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 - 17
Camphor based N-acyloxazolidinones as chiral auxiliary

Welcome back everyone. So, this particular module which is the continuation of earlier module of Enolate alkylation. Today, in lecture 17, we will be mainly talking about Camphor based N-acyloxazolidinone as a chiral auxiliary.

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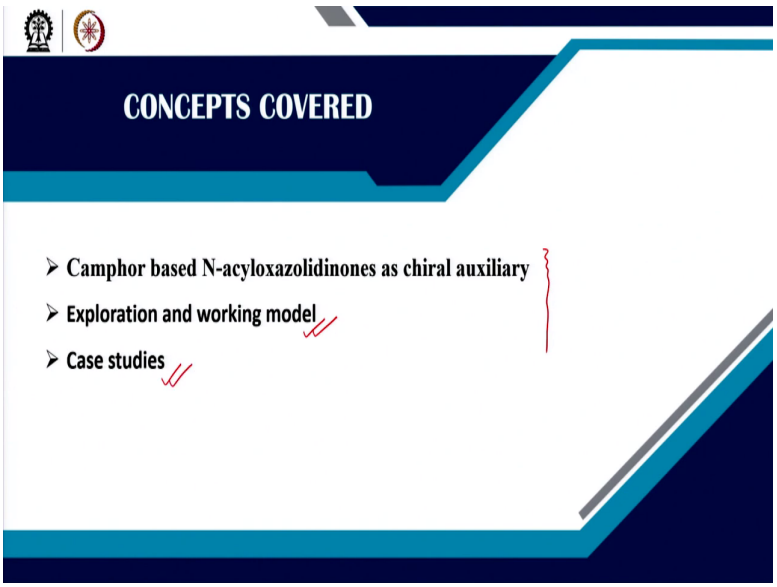

So, in this lecture our main content will be camphor based N-acyloxazolidinone, its structural features and how you can synthetically manipulate this auxiliary for enolate alkylation in asymmetric fashion. We will be mainly talking about its working model, what is the mode of asymmetric induction and particularly case studies, where such auxiliary based asymmetric alkylation was used for a natural product synthesis.

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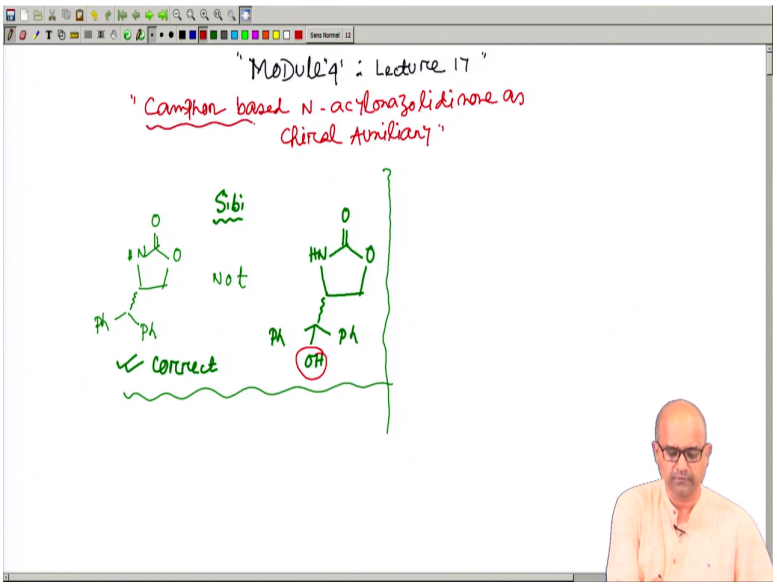

So, today we will be basically talking about lecture 17 and particularly in this module, we will be continuing our discussion on the enolate alkylation of oxazolidinone based systems and we have discussed in the last class couple of higher order oxazolidinones which are mainly inspired by Evan's oxazolidinone model.

And actually there is a small mistake in the last class. So, we talked about a oxazolidinones which was developed by professor Sibi; the correct structure is this one, where there is no hydroxy group appended here. But most probably in the lecture, it was drawn that a hydroxy group was present. So, please excuse me…….. I am sorry for that; the hydroxy group will not be there in the correct structure ok. So, now in the last class, at the end of the last class, we are basically talking about some N-acyloxazolidinone based auxiliary which are camphor based ok.

