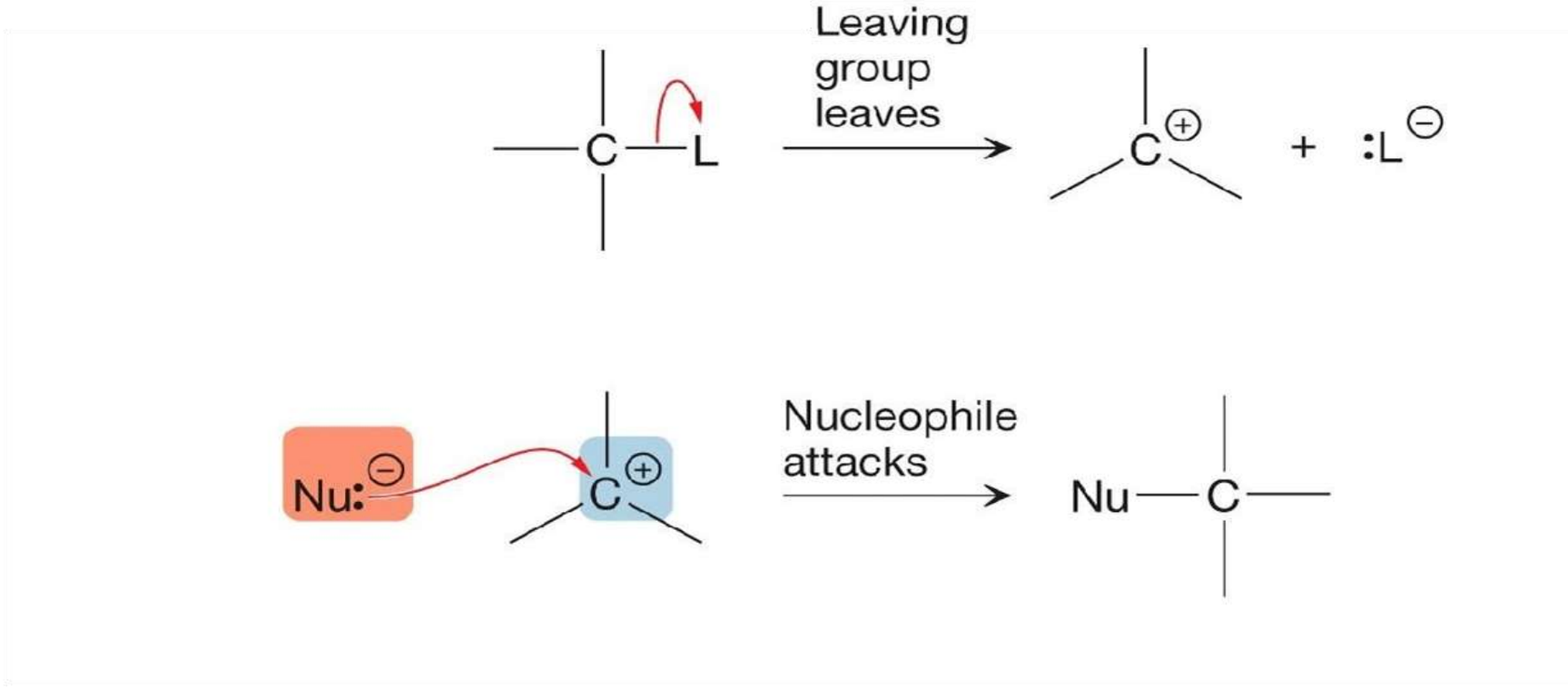
Nucleophilic Substitution reactions

S_N1: Substitution, Nucleophilic, Unimolecular

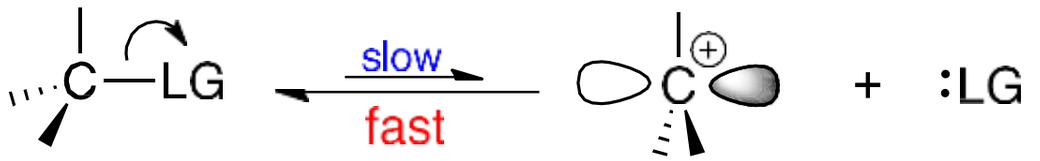
- A nucleophilic substitution reaction taking place in two steps is an example of a unimolecular nucleophilic substitution (S_N1) mechanism.



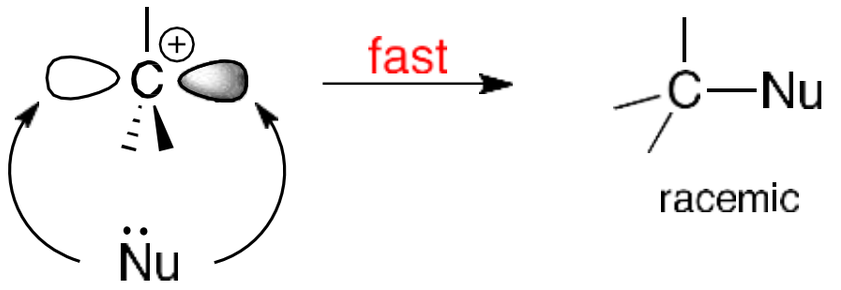
S_N1: Substitution, Nucleophilic, Bimolecular

- S_N1 reaction mechanism takes place in a two steps
- The C–L bond breaks first to give a **carbocation intermediate**
- This intermediate can then react with a nucleophile

Step 1

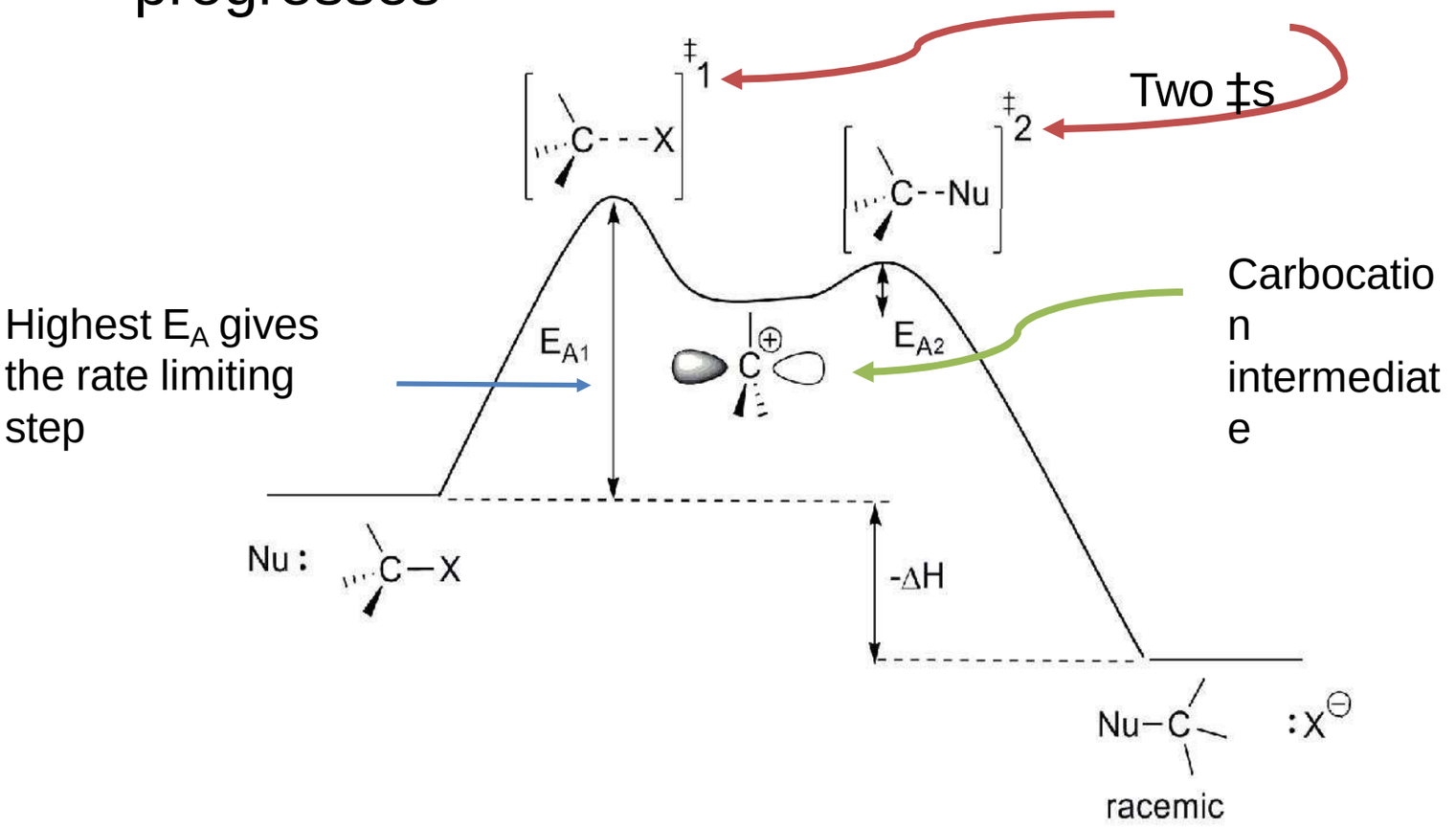


Step 2



S_N1: Substitution, Nucleophilic, Bimolecular

- S_N1 free energy diagram - maps ΔE as reaction progresses



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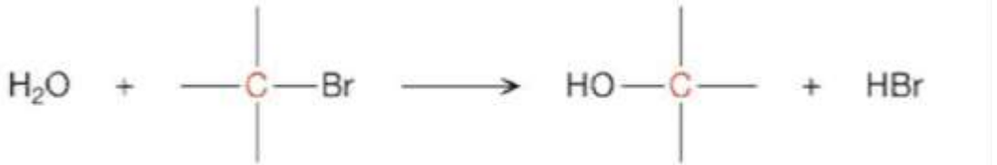
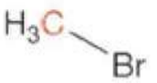
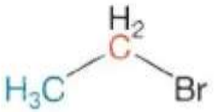
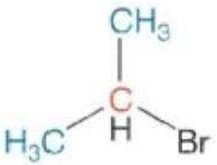
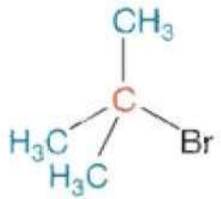
Factor 1: Structure of R-X/LG

- Empirical data for S_N1 reactions:

Relative Reaction Rates in the S_N1 Reaction:



Substrate				
Type of Carbon	Methyl	1°	2°	3°
Relative S_N1 Reaction Rate	~0	0.08	1	100,000

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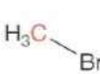
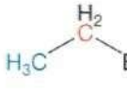
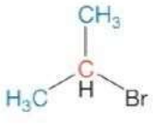
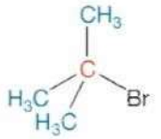
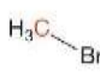
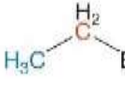
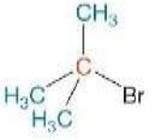
Factor 1: Structure of R-X/LG

- When S_N1 (top) compared with S_N2 rates (bottom), we see that the two reactions are opposite in their requirements for the structure of R-X

- For S_N1:
  $3^o > 2^o >> 1^o/CH_3$
  (never)

Substrate				
Type of Carbon	Methyl	1°	2°	3°
Relative S_N1 Reaction Rate	~0	0.08	1	100,000

Substrate				
Type of Carbon	Methyl	1°	2°	3°
Relative S_N2 Reaction Rate	4,000	80	1	~0

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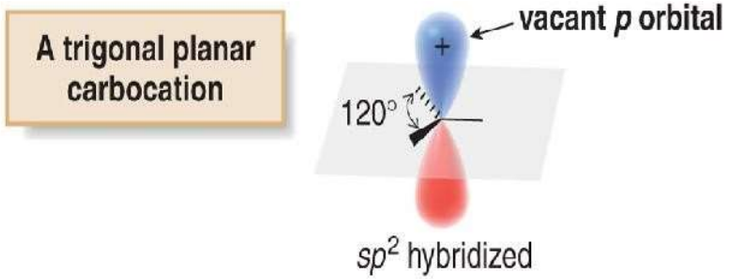
Carbocation Stability

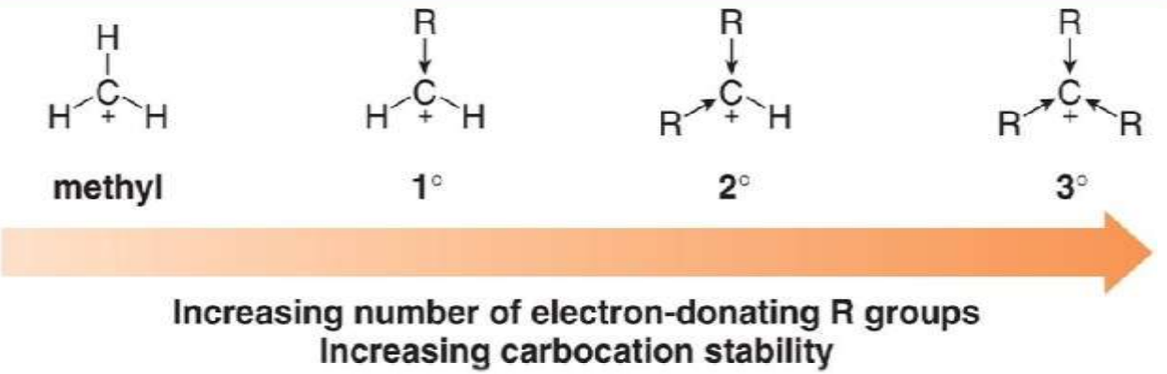
- Carbocations formed in S_N1 processes are sp^2 hybridized, trigonal planar species with an empty p-orbital
- This species is highly e^- deficient carbon and **very reactive**
- When we discuss a 'stable' carbocation, it is relative to other carbocations-–all of them are highly reactive!



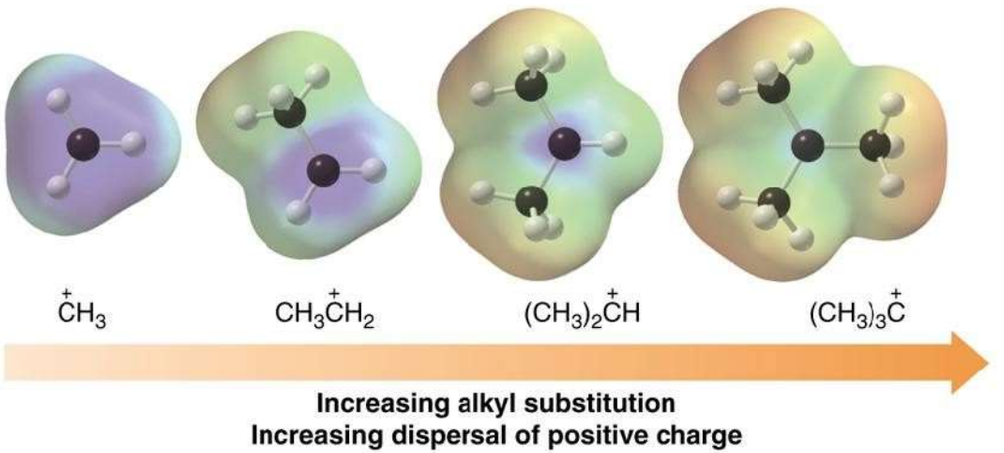
- A carbocation (with three groups around C) is sp^2 hybridized and trigonal planar, and contains a vacant *p* orbital extending above and below the plane.

Carbocation Stability

- Observed carbocation stabilities:



- Electrostatic potential plots show large difference in positive charge character:



- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.

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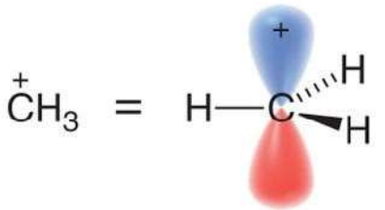
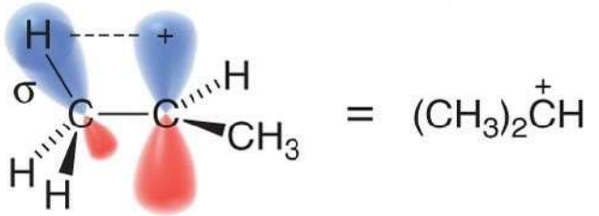
Carbocation Stability

- Carbocation stability is the result of **hyperconjugation.**
- **Hyperconjugation** is the spreading out of charge by the overlap of an empty *p* orbital with an adjacent σ bond.
- This overlap delocalizes the positive charge on the carbocation over a larger volume, thus stabilizing it.
- Here, $(CH_3)_2CH^+$ can be stabilized by hyperconjugation, but CH_3^+ cannot:



This carbocation has no opportunity for orbital overlap with the vacant *p* orbital.



Overlap of the C—H σ bond with the adjacent vacant *p* orbital stabilizes the carbocation.

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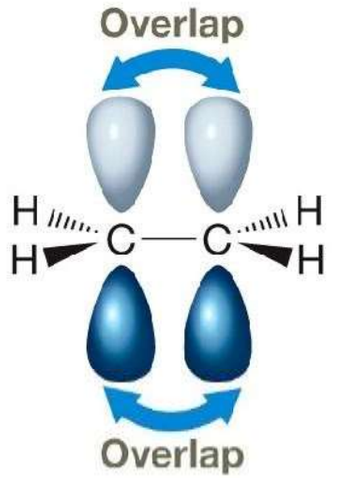
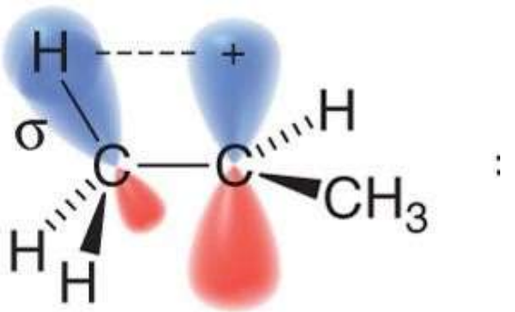
Carbocation Stability

- **Hyperconjugation** is a similar effect to the structure of a π-bond.
- A π-bond is the parallel overlap of two orbitals to make a stable bond
- The overlap of a 2-e^- σ-bond with the empty *p*-orbital is not as efficient, but stabilizes the empty orbital
- Note the back lobe of the sp^3 orbital is also in position to overlap and stabilize the empty *p*-orbital





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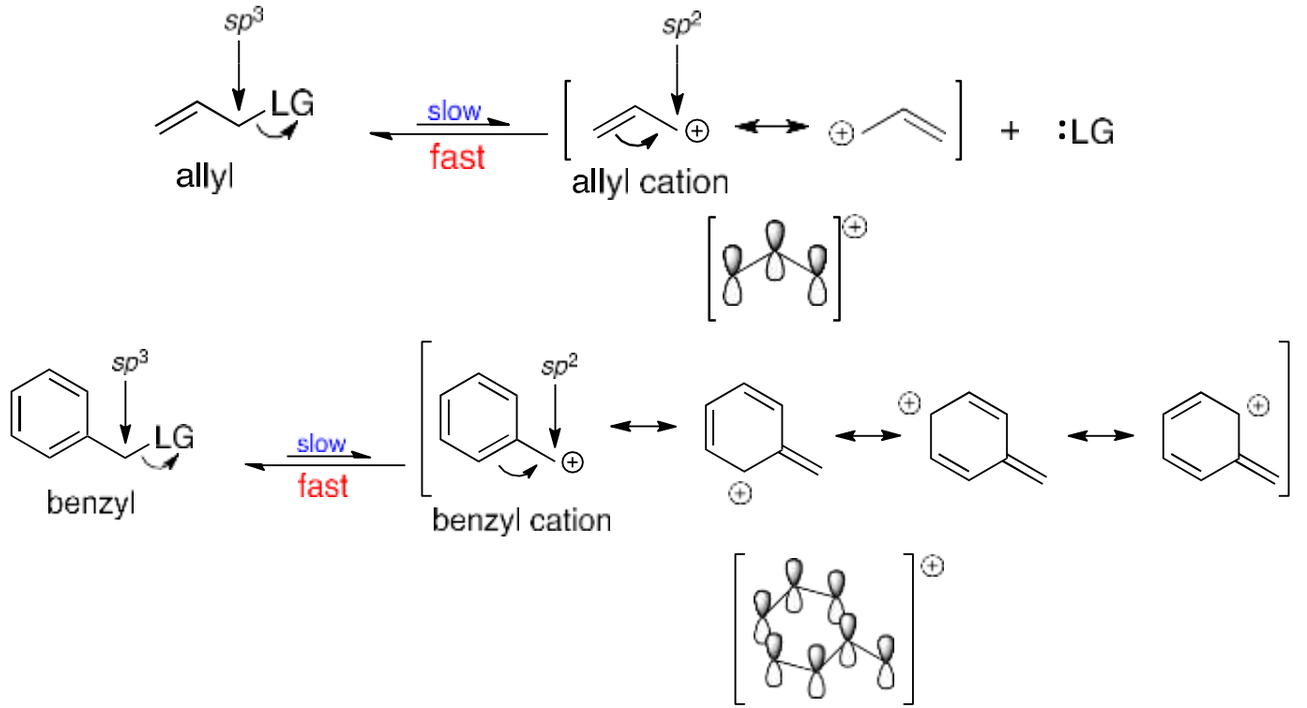
Carbocation Stability

- Benzyl and allyl carbocations are stabilized by direct conjugation and resonance contributors
- A 1^{o} allyl cation is about as stable as a 2^{o} carbocation
- A 1^{o} benzyl cation is about as stable as a 3^{o} carbocation



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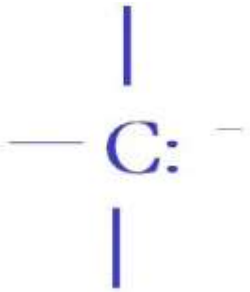
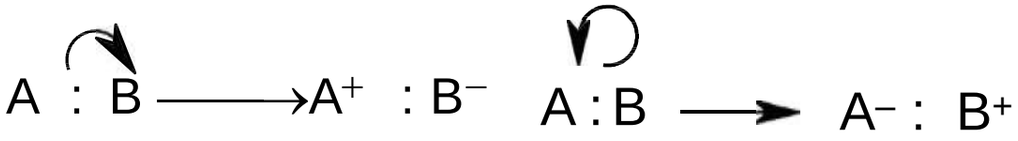
Carbanions



an anion in which carbon has an unshared pair of electrons and contains a negative charge. A carbanionis one of the reactive intermediates in organic chemistry.
The conjugate bases of weak acids, strong bases, excellent nucleophiles.

Bond Cleavage

Heterolytic Cleavage



+vely charged ion – carbocation

-vely charged ion – carbaanion

- Reactant → intermediate → product

A very important way of generating carbon nucleophiles involves **removal** of a proton from a carbon by a base. The anions produced are **carbanions**.

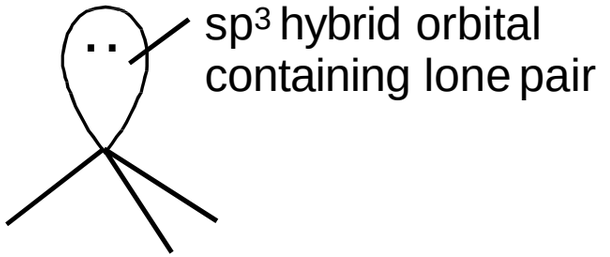
The negative charge gives good nucleophilic properties and it can be used in the formation of new carbon carbon bond.

Carbanion

- Pyramidal - sp^3 hybridised
  bond angle 109.28.geometery is thus tetrahedral

- Has eight electrons

- Stabilized by resonance or by inductive effect.

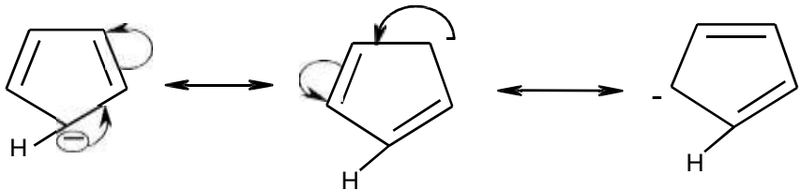


Tetrahedral structure of carboanion

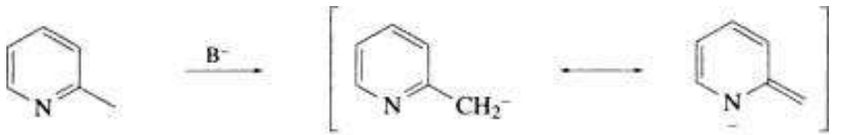
Stability of Carbanion

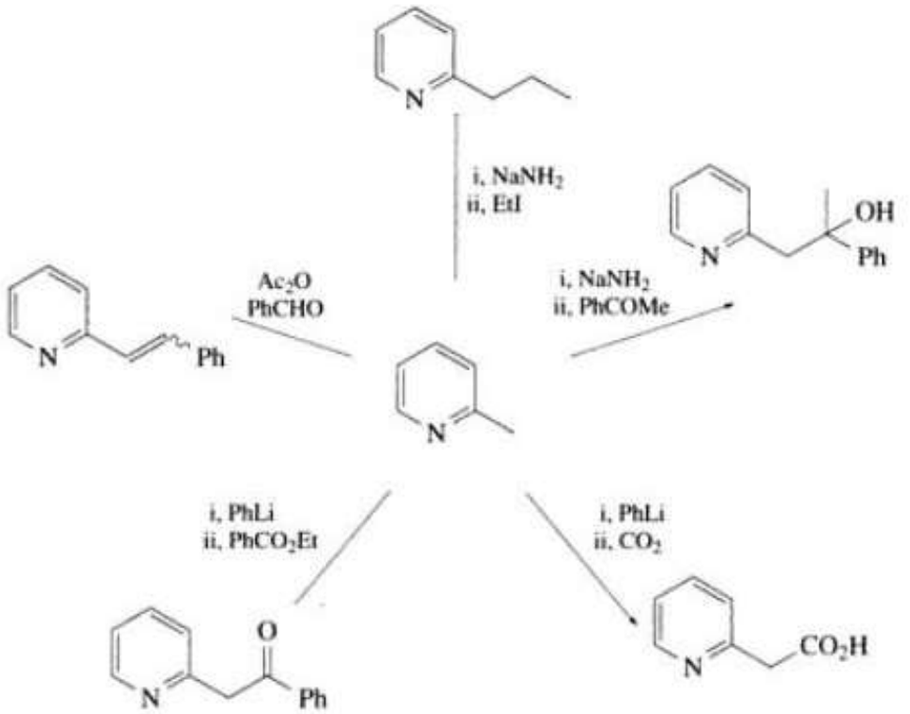
depends upon three factors:

(i) By resonance



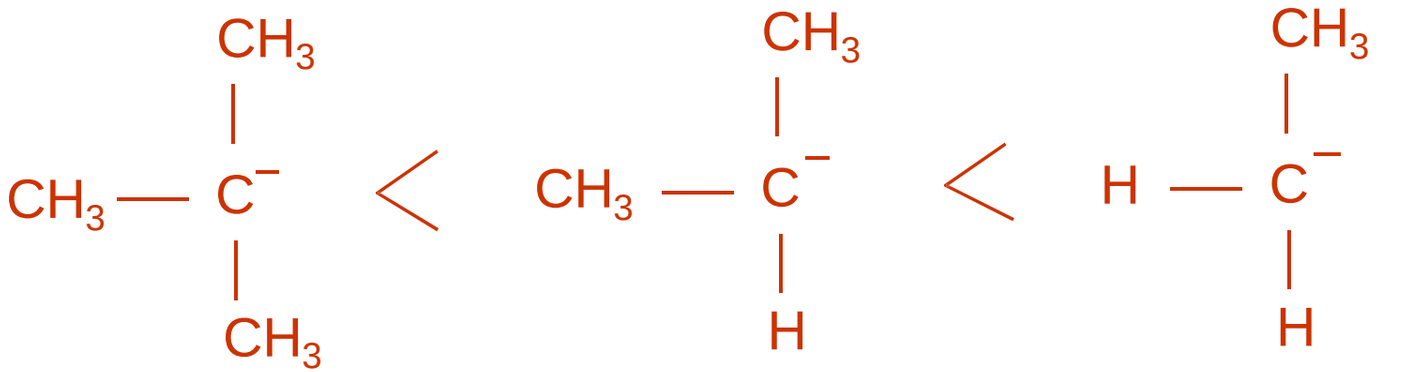
Cyclopentadienyl carbanion





Stability of Carbanion

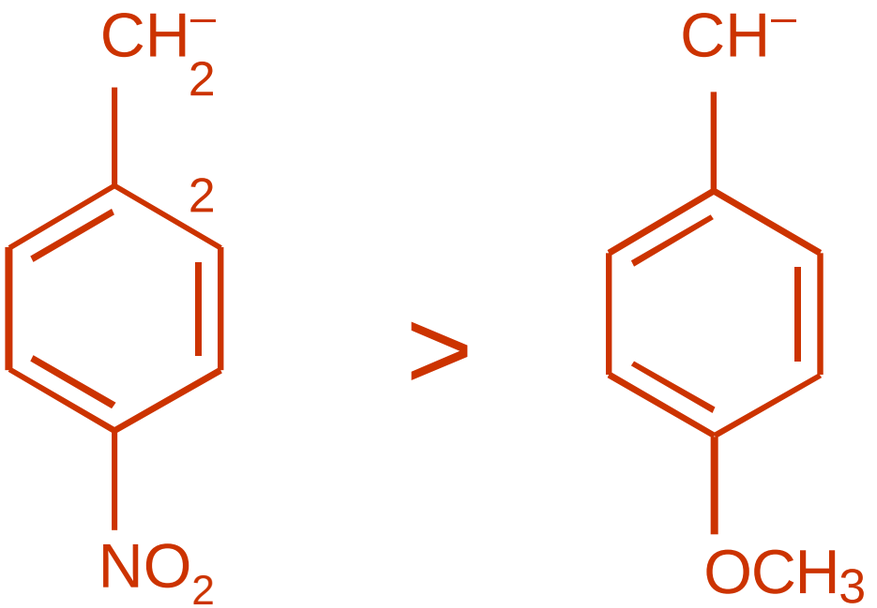
(ii) By inductive



3° 2° 1°

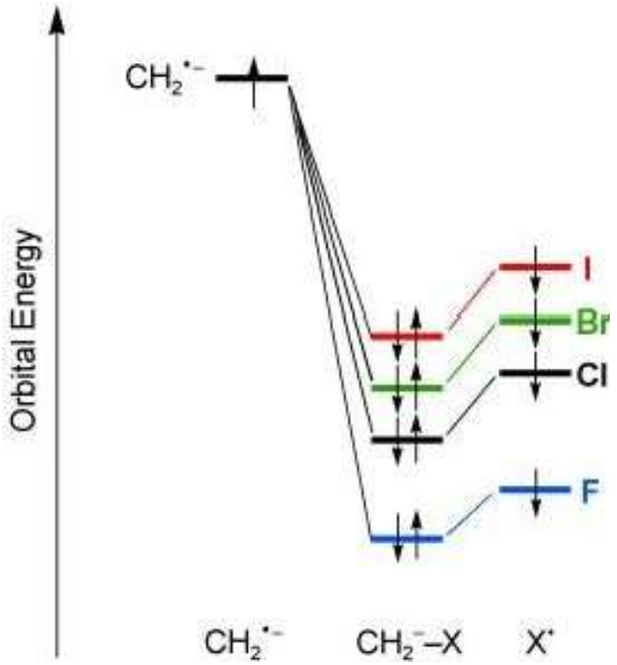
Stability of Carbanion

(iii) Electron-donating groups destabilize a carbanion while electron-withdrawing groups stabilize it.



