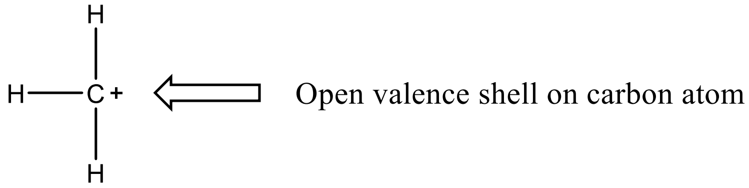
Organic reactive intermediate

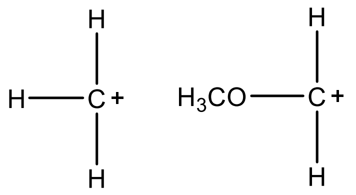
In chemistry, a **reactive intermediate** or an **intermediate** is a short-lived, high-energy, highly reactive molecule. When generated in a chemical reaction, it will quickly convert into a more stable molecule. Only in exceptional cases can these compounds be isolated and stored, e.g. low temperatures, matrix isolation. When their existence is indicated, reactive intermediates can help explain how a chemical reaction takes place. Reactive intermediates based on carbon are free radicals, carbenes, carbocations, carbanions, nitrenes, and benzynes.

A carbocation is molecule having a carbon atom bearing three bonds and a positive formal charge. Carbocations are generally unstable because they do not have eight electrons to satisfy the octet rule.

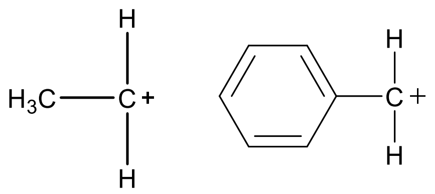


Carbocation Classification

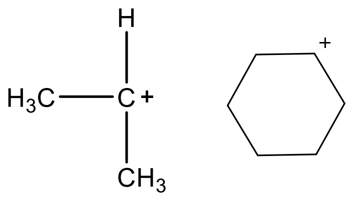
In order to understand carbocations, we need to learn some basic carbocation nomenclature concerning the number of carbon groups bonded to the open valence shell carbon. A carbocation in which the open valence shell carbon is not bonded to any carbon groups is termed a methyl carbocation. A primary carbocation (1^o carbocation) is one in which there is one carbon group attached to the carbon bearing the positive charge. (These groups are shown in red below.) A secondary (2^o) carbocation is one in which there are two carbons attached to the carbon bearing the positive charge. Likewise, a tertiary (3^o) carbocation is one in which there are three carbons attached to the carbon bearing the positive charge.



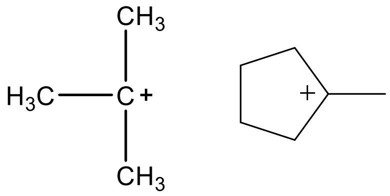
Methyl carbocations
No C–C$^+$ bonds



Primary (1^o) carbocations
One C–C$^+$ bond



Secondary (2^o) carbocations
Two C–C$^+$ bonds



Tertiary (3^o) carbocations
Three C–C$^+$ bonds

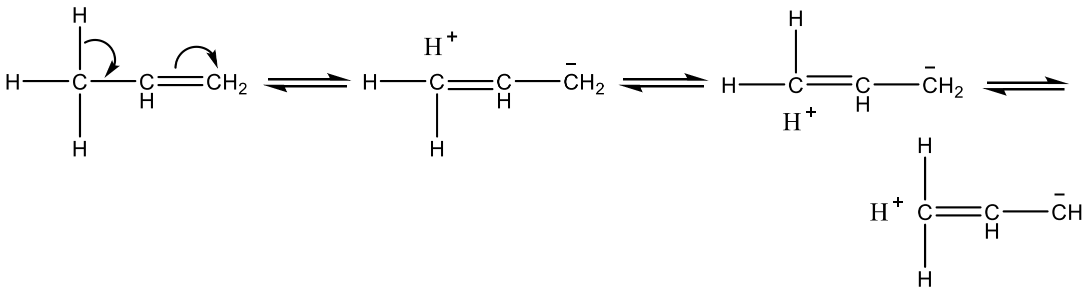
Carbocation Stability

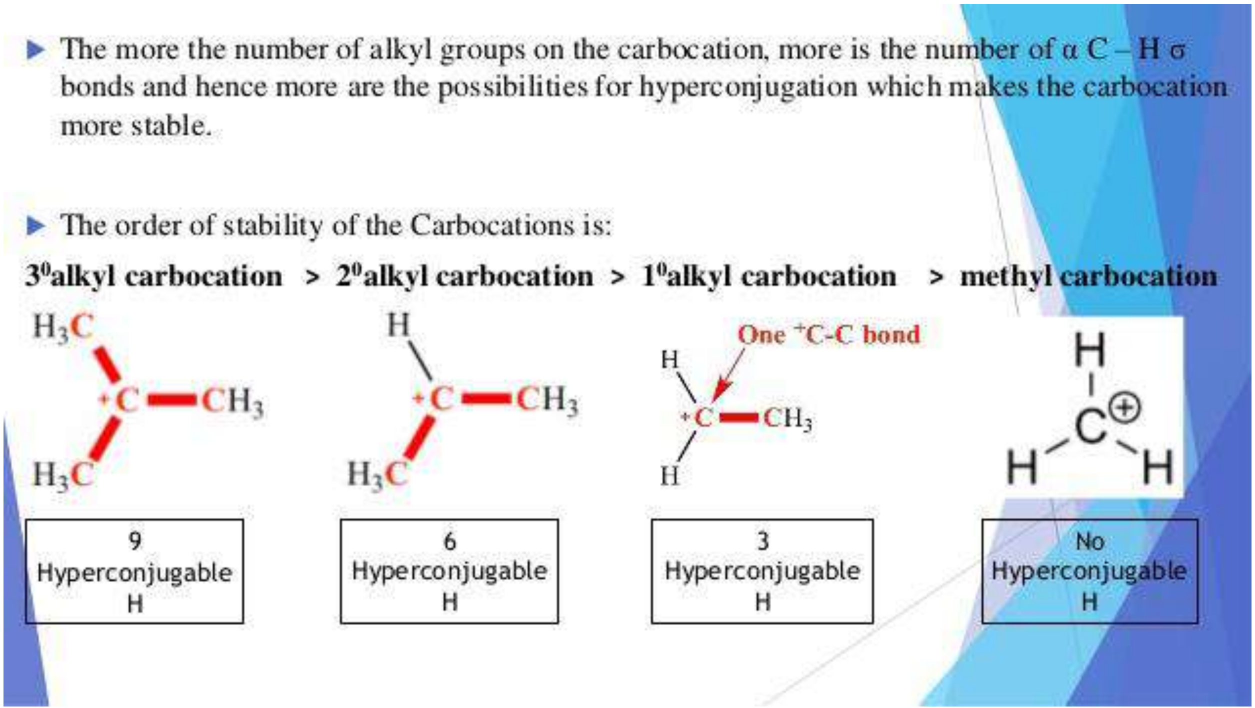
The stability order of carbocations bearing only alkyl groups is

$3^o > 2^o > 1^o > CH_3$

Cation stability is influenced by FOUR factors:

a) Hyperconjugation Increasing the number of alkyl substituents increases the stability of the carbocation. This is due to orbital overlap between the σ bond and the empty p orbital on the sp2 carbon.
When an alkyl group is attached to an unsaturated system such as double bond or a benzene ring, the order of inductive effect is actually reversed. This effect is called **hyperconjugation effect.**





- The more the number of alkyl groups on the carbocation, more is the number of α C – H σ bonds and hence more are the possibilities for hyperconjugation which makes the carbocation more stable.

- The order of stability of the Carbocations is:

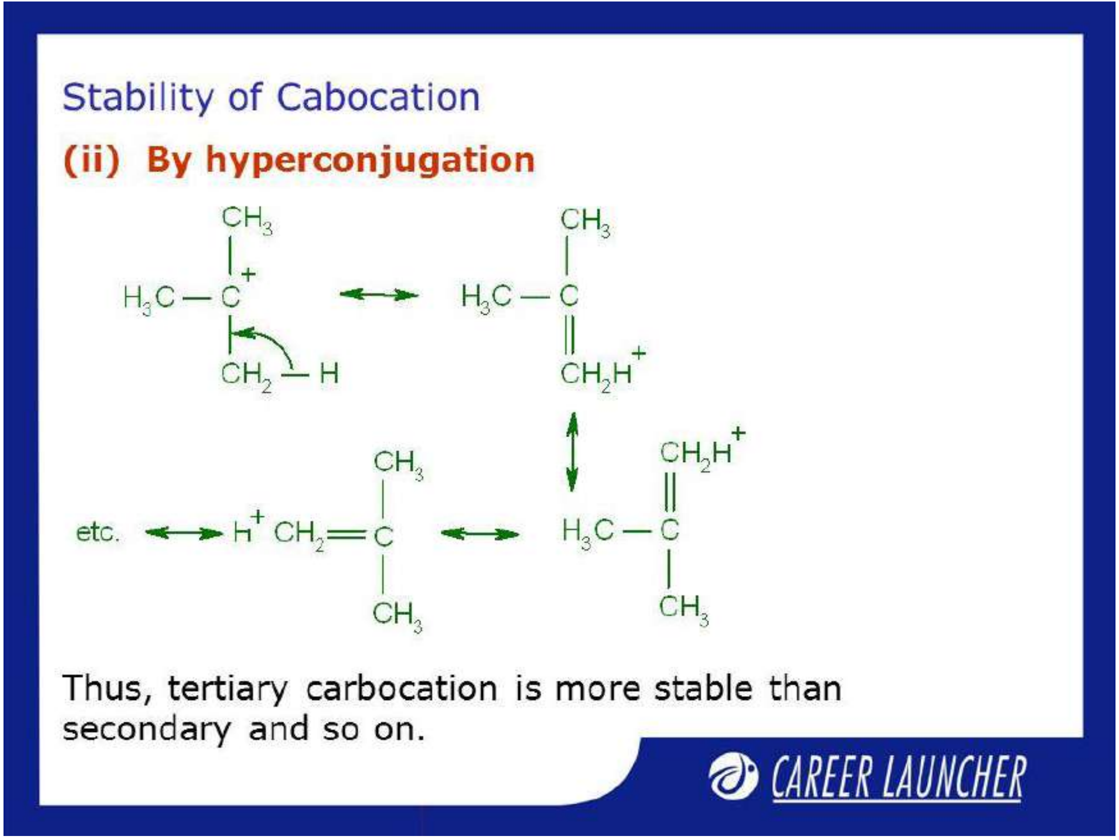
3^0alkyl carbocation > 2^0alkyl carbocation > 1^0alkyl carbocation > methyl carbocation

9 Hyperconjugable H

6 Hyperconjugable H

3 Hyperconjugable H

No Hyperconjugable H



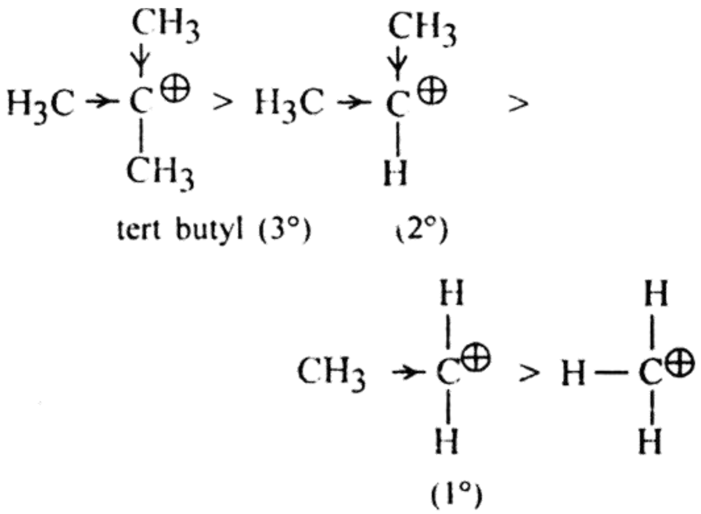
Stability of Cabocation

(ii) By hyperconjugation

Thus, tertiary carbocation is more stable than secondary and so on.

CAREER LAUNCHER

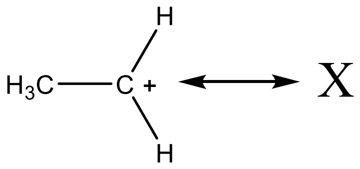
b) Inductive Effects Neighbouring alkyl groups contain electrons that are polarizable, and these can shift towards the positive charge. (Small Hydrogen substituents cannot do this as well).



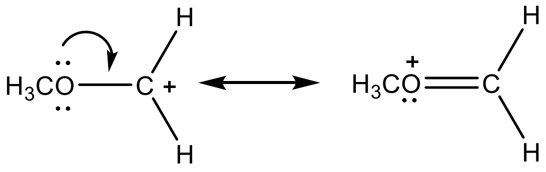
c) Resonance Effects Conjugation with a multiple bond or lone pairs of electrons increase the stability of a carbocation.

Therefore, allylic and benzylic systems are more stable than their saturated counterparts.

Be aware of the potential for heteroatoms to stabilize carbocations (since they can have lone pairs).

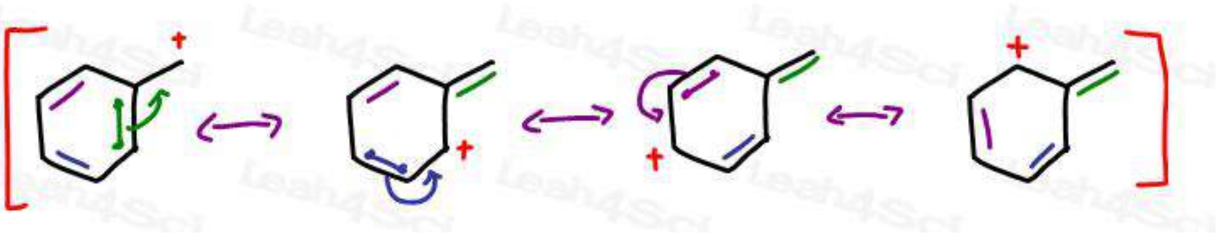


Lacks resonance.
A less stable carbocation.



Has resonance delocalization of the open valence shell. A more stable carbocation.

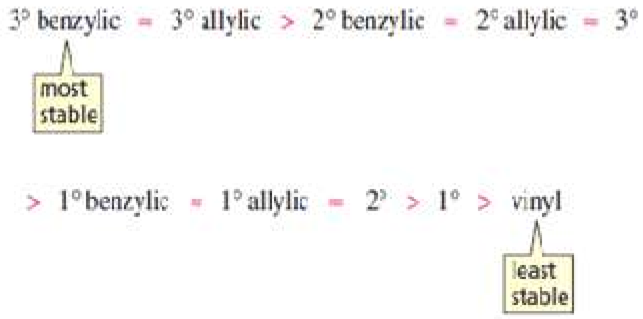
an allylic carbocation

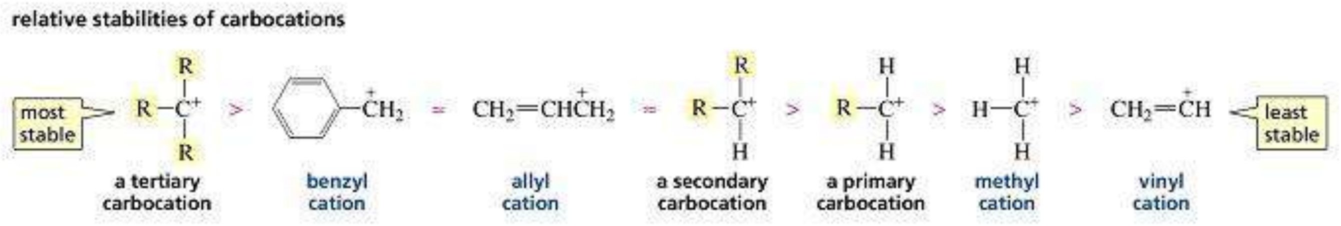


Benzylic carbocation

c) Hybridization also influences cation stability. The more s character in an orbital, the less stable the cation. Therefore, sp hybrid cations are very unstable.

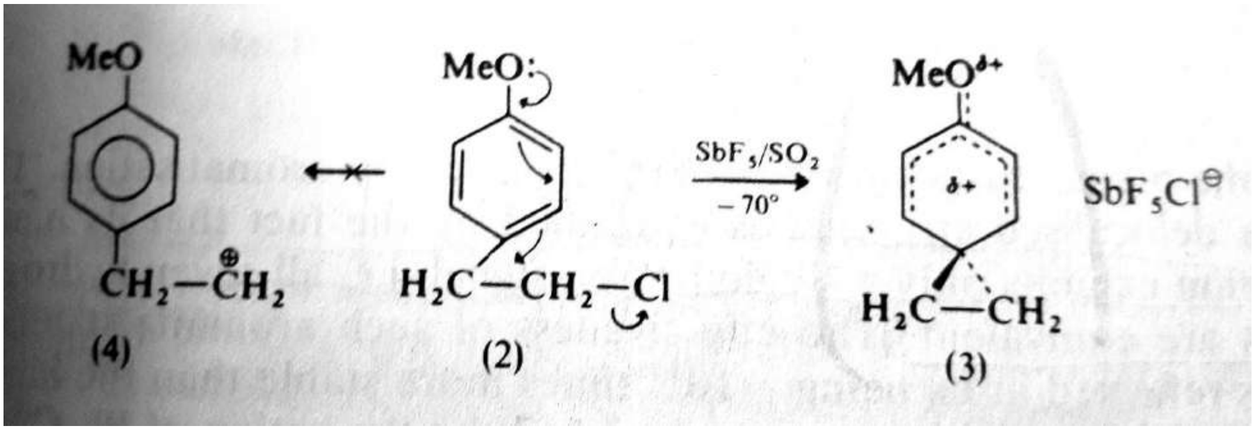
Due to the resonance stabilisation, a primary allylic or benzylic carbocation is almost as stable as a secondary alkyl carbocation and a secondary allylic or benzylic carbocation is about as stable as a tertiary alkyl carbocation.





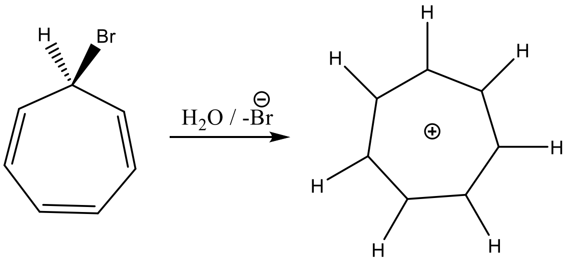
Delocalization Stability:

Bridged carbocation formation: for example: bridged phenonium ion

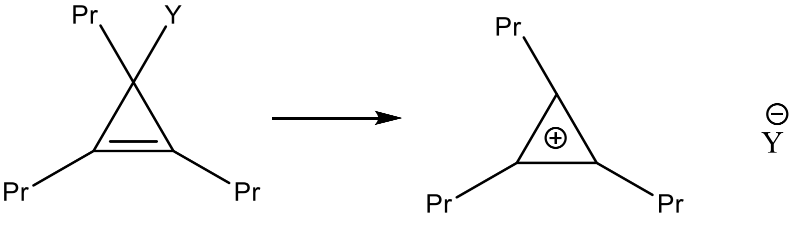


The Stability by Aromatation:

Carbocation from tropylium bromide compound:



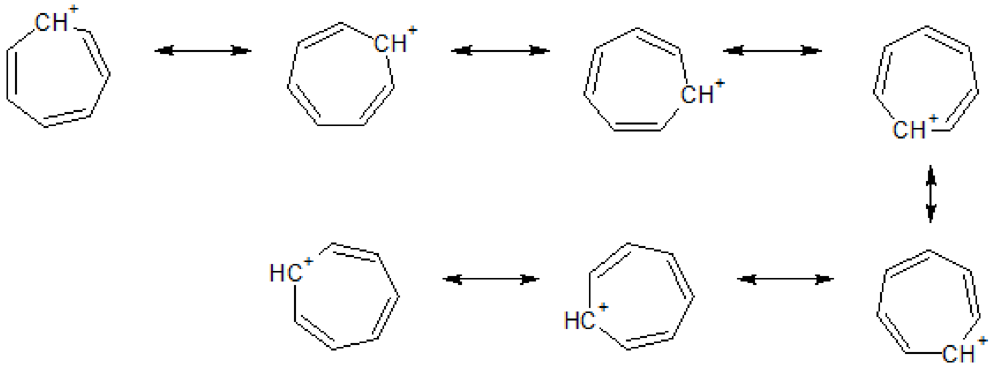
Tropylium cation



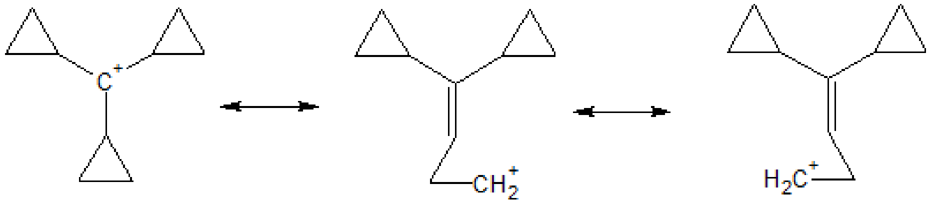
1,2,3- Tripropylcyclopropene

Cyclopropenyl cation

7 resonance structures for the tropylium carbocation



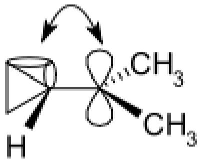
7 resonance structures for the tricyclopropyl carbocation



plus 4 more structures, 2 on each of the other 2 cycopropane rings

Due to overlapping of **cyclopropyl** ring's bond to vacant p-orbital at **carbocation**. It is a very special and important case of organic chemistry. They are **stable** due to bind bond conjugation. ... So, **cyclopropane** donate electron to **methyl carbocation** and stabilize it.

The bent bonds of the cyclopropane ring can overlap with the empty p orbital without steric hindrance.

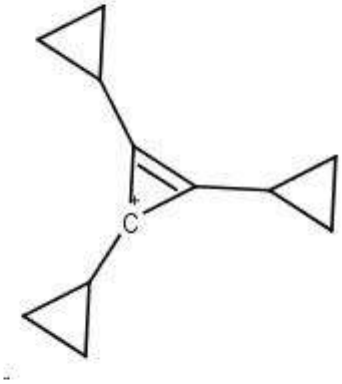


The positive charge on the carbon of **triphenylmethyl carbocation** is distributed uniformly over a number of structures. The aromaticity (i.e you can move the pi bonds around) of the phenyl groups allow for many possible **resonance structures**, and thus more potential for delocalization of the positive charge.

Hence, the triphenylmethyl cation, $(C_6H_5)_3C^+$ is stable because it has many resonance structures.
However, the resonance overlap of the π orbitals is not perfect because steric hindrance forces the ion to have a propeller shape.

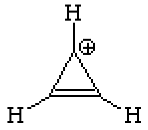
The most stable carbocation

Add the conjugation with cyclopropyl rings, and the most stable carbocation prepared to date is probably the tricyclopropylcyclopropenium cation.

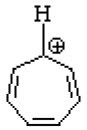


Arenium ions

Nothing beats the stability of aromatic cations like cyclopropenium and cycloheptatrienylium (tropylium) cations.



cyclopropenium ion



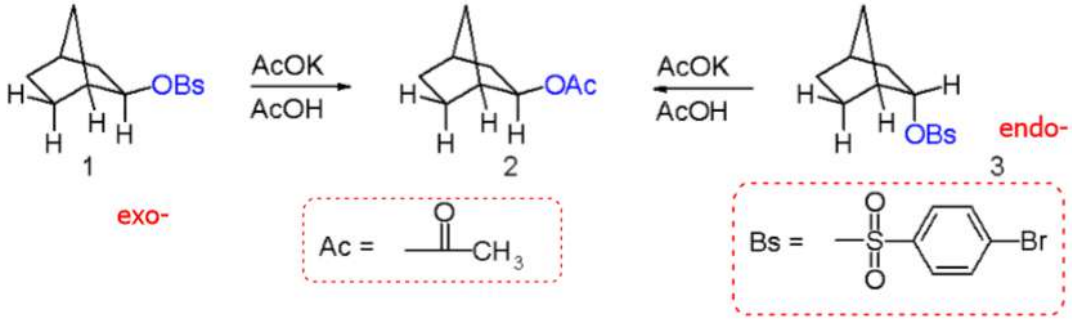
cycloheptatrienyl ion

tropylium is highly stable due to conjugated system, that being, it is resonance stabilized and the number of canonical forms of tropylium is more.

