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 - 03
Enolate alkylation of several carbonyl species
Lecture - 14
Evans oxazolidinone and related systems - IV

Welcome back everyone. So, today we will be talking about module 3 and lecture 14 is our main content today. And, today basically we will be talking about similar kind of things like Evans oxazolidinone and related system.

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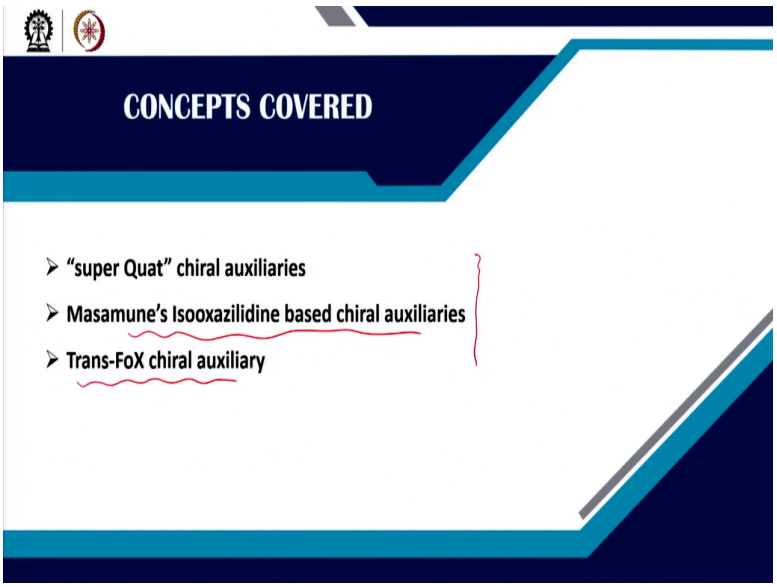

But, mainly we will be discussing higher order oxazolidinones like super Quat chiral auxiliaries, but mainly it will be focusing about Masamune's Isoxazolidine based chiral auxiliaries in the asymmetric alkylation. And, in the final part this, trans-FoX chiral auxiliaries which is also a modified version of Evans auxiliaries.

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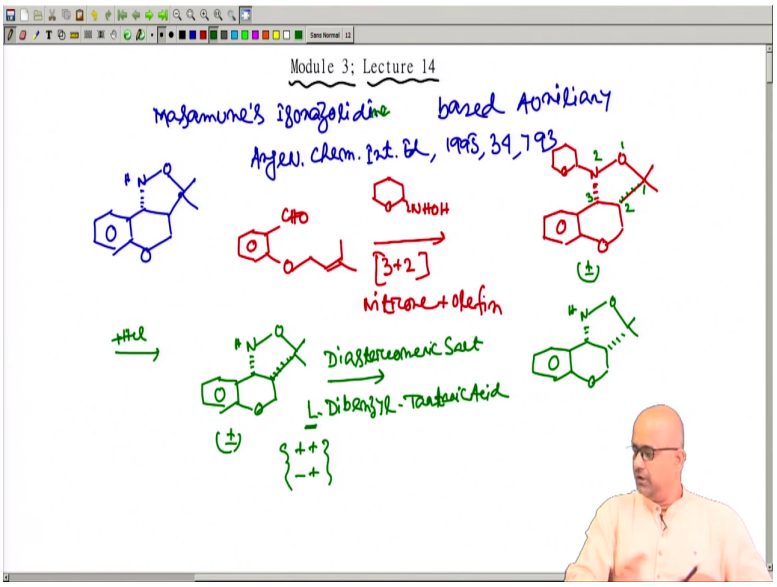

In this particular lecture which is lecture 14, under module 3 we will be basically talking about a different kind of auxiliary, but which is more or less similar like Evans based auxiliaries. But, this auxiliary structurally was little bit of different. This auxiliary was named as Masamune's isoxazolidine based auxiliaries, Masamune's isoxa…….. Now, this auxiliary was not definitely commercially available and you have to prepare this auxiliary.

This auxiliary was first invented by a Japanese scientist Masamune who published this paper in a Angewandte Chemie paper and which was published in 1995. And, the entire structure of such auxiliaries we are going to discuss now. The basic structure of this auxiliary was let me first write this structure.

This having an aromatic part and with this aromatic part a tetrahydro pyrone ring was there and with this pyrone ring, a 5 member fused oxazoline part was there ok. So, this is more or less you can say the modification of this Evans oxazolidinone part which is super Quat because you have this dimethyl group, the gem dimethyl part.

And, this is your N H means, where you can functionalize and this is the oxazoline, this is oxygen ok, so, isoxazoline. Now, this compound was usually prepared through a series of simple reaction. So, we will just talk about this corresponding salicylaldehyde was initially taken as a substrate which was alkylated with prenyl bromide to give you this compound.

