Organic Chemistry CH-401 Course

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Oxidation

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Oxidation

Oxidation is one of the most important & useful reactions in chemistry

Most of the chemicals are obtained by the oxidation of petrochemicals

Definition:

Inorganic Chemists & Organic Chemists differ in defining oxidation

Inorganic Chemists:

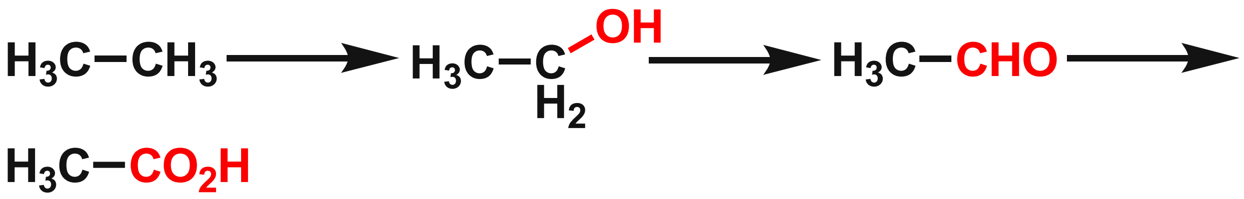
(1) Loss of electrons
(2) Increase in oxidation number

Organic Chemists:

The same rules can not be applied because

(1) Mechanisms of most of the oxidation reactions do not involve a direct electron transfer
(2) It is also not possible to apply oxidation number uniformly

Addition of oxygen



Replacement of hydrogen atom bonded to carbon with another, more electronegative element like oxygen

Elimination of hydrogen

Oxidation: Definition & Classification

Simplest Definition

Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen

The reverse is true for reduction

There is no oxidation without a concurrent reduction.

In organic chemistry, oxidation means organic substrate is oxidized

Reagents Based Classification

1. Metal based
2. Non-metal based

Substrates Based Classification

1. At Single carbon

   Alcohols to aldehydes to ketones

2. Vicinal Carbon

   Alkenes to diols, epoxides, ozonolysis

3. Hetero atom

   Oxidation of sulfur, nitrogen

4. Unfunctionalized Carbon atom

Oxidation

Metal Based Oxidation

Chromium based oxidation

Manganese based oxidation

Ruthenium based oxidation

Osmium based oxidation

Molybdenum based oxidation

Lead based oxidation

Titanium based oxidation

Non Metal Based Oxidation

DMSO based Oxidation

Iodine based oxidation

Epoxidation

Baeyer Villiger oxidation

Lead based oxidation

Oxygen/Ozone based oxidation

Selenium based Oxidation

Metal Based Oxidation

Chromium Based Reagents

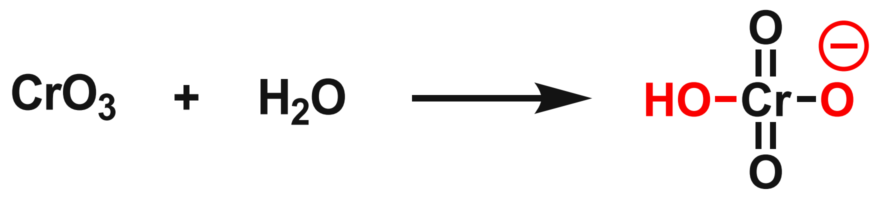
1. CrO_3
2. Jones reagent
3. PCC
4. PDC
5. Collins reagent
6. Chromyl chloride

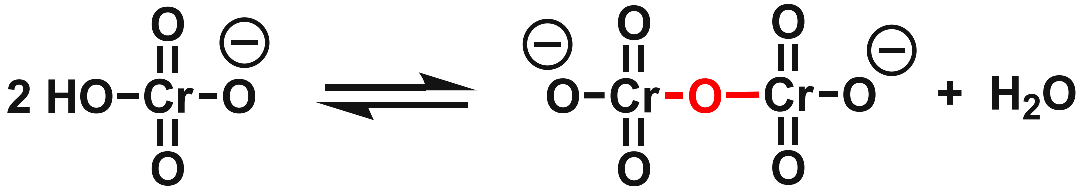
Reactivity & selectivity depends on the (1) Solvents & (2) Chromium ligands

Substantial selectivity can be achieved by choice of the particular reagent or conditions

The most widely employed transition metal oxidations are Cr(VI) based reagents

CrO3



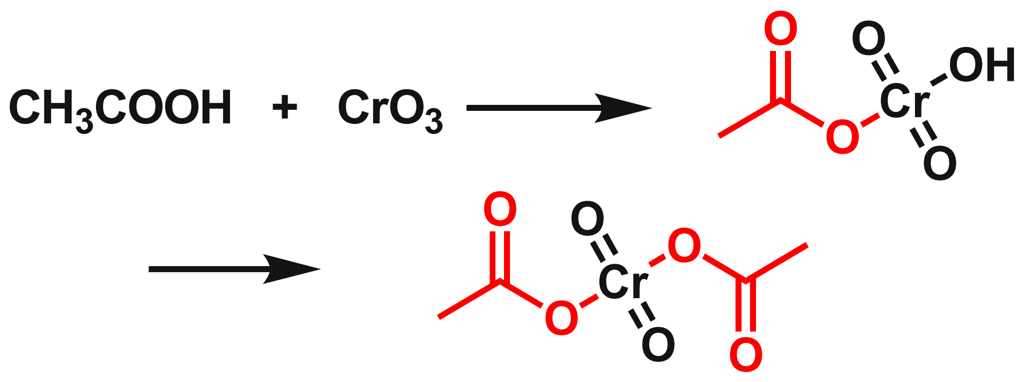


In dilute solution the chromate ion is present. As concentration increases the dichromate ion dominates

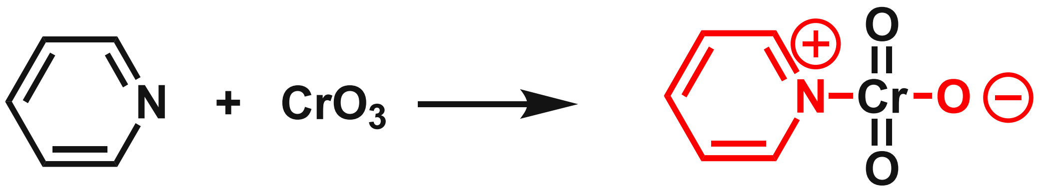
The extent of protonation of these ions depend on the *p*H

Chromium Trioxide

In **acetic acid**, CrO_3 exists as **mixed anhydride** of acetic acid & chromic acid

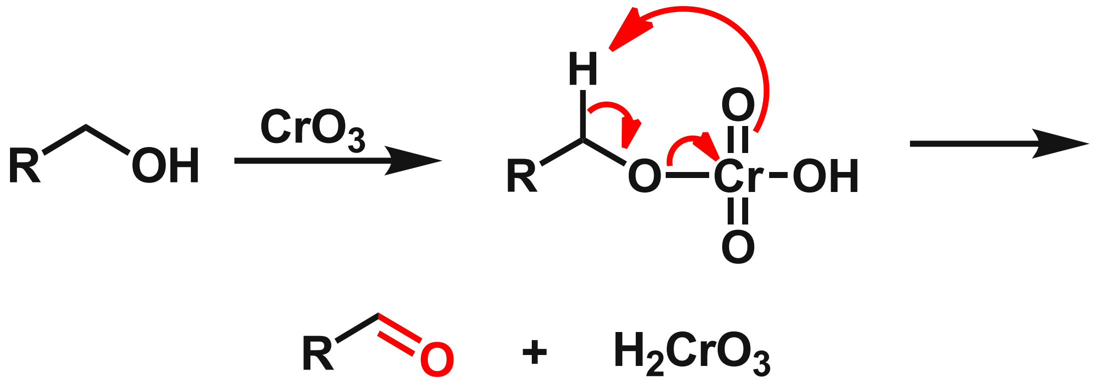


In **pyridine**, CrO_3 exists as an **adduct** involving Cr-N bond



Mechanism

The most common transformation effected on with Cr(VI) is the conversion of **alcohols into ketones or aldehydes**



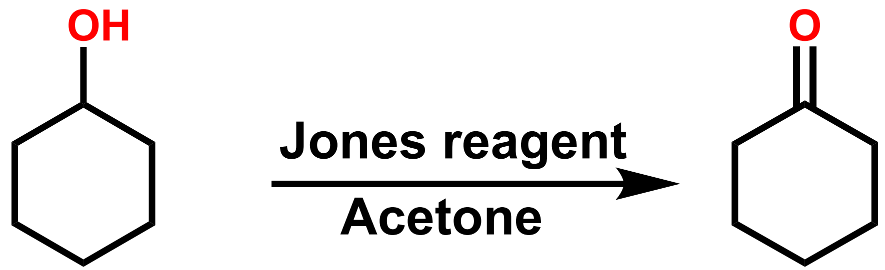
A variety of experimental conditions have been used for oxidation of alcohols by Cr(VI) on a synthetic scale

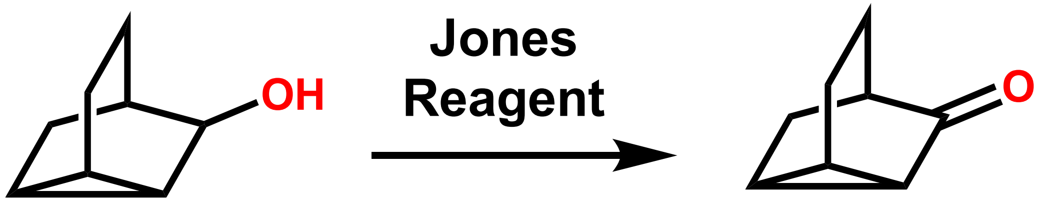
Jones Reagent

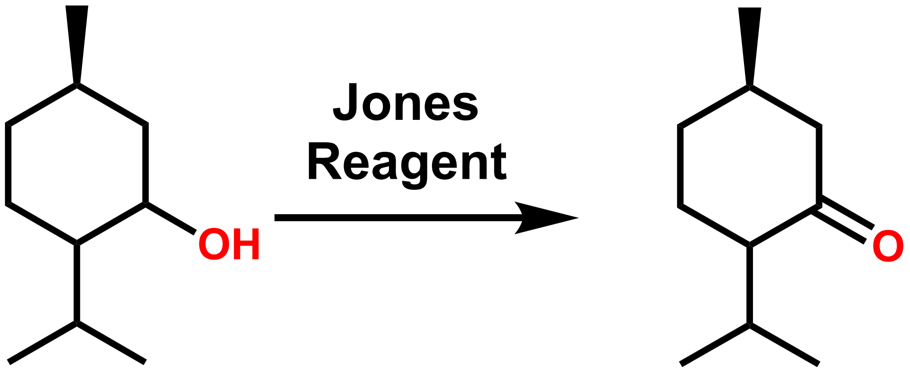
Jones Reagent: Acidic aqueous solution of chromic acid. Generally added to an acetone solution of the alcohol

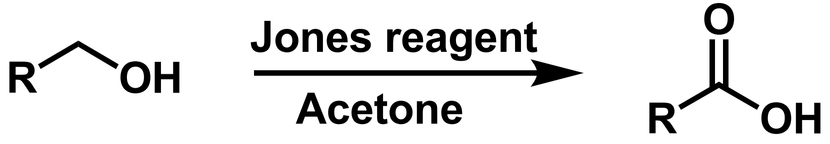
$$CrO_3 \; + \; H_2SO_4 \; + \; H_2O$$

Utility: Jones reagent can be used for oxidation of simple unfunctionalized secondary alcohols to ketones



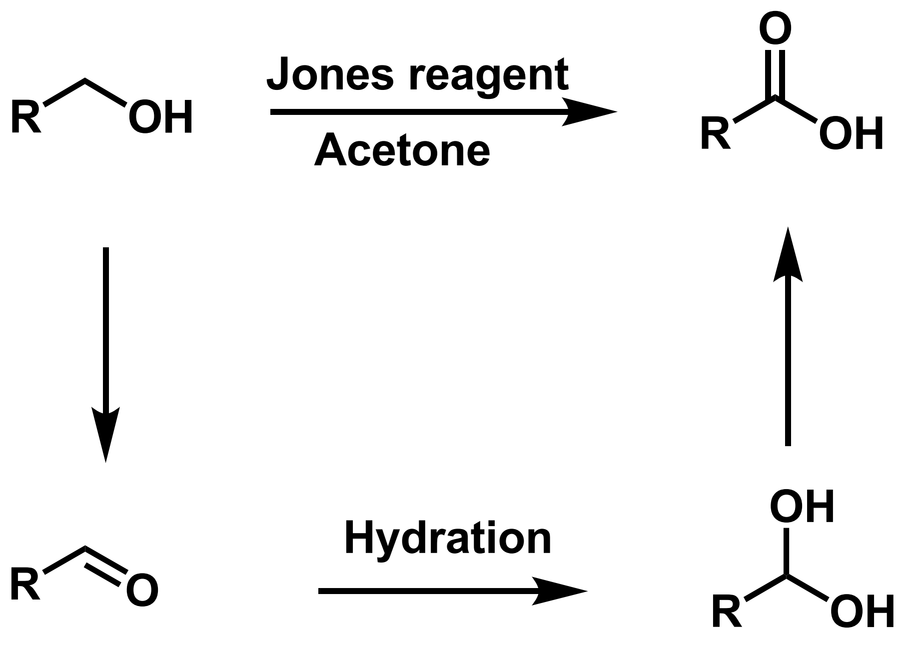






Jones Reagent

Saturated primary alcohols are oxidized to carboxylic acids



Advantages

(1) Cr(VI) ⟶ Cr(III)

Precipitate

Acetone can be decanted. Easy to work up

(2) Good reagent to oxidize primary alcohol to acid

Disadvantages:

(1) Not good for acid sensitive groups & compounds

(2) Under acidic condition dehydration may also take place

(3) Oxidation of primary alcohols can't be stopped at aldeh

CrO_3.2Pyridine (Collins reagent)

Preparation:

$$\underset{\text{(anh.)}}{CrO_3} + \underset{\text{(anh.)}}{\text{2 Pyridine}} \longrightarrow \underset{\text{(Solid)}}{CrO_3.\text{ 2pyridine}}$$

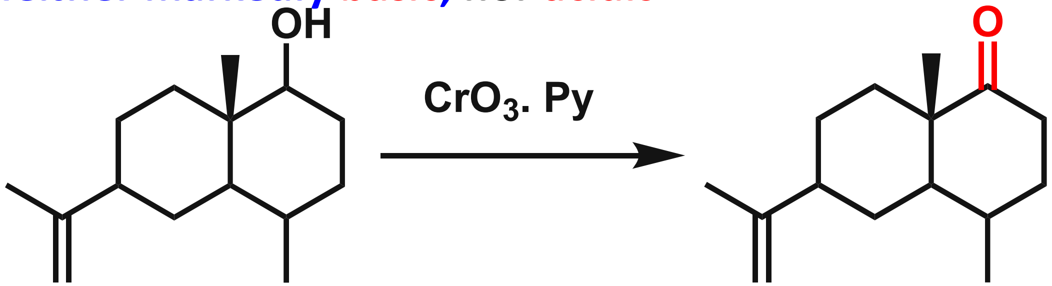
Uses:

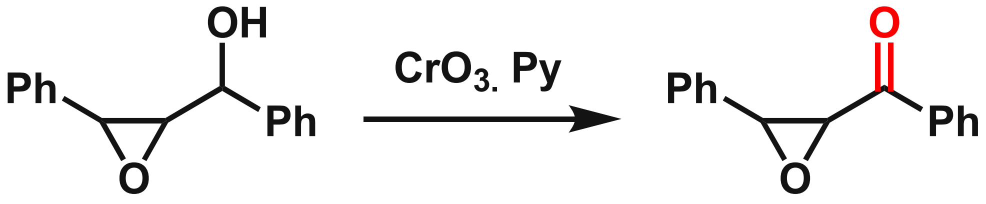
(1) Where other functional groups are susceptible to oxidation

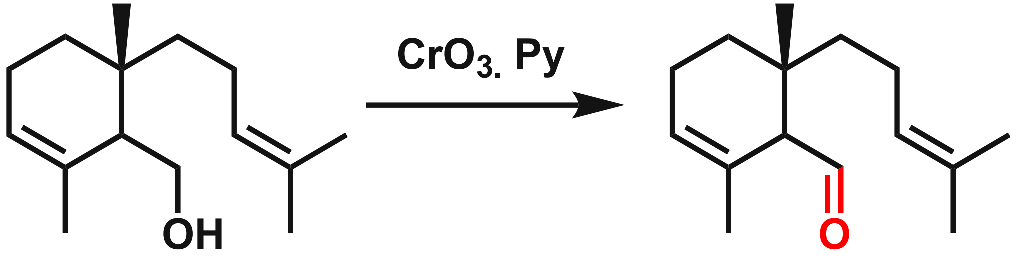
(2) When the molecule is sensitive to strong acid

(3) Primary & secondary alcohols are oxidized to aldehydes & ketones respectively in non-aqueous solution (Generally DCM was used) without over oxidation

(4) Neither markedly basic, nor acidic







The double bond did not migrate

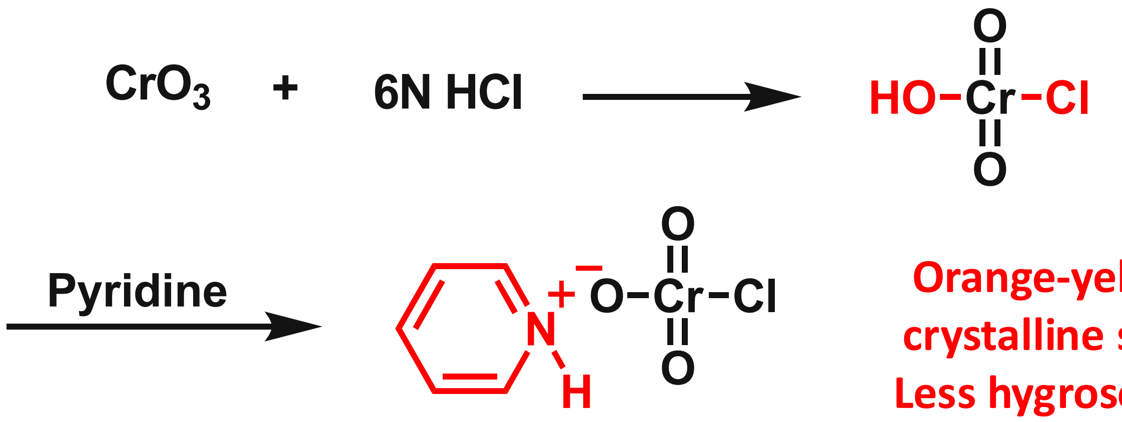
Disadvantages:

