I Oxidation Reactions

Objectives

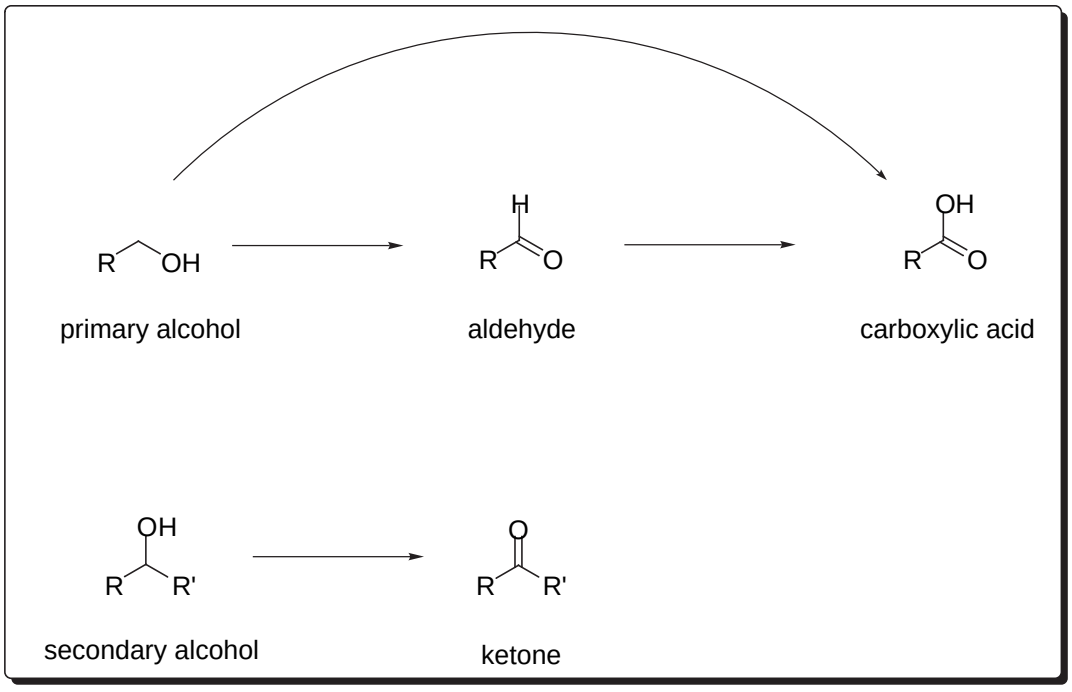
By the end of this section you will:

1) have an improved appreciation of some of the important selectivity issues involved in oxidation processes.
2) be aware of the wide range of methods available for carrying out a selective oxidation.
3) be able to make a judicious choice of reagent for a given oxidation.
4) be aware of the potential pit-falls (in particular side-reactions) in oxidation reactions.

Some Definitions:

Chemoselectivity	the reaction of one functional group in the presence of another
Regioselectivity	reaction at one point in an ambident functional group
Stereoselectivity	control of stereogenic centres in an absolute and/or (or both) relative fashion; control of double bond geometry.

I.A. Oxidation of Alcohols

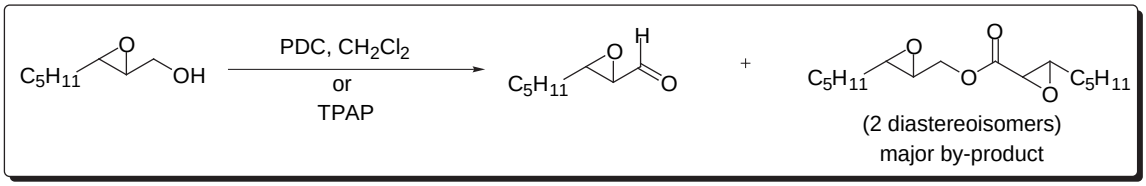


Issues of Reactivity and Selectivity.

1. Primary alcohols are generally more reactive than secondary alcohols and can sometimes be oxidised selectively.

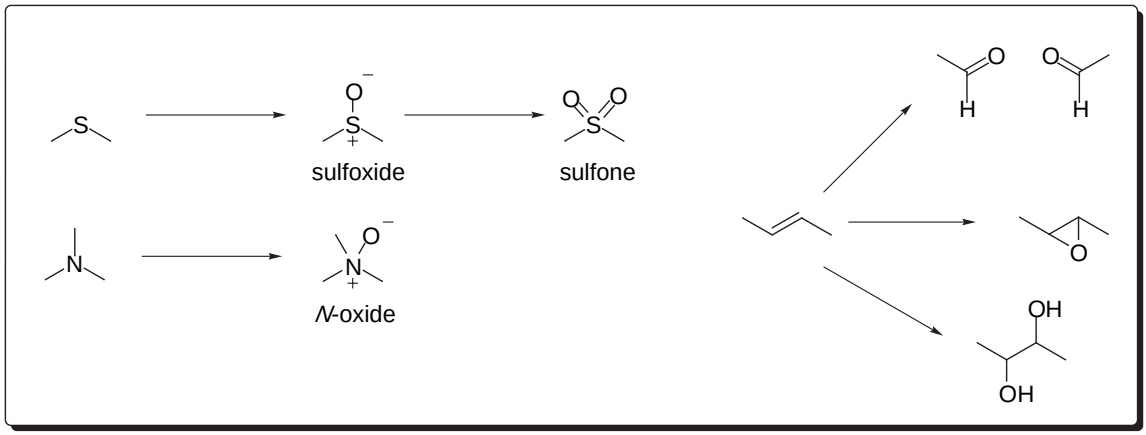
2. Chemoselectivity - oxidation of primary alcohols requires control as there are two potential products: the carboxylic acid and the aldehyde. Aldehydes are extremely important in organic synthesis; thus controlled oxidation from an alcohol to an aldehyde, avoiding over-oxidation to the carboxylic acid, is very important.

3. Aldehydes, and to a lesser extent, ketones, are reactive electrophiles. The presence of nucleophiles in the reaction mixture (*e.g.* the alcohol starting material!) can lead to side-reactions.

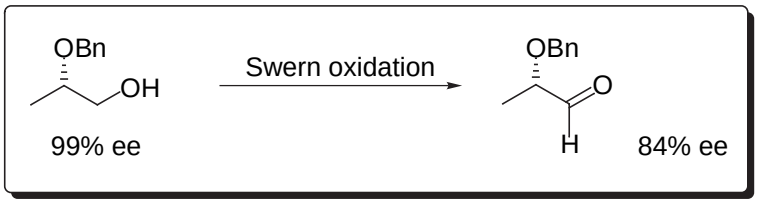


You should be able to draw a mechanism for the formation of the ester by-products.
When the alcohol was oxidised under Swern conditions, the ester by-product was not observed.
You should be able to rationalise this observation by the end of this section.

3. Other functional groups in a molecule can also be oxidised:



4. α-C–H protons next to a ketone, and even more so those next to an aldehyde, are relatively acidic (pK_a(acetone)~20). α-Stereogenic centres are therefore prone to epimerisation under oxidation reaction conditions, especially when there is a base present:



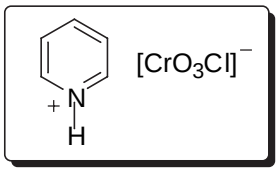
There is no general oxidant. A huge variety of oxidants is routinely used by synthetic chemists. Some of the most important types are found in the list below. Some of these you will have come across in earlier studies; some will be new to you. You should be able to answer all of the questions posed - if you can't, find solutions from the literature or ask me.

Common Oxidants

I.A.1. Middle → Late Transition Metals in a High Oxidation State

I.A.1.i Chromium Oxidants

a) **PCC** (pyridinium chlorochromate)



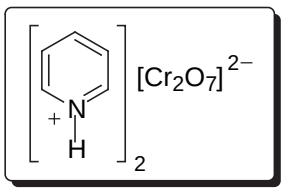
What is the oxidation state of Cr?

- Used to oxidise primary alcohols to aldehydes - over-oxidation is rarely a problem.
- Secondary alcohols are also readily oxidised to ketones.
- Relatively acidic reagent (more acidic than PDC and Collins) - can cause problems with acid-labile groups. Buffering the reaction mixture with NaOAc can help.

b) **Collins' Reagent** ($CrO_3 \cdot 2$ pyridine)

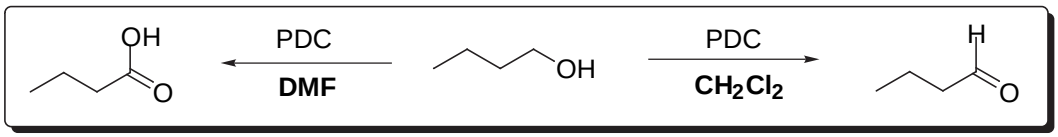
- Used to oxidise primary and secondary alcohols to aldehydes and ketones respectively.
- Non-acidic reagent (mildly basic) - acid-labile groups are tolerated.
- Requires a large excess of reagent for complete reaction.

c) **PDC** (pyridinium dichromate)



What is the oxidation state of Cr?

