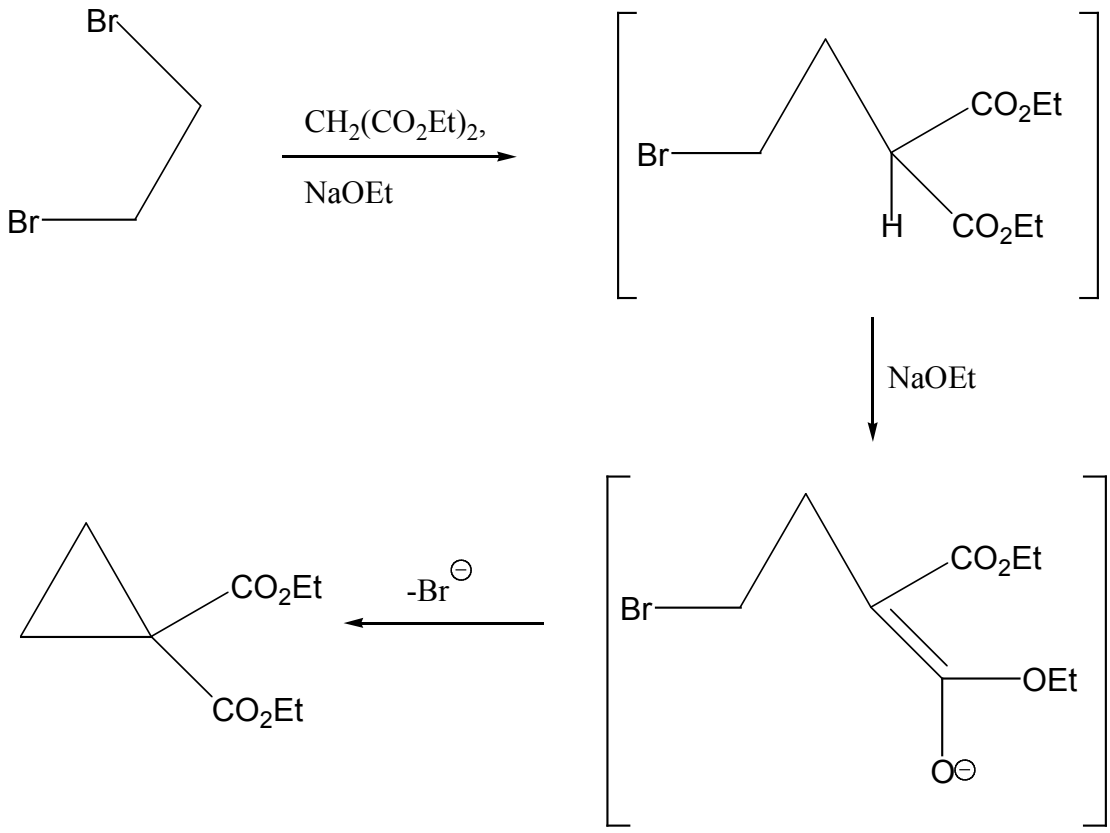
Alicyclic and Heterocyclic Chemistry. Lecture 6

Synthesis of three-membered rings (irreversible reactions only) contd

1. Deprotonation of the Conjugate Acid

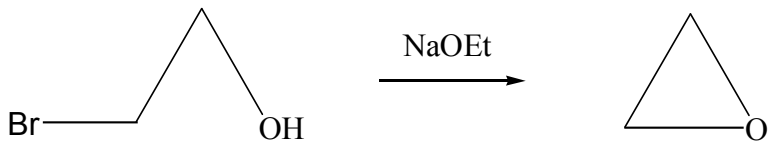
Good examples of this are the Perkin Synthesis (not to be confused with the unrelated Perkin Reaction) of cyclopropanes and the synthesis of epoxides from β-hydroxy halides.

Perkin Synthesis:



The group Br in this synthesis can be replaced by another good leaving one such as Cl, I, OTs, R_2S^+ or epoxide C-O etc. The two ester groups may be replaced by one or more groups which can stabilise an adjacent carbanion such as CN, COR, 2 x Ph, SO_2Ph, NO_2, Ph_3P^+ etc.

