Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

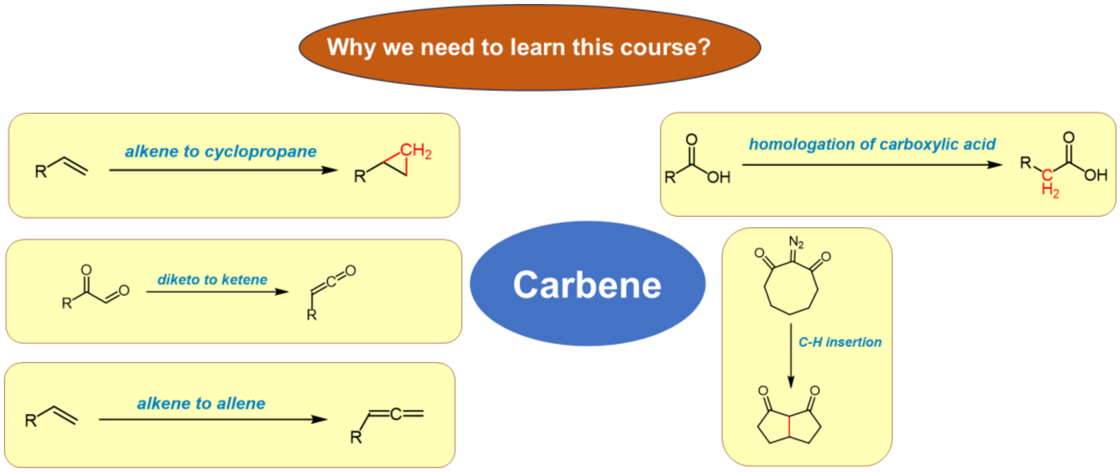
Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 11: Carbene

Welcome back to this NPTEL online certification course on molecular rearrangement and reactive intermediates. In today's class, I am going to talk about carbene. So, I am going to talk about the generation of carbene and their bonding and some of the reactions and rearrangements. So, let us go to the first slide of the today's topic. I am going to talk about the definition of carbene and then their structures, then I am going to talk about the singlet and triplet carbene. and what are the differences in the reactivity, will try to explain some of the facts through the molecular orbital diagram.

The lectures will end with several different generation methods of carbene. So, first thing is why we want to study carbene? I think once you try to study some topic, we should ask our self why? The answer is: by studying carbene you can able to learn how to convert this olefin to this corresponding cyclopropane. You can learn that how to convert this 1, 2-dicarbonyl compound to this corresponding ketene, and then from the ketene you can synthesize a variety of compounds. So, that is a reactive intermediate again.



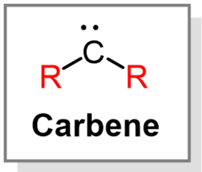
Then from alkene to allene, so that is the allene structure. Then homologation of carboxylic acid, starting from this carboxylic acid you can able to introduce this CH_2 group here. Then there is some reaction called C-H insertion. So, you can see from this diazo compound you can form this some sort of a fused 5-member ring. So, these are the different type of reaction you can only able to do if you can learn about carbene and their reactivity.

So, if you try to define carbene it is a divalent species. So, the most important thing having electron sextet that means, there are 6 outer electrons and it is an electron deficient species. So, it will be reactive because it wants to go to the octet. So, highly reactive and then it is short lived that means, if it is it is forms it will react first till it is forming a stable compound. And then of course, there are two covalent bonds, as I mentioned at the beginning.

➢ **Definition: Carbenes are neutral species containing a divalent carbon atom with an electron sextet.**

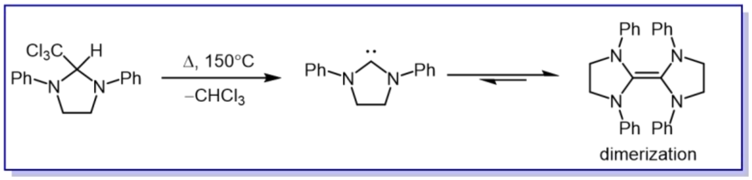
Characteristic of carbenes:

- ✓ Short-lived
- ✓ Highly reactive neutral
- ✓ Divalent
- ✓ Six valance electrons
- ✓ Two covalent bonds and two non-bonding electrons

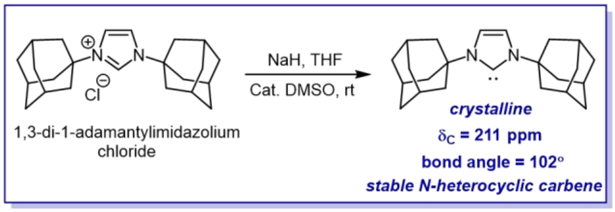


So, now I said the carbenes are short-lived and so that means, is that true for all the carbene? There are scientists who have tried to isolate them. So, the first effort was by Wanzlick. So, in 1960 when they tried to isolate the carbene from the pyrolysis of this compound which can release the chloroform. For end up instead of isolating this compound it actually forms a dimer. So, later Arduengo group actually realize that how to stop the dimerization.

