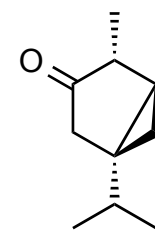
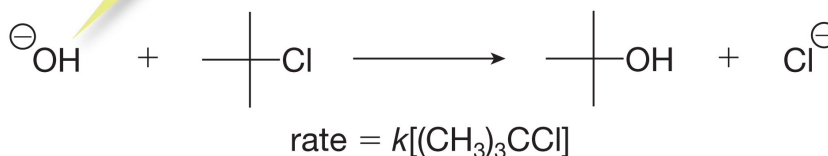


# S<sub>N</sub>1 Displacement Reactions



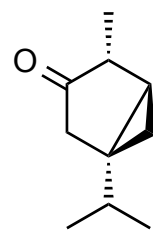
- Tertiary alkyl halides cannot undergo S<sub>N</sub>2 reactions because of the severe steric hindrance blocking a backside approach of the nucleophile.
- They can, however, react via an S<sub>N</sub>1 mechanism.
- For the reaction of HO<sup>⊖</sup> + (CH<sub>3</sub>)<sub>3</sub>CCl, the rate of the reaction is described by the following expression:

the nucleophile does not determine the rate of an S<sub>N</sub>1 displacement



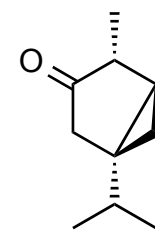
the rate of an S<sub>N</sub>1 reaction depends only on the concentration of the electrophile

# S<sub>N</sub>1 Displacement Reactions



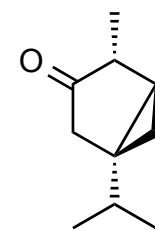
- Experiments show that the rate of this reaction is dependent only on the concentration of the electrophile ((CH<sub>3</sub>)<sub>3</sub>CCl).
- This type of reaction is designated S<sub>N</sub>1 (substitution, nucleophilic, unimolecular).
- Unimolecular refers to only 1 reactant involved in the rate determining step (RDS).
- This reaction must therefore proceed in 2 steps; one involving the electrophile, and one involving the nucleophile.

# S<sub>N</sub>1 Displacement Reactions

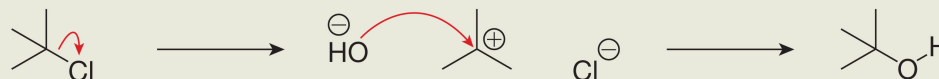


- Since only the electrophile is involved in the RDS, the leaving group must leave in the first, rate-determining step, and the nucleophile adds in the second step.
- Because the leaving group leaves first, this requires that an S<sub>N</sub>1 mechanism proceeds via a carbocation intermediate.
- The S<sub>N</sub>1 reaction is heavily dependent on the ability of the  $\alpha$ -carbon to stabilize a positive charge.
- If the carbocation is too difficult to form, the S<sub>N</sub>1 pathway becomes too slow. Either an S<sub>N</sub>2 reaction occurs or no reaction occurs.

# S<sub>N</sub>1 Displacement Reactions

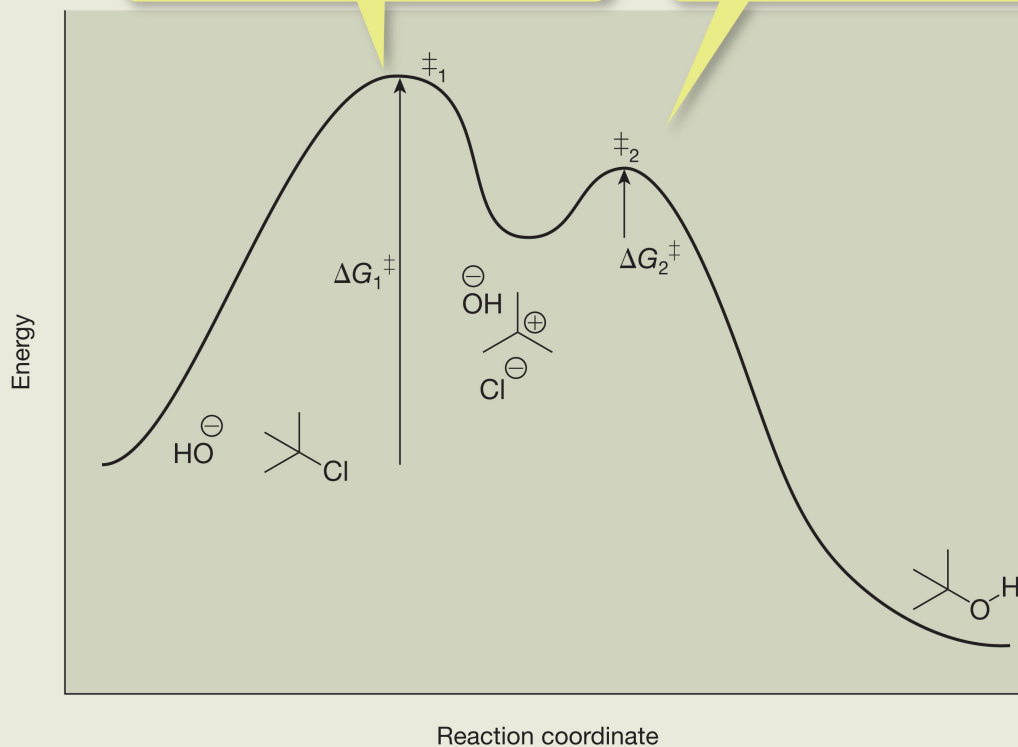


each step in the reaction has an activation barrier and a transition state



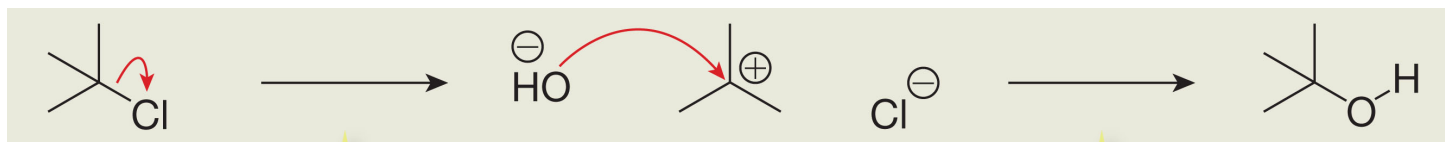
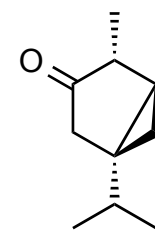
carbocation formation is rate-determining and has largest barrier ( $\Delta G_1^\ddagger$ )

addition of nucleophile to carbocation has smaller barrier ( $\Delta G_2^\ddagger$ )





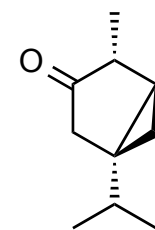
# Reaction Rates of S<sub>N</sub>1 Reactions



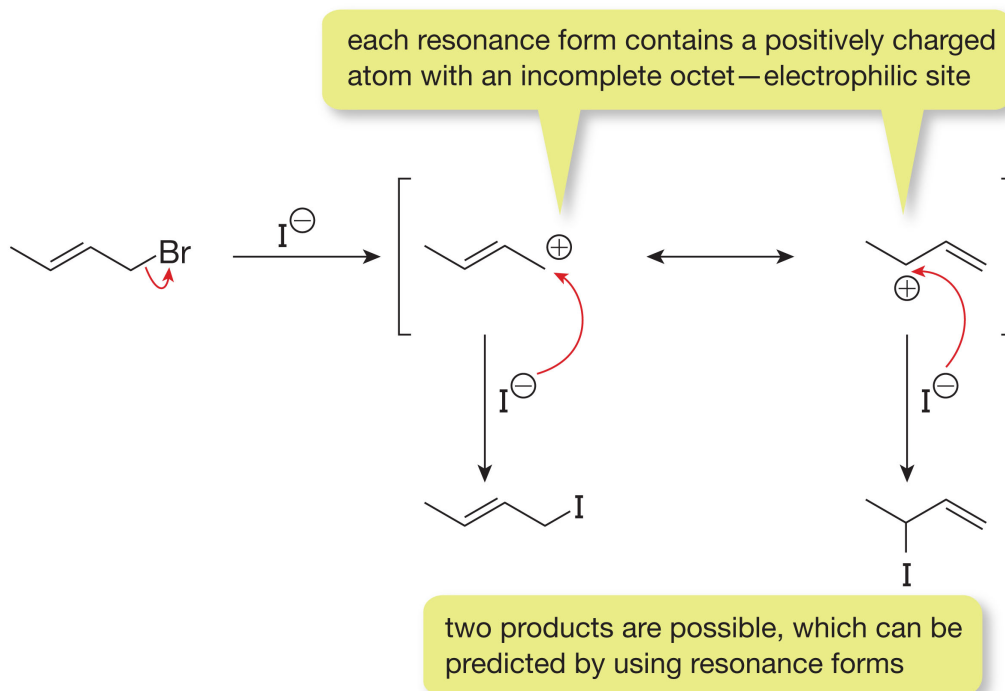
$$\text{rate} = k[(\text{CH}_3)_3\text{CCl}]$$

- What happens to the rate of production of (CH<sub>3</sub>)<sub>3</sub>COH if the concentration of OH<sup>-</sup> is held constant and the concentration of (CH<sub>3</sub>)<sub>3</sub>CCl is increased?
- What happens to the rate of production of CH<sub>3</sub>OH if the concentration of (CH<sub>3</sub>)<sub>3</sub>CCl is held constant and the concentration of OH<sup>-</sup> is increased?

