Substitution Reactions

Remember: Radical Substitution

1) **Homolytic bond breaking**

$$A-B \longrightarrow A\cdot \quad \cdot B$$

Example:

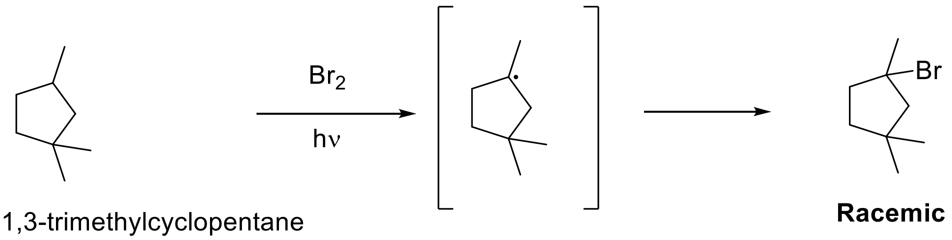
$$R\text{-}H + X_2 \xrightarrow{\text{light}} R\text{-}X + H\text{-}X$$

Proceeds by a radical mechanism

Alkane

X=F, Cl, Br
Not I

Alkyl Halide



1,1,3-trimethylcyclopentane

Racemic

Note: Although radicals are sp^3 hybridized, rapid inversion around the central C results in a loss of stereochemistry. Hence, the resulting product would be a racemic mixture.

2) **Heterolytic Bond Breaking (Ionic Substitution)**

$$M^{\oplus}\ Nu:^{\ominus} + R\text{-}X \longrightarrow Nu\text{-}R + :X^{\ominus}\ M^{\oplus}$$

Nucleophile
(Seeks positive
charge)

Alkyl Halide

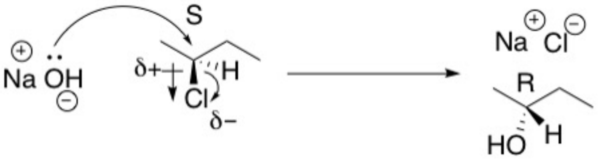
Nucleophile is a substance that seeks positive charge

Types of Nucleophilic Substitution (S_N)

S_N1 - rate depends on 1 concentration

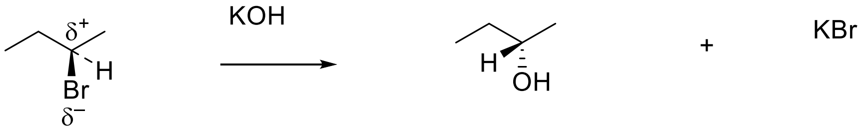
S_N2 - The rate is dependent on the concentration of the nucleophile and the nucleophile (2 concentrations)

Sn2 Mechanism



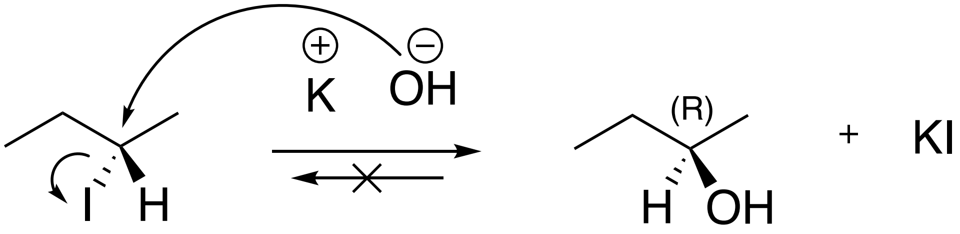
Reverse reaction will not occur.
OH$^-$ is a terrible leaving group
- **Rate**: Depends on concentration

- Inversion of configuration (**Walden inversion)**
- **Concerted**: The bonds of the starting material break at the same time as the product bonds form.
- **Stereospecific**: stereochemistry of the starting material determines the stereochemistry of the product.
- Works for $CH_3–X$, $R–CH_2X$, R_1R_2CHX.



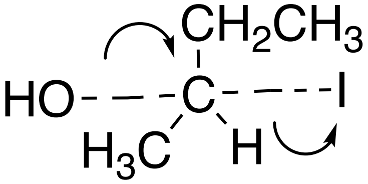
Another example of mechanism of S_N2 reaction

As such, the reaction below is not reversible:



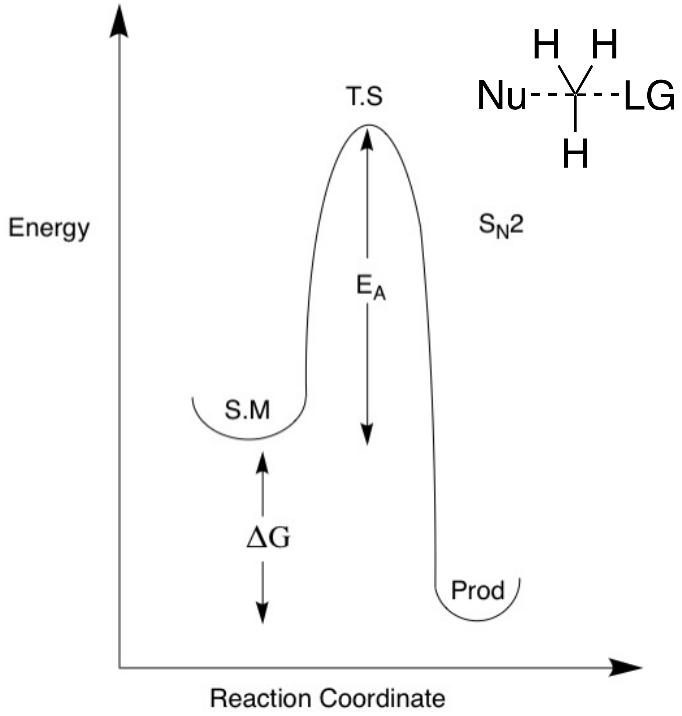
(S)-2-iodobutane

inverison of stereochemistry



S_N2 always inverts stereochemistry
Favored conditions are with less steric bulk, primary best and secondary okay

