Metal Mediated Synthesis - I

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Lecture – 8
Suzuki coupling reaction

Hello, welcome everyone. Today, we will continue discussing on those carbon-carbon bond formation reactions as you were discussing these are truly the greatest discovery of the organometallic chemistry. It has revolutionized the way the carbon-carbon bond can be formed.

Since carbon-carbon bond is fundamental or the backbone of organic compounds to be able to do synthesize this carbon-carbon bond in a controlled fashion is a fair amount important we have named those reactions we have seen those named reactions mainly based on the reagent that is used the same carbon-carbon bond formation reactions are named differently for example, as we have seen in the last class if a aryl halide usually aryl halide is the one coupling partner aryl halide such as aryl bromide chloride iodide or even aryl diazonium salt aryl OTf mesylate nonaflet or whatever it is.

If your electrophile is aryl halide keeping that as constant if we have the other partner. So, to speak the trans metalating reagent is differing, then the name reaction will appear various name reaction will appear for example, if the trans metalating reagent is bo aryl boronic acid or any boron partner then that reaction is called the Suzuki reaction. If it is a stin reagent, of course, aryl halide is constant that reaction is called Stille.

If it is zinc reagent that is used for trans metallation that will be called Negheshi reaction. If we do have silicon as a trans metalating reagent organosilicon reagent is used that reaction will be called the Hiyama reaction. If it is lithium or magnesium reagent is used, then those reaction will be called Kumuda reaction or Kumuda coupling reaction now we in the last class we have seen some examples of Kumuda coupling. We have started discussing also about the Suzuki reaction we have seen the beautiful example of the Suzuki reaction where even sp 2 are halide such as alkenyl halide was reacted with alkenyl boronic acid to give you the sp 2 sp 2 coupling.

Where 2 alkenyl partners can be associated to form the carbon-carbon bond these reactions are extremely successful and extremely valuable as a we were discussing the stereo centers re remain intact or the studio control e is given or its controlled by the starting materials also, another very important feature of the Suzuki reaction is you can have wide functional group into your 2 partners and the reaction will proceed smoothly without any problem with the functional group as we were discussing for Kumuda coupling where organo lithium or organo magnesium or grignard reagent are used the problem could be the functional group tolerance.

If you have functional group that is in you know incompatible with the grignard reagent those reaction will be problematic, but for Suzuki reaction no such problem appears and it works beautifully like this. Now today we will continue discussing on the functional group tolerance of the Suzuki reaction.

And also the carbonylative Suzuki reaction let us first discuss one functional group tolerance where we will see in presence of acidic functional group how Suzuki reaction is working beautifully. So, first will take an example where we will see that the reactions are occurring in presence of acidic functional group.

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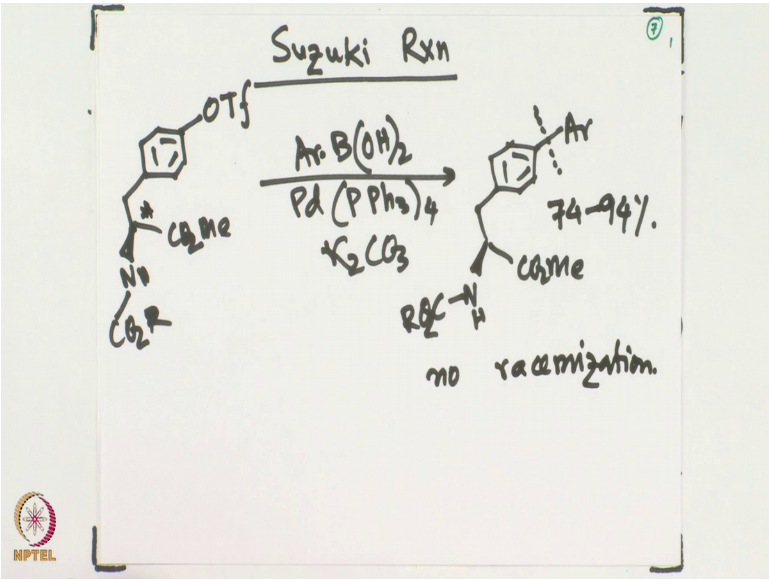

So, this is again continuation on Suzuki reaction the example that we have in hand is OTf these are acidic of course, now if you want to react with aryl boronic acid the aryl group can be also having different functional group in presence of palladium tetrakis we will get the product that we are looking for the digit carbon-carbon bond formation between the aryl group and this carbon center this carbon center and the carbon center of aryl group forms the bond to give you the desired product and the yield.

