Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

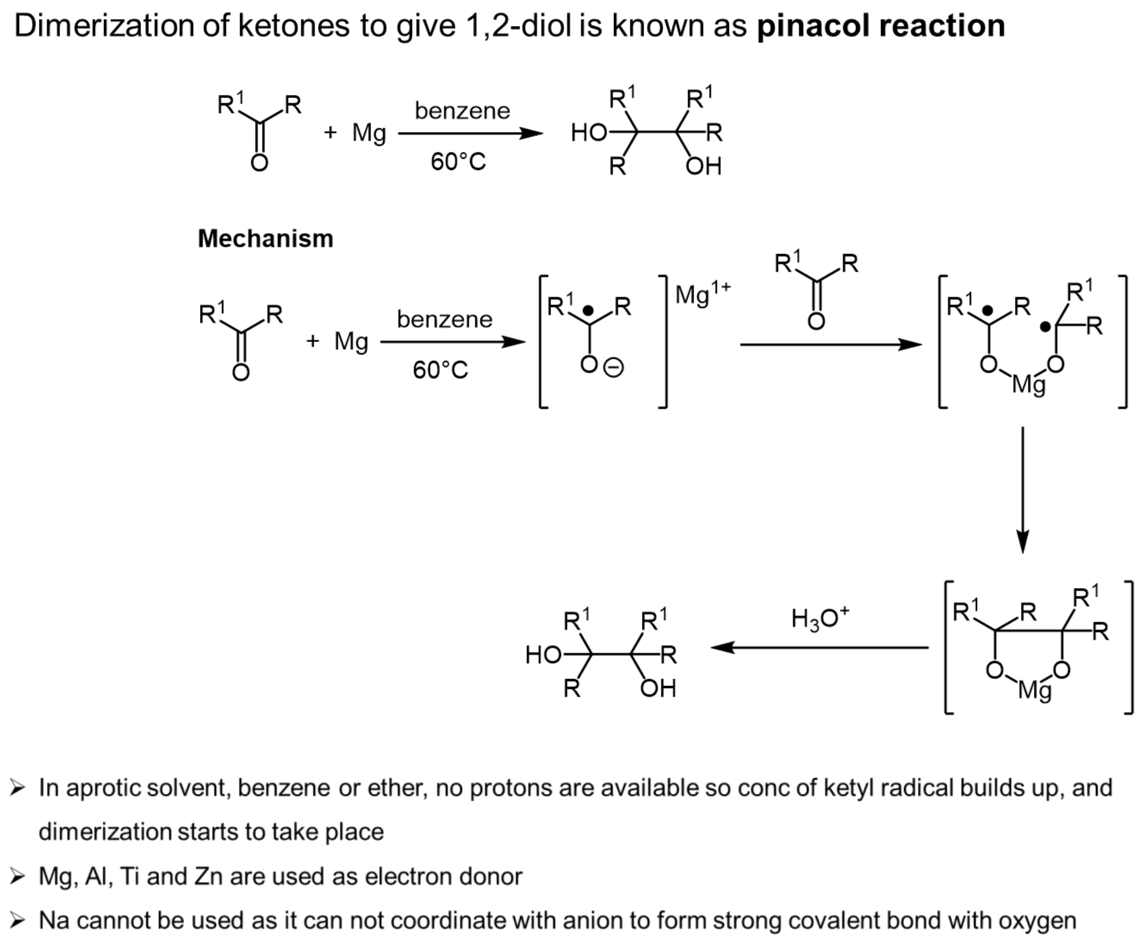
Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 23: Radical Continued

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. We are still continuing with the radical chemistry. In the last class, I talked about some of the single electron reduction reactions using sodium and lithium. You have learned about the Birch reduction, and you have seen how things are different if you have an electron-withdrawing group versus an electron-donating group. In today's part, we are going to continue to learn some of the other single electron reduction reagents and some of the reactions. So, I am going to start with the pinacol reaction at the beginning; I think you guys have already heard about that reaction before.

So, I am going to talk about the pinacol reaction and the mechanism, then the McMurray reaction, the Barbier reaction, I think you have already heard about the Sandmeyer reaction, and then the Meerwein arylation. So, there will be a single electron transfer going to happen and it going to form some sort of radical intermediate. So, let us start with the Pinacol reaction. If you remember, you know, when I was talking about the Pinacol-pinacolone rearrangement, at the time, I talked about this particular reaction. You know how to make Pinacol because once you go for Pinacol-pinacolone rearrangement, then before that you have to make the starting material. So, the starting material can be synthesized from the corresponding carbonyl compound if you use magnesium. So, here, the magnesium is in the presence of an aprotic solvent. So, what is going to happen? it is going to form a compound called pinacol. You can see this is literally first there is a reduction some sort of reduction of the carbonyl group and then there is a dimerization happening here.