- Less acidic than PCC and less basic than Collins' reagent.
- Secondary alcohols are oxidised to ketones.
- Primary alcohols can be oxidised to either aldehydes or carboxylic acids depending on the substrate and solvent:



d) Jones Oxidation (aq. H_2SO_4, acetone, CrO_3)

- Oxidises secondary alcohols to ketones.
- Primary alcohols are oxidised to carboxylic acids.
- Strongly acidic reaction conditions are a problem with acid-labile groups.

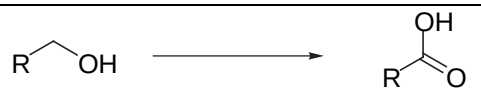
Advantages of Chromium Oxidants

- Relatively mild conditions
- Easy work-up procedures

Disadvantages of Chromium Oxidants

- Work-up can be messy on large scale
- Often require a large excess of the Chromium reagent
- Chromium reagents are toxic and mutagenic

Summary

Transformation	Chromium reagent
	PCC, Collins', PDC (in CH_2Cl_2)
	PCC, Collins', PDC, Jones
	Jones, PDC (in DMF)

References

1) S. V. Ley and A. Madin in *Comprehensive Organic Synthesis*, Eds. B. M. Trost and I. Fleming, Pergamon, Oxford, 1990, vol. 7, pp 251-289.

2) F. A. Luzzio, *Org. React*., 1998, **53**, 1-221.

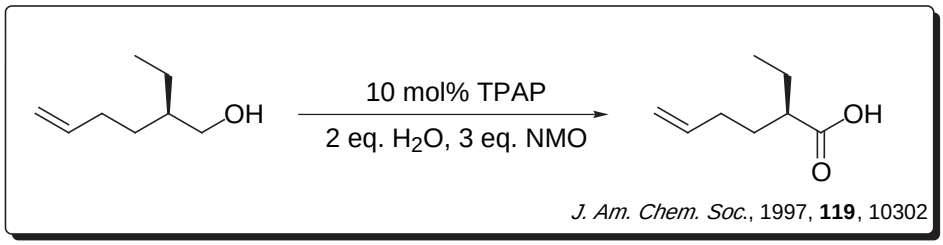
I.A.1.ii Ruthenium Oxidants

TPAP (tetrapropylammonium perruthenate) [$Pr_4N^+RuO_4^-$].

Chromium oxidants are usually used in stoichiometric quantities (and often in excess). A method which employs the transition metal oxidant in sub-stoichiometric amounts is highly desirable for many reasons including *atom economy* (see later). TPAP is the most widely used of these reagents.

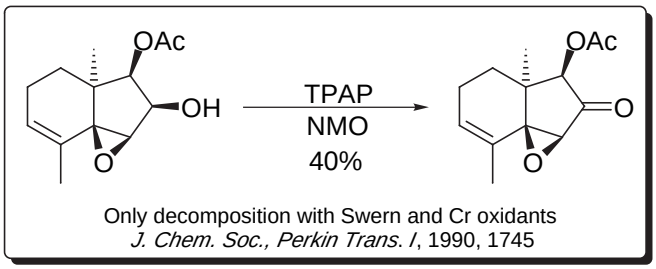
- *N*-methylmorpholine-*N*-oxide functions as the stoichiometric oxidant for recycling the catalyst.
- Primary alcohols are oxidised to aldehydes.
- Over-oxidation to the carboxylic acid is rare although can be induced by omitting the molecular sieves that are used to remove H_2O from the reaction.

How might the presence of H_2O allow further oxidation of an aldehyde to the carboxylic acid?



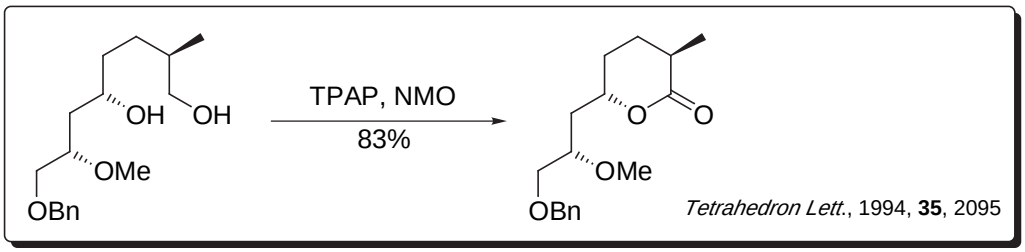
J. Am. Chem. Soc., 1997, **119**, 10302

- Secondary alcohols are oxidised to the corresponding ketones



Only decomposition with Swern and Cr oxidants
J. Chem. Soc., Perkin Trans. I, 1990, 1745

- Primary alcohols react more rapidly than secondary alcohols - this can be exploited in a useful synthesis of lactones:



Tetrahedron Lett., 1994, **35**, 2095

What are the intermediates in this reaction?

References

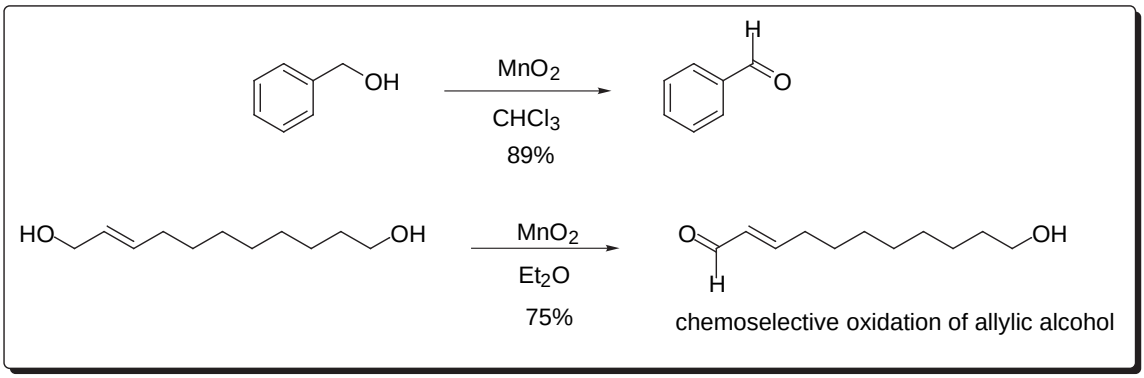
1) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* 1994, 639-666.

I.A.1.iii Manganese Oxidants

Manganese dioxide (MnO_2)

What is the oxidation state of the metal?

- mild oxidant
- oxidises allylic, propargylic and benzylic alcohols (*i.e.* activated alcohols) to aldehydes or ketones:

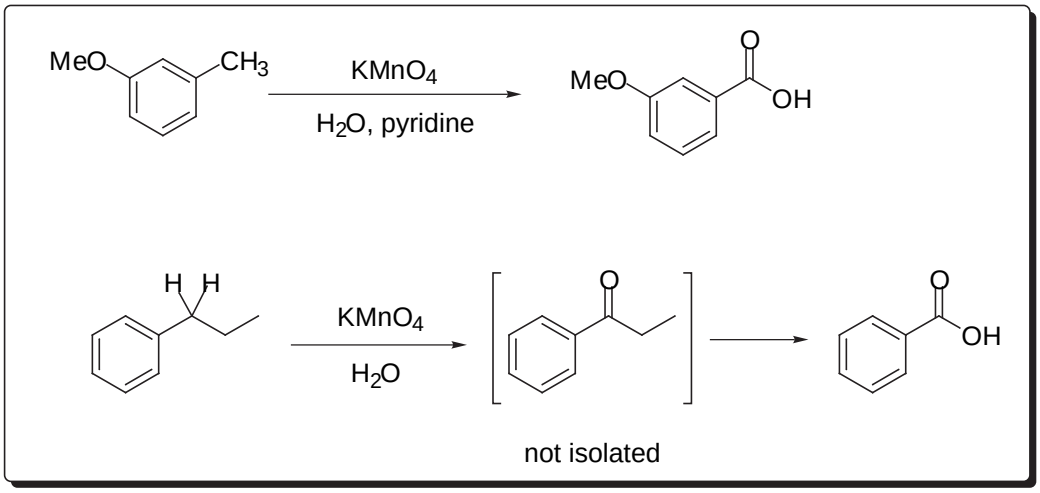


chemoselective oxidation of allylic alcohol

Potassium Permanganate ($KMnO_4$)

What is the oxidation state of the metal?

- A general and very powerful oxidant especially when used in aqueous solutions. Tends not to be very chemoselective, which limits its use.
- Can be used to oxidise the benzylic position of aromatic systems to carboxylic acids



not isolated

- The oxidising power of $KMnO_4$ can be tempered by using the reagent in organic solvents.

Why does $KMnO_4$ dissolve in benzene when a crown ether such as 18Crown6 is added?

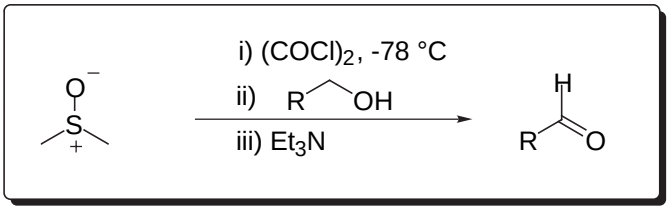
- Biphasic conditions have also been used. A phase transfer catalyst such as $BnNBu_3^+Cl^-$ is used to transfer the anionic oxidant into the organic phase.