For these reactions are usually very high seventy 4 percent to ninety 4 percent and no racemization that is very important because you have a stereo center at this site we do not get any racemization. So, that is a very beautiful things one should be very very proud of that form the Suzuki reaction now for the Suzuki reaction also, we know that there are variety of coupling partner that can be utilized during these reaction for example, we can have alkenyl coupling partner.

For example, alkenyl halide as well as boronic acid in between if we are to we are to insert or we are interested in having a carbonyl in between the halide partner as well as the boronic acid partner we can have the carbonyl relative Suzuki coupling to give the ketone compound that is again a powerful reaction.

Let us say for example, if one is interested in synthesizing you know benzo phenone. So, one of the aryl halide and aryl boronic acid you want to put in between carbonyl. So, that can be done that is a beautiful example of a Suzuki reaction another problematic coupling partner could be alkenyl halide along with you know aliphatic aryl boronic acid aliphatic boronic acid and then you have a carbonyl in between indeed those reaction even works quite beautifully for the Suzuki reaction. Let us look at one of the example of form of this carbonyl native Suzuki reaction where carbon monoxide is used in conjunction with the traditional coupling partner of the Suzuki reaction carbonylative Suzuki reaction.

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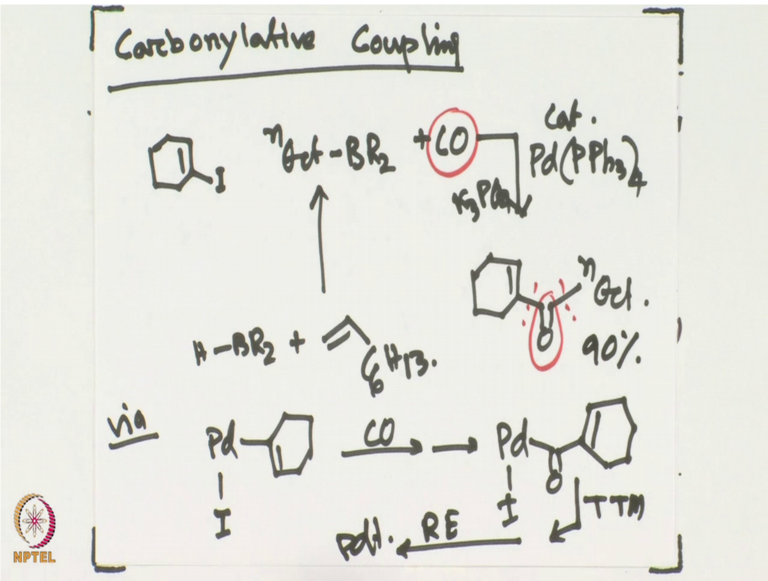

Carbonylative coupling; now what we have in hand is an alkyl halide such as this one and we have an aliphatic pa coupling partner again these are usually traditionally difficult coupling partner because in sp 3 carbon center is there and you can get a predominantly other side product that is that might be happening in these cases, but palladium PPh 3 4 that in palladium Tetrakis usually referred as in presence of potassium phosphate as a base we do not need stronger base phosphate is good enough we do see that you know your carbonyl group is getting incorporated.

So, this carbonyl group is the same over here and it is getting incorporated overall you can synthesize these octal bro boron reagent starting from H-BR 2 and reacting to it with your olefin reagent corresponding olefin reagent now if you look at carefully what we have seen right. Now is alkenyl coupling partner and alkenyl halide that is a very challenging coupling partner along with alkyl boronic acid reagent or boron reagent alkyl boron reagent these 2 partner put together in between carbon monoxide is placed that is a very reliable way to synthesize any ketone compound.

