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 - 28
Chiral relay systems in amino acid derived enolate alkylation

So, welcome students. In this module which is a continuation of the earlier module and particularly lecture 28 we will mainly be focusing on Chiral relay systems in different amino acid derived enolate alkylation. Last class we just given you a brief hint of this relay system.

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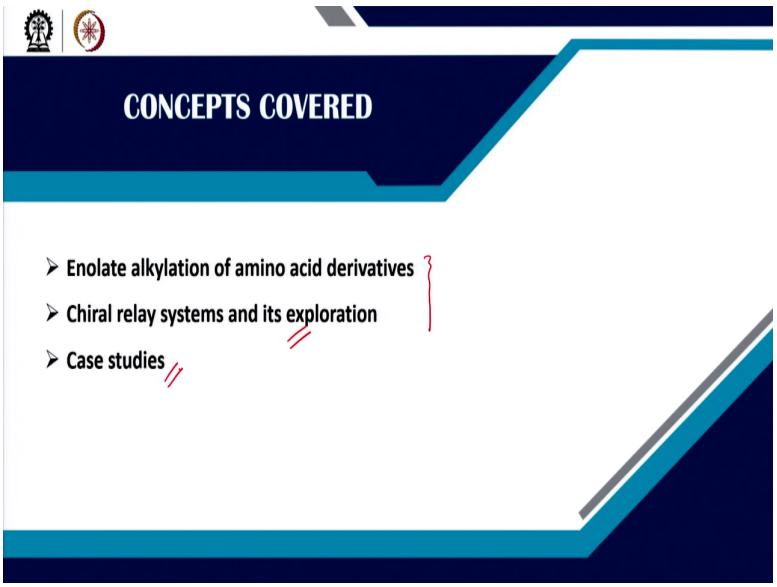

Main concept which we are going to cover chiral relay systems and it is exploration and different case studies and origin of asymmetric induction.

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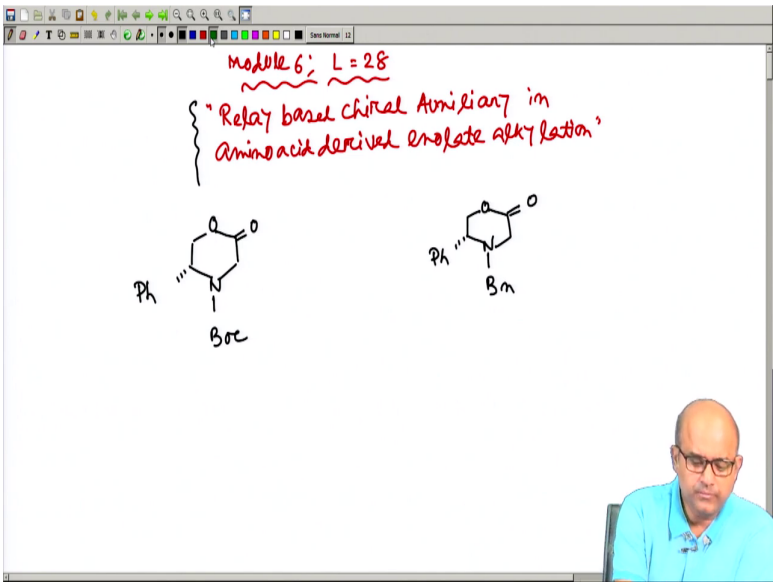

And, in the last class we are basically discussing that amino acid derived enolate and it is alkylation, and at the end we have started a new topic which we are calling as a relay based chiral auxiliary in amino acid derived enolate alkylation. This is first inventory Professor S G Davies.

Let me recapitulate the whole thing little bit, we have said that if you have a cyclic amino acid derived enolate system. Let us focus on example something like this you have a N-Boc protected thing and this is your this part. And, you can also have a similar kind of thing, where just you change the protecting group of the nitrogen from Boc to an alkyl group like benzyl.

