Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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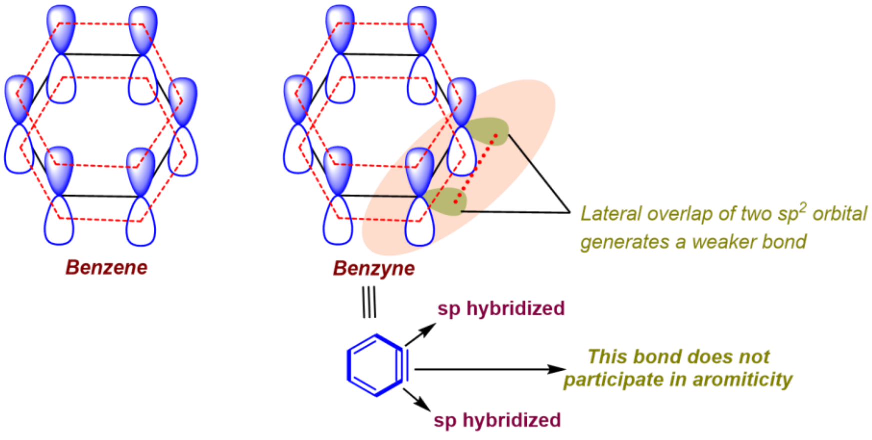
Lecture 28: Benzyne

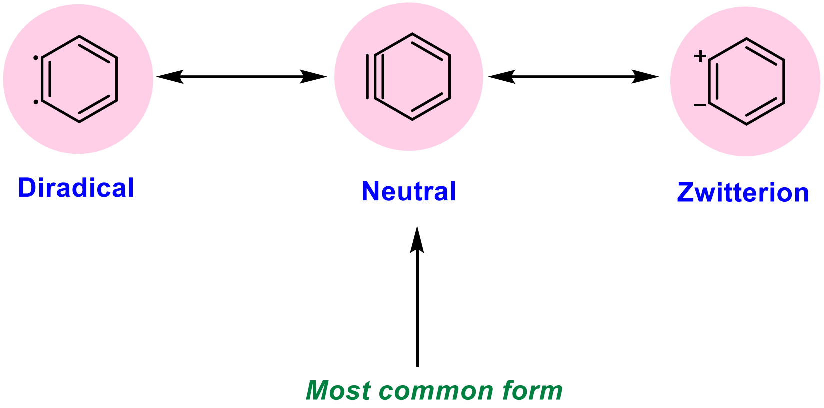
Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In this course, in the last couple of classes we have learned about the carbocation, we have learned about the carbanion, I talk about the free radicals, I also talk about the carbene, and nitrines. Also, in the last classes I was talking about some of the important reactions of radical chemistry like the hydrogen atom transfer, then the halogen atom transfer. But, in today's class, I am going to start with another reactive intermediate which is called benzyne or arynes. So, I am going to talk about how the benzynes or arynes can be formed from the different starting substrates. So, let us first talk about some of the introductions.

So, I am going to talk about or try to introduce the benzynes and try to do some sort of a comparison study with the acetylene, then I am going to talk about the different methods for the generation of benzyne. So, first, if you think about a benzyne or arynes. In general, this is a benzene ring. So, it is kind of a π cloud in this benzene ring. We know about it. So, this is aromatic compound. So, now what is happening, once you go to benzyne. So, you can see, one of the side, one of these two carbon there will be another extra bond. So, it looks like a triple bond which is in a strained position.



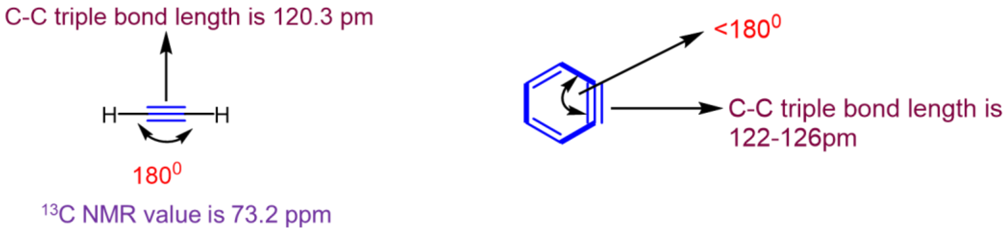
- Strained energy is about ~63 kcal/mol and $\nu_{C\equiv C}$ is 1846 cm^{-1}
- It obeys Huckel's (4n + 2) π rule, thus aromatic

People can write also this structure as a plus minus. So, we can use this type of zwitterionic structure of arynes, when we try to explain some of the reactivity. Also, there is another approach; people use for writing as a di-radical. As this is a formation of a bond we can think about two radicals. So, now if you try to think about the structure of benzyne, we know about the benzene structure.



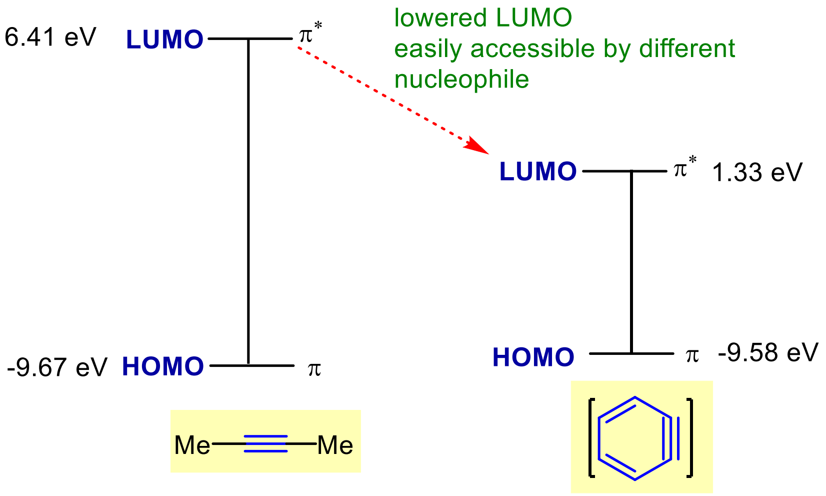
As I was telling you, it is forming. So, these three π-bond forming a π cloud here. Now, what happens once there is the formation of the extra bond? So, these sp^2 orbitals are forming an overlap. So, this sp^2 orbital and this sp^2 orbital, are forming overlap here and forming a weaker bonds, we call this bonds are weaker bonds which is formation happening.

