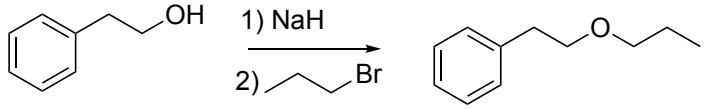
Synthesis of Ethers

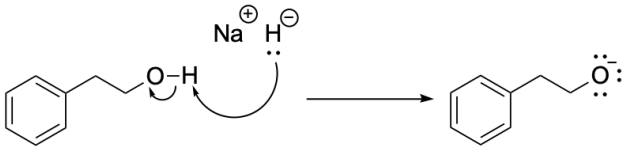
Williamson Ether Synthesis:

- Case One: S_N2 reaction with either a primary alcohol and strong base →alkoxide with a primary halide via S_N2
- Case Two: 2º/ 3º alcohol with a strong base → alkoxide reacting with a 1º halide via S_N2

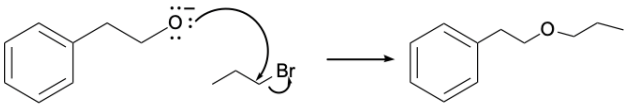
- **Case One:**
  - Overall Reaction:



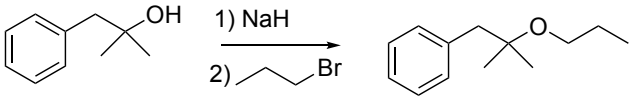
  - Step One: React with Strong Base



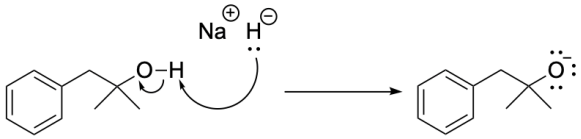
  - Step Two: React with Primary Halide



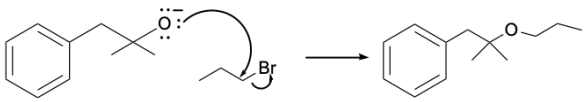
- **Case Two:**
  - Overall Reaction:



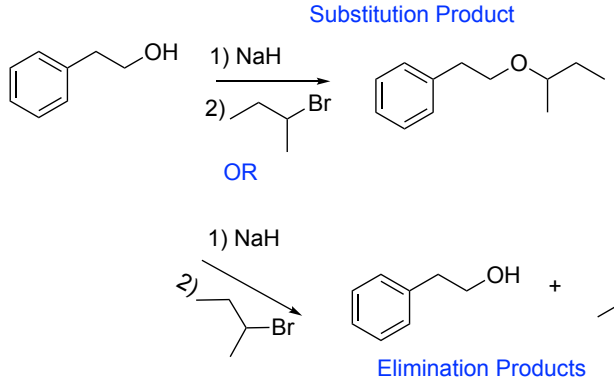
  - Step One: React with Strong Base



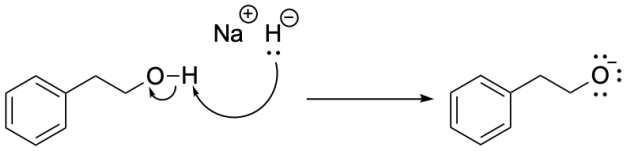
  - Step Two: React with Primary Halide



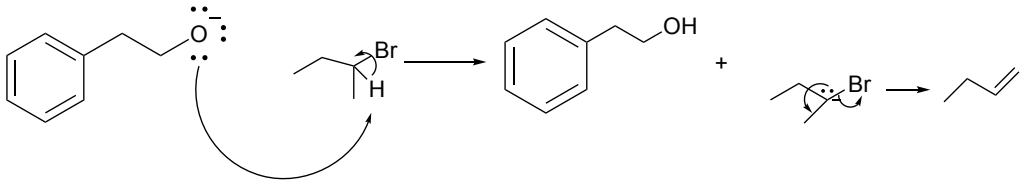
- Important Note: Alcohol with a strong base → alkoxide reacting with a 2º/3º halide will **NOT** always yield an ether product
    - Overall Reaction(s):



    - Step One: React with Strong Base



    - Step Two: Competition between S_N2 and E2 Reactions

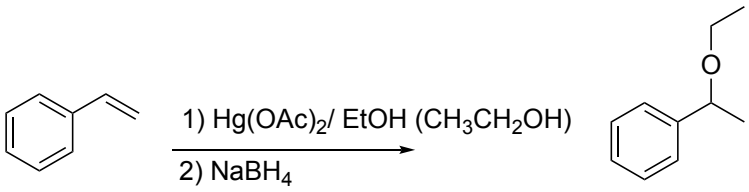


E2 Reaction Mechanism

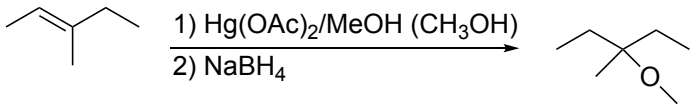
Reaction of Ethers: Alkoxymercuration

- Similar to oxymercuration-demercuration, Markovnikov addition of an alcohol to an alkene, but instead, we're adding a radical
- Sodium borohydride ($NaBH_4$) is to remove the mercury group

