Learning Guide for Chapter 16 - Ethers and Epoxides

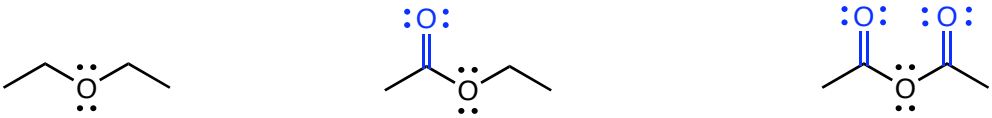
I. Introduction to ethers, sulfides, and epoxides
II. Nomenclature of ethers
III. Synthesis of ethers and sulfides
IV. Reactions of ethers and sulfides
V. Synthesis of epoxides
VI. Reactions of epoxides
VII. Review of reactions

I. Introduction to ethers, epoxides, and thioethers

Defintion and examples of ethers and thioethers

Describe an ether functional group: contains C-O-C w/no C=O on those C's

How is an ether different from an ester or anhydride?

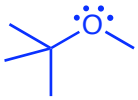


ether ester anhydride

What is the most common ether? What is it used for?

diethyl ether  solvent, starter fluid, early general anesthetic

What ether is used as an additive in gasoline? Why? Why has its use declined?

MTBE  increases octane rating; environmental concerns

What does a thioether look like? What else are they called?

 also called sulfides

What do thioethers often smell like?

oysters that have been left in the fridge too long

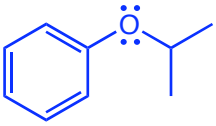
What thioether did we use in the reaction of alkenes with ozone?

 = $(CH_3)_2S$ dimethyl sulfide

Classifications of Ethers

Draw an example of each of the following:

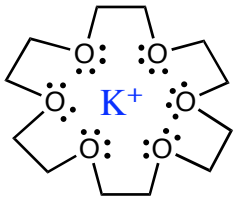
alkyl ether  alkyl groups on both sides

aryl ether  aryl group directly attached to the O

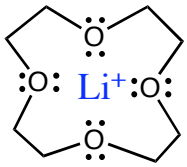
cyclic ether  THF O in a ring 4 or more

epoxide  O in a three-membered ring

What are crown ethers useful for?



CN^-



F^-

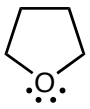
removing ions from solution

carrying anions into solution

[18]-crown-6 [12]-crown-4

Physical Properties of Ethers

Put the following compounds in order of their boiling points.

3 

dipole

66°C

1 

Van der Waals

-42°C

5 

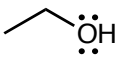
H-bonding

100°C

2 

dipole

-25°C

4 

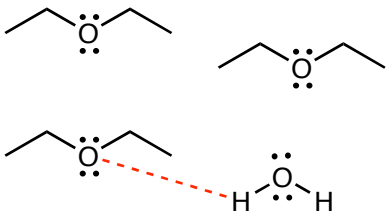
H-bonding

78°C

Why are ethers good solvents?

intermediate polarity - can dissolve nonpolar and polar compounds

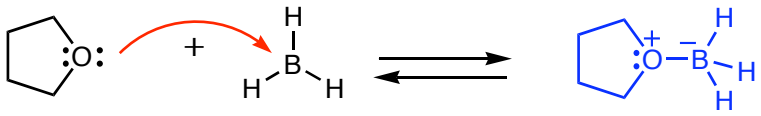
Can ethers undergo hydrogen bonding with each other? What about with water?



no H-bonding - no H on EN atom

can H-bond w/ H_2O
and other H-bonding donors

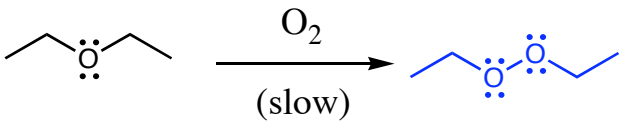
How can ethers stabilize electron deficient compounds?



Are ethers flammable? yes! and very volatile

What can happen when ethers are exposed to air for a long time?

form organic peroxides - shock sensitive



sold with inhibitors; don't open old bottles!

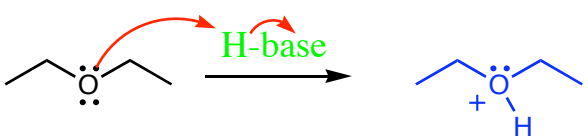
<u>Reactivity of Ethers and Thioethers</u>

Which of the following will ethers react with?

acids (circled) bases (X) nucleophiles (X) electrophiles (X) oxidizing agents (X) reducing agents (X)

least reactive functional group!

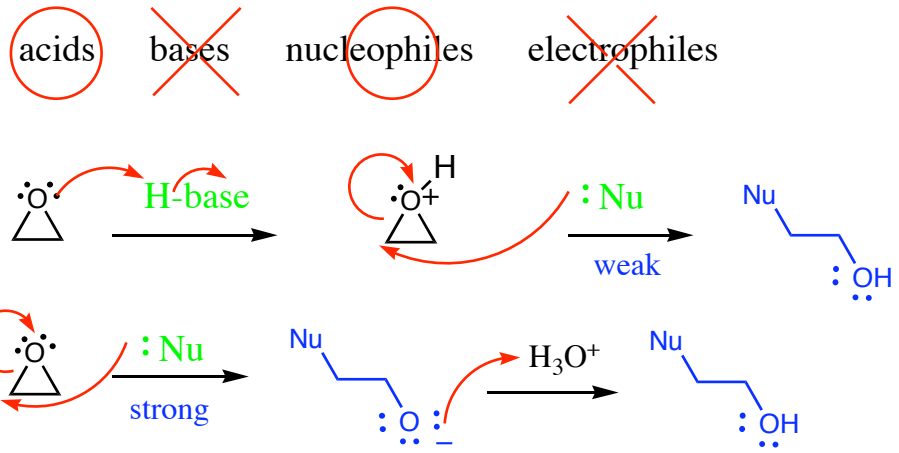
(another thing that makes them good solvents)



what happens next depends on the conjugate base of the acid

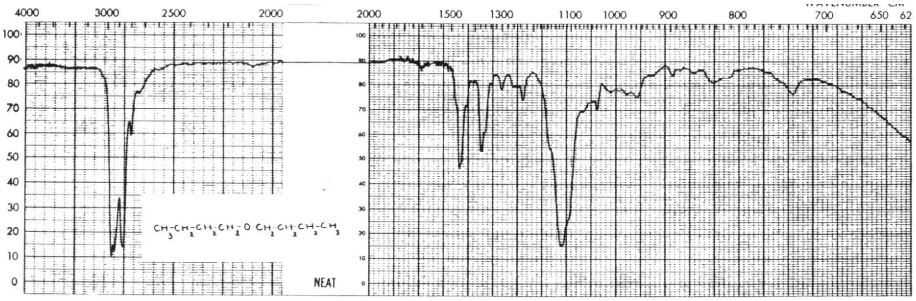
pKa - 3.6 so H-base has to have a pKa less than -3.6

Which of the following will epoxides react with?



