

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

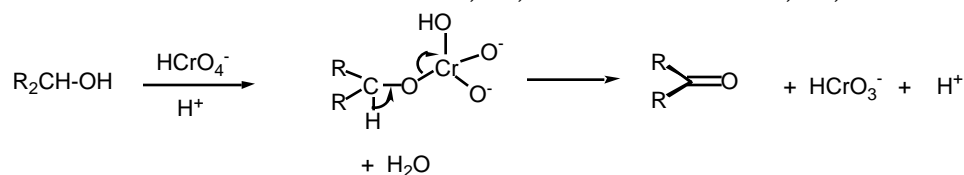
II Non-Metal Based Reagents

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.



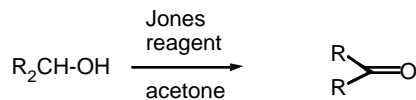
Jones Reagent (H_2CrO_4 , $\text{H}_2\text{Cr}_2\text{O}_7$, $\text{K}_2\text{Cr}_2\text{O}_7$)

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

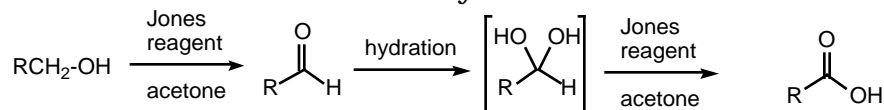
Org. Syn. Col. Vol. V, **1973**, 310.

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

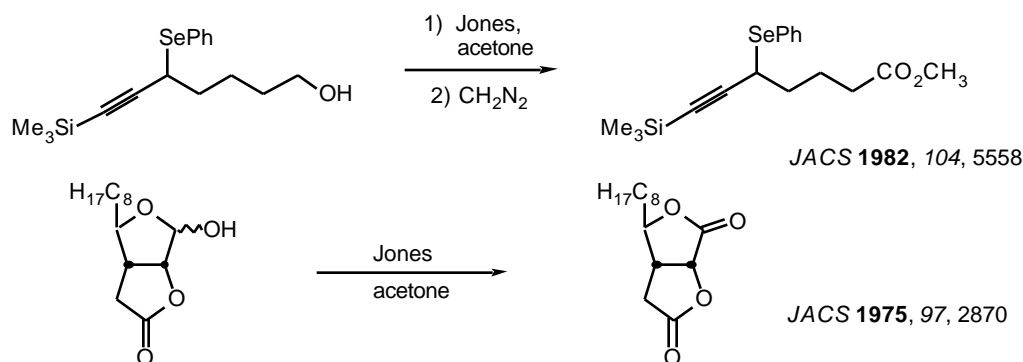
- 2°- alcohols are oxidized to ketones



- saturated 1° alcohols are oxidized to carboxylic acids.



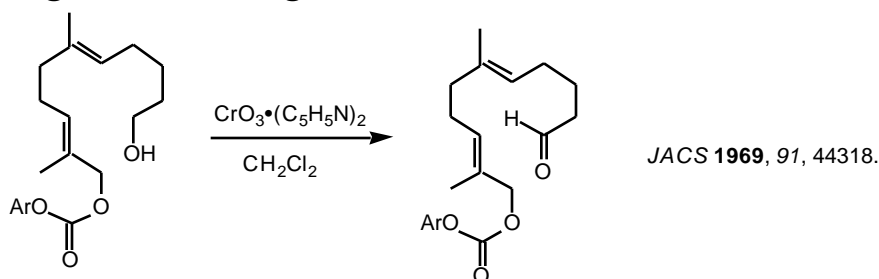
- Acidic media!! Not a good method for H^+ sensitive groups and compounds



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.

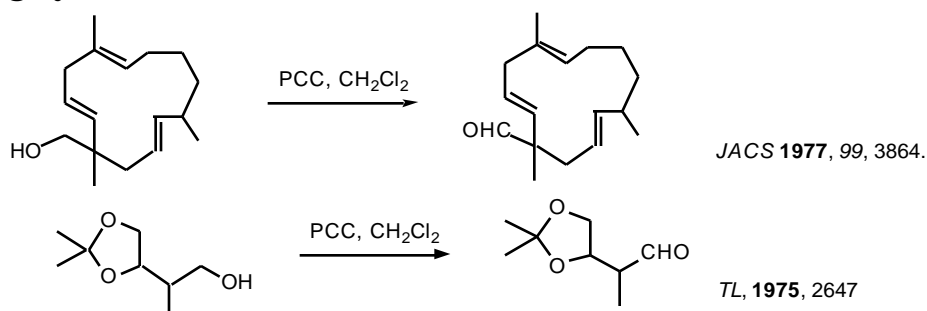
Pyridinium Chlorochromate (PCC, Corey-Suggs Oxidation)

TL 1975 2647

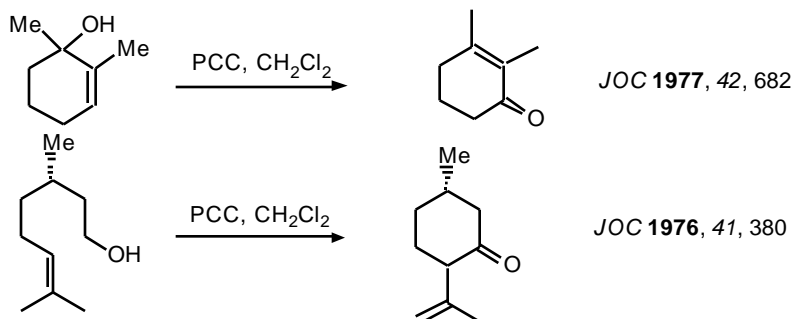
Synthesis 1982, 245 (review)

CrO₃ + 6M HCl + pyridine pyH⁺CrO₃ Cl⁻

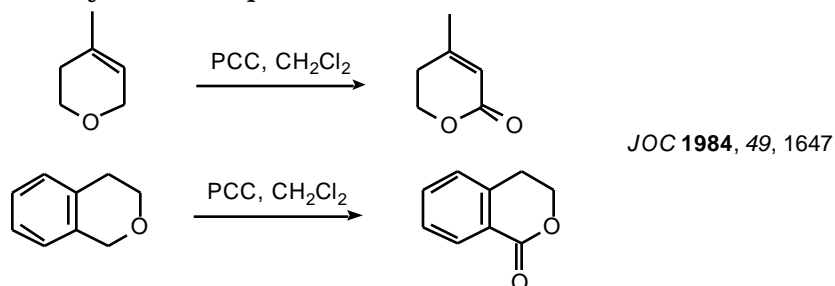
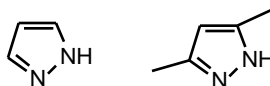
- Reagent can be used in close to stoichiometric amounts w/ substrate
- PCC is slightly acidic but can be buffered w/ NaOAc



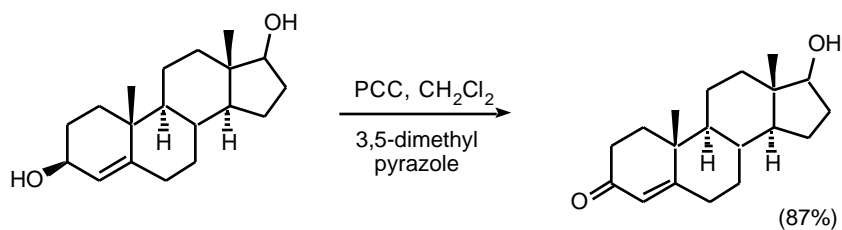
- Oxidative Rearrangements



- Oxidation of Active Methylene Groups

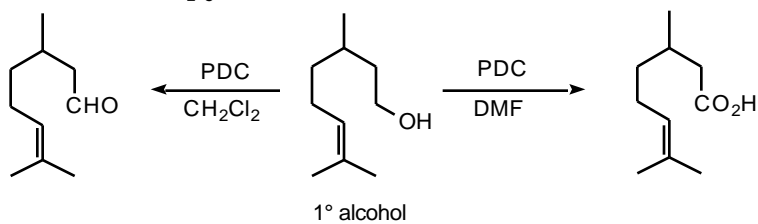

 - PCC/Pyrazole PCC/ 3,5-Dimethylpyrazole
JOC 1984, 49, 550.


- selective oxidation of allylic alcohols



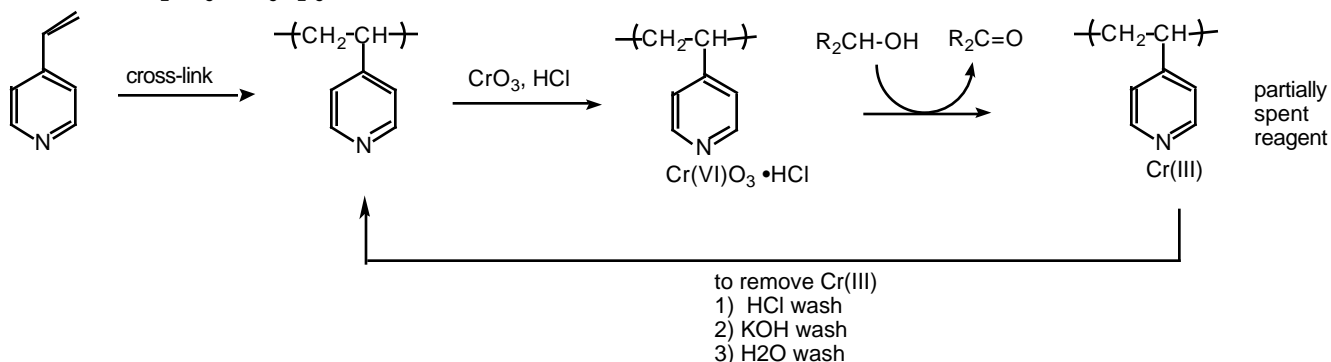
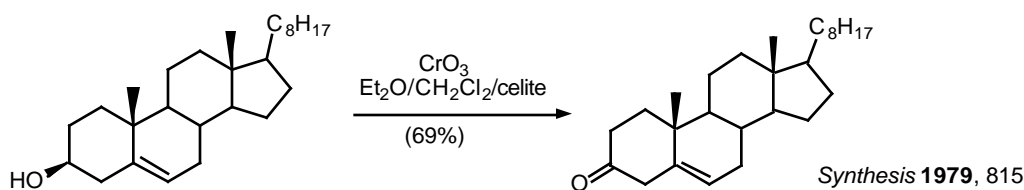
Pyridinium Dichromate (PDC, Corey-Schmidt Oxidation)

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

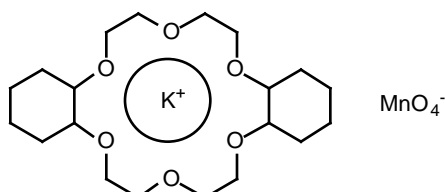
- ether is the solvent of choice

Manganese Reagents

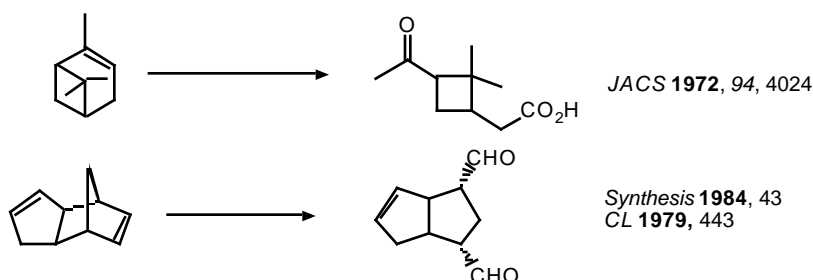
Potassium Permanganate

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

(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

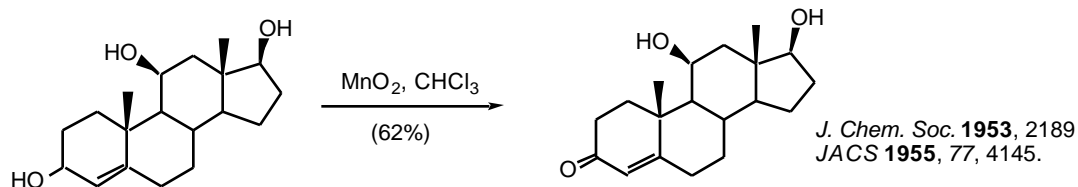
- heterogeneous reaction in benzene
- 1° alcohols are oxidized to acids
- 2° alcohols are oxidized to ketones
- multiple bonds are not oxidized

