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 - 16
Helmchen's auxiliary, Oppolzer's sultam based auxiliary

So, welcome back everyone. So, this module is left 4 and particularly in the beginning of this module which is lecture 16, we will mainly talk about couple of interesting auxiliaries which is the first one will talk about Helmchen's auxiliaries and Oppolzer's sultam based auxiliaries.

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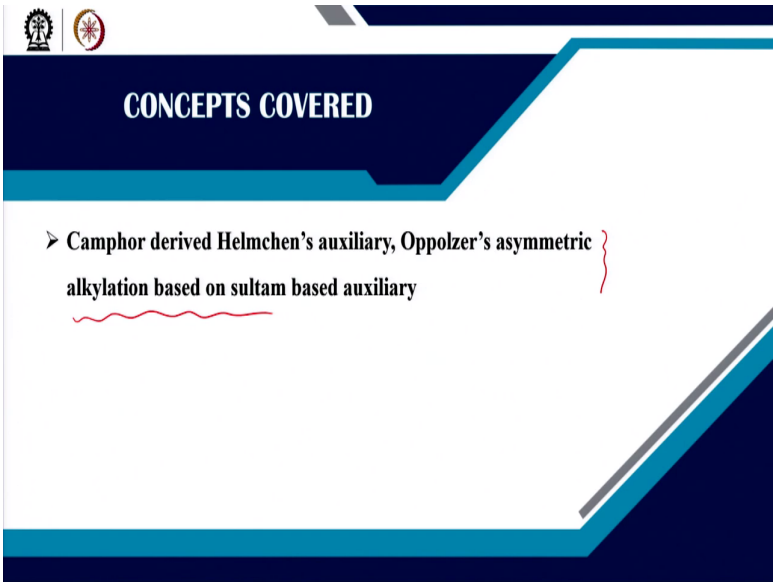

So, main content will be covering through these two auxiliaries. And, probably at the end we will try to talk about the Boeckman Junior's auxiliaries which is also basically a camphor derived auxiliary ok. So, let us start.

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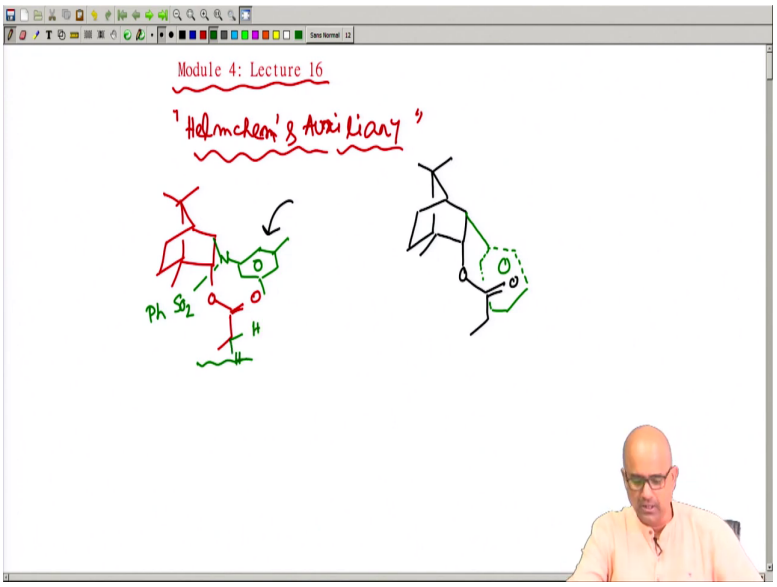

Today, we will going to start a new module, but definitely in the this particular lecture 16, we will be mainly discussing Evans oxazolidinone we have already talked about. But, it is not exactly the same auxiliaries, but first we will try to talk about auxiliaries which is derived by a German scientist whose name is Helmchen.

And, this Helmchen's auxiliaries was camphor derived auxiliaries, I am sorry just give me a time. This Helmchen's auxiliary, let me just try to give you a. So, this auxiliary was derived from a camphor based starting material and it usually gives pretty good selectivity. Normally, the this is also kind of a carboxylic acid derived structure which are condensed with the camphor based auxiliaries.

