Metal Mediated Synthesis - I
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Lecture - 13
Assymetric Heck reaction & Introduction to Buchwald-Hartwig coupling reaction

Hello everyone. So, we will start discussing on the heck reactions stereochemistry or stereoselectivity. We were discussing in the last class we have seen how the syn addition and syn elimination is controlling the regioselectivity as well as the stereo selectivity of the heck product. We have seen if we are starting from the syn or the cis substituted olefin, after the product formation; those two substituent where we are starting from, those substituents will be diagonally opposite to each other. We have seen about that let us look at some of the real example to fill the stereo selectivity during the heck reactions.

So, we will first of all discuss some of these aryl halide reacting with olefin.

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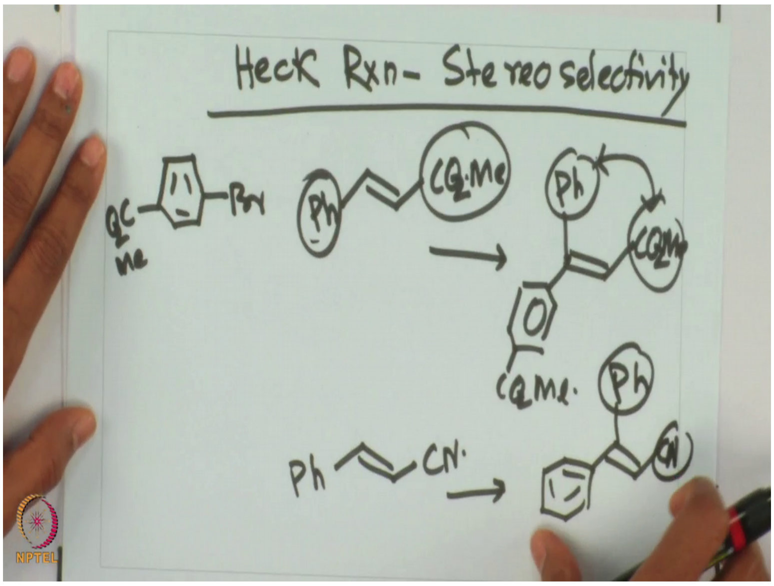

So, we are taking a aryl bromide along with CO 2 Me electron, withdrawing or connection deficient one. Now what would be the product formation from this reaction. Well, I think by now you should be able to predict it CO 2 Me on this side the phenyl substituent will be on the same side phenyl. And CO 2 Me were opposite to each other. Now they should be on the same side, and then your aryl group should come into picture for this sort of reaction, right.

Similarly, so, what we have seen now? We have our aryl bromide, adding to the less substituted olefinic site. And the substituent at that site is going to be the other way around with respect to the alpha site. So, that is all the stereochemistry is about. Let us look at some more example of this type of reaction. We have the same let us say cino with you know similar substrate it will again give the similar type of product where cino and phenyl now are with same with respect to each other. We can have some more substituent in the process.

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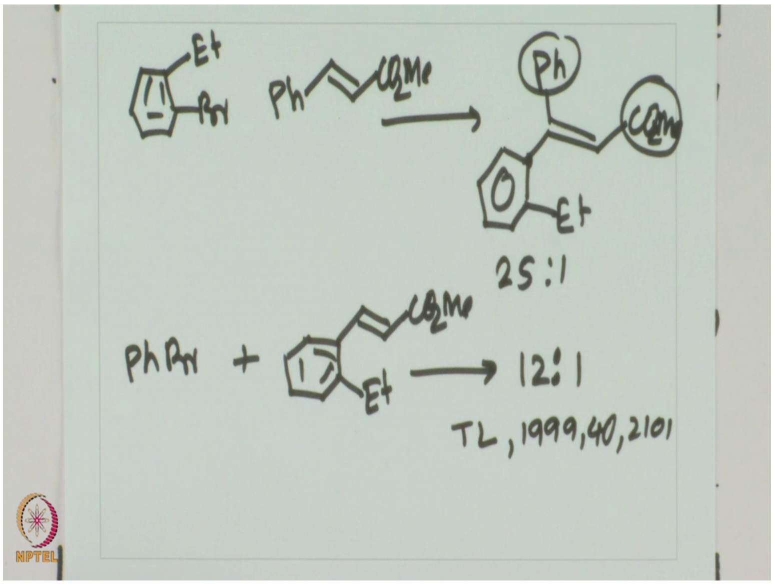

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Let us look at the bromide which is substituted at the ortho position, well is the atom is going to be different, hopefully not because again the syn elimination or beta hydride elimination requirement is the syn geometry between the living group, and the and the palladium center and therefore, once again they will be giving the same product as one would expect, the phenyl and CO 2 Me should be on the same side. And the aryl incoming aryl group can be on the other side the substituent at this ortho position with not hampering too much of the selectivity.