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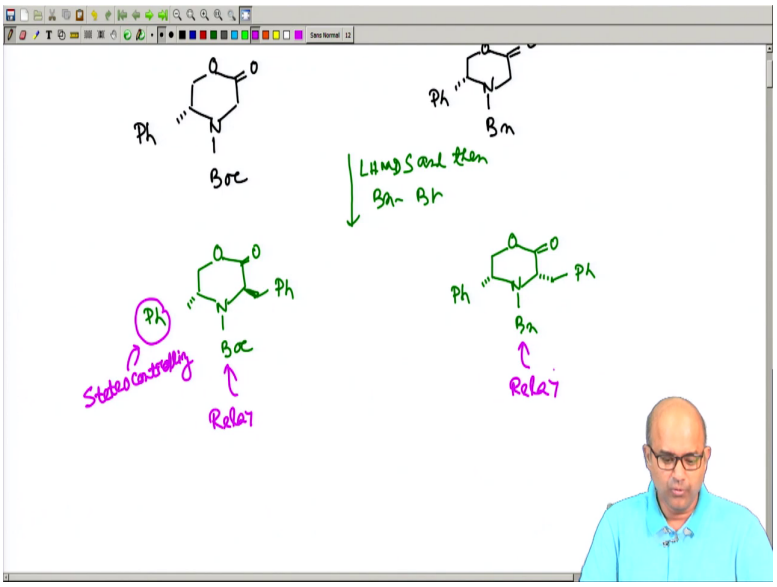

And, these two systems we have discussed in the last class and we have said that if in both the cases you actually treat the compound both the compounds with a base like LHMDS and then treat with benzyl bromide as an electrophile you have a different product stereochemistry.

In the first case, when you have a Boc…… this Boc case you are going to get the electrophile attack from the beta phase, ok. And, in the second case when you have a benzyl this case you will basically getting a cis-product and we have given you an explanation mainly based on a relay kind of phenomena. And we have said that this is nothing ……..I mean this is simply you have to draw the enolate geometry in both the cases.

Now, the idea that what I am trying to explore or trying to recapitulate this is the initial steric directing group; so, this is we called stereo controlling group in the normal auxiliary; in the conventional auxiliary this seems to be the stereo controlling group ok. And, the Boc group……. Boc group is the relay. The Boc group is relay or the benzyl group seems to be the relay part, ok.

Even you can change the benzyl group to other alkyl group you can get a similar kind of phenomena.

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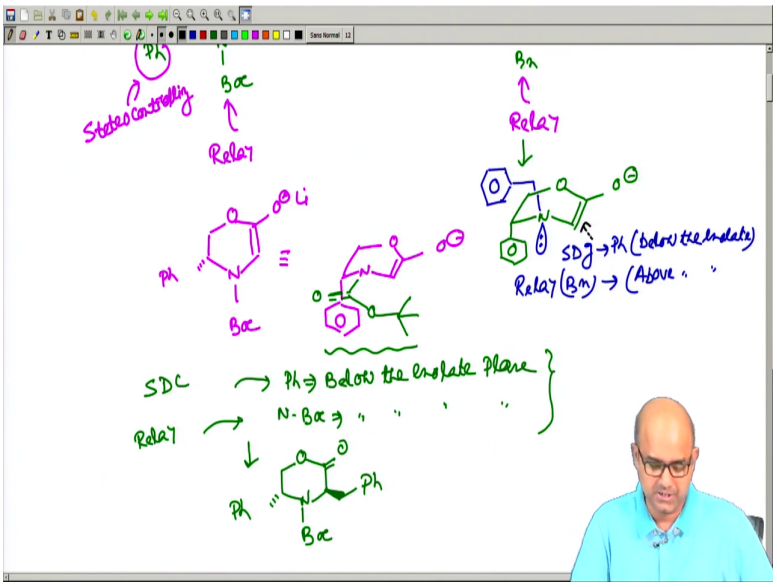

Now, explanation wise what we said now, again we can go back to the structure. So, initially for this case once you abstract the proton with a base you basically get the corresponding enolate O minus Li plus and then you have a phenyl here and you have a Boc here.

