

# Oxidation Reactions

## Oxidation Reactions

Key words: oxidations using chromium and manganese reagents, cleavage of double bonds with ozone and osmium tetroxide, oxidations with aluminum isopropoxide, peracids,

## Introduction

### Definition

Broader definition of oxidation and reduction respectively refer to the **loss and gain of electrons**, or an **increase in oxidation number** (oxidation) and a **decrease in oxidation number** (reduction).

In organic chemistry, the **gain of oxygen or loss of hydrogen** is often referred to as oxidation.

In practice, a series of functional groups have been qualitatively identified in the order of increasing oxidation state. Then, oxidation is referred to as the conversion of one functional group higher in the sequence to another lower in the list.

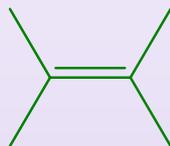
Conversion within a group are neither oxidation nor reduction.

It is summarized in following table.

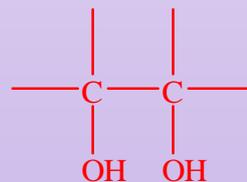
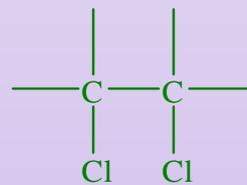
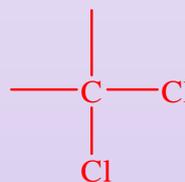
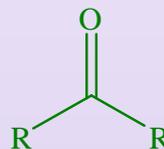
**This module has been organized based on the reagent that are used for oxidation reactions**

Table summarizing functional groups arranged according to oxidation state.

RH



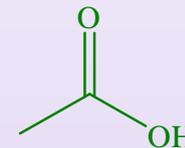
ROH  
RCl  
RNH<sub>2</sub>  
etc.



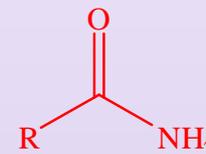
etc.

reduction

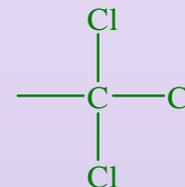
oxidation



CO<sub>2</sub>



CCl<sub>4</sub>



etc.

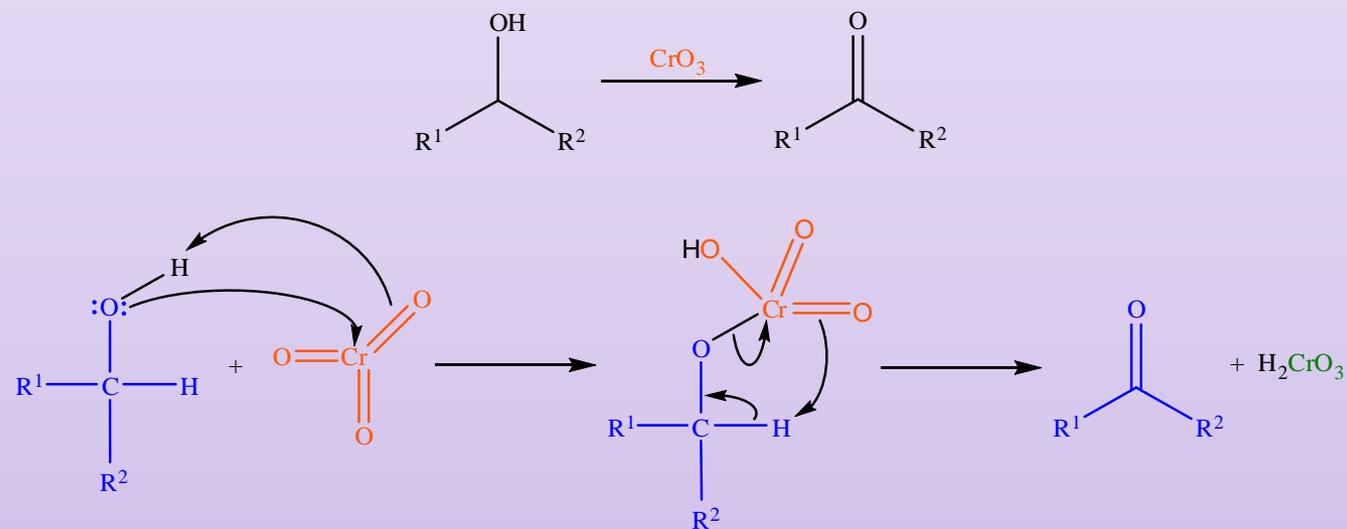


## I. Oxidation of alcohols using Cr(VI) reagents

For oxidation of alcohols to corresponding carbonyl compounds, generally **Cr(VI)** reagents such as  $\text{K}_2\text{Cr}_2\text{O}_7$ , **Jones reagent**, **PCC** etc., are employed.

□ Oxidation of alcohols to carbonyl compound occurs via **Cr(VI) acid monoester**.

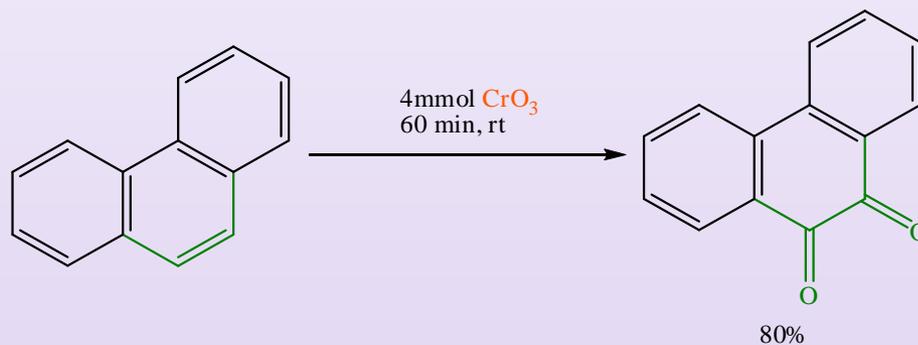
Mechanism is as follows.



Oxidation of fused aromatic system is generally carried out using  $\text{CrO}_3$  reagent

Juaristi M. et al, *Can.J.Chem.*,  
**1984**, 62, 2941

Example for chromium oxide based oxidation

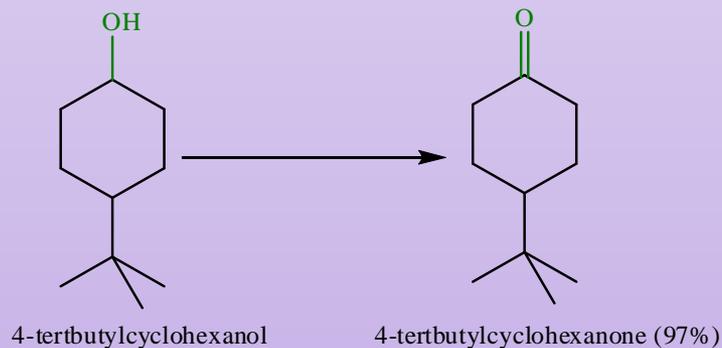
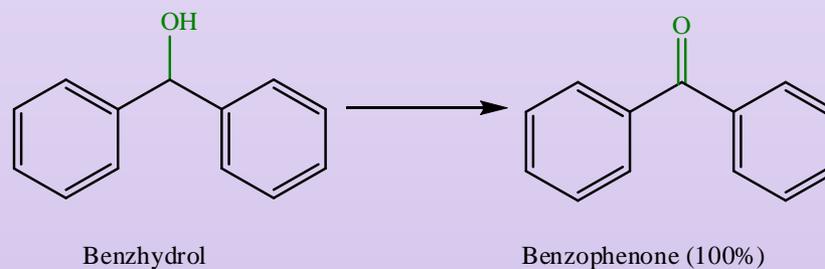
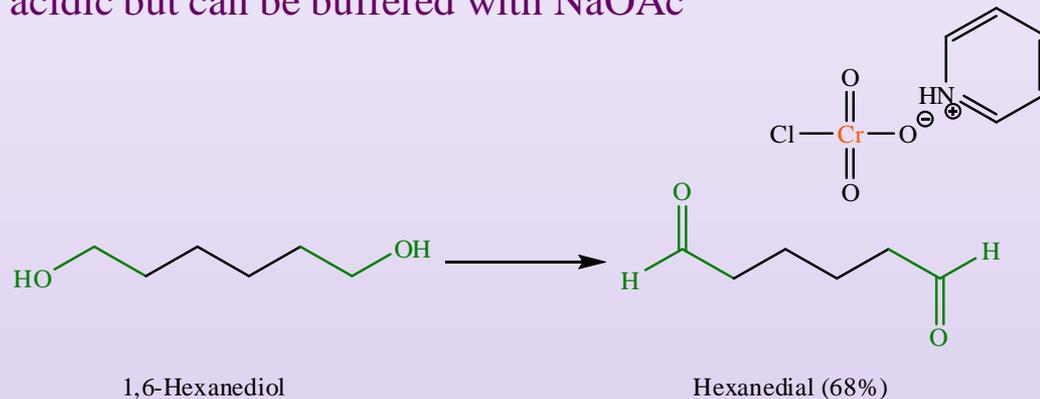


Reagent can be used in close to stoichiometric amounts with substrate

Corey E J & Suggs W,  
*Tet.Lett.*, **1975**, 16, 2647

**PCC** (pyridinium chlorochromate) is other efficient reagent used widely for oxidation of primary and secondary alcohols.

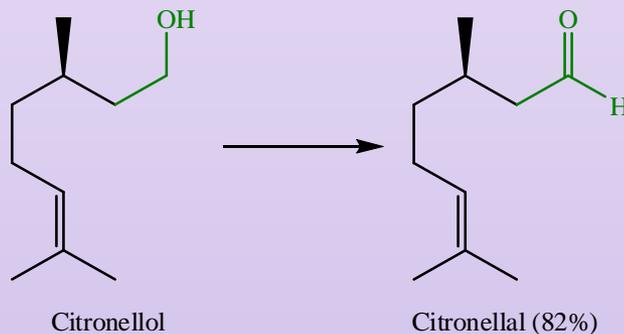
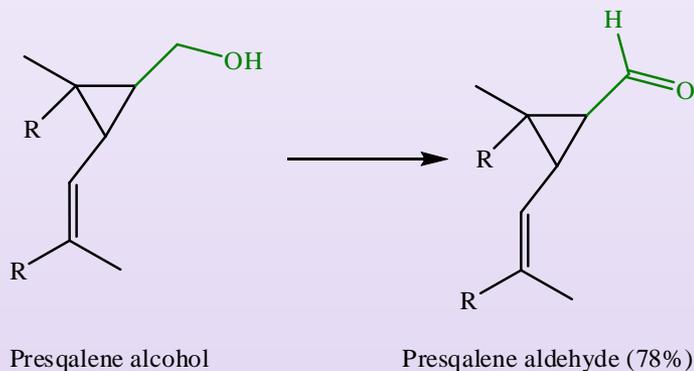
E J Corey and W Suggs in 1975 suggested PCC as oxidizing agent. PCC is slightly acidic but can be buffered with NaOAc



Corey and Suggs used following method for preparation of PCC.

100g (1mol)  $\text{CrO}_3$  is added to conc.  $\text{HCl}$ , rapidly with stirring over 5 min time. Homogenous solution obtained is cooled to  $0^\circ\text{C}$ . To this, 1mol of pyridine is added. Yellow-orange solid obtained is filtered and dried in vacuum.

This solid is PCC and is not hygroscopic. It can be stored at room temperature.



In this reaction, double bond is not affected.

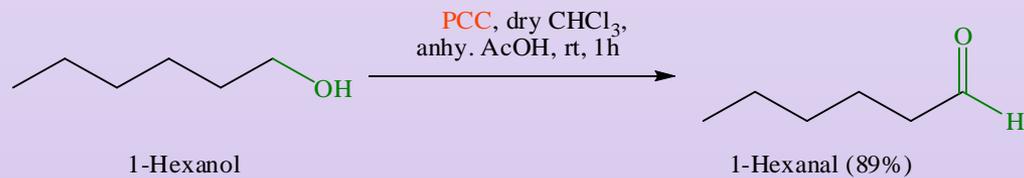
PCC is used particularly for the oxidation of primary alcohol to aldehyde. It does not have any effect on C=C or any other easily oxidizable functional groups.



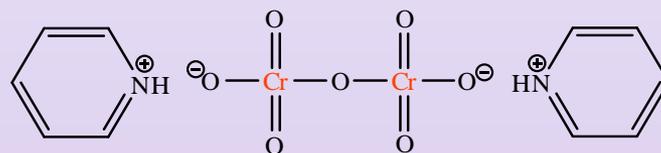
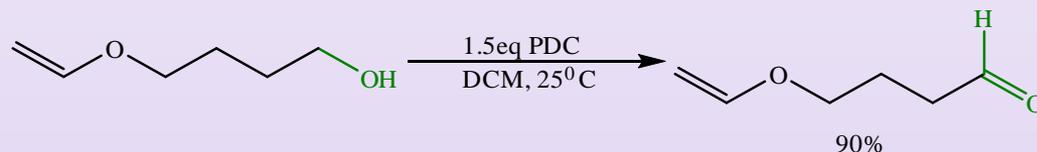
PCC is used in aprotic solvents, usually, dichloromethane.

As no water is present in the reaction mixture, no aldehyde hydrate is formed which is oxidized to carboxylic acid in presence of Cr(VI)

Agarwal S; Tiwari H  
P; Sharma J P,  
*Tetrahedron*, **1990**, 46,  
4417



□ Another similar oxidant is **PDC** (pyridiniumdichromate)



pyridiniumdichromate

Since **PDC** is **less acidic** than **PCC** it is often used to oxidize alcohols that may be sensitive to acids.

In methylene chloride solution, PDC oxidizes primary and secondary alcohols in roughly the same fashion as PCC, but much more slowly.

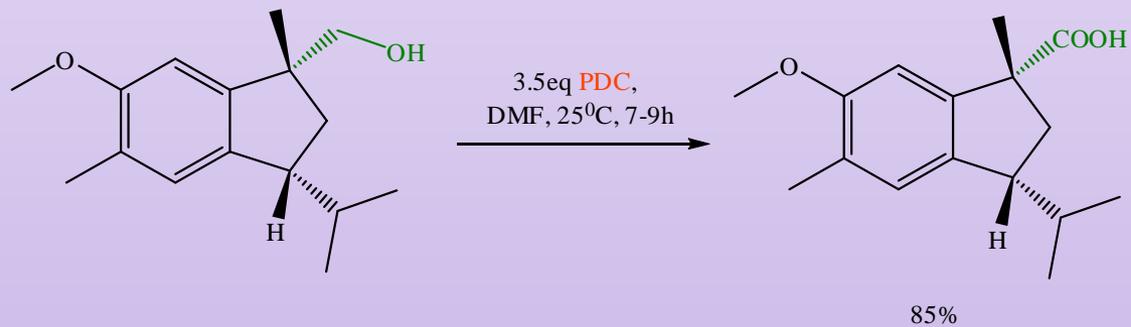
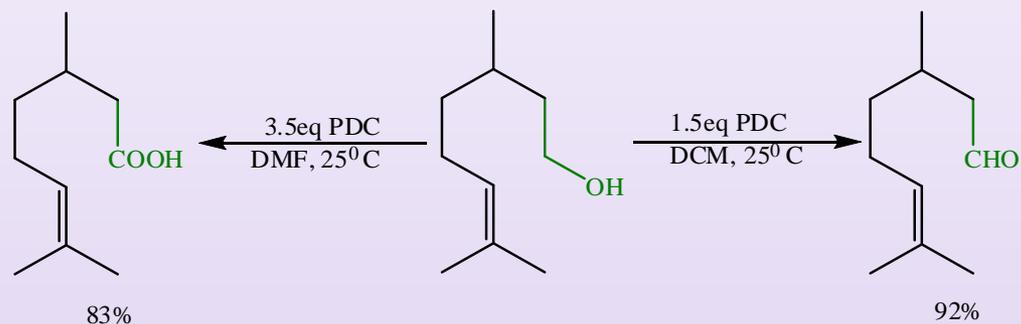
However, **in DMF** solution saturated **primary alcohols** are oxidized to **carboxylic acids**.