And if you think about this bond, this bond is not part of the aromatic system. So, that is why this type of benzynes is also aromatic. But again the thing is this particular triple bond-like character is going to look like a triple bond, but there are some differences from an alkyne. And then, these carbons where these bonds formation are happening, these are sp hybridized. Also, you can see there are strain energy of about 63 kcal/mol. So, that is the another important thing that you are literally putting an alkyne in a strain position. We also going to learn about it there, you can see the frequency of this bond is 1846 cm^{-1} which is kind of lower compared to an alkyne. If you think about alkyne also the bond length, compared to the normal alkyne, this bond in the case of an aryne is weaker. You can see, that it has a longer bond length and you can see from the carbon NMR values also. So, these cases it is getting even more deshielded. And, then the frequency, as I mentioned in the case of benzyne is 1846 cm^{-1}, but normal alkyne going to come around 2150 cm^{-1}. So, you see what is happening in the case of Benzyne, there is a triple bond-like character, but it is a weaker triple bond.



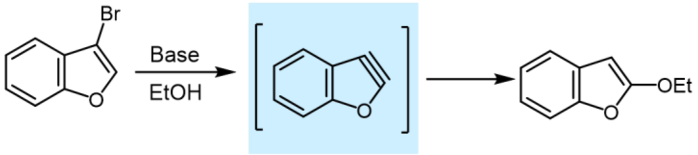
The vibrational frequency of the triple bond in benzyne was assigned by Radziszewski to be 1846 cm^{-1}, indicating a weaker triple bond than in unstrained alkyne with a vibrational frequency of approximately 2150 cm^{-1}

So, that is why, if it is a weaker bond that means, it is going to be much more reactive compared to normal alkyne. The other important factor is if you come from alkyne if you try to think about the molecular orbital. So, there is a HOMO and there is a LUMO. So, in the case of benzyne, the LUMO energy is decreasing. So, this is the LUMO energy that is coming down. It was 6.41 eV. Here it is coming to now 1.33. So, there is a stabilization of this π* orbital here. As the LUMO energy is lower in the case of benzyne. Now the nucleophile can able to access this LUMO because the nucleophile has to give electron density to the π* orbital to form a bond. So, if the nucleophile has to approach towards benzyne, it has to form this bond and it has to give electron density to the LUMO orbital. So, that is why because of the lowering of the LUMO, now different types of nucleophiles can access.

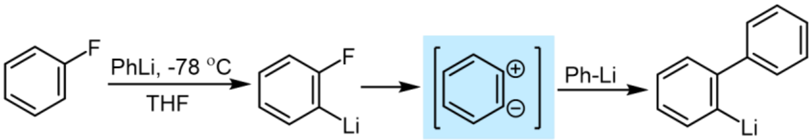


I am going to talk about the different types of nucleophiles and how they are forming bonds. But before I going to talk about them I am just going to talk about how these things were discovered. So, in 1902, the initial discovery by Stoermer and Kahlert who first proposed the existence of Arynes. They mention the existence of Arynes, when they are trying to get ethoxybenzofuran starting from the 3-bromo benzofuran, they able to get this ethoxybenzofuran . So, that time, they mention that this might be going through some sort of an aryne intermediate. Then, later on Wittig who also find out that once you start from then fluoro benzene using phenyl lithium what is happening first? First there is a proton next to the fluorine which is the more acidic one getting abstracted. Then, formation of this corresponding lithium and then there is a elimination happening to get to this type of plus minus or some sort of a benzyne species going to form. Now, once this is forming a benzyne, the phenyl lithium is already present in the reaction. It is a nucleophile. So, that can also attack here and then from the corresponding lithium which can get protonated. So, now you can think about that.

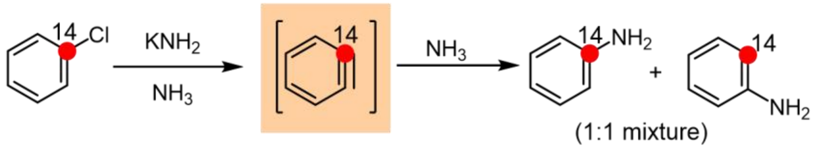
- Stoermer and Kahlert in 1902 first informed about the existences of arynes.



- Wittig et al. informed the formation of biphenyl in the reaction of fluorobenzene with phenyl lithium



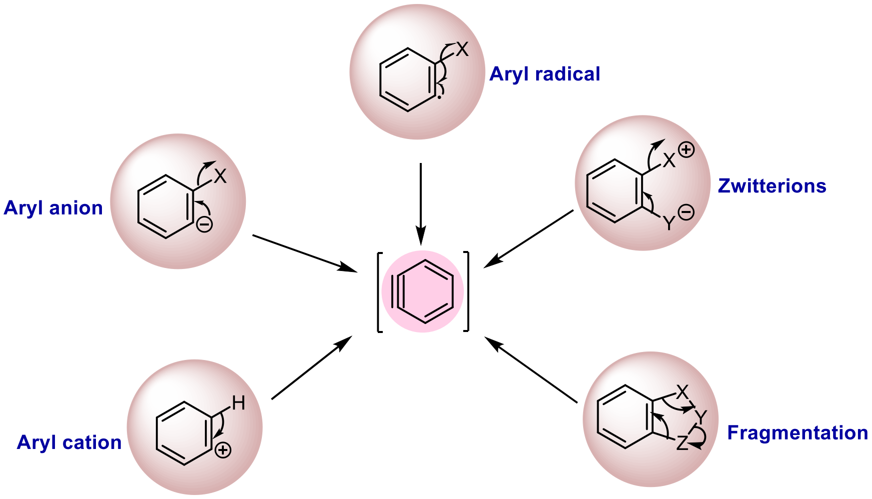
Another experiment was done by John Roberts. So, here the important thing is that they started with the 14-labelled. So, this carbon in the chlorobenzene which is the ipso carbon actually14-labelled. Now in the presence of the KNH_2 or potassium amide, what is happening here? It is actually going for the very similar things, you have seen for the n-butyllithium case. It is going to abstract this proton which is the acidic proton. And going to form this benzyne. Now, if the benzyne formation is happening, here the nucleophile is ammonia. So, ammonia can attack from this side and it can also attack from this side because there is really no difference in attacking from these two sides. So, that is how what is happening in the product it can able to get to aniline, where it is attached to the C-14 carbon or if you go to the other product where it is the next carbon means it is the α and this is the β or the ortho carbon. So, this is kind of indicating that it is going through some sort of an aryne intermediate from there the nucleophile can attack from either side as there is no preference you will end up getting a 1:1 mixture of both the products.



