Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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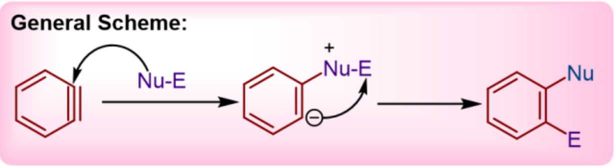
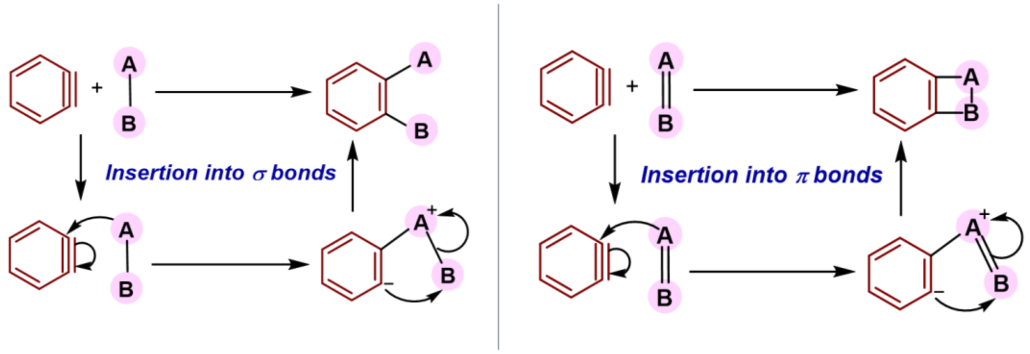
Lecture 30: Benzyne

Welcome back to this NPTEL online certification course in “reactive intermediate and molecular rearrangement”. So, in the last two classes, I was talking about benzyne. So, in the first class, I talked about the different methods by which you can generate benzyne. In the second class, I was talking about the different reactions of benzyne. If you form a benzyne then if you use a diene, it can participate in a Diels-Alder reaction. Then there are [3+2] cycloaddition, and there are some of the [2+2] cycloaddition reactions.

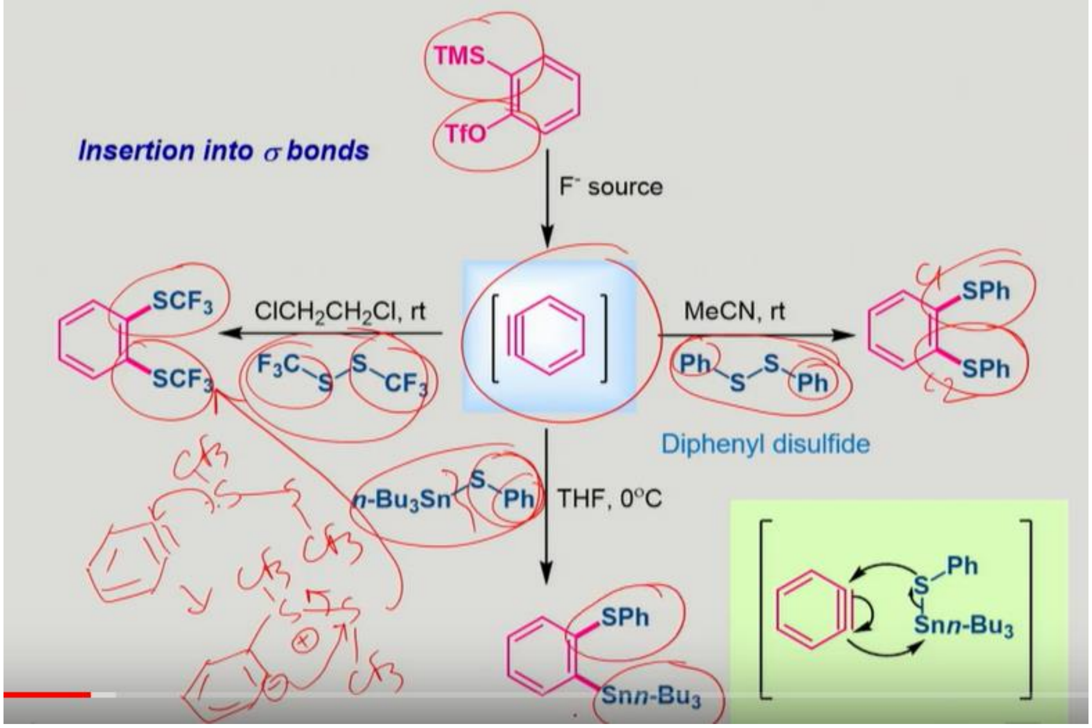
So, in today's class, we are going to learn some other reactions using benzyne. So, we are going to start with the insertion reaction, which is a very important reaction we will see several times in the GATE and JAM examinations. Then, we are also going to discuss some of the molecular rearrangements. I think some of the molecular rearrangements you have already learned in the previous classes in the case of carbocation or carbanion. Again you are going to see here, that if you have a benzyne in the reaction then how is this reaction going to happen? And then we are going to talk about the multicomponent reaction. Multicomponent reaction means one component will be benzyne and there will be two or three other components going to form a complex product.





So, let's start with the insertion reaction. So, in the first part of the insertion reaction, there are two different types we can talk about, first if see this A and B The bond between A and B has to be weak so that if one of them A or B could be a nucleophile, then it can attack the benzyne to generate this type of carbanion here. Now, this carbanion can attack B, followed by the cleavage of this A-B bond. In the end part A is coming to this carbon and part B is coming here. So, at the end, you are making 1,2-disubstituted benzene. So, this is a very important method and then there is another class if A and B have a π-bond. Again if one of them is nucleophilic, then it can attack the benzyne to generate this carbanion here. That carbanion can attack B then this charge goes back to neutralize the charge on A to generate this type of compound. We are going to discuss each of these different classes.

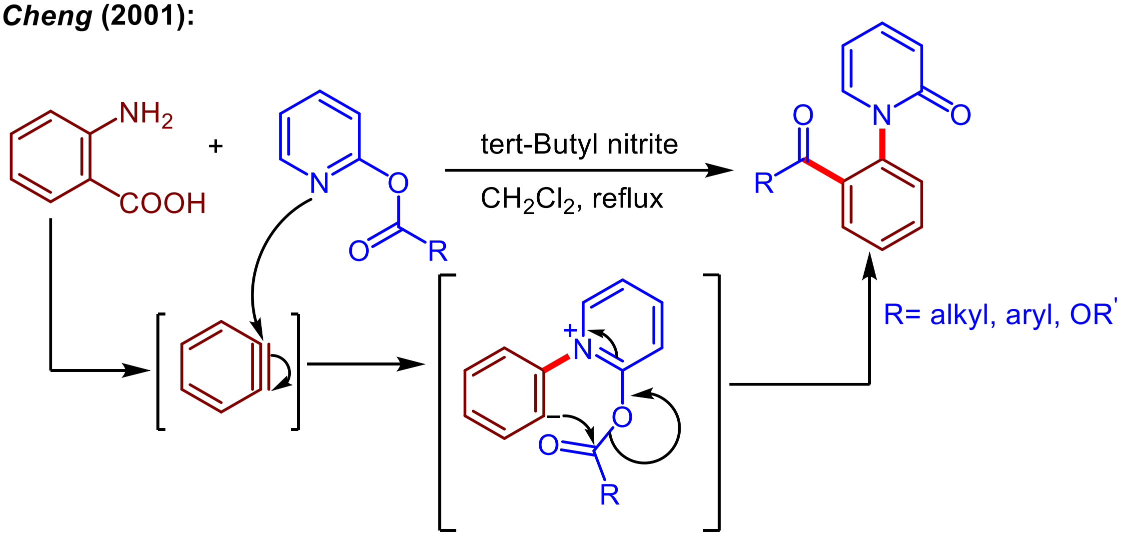
So, the first reaction you can see here, first we are generating benzyne, again you have this OTf and TMS the Kobayashi method I have already discussed in the beginning classes. Using a fluoride source, it could be a CsF or KF you have seen the generation of benzyne. Now if you treat with this particular type of compound, some sort of disulfide. If you treat this disulfide compound with a CF_3 group here these SCF_3 groups are coming to C1 and C2 position. We have already talked about this type of mechanism in the previous slide. I am still trying to show you one more time that if you have this SCF_3, sulfur is attacking as a nucleophile. Then it is generating a positive charge here, there is an anion here. So, this can attack the sulfur, there is a cleavage of the S-S bond to give the charge back and that can end up giving this particular product. Again, if you have diphenyl disulfide, two phenyl groups here can also be used to make this particular product. It is going to insert the two SPh groups in C1 and C2. So, you have C1 and C2 SPh groups. Now, if you have a scenario



here, where you have tributyltin on one side and SPh on the other side. Again the tin and the sulfur bond is the weak bond. So, tributyltin and SPh will be on these two carbons through the cleavage of this bond as you can see in the mechanism.