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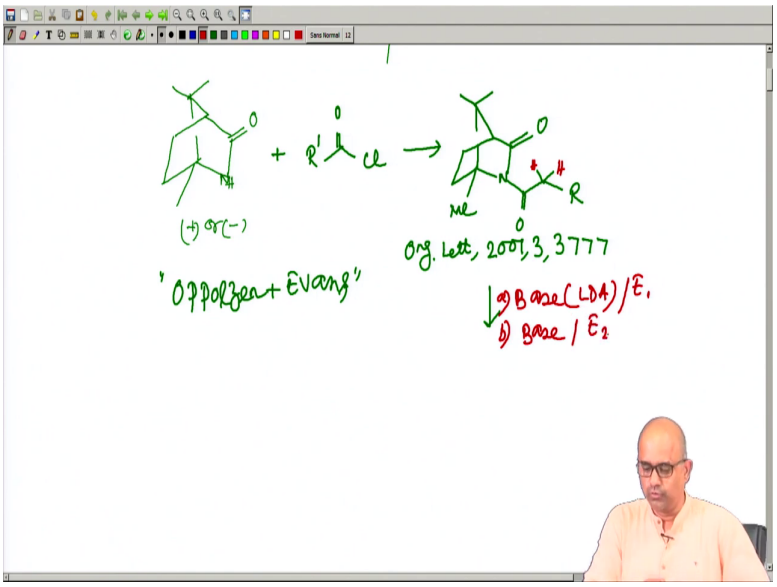

And this auxiliaries, we will be going to discuss in today and particularly, this auxiliary if I draw the structure, you will find that these structures are pretty unique and also in the last class, we said that these auxiliaries are mainly inspired from the design of Evans as well as Oppolzer.

Because in the Oppolzer's, main auxiliary is camphor based auxiliary and Evan's auxiliary is oxazolidinone auxiliary. So, this is kind of a camphor framework. But in the camphor framework, a nitrogen was deliberately taken here and then, this was kind of the amide and this kind of compound was initially chosen as the main precursor.

So, any of the enantiomer either plus or minus which we will discuss little bit later on; but first try to talk about the design aspect. So, this compound, it basically served as a the oxazolidinone precursor. Now, as you can easily imply it or easily find that these auxiliaries initially you have to couple with corresponding acid or acyl derivative. So, once you try to covalently attach your compound which we will be trying to do the enolate alkylation, whose structure will be something like this.

So, here you have this acyl group linked ok; something like this, definitely because you need to have a abstractable hydrogen. So, this is the compound which was now this result was initially reported in *organic letter* paper which was published in 2001. As I said this was mainly inspired by the work of Oppolzer as well as Evan's. So, in principle this is a basically

combination of Oppolzer's camphor based auxiliary, whose drawing we have earlier shown to you and Evan's the very famous Evan's auxiliary which also we have shown to you.

Now, let us see once you have this auxiliary, this particular auxiliary, what you can do ok. Now, this auxiliary is there with you fine and then definitely you would like to do the hydrogen abstraction. Now, hydrogen abstraction, we can use the different color pen yeah.

So, this will be the abstractable hydrogen which usually you can be abstracted by base, normal bases like LDA or other bases and then, actually you can do a two round of successive alkylation. So, let us say first you use base LDA and you use an electrophile one and second, we use similar base and then, you use electrophile 2.

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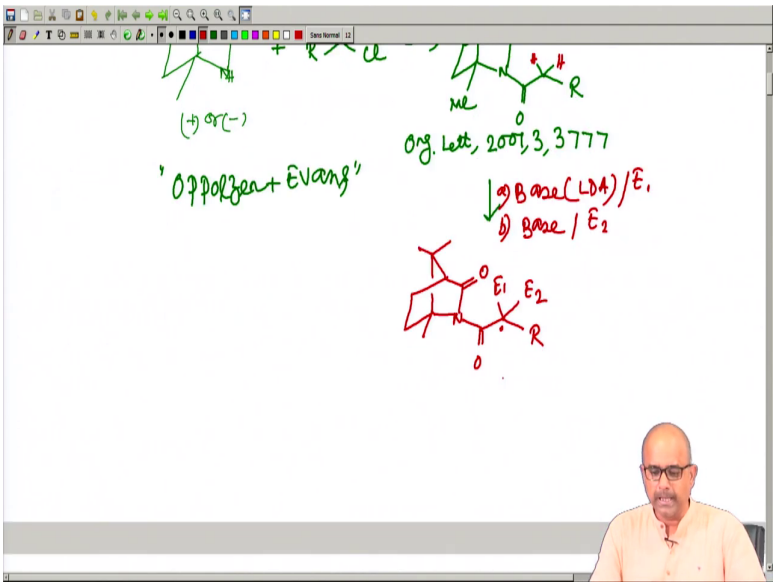

