Heterocyclic Chemistry
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Lecture - 20
Transition Metal Catalyzed Cross Coupling (Contd.)

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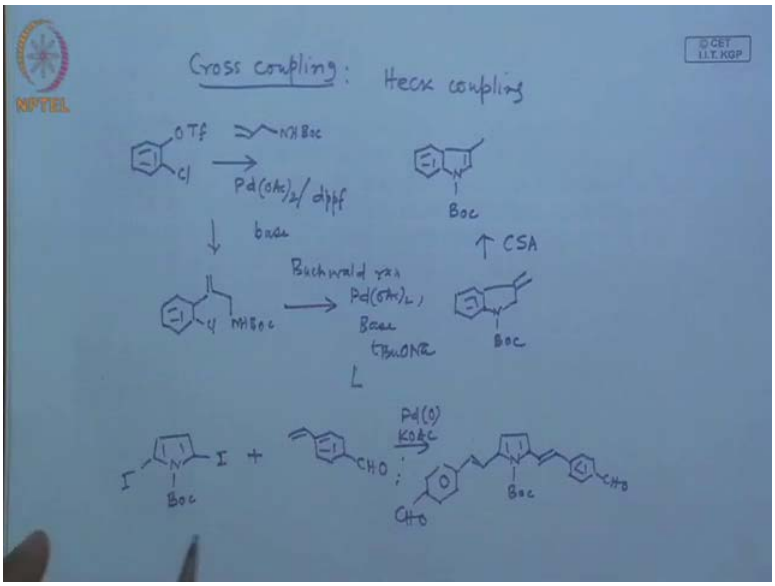

Good morning, we continue Cross Coupling reaction. Cross coupling, but today the discussion would be is restricted to the up force heterocyclic compounds. So, while we do, so we have to up certain things in our mind, namely the complication that can arise during the heterocyclic coupling; what are the possible problems, in heterocyclic chemistry. When we come from the know, normal areal chemistry or aphetically chemistry, the presence of the nitrogen. Presence of the nitrogen actually complicates the lignum selectivity, but cross coupling inheritably lignum specific except fake reactions right.

So, that means lignum chemistry should be stop at the earlier stage, when you make the oregano metrics or when you make the oregano halides, clefts, extra that is number 1. Number 2 that also to be noted, the variations of ligands, so while we proceed, we will see some ligands are unique and I mean literature may be there are about 1000 different ligands. But, of course, out of which may be 10 different or 15 different are very useful.

So, while we do this exercise of first topic in heterocyclic chemistry, we will come across of the ligands which are very popular. Other than, Secondly, thirdly you have to also know the compatibility with other functional groups, there are many functional groups which could compatible and may not be compatible. These are the important things, you have keep it in mind, while you choose a particular cross coupling reaction.

In the first class or in the last class, we said that the cross coupling would be privatize like, in terms of number of applications extra, Suzuki first may be the next is negasi then hake then other special coupling like Kumdha, Stella all these things, there are more coupling that involves carbon hydrogen carbon that is group carbon coupling. So, these are the thing, you have to have in mind you know, where you are given total synthesis for example, you have to have available options in hand.

And then you have to have power of choosing one of them, in favor of others. So, but for simplicity sake we drop out today, applications of hake reactions. So, by now all of us know, what are requirements of hake reactions that an alpha right alpha is required and an alkyl halide or trifectas or I mean any other proud of functional groups, salpointe also sometimes another carbonates all these things. At the same time, you have to have also one more thing that is a palladium most of an, then suddenly we will use extra, but let us look at one of the indorse synthesis.

This is the final in dole would be let us say, Boc this one we make, all other this one we want to make. So, what should be a starting material, and obvious starting material in all of these cases are namely benzyls, in the most of the cross coupling reactions one of the starting materials should be benzyls. And in this case, you have trifectas on one side chlorine on other side right. So, what next, so by looking at what have to see and there are, so many possibilities.

First of all I mean you have to think of all of these possibilities, one of the cross you have to talking about the continuous hake coupling. So, one of the reactions should be the perfectly, alright then what should be other one, hake coupling gives you a carbon single bond. So, what could be other; that means, other possible reactant at one point what will you find, you have to make carbon nitrogen bond. So, book called coupling could be one of this possibilities, other possibilities anything like.