IR Spectra of Ethers

What band do ethers have that alkanes don't? C-O 1300-1000 cm^{-1}



What other compounds have this band? How can they be distinguished from ethers?

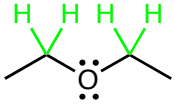
esters - also have C=O band

alcohols - also have OH band

anhydrides - also have 2 C=O bands

NMR Spectra of Ethers

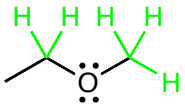
What chemical shift are the H's next to the O in an ether? 3-4 ppm



4H quartet at 3-4 ppm

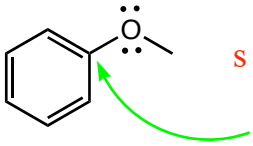
How will the spectra of a symmetrical ether and a nonsymmetrical ether be different?

symmetrical - 1 peak at 3-4 ppm; unsymmetrical - 2 peaks at 3-4 ppm



q and s at 3-4 ppm (might overlap)

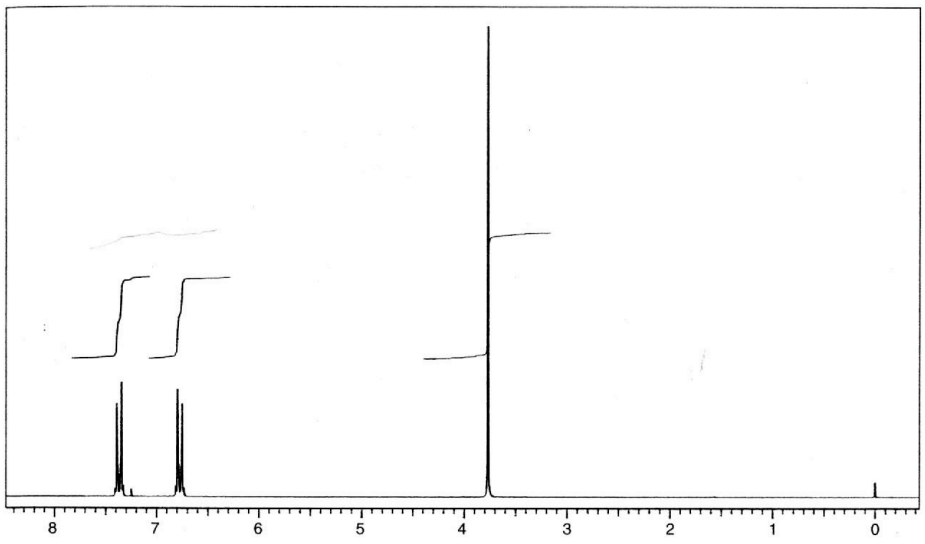
What will happen with an aryl ether?



s at 4-6 ppm

no H's next to O on aryl side

Deduce the structure of the compound which gave the following spectrum.

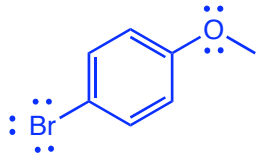


C_7H_7BrO

a - 2H d ~7 ppm aromatic

b - 2H d ~7 ppm 4 aromatic H's - 2 substituents

c - 3H s 3-4 ppm 3H's next to O



4-bromoanisole

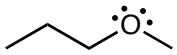
II. Nomenclature of ethers

Common names

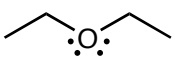
How are common names for ethers constructed?

substituent + substituent + "ether"

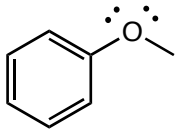
Give common names for the following ethers.



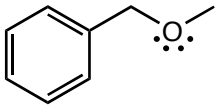
methyl propyl ether



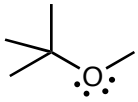
dimethyl ether



methyl phenyl ether

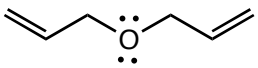


benzyl methyl ether



tert-butyl methyl ether

MTBE - oops



diallyl ether

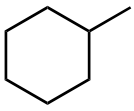
IUPAC names

Are ethers principle groups? no - don't change the ending

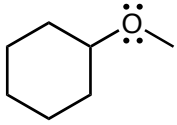
What part of the ether is considered a substituent?

the O plus the smallest carbon chain connected to it

How are ether substituents named?



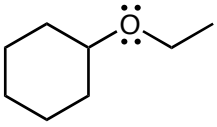
methylcyclohexane



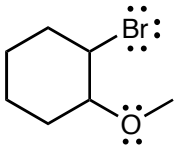
methoxycyclohexane

change "yl" to "oxy"

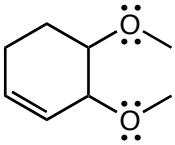
Name the following compounds.



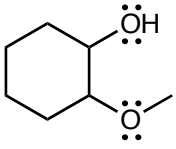
ethoxycyclohexane



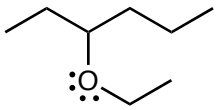
1-bromo-2-methoxycyclohexane



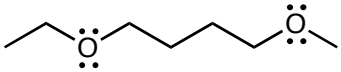
3,4-dimethoxy-1-cyclohexene



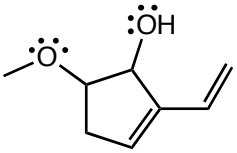
2-methoxy-1-cyclohexanol



3-ethoxyhexane



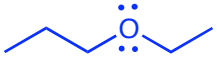
1-ethoxy-4-methoxybutane



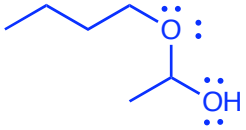
5-methoxy-2-vinyl-2-cyclopentene-1-ol

Draw structures for the following:

1-ethoxypropane

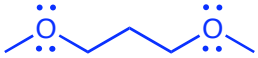


1-butoxy-1-ethanol

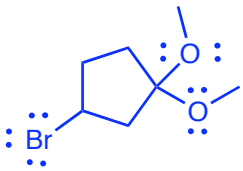


4-propoxy-1-butene

1,3-dimethoxypropane



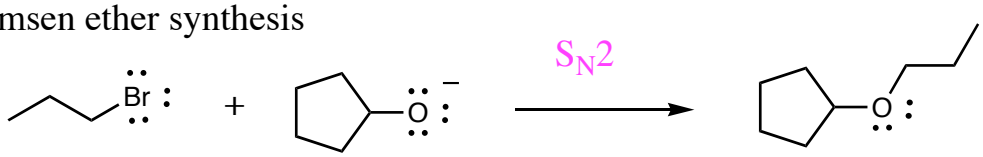
3-bromo-1,1-dimethoxycyclopentane



III. Synthesis of ethers and sulfides

What starting materials and reagents are needed for each of the methods of ether synthesis?

