Chapter 7 Oxidation and reduction

OXIDATION

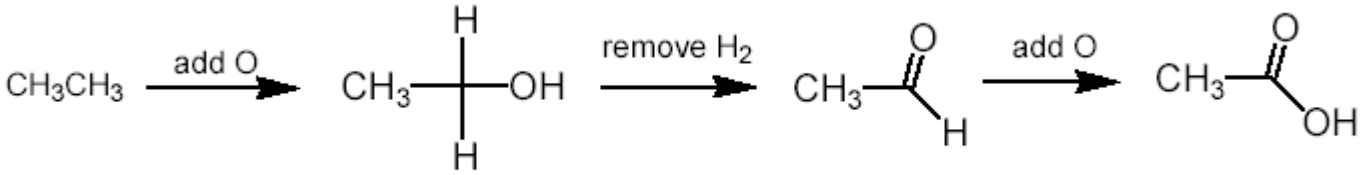
Definition:

The addition of oxygen

The removal of hydrogen

The removal of electrons

Exampl
e:



I. Oxidation of alcohols to aldehydes or ketones

A) Transition Metal oxidants

B) DMSO-based Oxidation

C) Other Useful oxidants

II. Oxidation of alkenes

A) Epoxidation

B) Dihydroxylation

C) Oxidative Cleavage

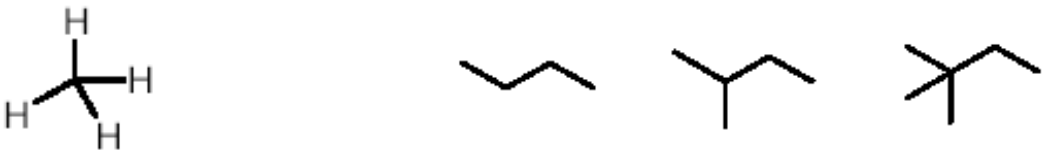
Oxidation levels in organic chemistry:

Level 0: Each carbon has *zero* bonds to elements more

elec ve than itself

Level 0

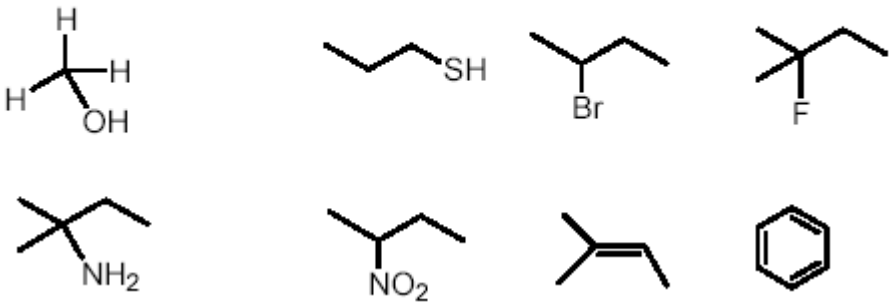
Hydrocarbon Oxidation Level



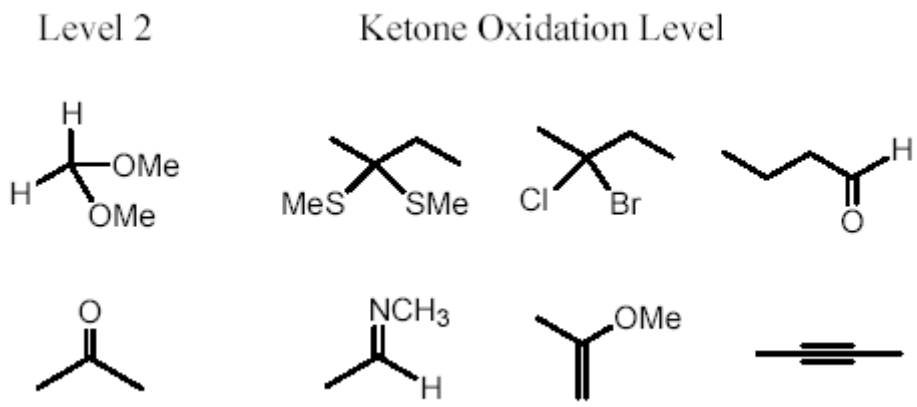
Level 1: Containing carbon atoms that have *one* bond to an electronegative atom.

Level 1

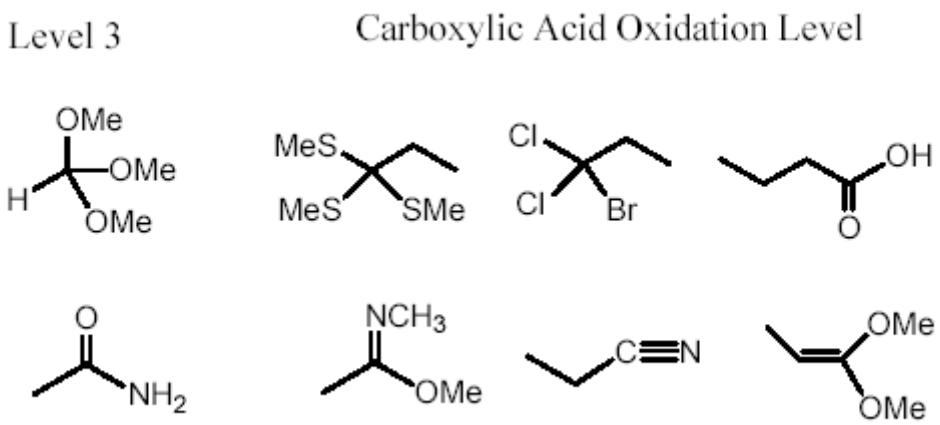
Alcohol Oxidation Level



Level 2: Containing carbon atoms that have *two* bonds to electronegative atoms.



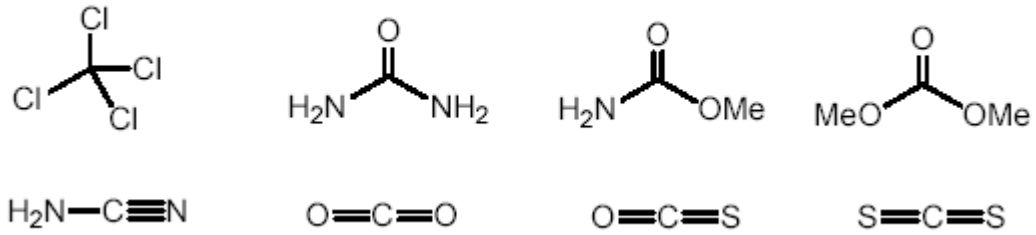
Level 3: Containing carbon atoms that have *three* bonds to electronegative atoms.



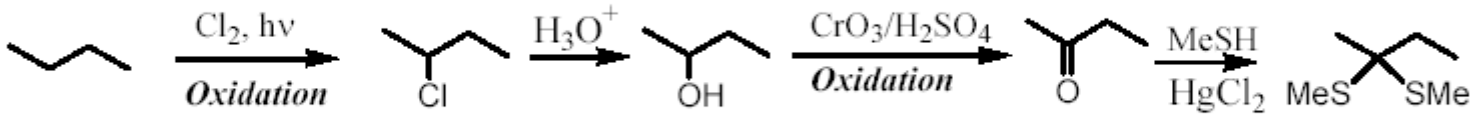
Level 4: Containing carbon atoms that have *four* bonds to

electronegative atoms.

Level 4 Carbon Dioxide Oxidation Level



Examples:



Level 0 Level 1 Level 2

I. Oxidation of alcohols to aldehydes and ketones

A) Transition-metal oxidants

1. Chromium-based oxidation reagents

a) Jones Reagent (Chromic acid, an orange solution)

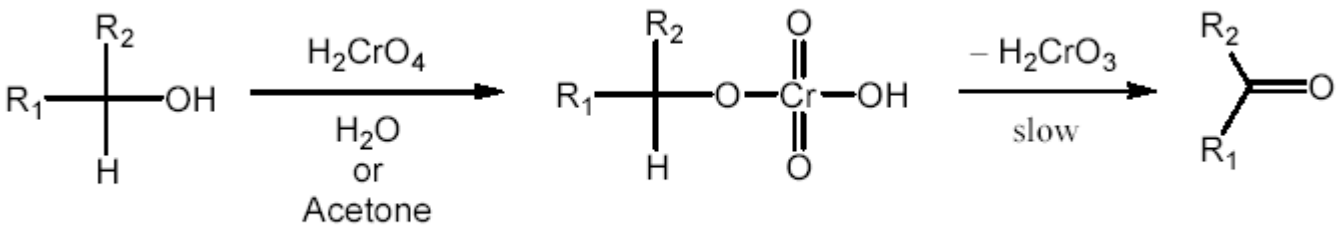
Preparation:

- $Na_2Cr_2O_7$ / H_2SO_4 or CH_3COOH / H_2O
- CrO_3 in aq. H_2SO_4 / acetone

$$H_2Cr_2O_7 \overset{H_2O}{\rightleftharpoons} 2\ H_2CrO_4$$

Acetone solvent serves to protect substrate from over oxidation.

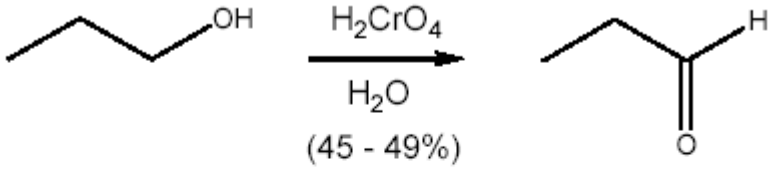
Mechanism:

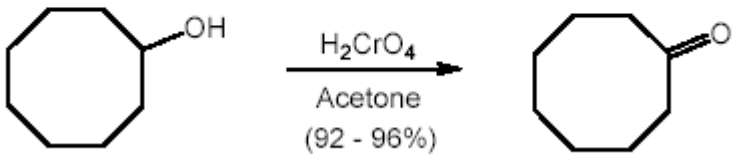


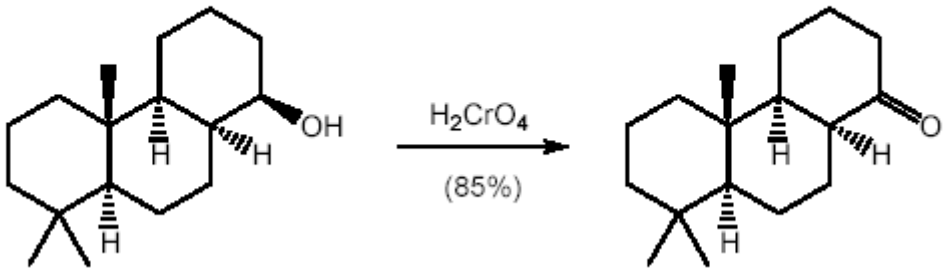
Chromate ester

- Alkenes are not oxidized under the Jones oxidation conditions

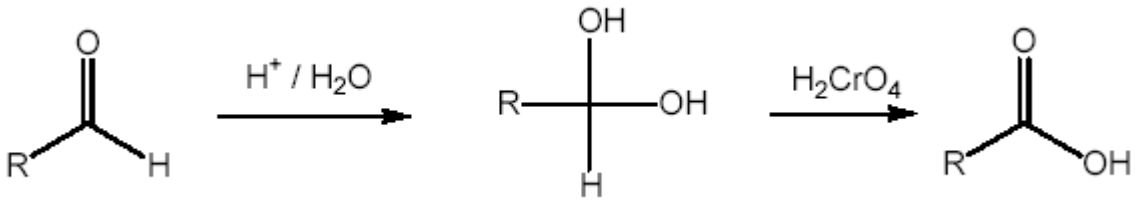
Examples:







Note: Over oxidation of alcohols to acids (water is present)



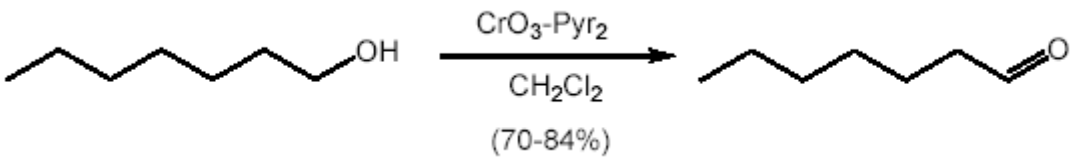
1. Chromium-based oxidation reagents

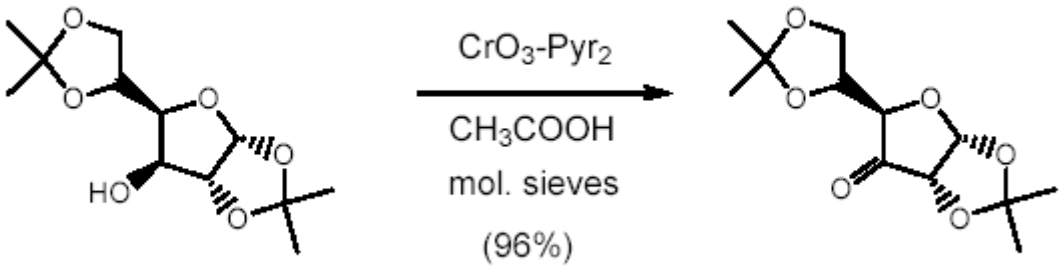
b) Collins Reagent (CrO_3-Pyr_2)

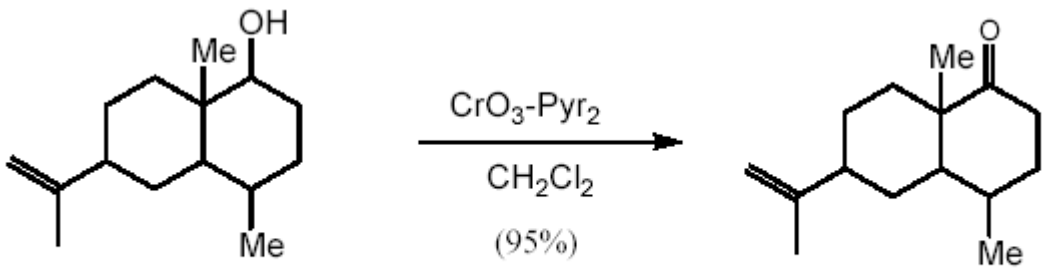
Preparation: Add CrO_3 to pyridine, not the reverse (inflames)

- A hygroscopic, stable, deep red crystalline complex which can be stored for a short period of time
- Neutral conditions
- Oxidation in dichloromethane at room temperature
- No over-oxidation to acids observed
- Good for acid sensitive substrates
- Large excess of Collins reagent is required

Examples:

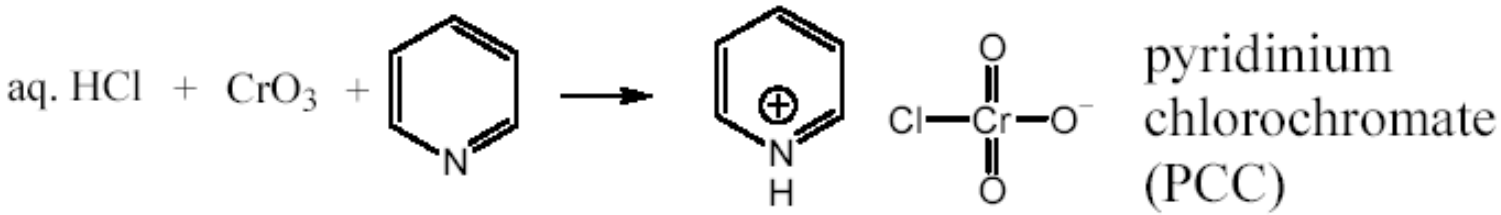






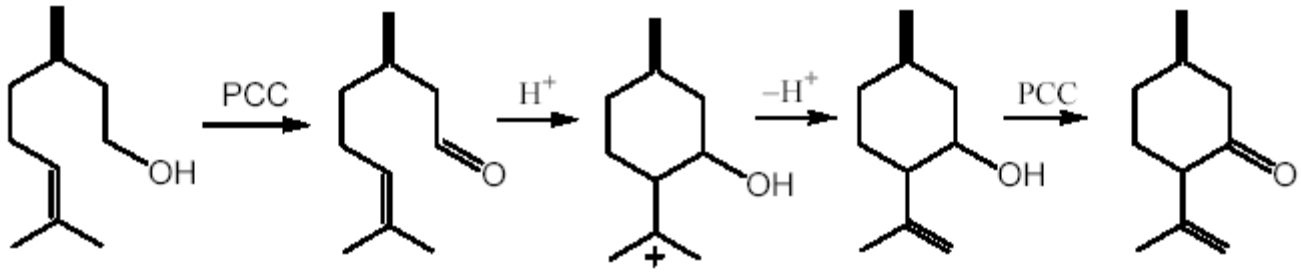
1. Chromium-based oxidation reagents

c) PCC

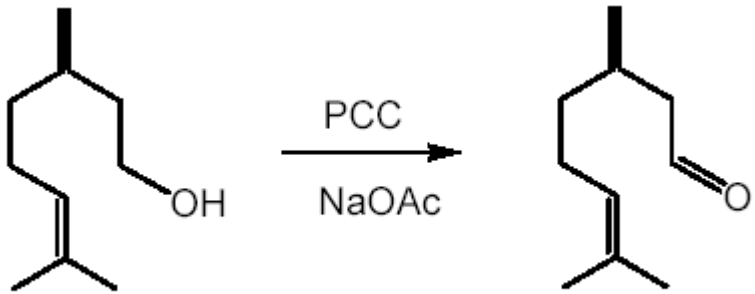


- Excess of oxidant is NOT required
- No over-oxidation observed
- PCC is slightly acidic which can cause side reactions

Example:

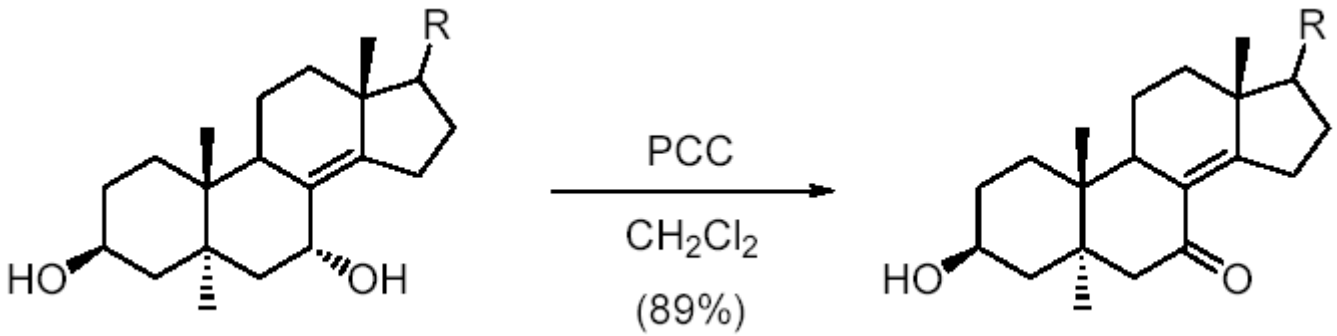


To avoid side reactions, PCC reaction can be buffered with sodium acetate



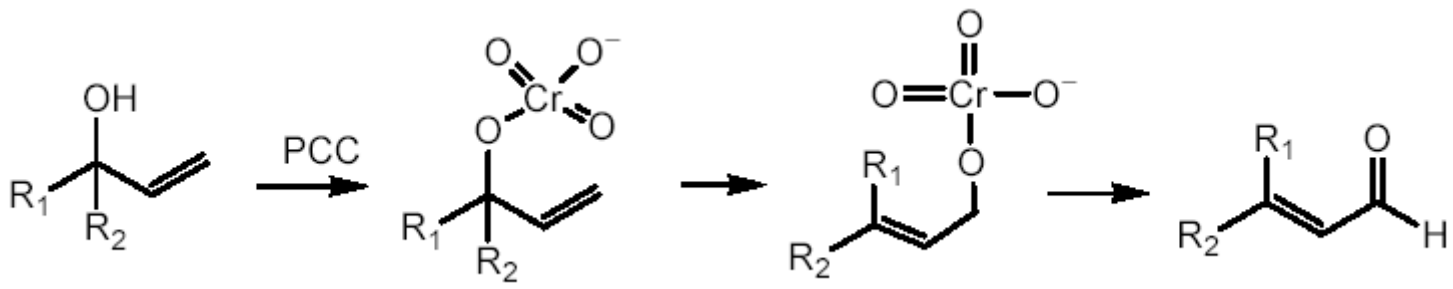
Fast oxidation of allylic alcohols

Example:

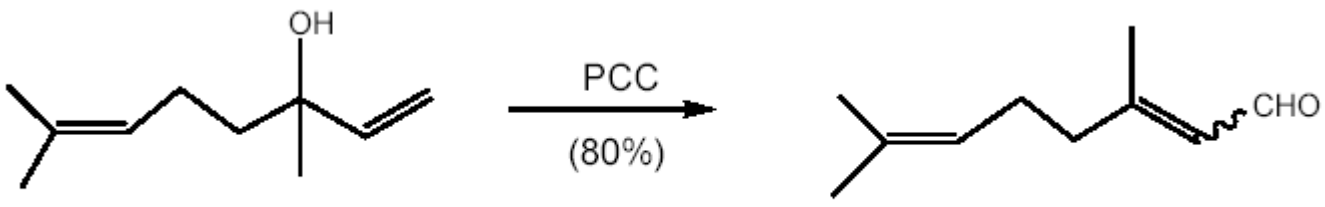


- Tertiary allylic alcohols undergo oxidative rearrangement to give α,β-unsaturated aldehyde

Mechanism:



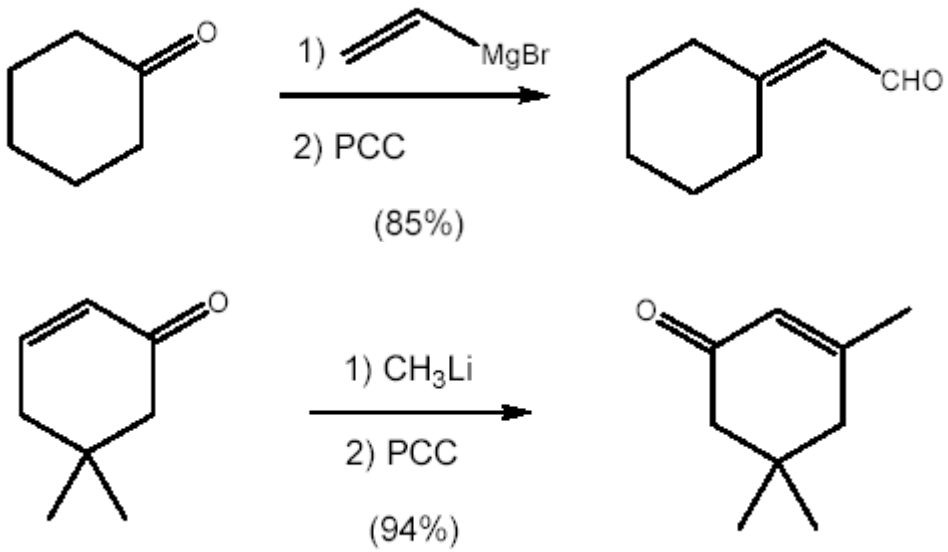
Example:



E/Z mixture

Useful for preparation of α, β-unsaturated aldehydes and ketones from ketones

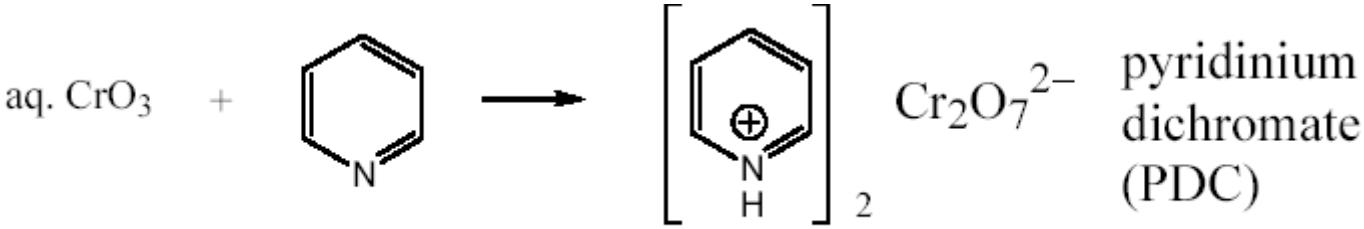
Examples:



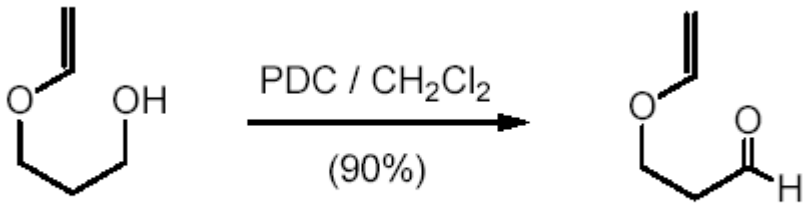
- Drawback: high toxicity and environmental hazards associated with chromium compounds

1. Chromium-based oxidation reagents

d) PDC



- PDC is neutral, stable, and commercially available
- PDC oxidation slower than PCC

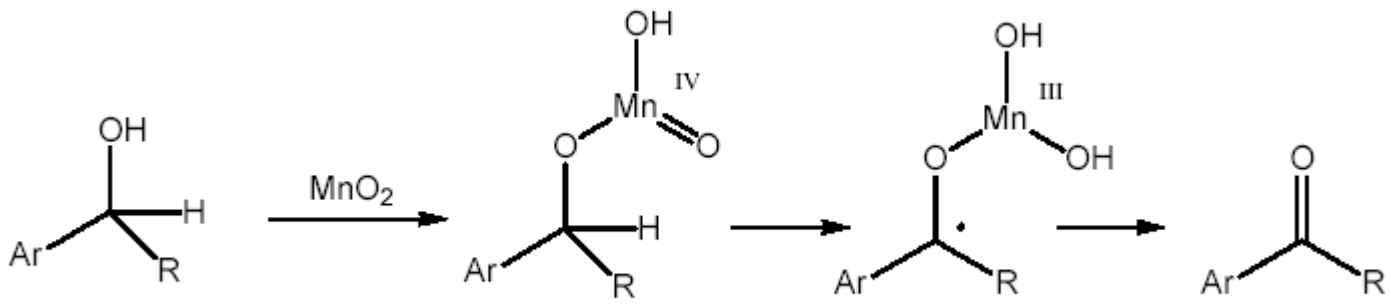


A) Transition-metal oxidants

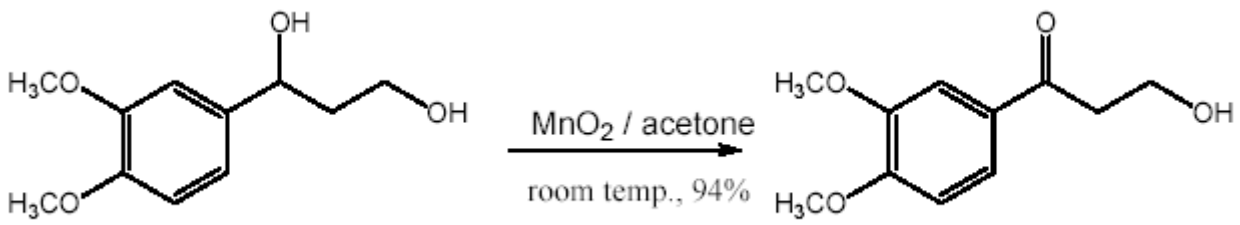
2. Manganese

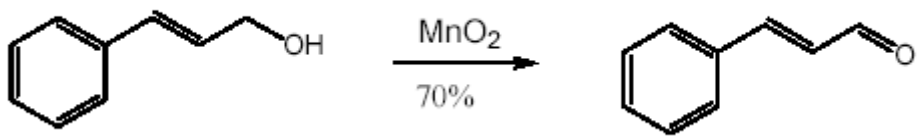
a) Manganese Dioxide (MnO_2)

Mechanism:



- Very mild oxidant
- Selective oxidation of allylic and benzylic alcohols





b) KMnO4

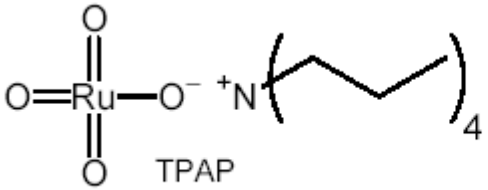
$KMnO_4$ / H_2SO_4

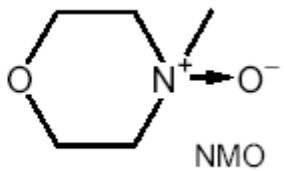
- Good for oxidation of alcohols to acids
- Reaction runs in aqueous solution (insolubility of $KMnO_4$ in organic solvents)
- Can oxidize carbon-carbon double bonds
- Other permanganate reagents: R_4NMnO_4, $BaMnO_4$ (soluble in organic solvents)

A) Transition-metal oxidants

3. Ruthenium (Ru)

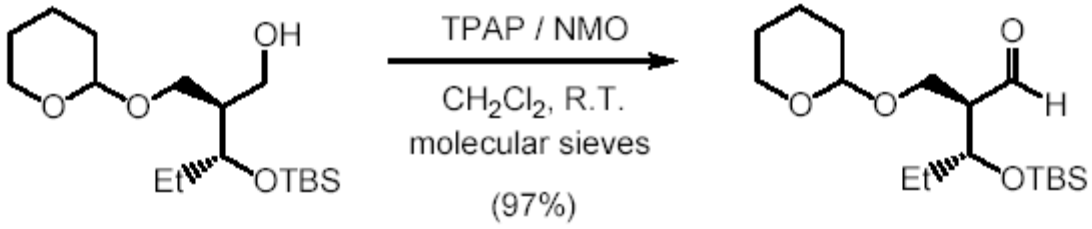
Tetra-*n*-propylammonium perruthenate (TPAP)/*N*-Methylmorpholine *N*-oxide (NMO)



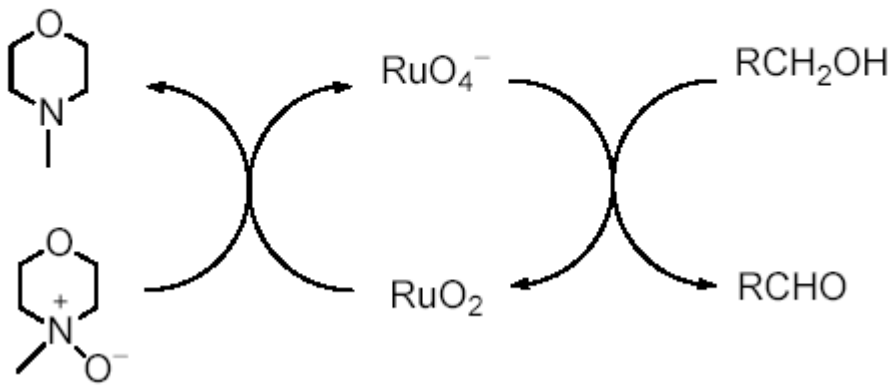


- Mild conditions
- Catalytic: only 0.5 – 5 mol % of catalyst is required: Good for large scale oxidation
- Do not oxidize olefins
- Potential oxidation of nitrogen and sulfur containing function groups

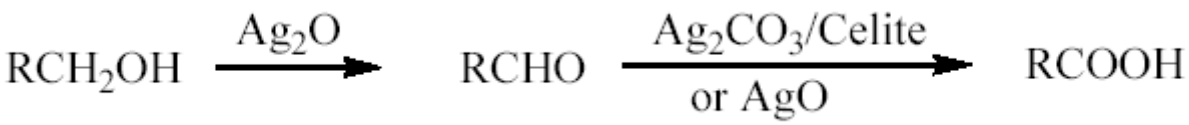
Example:

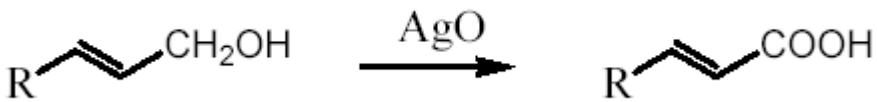


Catalytic cycle:



4. Silver (Ag)



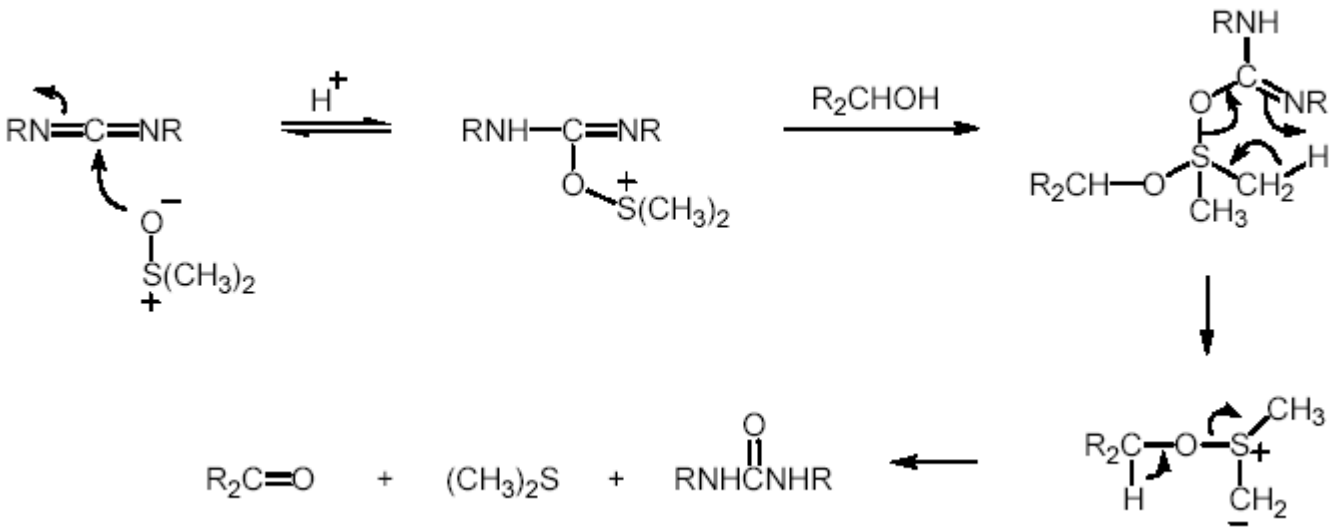


I. Oxidation of alcohols to aldehydes and ketones

B) Oxidation Based on Dimethyl Sulfoxide (DMSO)