In this case, we have reflect, so it could be I mean any of these coupling reactions, hakes, Suzuki all these things. And now, you have to again sequence the two reactions for an example, you have to sequence the one of the cross couplings and the book called coupling, involves a formation of a carbon nitrogen bond. Now, between the two which one is more facial, that we have to understand, which one is more facial I will whatever may be the case but one thing is very clear, that fluffed is more reactive, than the corresponding carbon bond that we all know because reactivity of fluffed is very similar to that of corresponding grommets.

So, that way; that means, this reaction should be that is, so then anything could be used in this case these B Boc allium haling is used. And the catalyst is of course, palladium acetate and what else we need, normally what is that base, very good base I would not mention because in most cases bases are used, but also you have to have sort of reducing agents which could be first fill login's.

And in this case d p p f these are very useful, I don't know, I have no idea, what is the clue of using this one, this is diphenyl first pine furuncle, why suddenly farcical I have no idea, if anybody know just you can give me idea why I mean of all available this particular one is useful in many, many cases. If you use or substitute any other encore very poor all the reactions do not go at all. So, any case, so once do this and there is a tricky reactions actually, by Cong low right first subsequent.

So, how does acetone coupling, see these case basically, what we need first pill we required to make this catalyst loge and make the catalyst 0 that is it, no other role while there are of course, increasing the bite angle, that is any case, we make you just if you have a chance for look at a literature you just look at. And what will see, and what should be then will you see, there is evening reaction actually this is bond. Normally, what you see this hake reaction, this arrival group is deliver to the lax electro deficient carbon ((Refer Time: 09:02)).

In this case and this arrival group has been transferred to the actually, more hindered, but yet, this is more electro positive carbon. Like just recall very first reaction, arrival bromate and quilts, if you do the hake reactions arrival group goes to debate positions, the one the most that is more electro deficient. So, in this case this also potentially more

electro deficient compare to the terminal one, and then you have chlorine. Now, once you have this, then one kind quick to see what is the other thing, again what you need.

Now, this is called Buchwald reactions Buchwald or sometimes Buchwald hot we reaction. What is required again, this is required first palladium in this case palladium acetate and a base, normally I do not know what, why again sodium tertiary beta side. This is h favorite Boc for favorite base, sodium tertiary beta side, like our tertiary lithium beta side. So, then must be some reasons though, may be it is actually cheaper than lithium possibly, and what else one more thing and a ligand is used and this in this.

So, once you have this then so one can quickly write the product is this, so this is a just basically NH attacking the chlorine, what should be the next one, next step, isomerizes all of us can guess, these isomerizes here should be pretty easy. Because, advertising is driving force and this is take compensative acid organic solvent, compensative acid; obviously, it is soluble in organic solvent, so it can be aromatized.

So, this reaction basically gives the applications of hex reactions, as well as the burp called, but point is that, if you fix the region chemistry is begin; that means, authorize substitute, there is no other arrest of the things are almost like, region selective and the reaction is very good. Let me take up one more example like, even to functionalize parole, is a 5 membered Boc and idiom here, on both side. Now, you see, you have alphenolic aldehyde.

And once again, this condition are very similar I should write for idiom 0, the combinations are different in different cases, like in this case the base potassium acetate, potassium acetate all these things. So, results are again results are similar to all other cases, but then choosing this example what we like to show you, that the reactions are very useful. So, you have to identify, other things of course, other things are there like solvent et cetera, et cetera, heat et cetera.

So, what is the lesson we learn from this, that is what we have to learn, write any idea basically a simple hake reactions. So, you have this is a double hake; that means, number 1; that means the double hake can be done, in same reaction port, on the same starting on the starting material. Number 2, that this arrival group is very transverse to the less hindered carbon, less when we have small difference in electro negativity or electro density, that this terrific effects actually dominates the region chemical outcome.

And what you speed learn from here, aldehyde aromatic aldehyde very soared to kneads radiations oxidation, benzyl aldehyde if you kept in a air, it undergoes oxidation all kinds of thing. That means, actually handling with aldehydes is quite tough, so; that means, it is basically displaying mildness of reactions mildness means hake reactions would be, tolerable for I mean could be useful for sensitive functional groups, aster aldehyde, Sinead there do not get reacted during the process.