Epoxide synthesis:

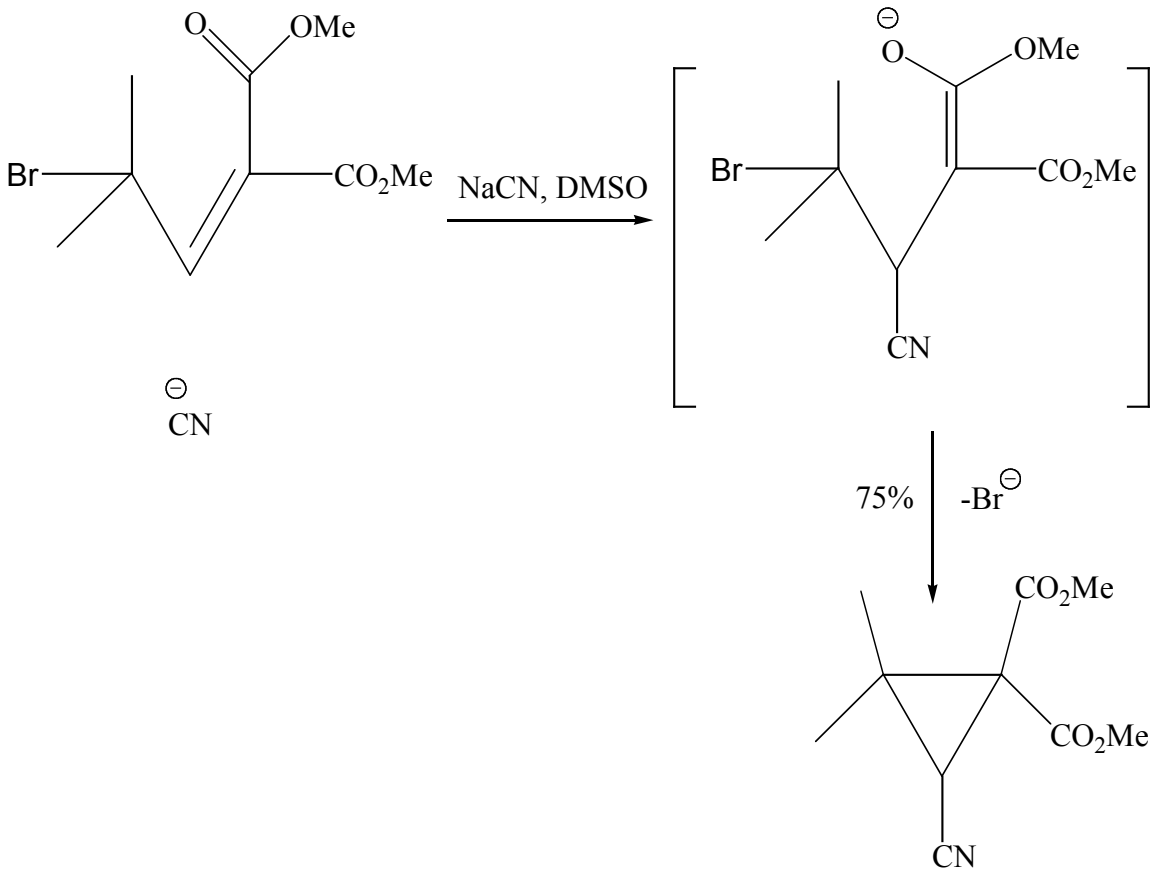


Again Br may be replaced by another good leaving group.

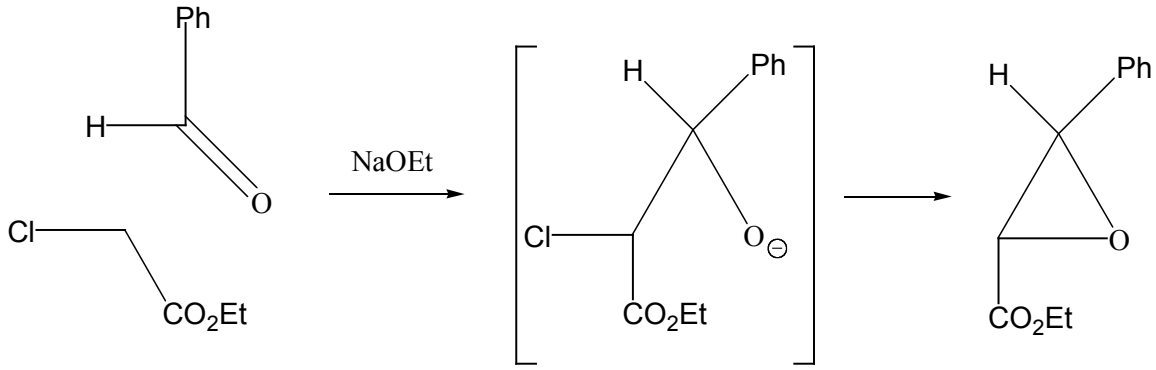
2. Addition of a Nucleophile to an Unsaturated Precursor

The nature of the nucleophile and the precursor may be quite diverse as the following examples show.