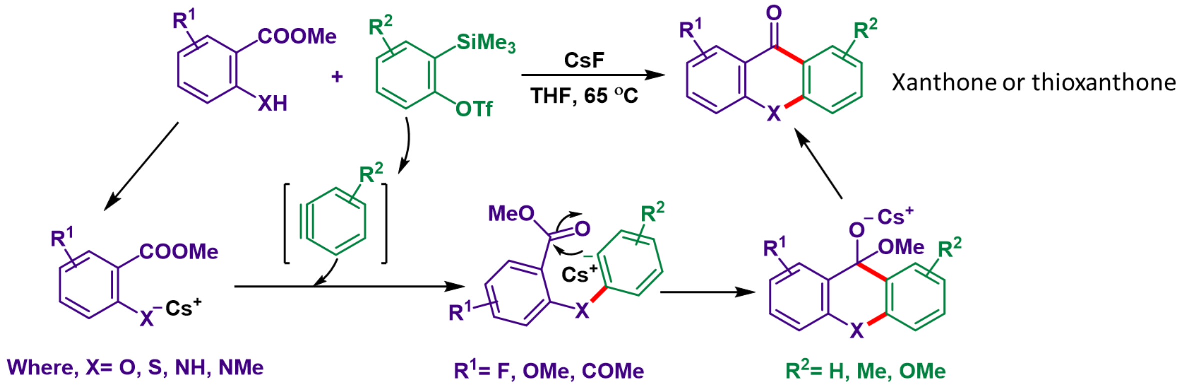
Then there is another interesting reaction here. We are starting with this anthranilic acid; we have already learned that if we use tert-butyl nitrite it is going to generate the corresponding diazonium salt here. So, it is going to form a zwitterion, and from there, it is going to get rid of N_2. So, it is going to generate this benzyne. Now once the benzyne was treated with this particular compound here you can see the pyridine nitrogen is nucleophilic. So, it is going to attack here to generate this carbanion here. So, this nitrogen already has a positive charge So, this carbanion can attack the carbonyl, once it is attacking it is going to form O^-. Finally, it is going to come back. You are cleaving this C-O bond. So in the end you are forming this type of compound. So these two parts are getting chopped here and this part is getting to this carbon. If you say C1 and C2 then the rest of the part the RCO, it could be acetyl or it could be benzoyl depending on the groups you have are going to go to the C2 carbon. So, again both of these fragments are getting inserted into the benzyne ring.

***Cheng* (2001):**



Another example here, we are not starting with anthranilic acid, but here you can see there is an X-H it could be sulfur, NH or it could be oxygen. Then you have a benzyne source, you have a trimethyl silane, and the OTf group. In the presence of cesium fluoride, the F^- going to attack the silicon to generate a carbanion and is going to get rid of the OTf to form the benzyne. Now, once you have cesium fluoride that can able to abstract this proton from the X-H to generate the X- and Cs+. Now the X- is going to attack the benzyne to generate a carbanion. So, that is going to attack this ester. Finally, it will generate this O-, Cs+, and