And, this is normally an ester based precursor where esters are treated with base and then they generate the enolate. Now, initially this could be a camphor based things and then at this point you do have a O, this C double bond O and this thing. So, this part is your initial precursor where from you will generate the enolate fine. And, now this auxiliary also does have a couple of other structural patterns, write in a different color.

You have a nitrogen; with this nitrogen you have a sulphonamide thing; SO2 Ph ok. And in this part, this is basically having an aryl ring ok. This aryl ring means a methyl and a methyl. Now, this structure in a two-dimensional fashion is very difficult to visualize. But this pyrene, this pyrene and this CO are basically top to bottom stacked one another. I mean if you can see it, let me try to give you a view in this way that this.

So, this is the O, C double bond O and this and this aryl ring here was kind of having this kind of. It means that the it is kind of a two-layer structure. The first layer is the O O C O. In the back side this aryl ring occupies. It is kind of a two piece of sandwich of the bread ok. This is the top layer and this is the bottom layer. Now, fine now what Helmchen's did? He first synthesized this kind of sulphonamide derived ester ok. So, this O O CO part. Now, you have this 2 hydrogen which you can abstract with the base for the enolate part ok.

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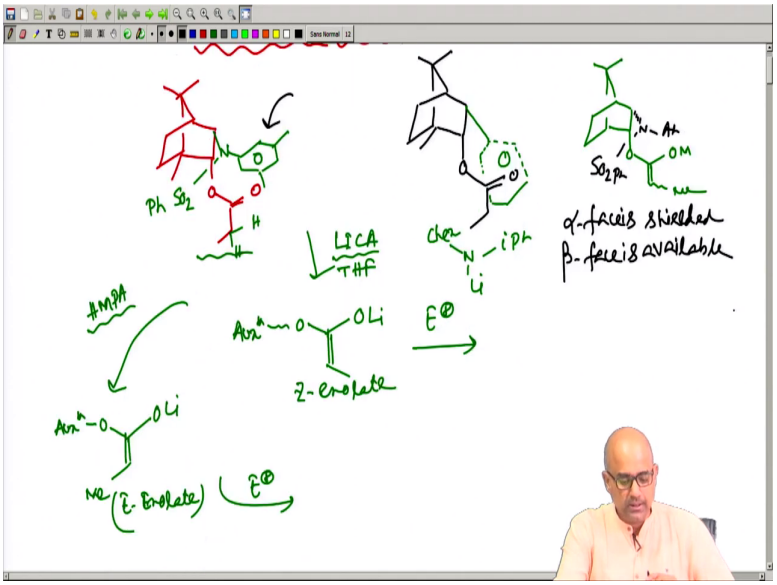

So, now let us take this first this auxiliary and you; what it with the base? Usually, the basis which was taken by Helmchen's is a LICA; LICA means Lithium, Isopropyl and this part is your Cyclohexyl with the Amide. Now, this base we already we have knowing it. Now, first you react this base with a LICA and THF solvent. If you remember the Zimmerman Traxler transition state sorry the Ireland model, in normal cases you get the cis enolate.

So, now, this part is the enolate. So, basically what you will get? You get this methyl is here, you have this O Li, O Li means the enolate and then this and this part is your another O with the auxiliary. So, this if you can now check the CIP thing; so, basically this is basically you are give you the cis enolate or the now this is one enolate.

On the contrary, you can actually take a more coordinating solvent with HMPA and HMPA basically solvates excess lithium as a counter ion. And, by changing the solvent, you eventually can generate another enolate geometrically different. You take this and then you take this. Just positioning the methyl in one case is cis, one can be trans with the auxiliaries.

