

Chapter 18: Ethers and Epoxides; Thiols and Sulfides



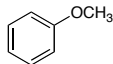
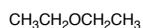
alcohols



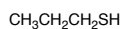
ethers



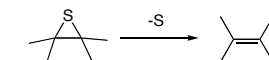
epoxides



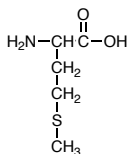
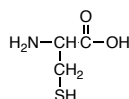
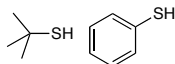
thiols
(mercaptans)



sulfides
(thioethers)



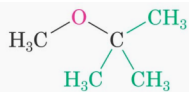
episulfides
unstable



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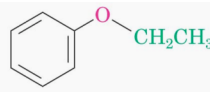
18.1 Naming Ethers

Simple ethers are named by identifying the two organic substituents and adding the word *ether*



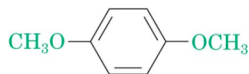
tert-Butyl methyl ether

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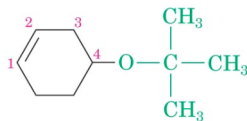
Ethyl phenyl ether

If other functional groups are present, the ether part is considered an alkoxy substituent



p-Dimethoxybenzene

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4-tert-Butoxy-1-cyclohexene

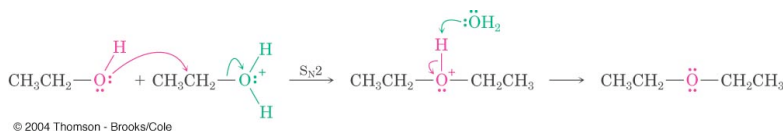
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18.2: Structure & properties of ethers:

The oxygen of ethers is sp^3 -hybridized and tetrahedral
The ether oxygen is a weak Lewis base
Ethers have small dipole moments and are relatively non-polar
Inert to a wide range of reaction conditions- good solvents

Synthesis of ethers:

Symmetrical ethers can be prepared by treating the corresponding alcohol with a strong acid



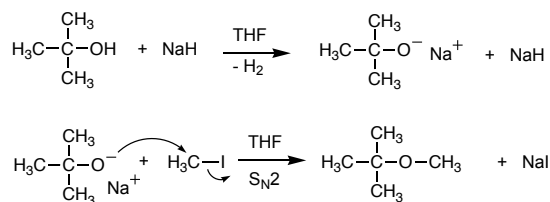
Limitations: must be symmetrical
works best for 1° alcohols

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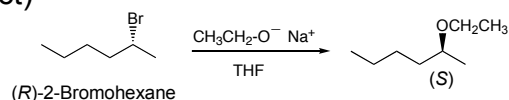
18.3: Williamson Ether Synthesis

Reaction of metal alkoxides with alkyl halides or tosylates to give ethers. This is an $\text{S}_\text{N}2$ reaction.

Alkoxides are prepared by the reaction of an alcohol with a strong base such as sodium hydride, NaH



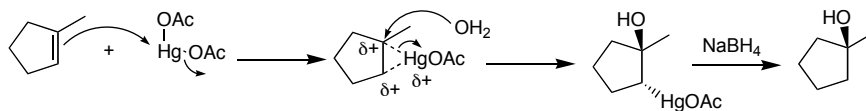
Few restriction regarding the nature of the alkoxide
Works best for 1° alkyl halide or tosylate; E2 elimination is a competing reaction with 2° halides and tosylates
 3° halides undergo E2 elimination (vinyl and aryl halides do react)



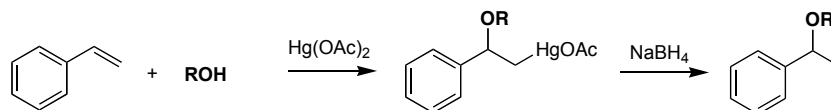
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18.4: Alkoxymercuration of alkenes

Recall oxymercuration (Chapter 7.4): overall Markovnikov addition of H-OH across the π -bond of an alkene



Alkoxymercuration: replace water with an alcohol to get the Markovnikov addition of H-OR across the π -bond of an alkene



Few restrictions regarding the nature of the alcohol or alkene

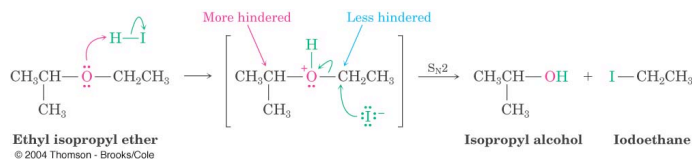
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18.5: Reactions of Ethers: Acidic Cleavage

