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 - 13
Evans oxazolidinone and related systems - III

Welcome back students. So, in this module, which is module 3 will be talking about lecture 13 and normally we are again continuing this Evans oxazolidinone and related systems.

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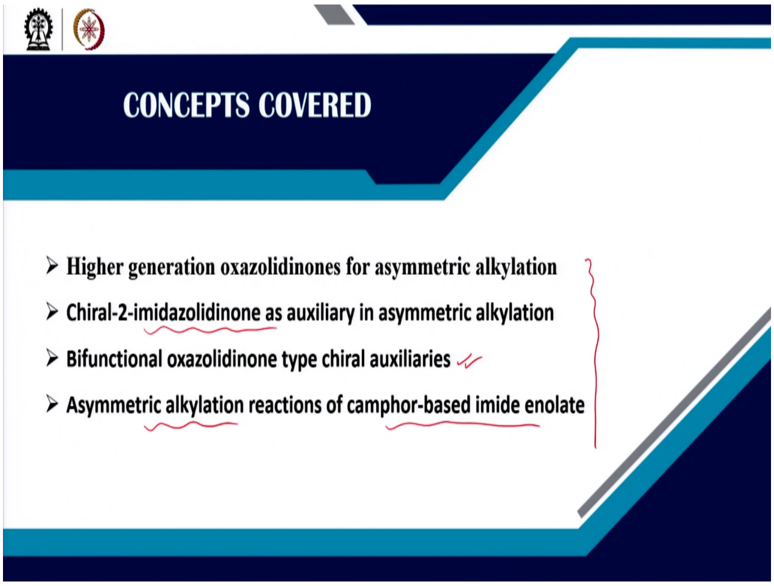

Today's class we will be mainly trying to cover higher generation oxazolidinone for asymmetric alkylations and we will try to talk about few different structural variations of this oxazolidinone. Mainly imidazolidinone and other structural variants, we also talk about bifunctional oxazolidinone, where you can have two units of electrophile can approach. And then asymmetric alkylation of camphor-based imide enolates, which are also pretty good variation of these things.

And probably in the final part we will talk about some of the limitation of Evans oxazolidinone based auxiliary and how you can solve this approach by designing a super quat auxiliaries.

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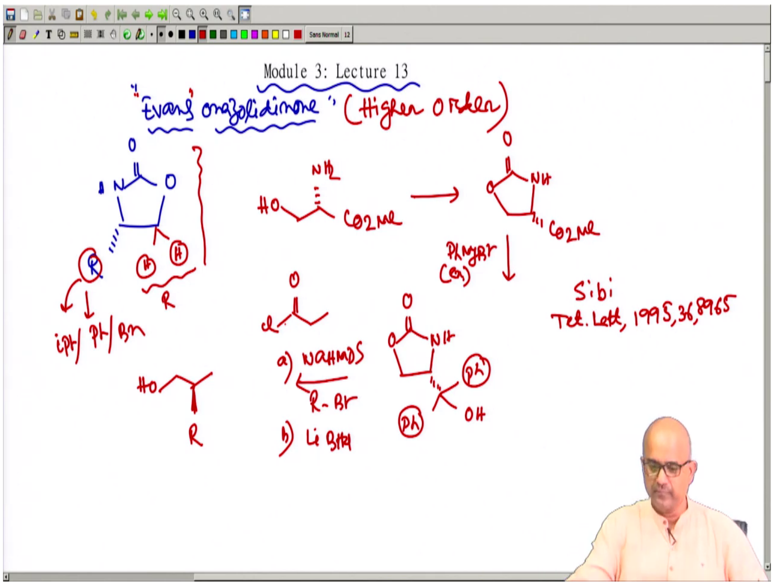

So, today we will be discussing lecture 13 in under the module 3. And today also will be mainly discussing about the Evans oxazolidinone based method and some of its higher variation.

Now, as I said, Evans oxazolidinone method is very powerful mode of asymmetric alkylation of enolates and this is a most versatile method and we are still using this method as a tool because since last 35 years or more. And as I told you the basic structural features of this Evans oxazolidinone, if you recall your memories are having some R group here.

In the last class you said that usually this H, we usually keep it as a normal hydrogen, but still this groups also you can replace, you can replace the hydrogen with a different R groups or you can change these R to a bigger R group. Now, today I will be mainly trying to discuss higher order oxazolidinone or different variations of oxazolidinone, which are mainly based on Evans method, but some other researchers, have took this idea and they have designed couple of higher order oxazolidinone.

And few cases their selectivity seems to be as comparable with the original one. So, one such oxazolidinone we are now discussing which was initially prepared from a serine ester, this is the amino acid serine which carboxylic acid group was converted to a methyl ester ok. And then this serine this amino alcohol is already having a CH2 OH group. So, this was basically condensed by the diethyl carbonate method, which we have discussed in the previous class.

And then now you can see that this CO2Me was here. Now this CO2Me means this ester. So, this ester you can actually introduce different group and here what people do they use excess phenyl magnesium bromide excess. Now, this ester so if you use excess phenyl magnesium bromide, this will actually react and you will get one phenyl here, one phenyl here and tertiary alcohol. Now, you can see instead of a normal isopropyl, earlier we have used to have isopropyl or a phenyl or a benzyl.

