

# Module I

# Oxidation Reactions

## Lecture 1

### 1.1 Osmium Oxidants

#### 1.1.1 Introduction

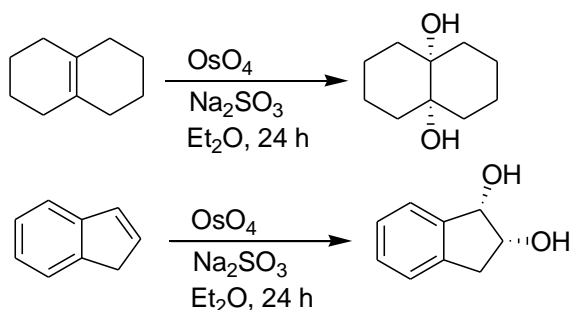
Osmium is the densest (density  $22.59 \text{ g cm}^{-3}$ ) transition metal naturally available. It has seven naturally occurring isotopes, six of which are stable:  $^{184}\text{Os}$ ,  $^{187}\text{Os}$ ,  $^{188}\text{Os}$ ,  $^{189}\text{Os}$ ,  $^{190}\text{Os}$ , and  $^{192}\text{Os}$ . It forms compounds with oxidation states ranging from -2 to +8, among them, the most common oxidation states are +2, +3, +4 and +8. Some important osmium catalyzed organic oxidation reactions follow:

#### 1.1.2 Dihydroxylation of Alkenes

*Cis*-1,2-dihydroxylation of alkenes is a versatile process, because *cis*-1,2-diols are present in many important natural products and biologically active molecules. There are several methods available for *cis*-1,2-dihydroxylation of alkenes, among them, the  $\text{OsO}_4$ -catalyzed reactions are more valuable (Scheme 1).

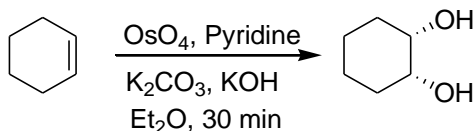
*OsO<sub>4</sub> vapours are poisonous and result in damage to the respiratory tract and temporary damage to the eyes. Use OsO<sub>4</sub> powder only in a well-ventilated hood with extreme caution.*

Y. Gao, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, New York, 1995, 6, 380.



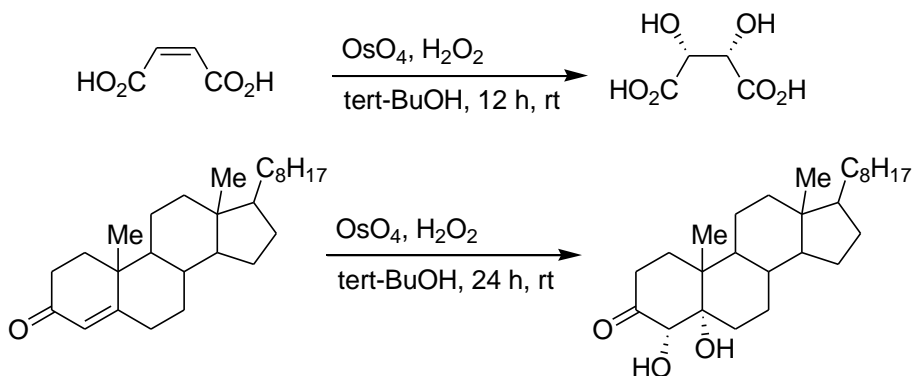
Scheme 1

The use of tertiary amine such as *triethyl amine* or *pyridine* enhances the rate of reaction (Scheme 2).

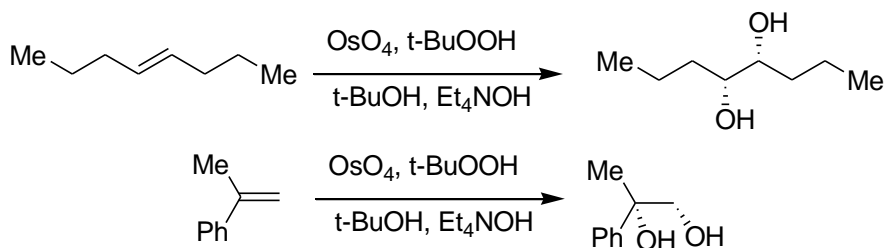


Scheme 2

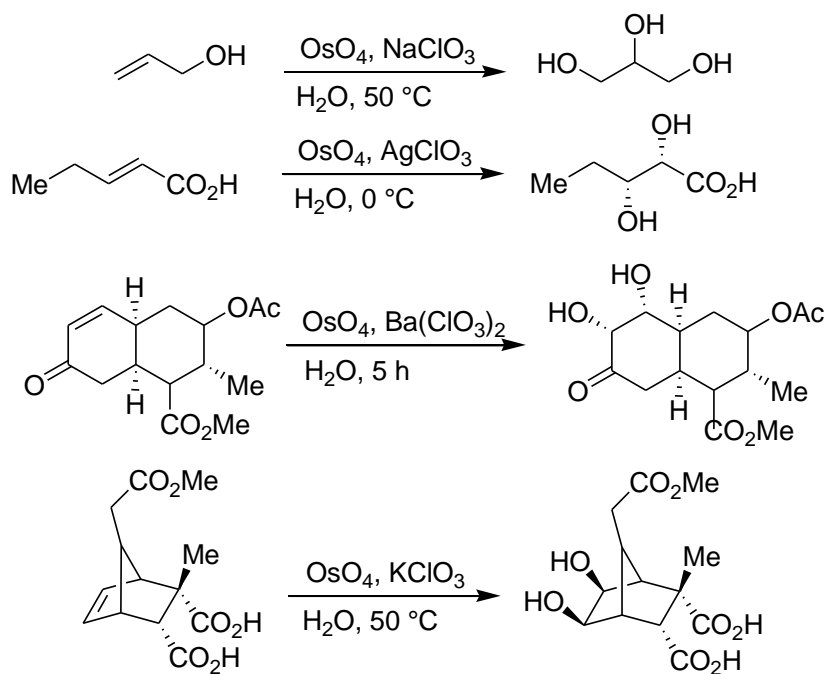
Catalytic amount of  $\text{OsO}_4$  can be used along with an oxidizing agent, which oxidizes the reduced osmium(VI) into osmium(VIII) to regenerate the catalyst. A variety of oxidizing agents, such as hydrogen peroxide, metal chlorates, *tert*-butyl hydroperoxide, *N*-methylmorpholine-*N*-oxide, molecular oxygen, sodium periodate and sodium hypochlorite, have been found to be effective (Scheme 3-7).



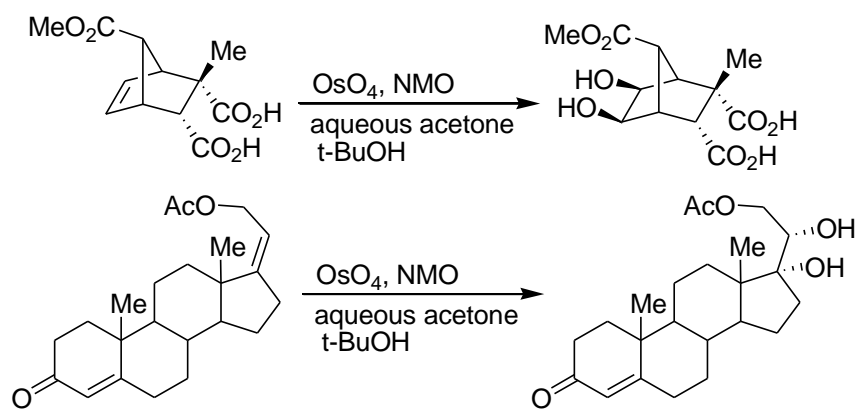
Scheme 3



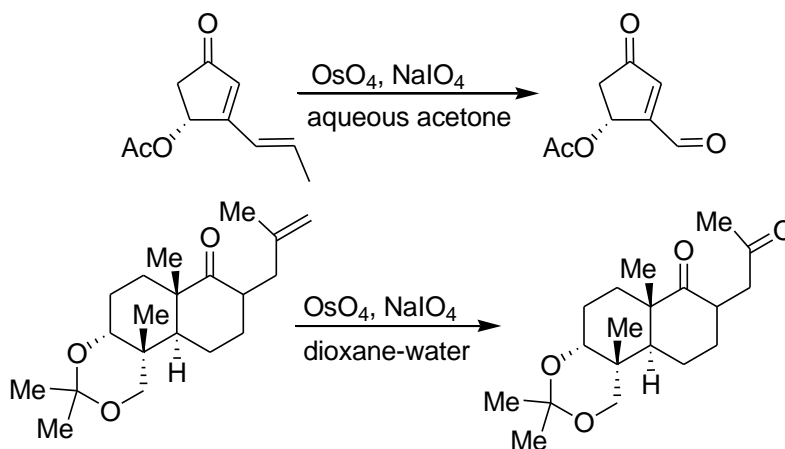
Scheme 4



Scheme 5



Scheme 6

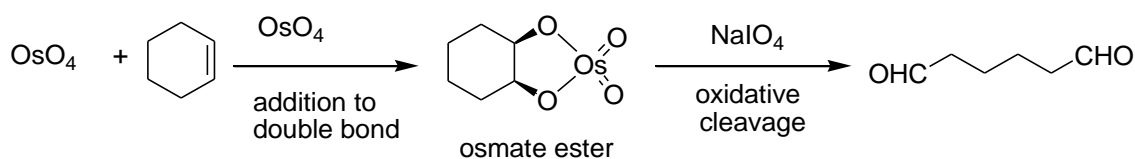


Scheme 7

In the latter case, the resultant diols undergo oxidative cleavage to give aldehydes or ketones. This reaction is known as *Lemieux-Johnson Oxidation*.  $\text{NaIO}_4$  oxidizes the reduced osmium(VI) to osmium(VIII) along with the oxidative cleavage of the diols.

## Mechanism

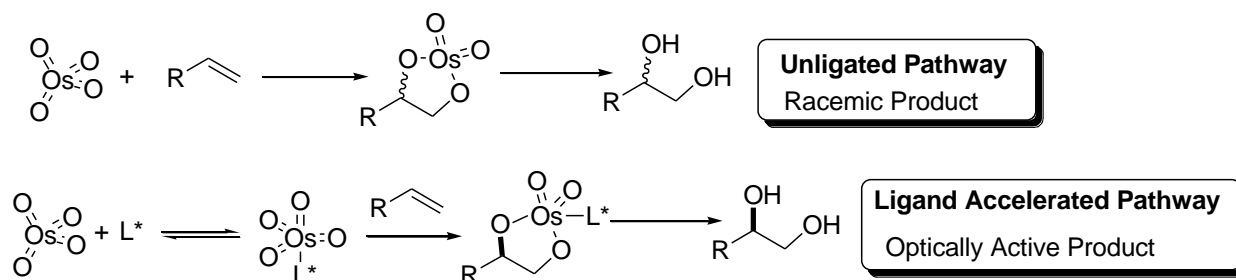
The reaction involves the formation of cyclic osmate ester, which undergoes oxidative cleavage with  $\text{NaIO}_4$  to give the dicarbonyl compounds (Scheme 9).



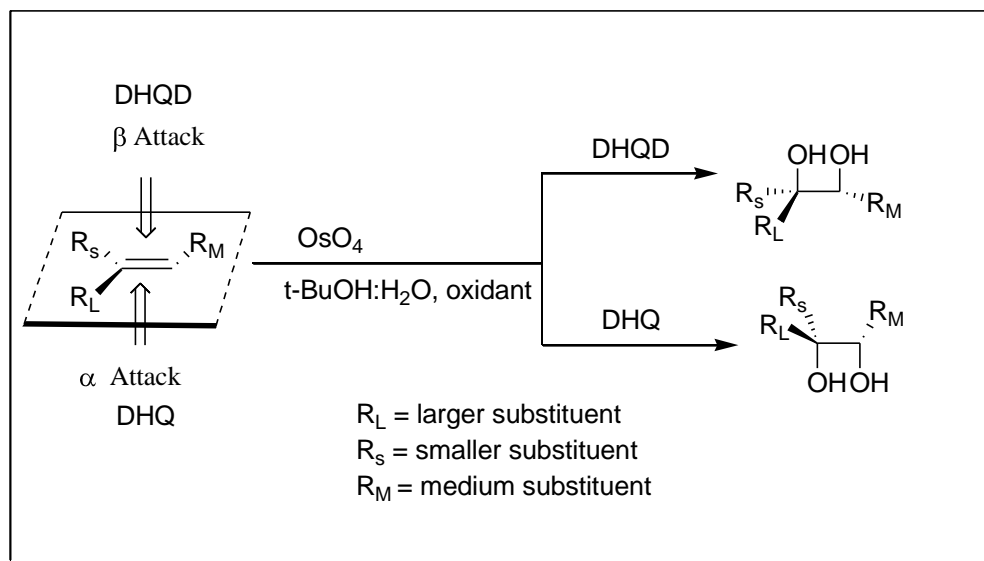
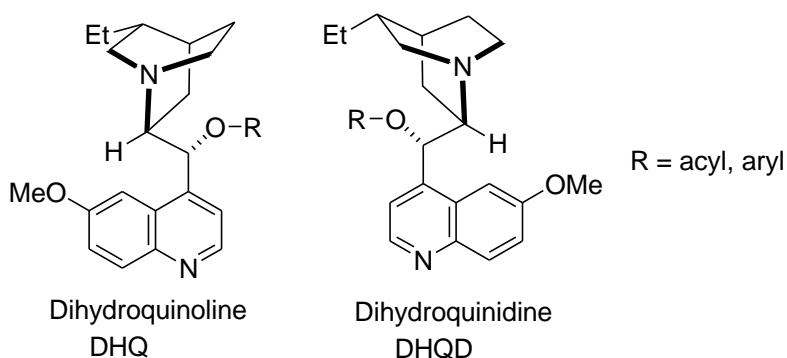
Scheme 9

### 1.1.3 Sharpless Asymmetric Dihydroxylation

Although osmylation of alkenes is an attractive process for the conversion of alkenes to 1,2-diols, the reaction produces racemic products. Sharpless group attempted to solve this problem by adding chiral substrate to the osmylation reagents, with the goal of producing a chiral osmate intermediate (Scheme 10). The most effective chiral additives were found to be the cinchona alkaloids, especially esters of dihydroquinidines such as DHQ and DHQD. The % ee of the diol product is good to excellent with a wide range of alkenes.



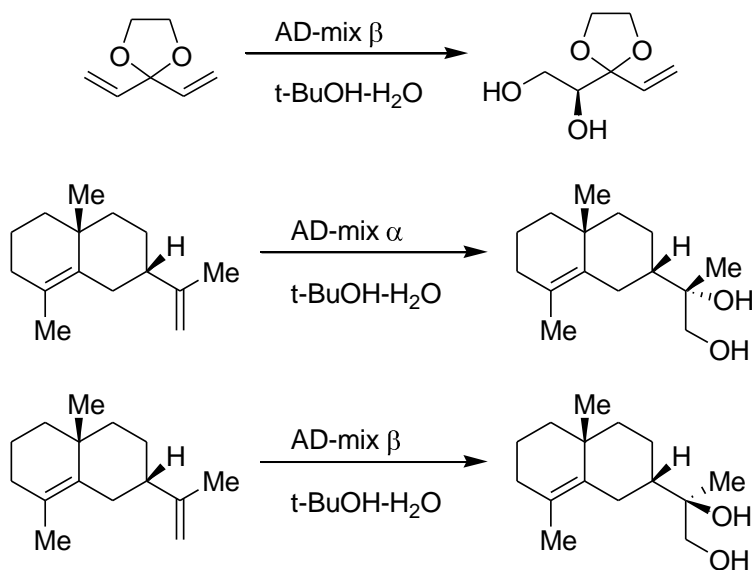
Scheme 10



Scheme 11

If the alkene is oriented as shown in Scheme 11, the natural dihydroquinidine (DHQD) ester forces delivery of the hydroxyls from the top face ( $\beta$ -attack). Conversely, dihydroquinoline (DHQ) esters deliver hydroxyls from the bottom face ( $\alpha$ -attack).

The reactions are generally carried out in a mixture of *tert*-butyl alcohol and water at ambient temperature (Scheme 12).



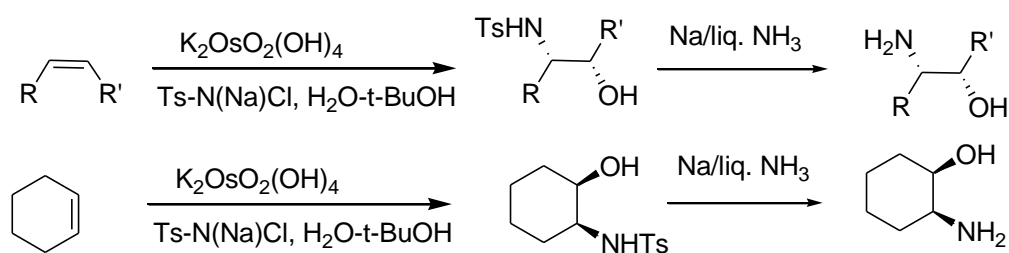
Scheme 12

**Features:**

- The reaction is stereospecific leading to 1,2-*cis*-addition of two OH groups to the alkenes
- It typically proceeds with high chemoselectivity and enantioselectivity
- The reaction conditions are simple and the reaction can be easily scaled up
- The product is always a diol derived from *cis*-addition.
- It generally exhibits a high catalytic turnover number
- It has broad substrate scope without affecting the functional groups

### 1.1.4 Aminohydroxylation

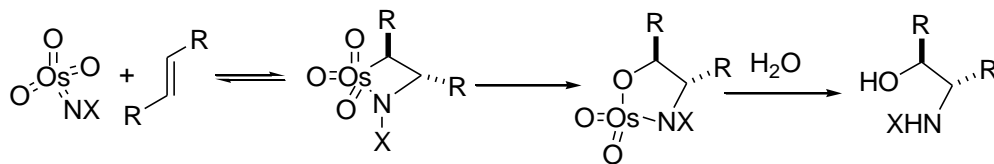
Similar to *cis*-1,2-dihydroxylation, *cis*-1,2-aminohydroxylation of alkenes has been developed by reaction with chloroamine in the presence of catalytic amount of  $\text{OsO}_4$ . In this process, alkene reacts with chloroamine in the presence of  $\text{OsO}_4$  to give sulfonamides that is readily converted into the *cis*-1,2-hydroxyamines by cleavage with sodium in liquid ammonia (Scheme 13). This process provides a direct *cis*-aminohydroxylation of alkenes, but the major problem is the poor regioselectivity for unsymmetrical alkenes.



Scheme 13

### Mechanism

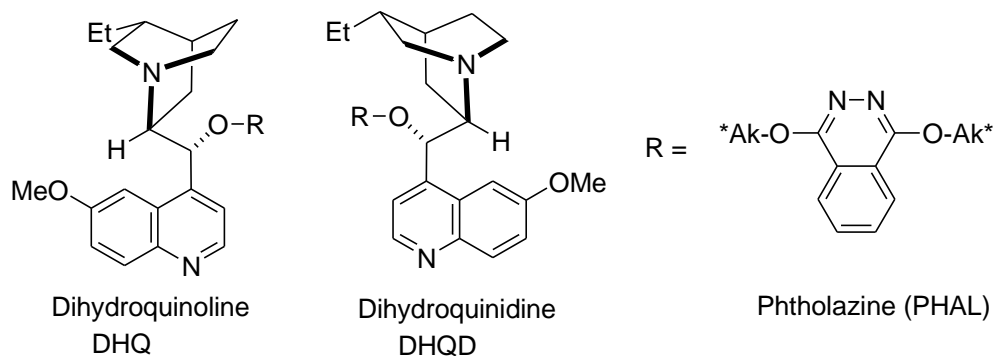
The catalytically active species in the reaction most likely is an imidotrioxo osmium(VIII) complexes, which is formed *in situ* from the osmium reagent and the stoichiometric nitrogen source, i.e. chloroamine (Scheme 14). Experiments under stoichiometric conditions have been shown that imidotrioxo osmium(VIII) complexes transfer the nitrogen atom and one of the oxygen atoms into the substrate. The major regioisomer normally has the nitrogen placed distal to the most electron withdrawing group of the substrate.



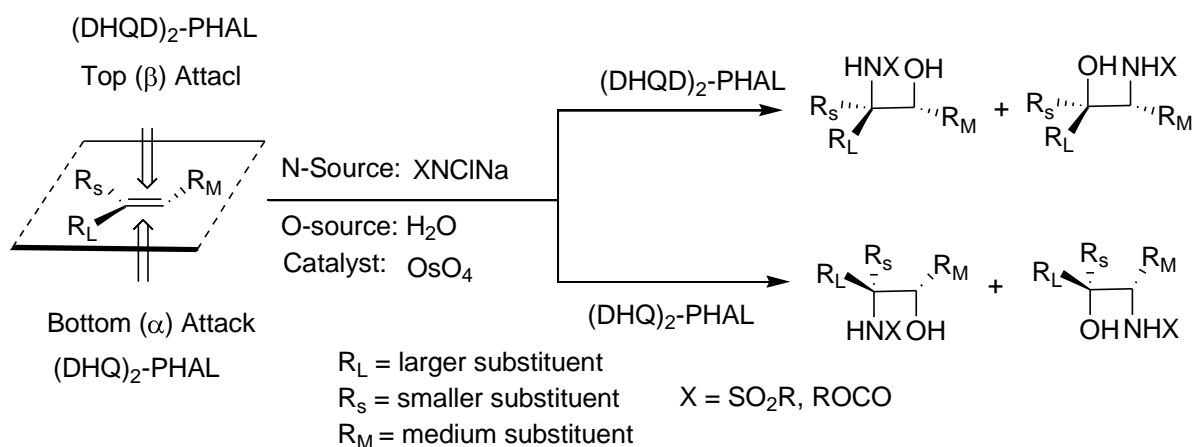
Scheme 14

### 1.1.5 Asymmetric Aminohydroxylation

The asymmetric *cis*-1,2-aminohydroxylation of alkenes with chloroamine has been explored using the chiral osmium catalyst derived from OsO<sub>4</sub> and cinchona alkaloids, dihydroquinidine ligands (DHQD)<sub>2</sub>-PHAL and dihydroquinine ligands (DHQ)<sub>2</sub>-PHAL.



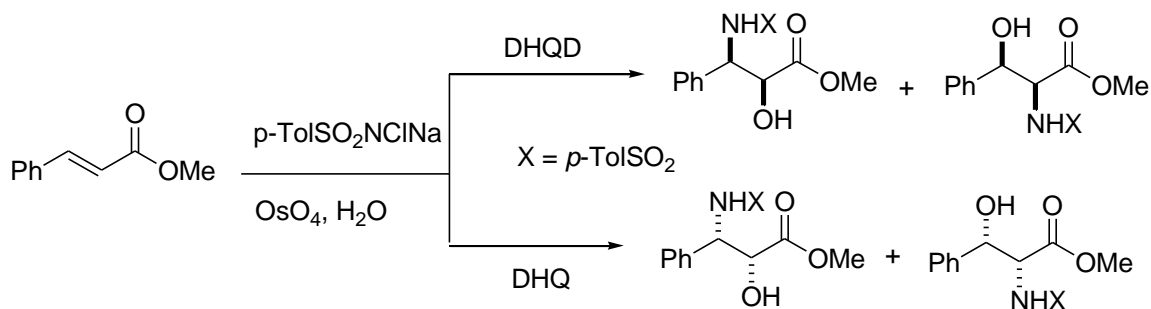
The face selectivity for the aminohydroxylation can too be reliably predicted (Scheme 15).



Scheme 15

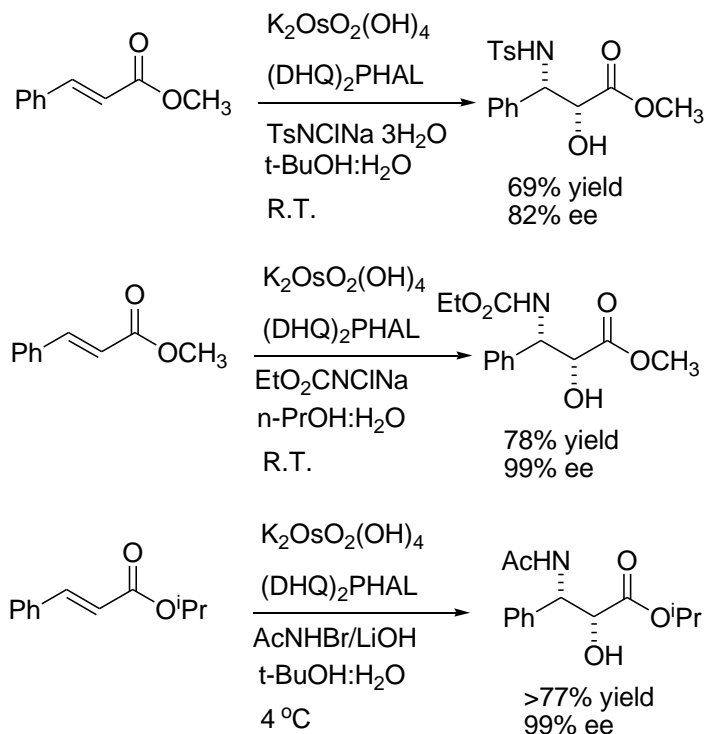
An alkene with these constraints receives the OH and NHX groups from above, i.e. from the □-face, in the case of DHQD derived ligand and from the bottom, i.e. from the □-face, in the case of DHQ derivative. For example, the asymmetric aminohydroxylation of methyl cinnamate gives the following face selectivity based on the chiral ligand (Scheme 16).





Scheme 16

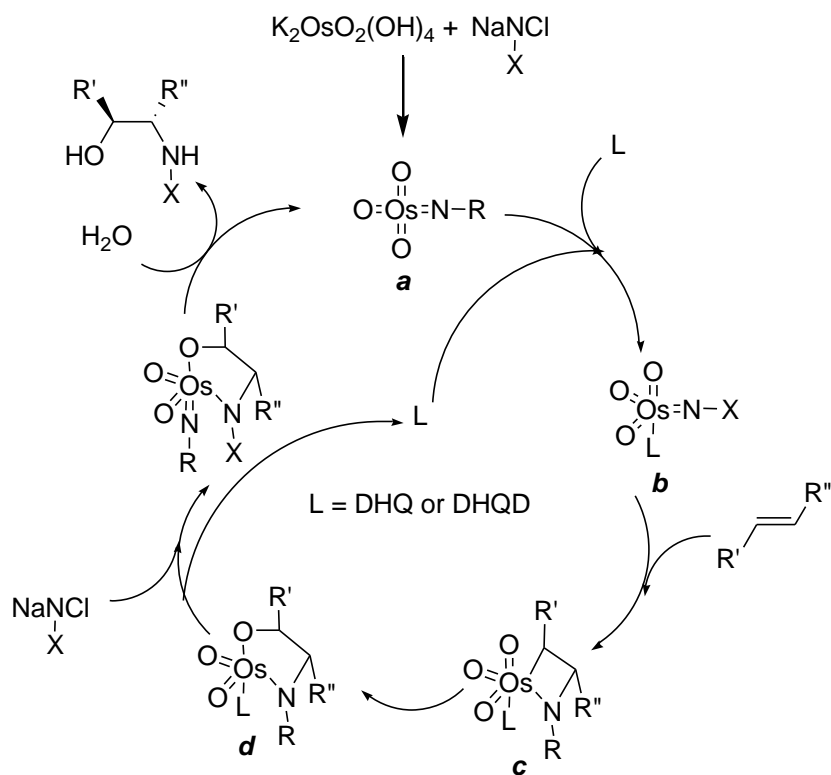
With respect to the yield, regio- and enantioselectivity, reaction depend on number of parameters, e.g. the nature of starting material, the ligand, the solvent, the type of nitrogen source (sulfonamides), carbamates and carboxamides as well as the size of its substituent. For some examples (Scheme 17):



Scheme 17

## Mechanism

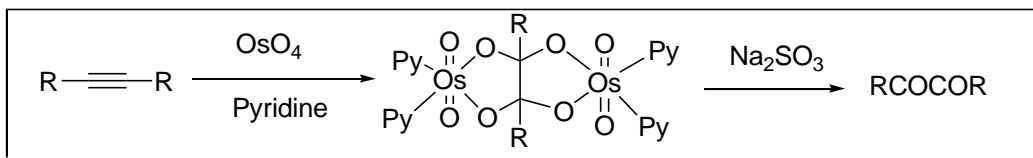
OsO<sub>4</sub> may undergo reaction with chloroamine to give an active imido-osmium intermediate **a** that could readily co-ordinate with chiral ligand 'L' to afford chiral imido-osmium intermediate **b** (Scheme 18). The latter may react with alkene to yield **c** via (2+2)-cycloaddition that may rearrange to give **d** that could undergo hydrolysis with water to give the target hydroxylamine derivative.



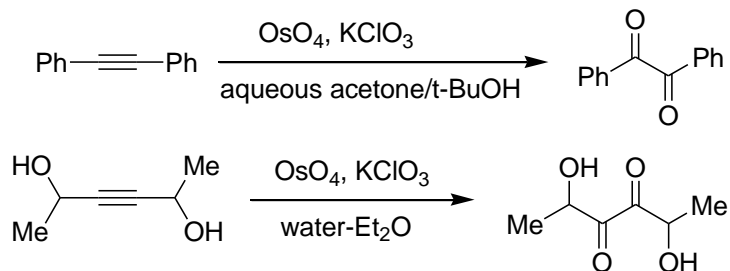
Scheme 18

### 1.1.5 Reaction with Alkynes

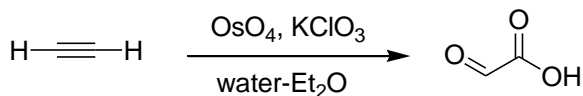
Alkynes react with OsO<sub>4</sub> in the presence of tertiary amines such as pyridine to give osmium(VI) ester complexes, which on hydrolysis with sodium sulfite yield the corresponding carbonyl compounds (Scheme 19-20). In the case of terminal alkynes, carboxylic acids are obtained (Scheme 21)



Scheme 19

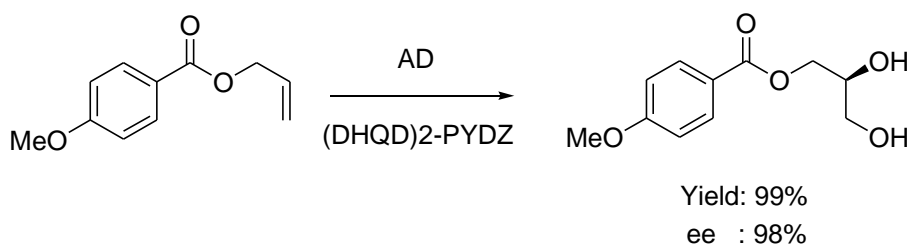


Scheme 20

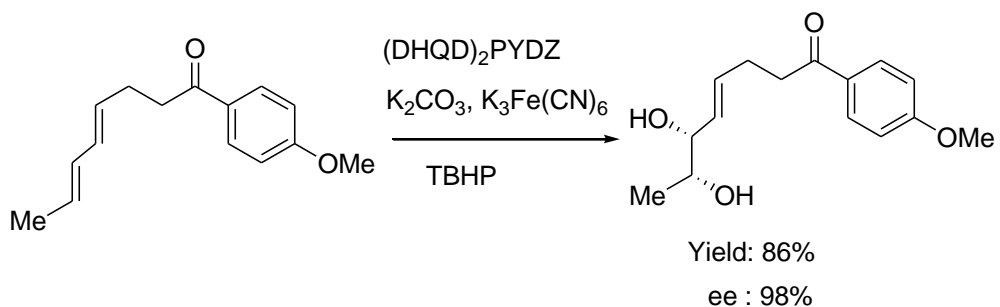


Scheme 21

### Examples:



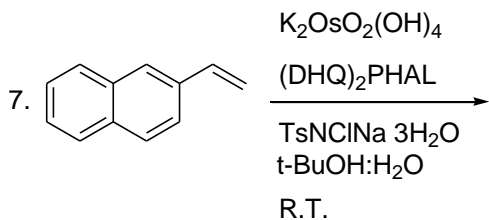
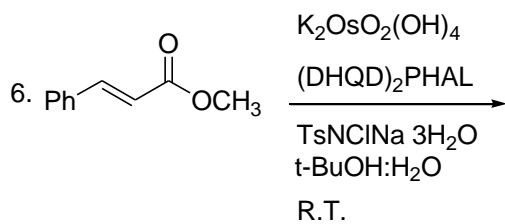
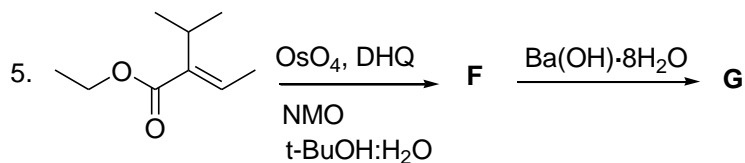
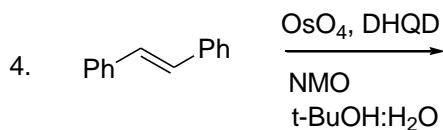
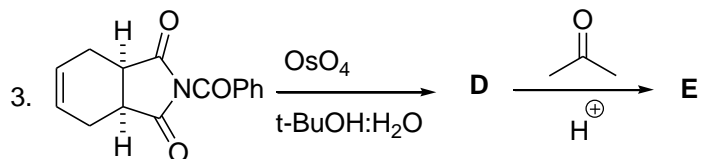
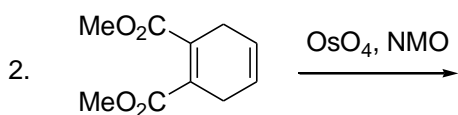
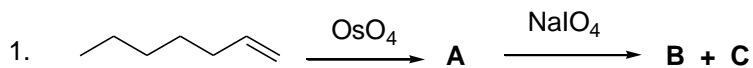
E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1995**, 117, 10805.



A. Guzman-Perez, E. J. Corey, *Tetrahedron Lett.* **1997**, 38. 5941.

## Problems

Give the major products for the following reactions:



**Text Book**

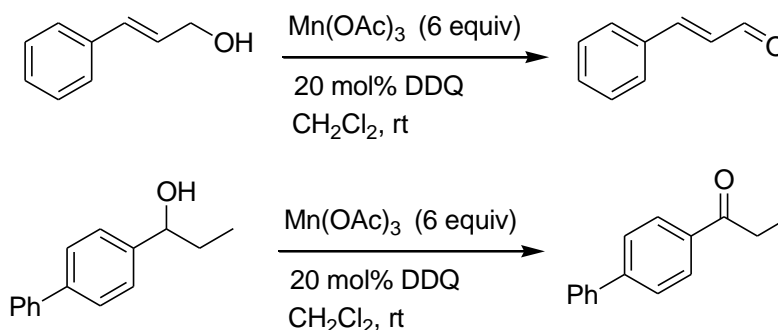
J. Clayden, N. Creeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 2001.

**Lecture 2****2.1 Manganese Oxidants****2.1.1 Introduction**

Manganese (Mn) is the 12<sup>th</sup> most abundant element (0.1%) on earth's crust with atomic number 25. Though manganese exists with the oxidation states from –3 to +7, the common oxidation states are +2, +3, +4, +6 and +7. The +2 oxidation state, which has a pale pink color due to spin forbidden *d-d* transition is found in living organisms for essential functions. The manganese in the oxidation state +7 is deep purple in colour and a strong oxidizing agent ( $\text{Mn}^{+7} + 5\text{e}^- \rightarrow \text{Mn}^{+2}$ ).

