Organic Chemistry II with Dr Roche

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Text   (a) "Organic Chemistry" Wade, 4….8th Editions
                         (b) Solution Manual, 4…..8th Eds

                         (organic model kit)

Do the problems in the book

Learn as you go along

Aim for understanding, not memorization

Ethers and Epoxides

Ethers are a class of compound of the general formula   R-O-R'.

R and R' can be alkyl or aryl.

Structure
Ethers can be thought of as alkyl analogues of water.

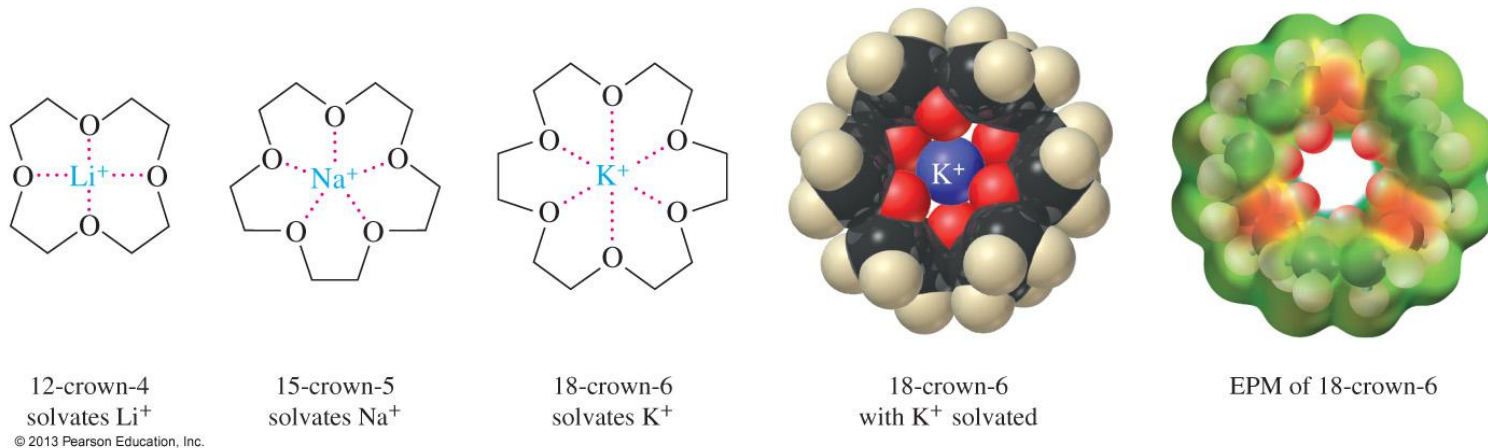$$H-\ddot{O}-H \qquad R-\ddot{O}-R$$

Uses
Since ethers are relatively unreactive and are strongly polar (due to the lone pairs on the oxygen), they are commonly used as solvents for organic reactions. (Diethyl ether and THF, the Grignard reaction).

Ethers will often form complexes with molecules that have vacant orbitals, enabling 'unstable' molecules to be used as reagents.

E.g. Hydroboration uses BH_3.THF
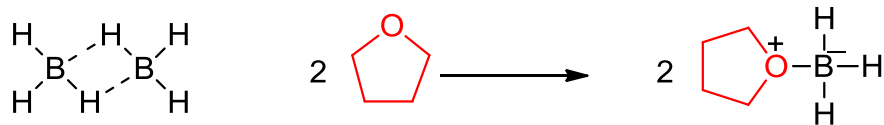
Crown ethers are *macrocyclic* ethers, which help to solvate metal cations, and thus allow inorganic salts to dissolve in organic solvents.

12-crown-4
solvates Li^+
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15-crown-5
solvates Na^+

18-crown-6
solvates K^+

18-crown-6
with K^+ solvated

EPM of 18-crown-6

18-Crown-6 is the ideal size to incorporate a potassium ion, and allows organic solutions of ionic potassium salts to be prepared (*purple benzene*).
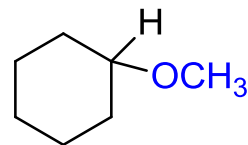
Nomenclature of ethers

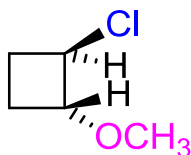*Common* names of ethers add the suffix *ether* after naming the groups on either side of the oxygen.

