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 - 06
Several methods for alkylation of amino acids derived enolates
Lecture - 31
Najera's auxiliary, Davies diketopiperazine and related system

Welcome everyone. So, today in this lecture 31 which seems to be the final lecture in this amino acid derived enolate alkylation. We will be mainly talking about Najera's auxiliaries and related system.

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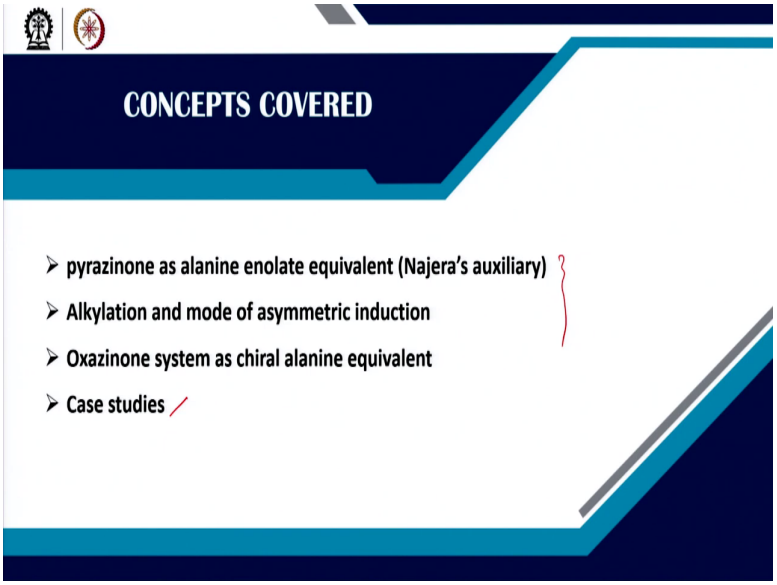

Now, the main content which we will be going to cover in the system is pyrazinone based auxiliaries and oxazinone based auxiliaries which can be used as an alanine equivalent ok. And then we will be talking about some case studies how these auxiliaries can be prepared and how these auxiliaries can be synthetically manipulated to create di alkylated alanine derivatives.

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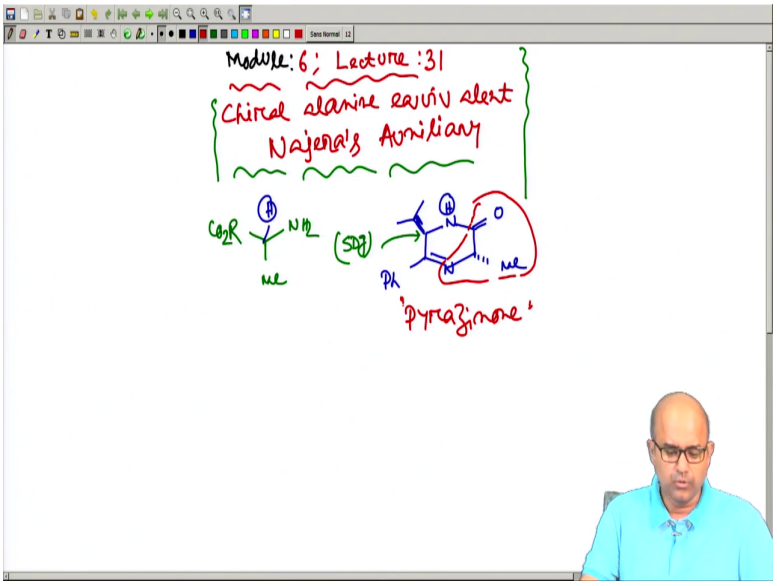

So, today we will be mainly discussing the lecture 31 which falls under module 6 and today it will be the last lecture for this alanine sorry this amino acid based enolate and its alkylation. And today mainly we will be talking about chiral alanine equivalent. Till now we talked about chiral glycine equivalent, but there are few reports where a chiral alanine equivalent also have been reported and this mainly this alanine equivalent is sometimes found to be pretty useful, because if you want to alkylate an enolate on alanine derived precursor.

Let us say we talk about simple alanine and based amino acids and if you have something to pick up this hydrogen and then how you can do it ok and in this regard Najera's auxiliary seems to be the most superior in the very beginning class I mean the initial part of this amino acid based alanine equivalent. We talked about this some of the auxiliaries like Schollpf's bis lactim ether, and Williams oxazinone and other relay system then we also pointed out Najera's auxiliary.

