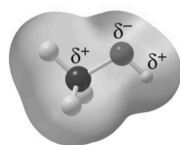
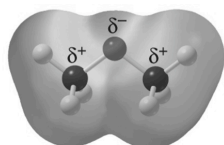


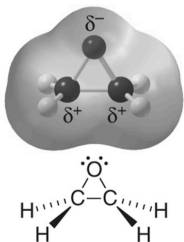
# Alcohols, Ethers, & Epoxides



CH<sub>3</sub>OH



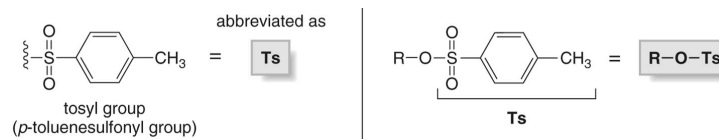
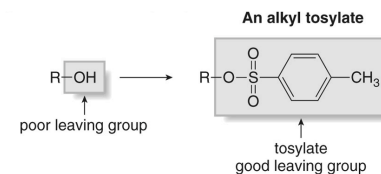
CH<sub>3</sub>OCH<sub>3</sub>



Chapter 9

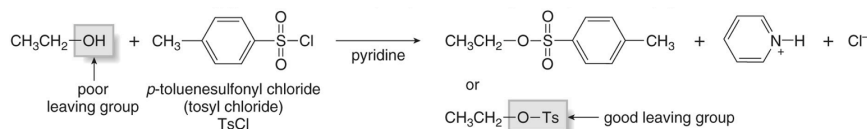
## Tosylate as Leaving Group (Review)

- Alcohols can be converted into alkyl tosylates.
- An alkyl tosylate is composed of two parts: the alkyl group R, derived from an alcohol; and the tosylate (short for *p*-toluenesulfonate), which is a good leaving group.
- A tosyl group, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub><sup>-</sup>, is abbreviated Ts, so an alkyl tosylate becomes ROTs.



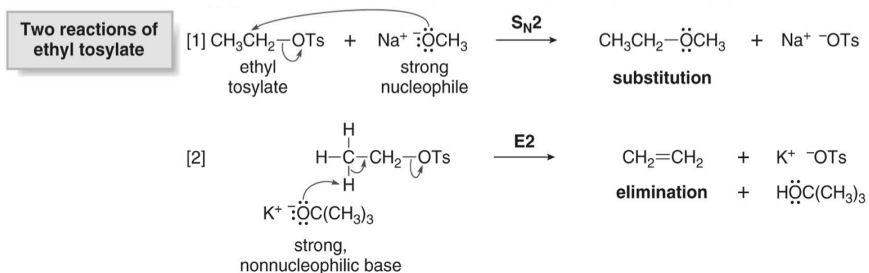
## Formation and Use of Tosylates (Review)

- Alcohols are converted to tosylates by treatment with *p*-toluenesulfonyl chloride (TsCl) in the presence of pyridine.
- This process converts a poor leaving group (-OH) into a good one (-OTs).
- Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H, TsOH) is a strong acid (pK<sub>a</sub> = -7).



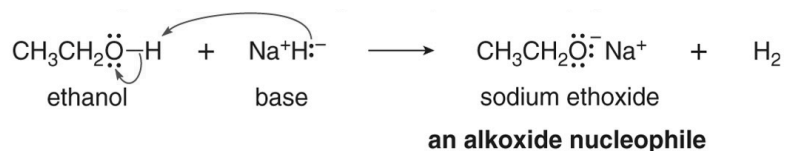
## Substitution and Elimination of Tosylates (Review)

- Because alkyl tosylates have good leaving groups, they undergo both nucleophilic substitution and β elimination, exactly as alkyl halides do.
- Generally, alkyl tosylates are treated with strong nucleophiles and bases, so the mechanism of substitution is S<sub>N</sub>2, and the mechanism of elimination is E2.



