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 - 05
Enolate alkylation of carboxylic acid derivatives
Lecture - 21
Meyer's oxazoline based alkylation - I

Welcome everyone. So, we will be going to start a new module 5, the basic idea was basically we will be trying to talk about Enolate alkylation of mainly Carboxylic acid derivative in this module and in the first lecture 21 we will be talking about Meyer's oxazoline based alkylation.

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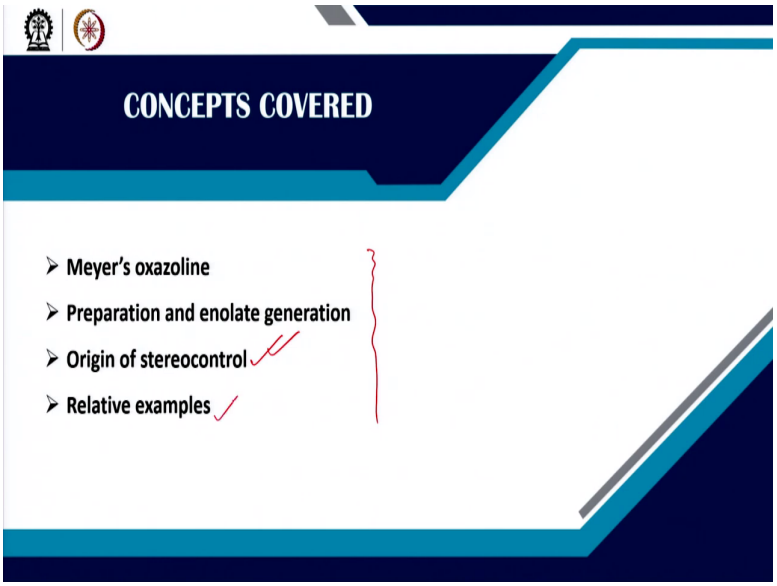

The main content which we are going to cover today what are Meyer's oxazoline its again a chiral auxiliary and particularly it is very useful for a carboxylic acid derived substrate's enolate generation and how you can alkylate in asymmetric fashion to this enolates.

Origin of stereocontrol we will be discussing and definitely we will talk about few case studies with relative examples.

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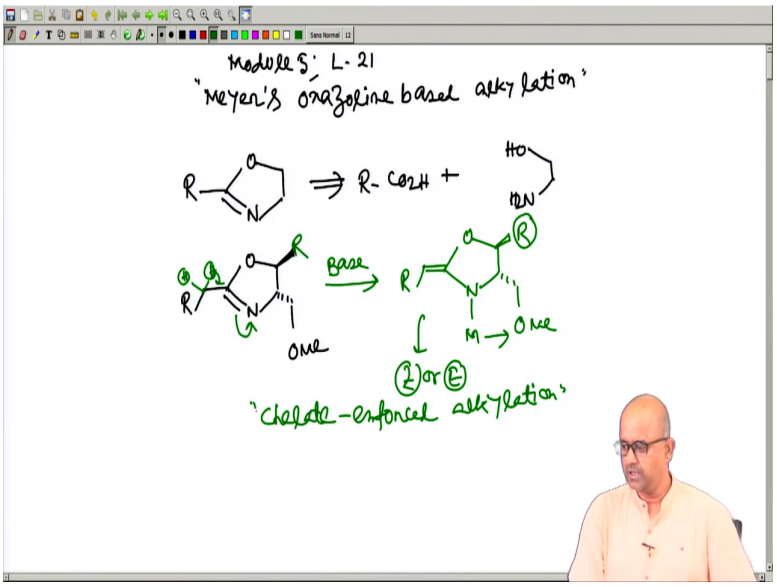

So, we will be discussing Meyer's oxazoline based alkylation now what are oxazolines? Oxazolines are usually a functional group which does have a structure something like this ok and usually this oxazolines can be easily prepared from corresponding carboxylic acid with a simple amino alcohol when they reacted with carboxylic acid.

We will discuss those methods little bit later on. Now in the Meyer's oxazoline method let me try to draw the Meyer's oxazolines method, which was first invented by late Professor Albert I Meyer's from University of Colorado. Now this is the structure of the Meyer's oxazoline now in this case the carboxylic acid derivative has an alpha hydrogen adjacent to this thing.

Now, what is happening initially, if you treat with base the hydrogen will be abstracted and the moment it abstracted it basically comes here and gives you a negative charge on the nitrogen ok. So, that basically let me try to see the structure it will give you this N this if you have a something R group here something R group here. And then you have a OMe you have a metal containing thing if you are using a metal containing base.

Now this gives you a chelation. So, a rigid chelate is forming basically the enolate could be Z or could be E and the incoming electrophile it is mainly controlled by this alkyl group here. So, this is again an example of chelate enforced alkylation and as you are forming a ring or annule. So, chelate enforced intra annular alkylation you can say.

