Oxidations

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

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

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

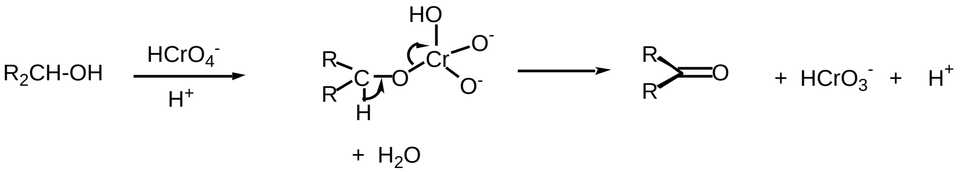
III. Epoxidations

Metal Based Reagents

Chromium Reagents

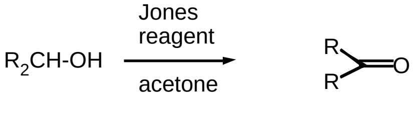
- Cr(VI) based
- exact stucture depends on solvent and pH
- Mechanism: formation of chromate ester intermediate

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

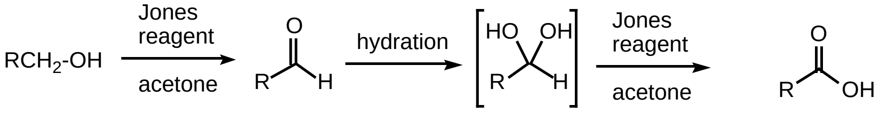


Jones Reagent (H_2CrO_4, $H_2Cr_2O_7$, $K_2Cr_2O_7$)
  J. Chem. Soc. **1946** 39
  Org. Syn. Col. Vol. V, **1973**, 310.

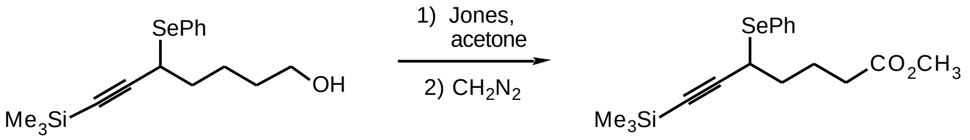
- $CrO_3 + H_2O \rightarrow H_2CrO_4$ (aqueous solution)
  $K_2Cr_2O_7 + K_2SO_4$
- Cr(VI) → Cr(III)
  (black) (green)
- 2°- alcohols are oxidized to ketones



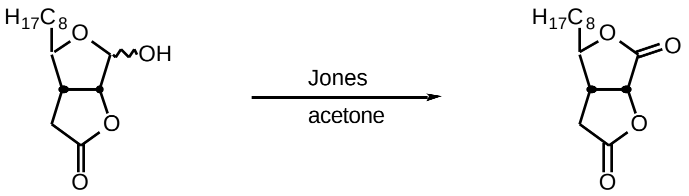
- saturated 1° alcohols are oxidized to carboxylic acids.



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



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

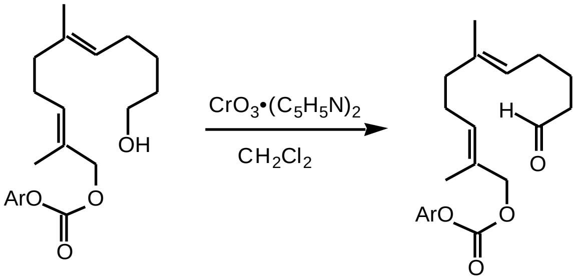


JACS **1975**, *97*, 2870

Collins Oxidation (CrO_3•2pyridine)

TL **1969**, 3363

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



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

CrO_3 catalyzed (1-2 mol % oxidation with $NaIO_6$ (2.5 equiv) as the reozidant in wet aceteonitrile.

oxidized primary alcohols to carboxylic acids.

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

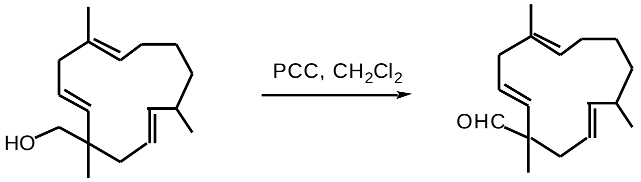
Pyridinium Chlorochromate (PCC, Corey-Suggs Oxidation)

TL **1975** 2647

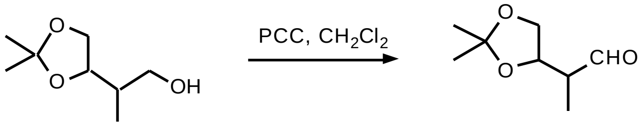
Synthesis **1982**, 245 (review)

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

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

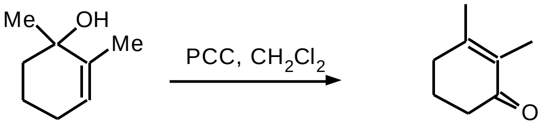


JACS **1977**, *99*, 3864.

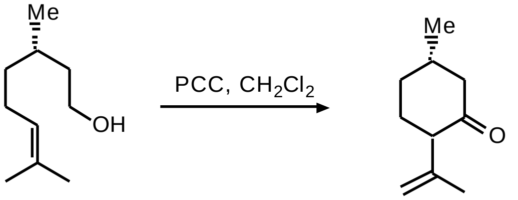


TL, **1975**, 2647

- Oxidative Rearrangements

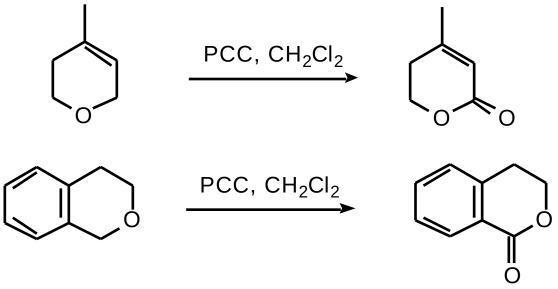


JOC **1977**, *42*, 682



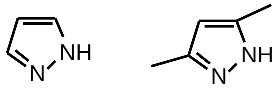
JOC **1976**, *41*, 380

- Oxidation of Active Methylene Groups

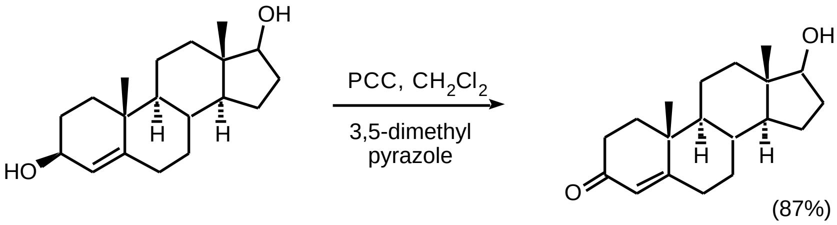


JOC **1984**, *49*, 1647

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

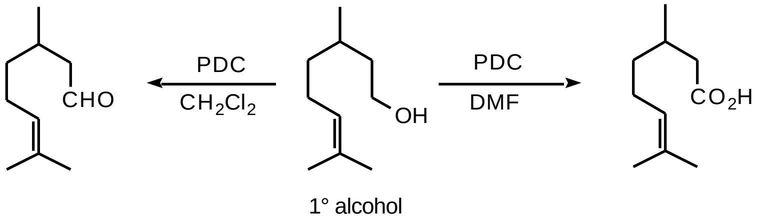


  - selective oxidation of allylic alcohols



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

- $Na_2Cr_2O_7 \cdot 2H_2O + HCl + \text{pyridine} \rightarrow (C_5H_5N)_2CrO_7 \downarrow$



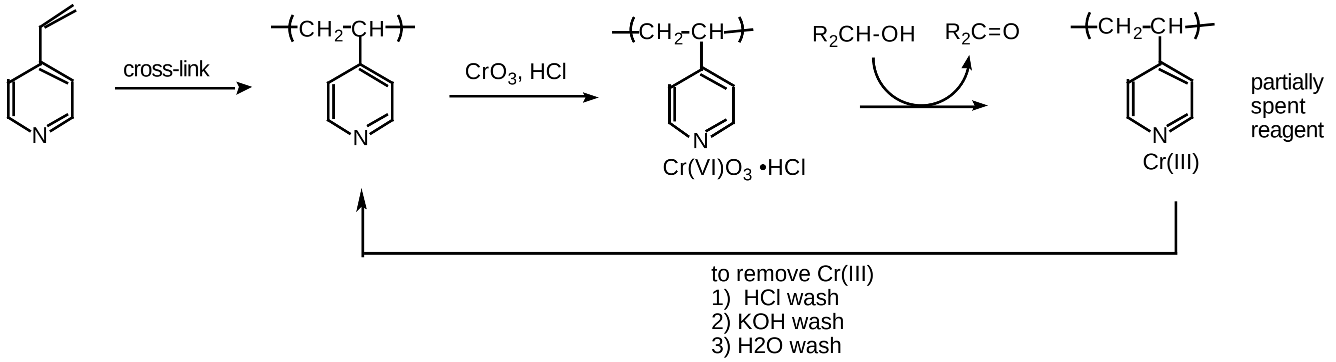
-allylic alcohols are oxidized to α,β-unsaturated aldehydes

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

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

- improved yields due to simplified work-up.

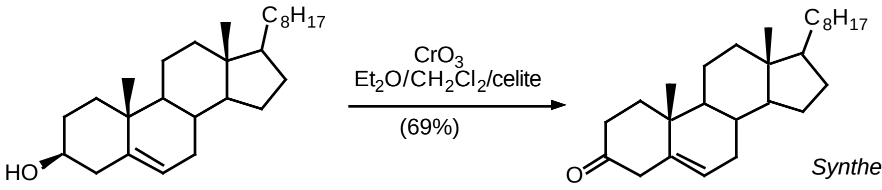
PCC on polyvinylpyridine : *JOC*, **1978**, *43*, 2618.



$CrO_3/Et_2O/CH_2Cl_2$/Celite

Synthesis **1979**, 815.

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



Synthesis **1979**, 815

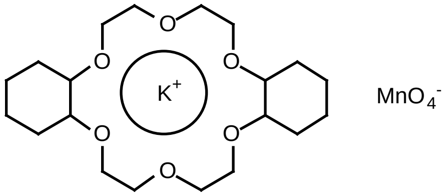
H_2CrO_7 on Silica

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

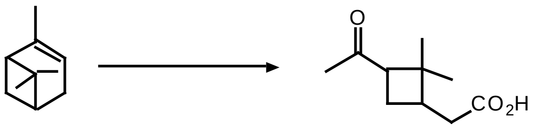
Manganese Reagents

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

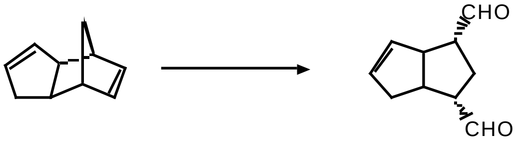
JACS **1972** *94*, 4024.



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



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



Synthesis **1984**, 43
CL **1979,** 443

Sodium Permanganate

TL **1981**, 1655

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

Barium Permanganate ($BaMnO_4$)

TL **1978**, 839.