Now, Najera's auxiliaries are in principle are basically an amino acid derived enolate system and these are usually the structural part. If I write you will come to know these are usually an alanine equivalent though stereo center is not important here. So, first these compounds are basically pyrazinone based compound and the main structural part is this part ok.

And this NH group usually they actually protect it, but we will discuss those things little bit later on. Now the main feature for this part this isopropyl group is the stereo controlling or stereo directing group as we have discussed earlier and you can easily now see that this is the

alanine part. This is the alanine part we are talking about. Stereo center seems to be not very important. This is the now how this compound this kind of pyrazinone.

So, this compounds are named as pyrazinone. So, this pyrazinone was named as Najera's pyrazinone. Now let me go through how these pyrazinones are prepared and how you can do enolate alkylation based on this.

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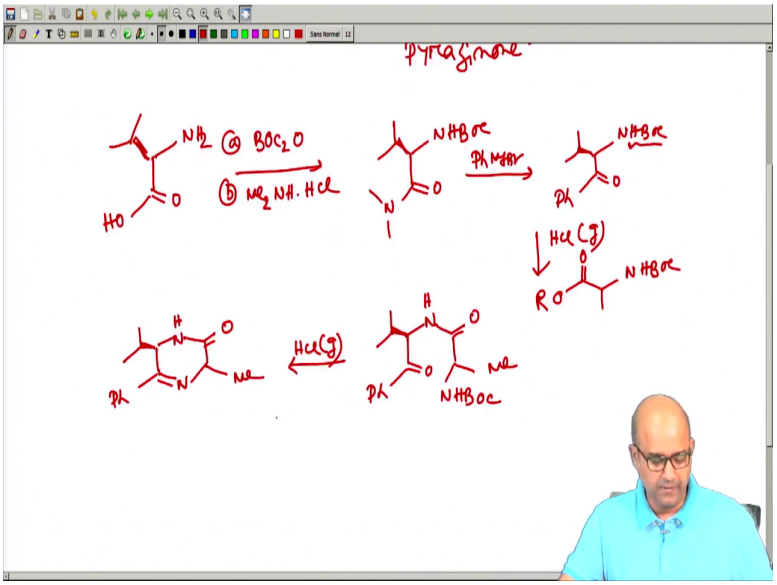

Such pyrazinone was usually prepared starting from the corresponding valine amino acid because you can see that valine contains an isopropyl group which is acting as a steric directing group.

In the reaction course first this was reacting with Boc anhydride. So, that free amine was protected as its mono Boc derivative. Second this carboxylic acid was reacted with dimethyl amine HCl. So, basically it will give you corresponding let me write it. This is NHBOC. This is the isopropyl group and this becomes corresponding amide derivative. Now this amide derivative was reacted with phenyl magnesium bromide.

So, amide on reacting with Grignard will give you corresponding ketone, this is well known in our UG days. So, you will eventually get COPh. Now with this compound in your hand if you now take a gaseous HCl, this was can actually be done and take the suitably protected alanine derivative like this any NH Boc and let us say CO2P. This is the suitable alanine derivative ok.

Now, this and then you just try to do a simple peptide coupling. So, means this HCl gas was usually required to free up one of this NH Boc. So, this NH Boc this become amine and then it can be coupled with the other acid. Now let me try to draw the product which we are going to get at the very beginning. You have this ketone Ph CO Ph this isopropyl is there and then see this NH Boc this Boc sorry this Boc is becoming free.

So, you get this NH and then this NH with sorry we just did a wrong structure. So, this will be CO and this will be the COO different R group…….. ok. So, this amine reacts with this carboxylic acid derivative. So, you now get NH C double bond o and this is your methyl of the alanine and this NH Boc remains same ok. A further round of gaseous HCl treatment will remove this Boc and then condense these two things ok.

So, finally, you will be getting let me write NH your isopropyl part is there, your phenyl is there. You get the imine bond and you get the C double bond O and a methyl.

