Metal Mediated Synthesis - I

Prof. Debabrata Maiti
Department of Chemistry
Indian Institute of Technology, Bombay

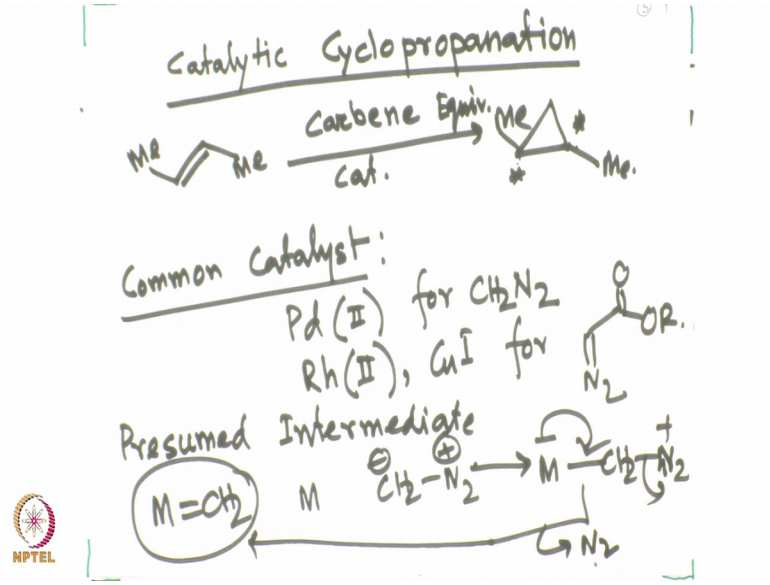
Lecture – 06
Catalytic cyclopropanation reaction & Introduction to cross coupling reaction

Hello everyone, welcome back to today's class. So, today we will be continuing discussing on catalytic cyclopropanation reaction. In the last class, we have just introduced the topic. Today we will discuss more about it and mainly the asymmetric version as well as well as some industrial application of this catalytic cyclopropanation reaction. See the cyclopropanation reaction is nothing, but creating cyclopropane ring from an olefin.

Traditionally, it is done with carbine. Now if you have an olefin and you are reacting the carbene equivalent with it one would expect them to form a cyclopropane ring as we have seen that palladium catalyzed methods are usually used where diazomethane is the starting material from which palladium carbene is forming on the other hand also, it could be possible that rhodium or copper be used for such processes.

Usually for rhodium and copper we do see diazo; diazo esters are used as starting materials today lets try to look at the cyclopropanation reaction in more detail and let us try to discuss it along its mechanism. At first, we look at one of the example and then how the metal carbene is forming from the diazomethane or diazo ester and then how they are being utilized for this cyclopropanation reaction.

(Refer Slide Time: 02:15)



We are going to discuss that let us discuss cyclopropanation the usually from a carbene what we see that that it is reacted with olefin to give the cyclopropa propane ring and of course, in this two center you can set the stereochemistry often we are we will be talking about the diastereo selective synthesis for such compound the common catalyst that is used for this purposes is palladium 2 for diazomethane as the starting material rhodium 2 for and copper wire one for diazo ester that is nothing, but this reagent as the starting material.

