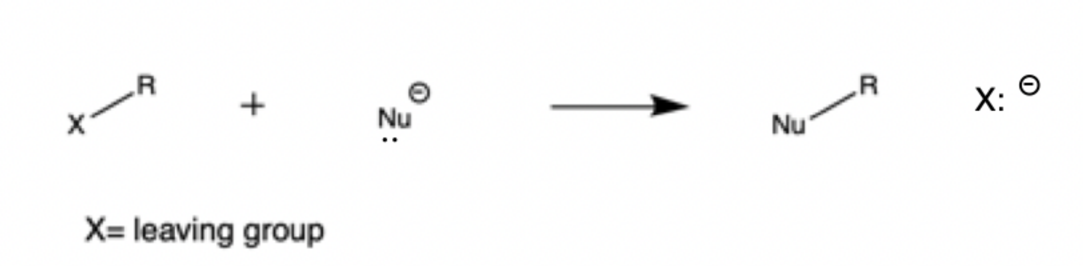
CHEM 261 October 19, 2023

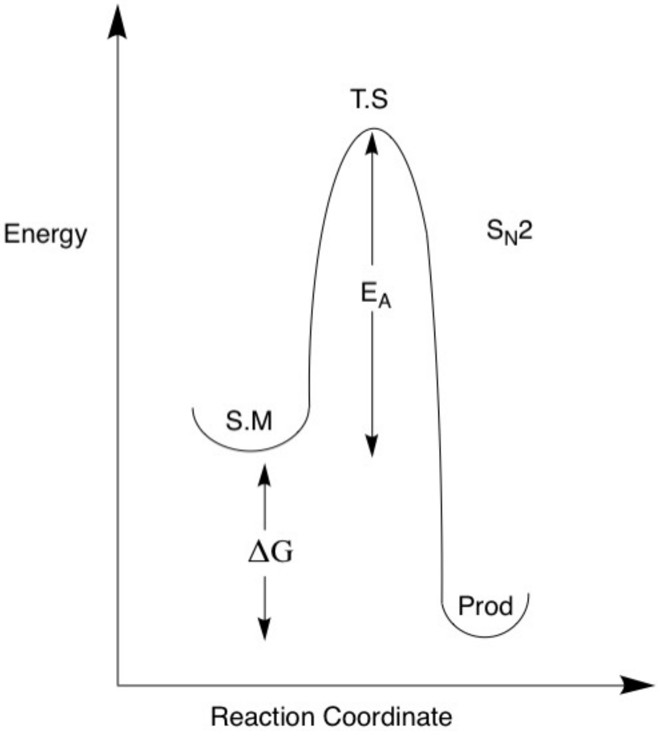
Recall the following about substitution reactions:



Characteristics of S_N2 reactions:

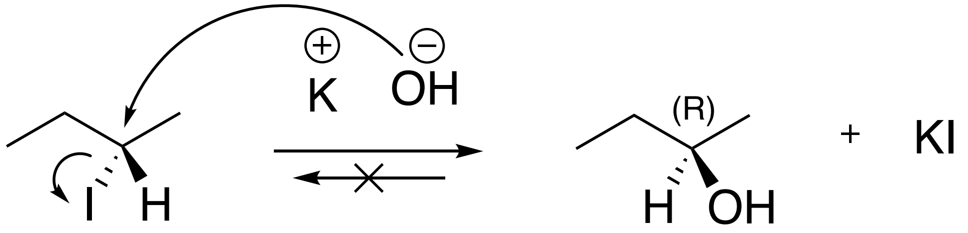
- Concerted
- Stereospecific
- Rate dependent on the concentration of nucleophile and substrate
- Works for 1° and 2° but not 3°

Energy Diagram of S_N2 Reaction



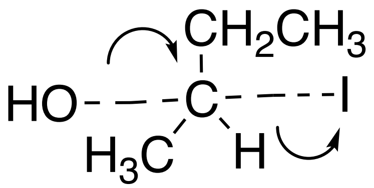
There is no intermediate in the S_N2 reaction, as it is concerted.
The only step is the rate determining step.

