Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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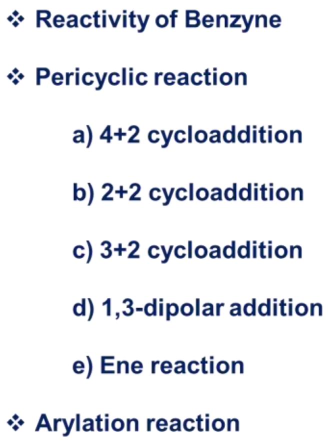
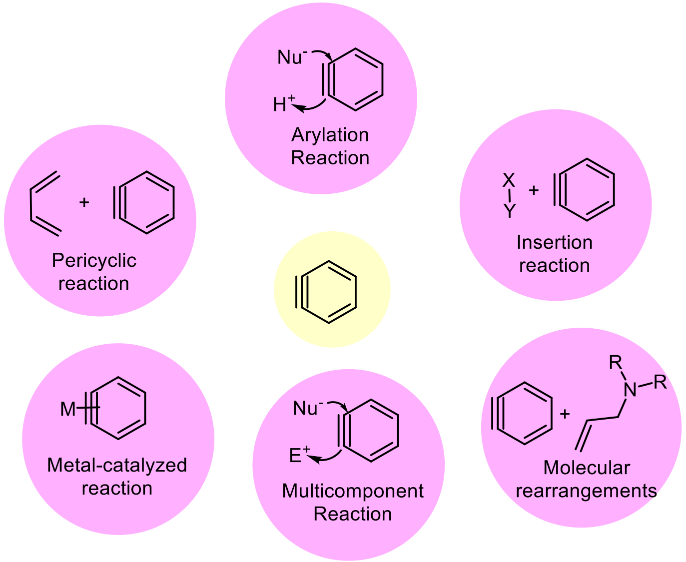
Lecture 29: Benzyne (Continued)

Welcome back to this NPTEL online certification course in the molecular arrangement and reactive intermediates. In the last class, I started talking about benzyne and I have shown you that there are several methods, of how you can make benzyne. In today's class, my main focus is what are the different reactions about benzyne. We are going to learn about different type of reaction which was done using benzyne. So, I am going to show you different type of pericyclic reaction that will be see the major type of reaction you are going to see using benzyne. And then, there are some sort of arylation reaction. I think, I already talked about some of the reaction, when I was starting with the benzyne that if you use some sort of a phenyl lithium, which is actually used for the formation of benzyne. At the same time, it can act as a nucleophile. So, let us start with first with the pericyclic reaction. So, I am going to talk about the different reaction about benzyne. So, I think as I mentioned in the today's class my main focus will be the pericyclic reaction. I am going to talk about some of the [4+2] and [2+2] and then, some of the ene reaction and, [3+2] reaction. And then, there will be other reaction is the arylation reaction.



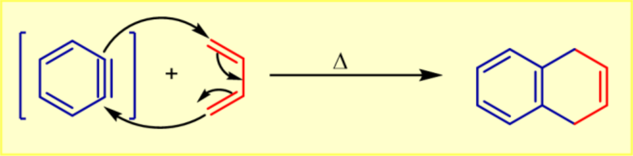
- **Reactivity of Benzyne**
- **Pericyclic reaction**
  - **a) 4+2 cycloaddition**
  - **b) 2+2 cycloaddition**
  - **c) 3+2 cycloaddition**
  - **d) 1,3-dipolar addition**
  - **e) Ene reaction**
- **Arylation reaction**

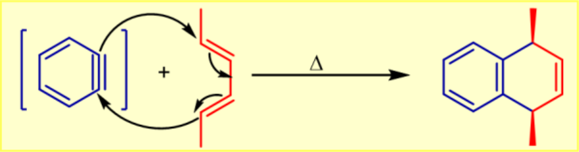
I am going to talk about some of the reaction today and some of the reaction in the next class. There will be an insertion reaction.I am going to talk about some of the molecular rearrangement using benzyne, multi-component reaction and, very briefly about the transition-metal catalyst reaction.



So, let us start with the pericyclic reaction. We all know about the [4+2] cycloaddition and we have already learned this in the pericyclic reaction course. So, here, what is going to happen? If you have remember the [4+2] cycloaddition. So, there will be a diene and, there will be a dienophile. If you remember, we always mention that the dienophile has a electron withdrawing group, and then, the diene will have electron donating group. Then, we also talk about if you remember that this cannot be always a double bond, that can be also a triple bond. If you remember, we always talk about this type of things. When you talk about it could be H or it could be R or R'. So, again, I think we already talk about this type of reaction in the pericyclic course. So, here what is going to act? So, that your benzyne is going to act as a dienophile. So, now, if you take a diene and heat up, it is going to participate in a Diels-Alder reaction, a [4+2] cycloaddition reaction to form this product. Again, I think, if you see the major difference here what is happening in every single product your one benzene is going to get attached. If you remember in case of the [4+2] cycloaddition reaction, we form a corresponding cyclohexane with a cyclohexene. Here, what is going to happen? With the cyclohexene you see a benzene is going to get attached. Again, all the rule what you have learned for the [4+2] cycloaddition reaction will be remain same that once you have a substitution here. So, here, you have a methyl and, if you remember once you talk about the [4+2], they come in a facial approach of both the dienophile and diene. So, both the groups in the diene which are substituted will be up.