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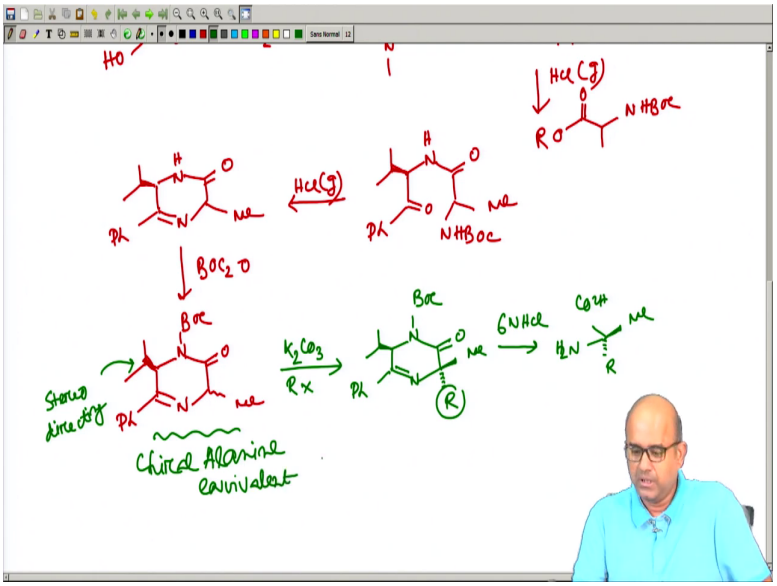

Now, the free amine was not kept as it is the free amine was treated with the Boc anhydride again. So, this will be the final compound or final pyrazinone which was prepared by Najera and this is now regarded as a Najera's auxiliary.

So, in this auxiliary you can now easily see that the main component was this part. So, this isopropyl group act as a stereo controlling element. It is a stereo controlling or stereo directing right. The hydrogen you can easily abstract from this thing. The beauty of this

system was you can actually use inorganic base not like a very strong base like LHMDS or LDA those are very expensive. You can use simple potassium carbonate as a base to enolize this system ok.

And then you react with RX as an electrophile. So, the moment you subject to base first you generate the enolate and then by virtue of the existing stereo center which is the beta isopropyl group. You will actually get the methyl is already there and the incoming electrophile in the form of R you will actually create this quaternary stereo center. Now, so this R will be below as this isopropyl group is above.

And finally, hydrolysis of this thing can be done by 6 N HCl and what you will get? You get an alkylated alanine derivative whose structure will be this. So, such thing was pretty nicely manipulated and this Najera's auxiliary served as a very good starting point for this asymmetric alanine equivalent. So, this compound you can call it as a chiral alanine equivalent.

Same like glycine we have earlier seen, this is chiral alanine equivalent. So, once you have this chiral alanine equivalent as we just now said. Now we can actually synthetically manipulate such alanine equivalents and you can create the alkylated alanine derivative.

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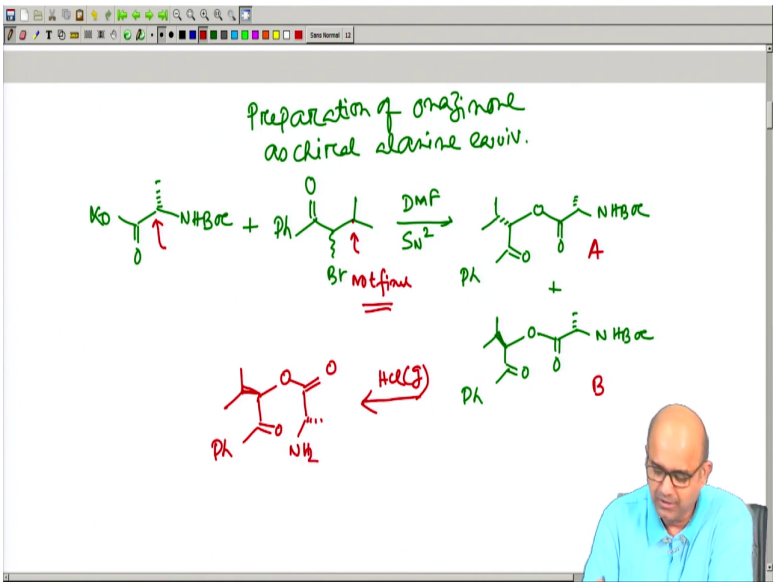

Now the similar line of thinking Professor Najera also prepare a oxazinone based derivative. We just trying to talk about oxazinone, earlier we have talked about pyrazinone. So, this is

oxazinone preparation of oxazinone and these are also used as a chiral alanine equivalent. Now let me go to the synthetic part and actually this oxazinone equivalent I just try to go quickly. So, the alanine part was there though I have mentioned the stereo center, this is not actually not required.