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

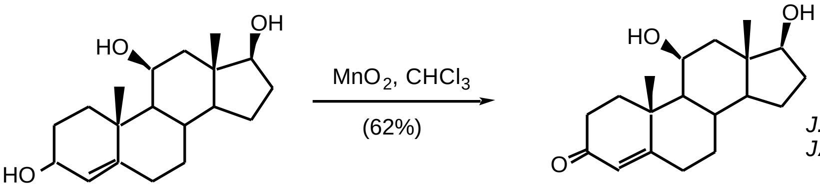
Barium Manganate

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

Manganese Dioxide

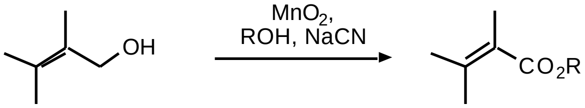
Review: *Synthesis* **1976**, 65, 133

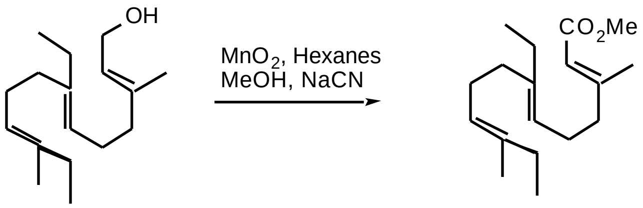
- Selective oxidation of α,β-unsatutrated (allylic, benzylic, acetylenic) alcohols.
- Activity of MnO_2 depends on method of preparation and choice of solvent
- cis & trans allylic alcohols are oxidized at the same rate without isomerization of the double bond.



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

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

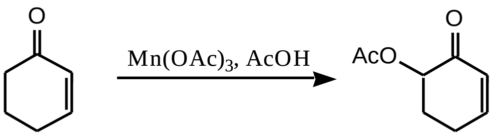




*JACS***1968**, *90*, 5616. 5618

Manganese (III) Acetate α-hydroxylation of enones

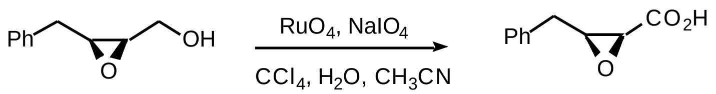
Synthesis **1990**, 1119 *TL* **1984** *25*, 5839



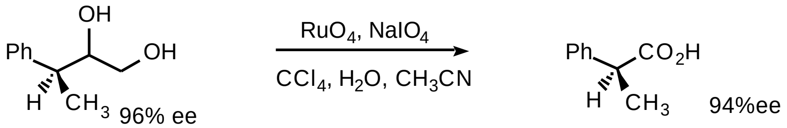
Ruthenium Reagents

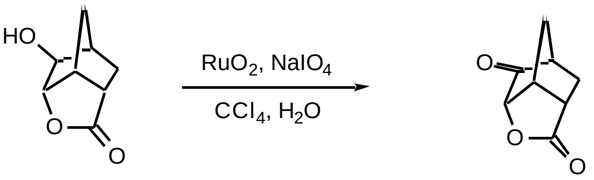
Ruthenium Tetroxide

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



JOC **1981**, *46*, 3936





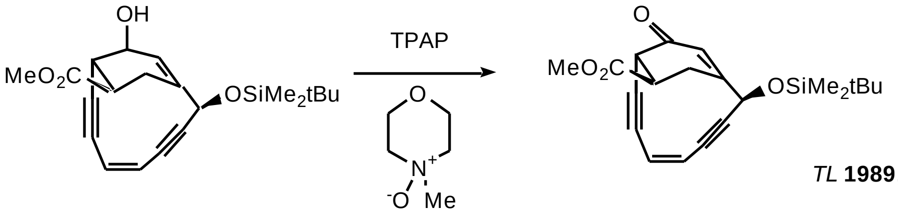
TL **1970**, 4003

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

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

Synthesis **1994**, 639

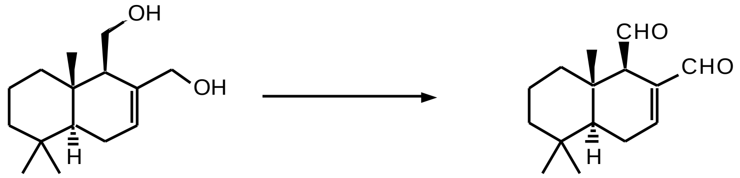
- mild oxidation of alcohols to ketones and aldehydes <u>without</u> over oxidation



TL **1989**, *30*, 433

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

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



JCS P1 **1984**, 681.

$Ba[Ru(OH)_2O_3]$

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

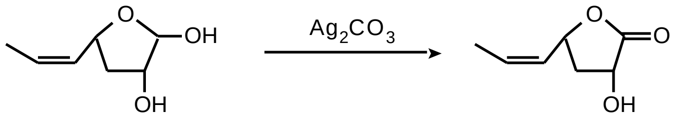
$(Ph_3P)_3RuCl_2$ + Me_3SiO-$OSiMe_3$

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

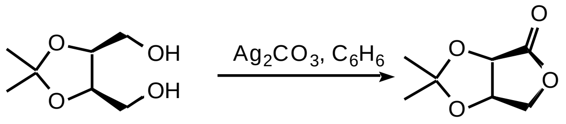
Silver Reagents

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

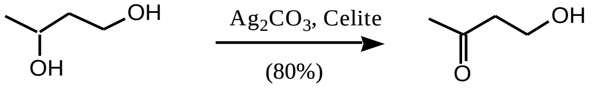
- oxidation of only the most reactive hydroxyl



JACS **1981**, *103*, 1864.
mechanism: *TL* **1972**, 4445.



- Oxidation of 2° alcohol over a 1° alcohol

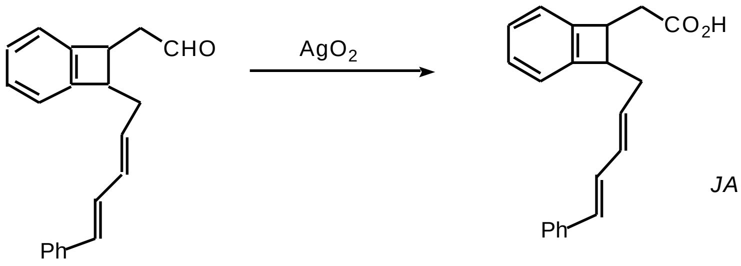


JCS,CC **1969**, 1102

Silver Oxide (AgO_2)

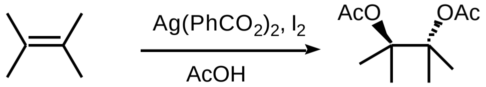
- mild oxidation of aldehyde to carboxylic acids

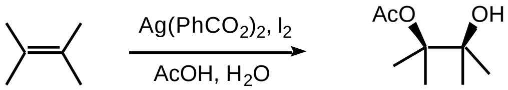
$$\text{RCHO} \xrightarrow{AgO_2,\ NaOH} \text{RCO}_2\text{H}$$



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

Prevost Reaction $Ag(PhCO_2)_2$, I_2





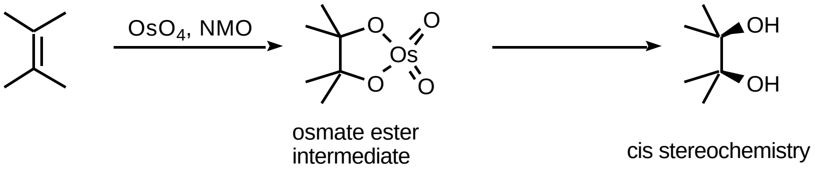
Other Metal Based Oxidations

Osmium Tetroxide OsO_4

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

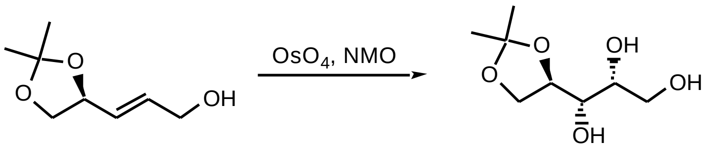
-cis hydroxylation of olefins

old mechanism:



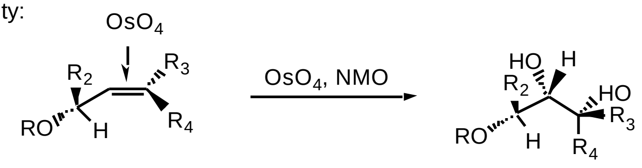
- use of R_3N-O as a reoxidant

TL **1976**, 1973.

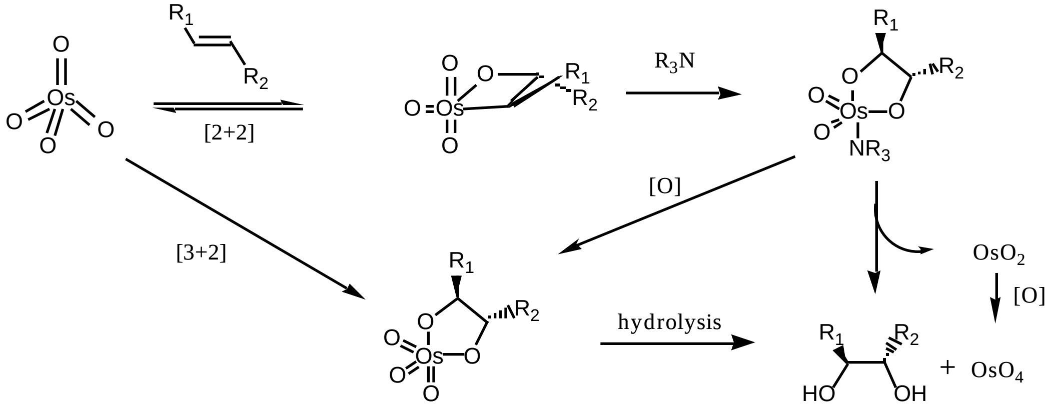


TL **1983**, *24*, 2943, 3947

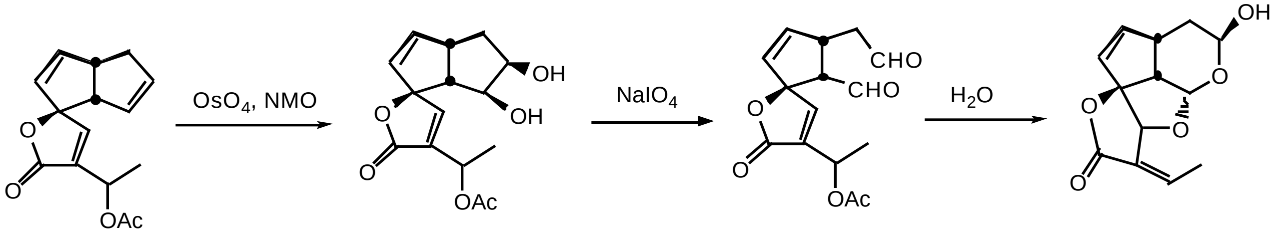
Stereoselectivity:



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



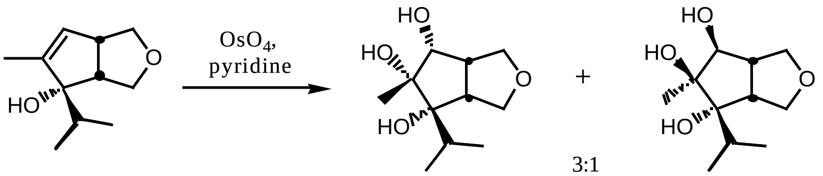
- Oxidative cleavage of olefins to carboxylic acids.
  JOC **1956**, *21*, 478.
- Oxidative cleavage of olefins to ketones & aldehydes.

