

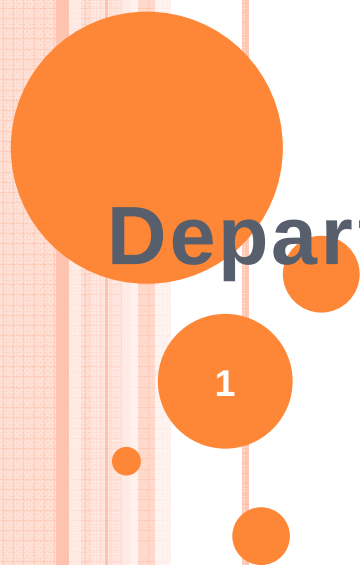
CHAPTER 4

Reactive Intermediates

LIMING JIANG

**Department of Polymer Science and
Engineering, ZJU**

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OUTLINE

Definition: a reaction intermediate or an intermediate as a molecular entity (atom, ion, molecule...) with a lifetime appreciably longer than a molecular vibration that is formed (directly or indirectly) from the reactants and reacts further to give (either directly or indirectly) the products of a chemical reaction.

Main carbon reactive intermediates:

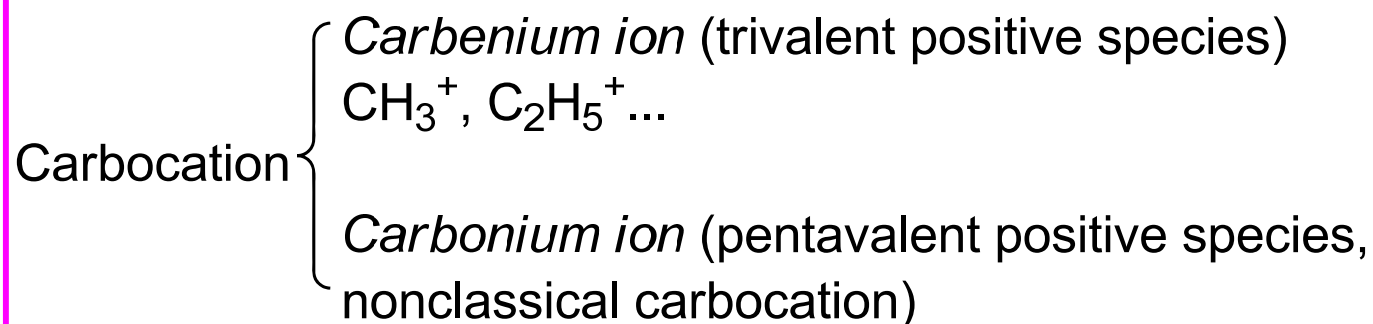
- Carbocations and their stabilized equivalents such as oxonium ions
- Carbanions and their stabilized equivalents such as enolates
- Free radicals
- Carbenes

Common features

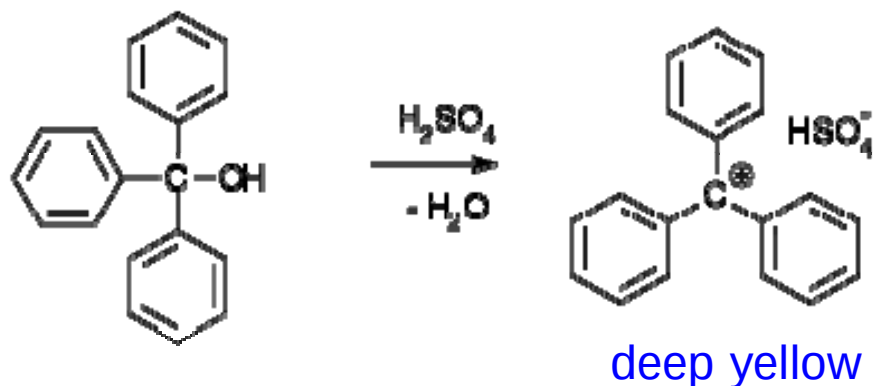
- ◆ Low concentration
- ◆ Do not obey the Lewis octet rule with the exception of carbanions, hence the high reactivity
- ◆ Often generated on chemical decomposition
- ◆ It is often possible to prove the existence of this species by spectroscopic means
- ◆ Cage effects have to be taken into account
- ◆ Often stabilisation by conjugation or resonance
- ◆ Often difficult to distinguish from a transition state
- ◆ Prove existence by means of chemical trapping

4.1 CARBOCATIONS

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



Norris and
Kehrman (1902):



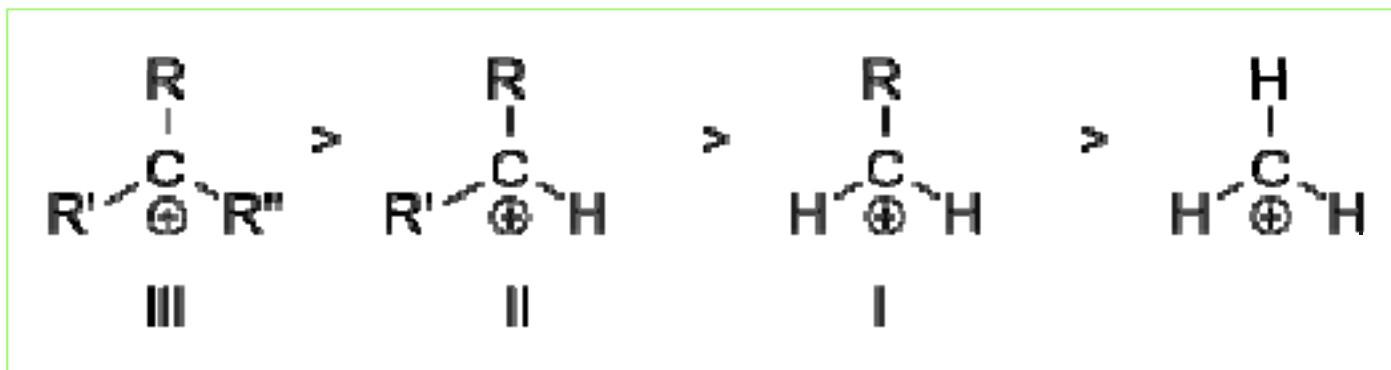
In 1962 Olah directly observed the *tert*-butyl carbocation by NMR as a stable species on dissolving *tert*-butyl fluoride in magic acid.

I. STRUCTURE AND 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*.

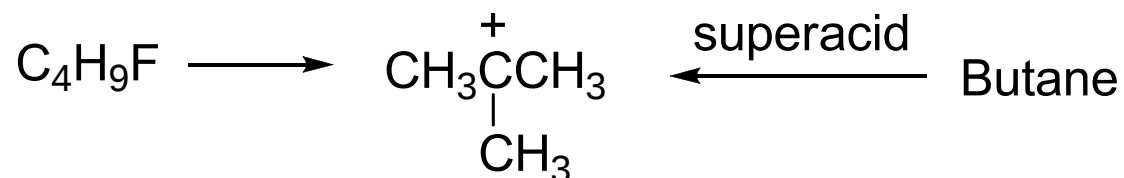
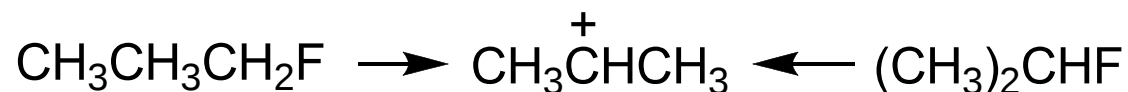
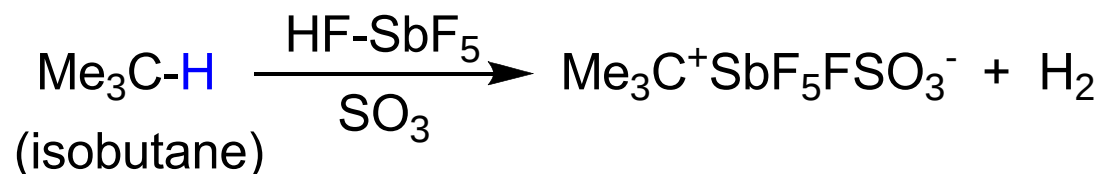
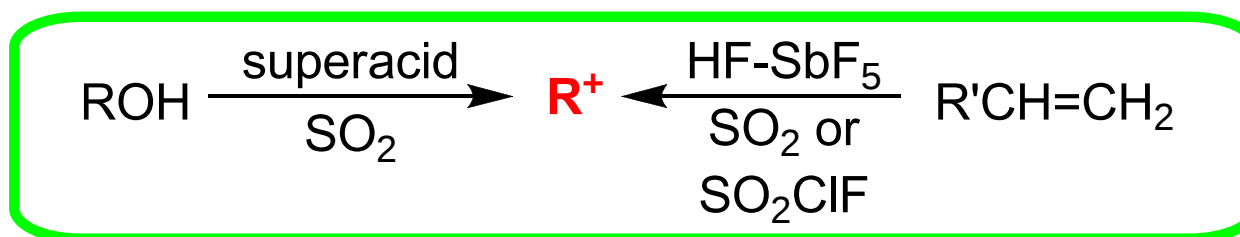
A. Simple alkyl carbocations

Stability: tertiary > secondary > primary

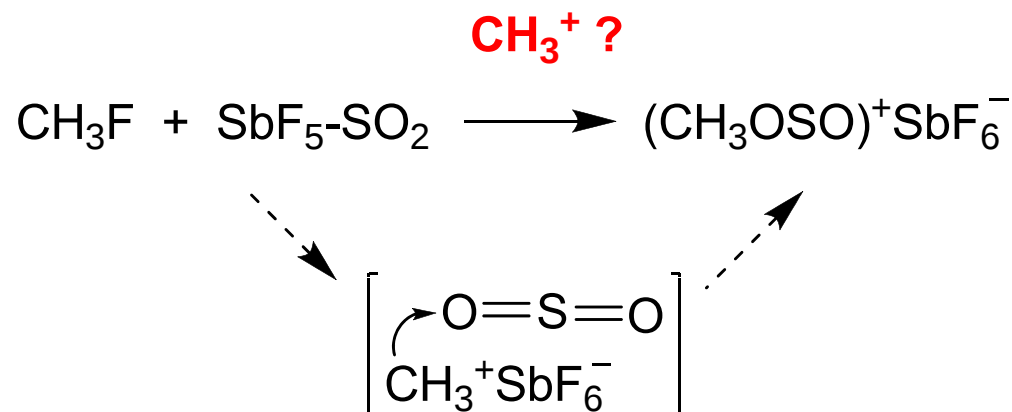


The most stable of all alkyl cations is the *tert*-butyl cation. Methane, ethane, and propane, treated with superacid, also yield *tert*-butyl cation as the main product.

No matter how they are generated, study of the simple alkyl cations has provided dramatic evidence for the stability. Both propyl fluorides gave the isopropyl cation; all four butyl fluorides gave the *tert*-butyl cation. Butane, in superacid, gave only the *tert*-butyl cation.

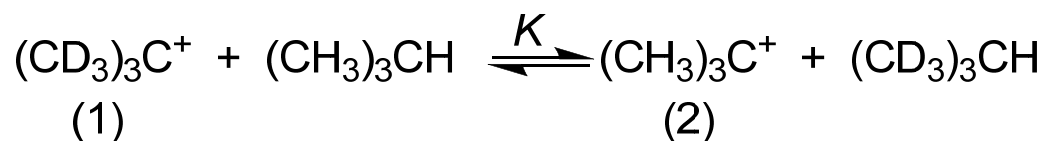
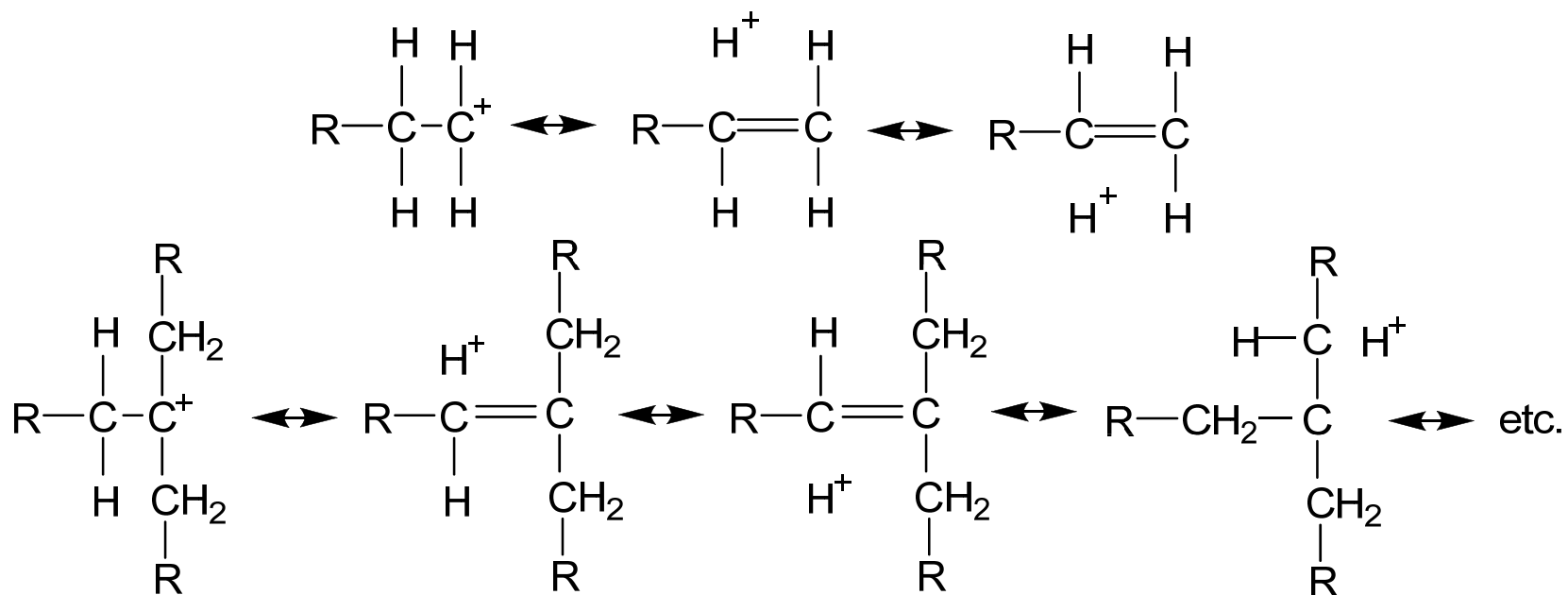


To date, no primary cation has survived long enough for detection.



◆ **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.

◆ **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*.



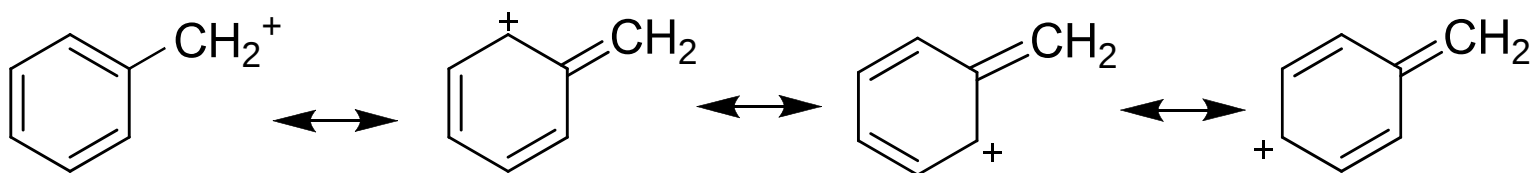
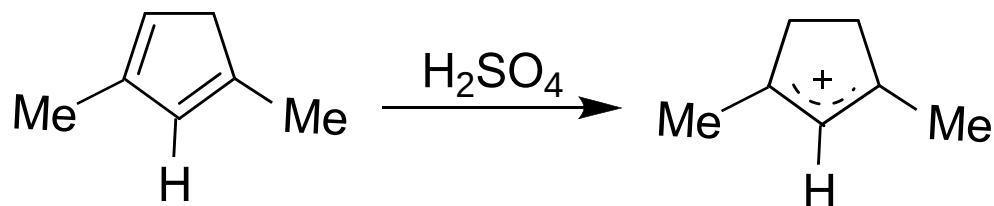
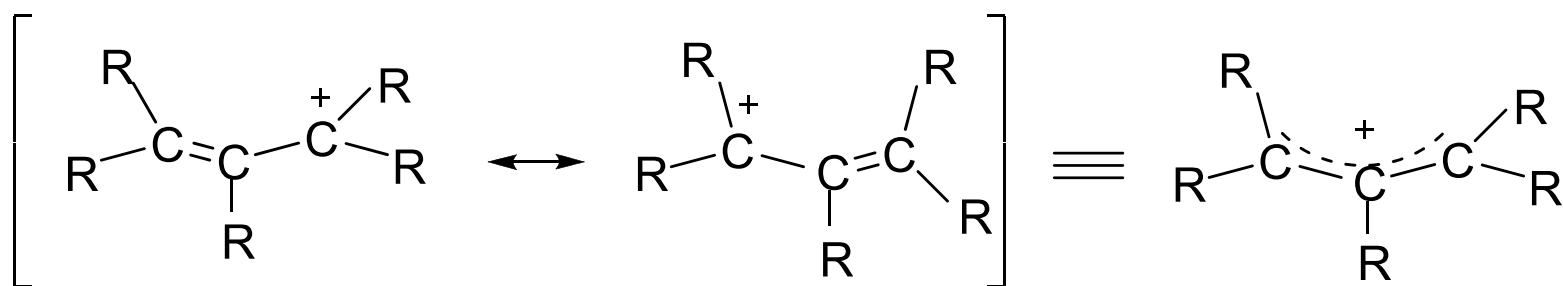
$$K_{298} = 1.97 \pm 0.20$$

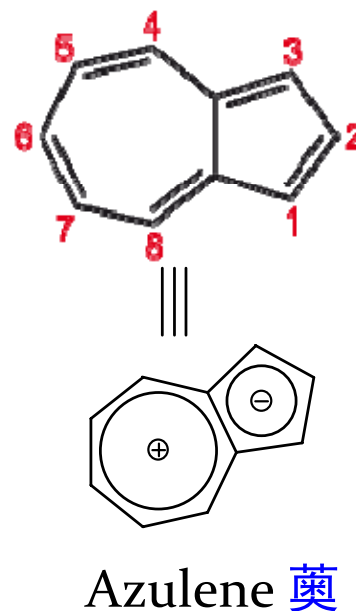
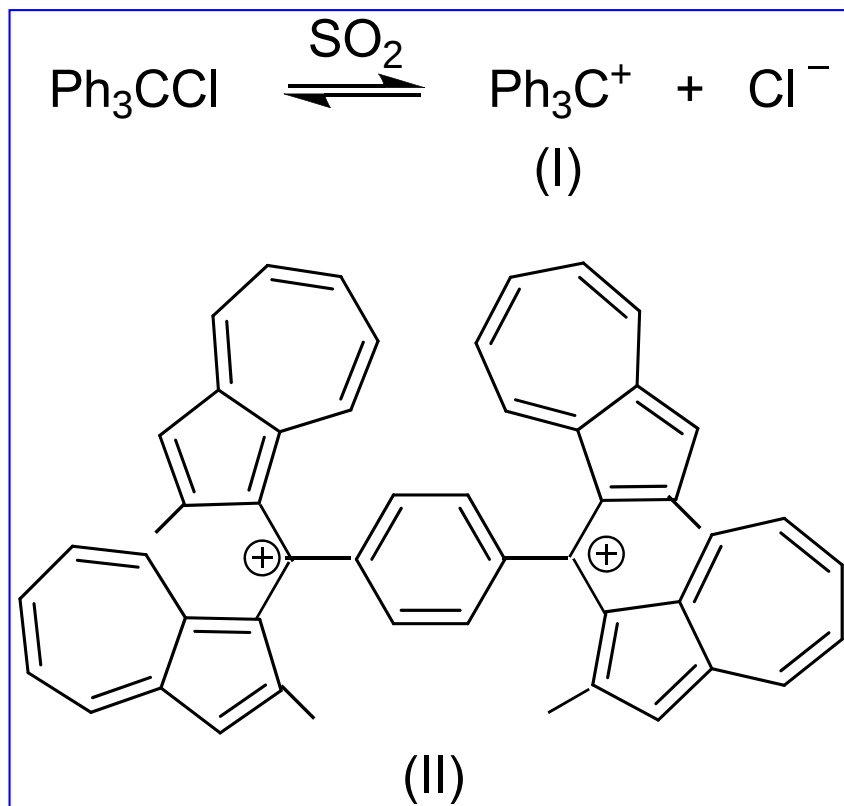
K is 1.97, showing that 2 is more stable than 1. This is a secondary **isotopic effect**; there is less hyperconjugation in 1 than 2.