So, two carbon electrophile bond, you can actually create the mode of asymmetric induction and other technical details, I will be sharing with you just in a short while. So, you can easily say that this will be your NCO and 2 hydrogens will be abstracted, you get 2 carbon electrophile bond ok. Now, so, you are basically having a quaternary stereo center at this point; then later on, you can remove the auxiliaries. This is one of the way you can functionalize this auxiliary.

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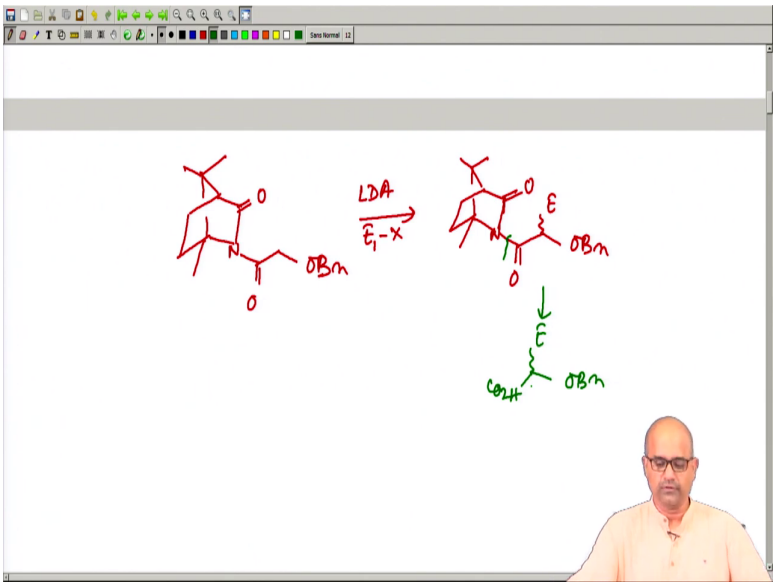

In addition, other way also you can functionalize which is very simple, we earlier did similar kind of exercises. If you remember the Evan's part, we actually have performed some alkylation of this kind of substrate which is nothing but a glycolic acid compound ok.

Now, here also similar thing and you treat with a base like LDA and react with a simple electrophile E1 with a X means a leaving group and you will find that you can basically alkylate the corresponding glycolic acid and later on this glycolic acid, you can remove the auxiliaries. And once you remove the auxiliaries, what you will get? You will basically cleave this bond and you can end up with simple lactic acid kind of derivative. Anyway, this was the synthetic part. Now, we will be explaining what is the origin of asymmetric induction for such auxiliary.

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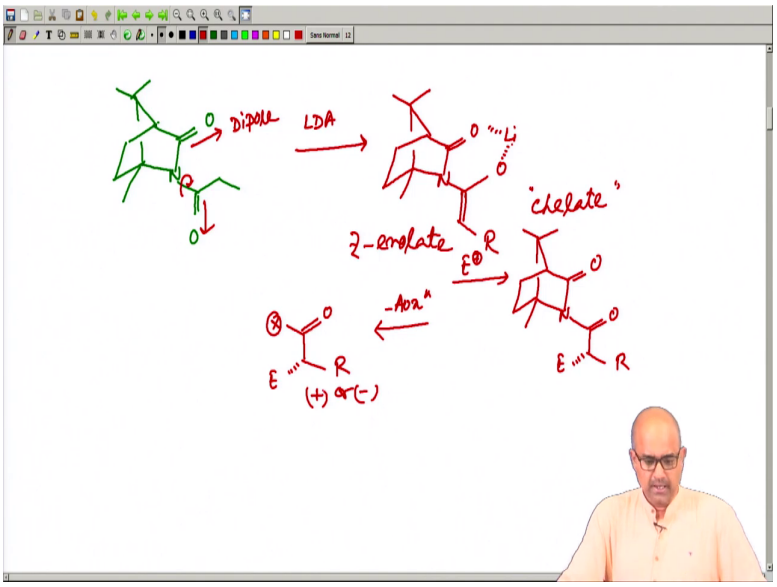