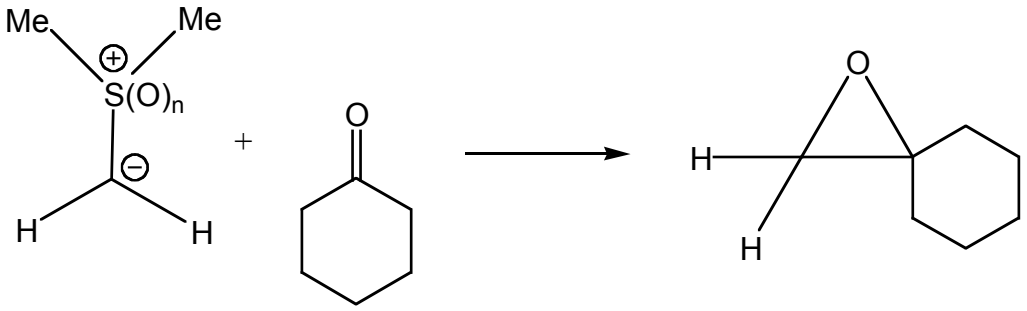
Cyclopropane synthesis:



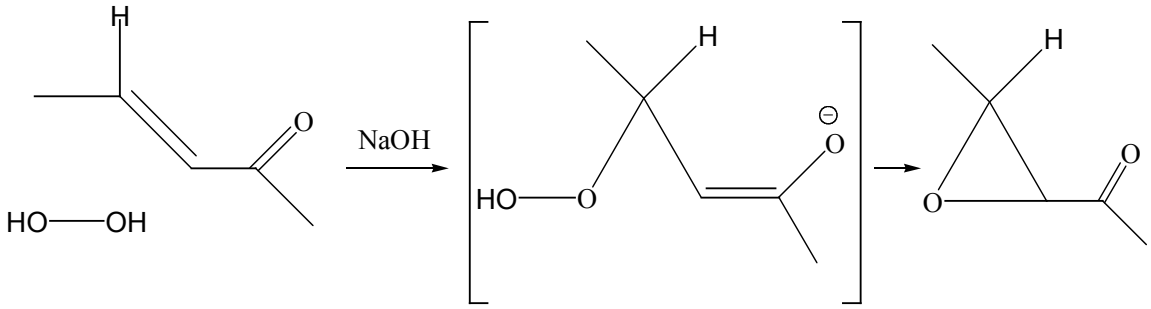
Epoxide synthesis (Darzen's Glycidic Ester Synthesis):



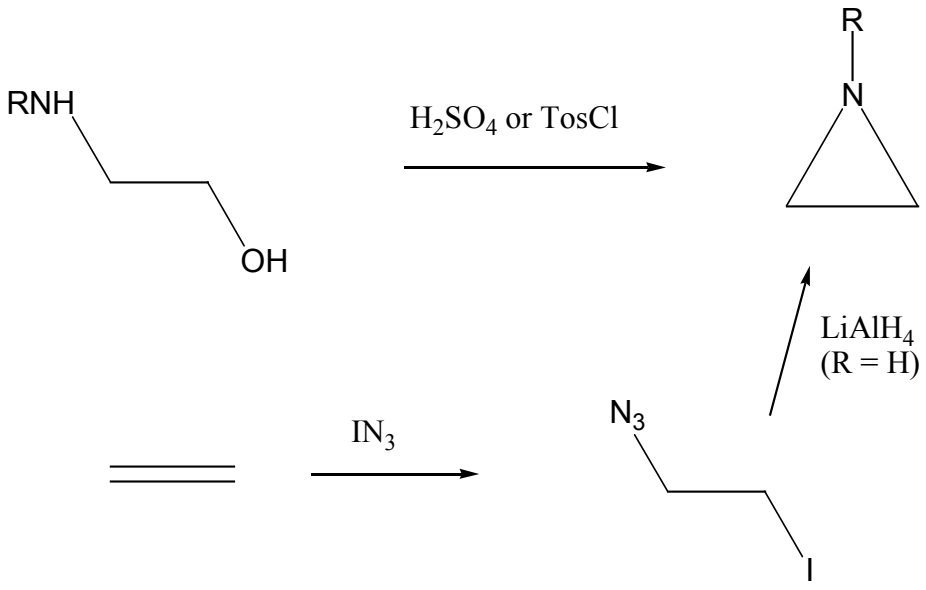
A related, more modern reaction, equivalent to the Darzen's synthesis, uses a sulphonium (n = 0 below) or sulphoxonium (n =1 below) ylide where the sulphonium or sulphoxonium group acts as the leaving group instead of chloride in the Darzen's process. Here there is no need to have an electron withdrawing ester next to the leaving group:



Epoxide synthesis:



Aziridine synthesis: The synthesis of the corresponding aziridines is similar but here an amino group beta to a leaving group is usually sufficiently nucleophilic to displace the halide without the need to generate an anion.

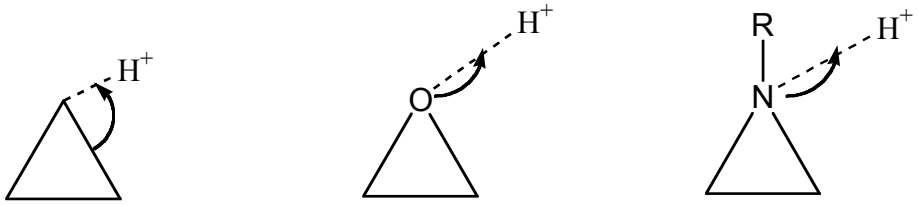


Reactivity of Cyclopropanes, Oxiranes and Aziridines

Because of the ring strain in these compounds they are most susceptible to ring opening which may occur by electrophilic reaction, concerted reaction (cyclopropanes only), nucleophilic reaction, cheletropic reaction (aziridines only) and electrocyclic reaction.

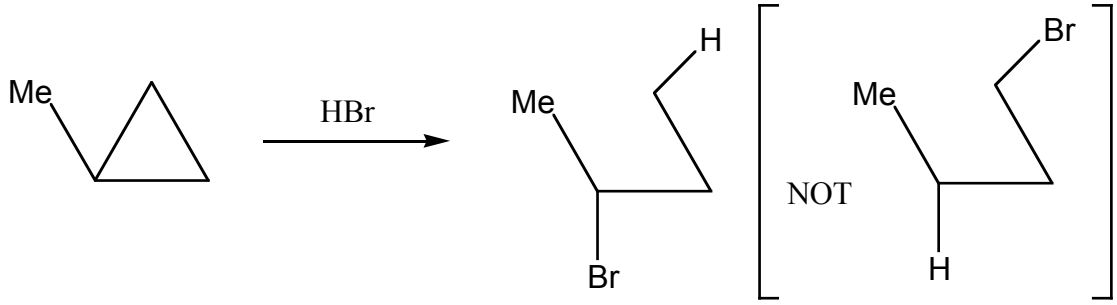
Electrophilic Ring Opening

Electrophiles must attack cyclopropanes at the C-C bonds whereas for epoxides and aziridines the presence of lone pairs of electrons on the heteroatoms make these atoms the sites of attack on the heterocyclic compounds.

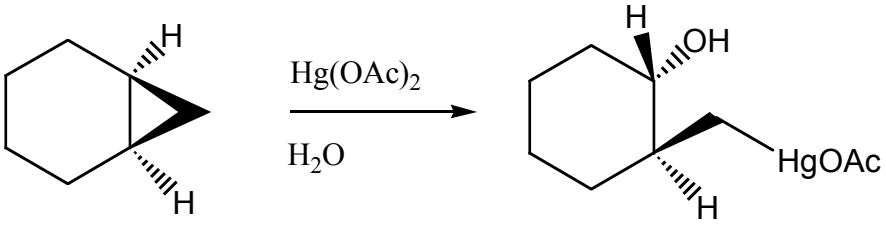


In every case the ultimate result is the breaking of a bond (C-C, C-O or C-N) in the ring.