Now, these two enolates have been generated fine. Next part will be yours. So, this I will write let us say this way I write as a Z enolate. If you I did not count the cis or the CIP rule, anyway CIP rule you can apply. So, one will be Z, one will be fine; that is for sure. Now, electrophile I will be now reacting with both the cases. Now, the point is the electrophile will be approaching from which face that will be governed by the existing stereo centre of this thing.

Now, here you can find that as more or less it looks like that the alpha face of this enolate, like you have the enolate generated here. The top face you basically have that two gem diethyl group, but the bottom face we will write it again. Bottom face means the endo face of the bridge bicyclic thing. So, this is your enolate part which you can simply write O and then this is the O metal and this is the typical geometry you can write ok.

Now, here you can see that this is an endo part. You have a N, you have a sulfonyl group, pretty bulky sulfonyl group SO2 Ph and you have a N aryl. So, this is basically blocked the alpha face ok. So, now you can write the alpha face is shielded. Alpha face is always shielded by this bulky N CO2 Ph group. So, beta face of the enolate is available, beta face is available.

So, this was the main factor. Now, in this case whether Z enolate or E enolate both will let the electrophile will attack from the beta face. What could be the final stereochemistry?

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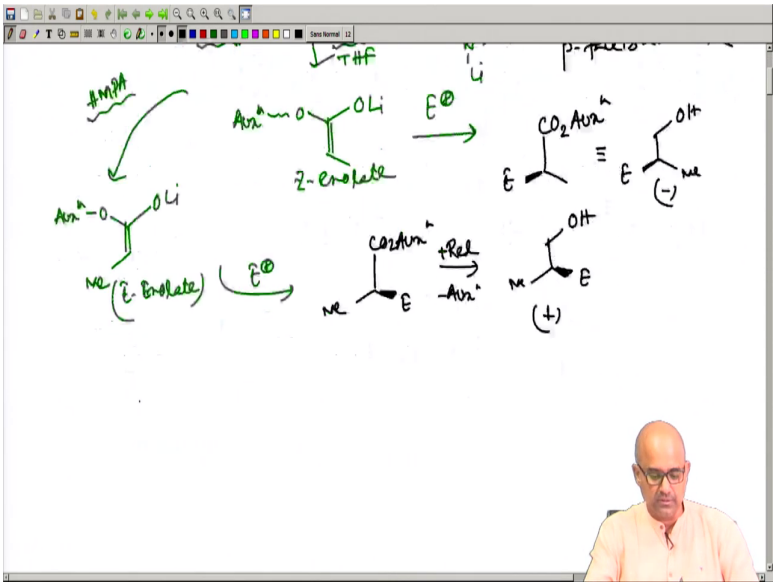

So, in this case now, we can write that the enolate the way we have been written this. So, a methyl is here and then your electrophile will be like this ok. And, then after your everything you can remove it. This will be your auxiliary means, CO2 auxiliary. This part you will be removing it ok. So, you get 1 enantiomer and now let us see what could be the you can do a simple electrophile. So, you can remove the auxiliaries by a reductive cleavage. So, Me ….E and let us say you get a CH2OH fine.

Now, in this case the enolate was drawn in basically this way. So, methyl will be in this way fine. You have your E, means electrophile and this part is the same CO2 auxiliary. Now, the next is reductive removal, you can do it reduction. So, auxiliary is getting removed. Now, let us see what will we get? You get methyl, you get this electrophile CH 2 ..H. Now, these two compounds, these two compounds are same or these two compounds are different.

These two compounds are basically enantiomeric to each other ok. See these two compounds are enantiomeric to each other. So, means if you get 1 enantiomer plus here, you get a minus enantiomer here. So, eventually the enolate geometry has a role because, means that the enolate geometry means this methyl is positioned in this way. So, electrophile trajectories from this way, for Z enolate methyl is this way. So, electrophile trajectory is this way, that basically will give you that the feature or the main feature is enantiodivergent. Sorry, let me just do the little bit.