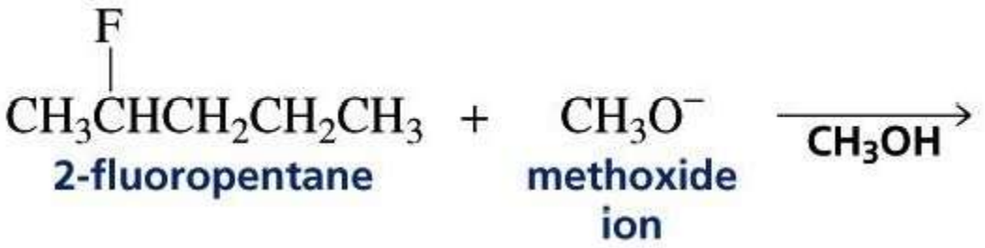
- An ordering of some important substituents with respect to their ability to stabilize carbanion can be established.

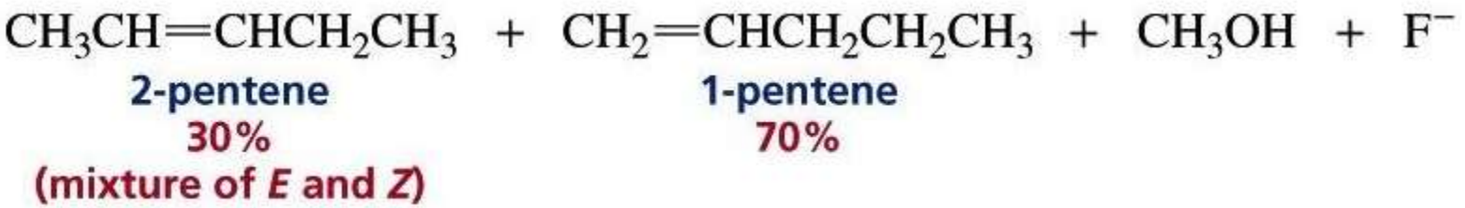
NO_2> COR>CN-CO_2R>SOR>Ph-SR>H>R



- F stabilizes CH_2X^- *more* effectively than Cl, Br, and I because of the fluorine electronegativity.

Consider the elimination of 2-fluoropentane …

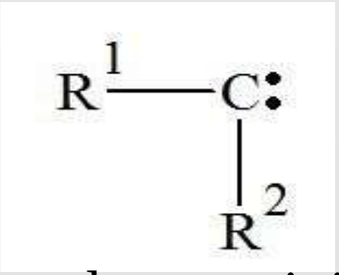




CARBENES

CARBENES

Introduction



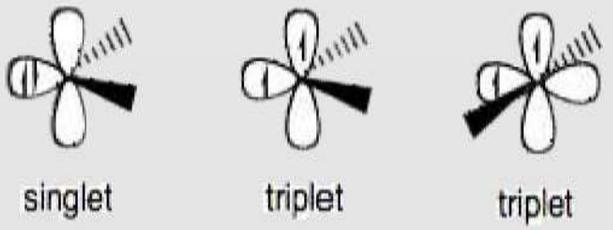
• A carbene is a molecule containing neutral carbon atom with a valence of two and two unshared valence electrons.

•Carbenes are uncharged, electron deficient molecular species that contain a divalent carbon atom surrounded by a sextet of electrons, and two substituents.

Types of Carbenes

- Carbenes are called singlet or triplet depending on the electronic spins they possess.
- Triplet carbenes are paramagnetic. The total spin of singlet carbenes is zero while that of triplet carbenes is one.
- Bond angles are 130-150° for triplet methylene and 100-110° for singlet methylene.
- Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

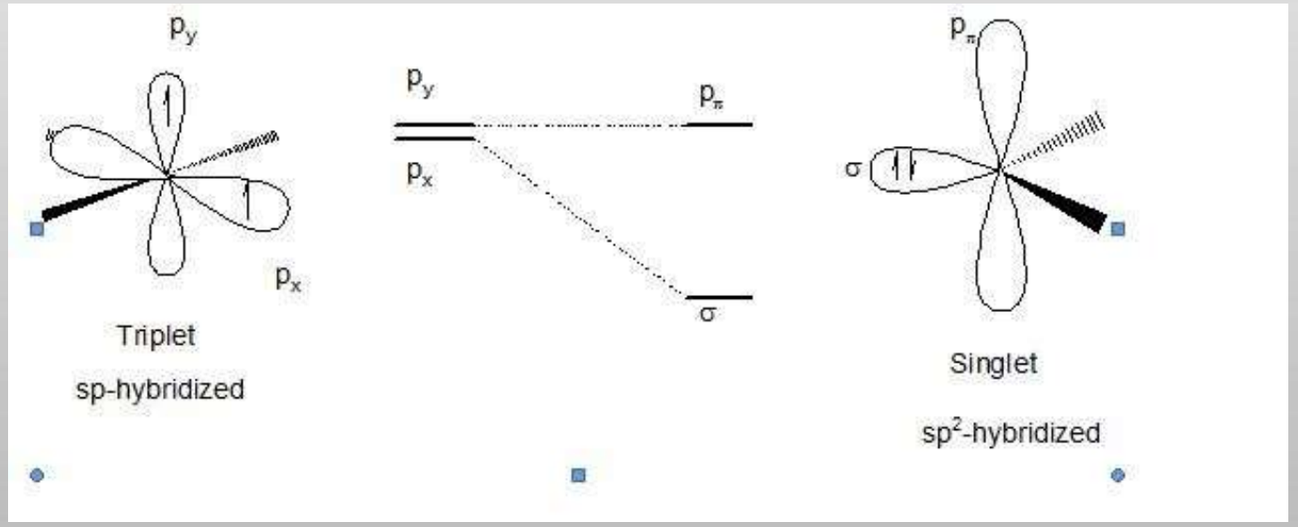
Structure and bonding



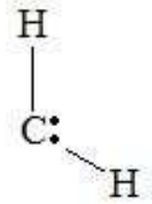
- Singlet carbenes are spin-paired. This molecule adopts an sp^2 hybrid structure.
  - Eg- :CH2 :CHPh :CHPh2 :CHR
- Triplet carbenes have two unpaired electrons.
- Most carbenes have a nonlinear triplet ground state, except for those with nitrogen, oxygen, or sulfur atoms, and halides directly bonded to the divalent carbon.
  - Eg:- :CCl2 :CHCl :C(OMe)2

- Singlet state: carbocation-like in nature, trigonal planar geometry,electrophiliccharacter. . Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles .

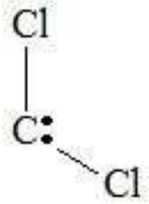
- Triplet state: diradical-like in nature, linear geomtry and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.



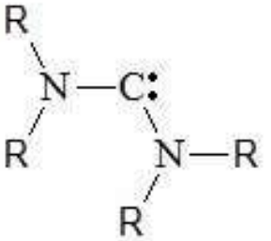
Carbene Examples



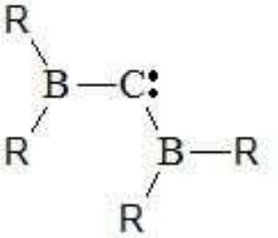
methylene



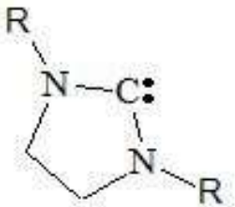
dichlorocarbene



diaminocarbenes



diborocarbene



cyclic diaminocarbenes

Formation of carbenes

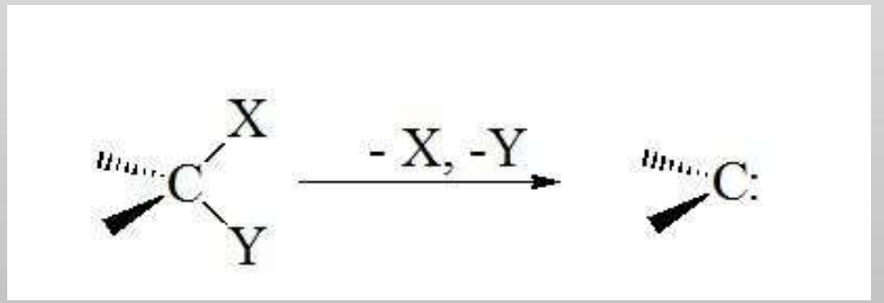
- Cabenes are formed by reactions of halogenated compounds with bases.

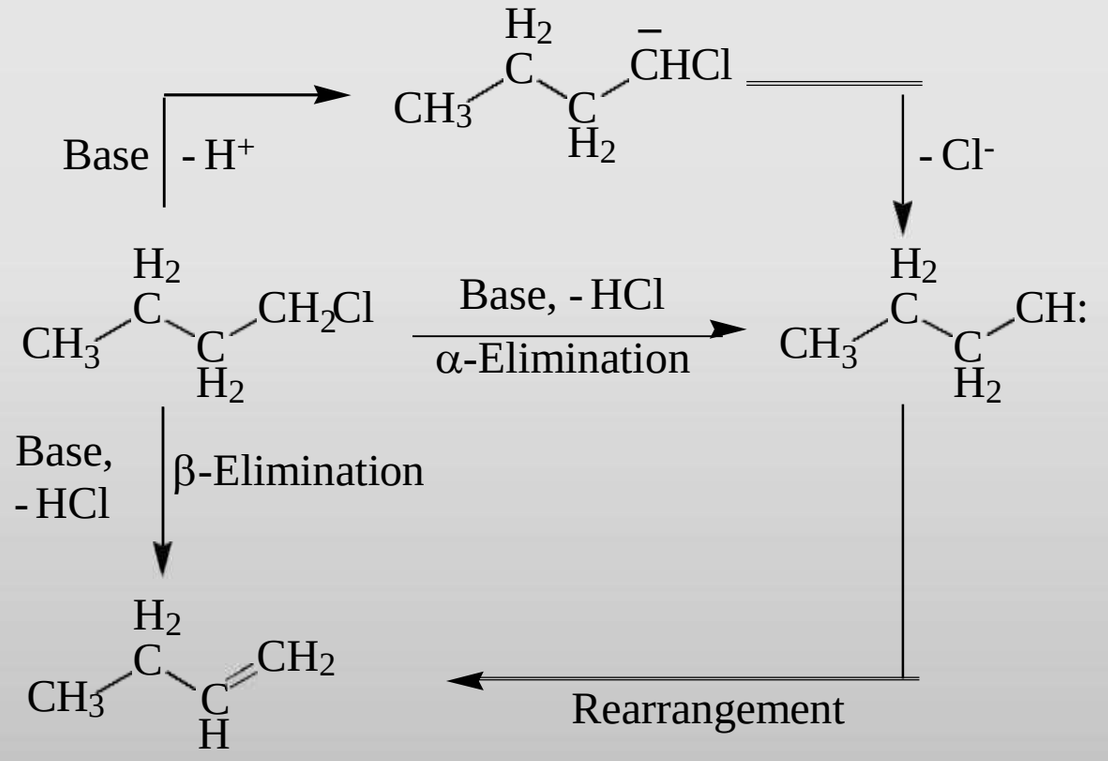
1. α elimination of chloroform with base
2. Thermal decomposition of diazo compounds

3. Metal(Rhodium or copper – catalysed decomposition of diazo carbonylcompound

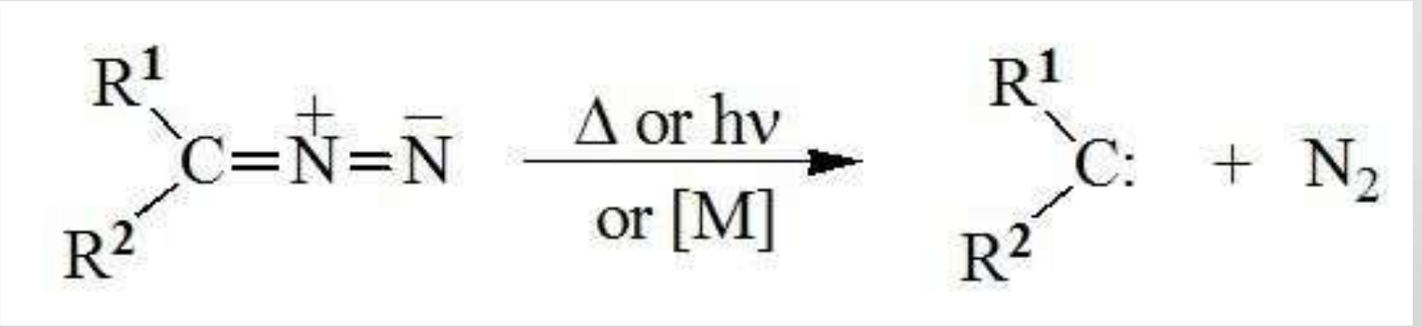
α-elimination of HX or X2 from an organic halide

- α elimination means the eliminations in which both the proton and the leaving group are located on the same atom.
- A strong base removes an acidic proton adjacent to an electron withdrawing group to give a carbanion.
- Loss of a leaving group from the carbanion creates a carbene.
- One of the best known elimination reactions occurs when chloroform is treated with base, forming a dichlorocarbene.
- The more common dehydrogenations (to form alkenes)are called beta(β) eliminations because the hydrogen and the halogen are lost from adjacent carbon atoms.



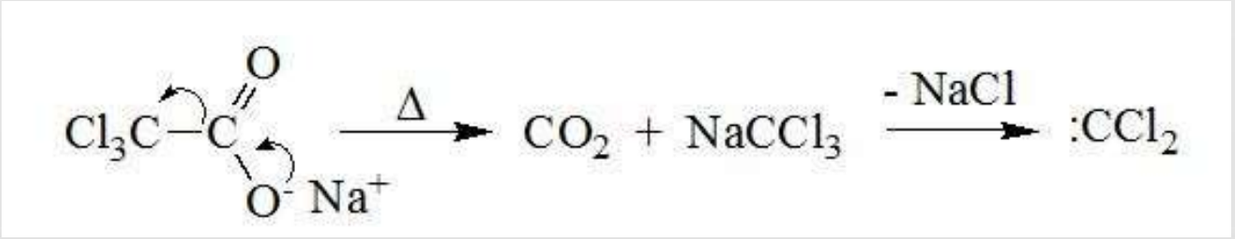

Base
- H+
- Cl-
Base, - HCl
α-Elimination
Base,
- HCl
β-Elimination
Rearrangement

α-elimination of N_2 from diazo-compounds

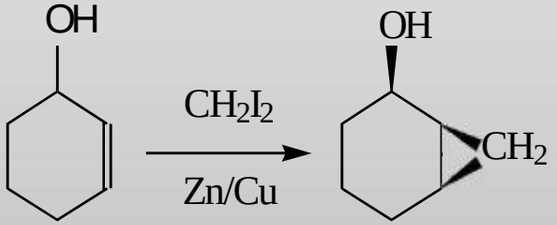


Carbene generation via α-elimination under mild non-basic conditions:

- Thermolysis of sodium trichloroacetate:

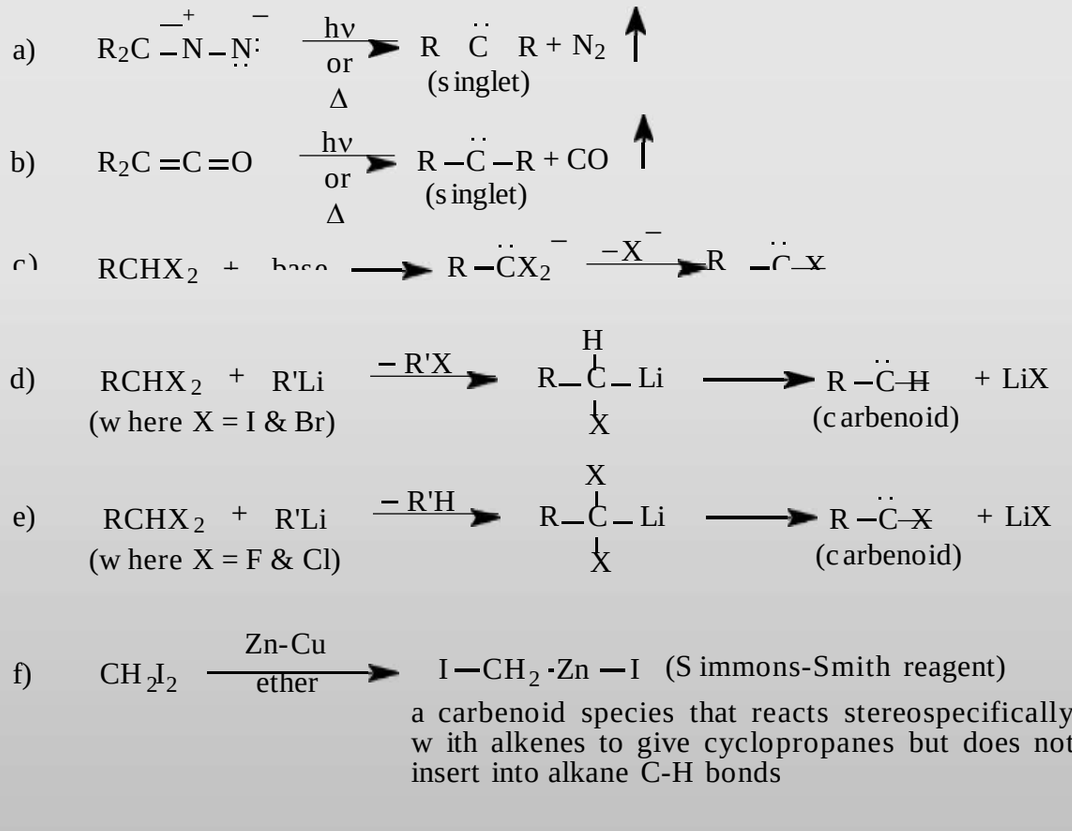


- The Simmons-Smith reaction:



$CH_2I_2 + Zn \longrightarrow :CH_2 + ZnI_2$

Formation reactions of carbenes



Generation and fate of reaction intermediates

REACTION INTERMEDIATES

- A reaction intermediate or an intermediate molecular entity (atom, ion, molecule..) with a lifetime appreciably longer than a molecular vibration that is formed (directly or in directly) from the reactants and reacts further to give (either directly or indirectly) the products of a chemical reaction.
- Main carbon reactive intermediates:
  - ✓Carbocations and their stabilized equivalents such as oxonium ions.
  - ✓Carbanions and their stabilized equivalents such as enolates.
  - ✓Carbenes
  - ✓Free radicals
  - ✓Nitrenes

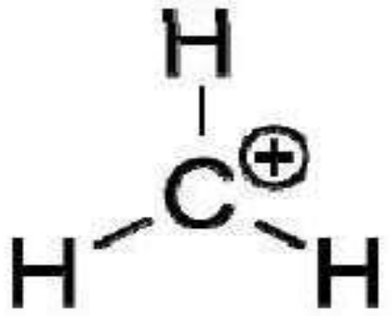
CARBOCATIONS

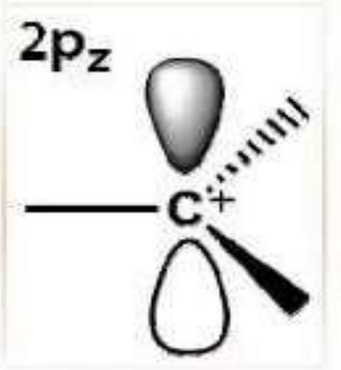
A carbocation is an ion with a positively-charged carbon atom.

Carbocation

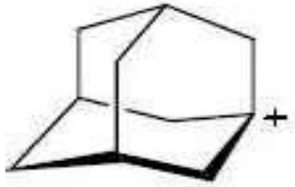
- Carbenium ion (trivalent positive species) CH_3, C_2H_5
- Carbonium ion (pentavalent positive species,non classical carbocation)

CARBOCATION STRUCTURES: PLANAR SP^2 HYBRID

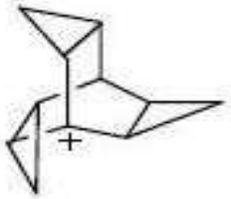




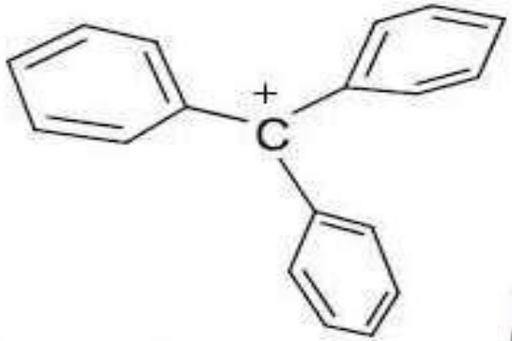
tert-butyl cation
demonstrating planar geometry



adamentyl



1-trishomobarrelyl

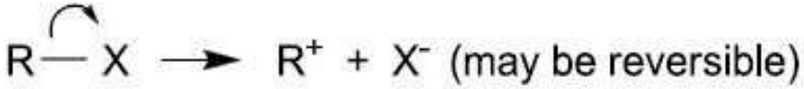


triphenylmethyl
propeller-shaped

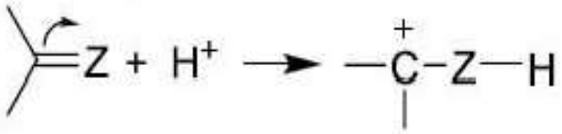
II. The Generation and Fate of Carbocations

Two general ways to form carbocations:

i. A direct ionization:

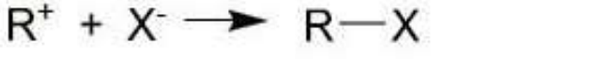


ii. Addition of a positive species toan unsaturateraed system:

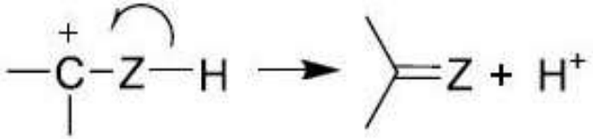


The reaction of carbocations:

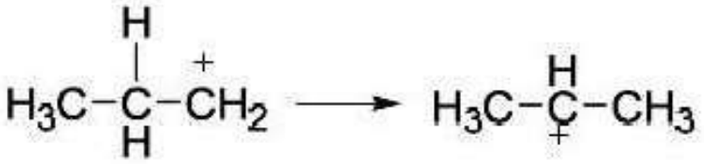
i. Combination with a species possessing an electron pair.

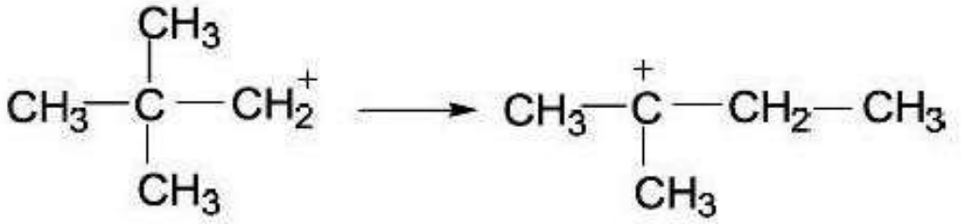


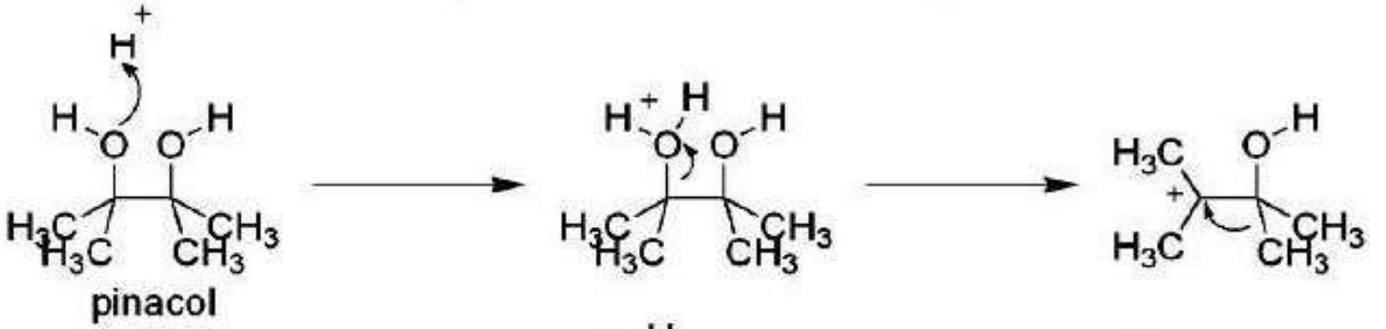
¨ The carbocation may lose a proton from the adjacent atom.



iii. Rearrangement

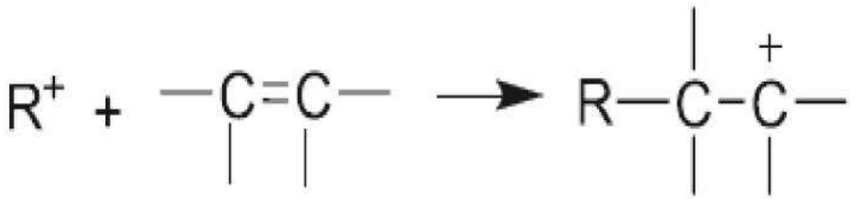




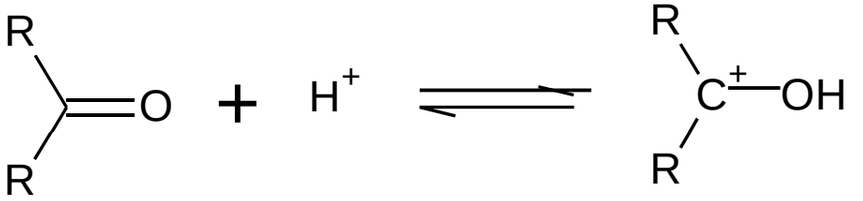


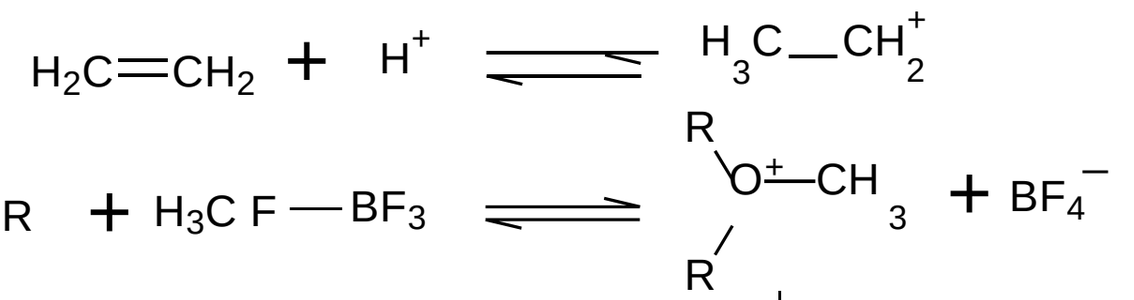
iv.