Now, what I am saying that this is your stereo controlling group, this is your relay group. Now, let me try to draw this structure in a little bit of different way let me just try to put it in a simple planar or even a half chair way also you can do it, ok. So, like this I mean this is not very good drawing, but still you can explain it ok this is your O minus enolate and in this case the phenyl group, which is the steric controlling group seems to be the alpha or in the below.

Now, here we are saying that this particular Boc group cannot occupy the above place because that will give you a non-bonding interaction with this ring hydrogen atom. So, then this actually will give an orientation something like this it is CO and then O. And the tertiary butyl group which actually stays apart from the phenyl group because this CO-O you can control it.

So, what does it mean? It means that the phenyl ring the phenyl is below the plane of the enolate below the enolate plane. Even N-Boc…….. this N-Boc also occupies below the enolate plane. Now, that means, that the initial auxiliary or stereo controlling group which is we can now write as a stereo directing group and this N-Boc is the relay group both are occupying below the plane and that is what the alkylation always took place from the above.

So, means final product which we are you are going to get. So, we will be having the benzyl as the above way ok…… Ph N-Boc and Ph. So, this is the thing we have explained here, ok. Now, in the second case when you have a typically benzyl group, now you can see the enolate for such compound you can also write the similar kind of enolate structure. If the drawing will be something like this you have a nitrogen you try to have a half chair kind of thing ok. So, this is your O minus, fine and then this phenyl is below as we can identify.

Now, the other here you have a benzyl now this benzyl has to be shifted in this way because there is no other way. This could be the most stable arrangement for such compound with this lone pair here. Now, why it is? It is basically to avoid the 1,2- steric interaction between this phenyl and this N-benzyl. So, what does it gives you this gives you the original steric directing group which is the phenyl which is actually below the plane.

This is below the enolate fine, this is already we have established and the relay group the relay group now becomes the benzyl. The relay group is the now benzyl group. Now, benzyl group is where now this is above the enolate plane above the enolate plane. Now, what does it mean? It means that when the electrophile seems to be approaching to the enolate electrophile now when it seems to be approaching to the enolate.

It usually prefers the this below approach because the adjacent or proximal group is the benzyl group. So, benzyl group now controls the relay or acting as an auxiliary kind of thing. Now, these things are pretty well established in the Professor Davies's original paper.

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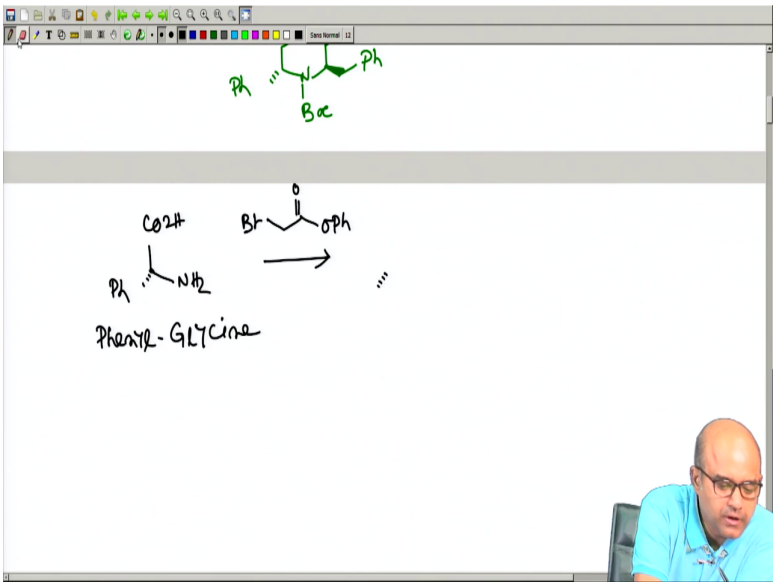

Now, let me try to think in different way that how such compounds can usually be prepared. Now, usually this kind of compounds can be prepared starting from a simple phenyl glycine as phenyl. So, if you have an amino acid amino this amino acid which is a phenyl glycine. Now, this phenyl glycine was the main precursor for making all the or preparing all the chiral relay system when you have an auxiliary.