You can have di aryl ketone you can have di alkyl ketone you can have alkenyl alkyl ketone these are very very interesting compound and specifically if you are looking to synthesize a bigger molecule which has ketone in it. Of course, there are plenty of natural product with ketone moiety and plenty of pharmaceutical you know industrial applicable molecule industrial important molecule that has ketone campa ketone unit in the molecule and these compounds can potentially be synthesized for corresponding coupling partner for the Suzuki reaction.

So, that is actually giving us a lot of control into the ketone formation; let us look at the mechanism briefly of course, it is a simple mechanism, but let us look at any way that will give us a good feeling that how this reaction might will be proceeding. So, it occurs via a palladium iodo and alkenyl unit.

Of course you have reacted co what you get over past it is your coordination with the palladium and eventually you will get palladium iodo with a co in there from wherein you will get trans metallation trans metallation and reductive elimination to give you the product and this is nearly ninety percent yield. So, what we have seen that alkenyl halide will undergo oxidative addition to give the palladium iodo and alkenyl unit now carbon monoxide will then come and interact with metal center to give the metal carbonyl bound alkenyl iodo compound from there on carbon monoxide will insert in between the palladium carbon bond of the alkenyl unit to give the type of intermediate.

So, alkenyl co palladium intermediate and iodo is of course, attached to it palladium subsequently what will happen as you know trans metallation from the boronate or boro aryl boron partner or alkali alkyl boron. In this case will come trans metallation in presence of a base will happen to give rise to the intermediate from which a reductive elimination will give the desired product and as you have seen the yield for these reactions are quite good. So, essentially what we have seen.

So, far that Suzuki reaction is quite versatile it can tolerate various functional group it can even tolerate a in enantiomer or you know stereocenter can be can be retained during the process we have seen also the also not only the stereocenter also the geometry and stereo control you can have if you are starting with a trans olefin or trans alkenyl halide you will end up with the same compound or without changing the geometry at the coupling partner.

So, as you have seen 2 alkenyl hala one alkenyl halide and another alkenyl boron reagent giving you the control completely with respect to the reagent during the reaction no racemization or isomerization of the partners or substituent is happening during the Suzuki reaction and most importantly any reaction that you can think of anywhere any carbon-carbon center is.

There you can split it into half and one side could be halide the other side would be could be the boron reagent and if you want to put a palladium for example, simple palladium tetrakis most often work if you want to put them together you can get it done in presence of a base under very mild condition and a standard organic solvent you can usually get the product quite efficiently this demonstrate the efficiency.

And the is of the formation of this desire carbon-carbon product that one may be interested in the problem with the Kumuda coupling was the functional group intolerant Kumuda coupling each functional group intolerant because it is dealing with organolithium and your grignard reagent no such problem happens for this Suzuki reaction in all these cases usually we are using a compound or using a palladium compound which is in palladium to plus oxidation state, but we are not interested in palladium in 2 plus oxidation state for the catalysis.

We need palladium 0. So, one way or the other usually by the help of or by taking the help from the starting material for example, in the first case we have seen organolithium reagent or grignard reagent will help form the palladium 0 from palladium 2 and that palladium 0 in c 2 form will go on with the catalytic cycle to give you the oxidative addition trans metallation and reductive elimination.

So, once a again although we are using palladium 2 as the starting material we need to have palladium 0 formation during the process otherwise catalytic cycle will not go on usually for this standard carbon-carbon coupling reaction or carbon-carbon bond formation reaction we have the starting material helping us out for palladium 0 formation then again the question simple question is why do not we use the palladium 0, directly from the market indeed there are plenty of palladium 0.

Stores that is available the problem of those palladium 0 source which are commercially is in order to stabilize palladium 0 they need to have a ligand associated with palladium now the for your desire carbon couplon coupling reaction you need another palladium ligand complex not the ligand that comes from the market. So, you need your desired phosphine ligand; for example, to be associated with the Suzuki reaction or Kumuda reaction now that ligand that special ligand of yours for your desired reaction may compete with the market available palladium 0 ligand.

Now that since that there is a competition because the ligand has to be good in order to stabilize palladium 0 from the market now your desired ligand and the ligand from the market for palladium 0 competes. So, your overall desired you know catalytic cycle can be problematic therefore, it is desirable that you start with palladium 2. Now let us move on of course, we will come back with some more example in latter classes for Suzuki reactions and the and the application of these as we also have discussed that.

