Metal Mediated Synthesis - I
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Lecture - 11
Sonogashira coupling reaction

Hello, welcome everyone. So, I hope you are enjoying the carbon carbon bond formation reactions. It is amazing what this organometallic chemistry can do for these carbon-carbon bond formation reactions.

We have seen the Suzuki reactions that is quite great we have seen thenegishi reaction; we have seen also the kumada coupling reaction. Today we will briefly discuss say the each of these areas are quite huge and it has been studied over the last few decades enormously, There is always a limitation of time; how much we can discuss each of this reaction.

But it is essential perhaps from the course perspective to discuss each of them briefly and try to convey the main messages that is there for these carbon carbon coupling reactions. And then if time allows maybe each of them we can come back separately and discuss in a greater detail.

Today, we will like to introduce two reactions namely sonogashira reactions and Heck reaction. In sonogashira reaction, it is a very powerful transformation where a terminal alkyne is reacted with organo halide; mainly aryl halide and vinyl halide. So, sonogashira reactions are quite effective for such transformation and it has been quite widely used irrespective of industry and academy. Let us look at the sonogashira reaction; the reaction mechanism and what are the important features of this reaction that will be interesting from the course perspective

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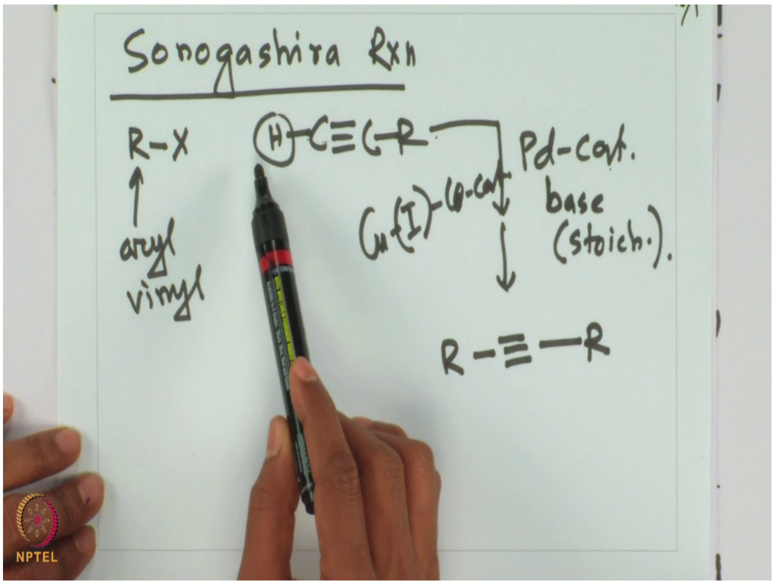

So, sonogashira reaction; sonogashira you are taking R X; this R is aryl or vinyl that is it. And you are having a terminal alkyne; so, this H is there, overall you will get a palladium catalyst usually nowadays lot of variations are there; copper one; co catalyst, not cobalt this is a co catalyst and a base which is usually stoichiometric amount; that is for example, triethylamine and so on; overall you get the product formations which is a internal alkyne.

So, essentially from a terminal alkyne you get an internal alkyne in the process and that is helped by the palladium catalyst. One as you look at the reaction, you can imagine that palladium catalyze catalyst will undergo oxidative addition into this R X bond and subsequently you know; this alkyne will interact. The way alkyne will interact is copper will be you know inserted into this copper acetylate intermediate will be forming and then that will be transmetallating into the palladium. We will draw the mechanism and subsequently reductive elimination will be happening.

So, what we will be discussing now is the reaction mechanism of this sonogashira reaction. As we tell that it is a R X aryl halide or vinyl halide; it will undergo oxidative addition with metal; that means, palladium in involvement with palladium. After that acetylene unit; terminal acetylene unit or terminal alkyne has to interact with the palladium. The transmetalation will not happen directly, it will need that usually I mean nowadays various options are available, some traditional variation from this sonogashira reactions are done.