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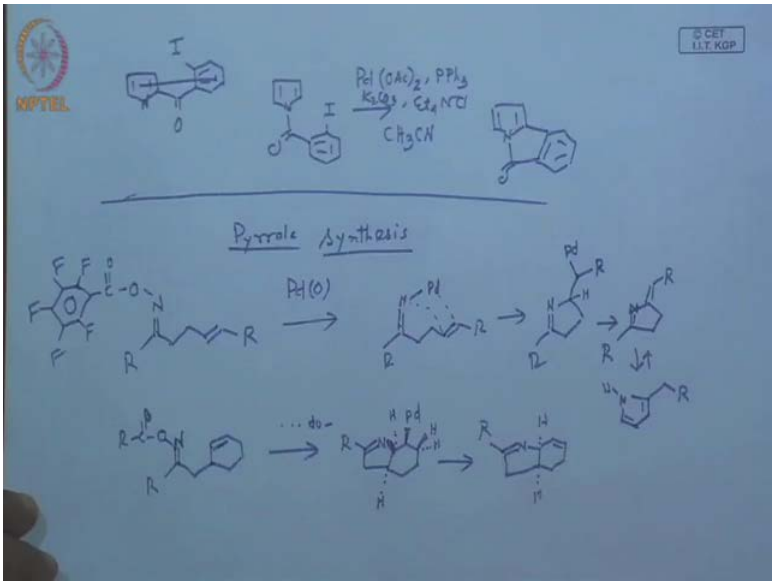

And this background let as say, one more example will sight here, this is something sorry. So, sort of benzyl kind of things, and mesa ketone, once again palladium acetate, palladium acetate means other combination of course, triton alpha Simon and what else, this is a base and tetra in this case tetra ethyl ammonium chloride and of course, there is solvent is required. So, all these recipes are in different these recipes are in different in different cases. In fact, you have to optimize the reaction conditions you know, from time to time.

Now, what is in the product, cyclization why because hake reactions requires a alpha double bond, this is just a yes, what you said is very right. Actually, the product would be 1, 2, 3, 4, 5, so another 5 membered would be form, another 5 membered and fuse these are the just example where, you have participation of these double bond of the aromatic system; that means, the hake reactions are not restricted to already lapping

double bond. It would be, double bond of the aromatic system it could be double bond of the heterocyclic system.

And, actually I am looking for this structure for s pause, and it is the example, we have used s pause I do not have with me, some of the day I will give you. Then latest ((Refer Time: 17:18)) hake reactions in hake reactions could be one of these things is parole synthesis. So, far we have taken up the examples where the heterocyclic rings should be functionalized, but in this one that we are talking about, is parole synthesis is in hake reactions, it is very typically, non typical reactions. What is the reactions, if I write will we see, apparently it is very easy to work, very easy to reanalyze and this is group here say, so fluorine, so fluorine here.

So, pent flour, let us see I said my first answer cut list, yes I mean you can use benzyl all depends on the many of times, there is no justification many times we blindly do trial in a error that is it. And this something very interesting reactions actually, again palladium I write palladium 0, the source is palladium acetate and the corresponding tri phenol chloral, trial supine. And then many times we used tri alumni also all of us know tri alumni also reduces, palladium two, then ammonia then commons TME all these things and certain amount of temperature certain degree of temperature is also required.

But, what do we expect out of this reactions, what is this is the structure now, what we expect. This case what is our expectation, actually this very this reaction was developed in let it is published upscale ((Refer Time: 19:41)) do not read at all, there is another call chemistry letters. How many of you know of, who publish that actually, it is published by Japanese the chemistry letters, chemistry records, burton chemical society of Japan then kempharnbol all these you know there are quite of you general published by Japan.

Chemistry let us, actually also useful very famous for the Japanese before, like they all of us know they are very patriotic and they try to publish in their own general. And any good work, like mukham alolcondosensen was hipped first in chemistry letters, then elsewhere. So, similarly this reaction actually published in chemistry letters first, then bulkensom of Japan, then slowly sometet hydron joshi all this things. Now, very nice reactions, so I mean people did not think about it, you wouldn’t think about it, and this is unusual.

I mean other anything can be sort of, but we have a palladium 0 mind it, we have a palladium 0 means, it will basically under go very first stable it under go acidity addition where hake that is it; that means, that across the single bond. Single bond, which is weaker, weakest that is very obvious right, but it was not obvious till, Nebraska discovered this, k Nebraska or n narasaka discovered this.

So, this structure obvious reactions and all of us know, more readily available, easily available we have ketone do the actmisine and fictionalize we get it; that means, getting the starting material is, so easy. That means, and the then you have a nitrogen now, in the construction of nitrogen heterocyclic then visible. I mean all these things are, so visible, so obvious, but most of the time the obvious reactions are not discovered. So, you have to discover this obvious reactions and ihaunchualiy; that means, nitrogen and then palladium I will not write oxidation state.