So, we first take the corresponding potassium salt of alanine ok, potassium salt of alanine and then this potassium salt was reacted with an alpha bromo ketone derivative. This you can easily prepare. Now this is simple SN2 reaction in a DMF solvent, this potassium salt O minus react with this alpha bromo ketone alpha bromo ketones are very good SN2 substrates probably all of us know it.

Now, this SN2 actually as there is a stereo center here this stereo center is there. So, basically you will get a two different diastereomers ok. Now let me try to explain that what are the compounds you will get. So, this isopropyl I just from this isopropyl I just draw it COPh fine and then O C double bond O this methyl NH Boc ok plus you get the other dash tumor. I will explain that how you can get this two compound NH Boc.

Now, this stereo center is fixed as we initially talked. This stereocenter is not fixed means that this is a racemic compound ok, this is basically a racemic compound. So, what you will eventually get this O minus when it comes here just this way you can basically get both the stereo isomers. So, this is below this is above ok fine.

Now the point is for this compound for this particular compound one and compound two these are diastereomers in nature. So, these two compounds you can basically separate them out. So, let us say compound A and let us say compound B. So, if you can separate them out and you take any of this compound let us say I take compound B ok. So, if I take compound B and then I just treat with gaseous HCl to hydrolyze this NH Boc.

So, now my isopropyl group is above. So, I can have this structure I will have O, I will have a COPh fine and then now we will have this C double bond o, this methyl is there and you have a NH2. Now this ketone and this amine will then condense.

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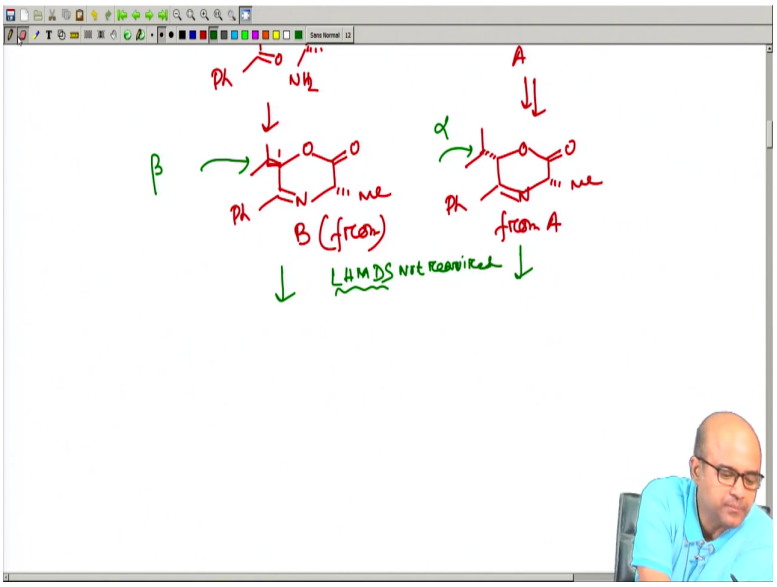

So, you will basically get this isopropyl group is there O this imine Ph NCO methyl so this oxazinone. So, this you will get from compound B fine from compound B from B.

So, now, see both form a this form a both the oxazinones you can get. Now both the oxazinones have similar kind of structural features, only difference is the steric directing group ok. Now you can now eventually see that this compound is having beta isopropyl group. This compound is having alpha isopropyl group means that once you generate the enolate.

Now, let us say what you can do it from both the compound right, both the compound can serve as a enolate structure now. So, so take compound B and A both treat with LHMDs or other base, but here LHMDs was not required as I said not required. Simple basis like potassium carbonate can be sufficient ok. So, you can just simply remove the LHMDs. In the case of pyrazinone we have used potassium carbonate. So, this potassium carbonate also can serve as a required base.

