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 - 11
Evans oxazolidinone and related systems

Welcome back students and today actually we are going to start a new module. This is module 3 and particularly in this module, we will talk about a little bit of different systems and its Enolate alkylation. And, particularly in this lecture we will be trying to talk about Evans oxazolidinone based systems and related systems.

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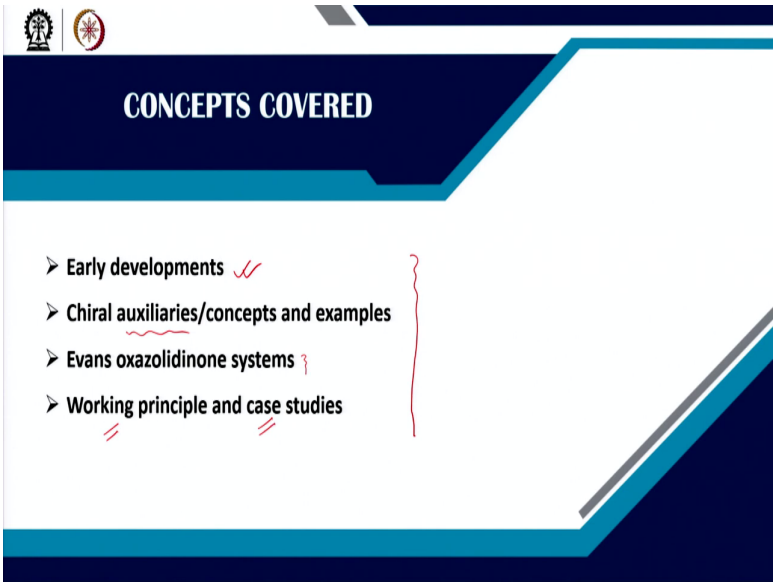

The main contents which will be covered in this part is the early developments, how this oxazolidinone based auxiliaries being developed by different scientists. The early part we will also talk about what do you mean by chiral auxiliaries, their concepts and examples. And, then we will slowly coming into Evans oxazolidinone systems, its working principle and different case studies. But, as it is an introductory lecture, we will try to be as brief as we can.

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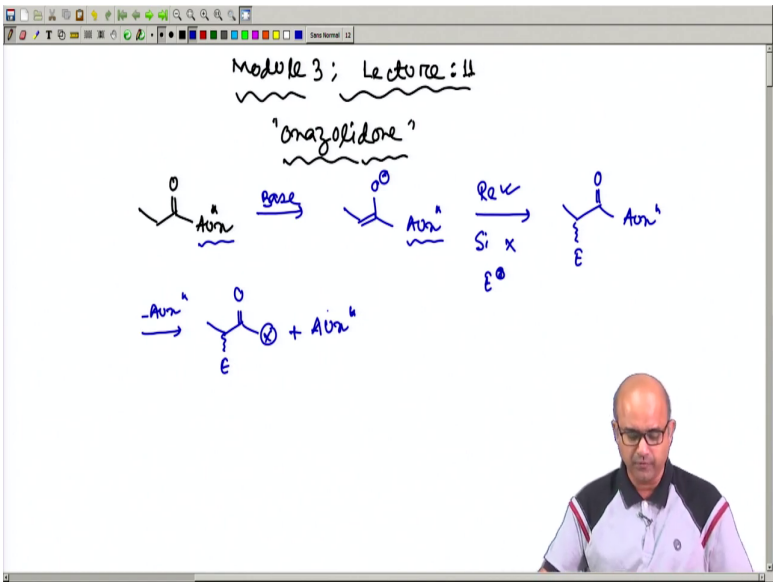

Welcome back students and particularly today we will be going to start a new module and in this module the main idea was we will be trying to talk about couple of auxiliary based asymmetric alkylation.

If you remember the very beginning of the class when we talked about how you can create new stereogenic center in the enolate alkylation, one of the idea was you generate the enolate or start with a enolate system or carbonyl compound, where this carbonyl compound was covalently attached to an auxiliary or a functional group ok. Now, this auxiliary contains a pre-existing stereo center, you generate the enolate with the help of base as usual you get Z or E enolate and then the auxiliary contains stereogenic element.

So, now this auxiliary basically controls the whether *Re* face will be favored or *Si* face will be disfavored ok. And, then you actually can do enolate alkylation based on this auxiliary and you create new stereogenic center by using simple electrophile. And then finally, you can remove the auxiliary, you can remove the auxiliary and then you will basically get the different kind of functional group plus the auxiliary actually you can reuse, you can reuse the auxiliary.