But usually what is happening is copper is helping in the transmetalation process overall of course, you need a stoichiometric amount of base for deprotonation of the alkyne upon binding with copper. And subsequently it will be able to transmittal it and in the final state; we will see the reductive elimination between the R X, R group of the R X and the alkyne unit to give you the terminal olefin a terminal alkyne to that internal alkyne product.

Let us look at the mechanism which should be simple at this point since we were discussing these reactions quite similar reactions previously.

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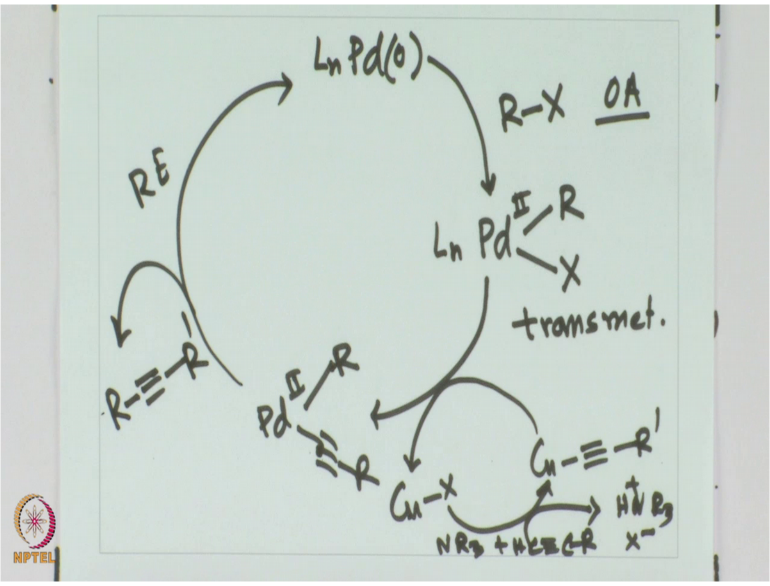

Reaction mechanism will involve against ligand palladium 0 complex; it will react with R X that is the step which is oxidative addition and from there we have ligand palladium R and X intermediate; this is the oxidative addition intermediate. We will have from there the transmetalation; so that is transmetalation; I think that is the main interesting aspect; we have copper acetyl intermediate acetyl at intermediate to give you overall copper X comes out and in the regeneration stage, we have a stoichiometric amount of base plus let us see the starting material and over here we have H N; R 3 X minus coming out.

During the transmetalation step of course, this is a palladium II; during the transmetalation again it is the palladium II and acetyl intermediate is involved. So, palladium 0; oxidative addition intermediate interacts with R X to give you the palladium two intermediate. Now this copper acetyl exchanges with the X; so, acetyl intermediate goes out; the X gets associated with copper copper X comes out. Now which copper X then react with the starting copper X or the regenerated copper X react with this amine and the acetylene or the terminal alkyne to give the copper acetyl intermediate

From there on its the simple reductive elimination that is the product formation between this carbon center and that carbon center; this could be a sp II; sp carbon center usually that will give you the desired internal alkyne that you are looking for. So, what we have seen so far is a starting from let us say bromobenzene and the terminal alkyne, you will be getting aryl substituted internal alkyne. So, if you are taking phenyl acetylene and aryl bromide; you will get aryl phenyl acetylene compound.

Well, these are really amazing transformation and it works beautifully if the catalyst loading can be very low. And nowadays different variation of palladium free copper free, sonogashira all those different variation of the sonogashira reactions are also available. But reaction works best when it is used in conjunction; in combination; that means, both palladium and copper are used together. And these palladium and copper can be used in catalytic amount, but you need stoichiometric amount of base because the deprotonation of phenol acetylene requires the base.

Let us look at how this deprotonation will be happening during these processes. So, transmetalation is one of the most interesting step let us look at; so you start with copper X.