Hans-Werner Wanzlick
1960



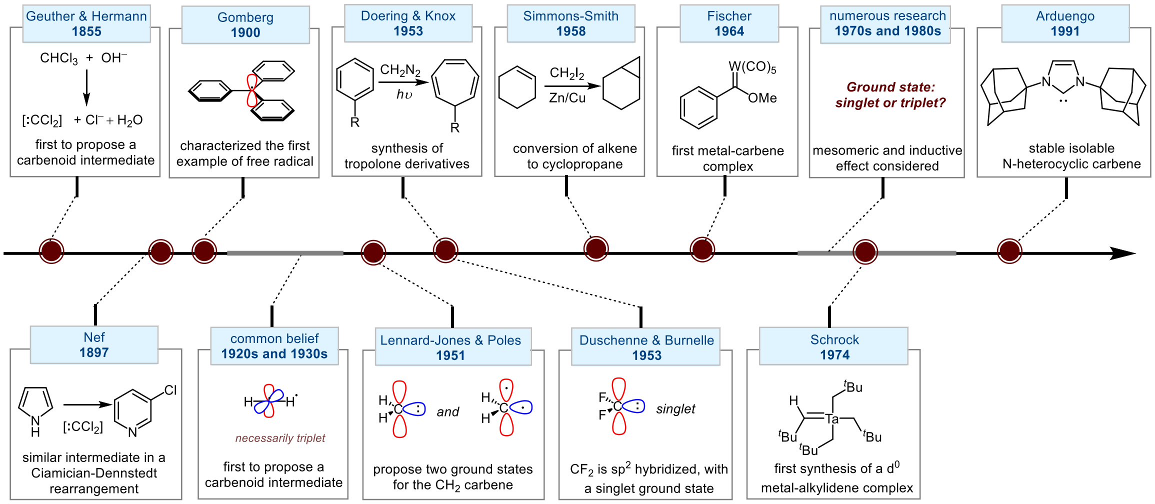
Anthony J Arduengo
1991



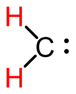
So, what they have done in this imidazolium chlorides they introduce this adamantyl group. So, once you introduce this adamantyl group here now it will be very difficult to form a dimer. So, using sodium hydride they can able to abstract this proton which can able to end up generating a carbene species. So, this carbene is well characterized, and you can get the X-ray crystal of this. From there we can able to calculate the bond angles and all other fact. So, it turns out that this is a singlet carbene. So, now, we are going to try to classify the carbene into a singlet and triplet. So, before going to the classification, let's go through some of the discoveries. Of course, so this is a discovery timeline, and I cannot read every single thing. I am just going to highlight some of the important discoveries.

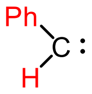
So, this is for your understanding of how this chemistry actually developed. So, in 1855, Geuther and Hermann were actually able to report first and propose the carbenoid intermediate. So, they are the first to propose that. Using chloroform and sodium hydroxide, they propose the formation of the $:CCl_2$. Later, Nef introduced this particular transformation using the particular carbene, which can give you this 3-chloropyridine.

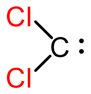
Then, Gomburg in 1900 actually discovered that. So, this is a first example of a free radical. Later on, there were several different discoveries about the diazomethane for ring expansion of benzene. to the tropolone it is a one of the important discoveries. Then Simmons-Smith reaction for converting this double bond to cyclopropane.

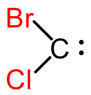


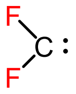
Then another important discovery: formation of this metal-carbene complex is so great Fischer carbene and then the Schrock which actually found the d^0 metal alkylated complex called Schrock carbene. Of course, there are numerous research and then as I mentioned that, Arduengo group actually first found the stable isolable carbene. After that in the last 3 decades there are lot of discovery in this area and lot of new reactivity was discovered. So, there are the nomenclature of the carbene we can talk about. So, if you just a CH_2 carbene we call it methylene.


methylene


phenylcarbene

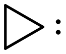

dichlorocarbene

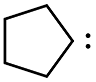

bromochlorocarbene


difluorocarbene

$H_2C{=}C:$

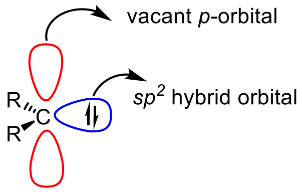
vinylidene


cyclopropylidene


cyclopentylidene

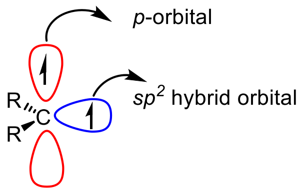
If it is from a phenyl and a hydrogen here attached with the carbene we call it phenylcarbene. If it is a dichloro here we call it dichloro carbene then the bromochloro and difluoro carbene. But if it is coming from a cyclic ring like if 3 membered or 5 membered, we call it cyclopropylidene or cyclopentylidene respectively. Very similarly, if you have a vinyl group with a carbene we call it vinylidene. So, that is some sort of a difference in the nomenclature.

So, now I came back that the topic I was trying to discuss that the difference between singlet and triplet. That means, once we write something like this, we are not specifying anything here; we are just saying this is a carbene. But now we have to kind of from there we have to come back and try to discuss that there are two different types one is called singlet carbene and one is called triplet carbene. In the next couple of slides, we are going to learn what will be the structure, what will be the bonding, what will be the hybridization, what will be the bond angle. So, in general what we are seeing here generally in this carbene has sp^2 hybridization for this carbon.



singlet *carbene*

Total no. of unpaired electron = 0
Total spin (S) = 2s + 1
= 2x0 + 1
= 1
i.e. singlet

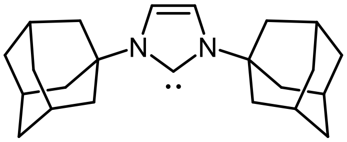


triplet *carbene*

Total no. of unpaired electron = 2
Total spin (S) = 2s + 1
= 2x1 + 1
= 3
i.e. triplet

Now you can see there is a vacant p-orbital here. And now these 2 electrons which of these actually are pair of into this sp^2 hybrid orbital, and here you can see the number of unpaired electrons is 0. So, the total spin actually 2s+1 going to give you 1 which is that is why we call it singlet. Once you come to in case of triplet, instead of pairing now each electron is in the sp^2 hybrid orbital and the other one is in the p-orbital. So, now you have 2 unpaired electrons here.

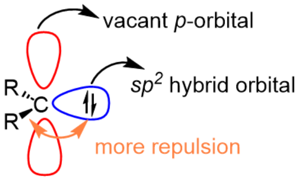
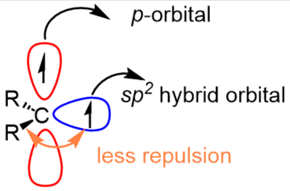
So, the number of unpaired electrons is 2, and if you take the total spin, it will be half plus half will be 1. So, (2x1)+1 is going to give you 3; it is called triplet. So, now, in general, if you see the carbenes like: CH_2, $:CHPh$, $:CHR$, $:CPh_2$ these are mostly triplet carbenes. But if you see something like a like a group which can give have a non-bonding electron like have a lone pair like CCl_2, CHCl or $C(OMe)_2$ you can see or here with you have a nitrogen next to this carbene. So, in these cases you can see these are forming singlet carbene.

Type 1: triplet carbene	**Type 2: singlet carbene**
bond angle 130°–150° observable by ESR	bond angle 100°–110° all electrons paired
$:CH_2$	$:CCl_2$
$:CHPh$	$:CHCl$
$:CHR$	$:C(OMe)_2$
$:CPh_2$	

So, we can understand some of the presence of this group versus you have a Cl versus you have a CHPh. So, now, we try to even understand why if you have a 2 chlorine or why if you have a just phenyl ring why they are being a singlet? So, now, we are actually trying to understand them very detail. We first have learnt that they have a sp^2 hybridization. Now, the important concept is about the bond angle. So, you can see that in case of triplet the bond angle between R-Ĉ-R.

So, we are talking about this particular bond angle here. So, now, you can see this bond angle we are talking about is 130° to 150°. So, now, the question comes why in case of the singlet the bond angle is 100° to 110° and in case of triplet it is 130° to 150°. So, what is happening in case of singlet? In case of a singlet, you have 2 electrons paired up in this orbital and this is sp^2 hybrid orbital. So, now, there is a repulsion between this bonding pairs and this 2-electron pair which is in this hybrid orbital.

