

Chapter 2: Substitution Reactions

In a substitution reaction, one atom or group of atoms is replaced by another atom or group of atoms. In more specific terminology a Leaving Group (LG) is replaced by a Nucleophile (Nu).



Substitution reactions follow one of two mechanistic pathways: S_N1 and S_N2 .

S_N1 Reactions



- Starting material rate of reactivity (carbon attached to LG): 3° (fastest) $>$ 2° $>$ 1° (slowest)
- Weak nucleophiles – often have no formal charge
- Acidic to neutral conditions
- Polar solvent (protic or aprotic)
- Carbocation intermediate formed
- Step-wise mechanism
- First order kinetics (rate depends only on concentration of substrate)
- Results in a mixture of inversion and retention of configuration

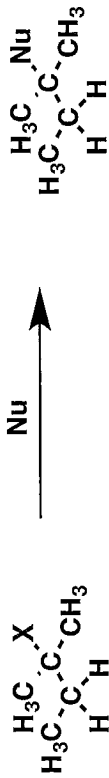
S_N2 Reactions



- Starting material rate of reactivity (LG degree of substitution) 1° (fastest) $>$ 2° $>$ 3° (slowest)
- Strong nucleophiles (often have a formal charge of -1)
- Basic to neutral conditions
- Polar aprotic solvent increases rate
- No intermediate – Transition State only
- Concerted mechanism
- Second order kinetics (rate depends on concentration of substrate and nucleophile)
- Proceeds with inversion of configuration

S_N1 With A Halide Leaving Group

General Reaction:



X = good leaving group

Nu = weak Lewis bases

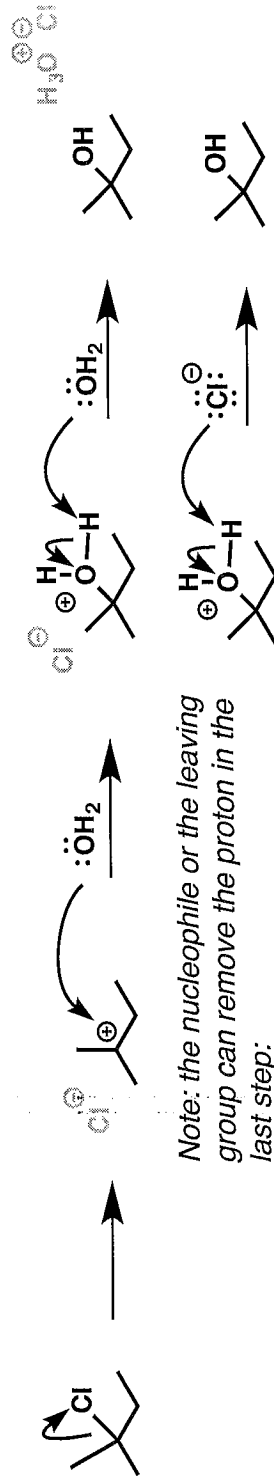
Examples: Cl, Br, I, ⁻OSO₂R

Examples: H₂O, ROH, RCOOH, RCOONa

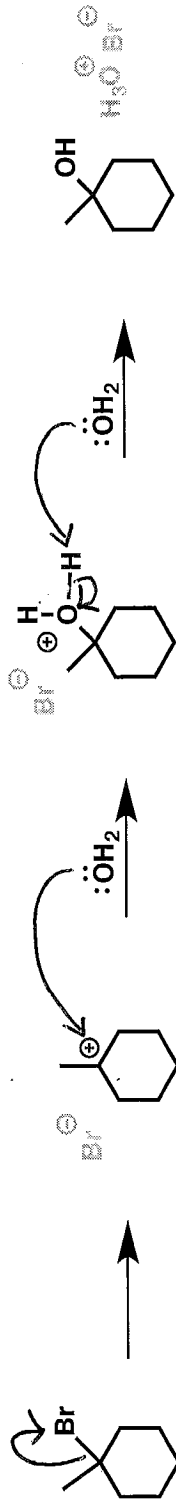
Mechanism Basics Box:

- Leaving groups (X) include halogens such as Cl, Br, and I in addition to alkyl sulfonates
- Typical nucleophiles (Nu) are weak Lewis bases and have lone pair electrons on an electronegative atom, but may also be negatively charged species in a small number of instances.
- The starting material (substrate) has a leaving group that is typically tertiary (3°), allylic (3°, 2°, or 1°) and to a lesser extent secondary (2°)
- The reaction proceeds via an achiral carbocation resulting in a racemic mixture
- The intermediate carbocation may rearrange to a more stable carbocation through hydride or alkyl shifts.