**2.1.2 Manganese(III) Reagents and Catalysts****2.1.2.1 Selective Oxidation of Benzylic and Allylic Alcohols**

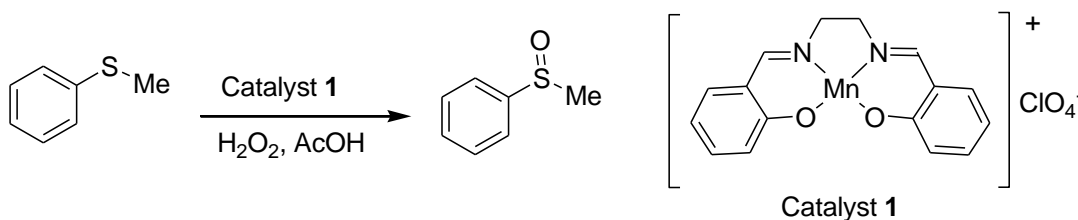
A combination of  $\text{Mn}(\text{OAc})_3$  and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been used for the selective oxidation of benzylic and allylic alcohols. The reaction works under mild conditions (Scheme 1).



Scheme 1

### 2.1.2.3 Oxidation of Sulfides to Sulfoxides

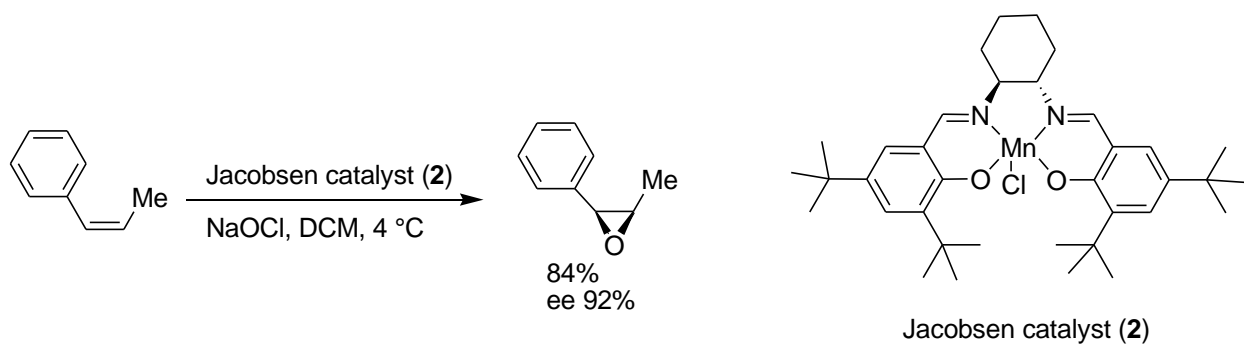
Oxidation of sulfides to sulfoxides is one of the important transformations in organic synthesis. Sulfides could be selectively oxidized to sulfoxides in good yields with hydrogen peroxide in the presence of a manganese(III) Schiff-base complex **1** under ambient conditions (Scheme 2).



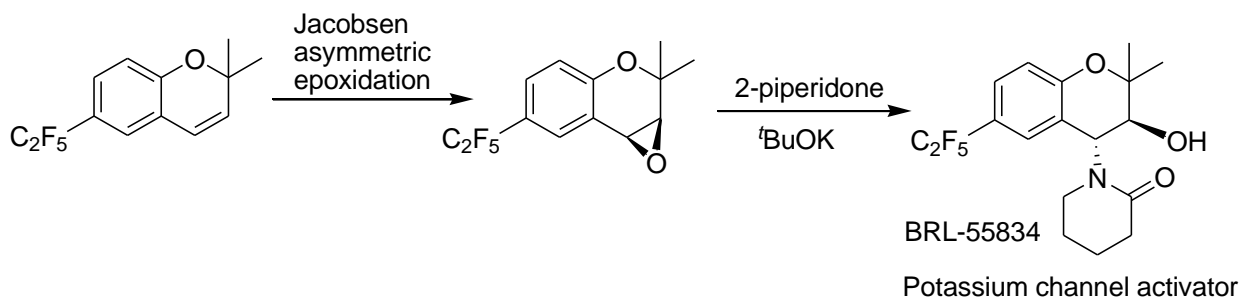
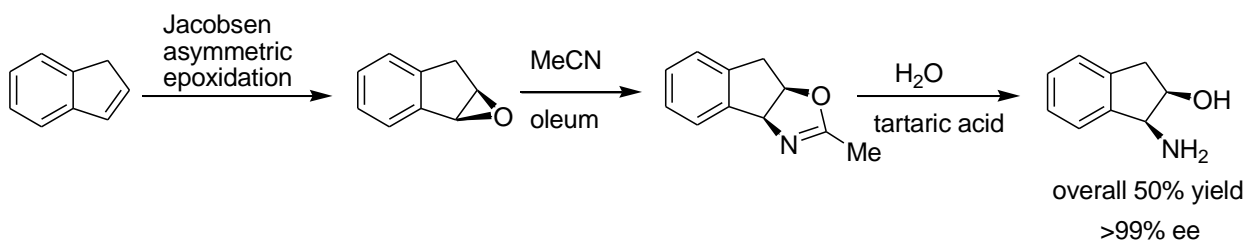
Scheme 2

### 2.1.2.4 Asymmetric Epoxidation of Alkenes

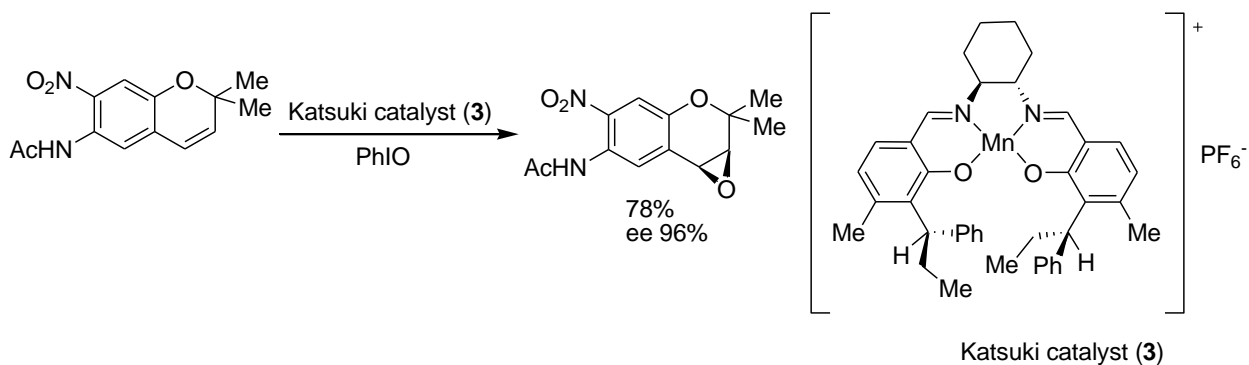
Jacobsen and Katsuki groups have explored asymmetric epoxidation of unfunctionalized alkenes using chiral Mn(III)-salen complexes in the presence of terminal oxidants such as  $\text{PhIO}$  and  $\text{NaOCl}$  (Scheme 3-4). The most interesting feature of the reaction is that simple alkenes are oxidized with high asymmetric induction. This process has now been extensively used in pharmaceutical industries.



### Examples for Applications



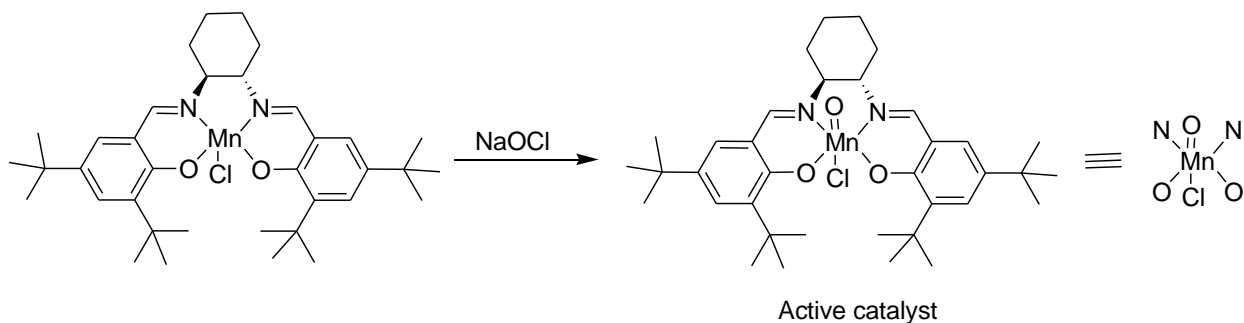
Scheme 3



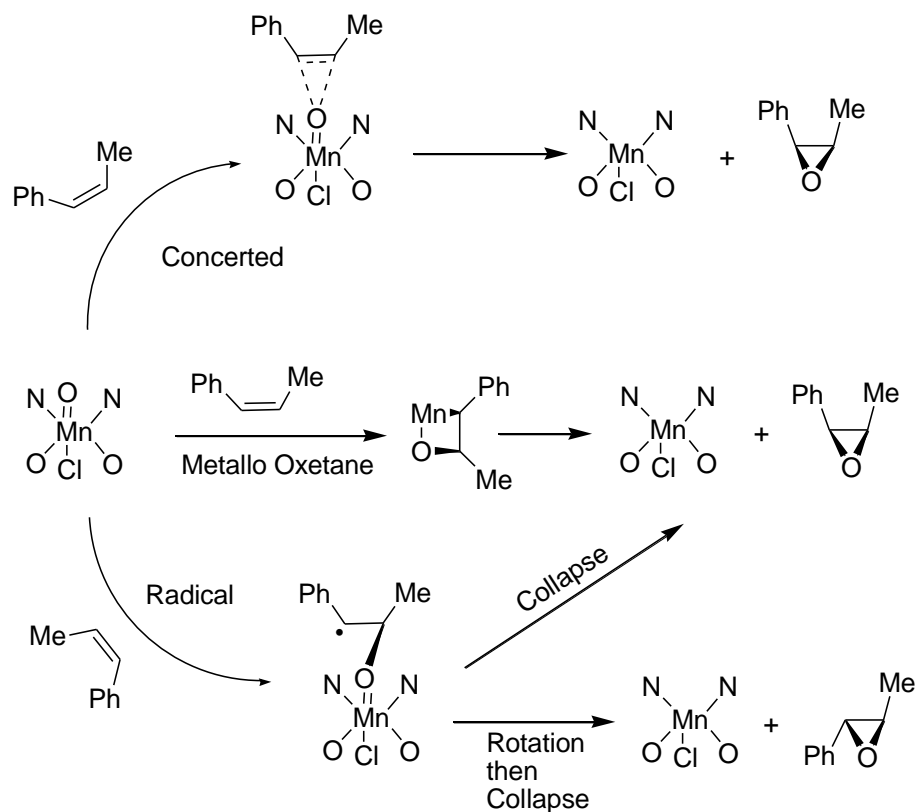
Scheme 4

## Mechanism

The mechanism of this reaction is not fully understood but it has been proposed that the oxidant oxidizes Mn(III)-salen to Mn(IV)-salen, which oxidizes the alkene (Scheme 5). There are three possible reaction pathways such as concerted, metallo oxetane and radical pathway but the most accepted one is the concerted pathway.



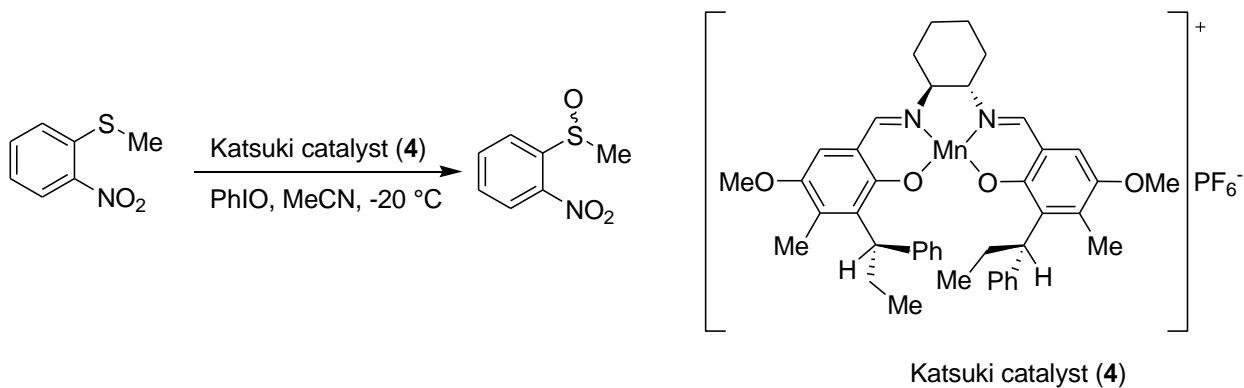




Scheme 5

### 2.1.2. 5 Asymmetric Sulfoxidation

The above described Katsuki catalytic system is also effective for the asymmetric oxidation of sulfides to sulfoxides (Scheme 6). The oxidation of aryl alkyl sulfides has been extensively studied with moderate to high enantioselectivity.



Scheme 6

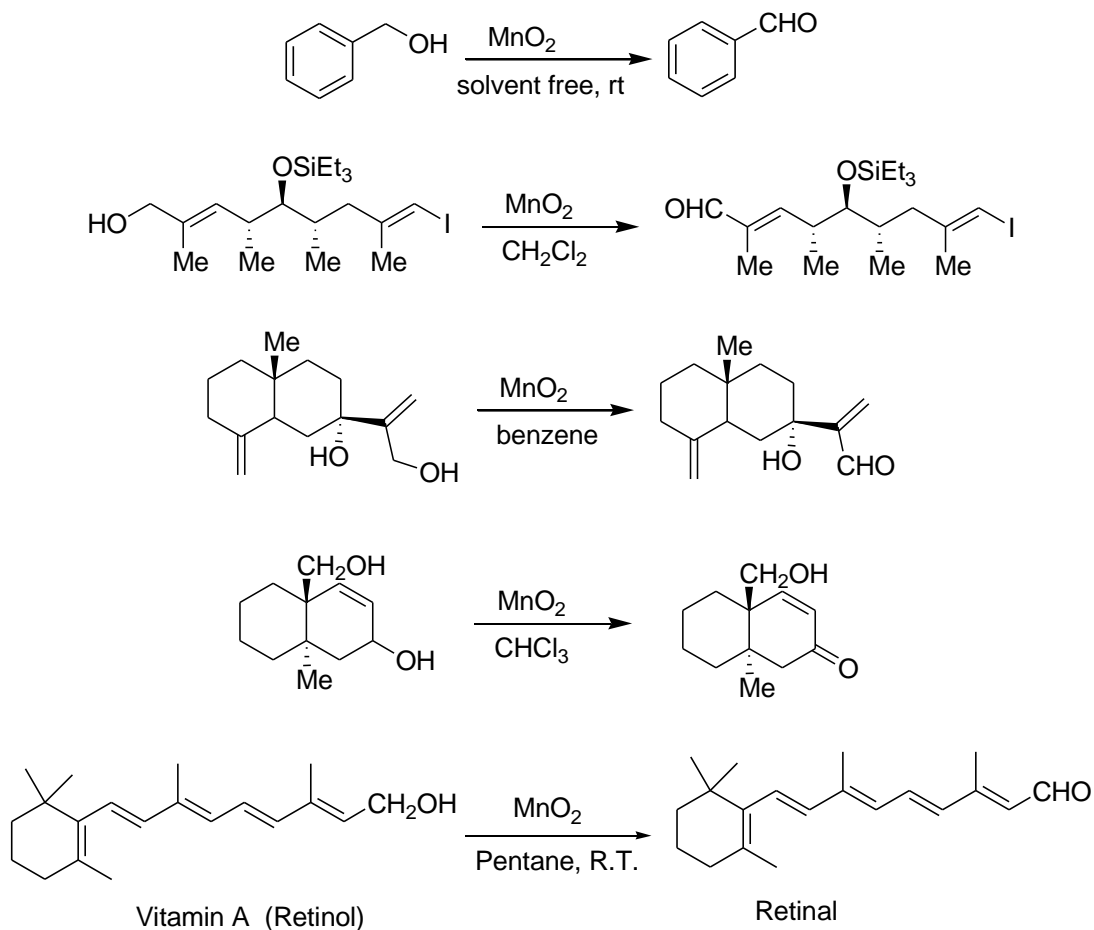
### 2.1.3 Mn(IV) Reagents as an Oxidant

MnO<sub>2</sub> is a useful selective oxidizing reagent in organic synthesis. It is commercially available, and it can also be prepared by the reaction of MnSO<sub>4</sub>·4H<sub>2</sub>O with KMnO<sub>4</sub> in aqueous NaOH.

G. Cahiez, M. Alami, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette Ed., New York, 1995, 5, 3229.

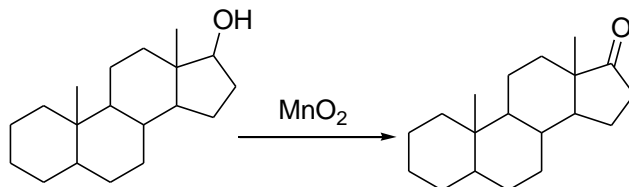
#### 2.1.3.1 Oxidation of Alcohols

MnO<sub>2</sub> can selectively oxidize allylic and benzylic alcohols to the corresponding carbonyl compounds (Scheme 7). The advantage of this method is that the reaction takes place under mild and neutral conditions, also carbon-carbon double and triple bonds are unaffected.



Scheme 7

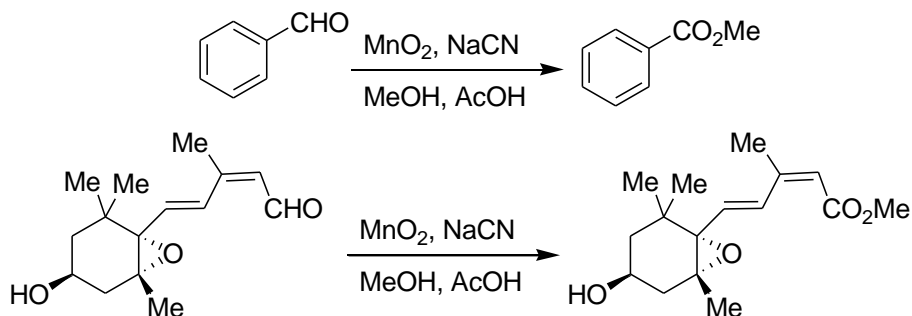
Furthermore, at elevated temperature, saturated secondary alcohols can be oxidized to ketones (Scheme 8).



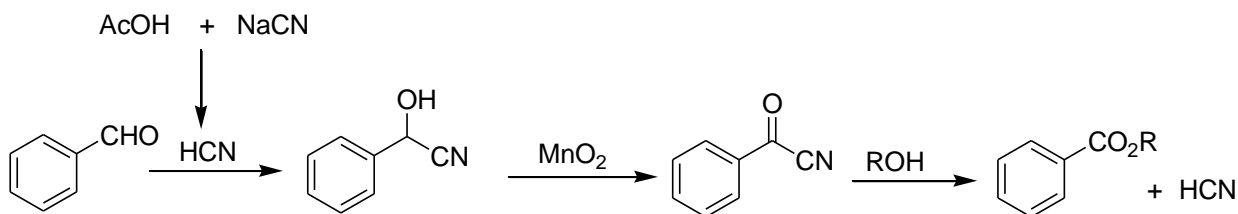
Scheme 8

### 2.1.3.2 Oxidation of Aldehydes to Esters (Corey-Gilman-Ganem Oxidation)

The aldehydes can be selectively oxidized to esters in presence of  $\text{MnO}_2$  and hydrogen cyanide in methanol at ambient temperature (Scheme 9). The aldehyde undergoes reaction with  $\text{HCN}$  to give cyanohydrins, which proceeds further oxidation to acyl cyanide. The latter on alcoholysis leads to corresponding  $\alpha,\beta$ -unsaturated carboxylic ester.



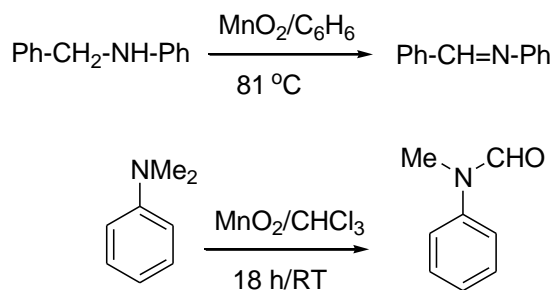
#### Mechanism



## Scheme 9

## 2.1.3.3 Oxidation of Amines

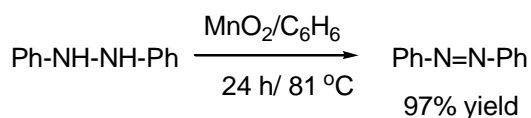
The oxidation of amines can lead to various products depending on the nature of the starting compound. This section describes the oxidation of amines to imines and amides (Scheme 10).



Scheme 10

## 2.1.3.3 Oxidation of Hydrazo Compounds

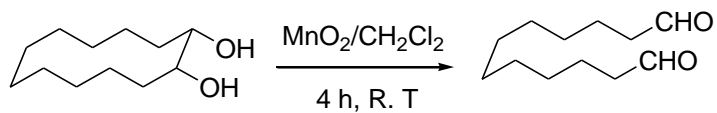
Hydrazobenzene can be oxidized to azobenzene with high yield (Scheme 11).



Scheme 11

## 2.1.3.4 Oxidative Cleavage of 1,2-Diols

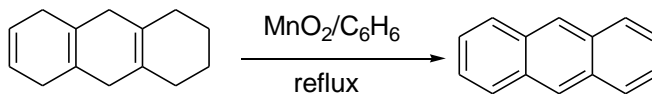
1,2-Diol undergoes oxidative cleavage to afford aldehydes or ketones (Scheme 12).



Scheme 12

### 2.1.3.5 Aromatization

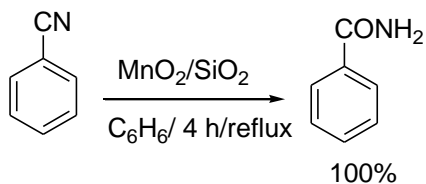
$\text{MnO}_2$  has been widely used for the dehydrogenation and aromatization reactions (Scheme 13).



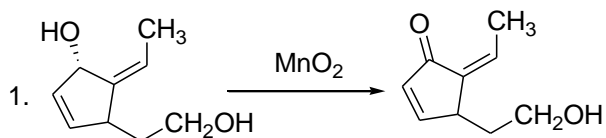
Scheme 13

### 2.1.3.6. Conversion of Nitriles to Amides

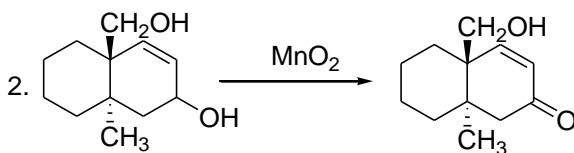
Nitriles are readily converted into amides in the presence of  $\text{MnO}_2$  under reflux conditions (Scheme 14).



Scheme 14

**Examples:**

K. M. Brummond, P. C. Still, H. Chen, *Org. Lett.* **2004**, 6, 149.



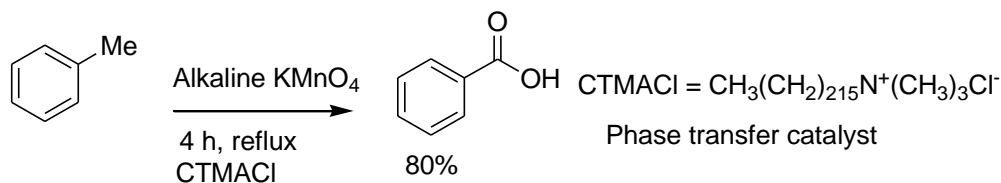
P. C. Mukharji, A. N. Ganguly, *Tetrahedron* **1969**, 25, 5281.

**2.1.4 Mn(VII) Reagents as an Oxidant**

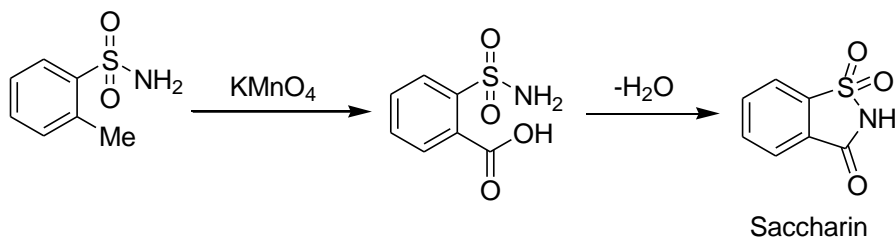
Potassium permanganate ( $\text{KMnO}_4$ ) is a strong oxidizing agent, and its reactivity depends on whether it is used in acid, neutral or basic conditions. In acid solution, Mn(VII) is reduced to Mn(II), while in basic and neutral conditions,  $\text{MnO}_2$  is usually formed.

**2.1.4.1 Oxidation of Aromatic Side Chains**

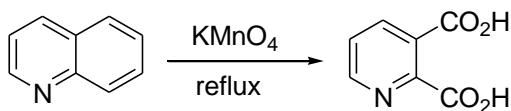
Alkyl side chain present in aromatic ring is readily oxidized to carboxylic acids (Scheme 15).



Scheme 15

**Application in the synthesis of Saccharin****2.1.4.2 Oxidation of Aromatic Rings**

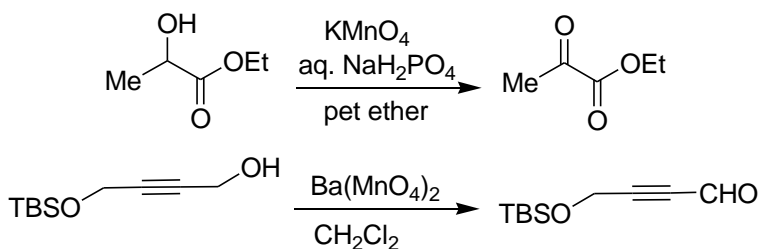
Benzene ring can be cleaved if it is fused to heterocyclic ring system. Thus, quinoline and isoquinoline can be oxidized to dicarboxylic acids in the presence of alkaline  $\text{KMnO}_4$  (Scheme 16).



Scheme 16

**2.1.4.3 Oxidation of Alcohols**

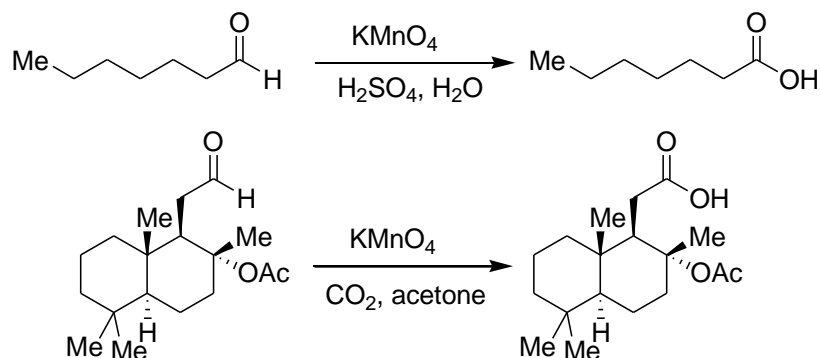
Alkaline  $\text{KMnO}_4$  and barium permanganate selectively oxidize alcohols to aldehydes and ketones (Scheme 17).



Scheme 17

### 2.1.4.4 Oxidation of Aldehydes

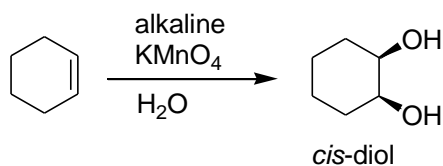
Aldehydes are oxidized to carboxylic acids with good yield at ambient temperature (Scheme 18).



Scheme 18

### 2.1.4.5 1,2-Dihydroxylation

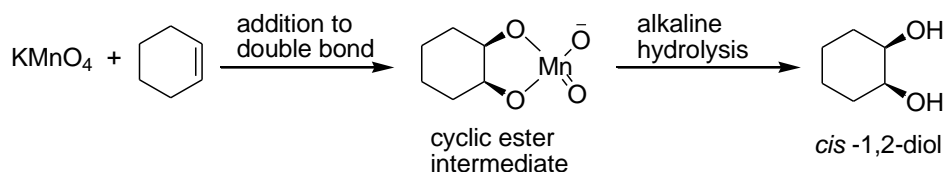
The alkaline KMnO<sub>4</sub> is most commonly used for selective *cis*-dihydroxylation from the less hindered side of the double bond (Scheme 19).



Scheme 19



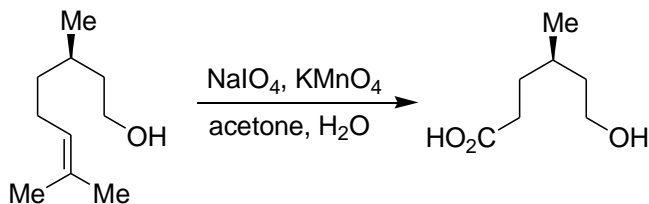
The permanganate ion adds to the double bond to form a cyclic ester, which after alkaline hydrolysis gives the desired *cis*-1,2-diol (Scheme 20).



Scheme 20

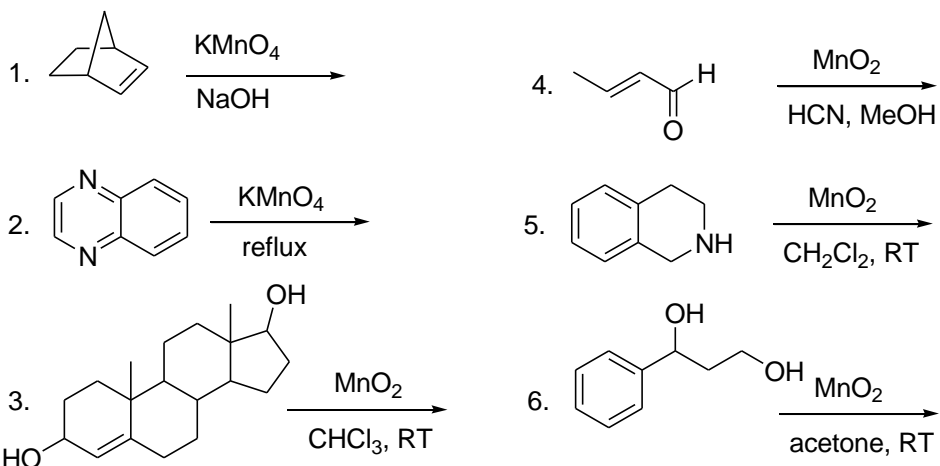
### Lemieux-von Rudloff Reagent

Mixtures of sodium periodate ( $\text{NaIO}_4$ ) and potassium permanganate ( $\text{KMnO}_4$ ) in aqueous organic solvent used for oxidative cleavage of a double bond.

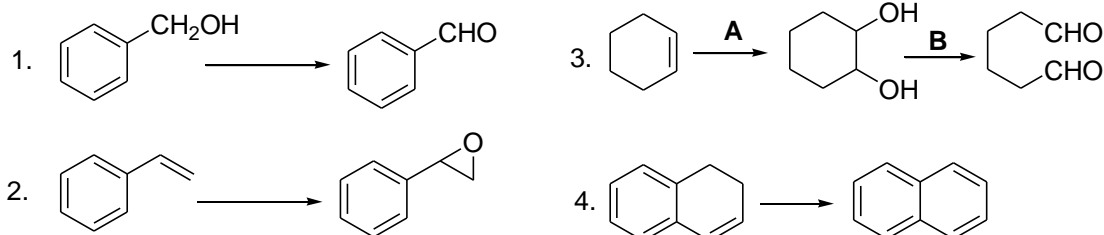


### Problems

1. Provide the major product for the following reactions:



2. Give suitable reagent and reaction conditions for the following transformations.



### Text Book

M. B. Smith, J. March, *Advanced Organic Chemistry*, 5<sup>th</sup> ed., John Wiley and Sons, Inc., New York, 2001.

## Lecture 3

### 1.3 Chromium Oxidants

#### 1.3.1 Introduction

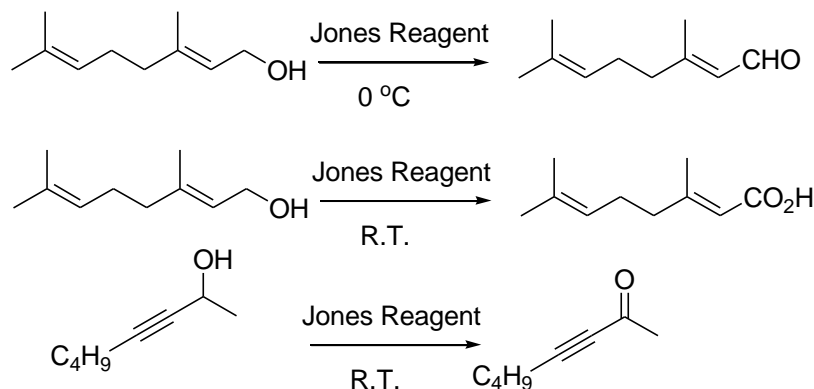
Chromium is the 21<sup>st</sup> most abundant element in Earth's crust with atomic number 24. Naturally occurring chromium composed of three stable isotopes;  $^{52}\text{Cr}$ ,  $^{53}\text{Cr}$  and  $^{54}\text{Cr}$  with  $^{52}\text{Cr}$  being most abundant. It has an electronic configuration of  $3d^5 4s^1$  and exhibits a wide range of oxidation states, where the +3 and +6 states are commonly observed. This section describes some of the important chromium mediated/catalyzed oxidation of organic substrates.

#### 1.3.2 Chromic Acid Oxidation (Jones oxidation)

The combination of  $\text{CrO}_3$  and sulfuric acid is often referred as Jones reagent, and the oxidation of alcohols with this reagent in acetone is called Jones oxidation. The reagent is selective as it is useful for the oxidation of alcohols, which contain

carbon-carbon double or triple bonds, allylic or benzylic C-H bonds (Scheme 1). The reaction is carried at 0-20 °C to give the corresponding carbonyl compounds.

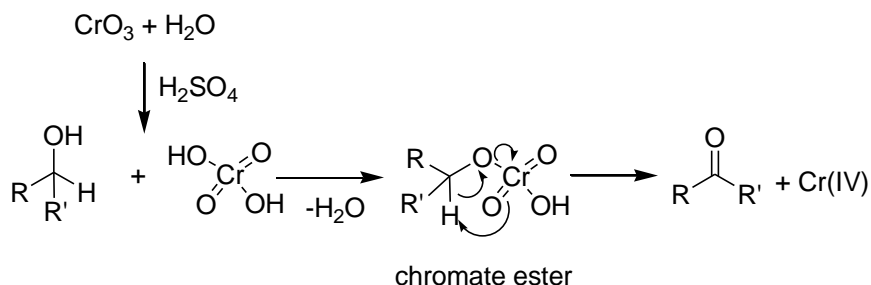
F. Freeman, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 2, 1261.



Scheme 1

## Mechanism

In aqueous acid,  $\text{CrO}_3$  forms chromic acid, which oxidizes the alcohols to carbonyl compounds (Scheme 2).