So, this was the main concept which probably we will be using in subsequent slides. And, actually if I give you different name of the auxiliaries, there will be pretty there will be numerous auxiliaries which is which are known in the literature. And, we will be talking few

of the auxiliaries which are very widely explored Evans oxazolidinone, seems to be one of the most widely explored.

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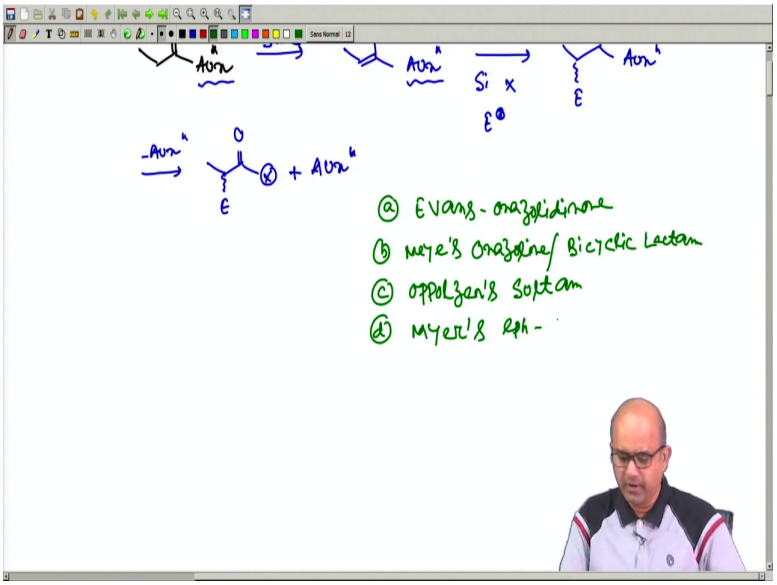

Then there are auxiliaries which have been derived based on different functional groups, this Myer's auxiliary. And, Myer's have developed several auxiliaries, the oxazoline based auxiliaries, then bicyclic lactam based auxiliaries. And, actually in all of these auxiliaries either different kind of carbonyl groups either an aldehyde or a acid or an acid chloride have been coupled.

And, then you in each of every cases the auxiliaries contain some pre-existing chiral center. Then you have this Oppolzer's sultam based auxiliaries, we will be trying to give all I mean a short discussion on different auxiliaries. And, this there is another Myer's auxiliaries, which is ephedrine based of auxiliaries. We will be discussing those auxiliaries slowly. Today at the very beginning, we will try to discuss about this Evans oxazolidinone and related auxiliaries.

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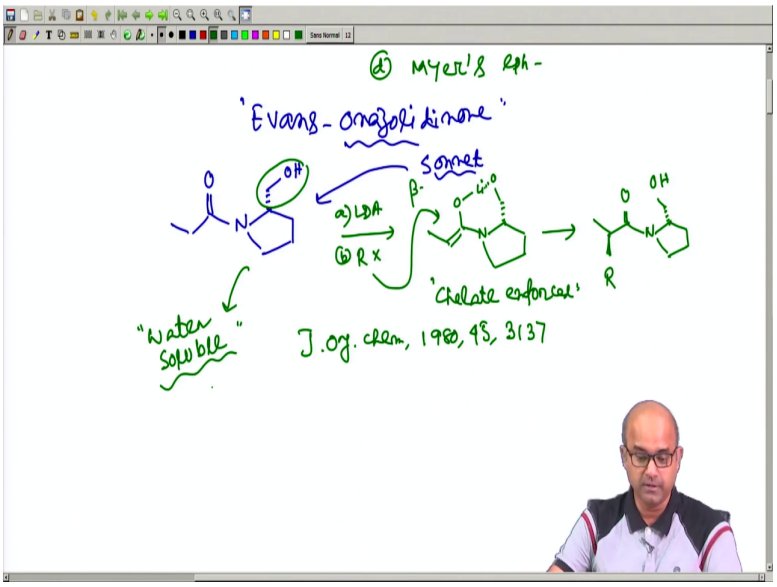

Now, such an auxiliary is first derived by Professor Evans, David Evans, but before that such of auxiliaries are usually have found application in the field of enolate alkylation. And, it was initially devised from a simple proline based compound ok and this was first reported by Sonnet. So, Sonnet's chiral prolinamide based thing, now you see this part is the proline part.

So, once you have this proline, the carboxylic acid reduced to corresponding alcohol and then this amine part, you condense with acyl chloride ok. The idea was very simple, you treat with a base LDA and treat with RX. Now, such auxiliary actually first you what you get? You get the O minus or corresponding lithium salt.