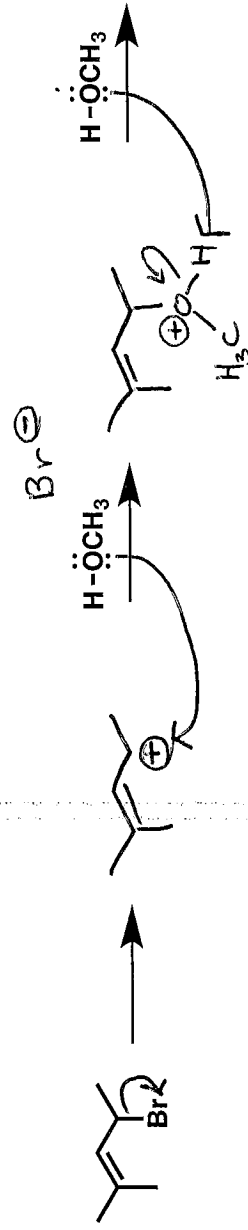
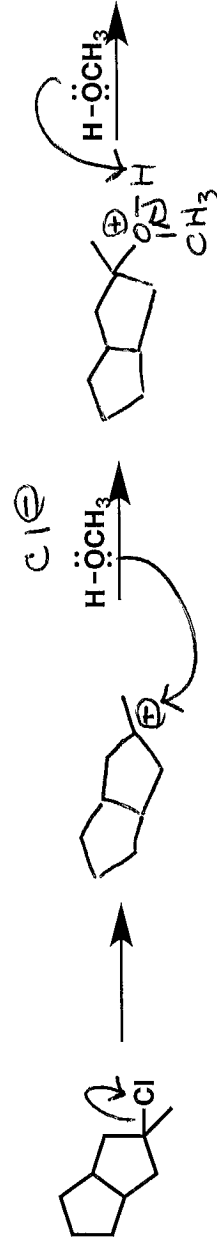
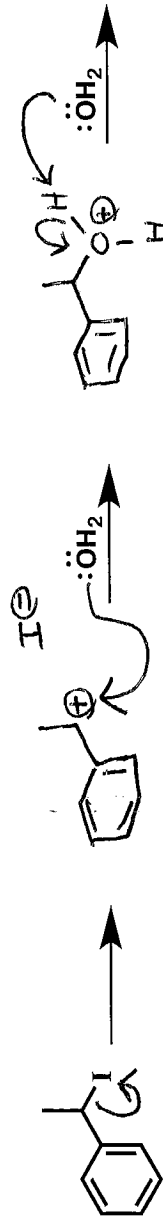
General Mechanism:

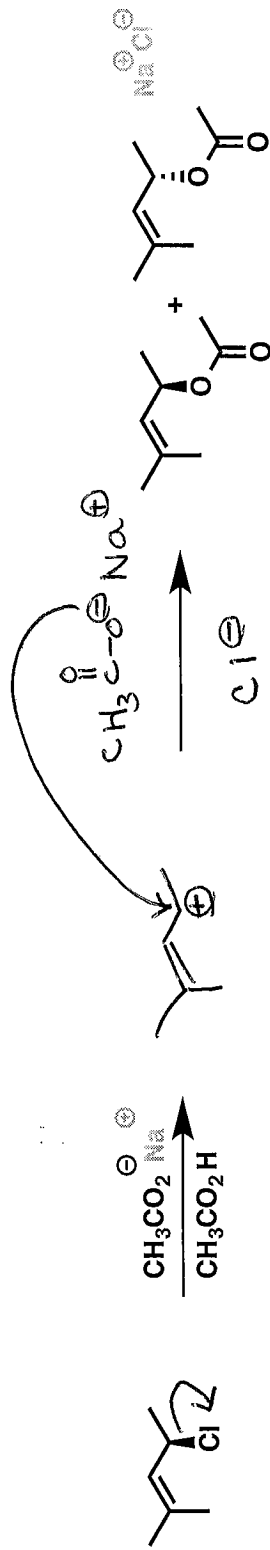


Fill in the missing arrows.