So, this is giving the selectivity 25 to 1 if we are using palladium acetate tetra butyl ammonium chloride and dicyclohexylmethylamine as a base. Now this this is of course, reported by buckwald in 1989, if you are taking a aryl bromide or phenyl bromide during this reaction, what we get is you know 12 to one selectivity. And in this case selectivity is thermodynamic control. So, we are taking the other one what we get is 12 to 1 selectivity with respect to the product formation, but in this case you see the other way around the same product we are getting, but starting with the this substituent.

At this side, its it is not rotating on the other side phenyl is actually coming and adding from this side. So, the selectivity in these case is thermodynamic in nature. And that that is by cunning TL, this is TL you can refer to 1989 40 to 101. That is interesting. Now will with respect to that we will of course, as you can see this is always not going to be the very strict rule depending on the thermodynamic factor also. One need to look at the product formation carefully. But overall this rules remains very simple the same similar, side substituent you know goes diagonally opposite during the heck reaction.

Let us look at one more example with the hetero cycle, because the heck reaction is widely used reaction. It is tolerant to a variety of functional group ester ketone you know nitrile acid everything almost every you know every functional group can be tolerated under the heck condition, which is a relatively milder condition for this sort of you know carbon carbon bond formation reaction. So, it is quite general and applicable for a wide variety of substrate. Let us look at one example where hetero cycle is involved and similarly disubstituted olefin is reacted for this purpose.

With a hetero cycle such as indole, one would say that usually the reaction gets perturbed because the hetero cycle hetero atom are problematic usually for any.

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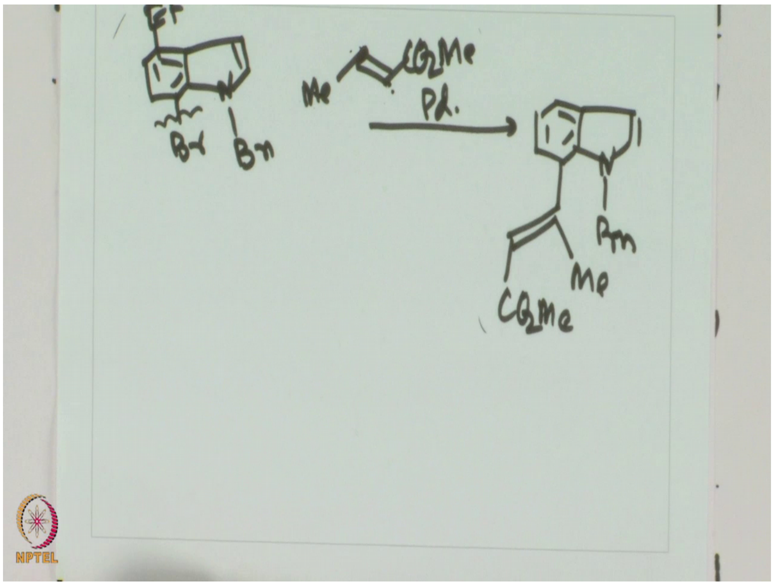

You know, metal containing reaction, but heck reaction is such a mild one and such a beautiful reaction that it works in presence of course, this is catalytic element of palladium acetate or otolyl phosphine and triethylamine as a base and acetonitrile as a solvent at 115-degree c. We do get this product formation where n benzyl of course, is retained. And then over here you see methyl and CO 2 Me are trans to each other, during the product formation methyl and CO 2 Me are cis to each other.

So, what else you have seen. So, this is the site where this aryl group is getting in this is the not that side, because electron withdrawing group at this center. So, the aryl group is joining here, whether methyl will be this side with or it will be on the other side of course, as you seen the methyl is now at the same side as CO 2 Me. So, during this you know syn elimination product formation requirement.

