Important Heterocyclic Systems

The description of each heterocyclic system is then arranged under the following headings:

A structure, physical properties, and spectroscopic properties

B chemical properties and reactions

C Synthesis

D important derivatives, natural products, drugs, biologically active compounds, and industrial intermediates

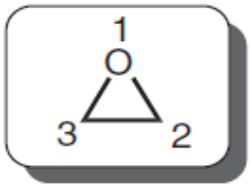
E use as reagents, building-blocks, or auxiliaries in organic synthesis.

Three-Membered Heterocycles

The properties of three-membered heterocycles are mostly a result of the great bond angle strain (BAEYER strain). The resultant ring strain imparts to the compounds high chemical reactivity. Ring opening leading to acyclic products is typical. As set out above, the heterocycles will be treated in decreasing priority, starting with those with one heteroatom.

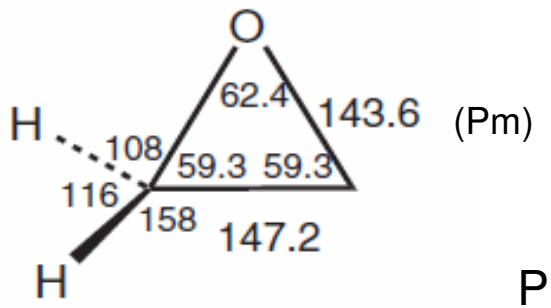
The parent system of the three-membered heterocycles with one oxygen atom is oxirene [1]; the corresponding saturated heterocycle is oxirane.

Oxirane



Oxiranes are also known as *epoxides*. Microwave spectra as well as electron diffraction studies show that the oxirane ring is close to being an equilateral triangle (see Figure 3.1a).

The strain enthalpy was found to be 114 kJ mol^{-1}. The ionization potential is 10.5 eV; the electron which is removed derives from a nonbonding electron pair of the O-atom. The dipole moment is 1.88 D with the negative end of the dipole on the O-atom. The UV spectrum of gaseous oxirane has $\lambda_{max} = 171$ nm ($\lg \varepsilon = 3.34$). The chemical shifts in the NMR spectrum are $\delta_H = 2.54$, $\delta_C = 39.7$. With a rise in the s-orbital component of the relevant C–H bonds, the ^{13}C–H coupling constant increases. The value of 176 Hz for oxirane is much greater than for aliphatic CH_2 groups. To explain this fact, one can imagine that the bonding MO of the C–O bonds are formed by interaction of the HOMO of an ethene molecule with an unoccupied AO of an O-atom, and also through interaction of the LUMO of the ethene molecule with an occupied AO of the O-atom (see Figure 3.1b).



(Pm)

Pm (Picometer): 10^{-12} m

The dipole moment is 1.88 D with the negative end of the dipole on the O-atom.

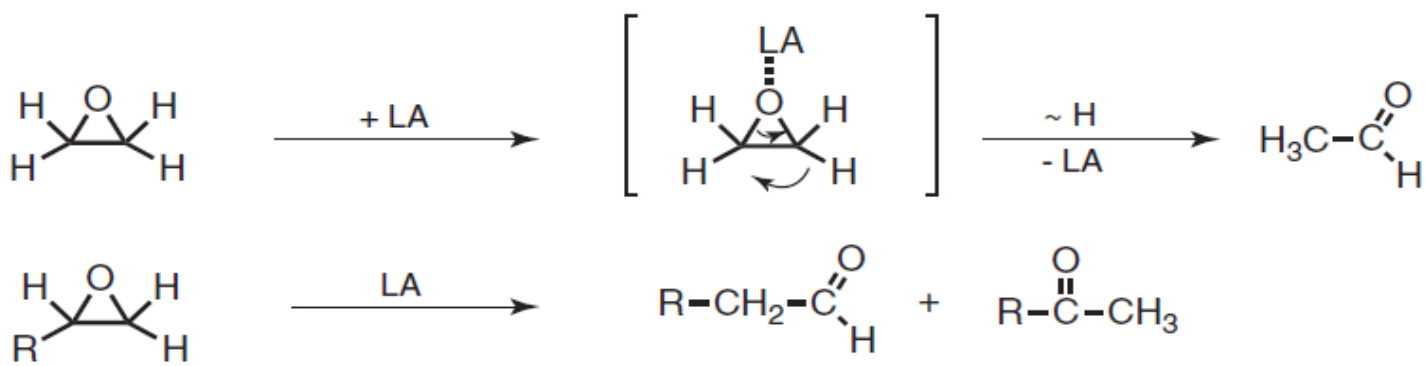
in the NMR spectrum are $\delta_H = 2.54, \delta_C = 39.7$.