Dimerization of ketones to give 1,2-diol is known as **pinacol reaction**

Mechanism

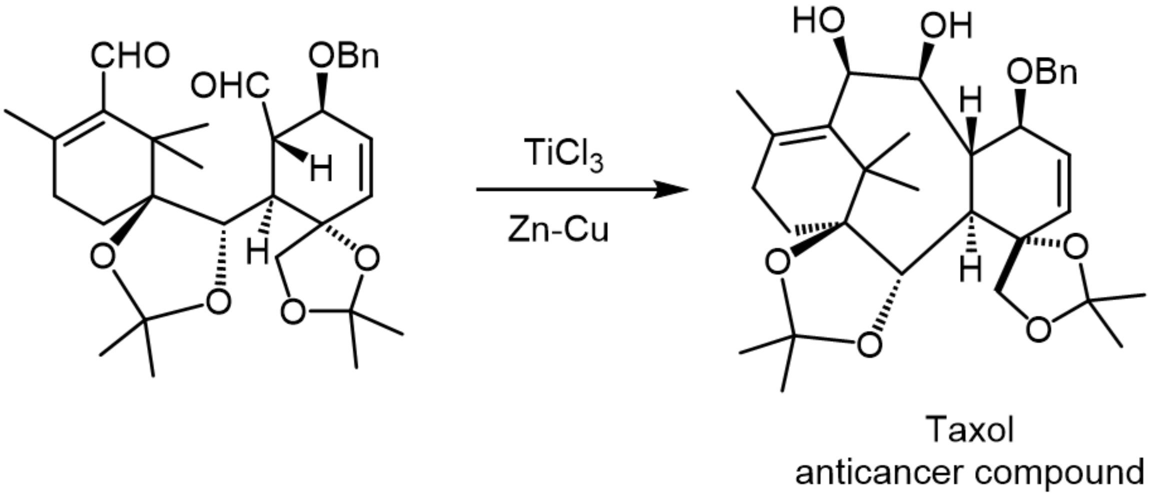
- In aprotic solvent, benzene or ether, no protons are available so conc of ketyl radical builds up, and dimerization starts to take place
- Mg, Al, Ti and Zn are used as electron donor
- Na cannot be used as it can not coordinate with anion to form strong covalent bond with oxygen

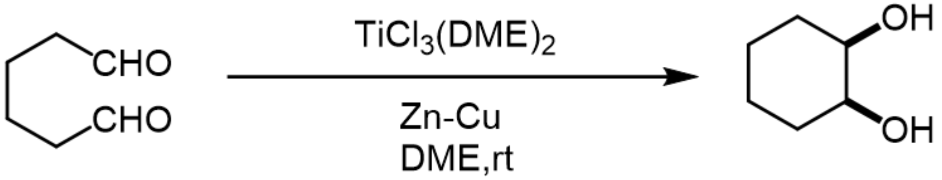
So, now, we are trying to understand the mechanism what is happening again the magnesium here acting as a single electron transfer agent which first after the single electron transfer happen you can see it is forming this minus and there is a radical on the carbon. Again there will be another reduction happening in place of. So, now what is going to happen the magnesium(I) going to convert to magnesium(II) and then you end up making this type of radical species which after the radical recombination reaction. So, we call this type of reaction as a radical recombination reaction once they combine it going to form this compound and then once you put H_3O^+ it is going to form the corresponding pinacol. So, it is a very important reaction and you can see we can easily make this type of pinacol from starting from the corresponding carbonyl compound.

Now, the important factor as I mentioned it is done in the in aprotic solvent. So, like benzene or ether. So, there is no protons are available. So, that concentration of the ketal radical will be built up because once you are putting magnesium there, it is generating this ketal radical. Once the ketal radical getting built up that it can participate in the dimerisation.

Again it is not the only magnesium works here there are other metals here I have mentioned aluminum, titanium, zinc and also can be used for this reaction. And you can also see I am going to explain that the samarium can be also used for the pinacol reaction as well. And again I think the question arises why not sodium, why we are using this magnesium. The important thing is the sodium cannot coordinate with the anion to form the strong covalent bond with the oxygen. So, that is why the magnesium is the preferable one instead of the sodium.

Again as I mentioned the titanium can be used the low valent titanium as I am saying because you are using zinc copper as a reducing agent. So, that it can be a low valent titanium it is not the titanium chloride titanium(III) it is going to be titanium(II). So, who is going to participate in the pinacol coupling? You can see in this molecule, which can be converted to the taxol, which is an anti-cancer compound here. So, in the synthesis if you see in this molecule there is two aldehyde group here. So, in the presence of titanium trichloride and then zinc copper couple, they can participate in a pinacol coupling to form this compound.

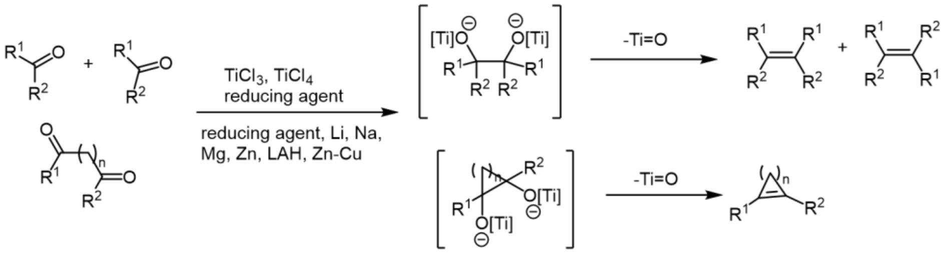




As the titanium going to coordinate with the two of the oxygen atom. So, that is why what is going to happen, as I mentioned, the titanium is going to coordinate correctly. So, that is why you will end up seeing them in the same phase both the alcohol. Again there is another example here. So that is again an intermolecular reaction happening in intermolecular pinacol formation.

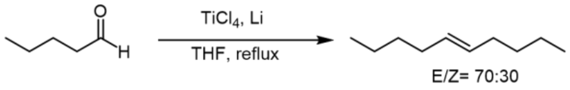
So, again both the aldehyde in place of the titanium and then titanium plus(III) and zinc copper as a reducing agent it can form this cyclohexane 1, 2 diol again both the OH in the same site as the titanium is forming a complex with it. It is not always that for every product that is going to happen also, and it also depends on the structure and the functional group , how the different types of the groups in the aldehyde are present. So, depending on that you can see sometime also the anti-alcohol also forms. So, we have learned about the titanium triploid and the and the zinc copper couple. So, now we go. We are going to learn that if you take a carbonyl group here, especially you can see here this R1, R2, and you can see this could be a ketone, and mostly for the ketone, I am going to talk about the McMurray coupling reaction.

The treatment of carbonyl compounds with low-valent titanium led to olefinic coupled products. In the following years, McMurry investigated the scope and limitation of the process, and today the reductive coupling of carbonyl compounds using low-valent titanium complexes to form the corresponding alkenes is known as the **McMurry coupling**.