And, then here the basic idea was as its having a CH2OH. So, this also gives you extra coordination and due to this coordination as this forms a very rigid chelate and this CH2 OH is alpha. So, definitely your electrophile or this RX will be coming from the beta face attack. And finally, what you will get? You actually get this Me; R will be opposite to the existing chiral center in the proline part.

But, this is a chelate enforced annulations. This was the main factor which we are already talking about. So, chelate enforced is the and this was reported long ago almost 40 years ago in a JOC paper 1980. And, this was the documented evidence, first reported by Sonnet. Now, with the help of Sonnet these compounds are definitely good, but the main difficulties for these compounds source, this compound seems to be pretty much water soluble.

And, as these compounds are pretty much water soluble, the during aqueous workup or when you are doing an extractive work after this reaction is over, this is very difficult to recover the auxiliaries, very difficult to recover the auxiliaries. But, they seem to be quite applicable and in many cases this compounds, I mean this Sonnet's prolinamide based auxiliaries where found application in the literature, Sonnet's prolinamide.

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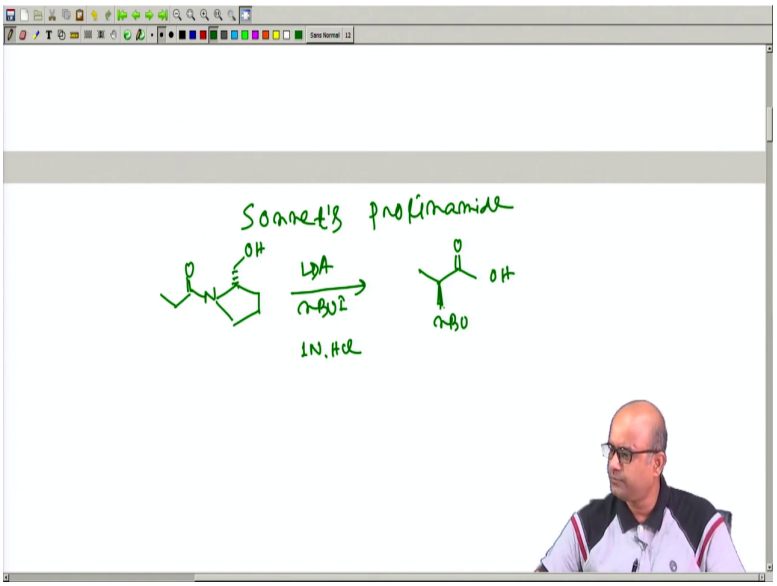

A very classic example as just now we talked about is something like this, a typical proline based system. You react with LDA, then react with n-butyl iodide and eventually what we will get? n butyl iodide as electrophiles, it will be coming from the beta attack and then you eventually this amide part, you can actually quench or cleaved by simple 1 normal HCl.

So, what you will get? You basically get corresponding CO2H. So, such alkylated acid you can eventually get and this was the initial application for this prolinamide part. Now, after that after this prolinamide part, as I said these compounds are very difficult to recover.

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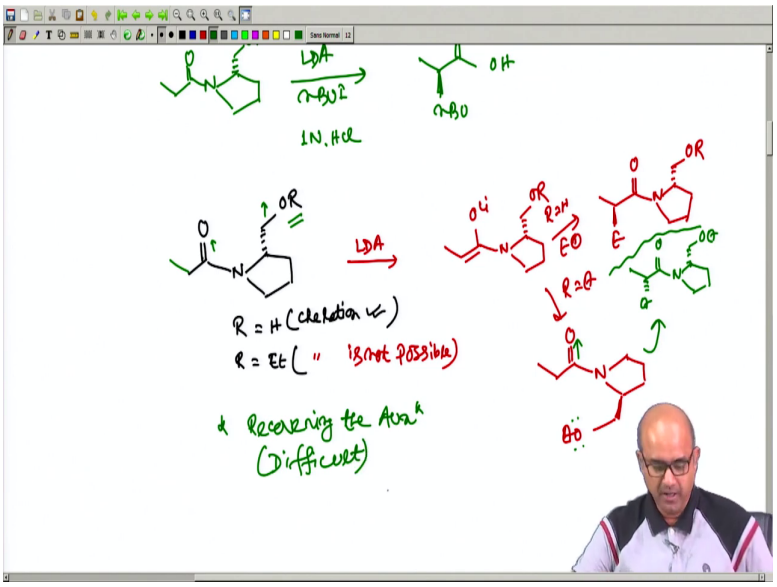

But, let me explain few interesting application of initial derived such system and this application was definitely give you a much more control. Now, here I will try to put a OR, now this in this case let me try to give the first case R is hydrogen. I mean there is OH, free OH; in another case this R is ethyl. Now, first case hydrogen is there.

