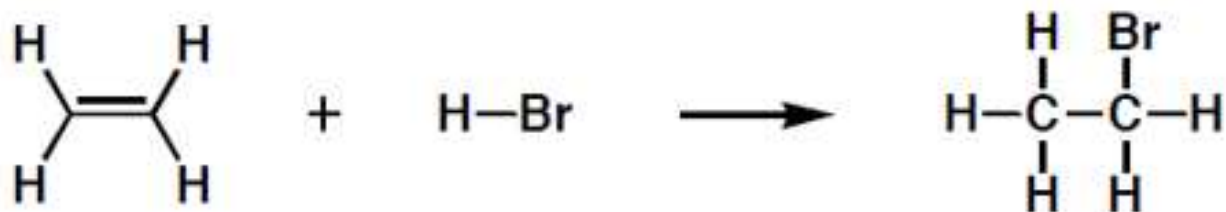


UNIT 4

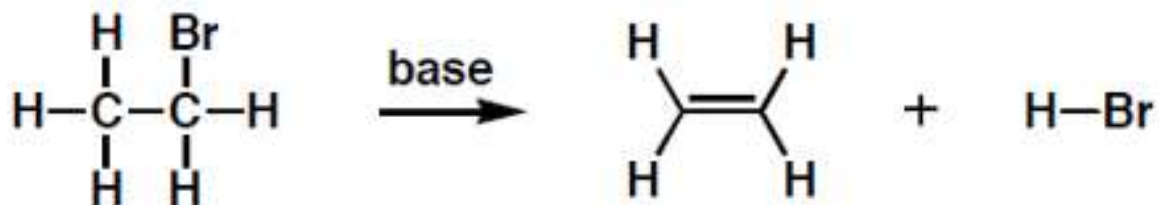
MAJOR ORGANIC REACTIONS

Kind of organic reaction

a. Addition



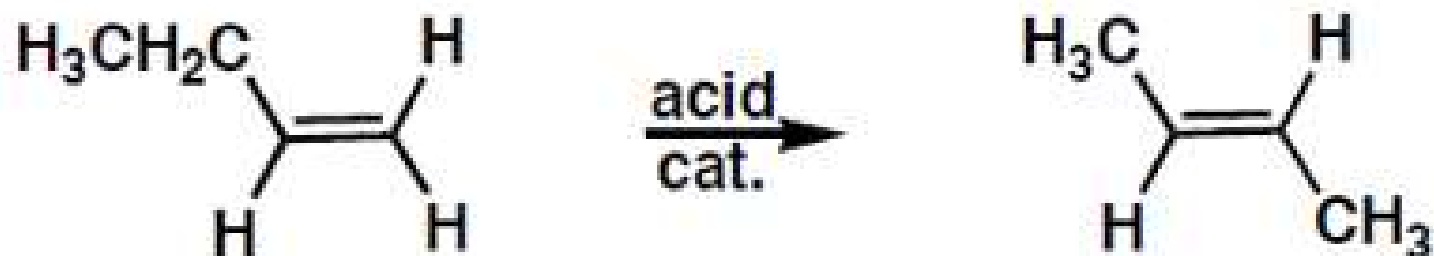
b. Elimination



c. Substitution



d. Rearrangement



Curved arrows indicate breaking and forming of bonds

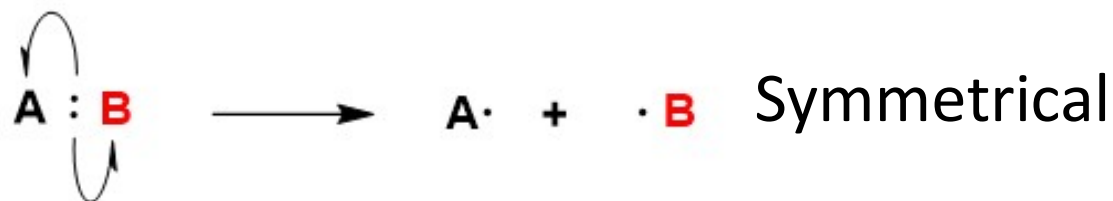


Arrowheads with a “half” head (“fish-hook”) indicate homolytic and homogenic steps



Arrowheads with a complete head indicate heterolytic and heterogenic steps

Bond breaking



Bond making



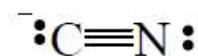
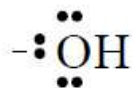
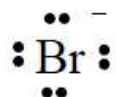
Nucleophile (Nu): - is a substance that is nucleus-loving.

has a negatively polarized, electron rich atom and can form a bond by donating electrons.

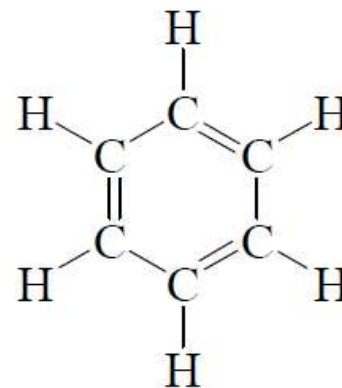
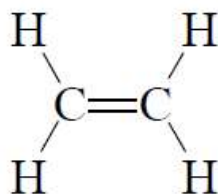
Characteristics: Nucleophilic atoms have either lone pairs or pi bonds that can be used to form new bonds to electrophiles

Nucleophile Examples

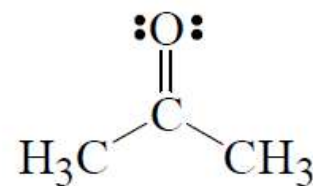
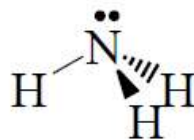
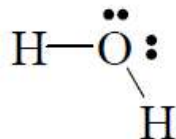
Anions



Pi bonds



Atoms with lone pairs



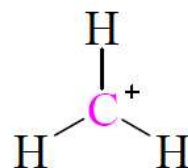
Electrophile (E): - is a substance that is electron-loving.

has a positively charge, electron poor atom and
can form a bond by accepting a pair of electrons
from nucleophiles.

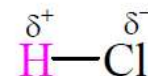
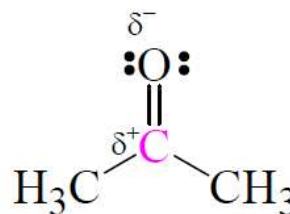
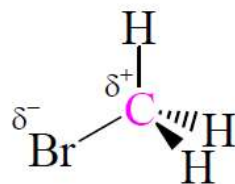
Characteristics: Electrophilic atoms have Positive charge, a partial positive charge, or be very polarizable

Electrophile Examples

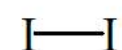
- Charged:



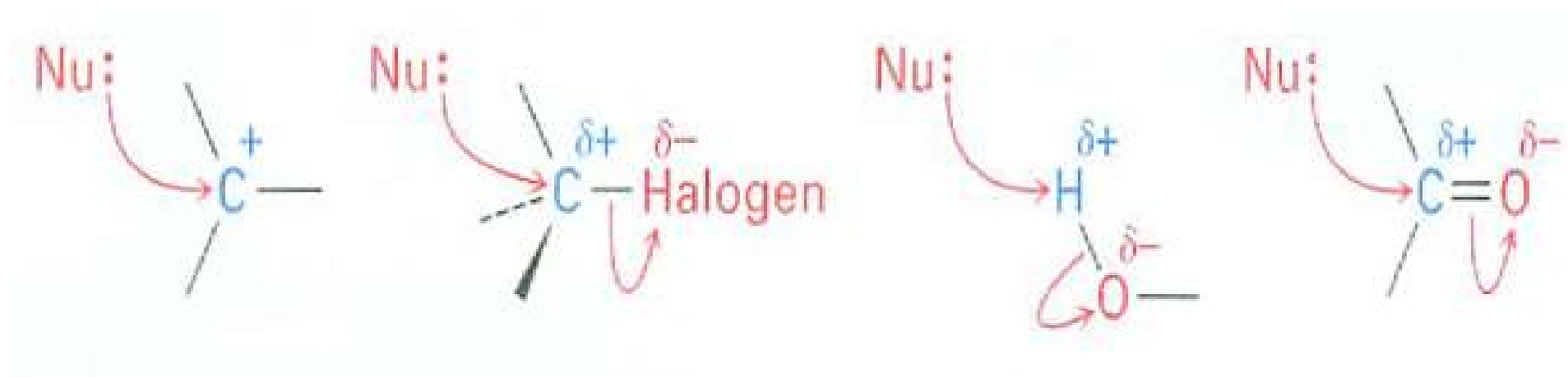
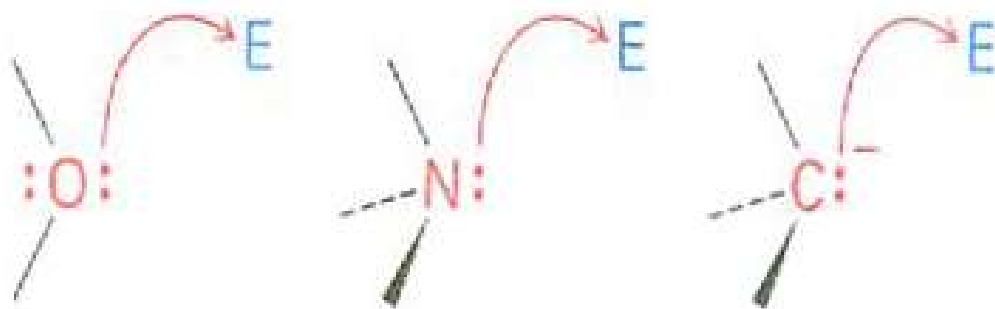
- Polar:

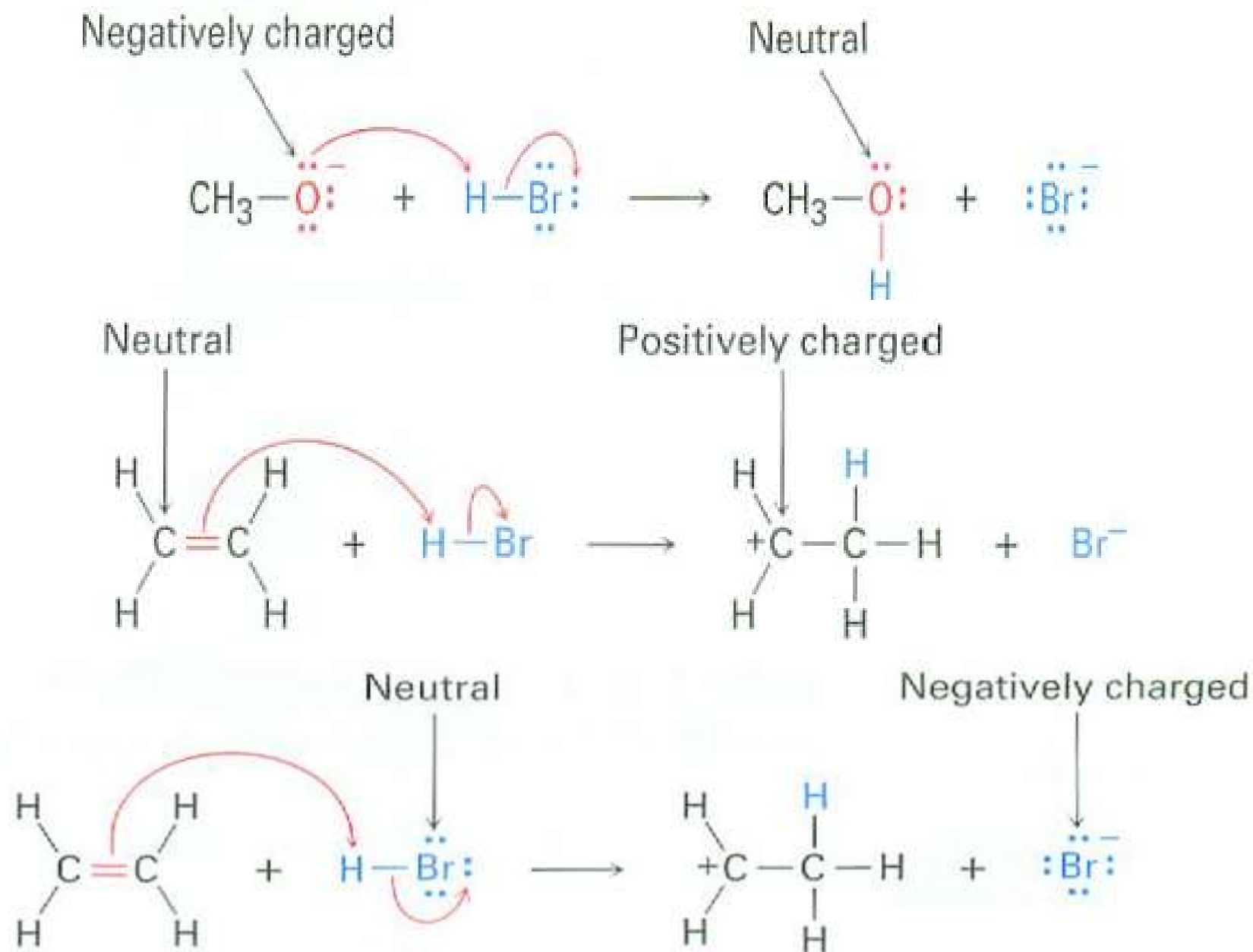


- Polarizable:



Electrons move from a nucleophilic source (Nu) to an electrophilic sink (E)

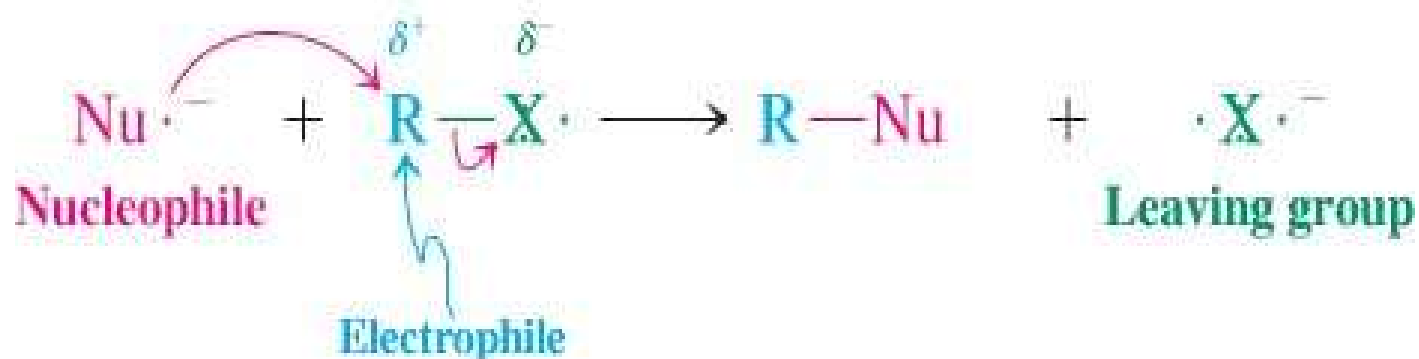




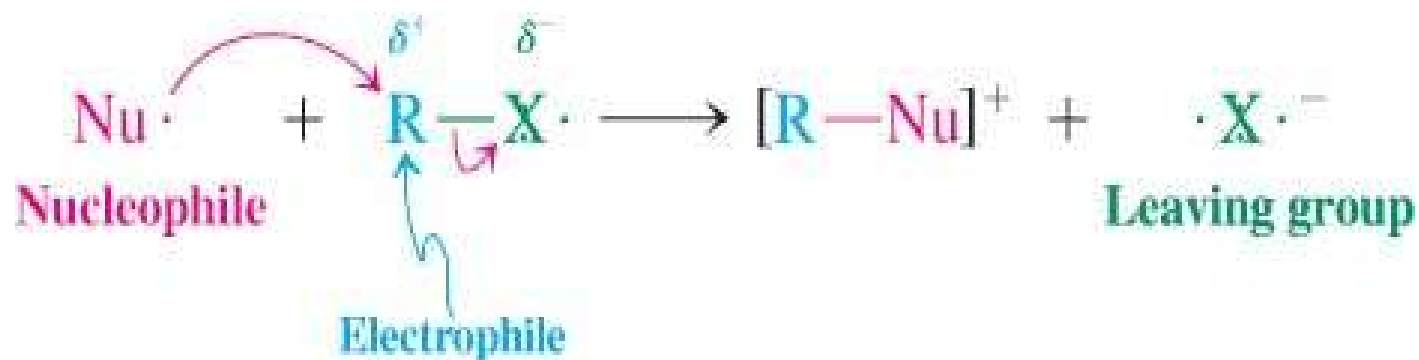
The octet rule must be followed during electron movement.