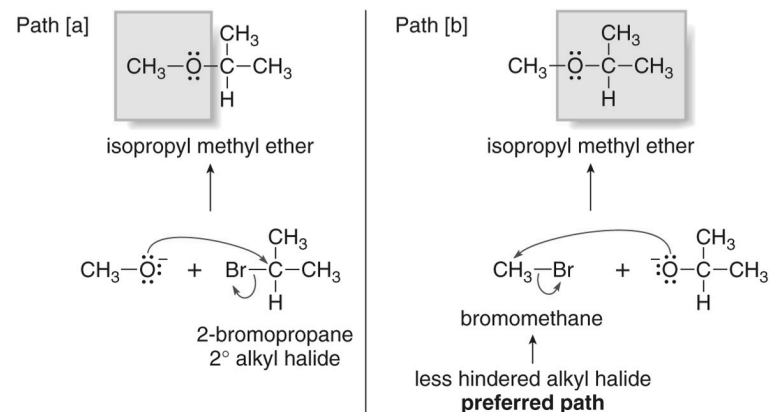
## Preparation of Alkoxides (Review)

- An **alkoxide** salt is needed to make an ether.
- Alkoxides can be prepared from alcohols by a **Brønsted-Lowry acid-base reaction**.
- For example, sodium ethoxide ( $\text{NaOCH}_2\text{CH}_3$ ) is prepared by treating ethanol with  $\text{NaH}$ .



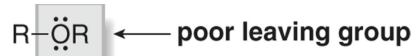
## Williamson Ether Synthesis (Review)

- In theory, unsymmetrical ethers can be synthesized in two different ways. In practice, one path is usually preferred.
- Consider the 2 possible paths, a & b below. **The path involving alkoxide attack on a less hindered alkyl halide is preferred.**

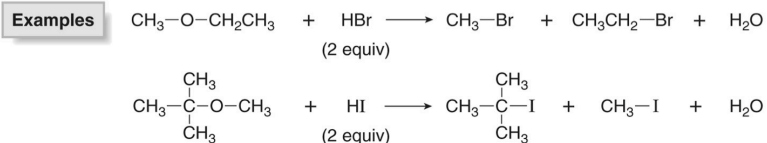
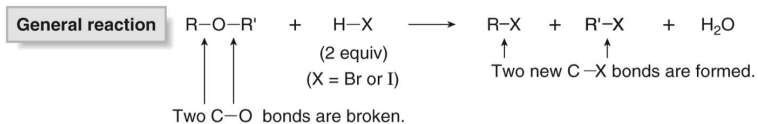


## RO- as a Leaving Group in Ethers (Review)

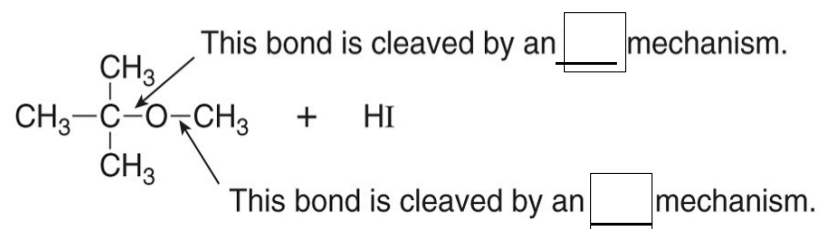
- Like alcohols, ethers do not contain a good leaving group.
- Ethers undergo fewer useful reactions than alcohols.