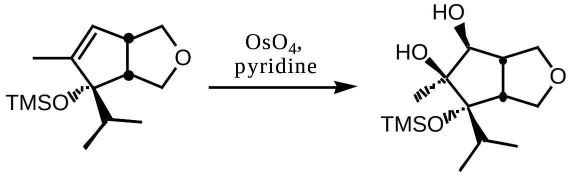


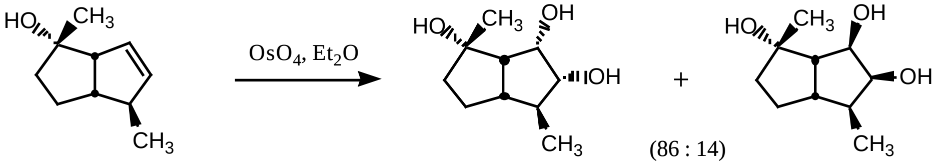
JACS **1984**, *105*, 6755.

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

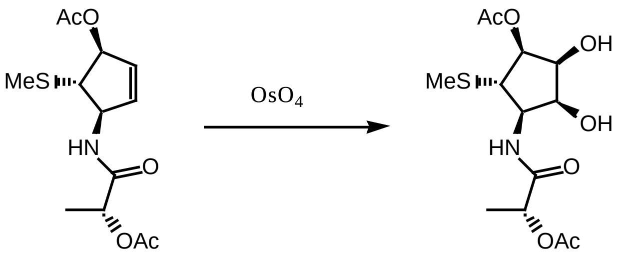
-by hydroxyl groups



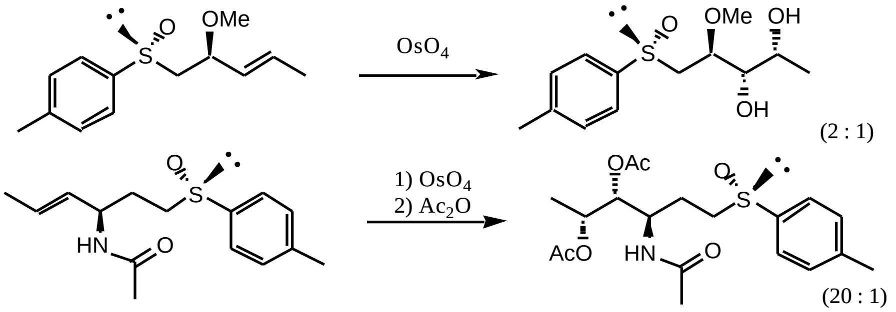




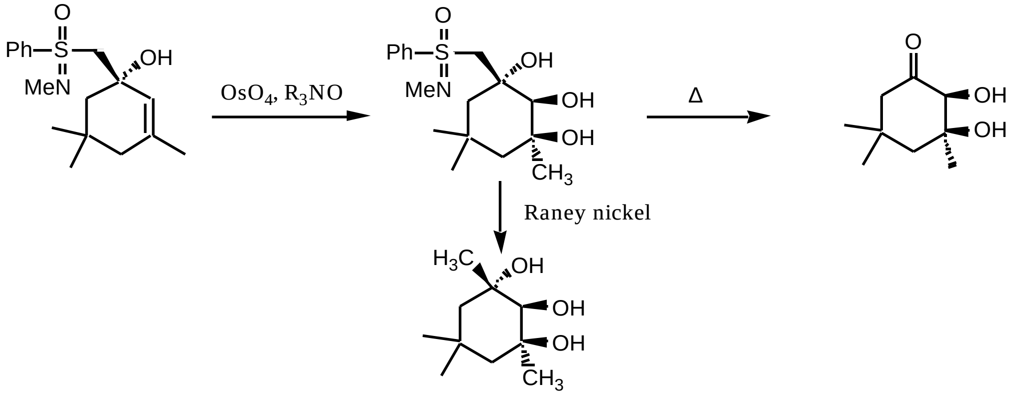
- by amides



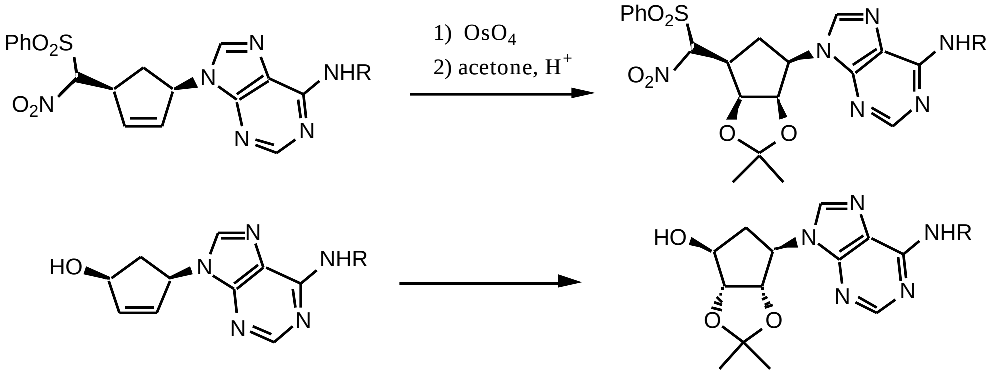
- by sulfoxides



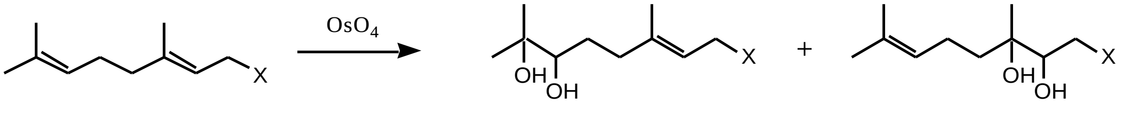
- by sulfoximines



- By nitro groups

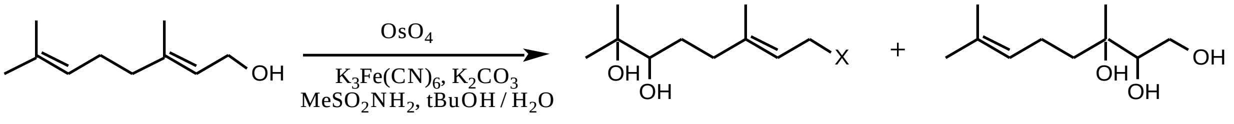


- OsO$_4$ bis-hydroxylation favors electon rich C=C.



X= OH	80 : 20	(directing effect ?)
= OMe	98 : 2	
= OAc	99 : 1	
= NHSO$_2$R	60 : 40	(directing effect ?)

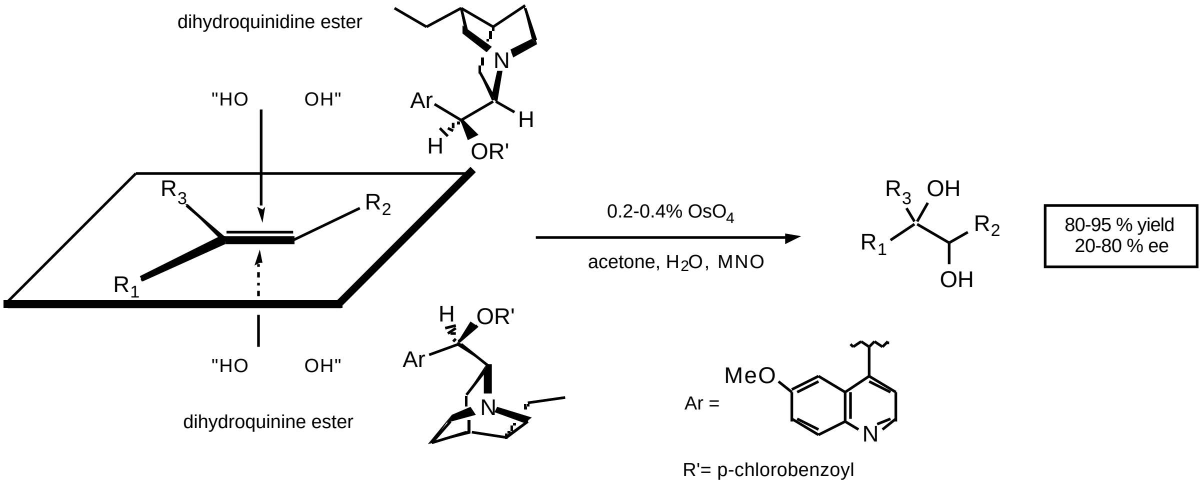
- Ligand effect:



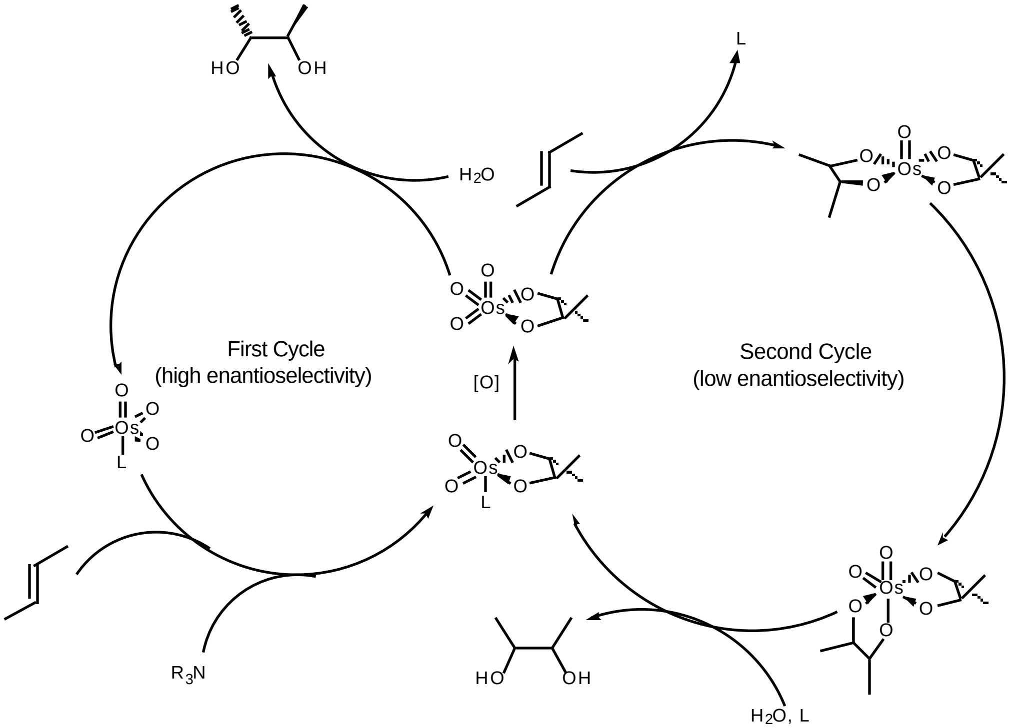
OsO$_4$ (no ligand)	4 : 1
Quinuclidine	9 : 1
DHQD-PHAL	> 49 : 1

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

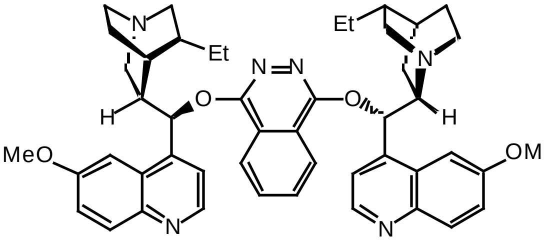
- Ligand pair are really diastereomers!!