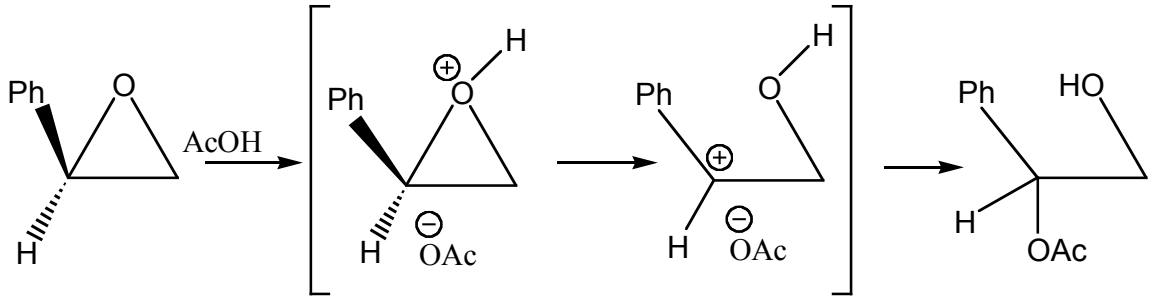
Cyclopropanes: Because of the π-like nature of the C-C bonds, cyclopropanes behave to some extent like alkenes and suffer electrophilic attack. Just as for alkenes such attack occurs in a Markovnikov manner:



The reaction also proceeds with inversion of configuration in many cases so that a free carbocation is probably not formed but rather an ion pair:

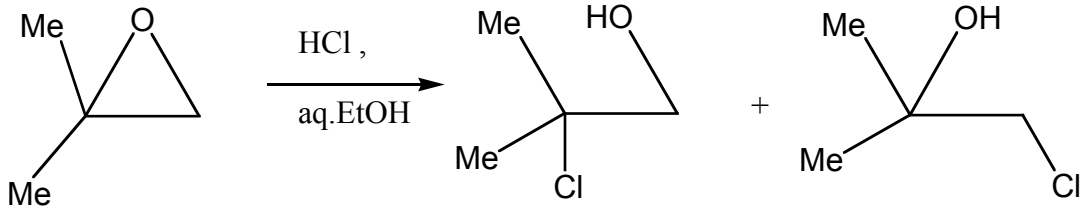


Epoxides: With epoxides the electrophile (usually H^+ but may be Lewis acids) attacks the oxygen first, making the C-O bonds more susceptible to cleavage. The regiochemistry of the subsequent attack, however, is not as simple as with cyclopropanes. With aryl epoxides the reaction proceeds through most stable carbocation as expected:



(Ion pair formation is again implicated in this case since the product is not totally racemised).

However, with alkyl epoxides the regiochemistry is not so clear-cut with one quarter of the product mixture being derived by S_N2 attack on the protonated epoxide which favours a less hindered approach by the chloride anion:



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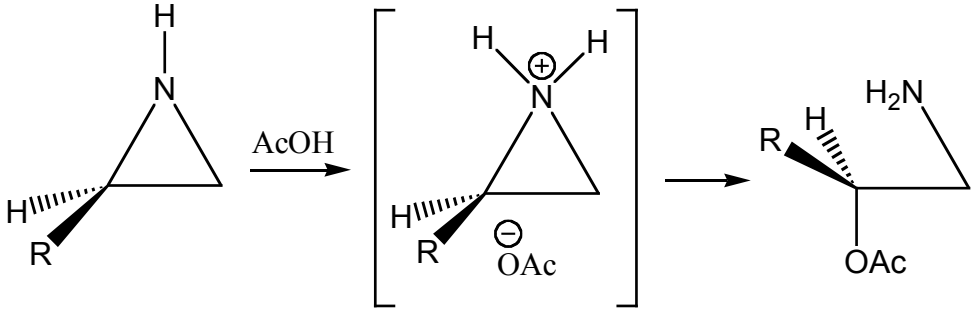
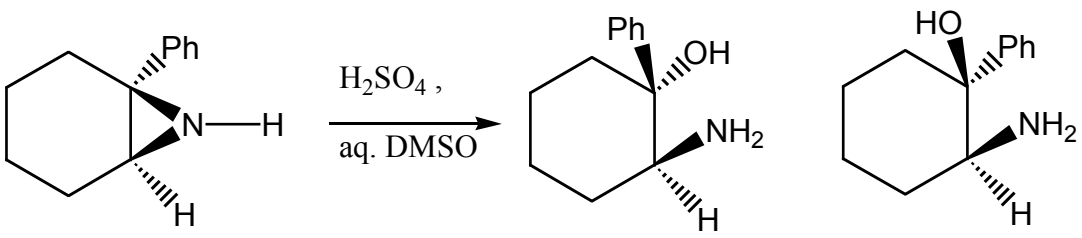
Aziridines: Protonation of the nitrogen of aziridines also weakens the adjacent (C-N) bonds but the relative stability of ammonium salts over oxonium salts means that carbocations are not formed in the acid-catalysed ring opening of aziridines which undergo generally clean S_N2 cleavages:



For example:



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