Now, how you can prepare this compound? So, you take a corresponding phenyl bromoacetate which is this, ok. So, initially it was like that this carboxylic acid and so, first you actually get the……. no we did some mistake. So, I will just try to point it out I am sorry.

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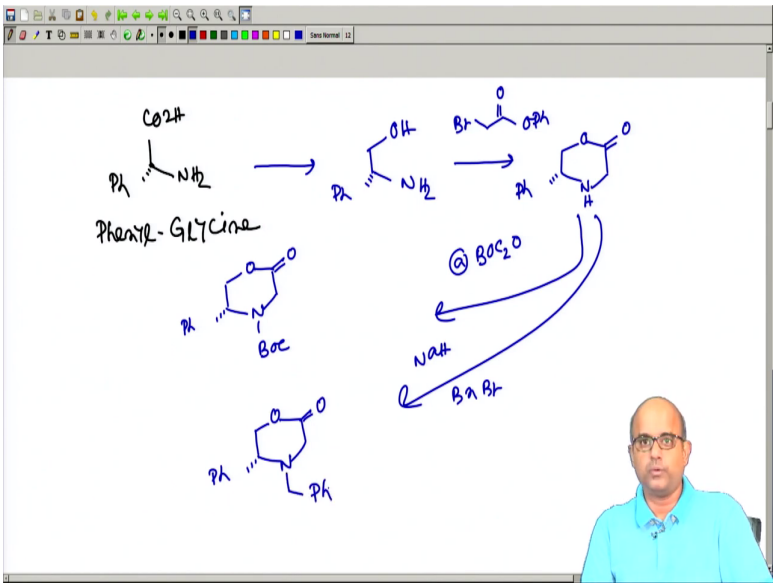

So, first you take this corresponding phenyl glycine and you reduce the corresponding phenyl glycine to it is amino alcohol by simple $I_2/NaBH_4$ reduction, yeah. Here you need this thing CH2OH and then you treat this compound with corresponding this bromoacetate ok, this phenyl bromoacetate.

Now, initially you can have a stepwise mechanism or other mechanism. So, means that this CH2OH is going to condense with this and this Br is with condensed with NH2 through normal SN2 pathway. So, you will be getting the cyclic oxo ……..kind of compound which is nothing but a chiral glycine equivalent. So, you have a free NH.

Now, take this compound take this compound and then if you are reacting with a Boc anhydride Boc whole 2.. O you are going to get the corresponding Boc derivative; Boc

derivative means your phenyl your N-Boc one of the precursor, which is required for this chiral relay.

And then if you are trying to use the same precursor and react with a sodium hydride and benzyl bromide just that will give you the N alkylated product. So, you get ON this portion remains as it is CO-N benzyl. So, these two precursors you can easily make by this way.

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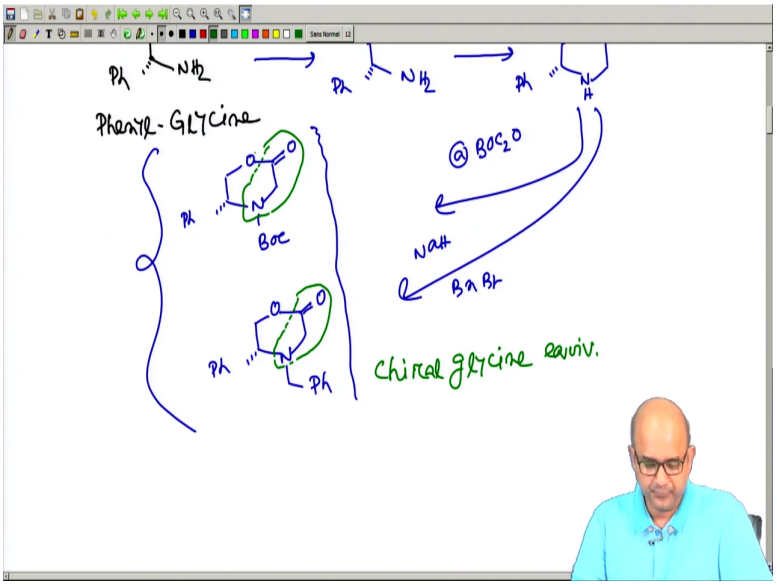

And, then the mode of alkylation you we have just now explained. So, phenyl glycine can basically give you these 2 precursors. Now, once the alkylation was done then you can basically hydrolyze these things with a standard way. Now, we will explain few other things similar kind of chiral relay.