Williamsen ether synthesis

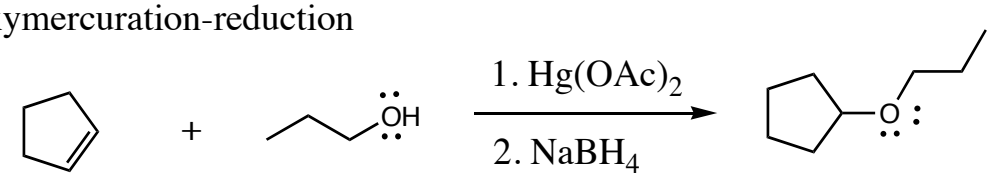


alkyl halide or tosylate

alkoxide

S_N2 reaction

alkoxymercuration-reduction



alkene

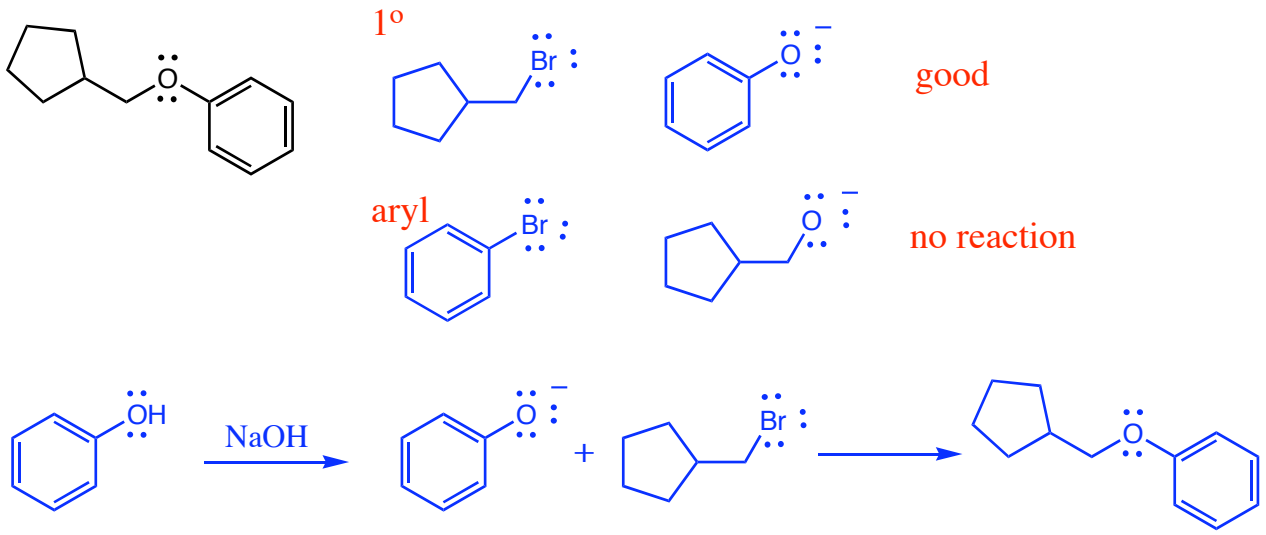
alcohol

oxymercuration-reduction with an alcohol instead of water

What is the main limitation of the Williamsen ether synthesis?

the alkyl halide or tosylate must be 1°

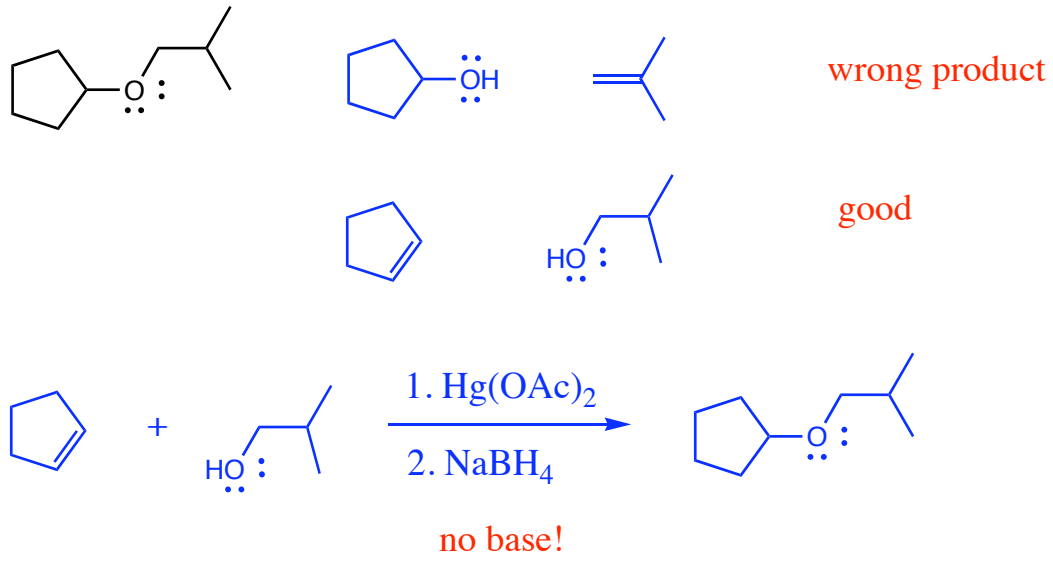
Synthesize the following ether by the Williamsen ether synthesis.



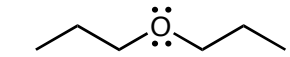
What is the main limitation of the alkoxymercuration-reduction reaction?

ether always goes to the more substituted side of the alkene
equally substituted - two products

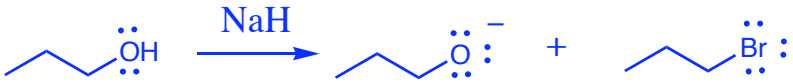
Synthesize the following ether by alkoxymercuration-reduction.



