

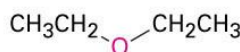
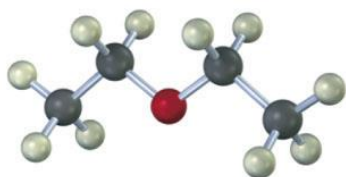
13: Ethers and Epoxides; Thiols and Sulfides

Fall, 2014 by Dr. Isam Al Naser

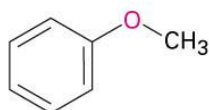
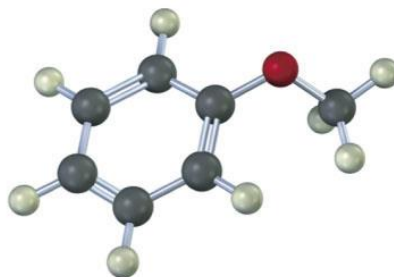
Based on McMurry's *Organic Chemistry*, 7th edition

Ethers and Their Relatives

- An **ether** has two organic groups (alkyl, aryl, or vinyl) bonded to the same oxygen atom, $R-O-R'$
- Diethyl ether is used as an anesthetic and industrially as a solvent
- Tetrahydrofuran (THF) is a solvent that is a cyclic ether
- *Thiols* ($R-S-H$) and *sulfides* ($R-S-R'$) are sulfur (for oxygen) analogs of alcohols and ethers



Diethyl ether



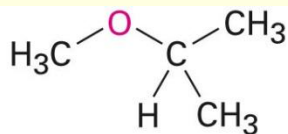
Anisole
(methyl phenyl ether)



Tetrahydrofuran

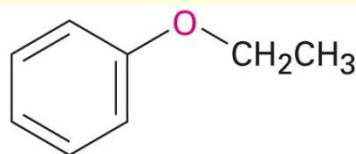
18.1 Names and Properties of Ethers

- Simple ethers are named by identifying the two organic substituents and adding the word *ether*
- If other functional groups are present, the ether part is considered an alkoxy substituent
- R–O–R ~ tetrahedral bond angle (112° in dimethyl ether)
- Oxygen is sp^3 -hybridized

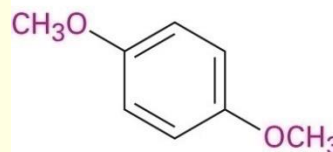


Isopropyl methyl ether

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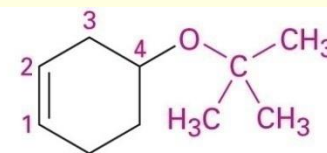


Ethyl phenyl ether



***p*-Dimethoxybenzene**

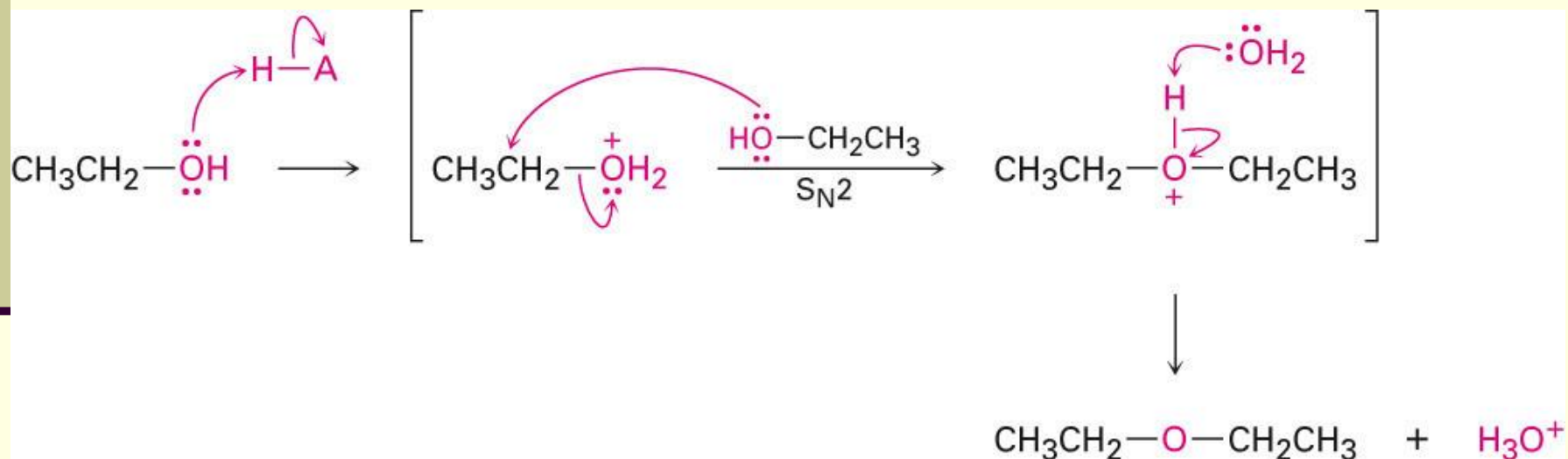
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4-*tert*-Butoxy-1-cyclohexene

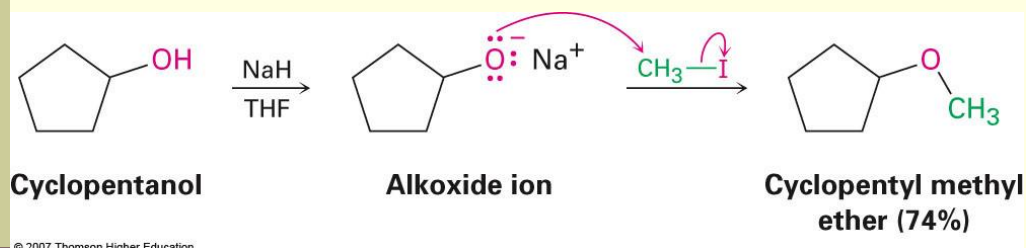
18.2 Synthesis of Ethers

- Diethyl ether prepared industrially by sulfuric acid-catalyzed dehydration of ethanol – also with other primary alcohols



