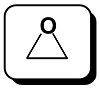
Functional Group Interconversions - Lecture 6

Section 7: Oxidation of C=X bonds

7.1 *Epoxidation of Alkenes*

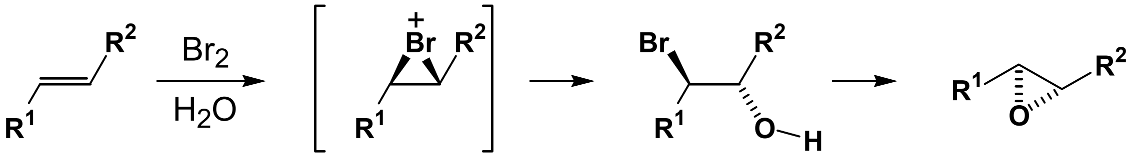
Epoxides are VERY useful in synthesis - the strain of the three membered ring makes these cyclic ethers very reactive. They react stereospecifically with nucleophiles (ring opening occurs with inversion of configuration in an S_N2 manner), and usually we see excellent regiocontrol for attack at the less hindered end as well. Thus there's a lot of interest in methods for their preparation.

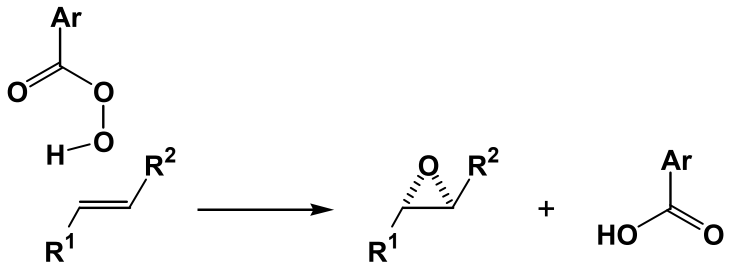


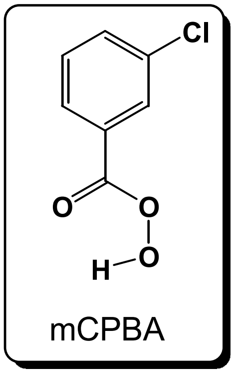
7.1.1 *Epoxidation of unfunctionalised alkenes*

One way to form epoxides is by halohydrin formation followed by treatment with base - you'll meet this in more detail later in the course. As you saw in first year, epoxides can also be prepared directly from alkenes by reaction with peracids. The reactions are concerted and so are stereospecific - the epoxide is formed with retention of olefin geometry. Since the peracid is a source of electrophilic oxygen, the reaction works best with electron poor peracids (*e.g. meta*-chloroperbenzoic acid, mCPBA) and electron rich alkenes.

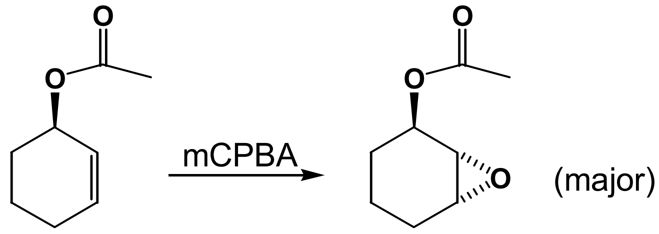
The reactions are also stereoselective and will attack the less hindered faces of alkenes.





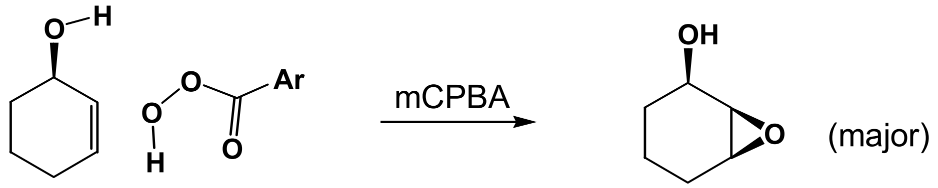


e.g.