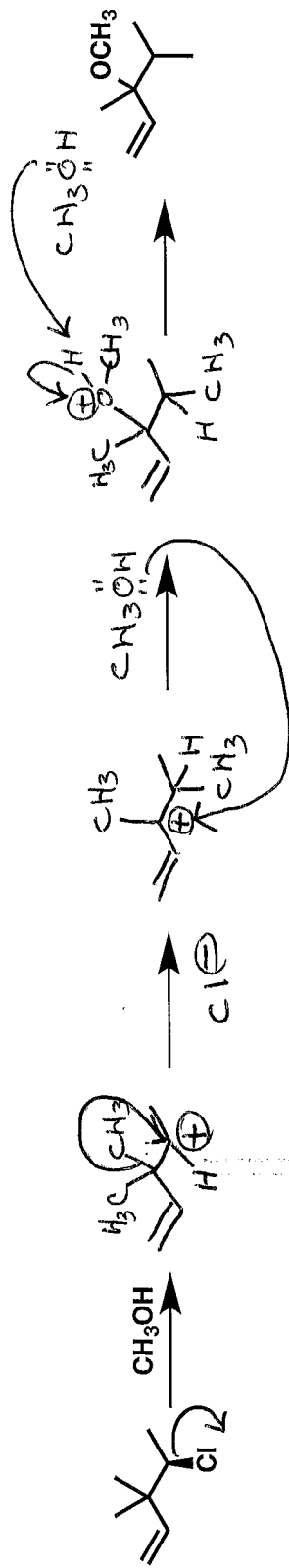
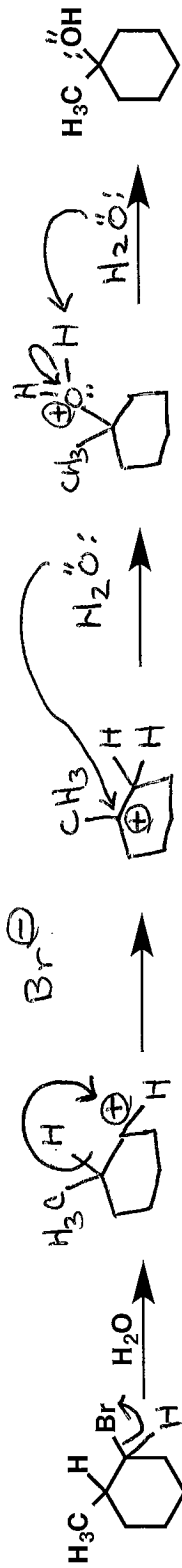
Fill in the missing mechanism arrows and intermediates.

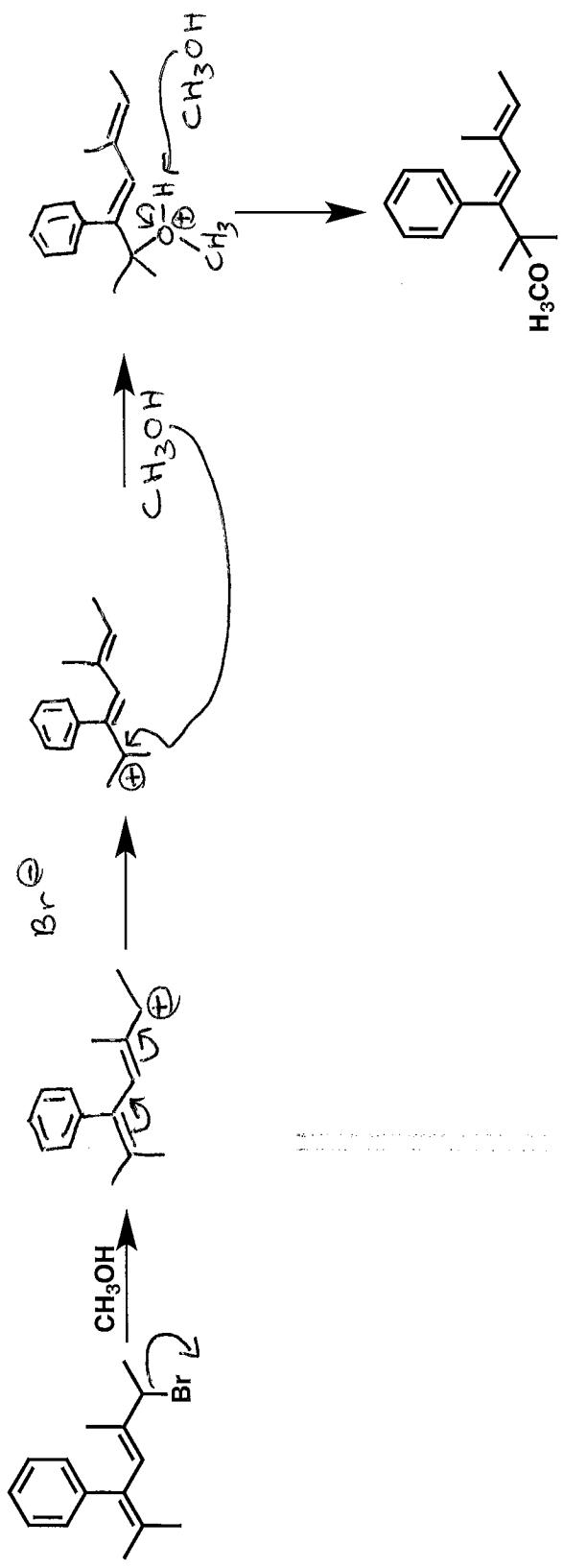
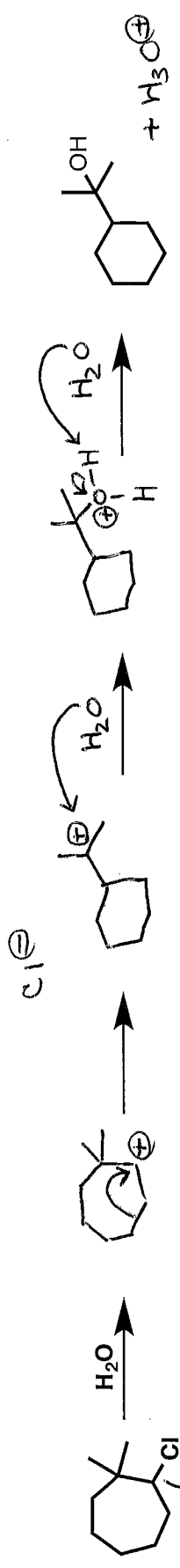
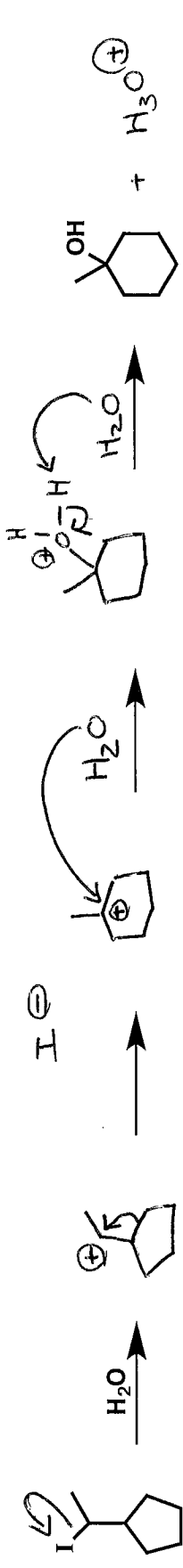