Now, you have a two phenyl group which definitely has much more steric bulk and this compound was first invented by professor Sibi and he actually reported this compound in a tetrahedron letter paper in 1995 almost after 10 years of the original work of Evans. So, this is the original references, if some of you are interested. The rest of the things are very much similar.

So, you have a this oxazolidinone you react with a base NaHMDS was preferred, you react with an electrophile and then you do with the reductive cleavage like lithium borohydride and everything remains similar. You will actually get this as this is the below. So, you get R on the above and you then, first actually you have to react with this initial this acyl chloride, which is the acid chloride ok.

So, these things are pretty much simple and you can just synthetically manipulate such oxazolidinone in a quite efficient way.

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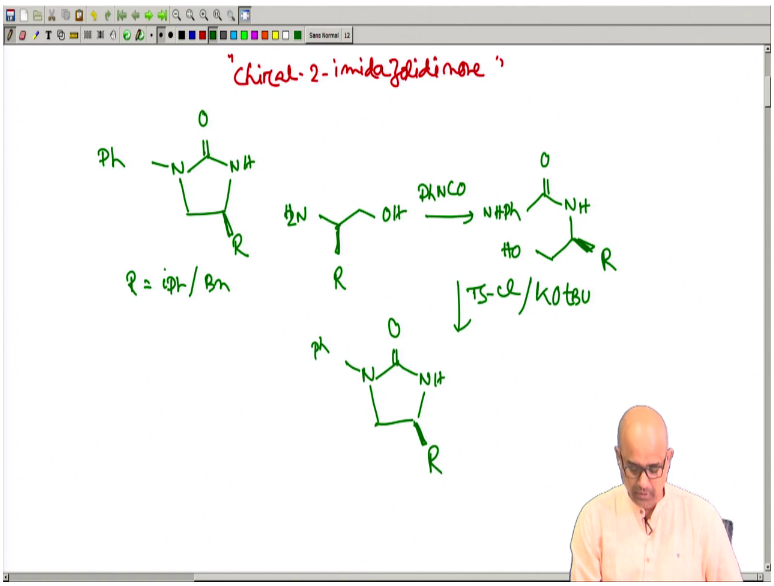

Then in line of similar analogy there are other compounds, which are also designed and synthesized. So, one such auxiliary will be talking about which is basically based on chiral-2-imidazolidinone. Now, this chiral-2-imidazolidinone if I write their structure you will find that the structure was basically based on the normal structure of the Evans oxazolidinone.

But they put a cyclic urea kind of derivative. Instead of the ring oxygen now put a nitrogen and that basically gives you …….. So, oxide is replaced by a imidazolidinone, more or less the design part was similar, this R group which is the steric directing element synthesis you can easily make this compound starting from this amino alcohol which is the commercially available as well as you can make in the lab.

First, this compound was reacting with phenyl isocyanate and this amine group is a much more nucleophile and you actually get this cyclic, you sorry this acyclic urea derivative at the very beginning. The reaction mechanism you can eventually try to find it out which seems to be not that much difficult and then you have these things ok. So, more or less this is very simple and then with this alcohol, amino alcohol what you do? You first react with tosyl chloride.

And tosyl chloride means this CH2 OH will be replaced by a tosyl group and then you treat with potassium tertiary butoxide. So, it will be tossing means a leaving group, you have N minus and then you actually react you actually get the your desired cyclic imidazolidinone. So, Ph is here and you have this R, sorry we did some mistake the R will be actually on this carbon fine I just, yeah R will be on sorry R will be on this carbon.

So, with this imidazolidinone in your hand rest of the part are absolutely similar. So, let us focus on what you can do with this imidazolidinone.

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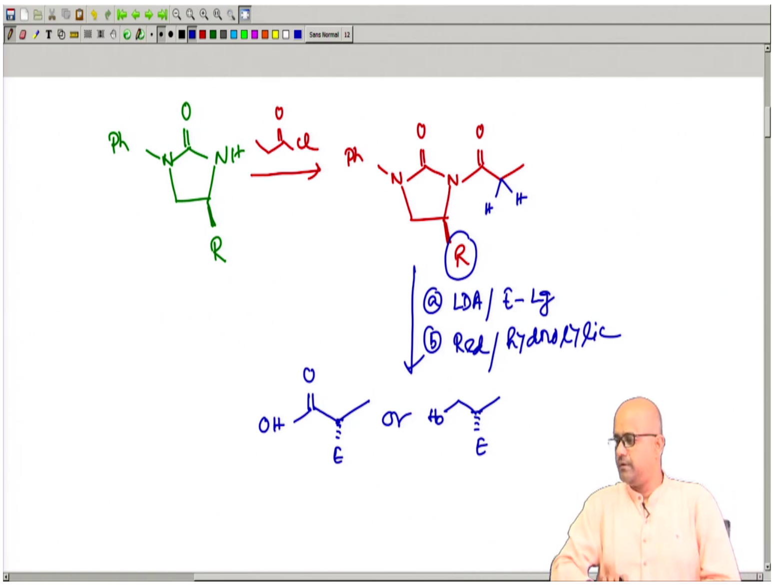

So, you have this imidazolidinone which you made just now, your NH is there and you have this group which is acting as a stereo controlling element so, first condensed with this your acid chloride or carboxylic acid derivative.

