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 - 12
Evans oxazolidinone and related systems - II

Welcome everyone. So, today we will be talking about this module 3 and we are mainly discussing the Evans oxazolidinone based alkylation of enolate system and this will be our lecture 12.

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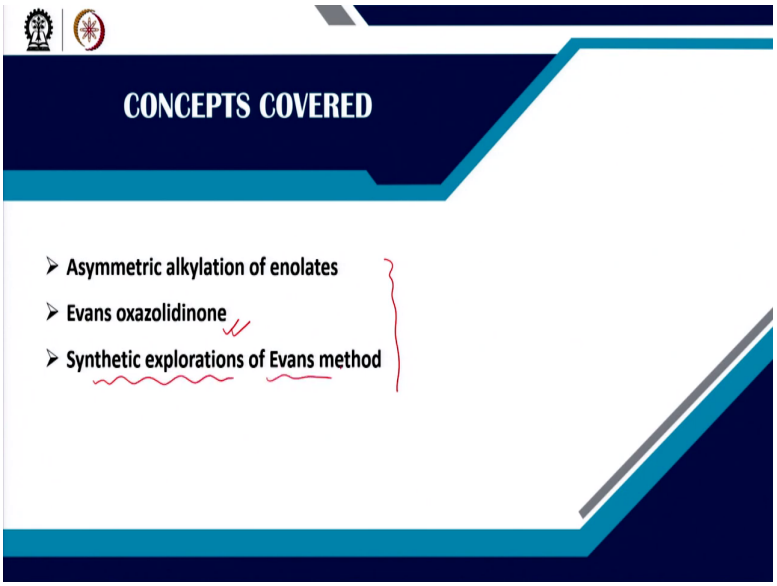

And today's lecture we will be mainly trying to cover different concepts of asymmetric alkylation and mainly we will be focusing about Evans oxazolidinone which we have just started in the last week.

We will be talking about several features of its and mainly we will be trying to discuss about synthetic explorations of this Evans method ok.

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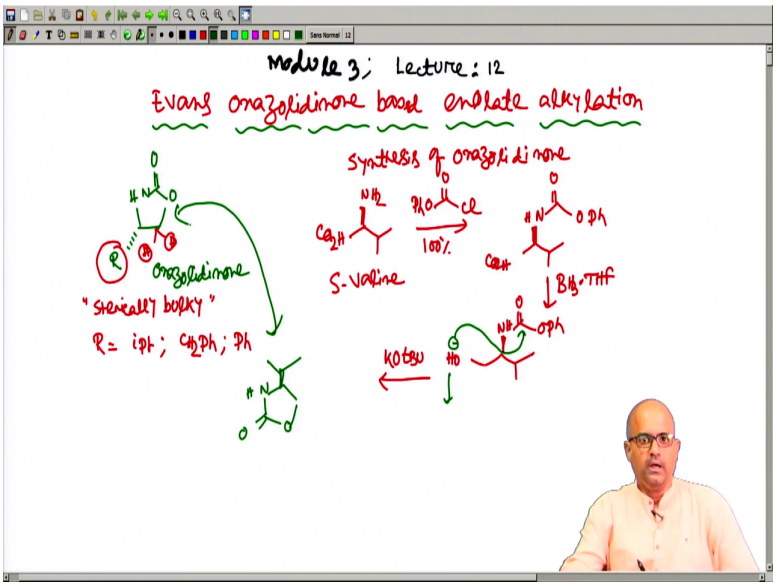

Welcome back students. So, today we will be continuing with our module 3 lecture 12; and the last class we actually have discussed the Evans oxazolidinone based asymmetric alkylation of an enolate species.

And we said that this oxazolidinone, if you simply write the structure of those compounds. Usually this compounds have a basic structure which are something like this and this compounds are usually commercially available even you can make this compounds in the lab also. Now this oxazolidinone the basic features we have already discussed this basically having a stereogenic carbon containing group here and this R group which is usually a sterically bulky group was chosen.

And nature of this group usually dictates the asymmetric induction. Now in usual cases R is normally isopropyl or you can take benzyl means this CH2 Ph. Other group also was chosen like phenyl or something like that. In few cases like higher order oxazolidinone this CH2 also can be substituted with different alkyl groups ok.

Now, first start with the simple oxazolidinone which are having basic structures. How you can prepare those oxazolidinones. I mean definitely if you are having enough funds of in your lab then you can definitely buy those oxazolidinones. Now you can also make those oxazolidinones starting from simple commercially available amino acids. So, let us talk about some usual synthesis of how this compounds are made.

We choose enantio pure amino acids which seems to be commercially available, like this amino acid which is S valine and is known to all of us. Now this S valine was initially reacted with this compound, this aryloxy chloroformate and so this nitrogen group this amine group was kind of protected with loss of HCl and then your remaining part was intact. So, this and this stereo center remains same ok.

And the yield is almost quantitative 100 percent yield the initial case and then now this compound this free carboxylic acid was reduced with borane THF. So, this reduction everything remains same this NH and this C double bond to oph remains as it is. This isopropyl group, then you are basically reducing this carboxylic acid group to this alcohol.