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

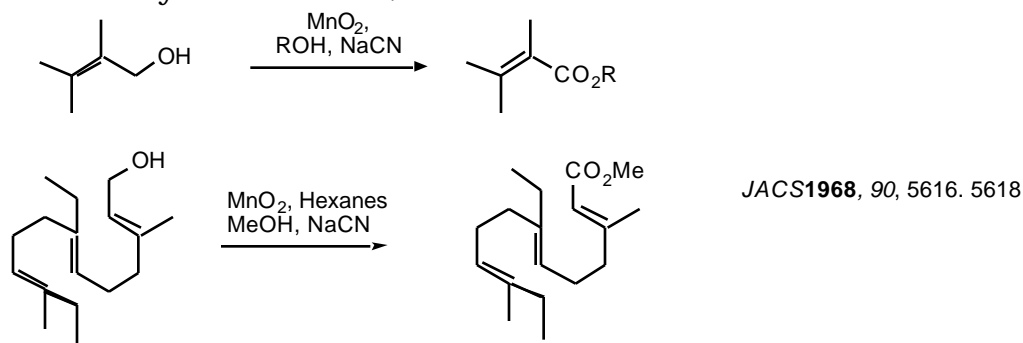
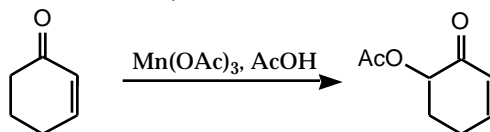
- Oxidation of 1° and 2° alcohols to aldehydes and ketones- No over oxidation
- Multiple bonds are not oxidized
- similar in reactivity to MnO₂

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

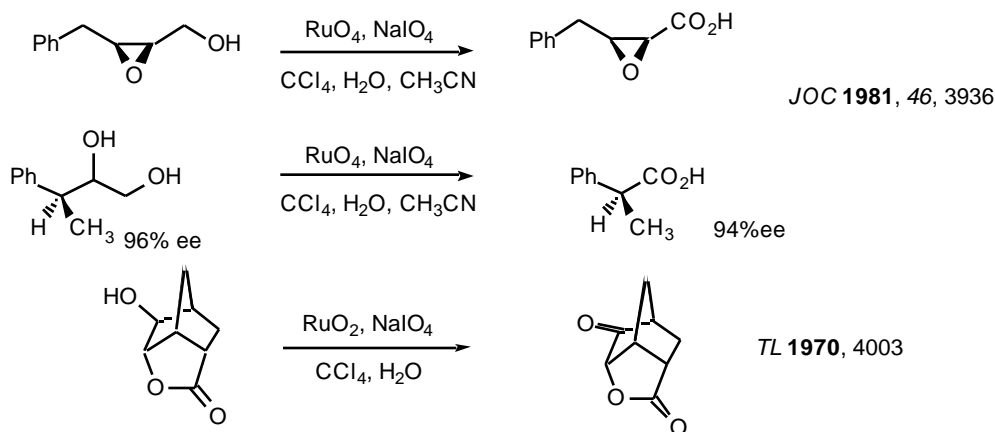
- Selective oxidation of , -unsaturated (allylic, benzylic, acetylenic) alcohols.
- Activity of MnO₂ depends on method of preparation and choice of solvent
- cis & trans allylic alcohols are oxidized at the same rate without isomerization of the double bond.



- 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.

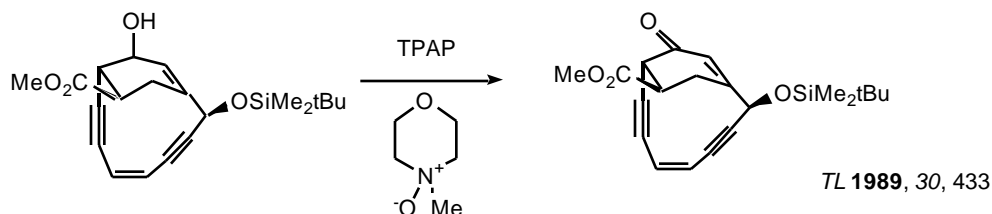


Tetra-*n*-propylammonium Perruthenate (TPAP, $\text{nPr}_4\text{N}^+ \text{RuO}_4^-$)

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

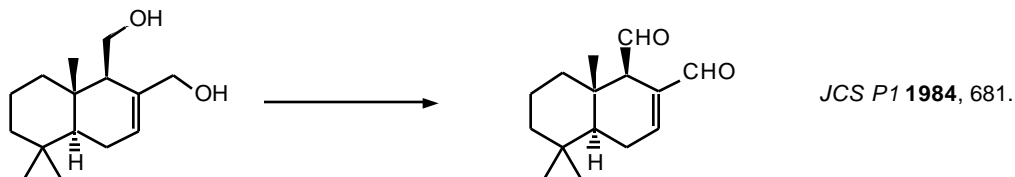
Synthesis **1994**, 639

- 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)

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

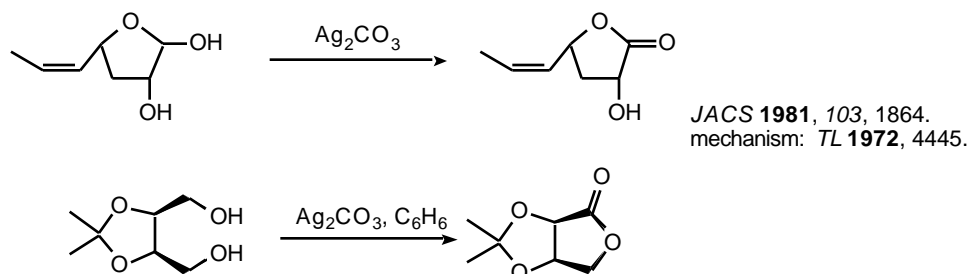
- oxidation of benzylic and allylic alcohols TL **1983**, 24, 2185.

Silver Reagents

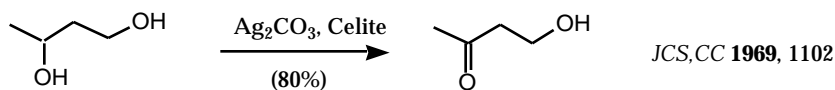
Ag_2CO_3 (Fetizon Oxidation) also $\text{Ag}_2\text{CO}_3/\text{celite}$

Synthesis **1979**, 401

- oxidation of only the most reactive hydroxyl

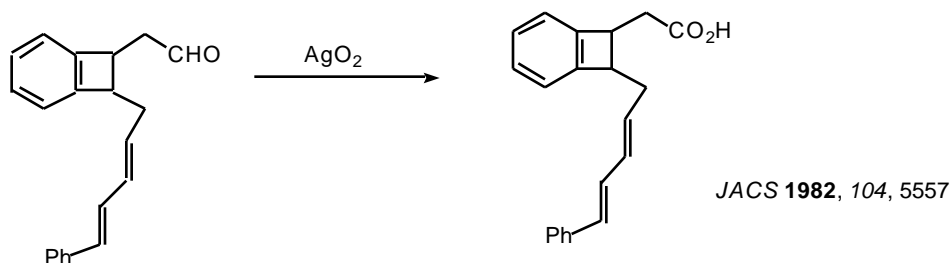
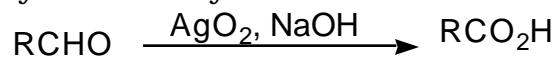


- Oxidation of 2° alcohol over a 1° alcohol

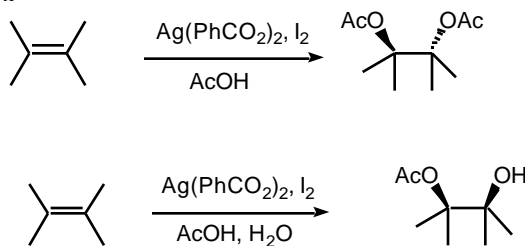


Silver Oxide (AgO_2)

- mild oxidation of aldehyde to carboxylic acids



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



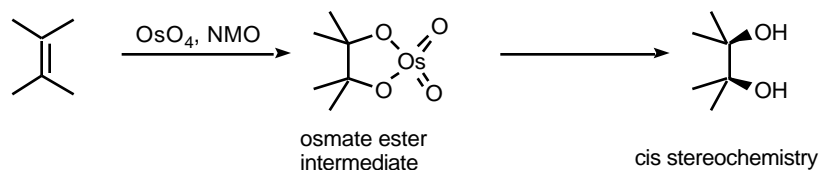
Other Metal Based Oxidations

Osmium Tetroxide OsO_4

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

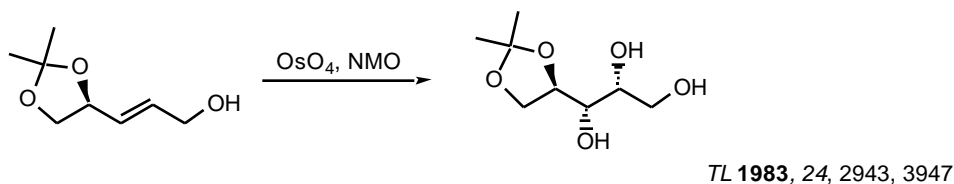
-cis hydroxylation of olefins

old mechanism:

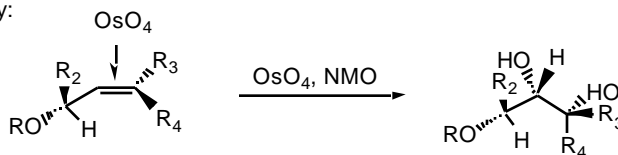


- use of $\text{R}_3\text{N-O}$ as a reoxidant

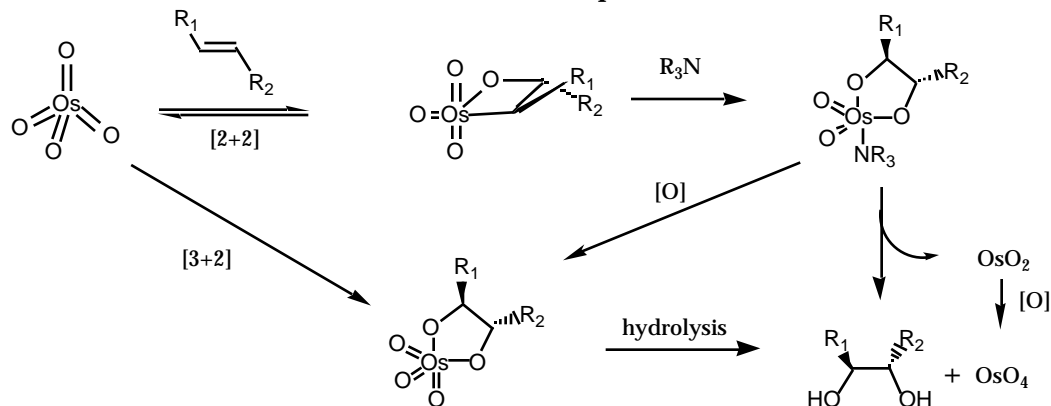
TL **1976**, 1973.



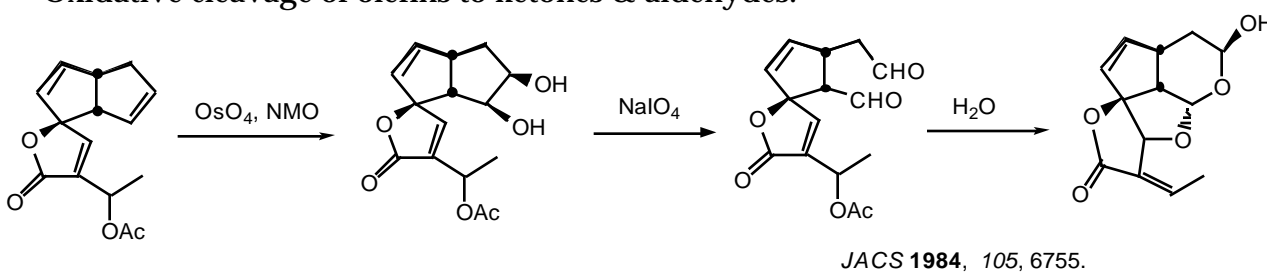
Stereoselectivity:



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

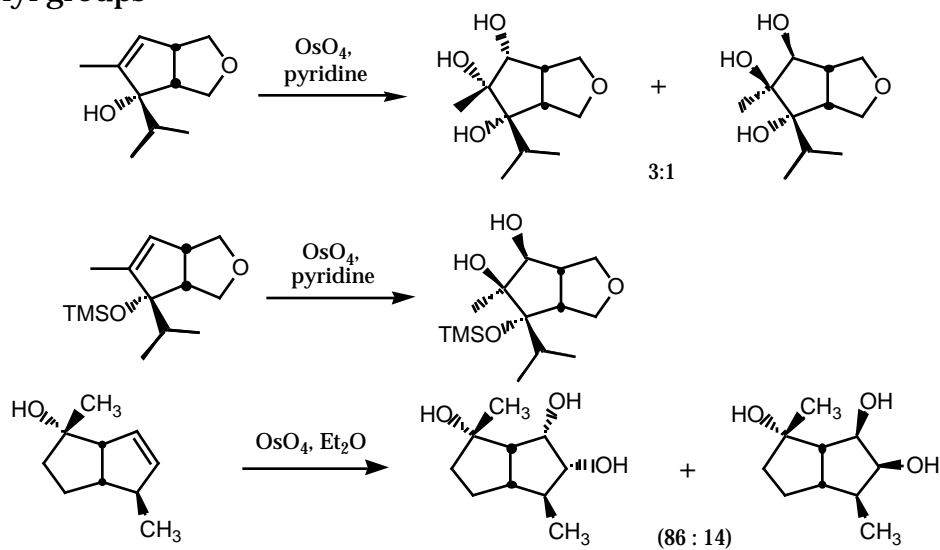


- Oxidative cleavage of olefins to carboxylic acids.
JOC **1956**, 21, 478.
- Oxidative cleavage of olefins to ketones & aldehydes.