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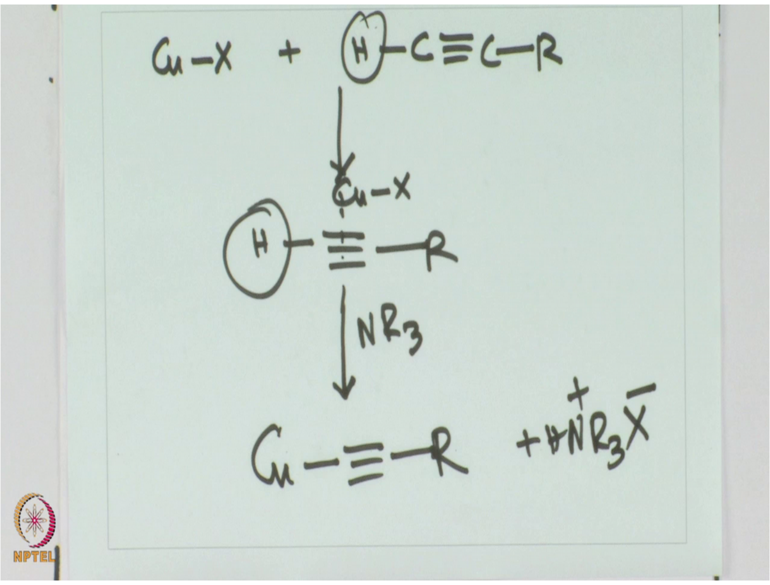

And then react with acetylene; terminal acetylene or terminal alkyne and overall you have first step as alkyne interacting with copper X. Now itself this deprotonation will not be possible; deprotonation from here will not be possible. It is required to have the copper interaction and therefore, it is now acidic enough for triethylamine to deprotonate.

So, without copper this deprotonation just by; I mean will not be possible, once it is interacting with copper then the pk value goes down; the lower pk value ensures that it can now be obstructed, this proton can be obstructed by this amine. In the process you have copper; acetylene intermediate formation and you get H N R 3 X; H and R 3 X, you overall get from this process.

Now, this is very simple; so the role of copper we do understand now, the copper role is mainly in the transmetalation step. And the role of palladium is also very simple; it holds that catalytic cycle together; it gives the oxidative addition then transmetalation and the palladium center and then reductive elimination happens to give the product.

It is a very simple and clean and efficient method; how efficient it is? Well, you can see it if you have two halide; in one substrate. Let us say alkenal halide; you are reacting with one equivalent of aryl halide selectively only one halide can be displaced. So, one type of aryl you can introduce in one end and on the other end you can introduce another one.

Let us say you have divinyl halide and you try to react it with two different alkyne, you would be able to do that. Let us look at one such example where this reaction is facile and one can do this reaction quite efficiently this sonogashira reactions.

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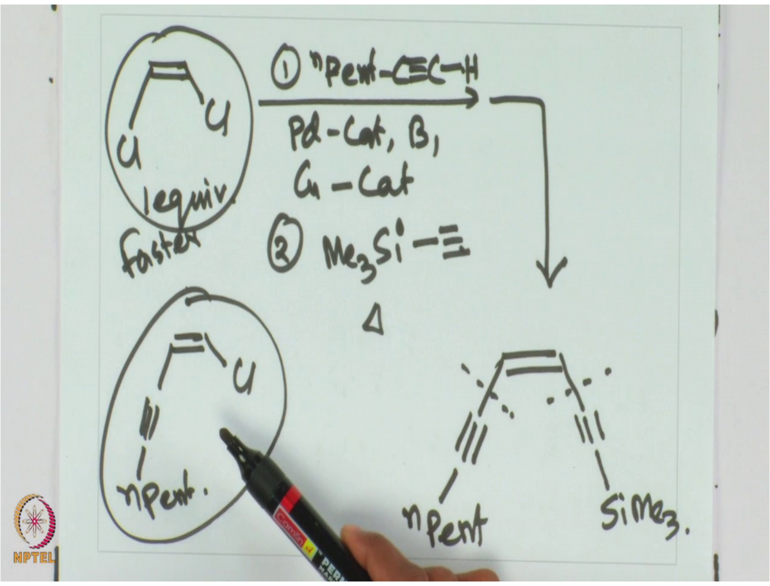