* loss of stereochemistry with S_N1 reactions

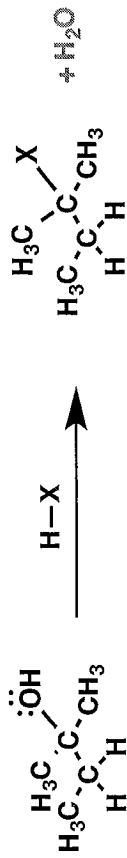
Fill in the missing mechanism arrows and intermediates. Be on the lookout for hydride shifts, methide shifts, ring contractions and ring expansions that can occur with carbocations.





S_N1 Reaction With An Alcohol Leaving Group

General Reaction:

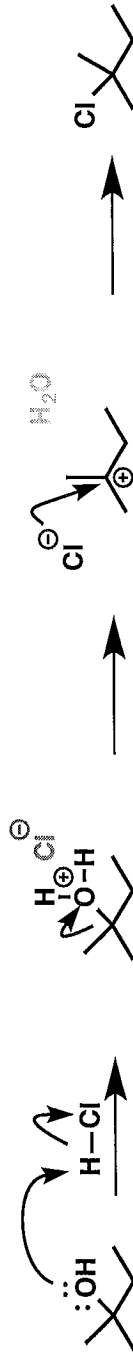


HX can be HCl, HBr, HI

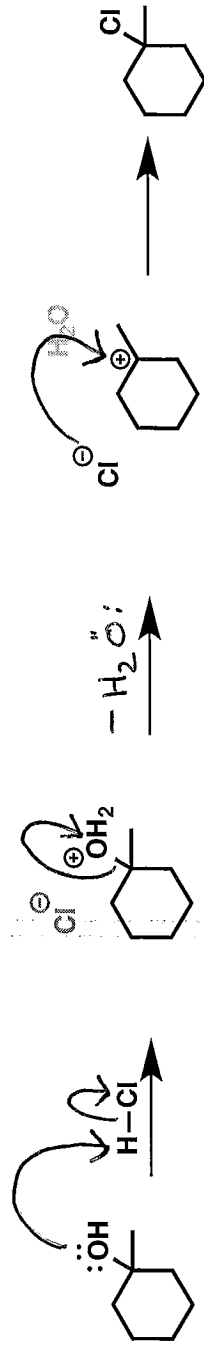
Mechanism Basics Box:

- See mechanism box for S_N1 with a halide leaving group

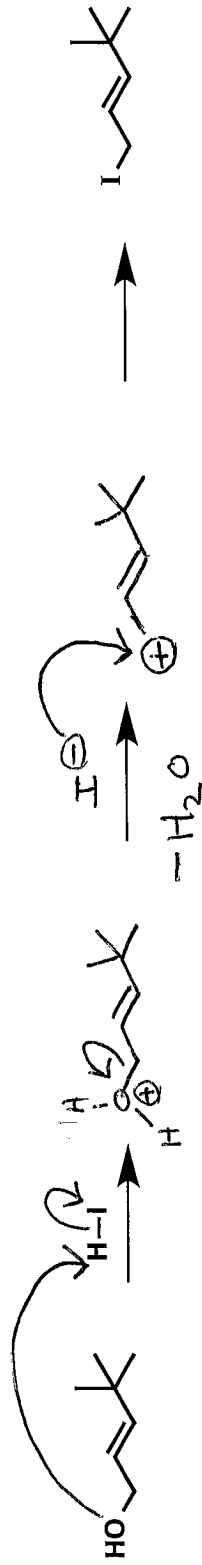
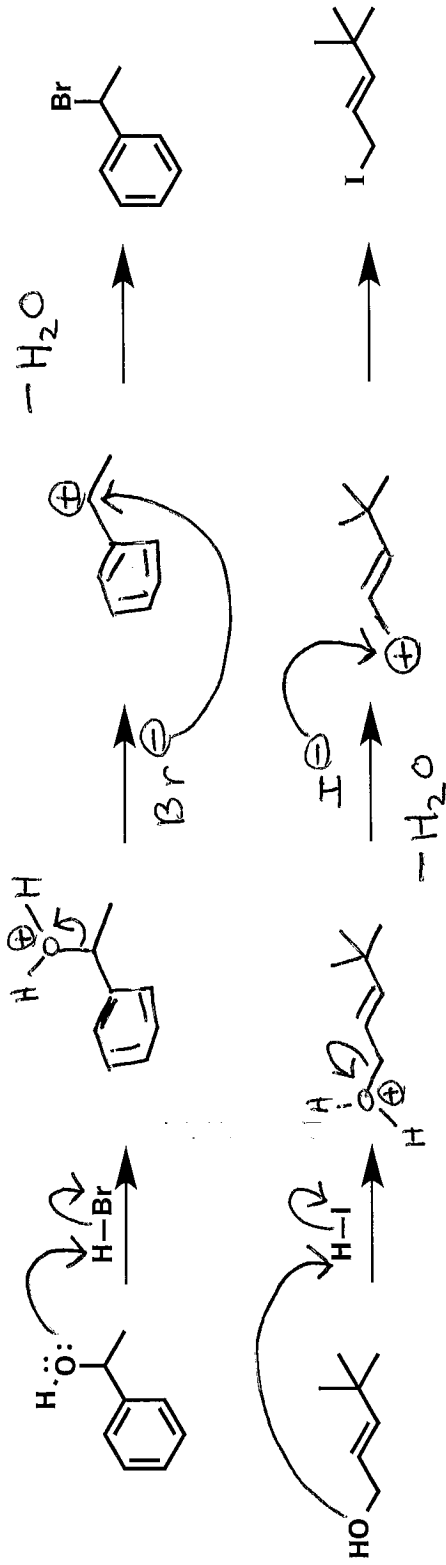
General Mechanism:



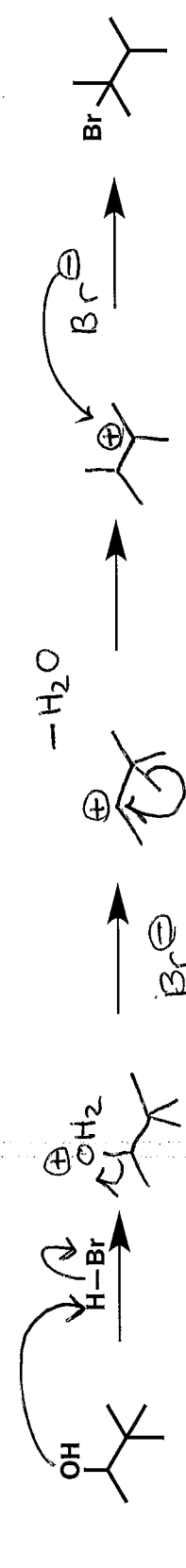
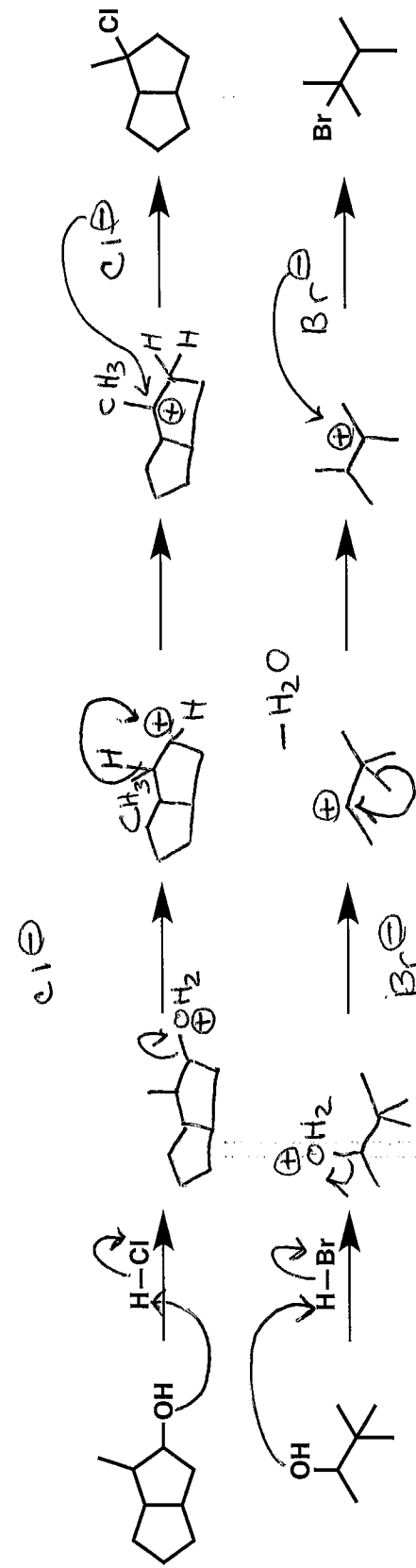
Fill in the missing mechanism arrows