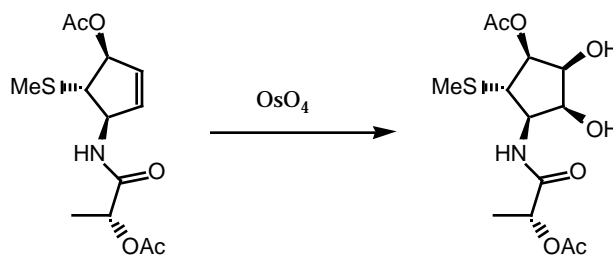


- Substrate directed hydroxylations:
-by hydroxyl groups

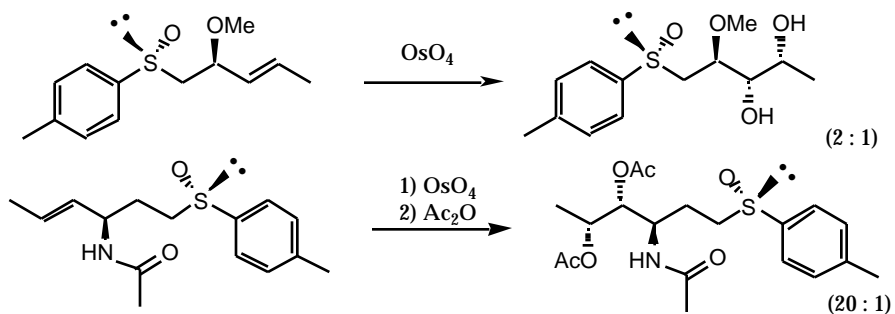
Chem. Rev. **1993**, 93, 1307



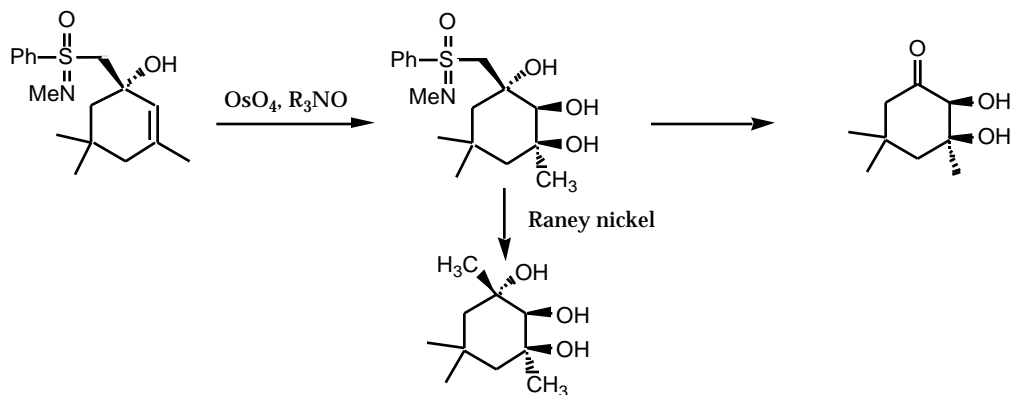
- by amides



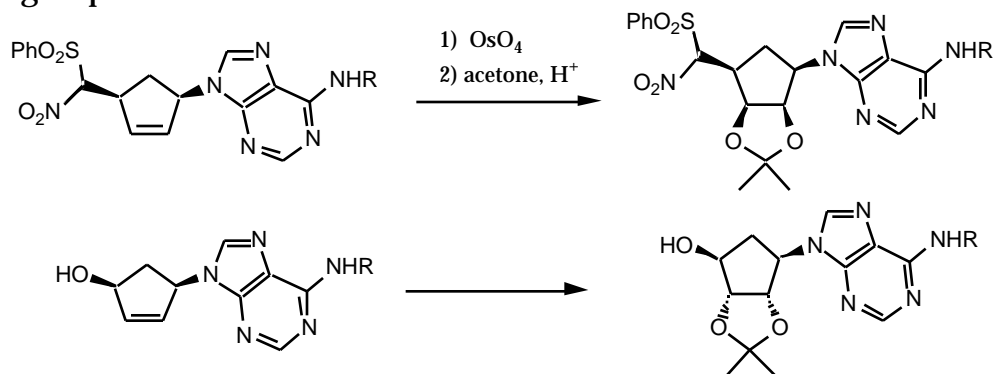
- by sulfoxides



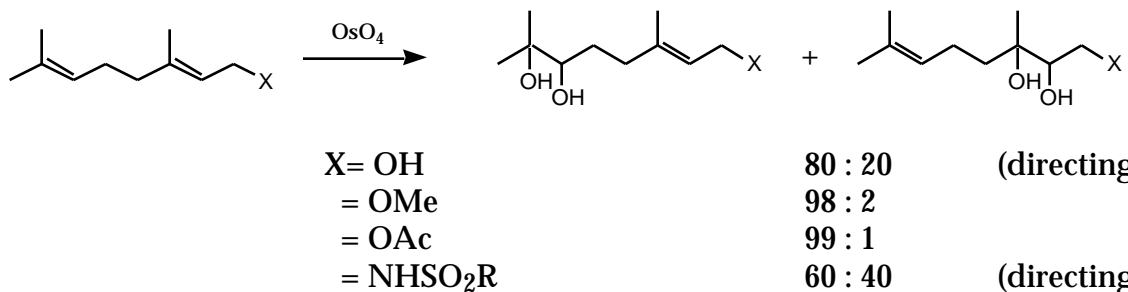
- by sulfoximines



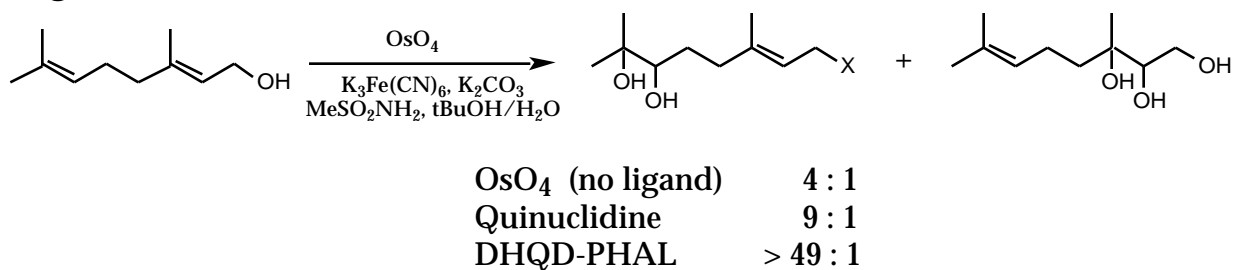
- By nitro groups



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



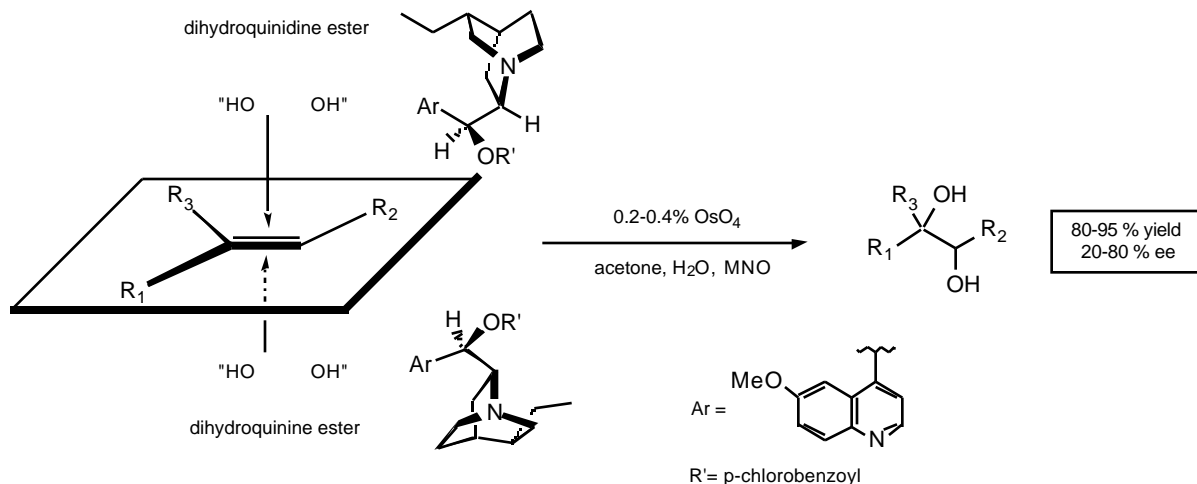
- Ligand effect:



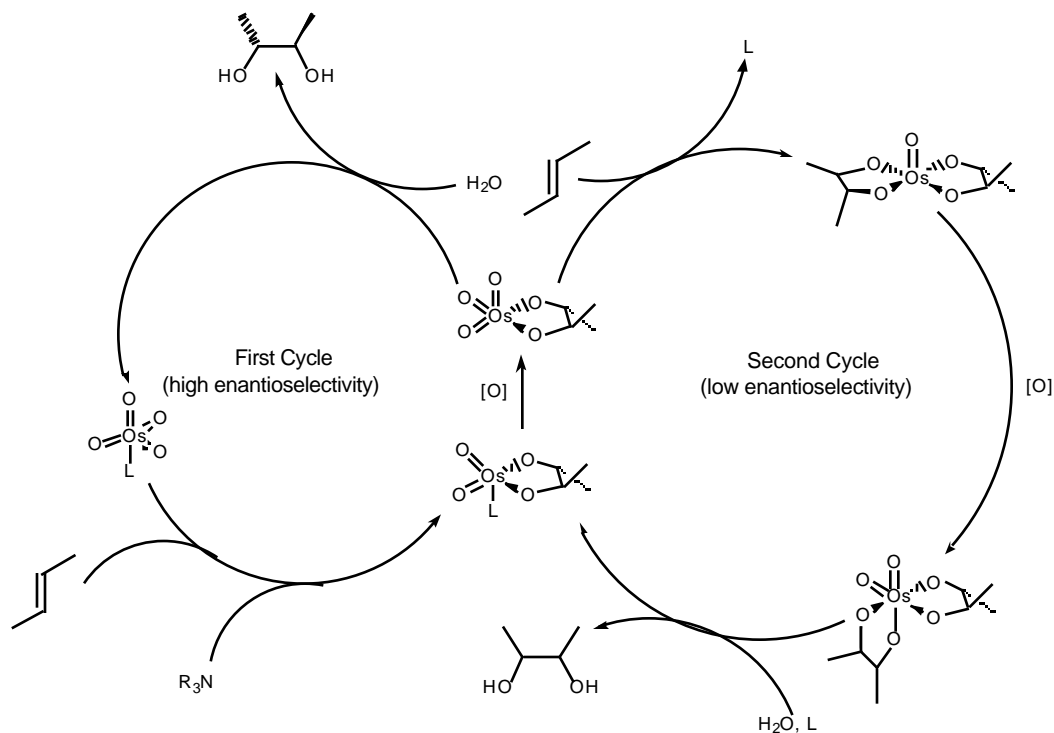
Sharpless Asymmetric Dihydroxylation (AD)

- Ligand pair are really diastereomers!!