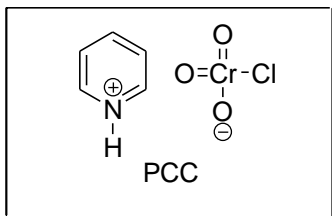


Scheme 2

### 1.3.3 Pyridinium Chlorochromate (PCC) Oxidation

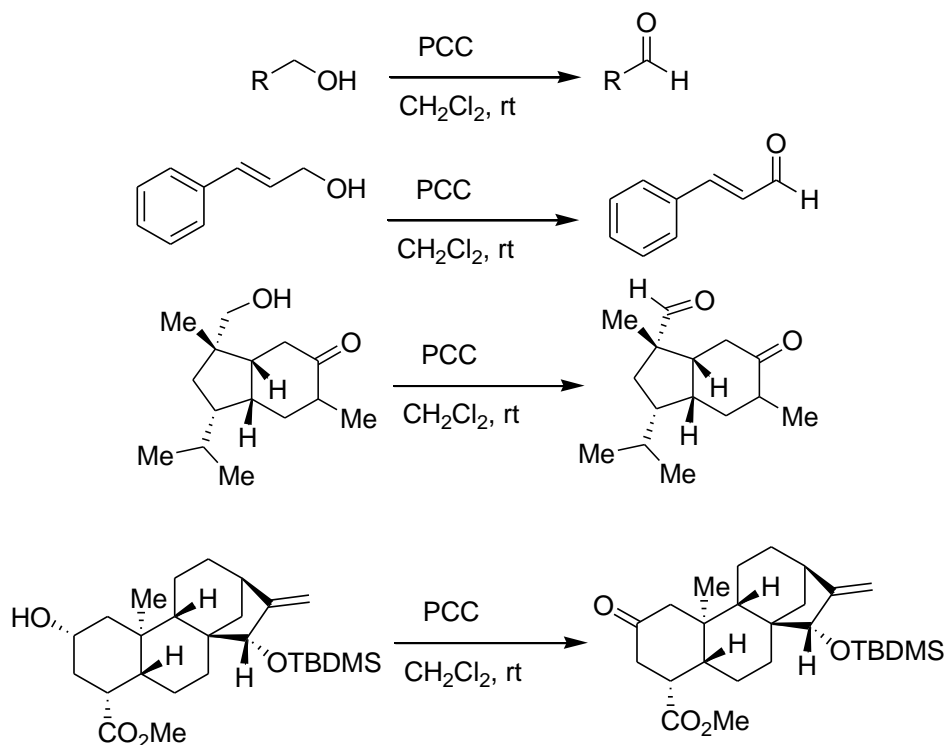
This reagent is obtained by adding pyridine to a solution of  $\text{CrO}_3$  in hydrochloric acid. PCC oxidizes primary and secondary alcohols to aldehydes and ketones, respectively (Scheme 3). As PCC is slightly acidic so it may affect the acid

sensitive groups. The powdered NaOAc is used along with PCC for the oxidation of the substrate containing acid labile groups. PCC is commercially available and could also be prepared.



G. Piancatelli,, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 4356.

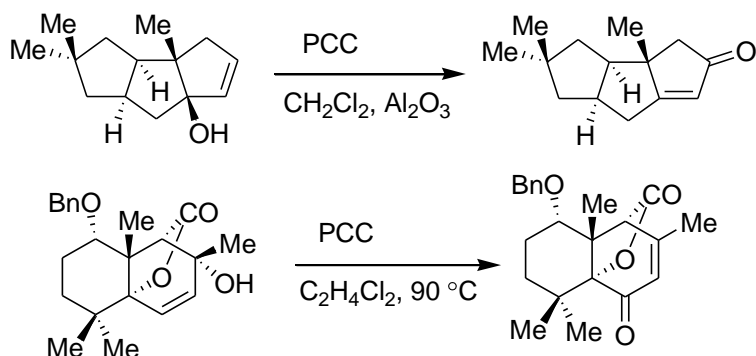
### Oxidation of Alcohols



Scheme 3

Another important use of PCC is the transformation of allylic tertiary alcohols to  $\alpha,\beta$ -unsaturated ketones (Scheme 4). This reaction is thought to proceed *via* a [3,3]-sigmatropic rearrangement of allylic chromate ester to give new allylic

chromate ester, which then undergoes oxidation to give the  $\alpha,\beta$ -unsaturated ketone.

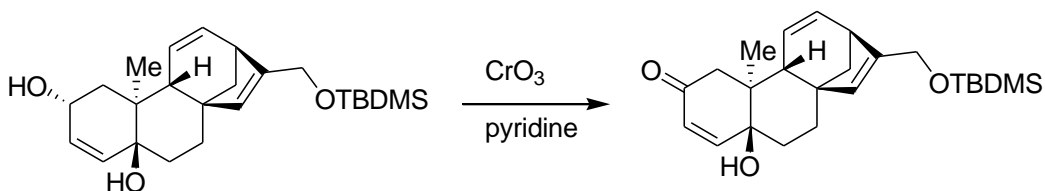


Scheme 4

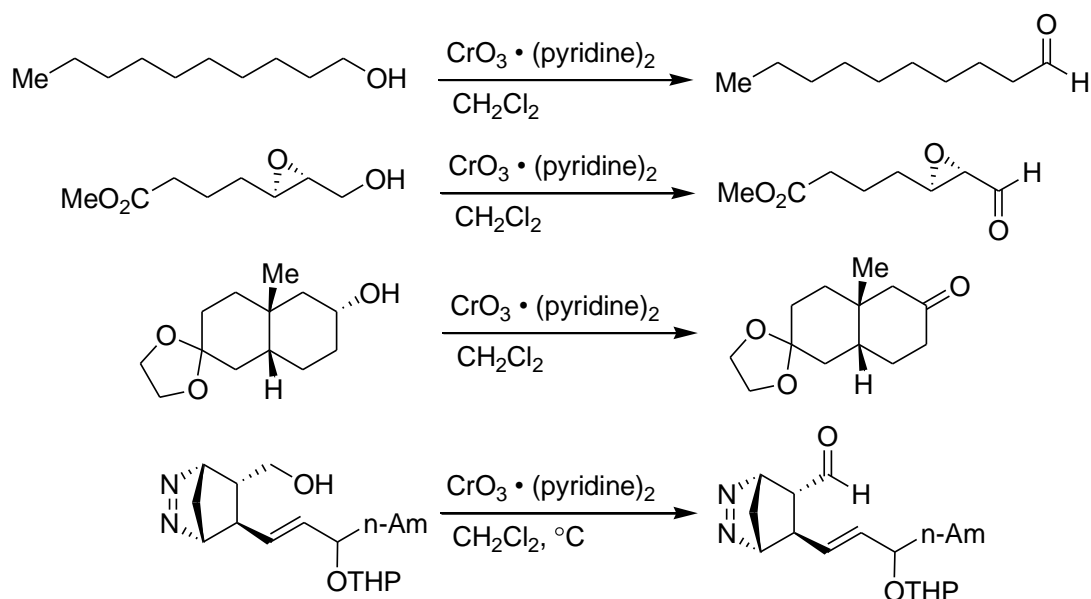
### 1.3.4 Sarrett's Oxidation

The Sarrett's reagent is a mixture of  $\text{CrO}_3$  and pyridine. This reagent also oxidizes the primary and secondary alcohols to aldehydes and ketones (Scheme 5). The acid sensitive groups and other oxidizable groups remain unaffected but the only problem is the removal of excess pyridine after the reaction.

F. Freeman, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 5, 2272.



Scheme 5



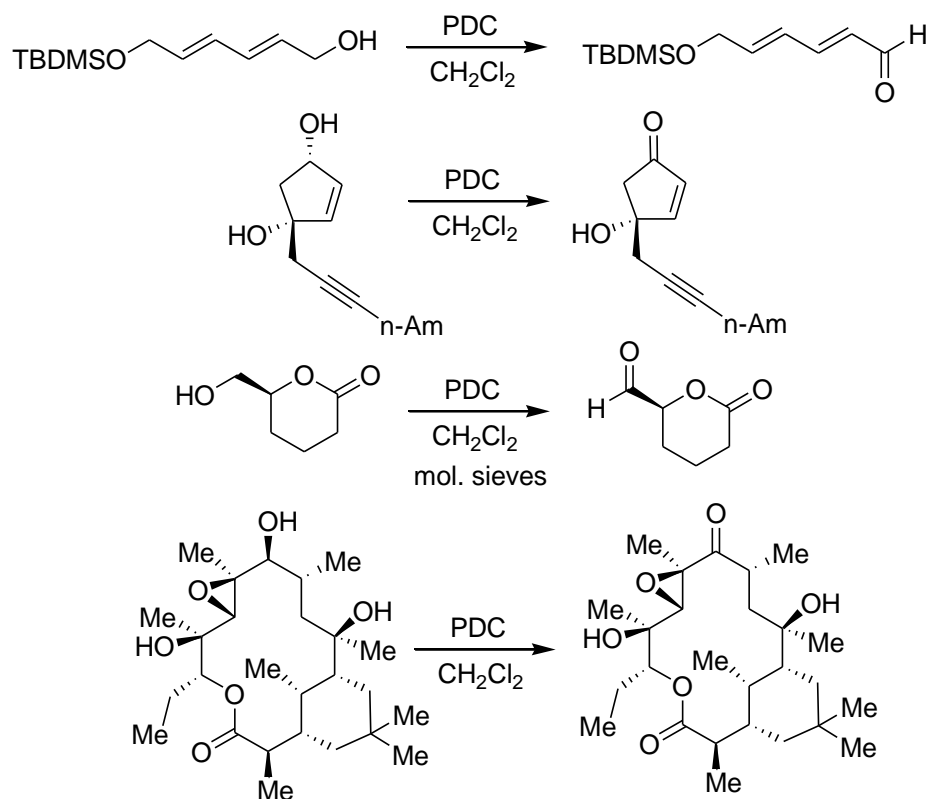
Scheme 6

### 1.3.5 Collins-Ratcliff Oxidation

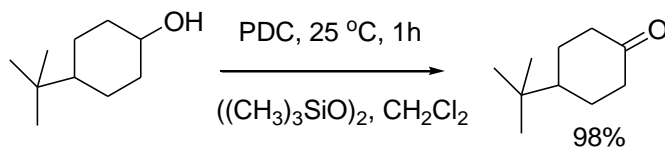
A 1:2 mixture of  $\text{CrO}_3$  and pyridine in dichloromethane (DCM) is known as Collins reagent or Collin-Ratcliff reagent. It also oxidizes the primary alcohols and secondary alcohols to aldehydes and ketones, respectively (Scheme 6). This reaction works under mild reaction condition without affecting other functional groups and the only disadvantage is the excess use of the reagent.

### 1.3.6 Pyridinium Dichromate (PDC) Oxidation

Pyridinium dichromate (PDC),  $(\text{C}_5\text{H}_5\text{NH}^+)_2\text{Cr}_2\text{O}_7^{2-}$ , oxidizes alcohols under neutral condition without affecting other functional groups (Scheme 7). Primary alcohols are oxidized to aldehydes with excellent yield. Allylic alcohol can be oxidized to  $\alpha,\beta$ -unsaturated carbonyl compounds. Excellent yields are obtained by the oxidation of secondary alcohols by using trimethyl silyl peroxide and PDC (Scheme 8).



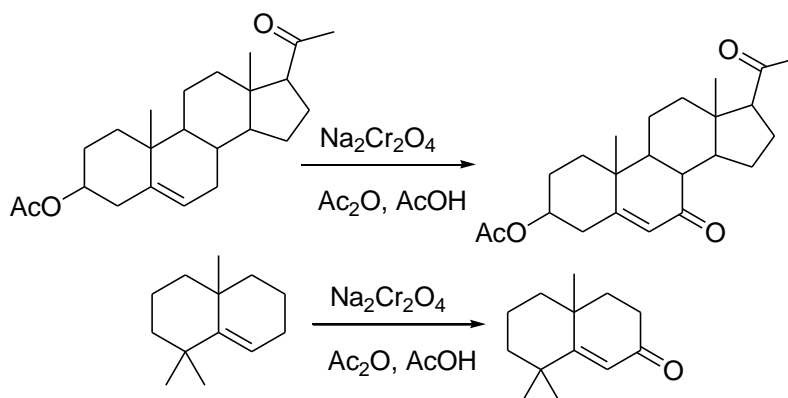
### Scheme 7



### Scheme 8

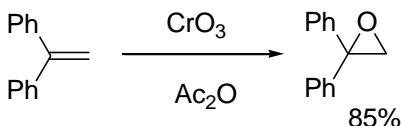
### 1.3.7 Oxidation of Alkenes

Chromium based reagents are used for the oxidation of alkenes to afford  $\alpha,\beta$ -unsaturated carbonyl compounds and epoxides depending the nature of substrates and reactions conditions. For example,  $\text{Na}_2\text{Cr}_2\text{O}_4$  has been used in acetic anhydride for allylic oxidation of cyclic alkenes to afford  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 9).



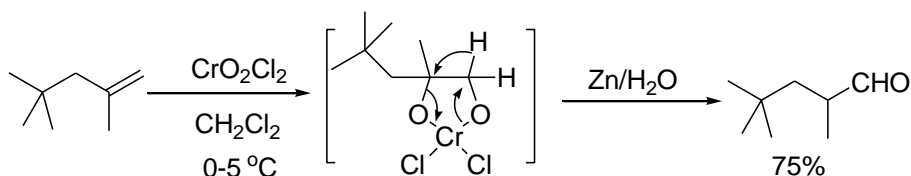
Scheme 8

$\text{CrO}_3$  in acetic anhydride or acetic acid has been found to transform alkenes to epoxides (Scheme 9).



Scheme 9

Alkenes can be oxidized by chromyl chloride at low temperature to afford carbonyl compounds (Scheme 10).

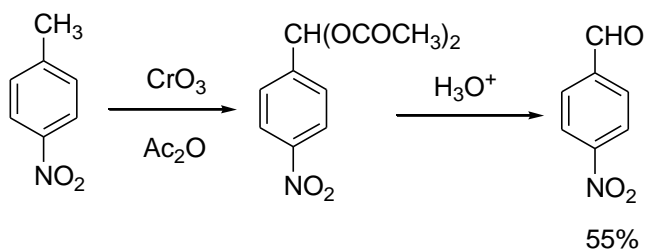


Scheme 10

### 1.3.8 Oxidation of Aromatic Side Chains

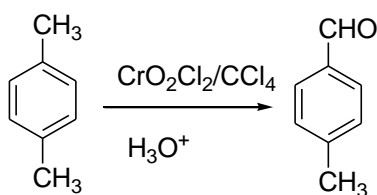
The selective oxidation of alkyl chains attached to an aromatic ring can be carried out with  $\text{CrO}_3$  in acetic anhydride. Thus, *p*-nitrotoluene is converted into *p*-nitrobenzylidene diacetate, which on hydrolysis in the presence of acid gives *p*-nitrobenzaldehyde (Scheme 11).





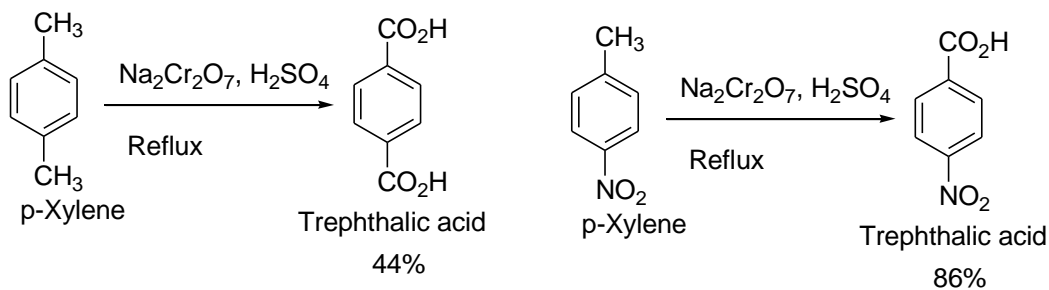
Scheme 11

Chromyl chloride can oxidize *o*-, *m*-, or *p*-xylenes to give tolualdehyde in 70-80% yield (Scheme 12).



Scheme 12

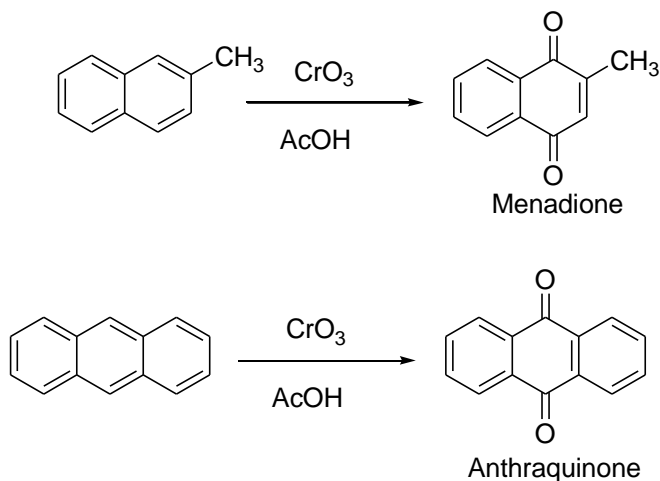
Several studies focus on the oxidation of aromatic alkyl side chains to give carboxylic acids (Scheme 13).



Scheme 13

### 1.3.9 Oxidation of Aromatic Ring

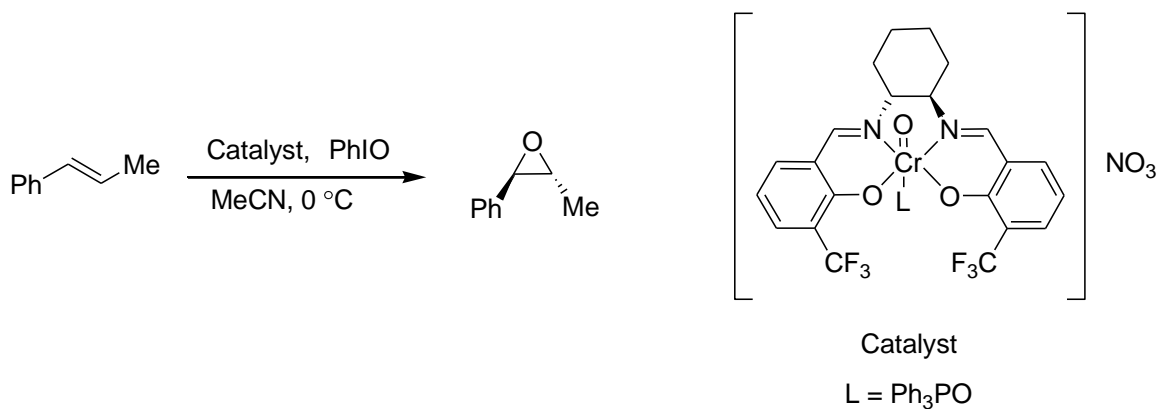
Chromium based reagents are extensively used for the partial oxidation of cyclic hydrocarbons to the quinones (Scheme 14).



Scheme 14

### 1.3.10 Asymmetric Epoxidation

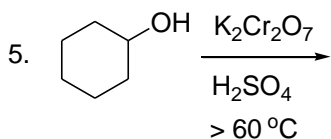
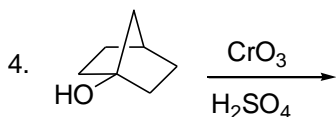
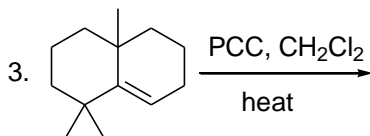
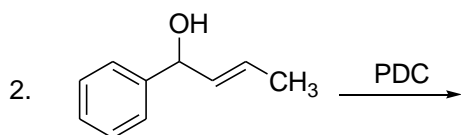
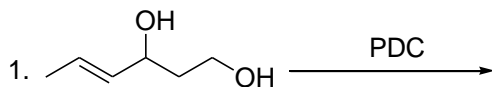
Chiral chromium(VI)-salen complex has been studied for asymmetric epoxidation of *trans* alkenes (Scheme 15). The reaction works in both catalytic and stoichiometric mode but the stoichiometric mode works slightly well than catalytic mode.



Scheme 15

## Problems

1. Give the major product for the following reactions:



2. Provide suitable mechanism for the oxidation of aldehyde to carboxylic acid with chromic acid.
3. How will you transform toluene to benzaldehyde? Discuss with mechanism.

## Text Book

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> edition, McGraw Hill, New Delhi, 2004.

## Lecture 4

### 1.4 Selenium and Aluminium Oxidants

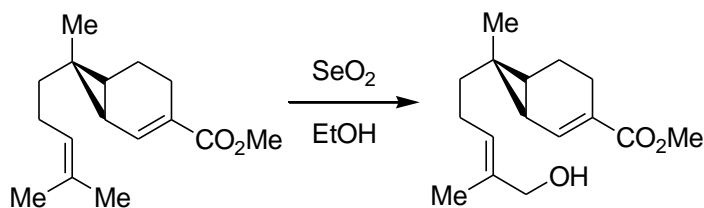
#### 1.4.1 Selenium Dioxide

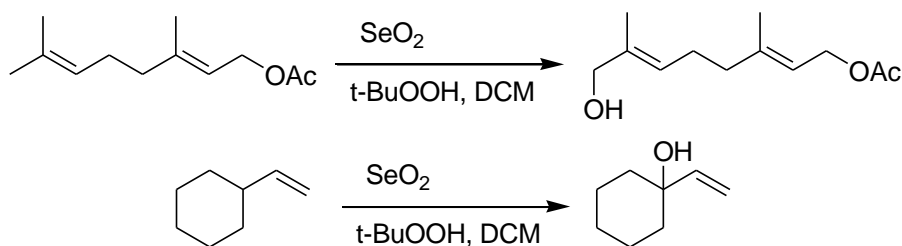
Selenium dioxide ( $\text{SeO}_2$ ) is a colorless crystalline solid. It is soluble in solvents like dioxane, ethanol, acetic acid and acetic anhydride. It is extremely poisonous and should be carefully handled while working with it. However, it is very selective oxidant.

William J. Hoekstra, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons Inc., L. A. Paquette, Ed., New York, 1995, 6, 4437.

##### 1.4.1.1 Allylic Oxidation

Allylic oxidation is an important organic transformation because it provides a direct access to the allylic alcohols from the readily available alkenes (Scheme 1).  $\text{SeO}_2$  is found to be an effective reagent for this transformation. The stoichiometric as well as catalytic amount of  $\text{SeO}_2$  can be used but the later requires an oxidant such as *t*-BuOOH to reoxidize the reduced selenium(II) to  $\text{SeO}_2$ . The reactivity order in ethanol solvent is as follows  $\text{CH}_2 > \text{CH}_3 > \text{CH}$  but the order may change depending on the reaction conditions.

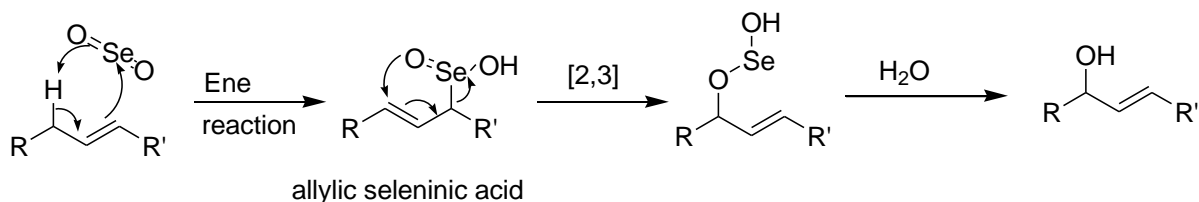




Scheme 1

### Mechanism

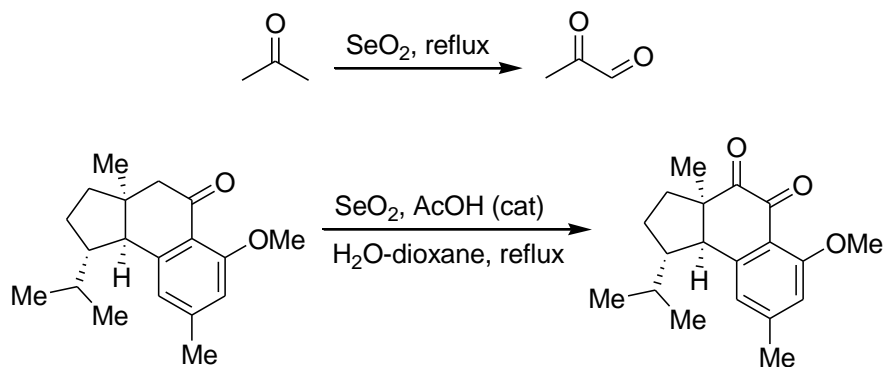
The reaction proceeds *via* ene reaction of allylic compounds with  $\text{SeO}_2$  to afford allylic seleninic acid that undergoes [2,3]-sigmatropic rearrangement to give selenium ester, which on hydrolysis gives the desired alcohol (Scheme 2).



Scheme 2

#### 1.4.1.2 Oxidation of Carbonyl Compounds (Riley Oxidation)

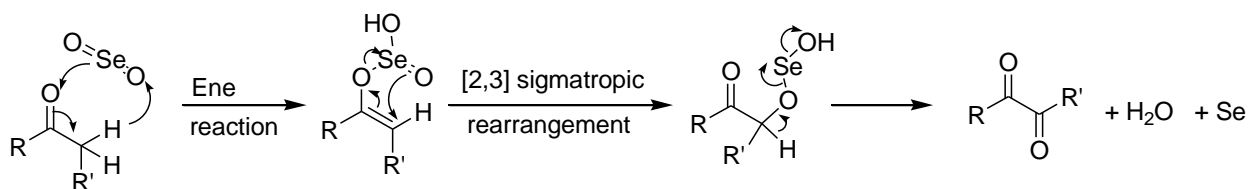
$\text{SeO}_2$  oxidizes active methylene or methyl group present adjacent to the carbonyl group to give 1,2-dicarbonyl compounds (Scheme 3). This reaction is called **Riley oxidation**. It has been widely used for the synthesis of natural products and biologically active compounds.



Scheme 3

## Mechanism

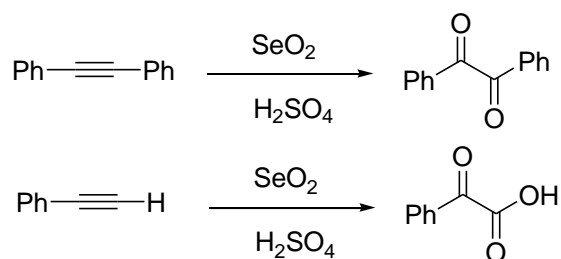
The proposed mechanism is similar to that of allylic oxidation i.e. ene reaction followed by [2,3]-sigmatropic rearrangement and then elimination gives the desired 1,2-dicarbonyl compounds (Scheme 4).<sup>1</sup>



Scheme 4

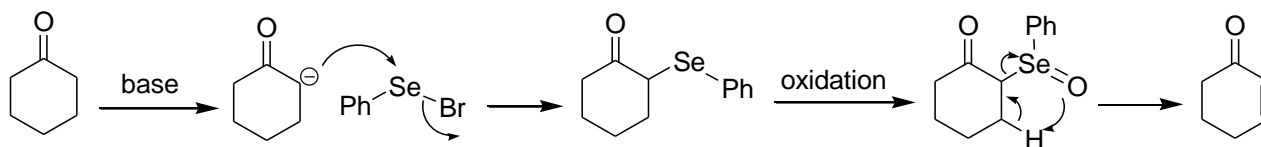
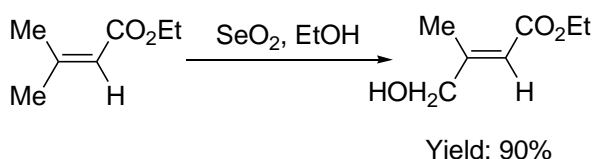
### 1.4.1.3 Oxidation of Alkynes

In the presence of acid,  $\text{SeO}_2$  oxidizes alkynes to give 1,2-dicarbonyl compounds. Internal alkynes can be converted into 1,2-diketones, whereas terminal alkynes are transformed into glyoxylic acid (Scheme 5).

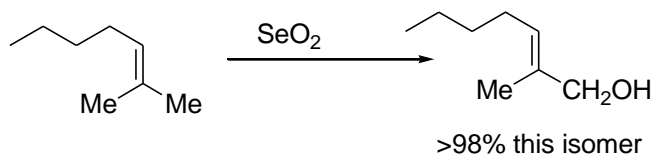


Scheme 5



**Mechanism****Examples**

R. W. Curley, Jr., C. J. Thomas, *J. Org. Chem.* **1986**, 51, 256.

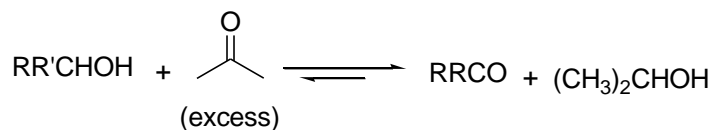


H. Rapoport, U. T. Bhalerao, *J. Am. Chem. Soc.* **1971**, 93, 4835.

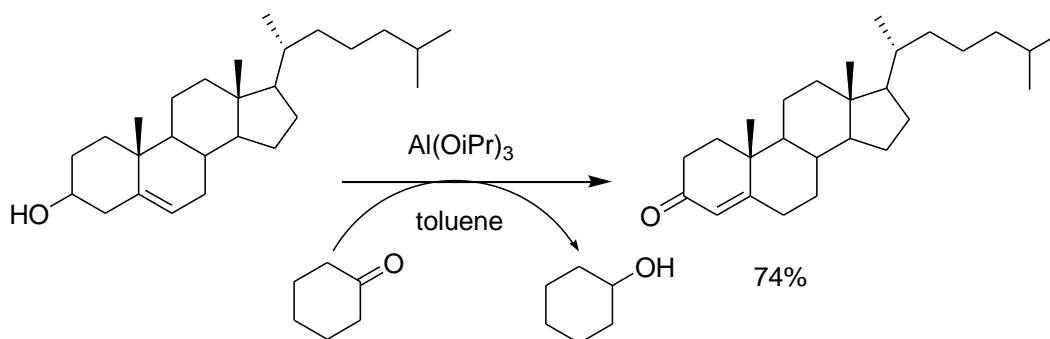
### 1.4.2 Oxidation of Alcohols with Aluminium Alkoxides (Oppenauer Oxidation)

Aluminium triisopropoxide and aluminium tributoxide have been found to be effective reagents for the oxidation of secondary alcohols to ketones in the presence of ketone such as acetone. Acetone acts as a hydrogen acceptor, and it is transformed into 2-propanol. The presence of excess of acetone drives the reaction towards the oxidation product. The use of inert solvent such as benzene, toluene or dioxane minimizes the side products and also helps to raise the reaction temperature.



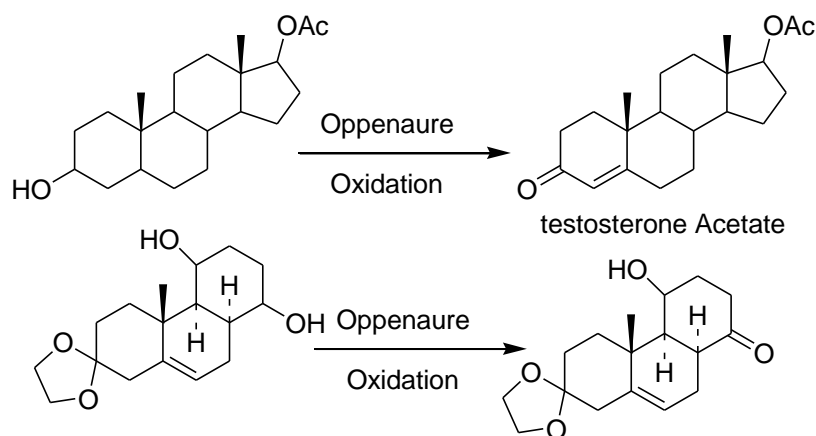


The  $\alpha,\gamma$ -double bonds generally migrate into conjugation with the carbonyl group under the reaction conditions (Scheme 8). For example, cholesterol is oxidized to cholestenone with the migration of the double bond in the presence of cyclohexanone, which acts as hydrogen acceptor.



Scheme 8

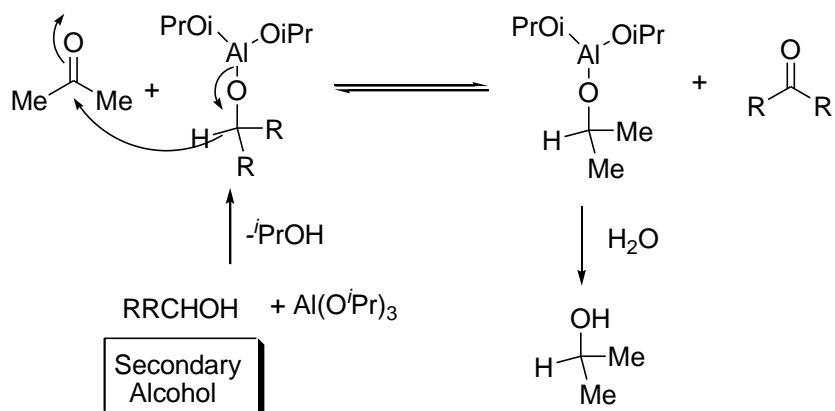
The reaction conditions are compatible with acetals, acetates and benzoates. However, formate can be oxidized as free alcohol to give ketone. The oxidation of equatorial hydroxyl groups are favored compared to the axial hydroxyl groups (Scheme 9).



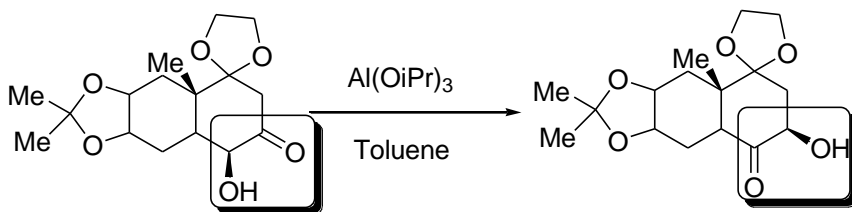
Scheme 9

**Mechanism**

The reaction is performed by refluxing a secondary alcohol with acetone in the presence of  $\text{Al}(\text{O}^i\text{Pr})_3$ . The latter serves only to form the aluminium alkoxide of the alcohol that is oxidized through a cyclic transition state at the expense of acetone to a ketone and 2-propanol.