In both solvents allylic alcohols are oxidized efficiently to conjugated enals and enones respectively.

Stanfield C F, et al, *J. Org. Chem.*, **1981**, 46, 4797

Corey E J & Schmidt G, *Tet.Lett.*, **1979**, 20(5), 399

## examples

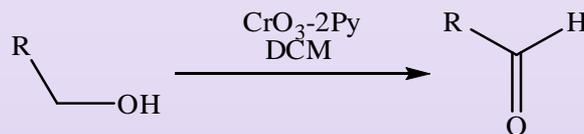


Collins reagent can be prepared and isolated or generated in situ.

Isolation of reagent often leads to improved yields.

□ Collins reagent is the mixture of **chromium trioxide** with **pyridine** in **dichloromethane**.

It is used to **selectively oxidize primary alcohols to aldehyde**, and will tolerate many other functional groups in the molecule.



It can be used as an **alternative to Jones reagent** and **PCC** in oxidation of secondary alcohols. Moreover, Collins reagent is especially useful for oxidations of **acid sensitive compounds**.

This complex is both **difficult** and **dangerous to prepare**, as it is very **hygroscopic** and can inflame during its preparation.

It is required to be used in a **sixfold excess** in order to complete the reaction.

## examples

one of the steps in the synthesis of [prostaglandin F2 \$\alpha\$](#)  employs Collin's reagent as oxidant

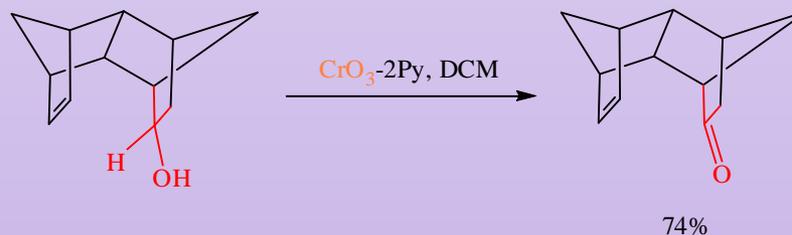
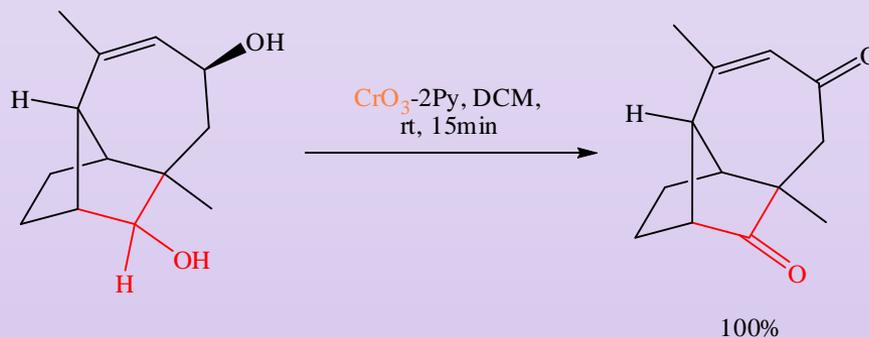
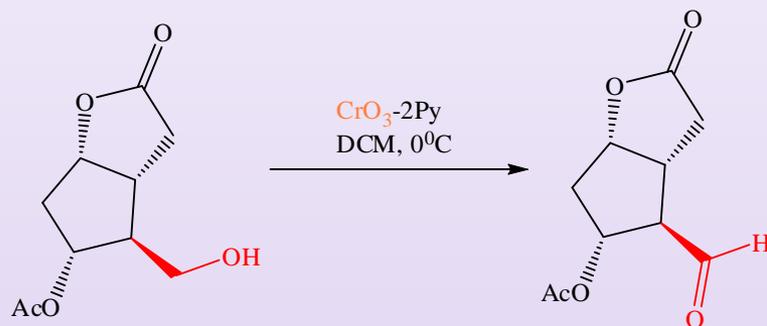
Corey E J, *JACS*, **1969**, 91, 5675

one of the steps in synthesis of longifolene employs Collin's reagent as oxidant

McMurry J E, *JACS*, **1972**, 94, 7132

one of the steps in synthesis of [triquinacene](#) employs Collin's reagent as oxidant

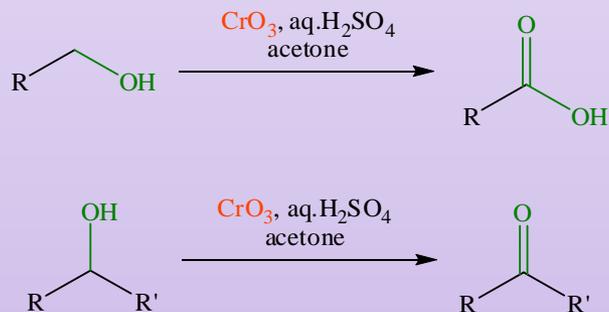
Woodward RB, *JACS*, **1964**, 86, 3162



Jones described for the first time a convenient and safe procedure for a chromium (VI) based oxidants, that paved way for some further developments such as Collins Reaction and pyridinium dichromate.

□ Jones reagent is used for the oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively, that do not contain acid sensitive group.

It is chromium oxide, sulfuric acid and acetone. A mixture of potassium or sodium dichromate and dilute sulfuric acid can also be used.



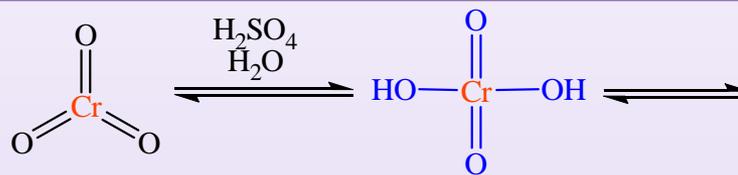
Mechanism :

Chromium trioxide or sodium dichromate with dilute  $\text{H}_2\text{SO}_4$  in situ forms chromic acid .

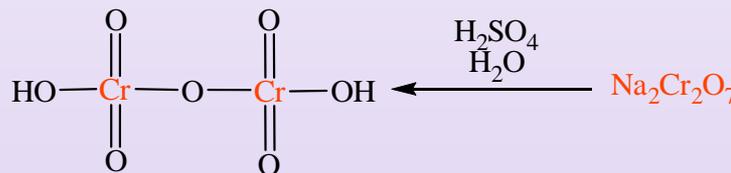
Chromic acid and alcohol then through chromate ester gives carbonyl compound in presence of base (water in this case).

The intramolecular reaction occurs by way of  $\beta$ -elimination through cyclic transition state.

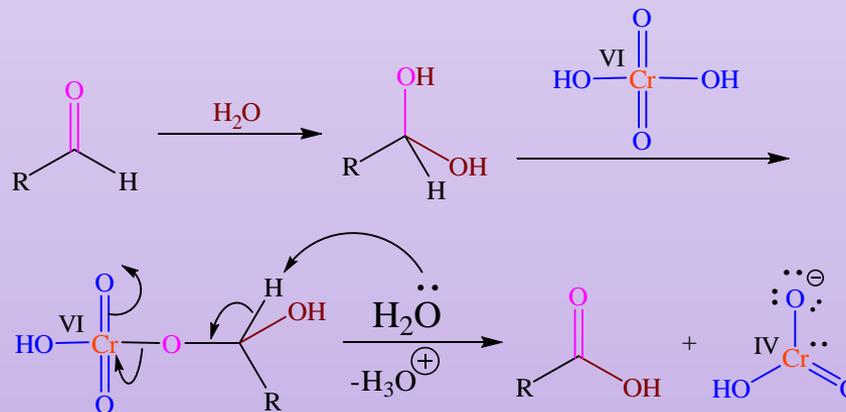
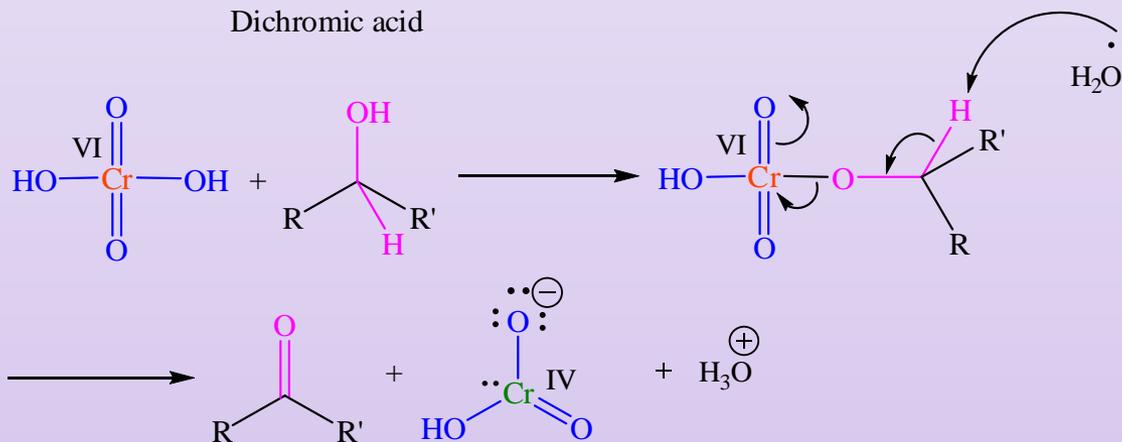
Aldehydes can form hydrates in presence of water and further oxidized to carboxylic acid in presence of  $\text{Cr(VI)}$  reagents.



Chromic acid



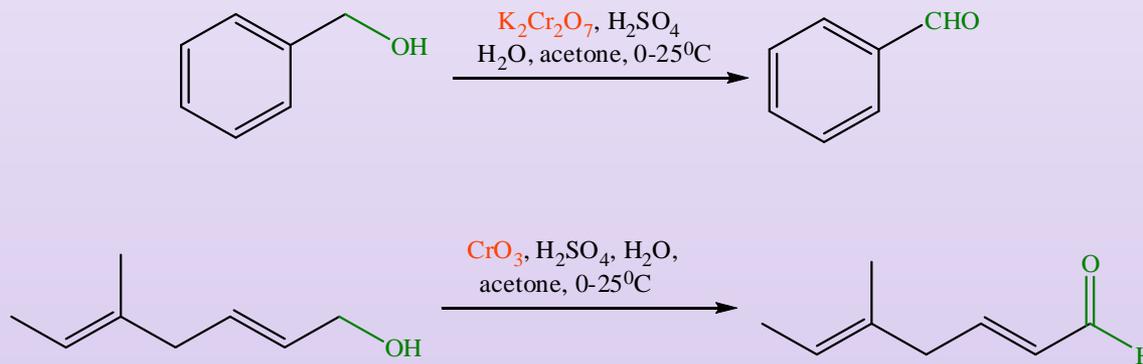
Dichromic acid



The Jones reagent is prepared by adding **chromium trioxide** to **dilute sulfuric acid** in **acetone** and is added to the alcohol at 0-25°C.

The **excess Cr(VI)**, if any is remained, is **destroyed** in the reaction **workup** by adding **isopropyl alcohol**.

The oxidation of **primary allylic** and **benzylic alcohols** gives **aldehydes**. Some alcohols such as benzylic and allylic alcohols give aldehydes that do not form hydrates in significant amounts; these can therefore be selectively oxidized with unmodified Jones Reagent to yield aldehydes.



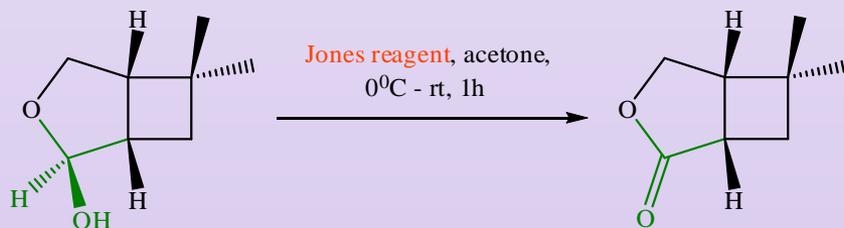
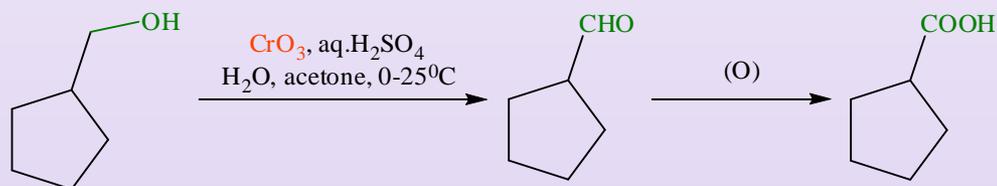
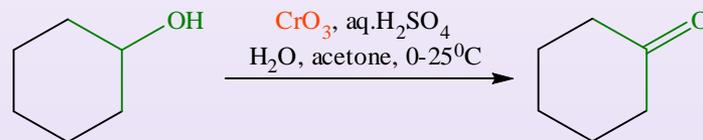
For the synthesis of aldehydes, the Collins Reaction or use of more modern although more expensive chromium (VI) reagents such as PCC and PDC can be an appropriate choice.

Tertiary alcohols cannot be oxidized by this reagent.

It is a powerful oxidizing reagent and exhibits only poor chemoselectivity.

oxidation of secondary alcohol gives ketone  
whereas primary alcohol  
is oxidized to aldehyde  
first and then to  
carboxylic acid.

Panda J; Ghosh S &  
Ghosh S, *ARKIVOC*,  
2001(viii), 146



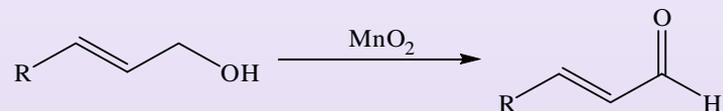
## II. Oxidation using Mn reagents

### (a) Mn(IV) reagent

Activity of  $\text{MnO}_2$  depends upon method of preparation and choice of solvent

$\text{MnO}_2$  is used widely as oxidant in organic synthesis.

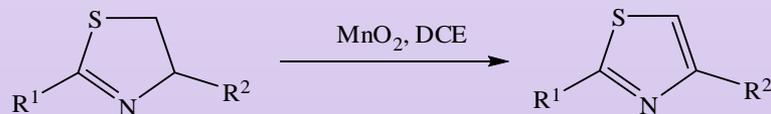
It oxidizes allylic alcohols to corresponding aldehydes or ketones.