Addition

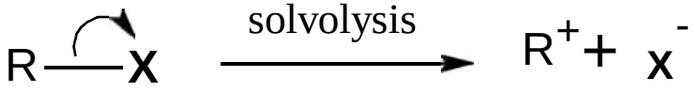


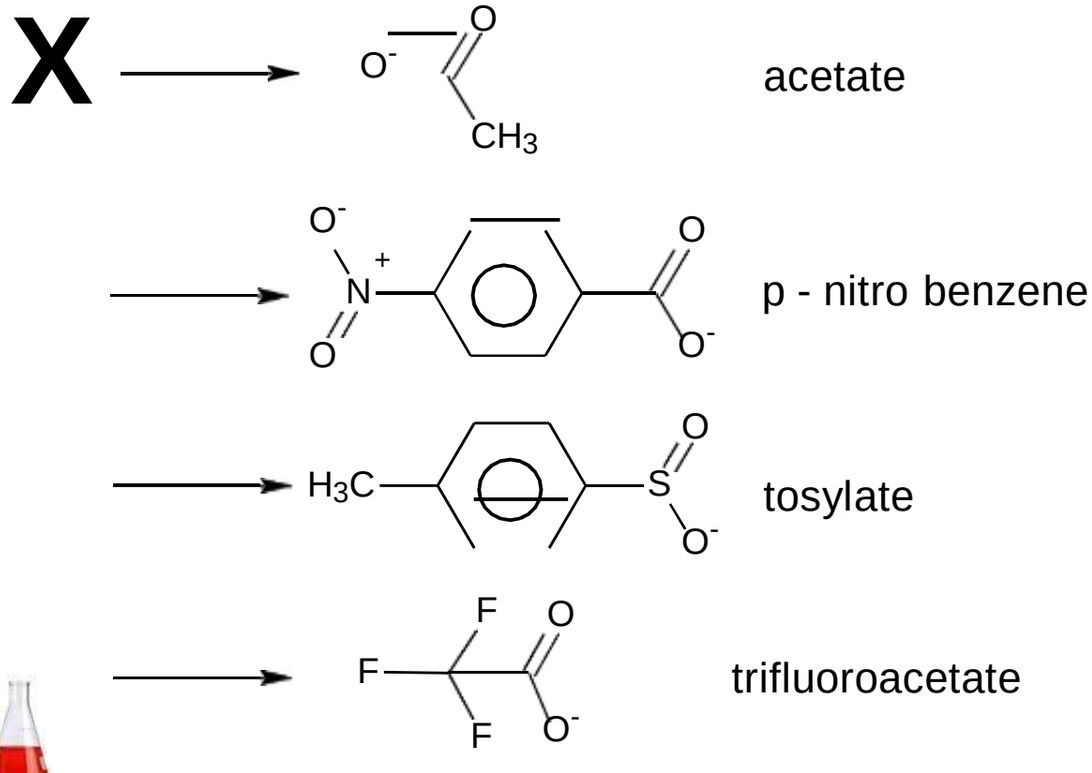
By the addition of a cation to a neutral molecule.



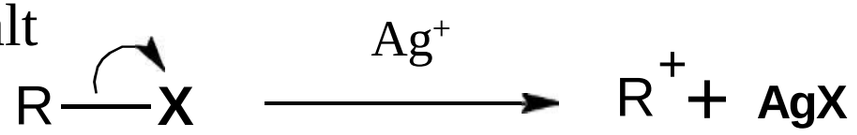


V. By the heterolytic fission of a C-heteroatombond.



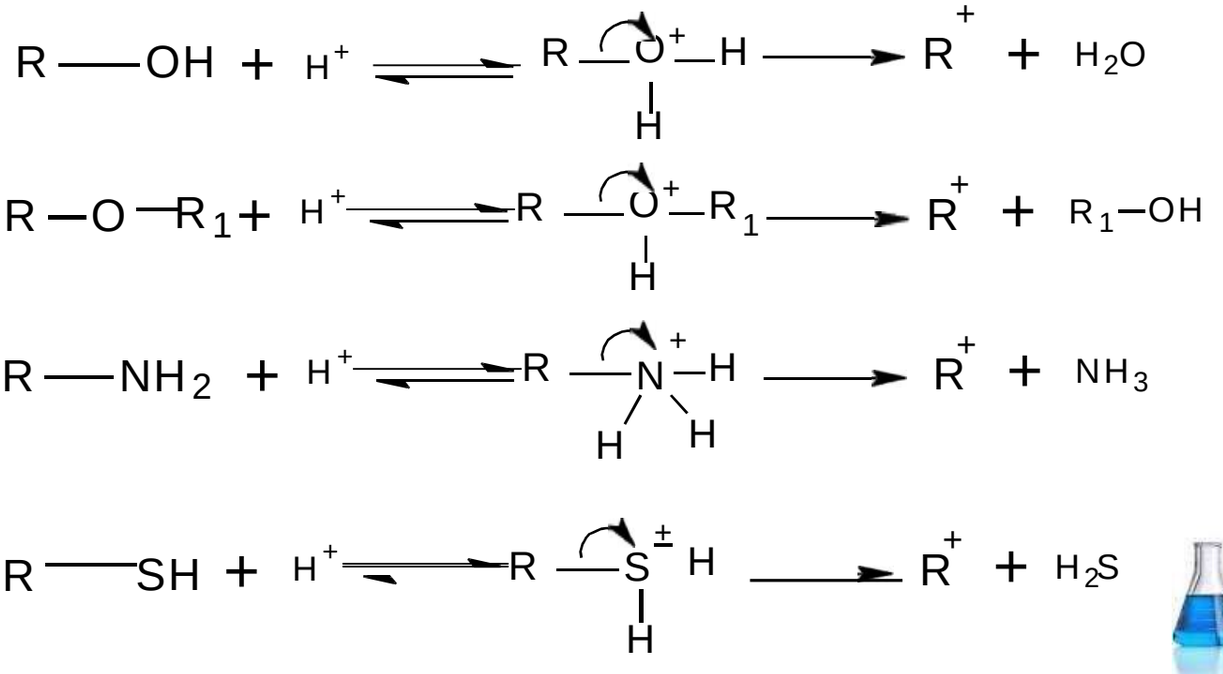


Vi. By the heterolysis fission of a C- heteroatom bond to form onium salt

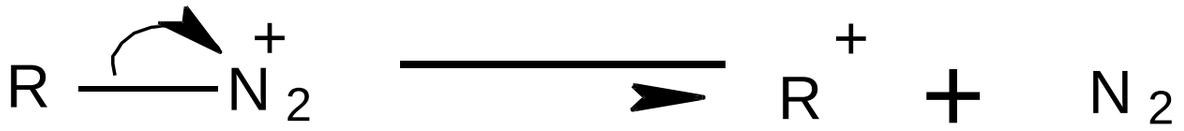


X ⟶ Cl, Br and I

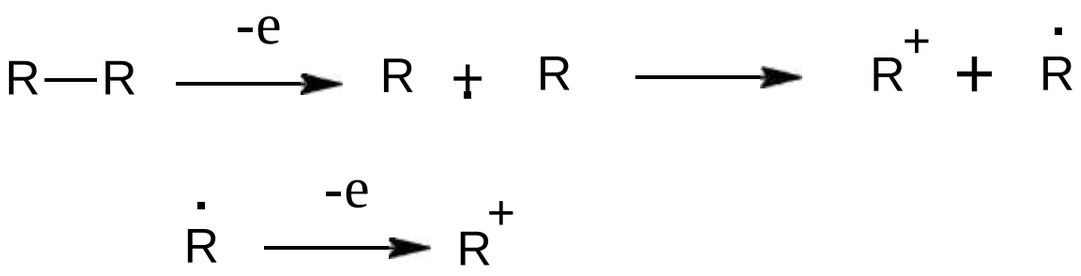
Onium salt Carbocation



- By the heterolysis of alkyl diazonium salt



- By the removal of an electron from a neutral molecule or a free radical

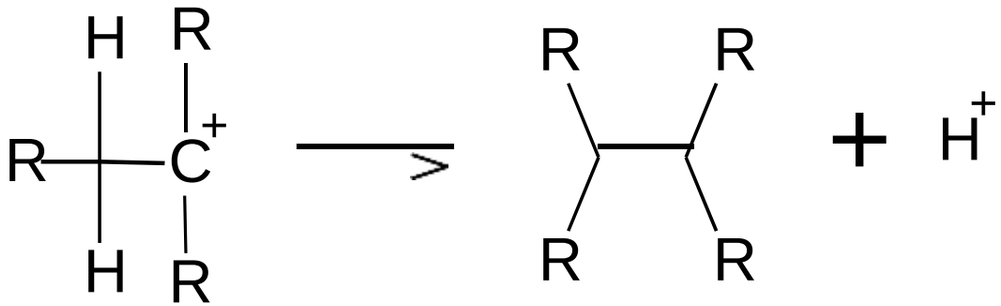


REACTIONS OF CARBOCATION

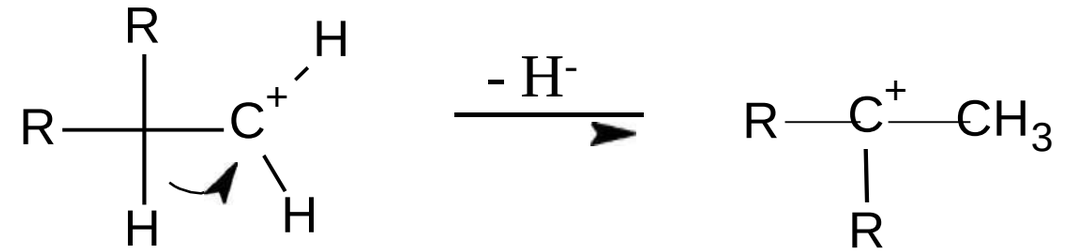
- R^+ cation act as an electrophile to react with nucleophiles. For Eg;

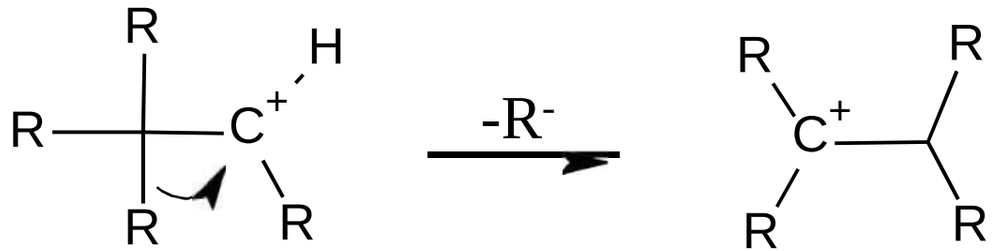
$$R^+ + Nu^- \longrightarrow R\ Nu$$

- Some carbocations act as Bronsted acid to lose a proton . For Eg;

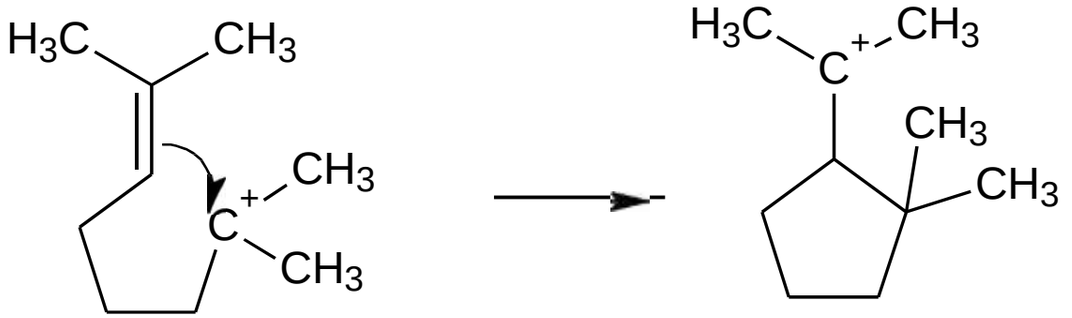


- 1º or 2º-carbocation often undergo Wagner –Meerwein rearrangement by an anionotropic 1,2- shift of a hydride or an alkyl anion. For Eg;





- Internal alkylation of a C=C bond sometimes may take place with a carbocation.



- Fragmentation of carbon chain of carbocation is also known.

- Carbocations can be reduced to a free radical or carboanions by cathodic reduction.

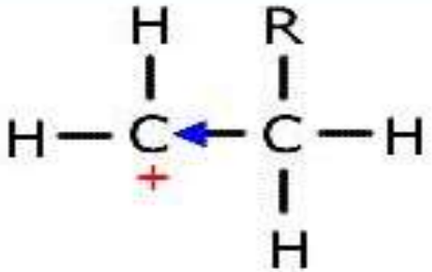
STABILITY

In solution, the carbocation may be free (this is more likely in polar solvents, in which it is solvated) or it may exist as an ion pair. Ion pairs are more likely in nonpolar solvents.

A. Simple alkyl carbocations

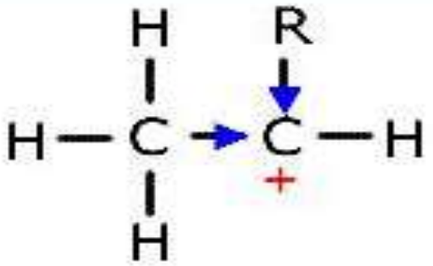
Stability: tertiary > secondary > primary

Carbonium ion stability



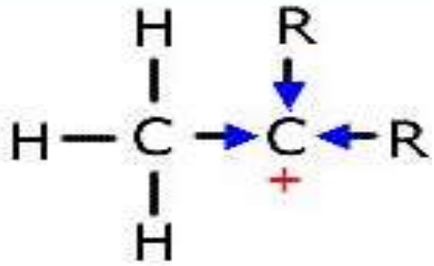
Primary carbonium ion

Induction from one alkyl group only



Secondary carbonium ion

Induction from two alkyl groups gives better stabilisation than primary

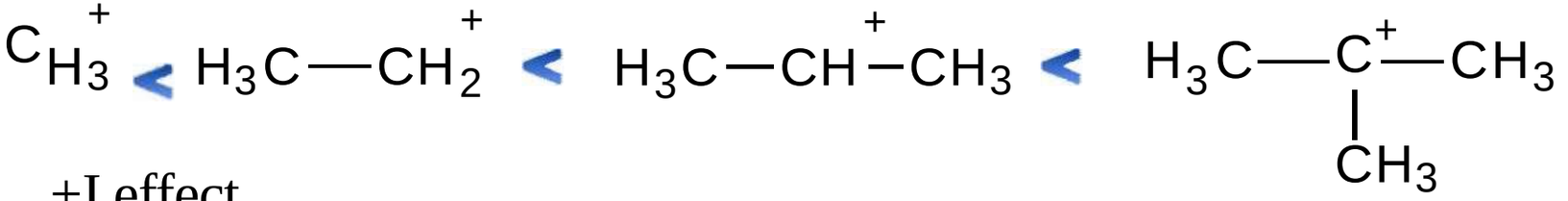


Tertiary carbonium ion

Induction from three alkyl groups gives even more stabilisation

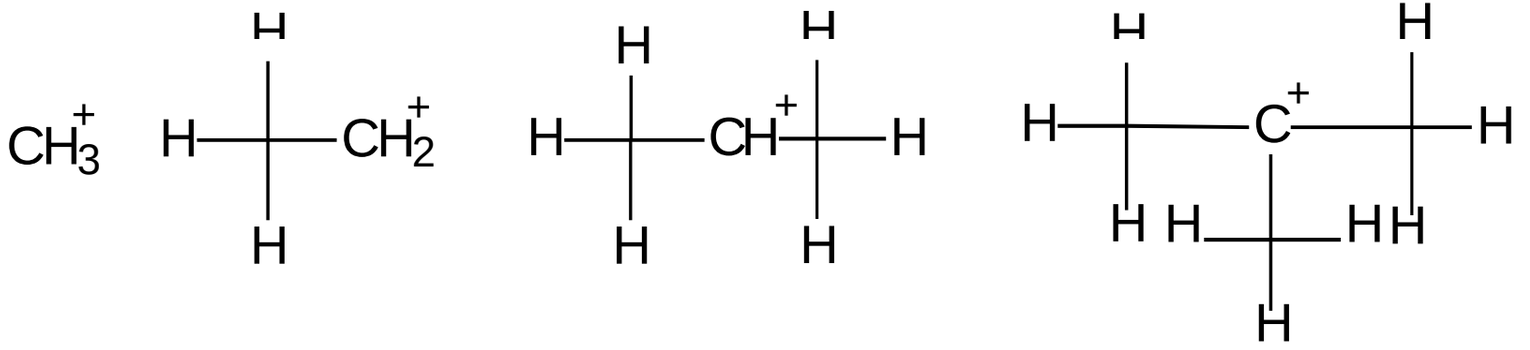
increasing stabilisation by induction

- The most stable of all alkyl cations is the *tert-butyl cation.*
- *Methane*, *ethane*, and *propane*, treated with superacid, also yield *tert-butyl cation* as the main product.
- **The Field Effect:** The electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons.



+I effect

- **Hyperconjugation:** Tertiary carbocations are more stable (and form more readily) than secondary carbocations; primary carbocations are highly unstable because, while ionized higher order carbons are stabilized by hyperconjugation, unsubstituted (primary) carbons are not.



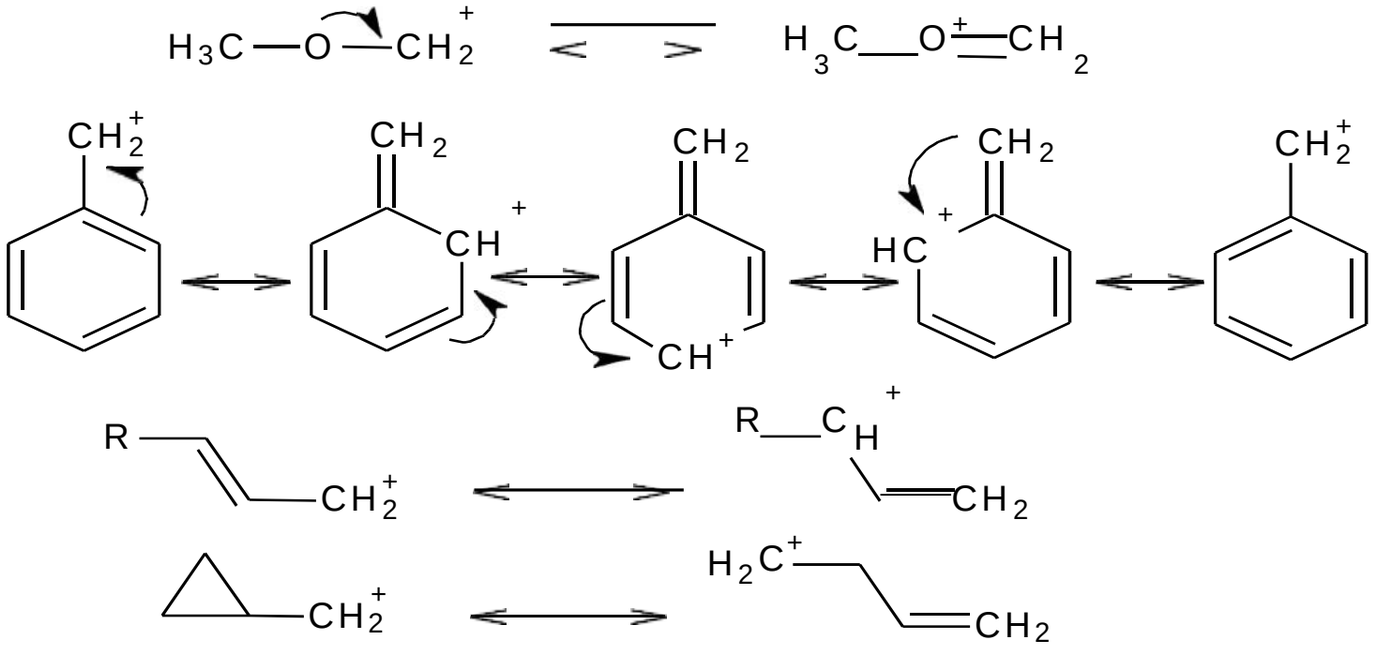
NONE

Three for 3C-H bonds

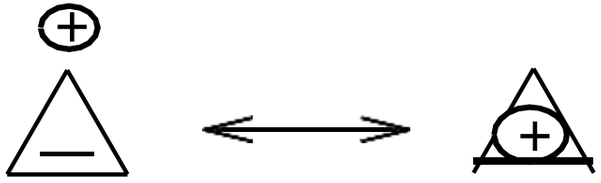
Six for 6C-H bonds

Nine for 9C-H bonds

+R groups stabilize the carbocations. Foreg;



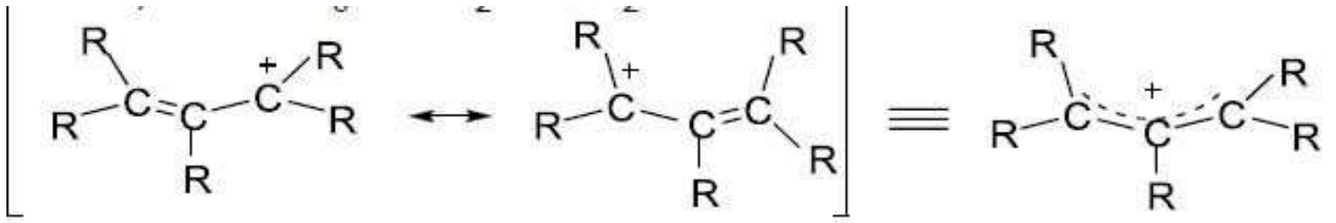
Some carbocations are stabilized due to aromatization. For eg;

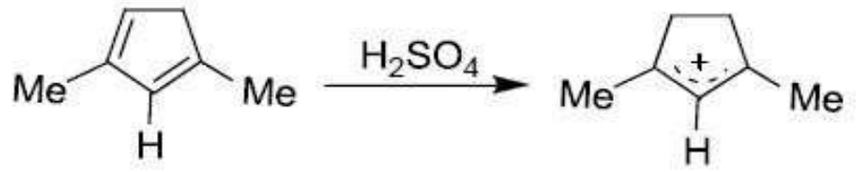


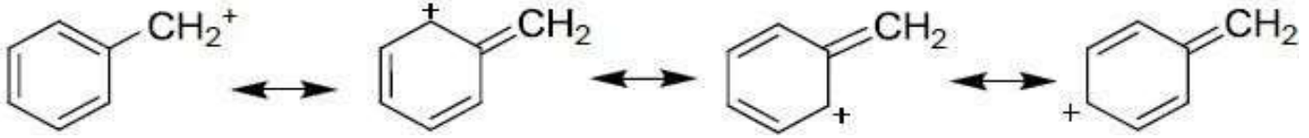
Cyclopropenyl cation is stable due to aromatization

STABLE ALLYLIC-TYPE CATIONS

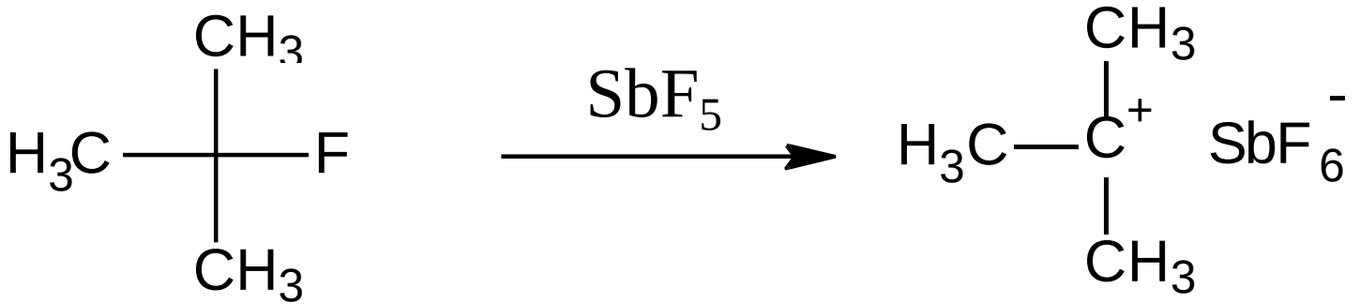
- Allyl cation and benzyl cation are more stable than most other carbocations.
- Molecules which can form allyl or benzyl carbocations are especially reactive. Stable allylic cations have been obtained by the reaction between alkylhalides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.





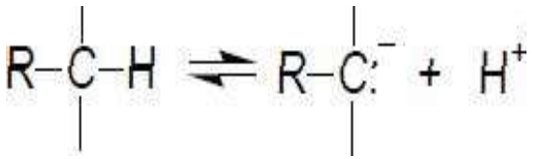


- **Detection of carbocation:** Formation of carbocation can be detected by NMR spectroscopy as the cation formation shifts the proton signals appreciably downfield due to deshielding of protons. For example;

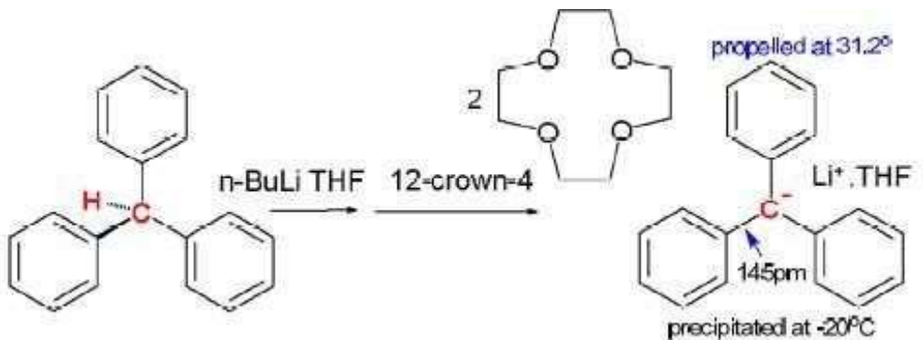


CARBANION

- 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.**

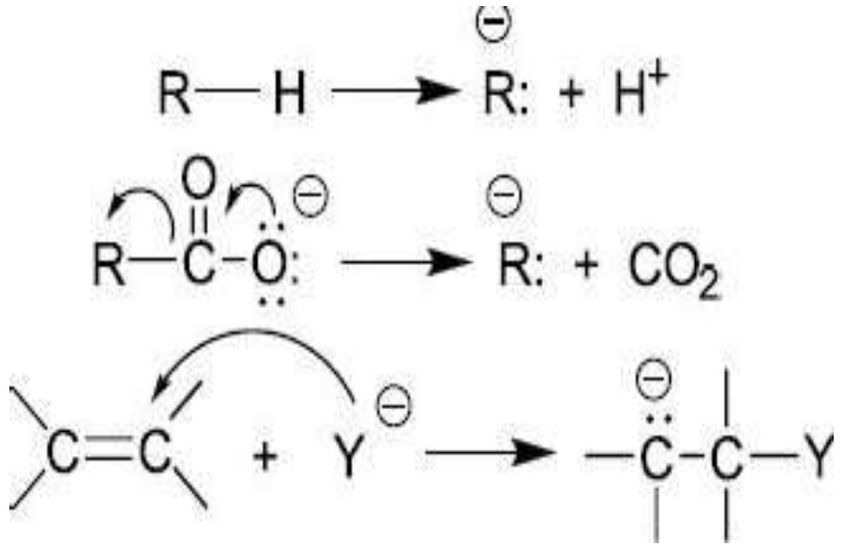


- Stable carbanions do however exist although in most cases they are reactive.
- Olmstead(1984):

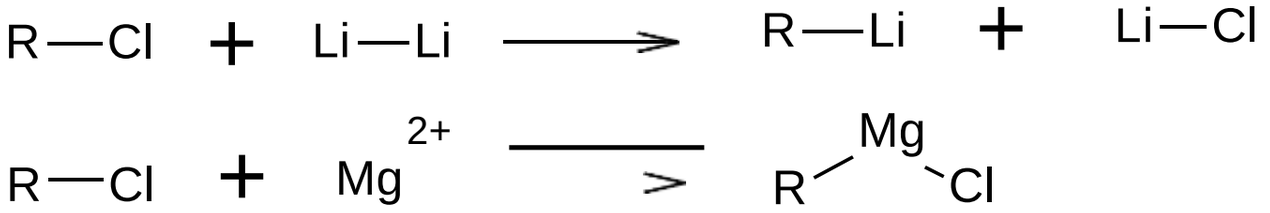


THE GENERATION AND FATE OF REACTIONS CARBANIONS

- A group attached to a carbon leaves without its electronpair.
- A negative ion adds to a carbon-carbon double or triplebond.

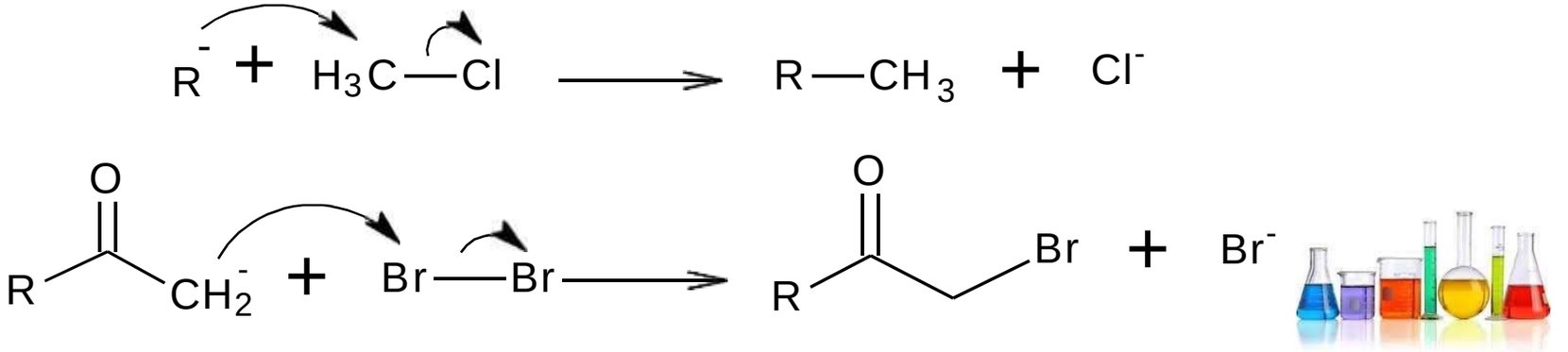


- Strongly reduced metals like Na or Li or Mg can convert alkyl halide to alkyl sodium or alkyl lithium or Grignard reagent.