Example 1:



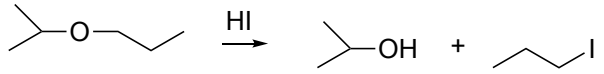
Example 2:



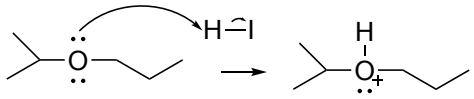
Acidic Cleavage of Ethers

- Start with an ether and produce an alcohol and halide
- **Case One:** 1º and 2º radicals attached to the ether group will proceed via S_N2
- **Case Two:** 3º radicals attached to the ether group will proceed S_N1 or E1 due to steric strain and stability of a 3º carbocation
- Acid used: either HI or HBr because those are the only two acids strong enough to cleave

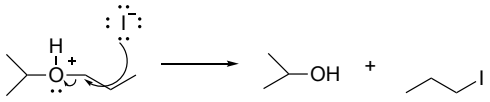
- **Case One:**
  - Overall reaction:



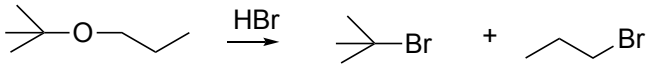
  - Step One: Lone pairs from oxygen deprotonate hydroiodic acid



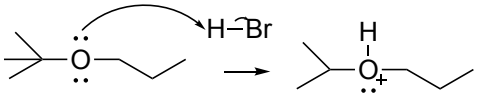
  - Step Two: Iodine attacks the least substituted carbon via an S_N2 mechanism



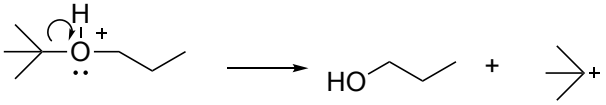
- **Case Two:**
  - Overall Reaction:



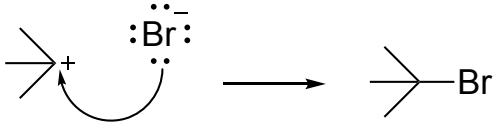
  - Step One: Lone pairs from oxygen deprotonate hydrobromic acid



  - Step Two: alcohol group leaves generating a 3º carbocation



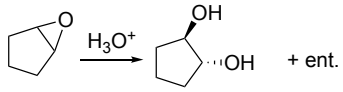
  - Step Three: Bromide Ion attacks the carbocation



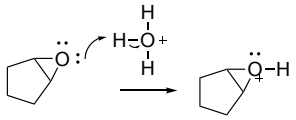
Acid Catalyzed Epoxide Ring-Opening

- Acids Used: HCl, HBr, or HI, or H_3O^+

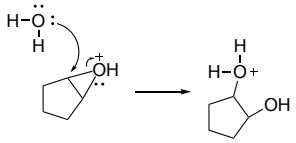
- **Case One: 1º or 2º will proceed via S_N2 and trans-stereospecific → racemic mixture**
  - Overall Reaction:



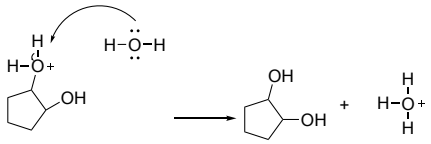
  - Step One: Lone pair of oxygen deprotonates H_3O^+



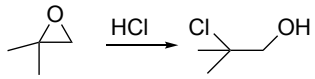
  - Step Two: Lone pair of oxygen from the resulting H_2O molecule attacks one of the carbons bonded to the hydroxyl group resulting in a ring opening event



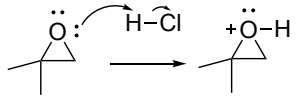
  - Step Three: Proton transfer from a H_2O molecule, generating a H_3O^+ molecule



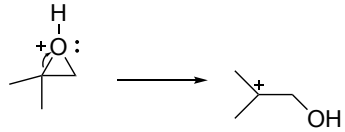
- **Case Two: 3º will proceed via S_N1**
  - Overall Reaction:



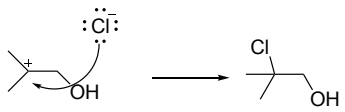
  - Step One: Lone pair of oxygen deprotonates HCl



  - Step Two: Electrons deposit onto hydroxyl group, → 2º carbocation and ring opening event



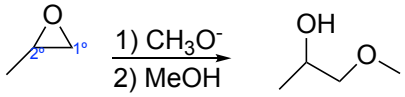
  - Step Three: Chloride ion attacks carbocation