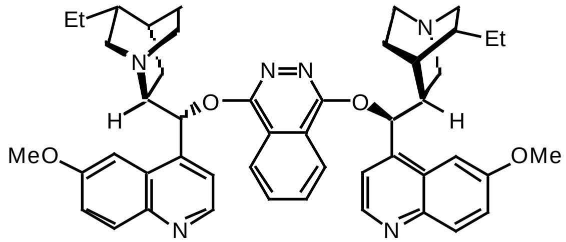
Mechanism of AD:



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



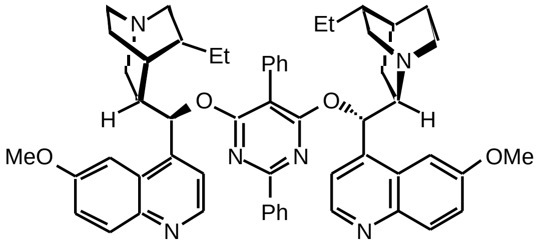
$(DHQD)_2$-PHAL



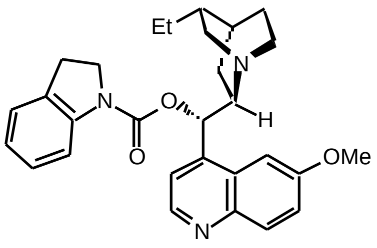
$(DHQ)_2$-PHAL

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

- Other second generation ligands

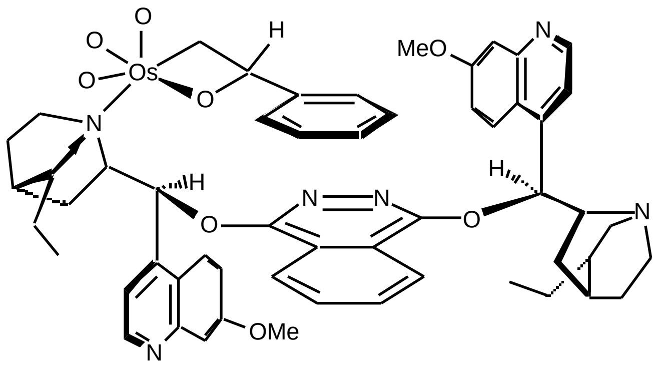


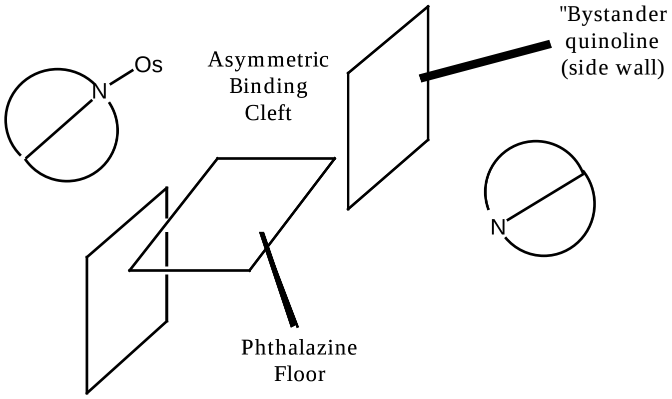
PYR



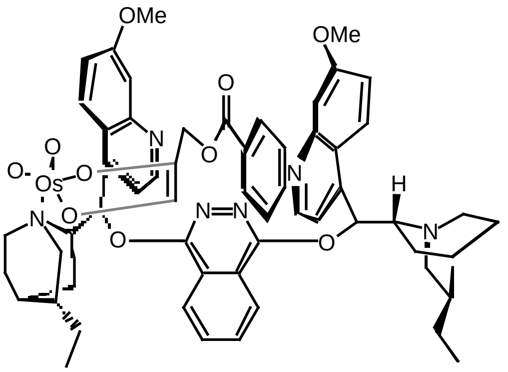
IND

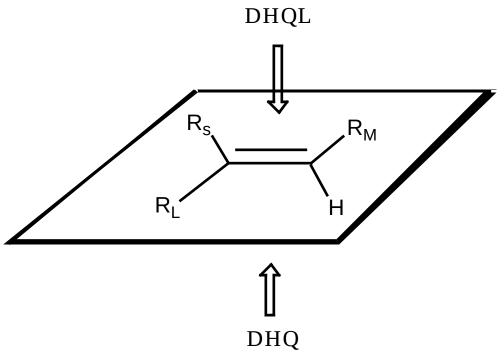
Proposed catalyst structure:



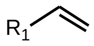
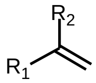
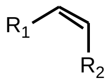
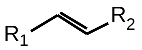
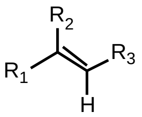
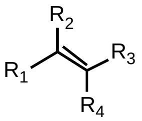


Corey Model: *JACS* **1996**, *118*, 319
Enzyme like binding pocket;
[3+2] addition of OsO_4 to olefin.





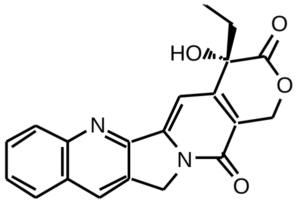
R_L large and flat,
i.e Aromatics work particularly well

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

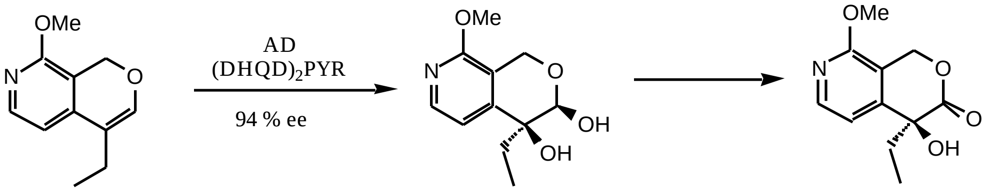
"AD-mixes" commercially available pre-mix solutions of Os, ligand and reoxidant

AD-mix α (DHQ)$_2$PHAL, $K_3Fe(CN)_6$, K_2CO_3, K_2OsO_4 (0.4 MOL % Os to C=C)

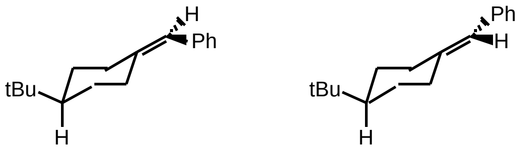
AD-mix β (DHQD)$_2$PHAL, $K_3Fe(CN)_6$, K_2CO_3, K_2OsO_4



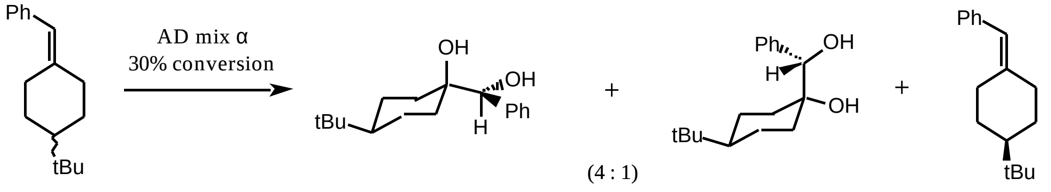
Campthothecin



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



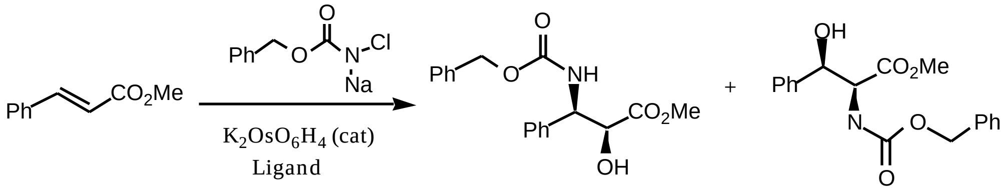
olefins with axial dissymmetry



enriched

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

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



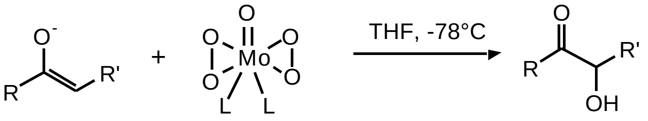
Ligand= PHAL 4:1
AQN 1:4

Molybdenum Reagents

MoOPH [MoO_5•pyridine (HMPA)]

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

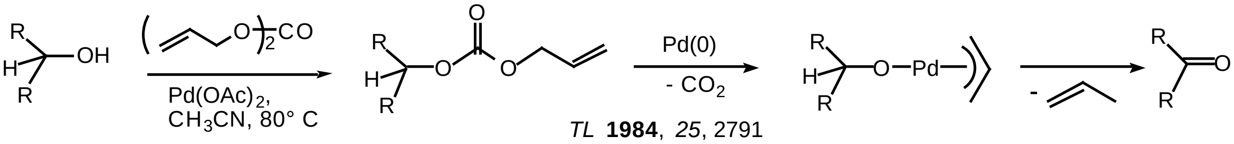
- α-hydroxylation of ketone, ester and lactone enolates.



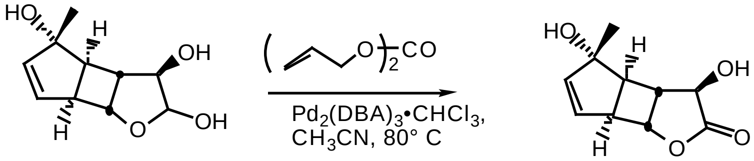
Palladium Reagents

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

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

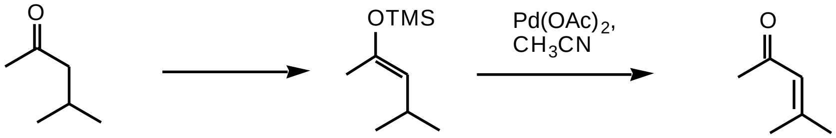


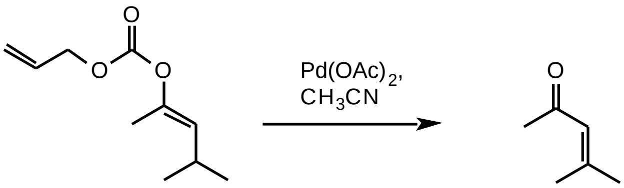
TL **1984**, *25*, 2791
Tetrahedron **1987**, *43*, 3903

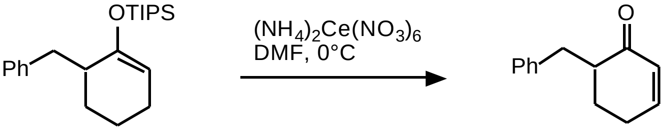


JACS **1989**, *111*, 8039.