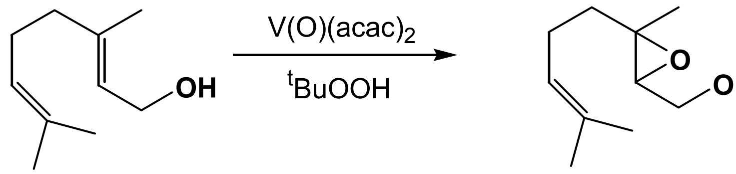


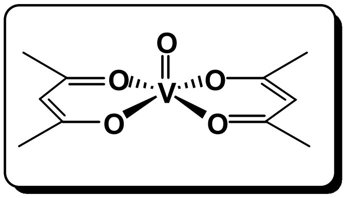
7.1.2 *Epoxidation of allylic alcohols*

Hydroxyl groups of allylic alcohols can be used to direct epoxidation to that alkene. In the case of mCPBA, this can lead to stereoselective directed epoxidation (*e.g.* to the same face of a cyclic allylic alcohol):



Certain transition metal salts can also bind to the oxygen and a peroxide species, delivering the oxidant solely to the adjacent alkene even in the presence of others! One of the first systems for this was “vanadyl acac” / ^tBuOOH:



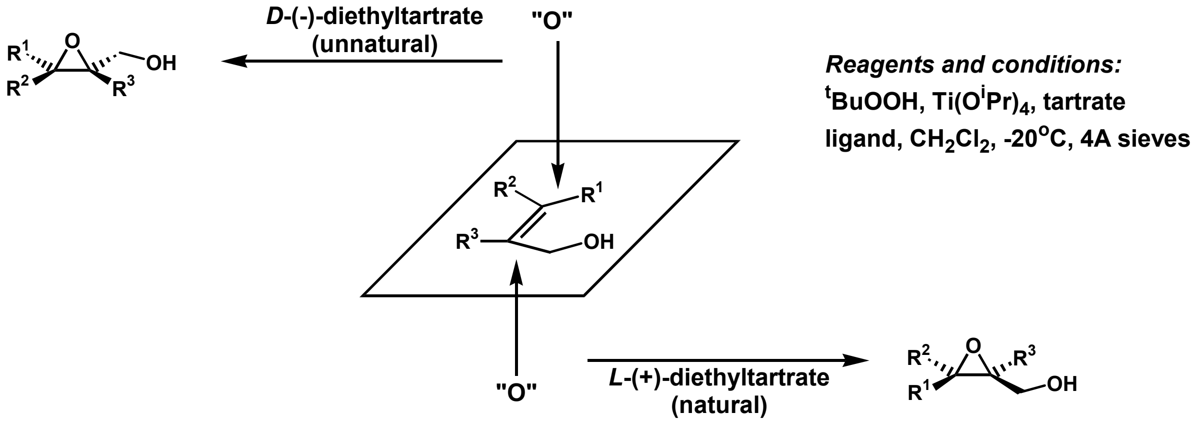


Not surprisingly, the addition of a metal bearing chiral ligands allows an asymmetric variant of this reaction: the ***Sharpless asymmetric epoxidation (AE) reaction***. Professor K Barry Sharpless (Scripps Research Institute, La Jolla) was awarded the 2001 Nobel Prize for this and his equally useful AD reaction (see later!)

The reagents for the reaction are ^tBuOOH, $Ti(O^iPr)_4$, (+) or (-)-diethyl tartrate and 4Å molecular sieves (essential for catalytic activity). Because the metal is bound directly to the hydroxyl group, very good levels of asymmetric induction are observed. The reaction is also extremely predictable - all examples to date fit the mnemonic shown on the scheme below.

This was really the first general, reliable and practical asymmetric reaction, and is done on industrial scale (hundreds of gallons). Nowadays there are also reagents which can epoxidise unfunctionalised olefins but they are neither as general nor as reliable as the Sharpless AE.

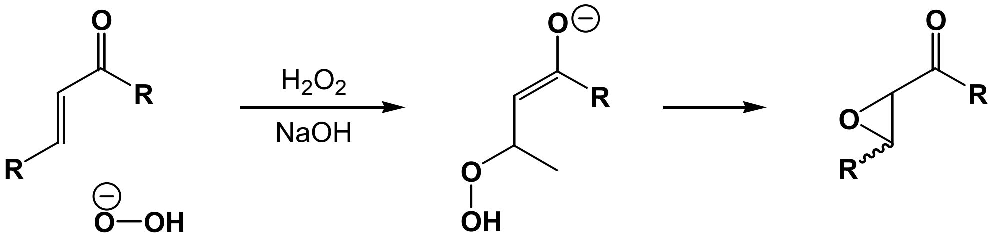
Katsuki-Sharpless asymmetric epoxidation of allylic alcohols



Reagents and conditions:
^tBuOOH, $Ti(O^iPr)_4$, tartrate ligand, CH_2Cl_2, -20°C, 4A sieves