Now, let us start with initial auxiliary and both the auxiliaries, you can synthesize in the lab or even you can make in the lab. So, first try to draw one auxiliary first, whose structure is the camphor part; I mean kind of camphor part, then you have this carbonyl here and you have this N here ok.

Now, you put the acyl group here. Now, you can easily see that by based on our earlier assumption, the dipole CO dipole is this way and this CO dipole is this way. So, dipole-dipole repulsion will definitely try to give this conformation as a major conformation. But fine, but as like earlier cases, we have to consider the chelation. So, now you treat with a base LDA ok.

So, the moment you try to put the base LDA that basically will force your compound and now, you will see that this particular bond will undergo rotation and rotation means then you get enol. So, usually, Z-enolate was the major product which you can explain through the Ireland model.

Now, see here you have to consider the rigid chelate. So, this is the rigid chelate is formed. The moment you form the rigid chelate, so now, you can you have to identify that which face of the electrophile is easily accessible. Now, you see, I will just try to put a reaction arrow and the electrophile. Now, definitely the camphor, the top face seems to be the blocked. Now, let us come to the model.

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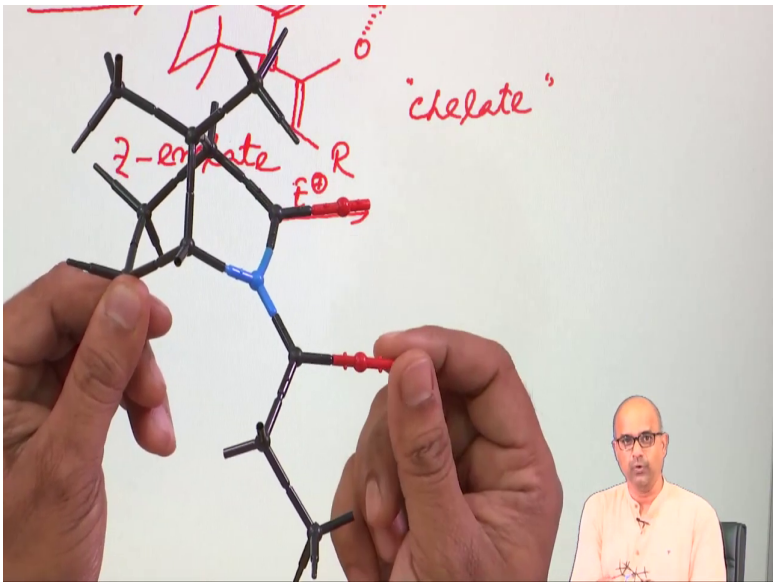

So, you can see that here the structure which I have drawn, it is basically you can visualize it as a ball stick model. The red color on this part is the CO initially and then, this is another CO. Now, here the initial structure was something like this which basically minimize the dipole-dipole repulsion ok. This is opposite. Now, the moment you have this base, it forms the chelate. Now, you see you get the chelating thing. Now, the enolate, once you have the enolate, you will find that the top face of the enolate seems to be blocked by this 2 gem dimethyl group ok.

So, this two gem dimethyl group will be blocking the top face of the enolate fine. So, now, with this information in the hand, so now, you can easily try to formulate that what structure of the alkylated product will you get. So, everything remains same; you have N, you have C double bond O, C H2R and enolate will be coming from this E ok. So, after you take these things and you if you can now remove the auxiliaries, this is similar like other way. So, what you will get? You get this CO, this R, this is the carbon electrophile bond and just write any functional group X. So, you can basically get different kind of…….

So, this enantiomer, you will be getting either plus or minus depending on which auxiliary you have taken. Eventually, the initial auxiliary which you have drawn, you can get the corresponding enantiomeric auxiliary whose structure also we can just write.