John D. Roberts

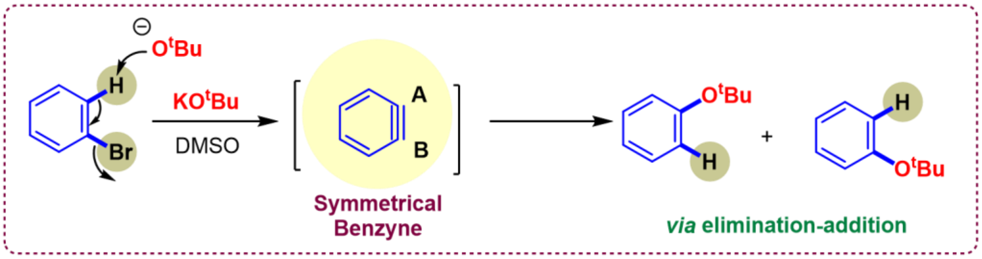
- John D. Roberts in 1953, performed a ^{14}C labelling experiment which identified the existence of neutral benzyne intermediate

So, in today's class, my focus will be what are the different methods how you can able to generate this aryne or benzyne. So we are going to learn about the different methods. So let us start with this method as I was telling you. You have some aryl halide here and you are using a strong base for deprotonation and then, there is an elimination happening which can generate the benzyne. We are going to talk about a method where you can also generate some sort of aryl cation. Then, there will be proton abstraction and you can generate aryne. Also, there could be a fragmentation. We are going to talk about some of the fragmentation reactions where after the fragmentation of this bond you are going to form a new bond here that is going to end up forming your arynes or there could be a zwitterion. So, if there is a formation of this plus-minus, if you have a compound that has a plus and has a minus, and then this one going to come back here and this is going to get out we are going to talk about some of this reaction. And, at the end, I am going to also discuss some of the reactions using aryl radical. If you have a halogen that can make a radical then now two radicals can form a bond which can end up making benzyne. From 1, 2 substituted means if you have two groups here which can form a radical. If you have X, they can form radical and then they can form a bond, it can end up making a benzyne.



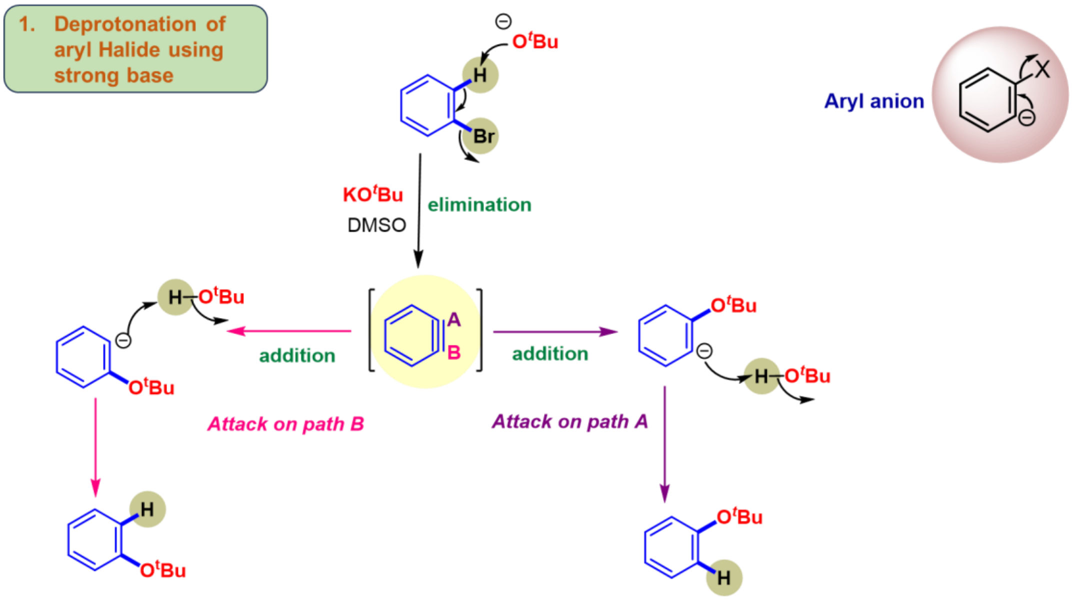
So, the first example here, using potassium tert-butoxide in DMSO starting from the bromobenzene. So, here, what is happening, starting from the bromobenzene, this proton is the acidic proton is getting abstracted in the presence of potassium tert-butoxide, which is forming this symmetrical benzyne. As you can see, both sides can be equally getting attacked. And again in the medium you have the tertbutanol. So, that can attack from either side or this side correct as I mentioned. So, you end up getting both products.

1. Deprotonation of aryl Halide using strong base

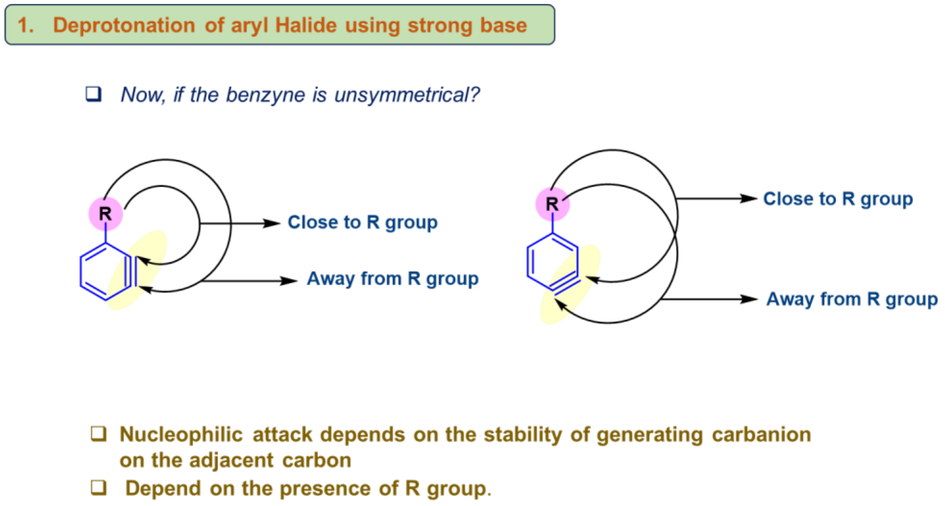


So, what is happening, this method is called elimination addition. First elimination happening of this bromine and then addition happening about the tertbutanol. Again we are trying to show the mechanism here. So, I think once the tert-butoxide taking this proton, it can form the benzyne. Now the attack through path B or path A, it can give you the same product.