(1) Must use a large excess of the reagent

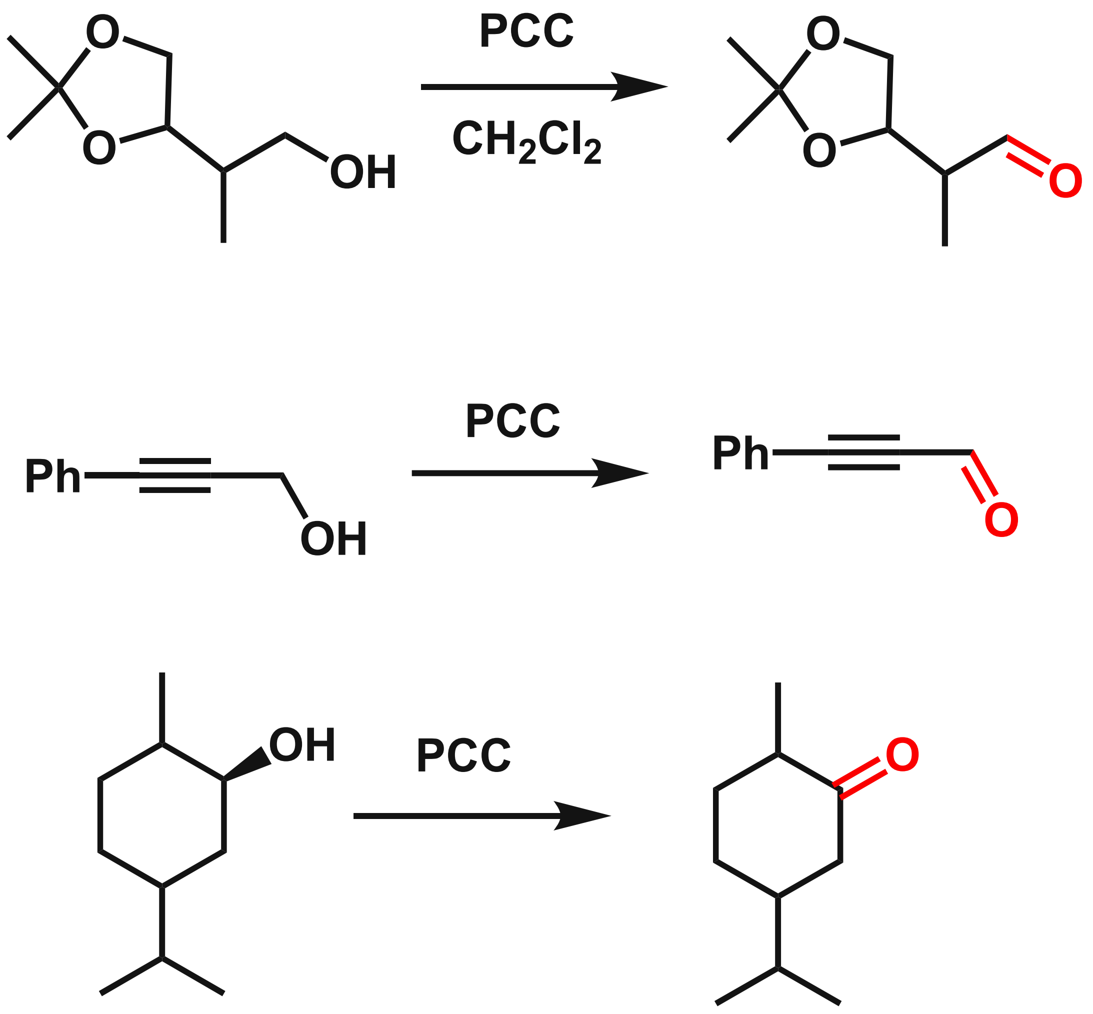
(2) It is moisture sensitive & loses its activity in aque
solution

Pyridinium Chlorochromate (PCC)

Preparation:



Orange-yellow crystalline solid, Less hygroscopic



Advantages

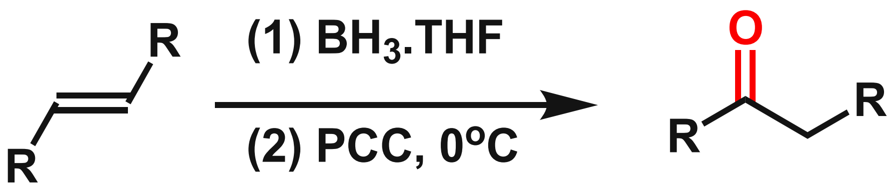
(1) Reagent can be used in stoichiometric amounts with substrate

(2) It is less hygroscopic. So, it can be stored for a long time

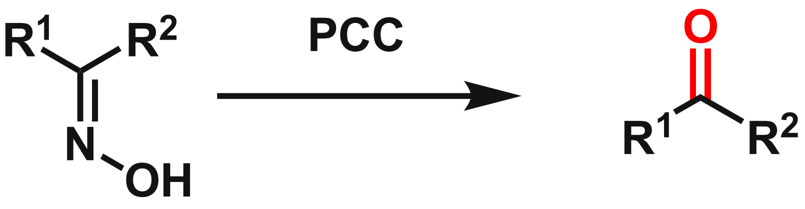
(3) PCC is slightly acidic, but can be buffered with NaOAc

Pyridinium Chlorochromate (PCC)

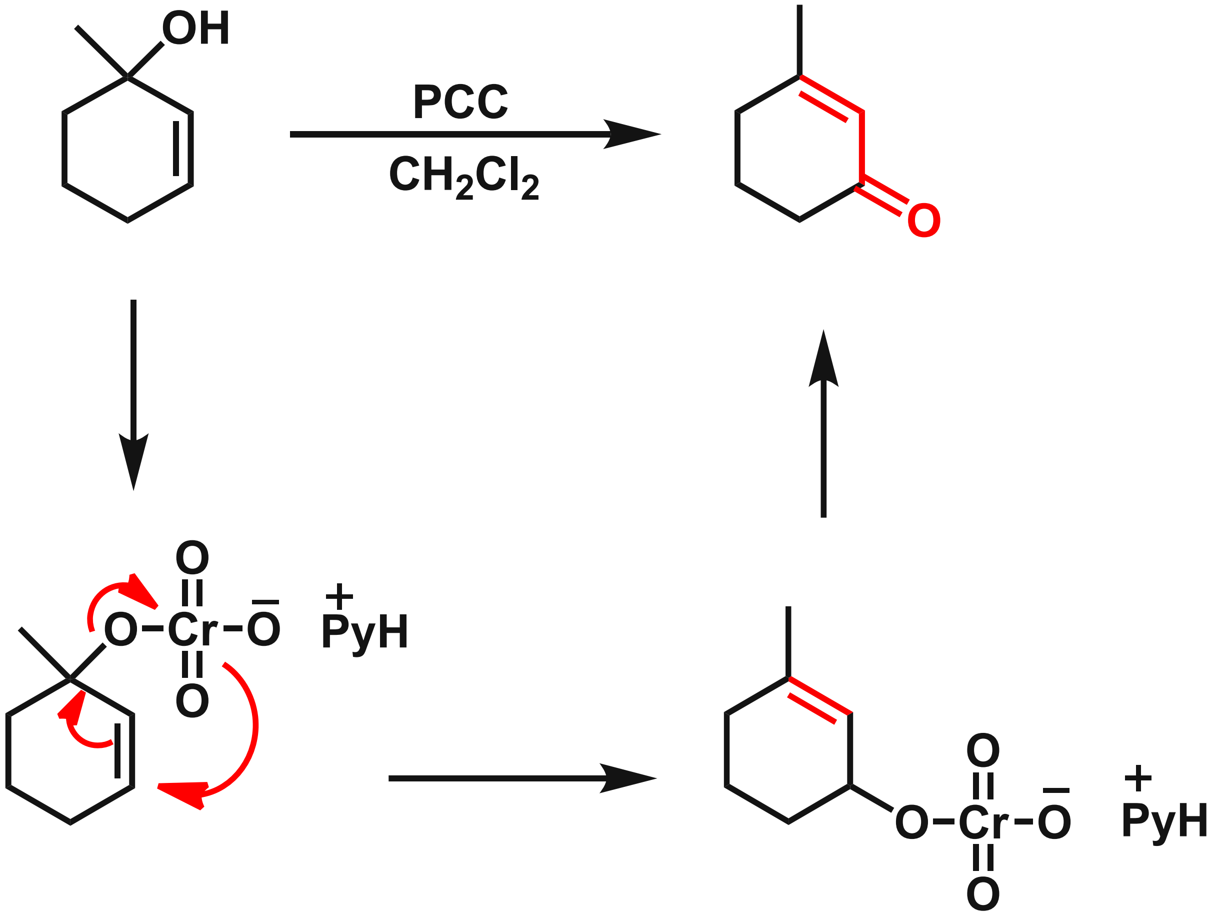
Oxidation of Organoboranes:



Deoximation:

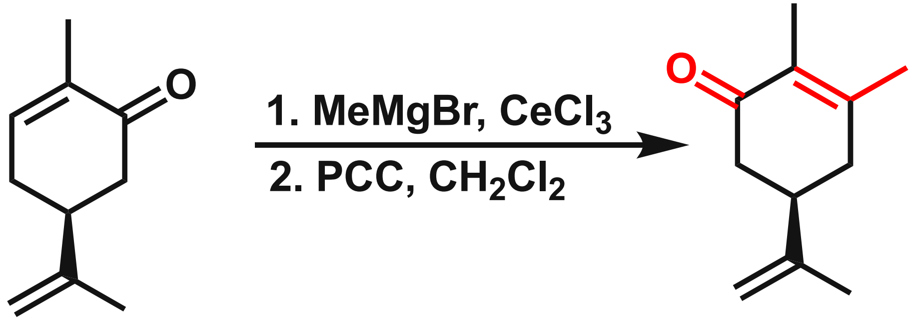


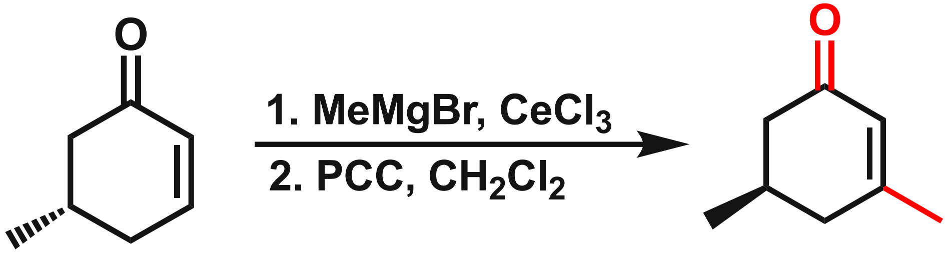
Oxidation of tertiary allylic alcohols:

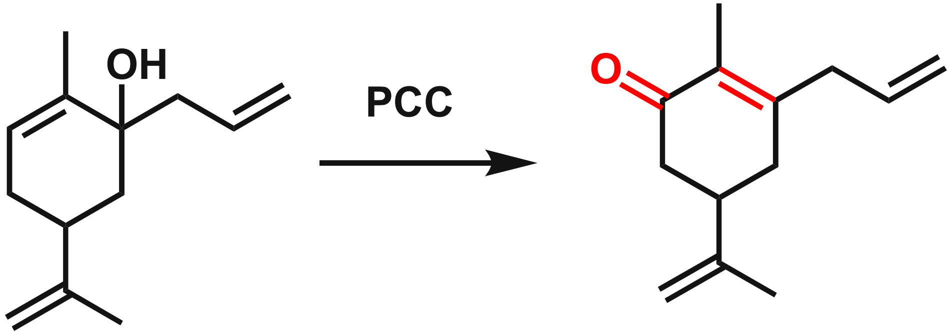


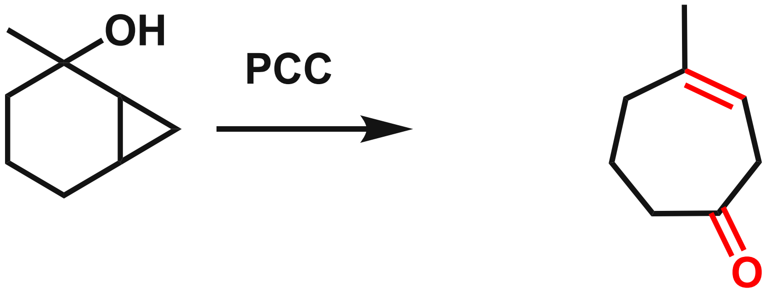
Pyridinium Chlorochromate (PCC)

Oxidation of tertiary allylic alcohols:

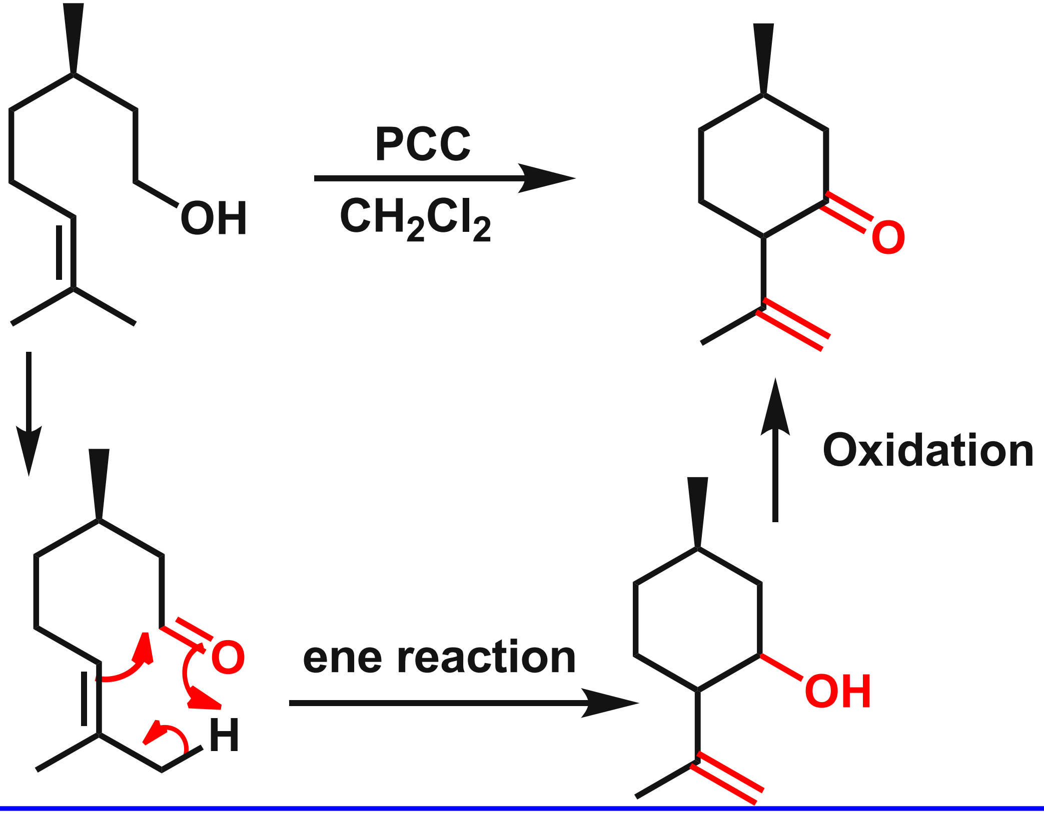




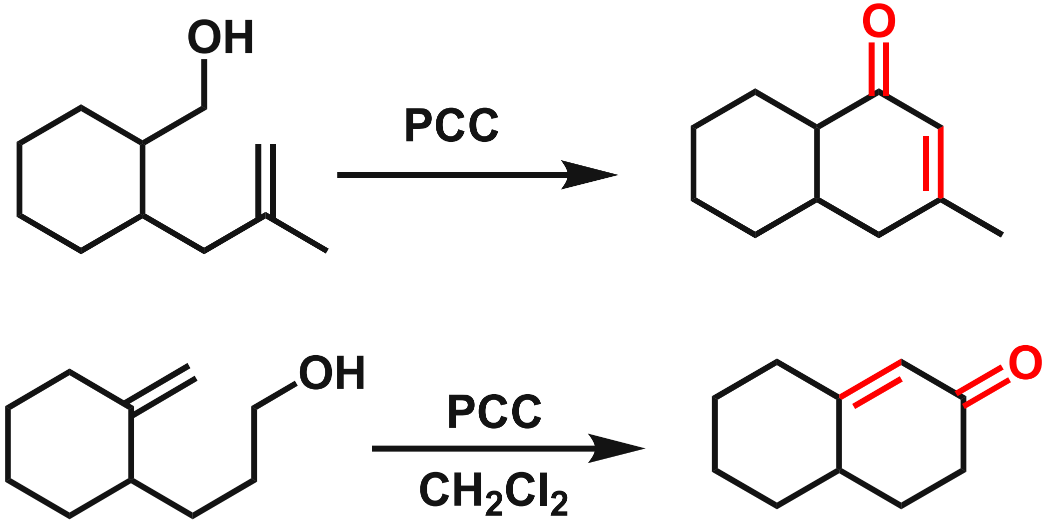




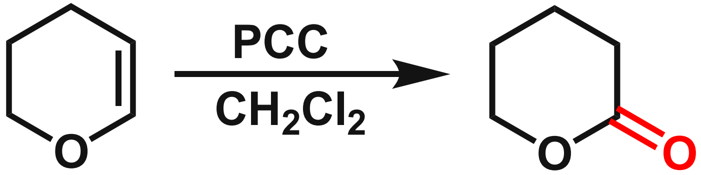
Oxidative cationic cyclization:

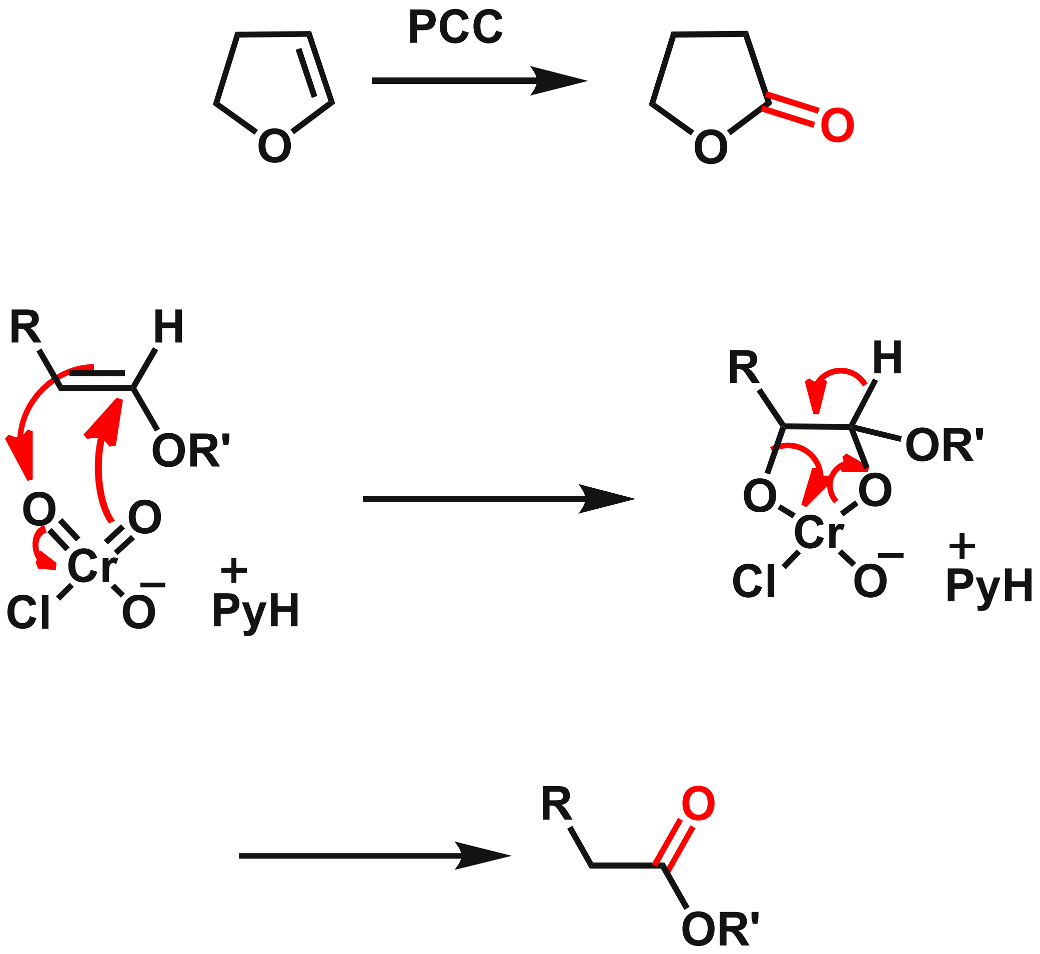


Oxidative cationic cyclization:



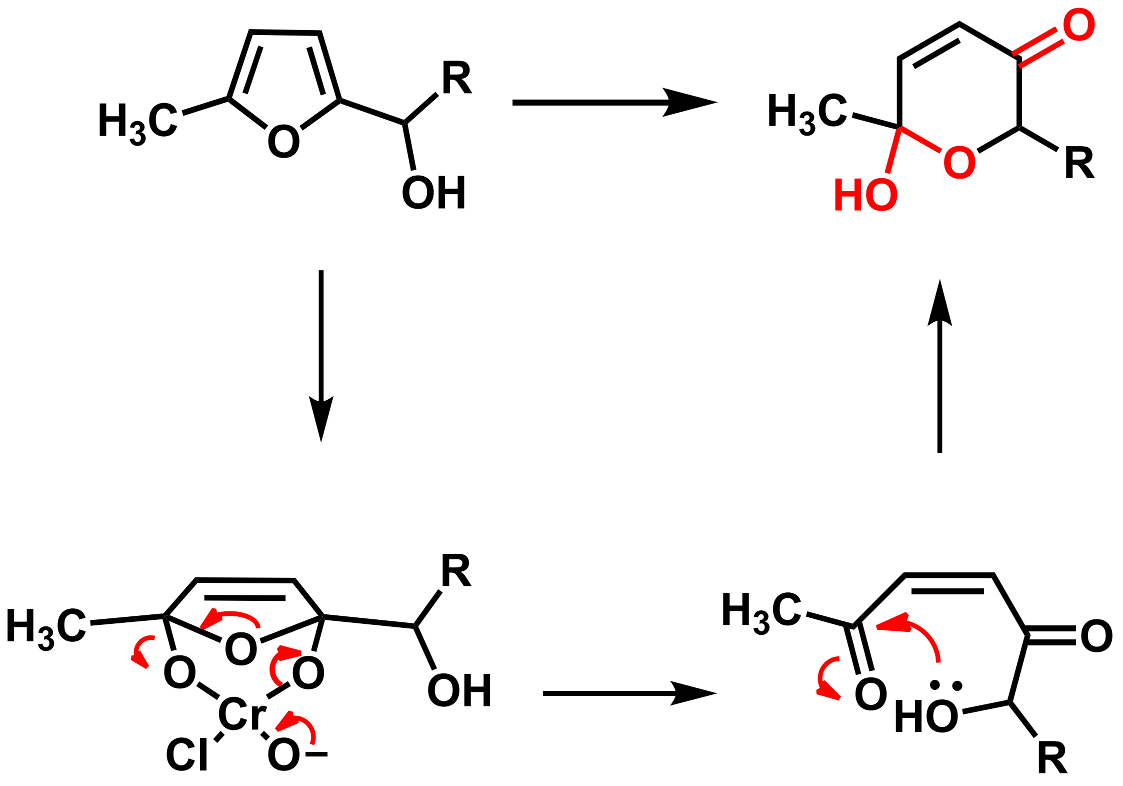
Oxidation of enol ethers to lactones:



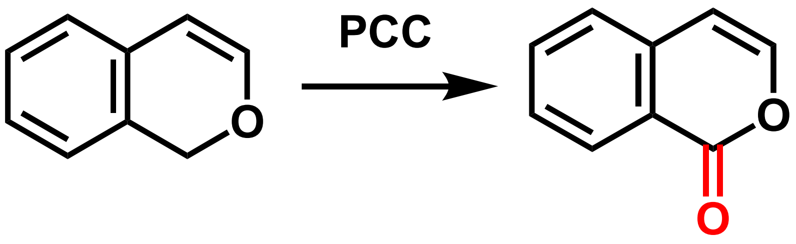


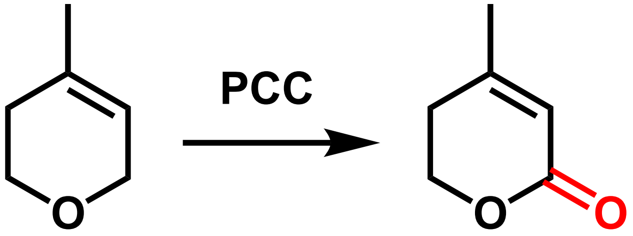
Pyridinium Chlorochromate (PCC)

Oxidation of furan ring system:



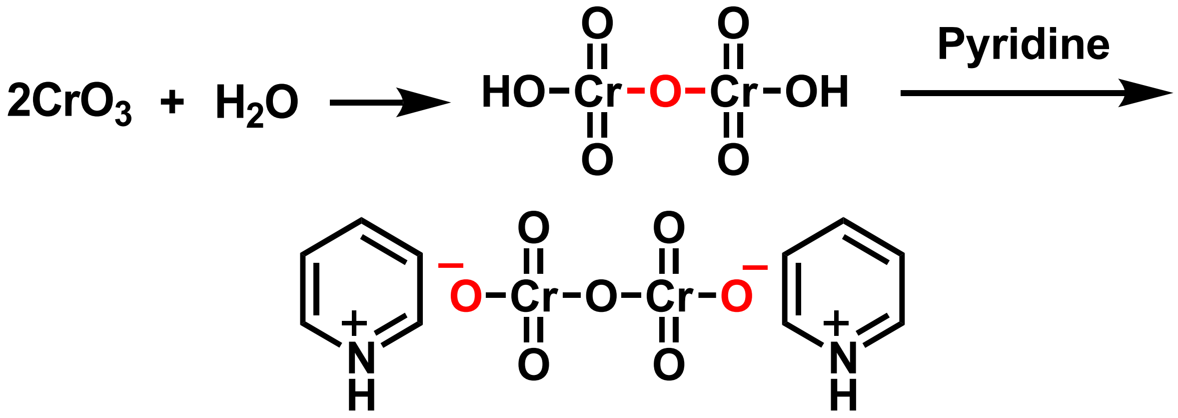
Oxidation of active methylene group:





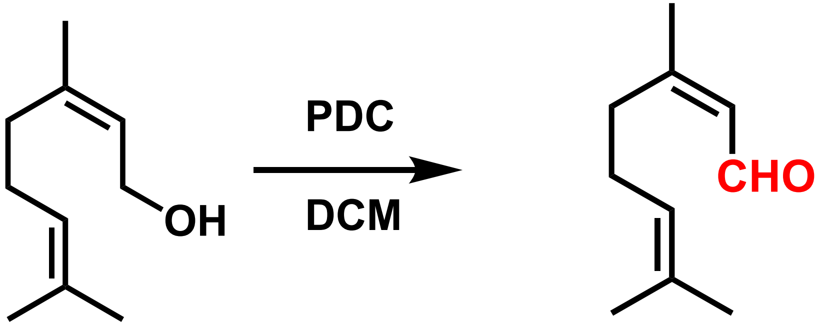
Pyridinium Dichromate (PDC)

Preparation:



Solubility:

Soluble in water, DMF, DMSO, dimethylacetamide. It is sparingly soluble in dichloromethane



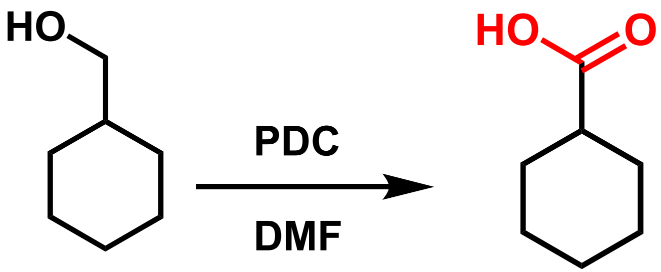
Advantages:

(1) Excellent reagent for oxidation of allylic alcohols

(2) There is no over-oxidation of aldehydes

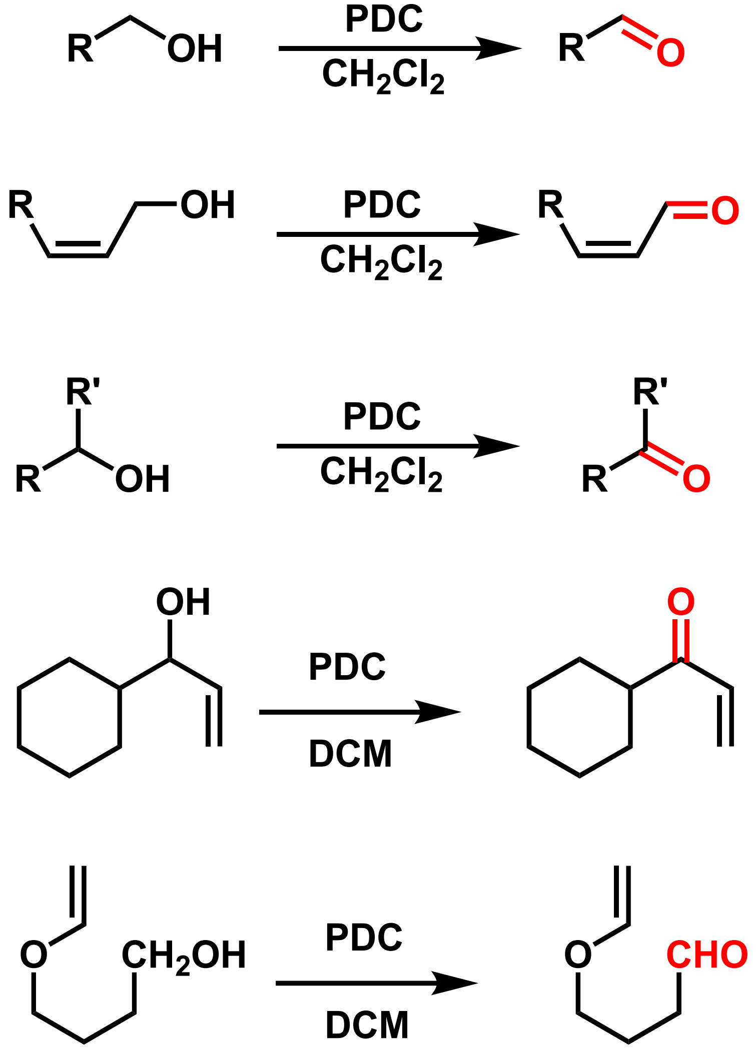
(3) No *E*/*Z*-isomerization

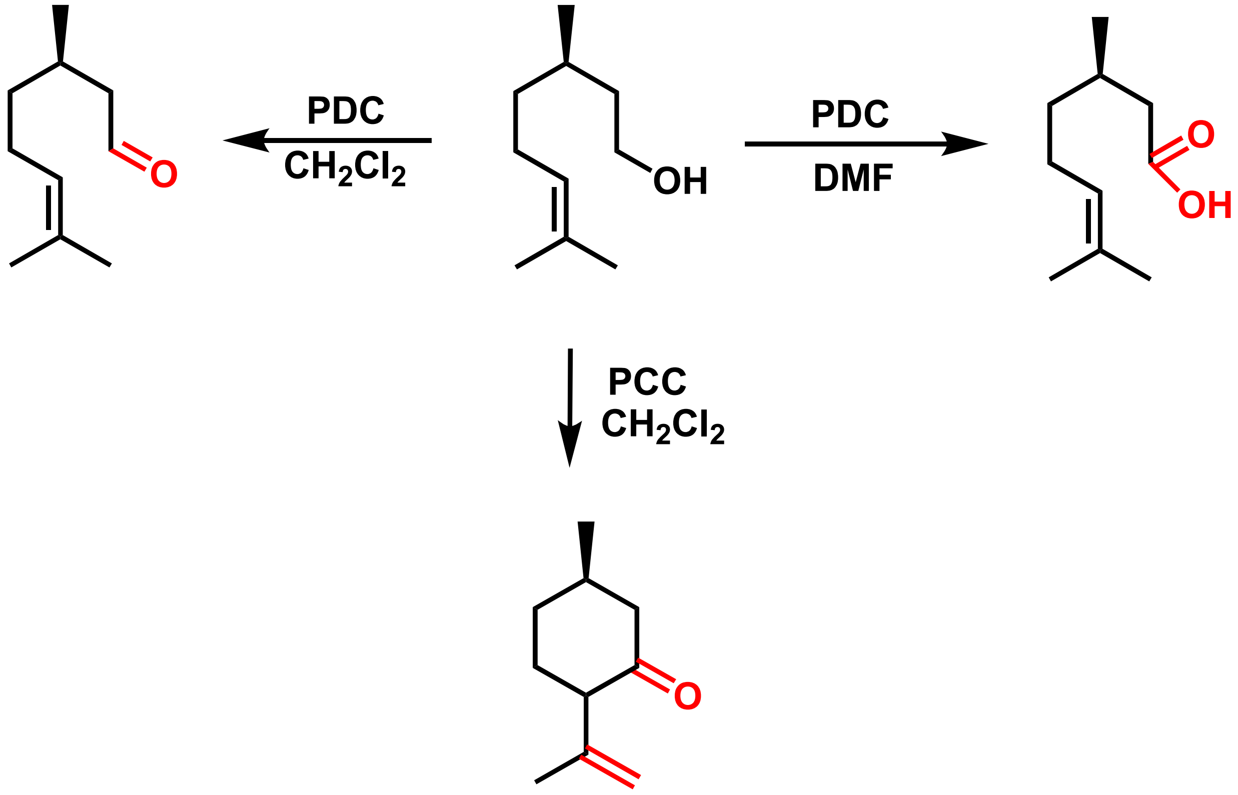
(4) Unlike conjugated aldehydes non-conjugated aldehydes are readily oxidized to acids by PDC in DMF at 25^{o}C



Pyridinium Dichromate (PDC)

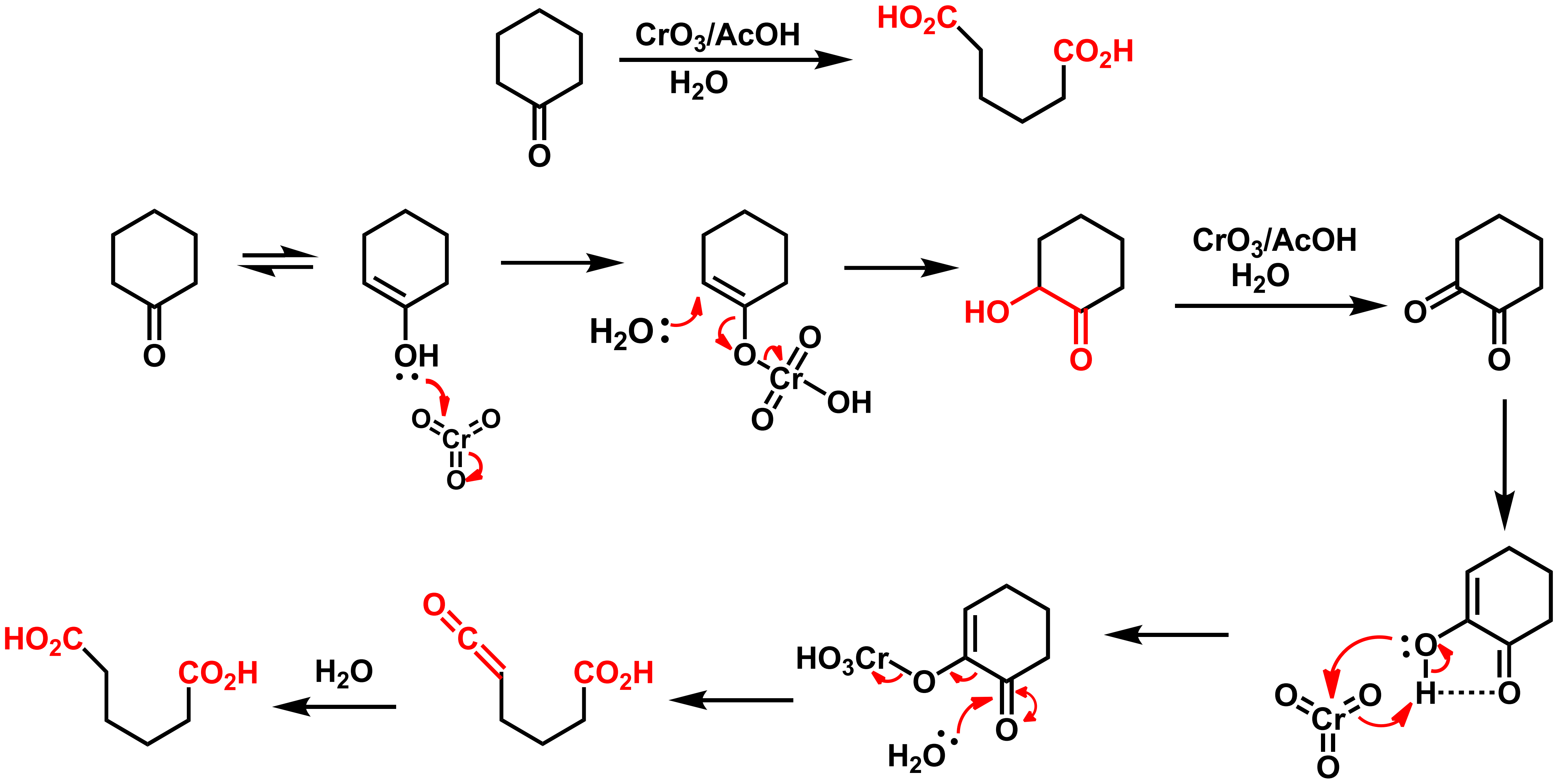
Utility:



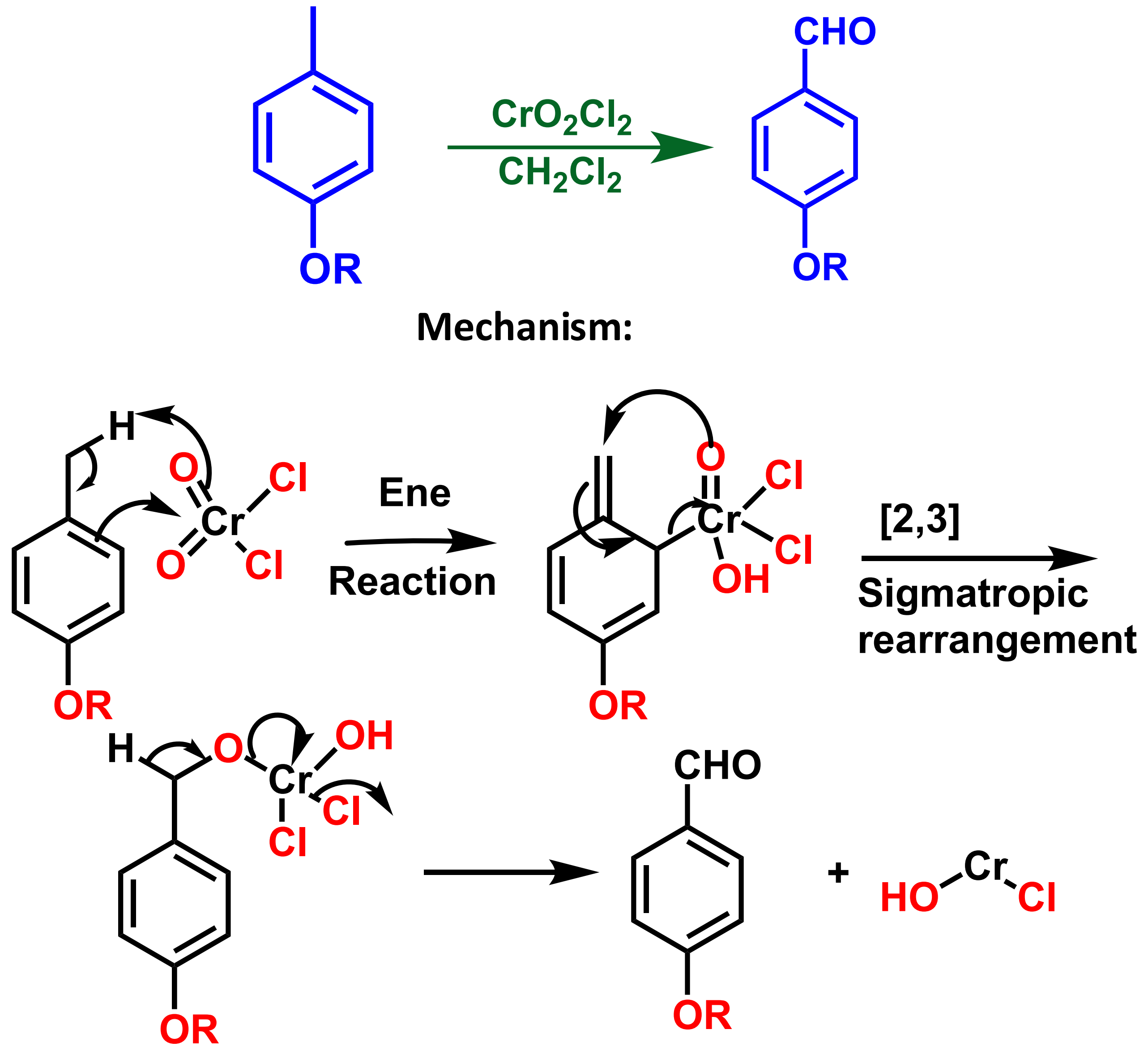


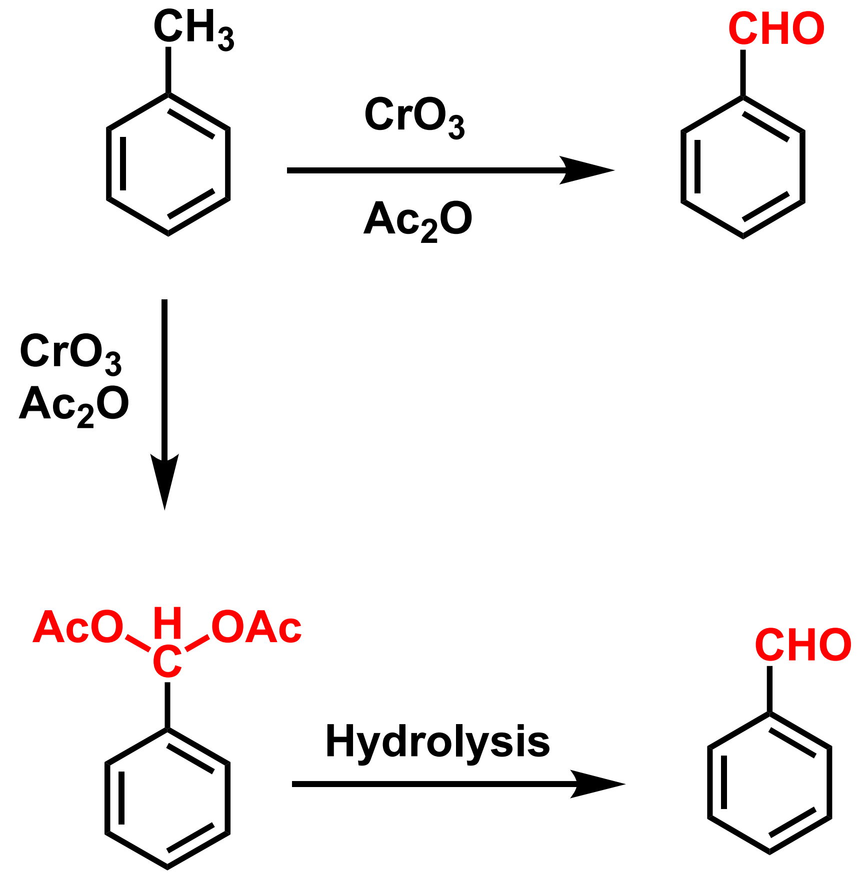
This reaction is complicated by the cationic cyclization when PCC was used

