REACTIVE INTERMEDIATES

Many organic reactions involve formation of transient intermediates that have a vital role in the overall processes. These intermediates have lifetimes appreciably longer than a molecular vibration (upward from 10^{-12} sec.) and most are present (at least in solution) only as intermediates which are converted to more stable molecules. However some are more stable than others. These intermediates may be formed by attack of various reagents on substrate, by dissociation of organic compounds, or by promotion of molecules to excited states by absorption of light or interaction with high energy radiations, such as alpha, beta or gamma rays. The four types of species are carbonium ions, free radicals, carbanions and carbenes. Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon like nitrenes. The following summary describes the important intermediates.

Carbonium ions:

These are carbon cations. These are the species in which a trivalent carbon atom having positive charge and holding six electrons. They are fragment of a molecule in which a group and a pair of electrons have been removed from one of the carbon atoms. The positively charged carbon atom of a Carbonium ion is in sp^2 state of hybridization so that the ion is planar.

Carbanions:

These are carbon anions. They are formed by the removal of one of the groups attached to carbon atom without removing the binding pair of electrons. Like amines, with which they are isoelectronic, carbanions are non-planar with pyramidal structures.

Carbon radicals:

These (free radicals) are formed from normal carbon compounds by the removal of an attached group along with one of the two bonding electrons. Most carbon radicals are uncharged, although both anion and cation radicals are known. Radicals are intermediates between carbonium ions and carbanions.

Carbenes:

These are fragments of molecules in which two groups attached to carbon have been removed along with one pair of bonding electrons. These are neutral divalent species with an electron pair. One interesting feature of carbene structure is that it may exist in two distinct states, singlet or triplet depending upon the pair spin, whether they have parallel or paired spin.
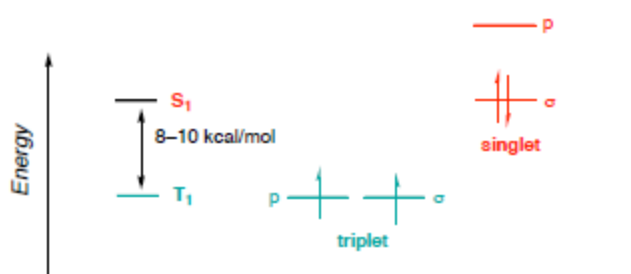
CARBENES

Carbenes are a family of organic molecules composed of a neutral divalent carbon atom linked to two adjacent groups by covalent bond and has 6 valence electrons, 2 of which are non bonding. Since carbon atom is surrounded by a sextet rather than an octet of valence electrons, it is electron-deficient and, hence, is electrophilic in nature. These are highly reactive species practically all having lifetimes considerably under 1 second. Carbenes have been isolated only by entrapment in materials at low temperature (77K or less). The parent specie CH_2 is usually called methylene, though derivative are more often named by carbon nomenclature. Thus CCl_2 is called dichlorocarbene, though it can also be called as dichloromethylene. In general a carbene is neutral. The two non bonded electrons of a carbene can be either paired or unpaired. These electrons can either occupy the same sp^2 hybridized orbital to form a singlet carbene (with paired electrons), or two different sp^2 orbitals to from a triplet carbene (with unpaired electrons). The chemistry of triplet and singlet carbenes is quite different but can be oversimplified to the statement: singlet carbenes usually retain stereochemistry while triplet carbenes do not.
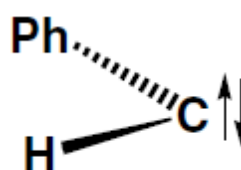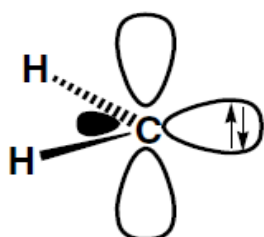
Carbenes are called singlet or triplet depending on the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they persist long enough. The total spin of singlet carbenes is zero while that of triplet carbenes is one (in units of \hbar). Bond angles are 125-140° for triplet methylene and 102° for singlet methylene (as determined by EPR). Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

Generally carbenes are expected to be triplet carbenes (Hunds rule), but substituents can change this. For simple hydrocarbons, triplet carbenes usually have energies 8 kcal/mol (33 kJ/mol) lower than singlet carbenes (see also Hund's rule of maximum multiplicity), thus, in general, triplet is the more stable state (the ground state) and singlet is the excited state species. Substituent's that can donate electron pairs may stabilize the singlet state by delocalizing the pair into an empty p-orbital. If the energy of the singlet state is sufficiently reduced it will actually become the ground state. No viable strategies exist for triplet stabilization. Due to electron repulsion, there is an energy cost in pairing both electrons in the σ orbital. If the small energy difference between the σ and p orbital exists, the electrons will remain unpaired (triplet).

If a large gap is present between the σ and p orbitals the electrons will pair in the σ orbital (singlet).
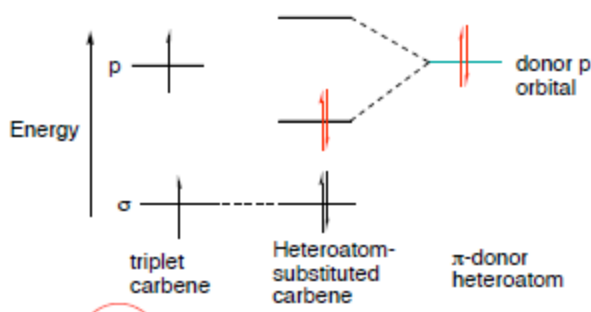

The p orbitals of carbenes substituted with p-donar atoms (N, O, Halogen) is raised high enough in energy to make the pairing of the electrons in the σ orbital energetically favourable. As a result, these carbenes are often in the singlet state.
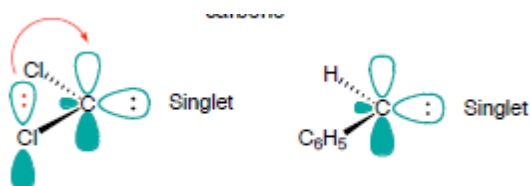
Reactivity of Carbenes:

Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, 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.

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with cis-2-butene or with trans-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product: cis from cis and trans from trans, which proves that the methylene is a singlet. If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.
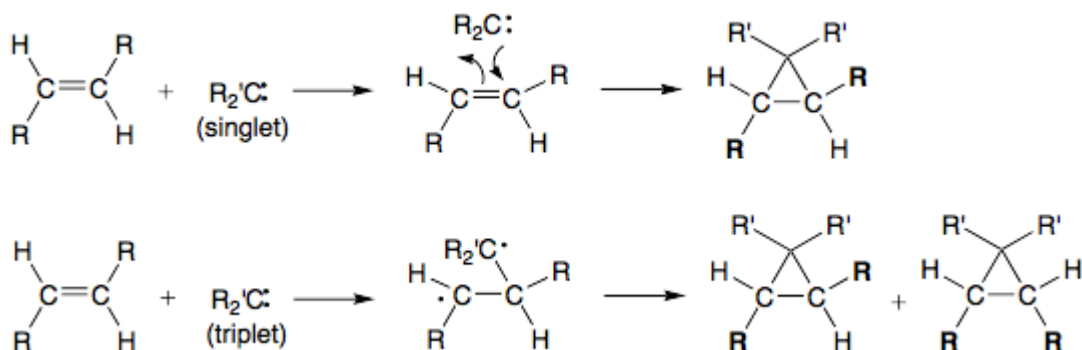
The structural features that determine whether a singlet or a triplet state corresponds to the lower energy form of the carbene molecule may be summarized by the rule that, with few exceptions, carbenes having only carbon or hydrogen atoms attached to the divalent (carbene) carbon atom have triplet ground states, whereas those with nitrogen, oxygen, and halogen substituents have singlet ground states. Examples of triplet carbenes are methylene (H−C−H), phenylmethylene (C₆H₅−C−H), diphenylmethylene (C₆H₅−C−C₆H₅) and propargylene (HC≡C−C−H). Carbenes with known singlet ground states are methoxymethylene (CH₃O−C−H), chloromethylene (Cl−C−H), and phenylchloromethylene (C₆H₅−C−Cl).

CARBENOID SPECIES:

A species that, when undergoing reaction, has the characteristics of a carbene, but in fact is not a free carbene. For example, the carbenoid species, iodomethylzinc iodide, reacts with ethylene to yield the same product, cyclopropane, as the reaction of ethylene with methylene, a free carbene.
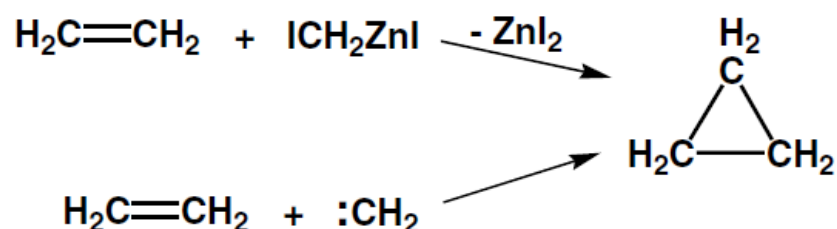
Methods of Generations of Carbenes

Carbenes are formed in two ways, though other pathways are also known.