III. NON-CLASSICAL CARBOCATIONS 非经典碳正离子

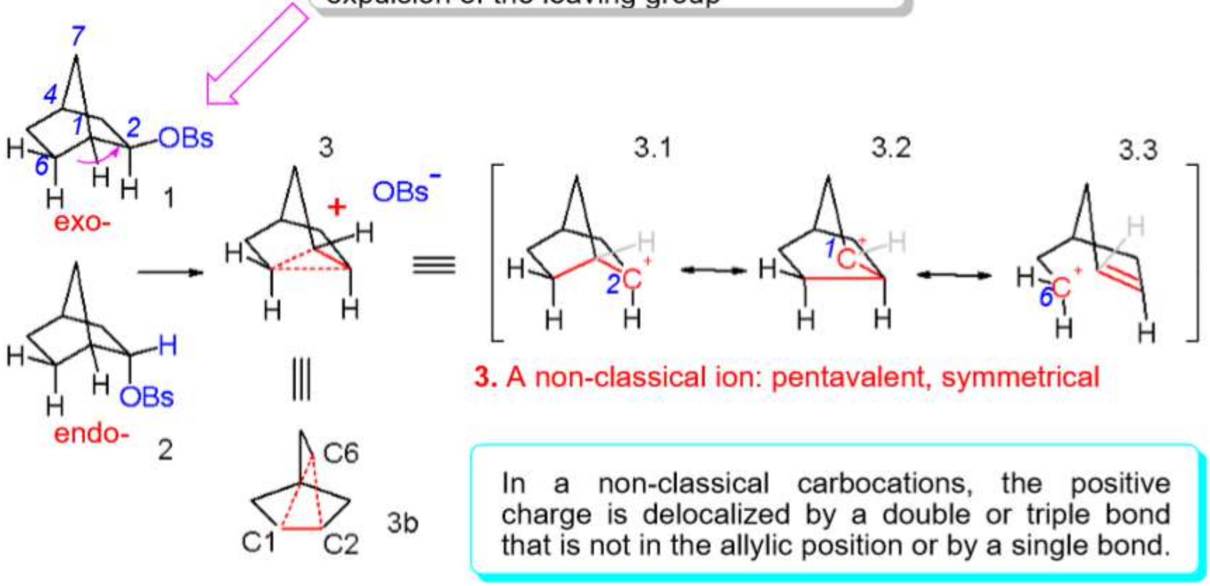
Non-classical ions are a special type of carbonium ions displaying delocalization of sigma bonds in 3-center-2-electron bonds of bridged systems.

S. Winstein (1949): Acylation (solvoysis) of norbornyl brosylate



A key observation is that in this nucleophilic displacement both isomers give the same reaction product an exo-acetate 2. Also the reaction rate for the exo-reaction is 350 times the reaction rate for the endo reaction.

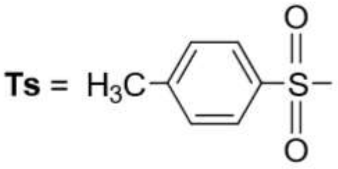
Sigma electrons in the C1-C6 bond assist by neighbouring group participation with the expulsion of the leaving group



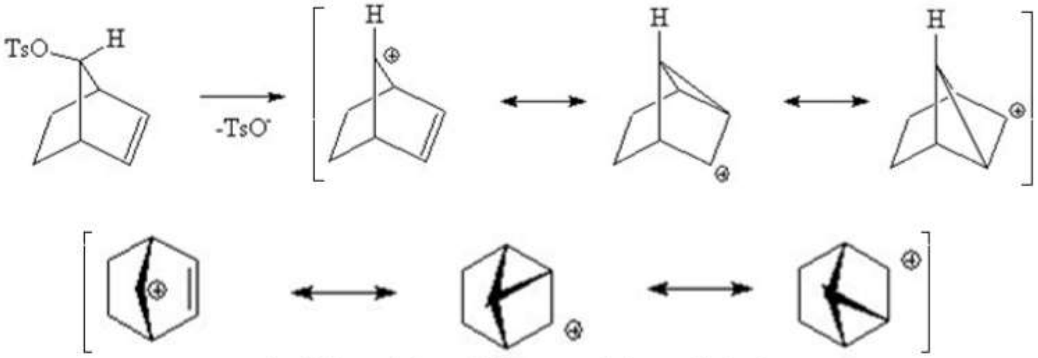
3. A non-classical ion: pentavalent, symmetrical

In a non-classical carbocations, the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond.

B. NGP BY AN ALKENE (C=C AS A NEIGHBORING GROUP)

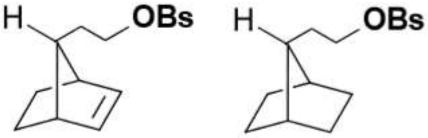


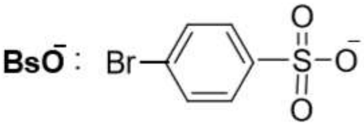
The rate of acetolysis	100	1
Configuration	retention	retention



(a different view of the same intermediates)

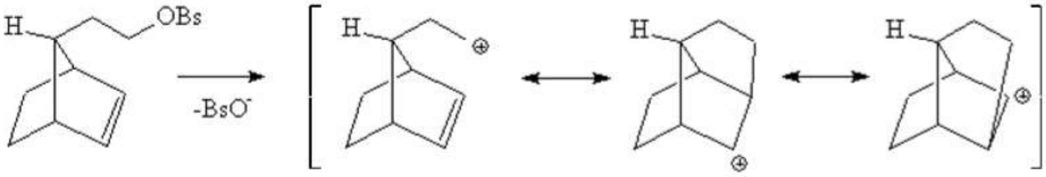
EVEN IF THE DOUBLE BOND IS MORE REMOTE FROM THE REACTING CENTER THE ALKENE CAN STILL ACT IN THIS WAY.





	(A)	(B)
Relative rate of acetolysis	140,000	1

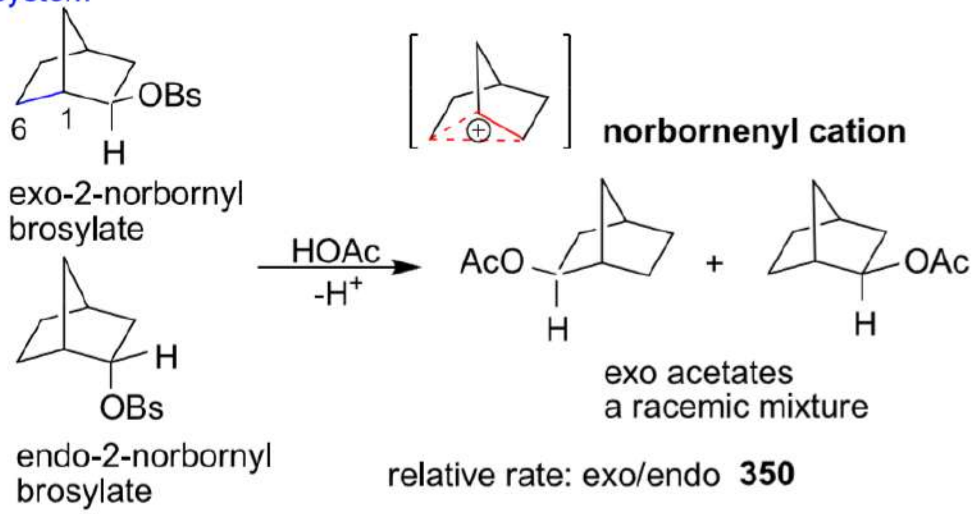
(A): β-(syn-7-norbornenyl) ethyl brosylate



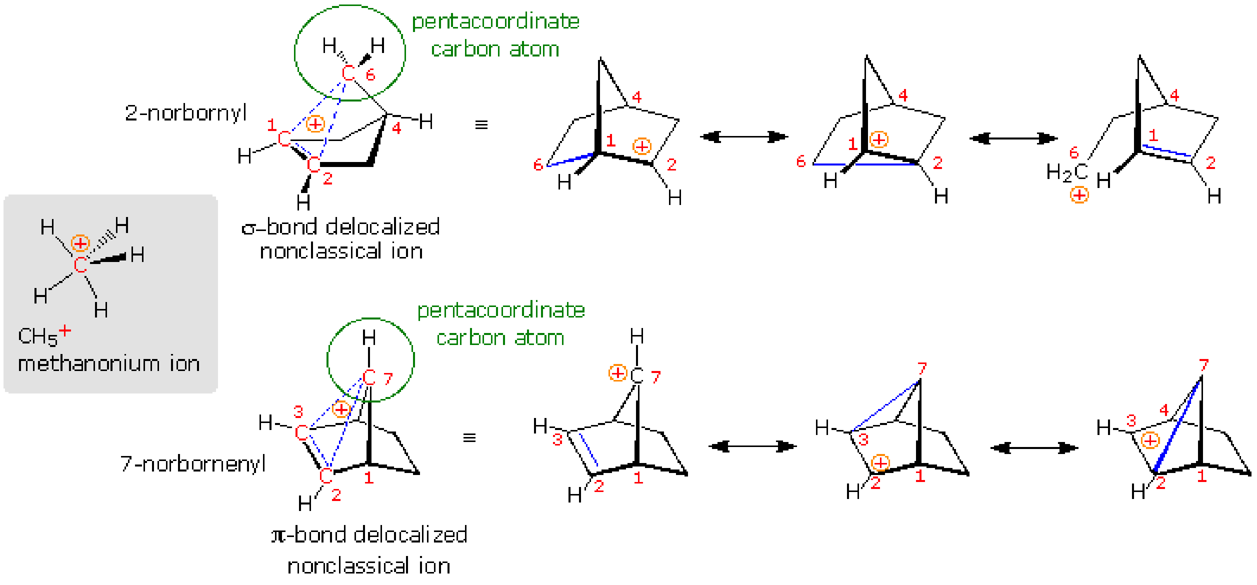
a different view of the same carbocation:

E. The C-C single bond as a neighboring group

i. The 2-norbornyl system



relative rate: exo/endo **350**



2) Formation of carbocations

a) ionization

Unimolecular ionization results in a **carbocation** and a **leaving group**.

If the carbocation leads to a substitution product = **S_N1** reaction.
If the carbocation leads to an elimination product = **E1** reaction.

In both cases the *ionization* is the **rate determining step**.

E.g. Acid catalysed dehydration (loss of water)

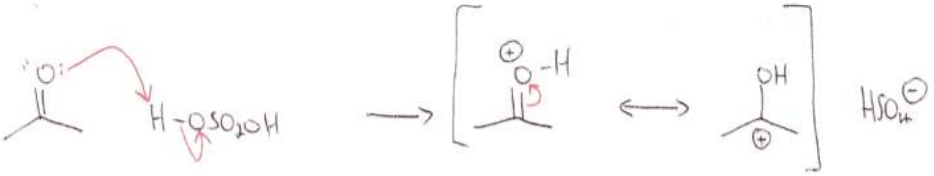
The protonation (and deprotonation) occur **faster** than the loss of water from the protonated alcohol.

b) Addition of an Electrophile to a π bond

A common way to generate cations is an **addition** of a Lewis acid (often a H^+) to a π bond.

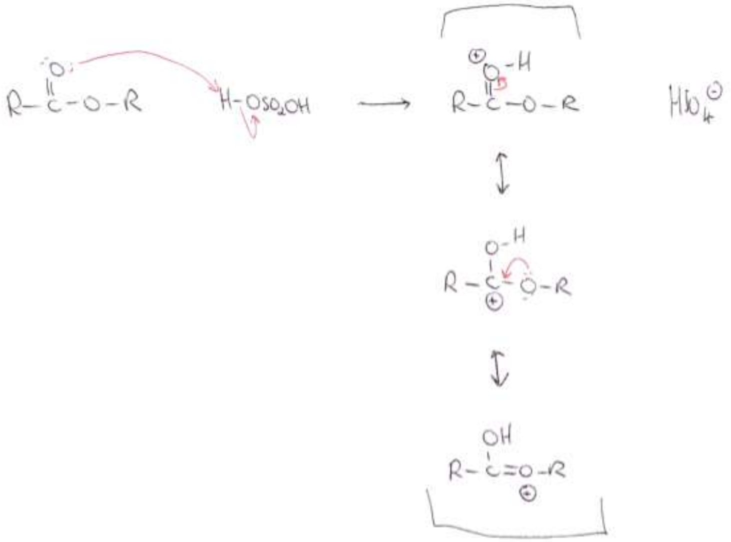
E.g. protonation of an alkene:

E.g. protonation of a carbonyl group:



In acid, carbonyl compounds become protonated on the O, although there is significant +ve charge on the carbon (activated carbonyl complex towards nuc attack).

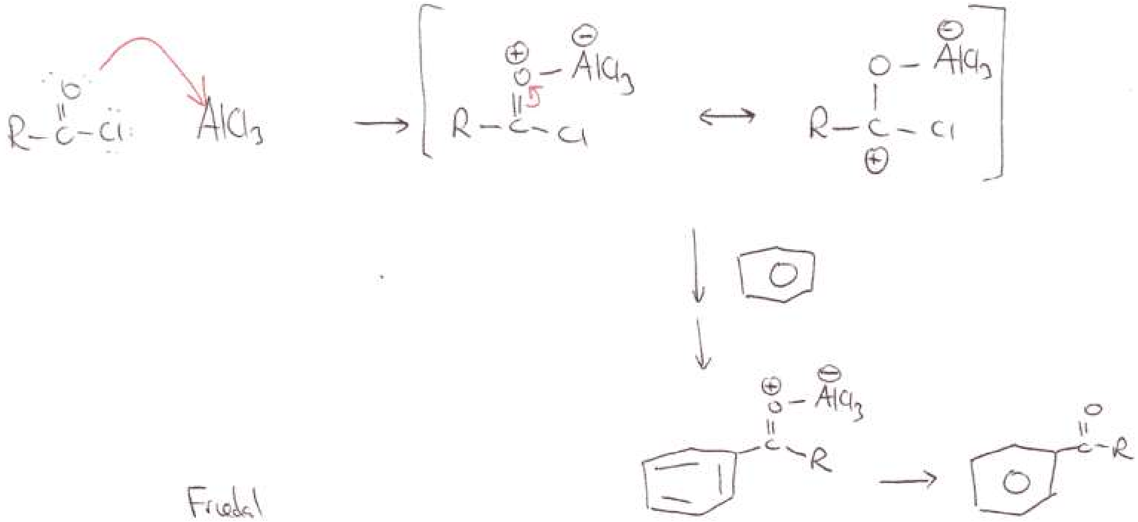
Protonation of **Esters** occurs at the **carbonyl oxygen** as this leads to an extensively delocalised cation.



Reaction of a carbonyl compound with a Lewis acid.

The **basicity** of the carbonyl **oxygen** allows reaction with Lewis acids such as $AlCl_3$, BF_3 and $SnCl_4$, leading to complexes which are usually reactive intermediates.

E.g.



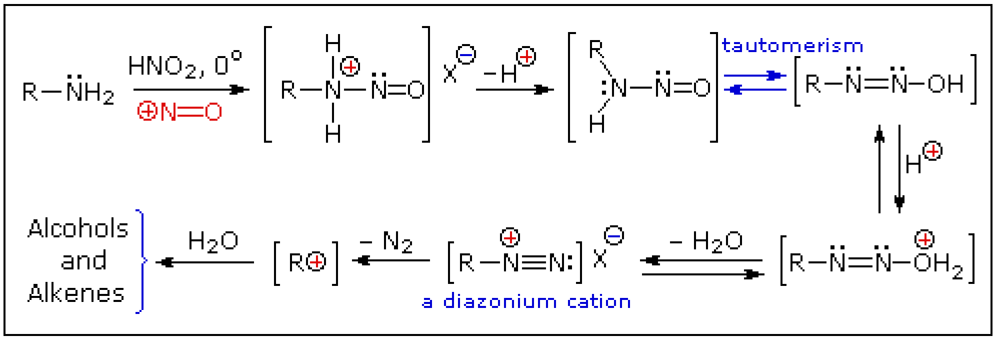
Friedel Crafts Acylation.

c) Reaction of an alkyl halide with a Lewis Acid

E.g. $AlCl_3$ with 2-chloropentane.

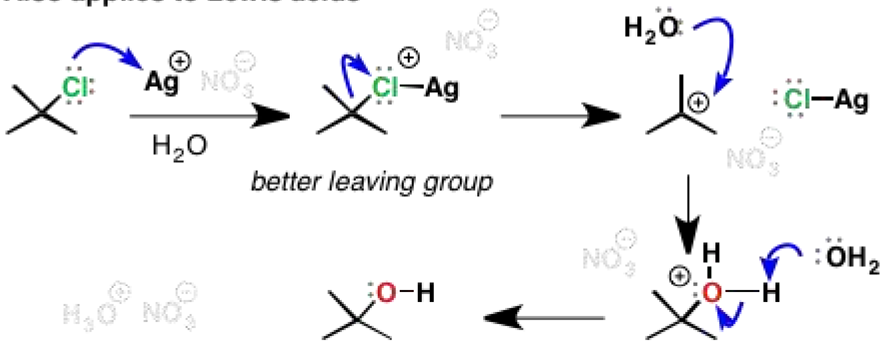
The LA removes the chloride to generate the **carbocation**.

d) Carbocation from diazo compounds



e) Carbocation from silver ion with alkyl halides

Also applies to Lewis acids



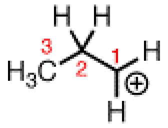
One advantage of Ag+ here with halides such as Cl, Br, and I is that silver halide salts are insoluble in water, driving the reaction to completion

$FeCl_3$, $AlCl_3$, $FeBr_3$, $AlBr_3$, BF_3 are other examples of Lewis acids tha can be used to make functional groups into better leaving groups

Reaction of Carbocation

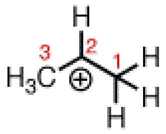
Carbocations are stabilized by neighboring carbon atoms.

The stability of carbocations increases as we go from primary to secondary to tertiary carbons. carbocations become more stable as you increase the number of electrons donating groups attached to them. **Alkyl groups are a perfect example:**

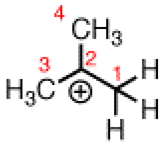


Primary carbocation

(least stable)



Secondary carbocation

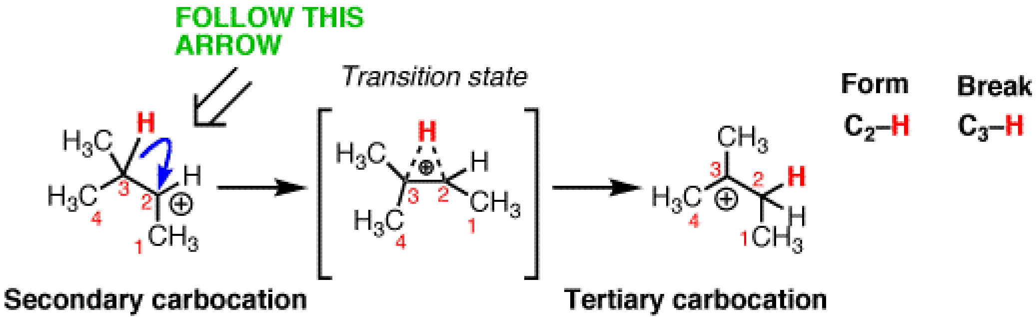


Tertiary carbocation

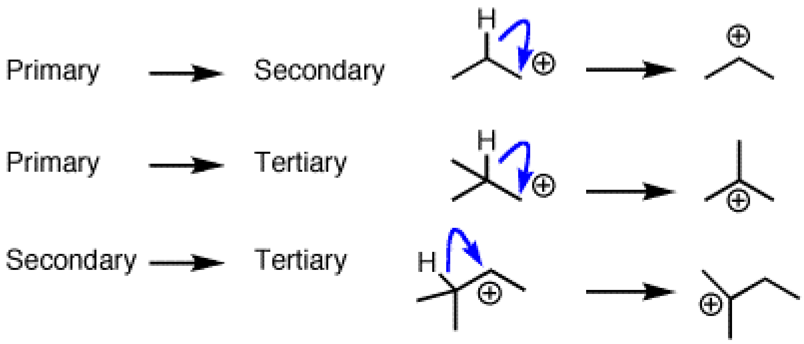
(most stable)

One rearrangement pathway where an unstable carbocation can be transformed into a more stable carbocation is called a **hydride shift.** Look at the diagram below.

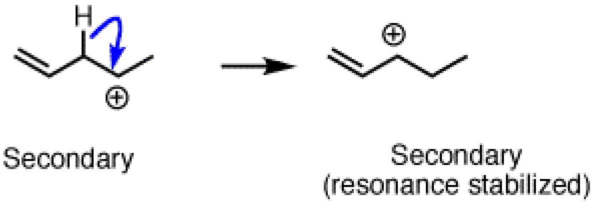
One pathway rearrangements can occur through is a *hydride shift.*



Some examples of "allowed" hydrogen rearrangements
(note: "hidden" hydrogens not drawn!)

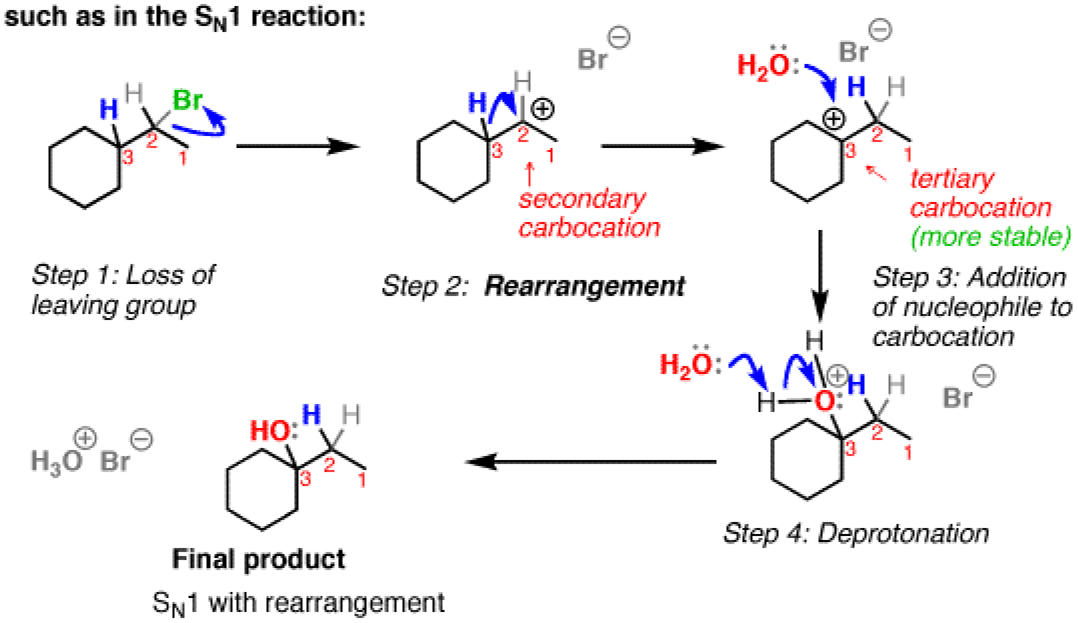


Note: Carbocations with the same substitution pattern can rearrange if it results in a resonance-stabilized carbocation



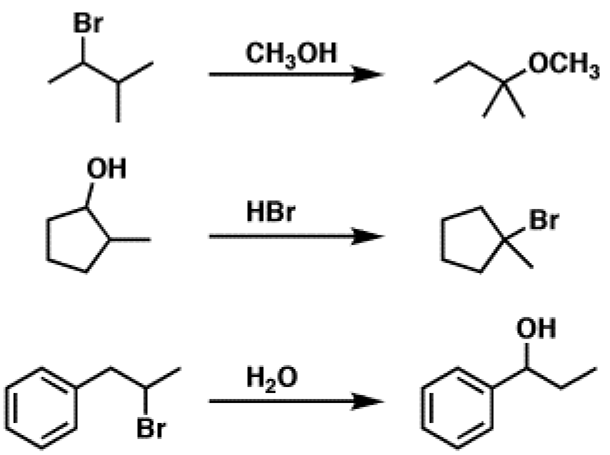
Now we're ready to show how the rearrangement reaction occurs with the SN1. Recall that the first step in the SN1 is that the **leaving group leaves** to give a carbocation. In the case below, the carbocation that is formed is **secondary**, and there's a **tertiary** carbon next door. Therefore, a **rearrangement** can occur to give the more stable tertiary carbocation, which is then attacked by the nucleophile (water in this case). Finally, the water is deprotonated to give the neutral alcohol. So, this is an example of an **S$_N$1 reaction with rearrangement**.

Rearrangements can accompany reactions where carbocations are formed, such as in the S_N1 reaction:

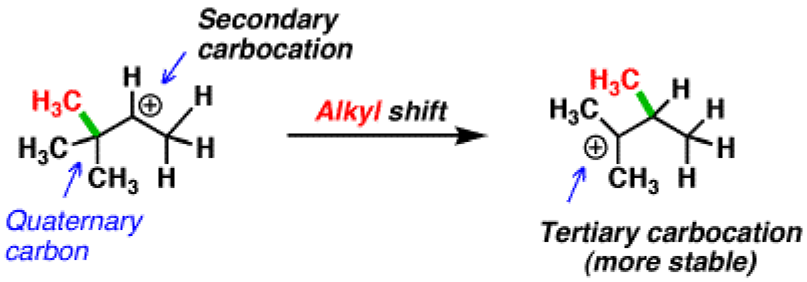


I’ve given some more examples of SN1 reactions with rearrangements below. See if you can draw the mechanisms! In the next post we’ll talk about a slightly different rearrangement pathway with substitution reactions.

Some other examples. Can you draw mechanisms?