## Reaction of Ethers with Strong Acid

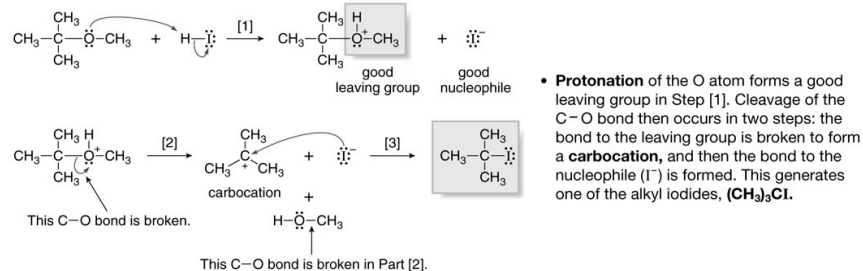


## Mechanism of Ether Cleavage (Review)



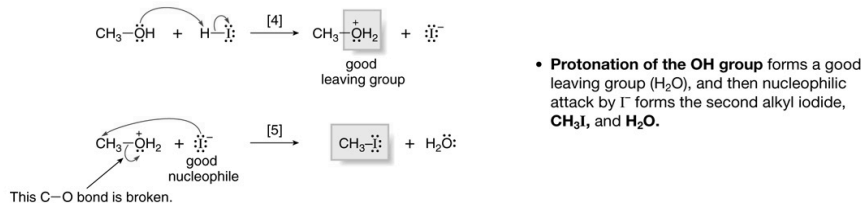
## Mechanism 9.9 Mechanism of Ether Cleavage in Strong Acid— (CH<sub>3</sub>)<sub>3</sub>COCH<sub>3</sub> + HI → (CH<sub>3</sub>)<sub>3</sub>CI + CH<sub>3</sub>I + H<sub>2</sub>O (Review)

**Part [1]** Cleavage of the 3° C–O bond by an S<sub>N</sub>1 mechanism



- **Protonation** of the O atom forms a good leaving group in Step [1]. Cleavage of the C–O bond then occurs in two steps: the bond to the leaving group is broken to form a **carbocation**, and then the bond to the nucleophile (I<sup>−</sup>) is formed. This generates one of the alkyl iodides, **(CH<sub>3</sub>)<sub>3</sub>CI**.

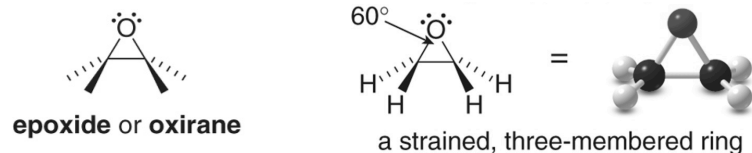
**Part [2]** Cleavage of the CH<sub>3</sub>–O bond by an S<sub>N</sub>2 mechanism



- **Protonation of the OH group** forms a good leaving group (H<sub>2</sub>O), and then nucleophilic attack by I<sup>−</sup> forms the second alkyl iodide, **CH<sub>3</sub>I**, and **H<sub>2</sub>O**.

## Epoxides (Review)

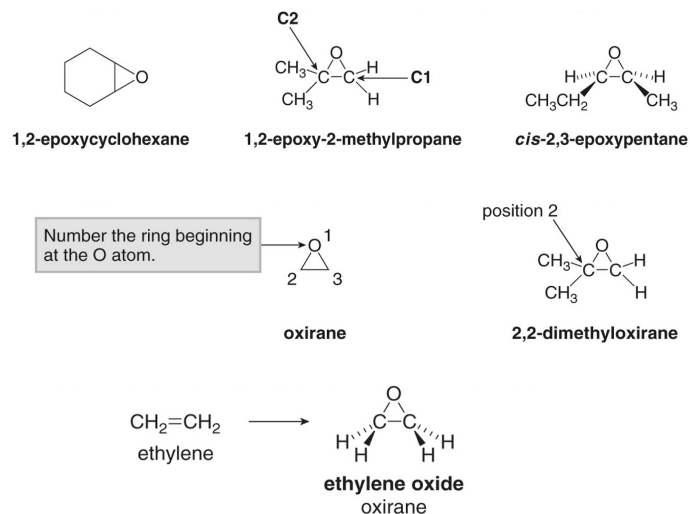
- Epoxides are ethers having the oxygen atom in a three-membered ring. Epoxides are also called oxiranes.



- The C–O–C bond angle for an epoxide must be 60°, a considerable deviation from the tetrahedral bond angle of 109.5°.
- Thus, epoxides have angle strain, making them more reactive than other ethers.

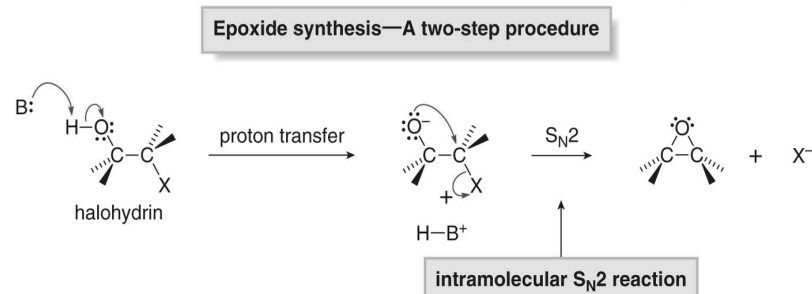
## Naming Epoxides (Review)

- Epoxides can be named in three different ways: epoxyalkanes, oxiranes, or alkene oxides.