How do phase transfer catalysts function?

I.A.2. Activated Dimethyl Sulfoxide Oxidations

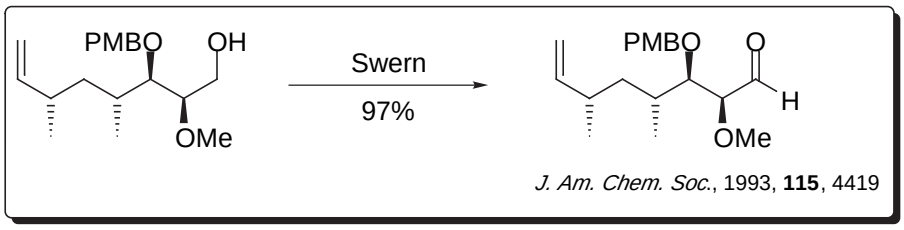
There are a wide variety of oxidation methods based on activation of DMSO. The most widely used is the so-called Swern oxidation:

- very mild method of oxidation
- over-oxidation to the carboxylic acid is not a problem



What is the mechanism of this reaction?

Example from Nicolaou's synthesis of rapamycin:



J. Am. Chem. Soc., 1993, **115**, 4419

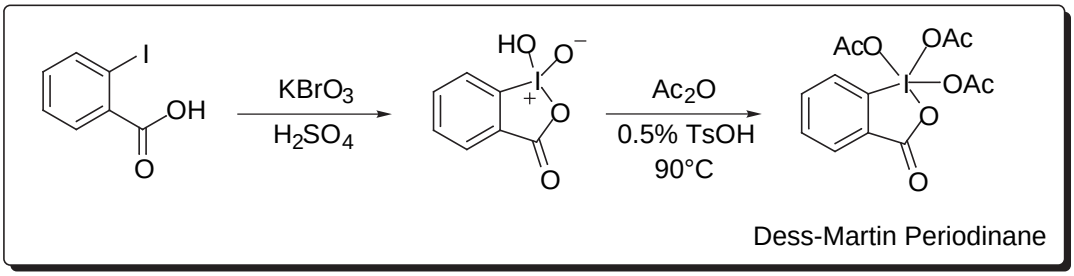
References

1. T. V. Lee in *Comprehensive Organic Synthesis*, Ed. B. M. Trost, I. Fleming, Pergamon, Oxford, 1990, vol 7, pp 291-303.
2. T. T. Tidwell, *Org. React.*, 1990, **39**, 297-303.

I.A.3. Hypervalent Iodine Oxidising Agents

There are a wide number of hypervalent iodine reagents (iodine in +3 and +5 oxidation state). The most important for oxidation purposes is **Dess-Martin Periodinane (DMP)** so-named after its discoverers.

Readily prepared from 2-iodobenzoic acid:

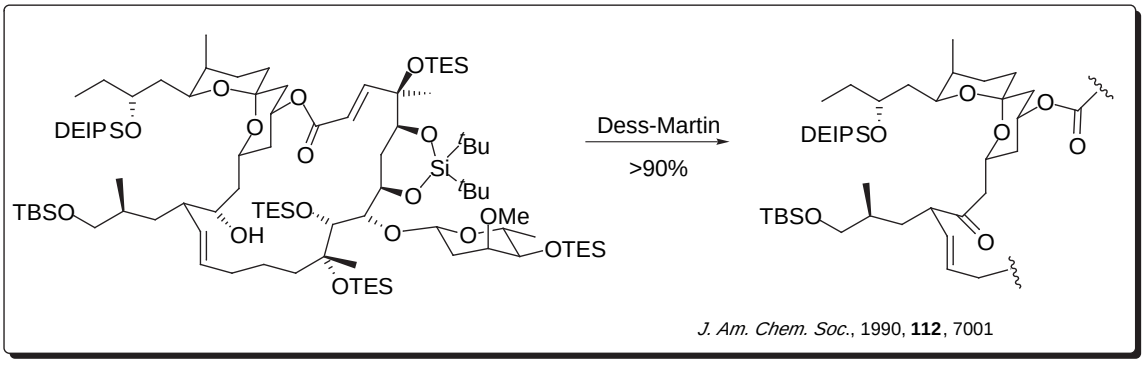


Preparation:

i) R. E. Ireland, L. Liu, *J. Org. Chem*., 1993, **58**, 2899.

ii) S. D. Meyer, S. L. Schreiber, *J. Org. Chem*., 1994, **59**, 7549-7552.

- DMP is a very mild oxidant and is especially useful for oxidising molecules containing very sensitive functionality. In the following example taken from Evans' synthesis of cytovaricin, Dess-Martin periodinane oxidised the only available secondary alcohol to the corresponding ketone in excellent yield. No problems associated with epimerisation of the α-stereogenic centre or migration of the proximal olefin into conjugation were encountered.

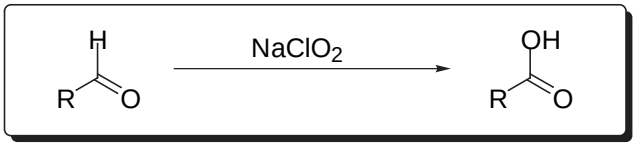


- Reaction conditions are either neutral or slightly acidic.
- Very chemoselective oxidising alcohols to aldehydes and ketones.
- Over-oxidation to the carboxylic acid is not a problem.
- Selectively oxidises alcohols in the presence of sulfides.

I.A.4 Oxidation of Aldehydes to Carboxylic Acids

Sodium Chlorite ($NaClO_2$)

- It is often more efficient to prepare a carboxylic acid from the alcohol in two steps proceeding through the aldehyde.
- Sodium chlorite (household bleach) is one of the mildest methods for achieving this:



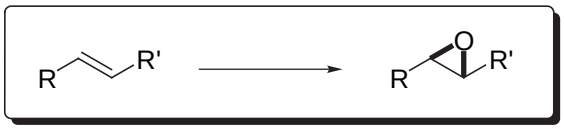
- A by-product from this reaction is HOCl which is a good source of electrophilic chlorine. This may be a problem when the substrate also contains olefin functionality. To circumvent such problems, add a more electron-rich olefin such as resorcinol (1,3-dihydroxybenzene). This then acts as a sacrificial *electrophile scavenger*.

Summary of Alcohol Oxidation Methods

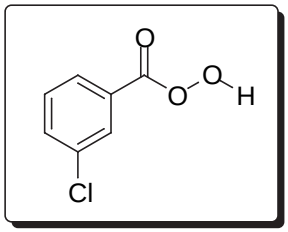
Alcohol → Aldehyde	**Comment**
PDC (in CH_2Cl_2),	stoichiometric in Cr, neutral reaction conditions
PCC	stoichiometric in Cr, mildly acidic
Collins	stoichiometric in Cr, mildly basic
TPAP	catalytic in Ru
Swern	mild
DMP	mild
MnO_2	only oxidises activated alcohols
Primary Alcohol → Carboxylic Acid	
PDC (in DMF)	mild
Jones	acidic reaction conditions
$KMnO_4$	usually suffers from lack of chemoselectivity
Aldehyde → Carboxylic Acid	
$NaClO_2$	mild

I.B Epoxidation of Olefins

For a general review: A. S. Rao in *Comprehensive Organic Synthesis*, Eds. B. M. Trost, I. Fleming, Pergamon, Oxford, 1990, Vol. 7, Chapter 3.1, pp 357-387.

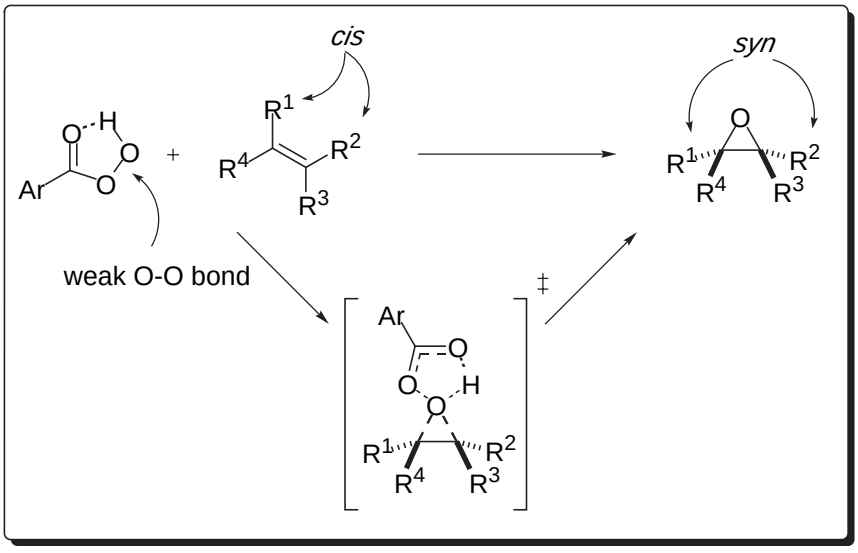


I.B.1 *meta*-Chloroperbenzoic acid (*m*CPBA)