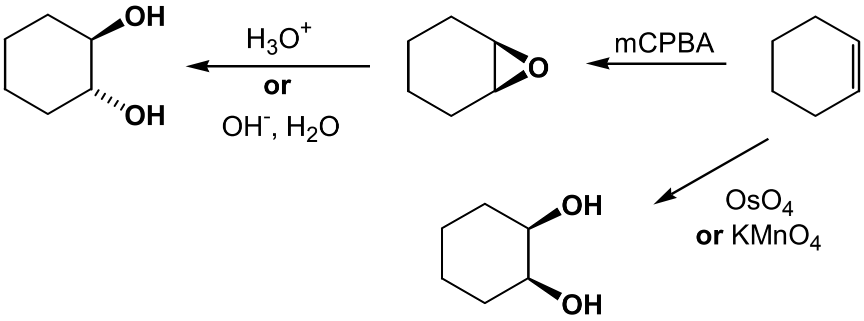
7.1.3 *Epoxidation of α,β-unsaturated carbonyl compounds*

These electron deficient alkenes don't react so well with electrophilic oxidants such as mCPBA, but they'll react nicely in a Michael fashion with peroxy anions. Intramolecular nucleophilic displacement furnishes the epoxide. Note that since we go through an enolate intermediate, the initial olefin geometry does not have to be preserved in the product.



7.2 *Formation of 1,2-diols*

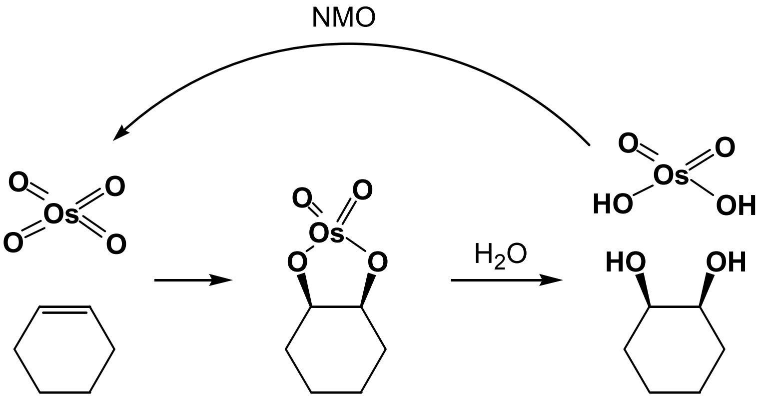
Ring opening of epoxides with acidic water gives rise to 'trans'-diols overall in two steps from alkenes. Perhaps more important are the reagents which will cis-dihydroxylate olefins directly in one step - alkaline permanganate and osmium tetroxide.

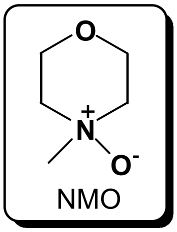


Both OsO_4 and $KMnO_4$ react *via* a similar mechanism, which is effectively a concerted cycloaddition to the alkene to generate a metal ester, which is then hydrolysed. We'll concentrate more on the osmium tetroxide, since this is the milder and more widely used agent.

Osmium tetroxide is a very toxic solid with a high vapour pressure, which makes it dangerous to handle. Its also very pricey, so its no surprise that people have sought co-oxidants capable of reoxidising the Os(VI) back to Os(VIII). NMO is often the co-oxidant of choice.

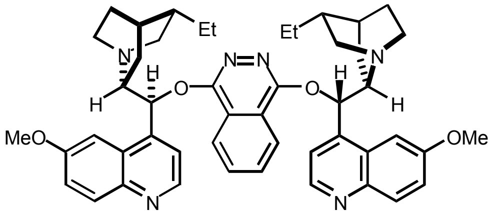
As discussed above, the reactions are stereospecific for cis-dihydroxylation of the olefin. They are also stereoselective - attack again occurs on the less hindered face of cyclic olefins. Electron rich alkenes generally react fastest.





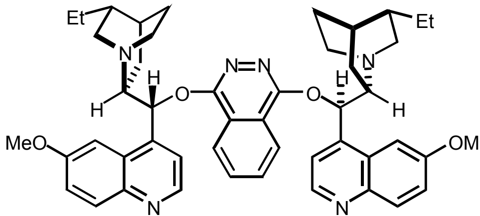
An asymmetric catalytic version of this reaction would be of great value. Guess who developed it? That man again - Sharpless. Actually the key discovery that enabled Sharpless to develop his system was made by Professor Griffith here at IC - that quinuclidines could accelerate the addition of OsO_4 to alkenes. Thus, add a chiral quinuclidine and you should get fast, asymmetric dihydroxylations. Aldrich now sells AD-mixes which contain the osmium, chiral ligand, co-oxidant and buffer for a reaction - just add water! OK, and tert-butanol and alkene.