Chromium Based Oxidation



Etard Reaction

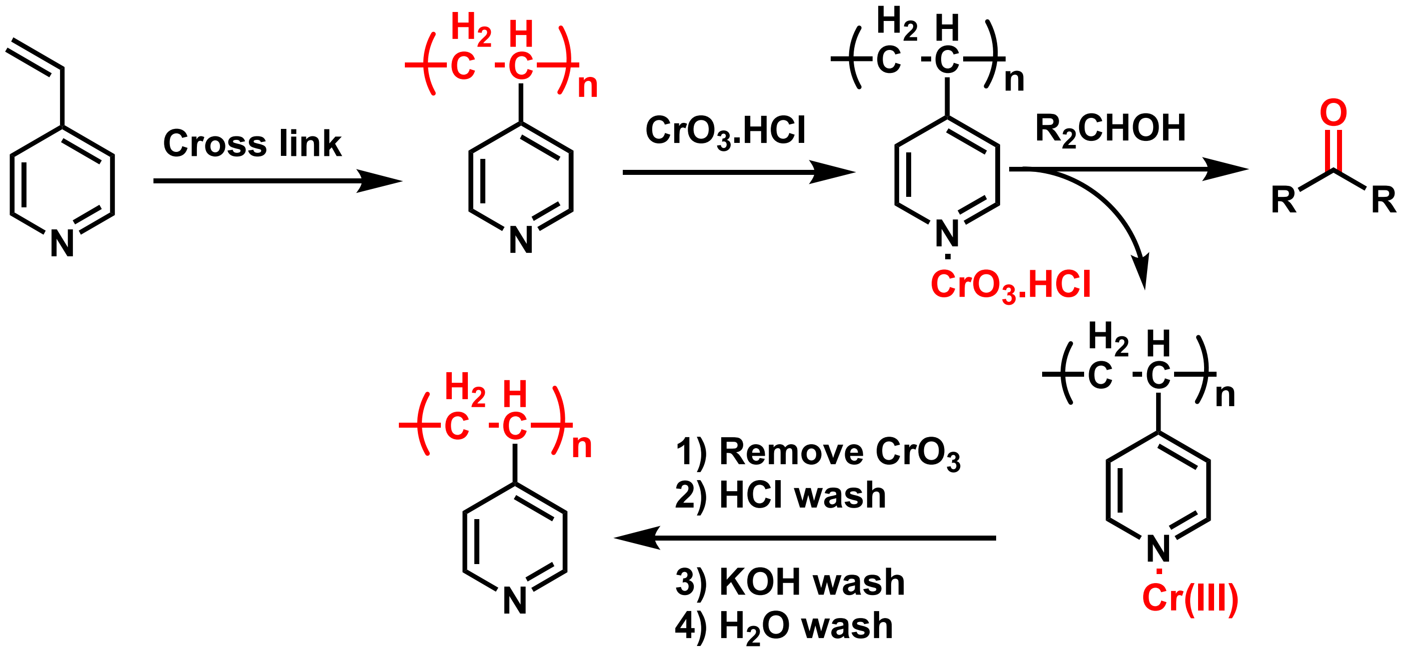




Supported Reagents

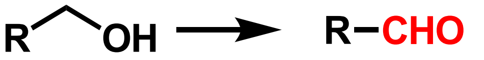
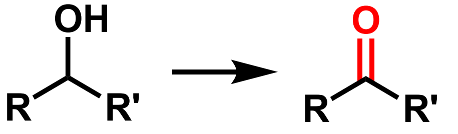
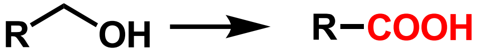
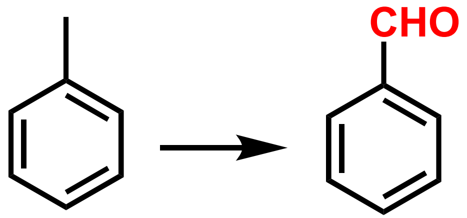
(1) PCC on alumina

(2) PCC on polyvinylpyridine



Advantage:

Improved yields due to simplified work up

Transformation	Chromium reagent
	PCC, Collins reagent, PD in DCM
	PCC, Collins reagent, PD Jones reagent
	Jones reagent, PDC in DMF
	Etard reaction

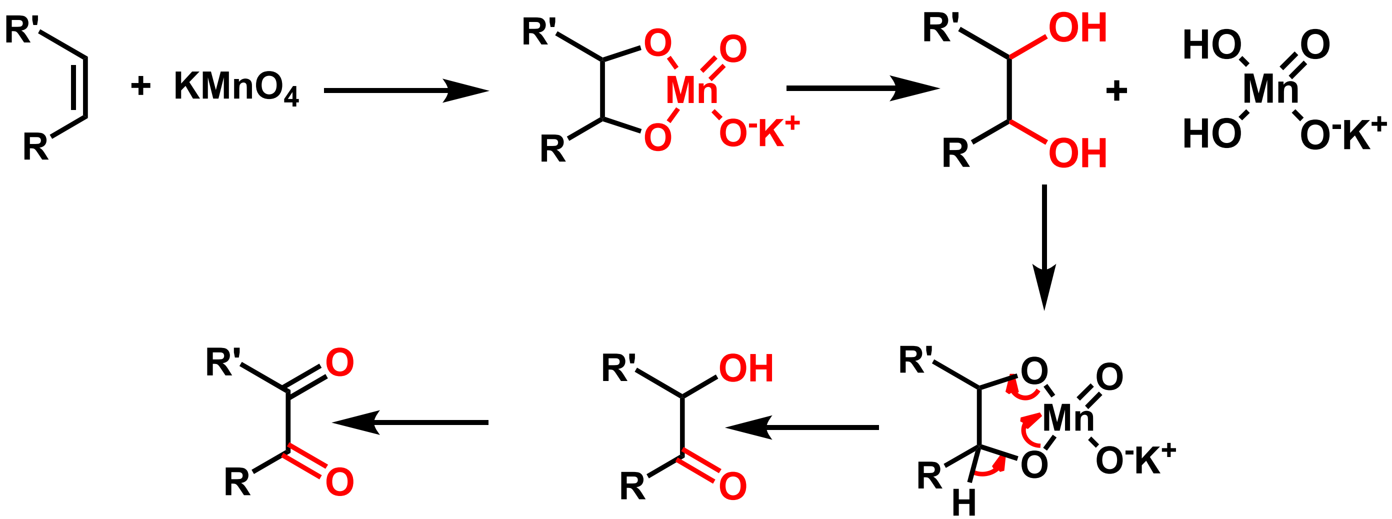
Manganese Based Oxidation

$KMnO_4$ MnO_2 $Mn(OAc)_3$

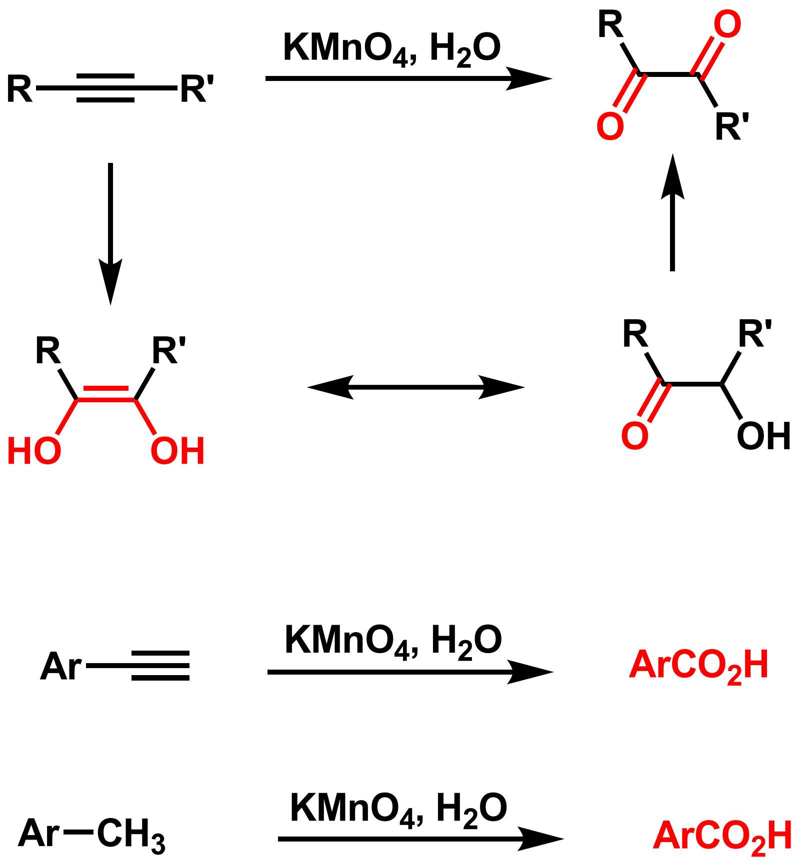
Potassium permanganate $(KMnO)_4$

Under mild condition $KMnO_4$ can effect conversion of alkenes to glycol

$KMnO_4$ is such a powerful oxidant that it can cleave the glycol further. So, careful control is required

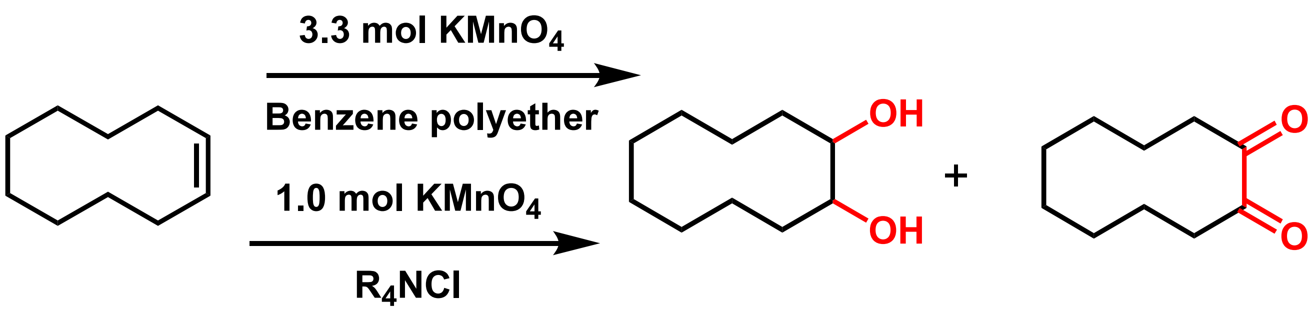


In water medium:

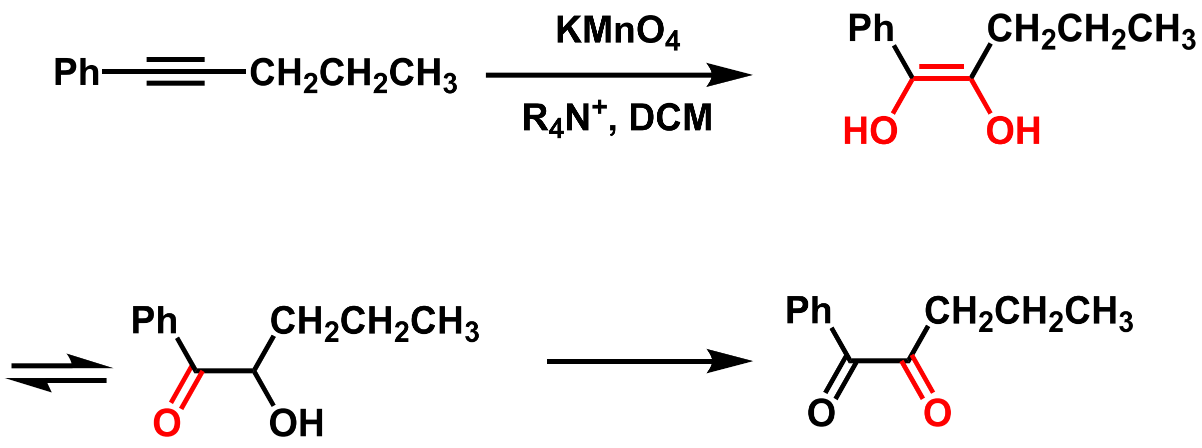


Potassium Permanganate

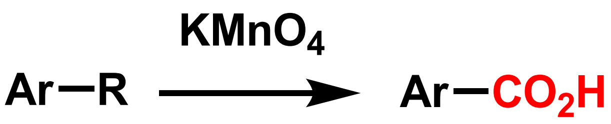
In Organic Solvents:



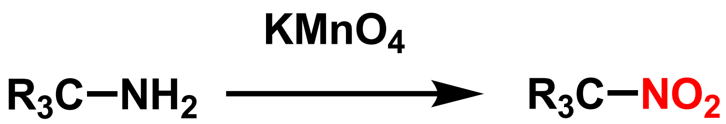
Oxidation of acetylenes:



Oxidation of aromatic side chain:

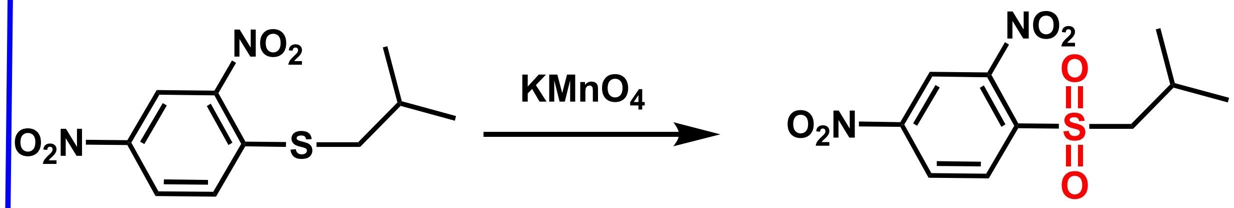


Oxidation of amino compounds:



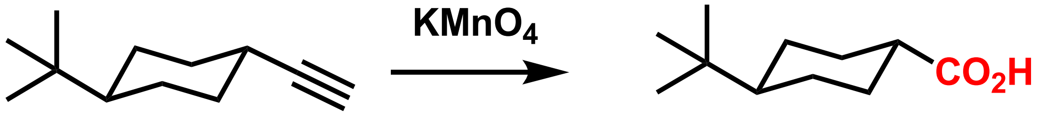
Tertiary alkylamines can be oxidized to nitro compounds

Oxidation of sulphides:

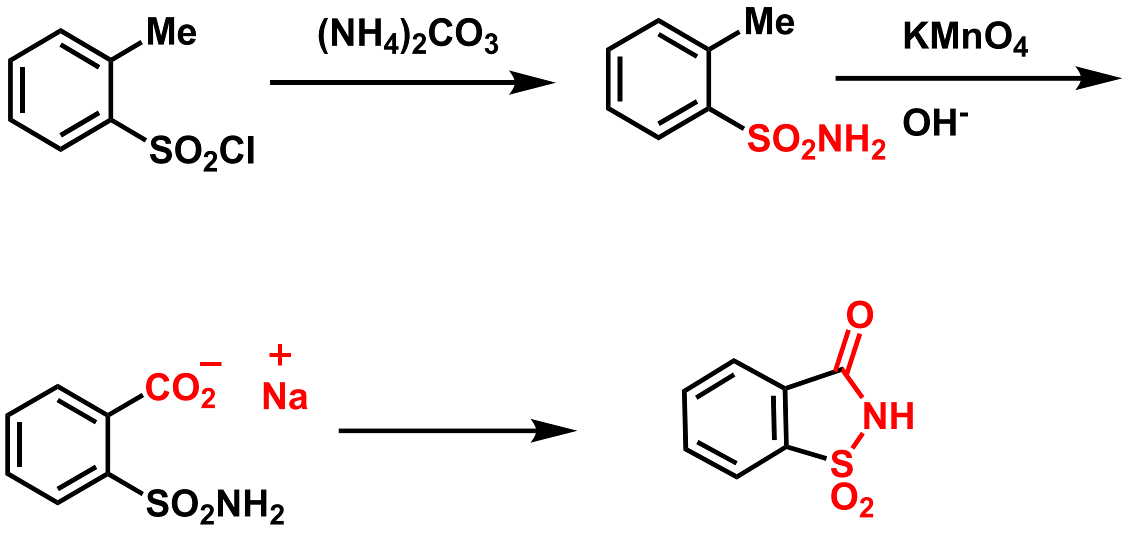


$KMnO_4/MnO_2$

Oxidation of terminal alkynes:



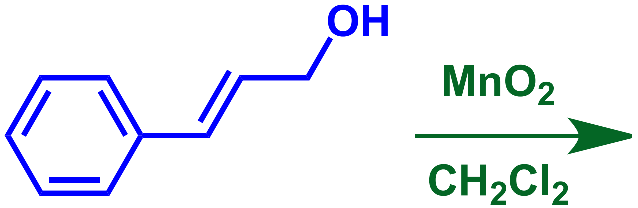
Application in the synthesis of Saccharin:



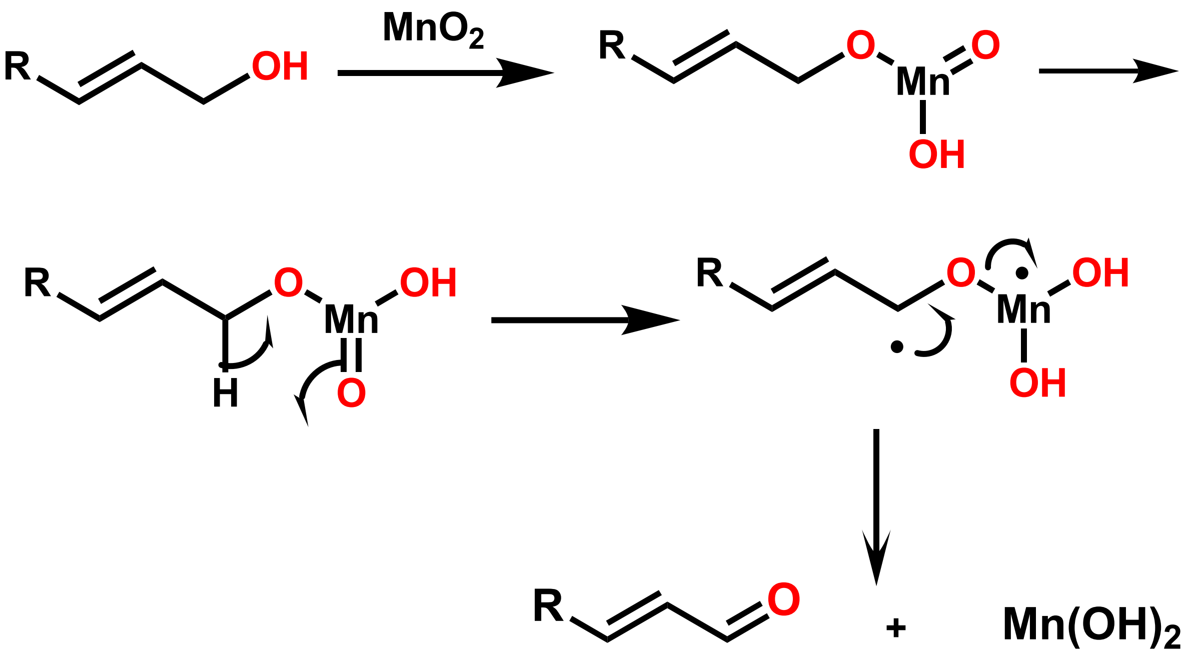
Saccharin

Manganese dioxide (MnO_2)

