Metal Mediated Synthesis - I

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Lecture – 10
Asymmetric Suzuki coupling reaction

Hi everyone, how are you doing? So, you remember what we were discussing in the last class? We were trying to discuss the problems basically with the alkyl halides we have seems that alkyl halide is truly one of the most difficult partner we have in the carbon – carbon bond formation reaction. The problem with alkyl halide is simply they do not want to give the desired product.

If you take an alkyl halide the metal complex of course, which is in lower oxidation state will oxidatively add to the carbon halide bond into the alkyl halide will give let us say palladium 0 will give palladium 2 plus oxidative addition complex, but we as have seen in the last class subsequently it will undergo or it may undergo a beta hydride elimination giving rise to the olefin as the side product. Once beta hydride elimination is going on, the desired carbon – carbon coupling product using alkyl halide as a starting material is going to be questionable.

So, mainly the beta hydride elimination is one of the problems that we have seen in the last class. Well, there is a way to solve this problem and simply if you take a bulky phosphine ligand which is bulky; that means, that it will not allow the beta hydride elimination to be facile, because for beta hydride elimination you will need the increased number of coordination site at the metal center. If the ligand is bulky such process such as beta hydride elimination will be somewhat retarded. So, by having a bulky phosphine ligand, one can think of reducing the beta hydride elimination product formation, so, to speak the olefin formation from alkyl halide and therefore, alkyl halide can gives rise to the desired carbon – carbon coupling product.

We have seen that alkyl act alkyl coupling in the last class like Suzuki coupling involving sp3 sp3 carbon center, sp3 alkyl halide and sp3 alkyl boron reagent that was using to give the long chain alkyne product at the same time such method is not really valuable or not really useful for secondary and tertiary halide. Such palladium and let say

tricyclohexylphosphine reactions are good for primary alkyl halide, but secondary alkyl halide what happens these reactions are really terrible that is mainly due to the fact that the oxidative addition into alkyl halide is occurring by SN 2 mechanism as you know for oxidative addition into any alkyl halide aliphatic any other aliphatic substrate or even aryl halide. We have 3 different mechanism possible SN 2 reaction of course, radical reaction and concerted processes for oxidative addition.

Often for alkyl halide we have this SN 2 reaction; that means, if you are having the carbon bromide bond that carbon centre where bromine is associated with the substrate over there we will have a inversion during the during this oxidative addition. So, if that is happening you can imagine that secondary and tertiary halide will not undergo such SN 2 reaction and that is the main reason why secondary and tertiary halide are problematic substrate for Suzuki reaction or for any usual carbon – carbon bond formation reaction involving palladium. Well, we have shown that also with a suitably designed substrate where alpha carbon and beta carbon are having 2 deuterium; 1, 1 deuterium each and once we are doing oxidative addition to this alkyl halide we have seen the inversion in the alpha center.

Now, as we are trying to discuss that there is a way out to incorporate the secondary and tertiary halides and what is that well we need to change the reaction mechanism we cannot rely on palladium catalyst to do this thing because it relies on a SN 2 mechanism for alkyl halide to undergo oxidative addition. On the other hand if we take a different metal such as you know nickel which promotes or which prefers a radical pathway due to it is mainly due to it is electronic configuration if you look at you know with the nickel lot of reactions are indeed radical in nature. What we can then expect that both primary secondary and tertiary halide can participate in to the carbon – carbon bond formation reaction. Indeed not only that although it is a radical reaction with a suitable ligand with a chiral ligand we might will be even able to control the carbon bond formation in a sterio control fashion.

So, will see those asymmetric versions of those carbon – carbon bond formation reaction today, as well as introducing the nickel for the tough or most difficult carbon – carbon bond formation reaction. Lot of these reactions or lot of these studies are done by professor (Refer Time: 06:44) who is now at (Refer Time: 06:47).