And, then this compound was reacted with this cyclic oxime type of thing ok, this tetrahydrofuran oxime type of thing. Now, the now how this compound was prepared? There is another story, but now this compound basically hydroxylamine it basically undergoes a 3 plus 2 nitrone cycloaddition. So, 3 plus 2 dipolar cycloaddition. You first generate a nitrone from this hydroxylamine and you have an olefin.

So, nitrone plus olefin cycloaddition was initially used. Now, once this cycloaddition was done, let me try to use this thing and then I will give you how this. If you are not familiar with this nitrone olefin cycloaddition; so, please give a search in the textbook or in the internet based thing. So, we have this, you have this and then this dimethyl, but this hydrogen was not there, I wrongly have written it. So, there will be a this THP; so, this THP ring was there ok.

Now, how this happening? Basically, you are basically creating 2 extra bond which is this nitrone basically is coming from here and this olefin is the this gem dimethyl. So, this so, you have C plus N O minor. So, this is the nitrone. So, this is the 3 1 2 3 and this is the 1 and 2. So, 3 plus 2 cycloaddition ok. So, you get this kind of oxazoline ok.

Now, this oxazoline you get a racemic oxazoline ok fine. Now, this THP part was removed by simple hydrolysis. So, you treat with HCl, aqueous HCl and then with this hydrolysis your THP part was removed. And you get the oxa isoxazoline NH, this is oxygen, this, this, this ok. Now, this oxazoline is a plus minus racemic mixture ok. Now, you have to resolve this compound.

And, how this compound was resolved? Actually, this compound was resolved with by making diastereomeric salt, diastereomeric salt formation with this L dibenzyl or dibenzoyl tartrate. Anyway, this is a definitely a simple resolution technique, the dibenzoyl tartaric acid salt formation by treatment. Now, what happen? This plus minus and you have a L means a single enantiomer that basically gives you a plus plus and minus plus.

Now, these two are diastereomers and diastereomers have different melting points. So, you can basically separate with those two diastereomers. And, after this diastereomers diastereomeric separation you actually can create this enantiopure cis compound which was used as a Masamune's isoxazolidine based compound ok.

Now, this is the structure N H your O, this, this. A slight change we will be calling this as isoxazolidine not the one, because you do not have any oxazolidinones ok. So, isoxazolidine, fine. So, with this auxiliary now your job starts that how you can synthetically use those oxazolidines.

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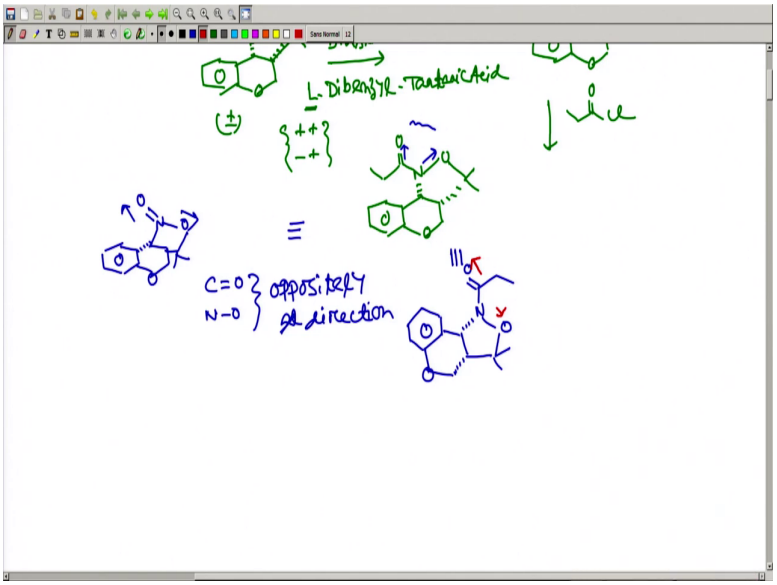

Now, definitely the next part will be reacting with the acid chloride. So, we treat with simple acid chloride or carboxylic acid derivative, where you want to create or do the enolate alkylation. So, definitely it will be N, oxygen, this, this, CO, CH2, CH3. Now, with little bit difference in the structural part than the Evans, because in Evans case you have a chelating group.

But, here you do not have a chelating group. So, what could be the main factor now? I mean, what could be the origin of asymmetric induction? Now, this structure the way you we have drawn, it basically gives you the fact that the CO dipole is this way and this NO dipole is this way. So, there will be a severe electronic repulsion, but in the Evans case you usually have chelate enforced annulation.

So, formation of the chelate basically over rules this electronic repulsion. But, in this case definitely there is no formation of chelate. So, what could be now you can think about, you have to write a different structural confirmation. This kind of different structural conformation, I will try to write in this way ok. We will try to put this. We will try to put this nitrogen, then C double bond O.

And, this oxygen will now try to write in this way. Now, it means that we are basically trying to feature it in this way here and this dipole should be in oppositely aligned. So, C double bond O and N O, this dipole should be oppositely aligned. So, drawing was definitely bit of crucial oppositely aligned. So, this or opposite direction. This was the main factor which seems to be seems to be responsible.