1. Deprotonation of aryl Halide using strong base



But I think this is an unsubstituted compound here. If your bromobenzene is substituted now, you are going to see some difference in the selectivity. So, now the question comes, as I mentioned if your benzyne is unsymmetrical which I mentioned in the previous slide. So, now you have to think about if the benzyne is unsymmetrical, now it depends on what group is attached to the aromatic ring. If it is an electron-withdrawing group or if it is an electron-donating group. So, mostly you are going to see that there will be some sort of anion going to generate. Now based on the stability, you will see that different types of products will be formed. One will be major and one will be minor. So, now if you think about you have a R group here, now if there is a benzyne here, the nucleophile can approach from this side or can approach from this side. So, we are going to talk about if it is attacking from this side what will be the preference, and if it is attacking from the other side what will be the preference? So, again if you have a benzyne, if you have R group here and benzyne is forming in this position. So, now, there could be attack from the para position or attack from the meta position.

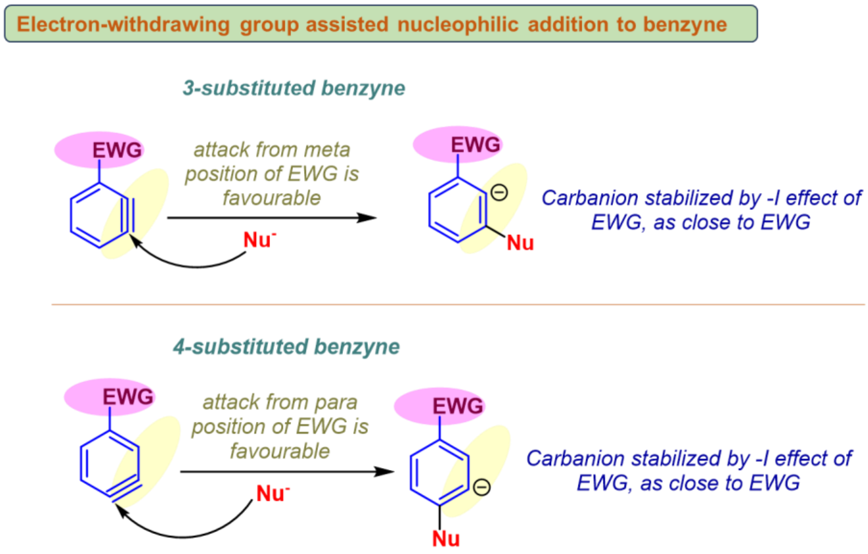


1. Deprotonation of aryl Halide using strong base

- *Now, if the benzyne is unsymmetrical?*

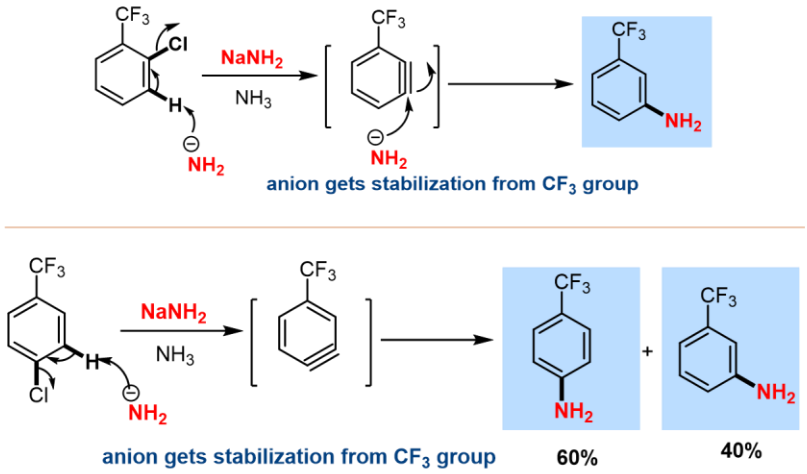
- **Nucleophilic attack depends on the stability of generating carbanion on the adjacent carbon**
- **Depend on the presence of R group.**

So, we are going to discuss first with electron-withdrawing. So, as soon as you have an electron-withdrawing group here that has a -I effect, we know about that group that has a -I effect. Now, once the nucleophile can attack from this side if we attack this side is generating this carbanion here. So, now, this can get more stabilized because of the -I effect of the electron-withdrawing group. Compatibly if you try to attack here in these cases that means, in these cases, this will be the meta attack. So, this will give a major product, but at the same time, you will get some attack from this side so that means your minor product. Where you will see what is happening, nucleophiles will be here and you will generate an anion here some sort and from there it can get protonated. So, this will be your major may be close to 70 % and that will be the minor close to 30 %. Now, the case is, if you have a 4-substituted scenario, there is a two possibility it can go for a *para* attack versus a *meta* attack. Now, what is going to happen if it is going for a para attack it will generate a carbanion here, if it is going for a meta attack means attacking from this side then it is generating carbanion here. Now, if you think about the electron-withdrawing group have a -I effect. So, the -I effect means that will be going to stabilize more this carbon because it is close to EWG. This is a para position, this will be far. So, if this is the carbanion which is forming here. So, that can be stabilized more because this is in the meta position formation happening versus this negative carbon formation in the para position. So, it is far from this electron-withdrawing group. So, that is why, this will be the major product.

