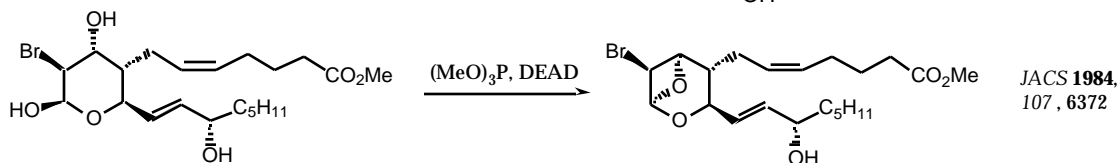
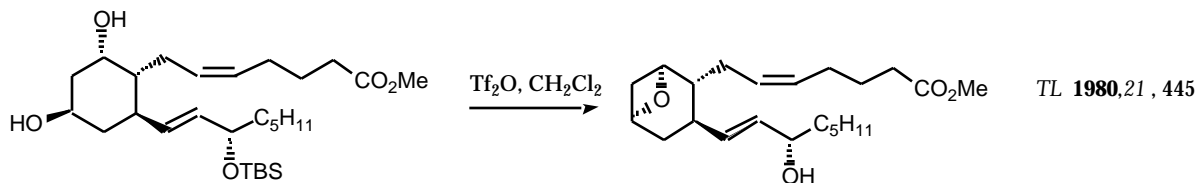
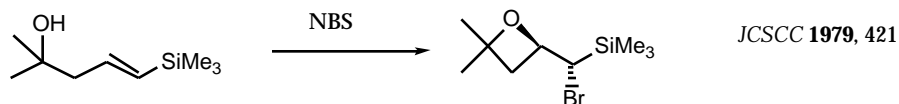
Oxatanes *Organic Photochemistry* **1981**, 5, 1

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

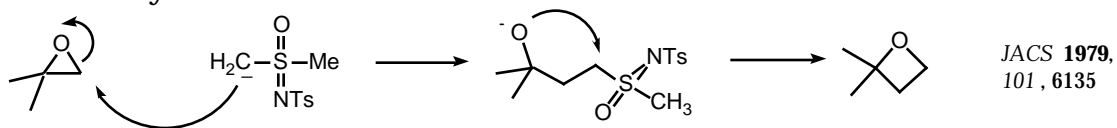




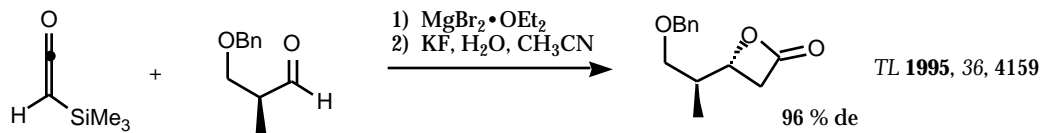
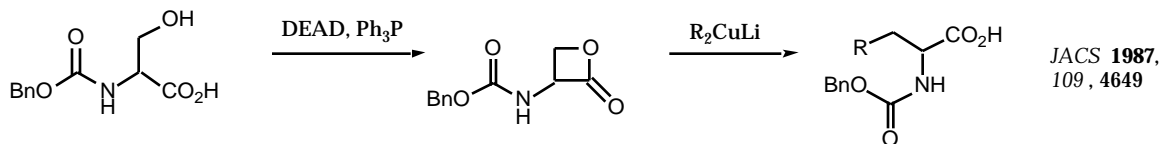
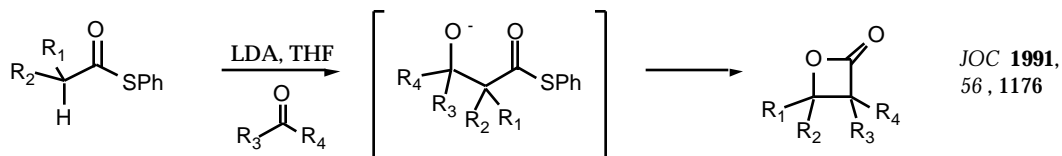
- S_N2 reaction



- sulfur ylides



-Lactones



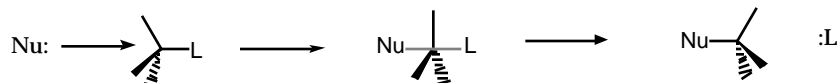
Baldwin's Rules (Suggestions) for Ring Closure

JOC 1977, 42, 3846

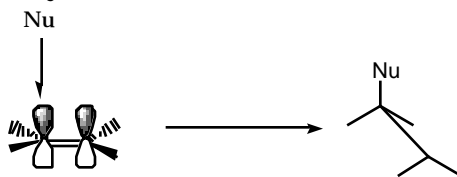
JCSCC 1976, 734, 736, 738

Approach Vector Analysis

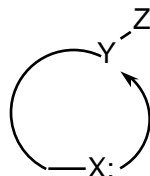
- for an S_N2 displacement at a tetrahedral center, the approach vector of the entering nucleophile is 180° from the departing leaving group



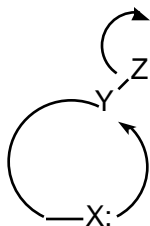
- for the addition of a nucleophile to an Sp^2 center, the nucleophile approaches perpendicular to the π -system.

*Nomenclature*

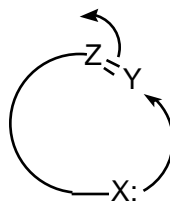
1. indicate ring size being formed
 - 3 membered ring = 3
 - 4 membered ring = 4
 - etc.
2. indicate geometry of electrophilic atom
 - if Y = Sp^3 center; then **Tet** (tetrahedral)
 - if Y = Sp^2 center; then **Trig** (trigonal)
 - if Y = Sp center; then **Dig** (digonal)



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



Exo



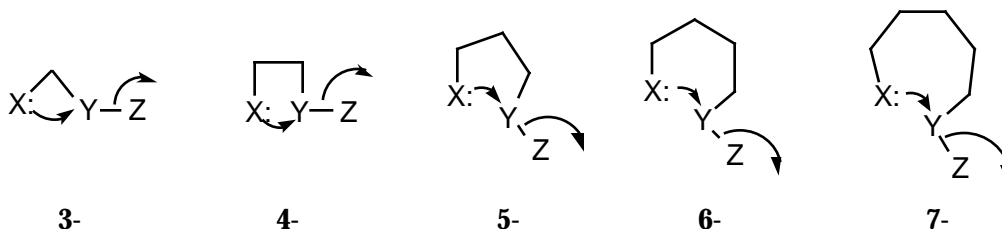
Endo

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.

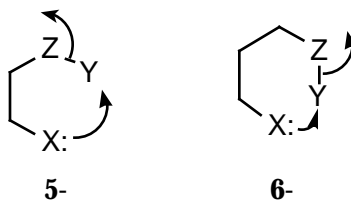
Rules (Suggestions) for Ring Closure

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



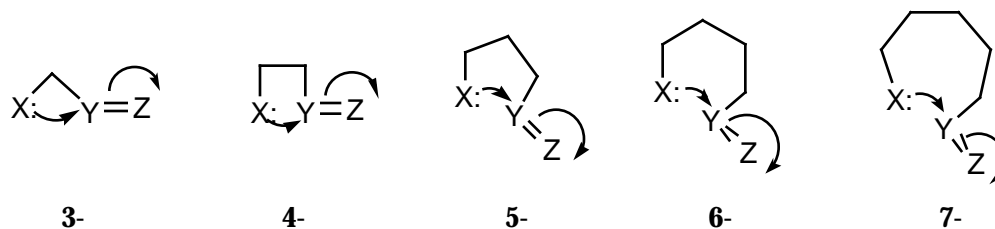
-----Favored-----

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



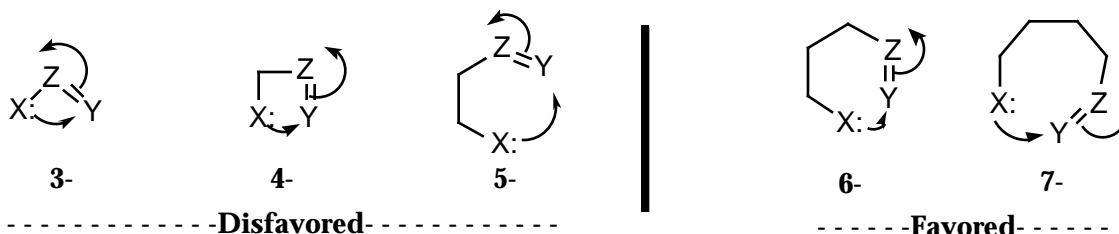
-----Disfavored-----

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

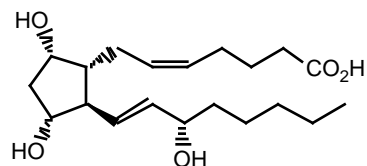
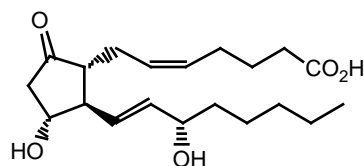
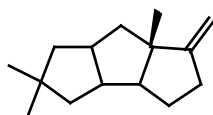


-----Favored-----

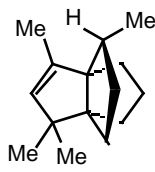
- **3-Endo-Trig**, **4-Endo-Trig** and **5-Endo-Trig** are disfavored; **6-Endo-Trig**, **7-Endo-Trig**, etc. are favored



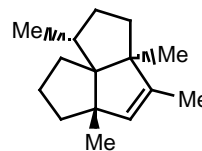
5 Membered Rings

PGF₂PGE₂

Hirsutene



Modhephane



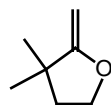
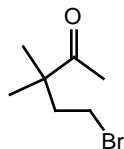
Isocumene

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

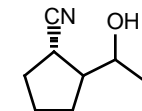
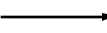
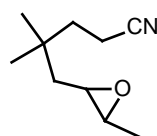
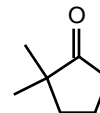
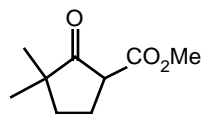
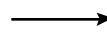
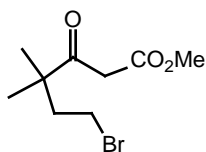
Synthesis **1973**, 397; *ACIEE* **1982**, 21, 480;

Intramolecular S_N2 Reaction

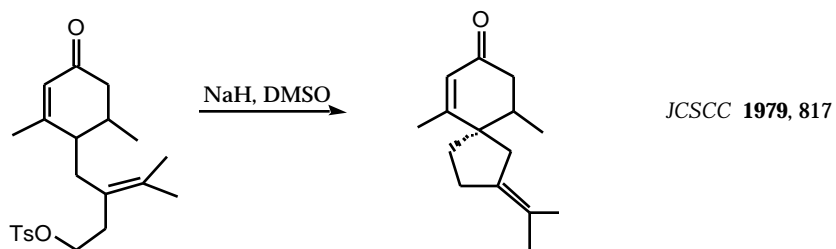
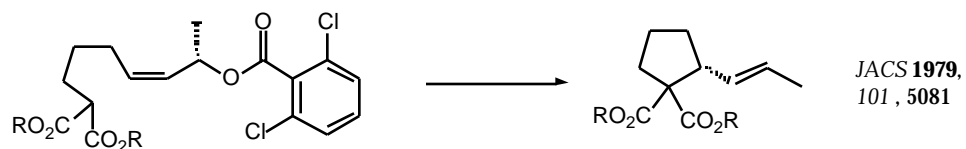
5-exo-tet: favored



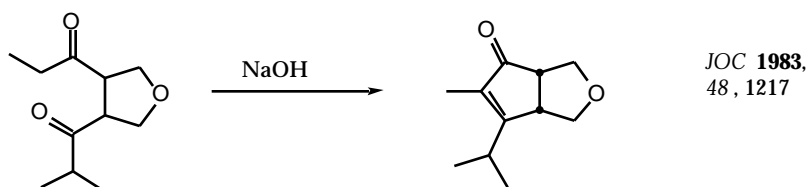
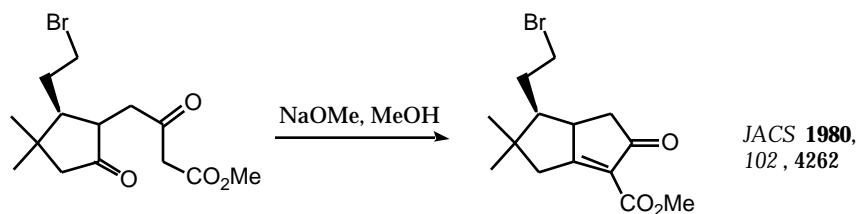
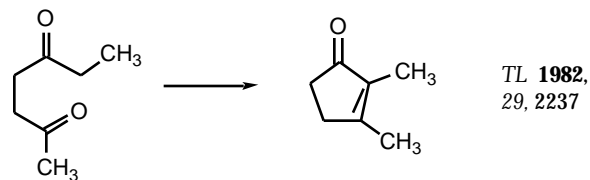
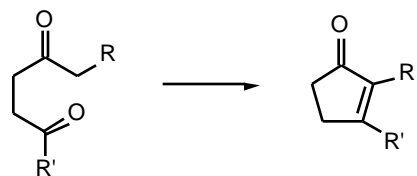
JCSCC **1973**, 233



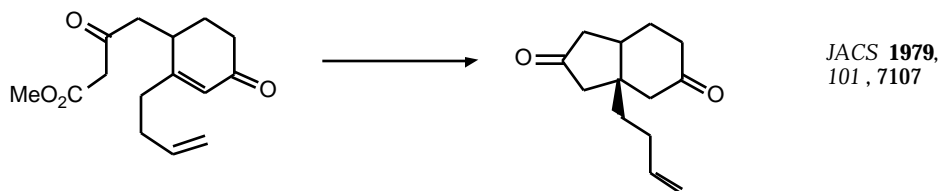
JACS **1974**, 96, 5268



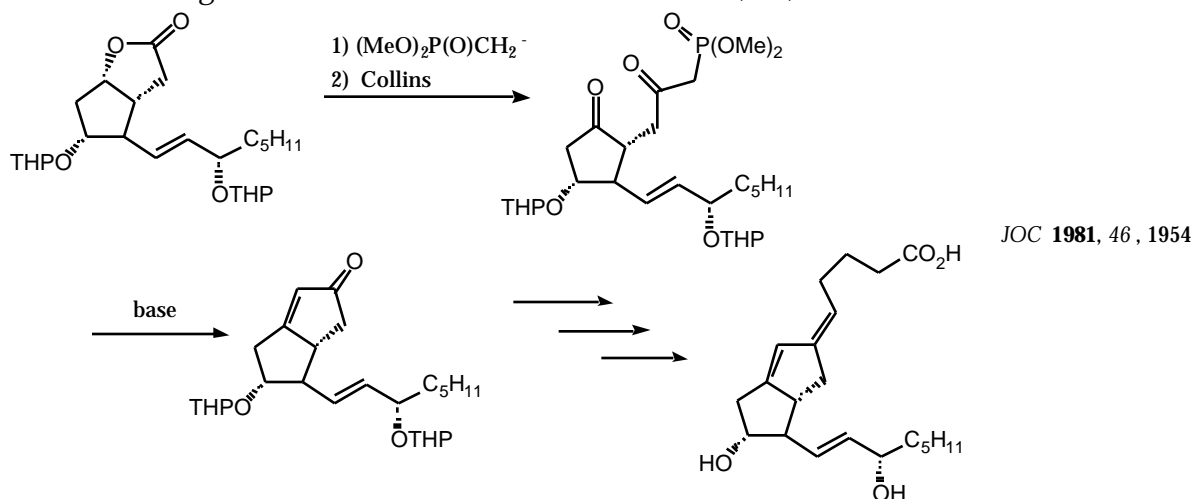
Intramolecular Aldol Condensation 5-exo-trig: favored
intramolecular aldol condensation of 1,4-diketones



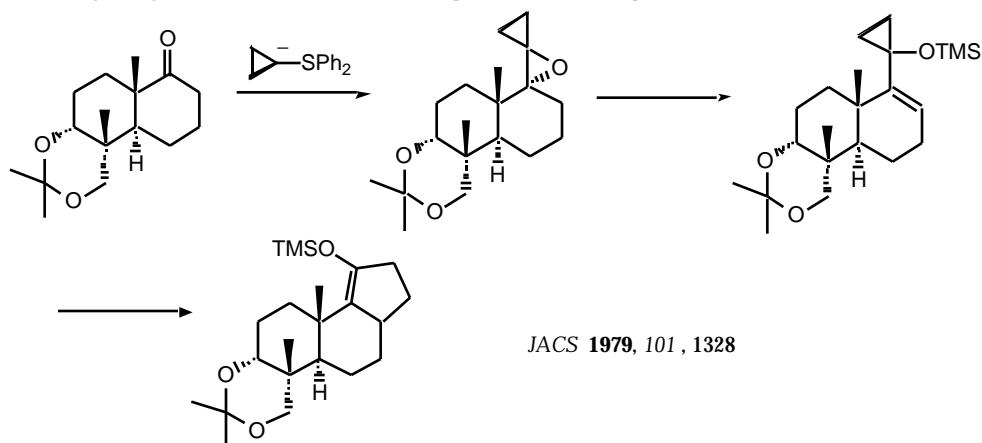
Intramolecular Michael Addition 5-exo-tet: favored
Organic Reactions **1995**, 47, 315-552



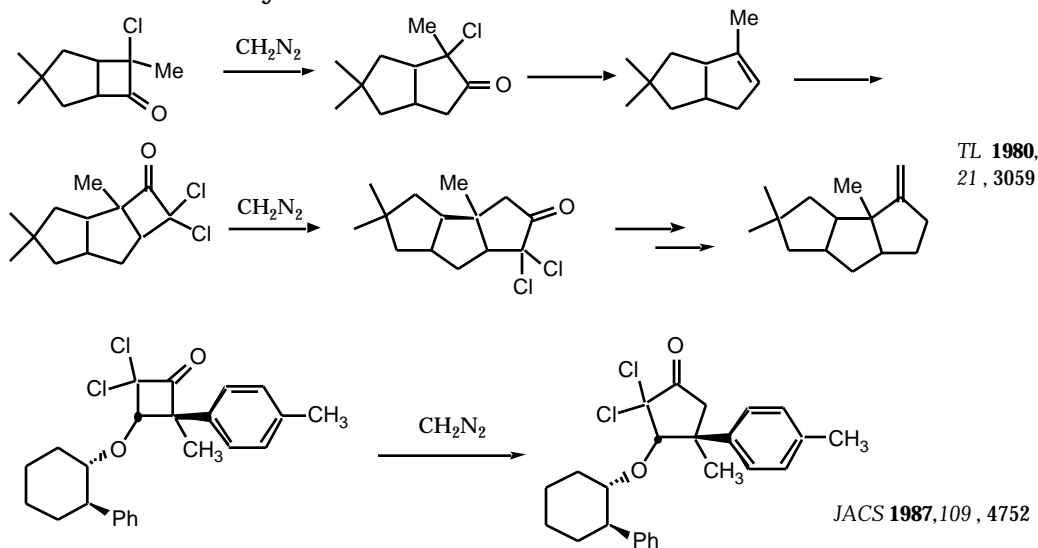
Intramolecular Wittig Olefination

Tetrahedron **1980**, 36, 1717

Ring Expansion Reactions

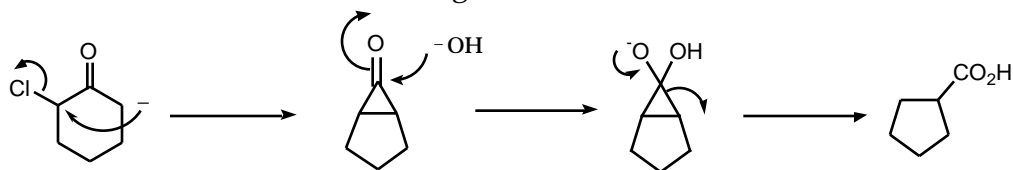
- 3 5: Vinyl Cyclopropane Rearrangement *Organic Reactions* **1985**, 33, 247.

- 4 5: Reaction of cyclobutanones with Diazomethane

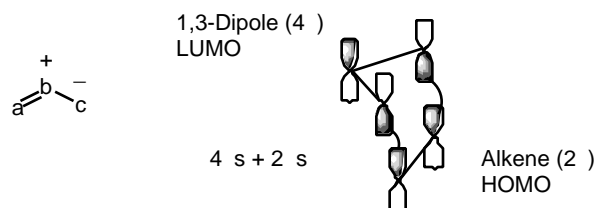


Ring Contraction Reactions

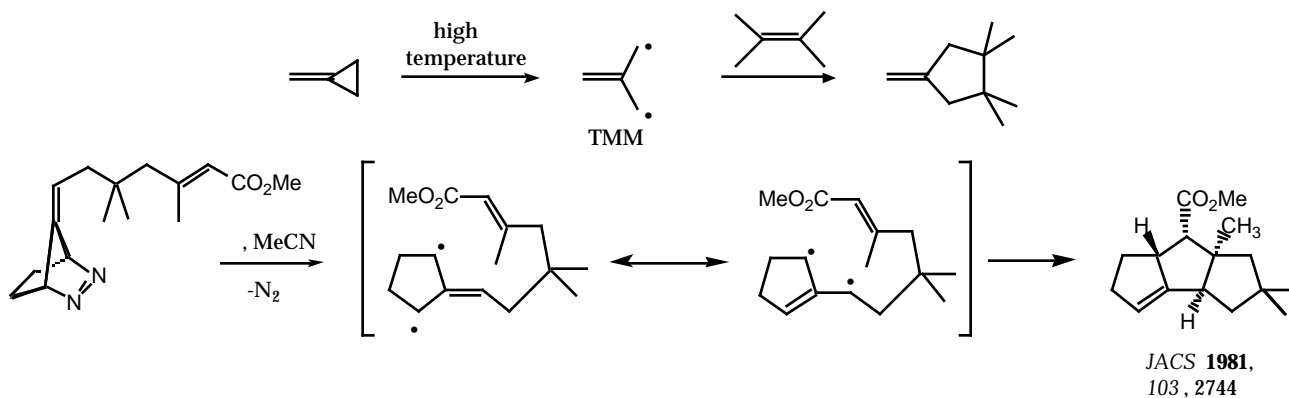
- 6 5: Favorskii Reaction *Organic Reactions* **1960**, 11, 261



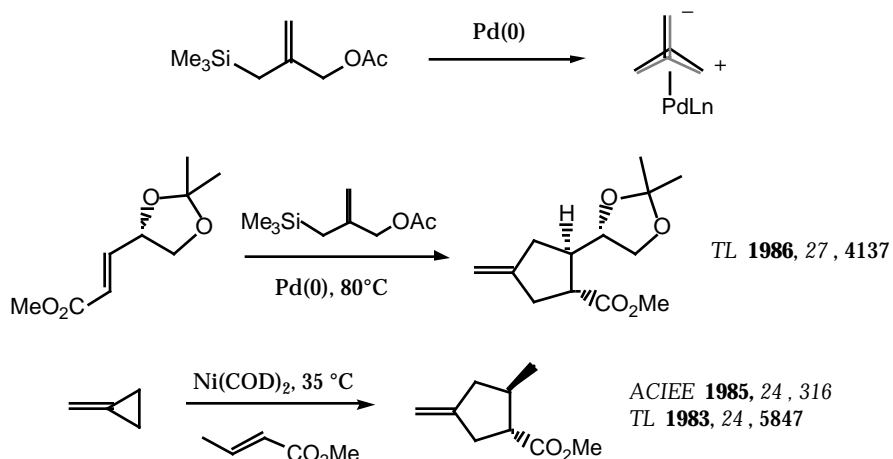
1,3-Dipolar Addition to Olefins *1,3-Dipolar Cycloaddition Chemistry*, vol 1 & 2 (A. Padwa ed.) (Wiley, NY 1984); *ACIEE* **1977**, 16, 10. *Chem Rev.* **1998**, 98, 863.