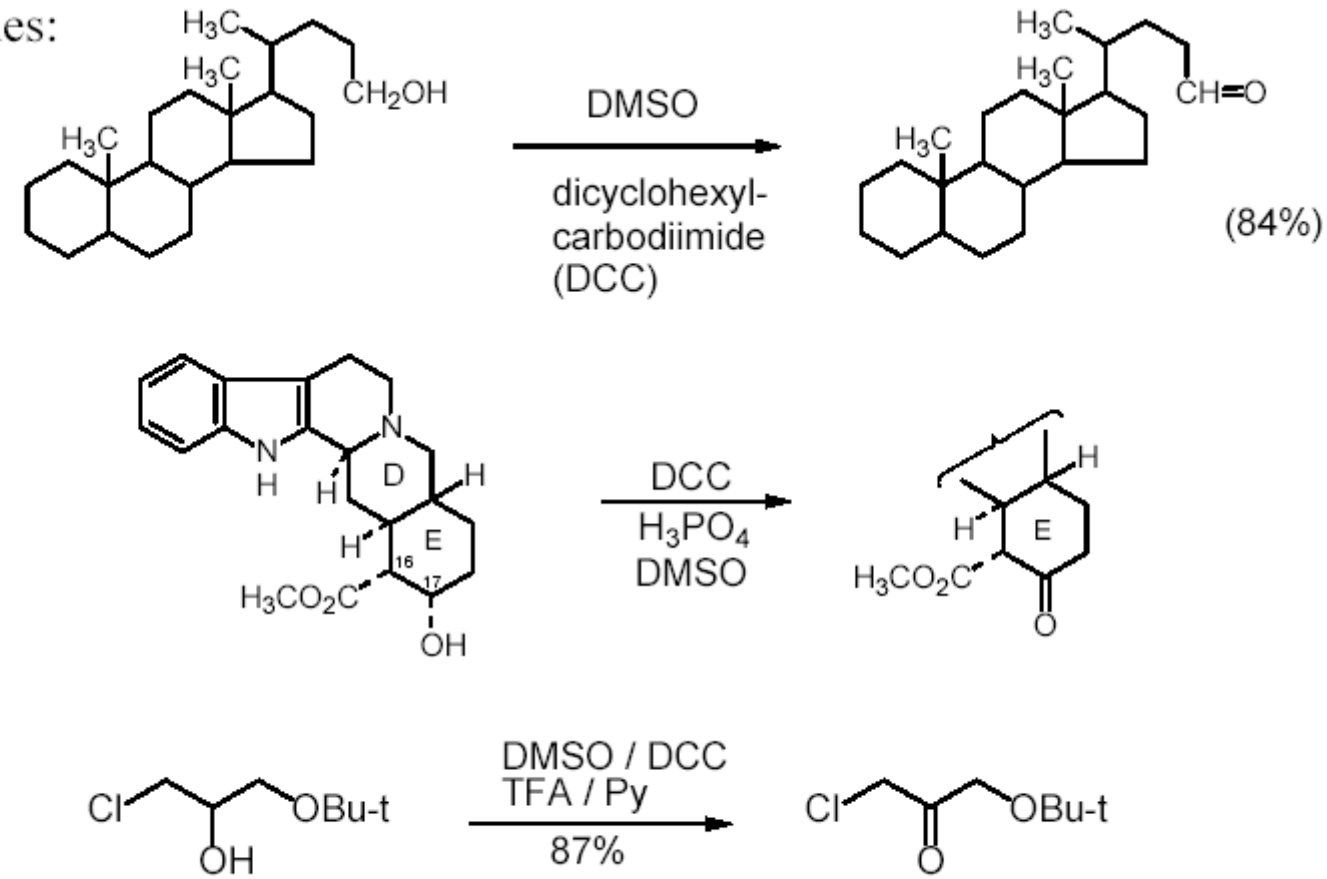
1. Ptitzner-Moffatt Oxidation (DMSO-Carbodiimide)

Mechanism:



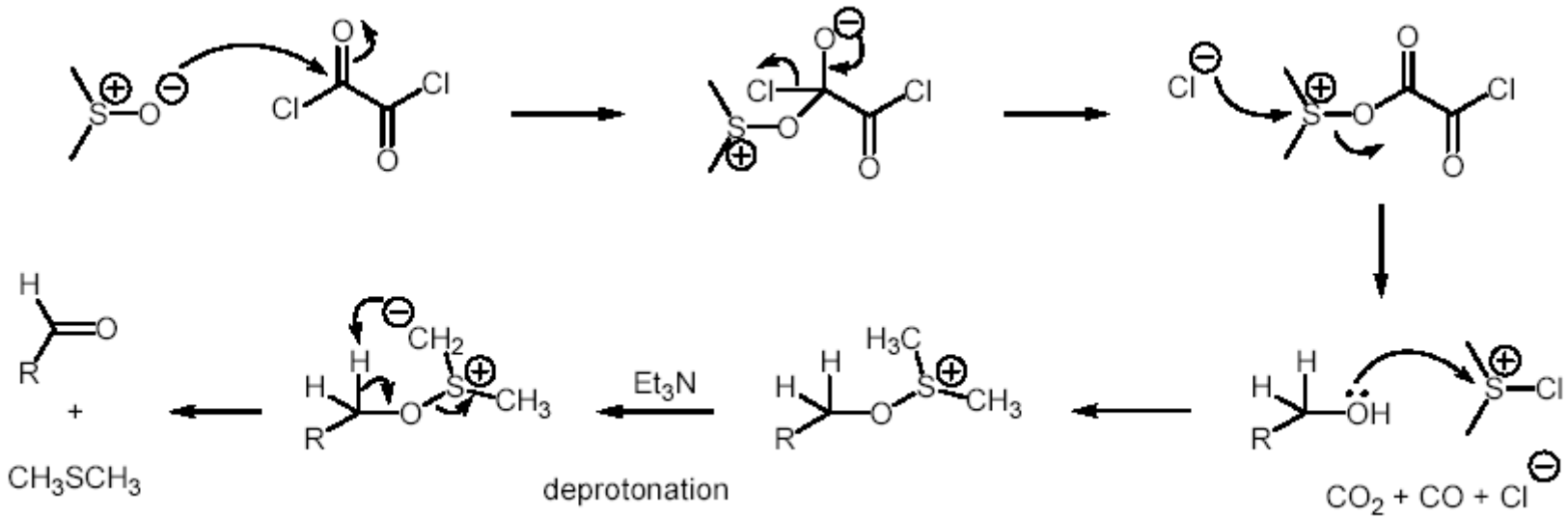
- Good for molecules that are sensitive to transition-metal oxidants (eg. Indoles)
- Less reactive than transition-metal oxidants
- Acidic conditions

Examples:



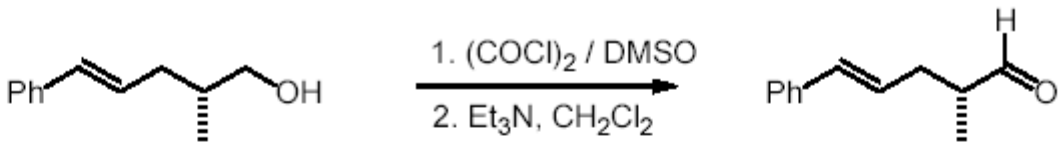
2. Swern Oxidation (DMSO-Oxalyl Chloride)

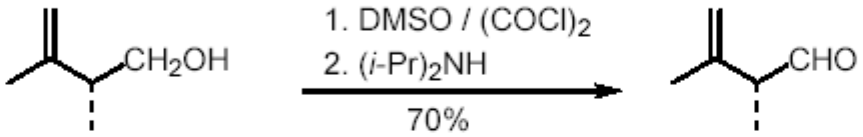
Mechanism:

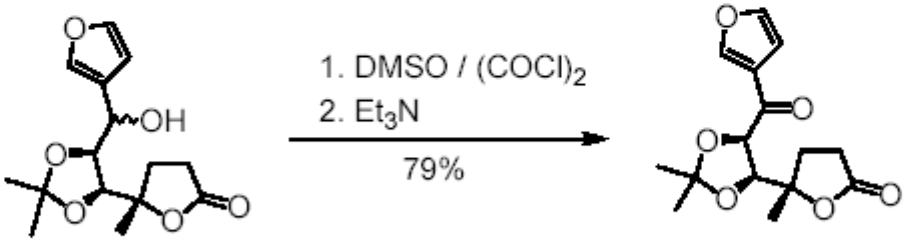


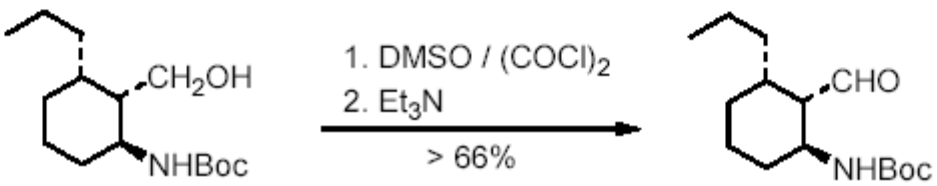
- More reactive than the Ptitzner-Moffatt conditions
- Requires very low temperature (−78°C) for activation of alcohols
- Neutral conditions: little racemization of α-chiral center
- Formation of side-product ($ROCH_2SCH_3$)

Examples:





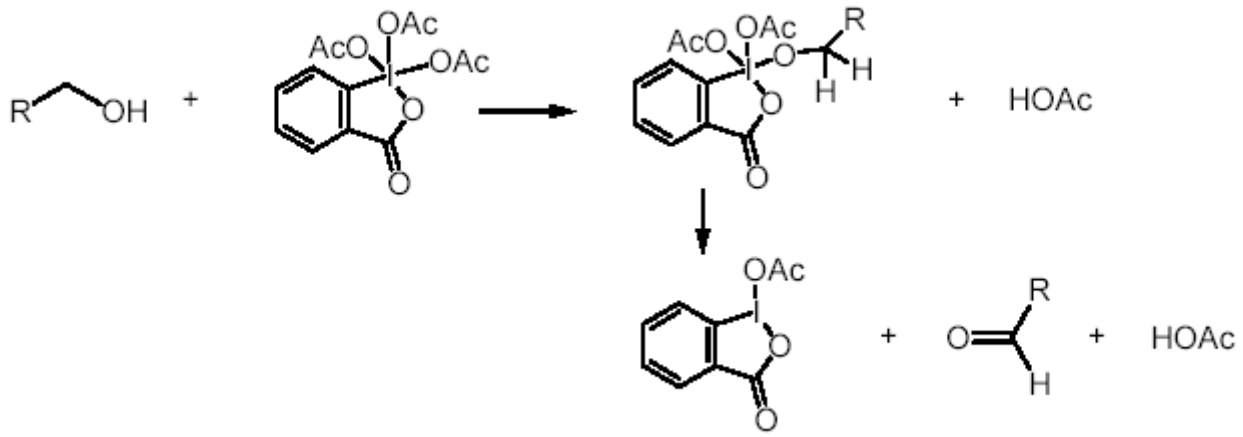




Other oxidants cleave diol C–C bond

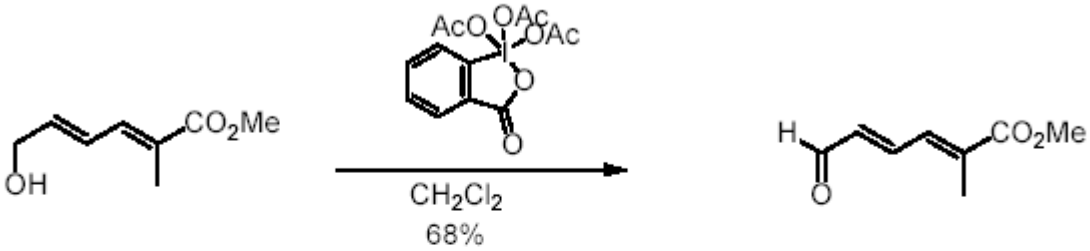
C) Dess. Martin Periodinane: a hypervalent iodine(V) oxidant

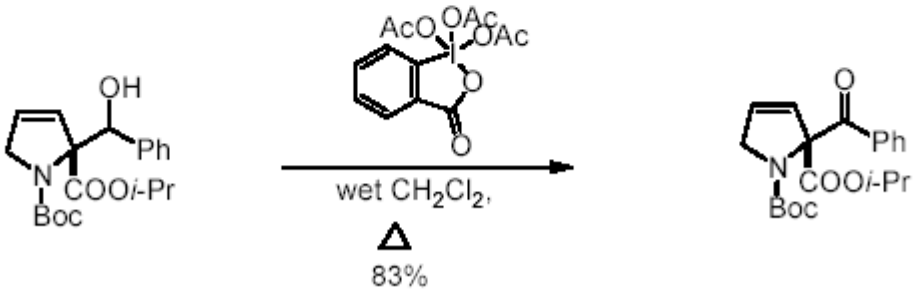
Mechanism:



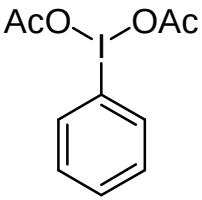
- Very mild condition: tolerate a large number of functional groups
- Wet solvent (CH_2Cl_2) increase the rate of oxidation and essential for oxidation of hindered 2° alcohol
- Require stoichiometric amount of reagents: not practical for large scale
- The intermediate for preparation of the reagent is explosive

Examples:

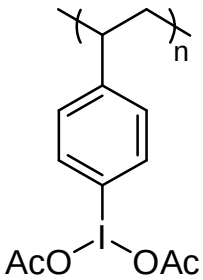




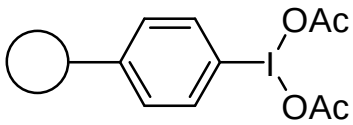
Hypervalent iodine



1



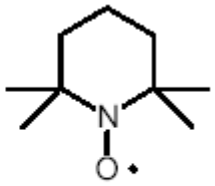
2: PSDIB



3: MPDIB

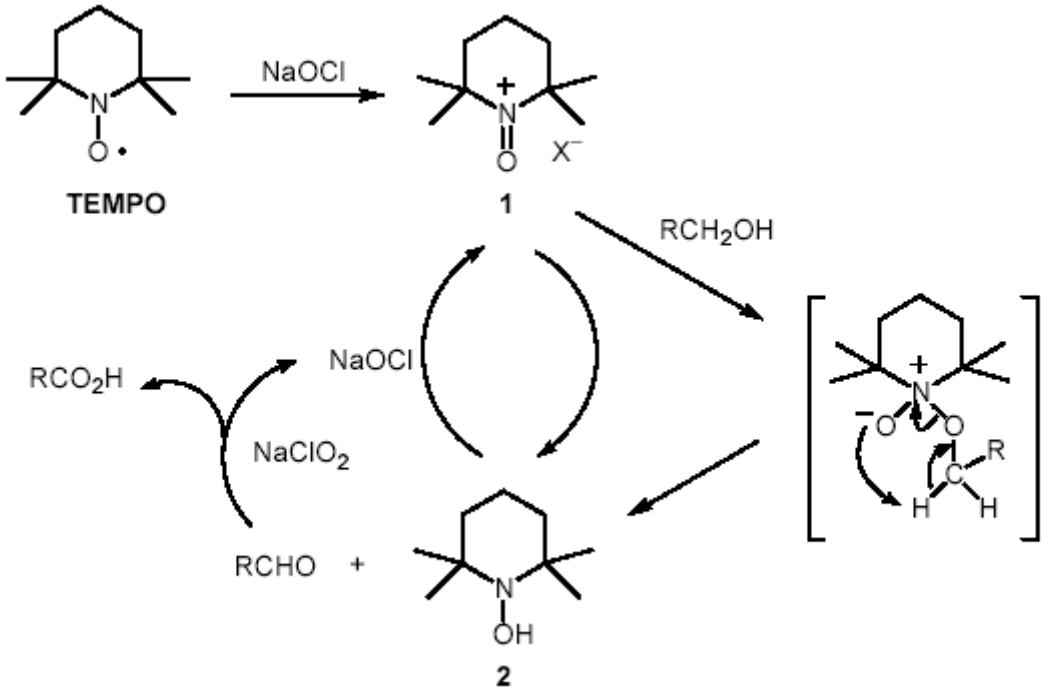
D) Oxoammonium salts:

2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) and NaOCl (bleach) catalyzed oxidation of primary alcohols to carboxylic acids with sodium chlorite ($NaClO_2$)

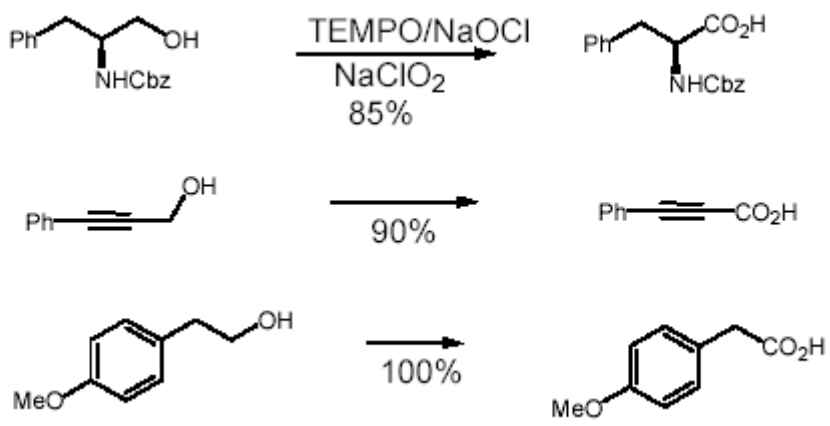


(TEMPO)

Mechanism:

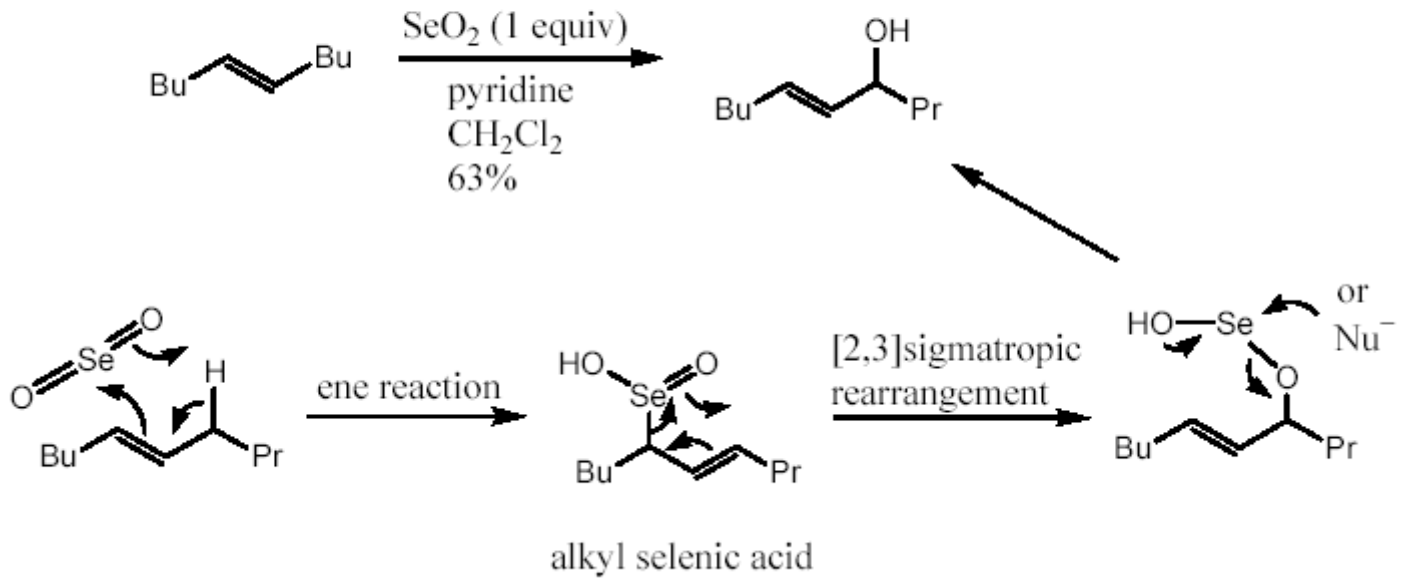


Examples:



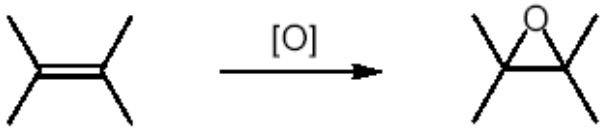
Other oxidation reactions:

Allylic oxidation with SeO_2:



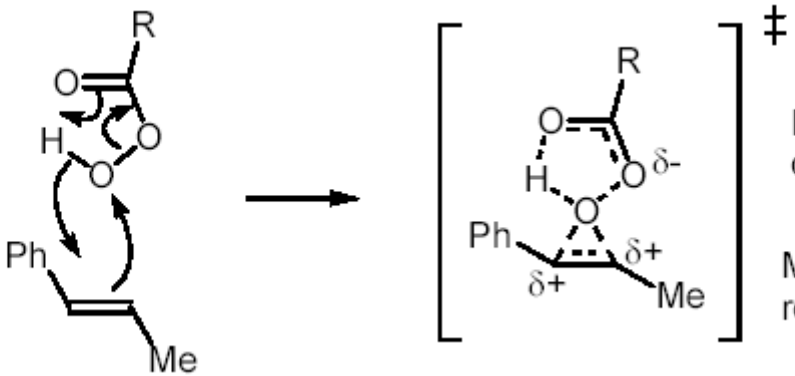
II. Oxidation of Alkenes

A) Epoxidation



1. Peracids (RCO_3H): prepared from RCO_2H and H_2O_2

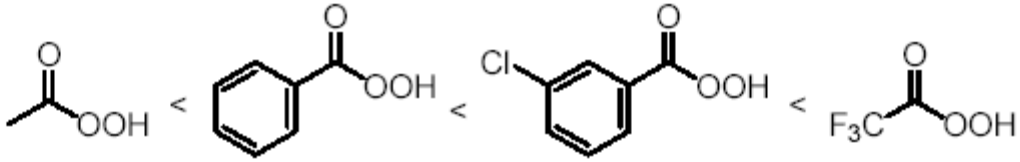
Mechanism:



Higher activity for more electron-deficient R group

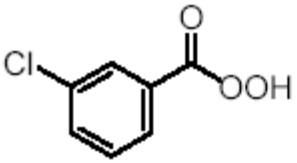
More electron-rich C=C bond reacts faster

Reactivity:



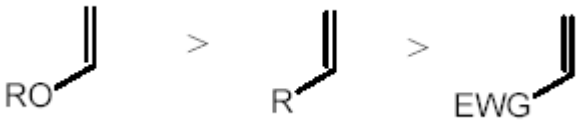
pK_a of acid (RCO_2H):	4.8	4.2	3.9	0

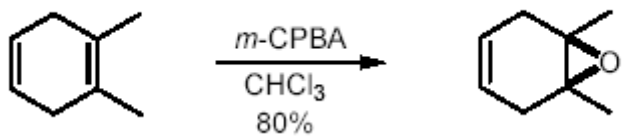
The lower the p*K*a, the greater the reactivity (i.e., the better the leaving group)

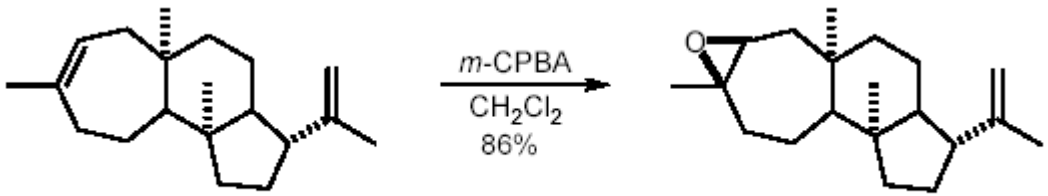


m-CPBA (*m*-chloroperbenzoic acid)
commercially available

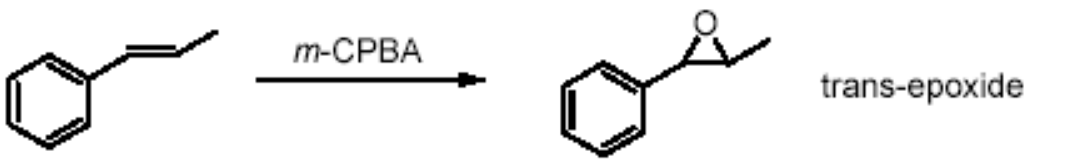
- Chemoselectivity: most nucleophilic C=C reacts fastest.

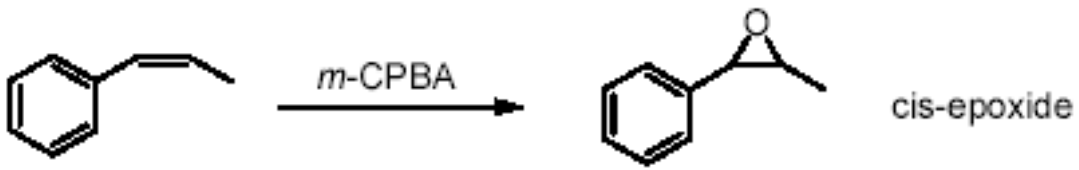




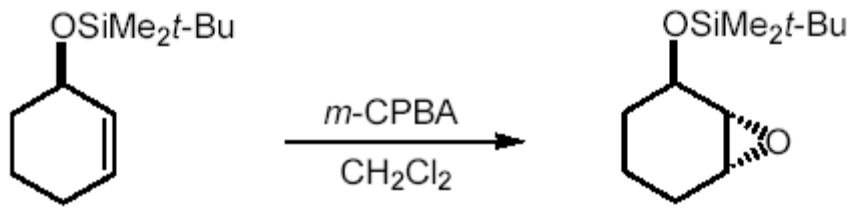


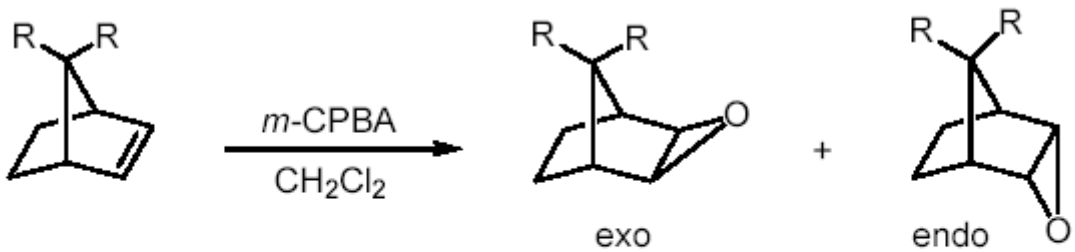
Stereochemistry of olefins is maintained (stereospecific!).





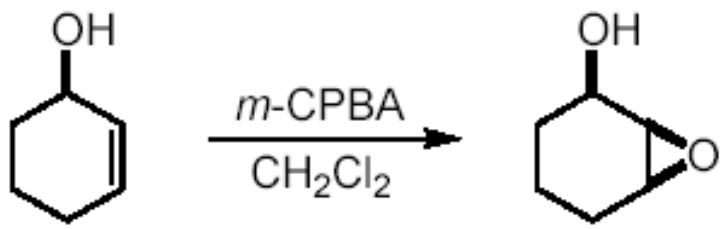
Sensitive to steric: Epoxidation preferentially occurs at the less hindered side.

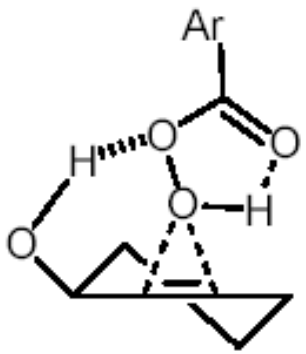




R = H	25°C, 20 min	99%	1%
R = CH_3	25°C, 24 h	<10%	90%

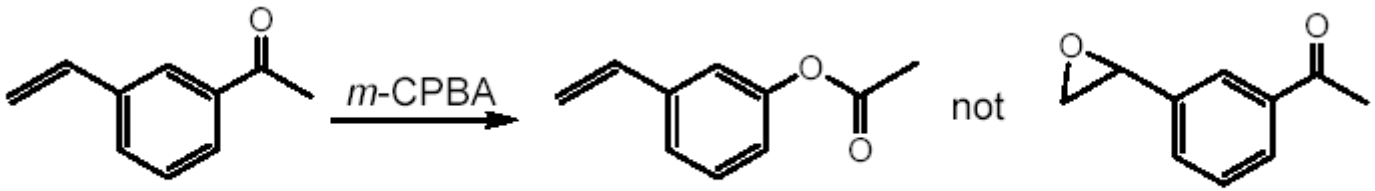
Directed by allylic OH and NHCOR groups



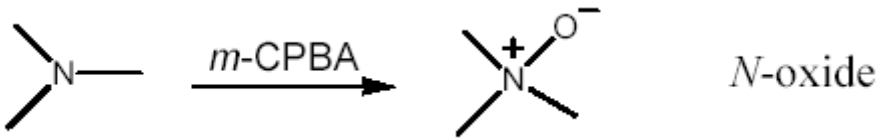


Common side reactions:

Baeyer-Villiger reactions of ketones and aldehydes

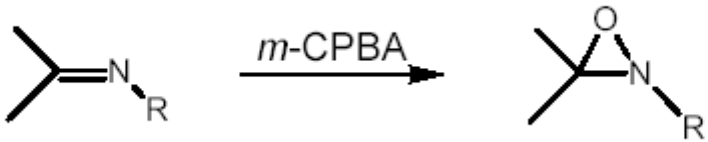


Oxidation of amines



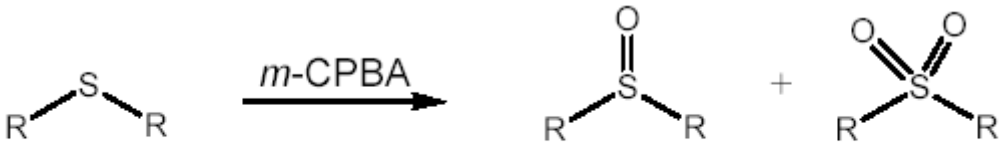
N-oxide

Imine oxidation



oxaziridine

Sulfur oxidation

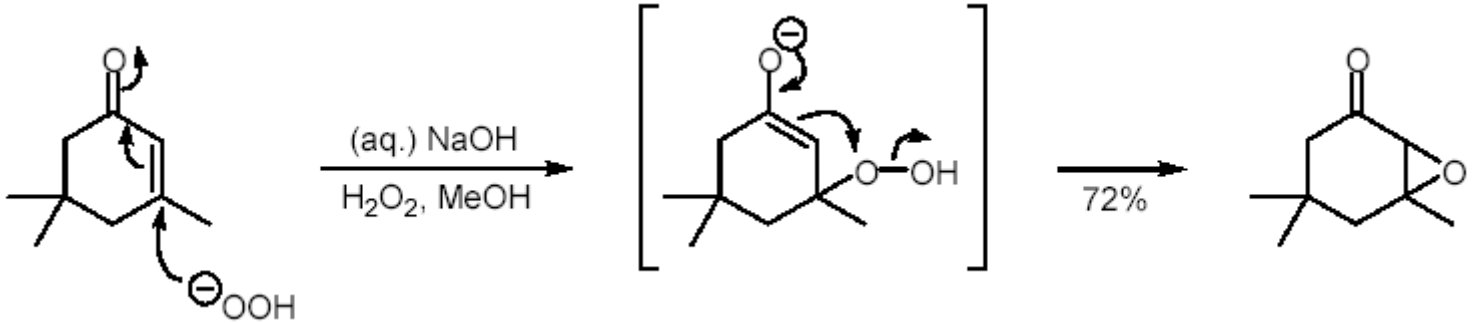


sulfoxide sulfone

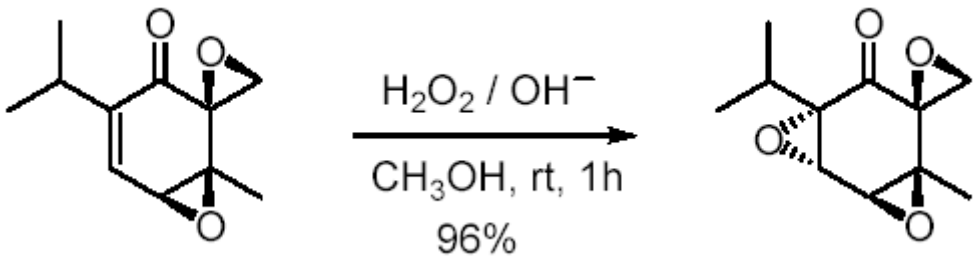
2. Hydroperoxides under basic conditions (H_2O_2 / NaOH)

Good for electron-poor alkenes

Mechanism:

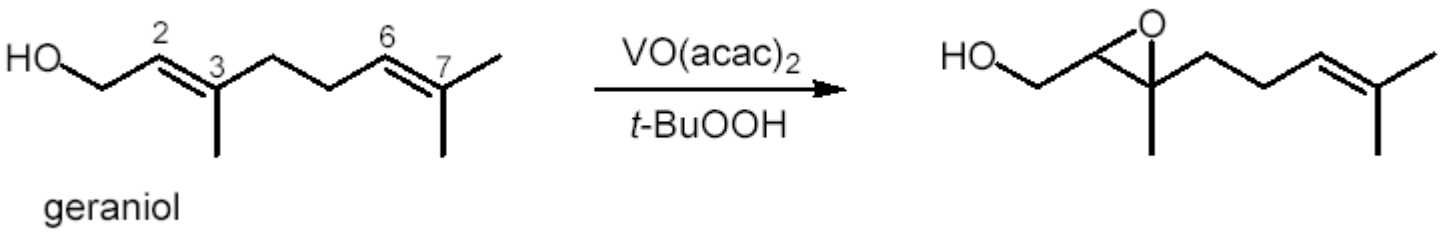


Examples:

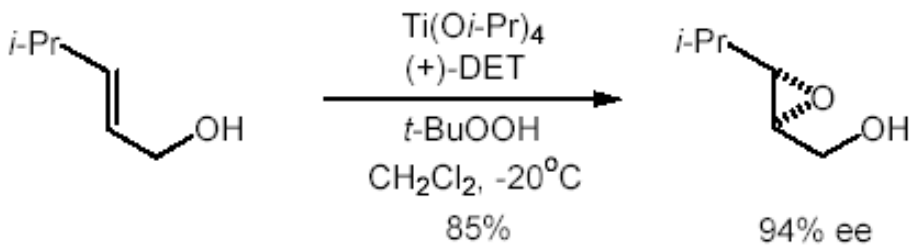


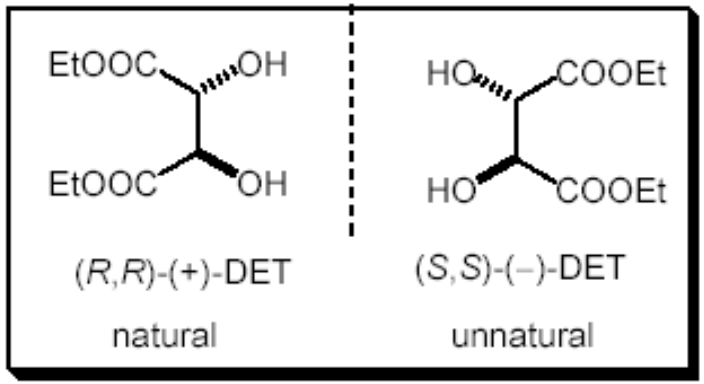
3. Hydroperoxides with transition metal catalysts

a) Vanadium: $VO(acac)_2$ / *t*-BuOOH

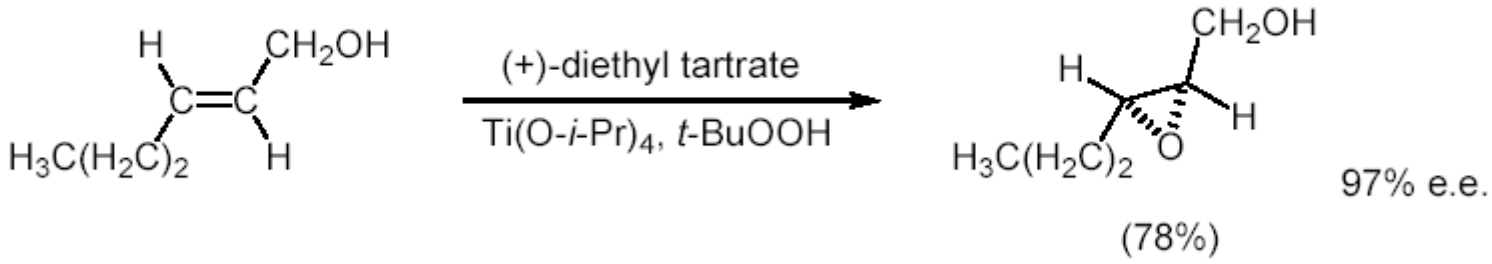


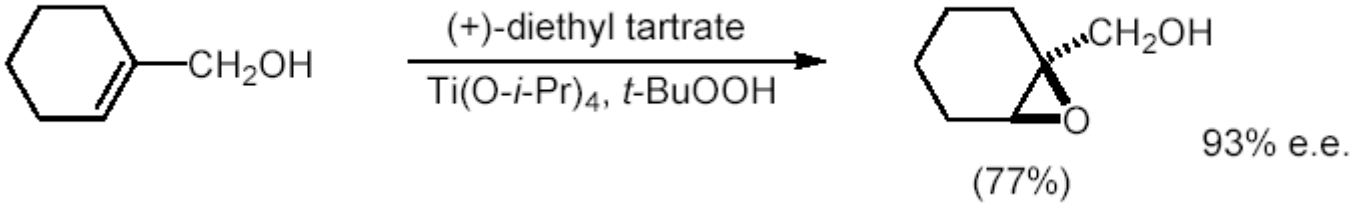
b) Titanium: $Ti(O\mathit{i}\text{-}Pr)_4$ / *t*-BuOOH / diethyltartrate (DET)
Sharpless catalytic asymmetric epoxidation (AE)





