Advanced Transition Metal Organometallic Chemistry
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Lecture – 35
C–C Cross Coupling Reactions

Welcome to this course on, Advanced Transition Metal Organometallic Chemistry. Today we are going to take up one important topic which is also a Nobel Prize award-winning discovery with regard to the application of organometallic chemistry. As we had said in the beginning of this course that organomentallic chemistry had has tremendous prospects in various applications type reactions and today we are going to be talking of one such reactions which are the CC cross coupling reactions.

Now before I proceed further let me just retaliate the fact that worth of a field are worth of any field for that matter resides on the ability of that particular field to translate from the confines of the laboratory to something that of more bigger or randol application space. So this transformation or this translation from laboratory to industry or laboratory to clean a clinic where the scope of this discovery is validated, that is very important for gauging the importance of a particular field.

So from that perspective organometallic chemistry is really very important, because the field itself is about 100 to 150 years old and one can see that this field has given rise to about eight or nine Nobel Prize award winning discoveries, which have been, recognized as impactful findings, by the Society at large and that speaks volumes of the importance of this area.

So, with that in the backdrop, let me just take up one of the first translational example of a simple laboratory result that could go past beyond the confines of the laboratory walls and end up making a significant impact in the society at large and that was duly recognized by its impact by controlling the awarding the Nobel Prize in 2010.

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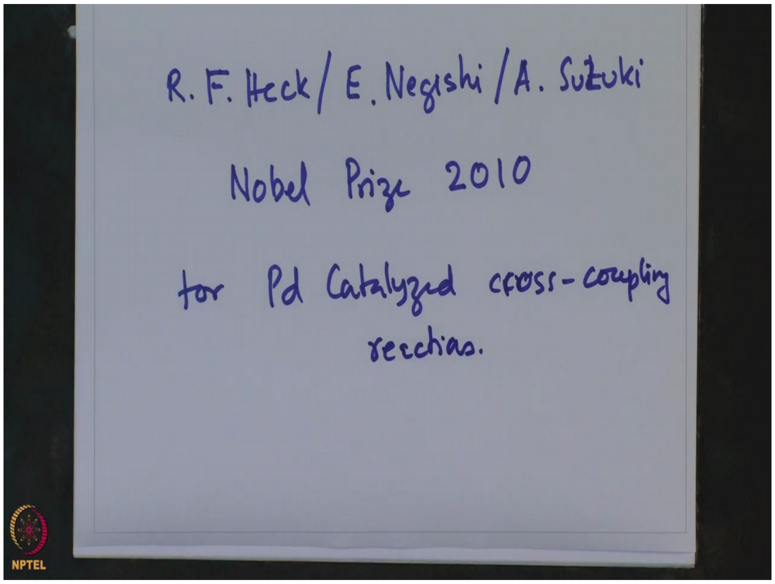

R. F. Heck / E. Negishi / A. Suzuki

Nobel Prize 2010

for Pd Catalyzed cross-coupling
reactions.

The recipient of which was R.F.Heck E.Negishi and A.Suzuki, Nobel Prize winners in 2010 for palladium catalyzed cross coupling reactions. Another interesting thing about them is, all three are Professors, Professor Heck was from US and Professor Negishi and Professor Suzuki were from Japan, so that sort of also speaks volumes about the fact that all the ideas which transform the world, originate in the confines of the library, laboratory.

So you know sometimes, we are very skeptical about kind of ideas people try around in academia but there are many such instances where these ideas so thought sought to is not so important indeed went on to prove everybody wrong and made very impactful discoveries, okay. So today we are going to talk about, one such very impactful translation of organometallic research which is this palladium catalyzed CC cross coupling reactions.

Now to begin with people had this notion that CC bond forming reactions are to make carbon-carbon bond is in the domain of organic chemists and so people always had reservation about what organometallic chemists or inorganic chemists are doing in this area but the thing is that the inorganic organometallic contribution to this CC bond forming reaction is the fact that they made the bond forming reaction catalytic.