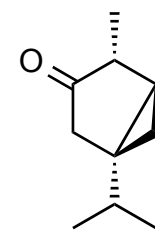
# Carbocation Stability



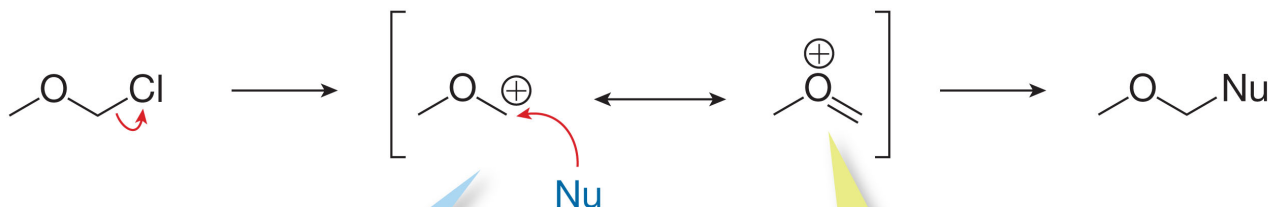
- Recall that carbocations are stabilized by charge delocalization (Chapter 8).
- Substrates that form resonance stabilized cations tend to undergo  $S_N1$  reactions and may form more than 1 product.



# Carbocation Stability



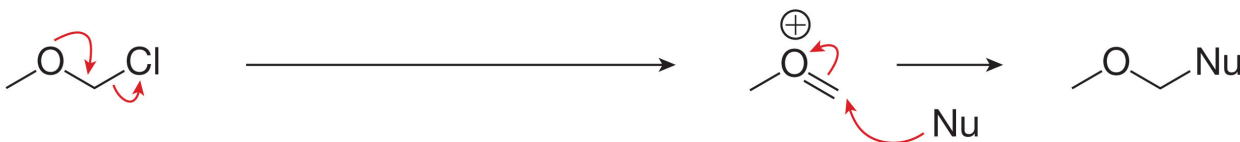
- A very common family of  $S_N1$  reactions involves the oxonium ion ( $=O^+-$ ).



This resonance form has an incomplete octet on carbon. Nucleophiles add to that position.

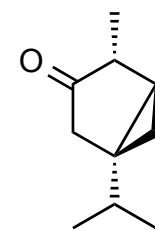
This resonance form (oxonium ion) has full octets.

The mechanism is usually written using the best resonance form as it most closely resembles how the molecules actually react.

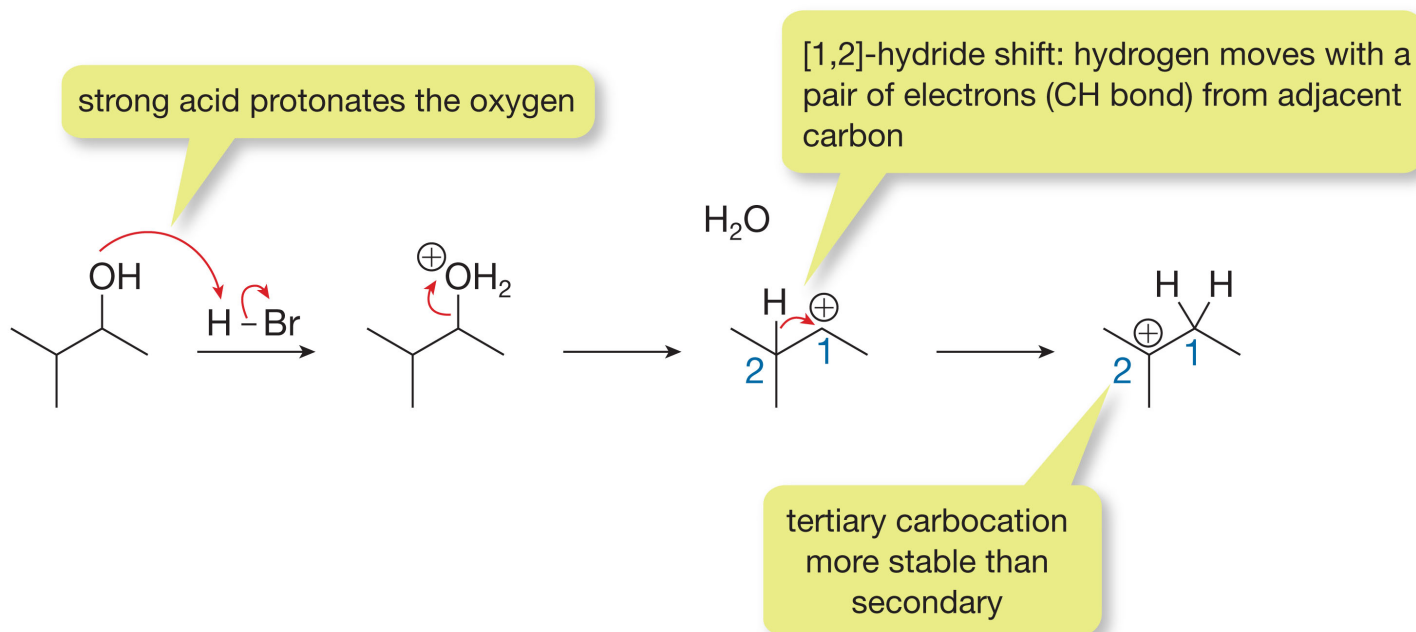


mechanism usually depicts only one resonance form

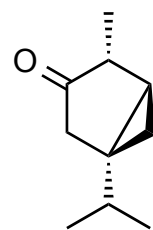
# Carbocation Rearrangements



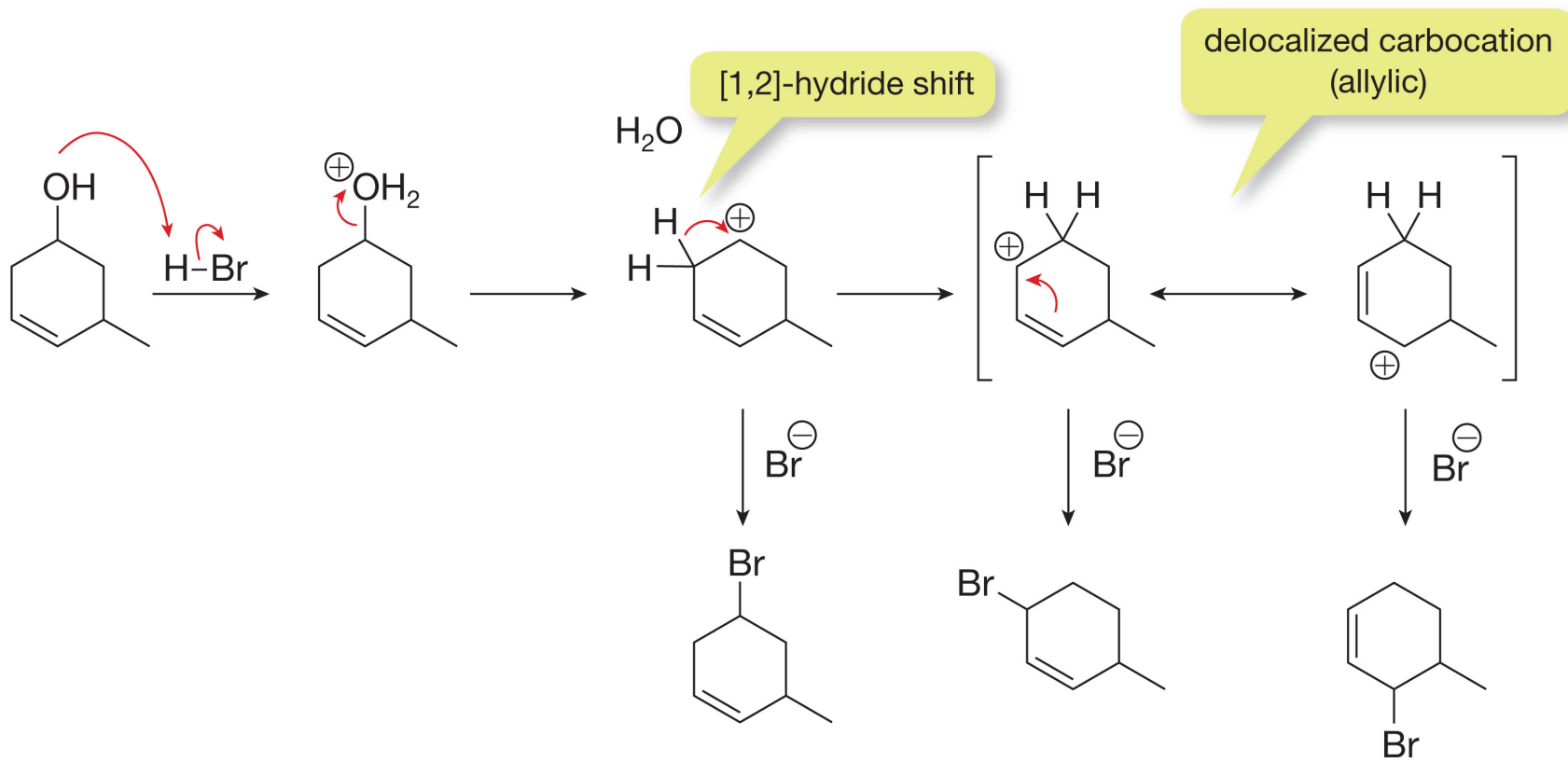
- Recall that carbocations are also prone to rearrangement reactions (Chapter 8).
- Because carbocations are high-energy intermediates, they rearrange to form a more stable cation:



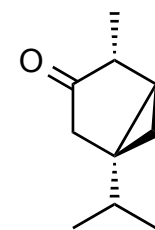
# Carbocation Rearrangements



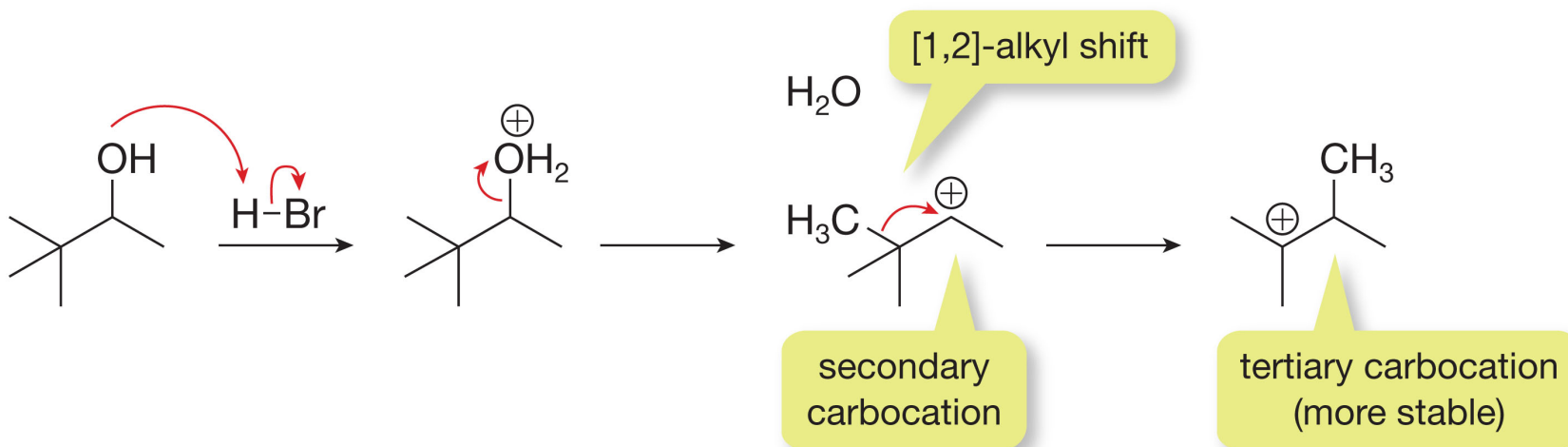
- Cations can also rearrange to give charge delocalized carbocations.