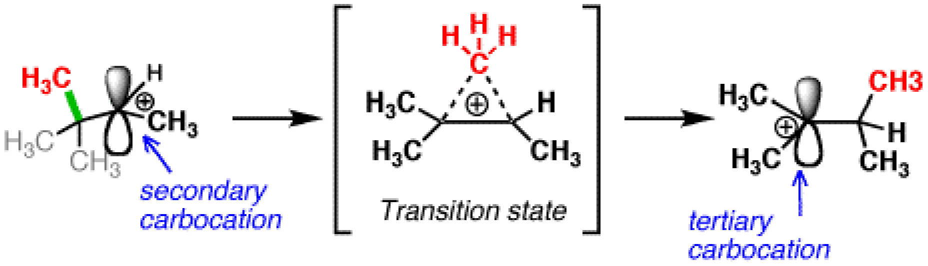


The most common situation where alkyl shifts can occur is when a **quaternary carbon** (that’s a carbon attached to 4 carbons) is adjacent to a **secondary carbocation**.



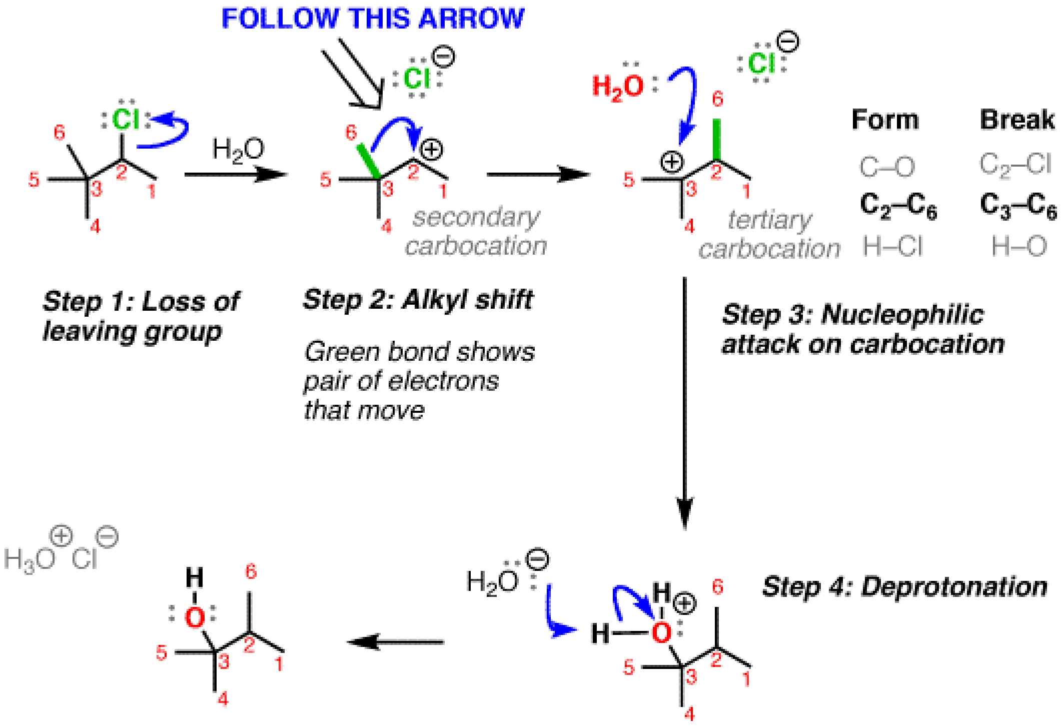
In the transition state, there are partial bonds between the carbon being transferred and each of the two adjacent carbon atoms. Then, as one bond shortens and the other lengthens, we end up with a (more stable) tertiary carbocation.

How an alkyl shift works:



Here’s an example of an S_N1 with an alkyl shift (note that the CH_3 groups here are just shown as lines).

S_N1 With Alkyl Shift:



Form	Break
C–O	C_2–Cl
C_2–C_6	**C_3–C_6**
H–Cl	H–O

Step 1: Loss of leaving group

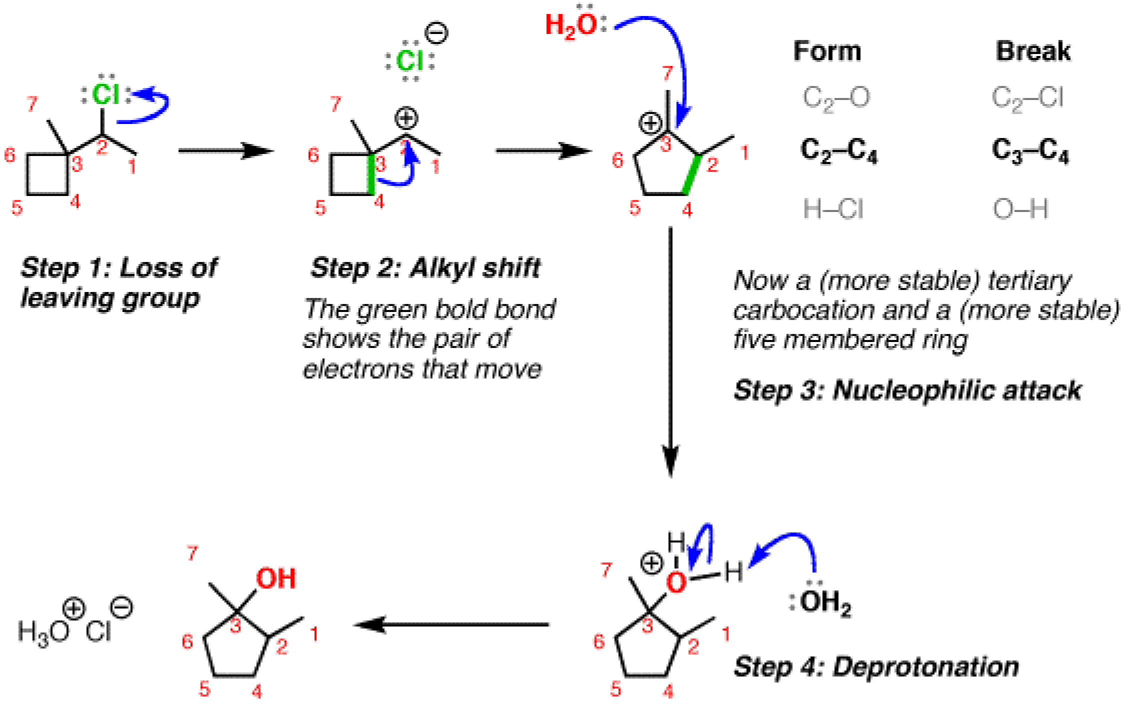
Step 2: Alkyl shift

Green bond shows pair of electrons that move

Step 3: Nucleophilic attack on carbocation

Step 4: Deprotonation

Here's an example of an S_N1 where an alkyl shift leads to ring expansion.



Form	Break
C_2–O	C_2–Cl
C_2–C_4	**C_3–C_4**
H–Cl	O–H

Step 1: Loss of leaving group

Step 2: Alkyl shift

The green bold bond shows the pair of electrons that move

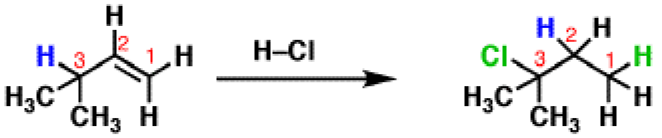
Now a (more stable) tertiary carbocation and a (more stable) five membered ring

Step 3: Nucleophilic attack

Step 4: Deprotonation

In exploring reactions that proceed along the carbocation pathway, every once in a while you might see an example of an addition reaction that looks a little… strange. The alkene is gone, two new bonds have formed, but the positions of the new bonds is a little out of the ordinary. Like in this example:

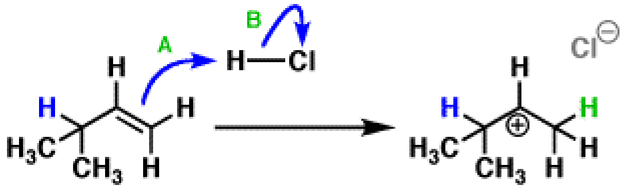
An addition reaction with a twist



How did that chloride end up on C-3?

Form	Break
C_1–H	C_1–C_2 (π)
C_2–H	C_3–H
C_3–Cl	H–Cl

Step 1 - attack of alkene on H-Cl (arrows A and B)



Observation: secondary carbocation

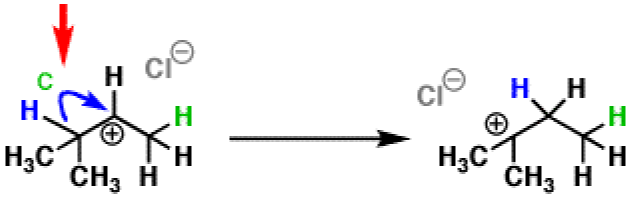
Form	Break
A C_1–H	A C_1–C_2 (π)
C_2–H	C_3–H
C_3–Cl	B H–Cl

Step 2 - rearrangement (arrow C)

Recall the order of carbocation stability: tertiary > secondary > primary

Migration of the C-H bond from C_3 to C_2 results in a more stable carbocation!

This arrow says, "break the C_3–H bond and form a new C_2-H bond"



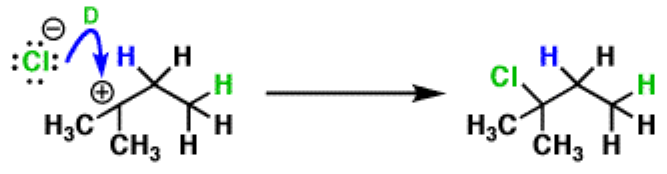
Secondary carbocation

Tertiary carbocation

a more stable carbocation

Form	Break
A C_1–H	A C_1–C_2 (π)
C C_2–H	C C_3–H
C_3–Cl	B H–Cl

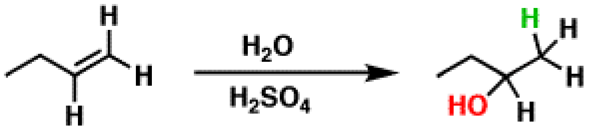
Step 3 - Attack of nucleophile (arrow D)



Tertiary carbocation

Form	Break
A C_1–H	A C_1–C_2 (π)
C C_2–H	C C_3–H
D C_3–Cl	B H–Cl

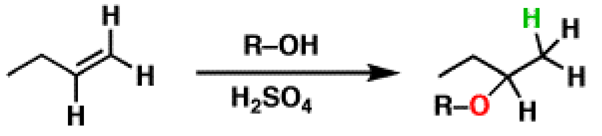
Hydration of alkenes (with acid catalyst)



(often written $H_3O^{\oplus}$)

Form	Break
C–H	C–C (π)
C–OH	H–O

Addition of alcohols to alkenes (with acid catalyst)

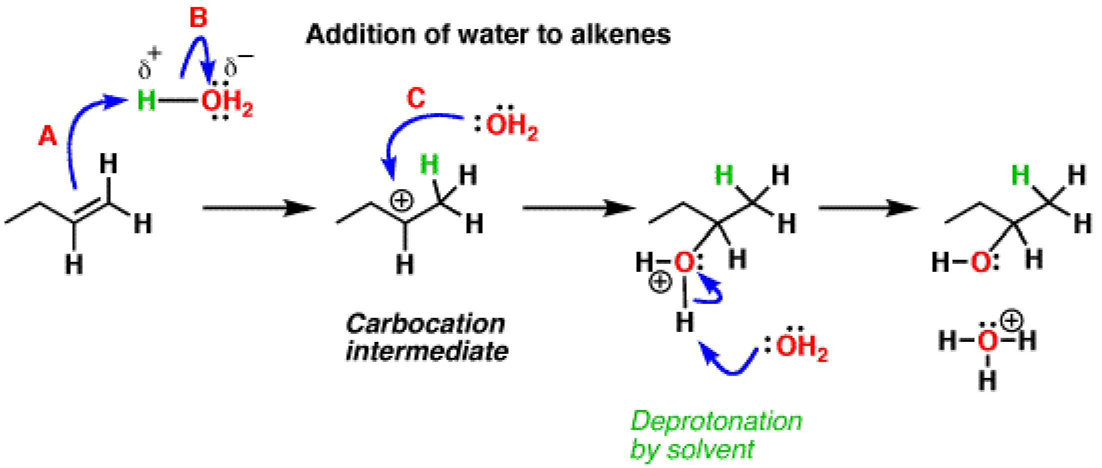


("$H^{\oplus}$" is often written as the acid here)

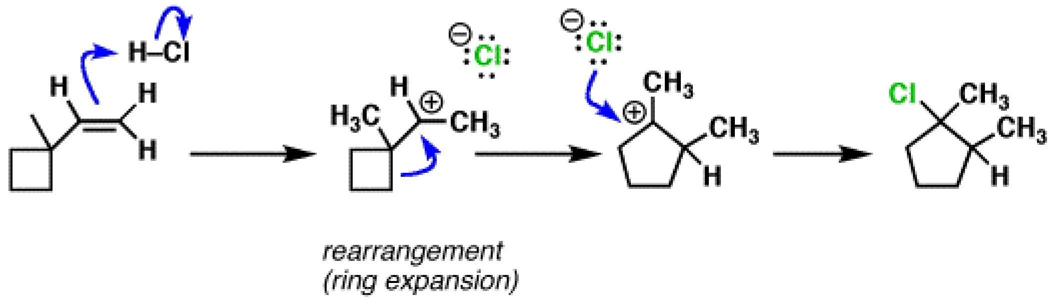
Form	Break
C–H	C–C (π)
C–OR	H–O

Since our nucleophile is neutral, it will bear a **positive charge** after attacking the carbocation. This positive charge can be removed through deprotonation by a weak base. One little assumption here: we are using H_2O (or ROH in the second case) as solvent, so there is a whopping excess around to act in this capacity.

Addition of water to alkenes

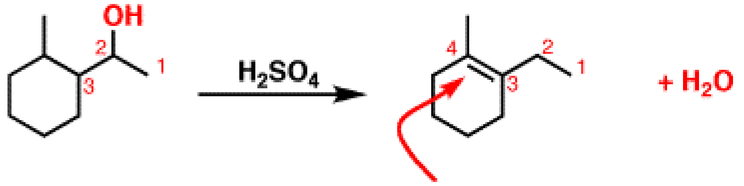


Ring expansion example:



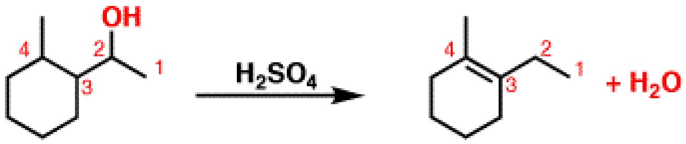
One last (weird) reaction to show you with respect to elimination reactions. Can you see what's weird about it?

An elimination reaction... but something is weird about it



How did the double bond get **here?**

Eliminations (E1) Can Occur With Rearrangement!

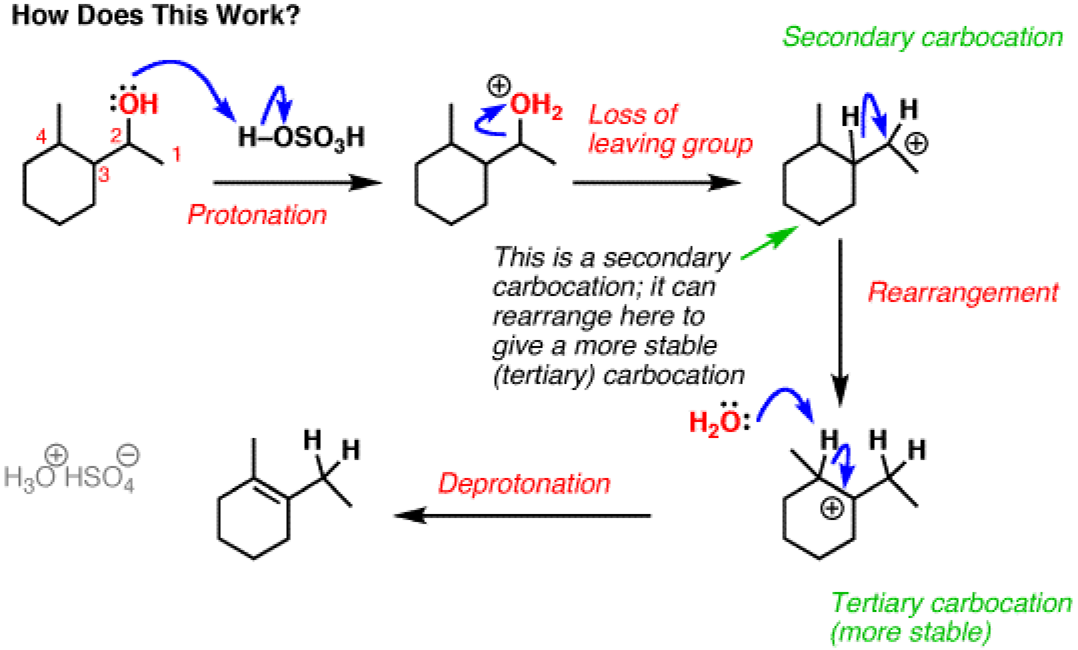


Form	Break
C_3–C_4 (π)	C_2–OH
O–H	C_4–H
C_2–H	C_3–H

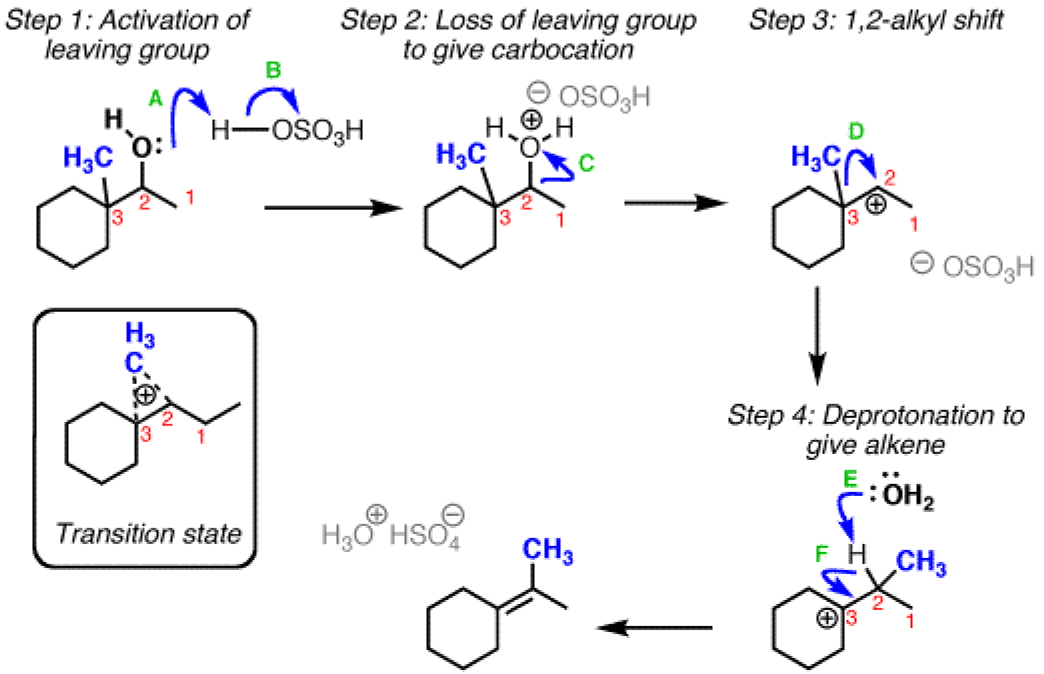
notice the extra set

Well, we start by protonating the alcohol. This allows for water to leave in the next step, which is going to form a carbocation. **Here's the thing:** the carbocation is **secondary**, and we're adjacent to a **tertiary** carbon. So, if the hydrogen (and its pair of electrons) were to migrate from C3 in our example to C-2, we'd now have a tertiary carbocation, which is **more stable**. Then, a base (water in this example) could remove C-H, forming the more substituted alkene (the Zaitsev product in this case). And that's how the alkene ends up there.

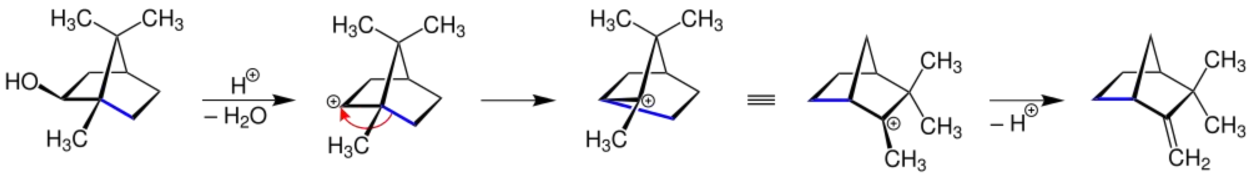
How Does This Work?



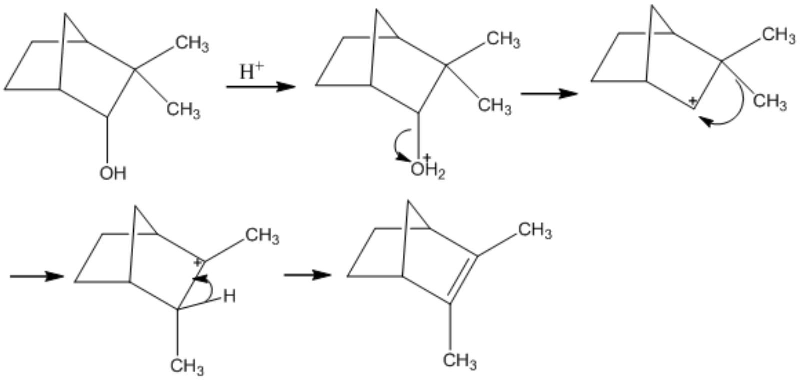
Elimination (E1) With Alkyl Shift

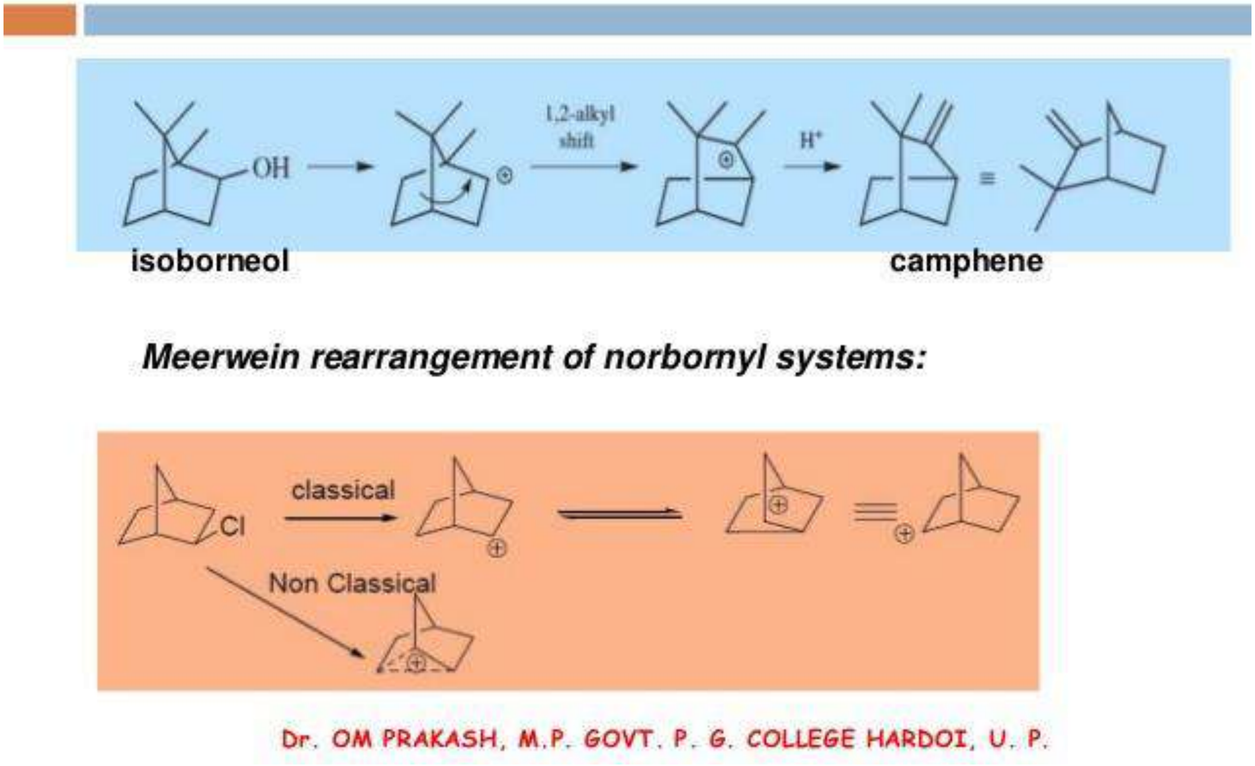


A **Wagner–Meerwein rearrangement** is a class of carbocation 1,2-rearrangement reactions in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon. The rearrangement was first discovered in bicyclic terpenes for example the conversion of isoborneol to camphene.