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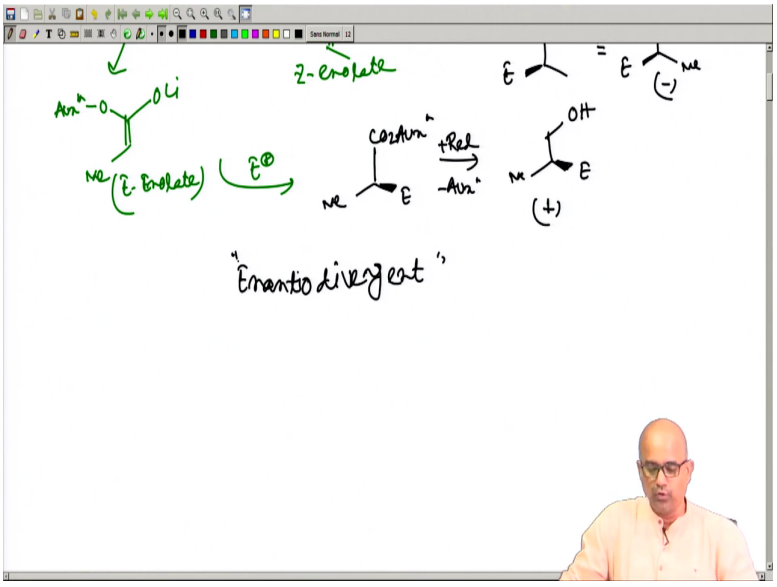

So, this idea is enantiodivergent means that both the enantiomer of the target molecule you can access by controlling the geometry of enolate. So, this gives you a pretty good idea and Helmchen's auxiliary was mainly followed by this principle ok. I hope it will be quite clear to you.

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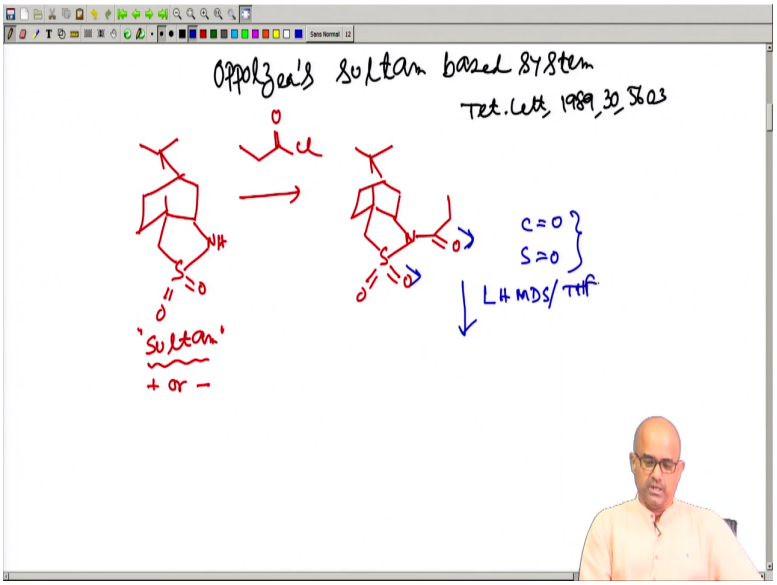

Now, next we will be trying to discuss a similar kind of auxiliary which was again derived or devised by Oppolzer. And, this is named as Oppolzer's sultam based auxiliaries. Now, in the Oppolzer's sultam based auxiliary, sultam based system. This was also very good auxiliaries. This was first reported by Prof. Oppolzer's in *Tet Lett* paper in 1989. The volume was 30 and page number was 5603.

Oppolzer system was very similar, let me draw the sultam first. Sultam actually a camphor derived compound and this is basically a sulphonamide. And, the sulphonamide was judiciously chosen mainly due to the fact that this one of this sulphone oxygen can undergo chelation. So, this is the sultam and sultam is commercially available or even you can buy in the I mean you can make the compound in the lab. Sultam plus or minus, both the enantiomers are available ok.