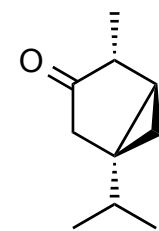
# Carbocation Rearrangements



- If there is no adjacent hydride, an alkyl or aryl group can also migrate.

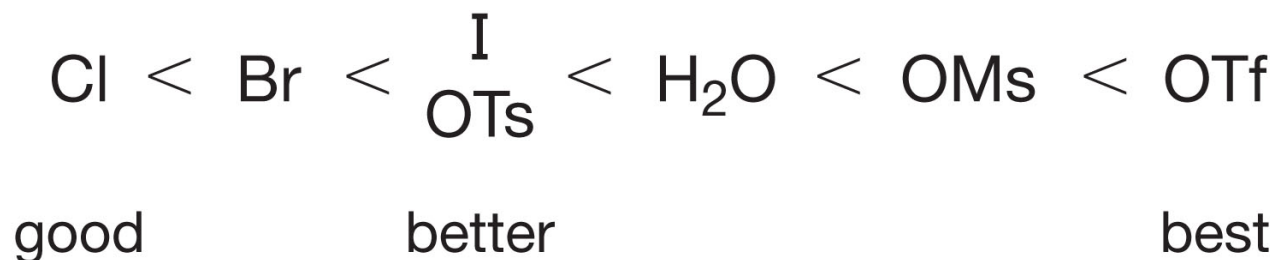


# Leaving Groups in S<sub>N</sub>1 Reactions

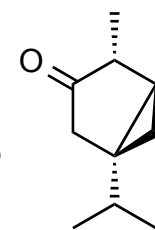


- Because the leaving group is involved in the RDS for **both** S<sub>N</sub>1 and S<sub>N</sub>2 reactions, its nature has a large influence on their reaction rates.
- Therefore, good leaving groups accelerate both S<sub>N</sub>1 and S<sub>N</sub>2 reactions.

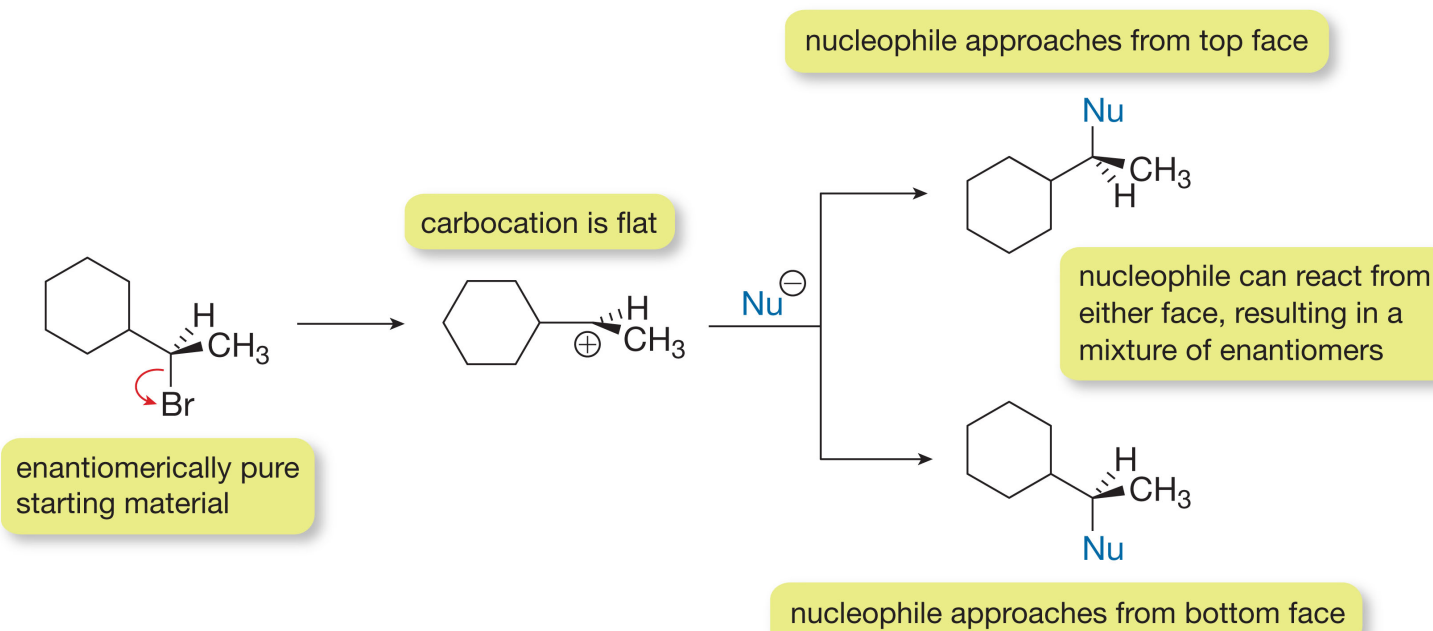
approximate order of leaving group ability



# Stereochemistry of $S_N1$ Reactions

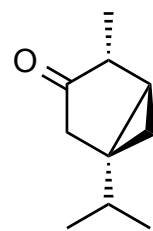


- Unlike  $S_N2$  reactions where the nucleophile does backside attack at the  $\alpha$ -carbon, in  $S_N1$  reactions the nucleophile is free to attack from either side.
- In  $S_N1$  reactions the nucleophile is attacking a **planar** carbocation, so it is free to attack from either side.

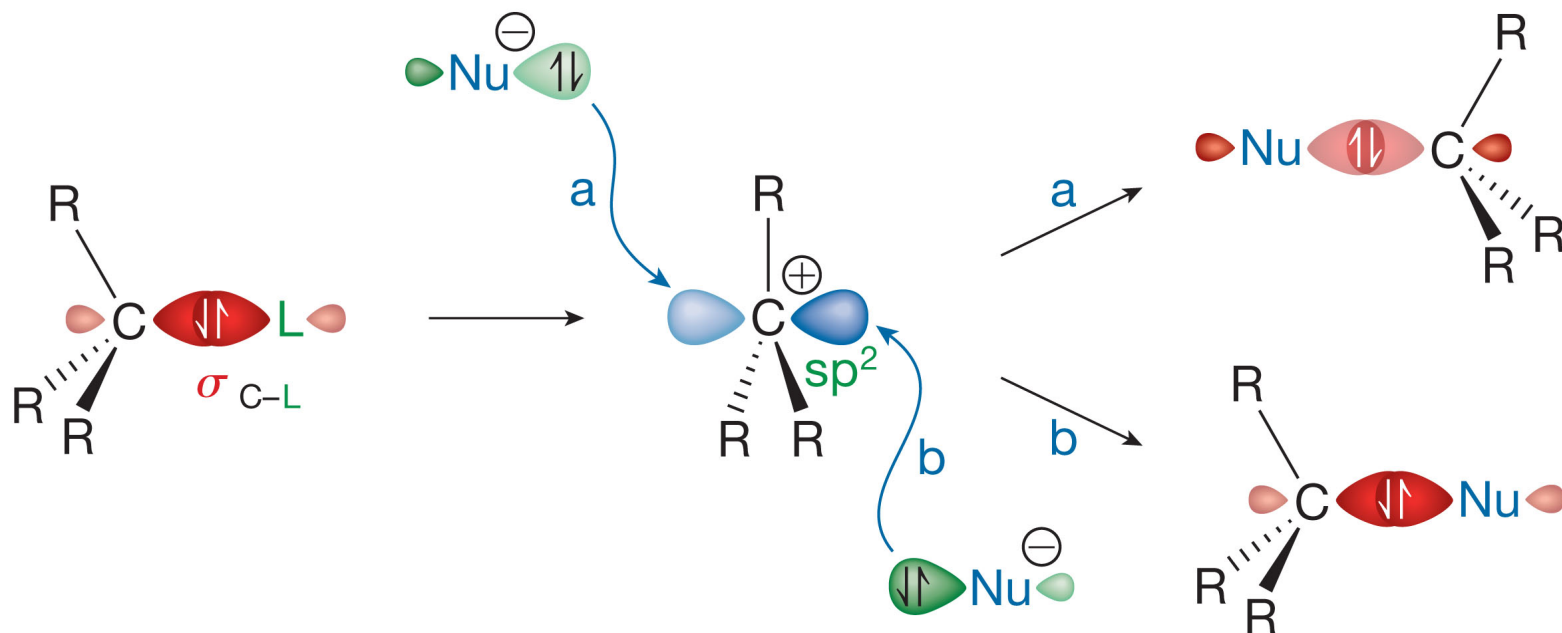




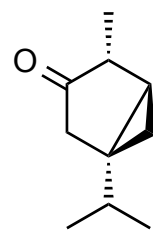
# Stereochemistry of $S_N1$ Reactions



- To form a new bond, the HOMO of the nucleophile must overlap with the LUMO of the carbocation electrophile.