IUPAC names ethers by taking the more complex alkyl group as the root name, and naming the remaining part as an *alkoxy* group.
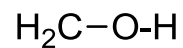
$H_3C-O-CH_2CH_3$
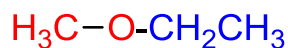
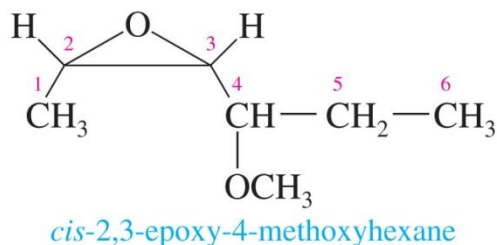methoxyethane

methoxycyclohexane

trans-1-chloro-2-methoxycyclobutane

H_2C-O-H
$H_2C-O-CH_2CH_3$

2-ethoxyethanol

Cyclic Ethers

Naming these **heterocyclic** compounds depends on the ring size and number of oxygens.
(It *can* be confusing at first…)

Epoxides

These 3 membered rings are named using the term *epoxy* as a substituent.
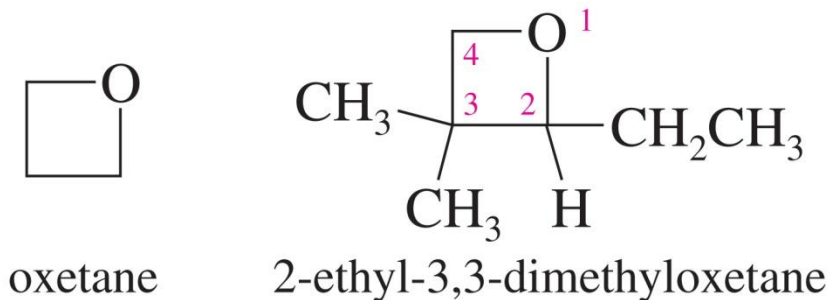

cis-2,3-epoxy-4-methoxyhexane

(*cis* refers to the substituents, not the epoxide which <u>must</u> be cis/syn).
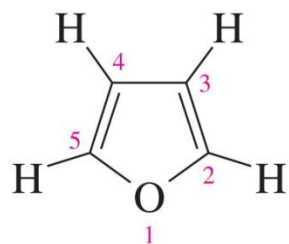
Epoxides have considerable *ring strain*.

Oxetanes

These are four membered rings with one oxygen.

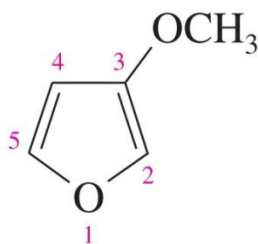oxetane   2-ethyl-3,3-dimethyloxetane

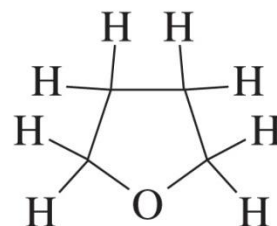Oxetanes have ring strain, but not as much as epoxides.

Furans

These are five membered rings with one oxygen and two double bonds. (Furan is an *aromatic* molecule).
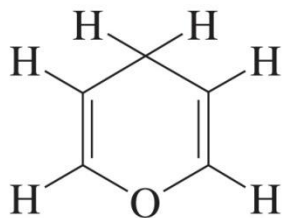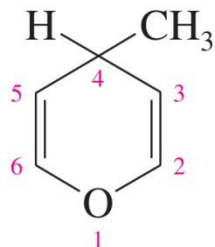
furan

3-methoxyfuran

tetrahydrofuran (THF)
(oxolane)

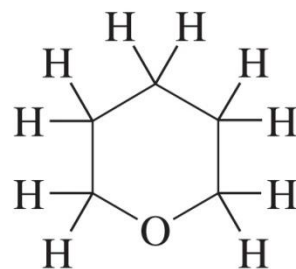© 2013 Pearson Education, Inc.

Pyrans

These are six membered rings with one oxygen and two double bonds.

pyran

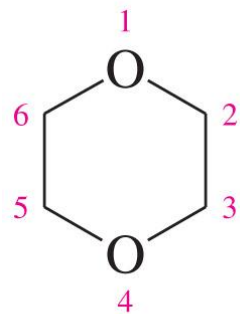4-methylpyran
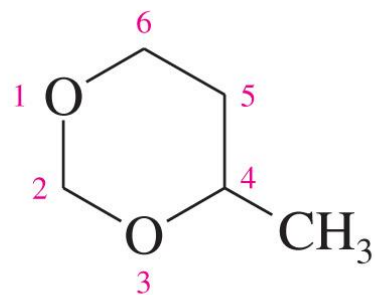
tetrahydropyran (THP)
(oxane)