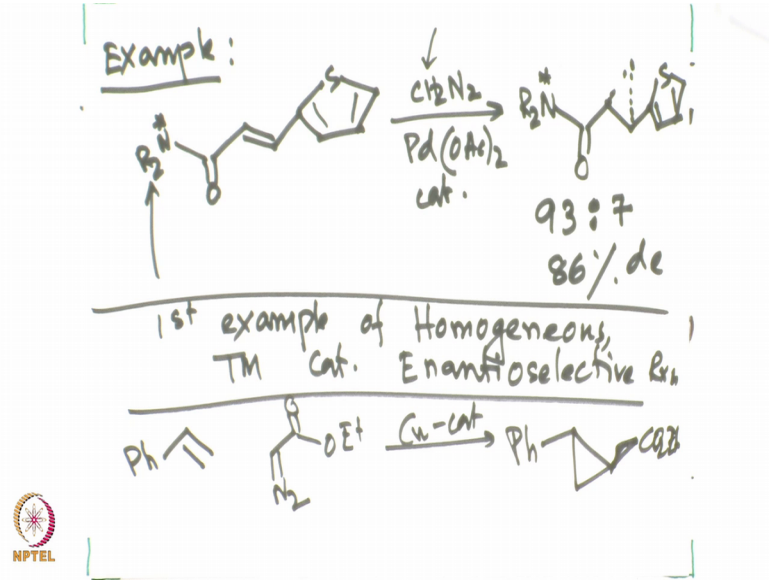
Now, also it becomes important how these reactions are working we can have presumed intermediate intermediate for these cases which is nothing, but a metal carbene equivalent of course, that is what is forming, but how it might will be forming; let us look at from the diazomethane one. So, CH 2 minus and N 2 plus what you might will get in the process is m minus CH 2 and N 2 plus reagent overall you end up getting m CH 2 plus of course, N 2 comes out from these reactions.

So, what we have seen right now is diazomethane reacting with metal to give them metal carbene intermediate of course, one would argue maybe it is the free carbene that is doing the chemistry can we have some sort of mechanistic proposal or mechanistic proof evidence in support of metal carbene formation; of course, nowadays there a lot of study being done will we will discuss the first example where such metal carbene formation

could have been possible or some evidence has been gathered in favor of metal carbene formation.

Let us look at one more example to discuss these metal carbene as the as the reactive intermediate for this cyclopropanation reactions.

(Refer Slide Time: 04:35)



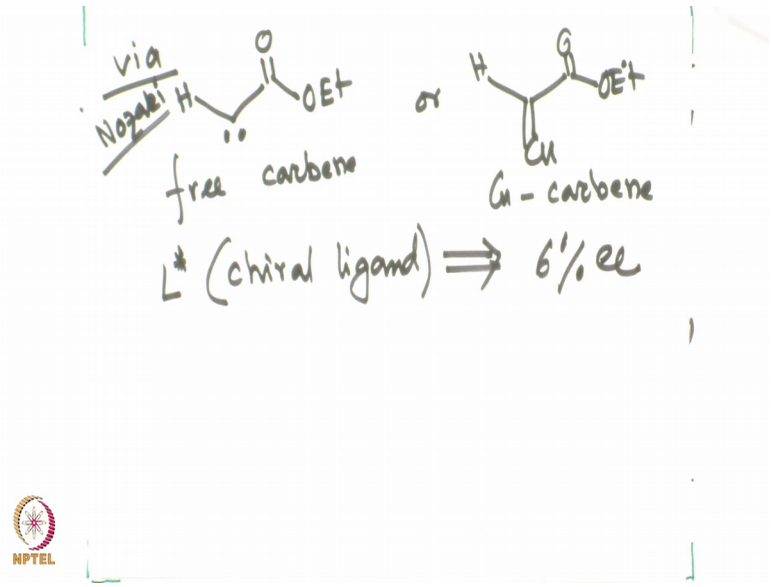
So that one examples that would like to discuss is where you have a chiral enantiopure auxiliary along with the substrate and now with this substrate if you are taking you know if propene or you know the olefin double bond what you would expect in presence of diazo methane and palladium acetate to as catalytic amount of course, to form in presence of the chiral auxiliary chiral auxiliary as is in here this is the chiral enentiopure auxiliary and from there on you would imagine to form a cyclopropane ring because this CH 2 is coming into picture and overall you get the product that one would expect now in this case we get ninety three is to seven diasteriomery; so, therefore, 86 percent de which is quite interesting for such reactions. Now still one would argue for these reactions how this reaction might would be happening how what would be the procedure is it the free carbene that is forming.

Or the metal carbene intermediate is generated during these reactions in order to prove

that or the first evidence that came forward for such involvement of a metal carbene intermediate a is the one where copper issued, let us try to look at the first example where metal carbene could have been proposed or the evidence has been gathered in support of metal carbene intermediate for the N cyclopropanation reactions. So, the first example of homogeneous reaction homogeneous transition metal catalyzed enantio selective reaction now one example that comes into mind or in the literature that is the diazo ester reaction in presence of copper catalyst to give the cyclopropane that one would expect in these case and that is this reaction now still even if you are getting this product cyclopropane.