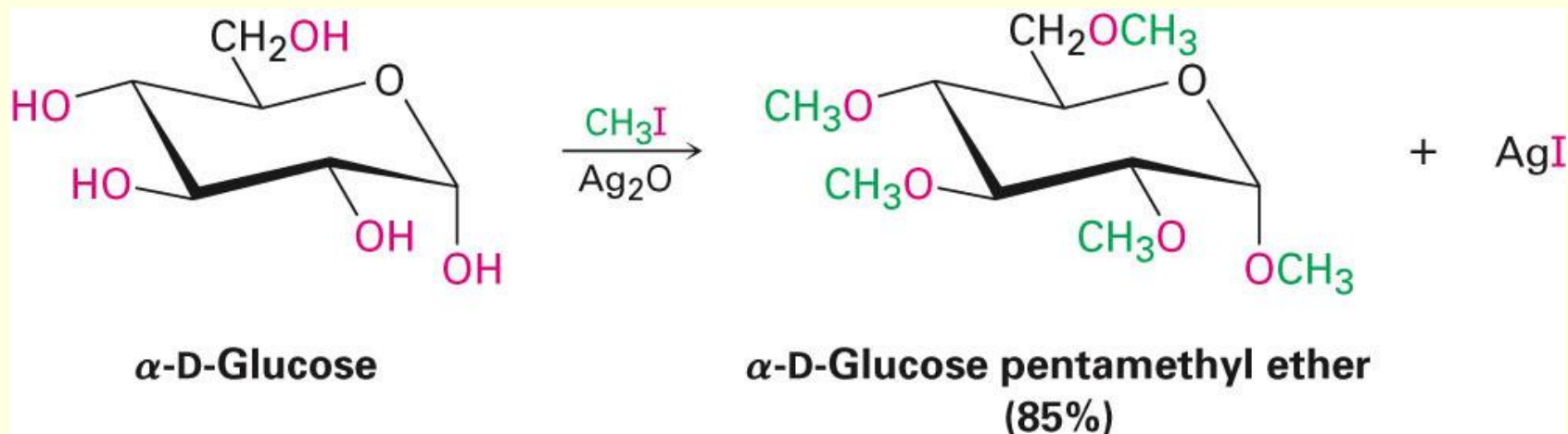
The Williamson Ether Synthesis

- The Best method for the preparation of ethers
- Reaction of metal alkoxides and primary alkyl halides or tosylates in SN2 reaction.
- Alkoxides prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH

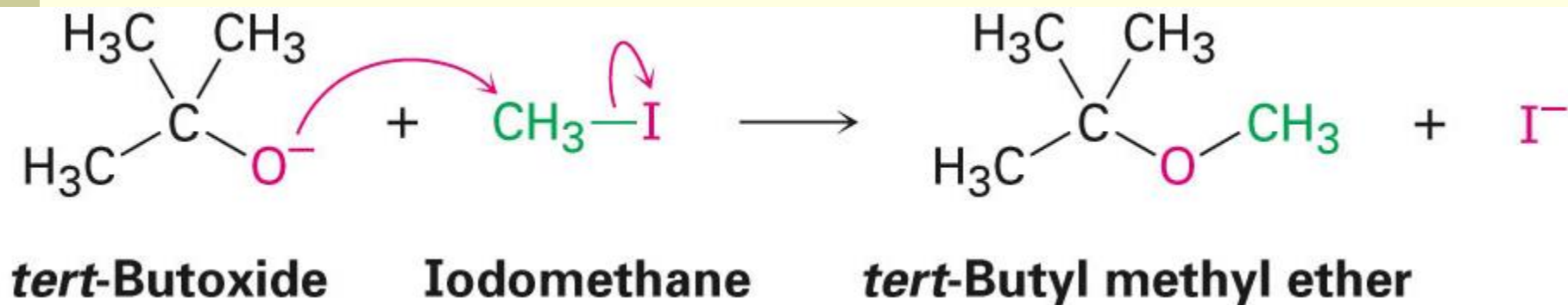


Silver Oxide-Catalyzed Ether Formation

- Reaction of alcohols with Ag_2O directly with alkyl halide forms ether in one step
- Glucose reacts with excess iodomethane in the presence of Ag_2O to generate a pentaether in 85% yield

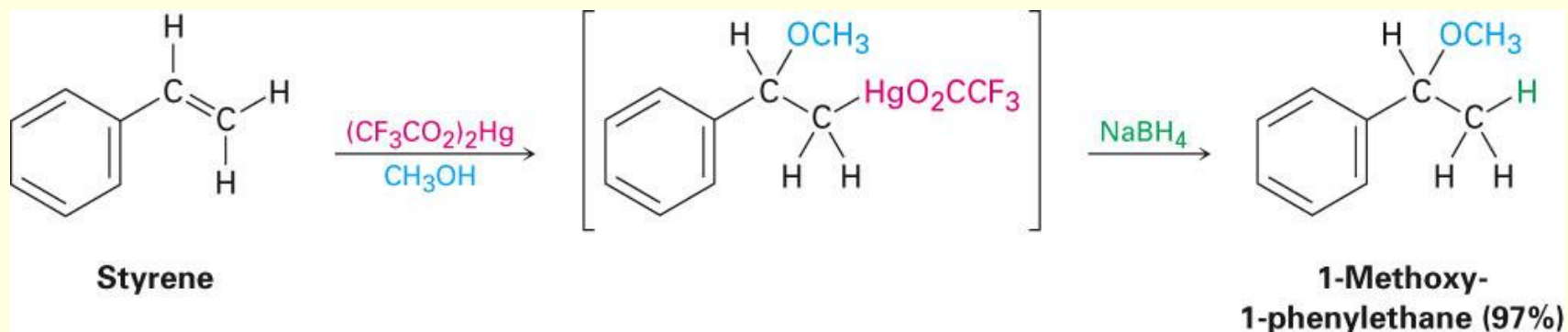


- Tert-butyl methyl ether, a substance used in 1990 as Octane booster in gasoline
- Is best prepared by reaction of tert-butoxide ion with iodomethane.

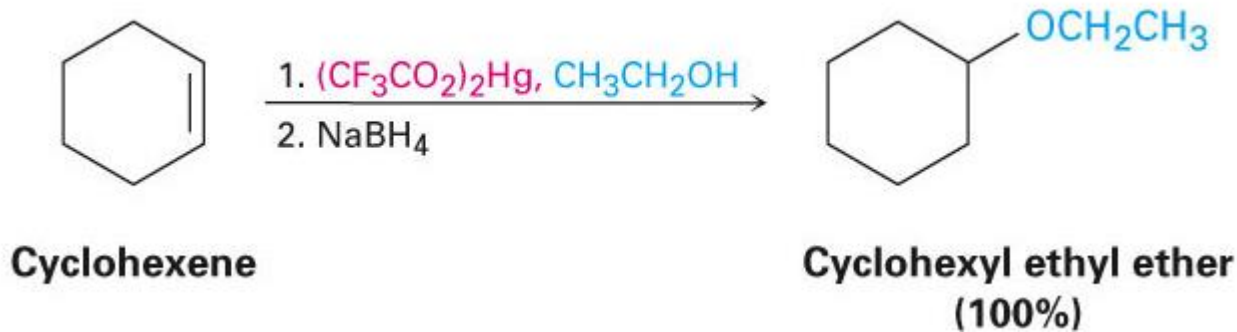


Alkoxymercuration of Alkenes

- React alkene with an alcohol in the presence of mercuric acetate or trifluoroacetate
- Demercuration with NaBH_4 yields an ether
- Overall Markovnikov addition of alcohol to alkene