Now, take any of this enantiomer and then you react with a similar acid derived acid chloride or something, the same way we do in the Evans method ok. So, let us try to do it. So, this CH2 S double bond O, double bond O and you see N. So, then you basically get N, C double

bond O, CH2, CH3. Now, idea was again the similar because as you can see that this dipole is this way, this dipole is this way.

So, 2 so, C double bond O and S double bond O are on the similar side. So, electronic repulsion is there. But, as there is a formation of chelation that probably will give you the absolute asymmetric induction.

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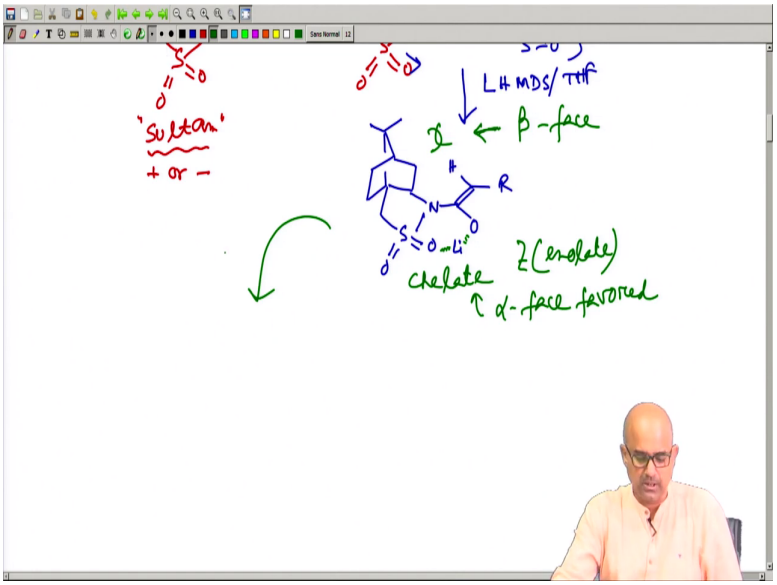

Now, in this case you try to generate the enolate LHMDS with THF solvent and definitely you can control the enolate geometry, Z enolate is normally formed which follows the Ireland transition state, as all of us are familiar. So, you try to use this methyl and this S double bond O, double bond O fine. Now, N ok and now you see this O and this is the R. This is your enolate structure.

Now, here I will just put lithium to give you the chelate formation. So, this is the rigid chelate which is already having a rigid camphor backbone structure and that gives you a quite. Now, your electrophile, electrophile. So, as this is said this is a definitely a Z enolate, Z enolate. Now, electrophile has to be approach usually in these cases electrophile will always approach from the below face, because the top face seems to be blocked by this gem dimethyl.

So, this beta face attack or top face attack, a beta face attack is blocked have a steric crowding. The alpha face is usually preferred; alpha face attack is favoured.

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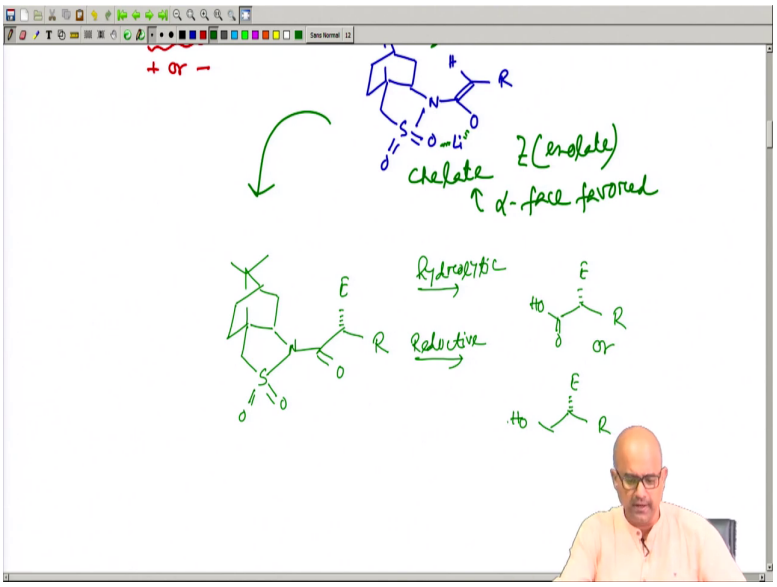