It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be. 电荷越集中，荷电物种越不稳定

B. 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 alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF .





The blue color of the mushroom *Lactarius indigo* is due to the azulene derivative (7-isopropenyl-4-methylazulen-1-yl)methyl stearate

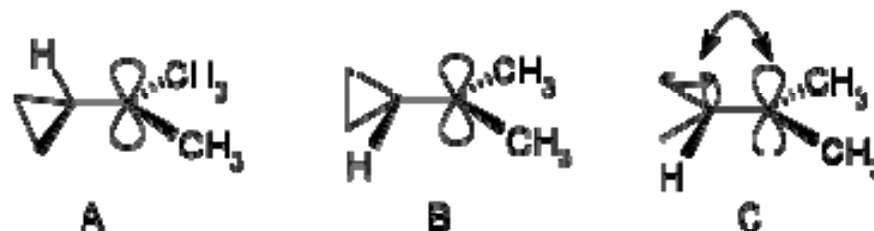
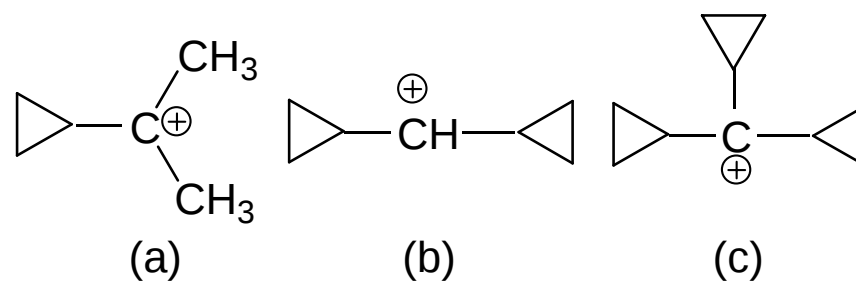
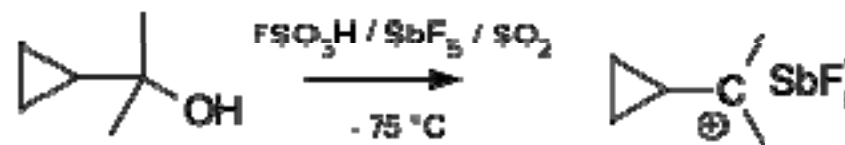
Both triphenylmethyl (I) and diphenylmethane cations have been isolated as solid salts and, in fact, $\text{Ph}_3\text{C}^+\text{BF}_4^-$ and related salts are available commercially. Positively charged benzylic carbon (II) is stabilized by two azulene rings.

C. CYCLOPROPYLMETHYL CATIONS

Cyclopropylmethyl cations are even more stable than the benzyl type. Compound (c) has been prepared by solution of the corresponding alcohol in H_2SO_4 . Compounds *a*, *b*, and similar ions have been prepared by solution of the alcohols in $\text{FSO}_3\text{H}-\text{SO}_2-\text{SbF}_5$.

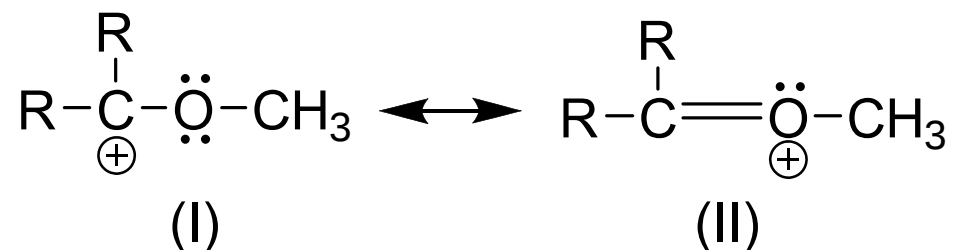
^1H NMR spectrum of a dimethyl derivative (a), identical signals are found for the two methyl groups.

J. Am. Chem. Soc. 1970, **92**, 3234–3235

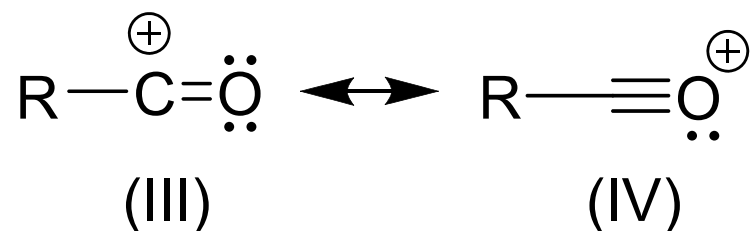
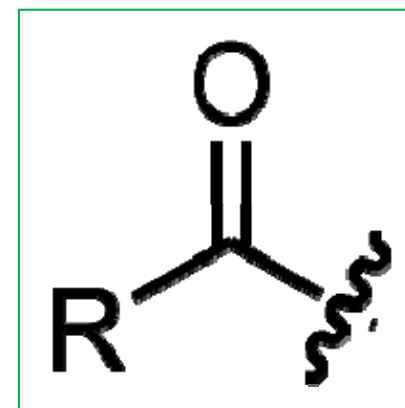


E. OTHER STRUCTURAL TYPES

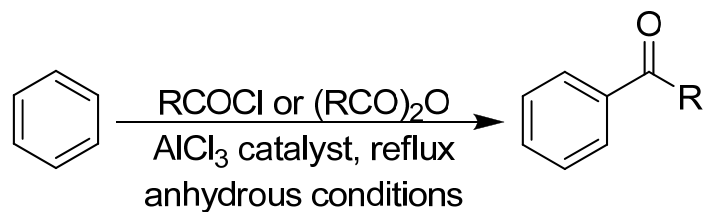
Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair.



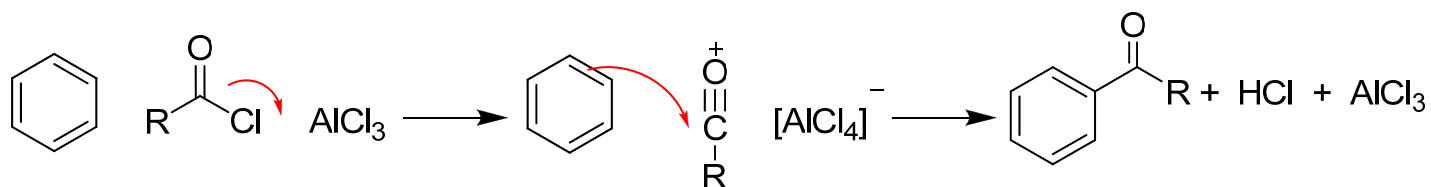
◆ Simple **acyl cations** (RCO^+) have been prepared in solution and the gas state. The acetyl (CH_3CO^+) is about as stable as the *tert*-butyl cation. The 2,4,6-trimethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4 .



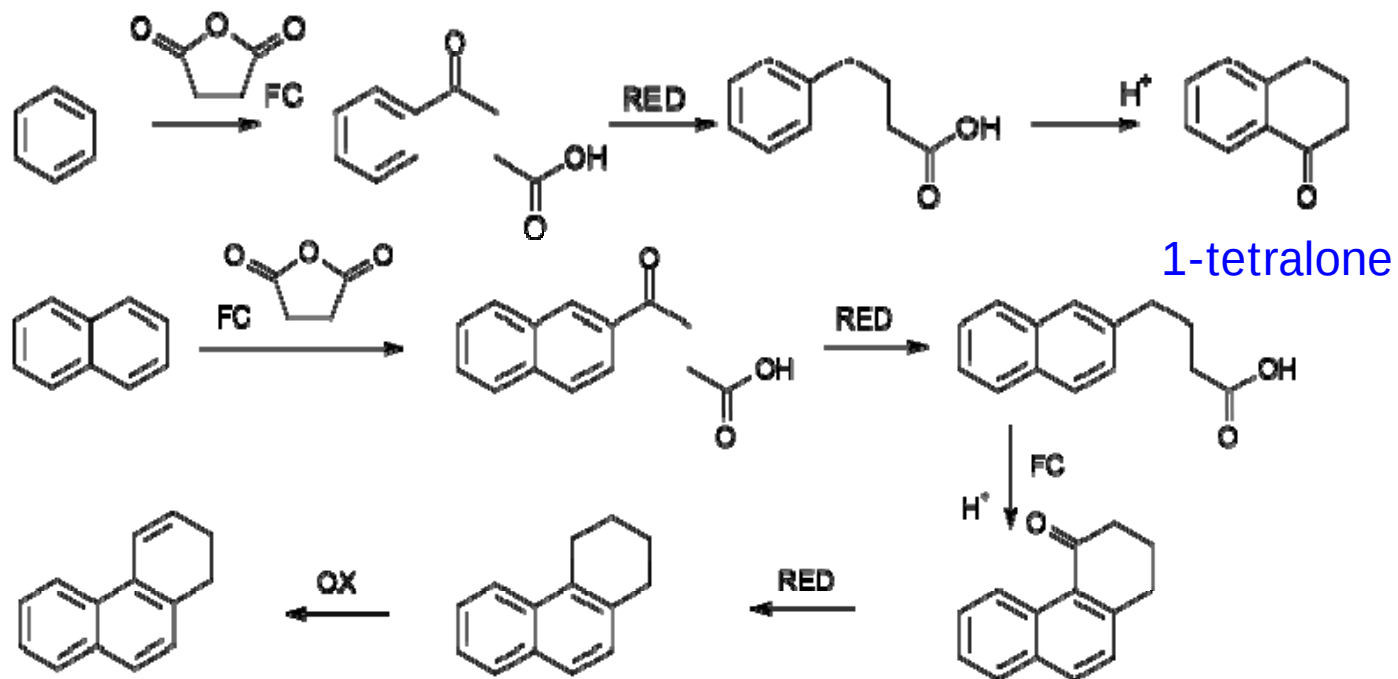
◆ Friedel-Crafts acylation



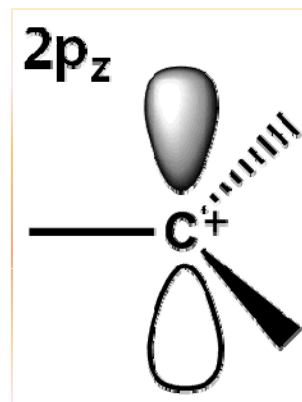
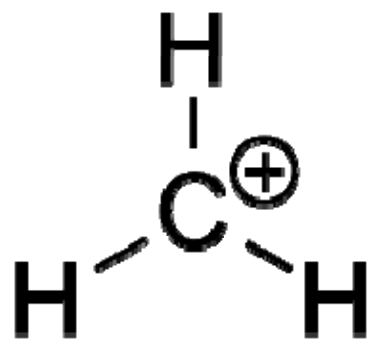
Mechanism:



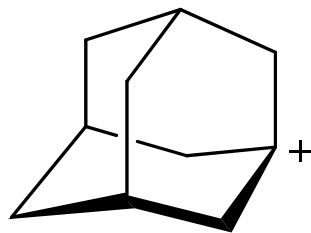
Haworth
reaction:



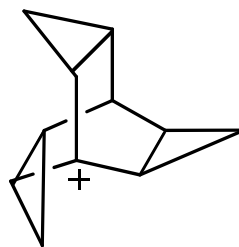
Carbocation Structure: planar sp^2 hybrid



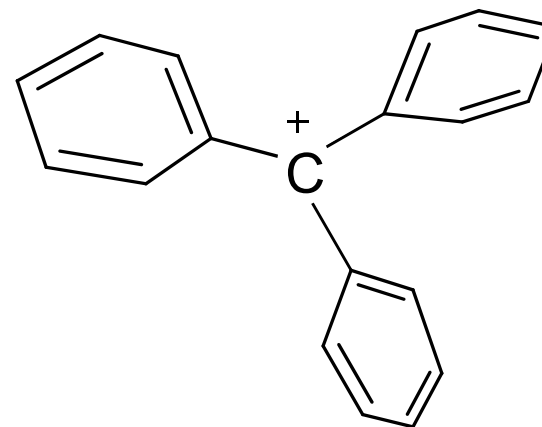
tert-butyl cation
demonstrating
planar geometry



adamantyl



1-trishomobarrellyl



triphenylmethyl
propeller-shaped

◆ An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge. *This shift approximately correlates with electron density on the carbon.*

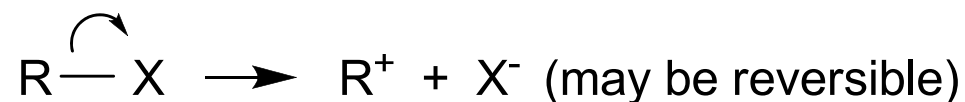
TABLE I. The ^{13}C chemical shift values for the charged carbon atom of some carbocations in $\text{SO}_2\text{ClF-SbF}_5$, $\text{SO}_2\text{-FSO}_3\text{H-SbF}_6$, or $\text{SO}_2\text{-SbF}_5$.

ion	Chemical shift, ppm	°C	ion	Chemical shift, ppm	°C
Et_2MeC^+	-139.4	-20	$\text{C}(\text{OH})_3^+$	+28.0	-50
Me_2EtC^+	-139.4	-60	PhMe_2C^+	-61.1 High	-60
Me_3C^+	-135.4 High	-20	PhMeCH^+	-40	-60
Me_2CH^+	-125.0	-20	Ph_2CH^+	-5.6	
Me_2COH^+	-55.7	-50	Ph_3C^+	-18.1 Low	-60
$\text{Me}_2\text{C}(\text{OH})^+$	-1.6	-30	$\text{Me}_2(\text{cyclopropyl})\text{C}^+$	-86.8	-60
$\text{HC}(\text{OH})_2^+$	+17.0 Low	-30			

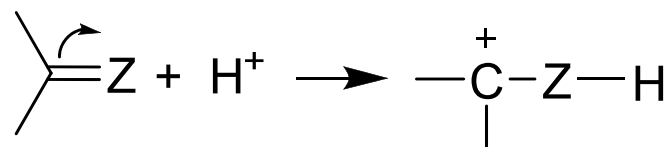
II. THE GENERATION AND FATE OF CARBOCATIONS

Two general ways to form carbocations:

i. A direct ionization:

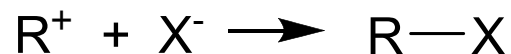


ii. Addition of a positive species to an unsaturated system:

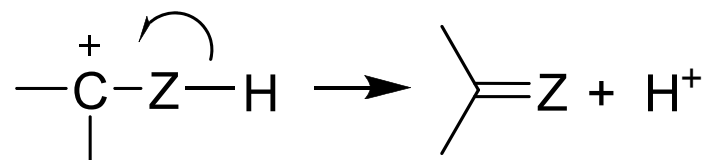


The reaction of carbocations:

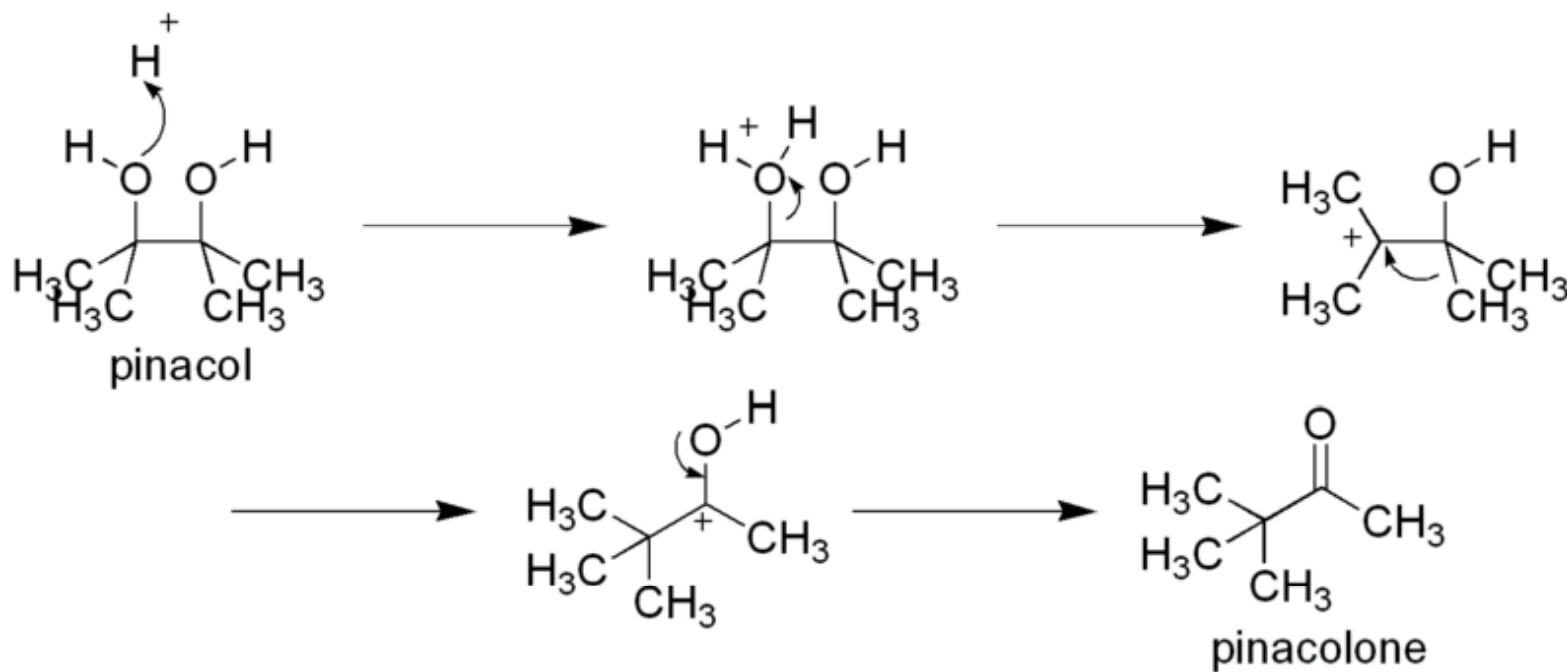
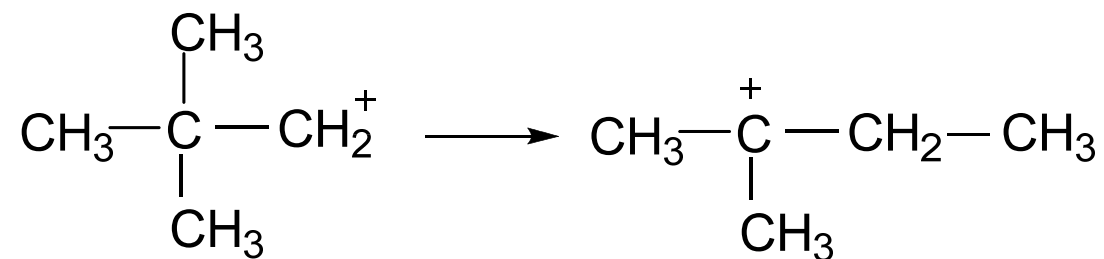
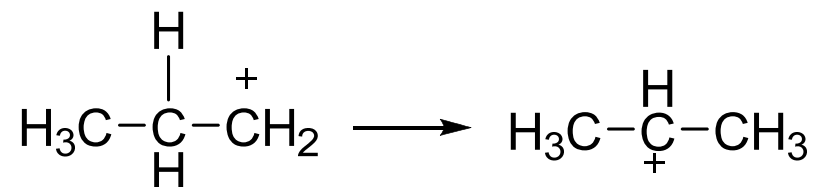
i. Combination with a species possessing an electron pair.

