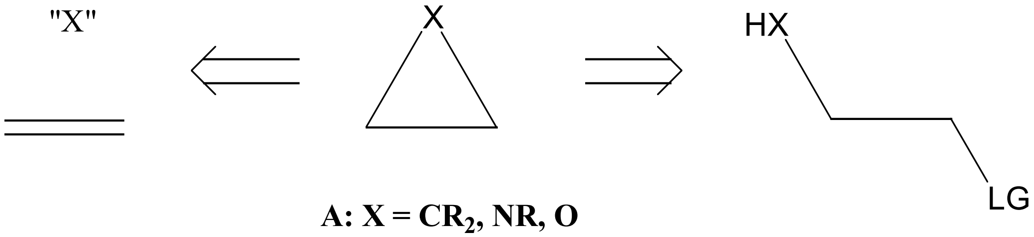
Alicyclic and Heterocyclic Chemistry. Lecture 5

Synthesis of three-membered rings (irreversible reactions only)

Because of the ring strain in three-membered rings they cannot be made in any sensible yield from open chain precursors by reversible reactions since any equilibrium would favour the open chain precursor rather than the cyclic compound.
If we represent cyclopropanes, epoxides and aziridines by the generic formula **A** then there are two main approaches to the syntheses of these compounds, namely, the addition of "X" to a double bond and the displacement of a neighbouring leaving group by anionic X^- derived from the parent XH compound:



A: X = CR_2, NR, O

Additions of "X" to a Double Bond

In each case "X" represents an atom bearing a sextet rather than octet of electrons which is therefore exceedingly reactive and a transient species. In the case of X=O such a species is not used but instead an equivalent to it is employed.

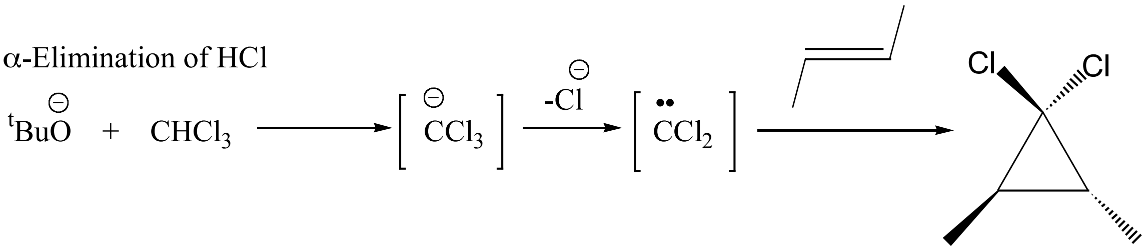
This approach includes the addition of carbenes or carbenoids (X = CR_2) to double bonds, the analogous addition of nitrenes (X = NR) and the formal addition of "oxene" (X = O) using a peracid as the equivalent of this species.

1. Carbene Additions.

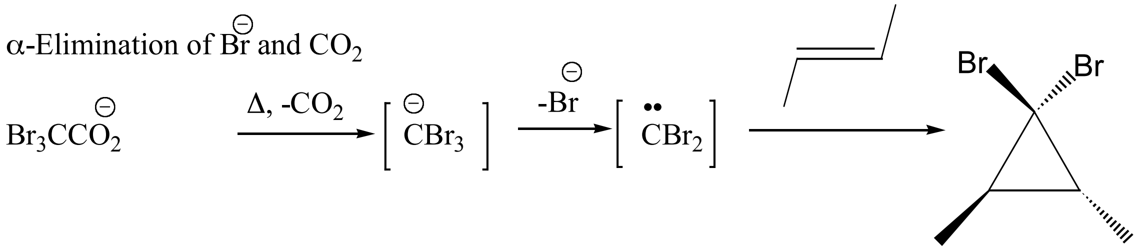
Since carbenes are transient species we must generate them in the presence of the alkene with which they will react. Thus, we must look at their generation as well as their reaction. Three general methods for producing carbenes are by the α-elimination of HX from halo compounds, the α-elimination of XY from substituted halo compounds and the α-elimination of N_2 from diazo compounds

Note below that whereas the additions of the dichlorocarbene and dibromocarbene are both stereospecific (the geometry of the double bond is retained in the product cyclopropane), that of ethoxycarbonylcarbene is not. The reasons for this difference will be explained in my course on reactive intermediates in the third year; suffice it to say at this point that dihalocarbenes add stereospecifically and most other carbenes give mixtures of stereoisomers.