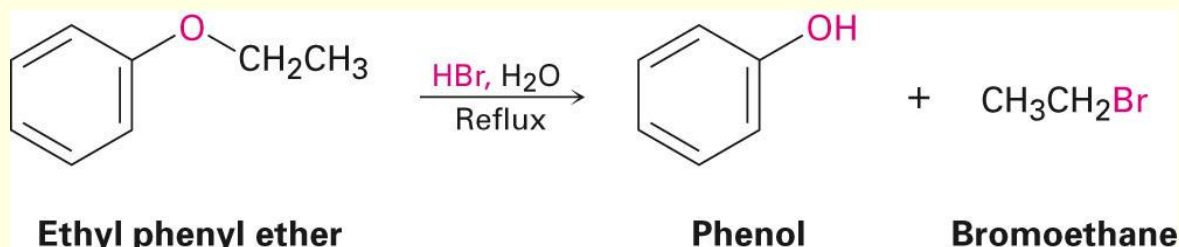


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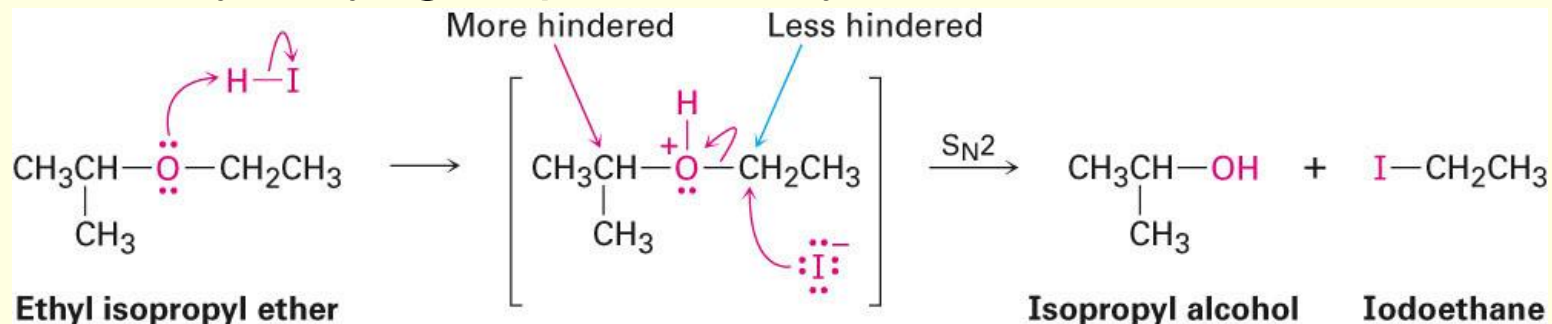
18.3 Reactions of Ethers: Acidic Cleavage

- Ethers are generally unreactive
- Only Strong acid will cleave an ether at high temperature
- HI, HBr both work well, but HCl does not cleave ethers.



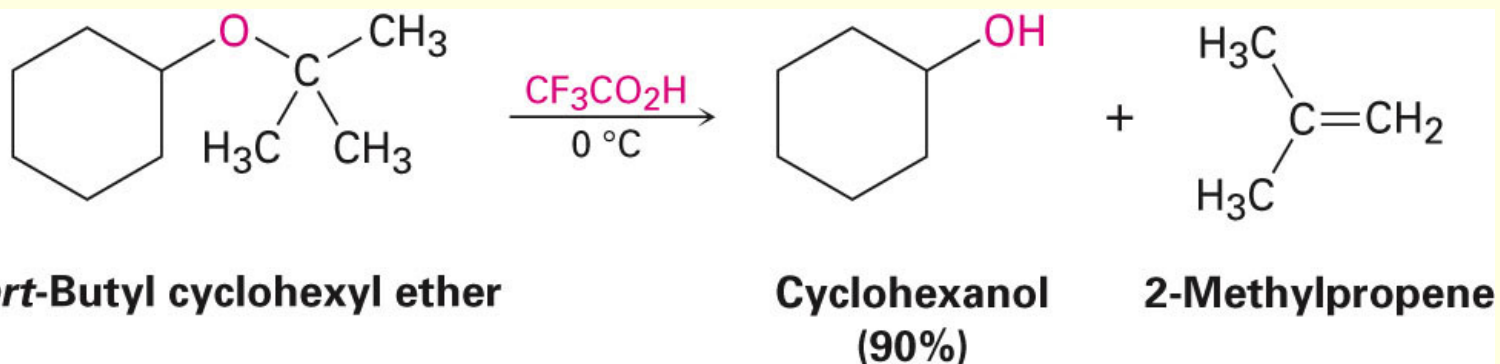
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Acidic ether cleavages are typical S_N1 or S_N2 Depending on the structure of substrate. Ether with only primary and secondary alkyl groups react by an S_N2 mechanism.



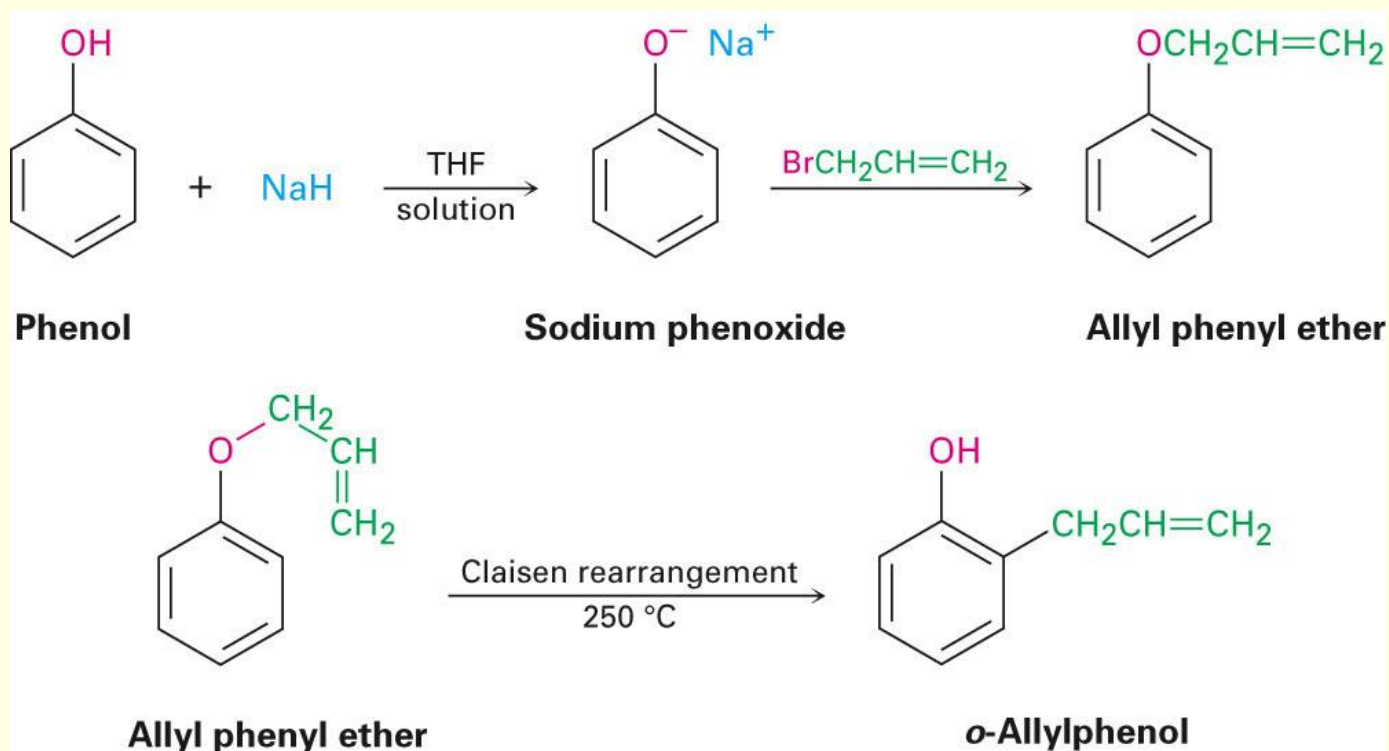
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- Ether with a tertiary, benzylic, or allylic group cleave by an S_N1 mechanism because these substrates can produce stable intermediate carbocations.



