16.9
Preparation of Epoxides:
A Review and a Preview
Epoxides are prepared by two major methods. Both begin with alkenes.

- Reaction of alkenes with peroxy acids (Section 6.18)
- Conversion of alkenes to vicinal halohydrins, followed by treatment with base (Section 16.10)
16.10
Conversion of Vicinal Halohyrdrins to Epoxides
Example

\[
\text{H} \quad \text{OH} \quad \text{Br} \quad \text{H} \quad \text{H} \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\]

\[
\text{NaOH} \quad \text{H}_2\text{O} \quad \text{O} \quad \text{O}
\]

(81%)
Example

via:

\[ \text{NaOH} \rightarrow (81\%) \]
Epoxidation via Vicinal Halohydrins

\[ \text{Br}_2 \xrightarrow{\text{H}_2\text{O}} \]
Epoxidation via Vicinal Halohydrins

\[
\text{Br}_2 + \text{H}_2\text{O} \rightarrow \underset{\text{anti addition}}{\text{Br}} \underset{\text{inversion}}{\text{OH}} \rightarrow \text{NaOH} \rightarrow \text{O}
\]

corresponds to overall syn addition of oxygen to the double bond
Epoxidation via Vicinal Halohydrins

 corresponds to overall syn addition of oxygen to the double bond
Epoxidation via Vicinal Halohydrins

H₃C
\[\text{anti addition}\]
H
\[\text{inversion}\]
H
\[\text{corresponds to overall syn addition of oxygen to the double bond}\]
16.11
Reactions of Epoxides:
A Review and a Preview
Reactions of Epoxides

All reactions involve nucleophilic attack at carbon and lead to opening of the ring.

An example is the reaction of ethylene oxide with a Grignard reagent (discussed in Section 15.4 as a method for the synthesis of alcohols).
Reaction of Grignard Reagents with Epoxides
Example

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{MgCl} & \quad + \quad \text{C}_2\text{H}_4\text{O} \\
& \quad \quad \downarrow \\
& \quad \quad \quad \text{1. diethyl ether} \quad \quad \quad \text{2. H}_3\text{O}^+ \\
& \quad \quad \downarrow \\
\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} & \quad \quad (71\%) 
\end{align*}
\]
Reactions of epoxides involve attack by a nucleophile and proceed with ring-opening.

For ethylene oxide:

\[
\text{Nu—H} + \text{H}_2\text{C—O—CH}_2 \rightarrow \text{Nu—CH}_2\text{CH}_2\text{O—H}
\]
In general...

For epoxides where the two carbons of the ring are differently substituted:

Nucleophiles attack here when the reaction is catalyzed by acids:

Anionic nucleophiles attack here:
16.12
Nucleophilic Ring-Opening
Reactions of Epoxides
Example

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{O} & \quad \text{O} \\
\downarrow & \\
\text{NaOCH}_2\text{CH}_3 & \quad \text{CH}_3\text{CH}_2\text{OH} \\
\downarrow & \\
\text{CH}_3\text{CH}_2\text{O} & \quad \text{CH}_2\text{CH}_2\text{OH} \\
(50%) & 
\end{align*}
\]
Mechanism

\[ \text{CH}_3\text{CH}_2\text{-}\text{O} \rightarrow \text{H}_2\text{C} - \text{CH}_2 \text{O} \]

\[ \text{CH}_3\text{CH}_2\text{-}\text{O} - \text{CH}_2\text{CH}_2\text{-}\text{O} \]
Example

\[
\begin{align*}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{O} & \\
\downarrow & \\
\text{KSCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \\
\text{ethanol-water, 0°C} & \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S} & \text{CH}_2\text{CH}_2\text{OH} \\
\text{(99%)} & 
\end{align*}
\]
Inversion of configuration at carbon being attacked by nucleophile

Suggests $S_N2$-like transition state
Stereochemistry

Inversion of configuration at carbon being attacked by nucleophile

Suggests $S_N2$-like transition state

(70%)
Stereochemistry

\[ \text{Reactant} \xrightarrow{\text{NH}_3, \text{H}_2\text{O}} \text{Product} \]

\((70\%)\)
Anionic nucleophile attacks less-crowded carbon

consistent with \( S_N2 \)-like transition state

(53%)
Anionic nucleophile attacks less-crowded carbon

\[
\text{MgBr} + \text{H}_2\text{C} = \text{CHCH}_3 \Rightarrow \text{CH}_2\text{CHCH}_3\text{OH}
\]

1. diethyl ether
2. \(\text{H}_3\text{O}^+\)

(60%)
Lithium aluminum hydride reduces epoxides

$$\text{H}_2\text{C} - \text{CH}((\text{CH}_2)_7\text{CH}_3)$$

Hydride attacks less-crowded carbon

1. LiAlH$_4$, diethyl ether
2. H$_2$O

$$\text{H}_3\text{C} - \text{CH}((\text{CH}_2)_7\text{CH}_3)$$

(90%)
16.13
Acid-Catalyzed Ring-Opening Reactions of Epoxides
Example

\[ \text{H}_2\text{C} - \text{CH}_2 - \text{O} \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{H}_2\text{SO}_4, \ 25^\circ\text{C} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH} \]

(87-92%)

\[ \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3 \quad \text{formed only on heating and/or longer reaction times} \]
Example

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{O} & \\
\text{HBr} & \quad 10^\circ\text{C} \\
\text{BrCH}_2\text{CH}_2\text{OH} & \\
(87-92\%) & \\
\end{align*}
\]

\text{BrCH}_2\text{CH}_2\text{Br} \text{ formed only on heating and/or longer reaction times}


Mechanism
Mechanism

H₂C—CH₂

Br

H₂C—CH₂

Br

CH₂CH₂—O—H
Figure 16.6
Acid-Catalyzed Hydrolysis of Ethylene Oxide

Step 1
Figure 16.6
Acid-Catalyzed Hydrolysis of Ethylene Oxide
Figure 16.6
Acid-Catalyzed Hydrolysis of Ethylene Oxide

Step 3

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{O} & \rightarrow \text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]
Acid-Catalyzed Ring Opening of Epoxides

Characteristics:

- Nucleophile attacks more substituted carbon of protonated epoxide.
- Inversion of configuration at site of nucleophilic attack.
Nucleophile attacks more-substituted carbon

consistent with carbocation character at transition state

(76%)
Stereochemistry

Inversion of configuration at carbon being attacked by nucleophile

Inversion of configuration at carbon being attacked by nucleophile

(73%)
Stereochemistry

Inversion of configuration at carbon being attacked by nucleophile

(57%)
Stereochemistry

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H} \\
\text{H} & \quad \text{R} \\
\text{R} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{H}
\end{align*}
\]

\[\text{CH}_3\text{OH}\] \quad \text{H}_2\text{SO}_4

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{H} \\
\text{H} & \quad \text{R} \\
\text{S} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{H} \\
\text{H} & \quad \text{R} \\
\text{S} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
\]
anti-Hydroxylation of Alkenes

\[
\text{CH}_2=\text{CHH}_2 \xrightleftharpoons{\text{CH}_3\text{COOH}} \xrightarrow{\text{H}_2\text{O}, \text{HClO}_4} \text{HO-CHCH}_2\text{CHCH}_2\text{OH}
\]

(80%)