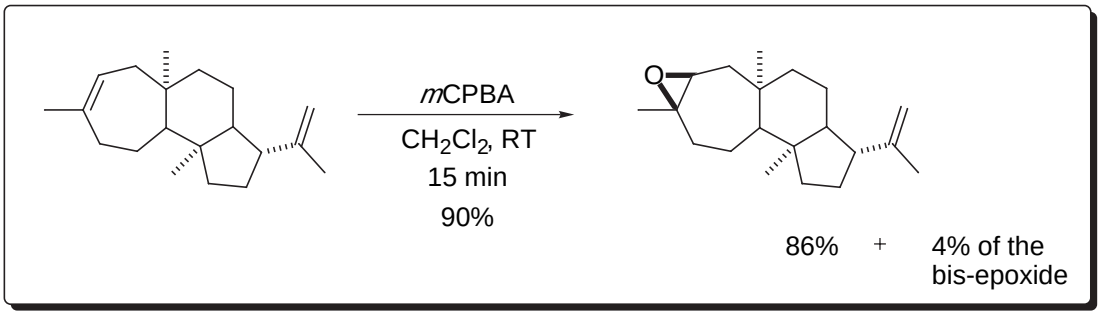
General oxidant - **electrophilic** therefore reacts preferentially with electron rich C=C

Epoxidation of olefins is a *syn*-stereospecific process:



Rate of epoxidation is related to the nucleophilicity of the olefin - the more substituted or electron-rich the more reactive: tetra/trisubstituted > disubstituted > monosubstituted olefins.

Regioselective Epoxidation

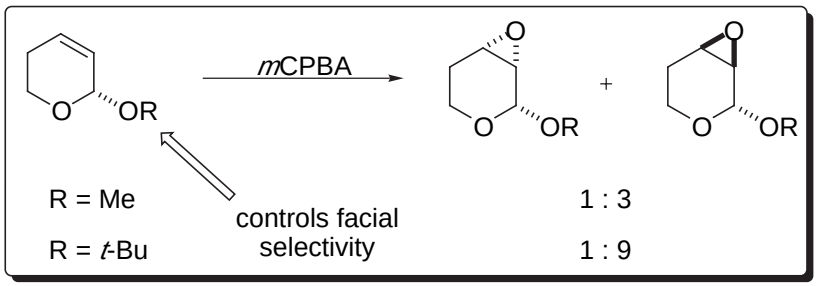


Rationalise the stereoselectivity of this epoxidation.

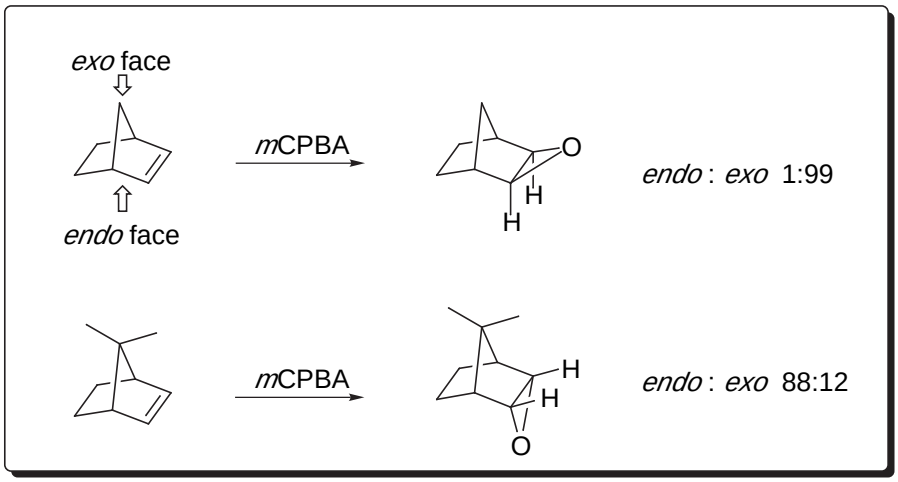
Diastereoselective Epoxidation

Steric hindrance is an important means for controlling the facial selectivity of reactions:

Example 1



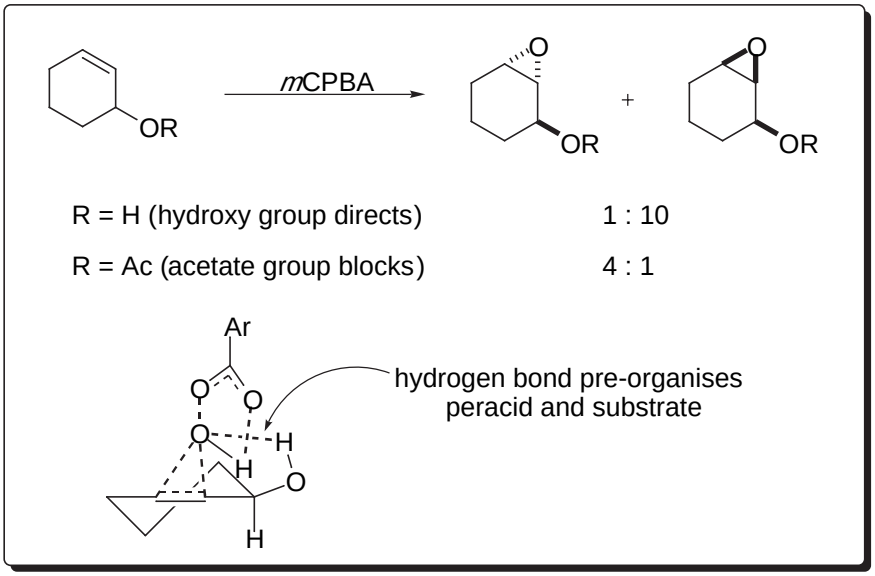
Example 2



Directed Epoxidation

In non-coordinating solvents, the hydrogen bonding capability of the peracid can be used to *direct* the epoxidation if there are hydrogen bond acceptor groups in close proximity to the olefin. This method, the so-called Henbest epoxidation, can sometimes overcome the inherent steric bias of the substrate.

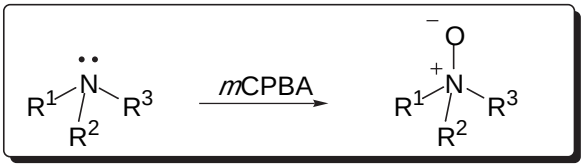
Example:



Heteroatom Oxidation

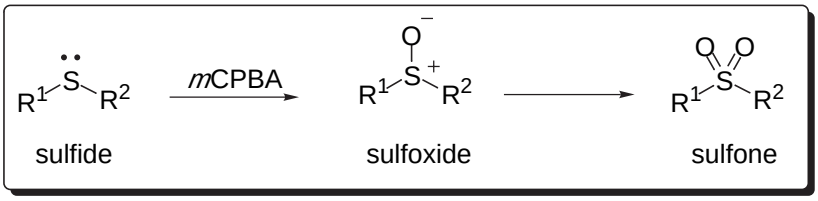
Amines

Tertiary amines are readily oxidised to amine oxides

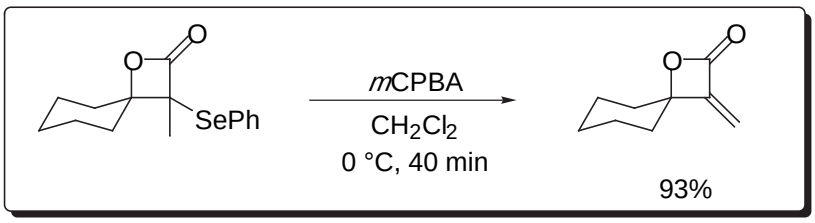


Oxidation of chalcogens

Sulfides are readily oxidised to sulfoxides (over-oxidation to the sulfone can be a problem):



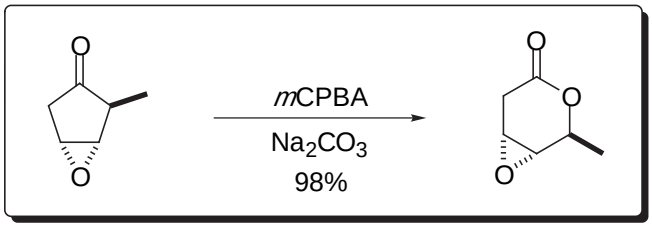
Selenides are even more readily oxidised to the corresponding selenoxides at low temperatures. Further oxidation is not a problem as the selenoxide readily undergoes *stereospecific* elimination on warming. This is a very useful method for preparing olefins.



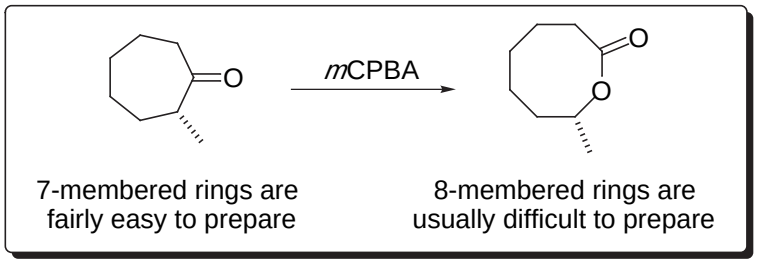
What is the mechanism of this transformation?