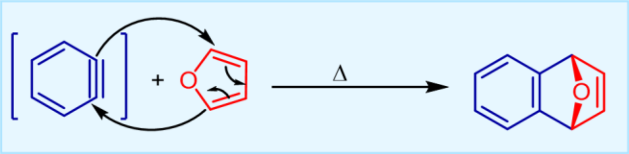
4+2 cycloaddition reaction

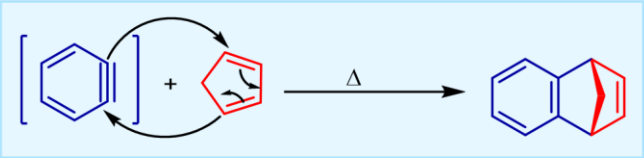




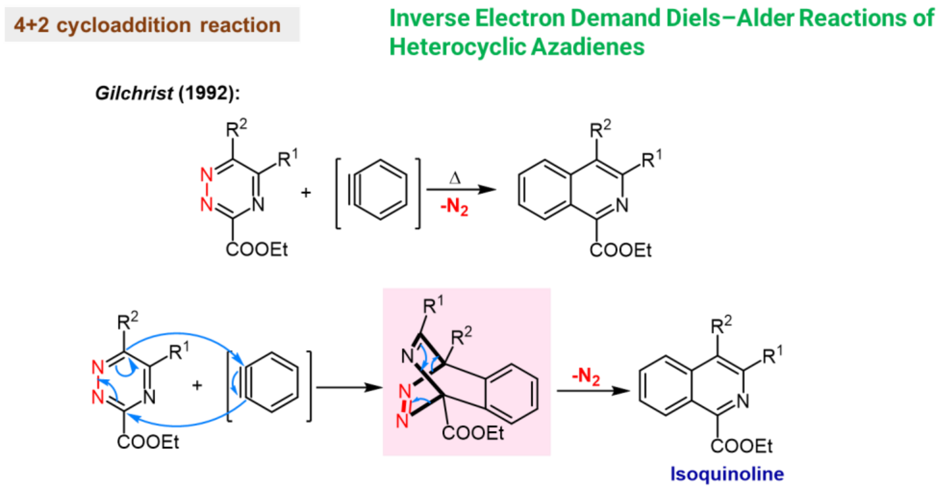
Again, this reaction will be more reactive, if you have some sort of a diene or if you have a ring like furan or the cyclopentadiene, what is going to happen? So, in case of the cyclopentadiene, if it is a ring form versus a chain form, like open form versus a closed form. The closed form will be much more reactive because you can see, this is already in the cisoid conformation. If you have 1, 3 diene, then in that case, there has to be rotation to make sure that they can be in the cisoid conformation for the reaction to happen, but here this is going to happen. So, now, it can form this [4+2] product. Here, also if you have a furan, it can also go through the [4+2] cycloaddition to get to this corresponding product.

4+2 cycloaddition reaction

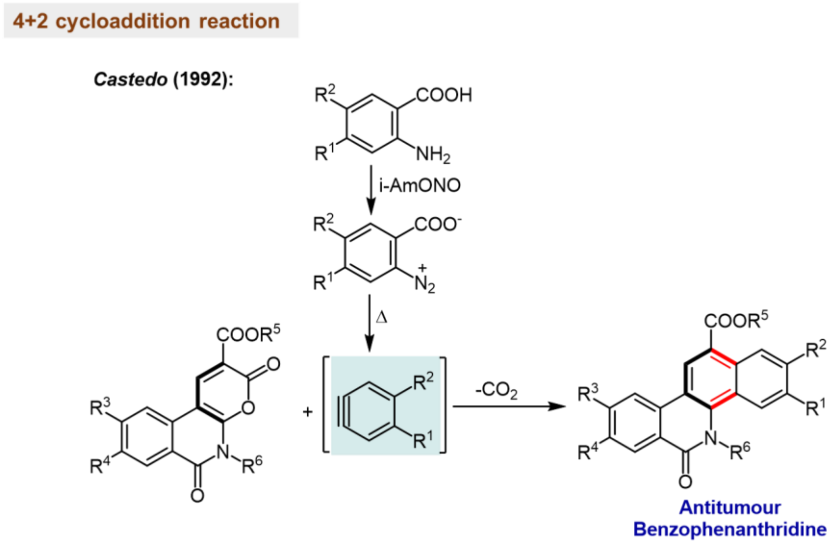




So, I think, if you have learned in the [4+2] cycloaddition, there are two different types. We talk about the normal [4+2] cycloaddition, one we talk about a inverse electron demand Diels-Alder reaction. I think, we also talk about the difference that once you talk about the normal Diels-Alder reaction versus the inverse electron demand Diels-Alder reaction. The one of the difference you have seen the type of the functional group or the nature of the diene and dienophile. I think, in case of the normal, we talk about that, here will be electron donating group, some sort of electron donating group will be here and there will be electron withdrawing group. But, in case of inverse electron demand you will see there will be electron withdrawing group attached here. It could be attached in the terminal position or you will see there could be a nitrogen in this position which can be pulling electron density like some sort of imine or you will see in some case instead of electron withdrawing group you might see some case of carbon group here and now you will have a electron donating group here. So this is an inverse electron demand. Now, if you think about a benzyne, as a some sort of cation and anion that means, it can act as a dienophile for both type of reaction for a normal Diels-Alder reaction as well as for an inverse electron demand Diels-Alder reaction . I think this type of reaction already taught you in the inverse electron demand reaction. What is happening? Benzyne is acting as a dienophile. So, once the benzene acting as a dienophile, first [4+2] cycloaddition is going to form this compound. But, this is not to stay there because this is going to release N_2. So, you can see this arrow push to form this $N \equiv N$. So, that will remove the N_2. Then, this bond going to form the new bond going to form and at the end, you end up generating a isoquinoline.

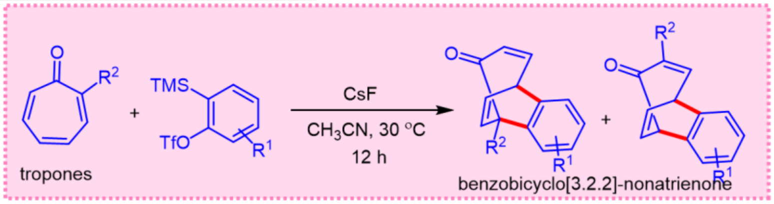


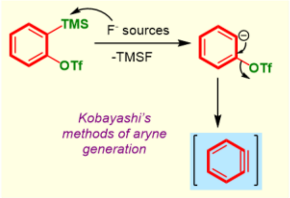
There is another example here. I think we start from this compound and generated this N_2+ and COO- and then, what is going to happening? Now it is going to generate the corresponding benzyne. It is very similar this in this anthranilic acid scenario. So, if you have this anthranilic acid, it is generating this corresponding benzyne and now, it is participating in a Diels-Alder reaction. Again, you will see that in this particular cases, your diene also have electron withdrawing group. So, this can participate in a [4+2] cycloaddition and, then after that, there will be a release of CO_2. So, this part we will going to get out. So, this 4 carbon 1, 2, 3, 4 and then this benzene will have this 1, 2 carbon. So, now you can see that these 4 carbon here 1, 2, 3 and 4 and this will be the your 1 and this will be your 2 and then, the CO₂ getting out to form this corresponding product.

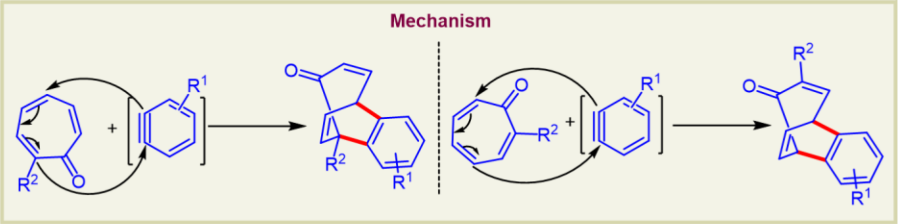


So, there is a another important reaction. starting from the tropones. So, the tropones can be also used in the Diels-Alder reaction. You can think about the tropones having this type of two double bonds in a cisoid form. So, that can participate in a Diels-Alder reaction to form this benzobicyclo[3.2.2]-nonatrienone structure. Sometimes people write this type of mechanism. But, you can also think about a some sort of a concerted way of forming this product or you think about there is a plus and minus then, this can attack here. This can push the electron density and attack here and form this product. or you can think about as I mentioned like a pericyclic reaction going through a concerted mechanism. But, if you think about this molecule, one of the important fact is there is two different set of diene. You can consider this is a one set of diene and this is other set of diene. So, the reaction can happen from the both side. So, you end up making both the products. And, we also know that about the formation of this benzyne from here. How the benzyne is forming? I think, this is a Kobayashi technique. I have already taught you in the first lecture that CsF is going to attack to the silicon, then it can go for elimination of this triflate to form this corresponding product.

4+2 cycloaddition reaction

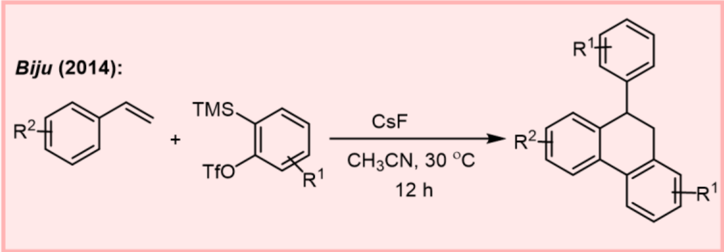


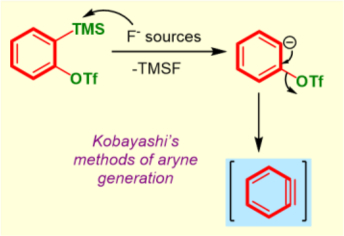




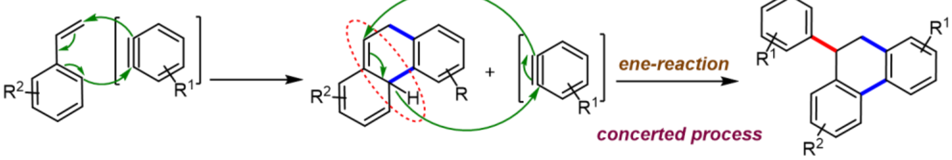
Professor Biju from IISC discovered this reaction. If you start with the corresponding styrene and again you are using this very similar type of benzyne which you are generating from the Kobayashi technique. Now they can take part in this type of [4+2] and then, there will be a ene-reaction happening which is a concerted process. So, this another molecule of the benzyne giving electron density here and this is I think you have learned in the ene-reaction, this hydrogen is going to find. So, if you think there is a enophile, generally if you have learned in ene reaction, we have taught you the carbonyl ene reaction where you have a carbonyl which can take the proton and then the other side is going to get attacked. So, the very similar thing happening here. Here, you have the benzyne. You can think about benzyne as a plus and minus, then you will get your answer and then, after the concentrated process it is forming this corresponding product.

4+2 cycloaddition reaction





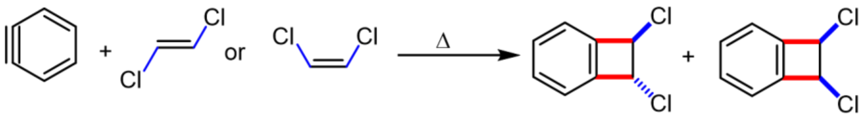
Proposed mechanism:



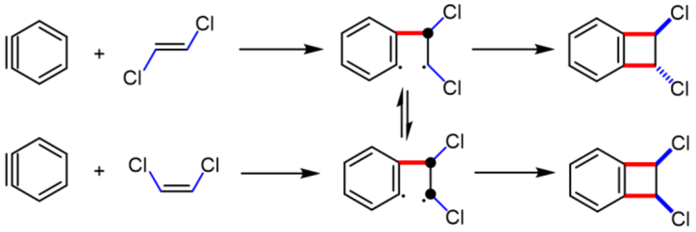
Benzyne, the other thing is, if the benzene can participate in a [2+2] cycloaddition, but the [2+2] cycloaddition reaction when it is happening using the cis or the trans they are giving. So, if you use this 1, 2 dichloroethane, if you use cis versus a trans, what is happening? you end up still getting the similar type of product selectivity. you still able to get the both cis and trans that means, the both syn and anti. So, this will be your syn and this will be your anti. So, using this, either using the trans or cis, you end up getting the mixture of both. So, now, the question comes what is happening here. So, this is going through some sort of a di radical formation. So, it is formation of the some sort of di-radical happening that is why once you have this di-radical. There is a chance of the bond rotation, as there is a chance of bond rotation is happening. So, if you think about the bond rotation is happening, that is why I think in this case because of the bond rotation you end up getting the mixture of products. So, both anti and syn product is going to form.

2+2 cycloaddition reaction

***Jones and Levin* (1969):**



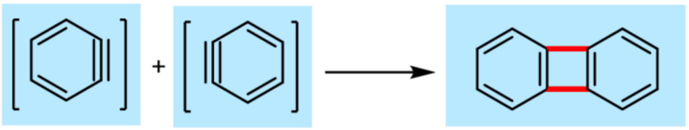
Why both the 1,2-dichloroethylene give mixture of stereoisomer?



So, the other thing is that if you are forming benzyne and if you have nothing else in the reaction, benzyne can dimerize themselves to form this biphenylene. So, it can form this biphenylene and it was already confirmed. If you are doing a some sort of a reaction using benzyne and you can see some sort of a by-product biphenylene is formed.

2+2 cycloaddition reaction

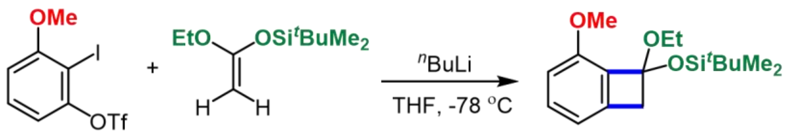
❖ A class of 2+2 cycloaddition is the formation of biphenylene.



Benzyne m/e 76 ***Biphenylene m/e 152***

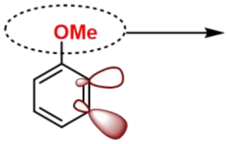
Other important reaction that if you have a benzyne, now the question comes if you are trying to do a [2+2] cycloaddition reaction using this. Some sort of a vinyl and OTMS group is here. So, what is going to happen in presence of the butyllithium. It is going to generate the corresponding the benzyne. Now, it is going to go for a metal halogen exchange to generate a anion here. It will be a minus. Now, the triflate is going to get out and it is going to generate the corresponding benzyne. So, now the question arises that where the nucleophile is going to get attacked because now if you have this part. You have a head and you have a tail. So, it is going to form the bond with head with head or will be head with tail. So, that is the question we have to answer because the product we are seeing, it is a head to head product formation.

2+2 cycloaddition reaction



Keisuke Suzuki

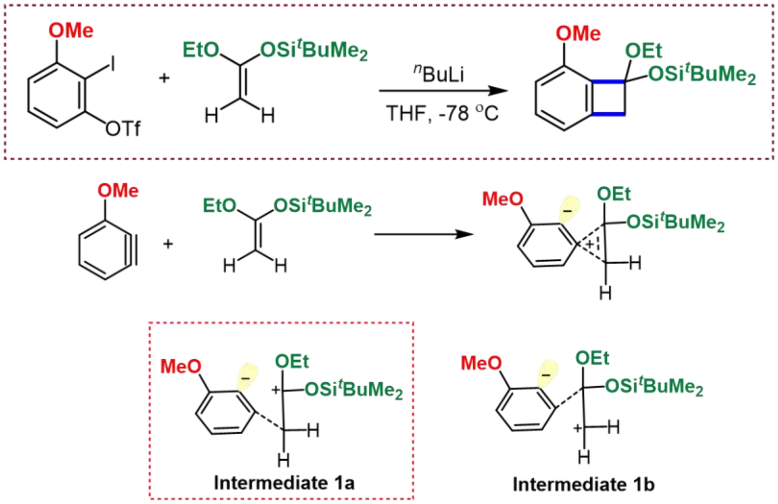
Regioselective reactions of substituted benzynes



Inductive electron withdrawing effect
of alkoxy group enhanced the
electrophilicity
at the rn-position relative to the o-
position

So, what is happening here? Now if you think about that we already taught you that if you have OMe group then it has a inductive effect. So, now if you think about a mechanism where you can either think about forming bond here. Now, you can think about when it is attacking it is going to prefer attacking in this position because now it will generate a minus in this position. So, it is going to generate a minus in this position. So, that is going to be stabilized. If you remember I told you that if you have a OME group, it has a -I effect. It is going to stabilize the anion in the ortho position. So, that is how now if you is attacking from this side you can see here, once it is forming then now this you are generating in a negative charge here which is going to attack here to form this corresponding product. The mechanism is shown here that as I mentioned first you form this benzyne and, now you can think about that there will be two possibility here. It can either go for intermediate like this. Where it can attack from here or it can form some sort of intermediate like. You can think about that this intermediate can be written in the two different ways. You can write a positive charge. So, of course, there will be a negative charge in the ortho position that is confirmed. Now, the question you can write a intermediate where there will be positive charge in this position that means what I was trying to show you that it is going to attack. We already know that if you have this type of; with the silicon and R then, this we already know that it is a some sort of a TMS enol ether which is going to take part in a reaction through this. So that means, if you think about intermediate A which will be much more better stabilized because you are generating a positive charge next to oxygen. So, it is going through this intermediate and, it is going to form this product.

2+2 cycloaddition reaction

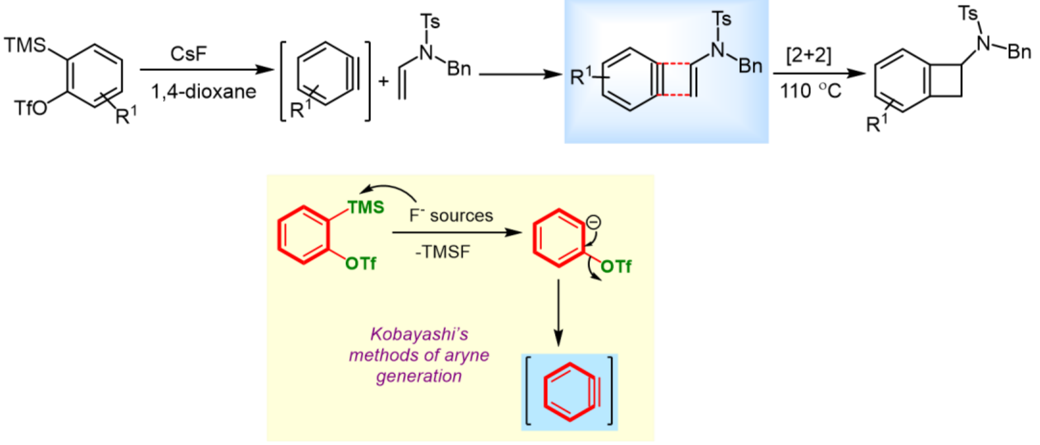


Keisuke Suzuki

Then there is another important [2+2] reaction again. What we are saying here that after the the benzene formation from the Kobayashi method, you have a some sort of enamine. Again if you remember the reactivity of enamine, we know the reactivity of enamine that it is going to react with something like this. It will going to generate this minus here which going to add to this imine and going to form this corresponding product. So, I think, I can write it down here. Attacking here and forming the corresponding and you have a R¹ here of course, forming the corresponding product.

2+2 cycloaddition reaction

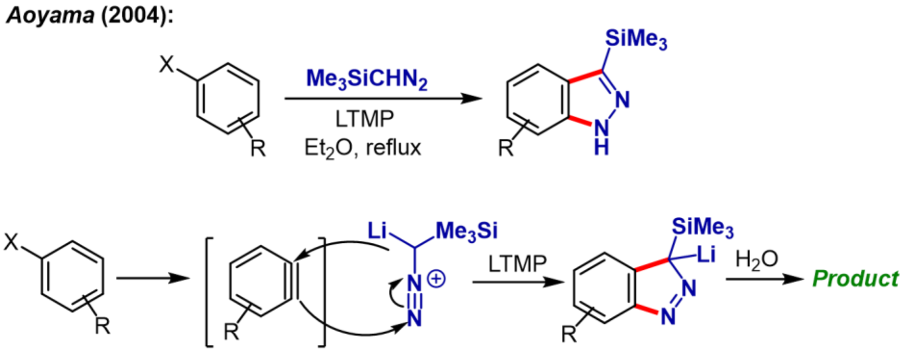
***Hsung* (2009)**



Again, there is another method of [3+2] cycloaddition. So, starting from here using the benzyne and if you use this TMS diazomethane it is going to form this product here.

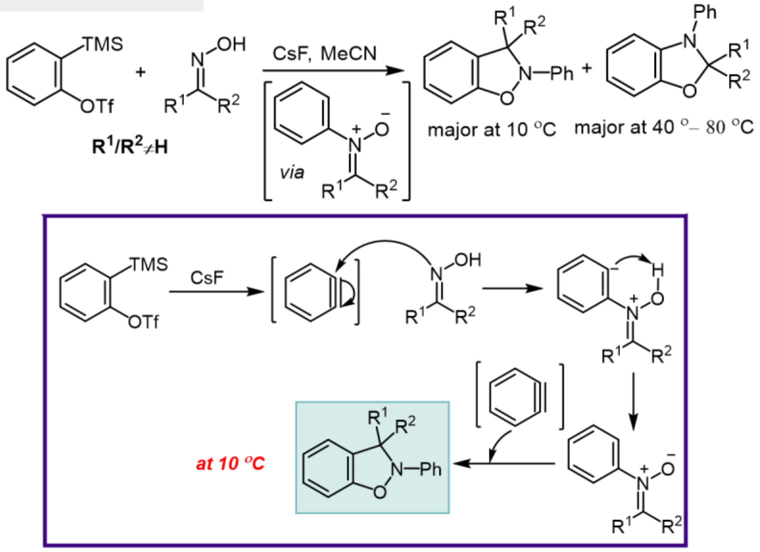
Let me try to understand what is happening here. First thing is that if you have this LTMP, if you don't know what is the structure of LTMP, I am going to show you. This is a tetra methyl here and there is a lithium on the nitrogen. So, it is going to look like something. Something means you have some sort of a hindered base here that means it can only go for a proton abstraction. So, it is going to act as a base not as a nucleophile. So, if you act as a base, what is going to happen? It is going to abstract the proton from here. It is a very strong base. Then, what is going to happen? It is going to form a benzyne and now this corresponding lithium which is there, because this LTMP can also abstract proton from this. So, this CH proton in the Me_3SiCHN_2, this proton is going to get abstracted. So LTMP is going to get form a lithium which is going to attack to the benzyne and now it is going to form this in negative here, which is going to come back and attack in the nitrogen to neutralize the charge to form this compound and, again you have a LTMP already in the reaction. So, that can now going to abstract this proton which was there to form this lithium which can now form this C-N bond and form the N- here. So, you will see there is a silicon here, TMS group and a minus which is going to take a proton to get to the corresponding product.

3+2 cycloaddition reaction



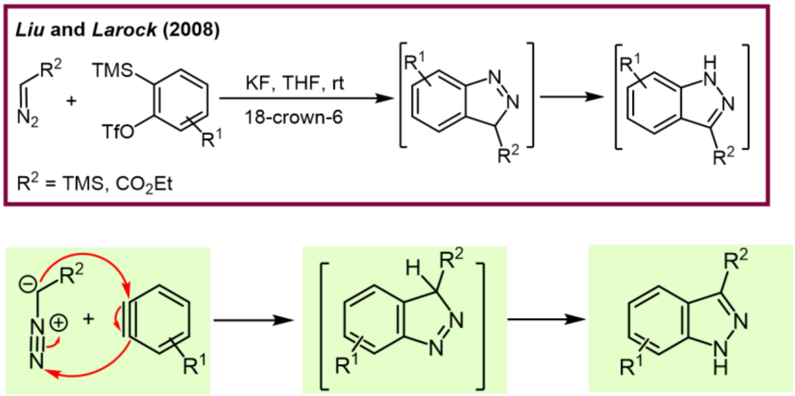
So, now, I am going to talk about this [3+2] cycloaddition reaction. Here you can see. Starting from this corresponding the TMS and triflate, we can generate this corresponding benzyne using the Kobayashi method. Now, you have this compound here. Which can be synthesized from the corresponding carbonyl and the hydroxylamine. and, once you have this compound what is going to happen? This is going to first attack to the corresponding benzene because the nitrogen have a lone pair, it is going to attack to the benzene and generate this compound. This minus can take this proton to form this sort of intermediate and now you can think about once you are forming this, this is again becoming a 1,3 dipole. You can write them 1 2 3. So, this 1,3 dipole can take another benzene and then going to form this product. So, it is happening there, first there is a [3+2] cycloaddition, first there is a attack of this nitrogen then there is a [3+2] cycloaddition happening in this test to get to this product.

3+2 cycloaddition reaction



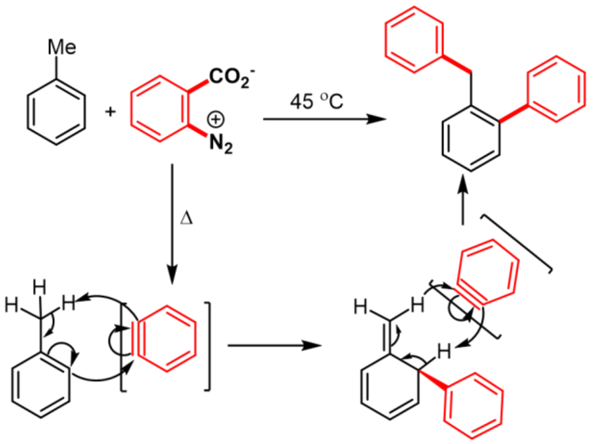
Again, there is another important method here, again using this different type of diazomethane. So, what is happening again? If you remember that if you have a diazomethane, we always think about there is a negative charge. This can attack here, to the double bond and, then what is going to happen this can come back and add here. It can form this and, then further what is going to happen? There is this proton can be abstracted to form this corresponding N-H. It will be N- and, it is going to take proton to form the corresponding N-H.

1,3-dipolar cycloaddition reaction

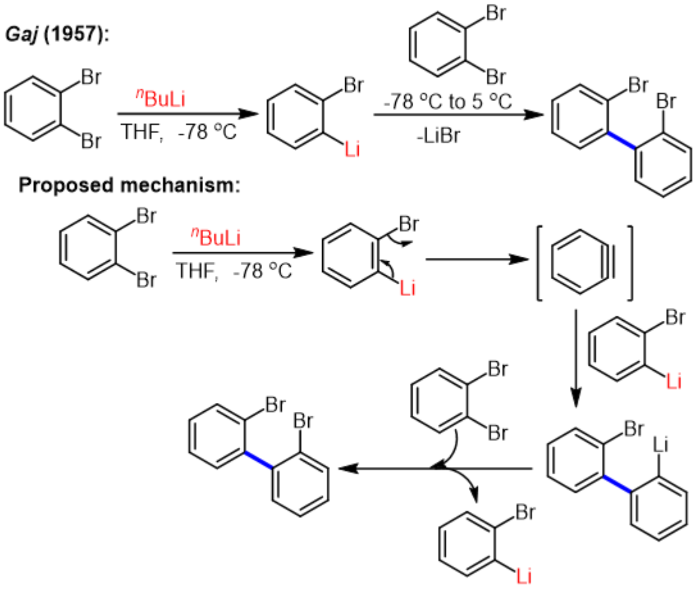


So, there is a example here. The double benzyne ene reaction is happenning. First there is a formation of benzyne from this corresponding Zwitterionic, starting from the anthranilic acid. Once the benzyne formation is happening, what is happening here? So, first thing is, it can take this methyl proton here. From the benzyne have a, if you think about a plus and minus. then, it can take this proton here through very similar to the corresponding ene reaction. Now, it can take the positive part and after that what is going to happen? In this test there is another benzene can take part to participate in another round of ene reaction here. So, it can act as a enophile to form this corresponding product here, after the two successive ene reaction. So, I talk about some of the pericyclic reaction.

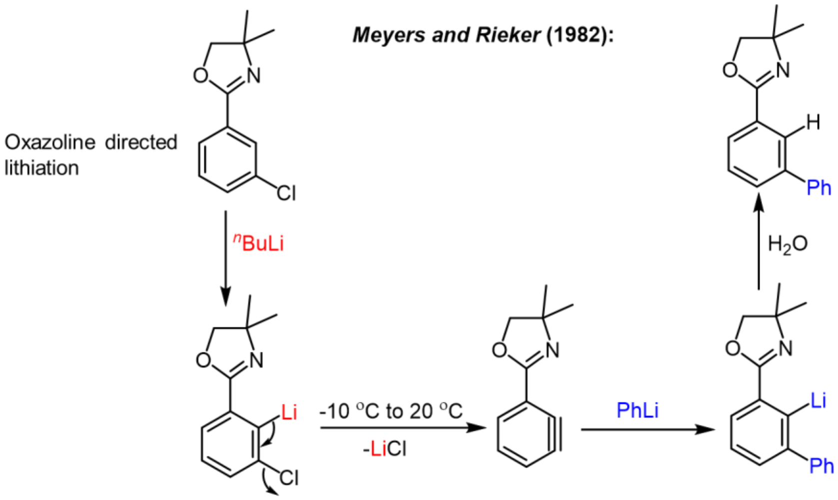
Double benzyne ene reaction



Now, I am going to talk about the arylation reaction. So, starting from this 1,2-dibromobenzene, if you use a butyllithium, it is going to go for the metal halogen exchange to generate the corresponding lithium here and, now it can able to react with another compound. So, I think, this can form a benzyne and this can attack here you have seen in the mechanism. First thing the metal halogen exchange, formation of the benzyne then, this corresponding lithium which is formed in the reaction going to attack to the benzyne to generate a corresponding lithium which can take a bromine from the corresponding dibromide to get to the corresponding product.

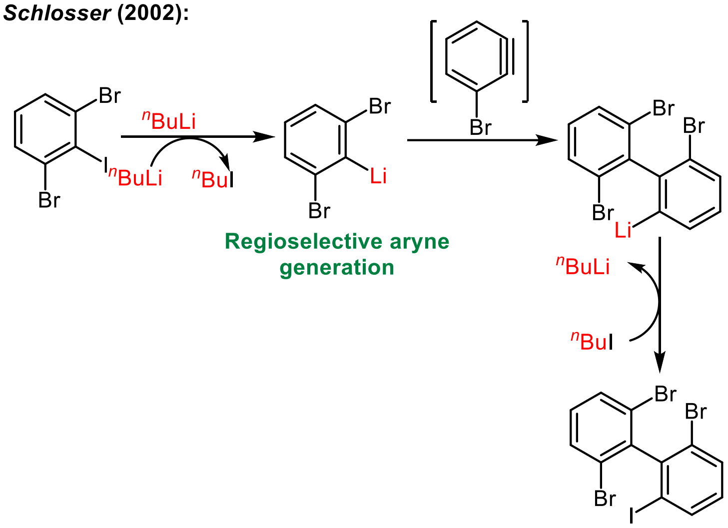


Then there is a another reaction, where the oxazoline can act as a directing group. I think, I am going to talk about this about the directing lithiation when I am going to talk about the organo lithium compound. Using a directed lithiation, you can able to form this corresponding lithium here by removing this C-H bond. It can form this corresponding lithium. Now, what is going to happen? It can get rid of the corresponding chlorine to form this benzene. So here, if you take a phenyl lithium in the reaction, the phenyl can attack here and this corresponding lithium formation is happening here because this can stabilize this corresponding negative charge formation happening in the ortho position, which can further get protonated to this compound with a very high regioselectivity.



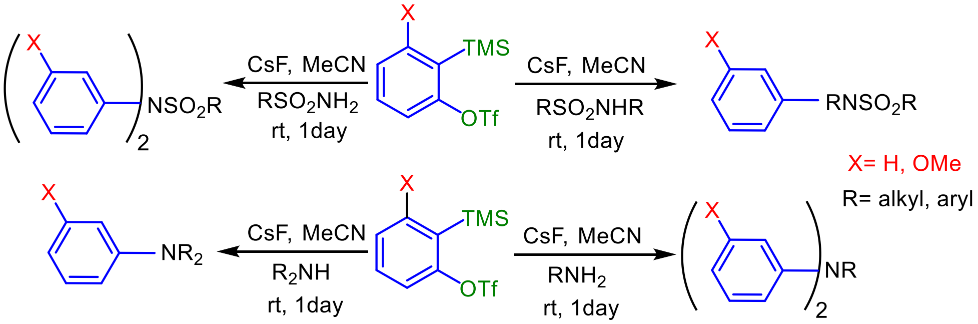
Then, you can see very similar reaction here. You have the bromo and bromo and, a iodo. So, first the weaker the C-I bond is going to get cleaved in presence of butyllithium. So, metal halogen exchange then after that what is going to happen? it is going to get rid of one of the bromine to form this corresponding aryne. Now, what is going to happen once you form the aryne, you already have this corresponding lithium in the reaction. So, this lithium can act as a nucleophile and going to attack here. You can see here, this is going to attack here to form this sort of a intermediate species which is going to take the the iodine from the butyl iodide. If you add a butyl iodide, this lithium can take iodo from there to form this product. Because you can see what is happening in the reaction medium? Already you have generating a butyl iodide. Because you have a butyllithium here. First thing, you have a butyllithium, you have this n-butyl iodide and, then that n-butyl iodide was there. So, there you can see that again this can getting exchange here, get to this corresponding product.

***Schlosser* (2002):**



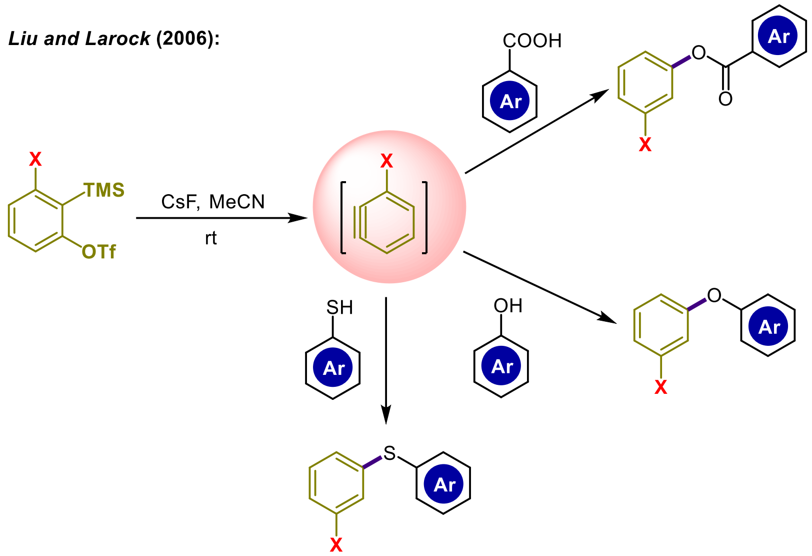
The other important technique is that if you have these corresponding benzyne, if you have generate from the Kobayashi technique. then, if you add a corresponding nucleophile, suppose if you have a benzyne like that. Now we are talking about a nucleophile suppose you think about amine as a nucleophile. So, if it is a primary amine then what is going to happen? This is going to attack here. Once it is going to attack if you remember it is going to form some sort of anion here, now this can take this proton from here. So, after you form the product, what is your product? In the product also you have another H here and N-R. So, this is not going to stop here. So, if you take a primary amine, this can take for another reaction with a benzyne. You can take another benzyne and do very similar type of reaction. So, at the end, what is happening? you end up forming a tertiary amine and you have two aryl ring here. So, you can see, here if you started with this type of primary amine, you end up making a a product where you have two different aryl ring which is attached. You are making a corresponding tertiary amine.