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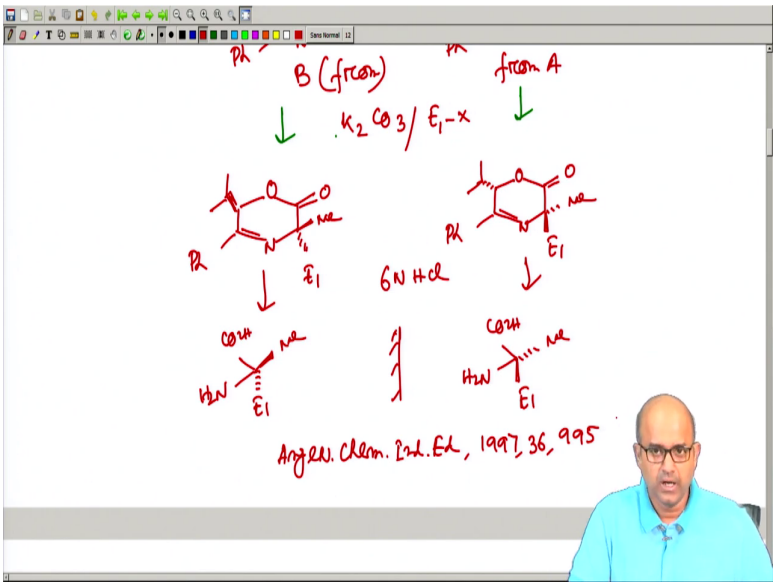

So, take simple potassium carbonate ok and then you add the electrophile as a E1-X. The first case the isopropyl group is above ok. So, as the isopropyl group is above, you write isopropyl group above. Isopropyl group is above that means that the incoming electrophile will be below. So, you have E1 and methyl now becomes above fine.

In this case as isopropyl group is below we will have opposite stereochemistry. We have E will be E1 will be above and methyl will be below. So, try to get the logic that is the beauty of this oxazinone auxiliary even you can get both the stereo isomers or both the enantiomers of the di alkylated alanine derivative fine and next you just hydrolyze both the thing with 6 normal HCl.

So, in this case E1 methyl then your CO2H your H2N. In this case you get the other enantiomer E1 methyl CO2H ……H2N. So, these compounds are enantiomer to each other ok. Now this was this was pretty interesting and this result of this Najera's auxiliary have been reported in a prestigious journal Angewandte Chemie international edition in English.

And this was reported 1997 little bit ago, but this gives you a good source of chiral alanine equivalent with the help of oxazinone as well as pyrazinone and both the compounds you can synthetically manipulate for couple of interesting purposes. We will try to give you one more example for this chiral glycine or chiral alanine equivalent.

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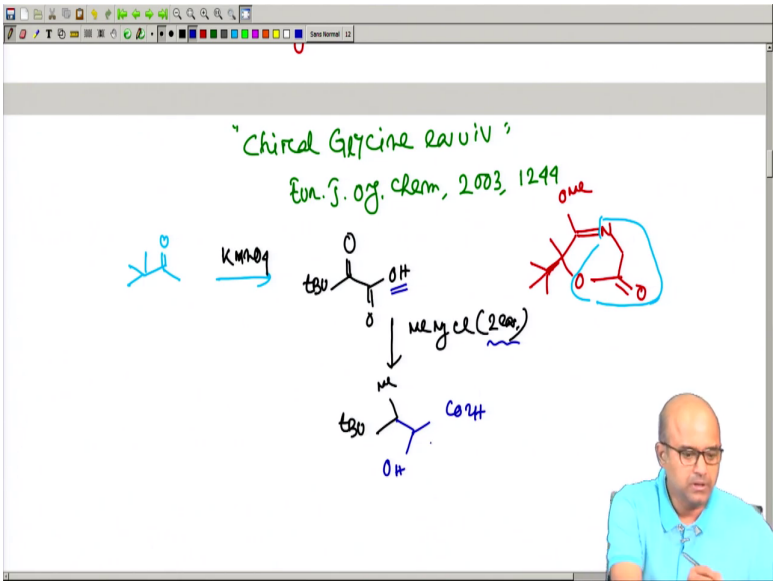

And we will probably just talk about one such example which is a chiral glycine equivalent a simple system which was reported in 2003. This was reported in a Euro journal of organic chemistry…… European journal of organic chemistry in 2003. So, little bit recent papers and now this particular work which was seems to be interesting and the idea that this kind of cyclic structure of a glycine derivative was usually seen for this compound.

This was the glycine part and actually this kind of compound contains a bulky tertiary butyl group at one of the end. So, this was the chiral glycine part you see this N and this is basically the glycine part the glycine part this is the chiral glycine equivalent. Now how this compounds are prepared it is a very simple chemistry, but the chemistry was quite interesting a tertiary butyl methyl ketone was used as a substrate.