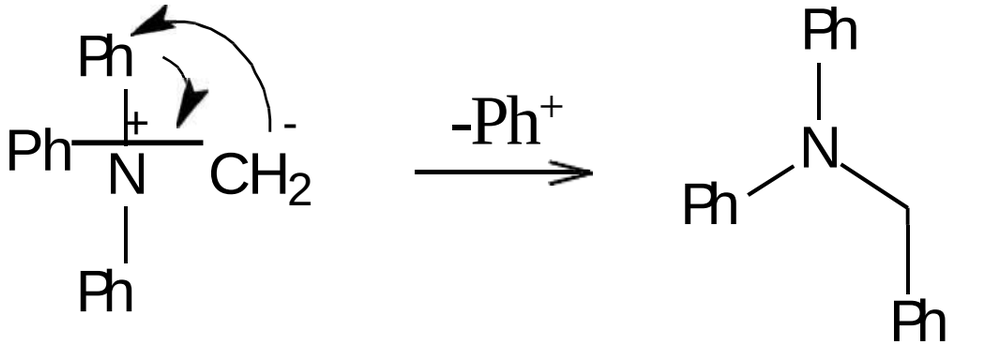


Reactions of carboanions

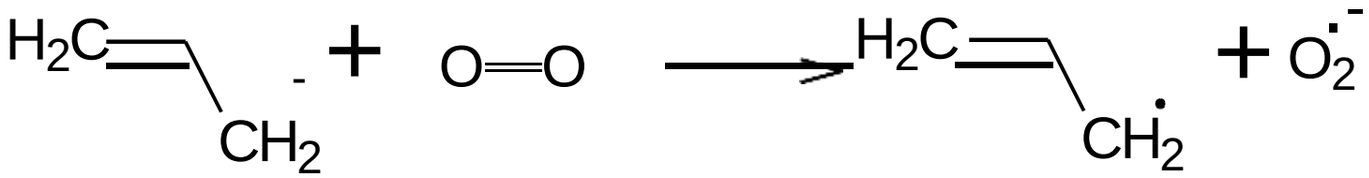
- Carboanions often act as a nucleophiles to react with electrophones species.



In rare cases ,the carboanions may undergo cationotropic 1,2-shift to give rearranged products, for eg;

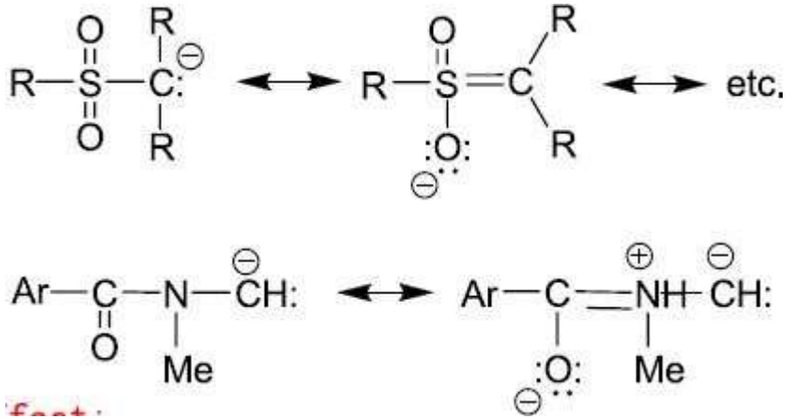


The carboanions may be oxidized to free radicals. For eg;



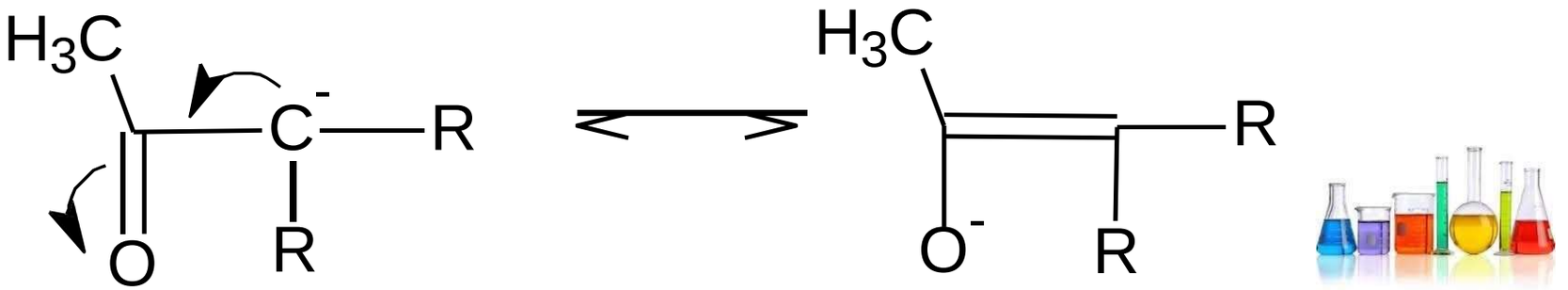
STABILITY AND STRUCTURE

- 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.
- Stabilization by sulfur or phosphorus.



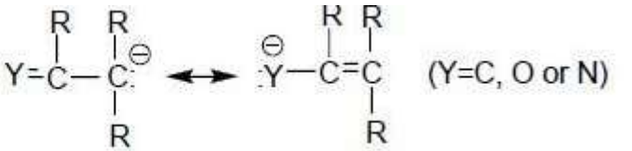
Field effect:

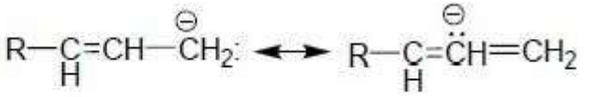
- Ylides are more stable than the corresponding simple carbanions.
- Carbanions are stabilized by a field effect if there is any heteroatom (O, N or S) connected to the carbanionic carbon, provided that the hetero atom bears a positive charge in atleast one important canonical form

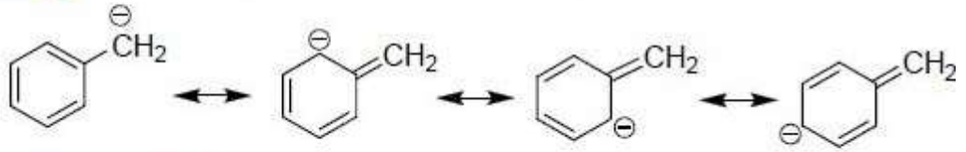


RELATIVELY STABLE CARBANIONS WITH CERTAIN STRUCTURAL FEATURES

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:

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

Factors determining the stability and reactivity of a carbanion:

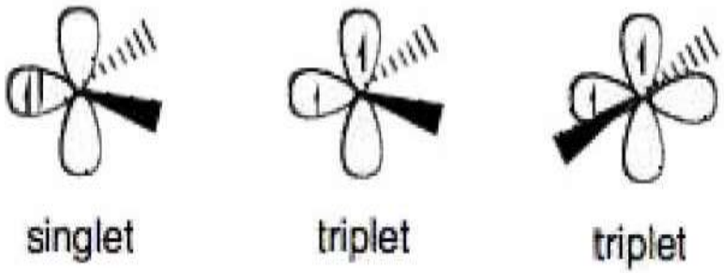
- The inductive effect: Electronegative atoms adjacent to the charge will stabilize the charge;
- Hybridization of the charge-bearing atom. The greater the ***sp3character*** of the charge-bearing atom, the more stable the anion;
- The extent of conjugation of the anion. Resonance effects can stabilize the anion. This is especially true when the anion is stabilized as a result of aromaticity

Detection

- Carboanions are type of CH_3^-, where the negative charge is not delocalized, due to conjugation can be distinguished from their ^1H NMR spectra.
- Formation of carbanions can be detected by the UV and Visible spectra of the different from the starting compounds.
- Trapping of carboanions with an electrophile may also show their formation of reaction.

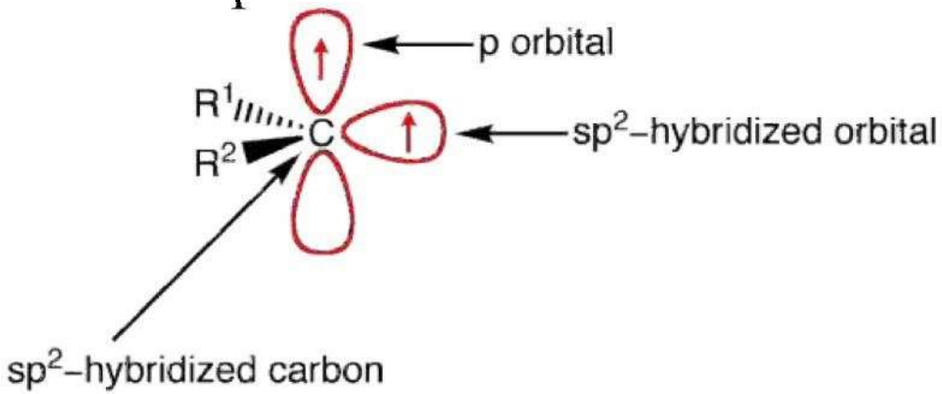
CARBENES

- A carbene is a highly reactive species containing a carbonatom with six valence electrons and having the general formula RR′C:, practically all having lifetimes considerably under 1 sec.
- Structure and bonding



the total spin=0	the total spin=1
Bond angle=102º	Paramagnetic ,may be observed by
For single	electron spin resonance spectroscopy
Methylene	

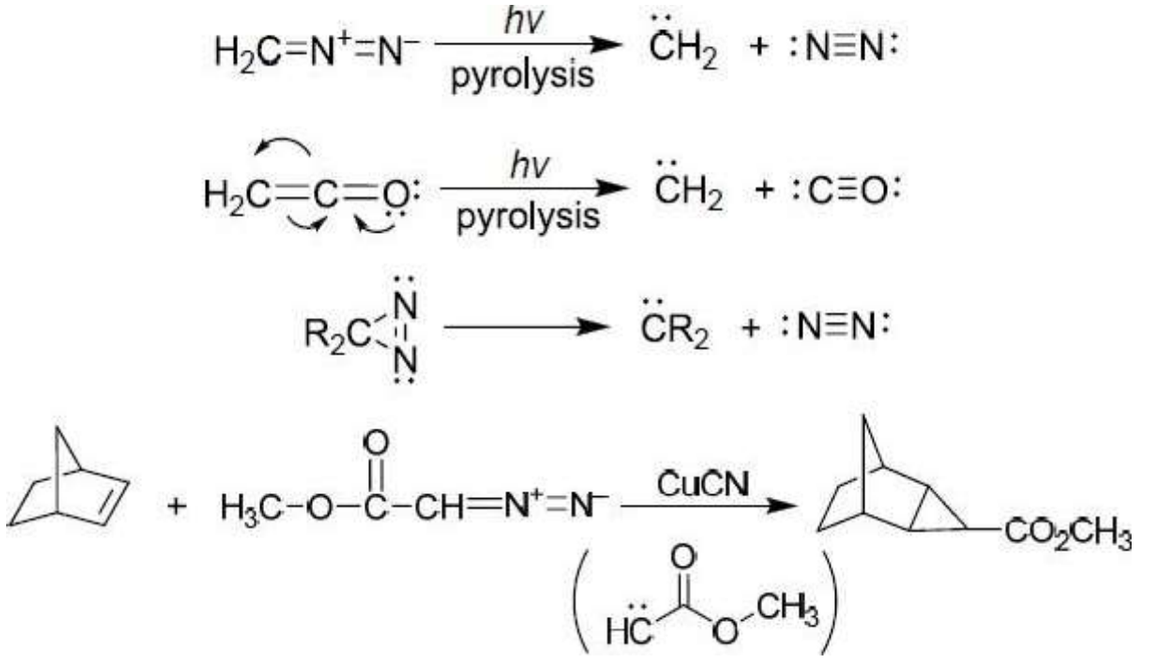
- Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.
- The C-atom in singlet carbene is sp^2 - hybridized in which the spin –paired electrons occupy an sp^2 orbital.
- Shape of carbenes is planar.



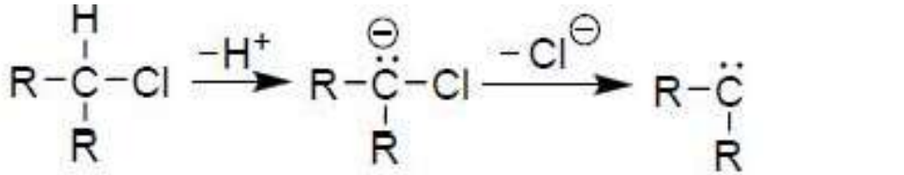
triplet carbene

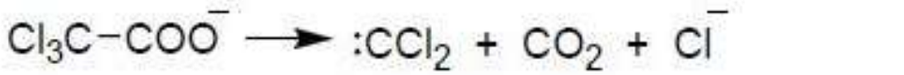
GENERATION AND FATE OF REACTIONS OF CARBENES

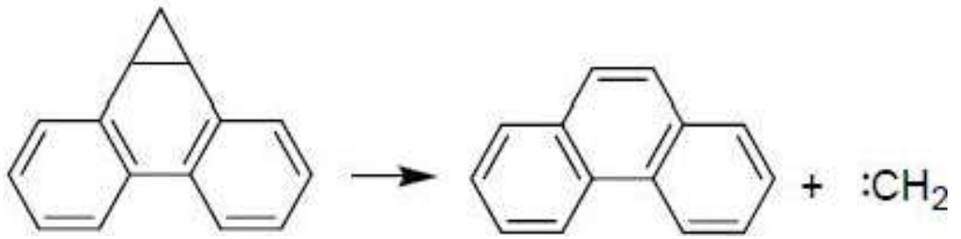
- Disintegration of diazoalkanes and their analogs, via photolytic,thermal, or transition metal (Rh, Cu)-catalyzed routes.



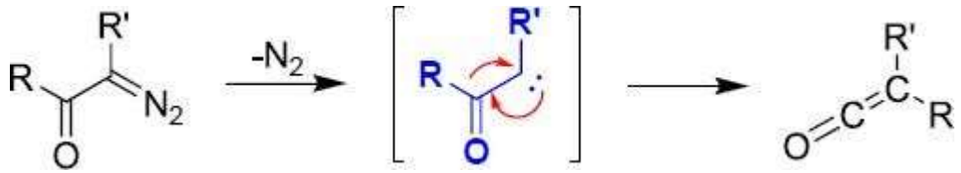
- Base-induced elimination



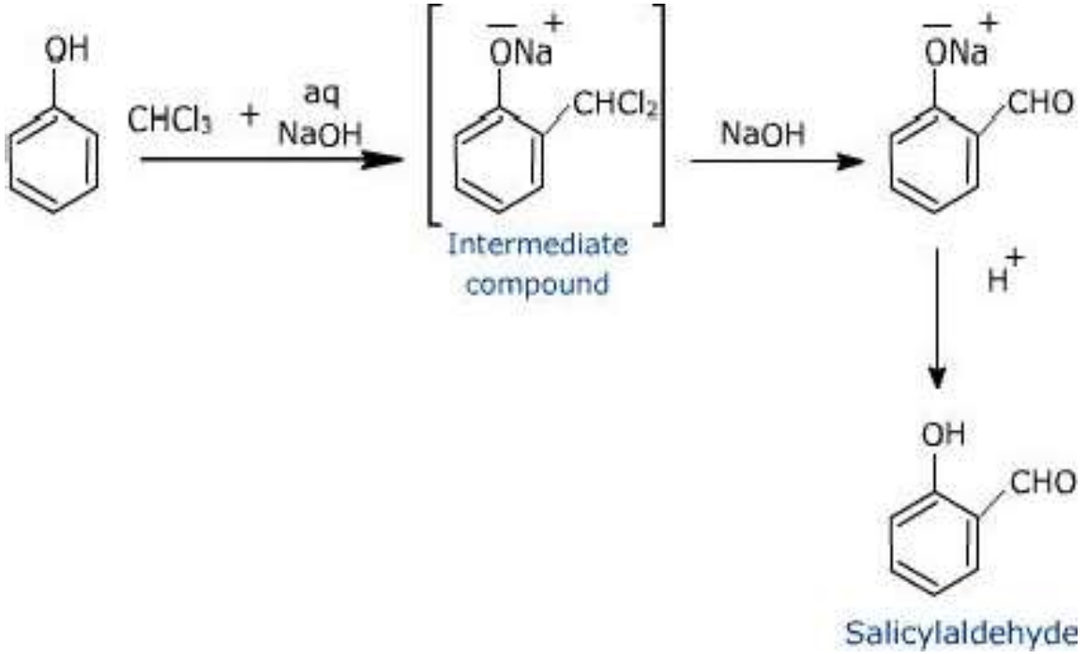




- Carbenes are intermediates in the Wolff rearrangement.



- Carbenes being the electrons-deficient species may take part in electrophilic aromatic substitution reactions. For eg; in Riemer –Tiemann reaction.



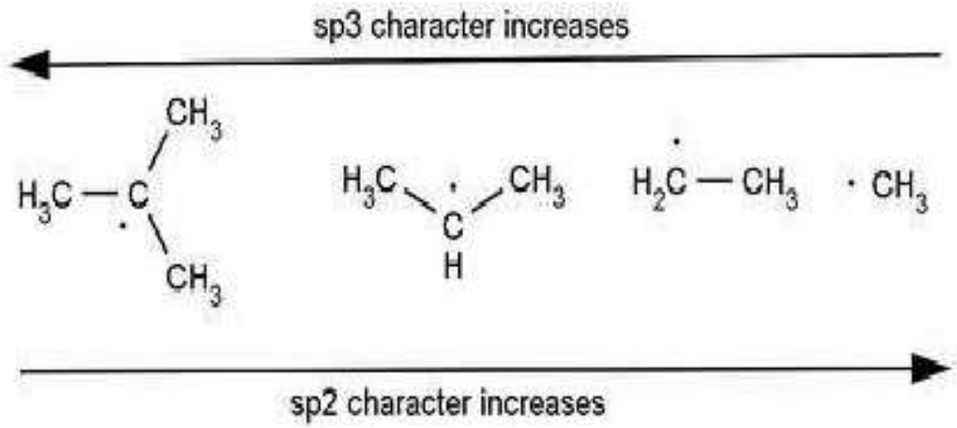
Detection

- Electron paramagnetic resonance spectroscopy(EPRS) can be used to detect the formation of the triplet carbenes.
- Rotational fine structure of the UV and Visible spectra can detect the formation of the singlet (bent form) or triplet(linear form) carbenes.
- π- Insertion reaction also can detect and distinguish the formation of singlet and triplet.

FREE RADICAL

- A free radical may be defined as a species that contains one or more unpaired electrons.
- Radicals play an important role in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes, including human physiology.
- The first organic free radical identified was triphenylmethyl radical, by Moses Gomberg (the founder of radical chemistry) in 1900.

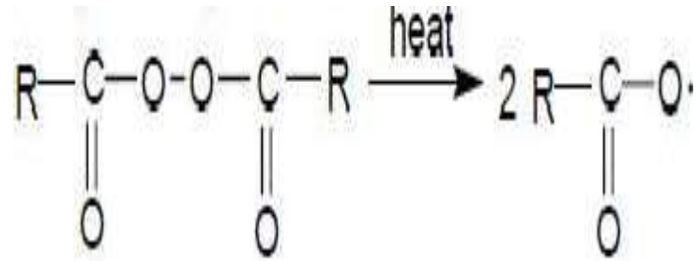
- A carbon -based free radical is a trivalent C-species having single p-electron in the valence shell.
- It has tetrahedral geometry where the C-atom is sp^3 hybridized.



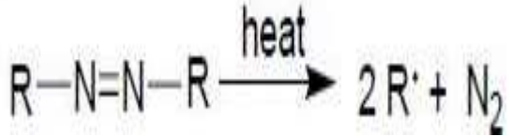
But essentially all alkyl free radicals are planar, it is just the relative difference.

GENERATION AND FATE OF REACTIONS OF FREE RADICALS

- Thermolysis or photolysis of organic peroxides and azo compounds generates free radicals.

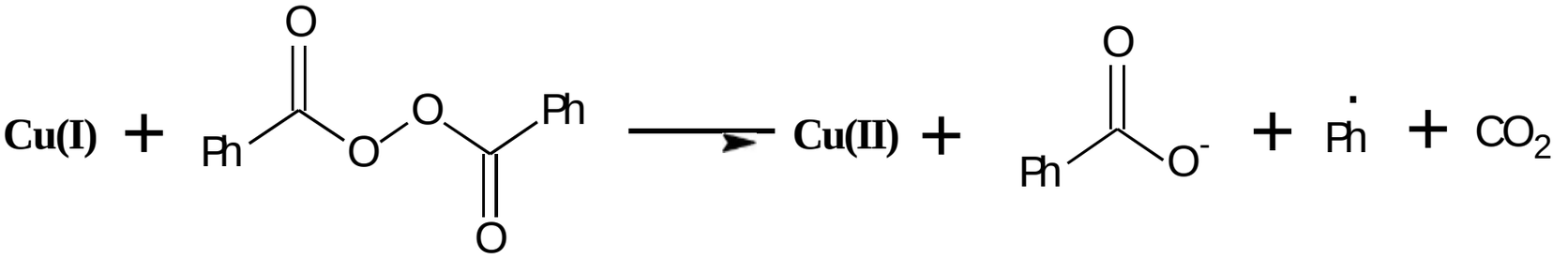


Alkyl peroxide Alkoxy radical



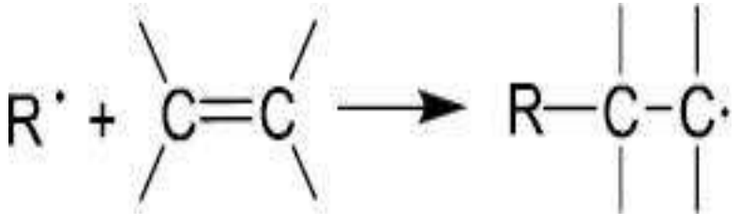
Azo Alkylnitrile

- Bimolecular redox reactions also generate free radicals. For eg;

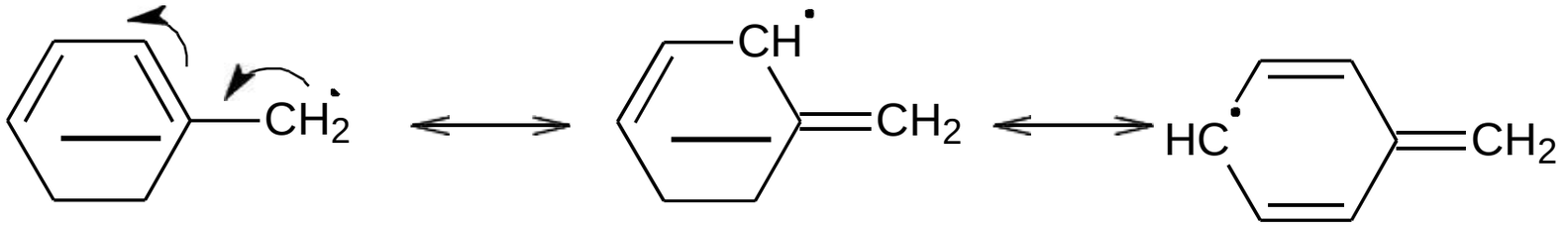


Stabilization of free radicals:

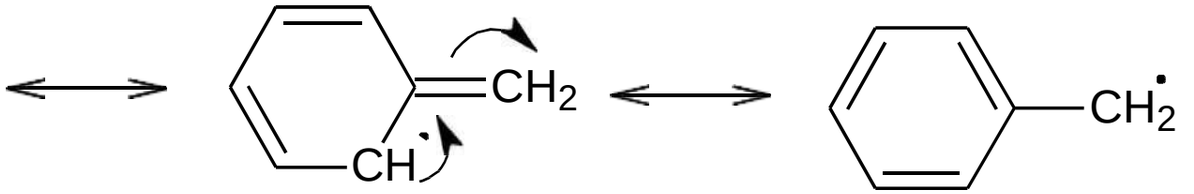
Resonance effect due to conjugation stabilizes the free radicals.



For aromatic

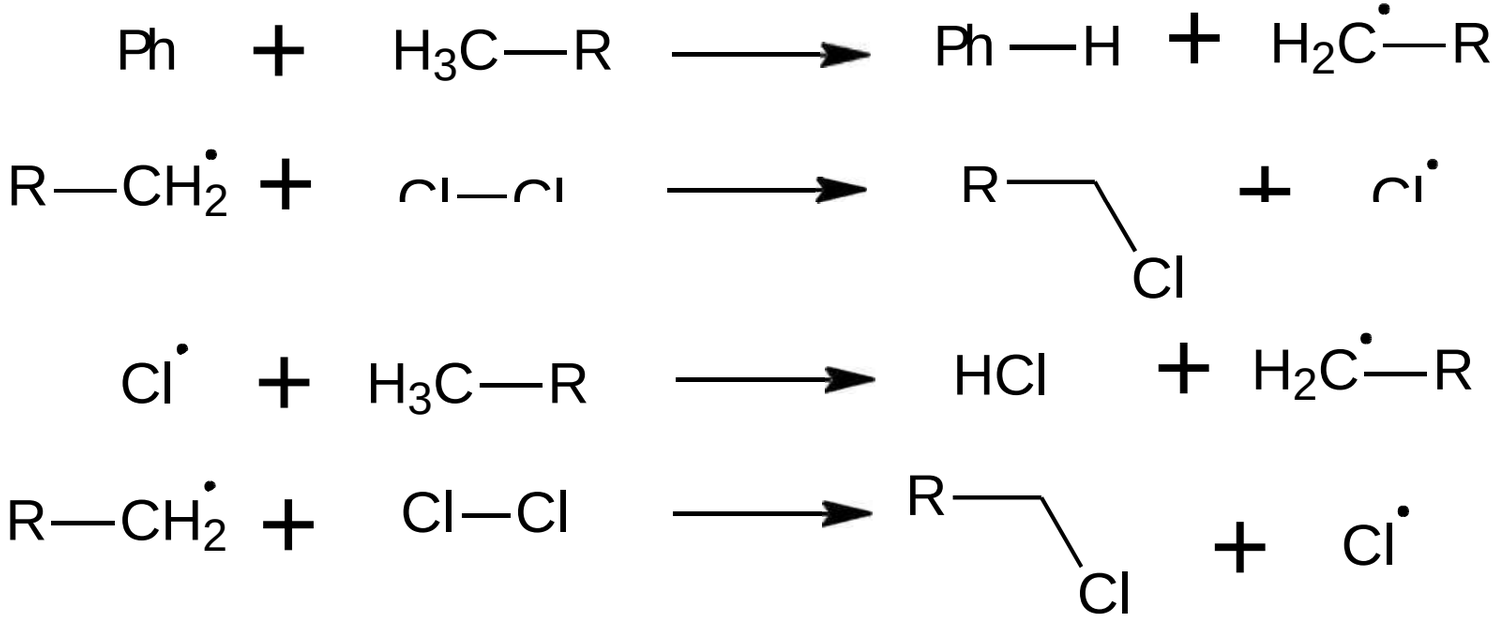


Benzyl radical

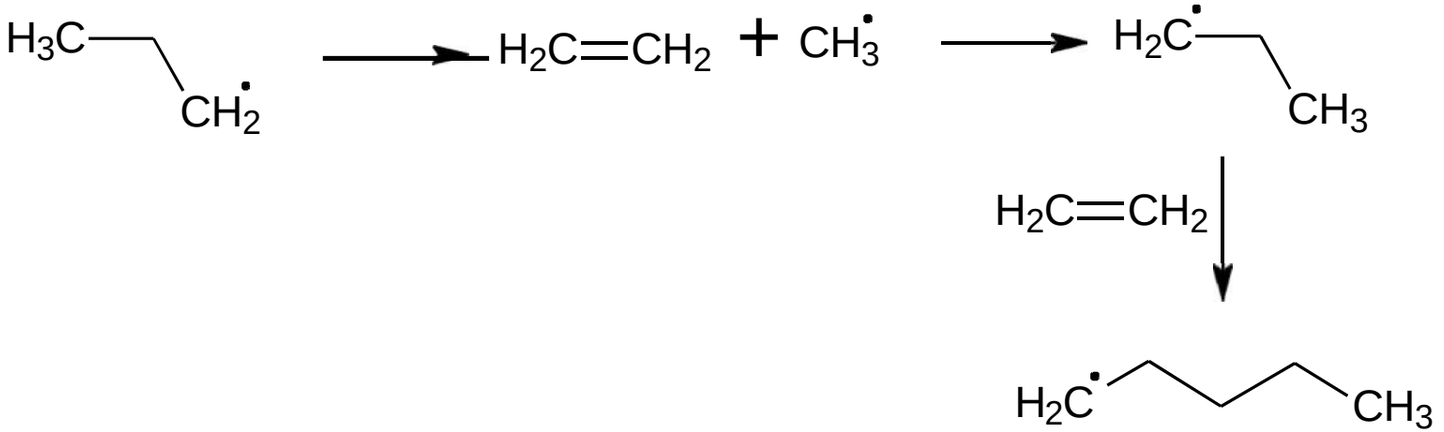


Reactions of free radical

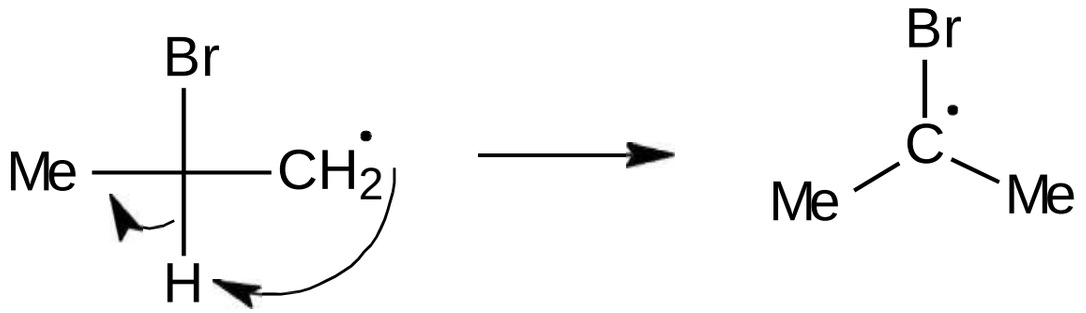
- Free radical often take part in radical-propagating reactions.