In the sense that you know, rather than being striking metric where a little amount of catalysts can form many such CC bonds so that is why this organometallic contribution did indeed find a lot of utility in the hands of organic chemists because this process being made catalytic now as a small amount of catalyst can make these cross cutting reactions in high turnover numbers and throughputs, okay.

Now, with that, let me just sort of take a look at the kind of reactions, actually CC cross coupling reactions and it represents a body of cross coupling reactions some of which are summarized over here.

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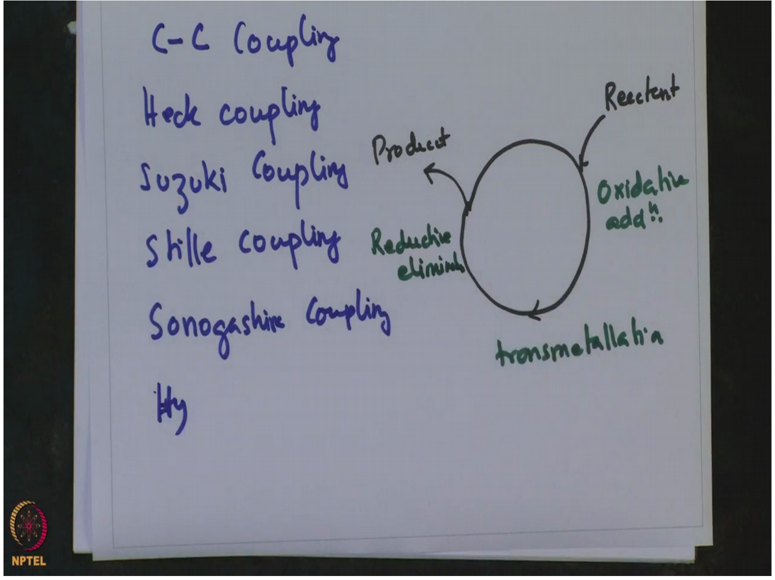

C-C Coupling

Heck coupling

Suzuki Coupling

Stille coupling

Sonogashire Coupling

Hy

Couplings are Heck coupling, Suzuki coupling, Stille coupling, Sonogashire coupling, these are all CC cross coupling reactions, and one may question that, then what is the difference, why they have different names, the answer to that is well they have different carbon nucleophiles, different types of carbon nucleophiles that are used in making the type of CC bond. However, the commonality of this cross coupling reaction is the follow a same catalytic pathway or similar catalytic pattern.

So now, one sort of can say that even though their names are varied, they proceed by the same catalytic pathway or in short they exhibit similar catalytic cycle. So any catalysis, you know, is represented or characterized by a catalytic cycle, where let us say, a reactant comes in and then a product goes out and that involves several steps so and so forth. And so it may, so all of these, different cross coupling reactions follow these similar same catalytic cycle and all of them exhibit three steps the first one is oxidative addition then comes trans metallation and third one is reductive elimination.

So, what you seen that even though the names are different, these sort of exhibit the same catalytic cycle and this catalytic cycle would have 3 different steps, oxidative addition, trans metallation and reductive elimination. Now and this negative elimination goes back to the active state of the catalyst. Now one thing, one sort of can look at the catalytic cycle and have some idea, well first step of oxidative addition is nothing but the substrate activation and the reductive elimination obviously is nothing but the product release.

So oh these so if you look at the catalytic cycle in a very intuitive way, so one can see that it has three steps, and which the first steps involves substrate activation and then the last step involves product release and there is an intermediate step as well, which is trans metallation and all of these happen in a cyclic fashion which represents the catalytic cycle. So now let me just dwell on the importance of these CC cross coupling reactions.

Now, the importance are many a and as can be sort of understood, because it has been awarded a Nobel Prize, so obviously it has several advantages, let me just sort of reiterate them.