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Dioxanes
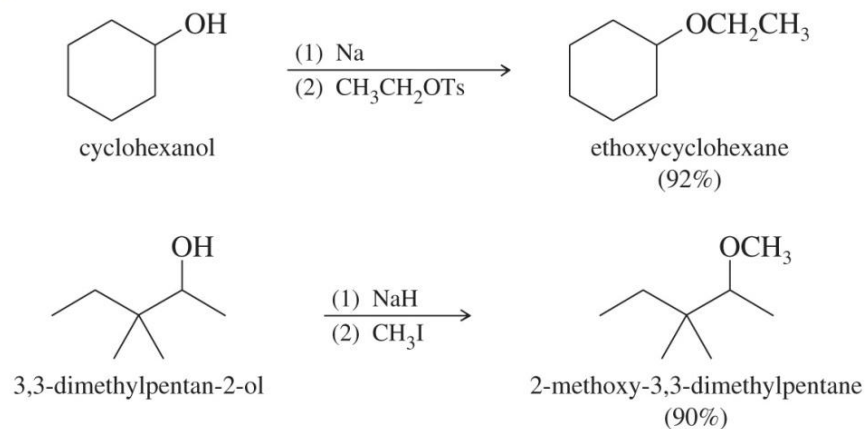These are six membered rings with two oxygens.

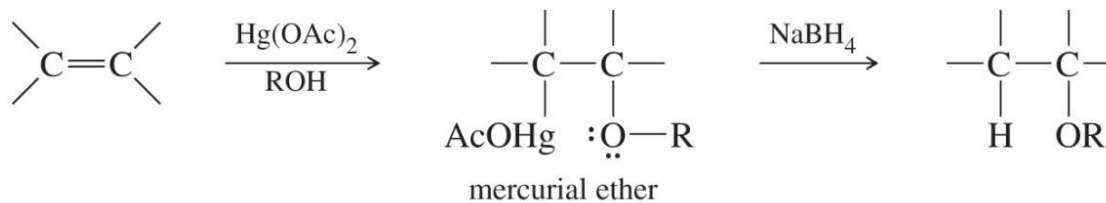1,4-dioxane   4-methyl-1,3-dioxane
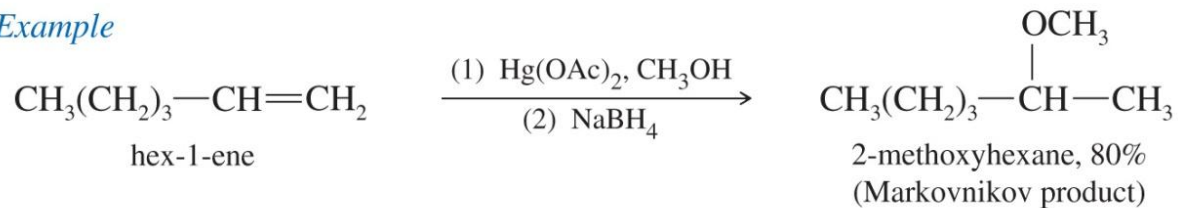
Ether Synthesis (Recap)

Williamson synthesis

Examples

cyclohexanol

(1) Na
(2) CH₃CH₂OTs

ethoxycyclohexane
(92%)

3,3-dimethylpentan-2-ol

(1) NaH
(2) CH₃I

2-methoxy-3,3-dimethylpentane
(90%)

Alkoxymercuration-Demercuration

mercurial ether

Example

CH₃(CH₂)₃—CH=CH₂

(1) Hg(OAc)₂, CH₃OH
(2) NaBH₄

hex-1-ene

2-methoxyhexane, 80%
(Markovnikov product)

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Bimolecular Dehydration of Alcohols

$$2\ R\!-\!OH \quad \underset{\longleftarrow}{\overset{H^+}{\longrightarrow}} \quad R\!-\!O\!-\!R \quad + \quad H_2O$$