4.1 Substitution reactions

Nucleophilic Substitutions



Nucleophiles attack electrophilic centers



There are two mechanisms of substitution: $\text{S}_{\text{N}}1$ & $\text{S}_{\text{N}}2$

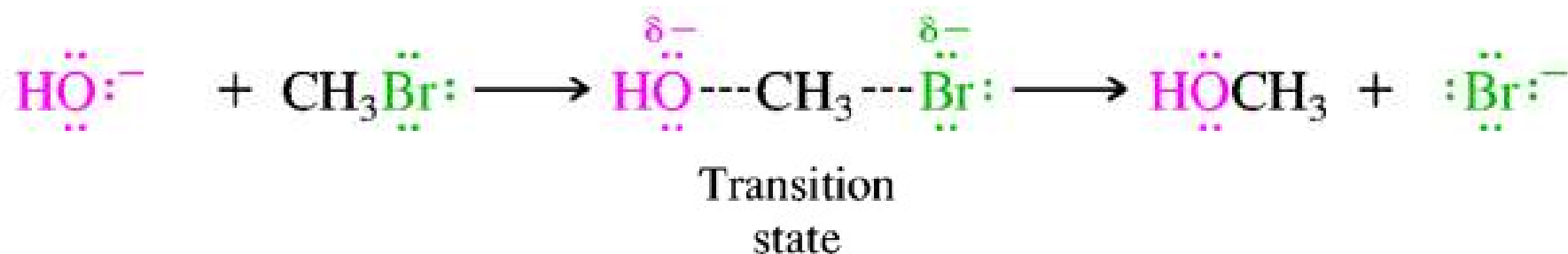
S_N2 Mechanism

- substitution **nucleophilic bimolecular**

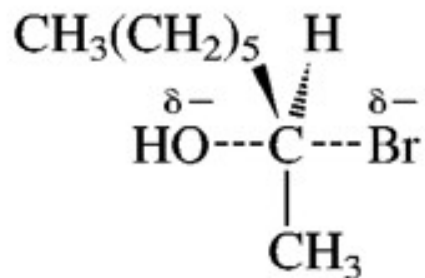
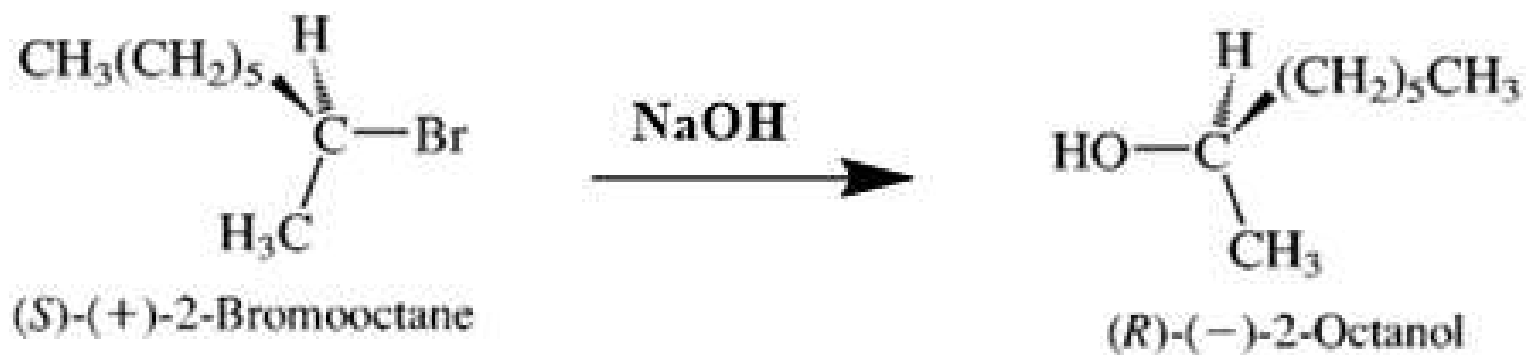
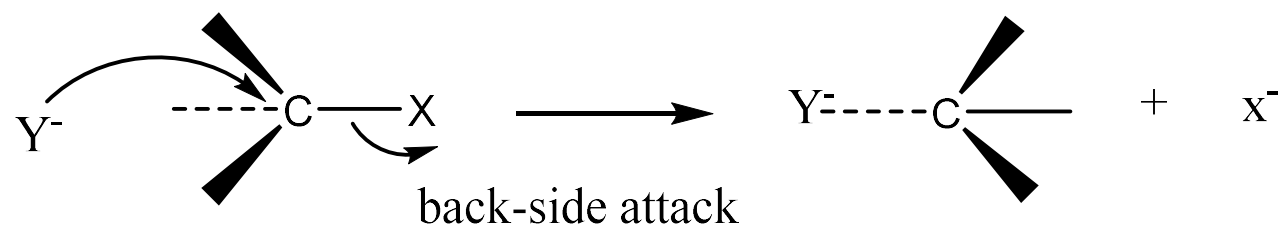


$$\text{Rate} = k[\text{CH}_3\text{Br}][\text{HO}^-] \quad \text{second order overall}$$

- It is a single-step process (concerted reaction) in which both the alkyl halide and the nucleophile are involved at the transition state.



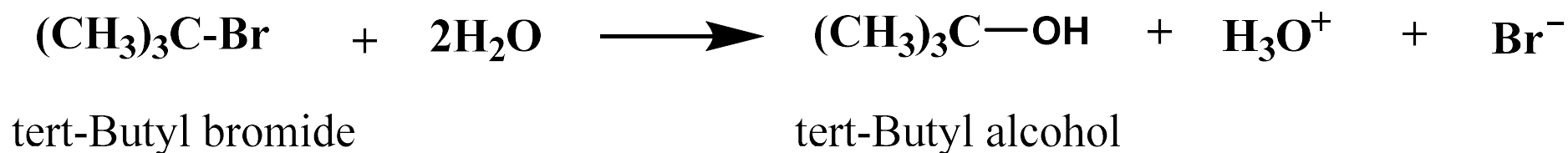
- S_N2 occurs with inversion of configuration with back side attack.



transition state

S_N1 Mechanism

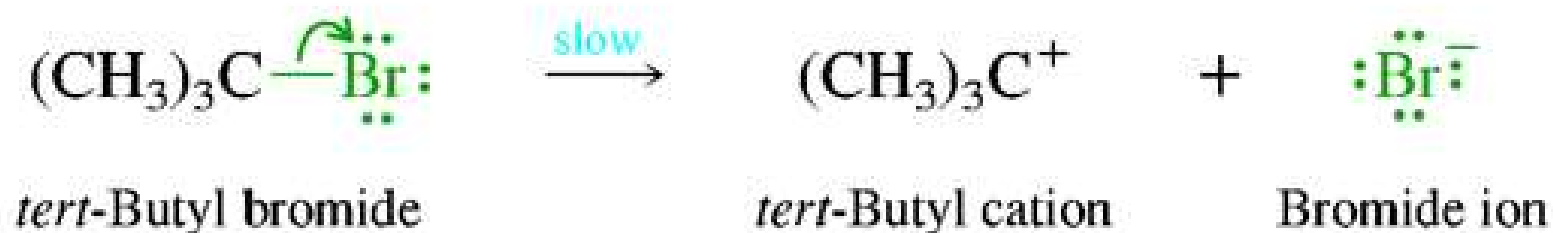
is Substitution nucleophilic unimolecular



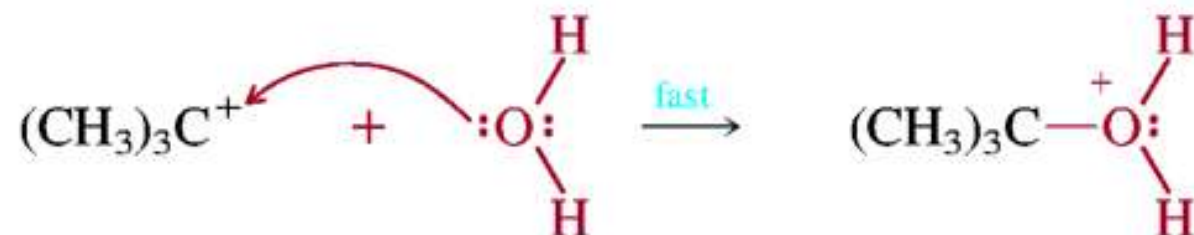
$$\text{Rate} = k[(\text{CH}_3)_3\text{CBr}] \quad \text{First order overall}$$

The rate depends on only the alkyl halide

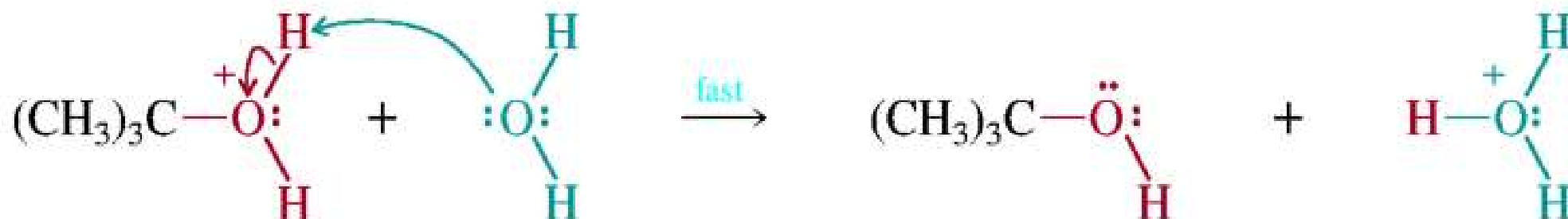
Step 1: The alkyl halide dissociates to a carbocation and a halide ion.



