# Metal Mediated Synthesis - I
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## Lecture – 16
## Oxidative cyclization process

Welcome back, so the, today's class will continue discussing on carbon nitrogen bond formation reactions. We have seen in the last class, that how Ligand can influence each and every process, each and every step of the palladium-catalyzed carbon-nitrogen bond formation reactions. Of course, if a very easy combination is there, let us say, aryl iodide is there and a very good you know I mean such as your aniline is there, then we can have corresponding diaryl amine synthesis pretty easily. So, it is all depends on the type of substrate we are dealing with. If the combination is very easy, 2 combination you need for cross coupling reactions, if these both the substrates are suitable for the coupling reaction we will get a reaction pretty easily.

However, if any of the component becomes difficult, then we really need to see what best we can do for increasing the yield and efficiency of these processes and that is where the Ligand design can be extremely crucial. If there is a easy combination you can get the reaction even with Triphenylphosphine, but lot of cases or most often than not what we have seen that the Triphenyl phosphene or other easily available Ligands which are, we are more familiar with are not sufficient or efficient enough to carry out the coupling reaction.

Remember, most important things for these type of coupling reaction is to reduce the palladium loading, reduce the time, reduce the temperature and every possible things, every possible parameters one can optimize to get these reactions going in a greener way or in a better way, that is something all are looking for.

Now, in order to get a lower catalyst loading or in order to get a better and more efficient reactions, we usually have to deal with a Ligand, we should have a system; we should have a catalytic system that is going to be very, very efficient and this is where Ligand plays a crucial role. If the Ligand metal complex is very efficient for a given process, then the overall palladium loading goes down and that means that, the removal of the palladium is not a big problem for a pharmaceutical industry. Well, of course, the cost of palladium one has to look at, once looking at any given reaction.

Now, we have seen for the biaryl phosphine ligand how it can bind with the palladium center and what it can do in doing the oxidative addition, amine binding deprotonation and the reductive elimination process. Let us, look back at those drawing once again to appreciate the fact how good this biaryl phosphine ligand might will be, for these palladium catalyzed carbon nitrogen bond formation processes. So, what we have right now is the same drawing what we have tried to do in the last class.

Now, we have it in (Refer Time: 03:49) draw fashion already ready.

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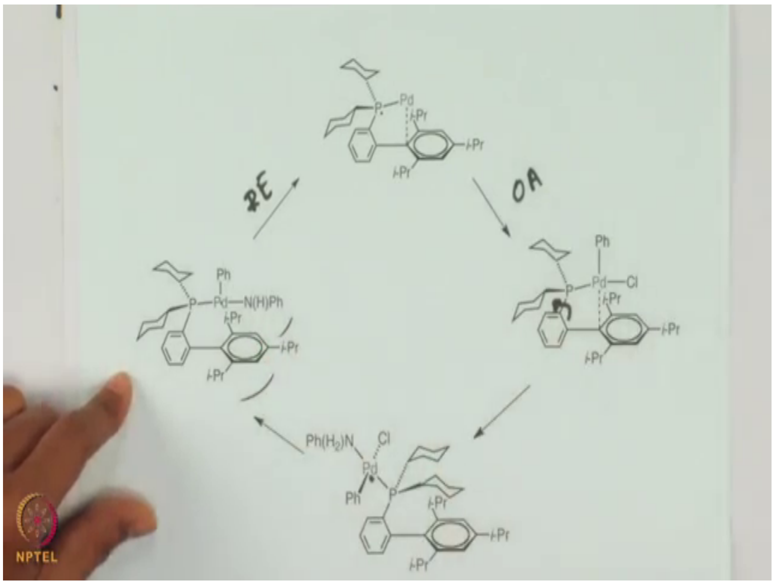

What we do see that, the palladium is coordinated with phosphine ligand and interacting with the bottom phenyl ring and from this conformation this palladium is on top of the phenyl ring, it is not the other side, palladium is not on the other side because it is having low coordination it prefers to have this coordination from the bottom phenyl ring.

Now, after this we will have the oxidative addition into aryl chloride or chlorobenzene in this case to give rise to an intermediate, where palladium is 1, 2, 3 and 4 coordinate and subsequently what we can have is the amine coordination method, but amine coordination in this geometry is not going to be possible, for them happens in palladium flip over on the other side while amine is coordinated with palladium. So, palladium is no longer towards the bottom phenyl ring. So, it is swipe or it is like showing away from the bottom phenyl ring.

So, basically a C palladium bond route, C P bond route gives rise to the orientation, where palladium is far from the bottom phenyl ring. In, under that condition we can have the deprotonation also pretty easily. Once, deprotonation is happening or happened then, it can come back because during the deprotonation will lose H C l overall and then it becomes a 3 coordinate from where, if we are to get a reductive elimination, we need to create an atmosphere which is sterically crowded, if it stays on the other way around after deprotonation, then it is less sterically crowded.

By bringing back the palladium on top of the phenyl ring, it again regains the steric crowd, which will be essential for the reductive elimination step. So, this is essential for the high efficiency and turnover number for the palladium to come back on this side and there is enough evidence in support of each of this step at this point in the literature.

Now, if you look at very carefully, the step before the reductive elimination, the materials before the reductive elimination. Let us, look at it once again, what is important and what can give rise to a pre catalyst like design from this transmetallation or deprotonation intermediate. Let us, look at it. If you look at this intermediate where you have palladium, Ligand, N H and phenyl, this orientation over here is extremely important to note, where we have the palladium over there and phenyl over there and phosphine ligand is coordinated with it. This is the aryl ring and this is the image and this is the ligand.

Now, keeping that in mind what people have done is, come up with a design for the pre catalyst. Let us, look at that pre catalyst design. So, remember we have a palladium, aryl, amine and a phosphine ligand coordinated with palladium. Now, how can you design the pre catalyst from such a orientation, which will be essential for our pre catalyst design.

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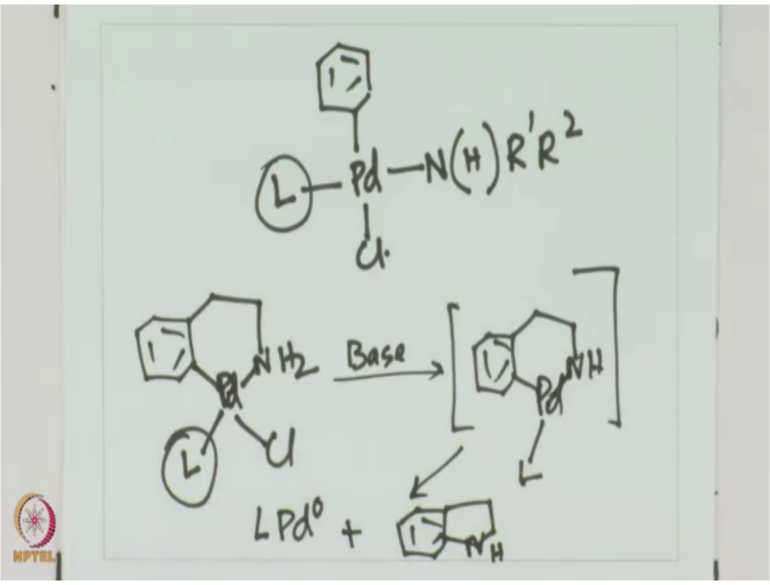

We do have a phenyl ring and we do have a palladium with it and then there is a Ligand with it. Now, before the deprotonation what we were having is N H R prime and R 2 and chlorine.

Now, looking at it, what scientist has designed, this is a once again by Buckwald group at M I T, if they have come up with a design which showed that if you can combined this aryl moiety with this amine. So, that means an intra molecular set up, where N H 2 is given, now palladium L C l, now this is the Ligand that biaryl phosphine ligand we are talking about, this is the same ligand we were talking about. What we have essentially done is the C palladium bond we kept it constant from the ortho position, we have attached the amine.

Now, this is a material which one can synthesize and stabilize and keep it without any problem in solid state. So, therefore, this material can be procured from the chemical company. Now, in presence of this, what can be done simply is we can get rid of H C l from this intermediate and therefore, what essentially we have is a palladium ligand and this deprotonation intermediate. From there on we will get Ligand palladium 0, after reductive elimination of the intermediate to give you the product like in the line.

Now, in this reaction, what essentially we have seen is very simply by putting the oxidative addition and amine coordination into the pictures and now design in a way so that your 2 coupling partner attached with each other. So, this is more of an intra molecular reaction. Of course, this reaction ideally we are not interested in because this is an easy reaction and taking advantage of this, we can get an oxidative addition into that amino aryl chloride moiety, where Ligand is attached with it.

Now, if we have this material readily available from commercial shows, at that point what we can have is the oxidative addition intermediate in presence of base and heating can give rise to the deprotonation, subsequently reductive elimination to from the product, which is something we are not interested with. This can come up in, let us say if we are using 1 mole percent of this catalyst, this can form in 1 mole percent, but what it gives you is a clean formation of Ligand palladium 0 in 1 mole percent. During the process we do get the indo line as the product.

Now, so what essentially in this case we are trying to come up with is, a method that gives you a clean let us say, one mole percent of palladium ligand 0 complex formation. This will be essential for very low loading and low and very high turnover number and frequency of the catalytic cycle because if the Ligand palladium 0 is complex, can be synthesized pretty easily, without any loss in efficiency that will be essential for a highly efficient reaction.

So, therefore, taking advantage of the known catalytic cycle a pre catalyst can be designed, which can readily supply the Ligand palladium 0 along with formation of the organic compounds, which is let us say will be formed in equivalent quantity as we need the Ligand palladium 0 species. For example, if we need 0.00 one mole percent of palladium for a reaction, then 0.001 percent of organic molecule will be generated, during the reaction which is negligible amount.

Now, 0.001 mole percent of this palladium with Ligand can be generated very efficiently and very precisely in the reaction mixture, that gives us the opportunity to do the reaction in very high efficiency for a given carbon nitrogen bond formation because the Ligand palladium 0 that it is getting generated during the process will be then participating in the real catalytic cycle. So, this is a method all to get, all to prepare the Ligand palladium 0 in C 2.

Let us, move on then the discussion of some other processes, where we will be seeing the role of metal, mainly early transition metal for the cyclisation processes. Now, we will bring a new topic at this point to discuss the cyclisation processes or oxidative cyclisation processes, where once again metal plays a critical role to bring 2 or more unsaturated moiety together, so that new carbon-carbon bond formation is happening.

Essentially in this next process oxidative cyclisation process, we would like to look at how, let us say for example, alkyne and olefin are put together to give rise to value added product. Then starting materials are readily available, but you need, one need some metal complexes to come up with the cyclisation process or a desired transformation process, which can gives the added value to these commodity chemicals.

Let us look at the oxidative cyclisation and discuss more on that right now. So, we are going to discuss oxidative cyclisation in the process of doing the cross, doing these transformations.

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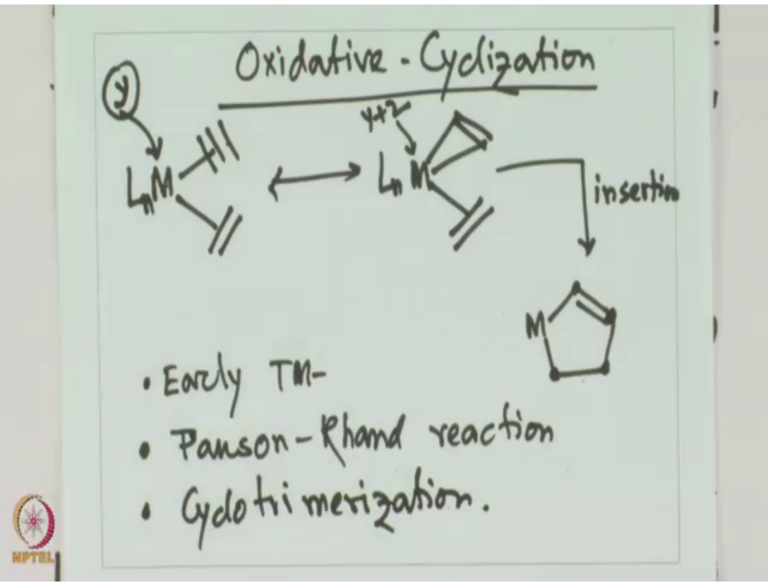

Oxidative - Cyclization

- Early TM-
- Panson-Rhand reaction
- Cyclotrimerization.

Oxidative cyclisation, now this is a process, where a Ligand metal will interact with alkyne and another alkyne or another olefins. Overall, if Ligand oxidation state is y for example and we will get in the product, Ligand metal oxidation state change to M plus 2. If it is, y it should be y plus 2 and along with it, we can have the olefin binding with it. So, overall alkyne and metal interacts to form a cyclopropene type metallo cyclopropene intermediate. Therefore, metal oxidation state goes up from y to y plus 2, subsequently we can have the insertion method; insertion process into this metallo cyclopropane ring to incorporate or to form a 5 member metallo cycle intermediate.

So, this 2 carbon centers are coming from this olefin and these 2 are from the alkyne. If it was a 2 alkynes, alkene and alkyne and then we should have another double bond over there. Usually, we have early transition metal for this processes, early transition metals are usually huge. Of course, another important thing we do we can discuss in this banner is the Pauson khand reaction, that is a very powerful technique and lot of natural product are synthesized by utilizing this technique, not only 2 partners we can also have up you know even the 3 coupling partners. So, we can have cyclotrimerization by utilizing this technique.

Well, essentially this method gives rise to a situation, where early transition metals are used to couple 2 or more unsaturated unit together to form the new carbon-carbon bonds essentially often gives rise to the cyclic compound formation which otherwise from these commodity chemical, from this easily available chemical would not have been possible. We have seen right now, an alkyne can be reacted with an olefin to give you the cyclopentene intermediate; mettallo metallo cycle intermediate.

We can also have 2 different sites, alkyne to gives rise to the cyclopentadiene type of intermediate and the metallacycle cyclopentadiene type of intermediate. Essentially we would deal with the early transition metal; we are also going to discuss the pauson khand reaction which is the extension of this type of reaction. Additionally, of course, one can think of 2 plus 2 plus 2 cyclotrimerization reaction by utilizing this technique to give the value added product formation. Let us look at the early transition metal processes or what are the different category of these processes that might will be involved in these oxidative cyclisation technique.

So, we are going to look at oxidative cyclisation processes, where this early transition metals are involved.

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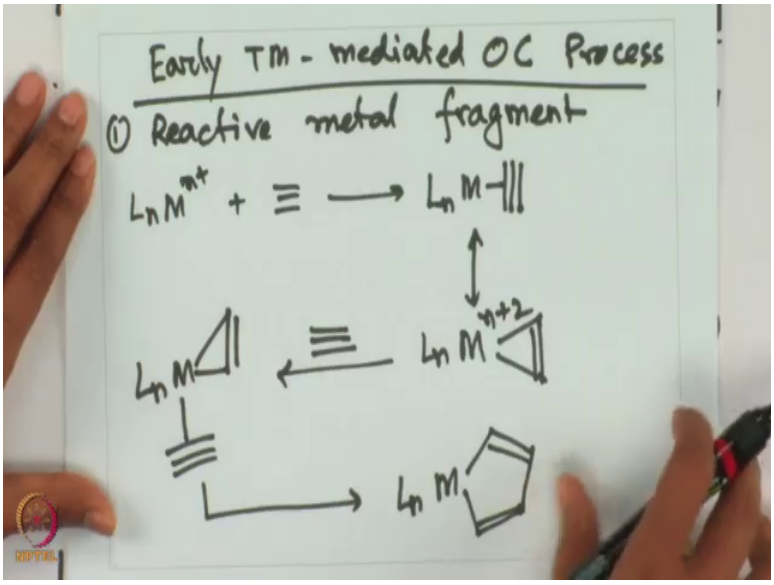

Early TM - mediated OC Process

① Reactive metal fragment

Early transition metal mediated oxidative cyclisation processes. Well, first we will deal with the reactive metal fragment. In this process, we will see that an alkyne is reacting with, for example, another alkyne to give you the metallacyclopentene intermediate. So, we have a Ligand metal reacting with an alkyne to gives rise to the Ligand metal alkyne interaction at the beginning, subsequently this intermediate. So, if it is metal m plus it would be an n plus at this stage, subsequently Ligand metal can give rise to the n plus 2, if it is n plus intermediate 2 to gives rise to this metallo cyclopropane intermediate.

From, there on another alkyne for example, can interact with this Ligand metal cyclopropane intermediate to form the cyclopropane alkyne interaction, subsequently insertion of this alkyne into the cyclopropane intermediate will give rise to the 5 members intermediate that can be further utilized for value added product synthesis. So, this is by (Refer Time: 20:04) and you can the comprehensive organic synthesis, book for this purpose chapter 9.5.

Now, this case what exactly we have seen is 2 different alkyne, 1 alkyne is interacting first with the metal centered forming the cyclopropane ring; metallo cyclopropane ring and subsequently this metallo cyclopropane ring interact with another alkyne to incorporate that as well. In the process we see a new carbon-carbon bond formation and 2 different metal carbon bond formation there. 2 new metal carbon intermediate and 1 new carbon-carbon bond formation process is happening.

In the process also we see that, if the early transition metal is starting with in class oxidation state it ends up with n plus 2 oxidation state in the process and once having this cyclopentadiene type of intermediate, this metallacyclo pentadiene intermediate can be further reacted because metal carbon; 2 metal carbon reactive intermediates or reactive bonds are there. Those can be, for example, protonated or other insertion reaction can be possible at those states.

So, let us look at other type of this oxidative cyclisation method that might will be involved during the reactions.

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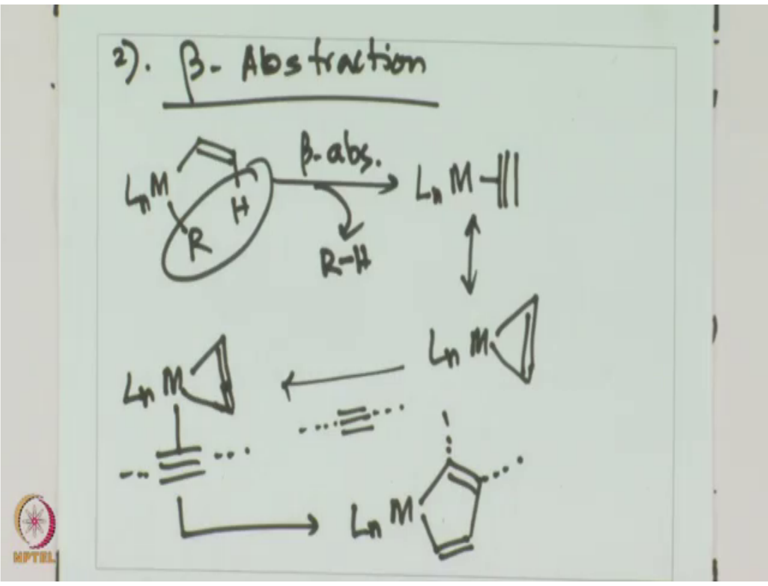

Another important thing that can happen is the beta abstraction. Well, that is a very novel technique reported by buckwald in 1993 in science paper. Where Ligand metal is reacted with olefin to form a Ligand metal alkenyl and alkyl intermediate together, from here on there is no option, but to or go undergo a beta abstraction. So, metal oxidation state is such that, it will not be undergoing a beta hydride elimination, only option it has is to undergo beta abstraction, so this is a beta abstraction process.

Overall, we get our H out of this process, but once again this is not a beta hydride elimination, this is beta abstraction. The electron required for metal center is not available for the beta hydride elimination. Therefore, only option that is available is beta abstraction and then Ligand metal this alkyne intermediate is formed from this, which can be essentially nothing but that what we have seen previously, it can undergo the cyclopropane ring formation, from there on a cyclo, you can have an alkyne it can be internal terminal, any different alkyne can be possible and Ligand metal alkyne. Then, interact with the cyclopropene intermediate to gives rise to a intermediate, where we can once again get the metallo cyclopentadiene, cyclo pentadiene species which can then be further reacted to give us the desired product that we might would be looking for.

So, this is the method which is a beta abstraction method and that is very powerful in delivering the desired compound starting from this Ligand metal, Ligand metal alkyl and alkyne intermediate intermediate. In this case, what we have seen that a beta instruction is the only process and thereby the starting process, kicks starting process with the beta abstraction gives rise to the metallacyclopropene intermediate, where oxidation of the metals state happens to by plus 2 and then another olefin or another alkyne can react to give the metallacyclo pentadiene intermediate. For example, what we have discussed today.

Yet, another type of this oxidative cyclisation it is possible. Let us, look at that. This is almost a mixture of method, which can be classified under the oxidative cyclisation process, so hybrid method for dealing with the oxidative cyclisation process.

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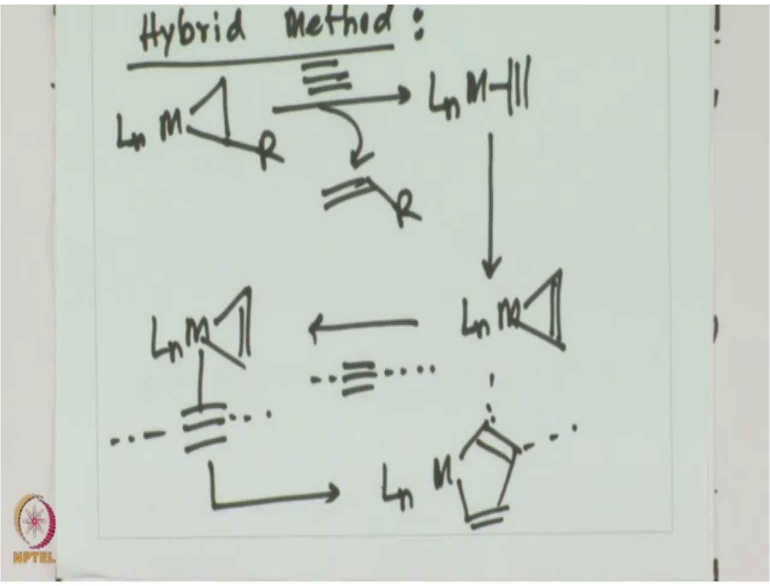

We are now looking at a method, which is a combination of these processes Ligand metal and al cyclopropane ring is there, from there on the alkyne will be reacted with it. During the process this olefin fragment will go out and overall we have Ligand metal alkyne species formation, which is nothing but once again this Ligand metal cyclopropane formation. From there on the alkyne can react, first it has to interact with the intermediate and subsequently we will see the incorporation of this alkyne into this metallacyclopropane intermediate, to form once again the similar processes.

So, from here on we will discuss various type of reactivity by utilizing this oxidative cyclisation technique that we will be discussing in the next class. Mainly, how to utilize this oxidative cyclisation process for really important organic transformation, we can discuss in the next class and we will also see, how various natural product or very complicated molecule can be generated by utilizing this technique can be of very useful scientific method.

We will discuss that in the next class, till then you please keep studying these oxidative cyclisation processes, bye-bye.