***Zhao and Larock* (2005):**



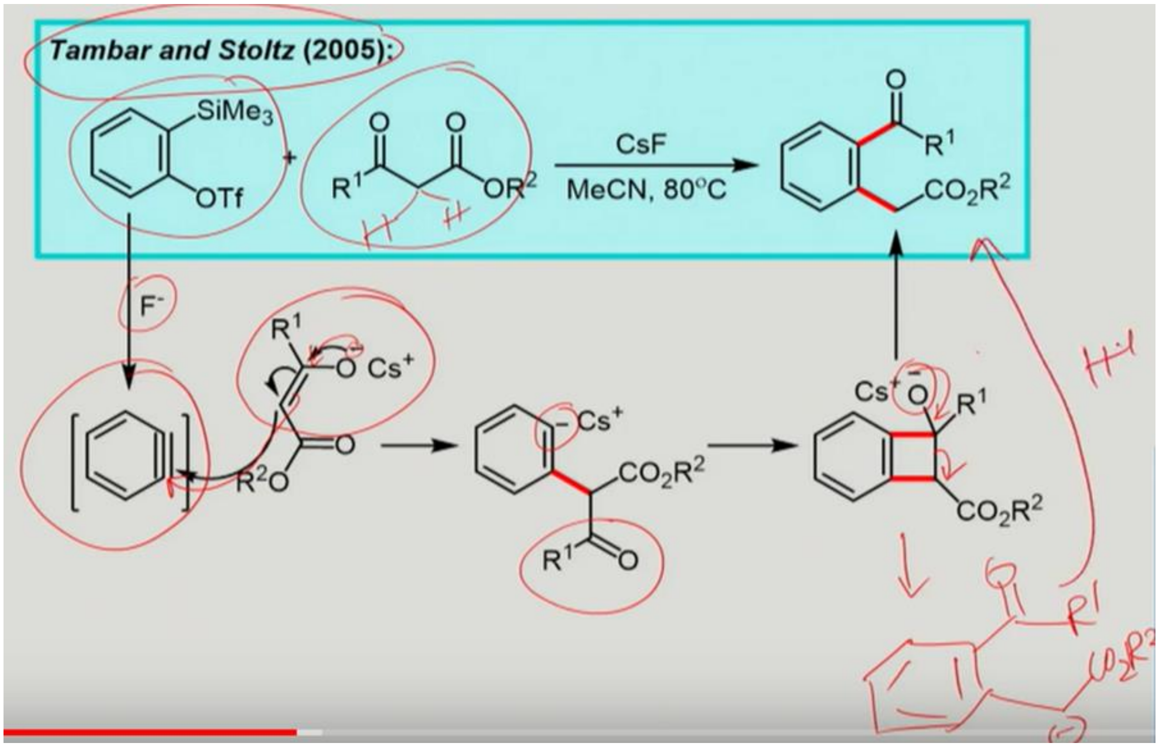
Where, X= O, S, NH, NMe

R^1= F, OMe, COMe

R^2= H, Me, OMe

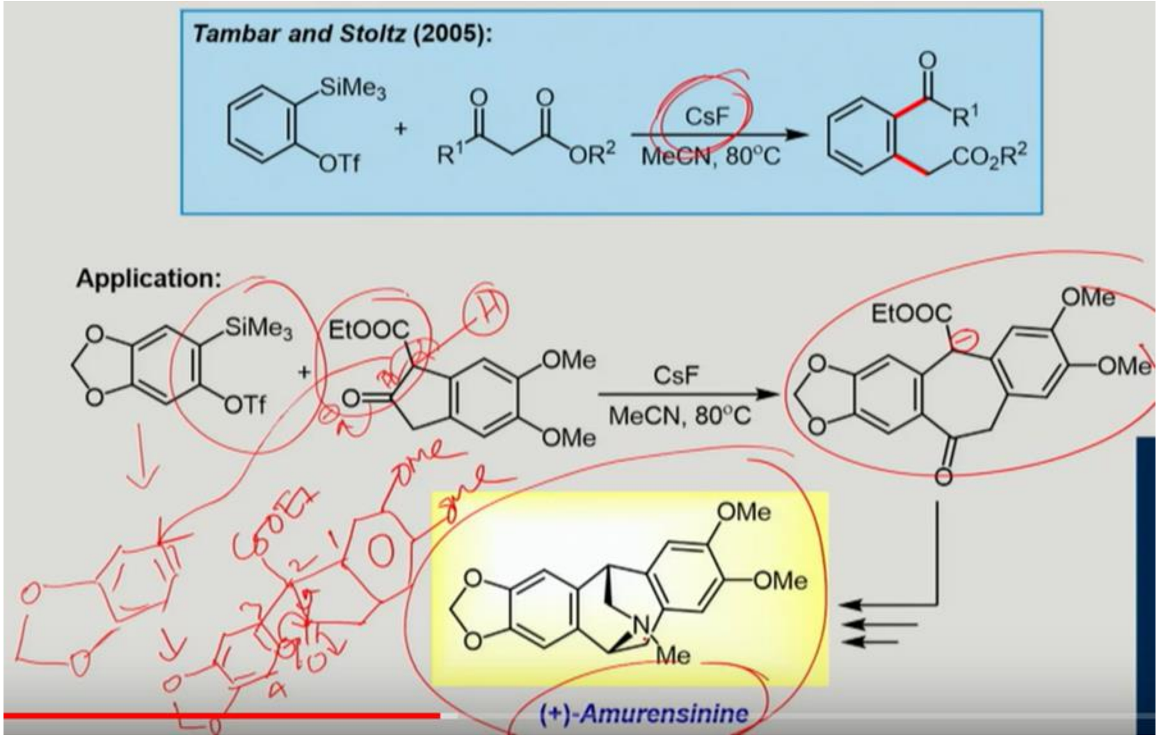
OMe It is going to come back and get rid of this OMe to form this type of xanthone or thioxanthone. So, if X is equal to oxygen, it is going to be the xanthone and if X is equal to sulfur it is going to be the thioxanthone.

Now, I am going to talk about a very important reaction developed by the Tambar and Stoltz group. So, the Stoltz group started working in this area, starting from the Kobayashi benzyne compound. So, in place of the cesium fluoride is going to generate the benzyne. Now, now you have this β-keto ester. So, we have already learned that this proton



in between this β-keto ester is highly acidic. So, now you are going to generate this type of cesium enolate which is going to come back. This minus going to come back here and going to attack through the carbon to form this carbanion here. Now that can attack the carbonyl group because between the ester and carbonyl, carbonyl will be more reactive. So, it is going to attack here to form this O^-. Now it can come back here and cleave this bond to form this minus which will take a proton to form the product.

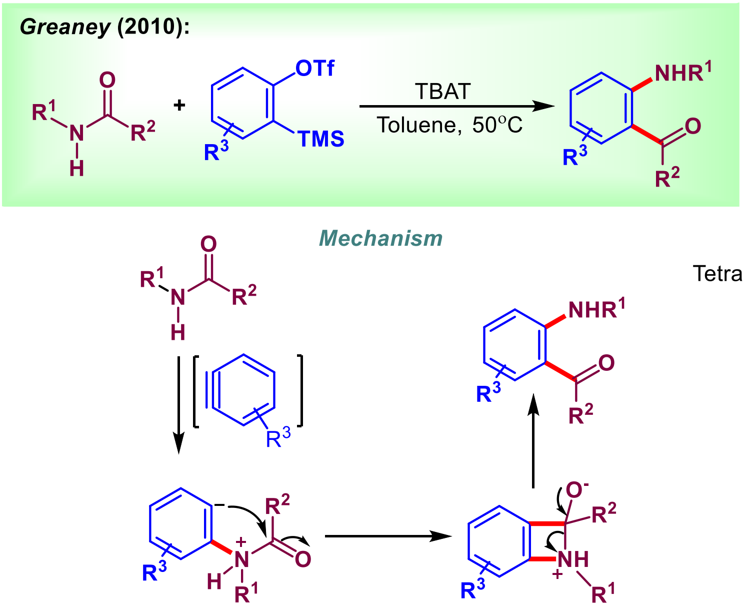
So, this chemistry was further used by the Stoltz group for the synthesis of important natural products. So, we are going to learn the important key steps used in this methodology. So, again from there you can see using the cesium fluoride, you can be able to generate a benzyne. Now, once you generate benzyne here let us try to write the mechanism and you have this β-keto ester, if you see this is your α- and β-position. So, we know that in β-keto ester this proton here will be acidic. So, this can form an enol here, which is going to come back and it is going to attack from this position to benzyne. once it is going to attack it is going to generate this compound. So, now you see the scenario where you have the CO_2Et then you have the CO and then you have the other phenyl ring which



have an OMe group here. So, the next thing is going to happen, you have this carbonyl group here. So, this negative charge going to attack here into the carbonyl group, then it will come back and finally go for a ring expansion to generate this carbanion which will generate this product. Once you cleave this now you can see the number of bonds 1, 2, and

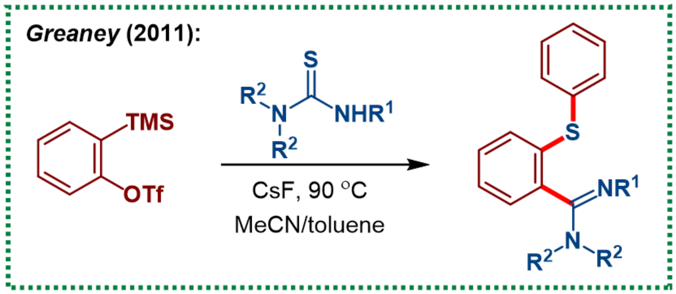
3 that are going to form here the bonds 4, 5, 6, and 7. So, that is going to form this particular compound and now once it gets an H^+ to form this particular product. From there after subsequent steps, you can able to synthesize this natural product.

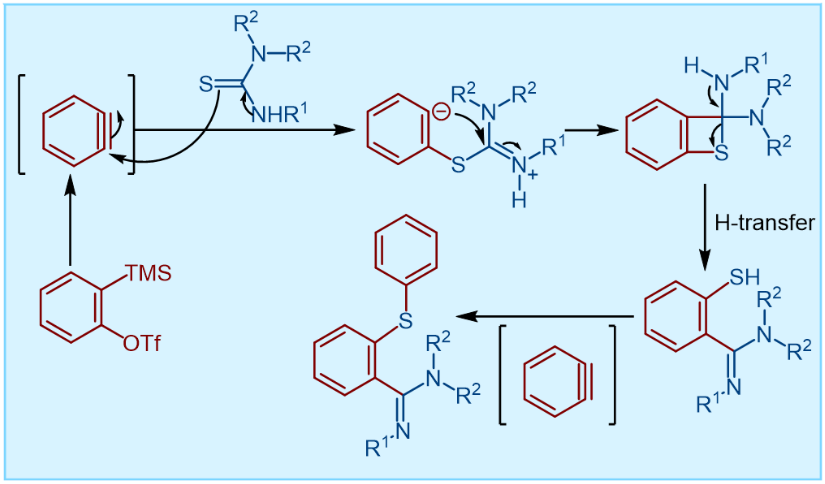
We are moving to another set of compounds, you have some sort of an amide here. If you have an amide again you have nitrogen having the lone pair so that is going to attack the benzyne first to generate this type of carbanion. And you have an N^+ so that carbanion going to attack this corresponding carbonyl group here. and then going to cleave this C-N bond. So, this type of intermediate species is going to cleave this C-N bond, at the end one carbon having the amine and another carbon having the carbonyl group. So, both these groups are getting inserted.