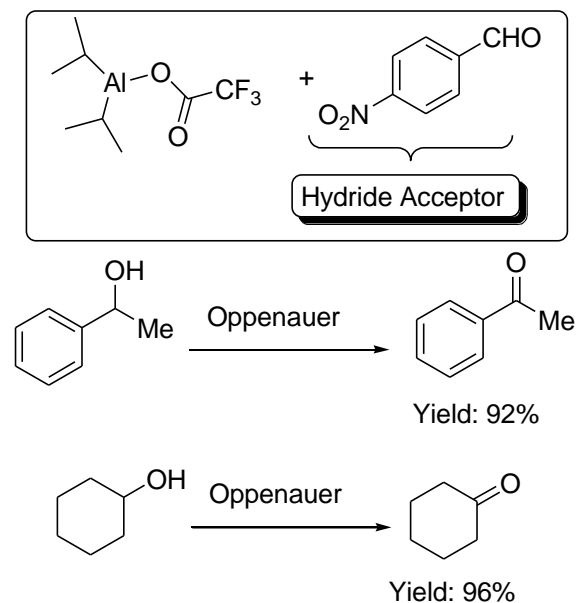


**An important feature of this reaction is the lack of over oxidation**

**Examples**

T. K. M. Shing, C. M. Lee, H. Y. Lo, *Tetrahedron Lett.* **2001**, **42**, 8361.

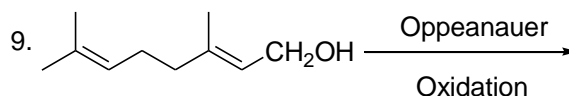
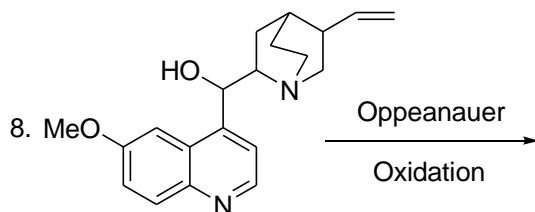
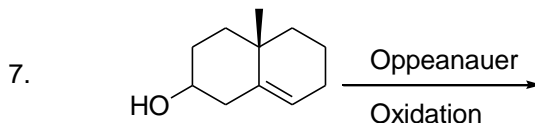
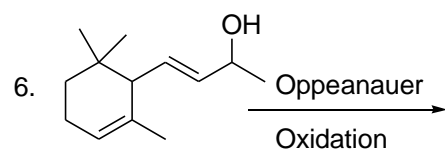
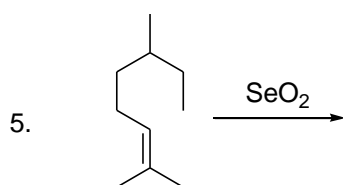
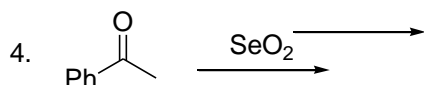
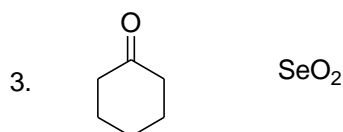
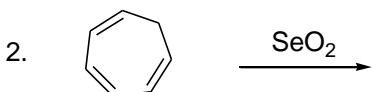
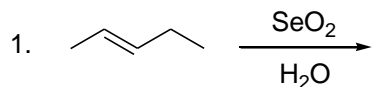
**New Oxidation System:**



K. G. Akamanchi, B. A. Chaudhari, *Tetrahedron Lett.* **1997**, 38, 6925.

## Problems

Give the major product for the following reactions:



## Text Book

M. B. Smith, J. March, *Advanced Organic Chemistry*, 5<sup>th</sup> ed., John Wiley and Sons, Inc., New York, 2001.

## Lecture 5

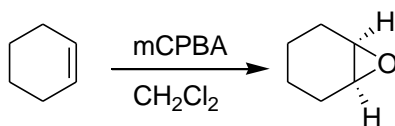
### 1.5 Peracids

#### 1.5.1 Introduction

A number of peracids having the general formula,  $\text{RCO}_3\text{H}$  have been used for the oxidation of organic compounds. Some of the common peracids are: peracetic acid ( $\text{CH}_3\text{CO}_3\text{H}$ ), perbenzoic acid ( $\text{PhCO}_3\text{H}$ ), trifluoroacetic acid ( $\text{CF}_3\text{CO}_3\text{H}$ ) and *m*-chloroperbenzoic acid (*m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}$ ). Peracids are usually prepared *in situ* by the oxidation of carboxylic acid with hydrogen peroxide.

#### 1.5.2 Epoxidation of Alkenes

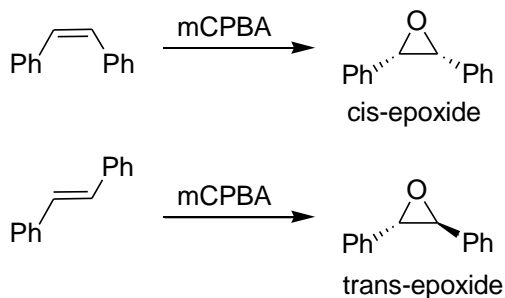
Epoxides are useful building blocks in organic synthesis as they react with a variety of nucleophiles resulting in opening epoxide ring. An effective route for the synthesis of epoxides is the direct conversion of alkenes to epoxides using peracids as oxidizing agent. *m*-CPBA is often used for this purpose because it is available commercially as a colorless crystalline solid. The reaction is carried out at ambient conditions in chlorinated solvent such as dichloromethane (Scheme 1). *m*-Chlorobenzoic acid is produced as a by-product, which can be removed by washing the reaction mixture with saturated  $\text{NaHCO}_3$  solution.



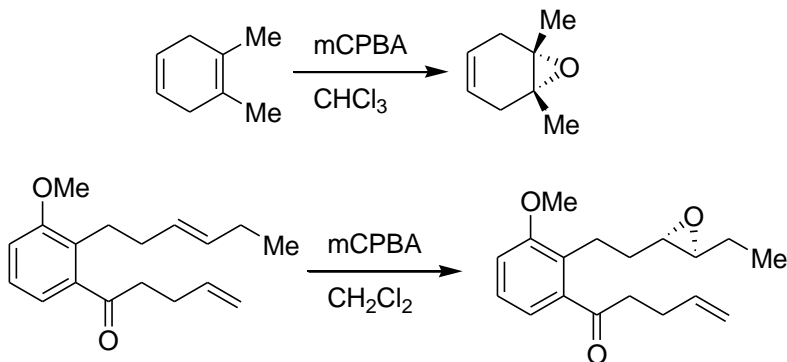
Scheme 1

The reaction is stereospecific leading to the *syn* addition of the oxygen atom to alkene. Thus, *cis* alkene gives *cis*-epoxide and *trans* alkene gives *trans*-epoxide (Scheme 2). The electron rich alkene shows greater reactivity compared to electron deficient alkenes toward *m*-CPBA. Thus, terminal alkenes exhibit slower reactivity compared alkyl substituted alkenes (Scheme 3). Peracid having

electron withdrawing substituent exhibits greater reactivity compared to that containing electron donating group. For an example, *m*-CPBA is more reactive compared to  $\text{PhCO}_3\text{H}$ .

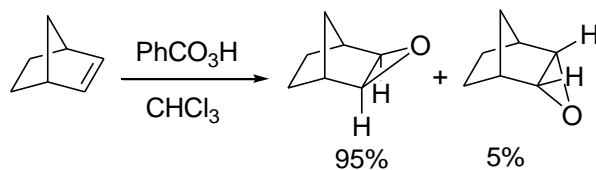


Scheme 2

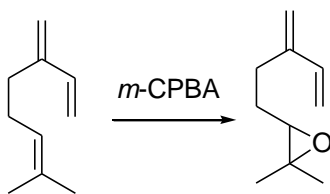


Scheme 3

In case of cyclic alkenes that are conformationally rigid, the reagent approaches from the less hindered side of the double bond. This is illustrated in the oxidation of norbornene (Scheme 4).



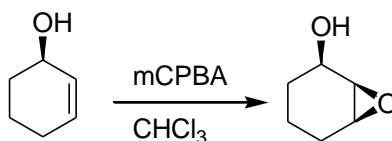
Scheme 4



Scheme 5

The isolated alkenes undergo reaction before the conjugated double bond. This is illustrated by the oxidation of  $\beta$ -myrcene (Scheme 5).

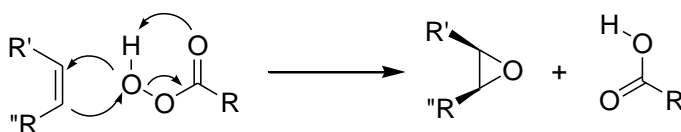
A suitable substituent particularly at the allylic position may control the direction of the new epoxide group (Scheme 6). This is due to the transition state electronic interaction between electron deficient *m*-CPBA and the direction group.



Scheme 6

### Mechanism

The reaction proceeds through a concerted pathway (Scheme 7). The reaction involves addition of an oxygen atom to the double bond with simultaneous proton transfer from oxygen to carbonyl oxygen.

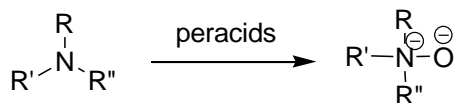


Scheme 7

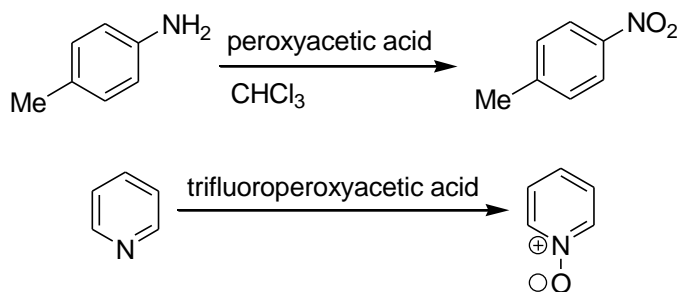
### 1.5.3 Oxidation of Amines

The tertiary amines and the aromatic nitrogen containing heterocycles could be oxidized to the corresponding N-oxides using peracids, which have great

synthetic utility (Scheme 8-9). The aromatic primary amines are oxidized to aromatic nitro compounds.



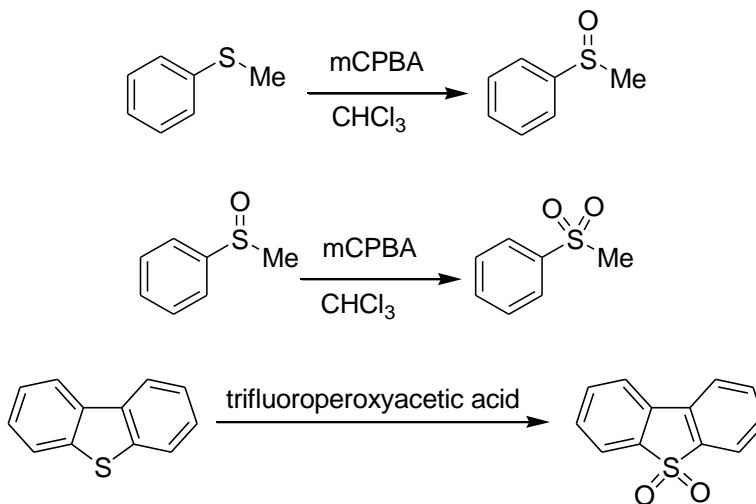
Scheme 8



Scheme 9

### 1.5.4 Oxidation of Thioethers

The thioethers could be oxidized to the corresponding sulfoxides and sulfones using peracids (Scheme 10).

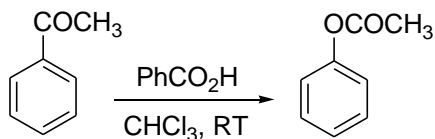


Scheme 10



### 1.5.5 Oxidation of Ketones (*Baeyer-Villiger Oxidation*)

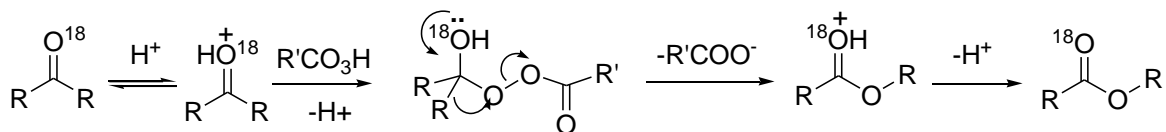
Ketones undergo reaction with peracids to give esters by insertion of oxygen (Scheme 11). The reaction is known as Baeyer-Villiger oxidation.



Scheme 11

#### Mechanism

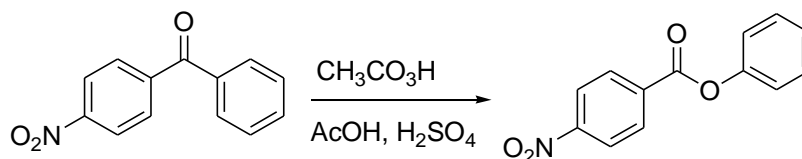
The first step involves protonation of carbonyl oxygen (Scheme 12). The addition of peracid to the protonated carbonyl group gives a tetrahedral intermediate. Elimination of the carboxylate anion and migration of R to the electron deficient oxygen atom occur simultaneously. The resulting protonated form of the ester loses a proton to yield ester. It is believed that the loss of carboxylate anion and migration of R are concerted. The labeling study with  $O^{18}$  suggests that the carbonyl oxygen of the ketones becomes the carbonyl oxygen of the ester.



Scheme 12

#### Migratory Aptitude

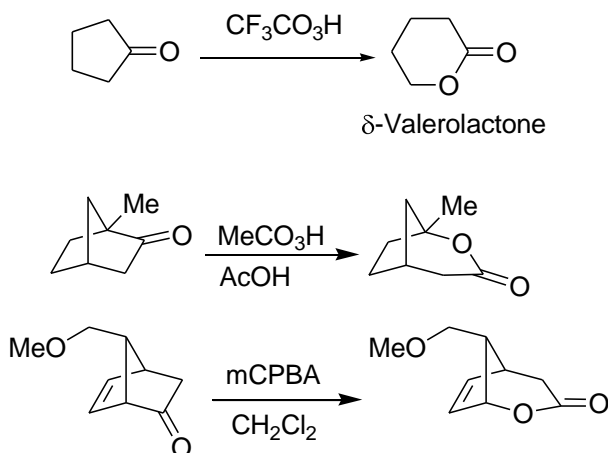
Aryl groups migrate in preference to methyl and primary alkyl groups. The order of preference for the migration of alkyl groups is  $3^\circ > 2^\circ > 1^\circ > \text{methyl}$ . The order of preference for the migration of aryl groups is  $p\text{-OMeC}_6\text{H}_4 > \text{C}_6\text{H}_5 > p\text{-NO}_2\text{C}_6\text{H}_4$  (Scheme 13).



Scheme 13

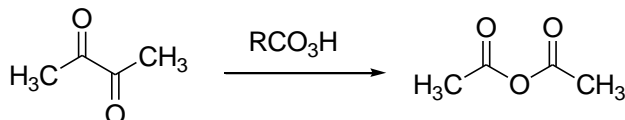
## Applications

Baeyer-Villiger oxidation has great synthetic applications as the reaction allows the conversion of ketones to esters. The reaction works well with cyclic and acyclic ketones (Scheme 14). For some examples, see:



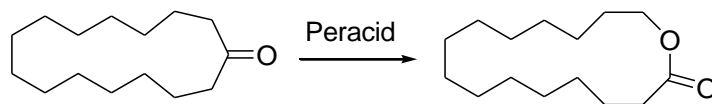
Scheme 14

Under these conditions, 1,2-diketones proceed reaction to give anhydride (Scheme 15).



Scheme 15

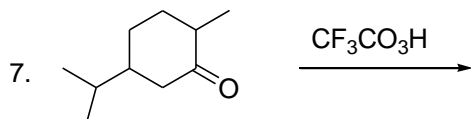
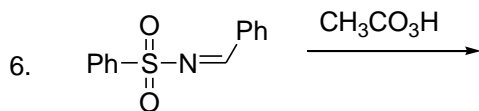
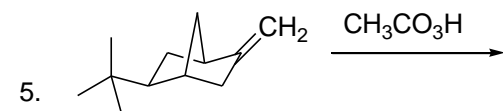
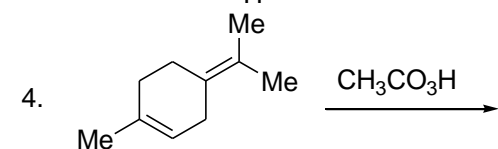
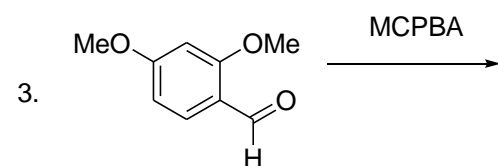
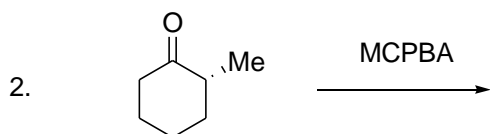
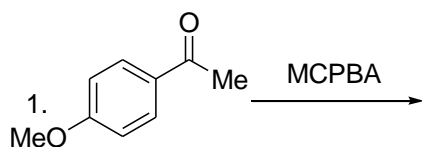
Baeyer-Villiger oxidation is a very useful protocol for the synthesis of large ring lactones that are otherwise difficult to prepare by intramolecular esterification of long-chain hydroxyacids (Scheme 16). For example, cyclopentadecanone can be readily oxidized to the corresponding lactone in good yield.



Scheme 16

## Problems

What major products would expect in the following reactions?



**Text Book**

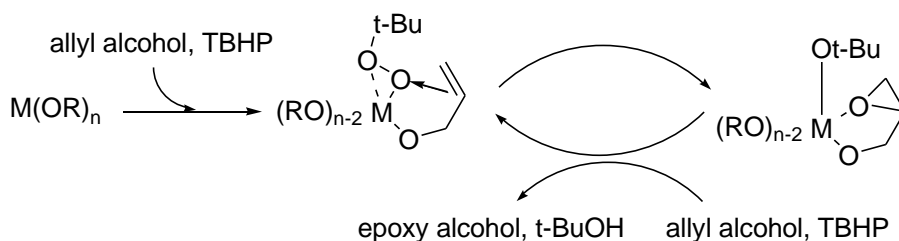
R. Brukner, *Advanced Organic Chemistry*, Academic Press, San Diego, USA, 2002.

**Lecture 6****1.5 Peroxides****1.5.3 Peroxides**

Peroxides are important oxidizing agent for the organic compounds. Aqueous  $\text{H}_2\text{O}_2$  and  $\text{t-BuO}_2\text{H}$  are commonly used hydroperoxides, which are commercially available. The lecture will discuss some of the important oxidation reactions performed with peroxide reagents.

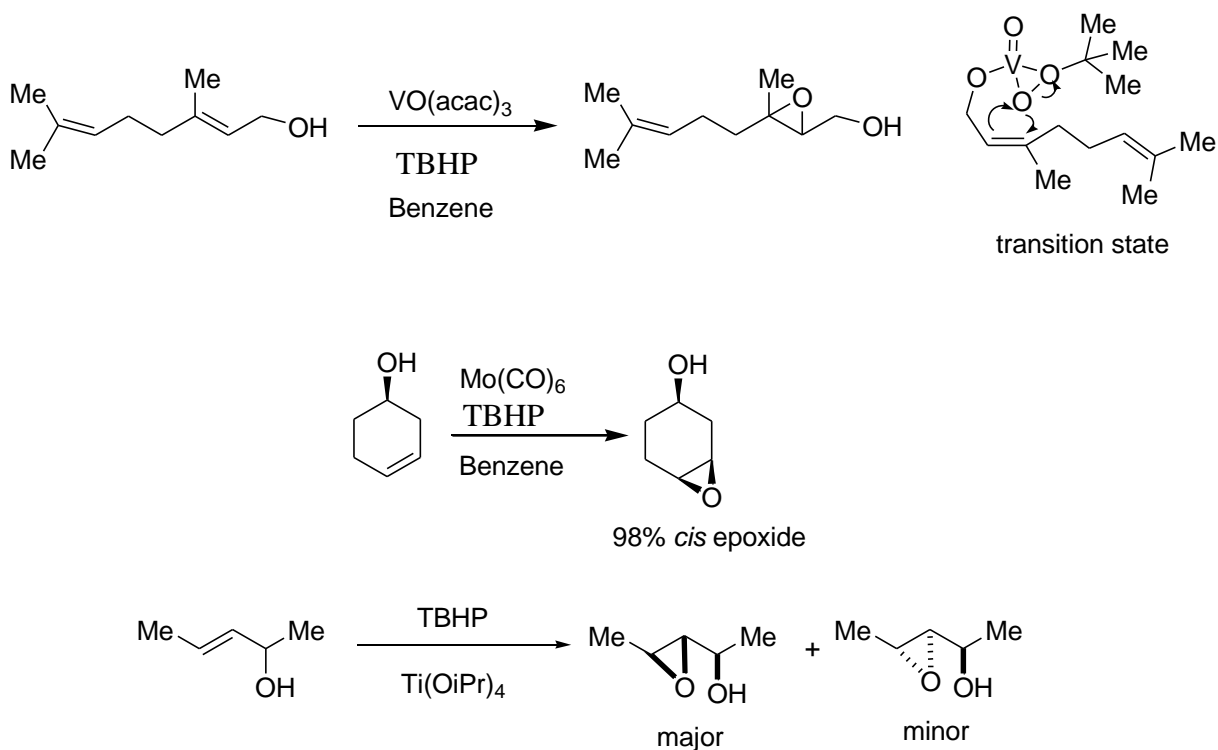
**1.5.3.1 Epoxidation of Allylic Alcohols**

Epoxidation of allylic alcohols is one of the most important processes in oxidation chemistry. Metal alkoxides with  $\text{t-BuOOH}$  (TBHP) provide an excellent method for the epoxidation of allylic alcohols (Scheme 1). The double bond selectively undergoes oxidation without affecting the OH group.

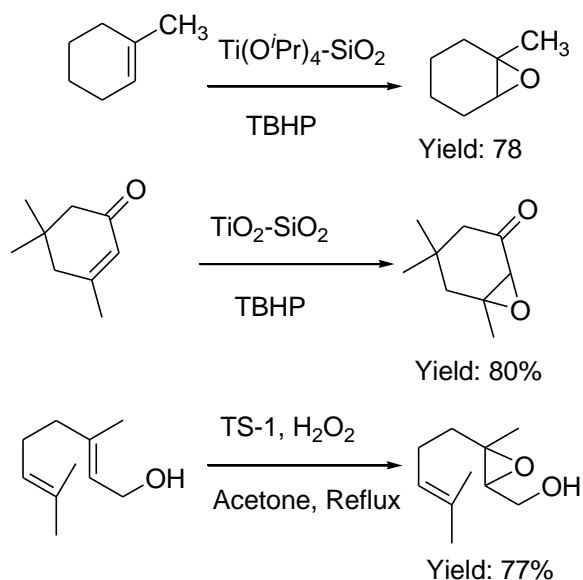


Scheme 1

For examples:



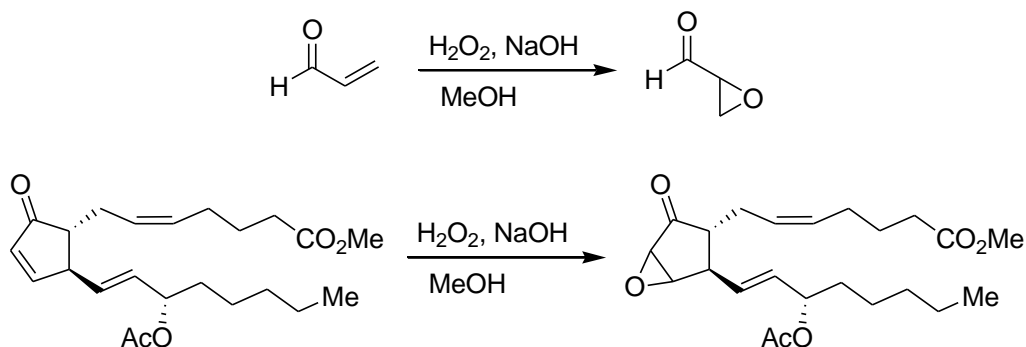
In addition to these homogeneous processes, effort has also been made to develop heterogeneous catalysts for the epoxidation of allylic alcohols with hydroperoxides (Scheme 2).  $\text{TiO}_2\text{-SiO}_2$  has been found to be superior to  $\text{V}_2\text{O}_5\text{-SiO}_2$  and  $\text{MoO}_3\text{-SiO}_2$  for this purpose. Both TBHP and  $\text{H}_2\text{O}_2$  (aqueous and urea  $\text{H}_2\text{O}_2$ ) have been employed as terminal oxidant. These systems also work for the epoxidation of unfunctionalized alkenes.



Scheme 2

### 1.5.3.2 Epoxidation of $\alpha,\beta$ -Unsaturated Carbonyl Compounds

Alkaline- $\text{H}_2\text{O}_2$  is used for the epoxidation of  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 3). The method is straight forward and the products are obtained in high yield.

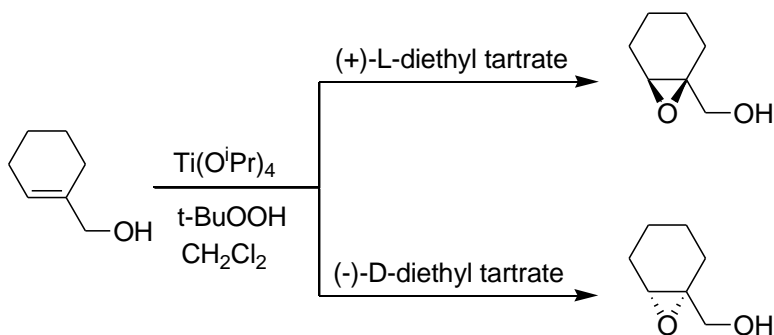


Scheme 3

### 1.5.3.3 Asymmetric Epoxidation

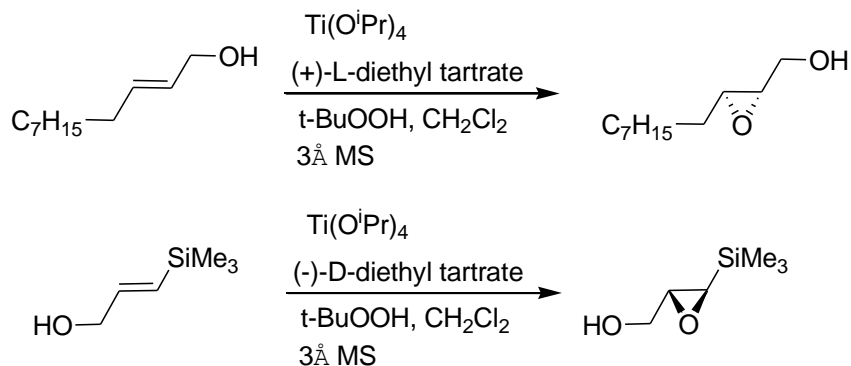
Asymmetric epoxidation is one of the most selective methods for the formation of enantiomeric products. The asymmetric epoxidation of allylic alcohols with *t*-BuOOH,  $\text{Ti}(\text{O}^i\text{Pr})_4$  and tartrate ester, called Sharpless asymmetric epoxidation, provides the epoxides with high enantiomeric excess and yield (Scheme 4). This

reaction has been used for the synthesis of many important natural products and biologically active molecules.



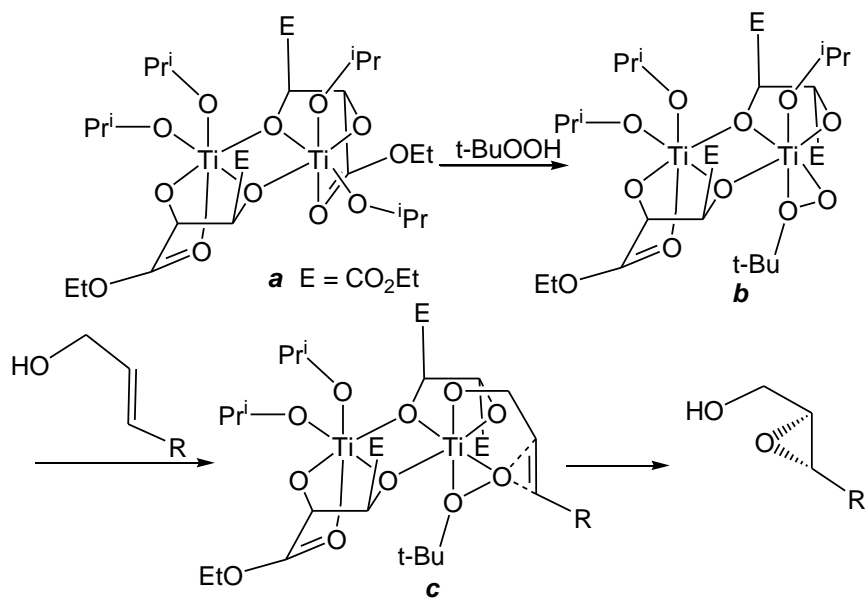
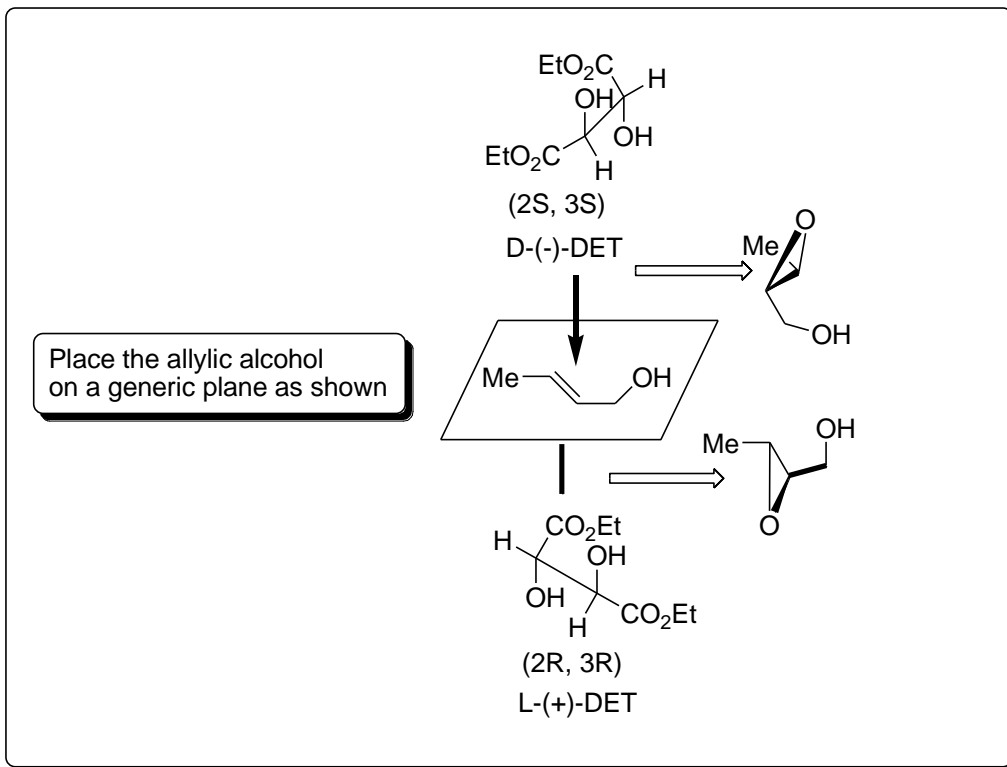
Scheme 4

The mnemonic rule for the absolute configuration of the epoxy alcohol is as follows, if the  $\text{CH}_2\text{OH}$  group is in lower right or upper left of the double bond then the epoxide is formed at the upper face of the double bond when (+)-L-diethyl tartrate is used and at lower face when (-)-D-diethyl tartrate is used (Scheme 5). The reaction works catalytically when  $3\text{\AA}$  or  $4\text{\AA}$  molecular sieves are used as an additive.



Scheme 5

## How to Predict Product Composition



Scheme 6

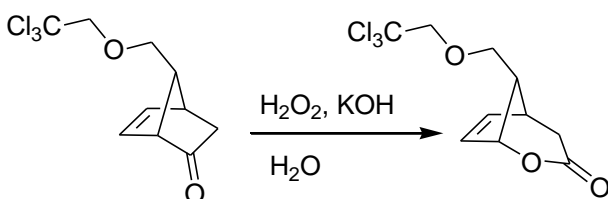
The diethyl tartrate (DET) and the  $\text{Ti}(\text{O}^i\text{Pr})_4$  react to form the dimeric complex **a**, which in presence of  $t\text{-BuOOH}$  replaces one isopropoxy group to form the



complex **b**. The complex **b** then reacts with the allylic alcohol to form the intermediate complex **c**, which is the active transition state intermediate and it transfers the active oxygen of the co-ordinated hydroperoxide to the allylic double bond (Scheme 6).

#### 1.5.4 Baeyer-Villiger Oxidation

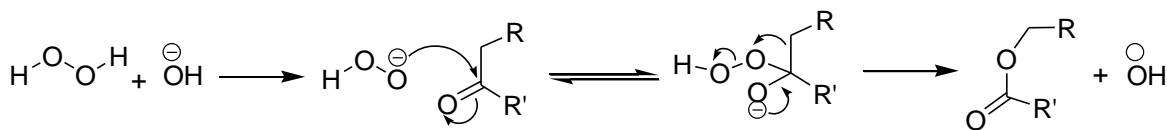
Alkaline peroxide could be used for the oxidation of ketones to give esters (Scheme 6).



Scheme 7

#### Mechanism

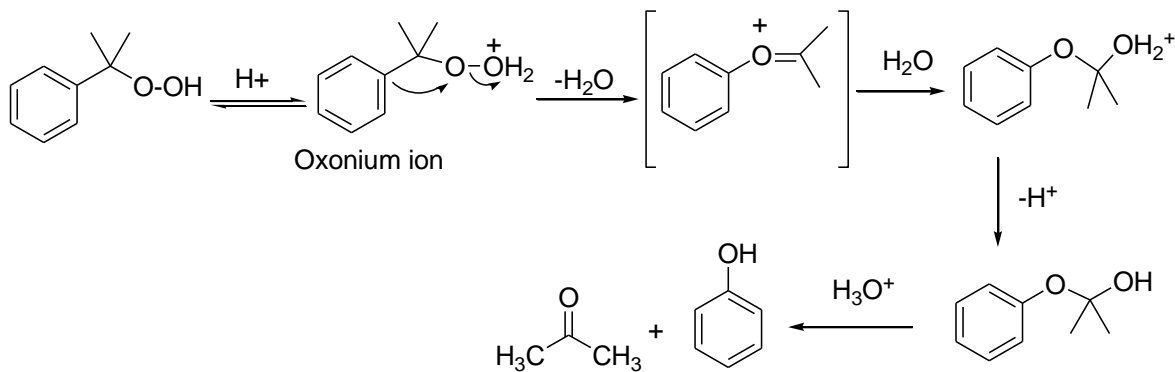
The mechanism for the alkaline hydroperoxide mediated oxidation of ketone to ester follows (Scheme 8).



Scheme 8

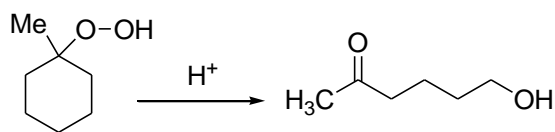
#### 1.5.5 Hyderoperoxide Rearrangement

Hyderoperoxide in the presence of strong acid such as  $\text{H}_2\text{SO}_4$ ,  $\text{HClO}_4$  and Lewis acids undergoes rearrangement as Baeyer-Villiger oxidation. For example, cumene hydroperoxide in the presence of  $\text{H}_2\text{SO}_4$  undergoes rearrangement *via* hemiacetal to give phenol and acetone (Scheme 9). The cumene hydroperoxide can be obtained by autooxidation of cumene. This is the commercial process used for the synthesis of phenol.



Scheme 9

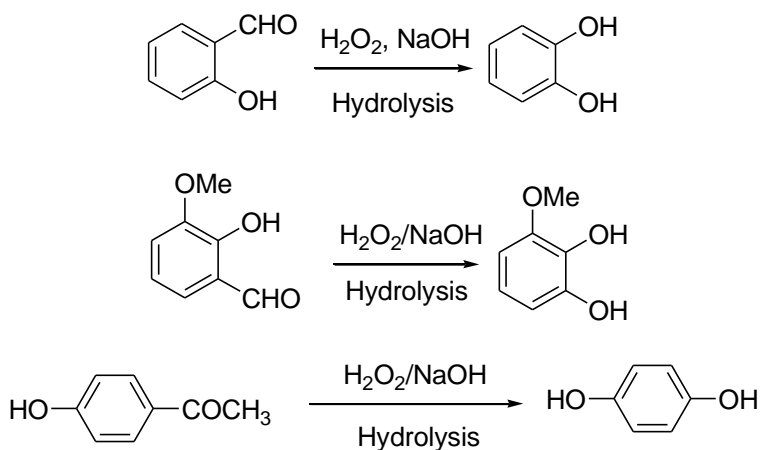
Under these conditions, 1-methylcyclohexyl hydroperoxide rearranges to give 7-hydroxyhept-2-one (Scheme 10).