Oxidation of silylenol ethers and enol carbonates to enones

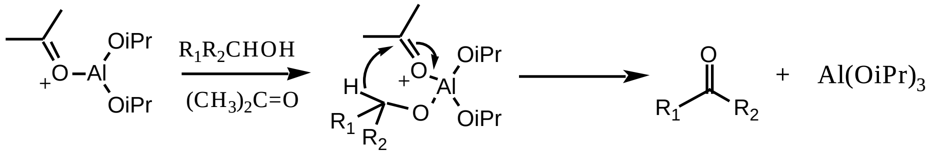






TL **1995**, *36*, 3985

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



Nickel Peroxide

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

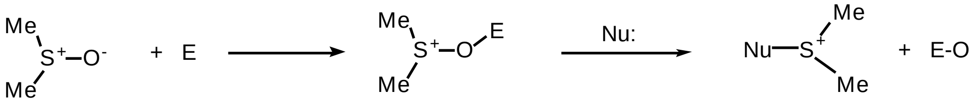
Thallium Nitrate (TNN, $Tl(NO_3)_3 \cdot 3H_2O$

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

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

Non-Metal Based Reagents

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

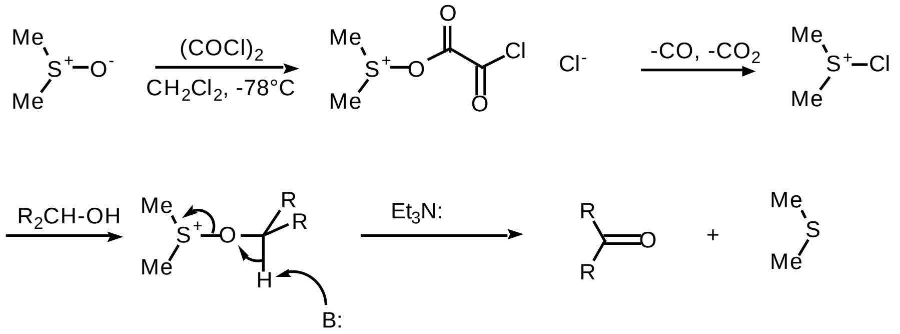


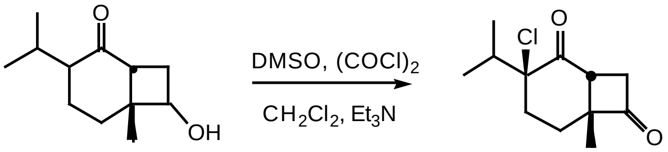
E= $(CF_3CO)_2O$, $SOCl_2$, $(COCl)_2$, Cl_2, $(CH_3CO)_2O$, TsCl, MeCl, SO_3/pyridine, F_3CSO_2H, PO_5, H_3PO_4, Br_2

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

Swern Oxidation

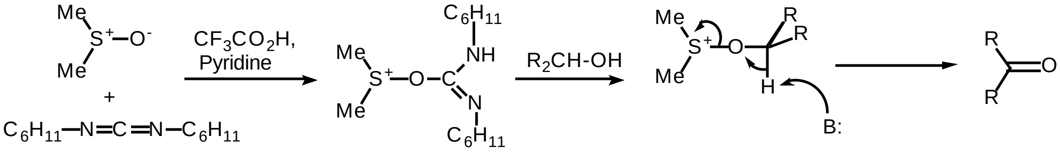
- trifluoroacetic anhydride can be used as the activating agent for DMSO

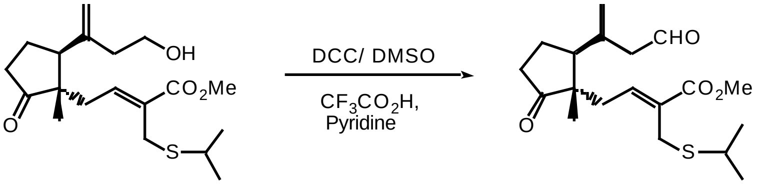




TL **1988**, *29*, 49.

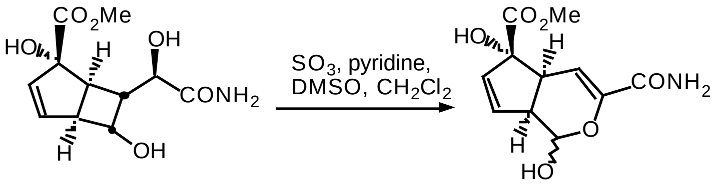
Moffatt Oxidation (DMSO/DCC) *JACS* **1965**, *87*, 5661, 5670.





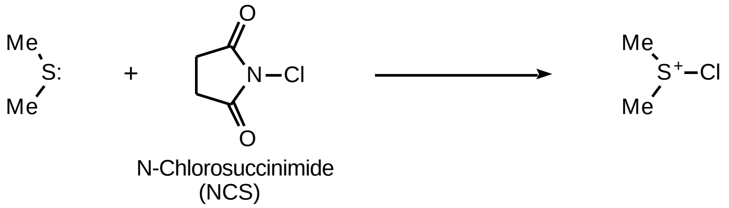
JACS **1978**, *100*, 5565

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



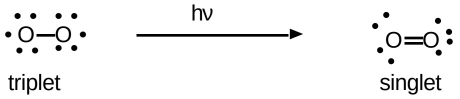
JACS **1989**, *111*, 8039.

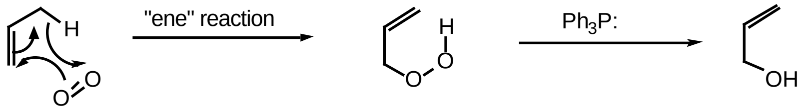
Corey-Kim Oxidation (DMS / NCS) *JACS* **1972**, *94*, 7586.



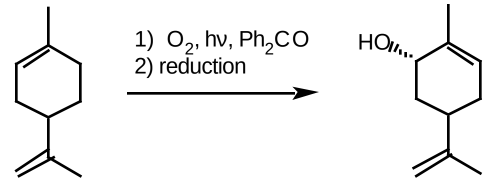
Oxygen & Ozone

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

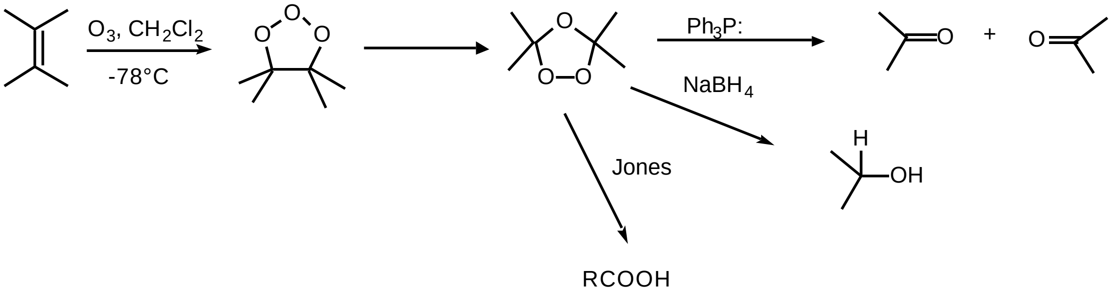




Tetrahedron **1981**, 1825

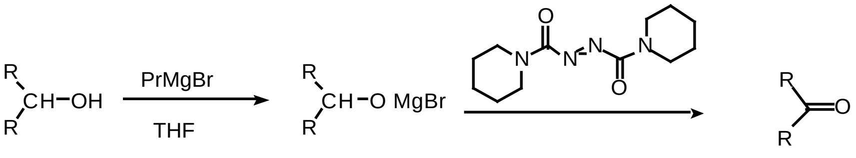


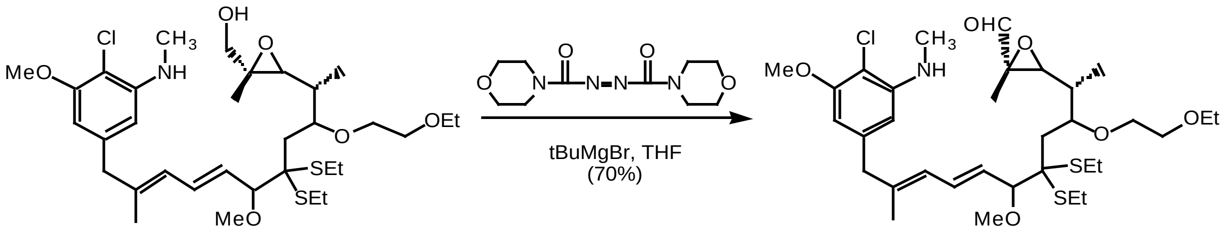
Ozone *Comprehensive Organic Synthesis* **1991**, *7*, 541



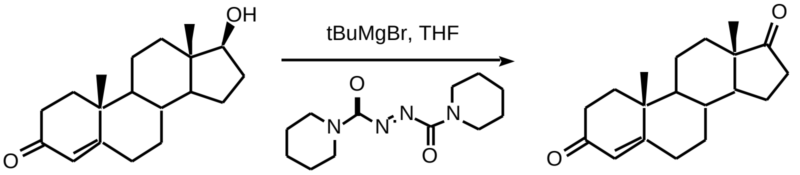
Other Oxidations

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



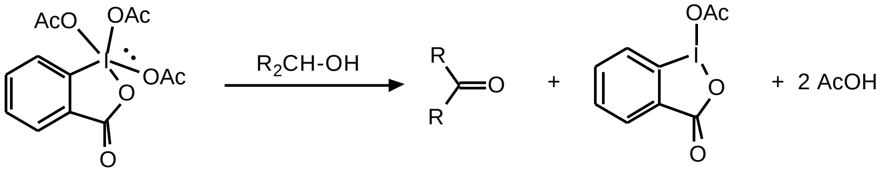


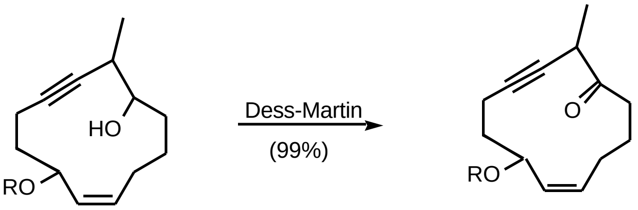
JACS **1979**, *101*, 7104



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

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

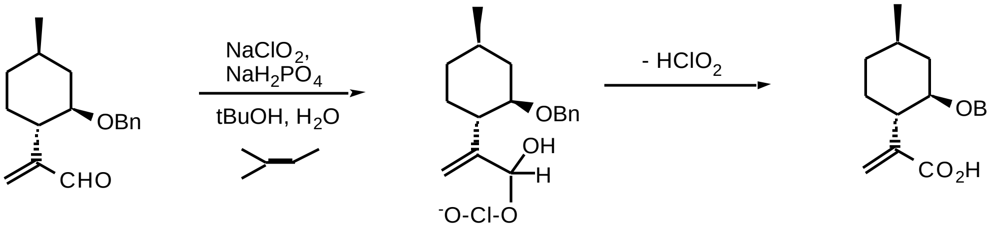




JOC **1991**, *56*, 6264

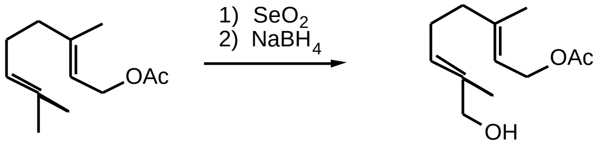
Chlorite Ion

-oxidation of α,β-unsaturated aldehydes to α,β−unsaturated acids.
Tetrahedron **1981**, *37*, 2091

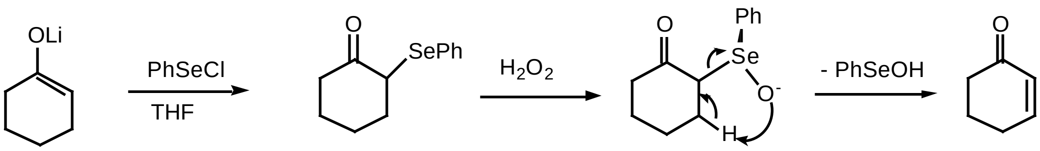


Selenium Dioxide

- Similar to singlet oxygen (allylic oxidation)



Phenyl Selenium Chloride



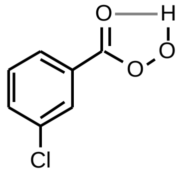
- PhS-SPh will do similar chemistry however a sulfoxide elimination is less facile than a selenoxide elinimation.