That does not mean that you know it is involved the copper carbene as an intermediate rather than free carbene perhaps one way to prove that at least that was the first evidence gathered in favor of metal carbene is if you add a chiral ligand if we introduce a chiral ligand for the metal center in this case for copper can we get any in enantio selectivity if you get any enantio selectivity during the process it. It could be suggestive of the fact that metal carbene is forming if it was a free carbine, you would not expect any enantio selectivity during this reaction during the reaction what we have just drawn. So, if any E is there, then one can argue in favor of a metal carbene species being the reactive intermediate for this cyclopropanation reaction. Let us look at what has happened in presence of the carbene as a you know in presence of a chiral catalyst used for this copper catalyzed reaction.

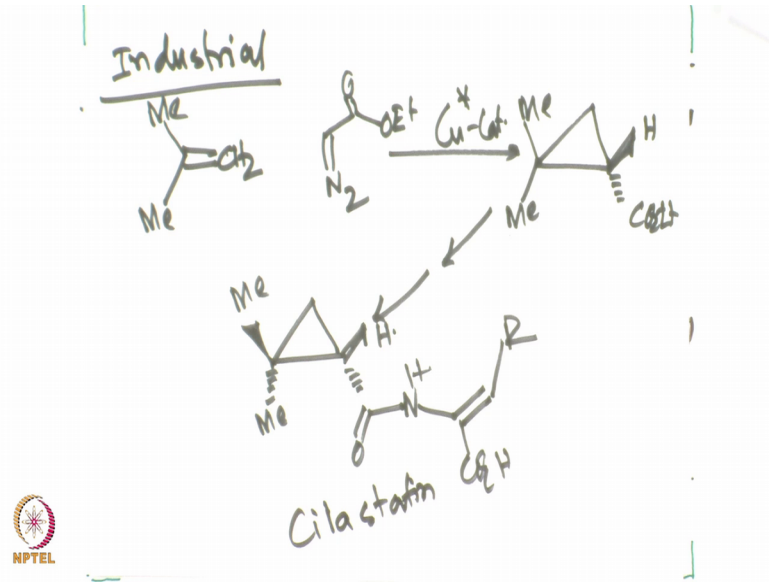
(Refer Slide Time: 08:31)



What if it is via a free carbine; the free carbene that you are expecting is this one ok. So, this is your free carbene or whether this is forming copper cut copper carbene intermediate is forming now of course, this you can name as copper carbine, right. This is done by Nozaki by the way. Now one a chiral ligand l star issued a chiral ligand is used what was observed is a modest very very modest 6 percent e e. So, this is the reaction that then proposed that since in presence of a chiral catalyst one can achieve some sort of e e although very modest at best, but still this is suggesting that carbene is involved metal carbene is involved, it is not the free carbene that is doing the chemistry indeed the metal carbene as the intermediate that is involved for this cyclopropanation reaction ok.

Now, let us try to look at one of the example where it is used in cyclopropanation reactions are used in industrial scale and therefore, one can justify the importance of these processes in indeed in medicinal chemistry lot of this cyclopropanation reactions are used quite routinely, let us look at one of those medicinally important or medicine that is utilized or produced by the cyclopropanation reactions.

(Refer Slide Time: 10:23)



So, industrial application in industry this is a reaction which is quite popular where diazo ester is used in presence of a copper chiral catalyst.