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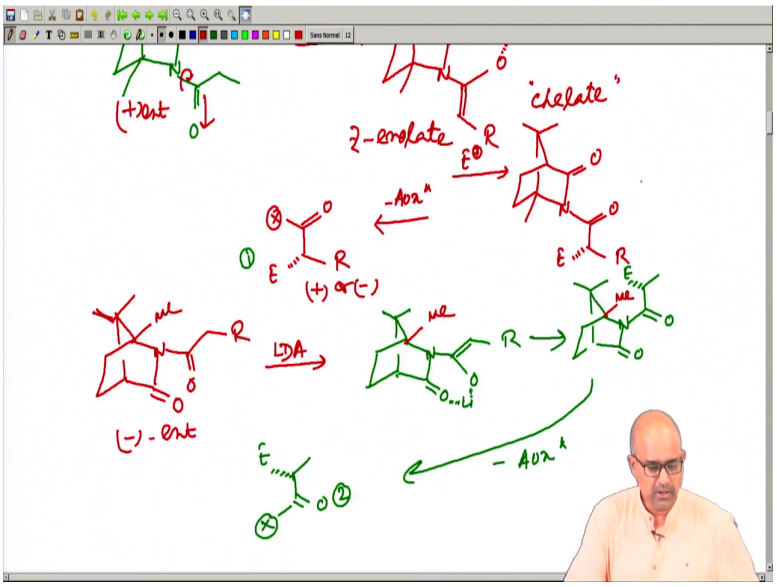

And everything remains same, but the top auxiliary or the green color auxiliary seems to be the enantiomer of the red color auxiliary. Now, the nitrogen will be here and the CO is here and this CO and CH2R. Now, both the dipole was we just put it in like this way. So, if this has to be plus enantiomer, this will be the minus enantiomer because you see the red compound and green compound are basically enantiomeric to each other.

Now, exactly for these things, you do the similar kind of reaction with LDA and here, also you will find that the enolate, after the enolate the electrophile will approach always from the below face. So, you can eventually try to draw the entire thing your dimethyl this, your N, you have this O, then your double bond, your R, here is your another CO and you basically get the metal chelation. So, everything remains same like as earlier.

Now, in this case, let me go to little bit above, but you can just make it short way. So, once you try to have this one, you everything was as it is; your nitrogen is here. You have this C double bond O, this, this and carbon electrophile bond is below. Now, from this green color thing, if you now extrapolate by removing this auxiliary means minus auxiliary. So, what we will be going to get? You get C double bond O, this your methyl; I mean any other group and you have this electrophile. So, this is EOX.

Now, compound 1 got in the earlier, compound 2 here. These are basically what? These are basically enantiomeric to each other. So, you can see that by choosing proper enantiomeric

auxiliaries, you can eventually access both the enantiomers of the alpha alkylated product through enolate alkylation.

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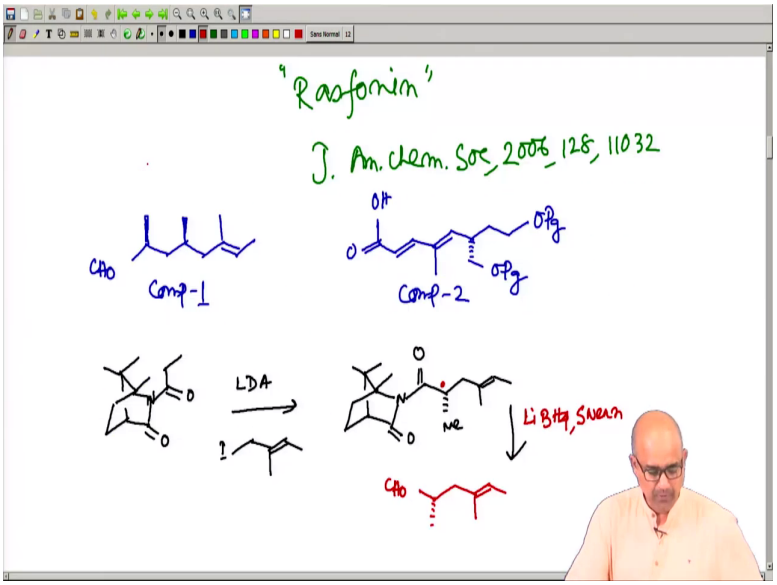

Now, this particular method was very much helpful for total synthesis of a molecule; the molecule structure we are not going to discuss. This molecule name is Rasfonin and this was reported in the synthesis was reported in a reputed journal '*Journal of American Chemical Society'*. This was reported 2006 is the volume number page number is this.