Now, let me try to keep this absolute configuration in the similar. So, we can do a better drawing that gives you a much clearer picture ok. So, first we try to put this nitrogen ok, then this is the C double bond O, this is the thing ok. And, then your oxygen here, then this part I put this, you have a gem dimethyl which is gives you the better hydrolytic stability, fine.

And, then now with this part your fine, you have this oxygen will be this initial tetrahydro pyrone will be there. Now, you can fuse the aromatic ring simple here. So, this way you can basically do the drawing. And, now if you do this drawing in this way, see the dipole is here being this and here is this. So, they are oppositely aligned or oppositely oriented ok. Now, the drawing in this way seems to be good and such structural information was quite important.

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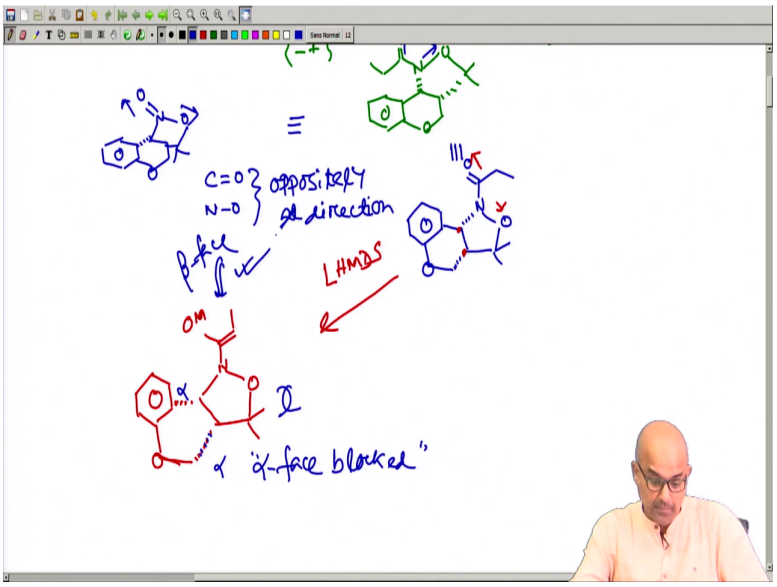

Now, next is your main enolate generation. So, treat with LHMDS, the usual base ok. The moment you have this of enolate generation, so, basically now we will write this N ok. So, this nitrogen you have this, you have this O metal. And, then definitely this is the enolate part ok fine. And, then rest of the part is this oxygen is there and then you have this gem dimethyl part, your remaining isoxazoline part you need to now fuse.

Now, asymmetric induction for that we need to now draw the redraw the structure in different way. Now, redraw means here as this is the absolute configuration of this center will be fixed ok. So, you can just redraw it and you find that this during the redraw the cyclohexane will be this, will be this. So, this will be your cyclohexane part ok. And, by keeping this absolute configuration exactly the same and then you put your oxygen here and now you can fuse your phenyl ring here.

So, this is the way you can draw the structure. Now, this structure once you draw, it means that this is alpha, this is alpha. That basically means that the enolate face, this alpha face seems to be blocked. Alpha face seems to be blocked as this contain say rigid dihydropyrone thing. Now, the beta face of the enolate, beta face of the enolate seems to be accessible ok.

So, alpha face you have this steric crowding, but beta face is accessible. Now, with based on this information or based on this stereo chemical drawing, your entire part you can now visualize.

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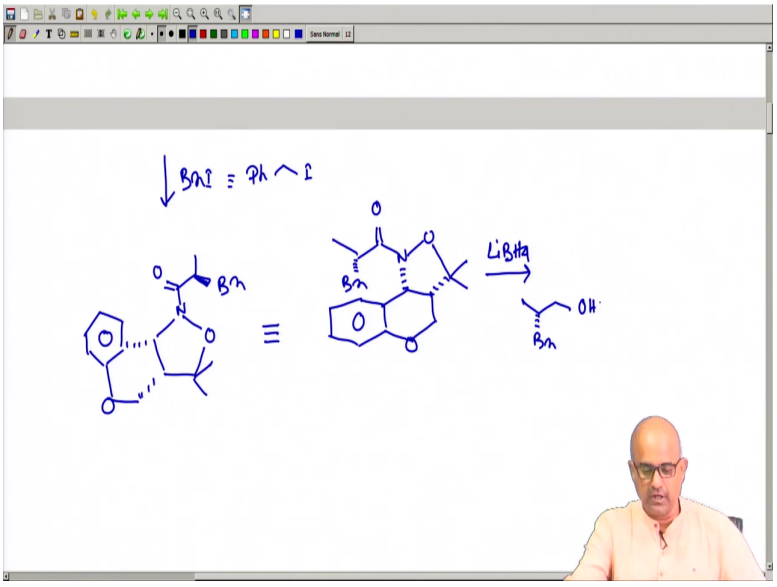

Now, you will let us say we react with a electrophile benzyl iodide. So, which is simple a Ph CH2 I. The moment you react with this compound by keeping everything similar, so, you have a N, you have C double bond O and then you just put that benzyl group on the beta, as beta phase is much more accessible. So, oxygen, this part, this part, gem dimethyl group and then you now draw the structure by keeping everything similar ok. Then you put your oxygen here and then you now draw the aromatic ring ok.