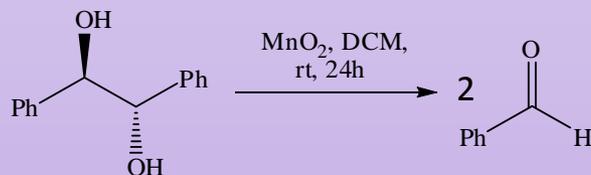
The configuration of double bond is preserved in the reaction.

Also, acetylenic alcohols and benzylic alcohols are oxidized under similar conditions.

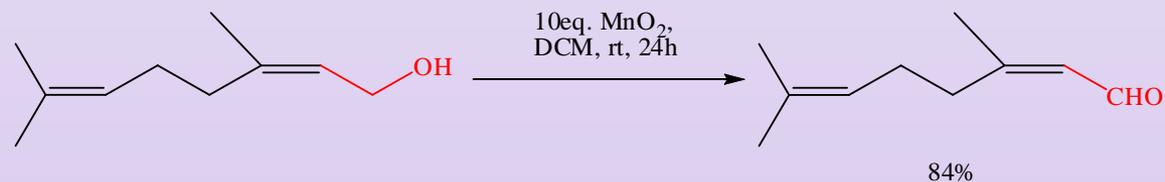
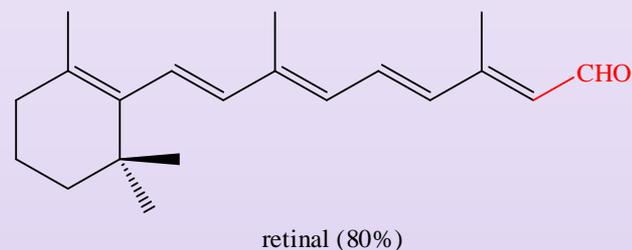
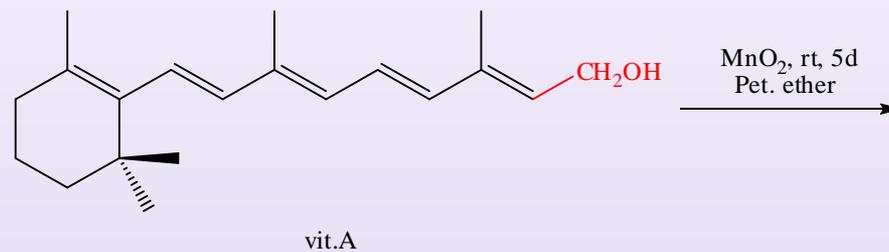
Applications of  $\text{MnO}_2$  are numerous. These include many kinds of reactions such as amine oxidation, aromatization, oxidative coupling, and thiol oxidation.



1,2-Diols are cleaved by  $\text{MnO}_2$  to dialdehydes or diketones.



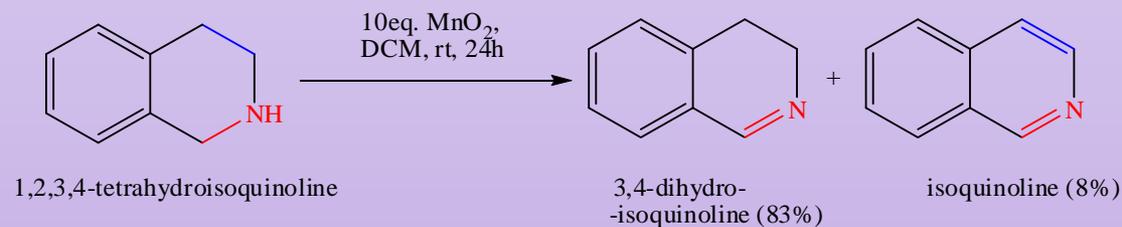
examples



oxidation of benzylic and allylic alcohol with  $\text{MnO}_2$  in mild condition

Aoyama T; et al,  
*Synlett*, **1998**, 35.

dehydration is also accomplished in good yields

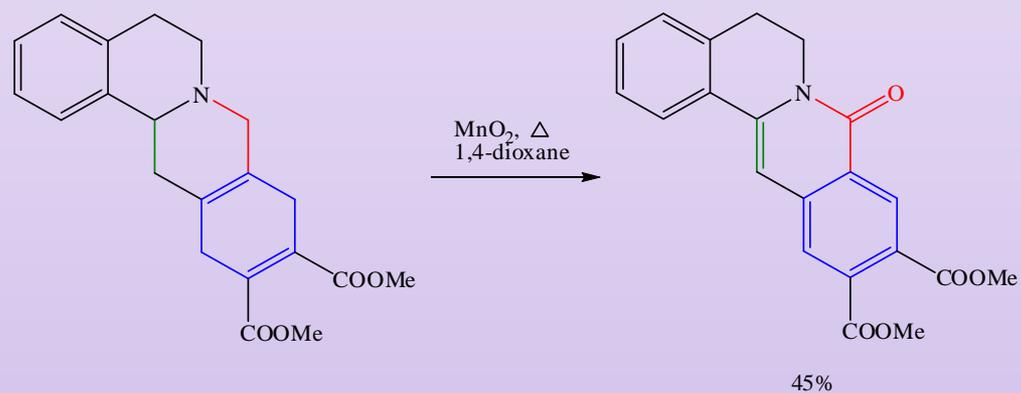
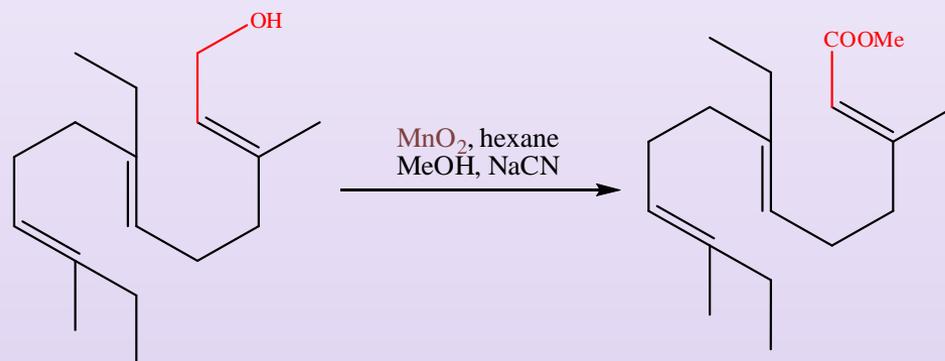


Oxidation of allylic alcohol  
to corresponding ester in  
methanolic solvent.

E J Corey; N W  
Gilman; B E Ganem,  
*JACS*, **1968**, 90, 5616

Husinec S; et al,  
*Tet.Lett.*, **2011**, 52,  
2733

## More examples



## (b) Mn (VII) reagents

Manganese can function as oxidant when it is in +7 oxidation state.

$\text{KMnO}_4$  is one such oxidant. It is a very strong oxidizing agent.

Alkyl side chains on aromatic rings are oxidized to carboxylic acid group. This method is more generally applied to methyl group, however, longer side chains can also be cleaved.

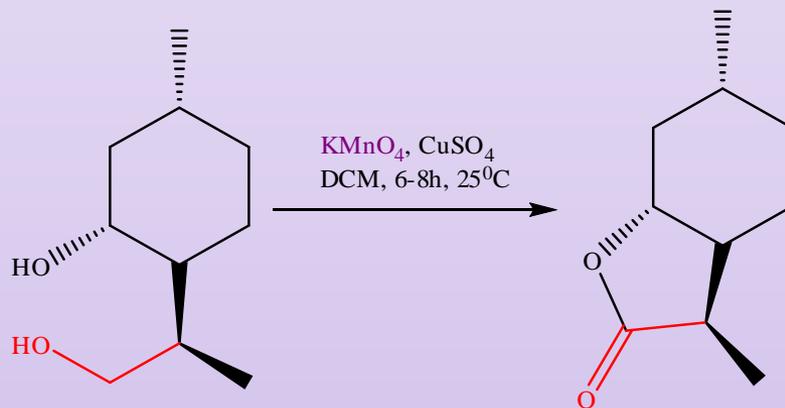
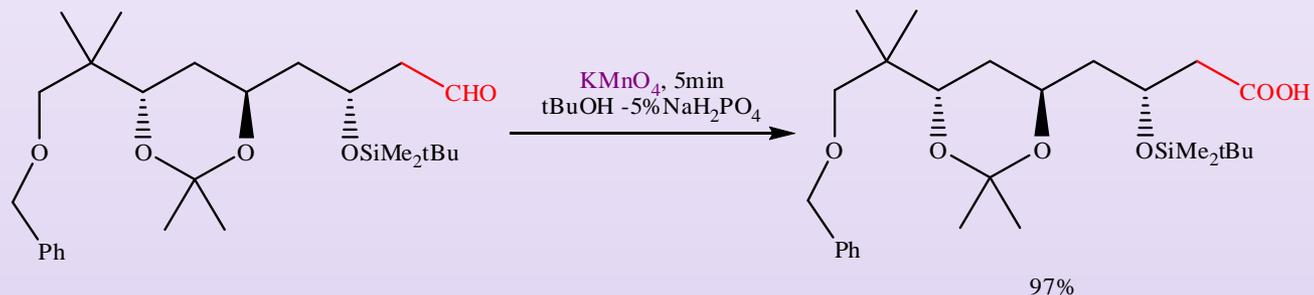
Tertiary alkyl groups are not oxidized and are usually accompanied by ring cleavage.

$\text{KMnO}_4$  is also used to oxidize primary alcohol and aldehyde to corresponding carboxylic acid.

Abiko A; Roberts J C;  
Takemasa T &  
Masamune S, *Tet.Lett.*,  
**1986**, 27, 4537

Jefford C W; Li Y;  
Wang Y, *Org. Syn.*,  
**1998**, 9, 462

Protected hydroxy aldehydes are oxidized to corresponding carboxylic acids with  $\text{KMnO}_4$  buffered with mixture of  $\text{tBuOH}$  and aq.  $\text{NaH}_2\text{PO}_4$

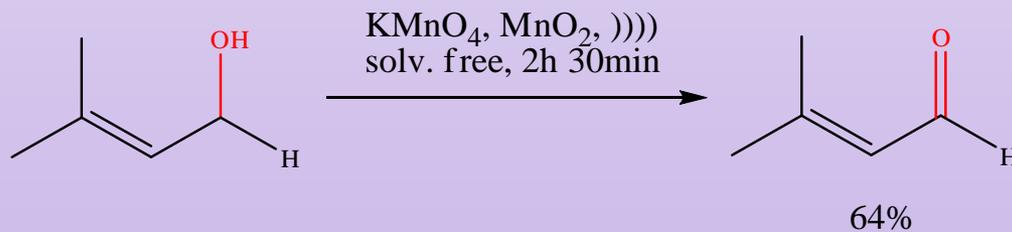
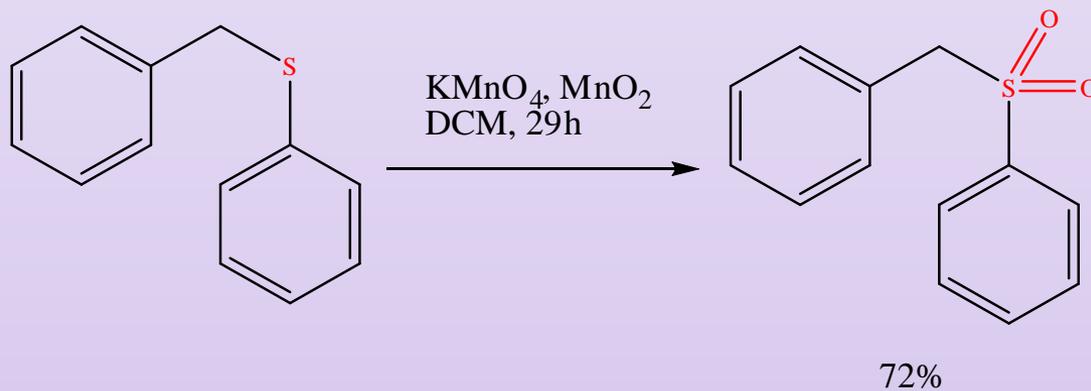
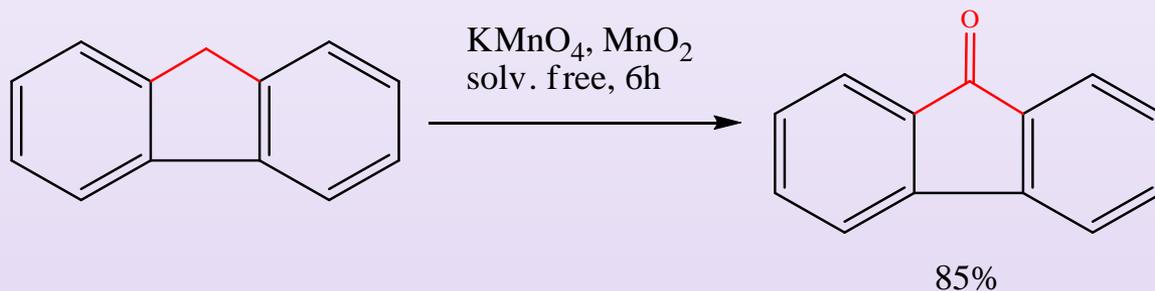


In this reaction  $\text{KMnO}_4$  first oxidizes primary alcohol to corresponding carboxylic acid which subsequently cyclizes to give a lactone.

oxidation using  $\text{KMnO}_4$   
supported on  $\text{MnO}_2$   
under heterogenous and  
solvent free conditions

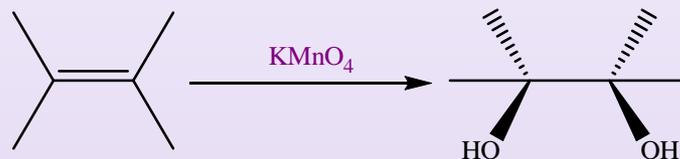
Shaabani A; et al, *Tet.*,  
**2004**, 6, 11415.

### More examples



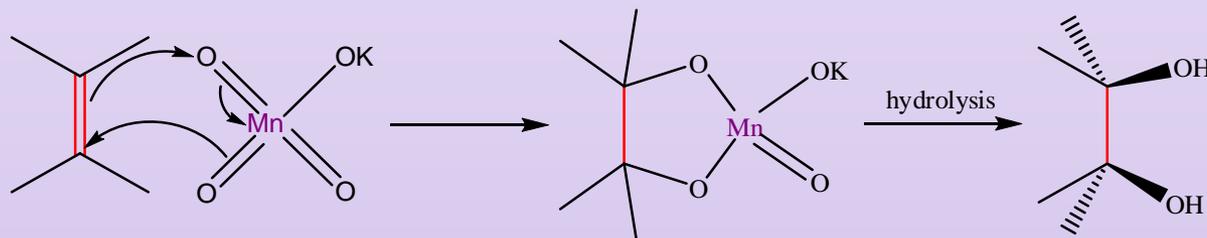
This reaction is also used as a qualitative test for the presence of double or triple bonds in a molecule, since the reaction decolourises the permanganate solution. It is sometimes referred to as [Baeyer's reagent](#).

Dilute solutions of  $\text{KMnO}_4$  convert alkenes into diols.



Dihydroxylation of alkenes using alkaline  $\text{KMnO}_4$  is a stereoselective syn addition of two hydroxyl groups across a double bond.