Due to this repulsion between this R group and this orbital, the bond angle is less compared to a triplet. Because in triplet now you have only single electron here. So, the repulsion will be less compared to comparative with the singlet. So, that is why you can see the bond angle will be higher. We have already clearly learned that singlet there has no unpaired electron.

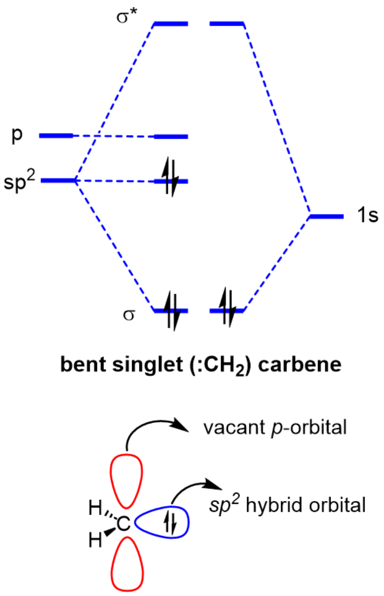
	Singlet carbene	**Triplet Carbene**
Structure and geometry		
Hybridization of central carbon	sp^2	sp^2
Bond angle	100 - 110°	130 - 150°
unpaired electron	Zero (0) *i.e.* diamagnetic	Two (2) *i.e.* paramagnetic
stability	higher in energy than triplet	lower in energy than singlet
Characterization	Not observable by ESR	observable by ESR
nature	Electrophilic / Nucleophilic	Diradical
examples	$:CCl_2$ $:C(OMe)_2$	$:CH_2$ $:CPh_2$

So, zero unpaired electron that means, these compounds will be diamagnetic. Now, here it is paramagnetic because you have 2 unpaired electrons. We know that to make a compound paramagnetic it has to have an unpaired electron. So, always you can see the singlet will be higher in energy compared to triplet. Triplet will be a more stable state compared to a singlet state.

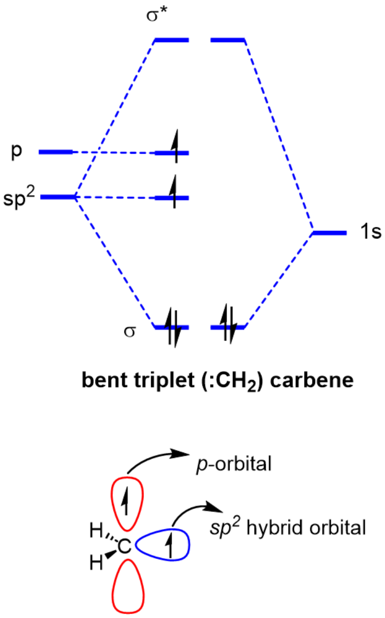
And as you can see these compounds are diamagnetic. So, you cannot see a peak in the ESR spectrum. But because the triplet is paramagnetic you can able to see the ESR spectrum. So, you can able to find out the generation of triplet carbene through the ESR spectroscopy. Then we are talking about the reactivity.

So, in case of singlet carbene as you can see, singlet carbene has a vacant p-orbital that means it can able to accept electron density, that means if you have a nucleophile, it can give electron density to this. and it has 2 electrons in the sp to hybrid orbital that means, it can also give these 2 electrons to electrophile. So, this can be both electrophilic and nucleophilic, but in case of triplet it is mostly acting as a diradical.

So, now I am going to show you some of this molecular orbital diagram about the singlet and triplets. So, again we are trying to show you that here you have this sp^2 orbital in the case of triplet which actually did not participate. So, it is actually this here in the same orbital as a pair. And, now it is actually you have this 1s orbital of this hydrogen if you talking about CH_2, then we are talking about the 1s orbital of the hydrogen which is actually forming two σ-bonds. So, this σ-bond means I am talking about this sp^2 hybridized bonds and there will be σ*, which is not filled. And, then you have very similarly if you come for the triplet carbene the only difference you can see, now you have one electron in the p orbital which is empty. For, singlet it was empty, but in case of triplet you have a single electron there.