Scheme 10

### 1.5.6 Dakin Reaction

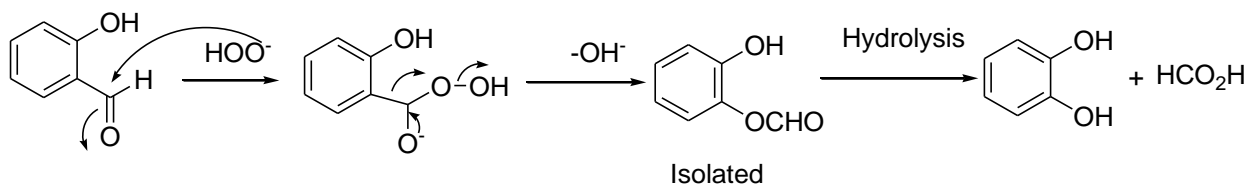
Phenolic aldehydes and ketones proceed reactions with alkaline  $\text{H}_2\text{O}_2$  to replace the aldehyde or acetyl group with OH group, which is called Dakin reaction. For example, salicylaldehyde is transformed into catechol in 70% yield (Scheme 11).



Scheme 11

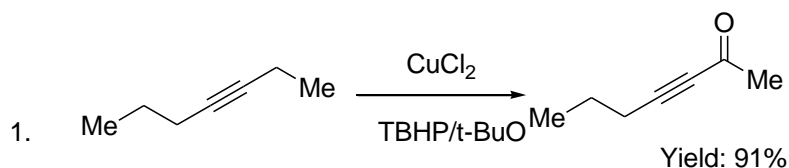
## Mechanism

The proposed mechanism is similar to that of Baeyer-Villiger oxidation (Scheme 12).

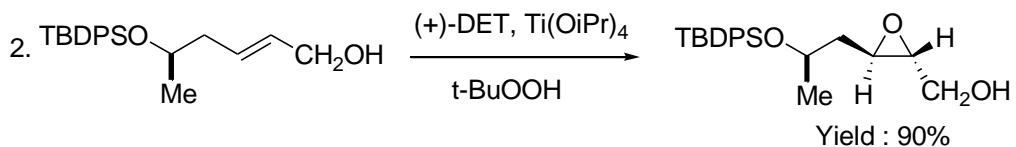


Scheme 12

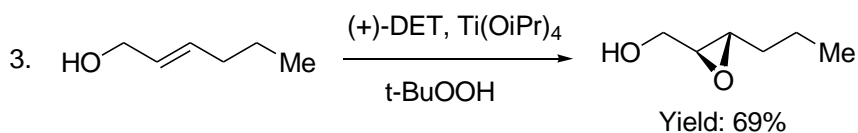
## Examples



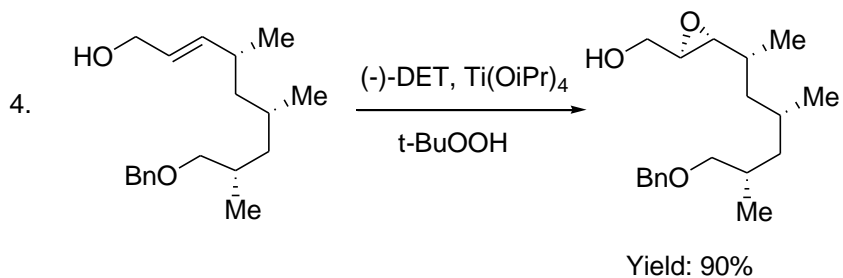
P. Li, W. M. Fong, L. C. f. Chao, S. H. C. Fung, I. D. Williams, *J. Org. Chem.* **2001**, 66, 4087.



R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin, S. J. Daisshefsky, *J. Am. Chem. Soc.* **2001**, 123, 10903.



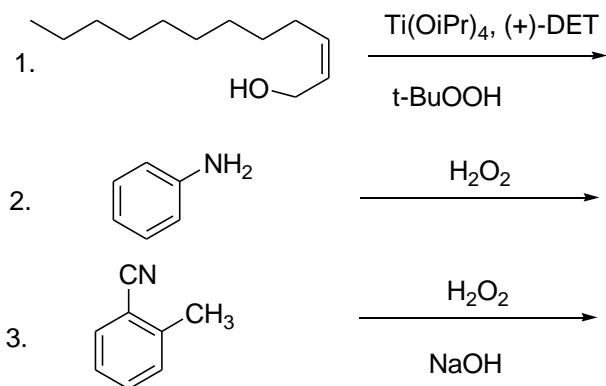
J. G. Hill, K. B. Sharpless, C. M. Exon, R. Regenye, *Org. Syn.* CV7, 461.

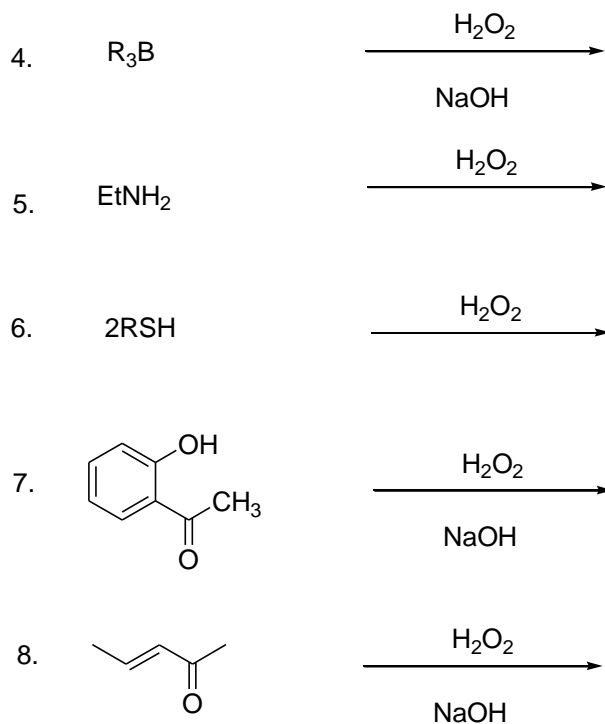


K. Ghosh, C. Liu, *Org. Lett.* **2001**, 3, 635.

### Problems

Give the major products in the following reactions.





### Text Book

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> edition, McGraw Hill, New Delhi, 2004.

## Lecture 7

### 1.6 Ozone, Lead Tetraacetate and Sodium Periodate

#### 1.6.1 Ozone

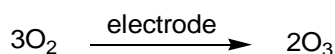
R. A. Berglund, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 3837.

##### 1.6.1.1 Introduction

Ozone is triatomic oxygen species with a characteristic smell and pale blue color. It is less stable and highly reactive and slightly soluble in water but more soluble in non-polar solvents such as carbon tetrachloride.

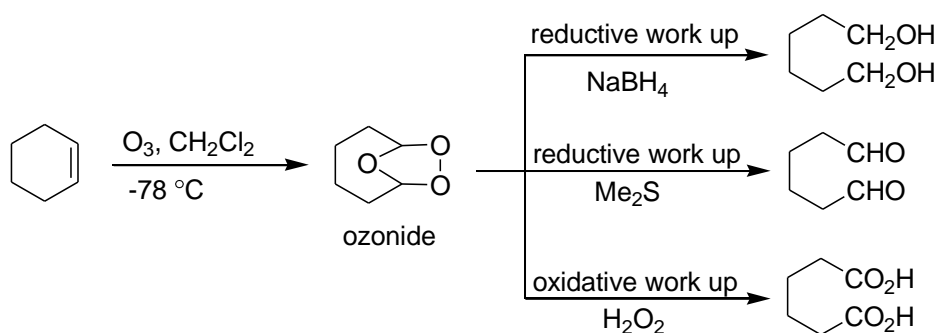
### 1.6.1.2 Preparation

Ozone is prepared by passing dry oxygen through two electrode connected with AC current.



### 1.6.1.3 Ozonolysis

The reactions of alkenes with ozone can produce alcohols, aldehydes, ketones and carboxylic acids depending on the reaction conditions (Scheme 2-3). This degradation of alkenes with ozone



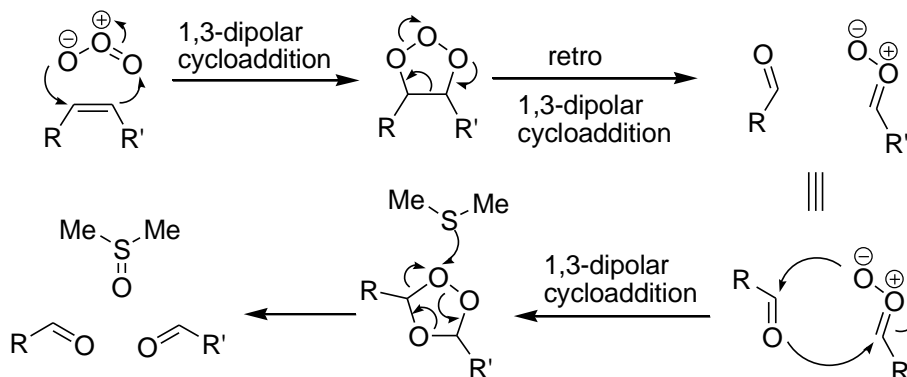
Scheme 1

is called ozonolysis. The reaction is performed in common solvents such as dichloromethane, methanol and acetone at  $-78\text{ }^{\circ}\text{C}$ . A reductive work up with  $\text{Me}_2\text{S}$  or  $\text{PPh}_3$  or thiourea or zinc dust produces aldehydes and ketones, whereas sodium borohydride ( $\text{NaBH}_4$ ) produces alcohols and the oxidative work up with  $\text{H}_2\text{O}_2$  provides acids.

Examples:



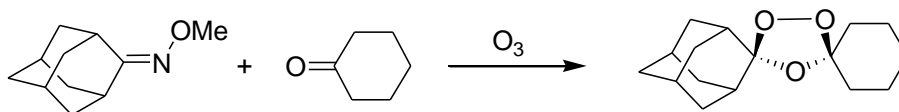
form the ozonide. The latter reacts with oxidizing or reducing agent to give the desired product.



Scheme 3

#### 1.6.1.4 Griesbaum Cross-Ozonolysis

The *O*-alkyl ketone oxime was ozonide in presence of an added carbonyl compound to give the cross-ozonide product. This reaction was discovered in 1995 by Karl Griesbaum and co-workers and hence called Griesbaum cross-ozonolysis reaction.



This reaction provides a widely applicable synthesis of both symmetrical and unsymmetrical tetrasubstituted ozonides that are otherwise generally inaccessible by common ozonolysis.

#### 1.6.2 Lead Tetraacetate(Criegee Reagent)

M. L. Mihailovic, Z. Cekovic, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 5, 2949.

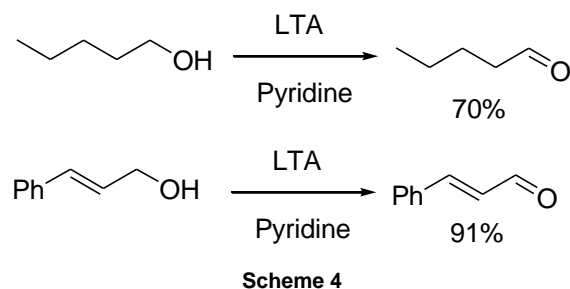
##### 1.6.2.1 Introduction



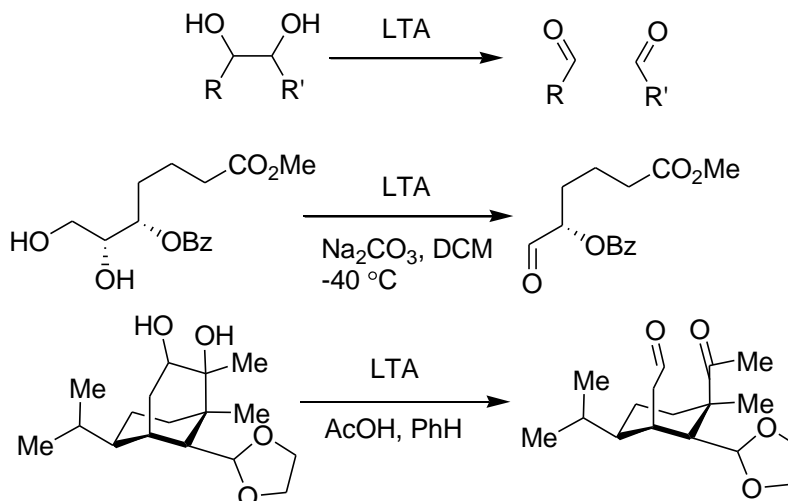
Lead tetraacetate (LTA) is one of the powerful common oxidizing reagents available with wide applications for organic synthesis. The reagent is very toxic, hygroscopic and turns brown due to lead dioxide formation on exposure to air. Therefore, the reagent is to be handled with extreme care in a chemical hood. It can be prepared by adding red lead oxide,  $\text{Pb}_3\text{O}_4$ , to a mixture of acetic acid and acetic anhydride at  $\sim 70^\circ\text{C}$ . Recrystallization of the crude LTA from AcOH can give colorless white crystals.

### 1.6.2.2 Reaction with Alcohols

LTA oxidizes alcohols to aldehydes and ketones in the presence of pyridine at ambient temperature. The reactions are efficient and over oxidation to carboxylic acids are not observed. For example, pentanol and cinnamyl alcohol can be oxidized to give aldehydes in the presence of pyridine with high yield (Scheme 4).



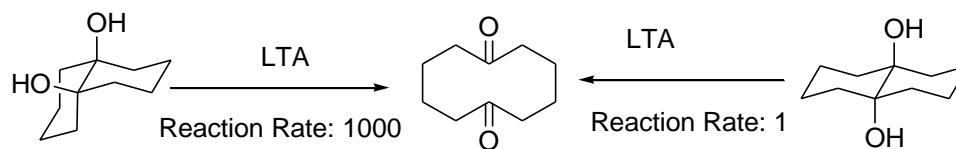
In the case of 1,2-diols, oxidative cleavage is observed to give aldehydes, ketones or both depending on the structure of the diols (Scheme 5). The reaction involves a cyclic intermediate and *cis*-1,2-diols exhibit greater reactivity compared to *trans*-1,2-diols. The reactions are performed in organic solvent such as benzene, toluene, dichloromethane and THF. When three or more hydroxyl groups are present on adjacent carbon atoms, then the middle one is converted into formic acid.



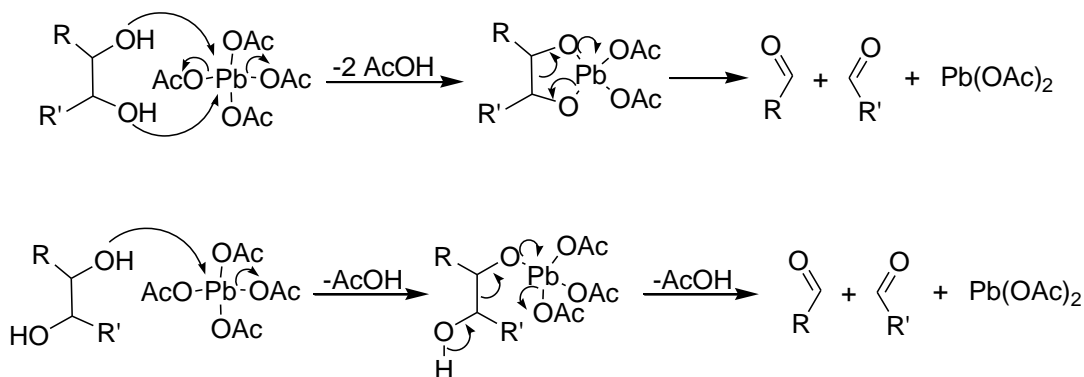
Scheme 5

### Mechanism

*Cis*-diols are cleaved more readily compared to *trans* diols (Scheme 6). Different mechanistic interpretations are thus proposed for the two processes (Scheme 7):

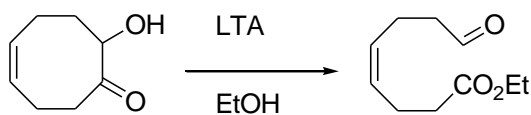


Scheme 6



Scheme 7

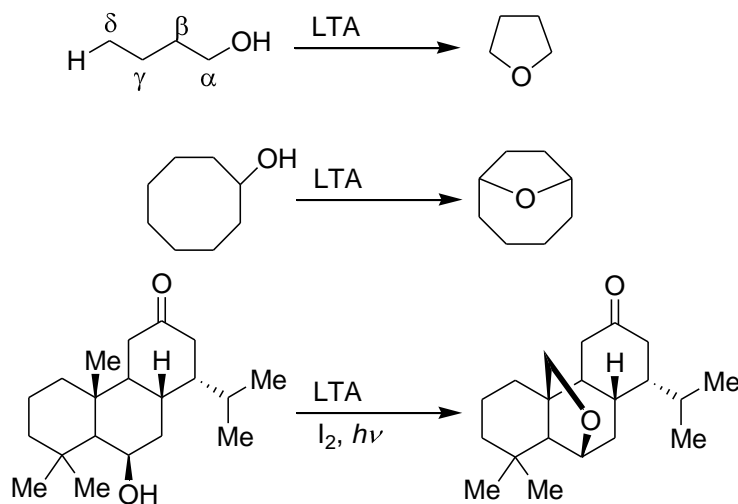
In addition, the reaction conditions can be used for the oxidative cleavage of the compounds such as  $\beta$ -amino alcohols, 1,2-diamines,  $\alpha$ -hydroxy carbonyl and 1,2-dicarbonyl to give similar results (Scheme 8).



Scheme 8

### 1.6.2.3 Cyclization of Saturated Alcohols

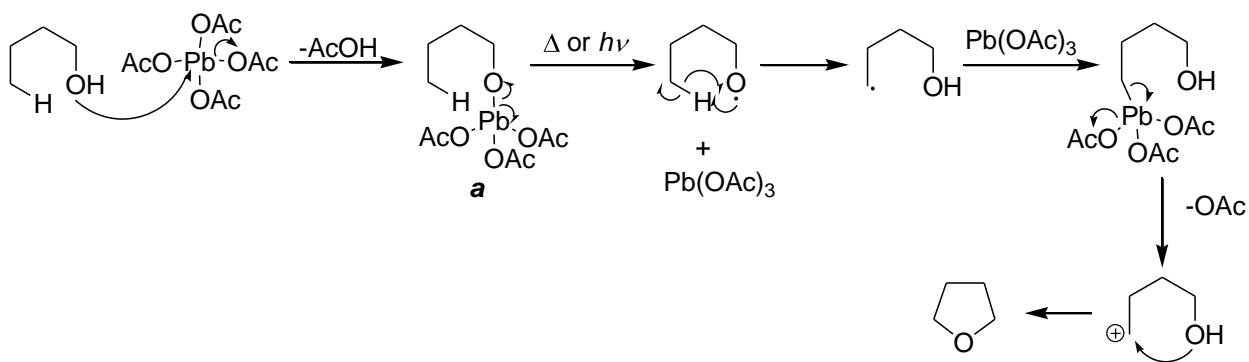
The alcohols having  $\delta$  hydrogen undergoes cyclization in presence of LTA *via* a radical pathway to give tetrahydrofuran along with low yield of tetrahydropyrans (Scheme 9).



Scheme 9

#### Mechanism

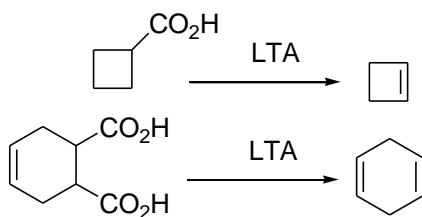
Reaction of the alcohols with LTA may give the intermediate **a**, which can undergo thermal or photochemical homolytic cleavage to give alkoxy radical **b**. The intermediate **b** may then lead to the formation **c** *via* abstract of  $\delta$  hydrogen abstraction, which may react with  $Pb(OAc)_3$  to give **d**. The  $Pb(III)$ -alkyl compound then undergoes heterolytic cleavage of C-Pb bond to generate alkyl carbocation that forms the cyclic ether by reaction with hydroxy group (Scheme 10).



Scheme 10

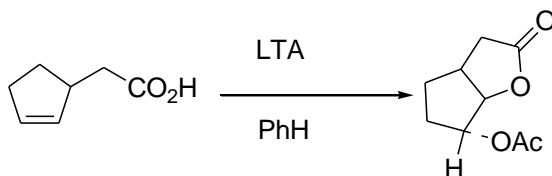
### 1.6.2.4 Reactions of Carboxylic Acids

Generally, the carboxylic acids with LTA undergo decarboxylation to give products such as esters, alkenes (Scheme 11).



Scheme 11

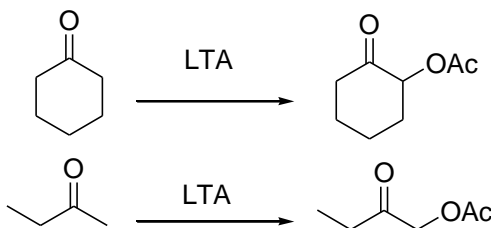
However, when a double bond is located nearby, lactone is obtained (Scheme 12).



Scheme 12

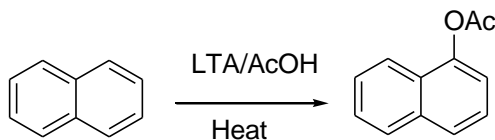
### 1.6.2.4 Acetoxylation

Ketones undergo reaction with LTA to give acetylated products at  $\alpha$ -position (Scheme 13). The yield can be improved with catalytic amount of  $\text{BF}_3$ .



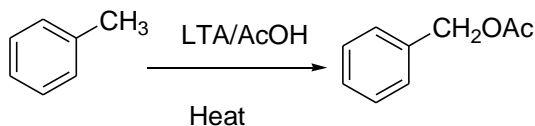
Scheme 13

Benzene derivatives having electron donating substituents could be acetylated on the thermal conditions (Scheme 14)



Scheme 14

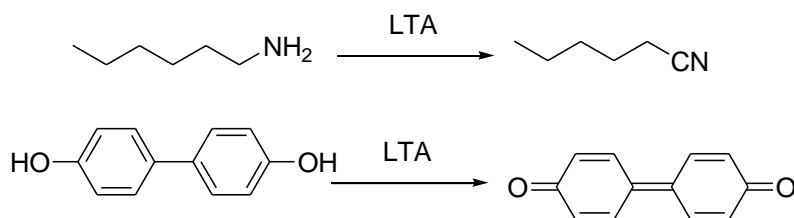
In case of alkyl benzene, the acetylation takes place at the benzylic C-H bond (Scheme 15).



Scheme 15

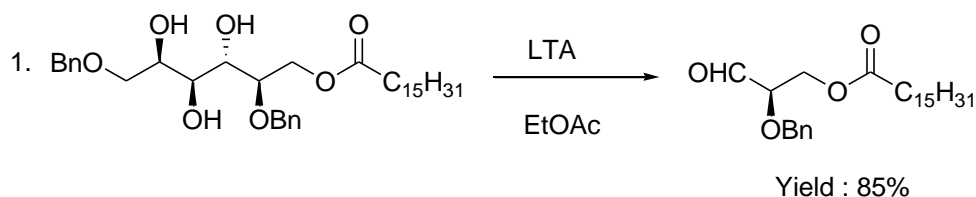
### 1.6.2.4 Dehydrogenation

Aliphatic amines readily undergo reaction with LTA to give nitriles, while the reactions of N,N'-disubstituted hydrazines afford azo compounds (Scheme 16). These reaction conditions are effective for the oxidation of 4,4'-dihydroxybiphenyl to afford diphenoquinone.

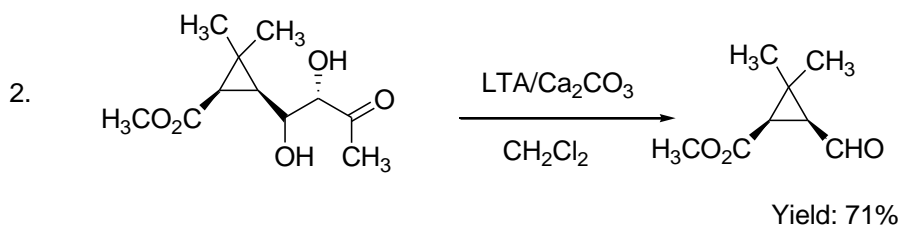


Scheme 16

### Examples



J. Xia, Y.-Z. Hui, *Tetrahedron: Asymmetry*, **1997**, 8, 451.



M. G. Banwell, G. S. Forman, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2565.

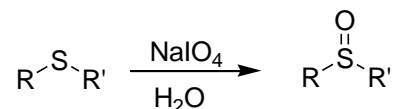
### 1.6.3 Sodium Periodate

#### 1.6.3.1 Introduction

Sodium periodate ( $\text{NaIO}_4$ ) is a sodium salt of periodic acid ( $\text{HIO}_4$ ). It is soluble in water and converts to sodium iodate ( $\text{NaIO}_3$ ) on heating.  $\text{NaIO}_4$  acts as oxidizing agent and mostly is used as a co-oxidant in oxidation reactions.

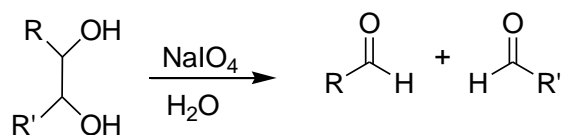
#### 1.6.3.2 Oxidation of Sulfide to Sulfoxide

Sodium periodate can oxidize sulfide to sulfoxide by treating sulfide with aqueous solution of  $\text{NaIO}_4$  at 0 °C.

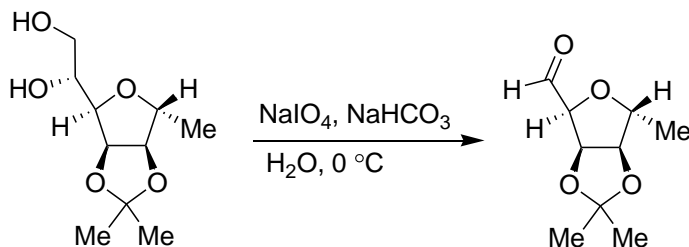


#### 1.6.3.3 Cleavage of Glycol

The  $\text{NaIO}_4$  can cleave 1,2-diol to give carbonyl compounds (Scheme 17). The LTA can also cleave 1,2-diol but LTA is soluble in organic solvents and sparingly soluble in water, in contrast,  $\text{NaIO}_4$  is soluble in water therefore the  $\text{NaIO}_4$  is used for those compounds, which are soluble in water i.e. most of the sugar molecules (Scheme 18).



Scheme 17

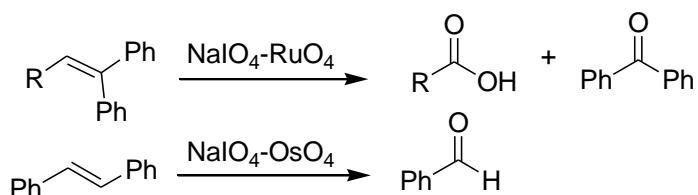


Scheme 18

$\text{NaIO}_4$  forms a cyclic intermediate with 1,2-diol that undergoes cleavage to give the carbonyl compounds.

### 1.6.3.4 Sodium Periodate as a Co-oxidant

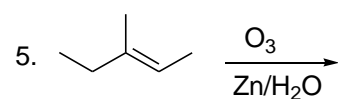
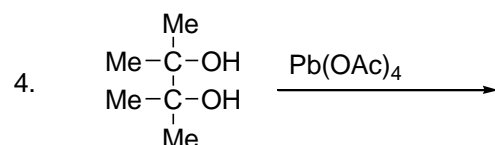
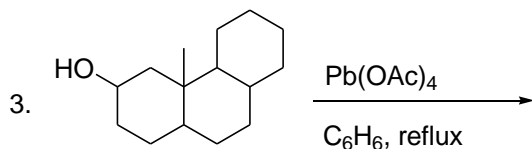
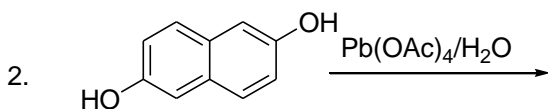
The  $\text{NaIO}_4$  is mostly used as a co-oxidant for a variety of metal catalyzed oxidation processes. It oxidizes the reduced metal to its active oxidation state therefore it reduces the use of stoichiometric amount of metal salt or complex (Scheme 19)



Scheme 19

### Problems:

Write the major products of the following reactions.





### **Text Book**

J. Clayden, N. Creeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 2001.

## **Lecture 8**

### **1.7 Molecular Oxygen**

#### **1.7.1 Introduction**

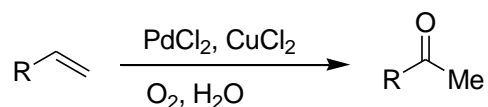
Oxygen is the most abundant element of Earth's crust. It is tasteless, odorless and very pale blue diatomic gas. Oxygen is important for oxidation reactions though molecular oxygen itself is not a good oxidizing agent. Advantage of using molecular oxygen is that it is abundant in nature and eco-friendly giving water as by product. A large number of catalysts have been used to activate oxygen for the oxidation of different functional groups. This lecture will discuss some of the important catalysts and methods.

#### **1.7.2 Palladium Catalyzed Reactions**

##### **1.7.2.1 Wacker Oxidation**

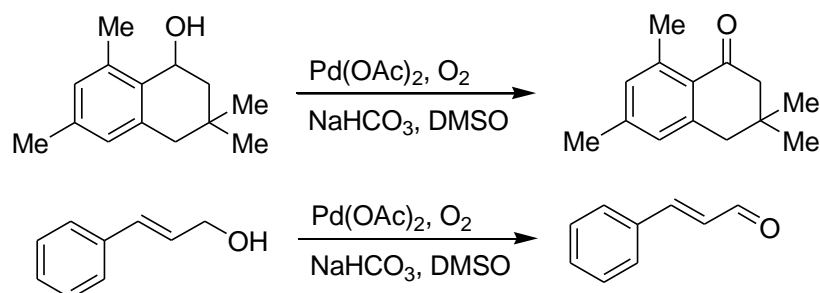
Wacker oxidation of alkenes to aldehydes or ketones is one of the most important industrial processes. In Wacker process, Pd catalyst is used in combination with O<sub>2</sub> and copper salt to transform alkenes to aldehydes or

ketones (Scheme 1). In these reactions, copper(II) oxidizes the reduced Pd(0) to palladium (II) to regenerate the catalyst, while the reduced copper(I) is reoxidized to copper(II) by oxygen. The oxygen incorporated in the alkene to give the carbonyl compound is obtained from water.

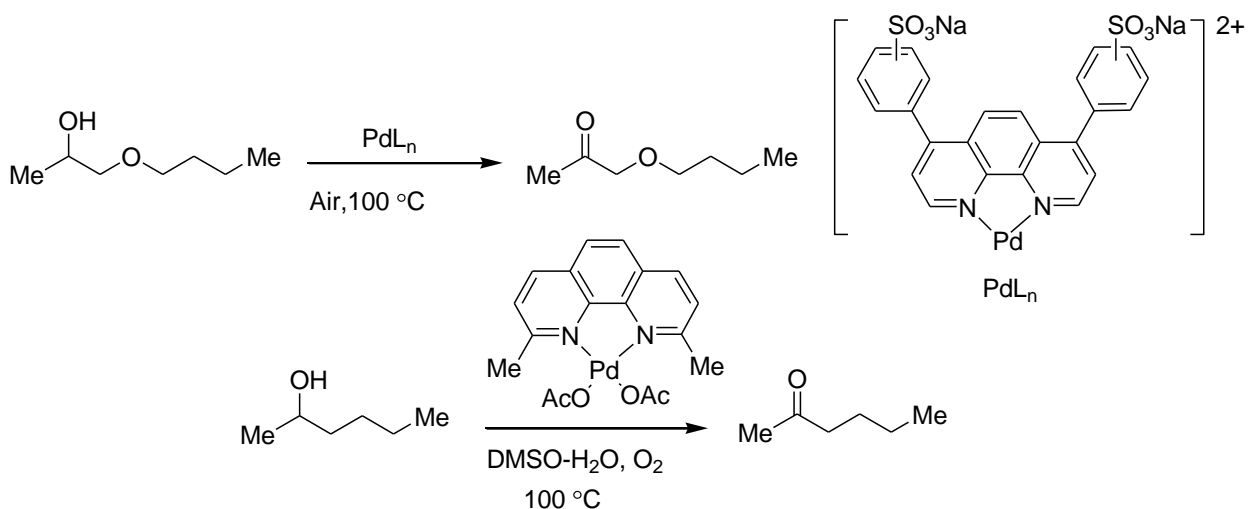


### 1.7.2.2 Oxidation of Alcohols

Palladium based catalysts have been extensively studied for the aerobic oxidation of alcohols to carbonyl compounds. For some examples, Pd(OAc)<sub>2</sub> with molecular oxygen in the presence of NaHCO<sub>3</sub> has been shown as effective protocol for the oxidation of allylic and benzylic alcohols to afford the corresponding carbonyl compounds (Scheme 2).



Scheme 2

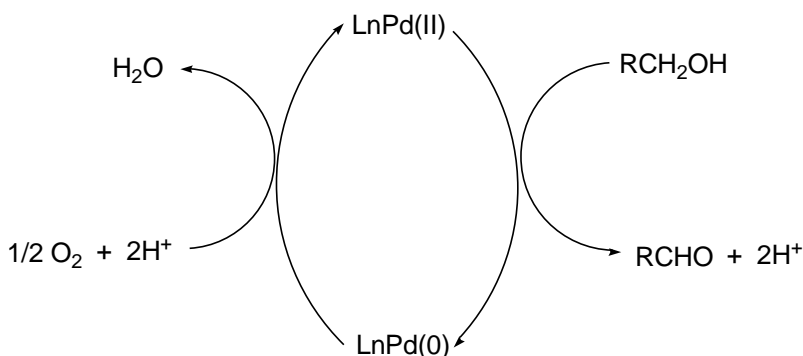


Scheme 3

Palladium complexes containing electron rich ligands such as phenanthroline have been found to catalyze the aerobic oxidation of secondary alcohols to give ketones (Scheme 3).

### Mechanism

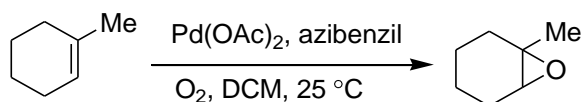
The palladium catalyzed oxidation of alcohols to carbonyl compounds with molecular oxygen can be explained as shown in Scheme 4. The palladium complex acts as an active catalyst and oxidizes the alcohols to carbonyl compounds. The reduced Pd(0) is reoxidized to Pd(II) by molecular oxygen to complete the catalytic cycle.



## Scheme 4

**1.7.2.3 Epoxidation**

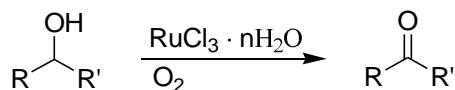
$\text{Pd}(\text{OAc})_2$  in combination with azibenzil has been reported for the epoxidation of alkenes in the presence of molecular oxygen. The aliphatic alkenes undergo epoxidation with moderate to good yield, while aromatic alkenes undergo C-C cleavage (Scheme 5).