And then you can see here we can have some intermolecular examples here. So, if you have two ketones present in the same molecule, it can intermolecularly also form the olefin. So, from ketone, you are making an olefin, or it could be a cyclic ring with a double bond. So, in the McMurry coupling, we are using the low-valent titanium again there is a low valent titanium is used. Again, we can see here there is a reducing agent. and then with the high valent titanium.

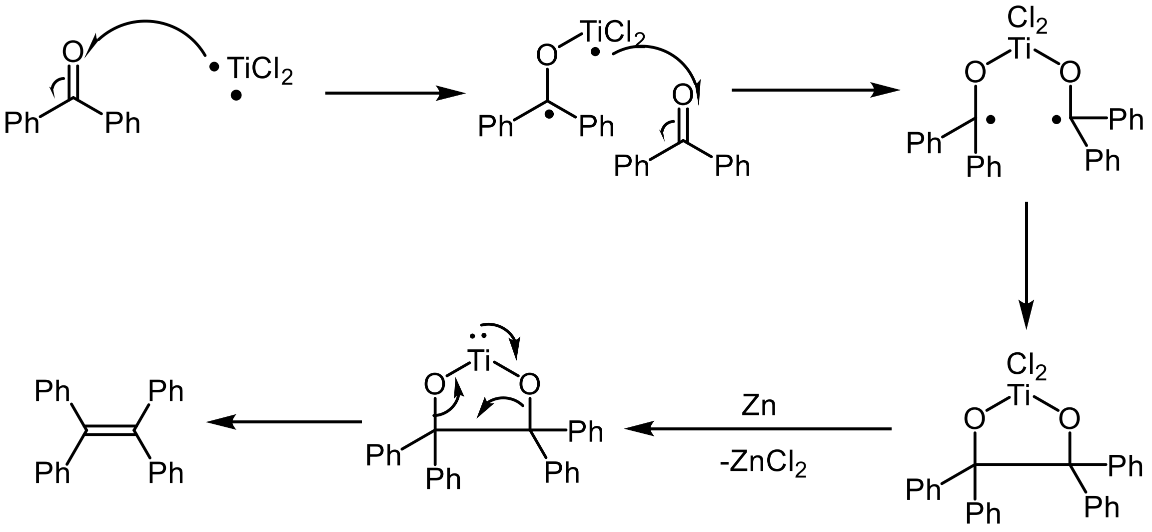
- **Low-valent titanium species** induce coupling of the carbonyls by single electron transfer to the carbonyl groups.
- The required low-valent titanium species are generated via reduction, usually with zinc powder in THF because it solubilizes intermediate complexes, facilitates the electron transfer steps, and is not reduced under the reaction conditions.
- Other the reducing agent employed: typically, lithium aluminum hydride, zinc-copper couple, zinc dust, magnesium-mercury amalgam, magnesium, or alkali metals



So, if titanium is going to get reduced to a low-valent titanium, then it can form some sort of a pinacol-type species here. From there, what is going to happen is the titanium dioxide is going to, you know, get out to form the corresponding olefin. So, literally two of this carbonyl group, you know, form a dimer here. This is a very important reaction because by starting from the carbonyl compound, you can make olefin. As I mentioned, low valent titanium is an important species that can participate in a single electron transfer.

So, the low-valent titanium is the one that can participate in single electron transfer, and then you know that species can be generated via the reduction, correct? So, you have to use a zinc powder or zinc copper couple. There are others you can use. also, here the lithium alumina hydrate can also be used. and then there is the magnesium-mercury amalgam the magnesium. So, there are different types of reducing agents that can be used with titanium for the McMurry coupling. Another important part you know part is that when you are using zinc powders in THF, it is solubilizing the intermediate complex, which facilitates the electron transfer steps you know faster.

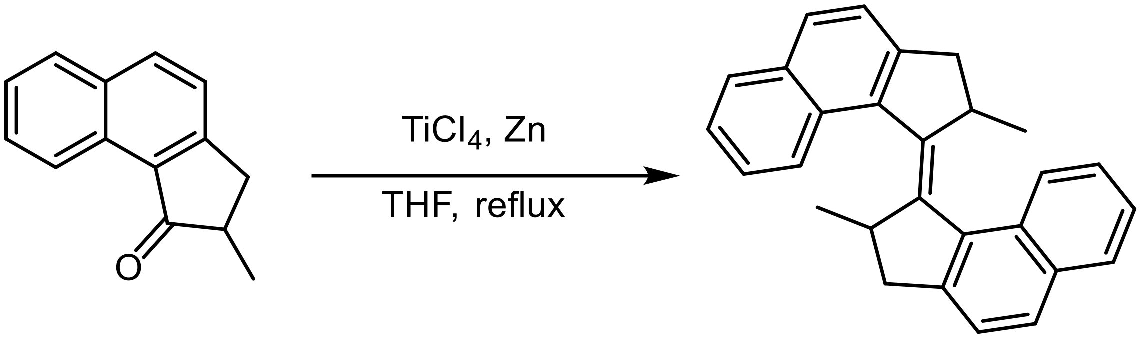
$$TiCl_4 + Zn \longrightarrow TiCl_2 + ZnCl_2$$



So, now I am going to talk about the mechanism, you know, of this reaction, you know, you know, how this transformation is happening again, you know, starting from this titanium. So, you can see titanium is getting, you know, reduced from the plus 4 to the plus 2 in place of the zinc-copper couple, and now, once you have the low valent titanium, it acts as a single electron transfer agent. So, now, it can able to transfer a single electron here. So, that can able to generate this ketal radical and then this titanium, you know, species which can again go for another sort of, you know, reduction very similar to the magnesium and then form this know species, which can now go for a radical recombination to forms the chelated complex with the two oxygen with the titanium. Now, I am sure here what is happening from this stage if you see titanium has already come to the Ti^{+4} from the Ti^{+2} after giving the 2 electrons.