Complete the mechanism by following the pattern (draw arrows and intermediate)

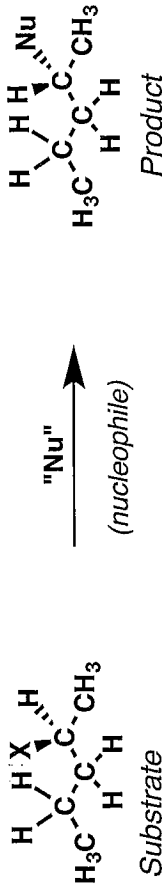


Draw arrows and intermediates. Be on the lookout for hydride and alkyl shifts!



S_N2 (Substitution Nucleophilic Bimolecular)

General Reaction:



X is a good leaving group
(Cl, Br, I, OTs, OMs)

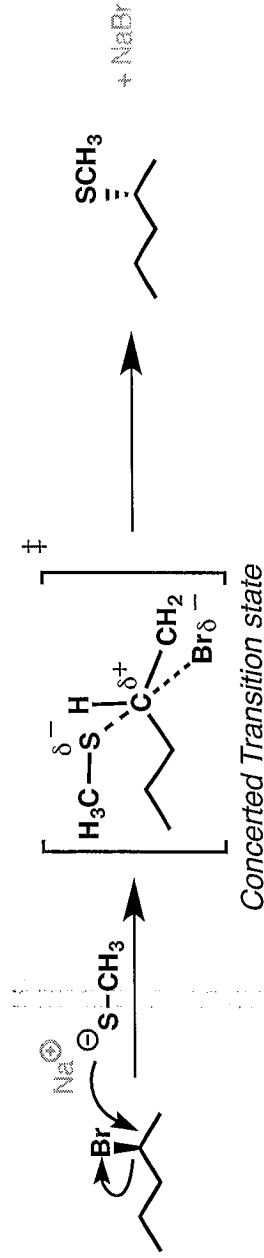
Nu is a nucleophile \ominus
Common examples: SH, CN, SR, N₃[⊖], HO[⊖], RO[⊖],

Cl[⊖], Br[⊖], I[⊖], F[⊖], RCOO[⊖], H-C≡C[⊖]

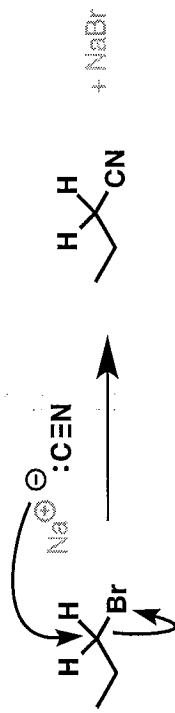
Mechanism Basics Box:

- Good leaving groups (X) are weak bases, such as halides (Cl, Br, I) and sulfonates (TsO, MsO)
- Works best with "good" nucleophile, generally negatively charged species such as \ominus CN and \ominus SH
- Main barrier to this reaction is *steric hindrance* on the carbon bearing the leaving group. The rate increases as steric hindrance decreases. For example tertiary (no reaction) \ll secondary $<$ primary $<$ methyl alkyl halides
- Reaction proceeds via a concerted backside attack, resulting in inversion of stereochemistry on chiral centers
- The rate law is bimolecular; depends both on concentration of nucleophile and substrate
- Reaction rate increased by use of polar aprotic solvents such as dimethyl sulfoxide (DMSO) or acetonitrile (CH₃CN) which increase nucleophilicity