So, now, by taking this as a starting point you can eventually try to write the compound that what could be the final stereochemistry or the absolute configuration of the compound. So, this, this and then everything was similar the sulfone, oxygen, sulfone, oxygen nitrogen, this and then you have C double bond O; if you can write in this way. And, then you put and you try to put the electrophile here and you put a R ok.

So, this is then you can eventually cleave the auxiliaries by numerous way the similar way. You can basically do it through hydrolytic cleavage as like Evans auxiliary, you can do a reductive removal ok. And, just you can get similar kind of compound, you can get either a carboxylic acid or you can get a corresponding alcohol.

So, different oxidation state of these compounds you can synthetically manipulate. Now, this is the initial findings and as I said the asymmetric induction you can quite easily explain. Now, such things the Oppolzer way actually was used by the synthetic organic chemist; mainly for a epothilone synthesis which is an anti-tumour drug molecule.

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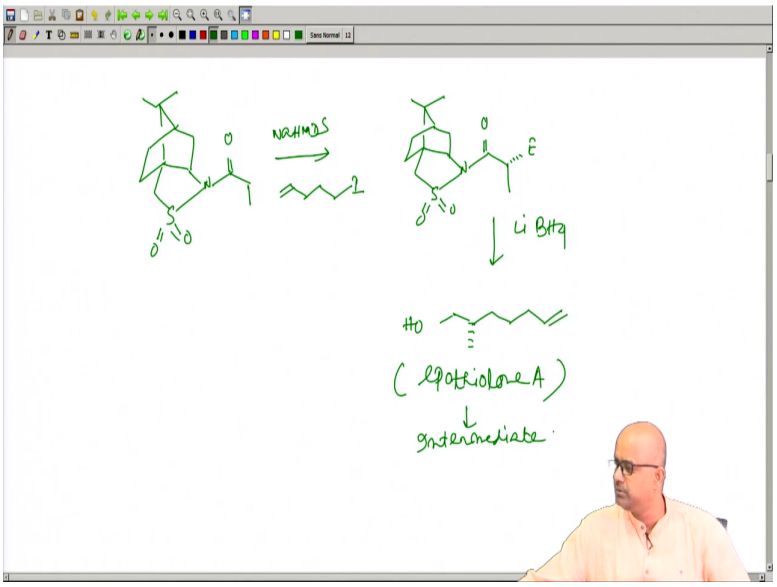

So, I will just try to give you the application of Oppolzer's synthetic route way route. So, this was the initial structure of this compound. Your sulfone S double bond O, S double bond O. You have this N which is there, this and then you have this CO, CH2, CH3. So, this part was there and then you react with base as all of us know similar kind of base NHMDS or other bases.

You take this base and then you take react with the electrophile, but in this case the electrophile was depending on the requirement. It was a kind of a long chain aliphatic iodo compound. There are 3 CH2 groups. So, this compound was chosen and everything remains quite similar as I said, the mode of asymmetric induction just now we have discussed. So, you will be having your S sulfone and then sulfone this thing, your C double bond O.

And, then you can choose actually you will get this and then your electrophile is will be actually this entire thing. So, anyway electrophile. So, you can remove the plus just yeah and then this compound can be synthetically manipulated. And, actually you will be later on getting this reductive removal by lithium borohydride. And, you get this alcohol which you can now try to get 3 CH2 and this.

Now, this was a particular intermediate for an antitumor compound epothilone A, the intermediate for this antitumor compound synthesis. So, such synthetic intermediate was used by I mean you can use the Oppolzer's route. So, Oppolzer's route now regarded as one of the

nice synthetic exercises. In continuation of the Oppolzer's pathway; so, Oppolzer have devised this route quite long ago and Evans also on the of the similar time.