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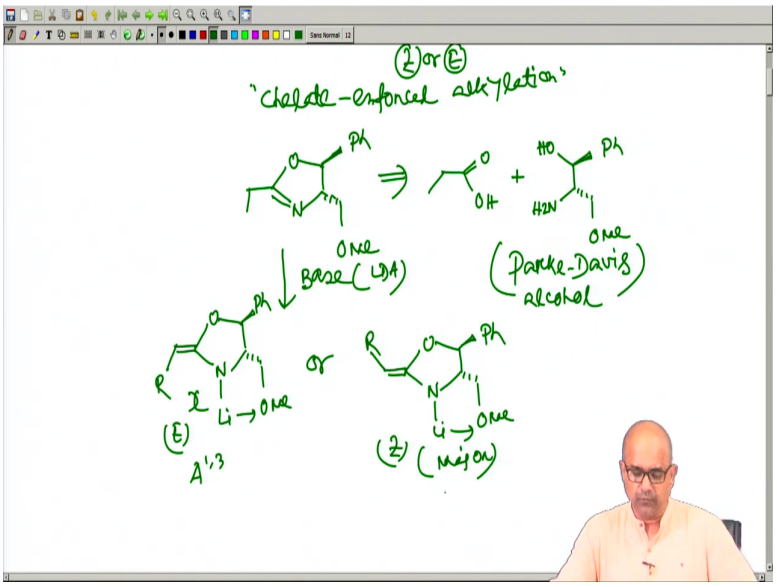

Now, let me try to give you some features of the Meyer's oxazoline based method. So, initially before we try to talk about the synthetic aspects, let me see how this oxazoline was. So, this is the parent oxazoline which was actually having this kind of structure.

Now, this oxazoline was mainly prepared by taking this propanoic acid, I will give you the detail method and this was the amino alcohol which was used. This amino alcohol was named as Parke Davis amino alcohol because, this Parke Davis alcohol was first synthesized by a pharmaceutical company Parke Davis and this is given to Professor Meyer to carry out some of his research.

So, this Parke Davis amino alcohol or Parke Davis alcohol was the main starting material. Now once you have this oxazoline, which you prepared then next part is your generation of the enolate ok. So, let me try to put a base and you abstract the enolate. So, you get this as one of the enolate with let us say if you treat with the lithium base like LDA kind of base you get lithium.

Now, you have a close proximity a methoxy group. So, a chelation cannot be avoided you get the chelation and you have a phenyl group here now what is this enolate? This enolate is usually an E enolate ok and you get another enolate which is the Z enolate. So, this, this, this OMe rest of the part are similar you have this phenyl.

Now, in this case actually this when you have this R group here, this kind of probably gives a strain mainly due to allylic 1,3 kind of strain allylic one three strain, but here such strain is minimized. So, Z enolate seems to be the major enolate which is forming here now once this Z enolate is formed next is your approaching of the electrophile.

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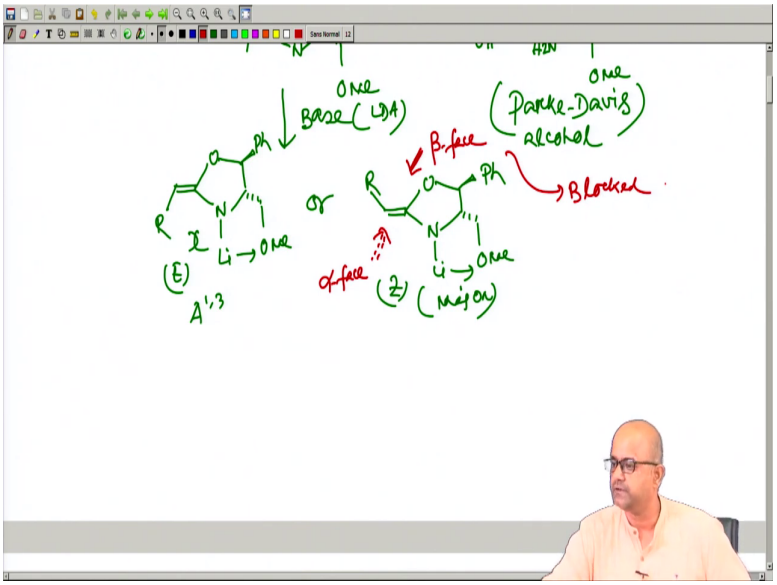

The approaching of the electrophile will be taking place mainly from the alpha face because the beta face seems to be blocked by the. So, beta face attack seems to be blocked by the bulky phenyl group. So, beta face attack is blocked. So, beta face attack is blocked. This was the general consideration or the working model for this Meyer's oxazolidinone sorry oxazoline based alkylation ok.