You get this product well that is quite interesting to know overall what we have been seen that during these processes to summarize again, if you have olefin less substituted position gets substituted. That position should be far from the electron withdrawing group, because that that is then it is going to be more electron deficient. In nature if the alpha position has having the electron withdrawing group the substituent will come at the beta position.

That is another thing, and if the substituent at alpha and beta position are thus are on the same side they will go opposite side to each other during the syn elimination, and the heck product formation. We have seen that functional group tolerance is beautiful it works almost for every different substituent, that you can think of even various heterocycles works out that is the you know that is the scope and the tolerance of this method is quite broad in general.

The problem still exists in this heck reaction. And those are incorporation of the aryl halide. Well, how do you incorporate aryl chloride into the reaction that remained one of the problems over long time. Once again professor greg (Refer Time: 08:46) has solved this problem of incorporation of aryl halide. Aryl chlorides in particular while taking tri you know tri tertiary butyl phosphine as a ligand. Now aryl chloride can be incorporated during this reaction. Well, that is that is a welcoming change for this reaction. So, people are still working on developing the existing issues or sorting out the existing issues in the heck reaction.

Well, I think we can keep on discussing more and more on this perhaps the healthier way to do it would be you keep studying from the literature and there are plenty of references, there are plenty of reviews out there. So, you can study more about that otherwise we can move on for now. And then discuss some other carbon hetero atom bond formation reactions which are equally important if not more compared to carbon carbon bond formation reactions. Let us look at the one of the most prominent carbon hetero atom bond forming reaction, and that is known as palladium catalyze reaction and named after hartwig and Buchwald. And so, Buchwald hartwig coupling reactions for the palladium catalyzed carbon nitrogen bond formation reactions.

Let us look at that. Well, I can again actually while introducing this topic. We must also look at few other issues, I think we were discussing in the last class that we should discuss a little bit of the anuncio selectivity you during the heck reaction. Well, before moving into the Buchwald hartwig coupling reaction let us look at the anuncio selective heck reaction. Which is again a various you know various application-oriented area and we have seen tremendous growth in this area as well and industry loves this area; particularly the asymmetric heck reactions.

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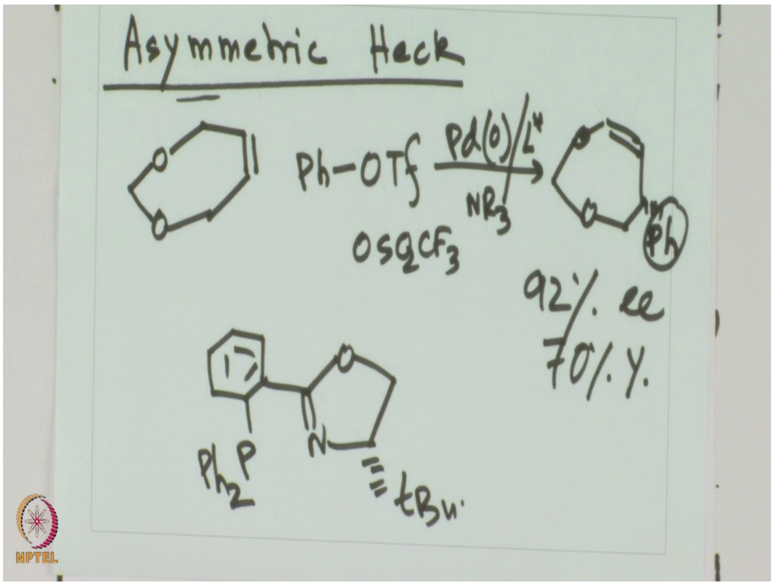

So, asymmetric coupling reaction well. The one example we would like to discuss with the fals ligand, where let us say the substituent is such that it is a cyclic one, and we have Ph OTf as the coupling partner OTf is nothing but OSO 2 CF 3.

And in during this process if you are taking palladium 0 ligand complex, and amine as a base in R 3 amine as the base what you get from these processes is quite also interesting. This is also gives you an idea that shifting can be possible shifting of the double bond can be possible. And you have a phenyl group at this position below the plane. This is a 92 percent e and 70 percent yield reaction. And the ligand that is required for this reaction is the falc reagent or falc ligand that is popularly known.