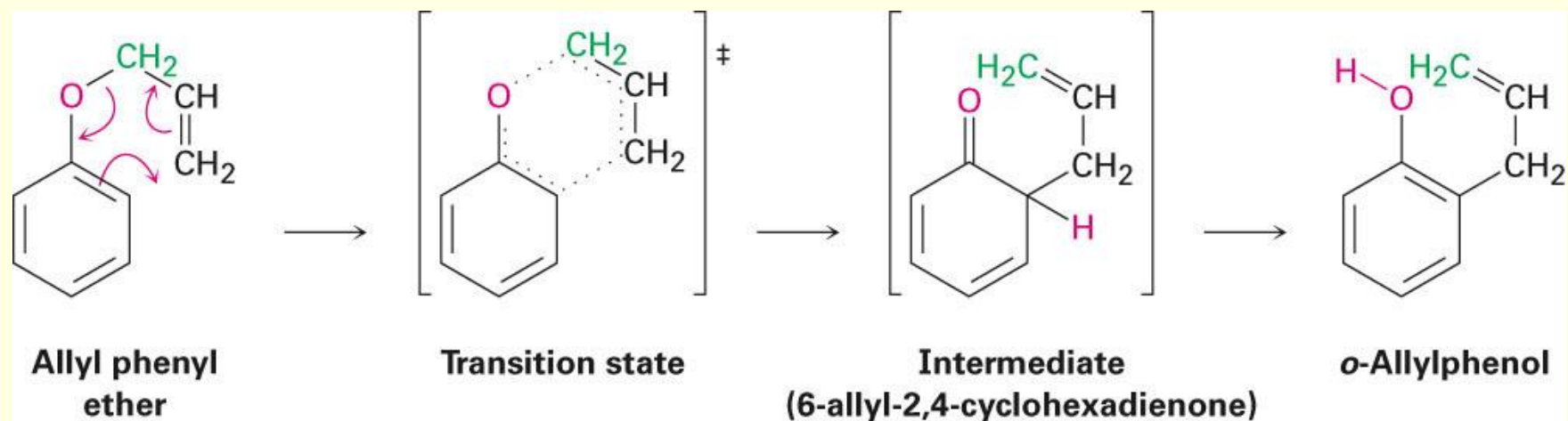
18.4 Reactions of Ethers: Claisen Rearrangement

- Specific to allyl aryl ethers, $\text{ArOCH}_2\text{CH}=\text{CH}_2$
- Heating to $200\text{--}250^\circ\text{C}$ leads to an *o*-allylphenol
- Result is alkylation of the phenol in an ortho position



Claisen Rearrangement Mechanism

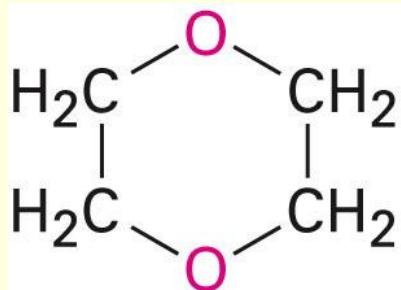
- Concerted pericyclic 6-electron, 6-membered ring transition state



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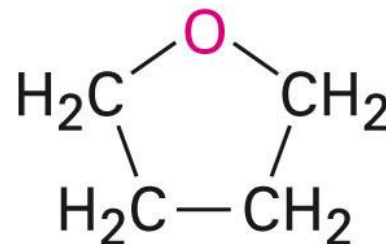
18.5 Cyclic Ethers: Epoxides

- The chemistry of the ether function group is the same, whether it's in an open chain or a ring
- Dioxane and tetrahydrofuran are used as solvents because of their inertness.



1,4-Dioxane

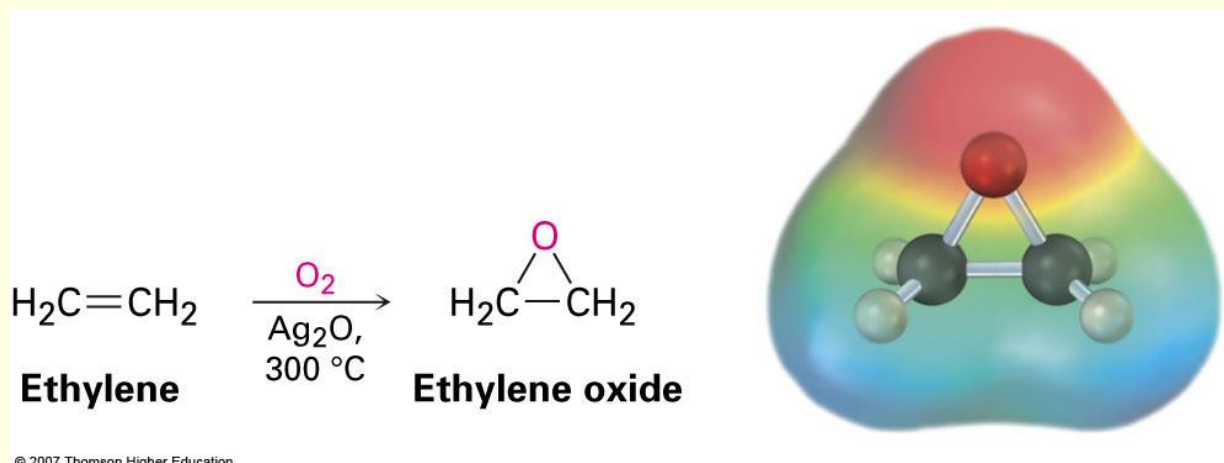
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Tetrahydrofuran