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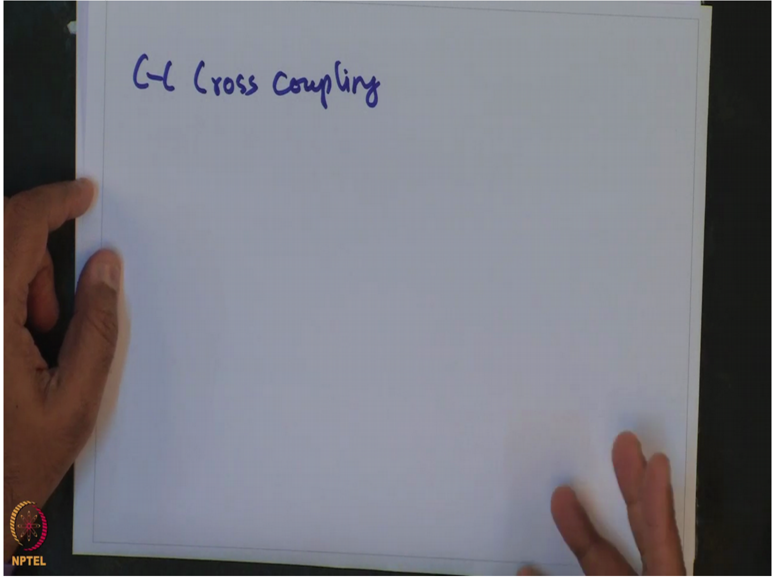

C-C Cross Coupling

So, this is about CC cross coupling reactions, so, so oh that means, that these carbon-carbon bond formed between the electrophile and the nucleophile in such a fashion that no homo coupling is observed, so homo coupling is completely sup, suppressed, now if one were to look at it, one may think that well when we make our cross coupling of two reagents obviously, statistically, there may be a possibility that one can get cross coupled product as well as no couple product and that will be governed by statistics.

However, the mechanism of these cross coupling reactions are such that, that there is absolutely no possibility of obtaining the whole couple product and that is the beauty of this method for making this highly selective cross coupling products. So, obviously as the name suggests cross coupling because of its selectivity of exclusively, a producing the cross couple product has made it very popular.

Also, you know, one thing about palladium, is the fact that it can carry out all those reactions as I mentioned that, oxidative addition, trans metallation, reductive elimination, which are individual part of a catalytic cycle, all it can be performed in a proper, in a sequential order, as a part of the catalytic cycle which makes this cross coupling reaction so popular.

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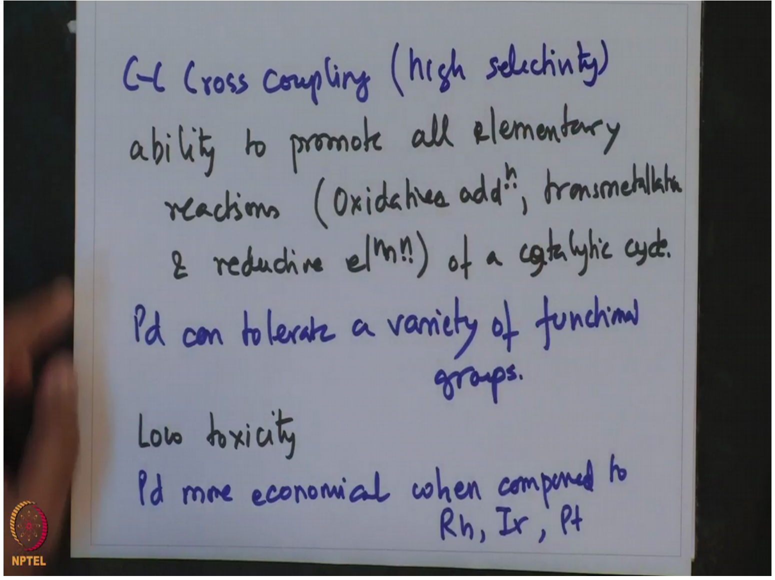

C-C Cross Coupling (high selectivity)

ability to promote all elementary reactions (Oxidative add^{n}, transmetallatn & reductive el^{mn}) of a catalytic cycle.