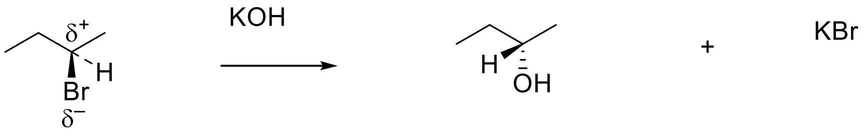
Energy Diagram of S_N2 Reaction



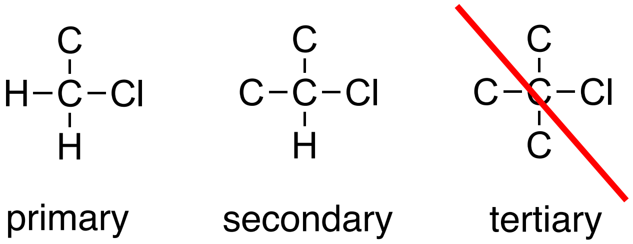
There is no intermediate in the S_N2 reaction, as it is concerted

Good Leaving Groups	Bad Leaving Groups
$RSO_3^- > I^- > Br^- > Cl^- >> F^-$ (due to solvation)	H^-, R^- (alkyl), $^-NR_2$, ^-OR, ^-OH, F^-

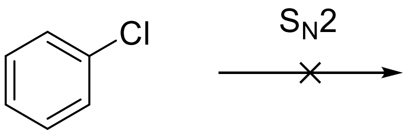
HOH, HOR are okay leaving groups, but need to protonate with acid before it can leave

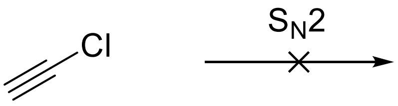


Leaving groups must be connected to a primary or secondary carbon (carbon that has at least one hydrogen, preferably 2)



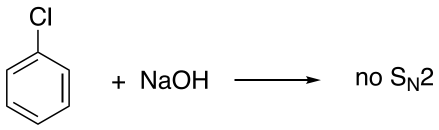
More examples of reactions that do not proceed via S_N2



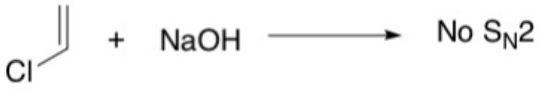


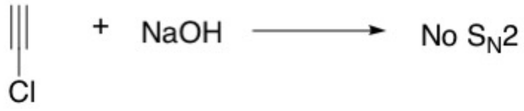
Example:

1)



2)



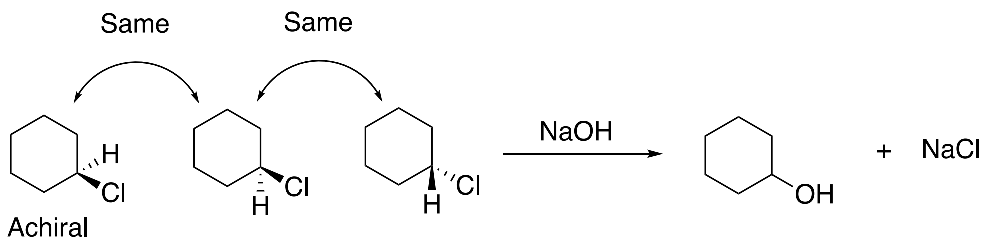


3)

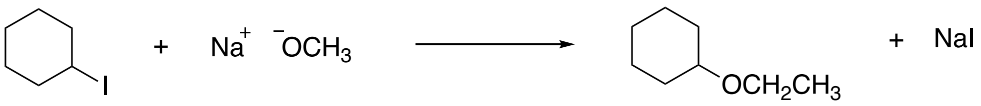
$Na^+\ {}^-OH + H_3C{-}O{-}CH_3 \cancel{\rightleftharpoons} Na^+\ {}^-OCH_3 + H_3C{-}OH$

Note: Methoxide (CH_3O^-) and hydroxide (${}^-OH$) are bad leaving groups

4)



5)



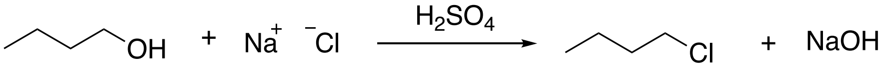
6) Neutral leaving group containing lone pair

$$\begin{tikzcd} H_3C-I \;+\; :NH_3 \arrow[r] & H_3C-\overset{+}{N}H_3 \;+\; I^- \arrow[d] \\ & H_3C-NH_2 \;+\; H^+ \end{tikzcd}$$

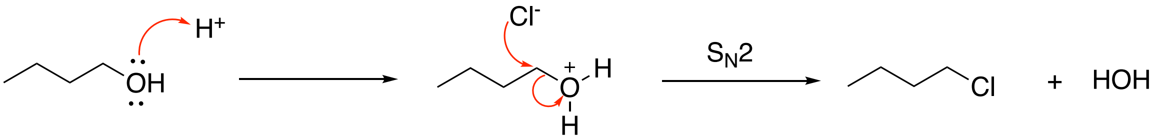
7)