So, R up here, R up here, what us what you think of next, is quite easy right intermolecular addition. So, 1, 2, 3, 4, 5, so; that means, nitrogen at here palladium at here, palladium at c, so the palladium right. So, what next that is all of us know, beta hydrogen elimination no when I say, so now, advanced level you have to all us think in two terms, little bit of the stereo, chemistry rogues chemistry all these things you have to kept in your mind.

BSE oxidation, then reductive elimination those are all five factors alright, when high class, you have to say that oxidation, then what. Then actually, sis knows, sis elimination sorry sis addition across a double bond, when have a optimal compound the both carbon and palladium and carbon and would add across the double bond sis action. That is first thing, that you have to kept in mind.

Then if there is a any system isomerism called complex et cetera, the possibilities then when the beta elements we are talking about, also we have to kept in our mind. That reaction proceed, I thing yesterday I told you something, sis sedimentation take place that is very critical step though, beta elimination are of an sis elimination. There is a palladium and the hydrogen should be oriented says, around this single bond.

Now, in this case in this case rogue chemical problem here, and so if you have hydrogen on this side that could be eliminated if it is, in the particular example, hydrogen eliminated from the side of the ring. So, you will have nitrogen double bond, this is R,

this R, then you have R up here. And then if you equilibrates with I mean any kind of let us say acids. So, what will find, will find a nice two substituted role, two substituted role.

So, nice reactions though, I mean it is coming up, but it is very interesting term of the chemistry, why I mean nowhere even today I mean you have come across many, many examples hake reactions. But, we have never come across a reactions where, a other carbon nitrogen bond is being used, that the unique of this reaction and one of these latest examples, would be you just see here apparently gain, so if this reaction known, then what is use of doing this, someone did this year or last year I thing.

Again all these things, any idea why first of all, if someone this did this reaction ((Refer Time: 25:53)) because you see here 1, 2, 3, 4, 5 there interrelationship nitrogen and the double bond 1, 5 sorry I thing nitrogen is here. Now, 1, 2, 3, 4, 5, so I mean chemistry wise it is not at all advancement right, but somebody done it, then up force is published by very good general. So, there are some thing then if you see the outcome will find, what next intermediate next intermediate, would be right this nitrogen gets pirated palladium nitrogen this end the palladium adds to the other end.

So, here is the palladium and if you recall, what I say said elements addition is sis. So, that means this beta let us say and this is beta so; that means, there is a hydrogen up here, and this hydrogen should be sis, all of us know, why may be tomorrow is bibore someone will catch you, why this is sis, trans is most stable no, you have to know this is very important information, that you have to know. Because, in stride chemistry a b ring is trans, b c ring is trans, c d ring is sis why. Because, sis hydrants are more stable, sis hydrant this called sis hydrant sis hydrant is more stable, some nominally more stable.

So, this is one this ((Refer Time: 28:06)), so now, what next beta no, sis beta elements if you remember that, then you will not make any mistake. So, that palladium is this side for sis side there is no hydrogen. So, there two hydrogen on this side this sis one should be eliminated that means, what you get you will get bicycle in dole will have a. So, this sort of things, this R here, and then R arrest of these things. So, what you now, you getting now is sort of bicyclic alcoholic compound. And then you have double bond here more double bond you can do all kinds of functions oxidation, all kinds of reactions we can do.

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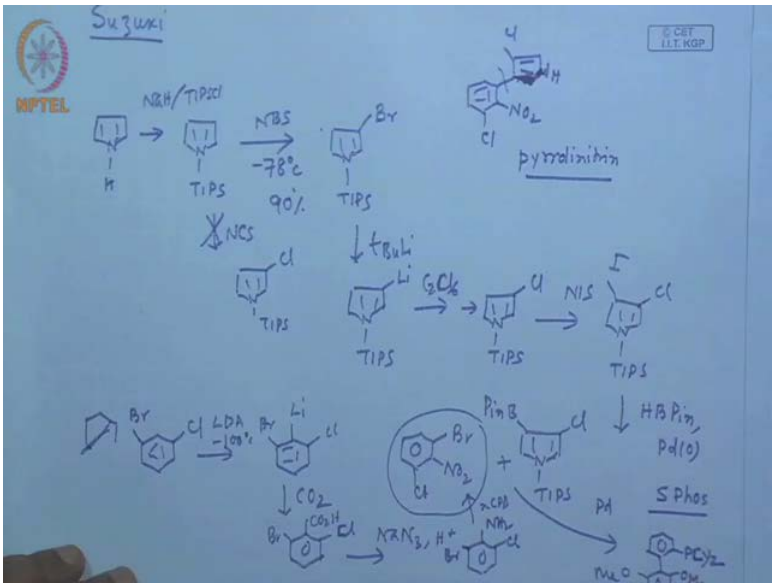