Mechanism of S_N2 Reaction



(S)-2-iodobutane

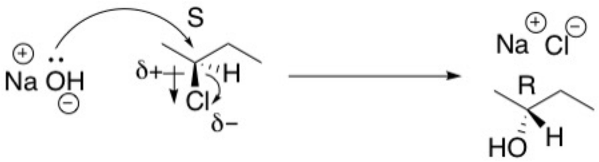
$\boxed{\text{inversion}}$ of stereochemistry



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

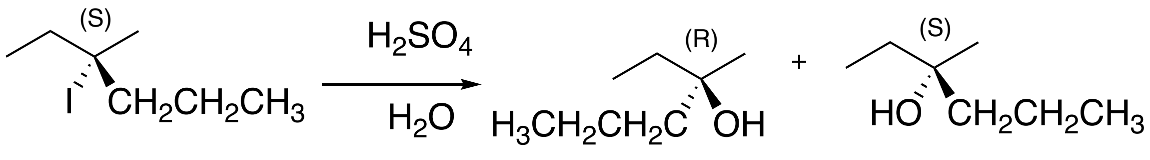
S_N2 Mechanism Example 2

Reverse reaction will not occur.
Inversion of configuration.



- **Concerted**: The bonds of the starting material break at the same time that the product bonds form.
- **Stereospecific**: stereochemistry of the starting material determines the stereochemistry of the product.