Examples

$$2\ CH_3OH \xrightarrow{\ H_2SO_4,\ 140\ °C\ } CH_3\!-\!O\!-\!CH_3 \quad + \quad H_2O$$

methyl alcohol

dimethyl ether
(100%)

$$CH_3CH_2OH \xrightarrow{\ H_2SO_4,\ 140\ °C\ } CH_3CH_2\!-\!O\!-\!CH_2CH_3 \quad + \quad H_2O$$

ethyl alcohol

diethyl ether
(88%)
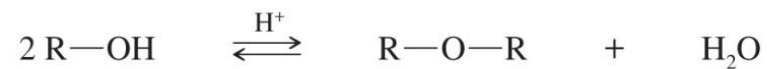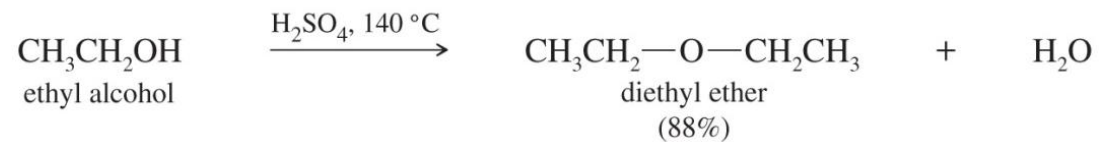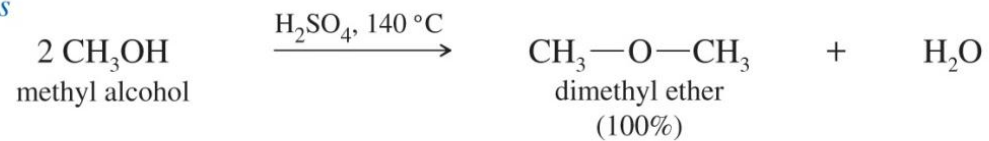
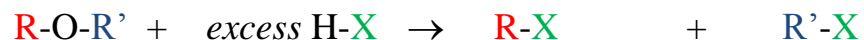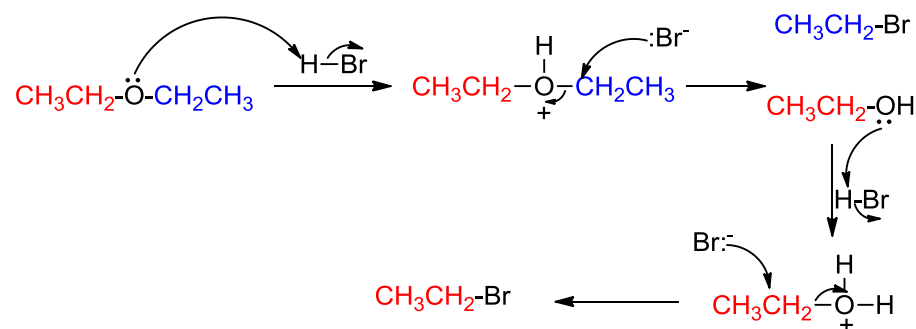## Reactions of Ethers

Typically ethers are stable and chemically inert, although they can undergo two types of reaction (*cleavage*, *oxidation*).

Cleavage

Ethers are cleaved by H-Br and H-I, generating the corresponding alkyl halides.

$$R\text{-O-}R' + \ excess \ H\text{-}X \ \rightarrow \ R\text{-}X \ + \ R'\text{-}X$$
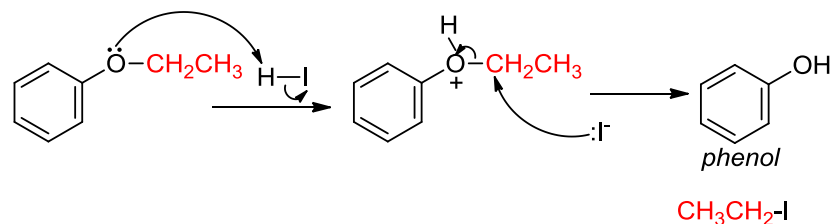
Ethers are stable to **bases**, but **acidic** conditions leads to the protonation of the ether oxygen, which then can undergo substitution reactions.

The alcohol produced reacts to generate a second molecule of alkyl halide.

Phenyl ethers are slightly different, and cleave to give alkyl halides and phenols.

phenol

CH_3CH_2-I

The reaction stops at the phenol stage since the sp^2 carbon of the C-OH bond does not allow the required S_N1 or S_N2 reactions to generate the second molecule of aryl halide.

Oxidation of Ethers

Ethers may auto-oxidize if left in the presence of oxygen for extended periods of time (**Dangerous** in the laboratory).