So, this will basically give you the entire compound which if you now wanted to redraw it, definitely you can do the redraw, just keeping the absolute configurations similar. And, just buying just drawing the redraw you can actually try to draw the structure again by little bit redrawing. And, the moment you redraw it, you put the oxygen and then you put this, you put this methyl and then you put N, CO, this, this and basically your benzyl now comes here.

It is basically redrawing these things and that can give you this. Now, once you are done, next is basically the reductive removal or other thing the reductive removal was done pretty nicely by treating with lithium borohydride. And what you will get? You actually get a similar kind of similar kind of product which you usually observed in the case of Evans auxiliary based methods also.

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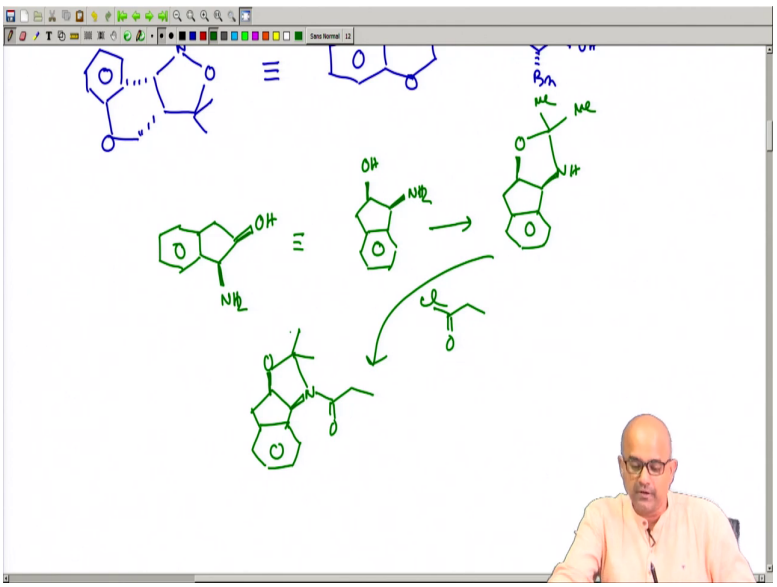

So, Masamune's isoxazolidine based method was usually pretty good. And, similarly based on this Masamune's oxazolidine method, other auxiliary was also reported. And, one such auxiliary we will now discuss which is based on the indanone based auxiliaries. So, this indanone based auxiliaries, which is basically based on the amino alcohol structure and this kind of 1, 2; 1 ,2 amino indanone ok.

Now, let me draw the structure in a different way. So, this was reported by one Indian scientist whose name is Arun Ghosh and we will try to draw the initial formulation with this kind of way, this is the OH. So, 1, 2 amino indanol and then this NH2, both are cis actually.

And, you have a pure enantiomer, enantiopure compound. And, then what was derived from this compound?

You just derivatize this compound, because you need to have this group which will react; sorry, you have a this is the CH2 which will be fine, this, this and this and then it is basically kind of O. And, this will be your NH which was protected as its acetonide derivative just by treating with acetone kind of thing.

Now, this is the compound, this is the auxiliary. Now, this is the auxiliary if you can now see with this auxiliary you react with simple compounds like our propionyl chloride ok, propionyl chloride and everything remains similar. So, take this compound and react with the propionyl chloride.

This part is the N H part. So, your N C double bond O, you can write in this way and this part is the O and you can close the ring and eventually this is having a gem dimethyl group. So, that basically gives you a better hydrolytic stability and like super Quat auxiliaries.

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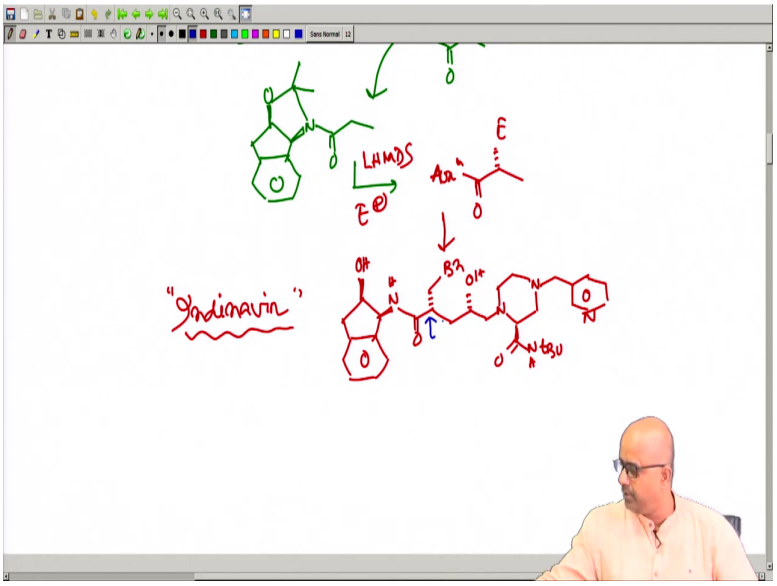

And, then you take this compound and then you react with a base similar like LHMDS or electrophile is your choice. And, definitely as this is completely blocked the beta phase; what we will get? You usually get this CO and then this part, this electrophile comes from the top the bottom phase you can write as auxiliaries. And, you can simply do a do a reductive cleavage.