Pd can tolerate a variety of functional groups.

Low toxicity

Pd more economical when compared to Rh, Ir, Pt

So, you know the individual you know successfully promotes or ability to promote, all individual steps, all elementary reactions, oxidative addition, transmetallation, and reductive elimination of a catalytic cycle. The second thing the third thing about is not only the catalyst can do that; the catalyst also is functional group tolerant. So the catalyst has is quite stable so Palladium as the catalyst can tolerate a variety of functional groups. I think, this is what makes a Palladium, so special about cross coupling reaction.

So scope of the substrate that palladium can use for its cross coupling reactions is what makes palladium so better metal than the other metals because other metals may be too reactive and sometimes may get affected, or poisoned by the functional group of the substrates, and then fail to carry out the cross coupling reactions. So it is the breadth of the Palladium with respect to the substrate, that it can affect the cross coupling by virtue of being functional group tolerant is what make palladium so special for performing special as a catalyst for performing the CC cross coupling reaction.

Another interesting thing about palladium is its low toxicity. Now this is a interest, important criteria, for any large scale production given the fact that there is a lot of Environmental Protection Agency which oversee the toxicity issues that may arise from large scale production of any chemical entity and from that perspective palladium makes the cut because it is not known, not known to be very toxic and also given the fact that palladium is extremely efficient in carrying out these CC cross coupling reactions at very low catalyst loading, that the toxicity issue does not surface.

So this is one of the strengths of palladium in terms of very low, low toxicity issues which makes palladium so successful in carrying out this cross coupling reaction. And also last but not the least, Palladium is more cheap, as compared to Rhodium, Iridium and Platinum more economical, Iridium, Platinum. So what is of economical importance is that palladium is way lot cheaper than other magic metals of catalysis which are magic metals of catalysis, Rhodium, Iridium and Platinum.

Palladium is way cheaper than that and that also sort of helps propel palladium in the scenario of CC cross coupling reactions. So, in all that palladium has certain advantages which makes it so popular for this cross coupling reaction, first of all that you know, it is highly selective, that it does not produce any kind of homo couple product. High selectivity and also that it has large broad subs, that it be able to carry out all the elementary steps of the catalytic cycles, which are, oxidative addition, trans metallation, reductive elimination, in a smooth way, as a part of the catalytic cycles.

So that also is a big deal. Also palladium offers a large substrate scope because, it is tolerant to the other functional groups on the substrate does not affect the catalyst, palladium does not have any toxicity issues or is low toxicity helps it even further and also last but not the least palladium is way cheaper than other magic metals of catalysis which are exorbitantly expensive, like rhodium iridium palladium, platinum.

So, that sets the ground for the palladium, mediated cross coupling reactions, and then we are going to be looking at comparing the effectiveness of palladium based cross coupling as opposed to the standard technology which existed at that time like the Grignard, reagent using cross coupling of CC bond forming reactions. So you know we are going to draw a conclusion in a completion of this catalytic CC coupling as opposed to the stoichiometric CC coupling.

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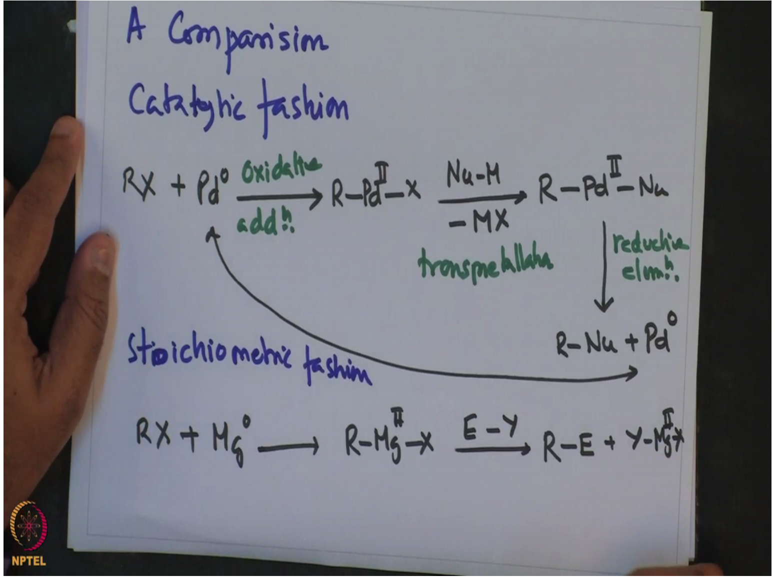