An issue of chemoselectivity: competing reactions - **Baeyer-Villiger Oxidation**

Ketones react with *m*CPBA to form esters, (the Baeyer-Villiger reaction). In this case *m*CPBA is behaving as a nucleophile.



This is a useful reaction for preparing medium ring lactones by ring-expansion.



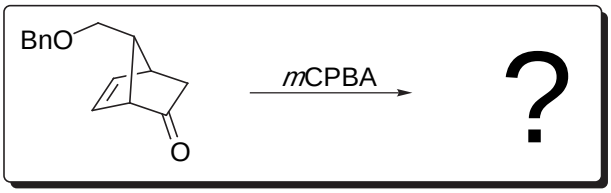
You should know the mechanism of this rearrangement reaction.

The reaction is *stereospecific* proceeding with *retention of configuration* at the migrating centre.

The migratory preference is (approximately) of the order:
3° alkyl > 2° alkyl > alkenyl, phenyl > 1° alkyl > methyl

Chemoselectivity can therefore be a problem.

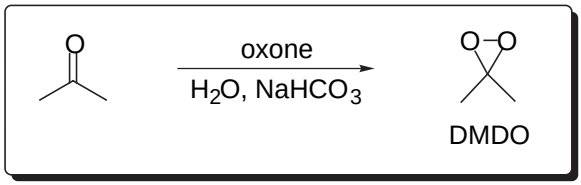
Predict potential products from the following transformation:



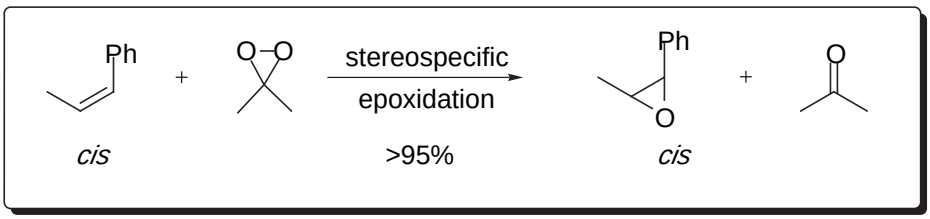
I.B.2 **Dimethyldioxirane** (DMDO)

Powerful, and yet frequently selective, electrophilic oxidant. Capable of oxidising very unreactive olefins. Reactions are carried out under mild conditions and the acetone by-product is inocuous and readily removed.

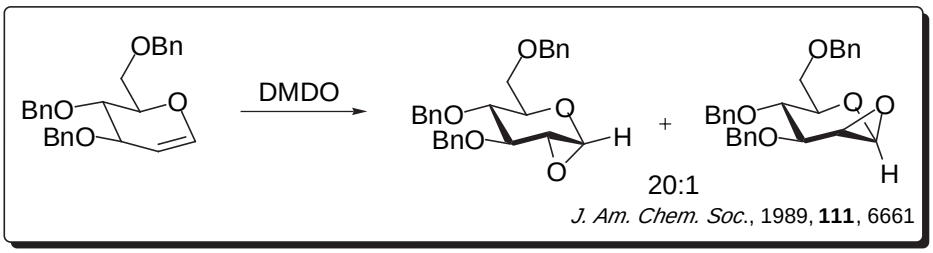
Preparation



Normally used as a dilute solution in acetone (impossible to isolate).



Although DMDO is a highly reactive epoxidising agent, reaction proceeds under very mild conditions which allows the isolation of some relatively unstable epoxides such as those produced from glycals (see example below).



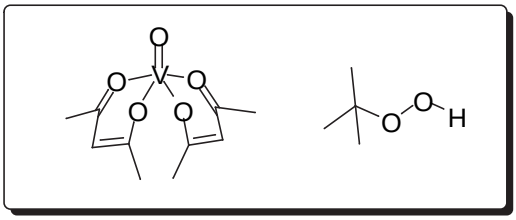
I.B.3 Directed Epoxidation Reactions

For a review of methods of asymmetric epoxidation: R. A. Johnson, K. B. Sharpless in *Comprehensive Organic Synthesis*, Eds. B. M. Trost, I. Fleming, Pergamon, Oxford, 1990, Vol. 7, Chapter 3.2, pp 389-436.

Directed epoxidation reactions, as their name implies are reactions in which the reagent containing the oxygen that is to be transferred to the substrate is tethered to the reacting substrate through a non-covalent interaction (*e.g.* H-bond or metal-ligand interaction). Typical substrates are allylic and homoallylic alcohols. The alcohol is critical for the reaction to proceed efficiently and is therefore important in the reaction mechanism.

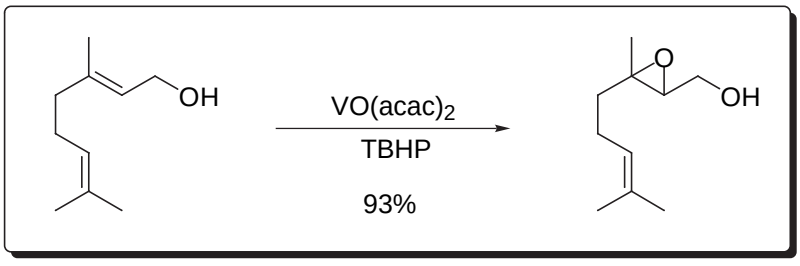
For a review of substrate-directable chemical reactions: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307-1370.

Vanadyl(acetylacetate) / *tert*-butylhydroperoxide ($VO(acac)_2$/TBHP)

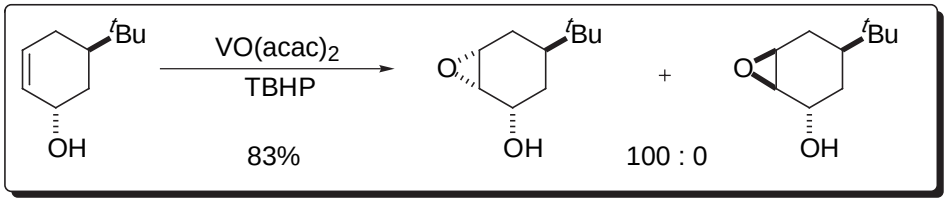


This combination of reagents will selectively epoxidise allylic alcohols in the presence of other (even more electron-rich) olefins.

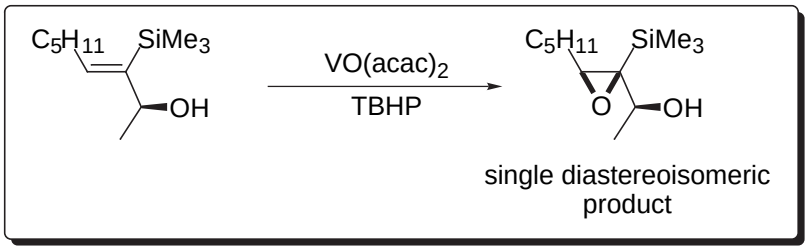
Example 1



Example 2



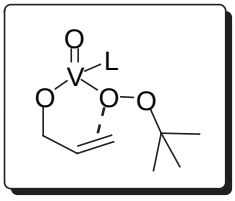
Consider the following highly diastereoselective reaction:



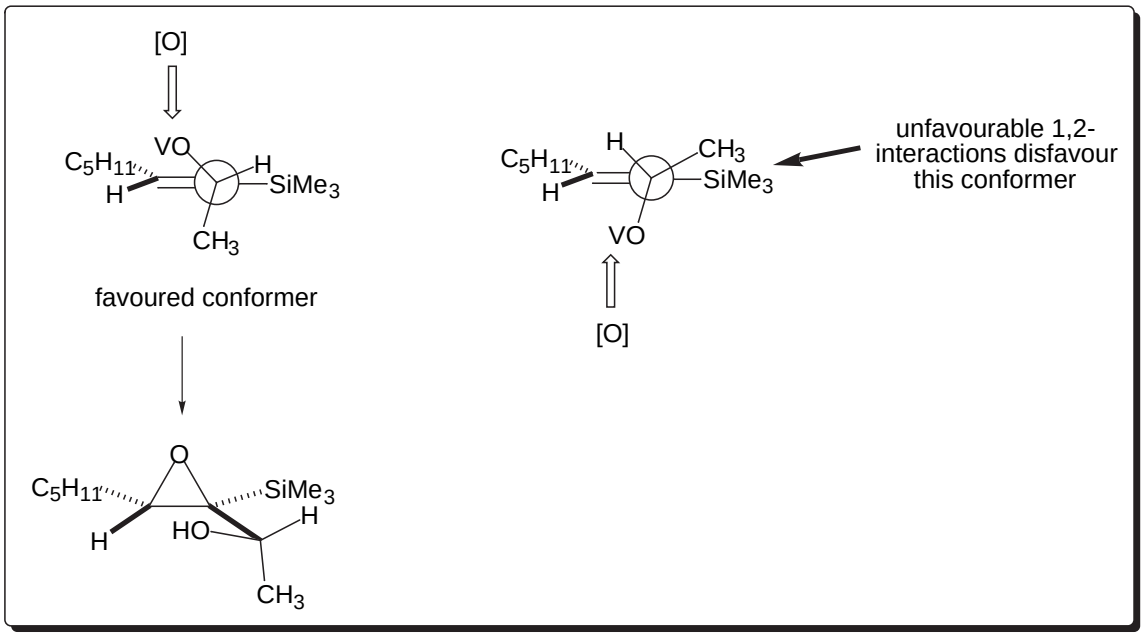
Q? Can we predict the stereochemical outcome of the reaction?

Notes: i) TBHP oxidises $VO(acac)_2$ to a Vanadium(V) species which coordinates the alcohol of the substrate *and* the hydroperoxide.

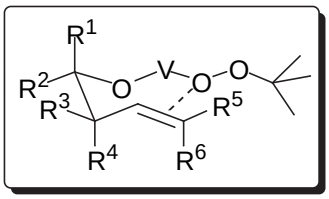
ii) the vanadium centre can therefore be thought of as a *template* in which the reacting substrates are brought together allowing an intramolecular reaction to proceed.



iii) computational calculations have shown that the ideal O-C-C=C dihedral angle is 50° thus there are two possible reactive conformers:

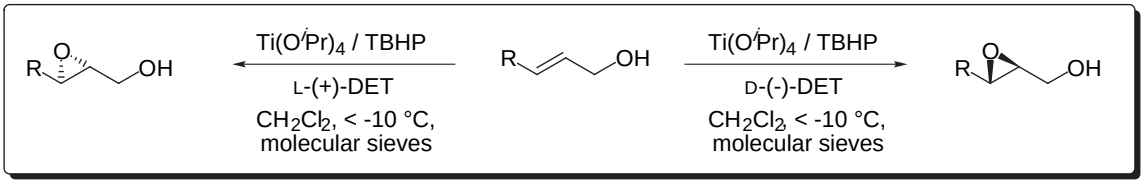


In the case of homoallylic alcohols the selectivity can be rationalised by invoking a chair-like T.S. which maximises the number of equatorial substituents:

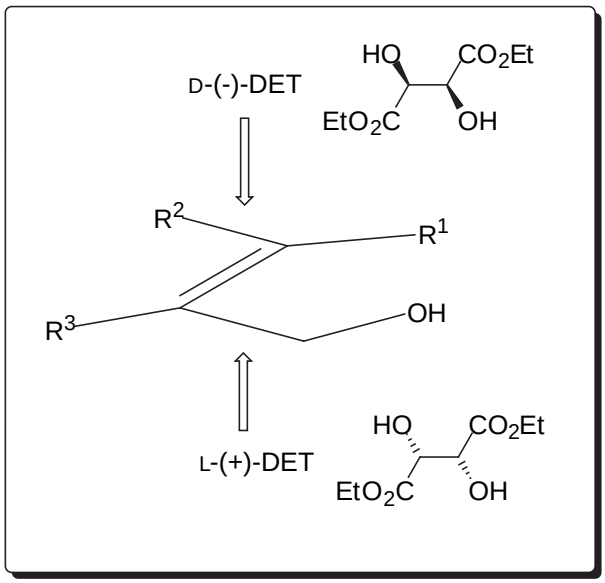


Sharpless Asymmetric Epoxidation

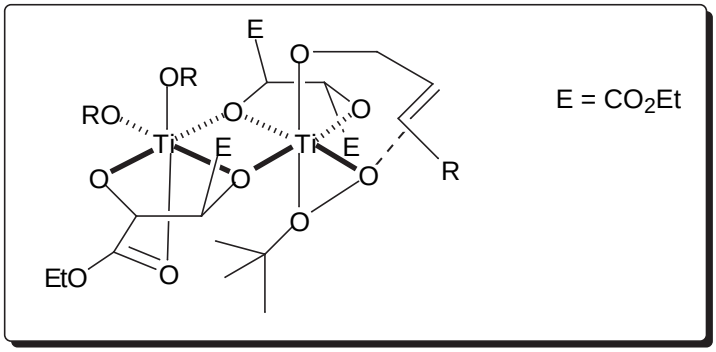
Titanium tetra-isopropoxide [Ti(O^iPr)$_4$] can also be used in place of VO(acac)$_2$ to effect a directed epoxidation of allylic alcohols. In the presence of a chiral ligand (such as diethyl tartrate) and under carefully optimised conditions, a catalytic enantioselective version was developed by Sharpless and is now known as the **Sharpless Asymmetric Epoxidation (AE).** Enantioselectivities are often in excess of 95% ee.



This is a very powerful reaction and can be applied to the majority of allylic alcohols. A useful cartoon has been developed to predict which ligand to use to access a particular enantiomer.



Again the proposed transition state has both the oxygen source (TBHP) and the substrate coordinated to a Titanium centre; the tartrate ligand creates the chiral environment.



I.B.4 Nucleophilic Epoxidation

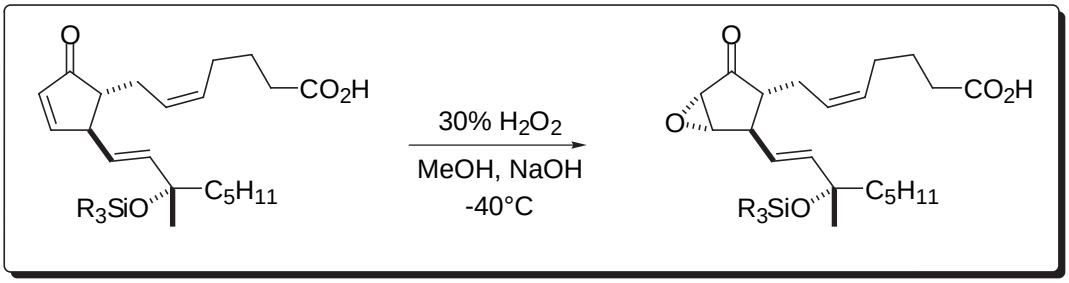
So far all the methods of epoxidation require nucleophilic olefins and the more electron-rich the better they react. α,β-Unsaturated carbonyl groups contain electron-deficient olefins which are therefore poor substrates for these electrophilic reagents. However, by exploiting the potential nucleophilic character of peroxides it is also possible to epoxidise this type of double bond.

Alkaline Hydrogen Peroxide or *tert*-Butylhydroperoxide

This combination of reagents generates a source of ROO^- which is a good nucleophile.

Why are peroxides more nucleophilic than alcohols?
What is the mechanism of this type of epoxidation?

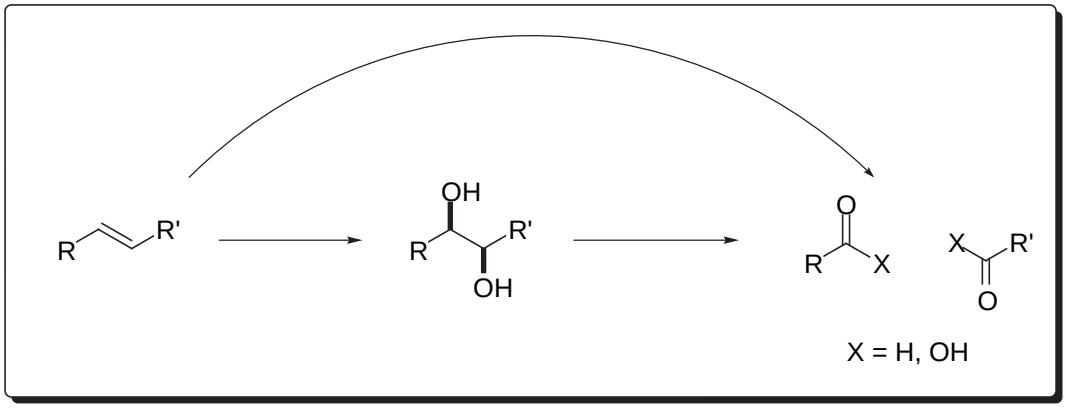
A chemoselective epoxidation reaction:



Summary

Epoxidation Method	Target Olefin
electrophilic reagents:	
*m*CPBA	electron-rich olefins, allylic or homoallylic alcohols
DMDO	electron-rich olefins epoxidised preferentially but will epoxidise most olefins
reagents requiring a directing group:	
$VO(acac)_2$ / TBHP	good for allylic and homoallylic alcohols
$Ti(O^iPr)_4$ / TBHP / DET	Sharpless ASYMMETRIC epoxidation of allylic and homoallylic alcohols
nucleophilic reagents	
TBHP / NaOH	α,β-unsaturated carbonyl systems

I.C Oxidation of Olefins



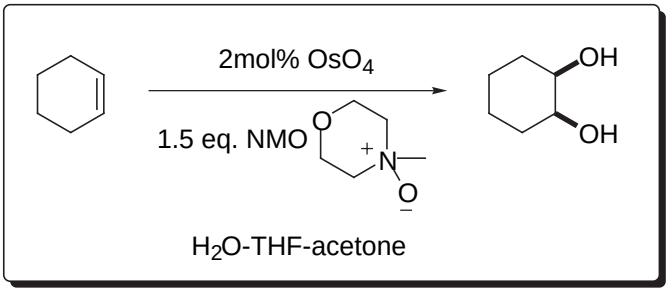
I.C.1 Dihydroxylation of Olefins

Osmium Tetroxide (OsO_4)

Osmium tetroxide reacts under very mild conditions and extremely selectively with most olefins to provide the corresponding diol. OsO_4 is an electrophilic reagent and therefore reacts most readily with electron-rich olefins.

The reaction is *stereospecific* providing the *syn* diol.

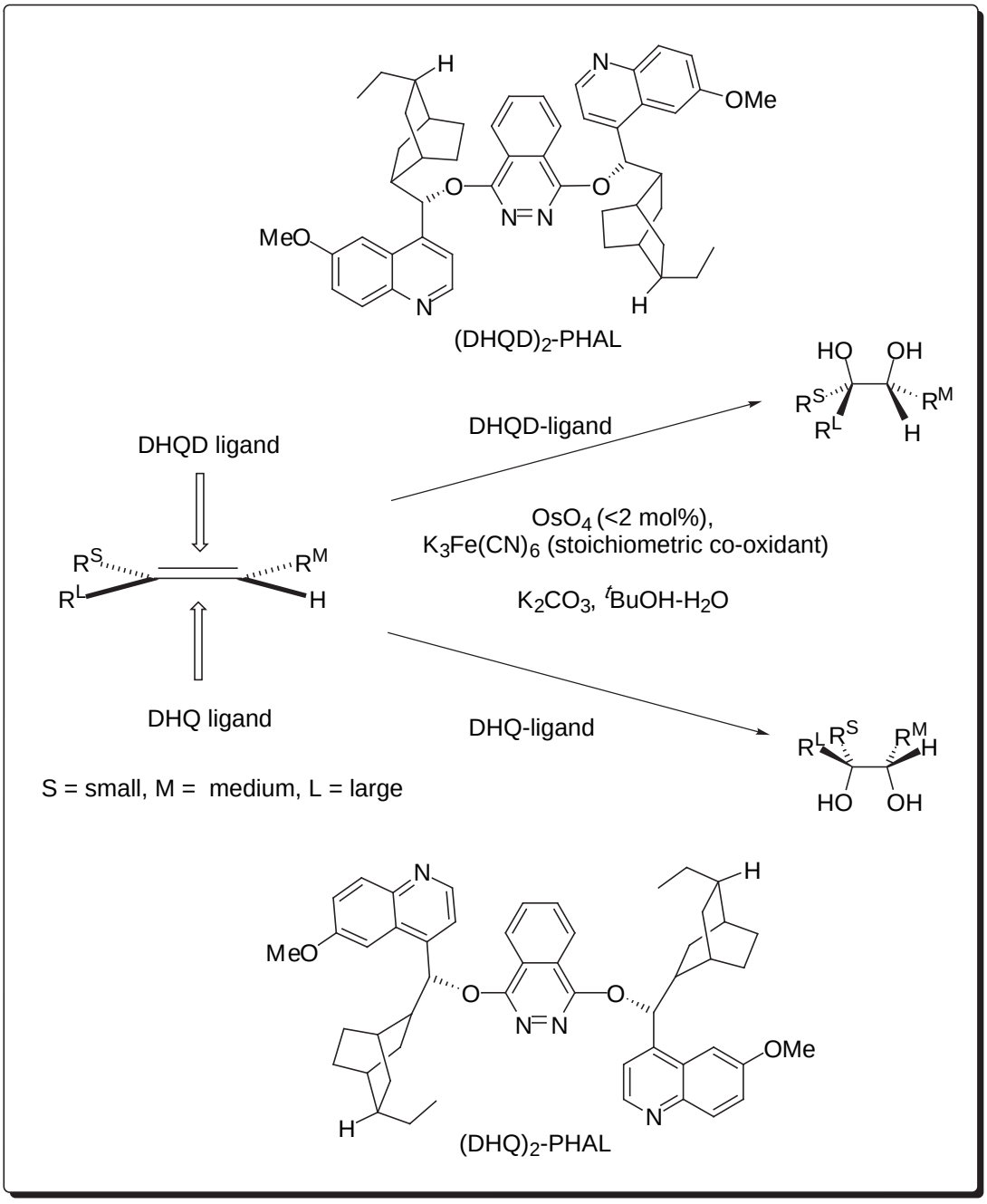
OsO_4 is very expensive and highly toxic. However it can be used in sub-stoichiometric amounts by employing a cheaper co-oxidant in stoichiometric quantities; the one that is most commonly used is *N*-methylmorpholine-*N*-oxide (NMO). These are the so-called Upjohn oxidation conditions:



Observation: the rate of dihydroxylation is increased by the presence of tertiary amines - an example of ***Ligand Accelerated catalysis****.* Therefore by using CHIRAL tertiary amines there is the potential for developing an enantioselective version of the OsO_4 dihydroxylation.

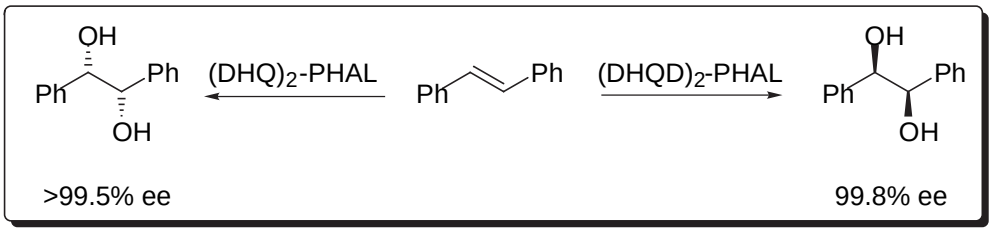
Sharpless Asymmetric Dihydroxylation

This is one of the most important and successful catalytic asymmetric processes developed to date. It is widely used, simple to carry out and is applicable to almost any alkene substrate. It is also relatively predictable in its outcome. The reaction is normally under REAGENT CONTROL *i.e.* the chiral ligand dictates the stereochemical outcome of the reaction irrespective of the stereochemistry already present in the substrate.

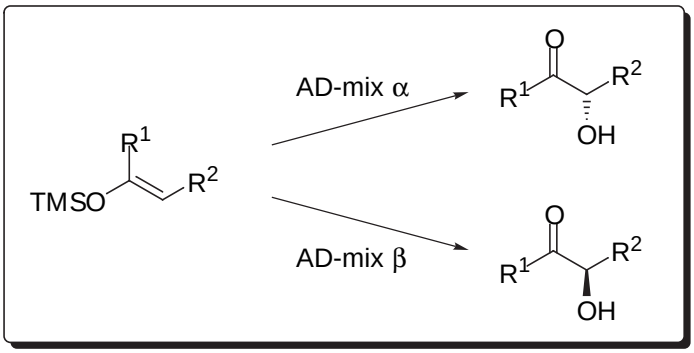


The ligand, K_2CO_3, $K_3Fe(CN)_6$ co-oxidant and source of osmium ($K_2OsO_4 \cdot 2H_2O$) are commercially available as AD-mix α (contains DHQ ligand) or AD-mix β (contains DHQD ligand) - just need to add solvent and substrate!

Example 1

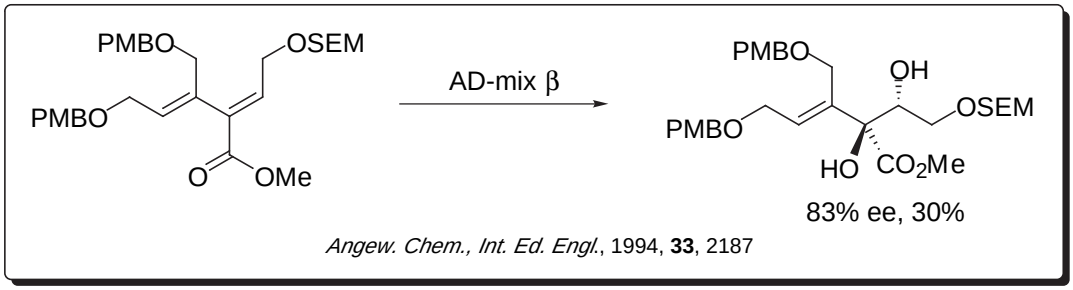


Example 2



Example 3

The Asymmetric Dihydroxylation of the diene below proved to be a key step in Nicolaou's synthesis of zaragozic acid A. The regioselectivity seems at first surprising. Think about the conformation that this molecule might adopt: the olefin that at first sight appears to be the less electron-rich is actually the more electron-rich and therefore that which partakes in the AD reaction.