You know aryl halide coupling partner or the or the oxidative addition also is dependent on the type of substituent we have in the in the electrophile if; for example, if you have a aryl bromide and those are ortho substituent they are 2 and 6 positions are having big or large substituent then those reactions will be problematic because it demands of the substrate slow drown the oxidative reaction similarly if it is a electron rich substrate we have problem during the oxidative addition.

So, electron deficient substrate will be will be preferred now when some time you see that some reaction required very very low loadings of palladium low amount of palladium even homeopathic amount of palladium will be good enough well then you have to see if whether it is really the catalyst control or the substrate control if the substrate combination is the easier one where your let us say aryl halide is electron deficient as well as the other partner is also electron deficient and therefore, reductive elimination is also faster as well as oxidative addition is also faster.

Those are not really the right reaction to compare because those are supposed to give you a very good turnover number, but if the ligand is very efficient then irrespective of the coupling partner you are supposed to get a very good turnover number that is why the ligand designing becomes very important now of course, as we know ligand plays a very important role for these carbon-carbon bond formation reaction even for any organometallic reaction if the ligand is way too bulky then of course, you have problem in oxidative addition you need ligand which is electron rich.

So, as you were seeing the Suzuki reaction is quite compatible with a number of coupling partners irrespective of the coupling reaction the name reaction of it you need a ligand which is very good for your oxidative addition and reductive elimination for oxidative addition to be facile you need an electron rich ligand which will be also not too bulky. So, you need a smaller elegant electron rich ligand, but on the other hand for reductive elimination what you need is a bulkier ligand because reductive elimination is going for a higher coordination number to a lower coordination number.

So, bulkier ligand will push the 2 coupling partner together and therefore, bulkier ligands will be will be very much promoting the reductive elimination at the same time you need to have a electron deficient ligand for reductive elimination because from a higher oxidation state to a lower oxidation state metal is going for oxidative addition lower oxidation to higher oxidation state it is coming.

So, palladium 0 is going to palladium 2. For example, for reductive elimination palladium 2 to palladium 0 one is going and therefore, the electron richness will be favored for the oxidative addition for the reductive elimination electron deficiency will be favored same way for the oxidative addition a smaller ligand will be preferred for the reductive elimination a bulkier ligand will be favored now this is the dilemma this is where the problem is for designing a ligand.

How a ligand could be electron rich as well as electron deficient how a ligand could be small as well as large. So, this is where the traditional problem comes and people have tried to address it by many different way one of the approach that found to be very successful is to use this by phenyl phosphine ligand whenever biphenyl phosphine ligand need to be bulkier the biphenyl unit coordinates or interacts with the metal center. So, to speak palladium in this case and whenever it need to be smaller the by phenyl ring can swing away.

And therefore, the palladium center is essentially looking at a smaller ligand both this ambivalent or bivalent characters in one sense it is bulkier in one sense it is smaller is crucial for the ligand designing and this remains a holy grail for the catalysis once again for the catalytic cycle you have oxidative addition trans metallation and reductive elimination the requirement for oxidative addition is completely opposite to that of the reductive elimination and this is exactly the point where the red ligand designing is. So, important and there is no suitable ligand for a variety of reaction because.

The requirement may change depending of the depending on the coupling partner nowadays one of the ligand that has shown the best result irrespective of the coupling partner and the type of reaction we are looking at is that bi phenyl by aryl phosphine type of ligand and there exists variation of those ligands which are found to be suitable for a number of reactions that is of interest both in industry and academia next we will briefly discuss the Negishi reaction of course, Negishi reaction means the zinc reagent will be used the best part of the Negishi reaction is these reactions are dependent on the zinc reagent, but zinc is not that nucleophilic compared to let us say organolithium or organo grignard reagent or you know rmgx therefore, functional group tolerance is going to be excellent for the Negishi reaction; let us try to look at the Negishi reaction.