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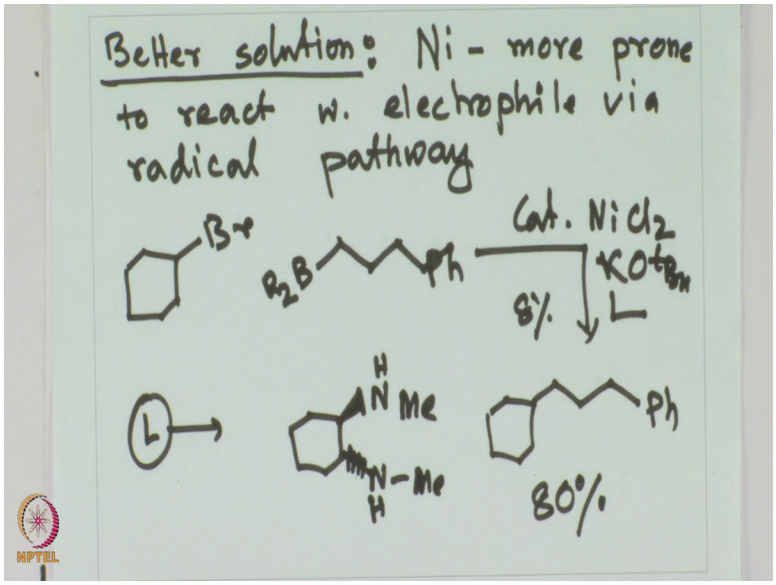

So, most difficult reaction we are trying to see the better solution we along the line while using the aliphatic substrate we are trying to have a better solution. What is the solution? Nickel which is more prone to react with electrophile via radical pathway that is the better solution compared to palladium and it works.

So, for example that previously what was not feasible as reaction secondary alkyl halide reacting with Br 2 1, 2, 3, let us say cut it down here with a phenyl and then the product that we are getting is going to be the one we would expect without much problem and this carbon – carbon bond formation reaction is happening by using catalytic amount of nickel chloride potassium tert-butoxide and 8 percent of a ligand that ligand L that is used in this case is the cyclohexyl diamine in dimethyl cyclohexyl diamine that is the one that is being used.

So, what we have seen right now is nickel as a catalyst now used for example, secondary alkyl halide which are not compatible with palladium because palladium cannot undergo oxidative addition in a reliable fashion to give the carbon – carbon bond formation product, oxidative addition will happen no problem, but you know the problem is we will end up having lot of side product as well that is one of the problem another problem is the of course, is a SN 2 reaction therefore, therefore, problem could be even more during the oxidative addition as well.

So, this is where nickel comes into picture and nickel helps us out for the overall process and we do see that a secondary sp3 center and a primary sp3 centered now reacted in presence of nickel catalyst and a ligand that we have used is the dicyclo cyclohexyl n,n, dimethyl cyclohexyl diamine that is now giving nearly 80 percent yield which is quite amazing for this type of carbon – carbon bond formation reaction.

As we were discussing previously we are not going to bring way too many examples at this point. We will come back maybe separately in future classes where we will discuss in more detail some of these things some of these carbon – carbon bond formation reaction, but, we will now touch to give an overview of the field overall and then try to move on with the next carbon – carbon bond formation processes. As we discussed there exist a number of these carbon – carbon bond formation processes some we have discussed some we will be discussing in future as well.

Let us look at the asymmetric version of these reactions where a chiral catalyst is used; that means, a chiral ligand is used. So, ligand will control the stereochemistry at where at the place where the carbon – carbon bond formation is going on. Once again nickel will be using as a catalyst and although these are radical mechanism still there will be an intermediate from which a of course, a radical intermediate will be formed from which phase of the radical you know this nickel catalyst join or from the bond organometallic complex that determined the stereochemistry into the product formation.

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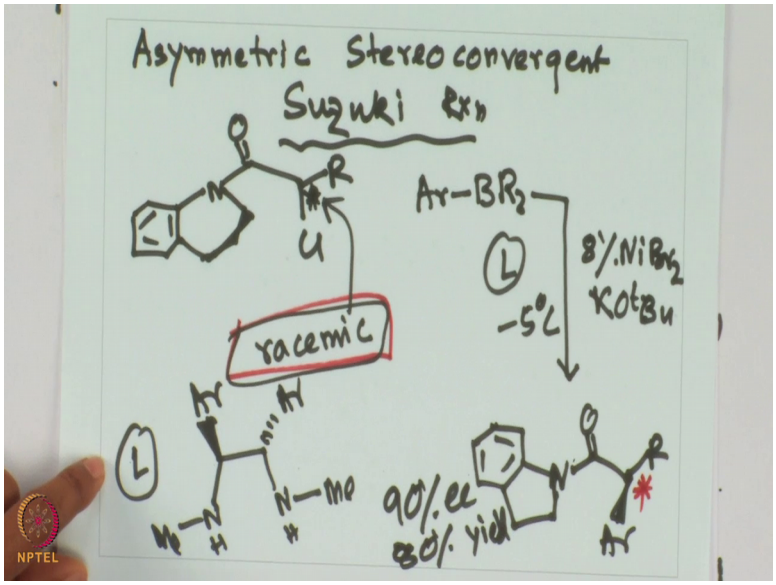

Let us look at asymmetric stereo convergent reaction asymmetric. Stereo convergent Suzuki reaction, what we are starting with is a racemic compounds. So, it is a 1, 2, 3, 4, 5 membered ring 1, 2, 3, 4 there is no carbon in between. So, this is the starting material and we are taking this. So, this center is racemised not a stereo center, this is a racemic center.