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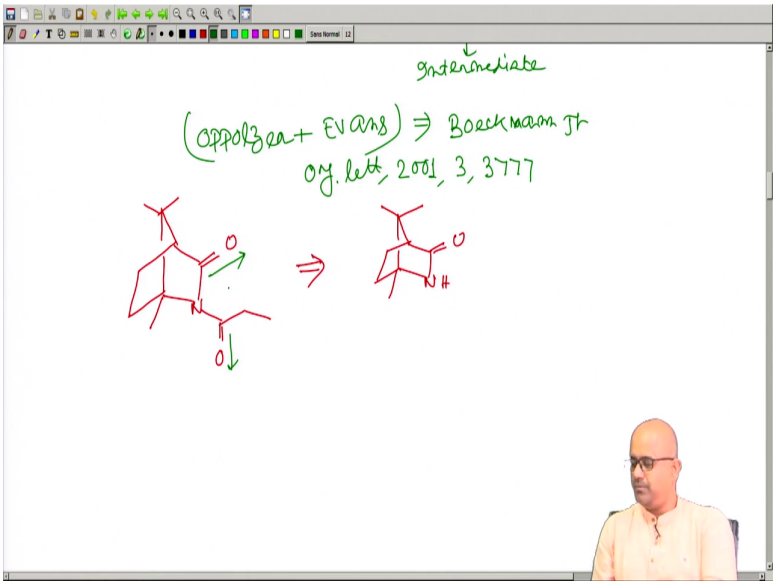

So, next this particular auxiliary which is now Oppolzer plus Evans, both the model has been combined together. And, that basically forces Boeckman Junior; another synthetic organic chemist who actually devised or designed an auxiliary which was first published in recent days in a *Org Lett* paper in 2006. I am sorry it is not 2006, it is basically 2001 and volume is 3, page number is 3777.

Now, what Professor Boeckman ……Boeckman Junior have been devised; let me first draw the structure, then you can understand that it is a combination of Oppolzer as well as Evans work. So, he actually took camphor derived or camphor type compound. Now, this oxazolidinone part was basically this amide was something like here. So, you can see this is the amide part ok. So, this is a one auxiliary.

Now, this auxiliary basically you can make in the lab or you can make in the lab. Now, what you need? You actually need this kind of cyclic oxazolidinone, this Me C double bond O, NH cyclic amide. Now, here also similar kind of logic is there that your dipole-dipole thing will probably try to give you this confirmation as this most preferred way ok. But the chelation; obviously, is coming into picture. Now, how this will be coming into picture?

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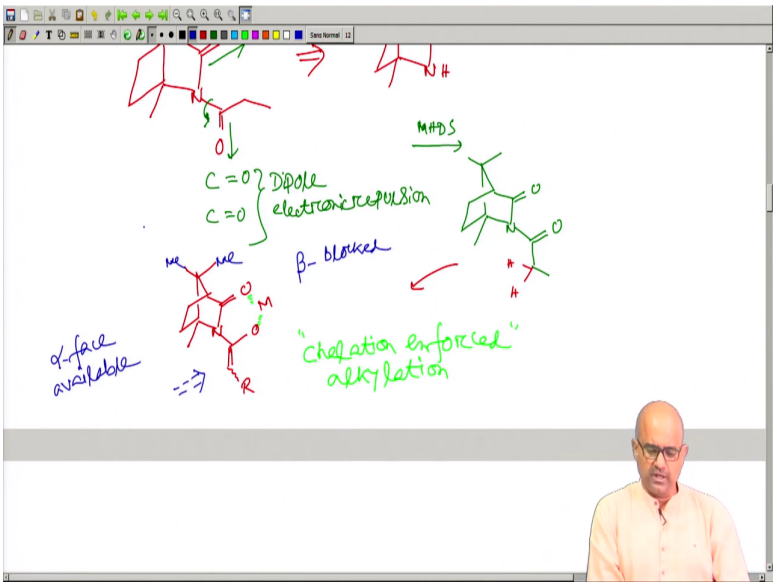

So, now if you try to focus that C double bond O and this C double bond O. These two dipole should be oppositely aligned ok, dipole-dipole thing. So, basically that gives you a strong electronic repulsion ok. Strong electronic repulsion which you already explained in the case of earlier work.