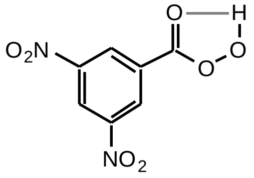
Peroxides & Peracids

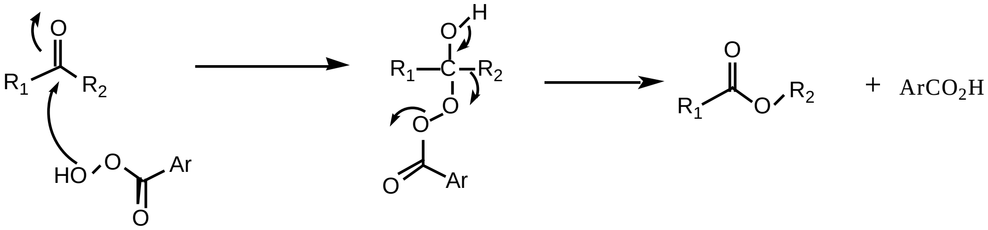
- R_3N: → R_3N-O
- sulfides → sulfoxides → sulfones

-Baeyer-Villiger Oxidation- oxidation of ketones to esters and lactones via oxygen insertion
Organic Reactions **1993**, *43*, 251 *Comprehensive Organic Synthesis* **1991**, vol 7, 671.

m-Chloroperbenzoic Acid, Peracetic Acid, Hydrogen peroxide

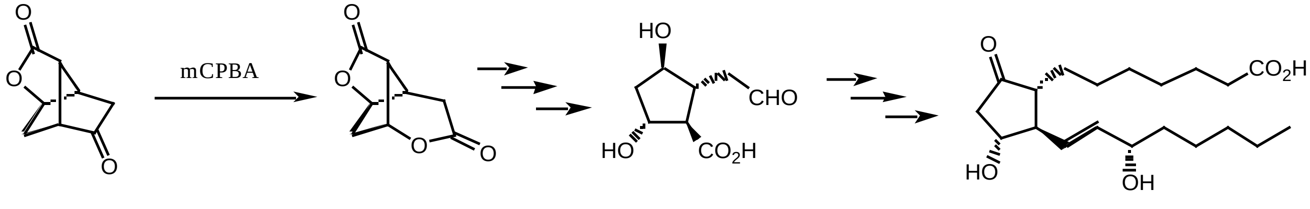




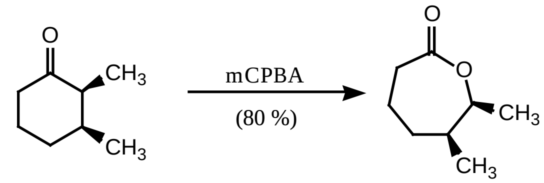


- Concerted R-migration and O-O bond breaking. No loss of stereochemistry
- Migratory aptitude roughly follows the ability of the group to stabilize positive charge:
  3° > 2° > benzyl = phenyl > 1° >> methyl

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



PGE$_1$



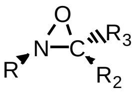
Tetrahedron Lett. **1977**, 2173
Tetrahedron Lett. **1978**, 1385

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

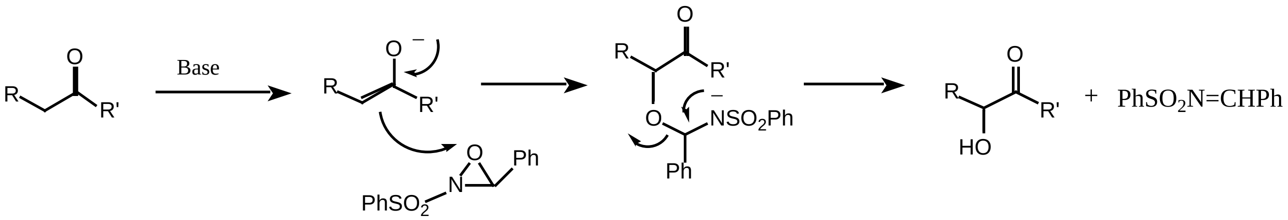
$$\text{RCHO} \xrightarrow[\text{acetone (aq)}]{\text{oxone}} \text{RCOOH}$$

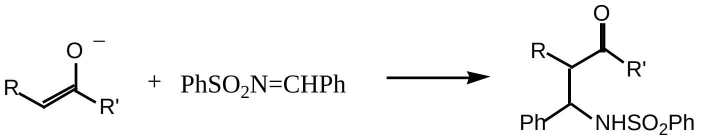
Oxaziridines

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



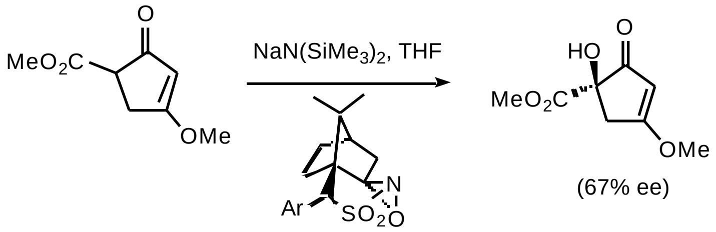
- hydroxylation of enolates





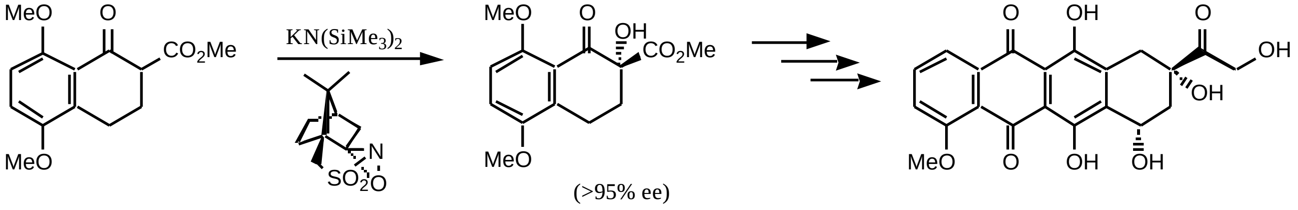
By-product
supresed by using
bulkier oxaziradine
such as camphor
oxaziradine

Asymmetric hydroxylations



(67% ee)

Tetrahedron **1991**, *47*, 173



(>95% ee)

- hydroxylation of organometallics

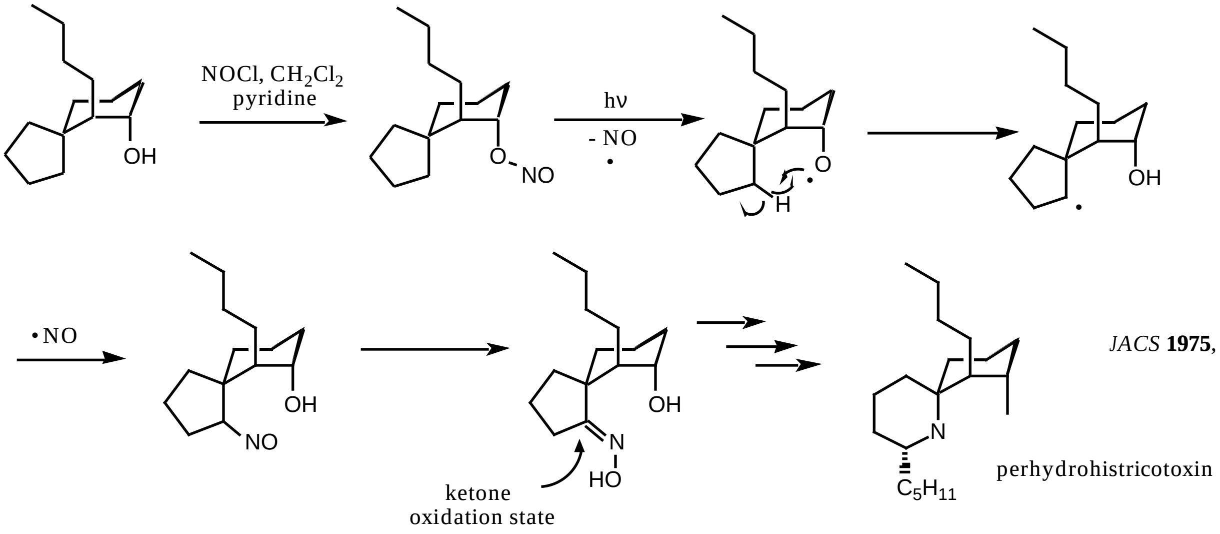
  R-Li or R-Mg → R-OH   *JACS* **1979**, *101*, 1044

- 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

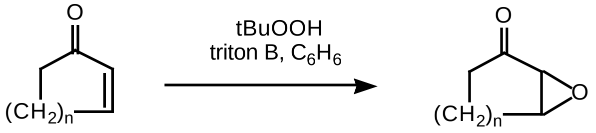


JACS **1975**, *97*, 430

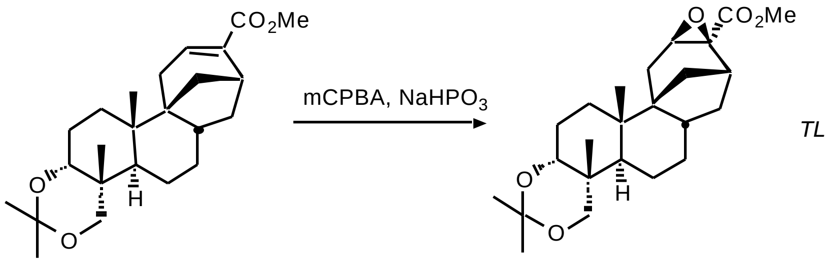
Epoxidations

Peroxides & Peracids

- olefins → epoxides   *Tetrahedron* **1976**, *32*, 2855
- α,β-unsaturated ketones, aldehydes and ester → α,β-epoxy- ketones, aldehydes and esters (under basic conditions).