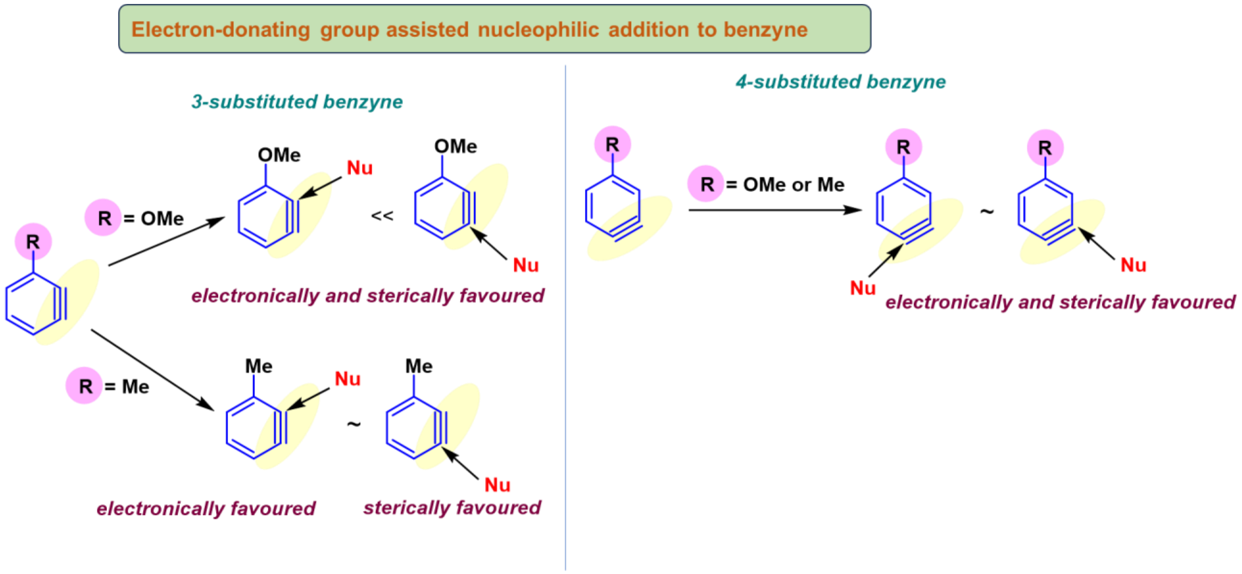


Then now, we are going to talk about a very similar scenario here. You have a CF_3 group, which is electron-withdrawing. You have a chloro there. Now, there is a possibility that the first thing is going to be, the sodamide going to abstract this proton to generate a minus which can eliminate this chlorine to form this corresponding benzyne. Now, the nucleophile can attack. As I have already told you in case of the formation of a benzyne in the ortho position, nucleophile is going to attack to the meta position to form the this product as a major product. And now, if it is in the para position what is happening, the selectivity is not same, there is two different possibility once this benzyne will form. So, the one which is attacking from this side will be the major. The para attack will be major product and the other one will be the minor product.

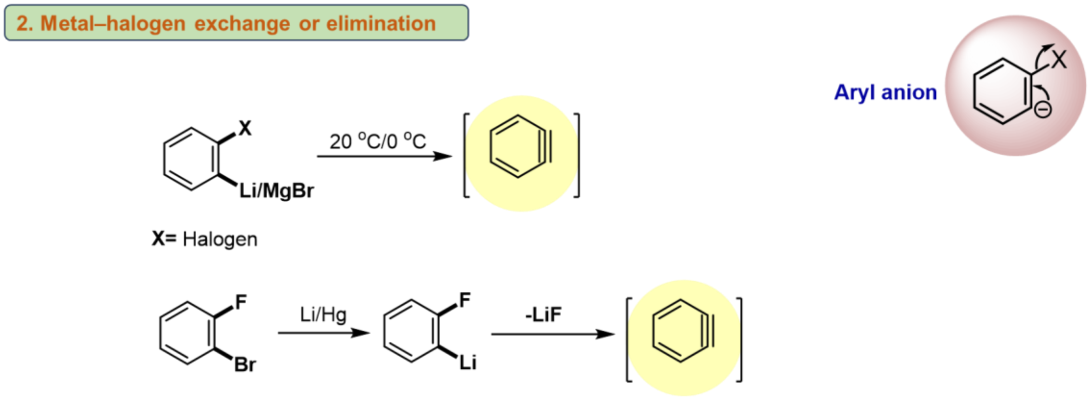
Electron-withdrawing group assisted nucleophilic addition to benzyne



So, now we are talking about the other scenario, where you have a methoxy group or you have a methyl group. So, what will be the changes there? Now we all know that the OMe group has a -I effect. And you can see, the -I effect will be the one which is going to be the controlling factor. So, because of the -I effect, the nucleophile always going to attack from this meta position and that will be the major product. But once you have something like a methyl which has a +I effect. In that case, what is going to happen, you can see there will be the nucleophile that can attack from this side of the ortho position or it can attack from the meta position. In both cases, you will see not much selectivity. Although, we can expect that electronically, it will favour that it is going to attack in the ortho position because the negative charge should be generated far from the methyl group. But this will be a sterically favour position because, if you are attacking in the ortho position, there is a steric effect happening between the methyl and the nucleophile. So, that can be avoided, if it is attacking from the meta position. So, that is why, you will see based on the size of the nucleophile, sometime you will not able to see much selectivity difference. In case of the 4-substituted one, as the charge will be forming far from this group. So, that's why, you will see that there is a steric and electronically both will be kind of not there and will be not much difference in the product selectivity.

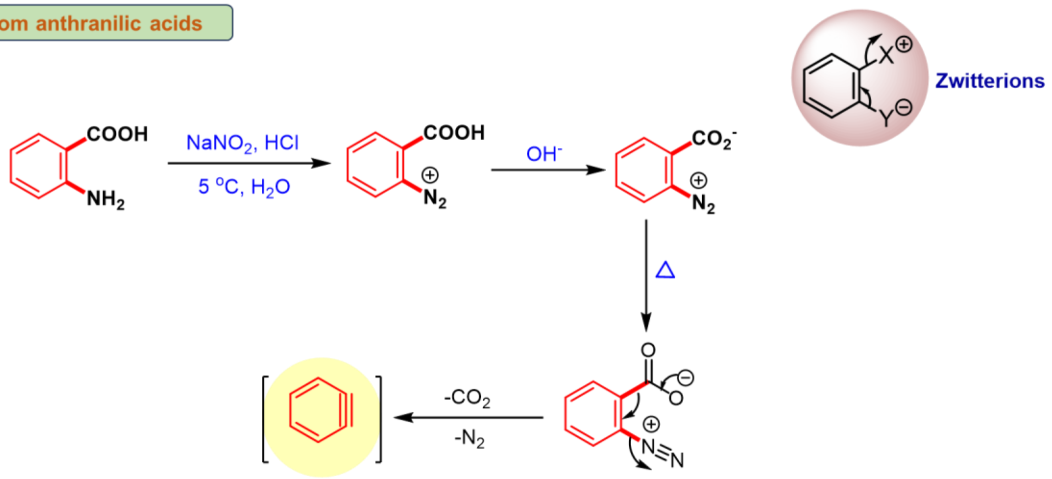


Of course, if you have a nucleophile which size is very much different, and based on that sometimes we have seen some selectivity, but not very much. So, the first thing I am going to start with the metal-halogen exchange. As I mentioned, if you have a halogen here, once you are generating this lithium through the metal halogen exchange, which I am showing here, just for a deprotonation. Then after, the next thing is elimination which is going to generate the corresponding benzyne.