Now, just talk about Suzuki reaction next most important reactions of course, is Suzuki reactions, I think let us say go to the jet product, at we are trying at target. This product in this case, is known as parolee nitrating; that means, a structure having a parolee unit here, sorry this is nitrogen and so what you will see, this is a parole if here. That means, 1, 2, 3, so 3, 4 dies up parole and the one of this substantially aromatic that you can see, I mean molecule and this known as parole nitrate.

So, how do you make it, so many things you ask our self, since it is the topic of the declass of coupling. So, you can just dived this molecule into two arrival groups. So, rheas is this one, once you have agree then we have to find out which one would be metaled wide, which one would be halogen; that means, one side we have halogen, other side we have metal. Then we have, so many things possible, possible et cetera, but since Suzuki is more Suzuki is expensive, but most reliable.

So; that means, we can talk about Suzuki then who which one, the Suzuki whether we should place borne on the pineal side or one the parole side, do you understand what I am saying there means borne could be replaced on the aromatic ring system or other side. But, how do I decide, how is it to right that is it, normally the accessibility which one is more easily accessible borne means you have to you know, so well studied in case of aromatic chemistry.

So, one can make it right, and maybe we will talk out little later then but see here, the important feature of this molecule that the parole is substituted in 3 or 4 positions or whereas, all of us know there are paroles are sustained to go in one direction at 2 and 5. So, how to drive the reactions 2, 3 and 4, one of the scientist did is basically started with halogen compound, who which was nicely obtained from simple parole, I will just give you the answer because this will take lot of time if we go back to discuss all this thing, tips try I try where.

One can do is sodium hydrate and tips chloride, that is perfectly alright. What was he discovered that if you do this reaction with NBS, NBS is a mind it NBS is a source of radical bromine, but if you do not eat heat if do not use to light, just a room temperature all though below room temperature, it is a ionic bromine ion. And parole is, so reactive you can actually, you carry out reactions minus 78 degrees centigrade now, question is where do attar, so bromine ion.

So, electronically we respect this auto cut the two position, but in this case very interestingly and yield is, so good in 90 percent 90 percent of yield and tips, that is the trick. Then means steady crowding of sailed group, has been used to make rogue specifically one substitute brome compound that is it, that is the trick. Then one would say, you can also n chore sanitize for introducing chlorine right because you need a chlorine here.

So, how do you do, obvious choice is n chore sanitize, but what is that the problem. Let us say, if the reaction fails, what is the problem n chore sanitize between the what is the difference between chlorine and bromine, which one is more oxidizing NCS chlorine is more oxidizing. So, actually it decomposes the whole material, so; that means, I mean they were unable to produce this by this one. So, what they have to do is, we have to convert this bromine to chloride, aromatic brome into chloride.

So, how do you do, tips now, so here something I mean, this such a simple molecule to took, so many steps actually, how do you do we have discussed all about. That is a betel lithium, so you get the lithium then c 2 c l 6. So, what we get; that means, now you have a 3 substituted parole, but we need group here, before to this one, in these case this 4 position is substituted in borne compound. And this was now, again NIS again NIS we have chlorine of here and indium here and tips.

And what next, you have to substitute adding by boron. And once again, what is the reaction, this is a boreal lesson reaction, boreal lesson reaction we do not have talk much. There are two is one of the very famous reagent is you said, no boreal lesson we can do we ignored also we can do now, this replayed during boreal lesson directly by pin coal pineal borne or dip in coal borne. So, then you have palladium 0, once again palladium 0, you see carbon bond palladium, also can be using palladium 0.

So, what we get is this tips and this and here, will have borne one pin coal borne, so this part is alright. So, when you have this part then aromatic part should be, then other aromatic part should be, this is chlorine, this is nitro and then this one should be then iodine bromine because you told that selective coupling. Now, see such simple ornamental compound, but it gives you lot of pain, why this is problematic, why it should be, so problematic you have to identify the right; that means, you have to put all these substituent side by side, no in continuous manner, so that is quite tough all of us know.