**1: α- Elimination of N₂ from diazo compounds**
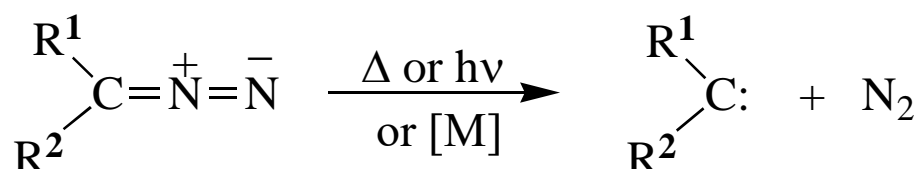
The yellow gas diazomethane, CH_2N_2 when exposed to light, heat or copper, facilitate the loss of nitrogen gas and the formation of the simplest carbene methylene. The process is driven by the formation of the nitrogen gas which is a very stable molecule.
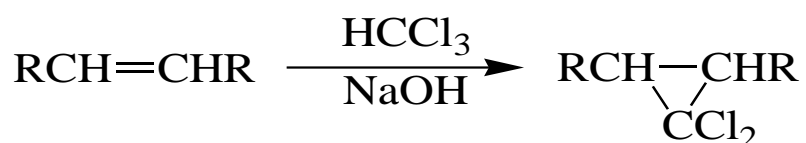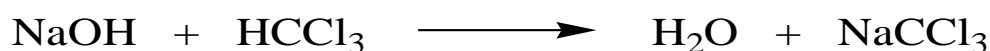
When the photolysis of diazo compounds is carried out at very low temperature in an un-reactive solid medium, it is often possible to prevent the resulting carbene from undergoing further reaction. Measurable amounts of the carbene may persist, therefore, in the solid medium, or matrix, for a long time. For example, methylene, the most reactive carbene of all, has been generated in a crystalline matrix of the inert gas xenon (cooled to the boiling point of helium) in which it persisted long enough to be studied. Many other carbenes have been produced by similar matrix isolation techniques.

2: α-Elimination of HX or X₂ from an organic halide.

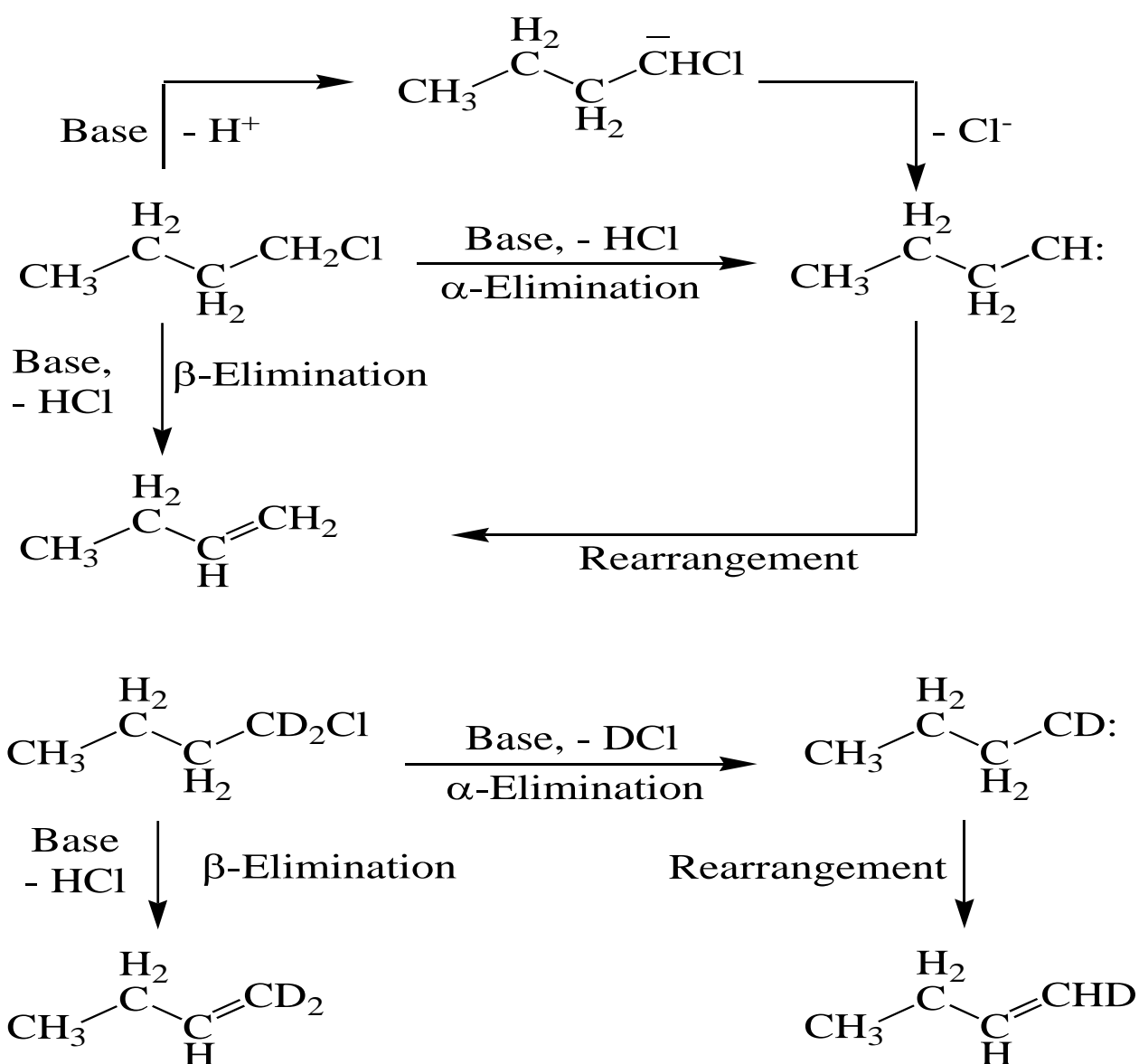In α-eliminations, a carbon loses a group without its electron pair, usually a proton and then a group with its pair, usually a halide ion in the presence of a strong base:
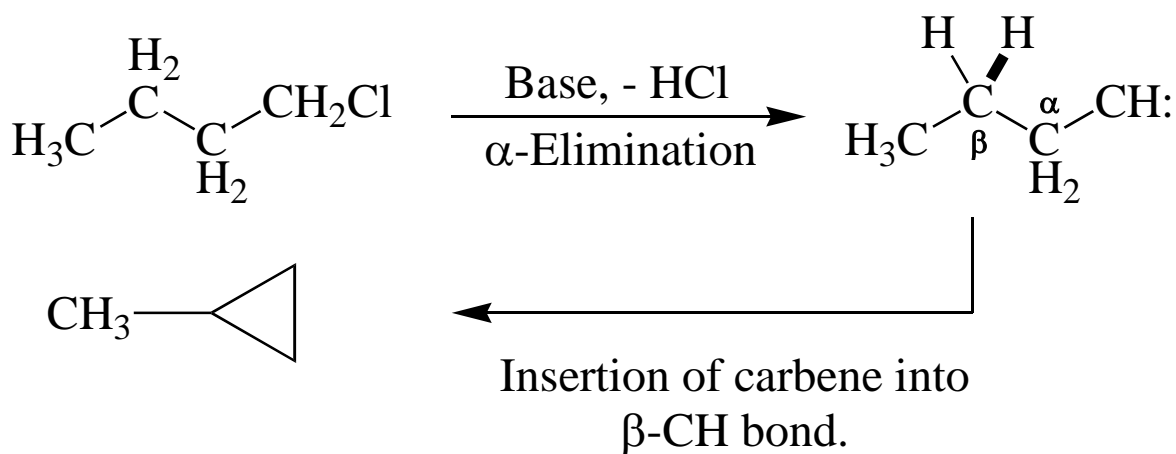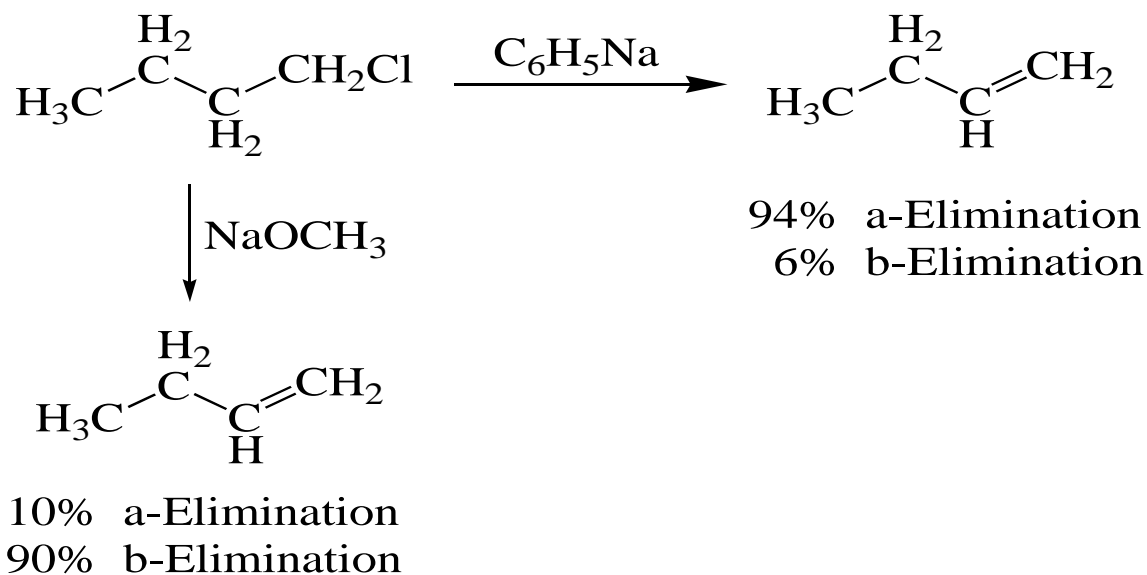
$$\overset{\prime\prime\prime\prime}{}C\overset{X}{\underset{Y}{}} \xrightarrow{\text{- X, -Y}} \overset{\prime\prime\prime\prime}{}C:$$
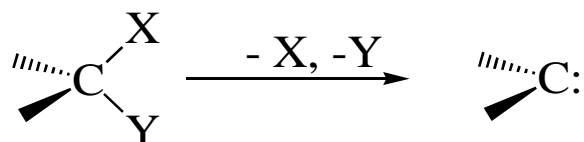
The most common example is the formation of dichloro carbene by treatment of chloroform with base.