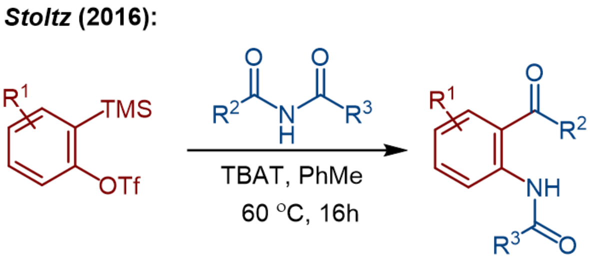
TBAT
Tetrabutylammonium difluorotriphenylsilicate

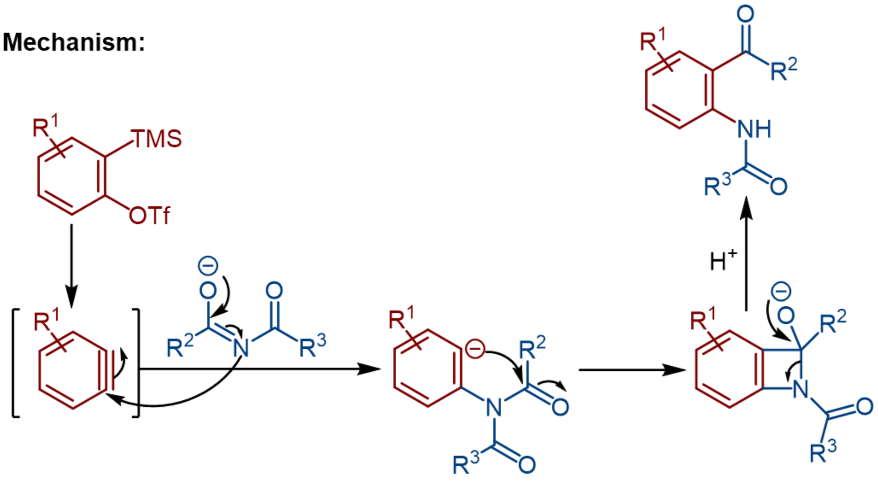
So, now if you have his particular compound here you can see you have some sort of a thiourea in that case what is happening here? Again once you have a sulfur the sulfurs are more nucleophilic here. So, sulfur is going to attack the benzyne. So, benzyne is forming again through the Kobayashi method using cesium fluoride. So, once the benzyne is formed thus it gets attacked by the sulfur to generate this carbanion and there is a positive charge on the nitrogen. So, the carbon going to attack this imine. Then it is going to form this type of intermediate species from there it is going to cleave this C-S bond and then it is going to form this intermediate. So, the one carbon will have the SH, and the other carbon will have this carbon-nitrogen double bond some sort of imine and there will be nitrogen here. So, as I have already taught in the previous class, if you have a thiophenol and if you have a benzyne the sulfur is ready to attack the benzyne. Then there will be an H^+ which will be taken by the benzyne to form finally this product.





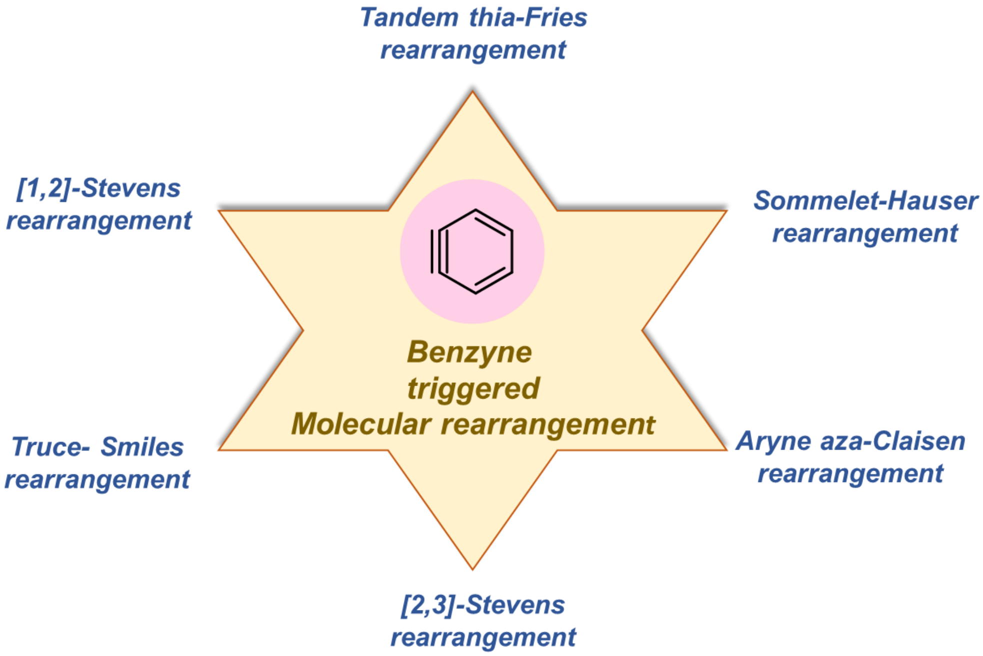
Then I am going to talk about the *N*-acetyl acetamide. So if you have an *N*-acetyl acetamide again from the Kobayashi's method the benzyne was synthesized then the benzyne is





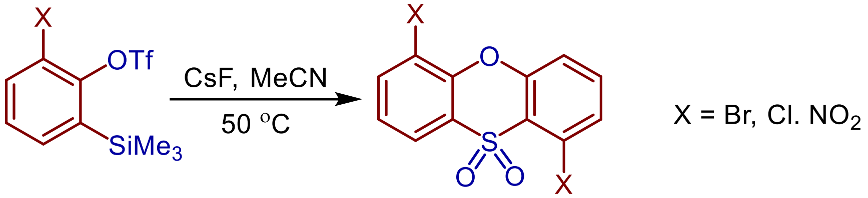
reacting with this *N*-acetyl acetamide. Again you can try to draw this resonance structure. You can see there will be O^- here and the N^+ which means now it can come back and it can attack through this nitrogen. It attacks through the nitrogen, then formation of this carbanion which is going to attack the carbonyl group here. The formation of this four-member intermediate, then cleavage of this C-N bond because this is the bond every case it is getting cleaved. All the insertion reactions you are seeing this is the bond that is getting cleaved. And then finally, it is going to put the acetyl group or the benzyl group in one carbon and the amide in the other carbon.

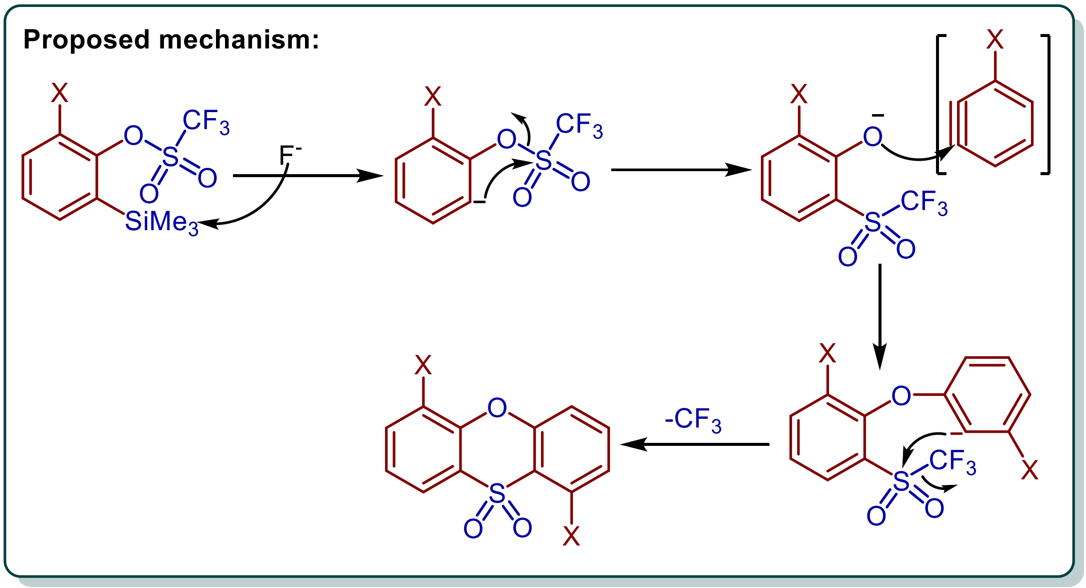
So, we have learned about the insertion reactions. Now, we are moving to a different type of rearrangement which was done using benzyne. We are going to talk about some of the thia-Fries rearrangement, then Sommelet-Hauser rearrangement. some Claisen rearrangement we are going to talk about, then two or three Stevens rearrangements, and also some Truce-Smiles rearrangement. I think some of these rearrangements already I have discussed, but now I am going to show you if there is a benzyne how this reaction taking place. So, this is a very interesting example.