Chemical properties of Oxirane

Apart from ring strain, a significant property of oxiranes is their BRÖNSTED and LEWIS basicity, for which the nonbonding electron pairs on the O-atom are responsible. When handling oxiranes, it should also be borne in mind that many of them are carcinogenic. The most important reactions of oxiranes are described below.

Isomerization to carbonyl compounds

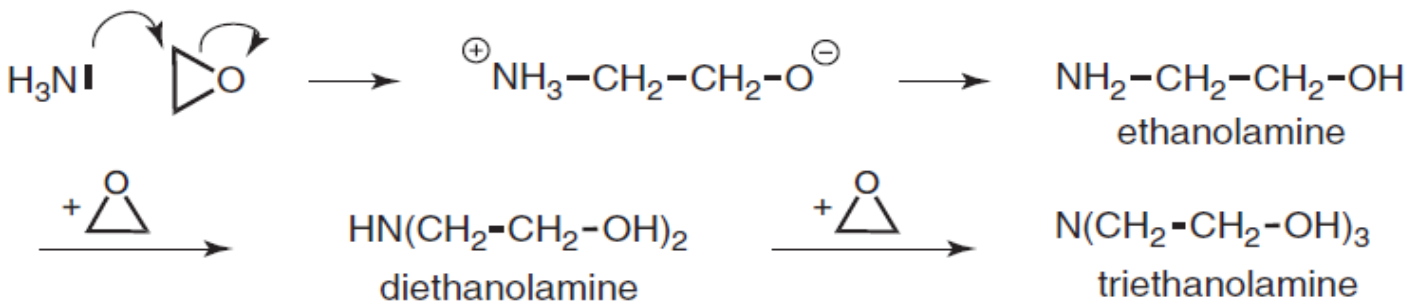
In the presence of catalytic amounts of LEWIS acids, for example, boron trifluoride magnesium iodide, or nickel complexes, oxiranes isomerize to give carbonyl compounds Oxirane itself gives acetaldehyde; mono-substituted oxiranes yield mixtures of aldehydes and ketones:



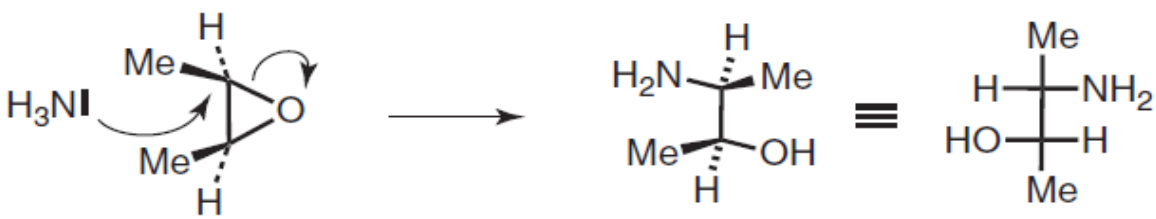
The nickel(II) complex $NiBr_2$ $(PPh_3)_2$ yields aldehydes regioselectively [2].