The reaction is believed to proceed through a cyclic permanganate ester intermediate.

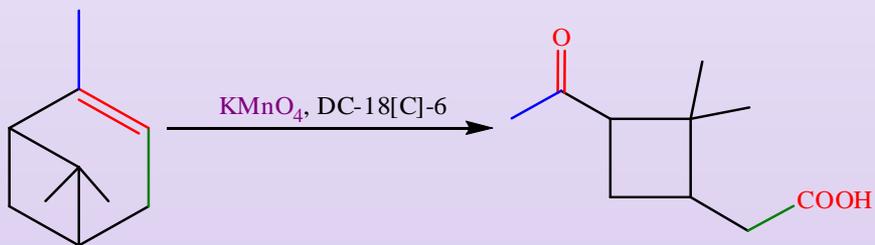
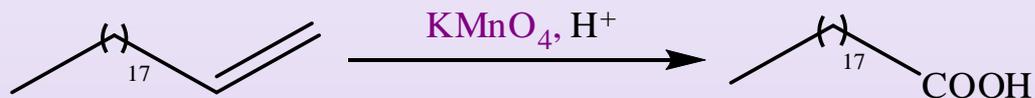


Though the presence of such an intermediate can not be confirmed by actual isolation. But, some of them are detectable spectroscopically also use of  $\text{Mn}^{18}\text{O}_4^-$  in the reaction lead to formation of 1,2-diols in which both the oxygen atoms were labeled. So, it can be concluded that both of them are coming from  $\text{Mn}^{18}\text{O}_4^-$ , and hence the presence of an intermediate cyclic permanganate ester can be confirmed.

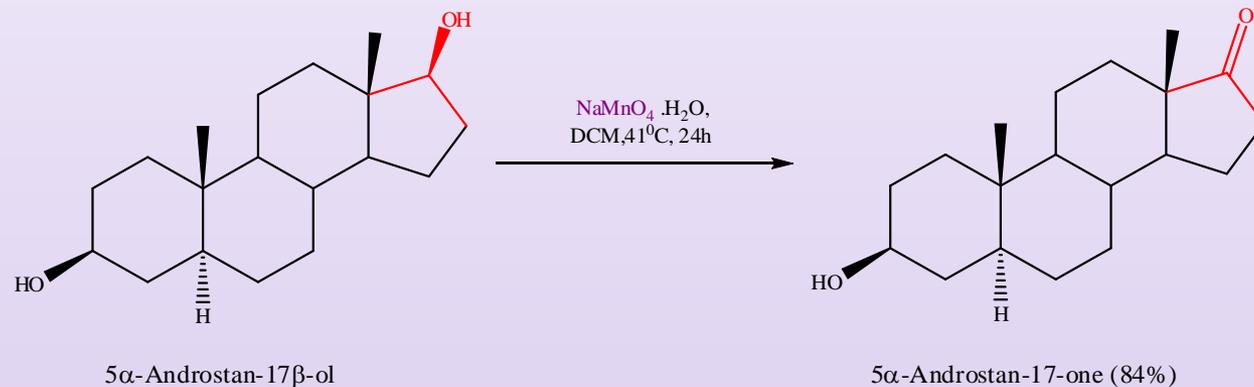
D J Sam; H E  
Simmons, *JACS*, **1972**,  
94, 4024

*Synthesis*, **1984**, 43,  
443

Under acidic conditions, the alkene double bond is cleaved to give a carboxylic acid.



$\text{NaMnO}_4$ , sodium permanganate is similar oxidant to  $\text{KMnO}_4$ . It oxidizes primary alcohol to acid and secondary alcohol to ketones but does not have any effect on multiple bonds.



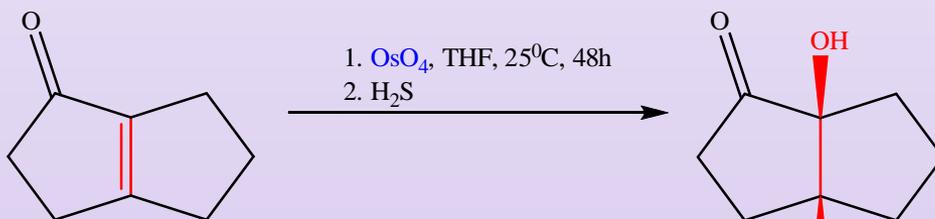
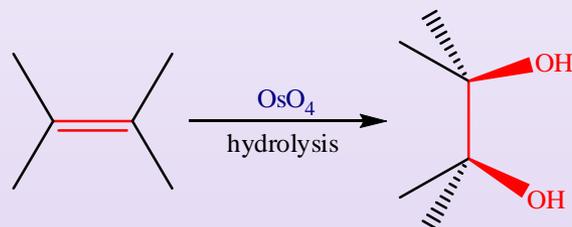
Menger F M and Lee  
C, *Tet.Lett.*, **1981**, 22,  
1655.

### III. Oxidation using Os reagent

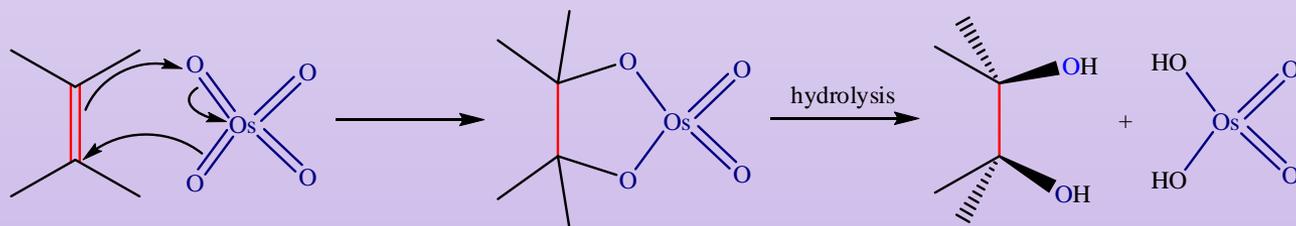
Os(VIII) reagent

p-electrons of olefins act as a nucleophile and forms favorable 5-membered ring as cyclic osmate ester by attacking  $\text{OsO}_4$ . This is considered as the origin of cis stereoselectivity. This osmate ester upon hydrolysis liberates cis diol and reduced osmium species.

$\text{OsO}_4$  is primarily used in cis dihydroxylation of olefins.

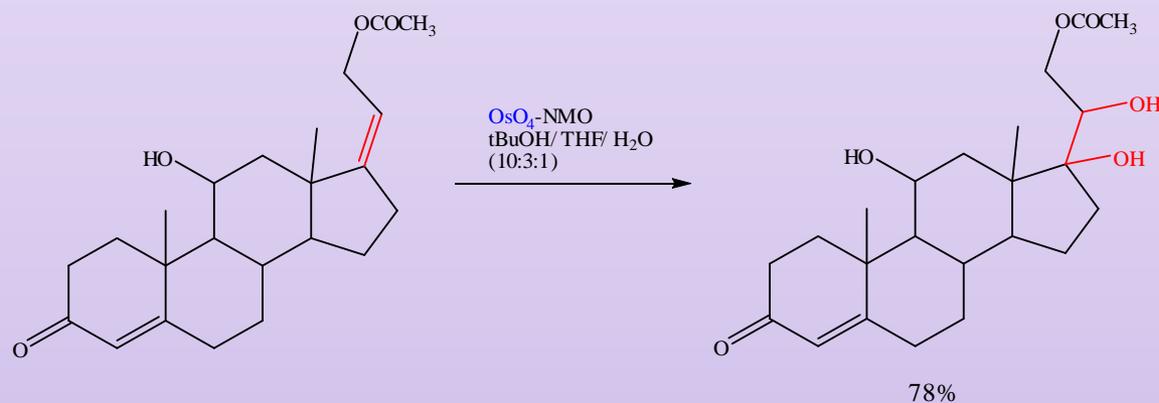
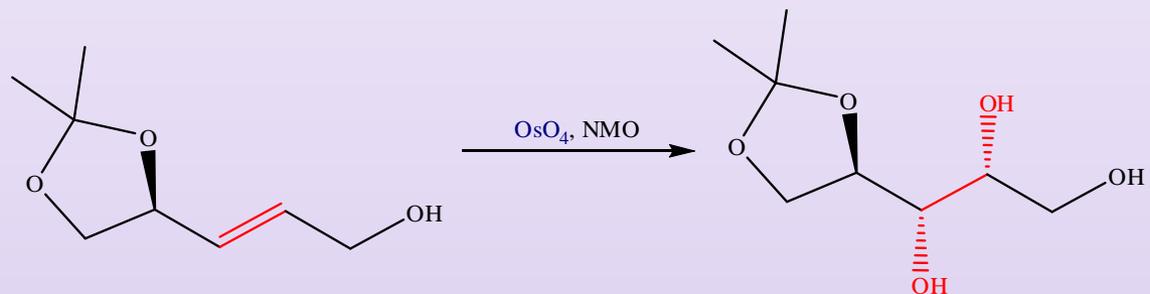


Mechanism of reaction goes through the formation of 5-membered cyclic ester intermediate.



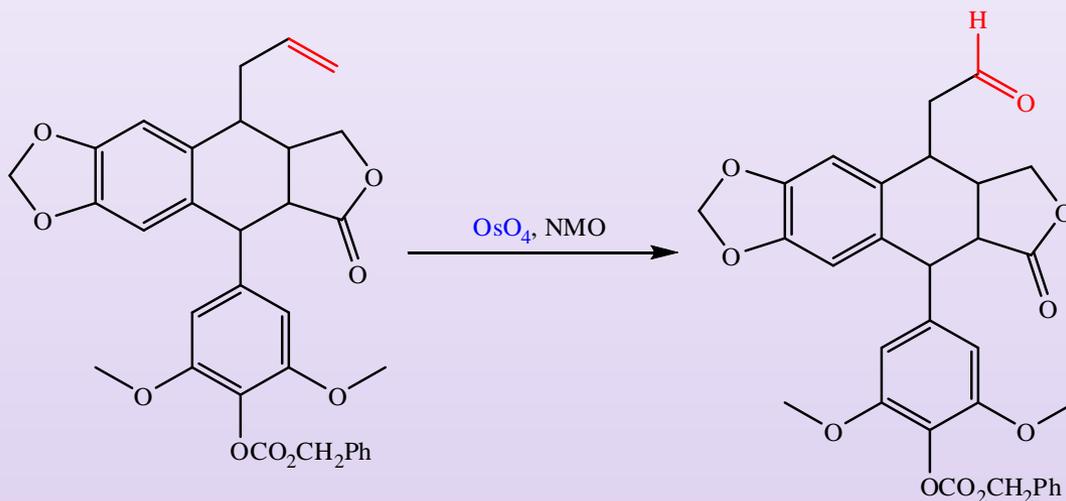
$\text{OsO}_4$  is toxic and is used in catalytic amounts in reaction. It can be reoxidized using co-oxidant such as NMO,  $\text{K}_3\text{Fe}(\text{CN})_6$ , etc.

NMO = *N*-methyl morpholine



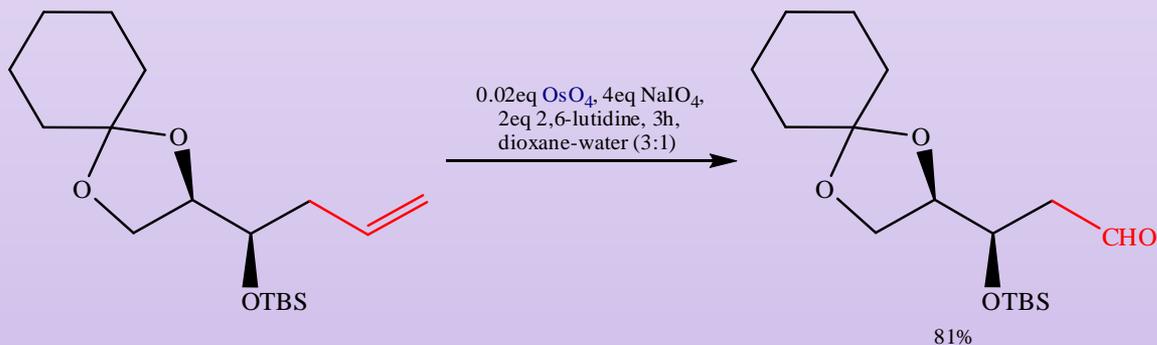
The use of NMO in catalytic  $\text{OsO}_4$  reactions was first reported for the introduction of corticoid side chain (an  $\alpha$ -ketol) in a steroid (as shown above).

$\text{OsO}_4$  is also used for oxidative cleavage of olefin. It forms carbonyl compound.



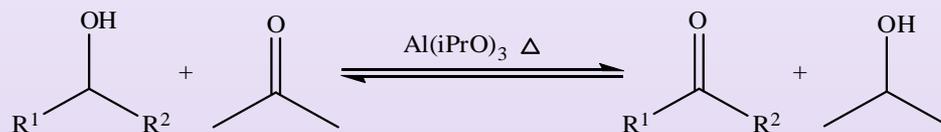
Oxidative cleavage of olefins using  $\text{OsO}_4$  -  $\text{NaIO}_4$  in presence of 2,6-lutidine

Yu W; Mei Y; Kang Y; Hua Z and Jin Z, *Org.Lett.*, **2004**, 6, 3217.



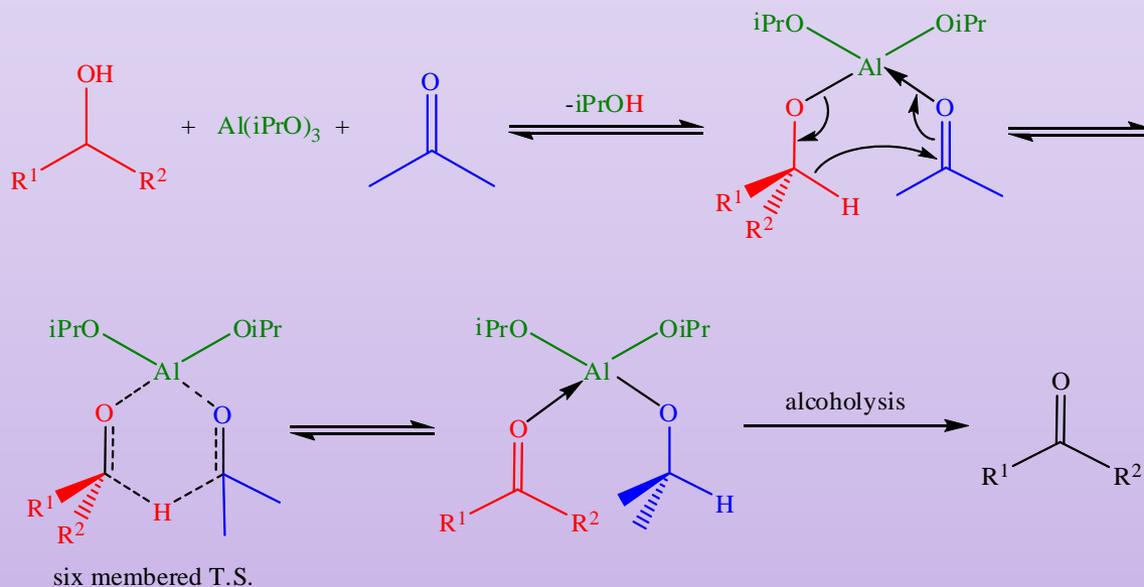
## IV. Oppenauer oxidation

Oxidation of primary and secondary alcohol with ketone in the presence of metal alkoxide to corresponding aldehyde or ketone is known as **Oppenauer oxidation**.