$$NaOH \ + \ HCCl_3 \longrightarrow H_2O \ + \ NaCCl_3$$

$$NaCCl_3 \longrightarrow NaCl \ + \ :CCl_2$$

$$RCH\!=\!CHR \ \xrightarrow[\text{NaOH}]{\text{HCCl}_3} \ RCH\!-\!CHR \atop \underset{CCl_2}{\diagdown\diagup}$$

How do we know that a carbene is formed?

$$H_3C-\underset{H_2}{C}-\underset{H_2}{C}-CH_2Cl \xrightarrow{C_6H_5Na} H_3C-\underset{H_2}{C}-\underset{H}{C}=CH_2$$

94% a-Elimination
6% b-Elimination

NaOCH₃

$$H_3C-\underset{H_2}{C}-\underset{H}{C}=CH_2$$

10% a-Elimination
90% b-Elimination

$$H_3C-\underset{H_2}{C}-\underset{H_2}{C}-CH_2Cl \xrightarrow[\alpha\text{-Elimination}]{\text{Base, - HCl}} H_3C-\underset{\beta}{C}\underset{H_2}{\overset{H\ H}{C}}-\underset{\alpha}{C}-CH:$$

$$CH_3-\triangleleft \longleftarrow$$

Insertion of carbene into
β-CH bond.

3: From ketenes:

The photolytic decomposition of certain ketenes, substances the molecules of which contain two carbon atoms and an oxygen atom joined by double bonds, gives carbon monoxide and carbenes, as shown below:

$$\underset{R'}{\overset{R}{>}}C=C=O \longrightarrow R-C-R' + CO.$$
ketene   carbene   carbon
                               monoxide
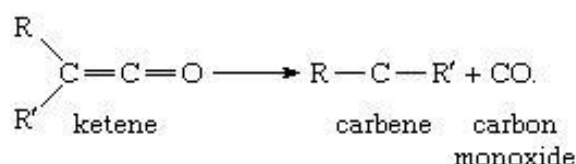
4: From cyclopropanes:

Under certain circumstances, cyclopropanes, can serve as carbene precursors in photochemical reactions. For example, 1,1,2,2,-tetraphenylcyclopropane is converted to diphenylcarbene by the reaction

$(C_6H_5)_2C=CH_2$ + $C_6H_5-C-C_6H_5$.
1,1-diphenylethylene   diphenylcarbene

1,1,2,2-tetraphenylcyclopropane
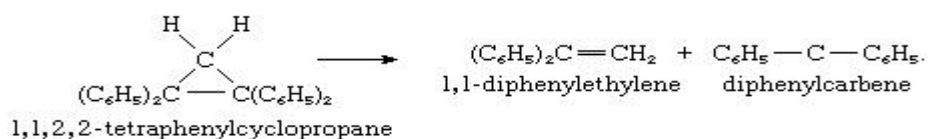
Reactions of Carbenes

1. Addition to multiple bonds:

The carbene is added either to double or to triple bond and forms a stable product. A carbene such as methlyene will react with an alkene which will break the double bond and result with a cyclopropane. The reaction will usually leave stereo-chemistry of the double bond
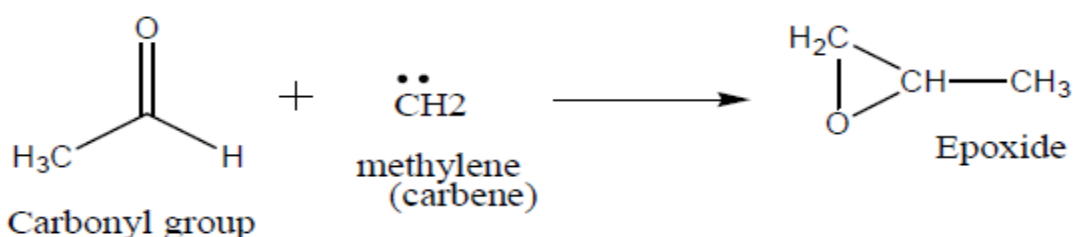
unchanged. As stated before, carbenes are generally formed along with the main reaction; hence the starting material is diazomethane not methylene.
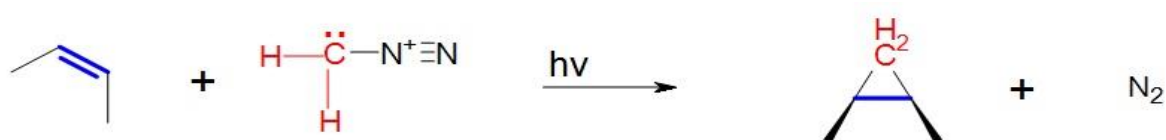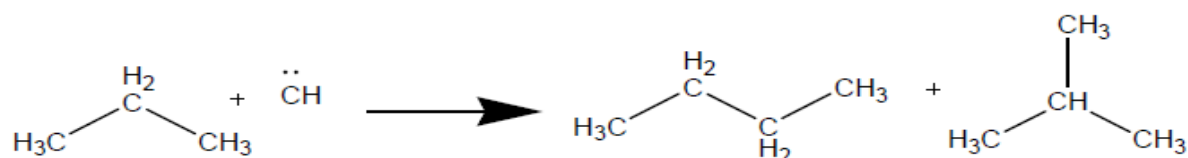

In the above case cis-2-butene is converted to cis-1,2-dimethylcyclopropane. Likewise,below the trans configuration is maintained.
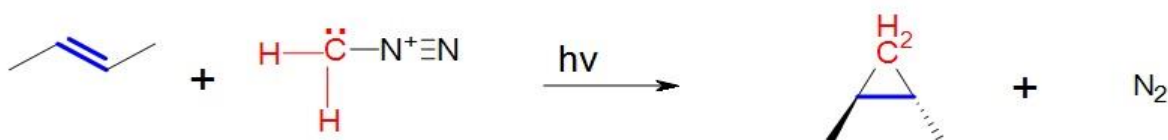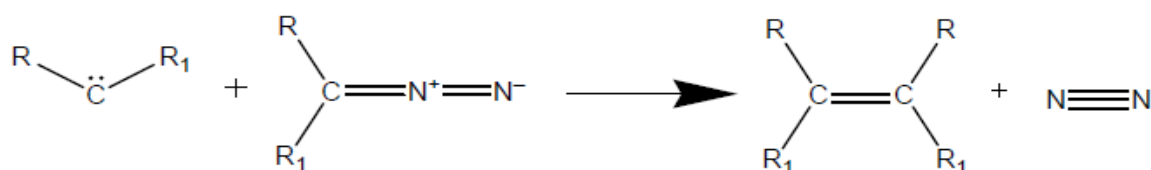

Another example is the epoxide formation.

**2. Insertion reactions:** Carbenes undergo insertion in C-H bond but not in C-C bond.

Normally carbenes do not undergo this reaction due to high reactivity they do not get the time to for dimmer and also due to high energy it easily dissociates.

3. Dimerization reaction

4. Rearrangement reaction
        Similar to above species carbenes undergoes rearrangement to form a stable product.
Examples
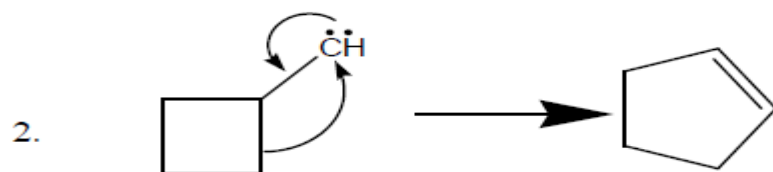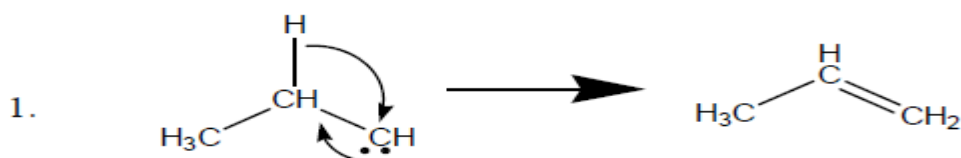
5. Abstraction reaction
        Carbene undergoes abstraction to form free radicals. Example- the reaction between methylene with ethane forms methyl and ethyl radical

$$H_3C-\overset{H_2}{C}-H \; + \; \ddot{C}H_2 \longrightarrow H_3C-\dot{C}H_2 \; + \; \dot{C}H_3$$
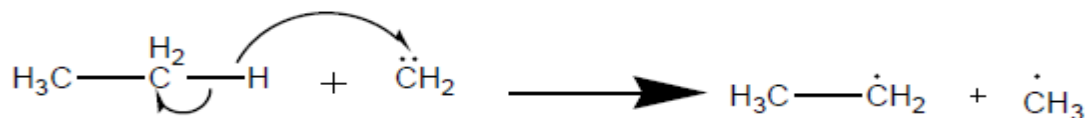
The Simmons-Smith reaction:

$$\xrightarrow[\text{Zn/Cu}]{CH_2I_2}$$
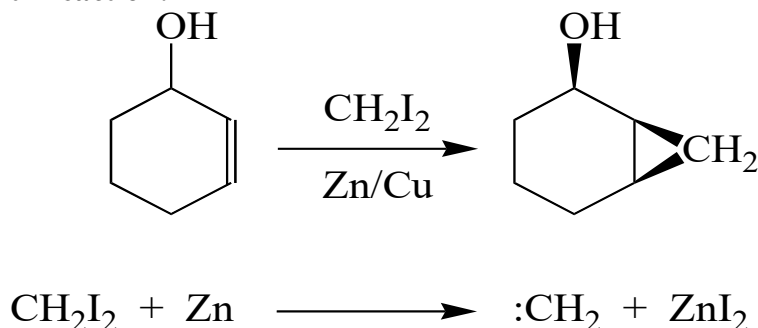
$$CH_2I_2 \; + \; Zn \longrightarrow :CH_2 \; + \; ZnI_2$$

Although the active carbene transfer reagent is thought to be the zinc carbenoid [$I_2Zn\cdots CH_2$] it seems that the organozinc reagents ICH_2ZnI and/or $IZnCH_2ZnI$ are formed first. Note the stereospecificity of the reaction.