Note: OH is never a leaving group but if you add a strong acid or the reaction happen in a strongly acidic condition (see next example), the reaction will occur

8)

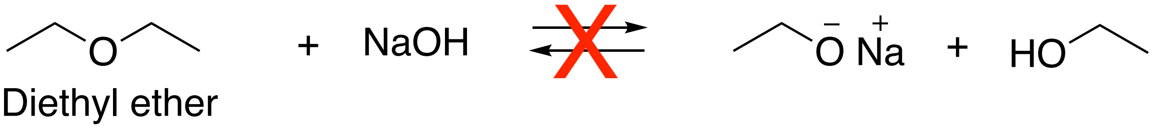


Mechanism:



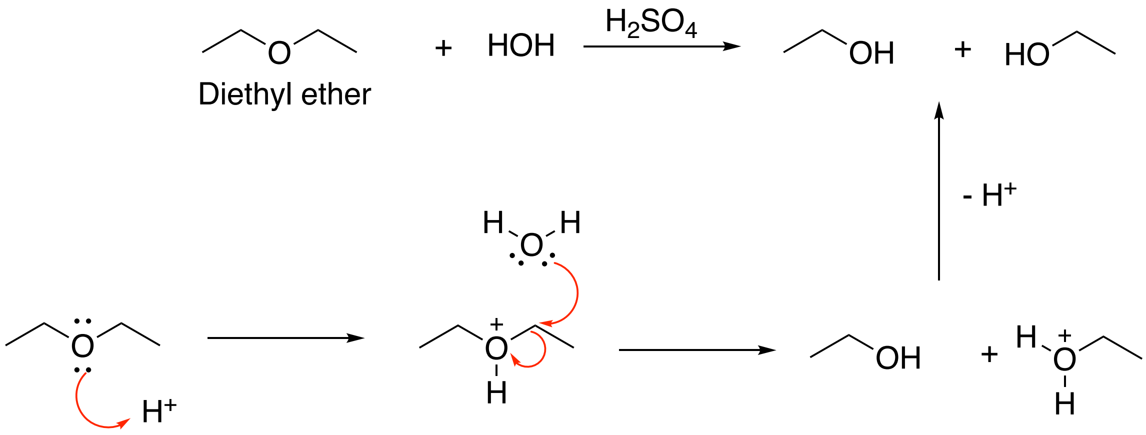
Note: The leaving group in this reaction is now HOH

9)

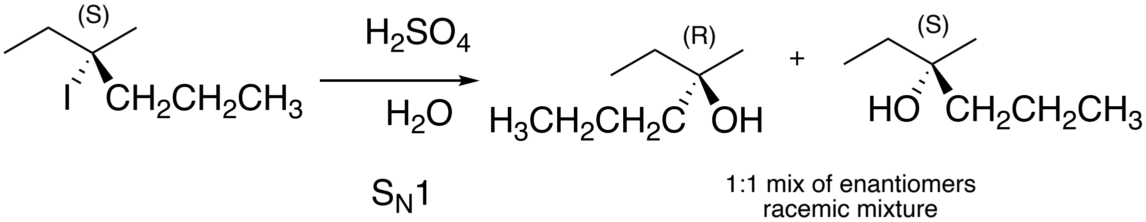


Note: Alkoxide ($^-$OR) or hydroxide ($^-$OH) are bad leaving group therefore no Sn2 reaction will occur on either direction. However, if the reaction happens in strongly acidic condition the reaction will occur. (see mechanism below)

10)



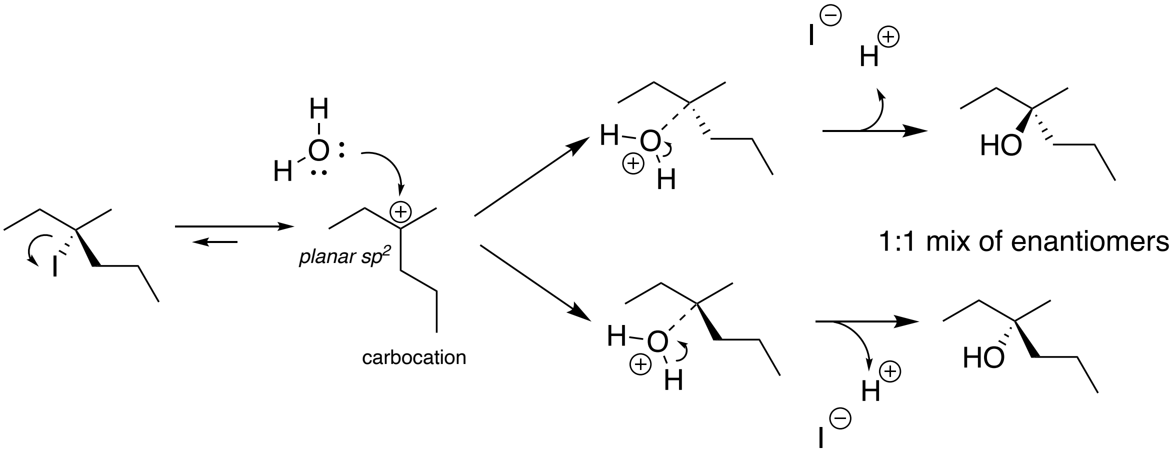
S_N1 Reaction:



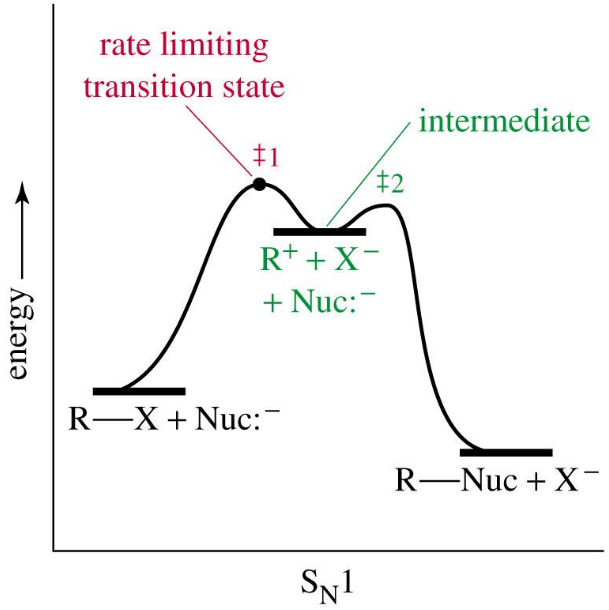
1:1 mix of enantiomers
racemic mixture

Characteristics of S_N1 reactions:

- Stepwise
- Carbocation intermediates
- Rate dependent on concentration of substrate only
- Not stereospecific
- Favoured by heat or acid
- Works for 3° and sometimes 2° but never 1°

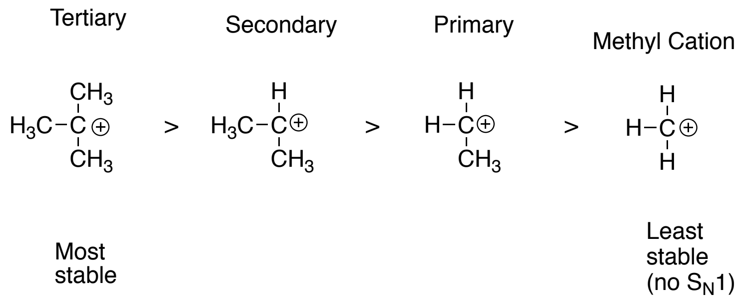


Energy level diagram of S_N1



Favored conditions are with stabilized carbocation – more substitution

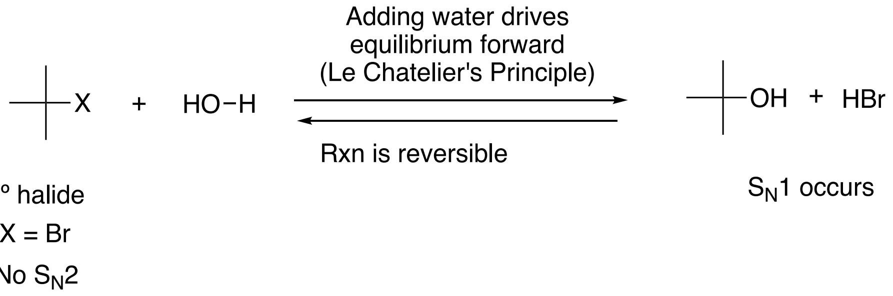
Carbocation Stability:



The 3 alkyl groups donate e^- density into the positive charge

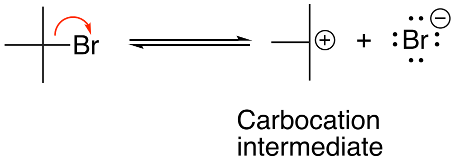
Example: Tertiary Halide

-No S_N2 possible, sterically crowded – does work by S_N1

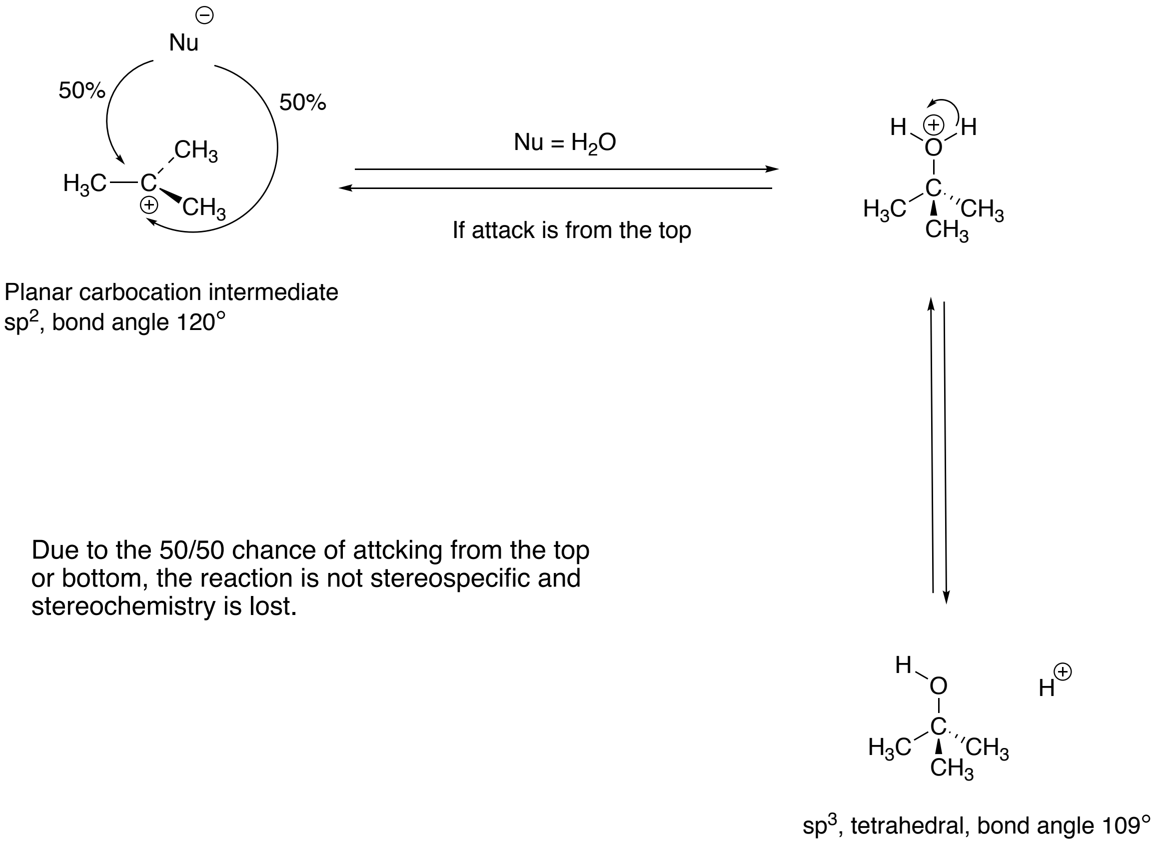


Mechanism of S_N1:

The bromine group leaves (Step 1) with its electrons from the covalent bond, leaving behind a reactive carbocation intermediate



Carbocation intermediate is planar, so the nucleophile can attack from the top or bottom

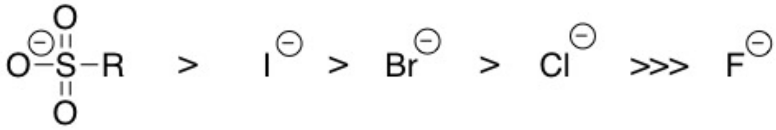


Due to the 50/50 chance of attcking from the top or bottom, the reaction is not stereospecific and stereochemistry is lost.

Summary of
S_N1 vs S_N2

	S_N1	***S_N2***
RDS	Unimolecular	Bimolecular
Main barrier	Carbocation stability	Steric bulk
Alkyl halides	3° > 2° >> 1°	1° > 2° >> 3°
Nucleophile	Neutral/weak	Charged/strong
Stereochemistry	Mixture	Inversion

Good leaving groups



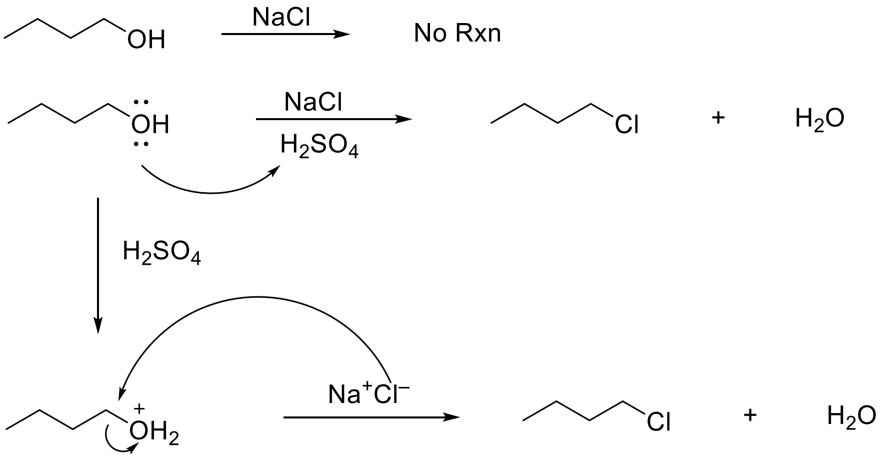
-OH or -OR can also act as leaving groups but they must first be transformed into H_2O or HOR by a strong acid

Never leaving groups: (negative charge not stabilized):

Fluorine, though electronegative, is a bad leaving group as it is small and poorly solvated.

Leaving group activation:

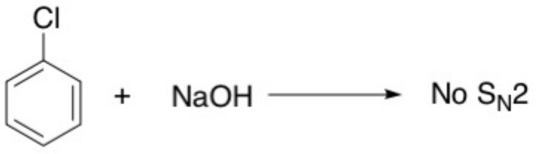
1) Protonation

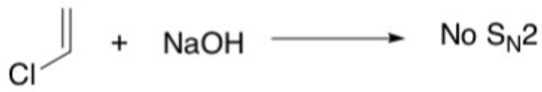


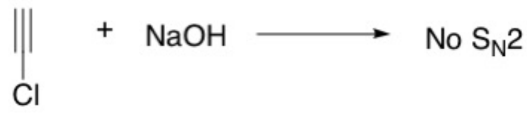
Highlights:

- H_2SO_4 is a proton (H^+) donor.
- ^-OH is transformed into a better leaving group via protonation of the O atom.
- Cl^- can then attack via S_N2, kicking off H_2O in the process.

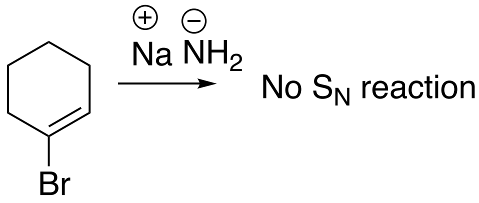
S_N2 will **not** occur on carbon sites that have multiple bonds.