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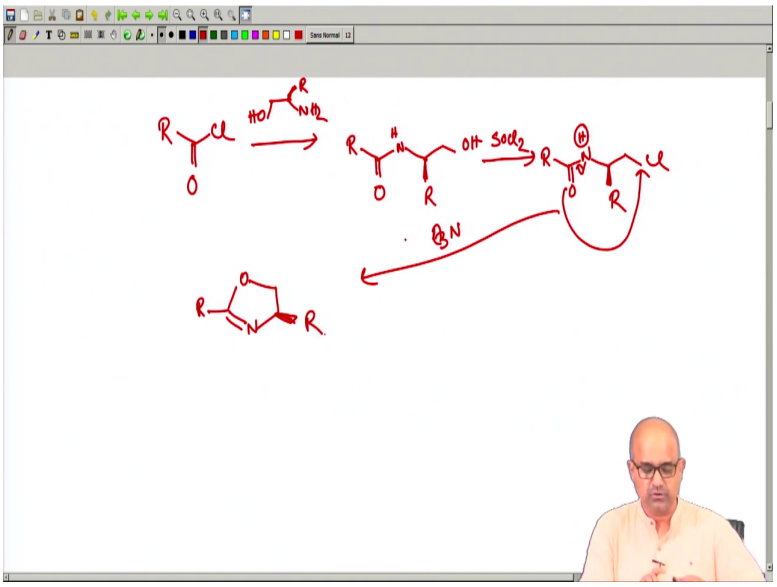

Now, coming to the preparation of this compound usually a very standard literature method was there you first take the acid chloride which you can easily convert easily prepare from the corresponding carboxylic acid, then you take a simple amino alcohol which could be your Parke Davis alcohol or something else you just write this R group ok this NH2 ok. And initially this acid and amine acid chloride and amine coupling will take place and you get the secondary amine NH.

Then you have this corresponding chiral center here and your CH2OH ok. This was later on converted to if you trying to do a step wise way a thionyl chloride which basically gives you this NH2 a sorry this CH2OH 2 a CH 2Cl ok and this part remains the same.

And then a base a simple base like triethylamine was used Et3N was used. Now what this base does this basically abstract this hydrogen this was abstract this hydrogen and then trying to give this thing as a O minus and this O minus then attack this CH2Cl through a intramolecular SN pathway, and then you will be getting this oxazoline as a main precursor.

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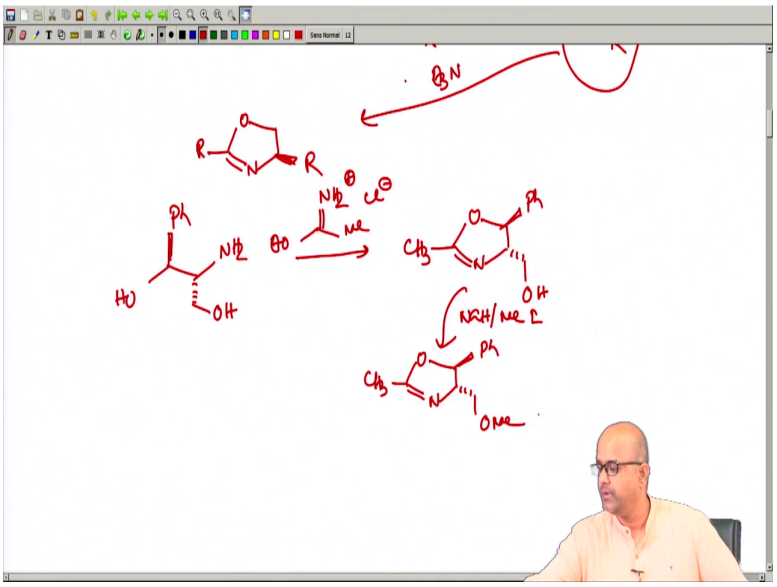

So, this was one of the method, but for the Meyer's oxazoline part we normally prepare this thing with a you take this amino alcohol or the Parke Davis alcohol which was given to you this. And then actually react with a amidine kind of derivative first this was basically acetonitrile derivative if you are interested I can give you the references or even I can explain the mechanism.

But this is the salt of this ethyl imidate of acetonitrile ok. Now this compound was initially reacting with this amino alcohol and that gives you this oxazoline at the beginning with this Ph and this CH2OH this CH2OH is later on converted to the corresponding methyl derivative by sodium hydride and methyl iodide treatment. This was very simple straight forward way of making this oxazoline in enantiomerically pure form. So, the moment you prepare the enantiomerically pure oxazoline next definitely we try to do some reaction.