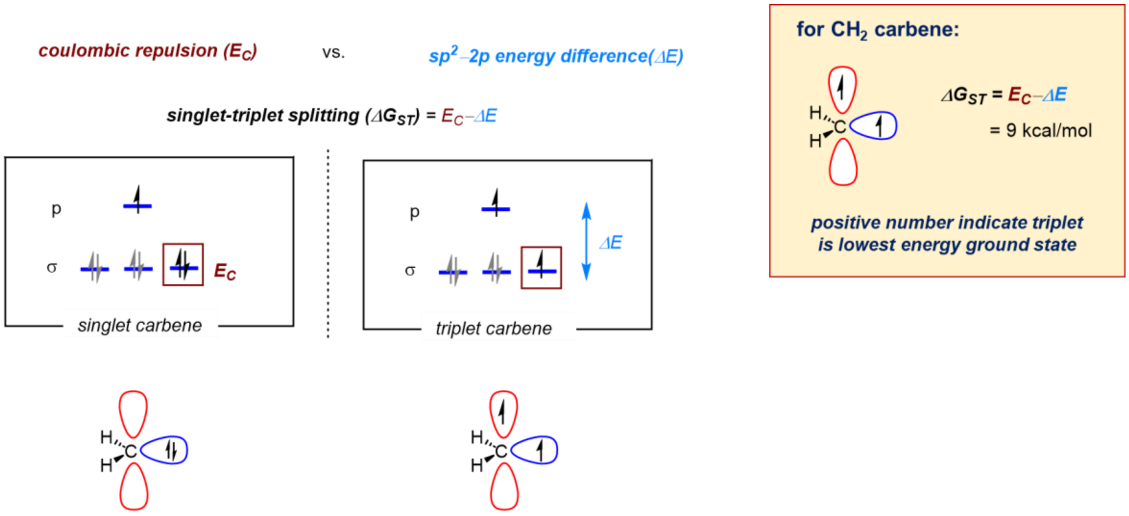


bent singlet (:CH_2) carbene



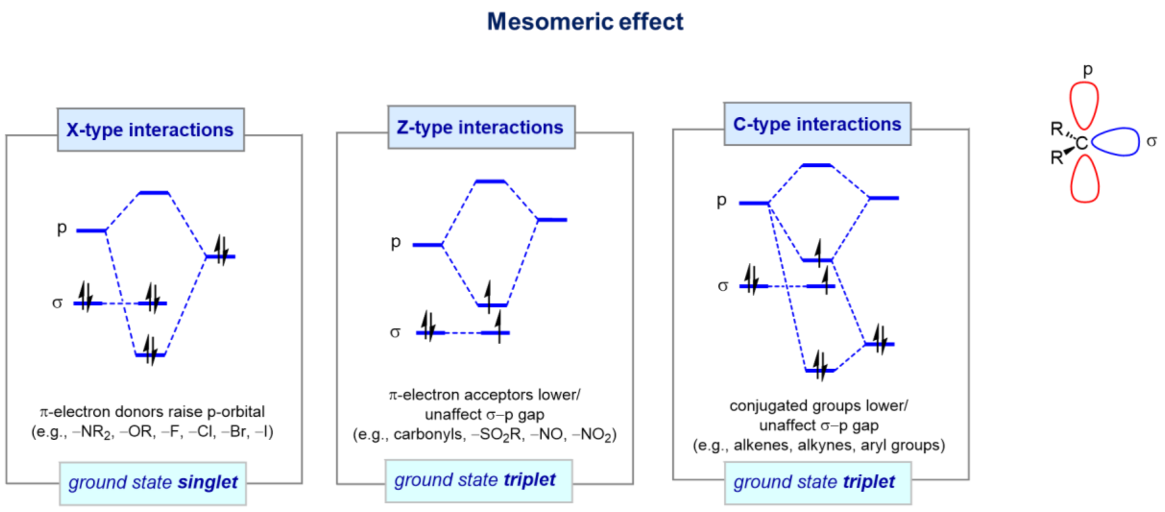
bent triplet (:CH_2) carbene

So, you have one electron in the sp^2 and one in the p-orbital. So, now I am going to talk about the factors that determine the multiplicity that means, we have learned that if you have a CCl_2 we are talking about a singlet if you have a CHPh I am talking about triplet, but is that is all or there is something else we can learn where we can able to use these values or understand that why something is triplet and why some of the carbenes are singlet. So, here we are going to learn about two important things one is the coulombic repulsion and the other is the sp to 2p energy difference. So, in case of the singlet carbene because the two of the electrons are paired up in this one orbital they can have a repulsion. So, this is called a coulombic repulsion and that is how this energy comes into the account and the other one is the gap between this σ and p that means, this is the σ means this is this hybrid orbital this is the p orbital which was empty, but then in case of singlet you have a one electron there.



So, now, the gap between this σ and p orbital is another factor for triplet carbene. Now, I am trying to explain you why that gap is important. because this singlet-triplet splitting is ΔG_{ST} actually is depend on the E_c and ΔE. So, what we are finding is that depending on the ΔE value if your ΔE values become higher and higher. So, if you ΔE become higher and higher than the ΔG_{ST} will be negative.

So, once you go from positive values of ΔG_{ST} towards the negative values you are going to slowly observe that this is happening because this ΔE that means, the gap of σ and P is getting increased as that is going to get increased it will slowly convert singlet carbene. So, that means, you can see here in case of CH_2 the value is 9 kcal/mol. Now, you can see that I am going to show you some more example there you can see that the values can go to even to minus values. So, now, I am going to tell you that based on the different type of groups around this carbene, we can classify them into three different types of interaction: one is X type, Z-type and then C-type interaction. So, here we are talking about the X-type interactions like CCl_2 carbene.



Mesomeric effect

X-type interactions

π-electron donors raise p-orbital
(e.g., –NR$_2$, –OR, –F, –Cl, –Br, –I)

ground state ***singlet***

Z-type interactions

π-electron acceptors lower/
unaffect σ–p gap
(e.g., carbonyls, –SO$_2$R, –NO, –NO$_2$)

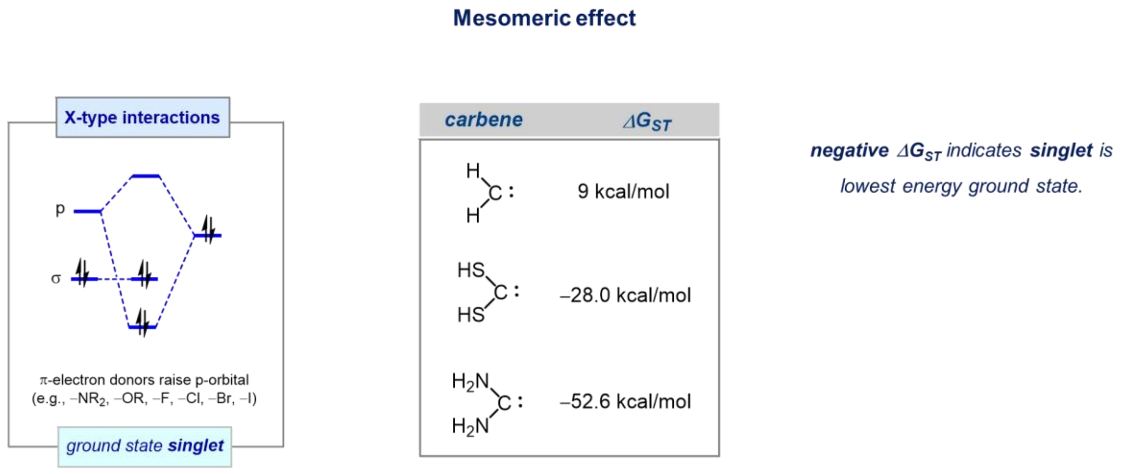
ground state ***triplet***

C-type interactions

conjugated groups lower/
unaffect σ–p gap
(e.g., alkenes, alkynes, aryl groups)

ground state ***triplet***

So, this type of carbene or CF₂. So, we are talking about this type of carbene here that means, you have a π-electron donor which can raise the p orbital like -NR₂, -OR, -F, -Cl. So, this type of group if it is present what is going to happen this can raise the p orbital that means, because you have a non-bonding electron which can be given. So, now this can raise the p orbital. So, that is how what is going to happen now you can see the gap between this. So, now if you have to be triplet then there is one electron from here to migrate to here to here.