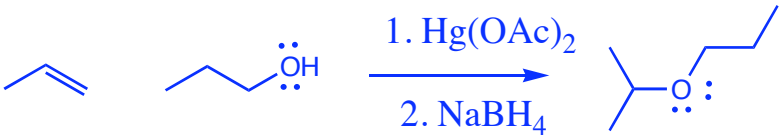
Synthesize the following ethers by either the Williamsen ether synthesis or alkoxymercuration-reduction. Explain why the other won't work!



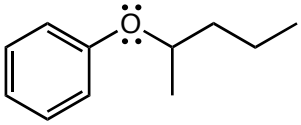
Williamsen



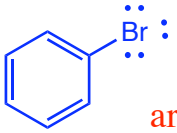
alkoxymercuration-reduction



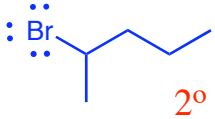
wrong product



Williamsen



aryl

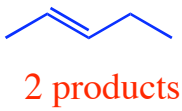


2°

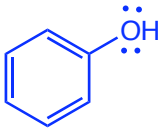
no reaction
or E2 products as well

alkoxymercuration-reduction

good



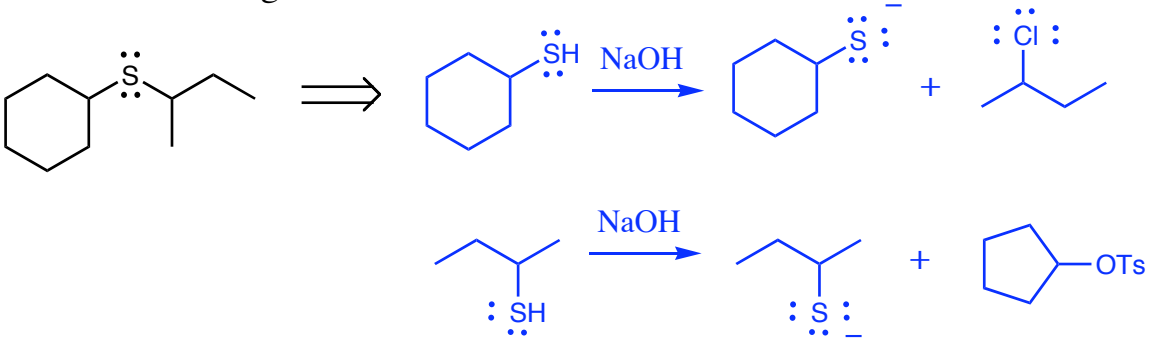
2 products



Which of these methods works for synthesis of sulfides? S_N2

What effect does the lower acidity of thiolate ions have? no E2, even with 2° RX or ROTs

Synthesize the following sulfide.

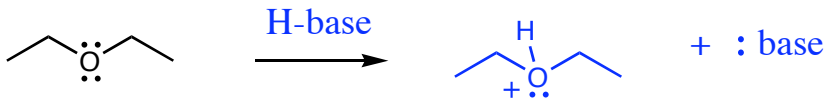


IV. Reactions of ethers and sulfides

Reactions of Ethers

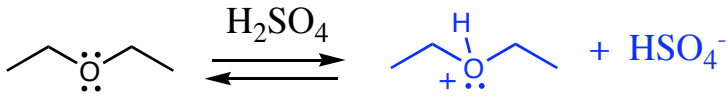
Are ethers highly reactive, or highly unreactive functional groups?

What kind of reagents do ethers react with? strong acids



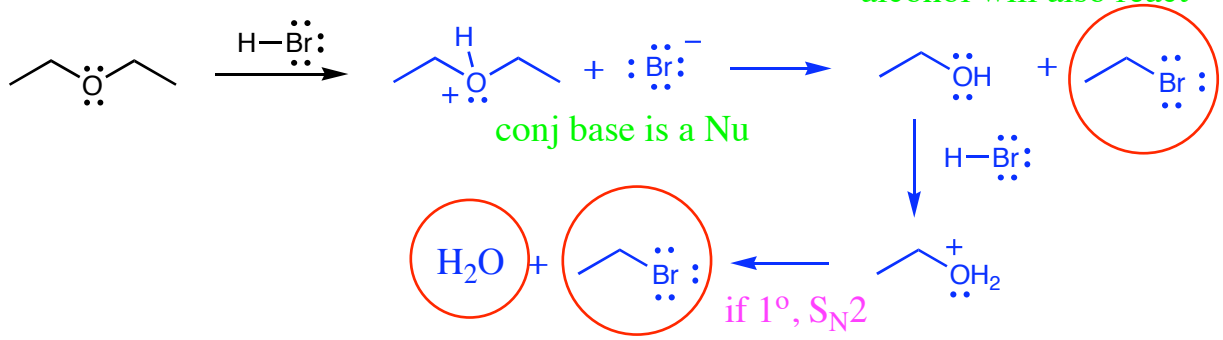
pKa = -3.6

Which of the following will give a new product?



protonates, that's all

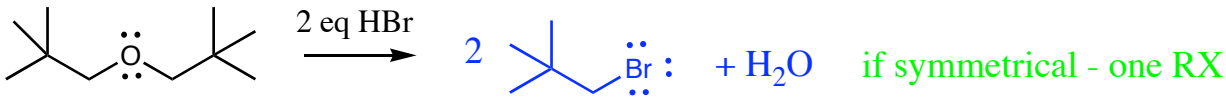
alcohol will also react



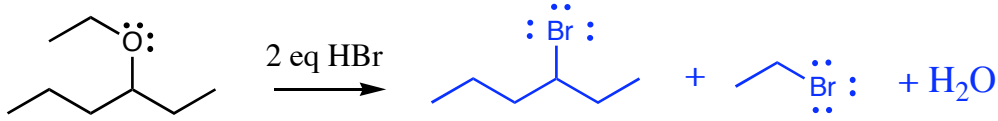
conj base is a Nu

if 1°, S_N2
if 3°, S_N1
if 2°, both

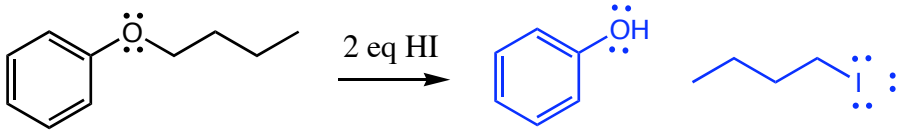
What products would the following ethers give?



if symmetrical - one RX



if unsymmetical, two RX



aromatic ethers give phenol, can't react

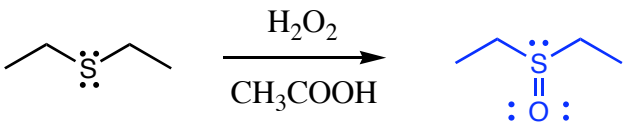
Is this a good way to make alkyl halides?

not really - makes two products, harder to make the ether first

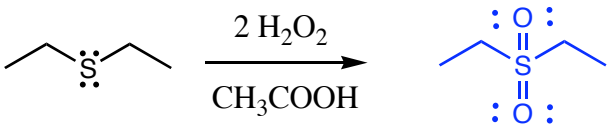
Reactions of Sulfides

What reaction can sulfides undergo that ethers cannot? oxidation

What can they be oxidized to?