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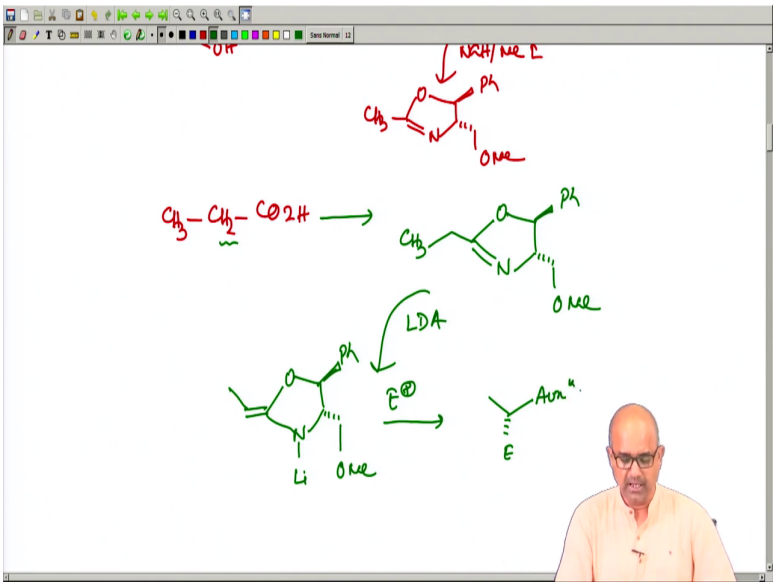

So, let me try to then take with a simple propionic acid. Now propionic acid the it is having an alpha hydrogen which can be easily abstracted. So, first you take this propionic acid and react with your make this kind of amidine derivative or the simple acid amine condensation like the in the thionyl chloride derivative you get the oxazoline.

So, oxazoline easily you can get. So, the moment you get the oxazoline you can eventually find that this structure was the oxazoline structure and actually oxazoline was used in carboxylic acid group protection. So, this oxazoline was used as a protecting group of the carboxylic acid. Now rest of the part is very simple you treat with a base definitely as you wanted to do it you get the Z enolate.

So, Z enolate means the methyl double bond your O your N. So, this is now the enolate which seems to be aza enolate kind of thing because the metal part remains with the nitrogen ok. So, you have this enolate. Now, electrophile will be definitely you take an electrophile the choice is yours the phenyl group as it is there the best possible way, if you write like this the it coming from the below of this group ok.

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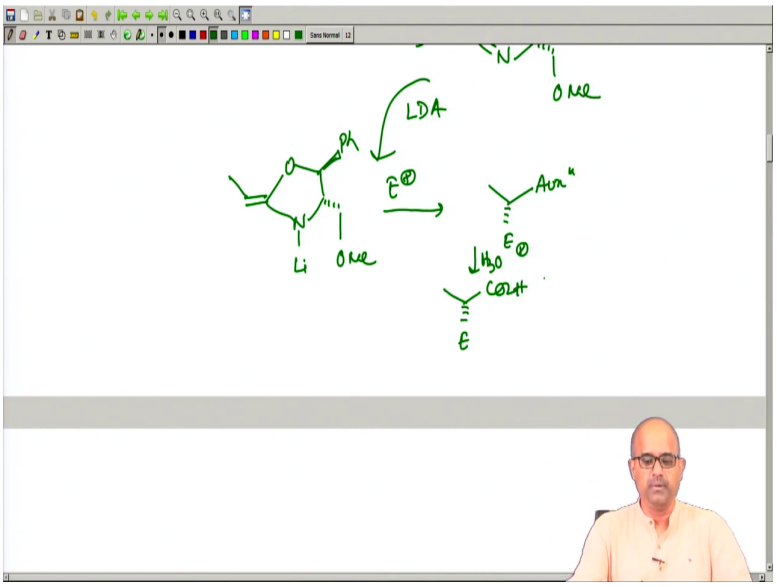

And then you have this oxazoline part, which you can write as an auxiliary and this auxiliary you can simply hydrolyze you can simply hydrolyze by H_3O^+ treatment and you actually get an alkylated carboxylic acid. So, this was in principle the Meyer's oxazoline method and this is a pretty interesting method and by using this oxazoline based method you can actually prepare a large number of enantiopure compound we will just next try to give you few examples.

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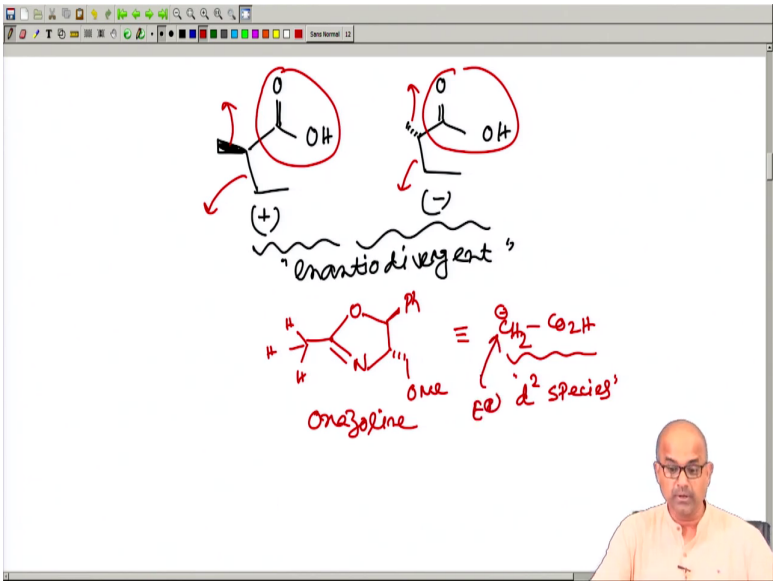