Rearrangement of alcohols under acidic condition

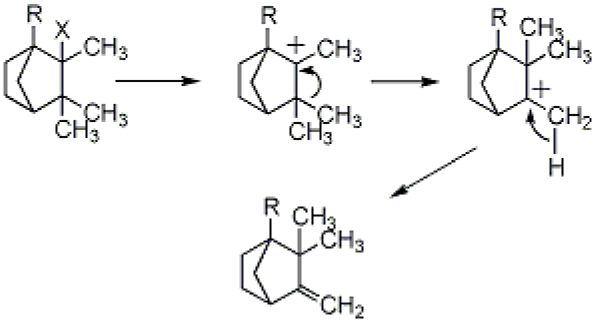




Meerwein rearrangement of norbornyl systems:

Dr. OM PRAKASH, M.P. GOVT. P. G. COLLEGE HARDOI, U. P.

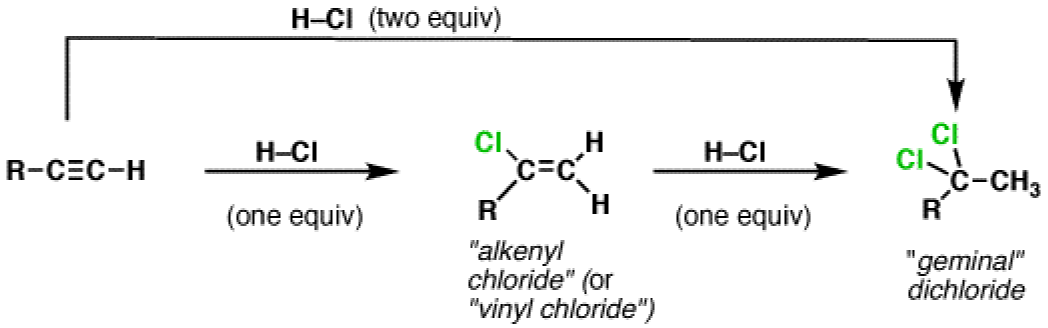
A special case of carbonium ion rearrangement in camphene hydrochloride derivatives involving the migration of a methyl group:



Addition of Acids To Alkynes

One equivalent of acid gives the alkenyl halide ("vinyl halide")

Two equivalents of acid gives the "geminal dihalide"



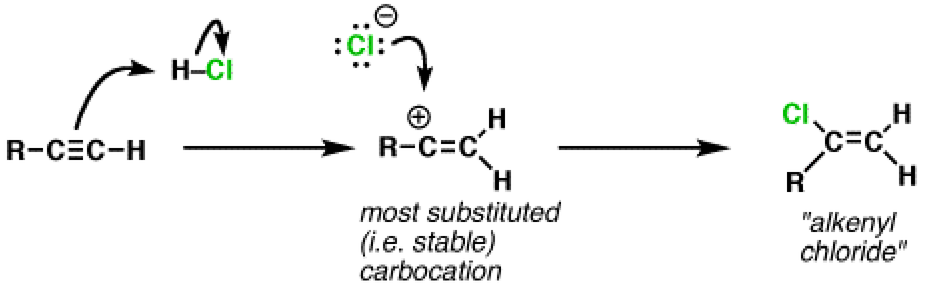
Same for HBr and HI

note: "Markovnikov" addition
(Cl adds to most substituted carbon)

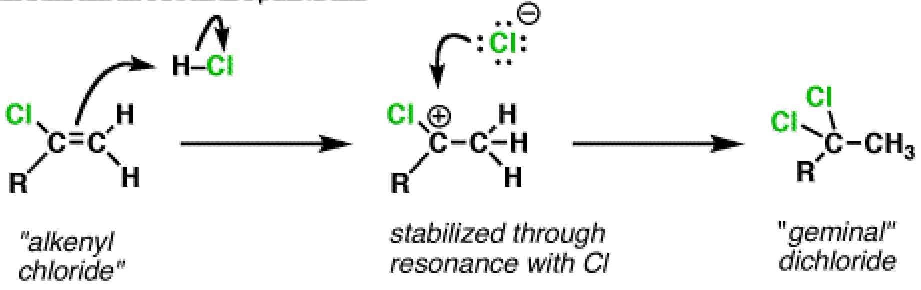
How It Works

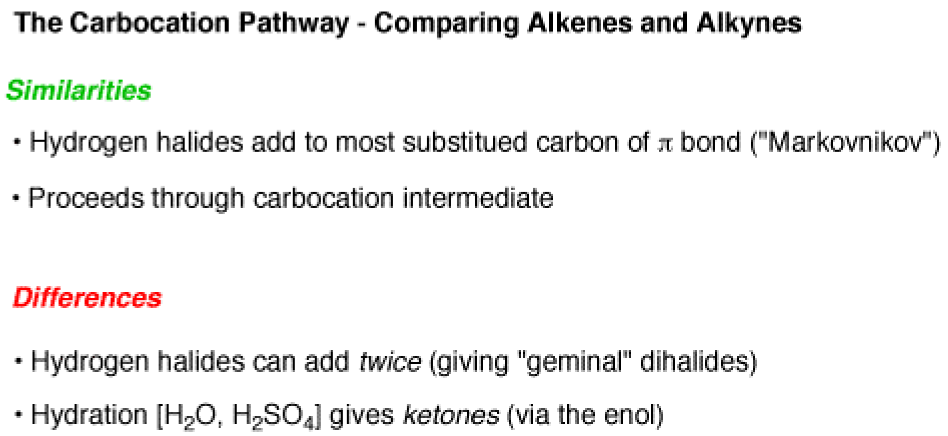
Mechanism still proceeds through a carbocation

Addition of first equivalent:



Addition of second equivalent:





The Carbocation Pathway - Comparing Alkenes and Alkynes

Similarities

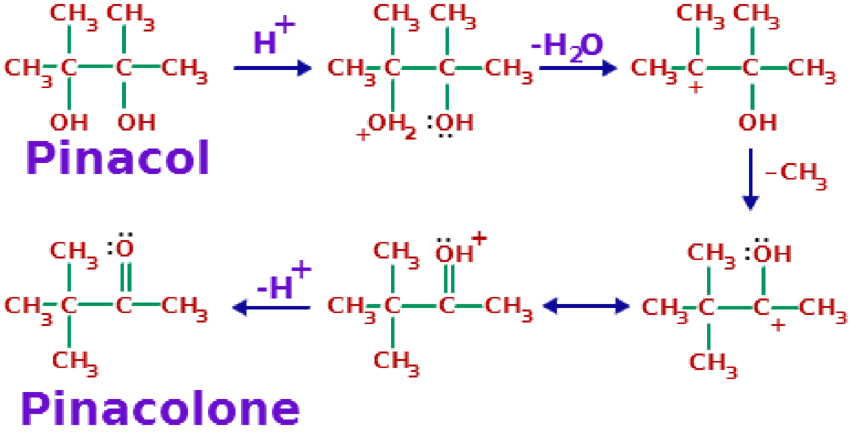
- Hydrogen halides add to most substitued carbon of π bond ("Markovnikov")
- Proceeds through carbocation intermediate

Differences

- Hydrogen halides can add *twice* (giving "geminal" dihalides)
- Hydration [H_2O, H_2SO_4] gives *ketones* (via the enol)

Pinacol / Pinacolon rearrangement:

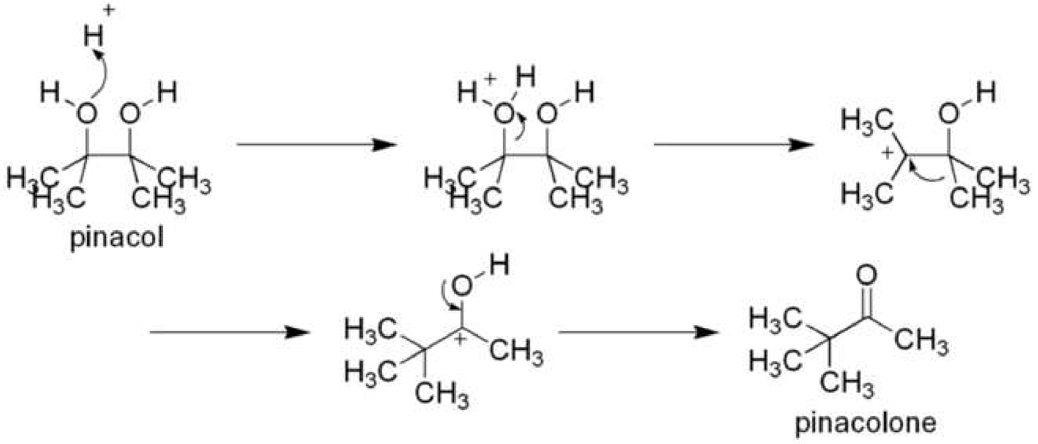
Eg: 1,2-dihydroxy compounds

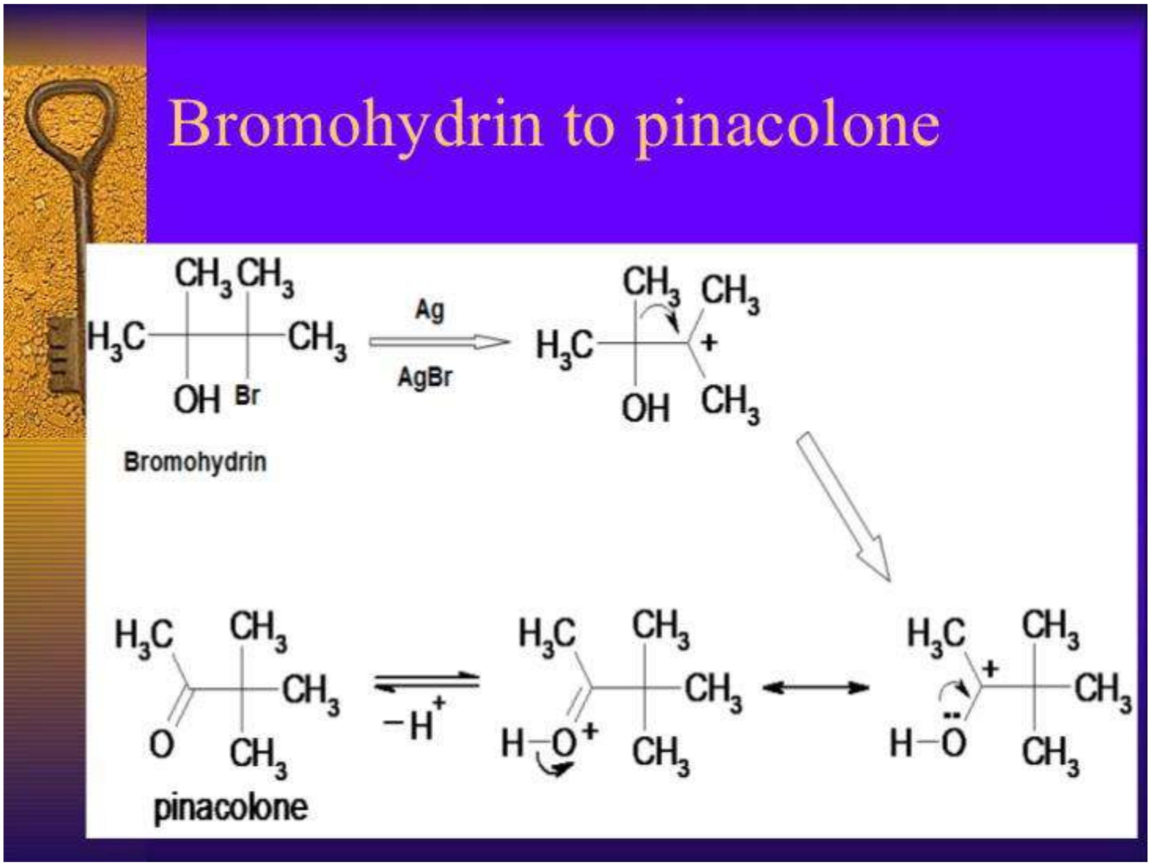


Carbocation is already tertiary

Then why should it rearrange?
The lone pair of electrons on the oxygen is another source to stabilize the carbocation.

Mechanism:

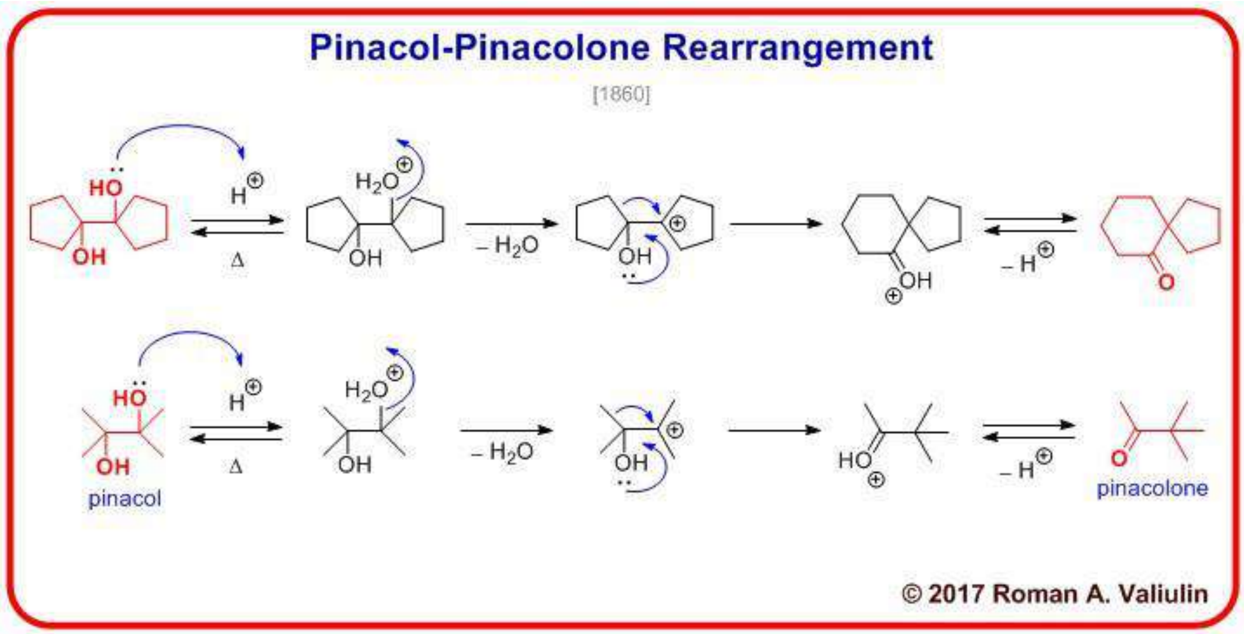


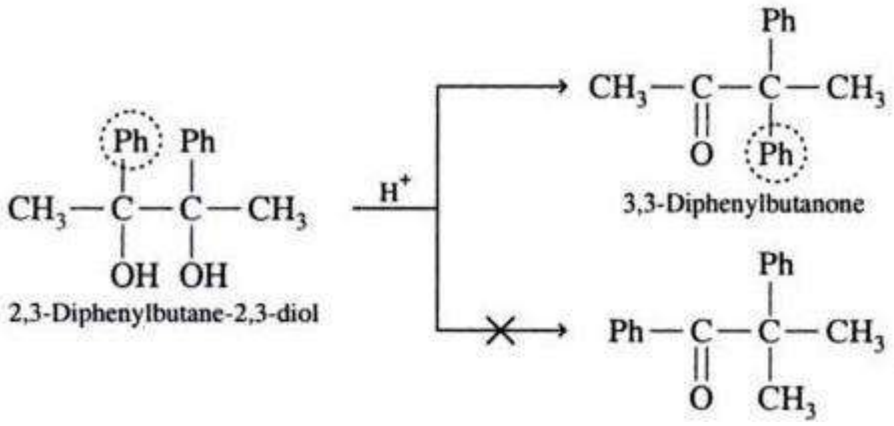


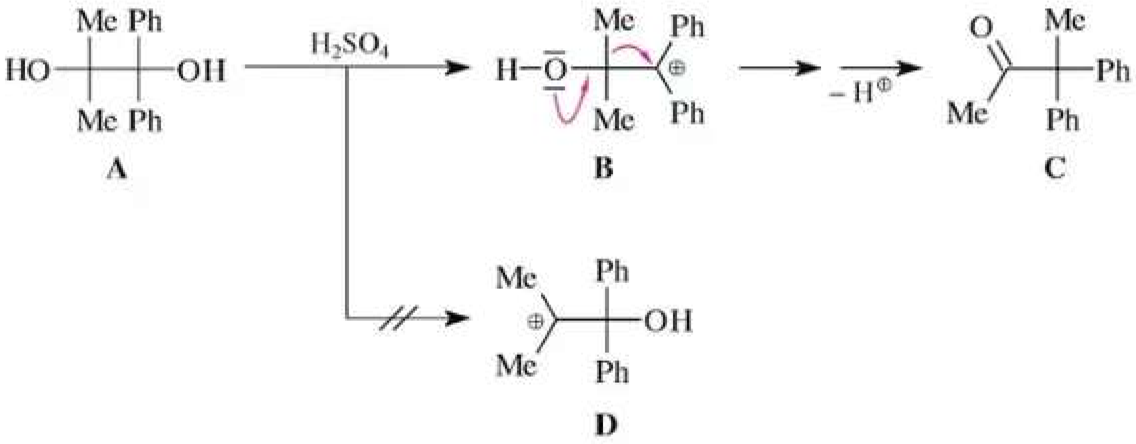
Bromohydrin to pinacolone

The carbocation formed as a result of loss of H_2O, pulls the migrating group, Lone pair on oxygen pushes the migrating group

Preparation of Spiro System:



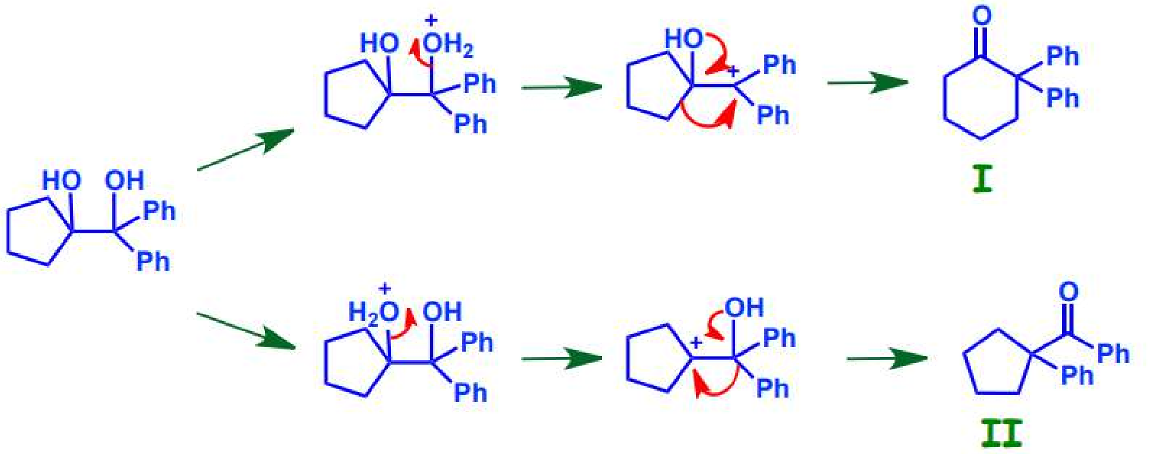




- **Migrating group preference:**

It doesn't matter when we have symmetrical diols & epoxides

It doesn't matter when we have unsymmetrical epoxides & diols

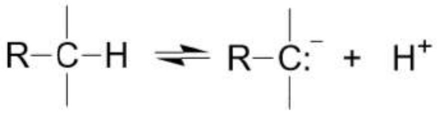


Only I is formed in quantitative amount because the carbocation is stabilized by two phenyl groups

Carbanions:

A **carbanion** is an anion in which carbon has an unshared pair of electrons and bears a negative charge usually with three substituents for a total of eight valence electrons.

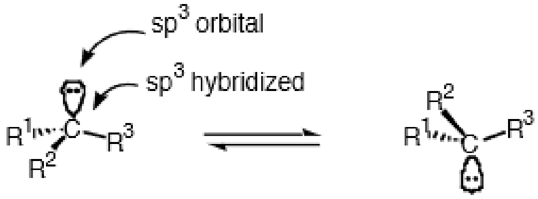
Formally a carbanion is the conjugate base of a **carbon acid**.



$$R{-}\underset{|}{\overset{|}{C}}{-}H \rightleftharpoons R{-}\underset{|}{\overset{|}{C}}{:}^{-} + H^{+}$$

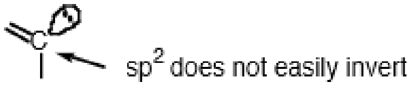
Carbanions are units that contain a negative charge on a carbon atom. The negative charge gives good nucleophilic properties to the unit that can be used in the formation of new carbon carbon bonds. Carbanions thus act as nucleophiles in substitution reactions, in carbonyl addition and substitution reactions, and in 1,4- addition (Michael) reactions.

structure:



-rapid epimerization of stereogenic carbanions, except when R_1 = OR

(Still, *JACS* **1978**, *100*, 1481 & *JACS* **1980**, *102*, 1201)



I. STABILITY AND STRUCTURE

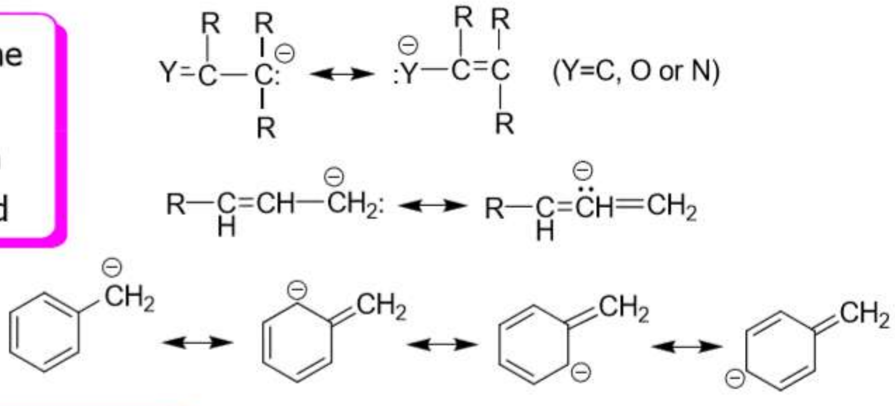
The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker is the acid, the greater is the base strength and the lower is the stability of the carbanion.

Factors determining the stability and reactivity of a carbanion:

- The inductive effect. Electronegative atoms adjacent to the charge will stabilize the charge;
- Hybridization of the charge-bearing atom. The greater the *s*-character of the charge-bearing atom, the more stable the anion;
- The extent of conjugation of the anion. Resonance effects can stabilize the anion. This is especially true when the anion is stabilized as a result of aromaticity.

RELATIVELY STABLE CARBANIONS WITH CERTAIN STRUCTURAL FEATURES

Conjugation of the unshared pair of electrons with an unsaturated bond



Carbanions increase in stability with an increase in the amount of *s* character at the carbanionic carbon.