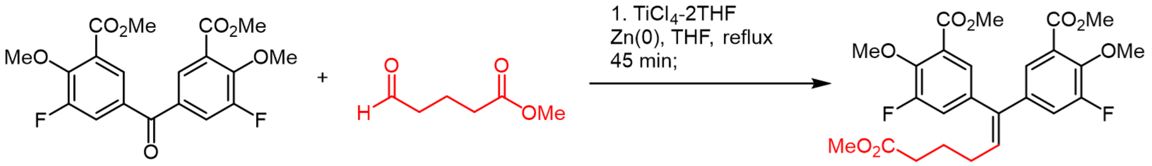
Now, what is going to happen from this intermediate now zinc going to again get from the zinc chloride now from in this intermediate it is going to make the titanium dioxide, you know, pushing the electron here, and you can see it is going to form the titanium dioxide and it is going to form the corresponding you know olefin. So, it will end up with benzophenone. You are making a tetra-substituted olefin here. There is an example here. So, you can see. So, this is used for the molecular motor.

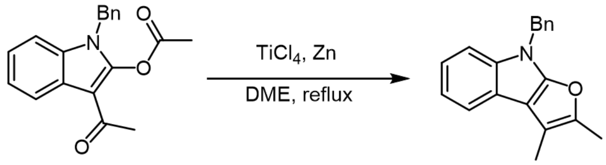
So, this is a very important skeleton. professor Ben Feringa received a Nobel prize for this discovery of molecular motors. So, that can be also synthesized. So, if starting from this compound this carbonyl compound using titanium tetrachloride and you know zinc in case of THF reflux it can end up making this compound. Through a very similar mechanism I have explained in the previous slide. It is going to form the Ti(II), then one electron transfer, then form the pinnacle type of complex, and then finally, it can you know titanium dioxide get out to get to the product.



molecular motor

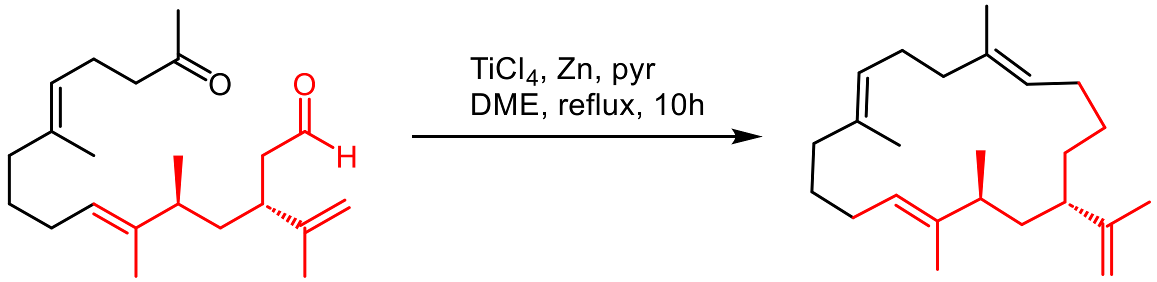
Now, the question comes if you have a if you have a like aldehyde versus you have a ester. and then another compound, you have a carbonyl group here, ok. So, again, in this reaction, you know there are two possibilities that can happen. One thing is that it can self dimerize. or they can do the intermolecular reaction. So, here, I think they can isolate this intermolecular product and also moderate to good yield in this reaction.





Again, what is happening is the titanium tetrachloride? In the case of the zinc, you can see in the 45 minutes, the reaction is over again. This aldehyde is getting reacted, not the corresponding ester. So, the aldehyde is finally forming a double bond with this carbon to make this type of tri-substituted olefins. Then there is an interesting example here. You can see this is an indole where in the C3 position, there is this acetyl group here, and then you have an acetate group here in the C2 position. And again you can, if you use the McMurry coupling reaction condition, it is going to end up making a substituted furan. Because, again, what is going to happen? carbon-oxygen double bond gets chopped here, both going to combine to form the double bond.

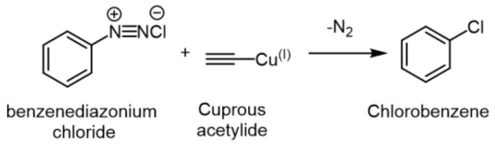
Another interesting example is here. this is an intermolecular reaction. you can see that on one side, there is an aldehyde, and on the other side, there is a carbon group here. Again in the presence of the titanium tetrachloride and the zinc. the zinc, as you know, reducing agent, can participate in the McMurray coupling to form this corresponding tri-substituted olefin.



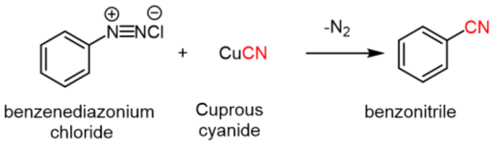
So, now I am going to move to another important reaction, where you are also going to see a formation of the radical species, called the Sandmeyer reaction. I am sure you have learned about this reaction in class 12. I am just going to take you to some of the steps again, and I am going to talk about some of the examples. this is the chemistry of benzenediazonium chloride. So, starting from the benzene diazonium chloride, Sandmeyer reported the formation of chlorobenzene using this copper acetylide.