Let me try to talk about a simple two compounds, which are actually enantiomeric to each other. So, you have this compound and also I take its enantiomer by this. Now with a simple logic you might think that to make this compound. Let us say is the that is plus and this minus unit both the chiral oxazoline, but the idea was not that even for a single oxazoline you can actually prepare both the target molecule.

So, it is basically a enantiodivergent way …….enantiodivergent means the process in which you can get a divergency and as the enantio means both the enantiomer you can make it now we will give you little bit of structural information for oxazoline. Now you can see that if you have to target like this part is coming from the oxazoline; obviously, the carboxylic acid part fine.

So, the electrophile could be either this could be an electrophile or this could be an electrophile same thing happens ok. Now we will just try to write the oxazoline in a different way. So, your oxazoline are this ok with proper group. Now what you are saying that we are saying that these oxazoline this hydrogen can easily be abstracted.

So, in principle the oxazoline you can write as a CH2 minus CO2H ok. Now how many carbons are there? This is a two carbon ok and this is a nucleophilic species that is why we call it as a d2 species in a synthetic terminology or synthon terminology these species are named as d2 species ok.

So, oxazolines can be regarded as a d2 species. So, oxazoline can be regarded as a d2 species. Now you can add your electrophile ok and you can do the synthesis. Now let us come to the particular problem which was given to you.

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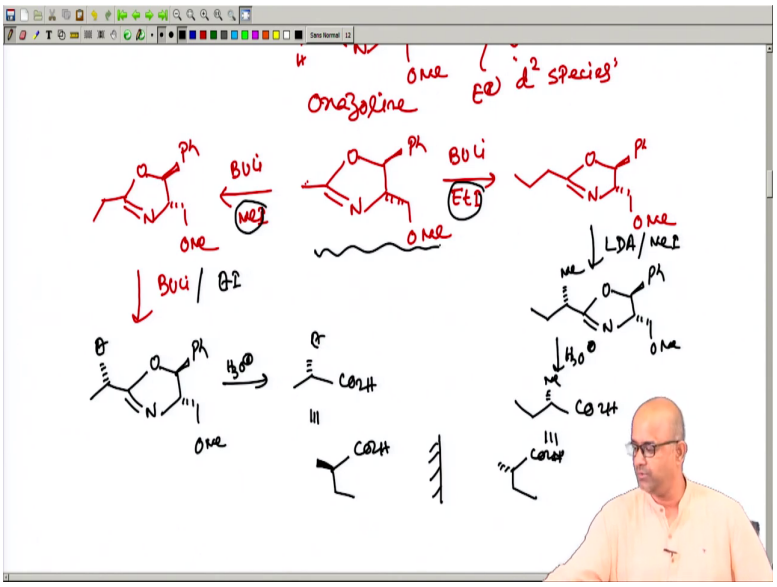

So, first we take the oxazoline at the very beginning. So, let me try to take a simple oxazoline, which is an acetic acid based oxazoline ok.

Now, here it is again a d2 equivalent definitely, but you are not creating any stereocenter here because there is no stereocenter formation. So, first you treat with base let us say butyl lithium also often used and then you use methyl iodide. A methyl iodide means you have a d2. So, you basically get this compound was at the very beginning OMe.

So, this is your starting auxiliary starting oxazoline. In the right hand side we will be doing a different thing you take BuLi, but we will be adding a one carbon extra electrophile now at the very beginning you it may not be clear to you, but once we finish the synthesis you can say why we did it that will be quite clear to all of you.

So, first is just basically making the higher homolog of this oxazoline. One case first we add methyl iodide one case ethyl iodide what is the logic? If you now see it here an ethyl a methyl an ethyl and methyl. So, one case we add the methyl first one case we add the ethyl first, fine.

Now, in this case methyl is already added. So, now, we want to add ethyl. So, the base; base is butyl lithium definitely and then you will be using an ethyl iodide now your asymmetric induction will come into picture ok. Now if you see the phenyl group is above. So, you can simply write the ethyl group in the below and then your oxazoline is this phenyl CH2OMe.

You can just do a hydrolysis by aqueous workup and you get ethyl CO2H. So, one product we got fine.

Now, in this case what we need to do? You just need to do LDA or butyl lithium and ethyl is already added now we need to add simple methyl. So, this the mode of stereo center asymmetric induction is remains similar methyl will be approaching opposite from the phenyl ring ok. So, your oxazoline is now this, this, this, this your Ph CH2OMe you just now do the hydrolysis H_3O^+.