Mesomeric effect

X-type interactions

π-electron donors raise p-orbital
(e.g., –NR$_2$, –OR, –F, –Cl, –Br, –I)

ground state ***singlet***

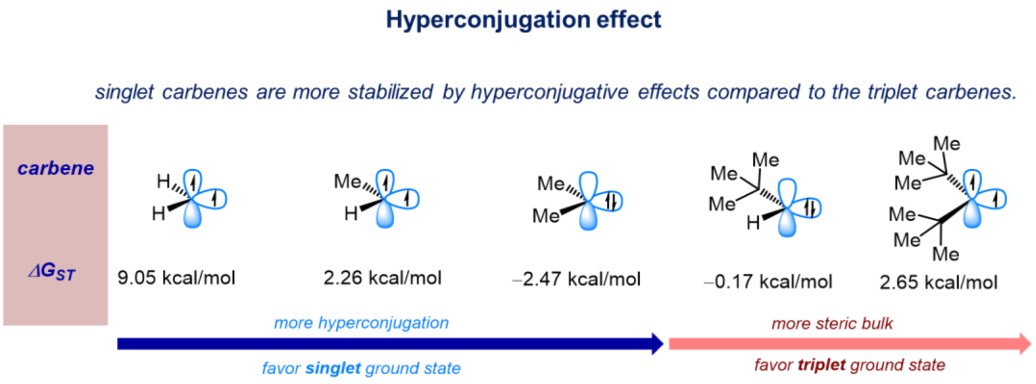
carbene	*ΔG_{ST}*
$H_2C:$	9 kcal/mol
$(HS)_2C:$	–28.0 kcal/mol
$(H_2N)_2C:$	–52.6 kcal/mol

negative ***ΔG_{ST}*** *indicates* ***singlet*** *is lowest energy ground state.*

Now that is getting very difficult because this gap is getting very increased. So, if this gap is increased that means it cannot possible so that means it is going to stay as a singlet curve instead of the triplet. Then the other interaction called Z-type interaction, we are talking about π-electron acceptors. So, previously π-electron donor, now π-electron acceptors and that means, you have to have carbonyls, -SO₂R, -NO those type of groups are there that can take the electron density. If you taking the electron density what is going to happen? Now your p is getting more stabilized instead of the destabilization.

So, now the gap between σ-p gap will be less. So, now it can able to easily go to the corresponding triplet so that means, in this scenario we will mostly see a formation of triplet carbene. Now, there is other type if we have a group where conjugated group. So, if you have a conjugated group then alkene, alkynes and aryls then depending on the different substitution on this alkene, alkynes and aryl it can either remain like a neutral like unaffected or it can lower that means, if it is going to lower then very similar things happen that it can give if the gap between this σ-p going to get decreased so that means, there is a formation of the triplet carbene. So, here are some of the values here you can see this is a triplet carbene which you mean having 9 kcal/mol. Now, you can see here once we introducing those groups which can have a lone pair or at the non-bonding electrons you are slowly going from triplet to singlet.

Again, I am trying to explain this that if you have a hyperconjugation effect. What is the hyperconjugation playing role? Again, hyperconjugation means giving electron density the CH electron density to the empty orbital. Now if you have a like as you are increasing the hyperconjugation means you are going from this direction that means the hyperconjugation increases that means 1 you have a methyl 3 hyperconjugation versus 6 hyperconjugation.

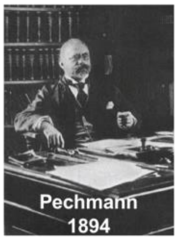


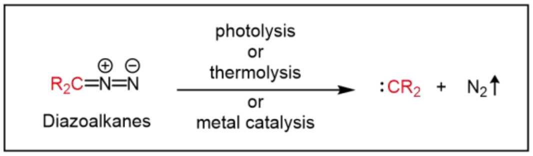
You can see a value become 2.26 to -2.47 that means, slowly it is going to singlet carbene. And now if you come to something like this type of scenario. So, here what is happening if you have this group like two tertbutyl group, then you can see the value is 2.65 kcal/mol. So, that means, in this case what we are seeing this carbene as a triplet.

So, that means, if you can think about the inductive effect, then you might think sir we are we have an inductive effect from the tertbutyl group that means, it is giving electron density. So, why it is triplet, because there is another effect called steric effect. So, that is also important I told you at the beginning that in case of singlet there will be a interaction I think I mentioned before that once you have this pair here and then you once you have this two R group here. I told you there is an interaction between this in the bond pair and this pair, which is in the sp² hybrid orbital. Because of that this angle was remember I was telling you this angle is 110° approximately. So, now, once you have a bulky group here because the steric will be even more once you put a tertbutyl group here. So, that is why it cannot achieve the geometry for a singlet that is why it is going to stay as a triplet. In case of triplet because of the less repulsion the angle can be up to 130 to 140°.

So, I have already talked about their geometry, their molecular orbitals and now I am going to talk about some of the method how to generate carbene. So, there are different methods like fragmentation reactions; I am talking about elimination reactions, and then you are going to find from organomercuric in a compound how to generate carbenes.

So, let us start about the diazo compound, I think this is a very important compound at the same time this compound is very explosive. So, if you are working in the laboratory, you should be very careful using what type of glassware you should choose. So, there is a particular glassware which is used for this particular compounds. So, this was discovered in 1894.





Diazomethanes are vey explosive, toxic
usually stored under lower temperature under solvent.

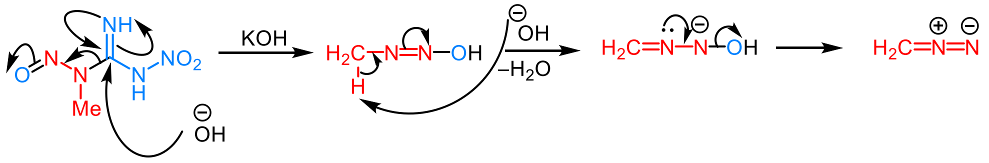

Resonance structure of 1,3-dipolar diazo compound

$$R_2C=\overset{\oplus}{N}=\overset{\ominus}{N} \longleftrightarrow R_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv N \longleftrightarrow R_2\overset{\ominus}{C}-N=\overset{\oplus}{N} \longrightarrow :CR_2 + N_2\uparrow$$

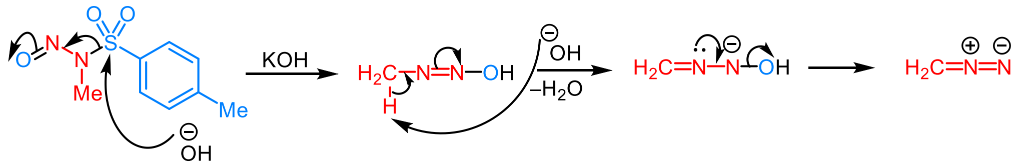
So, the structure of diazomethane is CH_2N_2. So, here I am talking about that this compound is always you can make an etheral solution of it and now once you take this diazomethane and go for a photolysis or thermolysis. or using metal catalyst. So, from this compound it will form this carbene, via photolysis, thermolysis or metal catalyst. You can see here that by I think we can able to draw the resonance structure of this compound. So, if you have CH_2 in place of R then that is the diazomethane it can form this N_2^+ and then minus and then finally, it can able to cleave this bond under photolysis or thermolysis to generate this corresponding carbene.