Now, this amino alcohol you treat with potassium tertiary butoxide as a base and what it does this base basically abstracts this proton and so it generates a O minus here and this O minus attack to this CO. So, eventually and then you get your desired oxazolidinone. So, you can just write the oxazolidinone in this way and you finally, get this compound. So, which is nothing basically, so these compounds are this compound where this R is isopropyl or starting from valine.

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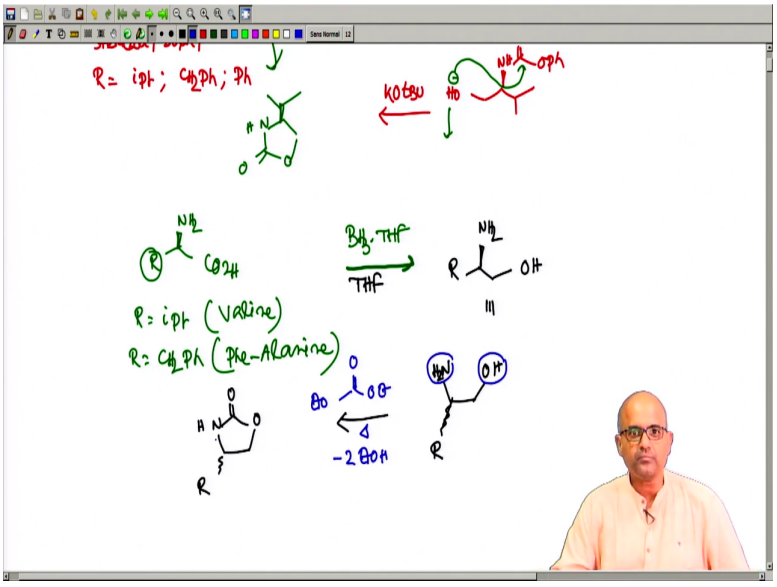

Now, there are definitely other way to make this compound, will try to give you another simple way which is also you can start from usually this amino acids kind of derivative. Let us take a simple amino acid, I put a very general structure where this R is your isopropyl or if

R is isopropyl you can take this compound is valine ok. If R is CH2 Ph or benzyl this compound is phenylalanine.

So, these amino acids are naturally occurring and absolutely you can use those amino acids. Now let us see how this synthesis was done. This is another way you can synthesize this compound. You just treat this compounds with simple borane THF. So, this carboxylic acid of this group is reduced and the solvent was THF ok. So, what you get you basically get this amino alcohol. So, this amino alcohol is usually you can use it.

Now, we will write this amino alcohol in a different way, so that you can think about the synthetic procedure. So, this could be your amino alcohol. Now this stereo center I just put in zigzag way because depending on which enantiomeric amino acid you have taken. Now this is the amino alcohol. Now what you need to do? You basically need to get the oxazolidinone whose structure is already we have talked about is something like this.

Now, basically this is the amino group ok and this is the OH group. So, basically you need to remove 1 hydrogen and 1 hydrogen here and 1 oxygen you need to basically incorporate. So, then usually you condense this compounds with a similar very simple compound which is a diethyl carbonate, which is carbonic acid ester and now by heating this compound a 2 molecule of ethanol is usually going to be released and you get this compound. This is also another method of repairing the this oxazolidinone.

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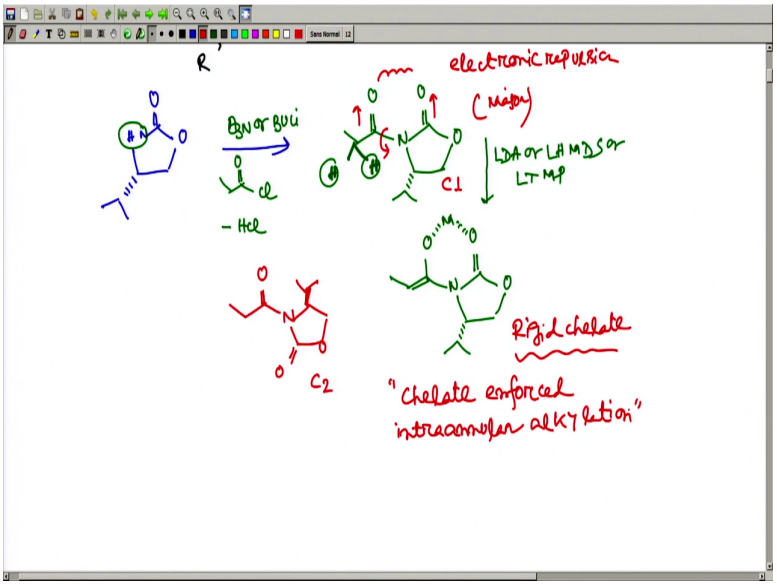

Now, next part, once this oxazolidinone was generated next was your how you can use this oxazolidinone for the asymmetric alkylation. We have already given you a hint in the last class, but still we can talk about little bit of next step. Now this oxazolidinone you have it. Now this is the contact point, this is the amino group this is the contact point.

So, your electrophile has to be approached from the opposite face. But, what is your substituted precursor? The precursor is basically carboxylic acid derivative and usually highly reactive carboxylic acid chloride was used and you need a base is like triethylamine or even stronger base like butyl lithium was used.