So, chelation is on, but in this case as is ethyl you will find that chelation is not possible. So, that basically gives you a different kind of working model then. So, let first generate the LDA, I mean the base. So, you basically get O Li double bond nitrogen, this CH2 OR. So, if R is H, you have a chelation, if R is not H there is no chelation. So, let first talk about if R is H and then you react with the electrophiles E plus.

So, what it will be happening? Your C O N and this will be above because this part is below. This is fine you get OR, this one. Now, in this case the second case if R is ethyl, you do have a different condition. And, actually in this case you find that the initial compound as a chelation is not possible, the first the starting precursor will undergo a rotation here. Now, why this rotation is happening?

The rotation is happening mainly to the fact that this CO, the dipole is this way and this oxygen also having a lone pair. Now, in this case both the dipoles are this way as well as this way. Electronic repulsion is definitely possible, but chelation overcomes that. But, in this case as there will be no chelation, this will be the most stable conformation isomers ok. Now,

you generate the enolate and then at the CH2O, it is above after the rotation. So, what it will be happening now, you basically get this ethyl is below and then CO N CH2 OR or OE t.

So, basically what we will get? You basically get two different enantiomers by creating the substitution pattern ok, by changing substitution pattern. Now, sometimes this model works fine. But, as I said after this reaction is over, the main difficulties are recovering the auxiliaries; because these auxiliaries are very much water soluble; recovering the auxiliary is difficult. So, this was one of the point you need to be taken care ok.

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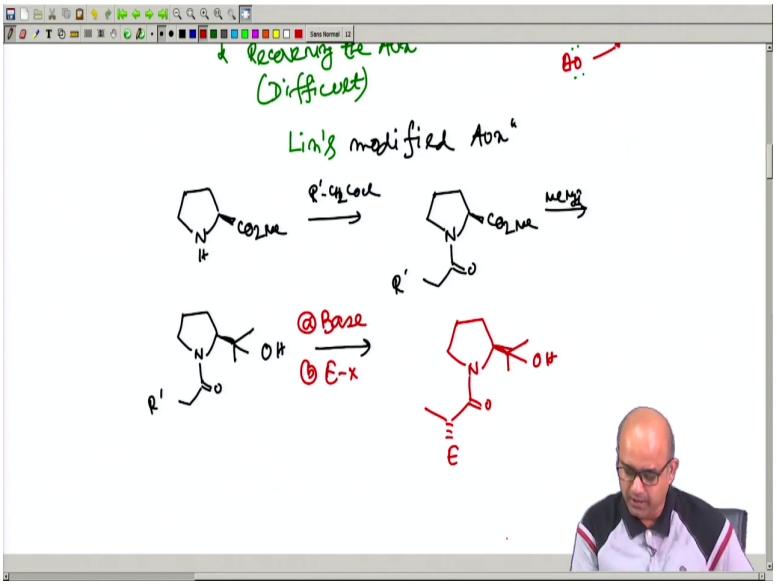

Now, this similar thing other people also working on these aspects; Lin, Professor Lin has come across with a new modified auxiliary. Now, let us see what Lin has tried to modified it. He took a proline derived compound, a proline methyl ester ok. And then first protect this proline with a acetyl chloride means this enol, enol was, amide was basically 2 CO CH2R. So, this enolate precursor was initially fused ok.

And, then you treat this ester group with excess methyl magnesium iodide. The moment you do it; actually what you will get? You will get the corresponding tertiary alcohol. So, methyl …..methyl……. OH and then you will get this. Now, everything was very much similar and then you treat with base, base means your LDA or something and then you use the electrophile, you can see that this is a pretty bulky group.

So, eventually the electrophiles will be trying to attack from the opposite face and so, what you will get? You will actually get this, this, this one. So, alpha attack is basically possible ok. So, this is the way you can do it. And then how to get rid of the auxiliary? You take the compound and doing a hydrolysis, after the hydrolysis actually you get this ethyl sorry, the electrophile, this is the electrophile and CO2H as the hydrolysis product.