So, usually what you create, you create the corresponding amide ok N CO these things and everything else are more or less similar, everything else is more or less similar the same way you have designed the Evans oxazolidinone. Now, you can see that this is the chiral controlling part; here you can abstract the hydrogen to generate the enolate.

So, what you do you can just straight watch write the similar condition, a base like LDA or something and then you can react with an electrophile, electrophile with a leaving group and then the rest is the way you want to cleave it. You can do a reductive cleavage you can do a hydrolytic cleavage the choice is yours and you can eventually get like. As the R group is above so you can write that the carbon electrophile bond seems to be on the alpha orientation.

And here you can choose your different functional group, if it is the hydrolytic cleavage you can get the corresponding hydroxyl acid and if you are doing a reductive cleavage you can get your corresponding alcohol. So, these things are almost quite similar ok, quite similar. And then similar kind of oxazolidinone or different variation all are mainly coming from.

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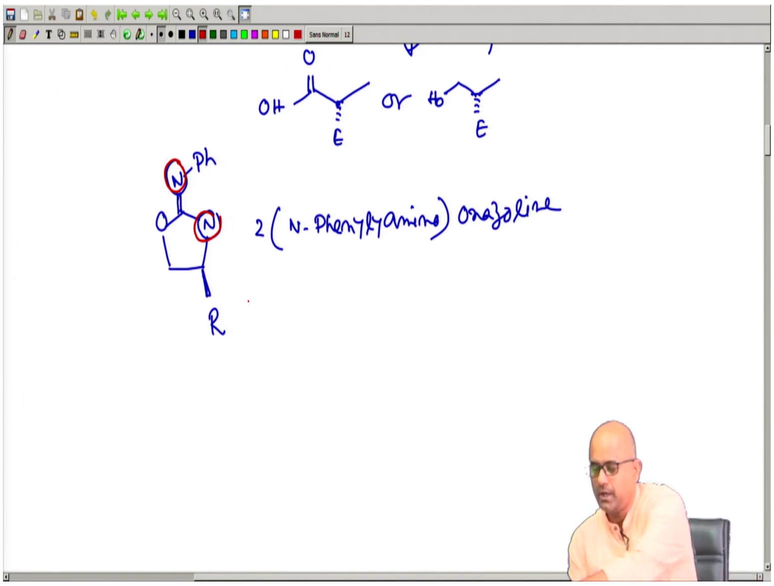

Now, this was a similar kind of things, where eventually you try to get this kind of compounds, also this is again a similar kind of thing. Instead of the amide you now have a N phenylamine oxazolines because nitrogen and things. So, these compounds are basically higher version of these things. So, we call this compound as a 2 N-phenyl amino N-phenyl amino oxazoline.

Now, rest of the part all remain same. Now, here the basic point is this nitrogen and this nitrogen they are actually involved in the chelation, this nitrogen and this nitrogen. Now, how you can make this compound? Again, a similar way you can actually prepare this compound.

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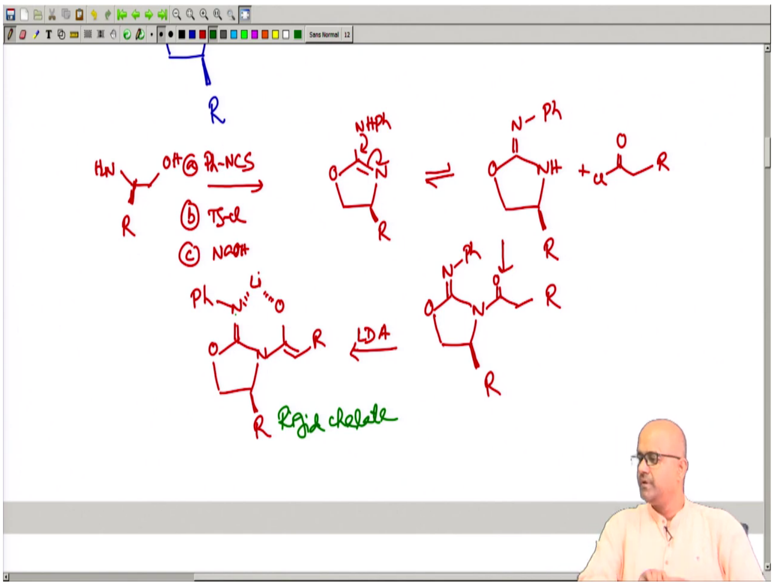

So, let us start with the preparation of this compound, you start with this corresponding amino alcohol which is very easily you can get it from commercial suppliers, react with Ph NCS ………phenyl isothiocyanate.

And similar like this isocyanate, you have this isothiocyanates and then like last time you have this compound then you react with procyl chloride and then react with a base, sodium hydroxide ok. And initially what you get? You have if you are not familiar with the mechanism, you can just give a try in your home, but I am sure you can eventually do it ok.

You initially get this compound and then this compound actually you can find that this compound easily undergoing some kind of abstraction of this hydrogen is basically kind of a tautomerization. And then which will eventually give you this amine in amine kind of tautomerization and that basically gives you this and this is your compound ok.

So, more or less this is the compound and then this compound you can fuse it or condense with your acyl chloride or the compound where you want to create the asymmetric center, through enolate alkylation. So, everything was more or less very much straight forward. So, based on is a simple concept of this Evans thing, you can create a numerous diversity ok.