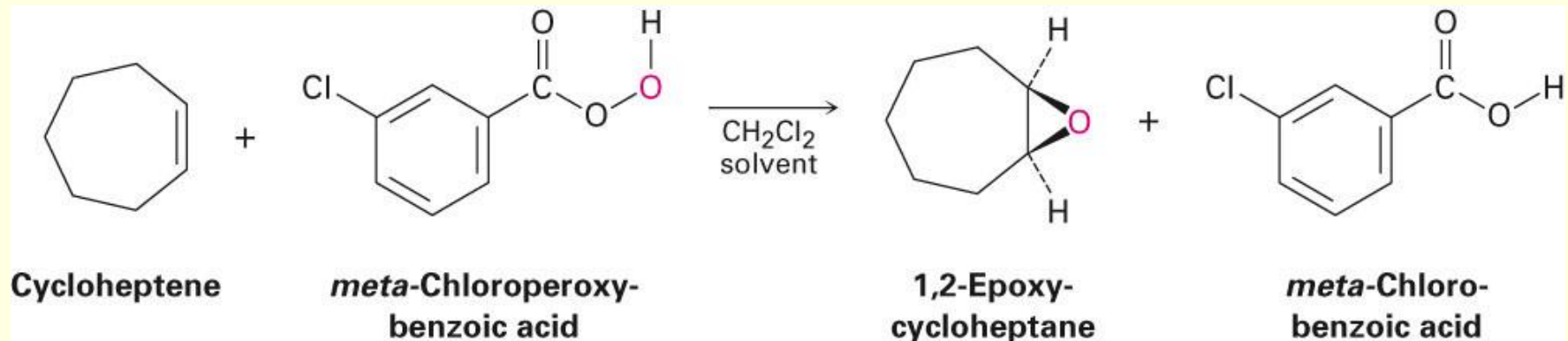
Epoxides (Oxiranes)

- Three membered ring ether is called an epoxide or oxirane (root “ir” from “tri” for 3-membered; prefix “ox” for oxygen; “ane” for saturated)
- Ethylene oxide (oxirane; 1,2-epoxyethane) is industrially important as an intermediate
- Prepared by reaction of ethylene with oxygen at 300 °C and silver oxide catalyst



Preparation of Epoxides Using a Peroxyacid

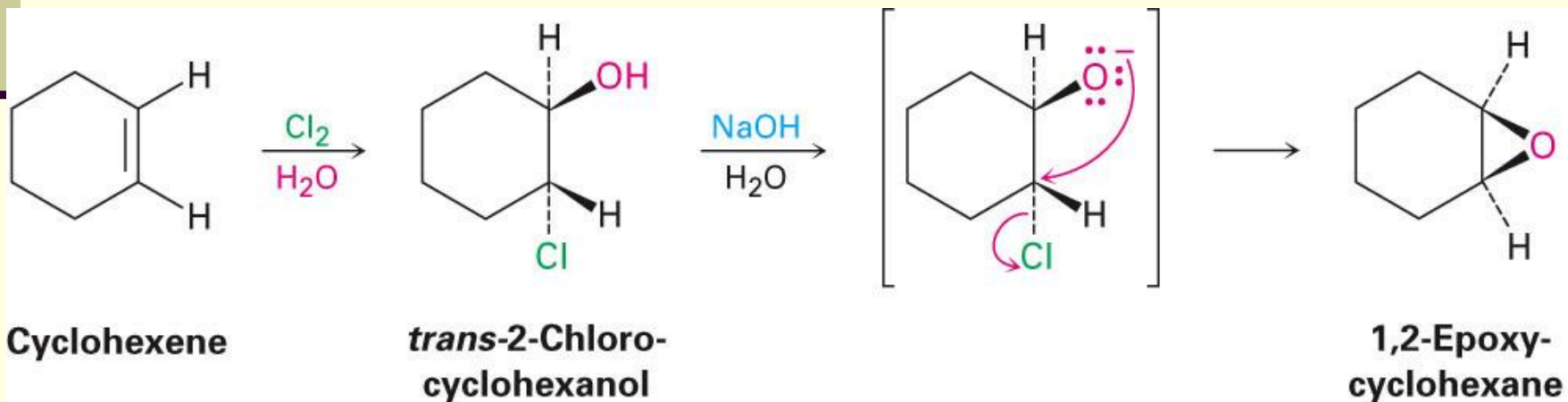
- Treat an alkene with a peroxyacid



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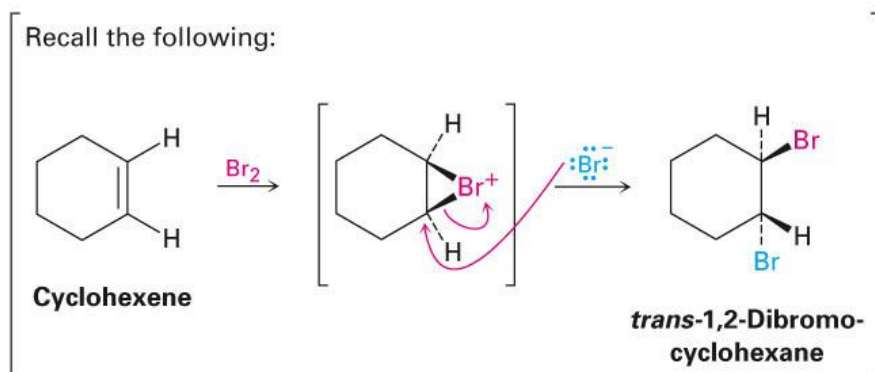
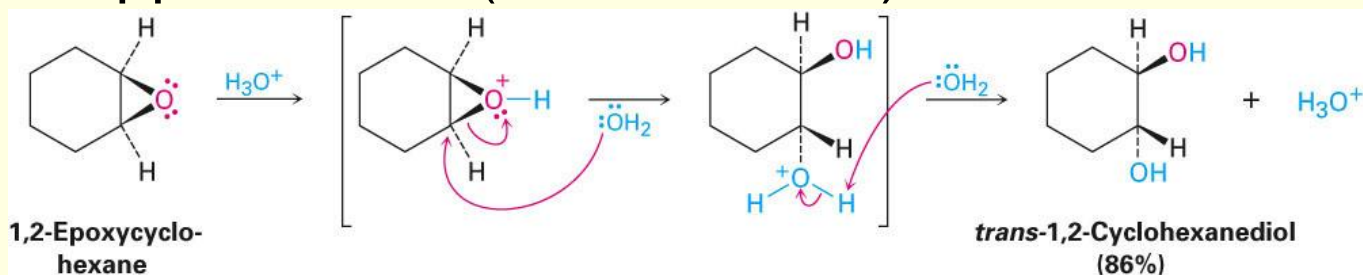
Epoxides from Halohydrins

- Addition of HO-X to an alkene gives a halohydrin
- Treatment of a halohydrin with base gives an epoxide
- Intramolecular Williamson ether synthesis
- The nucleophilic alkoxide ion and the electrophilic alkyl halide are in the same molecule.