REARRANGEMENTS
Wolff rearrangement:

This involves the carbene as an intermediate.

Acyl carbene   Ketene
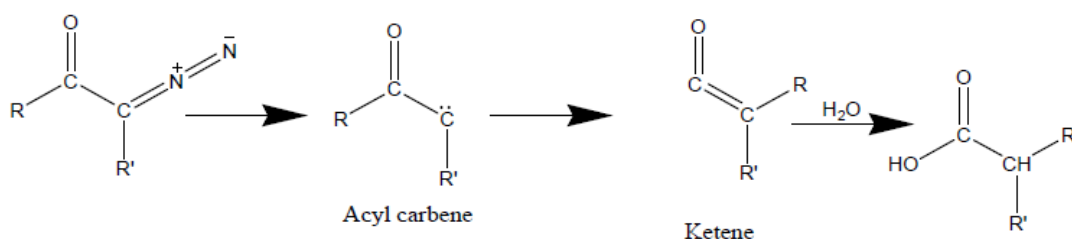
ARYNES

Arynes or benzynes are highly reactive species derived from an aromatic ring by removal of two ortho substituent. Arynes usually best described as having a strained triple bond; however, they possess some biradical character as well. The term aryne is most closely associated with ortho-aryne, however para- and meta-aryne intermediates have been described. Benzyne was first postulated by George Wittig in 1940 and experimentally confirmed by Roberts in 1953. The discovery of benzyne led to rapid developments in synthetic methodologies to make this highly reactive intermediate useful for organic synthesis.

In 1953 John D. Roberts performed the classic 14C labelling experiment, which provided strong support for benzyne. Roberts and his students performed the reaction of chlorobenzene-1-14C with potassium amide, and analyzed the 14C-label incorporation into the resulting aniline: equal amounts of aniline with 14C incorporation at C-1 and C-2 were observed. This result necessitated a symmetrical intermediate – now known as benzyne.

$$\xrightarrow[\text{(ii) } H_2O]{\text{(i) NaNH}_2}$$

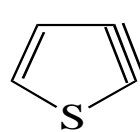• = ^{14}C label   50%   50%
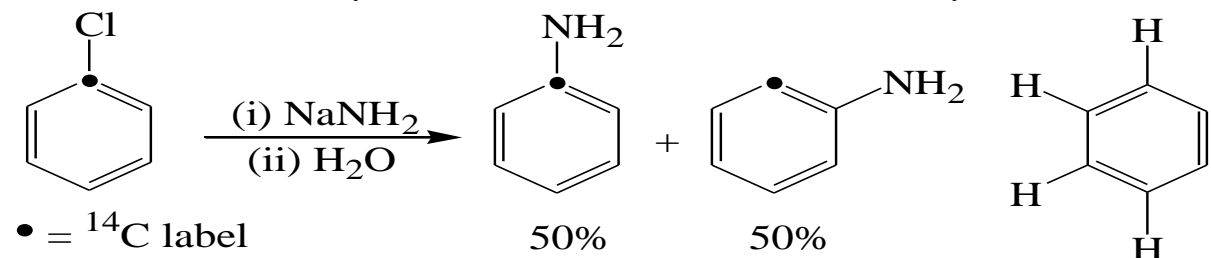
Benzyne is just one of a general class of reactive intermediates known collectively as 'arynes'. Arynes derived from aromatic species other than benzene are also known such as
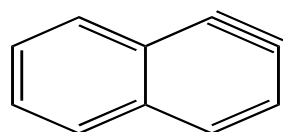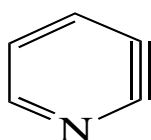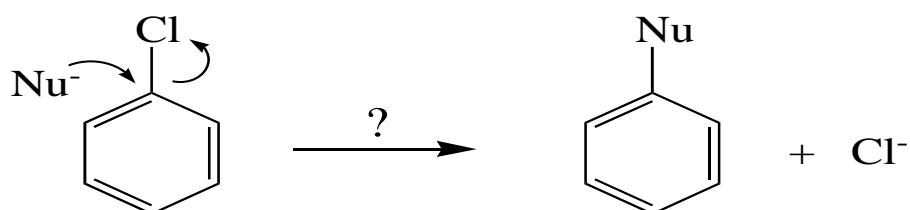
1,2- Naphthalyne   2,3-Pyridyne   2,3-Thiophyne

THE MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION - S$_N$Ar.

Can aromatic halides undergo S$_N$2-type substitutions with nucleophiles?

The answer is **NO**. In an S$_N$2 reaction the nucleophile must approach the reacting carbon from the rear - and this would require the electron-rich nucleophile to penetrate the aromatic Π-cloud, an extremely unlikely event. No examples of this kind of reaction are known.

Nucleophilic aromatic substitution, S$_N$Ar, can take place but it occurs by an addition-elimination mechanism and requires the presence of at least one substituent which is strongly electron-withdrawing by resonance to stabilise the anionic addition intermediate:
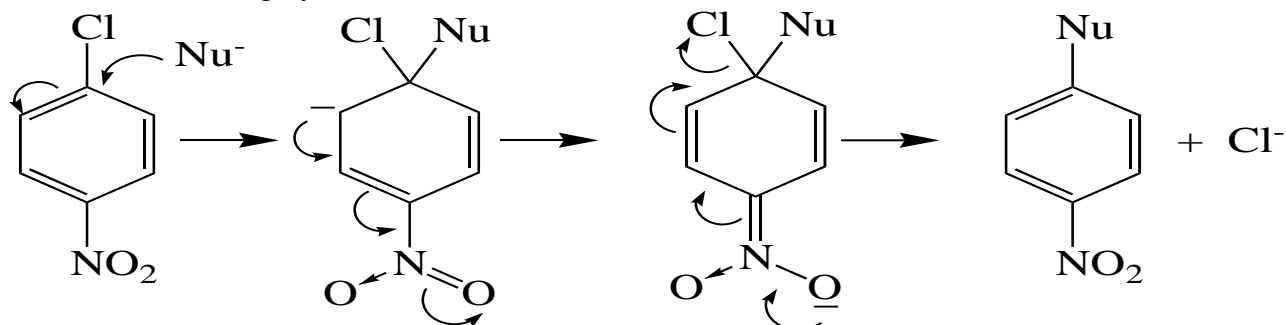
COMMERCIAL SYNTHESIS OF PHENOLS FROM HALOBENZENES:

The commercial process is difficult to reconcile with the accepted S$_N$Ar mechanism:
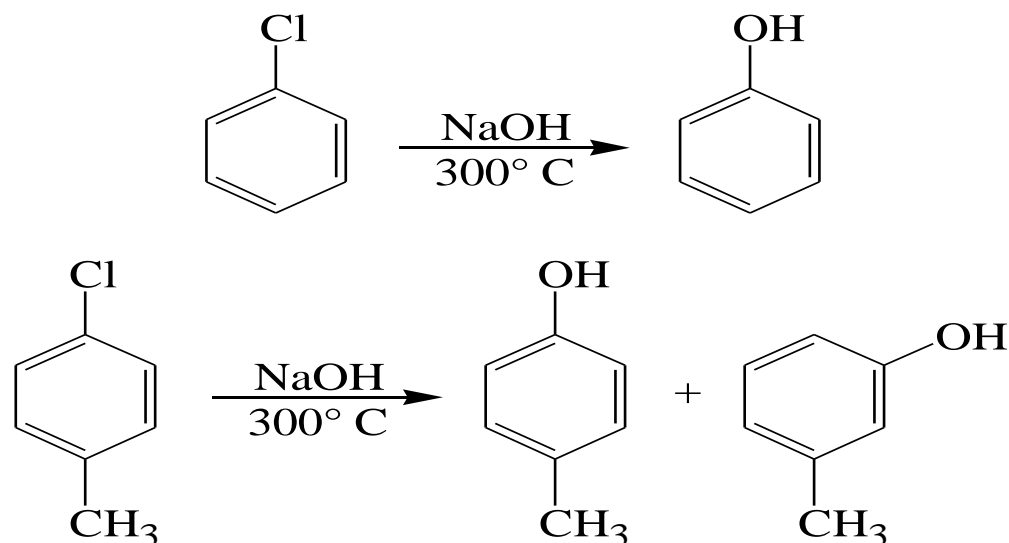
Suggested explanation - a different mechanism:

Benzyne
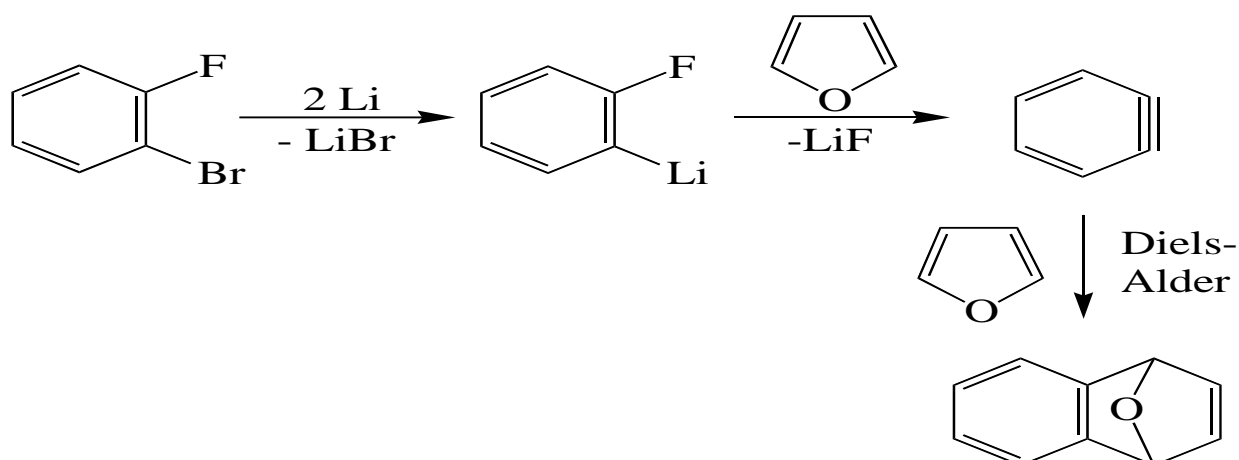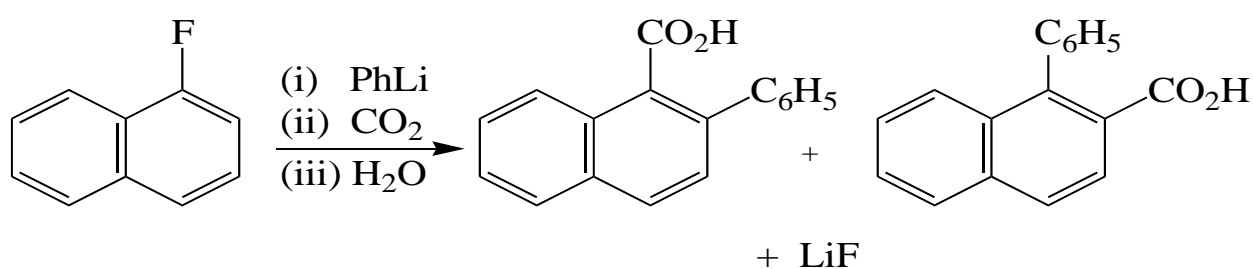intermediate
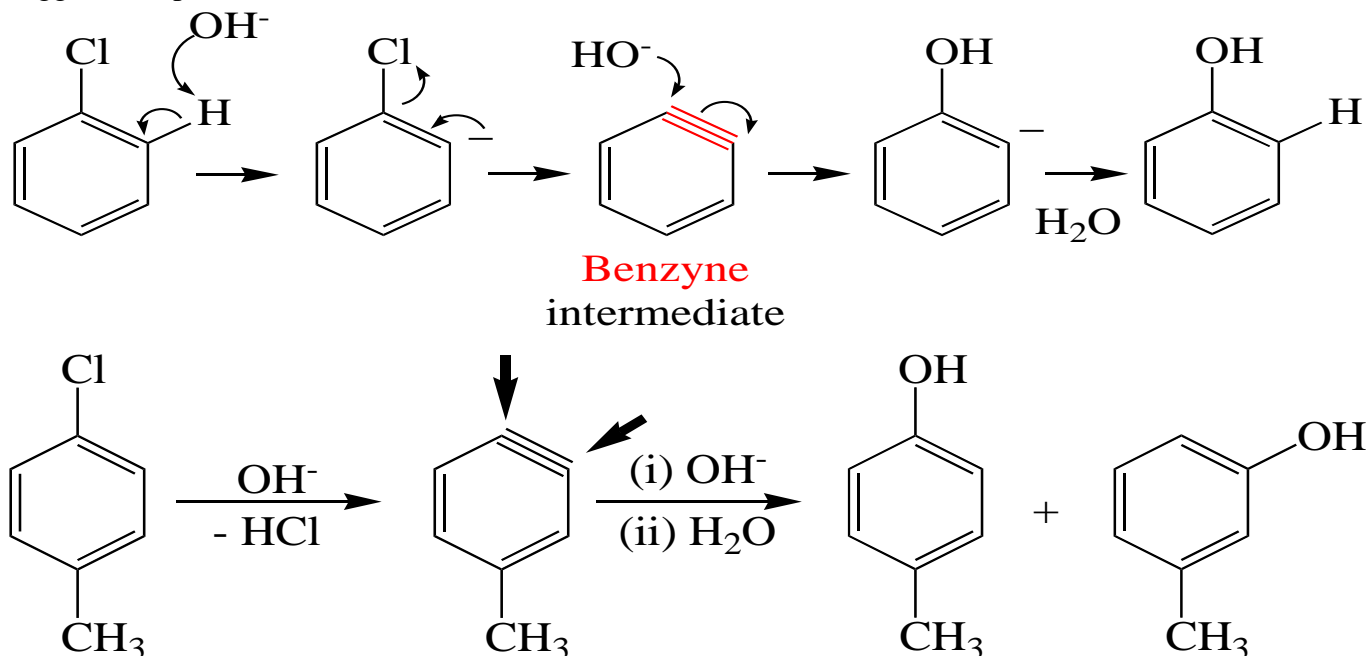
Methods of Preparations

o-Benzyne is an important reactive intermediate and many studies on its generation and reactions have been undertaken. Because of their extreme reactivity, arynes must be generated in situ. The generation methods most widely used is summarized here.

## 1. Treatment of halobenzenes with amide ion

A halide can be treated with a strong base such as an amide, to remove the o-aromatic proton and generate benzyne via an anion, o-halolithium or magnesium arenes readily undergo elimination to arynes. The α-elimination of LiF from lithiated fluoroarenes results in the formation of arynes. o-Cl- and o-F-copper reagents do not, and can be used in nucleophilic displacements, as in the following example
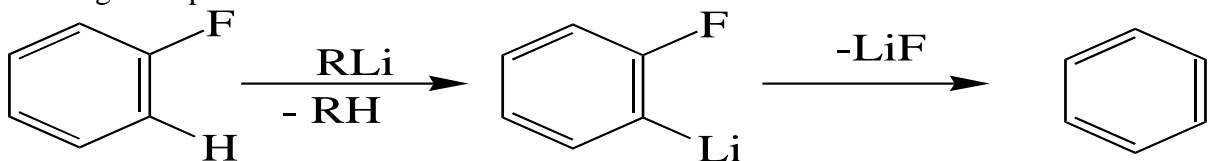
Two examples in which aryne intermediates are generated using this approach and then undergo further reaction are shown below:

For many synthetic applications of arynes it is necessary to generate the labile intermediate under mild conditions that don't require highly basic reactive organolithium reagents:
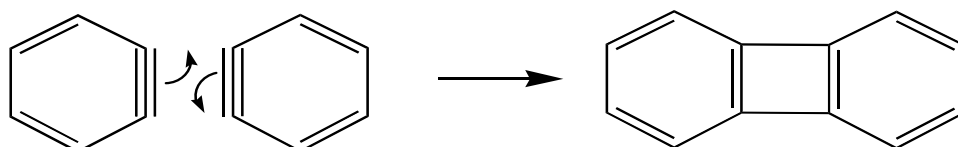
Benzothiadiazole -S,S-dioxide

Phthalic peroxy-anhydride
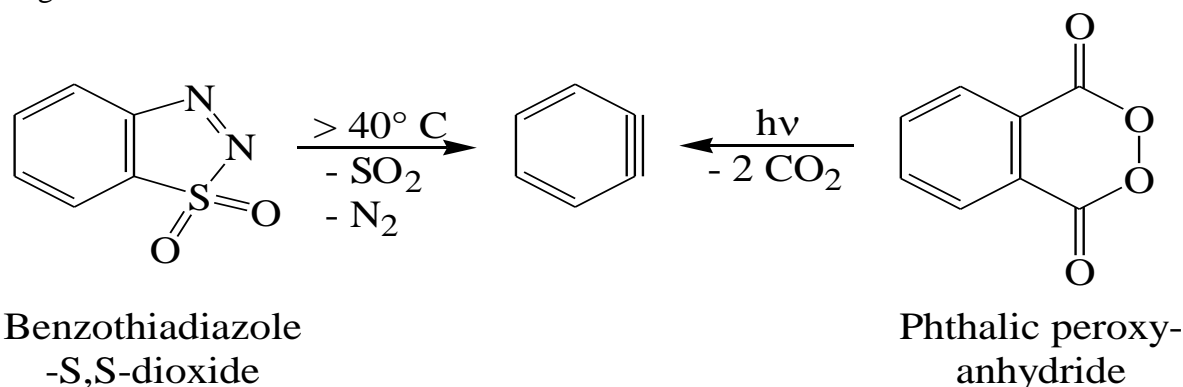
2.Thermal decomposition and photolysis:

Arynes may also be obtained from anthranilic acid, by decomposition of the internal benzenediazonium-2-carboxylate.