Now, this base basically picks up this hydrogen and this N minus reacts here with loss of HCl. You can actually get the corresponding oxazolidinone which was now coupled with your acid chloride. Now see this compounds are basically an amide derivative initially you have acid chloride now have a amide. Now the next part which is the hydrogen abstraction or your enolate generation. So, this is already we have discussed. So, you now treat with a pretty stronger non nucleophilic basis like LDA or even LHMDS or even LTMP.

So, those bases we have already talked about and as I said initially you get a chelated thing. So, you now write this your amide part this will this and this is your isopropyl group or other group. Now see the metal which is now forms a chelate here. So, this rigid chelate and you definitely have the which enolate you can eventually see this is the Z enolate, the other enolate would not be formed because that will give you the methyl here and that is interacting with the allylic 1 ,3 strain.

So, this enolate is the most stable one. Now we also discussed that in this conformation the of this amide if you draw in this way you see this CO dipole is this and this amide CO dipole is also this. So, there might be a strong electronic repulsion here ok. This electronic repulsion is there electronic repulsion. Now if such electronic repulsion is there that might force you because this bond if you allowed the rotation the usually probably the amide resonances is operating.

But, still if you can allow this rotation here, you will find that to minimize the dipole repulsion this compound might undergoing a rotation and that basically forces this group in the other way. So, this also another competing conformer. So, we can write this is conformer 1 this conformer 2, but usually this conformer was the predominant or major as it gives you a chelate.

So, this rigid chelate which was the main driving force for this high asymmetric induction ad we have already discussed such strategy in terms of chelate enforced, chelate enforced intra annular…… intra annular. Basically you are forming a cyclic transition state and you call it chelate enforced intra annular alkylation. At the beginning class we have discussed different mode of asymmetric induction.

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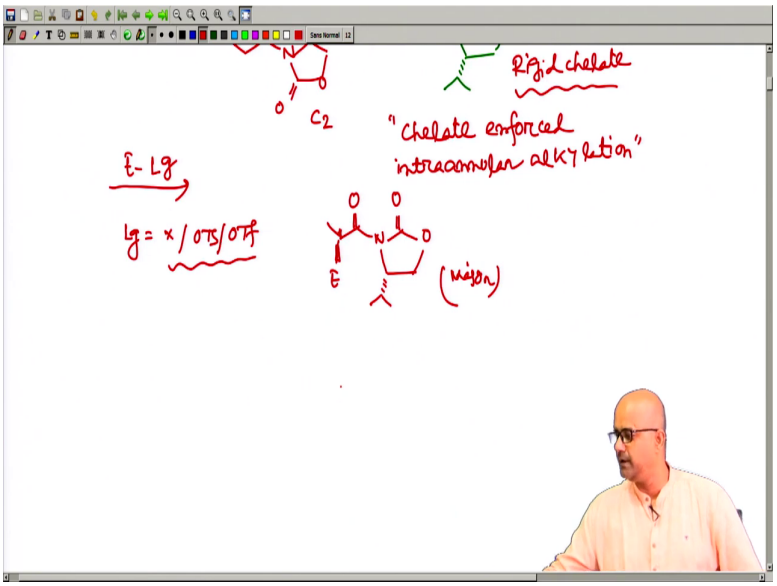

So, now you can see once this chelate was forming this C1 conformation then you treat the electrophile. Definitely the electrophile is your choice whatever electrophile you will be using and usually the electrophile has 2 components. A electrophile means a group alkyl group or something and then you have a leaving group. Now this leaving group mostly are halogens or O-tosylate O-triflate.

So, this are few leaving group and then after this alkylation you are basically getting a carbon electrophile new bond and as the enolate is planar sp2 and is it is the isopropyl group is in alpha. So, this carbon electrophile bond is now beta ok. Now once you get this as a major product your new stereogenic center formation was done. But what next? Next is to remove the auxiliary ok.

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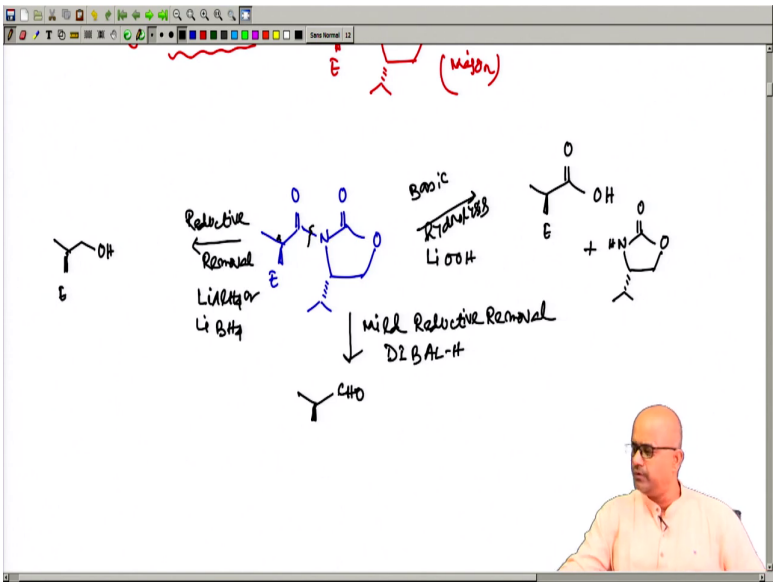

Now, for removing this auxiliary there are few important points you need to remember. We will just explain how you can remove those auxiliaries, once the alkylation was done. Now, the main important factor is sometimes you need to remove or you need to recover the auxiliaries because this auxiliary is very expensive.