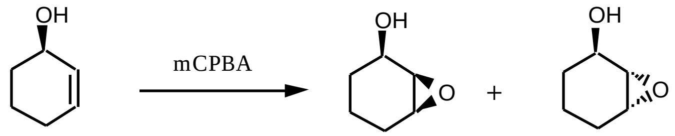


JACS **1958**, *80*, 3845

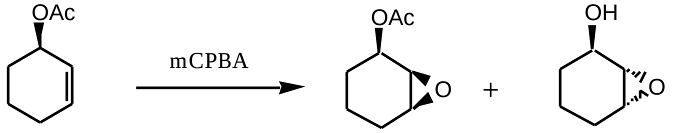


TL **1988**, *23*, 2793

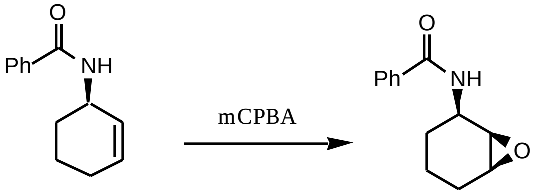
Henbest Epoxidation- epoxidation directed by a polar group



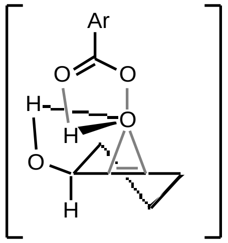
10:1 diastereoselection



1:4 diastereoselection



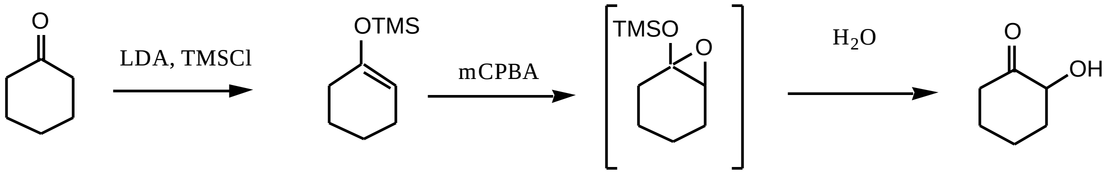
"highly selective"



proposed transition state:
-OH directs the epoxidation

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

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

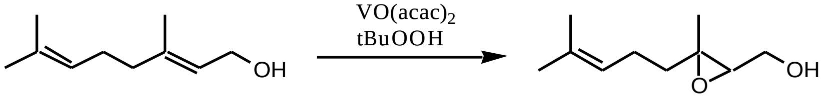


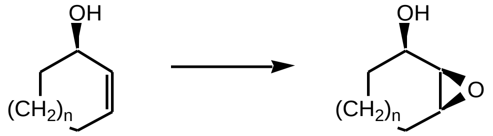
Sharpless Epoxidation tBuOOH w/ VO(acac)$_2$, Mo(CO)$_6$ or Ti(OR)$_4$

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

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

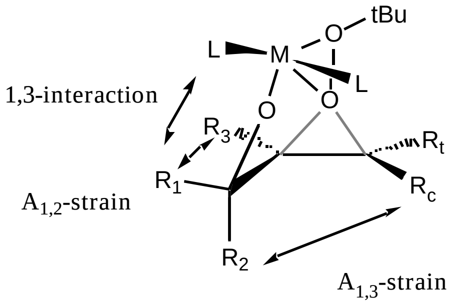
- Catalysts: VO(acac)$_2$; Mo(CO)$_6$; Ti(OiPr)$_4$
- Oxidant: tBuOOH; PhC(CH$_3$)$_2$OOH

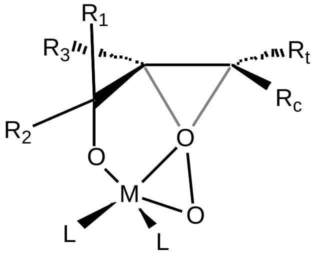




ring size	VO(acac)$_2$	MoO$_2$(acac)$_2$	mCPBA
5	>99%	--	84
6	>99	98	95
7	>99	95	61
8	97	42	<1
9	91	3	<1

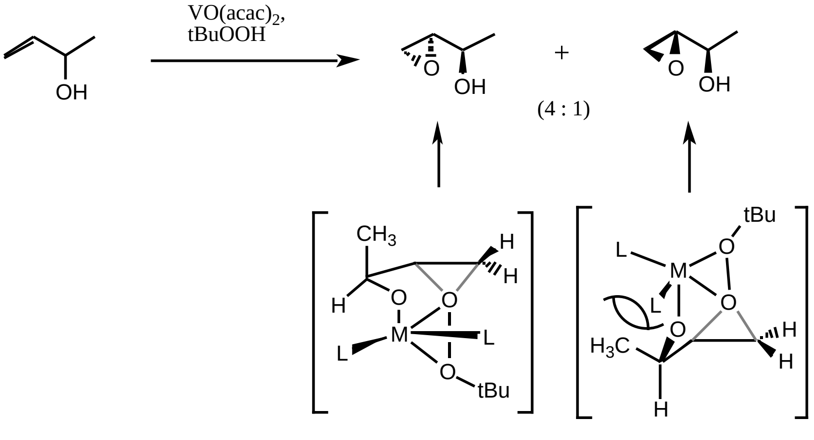
Acyclic Systems:

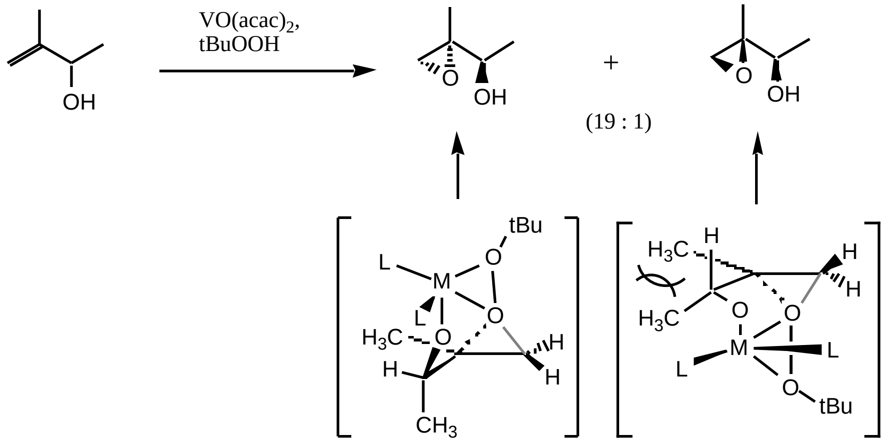


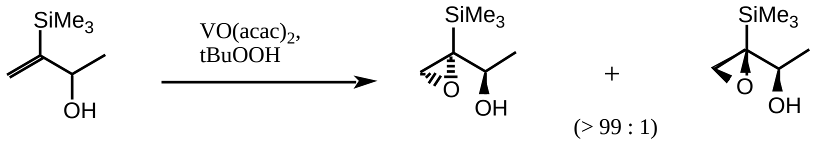


Major influences:

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

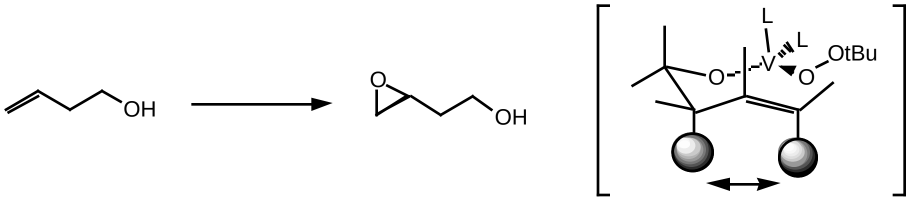






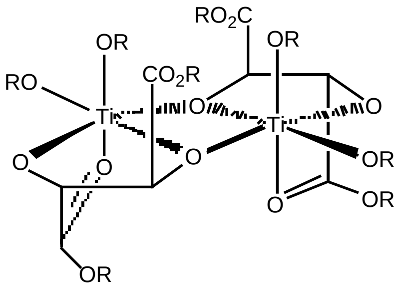
- Careful conformational analysis of acyclic systems is needed.

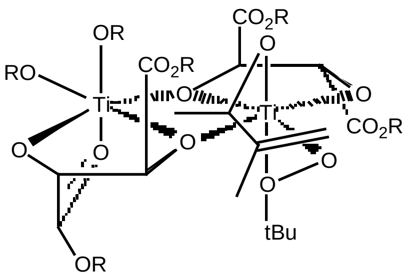
Homoallylic Systems



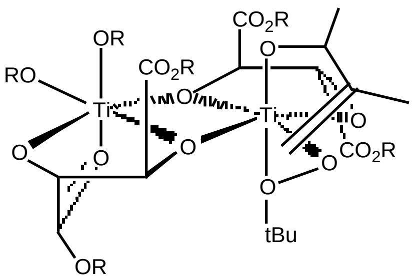
dominent stereocontrol element

Titanium Catalyst structure:





Disfavored

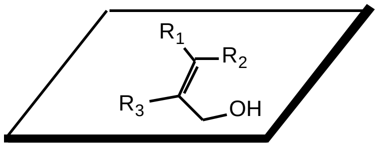


Favored

Asymmetric Epoxidation

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

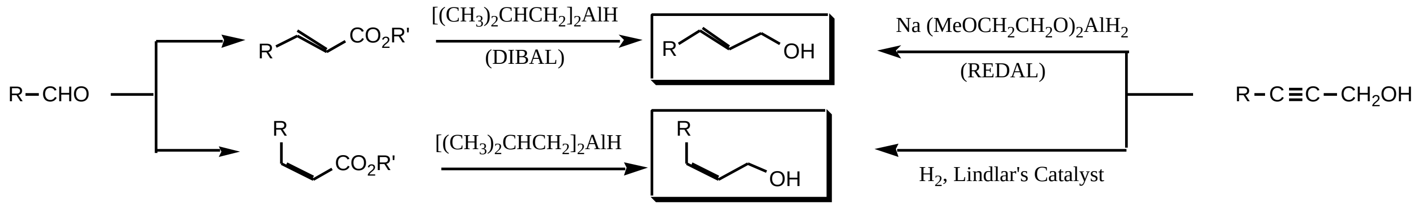
Empirical Rule



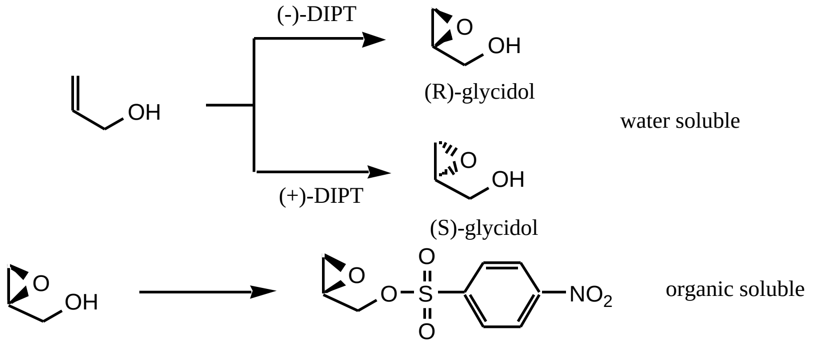
(+)- DET epoxidation from the bottom
(-)- DET epoxidation from the top

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

Preparation of Allylic Alcohols:



"In situ" derivatization of water soluble epoxy-alcohol

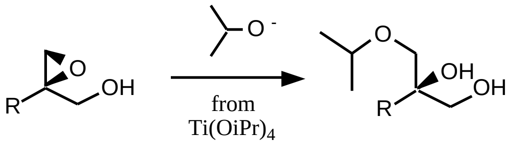


water soluble

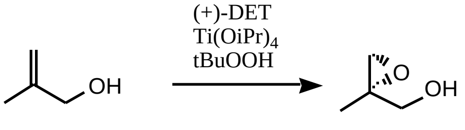
organic soluble

Alkoxide opening of epoxy-alcohol product

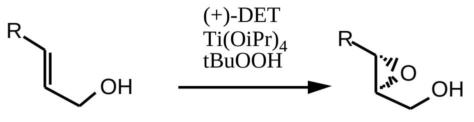
reduced by use of Ti(OtBu)$_4$ and catalytic conditions