Now, we are trying to react with a aryl boron reagent to get the product. Here, once again we are using nickel as the catalyst for example, nickel bromide we are using potassium tert-butoxide as the base at minus 5 degrees C we are taking and the ligand in this particular case the ligand we are using is the one developed nicely for this purpose and that works quite beautifully to give the product that we are looking for and in actual it gives in quite acceptable level of thus the enantio selectivity in these cases. We have this compound. Now, we have 90 percent ee for this compound and nearly 80 percent yield for this compound again. So, that is quite good right.

So, we have the product starting from a racemic one that is most interesting it is a racemic product, racemic starting material and here, we are able to generate the stereocenter 90 percent ee and 80 percent yield. So, that is I think it is quite amazing because you know this is a asymmetric stereo convergent reaction and that to a Suzuki reaction well you are forming a stereocenter and that too also sp3, sp3 in nature that that

is a I mean you know sp3 and particularly in this case sp3, sp2 carbon center between these two carbon center we are able to form and it is a very good reaction because this shows that it is not only possible to do such coupling reaction, we can control the stereochemistry at the center. It was crucial to have that ligand ethylene diamine with substituted with di aryl ethylene basically it is a ethylene diamine based ligand, but those aryl substituent are quite crucial for giving good yield and as well as the highs high selectivity for this reaction.

Let us look at one more example where once again we will have these stereo convergent reaction as stereo convergent is Suzuki reaction utilizing the racemic starting material once again and then we will get only one product and in very high enantio selectivity that is really a benchmark now for this kind of reaction to get these asymmetric reaction going starting from a racemic material we will come to that how that might will be forming.

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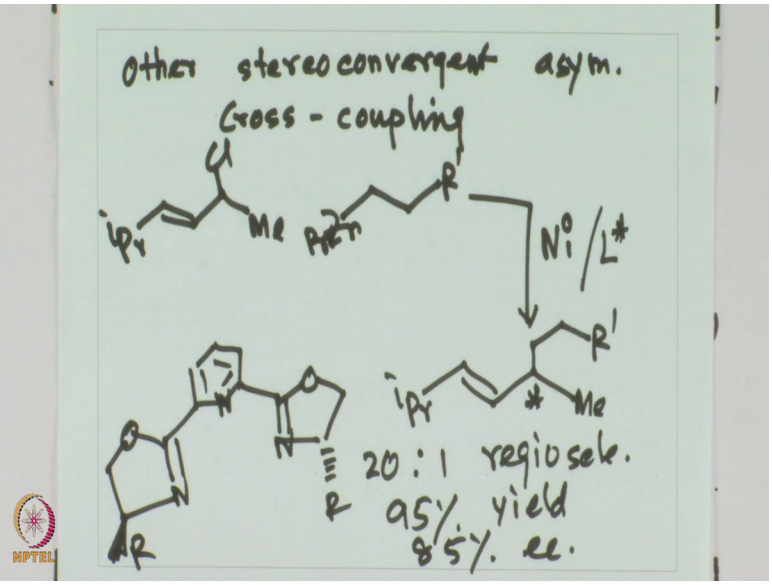

Other stereo convergent asymmetric cross coupling reaction, there are nowadays plenty of you know reports are there where we can do that. So, you can take basically now a organo zinc reagent. So, that is going to be your Negishi reaction once again with nickel no longer Suzuki we are talking it is a Negishi reaction we are talking with nickel now with zinc reagent we can get a once again the same you know expected product where now even we have a sp3, sp3 carbon center this is a the asymmetric center that will be

generated the selectivity is 20 to 1 and 95 percent that is the regio selectivity 95 percent yield and 85 percent ee wow, that is amazing.

And, what we have over here is a pi box type of ligand and that works quite beautifully for this type of reaction and you know this is this is quite amazing because you know this is a ligand controlled reaction where ligand is controlling the stereochemistry at the product. In the previous case what we have seen is mainly that we have a sp3 carbon center and then another sp2 aryl group is coupled it was a sp3, sp2 coupling with the palladium that that can be done quite efficiently by utilizing nickel catalyst once again it was a ethylene diamine based ligand.