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

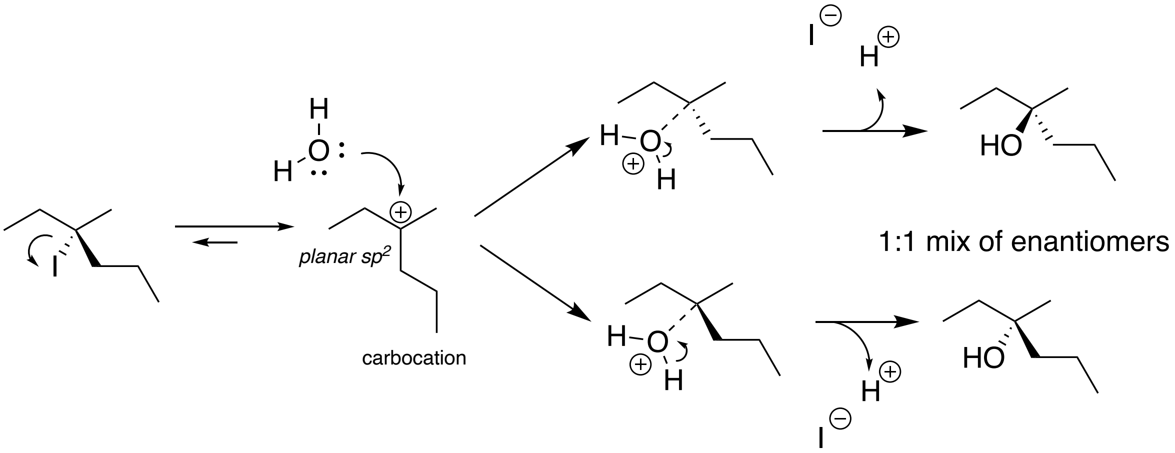


S_N1

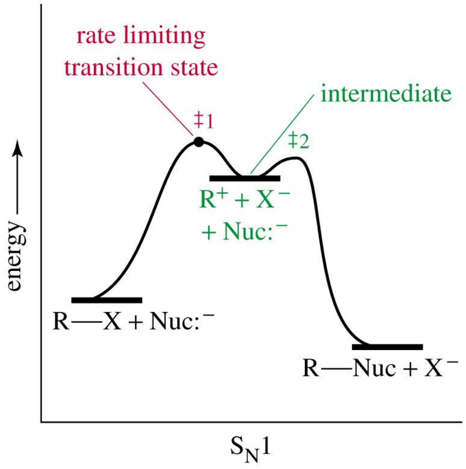
1:1 mix of enantiomers
racemic mixture

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°

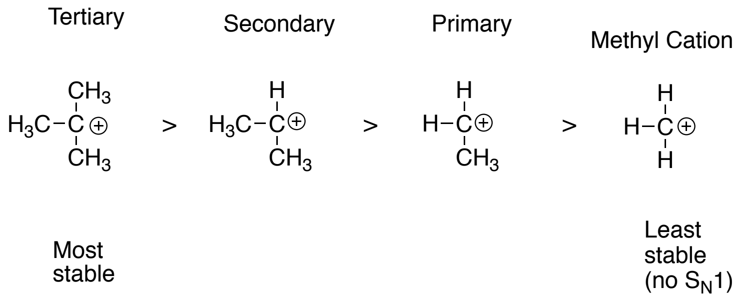


Energy level diagram of S_N1



Favored conditions are with stabilized carbocation – more substitution

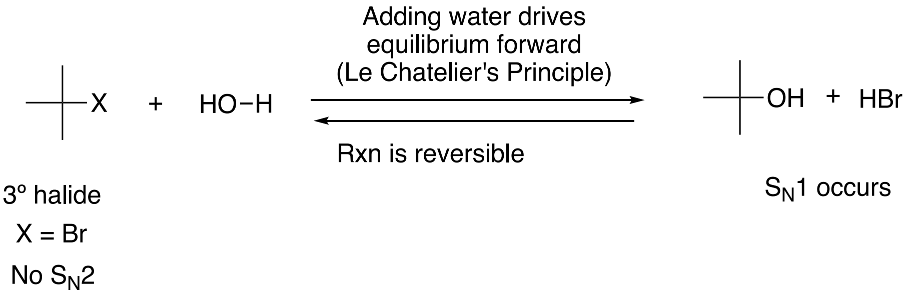
Carbocation Stability:



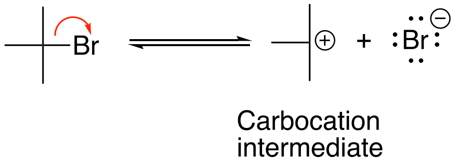
The 3 alkyl groups donate e^- density into the positive charge

Example: Tertiary Halide

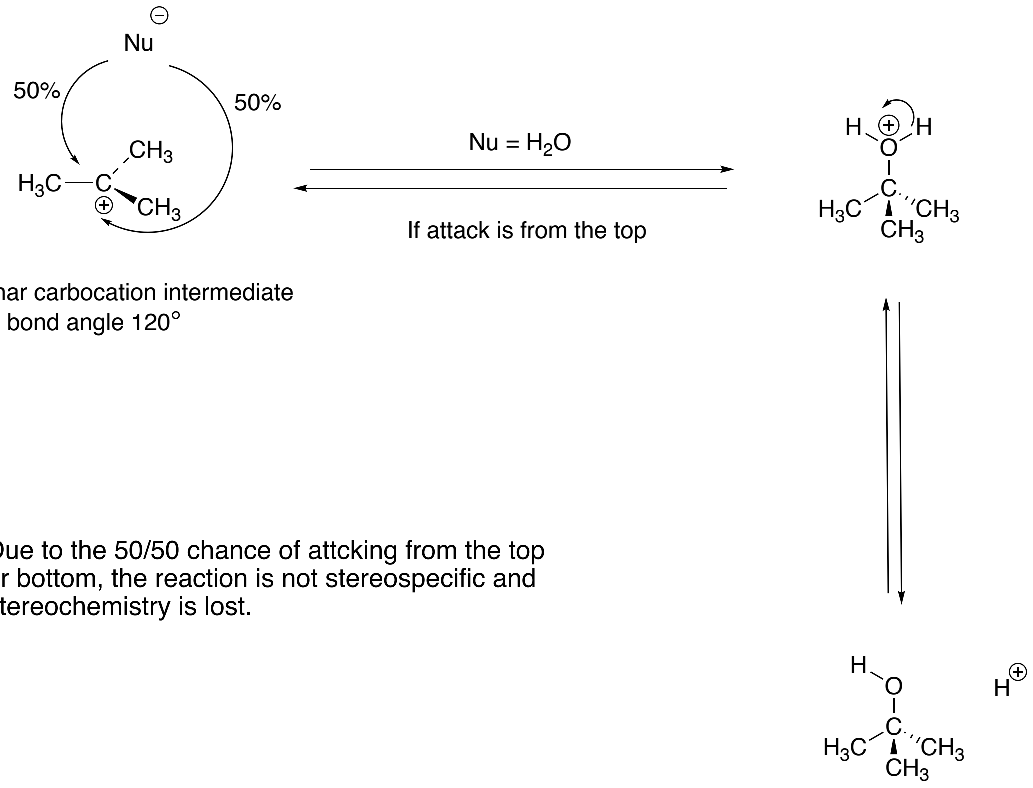
-No S_N2 possible, sterically crowded – does work by S_N1