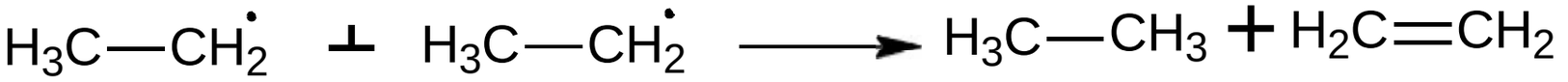
- In some cases, the free radical itself may be fragmented and trigger the propagation of a chain reaction. For eg;



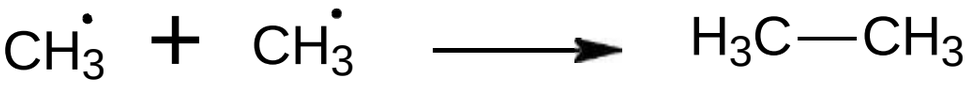
- Suitably substituted free radical may isomerize.for eg;



- Disproportion and radical coupling are the common reactions of the termination of free radicals. For eg;



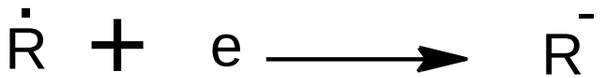
DISPROPORTIONATION



RADICAL COUPLING

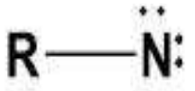
DETECTION OF FREE RADICALS

- By using electron spin resonance (ESR)
- Highly stabilized free radicals may be detected UV and visible spectroscopy.
- NMR spectroscopy can detect free radicals (by studying the overhauser effect).
- The unpaired electron in a free radical is accommodated in a single occupied molecular orbital(SOMO).
- If the SOMO is a high-energy orbital, the free radical shows a tendency to loose an electron.
- If the SOMO is a low-energy orbital ,it shows a tendency to accept an electron.



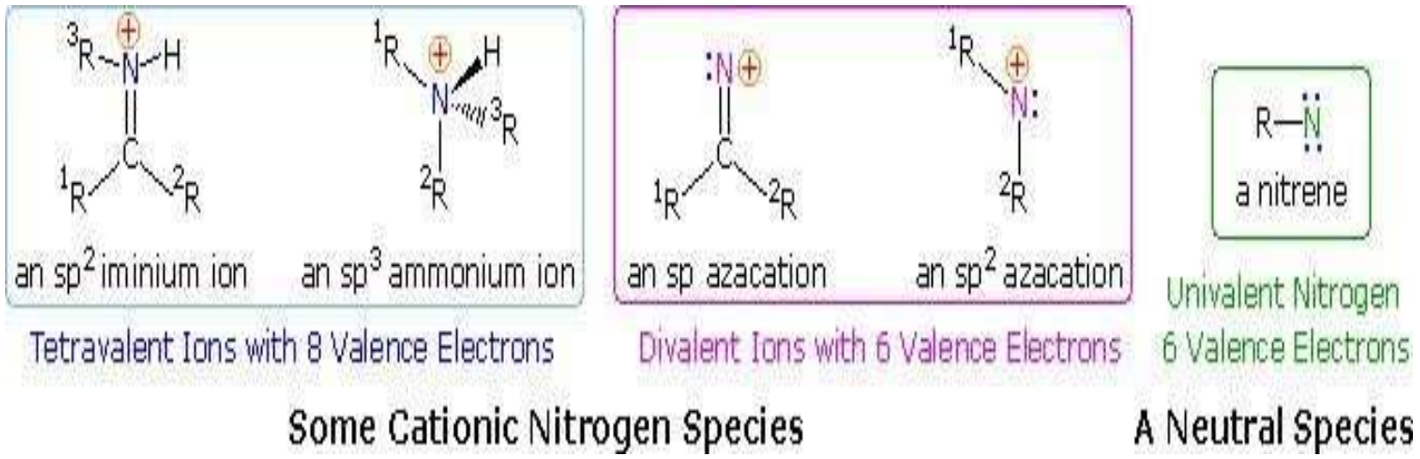
NITRENES

- These are neutral reaction intermediates where the central nitrogen atom is electron-deficient and has a sextet of electrons.



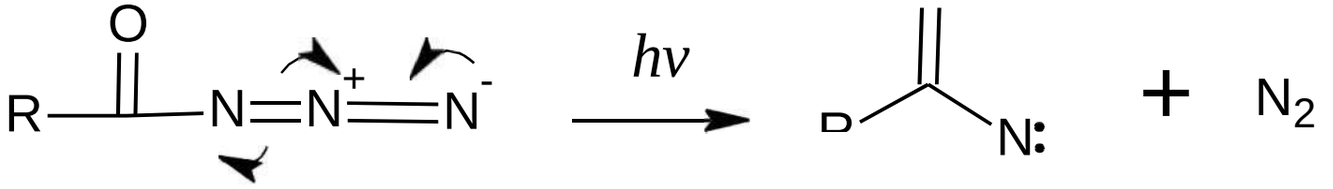
The structure of a typical nitrene group

- Sp^2 hybridized and planar in shape.



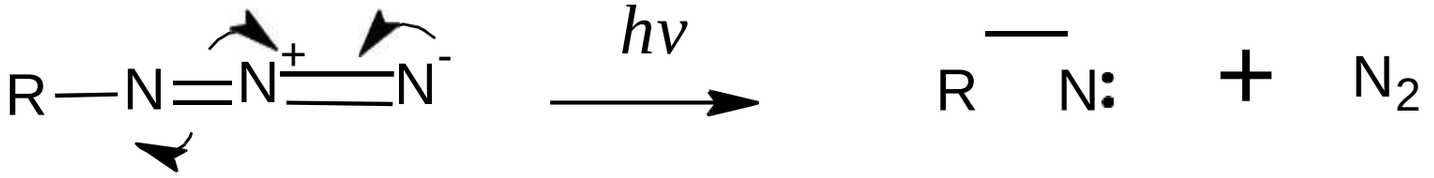
GENERATIONS OF NITRENES

- Like carbenes , these are also generated by protolytic,thermal, or base –catalysed α-elimination reactions. For eg;



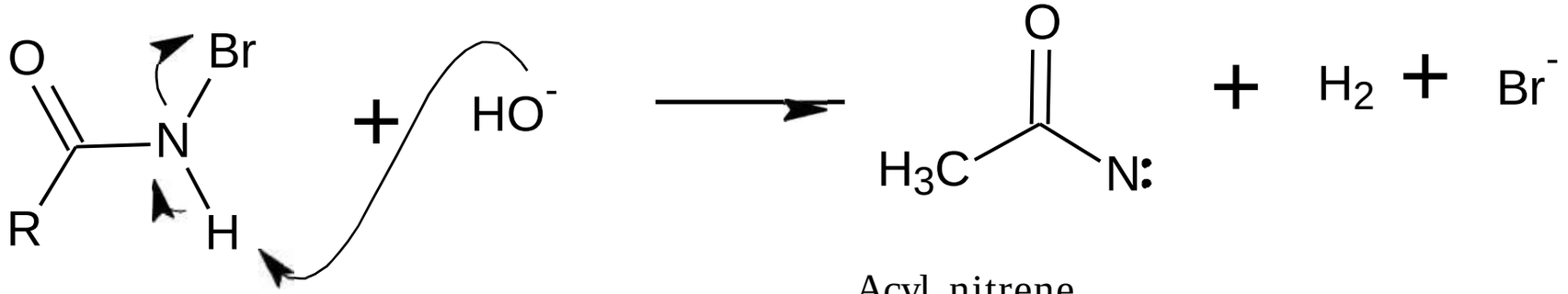
Acyl azides

Acyl nitrene



Alkyl azides

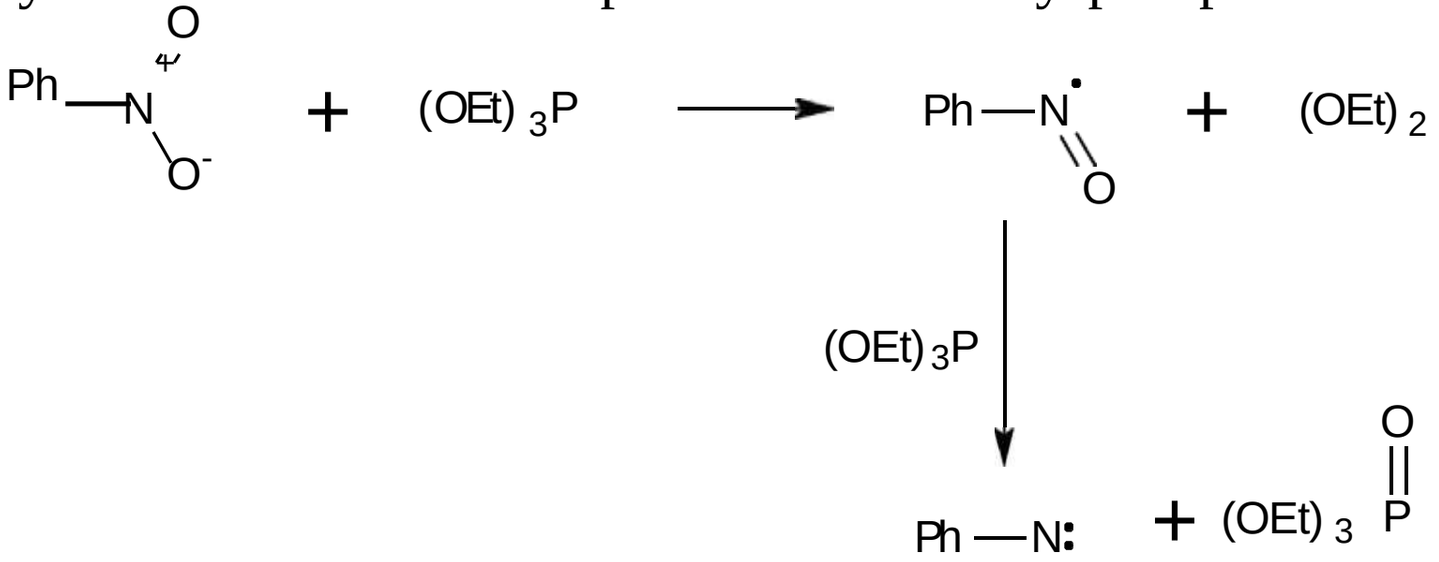
Alkyl nitrene



N-bromoamides

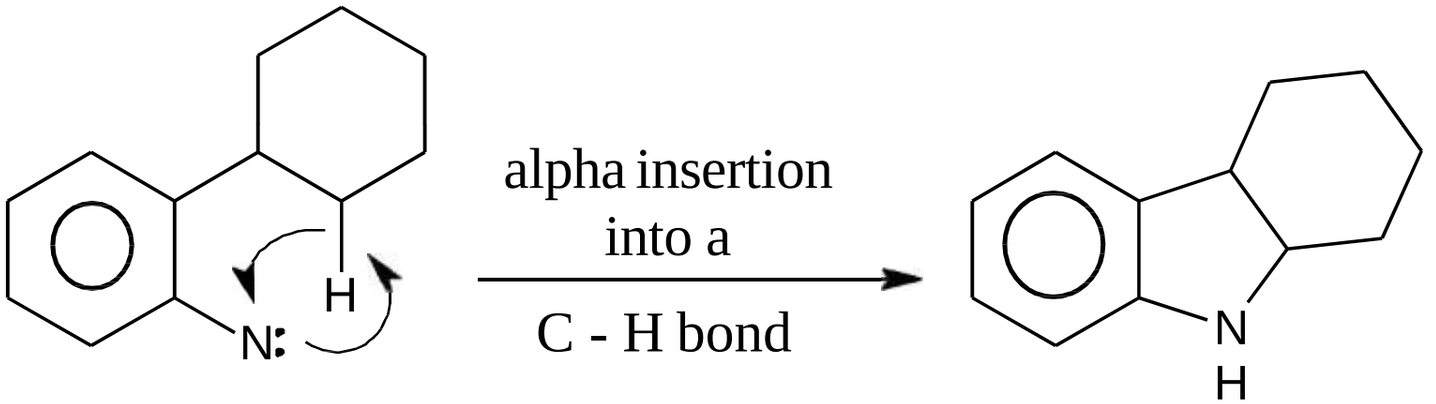
Acyl nitrene

- By reduction of nitro compounds with trialkyl phosphites.



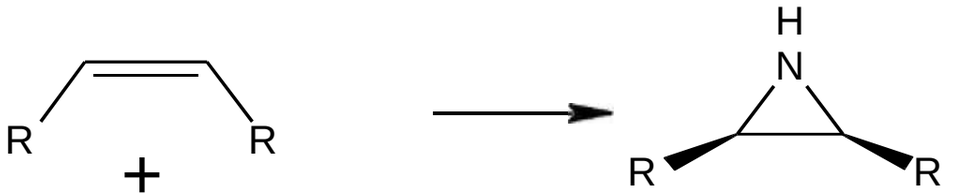
REACTIONS OF NITRENES

- Singlet nitrene undergoes a σ-insertion to give 2^0 - amines. For eg;



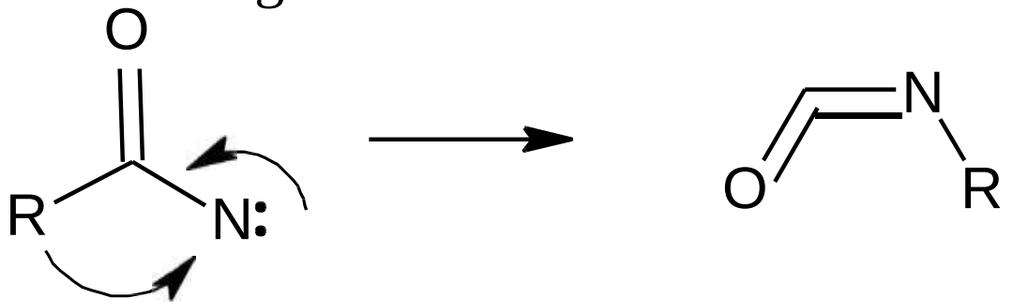
2^0-Amine

- π- Insertion of nitrenes into a C=C bond gives aziridines.



Singlet Nitrene

- Acyl nitrenes undergo skeletal rearrangement to give alkyl isocyanates.this rearrangements is involved in Crutius and Hoffmann rearrangements.



Acyl nitrene

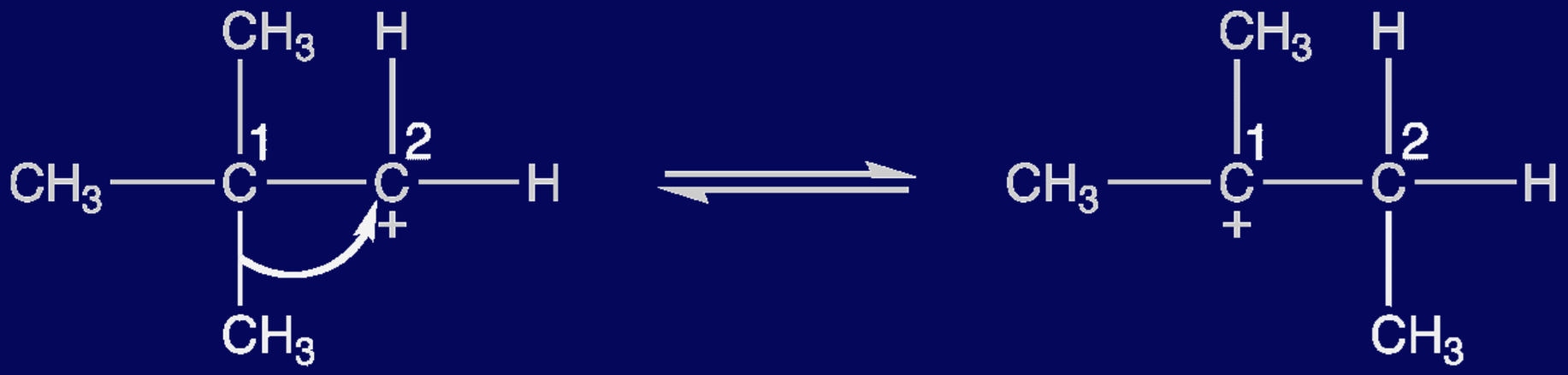
Alkyl isocyanate

Detection of nitrenes

- Triplet nitrenes can be detected and distinguished from singlet nitrenes, like carbenes ,by EPR.

Rearrangement reactions

- One atom or a group moves from one atom to another within same molecule
- Migration from a atom to adjacent atom is called 1,2-shift.

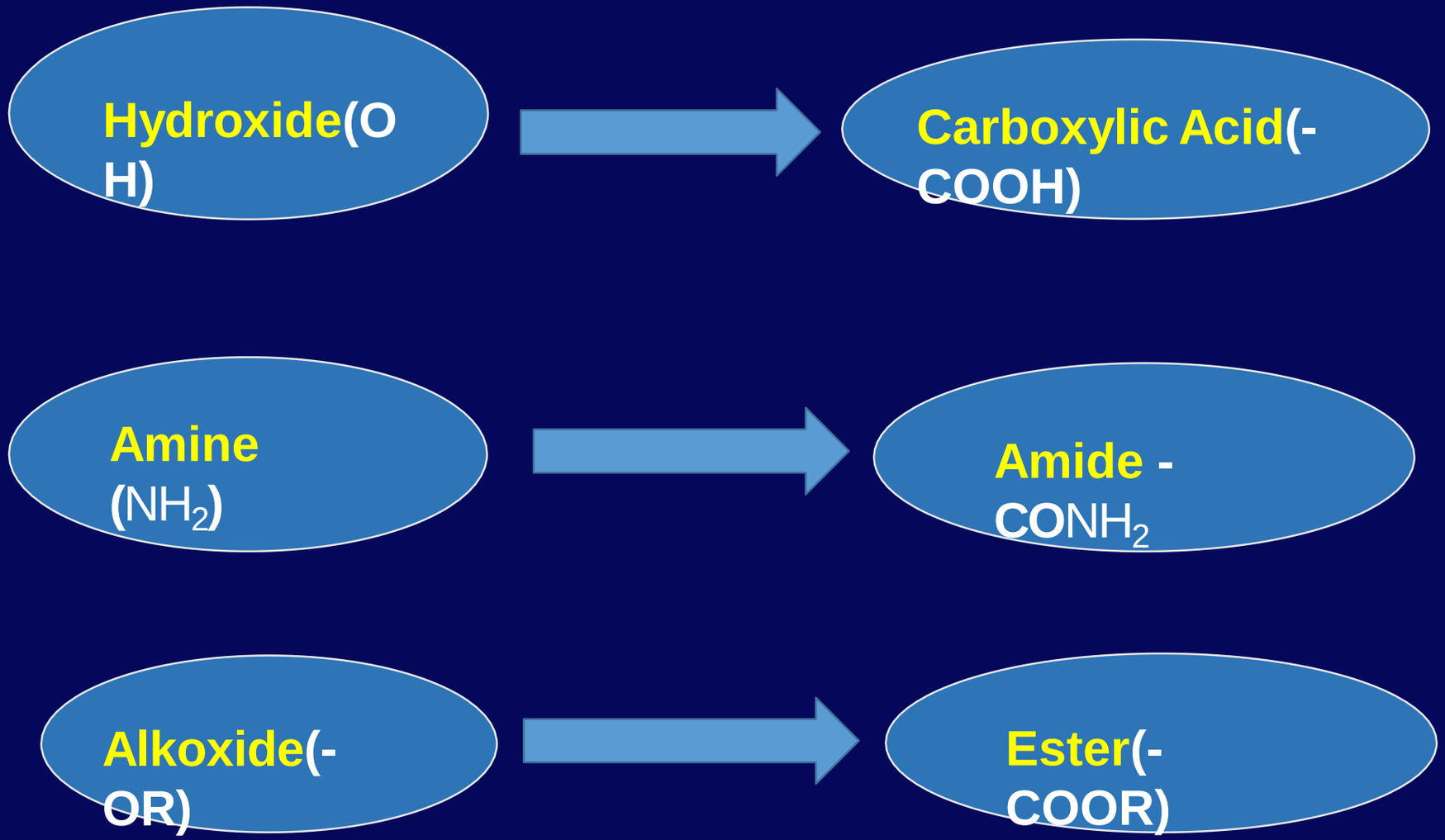


Listen Carefully

➢Favorskii Rearrangement

- Rearrangement of cyclopropanones and α- halo ketones, which leads to formation of carboxylic acids, or carboxylic acid derivatives.

Listen Carefully



Listen Carefully

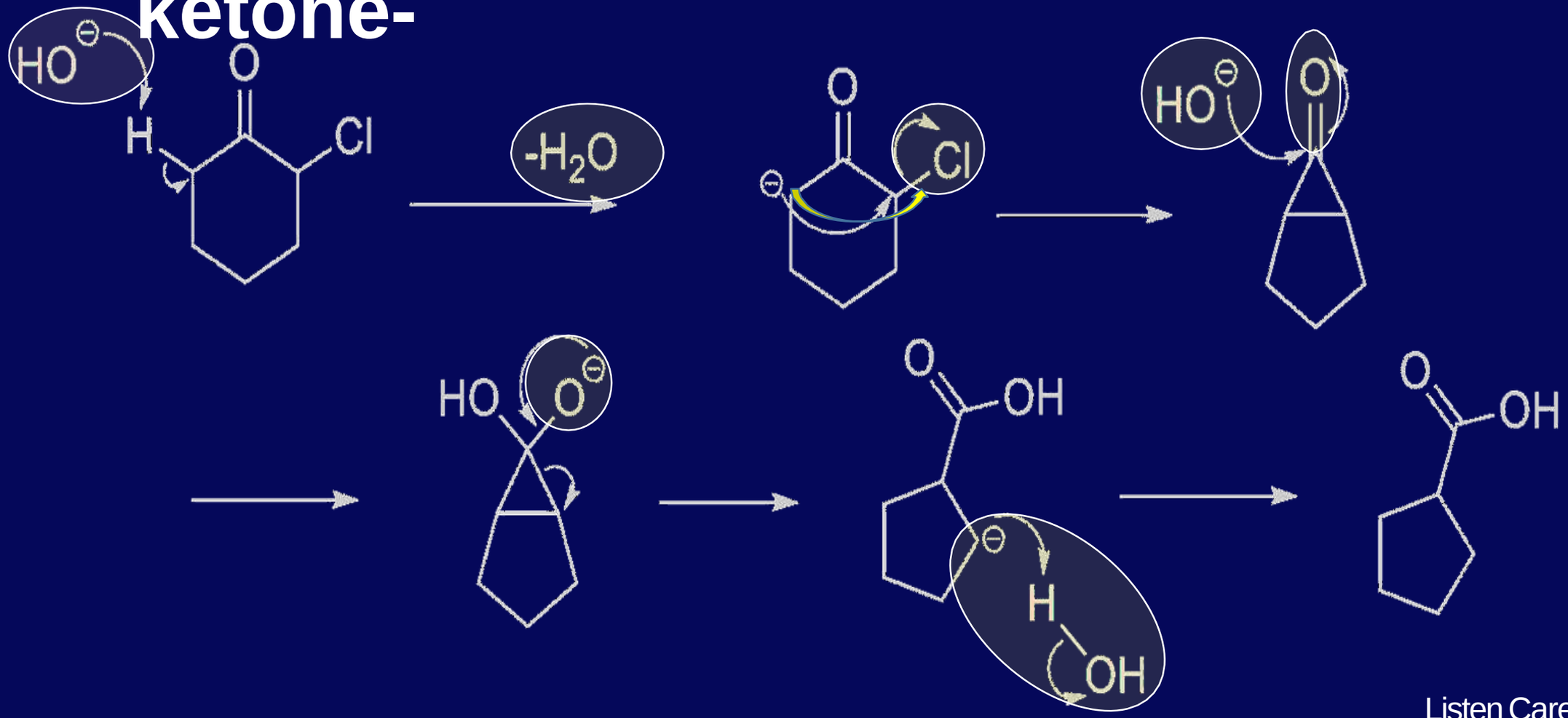
Cyclic α-halo ketones, the Favorskii rearrangement constitutes a ring contraction.

6-Membered

5-Membered

Listen Carefully

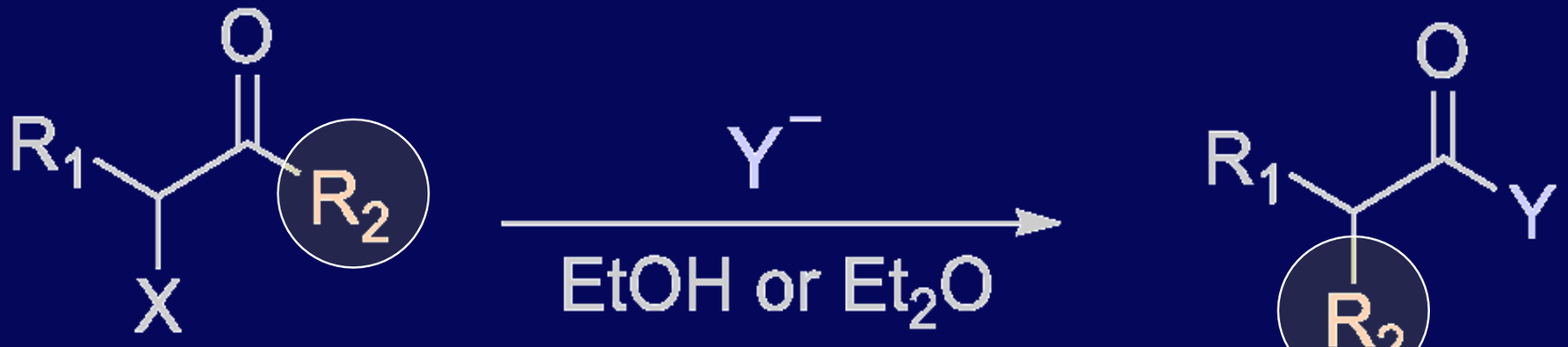
Mechanism of Cyclic α-halo ketone-



Listen Carefully

When there is a group on non-halogenated alpha position

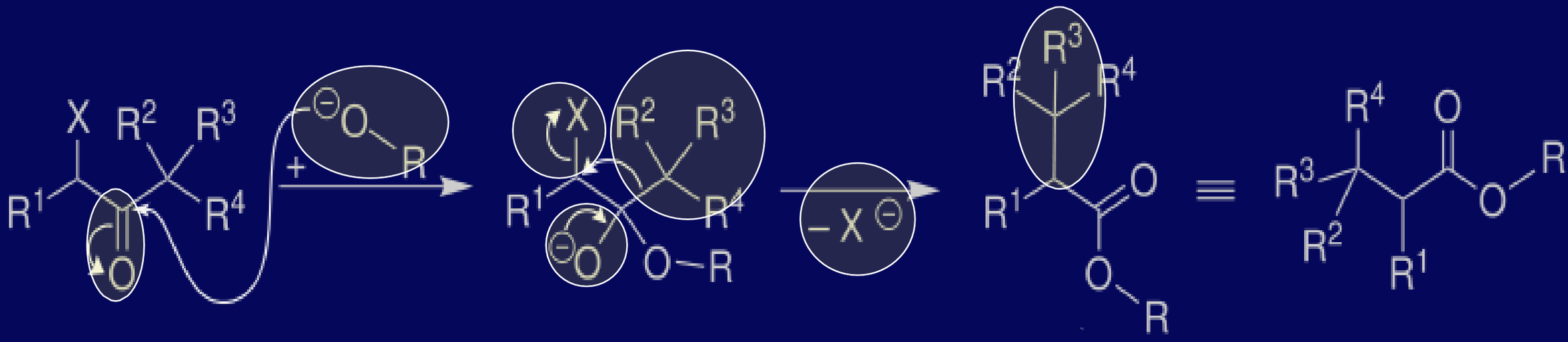
- When there is no α-Hydrogen then migration of the groupwill take place



Y = OH, OR, NR_2

Listen Carefully

Mechanism



R= H, CH_3 etc.
X= Cl, Br

Listen Carefully

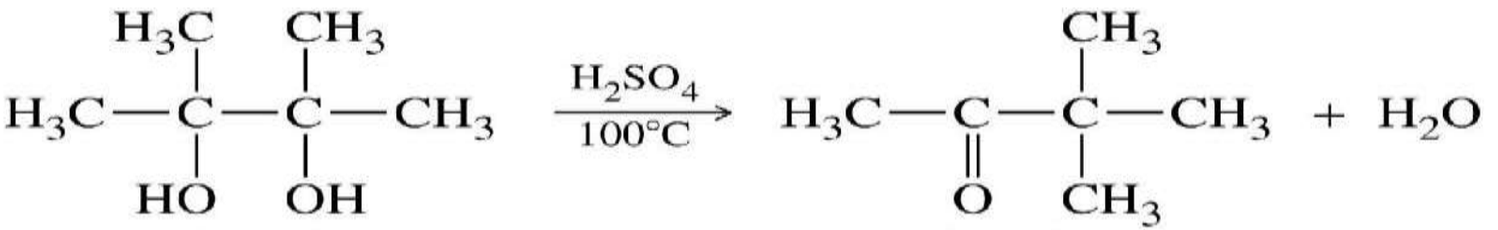
PINACOL-PINACOLONE REARRANGEMENT

Contents:

- Introduction
- Mechanism
- stereochemistry
- Migratory aptitude
- Applications
- References

Introduction:

- The conversion of pinacols(1,2-glycols) to ketones or aldehyde by means of mineral acids or zinc chloride is known as pinacol-pinacolone rearrangement.
- It is a anionic rearrangement i.e. migrating group moves from a carbon atom to an electron defecient carbon which has only six electrons in it's valence shell.
- Pinacol-pinacolone rearrangement is general for 1,2-glycols & the migrating group may be alkyl or aryl.