The substitution of aryldiazonium salts with halides or pesudohalides is known as the **Sandmeyer reaction.**

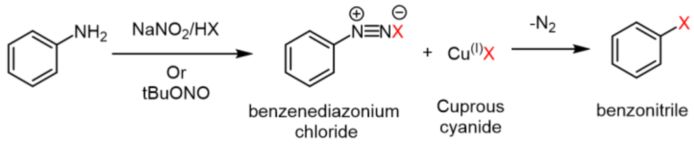
Sandmeyer (1884):



Sandmeyer (1884):



Sandmeyer reaction



So, what is going to happen? that the nitrogen get out to form this corresponding chlorobenzene. Also, it was mentioned that benzene diazonium chloride, in the presence of copper cyanide, can form the corresponding benzonitrile. So, starting from the aniline, how this benzenediazonium chloride formed? So, starting from aniline if you use $NaNO_2$ and any HCl, HBr, it is going to form the corresponding benzenediazonium chloride. In the presence of the copper(I) cyanide or the corresponding copper salt, what is going to happen? it can convert to the corresponding benzonitrile. So, now, depending on different types of partners with the copper, if you have an X equal to chloride, that can form the corresponding chlorobenzene. If you have a Bromo, that can form a bromobenzene. If it is a cyano, then it can introduce the cyano group here.

So, a couple of important facts are that, of course, their reactions start from the aryl amine or aniline via diazonium formation. So, for the diazonium formation, you need the $NaNO_2$ and corresponding HX depending on what X you want. So, the diazonium chloride is not isolated. It can be reacted in the same pot. That means you form the diazonium chloride, then add the copper salt, and under the appropriate condition, it is going to convert to the corresponding product. Again, the counter ion of copper salt has to be matched, which is very important. If you are using a reaction where you have to match the counter ion of the copper salt, that can be your product.

The general features of this transformation are:

☐ The required aryldiazonium halides are usually prepared from arylamines *via* diazotization using either $NaNO_2$/hydrohalic acid (HX) in water or alkyl nitrites (e.g., *tert*-butyl nitrite) under anhydrous conditions;

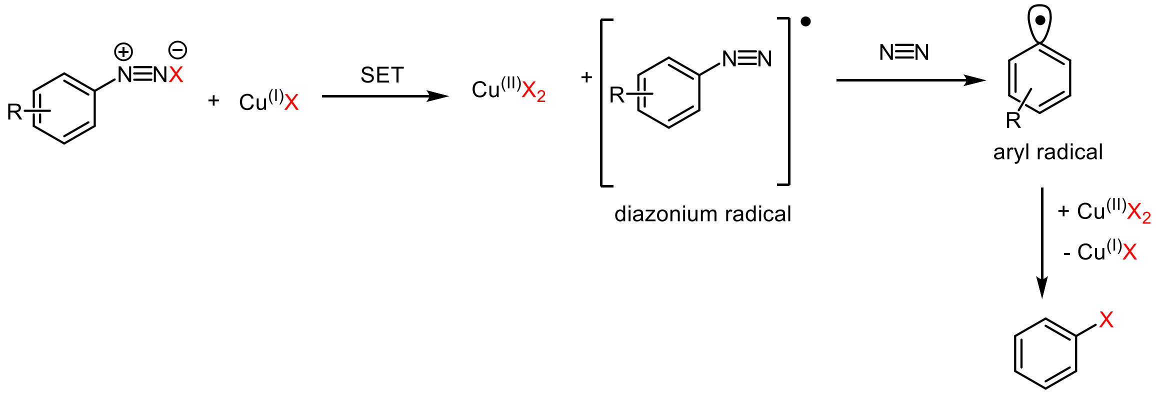
☐ The aryldiazonium halides are not isolated but reacted in the same pot with copper(I) chloride, bromide or cyanide to obtain the corresponding aryl chloride, aryl bromide, and aryl nitrile, respectively.

☐ The counter ion of the copper(I) salt has to match the conjugate base of the hydrohalic acid otherwise product mixtures are formed;

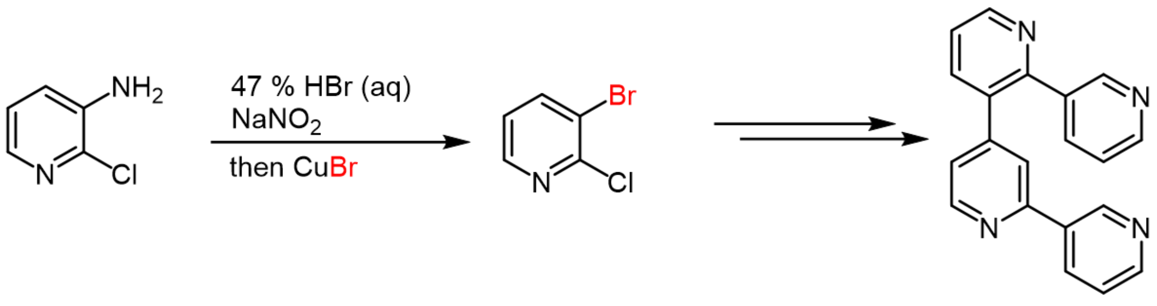
☐ The preparation of aryl iodides does not require the use of a copper(I) salts; simply adding KI brings about the substitution accompanied by the loss of dinitrogen; and

☐ The substitution pattern on the aromatic amine can be widely varied, both electron-donating and electron-withdrawing groups are tolerated.