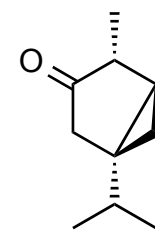


# $S_N1/S_N2$ Reactivity Continuum

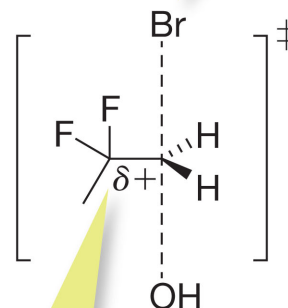
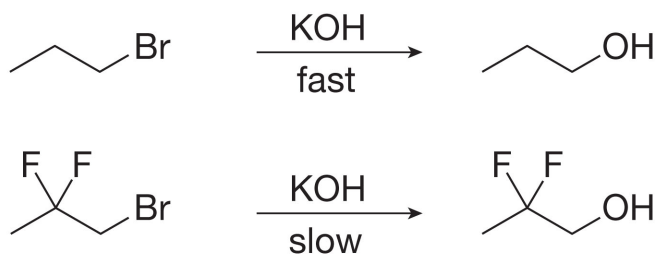


- It is important to remember that the  $S_N1$  and  $S_N2$  pathways represent extremes of a reactivity continuum, and that many substitution reactions display characteristics of both.
- Consequently, a particular substitution reaction may be more  $S_N1$ -like or more  $S_N2$ -like, without being purely one or the other.
- Consider the following examples:

# S<sub>N</sub>1/S<sub>N</sub>2 Reactivity Continuum



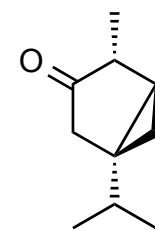
- S<sub>N</sub>2 reactions are sensitive to inductive effects, suggesting that the  $\alpha$ -carbon carries a partial (+) charge in the transition state.



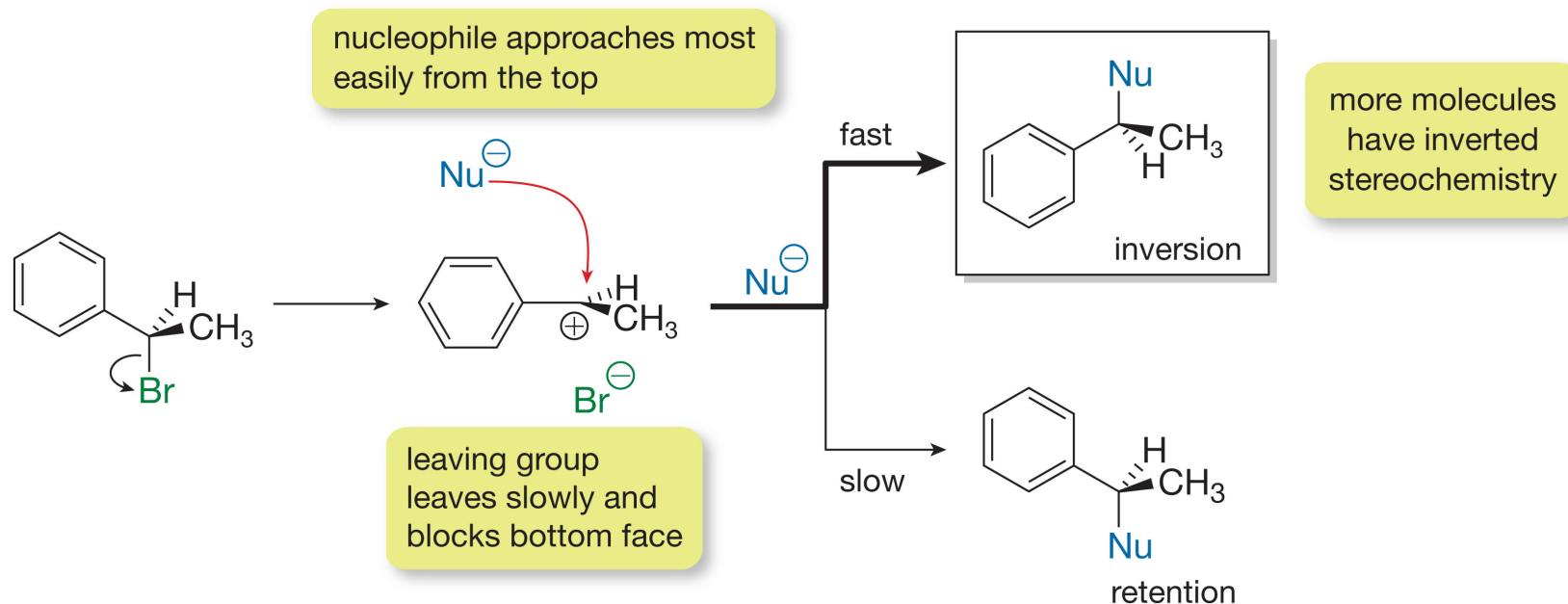
carbon leaving group bond breaks quickly, generating a small positive charge on the  $\alpha$ -carbon

fluorine atoms induce a larger  $\delta+$  on the  $\alpha$ -carbon which raises the energy of the transition state and slows the reaction

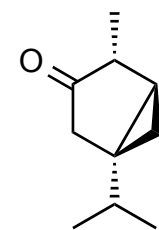
# $S_N1/S_N2$ Reactivity Continuum



- $S_N1$  reactions rarely produce completely racemic products from enantiomerically pure starting materials.

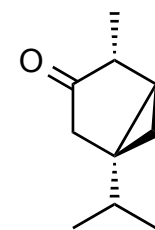


# Solvent Effects in $S_N1/S_N2$ Reactions



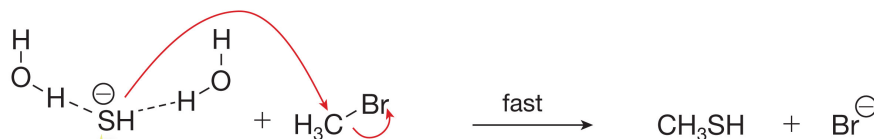
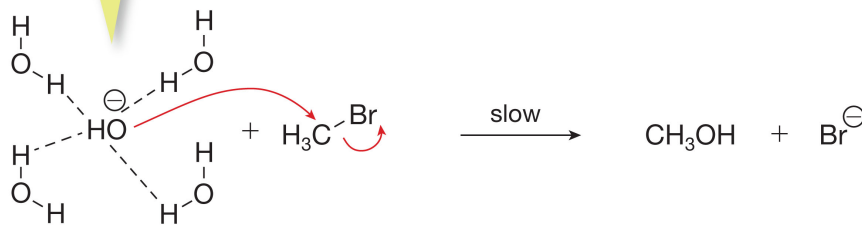
- Solvents can have a large influence on the reaction rates of substitution reactions.
- In general, polar **protic** solvents typically favour  $S_N1$  reactions and polar **aprotic** solvents enhance  $S_N2$  reactions.
- Polar protic solvents are those that are capable of acting as hydrogen bond donors (Chapter 2), of which  $H_2O$ , alcohols, and amines are good examples.
- Protic solvents can solvate anions very well through hydrogen bonding.

# Solvent Effects in $S_N1/S_N2$ Reactions



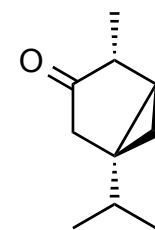
- Small anions have a high charge density and form strong hydrogen bonds with protic solvents. As a consequence, these ions are less nucleophilic.
- Large anions have a low charge density and do not hydrogen bond as well with protic solvents, making them more nucleophilic.

Small ions are well solvated and hydrogen bonded, and thus are less able to donate electrons.



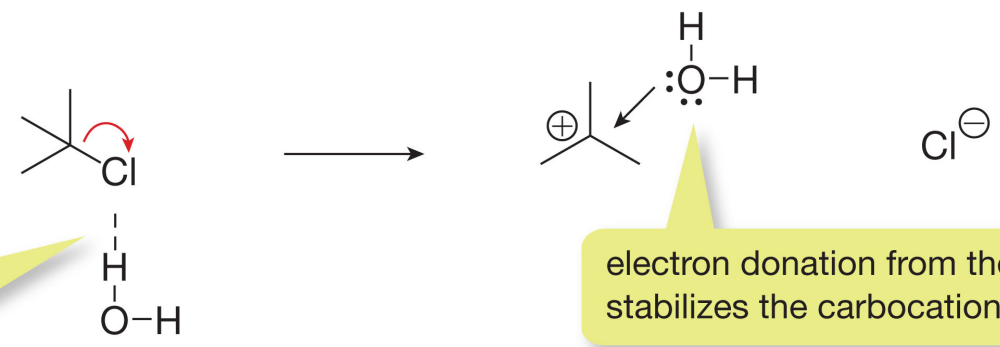
Large ions are poorly solvated and less hydrogen bonded, and thus are more able to donate electrons.

# Solvent Effects in $S_N1/S_N2$ Reactions



- Protic solvents help accelerate  $S_N1$  reactions in two ways:

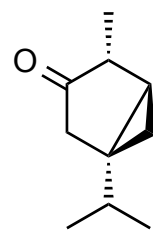
1. Donation of electrons from the solvent stabilizes the carbocation intermediate.
2. Hydrogen bonding from the solvent assists in the removal of the leaving group.



hydrogen bonding with the solvent helps the leaving group to leave

electron donation from the solvent stabilizes the carbocation

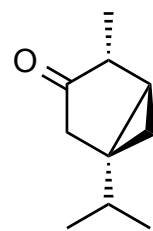
# Solvent Effects in $S_N1/S_N2$ Reactions



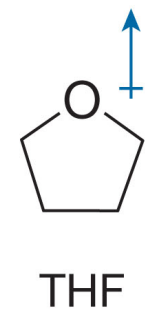
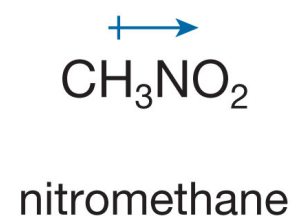
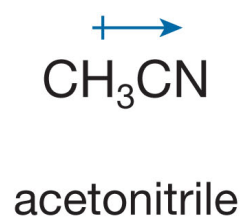
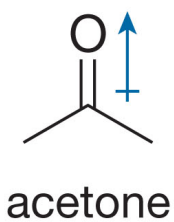
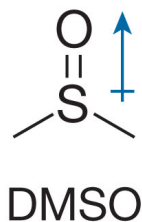
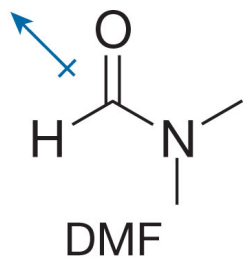
- Polar aprotic solvents do not have a hydrogen bonding group and therefore do not solvate anions well.
- Poorly solvated, negatively charged nucleophiles become much better electron donors, and so  $S_N2$  reactions are accelerated in aprotic solvents.
- Because polar aprotic solvents have Lewis base character, they are good at solvating metal cations.
- This tends to create 'naked' anions that are not impeded by their counter ions.



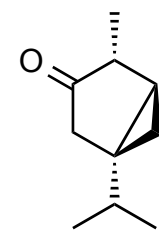
# Solvent Effects in $S_N1/S_N2$ Reactions



- Aprotic solvents are less effective at solvating carbocations, therefore these solvents slow the rate of  $S_N1$  reactions relative to the rate of the same reaction in protic solvents.
- The following are the most commonly used polar aprotic solvents:

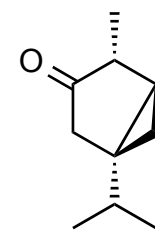


# Predicting $S_N1/S_N2$ Mechanisms



- To be able to predict which substitution mechanism is operating, there are 3 characteristics that need to be examined:
  1. Structure of the electrophile
  2. Strength of the nucleophile
  3. The solvent used
- Although good leaving groups are important to both pathways, they are not considered because they cannot help differentiate between the two mechanisms.

# Predicting S<sub>N</sub>1/S<sub>N</sub>2 Mechanisms



## 1. Structure of the Electrophile

- Structures that can sufficiently stabilize a carbocation – S<sub>N</sub>1.
- Electrophiles free from steric hindrance at the  $\alpha$ -carbon – S<sub>N</sub>2.

increasing  
rate of S<sub>N</sub>1

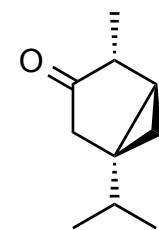
Compound	$\alpha$ -Carbon structure	Symbol	
CH <sub>3</sub> Br	methyl	Me	} <b>S<sub>N</sub>2 only</b>
CH <sub>3</sub> CH <sub>2</sub> Br	primary	1°	
(CH <sub>3</sub> ) <sub>2</sub> CHBr	secondary	2°	both S <sub>N</sub> 1 and S <sub>N</sub> 2 possible
(CH <sub>3</sub> ) <sub>3</sub> CBr	tertiary	3°	<b>S<sub>N</sub>1 only</b>

slow  
↓  
fast

fast  
↑  
slow

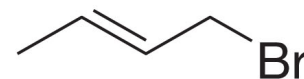
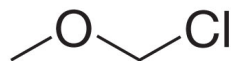
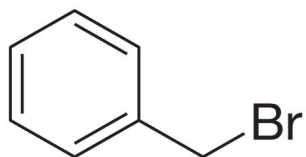
increasing  
rate of S<sub>N</sub>2

# Predicting $S_N1/S_N2$ Mechanisms



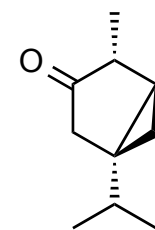
## 2. Strength of the Nucleophile

- For  $2^\circ$  substrates or those that can form charge delocalized carbocations, the nature of the nucleophile must be examined.

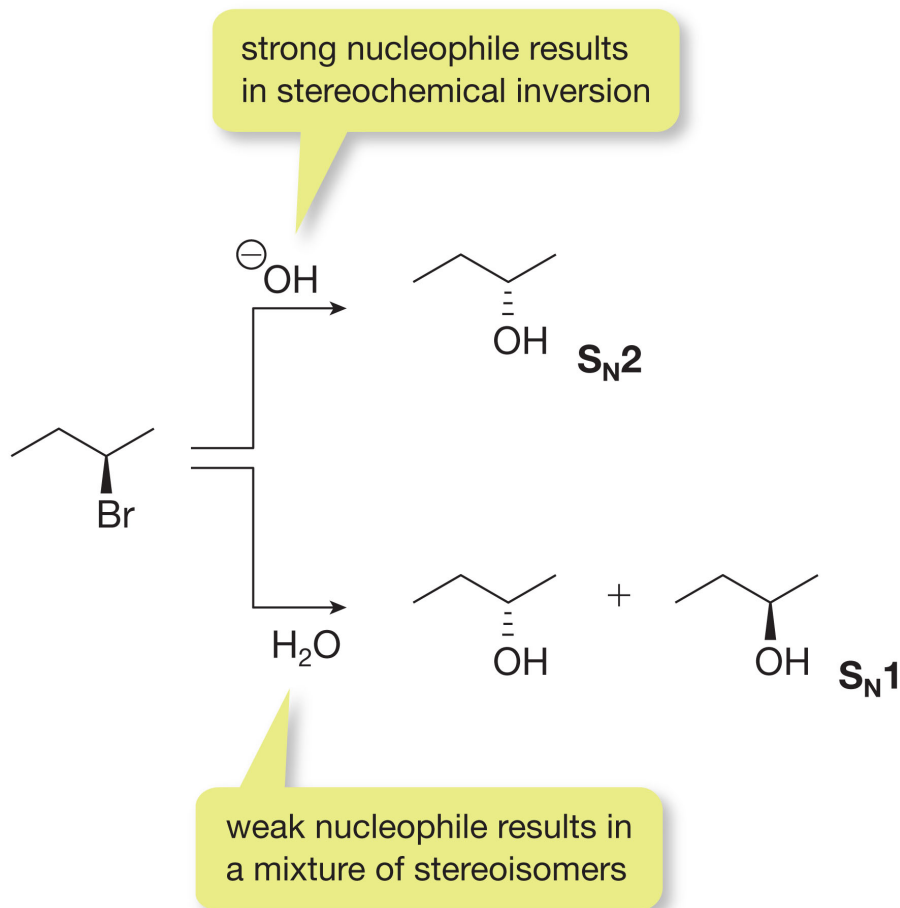


- Because nucleophiles are involved in the RDS of  $S_N2$  reactions, good nucleophiles favour  $S_N2$  reactions.
- Poor nucleophiles slow the  $S_N2$  reaction, which favours the  $S_N1$  reaction.

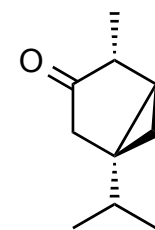
# Predicting $S_N1/S_N2$ Mechanisms



## 2. Strength of the Nucleophile



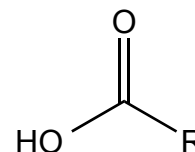
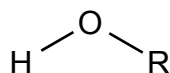
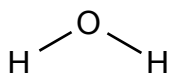
# Predicting $S_N1/S_N2$ Mechanisms



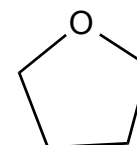
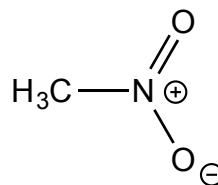
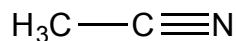
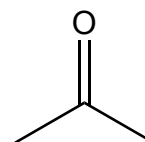
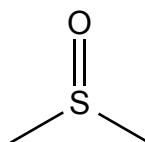
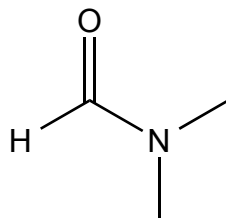
## 3. Solvent Used

- In general

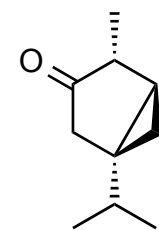
- Polar protic solvents –  $S_N1$  reactions



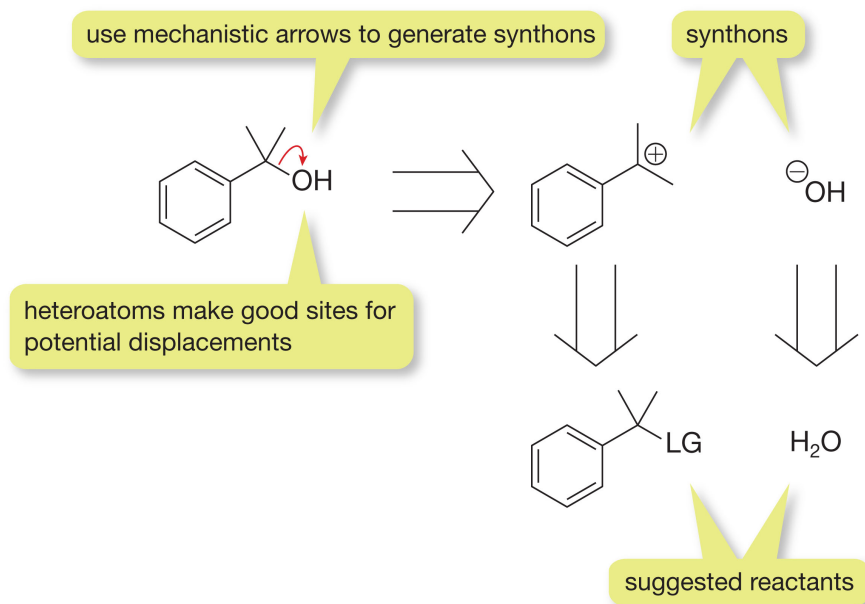
- Polar aprotic solvents –  $S_N2$  reactions



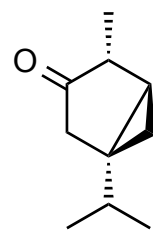
# Planning Substitution Reactions



- A systematic disconnection of bonds in a target molecule can aid in planning a synthesis.
- A synthesis can be planned by dissecting a target molecule into synthons.
- Synthons can give insight into the type of reactivity required for the individual components.

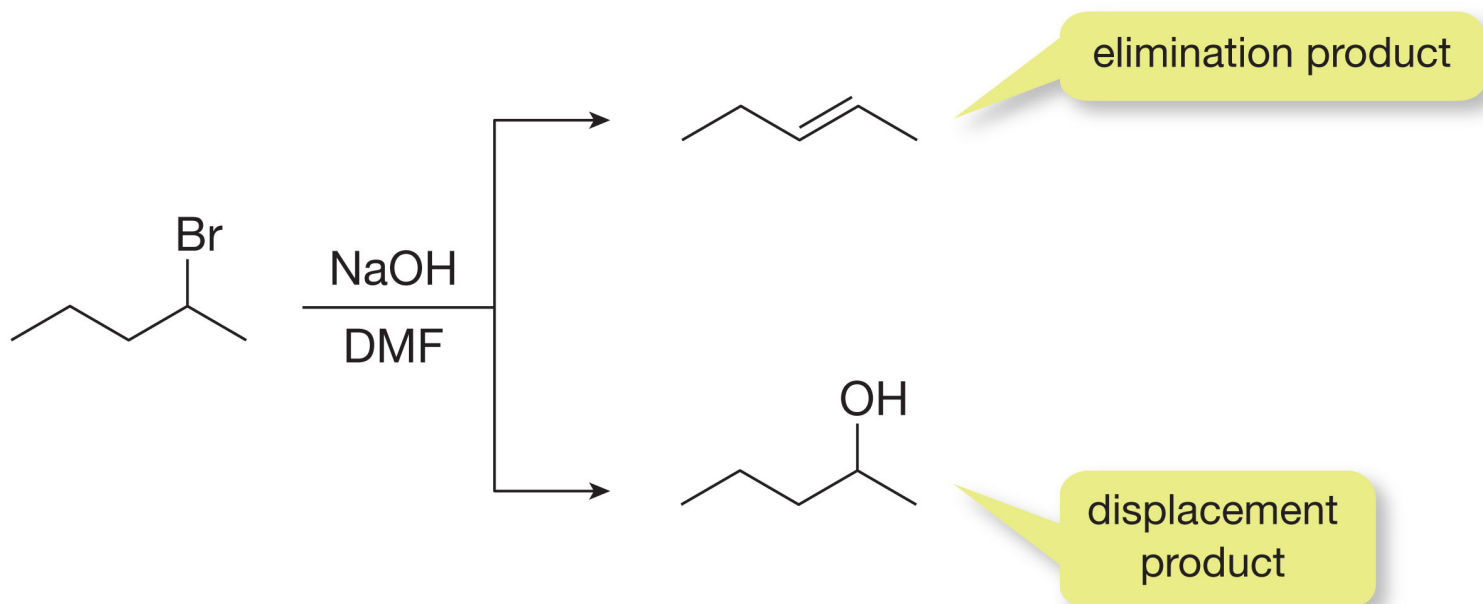


# Special Nu and E in Substitution Reactions.



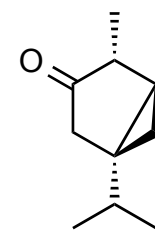
## Secondary Alcohols

- While  $\text{OH}^-$  is a good nucleophile in the preparation of alcohols, it is also a strong base which can lead to competing reactions (Chapter 12).

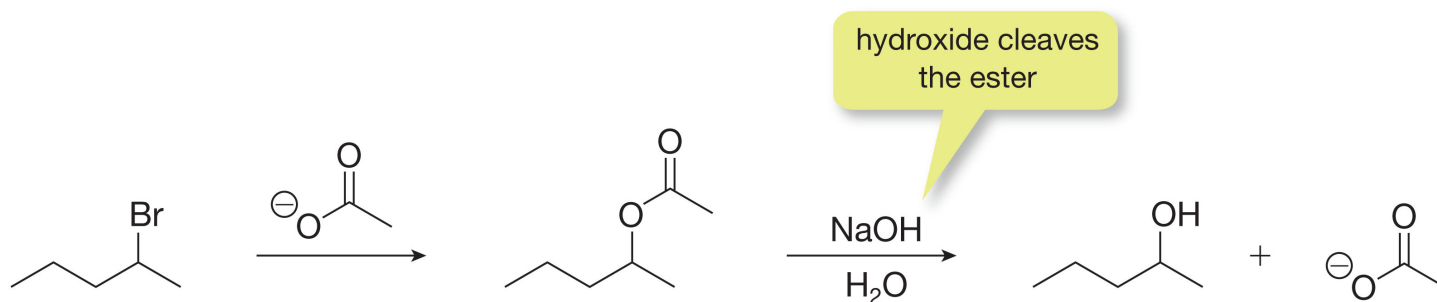




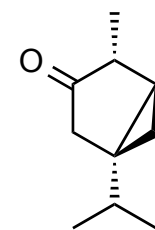
# Special Nu and E in Substitution Reactions.



- An alternative is to use a less basic nucleophile such as acetate to make a secondary alcohol in a 2-step sequence.

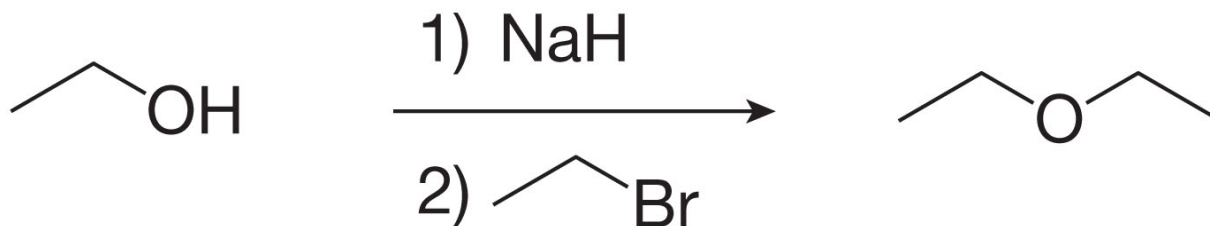


# Special Nu and E in Substitution Reactions.

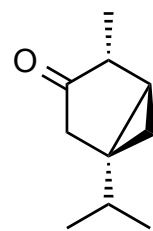


## Ethers

- The Williamson ether synthesis is an  $S_N2$  reaction between an alkoxide and an alkyl halide to form an ether.



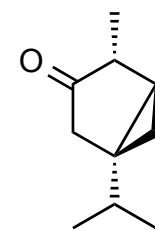
# Special Nu and E in Substitution Reactions.



## Epoxides

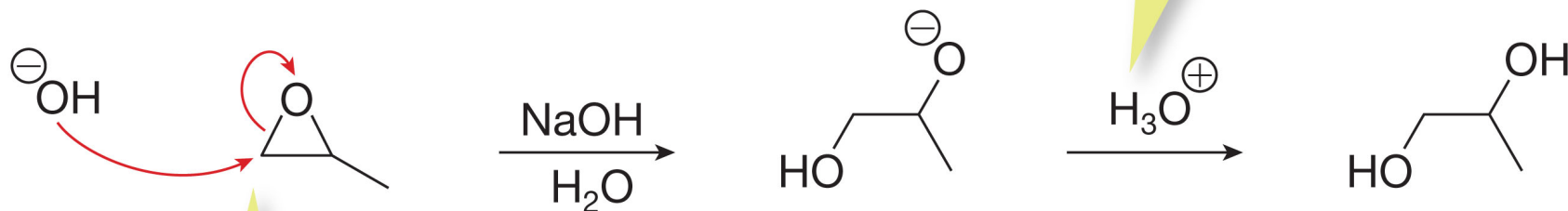
- Ethers are normally an unreactive functional group which is why they are often used as solvents.
- Epoxides are an important exception. They are reactive towards nucleophiles because of the large amount of ring strain (Chapter 8).
- The opening of an epoxide is regioselective. Where the nucleophile attacks is dependent on the reaction conditions.

# Special Nu and E in Substitution Reactions.



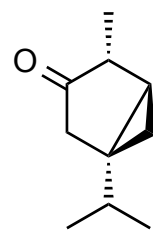
## Epoxides

- Under basic conditions, the nucleophile attacks the least hindered side ( $S_N2$ ).



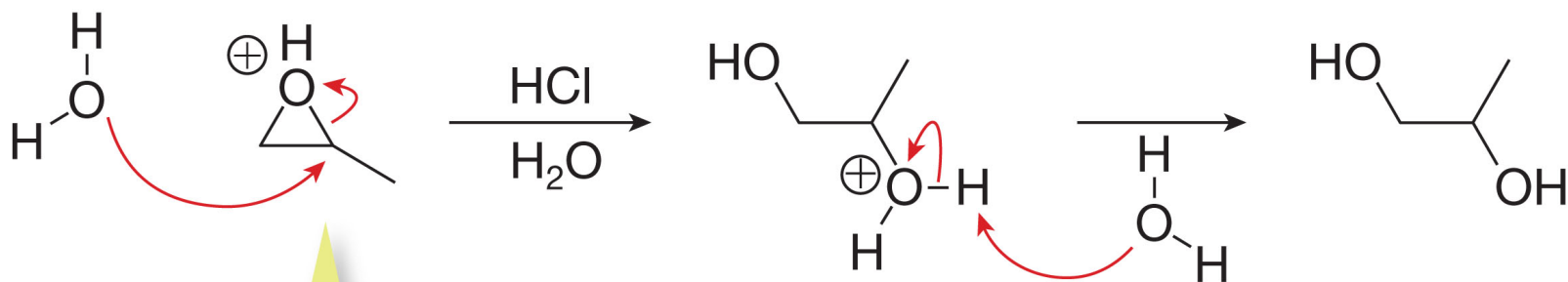
under basic conditions, the nucleophile attacks the less-hindered position

# Special Nu and E in Substitution Reactions.



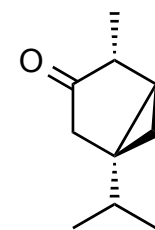
## Epoxides

- Under acidic conditions, the nucleophile attacks the more hindered side ( $S_N1$  like).