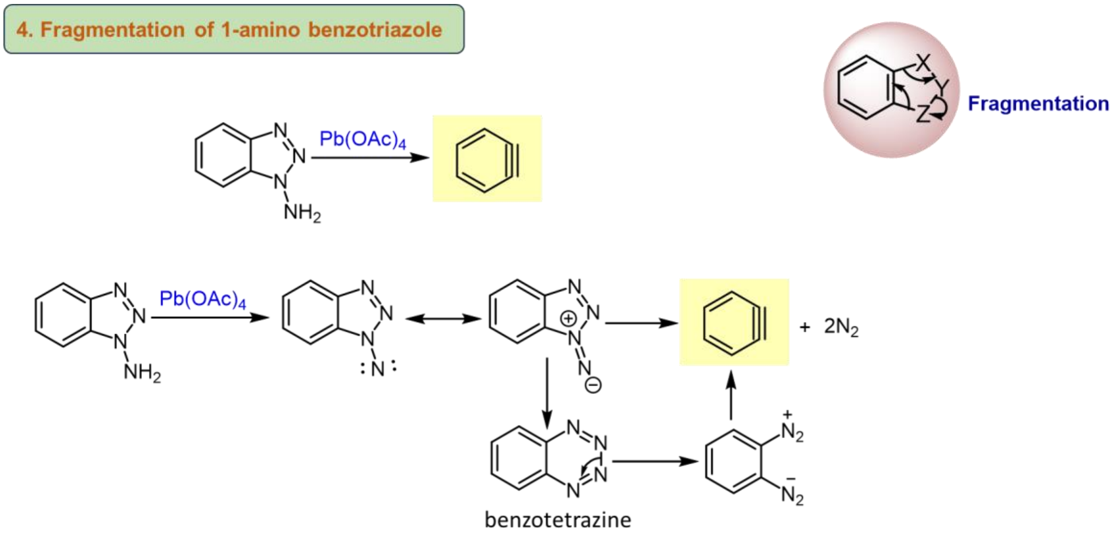
This is a very important method for the generation of benzyne starting from anthranilic acid. You can use $NaNO_2$, and HCl to form this diazo compound N_2^+. So, this diazonium chloride in the presence of OH^-, it is going to abstract the acid proton. So, now you can see, you have this zwitterionic scenario here. You have this CO_2^- and N_2^+. So, once you are going to heat this, CO_2 is going to get out from here. So, you can see this can come back, this can generate anion here and now this can throw the N_2 out. So, there will be N_2 and CO_2 which are going to get out to generate a corresponding aryne.

3. From anthranilic acids



Then the 1-amino benzotriazole. So, starting from this, 1-amino benzotriazole, using lead tetra acetate, it can also generate the corresponding benzyne. So, what is happening in the presence of the lead tetra acetate, it is generating a nitrene here. As the nitrenes are electron deficient. You might be familiar, I already talked about that. So, this lone pair, this nitrogen can give the lone pair to form this intermediate. From there, it can attack the other nitrogen, break this bond between this two nitrogen, where nitrogen is the positive, form this benzotetrazine, and then this benzotetrazine, there will be a fragmentation going to happen. This kind of fragment generates N_2^- and N_2^+, in one case it will be minus, and in one case it will be plus and then there will be two N_2 going to get out from here. And you are going to end up forming the corresponding benzyne. So, this is a method of fragmentation as I mentioned.

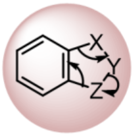
4. Fragmentation of 1-amino benzotriazole

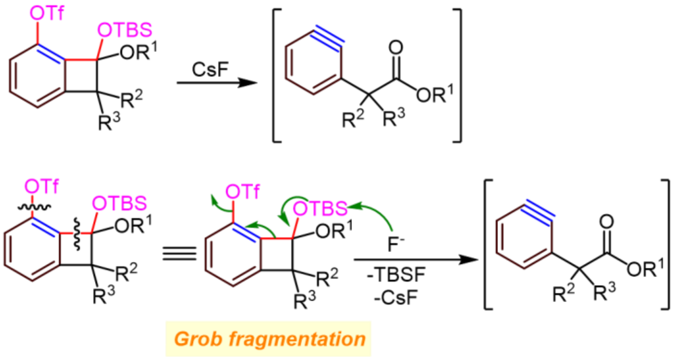


So, this is a another method of fragmentation. So, starting from this compound, you can see, there is a triflate here or OTF and there is this TBS protection.

So, once you have this TBS protection and if you are using cesium fluoride, it is going to attack on the silicon. So, once it is attacking on this, the F^- is attacking on it. What is going to happen now? It is going to form this. It is going to attack here and once it is going to attack to the silicon here. Now this can come back and it can allow this cleavage of this bond and there is a triflate is a very good leaving group. So, now, the triflate is going to get out and then it is going to end up forming this corresponding benzyne. So, this is called a some sort of a Grob fragmentation.

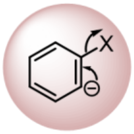
5. *Via* Grob fragmentation

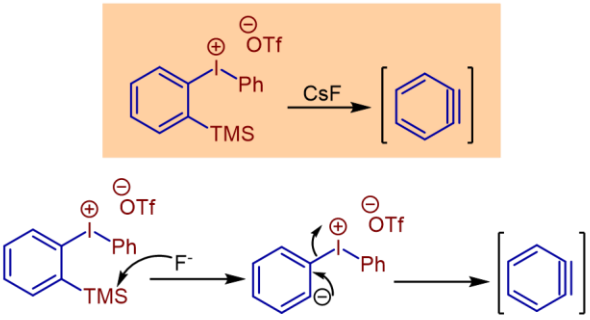




So, now you can see, we have started from this particular compound. Where you can see, this is a (trimethylsilyl phenyl)iodonium triflate. If you have iodonium triflate, what is happening? and you have a trimethylsilane here. Again, if you use this fluoride, I think I am going to also discuss these things in details when I talk about the silicon chemistry. So, there is a trimethyl group here. As the silicon having the vacant d orbital, the F^- going to attack on the silicon, and silicon fluorine bond is one of the stronger bond. Now it is going to form this penta-coordinated anionic complex and then, what is going to happen? It is going to break this bond and it is going to get out as a iodobenzene to form this corresponding benzene in the case of cesium fluoride.