The substrate we have in interest is a dichloride; the idea here is to put one alkyne here and a different alkyne here. Let us say you take one equivalent of this and then one of the alkyne let us say N pentanyl alkyne, you take one equivalent and you are doing palladium catalyst and you are taking a base, you are taking also copper catalyst; that is the first step. Second step; same part you can take another alkyne and then you of course, heat overall.

Overall what you will see this is one equivalent, this is one equivalent and this is also one equivalent. So, one equivalent will react with this one first to give the alkyne in one end, the other end will not be reacting at all that one will react with this one to give you know a symmetric or to differentially substitute an alkyne into that olefin starting material. So, in one hand for one equivalent alkyne it will be this and the other equivalent will give rise to the Si M e 3 product on the other hand.

So, what we are trying to tell that is; if we have multiple halide into your electrophile; each of those halide can be selectively reacted. Because the reactivity of the primary one or the first one is much more compared to the one that is undergoing the product formation, so we can selectively control the product formation very efficiently. And therefore, if you have alkenyl dihalide each of those halide can be selectively transformed to the alkyne; with the alkyne product to give the two differentially substituted alkyne into the final product. Therefore, let us look at once again you have alkyl dihalide; the intermediate that is involved in this case is this one, in pentile let us say.

Now, oxidative addition into this compound is faster compared to this one. Therefore, you will get if you take one equivalent, one equivalent; you will get the nearly 100 percent conversion for this product and subsequently this chloride will react with that one. So, oxidative addition is fast in this substrate compared to that one and that would lead to the product formation cleanly and in quite good here. In that next part well we are not going to discuss way too many example; one can take any number of example and discuss the efficiency and everything.

What in the sonogashira coupling reaction; we tried to discuss simply is we need a palladium catalyst, we need a copper catalyst, we need a base. We need two coupling partner ;one is halide electrophile; it could be aryl halide, it could be alkenyl halide. The other coupling partner that we need is the alkyne that has to be terminal alkyne; now that terminal alkyne CH bond will be displaced by this aryl halide; aryl partner or alkyl halide team partner.

That is the sonogashira reaction; palladium will help us in doing the oxidative addition into the electrophile. And the copper will help us deprotonate the alkyne and subsequently it will undergo the transmetalation step with the palladium and then the reductive elimination will give the product.

It is a beautiful reaction nowadays various variation is available, but overall what we see that we can control the substitution very efficiently. As we have seen with one example where two halides are there; selectively one halide at a time can be alkyne elated and the other halide can be remain intact. And that halide can be again substituted by yet another alkyne to give the di alkyne substituted olefin intermediate.

Now we would like to discuss another carbon carbon bond formation reaction which is again quite popular. As you know Suzuki and Heck both shared the Nobel prize along with the third partner; now this Suzuki reaction we have seen that is a noble reaction and Heck reaction now we will discuss.

Surprisingly, you know at the beginning when Heck was discovering the Heck reaction; he did not get enough support from the funding agency. I mean can you imagine that he has to quit from academics almost to do his chemistry. Richard Heck was quite convinced that this is a great reaction, but funding agency could not believe or did not believe him that it was a important enough reaction. There was a severe problem in funding, but as you know since then like 70s, 80s he kept on working on these reactions and it becomes quite popular over the years and subsequently in 2010 he got the Nobel prize; that is quite amazing

Well another sad thing is he passed away very recently after developing this carbon carbon bond formation to quite a great extent. So, today we will discuss the Heck reaction and that is the reaction between aryl halide and olefin. Previous reaction what we have seen? We have seen aryl halide and alkene sorry alkyne; terminal alkyne. Now we will see aryl halide and olefin that is the main part of the Heck reaction. Now the various development has been done, we will slowly look at that, but mainly the Heck reaction as it is that was what was discovered and then how it was developed subsequently we will now discuss; so, Heck reaction.