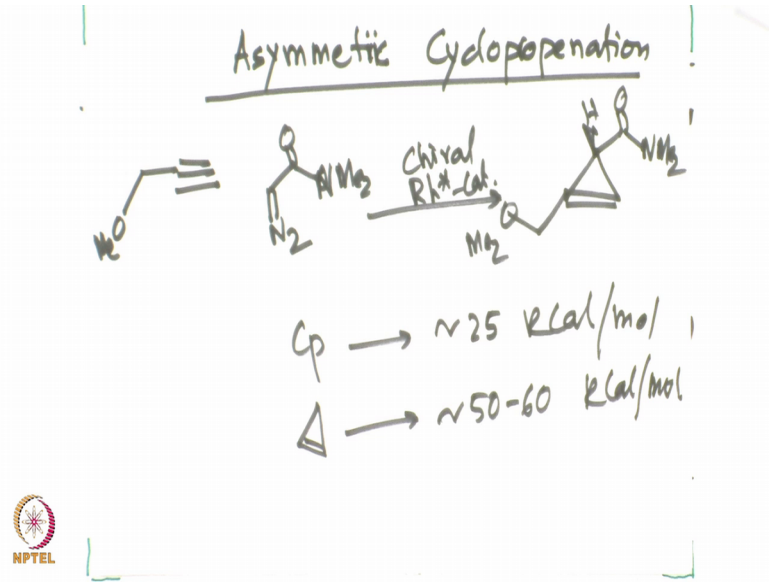
To get this intermediate which is an advanced intermediate for the drug that all of us are familiar with that is in the market that is called the cilastatin this is the structure of

cilastatin and as you know cilastatin is used as antibiotic in conjunction with carbopenane which inhibits the enzyme dehydopeptideg this is the cilastatin we are we are synthesizing by this cyclopropanantion method and once again this is used as in conjunction with carbon to inhibit the enzyme the hydropeptide edge.

So, these are antibiotic combination now. So, this is this is again cilastatin; cilastatin. Now of course, this is utilized and used and synthesized in multi gram scalar or rather kg scale cilastatin is a active component of the antibiotic. Now by this simple cyclopropanation reaction the main stereochemistry is set where we have seen that these copper catalyzed chiral copper catalysts is used for this cyclopropanantion reaction right from there, it can be further modified to get the cilastatin compound now of course, in addition to cyclopropane as the material one can think of cyclopropene preparation in those cases as one would expect.

We cannot use pro olefin right we must use alkyne instead of olefin if we have to get cyclopropene by a similar method that we have seen for a cyclopropane reaction, let us try to synthesize cyclopropene ring which is of course, is much more unstable and you know compared to cyclopropane how cyclopropane can be propene can be synthesized by utilizing the same technique.

(Refer Slide Time: 13:07)



So, let us just directly discuss asymmetric asymmetric cyclopropanation reaction cyclopropenation reaction cyclopropene ring formation we would like to discuss the reagent as we try to discuss you need is a alkyne and alkyne and let us say for example, diazo ester or rather amide let us say for example, and a chiral rhodium catalyst in this case its used to give the cyclopropene, I hope you can appreciate this method for this cyclopropene synthesis as you know cyclopropane ring strain is nearly something like 25 or 28 k cal per mole and cyclopropene is nearly 50 to 50 to 60 kcal per mole. So, this is very very you know very very strained molecule cyclopropene compared to cyclopropane.

So, overall in this part what we have seen today is the cyclopropanation reaction and then expanded the cyclopropanation methodology for the cyclopropenation reaction which are even more energy demanding and usually it is much more difficult to stabilize and prepare the cyclopropene, but the a rhodio.

For example, rhodium catalyzed when asymmetric version of this catalyst can be prepared by utilizing simple carbene type of chemistry both the cyclopropenantion and cyclopropanation reactions utilize carbene or metal carbene to be precise as a reactive intermediate for these reactions we have seen some evidences in favor of metal carbene as the reactive intermediate as opposed to the pre carbene for these cases this small molecule cyclopropane and cyclopropene are indeed very important structural building block for pharmaceutical or even for other industrial use and of course, for academic use as well.