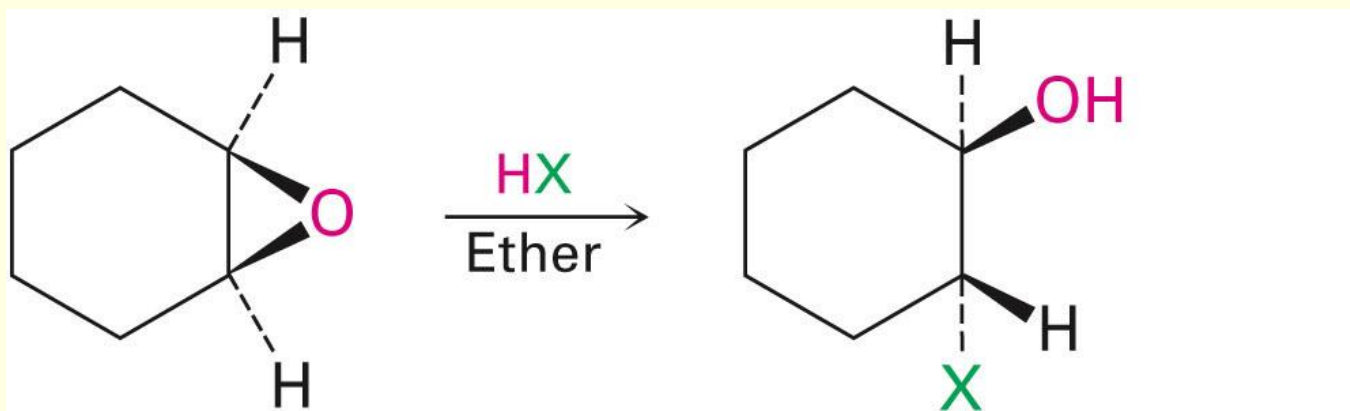
18.6 Reactions of Epoxides: Ring-Opening

- Water adds to epoxides with dilute acid at room temperature
- Product is a 1,2-diol (on adjacent C's: *vicinal*)
- Mechanism: acid protonates oxygen and water adds to opposite side (trans addition)



Halohydrins from Epoxides

- Anhydrous HF, HBr, HCl, or HI combines with an epoxide
- Gives trans product

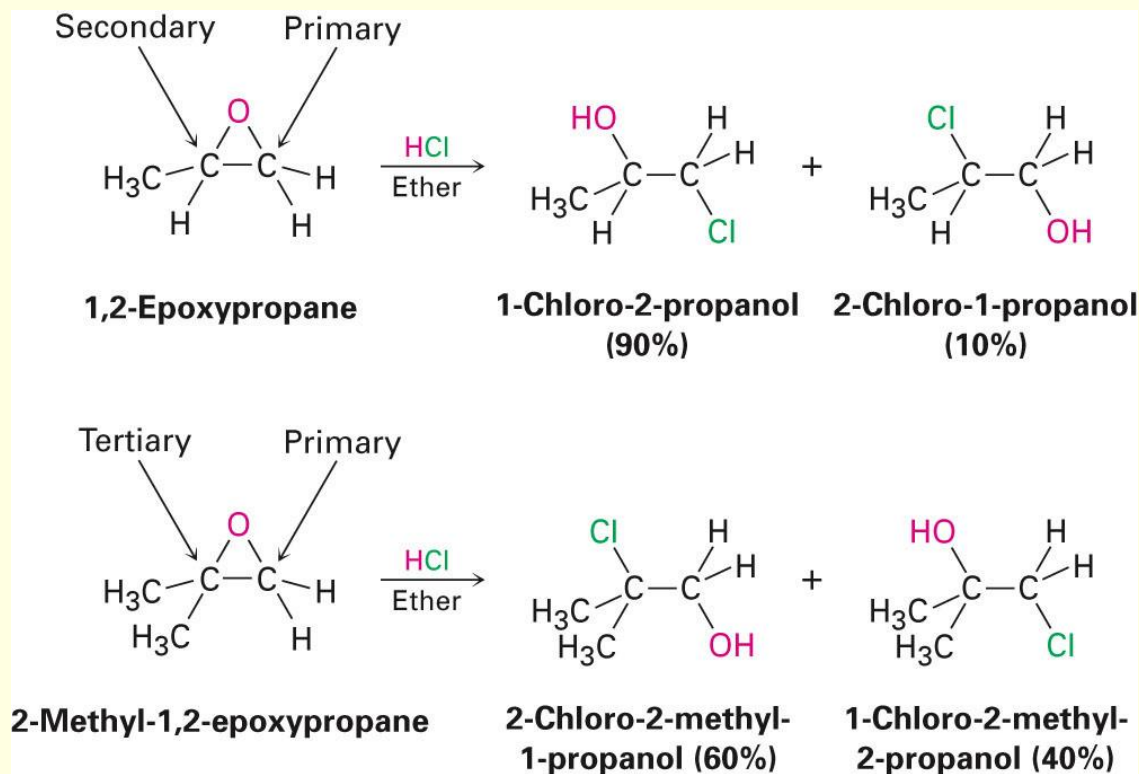


A trans 2-halocyclohexanol

where $X = \text{F, Br, Cl, or I}$

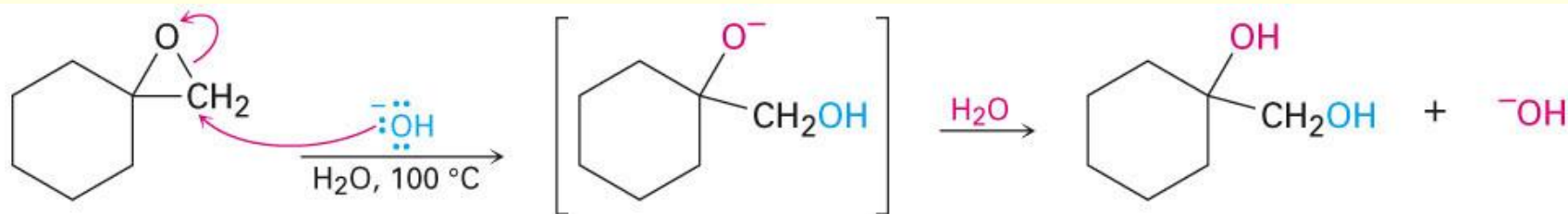
Regiochemistry of Acid-Catalyzed Opening of Epoxides

- Nucleophile preferably adds to less hindered site if primary and secondary C's
- Also at tertiary because of carbocation character .



Base-Catalyzed Epoxide Opening

- Epoxide ring can be cleaved by base as well as by acid.
- The Strain of the three-membered causes epoxides to react with hydroxide ion at high temperatures to give trans 1,2-diols

