Ethers & Epoxides

Reactions of Ethers

Ethers are relatively unreactive.

Ethers are often used as solvents in organic reactions.

Ethers oxidize in air to form explosive hydroperoxides and peroxides.

"Crown" ethers are useful as enhancers in nucleophilic substitution and other reactions

Crown Ethers

Crown Ethers

structure

cyclic polyethers derived from repeating —OCH_2CH_2— units

properties

form stable complexes with metal ions

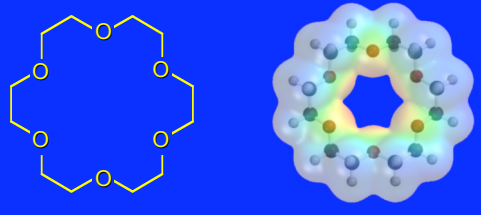
applications

synthetic reactions involving anions

naming

x = total # of atoms in ring: [x] Crown- # of oxygen atoms

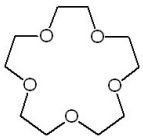
18-Crown-6



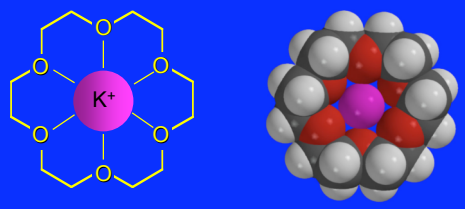
negative charge concentrated in cavity inside the molecule

Question

- What is the name of the crown ether show at the right?
- A) 12-crown-4
- B) 10-crown-5
- C) 15-crown-5
- D) 18-crown-6



18-Crown-6



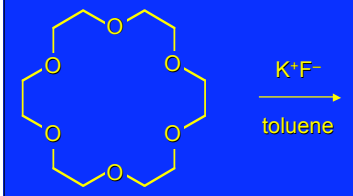
forms stable Lewis acid/Lewis base complex with K^+

Ion-Complexing and Solubility

K^+F^-

not soluble in toluene

Ion-Complexing and Solubility

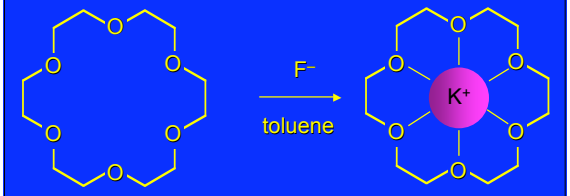


K^+F^-

toluene

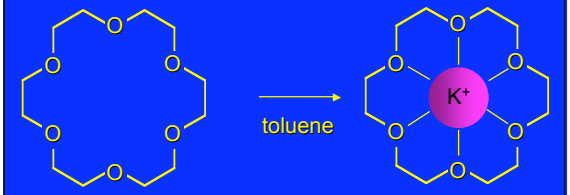
add 18-crown-6

Ion-Complexing and Solubility



18-crown-6 complex of K^+ dissolves in benzene

Ion-Complexing and Solubility



F^- carried into toluene to preserve electroneutrality

+ F^-

Application to organic synthesis

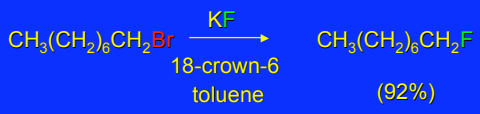
Complexation of K^+ by 18-crown-6 "solubilizes" potassium salts in toluene

Anion of salt is in a relatively unsolvated state in toluene (sometimes referred to as a "naked anion")

Unsolvated anions are very reactive

Only catalytic quantities of 18-crown-6 are needed

Example

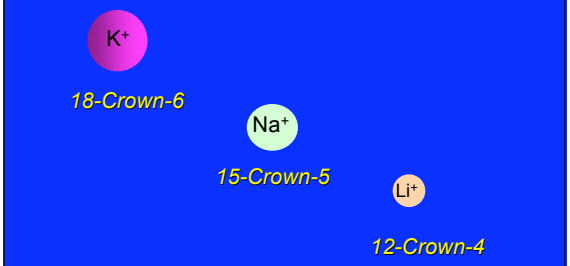


Question

- Which reaction is the best candidate for catalysis by 18-crown-6? (Which reaction proceeds faster in the presence of the crown ether than in its absence?)