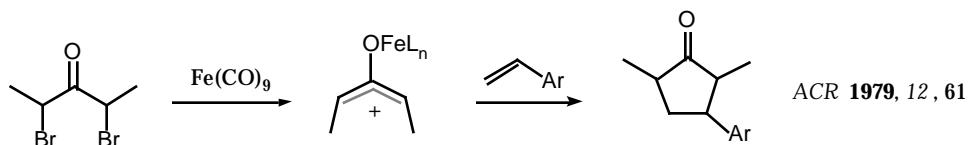
- trimethylenemethane (TMM) *ACIEE* **1986**, 25, 1. *Synlett* **1992**, 107.



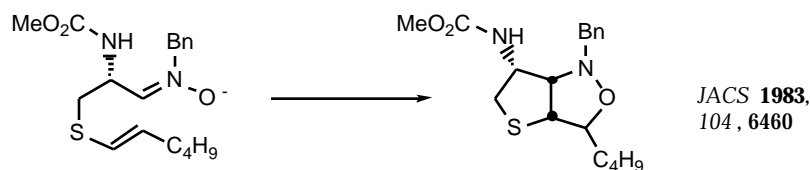
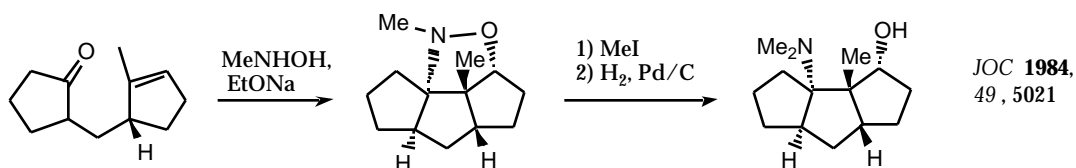
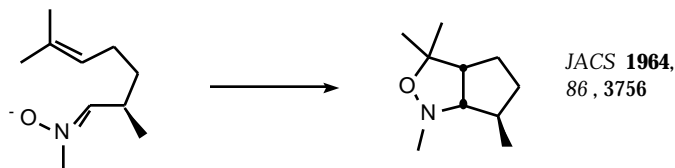
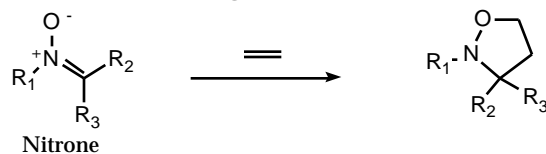
note: TMM usually reacts poorly w/ electron deficient olefins



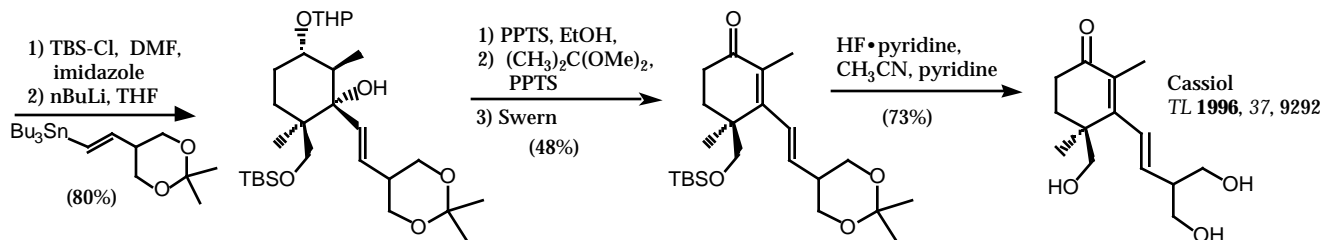
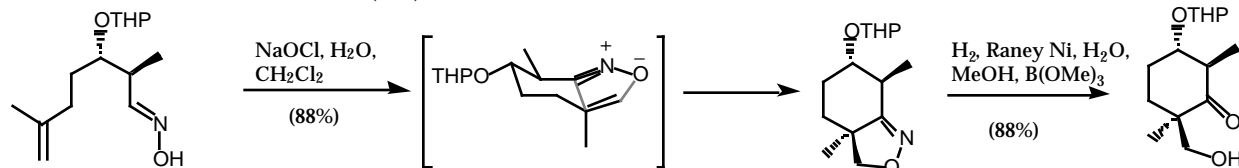
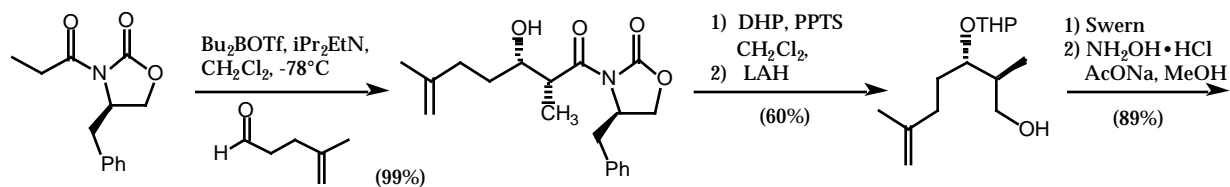
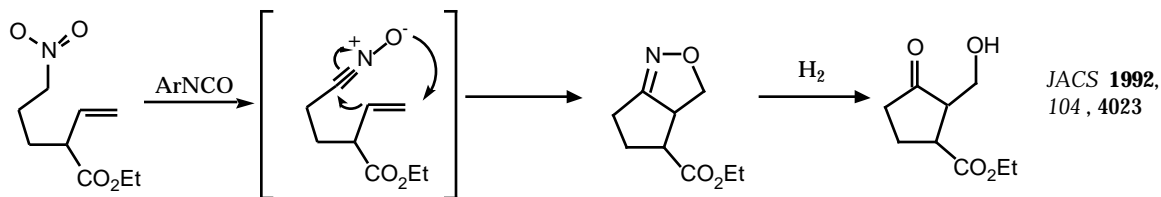
- , '-dihaloketones

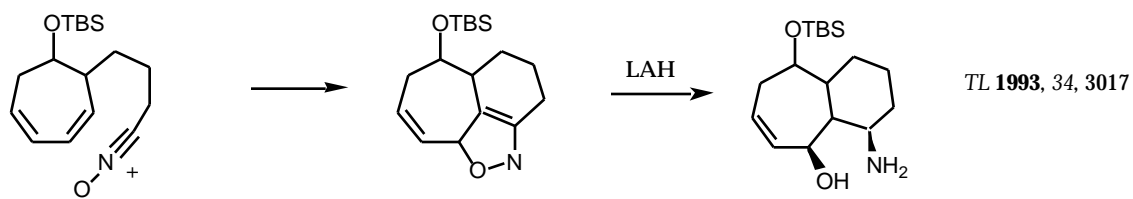


- nitrones ACR **1979**, 12, 396; *Organic Reactions*, **1988**, 36, 1

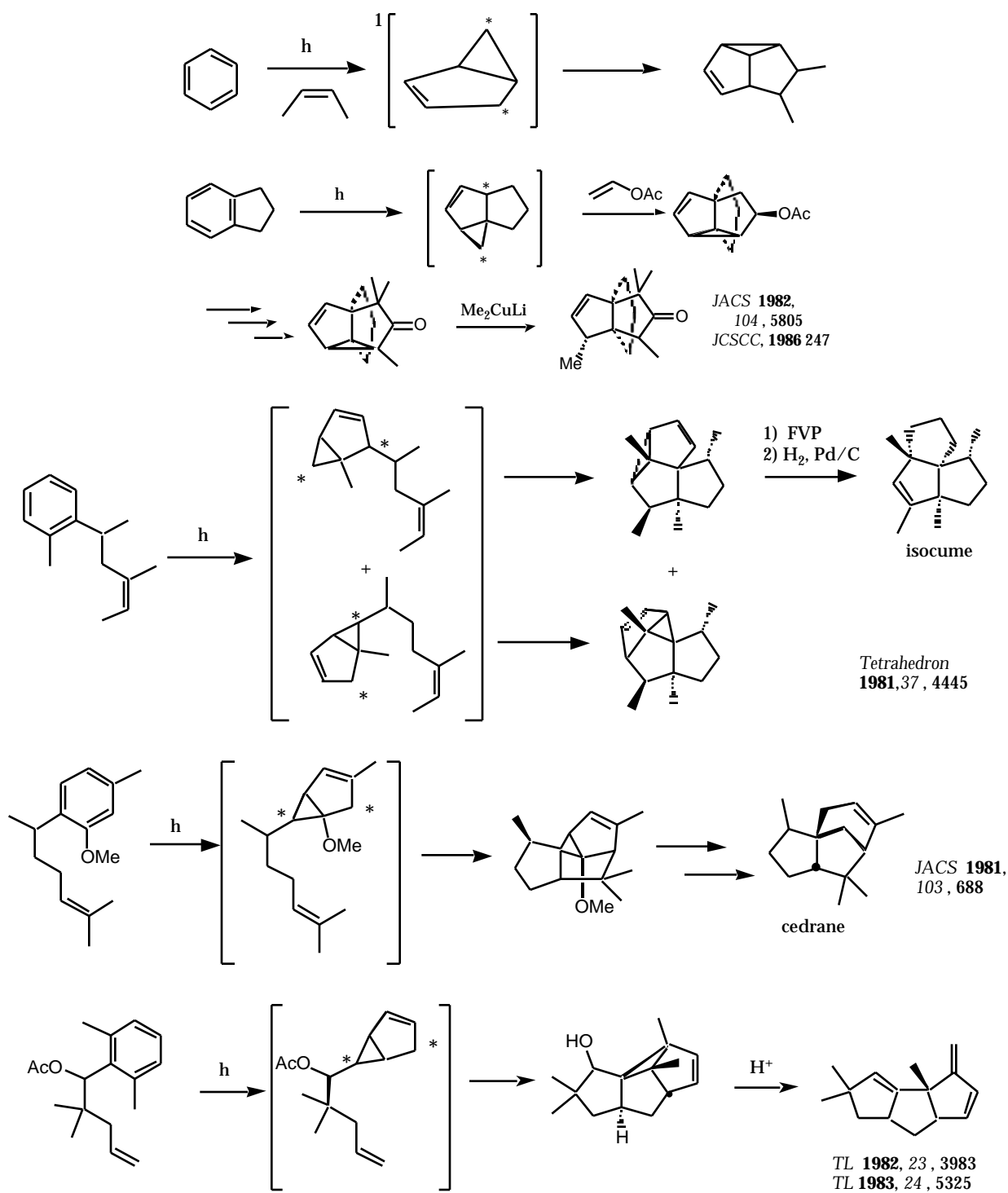


- nitrile oxides



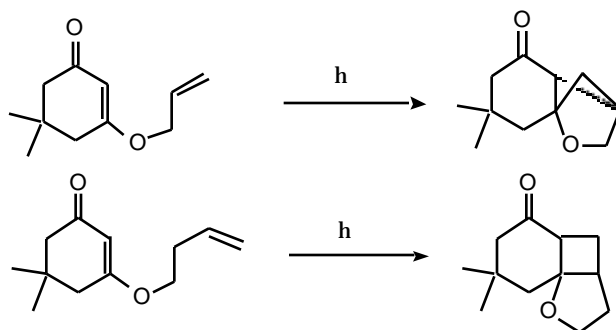


Arene-Olefin Photocyclization *Organic Photochemistry* **1989**, 10, 357
 - the photochemistry of benzene is dominated by the singlet state



Intramolecular Photochemical [2+2]

"Rule of Five"

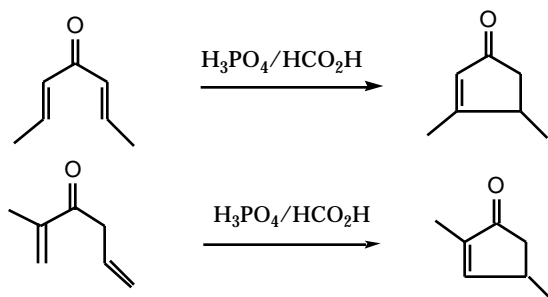


JOC **1975**, 40, 2702
JOC **1979**, 44, 1380

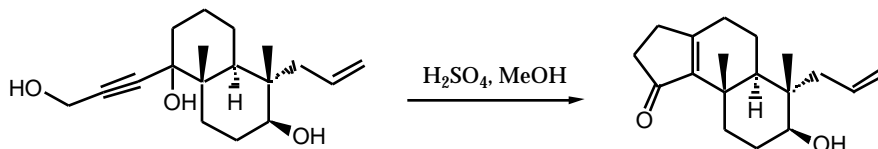
Nazarov Cyclization

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

- cyclization of allyl vinyl or divinyl ketones

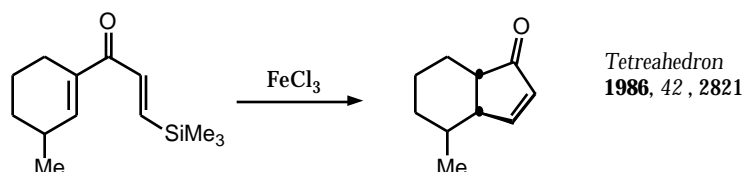


- 1,4-hydroxy-acetylenes



JOC **1989**,
54, 3449

- Silicon-Directed Nazarov



Tetrahedron
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 manner 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 systems
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

organoselenium & boron compounds

carboxylic acid derivatives (Barton esters)

reduction of organomercurials

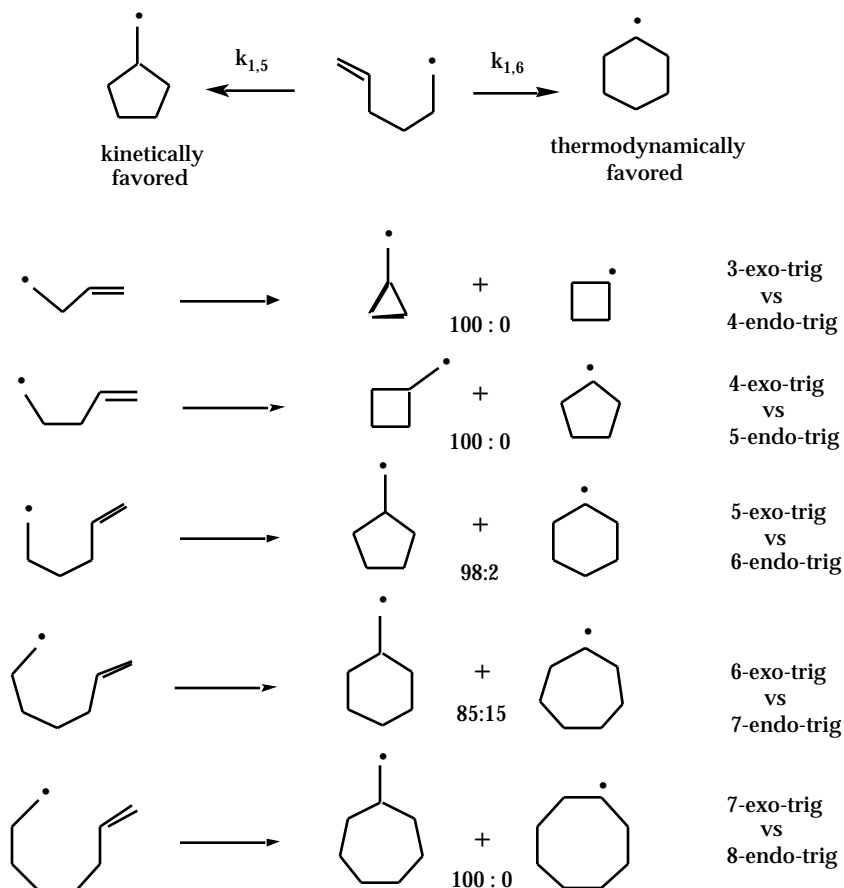
thermolysis of organolead compounds

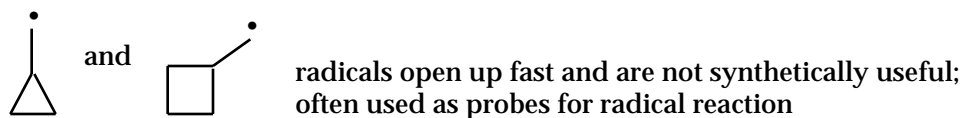
thermolysis or photolysis of azoalkanes.

Radical Ring Closure

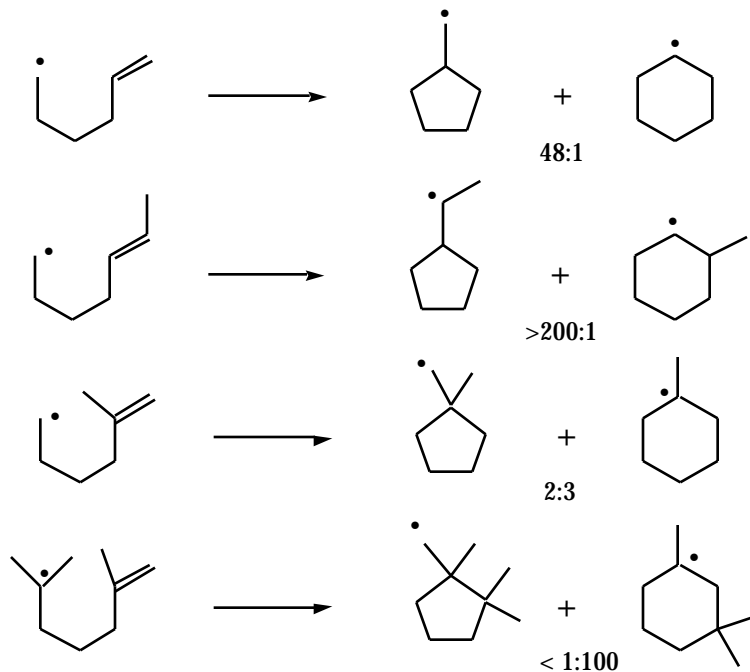
For irreversible ring closure reaction, the kinetic product will predominate.

Both the 5-exo-trig and 6-endo-trig are favored reactions, with the 6-exo-trig mode producing the most stable radical. However, the 5-exo-trig is about 50 times faster





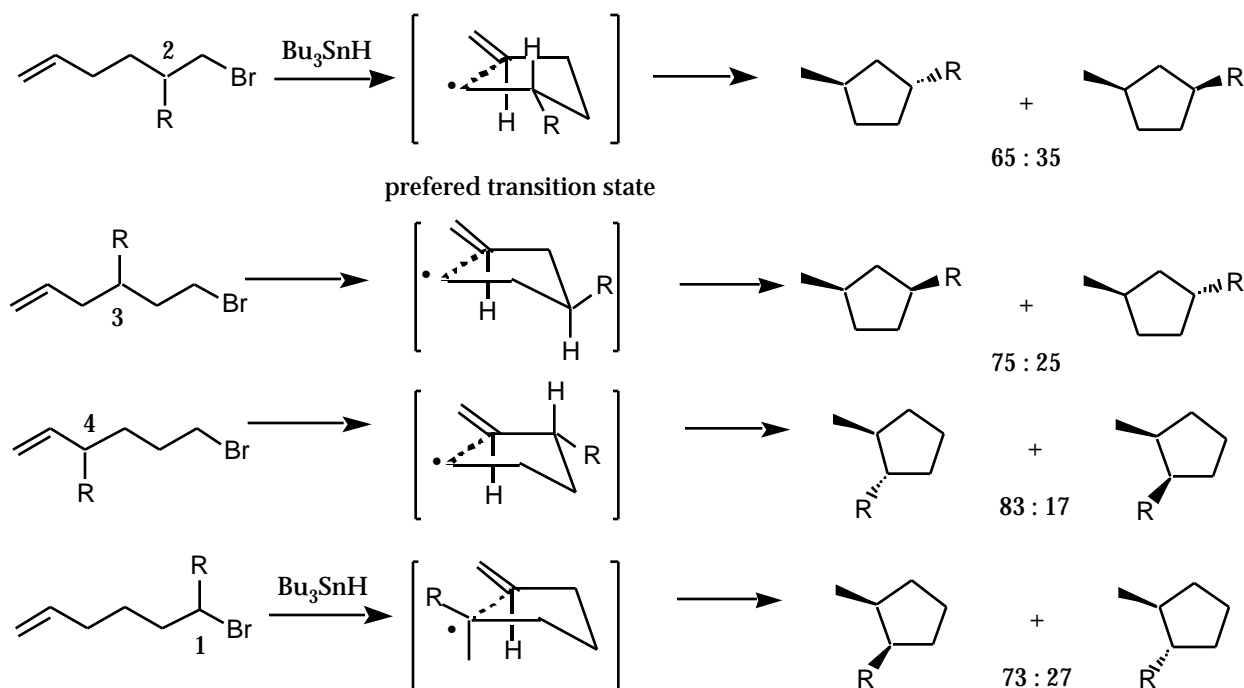
Effects of substituent on the regiochemistry of the 5-hexenyl radical cyclization

