Metal Mediated Synthesis - I

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Lecture - 15
Role of ligands and its influence in Buchwald-Hartwig coupling reaction

Hello, welcome back in the last class we were discussing these carbon nitrogen bond formation reaction, we have started working on that and today we will see the role of a ligand during these palladium catalyze, carbon heteroatom bond formation reaction in general or even that can be extended for different carbon bond formation reaction as well.

So, how the ligand design is important where the ligand plays the crucial role in the catalytic cycle; of course, as you see the common process that is involved for all these different metal catalyzed reaction is the oxidative addition into the sp2 x bond or even sp 3 x bond. We do have for example, oxidative addition into aryl halide for or to be more specific on aryl chloride because, those are the substrate which is readily available 1 would like to have those reaction going with aryl halide or aryl chloride.

Now, these reactions are more challenging because, oxidative addition into aryl chloride would require an electron rich palladium center; therefore, phosphine is used as a ligand usually almost every phosphine is efficient in doing the oxidative addition. So, oxidative addition may not be the most difficult of steps when palladium is involved with or palladium 0 is involved with a phosphine ligand, but then there must be other factor of course, you know at the same time even if oxidative addition is not a big problem, but 1 would like to have a very facile oxidative addition; therefore, very electron rich phosphine ligand as well as not too bulky phosphine ligand.

But on the other hand what we see that what we have seen as a ligand, those are usually bulky right; first particularly today's discussion we will focus on the bulk aryl phosphine ligand, this seems bulky but as it turned out those are not bulky enough for oxidative addition may not be a problematic at all usually they are not problematic for these for these biaryl phosphine ligands. Now then if not oxidative addition is problematic, but still they are big enough right, the amine coordination which might will be required for the catalytic cycle to be going.

So, amine coordination and deprotonation may also need the ligand role or amine coordination should not be in such a conformation. So, that the complex is use is becoming very bulky right. So, amine coordination should be from such a orientation such a geometry, where phosphine ligand might will not be hindering the amine coordination or the deprotonation event.

So, in 1 hand for the oxidative addition we need a smaller ligand and also for the amine coordination we do not want a bulky ligand because, that will be problematic for the amine coordination I mean approach becomes problematic. What then would be required for the reductive elimination? This is the most problematic as well as you know reductive elimination, will be required a bigger ligand because from palladium 2 oxidation state we will be forming the palladium 0.

That means, if you have a bulky ligand or a crowded atmosphere around the metal center the then the reductive elimination will be facile right. So, that to in order to go for that in 1 hand we need a smaller ligand for oxidative addition and amine coordination even for deprotonation on the other hand we need is a bulky ligand for reductive elimination. So, therefore, 1 must be having a balance between these 2 although this looks like a classical dilemma, but still 1 should have balance for these 2 fact, 1 side it should be small enough the ligand should be small enough on the other side ligands same ligand should be bulky enough.

So, this is where the biaryl phosphine ligand becomes very useful and it found to be traditionally very efficient, for example palladium catalyzed carbon heteroatom bond formation reaction. Today we will see the ligand system which is developed by Buchwald group at mit these are biaryl phosphine ligand there are many variations of these that are now available in the market, but we will take very fundamental 1 or very earlier 1 which are used and detailed mechanistic studies has been done, in order to get insight into the a mechanistic cycle. Let us look at the x phos s phos and ruphos these are the similar ligand series and how they are affecting into the palladium catalyzed carbon nitrogen bond formation reactions, so we are looking.

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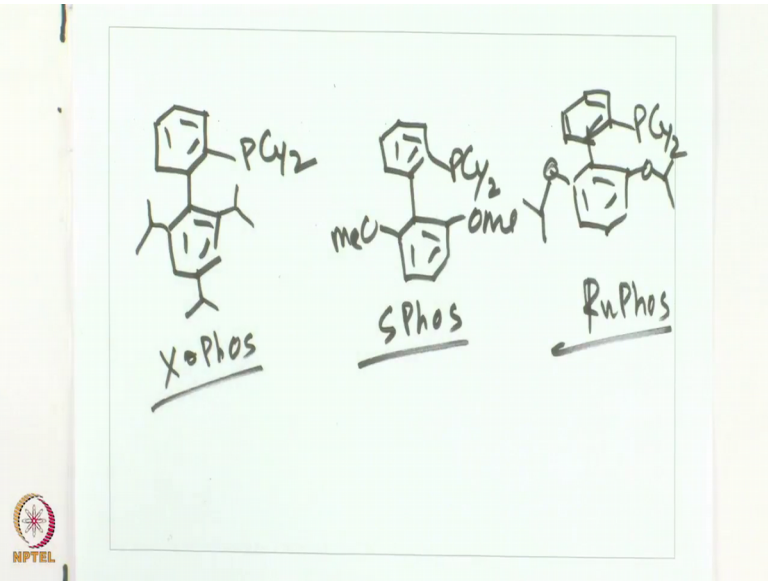

At first x phos this is all of the them are biaryl phosphine ligand cyclohexyl, now we have isopropyl this is x phos and we then have PCy 2 of course and ome this is usually called as Sphos and we have instead of methoxy isopropoxy, if 1 would have then we have the Ruphos version of it o isopropyl this is the Ruphos.

Now, of course there are many variations of this nowadays available, what we are looking at is these 3 different ligand and how or any of this ligand in generically we will represent that as biaryl and phosphine. So, just the biaryl unit we will draw and there could be different substituent we might will not get into details of that and then we will see how they may be participating into the reaction. Let us look back at the catalytic cycle that is involved during this reaction, what we need for this catalytic cycle is a ligand palladium 0 complex, let us look at the catalytic cycle which we tried to draw earlier.

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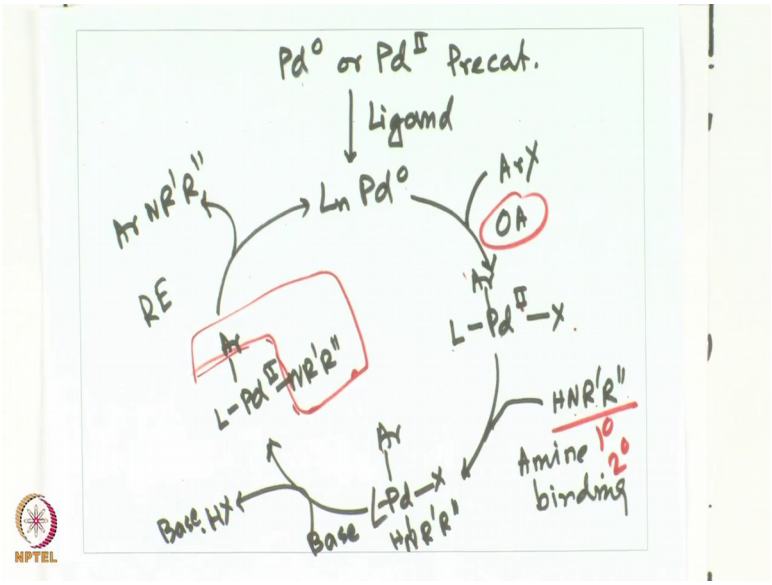

So, it is a palladium 0 or palladium 2 precatalyst that is required, the ligand as we said 2 equivalent of the ligand will be required, but 1 equivalent of ligand will be lost in the ligand phosphine oxide formation, 1 equivalent of ligand gets in usually with palladium in this case by aryl phosphine ligand, this palladium 0 will oxidatively add.

So, this is the oxidative addition step oxidatively add to give you the ligand palladium 2 at ARX intermediate. So, this is not from palladium 0 now you have a palladium 2 oxidation state now, there is an amine which is NHR prime primary or secondary whatever you want to have we can have 1 big primary or secondary. So, amine will coordinate as you see now it is becoming a overall 4 coordination, we can have the ligand here of course, so 4 coordination ligand aryl x and amine the base will participate into the reaction, overall to give you the deprotonation and Hx of course, Hx will go out it during the process.

So, you have you have aryl group and deprotonated, amine coordinated with palladium from which a reductive elimination will give rise to the product formation of the desired secondary or the tertiary amine right. So, what we do have seen in these cases, the similar transformation or exactly similar power transformation what we might will be seeing or we have seen for the carbon bond formation reaction, oxidative addition then trans metallation in these particular case amine binding and deprotonation that is what

happened of course, upon binding to the metal center amine Nh becomes more acidic deprotonation becomes viable.

So, you know you may not be able to deprotonate this amine without the metal in presence of a weaker base, but in presence of weaker base and the palladium as the metal this amine deprotonation becomes feasible and then we are looking for an intermediate, where palladium is there along with aryl and the amine from which reductive elimination can gives us the product formation.

Now, let us look at stepwise how this might will be happening in the biaryl phosphine case because, that will be critical for the success story of the palladium catalyzed carbon heteroatom bond formation reactions. So, these step fundamental steps 1 must remember oxidative addition, amine binding deprotonation and reductive elimination.

We will not be in the next slide and for the next discussion, we will not be drawing these catalytic step again will just draw this catalytic step with the ligand, with the hope that you will be able to follow what we have discussed right. Now oxidative addition amine binding deprotonation and the reductive elimination step, now in presence of the ligand where we will draw out how the biaryl phosphine ligand is associated into the catalytic cycle.

It is important to know that these are biaryl as you know are flexible ligand and also overall the carbon phosphorous bond can rotate around. So, therefore, the biaryl can in once a 1 time if this is the CP bond can rotate and therefore, the rotation can place the biaryl away from palladium or towards palladium.

This rotation of the biaryl moiety, the whole biaryl moiety that is caused by the rotation of the cp bond will be crucial for the high efficiency of this ligand. let us draw those different orientation to appreciate the ligand design in these particular cases for the biaryl phosphine type of ligand, for the palladium catalyzed carbon heteroatom bond formation reaction. So, we will see the ligand design in particular what we do have here is we need to draw it little careful yoks.

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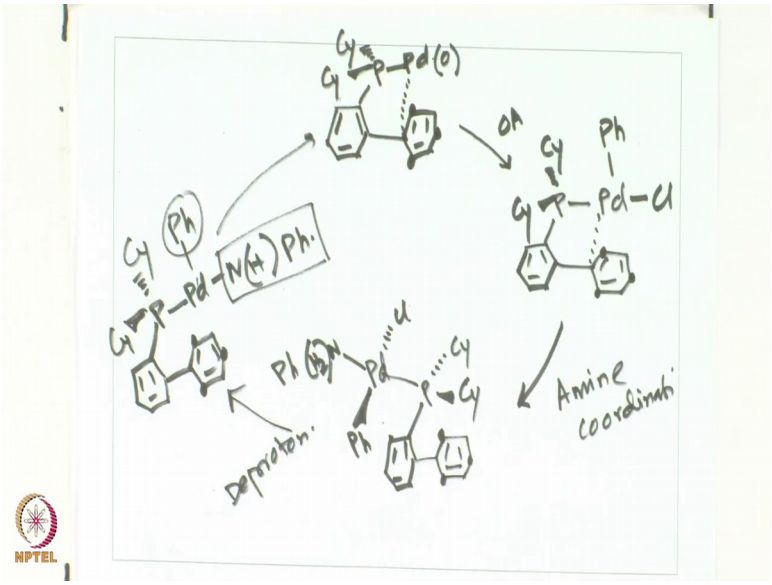

We do have a phosphine ligand, where p is there and let us say we have a cyclohexyl and another cyclohexylok. Now from there on there is a phosphine ligand now we have the palladium bond, now this palladium can interact with the pi electron cloud specifically that carbon center right and from there on of course, we do have the substituent at all these positions all these 3 positions specifically let us say if you are talking about x phos ligand.

From there on what we can have is the oxidative addition. Oxidative addition will gives rise to. So, here palladium is coordinated palladium is 0, catalytic cycle it has already entered phosphine is ligated with the palladium, now palladium is having only 1 phosphine ligand and therefore, the pi interaction from these biaryl unit will be participating to stabilize the palladium. So, there is this c palladium bond, bond pseudo bond formation that might would be happening in these cases essentially next step would be the oxidative addition where from this orientation we do see the phosphine interacting with palladium, and from the bottom ring we also do have the interaction with the palladium that leaves the oxidative addition to be very facile without any problem of course, we can have substituent at these position as well and we can have the cyclohexyl here and the and another cyclohexyl there.

Subsequently in this stage as you can see this is yes you know tetra coordinated palladium. Now the problem is of course, amine binding over here oxidative addition is

of no problem. So, phosphine is sitting or is coordinated with palladium, palladium is also interacting with the biaryl this lower ring and from at that orientation we can have the oxidative addition and that is what is happened there is enough room for this intermediate. Now from there on you cannot possibly happen amine binding because this is already very crowded.

You need a vacant coordination site you need a very less steric hindered intermediate. So, that now the amine binding can happen, what is also found that at this point cp bond rotation will leave the phosphine ligand you know on the other way around or other side let me draw in a little different way and therefore, you of course, you can have substituent at this position. Now you can have the palladium on the other side instead of the side where this biaryl interaction were possible, palladium is now placed on the away side from the biaryl moiety to give rise to the amine coordination.

So, this is the amine coordination intermediate where we have amine coordinated we have drawn a second primary amine and in lean for example, and from there on. So, this is amine coordination amine coordination or amine binding, and from here on a deprotonation you can have a deprotonation and overall during the deprotonation or after deprotonation, we can have an intermediate where palladium is back on the site where oxidative addition was happening, and you can have phenyl after deprotonation of course, both this h and 1 of the cl will be gone, and phenyl is over there from there on we can have the reductive elimination between these 2 intermediate.

So, what we have just seen is a very interesting diagram, where on one hand we have the biaryl the other phenyl ring which does not contain the phosphine, the non phosphine containing phenyl ring is participating in stabilizing the palladium 0 intermediate. That is the starting species mono-phosphine containing intermediate palladium 0 intermediate from where oxidative addition happen. So, the palladium is towards or it is sitting right on top of the phenyl ring which is not having the phosphine ligand.

Now, that is the conformation where oxidative addition occurs, but after oxidative addition for amine binding and deprotonation subsequent deprotonation one cannot afford to have the phenyl ring, non phosphine containing phenyl ring participating into the catalytic reaction and therefore, cp bond rotation brings the palladium away from the bottom phenyl ring and now once it is away, now it is only 3 coordinated 1 phosphine 1

aryl group and one halide. In that orientation amine coordination is possible. So, during the amine coordination this cp bond rotation happens, and it gives rise to that intermediate where 4 coordinate overall one amine, one phosphine, one aryl and one halide intermediate is participating. From there on deprotonation lives you the aryl amine intermediate and aryl palladium and amine deprotonated amine intermediate with h and x gone out during the deprotonation, and this step is responsible for the reductive elimination to give you the product formation.

So, palladium is basically swinging towards and away from the phenyl ring, to gives the product formation. Let us look at the cycle 1 more time carefully to get the real sense of it. What we do have over here is the phosphine ligand again it is coordinating with palladium, interacting with the biphenyl ring and from there on oxidative addition and amine coordination is going to happen. Oxidative addition happens no problem without any problem we can have oxidative addition, where palladium is interacting with the phenyl ring, but amine coordination cannot happen in this geometry.

So, therefore, the cp bond must rotate and palladium must be away from this phenyl ring. So, now, p palladium this bond is coming on this side, as you can see it rotates and we do have an intermediate. Then from where amine coordination can happen and deprotonation leaves an intermediate where aryl group and deprotonated amine are sitting with the palladium over there we do have of course, you know phenyl ring below.

So, this overall this geometry is pushing or it is very sterically crowded and therefore, once again deprotonation will be feasible from this intermediate, we do have both the oxidative addition facile, amine coordination facile, when it is away from the phenyl ring the bottom phenyl ring and then it comes back. So, it was in out in again with respect to the final ring to give rise to that the real active species, which is responsible for the catalytic cycle. So, this swing of the cp bond or the rotation above of the cp bond which brings the palladium towards the phenyl, away from phenyl and again towards the phenyl.

So, all these rotation all these flipping is important for a ligand to participate and therefore, these versatile behavior or the flexible behavior of the ligand is rooted for one of the region as is pointed out as one of the reason why these ligands are. So, efficient in these palladium catalyzed different coupling reactions. So, not only the carbon nitrogen

bond formation other similar type of reactions are other different carbon-carbon bond formation reactions are also possible by this biaryl phosphine ligand. So, in one hand it is less bulky in on the other hand it is more bulky. This flexible nature leaves the ligand in a unique position to be qualified both for oxidative addition trans metallation.

So, to speak here amine binding and the deprotonation and the reductive elimination all these steps although seemingly they requires different things in from the ligand, but still it is possible by one of the ligands such as this biaryl phosphine ligand, which sees a lot of application and this is quite popular in the literature as well and in industry and in academia. So, therefore, we have seen how this can be really bought into the picture let us look at little bit more in into these catalytic cycle. Once again let me emphasize that, palladium these amine palladium amine binding is more favorable, when the palladium center is distal to the non-phosphine containing ring.

So, binding is more favorable when the palladium center is distal to the non phosphine containing ring, by allowing some freedom of rotation around the pc bond amine binding and deprotonation will be facilitate that we have seen. Amine binding and deprotonation will is facilitate by allowing some freedom of cp rotation around this pc bond, and also we need to find a compromise between restricted rotation and free rotation around the pc bond that is also crucial.. And this is where you know we do not want a very easy rotation or very difficult rotation we need to compromise between restricted rotation around and the free rotation around the cp bond.

Well that is going to be very very true and therefore, we have seen in the next generation of the catalyst some substituents are put right at the ortho to that cp bond. So, so that it can further benefit the overall process let us look at again if another a substituent over there for example, methoxy over here that oxygen from the methoxy can also support a bit to the palladium. So, so that you know we can have a compromise between the restricted rotation and free rotation around the pc bond during these processes. Let us look at a little bit more we have seen how these ligands are efficient.

Now, in order to come up with a better version of the ligand what we really need to do for this reaction to be very efficient we need a palladium 2 catalystok because this is not. So, sensitive it does not come with a very sticky ligand that can compromise. So, we need a species which has a palladium 2. But at the same time it can have the ligand

palladium complex very easily right it all depends how easily we can get the palladium 0 ligand complex. Now as you have seen there are few steps that is required how 1 can prepare this palladium 0 ligand complex. We are usually starting with palladium 2 then using the phosphine ligand. So, one of the equivalent of the phosphine ligand is usually sacrificed as phosphine oxidized. So, that palladium 2 is converted to palladium 0.

Now, what if we do not want to sacrifice that, equivalent in addition we want it a very faster reaction for these processes; palladium 0 formation we want to be very fast without compromising the sacrificial amount of ligand. Now what we might will need is a design that can be called as precatalyst, but will be good enough or will be fast enough to give you the ligand palladium 0 intermediate.

So, by looking at the reductive elimination step and therefore, one has come up with a very interesting idea of the precatalyst that we will be discussing in the next class, how thinking about the reductive elimination step or rather having the reductive elimination intermediate one can think of having that as a readily available starting material for a desire palladium 0 ligand formation and that can participate into the catalytic cycle. We will discuss more on that in the next class. Pre catalyst design of the pre catalyst and how it can gives rise to the ligand palladium 0 intermediate, and what are the criteria, why we need a pre catalyst we will discuss much more in the next class.

Till then let us look at how this ligand has really influenced the metal catalyzed different carbon and carbon heteroatom bond formation ok. There are components of the ligand as we have discussed where ligand need to be smaller, yet big that is a fallacy, but still it can be solved by this for example, biaryl phosphine ligand that we have seen in today's class. Keep studying on that we will come back with these you know precatalyst design and how that has further revolutionized this area of palladium catalyzed carbon heteroatom bond formation reaction in particular, bye.