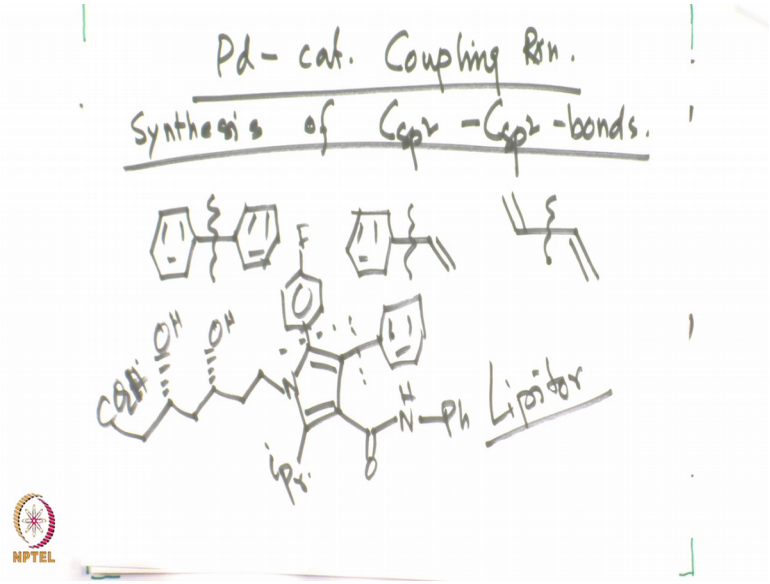
So, in the next part, we will try to discuss the carbon-carbon various carbon-carbon bond formation reaction of course, a carbon-carbon bond formation one can think of by various approach, but most often when a difficult carbon-carbon bond formation is talked about for example, sp 2 sp 2 bond formation reaction or you know sp three is sp bond formation reaction sp sp three bond formation reaction sp three sp three carbon-carbon bond formation reaction these reactions are extremely challenging and therefore, actually there exists no other organic transformation that can do it except using the organometal chemistry or organometallic intermediate.

So, organometallic intermediate has this kind of revolutionized the way this carbon-carbon bond formations are looked at nowadays it is you know indispensable to synthesize pharmaceuticals industrial other molecule different-different academic purposes

wherever you can think of synthesizing or introducing a new carbon-carbon bond usually the first thing that comes into mind is the organometallic chemistry where organometallic intermediate is doing wonder to do these carbon-carbon bond formation let us look at some of those example.

How one might would be thinking to prepare it both in industry and in academia that would be our next part of the discussion. So, palladium catalyzed first we will discuss the palladium catalyzed method of course, nowadays not only palladium a number of other metals had been used for these carbon-carbon bond formation reaction since historically and o overall expansion wise palladium played a key role for these difficult carbon-carbon bond formation reaction we will try to mainly focus on the carbon-carbon bond formation utilizing palladium as the active intermediate.

(Refer Slide Time: 08:04)



So, palladium catalyzed coupling reaction. So, most importantly synthesis of Csp 2; Csp 2 bonds right one, let us try to think about forming a by phenyl ring can this be form very easily without invoking organometallic intermediate I guess not can one synthesize this sp 2 sp 2 this short of bond or even you know this shorter bond what how one would think of forming these bonds remained completely under difficult situation and of course.

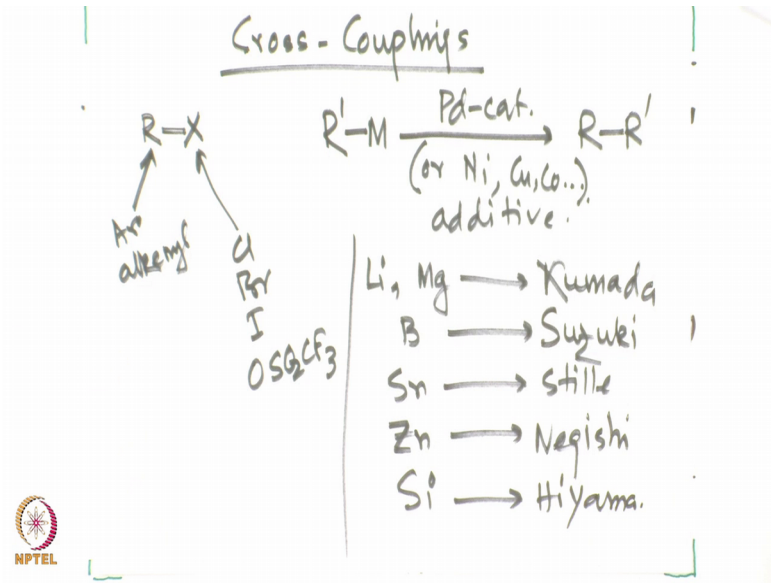
You know a number of drug molecule such as this which we and trying to draw here is a lipitor where you see this is one carbon-carbon sp 2 sp 2 bond formation and another for example, this one another carbon-carbon bond formation and you have a long chain of course, over there for this processes and overall CO2H; for example, overall this 2 difficult carbon-carbon bond formation reactions this is Lipitor are carried out by doing the so called cross coupling reaction or palladium catalyzed cause coupling reactions.