Now, these 2 examples you can actually treat them as a chiral glycine because if you now see these compounds are nothing but a chiral glycine equivalent, is it not? See this portion is the glycine part N CH2 CO. So, here you are abstracting the hydrogen generate the enolate and then you are doing the alkylation. These things are chiral glycine equivalent.

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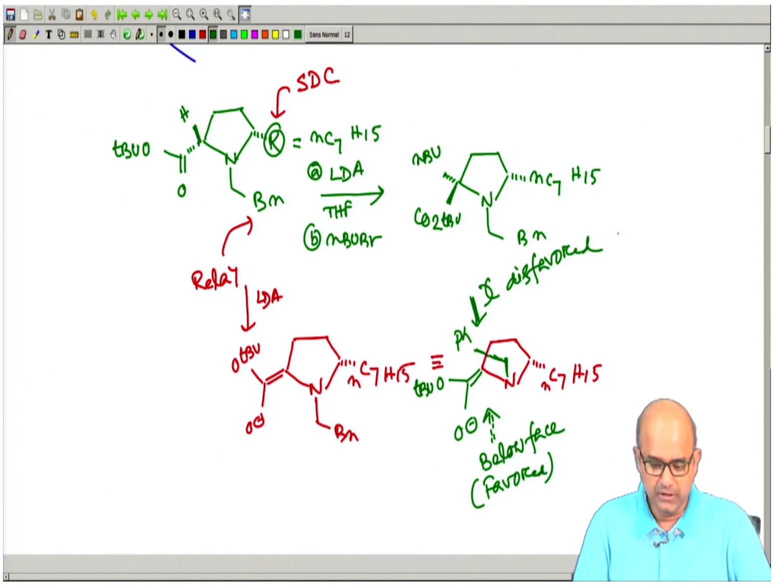

Now, based on similar kind of chiral relay other examples have been explored we just try to give you one such example which is based on a cyclic amino acid which is a proline based amino acid. A pretty bulky group is kept it here and this R-group is a heptyl group n C7 H15, this N group having a benzyl N-group having a benzyl and this portion is having a C double bond O tert butyl ester, ok.

So, this kind of proline derivative………. cyclin proline derivative was taken as the amino acid derived precursor where you want to abstract the hydrogen to generate the enolate. Now this compound was taken and reacted with LDA and THF solvent ok and the then next was the base sorry the base is there then the electrophile. The electrophile was reacted with n-butyl bromide.

First let me explain what product we are going to get and then we will explain what is the chiral relay mechanism here. So, this is the bulky n C7 H15 your N-benzyl is here ok and the CO2 tertiary butyl the ester group is there, the electrophile seems to be the below. Now, this seems to be relay. Now, what is exactly happening? You first analyze the starting material here this seems to your SDG or stereo steric directing group and this benzyl seems to be the relay group ok.

Now, initially if you now try to draw first abstract the hydrogen with a base means LDA. So, initially you will get enolate, which structure will be something like this O minus and O tert butyl. So, amino acid enolate ok this is the benzyl and this is your bulky n-C7 H15 group.

Now, how this enolate is properly looks like and then we can just have a little bit of simple planar geometry also you can do you can have another extended I mean envelope kind of thing by assuming the n-C7 H15 or the cyclopentane structure. Now, see this is this group is below. So, n-C7 H15 seems to be below, fine. And, as this group is below so, that basically forces the benzyl group go to a above position. So, this seems to be a benzyl group to avoid severe one to non bonded interaction.