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



Planar carbocation intermediate
sp^2, bond angle 120°

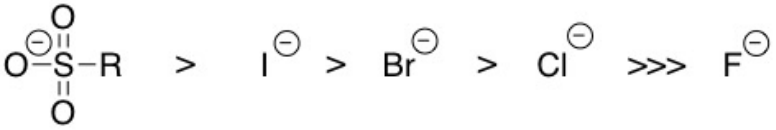
Due to the 50/50 chance of attcking from the top or bottom, the reaction is not stereospecific and stereochemistry is lost.

sp^3, tetrahedral, bond angle 109°

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



$^{\ominus}O-S(=O)_2-R > I^{\ominus} > Br^{\ominus} > Cl^{\ominus} \ggg F^{\ominus}$

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

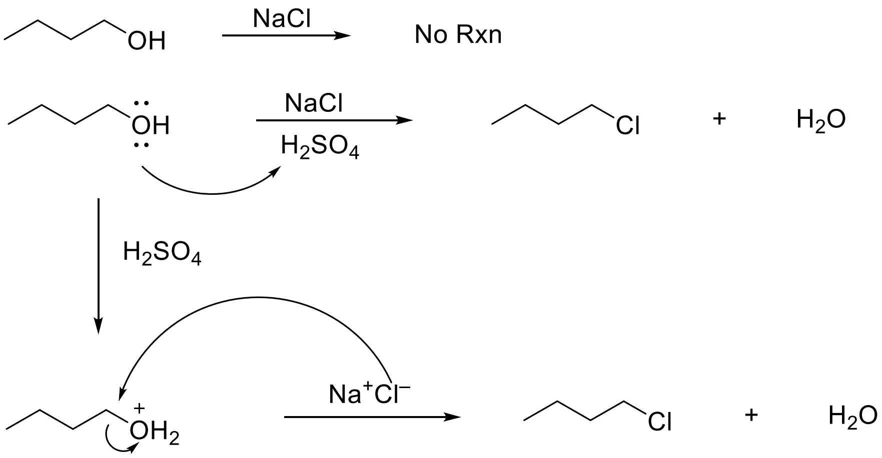
Never leaving groups: (negative charge not stabilized):

$F^{\ominus}$ $\overset{\ominus}{O}H$ $^{\ominus}OR$ $^{\ominus}NR_2$ $R\colon^{\ominus}$

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

Leaving group activation:

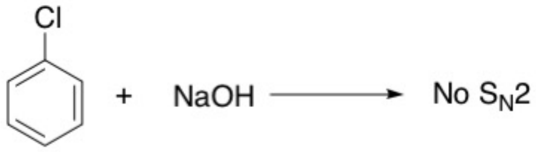
1) Protonation

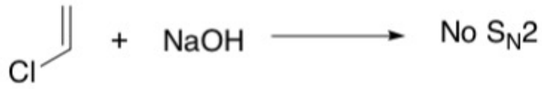


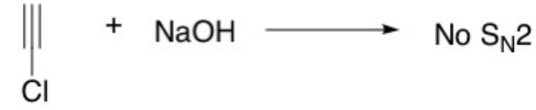
Highlights:

- 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.

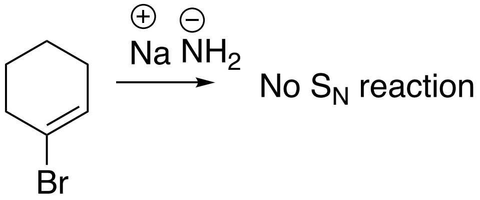
S_N2 will **<u>not</u>** occur on carbon sites that have multiple bonds.