Now, this compound and this compound you can just rewrite the compound and we will find that this compound corresponds to this compound and this compounds corresponds to CO2H and this. So, now, these two compounds are mirror image to each other. So, this was the it is basically a reagent controlled reaction. Reagent control means in one case methyl we add first and another case ethyl we add first and then the same sequences first is added methyl and ethyl, ethyl and methyl.

So, this is the enantio divergent which is coming from the same auxiliary or same starting material and through a reagent control or synthon control you can actually access both the enantiomers of the target molecule.

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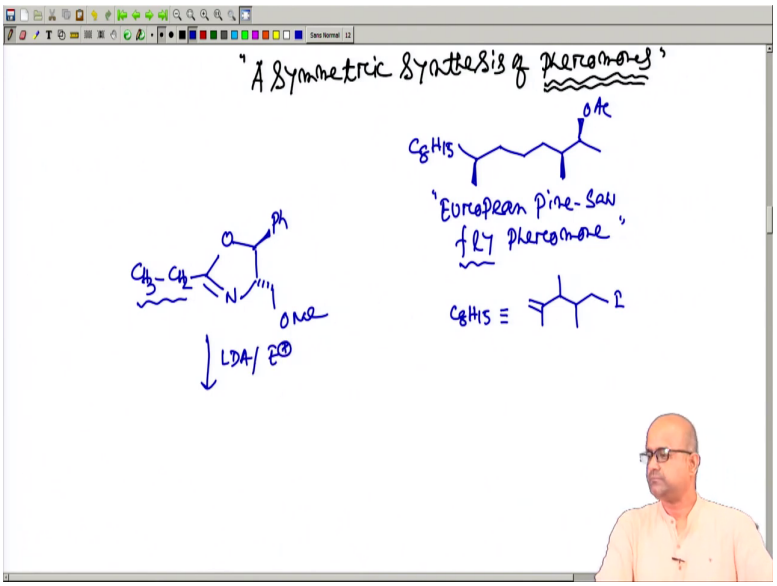

Now, such conceptual analysis we will be explaining little bit later on maybe not in this class, but we will be just switching over to one very interesting example for a real life synthesis of a pheromone molecule asymmetric synthesis of a pheromone molecule.

Now, pheromones are molecules, which are basically secreted by some insect as well as some of the mammalians also secrete the pheromones their main role is to give you a signature mark that this area belongs to me or I am here. So, in most of the cases pheromones are basically acting as a transmission agent and they basically try to attract the other counterpart during the usual mating time.

Now, one of the pheromone whose structure will be now I am writing this compound is isolated from European pine sawfly hormone ok. Now this compound structure is not that complicated, but there are 3 CH2 group and there is a methyl there is a OAc and there is a methyl here. Now this was the hormone sorry the pheromone, which was isolated from European pine tree, which have some fly hormone sorry the European pine sawfly and from there this pheromone was extracted.

So, this fly usually secretes some chemicals to attract their counterpart and this is the structure and this naturally occurring secondary metabolite actually synthesized by using this Meyer's oxazoline based method. Now we do not talk about the retro because it takes some time. So, I will just directly go to the synthesis how this compound was prepared.

Now, you can see the initial oxazoline, which you have taken is basically coming from the propanoic acid C3 ok and the C8 H15 ……the C8 H15 I should draw the structure this is a basically a primary iodide, but its structure is this its having a methyl here its having a methyl CH2 I this is the C8 H15 group ok and this C8 H15 group was there and now once you have this initial pheromone sorry the oxazoline you react with first base like LDA and this is the primary iodide you add the electrophile.

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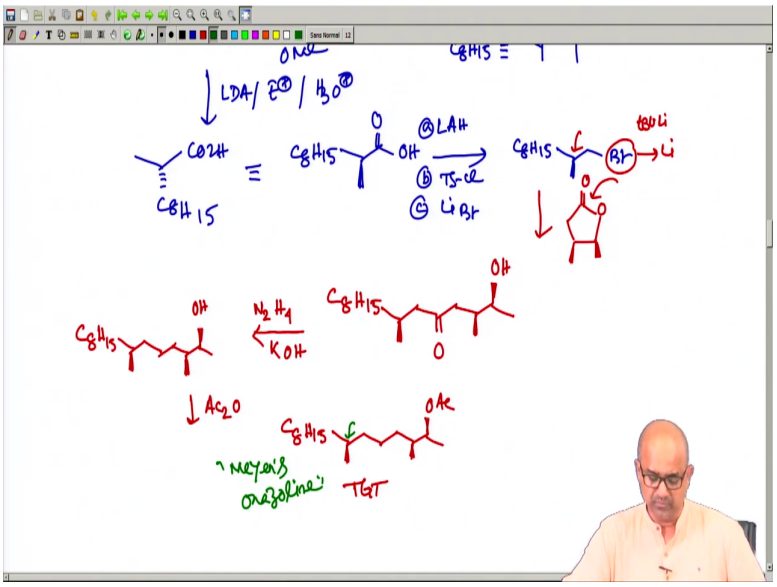

And then you do the hydrolysis with H_3O^+. So, eventually you can now see that the basic was you have you have this compound your C8 H15 will be there and you will get CO2 H right as it will be coming from the opposite of the phenyl group. So, which is definitely you can rewrite the compound C8 H15 then you put the methyl here your CO2H. This is simple you can eventually try to get this compound it with very good asymmetric induction.