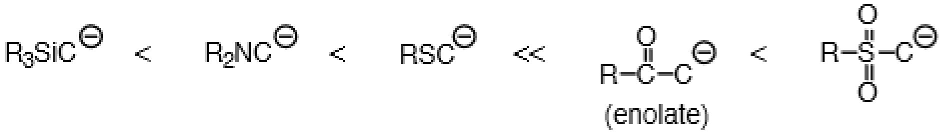
Stability:

$RC\equiv C^{-} > R_2=CH^{-} \approx Ar^{-} > RCH_2^{-}$

3° < 2° < 1° < allylic, benzylic

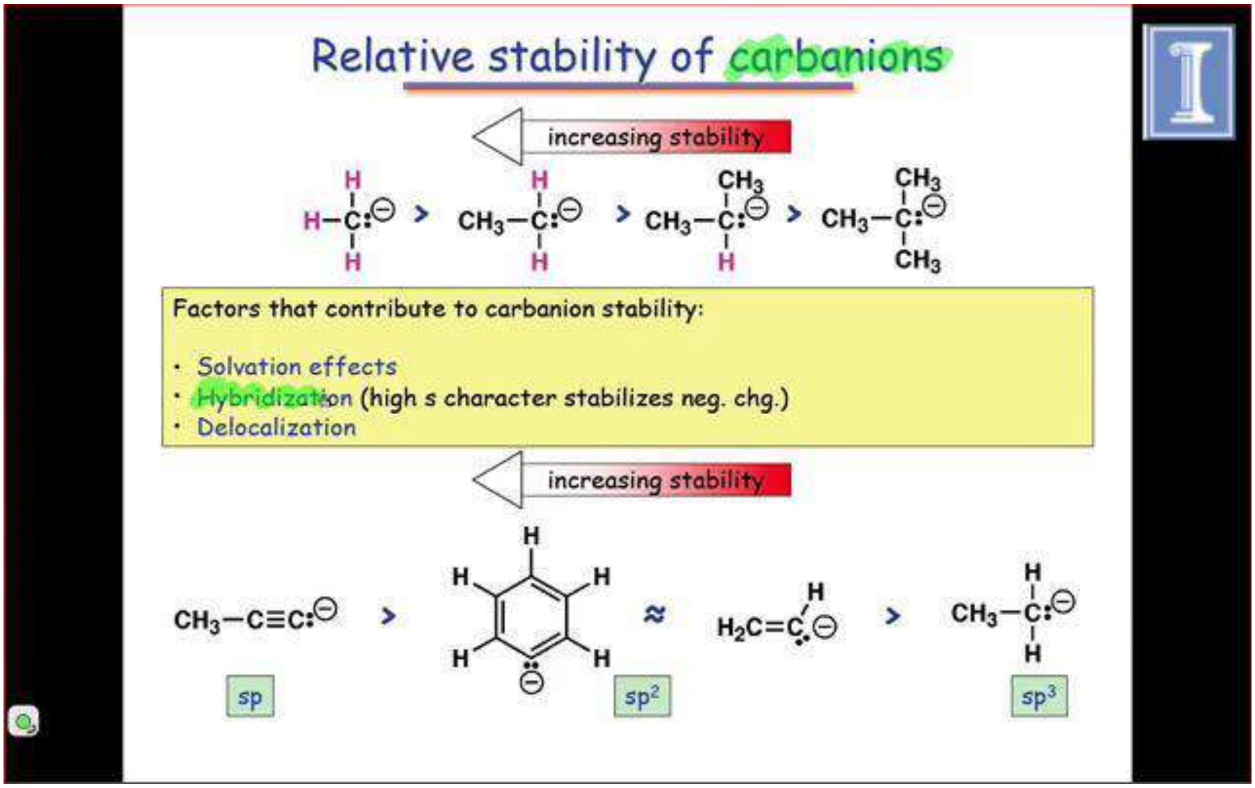
$sp^3 < sp^2 < sp$

[note: these trends are exactly opposite those of carbocations]



$R_3SiC^{\ominus} < R_2NC^{\ominus} < RSC^{\ominus} \ll R\text{-}C(=O)\text{-}C^{\ominus} < R\text{-}S(=O)_2\text{-}C^{\ominus}$

(enolate)



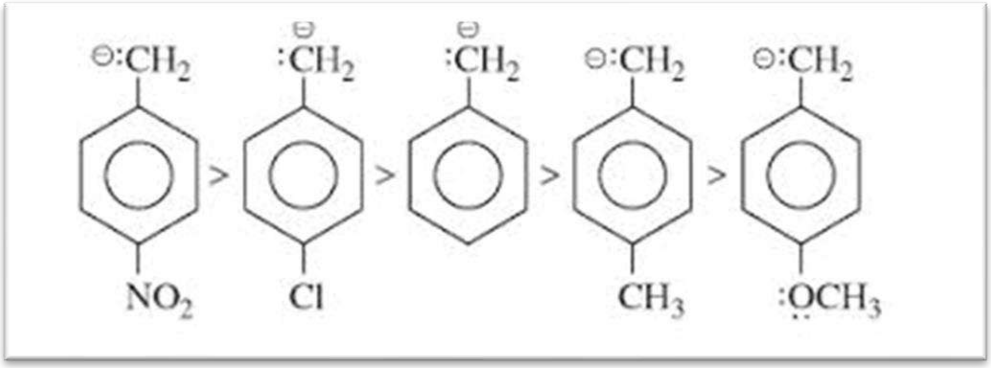
Relative stability of carbanions

increasing stability

Factors that contribute to carbanion stability:

- Solvation effects
- Hybridization (high s character stabilizes neg. chg.)
- Delocalization

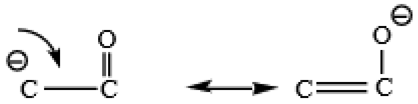
increasing stability

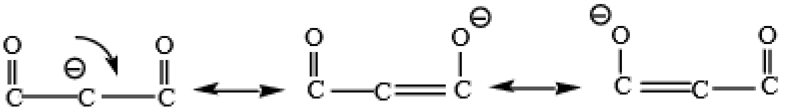


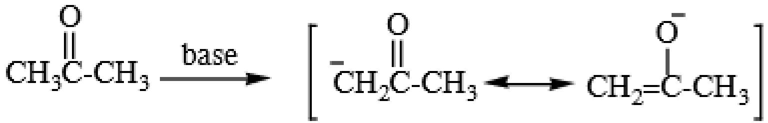
The negative charge on a carbanion is stabilized by neighboring electron withdrawing groups (WEG) such as carbonyl, nitro, and sulfone.

$$EWG = C{=}O \,,\, NO_2 \,,\, CN \,,\, SO_2$$

The stabilizing dispersal of the electrons into the EWG is shown in the examples below. Carbonyl functions are very effective in stabilizing adjacent negative charge and when two carbonyl groups are present (as in diethyl malonate or acetylacetone) a very useful carbanionic intermediate is produced. The intermediate is called an enolate. The dithane system is capable of stablizing the carbanion by dispersal of the charge into the d orbitals of the sulfur atoms.

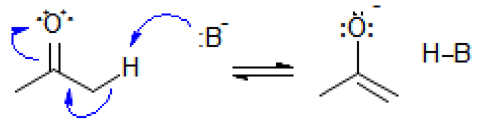


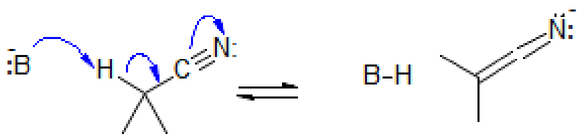


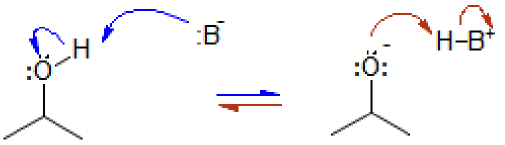


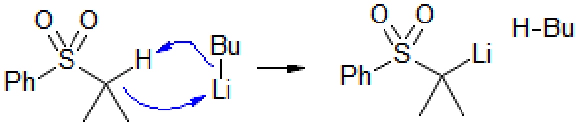
$$CH_3\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightarrow{\text{base}} \left[\,\bar{C}H_2\overset{O}{\overset{\|}{C}}\text{-}CH_3 \longleftrightarrow CH_2{=}\overset{O^-}{\overset{|}{C}}\text{-}CH_3\,\right]$$

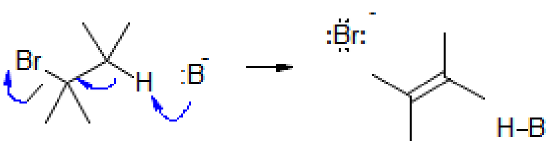
ketone enolate

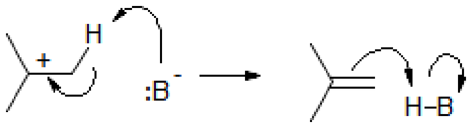


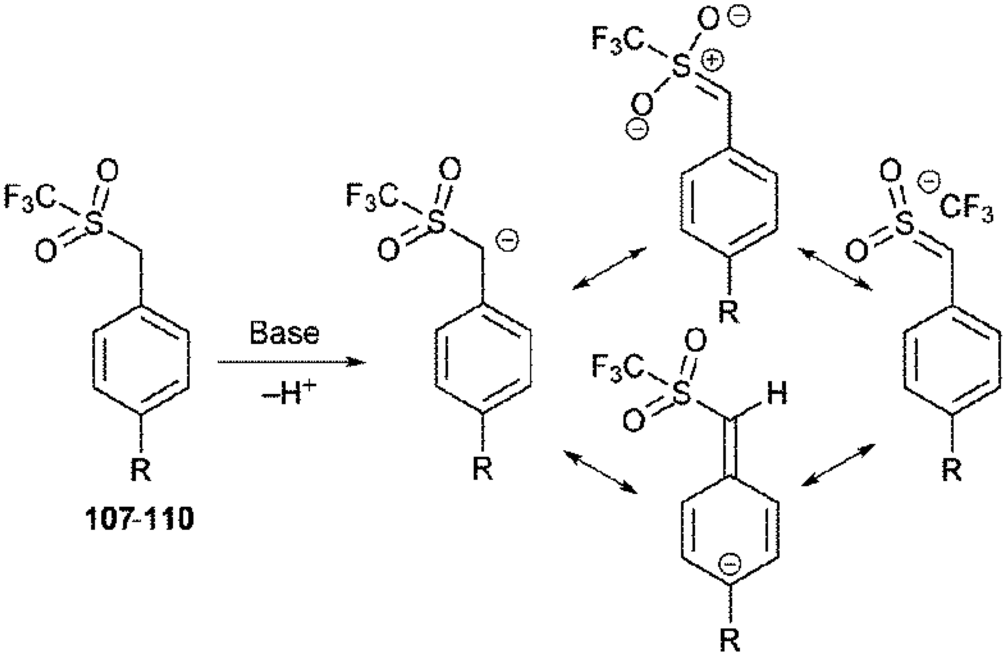






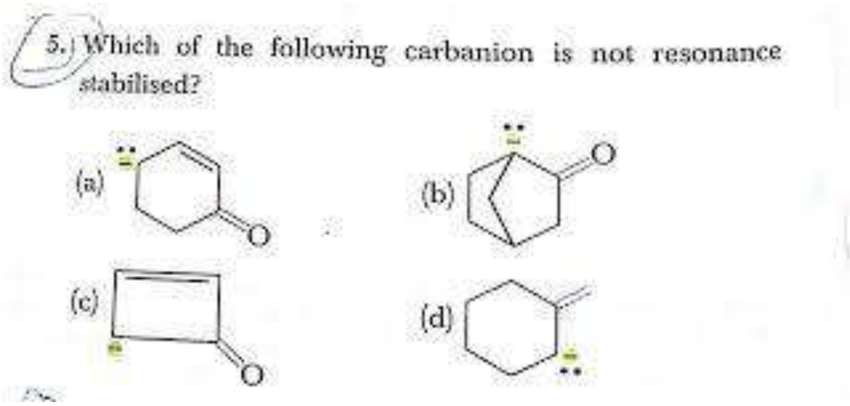






107-110

Compound	R	p*K*a (in DMSO)	p*K*a (in H_2O)
107	H	14.62	/
108	NO_2	9.46	/
109	SO_2CF_3	8.85	11.6
110	$S(O)(NSO_2CF_3)CF_3$	6.45	9.70



5. Which of the following carbanion is not resonance stabilised?

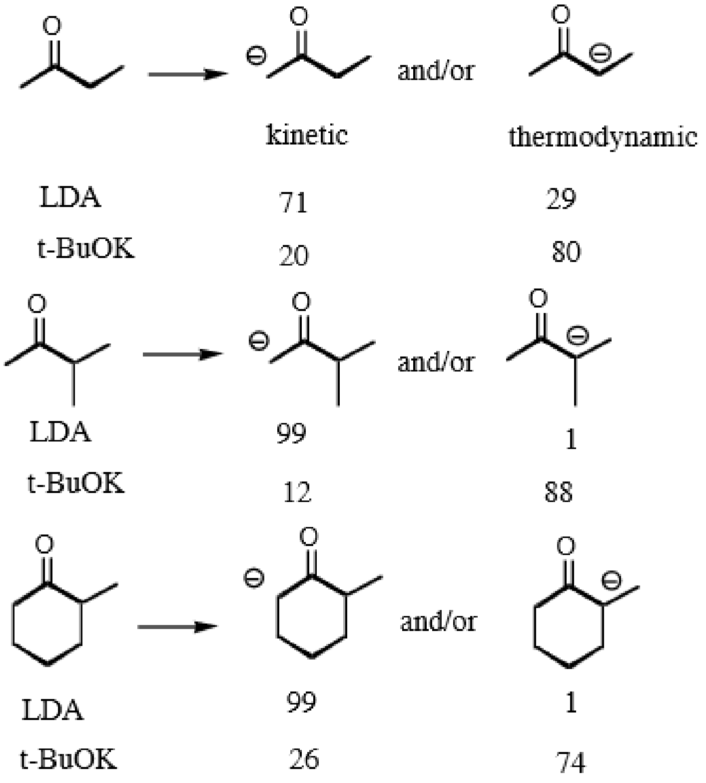
(a)

(b)

(c)

(d)

Whan carbanions are formed in unsymmetrical ketones, two carbanions is possible. One , the more substituted carbanion and more stable, is called the thermodynamic anion; while the least substituted and first formed anions is called the kinteic anion. LDA is a base of choice for formation of kinetic products while hydroxide and alkoxides give the thermodynamic anion.

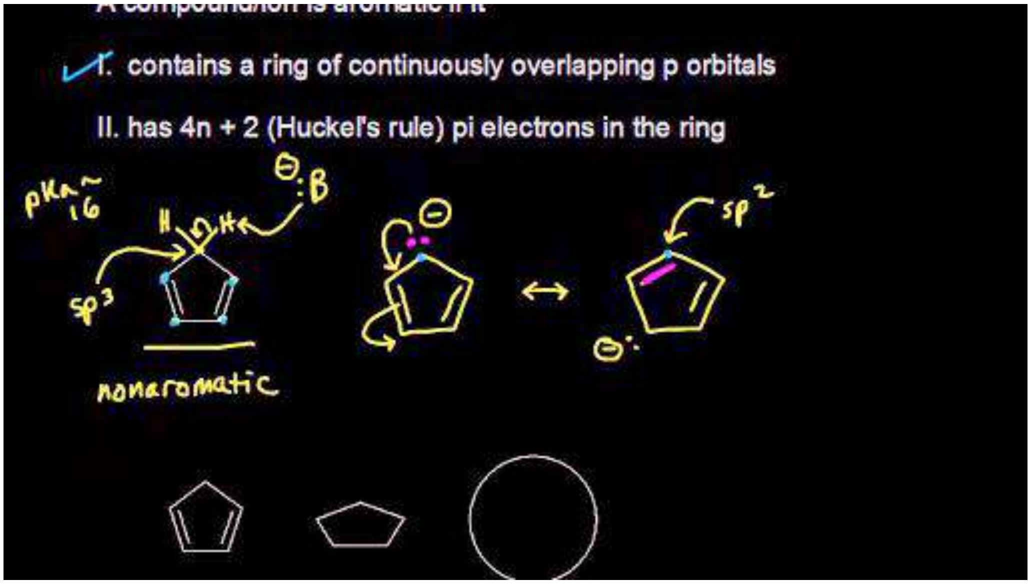


	kinetic	thermodynamic
LDA	71	29
t-BuOK	20	80

LDA	99	1
t-BuOK	12	88

LDA	99	1
t-BuOK	26	74

Stability of Carbanion by aromatization



A compound/ion is aromatic if it

✓ I. contains a ring of continuously overlapping p orbitals

II. has 4n + 2 (Huckel's rule) pi electrons in the ring

Solvents and Bases

The formation of carbanions can occur in several solvent systems. Very strong bases cannot be formed in protic solvents because they abstract a hydrogen atom from the solvent to form a hydrocarbon.

Commonly Used Solvents

Water, Alcohols---polar protic

Ether, THF, Hexane--covalent aprotic

DMSO, DMF, HMPA---polar, aprotic

The strongest bases are obtained from the reaction of metal with organohalogen compounds to give reagents known as Grignard reagents or organolithium reagents.

Bases

Organolithium reagents

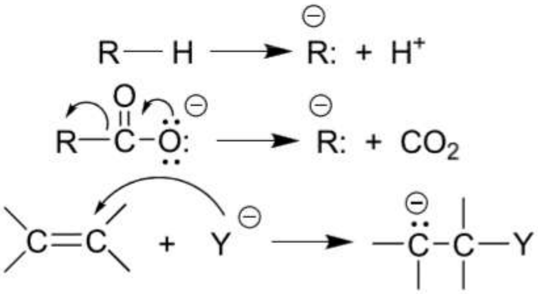
n-BuLi, PhLi, MeLi commercially available

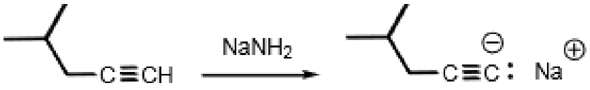
t-BuLi > sec-BuLi> n-BuLi in base strength

II. THE GENERATION AND FATE OF CARBANIONS

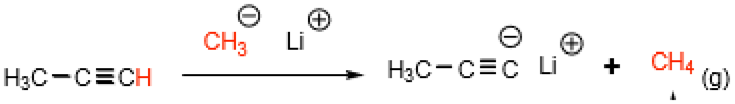
a) A group attached to a carbon leaves without its electron pair.

b) A negative ion adds to a carbon-carbon double or triple bond.



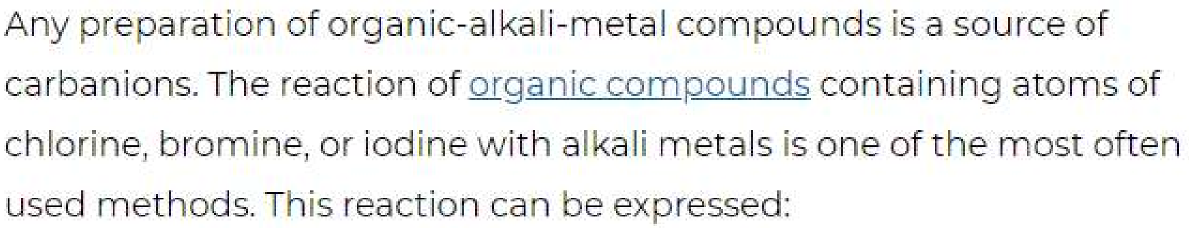


The first step is an acid-base reaction which produces the alkyne conjugate base, or alkynide ion (a nucleophile)

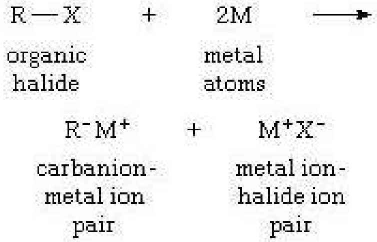


$$H_3C-C\equiv CH \xrightarrow{CH_3^{\ominus}\quad Li^{\oplus}} H_3C-C\equiv C^{\ominus}\quad Li^{\oplus} + CH_4\ (g)$$

c) Reduction of σ bonds



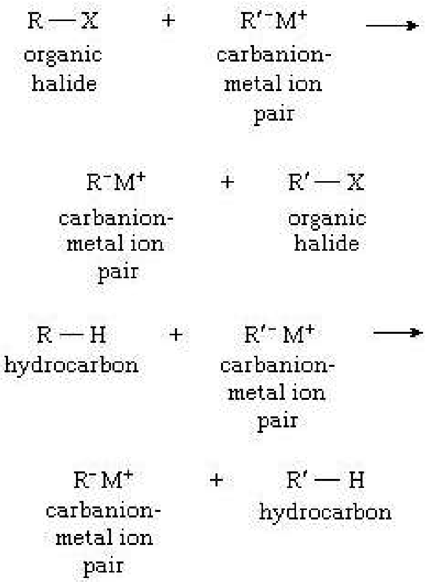
Any preparation of organic-alkali-metal compounds is a source of carbanions. The reaction of organic compounds containing atoms of chlorine, bromine, or iodine with alkali metals is one of the most often used methods. This reaction can be expressed:



$$\underset{\text{organic halide}}{R{-}X} + \underset{\text{metal atoms}}{2M} \longrightarrow \underset{\text{carbanion-metal ion pair}}{R^-M^+} + \underset{\text{metal ion-halide ion pair}}{M^+X^-}$$

in which R is an organic group; X is an atom of chlorine, bromine, or iodine; and M is an atom of an alkali metal.

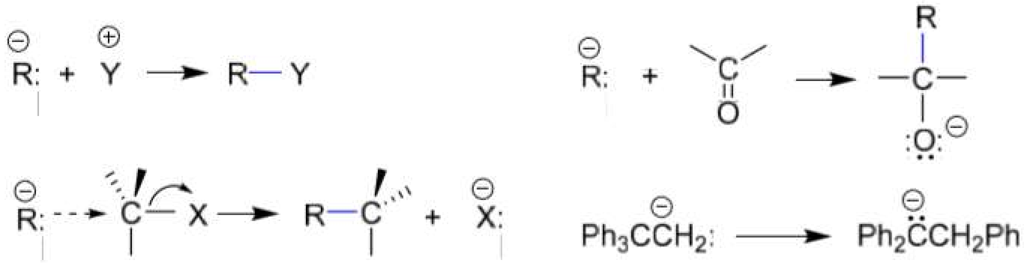
The conversion of one carbanion into another can be accomplished with either hydrocarbons or organic halides, as shown by the equations below:

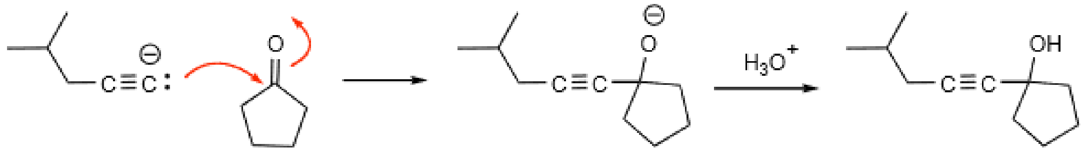


$$\underset{\text{organic halide}}{R-X} + \underset{\text{carbanion-metal ion pair}}{R'^{-}M^{+}} \longrightarrow \underset{\text{carbanion-metal ion pair}}{R^{-}M^{+}} + \underset{\text{organic halide}}{R'-X}$$

$$\underset{\text{hydrocarbon}}{R-H} + \underset{\text{carbanion-metal ion pair}}{R'^{-}M^{+}} \longrightarrow \underset{\text{carbanion-metal ion pair}}{R^{-}M^{+}} + \underset{\text{hydrocarbon}}{R'-H}$$

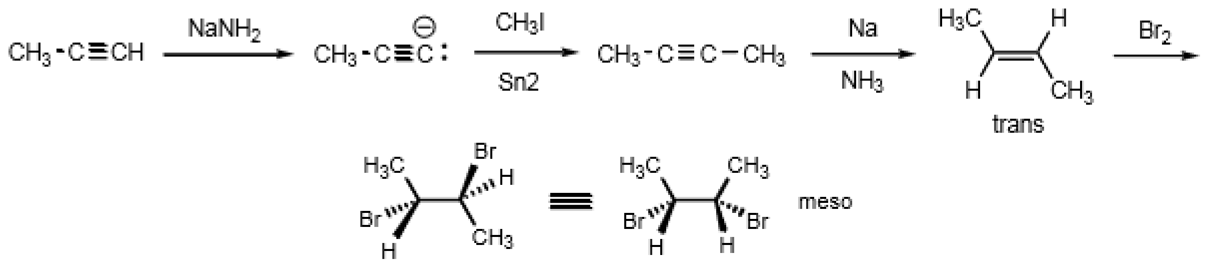
Reactions:

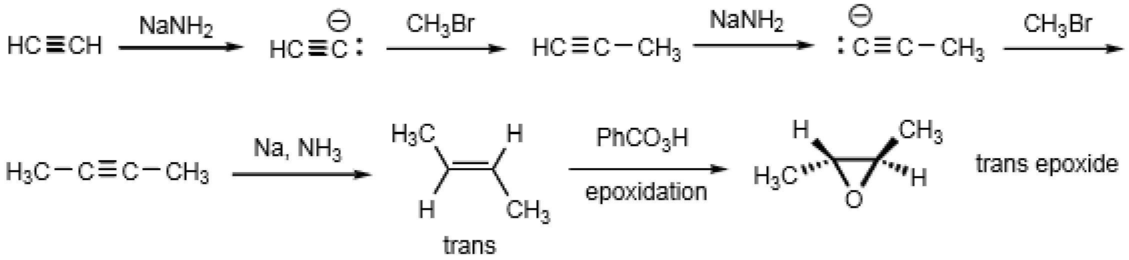


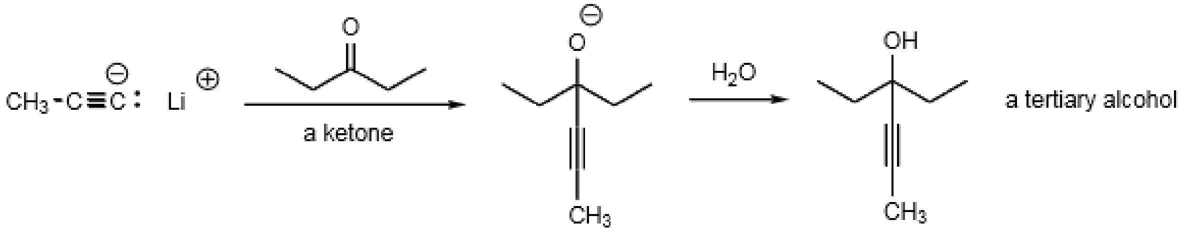


Nucleophilic attack on the ketone gives the alkoxide ion, which is the conjugate base of the 3° alcohol.

3° alcohols are produced from the reaction between carbon nucleophiles and ketones.


NaNH2
CH3I
Sn2
Na
NH3
trans
Br2
meso


NaNH2
CH3Br
NaNH2
CH3Br
Na, NH3
trans
PhCO3H
epoxidation
trans epoxide

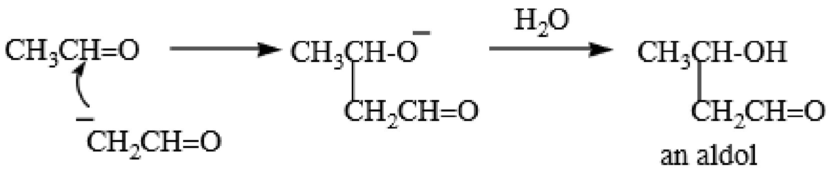

a ketone
H2O
a tertiary alcohol

Enolate Reactions with Carbonyl Groups

Aldol Condensation

An aldehyde or ketone that has a hydrogen next to the carbonyl group, an a-hydrogen, can form an enolate in basic solution, and the enolate can react by nucleophilic addition at the carbonyl group of another molecule. This process is a very important synthetic procedure and is known as the **Aldol Condensation.** The final product from aliphatic aldehydes or ketones contains both a carbonyl and an alcohol group. The product is called an aldol.