Step 2: The carbocation formed in step 1 reacts rapidly with a water molecule.



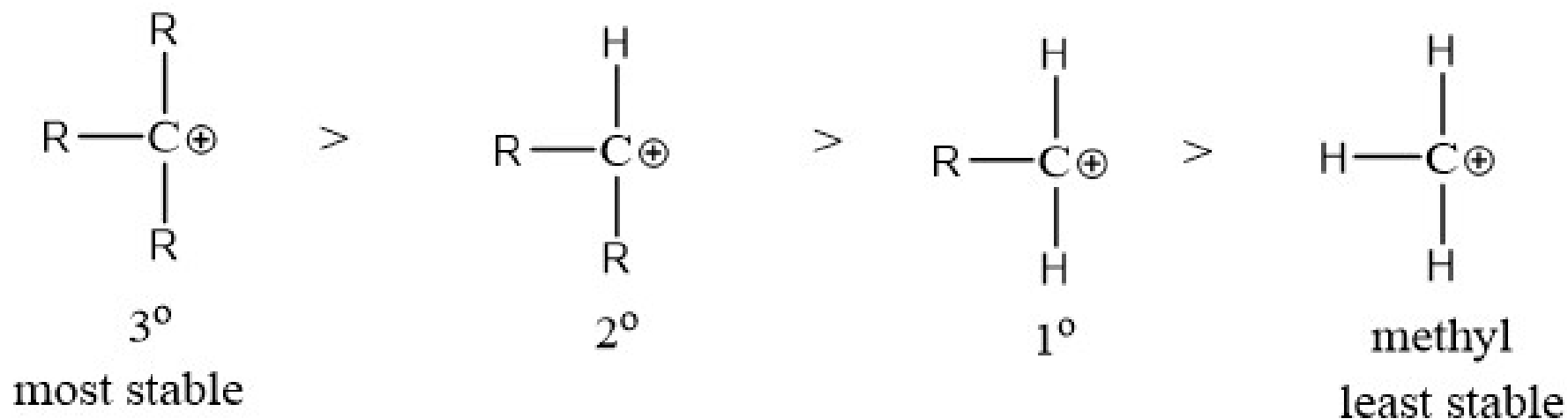
Step 3: This step is a fast acid-base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.



Carbocations are formed in SN1 reaction. Thus, the rate depends on the stability of carbocations.

Carbocation is a carbon cation $\begin{array}{c} + \\ \text{R}-\text{C}-\text{R} \\ | \\ \text{R} \end{array}$

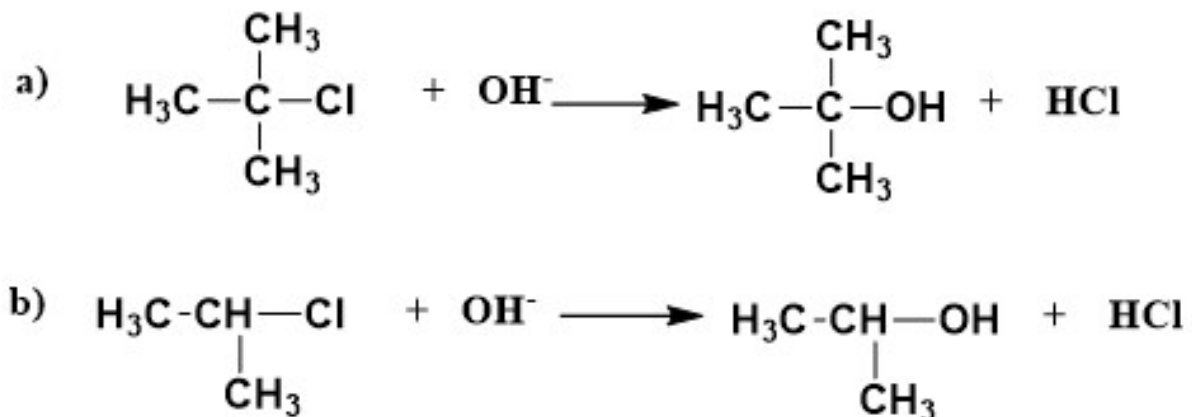
- The order of carbocation stability is: $3^\circ > 2^\circ > 1^\circ > \text{methyl}$



- Alkyl group stabilize carbocations by inductive effect.

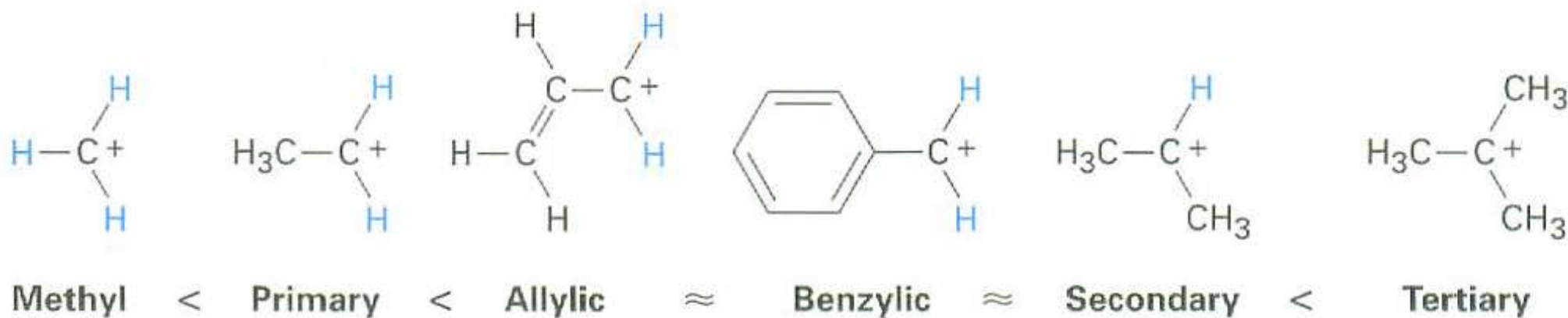


The more stable the carbocation, the rapid the reaction by SN1



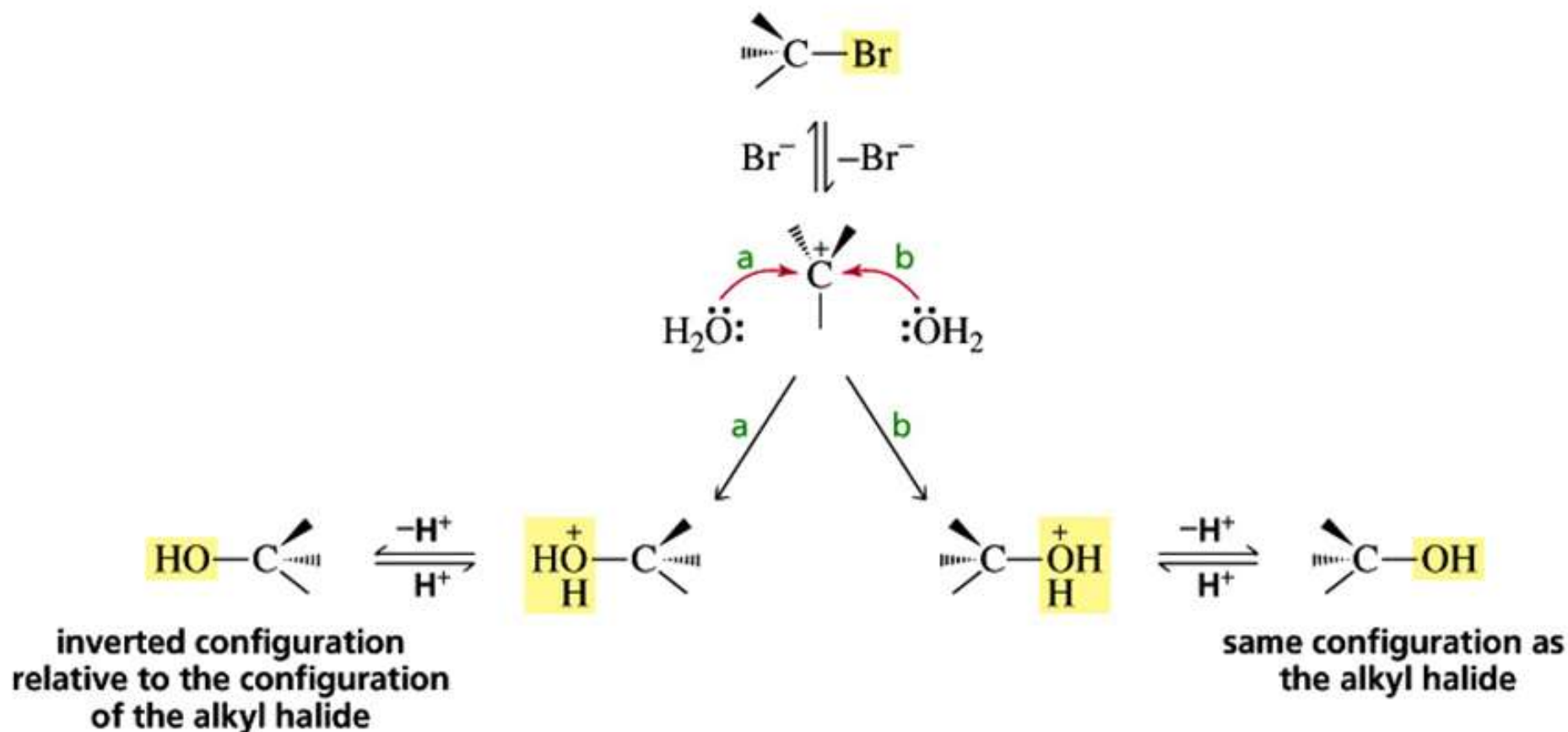
Reaction (a) takes place more rapidly than (b) since passes through more stable 3° carbocation.