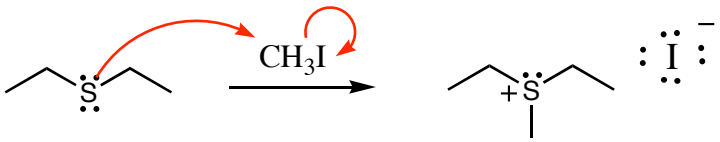
sulfoxides



sulfones

Which is a better nucleophile, S or O? S - larger

What happens when a sulfide acts as a nucleophile towards an alkyl halide?



alkylating agent
see biochem application p 642

V. Synthesis of Epoxides

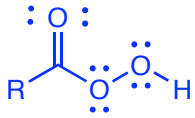
What are the two ways in which epoxides may be formed?

1) alkene + peroxy acid --> epoxide

2) halohydrin + base --> epoxide

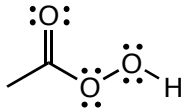
Epoxidation of alkenes

What do peroxyacids look like?



COOH with an extra O

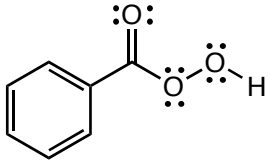
Which of the following peroxy acids are soluble in water or alchols? Which in low polarity solvents? How are they abbreviated?



peroxyacidic acid

water, alcohols

CH_3CO_3H

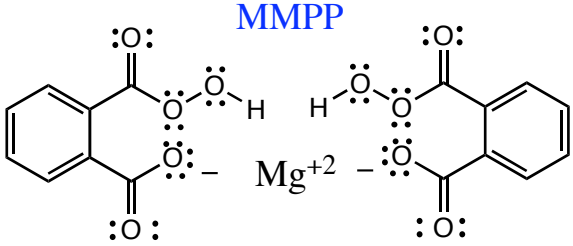


peroxybenzoic acid

low polarity solvents

$PhCO_3H$

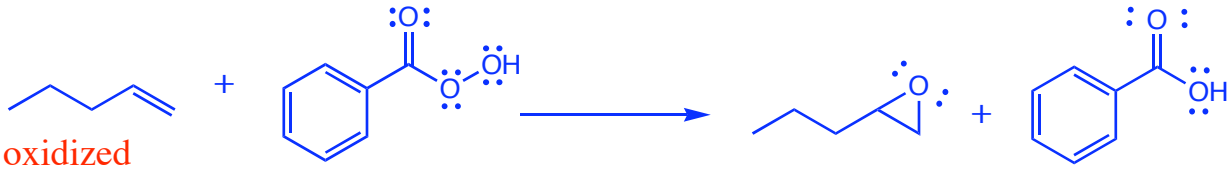
MMPP



magnesium monoperoxyphthalate

when used in low polarity solvents
product crystallizes out

Write a reaction of an alkene with a peroxy acid to form an epoxide.

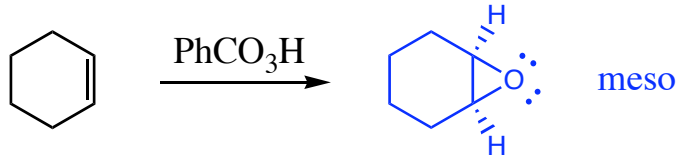


oxidized

reduced

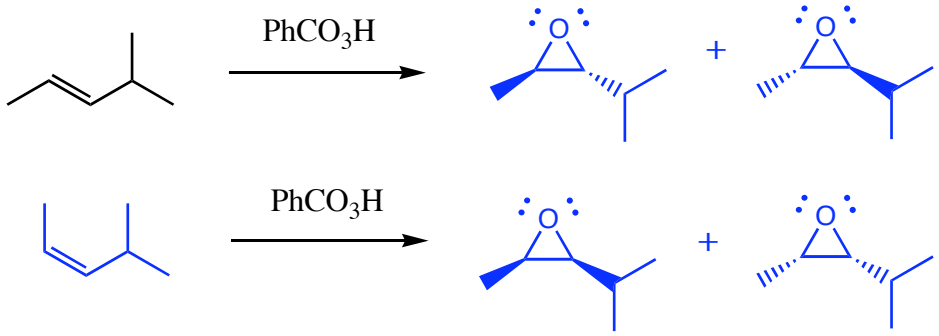
What gets oxidized and reduced in the reaction above?

What stereochemistry does this reaction have? Why?



meso

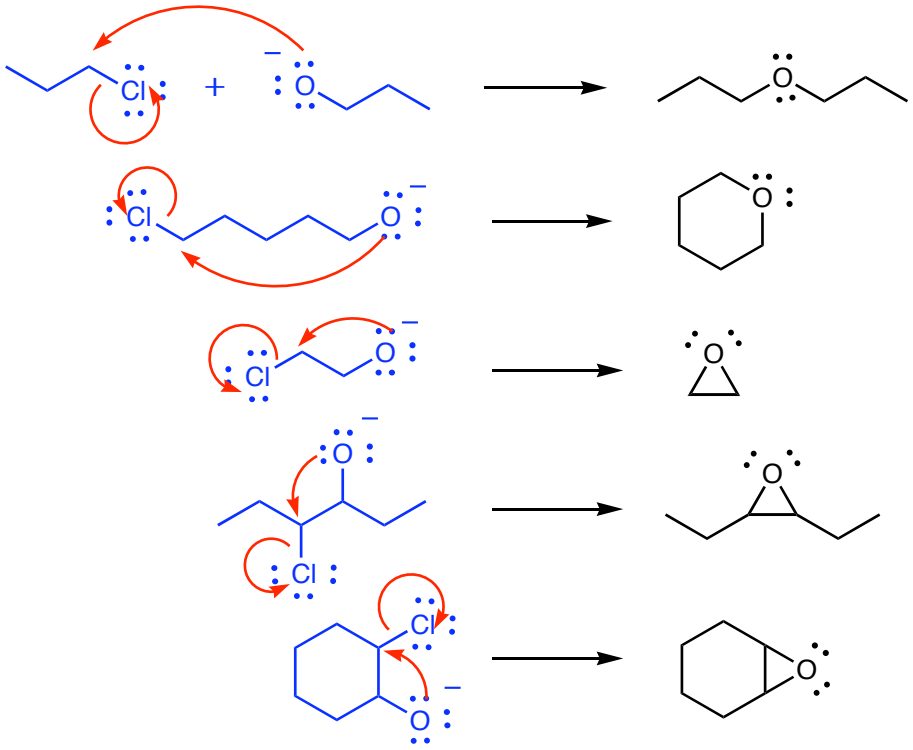
syn addition - O added to the same side
mechanism is electrocyclic, O connects to both C's at the same time