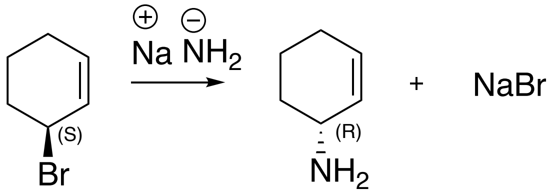




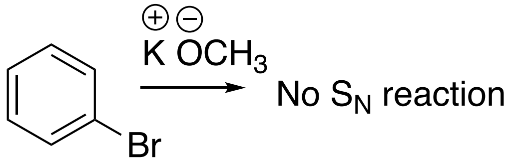
Example 1:



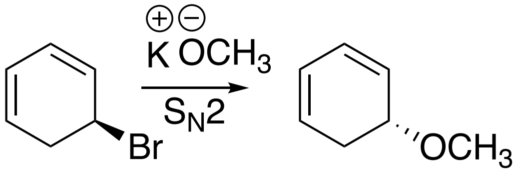
Example 2:



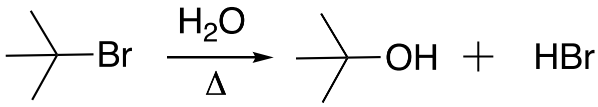
Example 3:



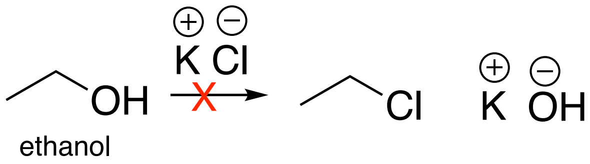
Example 4:



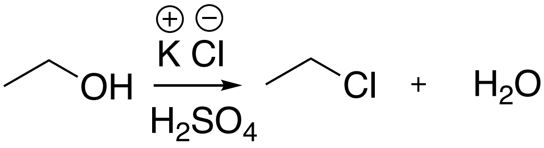
Example 5:



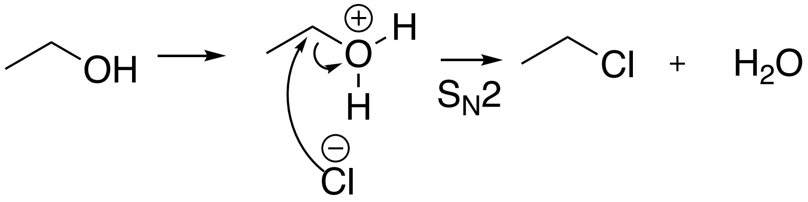
Example 6:



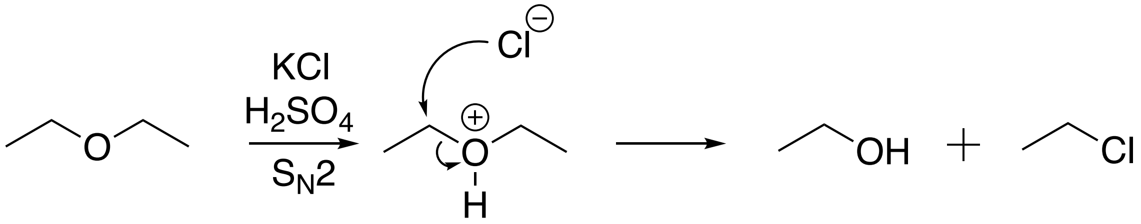
Example 7:



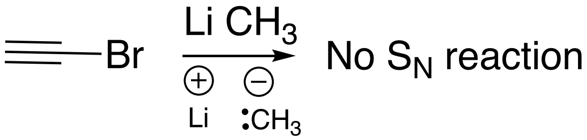
Mechanism:



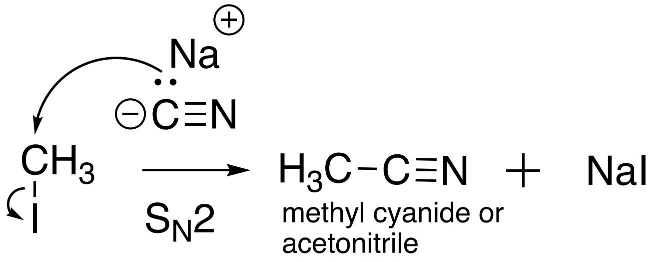
Example 8:



Example 9:

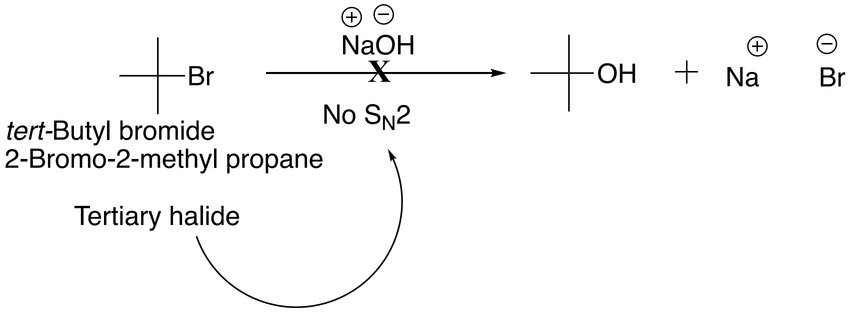


Example 10:



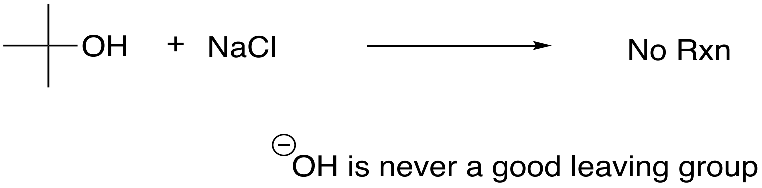
<u>REVIEW:</u> S_N yes or no? Examples

Ex #1) Will <u>NOT</u> proceed – no S_N

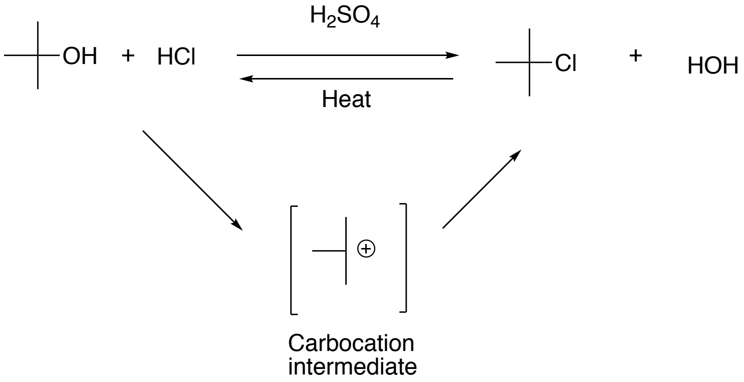


Note: alkyl groups stabilize carbocation intermediate by donating a negative charge
Note: will undergo elimination reaction (explanation of what this is comes later)

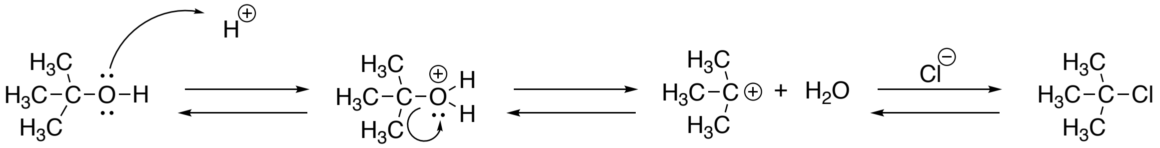
Ex #2)



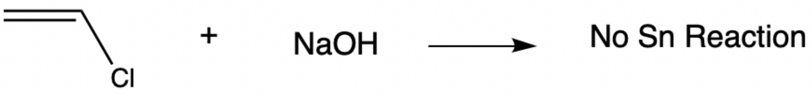
Ex #2a) Works with Acid as S_N1 Mechanism