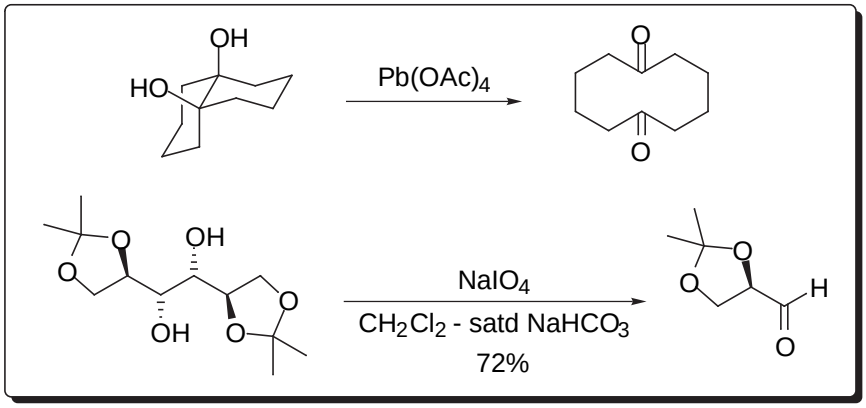
Angew. Chem., Int. Ed. Engl., 1994, **33**, 2187

For an excellent review of this area: H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483-2547.

I.C.2 Diol Cleavage

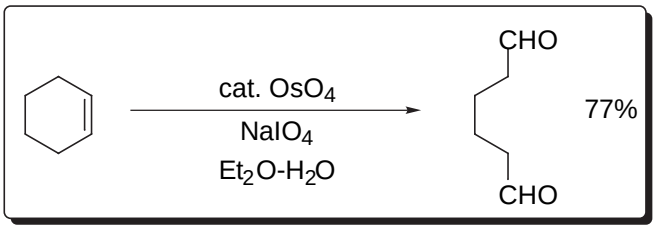
Lead(IV)Acetate ($Pb(OAc)_4$) and **Sodium Periodate** ($NaIO_4$)

Both these reagents are capable of cleaving 1,2-diols to the corresponding carbonyl groups.
Thus a dihydroxylation / diol cleavage protocol provides a two-step alternative to ozonolysis (see below).

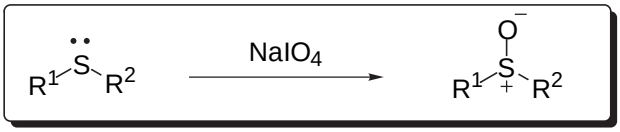


What is the mechanism of diol cleavage?

A one-pot (see later for the importance of this type of process) OsO_4 dihydroxylation - $NaIO_4$ diol cleavage has also been developed. The periodate has the added advantage of oxidising the Os(VI) back to Os(VIII) which allows the use of sub-stoichiometric quantities of OsO_4:

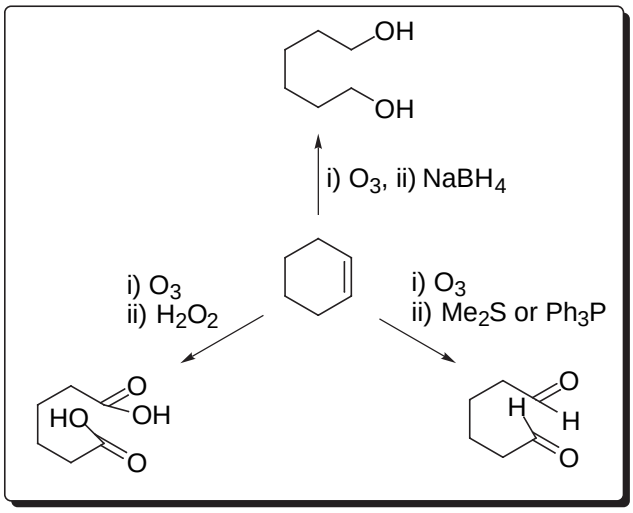


Sodium periodate is a good reagent for oxidising sulfides to sulfoxides - the use of 1 eq. of periodate allows the isolation of the sulfoxide without competing over-oxidation to the sulfone.



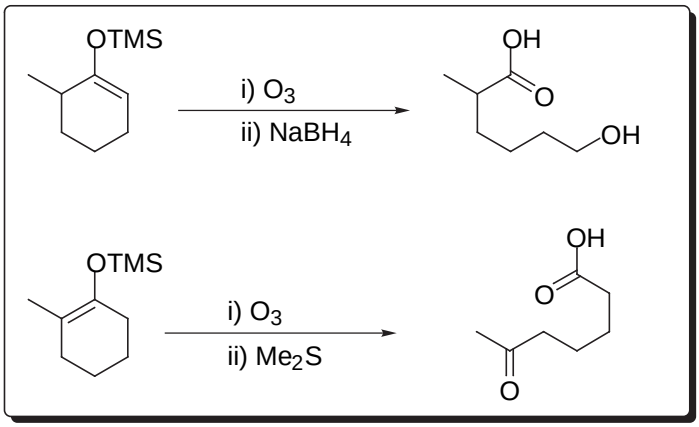
I.C.3 Direct Oxidative cleavage of Olefins - Ozonolysis

- The reaction of ozone (O_3) with olefins is the best method for the oxidative cleavage of double bonds.
- Mild and selective.
- O_3 is an electrophilic reagent and therefore reacts preferentially with electron-rich double bonds.
- A variety of work-up procedures (cleavage of the ozonide intermediate) further increases the versatility of this reaction:

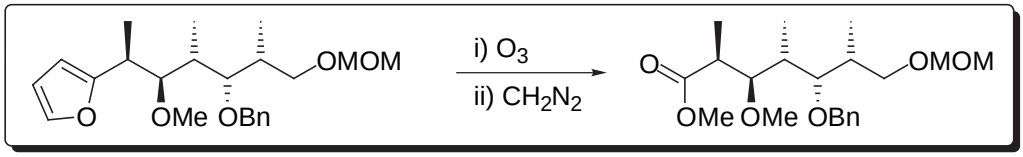


What is the mechanism of ozonolysis?

Example

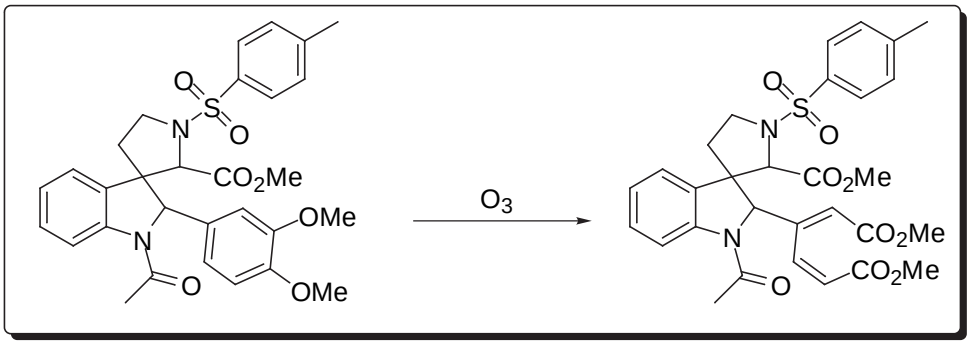


Aromatic compounds can also be ozonolysed although they often require more forcing conditions (destroying the aromaticity). A furan may be viewed as a *latent carboxylic acid* (see later for masking strategies):



Ozonolysis generates the carboxylic acid - *how might diazomethane form the methyl ester? (hint nitrogen gas is evolved)*

In Woodward's synthesis of strychnine, selective ozonolysis of the 1,2-dimethoxy aryl group released a (*Z, E*)-diene, an important synthetic intermediate.



Account for the regio- and chemoselectivity of this oxidation.

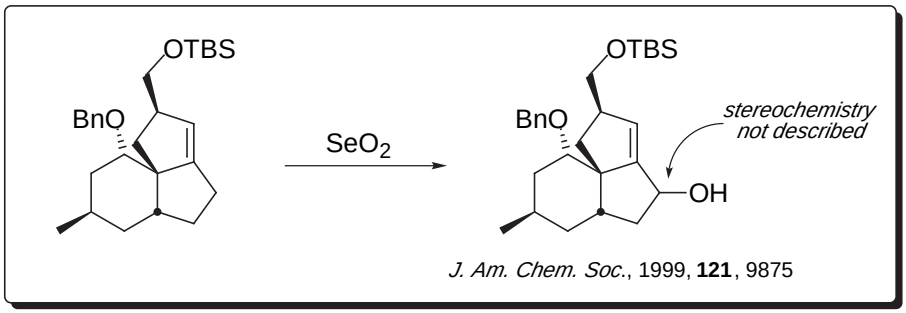
I.D Allylic Oxidation

Use selenium dioxide (SeO_2):

What is the mechanism for this transformation?

Allylic oxidations are not widely used in natural product synthesis. They are frequently not particularly high yielding and often require quite forcing conditions.

A recent example from Sha's synthesis of (+)–paniculatine:



SUMMARY

In this section I have concentrated on the most important oxidation reactions (there are many more), namely the oxidation of alcohols to aldehydes and carboxylic acids, and the various methods of oxidising olefins. It should be apparent that the multitude of reagents and reaction conditions now allows exquisite levels of selectivity, vital for the total synthesis of complex natural products which possess many reactive functionalities. Although the major reason for choosing one reagent over another is to carry out the desired reaction in as high a yield as possible, avoiding side-reactions, there is usually still a choice of reagents available to the user; often it is just a matter of trial and error (or many years of experience) before the optimum system is uncovered.