Now, of course, for cross coupling reactions as you know the reagent usually that is used is your organohalide reagent right for example, aryl bromide aryl chloride aryl iodide of course, nowadays aryl diazonium or even aryl carboxylic acid usually you have a aryl halide that is used traditionally and then depending on the other reagent other coupling partner the reaction are differing in their name right we are most familiar with for example, Suzuki reaction right which utilize a aryl boronic acid as the coupling partner now once that coupling partner is changed of course, aryl boronic acid in conjunction with aryl halide now once the aryl boronic acid change to aryl tin reagent that reaction is called the stili coupling right. So, the other coupling partner keeping the aryl halide constant if you change the other coupling partner the name of the reaction because those are the usual name reaction name of the reaction are changing.

So, aryl tin reagent should be called stilly reaction aryl or boronic acid reaction Suzuki reaction if one is using aryl zinc reagent that is called Nigishi reaction if it is a Stille reagent aryl Stelle reagent that is called the hiama reaction if it is you know lithium aryl organolithium reagent and the those are called Kumada coupling right lithium or magnesium reagent is used then those are called Kumada coupling.

So, with all these named reactions we will systematically discuss their pros and cons where is where a particular this bond formation carbon-carbon bond formation reaction good at where they fail what would be a ideal reagent that we would like to or idol types of reaction that one would like to use both in industry and in academia those are the one we will be discussing subsequently. Now let us define those organometallic reagent and the named reaction because those will be coming pretty often for our discussion, let us try to nail it down ok.

(Refer Slide Time: 22:20)

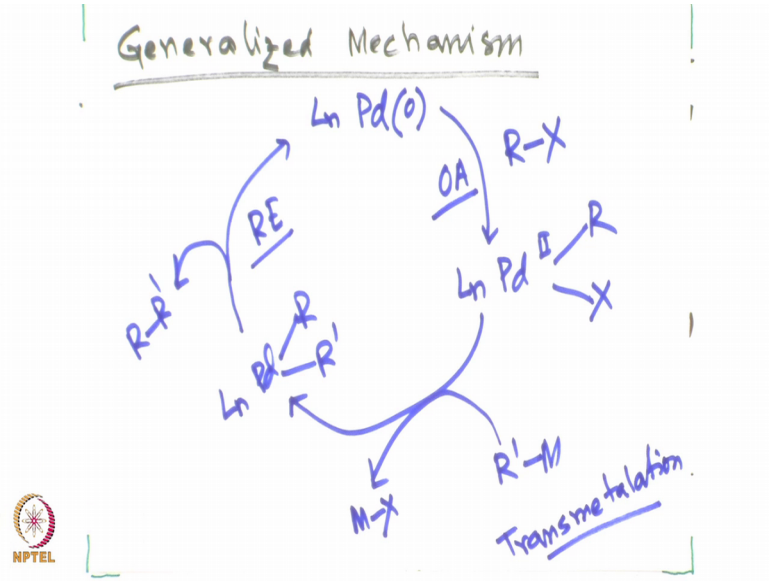


So, cross coupling reactions this is some part we will discuss in detail cross couplings usually it is a R X; R is early days it is aryl alkanyl nowadays of course, even the aliphatic are used Clo a halide x partner could be chloride bromide iodo OSO 2 C F 3 and so on. And you are the other partner based on which the name reaction is changing to give you overall R-R prime is the one which is usually called the transmetalating is reagent; let us say we are using palladium catalyst of course, we can use other such as nickel copper cobalt etcetera we need various additives depending on the reaction condition overall if it is a lithium and magnesium reagent that is called Kumada coupling if it is boron reagent that is called Suzuki coupling, right.