So, if you can remove sorry if you can recycle those auxiliaries it will be quite good in terms of cost economic matter. So, now see you need to actually clip this particular bond; this particular bond means this amide bond ok. And this stereogenic center has to be remain intact and usually there are different ways you can actually first one you can remove through a basic hydrolysis.

And in the basic hydrolysis it was usually found that a lithium hydro peroxide kind of compound was preferred was and then once you remove this auxiliary they you actually, this is basically amide hydrolysis and you get the corresponding acid with the auxiliary back.

So, this auxiliary again you can reuse for your next synthetic exercise ok. You can also do a reductive removal. In the reductive removal what you do you basically treat this alkylated auxiliary with a reducing agent. Now if you use a strong reducing agent like lithium aluminium hydride or even lithium borohydride or even sodium borohydride that basically will give you the corresponding CH2OH. So, different oxidation state in here you can get alcohol and here you can get carboxylic acid.

There are other ways if you try to do a reductive removal in a mild condition. Mild reductive condition like you doing a pretty mild or reducing agent like dibal-H or RedAl and in those cases if you use one equivalent you can actually stop at the aldehyde step. So, these are few conditions where you can try to remove it.

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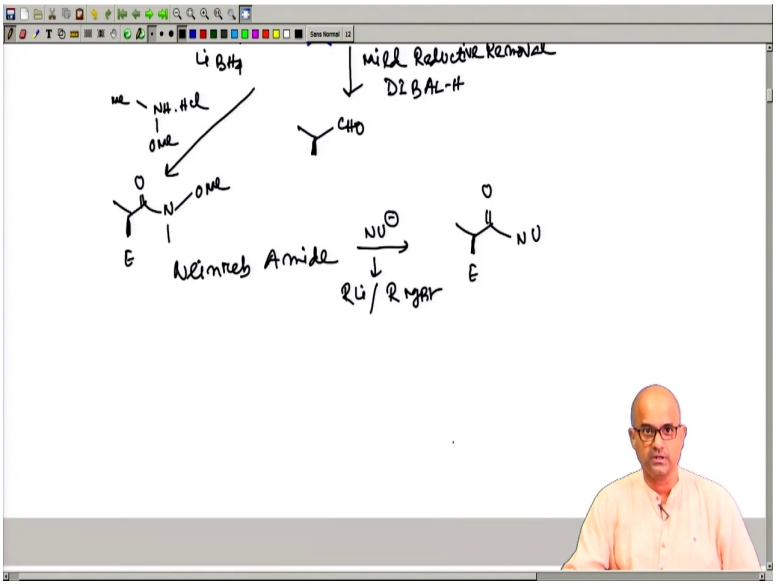

There is another important conditions if you can do a transamidation reaction. A transamination means you now treat this compound with a Weinreb amide derivative. This Weinreb amide derivative and that basically will lead to a corresponding Weinreb amide ok. And this Weinreb amide now you can this is Weinreb amide derivative and this Weinreb amide you can actually later on react with a various nucleophile to get the corresponding ketone.

So, this is …… if this Weinreb amide now you can treat with different nucleophiles species you can get the corresponding ketone. The nucleophiles are normally what nucleophiles are chosen an alkyl lithium or an alkyl Grignard aryl Grignard, those are usually chosen. So, these are way you can basically reductively cleave the auxiliaries, you can hydrolytically cleave the auxiliaries, you can do a mild reductive removal and even you can do a Weinreb amide based transamidation reaction.

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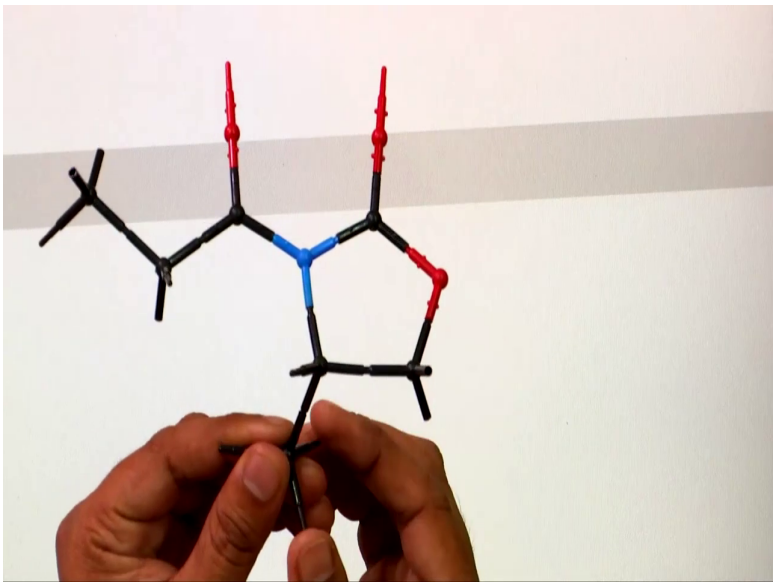

Now, coming to the typical model I will show you a model and then you can feel that this model basically a ball and stick model for this Evans auxiliary things. Now see the isopropyl group which I am holding with my two fingers. This is the isopropyl group.