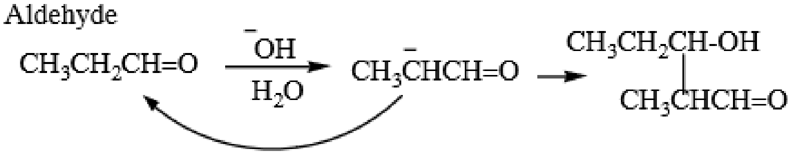
$$CH_3CH{=}O \xrightarrow{^-OH} {}^-CH_2CH{=}O \longleftrightarrow CH_2{=}CH\text{-}O^-$$



$$CH_3CH{=}O + {}^-CH_2CH{=}O \longrightarrow \underset{CH_2CH=O}{CH_3CH\text{-}O^-} \xrightarrow{H_2O} \underset{CH_2CH=O}{CH_3CH\text{-}OH}$$

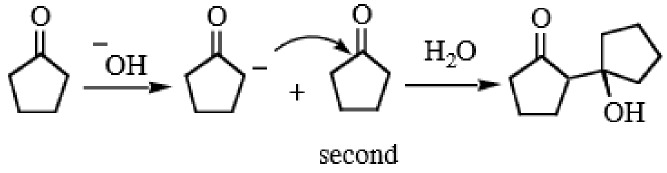
Some examples of the aldol condensation from aldehydes and ketones are shown below.

Aldehyde

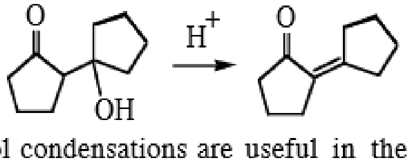


$$CH_3CH_2CH{=}O \xrightarrow[H_2O]{^-OH} CH_3\overset{-}{C}HCH{=}O \longrightarrow \underset{CH_3CHCH=O}{CH_3CH_2CH\text{-}OH}$$

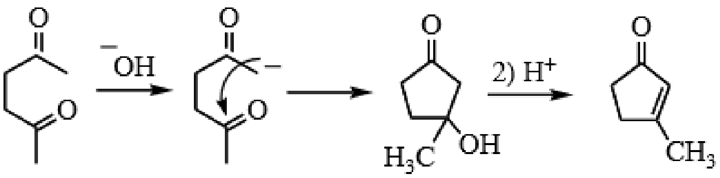
Ketone



The aldol products react readily with acid to undergo dehydration and give α,β-unsaturated carbonyl compounds that are also very useful in synthetic organic and biological chemistry.

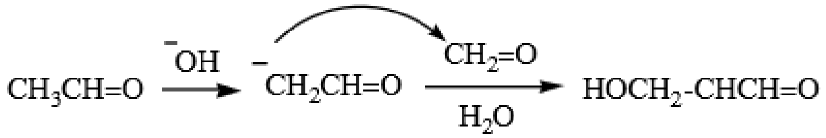


Intramolecular aldol condensations are useful in the formation of cyclic α,β-unsaturated ketones.

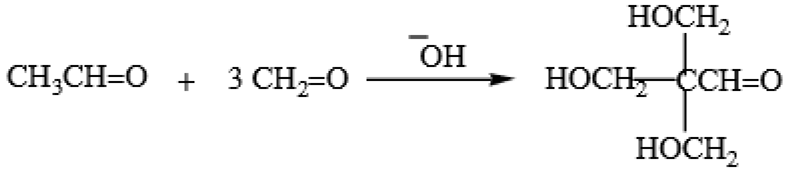


Crossed-Aldol Condensation

The main aldol condensation involves reaction between two aldehydes or ketones of the same structure. But, the procedure can be modified so that the enolate can react with another aldehyde of different structure. The requirement is that the other aldehyde has to be more reactive than the first and it contains no a-hydrogens. Formaldehyde, $CH_2C{=}O$, and benzaldehyde, PhCH=O, both meet these requirements and are useful in this procedure called the crossed-aldol condensation. All three of the α-hydrogens in acetaldehyde can react in a crossed-aldol condensation with formaldehyde.

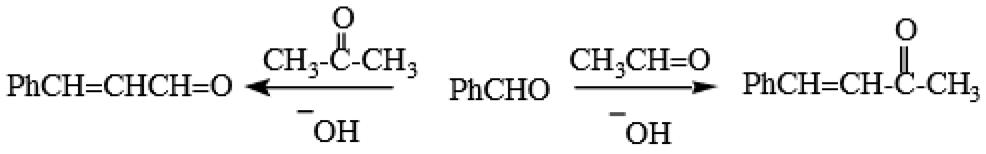


$$CH_3CH{=}O \xrightarrow{{}^-OH} {}^-CH_2CH{=}O \xrightarrow[H_2O]{CH_2{=}O} HOCH_2\text{-}CHCH{=}O$$



$$CH_3CH{=}O \;+\; 3\,CH_2{=}O \xrightarrow{{}^-OH} HOCH_2-\overset{\displaystyle HOCH_2}{\underset{\displaystyle HOCH_2}{C}}CH{=}O$$

Aromatic ketones bearing α-hydrogens give aldol reaction products readily, but in this case the aldol product spontaneously loses water to form the unsaturated ketone. When benzaldehyde is used in the crossed-aldol condensation the final product is the unsaturated aldehyde or ketone. Conjugation of the double bond with the aromatic ring is the reason for the spontaneous dehydration.

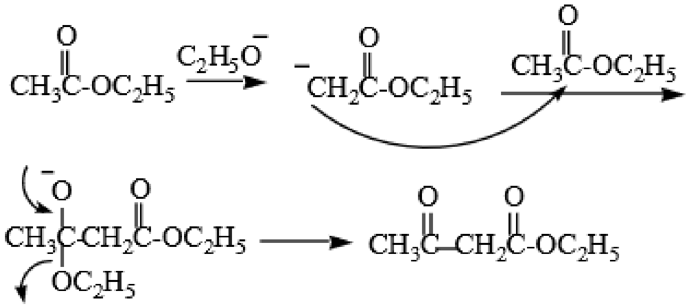


$$PhCH{=}CHCH{=}O \xleftarrow[{}^-OH]{CH_3\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}CH_3} PhCHO \xrightarrow[{}^-OH]{CH_3CH{=}O} PhCH{=}CH\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}CH_3$$

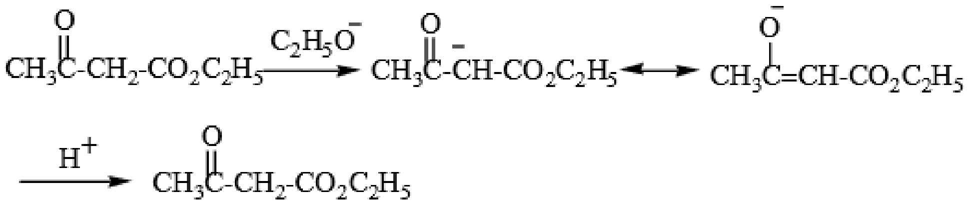
Esters

Claisen Condensation

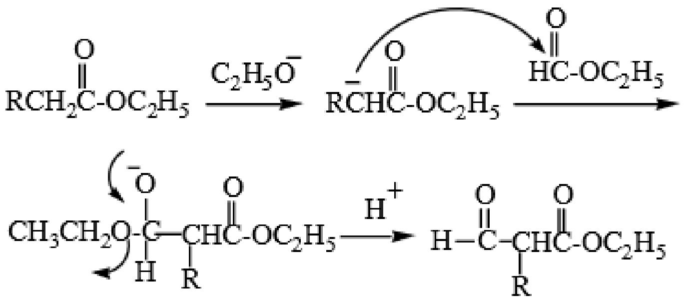
Esters, like aldehydes and ketones, give an aldol-type reaction. The a-hydrogen of the ester is removed by base to give the enolate. The enolate reacts with another molecule of the ester in an addition-elimination reaction characteristic of esters, which appears as displacement of the alkoxide. The resulting product is a β-ketoester. The reaction is known as the **Claisen condensation.**



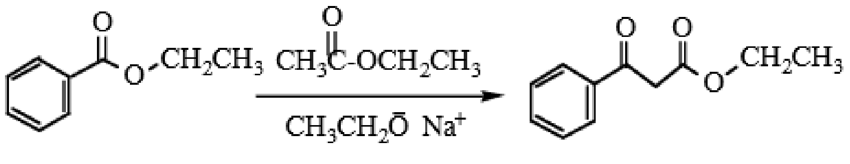
The α-hydrogens in the product β-ketoester are more acidic than the α-hydrogens in the starting ester. Thus a new enolate is formed that is more stable than the first enolate, thus helping the reaction go to completion.



Crossed-Claisen condensation occurs when a highly reactive ester with no α-hydrogens reacts with the enolate derived from another ester. Ethyl benzoate and ethyl formate are two frequently used esters that have no α-hydrogens.

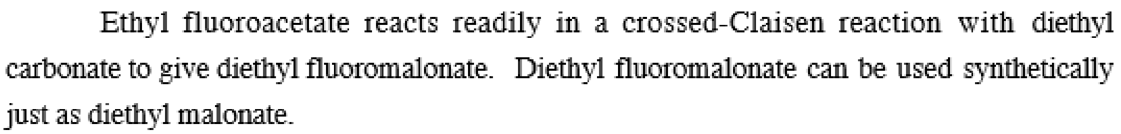


Claisen condensation of ethyl benzoate with ethyl acetate affords ethyl benzoylacetate in the crossed-Claisen method.

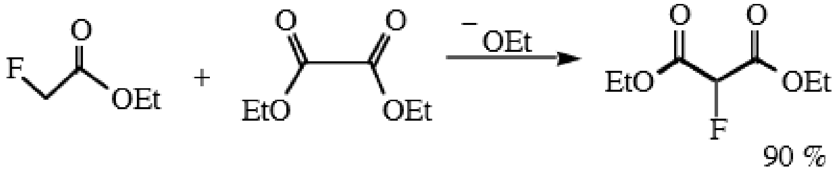


Intramolecular Claisen condensations go by the name of Dieckmann condensations and are useful for the preparation of five and six-membered rings.

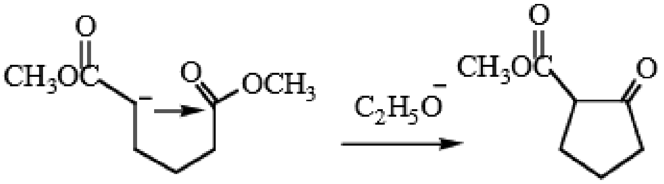
The **Dieckmann condensation** is the intramolecular chemical reaction of diesters with base to give β-keto esters. The equivalent intermolecular reaction is the Claisen condensation.

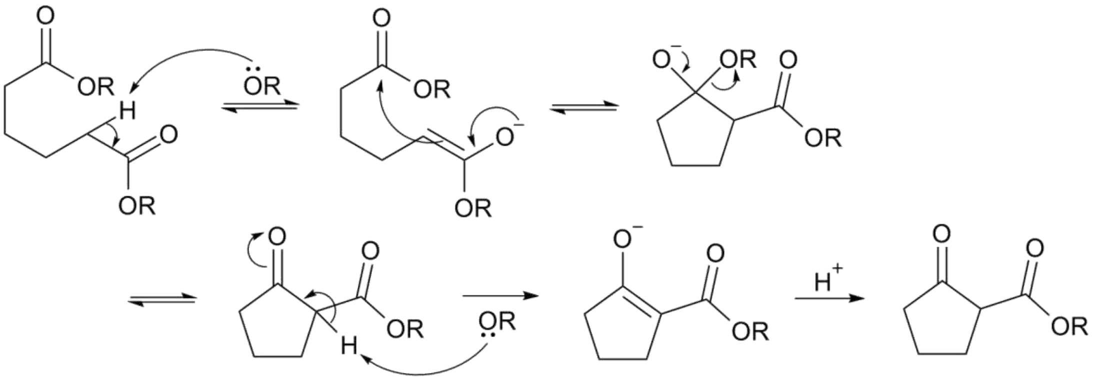


Ethyl fluoroacetate reacts readily in a crossed-Claisen reaction with diethyl carbonate to give diethyl fluoromalonate. Diethyl fluoromalonate can be used synthetically just as diethyl malonate.



Dieckmann condensation



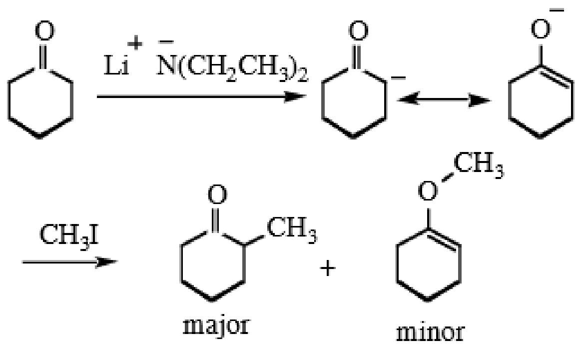


Deprotonation of an ester at the α-position generates an enolate ion which then undergoes a 5-exo-trig nucleophilic attack to give a cyclic enol. Protonation with a Brønsted-Lowry acid (H_3O^+ for example) re-forms the β-keto ester.

Enolate Anion Alkylation Reactions

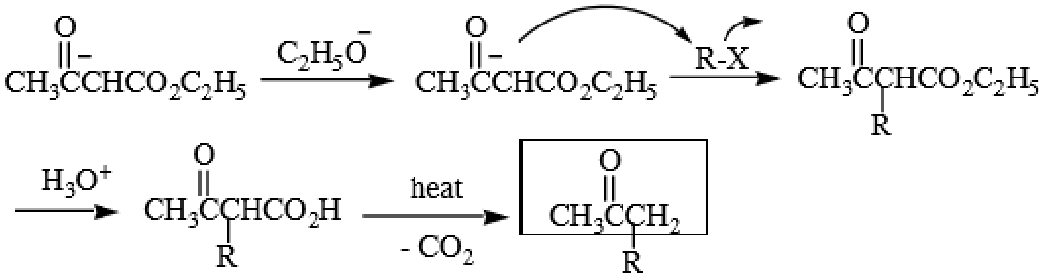
General Reaction

When strong anhydrous bases such as sodium hydride, sodamide or lithium diethylamide $LiN(C_2H_5)_2$, are used to prepare the enolate anions at low temperatures, the resulting enolate reacts very slowly with carbonyl groups and can be used as nucleophiles in the S_N2 reaction with primary alkyl halides. In the resonance stabilized enolate, a negative charge exists on both a carbon and an oxygen. Both sites are possible nucleophiles in the reaction but the carbon nucleophile predominates because it is a stronger nucleophile, but minor products from O-alkylation are found.



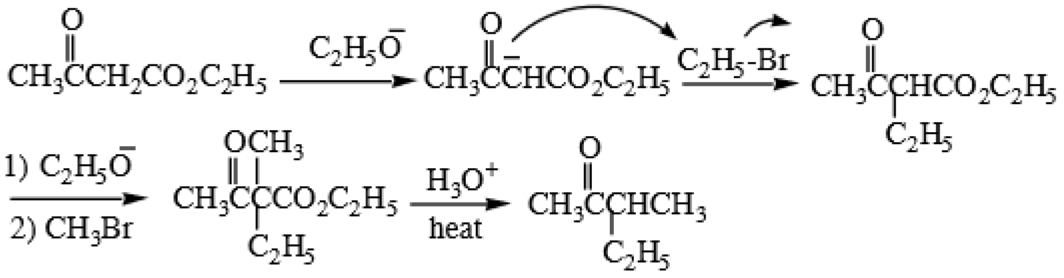
Ethyl Acetoacetate

The a-hydrogens of ethyl acetoacetate are acidic enough (pKa =11) to be removed by a variety of bases. The enolate anion can be used to displace a halogen in an alkyl halide. Hydrolysis of the product gives a β-ketoacid which loses CO_2 on mild heating. A derivative of acetone is the final product.



substituted acetone

Double alkylation of ethyl acetoacetate in sequential steps can provide a synthesis of highly branched derivatives of acetone after the hydrolysis and decarboxylation steps.

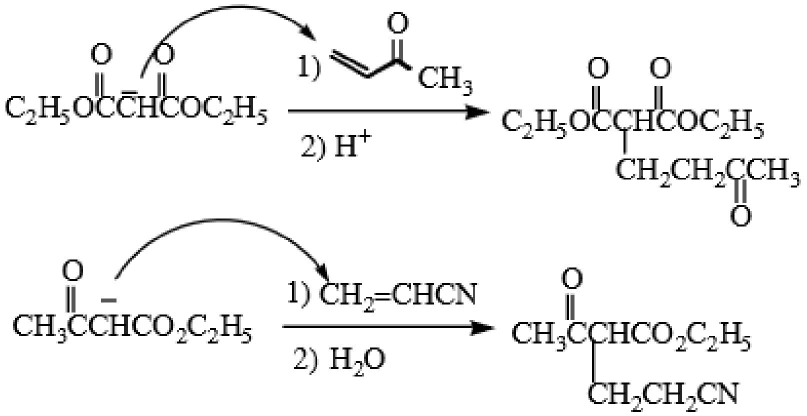


The Michael Reaction

Enolate Addition

Enolates may also be alkylated with α,β-unsaturated carbonyl substrates. The enolate adds in the 1,4 fashion to give a unit extended by three carbon atoms in a process known as the Michael reaction. Many α,β-unsaturated carbonyl systems may be prepared by the dehydration of aldol products. Examples of the Michael reaction using methyl vinyl ketone and acrylonitrile, two common units in the reaction, are shown below.

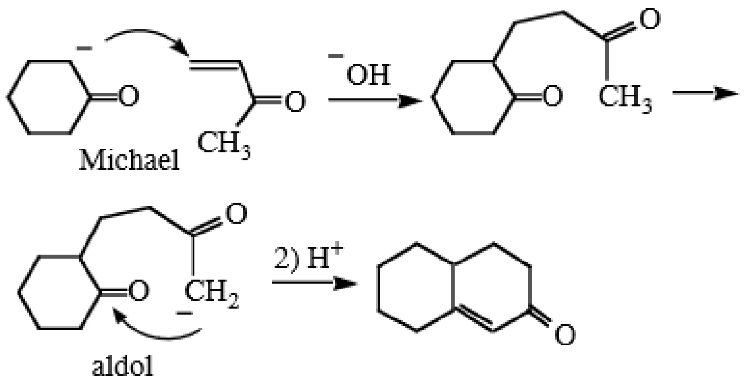
Michael Reaction



Robinson Ring-forming Reaction

A unique reaction that produces a new ring containing an a,b-unsaturated ketone is the Robinson reaction. When an enolate derived from a ketone reacts with methyl vinyl ketone, the enolate adds in the Michael reaction, then a second enolate in the ketone product is formed that cyclizes in an Aldol condensation to give the final product.

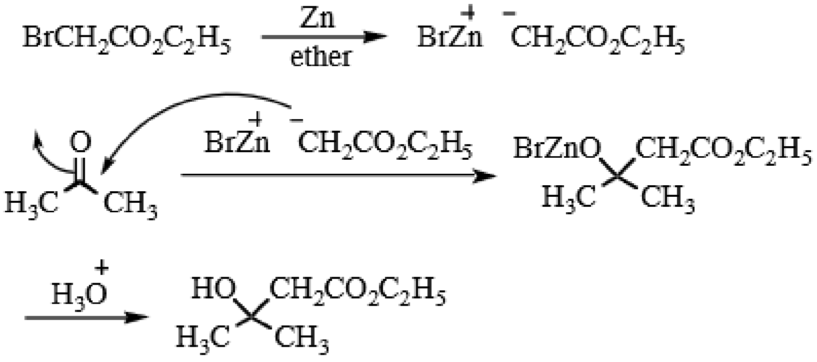
Robinson Reaction



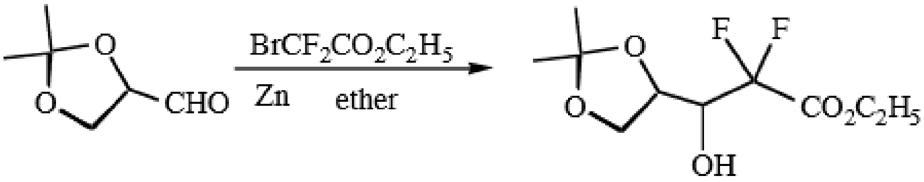
Reformatsky Reaction

Instead of forming the enolate from an α-hydrogen, an α-bromine atom can also be used. Zinc reacts with ethyl α-bromoacetate to form a zinc enolate that reacts at the carbonyl function of aldehydes and ketones to produce α,β-hydroxyester. The method is made easier by addition of the bromoester to a mixture of zinc and the carbonyl compound.

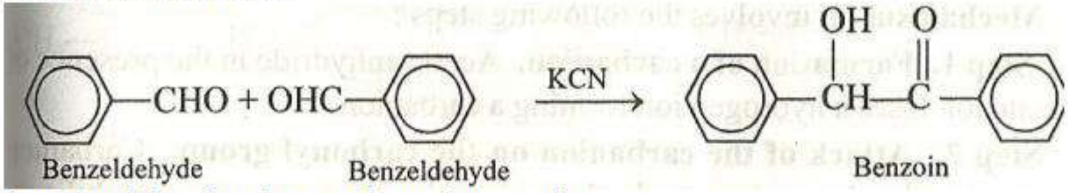
Reformatsky Reaction



Ethyl bromodifluoroacetate is used frequently in Reformatsky procedures to give high yields of alcohol products.

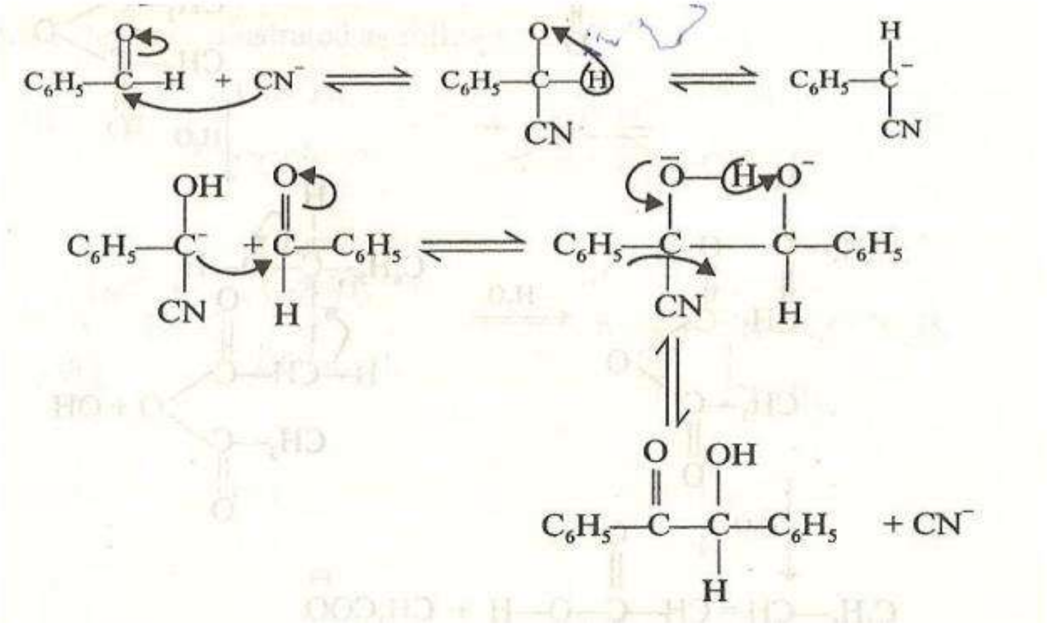


Benzoin condensation

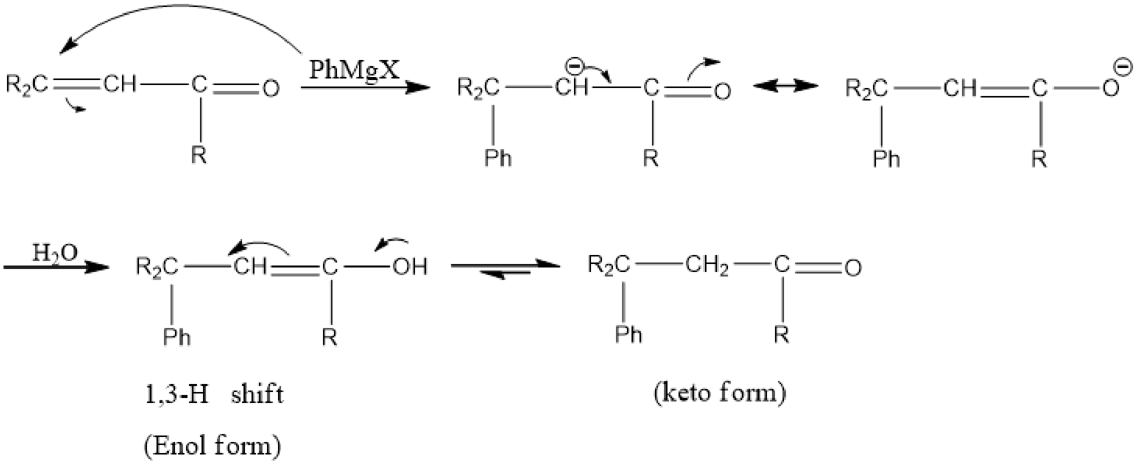


Step 1and 2 as in other condensation reactions.