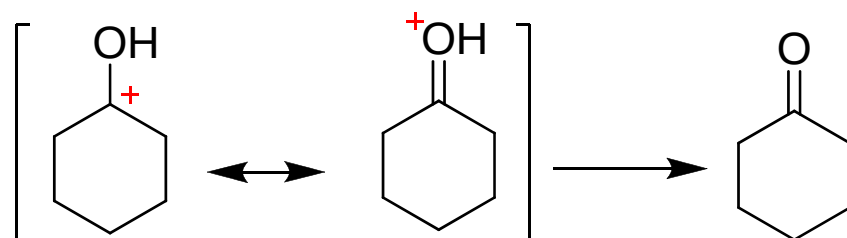
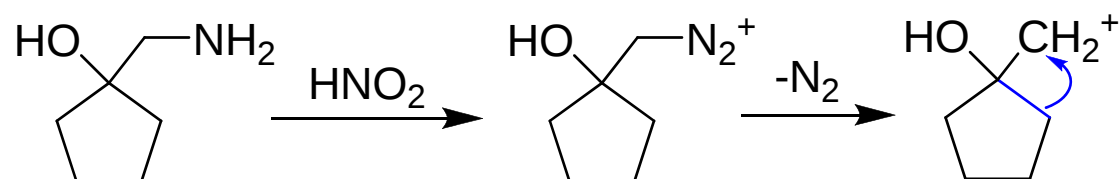
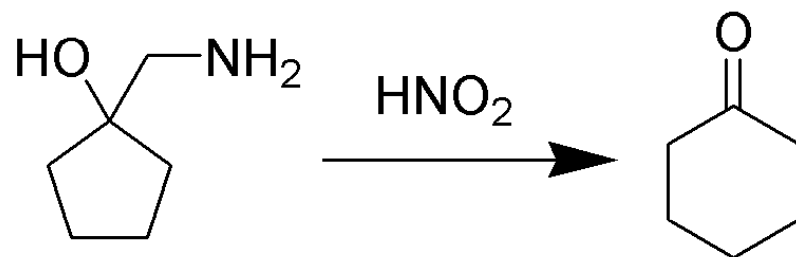


ii. The carbocation may lose a proton from the adjacent atom.

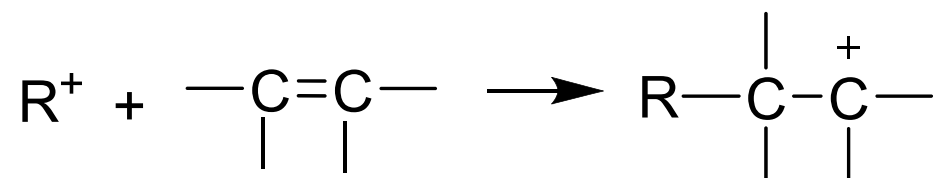


iii. Rearrangement





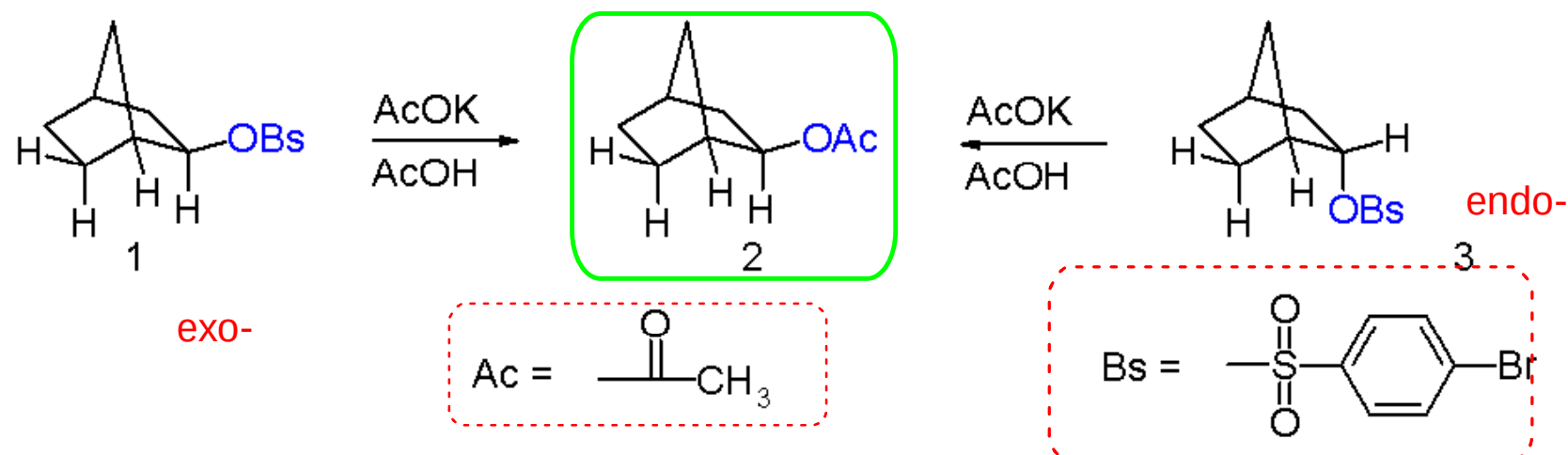
iv. Addition



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

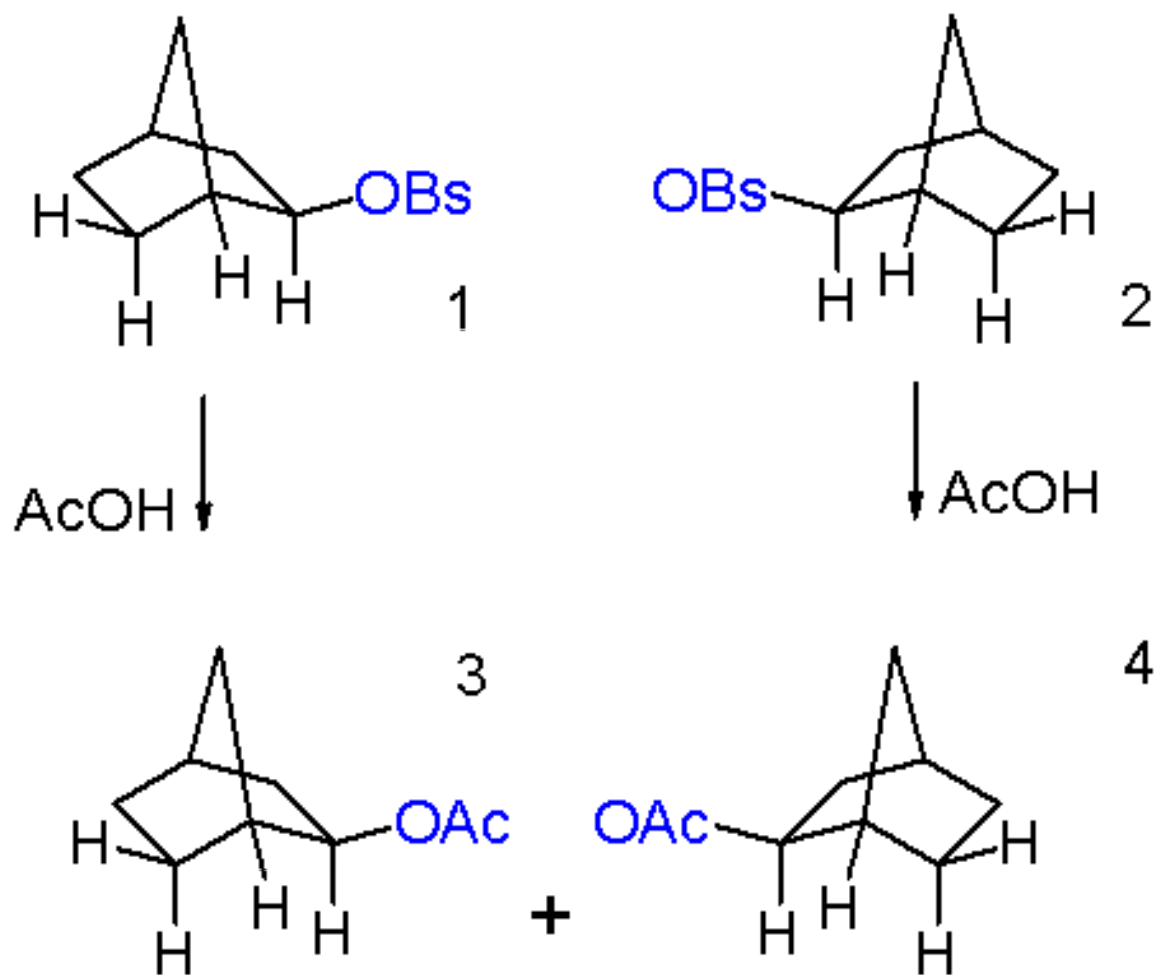
Non-classical ions are a special type of carbonium ions displaying delocalization of sigma bonds in **3-center-2-electron bonds** of bridged systems.

S. Winstein (1949): Acylation (solvolysis) of norbornyl brosylate 降冰片烷醇酯

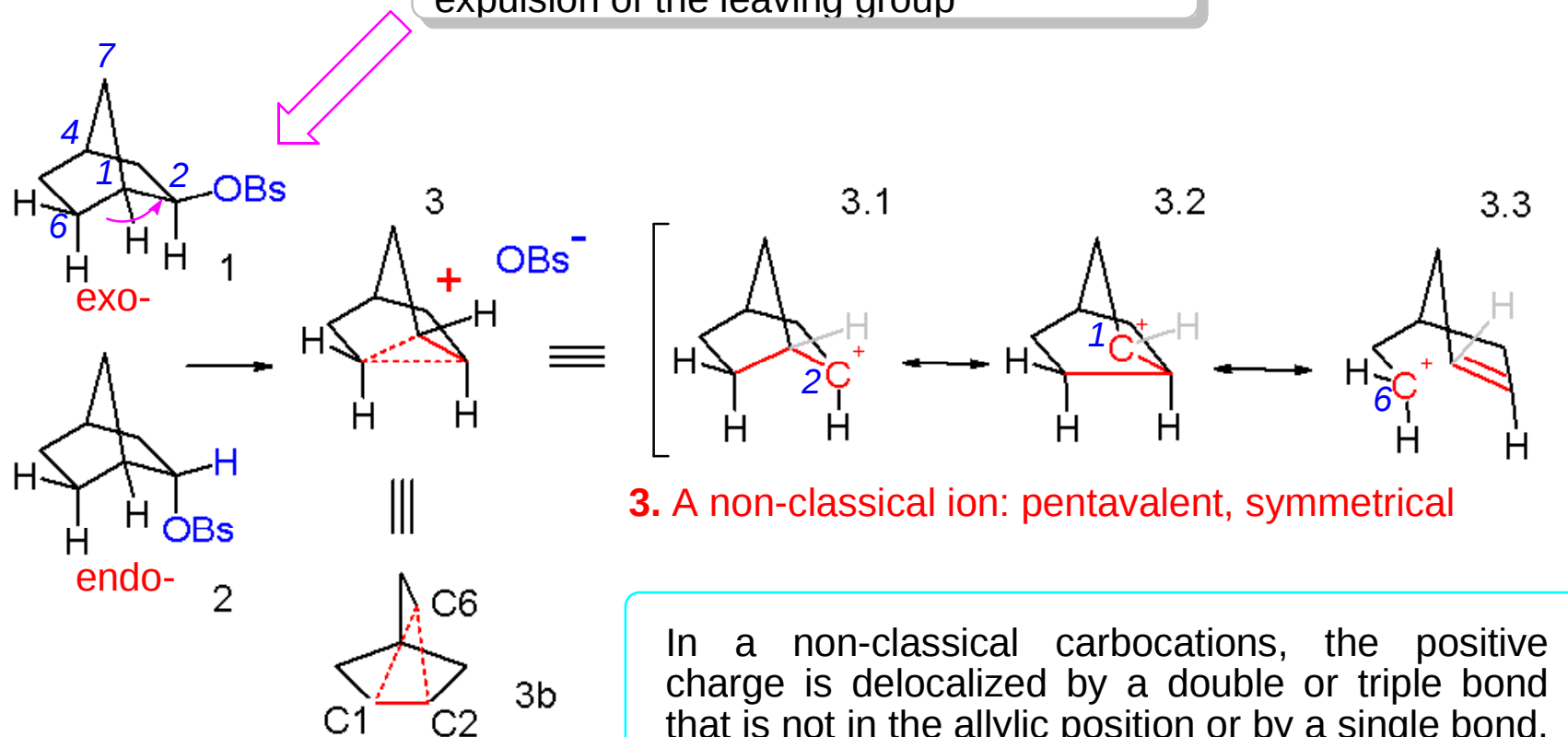


A key observation is that in this nucleophilic displacement both isomers give the same reaction product an exo-acetate **2**. Also the reaction rate for the exo-reaction is **350** times the reaction rate for the endo reaction.

In a related experiment both enantiomers **1** and **2** of the exo-brosylate on solvolysis give the same racemic reaction product. The optical activity of the reaction disappears at the same reaction rate as that of the solvolysis.

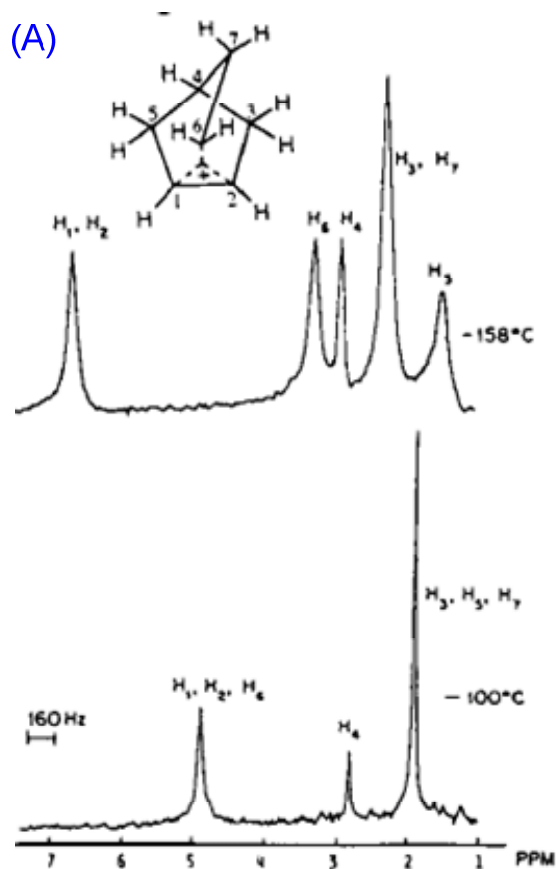
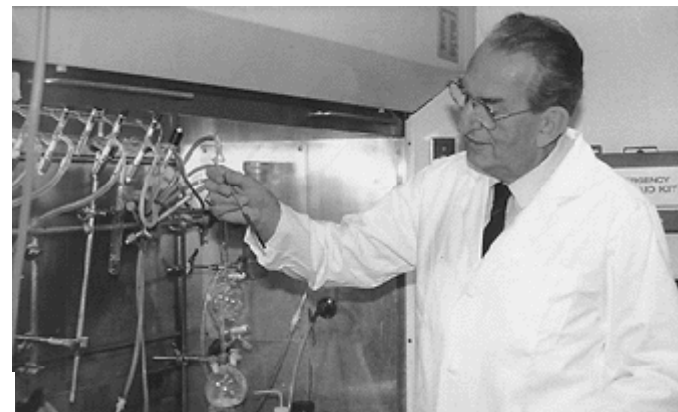


Sigma electrons in the C1-C6 bond assist by **neighbouring group participation** with the expulsion of the leaving group

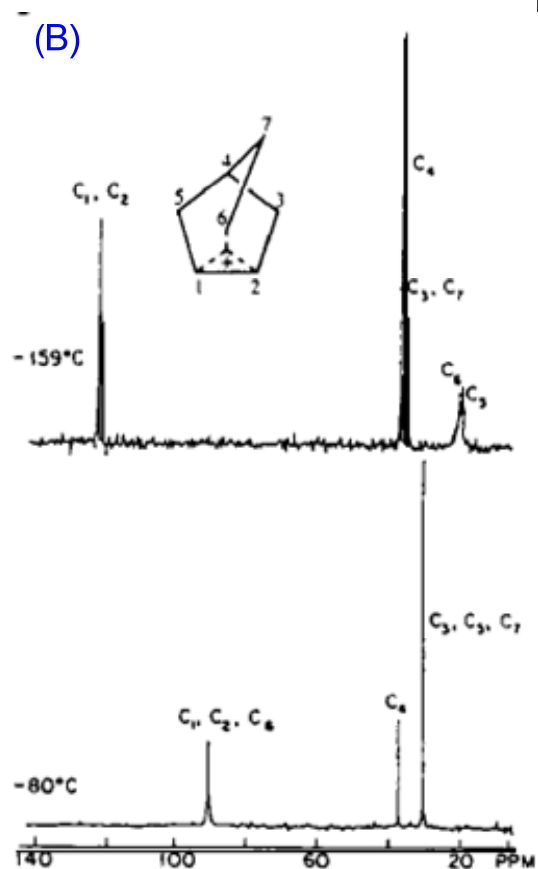


In a non-classical carbocations, the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond.