Now, by this method actually he has been able to report the synthesis of some compounds. And I just do not write the compound name, but this compound is an antiviral compound whose name is indinavir, as he is from India Professor Arun Ghosh who has reported the synthesis of an of this compound, his name is indinavir ok.

Now, indinavir structure maybe I can write it down just for your information when you can get the structures in some of the literature as well as some standard textbook also. So, everything else is remains similar, you have this OH as a potent antiviral compound, this N H is there, this is CO and, then this is your electrophile which is created by benzyl bromide.

And, then rest of the part are some of the other synthetic step was used. It is not only the simple asymmetric you know enolalate alkylation, but definitely other steps are used. But, this is the structure of this compound which seems to be a potent antiviral compound and this part is having a pyridyl group. Anyway, this compound is indinavir and the here this stereo center was created by this 2 amino indanol based derivative auxiliaries ok.

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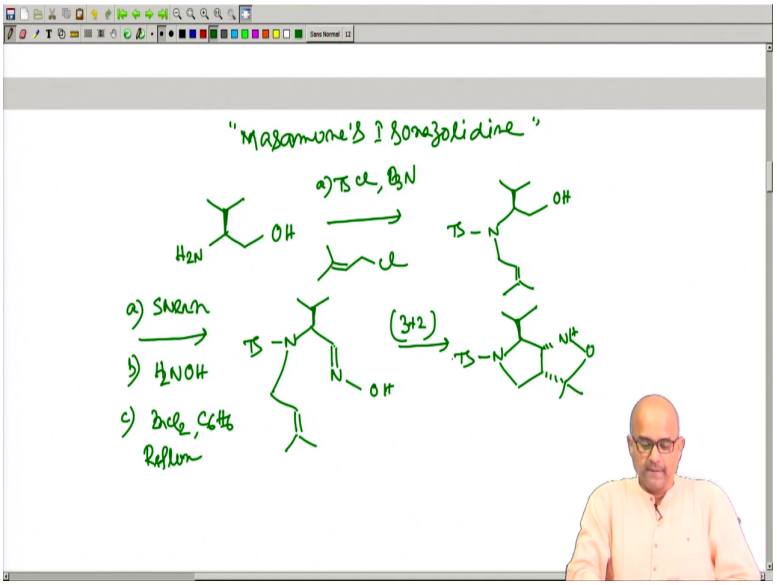

This is this auxiliary are quite interesting and then again we will try to talk about a similar kind of auxiliaries which again are derived by Masamune's; the Japanese scientist Masamune's. And, this time actually Masamune have been invented a isoxazolidine based auxiliaries, but earlier case this was having an amino alcohol; sorry an aromatic part. But, this time he did not have this aromatic part, you are simply having this aliphatic part.

Now, let me talk about or draw about this auxiliary. This is simple compound valinol. Now, valinol was react with tosyl chlorite which is a very simple reagent which usually converts this amine to its corresponding NTs. Because, amine is much more reactive than corresponding alcohol and then this compound was reacting with a prenyl bromide or prenyl chloride.

So, what was initially got first this N, this is the Ts and then this prenyl part is this ok and then this alcohol remains similar. And so, this is part is similar like this earlier reaction, you now will be doing a 3 plus 2 nitrone cycloaddition reaction. So, first he did a Swern oxidation which converts this alcohol to its corresponding aldehyde and then react with hydroxyl amine hydrochloride.

So, what was the compound he got is this fine and then CH double bond N OH ok, oxime thing. And, then you have this CH2 this, this, this. So, now, the point is this auxin part basically gives you 1 2 3 and this is 2 ok. So, this nitrone olefin cycloaddition next took place which was first you have to generate the nitrone by actually treating with the oxime with a zinc chloride. And, you can just treat it with olefin and do a reflux for 6 hours.

Thermal cycloaddition took place and then you actually get a bicyclic compound similar like earlier case. So, everything else remains similar as the valine, this part is there. And, then you have this and then you get this ok and then you have this N H and you have this part O O. It is more or less similar like what we prepared earlier ok. Now, with this compound in hand with this compounds in hand you can eventually now use this compound as the main auxiliaries for other purpose.