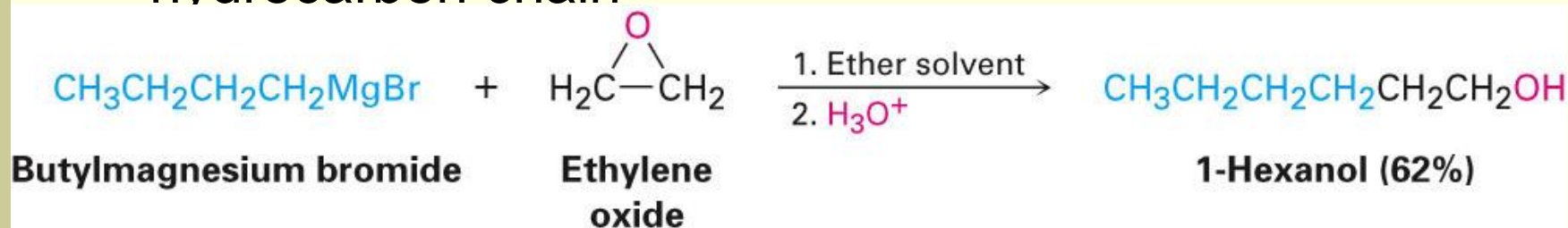


**Methylenecyclohexane
oxide**

**1-Hydroxymethyl-
cyclohexanol (70%)**

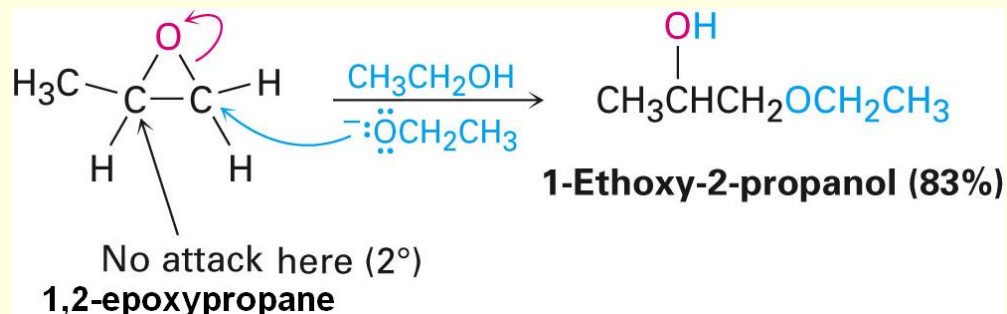
Addition of Grignards to Ethylene Oxide

- Asimilar nucleophilic ring-openinig occur when epoxides are treated with Grignard reagent's .
- Adds $-\text{CH}_2\text{CH}_2\text{OH}$ to the Grignard reagent's hydrocarbon chain



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Base-catalyzed epoxide opening is atypical $\text{S}_\text{N}2$ reaction the Nucleophile takes place at the less hindered epoxide carbon.



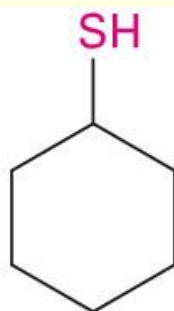
18.8 Thiols and Sulfides

- **Thiols (RSH)**, are sulfur analogs of alcohols
 - Named with the suffix *-thiol*
 - SH group is called “mercapto group”

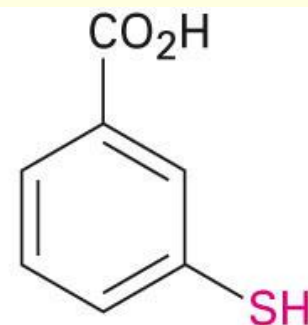


Ethanethiol

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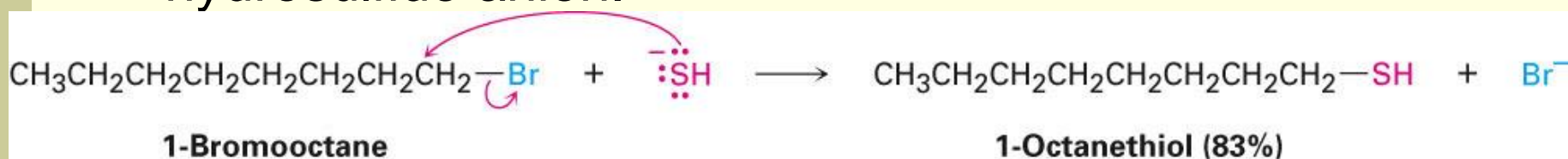
Cyclohexanethiol



***m*-Mercaptobenzoic acid**

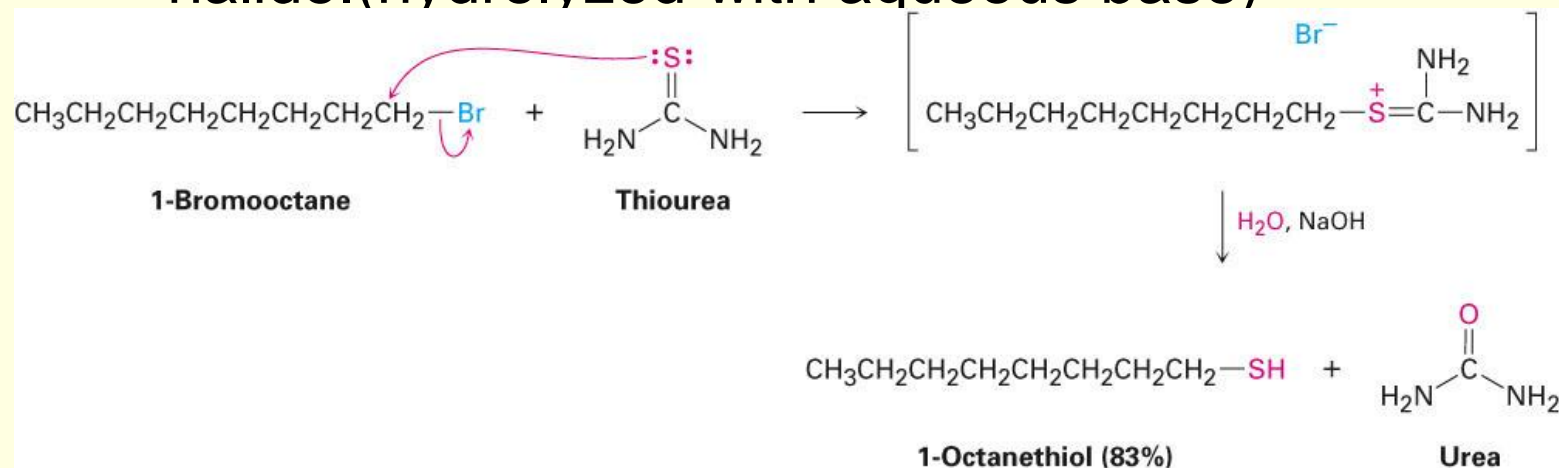
Thiols: Formation and Reaction

- Thiols are usually prepared from alkyl halides by S_N2 displacement with a sulfur nucleophile such as ⁻SH hydrosulfide anion.