So, then once again how to solve this problem, how to reduce the problem again lithiation; that is one of the modern technique, and most region selective. So, they begin with ((Refer Time: 38:14)) and if do the reaction for the LDA at minus 100 degree centigrade, what do you expect. See LDA reactions is driven by acidity as well as lesson, in this case because of the hydrogen groups here, the middle one is highly acidic, undergo lithiation. And that is if you like organ magnesium compound, if you treat lithuous compound with carbon dioxide sorry carbon dioxide, so what will you get, for the carboxyl acid, that is no problem at all carboxyl acid.

So, carboxyl acid and this is chlorine and this is bromine, now what. Now, we have to comport this carboxyl acid into nitro, how do you do simple right half man alright. So, but of course, they had by first, what they did they I thing use what is that quotes arrangement, quotes or smith azote and acid, what is it and what is it name, smith fine then smith fine. So, if you do this smith reaction, so you will get mean here this chlorine and this bromine here, then subsequently we can do this oxidation, they have done with to the, metal chore MCPB.

And then these two have been coupled, this borne compound and this is have been coupled and this standard reaction, standard other reagent radium 0 and ligand here. In

this case the ligand is S phos previous one was x phos. S phos is something like, this first been here cyclohexane and then you have arrival being two methoxy.

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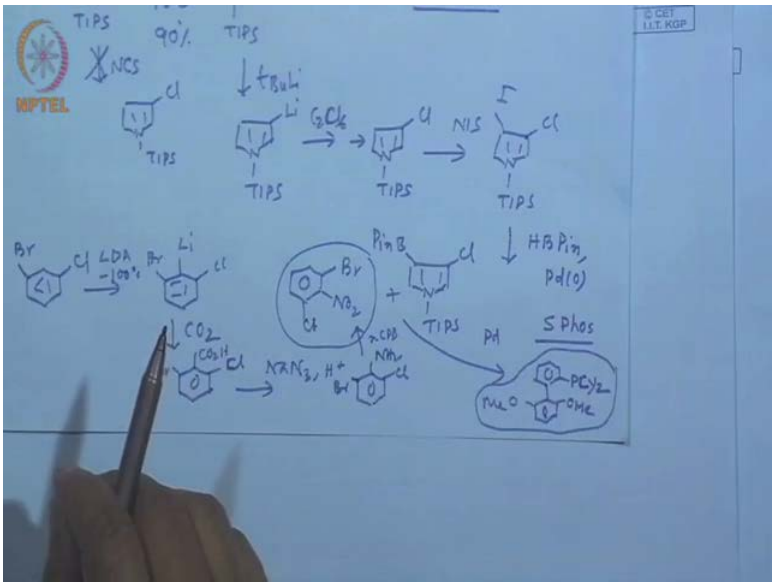

So, of course, there align to be named as S phos, why S phos there is no sulphide though, this one this is a ligand they have used for coupling this reaction. Not configuration, this S actually I came to know when one speaker come to our department and he gave a seminar. And he was booklover student, he said this name is given by booklover himself because there is only one single phosphorus. So, that is why it is called S phos.

So, Let us take up one more example, I have quite structure is like this, you have a bi pineal. Then one pineal carries two methaxi groups and ortho positions and other that whatever the position is, the other position is cyclic, di cyclic exile first page, I have many more examples. So, likewise negasicoupling is also pretty useful, I will just give you one examples for that would spiel to lasted the superiority of negasicoupling.

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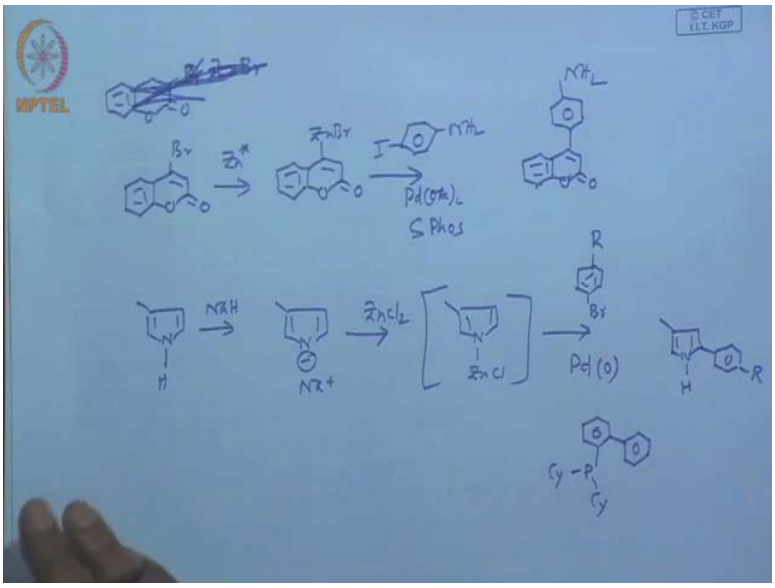

So, see here coumarone sorry this is I thing should not write here I thing just kept in mind, this 4 bromokumrine 1, 2, 3, 4 bromokumrine can be made of course, can be comported into the zinc compound. And what is the zinc, the most reactive zinc anybody remember zinc compound activated zinc, ester zinc, racy zinc, racy zinc racy himself very listen has done this. And then do this negasicoupling with ado anion, this palladium acetate again and ligand he also used ligand S phos.