A Comparision

Catalytic fashion

$RX + Pd^0 \xrightarrow[\text{add}^n]{\text{oxidative}} R-Pd^{II}-X \xrightarrow[-MX]{Nu-M} R-Pd^{II}-Nu$

transmetallation

reductive elim^n

$R-Nu + Pd^0$

Stoichiometric fashion

$RX + Mg^0 \longrightarrow R-Mg^{II}-X \xrightarrow{E-Y} R-E + Y-Mg^{II}-X$

So, the Palladium one in a category fashion starts from the reaction of the alkyl halide with a palladium 0 species giving the oxidative addition of R palladium two X, so this is the oxidative addition step, addition step, that I had been referring to in the catalytic cycle followed by nucleophile undergoing metathesis reaction which popularly known as trans metallation.

And that giving R Pd2 nucleophile and that undergoing reductive elimination giving R, a Nu class palladium 0, so this palladium 0 and this platinum 0, are the same species, so that is what a complete cycle and this third step is this, reductive elimination. Now as I had mentioned that the full step of oxidative addition is the cleavage of the RX bond by oxidative addition.

So this is indeed the substrate X activation step and the reductive elimination give rise to this final product which is R Nu, which is the cross couple product and that designates the reductive elimination step the whole thing being done in a cyclic fashion use catalytic what makes it more catalytic and hence it is more effective and the less amount of catalyst is required. So when we look at palladium mediated CC cross coupling which precedes in a catalytic fashion, let us look at how the magnesium or Grignard mediated stoichiometric reaction would proceed.

So the same coupling in stoichiometry fashion using grignard would involve RX+ magnesium giving R mg X, so this is again oxidative addition on magnesium to form the grignard and then electrophile E-Y giving R E + Y mg to X, now here we see that Bailey's this process is linear in the sense that it does not come back to its initiating step, that it is not cyclical. So, stoichiometric addition requires generation of large number of west because and also requires generation of large number of Grignard.

Because for exact amount of the R stoichiometric that much amount of the grignard is required for this coupling and as a result, you know, this is quite ineffective in compared to the catalytic fashion which palladium operates. So, one can sort of see a distinct advantage which comes with using the Palladium CC cross coupling reaction as opposed to that of using grignard which happens in stoichiometric fashion and that probably is the reason why the Nobel was awarded for palladium mediated cross coupling in 2010.

However, I would also like to note that about nearly about a century back when grignard was also in fashion or grignard came into the fore then grignard two was allowed, one the, given the Nobel Prize, for its ability to construct CC bonds so even though at a century later it may seem that the grignard is redundant to some extent as compared to palladium but in its own time grignard was also a Nobel Prize award-winning discovery about a century back.

So, one can see the depth of the field of organometallic chemistry and how it can turn out a very important our channel progresses or updates in the way fashioned carbon-carbon bonds can be constructed or moving from stoichiometric fashion using grignard to catalytic fashion using palladium about a century later. Now there is a concept of the Palladium in the cross coupling reaction.

So, the Palladium goes in a cyclic fashion which goes from palladium 2 to palladium 0. And then it will convert it back to palladium 2, so it is sort of a redox couple which goes from palladium 2 to palladium 0 and then back to 2.