Scheme 5

**1.7.3 Ruthenium Catalyzed Reactions****1.7.3.1 Oxidation of Alcohols**

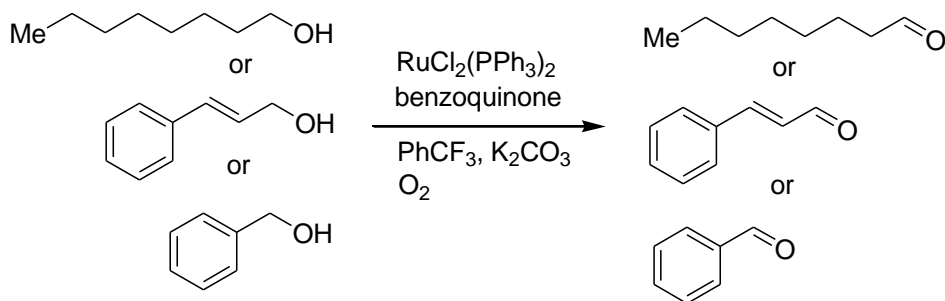
Ruthenium catalyzed aerobic oxidation of alcohol has been extensively studied.  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$  has been used for the oxidation of secondary alcohols to give ketones in the presence of oxygen (Scheme 6).



Scheme 6

Catalytic amount of  $\text{RuCl}_2(\text{PPh}_3)_2$  in combination with benzoquinone has been shown as an effective system for the oxidation of aliphatic, allylic and benzylic

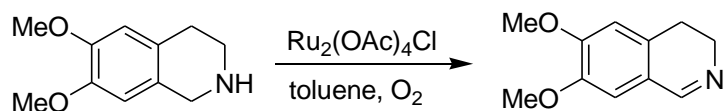
alcohols to provide aldehydes or ketones in the presence of molecular oxygen (Scheme 7).



Scheme 7

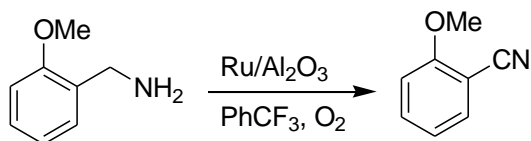
### 1.7.3.2 Oxidation of Amines

Binuclear ruthenium catalyst has been used for the oxidation of secondary amines to provide imines in presence of molecular oxygen (Scheme 8).



Scheme 8

Ruthenium supported on alumina has been used for the oxidation of primary amines to give nitriles with molecular oxygen (Scheme 9).



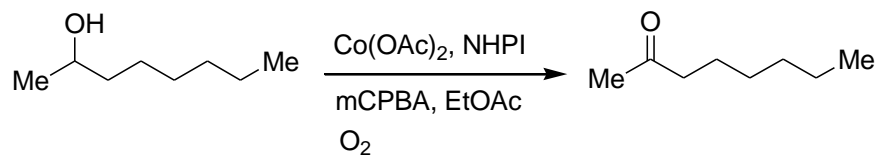
Scheme 9

## 1.7.4 Cobalt Catalyzed Reactions

### 1.7.4.1 Oxidation of Alcohols

Cobalt catalyst along with *N*-hydroxyphthalimide (NHPI) can oxidize alcohols to give carbonyl compounds in the presence of molecular oxygen. The reaction can

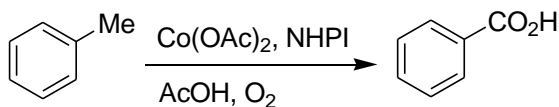
be performed at ambient conditions in the presence of catalytic amount of *m*-CPBA as an additive (Scheme 10).



Scheme 10

#### 1.7.4.2 C-H Oxidation Alkanes

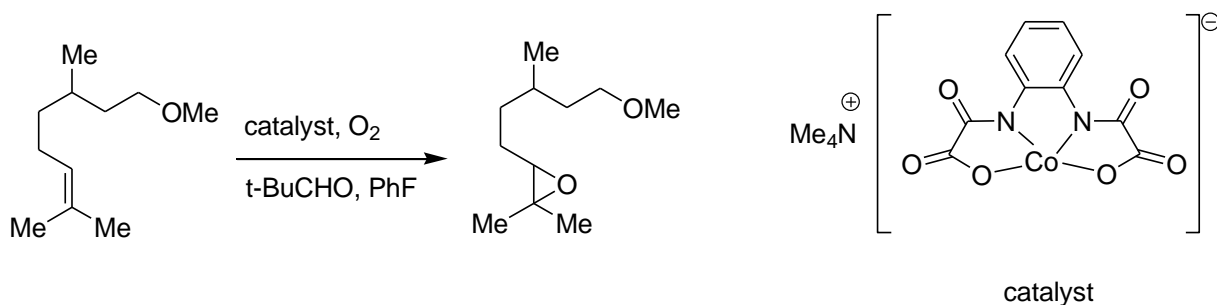
The oxidation of toluene is one of the important industrial processes. The toluene moieties could be oxidized to benzoic acid derivatives using cobalt catalyst in combination with NHPI in the presence of molecular oxygen (Scheme 11).



Scheme 11

#### 1.7.4.3 Epoxidation of Alkenes

Cobalt catalysts have been reported for the epoxidation of alkenes with molecular oxygen as a terminal oxidant. For example, Co(III) complex has been investigated for the epoxidation of alkenes in presence of pivalaldehyde and molecular oxygen (Scheme 12). In these reactions, the cobalt complex catalyzes the oxidation of the aldehyde to peracid with molecular oxygen and the peracid transfer the oxygen to alkenes.

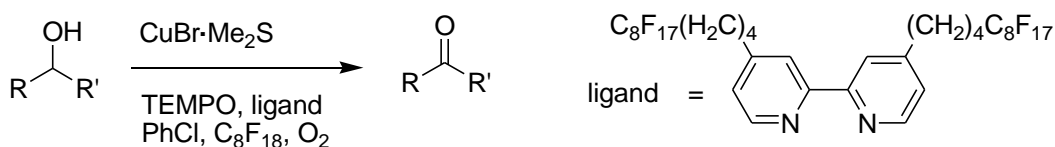


Scheme 12

## 1.7.5 Copper Catalyzed Reactions

### 1.7.5.1 Oxidation of Alcohols

Copper(I) complexes have been extensively explored for the oxidation of alcohols to aldehydes and ketones in the presence of molecular oxygen. Several studies have focused as functional model of galactose oxidase for the oxidation of primary alcohols to aldehydes. For example, copper(I)-complex with (2,2,6,6-tetramethylpiperidin-1yl)-oxyl (TEMPO) has been successfully found to catalyze the oxidation of primary and secondary alcohols to give aldehydes and ketones in fluorous biphasic system (Scheme 13). The fluorous phase having the catalyst can be recycled without loss of activity.



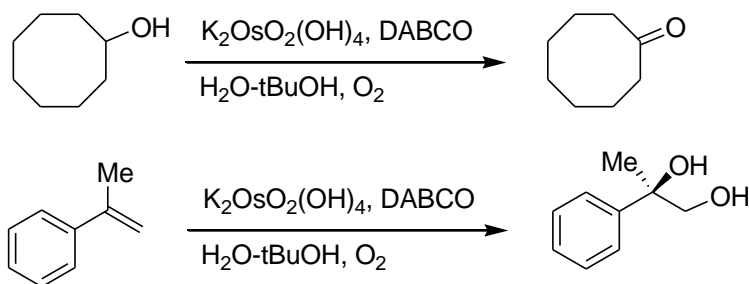
Scheme 13

## 1.7.6 Reactions with Other Catalysts

### 1.7.6.1 Osmium Catalyzed Reactions

The osmium-catalyzed oxidation of alcohols and dihydroxylation of alkenes has been explored with molecular oxygen as terminal oxidant. For example,

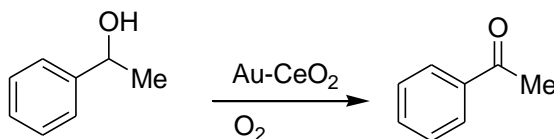
$\text{K}_2\text{OsO}_2(\text{HO})_4$  in combination with DABCO has been found to catalyze the oxidation of cyclooctanol to cyclooctanone in the presence of molecular oxygen (Scheme 14). This reaction condition has been demonstrated as effective system for the dihydroxylation of  $\alpha$ -styrene to afford the corresponding 1,2-diol in high yield.



Scheme 14

### 1.7.6.2 Gold Catalyzed Oxidation of Alcohols

Gold nanoparticles deposited on  $\text{CeO}_2$  nano crystals have been used as recyclable catalyst for the oxidation of alcohols to aldehydes and ketones in the presence of molecular oxygen (Scheme 15).

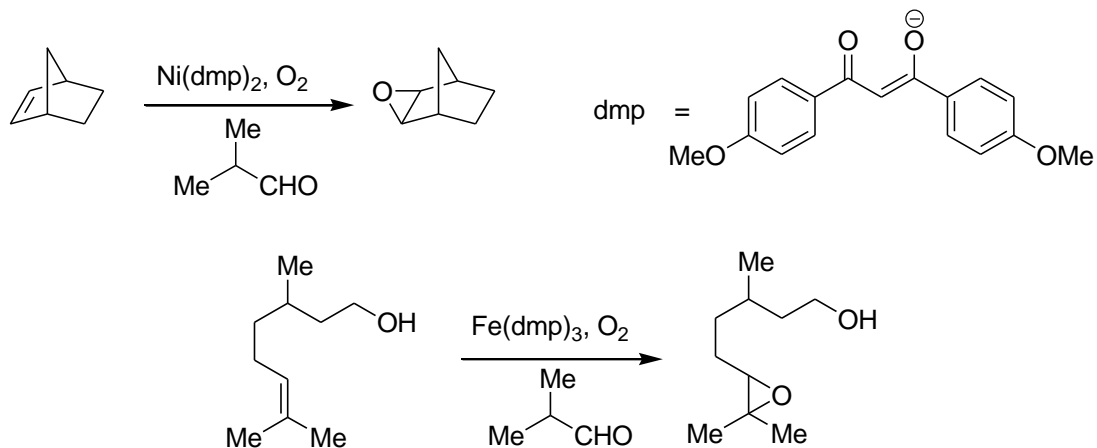


Scheme 15

### 1.7.6.3 Nickel and Iron Catalyzed Epoxidation

Nickel and iron based catalysts have been used for the epoxidation of alkenes using molecular oxygen as terminal oxidant in the presence of aliphatic aldehyde as a reducing agent. For example,  $\text{Ni}(\text{dmp})_2$  and  $\text{Fe}(\text{dmp})_3$  complexes have been shown to catalyze the epoxidation of substituted alkenes in the presence of *t*-butanal and molecular oxygen (Scheme 16). The aldehyde is oxidized *in situ* to peracid that transfers oxygen atom to alkenes to give the epoxides.



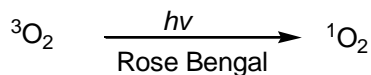


Scheme 17

## 1.7.7 Photooxidation

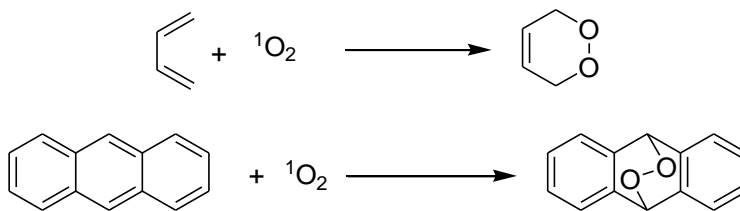
### 1.7.7.1 Excitation

The ground state triplet dioxygen ( $^3\text{O}_2$ ) could be excited to give singlet state dioxygen ( $^1\text{O}_2$ ) by photolytic energy transfer.



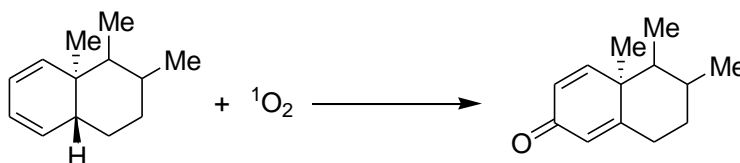
### 1.7.7.2 Cycloaddition

The excited singlet oxygen can undergo [4+2]-cycloaddition reaction with 1,3-diene to give cyclic peroxides (Scheme 18).



Scheme 18

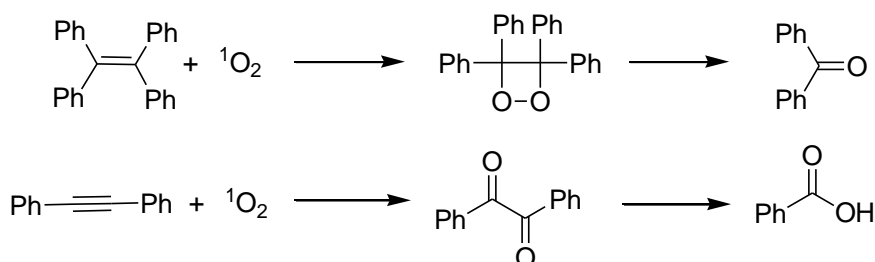
Cholestadiene does not give the similar expected peroxide but gives cholestidienone as the product (Scheme 19).



Scheme 19

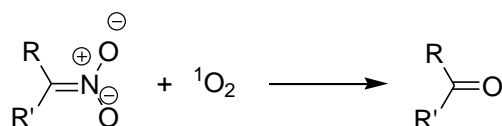
### 1.7.7.3 Oxidation of C-C Multiple Bonds

C-C multiple bonds could be oxidized by the singlet oxygen to give the corresponding carbonyl compounds or carboxylic acids depending on the nature of the compounds (Scheme 20).



Scheme 20

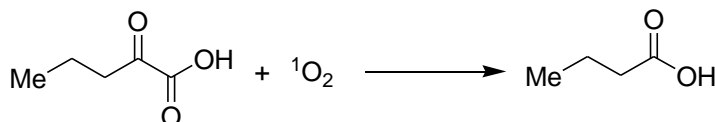
C-N double bond of nitronate can be oxidized to the corresponding carbonyl compound (Scheme 21).



Scheme 21

### 1.7.7.4 Oxidative Decarboxylation

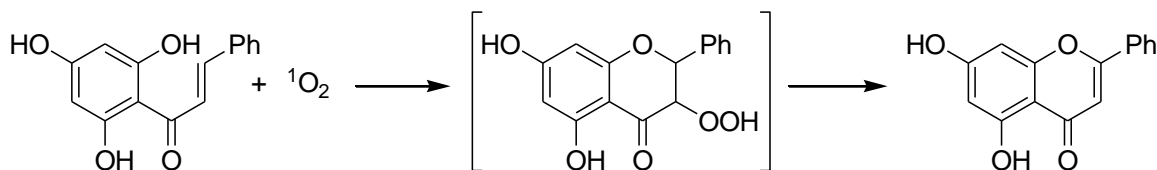
The carboxylic acids having  $\alpha$ -carbonyl groups can undergo oxidative decarboxylation to give carboxylic acid (Scheme 22).



Scheme 22

### 1.7.7.5 Oxidative Cyclization

Oxidative cyclization of chalcone with singlet oxygen gives flavanol (Scheme 23).



Scheme 23

#### Problems:

A. What major products would expect in the following reactions?

- 
- 
- 
- 
- 

B. Provide suitable mechanisms for the reactions mentioned in A.

#### Reference

T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, 105, 2329.

## Lecture 9

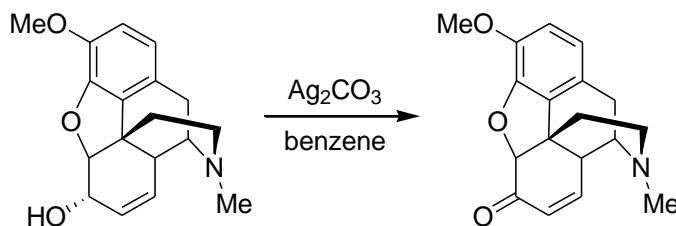
### 1.8 Other Metal Oxidants (Ag, Ru, Pd, etc.)

#### 1.8.1 Silver (Ag)

Silver in its metallic state is a grey shining soft metal and has a atomic number of 47. The stable oxidation state is +1.

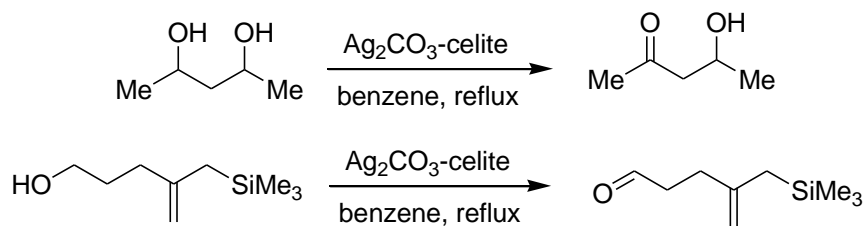
##### 1.8.1.1 Oxidation of Alcohols

Silver based catalysts are considerably investigated for the oxidation of alcohols to carbonyl compounds. For example, silver carbonate ( $\text{Ag}_2\text{CO}_3$ ) has been used for the oxidation of primary and secondary alcohols to give aldehydes and ketones, respectively (Scheme 1).



Scheme 1

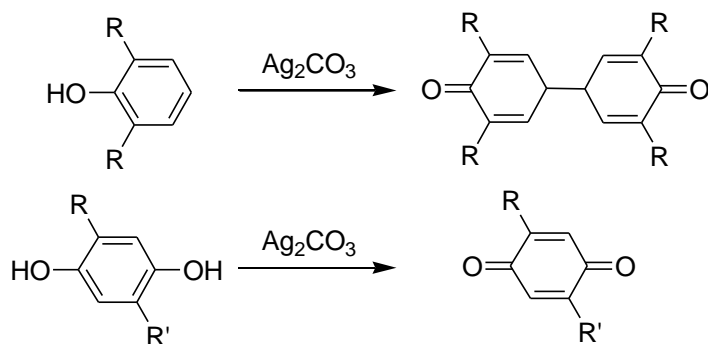
$\text{Ag}_2\text{CO}_3$  supported on celite is known as Fetizon's reagent. This reagent oxidizes alcohols selectively under mild reaction conditions (Scheme 2). The reaction is performed under apolar solvents such as benzene, heptane but the polar solvents hinder the oxidation.



Scheme 2

### 1.8.1.2 Oxidation of Phenols

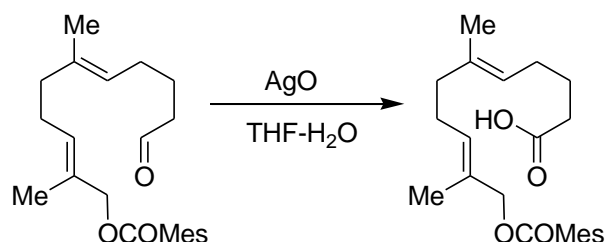
Phenols could be oxidized to a variety of products depending on the nature of substituent present in the aromatic ring. For example, 2,6-disubstituted phenols when treated with  $\text{Ag}_2\text{CO}_3$  undergoes dimerization to provide diphenoquinones, while substituted 1,4-catecols are oxidized to give substituted benzoquinones (Scheme 3).



Scheme 3

### 1.8.1.3 Oxidation of Aldehydes to Carboxylic Acids

Silver oxide ( $\text{AgO}$ ) has been found to catalyze the oxidation of aldehydes to give carboxylic acids in good yield (Scheme 4).



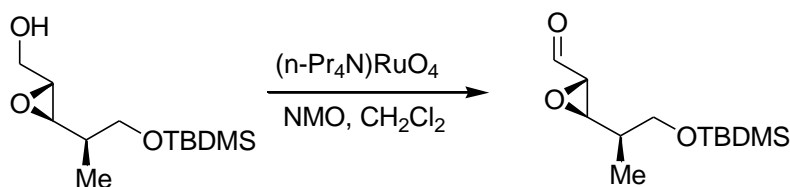
Scheme 4

## 1.8.2 Ruthenium (Ru)

Ruthenium is a rare transition metal and its atomic number is 44. It is comparatively less reactive metal. The common oxidation states of ruthenium are +2, +3 and +4. Ruthenium at +8 oxidation state is strong oxidizing agent.

### 1.8.2.1 Oxidation of Alcohols

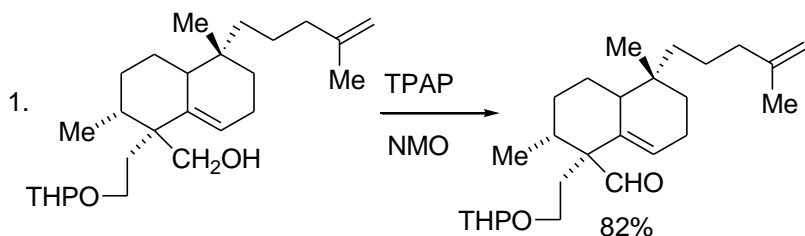
A variety of ruthenium catalysts have been used for the oxidation of alcohols to give carbonyl compounds. Among them, a quaternary ammonium salt of perruthenate ( $n\text{-Pr}_4\text{N}$ ) $\text{RuO}_4$  (TPAP) is one of the most useful catalysts (Scheme 5). Other catalysts such as  $\text{RuCl}_2(\text{PPh}_3)_3$ ,  $\text{RuCl}_3$  and  $\text{K}_2\text{RuO}_4$  are also effective for this functional group transformation.



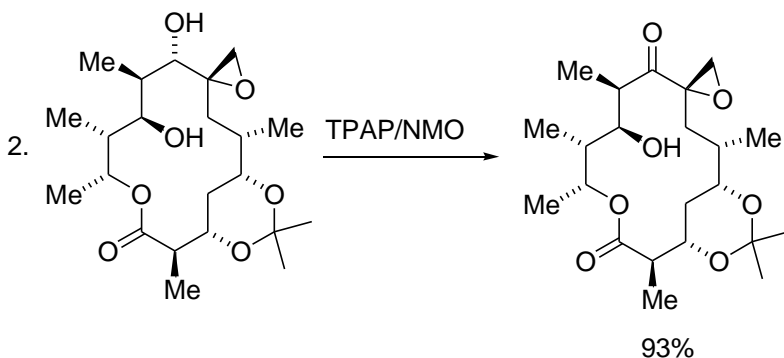
Scheme 5

S. V. Ley, J. Norman, *Encyclopedia of Reagents for Organic Synthesis*, JohnWiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 7, 4827.

#### Examples:

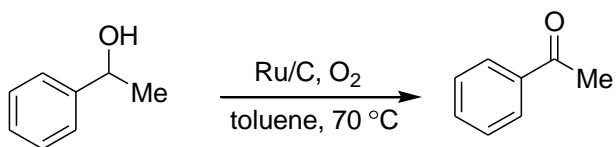


H. Miyaoka, M. Yamanishi, Y. Kajiwar, Y. Yamada, *J. Org. Chem.* **2003**, 68, 3476.

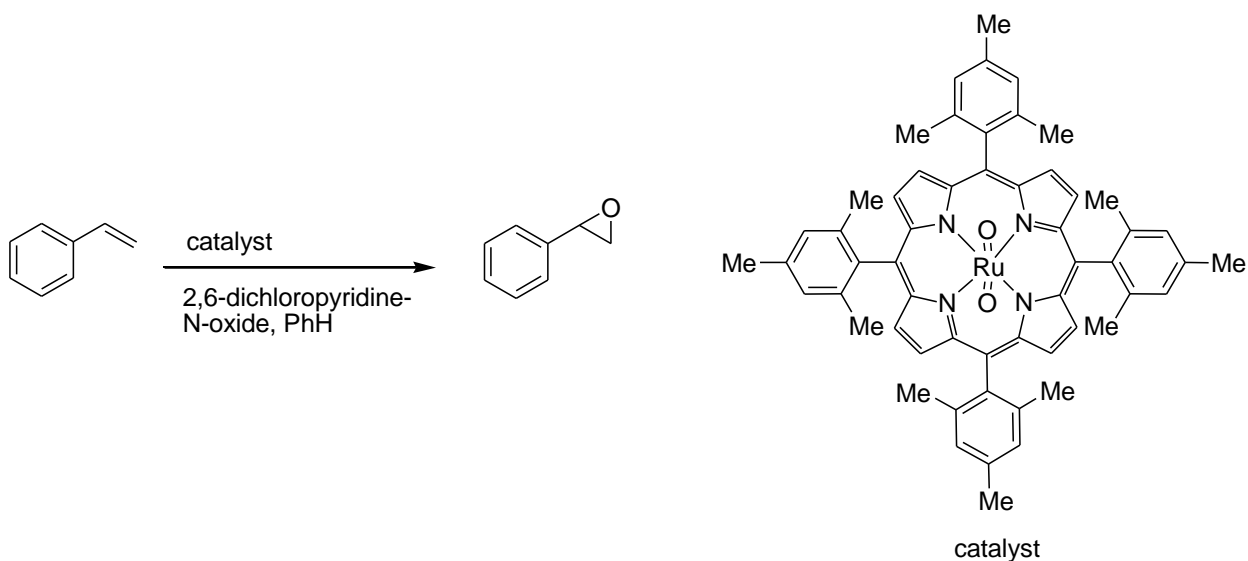


L. A. Paquette, H.-J. Kang, C. S. Ra, *J. Am. Chem. Soc.* **1992**, 114, 7387.

Ruthenium on charcoal (Ru/C) has been found to be a very efficient catalyst for the oxidation of alcohols to give carbonyl compounds in the presence of molecular oxygen (Scheme 6).



Scheme 6



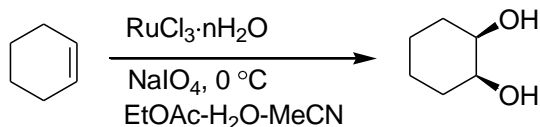
Scheme 7

### 1.8.2.2 Epoxidation

Ruthenium complexes containing porphyrin based ligands have been used for the epoxidation of alkenes. For example, ruthenium complex of tetramesitylporphyrinato (TMP) is very effective catalyst for the epoxidation of styrene in the presence of pyridine *N*-oxide as a terminal oxidant (Scheme 7).

### 1.8.2.3 Dihydroxylation

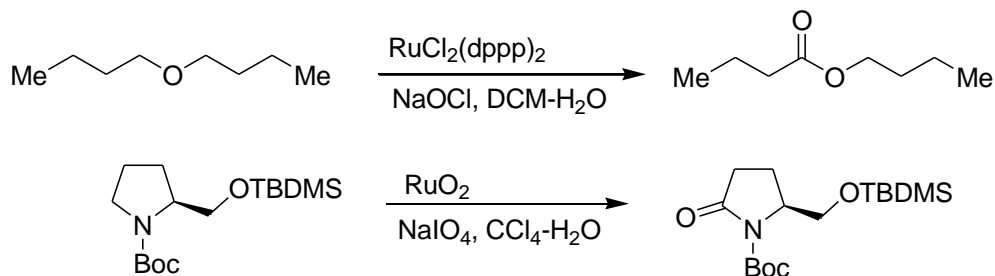
$\text{RuCl}_3$  in combination with  $\text{NaIO}_4$  can dihydroxylate the double bond efficiently to give *cis*-1,2-diols (Scheme 8). The reaction exhibits greater reactivity in a mixture of solvents.



Scheme 8

#### 1.8.2.4 $\alpha$ -Oxidation

The ethers and tertiary amines undergo carbonylation in its  $\alpha$ -carbon to give esters and amides, respectively (Scheme 9).

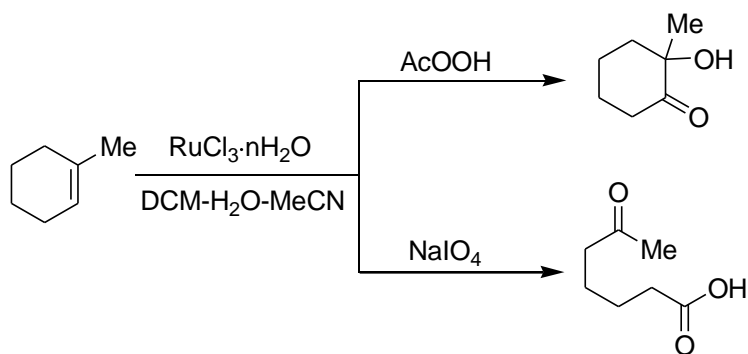


Scheme 9

#### 1.8.2.5 Synthesis of $\alpha$ -Ketols

The double bond could be oxidized to  $\alpha$ -ketol depending on the reaction conditions. Generally,





Scheme 10

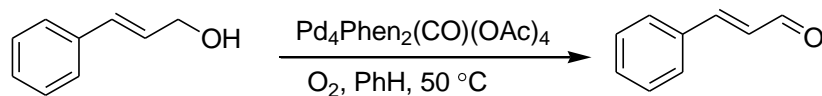
the co-oxidants play a crucial role. For examples, 1-methylcyclohexane can give 2-methyl-2-hydroxycyclohexanone and 6-oxoheptanoic acid depending on the nature of co-oxidant used (Scheme 10).

### 1.8.3 Palladium (Pd)

Palladium is the least dense metal in the platinum group and its atomic number is 46. The oxidation states of palladium are 0 and +2 and +4, among them, +4 is less common. The palladium was discovered by William Hyde Wollaston in 1803.

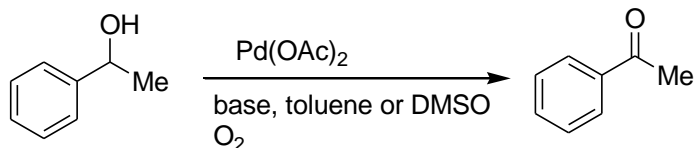
#### 1.8.3.1 Oxidation of Alcohols

Palladium based catalysts have been successfully used for the oxidation of alcohols in presence of a base under atmospheric oxygen. The reaction is selective and works without affecting other functional groups. For example,  $\text{Pd}_4$  cluster has been used for the selective oxidation of allylic alcohols to give  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 11).



Scheme 11

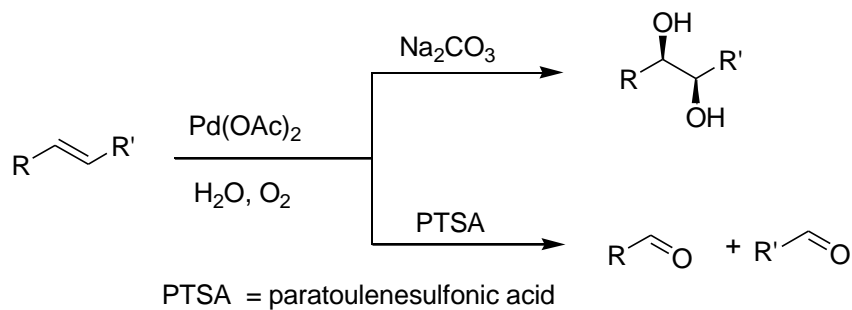
$\text{Pd}(\text{OAc})_2$  has been explored for the oxidation of benzylic and allylic alcohols to afford the corresponding aldehydes and ketones at moderate temperature (Scheme 12).



Scheme 12

### 1.8.3.2 Oxidation of Double Bonds

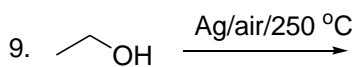
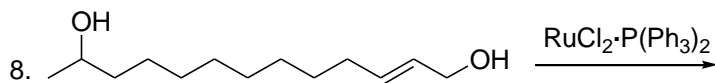
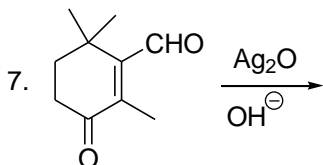
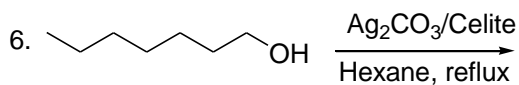
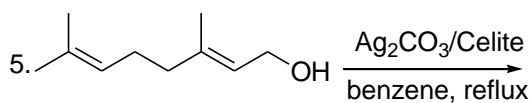
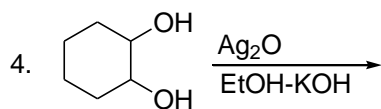
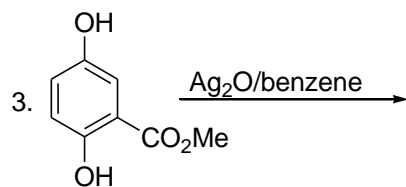
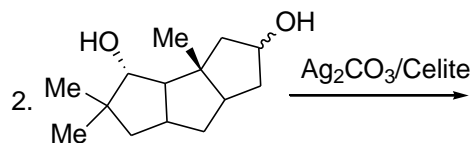
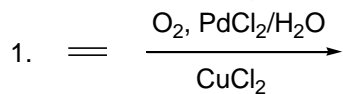
The alkenes could be oxidized selectively to give 1,2-diols or aldehydes or ketones depending on the reaction conditions.  $\text{Pd(OAc)}_2$  with molecular oxygen can oxidize alkenes to give 1,2-diols in basic conditions and aldehydes or ketones in acidic conditions (Scheme 13).



Scheme 13

**Problems**

For the reactions given below write the major products.



### **Text Books**

V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, Narosa, New Delhi, 2002.

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## **Lecture 10**

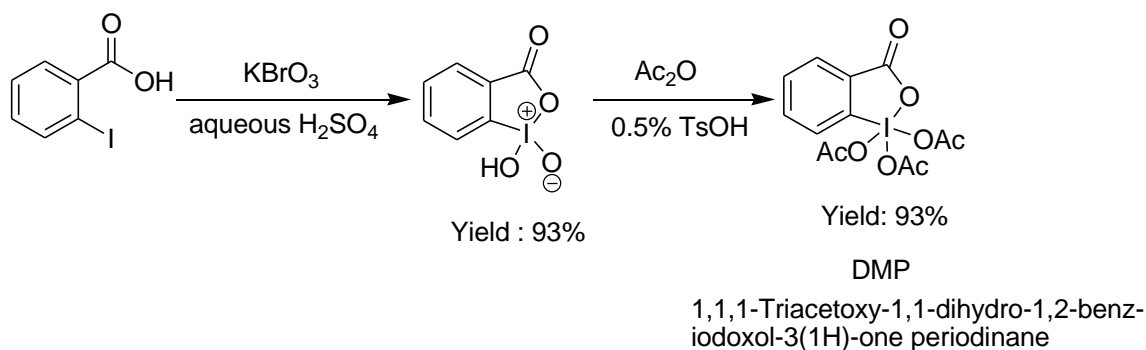
### **1.9 Other Nonmetal Oxidants (Dess-Martin, TEMPO and Dioxiranes)**

#### **1.9.1 Dess-Martin Periodinane (DMP)**

The Dess-Martin periodinane (DMP) is a hypervalent iodine compound developed by Daniel Benjamin Dess and James Cullen Martin. It is a selective oxidizing agent and works under essentially neutral conditions.

##### **1.9.1.1 Preparation**

The DMP is prepared by treating 2-iodobenzoic acid with potassium bromate and then acetylated with acetic anhydride in presence of catalytic amount of toluenesulphonic acid (Scheme 1). This reagent has indefinite shelf-life in a sealed container, however, hydrolysis occurs upon exposure to moisture.