Now, fine we can just write how you can do it. So, LDA; the moment you treat with LDA will now see that this was you basically get the corresponding enolate. Now, this enolate is

……… you have a lithium. So, you now write lithium and this was the chelate we are talking about ok.

Now, this cyclic chelate, now it is possible and this rigid chelate earlier we have done this chelate where this metal its basically involve this corresponding C double bond O.

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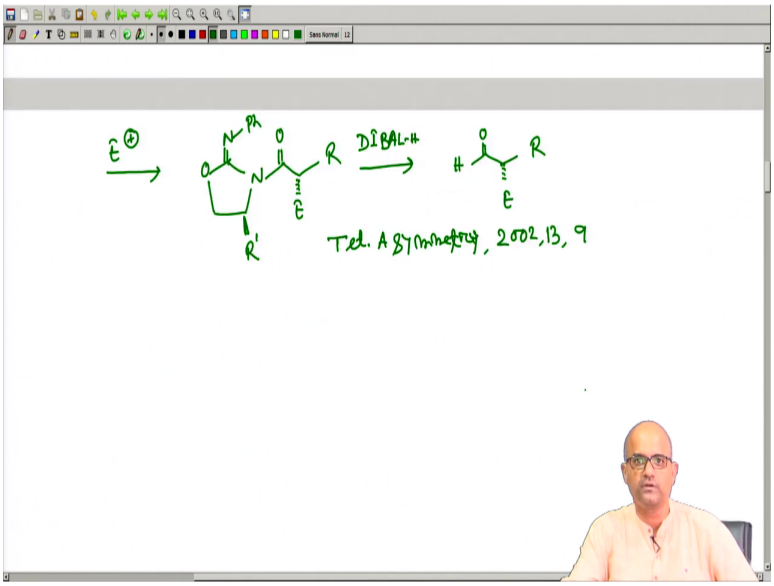

Now, this is C double bond N, rest of the part is very much similar and you can just take this rigid chelate, which you just now drawn in the earlier slide and then you react with electrophile.

This electrophile is your choice mostly highly reactive electrophiles like allyl bromide, benzyl bromide, methyl bromide or even methyl allyl or ethyl those kind of compounds you can use. So, now, you can see that the moment you react with the electrophile, the rest of the structure will just draw it again and as this group shields the top face you normally get these things as beta ok.

To have a differentiation you can put R and R prime just to differentiate. Now, you can eventually similar way you can reductively cleave it, you can reductively cleave it or you can in this case this was actually very mild. Reducing aging was used DIBAL-H and this DIBAL-H actually stops this reduction at the very initial stage and that will you will get the corresponding aldehyde.

Now, this was reported in a *Tetrahedron Asymmetry* paper, which is a journal well known in our asymmetric synthesis field; this is published in 2002, almost 20 years ago. The idea was taken from the Evans oxazolidinone based method and you can simply explore this technique by changing the different the base structure to a different structure, but the source of asymmetric induction and other way of mechanisms are almost similar.

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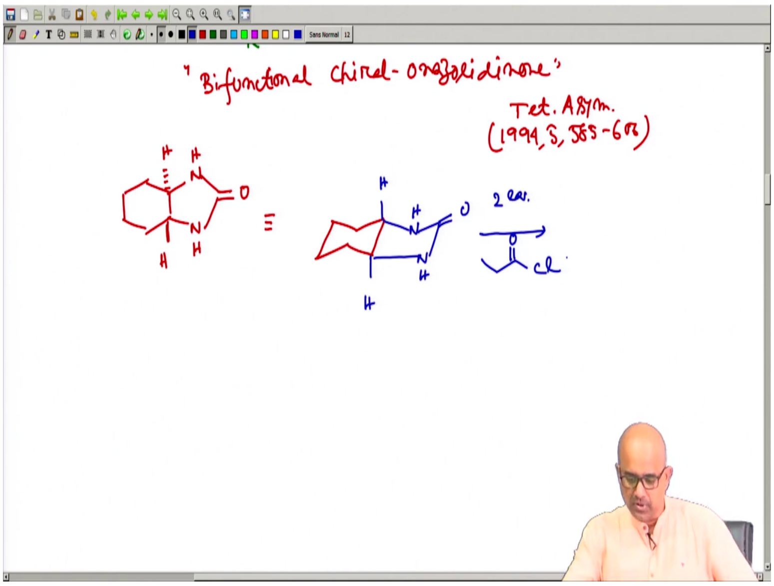

In a similar line of thinking next a bi functional chiral oxazolidinone, bi functional chiral oxazolidinone was also designed and this compound was pretty much interesting. And this was also reported in a tetrahedron asymmetry paper, which was reported in little bit earlier in 1994 volume is 5 and page number is 585 to 606.

Let me see what was done in this paper. In the original paper they have chosen a 6 member and a 5 member fused, this kind of cyclic urea ok. Now, this compound was chosen as a enantio pure compound, the corresponding trans compound was taken ok. Now, if you have to draw this compounds in its 3-dimensional form, the parent compound the first ring is a chair form ok.

And as a trans-fused the 5-member ring also is a chair form and you can eventually see this is the N and this is will write in this way and this will be the another N ok. So, this could be the structure and you have a one hydrogen here, one hydrogen here this is basically the trans structure just to show that these hydrogens are having trans one. Now, you have a hydrogen you have a hydrogen. Now, this compound was reacted with two equivalent of your acyl chloride where you want to generate the enolate.