Ligands for Sharpless asymmetric dihydroxylation, and mnemonic



$(DHQD)_2PHAL$

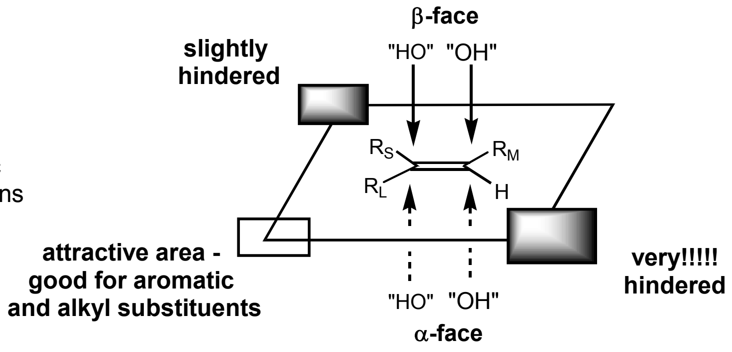
("β face" ligand)



$(DHQ)_2PHAL$

("α face" ligand)

mnemonic for predicting the sense of asymmetric induction in AD reactions

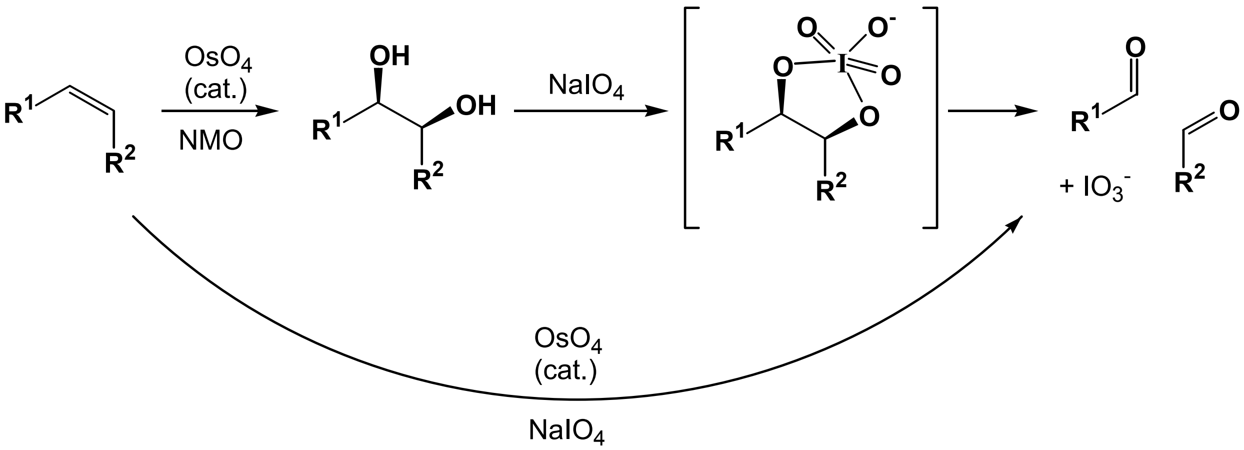


7.3 *Oxidative cleavage of alkenes*

Cleavage of alkenes is a useful reaction - we can use it to *e.g.* mask a carbonyl group through some reactions where they would normally react, or to manipulate an alkene created through another reaction such as a Diels-Alder reaction.

7.3.1 *Alkene cleavage via 1,2-diols*

One method of cleaving alkenes is via the 1,2-diols, commonly using periodate (either as periodic acid HIO_4 or sodium periodate $NaIO_4$). In fact, we can do the whole transformation in one pot if we use $NaIO_4$ as the co-oxidant for the OsO_4 dihydroxylation step (re-oxidising Os^{VI} to Os^{VIII}, i.e. regenerating OsO_4) as well as for the alkene cleavage.