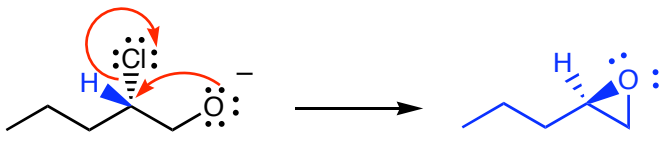
if you want this result, how do you get it?

Cyclization of halohydrins

We have seen how alkoxides react with alkyl halides to form ethers in the Williamson ether synthesis. How could this be used to make an epoxide?

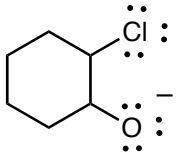


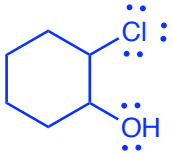
What is the stereochemistry of this reaction? Why?



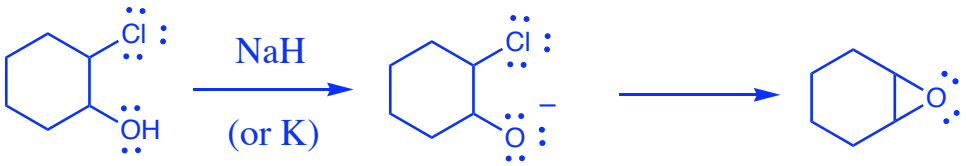
inversion - S_N2, attacks from the opposite side of the halogen

What does the starting material look like before the H is removed to make the alkoxide? What is this functional group called?

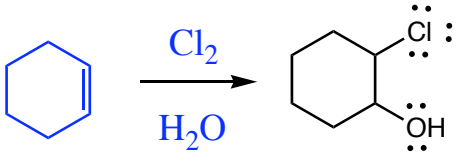
reagent we need: 

starting material:  halohydrin

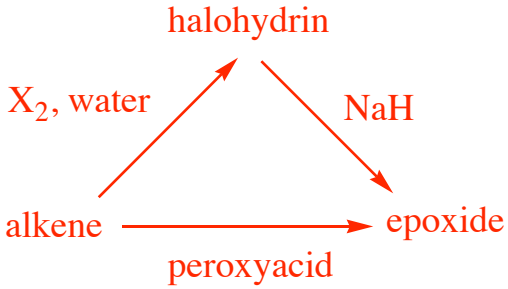
Write the entire reaction starting with the neutral starting material.



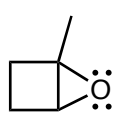
Where do halohydrins come from?



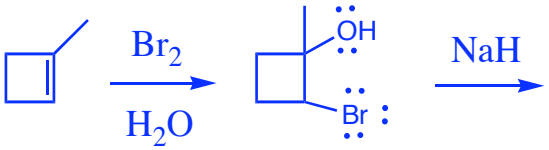
So, how are the two epoxide syntheses related?

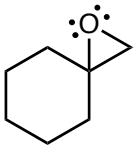


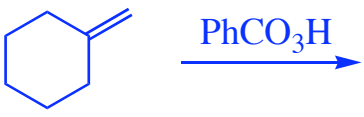
Show two ways each of the following epoxides could be formed from an alkene.

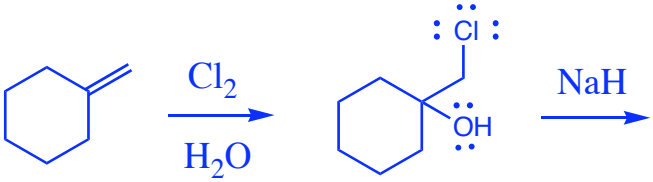


1) 

2) 



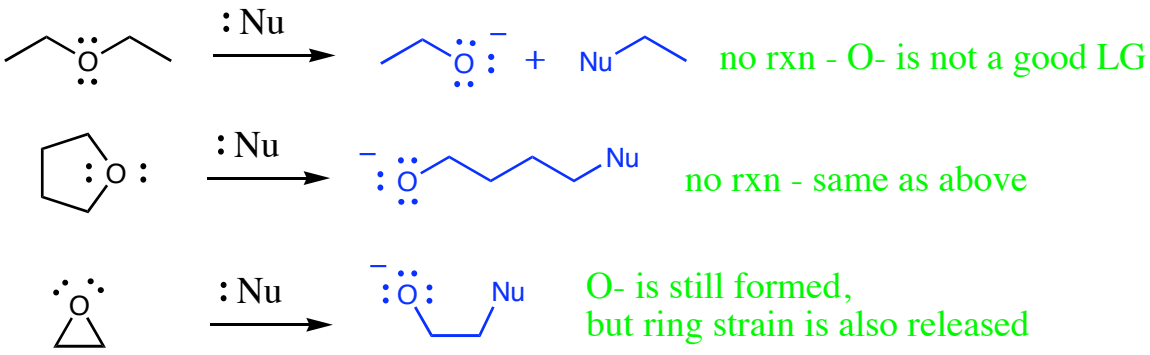
1) 

2) 

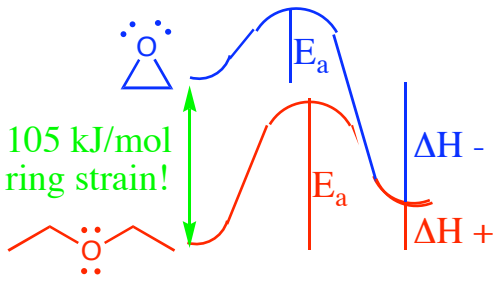
VI. Reactions of Epoxides

Reaction of epoxides with strong nucleophiles

Why are epoxides good electrophiles, while ethers are not?