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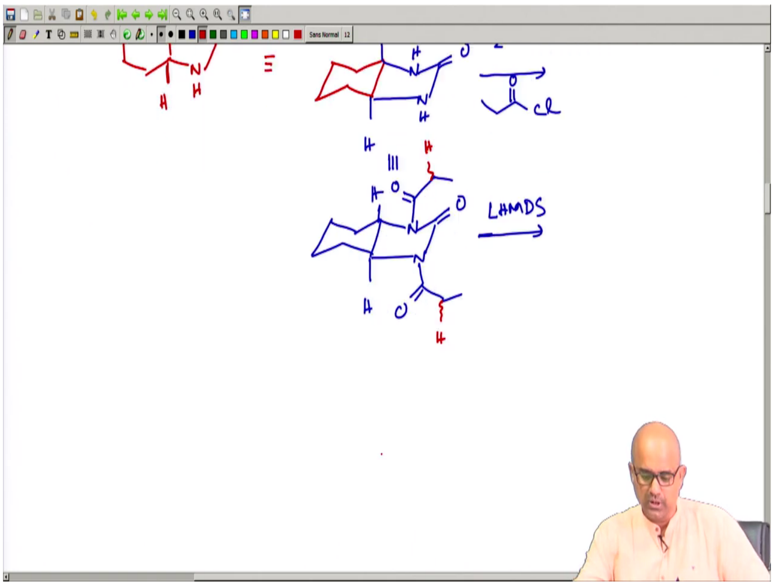

So, you can eventually write the entire structure in a 3-dimensional way, here the chirality was or the asymmetric induction was coming in a little bit of different fashion, I will just explain to you this and this. So now, you are having this CO CH2 this and you have another CO CH2R ok, this is the main thing.

Now, you can eventually have a chelation based on the drawing you have shown. Now, this way what drawing I have shown you can actually try to make it in much more comfortable way, because you have to bring two carbonyls on the similar side so that effective chelation can take place.

So, now let us we will be trying to do is generate with base like LHMDS. So, LHMDS will abstract these hydrogens from here as well as here as there are two competing things. Now, mostly if you try to react step wise thing that is better because once you it abstracts one hydrogen you get a chelate.

Now, the for the subsequent round you have to have this hydrogen abstraction, but this carbonyl will be involving in the chelation ok.

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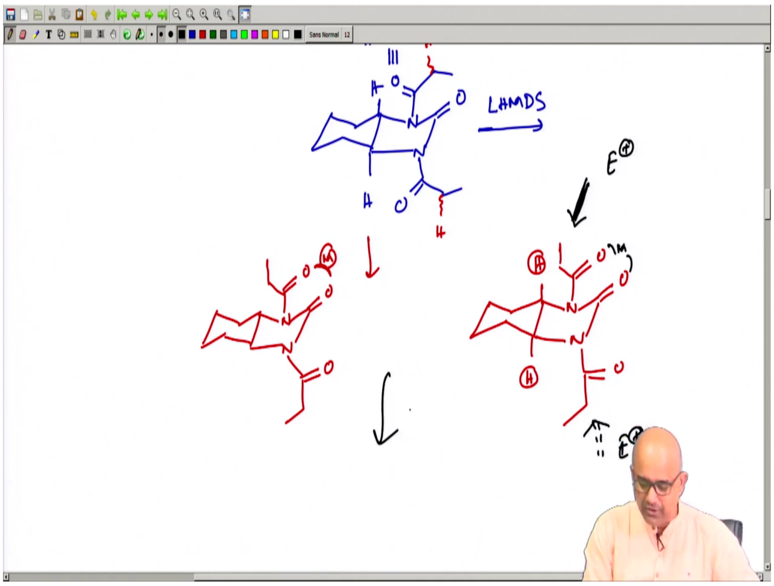

So, now, let us try to do the drawing in one such case and then that will be, just you need to do the drawing in a little bit feasible way. So, you can just visualize the chelation part. So, I will put the CO here and now here also I will try to put the CO and the enolate will have to put it.

So, this will be now will try to make the chelation ok, because now two of this amide I put in this way. Now, for the second round you also have to put it in this way ok. Now, in both these cases your enolate thing is will giving you the giving you the chelation. So, fine so but as chelation will make the transition state. So, this will be a simple metal here that gives a chelate

Now, if you do the second round of chelation. So, this carbonyl and this carbon will give you the another round of chelate ok. Now, I will try to write the asymmetric induction which will be most important thing in this part ok. So, you just try to think in this way as I said this and this and here also you will be having this and like this. Now, mostly by drawing of such structural conformations you will find that this usually, this once this forms enolate here, let us say.

And usually this entire this, this planar enolate everything is kind of blocked in this face. So, electrophile usually comes from this part for the top enolate fine. In this case, in this case actually if you have a chelate it seems that top face was blocked and now the enolate was more or less attacking from this one. So, this is kind of a self-sufficient model; in one case the electrophile seems to be coming from top and the bottom face coming from the bottom ok.

And then finally, what you are going to get you are basically going to get a……..