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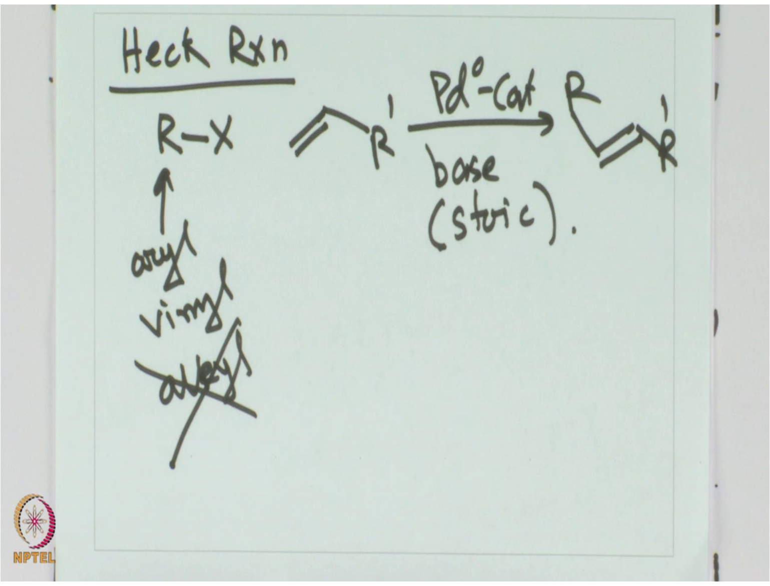

Now, the major part of the Heck reaction is R X; this could be aryl and vinyl on alkyl actually does not work. And it reacts with an olefin to give you the desired internal olefin or the olefin; usually it is an internal olefin that people are interested or people to get. So, you need base in stoichiometric equivalent; well that is a quite interesting reaction in its own right.

What we do see here is; you know aryl halide, as you can imagine it will undergo oxidative addition with palladium. And then olefin will coordinate beta migratory insertion into the olefin and then beta hydride elimination from the product that is formed after beta migration subsequently you will see the olefin is removed from the palladium.

So, overall in this reaction we will see palladium will oxidatively add to halide; aryl halide or alkenyl halide after oxidative addition we will see olefin will coordinate with the metal center. From there on insertion of the aryl or alkenyl part into olefin will occur; that is the beta migratory insertion. From that intermediate, we will see a beta hydride elimination to give you the; that is the thermodynamically stable product usually to give you the final olefin.

So, you start with the olefin; you end up with another olefin where your aryl or vinyl partner is incorporated into the process. Into the sonogashira reaction, you start with an terminal alkyne and the terminal CH bond is substituted by aryl or vinyl which is coming from the aryl halide or final halide.

So, terminal alkyne to internal alkyne you form in case of the sonogashira reaction; in case of a Heck reaction you start with one olefin, you get with a more substituted olefin and both the reactions as you can see are quite important for synthetic chemistry. Let us look at the simple steps of the Heck reaction; what we try to discuss right now.