Step 3, loss of CN^- ion



A **1**,**4**-addition is also called a **conjugate addition**



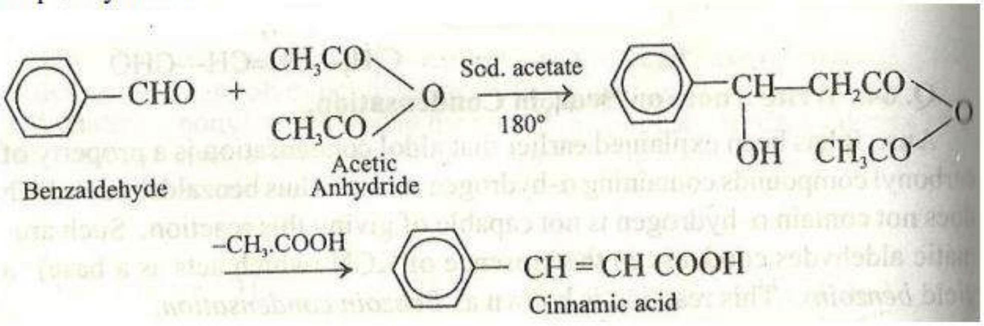
Perkins reaction

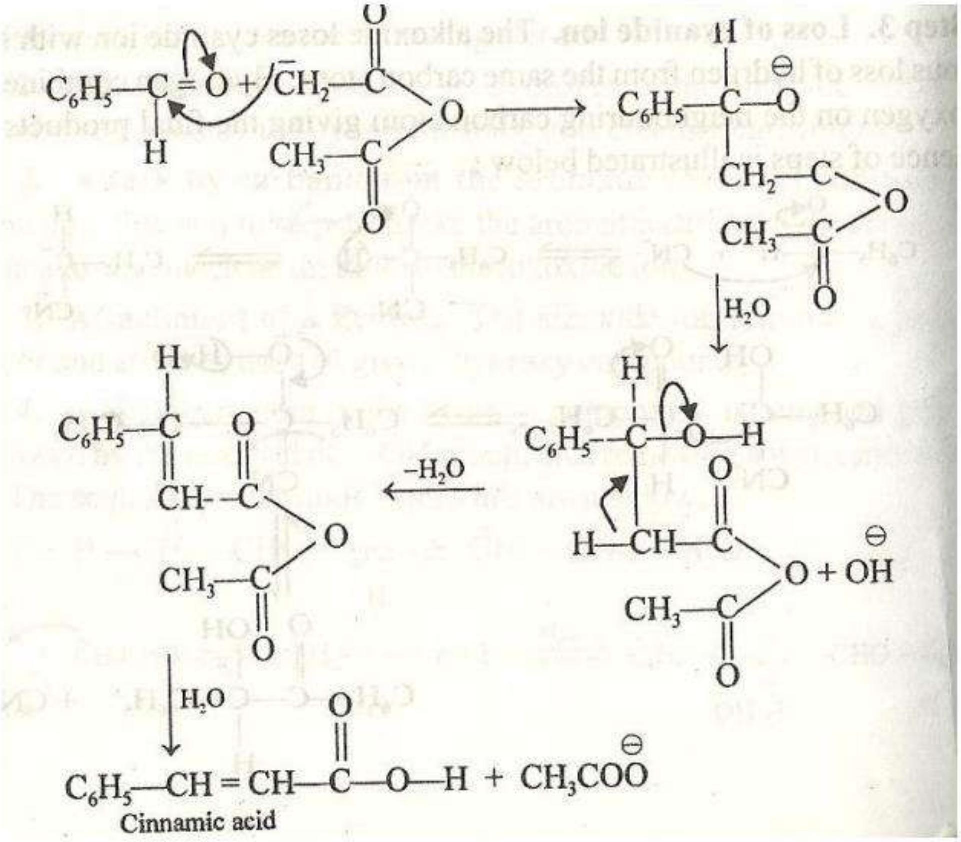
Step 1-2 as in others

Step 3: protonation of the alkoxide ion to form an aldol type compound.

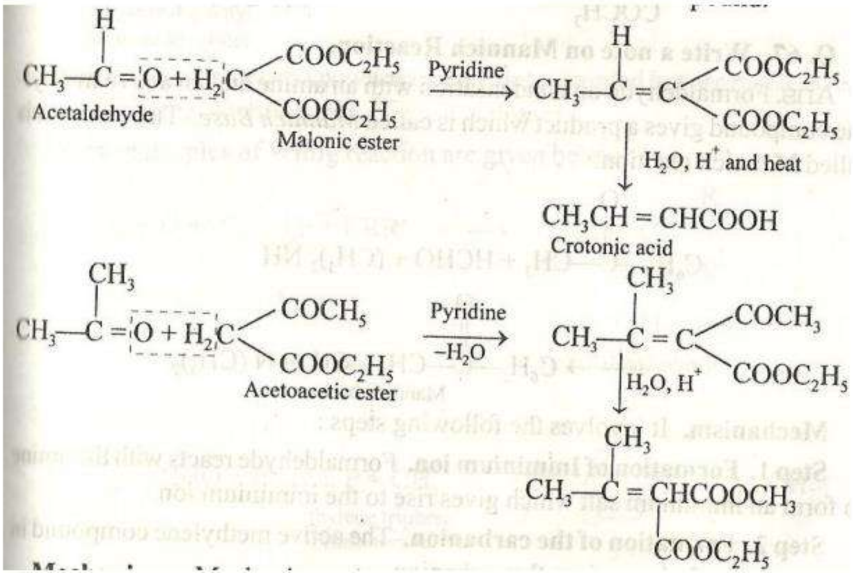
Step 4: dehydration, the hydroxyl group and neighbouring hydrogen are removed as water.

Step 5: hydration





Knoevenagal reaction

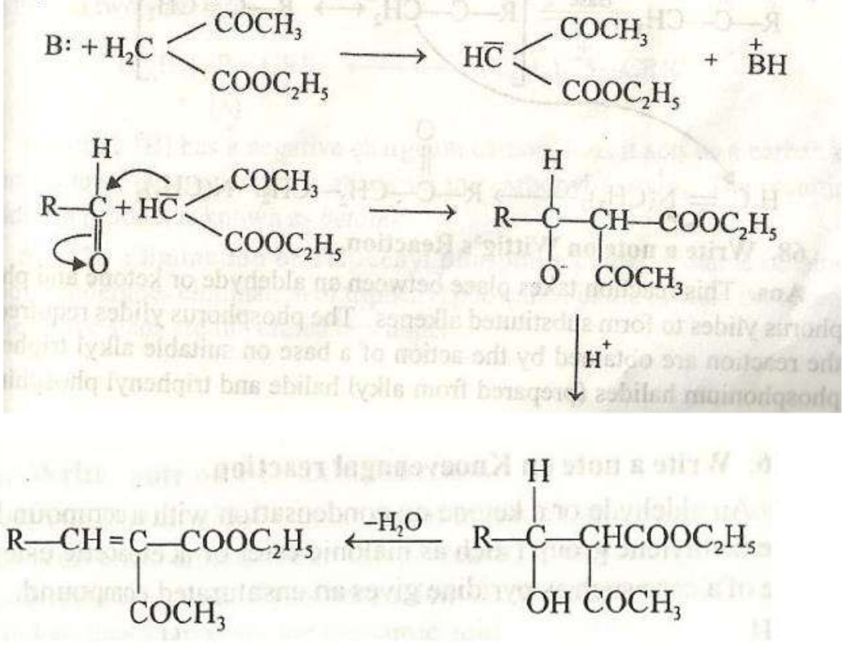


Mechanism

Step 1-2 as explained in other reactions

Step 3: protonation: - alkoxide accepts a proton to form hydroxyl compound.

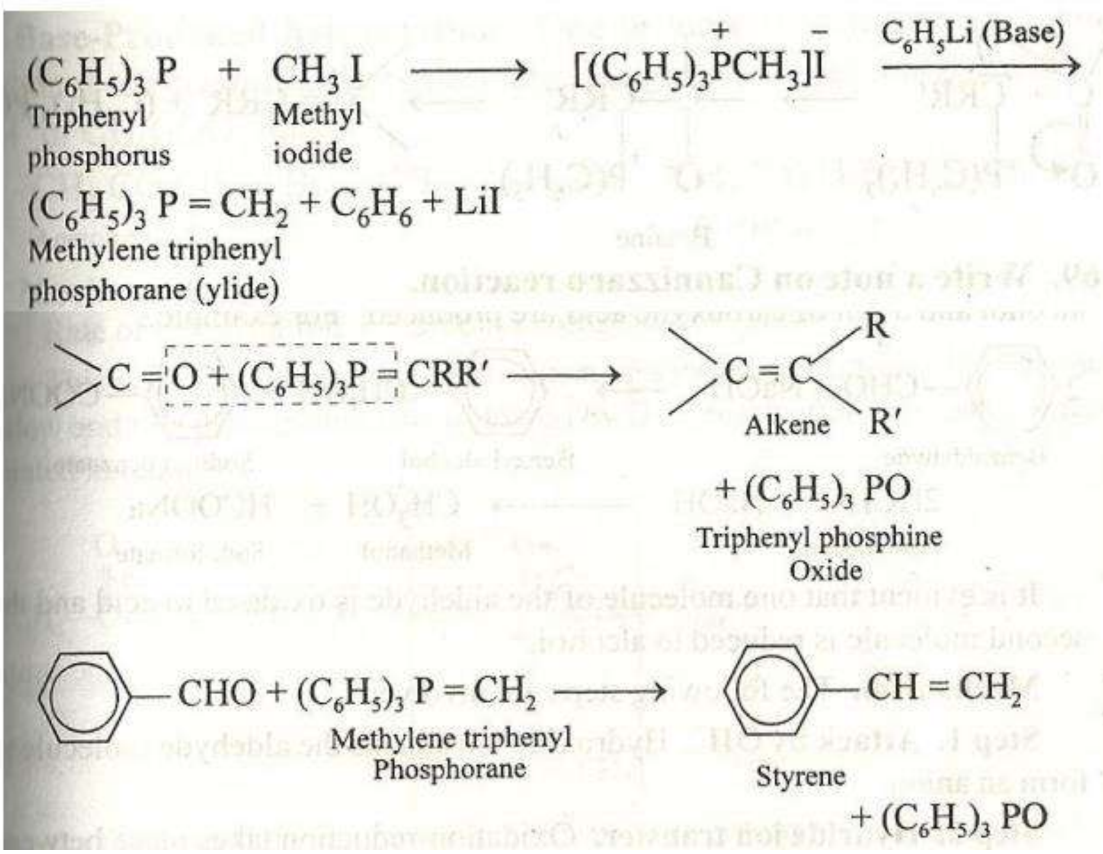
Step 4: involves dehydration



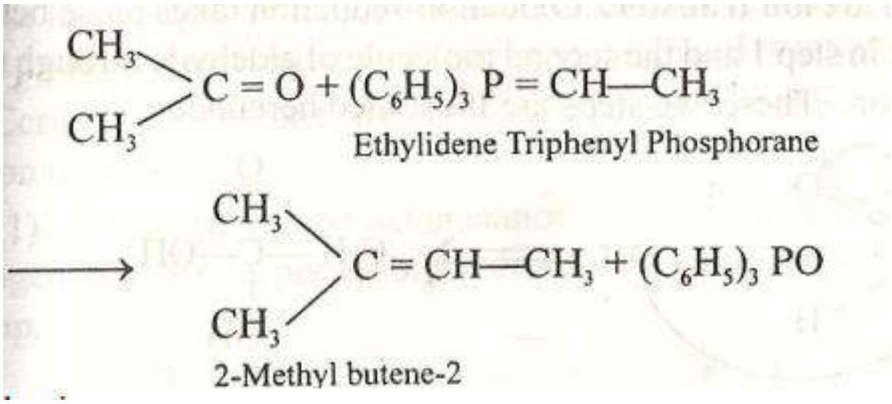
Witting's reaction

Reaction occurs between an aldehyde/ketone and phosphorous ylides to form substituted alkenes.

Phosphorous ylide is prepared by reacting a base with an alkyl triphenyl phosphonium halide as shown below



$$(C_6H_5)_3P + CH_3I \longrightarrow [(C_6H_5)_3\overset{+}{P}CH_3]\overset{-}{I} \xrightarrow{C_6H_5Li\ (Base)} (C_6H_5)_3P = CH_2 + C_6H_6 + LiI$$



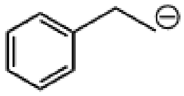
Rearrangements of Carbanions

Homoallylic rearrangements

The structures below represent allylic, homoallylic and homobenzylic. The "homo" means that there is one additional carbon atom. Some interesting rearrangements occur with the homoallylic systems.

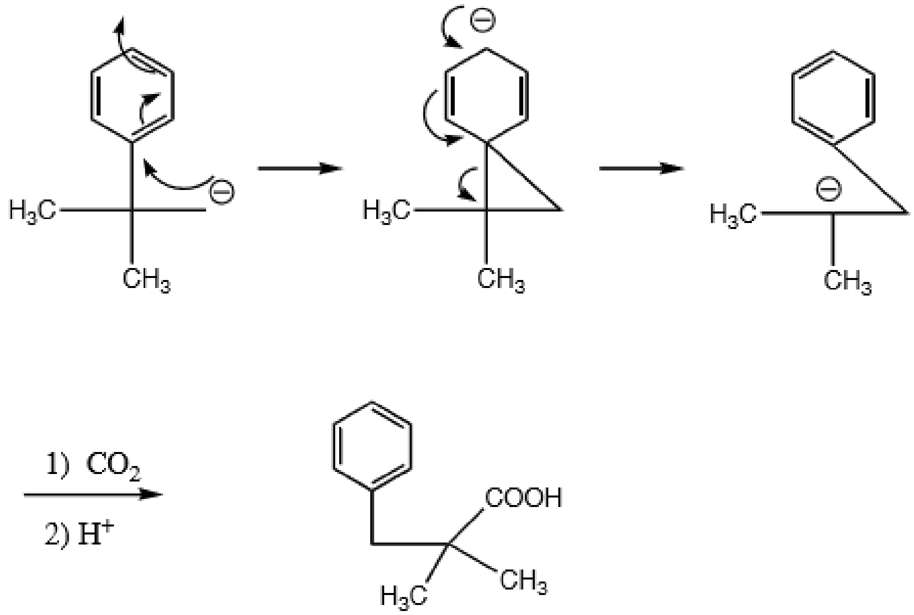
allylic

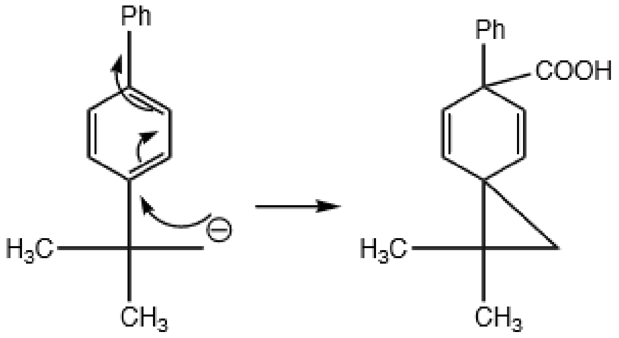
homoallylic



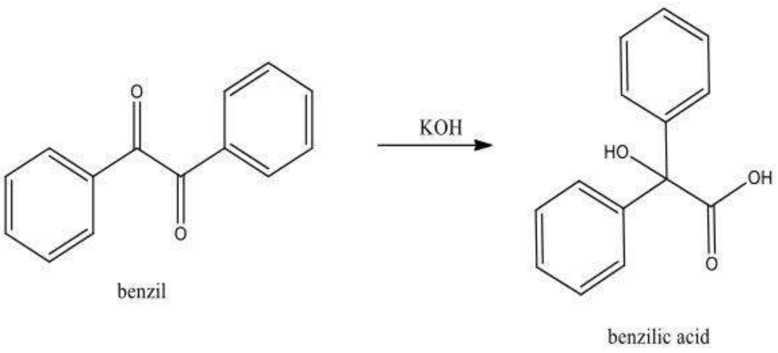
homobenzylic

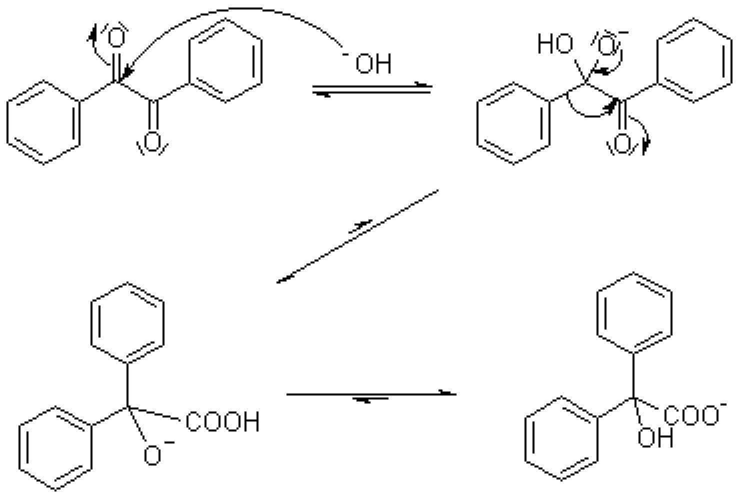
The examples below show a homobenzylic rearrangement where the carbanion interacts with the aromatic ring. The carbanion appears to insert between the ring and the carbon containing the two methyl groups. The mechanism of the rearrangement is proven by isolation of the cyclopropane structure when a para phenyl group is present.



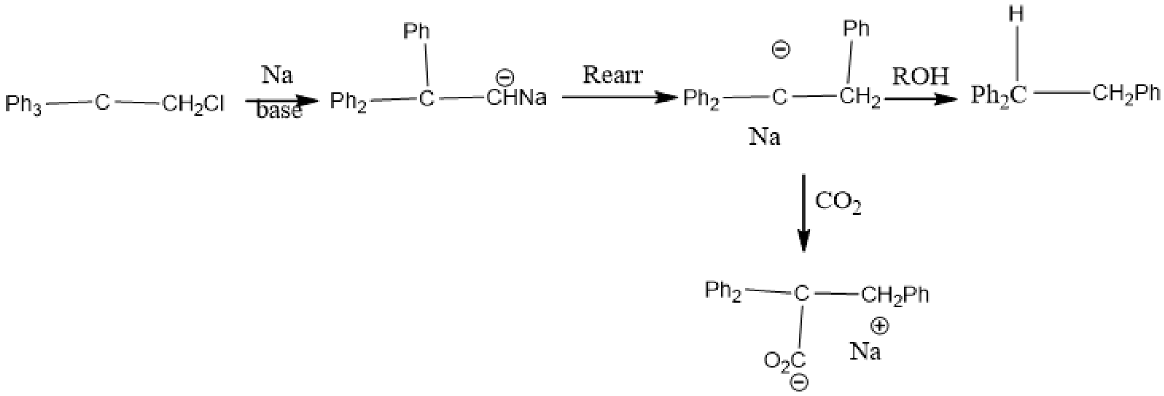


Rearrangement of benzilic acid

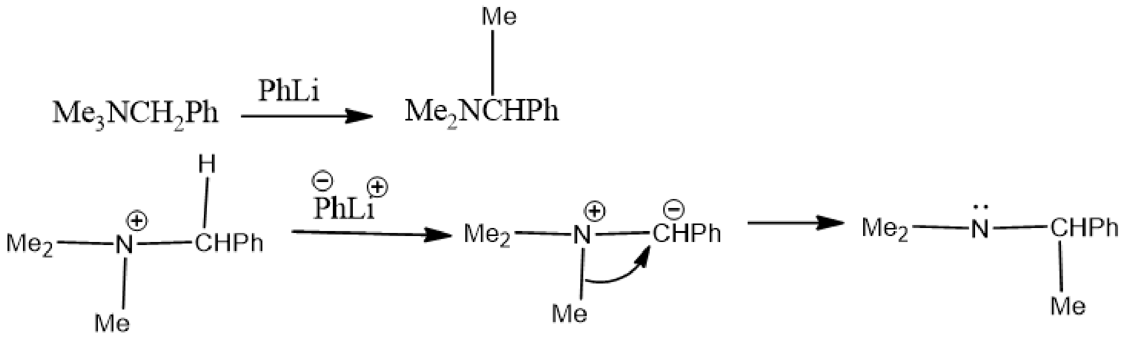




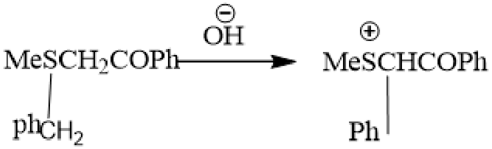
1, 2 aryls shift an adjacent carbon atom (carbon 1)

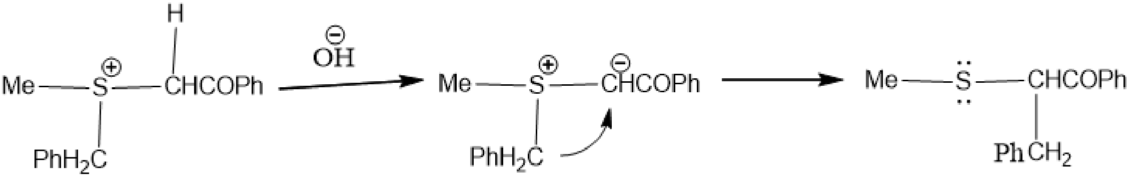


1, 2 alkyls shift from N to carbanion

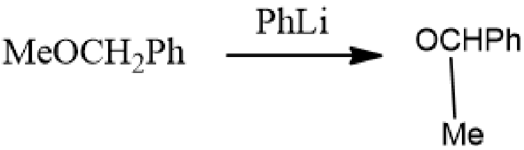


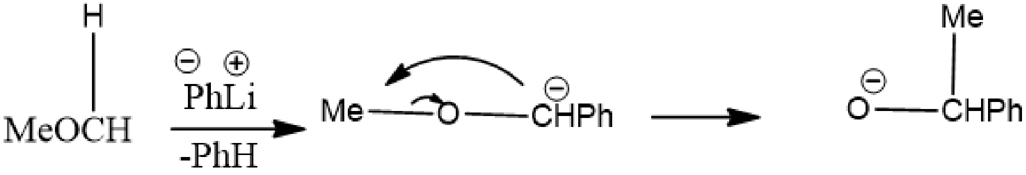
1, 2 alkyls shift from S to carbanion





1, 2 alkyls shift from O to carbanion



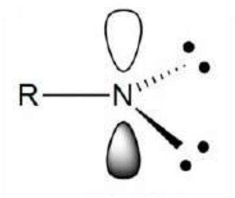


Nitrene

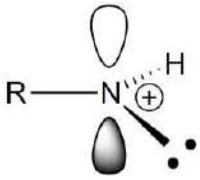
Structure & hybridization

Nitrenes are nitrogen analogues of carbenes. The nitrogen atom possesses only six valence electrons; in nitrenes the triplet state is lower in energy than the singlet state.

- Additionally, nitrenes can be protonated to give nitrenium ions that are isoelectronic with carbenes.