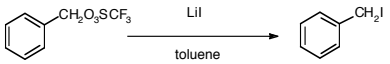
- A) Bromobutane + KCN (in toluene)
- B) Phenol + Br_2 (in water)
- C) Butanol + H_2CrO_4 (in water)
- D) $CH_3CH_2CH_2CHO + H_2$ (in ethanol)

Ion Size & Crown Ether Complexes



Question

- Which crown ether would provide the fastest rate for the following reaction?



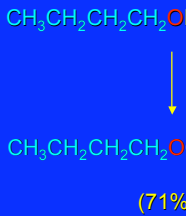
- A) 12-crown-4
- B) 10-crown-5
- C) 15-crown-5
- D) 18-crown-6

The Williamson Ether Synthesis

Just another S_N2 reaction →

primary alkyl halide (substrate) + alkoxide (nucleophile)

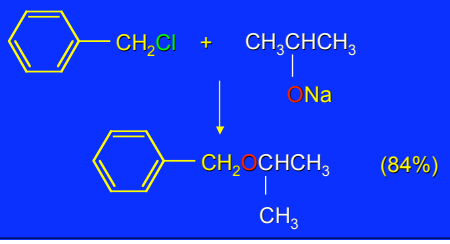
Example



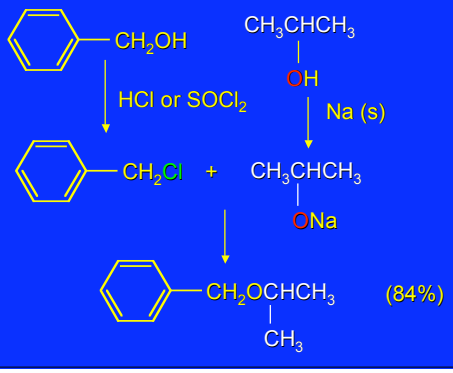
Another Example

Alkyl halide must be primary

Alkoxide ion can be derived from primary, secondary, or tertiary alcohol

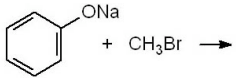


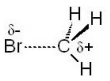
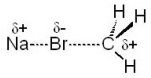
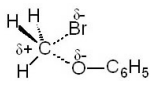
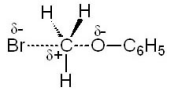
1° Halides & Alkoxides



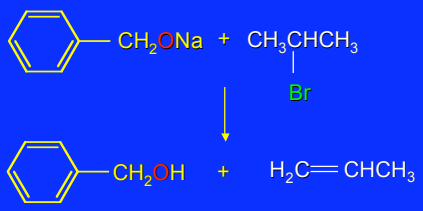
Question

- Which of the following best represents the rate-determining transition state for the reaction shown below?



- A) 
- B) 
- C) 
- D) 

What if the alkyl halide is not primary?
S_N2 vs E2



Elimination produces the major product.

Question

- The most effective pair of reagents for the preparation of *tert*-butyl ethyl ether is
- A) potassium *tert*-butoxide and ethyl bromide.
- B) potassium *tert*-butoxide and ethanol.
- C) sodium ethoxide and *tert*-butyl bromide.
- D) *tert*-butyl alcohol and ethyl bromide

Preparation of Epoxides

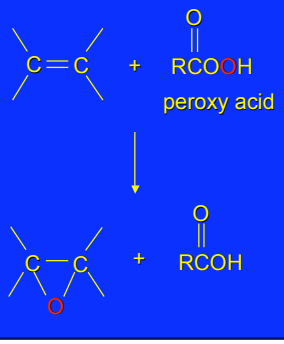
Preparation of Epoxides

Epoxides are prepared by two major methods. Both begin with alkenes.

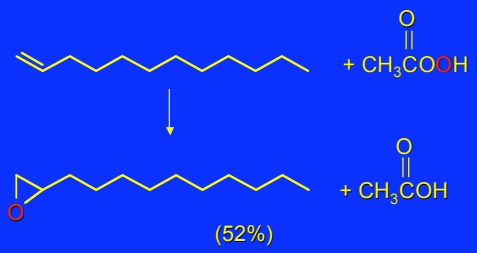
Reaction of alkenes with peroxy acids

Conversion of alkenes to vicinal halohydrins, followed by treatment with base.

Epoxidation of Alkenes

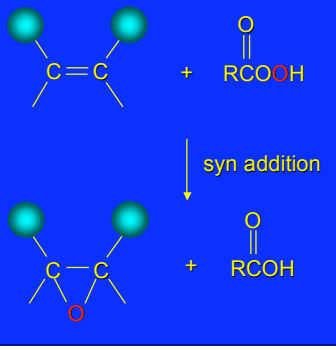


Example



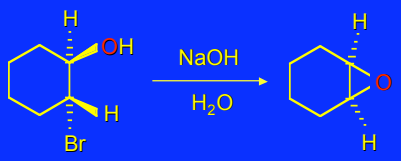
(52%)

Stereochemistry of Epoxidation



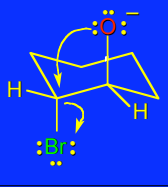
Conversion of Vicinal Halohydrins to Epoxides

Example

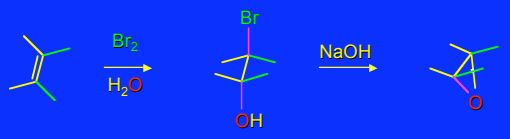


(81%)

via:



Epoxidation via Vicinal Halohydrins

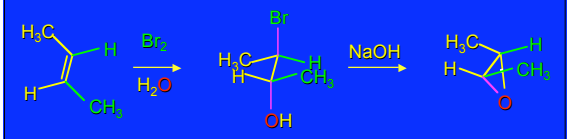


anti addition

inversion

Corresponds to overall syn addition of oxygen to the double bond.

Epoxidation via Vicinal Halohydrins



anti addition

inversion

Corresponds to overall syn addition of oxygen to the double bond.

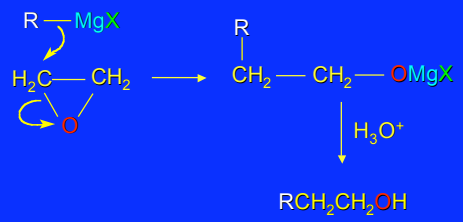
Reactions of Epoxides

Reactions of Epoxides

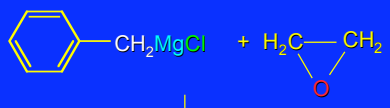
All reactions involve nucleophilic attack at carbon and lead to opening of the ring.

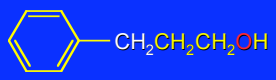
An example is the reaction of ethylene oxide with a Grignard reagent as a method for the synthesis of alcohols.

Reaction of Grignard Reagents with Epoxides



Example



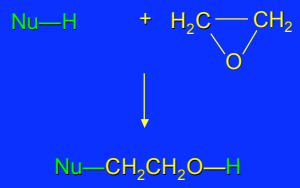


(71%)

In General...

Reactions of epoxides involve attack by a nucleophile and proceed with ring-opening.

For ethylene oxide:

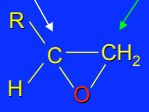


In General...

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

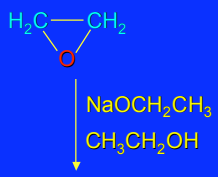
Nucleophiles attack here when the reaction is catalyzed by acids.

Anionic nucleophiles attack here. (less hindered)



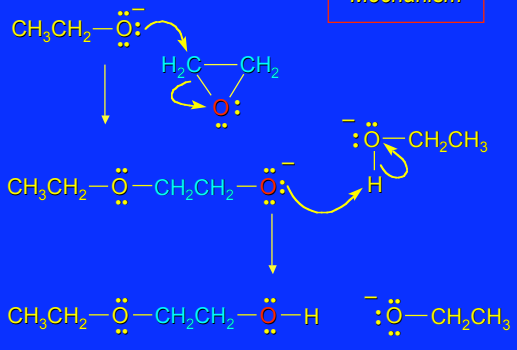
Nucleophilic Ring-Opening Reactions of Epoxides

Example

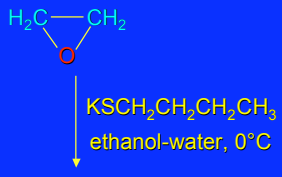


(50%)

Mechanism

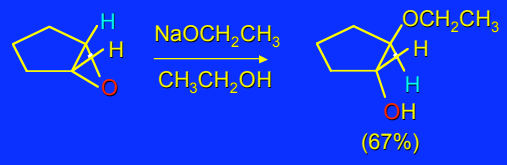


Example



(99%)

Stereochemistry

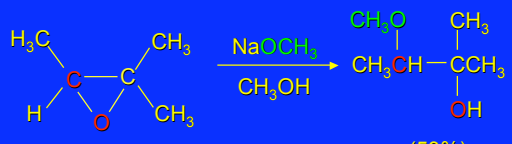


(67%)

Inversion of configuration at carbon being attacked by nucleophile.

Suggests S_N2-like transition state.

Anionic Nucleophile Attacks Less-crowded Carbon

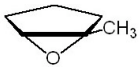


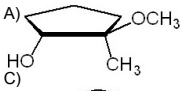
(53%)

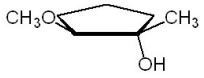
Consistent with S_N2-like transition state

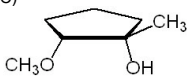
Question

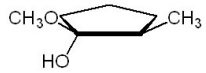
- What is the product isolated when the epoxide below reacts with $NaOCH_3$ in CH_3OH?



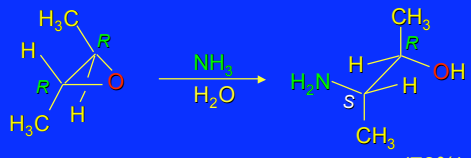
- A) 

B) 

- C) 

D) 

Stereochemistry

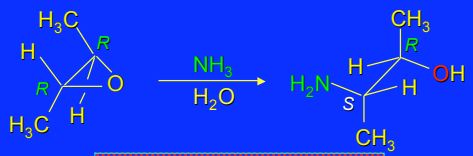


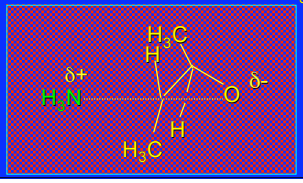
(70%)

Inversion of configuration at carbon being attacked by nucleophile.

Suggests S_N2-like transition state.

Stereochemistry

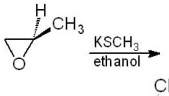


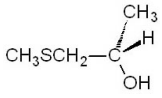


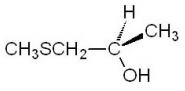
(70%)

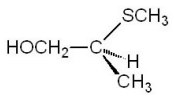
Question

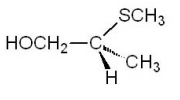
- What is the product of the reaction shown?



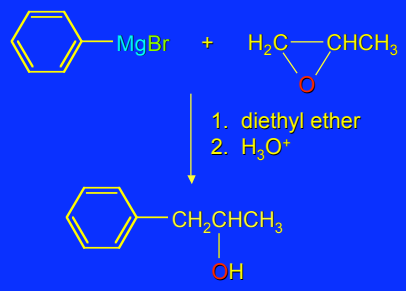
- A) 

B) 

- C) 

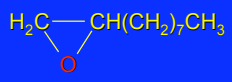
D) 

Anionic Nucleophile Attacks Less-crowded Carbon



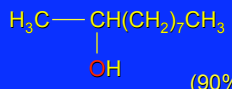
(60%)

Lithium Aluminum Hydride Reduces Epoxides



Hydride attacks less-crowded carbon

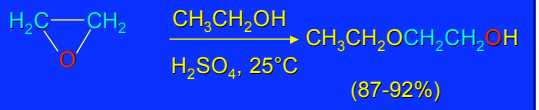
1. $LiAlH_4$, diethyl ether
2. H_2O



(90%)

Acid-Catalyzed Ring-Opening Reactions of Epoxides

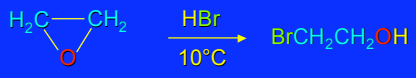
Example



(87-92%)

$CH_3CH_2OCH_2CH_2OCH_2CH_3$ formed only on heating and/or longer reaction times.

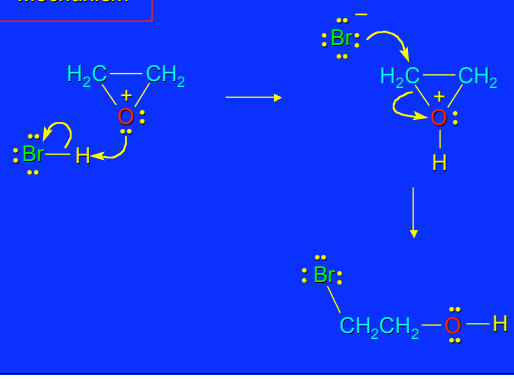
Example



(87-92%)

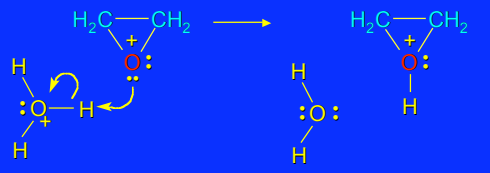
$BrCH_2CH_2Br$ formed only on heating and/or longer reaction times.

Mechanism



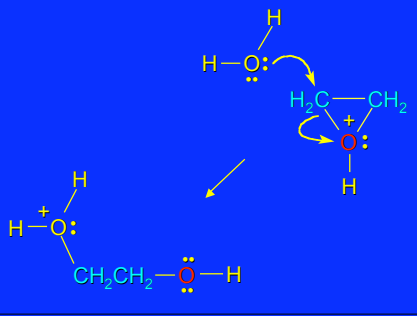
Acid-Catalyzed Hydrolysis of Ethylene Oxide

Step 1



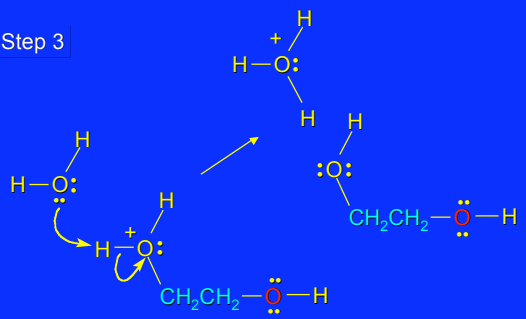
Acid-Catalyzed Hydrolysis of Ethylene Oxide

Step 2



Acid-Catalyzed Hydrolysis of Ethylene Oxide

Step 3



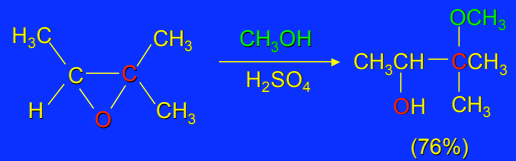
Acid-Catalyzed Ring Opening of Epoxides

Characteristics:

Nucleophile attacks more substituted carbon of protonated epoxide.

Inversion of configuration at site of nucleophilic attack.

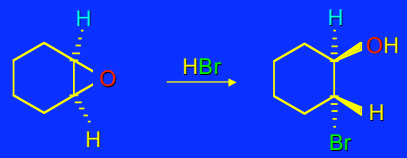
Nucleophile Attacks More-substituted Carbon



(76%)

Consistent with carbocation character at transition state

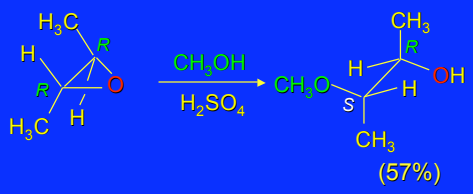
Stereochemistry



(73%)

Inversion of configuration at carbon being attacked by nucleophile

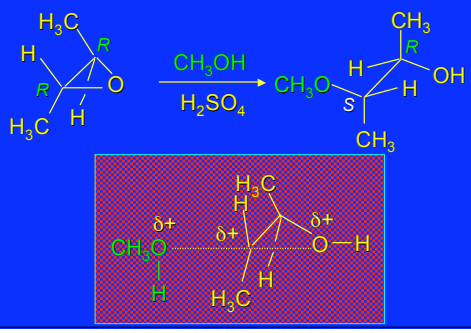
Stereochemistry



(57%)

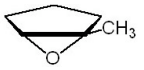
Inversion of configuration at carbon being attacked by nucleophile

Stereochemistry

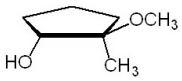


Question

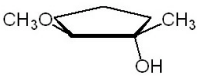
- What is the product isolated when the epoxide at the right reacts with CH_3OH and H_2SO_4?



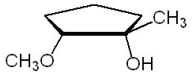
- A)



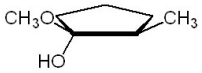
B)



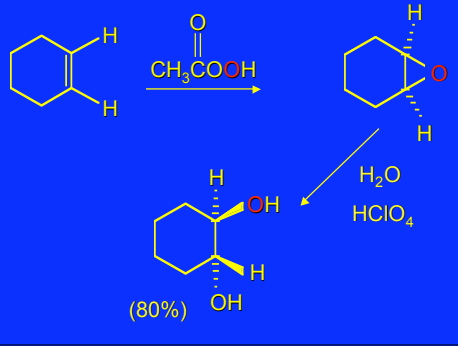
- C)



D)



anti-Hydroxylation of Alkenes



(80%)