Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3-sp3) bonds in asymmetric fashion

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Module - 04
Enolate alkylation of several carbonyl species
Lecture - 18
Myer's ephedrine, Chiral Weinreb amide equivalents and related systems

Welcome back friends; so, in particularly this module 4, we will be going to talk about lecture 18. And particularly in this lecture 18 we will be mainly focusing on Myers Ephedrine and other Chiral Weinreb amide based equivalent and its exportation in enolate alkylation.

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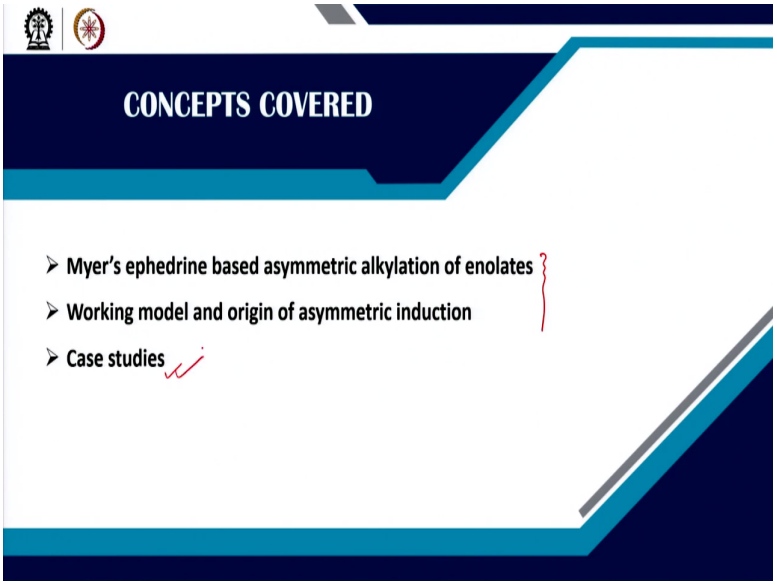

So, particularly today in this lecture our main focus will be seems to be the Myers ephedrine based asymmetric alkylation which again seems to be kind of an extension of Evans oxazolidinone. But this ephedrine acyclic; acyclic chiral auxiliaries, its working model and the origin of asymmetric induction. We will talk about some case studies definitely; so, let us begin.

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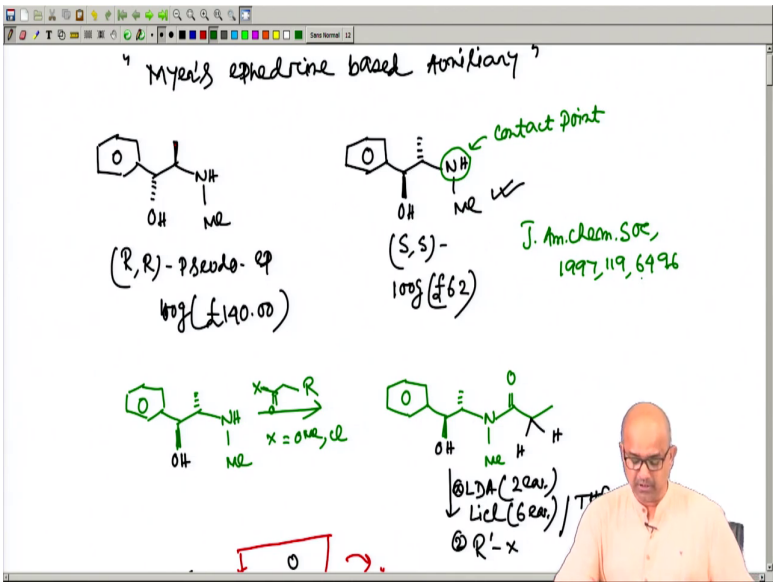

So, here we will be mainly talking about this Myers pseudo ephedrine based auxiliaries and we will try to give you a quite detailed understanding that how this Myers pseudo ephedrine based auxiliaries are used.

Now, let first draw some of the structures and how these auxiliaries are being used in the field of asymmetric enolate alkylation. So, very beginning let me first draw the auxiliary and mainly these auxiliaries are commercially available. So, these are usually based on one two amino alcohol backbone, these are the structural features yeah.

This is one of the auxiliary which is known and this is R, R pseudo ephedrine, pseudo ephedrine. And this auxiliary was definitely little bit costly the 100 gram price cost almost cost you something like 140 sterling pound which you can just convert to corresponding Indian rupees. So, this is the R,R and corresponding S,S auxiliary also are commercially available which will be just the (Refer Time: 02:55) of the initial auxiliary or the left-hand side auxiliary which we have just now drawn.

So, this is the S,S auxiliary and this auxiliary also was little bit less costly; so, 100 gram cost 62 sterling pound ok. Now, definitely you can see that one is almost twice then that the other one; so, probably this could be the cheapest one ok. Now, what is the main reaction pathway or reaction pattern, let me first draw the couple of structural features. So, this NH as like the other auxiliaries it should be your contact point fine.

So, where your acid or carbonyl compound will make a contact means you will be trying to do a covalent attachment here. It is you can easily see that the other part might acting as a chiral controlling agent or stereo controlling agent.

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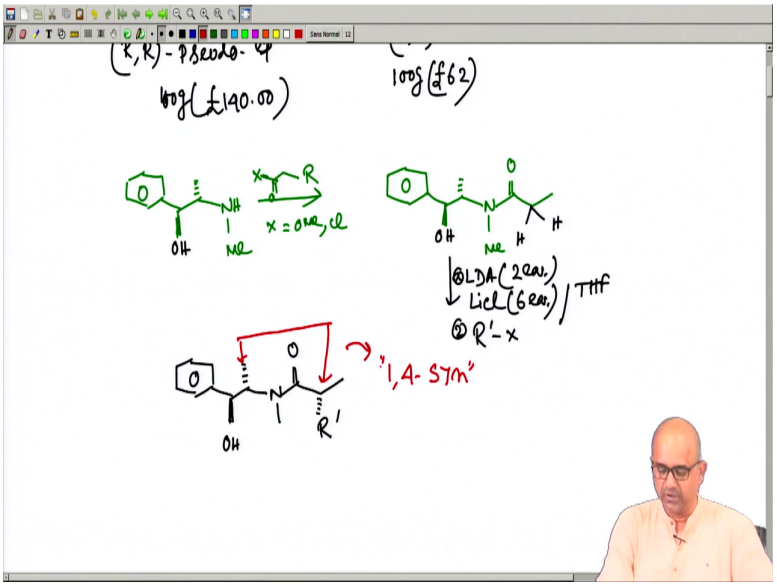

So, let me first draw the reaction sequences by taking any of this auxiliary. So, let me take the cheap auxiliary which is the S,S auxiliary and for such Myers ephedrine based auxiliaries you. We can also have a mnemonic device I mean that you can actually have a rule of thumb that which auxiliary gives you which stereo center in the final product. So, you first take the corresponding pseudo ephedrine SS pseudo ephedrine and then let us react to it the acyl derivative of your choice CH 2 R.

Now, usually X could be simple ester, if you try to react with ester, it could be acid chloride or something like that ok. So, you first make the covalent attachment or covalent bond formation and you will now have this N Me CO CH2 CH3 ok. Now, definitely you can now visualize that this could be the hydrogen which you are going to abstract abstracted for the enolate generation, enolate generation now.

So, for enolate generation LDA was used as a base; usually, two equivalent of LDA was used why usually this compounds do have a hydroxy group here ok. So, this definitely a having a proton source; so, definitely one equivalent goes here one equivalent goes to enolate generation ok. And then you also use lithium chloride as an ionic salt 6 equivalent extra. Now these 6 equivalent is needed to form a supra molecular enolate aggregates and then THF was

the solvent of choice definitely and then you use at the second reacting component is your electrophile the R x ok.

And what product you usually observe let me first draw the product then we will explain why this product was obtained. So, N then you have Me C double bond O, this is your methyl is there and here if you have the R prime this is the electrophile. Now, the rule of thumb is if this methyl is below your electrophile is below that is what sometimes we actually refer this as a 1 4 syn rule.

So, syn rule means this is the 1 carbon and this is the 4 carbon; so, we call it as a depending on the stereochemistry of the auxiliary of the methyl you always get the 1 4 syn. So, if in the starting compound you have the methyl above here, you get the electrophile above ok. Now this is a rule of thumb definitely there must be a logic behind that now what is the logic; now, for this logic we will try to draw the transition state to a different structure.

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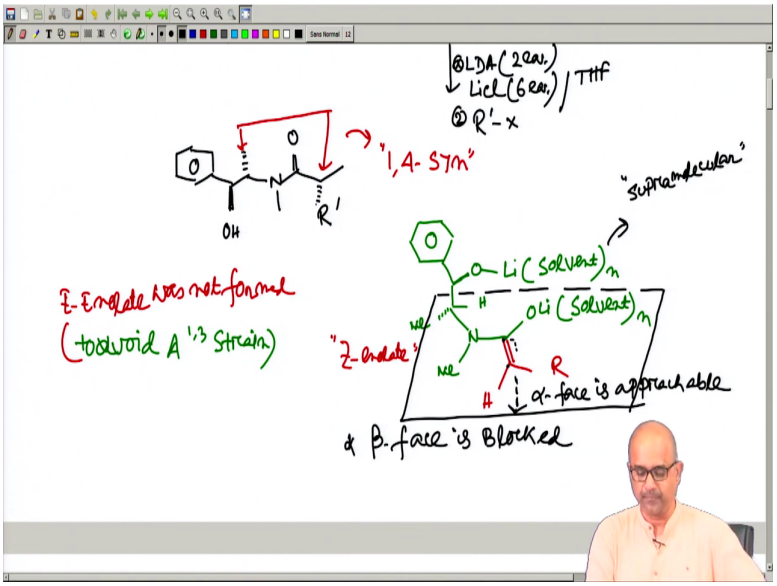

Now, this structure we will try to take some time, but definitely you can also practice with me when we are now see here we have this ok. Now, this hydroxy is above; so, you can just try to put the hydroxy above. Now, this is a free hydroxy; so, this we have extra lithium in form of base as well as lithium chloride also we added and this lithium seems to be have a supramolecular aggregate with other solvent molecule ok.

Now, next you have this part and then you do have your methyl here we try to put the hydrogen here ok. And then from this you have a nitrogen, this nitrogen you have a methyl ok and then you have this enolate, enolate means again a O Li. Now, this is also supposed to take part in the coordination because you have extra thing. Actually, some was usually not recommended for such, but ephedrine-based auxiliaries, now you can see this particular thing you will get enolate.

Now, there are certain features which you might be wanted to know that why this enolate was formed; now, this an enolate is what this enolate is Z enolate ok, Z enolate. Now, you can see that Z enolate was mainly formed if you put the R group here that gives you a severe allylic 1,3 strain. So, you can simply write that E enolate was not formed E enolate was not formed, why? To avoid allylic 1,3 strain, this was very simple which we already talked about.

Just try to emphasize if you put an alkyl group here that gives you allylic 1,3 strain; so, to avoid this you have this thing ok. Now, what we will try to do we will actually try to put this everything I mean this enolate this C, this carbon, this methyl, and this seems to be in a typical plane or one plane. So, let me try to assuming the plane where all the; so, this could be the plane of the enolate ok.

So, I just drawn a two dimensional plane and I am assuming that everything all these atoms are lying on this plane. And as this hydroxy group is above the plane by virtue of the pre-existing stereo center, you find that now this O Li seems to be highly solvated and that basically gives you the supramolecular aggregation. So, this supramolecular aggregation remember, in the very beginning class we talked about the enolate are form as a supramolecular aggregation.

So, also you have this lithium solvent here as well as here; so, the top face seems to be kind of highly we can write that beta face; beta face is blocked, blocked by whom? Blocked by mainly the supramolecular aggregation; now, see in this plane methyl is below ok. So, the electrophile electrophile normally approaches to this particular enol face of this I mean this sorry not this face in the alpha face; so, alpha face is approachable.

So, beta face is definitely blocked by the supra molecular enolate. Now, you can see that why this electrophile approach from the alpha face; this was the origin of the asymmetric induction for all these thing ok, I mean this particular pseudo ephedrine based enolate alkylation.

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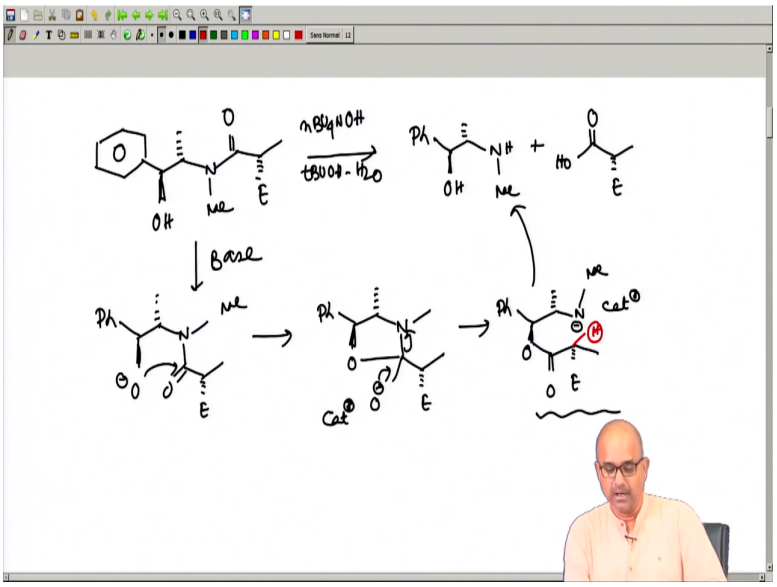

There are certain features which probably we will next explain that once this alkylation was done what step was used to remove the auxiliaries. And usually, the auxiliaries can be removed by different way similar like Evans or ephedrine based auxiliary, you can do a hydrolytic cleavage, you can do a reductive cleavage mainly these two are usually preferred or sometimes you can do a transamidation type of reaction.

Now, see here let me take a very general case you make a carbon electrophile bond in asymmetric fashion. Now, you want to remove this thing and usually what was done it was done with a tetra butyl in ammonium, ammonium hydroxide and in a tert butanol water solvent ok. Tert butanol water solvent to actually get rid of this auxiliary; so, you can get the auxiliary back which you can again reuse it.

So, this was the usual practice and if auxiliary you can get it back that is absolutely desirable and you can get the corresponding carboxylic acid back. So, this was the usual hydrolytic cleavage for such auxiliaries, but here there is a certain point which I want to mention. Now, after you treat with the base means this tetra butyl ammonium hydroxide there is a base ok. So, base also can deprotonate the pre hydroxy you, basically have this O minus the moment you have O minus and you can actually write the compound in a different way something like this ok.

So, now see you can write the initial compound in this way and you can find that this O minus probably will attack to the amide carbon. So, moment it attacks the amide carbon what

you will be expected to get? You basically get a cyclic structure and this cyclic structure will be having this O minus the tetrahedral intermediate the rest of the part is here. Now, O minus with the corresponding n bu 4 N plus the cation as a salt ok; now, this O minus comes back because the amide hydrolysis has to take place and actually put the negative charge on the nitrogen fine.

Now, what it will lead you that basically lead you this O this C O and then it puts the electrophile this carbon electrophile bond which we have created with the methyl. And then this methyl is there and then N is becoming minus and the cation is already there fine. Now, actually if you have this kind of compound which can also after the protonation can basically give you the hydrolysis, but here there is a point. The moment you generate this compound you can see that the newly created carbon stereo center contains an electron withdrawing group in its adjacent ok.

Now, this hydrogen this hydrogen which you have there in this compound as it is a typical basic medium; so, this hydrogen seems to be kinetically labile ok. Now, the base might give you abstraction and further reprotonation; so, that basically gives you a loss of enantiomeric purity and this was which we called competing enolate formation.

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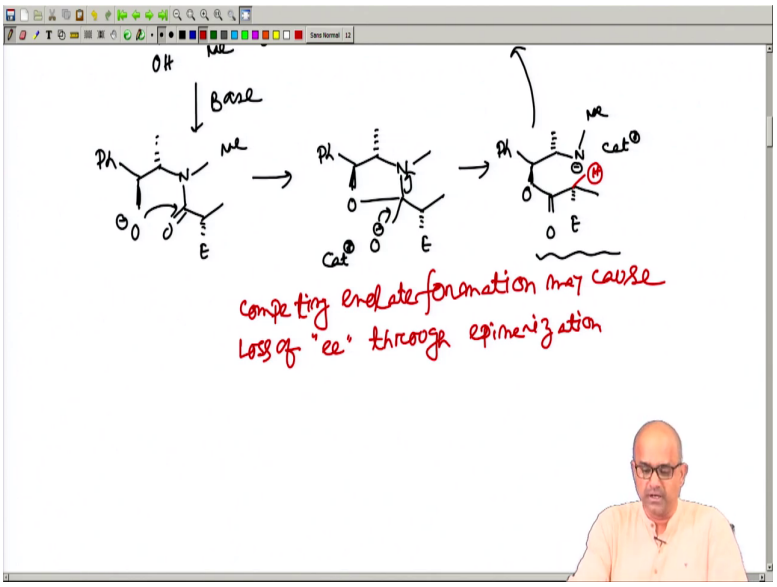

So, competing enolate formation was one of the major drawback in the hydrolytic cleavage in ephedrine based auxiliary system. So, competing enolate formation may cause it sometimes happen, but is not always happening may cause loss of enantiomeric purity and loss of ee we

can write enantiomeric excess through epimerization you can easily figure it. Now, this was one of the major drawback in most of the auxiliary cases and particularly for this ephedrine based auxiliary this seems to be one of the major drawback.

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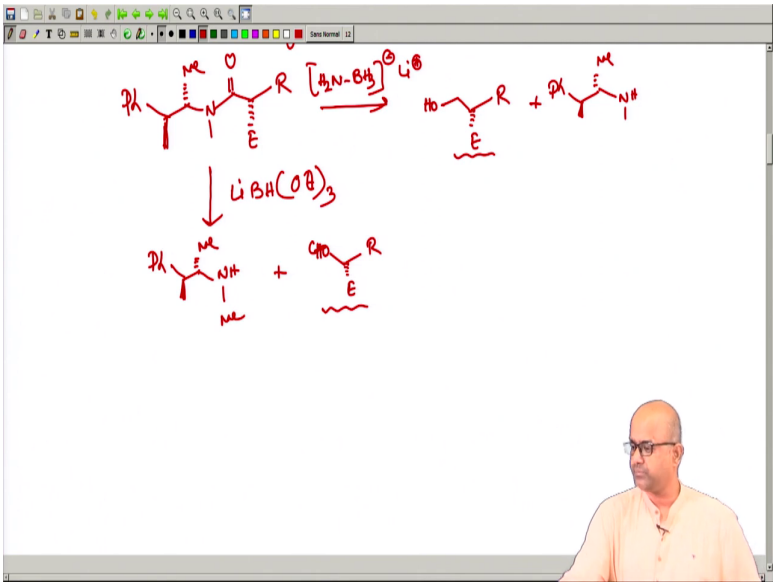

So, what people try to adopt it? They usually try to prefer through work in the other working model maybe you can talk about the reductive model, reductive cleavage which seems to be much milder. Now, in this case the reductive cleavage was definitely very much possible, let me talk about a general example something like this. And usually, the reductive model was usually done by a borane amine complexes; so, these complexes are commercially available.

So, you have H2N BH3 minus and lithium plus which is kind of a this hydroboration kind of reagent. But this BH3 minus will actually give you reductive cleavage and then you can get the reductive cleavage through E…….. R C H2OH your initial compound will be oxidized sorry reduced and the auxiliaries will be back ok. So, this was one of the way you can do it is pretty mild condition and normally other strongly reducing agent like lithium aluminium hydride lithium borohydride was not used here.

But other mild reagent if you try to use it like lithium tri ethoxy borohydride which seems to be pretty mild, and in this case actually the reduction stopped at the aldehyde level ok it does not go further. So, you can eventually stop the reaction here you can get this compound with the E and R CHO. So, different oxidation state you can actually get it, you can get the aldehyde, you can get the corresponding primary alcohol.

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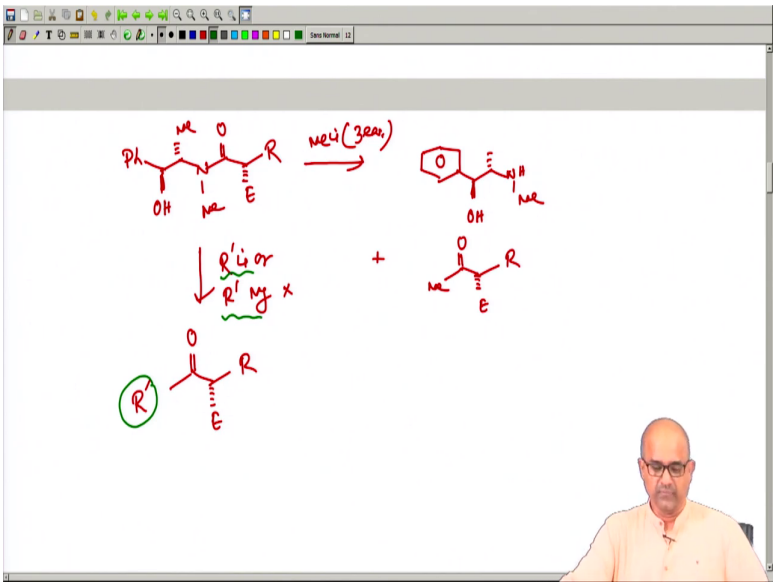

And also, you can create other functional group which was also we earlier explored in the case of Evans or related auxiliaries. Like in this case, you can explore in the similar way you can do a cleavage through let me try to write the general structure something like this you can do the cleavage through methyl lithium. So, if you have an amide; so, if you try to use methyl lithium and normally excess was used 3 equivalent, because one of the methyl lithium will take care by this hydroxy group.

And in this case initially the methyl lithium you know the amides will be reacted under this condition this ephedrine will be released ok. And then you get this and what product you will get you get the corresponding methyl ketone ok O R C O methyl. So, it all depends if you now instead of methyl lithium if you try to take any alkyl lithium like R prime Li or R prime Mg x, it is a general way of cleavage.

So, then in those cases what you will get you get the corresponding ketone as a final product. So, basically depending on your target you might choose this R prime as the choice of your alkyl lithium or the corresponding Grignard; so, this is the usual way you can do it. Now, in the Myers ephedrine based enolate alkylation seems to be quite interesting because it has been used in couple of industrial setup.

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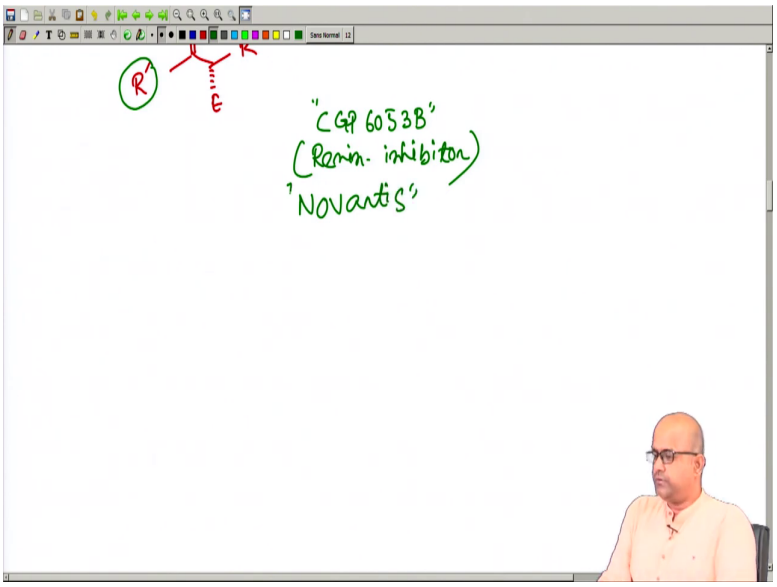

We will try to give one such example for a synthesis the molecule which whose name is CGP 6053B. It is a drug like molecule, and this molecule is acting as a renin inhibitor renin is an enzyme. It usually used in the treatment of heart disease and now this synthesis which was used by Novartis company……. Novartis use this process.

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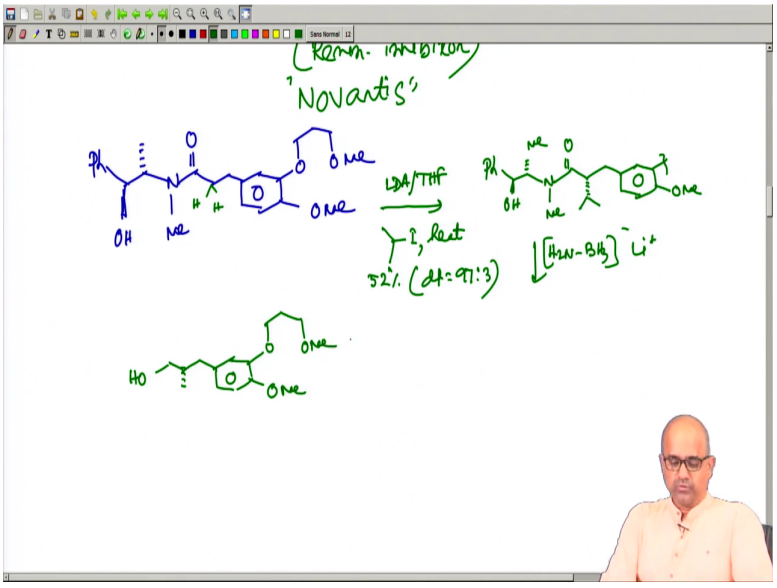

Now the structure of CGP 6053B……. I will draw it little bit later on, now first go to the synthesis because Myers ephedrine-based auxiliary was one of the key step for the synthesis.

So, initially you have this N methyl and this pseudo ephedrine was reacted with this aromatic compound which is the structural feature of the target molecule ok.

So, this part seems to be inert only active part was this hydrogen which will be now next reacted. So, fine LDA was the base of choice THF was used and then the electrophile was pretty important secondary iodide isopropyl iodide was used. And actually, as this isopropyl iodide even you can do it as a heat as a source because this iodide was not that reactive.

Yield was not that good 52 percent, but the diastereomeric ratio was 97 is to 3 the desired compound was obtained in a pretty good yield. Now, let me write the structure of the compound which you can eventually get and if you try to see the structure and the origin of asymmetric induction. So, methyl is alpha ok; so, 1 4 syn; so, isopropyl should be alpha fine. The model which we have explained earlier can now you can visualize it rest of the part remain similar; so, you can write the same thing ok.

Now, here what they did they basically try to do the reduction with amine borane complexes minus Li plus and what you will get you basically get the corresponding reduced product. So, this part you will get as a O Me and this is O, this O Me. Now, probably I should write the structure of this CGP thing; so, that you can compare that which part we have synthesized.

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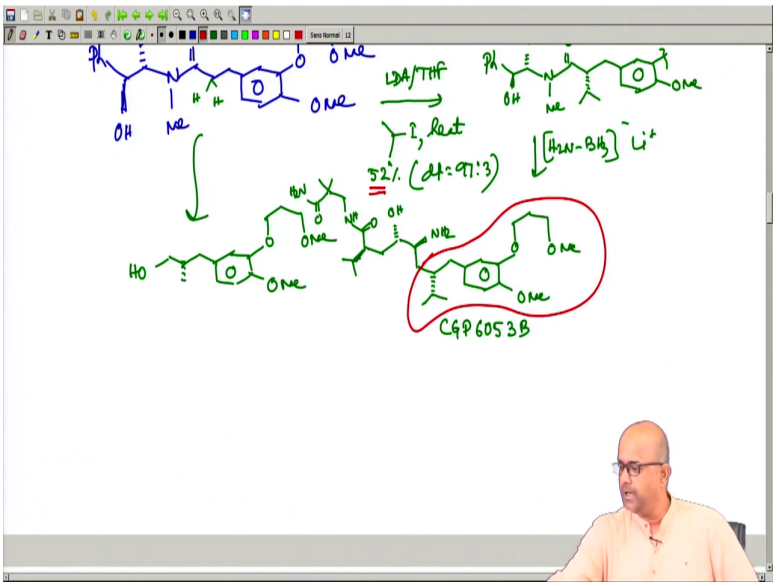

Now, CPJ sorry CGP 6053 B its structure was definitely little bit complicated, but nevertheless we will just try to draw its structure. And this part is this you have this isopropyl

part which just now we make then you have this ok, you have this NH2 here the structure was bit complicated and couple of stereo enters were there in the original structure OH ok.

Then you have CH2 you have a C double bond O, you have another isopropyl group here ok, and then ok let me try to write the structure little bit this way. So, CO then you have another NH and you have a CH2, you have a gem dimethyl, then you have a C double bond OH2 N amide. So, anyway this is the structure of this particular compound and you can easily find out that which part we are trying to make through this Myers ephedrine based auxiliary.

So, we actually prepare this part and Novartis prepared this compound in a pilot plant scale basically a in kg scale. So, this reaction was pretty much optimized and that gives you idea that such asymmetric enolate alkylation can even be used in the industrial setup where you need a bulk synthesis of several drugs or drug like molecule.

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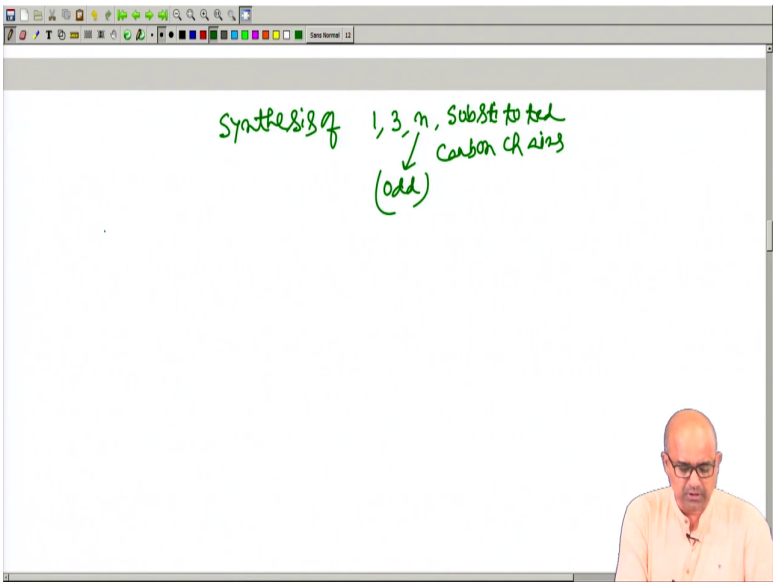

Now, one of the most significant application for this Myers ephedrine was actually synthesis of 1, 3 and N substituted carbon chain substituted and this is pretty interesting substituted carbon chain. Now, in this N seems to be odd number; so, means we are talking about 1 3 5 7 ok.

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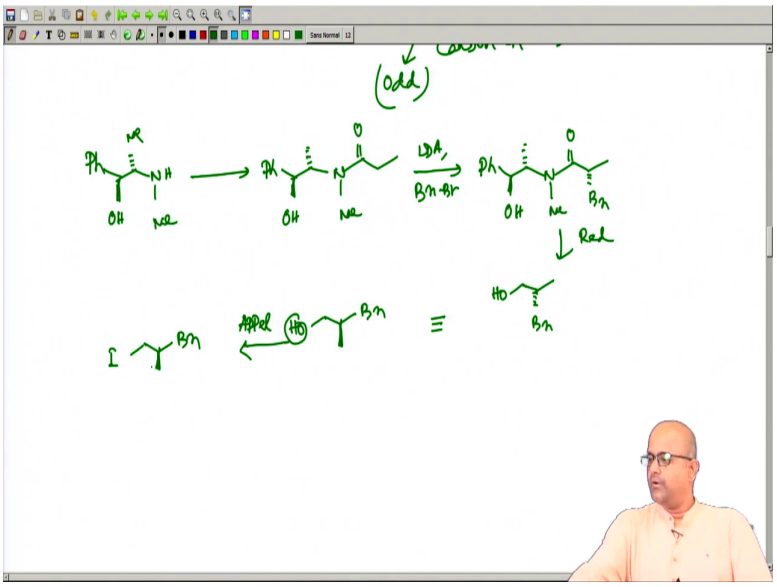

Now, let just try to be little bit of schematic presentation, you start with any of this auxiliary let us start with this particular auxiliary; so, methyl this is OH and this is NH me fine. So, first you condense or take this compound and react with the corresponding secondary amine to get the enolate precursor ok. The moment you get the enolate precursor everything seems to be ready you do a LDA and here you try to react with electrophile let say you react with benzyl bromide.

Now, fine now you can eventually choose that which way you want to react and now benzyl bromide is the electrophile. So, you will eventually what you get? You get N Me C double bond O and actually you get according to 1,4 syn thing your benzyl is here you get methyl fine. The reduction cleavage reductive cleavage you can easily do; so, what you will get you can get Bn methyl CH2 OH ok.

Now, this compound you can simply write in the other way, you can simply write this compound just by doing the absolute configuration analysis that Bn CH2 OH. Now, first what compound you have generated, now this free hydroxy group you can use as a electrophile by using a Appel reaction. Now, Appel reaction converts this alcohol to corresponding iodide.

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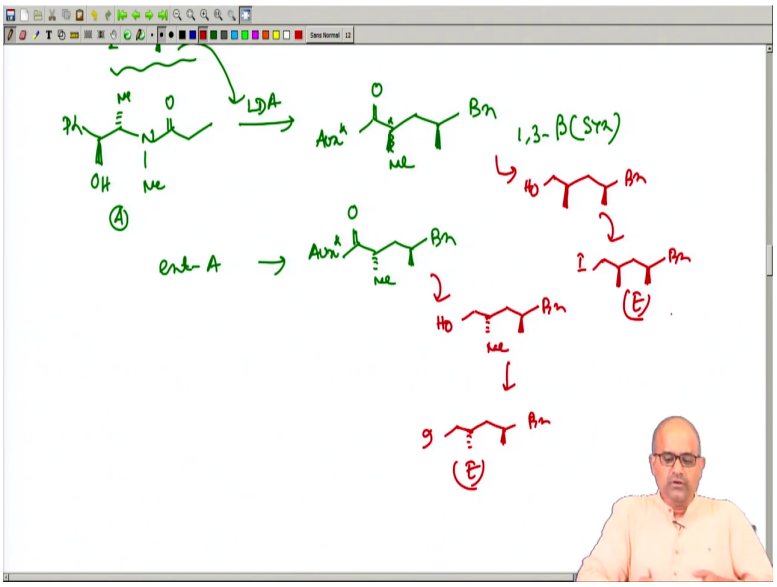

Now, in the second round of reaction what we will be now using you actually take this as an electrophile. And now we will be using the same auxiliary Ph OH, this methyl is there N Me C O these things ok; now, if you try to do the same thing LDA and this will be now your electrophile fine. Now, we can eventually you can just write this CO and now see you have to just put the auxiliary in this way; so, you can just write this auxiliary ok.

So, this will be now your you can just try to put the everything in this way I mean depending on the choice of which auxiliary you take. So, you fix this methyl in this way, the absolute configuration you can just take care of now this CH2 I. So, you can put the CH2 I this and the this methyl you already know; so, Bn. Now, you can see this methyl you can actually control you can actually control, if you take this compound.

If you take compound A you get once the isomer and if you take ent A means enantiomeric of this auxiliary. So, let say by using A you get both methyl are 1,3 beta 1,3 syn. Now, definitely if you take enantiomeric of A, you will get an opposite stereochemistry because the working model now seems to be just opposite; so, you definitely get the corresponding anti fine.

So, now see from this case from the first case after the reductive cleavage what will get? You get methyl, you get methyl, you get benzyl, you get CH 2 OH ok; now, in this case you get 1,3 anti. Now, this was repeatedly you can continue it, you can now again convert these things to the next round of electrophile right Bn CH2 I and this also you can convert one three anti Bn CH2 I. Now, this electrophile again you can further do the sequential alkylation.

So, this way you can eventually conclude now if you try to continue the reaction in such a way that one round of further round of auxiliary and reaction.

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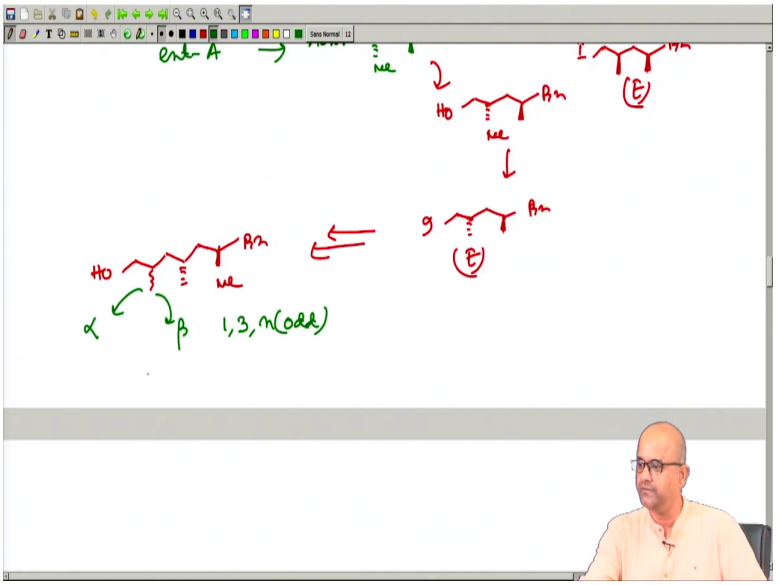

So, you can basically get this Bn is there just try to put this methyl is beta fine this methyl is alpha now you can see the further round of methyl you can get both alpha as well as beta. Now, what this methyl it could be alpha if you take one auxiliary it could be beta if you take one auxiliary.

So, this 1,3 and n, n means odd number; so, 1 3 5 then 7 you can basically create. So, sequentially this 1,3 syn or 1,3 anti-corresponding this dimethyl appendage you can easily create and such this 1,3 syn or 1,3 anti methyl was this kind of framework was usually abundant in many of the poly ketide natural product.

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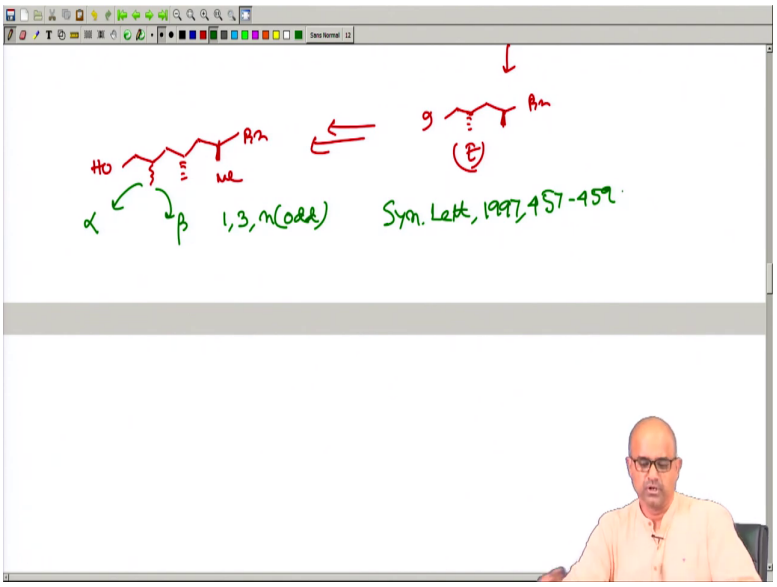

Now, this was Myer actually reported this finding in a very important paper which was published in syn Lett in 1997. And once this was published this method was very much applied by many of the synthetic chemist for using this work. So, for Myers asymmetric pseudo ephedrine based enolate alkylation; if you go back, you will find that this is the basic blueprint.

And actually, the initial work I forgot to tell about the references which was first published in a JACS paper in 1997; so, just after the Evans work. So, Evans oxazolidinone, they have already published their phenomenal work and then Myer came into picture. So, anyway we will be trying to continuing the Myers ephedrine based auxiliary and you can just try to go through the entire sequence of the reaction and if you have any difficulties just let me know.

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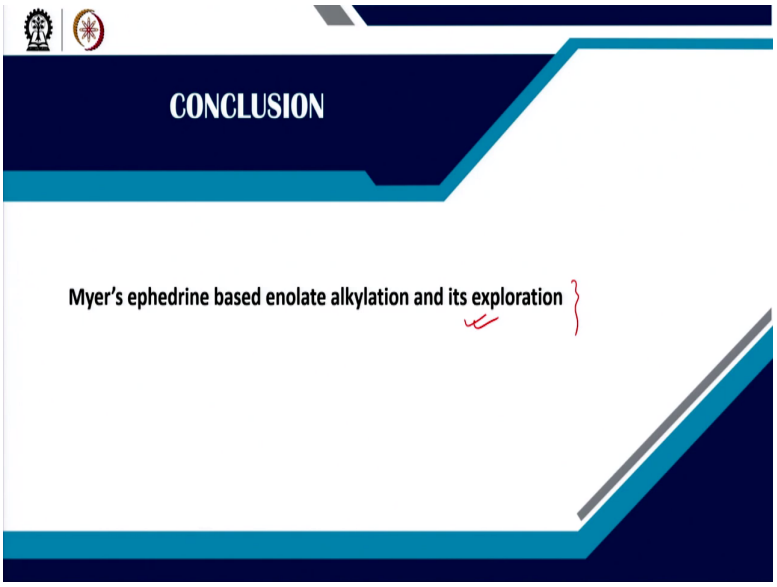

So, as a conclusion this Myers ephedrine based enolate alkylation and its structural features and synthetic exploration which you can find very useful in the field of asymmetric synthesis. We will try to explore few of its other features in the subsequent lecture and till then.

Thank you see you again.