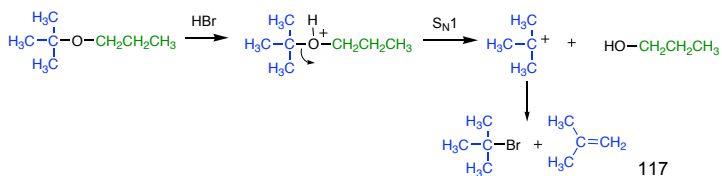
Ethers are generally unreactive

Ether bonds can be broken with strong acid (HI or HBr) and heat

The mechanism involves protonation of the ether followed by an $\text{S}_{\text{N}}2$ reaction with the halide acting as the nucleophile (works best for phenyl alkyl ethers $\text{Ph-O-CH}_2\text{R}$)

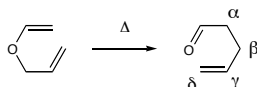


However:



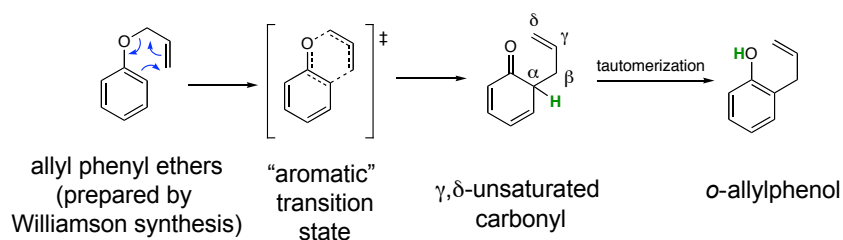
18.6: Reactions of Ethers: Claisen Rearrangement

Thermal rearrangement ($> 200^\circ \text{C}$) of allyl vinyl ethers to give γ,δ -unsaturated carbonyls



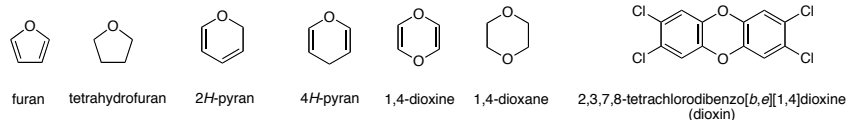
Member of a class of *pericyclic* reactions known as *sigmatropic* rearrangements (Chapter 30)

Allyl phenyl ethers rearrange to *o*-allylphenols



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18.7: Cyclic Ethers: Epoxides

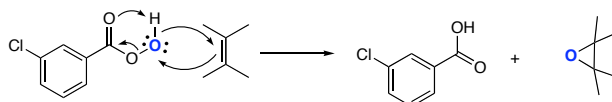
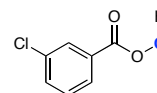


Epoxides (oxirane): three-membered ring, cyclic ethers;
the strain of the three-membered ring makes
epoxides electrophilic



Synthesis of epoxides from alkenes:

epoxidation with *m*-chloroperbenzoic acid
(mCPBA)

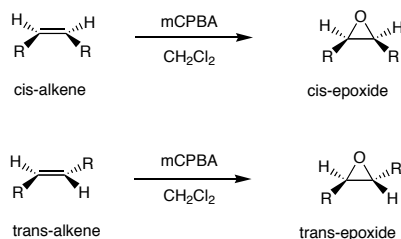


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Stereochemistry of the mCPBA epoxidation:
syn addition of oxygen.

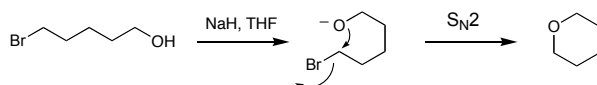
The geometry of the alkene is preserved in the product
(recall the cyclopropanation of alkenes, Ch. 7.6)

Groups that are trans on the alkene will end up trans on the epoxide product. Groups that are cis on the alkene will end up cis on the epoxide product.

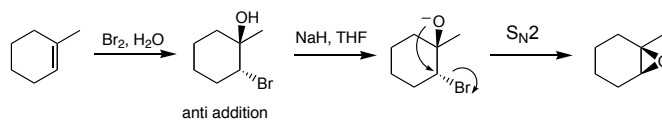


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Intramolecular Williamson Synthesis: general method for the synthesis of cyclic ethers: the alkoxide and alkyl halide are part of the same molecule



Epoxides from halohydrins

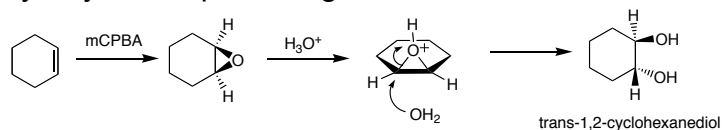


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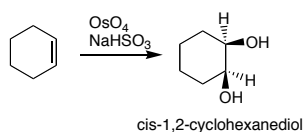
18.8: Ring-Opening Reactions of Epoxides