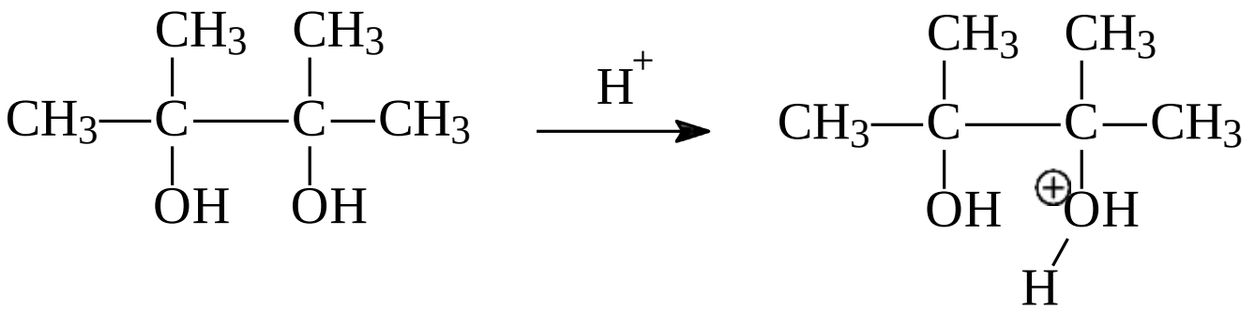


pinacol
(2,3-dimethyl-2,3-butanediol)

pinacolone
(3,3-dimethyl-2-butanone)

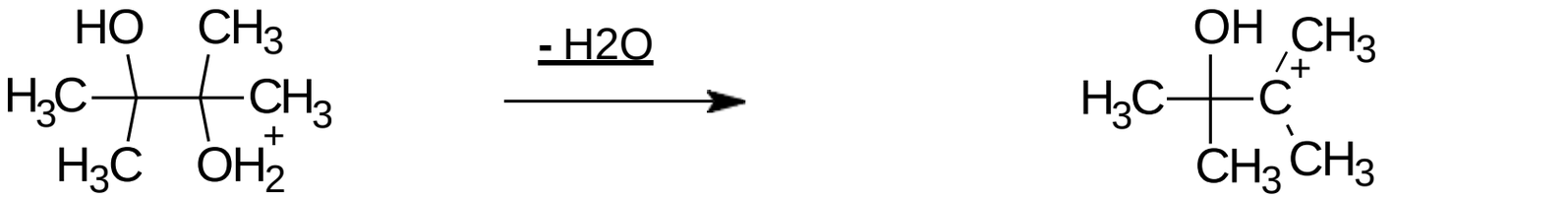
Mechanism:

- STEP-1:Initiation:-
- protonation of 1,2-diol.



2,3-Dimethyl-2,3-butane diol

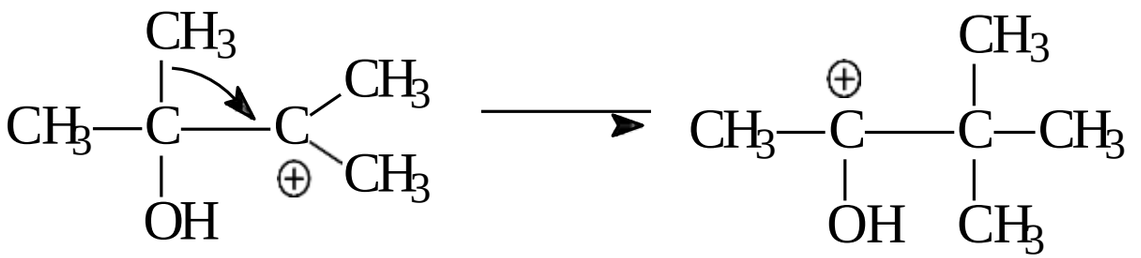
- Step-2:formation of carbonium ion by loss of water from protonated diol.



(3-hydroxy-2,3-dimethylbutan-2-yl)oxonium

3-hydroxy-2,3-dimethylbut-2-ylium

- Step-3:Rrearrangement of carbonium ion by 1,2-shift to give protonated ketone.



Carbonium ion

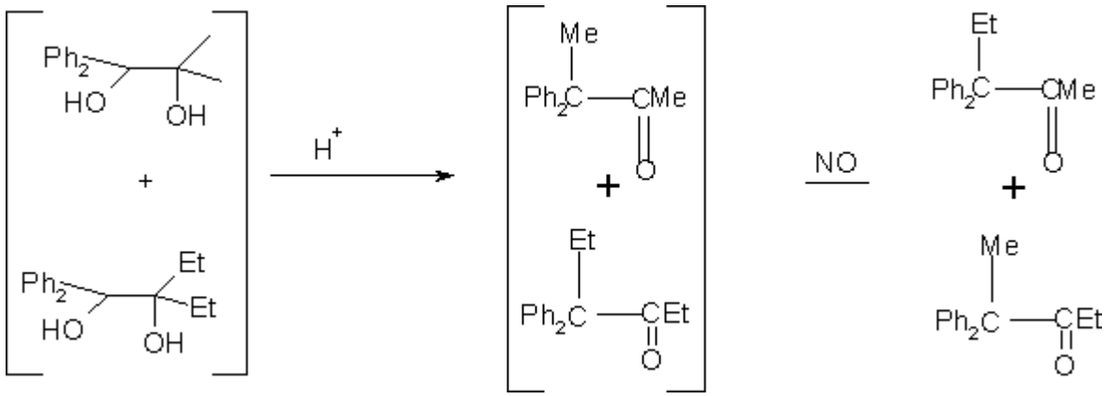
Protonated ketone

- Step-4:formation of ketone by loss of proton from protonated ketone.

pinacolone

Stereochemistry:

- It has been shown that the migrating group does not become free during the rearrangement .
- For e.g. taking two pinacols(48 & 49) that are very similar in structure but have different migrating groups,and rearranging them simultaneoesly in the same solution:no cross migration is ever observed.



- Similarly,if rearrangements in which there is a hybrid shift are carried out in a deuteriated solvent (e.g.D2O,MeOD,etc),no deuterium is incorporated into the new C-H(D) bond in the final rearranged product.

- In both cases the rearrangement is thus strictly intramolecular, i.e. the migrating group does not become detached from the rest of the molecule.

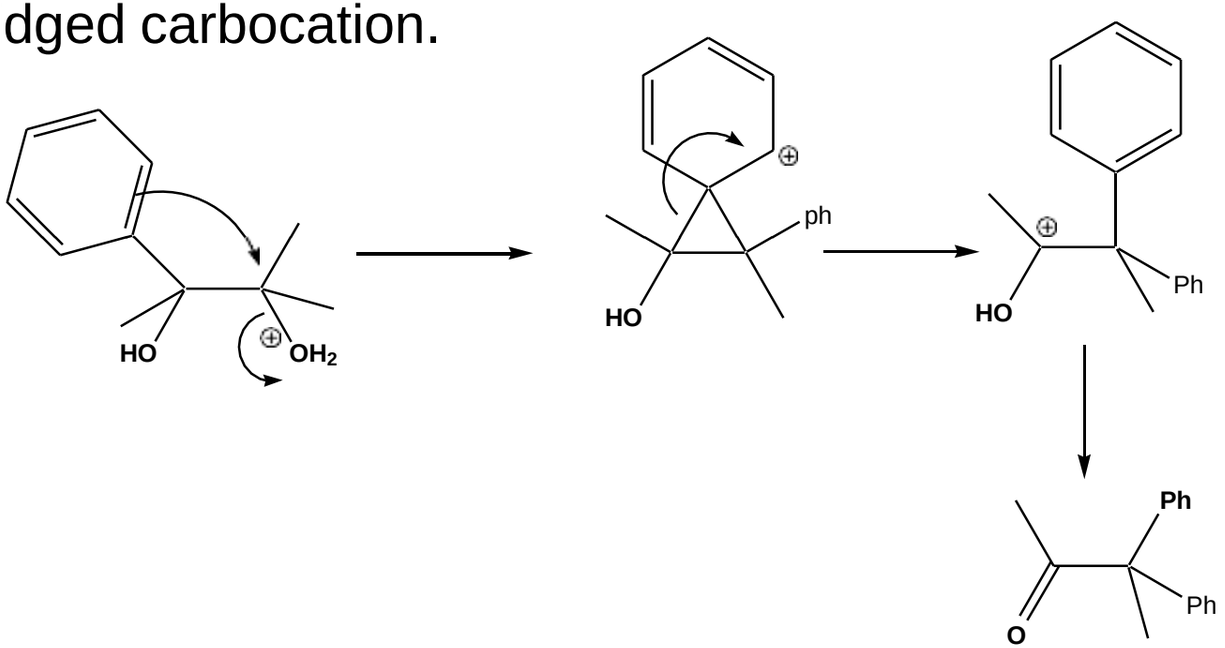
- This suggest there is no opportunity for it's configuration to change, i.e.retention of configuration.

Migratory aptitude : A general order of migratory aptitudes for the pinacol rearrangements is:

p-anisyl > *p*-tolyl > phenyl > *tert*.-alkyl > primary alkyl > H

- Aryl has greater migratory aptitude because it assists in the departure of leaving group (anchimeric assistance)

Via bridged carbocation.

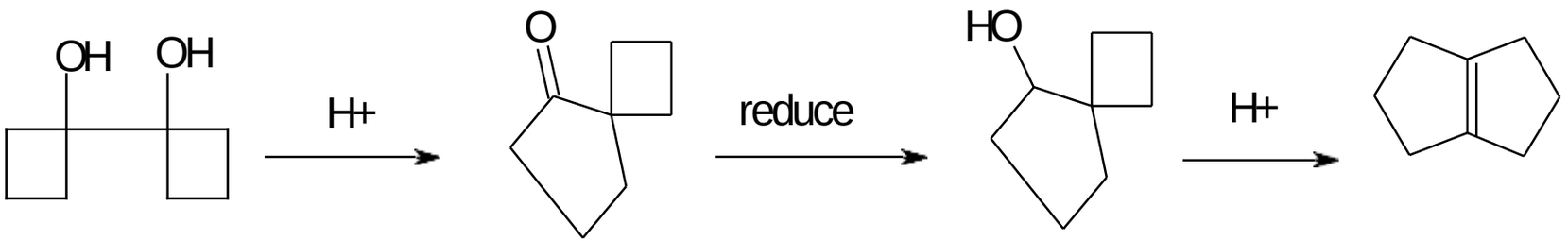


Electron donating groups at the ortho or para position will enhance the migratory aptitude while electron withdrawing groups will lower the aptitude for migration.

Applications:

- It is used in preparation of pinacolones**.**

- A nice synthesis of the bicyclic alkene on the right starts with a pinacol reaction.The ‘pinacol’ dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused to the remaining four membered ring.Reduction of the ketone then gives an alcohol that rearranges to the alkene.



- It is used in the preparation of furoscrobiculin B,a sesquiterpene
isolated from basidiomycetes of mushrooms.

- Pinacol rearrangement is also useful in preparation of Hydroxyphenstatatin,a antimitotic agent.

MOLECULAR REARRANGEMENTS

Key words: rearrangement reactions, migration to electron deficient nitrogen, electron deficient oxygen, electron deficient carbon. Migratory aptitude, cross-over experiments

Module Introduction

Rearrangment reactions are an interesting class of reactions wherein a group or an atom migration during the course of the reaction. While most of the rearrangements are designed in that fashion, it can also be undesirable in some cases. Depending on the reaction conditions, the nature of rearrangement (and the product) could also change.

In this module, various rearrangement reactions are presented. These are classified with respect the the migration origin and migration terminus.

Emphasis has been placed on examples involving skeletal rearrangements that are practically used in day-to-day organic synthesis.

I. *Introduction*

*Rearrangement reactions involve the migration of a group or an atom from one center (**migration origin**) to another (**migration terminus**) within the same molecule.*

In the above-mentioned generalized representation, atom-A is migration origin from where the migrating group " W" moves to atom-B (migration terminus)

These rearrangements can be roughly classified on the basis of the nature of the migrating group/atom,

i. Nucleophilic or Anionotropic: migrating group migrates with its electron pair.

ii. Electrophilic or cationotropic: migrating group migrates without its electron pair.

iii. Free radical: migrating group migrates with only one electron.

Of these most commonly found are nucleophilic one.

These rearrangements can take place in two possible modes,

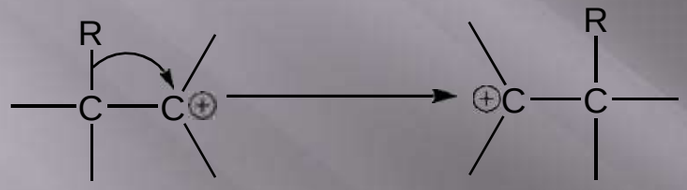
i. Intramolecular : In these migrating group do not completely detach from the migration origin and occurs within the same molecule.

ii. Intermolecular : In these migrating group is detached from the migration origin. In this case, migration of a group/atom can take place to different molecule.

II. *Origin of* 1,2-*rearrangement*

Different pathways through which 1,2-*rearrangement takes place are given below. Examples 1-3 involve* <u>*electron deficient carbon*</u> *atoms*

1.



2.

3.

4.

5.

Akey driving force in such rearrangement reactions comes from the conversion from a sextet to octet electronic configuration

Some General features of 1,2-rearrangement reactions

Reactions 1 *to* 3, a species with *valence electron sextet either carbocation or carbenium ion is involved. Thermodynamic driving force for an* 1,2-*rearrangement will be significant if rearrangement leads to a structure with octet on all atoms or generates some other more stable carbocation [reaction* 1*] i.e. if newly generated carbocation is stabilized electronically by its substituents than its preceding carbocation. Alternatively, reduction in angle strain can also provide the driving force.*

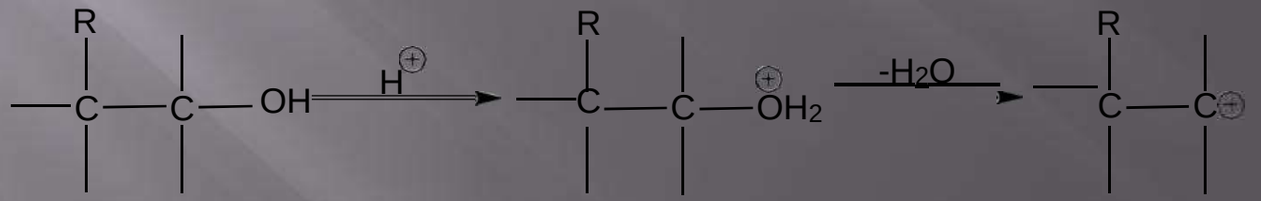
Reaction 4 *&* 5 *show second cause for occurrence of rearrangement. In reactions 4 and 5, atom* b *is bound to a good leaving group. Heterolysis of such a bond would provide a carbocation. Departure of the leaving group is then assisted by neighboring group. This sometimes gives a positively charged three membered ring I(as in reaction* 5*). Rearrangement in such reactions is possible only if group* x *is present at new position in product than in the reactant*

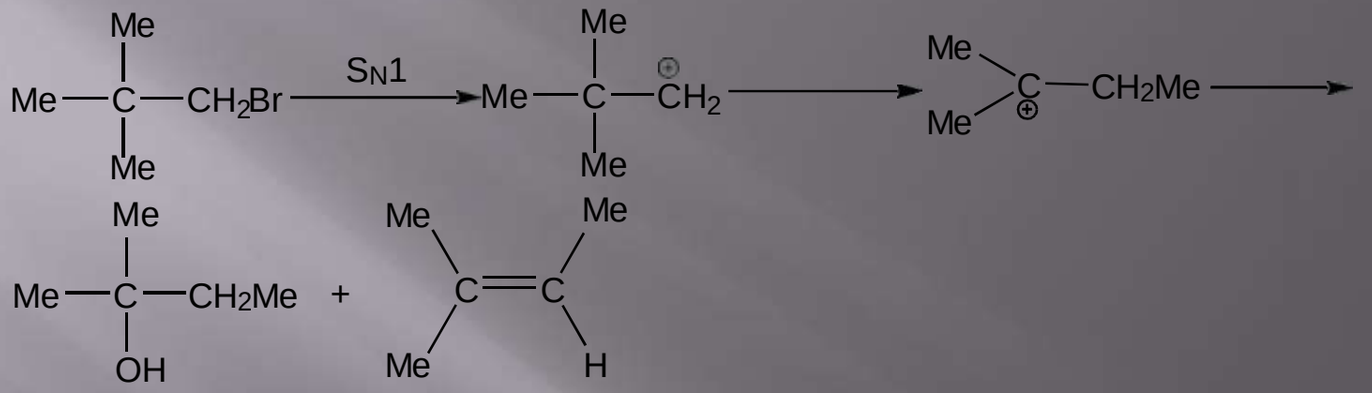
III. *Mechanism of nucleophilic rearrangement*

Broadly these reactions consists of three steps;

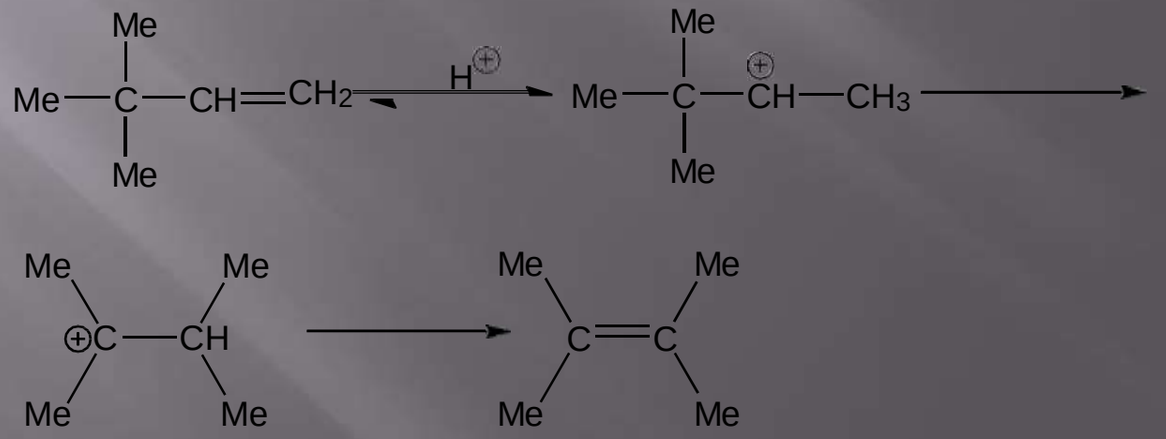
a)First step is ***generation of electron deficient centre*** *in the molecule. As the migrating group migrates with electron pair, the migration terminus must have an incomplete octet. This can be obtained in two ways ,*

i. Through carbocation: Carbocations can be formed in various ways. The most common being dehydration of alcohol. This step is similar to that of S_N1 *or* E1 *reaction.*





Rearrangement of carbocation is very important reaction in cracking of petroleum products.



ii. Through nitrenes : nitrenes can be formed by decomposition of acyl azides.

b)Migration: *Migrating group migrates to the electron deficient centre with its electron pair creating new electron deficient centre.*

c)In third step, newly formed electron deficient centre acquires octet either by accepting a nucleophile or excluding proton.

It is observed in many cases that either two or all three steps take place simultaneously. As seen in many cases S_N1 type of first step is commonly followed by rearrangement to give a more stable carbocation.

It is proved by the fact that the rate of reaction increases with the ionizing power of solvent and it is unaffected by concentration of base.

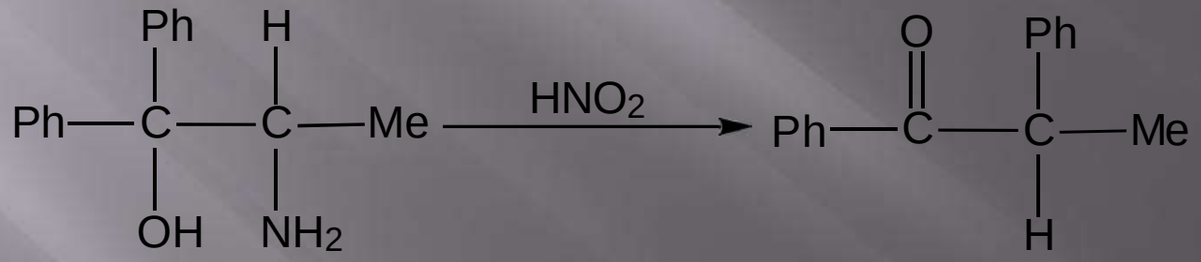
It has been shown that the rate of migration increases with degree of electron deficiency at migration terminus.

IV. *Nature of migration*

Majority of rearrangements are intramolecular.

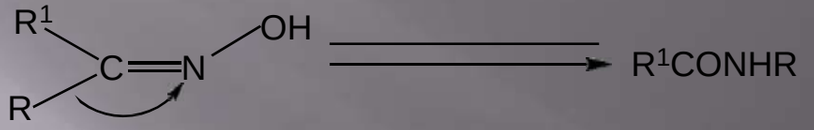
Cross-over experiments *are useful tools to establish the nature of rearrangement.*

Another form of evidence can be gathered by using a chiral migrating group. If the configuration at the migrating group is retained in the product, it is quite likely that the rearrangement is intramolecular.



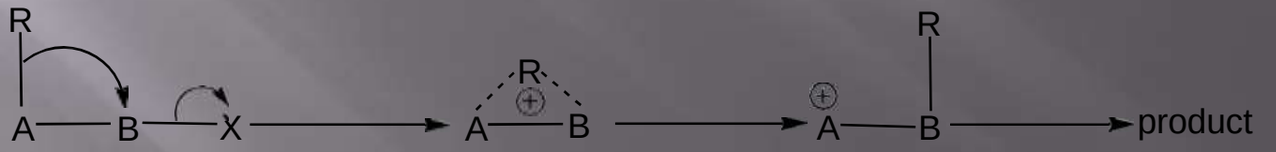
In this example inversion at the migration terminus takes place. The reaction involves diazotization and intramolecular 1,2-phenyl migration.

*Eg. In Beckmann rearrangement, only group **anti** to the hydroxyl migrates. This shows the concertedness of the reaction*



So, if racemisation is noticed, then it is probable that the first step takes place before the second step, as in S_N1 reaction.

And, if inversion occurs, then two steps might be concerted, as in S_N2.



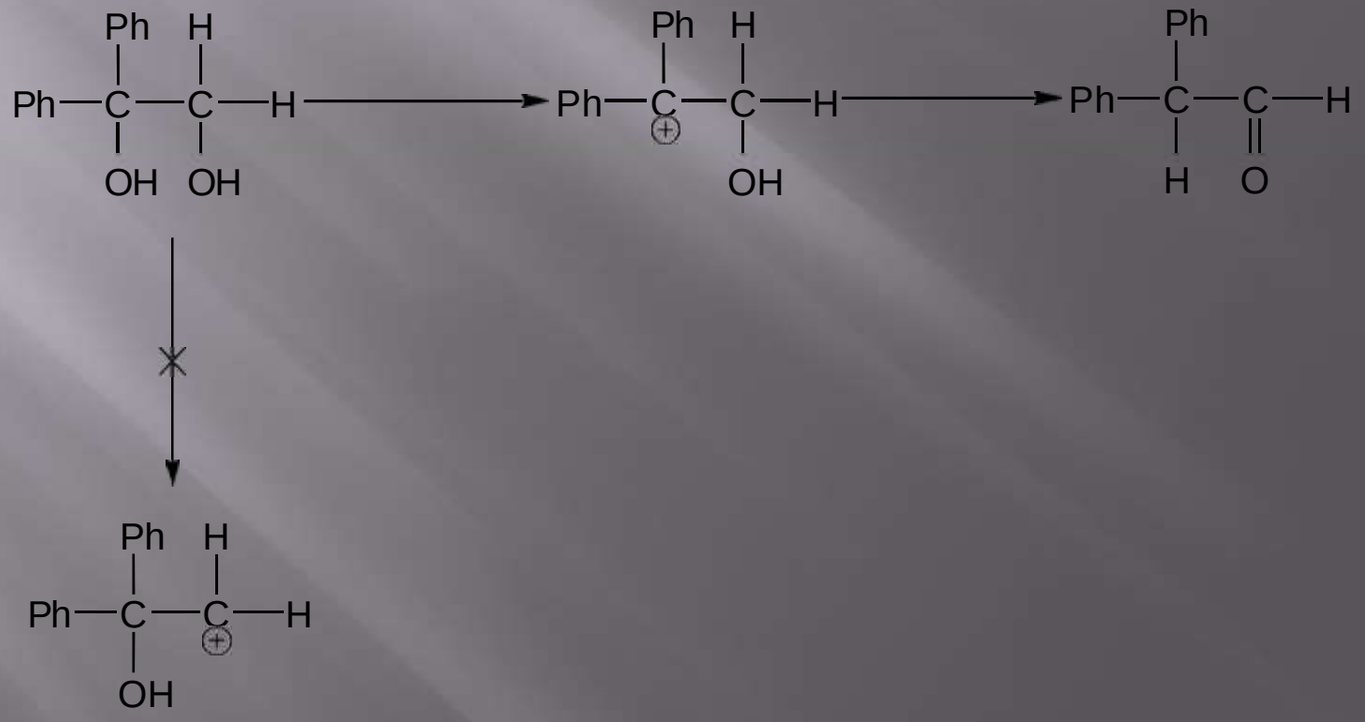
In this case, the neighboring group assists the departure of the leaving group, which in turn can increase the rate of reaction

V. Migratory aptitude

*In many reactions like **Hofmann**, **Curtis** (see later) etc., identity of the group that migrates is quite clear. However, in certain other reactions like **Beckman** rearrangement, there are more than one choice. In such situations the question of which group migrates depends on several factors (such as the geometry of molecule).*

*In the case of **Wagner-Meerwein** and **Pinacol** rearrangement, there are many choices, as substrate contains several groups, that have similar propensity for migration. Such reactions are used for the study of **relative migratory aptitude**.*

** In this example, hydroxyl group is lost from carbon bearing two phenyl groups as it provides a more stable carbocation. The stability of the carbocation is enhanced by group in the order aryl > alkyl >* H.



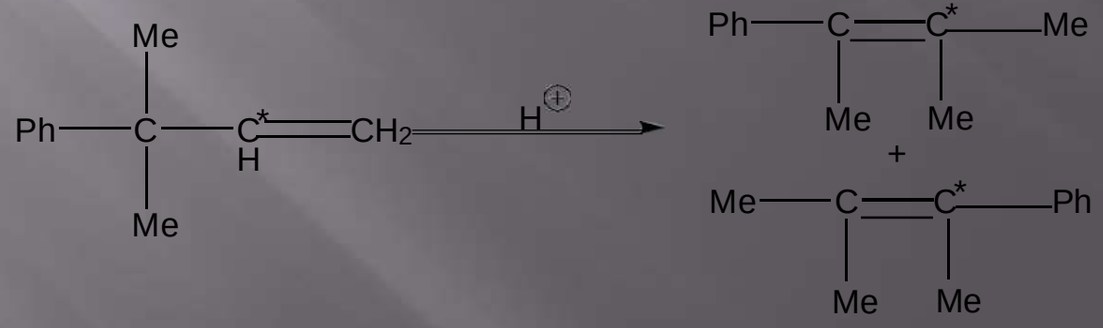
In order to study migratory aptitudes, the substrate should furnish same typeof carbocation wherein the migration occurs.

Many factors control migratory aptitude. These are (a) conformational features, (b) relative ability of the groups at the migration origin that can stabilize the developing positive charge.

In the following example, involving the decomposition of tosylate, onlyphenyl group migrates

The phenyl group in the following example assists the departure of the tosyl group

In a related alkene, upon treatment an acid, a competitive migration of themethyl and the phenyl groups are noticed



Some general trends in the migrating aptitude of different groups

Aryl groups exhibits higher propensity for migration than that of alkyl groups.