***Liu* and *Larock* (2003)**



And, if you started with the secondary amine then, there will be one benzene going to insert to get to the corresponding product. Again very similar thing here. You have a secondary amine here and you end up getting one benzene inserted. If your primary amine here, you will get two benzyne getting inserted. So, you end up making it corresponding tertiary amine.

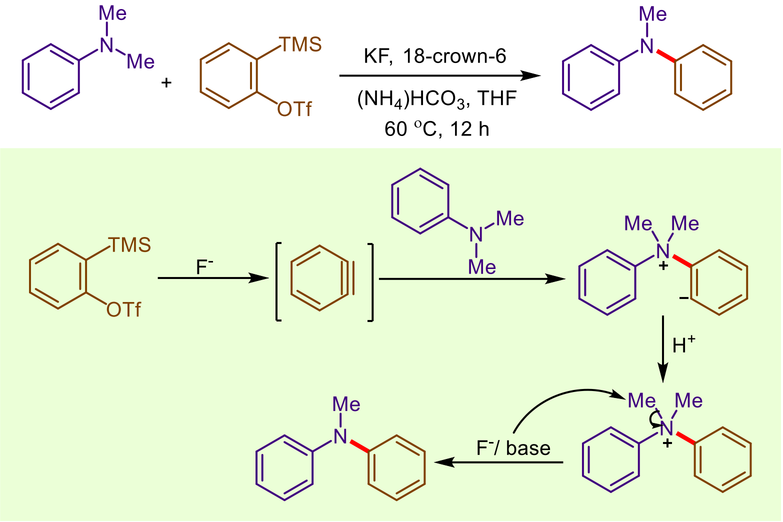
Now, the question comes what about other nucleophile, what about thiol or phenol or the carboxylic acid. Again in every cases what is going to happen? This nucleophile with the H. So, the nucleophile going to get attack here. So, once the nucleophile going to get attack, if you think about nucleophile having H, then the nucleophile going to get attack here, there will be minus which will take the proton. So if you have a thiol, then you end up making this product. So there will be S with aryl. If you have a phenol, then the oxygen going to get attack, then finally it will this, this proton going to transfer to that ring to form this product. If you have a corresponding carboxylic acid, what is going to happen? Now you have this oxygen going to attack here and generate this minus which will be taken by the proton.



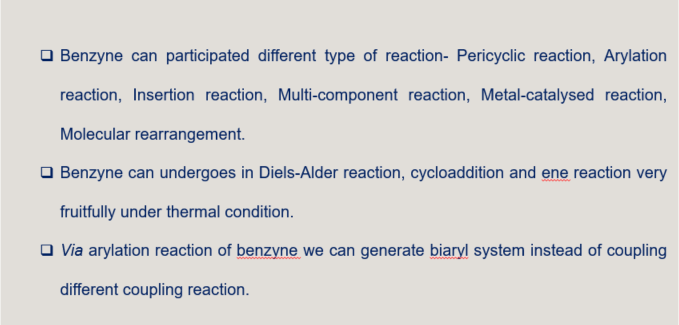
***Liu and Larock* (2006):**

Again the Biju group, so they work in the benzyne chemistry a lot. They have published this in the recent work that if you use this reaction with N,N-dimethyl aniline. What is happening here? If you use N,N-dimethyl aniline again, still you are seeing a product here that means you are one of the methyl is getting out and you are introducing one aryl thing here. So, they have generated the benzyne from the corresponding the TMS triflate using the method which was developed by the Kobayashi group using KF and 18-crown-6. So, here after the benzene formation, it is happening that the nitrogen has this lone pair, it can attack here and form this type of intermediate species which can get a proton. So, there is a H+, it can able to get here. Now you have this fluoride. So, if you have a fluoride that can or if a base. So, if a base or fluoride that can attack here take this methyl from this ammonium compound and then it can cleave this C-N bond to get to this product.

***Biju* (2013)**



So, in this particular part, I have talked about the different type of reaction using benzyne. So, I talked, I started with the [4+2] cycloaddition. Then, I told you in most of the cases the benzyne is acting as a dienophile. So, now if you take a diene it will going to participate in [4+2] and all the rules you have learned in the [4+2] still remain same. I talk about some of the ene reaction, some of the [2+2] cycloaddition, [3+2] cycloaddition and again I think in the future slide, I am going to talk about more about the arylation and also about the insertion reaction.



- Benzyne can participated different type of reaction- Pericyclic reaction, Arylation reaction, Insertion reaction, Multi-component reaction, Metal-catalysed reaction, Molecular rearrangement.
- Benzyne can undergoes in Diels-Alder reaction, cycloaddition and ene reaction very fruitfully under thermal condition.
- *Via* arylation reaction of benzyne we can generate biaryl system instead of coupling different coupling reaction.

And the first lecture also, I have shown some references. So, please go through this reference. So, there is a very important books by Biju. So, you can go through this, modern aryne chemistry. This is a very nice book to cover the chemistry of aryne. Again, thank you for coming to the class and I am going to see you guys in the next class.