Now, to minimize these things when you are trying to use a base metal containing base MHDS or something like this. So, what basically you are expecting now, that this will feature you this, this, this and this. And, now you have to draw in this way that you actually put through this way. The initial confirmation should be something like this ok.

So, you are basically allowing this bond to rotate. So, amide resonances might be bit of minimum factor. Now, if this conformation basically prevails and then you are trying to abstract the hydrogen ok and generating the corresponding enolate. So, let me draw the enolate structure by keeping this part. So, now, the enolate geometry definitely you can control. So, this carbonyl is there fine and this is there.

So, now you see enolate is you have a O and then let me just put a zig zag way either Z or E that I can control. So, now, here definitely it is a metal. So, now, this is the part which seems to be a very nicely designed. But, the idea was mainly coined either by Oppolzer as well as Evans, because the chelation enforced model.

So, now this chelation enforced, chelation enforced alkylation will be the main factor. And, definitely now the electrophile will try to approach from some phases. And usually it has been found that if it is designed in this way, definitely the 2 methyl group, 2 methyl group which is here that basically blocks the beta face. So, beta was usually blocked, that you can easily see you visualize. So, definitely alpha face seems to be much more available, alpha face seems to be available.

So, with this background information probably in the next class we will discuss this Boeckmen Junior's asymmetric enolate alkylation for this camphor derived auxiliary based system. And, it seems that this auxiliary based work which is read by the Professor Boeckmen Junior, it is like a combination of Evans as well as Oppolzer's work. And, this is also very nicely documented in this particular article ok. So, you can just go through this references. If you do not find this references just let me know.

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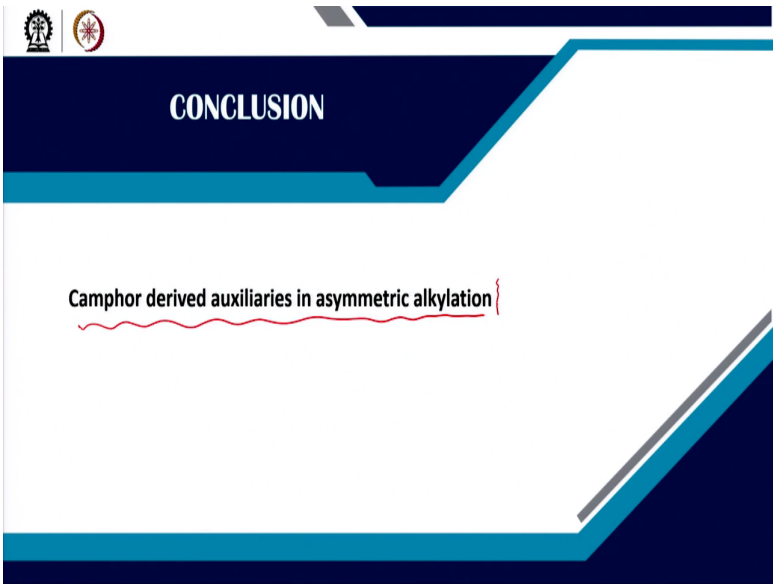

So, in the concluding remark, we can say that camphor derived auxiliaries also play a very important role in the field of enolate alkylation, particularly in the asymmetric fashion. And, as you can see that Oppolzer's auxiliary and Helmchen's auxiliaries are found very significant application. And, particularly in the final part we talked about Boeckmen Junior's auxiliaries which is also similar like camphor derived auxiliaries and we will talk about those auxiliaries in the subsequent section. So, we will talk about few more auxiliaries in the later part.

Thank you. Till then have a good time.