How do their energy diagrams compare?



epoxide: small E_a = fast - ΔH = exothermic

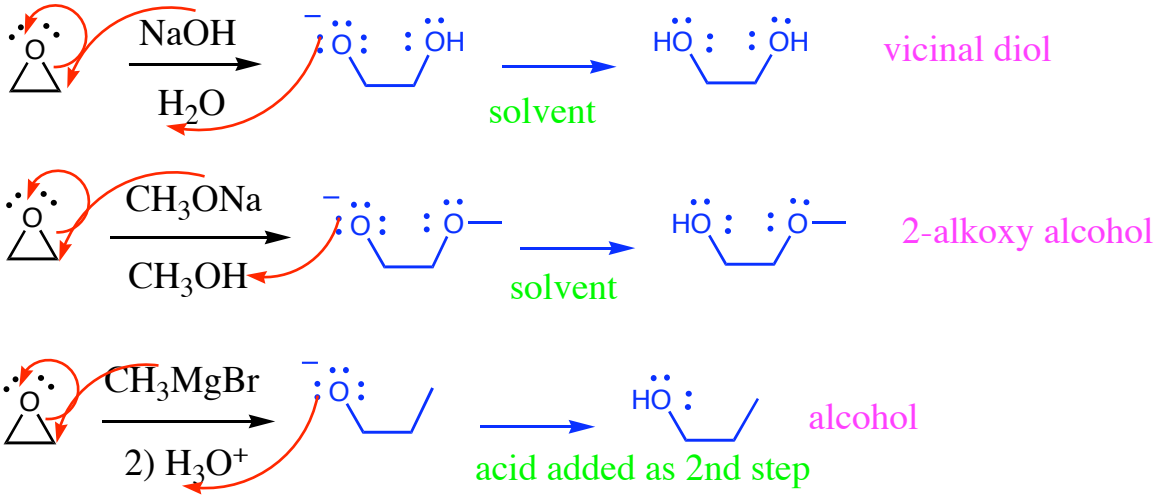
ether: large E_a = slow + ΔH = endothermic

since the epoxide starts out so much higher, it is
it is ok to form a charged product

What needs to happen to complete the reaction?

alkoxide needs to be protonated
source of H will depend on the Nu

What product is formed when each of the following nucleophiles is reacted with ethylene oxide? What is the proton source in each case?



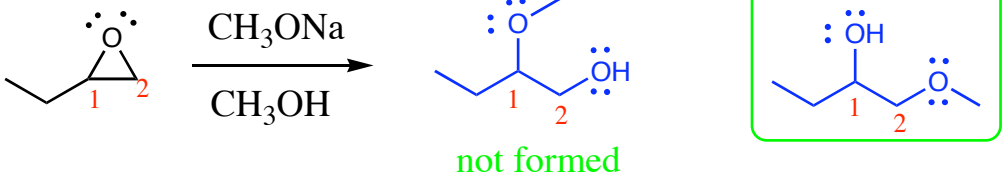
What other nucleophiles would attack epoxides?

any S_N2 Nu  

cyanide acetylide ions thiolate ions

If the epoxide is not equally substituted, which side will be attacked?

attack at C1 attack at C2



not formed

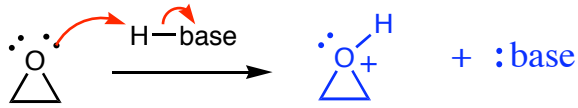
Write the two possible products.

How could we figure out which will be formed? by experiment

Knowing the answer, how can we make sense of it? sterics - less hindered side is attacked

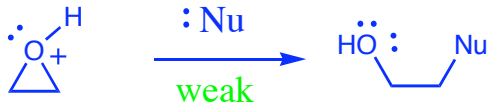
Reactions of protonated epoxides with weak nucleophiles

How can an epoxide react with an acid?



Which is a better electrophile, a neutral epoxide or a protonated one? Which requires a stronger nucleophile?

less reactive strong forms alkoxide - charged

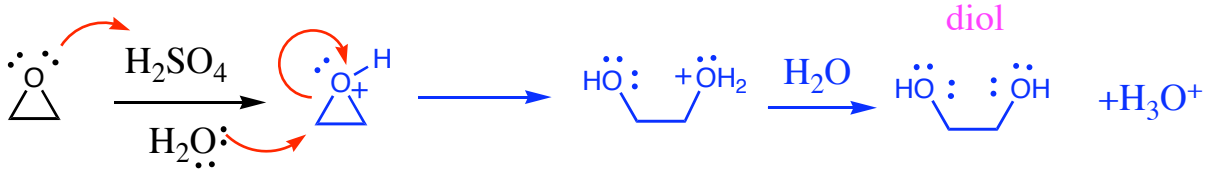


more reactive weak forms alcohol - neutral

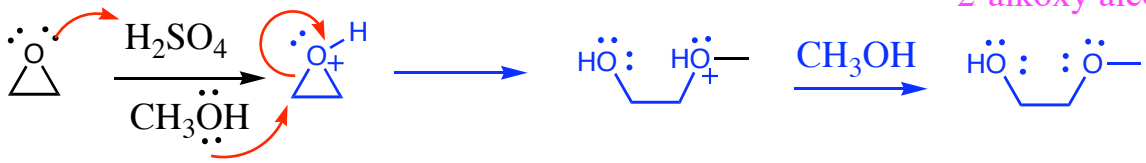
What kinds of weak nucleophiles would work?

S_N1 Nu water, alcohols

Show how a protonated epoxide would form, then react with water or an alcohol. What product is formed?



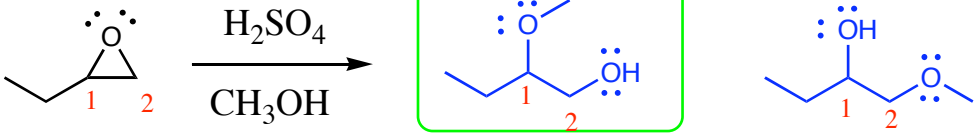
diol



2-alkoxy alcohol

What do you notice about the acid? catalytic

If the epoxide is not equally substituted, which side will be attacked?



attack at C1

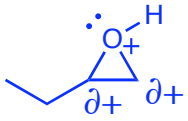
attack at C2

not formed

Write the two possible products.

How could we figure out which will be formed? by experiment

Knowing the answer, how can we make sense of it?