And obvious product, I thing all these couplings are, so will established and so what can we see is obvious product is this. Now, you have to understand of shy actually, you know this reaction is sight about or should be studied, what is the lesson we should learn from here. Once again the mildness of this reaction mildness all this cross coupling are very mild right because you see in most cases, if you handling with amine you have to do all kinds of protection, Boc, acetate, this thing, that thing, benzyl, all these things, but you do not require any protection for the amino group that is the advantage, one of this very advantage important advantage.

And then if you have lactone, like coumarin, coumarin is basically lactone that would undergo all kinds of reactions, you cannot use sodium hydroxide ((Refer Time: 44:59)) any strong base, you know these lactone open up, lactone ring also survives in during conditions that is the advantage. And, so this one of the example, let me give you one

more example called the Suzuki coupling, this is nice I thing I will give you one more. Let us say, you have a parole derivative.

And now, you sodium hydrate, so we know what happened, with sodium hydrate in the previous case this reaction what we see, that it would form a sodium salt. Now, you should create a zinc chloride. So, what do you expect transportation take place, so; that means, it should be this metal in fact, this transportation is very low temperature reaction. And once you have this, then let us say use an brome arisen R, so nothing happens, then you use palladium reagent. So, in this case I just write palladium 0.

And ligand very similar to S phos, very similar to S phos, the ligand S phos is nothing, but is a actually we called by pineal, with phosphorus and cyclohexane group and a cyclohexane group. And what are the other thing in S phos methaxi acid, but in this case no methaxi acid that is it. So; that means, the key punch changing ligands here and there you know, what are the available around just keep on optimizing things here, but then without ligand nothing happen, just both the reactants sit together and no reaction take place.

Then if you palladium; obviously, there is a reaction called negasi reaction, but question is, what does arrival group while, arriving does not break. So, this portion remains as it is right and after the work of the nitrogen, so what does it mean, that actually arisen take place at a carbon. Now; obviously, which carbon between you have to either 2 or 5, I said 2 or 5. So, it is the 5 that is it so; that means, the very selective and the reaction takes place like wise.

So, like weather this parole zinc this is specially, is very useful and there are, so many examples that have been work out and what else. So, I thing we have come to almost like an end and let me give you one more one or two more I thing I have one more examples. We turn next heproxtade hex, heproxtade Suzuki, heproxtade negasi and what do you did not talk about then still an what else sonoacirea fine I have an example of sonoaciera what, sonoaciera all of us know, basically yes sonoaciera good no doubt about it and is very useful. So, In heterocyclic chemistry once you have an basically I mean all other cross coupling reactions, if you have right the liquid reacting partner, the reaction take place without much problem.

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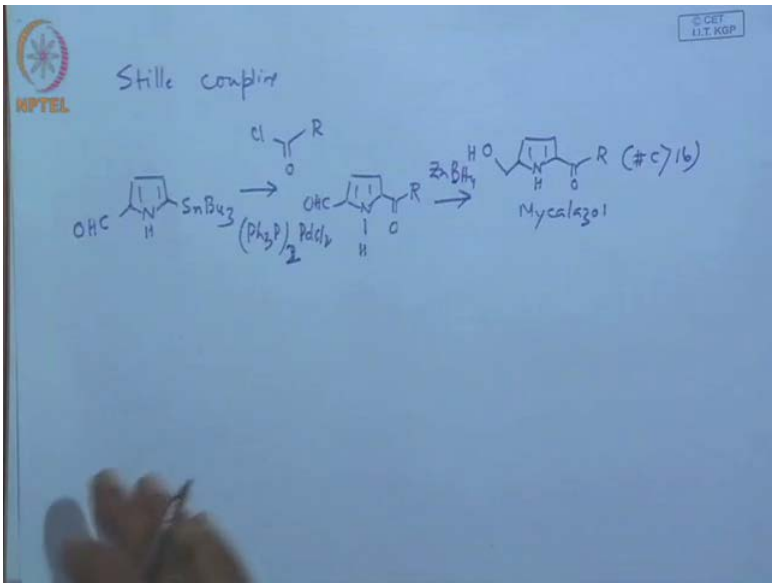