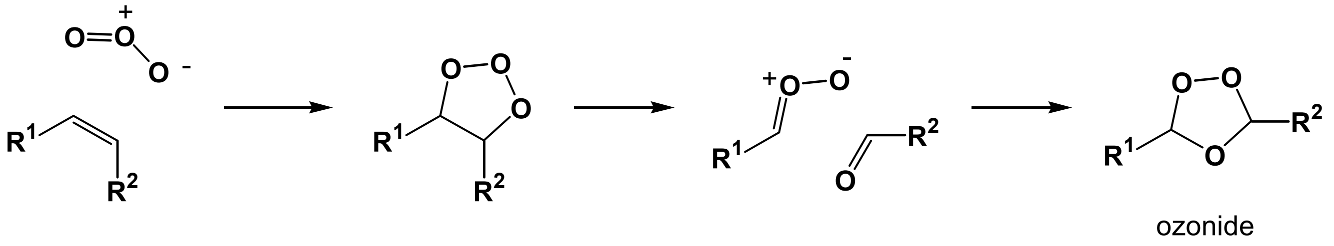


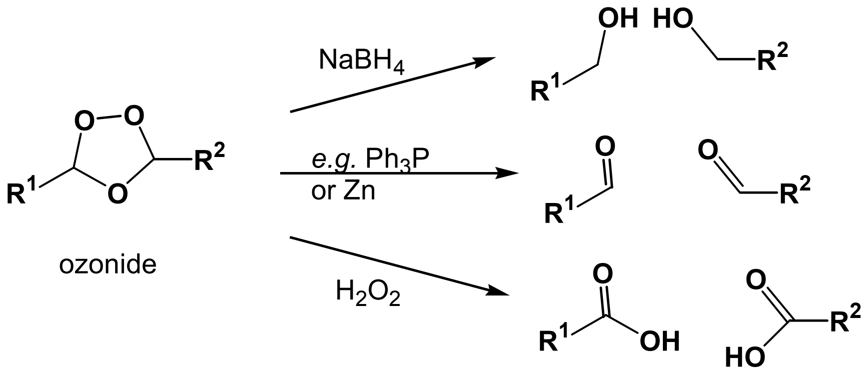
7.3.2 *Ozonolysis*

There are many reagents which will cleave alkenes, but most aren't selective only for alkene cleavage. Ozonolysis is one of the best methods for alkene bond cleavage. It is useful for both its experimental simplicity and the fact that one can manipulate the intermediates (ozonides) to give a range of products from a single precursor. Thus, treatment of secondary ozonides with sodium borohydride (care!) gives alcohols, mild reduction (with *e.g.* Zn or PPh_3) gives aldehydes/ketones and oxidative work-up with hydrogen peroxide gives carboxylic acids.

Ozone is prepared by passing an electrical discharge through a stream of oxygen, generating mixtures of 2-10% O_3 in O_2. Reactions are carried out in solvents such as CH_2Cl_2, AcOH or MeOH, often at 0^oC or below. Care is required as the ozonides are explosive! The reactions are often self-indicating, as the blue colour of ozone persists once the alkene is consumed.

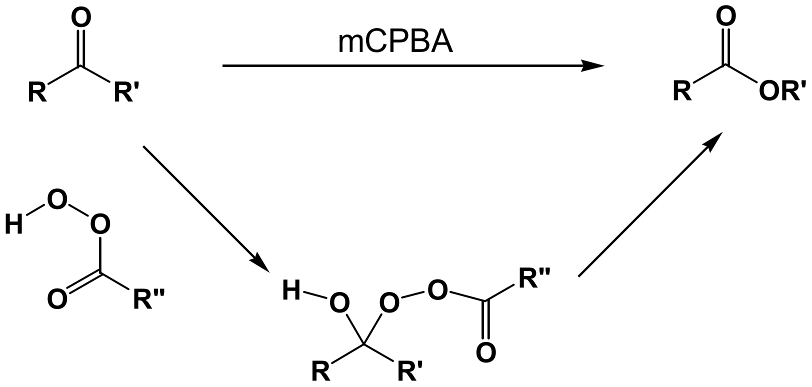
The mechanism involves [3+2] cycloaddition of the ozone to the olefin to give the primary ozonide; retro-[3+2] cycloaddition breaking a weak O-O bond to give a carbonyl and a carbonyl ylide (which can be trapped!); and finally [3+2]-cycloaddition in the reverse sense to generate the secondary ozonide. Note that ozone is electrophilic and will attack electron rich bonds preferentially.





7.4 *Oxidative cleavage of ketones*

The Baeyer-Villiger reaction, which you will have met in Dr Law's course in first year. The reagent is a peracid (usually mCPBA), and the reaction involves attack of the peracid on the ketone, followed by stereospecific migration of the alkyl group with retention of configuration to generate an ester. In unsymmetrical ketones, the order of migrating aptitude parallels roughly the ability to stabilise positive charge (3ry>2ry-phenyl-benzyl>1ry>>Me). The reaction works best with strained cyclic ketones, since the relief of ring strain helps to drive the reaction.



- migratory aptitudes: best positive charge stabilising group migrates
  ie H > tertiary alkyl > secondary alkyl > phenyl > primary alkyl >> methyl
- works very well for small ring ketones (cyclobutanones) or for bicyclic ketones: in both cases relief of ring strain drives the reaction
- reaction proceeds with retention of configuration at R'

Next time (Part 3: Wed 12th Jan 2005 at 11am): Protecting Groups

AA 18.11.04