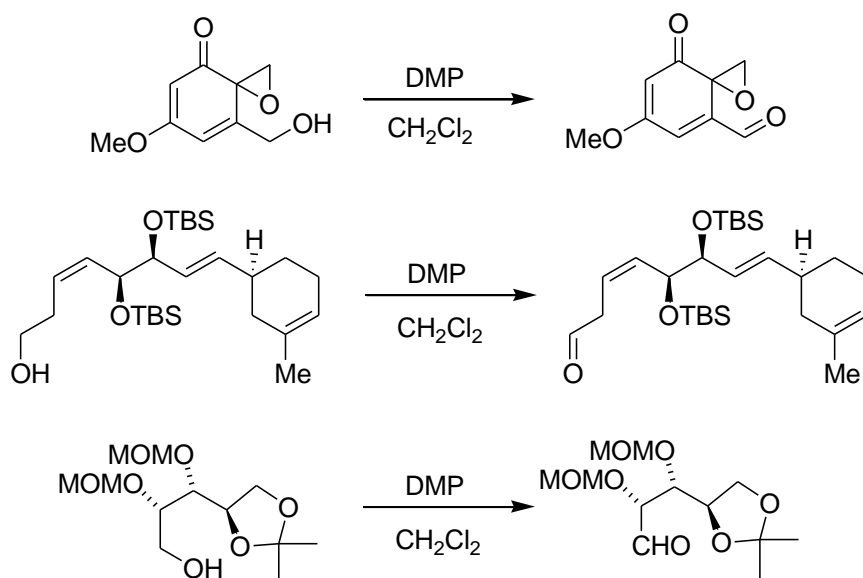


Scheme 1

R. J. Boeckman, Jr., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 7, 4982.

### 1.9.1.2 DMP Oxidation

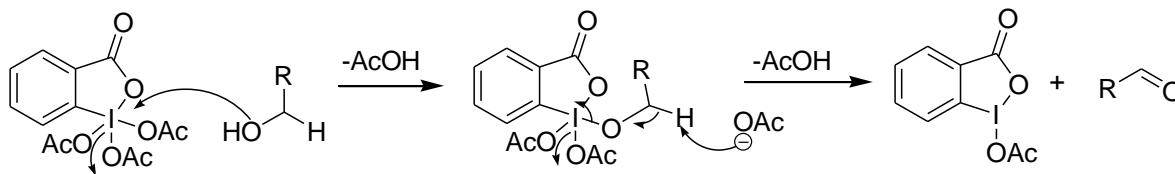
DMP oxidizes alcohols to give aldehydes and ketones under neutral or near neutral conditions. The reaction is mild and the alcohols can be selectively oxidized in presence of other sensitive functional groups at room temperature (Scheme 2). There is no over oxidation of the carbonyl compounds to carboxylic acids. Furthermore, simple product isolation makes this protocol much useful.



Scheme 2

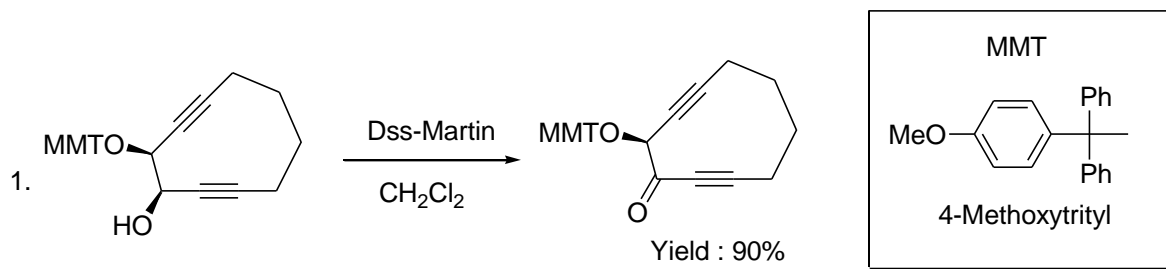
## Mechanism

The alcohol replaces labile acetate group from the iodine to give the intermediate **a** that can undergo reductive elimination by oxidizing alcohol to give the carbonyl compound (Scheme 3).

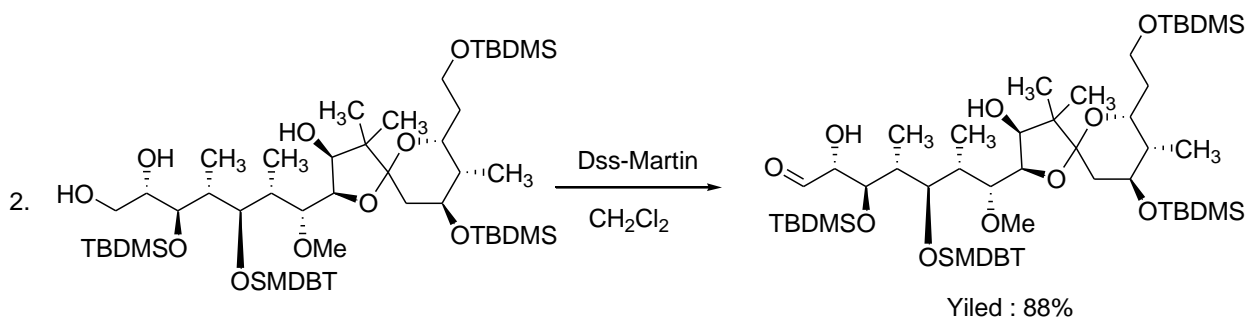


Scheme 3

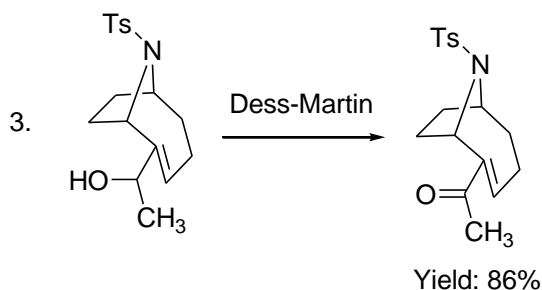
## Examples:



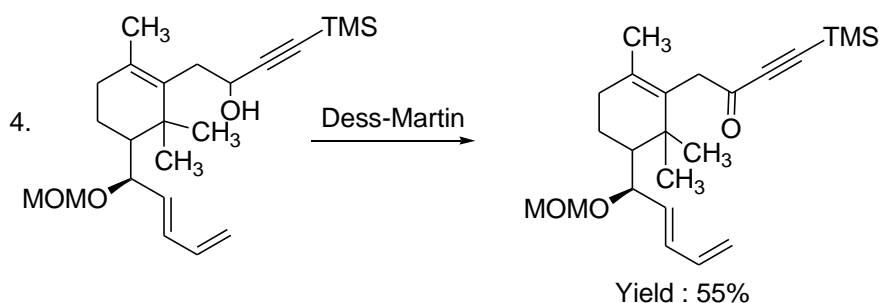
A. G. Myers, P. S. Dragovich, *J. Am. Chem. Soc.* **1992**, 114, 5859.



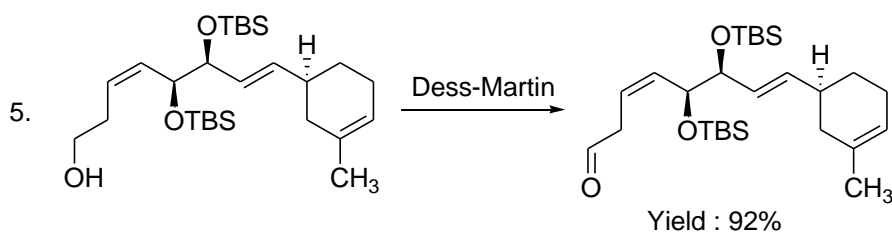
D. A. Evans, J. r. Gage, J. L. Leighton, *J. Am. Chem. Soc.* **1992**, 114, 9434.



M. Mori, T. Tomita, Y. Kita, *Tetrahedron Lett.* **2004**, 45, 4397.



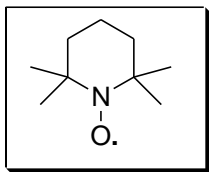
Y.-F. Lu, A. G. Fallis, *Tetrahedron Lett.* **1993**, 34, 3367.



P. A. Wender, S. G. Hegde, R. D. Hubbard, L. Zhang, *J. Am. Chem. Soc.* **2002**, 124, 4956.

### 1.9.2 2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO)

TEMPO is organic heterocyclic compound bearing a radical oxygen atom. This compound was prepared by Lebedev and Kazarnowskii in 1960 from the oxidation of 2,2,6,6-tetramethylpiperidine. In conjunction with other oxidizing agents, this reagent provides mild conditions for oxidations.

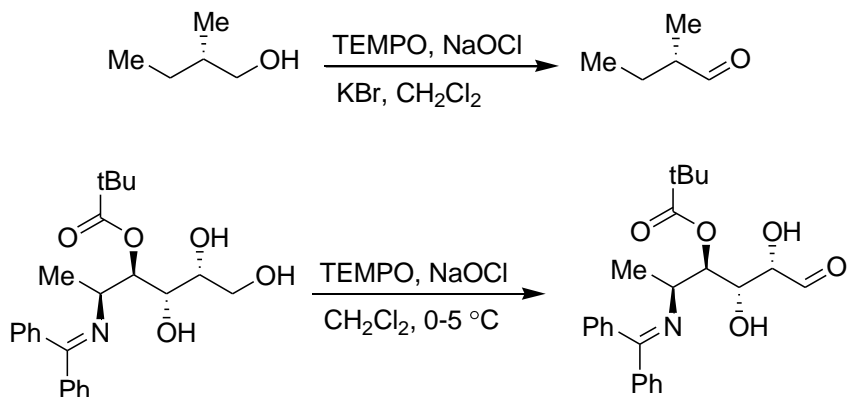


TEMPO

F. Montanari, S. Quici, *Encyclopedia Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 7, 4821.

### 1.9.2.1 Oxidation of Alcohols

TEMPO is a mild catalyst for the oxidation of alcohols to give carbonyl compounds (Scheme 4). NaOCl is usually used as a co-oxidant for the regeneration of the catalyst. The reactions with primary alcohols exhibit greater reactivity compared to secondary alcohols. Thus, primary alcohols could be chemoselectively oxidized in the presence of secondary alcohols.

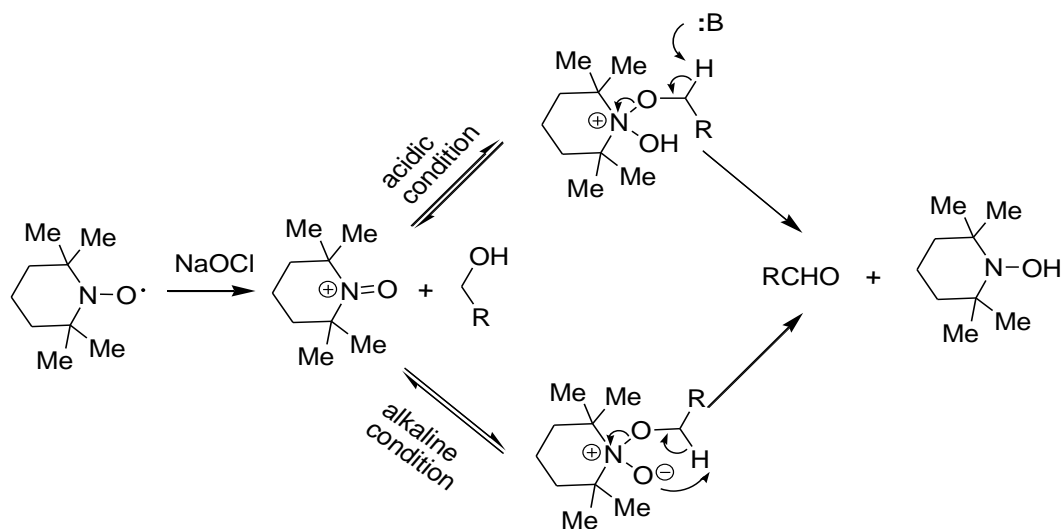


Scheme 4

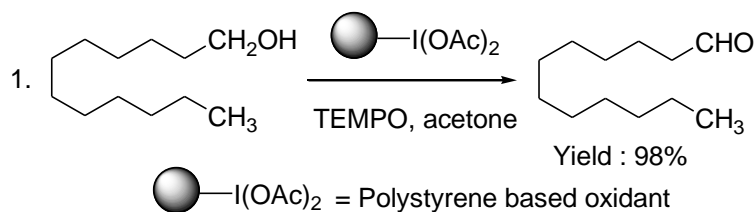
### Mechanism

The oxidation of nitroxyl radical gives the oxoammonium ion, which is the active species, in the TEMPO catalyzed reactions (Scheme 4).

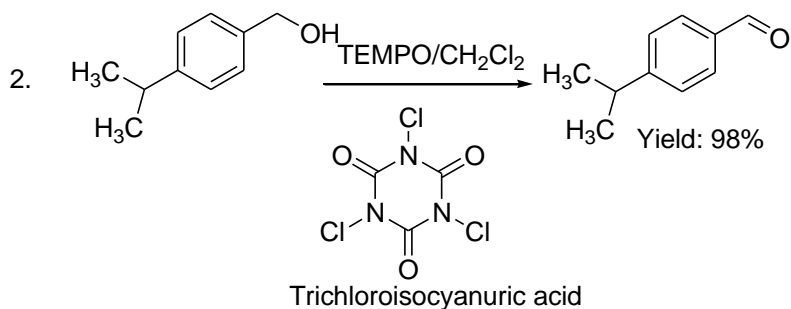




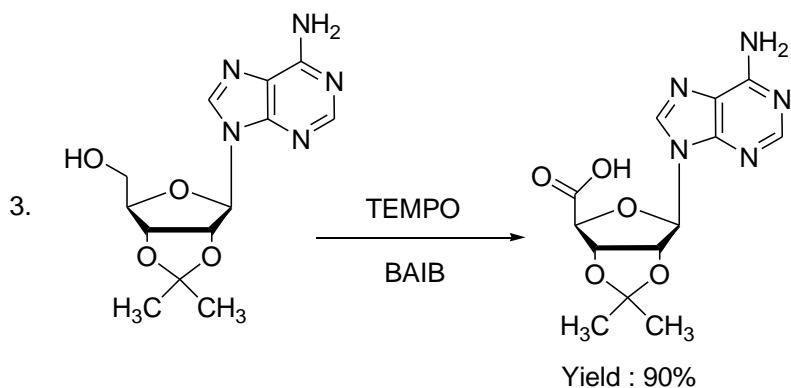
### Examples:



K. Sakuratani, H. Toga, *synthesis* **2003**, 21.



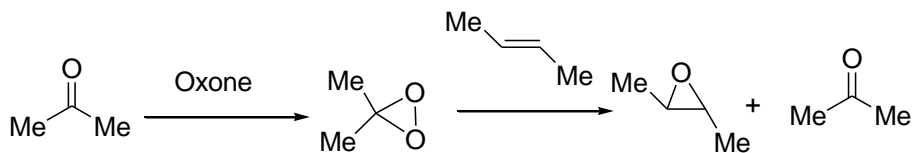
J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, 64, 293.



L. D. Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, 3, 3041.

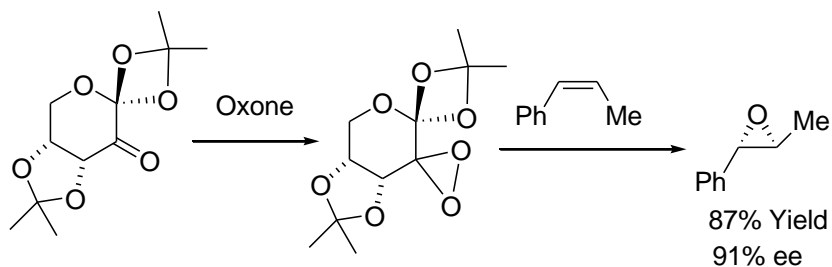
### 1.9.3 Dioxiranes

Dialkyl dioxiranes are versatile oxidizing agents that can be produced from oxone (potassium peroxymonosulfate) and ketones. Dioxiranes are extensively used for the epoxidation of alkenes (Scheme 3).



Scheme 6

If the ketones are chiral, chiral dioxiranes can be generated, which can be used as an effective chiral reagent for asymmetric epoxidation of alkenes with excellent enantioselectivity (Scheme 7).

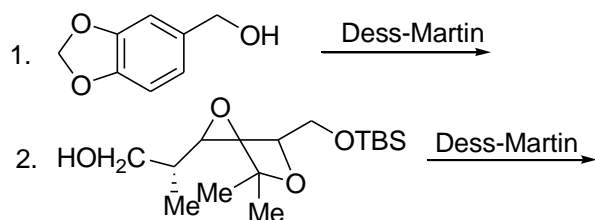


Scheme 7

J. M. Crandall, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **6**, 4265.

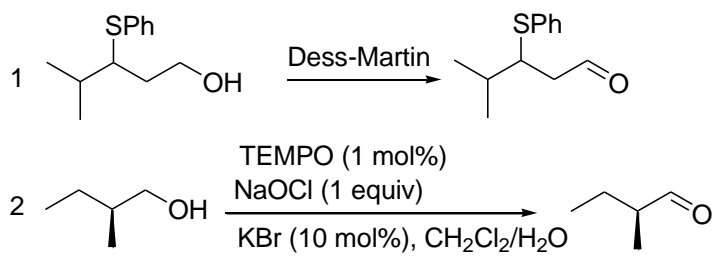
### Problems:

A. Complete the following reactions.



B. How will you prepare TEMPO?

C. Give mechanistic explanation for the following transformations.



### Text Book

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## Lecture 11

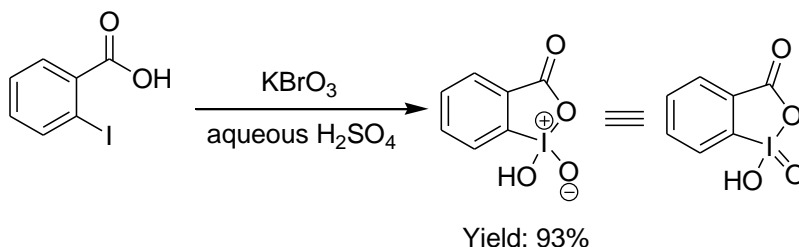
### 1.9 Other Nonmetal Oxidants (IBX and DDQ)

#### 1.9.4 2-Iodoxybenzoic acid (IBX)

2-Iodoxybenzoic acid (IBX) is an organic compound prepared by oxidation of 2-iodobenzoic acid with potassium bromate in aqueous sulfuric acid. This is used for the oxidation of alcohols to give carbonyl compounds. The only drawback is that it is insoluble in common organic solvents but soluble in highly polar solvent such as DMSO.

##### 1.9.4.1 Preparation

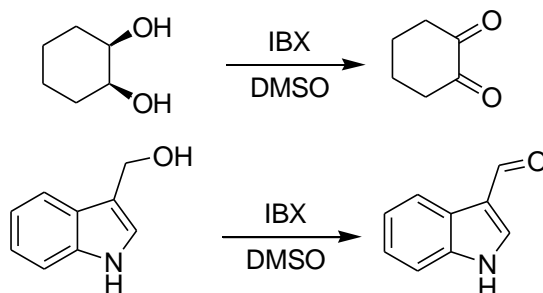
The oxidation of 2-iodobenzoic acid in aqueous sulfuric acid with potassium bromate gives IBX (Scheme 1).



Scheme 1

##### 1.9.4.2 Oxidation of Alcohols

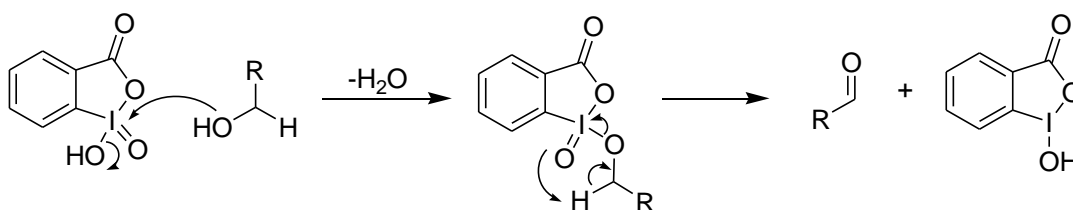
The alcohols are oxidized to aldehydes and ketones when treated with IBX (Scheme 2). The reaction occurs smoothly without affecting other functional groups.



Scheme 2

### Mechanism

The oxidation mechanism is similar to that of DMP reaction (Scheme 3).



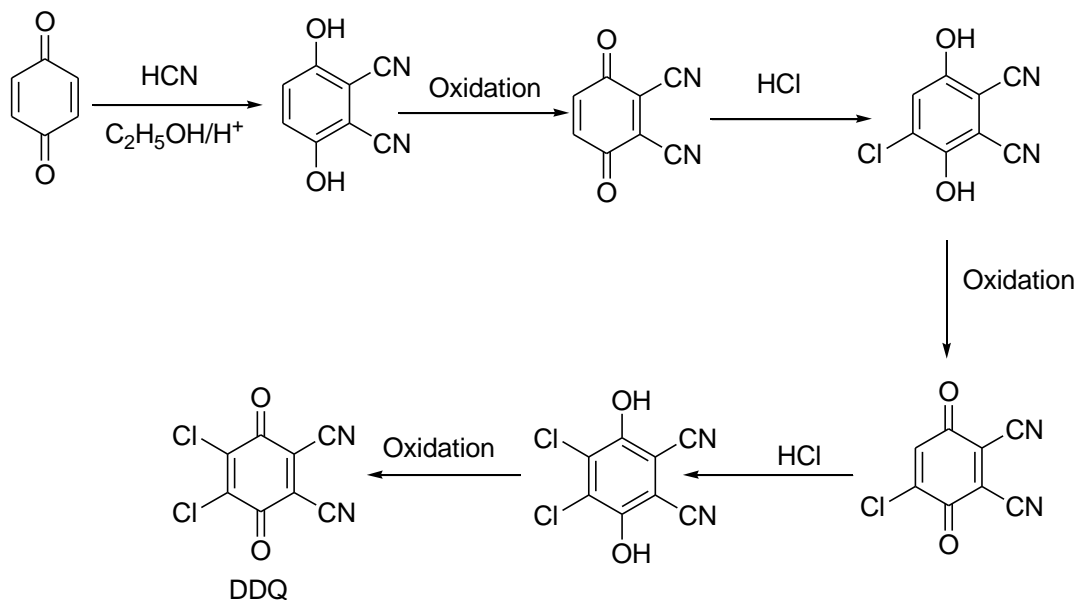
Scheme 3

### 1.9.5 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

Quinones are used for dehydrogenation reactions. Among them, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is an important reagent. DDQ is very reactive and used under anhydrous conditions because it decomposes in the presence of water. The reaction is carried out in inert solvents such as benzene, THF and dioxane. Solution of DDQ in benzene is red in colour because of the formation of charge transfer complex. After dehydrogenation, DDQ is reduced to hydroquinone that is a yellow solid and insoluble in benzene. Hence, the progress of the dehydrogenation can be monitored.

#### 1.9.5.1 Preparation

DDQ is very convenient to handle and is commercially available. It can be synthesized as described by Thiele and Ganther procedure from the reactions of benzoquinone with HCN/HCL followed by oxidation (Scheme 4).

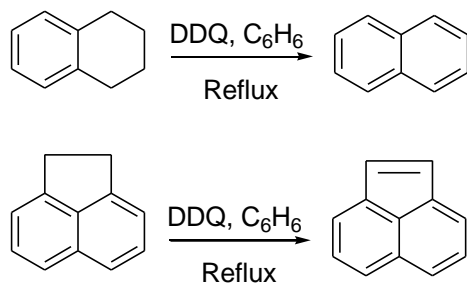


Scheme 4

D. R. Buckle, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **3**, 1699.

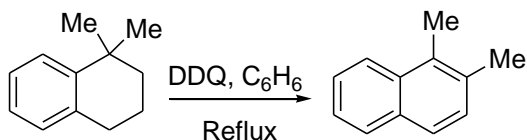
### 1.9.5.2 Aromatization

DDQ is an effective reagent for the dehydrogenation of hydroaromatic compounds to give aromatic compounds. The procedure can be applied for the synthesis heterocyclic compounds such as pyrroles, pyrazoles, indoles, furans and thiophenes. Many substituents do not interfere in the reaction. For example, using DDQ in boiling benzene tetralin and acenaphthene can be converted into naphthalene and acenaphthylene, respectively (Scheme 5).

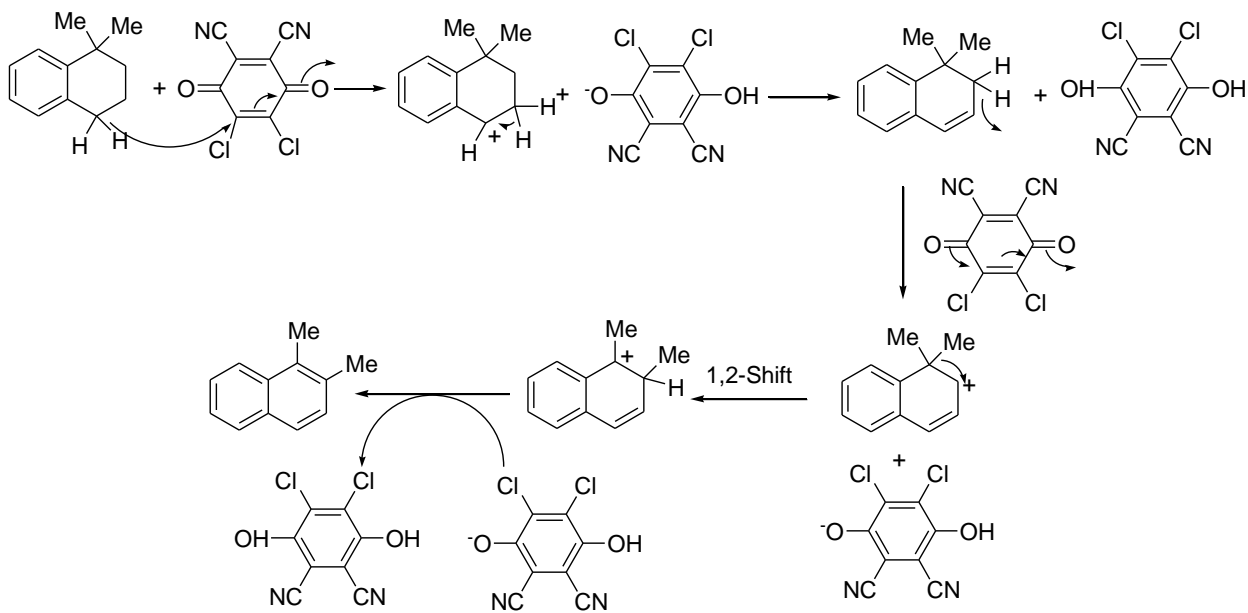


Scheme 5

In the case of hydroaromatic compound with blocking group rearrangement has been observed. For example, in 1,1-dimethyl-1,2,3,4-tetrahydronaphthalene, the aromatization takes place with 1,2-rearrangement of the methyl group (Scheme 6).

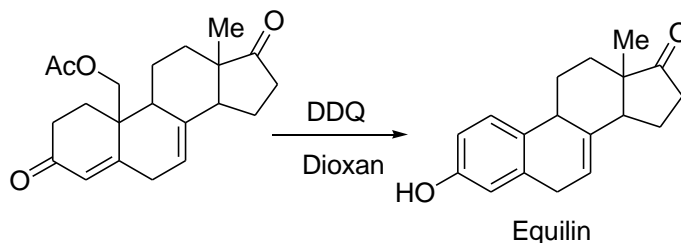


### Mechanism



Scheme 6

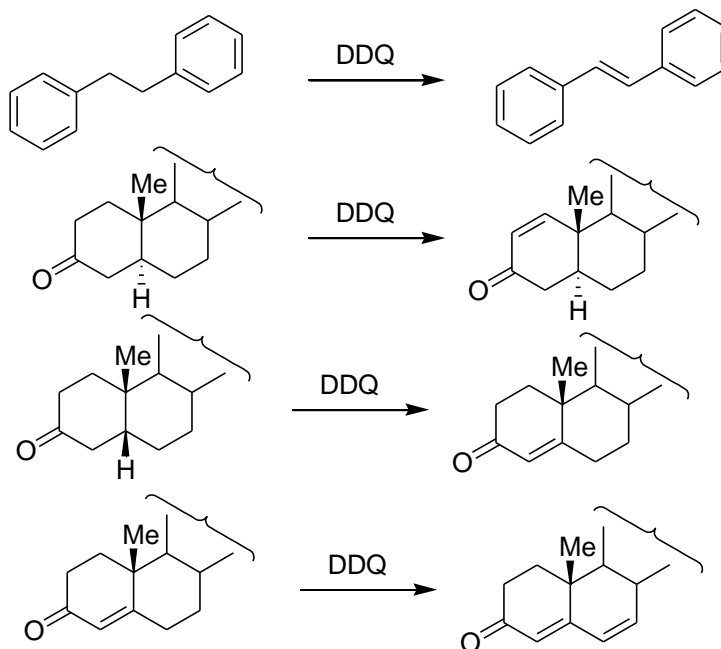
This process has been extensively used in steroid chemistry for aromatization. For example, DDQ has been used for aromatization in the synthesis of equilin (Scheme 7).



Scheme 7

### 1.9.5.3 Formation of Conjugated Double Bonds

DDQ is used for dehydrogenation of organic compound for extending conjugation (Scheme 8). For example, 1,2-diphenylethane can be converted into *trans*-stilbene in high yield. In a similar way, ketones can be transformed into  $\alpha,\beta$ -unsaturated carbonyl compounds, which have been considerably employed in steroid chemistry. The products are generally obtained in high yield and the substituents commonly encountered are not affected.

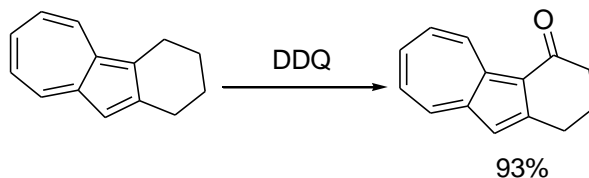


Scheme 8

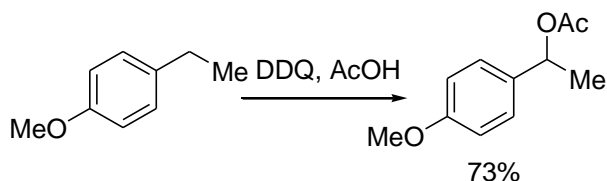


### 1.9.5.4 Allylic Oxidation

The oxidation of benzylic C-H bonds can be carried with DDQ to afford carbonyl compounds. The reactions in aqueous acetic acid proceeds *via* an intermediate benzylic acetate, which is hydrolyzed under the reaction conditions (Scheme 9). In some cases, the benzylic acetate can be isolated (Scheme 10).



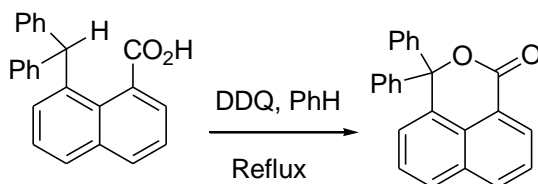
Scheme 9



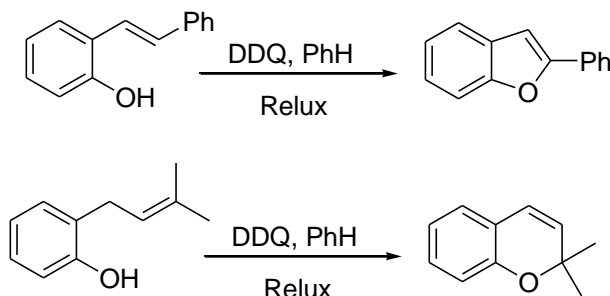
Scheme 10

### 1.9.5.5 Oxidative Cyclization

DDQ has been extensively employed for the cyclodehydrogenation reactions of phenolic and carboxylic acids. These processes afford effective route for the synthesis of oxygen heterocycles



Scheme 11

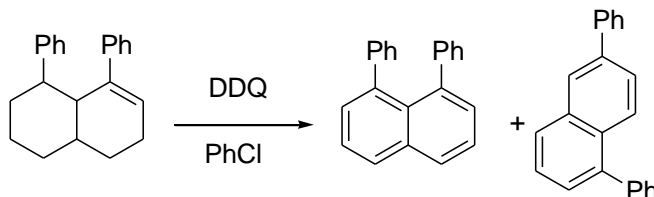


Scheme 12

such as coumarins, chromones, benzofurans and lactones. For example, 8-diphenylmethyl-1-naphthoic acid undergoes oxidative cyclization to give  $\alpha$ -lactone (Scheme 11). Likewise, DDQ can be employed for the cyclodehydrogenation of phenols (Scheme 12).

#### 1.9.5.4 Isomerization

The compounds that are difficult to dehydrogenate give a mixture of isomeric products (Scheme 13).

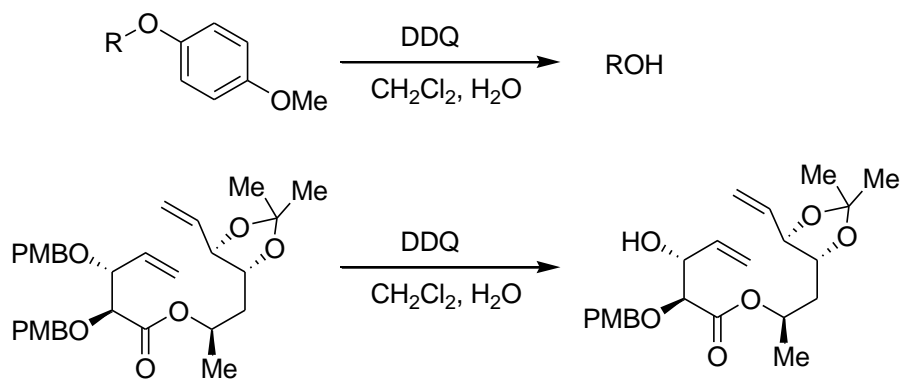


Scheme 13

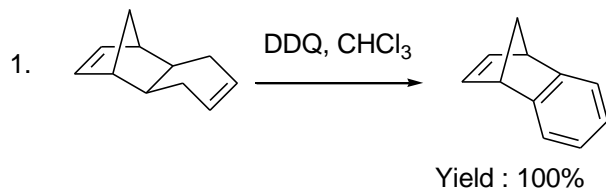
The isomeric products could be formed due to fragmentation of intermediate carbonium ion followed by ring closure and dehydrogenation.

#### 1.9.5.5 Deprotection of *p*-Methoxybenzyl Ethers

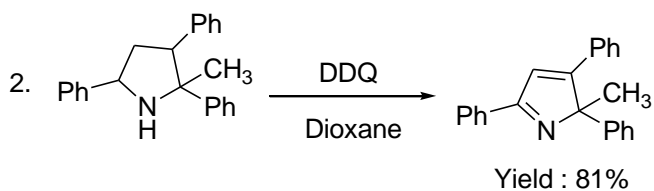
*p*-Methoxybenzyl ether could be deprotected selectively using DDQ in the presence of other protecting groups such as acetals, RO-Bn, RO-MOM, RO-MEM, RO-THP, RO-TBS, benzoyl, tosyl, acetate groups or epoxides (Scheme 14).