So, this is the enantiopure compound now rest to the synthesis was very easy first you react with lithium aluminium hydride that reduce the carboxylic acid to corresponding alcohol treat with tosyl chloride that gives CH2 OTs and then react with lithium bromide fine.

So, it will eventually give you another round of SN2 reaction and you will get a bromo compound. Now the Meyer's oxazoline part was up to this point, but fine as we have discussing you can basically write the remaining part of the synthesis to learn some new reaction.

Now, this compound was reacted with a enantiopure lactone now lactones are hydroxy ester we when they cyclize they gives you lactone. Now lactone and you are reacting with this bromine you first exchange with a lithium by treating with Tert Butyllithium now this basically act as a nucleophile ok. So, nucleophile reacting on an ester what is happening? That will basically give you a ketone right because all of us know that reaction of an ester with a Grignard if you use one equivalent that gives you a ketone.

So, C8 H15 this part is fine and then your CH2 then you get C double bond 2. So, this nucleophile is coming this carbonyl of this lactone ok. And then the two stereocenter which was already present in the molecule will remain same after opening one will be ketone this will be OH……. O minus and you can just do the aqueous workup. So, now, you can see we are almost close the final target molecule the structure is this ok. C8 H15 methyl CH2 CH2 CH2 three CH2 in between, but the carbonyl is not there.

So, carbonyl seems to be not required in the final target. So, you can do a reductive elimination reductive deoxygenation by hydrogen hydrate by Wolff Kishner reduction that is very trivial reaction the C8 H15 your methyl is here you have a CH2 CH2. So, 3 CH2 what was required was already there fine and you have the methyl.

So, rest what you need to do? You just treat with acetic anhydride because in the final molecule you have a acetate group in the target molecule. So, you have this you have this and then you react with O we get OAc. So, this is your target molecule. So, now, we can summarize this that this stereocenter was created by the Meyer's oxazoline method and such oxazolines are pretty useful synthetic intermediates mainly and they have been quite often used for the chiral new stereocenter creation through the enolate alkylation strategy.

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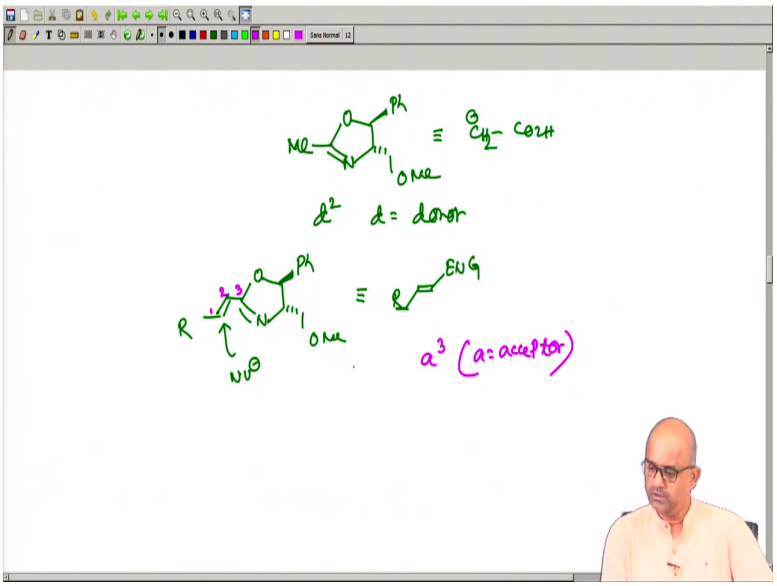

Now, before we end today's lecture I will just try to give you one extra feature of this oxazoline. Now we said that this oxazoline if you have a structure something like this usually

act as a d2 system…… d2 means why? Because this you can regarded as a CH2 minus CO2 H there is a 2 carbon it is a nucleophilic species fine.

So, d2 ……d stands for what? d stands for donor. Now there might be some oxazoline and we will now explore to other oxazoline where you can find that oxazolines of this kind of structural features now what does it mean? It basically says that oxazolines are prepared from an alpha beta unsaturated carboxylic acid. So, in principle these things are like a conjugate system something like this ok with an electron withdrawing group.