And this (Refer Time: 11:59) based phosphine amine real a ligand that is quite easy to prepare, though although it looks a little complicated, but the corresponding aldehyde and amino alcohol would give this starting material quite very easily and this tri triaryl substituted aldehyde. One can give this starting material very easily.

In this reaction what you have seen it is a cyclic internal olefin we have started, with there is a alpha position alpha carbon with respect to olefin which is having 2 which is having CH 2 unit. Now during this during this heck reaction what we have seen that that is alpha position CH 2, now is participating during the reaction. To get the double bond shifted at that alpha carbon and with respect to the olefin carbon center, now a new stereocenter is getting generated where ligand the falch ligand is controlling the stereochemistry at that side. And we have seen by utilizing this reaction. We have we can get a very good yield and high anuncio selectivity for this reaction.

You can draw ands here you can draw the mechanism of this reaction quite easily. Once again, this triplet will oxidatively add olefin will coordinate. And then beta migratory insertion will happen, and subsequently during the beta hydride elimination it is the other position that that gets the double bond not the more substituted position. And that is controlled by the hetero atom present in the molecule.

So, that sort of substituent that sort of rolling over of the double bond can happen, if you have a hetero atom at the part of the part of the ring or part of the molecule. That you also one should look out for. And this by doing this then we get an opportunity to create a stereocenter and the asymmetrical version of this reaction can be developed quite easily as you have seen for this particular case we have seen the first ligand is quite suitable for these cases.

We also can get some sort of rollover reaction some sort of you know oxidative addition, beta migratory insertion, and then a heck type of product formation shortly. With more example with 2 more example we will conclude on the heck reaction today, and then the next topic of discussion should be palladium catalyzed carbon nitrogen bond formation also known as buckwald hartwig coupling reactions. Let us look at 2 more examples with the heck reactions.

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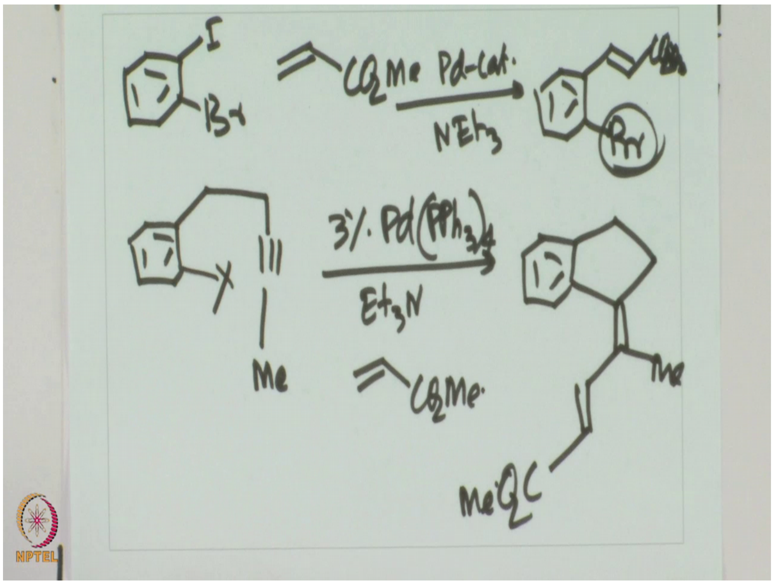

So, the another substrate that we it is quite interesting is the iodo bromo both iodo and bromo are present and selectively only one substituent. And that is the iodo since oxidative addition is faster over there. Once again, the here palladium catalyst palladium 0 catalyze triethylamine, and you can see the final product is even bromo containing or bromo substituted one that is quite interesting.

Other substituent that is quite also very interesting for our purpose is let us say if you have a x or you know substituted halogen substituted one and intra molecular alkyne is placed beautifully right in front of it. And in presence of palladium triphenyl phosphine or tetrakis let us say, we can have triethylamine as a base and this CO 2 Me as a substituent, what we can come over then is this product formation where you see that olefination occurring at the terminal state, and that is quite interesting, right. What is happening here? You have a substrate aryls halide along with that ortho substituted you have alkyne that is appended to it.