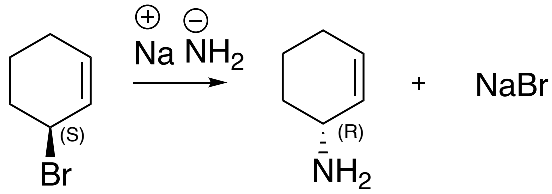




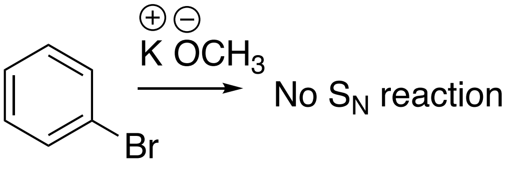
Example 1:



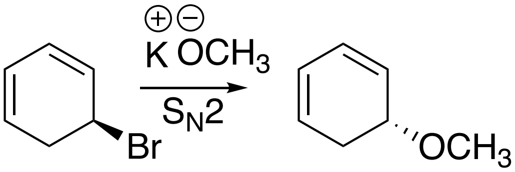
Example 2:



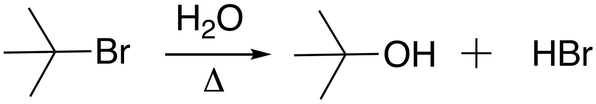
Example 3:



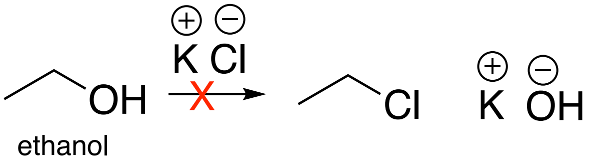
Example 4:



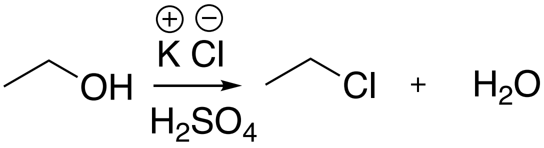
Example 5:



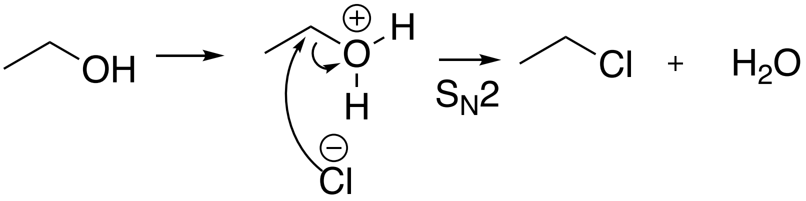
Example 6:



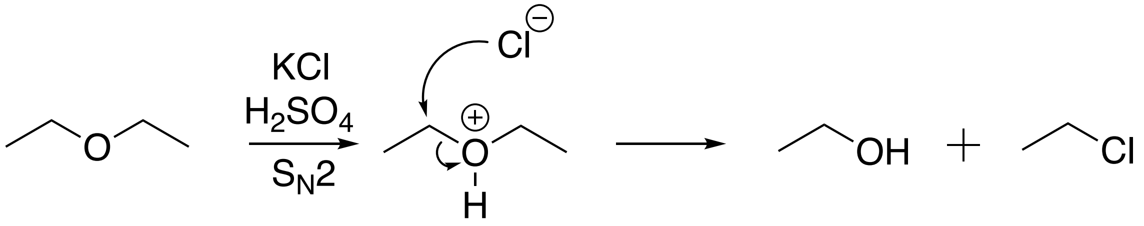
Example 7:



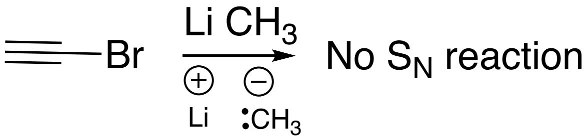
Mechanism:



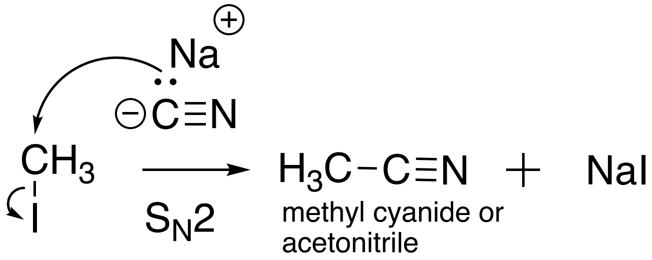
Example 8:



Example 9:

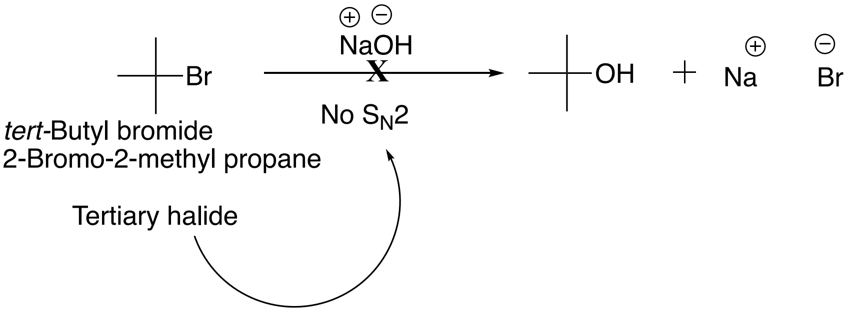


Example 10:



REVIEW: S_N yes or no? Examples

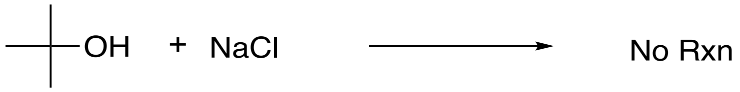
Ex #1) Will NOT proceed – no S_N



Note: alkyl groups stabilize carbocation intermediate by donating a negative charge

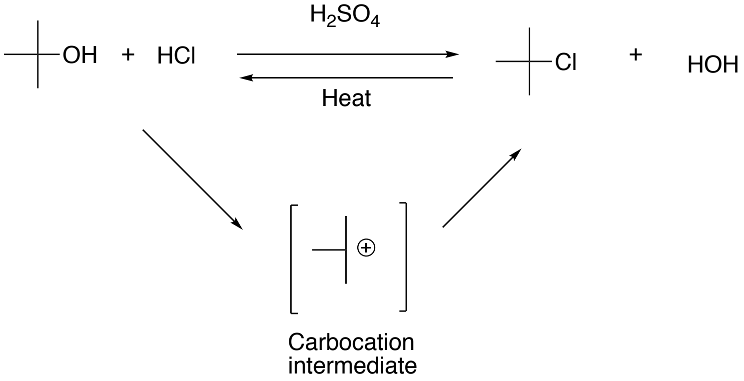
Note: will undergo elimination reaction (explanation of what this is comes later)

Ex #2)

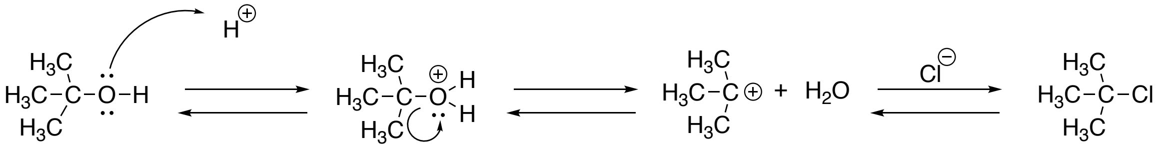


$^{\ominus}$OH is never a good leaving group

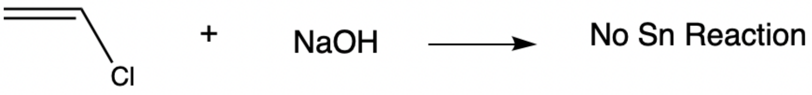
Ex #2a) Works with Acid as S_N1 Mechanism

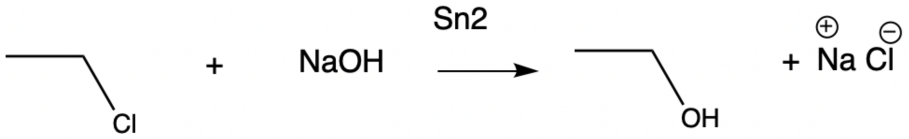


Mechanism:



Ex #3)

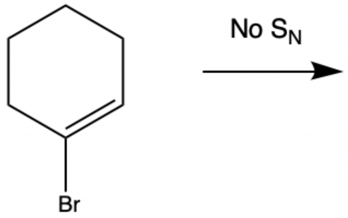




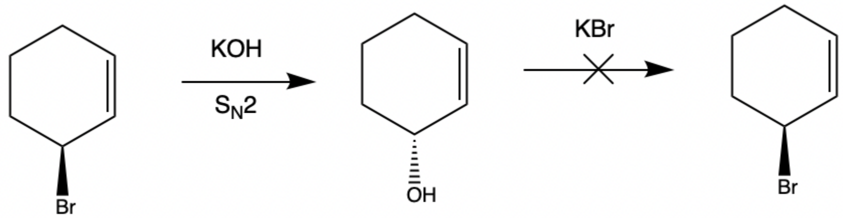
A carbon attached to a double bond cannot undergo a substitution reaction

The carbon with the leaving group must be sp^3 to undergo a substitution reaction

Ex #4)



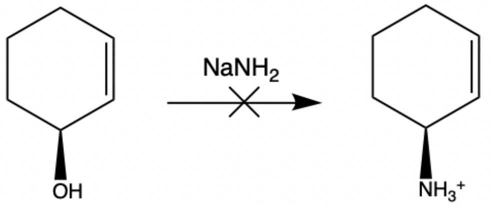
Ex #5)



OH$^-$ is a bad leaving group

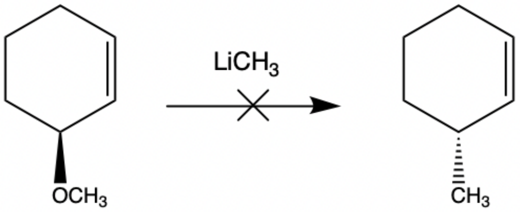
Inversion of stereochemistry indicates S_N2

Ex #6) Will not work



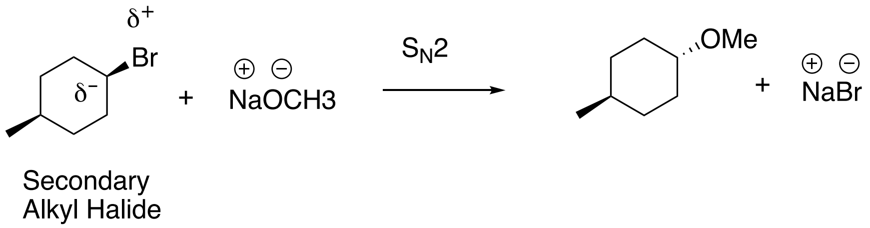
Note: these reagents will undergo an acid/base reaction rather than a substitution