Properties of benzyne:
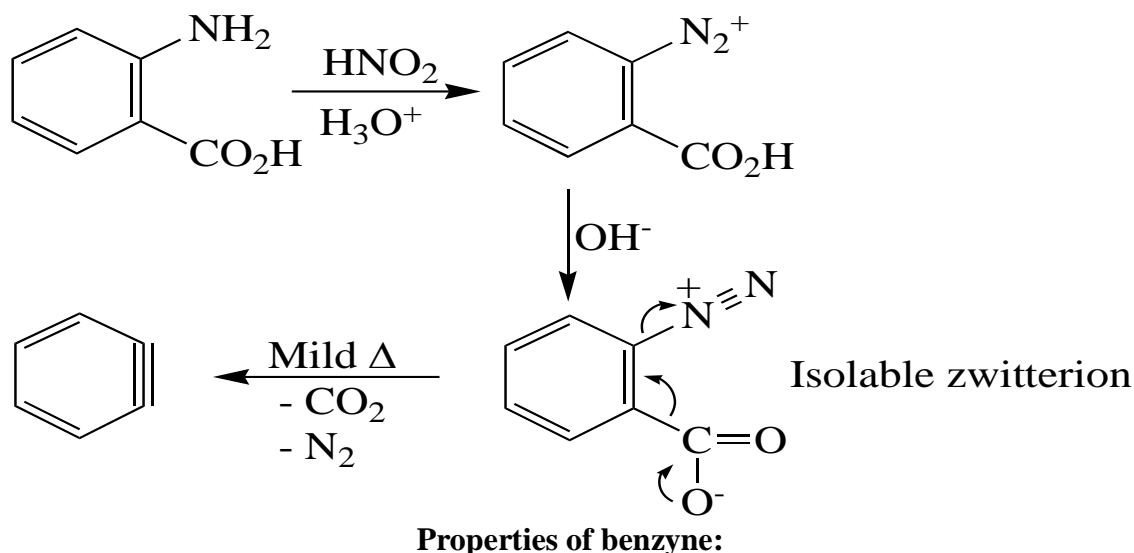
Free benzyne is very reactive and rapidly dimerises:

The lifetime of benzyne in the gas phase has been estimated to be at least 20 nanoseconds (2×10^{-8} seconds) by Mass Spectroscopic techniques. Some spectroscopic properties of benzyne have been determined by Orville Chapman using Matrix Isolation techniques:


$\nu(C\Box C)$ 2085 cm^{-1}

(2100 - 2260 cm^{-1})
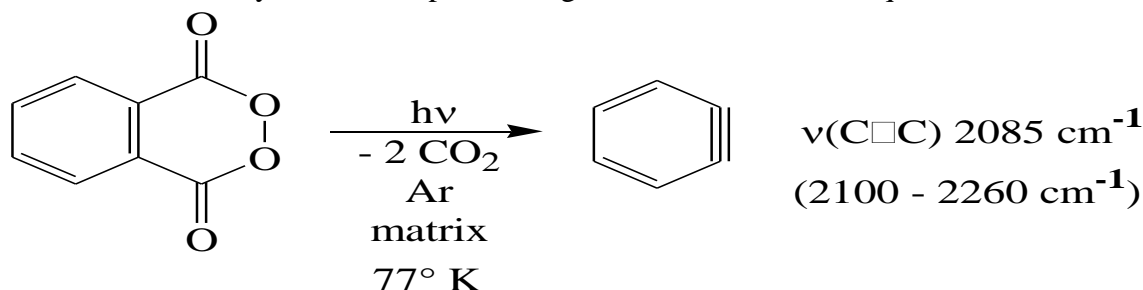
Theoretical calculations suggest that the strained 'bent alkyne' form of benzyne is lower in energy than the di-radical alternative:

(A)   (B)
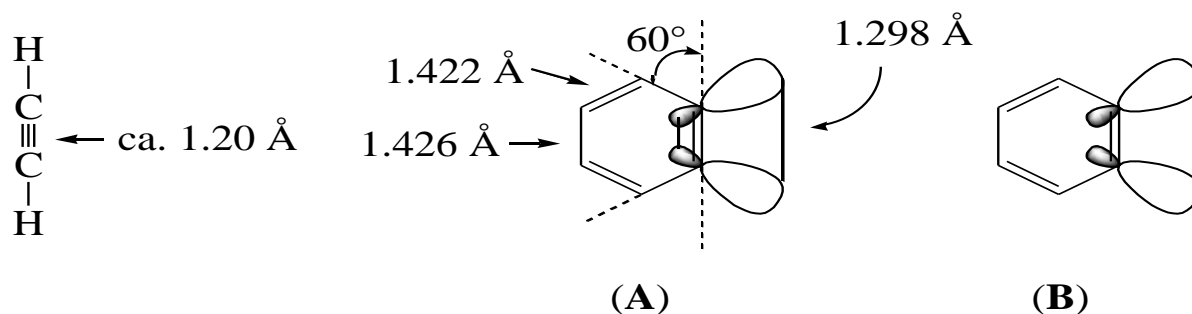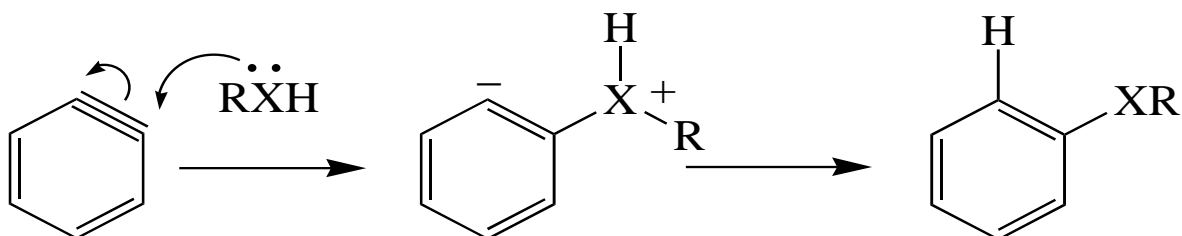
The calculations suggest that the π-overlap in the strained π bond is weaker and that the π^* component of the bond (*i.e.* the LUMO) is at lower energy than normal for a triple bond. Hence arynes behave as powerful electrophiles.
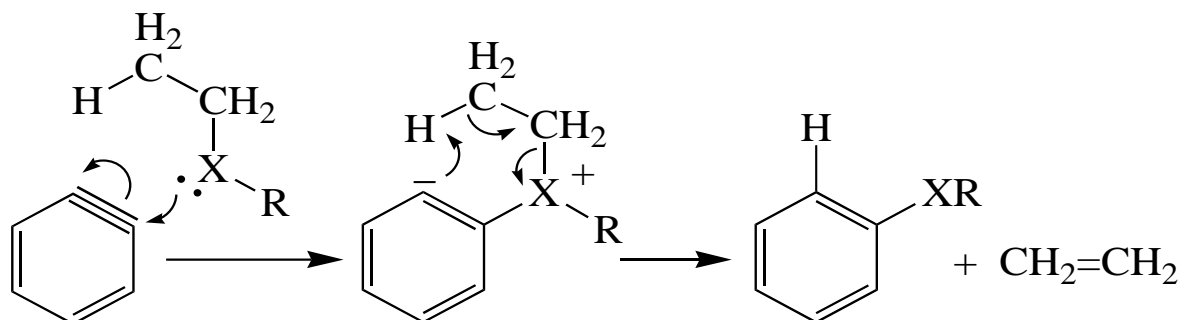
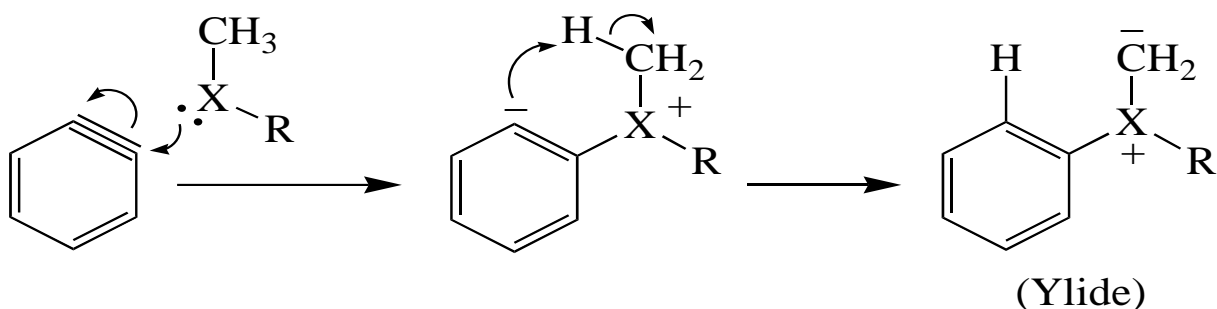### (1) Addition of nucleophiles to the triple bond.
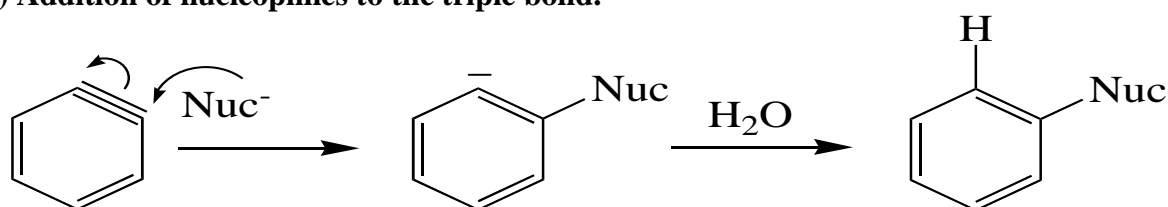
Nuc = Ph–C≡C⁻ (30%), [(EtO$_2$C)$_2$CH]⁻ (51%) etc.
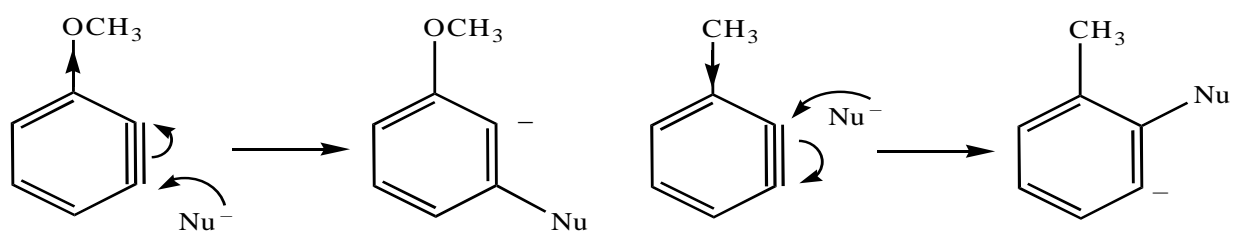
$RXH = H_2O$, ROH, RCO_2H, RSH, RNH_2 etc.