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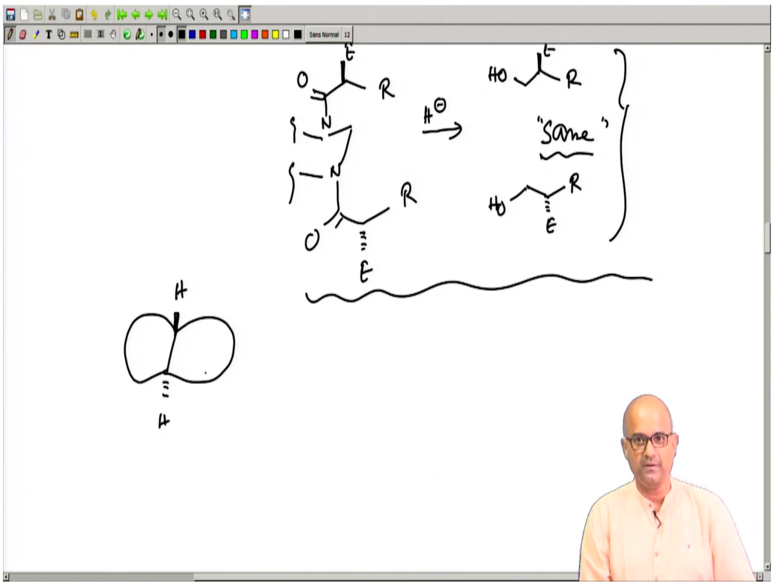

So, the top face, if you try to now write this N your C double bond if you now allow the rotation and this thing your R. So, electrophile is attacking from top ok, you get this in the bottom part I just write in this way, remaining part will just do not write ok. Now, in this case you write this way COR and this is the thing.

Now, you do a reductive cleavage or anything. So, now, say you are doing a reductive cleavage by hydride. So, what you will get you get the E in the top part R CH2 OH, fine. From the bottom what you get? E R CH2 OH; now this compounds are basically same. So, the idea was by doing a single enantiomeric auxiliary, which is having a bifunctional handle you actually create a two mole of same product with a same absolute configuration.

So, that was quite interesting and that is why we said that it is a bifunctional chiral oxazolidinone. Now, this bifunctional chiral oxygen is only possible as this compound is usually having this kind of structure and the stereo induction mainly governed by two independent ways, but two independent means they are complementary to each other.

The first case if the above attack takes place and in the second case the bottom face attack takes place, by mainly the virtue of the substrate, which is kind of having its own steric bias, because it is a bicyclic structure; you can coordinate with the similar kind of bicyclic structure where in the substrate directed asymmetric induction we talked about something like this kind of bicyclic structure.

Now, this kind of ring has its own flipping or now you can see that this ring structure was quite important. But anyway, this kind of ring structure gives you an own conformational bias and that basically gives you pretty much a controlling element. Now, with this idea you can also eventually try to explore a similar kind of oxazolidinone based on camphor-based things.

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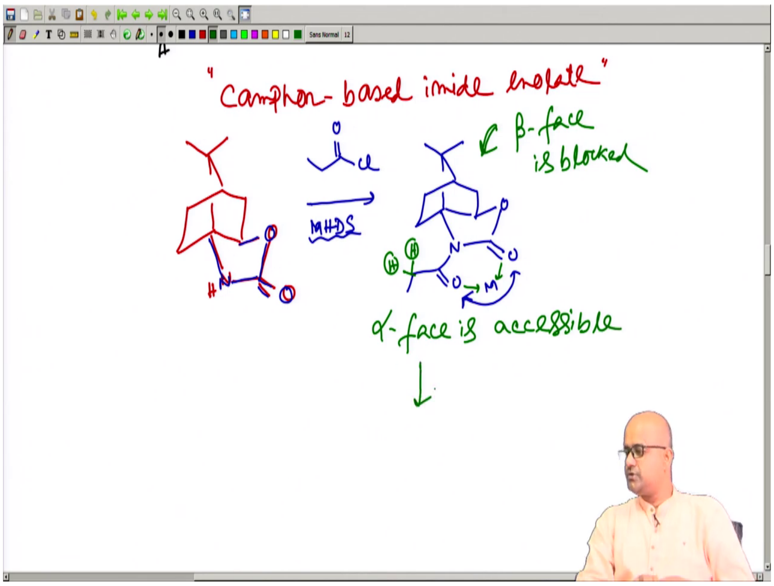

These are mainly derived from the by keeping the idea that Evans oxazolidinone was the main framework and you can just try to mimic the entire system with different backbone. Now, such camphor-based thing was usually chosen and you can see that the oxazolidinone was framed on this way. So, here is oxygen, where is nitrogen and then you have these things.

Now, see this is your enantio pure camphor and this part is the oxazolidinone. This blue color which I am now writing is the oxazolidinone and rest of the part is your camphor part, which is the chiral precursor ok. Now, everything will be now similar, you just condense with the corresponding acid chloride or your acid derivative.

So, you can simply write the synthesized derivative, which will now will have N this is the bond you will around N C O, this CH2, CH3 and then you have this O, you have this C double bond O. The idea was similar try to put both the carbonyl on the same orientation though the dipole-dipole repulsion is there, but your chelation which makes a pretty good thing.

So, now here once you treat the base like MHDS, lithium, potassium or sodium your metal forms a chelate. So, this chelate you give I have this kind of thing. Now, the idea was the enolate which is mainly generated by abstracting any of this two hydrogen, you have this enolate. Now, if you will find that the camphor the bridge structure is such that the top face seems to be blocked.