The reaction is completely reversible and can be driven to completion according to [Le Chatlier's principle](#) by addition of excess of ketone.

In the first step of the mechanism, alcohol, aluminium and acetone coordinates to form a complex. This complex then, via a six-membered chair like transition state transfers hydride from α-carbon of the alcohol to the carbonyl carbon of acetone to give the desired ketone as product.



▪ In 1937, Oppenauer discovered this reaction.

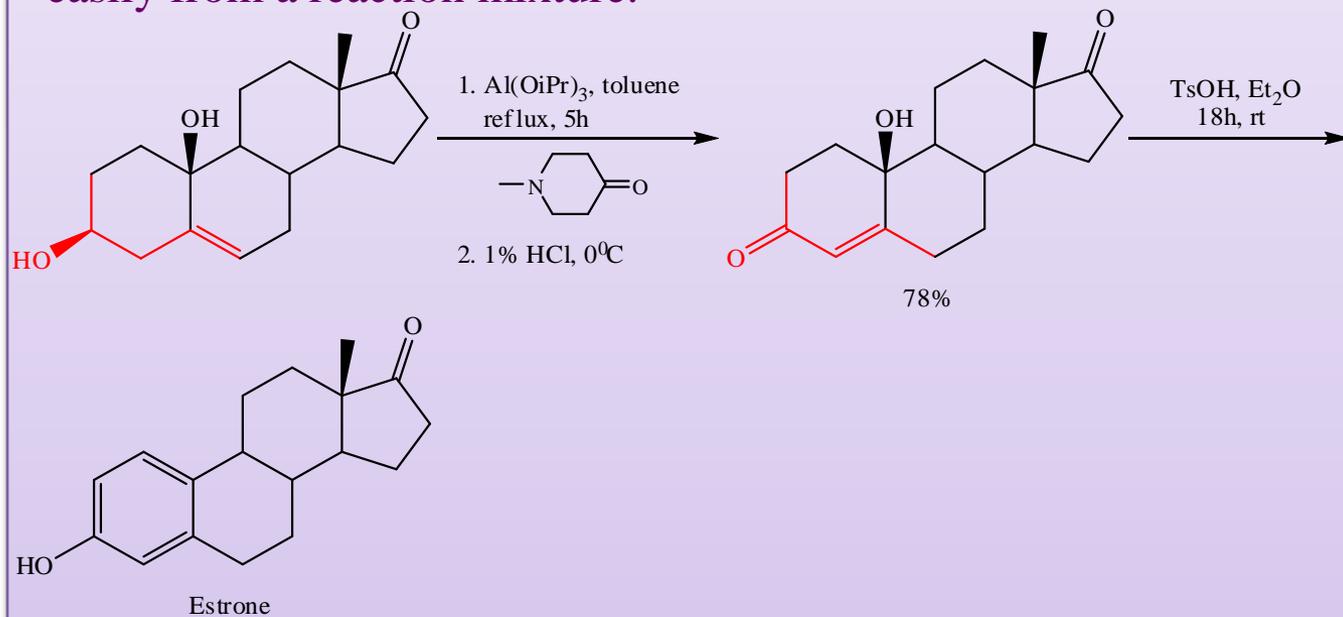
▪ Reaction is reverse of Meerwein-Ponndorf-Verley reduction.

Oppenauer oxidation has many advantages.

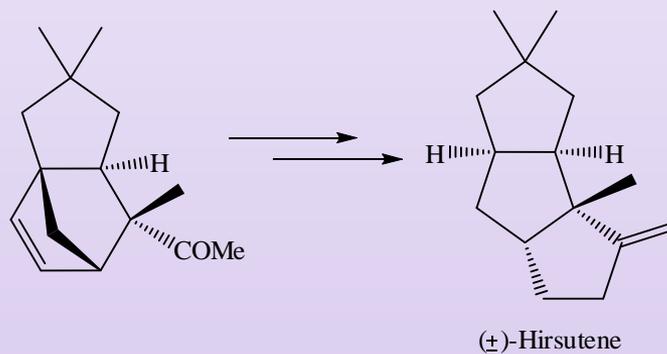
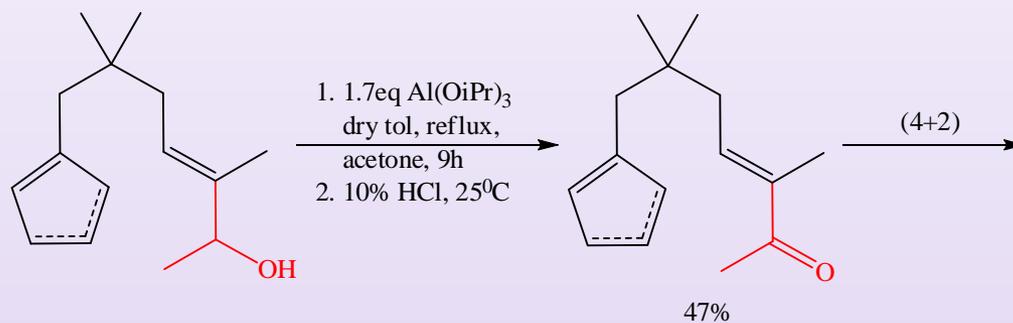
- mild reaction conditions.
- most functional groups are tolerated (If substrate contains basic nitrogen then use of alkali metal alkoxide is necessary instead of Al-isopropoxide).
- in order to achieve reasonable reaction rate, stoichiometric amount of Al-alkoxide to be used (Al-isopropoxide, Al-tertbutoxide, Al-phenoxide can be used).
- wide range of substrates are oxidized.
- secondary alcohols are oxidized faster than primary alcohols. Due to this secondary alcohols can be oxidized chemoselectively over primary ones.
- over oxidation to carboxylic acid does not happen.
- oxidation of 1,4 and 1,5-diols yields lactones.
- acetone is most often used as an oxidant but aromatic and aliphatic aldehyde are suitable as oxidants due to low reduction potential.

## Synthetic applications

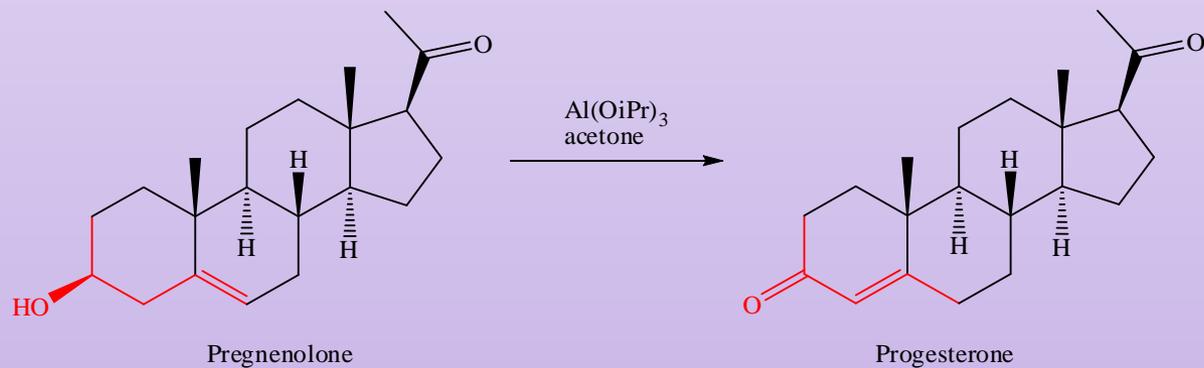
### Syntheses of Estrone from tetracyclic diol



Syntheses of linearly fused triquinane ( $\pm$ )-hirsutene.



syntheses of hormone progesterone



## Syntheses of steroid derivative

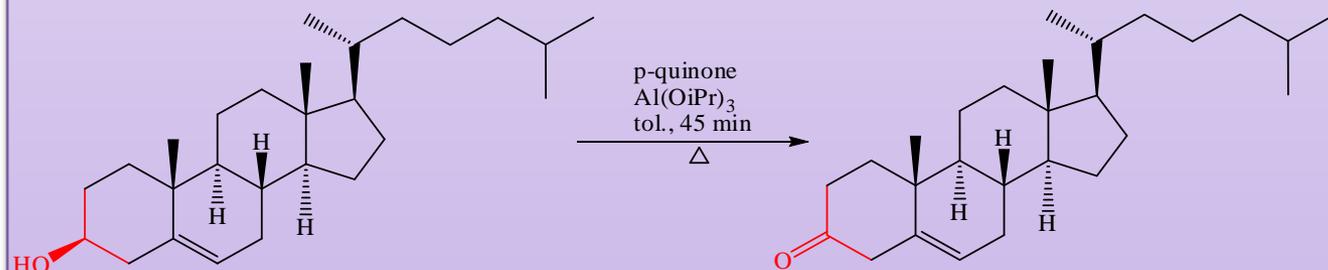
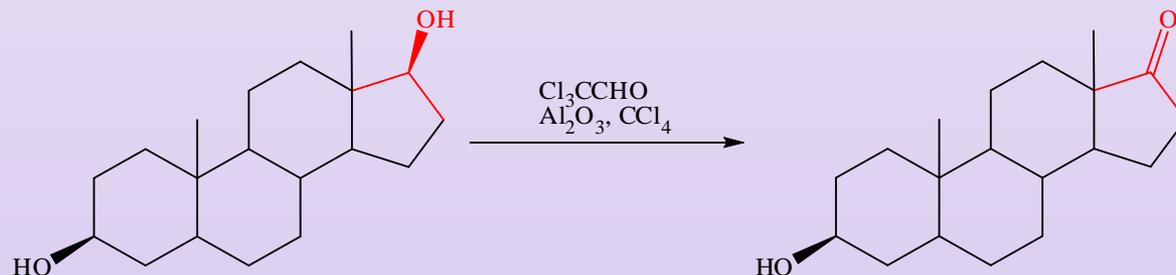
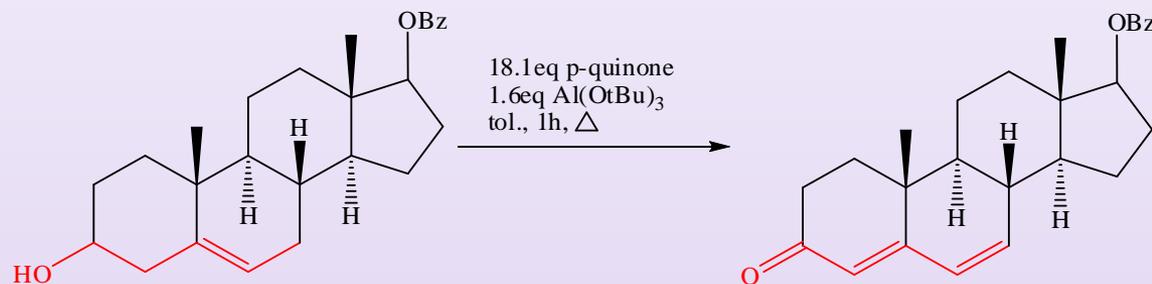
### Oppenauer oxidation using strong oxidant p-quinone

acetone, cyclohexanone or N-methylpyridinone gives over oxidation

trichloroacetaldehyde on alumina is used as oxidant.

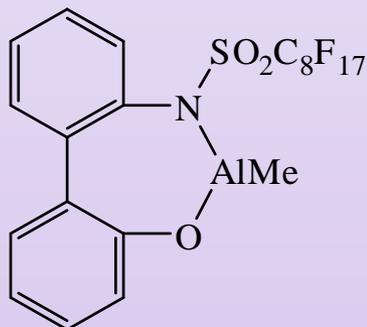
secondary alcohol gets readily oxidized over primary.

oxidation of cholesterol using p-quinone



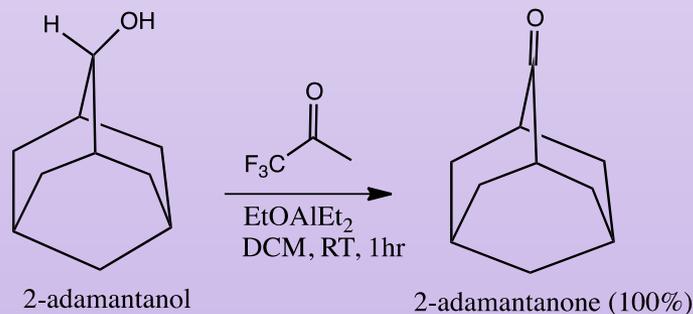
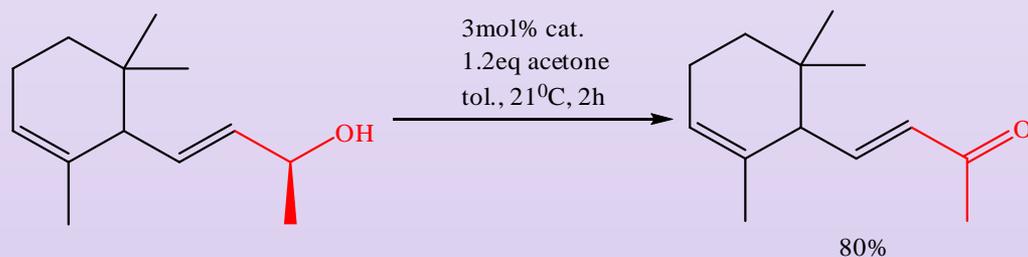
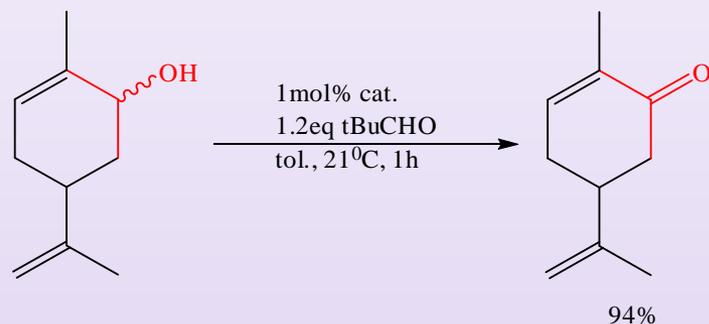
Ooi T; Otsuka H;  
Miura J; Ichikawa H;  
Maruoka K; *Org.*  
*Lett.*, **2002**, 4, 2669.

Catalyst:



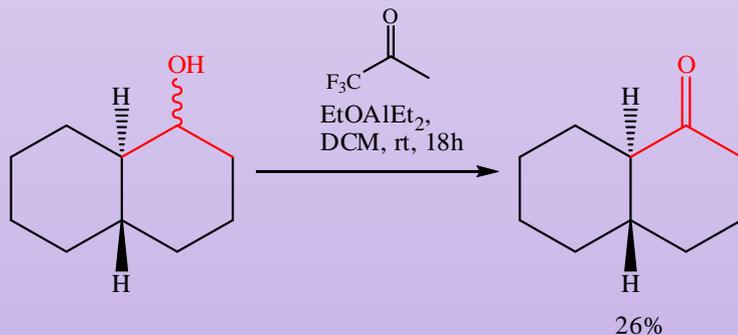
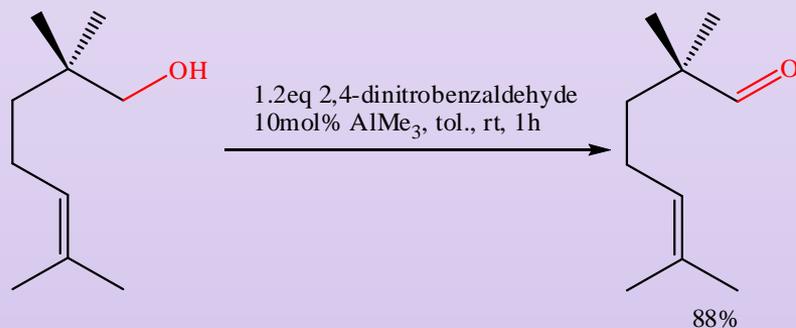
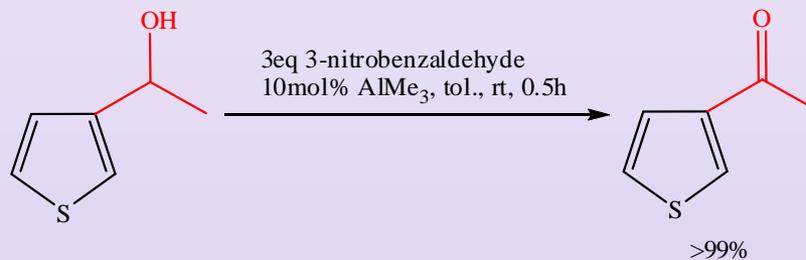
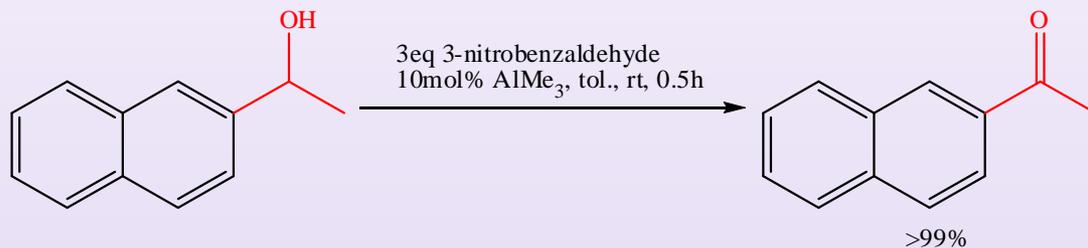
Mello R;  
Martinez-Ferrer J;  
Asensio G; Slena  
M, *JOC*, **2007**, 72,  
9376.

## Oxidation of Carveol:

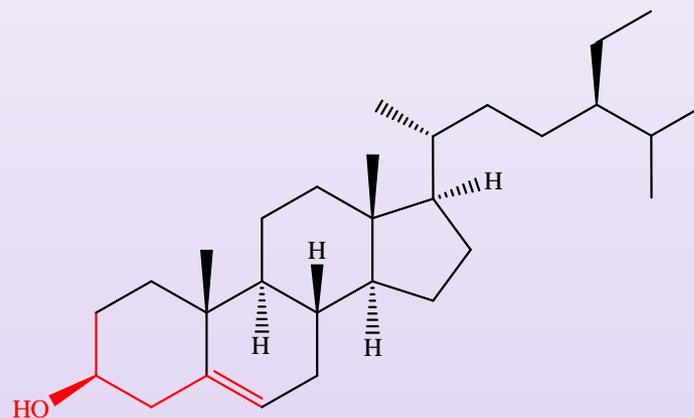


Graves C R; Zeng B  
S; SonBinh T N,  
*JACS*, **2006**, 128,  
12596.

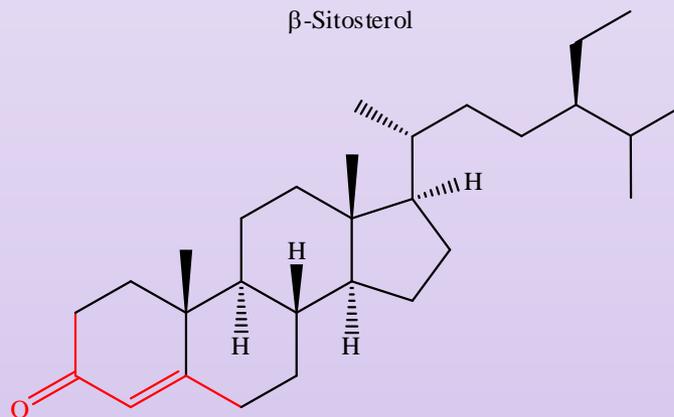
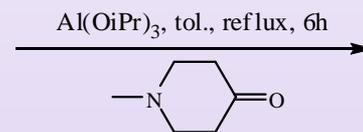
Mello R; Martinez-  
Ferrer J; Asensio G;  
Slena M, *JOC*, **2007**,  
72, 9376.



Raggio M L; Watt D  
S, *JOC*, 1976, Vol.41,  
No.10, 1873.



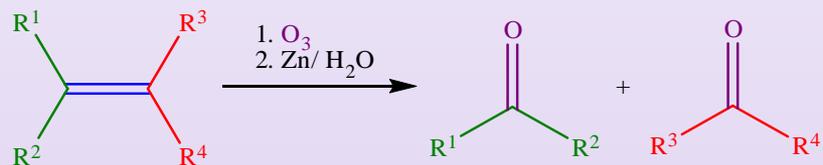
$\beta$ -Sitosterol



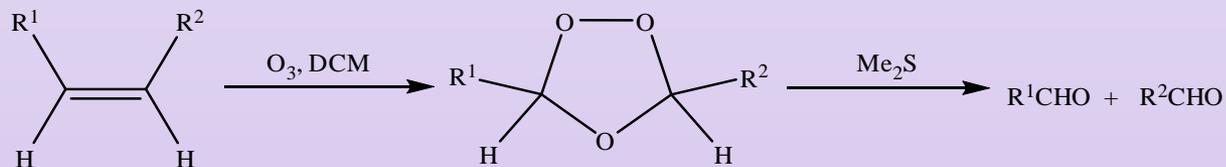
24-Ethylcholest-4-en-3one (71%)

## V. Ozonolysis

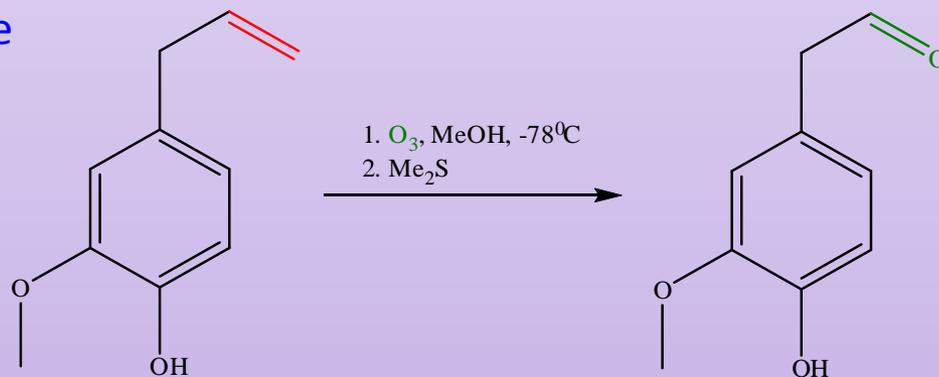
Ozonolysis involves the cleavage of olefins with ozone. It forms either carbonyl compound or carboxylic acid depending on work up procedure.



Ozonolysis is an oxidative cleavage (like permanganate). But, it is comparatively mild reaction and no overoxidation is seen.

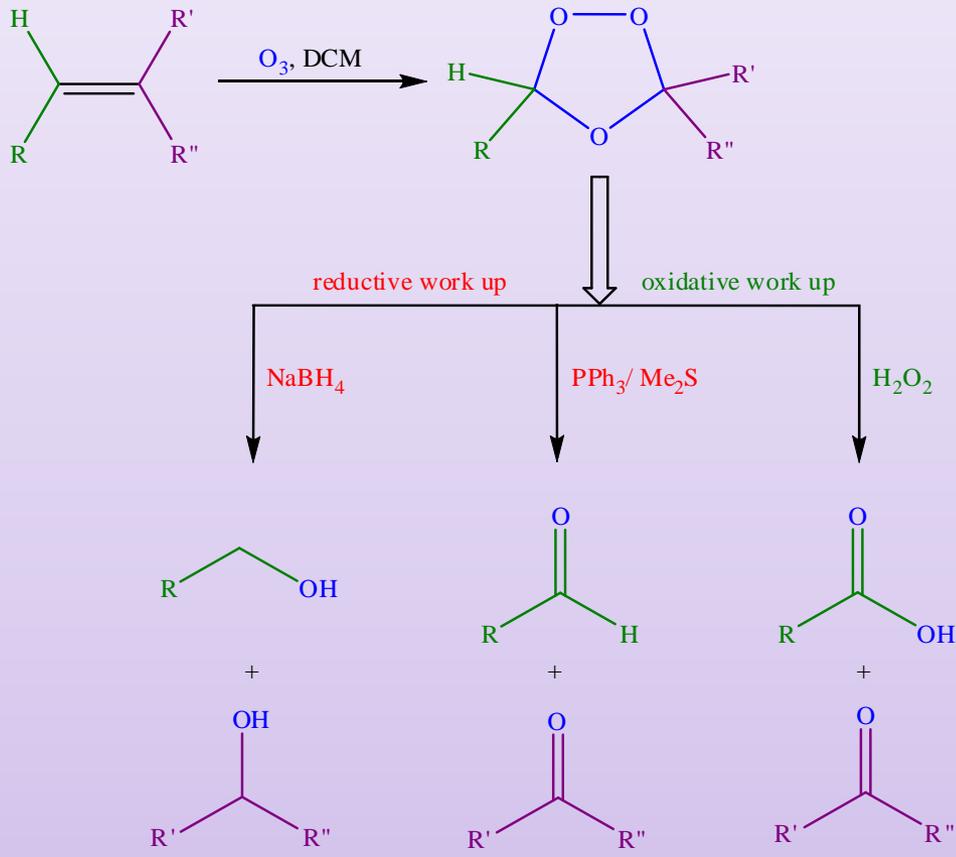


example



oxidation of eugenol to corresponding aldehyde

Reductive work up forms aldehydes and ketones while in oxidative work up aldehydes are further oxidized to corresponding alcohol.

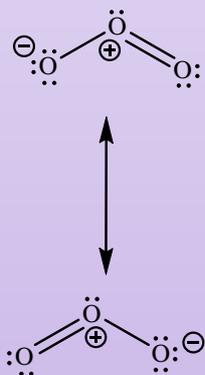


Overall result is that double bond is replaced by an ozonide ring.

work up of ozonide

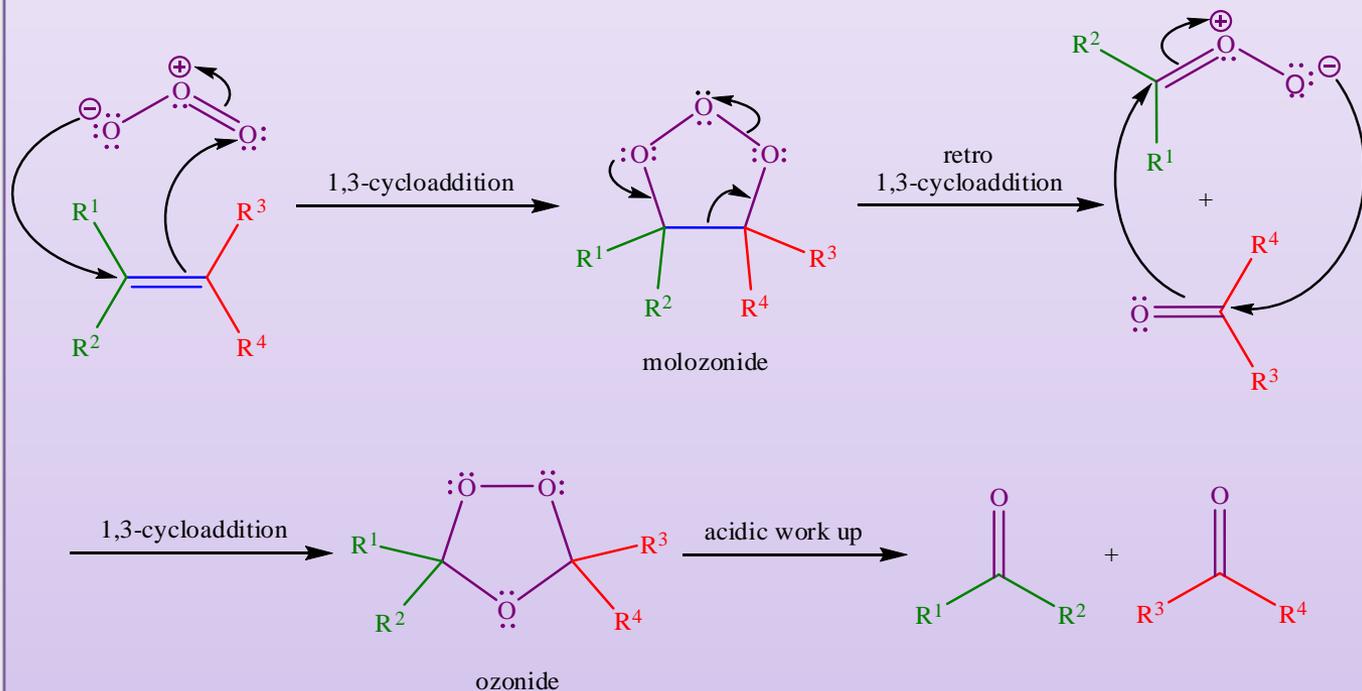
Ozone is high energy form of oxygen, produced when UV light or electrical discharge passes through oxygen gas.

Lewis structure has central oxygen positively charged and each outer oxygen has  $\frac{1}{2}$  negative charge.



Ozonolysis is a two step reaction.

First step is 1,3-dipolar addition of ozone across the double bond, to give molozone. It rapidly undergoes rearrangement to give ozonide.

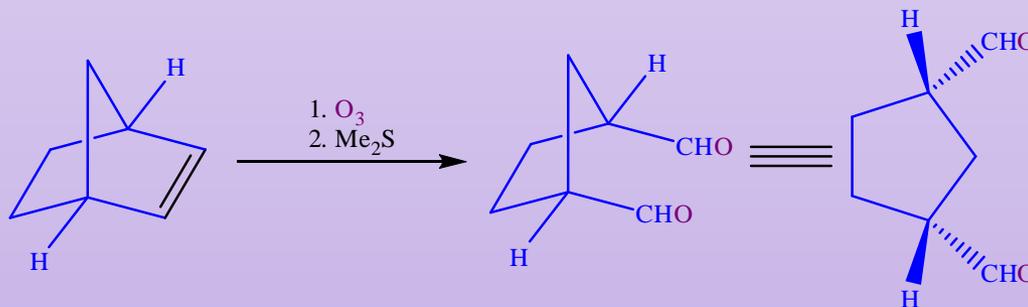
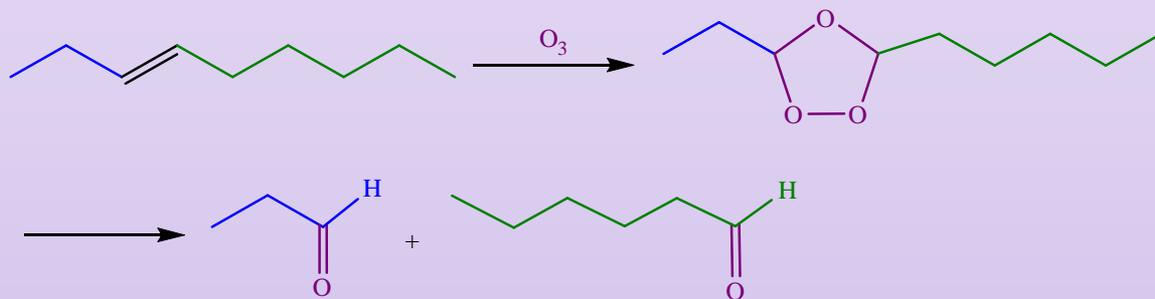
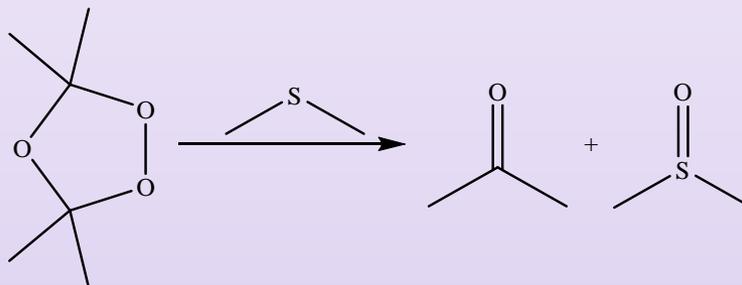


Second step is work up. Oxidative work up can be done by aqueous acid while reductive work up by zinc and water or dimethyl sulfide or  $\text{Pd-H}_2$ .

More details on  
ozonolysis reaction

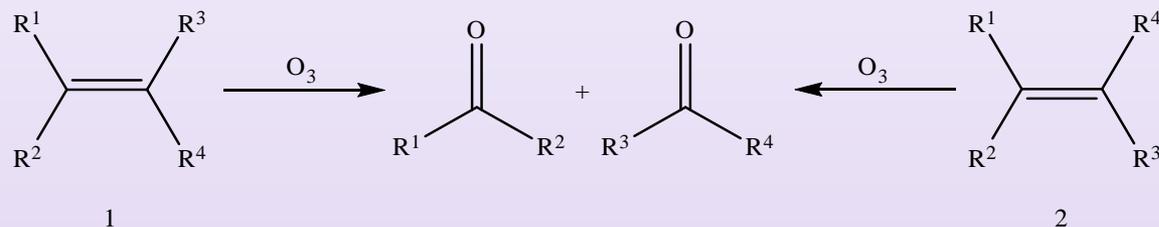
**Molozonide** or primary ozonide has peroxy linkage which makes it **unstable** and it undergoes rapid rearrangement to give ozonide.

On the other hand, ozonide is stable but is rarely isolated. It is reduced with mild reducing agents to give aldehydes or ketones.

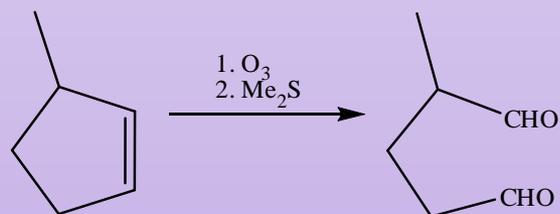
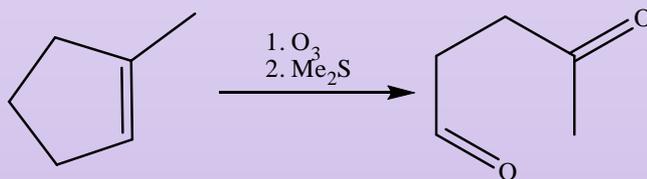
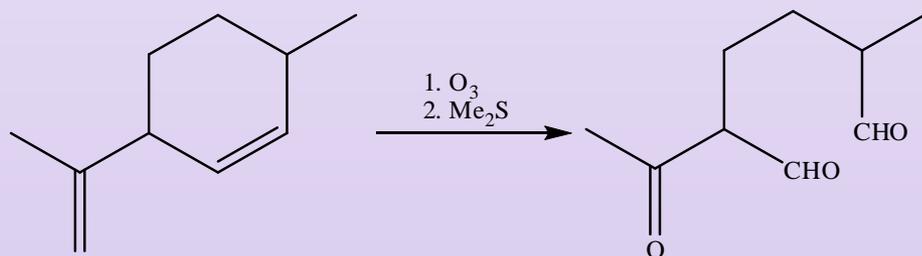


## Key facts about ozonolysis

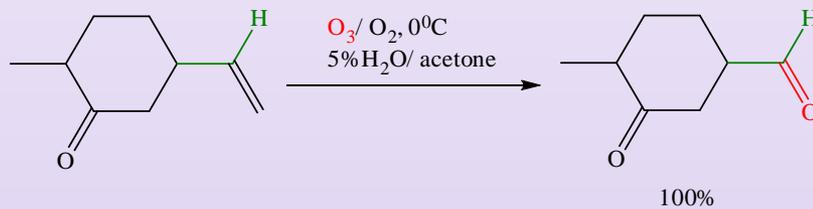
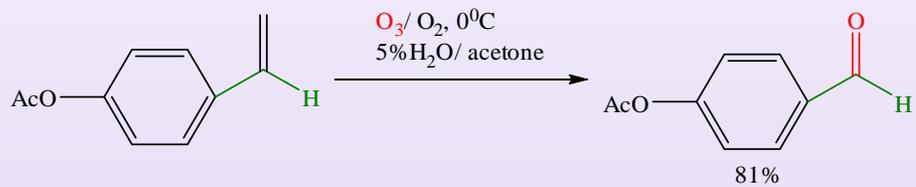
Ozonolysis does not afford information about stereochemistry of alkene. Thus, 1 and 2 give same carbonyl compound.



Ozonolysis is mainly used to determine the position of a double bond in an alkene.

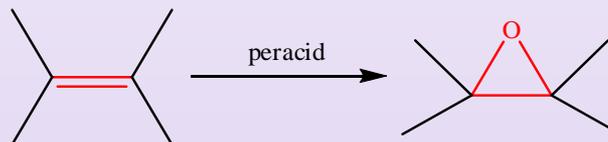


Schiaffo C E &  
Dussault P H, *JOC*,  
2008, 73, 4688.



## VI. Epoxidation

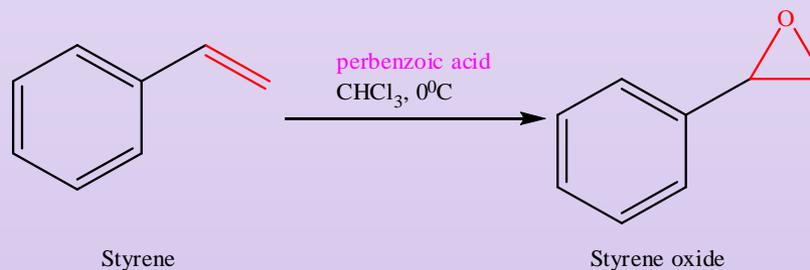
Epoxidation is a reaction in which  $C=C$  of an olefin is converted to an epoxide (or oxirane), a cyclic ether.



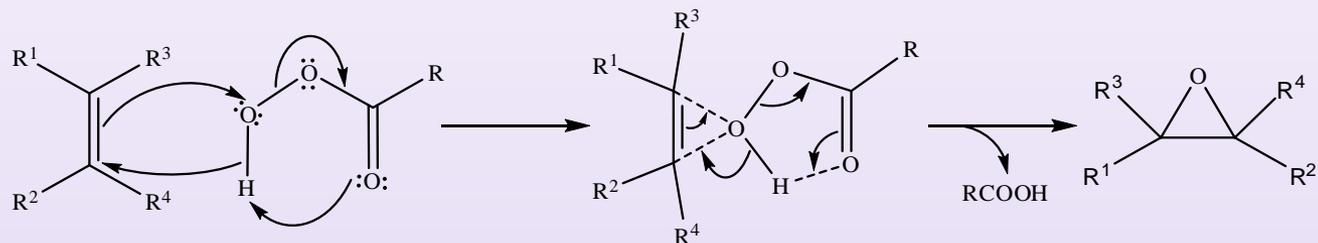
Commonly used reagents are peracid or peroxyacid, peroxide, etc.,

Addition of oxygen to  $C=C$  is syn stereoselective

epoxidation of styrene  
using perbenzoic acid



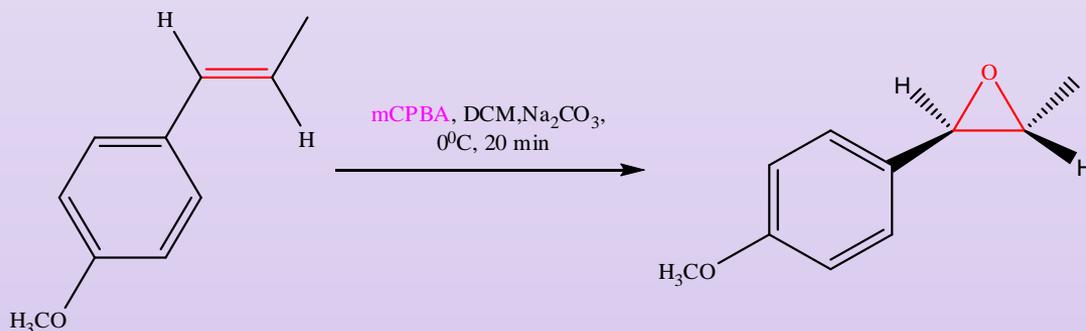
The reaction is an example of a concerted process (all bonding changes occur in one step)



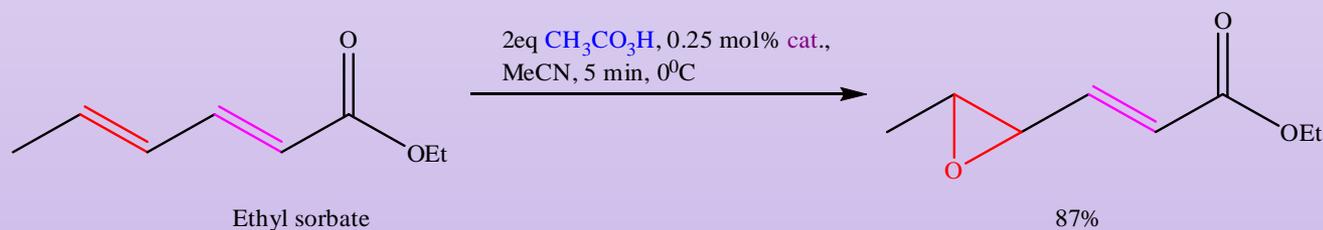
Since the reaction is concerted the stereochemistry of the alkene is preserved in the product.

For example if the alkyl groups of the alkene are cis then they are also cis in the epoxide.

*J.Chem. Edu.*, **2001**, 78.



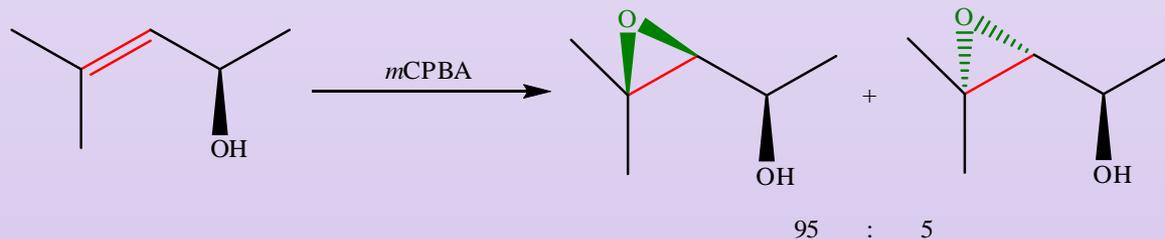
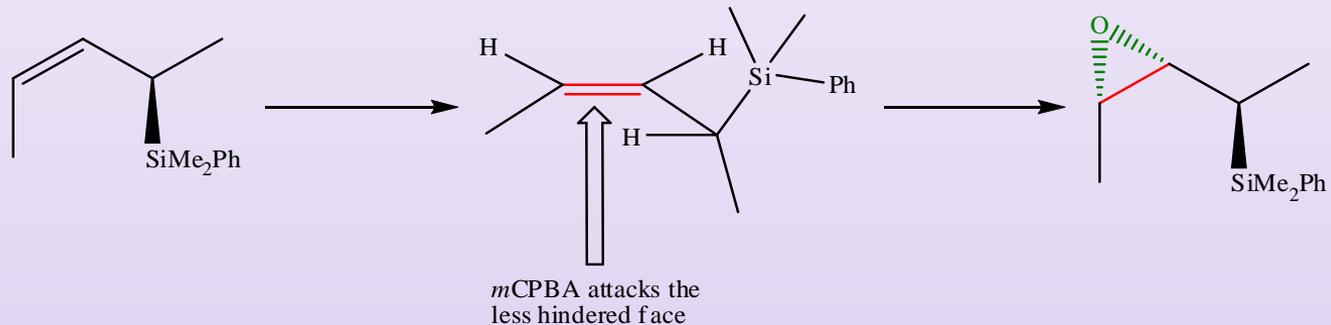
Dubois G; Murphy A  
and Stack T D P,  
*Org.Lett.*, **2003**, 5, 2469.



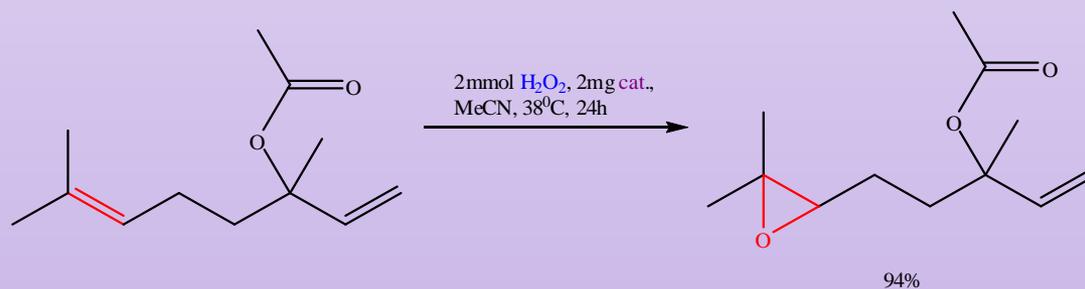
Catalyst:  $[\{(Phen)_2(H_2O)Fe^{III}\}_2(\mu-O)](ClO_4)_4$

only important conformer has H eclipsing double bond

Epoxidation of an olefin is distereoselective reaction. The reagent attacks alkene from less hindered face.



Villa de P A L; Sels B F;  
De Vos D E and Jacobs P  
A, *JOC*, 1999, 64, 7267.