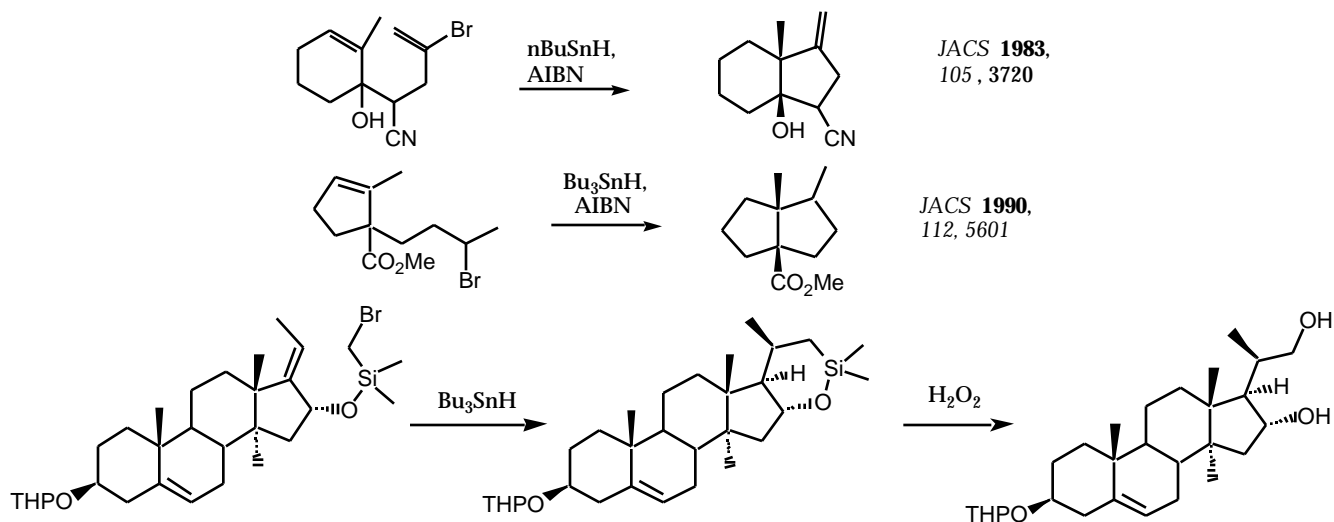


Stereochemistry of 5-hexenyl radical cyclization

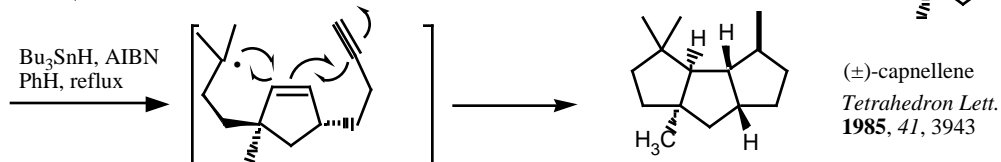
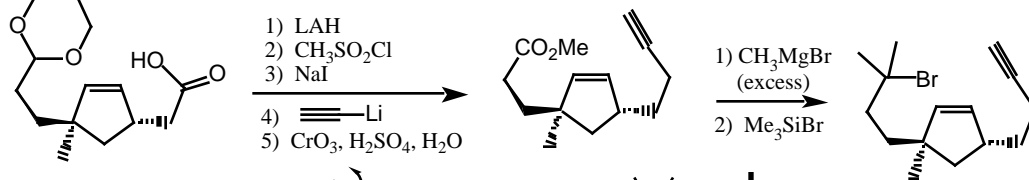
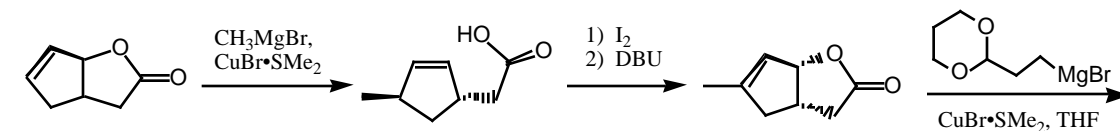
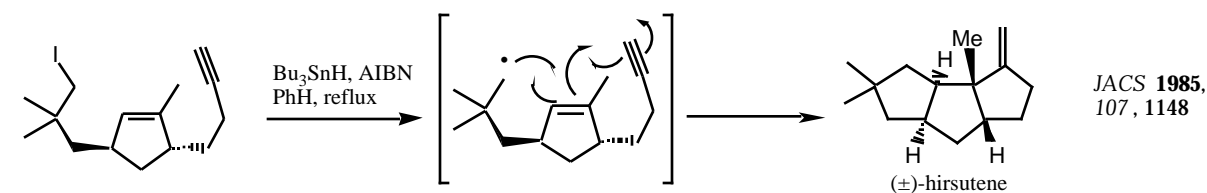
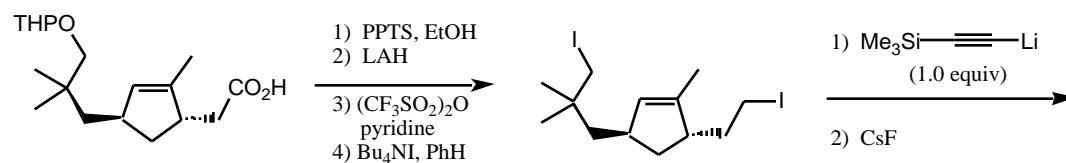
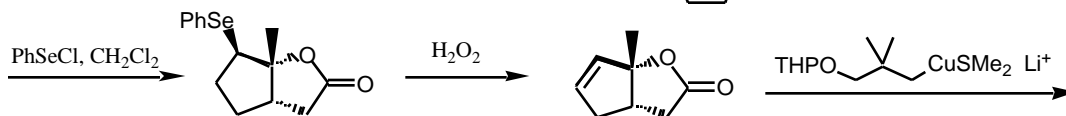
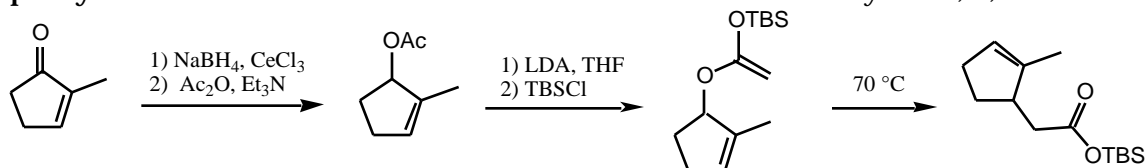
1-, or 3-substituted 5-hexenyl radicals give cis disubstituted cyclopentanes

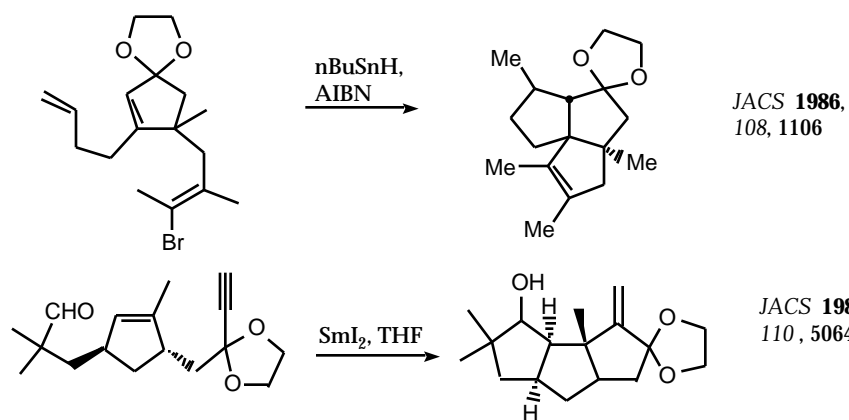
2-, or 4-substituted 5-hexenyl radicals give trans disubstituted cyclopentanes



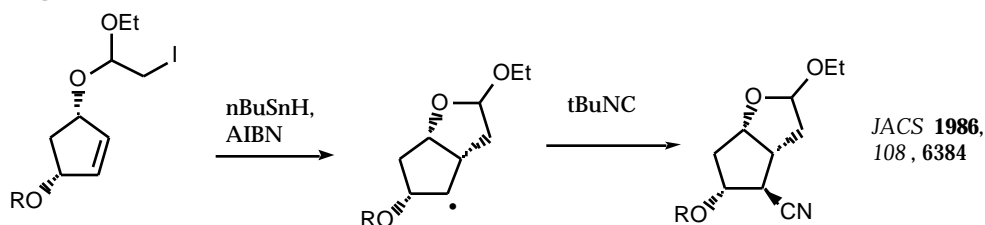


multiple cyclizations: D. Curran *Advances in Free Radical Chemistry* **1990**, 1, 121.

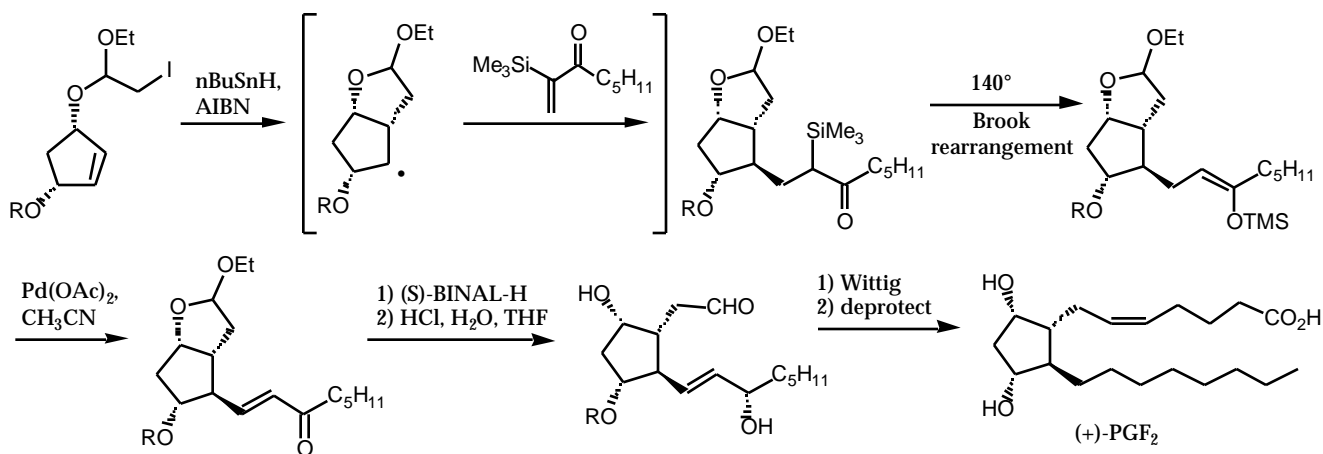




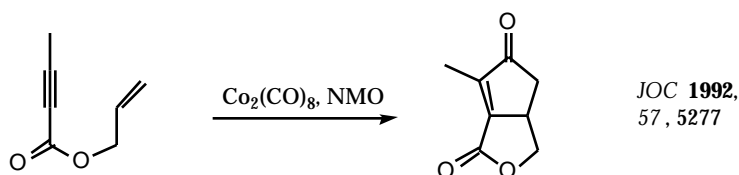
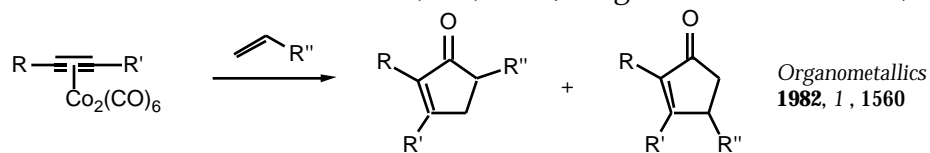
radical trapping

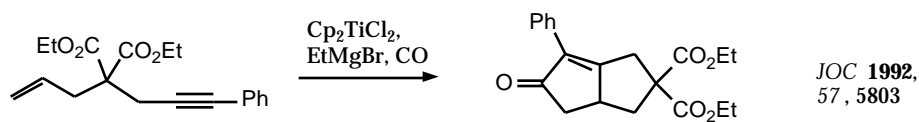


can also be trapped with acrylate esters or acrylonitrile.

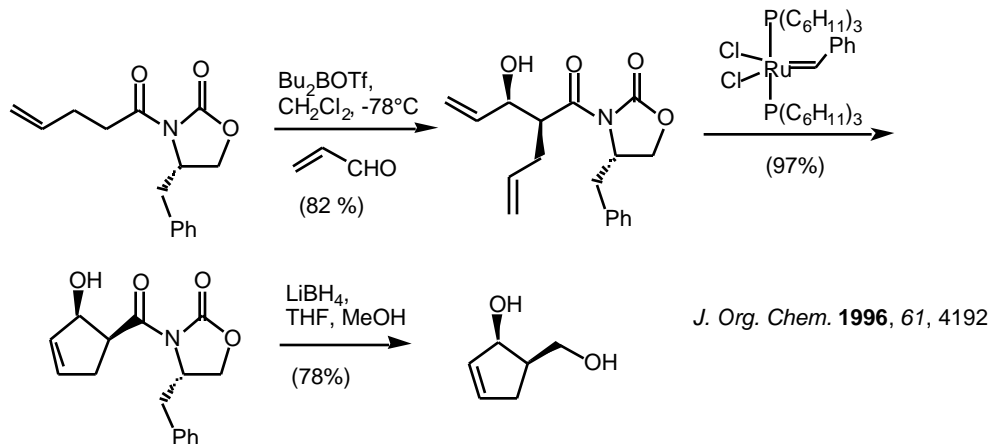


Paulson-Khand Reaction *Tetrahedron* **1985**, 41, 5855; *Organic Reactions* **1991**, 40, 1.





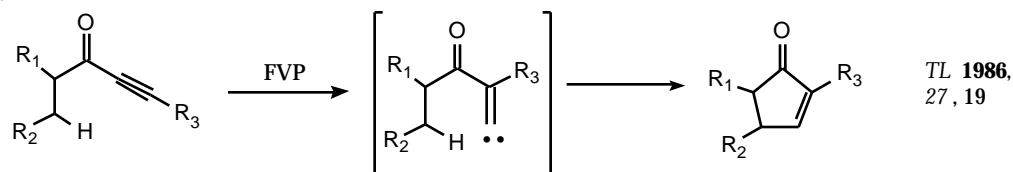
Ring-Closing Metathesis *Tetrahedron* **1998**, 54, 4413, *Acc. Chem. Res.* **1995**, 25, 446.



Diazoketones *Tetrahedron* **1981**, 37, 2407; *Organic Reactions* **1979**, 26, 361



FVP of Acetylenic Ketones



Six Membered Rings

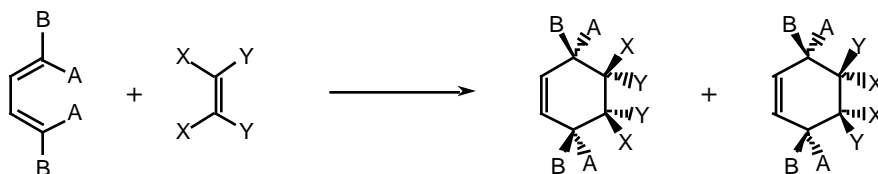
1. Diels-Alder Reaction
2. o-Quinodimethanes
3. Intramolecular ene reaction
4. Cation olefin cyclizations
5. Robinson annulation

Diels-Alder Reaction

ACIEE **1984**, 23, 876; ACIEE **1977**, 16, 10; Organic Reactions **1984**, 32, 1

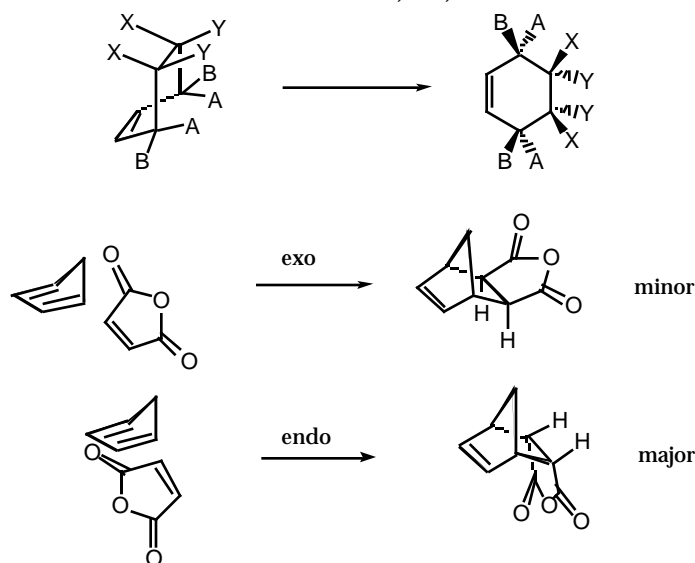
W. Carruthers *Cycloadditions Reactions in Organic Synthesis* (Pergamon Press, Oxford) **1990**

- reaction of a 1,3-diene with an olefin to give a cyclohexene.
- thermal symmetry allowed pericyclic reaction
- diene must react in 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

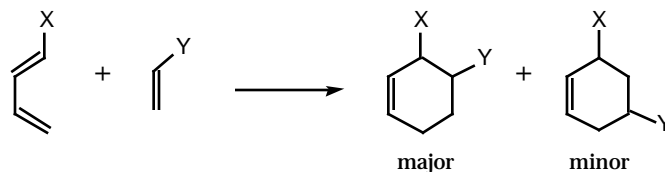


- Alder Endo Rule: In order to maximize secondary orbital interactions, the endo TS is favored in the D-A rxn.

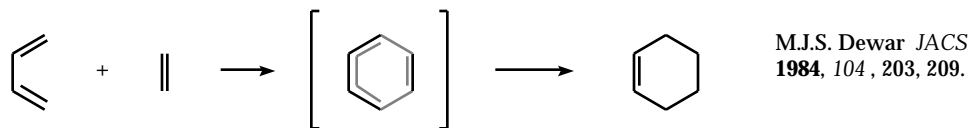
Tetrahedron **1983**, 39, 2095



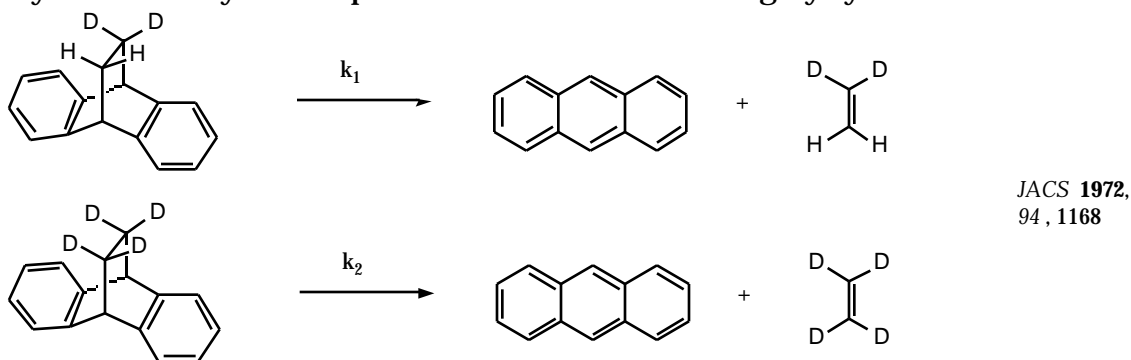
Orientation Rules



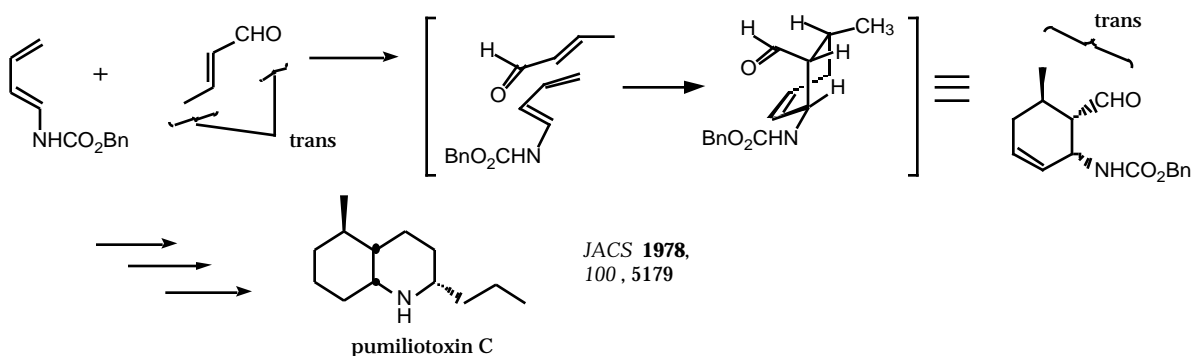
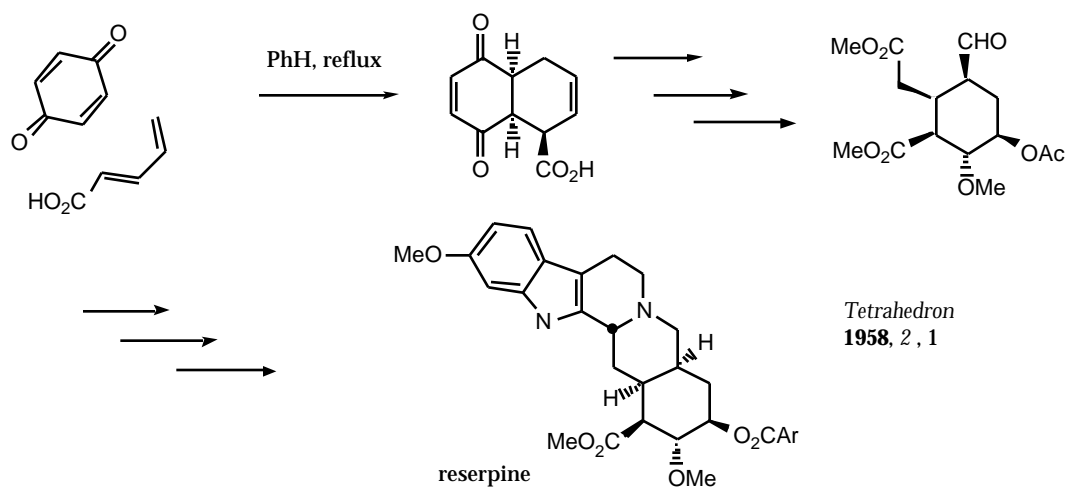
- The mechanism of the D-A rxn is believed to be a one-step, concerted, non-synchronous process.
- concerted- bond making and bond breaking processes take place in a single kinetic step (no dip in the transition state)
- synchronous- bond making and bond breaking take place at the same time and to the same extent.

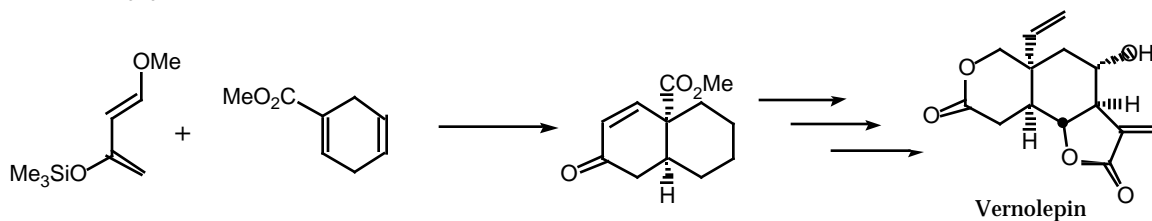
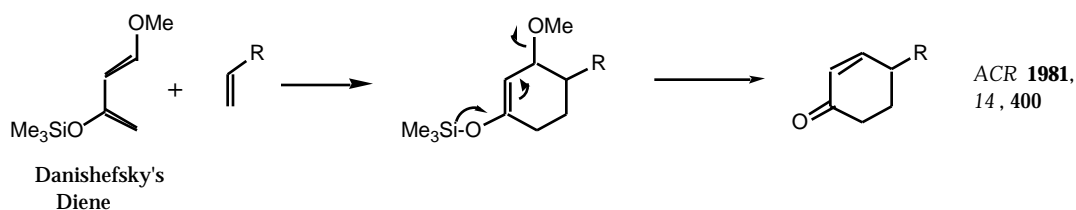
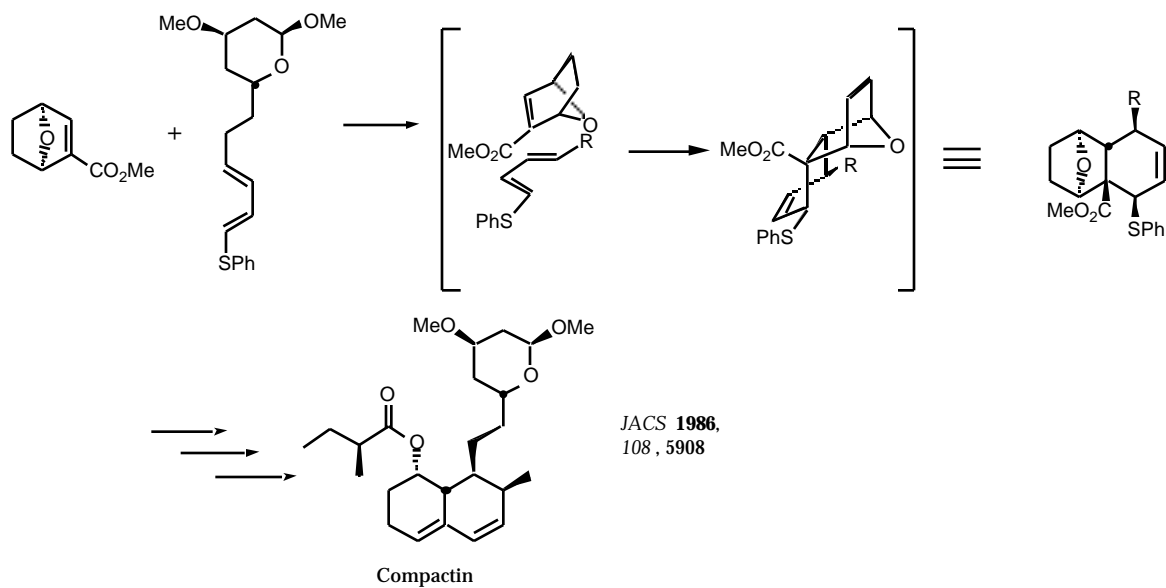


- study of secondary D-isotope effects have indicated a highly symmetrical T.S.

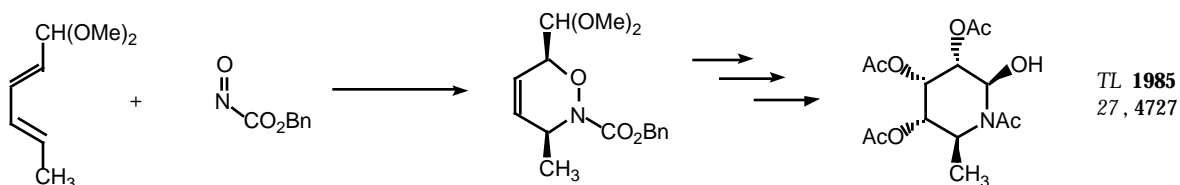
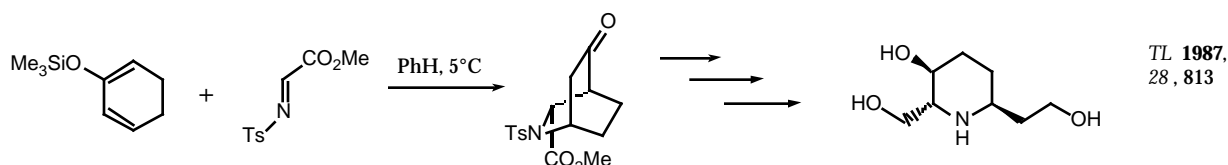
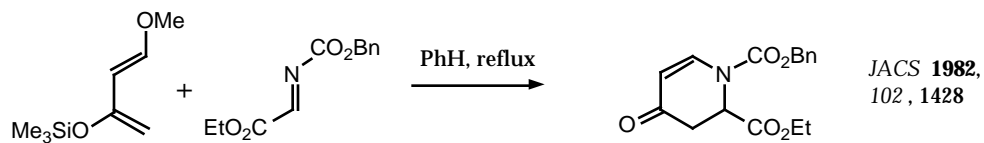


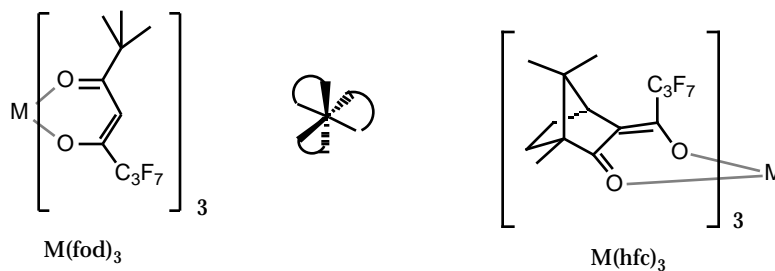
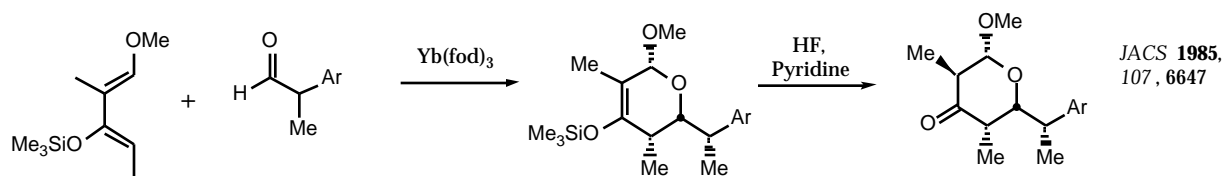
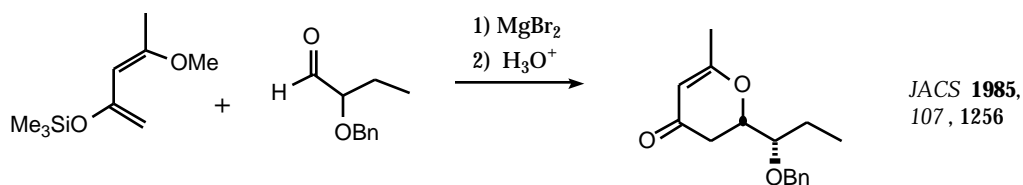
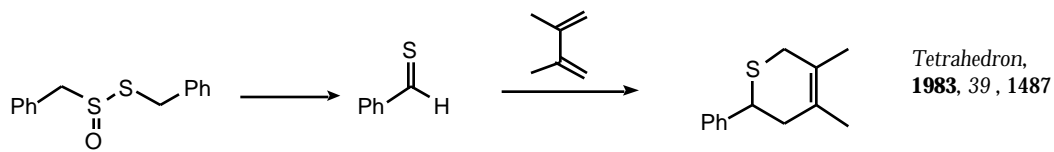
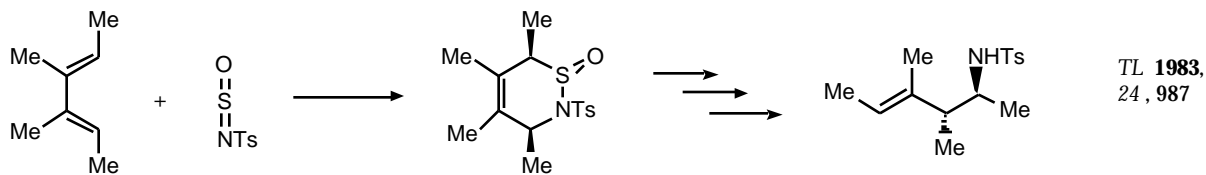
Diels Alder Reactions:



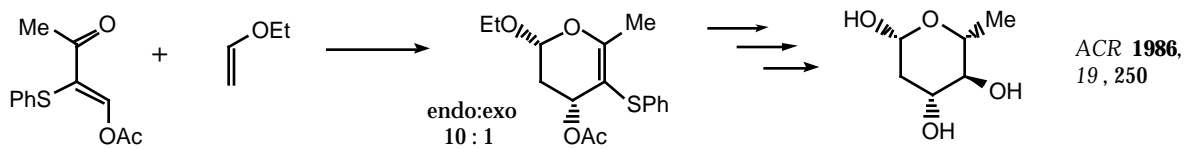
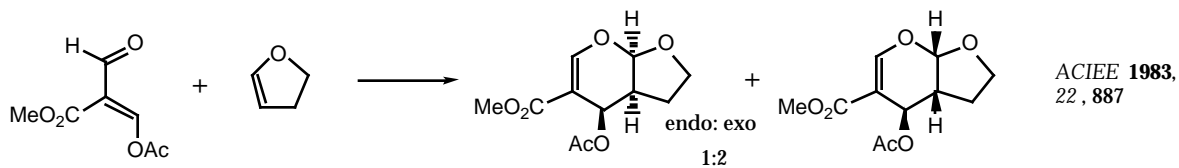


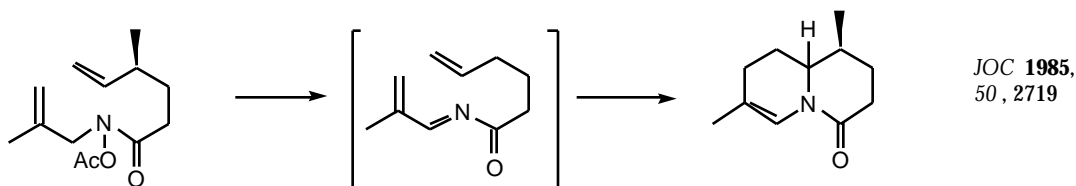
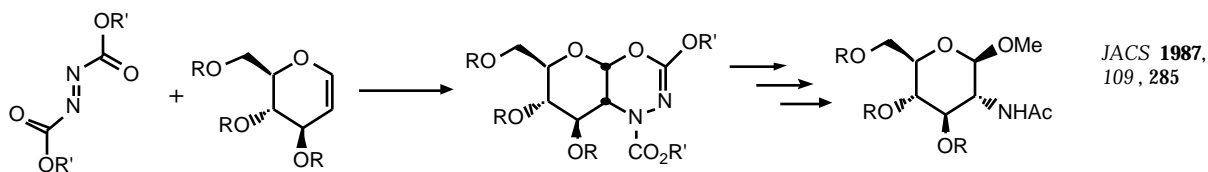
Hetero Diels-Alder Reactions - Heterodienophiles





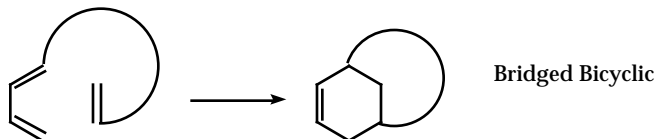
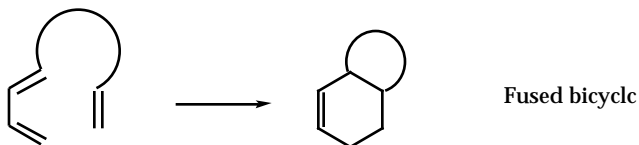
- Heterodienes





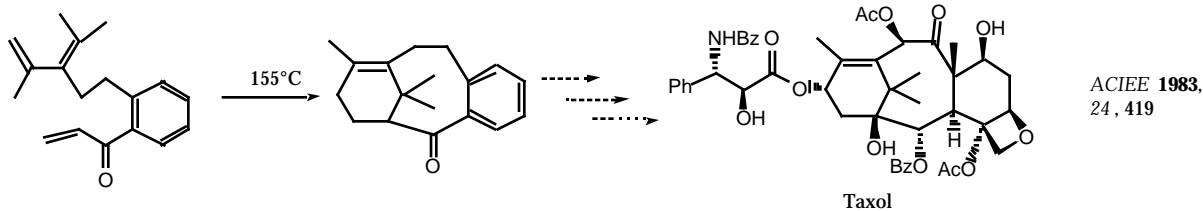
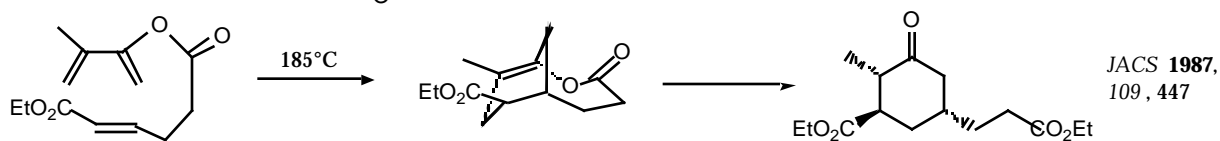
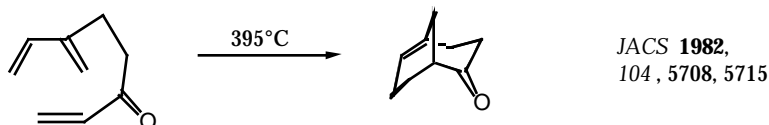
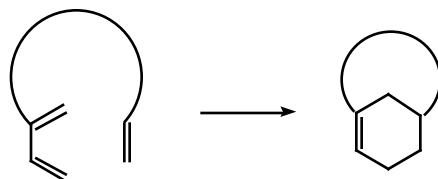
Intramolecular Diels-Alder Reactions (IDA)

- Type I IDA rxns

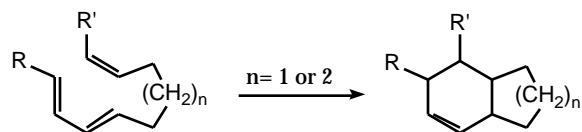


- Generally, for E-dienes, the fused product is observed unless the connecting chain is very long. For Z-dienes, either the fused or bicyclic products are possible.

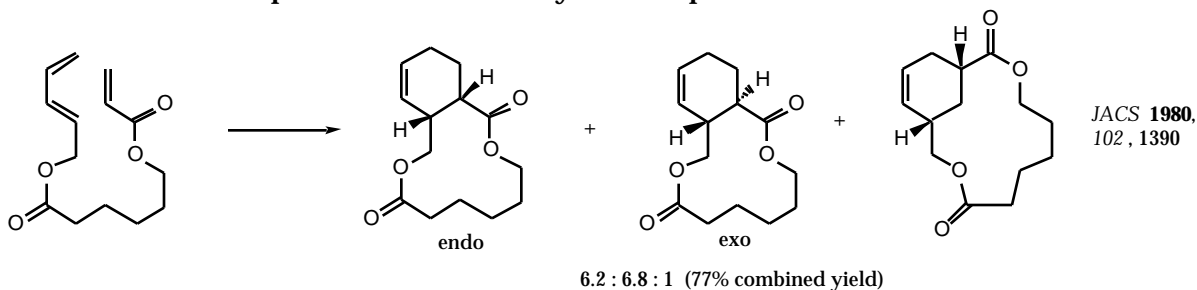
- Type II IDA rxns: gives bridgehead olefin



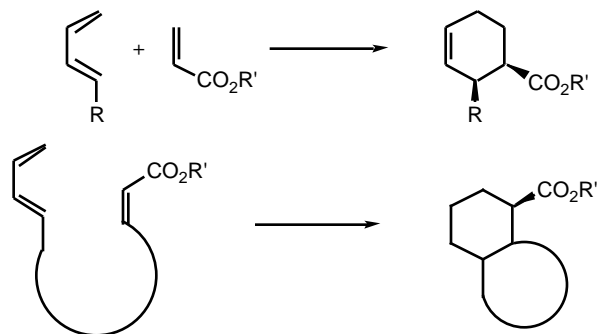
- IDA reactions to give fused 6•5 (hydroindene) and 6•6 (hydronaphthalene) ring systems are usually favorable reactions.



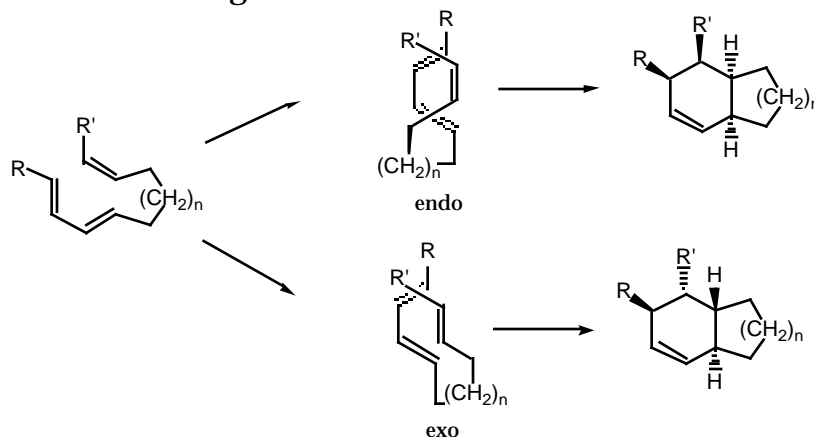
- Intramolecular D-A rxns that give medium sized rings (7,8,9, 10) are much less favorable.
- Intramolecular D-A rxn which form large rings are often favorable reactions with the diene and olefin portions act as if they were separate molecules



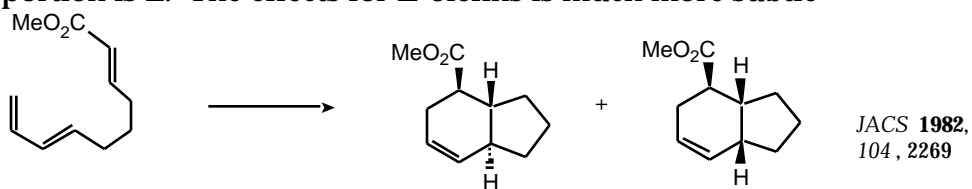
- Preference for endo or exo transition state depends on the substitution of the diene, dienophile and connecting chain.
- For intramolecular D-A rxns, geometric constraints can now reverse the normal regiochemistry of the addition as compared to the intermolecular rxn.



- for intramolecular D-A reactions, we will use endo and exo to describe the disposition of the connecting chain

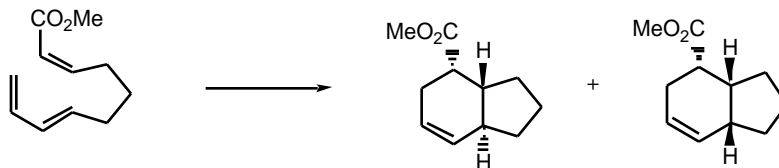


- Lewis acids can greatly effect the endo/exo ratio of IDA reactions especially when the olefin portion is E. The effects for Z-olefins is much more subtle



150°C
(RO)₂AlCl₂, rt

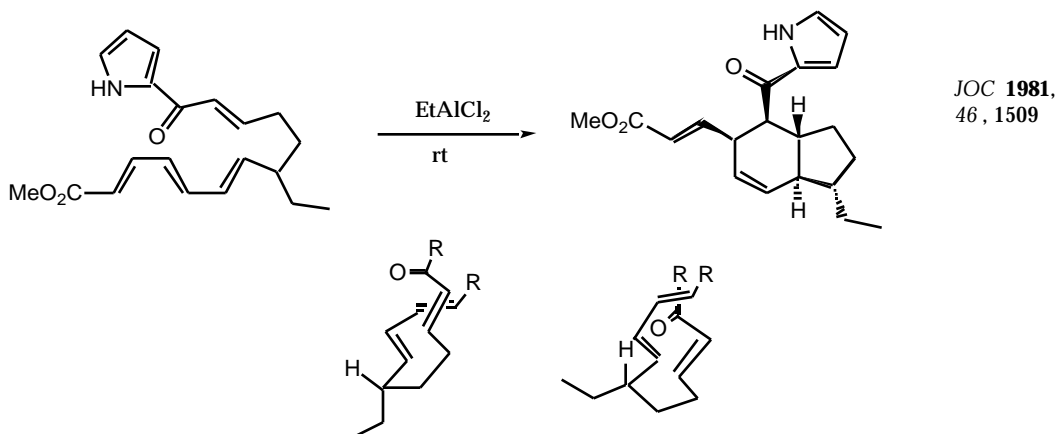
75 : 25	(75% combined yield)
100 : 0	(72% combined yield)



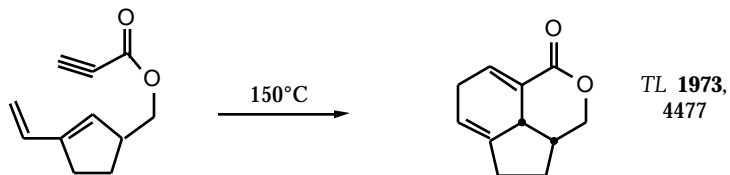
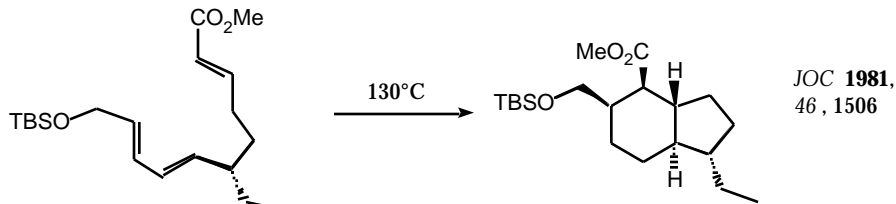
180°C
EtAlCl₂, rt

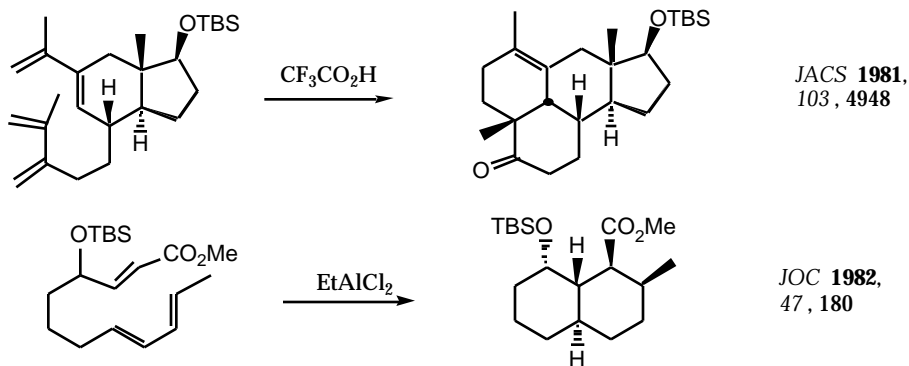
75 : 25	(74% combined yield)
63 : 37	(60% combined yield)

- the effect of substituents on the connecting chain can influence the stereochemical course of the IDA reaction



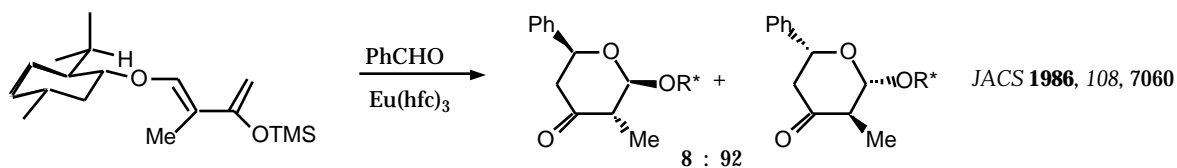
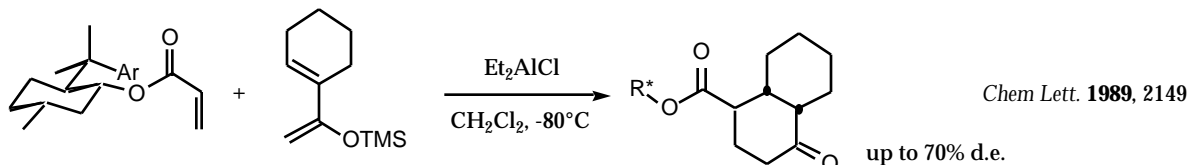
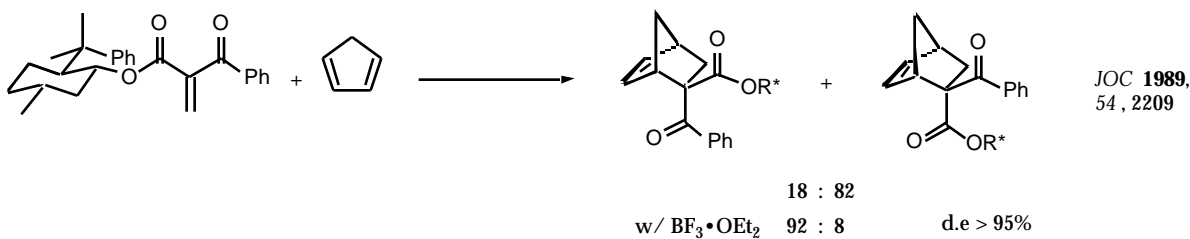
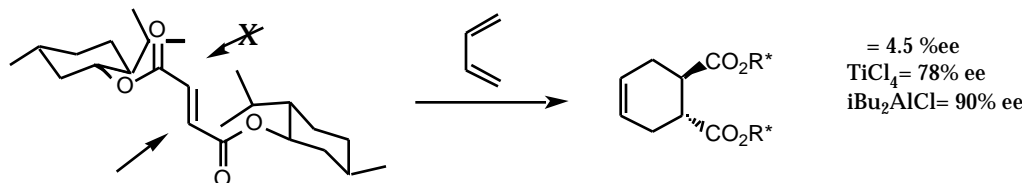
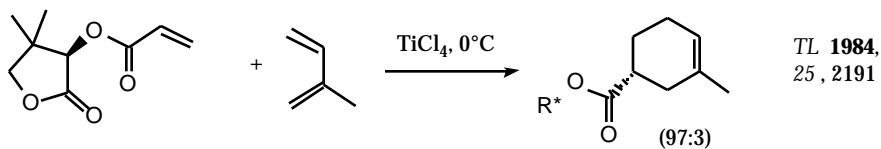
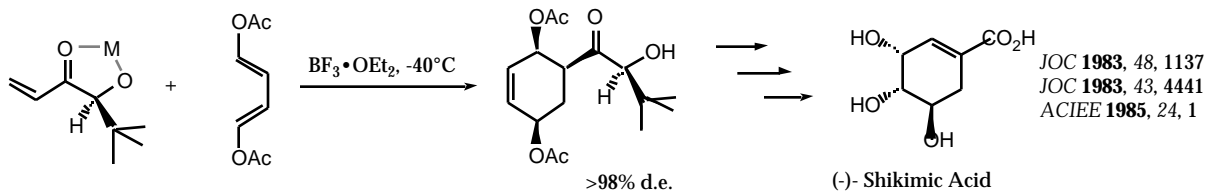
Intramolecular Diels-Alder Reactions:

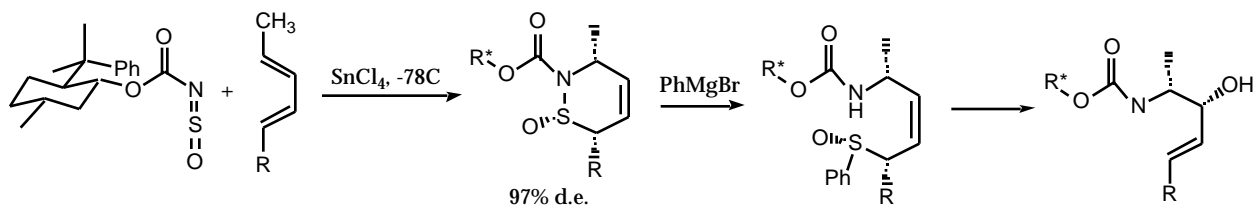




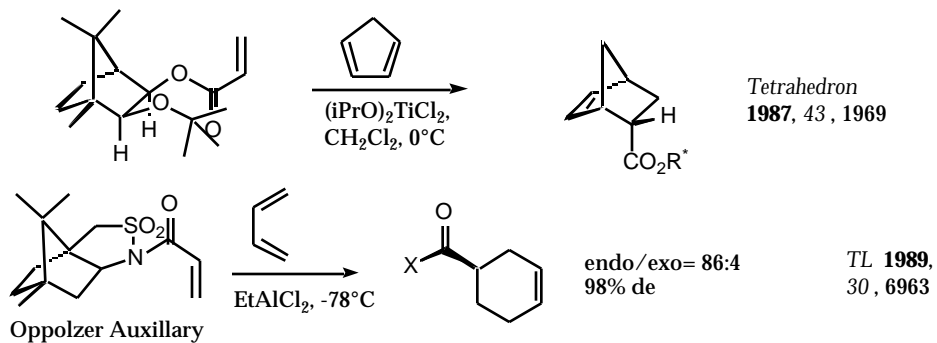
Asymmetric Diels-Alder Reactions

- Chiral Auxillaries

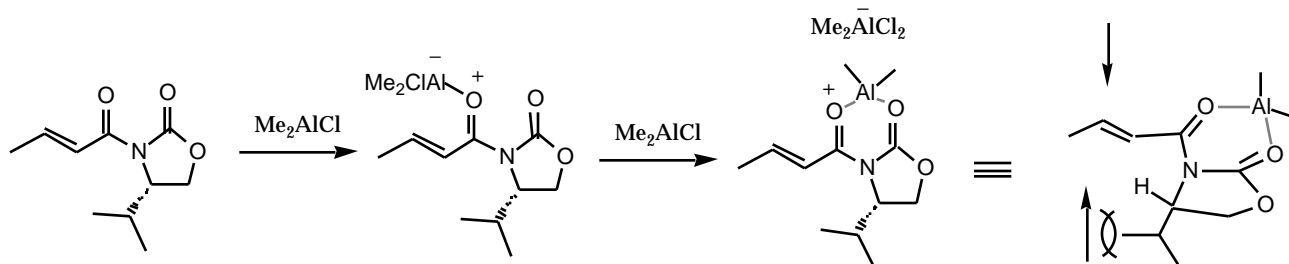
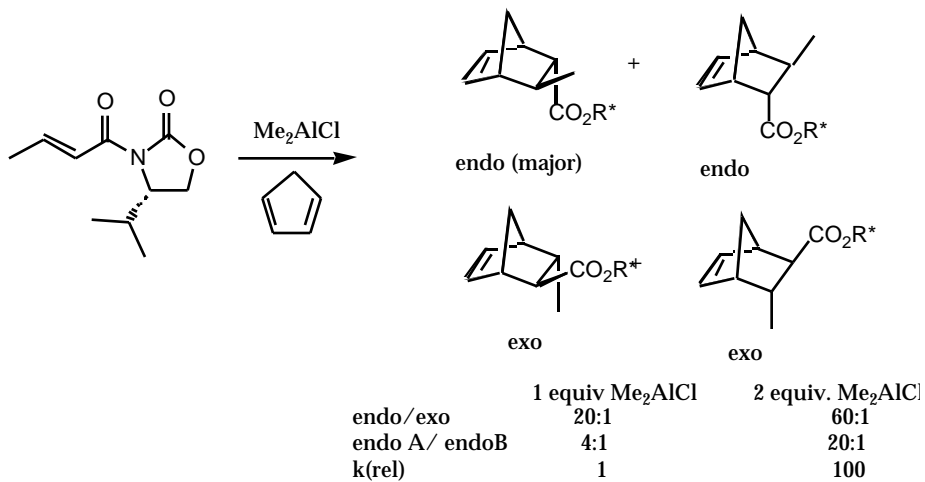
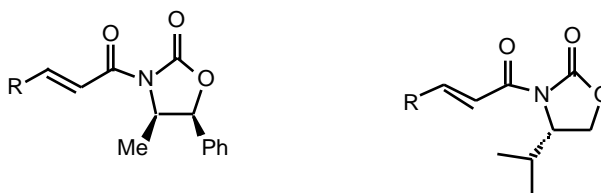
Chem. Rev. **1992**, 92, 953; Tetrahedron **1987**, 43, 1969

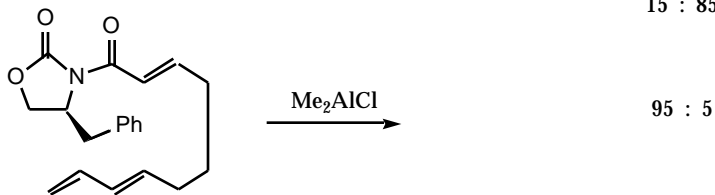
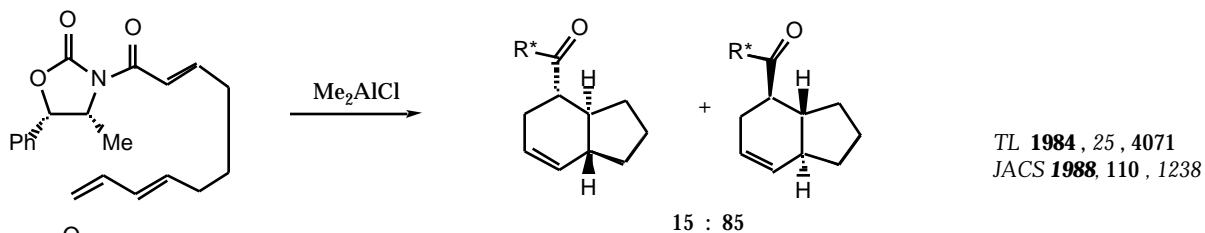
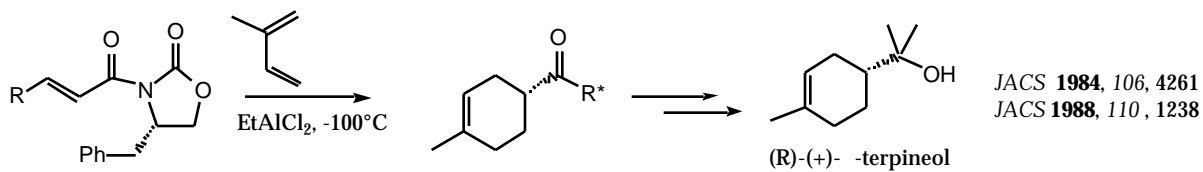


JCSCC, 1985, 1449
TL 1986, 27, 1853

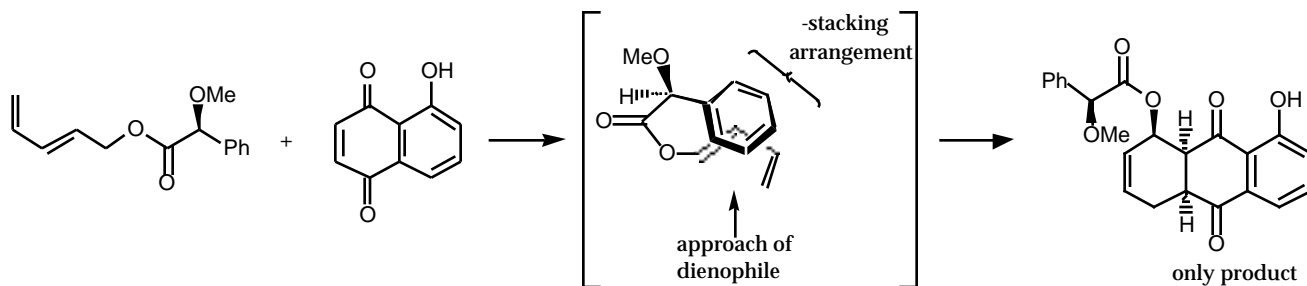
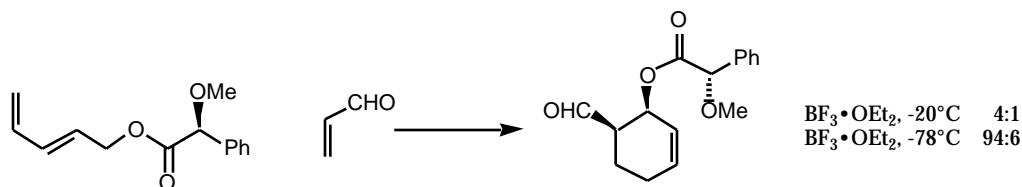
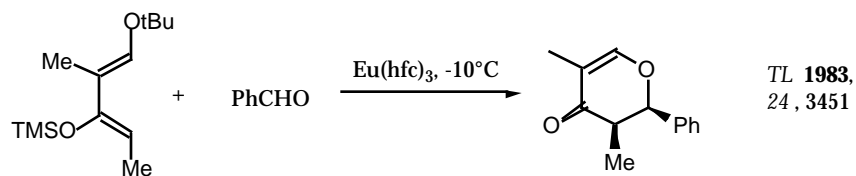
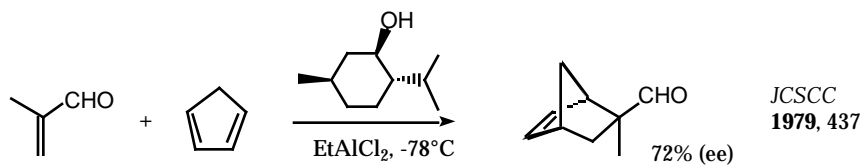


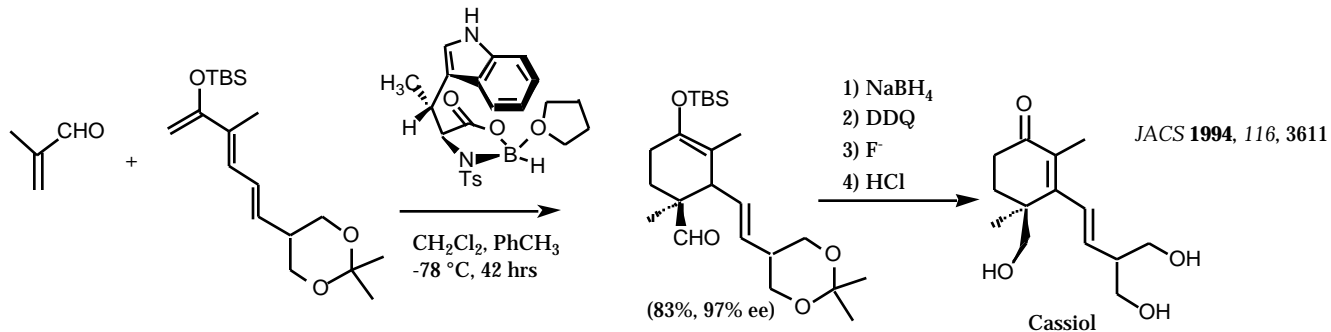
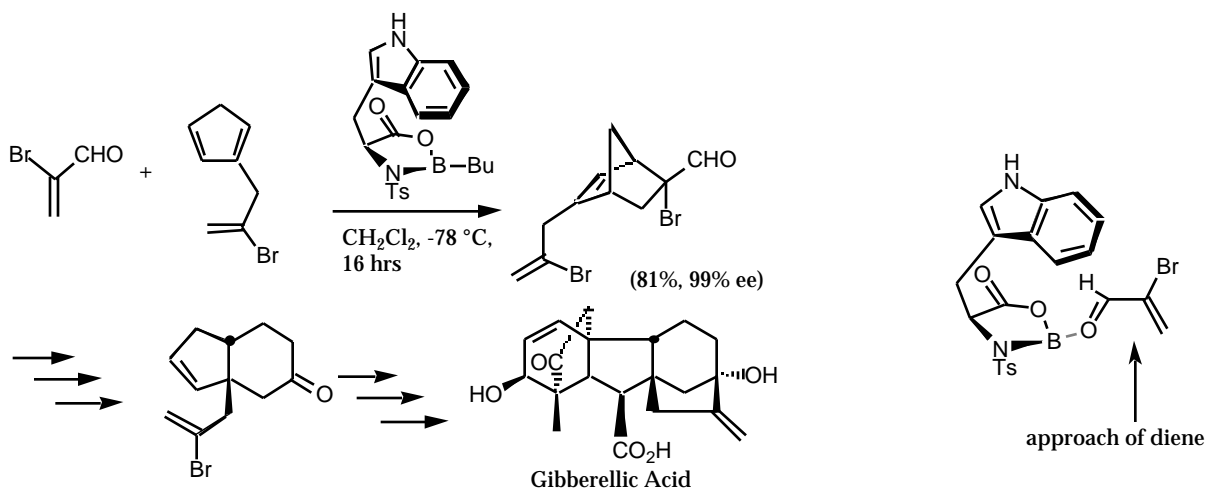
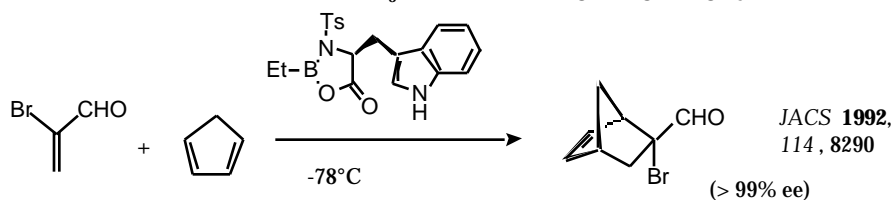
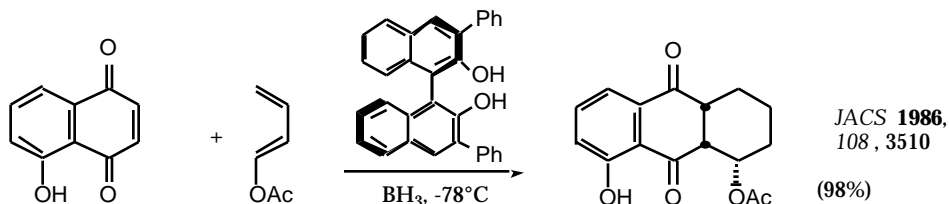
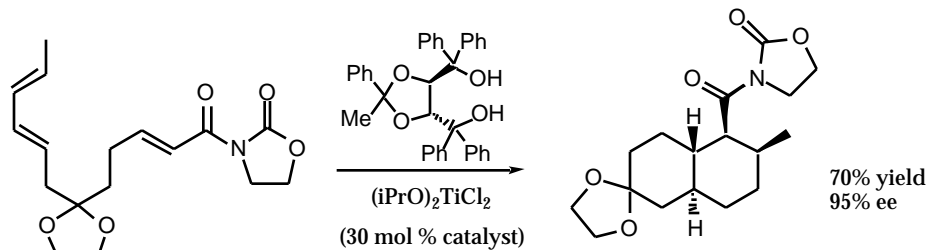
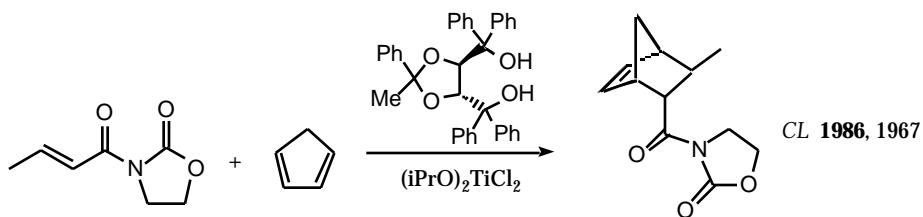
Evan's auxiliaries





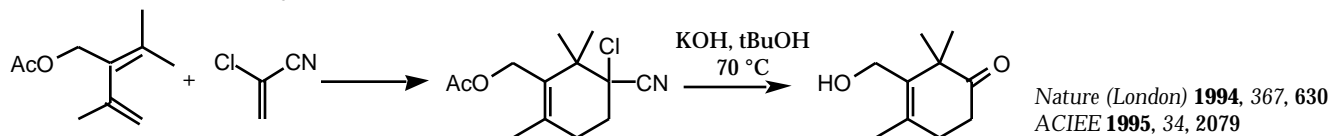
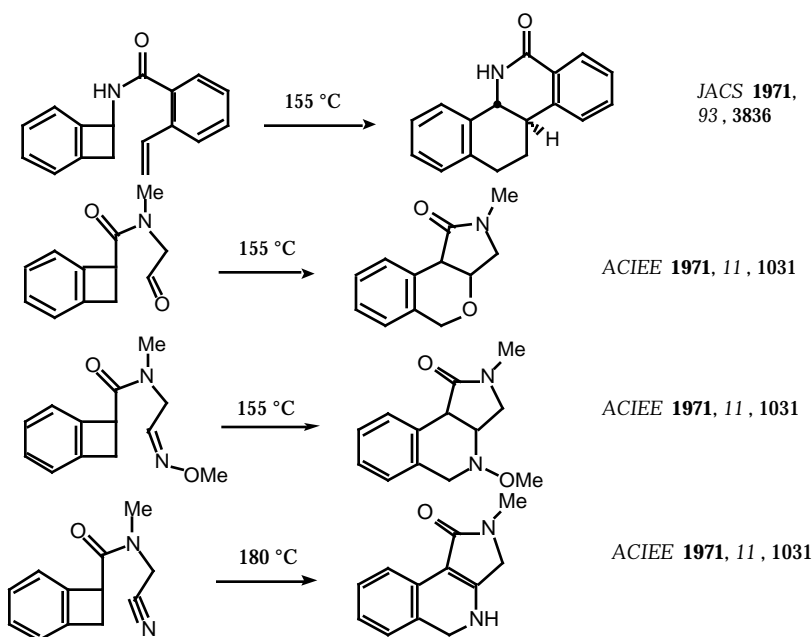
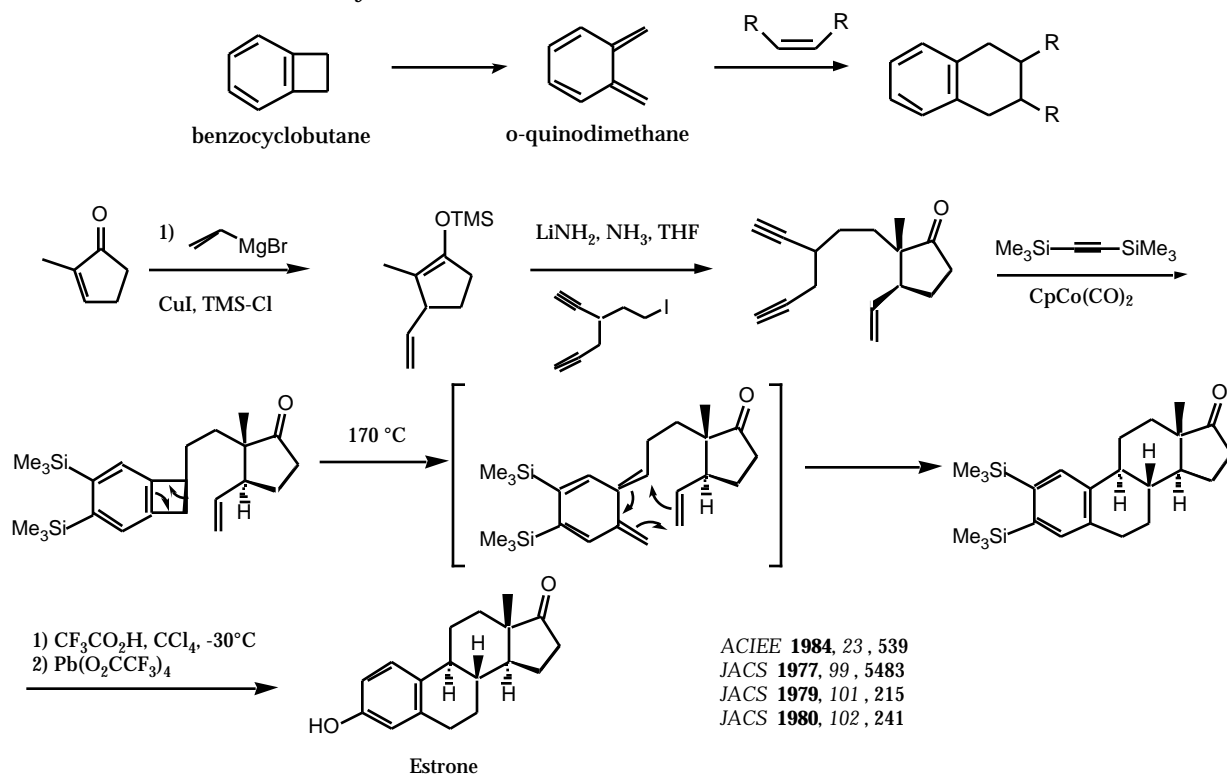
- Chiral Dienes

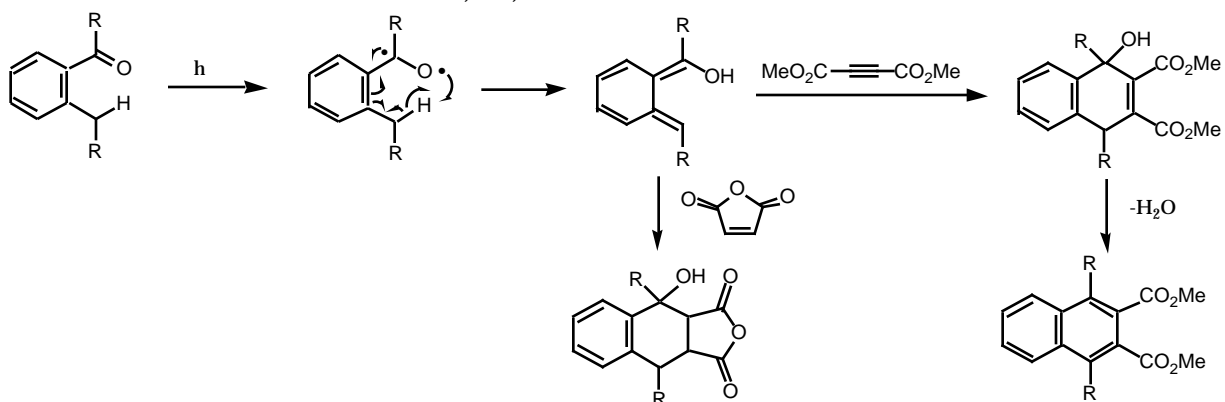
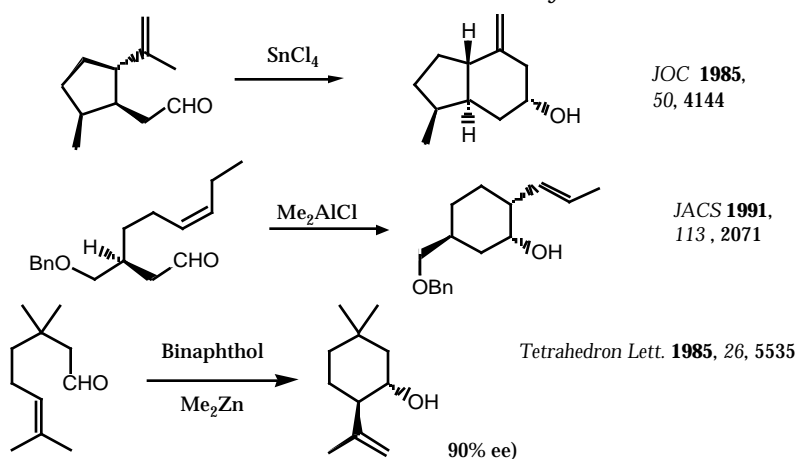
- Chiral Catalysts *Chem. Rev.* **1992**, 92, 1007; *Synthesis* **1991**, 1; *OPPI* **1994**, 26, 129-158



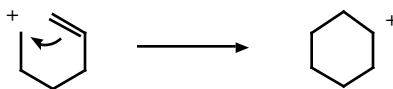
Ketene Equivalents in the D-A reaction

- ketenes undergo thermal [2+2] cycloaddition with dienes to give vinyl cyclobutanones.
- 2-chloroacrylonitrile as a ketene equiv. for D-A rxns.

ortho-Quinodimathanes Synthesis **1978**, 793; *Tetrahedron* **1987**, 43, 2873

Photoenolization *Tetrahedron* **1976**, 22, 405Intramolecular Ene Reactions *ACIEE* **1984**, 23, 876, *Synthesis* **1991**, 1

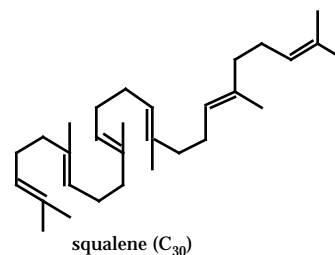
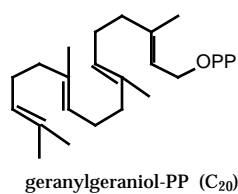
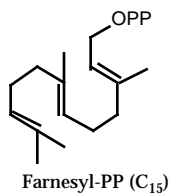
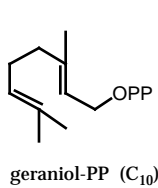
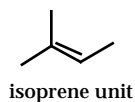
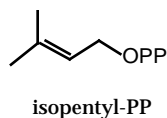
Polyene Cyclization

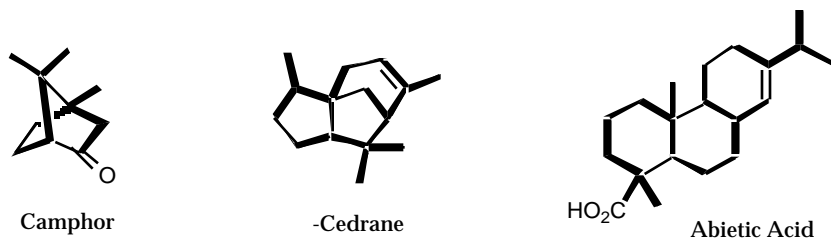


Terpene Biosynthesis

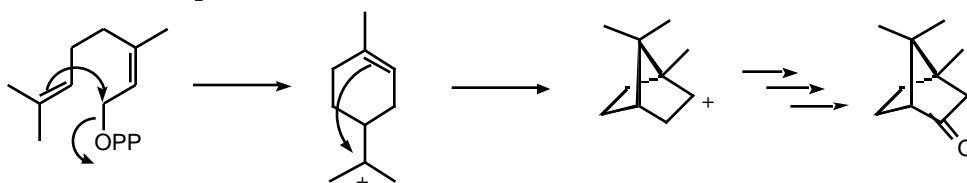
terpenes	C ₁₀	geraniol
sesquiterpenes	C ₁₅	farnesol
diterpenes	C ₂₀	geranylgeraniol
steroids	C ₃₀	squalene

- isoprene- basic building block

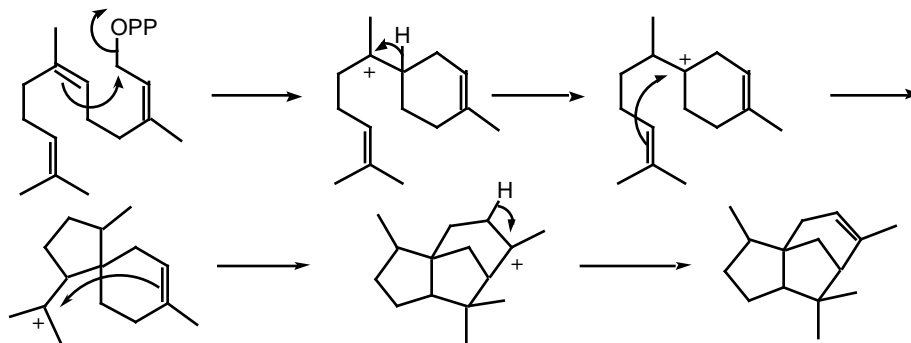




Biosynthesis of camphor:

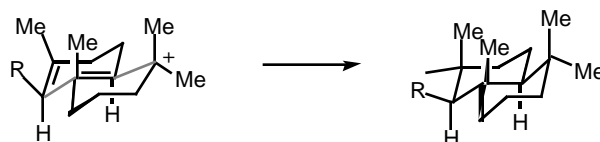


Biosynthesis of cedrane:

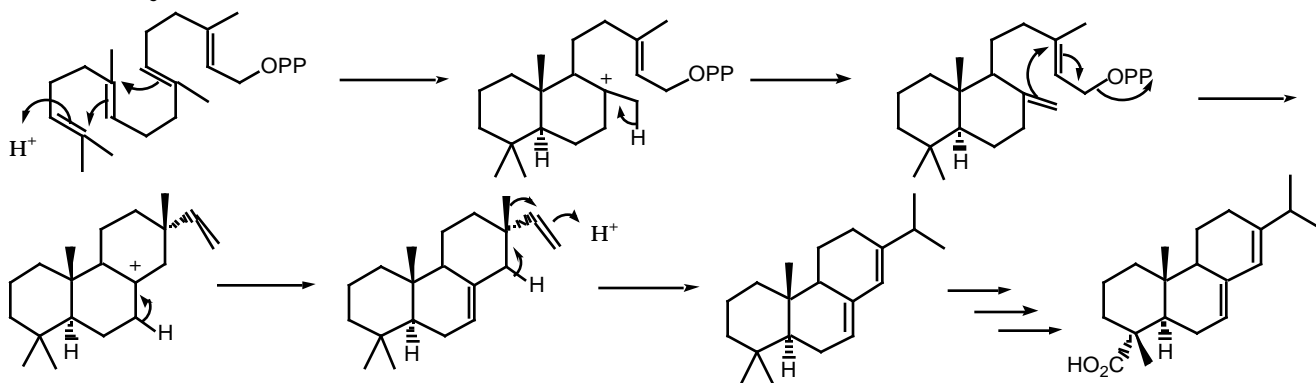


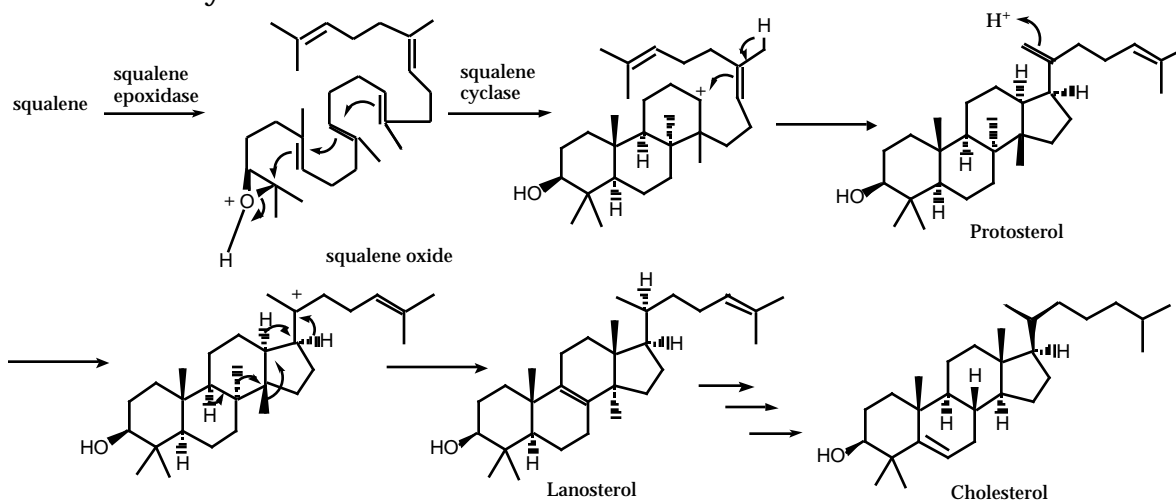
Stork-Eschenmoser Hypothesis- Olefin Geometry is preserved in the cyclization reaction, i.e. trans olefin leads to a trans fused ring junction

A. Eschenmoser *HCA* **1955**, 38, 1890; G. Stork *JACS* **1955**, 77, 5068

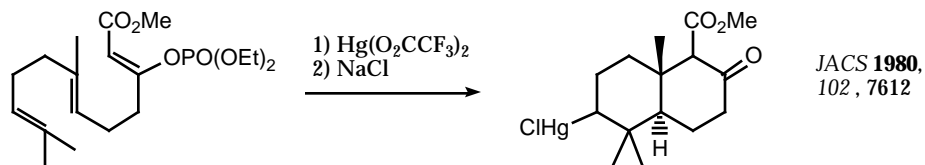
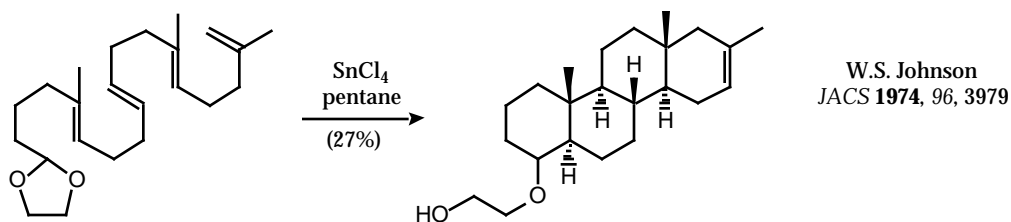
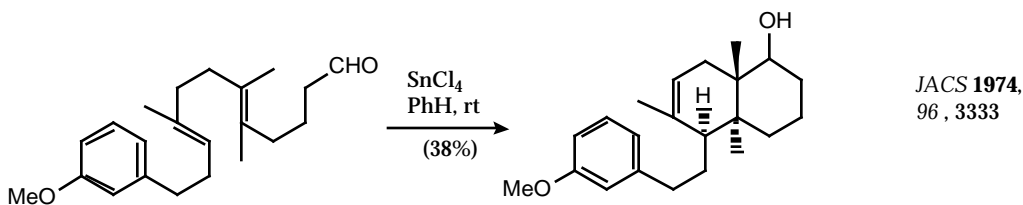
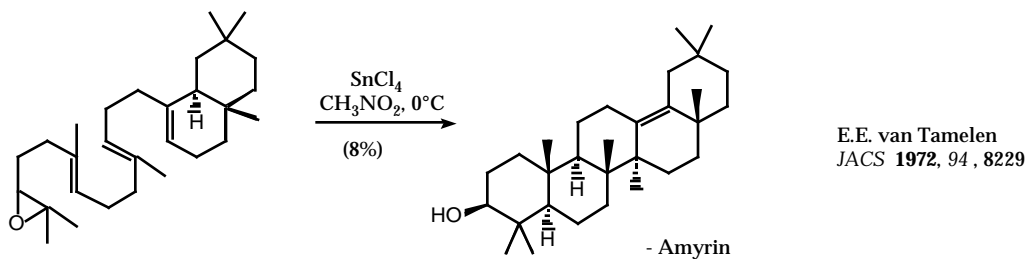


Biosynthesis of Abietic acid:

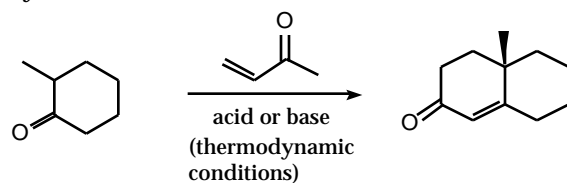


-Steroid Biosynthesis:

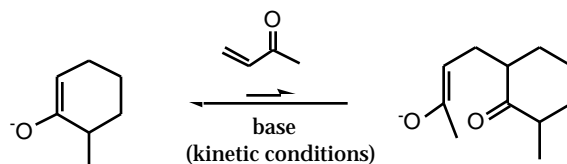
- Polyene cyclization in synthesis *ACR* **1968**, 1, 1; *Bioorg. Chem.* **1976**, 5, 51; *Asymmetric Synthesis* **1984**, 3, 341-409; *ACIEE* **1976**, 15, 9



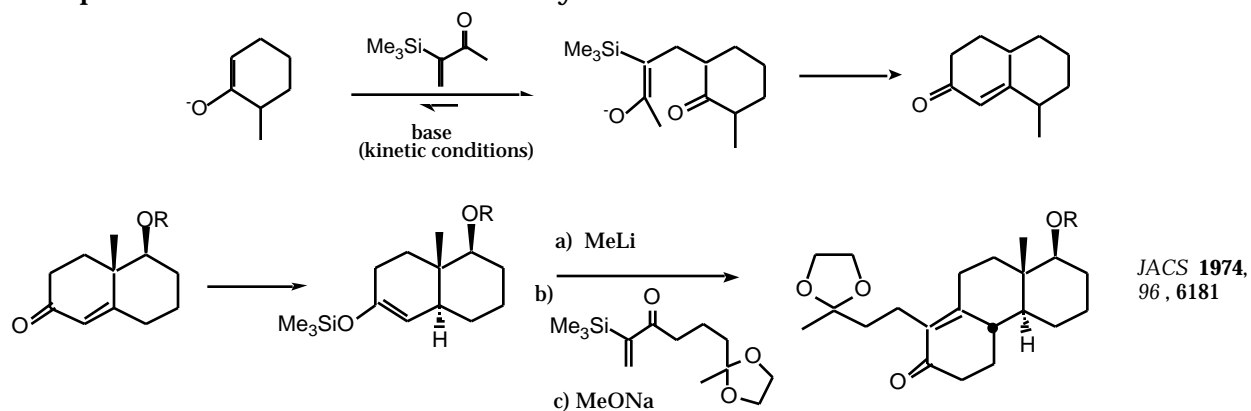
Robinson Annulation

Synthesis **1976**, 777; *Tetrahedron* **1976**, 32, 3.

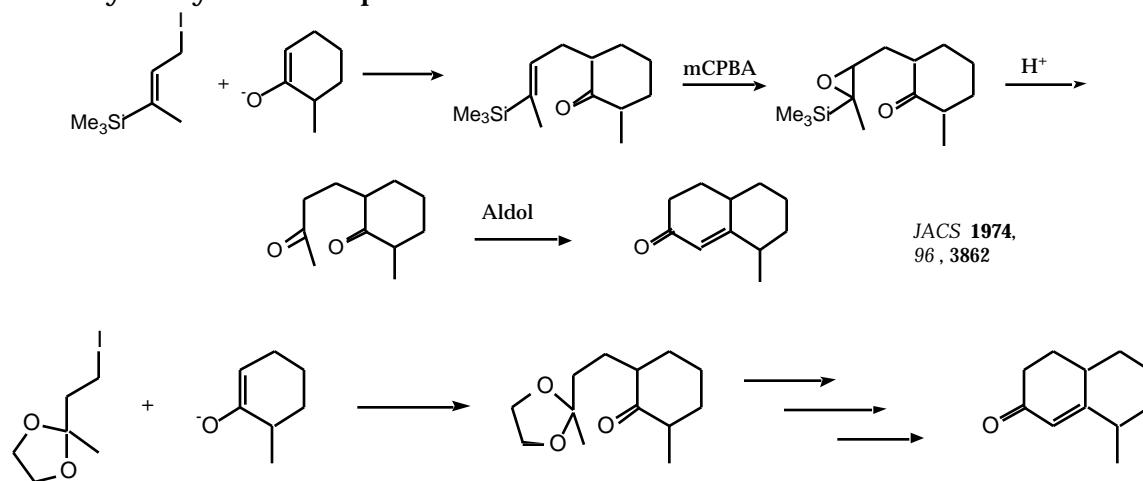
- unfavorable equilibrium for the Michael addition under kinetic conditions



- stabilizing the resulting enolate of the Michael Addition product can shift the equilibrium as in the case of the vinyl silane shown below

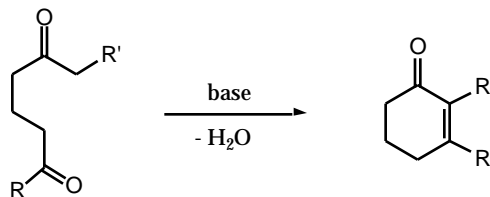


- Methyl Vinyl Ketone equivalents

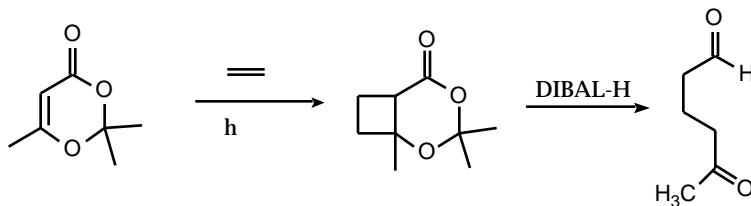


Intramolecular Aldol Condensation of 1,5-Diketones

6-exo-trig; favored process



- DeMayo reaction to 1,5-diketones

Intramolecular Alkylations (S_N2 reaction)

Radical Cyclizations

Acyloin Reaction

Birch Reduction *Organic Reactions* **1992**, 42, 1.

Aromatic Substitution (Carey & Sundberg, Chapter 11)

Intramolecular Wittig Reaction

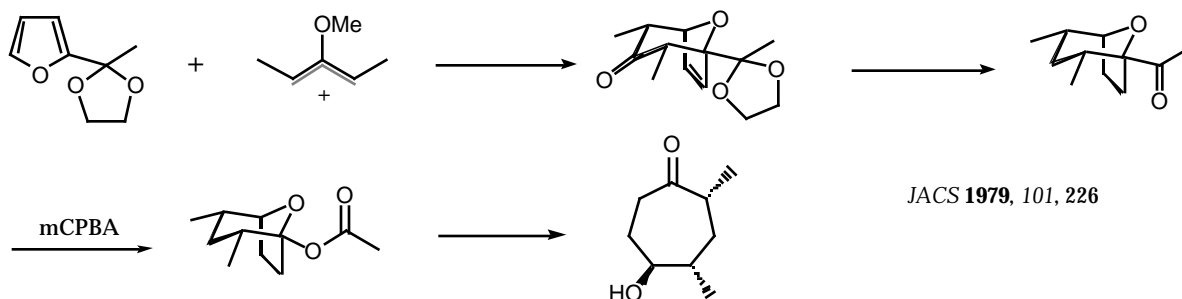
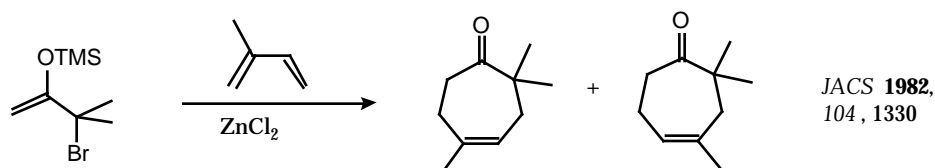
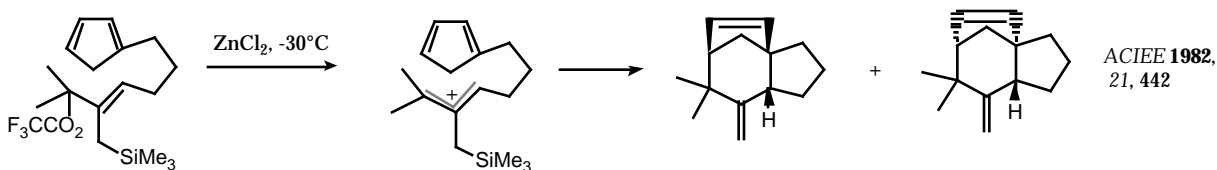
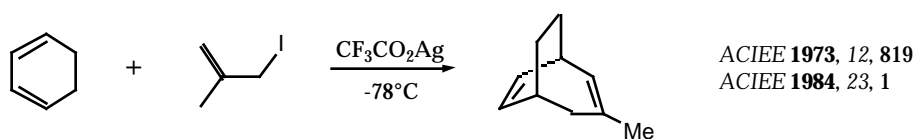
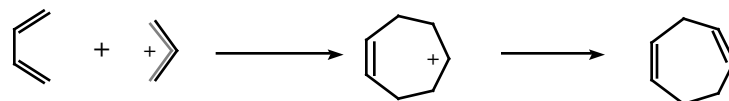
Sigmatropic Rearrangements

Medium Sized Rings

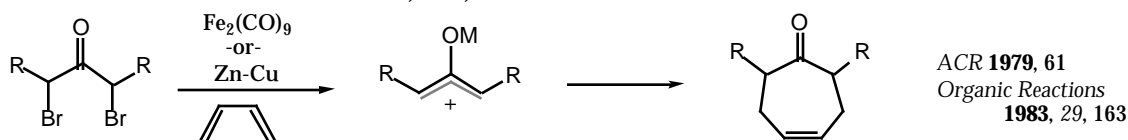
7-Membered Rings

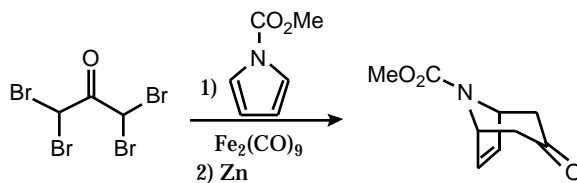
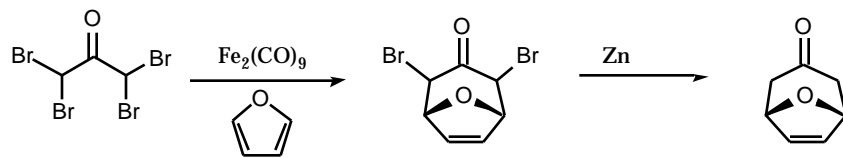
[4+2] cycloadditions

- [4+2] cycloadditions between dienes and allylcations leads to cycloheptadienes
review: *ACIEE* **1984**, 23, 1; *ACIEE* **1973**, 12, 819

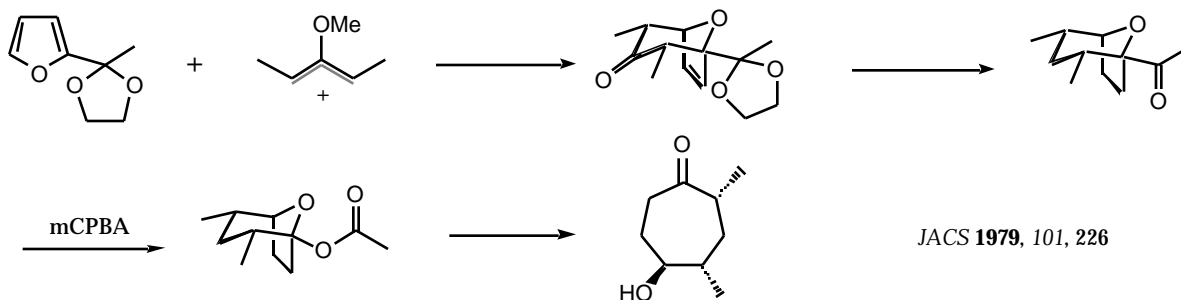


- Noyori [4+2] cycloaddition of α,β -dibromoketones and dienes
review: *ACR* **1979**, 12, 61

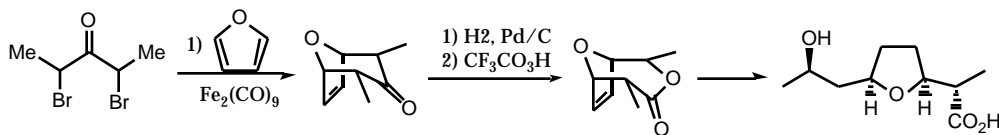




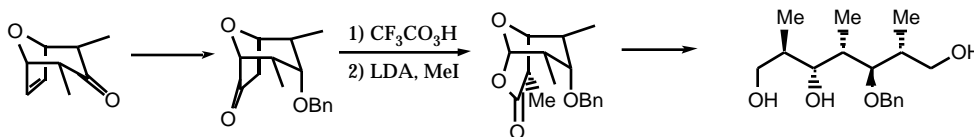
JACS **1978**, *100*, 1786
Tetrahedron **1985**, *41*, 5879



JACS **1979**, *101*, 226

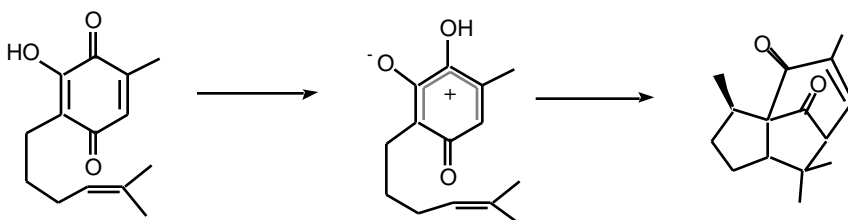
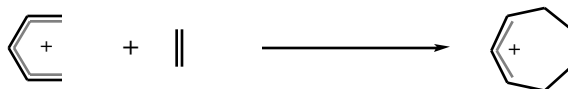


JACS **1972**, *94*, 3940
JOC **1976**, *41*, 2075

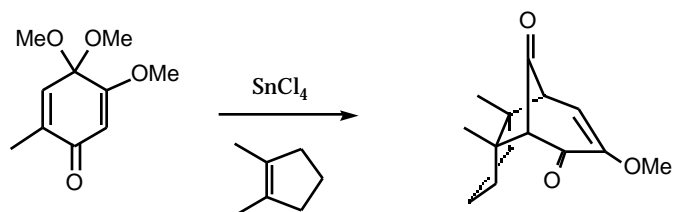


JCSCC **1985**, 55

- [4+2] cycloaddition between pentadienyl cations and olefins

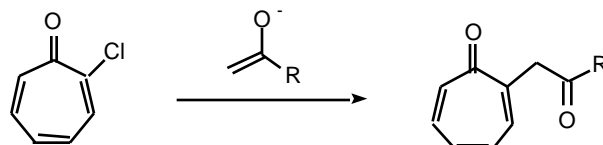


Tetrahedron **1966**, *22*, 2387
JOC **1987**, *52*, 759



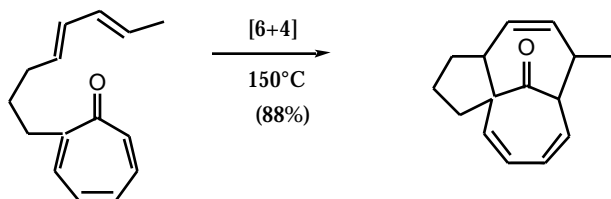
JACS **1977**, 99, 8073
 JACS **1979**, 101, 6767
 JACS **1981**, 103, 2718

Seven-Membered Rings from Functionalization of Tropone
Organic Reactions **1997**, 49, 331-425

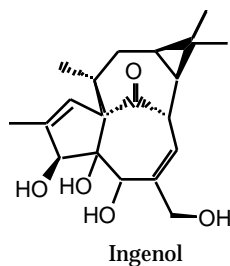


JOC **1988**, 53, 4596
 JACS **1987**, 109, 3147

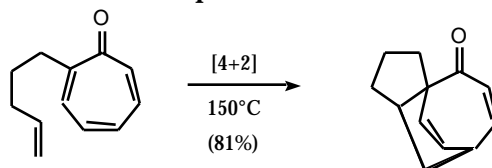
- [6+4] cycloadditions of tropones with dienes



JACS **1986**, 108, 4655
 JOC **1986**, 51, 2400

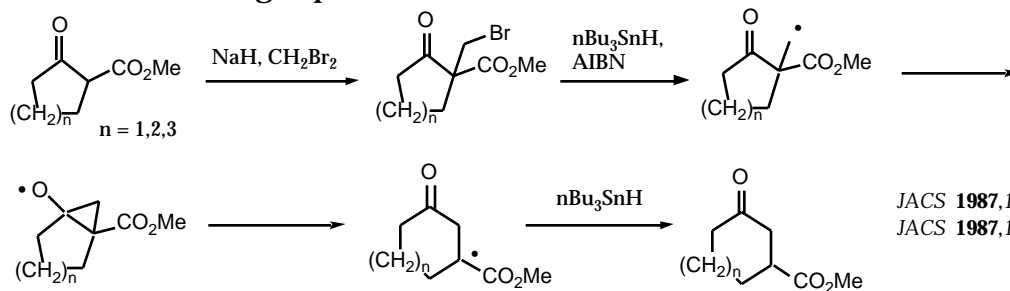


- [4+2] cycloaddition between tropone and olefins

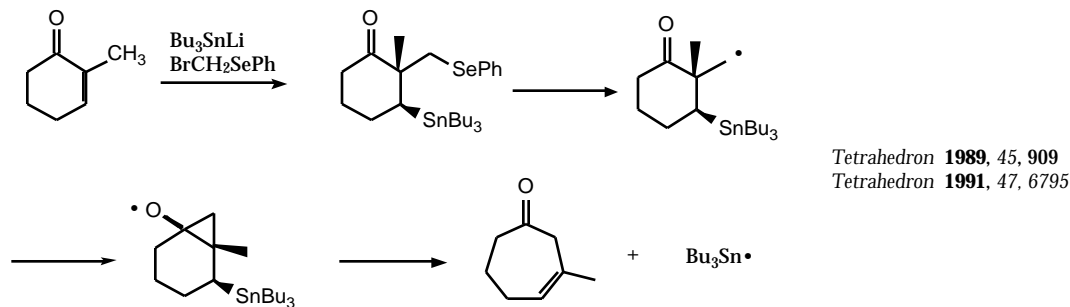


Radical Ring Expansion Reactions

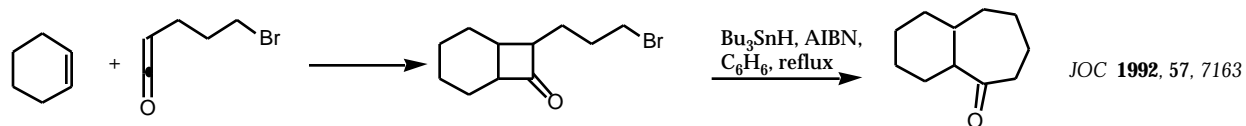
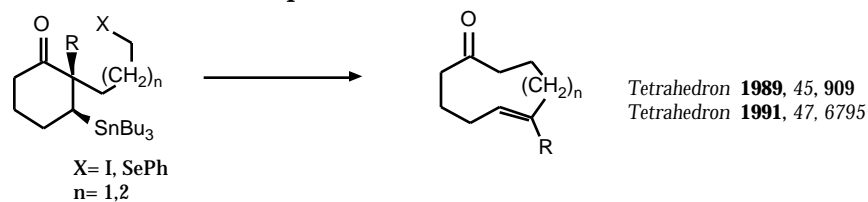
- one carbon ring expansions



JACS **1987**, 109, 3493
 JACS **1987**, 109, 6548



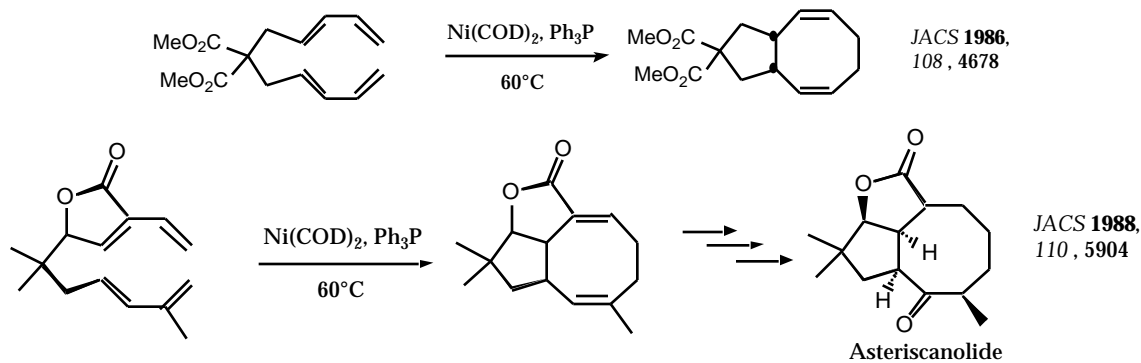
- more than one carbon expansion



Eight-Membered Rings

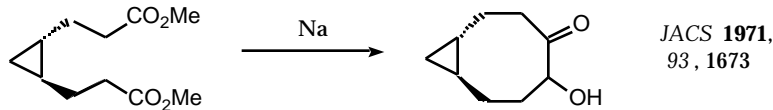
[4+4] Cycloaddition of Dienes

review: Tetrahedron **1992**, 48, 5757.

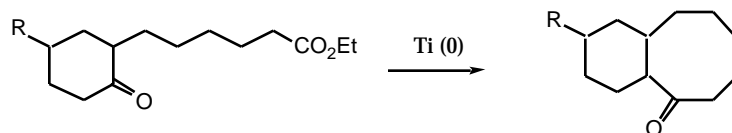


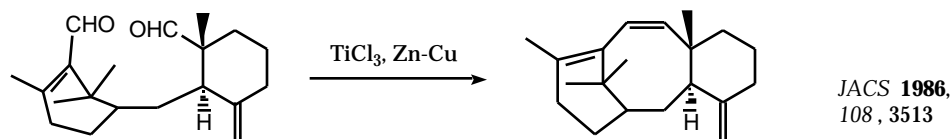
Carbonyl Coupling Reactions

- Acyloin Reaction

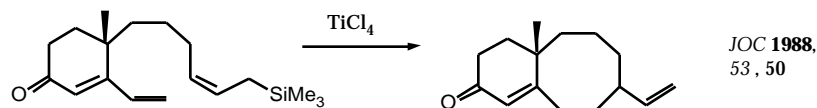
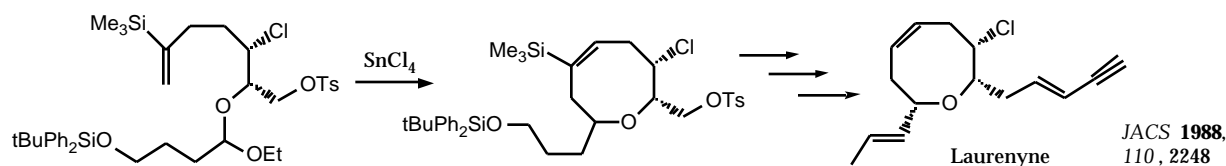
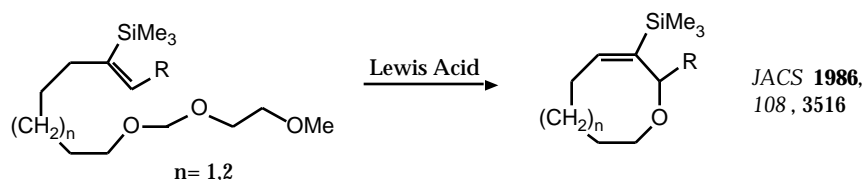
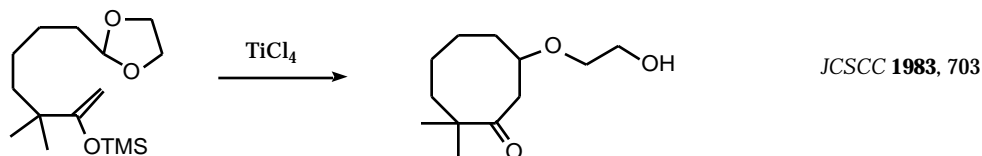


- McMurry Reaction

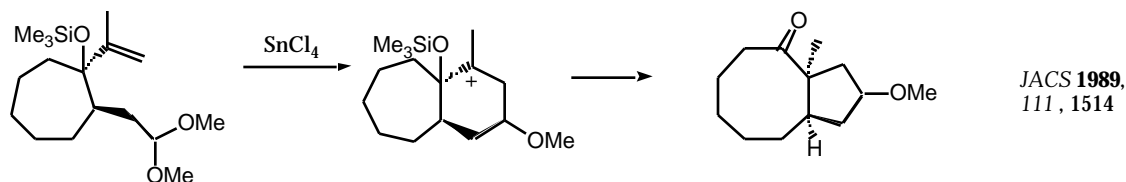




Aldol-like Condensations

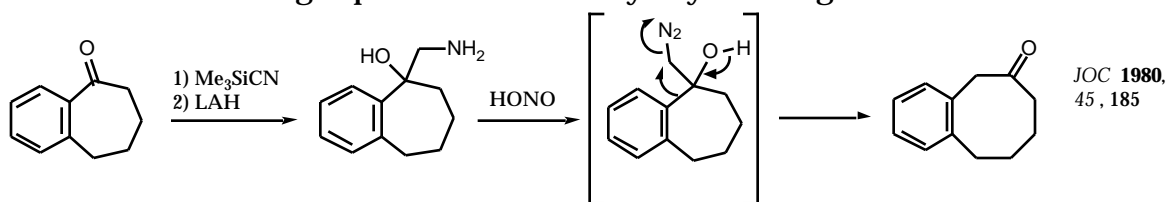


Pinacol Rearrangement



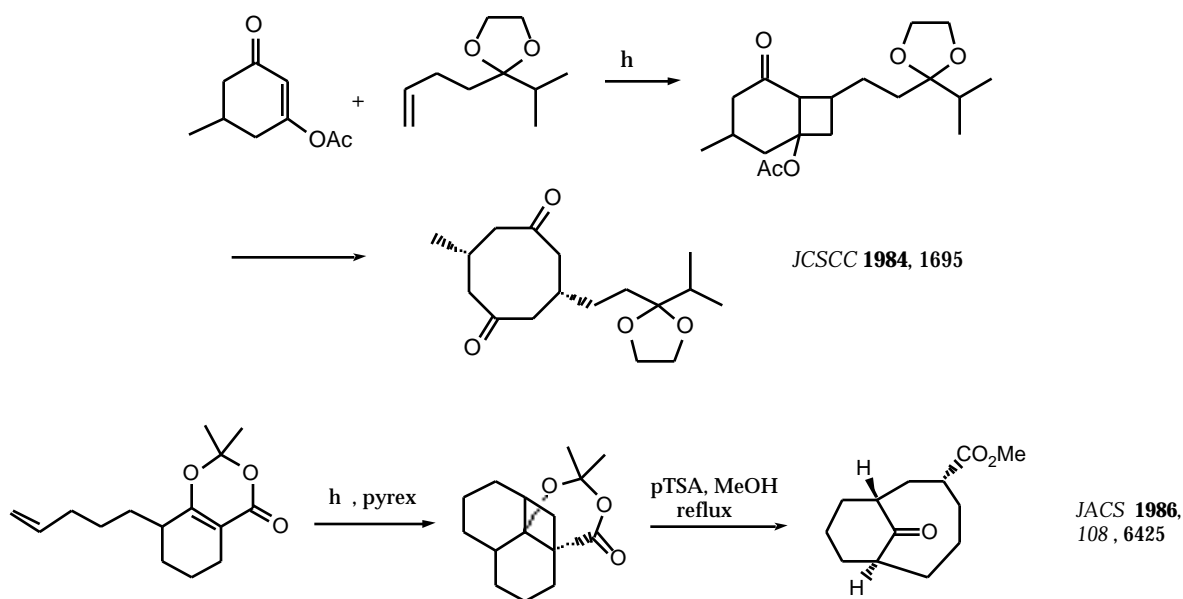
Tiffeneu-Demyanov Ring Expansion

- one carbon ring expansion for virtually any size ring



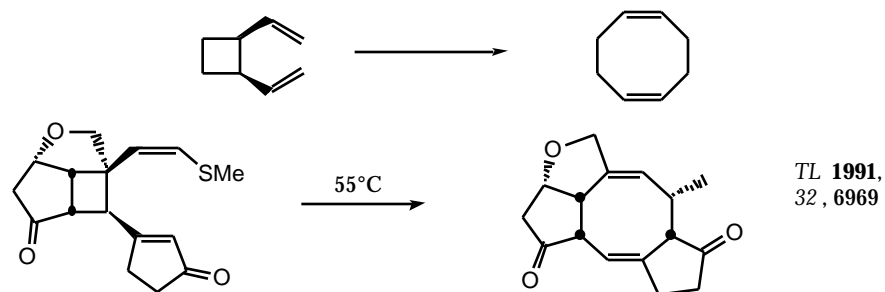
- also see Beckman and Schmidt rearrangements as a one atom ring expansion for the conversion of cyclic ketones to lactams.

DeMayo Reaction

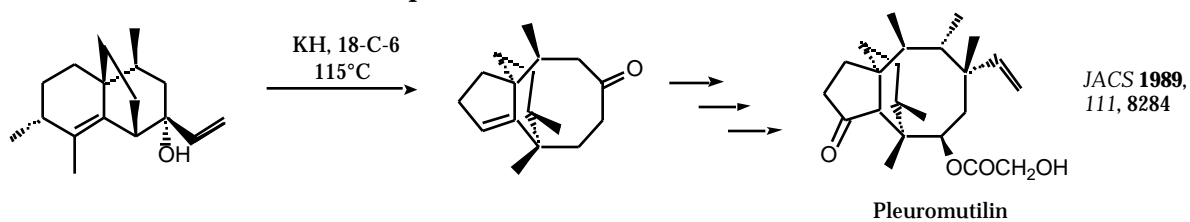


Ring Expansion/Contraction via Sigmatropic Rearrangements

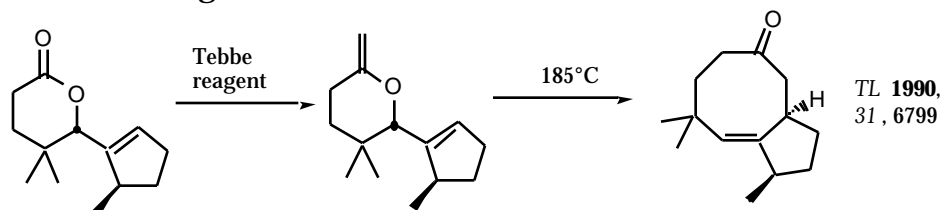
- Cope Rearrangement



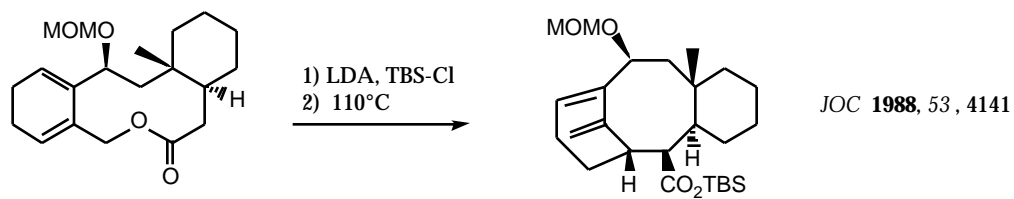
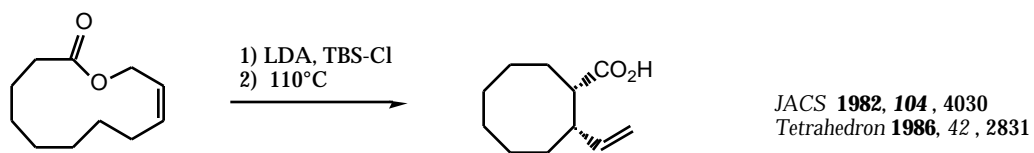
- Anion Accelerated Cope



- Claisen Rearrangement

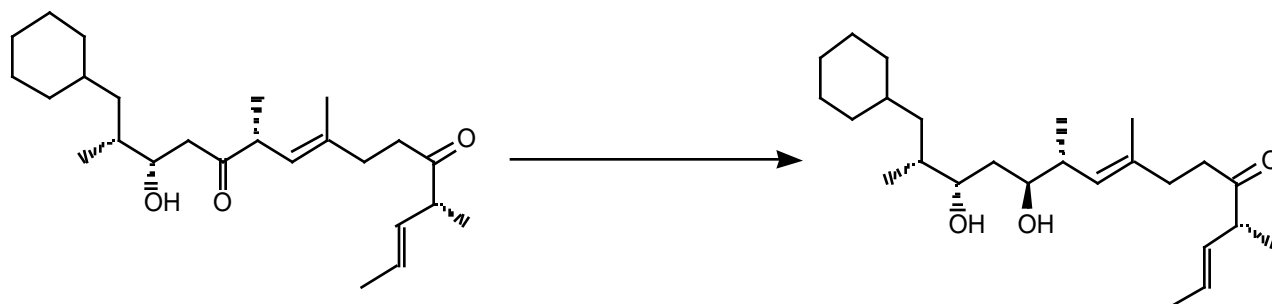
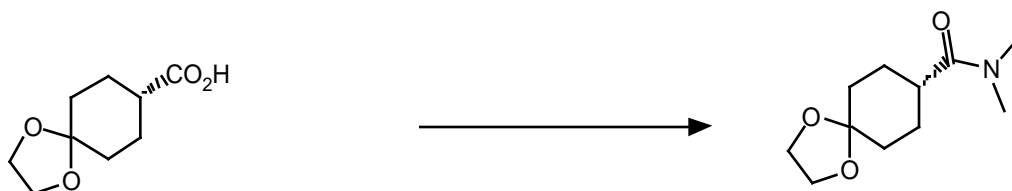
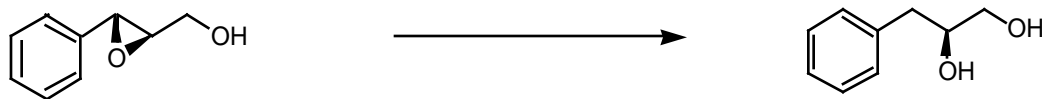
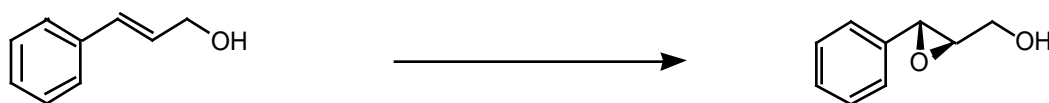
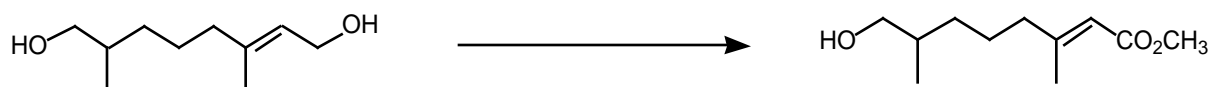


- Ester Enolate Claisen- 4 carbon ring contractions

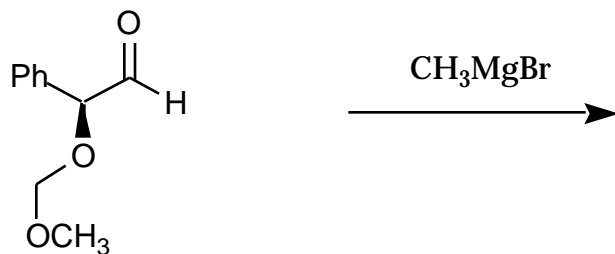
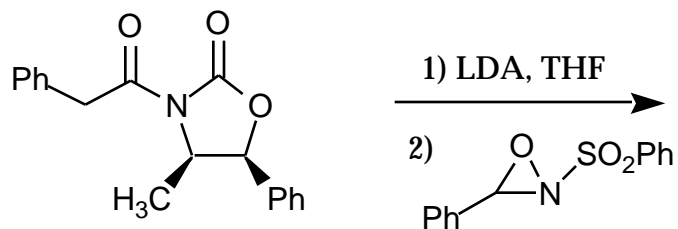
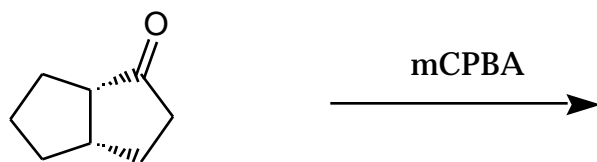
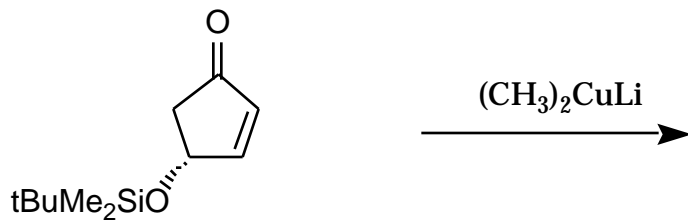
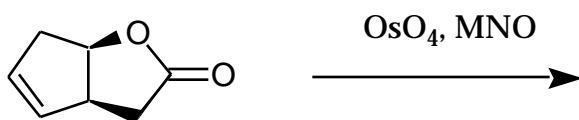


Exam 1

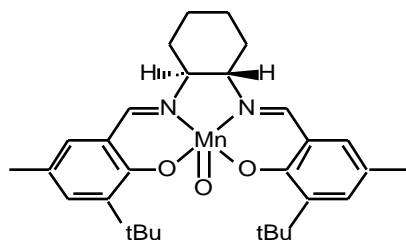
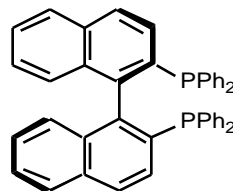
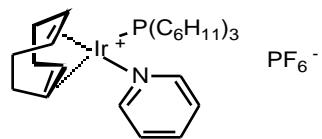
1. Give the reagent(s) necessary to carry out the following transformations. The stereochemistry of the products and reactants is as shown. (20 pts)



2. Give the product of the following reactions. The stereochemistry of the reactant is as shown. Give the proper stereochemistry of the major stereoisomer of the product. (20 pts)

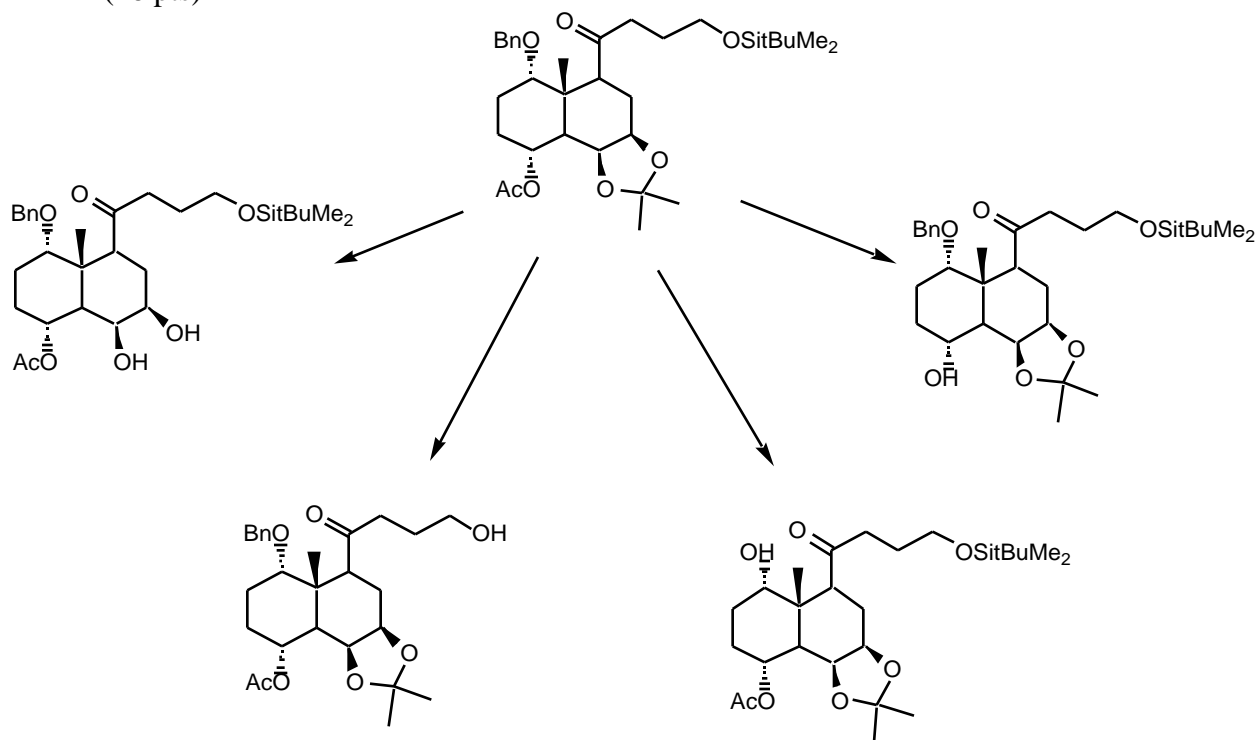


3. What are the following reagents used for. Please be specific. (8 pts each)

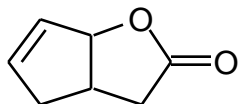


Bu_2BOTf , iPr_2NEt

4. Give the reagent(s) needed to selectively deprotect the substrate below to the desired product. (16 pts)



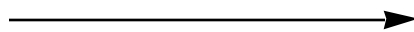
5. Provide the product and all intermediates for the following sequence of reactions. (20 pts)



1) LiAlH_4

2) MnO_2

3) $\text{tBuMe}_2\text{SiCl}$, pyridine



4) $p\text{CH}_3\text{C}_6\text{H}_3\text{SO}_2\text{NHNH}_2$

H^+ , C_6H_6 (- H_2O)

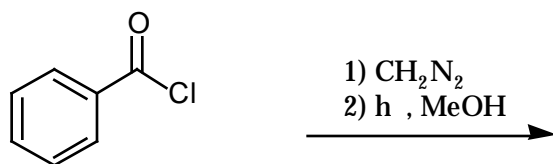
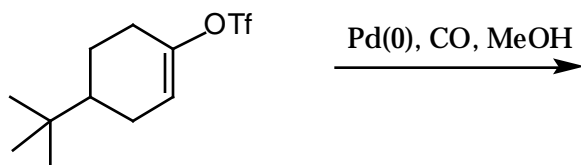
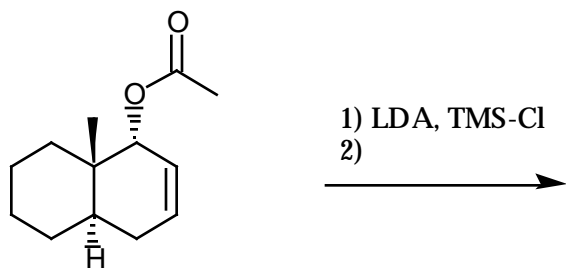
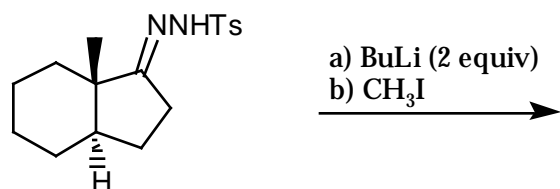
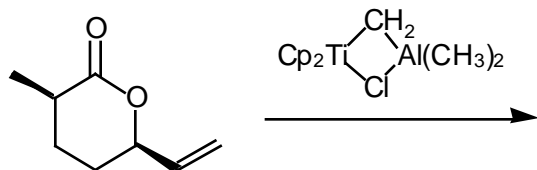
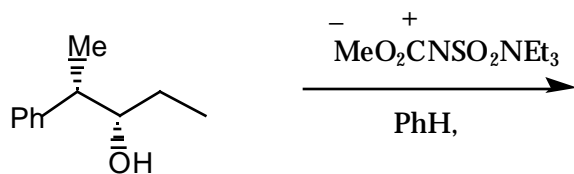
5) NaCNBH_3

6. Starting from cyclohexanone, provide a feasible synthesis target shown. Give all reagents and intermediates. (16 pts)

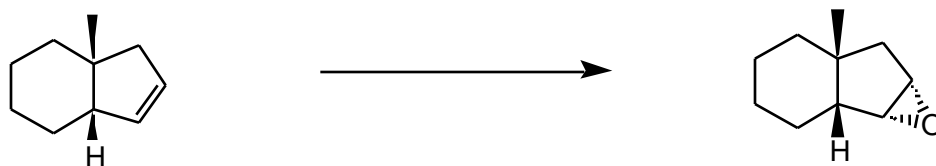
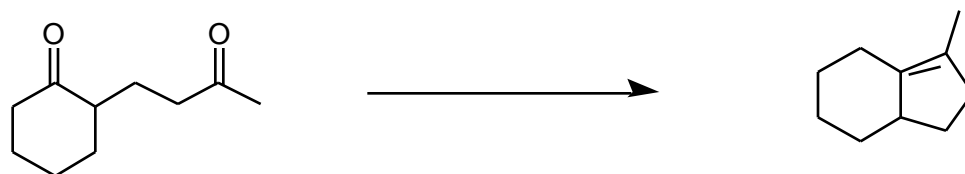
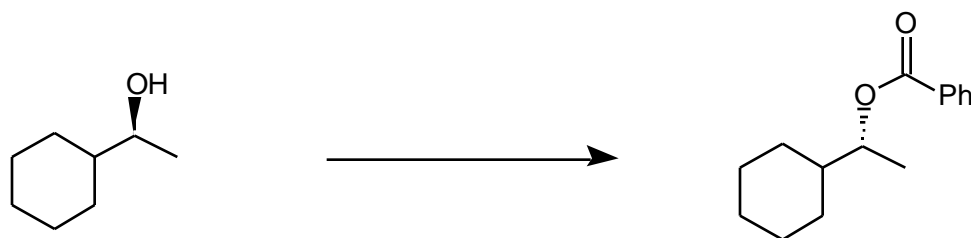
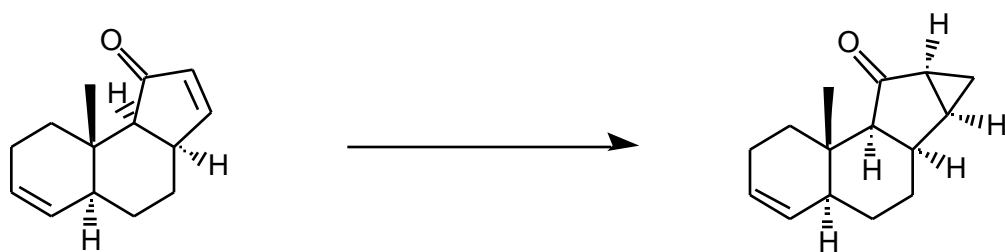
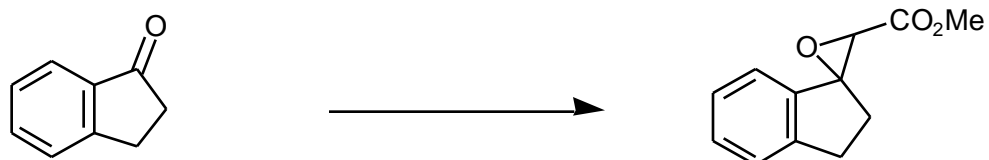
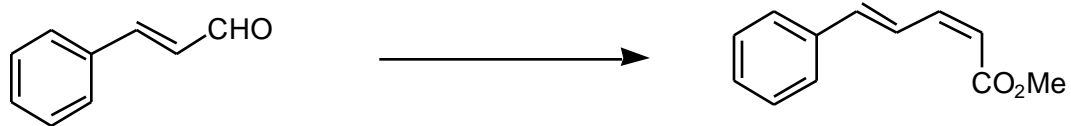


Exam 2

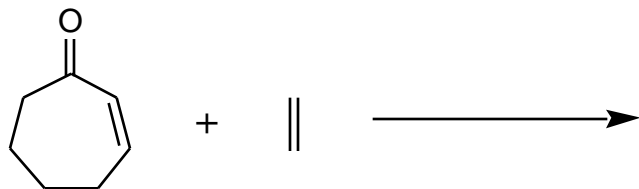
1. Give the product of the following reactions. The stereochemistry of the reactant is as shown. Give the proper stereochemistry of the major stereoisomer of the product. (24 pts)



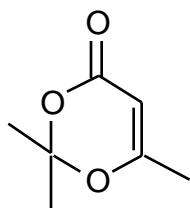
2. Give the reagent(s) necessary to carry out the following transformations. The stereochemistry of the products and reactants is as shown. (24 pts)



3. Give the expected product from a thermal and photochemical [2+2] cycloaddition of cycloheptenone with ethylene. Using MO's, clearly show why the photochemical and thermal pathways give different stereochemical outcomes. (12 pts)



4. Provide the product and all intermediates for the following sequence of reactions. (20 pts)



1) cyclopentene, h

2) DIBAL

3) $t\text{BuO}^- \text{K}^+$

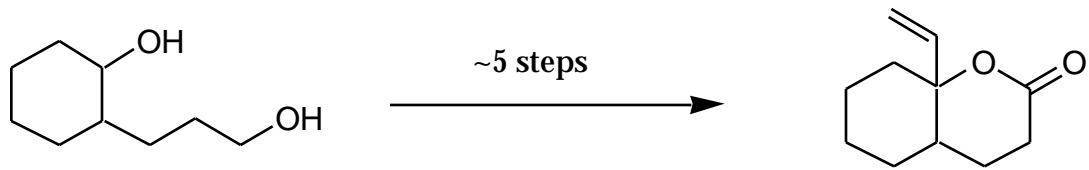


4a) $(\text{CH}_3)_2\text{CuLi}$

b) Tf_2NPh

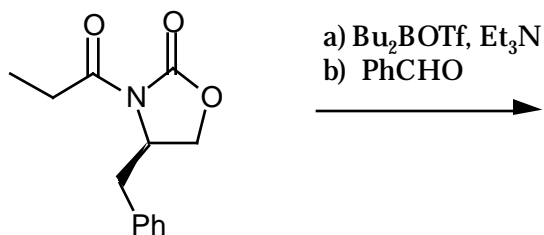
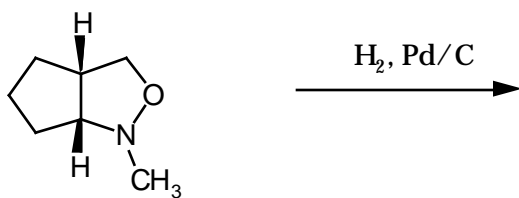
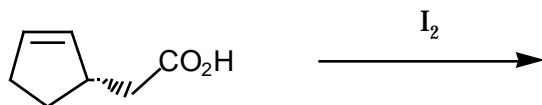
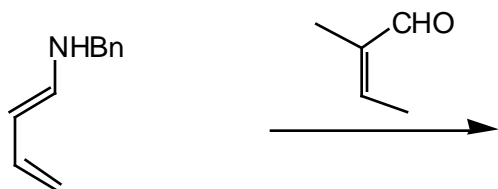
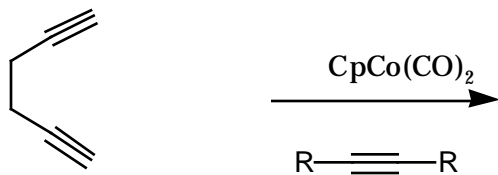
5) Ph_2CuLi

5. Complete the synthesis for the target shown. Give all reagents and intermediates. (20 pts).

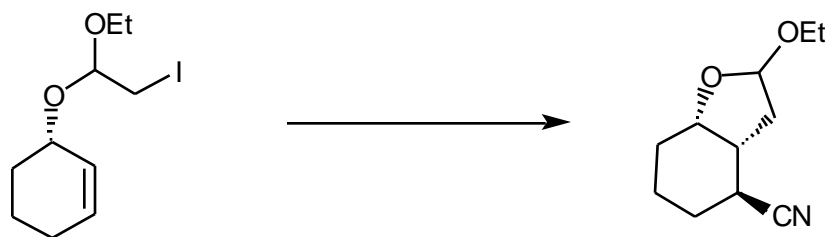
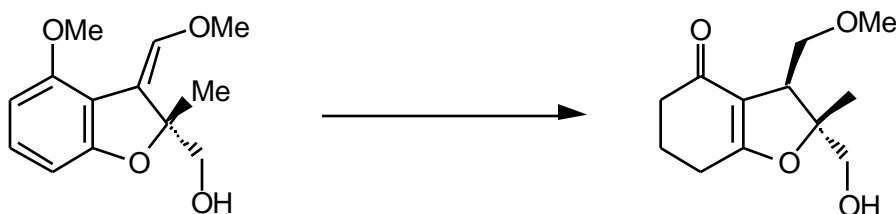
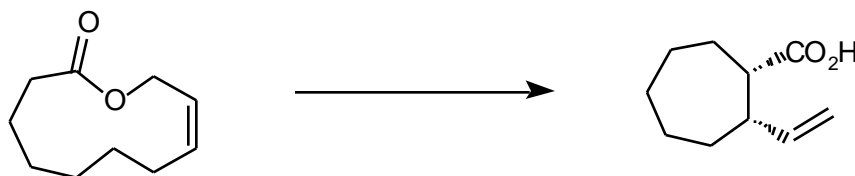
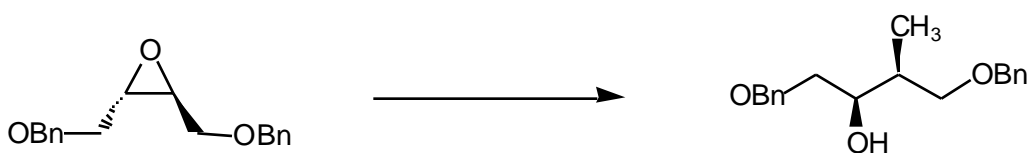
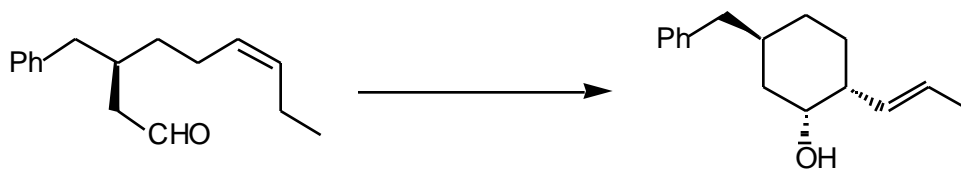


Exam 3

1. Give the product of the following reactions. The stereochemistry of the reactant is as shown. Give the proper stereochemistry of the major stereoisomer of the product. (20 pts)



2. Give the reagent(s) necessary to carry out the following transformations. The stereochemistry of the products and reactants is as shown. (20 pts)



3. Short Answers. (5 points each, 20 points total)

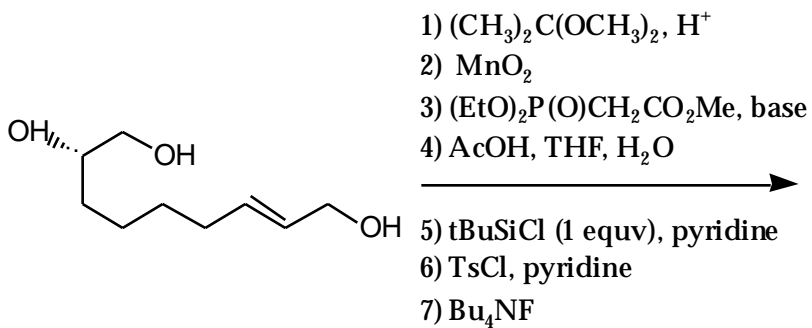
a. Define enantioselective and enantiospecific and give examples of each.

b. What is the Stork-Eschenmoser hypothesis?

- c. What are Baldwin's Rules (be general, do not give each specific rule)? Be sure to explain what are the basis of the rules and give one example each of a reaction that is favored and disfavored according to Baldwin's rule.

- d. Define umpolung and give an example.

4. Provide the product and all intermediates for the following sequence of reactions. (20 pts)



5. Complete the synthesis for the target shown. Give all reagents and intermediates. (20 pts).