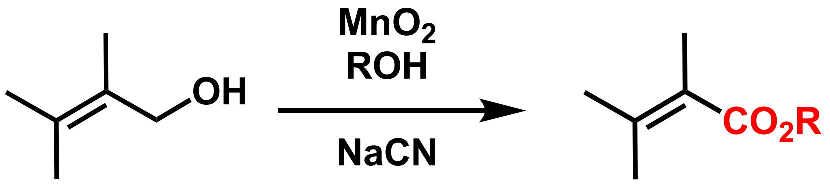
Selective oxidation of allylic & benzylic alcohols

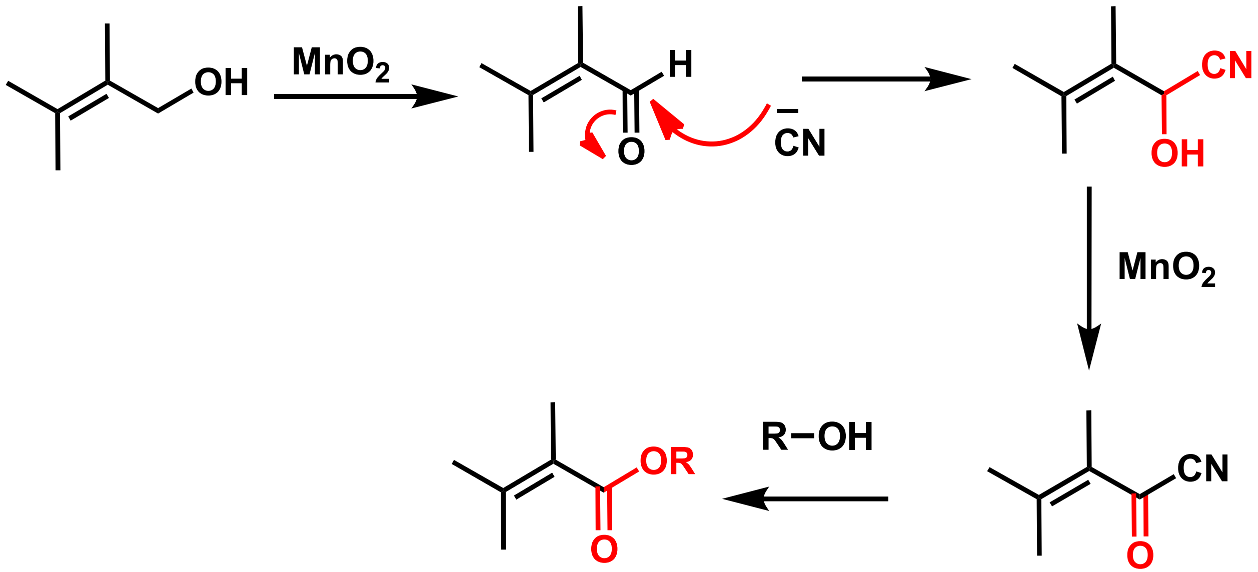


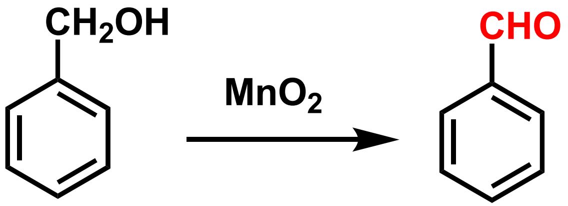
Excess of MnO_2 is required

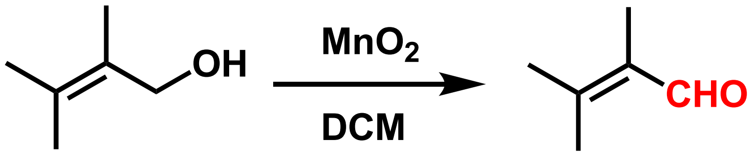


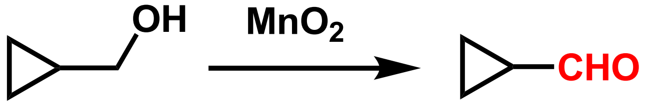
Manganese Dioxide

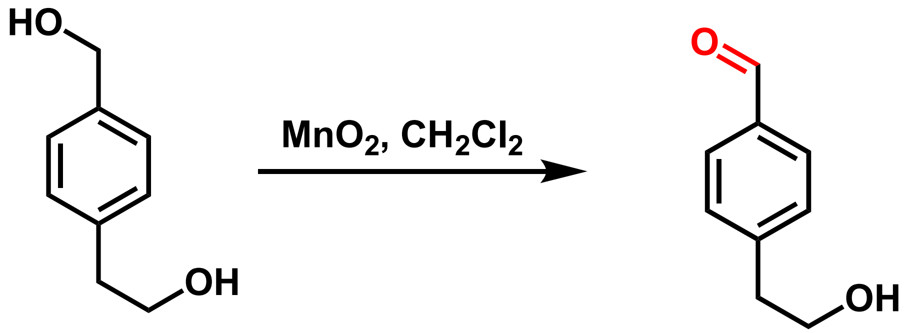


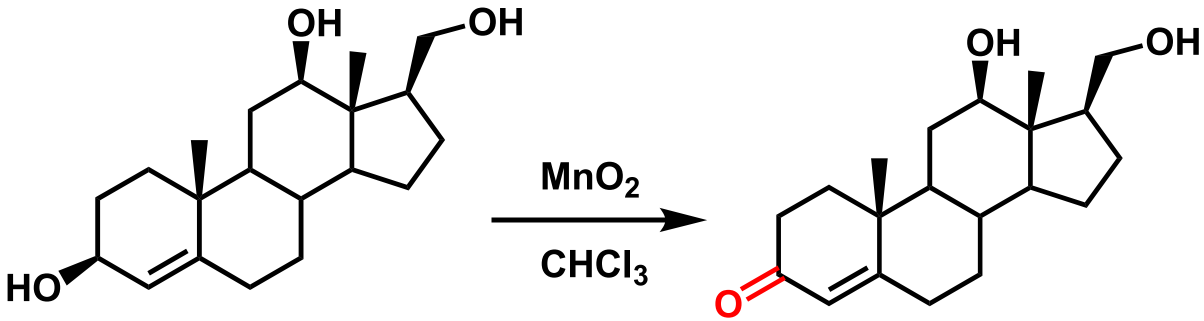




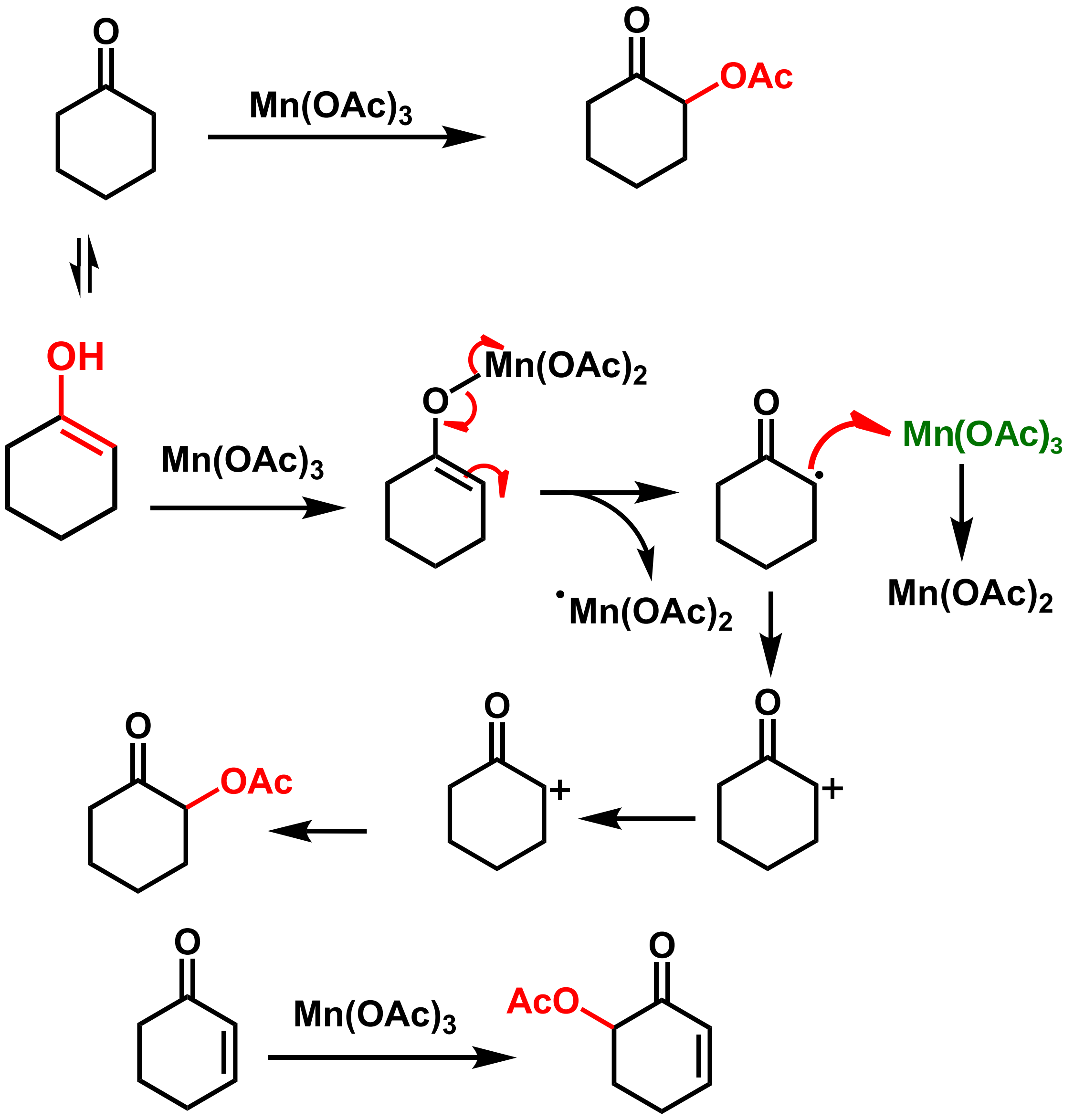


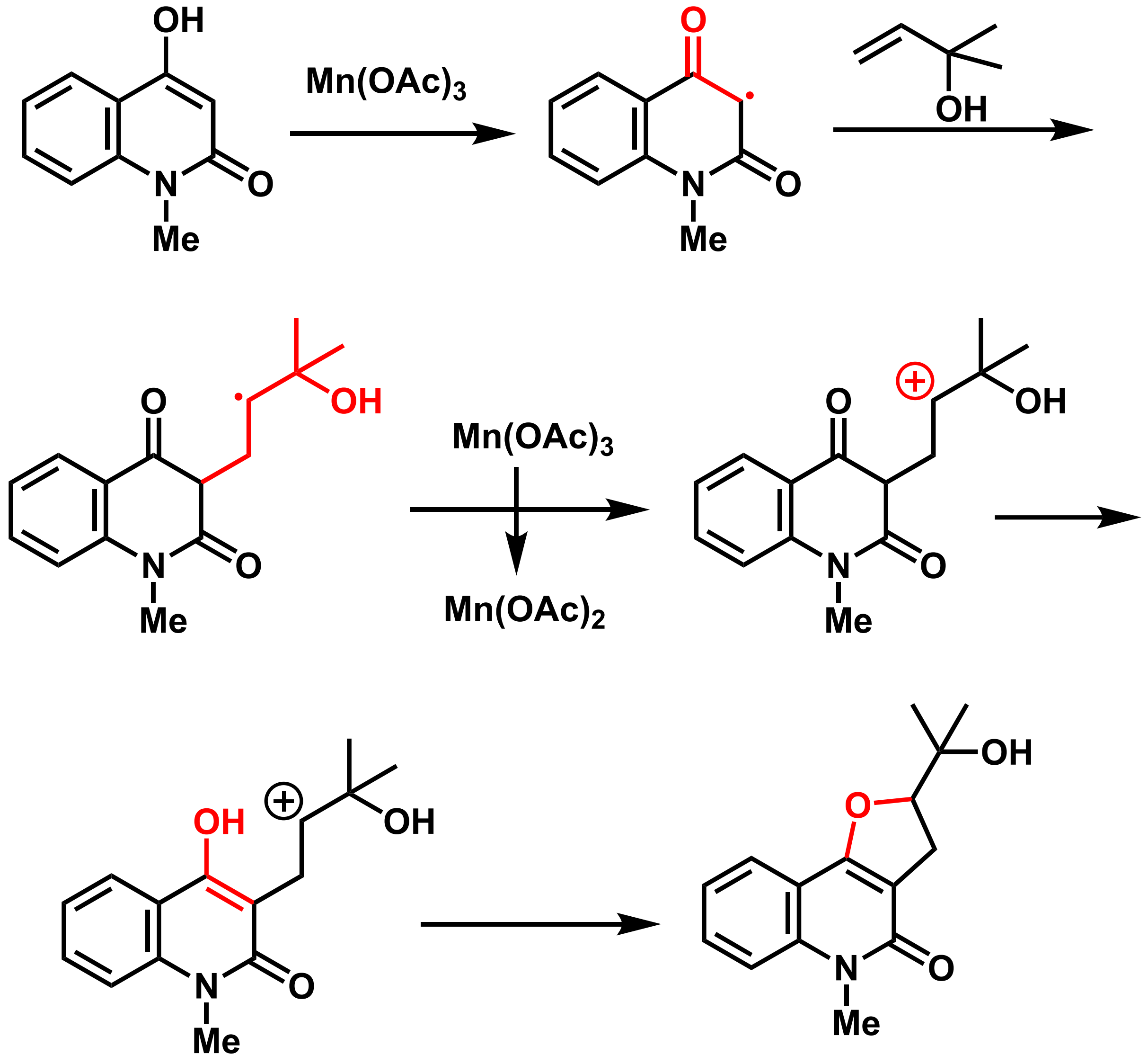




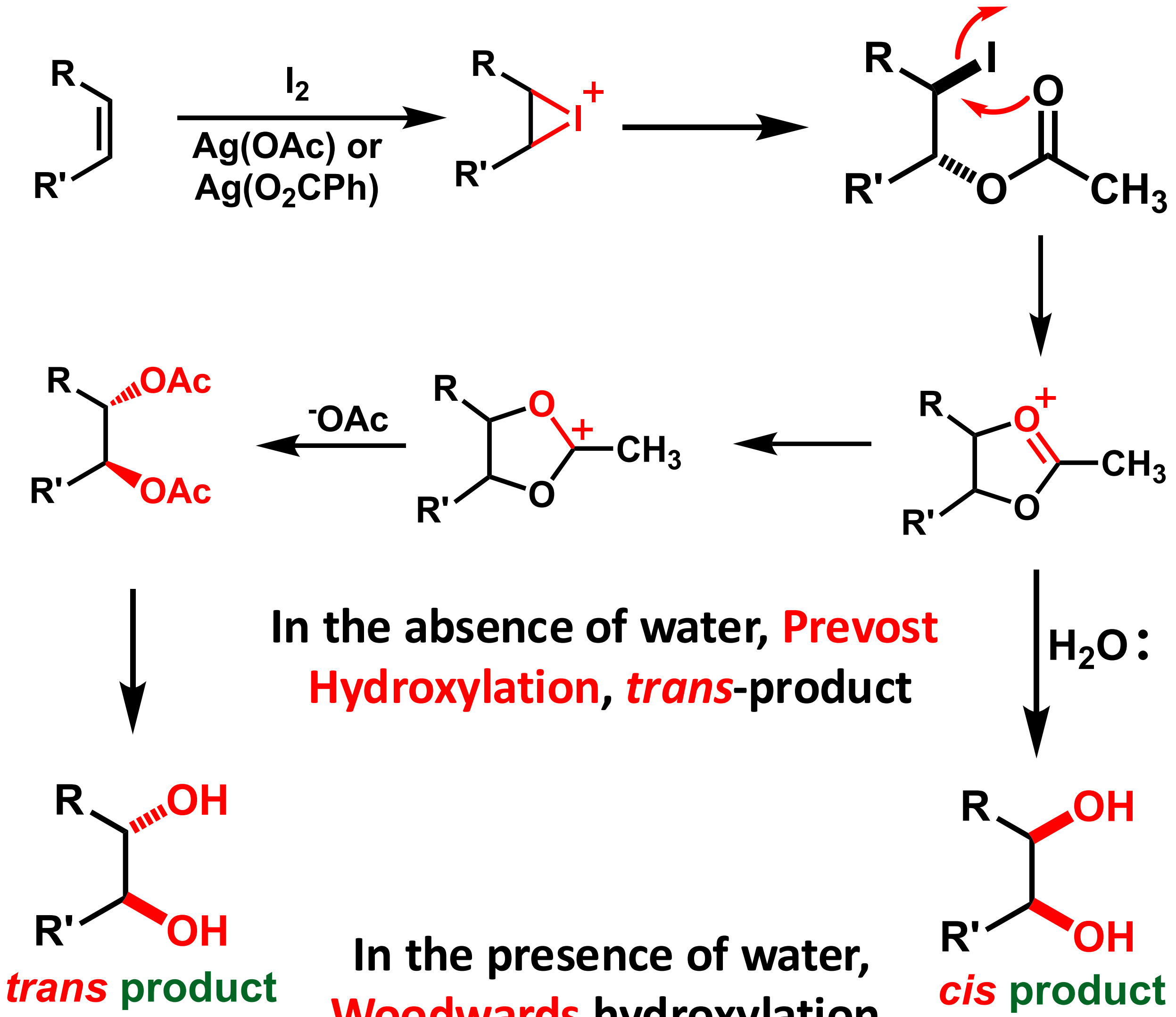


Manganese (III) Acetate [$Mn(OAc)_3$]





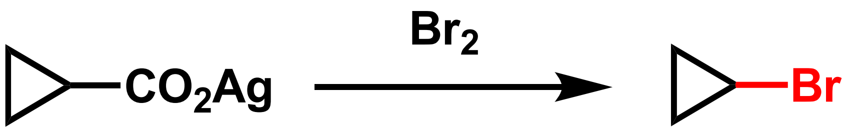
Silver Acetate



In the absence of water, **Prevost Hydroxylation**, *trans*-product

In the presence of water, **Woodwards** hydroxylation, *cis*-product

Hunsdiecker Reaction



Mechanism

$$RCOOAg + X_2 \longrightarrow RCOOX + AgX$$

$$RCOOX \xrightarrow{h\nu} RCO\dot{O} + \dot{X} \quad \text{(Initiation)}$$

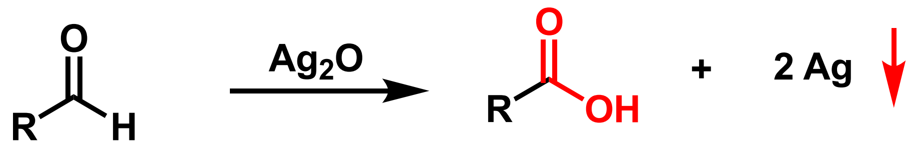
$$RCO\dot{O} \longrightarrow \dot{R} + CO_2$$

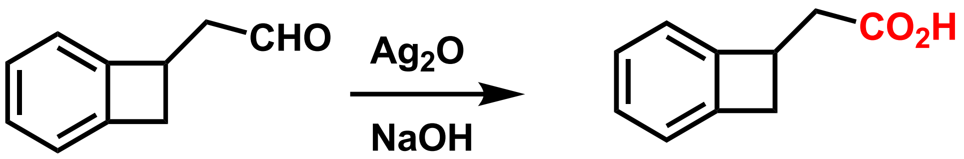
$$\dot{R} + RCOOX \longrightarrow RX + RCO\dot{O} \quad \text{(Propagation)}$$