Carbocation stability

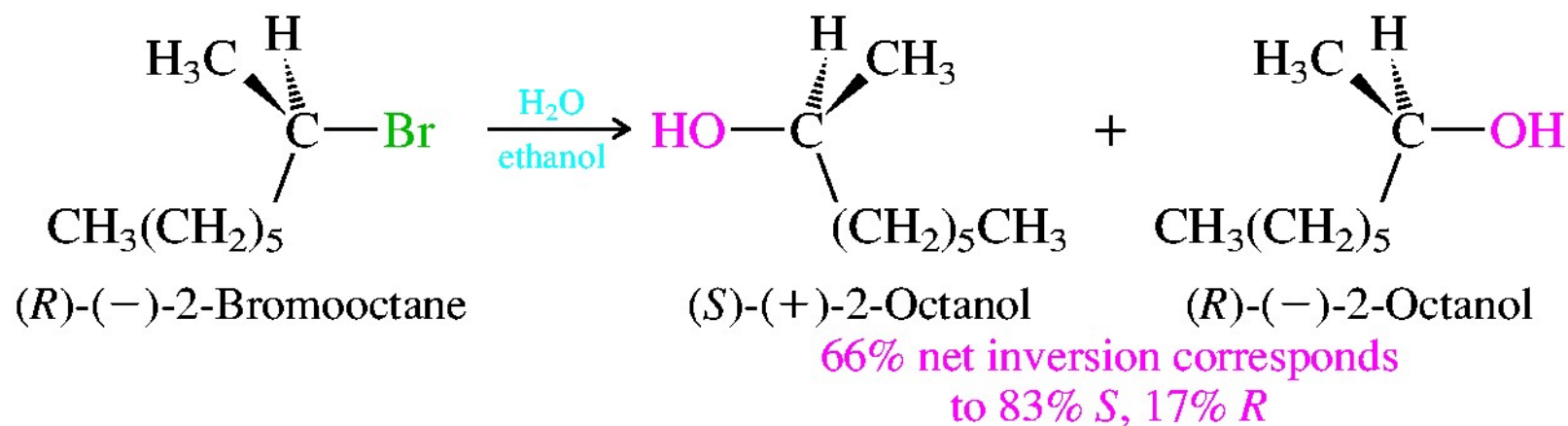


STEREOCHEMISTRY OF S_N1 REACTIONS

- S_N1 is not stereospecific
- Since carbocation has a trigonal planar structure, the Nucleophile can attack from front side or back side



A mixture of (R) and (S) products are possible= Racemization



Factors Affecting S_N1 and S_N2 Reactions

- A. The structure of substrate
- B. The concentration and reactivity of nucleophile
- C. The nature of leaving group
- D. The effect of solvent

Factors Affecting S_N1

A. The Structure of Substrate

- S_N1 depends on the nature of carbocations. The more stable the carbocation, the faster the reaction.
- In general, more highly substituted alkyl halides are more reactive toward S_N1 reaction than less substituted ones.

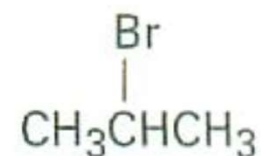
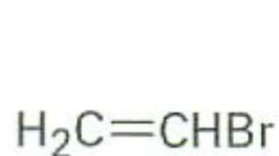
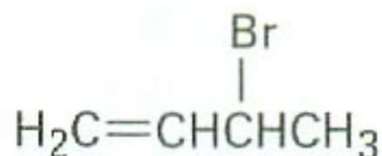
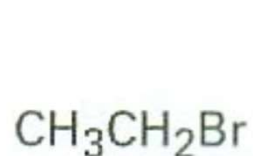
S_N1 reactivity rates follow the trend: $3^\circ > 2^\circ > 1^\circ > \text{methyl}$

E.g reaction of alkyl halides with acetic acid

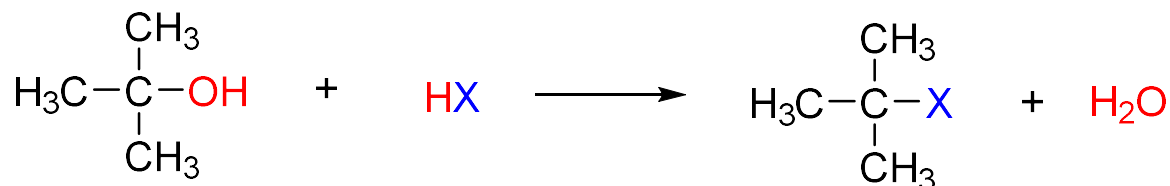
Table Relative reactivities

Substrate	Relative rate of S _N 1
CH ₃ CH ₂ Br (primary)	Too slow to measure
(CH ₃) ₂ CHBr (secondary)	1
(CH ₃) ₃ CBr (tertiary)	10 ⁵

Ex. Rank the following substances in order of their expected S_N1 reactivity:



B. The Concentration and Reactivity of Nucleophile



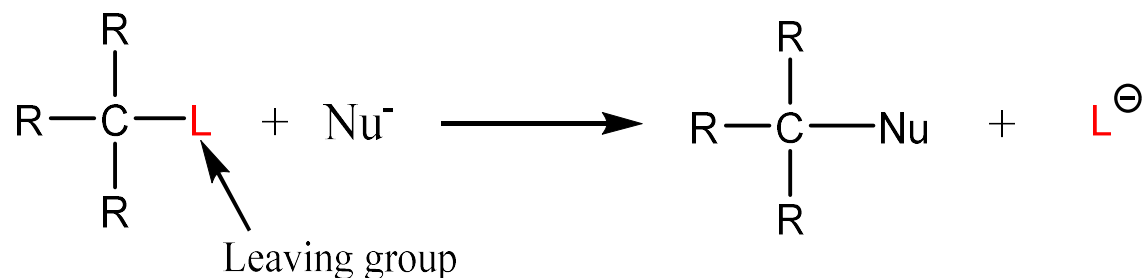
$$\text{Rate} = K [(\text{CH}_3)_3\text{COH}]$$

The same rate for X = Cl, Br, I

- Since the rate determining step in the mechanism for $\text{S}_{\text{N}}1$ does not involve the nucleophile, we would not expect the nucleophilicity to affect the rate.
- a change in the concentration of the nucleophile to have any effect on the reaction rate of a reaction occurring via the $\text{S}_{\text{N}}1$ path.
- Nucleophilic strength is the measure of the ability of the nucleophile to more rapidly attach or bond itself to the carbon releasing the leaving group.

C. The Nature of Leaving Group

The leaving group ability (LGA) is defined as the ability of the leaving group to be displaced and remain stable after departing.



- Leaving groups that are weak bases (coming from strong acids) are more stable after leaving the molecule and do not have any desire to return. However, the more basic the leaving group is (coming from weak acids), the poorer will be its ability to depart without wanting to return to the molecule.
- Good leaving groups are essential for $\text{S}_{\text{N}}1$ reaction. Some common leaving groups are:
 - Anions: Cl^- , Br^- , I^- , RSO_3^- (Sulphonate)
 - Neutral: H_2O , ROH , R_3N , R_3P
- Cl^- , Br^- , and I^- are good leaving groups with high LGA
- F^- comes from HF (a weak acid) is a very poor leaving group

D. The effect of solvent

- The solvent used in a substitution reaction will influence which pathway will be chosen.