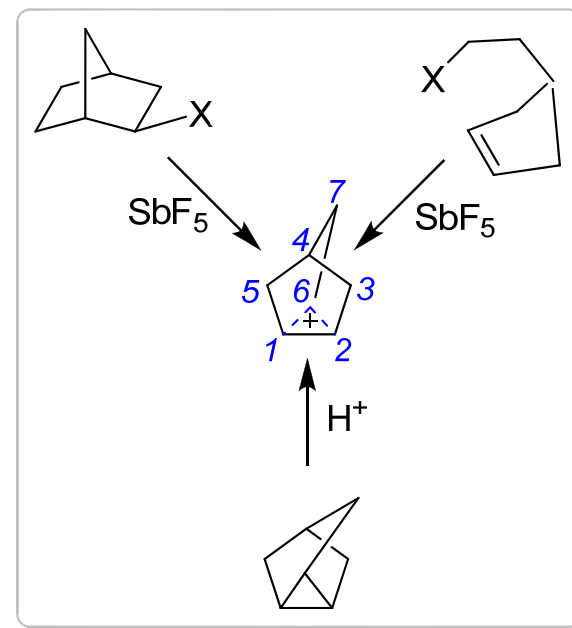
George A Olah (1964): direct evidence for the norbornyl cation by NMR analysis



(A) 395 MHz ^1H NMR of 2-norbornyl cation in $\text{SbF}_5/\text{SO}_2\text{ClF}/\text{SO}_2\text{F}_2$ solution.



(B) 50 MHz proton decoupled ^{13}C NMR of 2-norbornyl cation in $\text{SbF}_5/\text{SO}_2\text{ClF}/\text{SO}_2\text{F}_2$.

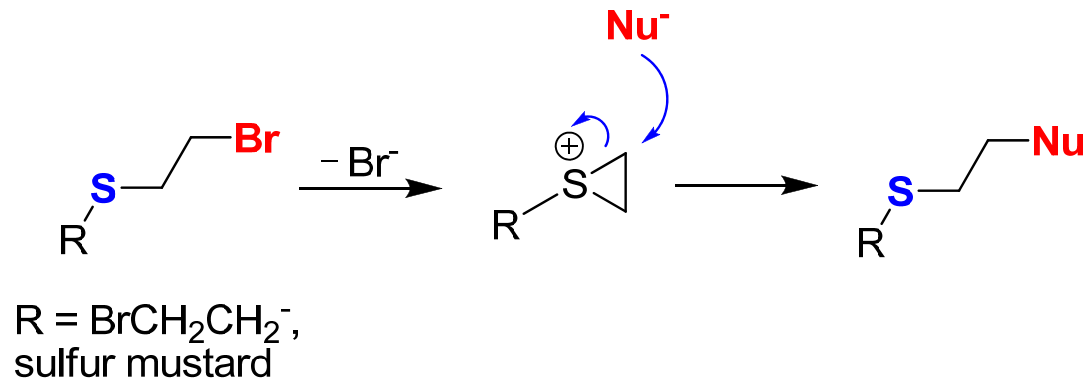


Olah, G.A., *J. Am. Chem. Soc.* **104**, 7105(1982)

IV. Neighbouring group participation (NGP) 邻基参与

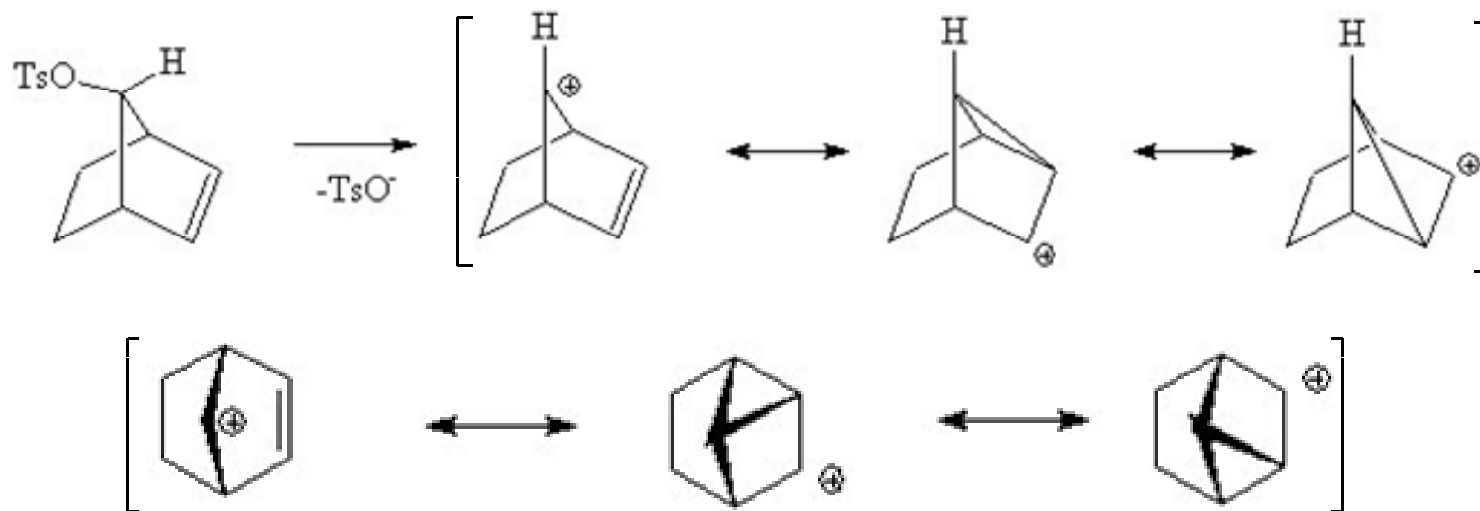
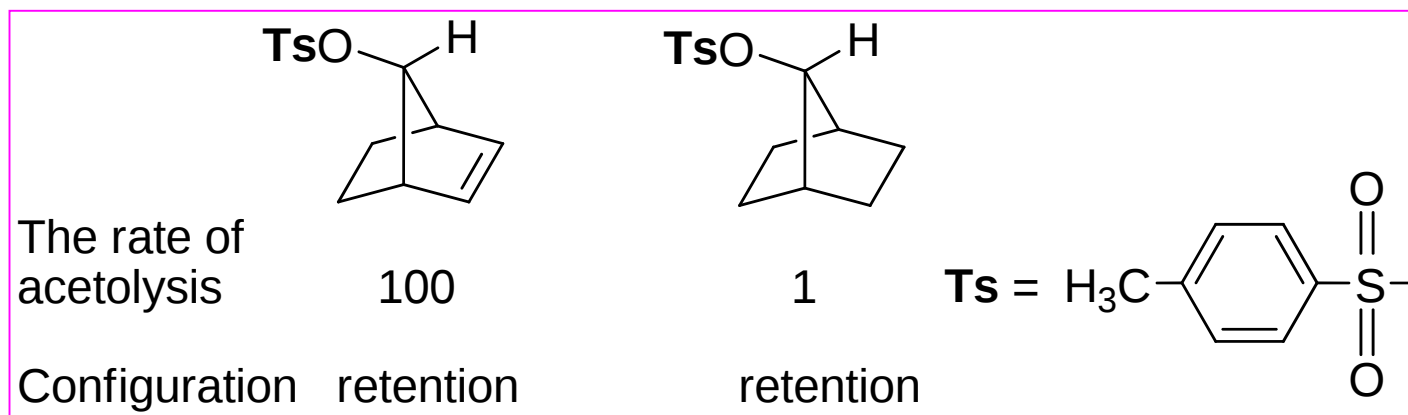
Neighbouring group participation or NGP has been defined by IUPAC as the interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a σ bond or π bond. When NGP is in operation it is normal for the reaction rate to be increased. It is also possible for the stereochemistry of the reaction to be abnormal (or unexpected) when compared with a *normal* reaction.

A. NGP by heteroatom lone pairs



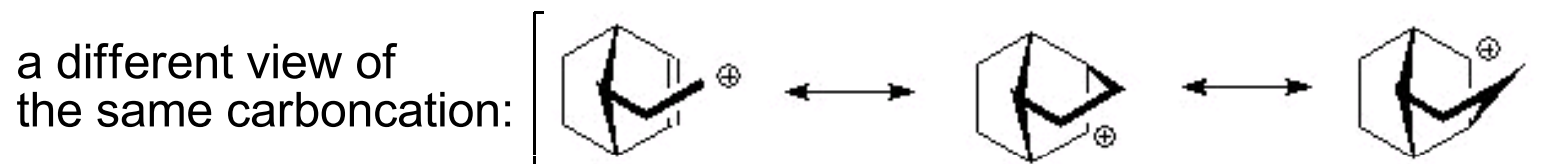
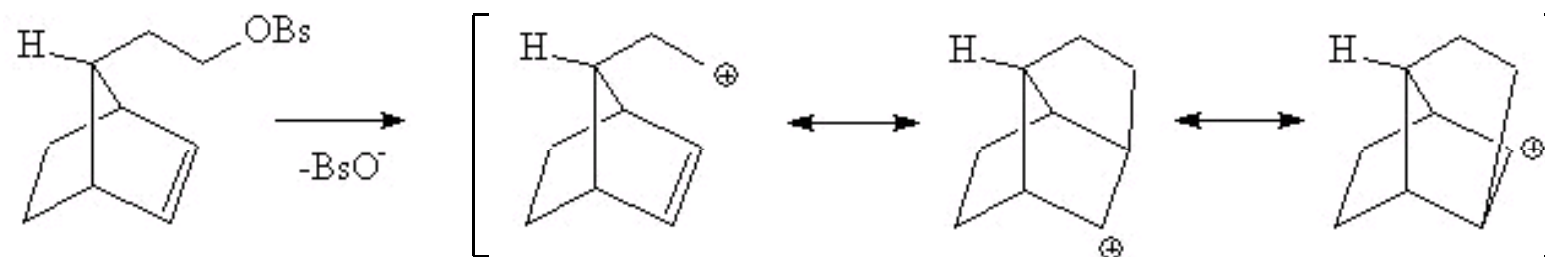
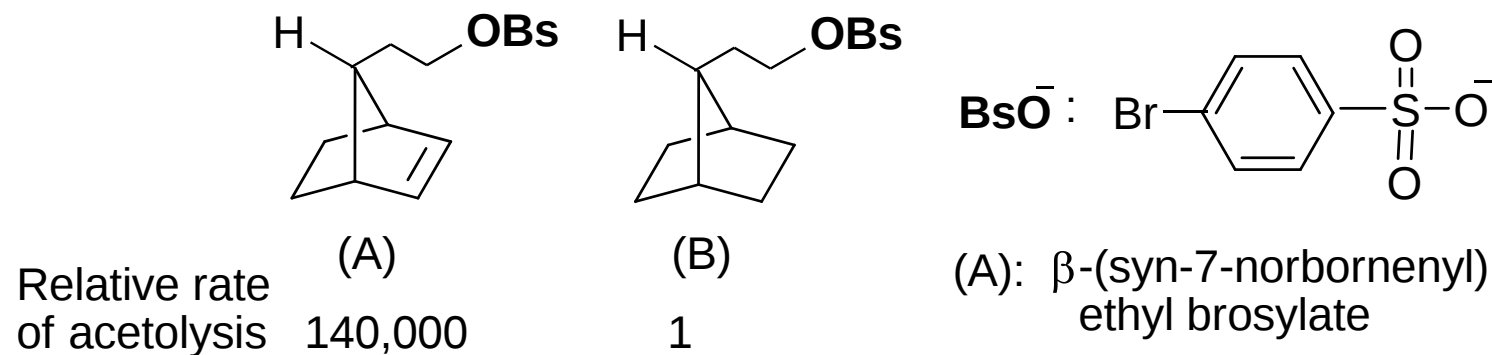
The rate of reaction is much higher for **the sulfur mustard** and a nucleophile than it would be for a primary alkyl chloride without a heteroatom. 芥子气

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



(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.

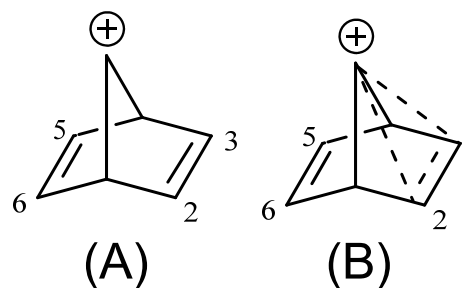


DISCUSSION

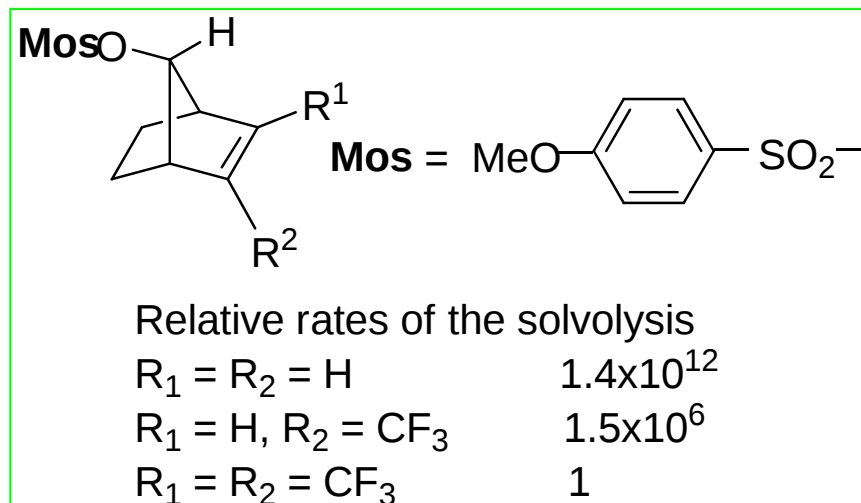
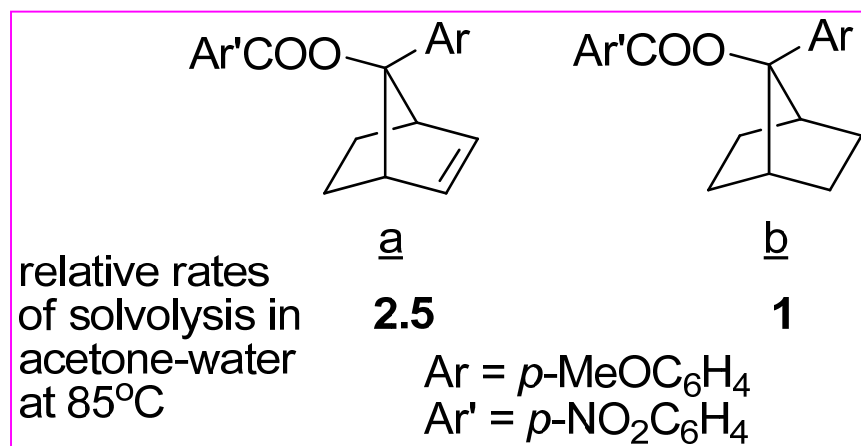
(i) Evidence for the non-classical cations.

(ii) A neighboring group lends anchimeric assistance only when there is sufficient demand for it.

(iii) The ability of C=C to serve as a neighboring group can depend on its electron density.

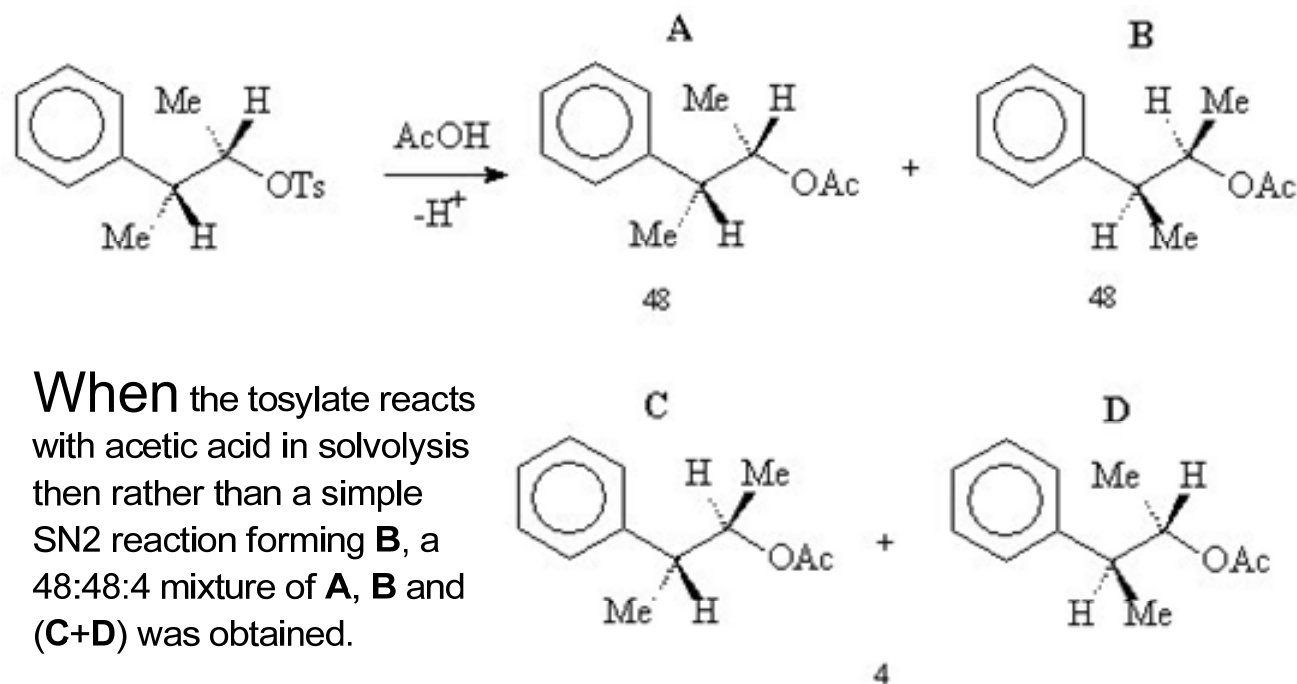
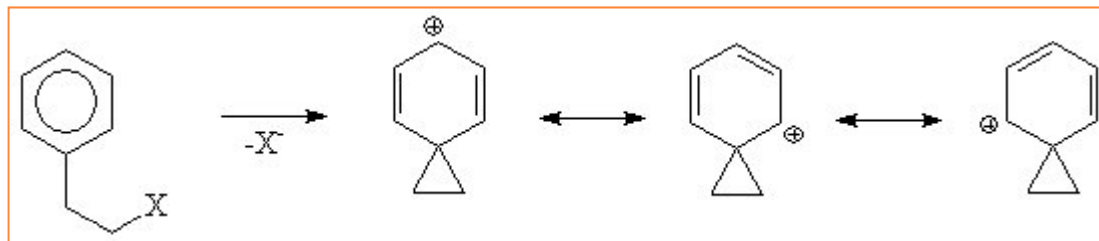


Norbornadienyl cation
 ^1H NMR:
 2 and 3 protons are not equivalent to the 5 and 6 protons.



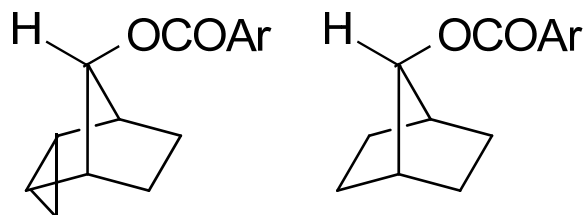
C. NGP BY AN AROMATIC RING

An aromatic ring can assist in the formation of a carbocationic intermediate called a **phenonium ion** by delocalising the positive charge.