Ex #7) will not work



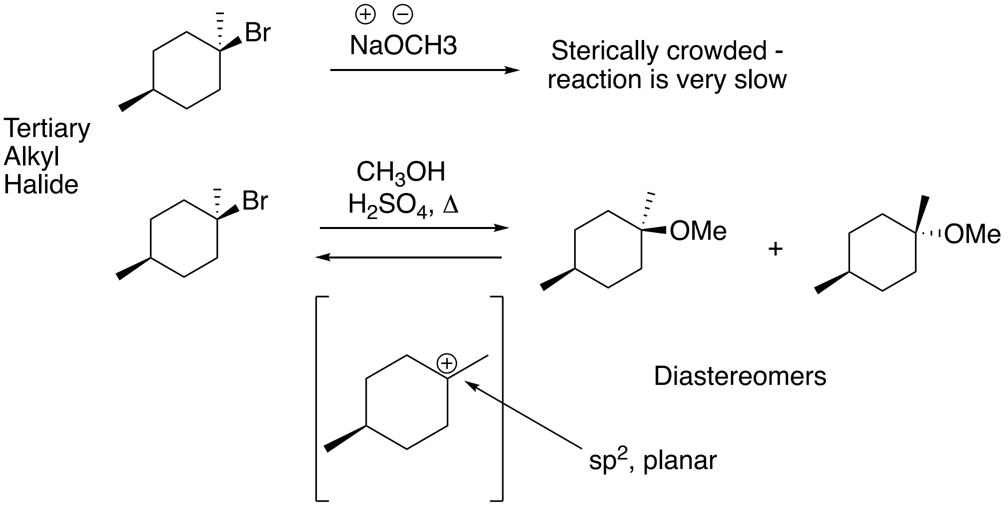
$^-OCH_3$ is a BAD leaving group

Ex #8)



–OCH_3 is a strong, negatively charged nucleophile, so it favors a S_N2 mechanism

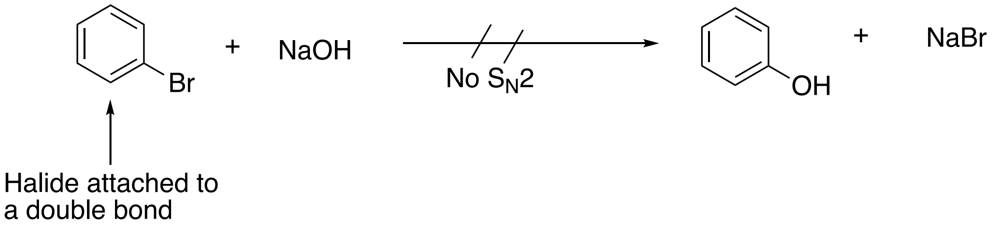
Ex #9)



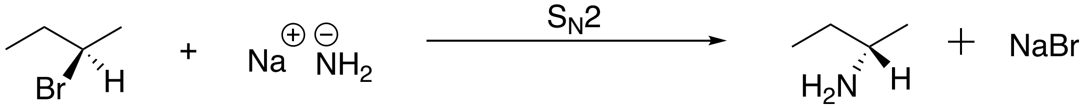
Note: the products are achiral

Extra examples:

Ex #1)



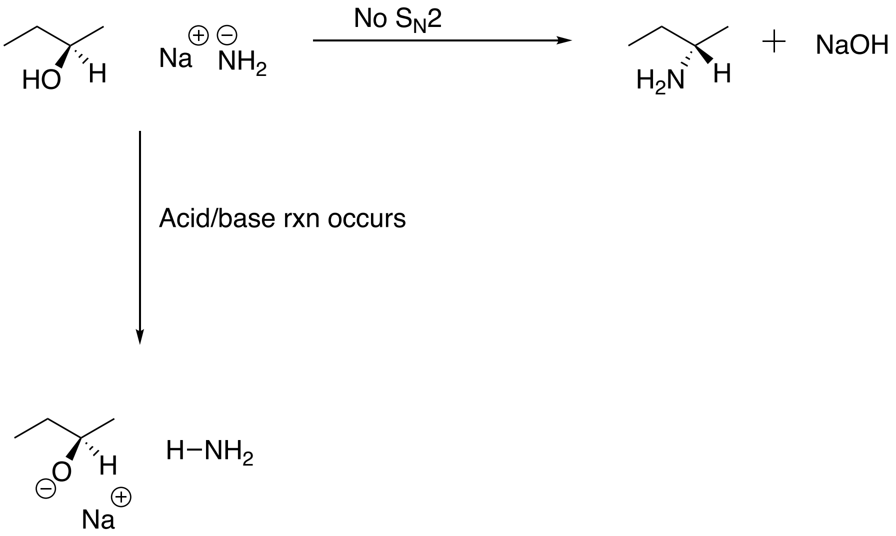
Ex #2) This one can work in principle



2-Bromobutane

Ex #3) The one below does NOT work

$^{\ominus}OH$, $^{\ominus}OR$, $^{\ominus}NR_2$ are never good leaving groups



In this reaction, the NH_2 species will pull off the most acidic proton (the one on the alcohol) to from an **alkoxide** instead of undergoing an S_N2 reaction,