hydroperoxide   dialkylperoxide
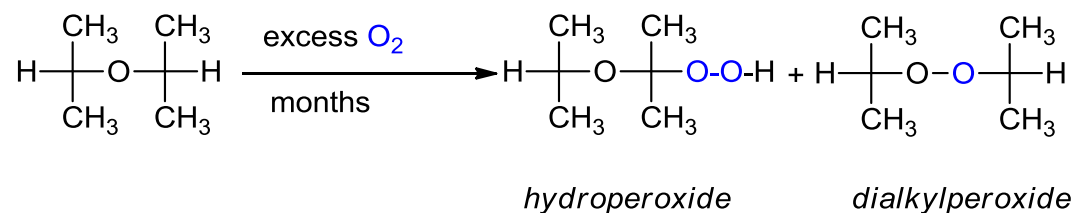
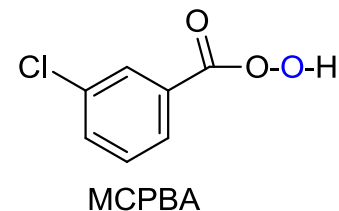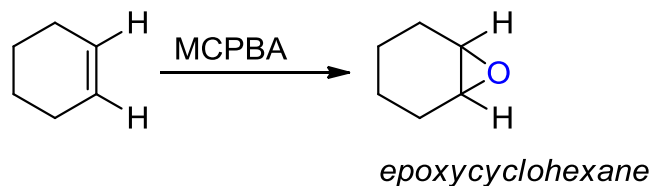The peroxides and hydroperoxides are unstable and explosive.

Epoxides

Unlike straight chain ethers, epoxides are very reactive (*release of ring strain*), and are useful intermediates because of their chemical versatility.
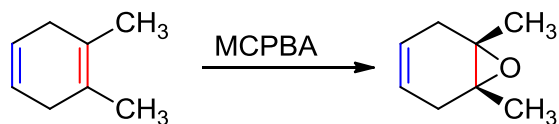
Synthesis

Recall alkene and peroxyacid → epoxide and carboxylic acid
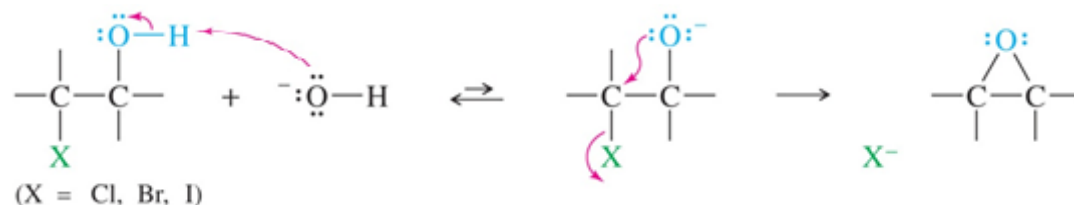
E.g.

epoxycyclohexane

MCPBA is one of the most common epoxidising reagents.
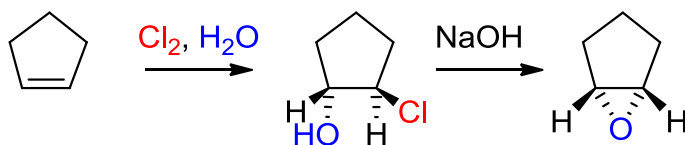
Epoxidations work better for *electron rich* double bonds.

Synthesis from Halohydrins

When halohydrins are treated with base, an *intramolecular* cyclisation occurs, and epoxides are formed.
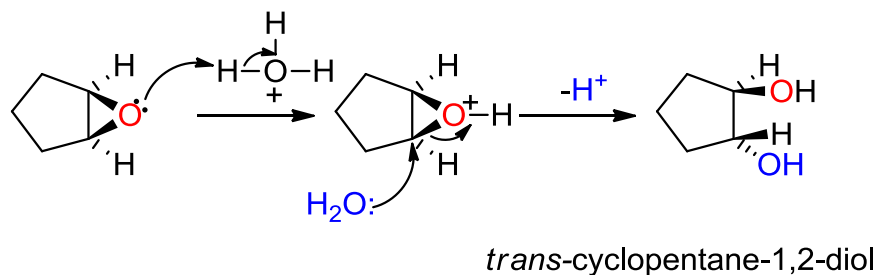

$(X = Cl, Br, I)$

Recall that halohydrins are produced from alkenes by reaction with halogens in the presence of water. (Chlorine water or related reagents).
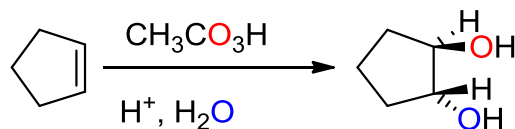

Acid Catalyzed ring Opening

Epoxides react to **release** their considerable (25kcal/mol) strain energy.
Recall that the acidic hydrolysis of epoxides gives **anti** diols.