Ring-opening reactions

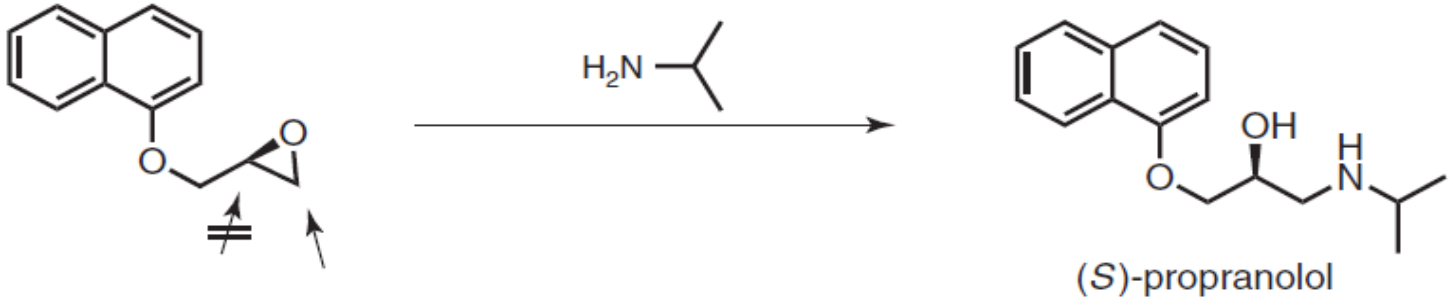
(a) N-Nucleophiles, for example, ammonia or amines, cause ring-cleavage of oxiranes to give amino alcohols, for example:



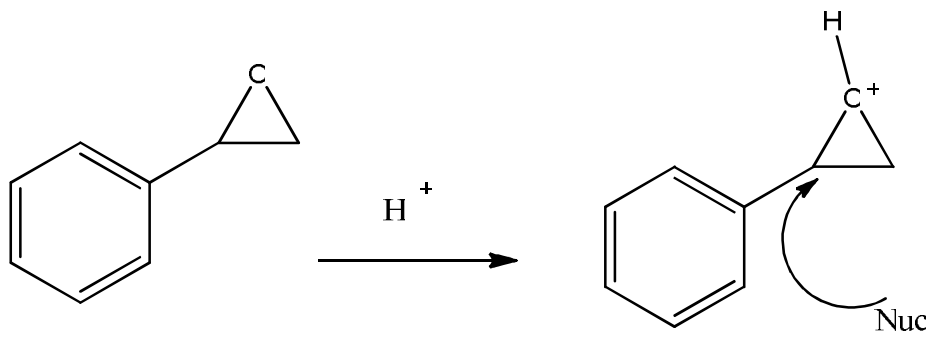
This process occurs as a concerted reaction, is stereospecific, and thus corresponds to the S_N2 mechanism of nucleophilic substitution at an sp^3-C-atom. For example, from *cis*-2,3-dimethy-l-oxirane, (±)-*threo*-3-aminobutan-2-ol is obtained by reaction with NH_3:



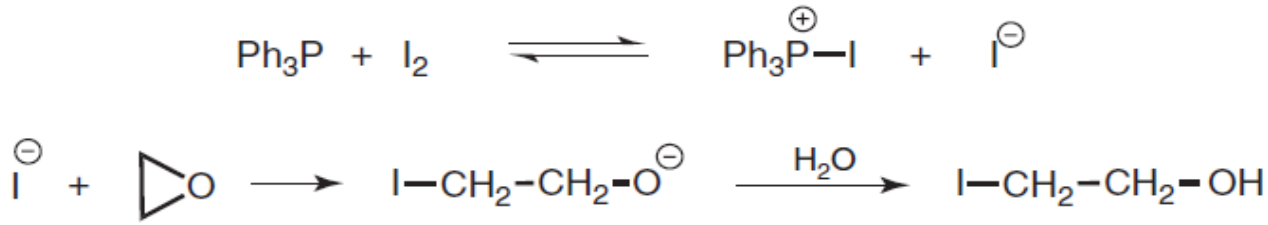
In unsymmetrically substituted oxiranes, ring-opening by attack of N-nucleophiles often proceeds via the less substituted oxirane C-atom, as illustrated by the key step of the synthesis of (*S*)-propranolol, a medicinally applied β-blocking agent [3]:



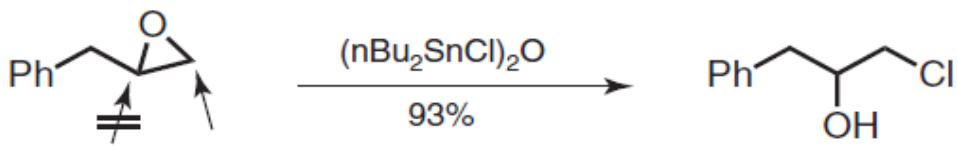
In Lewis acid-promoted reactions of styrene oxide with various amines, the site of ring-opening is dependent on the nature of the attacking nucleophile and of the Lewis acid catalyst [4].