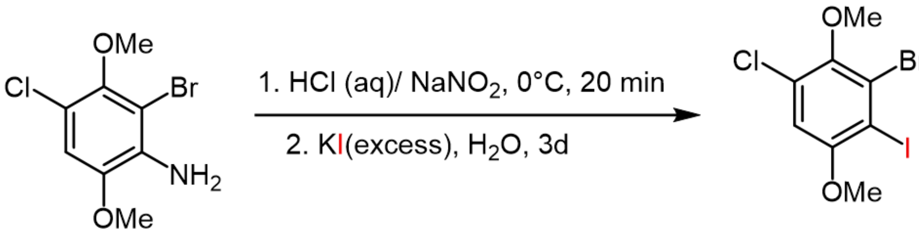
Based on the counter ion, that type of aromatic ring is going to form. If it is a chloride, it will be chlorobenzene; if it is a bromide, it will be a bromobenzene, and so on. The substitution pattern on the aromatic amine can be widely varied; both electron-donating and withdrawing groups are tolerated. So, that is also another important fact that if you have an electron-donating group or electron-withdrawing group with the aniline ring, in both cases this reaction works well. If you see the mechanism, what is happening? From here, the copper(I) is going for a single electron transfer.



it gives the single electron to the aryl diazonium salt, then it is going to go for a corresponding diazonium radical, then it is going to participate for a heterolytic cleavage to generate this aryl radical and N_2 will get out. Now, the aryl radical will going to take this X from this corresponding copper species to form this corresponding aryl halide or aryl cyanide. So, there are some examples here. In this pyridine, you can see there is an NH_2 group here, which can form the corresponding diazonium salt in the presence of the HBr and $NaNO_2$ and now in the presence of the copper bromide, it can able to introduce the bromine here in the C3 position of the pyridine and now it can be converted to the important compounds.

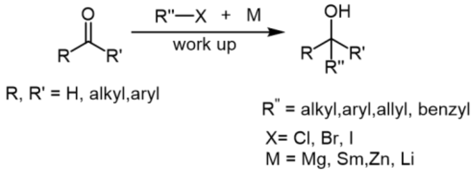


Nemertelline



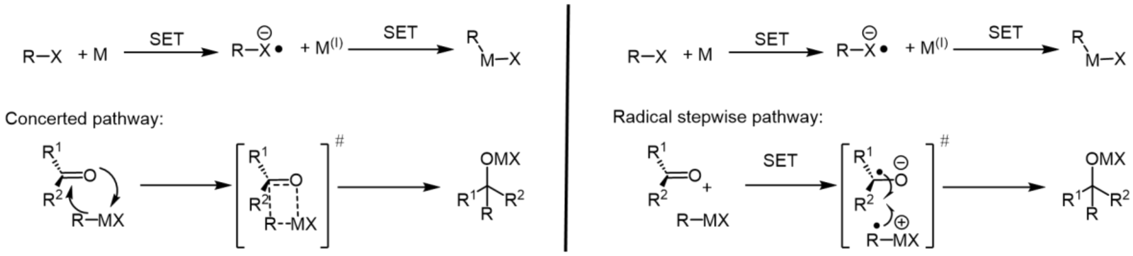
There is another example here. you can see, we have several different functional groups. We already have some bromo and chloro. they are an electron-withdrawing group. At the same time, we have some electron-donating groups like methoxy and amine here. this aniline is now going to convert to this corresponding iodo here. So, what is happening? we are using this corresponding potassium iodide instead of the copper iodide here, which can transfer the iodine here. So, I am going to talk about another important reaction called the Barbier coupling reaction.

- The Barbier reaction is an organometallic reaction between an alkyl halide (chloride, bromide, iodide), a carbonyl group and a metal.
- The reaction can be performed using magnesium, aluminium, zinc, indium, tin, samarium, barium or their salts.
- The reaction product is a primary, secondary or tertiary alcohol.



I think I am going to talk about this reaction again when I am going to talk about the Grignard reagent or the organozinc. when I am going to talk about the corresponding carbanion, where I am going to talk about the different types of organometallic species. So, first we will try to learn what is this reaction? So, this is a reaction between an alkyl halide and a carbonyl group in the presence of a metal. So, the metal is going to act as a single electron transfer agent. So, the reaction of the alkyl halide and carbonyl group is going to end up forming an alcohol.

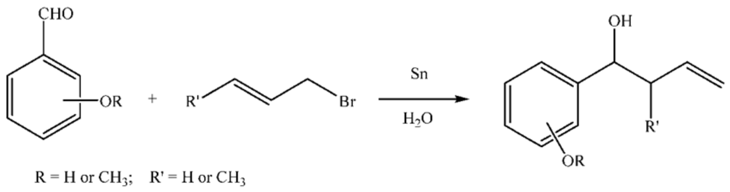
So, depending on what type of carbonyl group you are going to choose, you are going to end up making a secondary or tertiary alcohol or primary alcohol. So, literally, what is going to happen? you are going to form some sort of organometallic species using the corresponding alkyl halide, which is going to add to the corresponding carbonyl species, and once the organometallic species is added to a carbonyl species, after the protonation, it will convert to the corresponding alcohol.

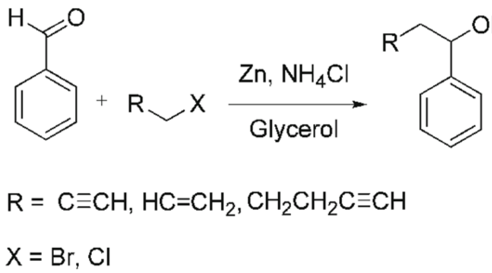


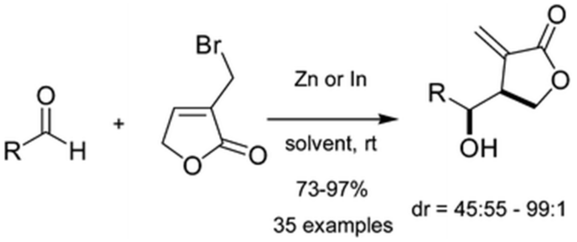
the mechanism is going through a single electron transfer, which means if you start from the RX, here the first thing is there will be a single electron transfer going to happen. So, once the single electron transfer happens from the metal, you expect the metal will be +1, and then there will be RX-dot, which is going for another single electron transfer to form this corresponding RMX. Now, once you form this, after that, there could be two different pathways, which means you know this can add to the corresponding carbonyl compound through a concerted pathway. once you take a H_3O^+, it is going to convert to the corresponding tertiary alcohol. starting here, there is another pathway that can be possible. it can go via stepwise pathway. what does it mean? it can also go through some sort of ketal type of radical, then there will be a radical recombination, and that is how it can go to the corresponding intermediate. From there, if you treat it with H_3O^+, it will go to the corresponding product.