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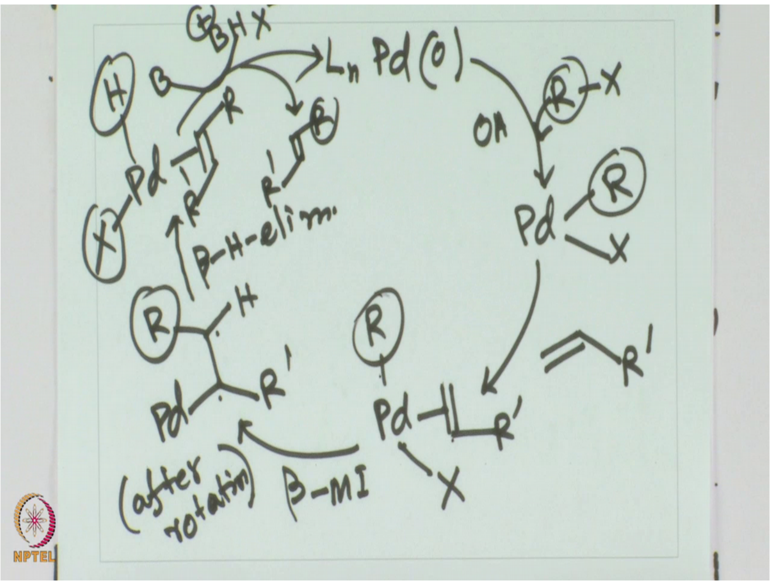

So Heck reaction intermediate and Heck reactions the reaction pathway Ligand palladium 0; that is crucial for the reaction; first step is oxidative addition. We will get our X and overall we will have palladium R X intermediate; which is same as before. It will react with olefin and from there on, we have olefin coordination just it is coordination and nothing else initially and now we are ready for beta migratory insertion.

Why it is a beta migratory insertion? In a moment, we will see the palladium will coordinate with one of these two carbon center; with respect to that palladium carbon coordinates; R is at the beta position. So, the intermediate we usually get is that one where we have R; this is the R that is over this or that is over that one. Now it gets at alpha beta; beta position it gets inserted.

So, this is the beta migratory insertion step from there on of course, you have to have after desired rotation where you will get to the right orientation. From here you will get beta hydride elimination to give the palladium olefin intermediate that is required for the product formation and you have H X; both H and X can leave out and the olefin is there that can again leave out from the product.

Overall, in the final step you will have this coming out to give you B H X minus B H plus X minus and the product formation that is R; olefin R prime; that is the cycle we are drawing. So, it is a simple catalytic cycle that you have seen; where palladium 0 oxidatively add to the aryl halide or olefin or alkenal halide. And subsequently what we do see is the olefin interaction with the palladium intermediate incorporation of the R group coming from aryl halide or from alkenal halide.

That R inserts into the olefin at the beta position with respect to the palladium center where it is attached with the substrate; that center is beta. And from there on after suitable rotation, what is required for the beta hydride elimination; we do see that it is the beta hydride elimination product gives you the olefin product which is coordinated with palladium along with hydride and ex halide that is coordinated.

If you give now a base; base will take to give B H X intermediate; B H plus and X minus intermediate, overall you regain or regenerate the palladium idiom for the next catalytic cycle and olefin also falls off from this intermediate. So, in this class so far we have seen two important reaction; sonogashira and the Heck reaction. We did not discuss too much about the Heck geometry or the product geometry, where R group will be migrating that aryl group whether it will give you 1, 2 product or a 1, 1 product.

Those control of the geometry for the product formation we would like to discuss in the next class. And also we will be discussing in detail the selectivity that will be obtained during the product formation. Heck reaction could be little bit more interesting in terms of understanding how the product formation and the product distribution are happening. Not only that this reaction we can have an asymmetric version, you are perhaps wondering how an asymmetric version can be introduced. We will be discussing that in the next class as well; you can do that as you know palladium can pretty much work along the ring or along the carbon side.

So, that could leave a option for the stereocenter generation; we will discuss about that. We will discuss some more example or the examples of the Heck reaction that we did not discuss too much today. In the next class, then I hope you will be able to remember this mechanism.

Based on this, we will be able to discuss more of the examples of the Heck reaction and the a symmetric version. Well till then keep studying this sonogashira and Heck reaction; we will come back soon with examples and discussion on the Heck reaction in the next class bye.