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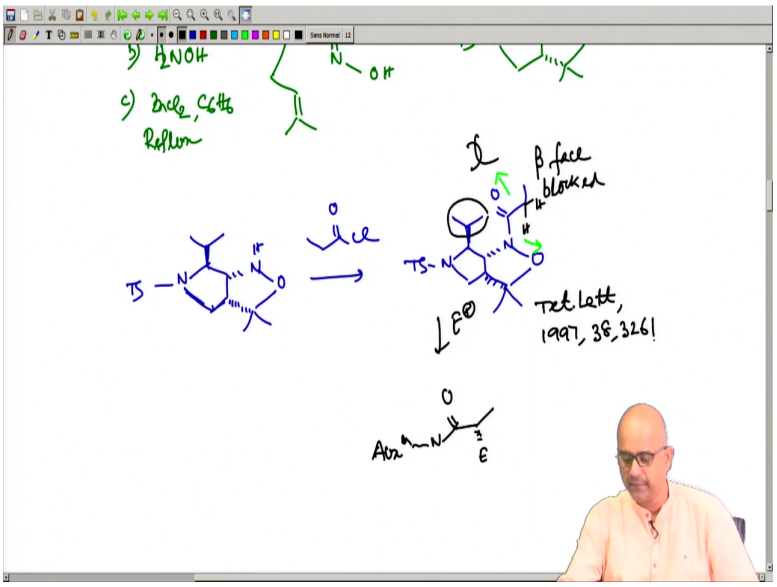

Now, let me try to draw the compound which was prepared just now. Now, this compound in the similar fashion the mode of asymmetric induction was quite important because, you do not have any chelation effect here also ok. So, fine you can now write this.

So, this is the thing fine and then you have this is NH, this is your O, this and this is the gem dimethyl group ok. And, now you react with your acyl chloride which seems to be the normal way. So, TS because here you want to generate the enolate, everything remains similar isopropyl group, your N. Now, C double bond O, this, this and here your oxygen this, this and this is your alpha fine.

So, now you can see that the earlier way this dipole is this way and this dipole is this. So, this would be the most prefer conformation. And, then this particular acetyl isopropyl group seems to be the main chiral controlling element as this is beta, your beta face seems to be blocked. So, electrophile will be attacking from the alpha face. So, now, you try to react in with this some electrophile.

So, you can simply write that beta face is blocked, beta face blocked because you have a bulky isopropyl group right. So, this is blocked. So, alpha attack of this enolate because, this is the 2 hydrogen, we are going to replace so, fine. So, now, you can simply write that this N C double bond O, this and your electrophile and this. So, electrophile is we were adding.

Now, this part is the simple auxiliary which you will removing the auxiliaries. Now, this is a very interesting work and this also reported by Professor Masamune in Tetrahedron Letter Paper in 1997, 38 page number 3261. So, this both the cyclic one and this one was one of the nice example for this Masamune's work. And, actually we can just try to give you a simple example how this compound was synthesized by using this particular thing.

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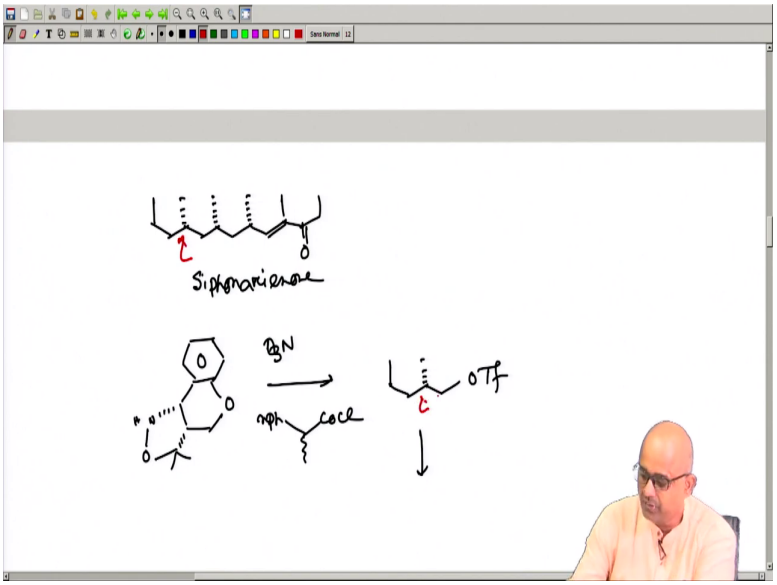

So, Masamune reported an asymmetric synthesis of a very interesting natural product, where you will find that this natural product having all this methyl group are 1, 3, 5 are all syn to each other. And, then you have this methyl, this CO, CH2, CH3. And, this compound was name is siphon aadinoine, that is pheromone compound actually. And now, what we trying to do? I will probably do not write everything in detail.

I will just give you the few claims that how you can synthesize this molecule by using Masamune's aromatic based auxiliary which earlier we talked about ok. So, this is the auxiliary, which was used by Masamune's, your N H ok, then your oxygen and this is your gem dimethyl group, so, which we discussed earlier ok. And, now this compound was actually reacted with a triethylamine and then you react with N propyl and this methyl with COCl. Now, this compound is racemic ok.