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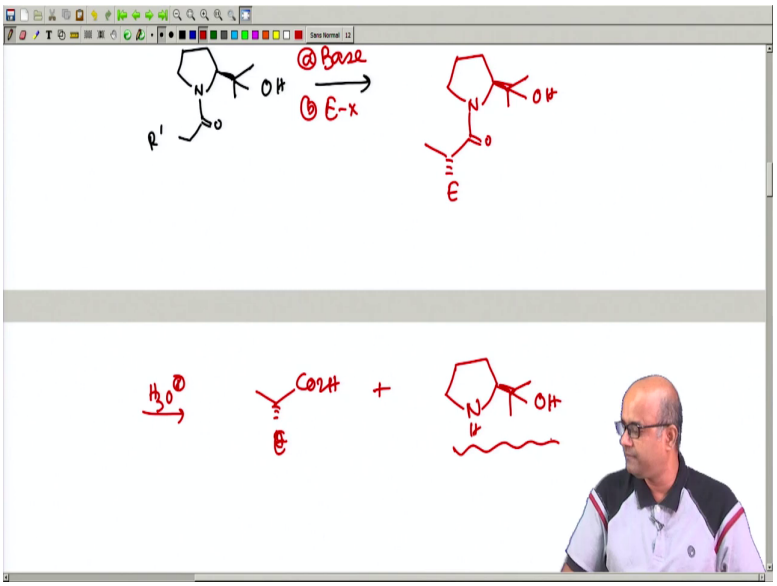

And, you can eventually recover the proline analog. Now, similar thing these things also this kind of compounds are pretty much water soluble. So, recovery seems to be bit difficult, but eventually you are not bothered that much because, proline is not that expensive. So, you can eventually try to deal with this part, this part pretty easily.

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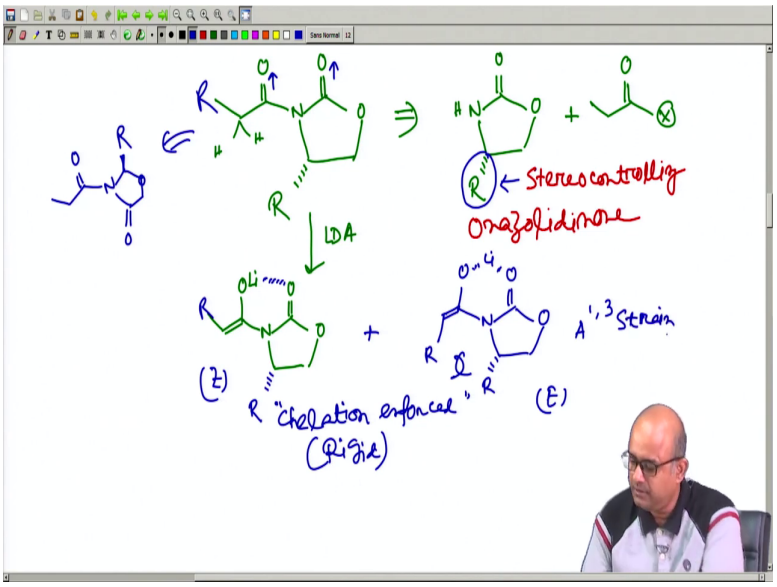

But, with this background information Professor Evans thinks that probably if you can try to do some other modification in the initial design part, that could be quite useful. So, Evans oxazolidinone was mainly based on the early works of Sonnet as well as Lin's work. And, without the proline part he actually now tried to came across a system something like this. Now, this kind of systems can easily be generated, if you have this oxazolidinone of this.

So, what you take? You first take this kind of oxazolidinone and then react with an acid chloride or acid derivative. Now, these compounds are now named as oxazolidinones, oxazolidinone. These compounds are pretty easily you can make in the lab also; you can make in the lab. Now, let us see what chemistry you can do it with this oxazolidinone. You can see that this oxazolidinones structurally they have a pre-existing stereocenter. So, this will be your stereocontrolling element.

So, in such case this oxazolidinone…….. the pre-existing stereocenter is the stereocontrolling element. Now, such case the design was has to be done in very efficiently and how this compound you can now see that, you take this oxazolidinone and generate the enolate by treating with a base like LDA.

The moment you treat the base, there are two abstractable hydrogens and you will be eventually generating this, this thing ok. Now, the initial starting compound, the oxazolidinone if you can see that the dipoles are aligned here, align here. So, these are basically in same direction.

So, eventually they tend to force in an opposite way to minimize the electronic repulsion. So, probably you can think that this kind of oxazolidinone might undergoing a rotation to give you this kind of structure, where the dipole-dipole repulsion is minimum ok. It looks quite possible ok, but here the main point is this oxygen forces this chelation. So, this was the controlling factor. So, the chelation controlled thing is basically overcome the dipole-dipole repulsion.

So, chelation enforced annulation or chelation enforced. So, this rigid chelate are actually main controlling factor. Now, coming to another point. Now, this enolate is Z if you take the, there could be another structure of the enolate where this group if this is R group, we can write R. This R could be facing the opposite same site of the oxazolidinone, chelation and everything seems to be happening chelation.