And, then you are having this enolate here is your O minus and here is your tert-butyl-oxygen, ok. Now, what does it mean? That means that now you can see that the enolate below face seems to be much more accessible below face because, the top face seems to be blocked by this N benzyl group below face is favoured. The top face, the beta face seems to be disfavoured while it is basically mainly due to the relay effect of the N-benzyl group.

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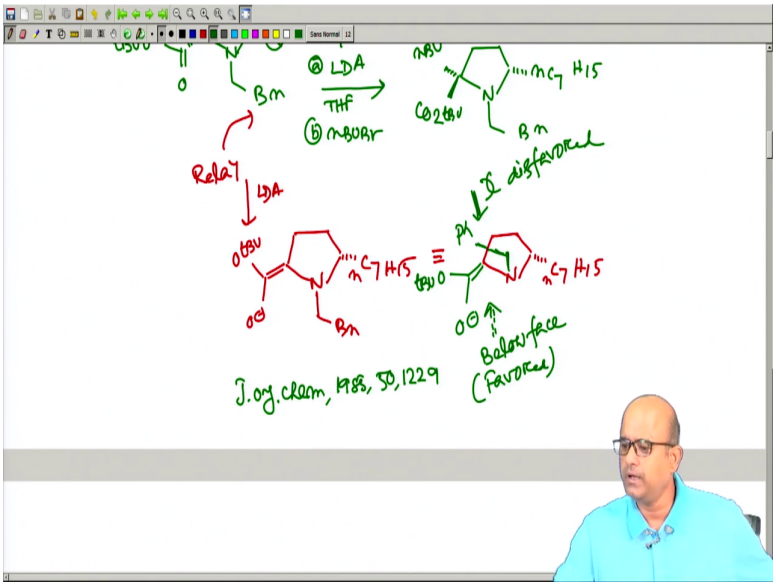

So, this relay effect in the cyclopentane system or a pyrrolidine system is also very well reported, but it is a reported in a JOC paper very well known Organic Chemistry paper. This appeared in 1985 volume is 50 and page number is 1229. So, such relay gives a pretty well defined steric parameter as well as controlling factor.

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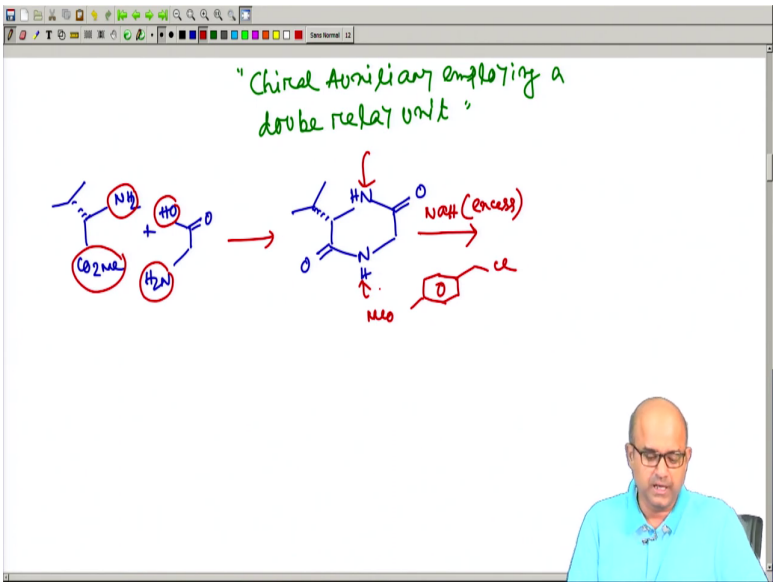

Now, till now we are talking about an auxiliary on a single chiral relay system. Now, next we will be just discussing a chiral auxiliary which employs a double relay unit employing a double relay unit. This was also quite interesting. This was again reported by Professor Davies.

Now, this thing seems to be just an expansion of or extension of Schollkopf bis- lactam ether. Now, let me just draw very quickly that how you can device such system. Initially bis-lactam kind of compound was taken. Now, this bis-lactam already we have synthesized or we have seen that how you can make this compound in the Schollkopf bis- lactim ether.