Now, over here what we have right now seen is a you know Negishi reaction using zinc as the reagent now in this reaction once again nickel is used, but we are even able to achieve sp3, sp3 which is again even much more challenging than any other carbon – carbon bond formation reaction.

We are able to do the sp3, sp3 carbon – carbon bond formation as you have discussed why sp3 carbon centers are challenging first of all oxidative addition could be problematic you know because the mechanism is different. usually it is a radical mechanism and then most importantly some side product formation can also happen during oxidative addition or transmetallation reaction once after the oxidative addition or trans metallation still beta hydride elimination is feasible. So, alkyl partner can undergo a olefin formation rather than going for the carbon – carbon bond formation.

Despite having all these problems this nickel catalyst what if we were able to show that it can form the product under the Negishi reaction condition where zinc is used as a one of the coupling partner by after having that reaction as if it was not sufficient we can also have even the stereo center controlled with the help of the ligand. Well, that is got to be amazing because you know to have the sp3, sp3 carbon center first of all in a in a non a symmetric fashion is also very you know challenging tasks, after having that we can control the stereochemistry get the asymmetric center in a you know set in a correct fashion that is that is quite interesting.

And, for this purpose we needed a tridentate ligand usually known as these are oxygelene

based best of ligand not the pi box sorry and once we have that we can go for the stereo center setting quite nicely with the right optimization we see that it gives the product in good yield and very high enantio selectivity. So, in this part what we have seen is these carbon – carbon bond formation reaction mainly we were initially discussing the palladium catalyzed reaction. Palladium still remained I guess undisputed you know king for this carbon – carbon bond formation reaction.

Nevertheless other metal can chip in can be of great help we did not discuss too much of different metals like cobalt you know ruthenium, rhodium, meridiem you know all other variety of metal that might will be helpful for this reaction even iron. But, we have seen just a glimpse of nickel what nickel can do if given a chance that nickel can solve some of those existing problem that we face in the literature and the main problem that we were discussing is to participate or is to make sure that sp3 carbon center is participating during this reaction and that can be done by a radical fashioned.

Nonetheless, although this is a radical mechanism still we can control the stereochemistry. If we start from the racemic mixture in a stereo conversion manner both r and s starting material is given to one product. How that might will be happening we need to look at, of course, as you could expect that radical will be forming first and then definitely the ligand is controlling the chemistry. Let us look at just simply to give an overview of what might be happening.

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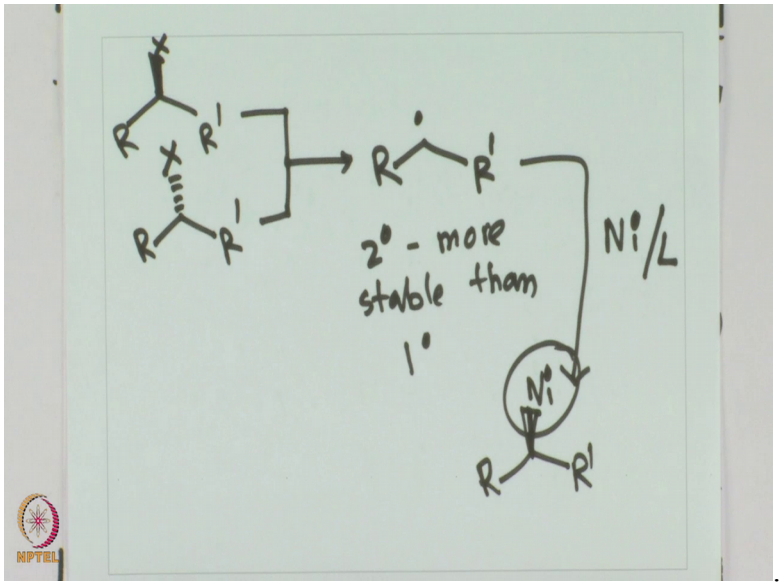

Let us say you have the starting material R, R prime with X up since it is a mixture R, R prime and X down. So, that is why if one is R another is s, but both of them will lead to the same intermediate and that is the radical intermediate. So, this is a 2 degree or secondary radical that is more stable than primary one which is expected. From there on this nickel and ligand; ligand is to remind you, ligand is a and you know of course, that there is a 2 stereocenter in ligand. So, this is basically a dias stereo marek or diasterio mark of the ligand person we are taking. Two stereo center are already there which is essential for the stereochemistry to be set and R prime what we get is the nickel.

So, ligand dependent cross coupling let us say for a particular ligand this. Now, nickel is above the plane because ligand has 2 stereo centers already in it only one geometry will be possible for the metal center to bind with it in a in a more preferable or more friendly manner and therefore, this is the intermediate. Since, one intermediate is forming from this from this radical intermediate this is the one which will control the stereochemistry of the product formation.

Now, during these processes we also should tell you that you know as all of us are familiar with for any asymmetric reaction you need two stereo centers; one stereo center could be in your product formation, another stereo center could be inside your ligand formation, but what is most important that for any of the a symmetric reaction when let us

say we are forming a enantiomer of course, as you know enantiomer are not separable by normal column because for separating any enantiomer you need another interaction for another stereo center. So, namely a chiral column, a column material that is having a chiral center already in it so, the material is already chiral.

So, your product enantiomer, 2 different enantiomers will interact with the chiral center in a different fashion and that is how we get the separation in chiral GC chiral HPLC; that means, chiral column containing GC chiral column containing HPLC. So, if your compound is having one stereo center, you need help from another molecule or another support which will help you identify or help you interact with that enantiomer differentially during the product isolation.

This is why, if you are taking 2 enantiomers of the same compound r and s and you are trying to run a column by normal column, you will not be able to separate them out, but that normal column material if there is a chiral center already existing then your compound r and compound s will interact with that chiral molecule differentially and therefore, will give the separation because the retention time will now differ for your r compound may interact with the column material which is a chiral material differentially compared to the s material and therefore, you will get the separation if you are carefully setting the reaction condition.

But, does not matter how careful you are if the normal column a what we run in for isolating a enantiomer will never be possible similarly if you take the enantiomer you want to do NMR a you want to run NMR you know experiment you will not be able to isolate or separate out or identify these enantiomer because NMR itself is not a chiral instrument that has chirality included into it. But, similarly same normal GC, normal HPLC, normal GCMS you will not be able to identify to enantiomers. But if you have a chiral column in GC, GCMS, HPLC or a chiral shift reagent in NMR you might be able to separate out or quantify the 2 enantiomers that you are dealing with.

So, remember 2 stereo centers are necessary for you know giving the product separation. Similarly, if this is where you need to have a chiral version of the ligand because ligand will interact with the with the 2 product that is r and s product if it is forming in differentially and therefore, the corresponding transition state that is leading to r product

and s product will be different in energy otherwise enantiomer transition state energy are the same.

So, unless there is a diastereo formation in one form or the other most often it is the ligand that is controlling the ligand controlling the interaction of the metal center with that substrate that is r or another substrate that is s depending on the ligand stereochemistry the energy of these corresponding transition state that will be diastereomeric in nature because now, you have a stereo center in the starting material also stereo center in the ligand and another stereo center the same let us say s stereo center in the starting material and r stereo center in the starting material. Now, this even if you take the racemic mixture of the starting material the ligand stereo center will determine which energy or which transition energy corresponding to the product formation is higher in energy. Therefore, that product formation will not be happening in larger amount if you are to get a enantiomer in a in high excess.

So, you always remember the 2 stereo centers are necessary for any asymmetric reaction although your product or starting material might will be controlling one stereo center or responsible for a one stereo center another stereo centers must be there at somewhere that is at the ligand stage usually. Otherwise, if it is a diastereomer that you are forming you may not have to worry about anything because you are forming distereomer; that means, the let us say 2 diastereomers having one is 1 or 1s or 2s another is 2s 1r.

So, that I mean if as long as that stereocenters are different at 2 different product they will have 2 different transition energy once you have such compound the 2 stereocenter in one molecule; that means, you will be able to isolate those compound by normal column chromatography. If you run a normal GC normal HPLC without any chiral column or even NMR will be a experiment you will be able to give you the or I will be able to help you identify the product. So, enantiomer are not separable by your column simple column or simple instrument like NMR GC HPLC, but enantiomers are separable if you have another help from the GC column or HPLC column or if there is a chiral shift reagent in the NMR.

Similarly, on the other hand the diastereomers are separable by normal column because 2 stereo centers are already. There you do not need any help this diastereomer can be

isolable or separable by in GC or in HPLC without any chiral column you should be able to do that. We might, will discuss these or their relative energies of different enantiomers and diastereomers what are the requirement on a different class. Till then keep studying, we will come back with some more of those carbon – carbon bond formation reaction in the next class. Bye.