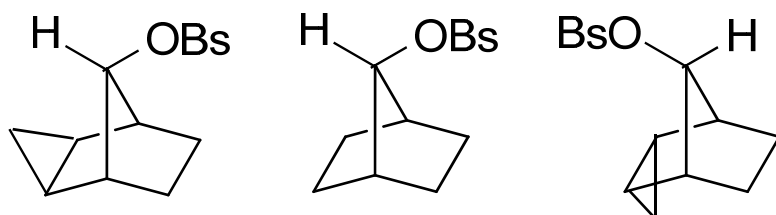


QUESTION: please give a mechanism which forms A and B.

D. CYCLOPROPYL AS A NEIGHBORING GROUP



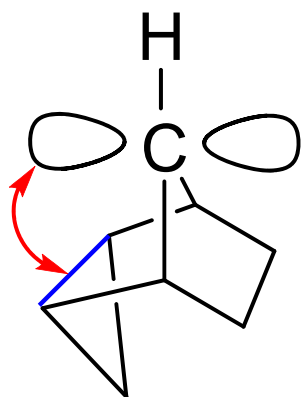
(A) (B)
(Ar = *p*-NO₂C₆H₄)



(C) (D) (E)

The relative rate of solvolysis

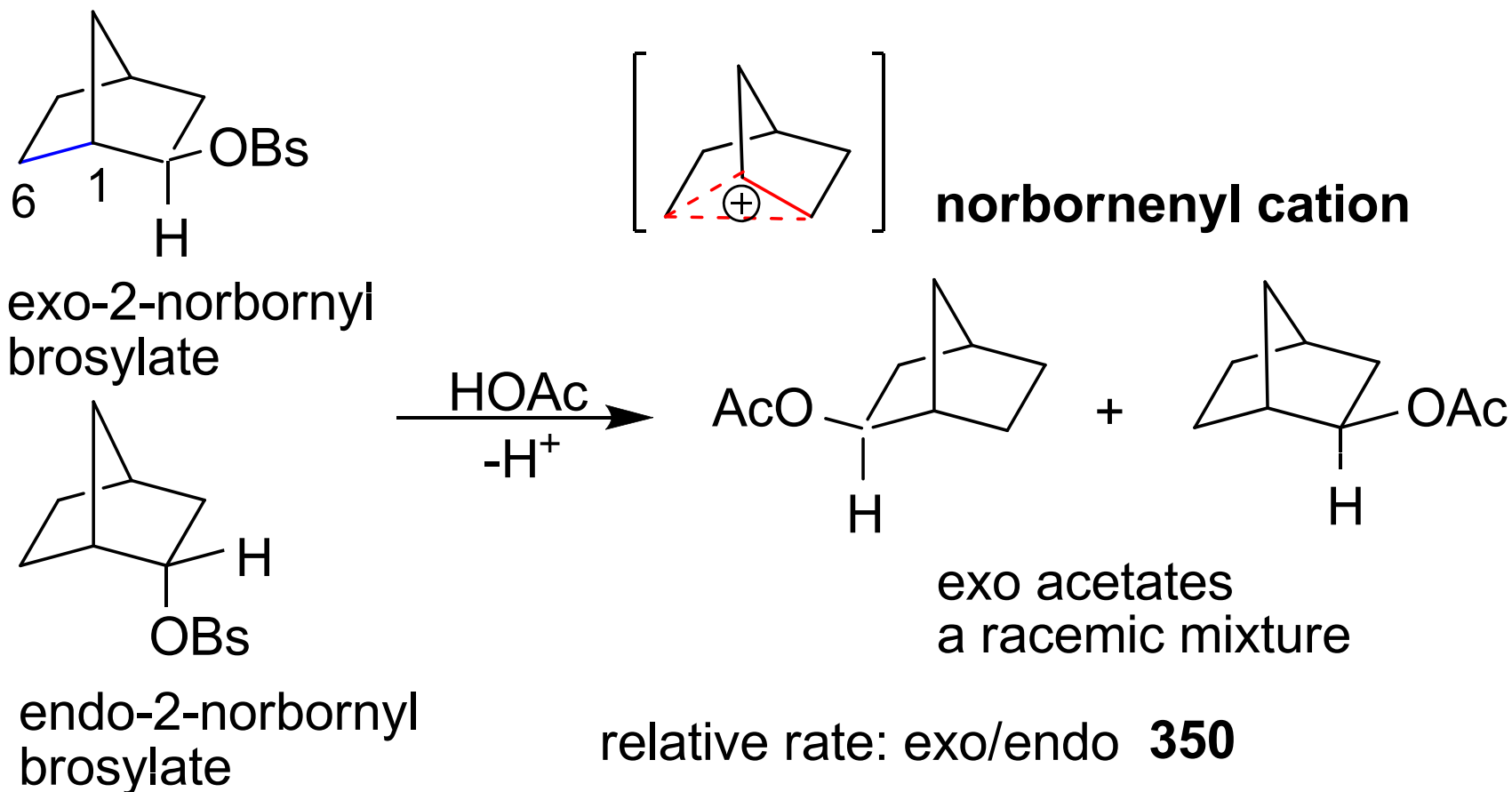
(A)	(B)	
10^{14}	1	
(C)	(D)	(E)
$1/3$	1	5



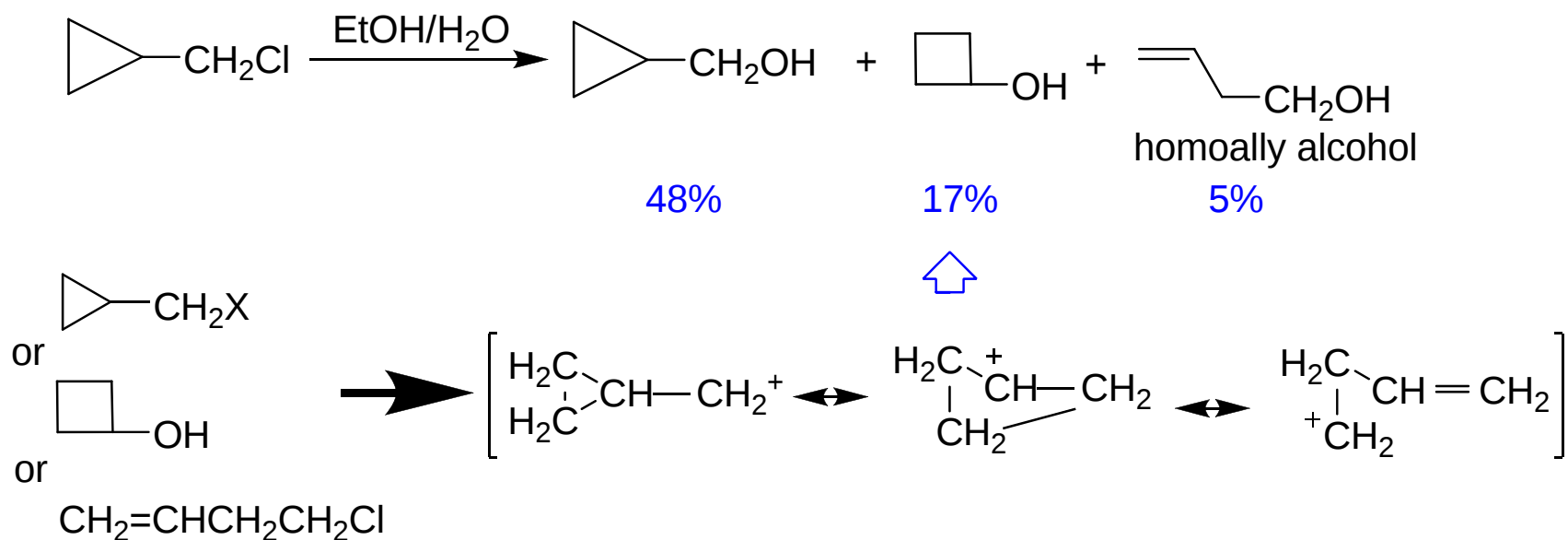
Where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.

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

i. The 2-norbornyl system

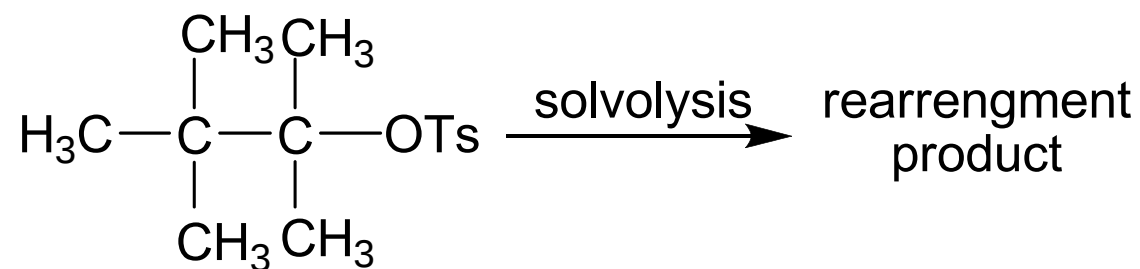


ii The Cyclopropylmethyl System

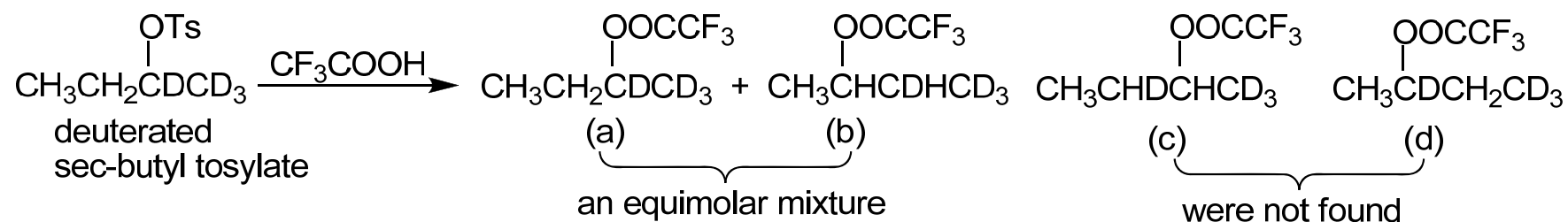
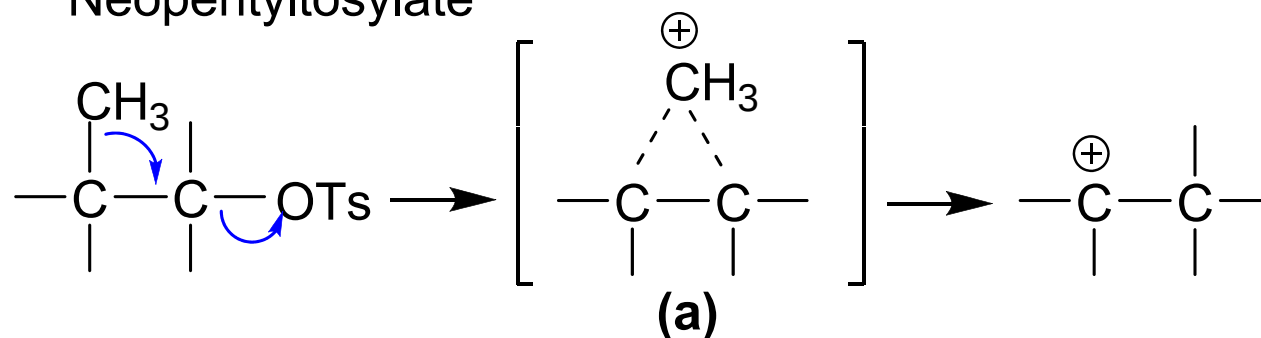


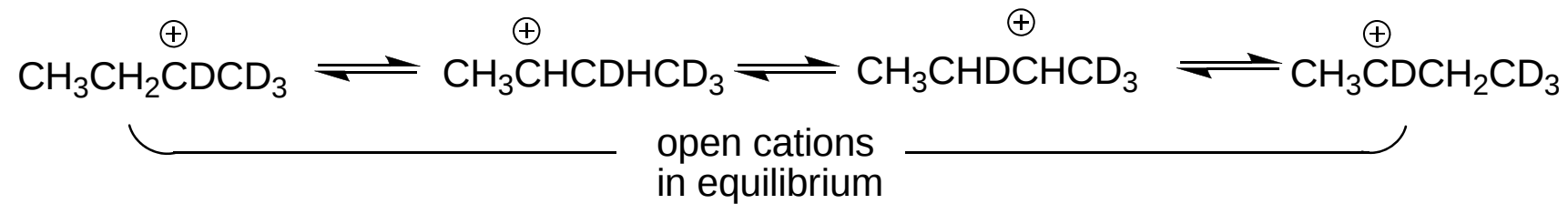
The carbocationic intermediate is delocalised onto many different carbons through a reversible ring opening.

iii. Methyl or Hydrogen as Neighboring Group

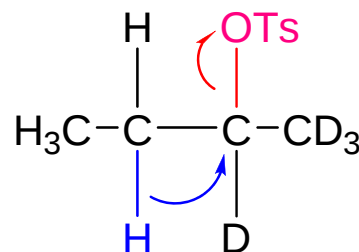
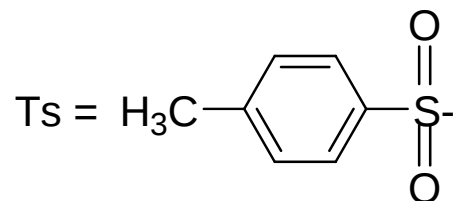


Neopentyltosylate

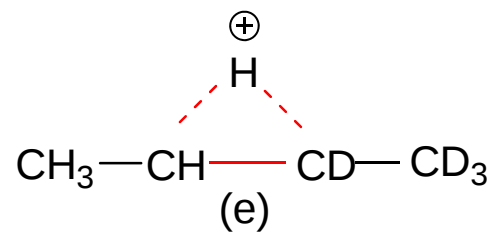




↑ no NGP by hydrogen



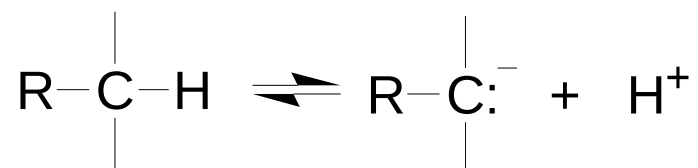
↓ NGP by hydrogen



4.2 CARBANIONS

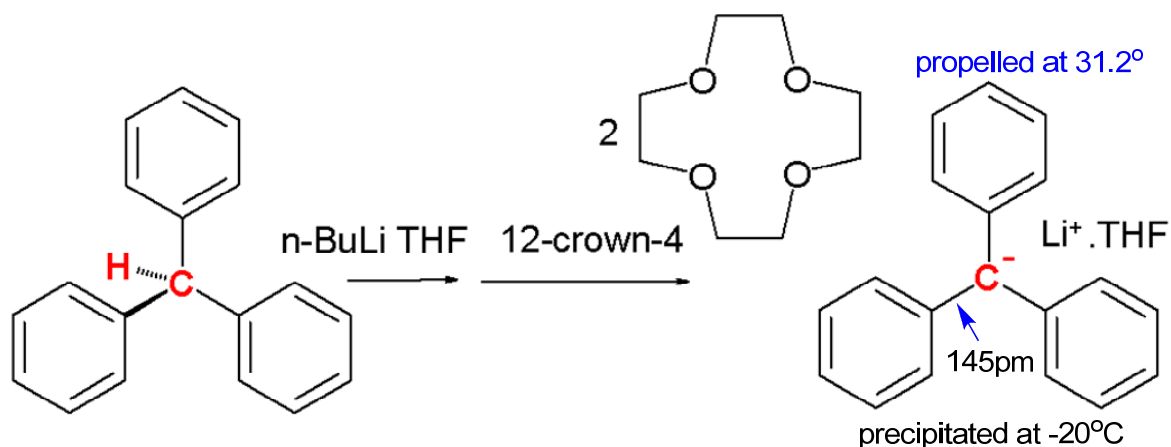
A **carbanion** is an anion in which carbon has an unshared pair of electrons and bears a negative charge usually with three substituents for a total of eight valence electrons.

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



Stable carbanions do however exist although in most cases they are reactive.

Olmstead (1984)



I. STABILITY AND STRUCTURE

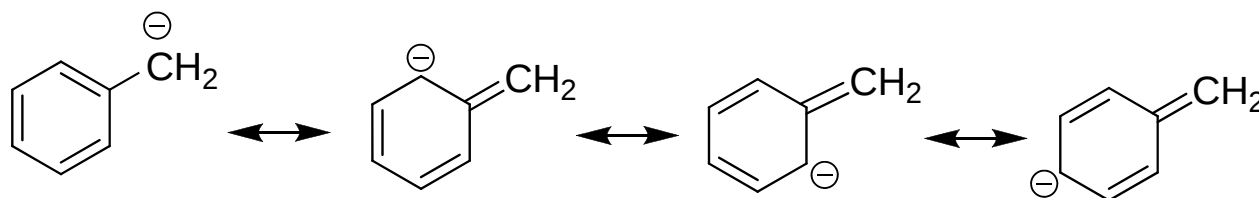
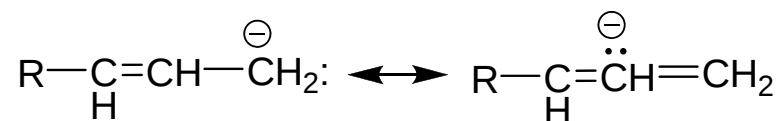
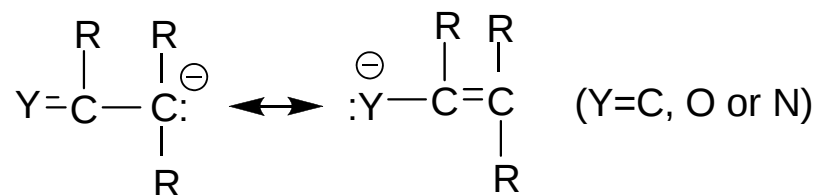
The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker is the acid, the greater is the base strength and the lower is the stability of the carbanion.

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

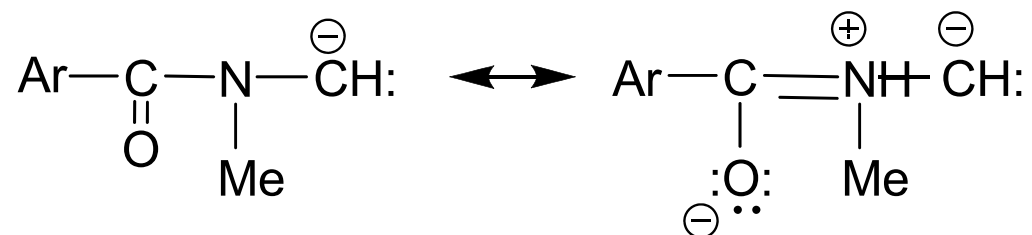
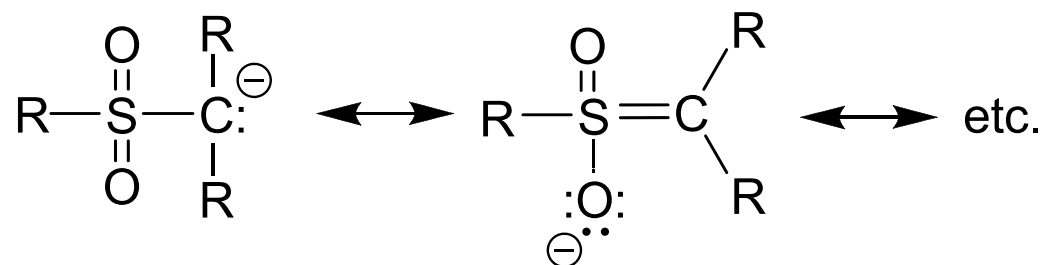


Carbanions increase in stability with an increase in the amount of *s* character at the carbanionic carbon.