Silver Based Oxidation

Ag_2O

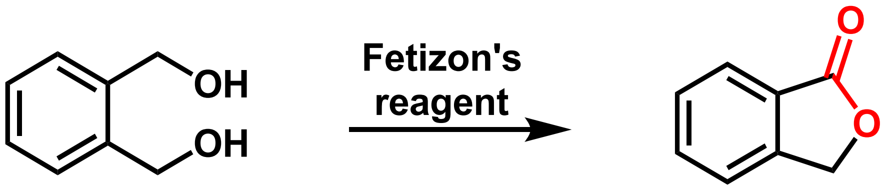
Mild oxidant to oxidize aldehyde to carboxylic acid

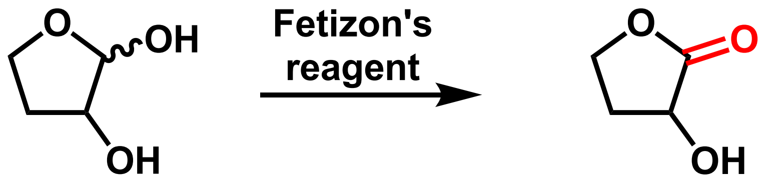




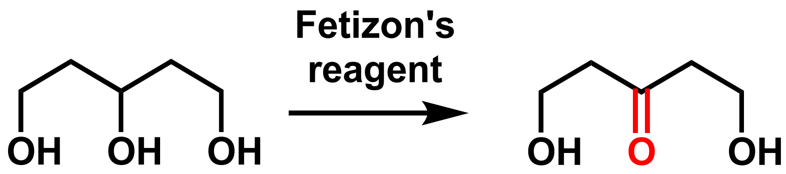
Ag_2CO_3 on Celite (Fetizon's reagent)

Conversion of diols to lactones

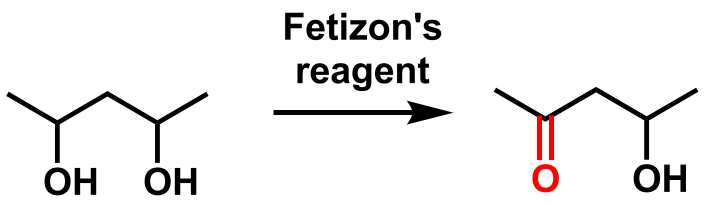


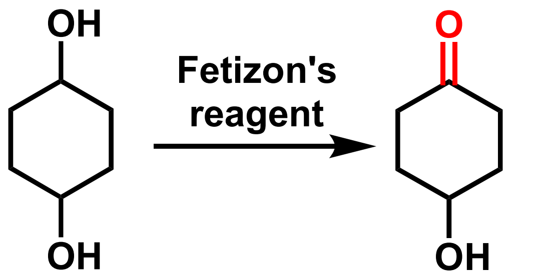


Highly selective:



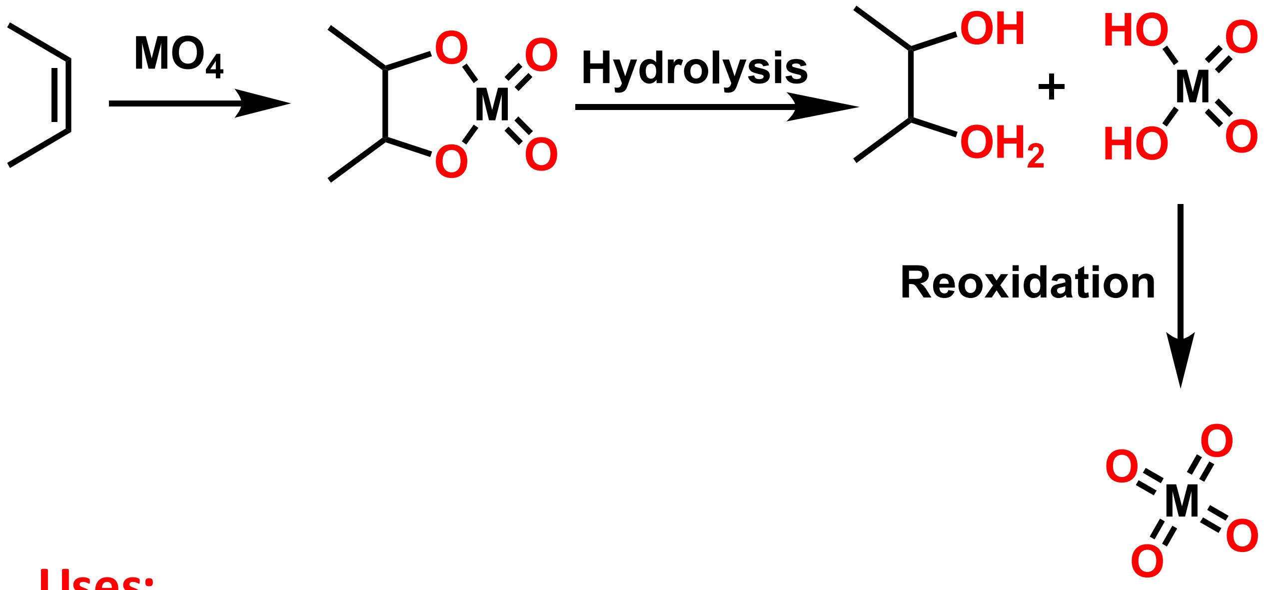
Mono-oxidation:





Osmium & Ruthenium Based Oxidation

Mechanism seems to be same in both cases

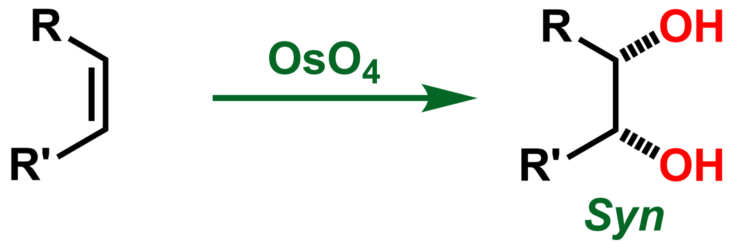


Uses:

Alkenes are generally oxidized to *cis*-diols

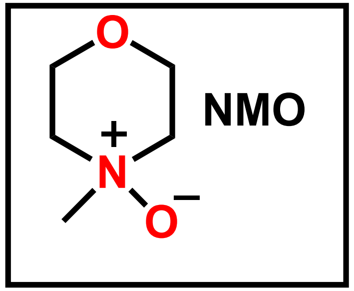
Alkynes are oxidized to diketones as in case of $KMnO_4$

Osmium tetroxide (OsO_4)



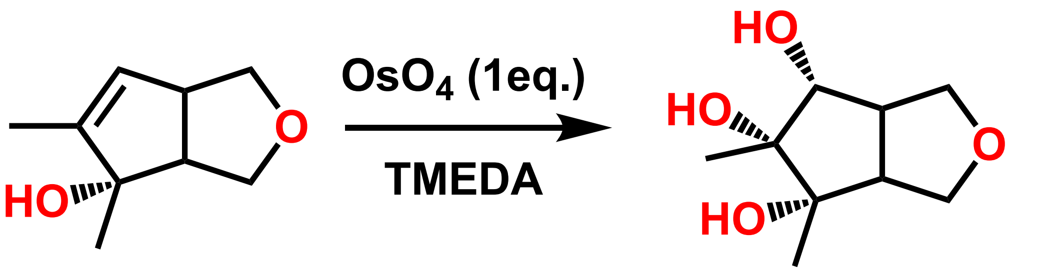
OsO_4 is highly toxic, cannot be used at industrial scale

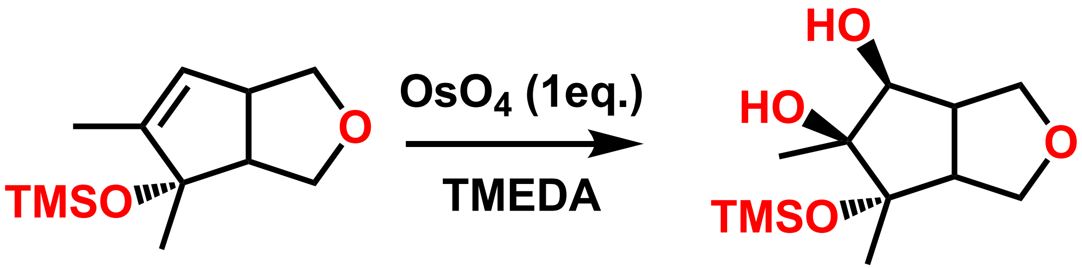
Use of NMO as co-oxidant along with catalytic amount of OsO_4 can be used for higher scale

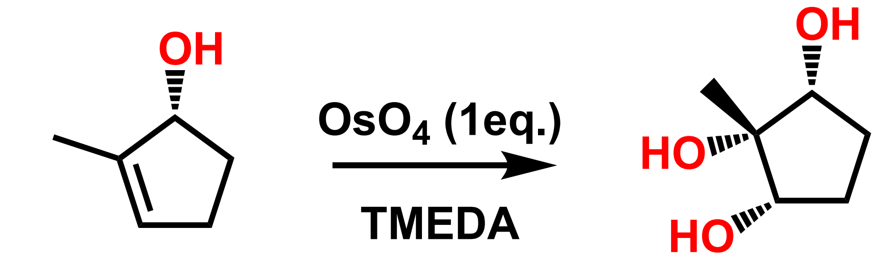


Osmium Tetroxide & Ruthenium Tetroxide

Directed by hydroxyl group





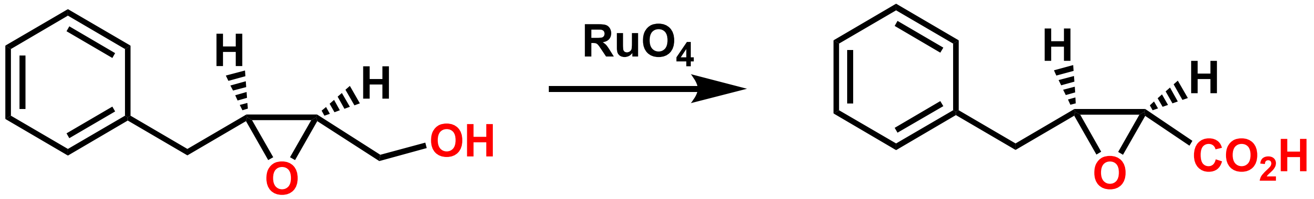


With catalytic amount of OsO4 and stoichiometric amount of NMO, opposite isomer was the major pdt.

Ruthenium tetroxide (RuO4)

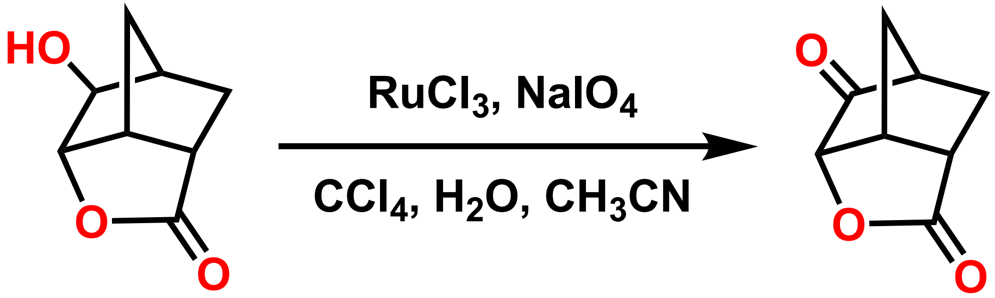
Prepared *in-situ* by mixing $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O

Primary Alcohols:



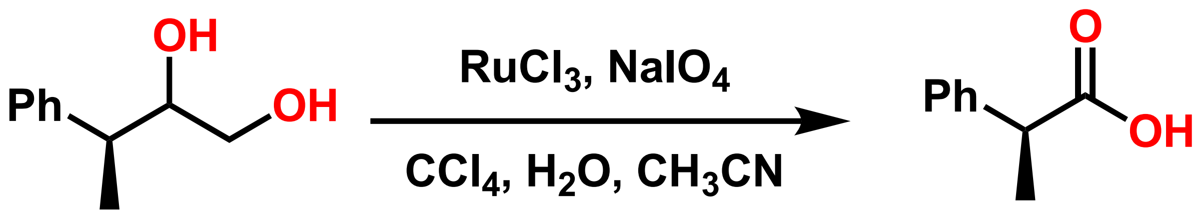
Secondary Alcohols:

Secondary alcohols oxidized to ketones

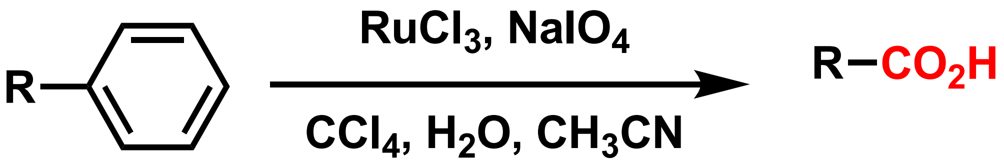


Diols:

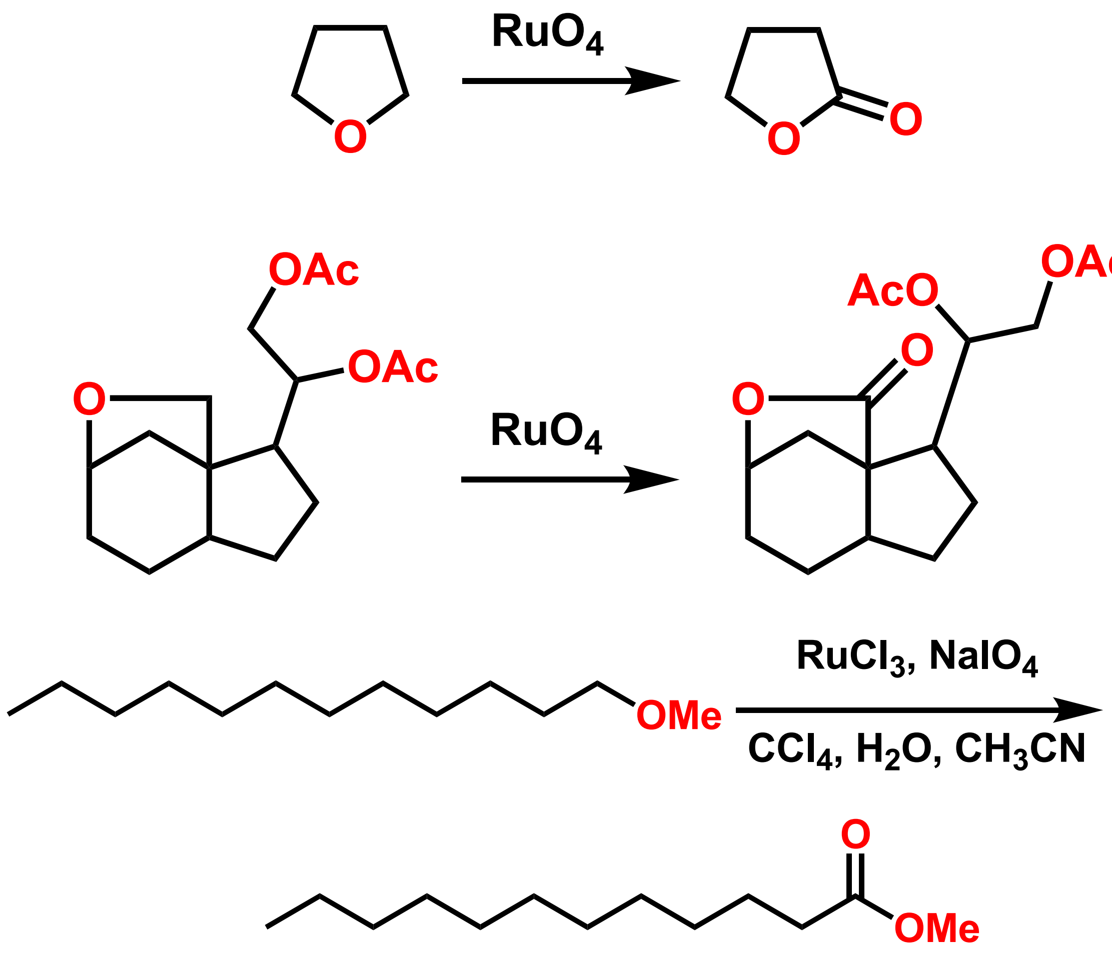
Diols are further oxidized to carboxylic acids



Oxidation of Phenyl Groups:



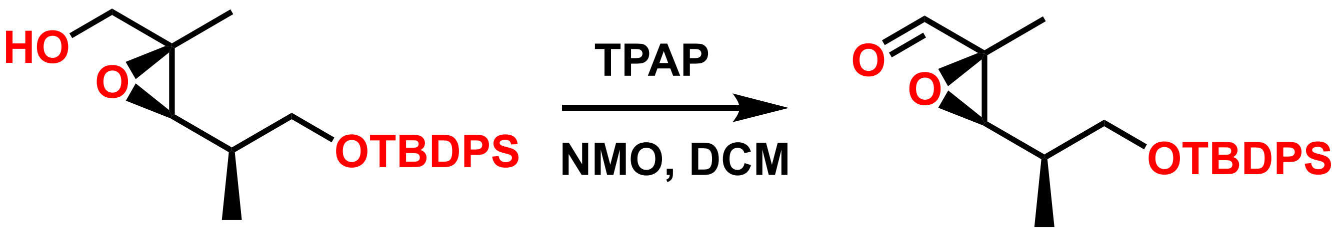
Oxidation of Ethers:

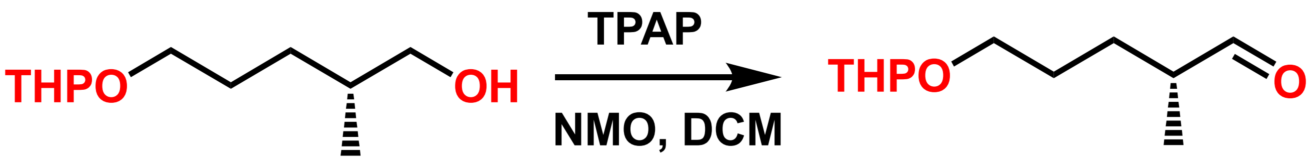


Tetra-n-propylammonium Perruthenate (TPAP)

A catalytic amount of TPAP with NMO as the co-oxidant oxidizes a range of functional groups

The performance of this reagent is improved by the addition of Molecular Sieves





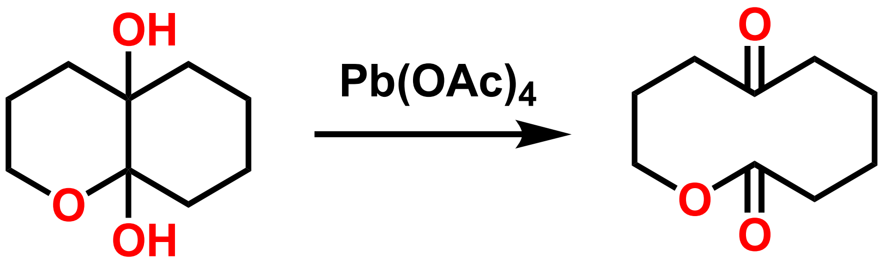
Groups tolerant are:

- Alkenes
- THP ethers
- Epoxides
- Lactones
- Silyl ethers
- Indoles

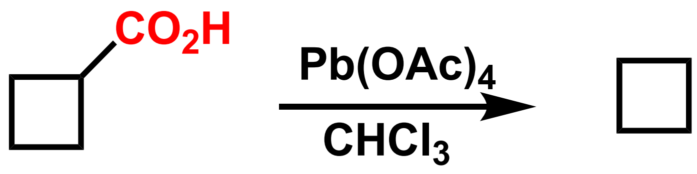
Lead Tetraacetate (LTA)