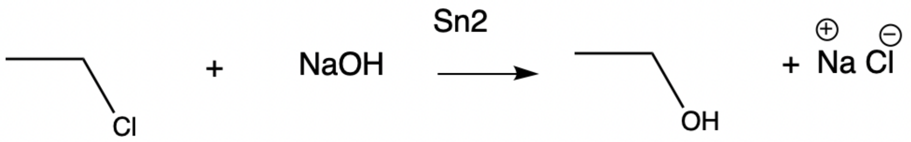


Mechanism:



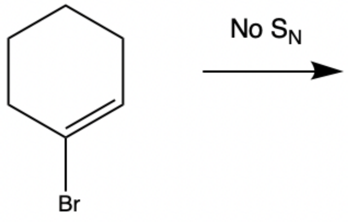
Ex #3)



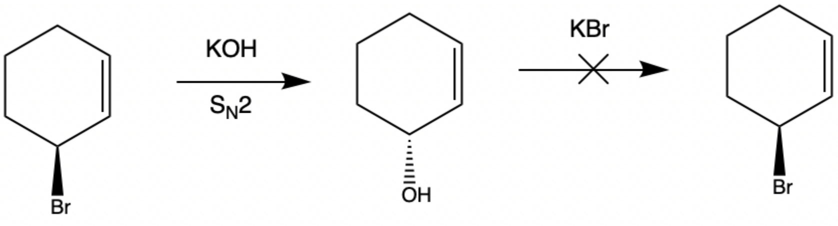


A carbon attached to a double bond cannot undergo a substitution reaction
The carbon with the leaving group must be sp^3 to undergo a substitution reaction

Ex #4)



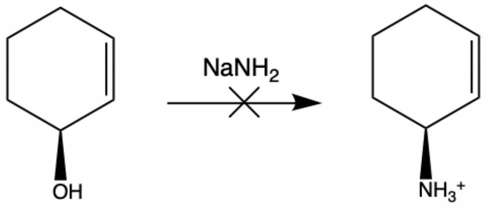
Ex #5)



OH^- is a bad leaving group

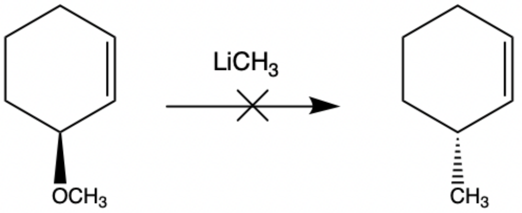
Inversion of stereochemistry indicates S_N2

Ex #6) Will not work



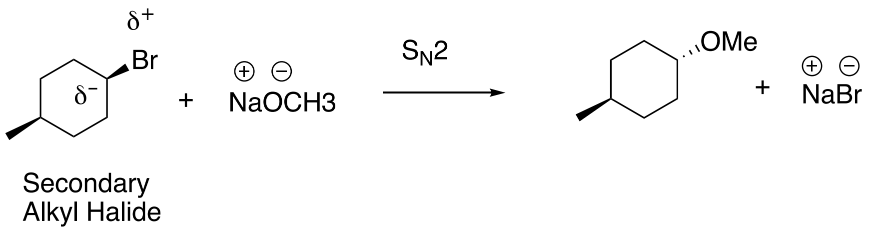
Note: these reagents will undergo an acid/base reaction rather than a substitution