So, now, we are going to see some of the examples here. first example is using tin. So, if you use tin as a single electron transfer agent. So, starting from this corresponding allyl bromide, it can generate this corresponding radical species here, which can add up here through some sort of a S_N2' type of reaction to get to this corresponding alcohol. Then there is example using the zinc, ammonium chloride.

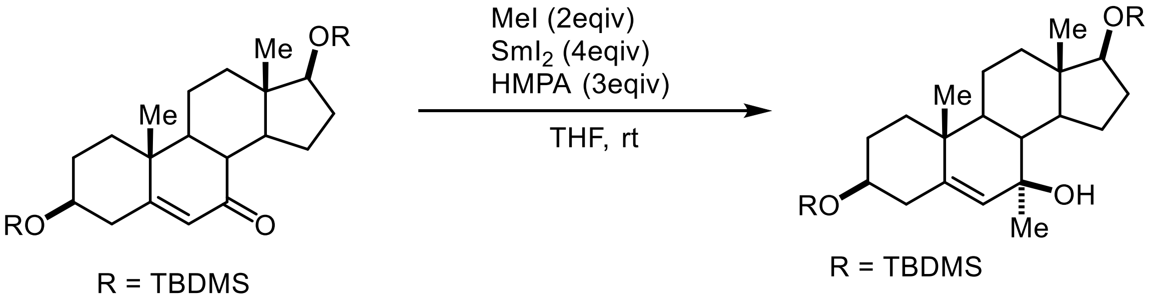
and then they used glycerol, which can quench the reaction. So, what is happening? So, they will be going to make the corresponding organozinc species, which is going to add to the corresponding aldehyde here to form the corresponding alcohol. Again I am going to talk about more details about how the organozinc is formed, when I am going to talk about the organozinc chemistry.







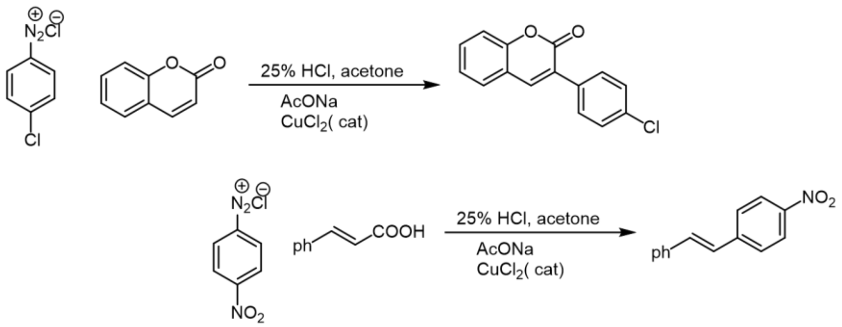
And then there is another example. here you can see in this case also, that this is going to be allylic bromide here if you use a zinc or corresponding indium. that can also form the corresponding organometallic species first. So, there will be a metal halogen exchange going to happen and then that organometallic species ready to add to the corresponding aldehyde. So, once it forms the organometallic species, as you see in a previous case also, it will be some sort of an SN_2’ type of reaction going to happen once you generate the corresponding zinc bromide. And, then it will come back here and it will go to add to the corresponding aldehyde to form this product.



So, there is an interesting example using samarium as I was trying to mention that this chemistry can be done with samarium. And, I think when I am going to talk about samarium in more details, I am going to also explain the Barbier coupling there as well. So, what is going to happen? in presence of samarium and the methyl iodide you can again end up generating the methyl samarium species. So, which can add to this? here you can see there is a possibility of 1, 2 addition or the 1, 4 addition, but what is going to happen? in the case of the samarium, it is going to participate in a 1, 2 addition.

So, if you see in this molecule there is two different way the nucleophile can approach to the carbonyl group; it can come either from the top face or it can come through the bottom face. Now, the question comes from which face the nucleophile will approach. So, as you can see in the top face, you have this methyl group, which is able to make a steric interaction with the nucleophile. For that, the nucleophile can prefer to come through the bottom face to get to this product as a major product.

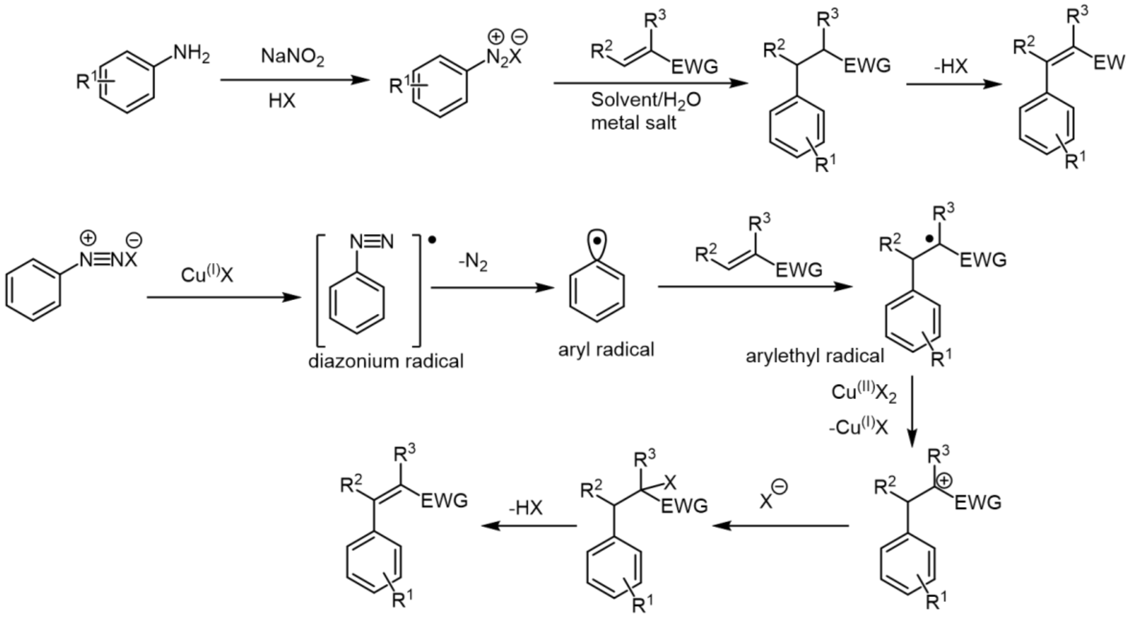
The arylation of substituted alkenes with aryldiazonium halides (formally the addition of an aryl halide to a carbon-carbon double bond) in the presence of a metal salt catalyst is known as the **Meerwein arylation**.