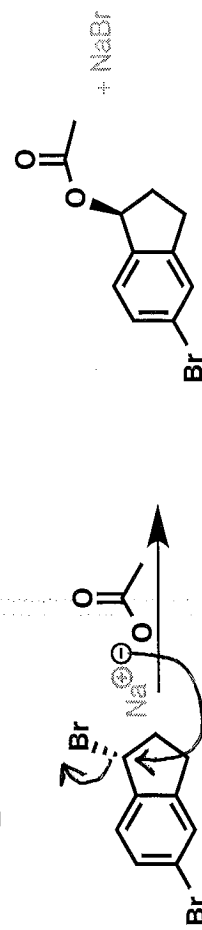
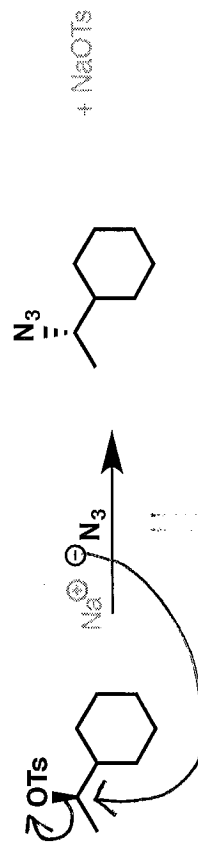
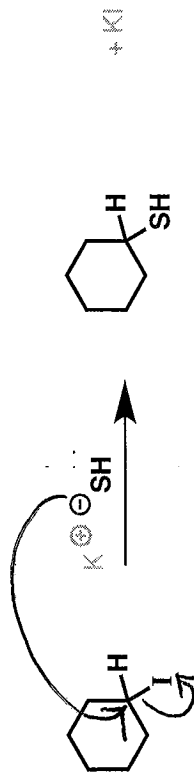
General Mechanism:



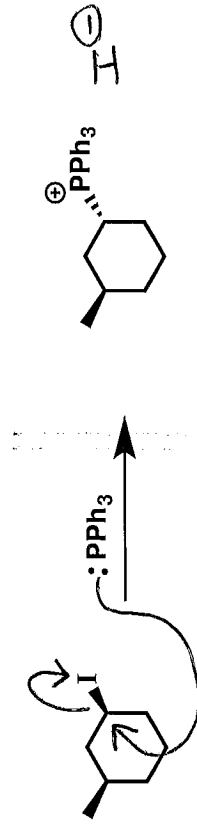
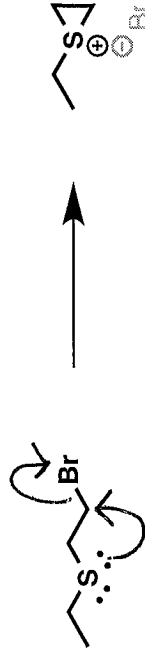
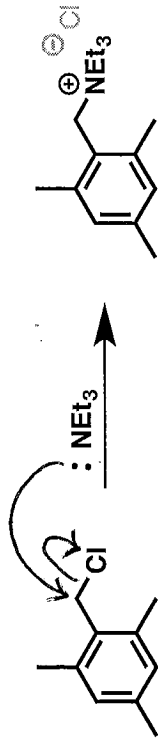
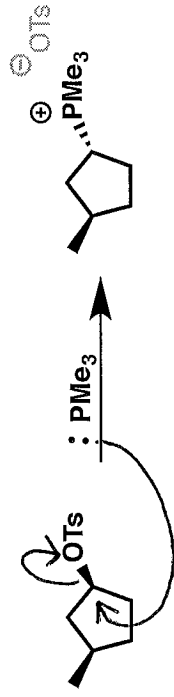
Given this example, fill in the arrows for the remaining examples.



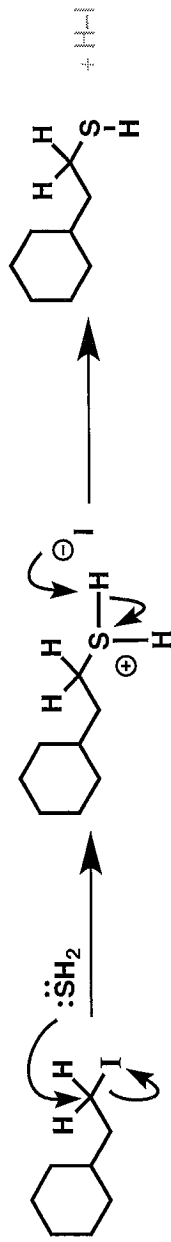
Fill in the missing arrows.