So, you can write that the top face or the beta phase face of this enolate is blocked by the camphor auxiliary. So, alpha face seems to be available, alpha face is easily accessible. So, fine by keeping this idea you can just correlate the entire thing.

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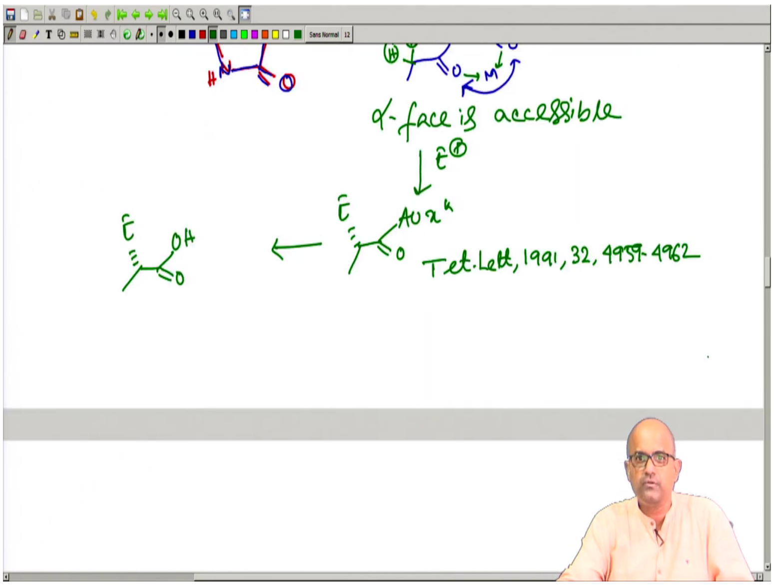

So, now, you can write this carbon electrophile, if you treat the electrophile will be here and then everything is your CO, you can write auxiliary ok. Now, this auxiliary you can just simply remove.

So, this all methods are basically the extension of Evans oxazolidinone based method. And you can; and this was reported also in a famous journal that *Tetrahedron Letter*, which was reported almost similar the time of Evans published after 5 years of Evans in 1991 actually and 4951 to 4962 is the page number. So, this all this features actually gives you a pretty good control in the overall geometry.

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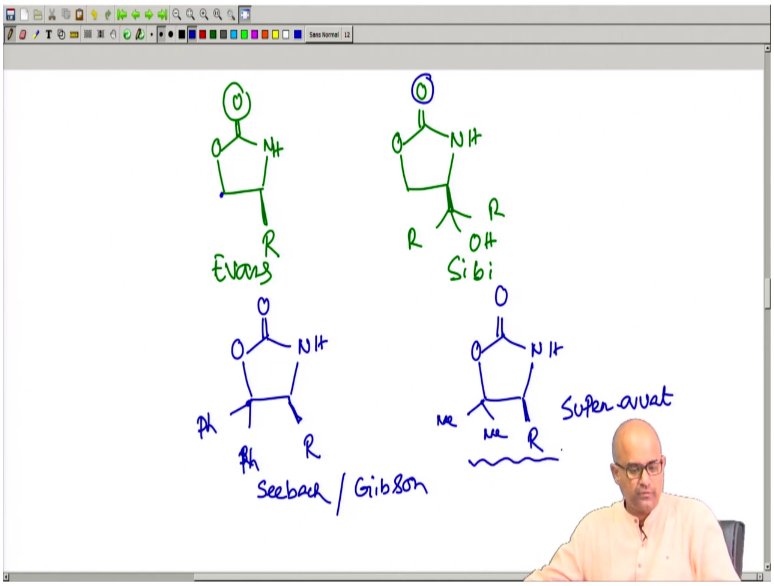

But now, we will try to give you something else in remaining few minutes, that how higher order or different variation of Evans or gradually known can be feature. So, this is the parent Evans oxazolidinone known. So, this is Evans one ok, and we already seen different oxazolidinone like this Sibi's work in this case, Sibi what it did he put it R R and OH, this was more like a Sibi's oxazolidinone.

Now, this atom has been replaced by oxygen to nitrogen in different way, just now we talked about fine. But by keeping the core structure similar, some people also developed some other oxazolidinone by having a much more things like this they put a phenyl, a phenyl and here they put a R. So, what is happening I am talking about these two hydrogen they have replaced by this phenyl, phenyl.

So, it means that they basically try to put more rigid framework here and by this two confirmation, you can basically expect a gem di methyl or gem di aryl effect which gives you extra rigidity ok. So, this was developed by see back, though I am not giving you the corresponding references, but such structures are see back as well as later on Gibson ok.

Now, such structures are very important definitely and then with this thing in mind, actually this simple gem dimethyl compound also have been derived and such auxiliaries are now named as super quat auxiliaries. Now, super quat auxiliaries, super quat or super quaternary auxiliaries; now, the super quat auxiliaries are usually very much hydrolytically stable.

Normally whatever sometimes this Evans oxazolidinone methods why you need to have the super quat auxiliaries, I will just try to give you a little bit of idea.