trans-cyclopentane-1,2-diol

This overall transformation (alkene → anti 1,2-diol) can be achieved in one step by reaction with aqueous peroxyacids.
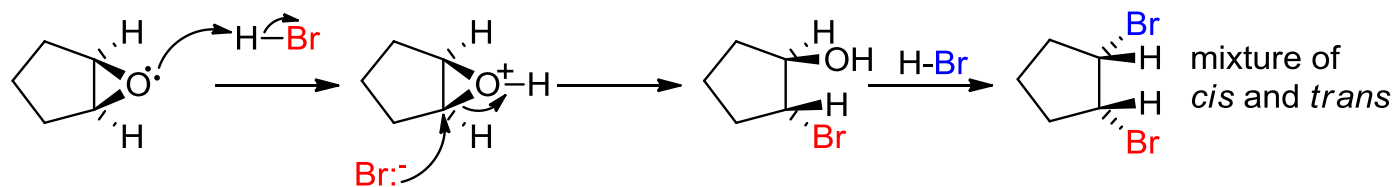

Epoxides can be ring opened by <u>alcohols</u> with acidic catalysis to generate alkoxy alcohols with **anti** stereochemistry.
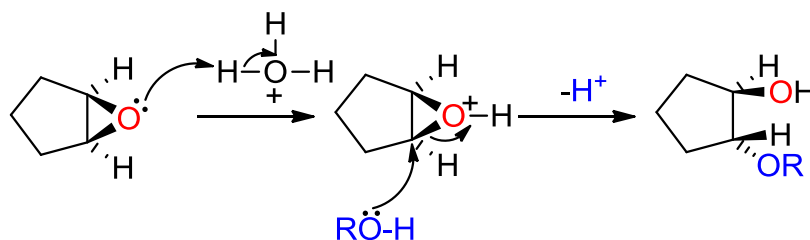
Hydrohalic Acids

Epoxides react with H-X to produce *halohydrins*, which react further with H-X to generate 1,2-dihalides.

mixture of *cis* and *trans*

(However it is synthetically easier just to add X_2 to an alkene).

Base Catalyzed Ring Opening
Normal ethers do not undergo nucleophilic substitution or eliminations because the alkoxide anion is **not** a good leaving group. (That is why acid catalysis is required).