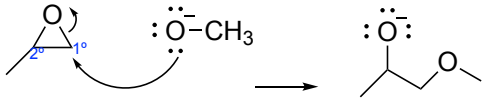
Base Catalyzed Epoxide Ring-Opening

- Only proceeds S_N2
- Base will attack the least substituted carbon participating in the epoxide

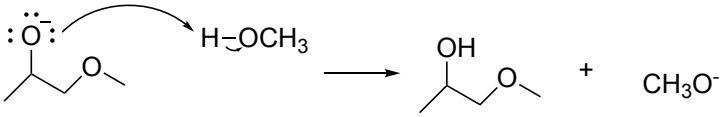
- **Case One: 2º and 1º Carbon**
  - Overall Reaction:



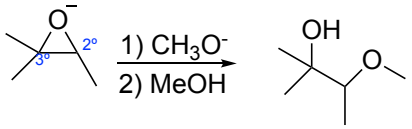
  - Step One: Lone pairs from the oxygen of the methoxide attack the least substituted carbon (1º in this case)



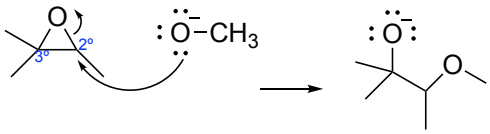
  - Step Two: Lone pairs from the negatively charged oxygen attack the solvent, methanol and deprotonate it



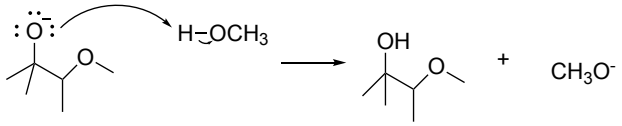
- **Case Two: 3º and 2º Carbon**
  - Overall Reaction:



  - Step One: Lone pairs from the oxygen of the methoxide attack the least substituted carbon (2º in this case)



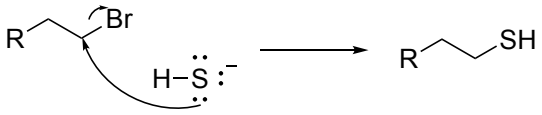
  - Step Two: Lone pairs from the negatively charged oxygen attack the solvent, methanol and deprotonate it



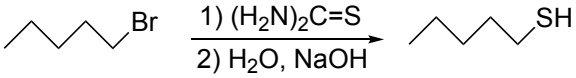
Thiols

Synthesis of Thiols

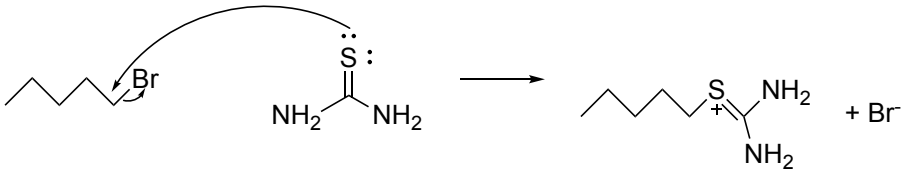
- Method One: Primary alkyl halide and hydrosulfide anion (**not preferred** because sulfide is normally produced in a higher amount than the thiol)



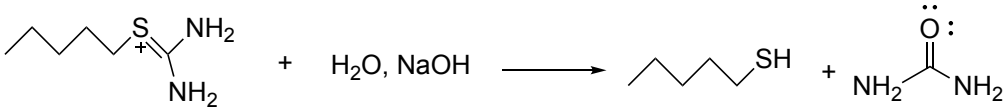
- Method Two: Primary alkyl halide with thiourea, then treat with hydroxide
  - Overall Reaction:



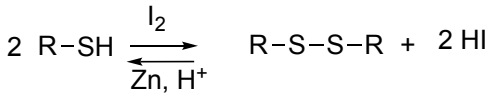
  - Step One: Primary alkyl halide with thiourea



  - Step Two: Treat with water and hydroxide



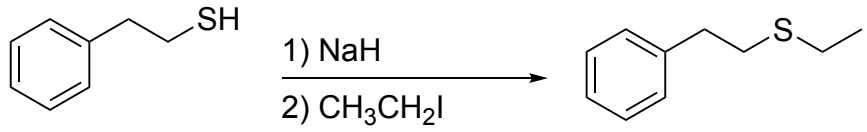
Interconversion of Thiols to Disulfides (Important Biochemistry Implications)



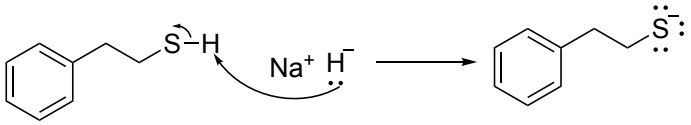
Sulfides

Synthesis of Sulfides

- Method: Start with a thiol
  - Overall reaction:



  - Step One: Treat with a strong base



  - Step Two: Treat thiolate ion with a primary or secondary alkyl halide