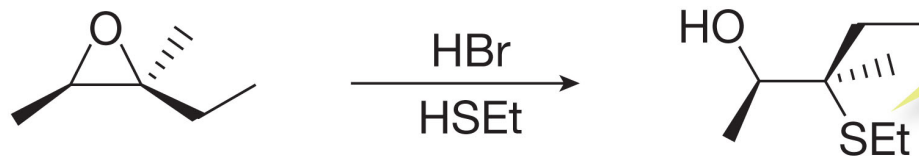
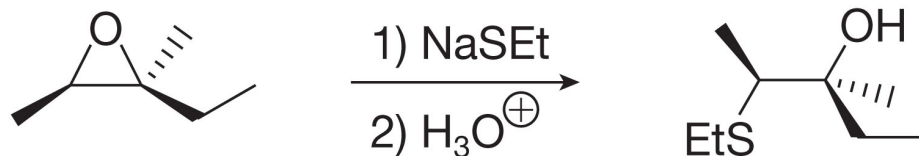
under acidic conditions, the nucleophile attacks the position that can best stabilize a carbocation

# Special Nu and E in Substitution Reactions.



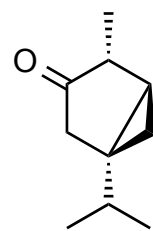
## Epoxides

- Reactions of nucleophiles with epoxides occur with inversion, regardless if it is under acidic or basic conditions.



under either acidic or basic conditions, inversion of configuration is observed

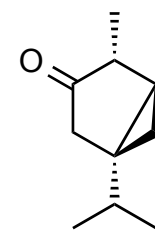
# Special Nu and E in Substitution Reactions.



## Carbon Nucleophiles

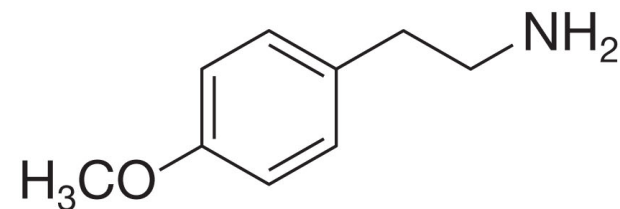
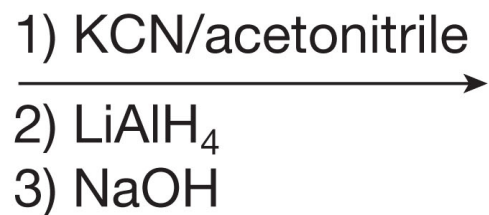
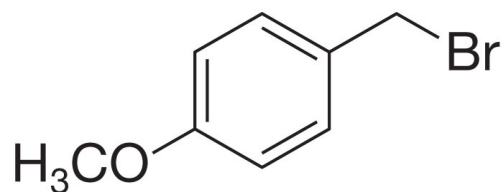
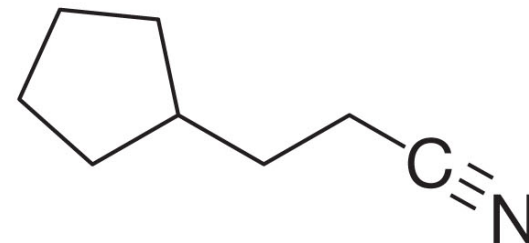
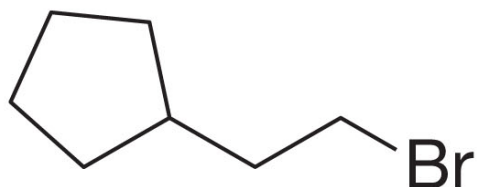
- Carbon nucleophiles are important as they allow us to form new carbon-carbon bonds.
- Some carbon nucleophiles are much too basic and cannot undergo controlled substitution reaction.
- The best carbon nucleophiles to use are those that stabilize the negatively charged nucleophilic carbon atom by resonance or induction.
- Typical carbon nucleophiles used in substitution reactions are acetylides and cyanides (Chapter 7), as well as enolates (Chapter 17).

# Special Nu and E in Substitution Reactions.



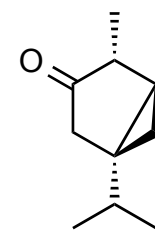
## Carbon Nucleophiles

- Nitriles:



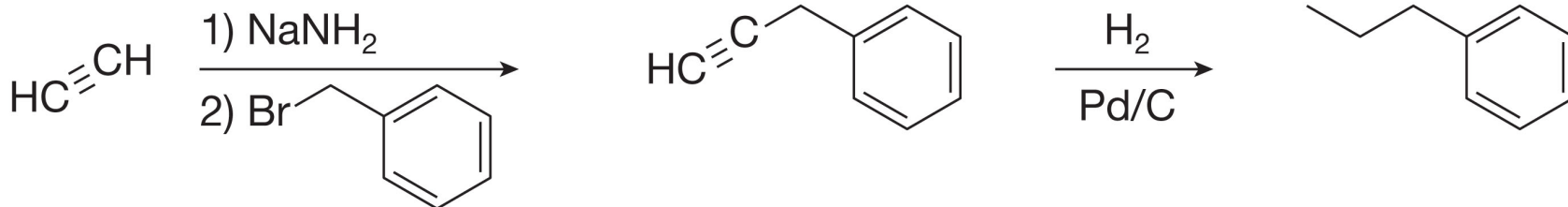
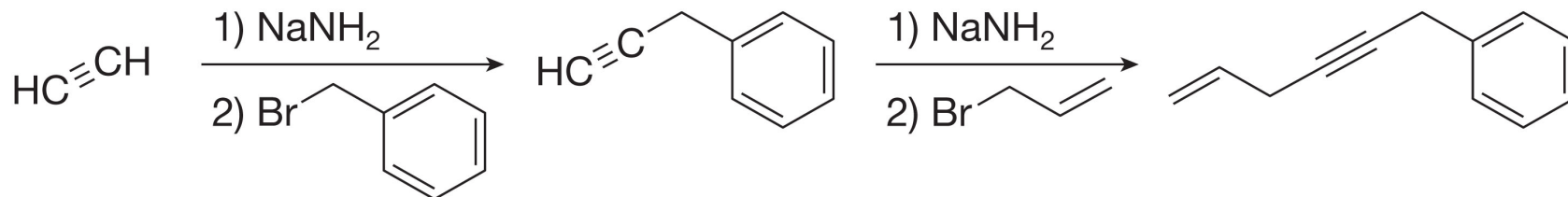


# Special Nu and E in Substitution Reactions.

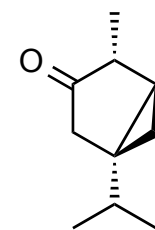


## Carbon Nucleophiles

- Acetylides:

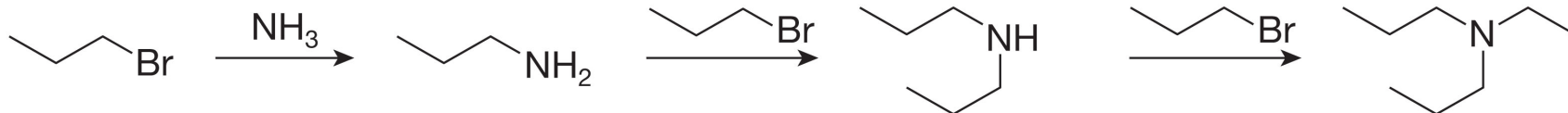
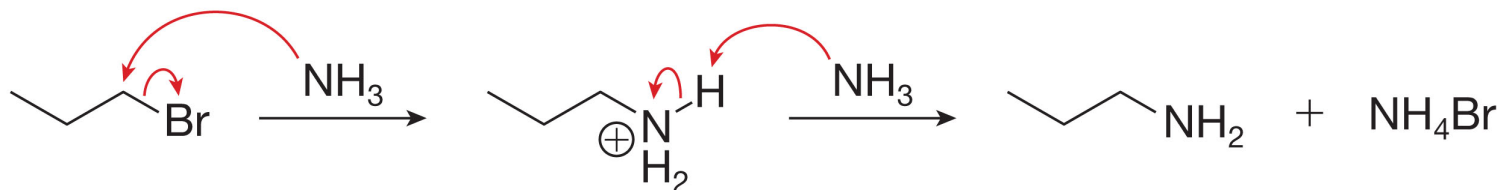


# Special Nu and E in Substitution Reactions.

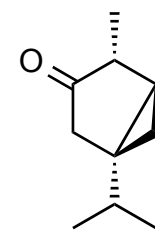


## Primary Amines

- Amines are also good nucleophiles, however, the reaction is difficult to control as over alkylation tends to occur.

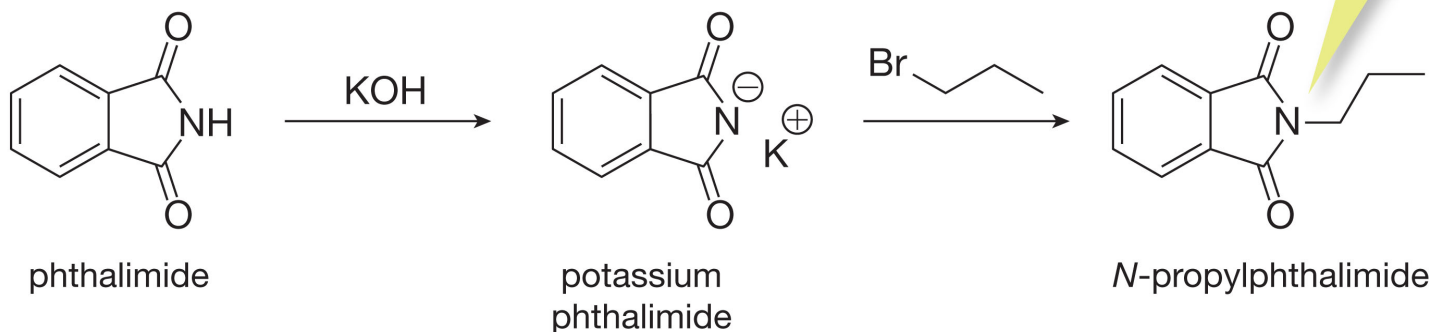


# Special Nu and E in Substitution Reactions.

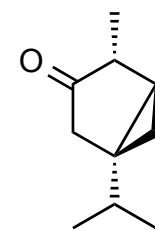


## Primary Amines

- To form primary amines without the risks of over alkylation, masked amines, such as phthalimide and azide, are used.
- Phthalimides:

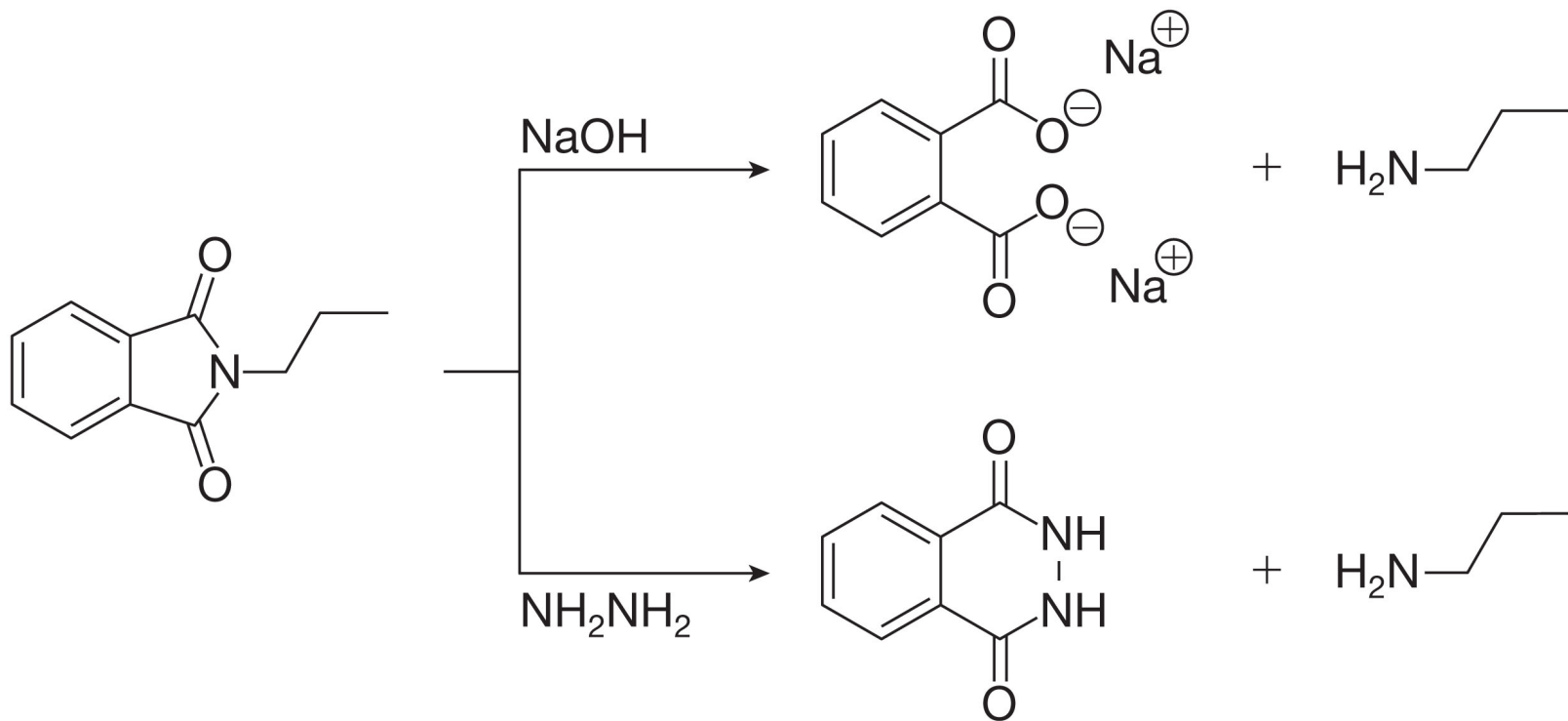


# Special Nu and E in Substitution Reactions.

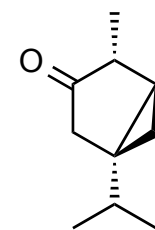


## Primary Amines

- Phthalimides:

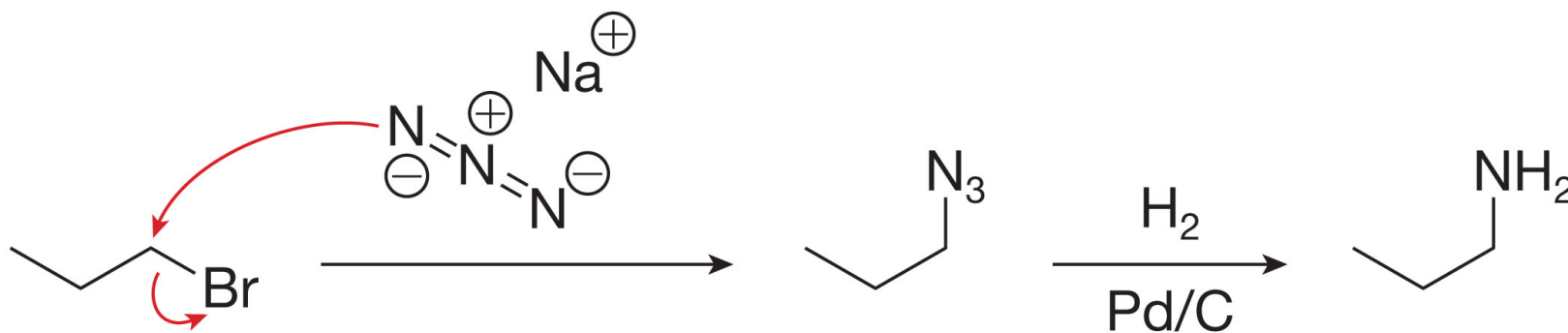


# Special Nu and E in Substitution Reactions.

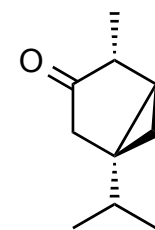


## Primary Amines

- Azides:



# Patterns in Nucleophilic Substitution Reactions.

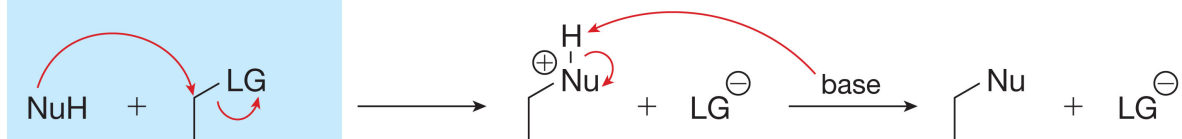


$S_N2$  reaction

Charged nucleophile



Neutral nucleophile



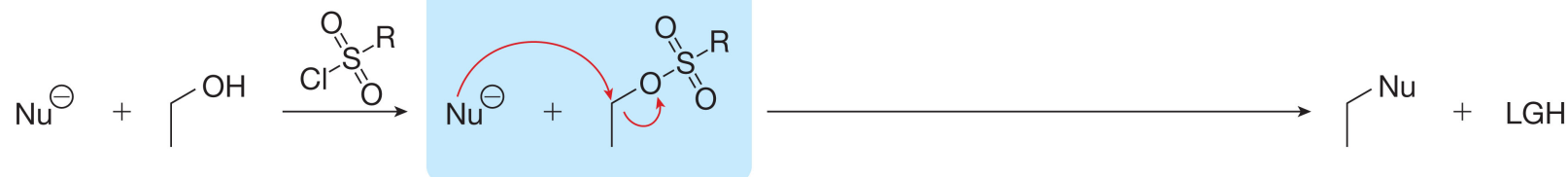
Acid catalysis charged nucleophile



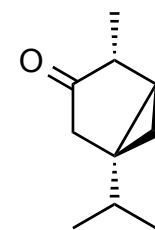
Acid catalysis neutral nucleophile



Sulfonate esters



# Patterns in Nucleophilic Substitution Reactions.



$S_N1$  reaction

$S_N2$



$S_N1$

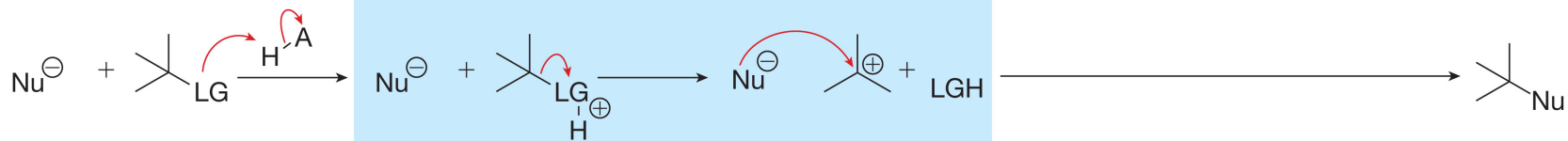
Charged nucleophile



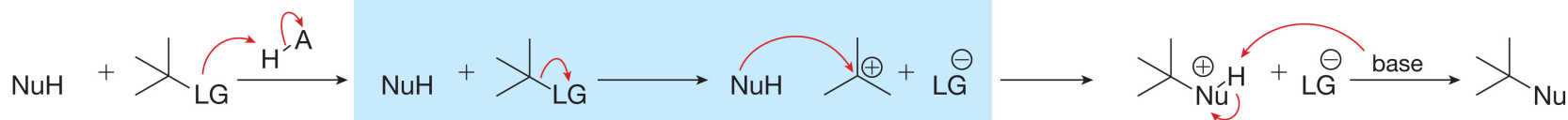
Neutral nucleophile



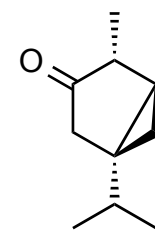
Acid catalysis charged nucleophile



Acid catalysis neutral nucleophile



# Patterns in Nucleophilic Substitution Reactions.



- General features of  $S_N1$  and  $S_N2$  reactions.

	$S_N2$	$S_N1$
Mechanism	One-step reaction (not including acid–base)	Two-step reaction (not including acid–base)
Rates	Rate depends on the concentration of both the nucleophile and electrophile $\text{rate} = k[\text{Nu}][\text{E}^{\oplus}]$	Rate depends only on the concentration of the electrophile $\text{rate} = k[\text{E}^{\oplus}]$
Electrophile structure and rate	Methyl > Primary > Secondary	Tertiary > Secondary
Nucleophile	Promoted by good nucleophiles	Promoted by weak nucleophiles
Stereochemistry	Inversion of configuration	Mixtures of stereoisomers
Leaving group	Good leaving groups give fast reactions	Good leaving groups give fast reactions
Solvent	Favoured in polar aprotic solvents	Favoured in protic solvents