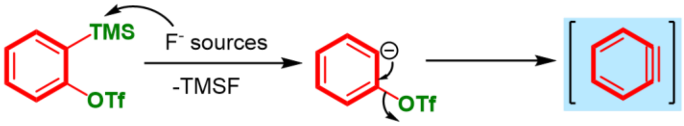
6. From phenyl(2-(trimethylsilyl)phenyl)iodonium triflates

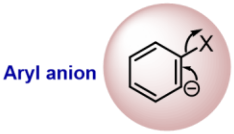




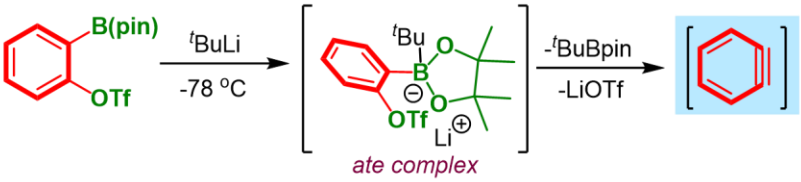
And there is another approach here. So, this is a very important method. So, it is a Kobayashi method for generation of aryne. So, there is one carbon having the TMS group and the next carbon is with a triflate. So, if you have triflate, the triflates are a very good leaving group. So, now, if the F^- is attacking on the TMS, as I mentioned in the previous slide. You can write as a negative charge here or write as a some sort of anion here, which can come back here and get rid of triflate to get to the corresponding anion. So, that means first fluorine going to attack to the TMS. Then, it is going to break this C-Si bond. You can write in this, something like in one sort or you can write this way in the stepwise manner that can generate the benzyne. So, this is a very important method used in lot of times for generation of benzyne. The other method using by hosoya. So, here you have a boronic ester instead of the silicon. borons are also electron deficient. So, if you have a F^-, it can attack to the boron. So, here, instead of F^-, you have *t*-butyl lithium. So, again, I think, the lithiums are a very good nucleophile. So, it can attack to the corresponding boron to form this boronate complex, which you can see here. So, we are going to discuss about the formation boronate complex in the classes, when I am going to talk about the boron. But generally, what you see, borons are trivalent, but if you increase the valence to tetravalent then, we generally call this type of complex as a boronate complex. So, from there, once is forming the boronate complex, this C-B bond become weaker. So, it can go into a break and you can write something like that very similar to the silicon going to form the benzyne and the triflate is going to come out.

7. Kobayashi's methods of aryne generation



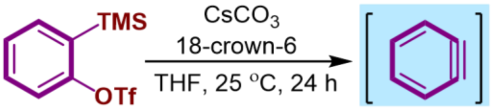


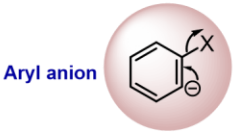
8. Hosoya's methods of aryne generation

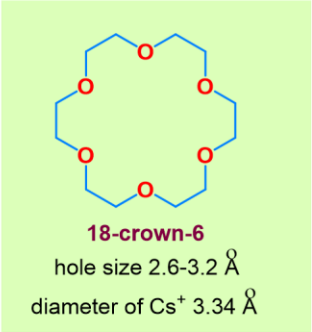


So, this is a another important approach. So, I think, this is a modification of the Kobayashi approach. Where you do not need to use the fluoride, using cesium carbonate and 18-crown-6, starting from this, the TMS and the triflate can able to form the benzyne. What is happening here? the Cs^+ is going to get into the 18-crown-6. and now, the carbonate which is there. So, the carbonate is going to attack to the TMS. Instead of the F^-, the carbonate can attack to the TMS and, once the carbonate is going to attack, you can see the nucleophile is attacking here, now it can form the benzyne and the triflate is going to get out to form the corresponding benzyne.

9. Fluoride source free aryne generation



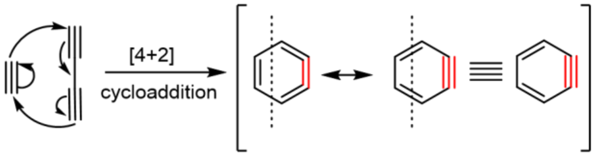


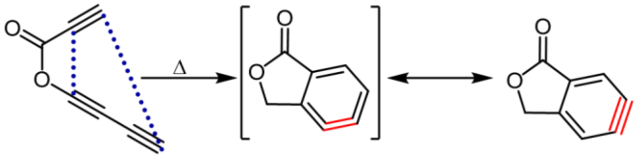


18-crown-6
hole size 2.6-3.2 Å
diameter of Cs^+ 3.34 Å

The other method of aryne generation is using the Hexadehydro Diels-Alder reaction. So, what is happening? if you see, there are 3 different alkyne. This can participate in the [4+2] cycloaddition and in the [4+2] cycloaddition, this can form this corresponding benzyne. You can think about the very same reaction here. You have the alkyne, you have alkyne. So, these 3 alkyne forming this cycloaddition, is a Hexadehydro Diels-Alder reaction, going to form the benzyne which can further take part in various transformations.

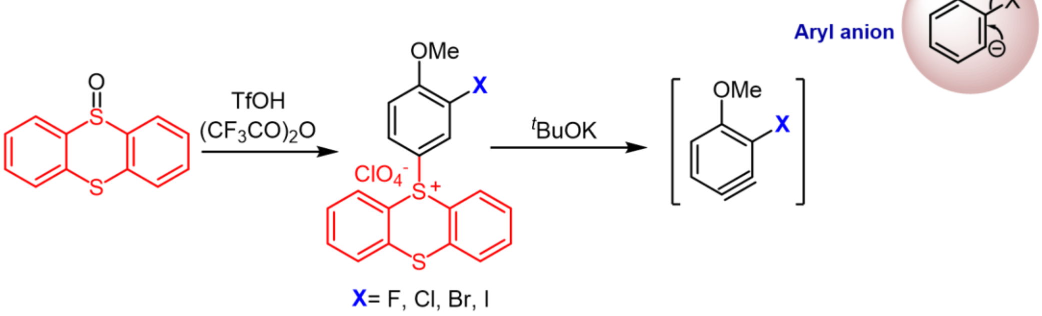
10. Using Hexadehydro Diels-Alder reaction





Another, important work here, so using the 5-arylthianthreniumyl perchlorate. So, this type of thianthrene molecule can act as a leaving group. So, these are thianthrene molecules. So, this thianthrene molecule can be synthesized starting from this compound using the trifluoroacetic acid and trifluoroacetic anhydride. If you take any type of aryl compound, it can go for some sort of Friedel-Crafts reaction and then it can form this type of compound, but the very important thing is that, these are very important leaving group. So, this can be used as an alternative to the halogens. So, now if you have a halogen in your molecule if you are using tert-butoxide. So, this has a better leaving group capacity. So, it can leave halogen there and at the same time forming a benzyne. So, you can think about the advantage of this reaction that it is leaving halogen, but it is taking this proton from here and, this is acting as a better leaving group to form this corresponding benzyne.