There are three major categories of solvent.

1. Polar Protic Solvents

2. Polar Aprotic Solvents

3. Non-Polar Aprotic Solvents

Polar Protic solvents

- are solvents in which at least one Hydrogen atom is bonded to either on Oxygen or a Nitrogen. This creates a polar molecule that will attract other molecules or ions using Hydrogen bonding.

- Water (H_2O)

- alcohol (R-O-H)

- amine (R-NH_2),

- Carboxylic Acids like formic acid, H-COOH , or acetic acid, CH_3COOH

are described as Polar Protic solvents.

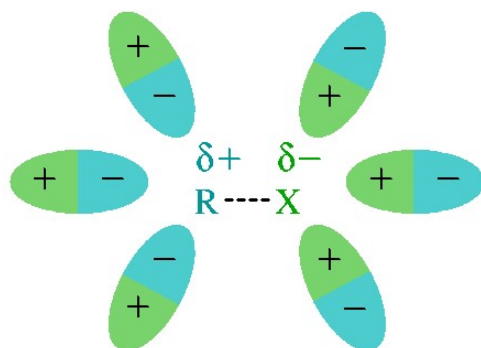
Polar aprotic solvents

- are solvents whose molecules exhibit a molecular dipole moment but whose hydrogen atoms are not bonded to an oxygen or nitrogen atom.
- no hydrogen bonding interactions can take place between particles.
 - aldehydes, ketones, Dimethyl Sulfoxide (DMSO), $\text{CH}_3\text{-SO-CH}_3$,
Dimethyl Formamide (DMF), $\text{H-CO-N(CH}_3)_2$ are polar aprotic solvent.

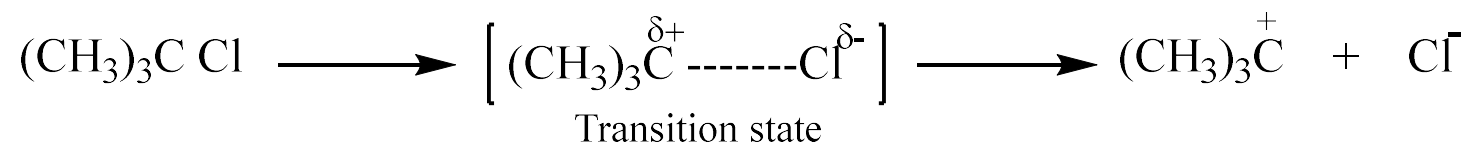
Non-polar aprotic solvents

- are solvents whose molecules have a zero molecular dipole and whose hydrogen atoms are not bonded to an oxygen or nitrogen.
- Examples include all the hydrocarbons (Alkanes, Alkenes, and Alkynes).

- Polar protic solvents are useful for SN1 reaction.
- According to the SN1 mechanism, a molecule of an alkyl halide ionizes to a positively charged carbocation and a negatively charged halide ion in the rate-determining step. As the alkyl halide approaches the transition state for this step, a partial positive charge develops on carbon and a partial negative charge on the halogen.



Polar protic solvents surround carbocations by hydrogen bonding to the charged species, which has the effect of stabilizing the intermediate.



$(\text{CH}_3)_3\text{C}^+$ become more stable with the help of protic solvent.

Factors Affecting S_N2

A. The Structure of Substrate

S_N2 is a single step reaction.

Large groups prevent the approach of a nucleophile in S_N2 reaction. The nucleophile must approach the alkyl halide from the side **opposite** the bond to the leaving group.



CH_3Br



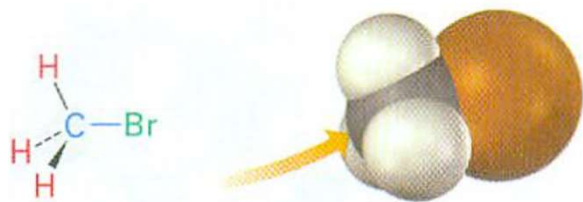
$\text{CH}_3\text{CH}_2\text{Br}$



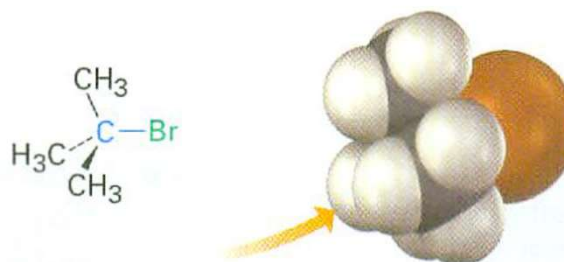
$(\text{CH}_3)_2\text{CHBr}$



$(\text{CH}_3)_3\text{CBr}$

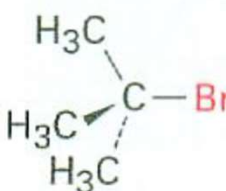
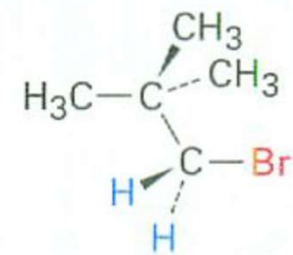

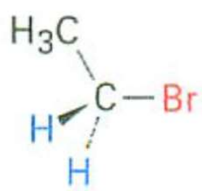



Easy approach of the nucleophile.



approach of the nucleophile is difficult



					
	Tertiary	Neopentyl	Secondary	Primary	Methyl
Relative reactivity	< 1	1	500	40,000	2,000,000

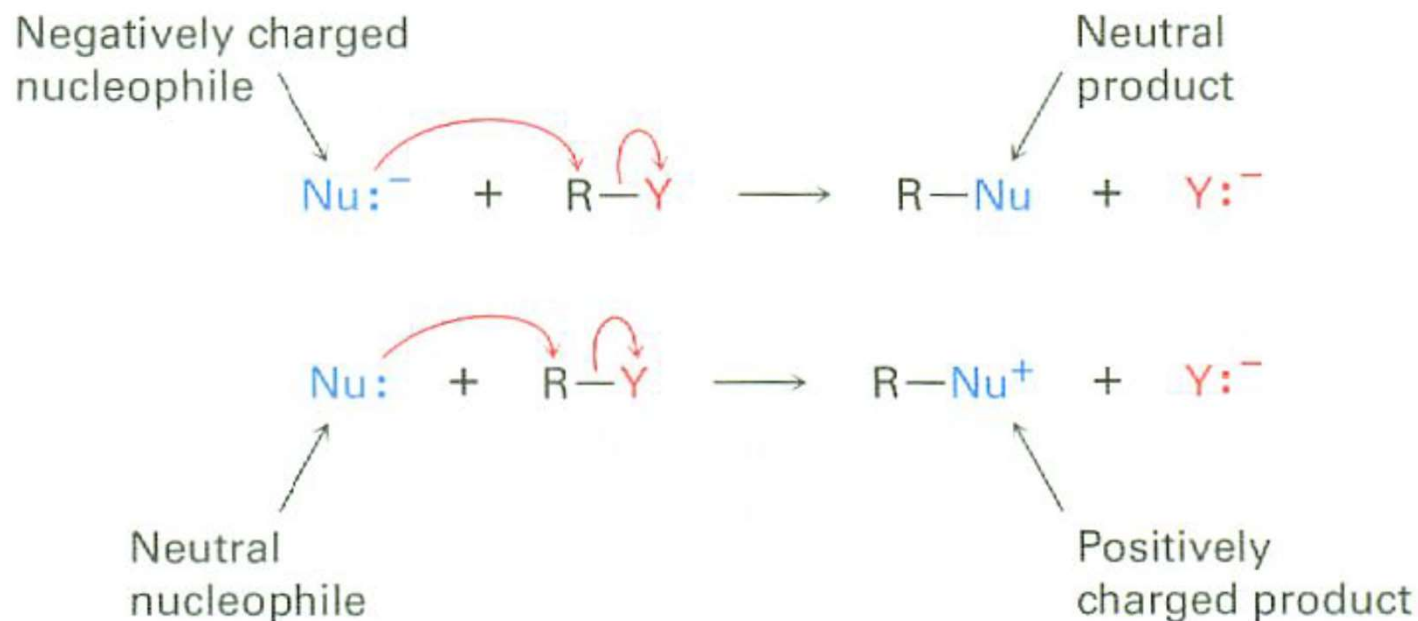
$\text{S}_{\text{N}}2$ reactivity rates follow the trend: **methyl** > 1° > 2° > 3°

B. The Concentration and Reactivity of Nucleophile



$$\text{Rate} = k[\text{CH}_3\text{Br}][\text{HO}^-] \quad \text{second order overall}$$

- The rate of $\text{S}_\text{N}2$ depends on the nature of nucleophile.
- Any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons.
- **Strong nucleophiles** will react more rapidly than poor or weak nucleophiles.