Migratory aptitude of hydrogen is unpredictable. Hence, mixture of migrated products are obtained.

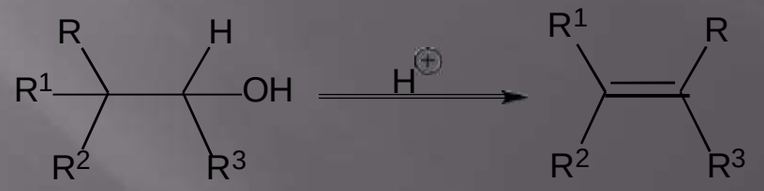
In the case of aryl groups, those with electron donating substituents at the meta or para positions migrates preferentially over those containing substituents at the ortho position.

Aryl group containing electron withdrawing groups show reduced migratory aptitude.

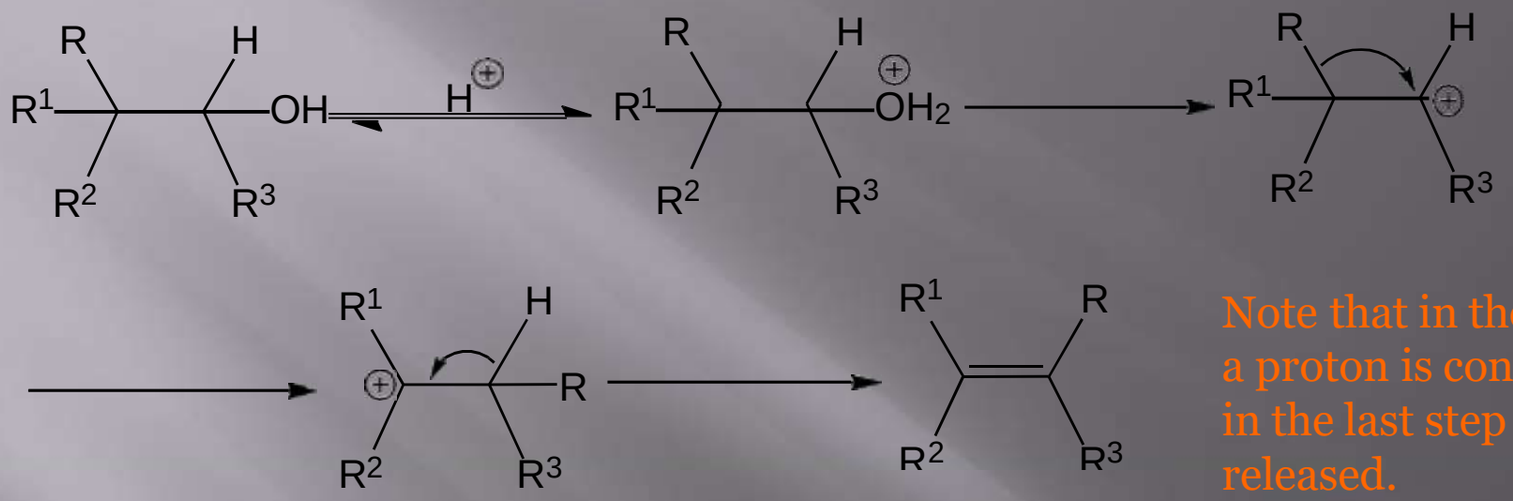
VI. *Reactions involving carbocations*

A. Wagner-Meerwein rearrangement:

When alcohol containing more than two alkyl or aryl group on β carbon are treated with acid, the product formed is generally a rearranged product, rather than simple substitution or elimination product. This reaction is called Wagner-Meerwein rearrangement. Newly generated carbocation is stabilized generally by loss of a proton to give olefin (and less often by nucleophilic substitution or loss of some other positive group).

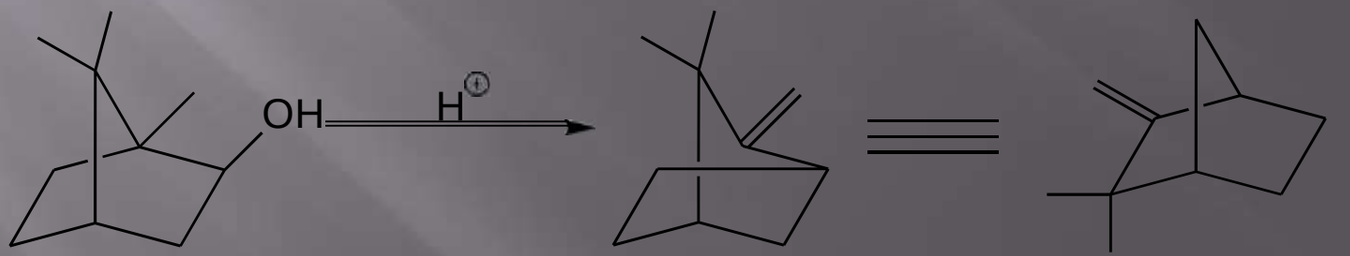


Mechanism involves rearrangement of the carbocation intermediate.



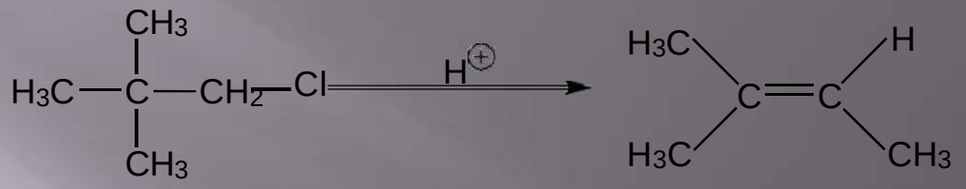
Note that in the initial step a proton is consumed and in the last step a proton is released.

The earliest examples of Wagner-Meerwein rearrangement was noticed in bicyclic terpenes.



Isoborneol

Camphene



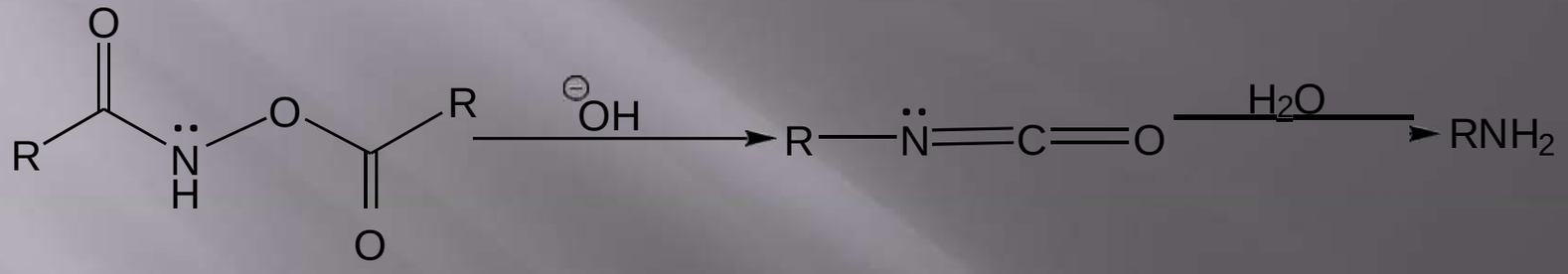
Camphenilol

Santene

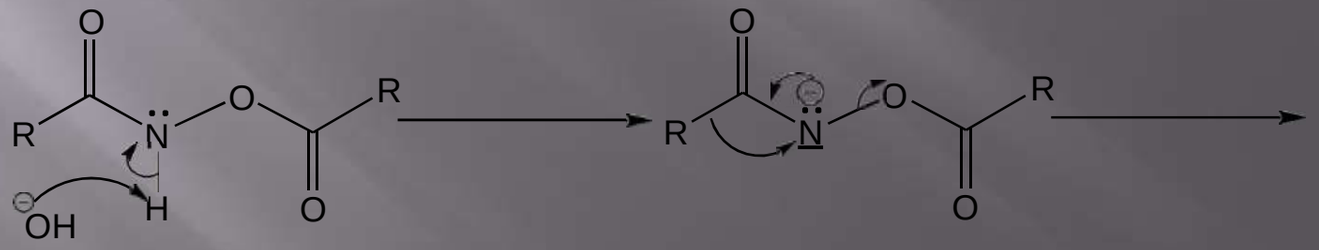
In these reactions, double bond is formed according to Zaitsev rule. Leaving group in this reaction can be hydroxyl or other leaving groups (like chloride) which renders carbocationic character to carbon atom. Direction of rearrangement is usually $3^0 > 2^0 > 1^0$.

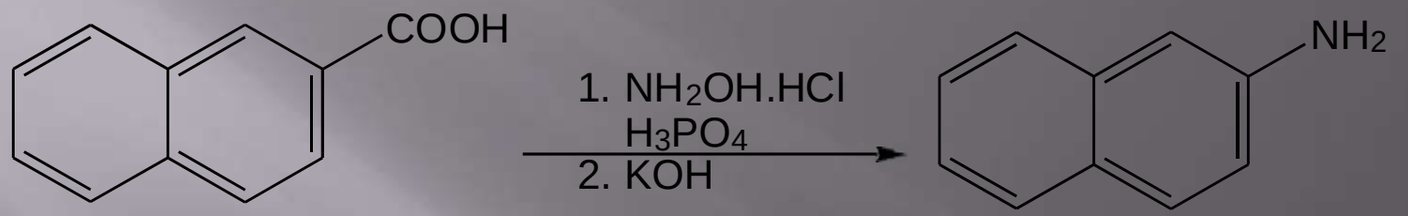
B.Lossen rearrangement:

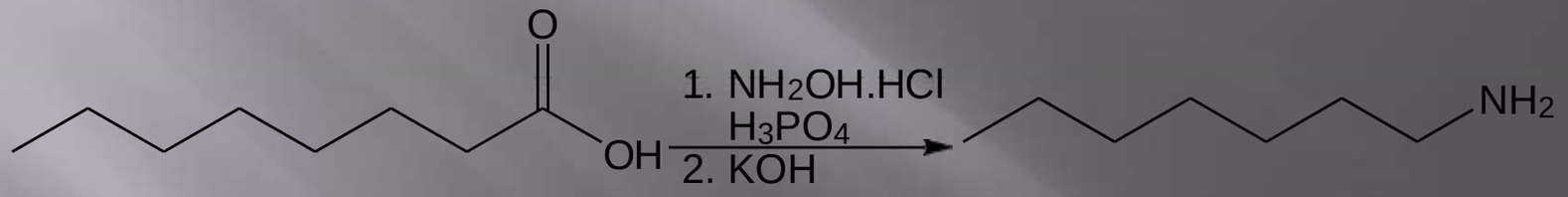
O-acyl derivatives of hydroxamic acids *on heating with a base concerts to the corresponding isocyanate. This reaction is known as Lossen rearrangement. The isocyanate thus produced can be further hydrolyzed to corresponding amines.*



Mechanism







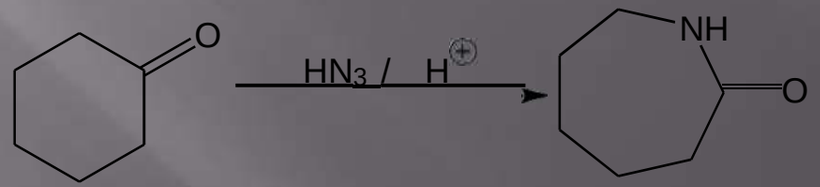
[*JACS*, 1953, 75, 2014]

C. Schmidt rearrangement :

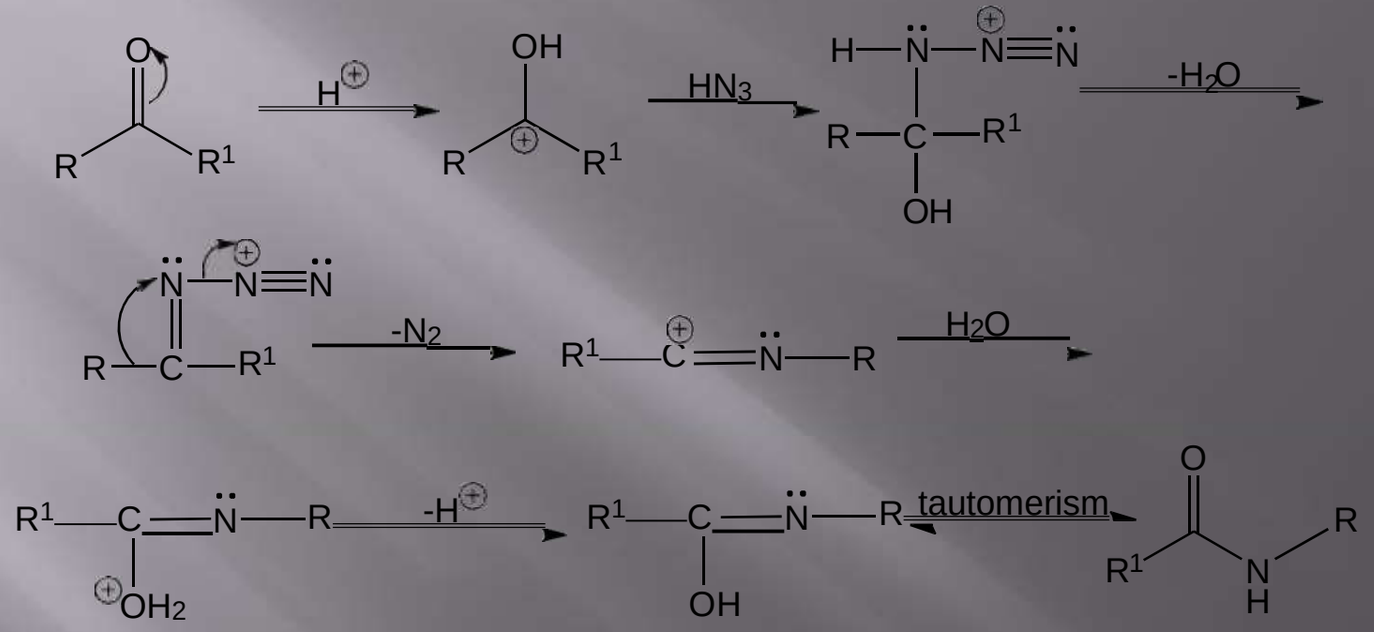
Reaction of carboxylic acid or aldehyde or ketone with ***hydrazoic acid***

in the presence of mineral or Lewis acid to give corresponding primary amine or amide is known as Schmidt rearrangement.

Cyclic ketones give lactams.



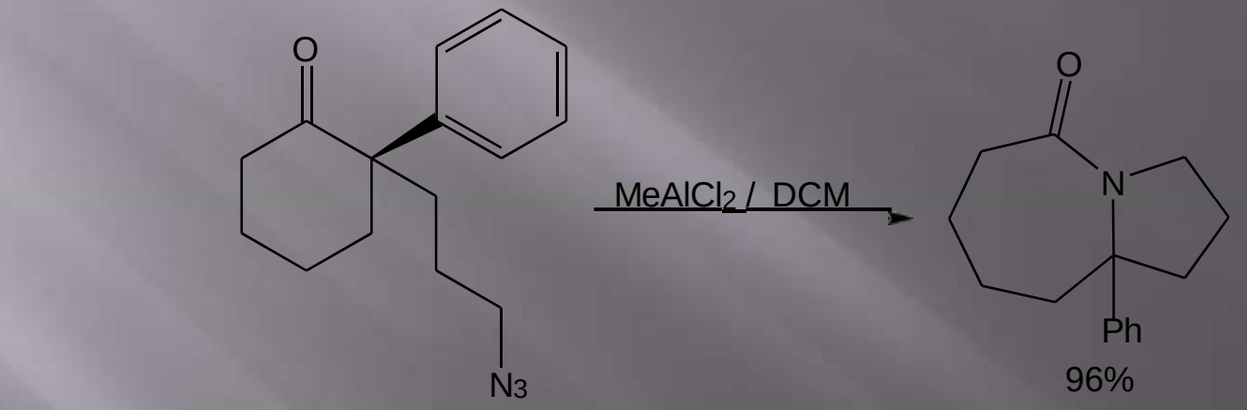
Mechanism is similar to that of Curtius rearrangement, except that protonated azide undergoes molecular rearrangement.

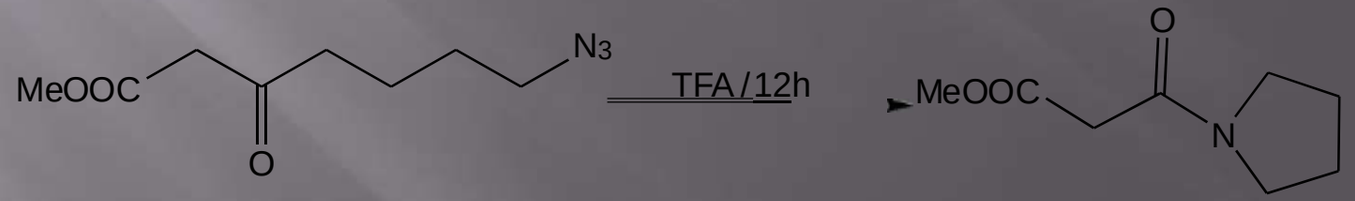


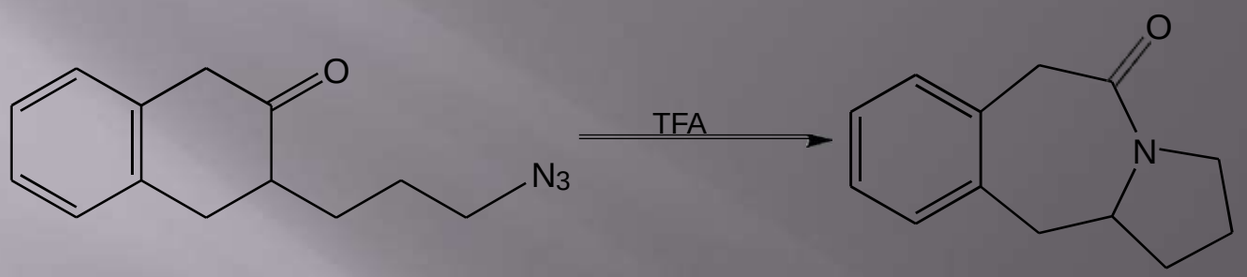
In reaction with ketone, ketone is activated by protonation for nucleophilic addition of azide group to it.

In the case of alkyl aryl ketone, the aryl group migrates preferentially except for bulky alkyl group.

Intramolecular Schmidt reaction can be used for the preparation of bicyclic lactams.



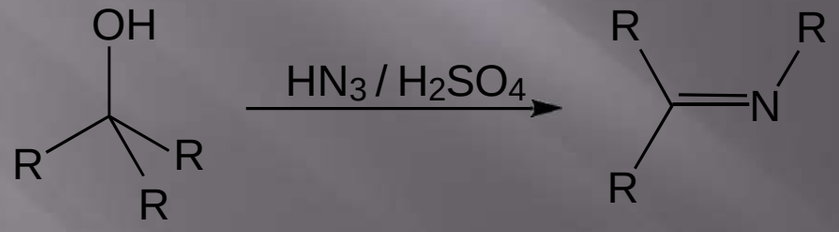




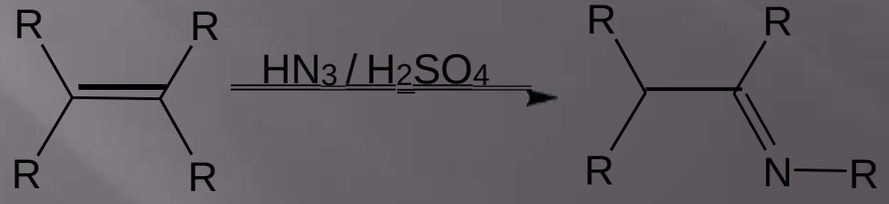
[*Org. Syn*., 2007, 84, 347]

Reaction of tert-alcohol (e.g.1) or olefin (e.g., 2) with hydrazoic acid under acidic condition to give substituted imines is also a form of Schmidt rearrangement.

E.g.,1

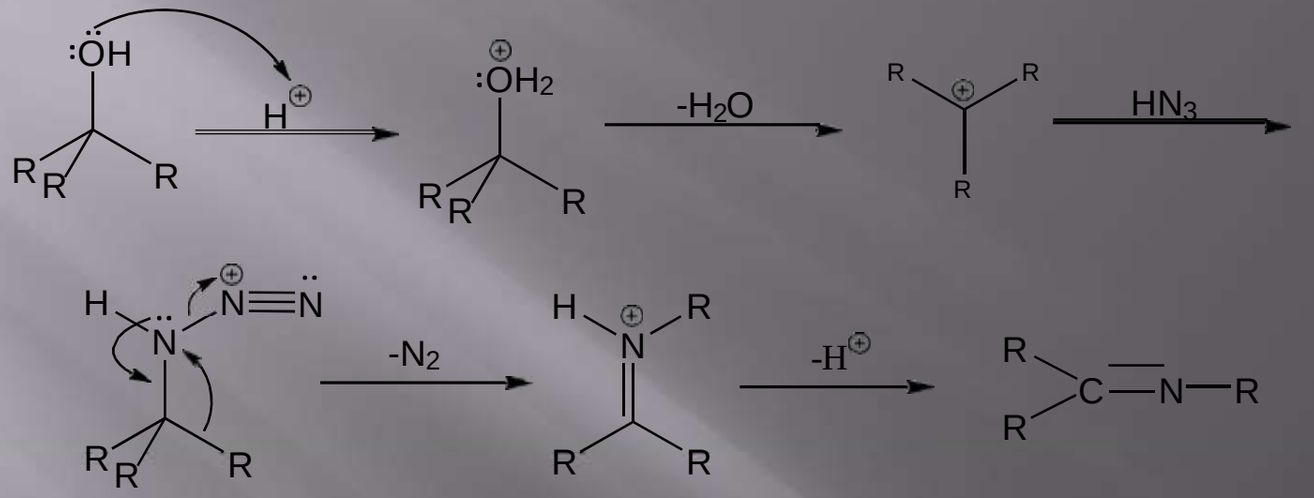


E.g.,2

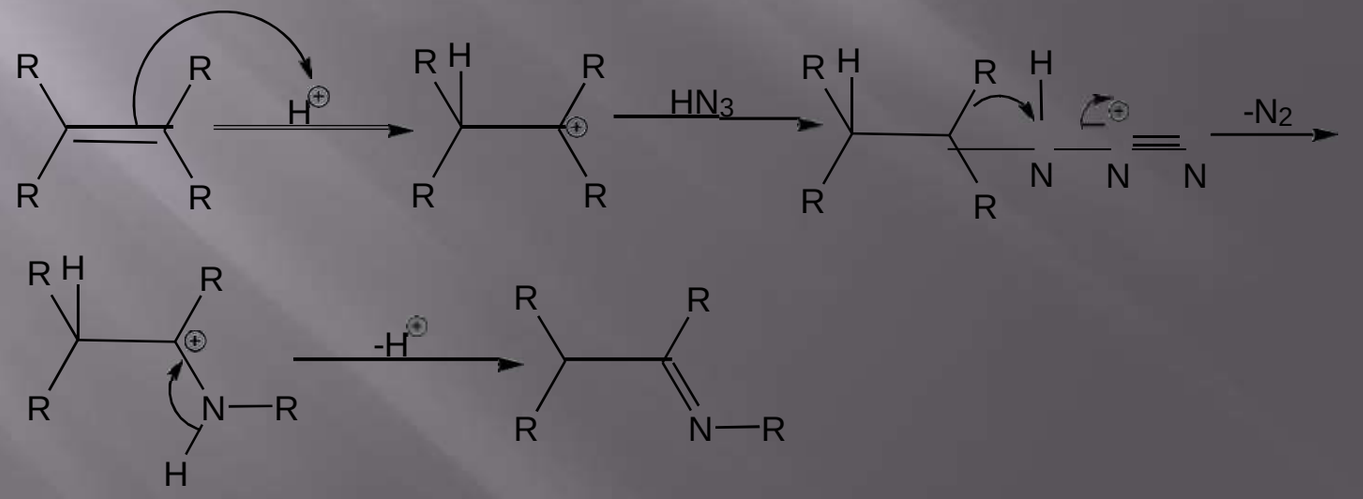


Mechanism of the reaction is as follows.

tert-alcohol

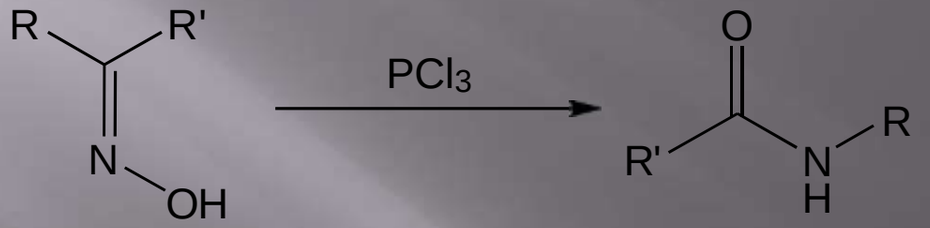


olefin



D. Beckmann rearrangement :

Oximes on treatment with Lewis acid or protic acid rearrange to give substituted amides. This reaction is called as Beckmann rearrangement.*

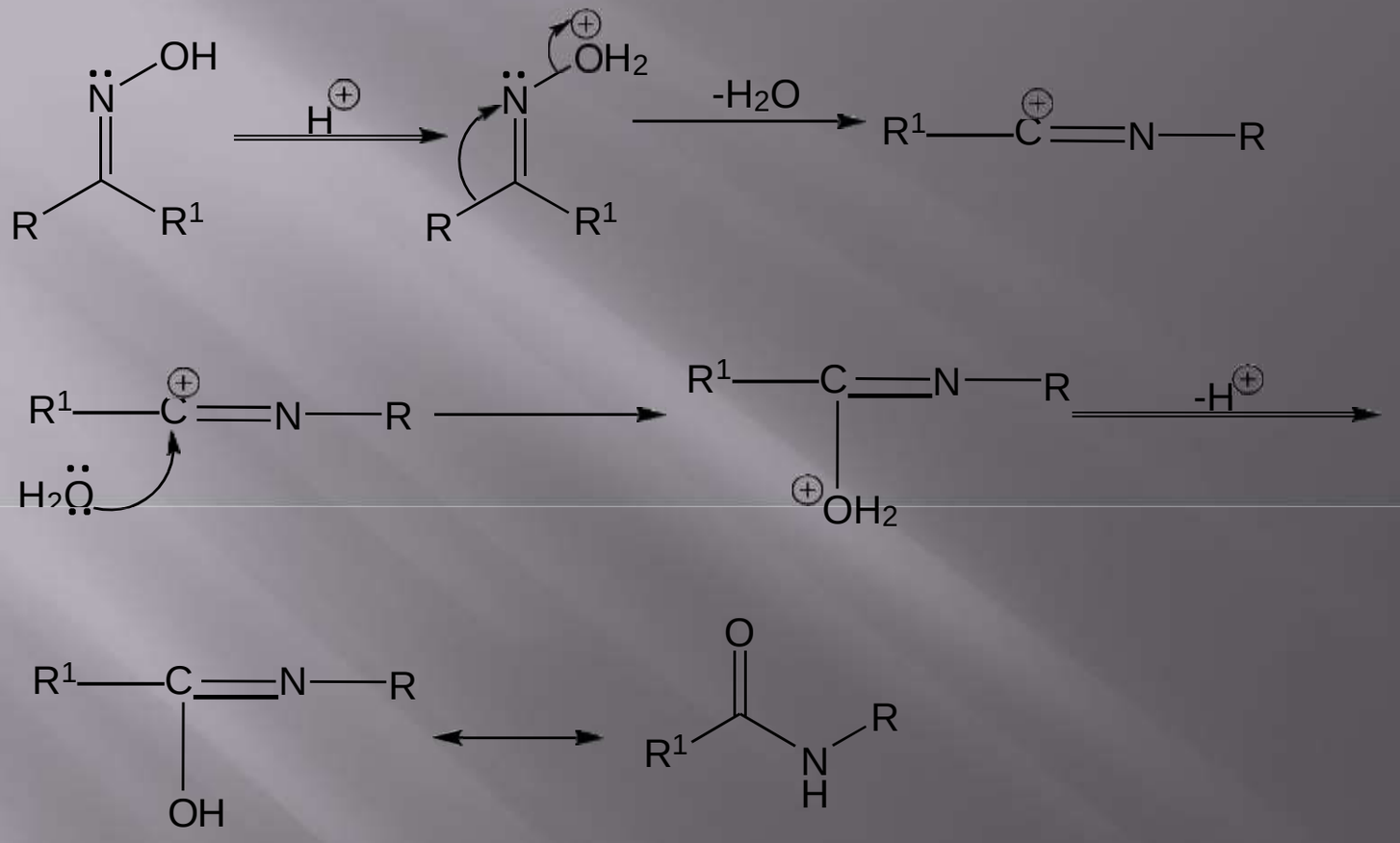


Generally group anti to hydroxyl migrates. However, there are several exception reported. R *and* R' *can be alkyl, aryl or hydrogen. (Hydrogen does not migrate under normal reaction conditions, but it migrates when the reaction is carried out with nickel acetate under neutral conditions.)*

Like Schmidt rearrangement, oximes of cyclic ketones give ring-expansion.