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



Mechanism of AD:

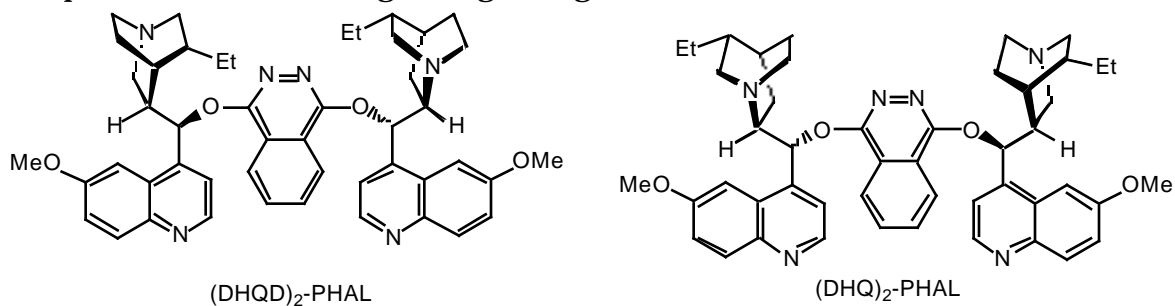


- K₃Fe(CN)₆ as a reoxidant gives higher ee's- eliminates second cycle

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

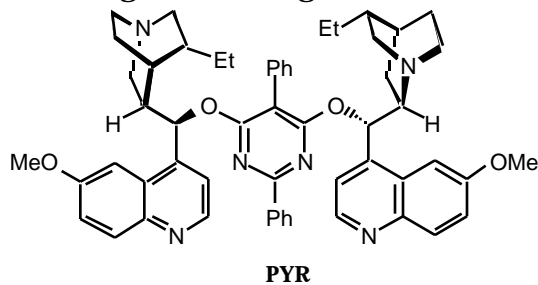
- Sulfonamide effect: addition of MeSO₂NH₂ enhances hydrolysis of Os(VI) glycolate (accelerates reaction)

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

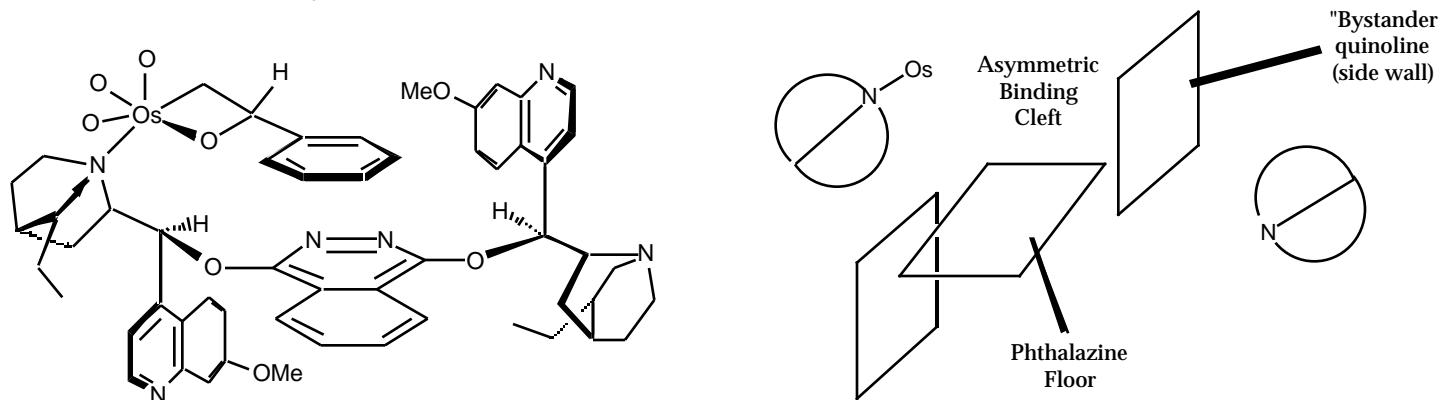


JOC **1992**, *57*, 2768.

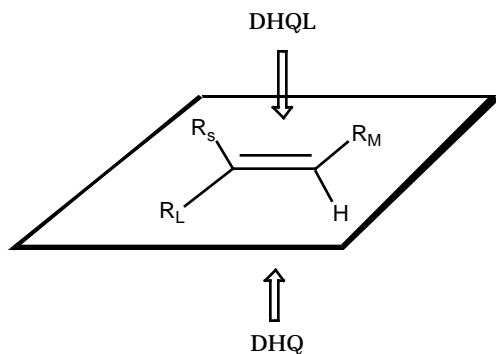
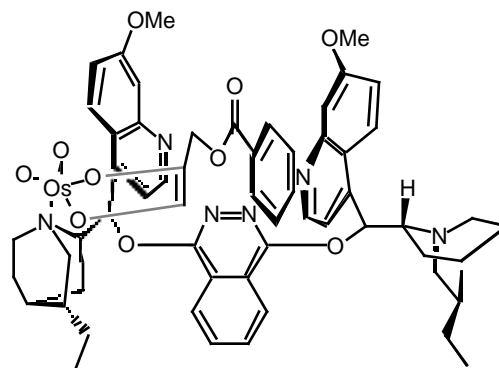
- Other second generation ligands






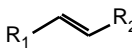
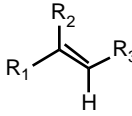
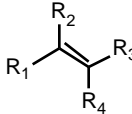
Proposed catalyst structure:



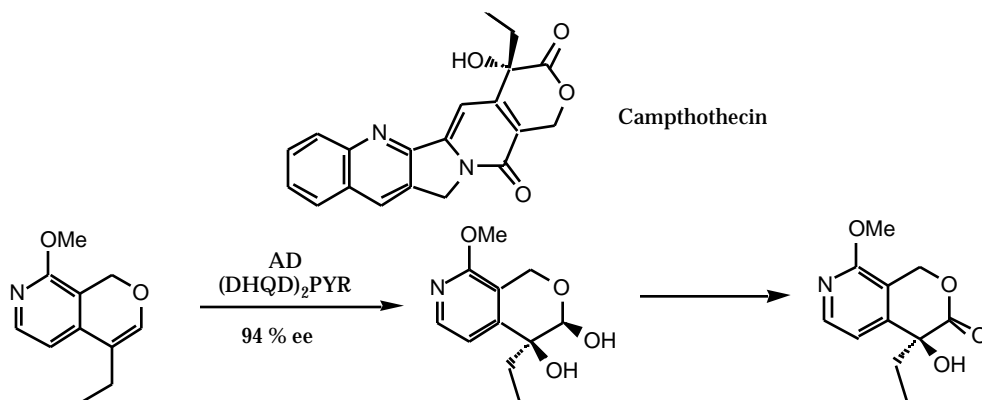
Corey Model: *JACS* **1996**, 118, 319
 Enzyme like binding pocket;
 [3+2] addition of OsO₄ to olefin.



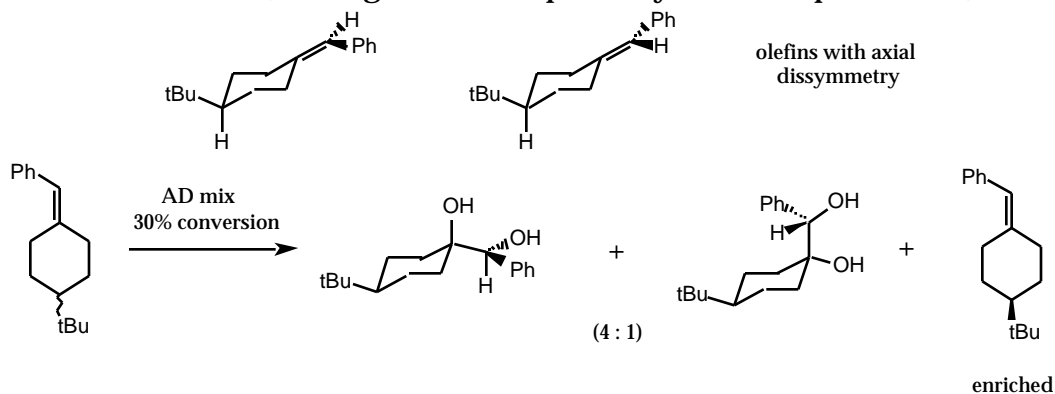
R_L large and flat,
 i.e Aromatics work particularly well

<u>Olefin</u>	<u>Preferred Ligand</u>	<u>ee's</u>
	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 %

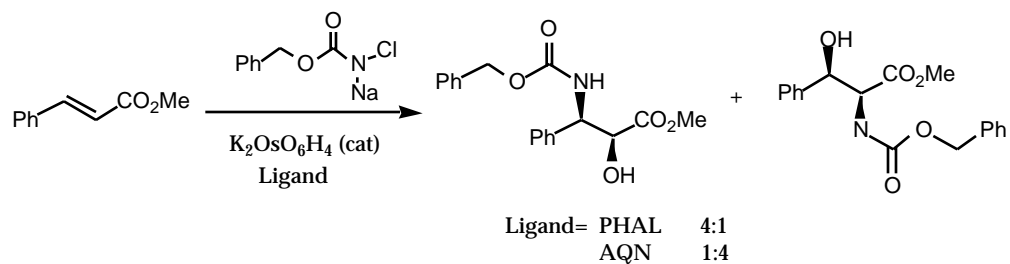
"AD-mixes" commercially available pre-mix solutions of Os, ligand and reoxidant
 AD-mix (DHQ)₂PHAL, K₃Fe(CN)₆, K₂CO₃, K₂OsO₄ (0.4 MOL % Os to C=C)
 AD-mix (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, K₂OsO₄



- 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

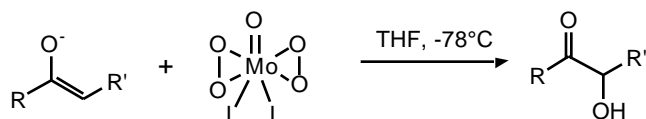


Molybdenum Reagents

MoOPH [MoO₅•pyridine (HMPA)]

JOC **1978**, 43, 188.

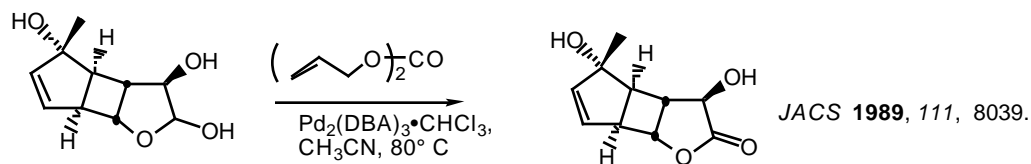
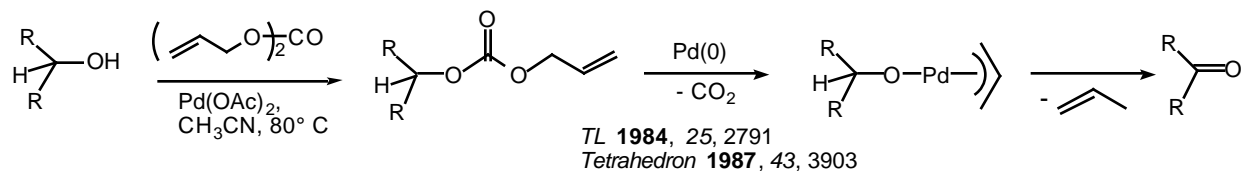
- α -hydroxylation of ketone, ester and lactone enolates.