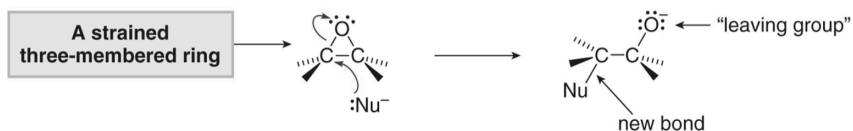
## Forming Epoxides from Halohydrins

- Organic compounds that contain both a hydroxy group and a halogen atom on adjacent carbons are called halohydrins.
- In halohydrins, an intramolecular version of the Williamson ether synthesis can occur to form epoxides.



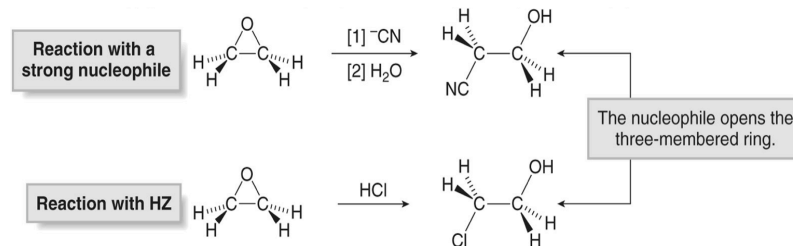
## Reactions of Epoxides

- Epoxides have the same type of leaving group as ethers,  $\text{OR}^-$ .
- However, epoxides do contain a strained three-membered ring with two polar bonds.
- Nucleophilic attack opens the strained three-membered ring, making it a favorable process even with a poor "leaving group".

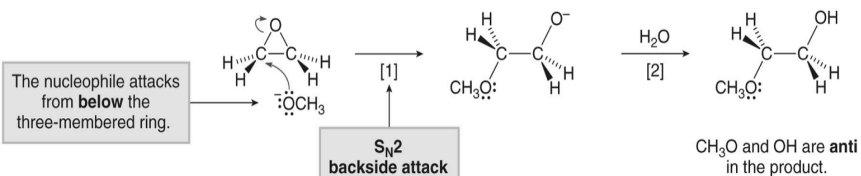


## Addition of Nucleophiles to Epoxides

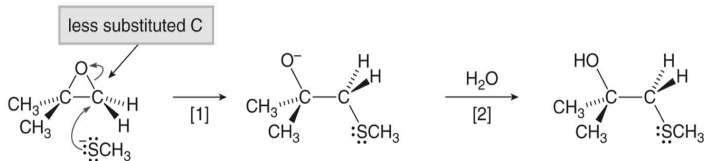
- Most nucleophiles can open an epoxide ring.
- Ring opening can happen under basic or acidic conditions.
- The two conditions lead to differences in the mechanism that can have significant stereochemical consequences for the products.



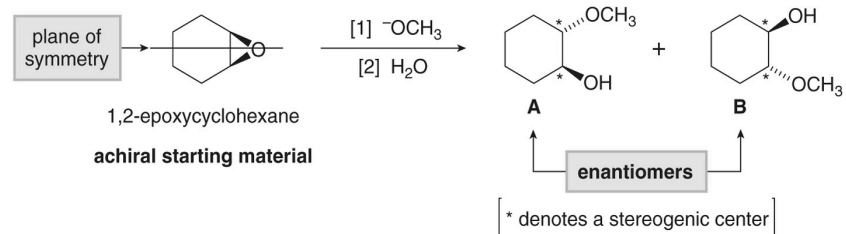
## Mechanism & Regioselectivity of Basic Epoxide Ring Opening



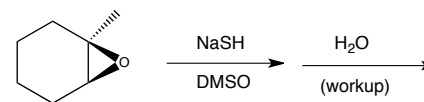
- In an unsymmetrical epoxide, the nucleophile attacks at the less substituted carbon atom.