Now, this aryl halide will undergo the oxidative addition, and then beta migrative insertion occurs into the alkyne, that gives rise to the cyclic product formation. And then the alkenal halide is right outside that cyclic rate, and from there on then the palladium intermediate will interact with the olefin methyl acrylate in this case, to give you the further substituted intermediate and the product formation right. So, oxidative addition rollovers you know beta migratory insertion, and then the palladium which is rolled over at that alkyne the methyl substituted carbon position that then can react with the olefin just like heck reaction. But in a little elaborate sense to give you know cyclic product formation in this particular case.

So, that is again one very interesting point. Also, another thing you have perhaps noticed that we are using triethylamine as a base is used for a number of heck reaction; that is, giving rise to s condition which is very mild right. Now of course, as we were discussing that initial reagent that we use for this any palladium catalyzed or almost all palladium catalyzed for this carbon carbon bond formation cross coupling type of reaction is the palladium 2 plus.

So, how palladium 2 plus is giving rise to palladium 0 in presence of base such as triethylamine is also a very interesting topic. And almost clear understanding is there at this point which suggests that triethylamine participate into the reaction to give the palladium 2 to palladium 0 catalytic cycle or the activation of palladium 2 to form the palladium 0.

Let us look at the mechanism by which triethylamine is participating for example, to give you the palladium 0 complex from palladium 2. Most common catalyst of course, is palladium acetate, right.

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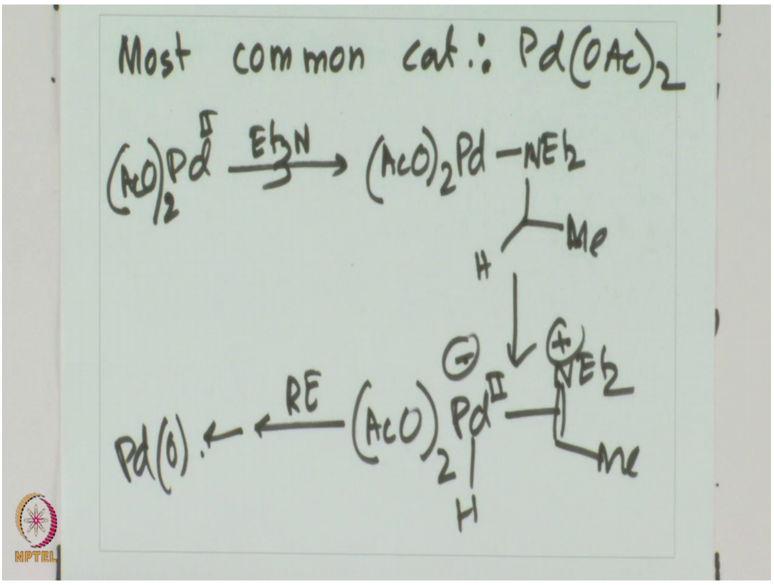

So, palladium acetate how palladium acetate is converted to so, this is in palladium 2 plus condition and triethylamine is coming into the picture. So, first question that comes into mind that is it going to bind of course, this has lone pair nitrogen has lone pair it will bind and the ethyl group let us draw it more of like that you have alpha beta beta hydride elimination is possible from here giving rise to an intermediate where palladium 2, and then tridiethyl I mean this cationic intermediate is formed.

This cationic and anionic intermediate form along with the hydride over there, and then overall, we will get the acetate coming into the picture. Then the reductive elimination can gives rise to the palladium 0 formation, because acetic acid and other things will give you the other side products from this reaction overall, then this will be giving you the palladium 0.

So, palladium 2 acetate reacts with triethylamine, and then this triethylamine coordination and the beta position beta hydride elimination gives right to the palladium to hydride type of intermediate. And from there of course, acetic acid will go out and acetate will react with that triethylamine to give you overall palladium 0.

So, as I was trying to tell you that earlier, we also have previously seen how palladium 2 to palladium 0 formation is occurring in in organolithium reagent or grignard reagent. Similarly, the almost in every palladium catalyze carbon carbon bond formation, we have one way or the other palladium 2 to palladium 0 formation. Therefore, to summarize this reaction then we have seen quite a few examples with a with demonstration of the regio and the stereo selectivity of the heck reaction.