Stability:



- 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 hetero atom (O, N or S) connected to the carbanionic carbon, provided that the hetero atom bears a positive charge in at least one important canonical form.

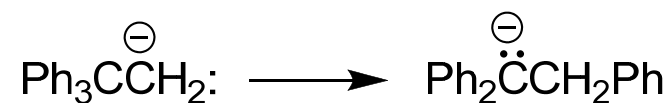
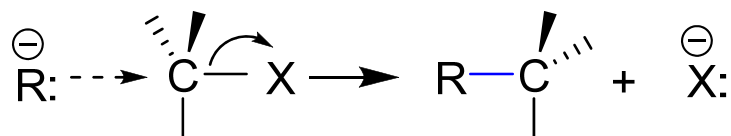
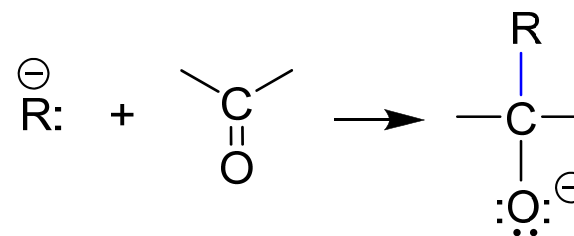
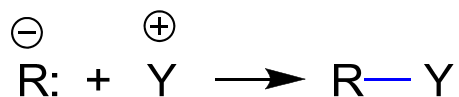
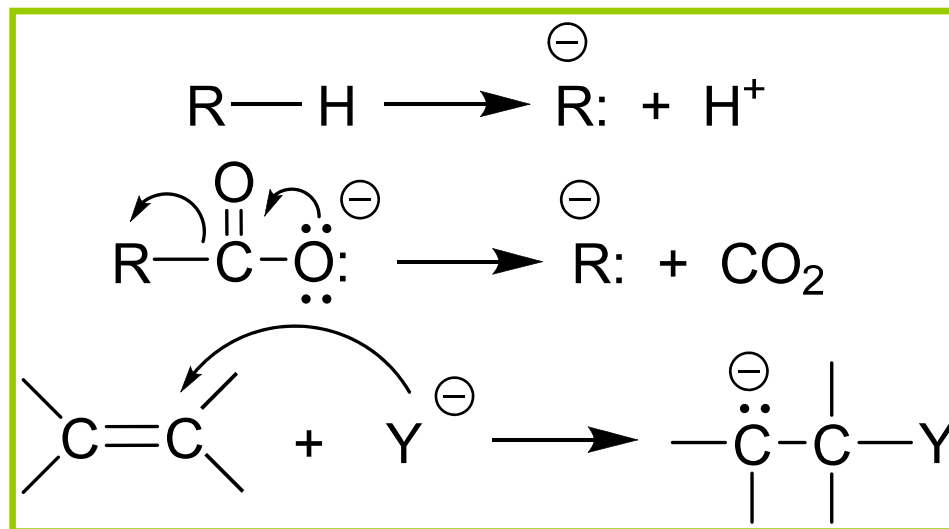


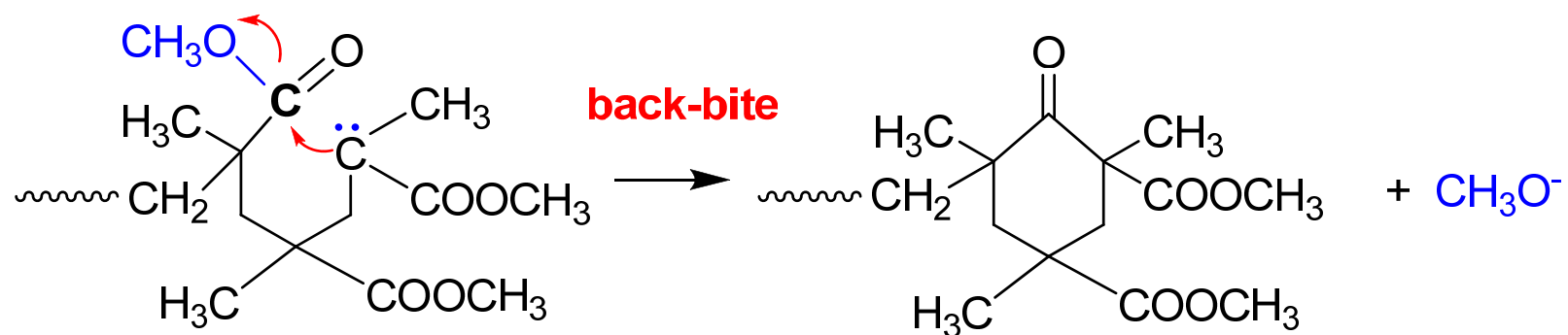
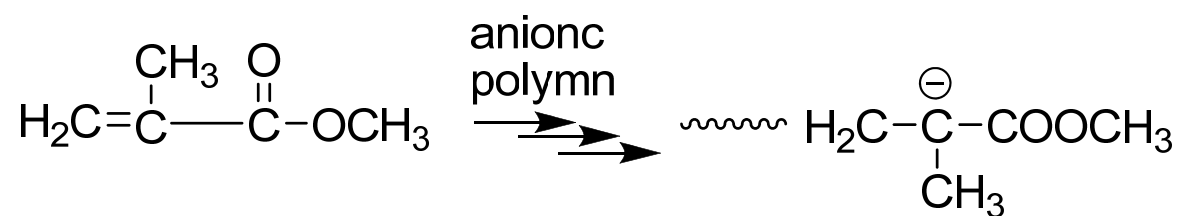
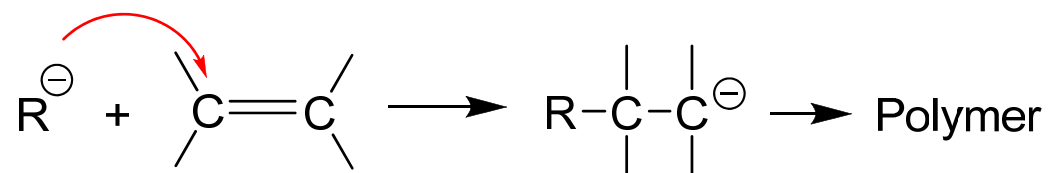
II. THE GENERATION AND FATE OF CARBANIONS

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.

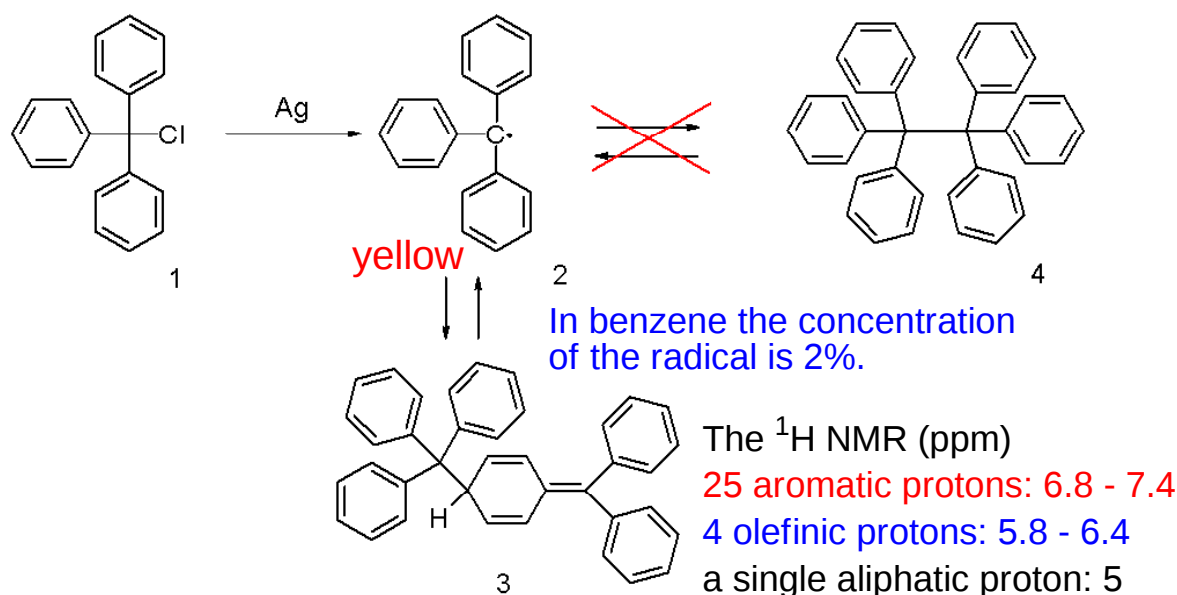
Reactions:





4.3 FREE RADICALS

- 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.



Moses Gomberg
1866-1947

I. STABILITY AND STRUCTURE

- Alkyl radical intermediates are stabilized by similar criteria as carbocations: *the more substituted the radical center is, the more stable it is.*

The stability order for radical: tertiary > secondary > primary

Hyperconjugation:

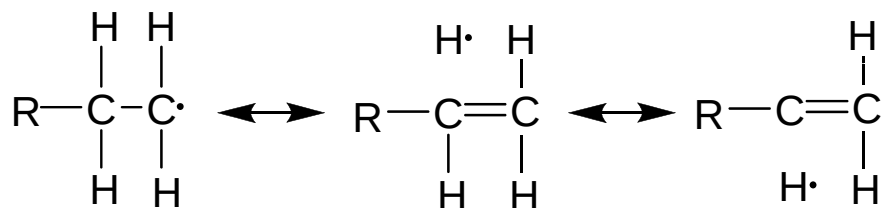
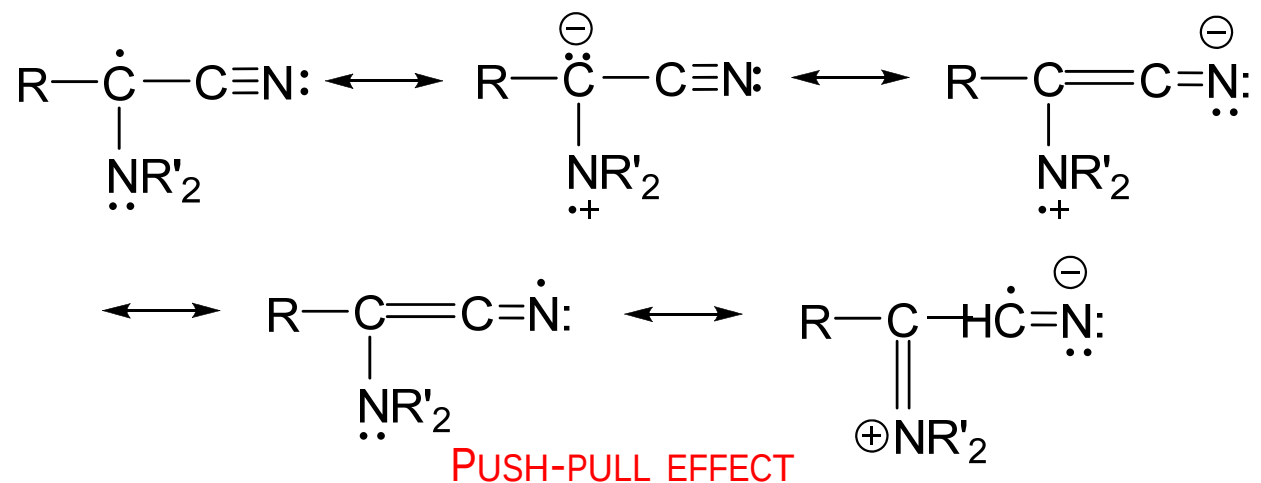


TABLE. The D_{298} values for R-H bonds

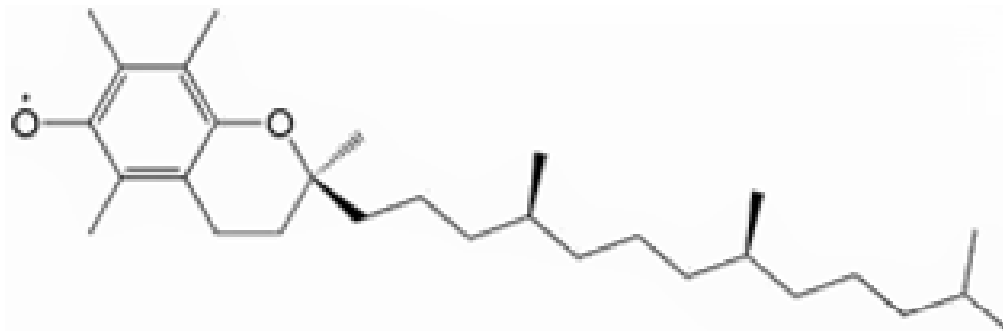
R	D (kJ/mol)	R	D (kJ/mol)	R	D (kJ/mol)
Ph	464	Et	419	Me ₃ C	401
CF ₃	446	Me ₃ CCH ₂	418	Cyclohexyl	400
CH ₂ =CH	444	Pr	417	PhCH ₂	368
Cyclopropyl	444	Cl ₃ C	401	HCO	364
Me	438	Me ₂ CH	401	CH ₂ =CH-CH ₂	361

Free radical stability is in reverse order.

♦ Radicals next to functional groups, such as carbonyl, nitrile, and ether are even more stable than tertiary alkyl radicals.



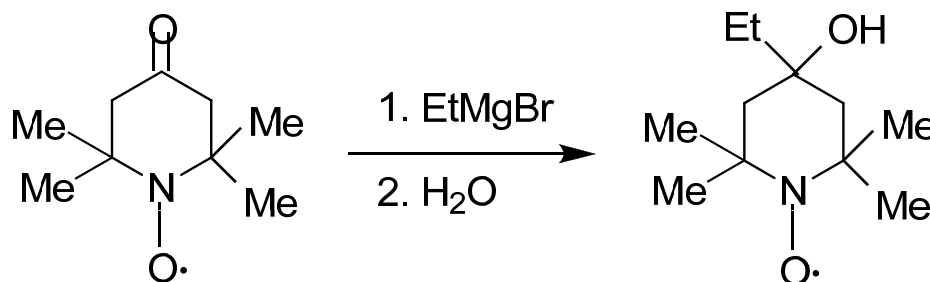
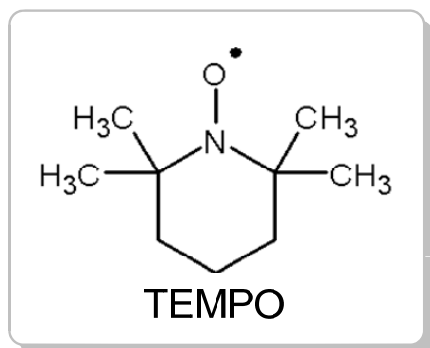
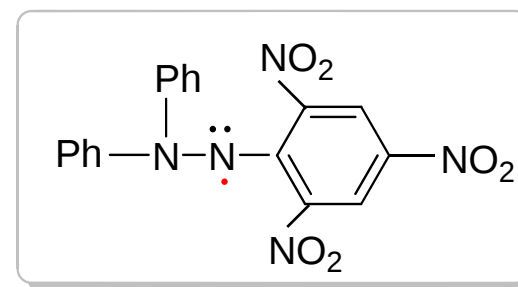
♦ Organic radicals can be long lived if they occur in a conjugated π system.



The radical derived from *alpha*-tocopherol

♦ **Persistent radical** compounds are those whose longevity is due to *steric crowding* around the radical center and makes it physically difficult for the radical to react with another molecule.

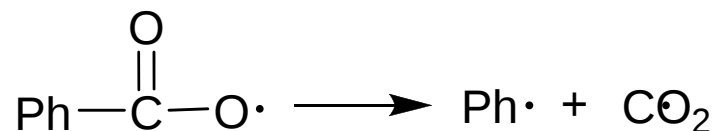
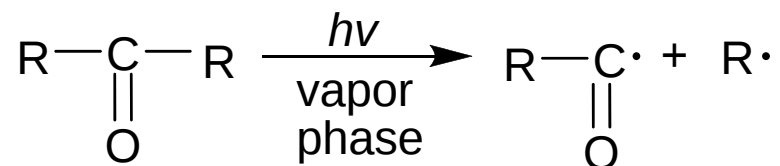
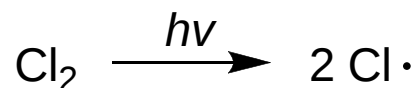
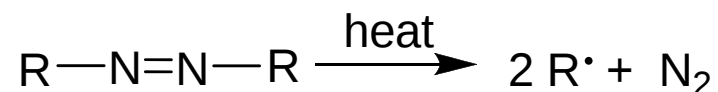
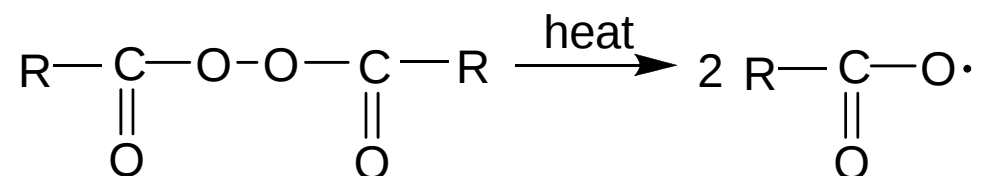
Examples: Gomberg's triphenylmethyl radical
2,2-Diphenyl-1-picrylhydrazyl (DPPH)
2,2,6,6-Tetramethylpiperidine-1-oxyl (**TEMPO**)



Application of TEMPO: as a radical trap, as a structural probe for biological systems in conjunction with electron spin resonance spectroscopy, as a reagent in organic synthesis, and as a mediator in controlled free radical polymerization.

II. THE GENERATION AND FATE OF FREE RADICALS

- The formation of radicals may involve breaking of covalent bonds homolytically, a process that requires significant amounts of energy.
- Homolytic bond cleavage most often happens between two atoms of similar electronegativity.



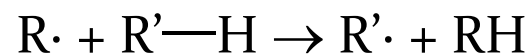
- Free radicals take part in **radical addition** and **radical substitution** as reactive intermediates.
- Chain reactions involving free radicals can usually be divided into three distinct processes: *initiation*, *propagation*, and *termination*.

Termination reactions → stable products

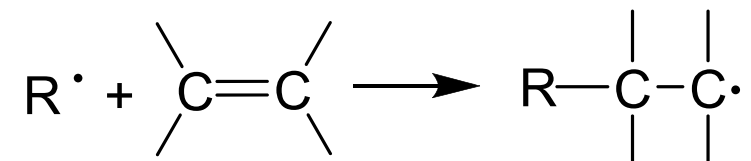


Propagation reactions → other radicals (which usually react further)

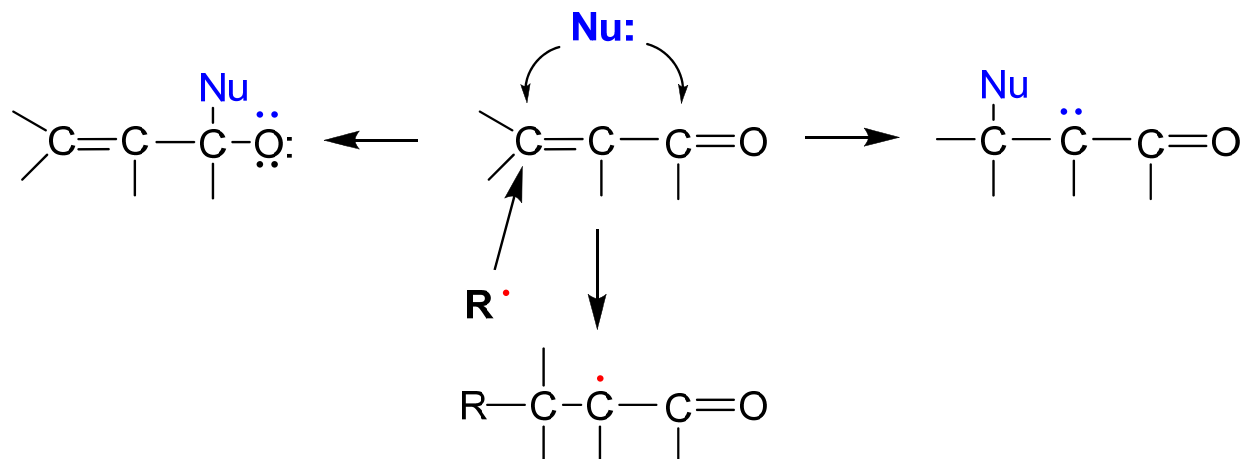
(iii) abstraction of another atom or group, usually a hydrogen atom:



(iv) addition to a multiple bond:

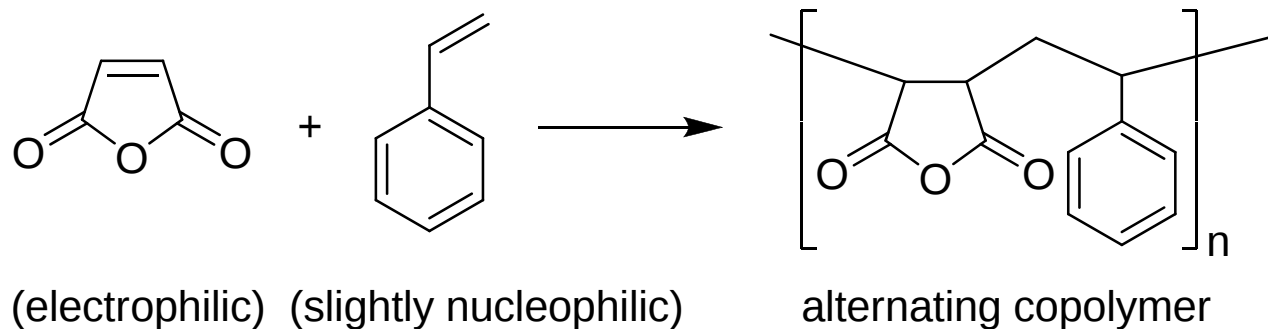


- Radicals attack double bonds, but unlike similar ions, they are not as much directed by electrostatic interactions.



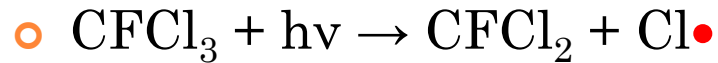
alpha-Radical carbonyl is relatively stable;
it can couple with another molecule
or be oxidized.

- The electrophilic/neutrophilic character of radicals



ATMOSPHERIC RADICALS — OZONE DEPLETION

- Refrigerants: **Freon**. Freon-11 is trichlorofluoromethane, while Freon-12 is dichlorodifluoromethane. Freon-113 (1,1,2-Trichloro-1,2,2-trifluoroethane).



These free radicals then react with ozone in a catalytic chain reaction which destroys the ozone:

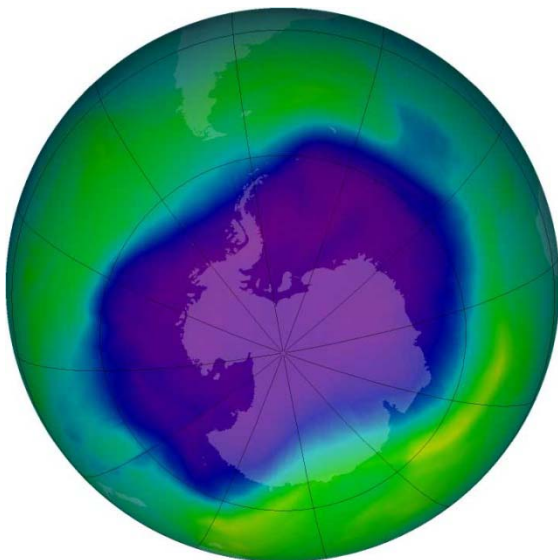
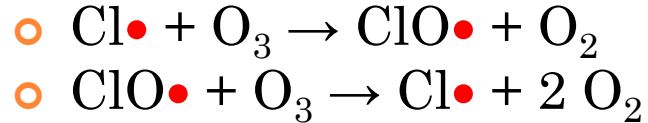
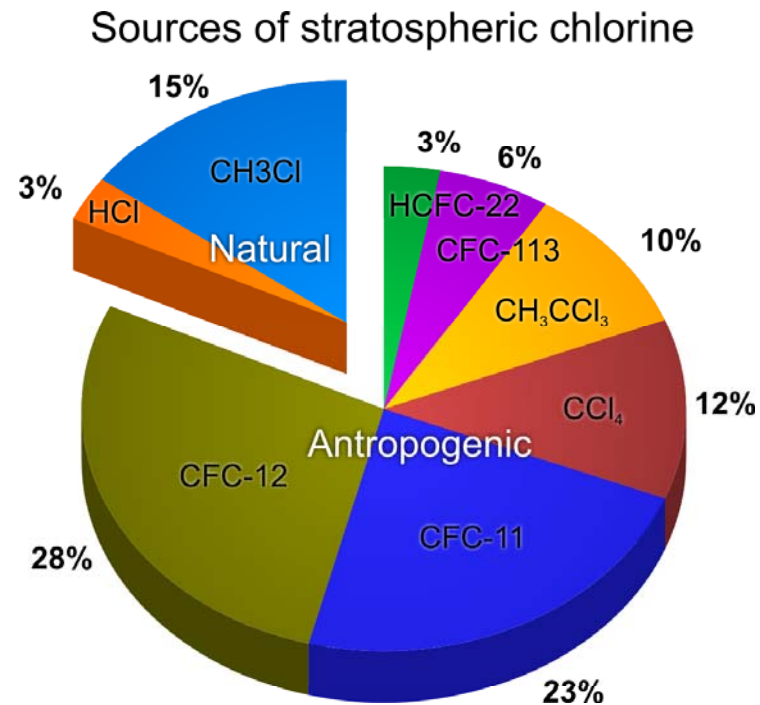


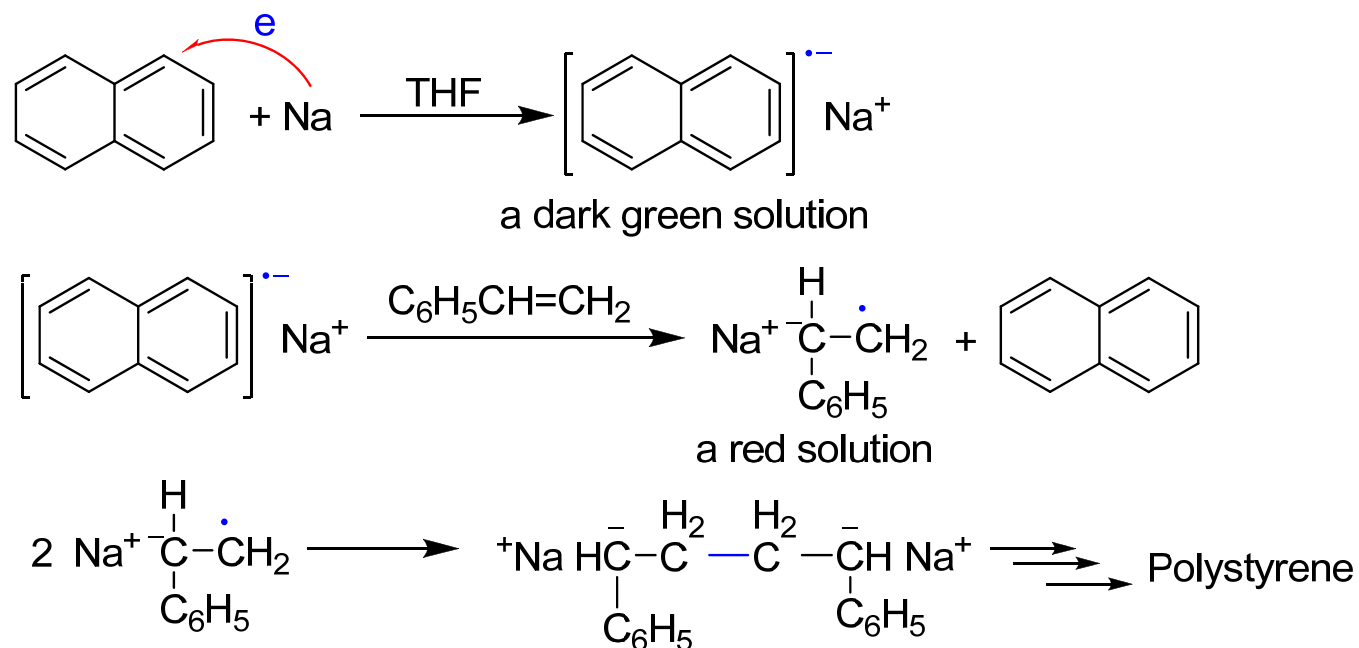
Image of the largest Antarctic ozone hole ever recorded (September 2006)



III. RADICAL IONS

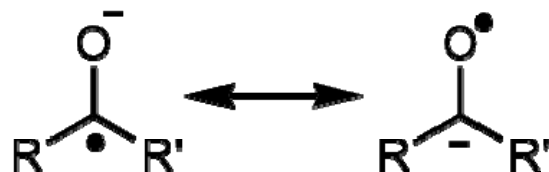
- A **radical ion** is a free radical species that carries a charge.
- Many aromatic compounds can undergo *one-electron reduction* by alkali metals.

Sodium naphthalenide: the reaction of naphthalene with sodium in an aprotic solvent.



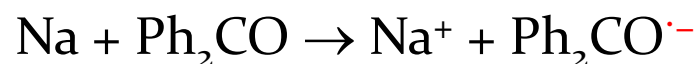
KETYL

- A **ketyl** group is an anion radical with the general structure $\text{C-O}^\bullet$ in which an oxygen radical is bonded directly to carbon.



Benzophenone radical anion

Sodium reduces benzophenone to the soluble ketyl radical, which reacts quickly with the water and oxygen dissolved in the solvent. The deep blue coloration qualitatively indicates dry, oxygen-free conditions.

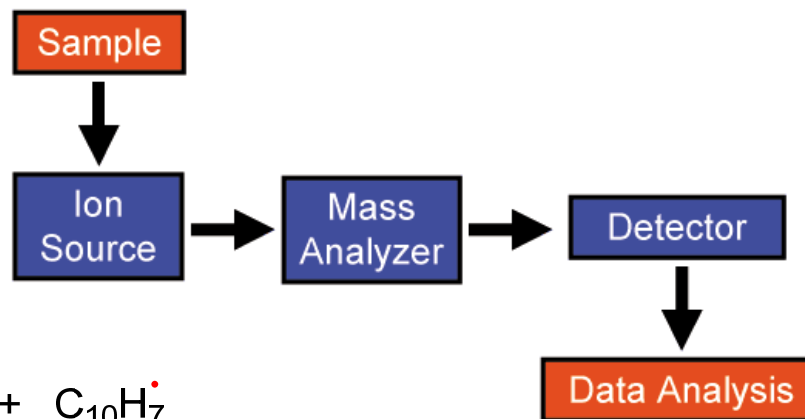
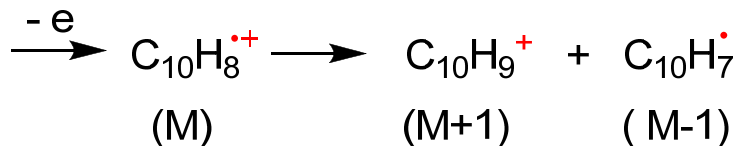
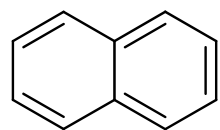
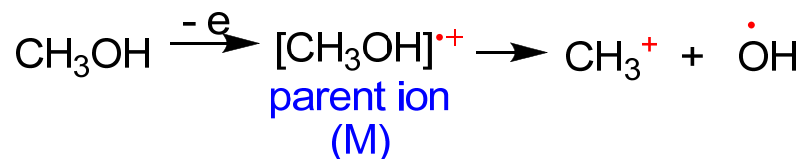


The intense blue coloration due to the benzophenone ketyl radical shows that the toluene is considered free of air and moisture.

RADICAL CATIONS

- **Cationic radical species** are much less stable. They appear prominently in mass spectroscopy (MS). When a gas-phase molecule is subjected to electron ionization, one electron is abstracted by an electron in the electron beam to create a radical cation $M^{\bullet+}$. *This species represents the molecular ion or parent ion and will tell the precise molecular weight.*

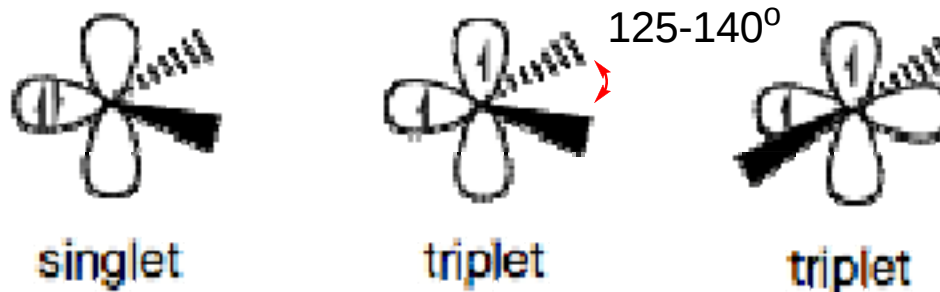
- Examples:



4.4 CARBENES

- A **carbene** is a highly reactive species containing a carbon atom with six valence electrons and having the general formula $RR'C:$, practically all having lifetimes considerably under 1 sec.

i. Structure and bonding



singlet
the total spin=0
bond angle = 102°
for single methylene

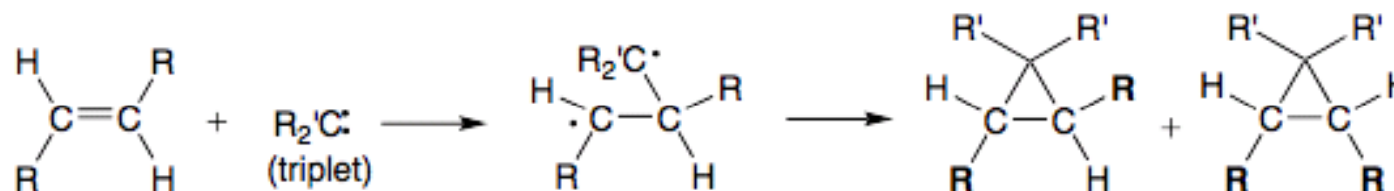
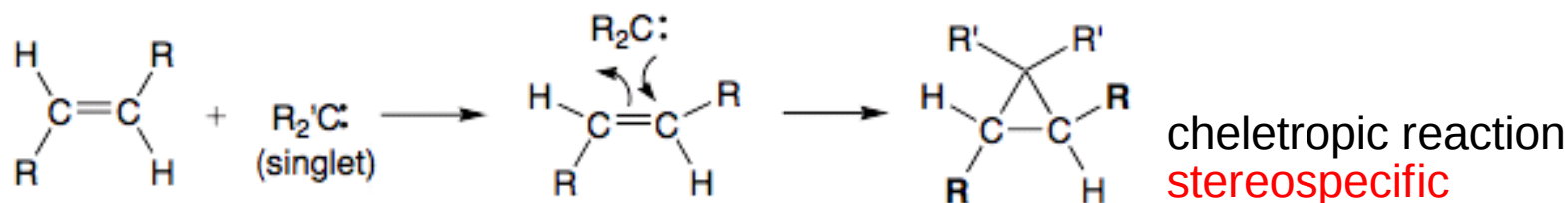
triplet
the total spin=1;
paramagnetic, may be
observed by
electron spin resonance
spectroscopy

Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

II. REACTIVITY

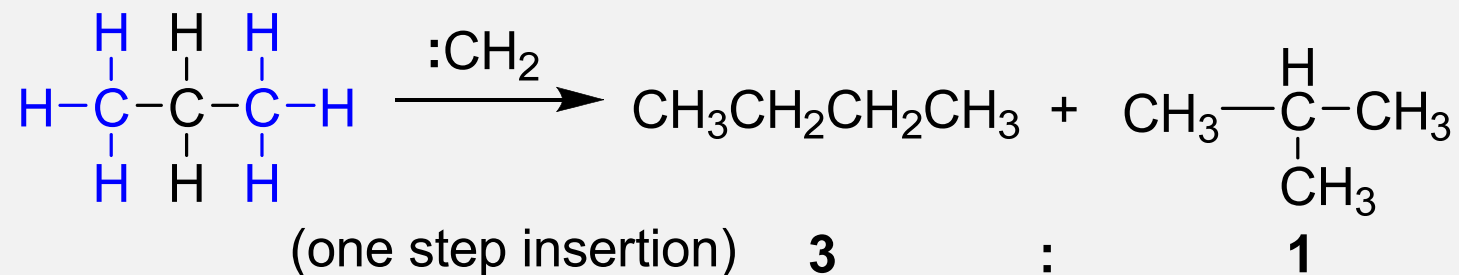
- Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in **cheletropic reactions**. **Singlet carbenes with unfilled *p*-orbital should be electrophilic**. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions.

Addition to C=C:

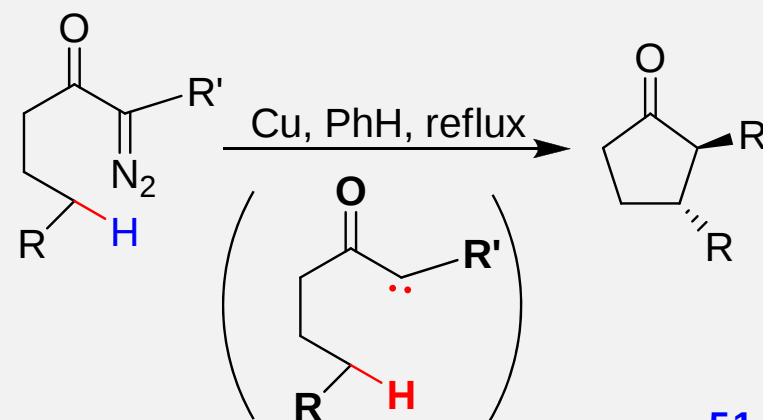


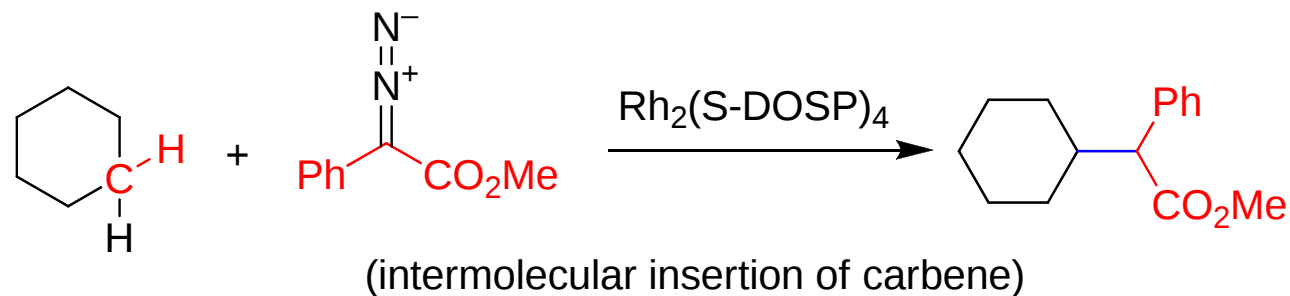
stepwise radical addition, may be **stereoselective**

INSERTION REACTION

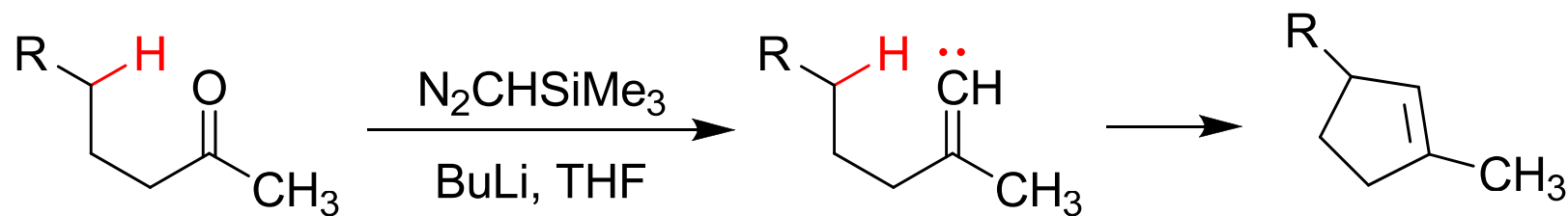


- The order of preference: X–H (where X is not carbon) > C–H > C–C
Insertions may or may not occur in single step.
- When an intramolecular insertion is possible, no intermolecular insertions are seen. *In flexible structures, five-membered ring formation is preferred to six-membered ring formation.*





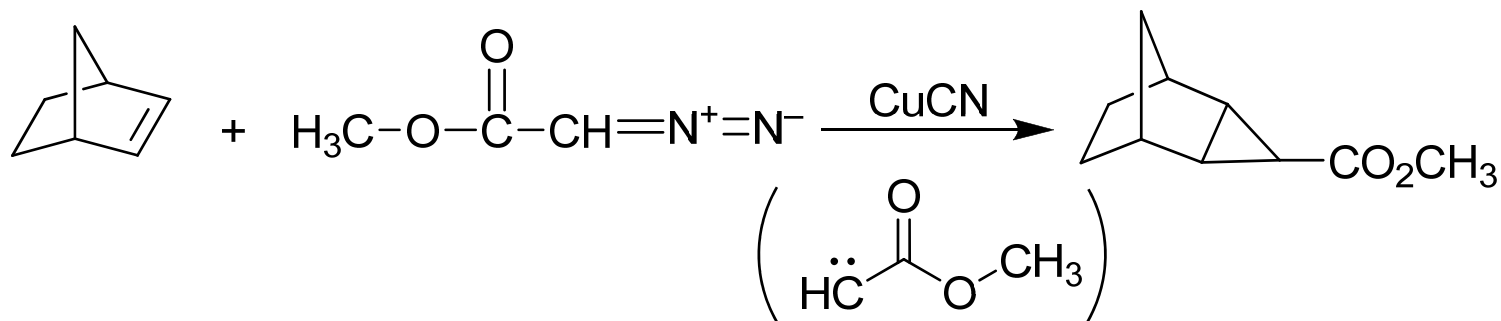
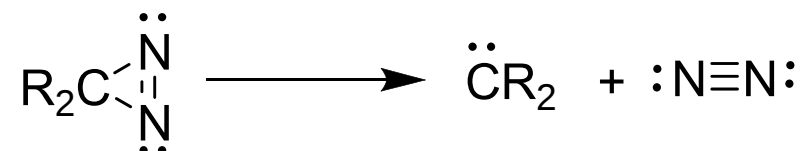
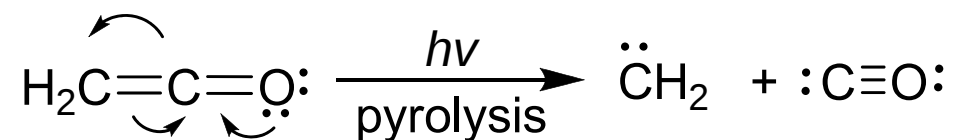
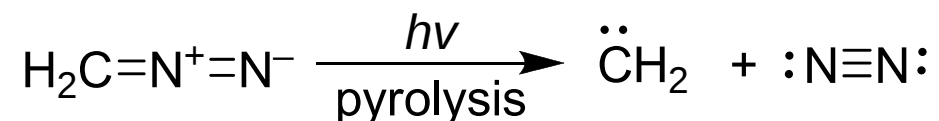
- **Alkylidene carbenes** are alluring in that they offer formation of cyclopentene moieties. To generate an alkylidene carbene a ketone can be exposed to **trimethylsilyl diazomethane**.



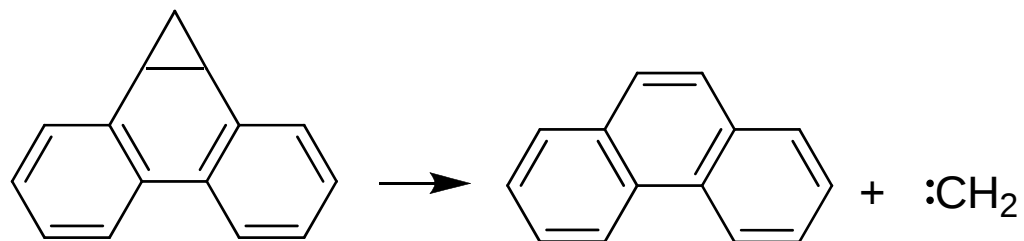
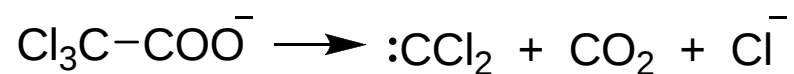
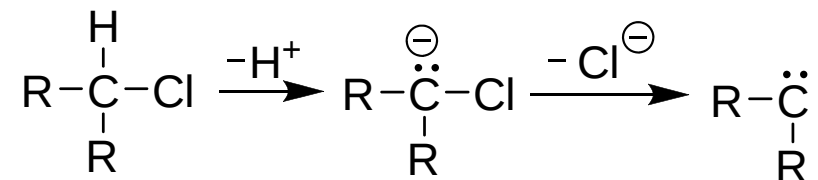
An alkylidene carbene

III. GENERATION OF CARBENES

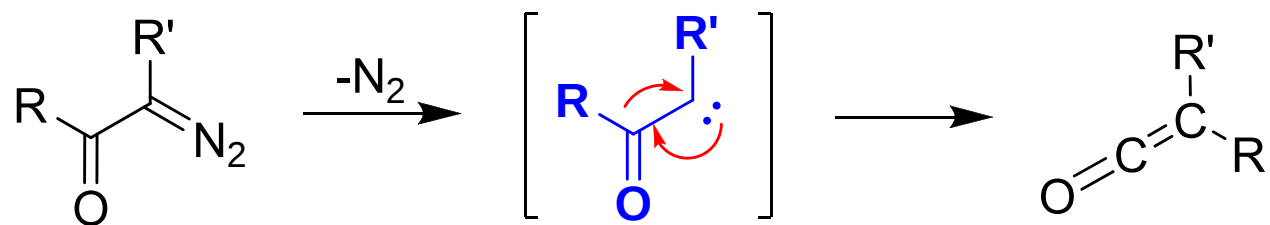
- Disintegration of diazoalkanes and their analogs, via photolytic, thermal, or transition metal (Rh, Cu)-catalyzed routes.



- Base-induced α -elimination

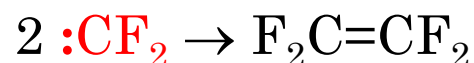
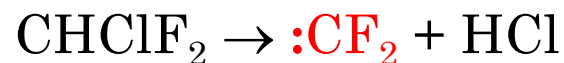
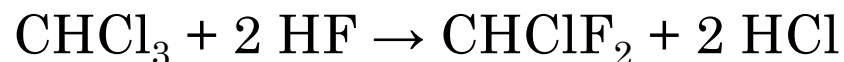


- Carbenes are intermediates in the *Wolff rearrangement*.

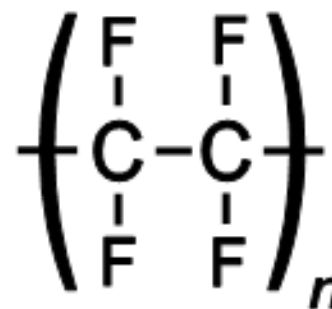


IV. APPLICATIONS OF CARBENES

- A large scale application of carbenes is the industrial production of **tetrafluoroethylene**. Tetrafluoroethylene is generated via the intermediacy of difluorocarbene:

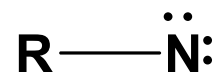


- Polytetrafluoroethylene (PTFE, mp 327°C the DuPont brand name **Teflon**) is a synthetic fluoropolymer of tetrafluoroethylene which finds numerous applications: used as a non-stick coating for pans and other cookware.



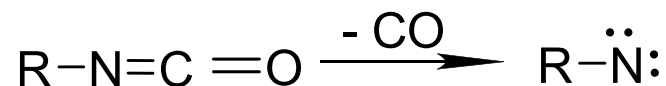
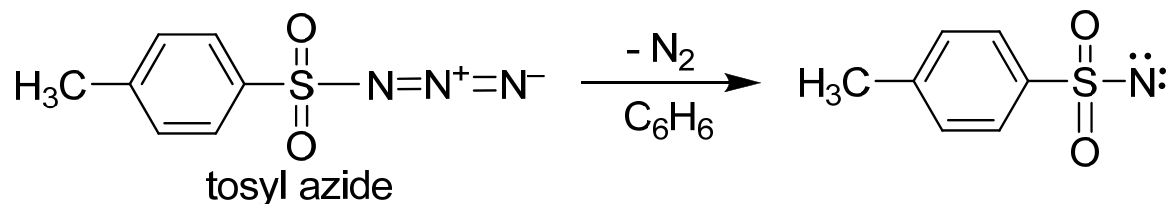
4.5 NITRENES

- A **nitrene** (**R-N:**) is the nitrogen analogue of a carbene. The nitrogen atom has only 6 electrons available and is therefore considered an electrophile. A nitrene is a reactive intermediate and is involved in many chemical reactions.



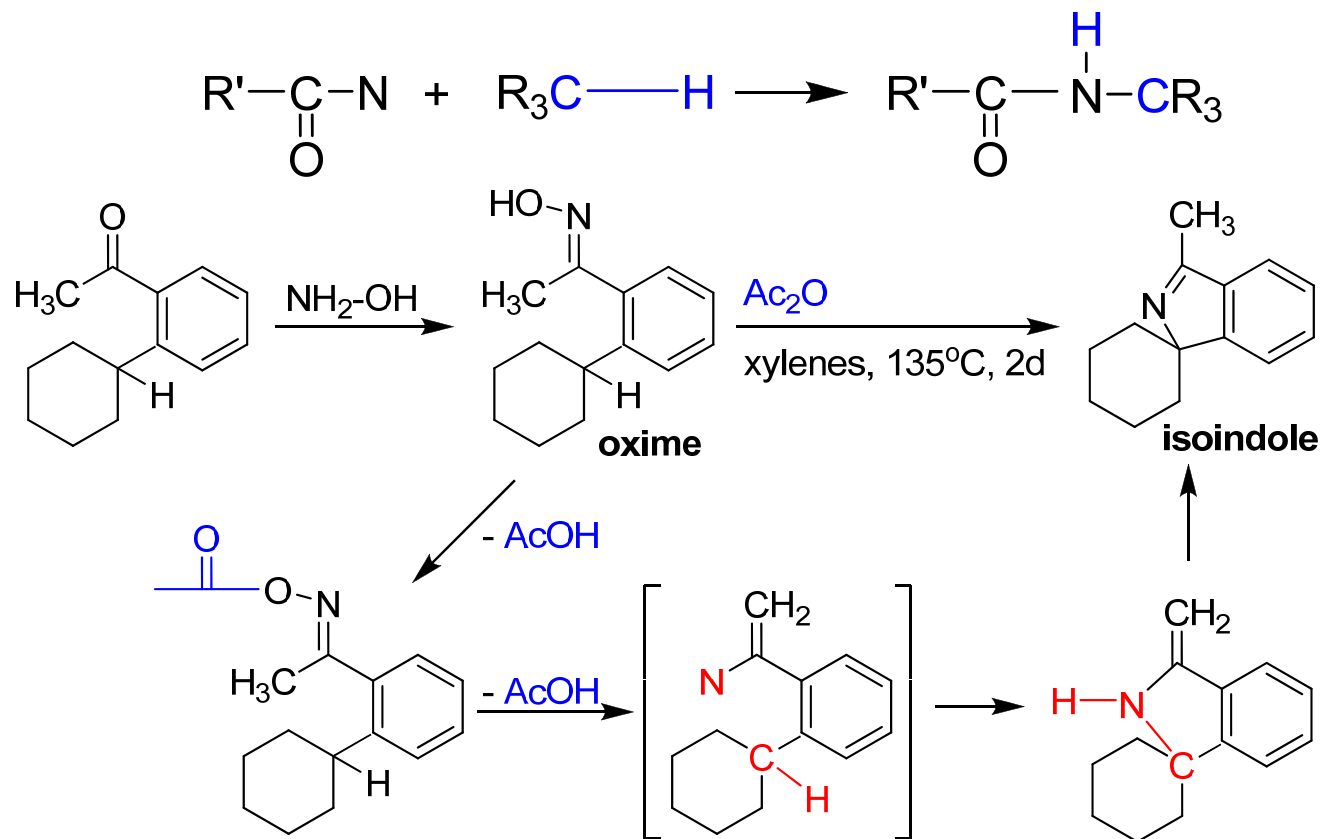
The structure of a typical nitrene group

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



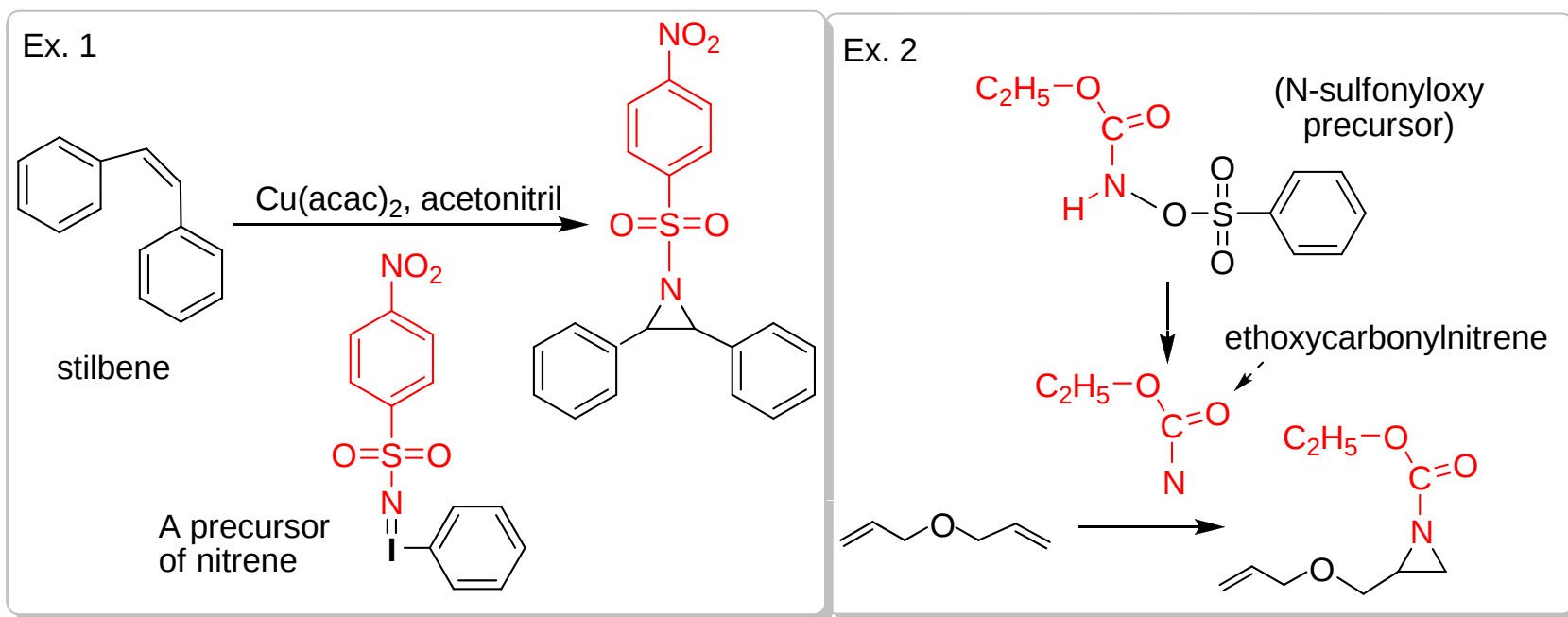
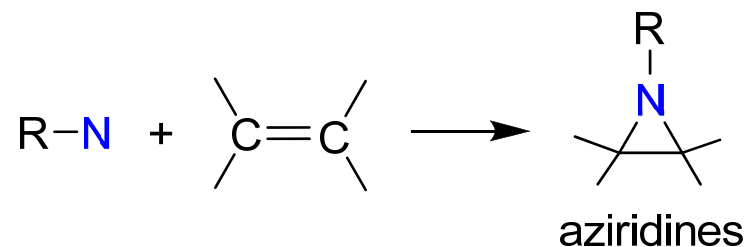
REACTIONS OF NITRENE

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



Org. Lett. **9**, 981(2007)

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



J. Org. Chem. **71**, 5876(2006)

Tetrahedron Letters, **25**, 4271(1984)