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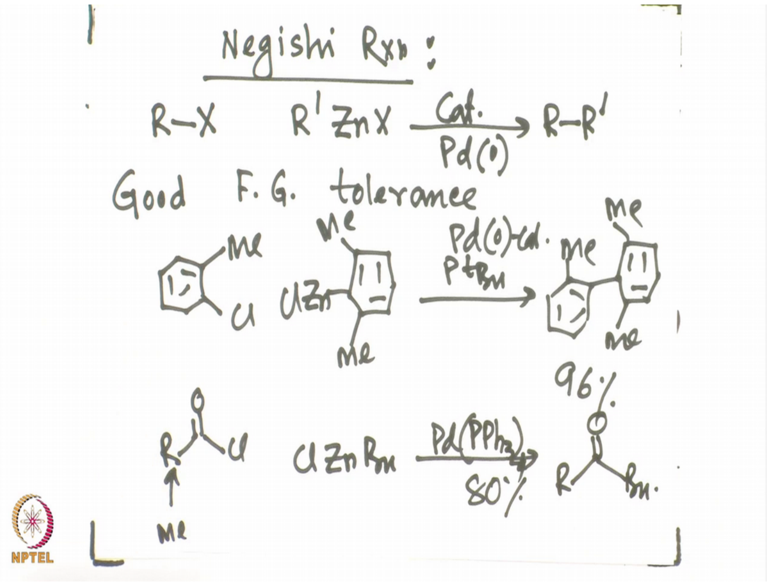

What are the coupling partner and what is the efficiency of these reactions Negishi reaction, we have R-X and R prime Z and X that will give you catalytic in presence of palladium 0 to give you R and R prime as we said these are good functional group tolerance if you have a bulky partner such as these and you can get the desired product in presence of palladium 0 catalytic amount and this methyl reagent this gives you 96 percent yield of the desired product.

Now of course, if these are very good for these coupling reactions and not only that we also would like to have the reaction where maybe let us say Kumuda reaction is failing for example, a ketone synthesis if you have a acid chloride and you are reacting with zinc reagent that when Negishi reaction you can get the corresponding ketone product on the other hand if the same reaction one is interested in doing under the organolithium or organo magnesium reagent or grignard reagent.

So, to speak Kumuda coupling those reaction will not be successful because they might will need to the tertiary alcohol formation one more addition on the desired product let us look at one of the example R CoCl, let us say R is methyl and reacting with chloro zinc butyl and in presence of palladium tetrakis, it gives 80 percent yield of RCo of butyl. So, these particular reagent where a ketone is formed starting from acid chloride and the organo zinc creation is going to be successful and can give good yield.

But the same reaction will not be successful for the Kumuda coupling reaction now this demonstrate the functional group tolerance of Negishi reaction zinc aryl zinc or organo zinc reagent is used once again for Negishi reaction one can have plenty of reaction or any reaction of their choice if they are ready to use this zinc reagent and functional group tolerance is you know its uncomparable its almost every functional group can be tolerated under the reaction condition reaction conditions are usually mild and therefore, desired product can be formed very easily.

So, so far we have seen Kumuda coupling Suzuki coupling and Negishi coupling in the next class will briefly discuss the Stille reaction the good things and the bad thing pros and cons of Stille reaction and then we also we would like to discuss what happens when alkyl halide were used why alkyl halides are very tough problem in the carbon-carbon bond formation reaction all these issues can be solved by suitably designed ligand because legand play the most crucial role during these processes with those discussions will be coming in the next class of those carbon-carbon bond formation reactions.

It is also most important for all of us to appreciate and understand the value ligand holds for these coupling reaction ligand is most crucial to cut down the cost although ligand itself can be little expensive, but compared to other things that is involved in the process even the ligand is expensive if we can cut down the palladium because palladium loading is most important to cut down because if in the in during the processes, let us say for a medicinal chemistry purpose if you are using huge amount of palladium irrespectively during the product formation some tiny amount ppm level of palladium will be left during the process even after running column and washing and every other processing

you would like to do ppm level co palladium may still left behind which will not be desirable if it is a drug molecule no drug approval will be possible if decent amount of palladium is left. So, therefore, a desired reaction can be only considered industrially viable medicinally viable if it requires very little amount of metal for example, palladium in particular. So, loading catalyst loading decreasing to a certain level is essential for employing the reaction for industrial as well as medicinal purposes will discuss more on those issues in the next class, till then, let us look at the Negishi reaction, let us read more example of the Negishi reaction also the pros and cons of each of these coupling reaction see you in the next class keep reading.