We have learned that if you have these two OTf and TMS in this scenario if you use a cesium fluoride it is going to generate a benzyne. But as soon as you have an X equal to bromo, chloro, or nitro they end up finding out this type of product and they also got an X-ray crystal structure that confirmed the formation of this product. Now, we have to find out what is happening here. Once you have an X equal to an electron-withdrawing group the F^- is attacking the TMS group to generate the corresponding carbanion. So, X is stabilizing this carbanion now instead of going for an elimination it is attacking the sulfur here.

Greaney **(2013):**

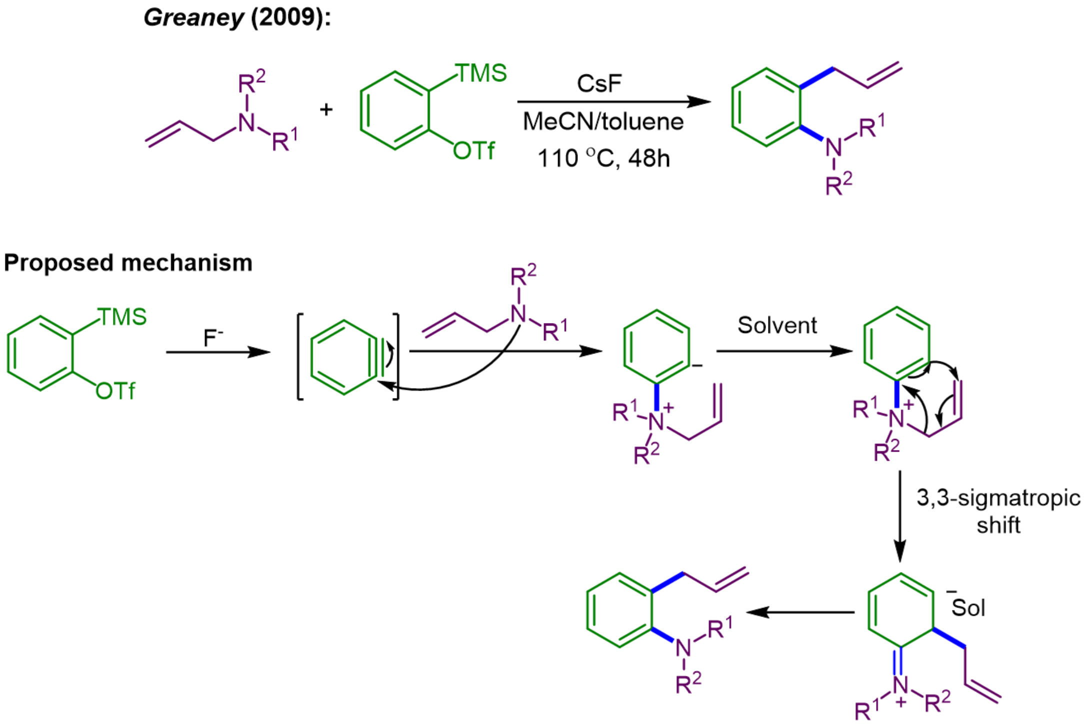



Proposed mechanism:

Then once it is attacking the sulfur it is going to attack here and then cleave this S-O bond to generate this O^- and this species. Now, this O^- is going to attack another benzyne to generate this carbanion species. again which is going to attack back to the sulfur and then get rid of the CF_3 and the SO_2 will be coming between these two aromatic rings. So, that is how they ended up making this product. So, from the starting material to the product you can see two different benzyne units reacted together to form this particular compound.

Another interesting example here if you start with allylic amine. So, in that case, the nitrogen having the lone pair it is going to be a nucleophilic center. So, it is going to attack the benzyne and generate this carbanion and then that carbanion can take a proton from the solvent. to generate some sort of a solvent negative charge, we are going to come back to that. And once it is forming this species, now you can think about that if you give them a numbering as 1, 2, 3 and then 1, 2, 3. So, we have learned about this [3,3] sigmatropic shift, and we have learned about this Claisen rearrangement. You can see this could be Aza-Claisen because there is nitrogen here. So, we have learned about this aza-Claisen reaction. So, it is going to break this C-N bond and in the end form this particular compound. So, you can see still benzene is still not aromatized, but there is hydrogen here, and if you remember we have abstracted a proton from the solvent.

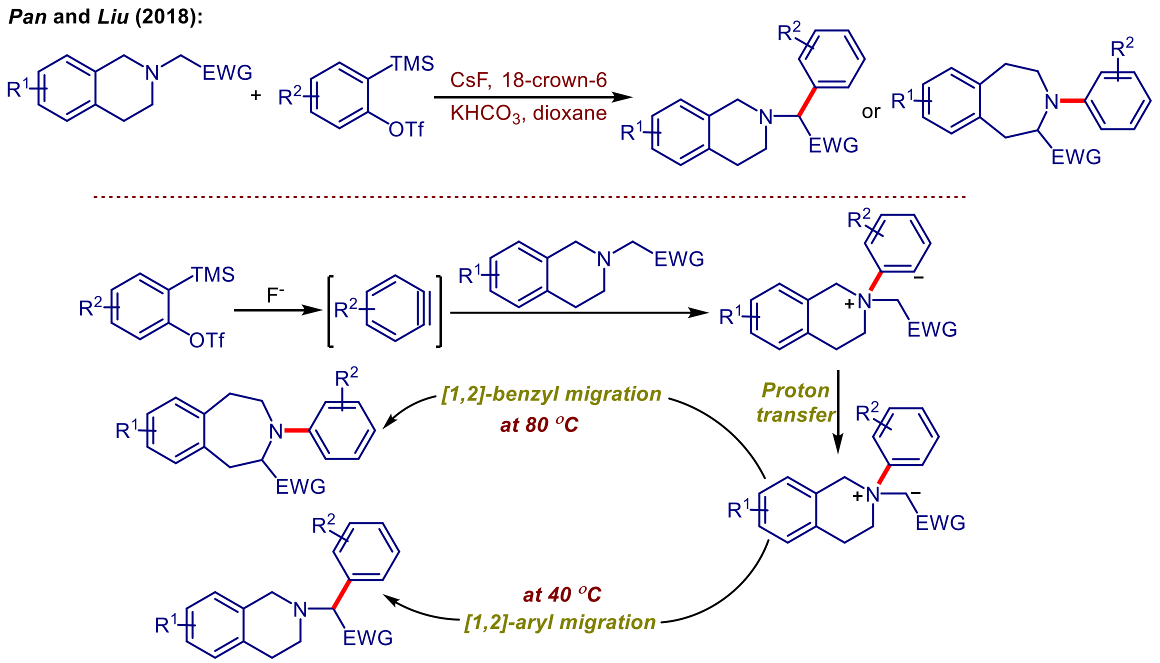
So, that negative part can take this proton and then finally going to form this product. Once you form the double bond here this goes back as aromatic and you have an amine and you have an allyl group in the next carbon.