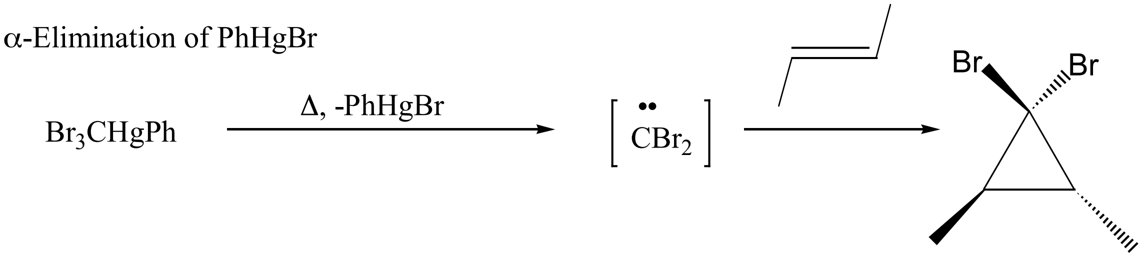
α-Elimination of HCl



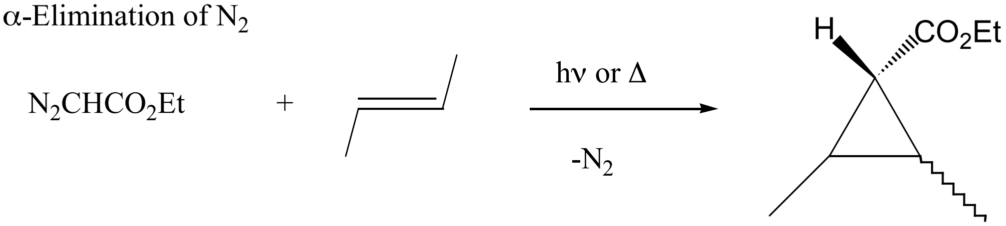
α-Elimination of $Br^{\ominus}$ and CO_2



α-Elimination of PhHgBr



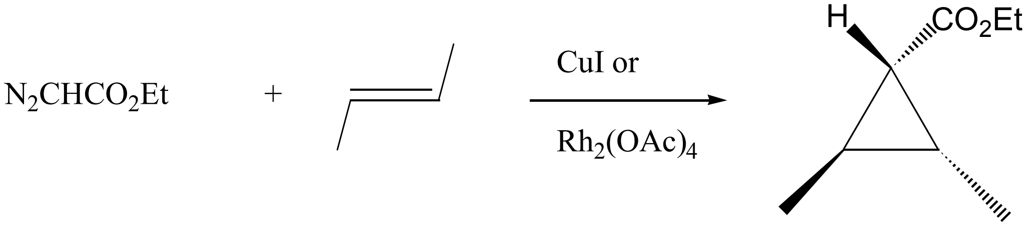
α-Elimination of N_2



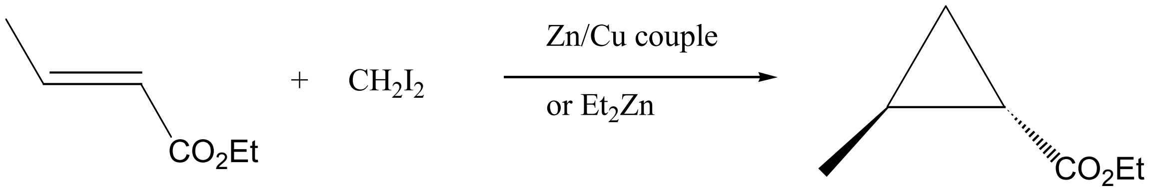
2. Additions of Carbenoids

When carbenes are complexed (very often in an indeterminate way) with metals they are called carbenoids and their reactivity is modified slightly; the most important modification is that carbenoids almost always add stereospecifically.