So, basically what initially happened? You make this diastereomeric salt and 2 diastereomers are there, because this is the racemic it will be having R and S and this is an enantiopure. So, you get R ,R or you get S, R. So, you can just separate the diastereomers and then you

normally separate it. And, then you once you do the there is no actually further reaction just this is this used as a reducing agent, sorry the resolution agent.

And, then you actually get this kind of compound where you convert the OH to triflet. Now, this is one of the electrophile for the subsequent step. Now, this compound you can see the first methyl was fixed. If you check this compound, this compound is having 3 methyl. So, first methyl was this is fixed. So, this is the first methyl, first methyl, this is the first methyl.

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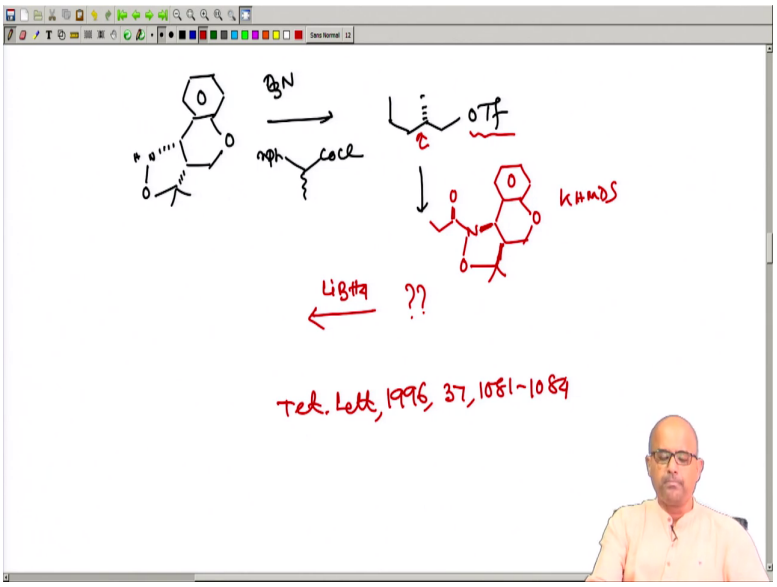

Now, take this compound with you and then you now apply the second step in the synthesis which is also now the Masamune's enolate alkylation method. Now, you take the other auxiliaries depending on your choice which stereo center you want to create. Now, this part you have to actually look it very carefully that which stereo center you need to create; so, N CO CH2 CH3.

Now, this triplet you have to generate the enolate. So, actually you treat with KHMDS ok and this is the electrophile. So, this is the leaving group, ok. So, you need to predict what product you will get. So, this is this you have to do it ok and then you next you remove the auxiliaries by simple treating with lithium borohydride.

So, what will be you will be getting that you have to write. Now, this thing you basically you need to do the practice and you need to take care. Now, this entire synthesis was reported in Tetrahedron Letter Paper which was published in 1996. If you are not getting those

references, you can let me know and I will basically help you to sending those references from my personal account ok.

And, this is usually the synthetic application of Masamune's method and this gives you a pretty good asymmetric induction in most of the cases.

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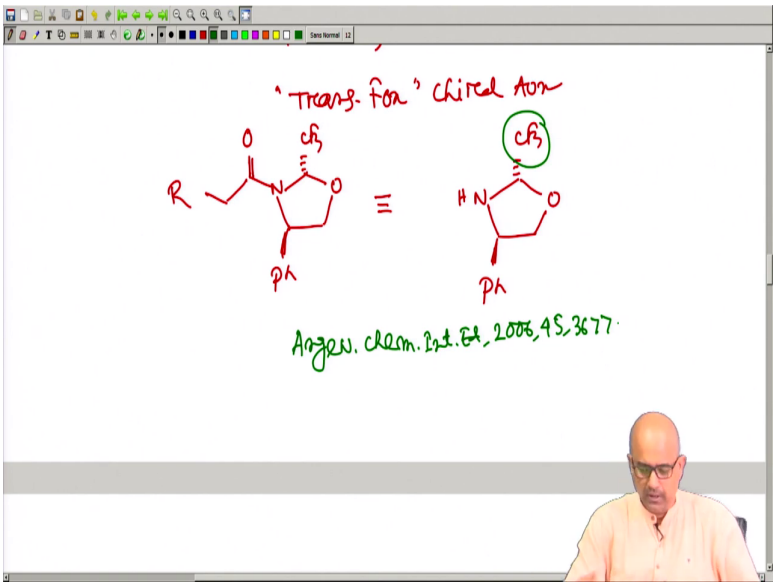

We will stop the lecture by just talking about one such thing which we just now called as a trans-Fox chiral auxiliary. Now, this trans-Fox chiral auxiliary was more or less a similar auxiliary, which was again coming from the structural variations of Evans. But, here the chelation was usually derived from a CF3 group, not the corresponding amide group. So, such structure was usually this kind of structure ok.