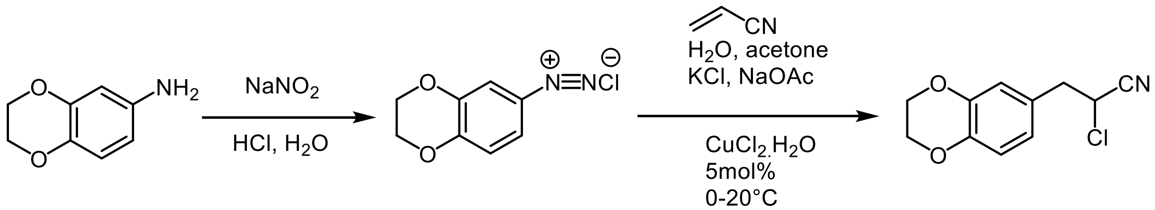
So, now I am going to talk about another important reaction of the radical chemistry, that is the Meerwein arylation. So, you are seeing that, in this particular topic I am going to talk about several different reaction where the single electron transfer is happening. So, there are different types of single electron transfer agent which can generate radical species and now that can participate in different types of reaction.

So, what is going to happen? In the reaction mechanism, first the aniline is going to convert to the corresponding diazonium salt in presence of $NaNO_2$ and X. Now, it is going to add to this α,β-unsaturated compounds. if you have electron-withdrawing group here, the aryl radical adds here . So, in general, this type of aryl radical is a nucleophilic radical that is going to add to the corresponding α,β-unsaturated compounds. And, then what is going to happen? after that it is going to get to this after the HX elimination.

So, let us try to understand the mechanism here. So, first copper is going to give a single electron to form this diazonium radical, then a heterolytic cleavage to generate allyl radical. This it is going to go for a 1,4-addition here. the radical will go for a 1,4-addition to generate a radical species. Now, what is going to happen? Now, it is going to the copper(II), and it is going to take one electron from here. So, it can going to convert the copper to the corresponding copper(I) and then, it is going to form the corresponding carbocation in this position.

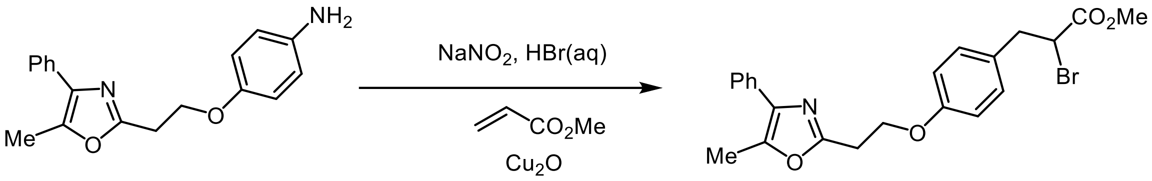


So, now, once it forms the carbocation, the X- which was there available, it going to attack here to form this species . So, there will be HX, there will be elimination reaction from here which is going to form the corresponding α,β-unsaturated compound. So, what is going to happen? Finally, you are able to insert the aryl ring here in the product. So, starting from the aniline, you are introducing aryl ring at end, into the α,β-unsaturated compound.



So, there is an example here. starting from this aniline $NaNO_2$ and HCl going to form this corresponding diazonium chloride, which is going to add here to this α,β-unsaturated compound if you are using KCl, it is going to form this corresponding chloride here. So, they actually want to get to this type of product. If you want to get to the olefin, then you can use some sort of bromide agent which can convert the corresponding bromide and in the reaction condition, there will be elimination going to happen to get to the corresponding olefin. There is another interesting example here.

I think they have also want to get to the corresponding bromo. So, this is α-bromo ester. So, here first thing is the formation of this diazonium chloride in the presence of the copper oxide and then this α,β-unsaturated compound; what is going to happen? It is going to generate a aryl radical. So, this aryl radical is going to add here first and generate a radical species.



So, now, the copper(II) to copper(I) takes 1 electron from here. So, minus 1-electron, CO_2Me, and then what is going to happen; you have the HBr where the Br- going to come here and from this corresponding product. So, in this particular chapter, I talk about the different types of single electron transfer agents, and I have already talked about the different types of pinacol reactions using different types of metals, like I have talked about using tin, using samarium, and using magnesium. And then also I talk about the McMurray reaction, the Barbier reaction, the Sandmeyer reaction, and I talk about the Sandmeyer reaction's different variation. you can see that depending on the counter anion, you can make corresponding aryl halide, which means corresponding chlorobenzene, bromobenzene, or benzonitrile. And finally, that aryl radical can be added to the α,β-unsaturated compound.

And, if you add a base then it can able to form the double bond at the end and if you do not add that then it will form the corresponding α-halo with an electron-withdrawing group. So, there are some of the key references here. You can go through them for this particular topic. And thank you so much for coming to the class, and I am going to see you guys in the next class. Thank you.