X = S, NR, PR


(Ylide)

X = S, NR, PR

SUBSTITUENT EFFECTS ON THE ADDITION OF NUCLEOPHILES TO ARYNES

Inductively electron-withdrawing substituents are *meta*-directing and inductively electron-releasing substituents are *ortho*-directing.

2. Cycloaddition reactions to the aryne triple bond:
Diels-Alder reactions of benzyne with 1,3-dienes in which the aryne triple bond behaves as dienophile are very common and an example involving furan as the diene has been described earlier.The stereochemistry of the product in the following thermally promoted Diels-Alder reaction with 2,4-hexadiene demonstrates the concerted nature of the addition.
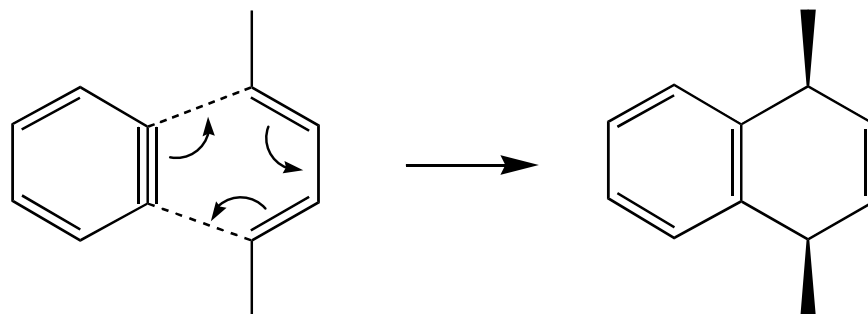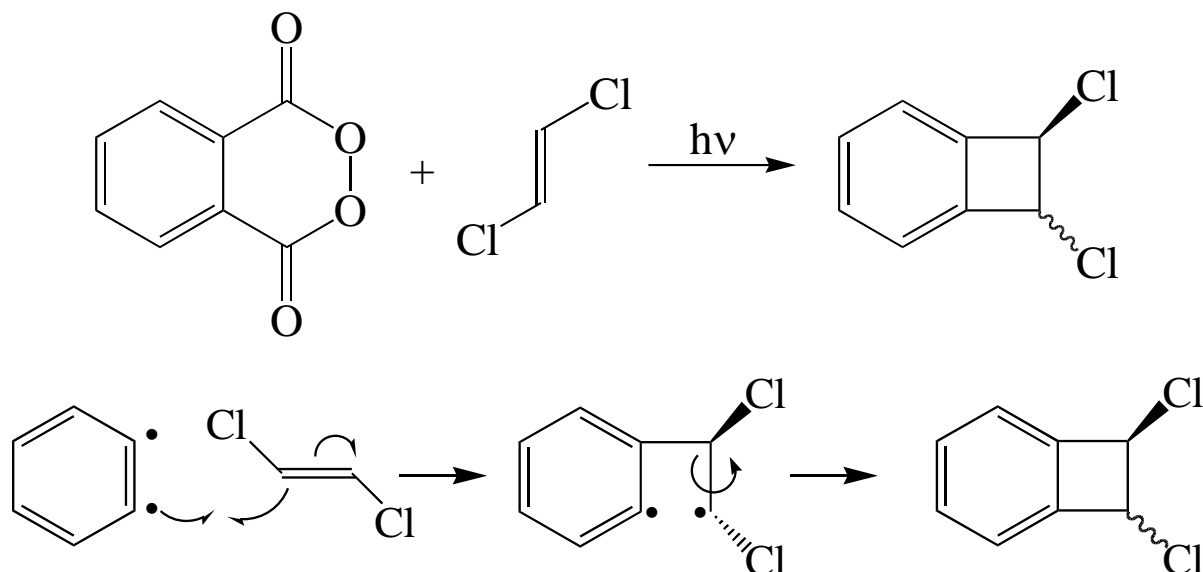
Arynes also undergo formal [2+2] additions to alkenes but many of these are stepwise rather than concerted processes. The loss of the alkene *trans*-stereochemistry in the product of the photochemically mediated cycloaddition illustrated above suggests that it proceeds via a photochemically generated diradical excited state of benzyne rather than by a concerted mechanism.

APPLICATIONS OF ARYNE INTERMEDIATES IN ORGANIC SYNTHESIS

Arynes have not been exploited in organic synthesis to the same extent as free radicals or carbenes but there are still many examples of the use of arenes in natural product synthesis:

Synthesis of an Aporphine alkaloid:
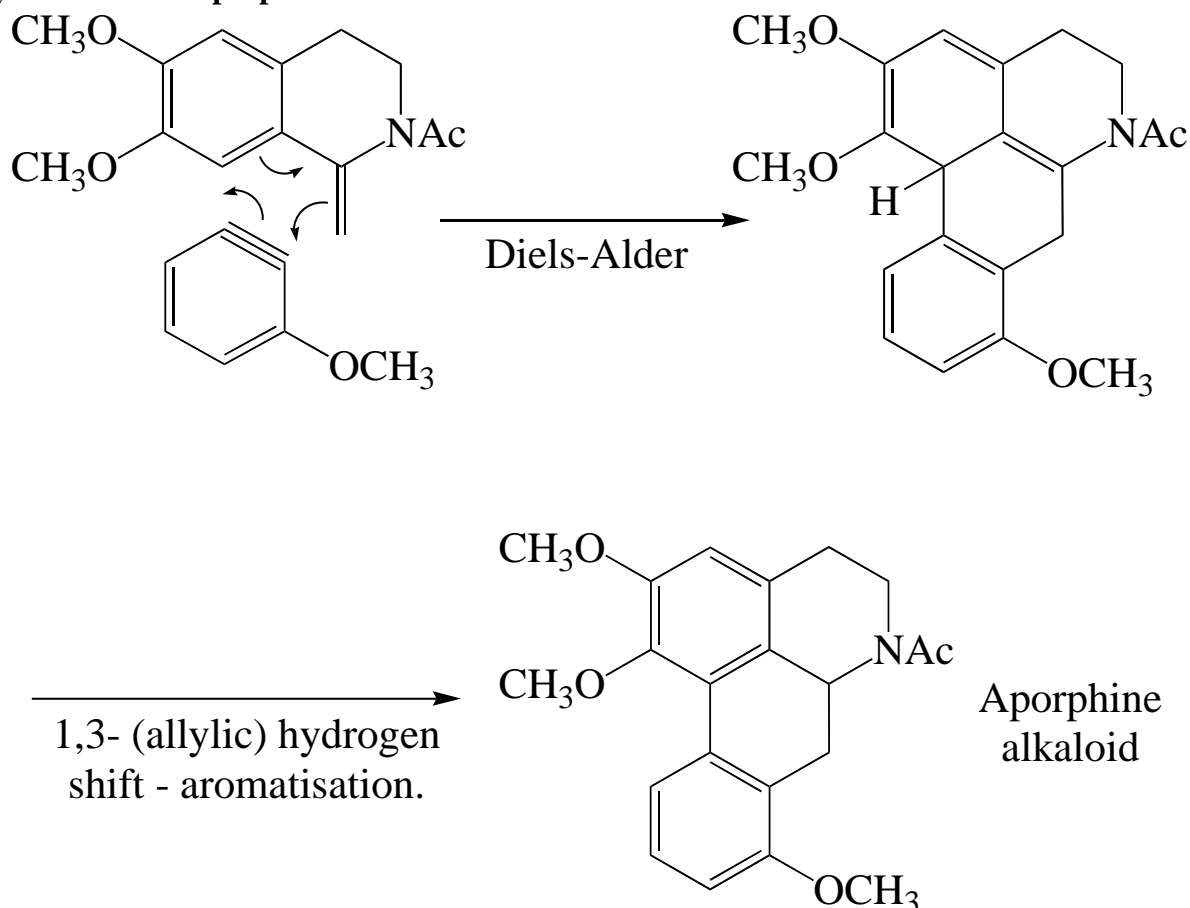
Note the unusual incorporation of a benzene double bond as part of the 'diene' component of the Diels-Alder reaction. 3,4-Pyridyne in the synthesis of Ellipticene, an anti-cancer alkaloid.