Now, this trans-Fox base auxiliary which are normally prepared from a different way, this auxiliary is having a general structure. If you now try to write the general structure of the auxiliaries which is also commercially available but, you can make it in the lab NH CF3O and then this with this, with this Ph. Now, see this is only difference is similar like Evans oxazolidinone, only difference is this CF3 group.

So, this was quite interesting, but obviously, as time may not with us; so, you can just give it a try in the corresponding references. It was reported in Angewandte Chemie International Edition and this was reported in 2006. So, this is quite interesting, but I can just give you the as mode of asymmetric induction how this reaction occurs ok.

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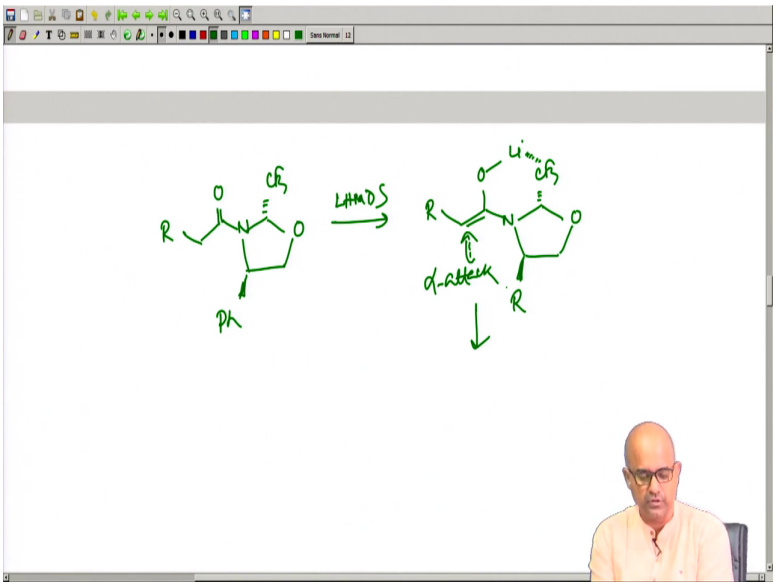

So, initially what happens? So, initially if you see this structure gives you a N C double bond O, this with R, then you have your CF3 with oxygen, with this phenyl ok. The idea was you treat with base definitely LHMDS and it has been found that this after the metal enolate generation, this lithium usually creates a chelation with this CF3 group.

So, fluorine being a very electron negative, it basically helps one of this fluorine out of the CF3; there will be definitely some chelation. So, that was the main idea for this entire thing. The mode of asymmetric induction will be definitely opposite. So, it will be alpha face attack, because beta face is blocked. So, alpha attack ok.

And, the reductive cleavage everything is kind of similar and then you can actually remove recover the auxiliaries in this way. So, anyway we will be talking some, we will be discussing few more interesting auxiliaries in the near future.

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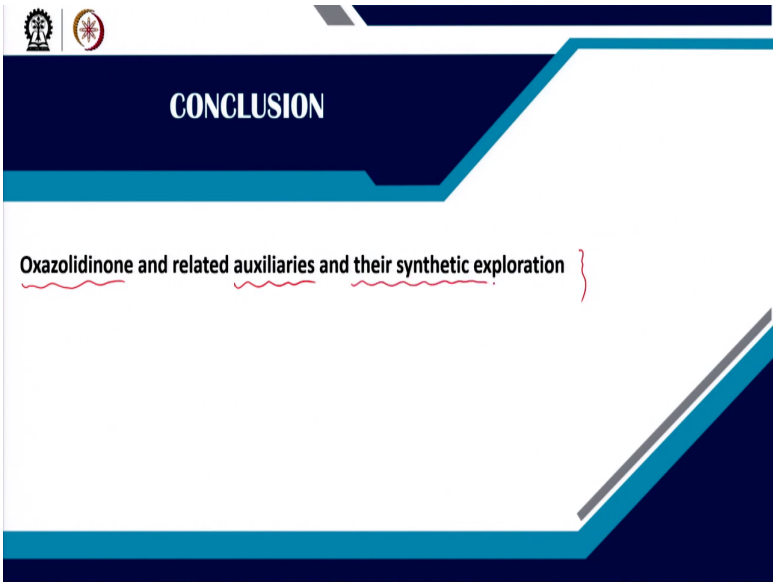

So, as a concluding remark we can say that many oxazolidinones are found their synthetic applicability in the asymmetric enolate alkylation and particularly the idea was initially started with Evans. And, such oxazolidinones have been structurally modified by several other researchers and numerous auxiliaries have been designed and synthesized.

And, they are all reported in the literatures and their synthetic expedition was definitely quite well known. And, they basically give you very nice stereo control in the enolate alkylation. In the subsequent section, so we will be coming with few more things.

So, thank you for today and thank you for listening me.

Thank you.