***Greaney* (2009):**

Proposed mechanism

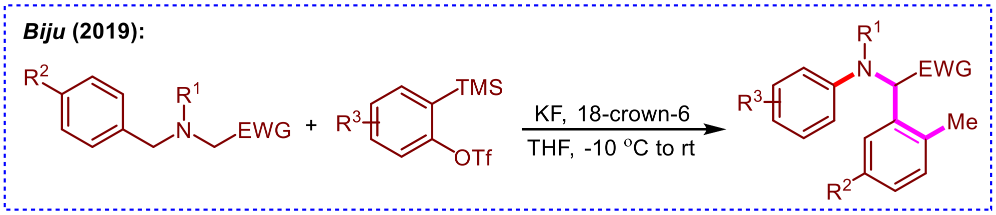
Another interesting reaction here is if you have started with a tertiary amine. So, this will be a Stevens rearrangement, now we are going to talk about the Stevens rearrangement. So, again the nitrogen has this lone pair that is going to attack the benzyne and going to form this particular intermediate species having this carbanion. Now, this carbanion going to find a proton which is going to be acidic. So, this will be acidic because it is next to N^+ and the electron-withdrawing group. So, it will form this anion here. So, after forming this anion there are two different things going to happen. At 40°C one thing going to happen and at 80°C something else going to happen. At 40°C let us try to learn what is happening here. So, now this minus going to attack here to this aryl ring some sort of if ipso substitution going to happen. This is going to attack here, this charge is going back and then finally, this carbon-nitrogen bond going to get cleaved. and that will end up giving you this particular product. You can clearly see that there is a 1,2-aryl shift, this aryl group now coming from nitrogen to the corresponding carbon with which the electron-withdrawing groups are attached and the rest of the things remain the same. Now, if you see at 80°C what is happening? If you increase the temperature, instead of the ipso substitution it is readily going to attack this carbon to cleave this C-N bond. Once that is happening you have a ring expansion going to happen. Instead of the six-member now



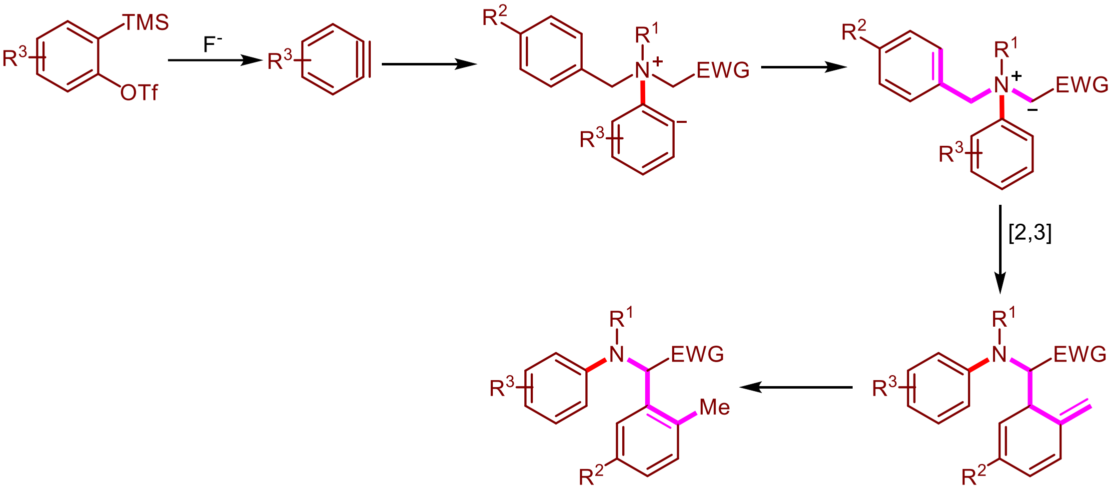
there will be a seven-member ring. So, these are the two different situations that can happen, In one case there is a 1, 2-benzyl migration, it happens through attacking here and cleaving the bond or there could be a 1,2-aryl migration. So, you end up getting both products depending on the reaction condition.

Then the next example is the Sommelet-Hauser rearrangement. Here you can see first in the case of a very similar condition of the Kobayashi group you end up generating benzyne. Now the benzyne is going to get attacked by this tertiary amine using the nitrogen lone pair to form this benzylic ammonium salt. If you remember, if you have a benzylic ammonium salt and if there is a carbanion generation happening then you remember about the Sommelet-Hauser rearrangement. So, we have learned that in this particular compound if you look into it there is a proton next to the electron-withdrawing group is the acidic proton. So, this proton getting abstracted to generate this carbanion. Now, you can see that there is a [2,3] rearrangement happening. So, this negative charge now going to attack here, this going to come back from this double bond and there will be cleavage of this C-N bond. So, once that is happening you end up getting to this particular intermediate. The next thing is very simple, this proton is going to get abstracted from here to go back to an aromatic compound that will end up giving to this particular product.

We are going to talk about the Truce-Smiles rearrangement here and how this reaction is happening. So, once you have this sulfonamide then that nitrogen is going to attack the benzyne to form this carbanion here which is going to attack the carbon ipso to the SO_2 group. You have learned this in the Truce-Smiles arrangement. So, it is going to attack here.

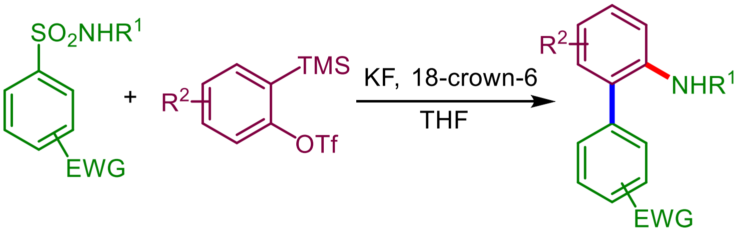


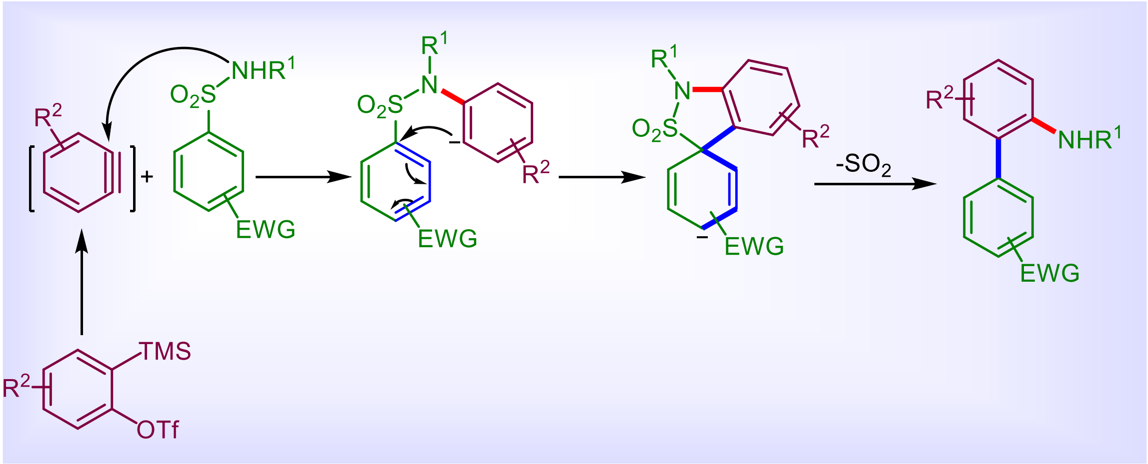
Mechanism:



And then it is going to form a carbanion here which is going to come back and cleave this C-S bond. Then SO_2 is going to get out to give this corresponding product after the protonation.