Now, this Z enolate, this E enolate. Now, you see in the case of E enolate, there will be severe allylic 1, 3 strain. So, for that reason the Z enolate seems to be the major product. So, Z seems to be the major product.

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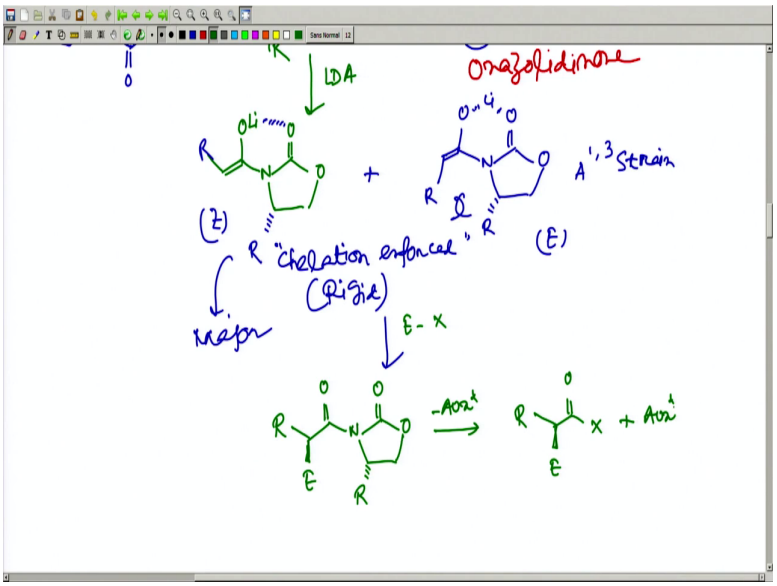

Now, once the enolate has been created, you can actually next do the alkylation. Now, in this case the alkylation as you can now try to explore, you treat with electrophile X ok. So, this group is below and then that basically forces your electrophile to attack from an opposite face of the existing group. So, eventually you will try to have this compound.

And then finally, you can remove the auxiliary or the oxazolidinone in a different way. Those cases will be talking in the subsequent classes, but actually you can now end up with getting such a compound with the oxazolidinone might be regenerating. Now, this is the most interesting way in terms of Evans thing. Now, what are the commercially available oxazolidinone?

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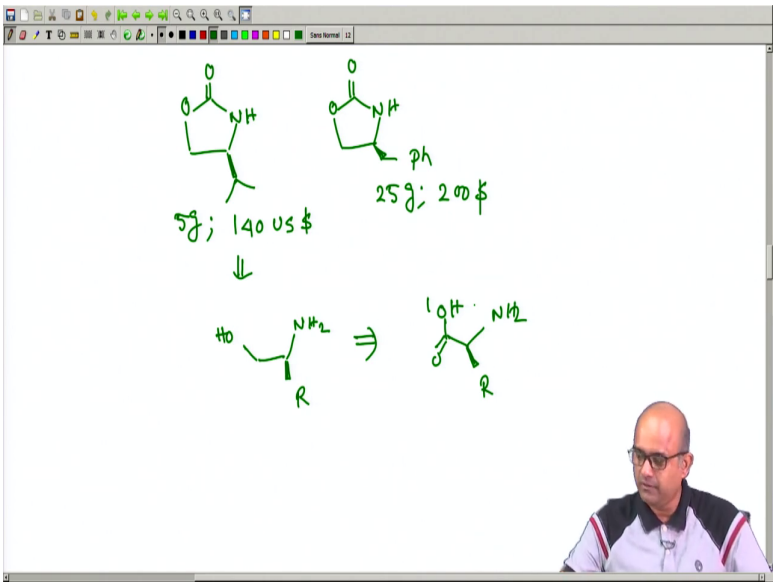

This most of the oxazolidinone nowadays are commercially available and if you are rich, you can I mean if your lab has enough funding, you can actually try to buy those oxazolidinone. Now, these oxazolidinone, the 5 gram oxazolidinone costs approximately 140 US dollar, may not be that much cheap also.

Now, you see this is an isopropyl group and mostly amino acids or these oxazolidinone have been chosen where you require, sorry this will be a NH part, the structure I just wrote in a wrong way NH and here also same NH. And, you see we will be having a phenylalanine all and this is also, this still 25 gram cost 200 US dollars.

Now, how you can generate this auxiliaries? This auxiliary can be generated if you now try to do a disconnection, you can see that this is can be easily prepared by this, this is a R CH2OH. So, this is what? This is amino alcohol and this can be easily prepared from the corresponding amino acid NH2 CH2 OH; sorry NH2 amino acid.