- Negative charged nucleophiles tend to be stronger than the neutral nucleophiles with the same central atom.
 - For example, OH^- is stronger than H_2O
- RO^- are better nucleophiles than R-O-H .
- Nucleophilicity usually increases going down a column of the periodic table
 - HS^- is more nucleophilic than OH^-
 - $\text{I}^- > \text{Br}^- > \text{Cl}^-$
- Negatively charged nucleophiles are usually more reactive than neutral ones. As a result, $\text{S}_\text{N}2$ reaction are often carries out under basic condition rather than neutral or acidic condition.
- Stronger nucleophiles will enhance the reaction rate of a reaction operating under $\text{S}_\text{N}2$ conditions.
- Increasing the concentration of the nucleophile will enhance the rate of an $\text{S}_\text{N}2$ reaction since kinetically the reaction is first order in respect to the nucleophile concentration.

Table 5.2 Relative nucleophilicities

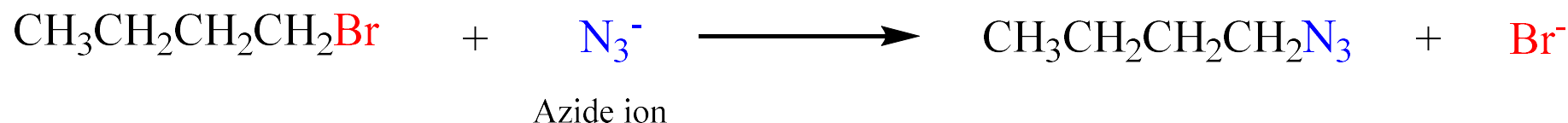
Very Good	I^- , HS^- , RS^-
Good	Br^- , HO^- , RO^- , NC^- , N_3^-
Fair	NH_3 , Cl^- , F^- , RCO_2^-
Weak	H_2O , ROH
Very Weak	RCO_2H

C. The Nature of Leaving Group

- The reaction rate of a reaction occurring via $\text{S}_{\text{N}}2$ path would increase with higher leaving group affinity (LGA) for the leaving group.
- This is the same effect as was observed for an $\text{S}_{\text{N}}1$ reaction.

D. The Effect of Solvent

- Polar Aprotic solvents are important in SN2 reaction.
- They lack OH groups and do not solvate anions very strongly, leaving them much more able to express their nucleophilic character.
- Polar Aprotic solvents do not solvate or encapsulate the nucleophiles, so they are free to approach the organic substrate.



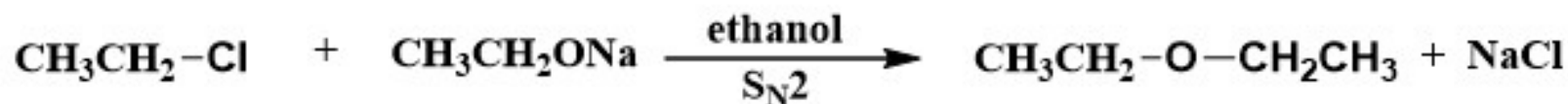
Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(\text{CH}_3)_2\text{S}=\text{O}$	48.9	Polar aprotic	1300
<i>N,N</i> -Dimethylformamide	$(\text{CH}_3)_2\text{NCH}=\text{O}$	36.7	Polar aprotic	2800
Acetonitrile	$\text{CH}_3\text{C}\equiv\text{N}$	37.5	Polar aprotic	5000

- The rate of the above reaction is high in polar aprotic solvents.
- The rate of an S_N2 reaction will be increased when Polar Aprotic solvents are used.

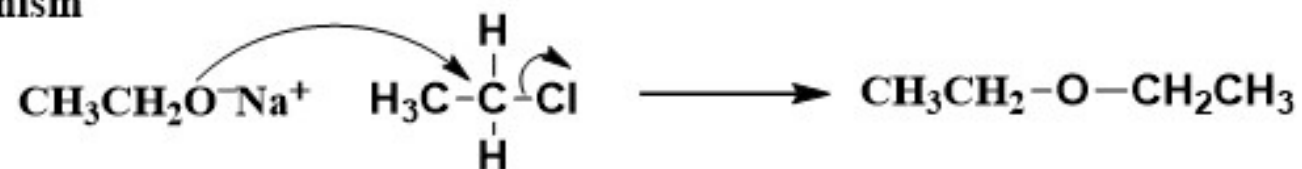
Applications of Substitution Reactions

1. Alkyl halides

- Williamson ether synthesis



mechanism



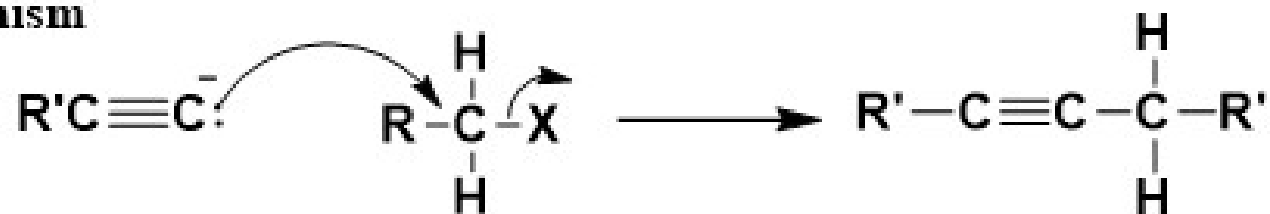
- preparation of primary amine



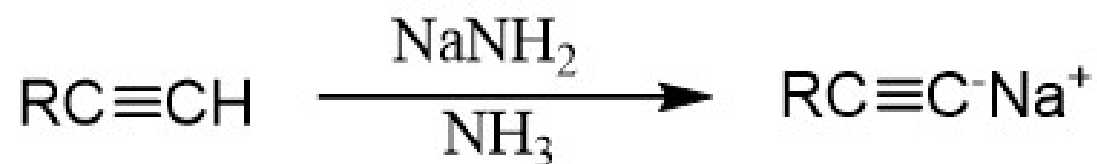
- Preparation of alkynes

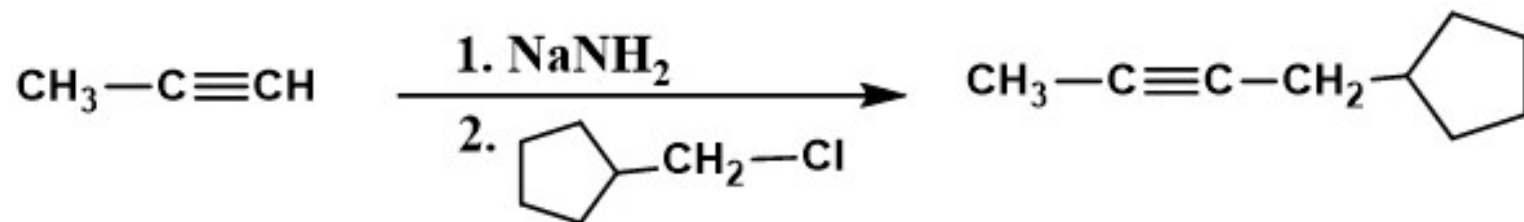


mechanism



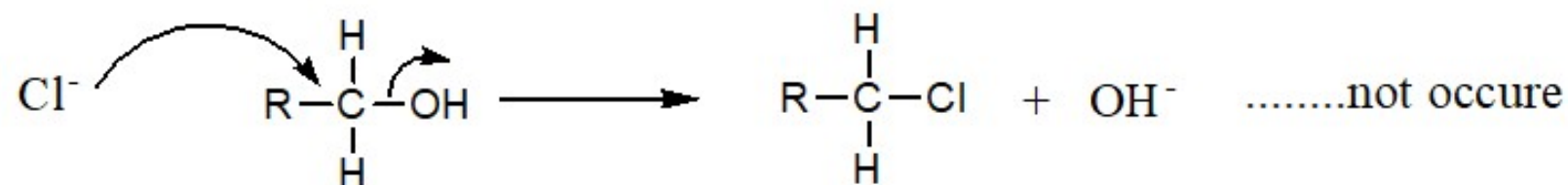
$\text{RC}\equiv\text{CNa}$ can be prepared from a terminal alkyne using strong base like NaNH_2