So, is the below of the plane the cyclopentane ring the blue color is the nitrogen then you have a C double bond O the amide oxygen red color is the oxygen. As oxygen the ring which is coming from the amino alcohol outside you have a CO which is coming from the acid chloride. You pick up or remove this 2 hydrogen to generate the enolate. Now see if you have this enolate if you try to get E enolate ……the severe 1,3 interaction that is what you always get the Z enolate.

Now, this 2 oxygen basically chelates with the metal you get a 6 member rigid chelate fine. And then the planar electrophile based on this particular group ok; this particular group as it is below the plane the electrophile comes from the opposite ok. So, this was the very simple ball and stick three dimensional model which will essentially can explain the origin of asymmetric induction for this system.

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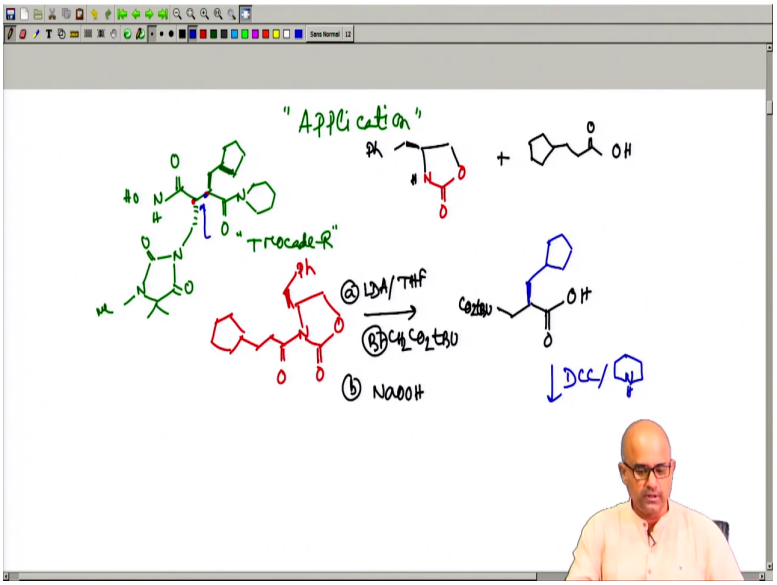

Now, we can talk about few more things and eventually the most important point in the Evans auxiliary was its application ok. Now in the application we will be definitely discuss few more examples and initially let talk about how this auxiliary based thing was used for synthesis of various important molecules like drug intermediates, drug like candidates, various chiral intermediates for natural product synthesis.

One such compound we will now just discuss the structure of this compound. I just try to write it down its a hydroxamic acid derivative and this compound structure was a bit bulky. Bulky means it basically is bit complicated structure, but ok we can just write it with a cyclo pentane ring and then this part this is having a amide ring or a piperidine kind of moiety cyclic amide and then with this part they are having a again a cyclic urea derivative.

So, this molecule is a drug molecule and this drug molecule name is Trocade R. I will write the structure is a having in methyl and this is to gem dimethyl ok, cyclic urea. Now this molecule …..name is Trocade R. It is a drug molecule and this molecule was actually it is a used as a matrix metalloproteinase inhibitor and this compound was used as an active drug molecule for treatment in the rheumatoid arthritis and the patients who are having a joint pain ok.

Now, this molecule if you can see this was basically used in industry to synthesize this molecule. These two stereo centers were actually being planned to use by Evans oxazolidinone based alkylation. Now let me talk about the forward synthesis in a very

straight forward way. So, it starts with this CH 2 cyclopentane based compound. There are these things and then you take the Evans oxazolidinone based oxazolidinone yeah.

And this oxazolidinone was actually made from corresponding phenylalanine derivative. See this is the oxazolidinone we have used. So, what you need? You basically need this particular oxazolidinone which you can prepare from the commercial source or you can make in the lab. See this phenylalaninol here ok this part.

And you need what? You need a this cyclopentane based carboxylic acid. So, it is a CH2 CH2. So, there are two CH2 CH2 CH2 CO2H ok. You just make the corresponding acid chloride and you do it and then what you need to do? You basically treat with LDA. You get the corresponding metal enolate THF is a solvent and then you react with electrophile which is Br CH2 CO2 tertiary butyl.

So, this bromine is the electrophile thing and after this reaction so initially you get this compound and then they actually first step is this and followed by a hydrolysis by sodium hydro hydro peroxide and then what will get? You basically get the corresponding this amide bond is means chiral auxiliary part was removed. So, we will write the simple thing CO2 H and this part is your electrophile electrophile means CO2 tertiary butyl.

Remember the tertiary butyl ester was not removed ok. And then this is the stereo center which is actually created by the auxiliary derived thing. Now in the molecule, so this stereo center was created by the Evans asymmetric alkylation with the oxazolidinone chemistry ok. Now next part was very simple you actually react with DCC and the compound is your pi paradigm which actually coupled with this 6-member amide.