Now, these amino acid if R is isopropyl, its valine, if it is CH2Ph its actually phenylalanine. So, this amino acid can easily act as a source of your chiral auxiliaries, few other chiral auxiliaries of similar structures are also reported or known in the literature.

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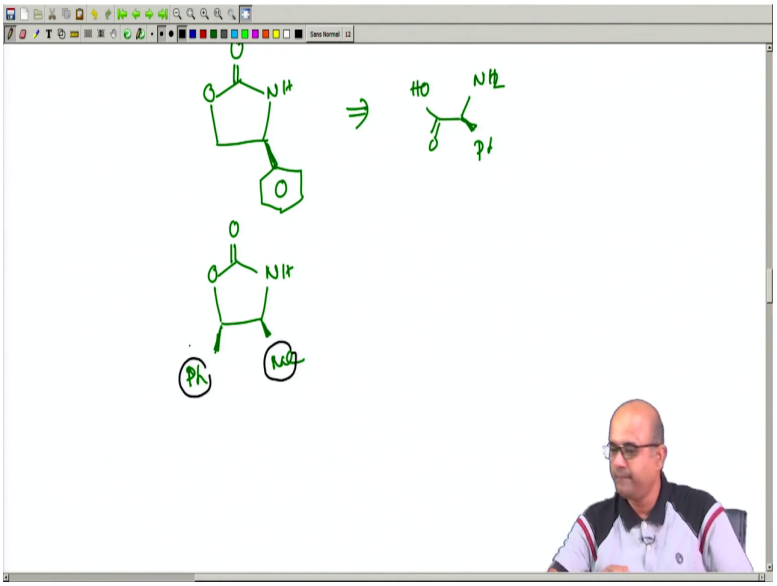

Such auxiliaries like if you try to take it the structure as such like you have a phenyl ring here. So, which is actually derived from phenylglycine and means this you can easily prepare from Ph NH2 and CO2H. So, you can prepare from phenylglycine and there is some unnatural thing also, means this is coming from amino alcohol. These all are commercially available and if you want to make in the lab, this also you can do it.

So, you can have a phenyl here, you can have a methyl here. So, now, see this kind of auxiliary is also pretty good as you have a steric directing approach and two position. This is a beta phenyl; this is a beta methyl. So, eventually the beta face seems to be completely blocked now, let us trying to give you a working model for this thing.

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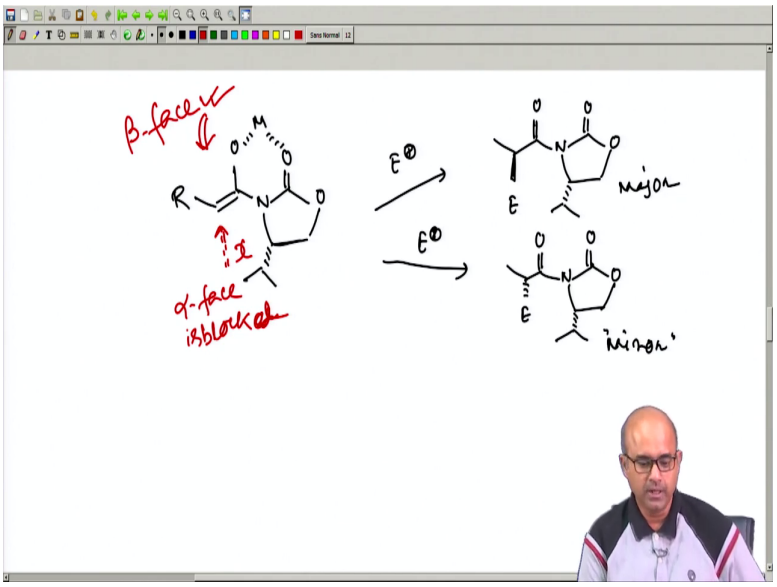

So, let us say you having a simple auxiliary which you are trying to do the asymmetric enolate alkylation, the isopropyl seems to be beta ok fine. This n I will write the enolate structure directly, because as you know the enolate structure. This will be metal. So, you have a coordination, you have a coordination fine. So, electrophile, electrophile will be now attacking. The electrophile will be definitely approaching from the beta face; means this is the beta.

And, then you will be having this. Now, you can write the entire auxiliary, C double bond O, this, this, this ok. And, then if you are trying to give an another competing model means if it attacks from the alpha, this will be having this structure, but that is that will be not possible; because it sorry. This will be sterically not favored, because the alpha face is already blocked.