In the very beginning and this tertiary butyl methyl ketone was first reacted with a potassium permanganate solution. So, this ketone group first actually oxidized not ketone the alpha methyl group was oxidized and then with this ketone actually ketones are much more reactive than the corresponding carboxylic acid. A two equivalent of methyl magnesium chloride was reacted.

Now, that basically give you a tert butyl is here and in this part two methyl was added and then you actually just one minute there is a tert butyl and then this sorry two not two methyl one methyl actually I just yeah there is a one methyl. There is a one methyl then you have this OH and this CO2 H. So, two equivalents were basically used that they have carboxylic acid. So, that can be taken part one of the acidic hydrogen.

So, you get this compound. Now there is a you will find that this tertiary butyl then methyl, then you have OH and CO2H. So, there is did I draw it right away just 1 minute. Just we will draw the structure one more time.

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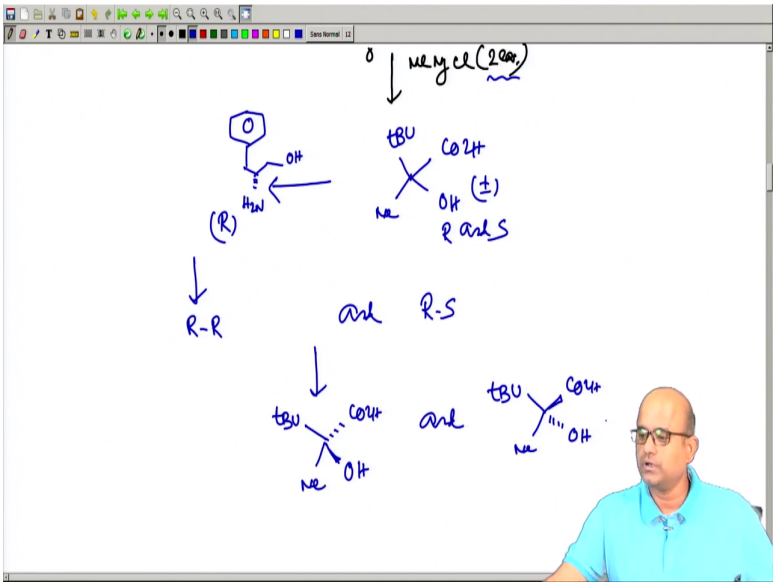

So, you have a methyl. You have a OH you have CO2H. We are talking about this carbon and then you have a tert butyl group fine ok. So, you basically get a racemic mixture plus minus mixture.

Now, this plus minus mixture was reacted with a diastereomeric or enantiopure amine to prepare the corresponding diastereomeric salt H2N….. CH2OH. Now this amine is enantiopure amine it actually reacts with this carboxylic acid to give you a corresponding two. So, let us say I write this is as a R amine and this you have R and S.

So, after this reaction you can eventually get this RR amide and RS amide. You can separate them this two out and then you simply hydrolyze this amide part and then you actually get both the enantiomeric thing tert butyl and then you get this methyl. You get CO2H and OH. So, you can get both the enantiomers you can get either this as well as this. This you can eventually just prepare.

So, with both the enantiomers you have prepared by diastereomeric salt or kind of a resolution. Next your job is how you can synthetically use a chiral glycine equivalent with this hydroxy acid.

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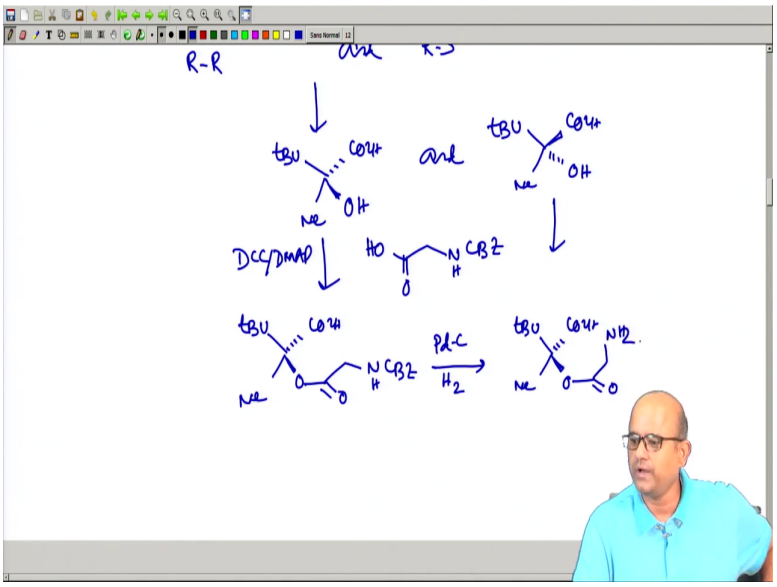