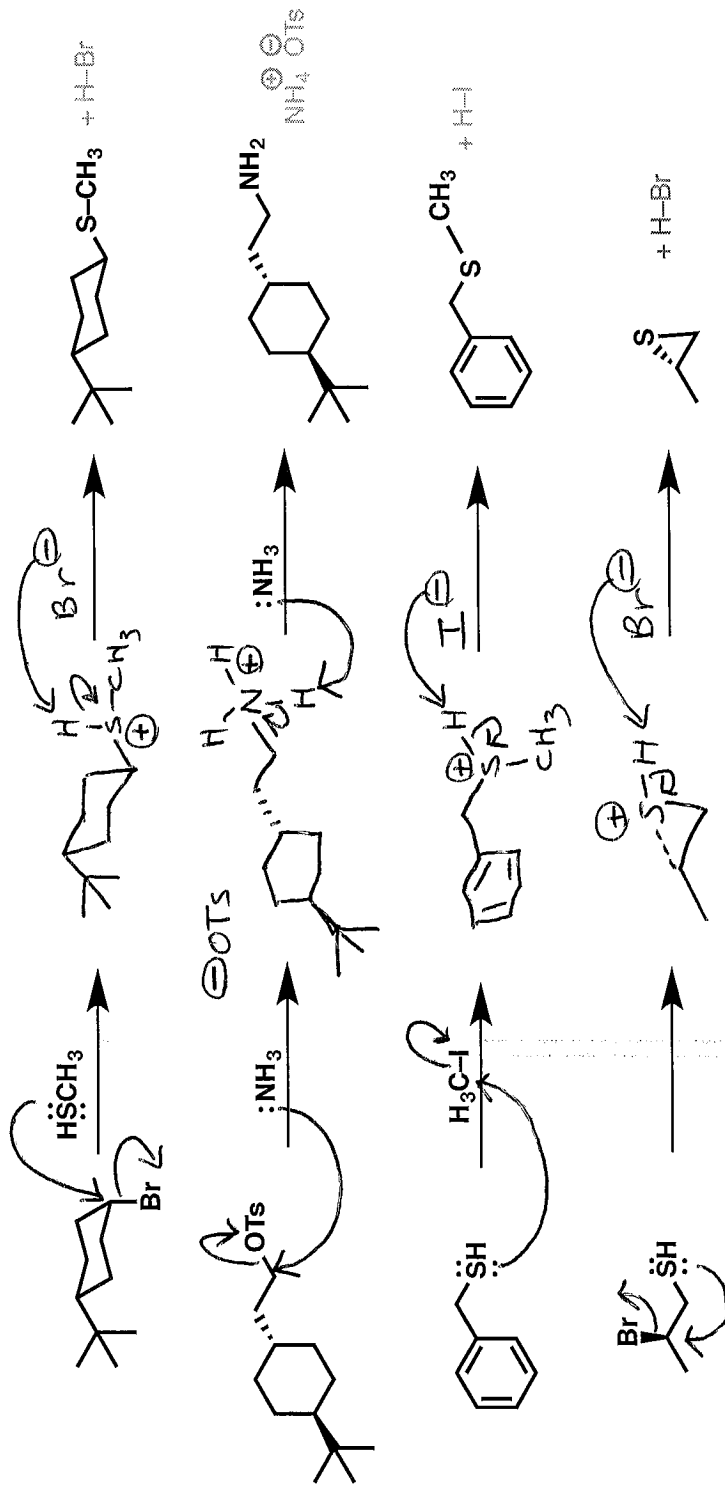
These examples show a neutral nucleophile reacting with the substrate. Fill in the arrows.



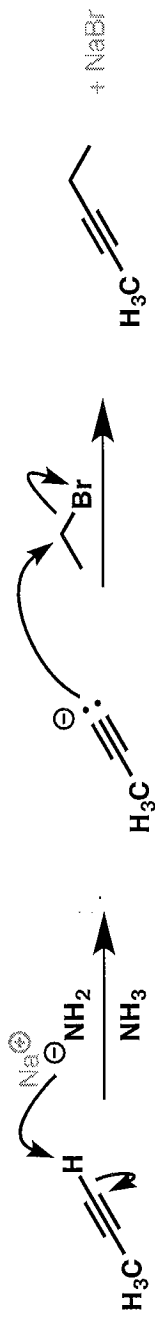
These examples have an S_N2 reaction followed by a deprotonation step.



Complete the mechanism by following the pattern (draw arrows and intermediate)



These examples begin with a deprotonation event followed by an S_N2 reaction.



Complete the mechanism by following the pattern (draw arrows and intermediate)