So, it will not allow the incoming electrophile to approach from the same face, this will be the major product; this will be the minor product. So, this kind of working model you can explain. And, if I have to draw, I can just try to give you a typical thing for such a drawing if I have to give a drawing yeah. So, see I just try to put a bulky group at position ok.

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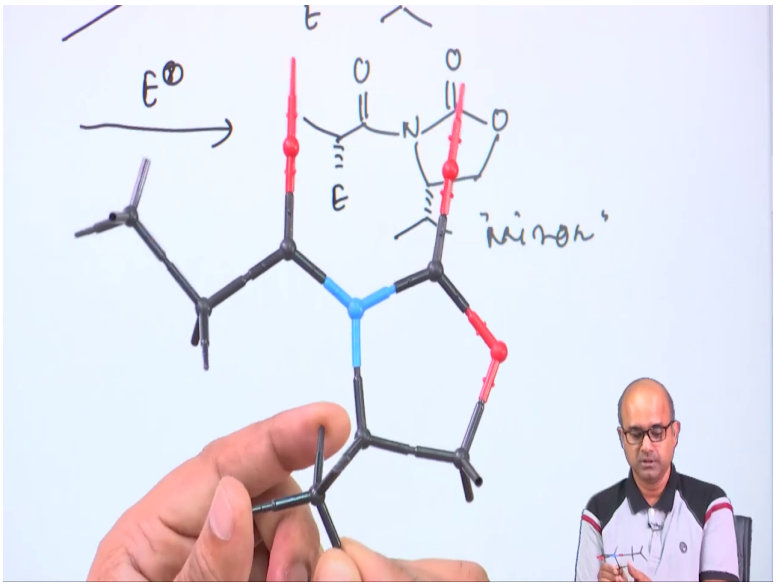

So, this is my auxiliary, CH3, CH2, this is CO, this is CO. So, metal coordinates here, the metal coordinates at this point ok. This is nitrogen, the blue color nitrogen, this is the oxygen and this part is your group, the group. So, this is below so, the iPr…. is below see. And, now definitely the electrophile cannot approach from here because, this face is blocked by this group; but it can attack from the other face.

So, this is the way you can explain it. So, I can now say that attack from beta face is favored, attack from alpha face of this enolate ok; let me try to because, it has to follow the Agami/Burgi-Dunitz trajectory as we explained earlier. So, this is blocked; so, alpha face is blocked. So, anyway in the in this way you can eventually explain that how you can get the very good stereocontrol.

Now, the finer details of this Evans oxazolidinone based thing, we will be explaining in the subsequent classes. And, how you can remove the auxiliaries in a straight forward manner will be continued in the subsequent section.

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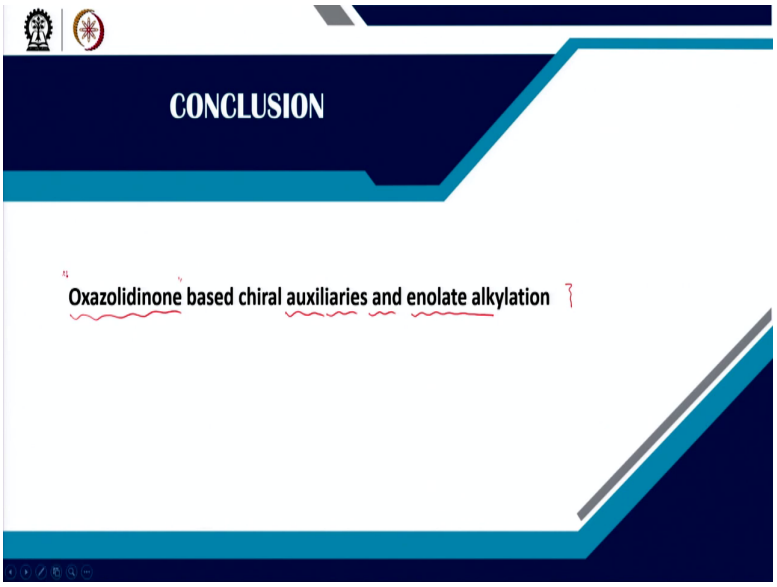

So, as a concluding remark you can see that we have talked about little bit of Evans oxazolidinone based systems. And, prior to that systems like Sonnet's prolinamide and Lin's proline based auxiliaries and, how Evans oxazolidinone based auxiliaries are better in terms of selectivity and product recovery than the earlier developed method.

The working principle we have already talked about that as this auxiliary have a pre-existing chiral centers that can act as a controlling element. So, we will talk about subsequent discussion on the Evans oxazolidinone based alkylation in the coming weeks…….

Thank you and see you again.