Heterocyclic Chemistry
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Lecture - 19
Transition Metal Catalyzed Cross Coupling

Good morning, so before we take up the topic Transition Metal Catalyzed Cross Coupling. We will actually continue on the previous class, that was on oregano magnesium and one of the applications was in the synthesis of heterocycles, which is again such kind it is an important topic, which will be talked about after few classes.

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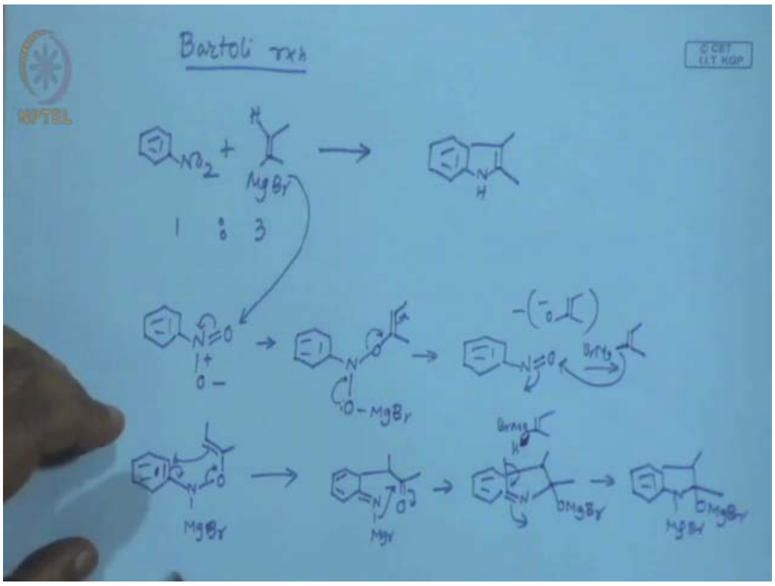

But, last time, we gave a reaction called bartoli reaction and say very useful reaction, if you recall, you have to identify the starting materials, the starting material nitro benzene and other portion is phenyl magnesium bromide. So, this is the thing and you do not have to do anything just mix them, but the ratio of the starting material should be one is to 3, that is the minimum and the product that you are going to get is straightway and straightway of course, this is this has as to be hydrogen.

So, phenyl magnesium straightway, you will get this indol is reaction what is the mechanism, mechanistically, actually there are 3 different steps, the first steps is a kind of unique reactions. And often we do not except, if you look at these nitro benzene structure, we often write this then this magnesium adds to the oxygen and nitrogen charges neutralized. So, result is result is we get an oxygen linked phenyl group nitrogen is now neutralized, these oxygen now is linked with magnesium bromide right.

Then what, then actually, this oxygen is picked up by the phenyl ((Refer Time: 03:04)), so phenyl push some other and what will find, we will find nitrous compound and of course, the other portion would come out as oxygen minus inlet, it comes out. And so essentially what we get is a nitrous benzene is intermediate, what next, we can except one more, this is minus that comes out then if you have magnesium bromide and again then the first equivalent is consumed.

Then the second equivalent mind it nitrous benzene as a unique property though, many it can be used as a decoder dynofield reaction takes place across the nitrogen double bond oxygen, then if you claim with that in corporate nitrogen in an cyclic munity. Then another reactions is developed by 2 scientist called Hiyasi one of them, other is Mackmillan both are organic chemist specialized in organo catalyze, if you do organic reaction with nitrous benzene, you will see oxygen is getting linked to the carbon not with nitrogen often, we custom to polarize, this nitrous bond towards this oxygen right.

And nitrogen gets positive charge that is just like carbonate but in this case the polarization is reverse manner, because of the agnatic link system. So, what will be getting now say double bond again nitrogen and oxygen then you have now, you have magnesium up magnesium here and this bromide. I think what next, I think all of you probably would anticipate right, what is the next possible reaction, the via have written I think is very apparent right.

It will undergo 3 3 sigma tropical elements, this one 3 3 sigma tropical elements, so you get a new now carbon carboun, bond formation, nitrogen magnesium and then you had this oxygen now, oxygen heat on. And then all us can understand, what will happen next, because nitrogen magnesium means polarized towards nitrogen, so like ship base kind of formation and eventually, what will get, you will get nitrogen appear as 5 member range then you have oxygen magnisiated and is.

Then probably next step is I think this proton transfer and this is where one more last equivalent of magnesium is consumed, that is reason why equivalent of magnesium’s are required all of us know magnesium also pickups the acidic hydrogen. So, it will picks up the acidic hydrogen and this will be polarized and essentially, you will be getting a dimagnecciated product, this is magnesium bromide up here and this is O magnesium.

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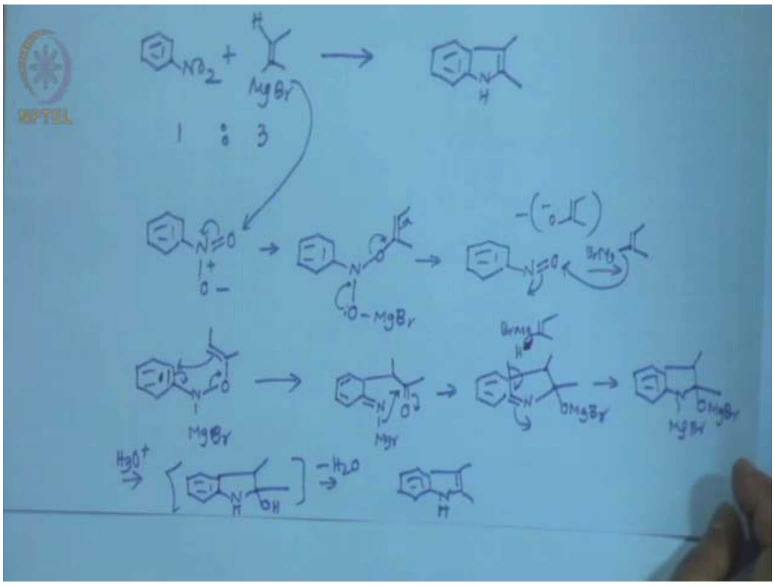

So, if you next is if you acidify during the workup, so all of us in case, what would happen, it would produce N H only one hand and other hand will have this O is up here, which ensure, which is not very stable, so under the reaction conditions, it would eliminate water, you will give this indol, this is very nice O l and its free versatile reaction.

There are lot of examples, which are will executed by this method and only thing, that organo magnesium reasons are sometimes very reactive towards many functional group, that is the disadvantage. And next most disadvantage is this use of excess amount, this oragno magnesium.

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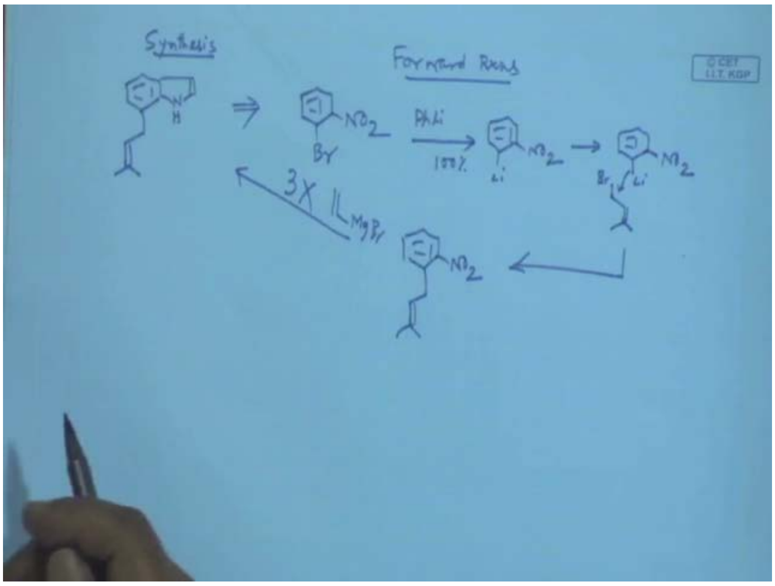

Now quickly just see whether, you can work out a reaction without bartoli reaction, suppose you are advise to make a prenailated indol, so how would you synthesis this, what is the starting point, obviously, see the most of us what will do will do a electro synthesis right. What was the first step starting electro synthesis, you have to look for some of the transforms, what are the transforms you have not talked about, so far.

Towards the end of the course actually, we will talk about construction of different heterocyclic, I mean so far, we have talk about only 2, one of them are ox gel by balvation method, second one is bartoli. So, other than that whatever your studied in B S C, so what could be the proper example indol synthesis, how many indol synthesis do know off, how many I said not, I know at least 10.

Obviously, fisel indol is first one the modification of fisel indol jab glinger method, glingman method, third one could be medallion synthesis, medallion indol synthesis, fourth one bartoli baby, fifth one nanijesco reaction very useful reaction, sixth I thought, I am not tell that is what I am trying to say sixth gasman synthesis gasman pal gasman synthesis, gasman indol synthesis. We studied in 1974 prof vaseema chatargi thought us and that was discovered in 1923, she thought us in 1974 actually remember.

What else may be more actually, if review these books by lee on namely name reaction, and hetero cyclic chemistry, you will find many more at the moment I cannot often, I cannot remember, frushner indol synthesis, frushner alovi frushner is the director of maxwell institute in germany. What he has done, he has basically formed the carbon carbon double bond pirol ray by macmali coupling all of us know macmali coupling and then one modification is there where you formed double bond by heating reaction.

So, know it has already, we 8 to more we have to collect, likewise we are actually developing one more, best one house analysis in our lab, we already done it, but examples are very few, so hopefully that also would then the other methods. So, that means, when you are given a problem on synthesis, I mean of course, this should be done, but one of the major steps is identifying the right transform, that means, the forward reactions for example, when I ask this question to you suggested that frushner indol should be applicable.

But, believe me it is not applicable, that is the a reason, you have to understand the key reaction mechanism, what is key the driving force, key driving force means you have to find out rate determining steps is a multiple steps, but one of the steps should be rate determining. Rate determining is very good for many many molecules, but it is not appropriate for the very simple molecule like this now, it is for simple molecule mean to say that 2 3 dyes un substituted, there is no substitution.

Students: ((Refer Time: 12:49))

Right it does not work, that means, you have to know dept of the all transform than only you to choice. And of course, and other point should be starting material. So, in this case your convenience, I suggest let us say the starting material is this one, our hetero synthesis falls down to benzenoide like this. Now what is the forward reaction, forward directions, forward reactions, so what you do, let us say I give you the answer the appropriate starting, but appropriate transform is bartoli reaction.

So, what is suggested step, next step suzuki coupling with suzuki coupling fine with corresponding bordigus acid, that is fine. So, we have to yes Suzuki coupling should be possibility, but there are so we to again know all this details, but how to make this suzuki bordigus acid, for simple one alive bordigus ((refer time: 14:20)), but it is un ((Refer Time: 14:22)).

So, may also takes place other side, most cases takes places, but one that has been worked out is starting from the oregano lithium compound. So, what you do, you make this lithium agent and lithium agent ossification and lithium can be done by since bromine already, there helical exchange and if you do phenyl lithium the reaction proceeds in 100 percent.

What next, you have to introduce thesephenyl group here, mine it most cases phenyl does not takes place unless you put kyouprasynod right. But, in some cases actually reactivity, so computable then directly do this lithium displacement, especially if it is alloy mixture software not the simple all kind software. So, product then would be just basically a phenyl and you have to take node of these thing stability of these lithiuo nitro benzene, because we have seen alcho lithium undergo additional to the nitro compound.

But, in these particular case stable probably controlling the temperature, you can stop further reaction of these and once is this done of course, next is quite essay right. Next step is very essay right, what is that phenyl magnesium bromide, so 3 equivalent of phenyl magnesium bromide, you can straight way go to this material. So, this is from the last class.

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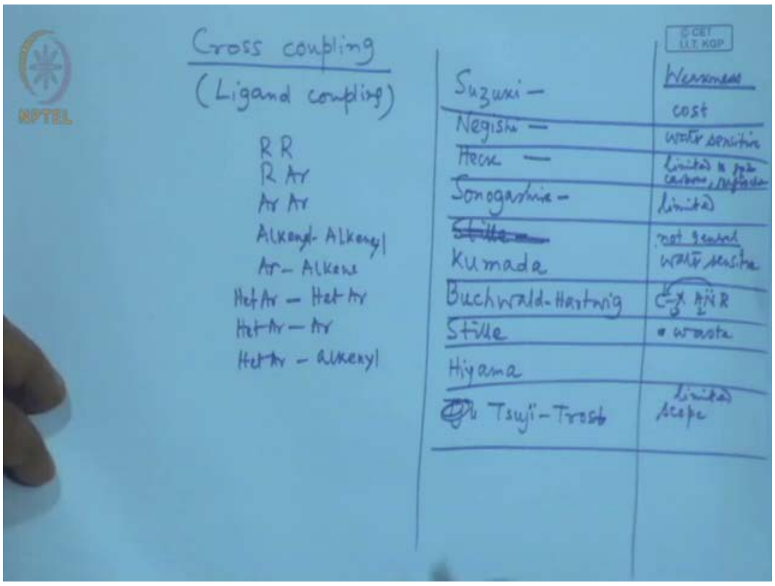

Now today’s topic is cross coupling is very important topic all of us know, in the last year, we talk about this, so since now, you have other people also from other section and also talk little bit about this. Just show what I will do give an over view of the cross coupling, than I selected example from pyroll in the next class, example from other classes. And there are first of all let us define, what is cross coupling, how do you defined, that is see whenever you start the topic, you have to first clarify the scope and the definition how mark we talk about.

When I say cross coupling, I think what does it mean.

Students: ((Refer Time: 17:38))

Let us say someone who is [FL], what do you mean by cross coupling from delhi iit is it thought was it thought.

Student: ((Refer Time: 17:51))

Who thought that

Students: ((Refer Time: 18:04))

What is the meaning of cross coupling.

Student: Cross coupling is formation of carbon bond.

No I am not taking there is, so many formation in organic reaction.

Students: ((Refer Time: 18:24))

That is you have to defined when I say cross coupling, what does implies cross coupling of what.

Students: ((Refer Time: 18:40))

Not really, so I think best thing would be organo material people writes, ever heard of this ligand coupling, if you remember this ligand coupling that would tell what is exactly cross coupling is.

Students: ((Refer Time: 19:04))

Right metals that means, that is it, the 2 different elegant on the metal surface undergo coupling, so it could be R R, it could be R Ar, it could be Ar A r, it could be alkene and alkene right. It could be I mean all possible combination, aril and alkene, what else, what is possible combination, now we know our domain is our scope is hetero aril hetero aril right. We have hetero aril aril so we can go on writing, so many things, then hetero aril and alkenyl, so instead of writing alkenyl.

So, you have, so many possibility, but when is say ligant coupling means actually, the reaction is taking place metal surface and the coupling take place on the metal surface. And most of an occurs all these ligant coupling or cross coupling is refers to the transition metal catalyze reaction, there are again more than 10 different reactions, just quickly review, what are the names 10 different names.

Students: ((refer time:21:04))

I am sure all of you know now, but when I say, so in the higher class, you have to prioritize means, which one is very good, which one is very bad.

Students: ((Refer Time: 21:18))

Yes I think in my mind this morning, I was going through review article on patental literature on cross coupling, what I am find is most of the example are from suzuri coupling, so suzuri coupling. And next most, which one is your saying, I would say negishi and next and heck and next

Students: ((Refer Time: 22:00))

And I will take sonegashira stille, I would take stille little later, kumada no at least this I will take something else buchwald hartarig, then I will take stille, anything else. There are other coupling actually, people call actually hiyama ate to be developed, Pucuhiyama who pucuhiyama, I do not have remembered, but I roughly remembered do you remember what is it, yes du pucuhiyama yes, I know and then one more is suji trost.

And so there are, I think of course, many other, but these are the main one, but now you have know little bit about this, strength and weakness of these all of us know they all most of them are transition materials catalyzed, And there are many more actually, quietly few, because frushner also is associated with the discovery and that is very similar to kumada reaction actually.

Kumada, we talk about little bit after these, but for example, suzuri coupling, what are disadvantages of weakness, what are the weaknesses of these, suzuri coupling let us talk about the weaknesses I think rest of the things strength.

Suzuri coupling, what do you suzuri coupling, suzuri coupling basically organo borons are more expensive that is it nothing else, because many cases you have to compound to organic magnesium all these organo metallic's to oragano borons or direct boray lesson is very expensive very few agents. So, that is basically cost is important as weaknesses for legacy coupling, there are many many strength, is there any weakness of these legacy coupling.

Legacy coupling is oragno zinc compounds are water sensitive when suzuri coupling can be carried out in water, but legacy coupling cannot be like oragno magnesium compound, similarly kumada coupling for example, water sensitive at not that general I heck coupling, what is the weaknesses of heck coupling is very good, what is that.

Students: ((Refer Time: 26:06))

Heck coupling involves the S P 2 and S P 3

Students: ((Refer Time: 26:18))

Right S P 2 and S P 2 right, no weak up, that means S P 3 S P 3 cannot be done, so that means limited, the scope is limited to S P 2 corbons. That is one more heck coupling is good for inter molecule reaction, but heck coupling is also gives to rigu isomerse, if you have double bond compound, you can have addition of alpha position or beta position, so rigu chemical problem, sonegashira is good is very good, but it is limited sonegashira is limited to only certain scope is limited that it.

And Buchwald reaction of course, it is not really involving the carbon carbon organs, if you recall Buchwald reaction actually requires a nitrogen that means, you have R something like this is to x would be. So, that means, somewhat restricted, but it is very useful hetro cyclic compound, hetro cyclic chemistry and stille, so many plus point stille is very good for total synthesis and very might reaction.

But, very expensive, but disposal problem, I should say disposal problem is more important stille is a heavy metal and disposingly in large quantity; that means, its not scaleable the scale of the reaction cannot be increased. Get lot of so say disposal problem waste, so waste is the material, hiyamais is not really into the chemical industries.

But, and this is an suji trost coupling is somewhat separate and again it is limited in scope and scope is limited, what it is means it always require aryle kind of assitate aryle compound, aryle oxygenated aryle compound, so that means, you have limited scope in the reaction. And for us and I think first 2 3 reactions are very useful, I should say 5 suzuri negishi and sonegashira and kumada and 1 2 3 4 5 6 and first 6 should be very useful, let us look at an example from say again petantral literature.

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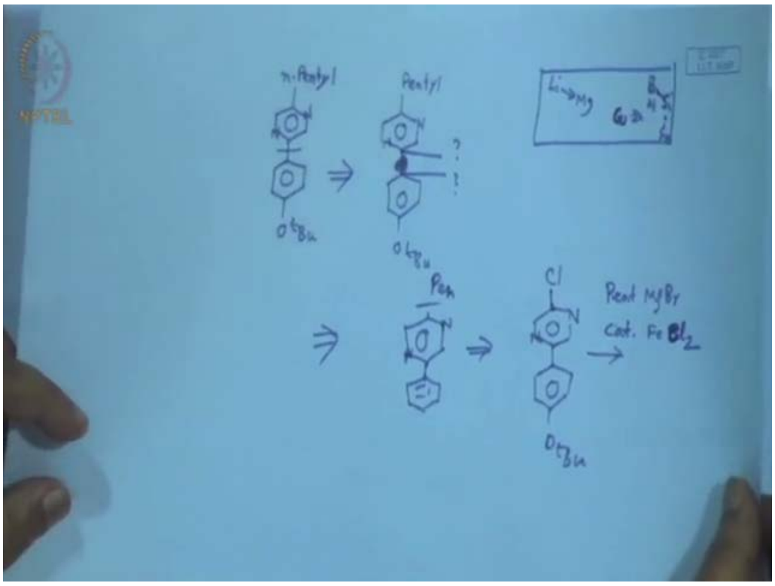

The target molecule is a hetro cyclic 1, its look like by arile, it is a pyragin divert, that means, nitrogns are 1 4 1 4, now you have substituent n pentyl and you have o todbeutyte. So, grossly looking, it is a biaryl, know what do you connect them, disconnect it, obviously, aryl S P 2 all these transition material well suited for S P 2 S P 2 connection right. So, this is show now you have to make choice, that is the hole trouble, the choice should be I mean whether, I mean we have since, so many possibilities.

So, many different kinds of couplings, which one be choose, making decision is a important, taking decision is important, should do, so you to actually learn all of the reaction in dept then only, you can do it. In these case, so which one is let us say you give me a suggestion, I will trying to defined, you who or other myself also, so that means, 2 units are of this right.

This is one of the electrolyses sorry, now you to put groups here, you have to fill the blanks, so we made a mistake in the first place actually, other possibility, we have not looked at, other possibility could be this is also pentyl, that means, we also think of at one point connection between the S P 2 and S P 3 tough.

Now, I mean suzuri negishi are now well developed for making C C bond between the S P 2 and S P 3, that means, the options are wide open now, so what can we do, this also possibility, now we are in the hetro cyclic chemistry class right. So, what we know, we know hetro cyclic molecule 2 position is very reactive, especially have nitrogen have 6 member system, that is what done one is choice is pentrial literature, choice is that you first makes this biaryl somehow.

Then you take this halogen of here understood, because all of us know that halogen next to nitrogen in 6 member pretty while, because of electro lowest density of carbon, so all additional element reaction takes place, so this is the subs right. The one side is now well choose n, so what should be the this, what I call this is acceptor, now you have to have donor right. What is the donor and donor coulde be again, just look at predict table, we have talk about it lithium, then diagonal replaced magnesium, then what do talked about, further lower down go to zinc is there, anything before zinc you had copper right.

Copper in one position right, group one, so copper that up to copper, we do not call actually this cross coupling reactions, so reactions of copper, because they are not metal catalyzed. So, we have now zinc then go to boron, poladin is a catalyst, it is not reacting actually donor, then comes aluminum yes limited I cannot ignore aluminum.

Students: ((Refer Time: 34:54))

No silicon then germanium is out, then tin these are the very few metals actually. So, we talk about the donor, you can concentrated on all of them sometimes I said before organo lithium directly displace this halogens, if normally does not work well, because you have now another nitrogen, so it can cause all calls of the problem. Magnesium also very similar, magnesium normally has less reactive, so make it more reactive, now we know that there are all possible transition metal catalyzed reactions, although is less reactive, now we know the cross coupling reactions, the kumada reactions, you can think of the kumada reactions, first let us think of the kumada reactions.

So, that means, so pentyl magnesium in this example, they have used magnesium bromide, what next you choose a right catalyst, what is the catalyst, kumada actually, yes originally used nickel catalyst. But, many other people like nakamura aloyi fussner, they have used iron and this example patent literature interestingly very interestingly, they use catalyst amount of ferrous bromide sorry, ferrous chloride, less expensive then directly commercially, available ferrous chloride and is not mentioned, since it is in patent literature, this was developed in 1984 by company called obhe industries. It is industrially suitable reaction is very useful magnesium and so quickly then summarize you know, what we talk about then you have to that means, halogen etc again quickly.

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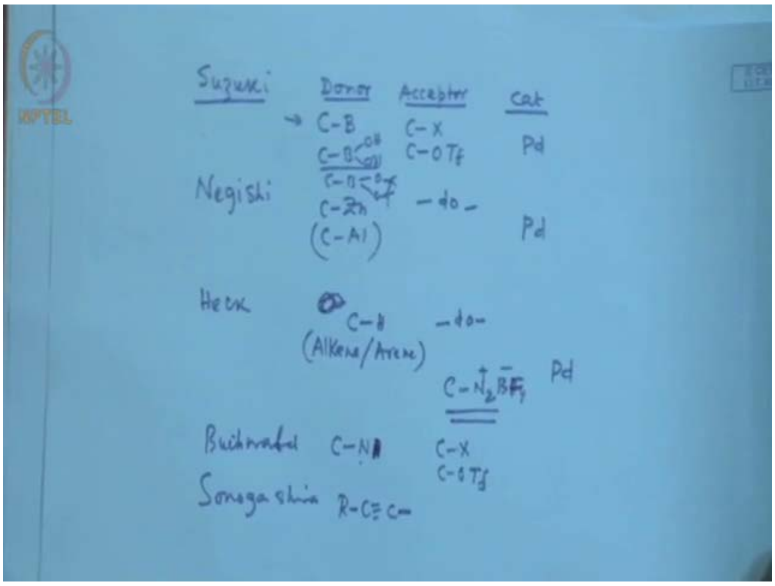

So, our first choice now hetero cyclic chemistry is Suzuki, so you have know the donor, what is the donor boron right. So, and accepter that is what also you to think about accepter, what are accepter could be C X halogen, what else trifoliate very good actually, organic chemistry such an important first subject you can suggest anything, if not done you can start doing it now will it be.

And recently I have seen carbon sulfur sulfonium ammonium salt carbonate all kinds of reuses, which little bit of living property, that means, is very difficult to actually evaluate on higher classes, anybody can just sir I seen this article somewhere this has displaced by this. Buy, of course, now you have to privatize, you have to give more important once to other, so this is thing then catalyst all of us know Suzuki means, often peradium and than is negishi primarily, it is carbon zinc.

So, this is accepters are odsum carbon zinc occasionally it is carbon aluminum, infact in older industry some of the reactions were, carried out with aluminum. And So, than palladium then someone say nickel or than I have to say might be most commonly is palladium, when palladium is 0 many many characteristics, than next choice heck, what is the donor carbon.

Student: Magnesium.

No no donor part, the donor part means, subscribe that the donate the alkyl groups aryl groups.

Students: ((Refer Time: 40:16))

In heck reaction carbon hydrogen S P 2 carbon hydrogen alkene that means, carbon hydrogen of alkene or if in arenes simple benzene is also do this reaction and accepter again same thing, anything else, one more yes. This dygenium salt are very useful and again it has a also reaction something like all heck mathsudh a reaction only different that, these case accepter is this would have done it, impact reference has appeared in swis book, because we have used an heck reactions of diginium salt in the synthesis of ary molecule.

So, is very useful, you just go through this written literature, you can find plenty of difference on review articles also on this and once, we did actually, this reaction has been partly developed by one ex faculty university, he left the university is now industry he did this action in water and one of the papers also he describes he do not need for palladium very expensive palladium. Just palladium charcoal that is used for hydrogenation that can also be used and I think we did once that was works well.

So, that is the reason why this reaction now is limit upto the corresponding scientist must together, so again palladium for boron I think you to know little bit of the Suzuki coupling here, this boron can be used as boronic acid derivative and then or this is one commonist one, other one is boron that Pensacola deliberates, this lot people are using actually, because of Pensacola deliberaty. And I think hiyama will not talk about, other thing then hetero cyclic chemistry that is most important is also Buchwald reaction and sonegashira, these are the 2 Buchwald, what is the donor is I mean.

So, carbon nitrogen I mean, donor accepter again halogen tatroflate most commonly, sonegashira, what is the donor is corresponding acetylene compound, these are the I think, I am not over view the other think these are the things 1 2 3 4 5, these 5 reaction are very useful in hetero cyclic chemistry. And let us look at all of you know the mechanism or should I talk about the mechanism I think, what is the mechanism, what are the steps let us say working mechanism, no detail mechanism, detail mechanism consist of 6 different steps right.

Oxydary addition then…

Students: ((Refer Time: 44:48))

No no isomaration, system isomaration, ligant system isomaration than insertion then migration. So, many things let me you can actually reaction mechanism, can we divide into 3 4 more than 6 different steps, but those are the approaches taken up by oragno metallic chemistry. For organic chemistry I think 2 3 steps are enough, one is oxydary addition, I think I say trans metal may be, you can insertion, whichever you like than radioactive element that is enough.

So, I do not have to tell them, now there are few tricky things remember, if you let us say you go for heck reaction, you will see something different sometime the outcome is not really as expected for example.

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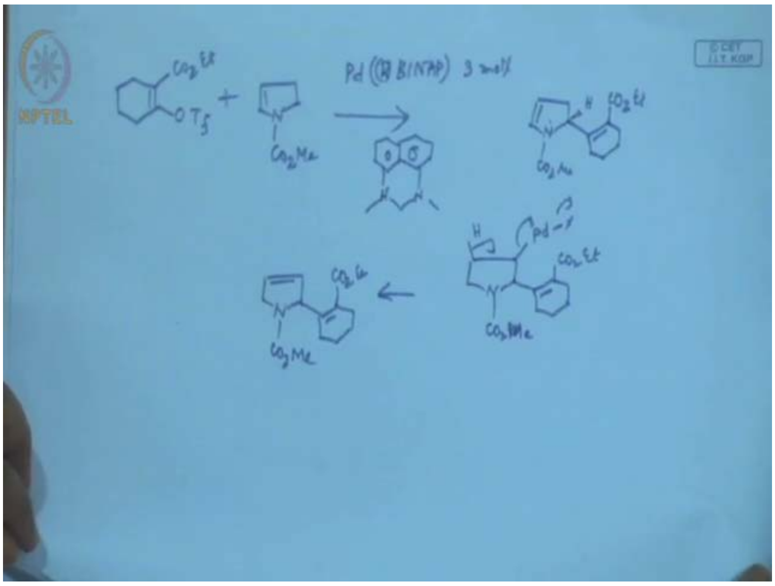

I have reaction, which right now, this is a trifled and then you have enamine and reaction conditions, that you have to sometimes little bit careful about this reaction conditions, these case palladium 0 with 1, I have here are binap, this is only 3 mole percent and there is amine a cyclic amine. So, all of us know as R binap, basically introduce caririty in the final product, binap first means these abnormally, I am given this as do u have to I think understand, what is the use I mean that there things you have to take note out.

In a reaction this kind, you write right catalyst additive also many times, you will see in heck reaction, especially in jacalibe lab often use a base, there is not commonly used what is that there is senior fellows, they do not use normal base like sodium carbonate sodium bicarbonate tri thallium, they use something little expensive.

Some of the reactions are very tricky sensitive to the reaction condition and cesium carbonate likewise see particularly base, base is required, what is the purpose of base in most cases your eliminating as net result like H B R or H I all these things. So, competent that occasionally, base is like tri thallium tri felon toxins, they used to reduce the palladium 0 fine. So, what is flicked product, it should be a what is the class of the reaction, the reaction should be categorized as what is the reaction heck reaction.

So, heck donor is halothane is here and this product you will find, so product will find next group again is comes from the trifled double bond is now moved to the other side. Normally heck reaction gives the alkenes, alkenyl hydrogen is substituted would have expected, this reaction on this side right. Conjugated double bond primarily, because of a step in heck reaction although, we have simple working mechanism oxidary elements, but there is a critical step also in heck reaction, what is that critical step which will accounts for this type isomaric compound.

Actually, Intermediate CO2oH CO2 write here, intermediate palladium some were here, so you have double bonded ester here and this is ester right. What is that next beta elements, that is thing, you have to remember that means, beta elimination takes place all of these, these are thing, you have to recall once, you have this beta elimination.

So, will have, you will get these and this is ome, what next same thing undergo isolation again palladation takes place other side and essentially, it will go the double bond, simply because you have nitrogen assist the stabilization of double bond, you said enamine structure.

Student: Is there possibility of double bond isomartion.

Isomartion both way right, there is possibility, but product will go to the most stable one right.

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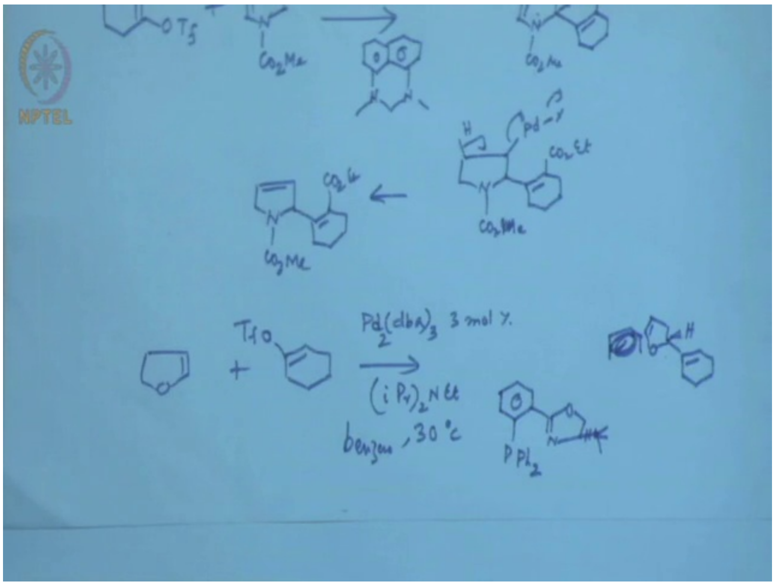

This is somewhat common also let me give me one more example from the 5 member hetero cycle, you have dihydro feron and trifled like these and trifled and do these reaction, in these case palladium D B A di benzyl acetone, this is only three more person mind it percentage requirement of the catalyst is very little. And So, and isoprofile ethyl amine and the temperature is only 30 degree sort of like room temperature and again base is required amine base, this is known as sometimes people say honig base.

And of course, anything else is missing, anything missing solvent benzene and ligant prosperous ligant. So, prosperous ligant in these case first di phenyl festeno benzene kind of molecule and once again an hetero cyclic kyral heterocyclic, its comes oxogenal hetero cycle. This is for introducing kyral center, so the product here would be this is acceptor part, donor part now, again a furan double bond undergo migration to this, like these is not heck reaction sometimes predictable sometimes not, but once it works it gives the world defined, the structure.

I think may be one more is I think stop here, next what will do more example, first will example for 5 member exam system, try to see what are the functional group that could be accommodated, than will see some of the things like total synthesis done, before I end let me give just little home work to do at home see, if you can do it.

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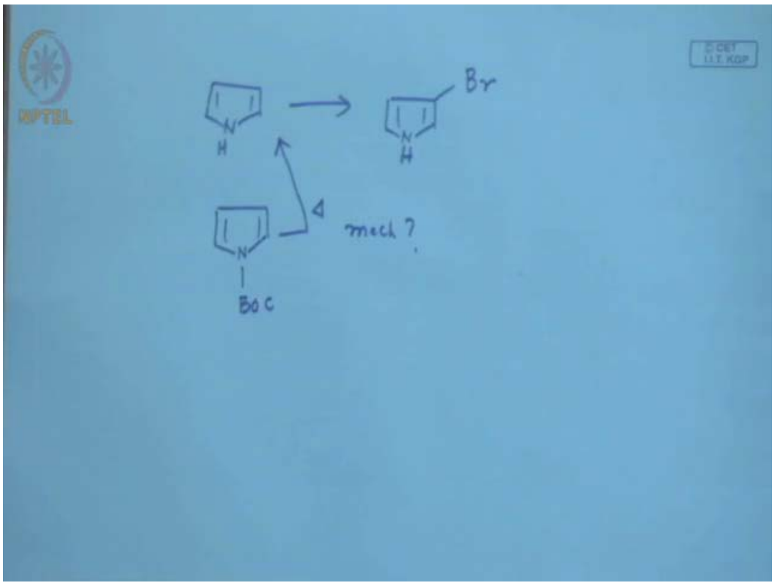

How to produce and one more these are all right. So, actually, discuss all these thing in next class, before that you just workout infect, this is interesting one again recent example one paper bases.