Now, in this particular paper, they have been using this enolate alkylation for preparing two fragments by this N-acyloxazolidinone based alkylation and the structure of this fragment, I was first trying to draw it; this is one fragment and in the another fragment, the structure was this. Anyway, we will just try to show you that how this method was applied to create these things. So, OP is basically the protecting group. Now, in this case this 2 methyl stereo center was created and in this case this stereo center was created by this enolate alkylation method. Now, let us see how it was done.

In the initial case, we for the compound 1, we write compound 1 and this is compound 2. Let me use a black color pen. So, the auxiliary which was chosen by professor Boeckman. This auxiliary was derived by professor Boeckman.

And let me try to draw the auxiliary, this one this C double bond O, this is N, this is CO, this is these things ok. So, this auxiliary was initially taken, but then everything was similar. You

can just apply the earlier working principle and base was LDA. Now, what is the electrophile? The electrophile was usually having this structure. So, the moment you have this electrophile, you do this reaction and your mode of asymmetric induction followed through a similar pattern which we have explained earlier.

And actually you will get this N CO and then, we put it methyl here and this is you get this compound. Anyway, this you can just try to visualize why this compound was generated. The origin of asymmetric induction you can basically explain through the earlier model. Now, this auxiliary was cleaved by reductive cleavage by lithium borohydride and then, we do a Swern oxidation. Then, what we will get? They basically get this aldehyde ok. So, this aldehyde was this one.

Now, see this is basically we are talking about this stereocenter, you can just invert it, you get the same compound. Now, probably in the earlier drawing, we did some mistake. Yeah, in actually this part, we did some mistakes. So, I am sorry for that. This methyl will not be here; this methyl will not be here because the enantiomeric one. So, this methyl will be at this point; this is the methyl. So, such silly mistake usually happens; once you are trying to draw the structure in the board, it usually ok; this is the methyl and fine.

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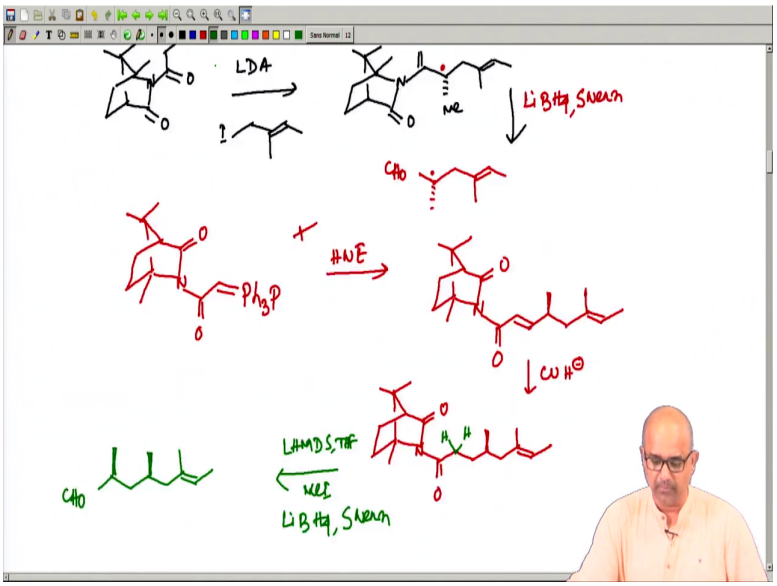

Now, once you get this aldehyde the moment you get this aldehyde, this aldehyde is actually this stereo center we are talking about. So, this stereo center can be created, but fine that this this stereo center you just keep it like this with the aldehyde and then, you can I mean

professor Boeckman applied another round of alkylation by taking the other enantiomeric auxiliary by taking this compound. But this compound initially, he actually takes some Wittig ylide. This compound was can be easily prepared.