Now this you take any of this hydroxy acid and then actually we react with the glycine derivative. The same kind of glycine derivative we earlier we used this NHCBZ. Remember the carene or the camphor derived tricycloaminolactone. Now in both the cases so then you I just write you one example. So, tertiary butyl then you have this methyl and then first this C O2H is there. So, this is the DCC/DMAP coupling,

So, you basically get this O fine. You get C double bond 2 and then you get CH2NH CBZ. Similarly you get another compound for this also ok. Now this CBZ you can easily remove or de benzyl it. Once you remove this CBZ and then you actually can condense with this CO2H which with this NCBZ.

So, now let try to write what you can do it. So, you can just do it with this palladium charcoal and hydrogenation. We can just de benzyl it these things. So, you can tert butyl, you can get methyl. You can get CO2 H. This is your oxygen. You get C double bond O CH2NH2 fine and then you just couple this carboxylic acid with the amine.

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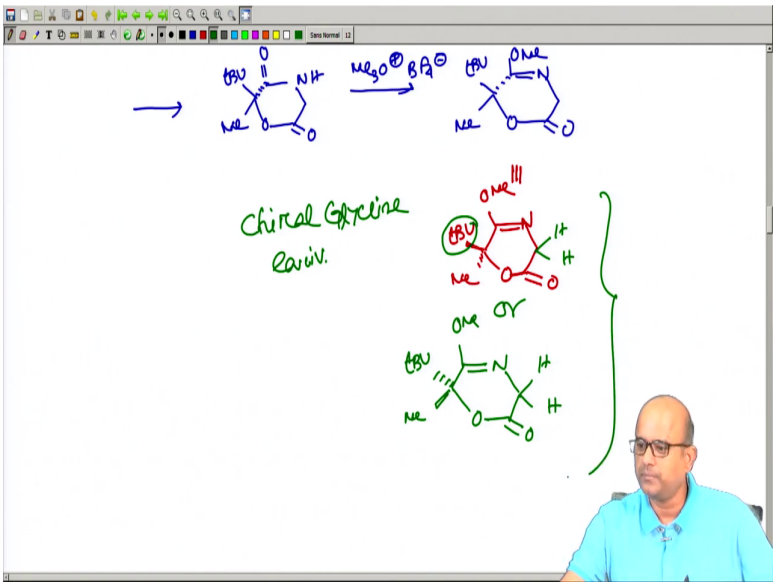

So, what you are going to get you get the cyclic structure. So, you get this kind of C double bond ONH. This is your oxygen, this is your C double bond O yes. So, the chiral glycine part you have a tert butyl and you have a this is your methyl fine. Now with this thing we will be next just do a Meerwein salt kind of things. So, you get the monolactimether. So, this monolactim ether means you will be now having this O me this Ome double bond NOC double bond O, so tert butyl and methyl.

Now, such compound you can eventually write in another way, other way means you can just change the stereo structure of this compound, in this way that you can put the stereo structure in this you can put in the planar way O C double bond O your nitrogen. This you have a O me, you put this tert butyl and methyl. So, it basically what it gives you? It gives you a chiral glycine equivalent.

And the tertiary butyl group being a bulky group this can control the enolate alkylation stereochemistry. So, this is your chiral glycine equivalent. Now such both the compounds actually we have started with this you can also start with this. So, both the enantiomeric of such compounds either this or even other one means here your tert butyl will be below methyl will be above you have O me.

We have double bond N O this you can actually have these things. Now the in principle both the compounds you can use as a enolate precursor or chiral glycine precursor for corresponding enolate alkylation.