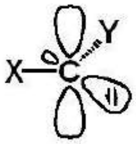


singlet

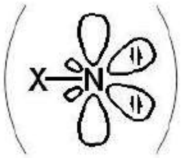


nitrenium ion

Singlet and Triplet States

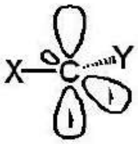


Singlet

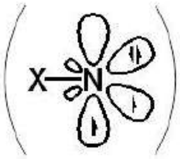


Singlet

- sp^2 hybridized carbon
- non-bonding electrons have opposite spin - occupy an sp^2 orbital
- XCY angle 100-110°



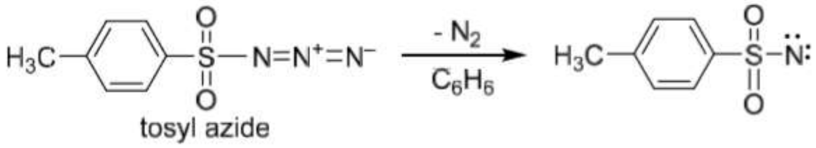
Triplet



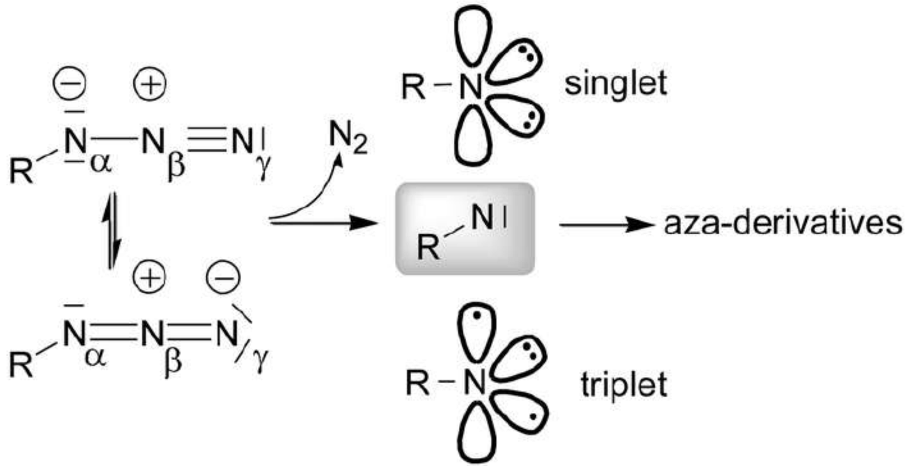
Triplet

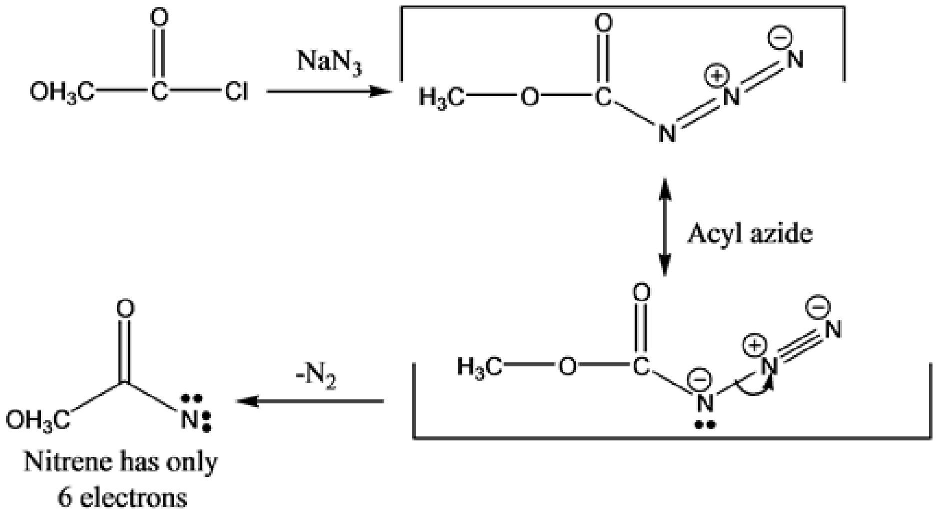
- sp^2 hybridized carbon (or sp?)
- non-bonding electrons have same spin – occupy an sp^2 and p orbital
- XCY angle 130-150°

- Formation of nitrenes
- from thermolysis or photolysis of azides.
- from isocyanates, with expulsion of CO.

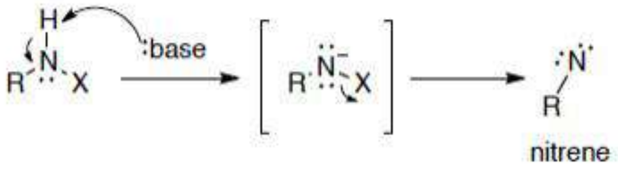


$$R{-}N{=}C{=}O \xrightarrow{-\,CO} R{-}\ddot{N}:$$



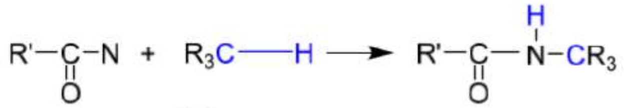


From 1,1-elemination

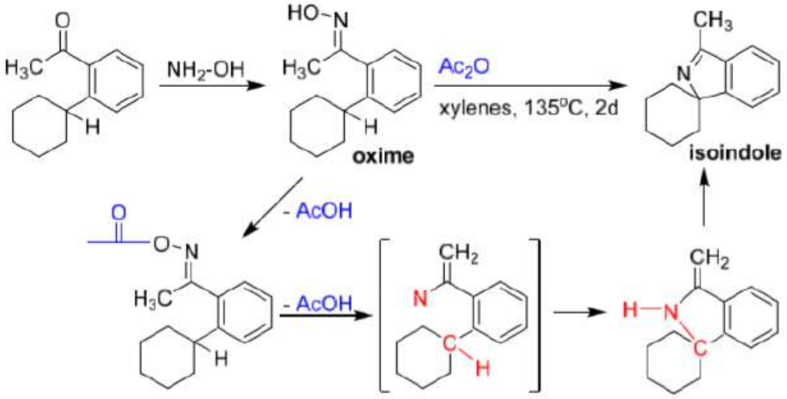


REACTIONS OF NITRENE

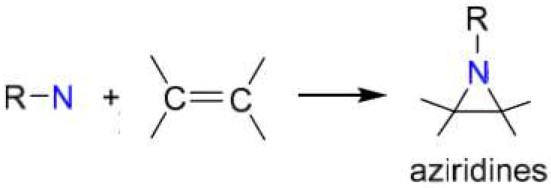
- **Nitrene C-H insertion.** A nitrene can easily insert into a C-H bond yielding an amine or amide.

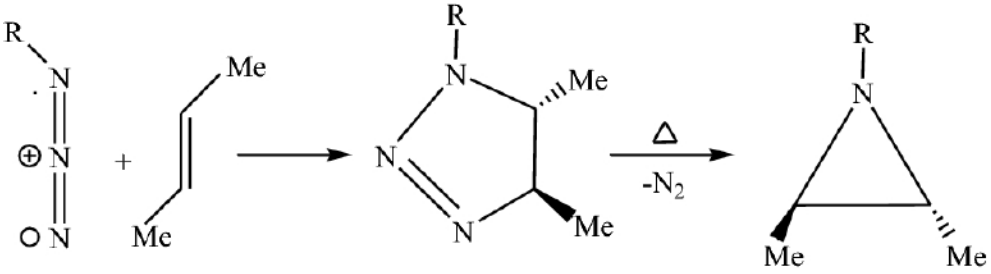


$$R'-\underset{\underset{O}{\|}}{C}-N + R_3C-H \longrightarrow R'-\underset{\underset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-CR_3$$



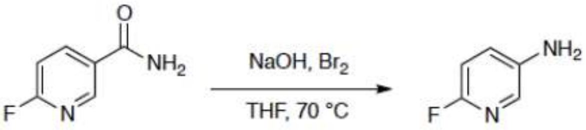
- **Nitrene cycloaddition.** With alkenes, nitrenes react to aziridines.



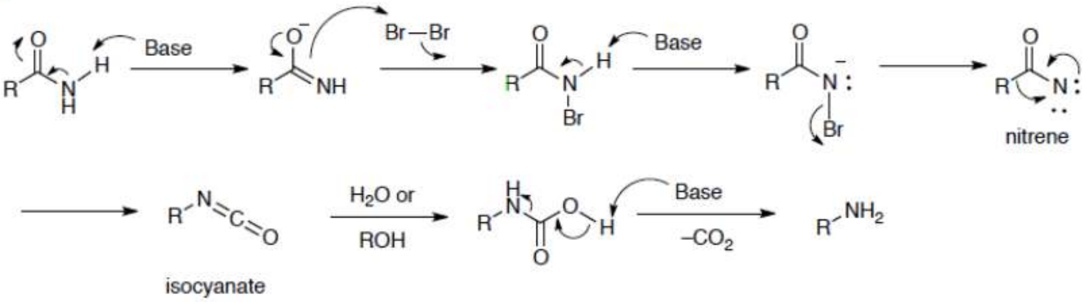


Rearrangements

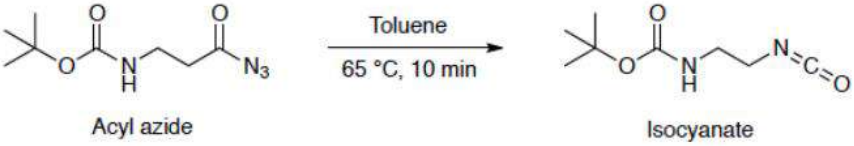
Hoffman rearrangement



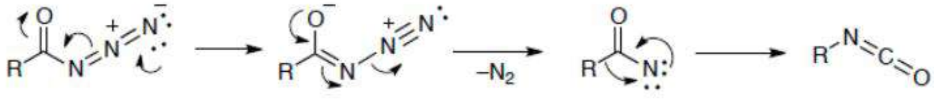
Mechanism



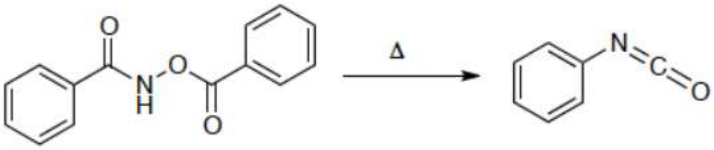
Curtius rearrangement



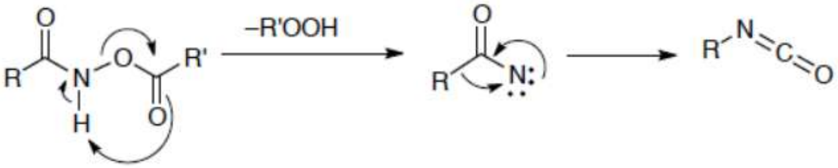
Mechanism



Lossen rearrangement

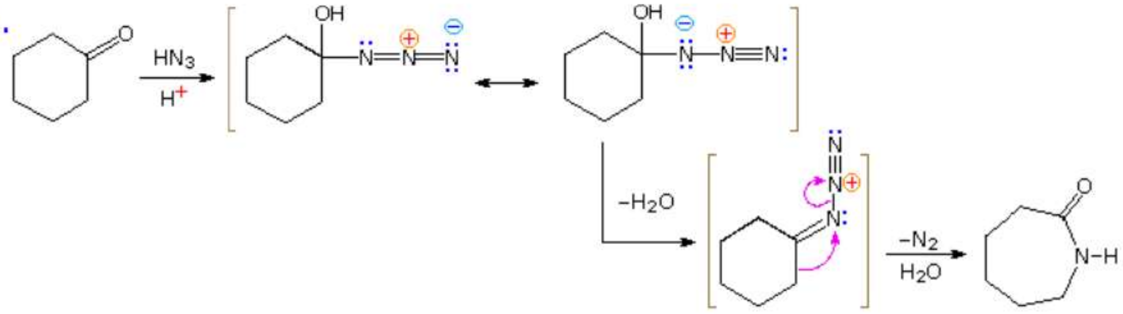


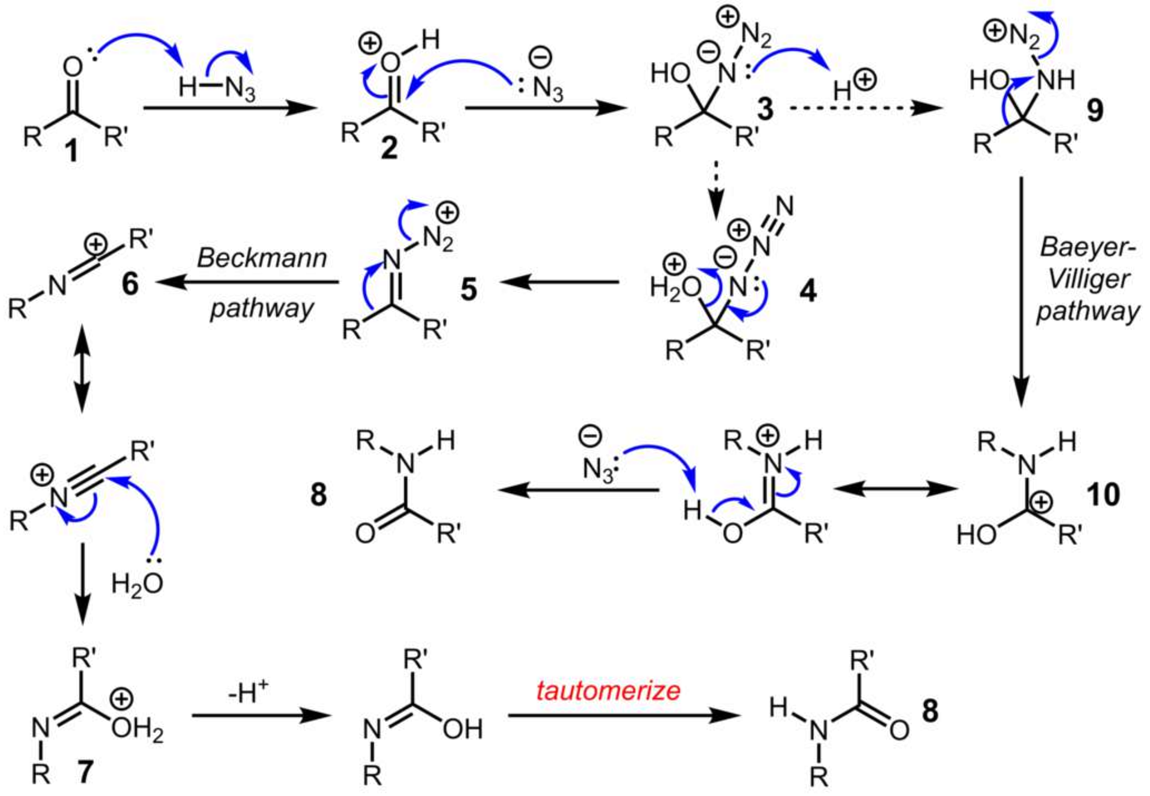
Mechanism



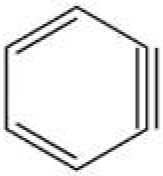
Schmidt Rearrangement of Ketones

1.



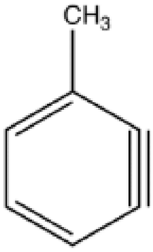


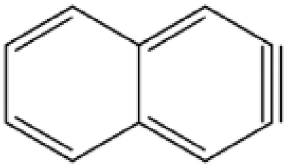
Benzynes



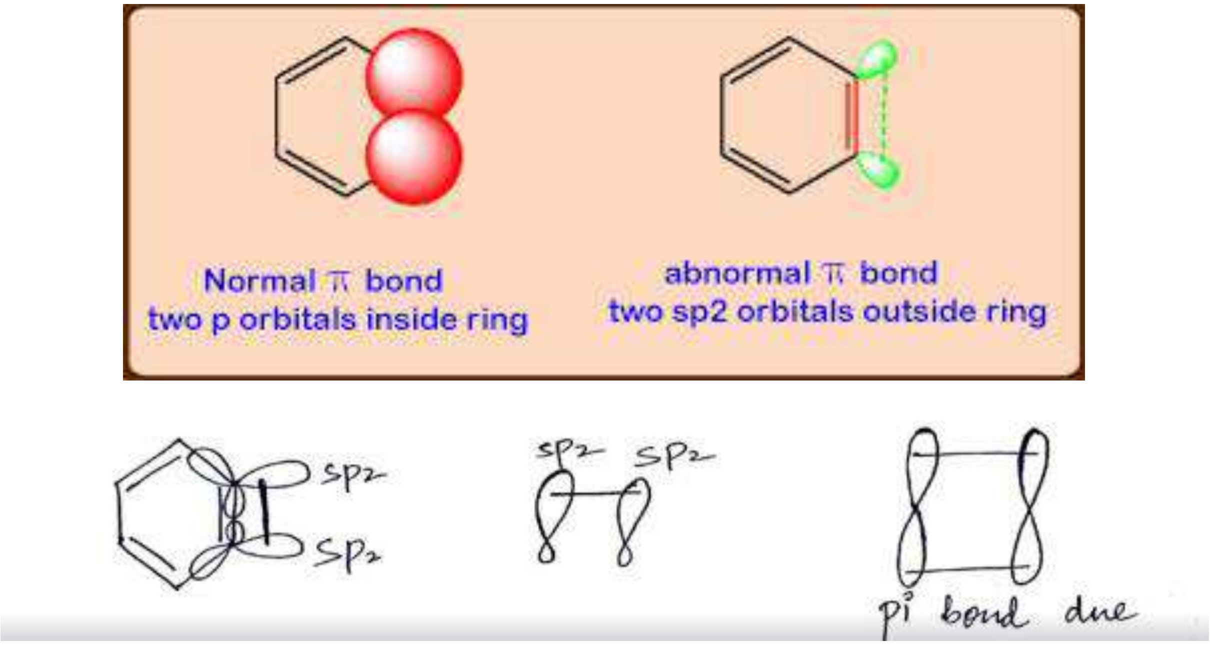
Derivatives are called benzynes or arynes

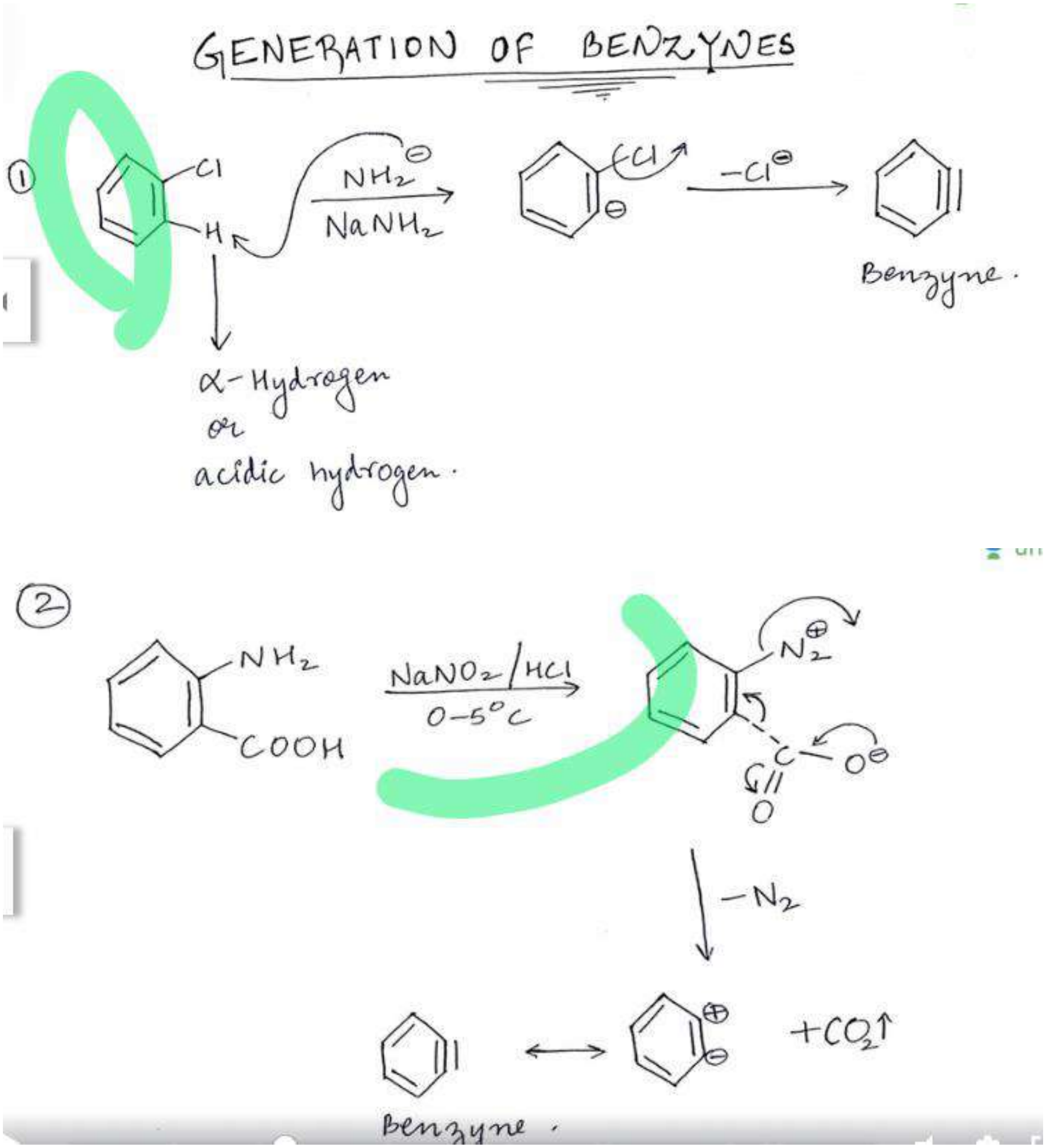
Eg:





If each triply bonded carbon atom in a benzyne molecule is sp-hybridized, as is typical of triply bonded carbon atoms, there would be severe angle strain in the molecule. It is more likely that each triply bonded carbon atom in a benzyne molecule is sp^2-hybridized, in which case two sp^2-hybridized orbitals that are not parallel to each other overlap laterally to form the pi bond that is not part of the loop of pi electrons **(2)**.





GENERATION OF BENZYNES

①

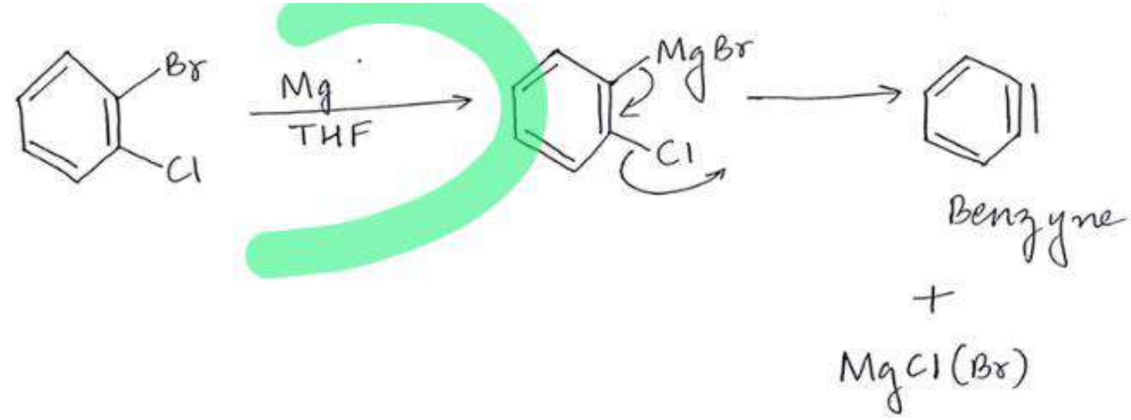
Benzyne.

α-Hydrogen
or
acidic hydrogen.

②

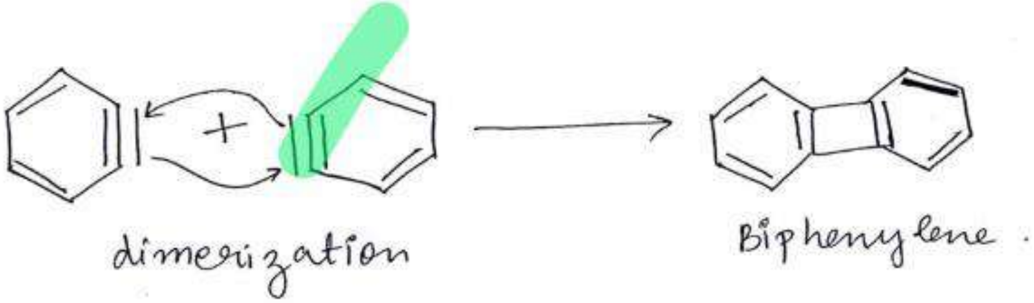
Benzyne.

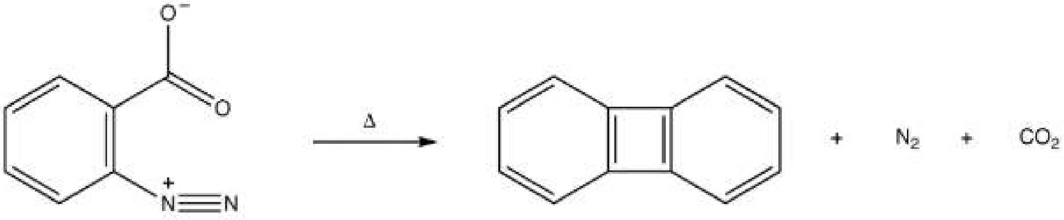
③.



In either case, the pi bond in a benzyne molecule that is not part of the loop of pi electrons would be very weak, which is consistent with the observation that, despite being aromatic, benzynes are extremely unstable and reactive. If generated in isolation, benzynes undergo rapid dimerization.

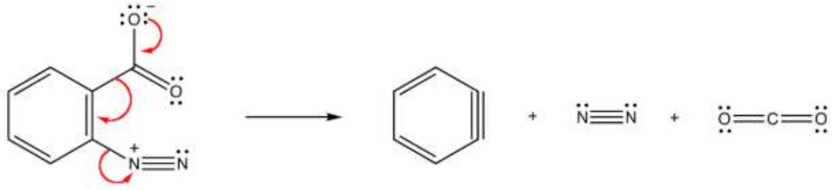
Dimerization in benzynes





mechanism:

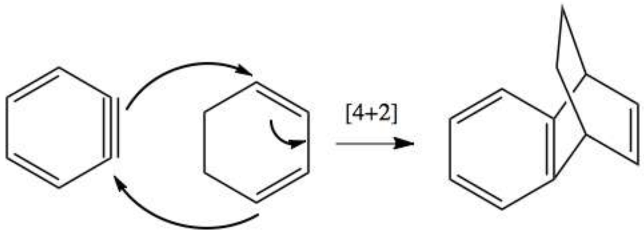
Step 1:



Step 2:

Synthetic Application of Diel's Alder Reaction.

Q Find the product.



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