So, this can now have regarded as an acceptor so, that a nucleophile can attack ok. Now in terms of carbon now this is a 1, this is 2, this is 3. So, you can now regard or you can now consider this kind of oxazoline as a3 system why a3? a stands for acceptor. Now this a three a or d model, which are very much common in the field of synthon concept.

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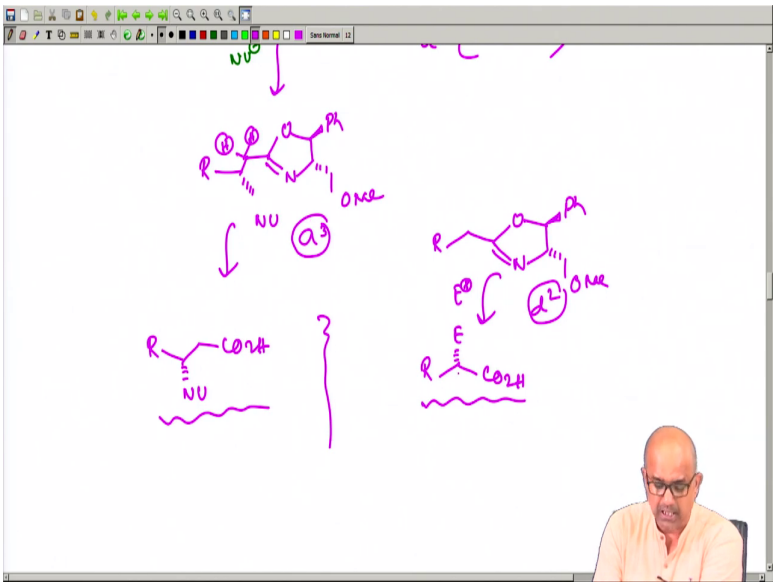

So, now this kind of oxazoline you can actually add some nucleophile. Now the mode of asymmetric induction again will be governed by this phenyl group. So, now, here if you try to use this thing the nucleophile carbon bond will be this way ok and then you can actually create this O N you might be expecting that you can do something else also because once the nucleophile is coming it can give you a aza enolate and you might expect that this hydrogen is now prone for the further round of alkylation that also conceptually you can think about.

But usually this Meyer's oxazoline reaction stopped here and so, it can basically give you a two different dimension a simple oxazoline like this like let us say if you are having this kind of oxazoline, which act as a d2 system a d2 system and after alkylation with electrophile you can get R your carbon electrophile bond in a stereochemical fashion then hydrolyze R CO2H.

Now, if you have this kind of auxiliaries as an a3 system what you get? You get this, you get this you get CH2 CO2H. So, different number of carbons you can actually create. So, here you get two carbon unit here you get three carbon unit and. So, different higher homolog of carboxylic acid, you can get sorry this could be a nucleophile because here you are reacting with a nucleophile.

So, this gives you an extra dimension of this entire Meyer's oxazoline based method. Now we will discuss subsequent application of this Meyer's oxazoline method in the next class and we talk about d2 system like this and we also talk about a3 system like this and how such compounds have been prepared and how they are synthetically manipulated through an alkylation mode or a nucleophilic addition mode to create a diverse set of enantiopure organic molecules.

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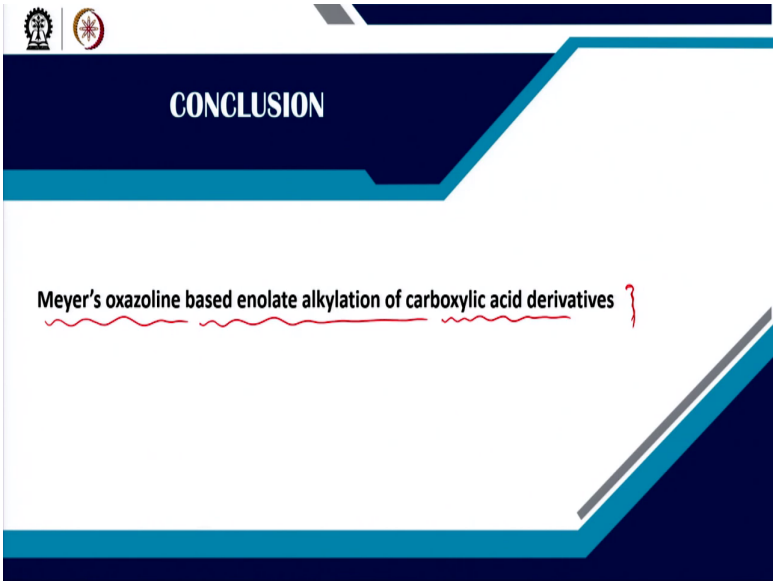

So, as a concluding remark we can say that Meyer's oxazoline seems to be one of the very useful method for selective alkylation of carboxylic acids in asymmetric fashion and particularly this gives you a very good stereo control. And once the alkylation was done you

can actually make use of that method for synthesizing very interesting enantiopure molecules in the subsequent section we will talk about few more examples.

Thank you.