We have seen that heck reaction can be made asymmetry; where we can have the rollover little bit and the alpha position as long as it is connected with the hetero atom that lone pair will help the rollover of the palladium so or so to speak the beta hydride elimination instead of the desired position what one would expect the other alpha position if it is having alpha CH bond, then that CH can give the double bond generation during the beta hydride elimination. During the beta hydride elimination also we have learned that these beta hydride elimination can only occur. If the palladium and the hydride are sync to each other.

In order to gain that sometime what we do see is the rotation of the substituent that might will be might will be there in the disubstituted olefin. And therefore, disubstituted olefins that substitution pattern or substitution relative positioning can be changing more often than not. We have also seen the stereochemistry and the regiochemistry is controlled by the substituent on the olefin.

If an electron withdrawing substituent is present that will give rise to the substitution. At the other carbon center of the olefin, because that is the more electrophilic center in nature. We have seen all these you go through more and more example I am sure you will be able to appreciate the far reach strategy, that that one have one can design during a complex molecule synthesis by utilizing the heck reaction.

So, I hope you will be keep studying on this we if required we can take and discuss more take more question or discuss more about it. In due course otherwise let us move on to the next topic that is palladium catalyze carbon nitrogen bond formation. Well, so far what we have discussed is all involving carbon carbon bond formation. Another wide area of research is the carbon hetero atom bond formation using the organometallic reagent.

This is a widely studied areas because number of drug molecules and pharmaceuticals or in industrial relevant compounds or even for the academic purpose. We need a carbon hetero atom bond formation carbon nitrogen, carbon oxygen, carbon sulfur, carbon phosphorus and so on bond formation we need to have.

Now, the reaction that has revolutionized this area is known as buckwald hartwig coupling or palladium catalyze carbon nitrogen bond formation. In these cases, we have aryl halide or we have alkenal halide, and then react it with amine the amine could be primary amine or secondary amine of course, tertiary amine does not come into picture. So, primary or secondary amine can be reacted with aryl halide for example, to give you the aryl amine or aryl substituted amine.

Now of course, there are quite a quite a lot of challenges in these areas, whether you take the primary amine or the secondary amine; whether to take the completely aliphatic primary amine or completely aromatic primary amine, whether to take disubstituted amine or that secondary amine aliphatic, or the aromatic, one or aliphatic aromatic combination.

So, all these makes it all these issues of amine and the you know the variety of amine that we can have, makes this process very interesting. Similarly, for the alcohol, we can have phenol or aliphatic alcohol. The aliphatic alcohol is having alpha substituted one, and beta substituted one. So, overall, we can have plenty of different issues that to discuss during this palladium catalyze carbon heteroatom bond formation reaction. Both the carbon nitrogen and carbon oxygen or even carbon sulfur bond formation reaction are usually broadly referred to as this buckwald hartwig coupling reaction, we can have alpha substituted alcohol, beta substituted alcohol. All these can react actually quite differently.

As one could imagine, the mechanistic things will be similar right as that of let us say for example, heck reaction we will have aryl halide. As we were saying aryl halide will oxidatively add to palladium to give the give the palladium 2 intermediate from their own amine or the alcohol coordination. And then deprotonation in this case, unlike the heck reaction deprotonation and then insertion will give you the product like intermediate from where you can you can dissociate the product from the palladium intermediate to give to generate the palladium 0 and the organic molecule.

Now we will we will discuss more on that in the subsequent class. So, I guess we will be discussing stepwise different issues with this carbon hetero atom bond formation reaction and also, about the ligand designing overall into this carbon carbon and carbon heteroatom bond formation reaction. Why it is important and the what has been really done to solve this existing problem of ligand designing

As I was discussing oxidative addition and reductive elimination are completely opposite with it is respect to each other therefore, ligand design can be very, very complicated issues for this metal catalyzed reaction. What are the aspects of ligand design in that we need to look at and how researchers has come up with different ideas, and some of them has revolutionized and they changed the way these palladium catalyze reactions in general are done not only that those ideas you can now be incorporated not only on palladium, but with variety of other metal, where any these new bond formations can be taking place.

With those discussions we will come to the next class, till then keep reading if you have any queries feel free to contact the or to me directly.

Thank you. Bye-bye.