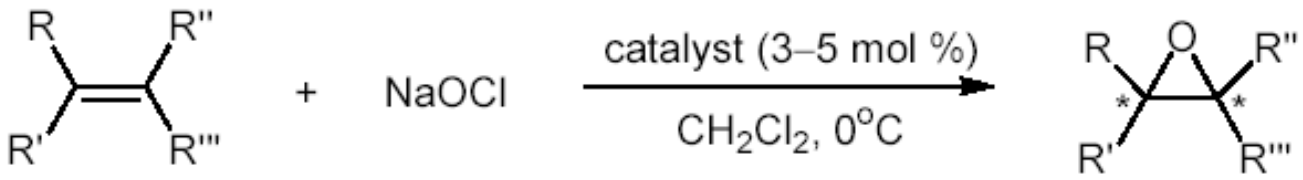
Examples:



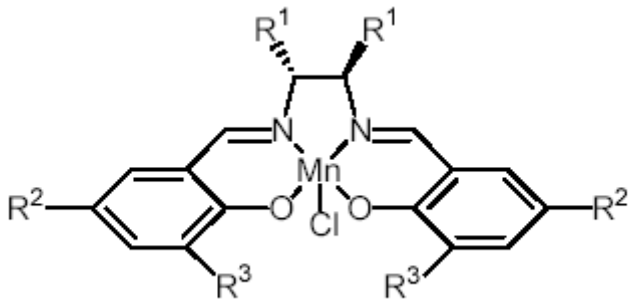


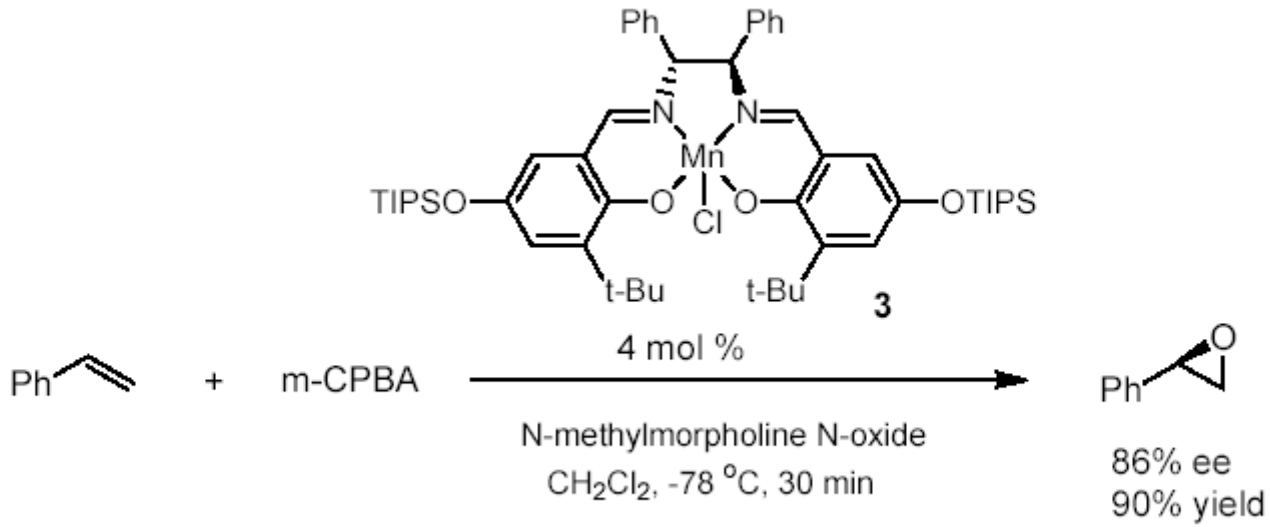
c) Manganese: (Salen)Mn(III) / NaOCl (Jacobsen epoxidation)

Stereoselective epoxidation of unfunctionalized olefins



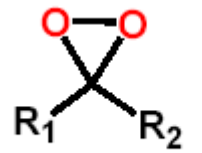
Jacobsen catalysts:



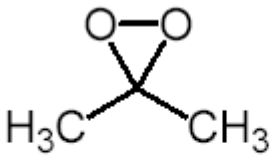


4. Dioxiranes

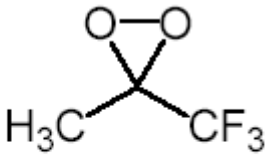
Dioxiranes: a new class of organic oxidants for epoxidation, C-H bond oxidation, and heteroatom oxidation reactions



dioxiranes



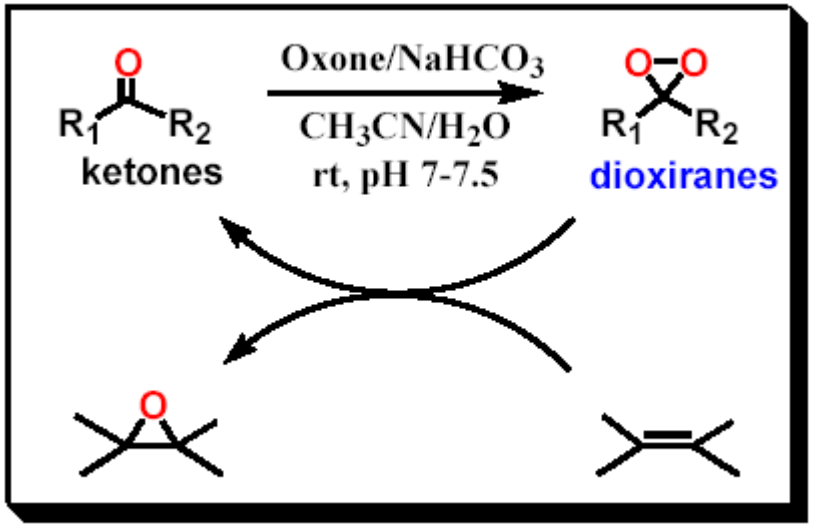
Dimethyldioxirane (DMDO)



methyl(trifluoromethyl)dioxirane

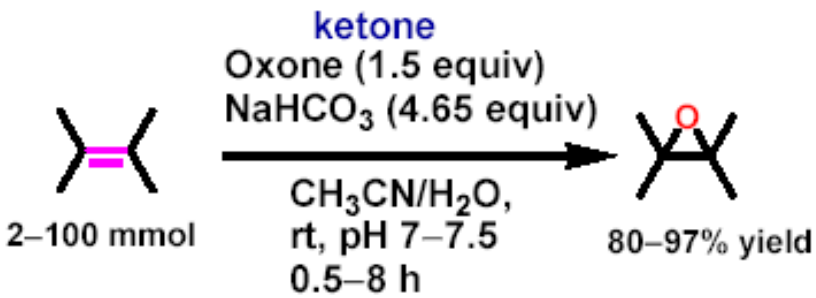
- Methyl(trifluoromethyl)dioxirane is about 1000 times more reactive than DMDO.
- Dioxiranes can be generated in situ from ketones and Oxone® (potassium peroxymonosulfate; $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)

Catalytic Cycle



Environmentally Friendly Process

Economical

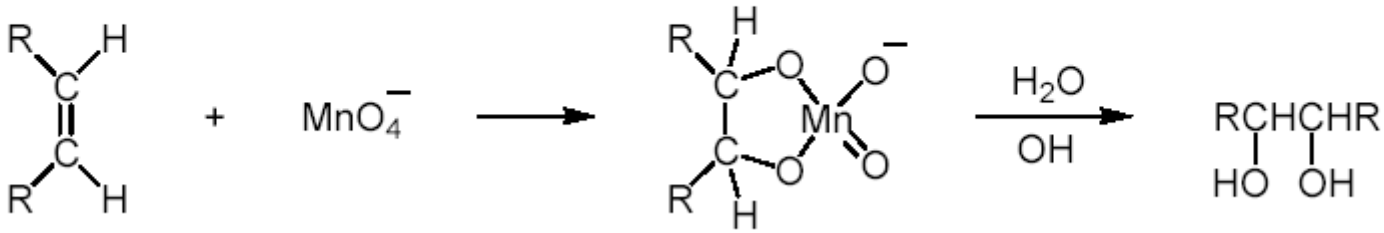


II. Oxidation of Alkenes

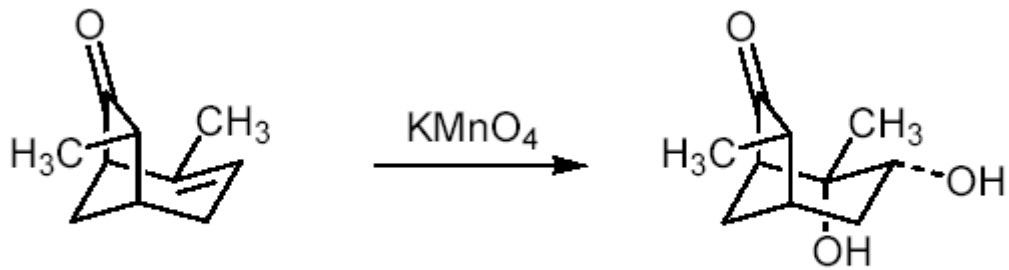
B) Dihydroxylation

1. $KMnO_4$:

- *Syn* addition



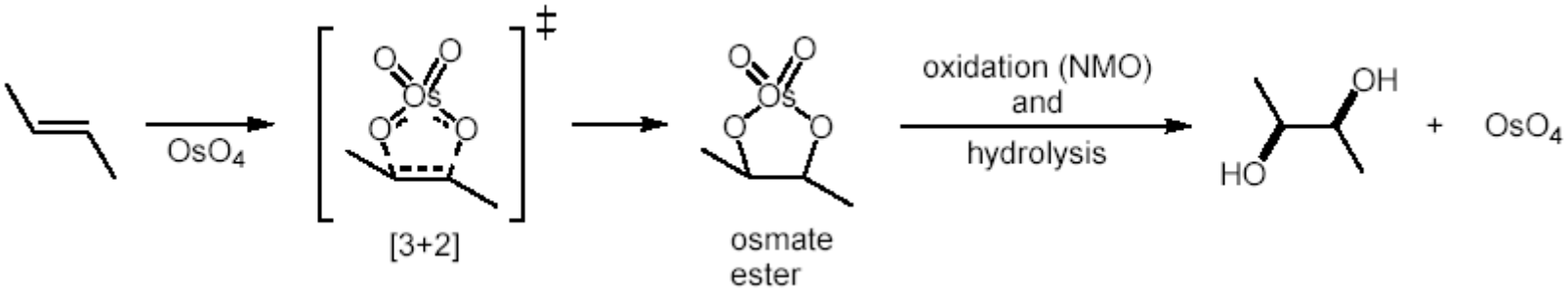
Examples:

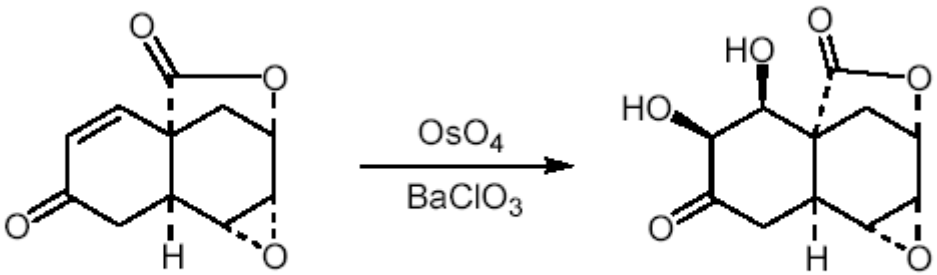


(58%)

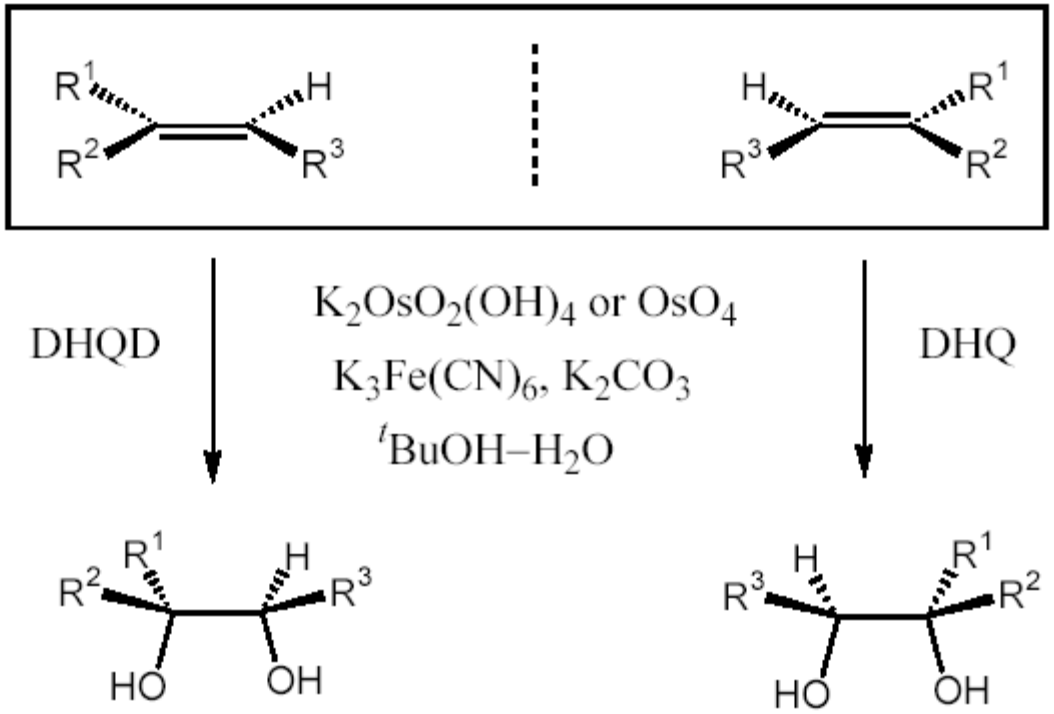
2. OsO4 :

- More selective than $KMnO_4$
- *Syn* addition
- Catalytic with OsO_4: *N*-methylmorpholine-*N*-oxide (NMO), *t*-butyl hydroperoxide or barium chlorate can be used as the stoichiometric oxidant
- Diastereospecific, with attack on the C=C from the less hindered face

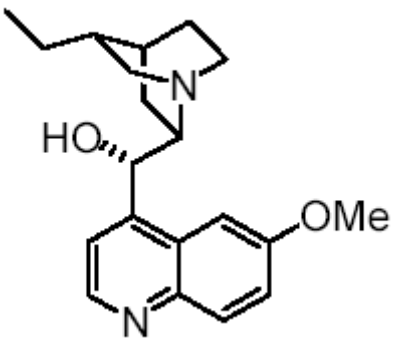




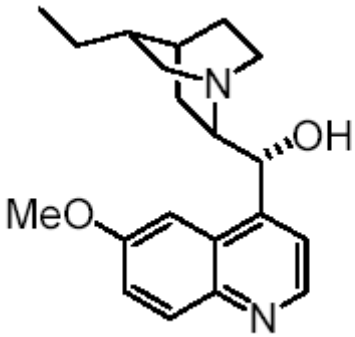
Sharpless Catalytic Asymmetric Dihydroxylation (AD)