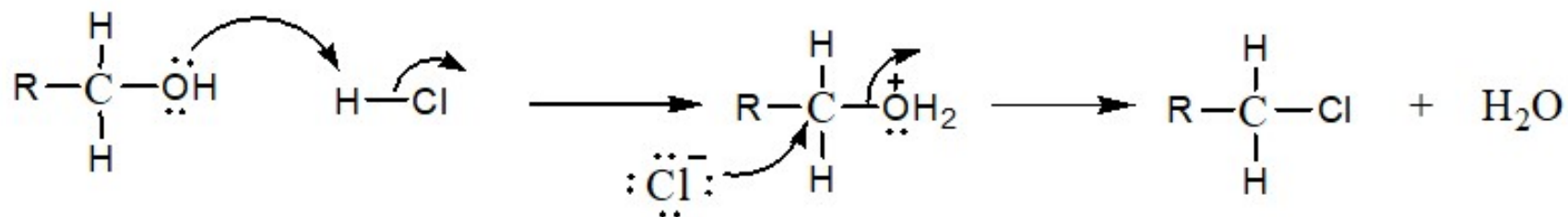


2. Alcohols

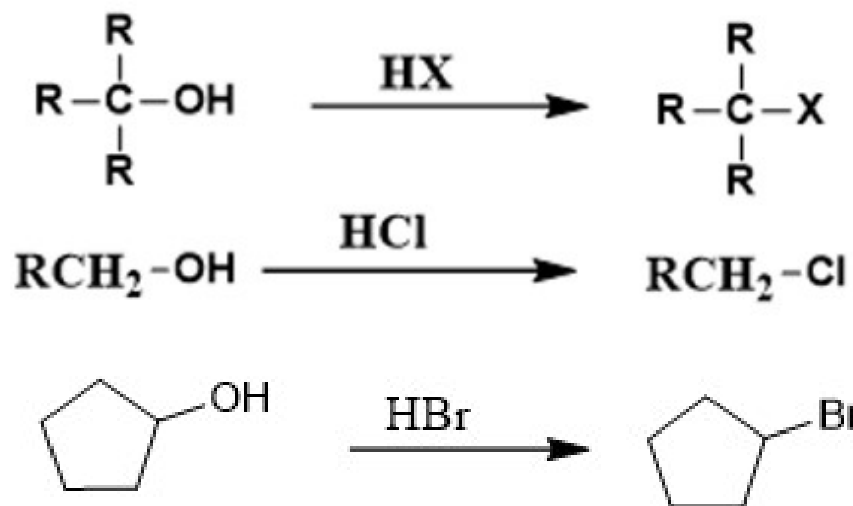
-OH is too basic to be displaced by a nucleophile



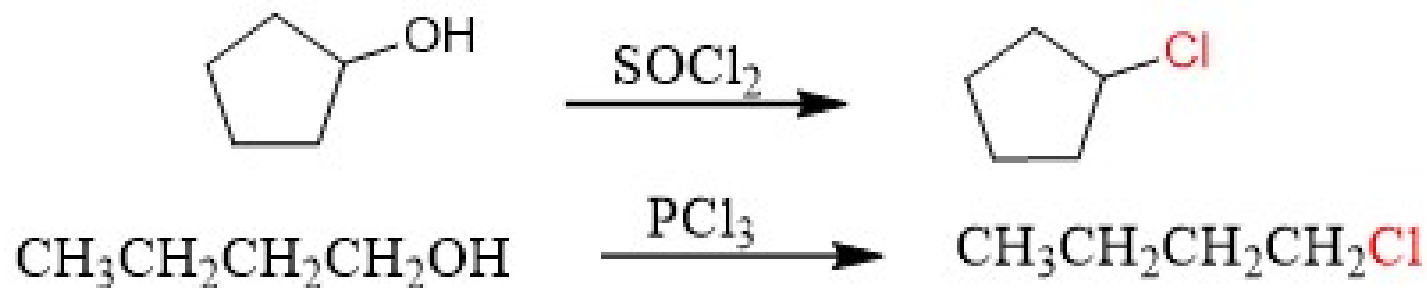
- Acid protonation change -OH to -OH₂⁺ (good leaving group)



Preparation of alkyl halide from alcohol



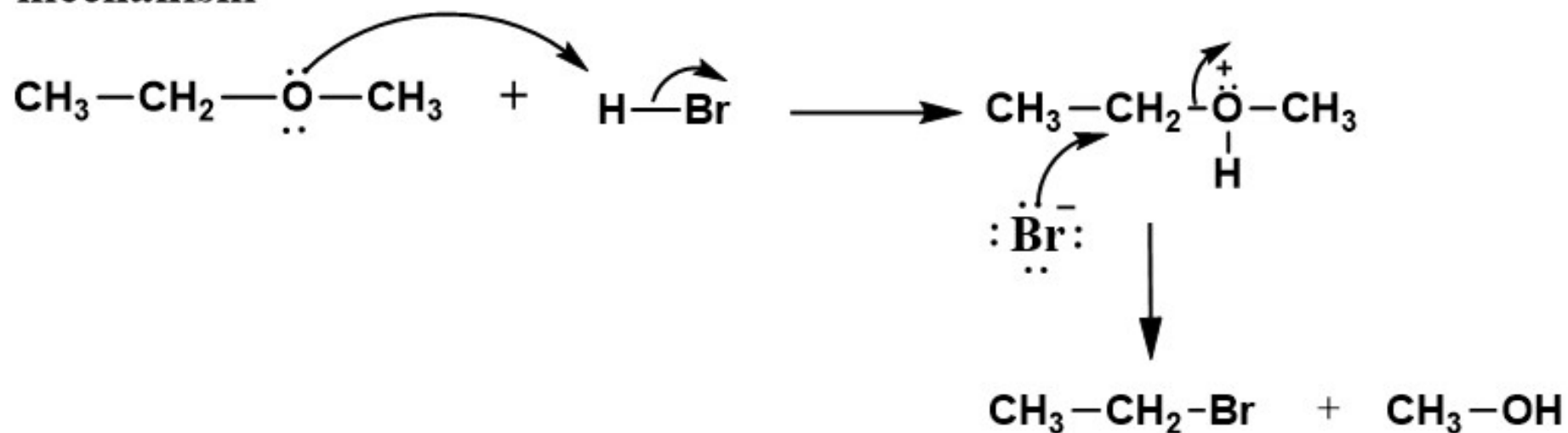
- Thionyl chloride (SOCl_2) and phosphorus halide (PX_3) are also used for this purpose



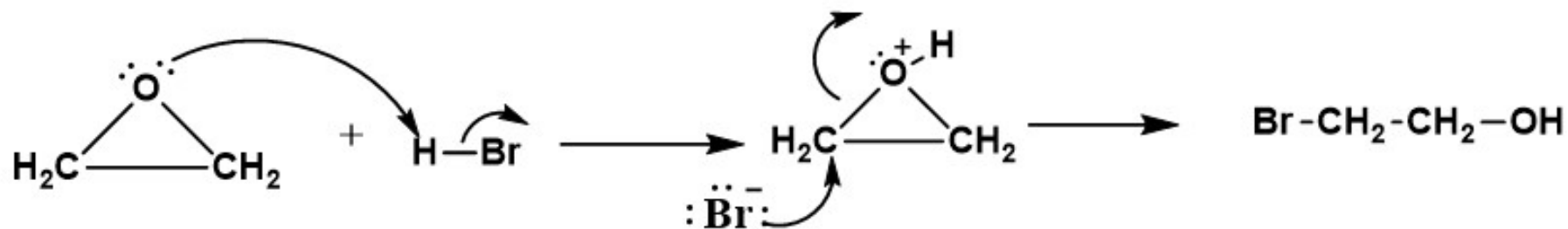
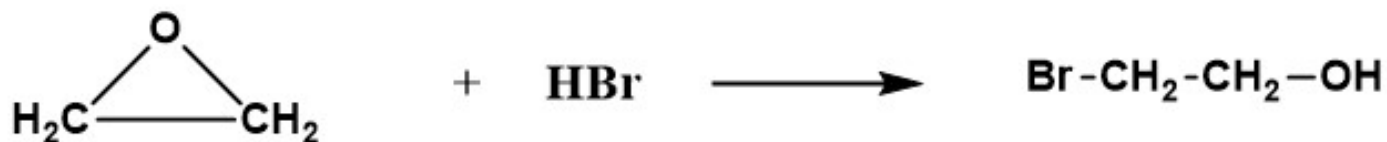
3. Ether



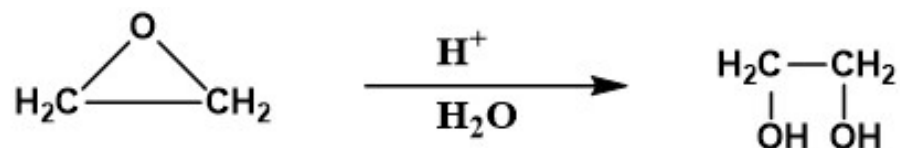
mechanism



4. Epoxides



Acid catalysed cleavage of epoxides



Mechanism