Carbenoids are most commonly generated from diazo compounds by treatment with Cu(I) salts or Rh(II) carboxylates:



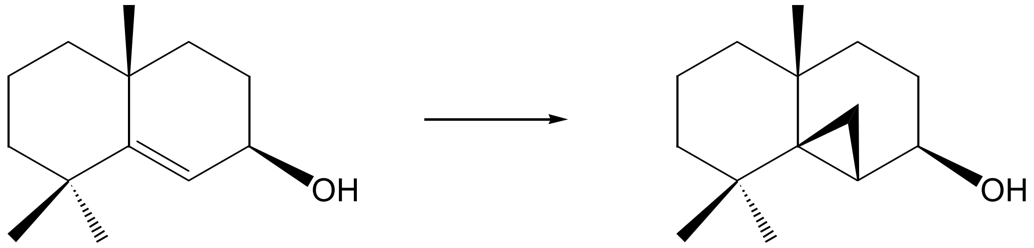
Another source of carbenoids is the Simmons-Smith reaction:



The mechanism of this reaction is still under investigation but evidence for the involvement of one of the zinc species in the following Schlenk-like equilibrium is strong:

$$2\ \mathrm{ICH_2ZnI} \rightleftharpoons \mathrm{(ICH_2)_2Zn.\ ZnI_2}$$

The active species commonly complexes with adjacent groups which can act as ligands to the zinc. In the following example the OH group delivers the CH_2 to the more hindered, upper face:



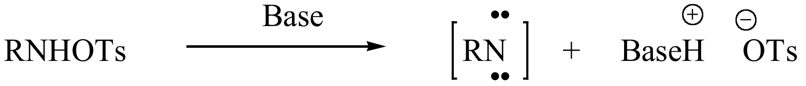
The Simmons-Smith reaction only works with the parent diiodide, CH_2I_2, and not with higher congeners, CR_2I_2, so that it can only be used to synthesize cyclopropanes which have at least one CH_2 group in the ring. It is, however, of very wide scope with respect to the alkene reactant.

3. Addition of Nitrenes

Nitrenes are, like carbenes, transient species and therefore are generated in the presence of the alkene trap in very similar ways to those used for the formation of carbenes i.e. by α-elimination reactions.

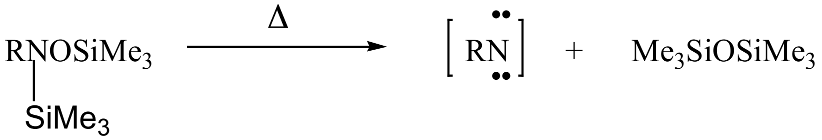
In the last two methods of generation, shown below, the reactions may be catalysed by transition metals when a nitrenoid may be invoked. However, the evidence for nitrenoids is less persuasive than for carbenoids.

α-Elimination of HX



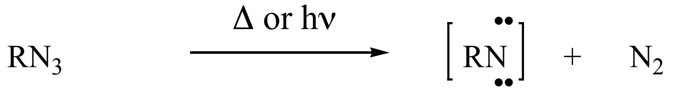
$$\mathrm{RNHOTs} \xrightarrow{\text{Base}} \left[\mathrm{R\ddot{N}}\right] + \overset{\oplus}{\mathrm{BaseH}}\ \overset{\ominus}{\mathrm{OTs}}$$

α-Elimination of XY

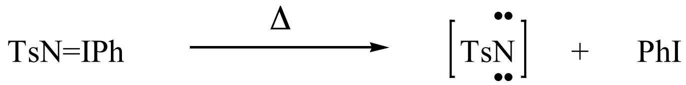


$$\mathrm{R\underset{SiMe_3}{N}OSiMe_3} \xrightarrow{\Delta} \left[\mathrm{R\ddot{N}}\right] + \mathrm{Me_3SiOSiMe_3}$$