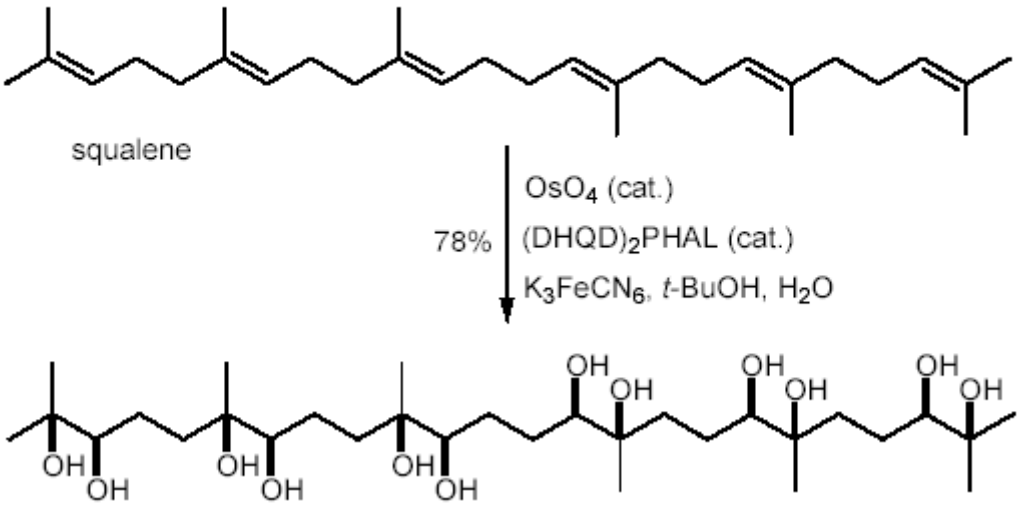
DHQD=



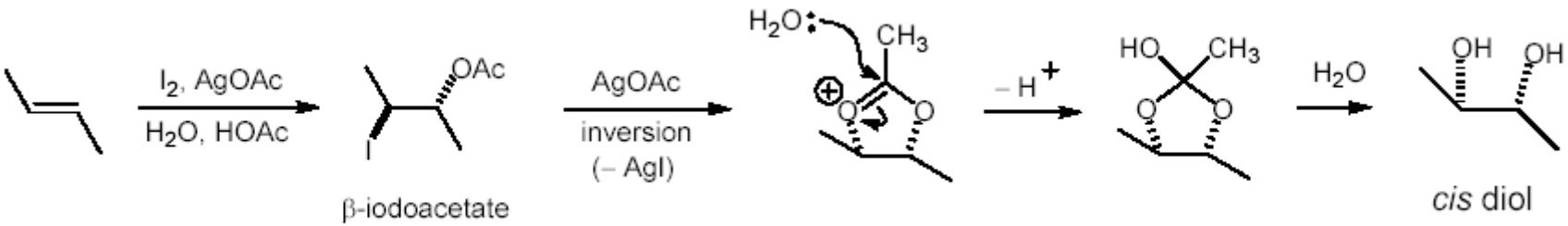
DHQ=



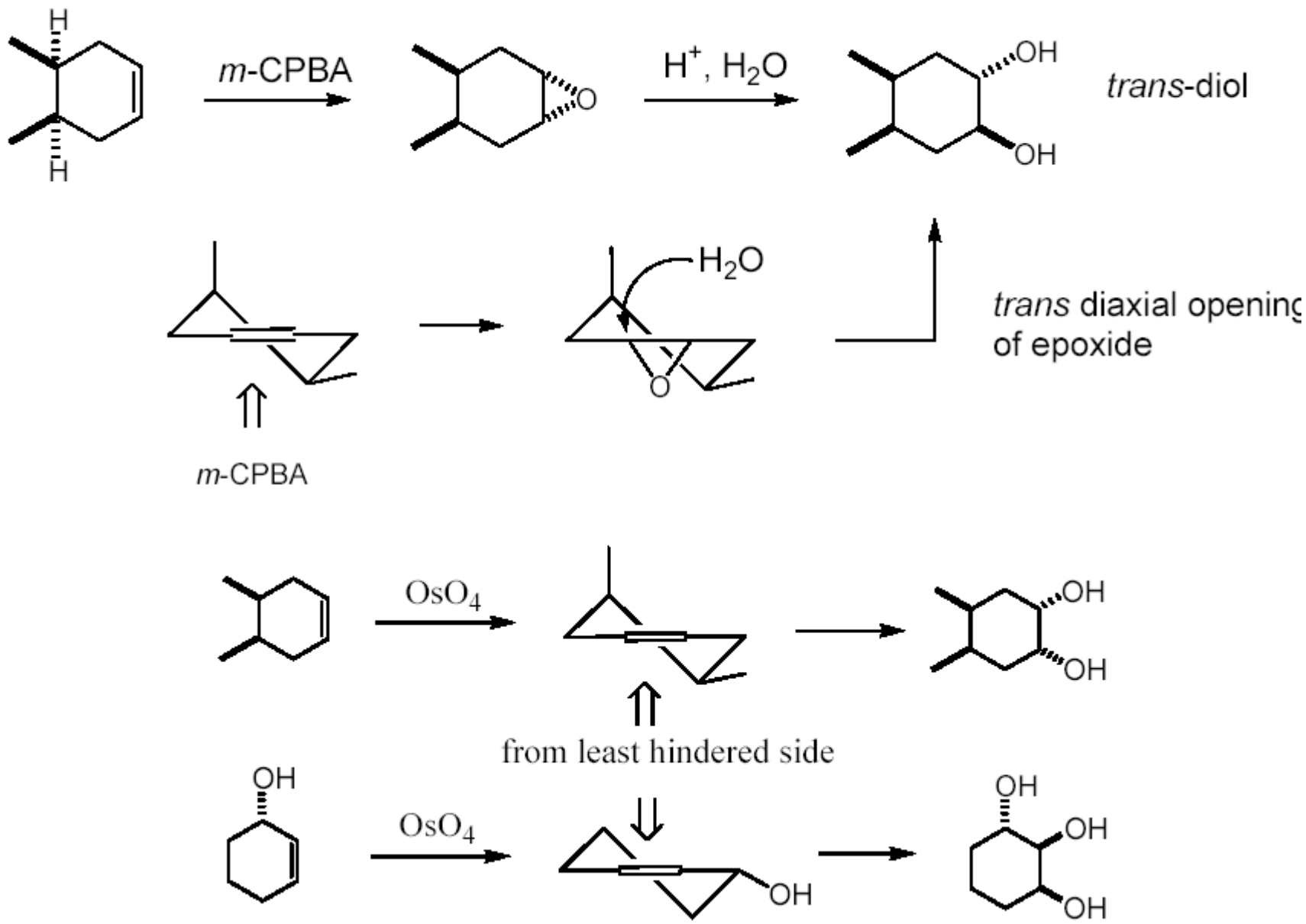
Example



3. Prevost reaction and Woodward hydroxylation

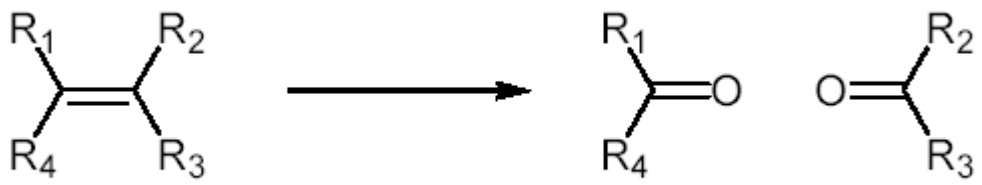


Comparison with *m*-CPBA and OsO_4 oxidation:

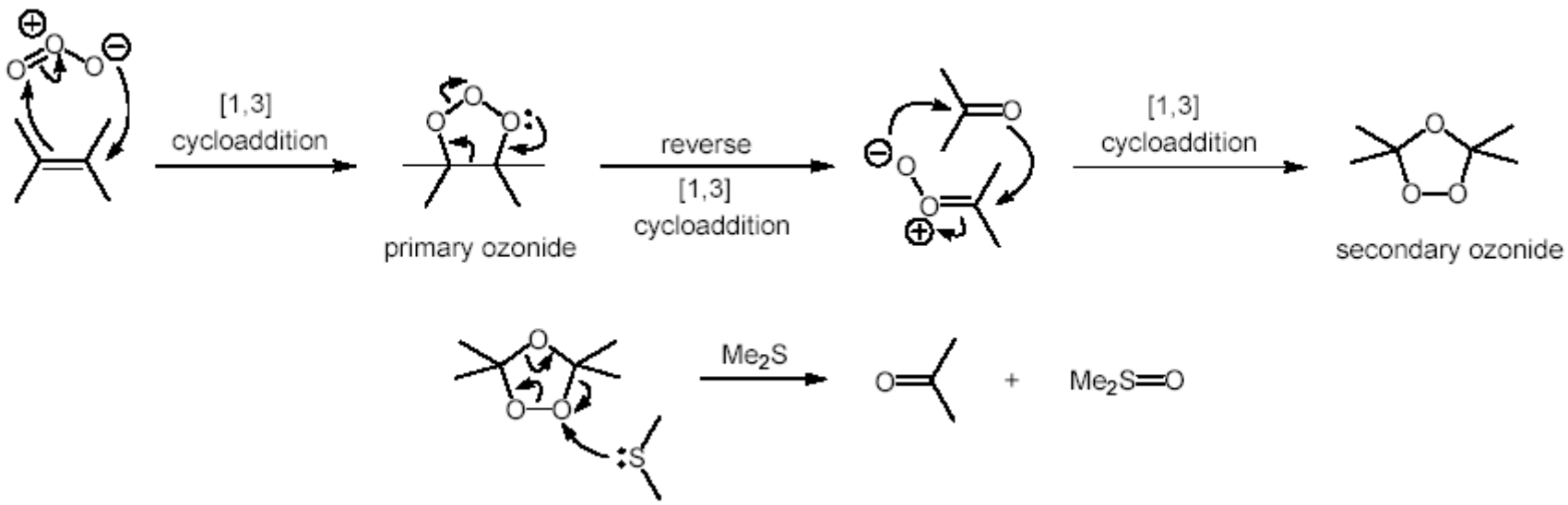


II. Oxidation of Alkenes

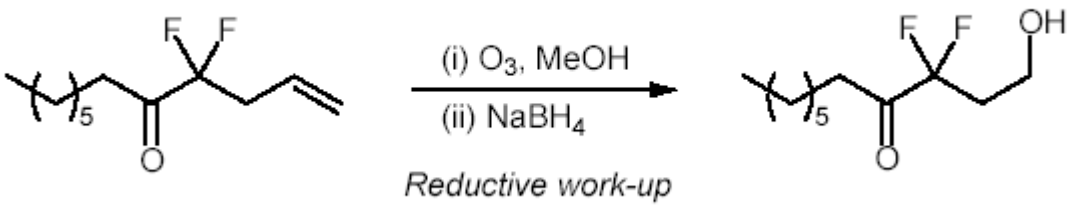
C) Oxidative cleavage of alkenes



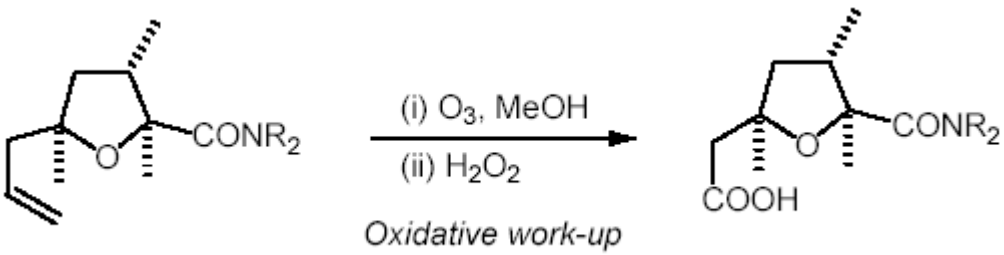
1. Ozone (O3)



Reductive work-up: Me_2S, Ph_3P, Zn/HOAc give aldehydes/ketones
$NaBH_4$ and $LiBH_4$ give alcohols



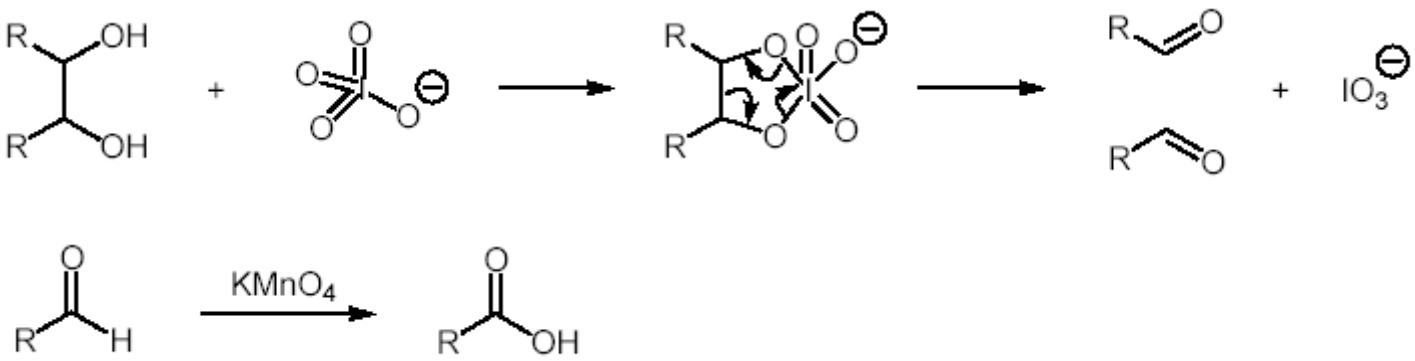
Oxidative work-up: H_2O_2, $KMnO_4$, Cr(VI), and RuO_4 give ketones, carboxylic acids



2. Transition metal oxidants

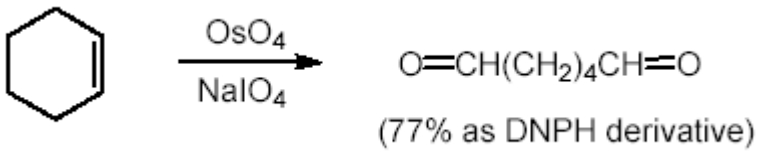
a) $KMnO_4$ / $NaIO_4$

- Form carboxylic acids



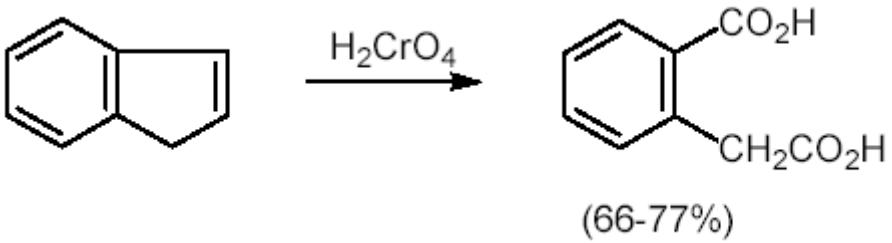
b) Lemieux-Johnson modification (OsO_4 / $NaIO_4$)

- Form aldehydes (no over oxidation)

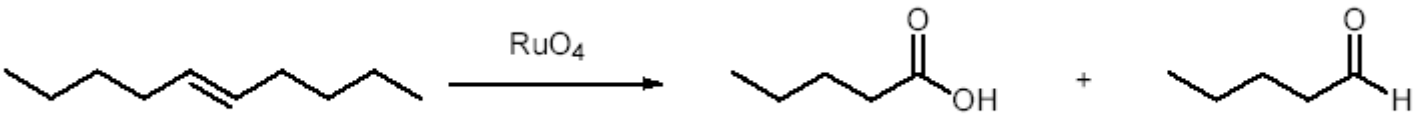


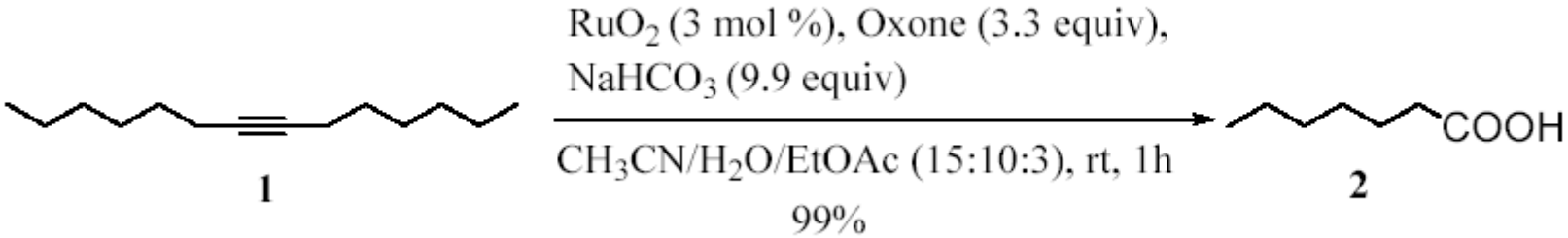
c) H_2CrO_4

- Form carboxylic acids



d) RuO_4 ($RuCl_3$ or RuO_2 / $NaIO_4$)





Reduction Reactions

I. Heterogeneous Catalytic Hydrogenation

II. Homogeneous Catalytic Hydrogenation

III. Group III Hydride Donor Reagents ($LiAlH_4$, $NaBH_4$)

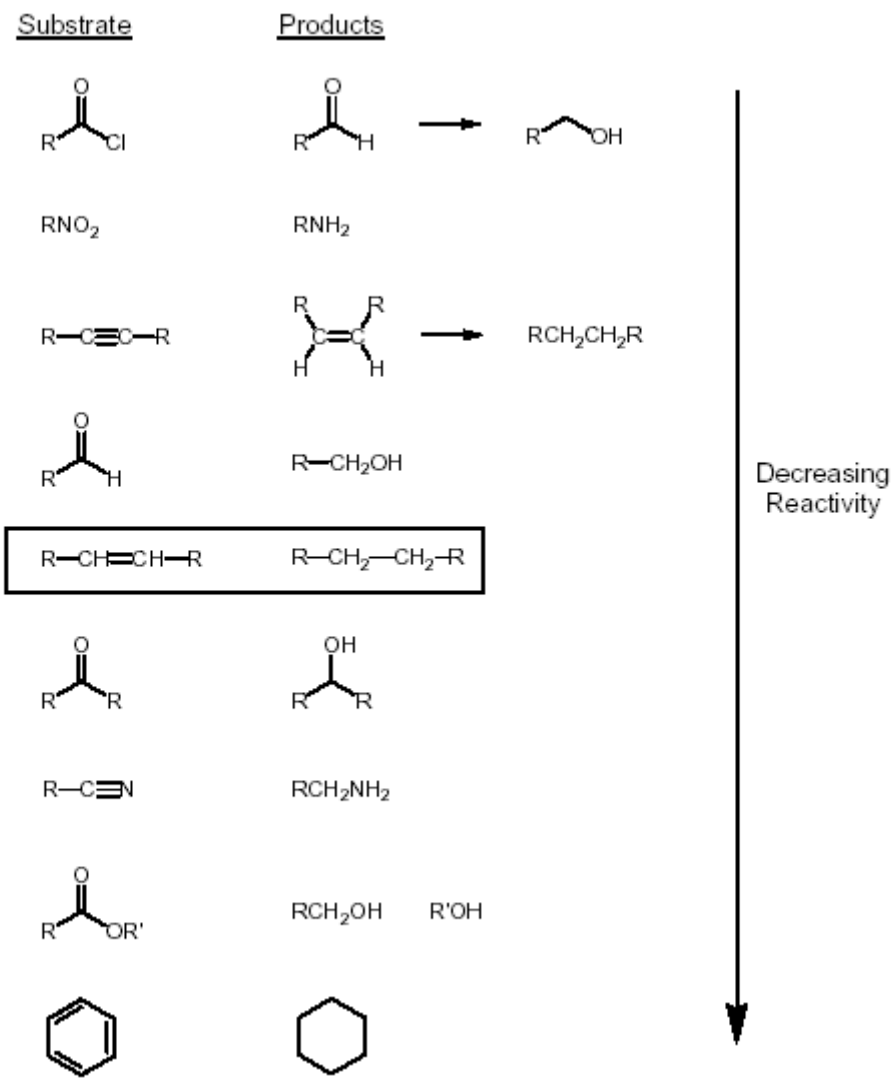
IV. Neutral Group IV Reducing Reagents (B_2H_6, AlH_3)

V. Chiral Reducing Agents

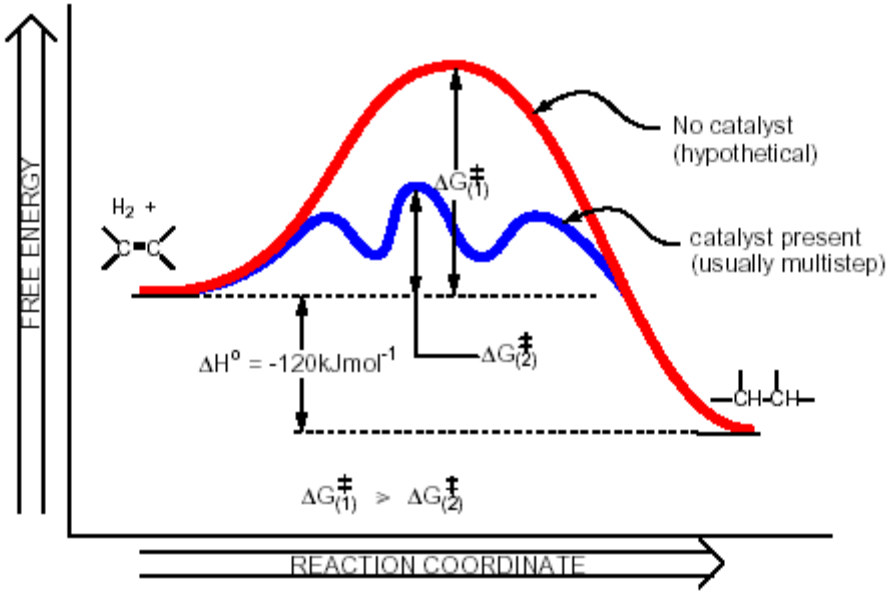
VI. Chemoselective 1,2- and 1,4-reductions

I. Heterogeneous Catalytic Hydrogenation

A. Approximate order of substrate reactivity in heterogeneous catalytic hydrogenatio



B. Catalysts:



1. Reactivity of hydrogenation catalysts (to C=C):
   Pd > Rh >Pt > Ni > Ru

2. The most common catalysts:
   a. **Palladium on charcoal** (5% or 10% Pd/C)

   b. Platinum – **Adam's catalyst**, the actual catalyst Pt is generated *in situ* under the hydrogenation conditions.

$$PtO_2 + H_2 \longrightarrow Pt + H_2O$$

C. Solvents:

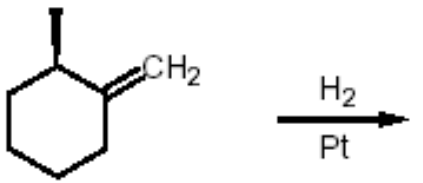
- Common solvents: Methanol (MeOH), ethyl acetate (EtOAc) and acetic acid (HOAc).
- Increasing the polarity of the solvent generally increases the activity of the catalyst.