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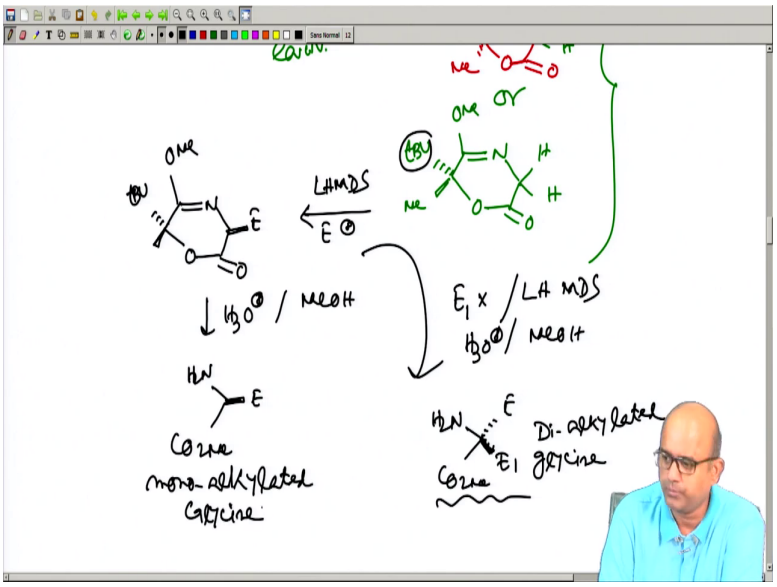

Take any of the compound take any of the compound and treat with base simple LHMDS and then use the electrophile. Now see as this group is the bulky one, this controls the stereo selectivity in the enolate alkylation. So, you can simply write the entire thing most of the remaining part will be very simple.

So, you have this ketone. Now see the electrophile will be definitely approaching from the above ok. So, then you can hydrolyze these things, hydrolyze this things H 3 O plus methanol. You can do a mono alkylation, you can do a di alkylation the choice is yours. The moment you do it you get E you get H2N you get CO2 Me.

So, mono alkylation and if you try to do a di alkylation means a second round of electrophile E1X, another round of base LHMDS followed by $H3O^+$, methanol treatment as tertiary butyl is above sorry below the E1 will be a below sorry E1 will be above E1. E1 will be above. Your E will be now below CO2Me and H2N. So, mono alkylated glycine…….. di alkylated glycine both you can make mono alkylated and di alkylated glycine……

So, both the compounds you can actually make. So, this way you can eventually prepare different kind of glycine derivative in enantiopure fashion. So, probably this makes you the amino acid based enolate and its alkylation. We will discuss subsequent things in the coming days.

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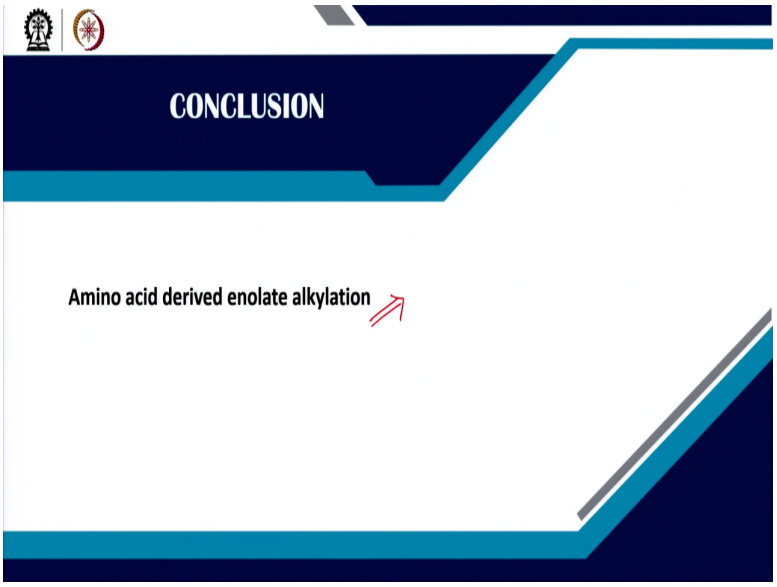

So, finally, you can see that such pyrazinone based and oxazinone based auxiliaries are very useful for making mono alkylated alanine as well as di alkylated alanine derivative in enantiopure fashion. In the subsequent section we will be talking about a ketone derived enolate as well as enamine derived and imine derived enolate.

Thank you and see you in the subsequent lectures.