Catalyst:  $\text{PW}_4\text{O}_{24}[(\text{C}_4\text{H}_9)_4\text{N}]_3$ -Amberlite IRA900

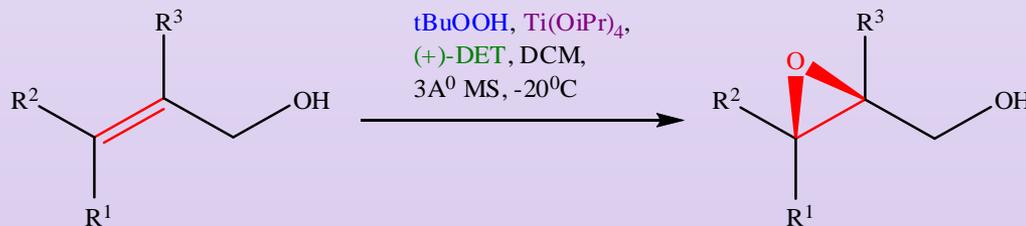
## Sharpless epoxidation

[K. Barry Sharpless](#) won the 2001 Nobel prize in Chemistry for his work on asymmetric oxidations.

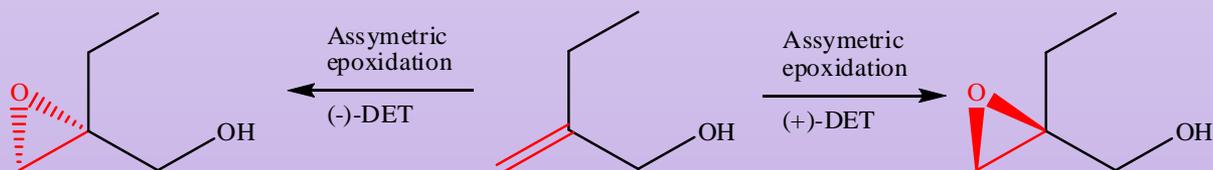
The Sharpless Epoxidation is an enantioselective and distereoselective epoxidation of allylic alcohols.

The stoichiometric oxidant is a hydroperoxide, usually *tert*-butylhydroperoxide in the presence of catalyst  $\text{Ti}(\text{O-isopropoxide})_4$ .

It allows the enantioselective epoxidation of [prochiral](#) allylic alcohols. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative.



The stereochemistry of the resulting epoxide is determined by the diastereomer of the chiral tartrate diester. Usually diethyl tartrate or diisopropyl tartrate are employed in the reaction.



## Advantages:

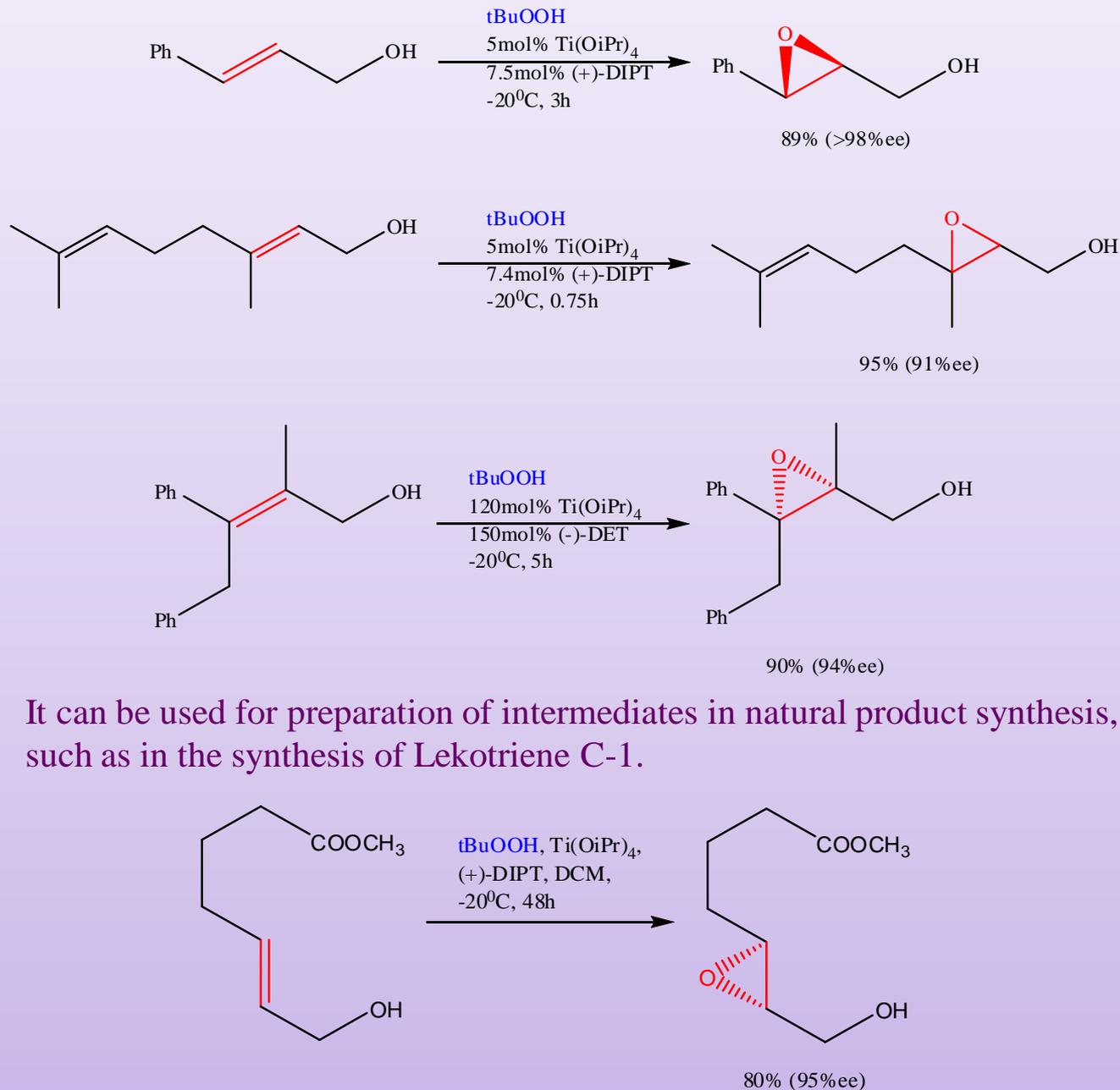
Epoxides can be converted into diols, aminoalcohols or ethers. The formation of chiral epoxides is a very important step in the synthesis of natural products.

Can be carried out with many primary and secondary allylic alcohols.

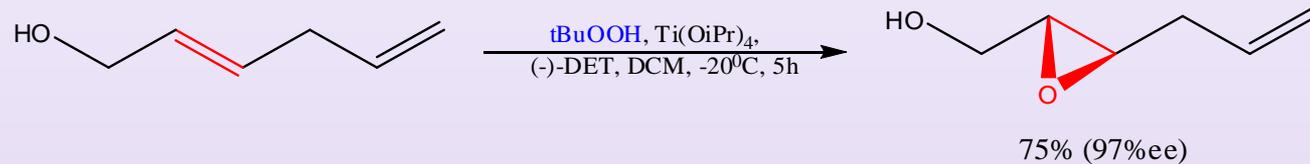
High enantiomeric excesses > 90%.

The products of the Sharpless Epoxidation are predictable using the [Sharpless Epoxidation model](#).

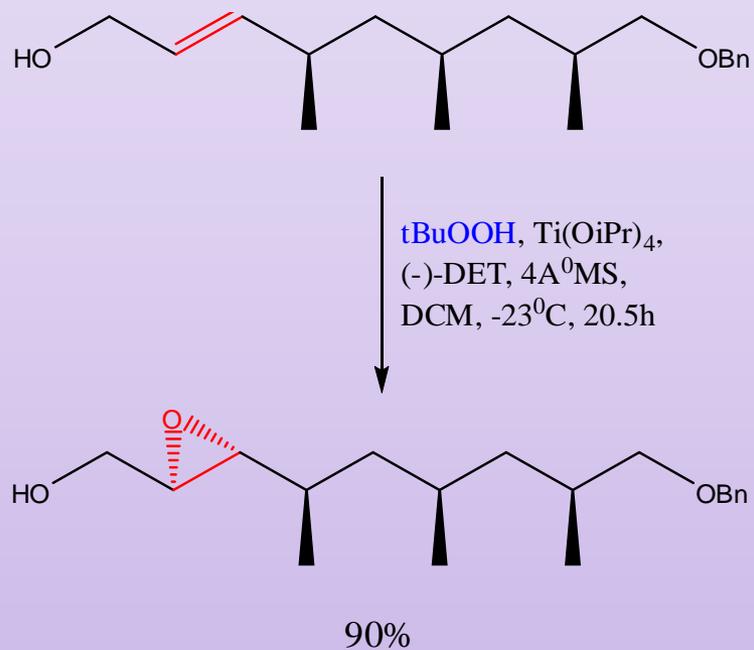
The reagents are commercially available and relatively cheap.



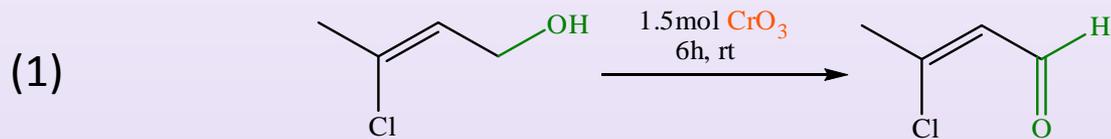
Robinson A and  
Aggarwal V K,  
*Angew. Chem. Int.  
Ed.* **2010**, *49*, 6673.



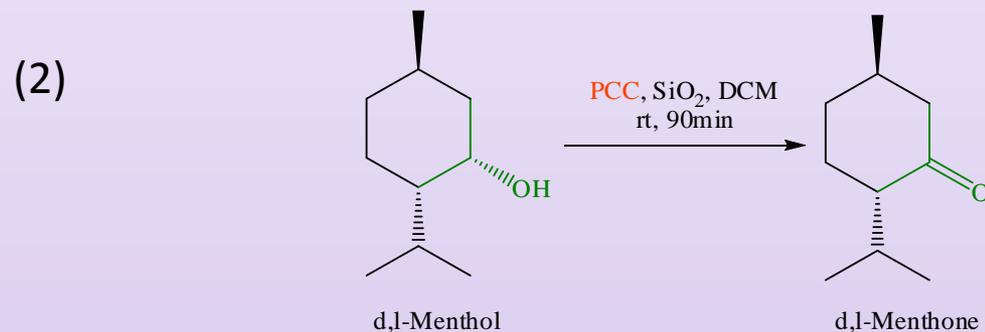
Ghosh A K and Liu C,  
*Org. Lett.* **2001**, *3*, 635.



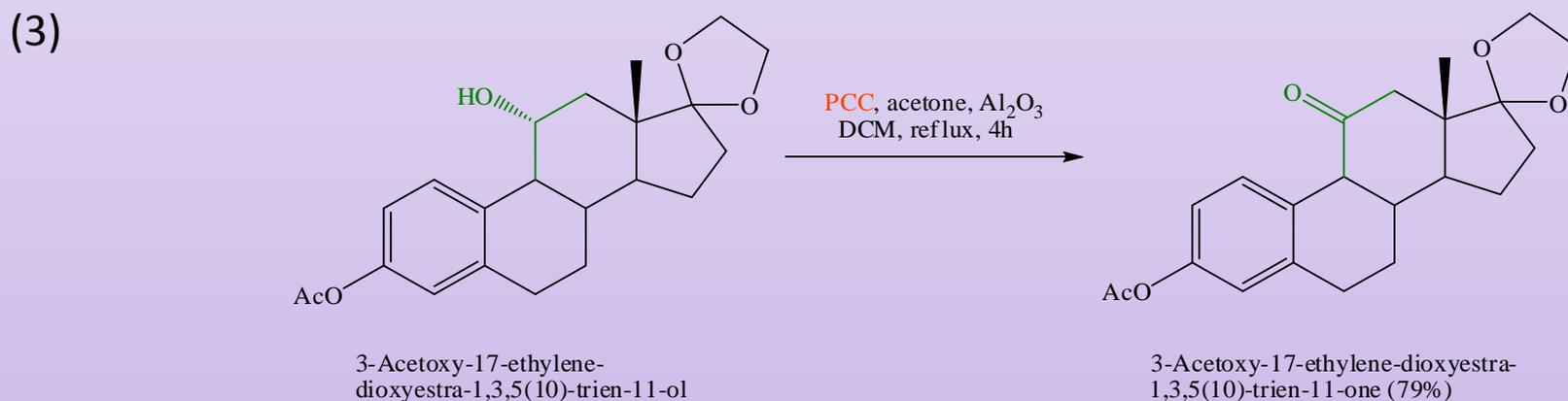
# Additional/Practice Problems

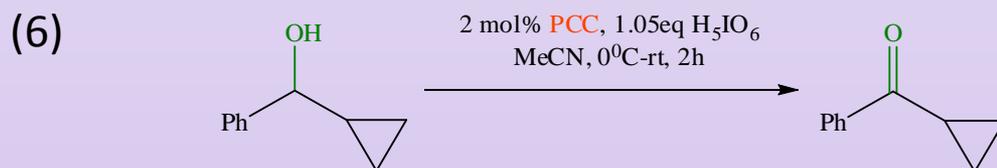
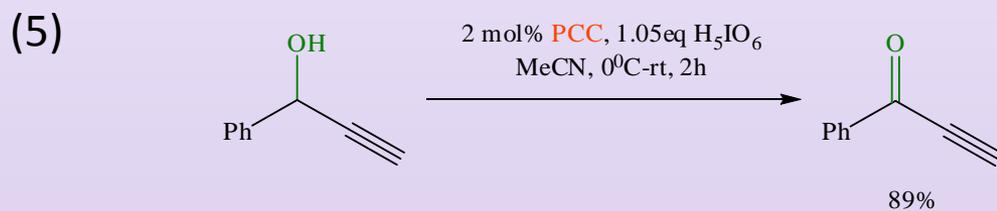
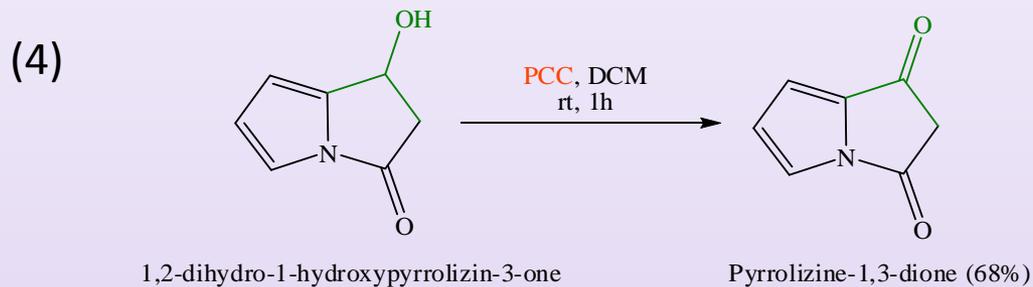


78% Zou J D; Xu Z N, *Tet.Lett.*, **2002**, 43, 6095



Luzzio F A, et al, *J Chem. Edu.*, **1999**, 76, 974.





Hunsen M, *Tet.Lett.*, 2005, 46, 1651