Lead tetraacetate is a very good reagent for glycol cleavage

Particularly LTA is useful for glycols that have low solubility in aqueous media



Carboxylic acids are easily oxidized by LTA



Mechanism

$$Pb(OAc)_4 + RCO_2H \longrightarrow RCOO\text{-}Pb(OAc)_3 + CH_3COOH$$

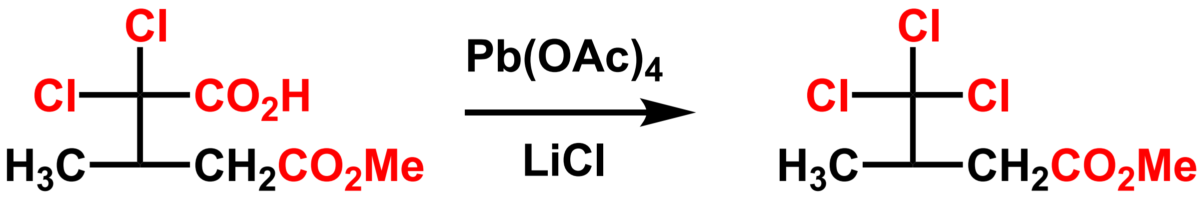
$$RCOO\text{-}Pb(OAc)_3 \longrightarrow \dot{R} + CO_2 + \dot{Pb}(OAc)_3$$

$$\dot{R} + \dot{Pb}(OAc)_3 \longrightarrow R^+ + Pb(OAc)_2 + CH_3COO^-$$

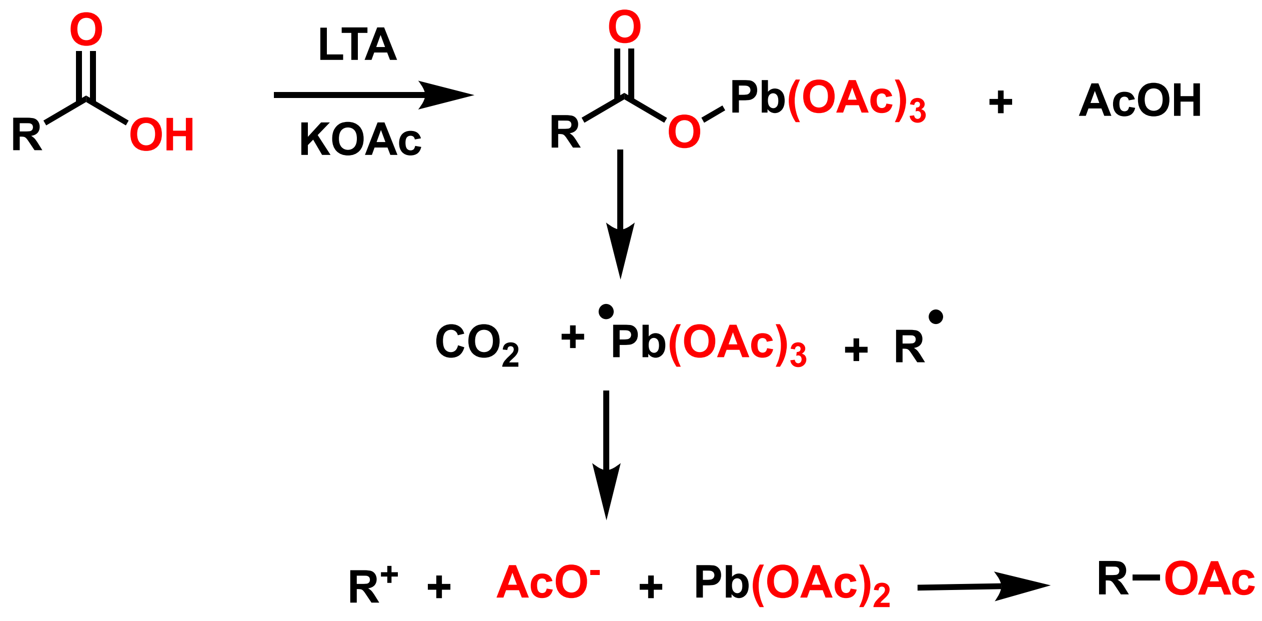
The reductive step is promoted by hydrogen donor solvents

Acetate arise by the capture of an acetate ion

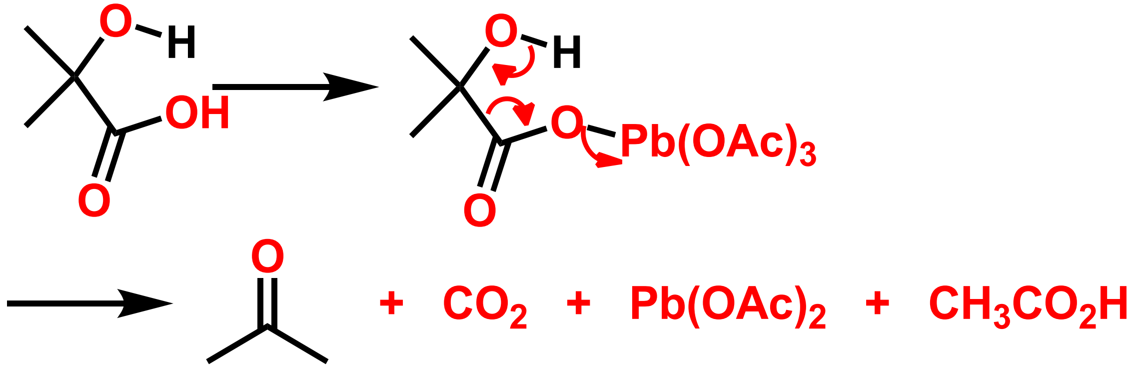
In the presence of lithium chloride, the product is the corresponding chloride



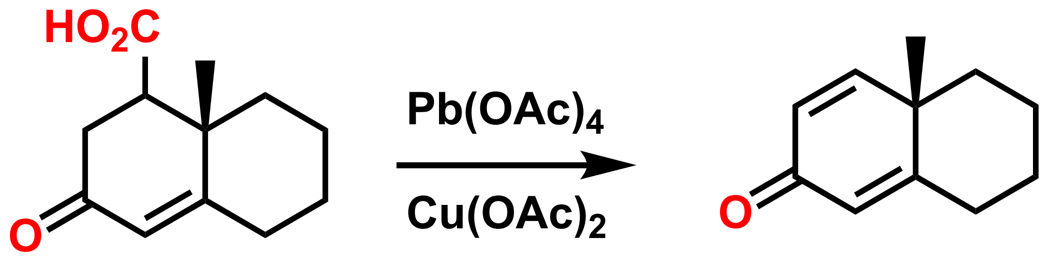
Lead Tetraacetate (LTA)



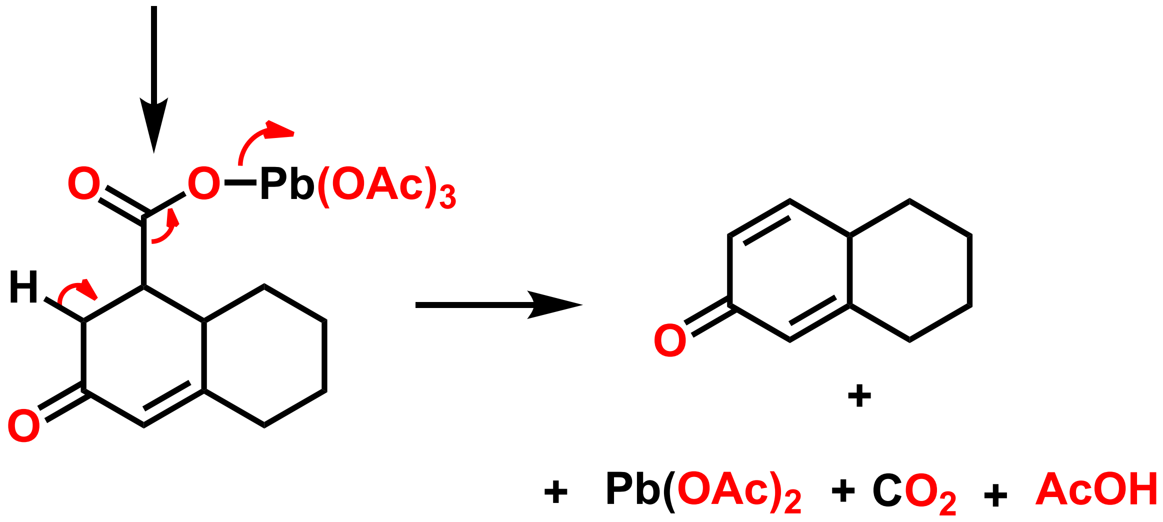
α- hydroxy carboxylic acids undergo oxidative decarboxylation to give ketone



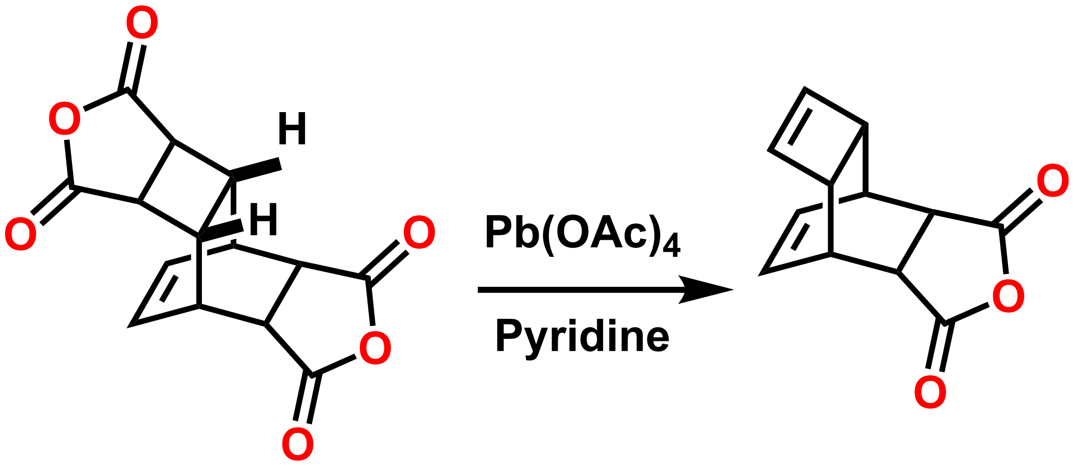
ν- keto carboxylic acid preferentially yield α,β–unsaturated ketone

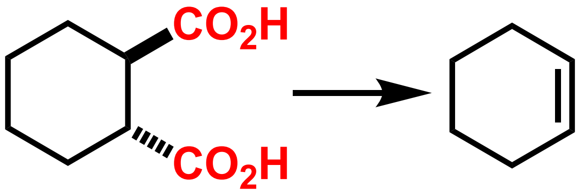


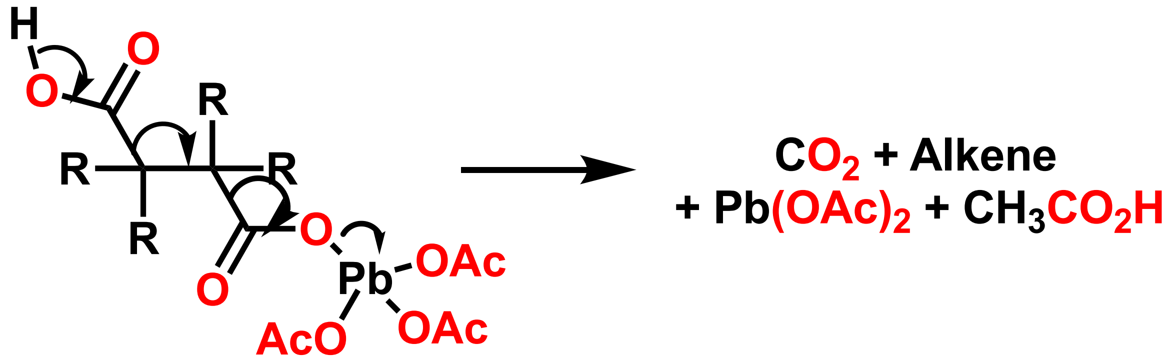
Presumably it goes via oxidation of carboxylic acid to the carbocation followed by loss of a proton

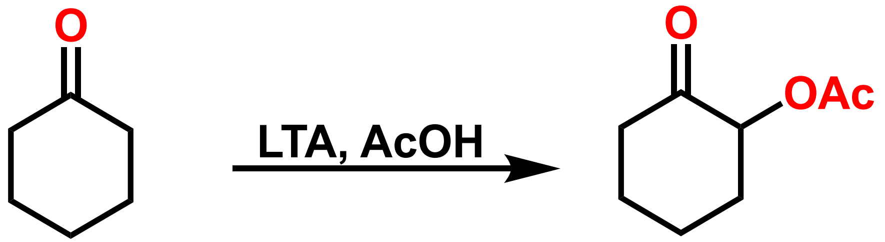


Lead Tetraacetate (LTA)

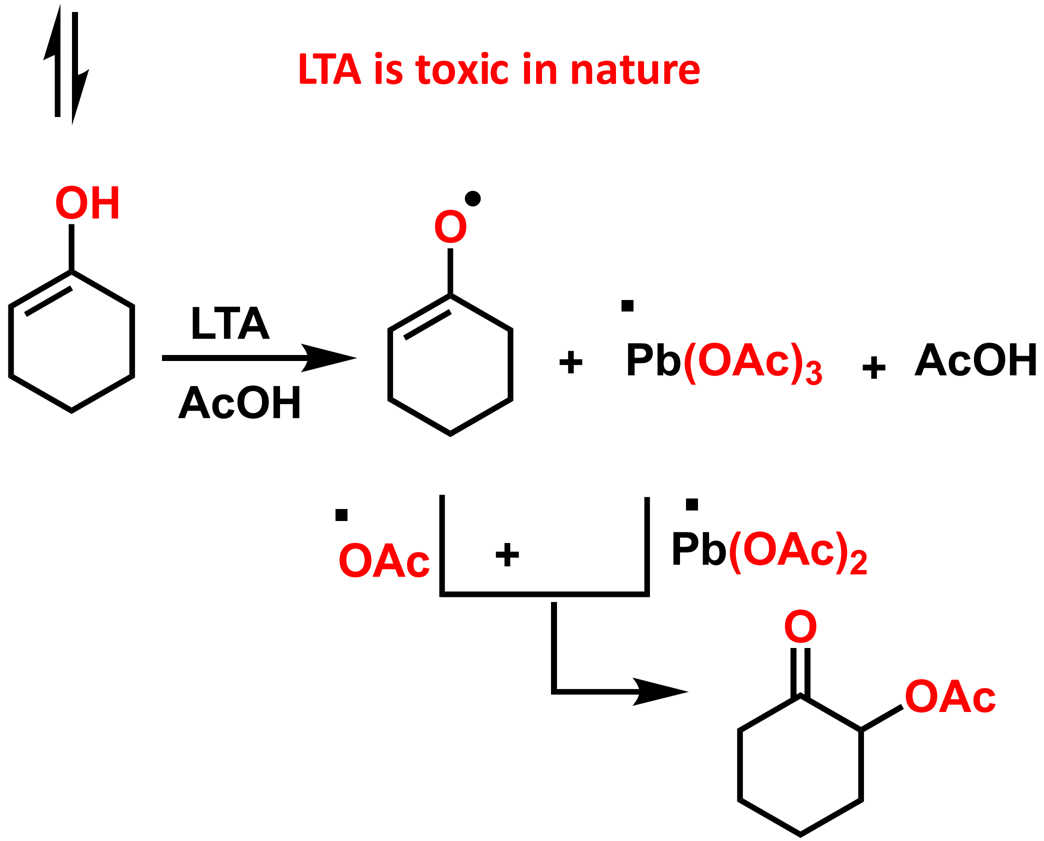






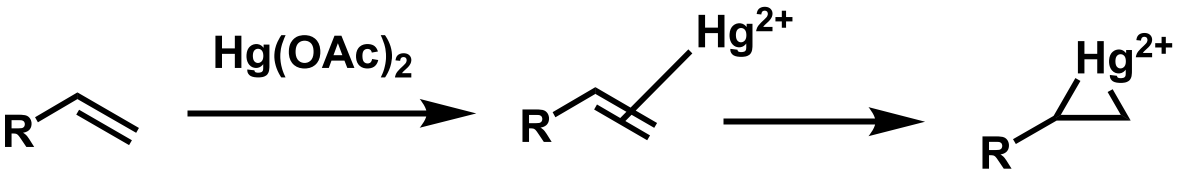


LTA is toxic in nature

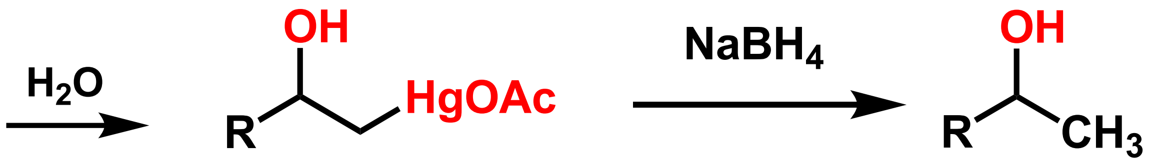


Oxymercuration

Addition of water to an alkene



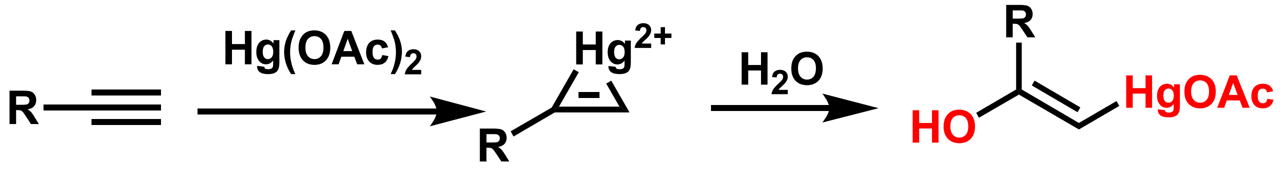
Mercurinium ion



When water is used as solvent, it opens the mercurinium ion and give alcohols

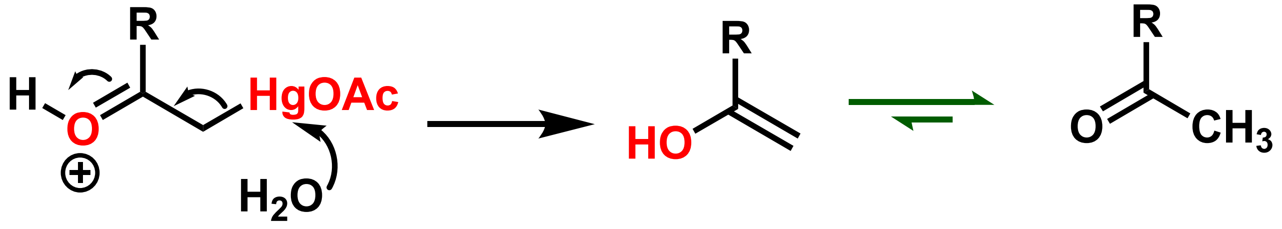
C-Hg bond is very weak and it can be easily replaced with hydrogen by reducing agents. Generally $NaBH_4$ is used

Addition of water to an alkyne



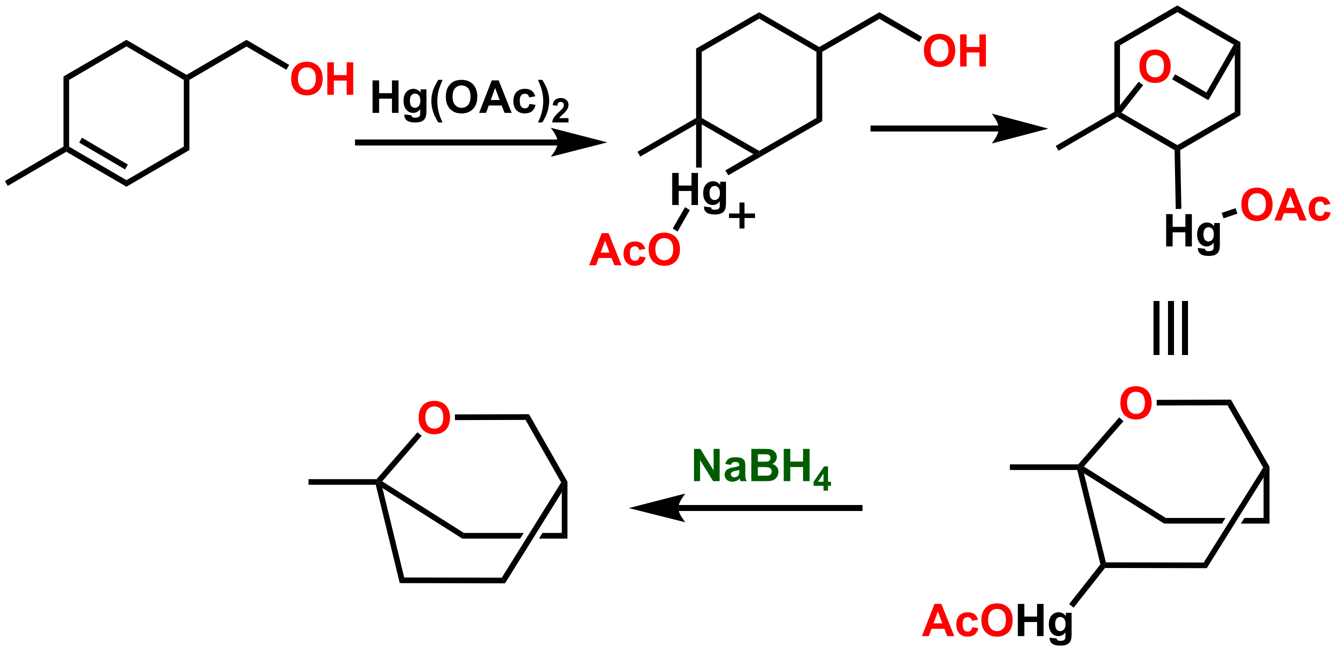
Addition of water to the intermediate leads to an enol which isomerizes to a ketone