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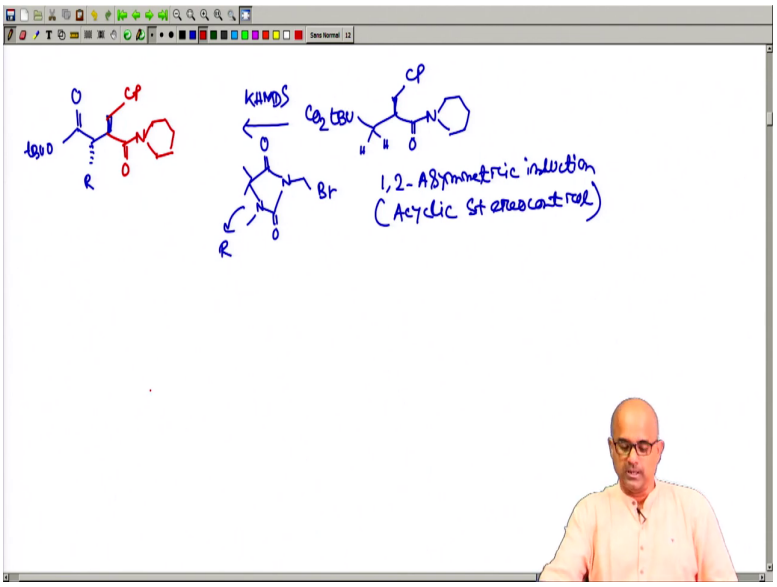

And you get the let me write the compound. It is your cyclopentyl structure and you get CON this piperidine. The structure everything was almost like similar you need to have another group which is this part ok and here also we will be doing a simple alkylation. This kind of concept was also we are already discussed earlier we treat with a base KHMDS.

You see there are hydrogens here. So basically now you can remove this hydrogen and you can get the enolate and the electrophile which now they have used in the industrial people. They use this particular part as the electrophile and then cyclic urea based electrophile, they have used and let me write the structure N methyl and then this C ON CH2 Br ok. Now this group was above. So, is a simple 1, 2 asymmetric induction which already we have discussed in the substrate directed alkylation and as this group cyclopentane group is beta. So, it is a pure case of acyclic stereo control ok.

And in this acyclic stereo control you get one to trans compound means finally, what you get you get C O tertiary butyl. This ester and then you get this entire group which you can now write as a let us say you write as a R. So, this R group is here and this you have this your cyclo will use a different color pen. You have this cyclo pentyl you write cyclo pentyl and this part is your pi pyridine part.

So, only part which is remains to be accomplished you just hydrolyze this tert butyl ester and introduce the hydroxamic acid. Now actually Trocade R was synthesized in a multikilogram scale by using this method and this method was quite useful as it was allowed a industrial

preparation for this molecule by applying a Evans asymmetric anodic alkylation as well as simple 1,2 asymmetric induction through an acyclic stereo control mode.

But, definitely there are many other ways to synthetically manipulate this Evans asymmetric alkylation based technique. We will be trying to use or we will try to explore such things.

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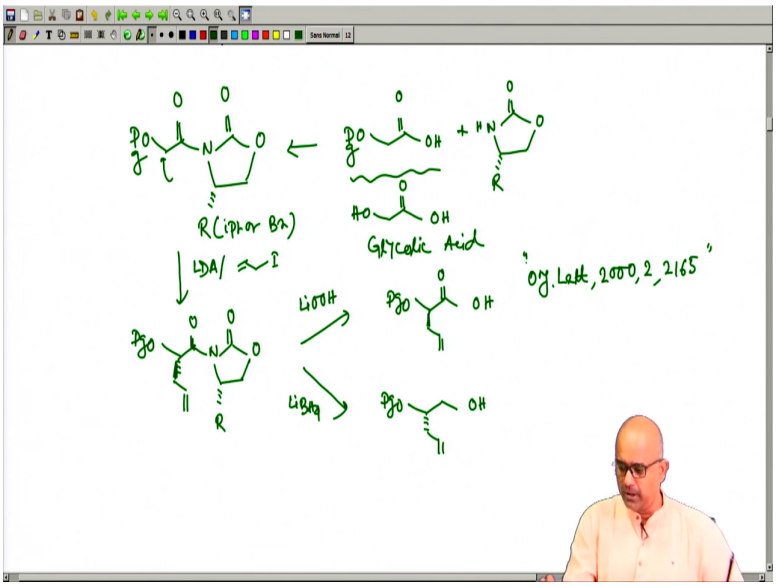

And next what we will trying to use it, we are basically will be trying to give you this Evans asymmetric anodic alkylation in the field of 1 minute this ok. So, you such compound was initially used as a precursor for.

Now, what is this compound? How you can prepare those compound? This compound was usually prepared this pgO stands for a protecting group ……OPg. So, you get basically this kind of carboxylic acid its derivative and use this oxazolidinone as a main source of thing ok. Now what is this?

This compound is basically a protected glycolic acid glycolic acid you can write the structure which you have already discussed in the self regeneration of stereo center. This compound is named as glycolic acid ok. Now what does it mean? It means that you now have an Evans oxazolidinone based on glycolic acid and in this part you want to create a new stereo center with the help of Evans oxazolidinone based method. Now what you do? You treat with base like LDA and treat with simple electrophile.