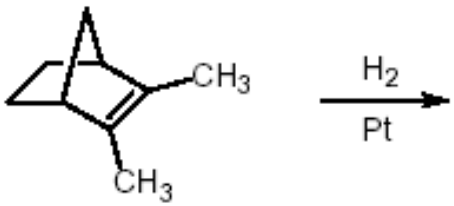
D. Pressure:

- Hydrogenation rate is proportional to pressure.
- High pressure – high reaction rate, but low selectivity.

E. Stereochemistry:

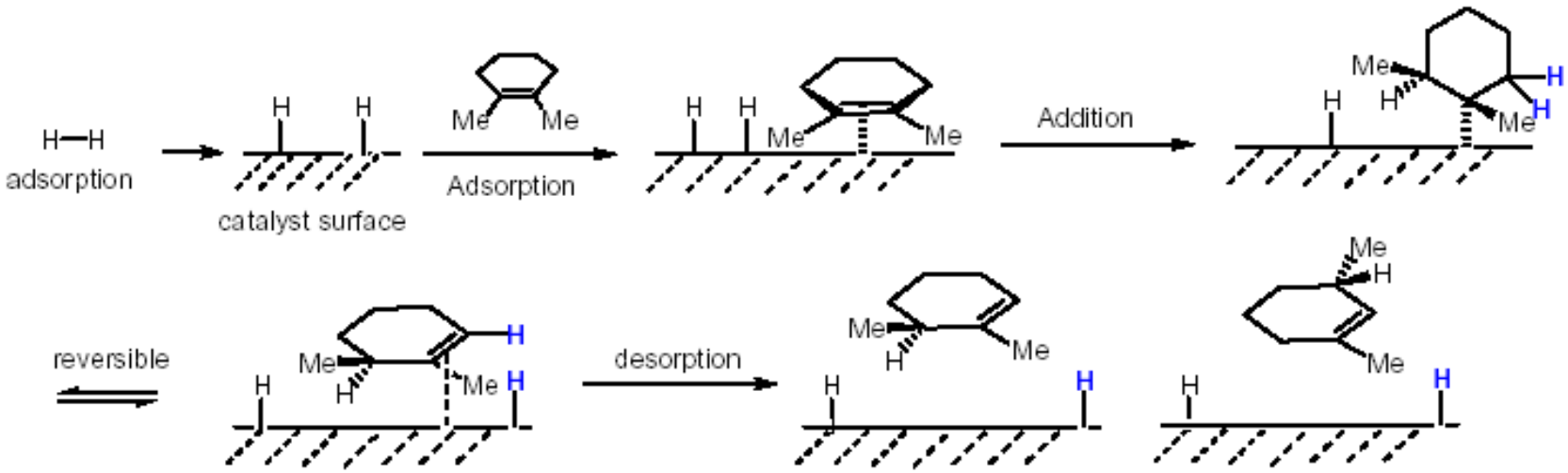
- Syn addition from the less hindered side:





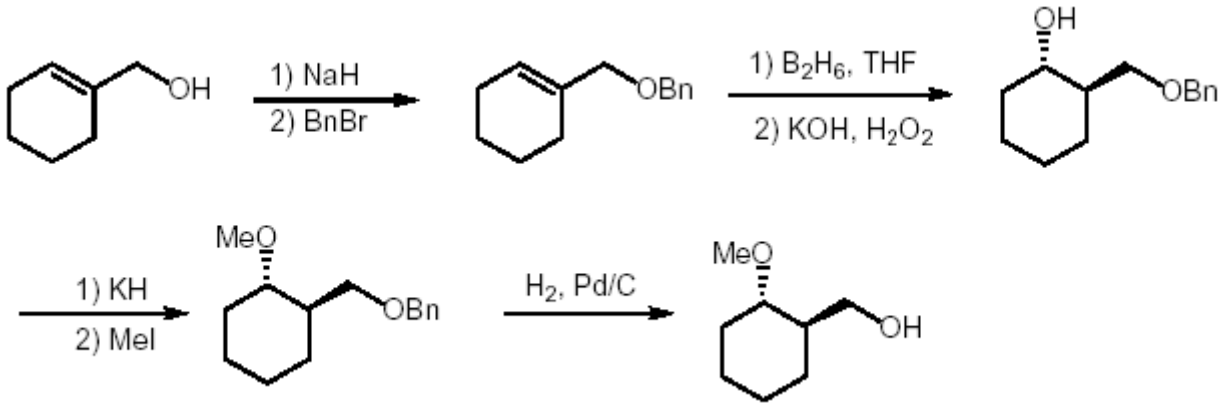
Mechanism: Why is it not perfect syn addition??

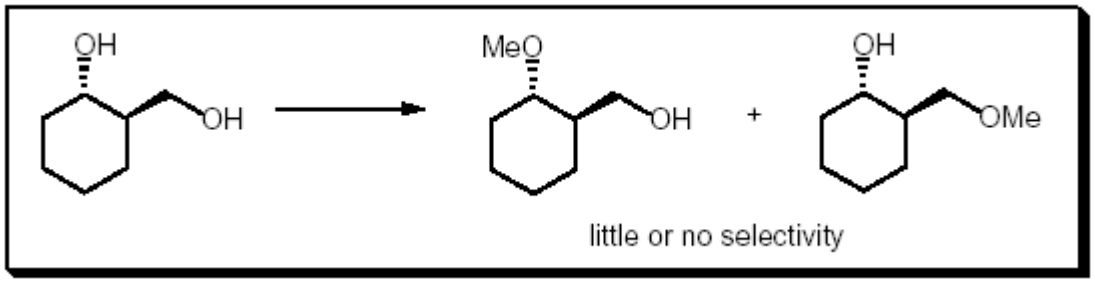
Stepwise addition from catalyst surface, and catalytic hydrogenation is reve



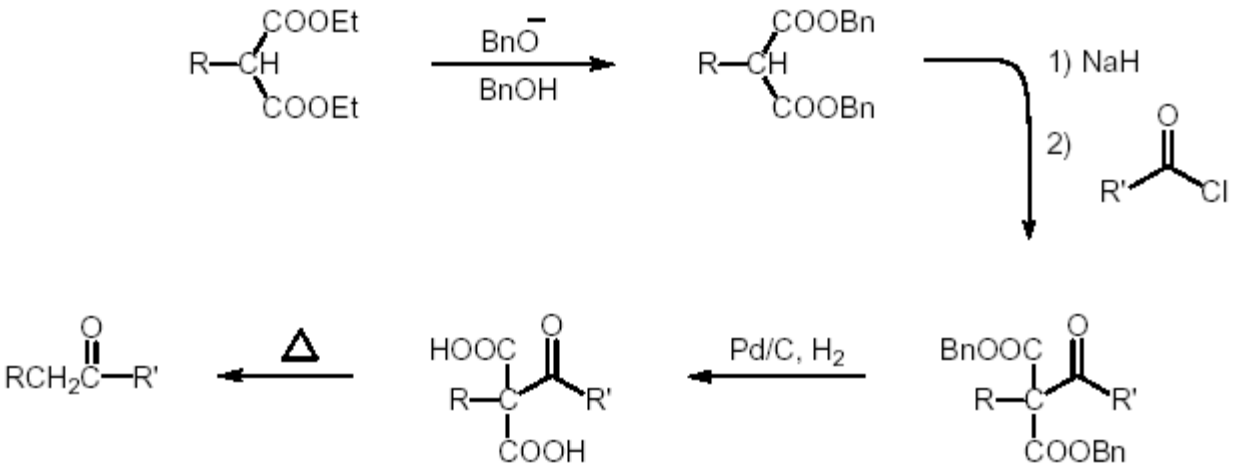
Applications of hydrogenolysis:

a) Benzyl groups can be used as a temporary protecting groups for alcohols and amin

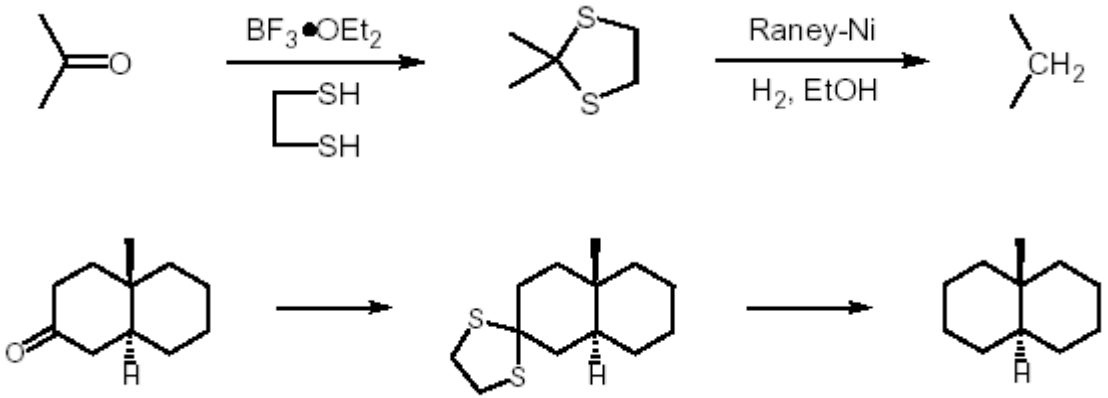




b) Benzyl esters can be used as temporary protecting groups for carboxylic acids. Deprotection occurs under neutral conditions.



c) Desulphurization: Conversion of C-S bonds to C-H bonds



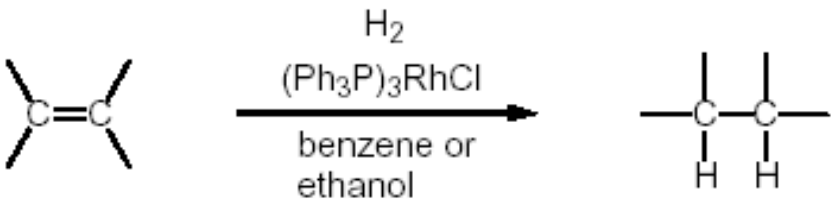
II. Homogenous Catalytic Hydrogenation

- Wilkinson's Catalyst: $(Ph_3P)_3RhCl$

Preparation:

$$RhCl_3 + Ph_3P \xrightarrow[\Delta]{EtOH} (Ph_3P)_3RhCl \downarrow$$

General reaction:



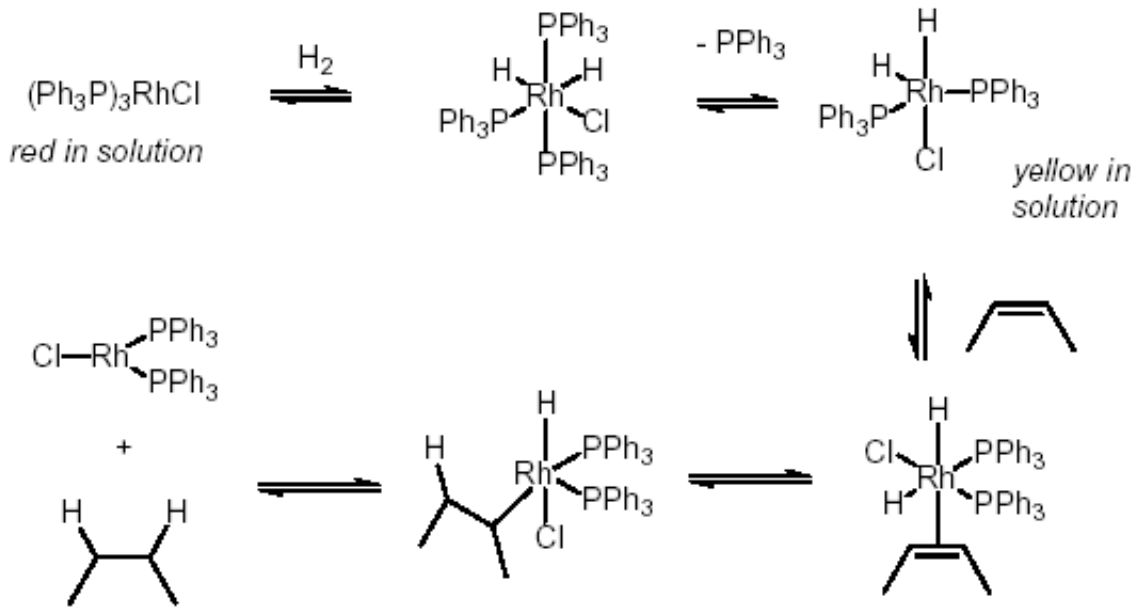
- Highly chemoselective for unhindered olefins:

Monosubstituted > disubstituted >>>> trisubstituted olefins

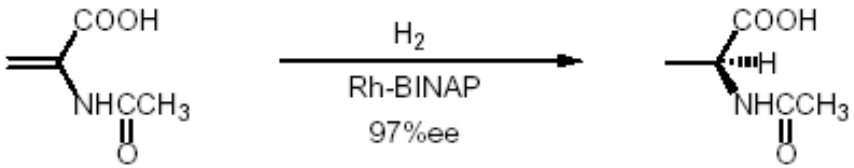
unreactive

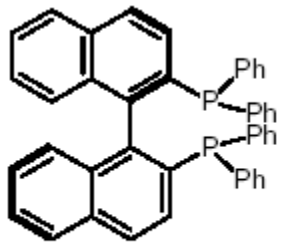
- Net syn addition.
- Compatible with sulphur containing functional groups.
- Can use chiral ligands for stereoselective hydrogenation.
- Selective for allylic alochols.

Mechanism:



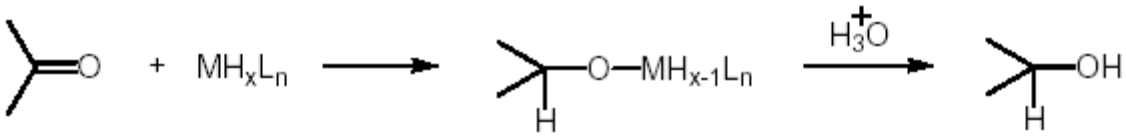
Examples:





(*R*)-BINAP

III. Group III Metal Hydride Donor Reagents (Boron and Aluminum)

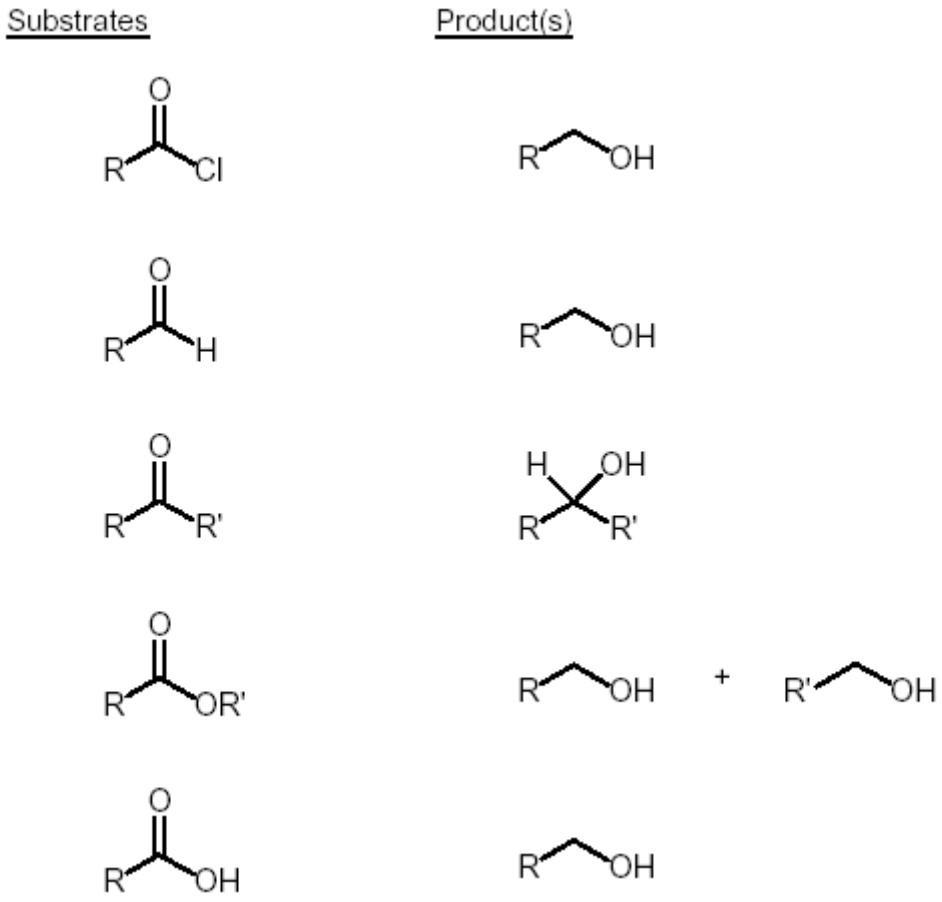


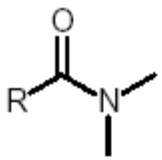
1) $LiAlH_4$ (lithium aluminum hydride, LAH)

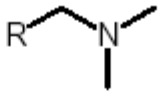
- A powerful reducing agent.
- Reactions are very exothermic.
- Reacts vigorously with water.
- Frequently causes fires. (Be careful with large-scale reactions)
- Used in anhydrous, aprotic solvents (diethyl ether, tetrahydrofuran [THF] or 1,2-dimethoxyethane)
- Hydrolysis of aluminum alkoxide salts can be difficult.
  - The formation of aluminum alkoxides which are insoluble under neutral conditions, traps products.