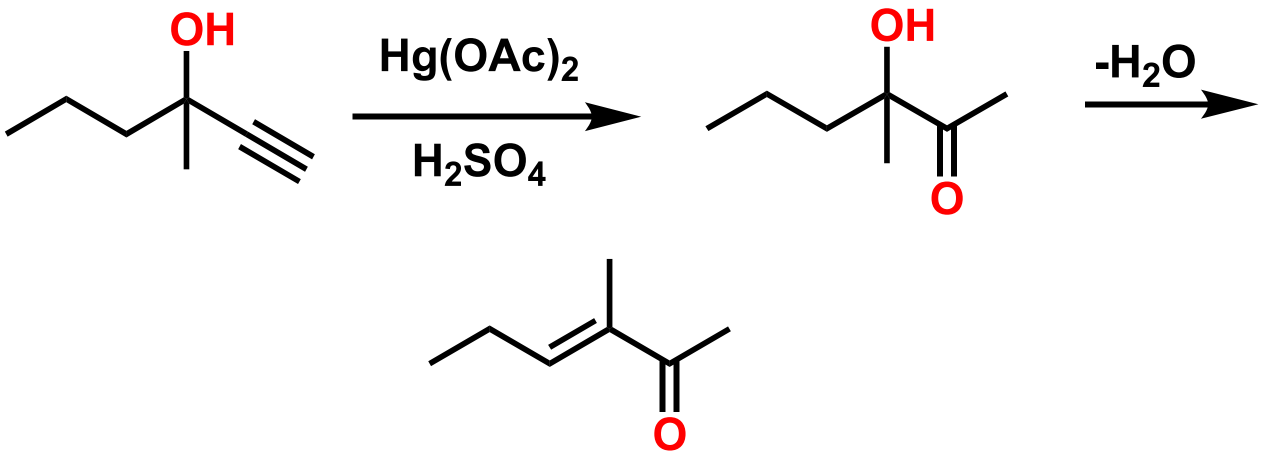
Since AcOH is the byproduct, this protonates the carbonyl group

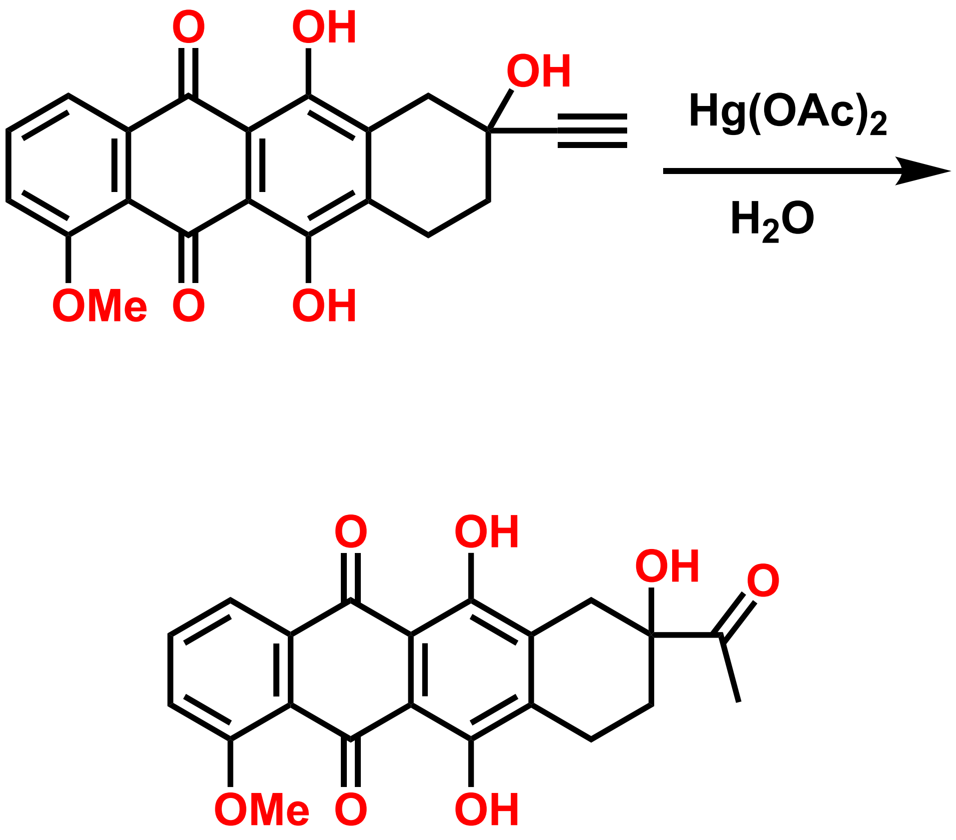


For hydration of alkynes, we do not need $NaBH_4$. Moreover, if you use $NaBH_4$ in the last step, it will reduce the ketone

Oxymercuration

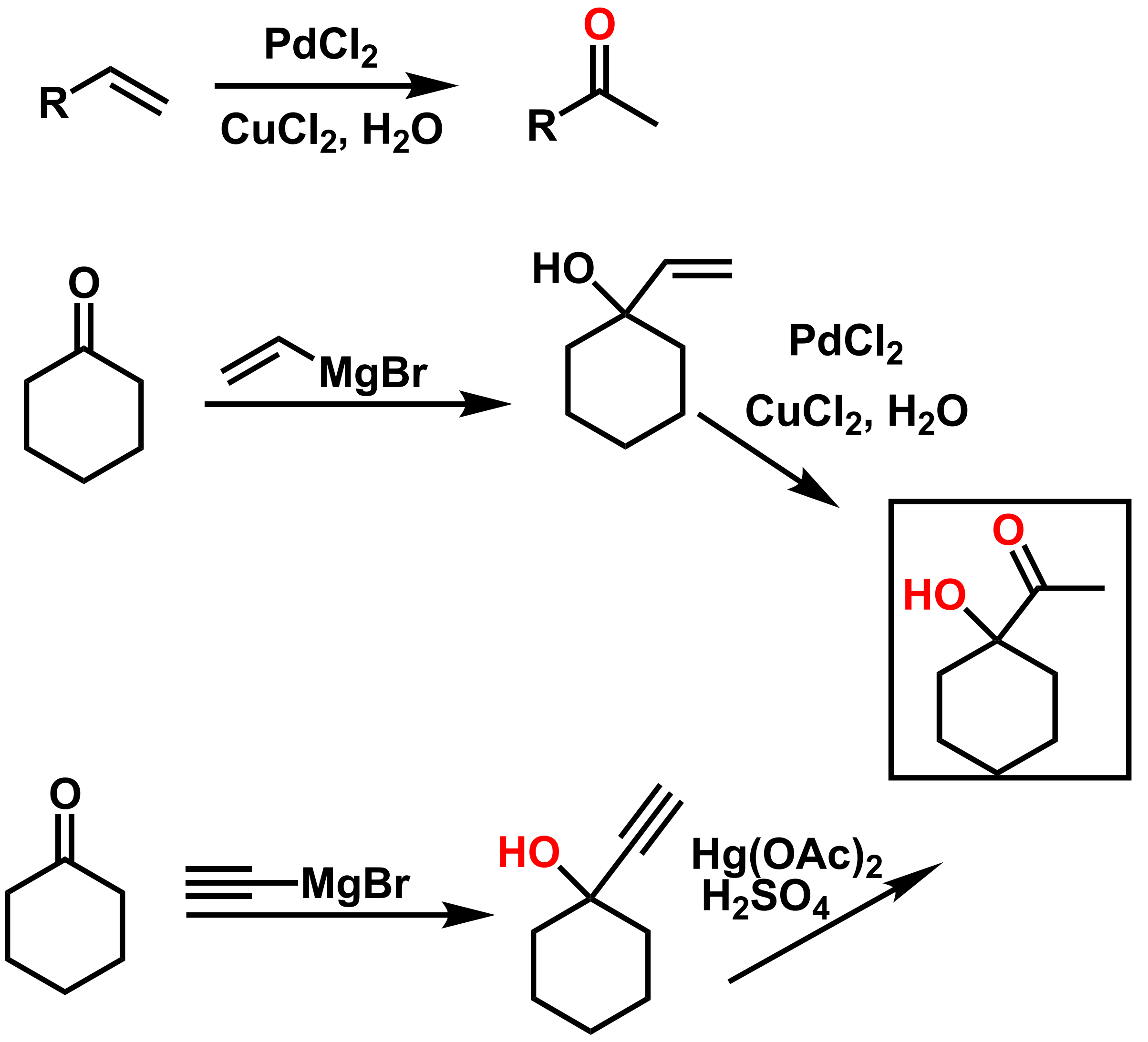




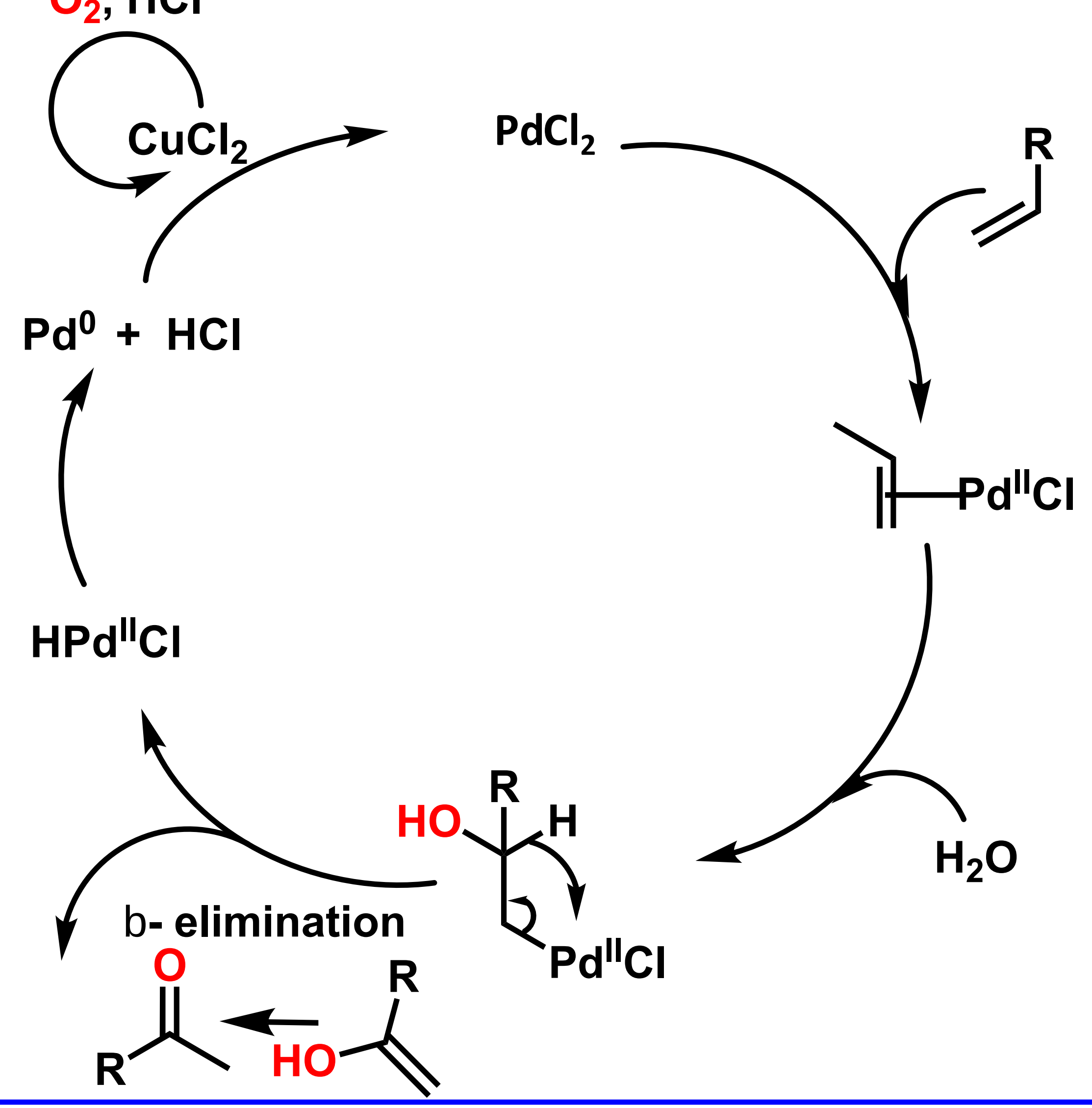


Deoxydaunomycinone

Wacker Process



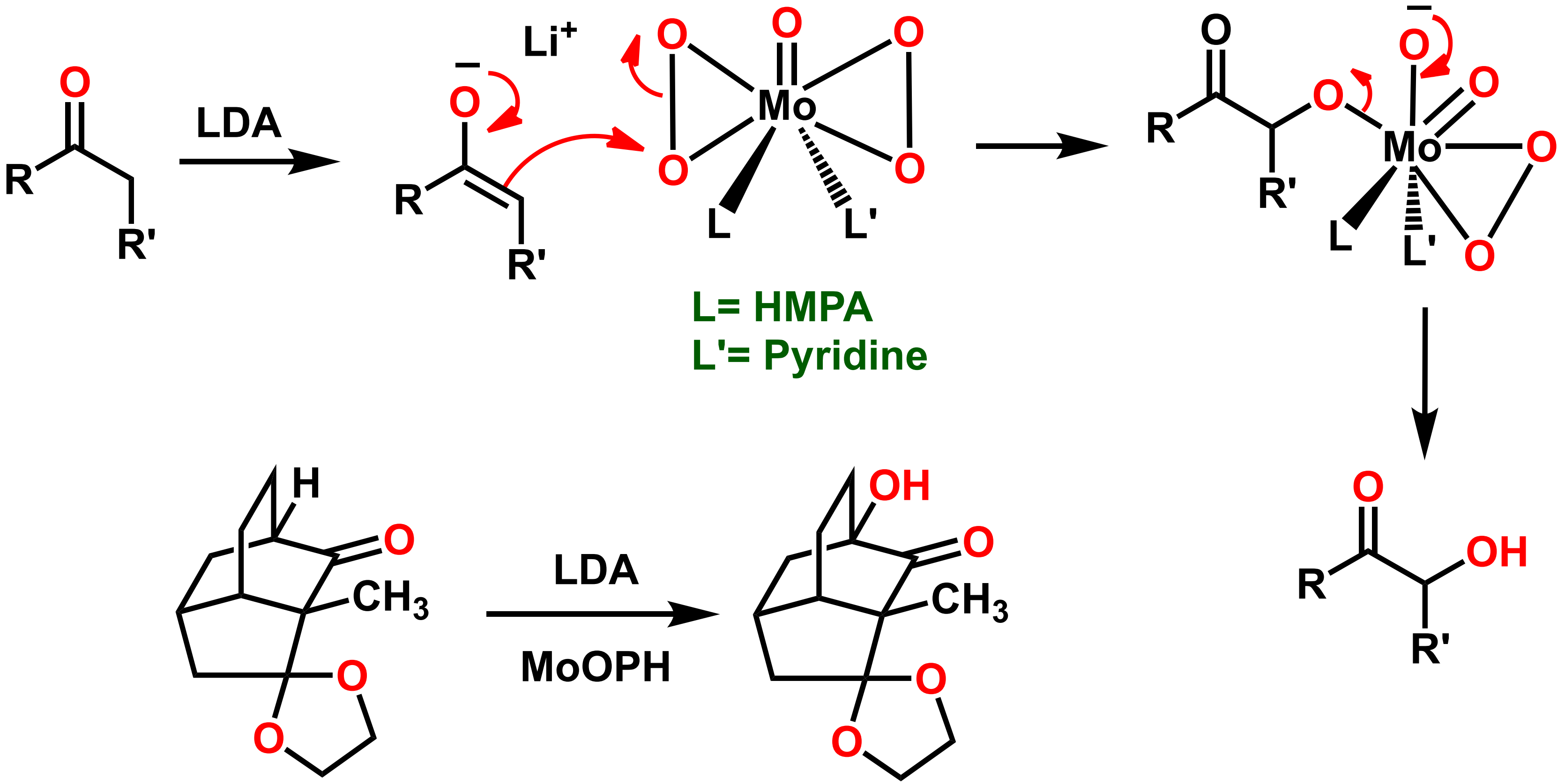
Mechanism



Molybdenum Peroxy Complexes

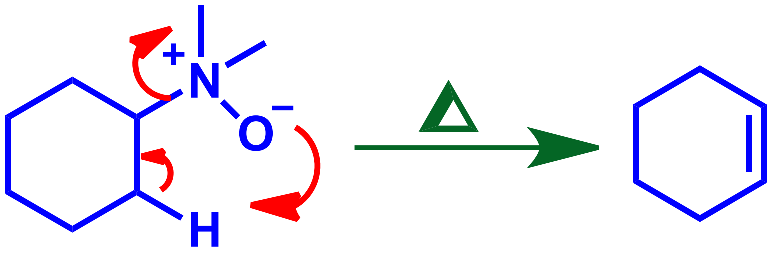
MoOPH (MoO_5. Py. HMPA complex)

It contains two electrophilic bridged peroxy ligands and a single oxo-unit

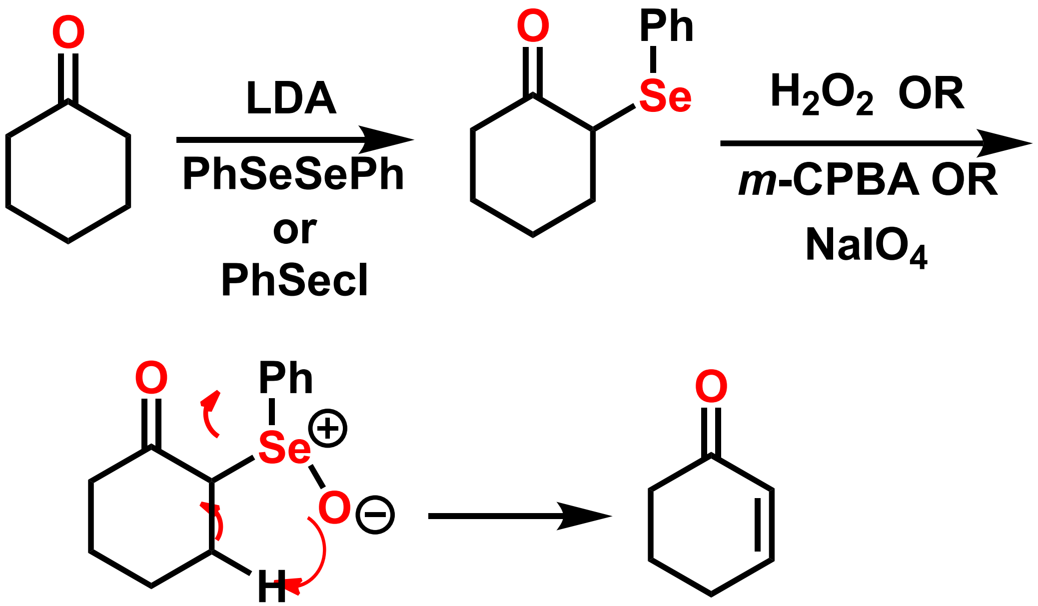


Selenoxide/Sulfoxide Elimination

Cope elimination



Selenoxide elimination



Sulfoxide elimination