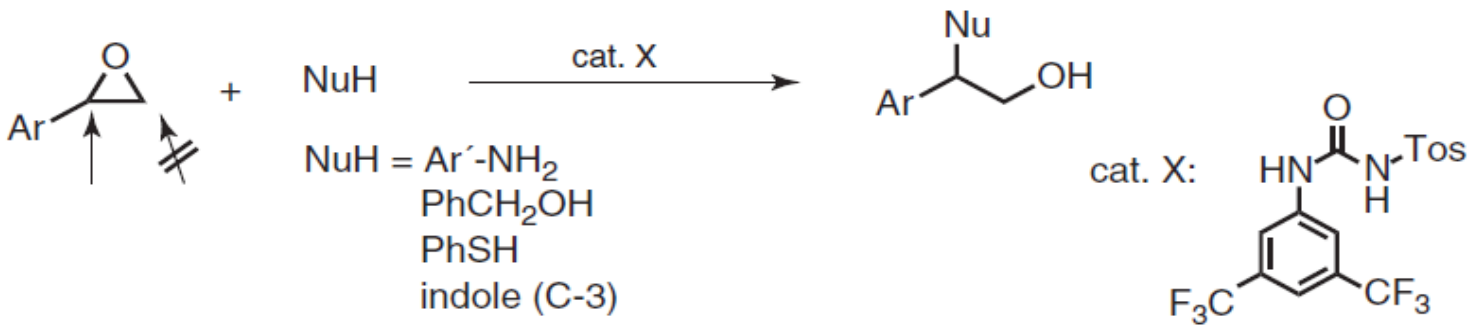
(b) Halogens react with oxiranes in the presence of triphenylphosphane or with lithium halides in the presence of acetic acid to give β-halo alcohols (halohydrins) [5], for example:



(c) The tin halide bis(chlorodibutyl)tin oxide effects regioselective conversion of mono-substituted oxiranes to CH_2-substituted chlorohydrins [6], for example:

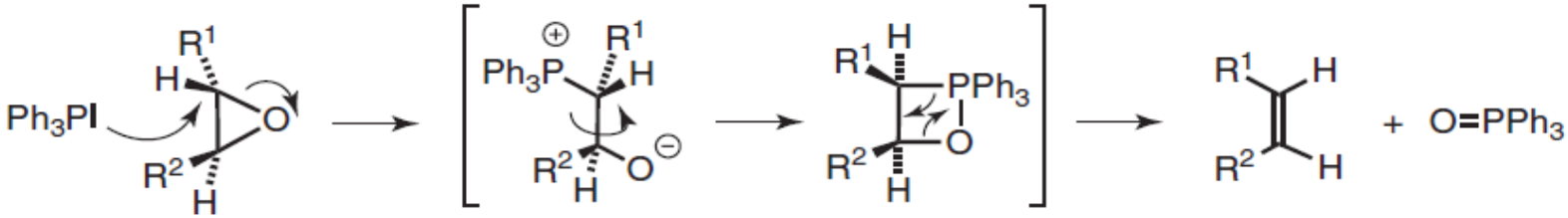


(d) The *N*-aryl-*N*′-tosyl urea **X**, designed as a tailor-made organocatalyst in a computer-led study [7], promotes regioselective ring-opening of aryl oxiranes by various N-, O-, S-, and C-nucleophiles through directed attack at the aryl-substituted oxirane position:



Deoxygenation to olefins

A number of reagents transform oxiranes to olefins with deoxygenation [10]. For instance, a *trans*-oxirane yields a (*Z*)-olefin on treatment with triphenylphosphane at 200 °C:



Since *trans*-oxiranes are stereoselectively formed from *trans*-olefins (cf. p. 23), the deoxygenation process allows the conversion of an (*E*)-olefin to a (*Z*)-olefin.