Now, this Wittig ylide and this aldehyde was kind of condensed through a Horner Wadsworth Emmons Olefination and this compound was initially if you try to do the Horner Wadsworth Emmons Olefination, you do the reaction and let me try to draw the structure, what you get? You get this N CO, this CO was there, you get the corresponding double bond and then, the stereochemistry was here; the stereochemistry which we have generated earlier through the alkylation fine.

Now, here is an interesting reaction because it is alpha beta unsaturated double bond, you can actually reduce through copper hydride system; only alpha beta unsaturated double bond will be reduced, the isolated double bond will not be reduced. That is the chemo selective reduction of the alpha beta unsaturated double bond, which you might have came across in your UG days.

Now, why it was done because you need to do the next round of alkylation. So, now, you can see the next round of alkylation was the set was ready because now you have this two hydrogen which you can do the enolate alkylation. So, first abstract the hydrogen through a base LHMDS was used and THF was solvent definitely and then, based on the structure what electrophile you need, you check the structure.

So, this part is this part; this methyl double bond, you have one methyl; you need another methyl. So, definitely the electrophile has to be a methyl iodide ok. So, the moment, you do the methyl iodide, you basically do the methyl iodide. So, methyl will be coming here and the rest of the state steps are very simple; you do the same lithium borohydride and you do the Swern oxidation. So, what compound you would next get? Actually lithium borohydride will just remove the auxiliaries. So, you will definitely get the required desired compound which we have initially drawn a methyl beta, a CHO, another methyl beta, this, this.

So, this is one of the intermediate which was prepared by applying this method and this was really a nice way of exploration for another intermediate which also we have drawn it here, the second intermediate this particular intermediate was also prepared through this asymmetric alkylation mode.

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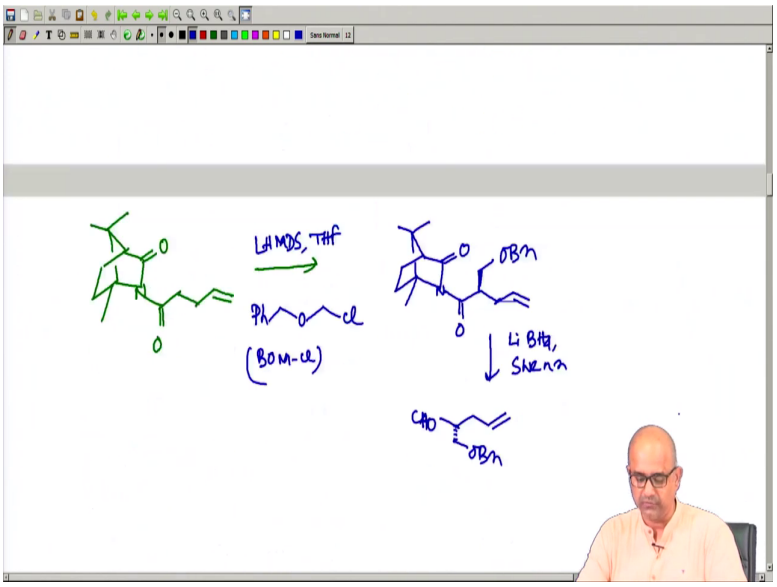

Now, how? For that purpose, professor Boeckman took this auxiliary, the one of the enantiomeric auxiliary which was available, this auxiliary ok. This auxiliary was first coupled with corresponding acid chloride; this acid chloride ok. So, this acid chloride was there.

Now, you go to the earlier part what was required basically you need mainly this stereochemistry ok. So, electrophile will be kind of this hanging group ok. So, what electrophile was chosen that was the important thing and the electrophile first is the base because LHMDS was your preferred base THF as a solvent and the electrophile was a bom chloride Ph CH2 O CH2 Cl. This is abbreviated as bom chloride which stands for benzyloxy methyl chloride ok.

So, now once you try to do the alkylation, you will eventually get this alkylation that model which already we explained with the model through the chelation mode. So, we write this this fine and so, your bomb group it was here OBn ok and then, this compound was again reductively cleaving the auxiliary by lithium borohydride and then, you do a Swern oxidation as earlier. So, you will see that this compound will now generate a CH2 OBn and this part you have this ok and then, you have a CHO here.