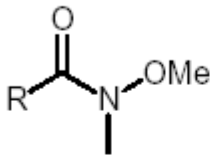
Reactions of LAH:

Reduction of carbonyl groups and other polarized multiple bonds.

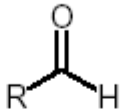


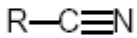


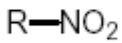


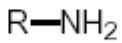


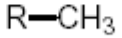
(a Weinreb amide)

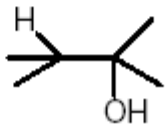




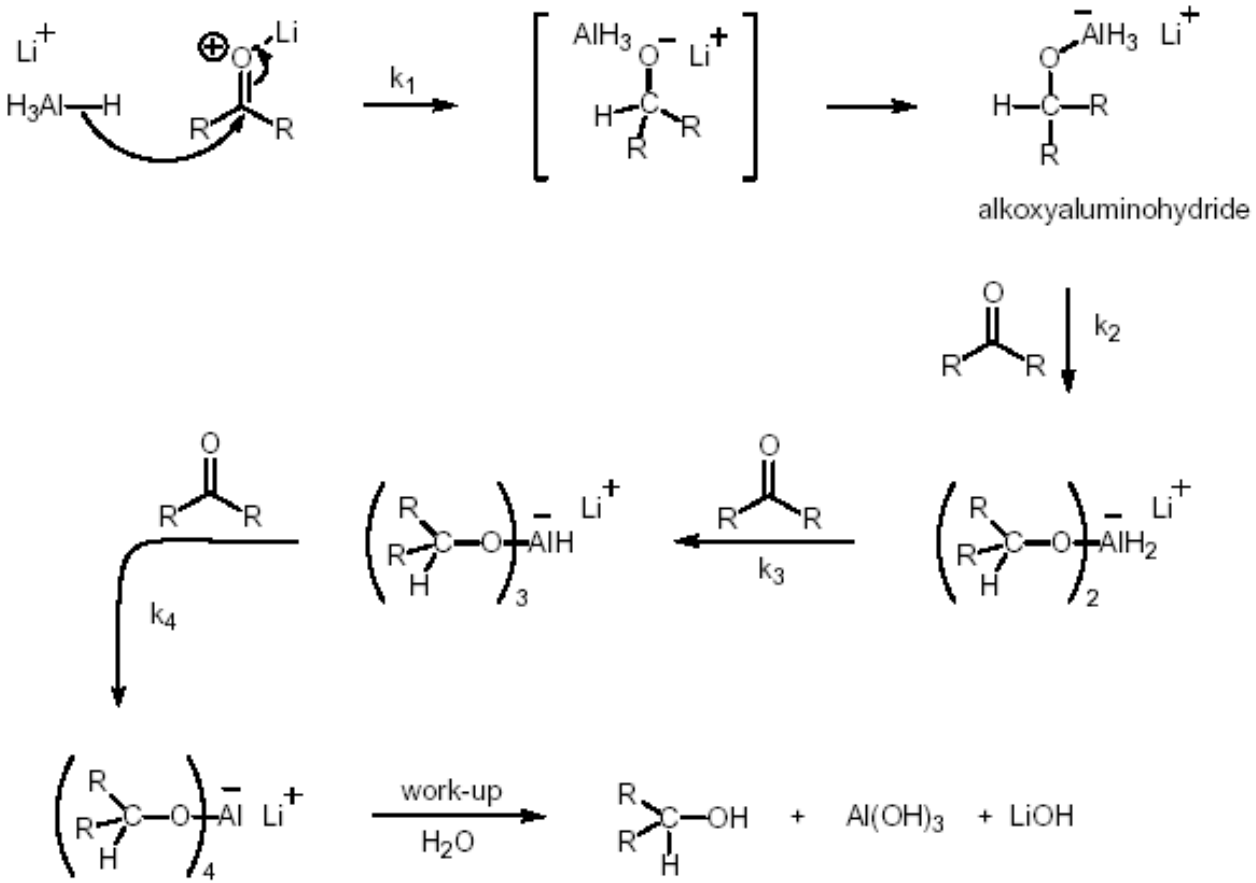




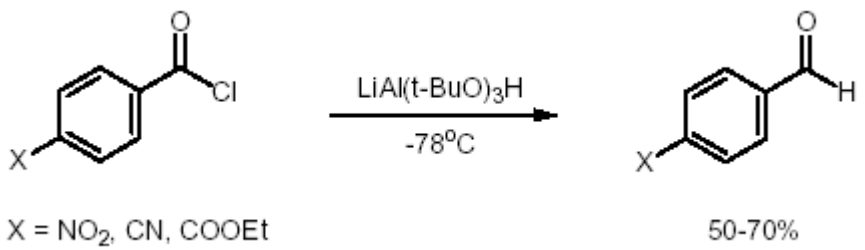




Mechanism of LAH reduction:

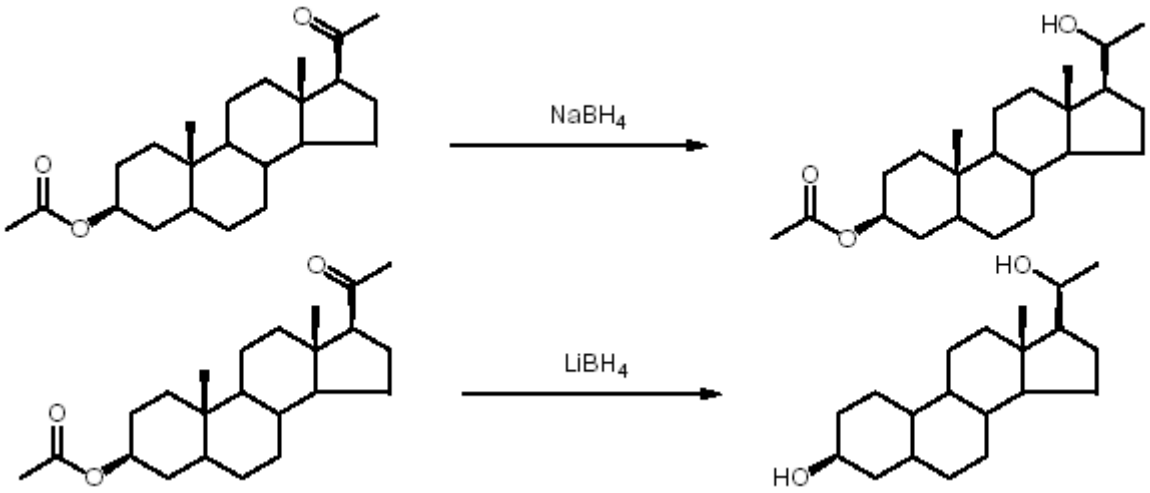


e.g.



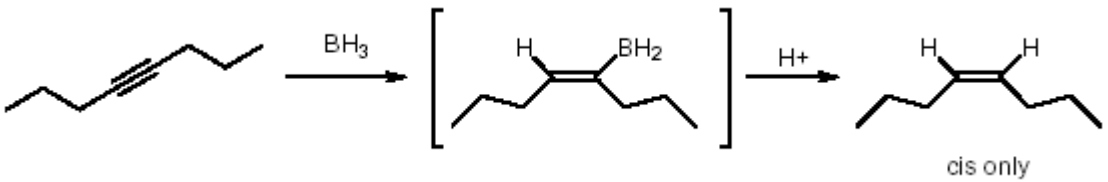
Sodium borohydride reduction:

- A milder reducing agent than LAH, therefore more chemoselective.
- $NaBH_4$ reduces ketones faster than α,β-unsaturated ketones.

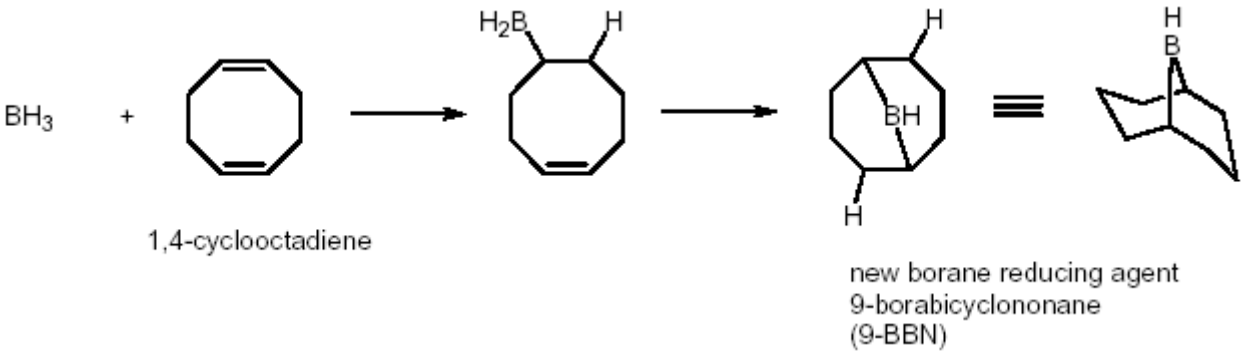


IV. Other group III metal reducing reagents:

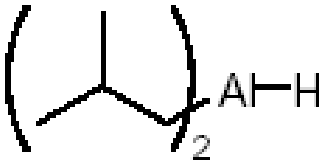
1) Diborane (B_2H_6) or Borane (BH_3·THF or BH_3·Me_2S)

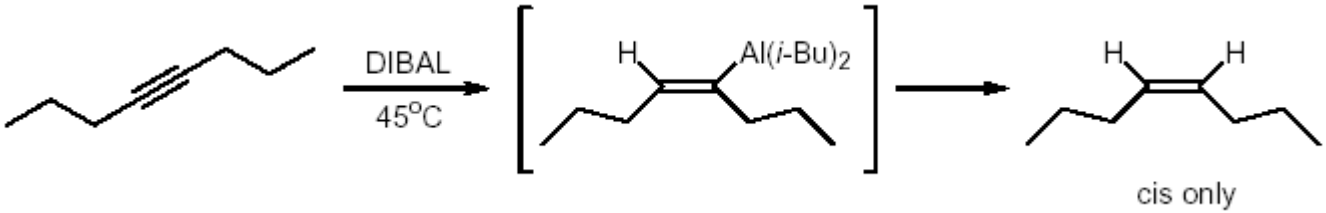


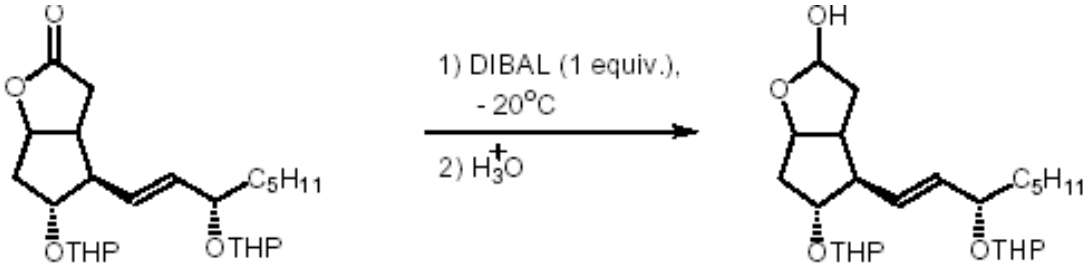
2) Complex boranes

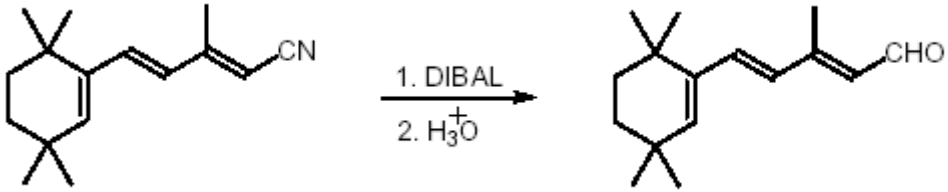


3) Diisobutylaluminium hydride (DIBAL or DIBAL-H or DIBAH)



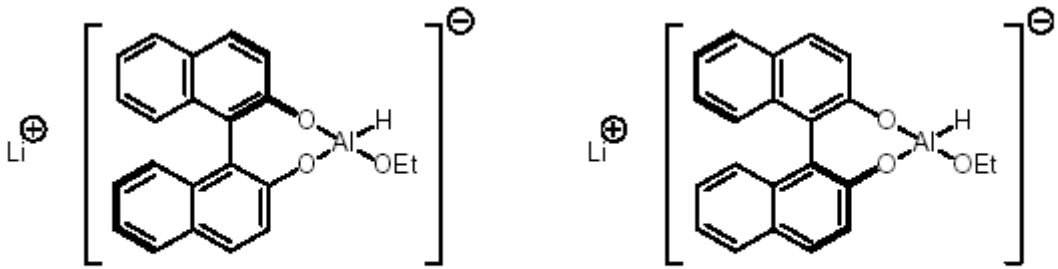






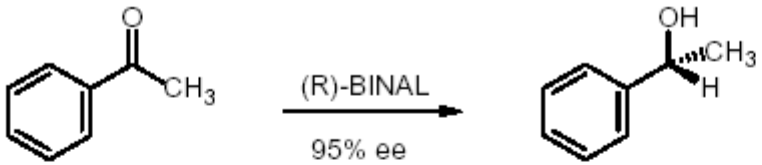
V. Chiral Reducing agents for asymmetric reduction

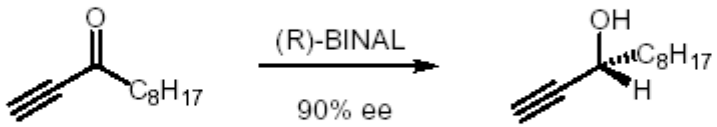
a) (*R*)- or (*S*)-BINAL-H

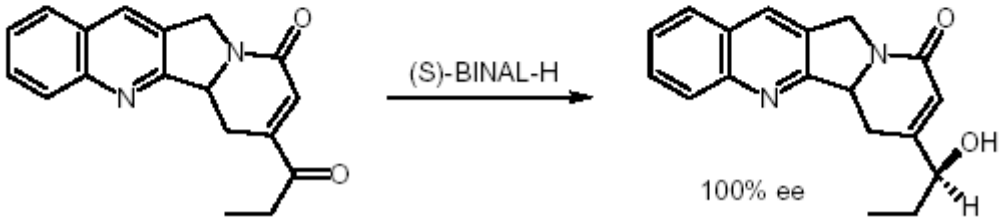


(R)-BINAL-H (S)-BINAL-H

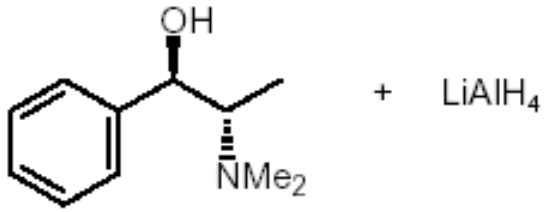
Examples:



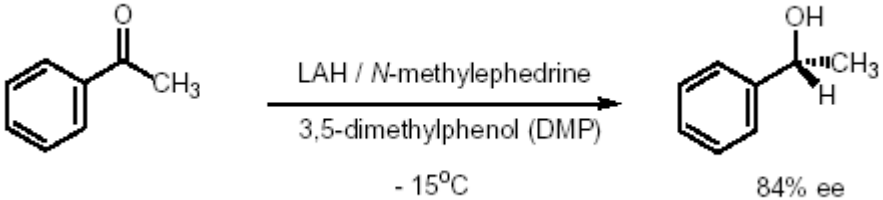




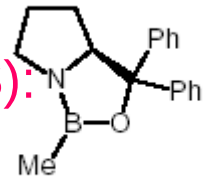
Chiral amino alcohol ligands for the preparation of chiral LAH *in situ*.

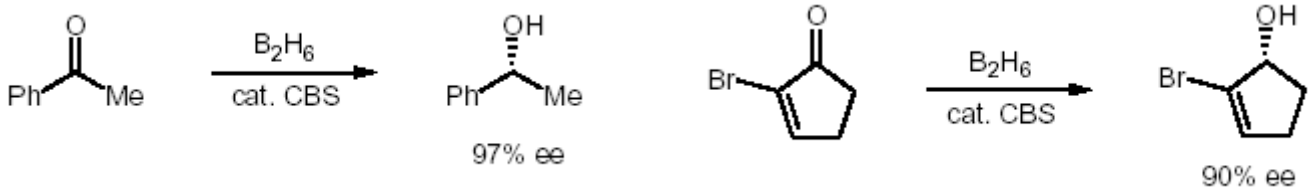


(-)-N-methylephedrine



Borane reduction in the presence of chiral catalyst(CBS):





VI. Selectivity: 1,2 vs. 1,4 (conjugate) reduction.