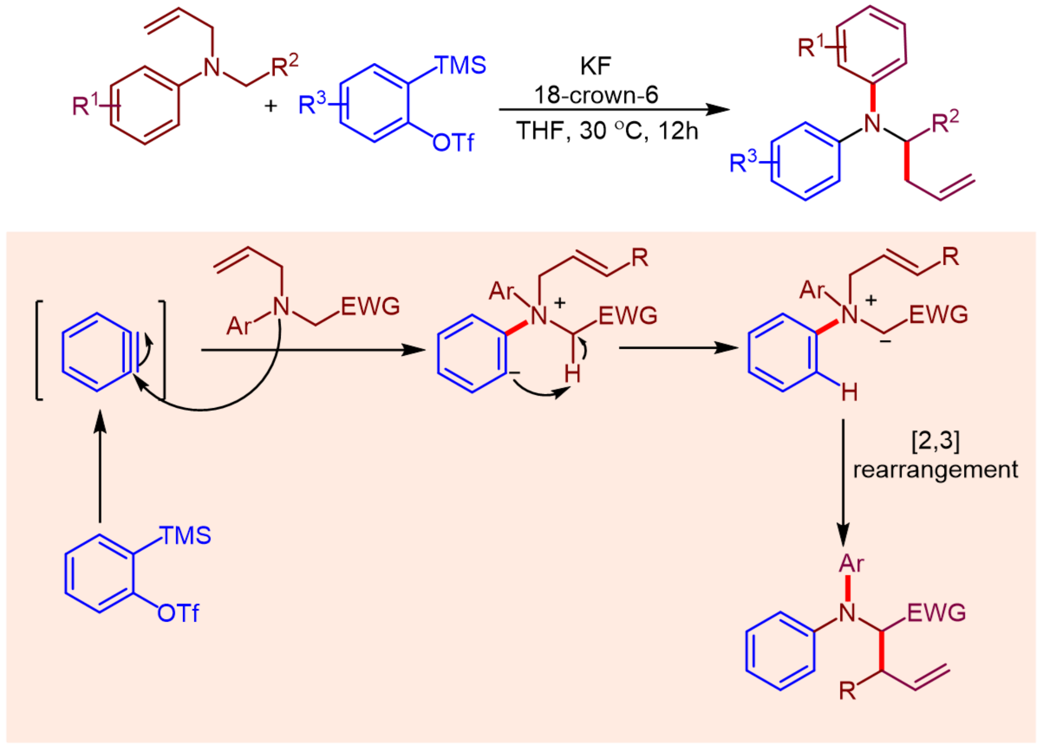
Greaney **(2016):**





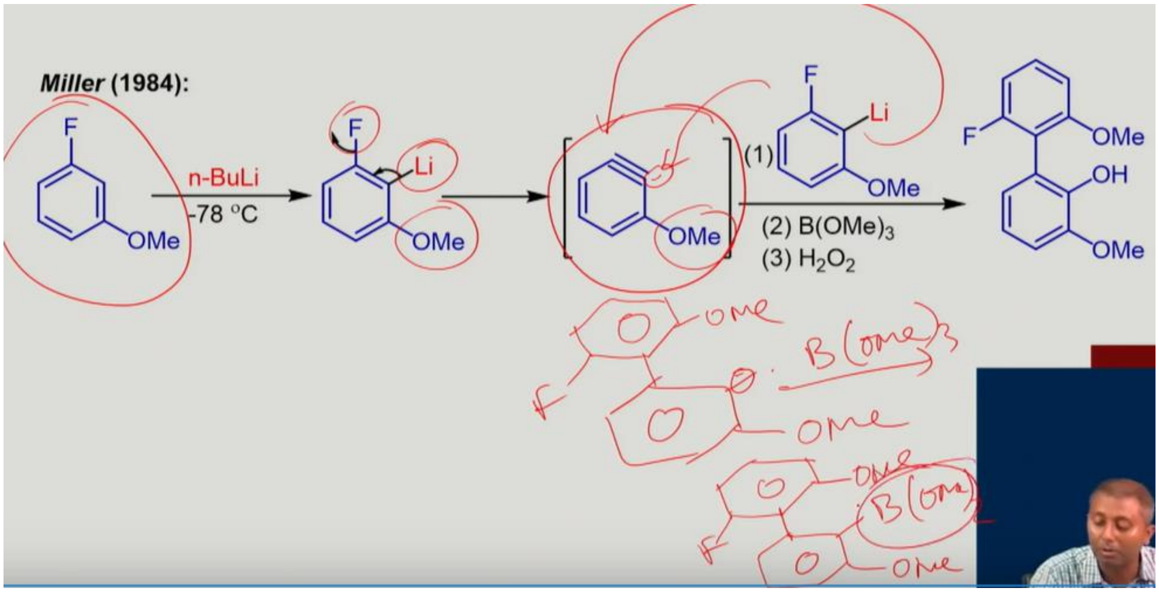
This work was done by Professor Biju from IISC Bangalore. This tertiary amine nitrogen lone pair is going to attack the benzyne to form this particular intermediate, now nitrogen having a positive charge and you have a carbanion. So, that can cleave this C-H bond because it is next to the electron-withdrawing group. So, this carbanion going to get generated. Once you have this scenario here, there is a plus and a minus and you have an allyl group here, that is going to participate in a [2,3] rearrangement. So, it is going to attack here and cleave this C-N bond to get to the corresponding product.

***Biju* (2016):**



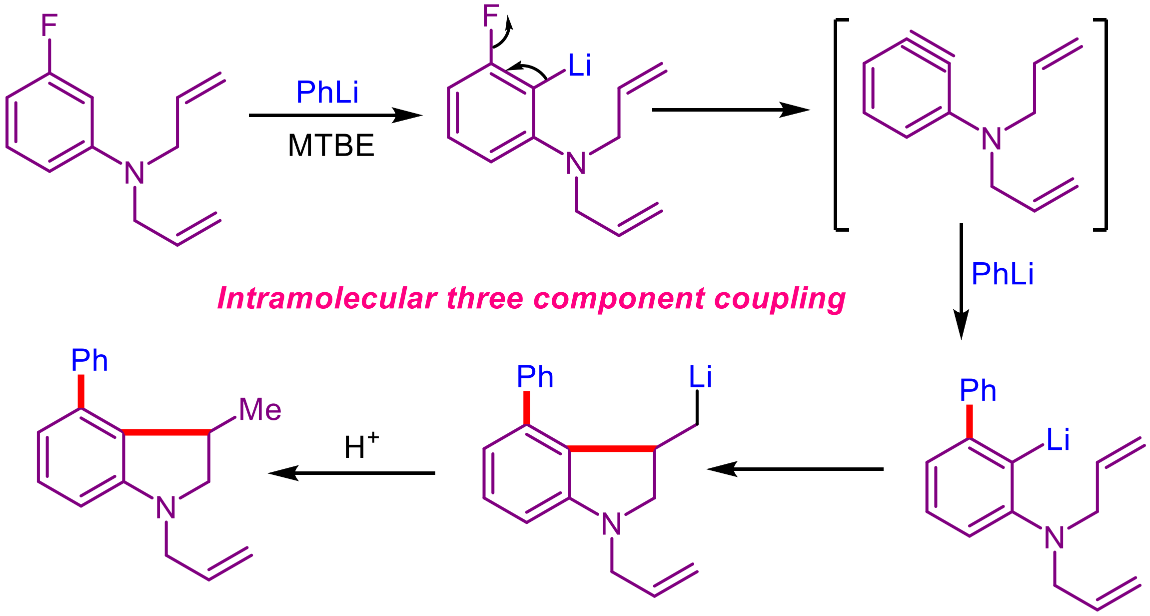
Then I am going to talk about some of the multicomponent reactions. Previously we have learned that if you have this particular compound with a C-F bond, if you use a strong base then it is going to abstract a proton. So, in this particular lithium which is forming here in between a fluoride and a methoxy, if you remember both fluoride and methoxy have a -I effect. So, this lithium going to form first, then it is going to end up making this particular benzyne. And then you have to understand there is organolithium in the reaction. So, that lithium is going to attack the benzyne again. Again the question comes where it is going to attack. It is going to attack in this position or this position? We have already learned that the meta attack will be favorable because this anion going to stabilize through the -I effect of the OMe group. So, that will end up generating this particular compound. So, it will generate a carbanion here at the beginning. So, you will see a carbanion here and then there will be OMe and then you have another aryl ring with a substitution of fluorine and OMe.