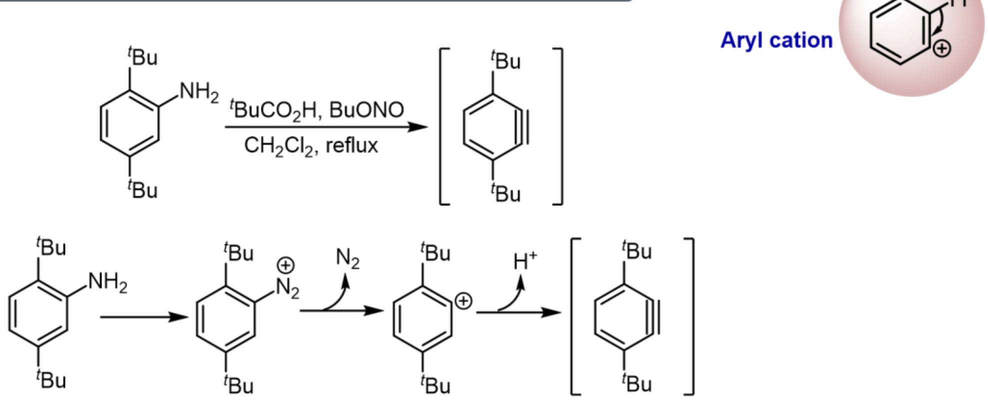
11. 5-Arylthianthreniumyl Perchlorates; a useful benzyne precursor



Thianthrene molecule act as a leaving group instead of halogen

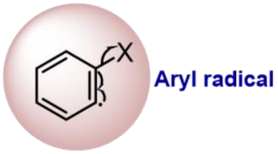
Then, there is an another method. If you start with this aniline here, where there is a tert-butyl group in the C-1 and in the C-4 carbon. First thing is formation of this diazonium salt and, then once you go for the reflux it is going to get rid of the N_2 and it is going to form the corresponding benzyne. So, for the mechanism is given, first there is a formation of this diazonium chloride in presence of the tert-butoxide in ^{t}BuONO. So, this is going to form the corresponding diazonium. Then, there will be N_2 going to get out and generates a carbocation. If you are using this corresponding acid then, there will be a counter anion. So, which can able to go for a proton abstraction to get to the corresponding benzyne.

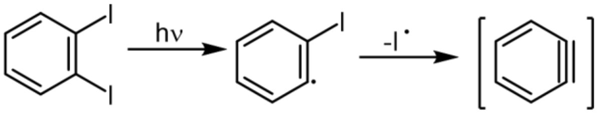
12. Decomposition of diazotized 2,3-di-^{t}butylaniline



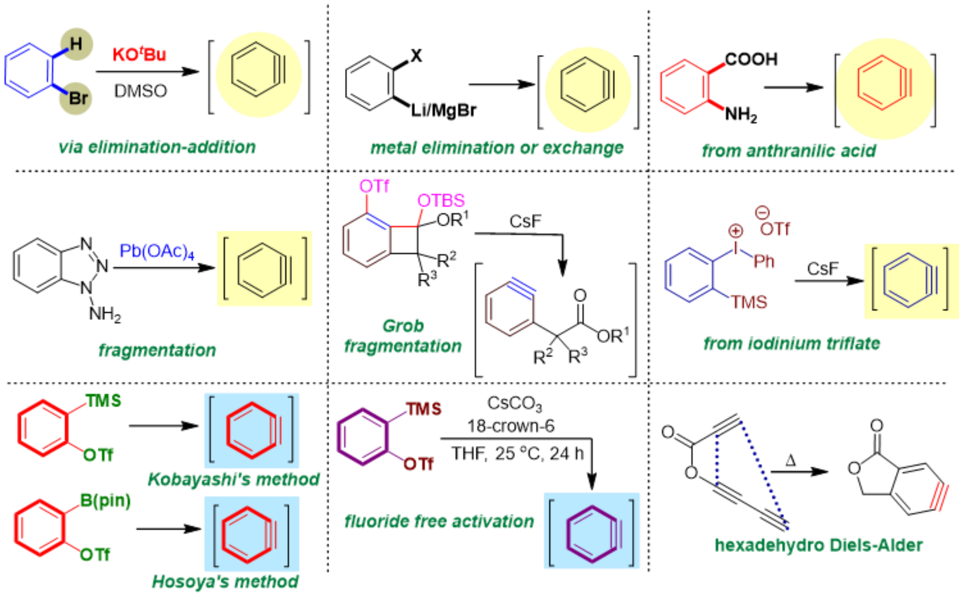
Then in as I mentioned that one of the other approach is the radical reaction under UV light. If you have 1,2-diiodobenzene, it can form the radical first we have already mentioned it. Now, it can form a bond. then the next thing, it can form a radical here. and then, both of the radical can go for a radical recombination to form this bond. So, what is going to happen? So, it is going to get rid of the two I•, which are going to form I_2.

13. Irradiation of 1,2-diiodobenzene

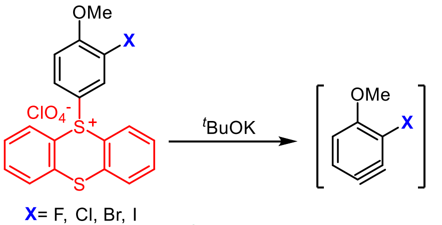




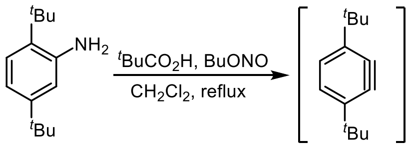
So, in the today's class, I am going to show you a summary that what are the different methods for the generation of arynes or benzyne. So, the first thing, I talk about via addition and elimination. So, you can see here, first thing what is happening? There is elimination happening. I think you can see, there is an elimination of this bromine. So, there is a base which is going to take this proton and form anion and then, this can come back and get rid of this bromine and, then there is the metal halogen exchange. So, if you have a metal halogen exchange. If you start with a dibromo compound and if you give some sort of Grignard some sort of magnesium, it can form the corresponding Grignard reagent. If you go for metal halogen exchange will generate the corresponding lithium now. It can form this benzyne. Starting from anthranilic acid, I talk about the formation of this zwitterion, you have seen that. Then the fragmentation chemistry, we talk about the generation of benzyne from the iodonium triflate, again you have seen the CsF going to attack on the TMS as I mentioned and then there will be cleavage of this C-Si bond and then there will be a elimination of this IPh to form the benzyne. And then, I talk about the fluoride free activation and then, this hexadehydro Diels-Alder reaction.



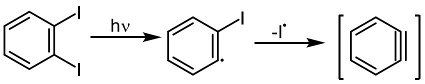
I talk about some of other method starting from these important compounds here which has a better leaving capacity compared to the halides. And again, from this starting from this iodobenzene.



from 5-arylthianthreniumyl perchlorates



from diazotized 2,3-di-^{t}butylaniline



from 1,2-diiodobenzene

So, here are the references for this particular topic and again thank you for coming to the class and thank you so much and I am going to see you guys in the next class.