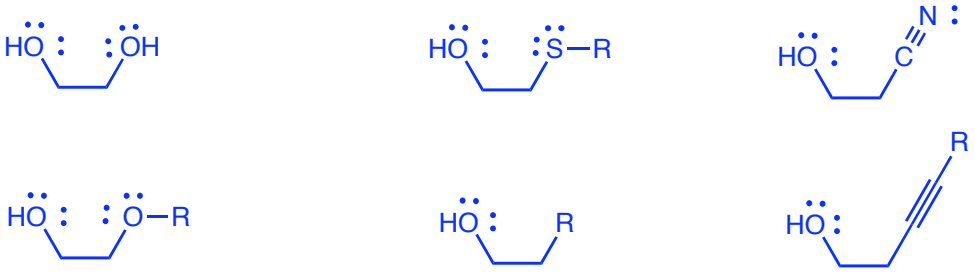


more substituted C has more of the + charge

<u>Synthesis using epoxides</u>

What kinds of products can be made using epoxides?

compounds with an alcohol next to something that can be attached using a Nu



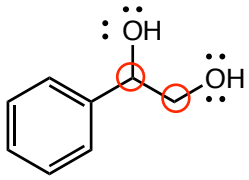
What steps should you take when designing a synthesis using an epoxide?

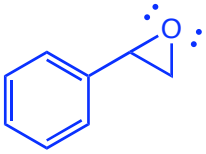
1) determine where the epoxide was

2) figure out what Nu(s) could be used

3) determine if the Nu will attack the correct side

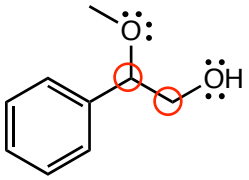
What reaction could be used to form the following products?

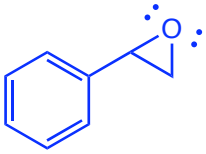




H_2SO_4 / H_2O or NaOH / H_2O

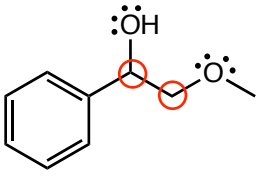
since both sides end up the same, it doesn't matter which side the Nu attacks

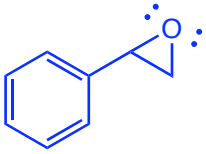




H_2SO_4 / CH_3OH or CH_3ONa / CH_3OH

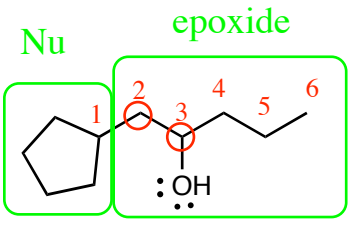
since the ether is on the more substituted side, acid and a weak Nu must be used

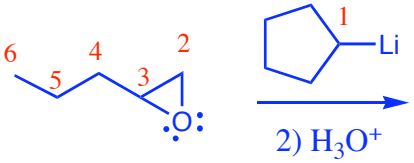


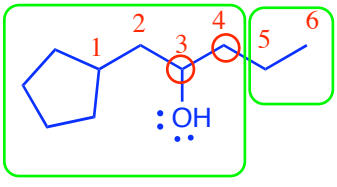


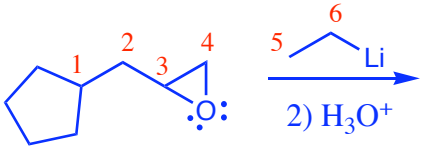
H_2SO_4 / CH_3OH or CH_3ONa / CH_3OH

now the ether is on the less substituted side, so a strong Nu must be used







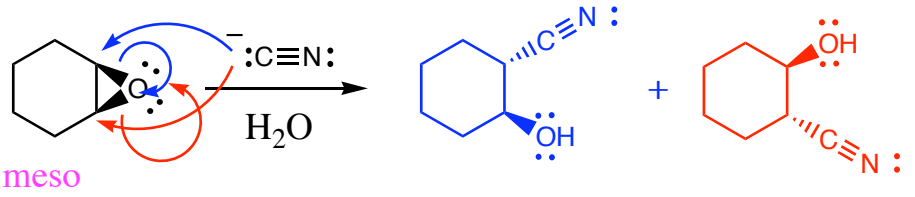


Nu must attack the more substituted side, but either side could be the Nu

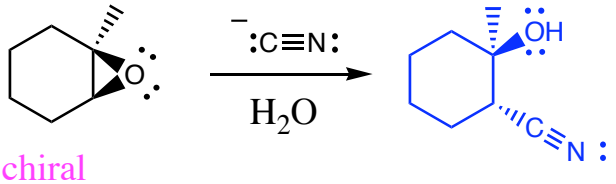
Stereochemistry of epoxide reactions

What is the stereochemistry of the addition of the Nu to an epoxide?

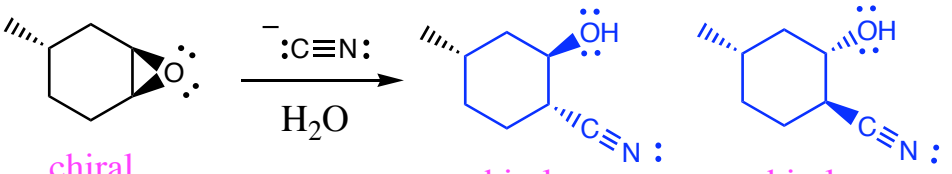
the carbon which is attacked it inverted; the other carbon stays the same



meso



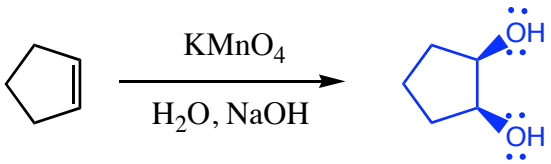
chiral

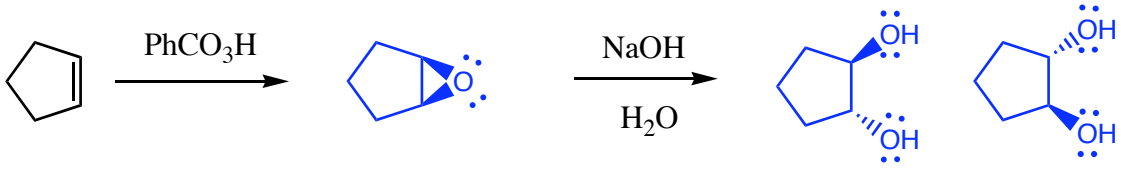


chiral chiral chiral

the idea is not to memorize these examples, but use the principles to predict stereochemical results in multiple situatons

Compare the stereochemistry of the following reactions.





How are these two reactions complementary?

hydroxylation gives cis diols

epoxidation, then hydrolysis gives trans diols