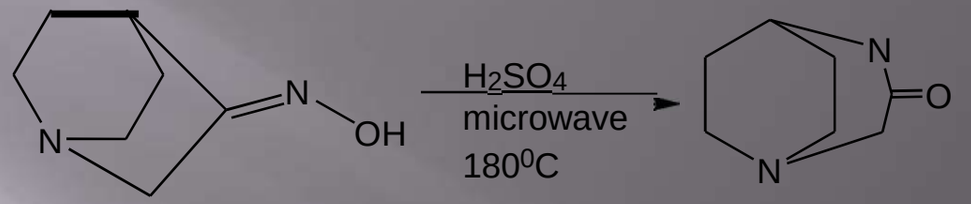
*Oximes are condensation product between hydroxylamine and an aldehydes/ketones

Mechanism of reaction

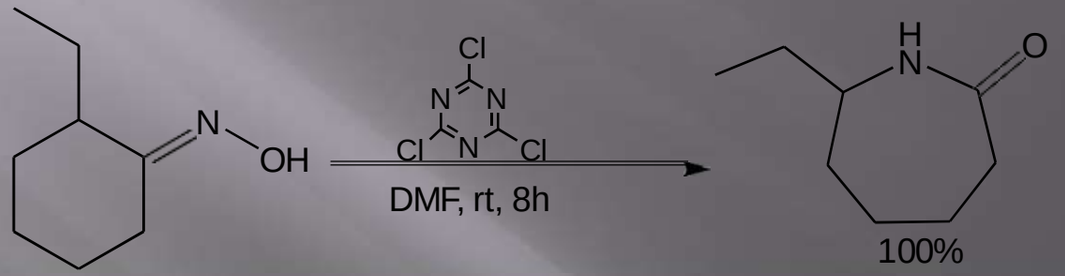


The proposed mechanism is supported by detection of nitrillium ion by NMR and UV spectroscopy.

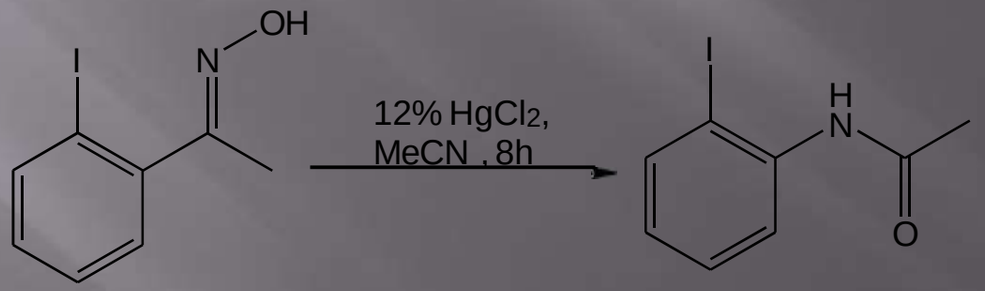
Examples



[*Syn. Comm.,* 2006, 36, 321]



[*J. Org. Chem.*, 2002, 67, 6272]

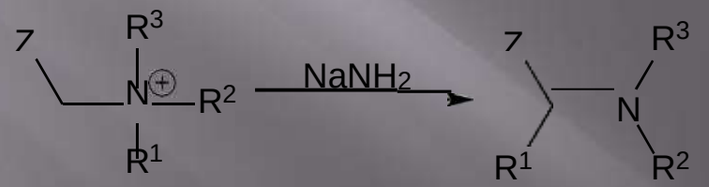


[*J. Org. Chem.*, 2007, 72, 4536]

IX. *Migration from nitrogen to carbon*

Stevens rearrangement :

In Stevens rearrangement, quaternary ammonium salt containing electron withdrawing group on α carbon atom when treated with strong base rearrange to give a tertiary amine.

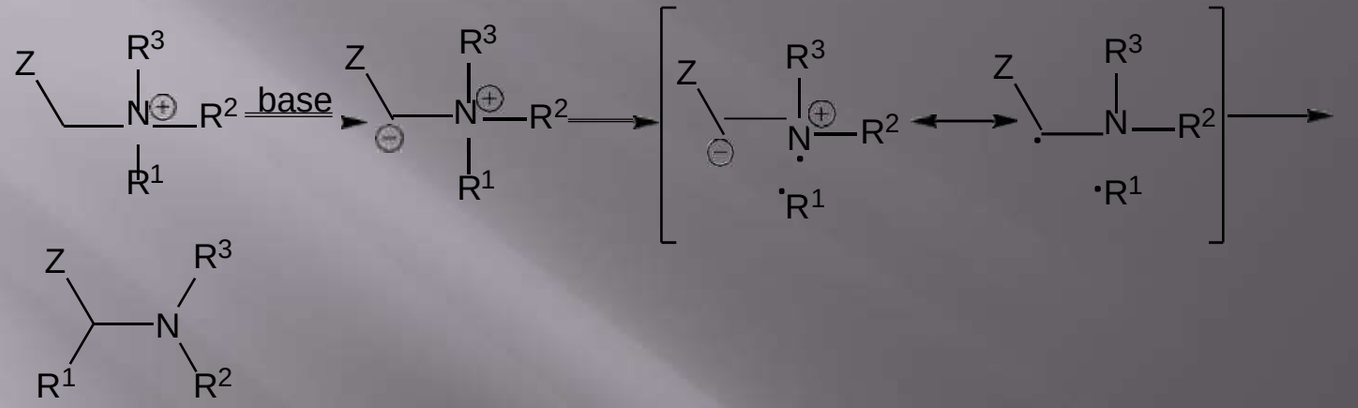


Rearrangement is intramolecular (as shown by cross over experiment).

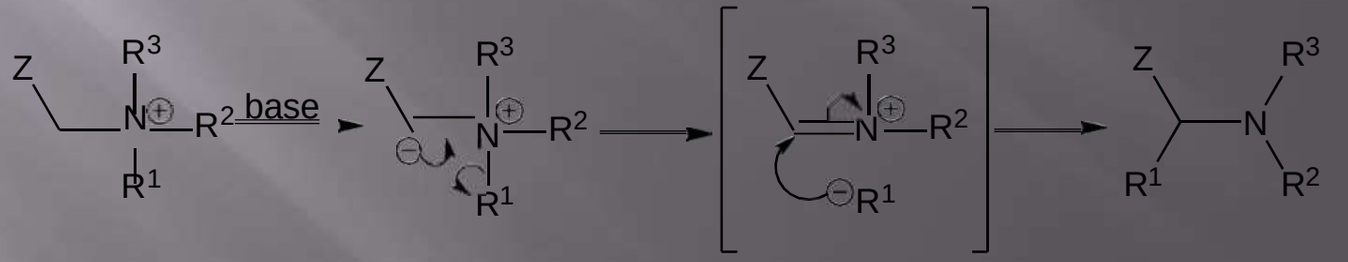
Also, retention of configuration was noticed in the product.

Two mechanistic pathways are possible. One involving radical pair in a solvent cage. Presence of solvent cage is important in order to explain retention of configuration.

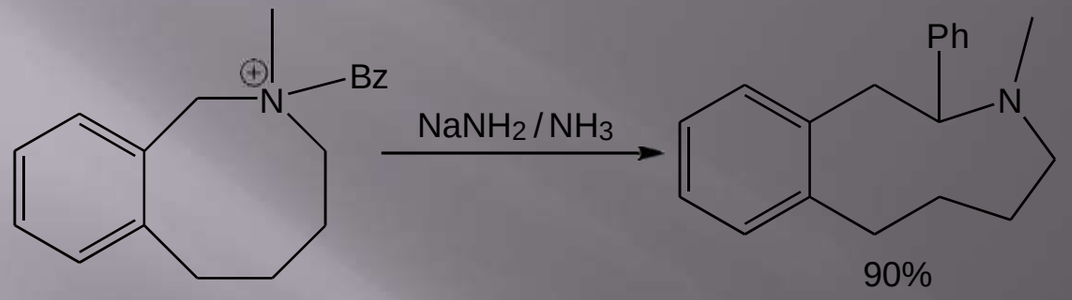
Involving ion pair in solvent cage.



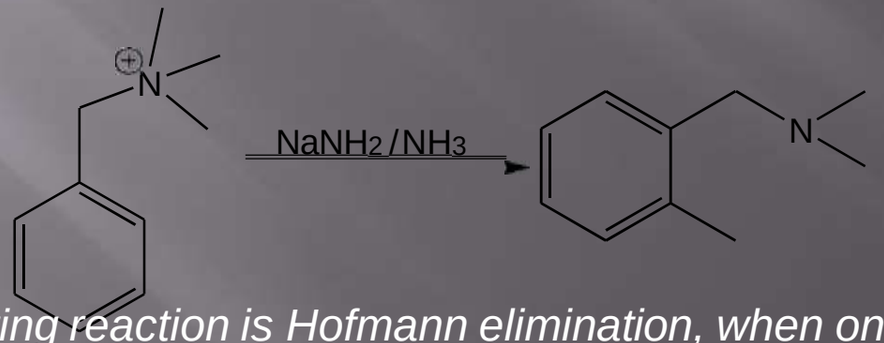
Involving an ionic pathway.



Reaction can be used for ring enlargement.

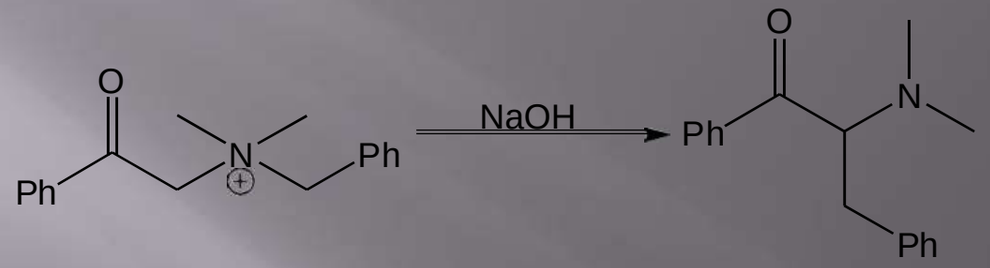


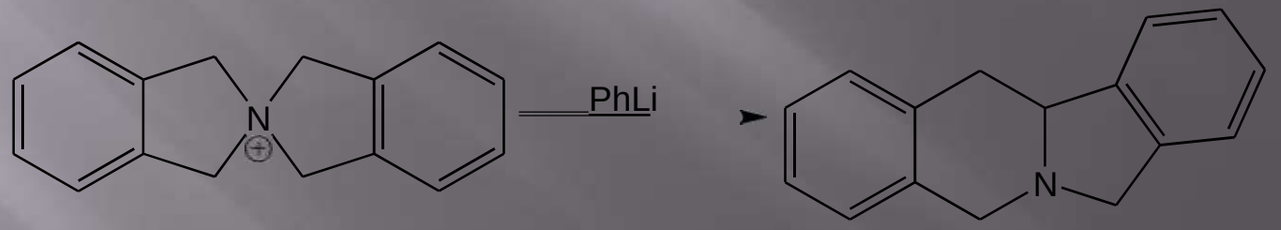
When Z group is an aryl group, the rearrangement is known as ***Sommelet-Hauser rearrangement****, in which reaction of tert-alkyl ammonium salt with* $NaNH_2$ *gives N,N-dialkylbenzylamine with ortho substituted aromatic ring (shown below).*

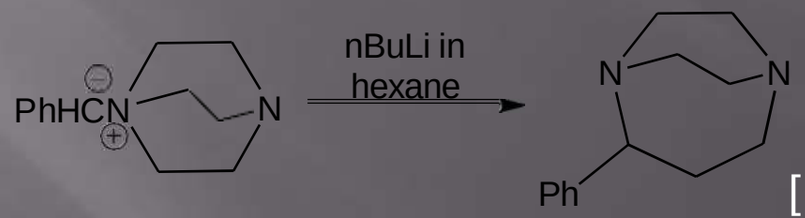


Another competing reaction is Hofmann elimination, when one of the alkyl group contains β *hydrogen atom.*

Some examples of Steven rearrangement are given below.







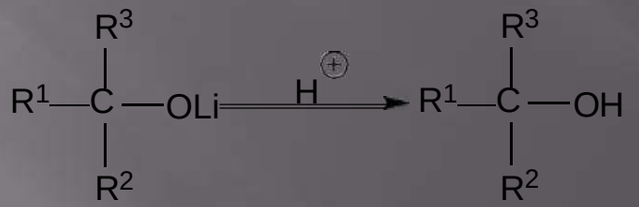
[*JOC*, 1974, 39, 130]

X. Migration from oxygen to carbon

Wittig rearrangement:

Ethers, on reaction with alkyl lithium rearrange in a similar manner to that of Stevens rearrangement to give alkoxy lithium. This reaction is called Wittig rearrangement.[Note: Witting reaction of phosphorous ylides are different]

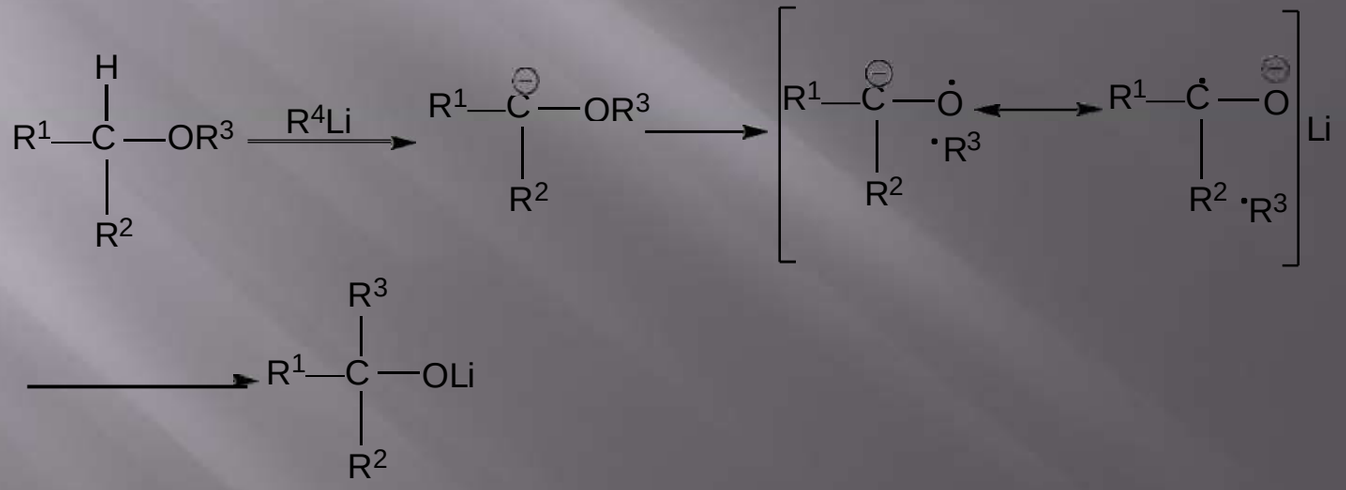
This alkoxy lithium can then be converted to alcohol.



R *may be alkyl, aryl or vinyl group.*

Migratory aptitude are allylic, benzyl>ethyl>methyl>phenyl.

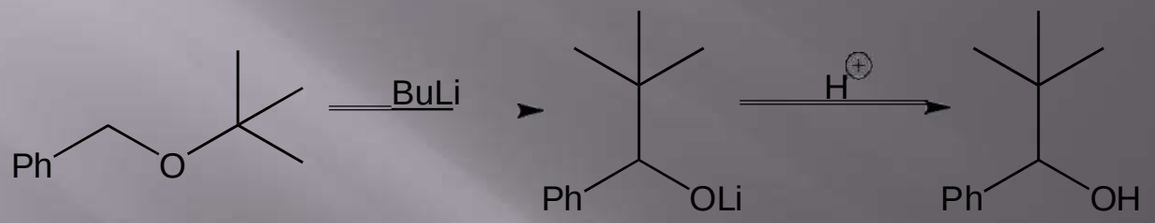
Mechanism is suggested to follow a radical pair pathway.

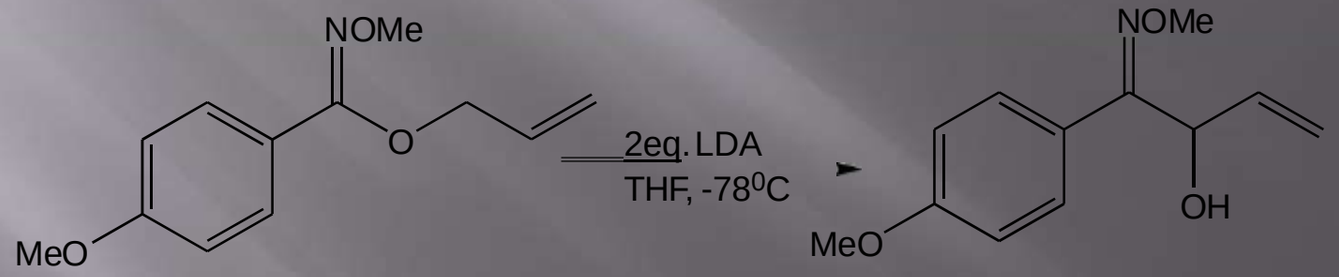


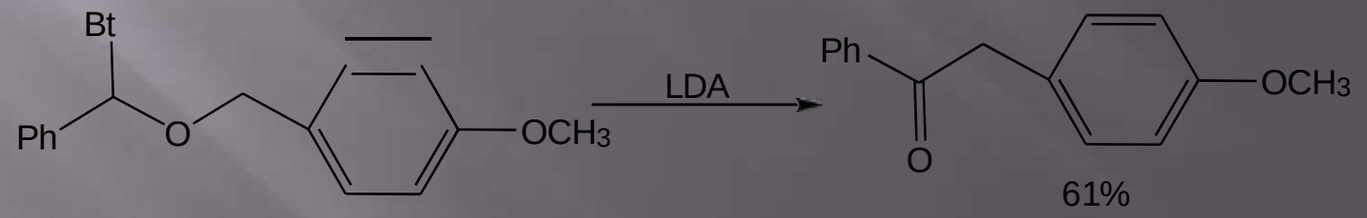
i.Reaction is largely intramolecular

ii.Migratory aptitudes are analogous to free radical mechanism.

iii.Product obtained is with retention of configuration.

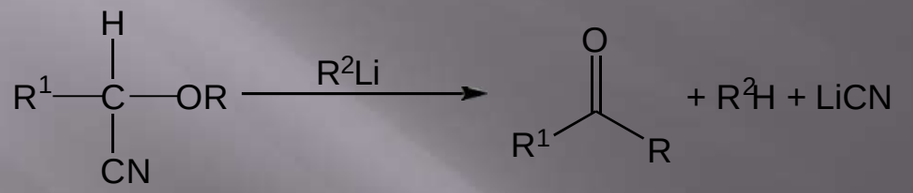


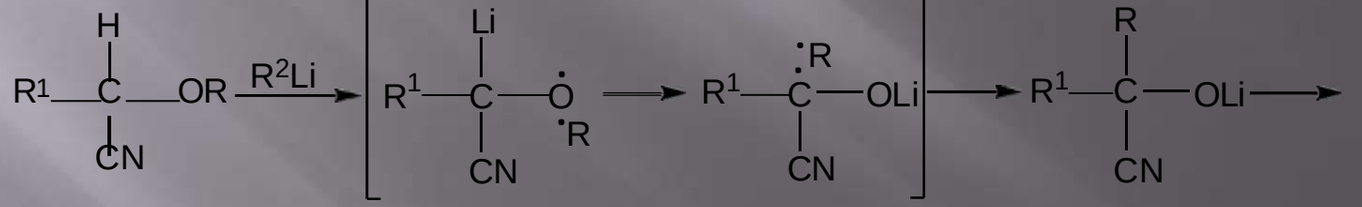


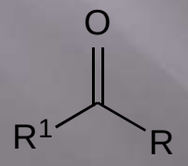


Bt : *benzotriazol-1-yl*

When R^2 *is a good leaving group and electron withdrawing functional group like* CN*, then this group is eliminated and ketone is formed.*







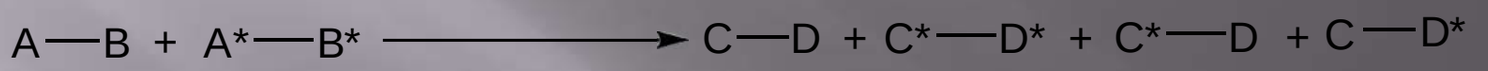
XI. *Crossover experiment*

The purpose of crossover experiment is to determine whether the given reaction takes place intermolecularly or intramolecularly i.e. whether reactant break apart to form intermediates, which diffuse away into solution before they combine to give product.

In this experiment two substrate differing in substituent are mixed together and are reacted under the same reaction condition and the product obtained is analyzed.

Illustration for cross-over experiments:

Consider, a simple reaction in which A-B *reacts to give* C-D.



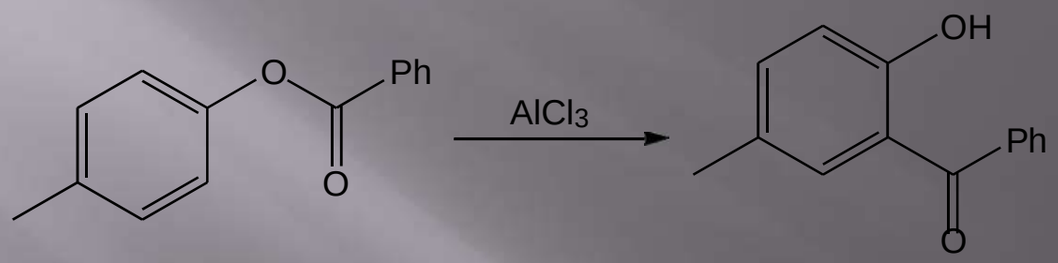
There are two possible of outcomes for the above reaction, as A, A are differently substituted (so are B and B*).*

One in which <u>no crossover of substituent</u> is seen. This is possible if reaction is <u>intramolecular</u>. [The reactant stay connected throughout the course of the reaction]

*The other possibility is that a <u>mixture of products</u> are obtained in the crossover reaction. This is possible in the case of **<u>intermolecular</u>** reaction.*

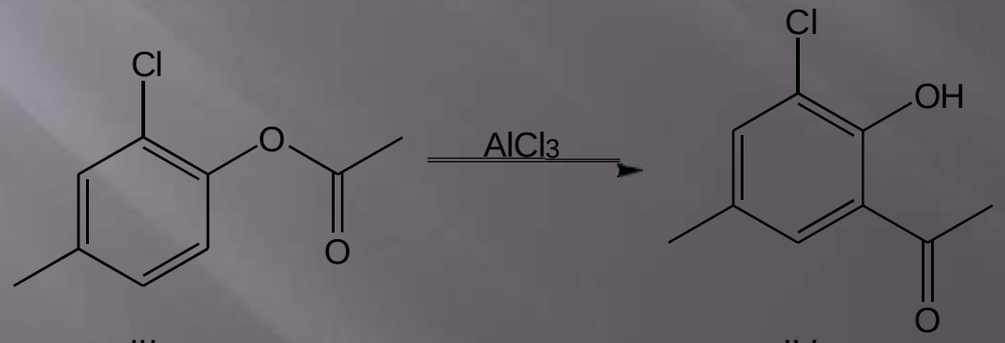
The experiment can be illustrated by considering Fries rearrangement.

p-Tolylbenzoate (I) *on rearrangement gives* 2-hydroxy-5-methylbenzophenone (II).



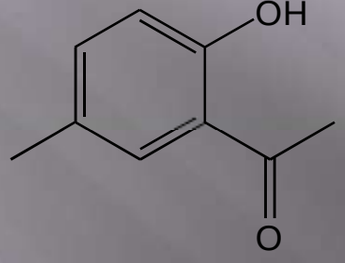
I II

In the similar reaction, o-chloro-p-tolylacetate (III) *give* 2-hydroxy-3-chloro-5-methylacetophenone (IV).

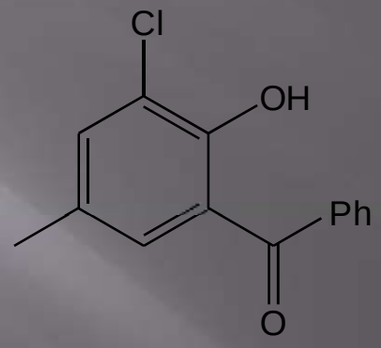


III IV

When I *and* II *are mixed together and product is analyzed,* V *and* VI*, along with* II *and* IV *are obtained.*



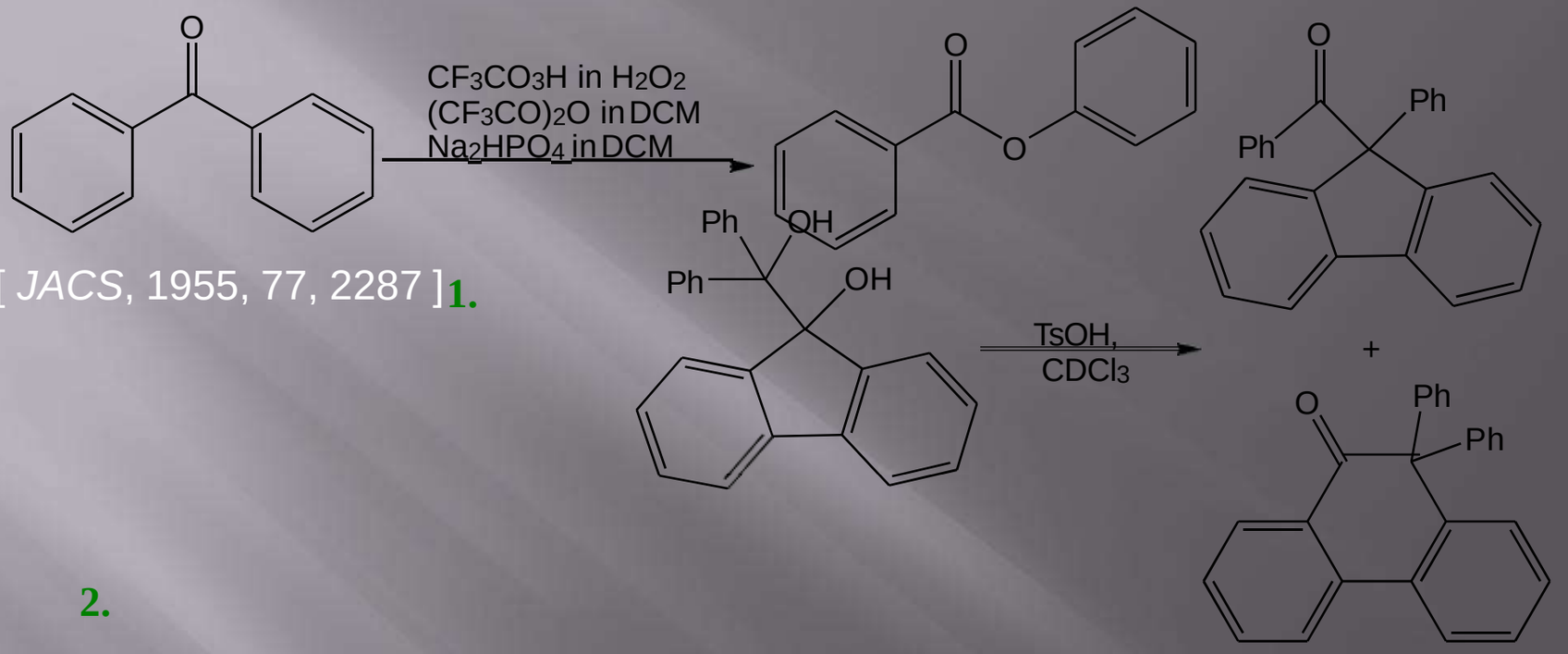
V



VI

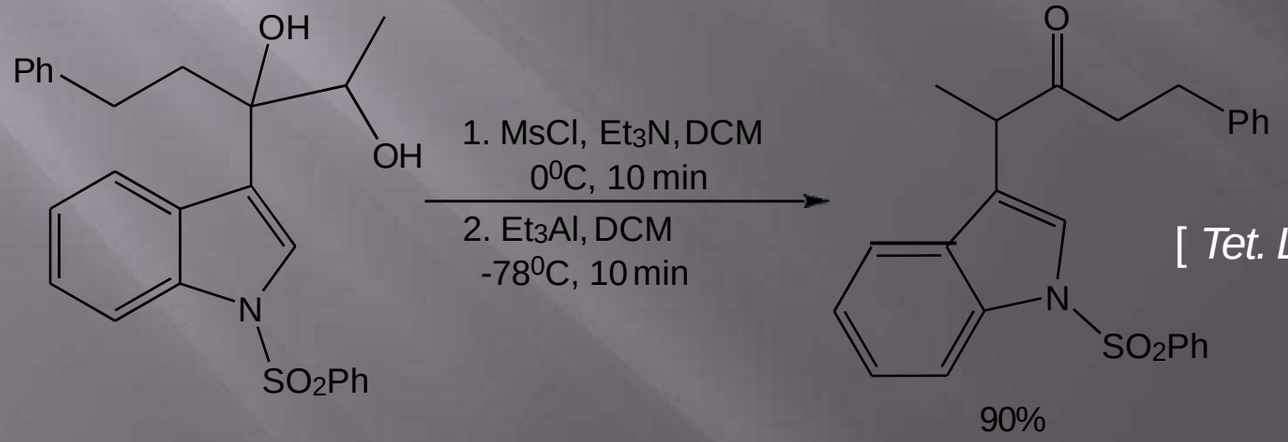
This shows that the reaction proceeds ***intermolecularly*** *and fragments are formed in solution.*

Home work: Propose a mechanism for the following pinacol reaction



[*JACS*, 1955, 77, 2287] **1.**

2.



90%

[*Tet. Lett.*, 2002, 43, 6937]