The one I will give you I think this is a from stille coupling reactions, you say natural product will talking about this is a piroal natural product, this is known as mycalazol, it is a merit natural product. And then we have a big carbon change here the carbon change containing, so more than I mean carbon number of carbon is more than 16 is a long carbon change and then we have on this side, we have an alcoholic here. So, how do you make it, first of all you have to know paroles are very, very reactive if you keep bottle of parole it will became black it becomes blacks right pallimination, so this kinds of oxidation all these things.

So, but they are found at in self-products, but most of the parole contents and elector relative group, in this case we have a carbonyl group. So, once a carbonyl group they are compound is disturbed, any case our problem is to synthesis this compound let us say. And synthesis this compound, so starting point starting material this would be home work for the next class for Friday, how to make the starting material.

In this case, so as I said say before at early stage you fix up the region chemistry all this problem. So, once you have two different groups, in this right position then the rest of reaction should follow the course of the reactions then in actually you reach the right target. So, once have tin then of course, you know what we are going to do, we were going to do stile coupling.

So, this the metalize, then now you have to have a halogenides, what is the halogenides hooligan contain compound what should be for a change, you will see nice now you do not have to have stile coupling, you do not have to have aphonic compound simple axial chloride also nothing else. Now, one this selective take place between in the tin and the corresponding halogen compound normally acidic, but in this case the axial chloride is perfectly alright.

And, so once you have this that is it nothing else, so this thing and in this case the palladium is the diaphone first Pinole palladium chloride and then of course, there must be ligand, but ligand is not. And hydrogen here, aldehyde and see once again aldehyde remains intact and this O and axial chloride. So, once you, so what next read action, no I should not say we have to say selective redaction, so how do you do selective reaction of this aldehyde to the corresponding alcohol.

So, you have ketone, you have aldehyde very similar reaction 2 and 5 are very similar position of the parole, see NH is not first of all protected. So, that scare of the three such aldehyde n h does not have to be protected. So, you have nice coupling, now it is just case of the basically select redaction case. So, suggested method, suggested reagent that would reduce only the aldehyde, you have been learning, so many redactions sinoboerhyded no sinoboerhyded requires acidic conditions.

What you said all by the way, yes there is a compound actually at this movement I have forgetting this structure. I say lithium aluminum hydrate titrated with something right, aphetic methodic group, methanol alright that the methaxi ethane may be can we just look at the radial sometime use, but I have no idea at the moment. But, the one I know they this people have used is something some body, also what heavily on the reagent from calcination of science bisireno.

Originally he was famous for using that reagent, zinc bore hydride, zinc has a stronger acidity towards, oxygen activate the aldehyde and in actually this. So, I think I will skip this one I will keep this, so samara what is samara let us say, what is knew about the cross coupling in heterocyclic chemistry. So, basically extension are applications of the heterocyclic chemistry, glorify the cross coupling reactions; that means, they more harsh tile they can be used anywhere in chemistry yes number one.

And number two most of the cases reactions are mild reactions, I mean protections of the groups especially nitrogen contain groups I did not give you one example, but the funnel is there the reaction does not go out funnel is acidic. So; that means, all this cross coupling reactions take place in slide the basic medium, basic also neutral medium, if the carboxylic acid is there, there is chance of reaction protection place, that you have to kept in mind.

Third thing is harsh tile and the fourth thing, what is the fourth thing summary, go back and see and tell me. Fourth thing is this right that cyclization of oxzine, I should say narasaka hake reaction by narasaka hake reaction; that means you can form carbon nitrogen single bond, that is important. And lastly, what I dint talk about, I had things that this, if recall andro hamiltonian also said that I have an example also, there are molecules you can synthesis by repetitive hake reactions or Suzuki reactions.

Let us see, you have a parole, you want to place four different substituent on the parole 2, 3, 4 positions, you can do one Suzuki and next Suzuki, then next Suzuki, then next Suzuki, you can go on; that means, they are not that suspect to sub stable effect, but eight sub stable. That means, if you want to put the fourth one, by Suzuki the yield deistically decreases. Then these all this Suzuki reactions also all this reactions are sensitivities steric effects. If recall undo Hamiltonian what did you made, no poliflence, then one point at he said that yields these are not good method because yield progressively decreases.