Stoicheometric vs Catalytic epoxidation:

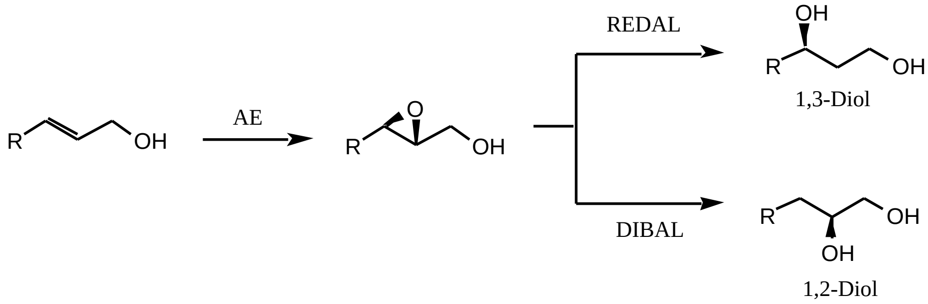


stoicheometric: 85% ee
catalytic (6-7 mol %) 47% yield >95% ee
in situ deriv. with PNB 78% yield 92 % ee >98 %ee after 1 recrystallization

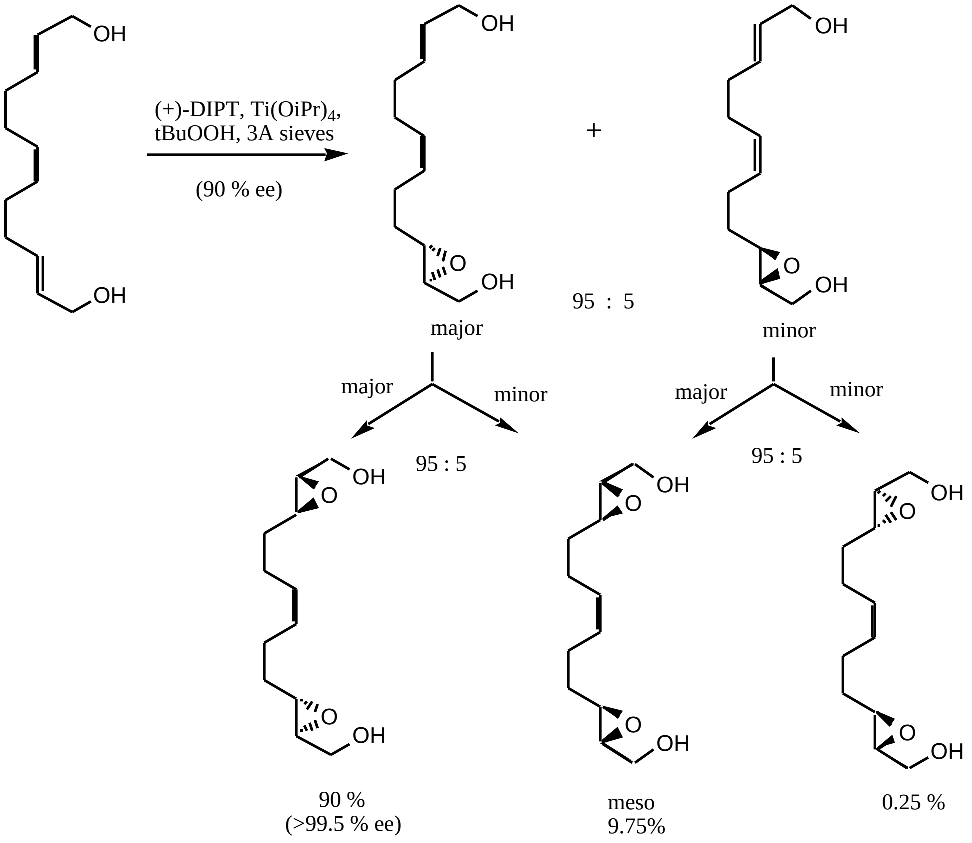


yields: 50 - 100 %
ee: > 95%

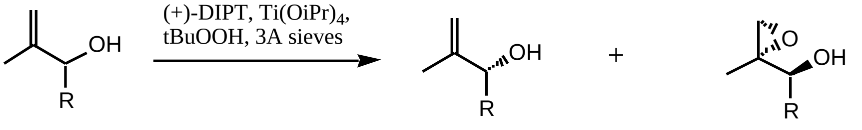
Ring Opening of Epoxy-Alcohols

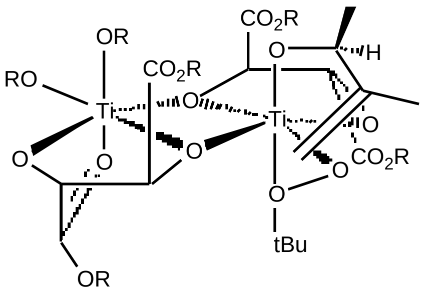


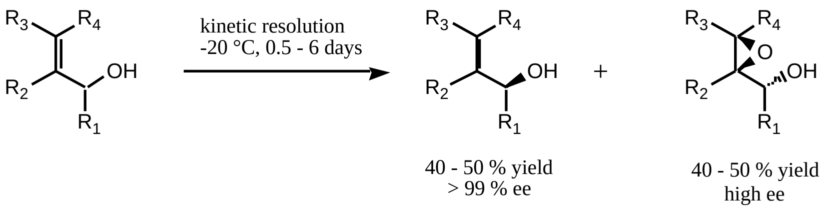
Two dimensional amplification



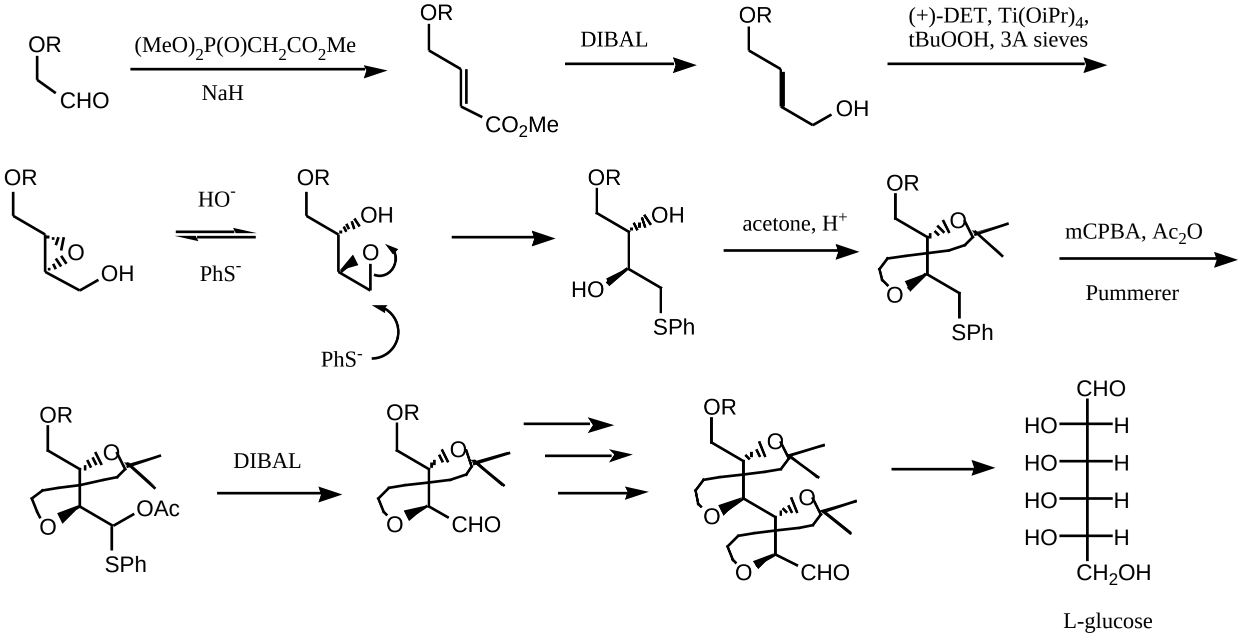
Kinetic Resolution of Allylic Alcohols







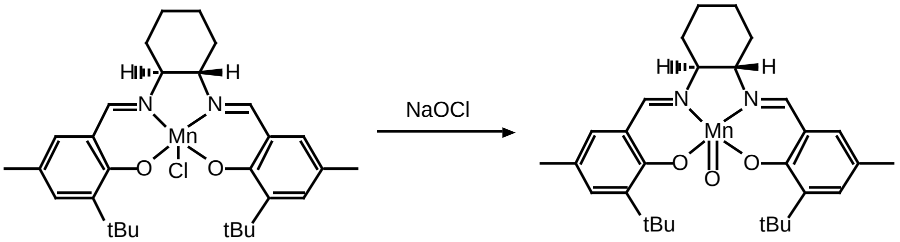
Reiterative Approach to the Synthesis of Carbohydrate

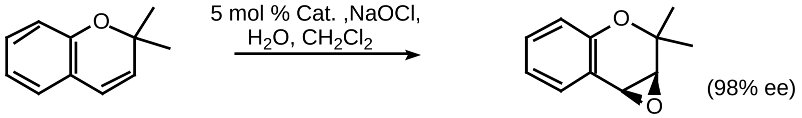


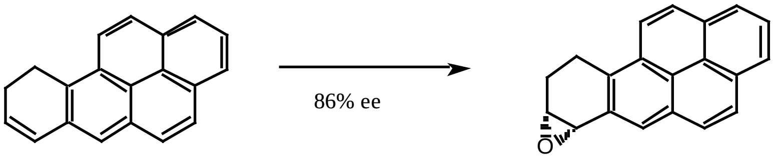
Jacobsen Aysmmetric Epoxidation

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

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

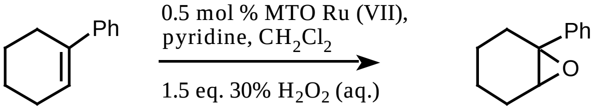






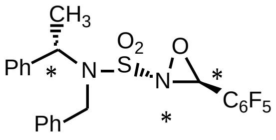
Methyltrioxoruthenium (MTO) Ru(VII)

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

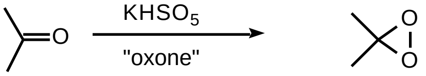


Oxaziridines

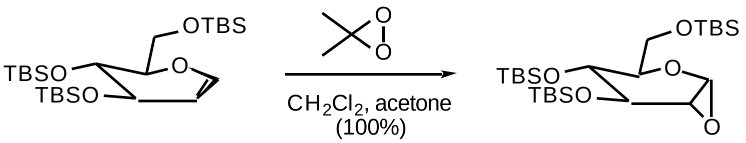
- Asymmetric epoxidation of olefins *Tetrahedron* ***1989*** *45* 5703



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

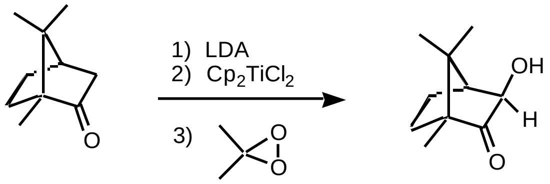


- epoxidation of olefins



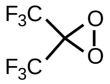
JOC **1990**, *55*, 2411

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



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

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



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

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