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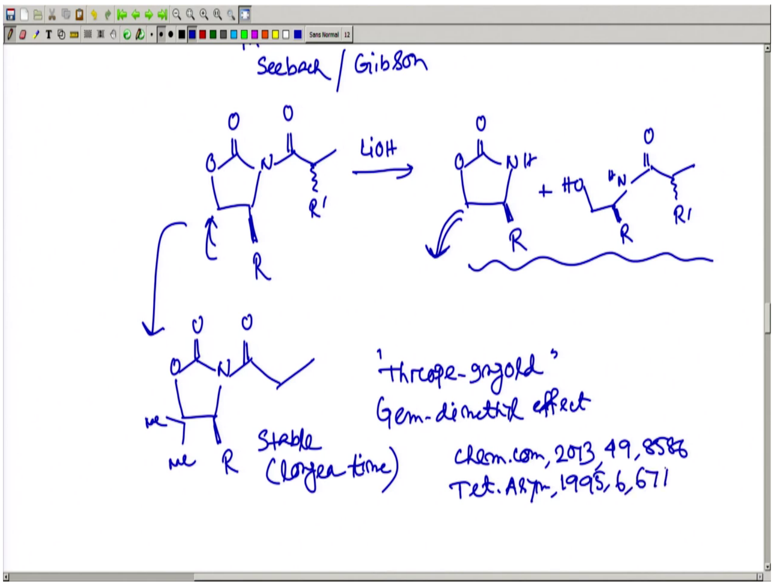

So, Evans auxiliary based method sometimes it happens that, if you have this Evans oxazolidinone based methods you are after this alkylation you do the alkylation and you get a stereo center here fine ok. And then you try to remove with a hydroperoxide or lithium hydroxide. Now, what happen your auxiliaries seems to you be regenerated with this ok. And you expect that hydrolysis takes place.

But sometimes this incomplete hydrolysis also takes place and that basically gives you this R with this NH and this CO with this R prime and this group. Now, this incomplete hydrolysis sometimes happens in such a way that you your reaction is not fully high yielding. So, this auxiliary you cannot get completely back ok.

And also, you want then further you want to hydrolyze this part you can get, but here you can get the amino alcohol. So, there certain complications in hydrolysis ok, if the hydrolysis is not complete. But then, so then they are trying to introduce some group here so that it gives you a better hydrolytic stability and hydrolysis is not at all a at all a problem and usually this compound seems to be quite stable.

And then after hydrolysis you do not have incomplete hydrolysis problem associated with this Evans auxiliary or similar kind of auxiliary. And also by changing this group here you are actually creating something like this, you have a gem dimethyl group ok.

Now, this gem dimethyl group puts a Thorpe-Ingold gem-dimethyl effect. So, this is probably all of you know it this Thorpe-Ingold gem dimethyl effect that basically gives you a rigidity in the system in this quat auxiliary and that was mainly responsible for this hydrolytic stability for this compounds.

So, you can do a couple of reaction and after that recycling seems to be quite easier. So, we will discuss those points in the subsequent sections and normally there are three factors, hydrolytic stability, the gem dimethyl effect which gives a conformational rigidity and obviously, the stability for longer time. So, normally this kind of compounds are quite stable, quite stable even better stable than the original one which was invented by the Evans.

So, this super quat auxiliaries usually reported by different people and we will discuss those compounds probably in later part. But you can if you can find it this is some references which you might find useful. This is reported in *Chem Comm* and then this is also reported in a *Tetrahedron Asymmetry* paper and which seems to be quite useful in terms of better hydrolytic stability.

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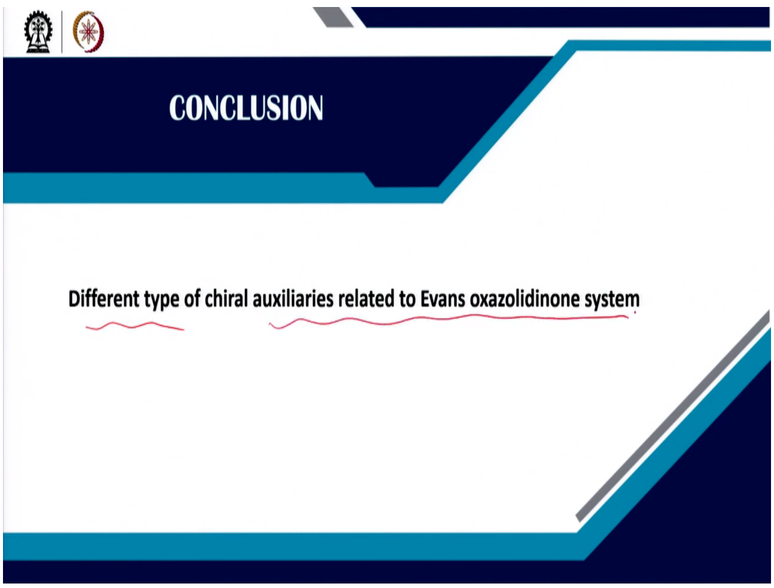

So, the conclusion or concluding remarks, different type of chiral auxiliaries related to Evans oxazolidinone systems we have discussed in today's class. And you can find that most of the oxazolidinone, which Evans initially designed have been framed on that structure. And more or less all are giving very good dash to selection in the asymmetric alkylation and the hydrolytic removal of the reductive removal seems to be operating in the similar fashion.

But in few cases like the super quat based auxiliaries which have been having a better hydrolytic stability and you can keep those auxiliaries for a longer time in the room temperature, they having a better self-life. So, ok well try to discuss those things in the subsequent sections.

Thank you all; thank you, see you again.