Suzuki reaction if it is tin that is Stille reaction if it is zinc that is Neghishi reaction and if it is silicon that is the Hiyama reaction overall then we have these at least five different type of reagent or five different type of starting material that is used for example, palladium catalyzed carbon-carbon bond formation process now overall there is a synergy there is some sort of harmony among these all five different type of reaction of course, we will discuss separately these palladium catalyzed carbon nitrogen bond formation or famously known as Buchwald Hartwig type of coupling and other reaction that is also under the cross coupling banner is the Shufa Sonogashira the reaction for example. So, those we will discuss separately.

Let us just simply we are trying to discuss these five reaction first and then we will come to those other reaction which are extremely useful for industry as well as in academic setup we will first try to look at if there is some sort of you know some sort of general mechanism for all these reaction all or each of these reaction on their own right have caught the imagination of the scientist in terms of its application its becomes really widely used at this point, but there exist a number of issues almost with every reaction we will try to touch upon those and the development that has been carried out over many many decades du during our time that we would like to discuss before going into details let us try to look at a generalized mechanism for all these processes.

(Refer Slide Time: 25:35)



So, generalized mechanism for these purposes, we will have palladium reagent as I was saying, it is not necessary to use palladium, but we will use palladium for a general mechanism. Mechanism is oxidative addition is the first step with R-X to give ligand palladium intermediate where R and X are attached to it from here we get Ln palladium R and R prime where this R prime is coming from this is where the trans metalating reagent that is organoboron reagent organolithium magnesium organotin organozinc or organo seleno selenium silicon reagents are important here m and x gives you a x overall in the process we get R-R prime as the product formation that is the reductive elimination and this step is called trans metalation. So, it is a oxidative addition trans metalation and reductive elimination. So, these are the key approaches for this processes overall we do

see that we do have a process where starting from a starting from an intermediate.

When we have we have a lower valent intermediate for example, palladium 0 from there on an oxidative addition with organohalide for example, aryl bromide gives rise to a palladium 2 intermediate at which now we see a trans metalation. So, after oxidative addition trans metalation usually proceeds with the R and R prime both the partner carbon partner on the palladium keeping the palladium tool oxidation state intact.

So, palladium 0 goes to palladium 2 in pre in during the oxidative addition and during trans-metallation palladium 2 oxidation state is maintained subsequently we do see that this palladium 2 intermediate undergo a carbon-carbon bond formation; that means, the product formation step between those 2 R and R prime. So, 2 sp 2 sp 2 carbon center for example, undergoes a reductive elimination to give palladium 2 to palladium 0 formation that regenerates the catalyst and one can see the product formation or. So, so to speak the carbon-carbon bond formation reaction that occurs subsequently.

So, by doing so, we are able to show that it is a palladium 0 to 2 0 catalytic cycle. So, 0 2 catalytic cycle that is involved and during these processes then one during the trans metalation process usually one would need a base that will discuss for other metal a similar plus 2 oxidation state if it is a for example, I mean nickel one it could be nickel one three catalytic cycle nickel is a little problematic case sometime depending on the substrate combination actually metal mechanism can change it is usually undergo, it is usually proposed to undergo a radical type mechanism.

But nonetheless you know it is a overall plus 2 oxidation state change usually pread gets predicted for these kind of reactions, but you know, it is extremely difficult to put a single mechanism for all that type of cross coupling reaction that.

We do see, but the one we discussed usually captures the field, but not necessarily exactly correct for all the reactions this is a oversimplified mechanism that we have drawn for all the different type of a cross coupling reaction or carbon-carbon bond forming reaction we are going to discuss we will discuss each of those topic in detail I might will be discussing briefly about one to three of these reaction and then come back and discuss this reaction in greater detail.

We will this start discussing briefly the Suzuki reaction and then maybe the Negishi reaction a in a bit and Stille reaction. In the next class, briefly we might will again after that we might will come back to these type of reaction in more detail to give you better idea about these processes keep studying these cross coupling reactions and their utility in the synthetic setup, bye-bye.