What is going to happen? This will be going to react with $B(OMe)_3$. Again we are going to talk about this in the boronic ester when I will talk about organoboron chemistry. It is going to form this $B(OMe)_2$. It forms a boronic ester. So, now if you use H_2O_2/NaOH you remember the hydroboration-oxidation reaction? The boronic ester now going to react with H_2O_2/NaOH to convert to the corresponding phenol.



Another important reaction here, first you treat this compound with phenyl lithium once you treat it with phenyl lithium again there will be proton abstraction from here. that is

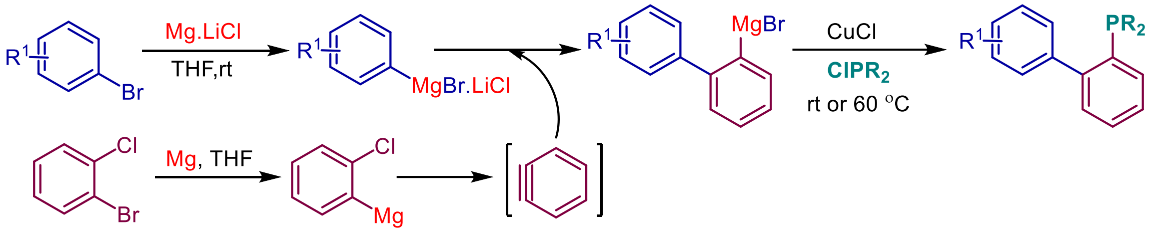
***Carson* (1997):**



going to form the corresponding benzyne. You already have a phenyl lithium in the reaction. So, it is going to attack here to generate this corresponding lithium. This lithium is ready for an intramolecular 5-exo-trig cyclization. Finally, that lithium takes a proton to get to the corresponding product.

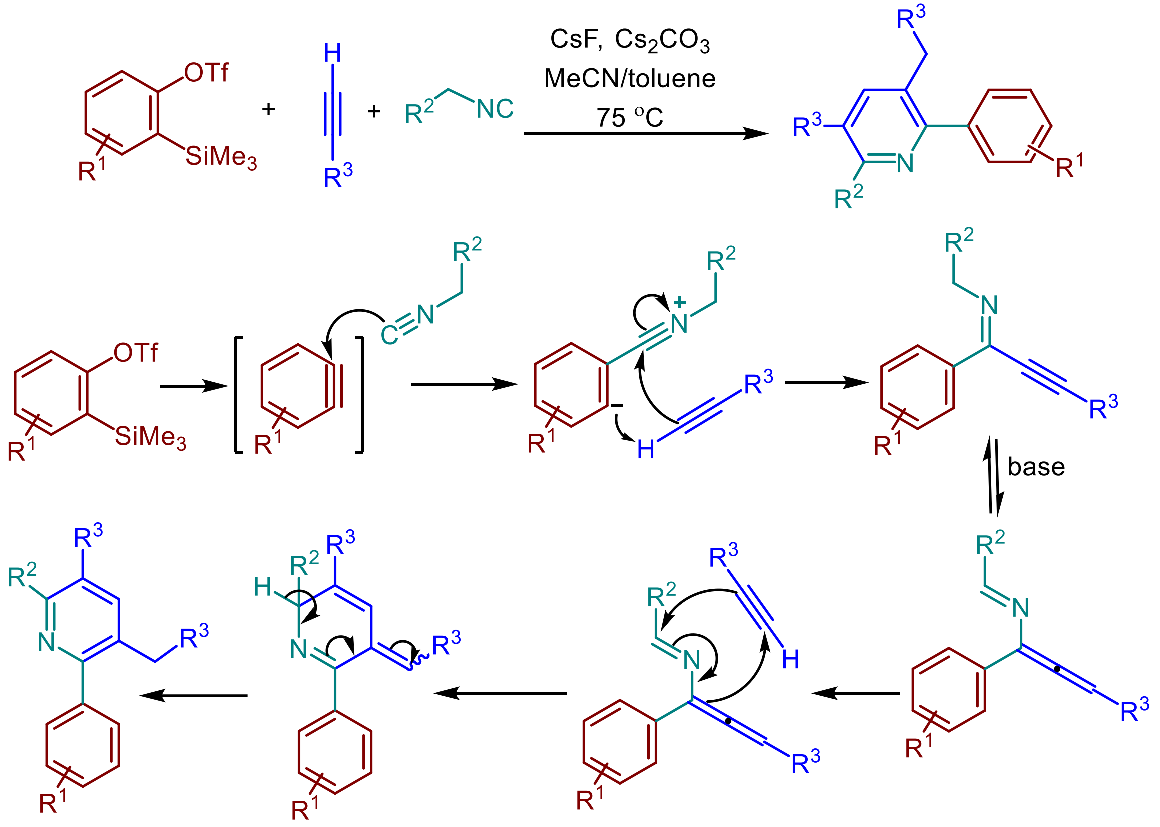
Here we started from the corresponding bromobenzene using the magnesium you can make the corresponding Grignard reagent. Starting from this 1, 2-bromochlorobenzene you have the corresponding magnesium. So, it is going to form the Grignard. Now, you have chlorine as a leaving group. So, it is going to participate in an elimination to form the corresponding benzyne which will be attacked by this Grignard reagent to form this sort of a species. In the presence of the copper chloride and this $ClPr_2$, it is going to install the phosphine. So, that is how a lot of Buchwald ligand was synthesized which was used in a cross-coupling reaction.

Buchwald **(2000):**



So, then the final one is the multicomponent reaction here. Again from this very similar Kobayashi method, it generates the corresponding benzyne which is getting attacked by isocyanide. If you remember the isocyanide you know always attacks through the carbon, not through the corresponding nitrogen. So, the isocyanide is attacking the corresponding benzyne. Once it is attacking the benzyne you can see here it is generating a corresponding carbanion and a nitrilium intermediate. Once it is attacking here you can see here you are generating this type of nitrilium intermediate. And now this minus which you are generating here going to take this proton because this is the acidic proton of the alkyne. So, the alkyne will be deprotonated in situ. So, once alkyne is deprotonated it is going to generate this particular compound in situ. A lithiated alkyne is going to form. Once the lithiated alkyne is formed that lithiated species going to attack the corresponding nitrilium intermediate. So, this C≡N going to get attacked by this organolithium. Once that is happening you have to neutralize the charge on the nitrogen to generate this species. So, you can see you have an imine and an alkyne here. Now, if you have a proton here in this position, you already have organolithium present in the reaction. So, that is going to abstract this proton to form an allene. Now, you can think that this is going to take part in a reaction with another alkyne. So, in a reaction with another alkyne, this alkyne electron density coming back here, this is moving here, this double bond is attacking here. So, now, it is forming this particular species and you can think about this. So, this particular carbon is attacking here and ends up forming a pyridine. So, in that pyridine, there are four carbons coming from here one, two, three, four these two carbons come from this place and this particular group is remaining here which can finally be converted to the corresponding alkyl group. After this deprotonation, this is getting converted to the corresponding alkyl group. So, that is how you starting from this type of isocyanide, alkyne, and this benzyne precursor you can able to make this 2-arylated and 3-alkylated product. So, you have substitution at the 2, 3, then 5, 6. So, you are making a pyridine with so many different substitutions. So, this is a very important reaction.

***Huang* (2009):**



So, in this particular part, we have learned about different types of insertion reactions using the benzyne. We have we have seen several different types of insertion starting from the disulfide to β-keto ester and many other variations. Also, we have learned some of the molecular rearrangement. We have seen some of the Claisen rearrangements using benzyne and some of the other rearrangements. And we have always seen if there is a nucleophilic partner it is going to attack the benzyne to generate a carbanion which going to attack the other part. These are the references, again I told you that please follow these books which have been given here, the "Modern Alkyne Chemistry" by Prof. Biju and some other books. Again thank you for coming to the class and I am going to see you guys in the next class.