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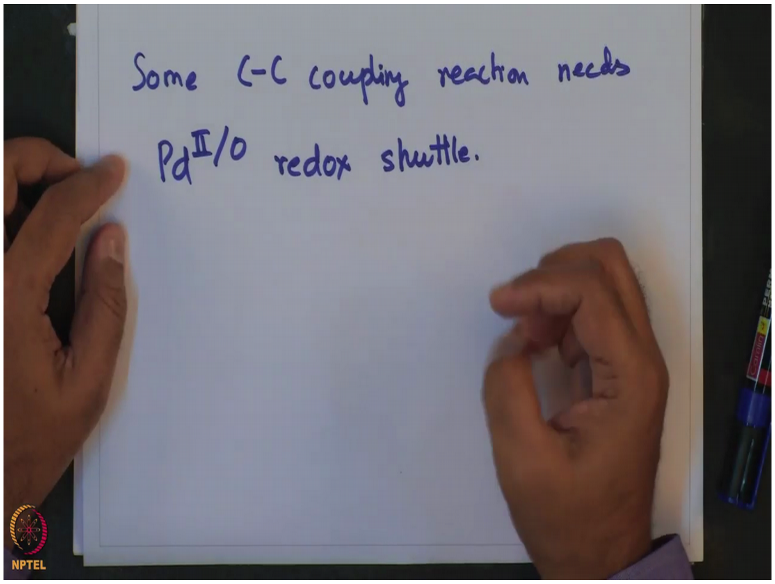

Some C-C coupling reaction needs $Pd^{II/0}$ redox shuttle.

So, some CC coupling reaction needs Palladium 2 to Palladium 0 redox shuttle, as we have been discussing about, and there are some literature reference about this cross coupling reaction occurring between palladium 2 to palladium 4, however the amount of literature which supports are which represent on palladium 2, palladium 0 , cross coupling reaction, is indeed way more than that of the Palladium 4 palladium 2 or shuttle.

So, with these I am going to stop our discussion on CC mediated cross coupling reactions using palladium and I would like to summarize what we have been talking about today. So, you know, we had discussed about why the importance of palladium mediated cross coupling reactions or the reason for the success of palladium in this variety of cross coupling reactions and what it comes to the fore, that there are several characteristics criteria which we went in favor of palladium.

For example, palladium can carry out all the elementary steps involving oxidative addition, trans metallation, and reductive elimination in a smooth fashion within a catalytic cycle which makes the CC cross coupling reaction so effective. Another interesting attribute about palladium catalyzed cross coupling reaction is that its selectivity it always produces the cross couple product and does not ever allow for any formation of any homo couple products as the selectivity is something, which has gone in favor of palladium.

In addition to that palladium has a wide substrate scope because you know it is a lead transition metal and it is tolerant towards functional group and as a result, the wide variety of substrate can be affected by palladium for carrying out the CC cross coupling reaction in a flawless manner.

Furthermore the Palladium has low toxicity and also has quite a high turnover numbers for carrying out these cross coupling reactions.

And because of which this palladium mediated cross coupling reaction are not that, does not have much of toxicity issues, which environment production agencies are always concerned about and also as compared to the other magic metals of catalysis like rhodium, iridium and platinum, palladium, is way cheaper and so can be effectively used in performing these cross coupling reaction in a more larger scale.

A distinct advantage of palladium with regard to the other grignard, for example, which can perform the stoichiometric reaction is the fact that, palladium is able to carry out this cross coupling reaction in a catalytic fashion which means that with a small, small amount of catalyst which has a high turnover number and high activity it can carry out, many more catalyst, catalysis.

And lastly one needs to say that this cross coupling is affected by palladium undergoing a redox palladium 2 palladium 0 shuttle, as though there is some talk about this cross coupling for certain system proceeding by palladium 2 and palladium 4 a redox couple. So with this I would like to conclude today's talk on CC a cross coupling reaction. We have just started embarking on this journey and we are going to take up these easy cross coupling reactions and look at a variety of reactions which falls under this purview in the next class.

So, I once again thank you for patiently listening to this class to this topic and I look forward talking about this topic in much more detail in greater depth and breadth in the next class, till then, thank you and goodbye.