So, for the stereo chemistry, the required stereo chemistry was being created and later on, further functional group manipulation, we can actually do it and that should not be a big issue. You can see the structure what was required. The structure required was actually a

hydroboration and this part was normally done by a Wittig olefination Wittig olefination. Anyway, so with this information, we can just next continue the steps.

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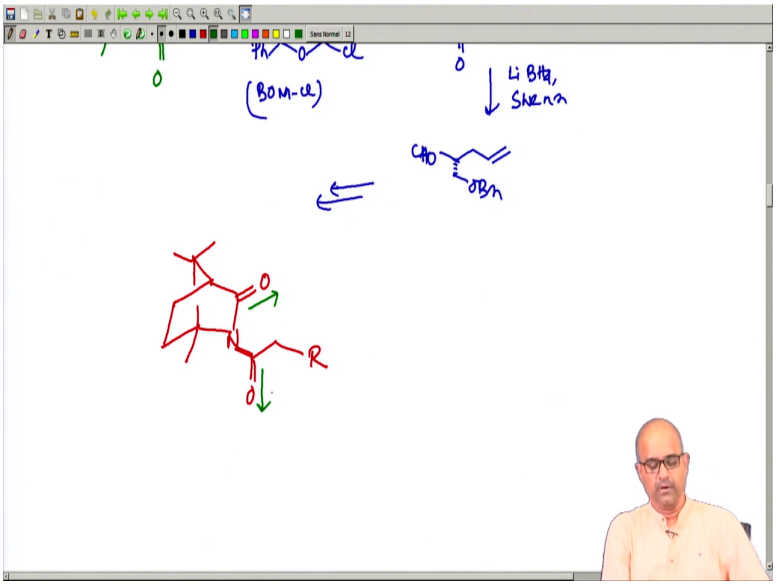

Anyway, these steps are pretty simple probably; I am not going to do it. So, what I am trying to say that such auxiliary based on camphor derived in N-acyloxazolidinone which the base structure was mainly this kind of thing which was actually an amalgamated or amalgamation of this Evan's as well as Oppolzer thing. So, this was the main structure of the auxiliary. And the model which through for the reaction proceeds is basically the chelation control model because normally if you try to again analyze, this is the dipole is oriented in this, this dipole is oriented in this ok.

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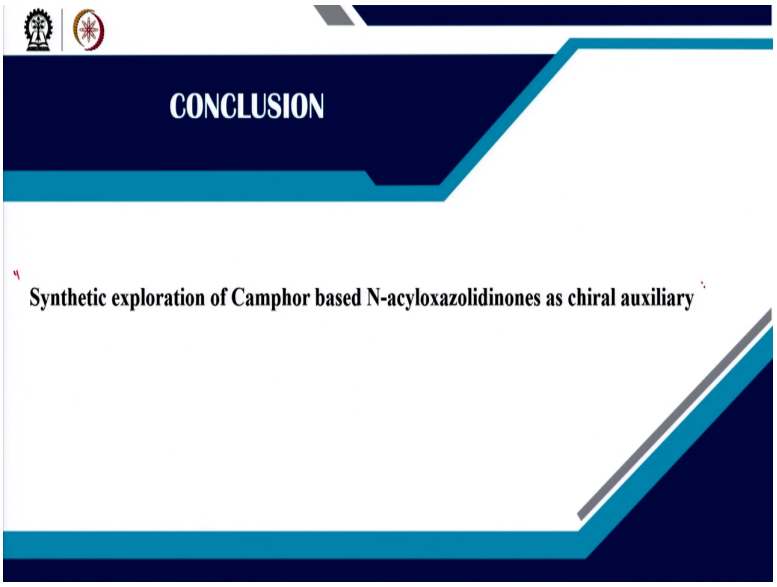

So, as a concluding remark, we can say that such oxazolidinone which seems to be a combination of Oppolzer's Camphor based auxiliary as well as Evan's oxazolidinone serve as a very good useful synthetic tool and you can actually control the enolate alkylation in the asymmetric fashion by using such auxiliaries. So, we will discuss about some other auxiliaries in the subsequent lectures; till then.

Thank you and goodbye.