Let us say you treat with allyl iodide as a good electrophile ok. So, after the initial thing what you will get? You basically get this electrophile will approach from the above phase because the R group. This R group might be isopropyl or a benzyl group ok and then you can simply write the compound which you will get and then you can remove the auxiliary by different way. Let us say you can do a reductive elimination or a hydrolytic thing.

See if you do a hydrolytic elimination hydrolytic cleavage lithium per hydroxide. What you will get? You basically get the alpha alkylated acid. This kind of acid now this kind of acid is basically a lactic acid derivative enantiomer chiral lactic acid ok or if you want to do a reductive cleavage like lithium boro hydride you can get compound something like this which is a 1,2 diol protected things in (Refer Time: 30:29) fashion.

Now, such compound or such method was reported in the literature in 2000. So, the idea was not very old …….kind of 20 years old and Evans actually invented this auxiliary in 1996, but this was reported in 2000. So, Evans auxiliary based asymmetrical alkylation was still a very popular method and let try to give you some of the home task which you can eventually try to solve it.

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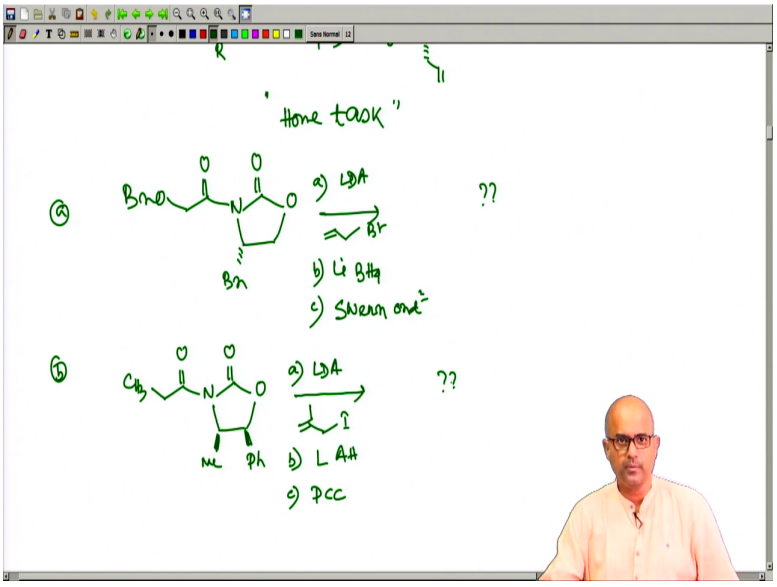

When you do some practice in your laser time. So, let write a compound something like this which is basically based on the Evans oxazolidinone based thing. You have this compound which is just now we said. So, assignment 1; so what are the things you are doing basically

here? You treat with LDA treat with allyl bromide fine and then you react with lithium boro hydride and then I will be giving you some extra things, you will do a Swern oxidation.

So, you can you have to write the product what you are going to get fine. Assignment number 2 again based on a similar kind of concept and actually in subsequent classes we will also do some solved assignment analysis based on this concept. So, now you can eventually see this is another auxiliary. Now this auxiliary is similar, but as a methyl and a phenyl both are beta. So, you can eventually try to correlate the beta face is completely blocked by this 2 group which occupies the beta phase of the enolate fine.

What is the condition? The condition was LDA fine and we use a very strongly reactive meth allyl iodide as an electrophile and then we react with lithium aluminium hydride followed by a PCC oxidation. So, you need to predict the product. Now there are few very simple problems which you can which you can analyze.

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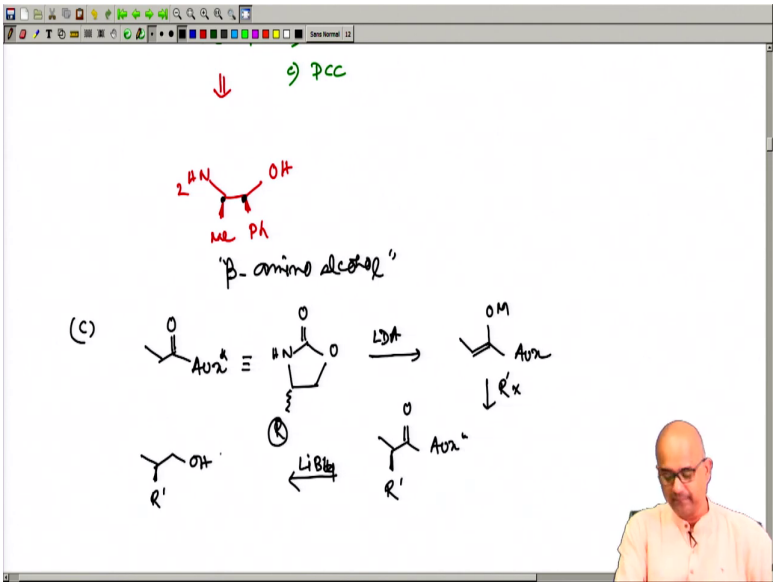

Now, in continuation of the second problem you can actually eventually think that how this auxiliary was generated. This auxiliary was usually prepared from a compound something like this which are actually beta amino alcohol. This kind of beta amino alcohol which is basically this now see this particular point this and this they are. So, this beta amino alcohol is also commercially available and this beta amino alcohol are very good a very good alternative for the normal amino alcohols and asymmetric induction seems to be kind of

comparable because as both the groups are having a similar kind of stereo steric sense of preferences.