α-Elimination of N_2 or PhI

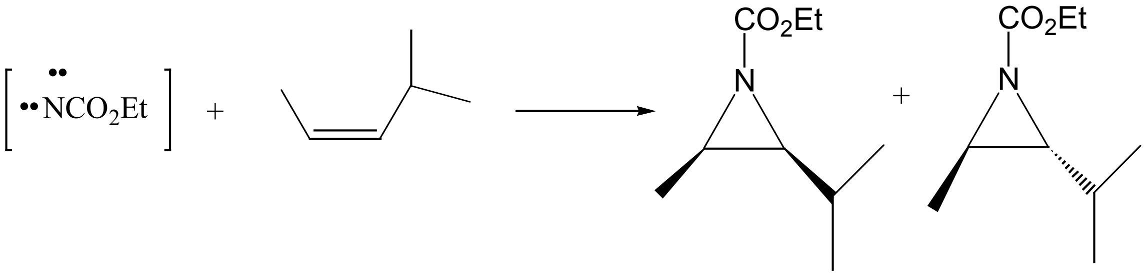


$$\mathrm{RN_3} \xrightarrow{\Delta \text{ or } h\nu} \left[\mathrm{R\ddot{N}}\right] + \mathrm{N_2}$$



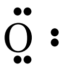
$$\mathrm{TsN{=}IPh} \xrightarrow{\Delta} \left[\mathrm{Ts\ddot{N}}\right] + \mathrm{PhI}$$

Nitrenes generally react in a non-stereospecific fashion:



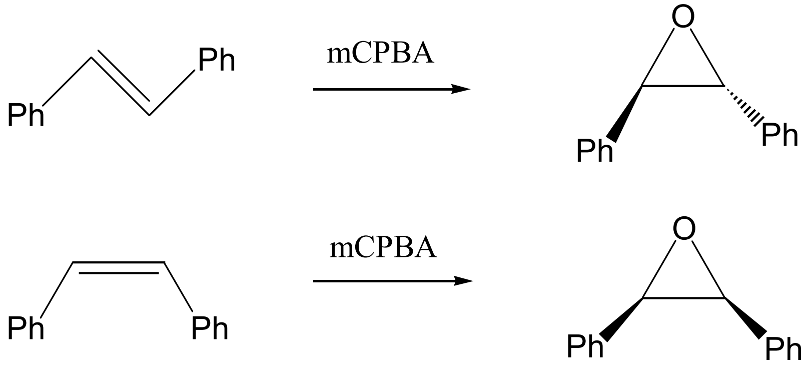
4. Epoxidation

Epoxidation is the formal addition of the unknown “oxene”:

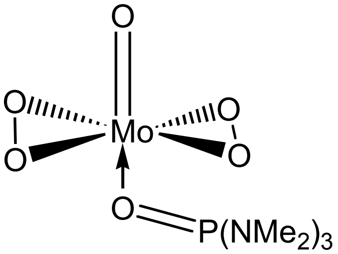


$$\mathrm{\ddot{O}:}$$

The most common reagents which transfer oxygen to double bonds to produce epoxides are peracids (sometimes called peroxyacids) and combinations of peroxides and transitions metals. You should already be familiar with the use of monochloro-perbenzoic acid (mCPBA) which reacts with alkenes stereospecifically:

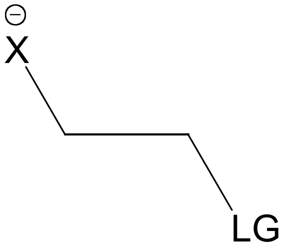


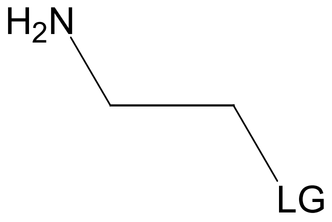
The combinations of transition metals with peroxy compounds are various but the compound made from Mo(VI), hexamethylphosphoramide and hydrogen peroxide is useful for the epoxidation of a wide range of alkenes:



Displacements of a Neighbouring Group (Intramolecular S_N2 Reaction)

As noted above all these processes have a nucleophilic group, X (a carbanion, amine or alkoxy anion) in the same molecule as a leaving group:





$X = CR_2$ or O

The synthesis of the anionic precursors (carbanion or alkoxy anion) follows two main routes, either deprotonation of the conjugate acid or nucleophilic addition to an unsaturated precursor.