Ex #7) will not work



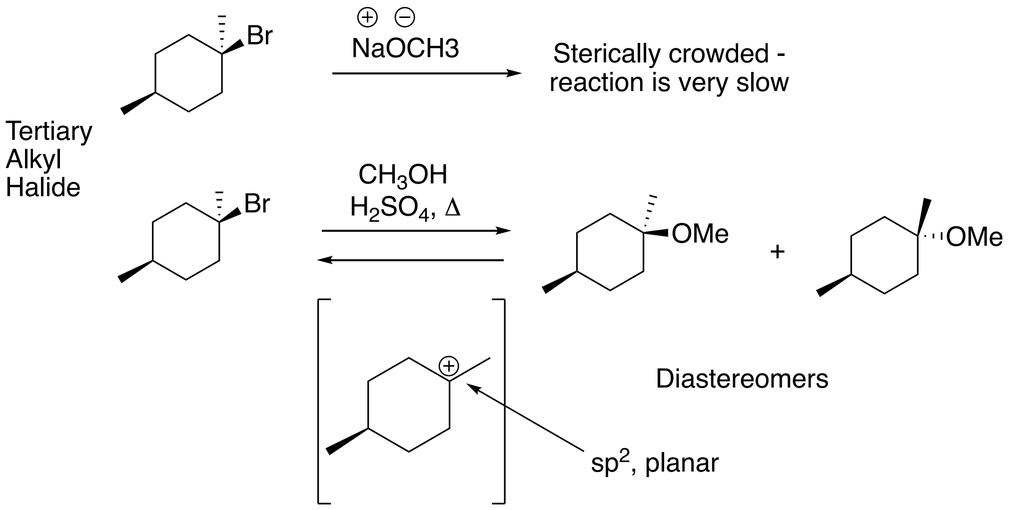
$^-$OCH$_3$ is a BAD leaving group

Ex #8)



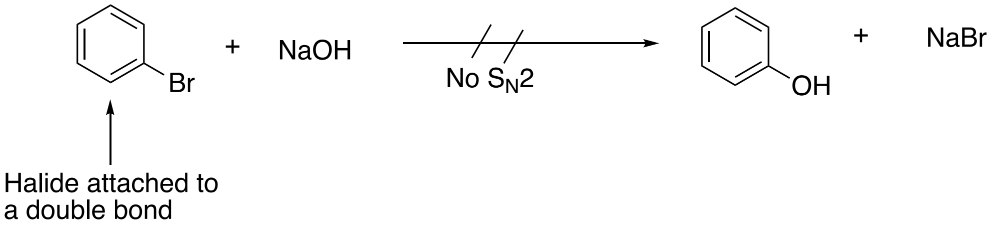
–OCH$_3$ is a strong, negatively charged nucleophile, so it favors a S$_N$2 mechanism

Ex #9)

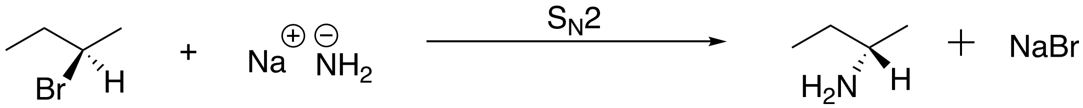


Note: the products are achiral

Extra examples:
Ex #1)



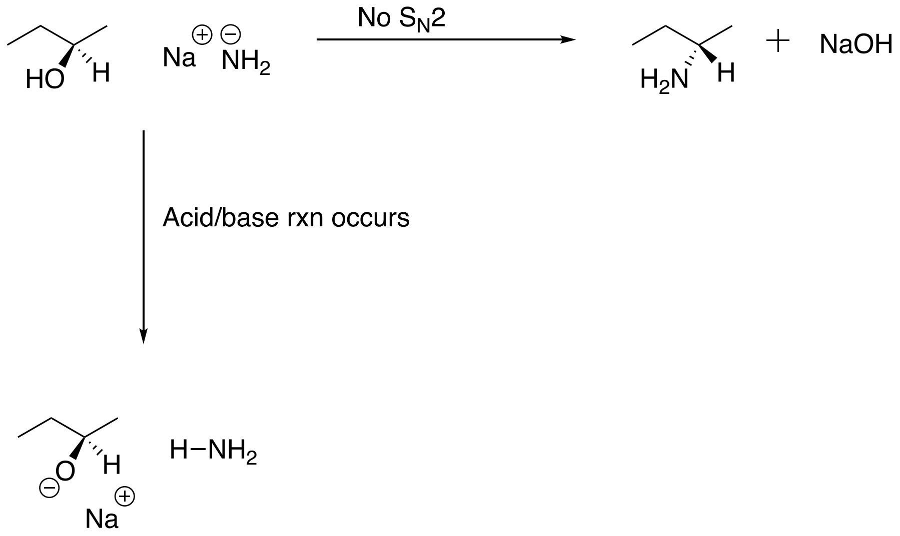
Ex #2) This one can work in principle



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,