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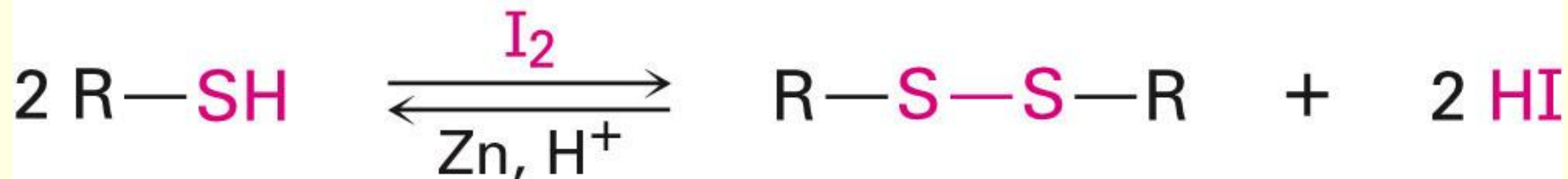
Thiourea is often used as nucleophile in the preparation of a thiol from an alkyl halide. (hydrolyzed with aqueous base)



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Oxidation of Thiols to Disulfides

- Reaction of an alkyl thiol (RSH) with bromine or iodine gives a disulfide (RSSR)
- The thiol is oxidized in the process and the halogen is reduced

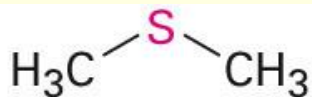


A thiol

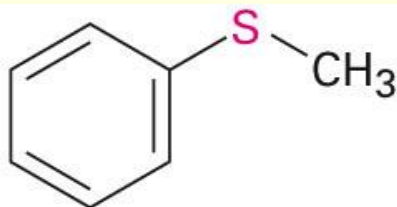
A disulfide

Sulfides

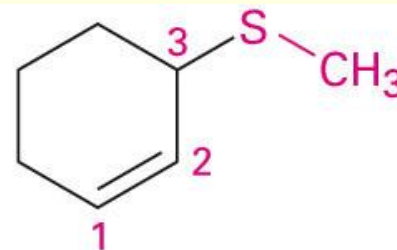
- **Sulfides (RSR')**, are sulfur analogs of ethers
 - Named by rules used for ethers, with *sulfide* in place of *ether* for simple compounds and *alkylthio* in place of *alkoxy*



Dimethyl **sulfide**



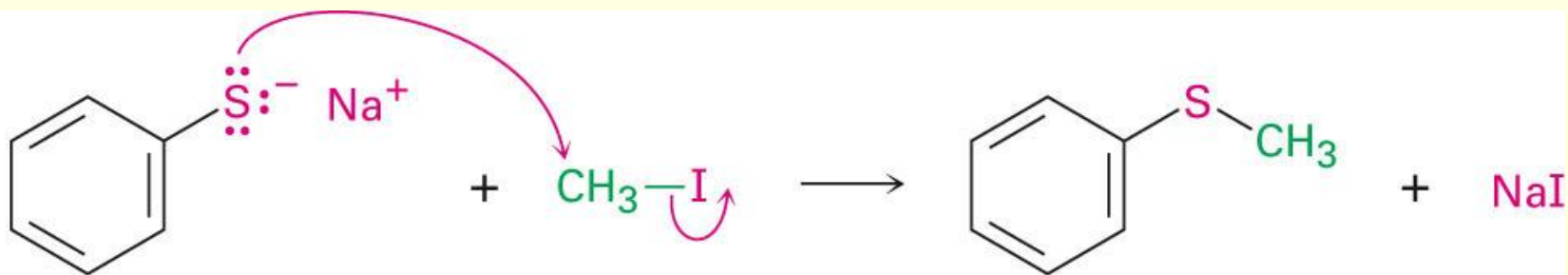
Methyl phenyl **sulfide**



3-(Methylthio)cyclohexene

Sulfides

- **Thiolates (RS⁻)** are formed by the reaction of a thiol with a base such as NaH
- Thiolates react with primary or secondary alkyl halide to give sulfides (RSR')
- Thiolates are excellent nucleophiles and react with many electrophiles

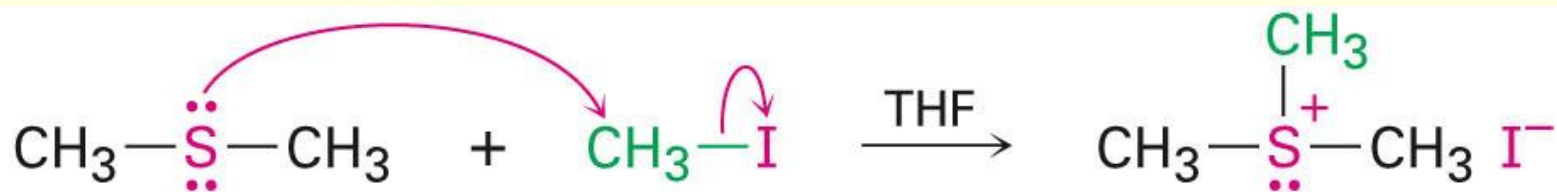


Sodium benzenethiolate

**Methyl phenyl sulfide
(96%)**

Sulfides as Nucleophiles

- Sulfur compounds are more nucleophilic than their oxygen-compound analogs
 - $3p$ valence electrons (on S) are less tightly held than $2p$ electrons (on O)
- Sulfides react with primary alkyl halides (S_N2) to give trialkylsulfonium salts (R_3S^+)



Dimethyl sulfide

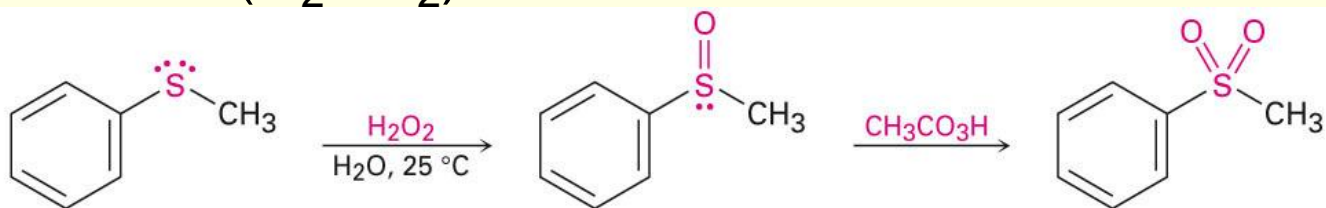
Iodomethane

Trimethylsulfonium iodide

- **Thiols, are stronger acids $pK_a=10$ than alcohols, and thiolate ions are weaker bases than alkoxide ions.** The larger thiolate ions are less well solvated than alkoxide ions, so in **protic solvents thiolate ions are better nucleophiles than alkoxide ions**
- Sulfides, therefore, react readily with alkyl halides to form **sulfonium salts—a reaction that an ether** cannot undergo because oxygen is not as nucleophilic and cannot accommodate a charge as easily.

Oxidation of Sulfides

- Sulfides are easily oxidized with hydrogen peroxide H_2O_2 to the sulfoxide (R_2SO)
- Oxidation of a sulfoxide with a peroxyacid yields a sulfone (R_2SO_2)



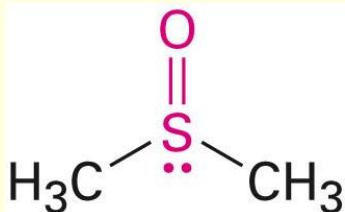
Methyl phenyl sulfide

Methyl phenyl sulfoxide

Methyl phenyl sulfone

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- Dimethyl sulfoxide (DMSO) is often used as a polar aprotic solvent
- It must be handled with care, it has markable ability to penetrate the skin.



Dimethyl sulfoxide
(a polar aprotic solvent)

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