Acid-catalyzed epoxide opening: protonation of the epoxide oxygen makes it more reactive toward nucleophiles

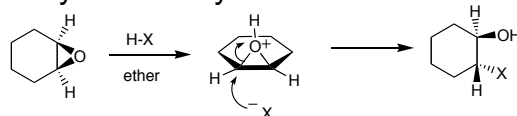
hydrolysis of epoxides give vicinal diols



complementary to dihydroxylation of alkenes



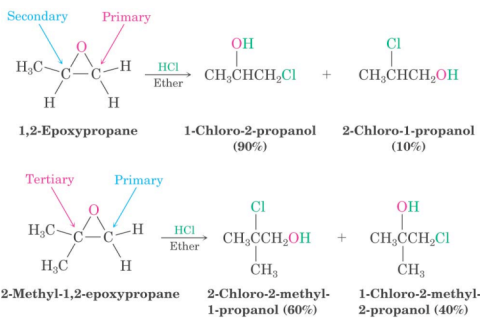
acid-catalyzed halohydrin formation from epoxides



Regiochemistry of acid-catalyzed epoxide openings:

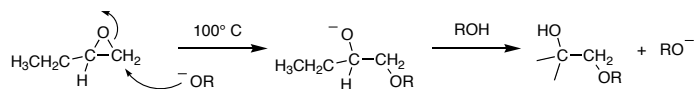
if the carbons of the epoxide are 1° or 2°, then the epoxide opening goes predominantly by an S_N2 mechanism and the nucleophile adds to the least substituted carbon

if either carbon of the epoxide is 3°, the epoxide opening goes predominantly by an S_N1 mechanism and the nucleophile adds to the 3°-carbon

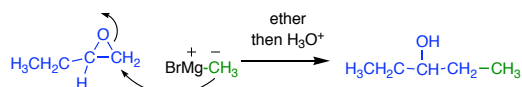


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Nucleophilic (base-catalyzed) epoxide opening:
Epoxide undergo ring-opening with nucleophiles via an S_N2 mechanism



Nucleophilic epoxide opening with Grignard reagents



The nucleophile will add to the least substituted carbon of the epoxide (S_N2 mechanism)

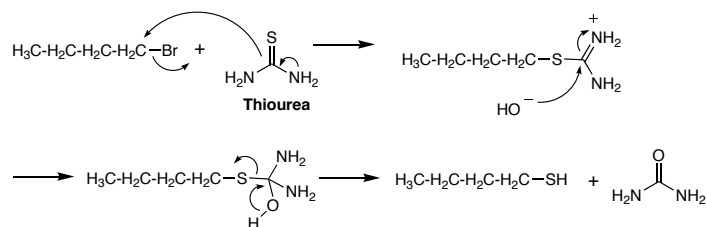
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18.9: Crown Ethers (please read)

18.10: Thiols and sulfides

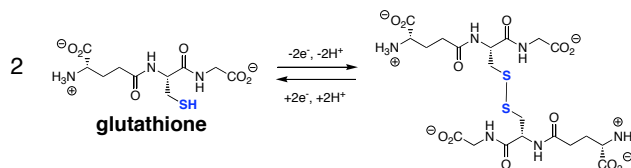
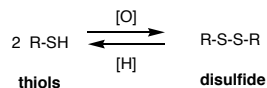
Thiols (mercaptans) are sulfur analogues of alcohols
Sulfides (thioethers) are sulfur analogues of ethers

Preparation of thiols from alkyl halides (S_N2):

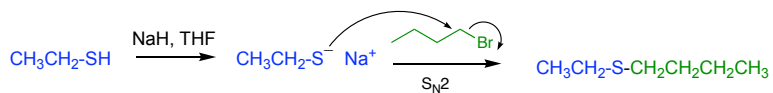


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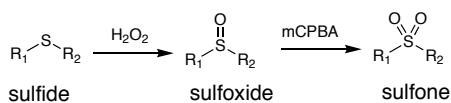
Thiols can be oxidized to disulfides



Thiolate ions (anions of thiols) are very reactive nucleophiles
Thiolates react with 1° and 2° alkyl halides to yield sulfides (S_N2), analogous to the Williamson ether synthesis