**Examples:**



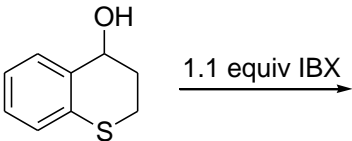
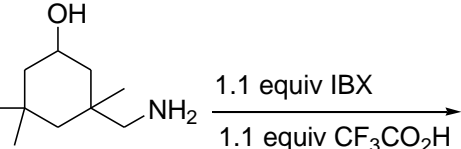
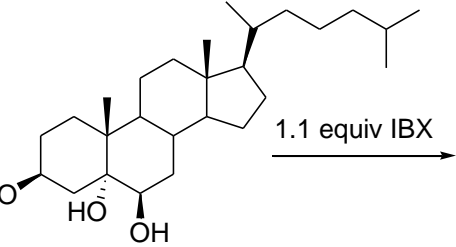
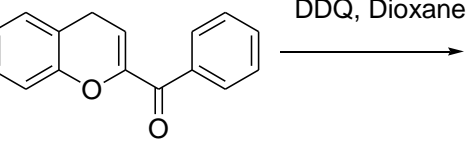
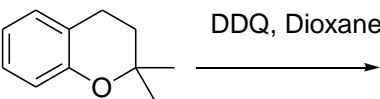
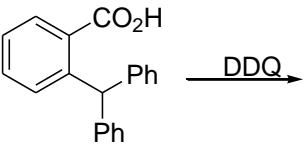
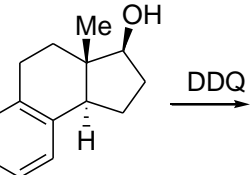
S. Cossu, O. DeLucchi, *Tetrahedron* **1996**, 52, 14247.



S. R. Cheruka, M. P. Padmanilayam, J. L. Vennerstrom, *Tetrahedron Lett.* **2003**, 44, 3701.

### Examples:

What products would you expect in the following reactions?

1. 
Oc1ccccc1S1CCCC1  $\xrightarrow{1.1 \text{ equiv IBX}}$
2. 
CN(C)(C)C1(C)CCCC1(C)O  $\xrightarrow[1.1 \text{ equiv CF}_3\text{CO}_2\text{H}]{1.1 \text{ equiv IBX}}$
3. 
CC(C)CCCC(C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C[C@H]5[C@@H](O)CC[C@@]2(C5)O  $\xrightarrow{1.1 \text{ equiv IBX}}$
4. 
O=C1C(=O)C2=CC=CC=C2O1C3=CC=CC=C3  $\xrightarrow{\text{DDQ, Dioxane}}$
5. 
CC1(C)OC2=CC=CC=C2C1  $\xrightarrow{\text{DDQ, Dioxane}}$
6. 
OC(=O)c1ccccc1C2=CC=CC=C2C3=CC=CC=C3  $\xrightarrow{\text{DDQ}}$
7. 
CC[C@H]1[C@@H](O)C[C@H]2C[C@@H]1C[C@H](C2)c3ccccc3  $\xrightarrow{\text{DDQ}}$

### Text Books:

V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, Narosa, New Delhi, 2002.

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

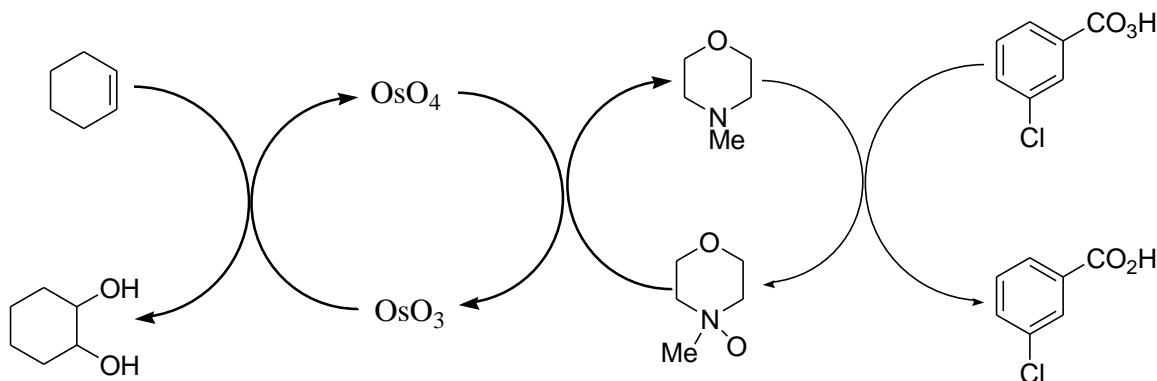
## Lecture 12

### 1.9 Other Oxidants (NMO, I<sub>2</sub>/RCO<sub>2</sub>Ag and NBS)

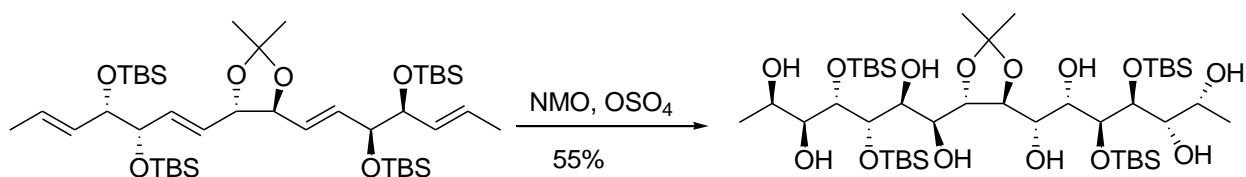
#### 1.9.6 N-Methylmorpholine-N-oxide (NMO)

NMO is a useful and relatively mild oxidizing agent. It is used as a co-oxidant with OsO<sub>4</sub> for hydroxylation of alkenes (Scheme 1). In the presence of oxidizing agent such MCPBA catalytic amount of NMO can be used.

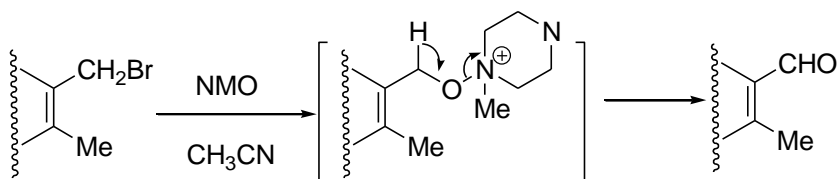
M. R. Sivik, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 5, 3545.



Scheme 1

**Examples:**

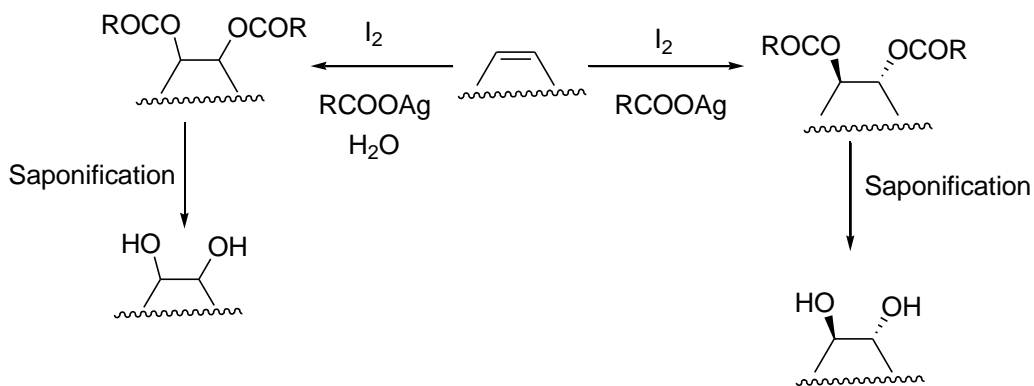
J. A. Marshall, S. Beaudoin, K. Lewinski, *J. Org. Chem.* **1993**, 58, 5876.



W. P. Griffith, J. M. Jolliffe, S. V. Ley, K. F. Springhorn, P. D. Tiffin, *Synth. Commun.* **1992**, 22, 1967.

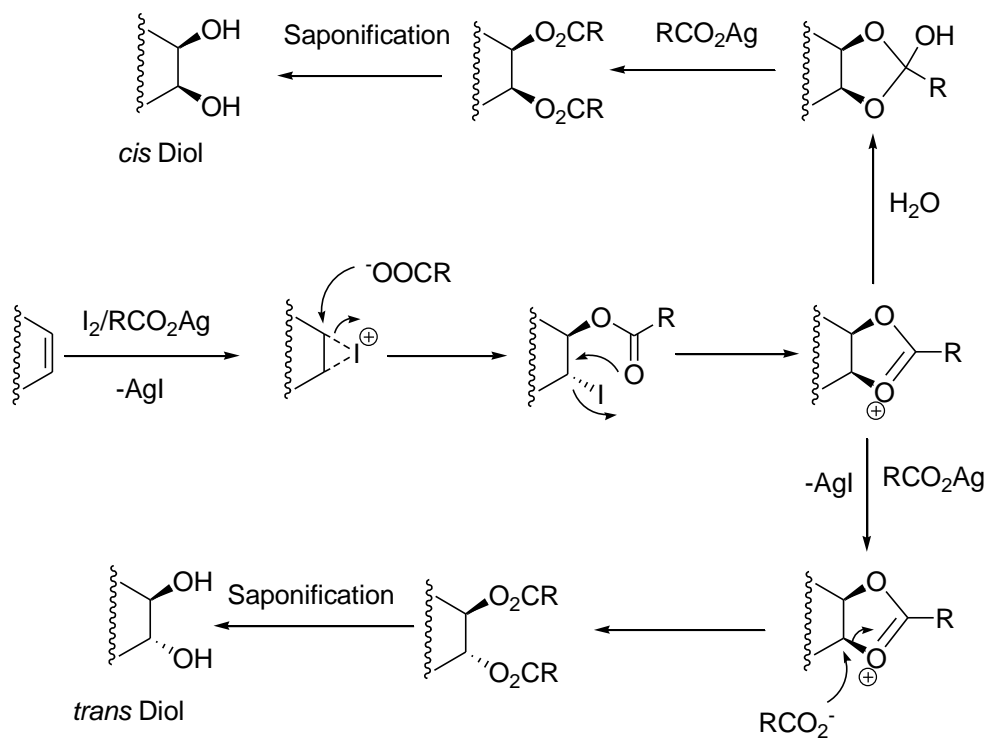
**1.9.7 Dihydroxylation of Alkenes ( $\text{I}_2/\text{RCO}_2\text{Ag}$ )**

Under anhydrous conditions a solution of iodine in  $\text{CCl}_4$  and equiv molar amount of silver acetate or silver benzoate transform alkenes into the diacetyl/dibenzoyl derivatives of the *trans* glycol, which on hydrolysis give *trans* diols. This reaction is known Prevost dihydroxylation of alkenes. In contrast, if the reaction is free from anhydrous conditions (in presence of water), *cis* diacetate or dibenzoate is obtained, which on saponification gives *cis* diols. This is called Woodward dihydroxylation of alkenes (Scheme 2-3).



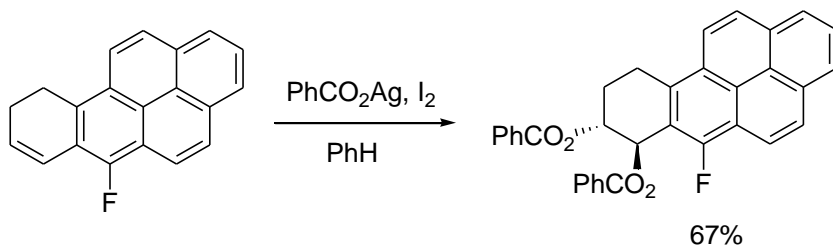
Scheme 2

### Proposed Mechanism

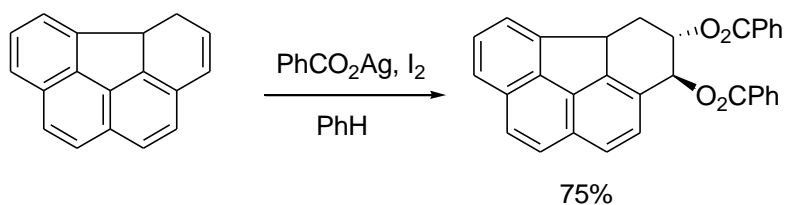


Scheme 3

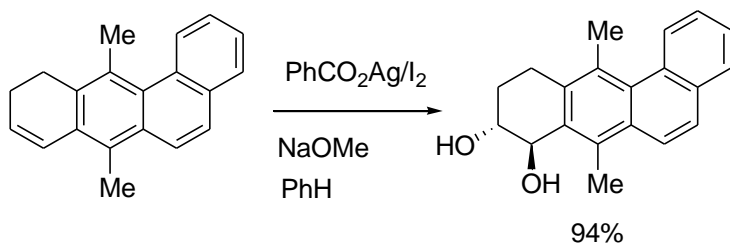
**Examples:**



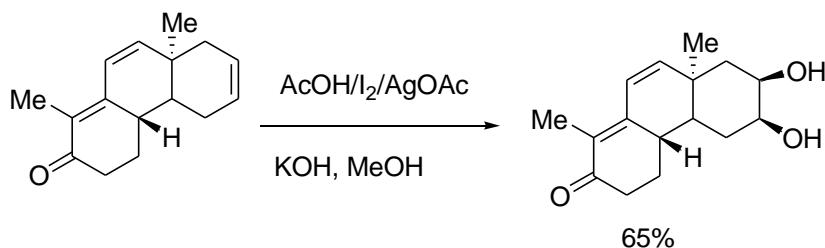
B. Zaje, *J. Org. Chem.* **1999**, 64, 1902.



H.-F. Chang, B. P. Cho, *J. Org. Chem.* **1999**, 64, 9051.



R. G. Harvey, P. P. Fu, C. Cortez, J. Pataki, *Tetrahedron Lett.* **1977**, 3533.



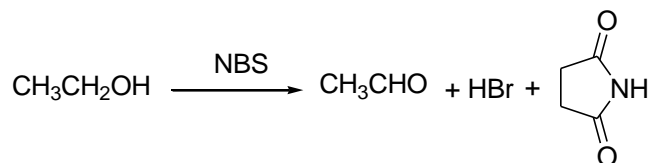
R. B. Woodward, Jr., F. V. Brutcher, *J. Am. Chem. Soc.* **1958**, 80, 209.



### 1.9.8 *N*-Bromosuccinimide (NBS)

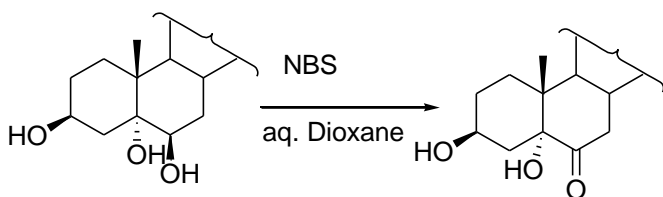
S. C. Virgil, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 1, 768.

NBS is mostly used as a brominating agent. It can also oxidize alcohols to aldehydes and ketones.



Scheme 4

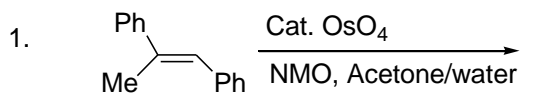
In the case of cholestane-3 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -triol, chemoselective oxidation has been observed.

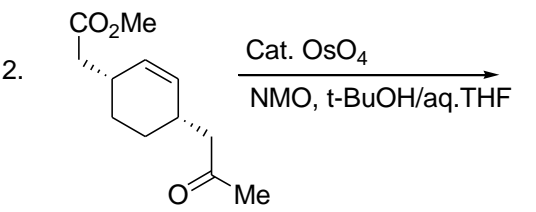


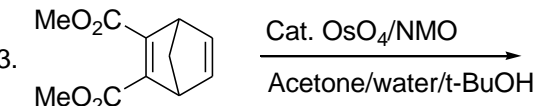
Scheme 5

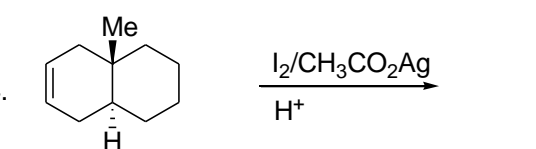
**Problems:**

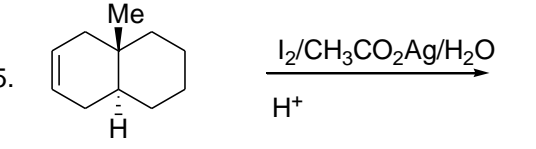
A. Predict the major products with mechanism for the following reactions.

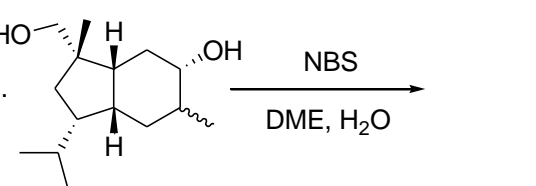
- 

1. CC(=C(c1ccccc1)c2ccccc2)O.OsO4>NMO, Acetone/water>CC(O)(O)C(c1ccccc1)c2ccccc2
- 

2. CC(=O)C1=CCCCC1CCOC(=O)C.OsO4>NMO, t-BuOH/aq. THF>CC(=O)C1(O)CCCCC1CCOC(=O)C
- 

3. COC(=O)C1=CC2(C1)C#NCC2C(=O)OC.OsO4>NMO, Acetone/water/t-BuOH>COC(=O)C1CC2(C1)C#NCC2C(=O)OC
- 

4. CC1=CC2=CC=CC2CC1.OI2>CH3CO2Ag, H+>CC1(O)C(O)C2=CC=CC2CC1
- 

5. CC1=CC2=CC=CC2CC1.OI2>CH3CO2Ag, H2O, H+>CC1(O)C(O)C2=CC=CC2CC1
- 

6. CC1=CC2=CC=CC2CC1.OI2>CH3CO2Ag, H2O, H+>CC1(O)C(O)C2=CC=CC2CC1

**Text Books:**

V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, Narosa, New Delhi, 2002.

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## Lecture 13

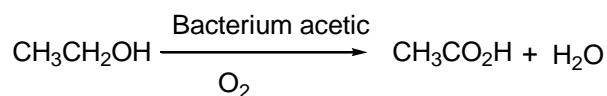
### 1.10 Bio-oxidations (Enzymatic or Microbial Oxidations)

#### 1.10.1 Introduction

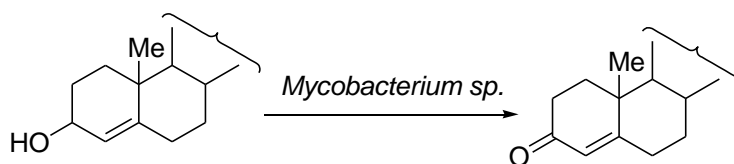
Enzyme catalyzed oxidation of organic molecules is one of the important processes in biological chemistry. In monooxygenase catalyzed processes, one of the atoms of the oxygen is incorporated in the substrate and the other is converted into water. In dioxygenase catalyzed reactions, both the atoms of oxygen are incorporated in the substrate. The advantages of the bio-oxidations are, (i) it uses the atmospheric oxygen as terminal oxidant, (ii) the reaction is performed in biological solvent i.e. water and (iii) the reactions are regio- and/or stereoselective.

#### 1.10.2 Oxidation of Alcohols

The oxidation of alcohol to acetic acid using *Bacterium acetic* in presence of air is a very well known reaction (Scheme 1). The process is employed to produce acetic acid by the well-known quick-vinegar process. Oxidation of cholesterol by *Mycobacterium species* affords cholest-4-en-2-one (Scheme 2).



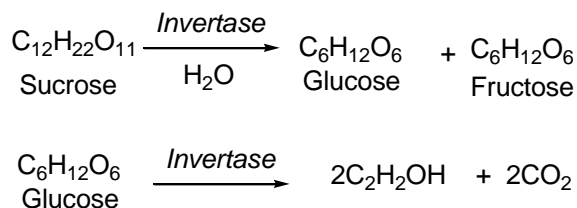
Scheme 1



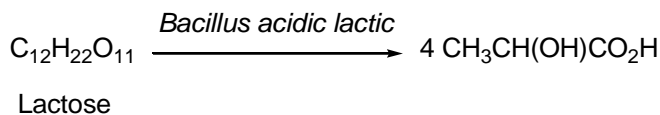
Scheme 2

#### 1.10.3 Oxidation of Sugar

The oxidation of sucrose to ethanol using yeast under air is also very well known reaction (Scheme 3). This process is employed to manufacture ethanol. Likewise, the formation of lactic acid has been shown from lactose in the presence of *Bacillus acidilactic* (Scheme 4). These reactions are referred as fermentation.



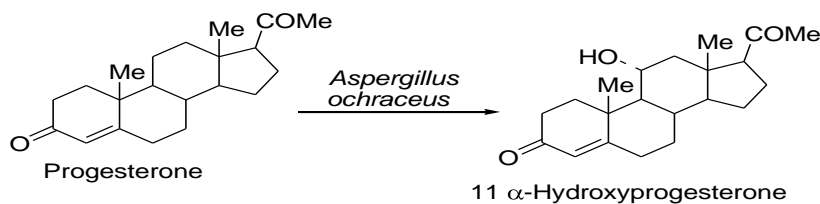
Scheme 3



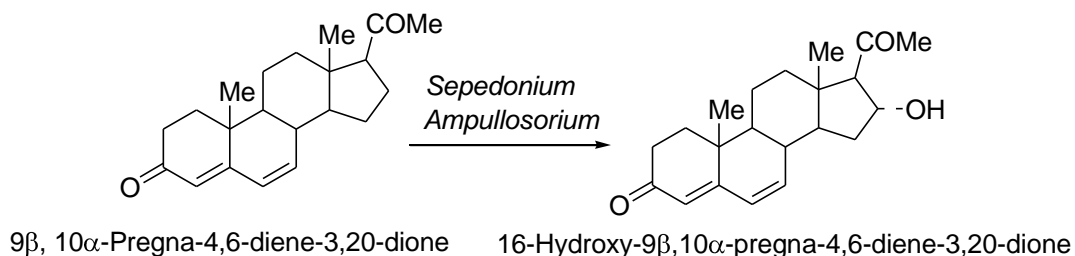
Scheme 4

#### 1.10.4 Aliphatic C-H Oxidation

The C-H oxidation of steroids, isoprenoids, hydrocarbons and alkaloids has been considerably investigated using microbial reagents. For example, progesterone has been converted into 11 $\alpha$ -hydroxyprogesterone by *Aspergillus ochraceus* (Scheme 5). Likewise, hydroxylation of 9 $\beta$ -10 $\alpha$ -pregna-4,6-diene-3,20-dione has been shown using *Sepedonium ampullosporium* to afford 16 $\alpha$ -hydroxy-9 $\beta$ -10 $\alpha$ -pregna-4,6-diene-3,20-dione (Scheme 6). The reaction can be performed in Kg

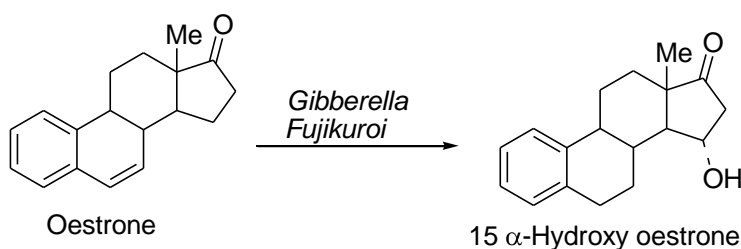


Scheme 5



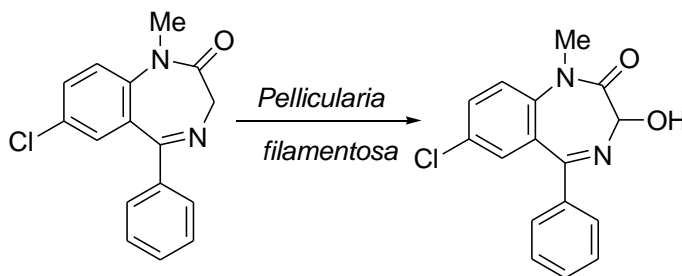
Scheme 6

scale with high yield. Furthermore, oestrone can be oxidized by *Gibberella fujikuroi* to afford 15α-hydroxy oestrone in 75% yield (Scheme 7).



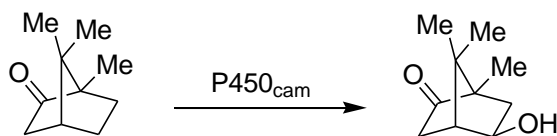
Scheme 7

Diazepam has been oxidized by *Pellicularia filamentosa* to give 7-hydroxy diazepam (Scheme 8).



Scheme 8

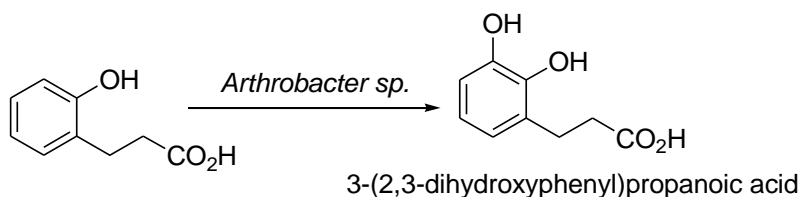
Cytochrome P-450 monooxygenases contain a heme co-factor and a bulky protein molecule and their name originated from the unusual property of forming reduced iron (ferrous)-carbon monoxide complex in which the absorption of heme group shifts from 420 nm to ~450 nm (P-450). It catalyzes the hydroxylation of (+)-camphor at 5<sup>th</sup> position to give 5-exo-(+)-camphor (Scheme 9).



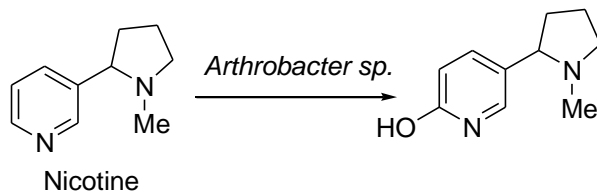
Scheme 9

### 1.10.5 Aromatic C-H Oxidation

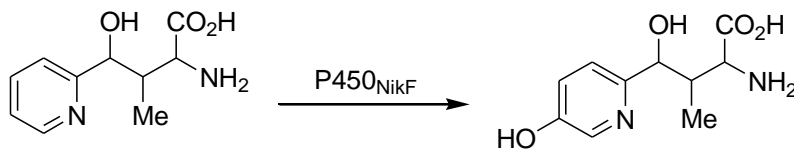
Enzyme obtained from *Arthrobacter species* catalyzes the oxidation of melilotic acid to afford 3-hydroxymelilotic acid in 20% yield (Scheme 10). Similarly, nicotine has been hydroxylated at position 6 by *Arthrobacter species* (Scheme 11).



Scheme 10



Scheme 11



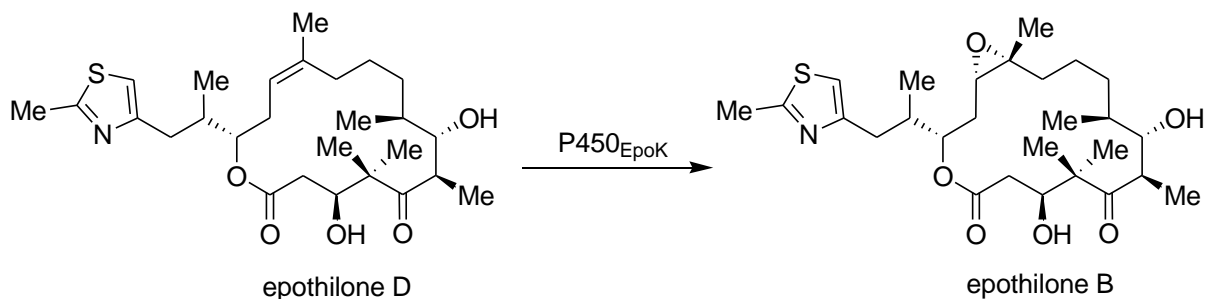
Scheme 12

The hydroxylation of aromatic compound has been reported by P-450 enzyme. The P-450<sub>NikF</sub> from *Streptomyces tendae* catalyzes the hydroxylation of 2-amino-4-hydroxy-4-(5-pyridin-2-yl)butanoic acid to 2-amino-4-hydroxy-4-(5-

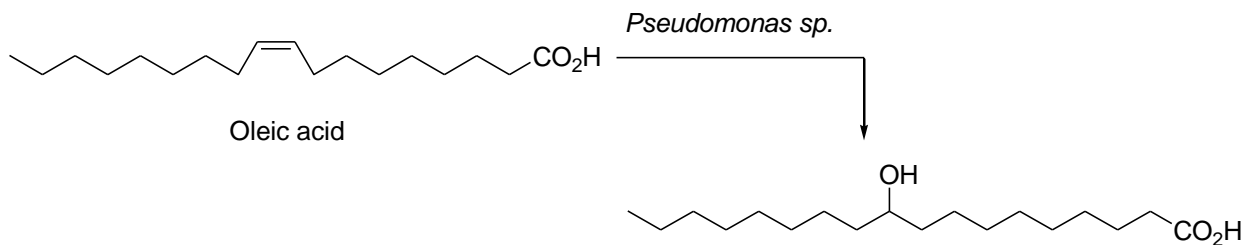
hydroxypyridin-2-yl)-3-methylbutanoic acid, which is an intermediate in biosynthesis of nikkomycin (Scheme 12).

### 1.10.6 Oxidation of Aliphatic C=C Bonds

The P-450<sub>EpoK</sub> from *Sorangium cellulosum* catalyzes the epoxidation of thiazole containing macrolactone epothilone D to give epothilone B (Scheme 13). While oleic acid undergoes oxidation in the presence of *Pseudomonas species* to give 10-hydroxystearic acid in 14% yield (Scheme 14).



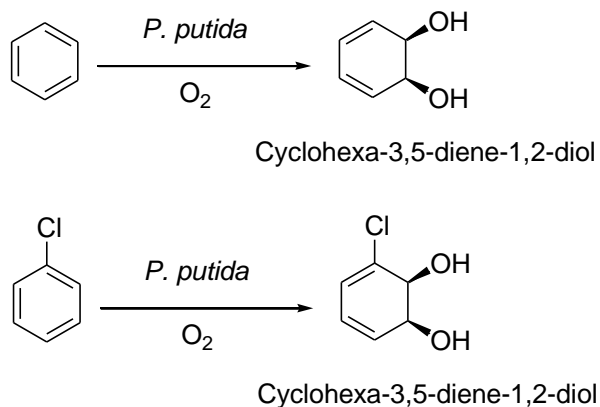
Scheme 13



Scheme 14

### 1.10.7 Oxidation of Aromatic C=C Bonds

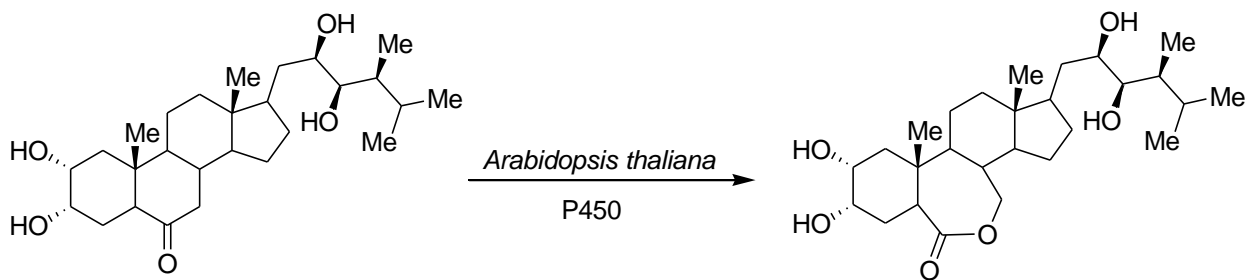
$\pi$ -Bond in benzene and chlorobenzene are converted into a *cis* 1,2-diol by *Pseudomonas putida* in the presence of air (Scheme 15). The *cis* diol obtained has been used for the synthesis of conduritol F and pinitol (antidiabetic agent).



Scheme 15

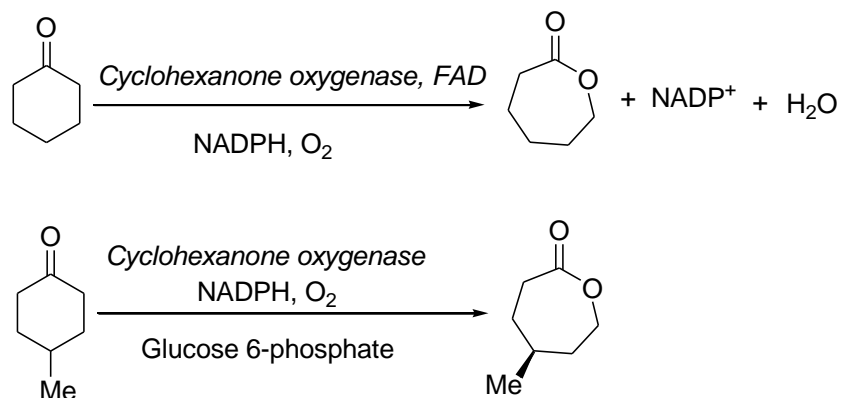
### 1.10.8 Baeyer-Villiger Oxidation

The Baeyer-Villiger oxidation has been reported by P-450 from *Arabidopsis thaliana*, which can transform castasterone to brassinolide (Scheme 16). In a similar way cyclohexanone oxygenase oxidizes cyclohexanones to give the corresponding lactones (Scheme 17).



Scheme 16

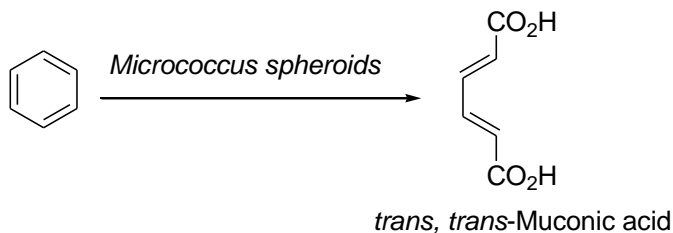




Scheme 17

### 1.10.9 Oxidative Cleavage of Benzene

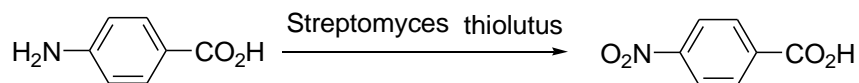
*Micrococcus spheroids* catalyze the conversion of benzene into *trans, trans*-muconic acid (Scheme 18).



Scheme 18

### 1.10.9 Oxidation of Amino Group

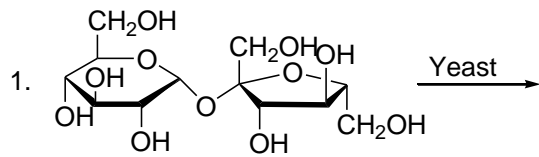
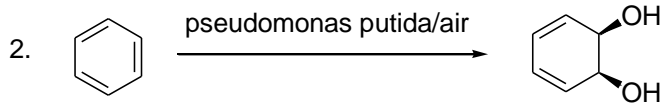
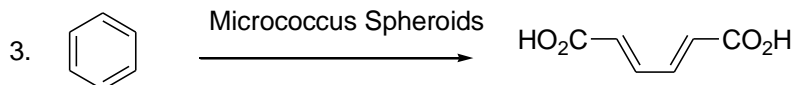
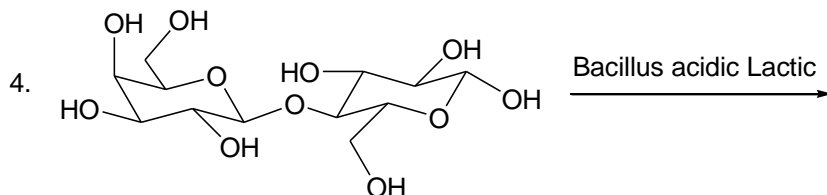
Amino group can be oxidized into nitro group by *Streptomyces thiolutus* (Scheme 19).



Scheme 19

## Problems

Complete the following bio-oxidation processes.

- 
- 
- 
- 

## Text Books

V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, Narosa, New Delhi, 2002.

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.