Epoxides are different though. The release of strain when an epoxide is opened more than compensates for the poor leaving group ability, and so epoxides **will** open under nucleophilic conditions.
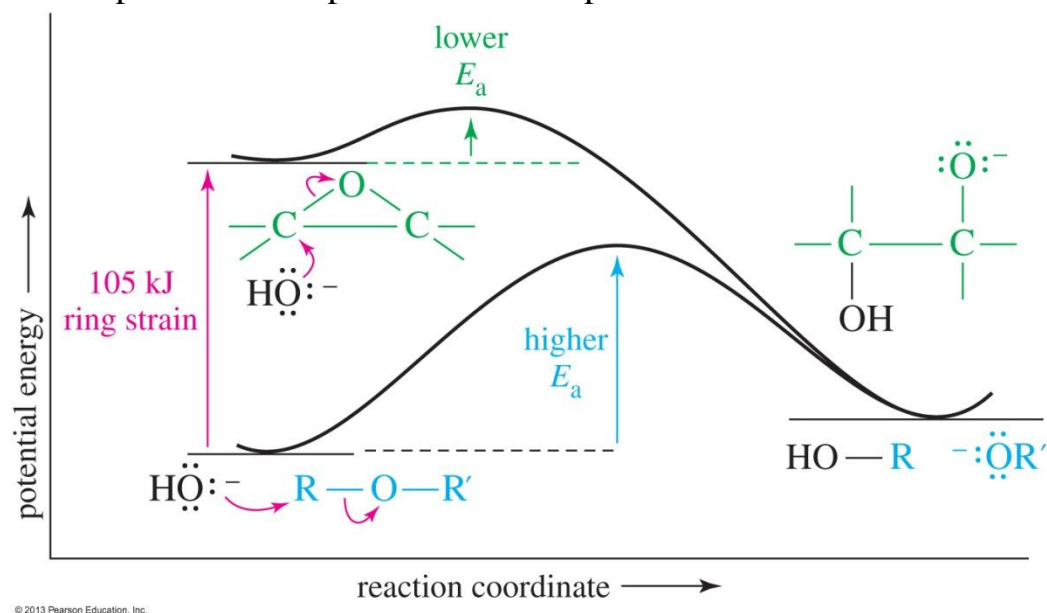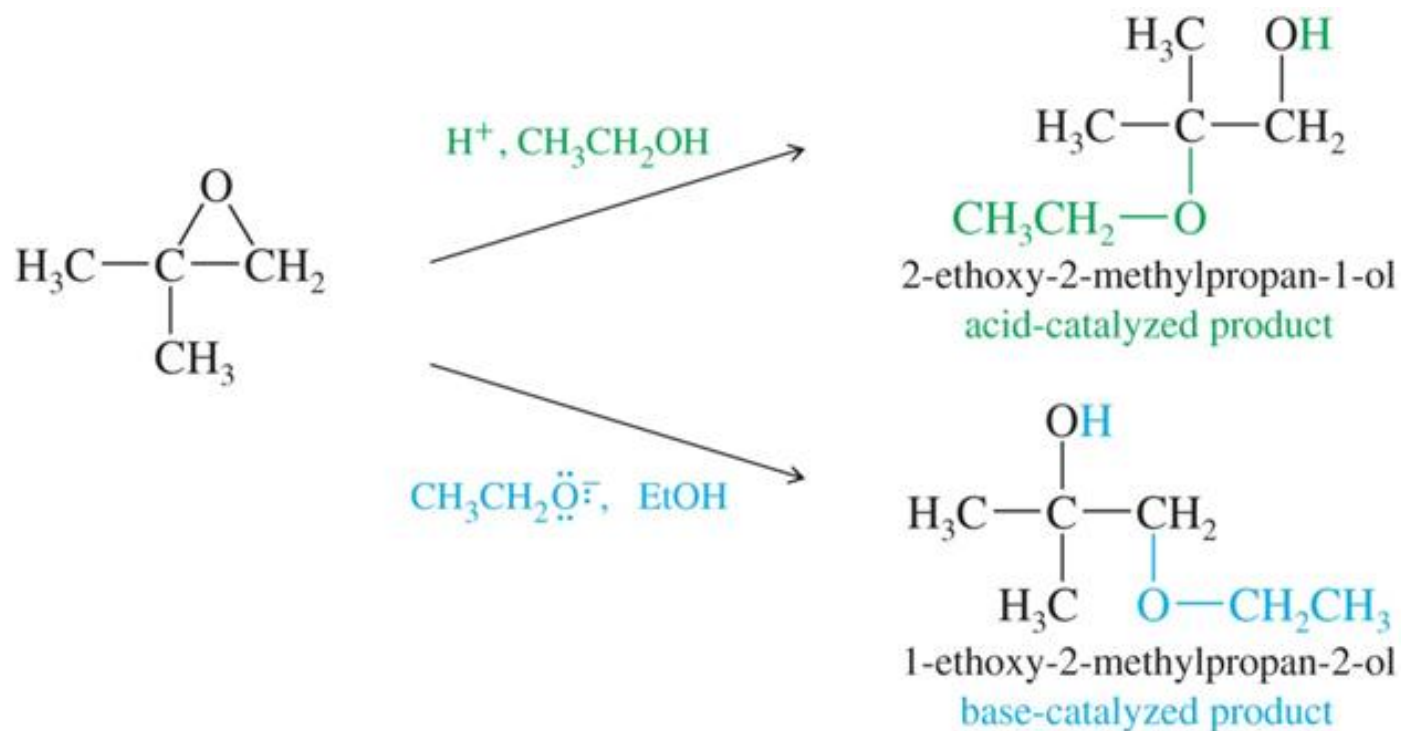

The *strained* epoxide has a lower E_a than the corresponding straight chain ether.

The reaction of hydroxide (or alkoxide) with a *symmetric* epoxide generates *anti* diols (or alkoxy alcohols) identical to those produced under acidic conditions.
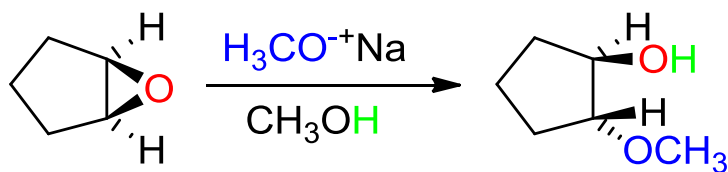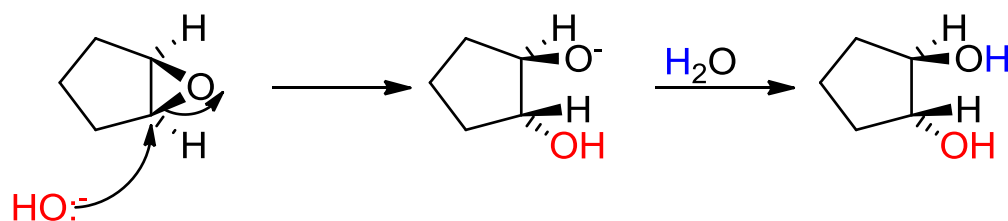
Orientation of Ring Opening

Unsymmetrical epoxides give products with *different* regiochemistry with **basic** opening compared to **acidic** opening.


H^+, CH_3CH_2OH

2-ethoxy-2-methylpropan-1-ol
acid-catalyzed product

$CH_3CH_2\ddot{O}^{\overline{\cdot}}$, EtOH

1-ethoxy-2-methylpropan-2-ol
base-catalyzed product

Why ?

Under *basic* conditions, the alkoxide simply attacks the *least sterically hindered* epoxide carbon in an S_N2 displacement.
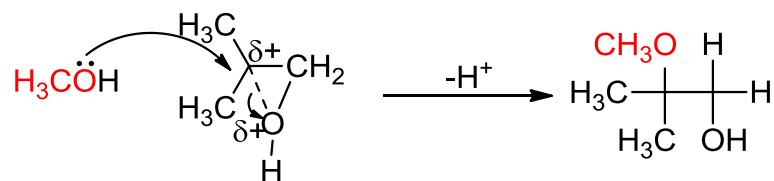

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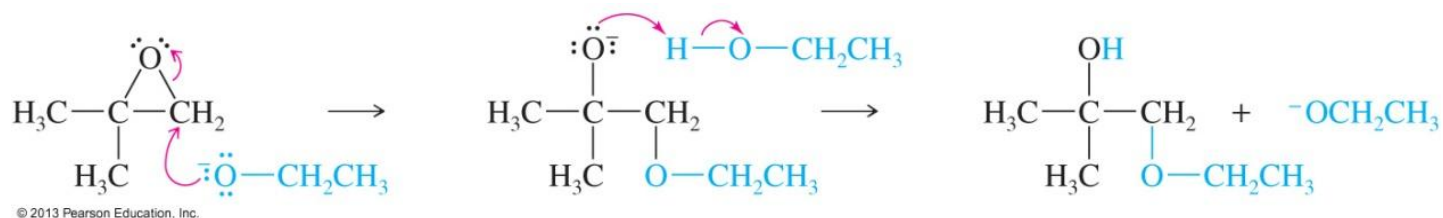
Under *acidic* conditions, the alcohol *seems* to attack the more hindered carbon, but it is more complicated…

The **protonated** epoxide has several resonance structures.

$$
\begin{bmatrix}
\text{(I)} & \longleftrightarrow & \text{(II)} & \longleftrightarrow & \text{(III)}
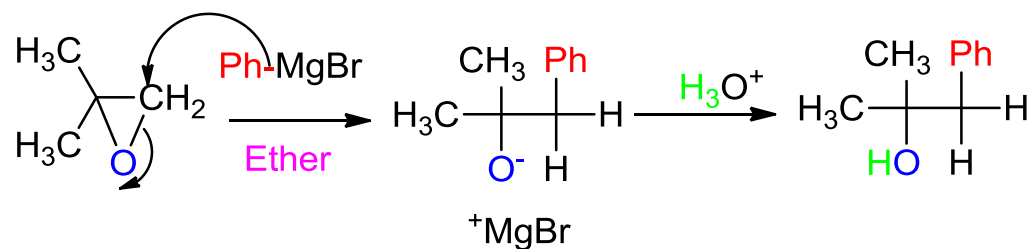\end{bmatrix}
$$
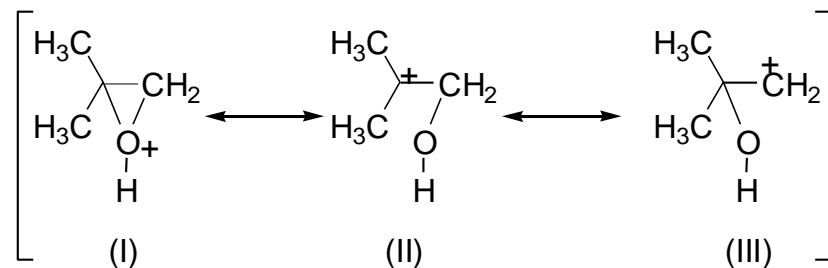
Structure II is a **major** contributor since the cation is *more highly substituted* and therefore more stable.

The nucleophile attacks the carbon with greatest positive partial charge.

Organometallic Reagents

Grignard and organolithium reagents also attack epoxides at the *least* hindered carbon to generate alcohols (after acidic workup). (Organometallics are typically strong bases – therefore basic conditions ring opening).