And you can simply apply the entire technique by using this way. Now let me try to give you another assignment which also seems to be quite possible ok. We will just try to give you another assignment. Now here I put an auxiliary, auxiliary means your oxazolidinone. This auxiliary basically you can choose your auxiliaries according to your preferences. So, you have the liberty.

So, this R is your main thing and this R could be isopropyl could be a phenylalanine sorry a benzyl group and the stereo center was important. I have not given any stereo center. Now such thing we know very well, you treat with LDA. So, it basically gives you a metal enolate, the auxiliary remains same. It is trying to give you a typical conceptual analysis of a normal problem.

Now, let us say you treat the electrophile and this electrophile definitely based on this auxiliary you will get; let us say this auxiliary having an alpha stereo center with the R. So, definitely you get a R prime here and then with your CO auxiliary fine. Now this auxiliary you have you can remove it. So, you can do a reductive removal let us say lithium boro hydride. Now what you will get? You get a R prime here R prime here. You get a CH2OH fine.

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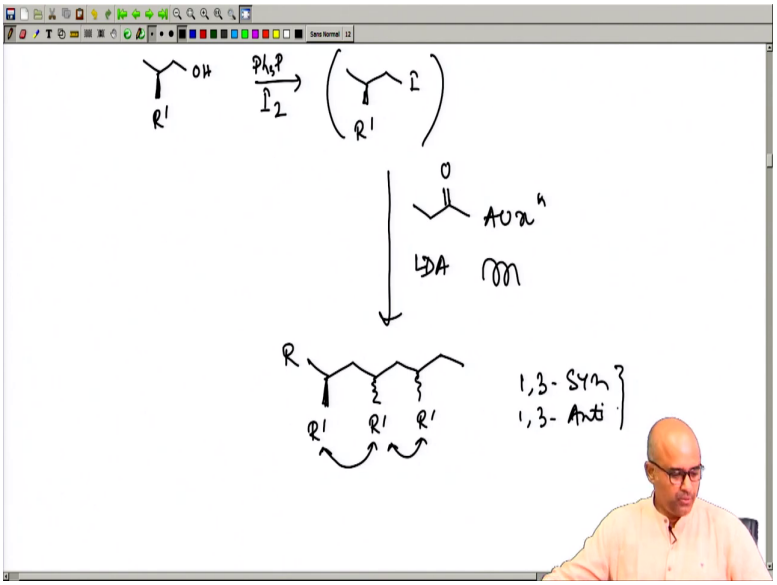

Now, with this CH2 OH with this CH 2OH we go to the next page with this CH2OH what you can do? Now this CH2OH with this methyl or R prime is fixed. You can actually convert this OH to an another electrophile by simple SN2 reaction. You can just do an Appel reaction by Ph3P…….. iodine. So, this now gives you a I fine.

Now, this you can use in a next round of alkylation. So, now, you can let us say you can try to use such auxiliary again for your you take the initial starting material this auxiliary and then you do a LDA and this electrophile this electrophile. Now eventually you can see that normally this series of alkylation you can happen and actually you will usually generate either syn or anti. This kind of series of 1, 3 either syn or 1, 3 anti based stereo chemistry depending on your choice.

So, you can basically do a repeated round of alkylation ok. So, this 1, 3 syn and 1 ,3 anti you can easily create. We will discuss those things in the next lecture or probably you can just take it as a home assignment. So, we will definitely discuss.

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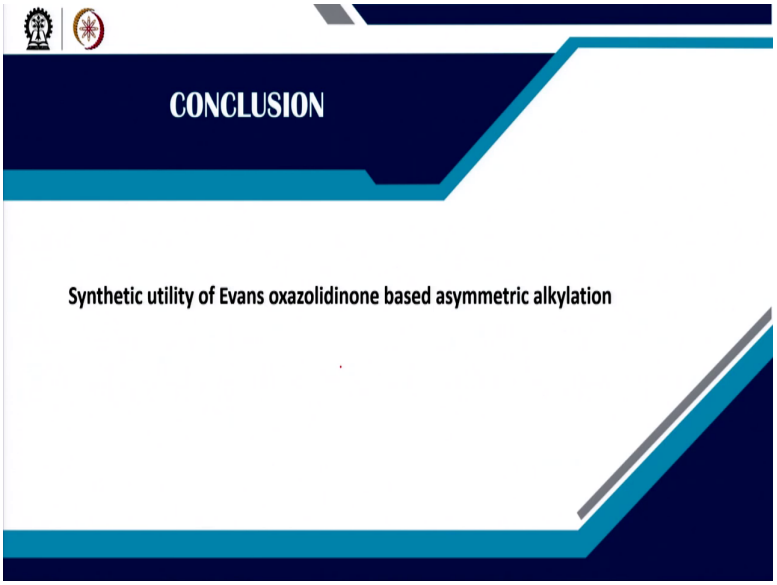

So, as a concluding remark we can say that Evans oxazolidinone based asymmetric alkylation is a very powerful method and very versatile method and in the subsequent lecture definitely will be talking about much more of its application in the field of organic synthesis. So, ok we will see you in the subsequent lectures.

Thank you everyone.