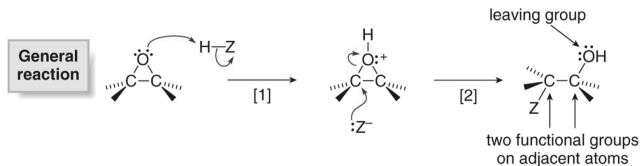
## Stereochemistry of Reaction of Epoxide Ring Opening



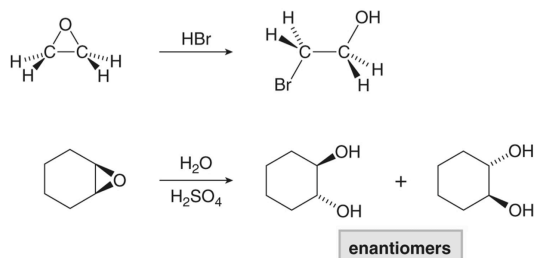
- Provide the mechanism and predict the major product of the following reaction:



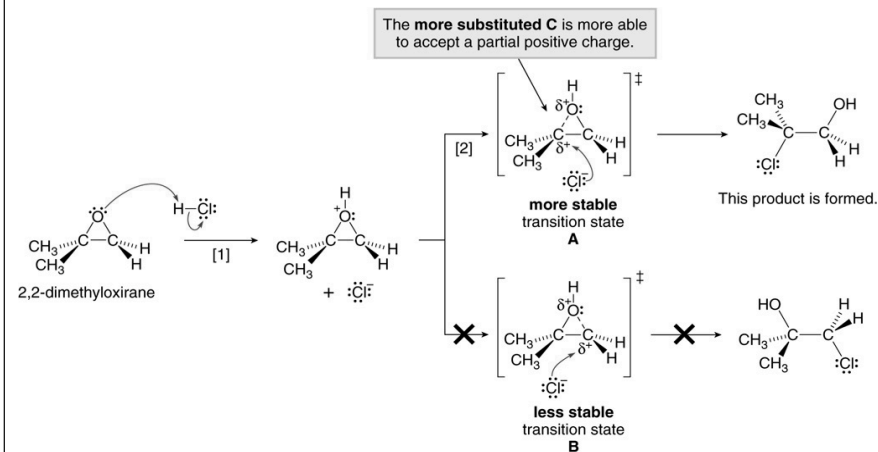
## Mechanism & Examples of Acidic Epoxide Ring Opening



### Examples



## Mechanism & Regioselectivity of Acidic Epoxide Ring Opening

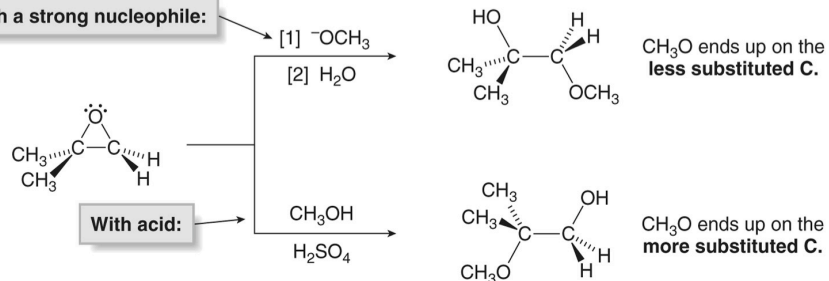


- Transition state **A** is lower in energy because the partial positive charge ( $\delta^+$ ) is located on the more substituted carbon. In this case, therefore, nucleophilic attack occurs from the back side (an  $S_N2$  characteristic) at the more substituted carbon (an  $S_N1$  characteristic).

## Summary of the Regioselectivity of Epoxide Ring Opening

- Ring opening of an epoxide with either a strong nucleophile (generally basic conditions) or an acid, HZ, is regioselective because one constitutional isomer is the major or exclusive product.
- The site selectivity of these two reactions is exactly opposite.

### With a strong nucleophile:



- With a strong nucleophile,  $:\text{Nu}^-$  attacks at the less substituted carbon.
- With an acid HZ, the nucleophile attacks at the more substituted carbon.