3,4-Pyridyne

- CO$_2$

Ellipticene
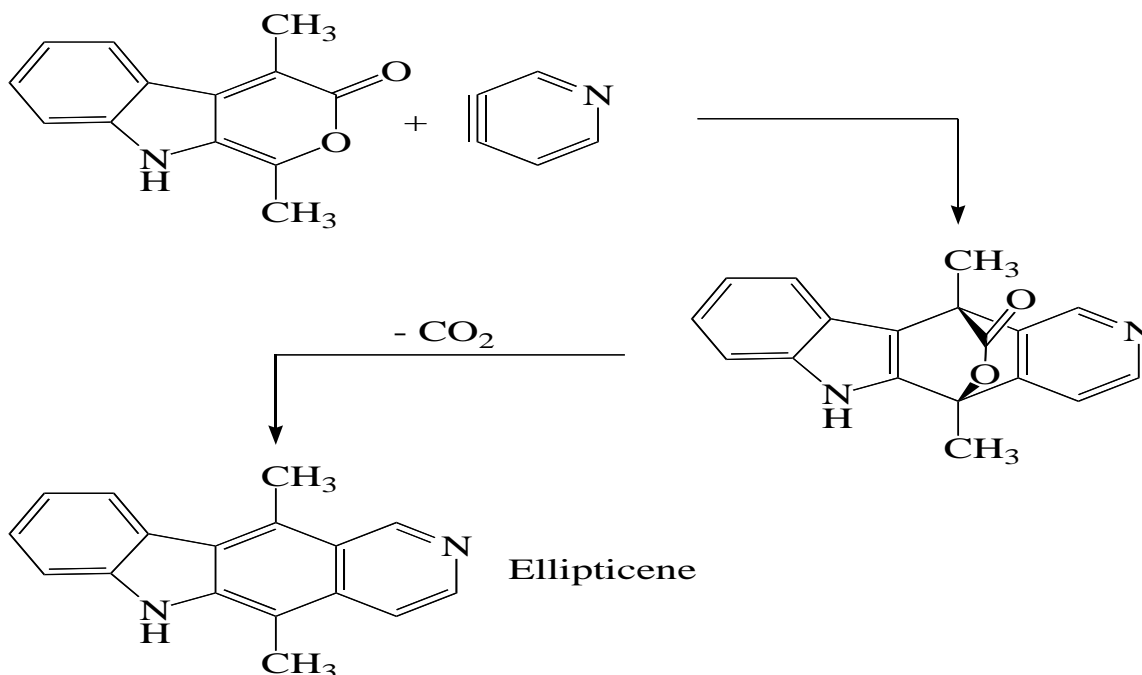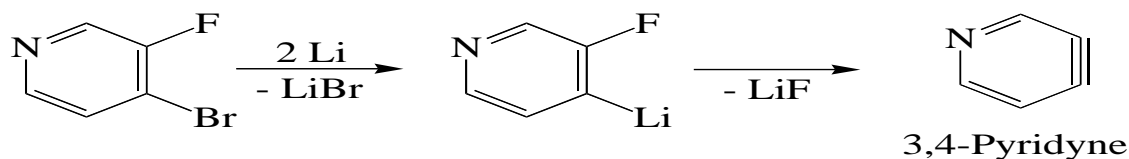
Nitrenes

Nitrenes are uncharged, electron-deficient molecular fragments containing a nitrogen atom with only six electrons in its valence shell. Both a singlet state, with two pairs of electrons and a low energy empty orbital, and a triplet state, with one electron pair and two electrons with parallel spins, are possible. These intermediates are analogous to carbenes with respect to electronic structure (isoelectronic), methods of formation and detection, and modes of reaction. In nitrenes the triplet state is lower in energy than the singlet state. As far as nomenclature is concerned :NH is generally known as nitrenes and replacement of H by Ph is known as phenyl nitrenes :NPh. Uncommon names are also known like azene, imene, or azocarbene.
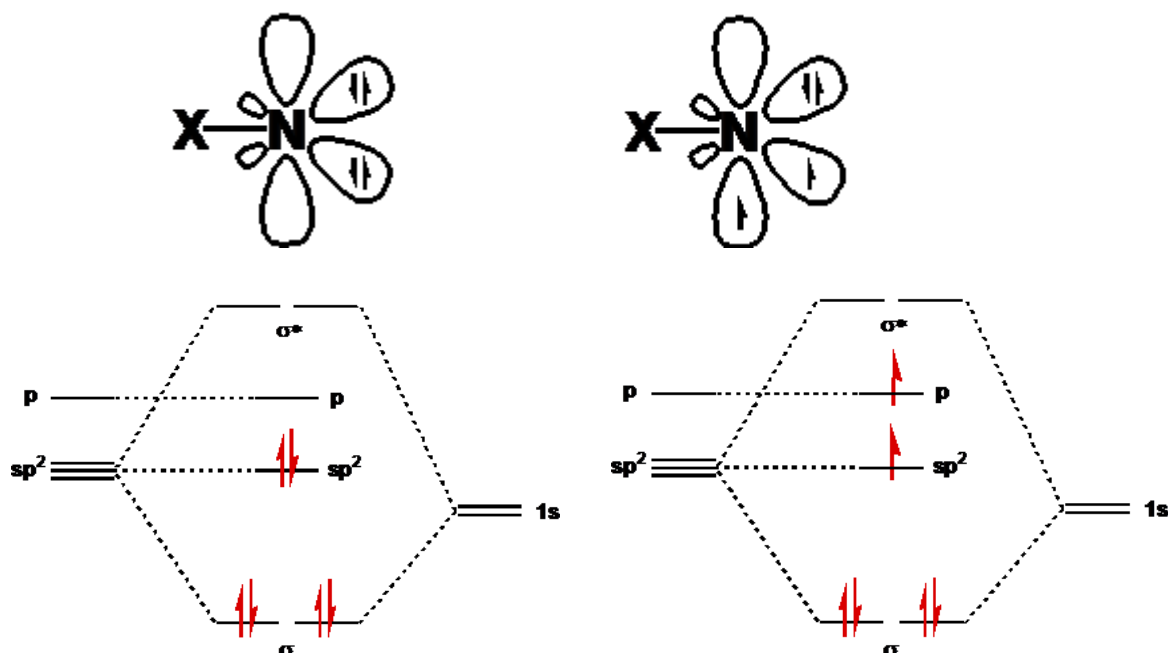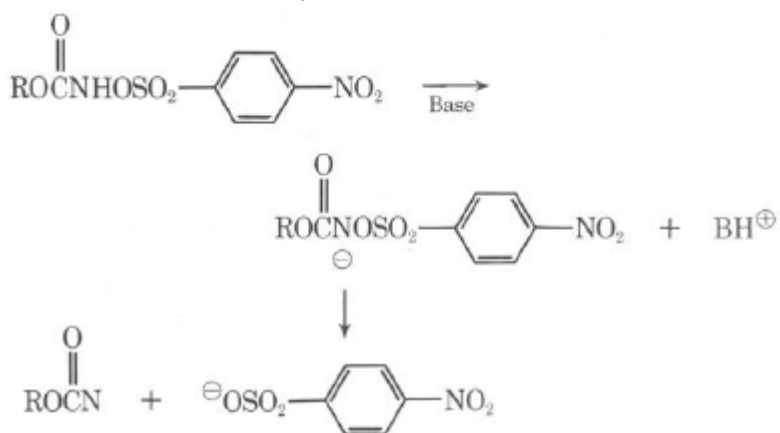

Triplet more stable than singlet (R=H, alkyl), Unless, added stabilization possible (X=O, N, S, halogen etc.)
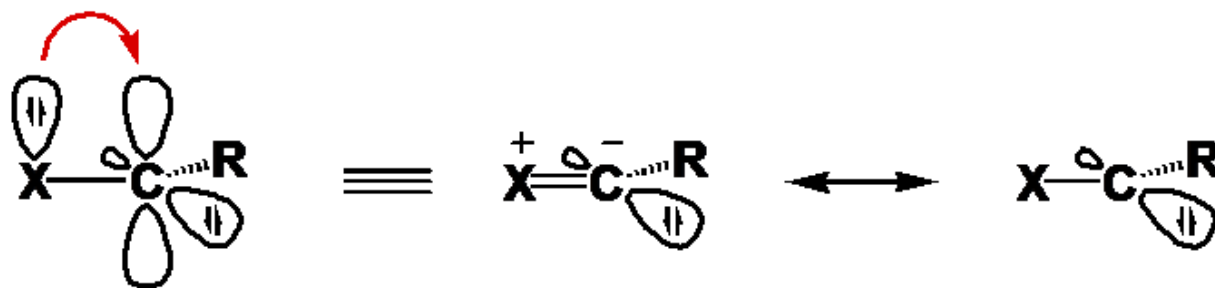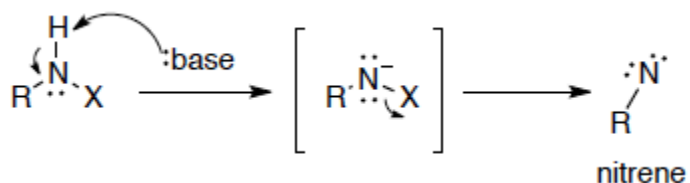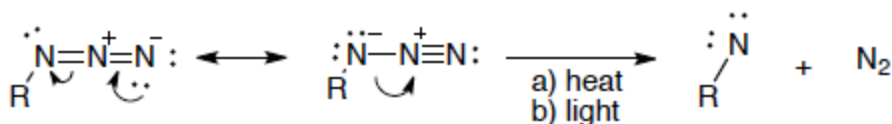
Methods of Generation of Nitrenes:

Nitrenes can be generated by the thermal or photochemical decomposition of hydrazoic acid, alkyl and aryl azides, sulfonyl azides, azidoformates, and cyanogen azide (eq. (1-5)). Ethoxy-cabonylnitrene, CH3CH2OCON, can also be produced chemically by base induced α-elimination from N-(p-nitrobenzenesulfonyloxy) urethane.

$$HN_3 \xrightarrow{h\upsilon/\Delta} HN + N_2 \tag{1}$$

$$RN_3 \xrightarrow{h\upsilon/\Delta} R N + N_2 \tag{2}$$

$$RSO_2N_3 \xrightarrow{h\upsilon/\Delta} RSO_2N + N_2 \tag{3}$$

$$ROCON_3 \xrightarrow{h\upsilon/\Delta} ROCON + N_2 \tag{4}$$

$$N_3CN \xrightarrow{h\upsilon/\Delta} NCN + N_2 \tag{5}$$

From 1,1---eleminaton

From azides:

Iminoiodanes: