Metal Mediated Synthesis - I

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Lecture – 14
Buchwald – Hartwig coupling reaction

Hello, welcome back. Today, we will discuss those carbon nitrogen bond formation reaction or more specifically carbon heteroatom bond formation reaction the first topic that we discussed today is the palladium catalyzed carbon nitrogen bond formation also known as Buckwald-Hartwig coupling. Let us look at the transformation first and the generalized mechanism and then we will discuss the role ligand can play in these palladium catalyzed carbon nitrogen bond formation reaction of course, the ligand designing or ligand planning could be similar for the other carbon-carbon or carbon hetero atom bond formation reactions as well.

Let's look at first the name reaction or let us define the reaction first what is usually called as Buckwald-Hartwig coupling. So, it is an aryl halide that is reacted with a primary or a secondary amine to get secondary or tertiary amine respectively in presence of palladium and phosphine ligand usually these reactions are found to be very efficient let us look at the name reaction.

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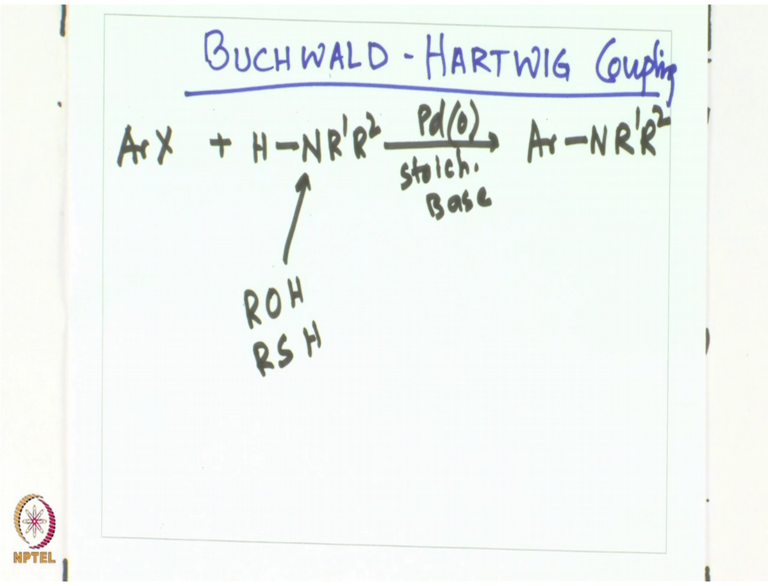

So, it is aryl halide that is reacted with an amine HNR prime and r dot. So, 2 different are substituent you can have you can have a primary or a secondary amine and palladium 0 stoichiometric amount of this that is required for this reactions and you get A r N R prime and R 2 ok.

Of course instead of amine one can have R O H, R S H, still it could be called as the Buckwald-Hartwig coupling the accent; in the last class, we were discussing different aspects of heck reaction; for example, and we have seen quite a few interesting topic emerging from such heck coupling reaction in today's class, let us first look at the catalytic cycle involved that for the palladium catalyzed carbon nitrogen bond formation reaction and then we will try to discuss the role of ligand or how the ligand is involved during the catalytic cycle is it just a ligand for the metal or ligand has conformational change that it is critical for giving very high yield; that means, turnover number both turnover number and turnover frequency may also get affected by this ligand.

Let us look at the catalytic cycle and stepwise we will look at what it takes for ligand to be efficient in this you know very important reaction also we would like to see one example how palladium is really getting incorporated or getting started into the catalytic cycle how palladium active species is formed during this catalytic cycle that is also another point of interest of today's lecture.

So, we will we will first discuss the catalytic cycle, let us look at it the catalytic cycle as you know would have the ligand palladium 0 that like similar to other carbon-carbon or carbon hetero atom bond formation reaction it is the palladium 0 that is the active species not the palladium 2 that that may used during the reaction, but the active species should be the reduced version from there. So, that is palladium 0 should be the real active species.

Let us start the catalytic cycle with palladium 0 as the starting material.

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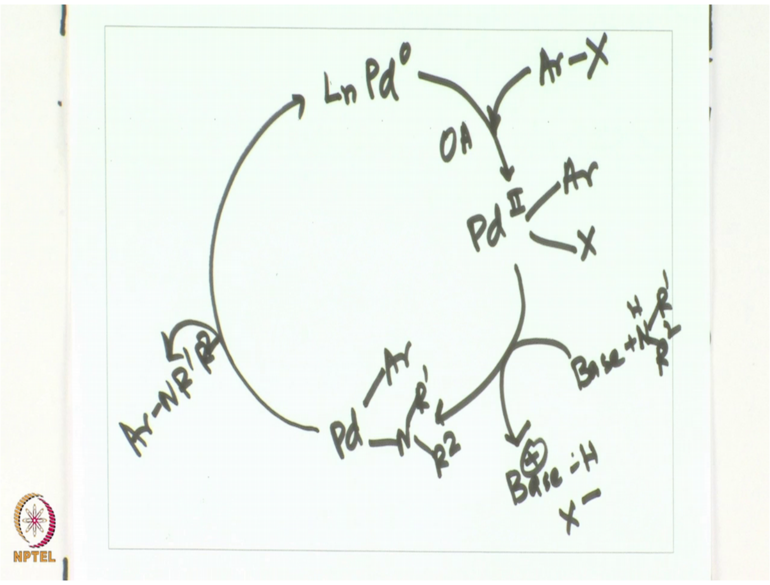

So, the catalytic cycle would have ligand palladium 0 and from there on the oxidative addition with Ar-X will gives rise to palladium 2 intermediate where palladium 2 Ar-X will be present and from there on, we will have a palladium A r N R prime and R 2 will be there subsequently what we will see that in this step of course, base and amine will come into picture h and r and r prime R 1 and R 2 in to be to be precise will come into picture and we will get base plus h of course, and then x minus and from there on we will see a overall catalytic cycle that is producing a r n r prime r two.

Of course as you can see in the catalytic cycle we have a very generalized mechanism here it is not stepwise we have not drawn this stepwise yet what we have shown this that palladium 0 will oxidatively add into Ar-X, then the amine will participate into the reaction and following you know I mean coordination and deprotonation, it will be transmetallated. So, from which the intermediate will gives rise to the product formation now that is definitely not that very simple as I have drawn in the mechanistic cycle right. Now it is little bit more complicated actually it is much more complicated although the transformation is very simple you need to one need to understand what goes on during the catalytic cycle.

Before getting into that let us try to take a look we will come back to the mechanism and discuss stepwise a little bit more one more step at least we will add and then we will try to try to look at the intricacies of the ligand design might we will be involved to facilitate the each and each on every of these of these step that is involved during these carbon nitrogen bond formation reaction let us look at one 2 simple example to get the feeling what really these reactions are about let us look at one palladium catalyzed carbon nitrogen bond formation reaction. So, technically any aryl halide one can take nowadays aryl iodide bromide chloride mesylate, anything can be used that is the great application or great reach outreach of these carbon nitrogen bond formation reaction.

Let's take a very simple reaction with aryl halide and an amine that is a secondary amine and let us see the product formation.

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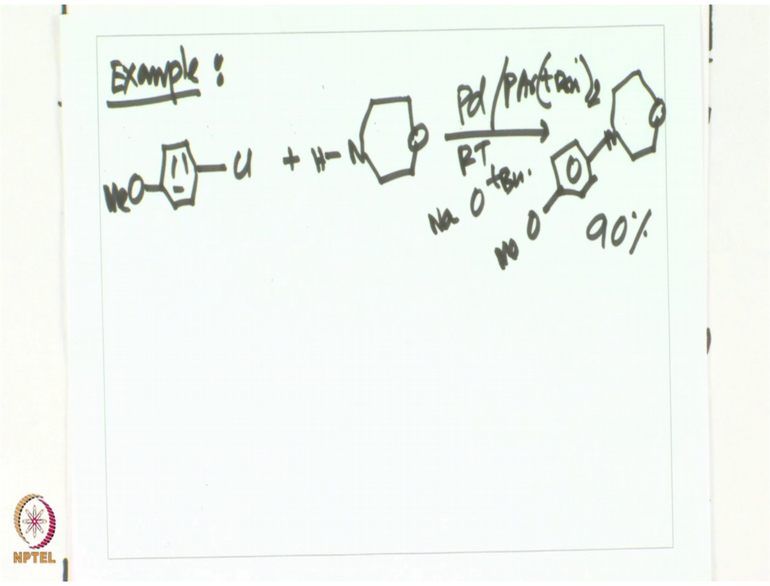

So, one example, we will come back with more example in due course we have an for example, aryl chloride of course, it is one of the most difficult substrate as one would understand and it reacts with morpholine and this is a pretty easy reaction for this sort of product formation we have ome and m this it is ninety percent yield palladium is used and phosphine aryl tributyl to this is not really the best ligand, but for this reaction it works quite and it can be done pretty easily of course, another another type of reaction could be. So, this is a very simple reaction right it is an aryl chloride, we are looking at and then a secondary amine one can take even the primary amine during the reaction to get the secondary amine.

So, secondary amine gives you the tertiary amine primary amine will give you the secondary amine right. So, any amine technically nowadays with the advanced catalytic system advanced ligand and very very highly designed ligand one can do almost every carbon nitrogen bond formation reaction by utilizing this palladium catalyzed carbon nitrogen bond formation well let us look at one hetero cycle synthesis which essentially is also an extension or the application of this method to get going the palladium catalyzed carbon nitrogen bond formation the key step and then we had a very interesting heterocycle formation we will we will synthesize indole very simply by utilizing this approach.

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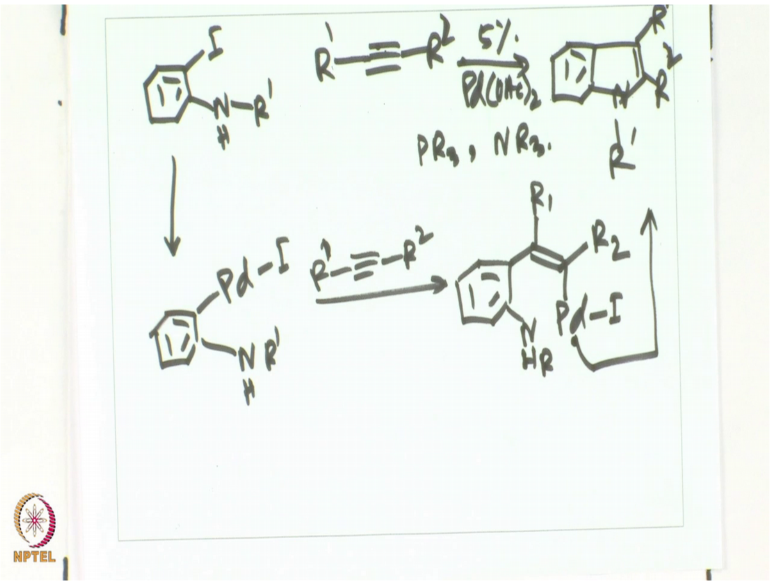

So, we have iodo N H R prime and an alkyne internal alkyne for example, we take the product we do get in these cases if you take something like 2 iodo aniline of course, in substitute that you can have then the product we get in this case is the indole that is a very powerful and very simple yet very powerful reaction for this class what is essentially happening of course, we need take palladium acetate in this case 5 percent of it.

And we take phosphine ligand and amine as this reaction works quite good what definitely happening in these cases is oxidative addition is occurring to give palladium oxidative addition intermediate and from there on what we have a beta migratory insertion of course, alkyne will coordinate and then we will insert. So, beta migratory insertion will give you rise to this intermediate where R 1 and R 2 is placed in a position before the before the final bond formation step. So, here we do have the beta hydride elimination from here on to give you the final product ok.

Now, what we have seen right now is if you have any iodo aniline 2 iodo aniline and substitution at any position and if it is interacting with an alkyne in presence of palladium then we basically will be able to enclose this one to give you the indole product formation.

So, oxidative addition at the aryl iodide and then binding olefin sorry alkyne binding and insertion with a migrated insertion finally, will give rise to an intermediate whereas carbon and nitrogen bond are very close they will go undergo a reductive elimination to give you the final product formation. So, by this way indole formation is made really very easy and one can get or one can expect the product formation quite efficiently by utilizing these palladium catalyzed carbon nitrogen bond formation process here carbon hydrogen bond formation process is not a direct with the aryl halide it is the aryl halide where it started and finally, alkyne gets inserted and it gives rise to the product.

Well, we are little bit deviating from our major discussion today that in palladium catalyzed carbon nitrogen bond formation will not discuss a lot of example in today's class, but what would like to discuss is why palladium is important and what oxidation state of palladium is taking part in to the catalytic cycle and the role of ligand during this catalytic reaction, let us look at the palladium palladiums salts or palladium sources that one can use for these type of reactions. So, well if we are talking about R 1 and R 2 NH.

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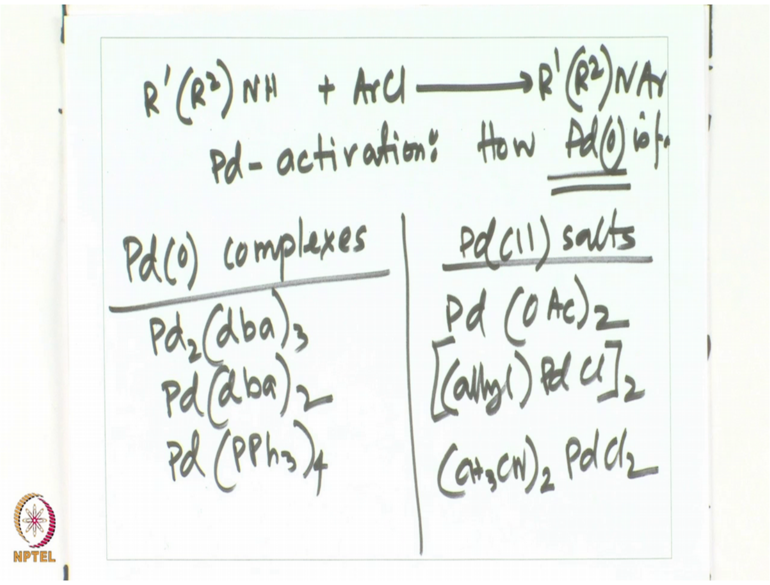

$R'(R^2)NH + ArCl \longrightarrow R'(R^2)NAr$

Pd- activation: How Pd(0) is f

Pd(0) complexes

$Pd_2(dba)_3$

$Pd(dba)_2$

$Pd(PPh_3)_4$

Pd(II) salts

$Pd(OAc)_2$

$[(allyl)PdCl]_2$

$(CH_3CN)_2PdCl_2$

So, this is the amine this could be primary and secondary amine for example, and for example, we are taking aryl halide to give R 1 R 2 NA r this is the palladium catalyzed carbon nitrogen bond formation reaction.

So, what we are trying to right now discuss it during these reacts and how palladium activation is happening; how do we form how do; how palladium 0 is form. So, that that is that is the main question how palladium 0 is formed during these during this reaction of course, one can use palladium 0 complex that is we were emphasizing previously palladium 0 complexes is are the one, let us say; for example, we can have palladium 2 deviate 3 we can have palladium dBa 2 these are commercially available palladium 0 source palladium pph 3 4 palladium tetrakis, but the problem is palladium 0 complexes are more active, but considerably less stable additionally the residual ligands for example, dBa or triphenylphosphine can bind to the palladium 0 and therefore, inhibiting its reactivity ok.

So, although palladium 0 is commercially available those we can buy such as palladium 2 db a 3 palladium dBa 2 aluminum tetrakis, but in order to stabilize them we have to pay the high price the ligand that comes with it, it does not want to go away during the reaction. So, it tries to stick around. So, for example, dBa tries to stick around for spin triphenylphosphine try to stick around, but those ligand, we are not very much interested in during the reaction although to stabilize starting material that is essential, but during the reaction we want one of our sophisticated ligand which is very efficient which can give very high turnover number and triumphant frequency, but those ligand placement at the palladium center becomes very very difficult.

And therefore, although palladium 0 is active, but of course, less stable compared to palladium 2, but still people want to have palladium 2 what are the palladium 2 short says we are usually using let us look at that 2 salts we have seen the examples with it previously, but to put it in the perspective palladium acetate usually we use lot of people huge aryl palladium chloride a diamond d species or acetonitrile this acetonitrile palladium chloride of course, palladium 2 shots are very stable all of them, but must be reduced to palladium 0 by hitting in presence of additives up. For example, final bronica acid I mean as you have seen in the last class or phosphine we have not seen the example of phosphine when it is used to reducing the play diem 2.

So, there exist a number of method that utilizes the in situ reduction of radium to delirium 0 formation; however, those methods few of them only we have seen in one case for example, when we were discussing about the Kumuda coupling organ lithium reagent was used or the reagent that is used for the reaction is participating in situ to reduce palladium to palladium 0 that we have seen.

In the last class we have seen also how amine can be participating by beta hydride elimination to reduce the palladium 2 to palladium 0 in today's class now we are going to see how phosphine can be involved phosphine the ligand itself the ligand which we need for our precious palladium catalyze different coupling reaction for example, carbon nitrogen bond formation reaction the ligand used in the reaction will be used or can be used as a reducing agent for palladium 2 to palladium 0 formation.

Let's look at how this reaction works because in almost essentially every cases one uses palladium acetate or palladium chloride or palladium allyl palladium species which are essentially palladium 2 species which cannot be the actives real active species the real active species must be palladium 0. So, therefore, how they are forming in the reaction that is essential to see, let us look at the process how phosphine is reducing palladium palladium 2 to palladium 0. So, we are talking about palladium activation.

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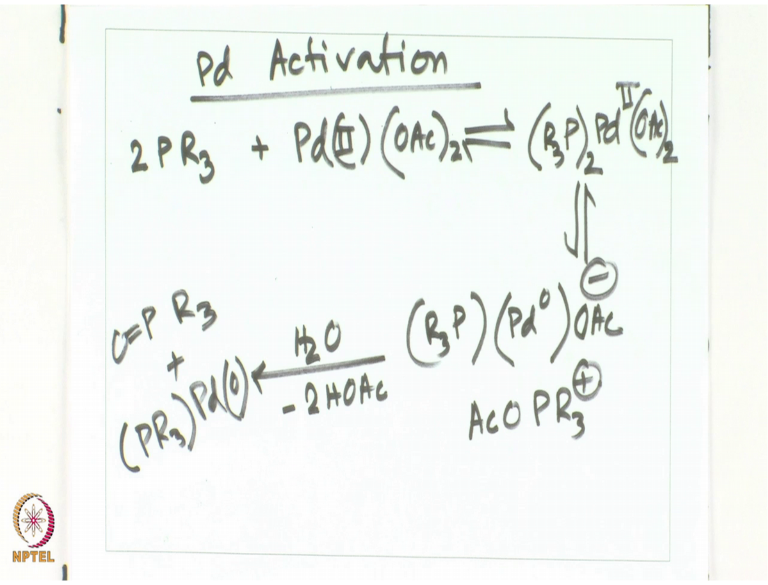

How do we form palladium 0?

So, what exactly we take for example is we take the phosphine ligand to equivalent of phosphine and we put palladium 2 salts and that is for example, palladium acetate we end up taking it is a reversible reaction we do see the binding of it n. So, diphenyl for example, 2 phosphine ligand binds with palladium 2 to give palladium dye acetate intermediate and from there on it is the formation of a cationic and anionic species that is critical for example, palladium 0 and then this acetate intermediate this should be a negatively charged intermediate along with acopr 3 plus this is a cationic intermediate.

So, essentially one of the phosphine over here and one of the acetate decides to leave the coordination site from the palladium; so, it is phosphine that is formed that is a cationic species and accordingly it is now a palladium 2 species to palladium 0 formation where acetate is coordinated it is got to be an anionic intermediate from which water participate.

So, trace amount of water is always good for this reaction and we need acetic acid for the reaction as well overall show this acetate and both the acetate forms the acetic acid the phosphine now. So, the proton comes from the water for both of those acetic acid information the oxygen that from water gets into phosphine to give rise to the phosphine oxide species as well as where we have now one of the phosphine incorporated into the palladium to give palladium 0.

So, what we have just now seen is then 2 equivalent or phosphine ligand which is very precious of course, 2 equivalent of phosphine ligand participating in reacting with palladium the palladium oxidation state is palladium two. So, 2 of those phosphine ligands bind with one of the palladium along with a palladium has 2 more acetate of course, it is a palladium 4 coordinate now what happens from there is one acetate and one phosphine leaves the coordination site to form a cationic intermediate and that leaves the palladium in palladium 0 state along with the acetate coordinated with it. So, it is an anionic intermediate. So, cation and anion formation; so, it is like almost ion pair formation happens right over there in presence of catalytic amount of water finally, what we see that a phosphine oxide is formed during the process and that lives out to the and that that gives rise to yet another equivalent of the palladium phosphine complex.

So, 2 phosphine ligand react with one palladium to give one phosphine one palladium species that is the real active species palladium is in now 0 state and in the process trace of phosphine oxide that gets going during the catalytic cycle now that is why that is also explain why we usually huge 2 equivalent of phosphate and one equivalent of palladium during the reaction right often we see that ten mole person for example, palladium and twenty mole percent of ligand that is a lot, but that is how it may be involved during the catalytic cycle. So, one equivalent of phosphine ligand usually if it is a bulky one is good enough for the real catalytic species, but another equivalent goes on activating goes for activation of these palladium 2 to 0.

We will see much more of those activation a little later on, but now we must see the stepwise mechanism of the palladium catalyzed carbon nitrogen bond formation or before getting into that let us look at the various ligand that might will be involved during the palladium catalyzed carbon nitrogen bond formation reactions. So, various ligand that is involved during the palladium catalyzed carbon nitrogen bond formation reaction.

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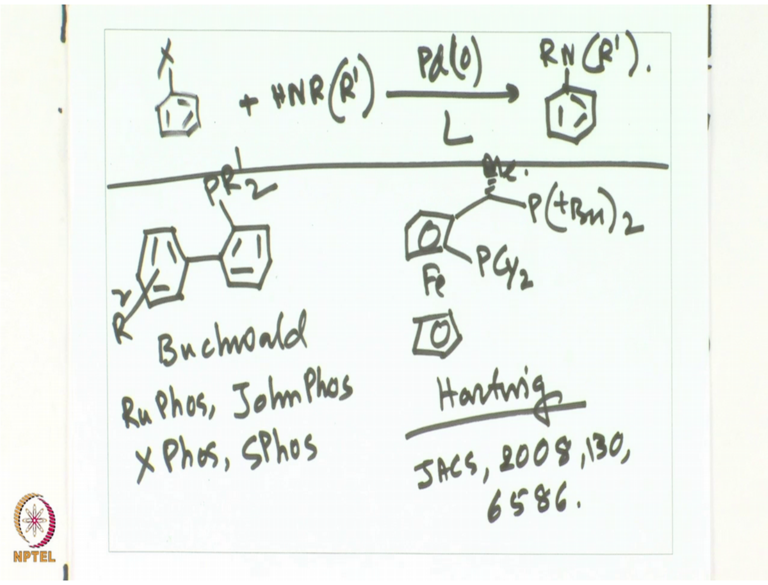

So, the reaction we are interested in is this x. Now these x are very useful aryl halide highlight and we are looking at HNR and R prime, we are of course, palladium 0 as the catalyst palladium 0 and ligand, we are taking base and some vendor of course, there what we get is N A r and R prime this is the species the ligand that is one of the most popular we are now going to draw different ligands that might will be involved. So, today's class will be mainly ligand centric how ligand is participating into the catalytic cycle in one case we will be discussing today and we have different r group in here.

So, we have a biaryl. So, this is a biaryl phosphine ligand there are substituent at various positions of this phosphine ligand. So, these are the ones which is used by Buckwald and the famous ligands are for example, ru phos john phos x phos of course, and s phos etcetera the other series of ligand which is ferrocene based ligand is popularized by Hartwig group, what we see there is also it is not a you know monos phosphine containing this is a mono phosphine containing bulky phosphine ligand, but this is a bisphosphine or bidentate chelation usually the joshi; first version of it anyway. So, this is popularized by Hartwig a reference one must write down jack's; for example, 2008, 130, 6, 5, 8, 6, alright; that is fine.

So, these are the ligand that it is used for these processes. So, there are plenty of other ligands that all is also involved we will discuss should. So, what we have seen is a biaryl phosphine ligand that is good for these purposes we will also we have also seen this ferrocene based ligands which is involved during the catalytic cycle, let me draw few more ligand which are very popular in this field specifically the carbon based ligand not only the phosphine ligand monodentate phosphine, we have seen biaryl phosphine, we have seen the bidentate phosphine which is very popular and very useful also the nowadays we do know that there are carbine ligand which is useful and very effective for this reaction as well and there are also baylor's ligand there is also ligand, there is a ligand.

So, a lot of different people have come up with a variation of these ligands and which are found to be quite efficient, but perhaps the most efficient trimend are the biaryl phosphine ligand that that we will be discussing in a moment how these reactions are you know affected by various ligands and what might will be one of the criteria to design the ligand to in order to get the high selectivity and high efficiency of the palladium catalyze carbon nitrogen bond formation reactions.

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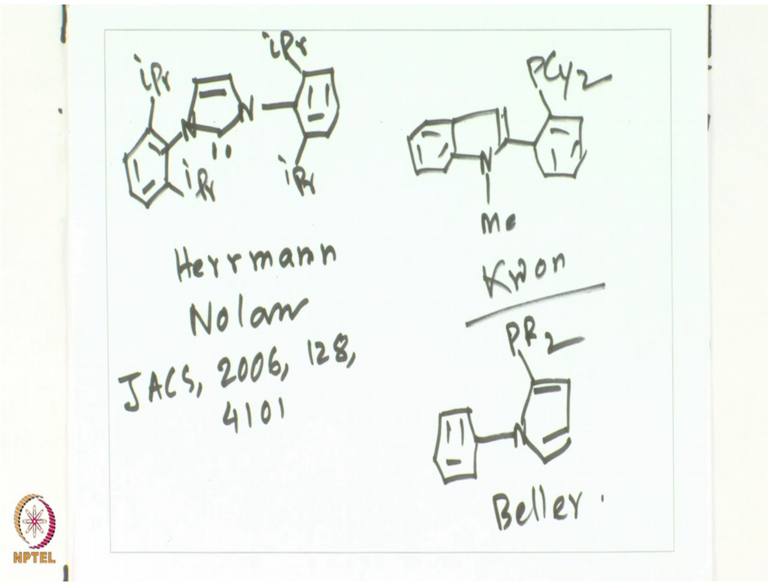

The other ligand that is involved in this process are the carbyne ligand where you know you do have these this isopropyl group. So, cipher si pr ligand of course, by herrmann and Nolan, these ligands are developed and put forward. So, we have isopropyl on the both side and these are the carbyne based ligand by herrmann and Nolan you can have a reference JACS, 2006, 128, 4101; of course, there are Kwon's ligand which is also very popular we have verkade ligand let us look at the Kwon's legand these are again based on mono dented phosphine ligand, but these are indole based quite pop quite efficient again.

So, this is Kwon's ligand we have Baylor's ligand which are again heterocycle based these are the again very very effectively ligand as well. So, we have seen what we have seen. So, far in today's class then for palladium catalyzed carbon nitrogen bond formation reaction we huge palladium 2 sats usually palladium 2 salts can be in situ converted to palladium 0 by sacrificing one equivalent of phosphine ligand which gets oxidized to palladium sorry phosphine oxide and in the process palladium 2 is reduced to palladium 0.

Water is needed catalytic amount or water is needed for this for the palladium 2 activation to give rise to the palladium 0 species. So, 2 huge element of ligand is utilized for the process one equivalent get going with the palladium another equivalent is sacrificed for phosphine oxide formation. So, palladium 2 although it is in plus 2 oxidation state it is reduced in c 2 to palladium 0 the readily available palladium 0 salts are not a great source for the vanadium catalyzed reaction because they usually comes with their own ligand such as dBa and triphenyl phosphene which are not the best ligand one can have for the various carbon hetero atom and carbon-carbon bond formation reaction.

So, one must huge palladium 2 without a strong coordinating ligand or you know which will not be good for the catalytic cycle now we have also seen how the palladium catalysis is used for carbon nitrogen bond formation reaction we have seen the overall simplified mechanistic side we will be discussing more about the ligand, how ligand is important.

In to these palladium catalyzed carbon hetero atom or in general any cross coupling reaction and what is perhaps one of the criteria we will take a case study specifically we will discuss the by aryl phosphine ligand which is developed by Buckwald group at MIT and then we will try to discuss the aspects of this ligand that is crucial for promoting high efficiency for this reaction. So, we will come back with that in the next class keep studying about these different metal catalyzed bond formation reactions bye-bye.