So, as I said that the synthesis of diazomethanes is a little bit tricky. So, that means, so that is why there are several groups found a different approach that means you can make diazomethane, but from a precursor compounds. So, one of them example is N-nitroso derivative of urea, using the *N*-nitroso derivative of urea using this compound. in presence of KOH, it can form this particular intermediate. So, let us try to understand what is the mechanism here, the OH- actually attacking here and then you can see.

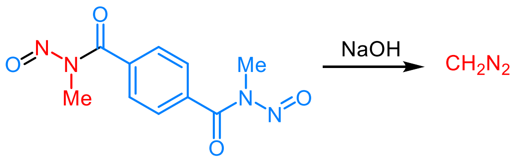
a) *from N-nitroso derivative of urea*



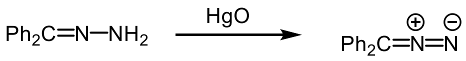
b) *from N-nitroso derivative of sulfonamides*



c) *N-nitroso derivative of amide*



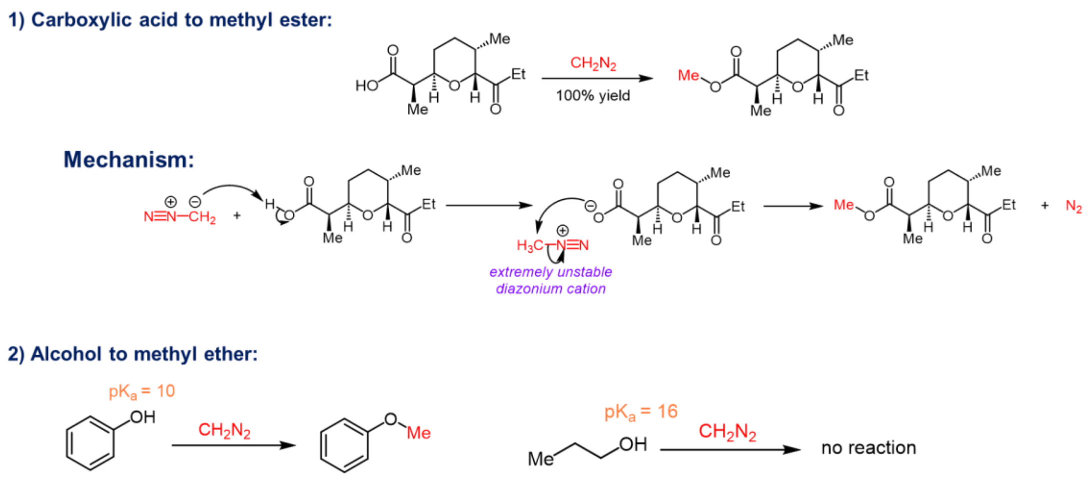
2) from hydrazone:



$$Ph_2C{=}N{-}NH_2 \xrightarrow{HgO} Ph_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$$

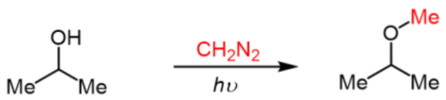
So, it will be forming the N^- then it is going to come back and get rid of this part which can take a proton to form this intermediate. Now, once this one getting treated in place of a base. is going to take this it is going to abstract this proton and then form this N- which going to finally, this lone pair of nitrogen can form this N=N to finally, form the diazomethane. From N-nitroso derivative of sulfonamides very similar thing happening here. In presence of KOH, it is cleaving this bond forming this intermediate and finally, forming diazomethanes. For N-nitroso derivative of amide again very similar thing base going to attack here this part going to come out and then from diazomethanes. From hydrazones also using mercury oxide also diazomethanes can be not a diazomethane, but it is a it is a diphenyl diazomethanes can be synthesized.

So, now I am going to talk about some interesting reactivity of diazomethane. So, diazomethanes are very much important compound as I said it is known for this particular transformation. So, if you want to transform this carboxylic acid to ester then diazomethane can be used.

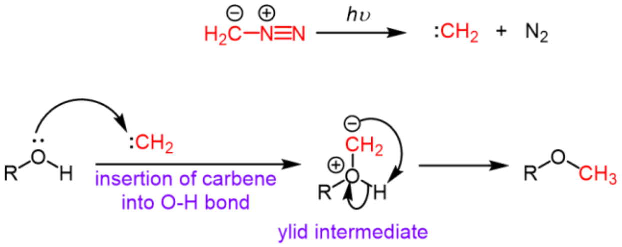


So, here what is happening the diazomethane has a CH_2^- it can abstract this acidic proton. then to form this corresponding O^- species. So, this O^- can attack here through the CH_3; release of N_2 can form this compound. So, now the question comes does the reaction happens if you have an instead of acid you have simple alcohol. So, if you have a just a when a n-propanol then there is no reaction is happening, but if you have a phenol the reaction still works that is because this depending on the pKa. So, depending on the pKa if the proton is little bit of acidic then only this reaction happens, but if you want to make this transformation. So, if you want to make this transformation working what will be the product? Let me just write down the product, then you can able to achieve it, but not just by using diazo methane you have to use hν or some sort of a UV radiation.

Methylation of alcohol:

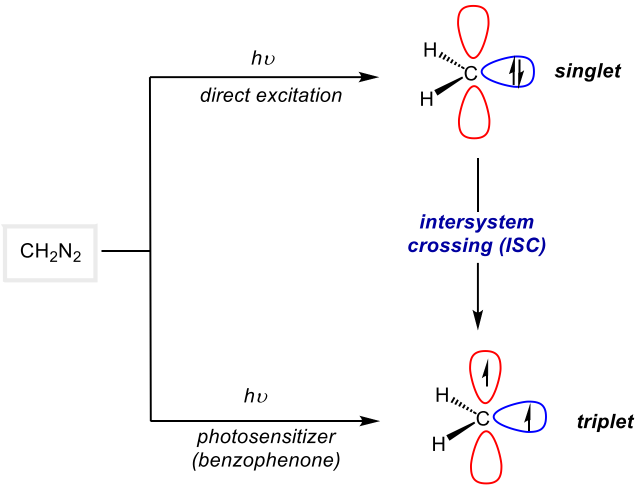


Mechanism:

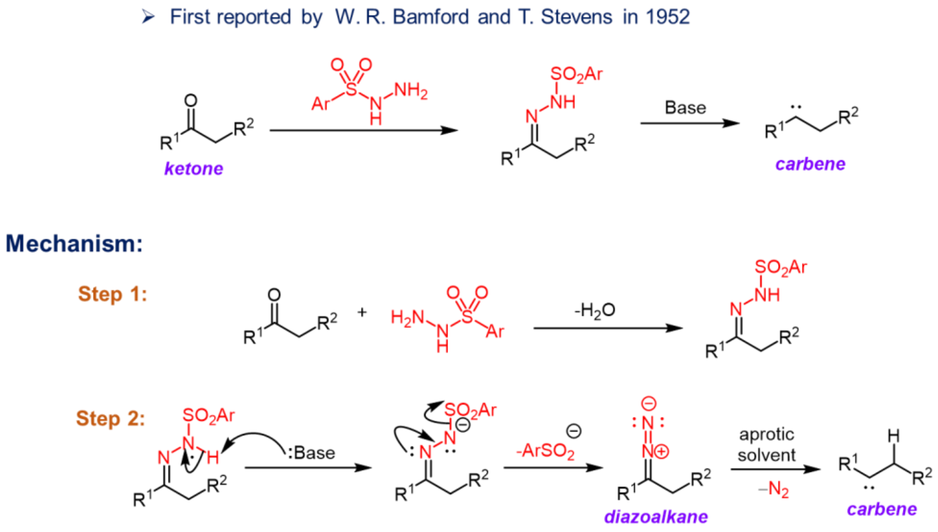


If you do that then you can able to convert this corresponding isopropanol to this -OMe product means corresponding ether. So, here what is happening in presence of light or in presence of the photolysis this can form the corresponding carbene. Now, carbene is going for a C-H insertion. I am going to discuss all these different types of reactions. So, here the carbene is going for a C-H insertion where this oxygen lone pair now can attack to the vacant orbital of this carbene followed by it can capture this proton get capture by this CH_2- to form this corresponding product.

Again, there are generation of carbene. So, here I am going to talk about the generation of carbene from diazo methane. If you use this hν under the direct excitation then it can generate a singlet carbene, but in place of photosensitizer it can convert to corresponding triplet carbene. So, you can use several different photosensitizers are known; I think benzophenone was used for this purpose.



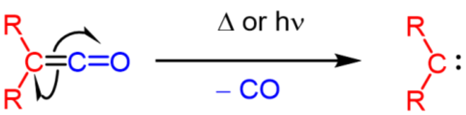
So, now, I am going to move forward and talk about the Bamford-Stevens reaction I think all of you are very familiar with these reactions. So, in the Bamford-Stevens reaction there is actually two different protocols in one case it can from a carbocation if you use a protic solvent; if you use a aprotic solvent then after formation of this hydrazone what is happening in place of base it is actually forming a carbene and from the carbene what is going to happen it is going to go for this the CH. So, this CH go for CH insertion which can end up forming this corresponding olefin. So, we have shown here the mechanism. So, in presence of base it is going to abstract this NH proton to form the N^- then release the SO_2Ar group then generation of this intermediate and then after that, the release of N_2 in place of aprotic solvent actually generate this carbene. And if you have a protic solvent then from here instead of carbene it will generate a carbocation and after that there will be a proton abstraction to go to very similar product.



- First reported by W. R. Bamford and T. Stevens in 1952

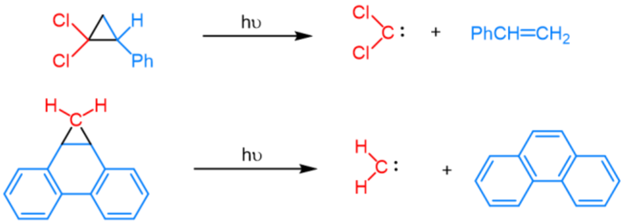
So, now I am going to talk about another method of generation of carbene from ketene. So, using ketene also if you can go for this the pyrolysis or in place of hν it can able to convert to this corresponding carbene, but again it was reported that in case of ketene, ketene can also go for polymerization in under those condition.

- ✓ Ketenes can eliminate CO molecule on thermolysis or photolysis to generate carbene.
- ✓ Since ketenes are not readily available precursor and polymerize under the reaction conditions, they are not widely used.



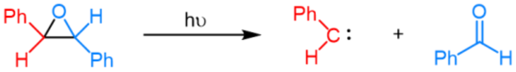
So, here are some other examples of generation of carbene from strained molecule. So, you can see from this strained cyclopropane it can actually goes for some sort of a you can able to draw maybe this type of arrow to show them that is happening. So, it is cleaving here and this bond can move this direction. So, that means, this part is getting out forming this corresponding dichloro carbene. It can happen here very similarly this part can chop under photolysis to form this CH_2 carbene or methylene.

from cyclopropane:

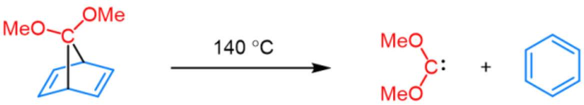


So, you can form the stereospecificity you can also find if it is a singlet or a triplet. Then from phenyloxirane under photolysis it can also cleave here to form this corresponding carbene and the benzaldehyde. And then again from this compound also it can get to the corresponding aromatic compound and it can able to form the corresponding carbene as well.

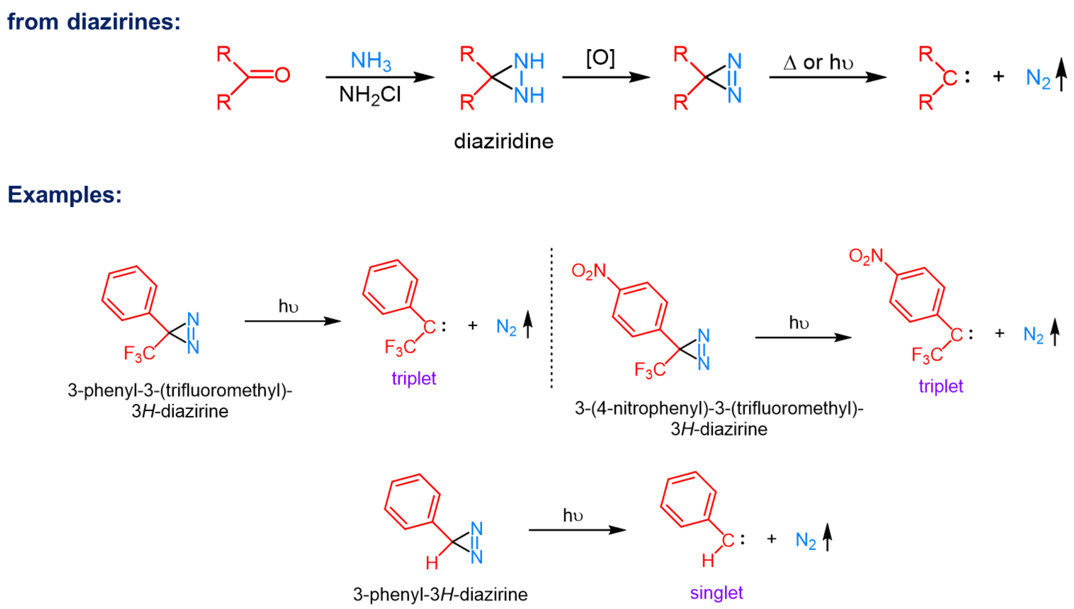
from phenyloxirane:



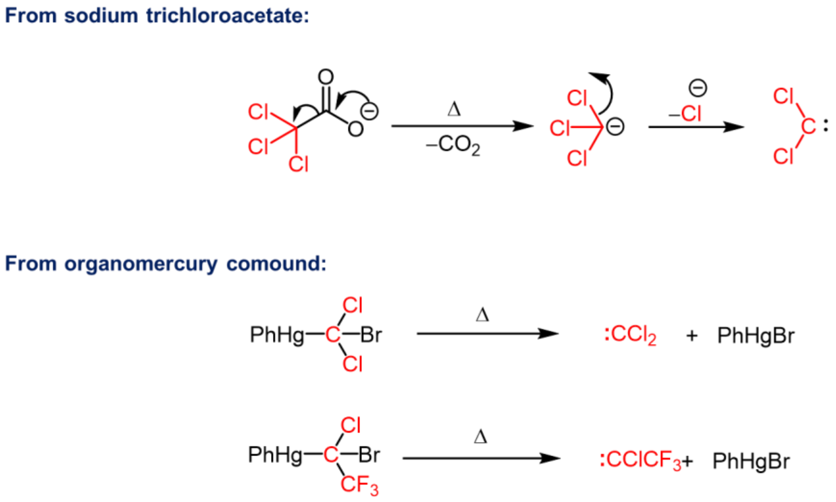
from norbonyl ketal:



So, there are other method to for the formation of the diazirines. So, diazirines is an important precursor which can also generate the carbene. Here you can able to synthesize from corresponding carbonyl to diaziridine which can further oxidize to corresponding diazirines and which can under photolysis or thermolysis can generate carbene. Here are some of the examples. So, depending on the different groups here that means, if you have phenyl and CF_3 it can generate triplet carbene under photolysis. Again, here we are showing that if you have a nitro group here also it is generating a triplet, but if you do not have CF_3 group here then under photolysis actually it is generating a singlet carbene.



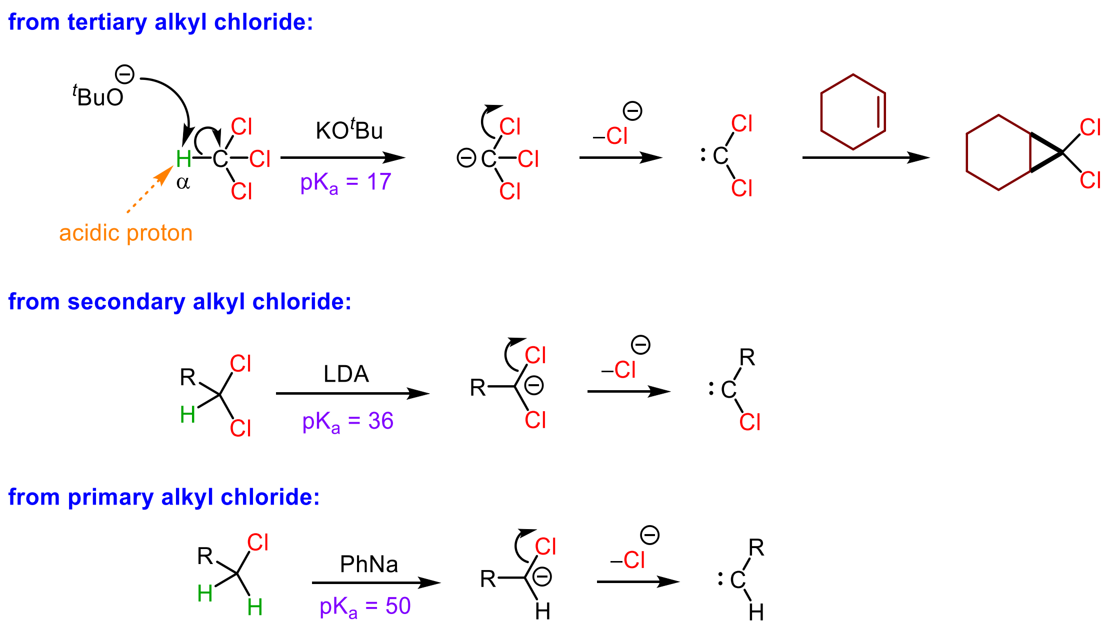
So, here are another method of generation of carbene through the as I mentioned that you are actually cleaving of the sodium trichloroacetate. That means, once this bond goes for a decarboxylation because this is going for a decarboxylation because you can see that the CCl_3^- is now going for α-elimination. So, first go for decarboxylation, then α-elimination to generate this corresponding dichloro carbene. or from organo mercury compound under heat it can also generate this type of dichloro carbene or this the chloro CF_3 carbene as well.



So, here is the example of α-elimination. I think α-elimination is a very important reaction and I think it was the one of the early discoveries of carbene were using NaOH and chloroform it can form this the dichloro carbene which is still useful in the organic synthesis.

Here is one of the important facts about it that if you have a trichloro compound like this then using potassium tertbutoxide you can abstract this proton to form this CCl_3^- then α-elimination from here to generate this carbene. So, what we are talking that from if you have a trichloromethane versus if you have a dichloro; the pKa of now this hydrogen is going to get change. That means, now what you will do you have to use stronger and stronger base. Once you have the monochloro versus dichloro versus trichloro the proton become more acidic. That means, you can use a milder base if you come here, but if you can come to this where you have a one chloro then you have to use more stronger base the pKa is. So, this is a literally alkane which have a pKa around 50. So, you have to use a stronger base to generate this corresponding anion which can go for α-elimination to generate the corresponding carbene. So, the final example here that if you have a strained alkene because if you have a strained alkene because of the steric things and. So, this π-bond becomes weaken because of the steric reason of these two different groups this π-bond become weaken because the p-p overlap because the overlap of this p orbital got disturbed because of the planarity issue. As a result, what happened so, because the energy got raised.

So, after heating this particular compound it forms this corresponding carbene.



In this part I actually teach you the definition of carbene different variety of carbenes and the singlet triplet carbene and their generation in the in the next class I am going to talk about different reaction and the rearrangement. Thank you for coming to the class and thank you and I am going to see you in the next class.