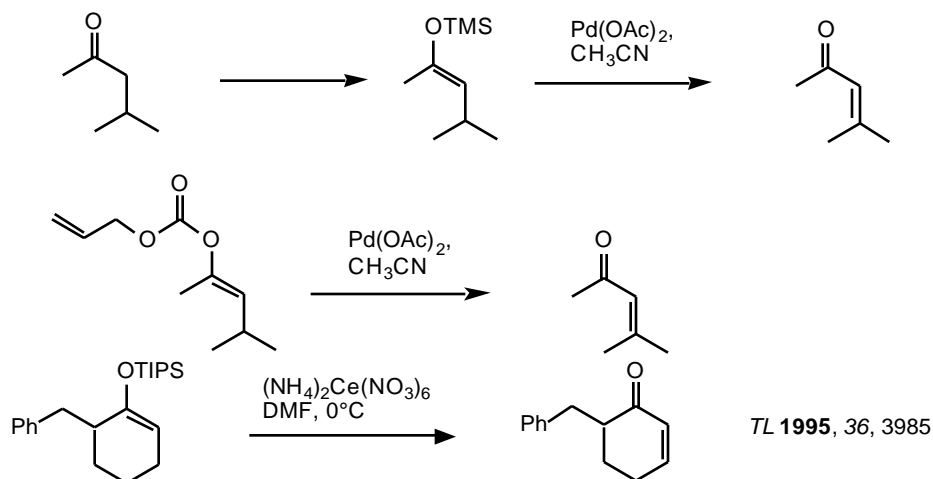
Palladium Reagents

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

Tetrahedron **1986**, 42, 4361

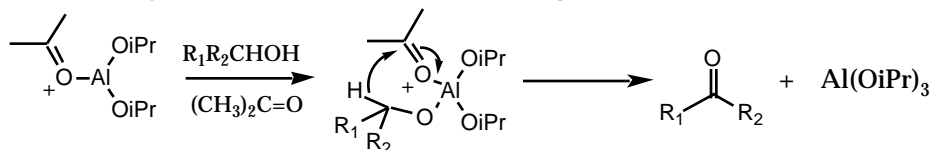


Oxidation of silylenol ethers and enol carbonates to enones



Oppenauer Oxidation

 Synthesis **1994**, 1007

 Organic reactions **1951**, 6, 207


Nickel Peroxide

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

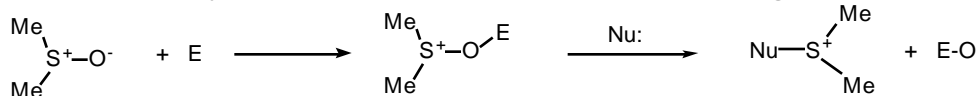
 Thallium Nitrate (TNN, Tl(NO₃)₃•3H₂O)

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

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

Non-Metal Based Reagents

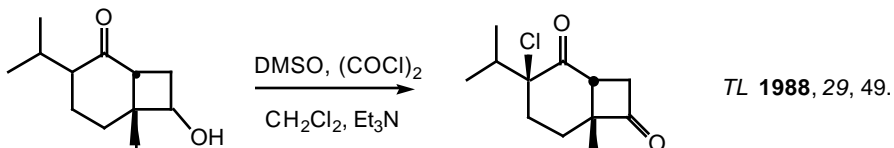
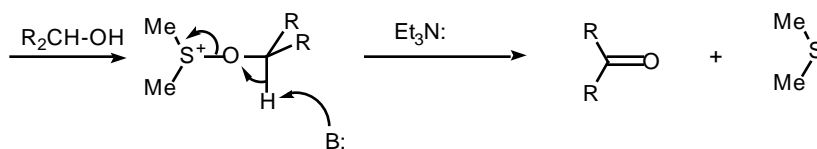
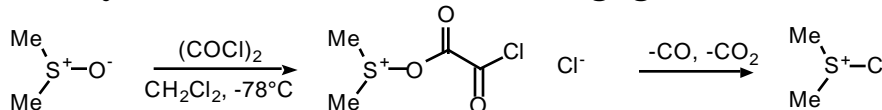
Activated DMSO Review: Synthesis **1981**, 165; **1990**, 857.

 Organic Reactions **1990**, 39, 297

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

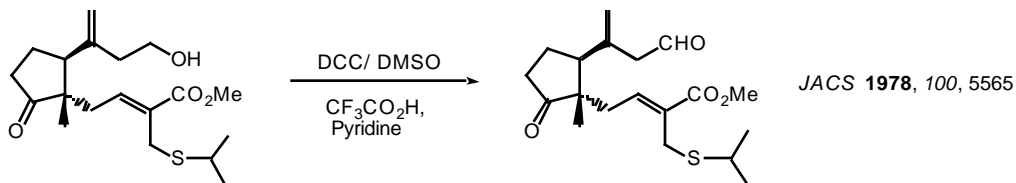
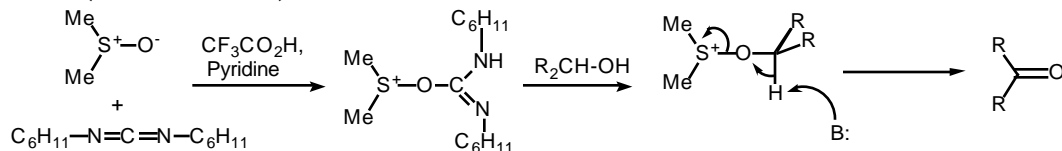
 Nu:= R-OH, Ph-OH, R-NH₂, RC=NOH, enols

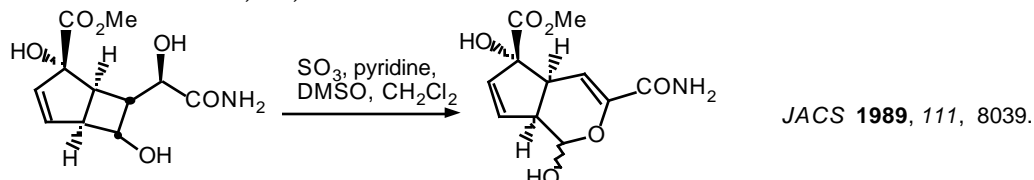
Swern Oxidation

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

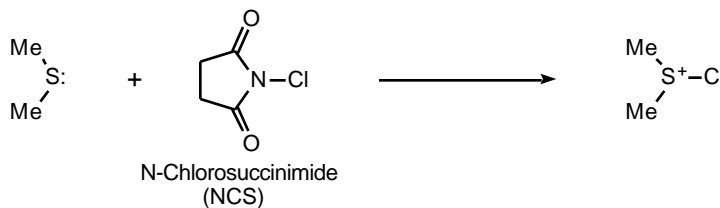


Moffatt Oxidation (DMSO/DCC)

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

 SO₃/Pyridine

 JACS **1967**, 89, 5505.


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

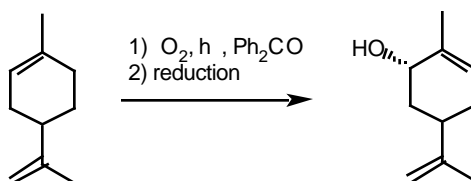
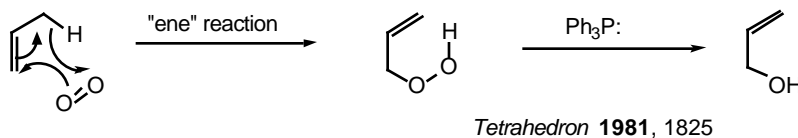
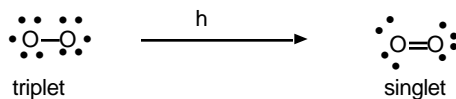


Oxygen & Ozone

Singlet Oxygen

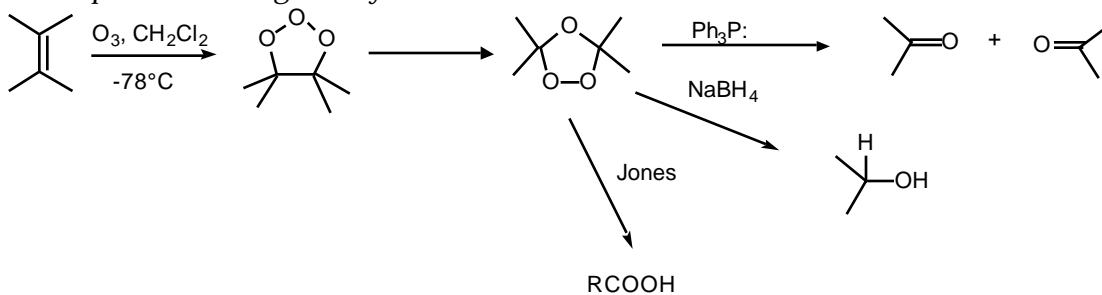
Acc. Chem. Res. **1980**, 13, 419

Tetrahedron **1981**, 37, 1825



Ozone

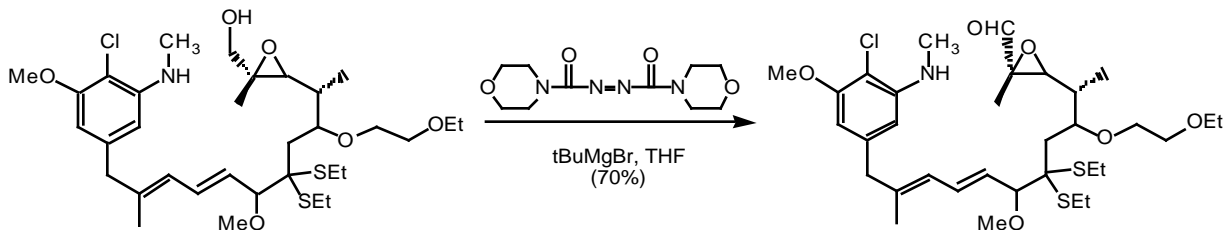
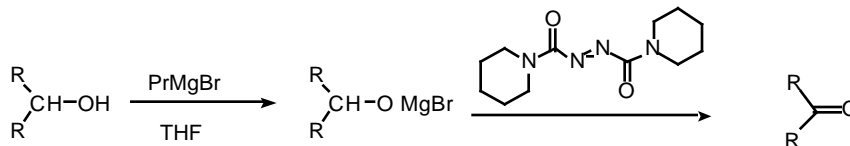
Comprehensive Organic Synthesis **1991**, 7, 541



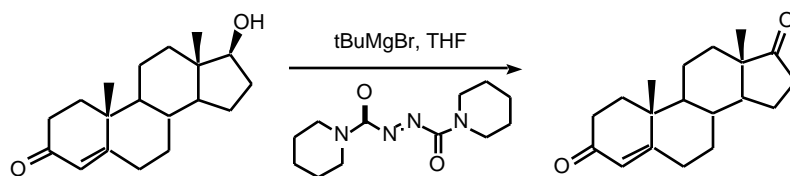
Other Oxidations

Mukaiyama Oxidation

BCSJ **1977**, 50, 2773



JACS **1979**, 101, 7104

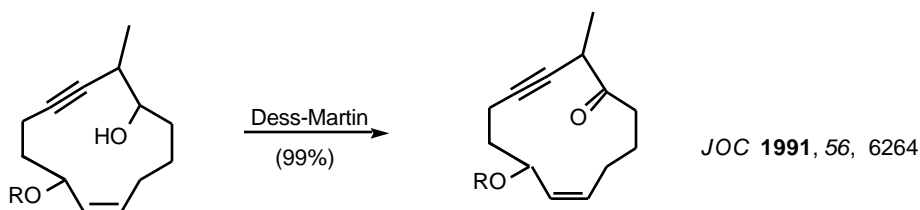
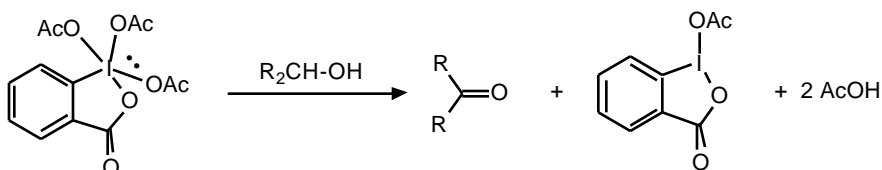


Dess-Martin Periodinane

JOC **1983**, 48, 4155.

JACS **1992**, 113, 7277.

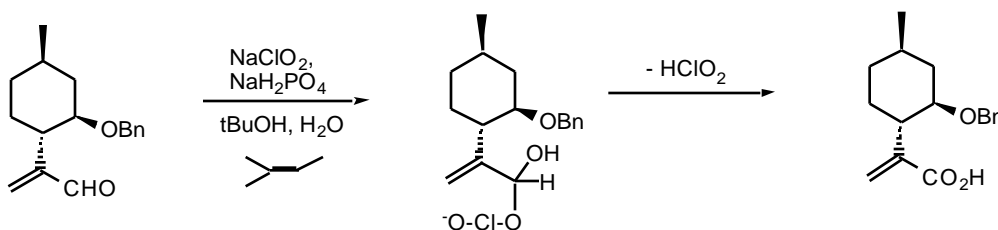
- oxidation conducted in CHCl_3 , CH_3CN or CH_2Cl_2
- excellent reagent for hindered alcohols
- very mild



Chlorite Ion

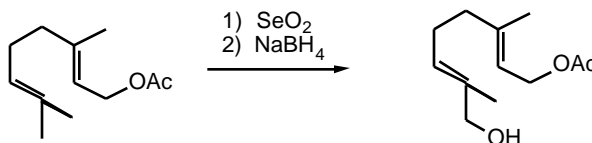
- oxidation of α,β -unsaturated aldehydes to α,β -unsaturated acids.

Tetrahedron **1981**, 37, 2091

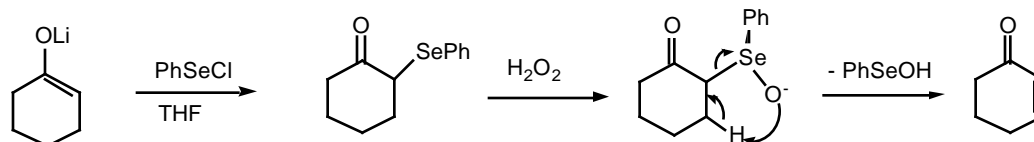


Selenium Dioxide

- Similar to singlet oxygen (allylic oxidation)



Phenyl Selenium Chloride

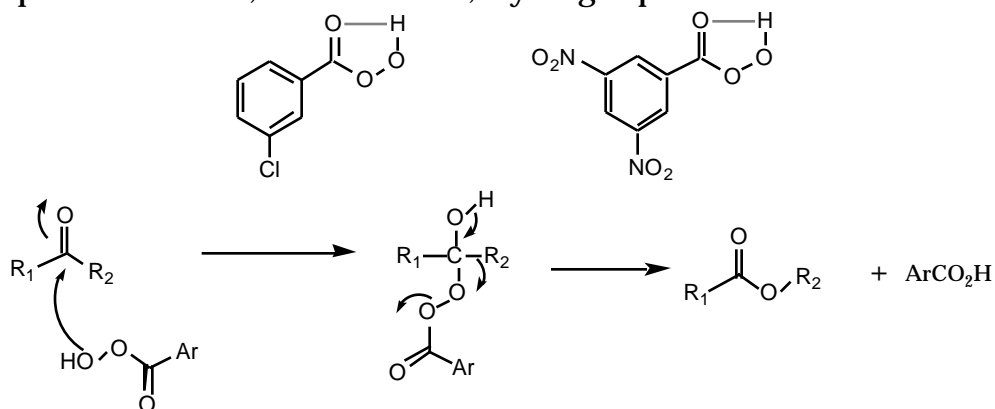


- PhS-SPH will do similar chemistry however a sulfoxide elimination is less facile than a selenoxide elimination.

Peroxides & Peracids

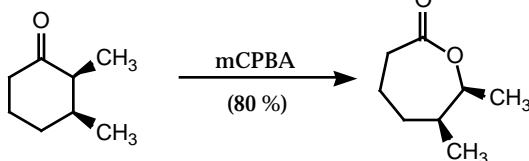
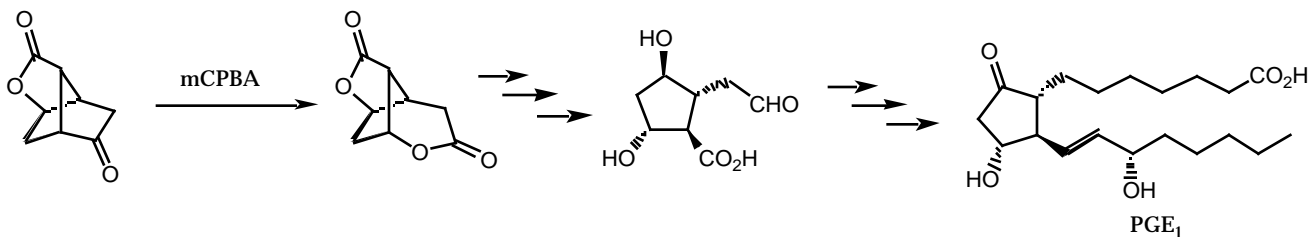
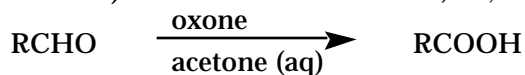
- R_3N : $\text{R}_3\text{N-O}$
 - sulfides sulfoxides sulfones
 - Baeyer-Villiger Oxidation- oxidation of ketones to esters and lactones via oxygen insertion
- Organic Reactions **1993**, 43, 251 Comprehensive Organic Synthesis **1991**, vol 7, 671.

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:
 $3^\circ > 2^\circ > \text{benzyl} = \text{phenyl} > 1^\circ \gg \text{methyl}$

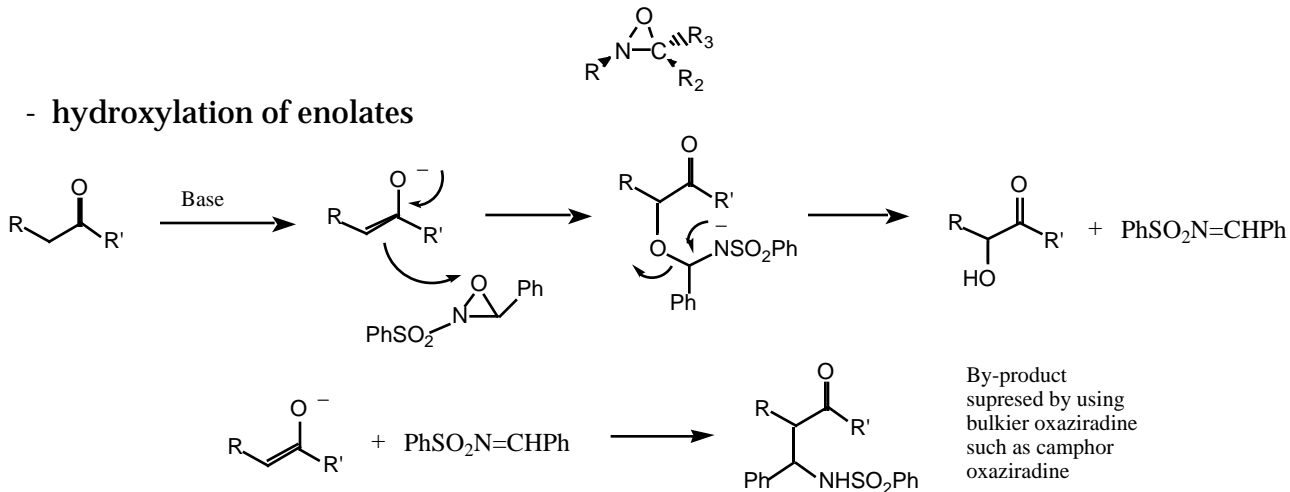
JACS 1971, 93, 1491

Tetrahedron Lett. 1977, 2173
Tetrahedron Lett. 1978, 1385Oxone (postassium peroxymonosulfate) *Tetrahedron* 1997, 54, 401

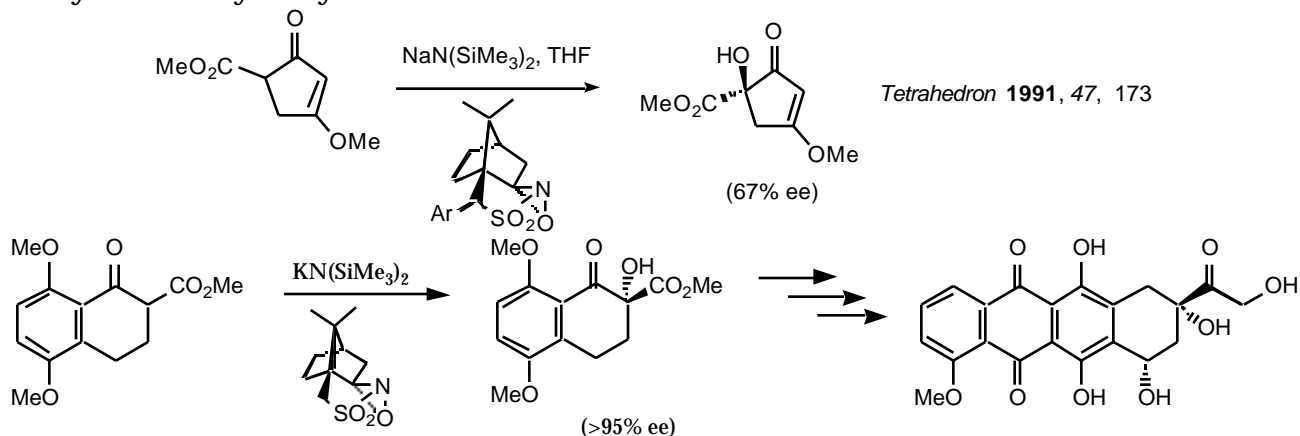
Oxaziridines

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

- hydroxylation of enolates



Asymmetric hydroxylations



- hydroxylation of organometallics

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

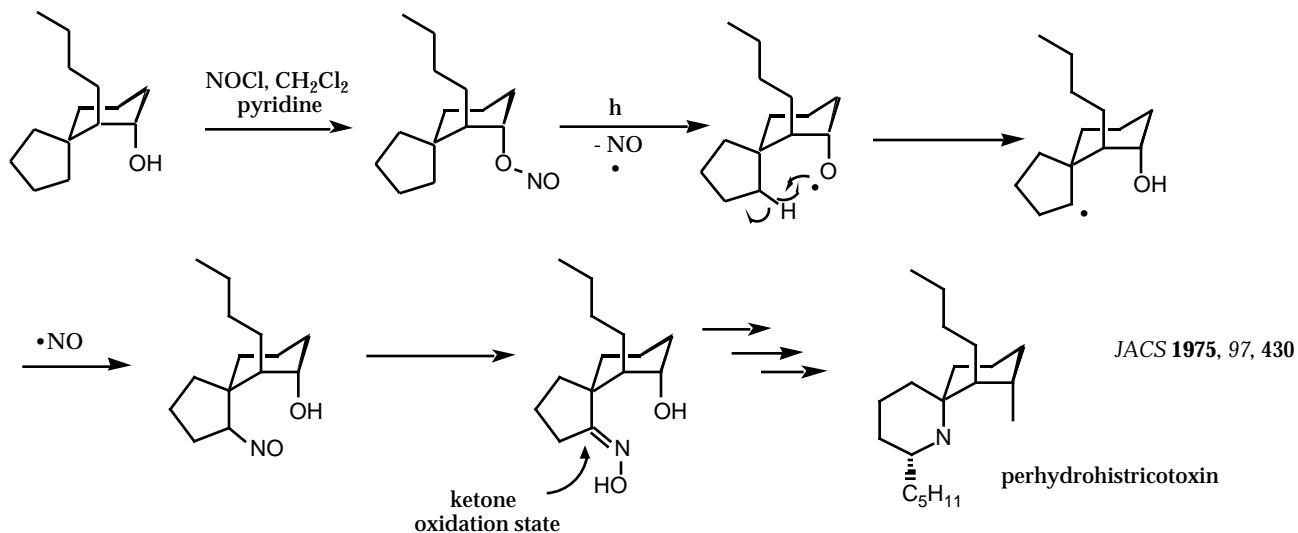
- Asymmetric oxidation of sulfides to chiral sulfoxides.

JACS **1987**, 109, 3370.

Synlett, **1990**, 643.

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

Barton Reaction

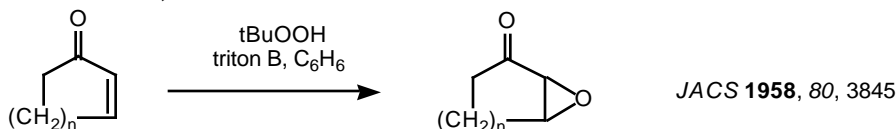


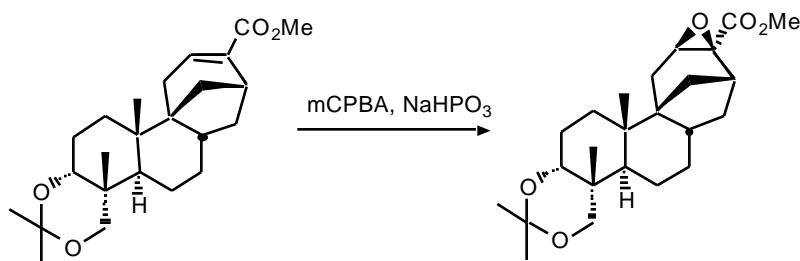
Epoxidations

Peroxides & Peracids

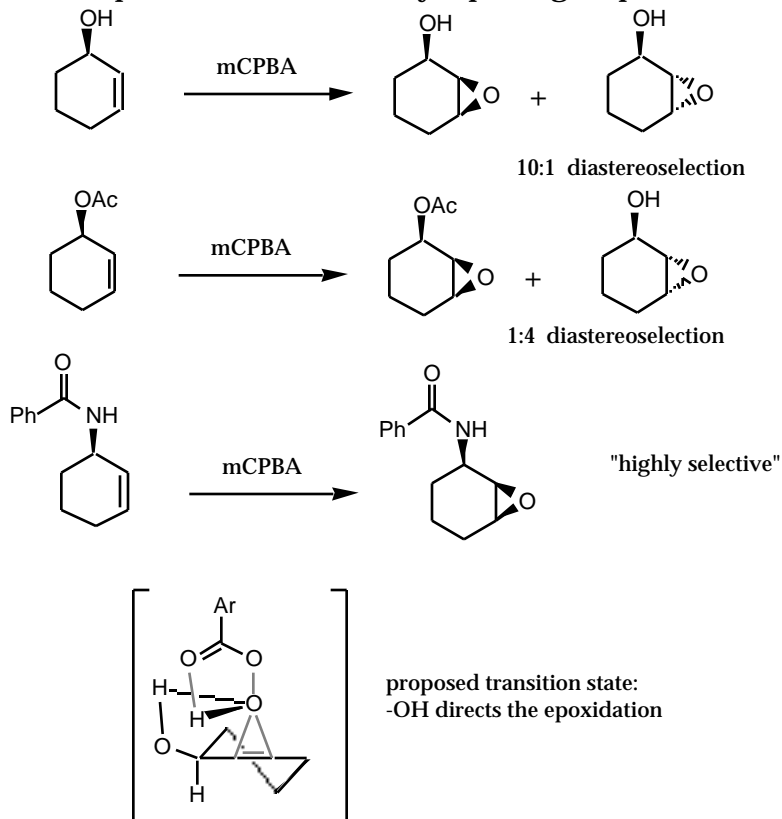
- olefins epoxides *Tetrahedron* **1976**, 32, 2855

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



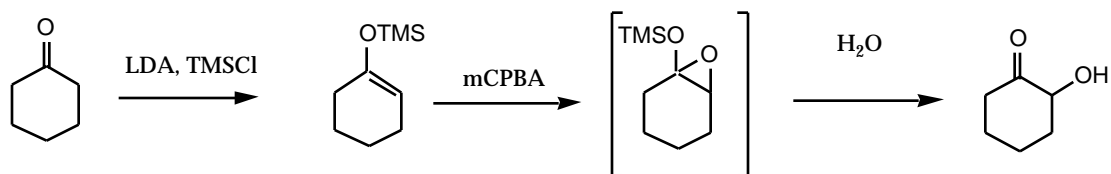


Henbest Epoxidation- epoxidation directed by a polar group



- 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

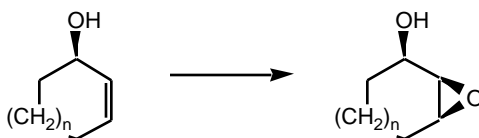
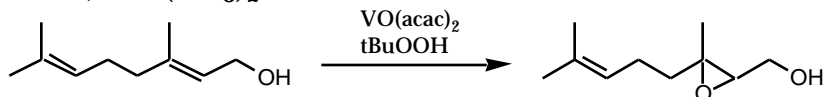
Synthesis, **1986**, 89. *Org. React.* **1996**, 48, 1-299.

Aldrichimica Acta **1979**, 12, 63

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

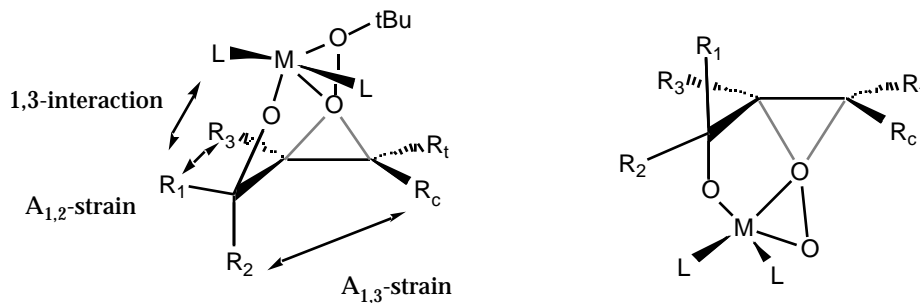
- Regioselective epoxidation of allylic and homo-allylic alcohols
- will not epoxidize isolated double bonds
- epoxidation occurs stereoselectively w/ respect to the alcohol.

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



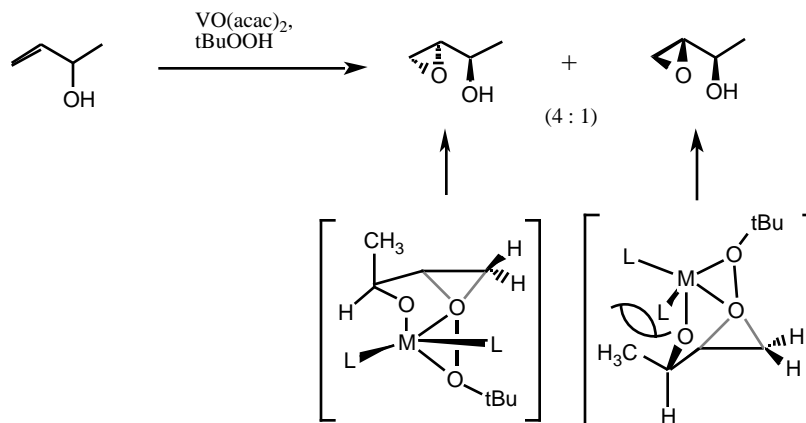
ring size	VO(acac) ₂	MoO ₂ (acac) ₂	mCPBA
5	>99%	--	84
6	>99	98	95
7	>99	95	61
8	97	42	<1
9	91	3	<1

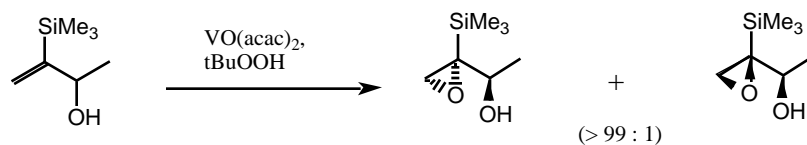
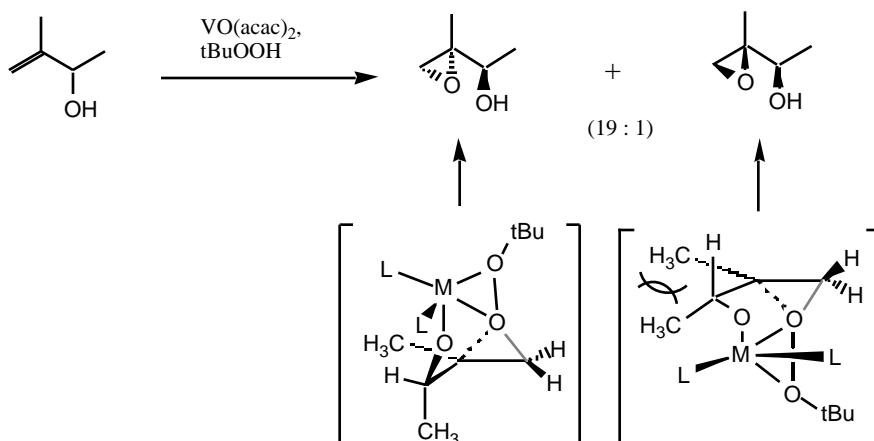
Acyclic Systems:



Major influences:

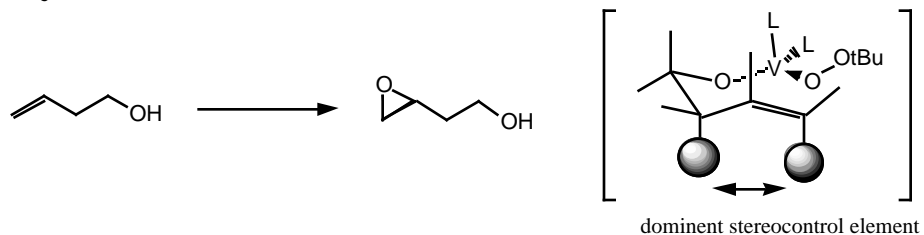
- A_{1,2}-Strain between R_g and R₁ (R_g and R₂)
- A_{1,3}-strain between R₂ and R_c (R₁ and R_c)
- 1,3-interactions between L and R₁ (L and R₂)



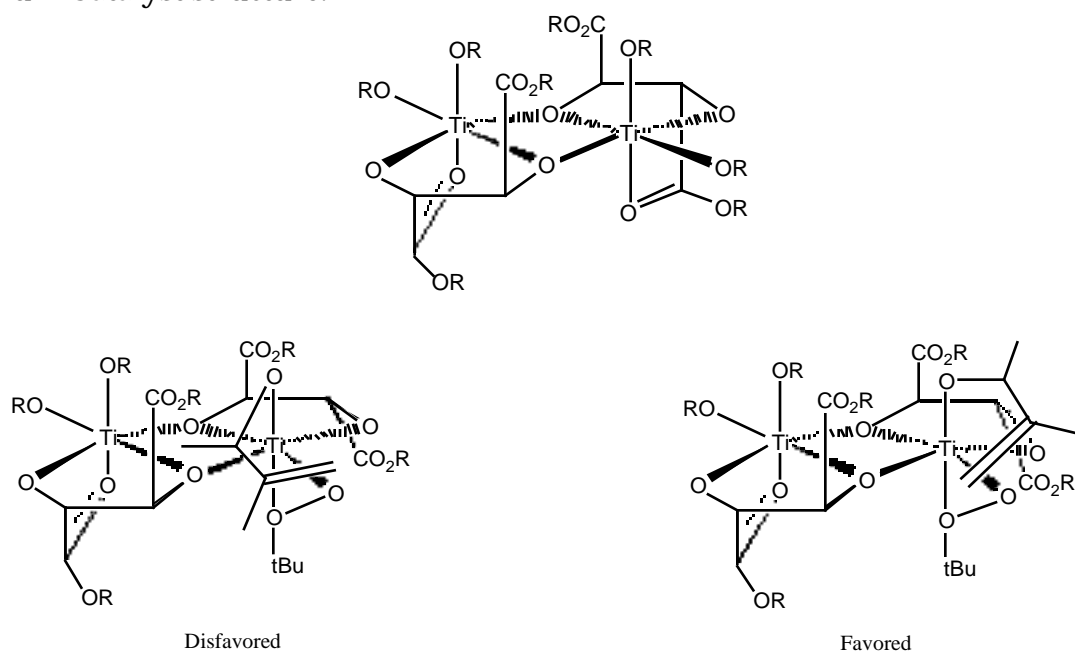


- Careful conformational analysis of acyclic systems is needed.

Homoallylic Systems



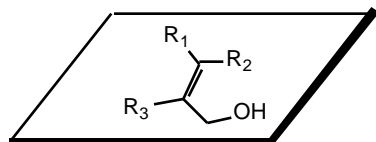
Titanium Catalyst structure:



Asymmetric Epoxidation

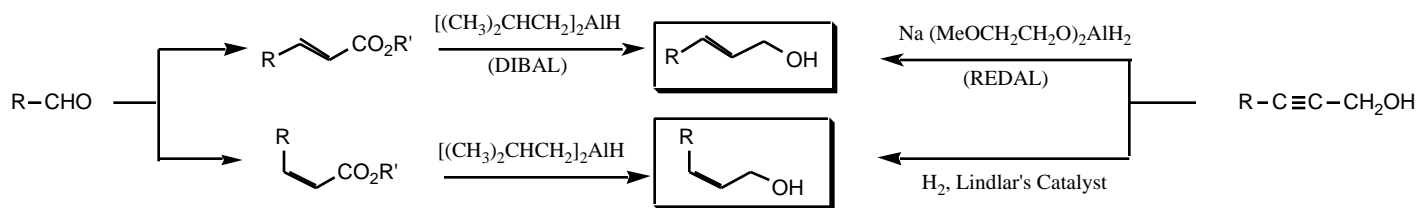
 tBuOOH, Ti(OiPr)₄, (+) or (-) Diethyl Tartrate, 3Å molecular sieves

Empirical Rule

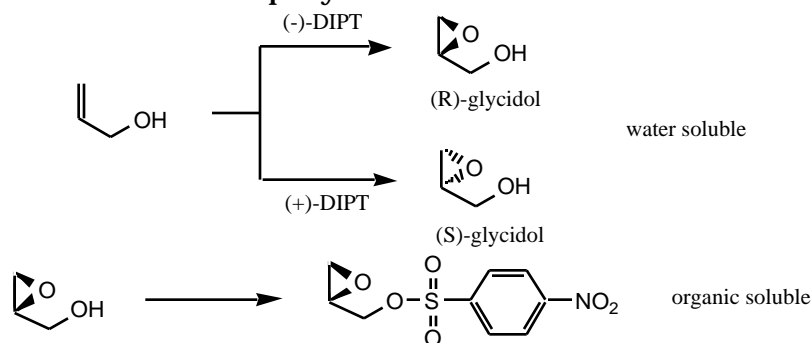

 (+)-DET epoxidation from the bottom
 (-)-DET epoxidation from the top

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

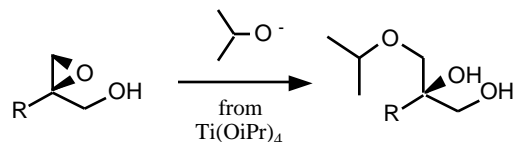
Preparation of Allylic Alcohols:



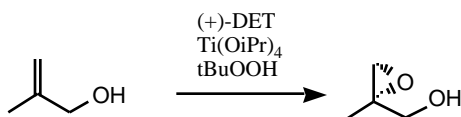
"In situ" derivatization of water soluble epoxy-alcohol



Alkoxide opening of epoxy-alcohol product

 reduced by use of Ti(OtBu)₄ and catalytic conditions


Stoichiometric vs Catalytic epoxidation:



stoichiometric:

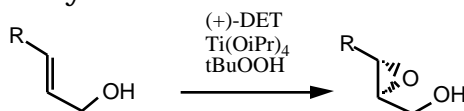
catalytic (6-7 mol %)

in situ deriv. with PNB

85% ee

47% yield >95% ee

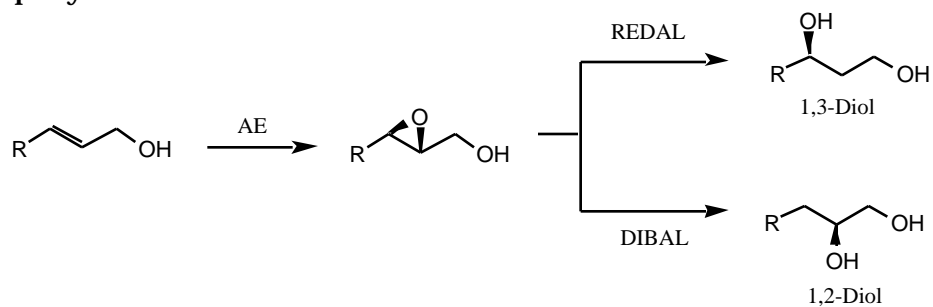
78% yield 92% ee >98% ee after 1 recrystallization



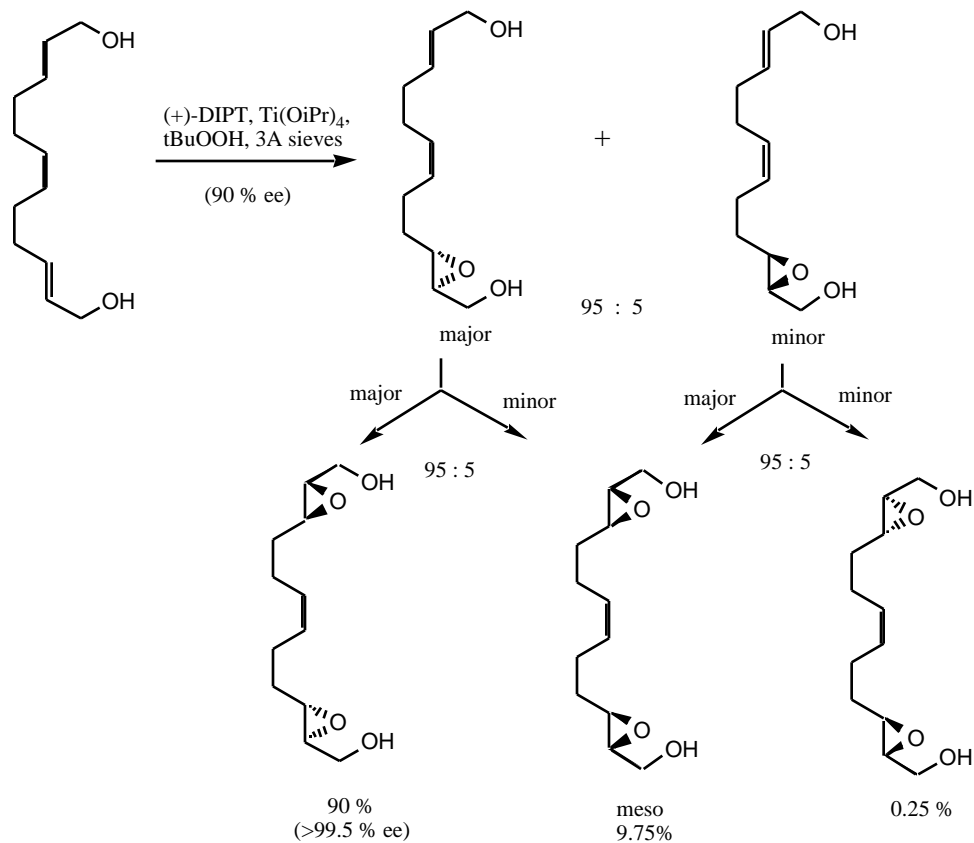
yields: 50 - 100 %

ee: > 95%

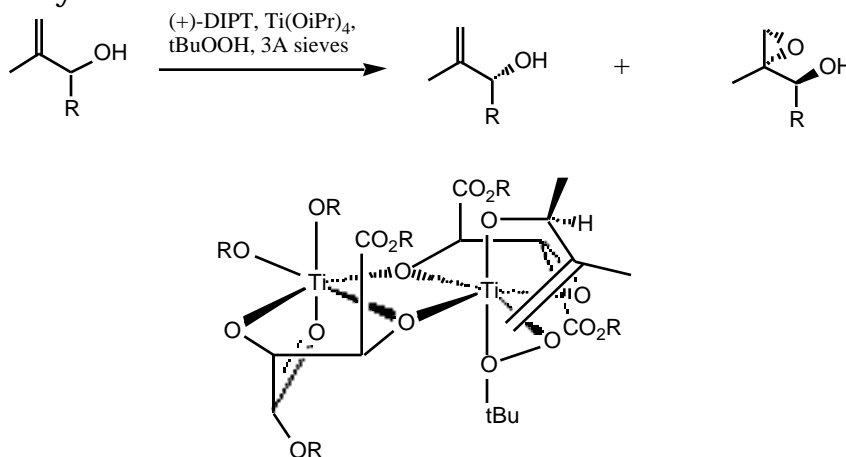
Ring Opening of Epoxy-Alcohols

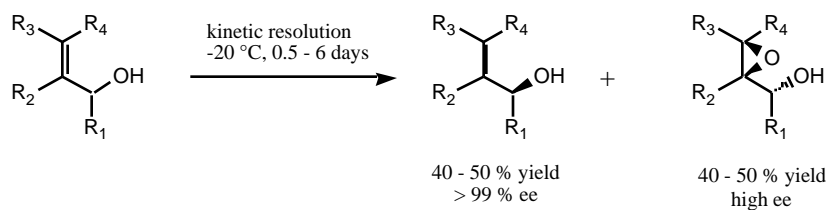


Two dimensional amplification

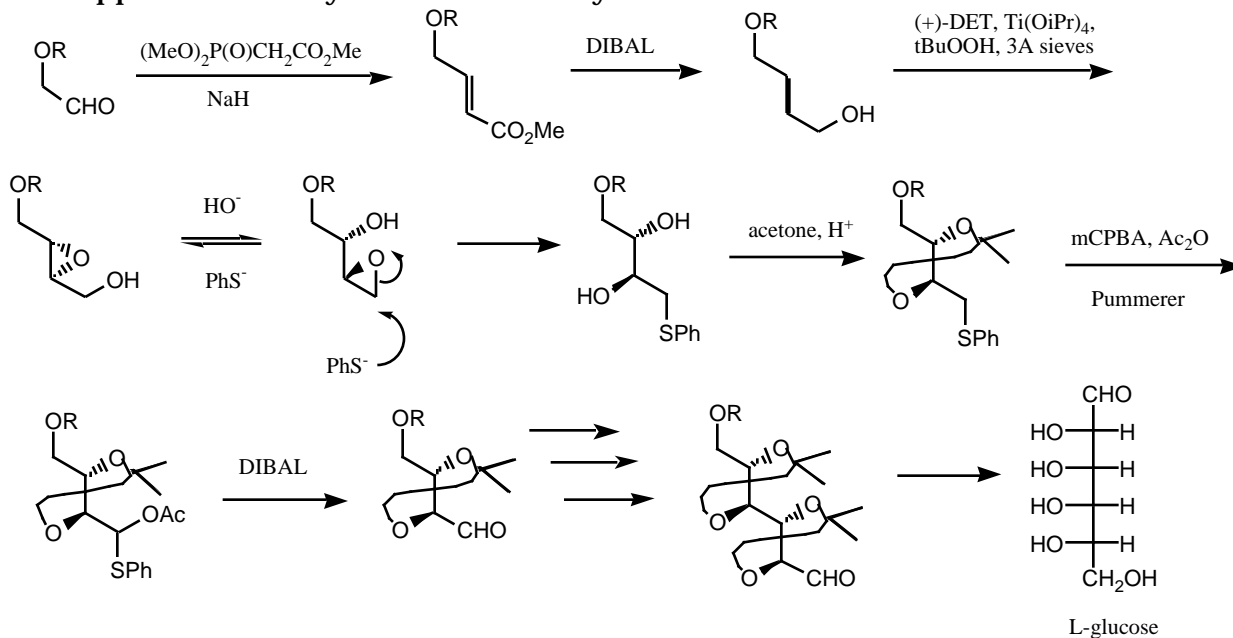


Kinetic Resolution of Allylic Alcohols





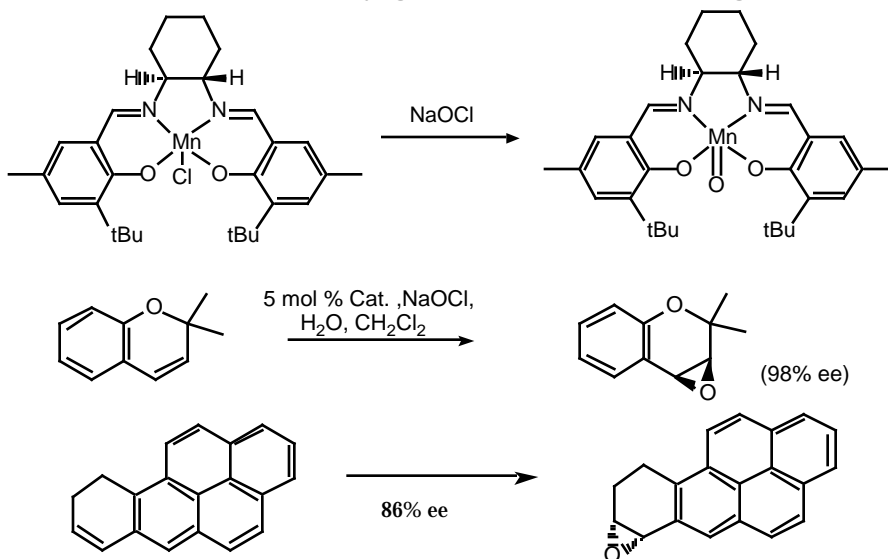
Reiterative Approach to the Synthesis of Carbohydrate



Jacobsen Asymmetric Epoxidation

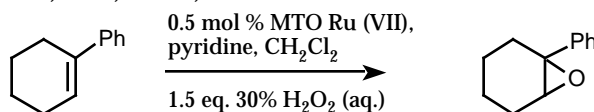
JACS **1990**, *112*, 2801; *JACS* **1991**, *113*, 7063; *JOC* **1991**, *56*, 2296.

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



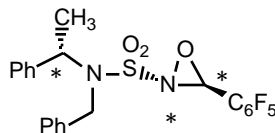
Methyltrioxoruthenium (MTO) Ru(VII)

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



Oxaziridines

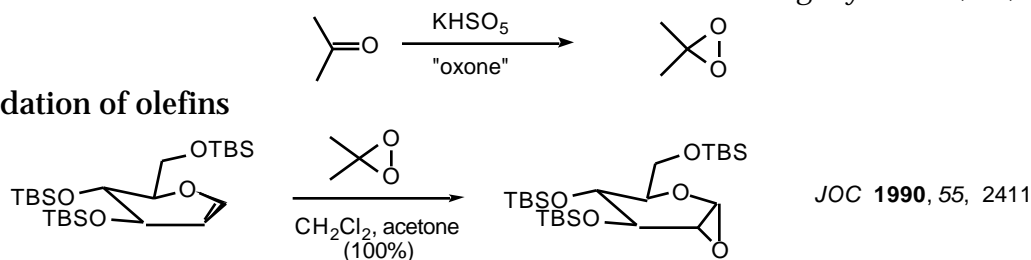
- Asymmetric epoxidation of olefins *Tetrahedron* **1989** 45 5703



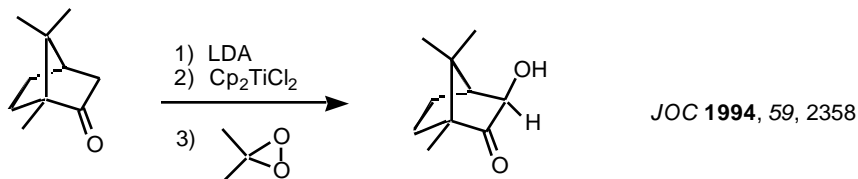
Dioxiranes (Murray's Reagent)

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

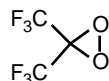
- epoxidation of olefins



- 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