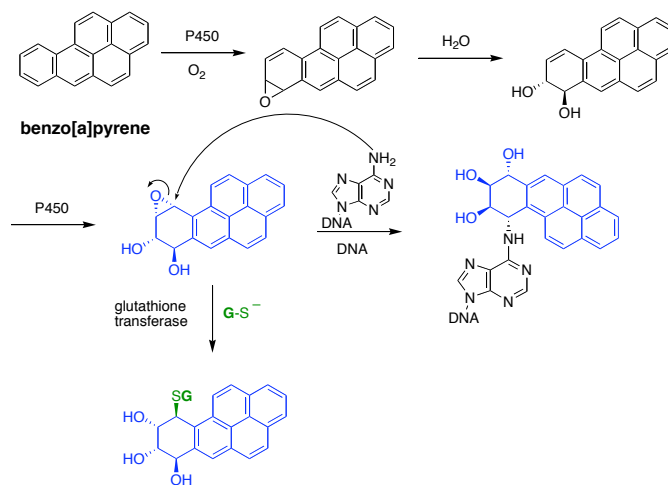


Sulfides can be oxidized to sulfoxides and sulfones



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Bioactivation and detoxication of benzo[a]pyrene diol epoxide:

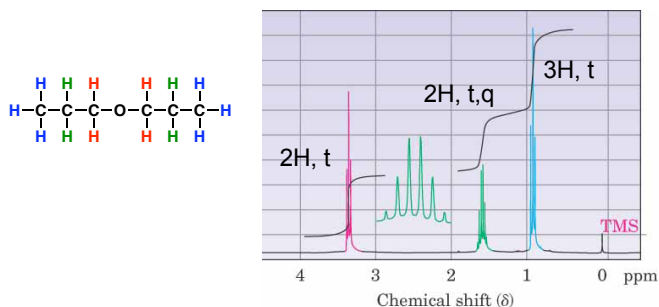


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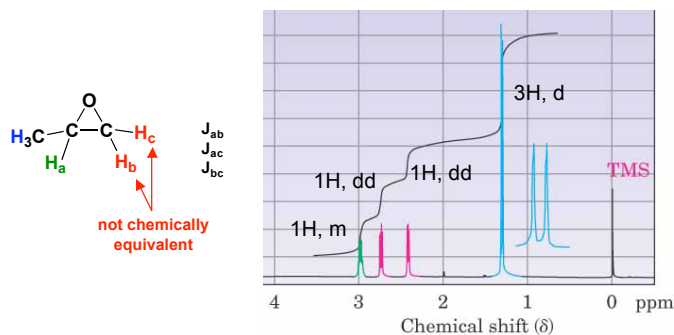
18.11 Spectroscopy of ethers

IR spectroscopy: not particularly diagnostic for the ether functional group. Strong C-O single bond stretch between 1050-1150 cm^{-1}

^1H NMR: protons on the carbons that are part of the ether linkage are deshielded relative to alkanes. The chemical shift of these protons is from $\delta = 3.5 - 4.5$ ppm



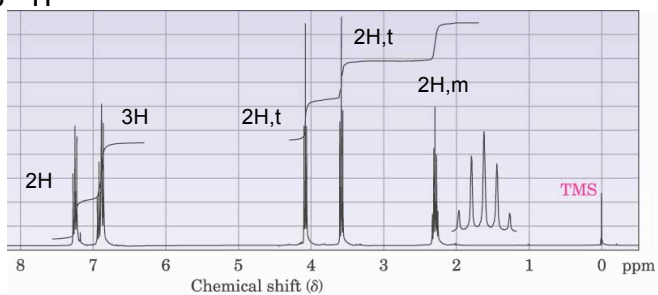
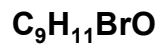
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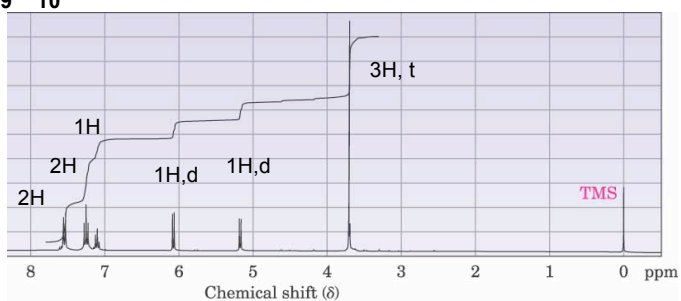
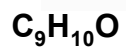
Protons on epoxide carbons are shield relative to those of a typical ethers ($\delta = 2.0 - 3.0$ ppm)

^{13}C NMR: the chemical shift of carbons that are part of the ether linkage are in the range of $\delta = 50 - 80$ ppm
Epoxide carbons are on the upfield side of this range ($\sim 40 - 60$ ppm)

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13C: 157.5
129.4
120.4
114.4
67.3
31.5
29.0



13C: 147.4
135.2
129.2
128.0
126.4
100.8
55.4

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