Now, see this kind of bis-lactam…… bis-lactam how you can prepare this kind of bis lactam definitely? You can prepare this bis lactam. If you have the corresponding let say this valine NH2 and this CO2Me or anything. So, this is the left part and the right part you simply need a glycine derivative, is it not? So, you have a glycine derivative this H2 N, fine. So, means that this NH2 this CO2H condenses and this NH2DCO2Me condenses to give you this bis-lactam, which we already employed in the Schollkopf bis-lactim ether.

Now, such a bis-lactam we call it such a bis-lactam what Professor Davies did? He takes this bis-lactam and reacted with sodium hydride excess or more than two equivalent and reacting with an alkylating agent which is nothing but a paramethoxy benzyl chloride.

Now, it means that this nitrogen will be alkylated, this nitrogen will be alkylated, fine. Now, the moment these two nitrogen is going to be alkylated there it is a chance that what will be the relative stereo orientation of this both incoming paramethoxy benzyl group.

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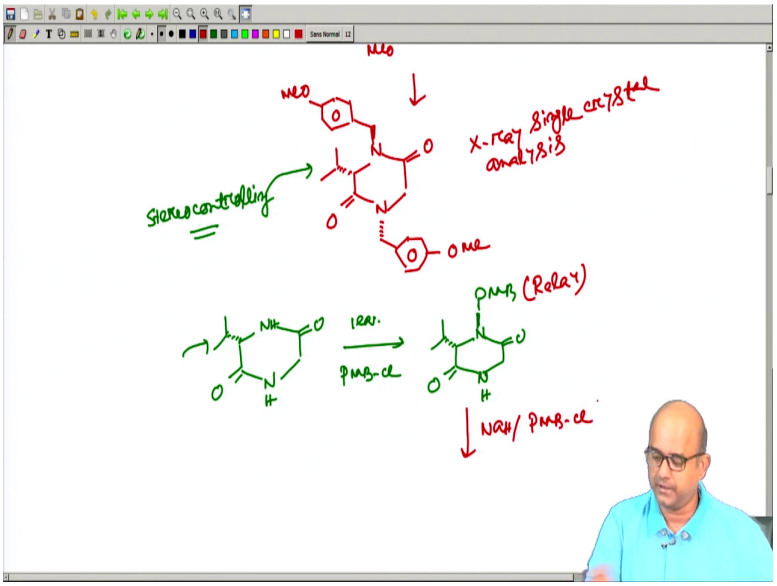

Now, what Professor Davies observed? That you will be having this nitrogen. It is basically a piperedine system 1, 4 nitrogen. This CO is there, this CO is there. This part is fine because you have pre existing isopropyl group. Now, here the structure which was reported by Professor Davies and later on also supported by X-ray structure you actually get this kind of structure.

Now, this structure implies that the first alkylation might took place in the top nitrogen. Now, as this top nitrogen contains an adjacent isopropyl group which is below; that means, that first PMB group becomes above. Now, the moment first PMB group above the second PMB group seems to be below because this group now controls the incoming orientation of the second group.

So, this was the main thing and eventually the such compound structure has been confirmed by X-ray single crystallography…… X-ray single crystal analysis. So, that was clearly indicative that such relay you can do it. Now, let me explain this relay in terms of little bit more thing.

So, first you have this isopropyl group. So, this isopropyl group seems to be the stereo controlling group in the normal auxiliary which was present any auxiliary let us Schollkopf bis-lactim ether. Now, first it has to be so, again we can draw the entire structure of this auxiliary first isopropyl you have this NH you have this C double bond O, this N. So, this is your general structure, ok, fine.

So, first one equivalent of PMB chloride this was probably the first approach takes place. Now, first attack means that as this is the steric controlling group the first group in PMB group occupies the we that CH2PMB ok it is not a CH2PMB it is just a PMB ok. So, you can just take it write this PMB and this will be above because this is a 1,2 interaction.

So, this was the first relay creation means your stereo controlling group and this group is now the relay. So, this is the relay group, ok. Now, second the same compound was again subjected to sodium hydride and PMB chloride.

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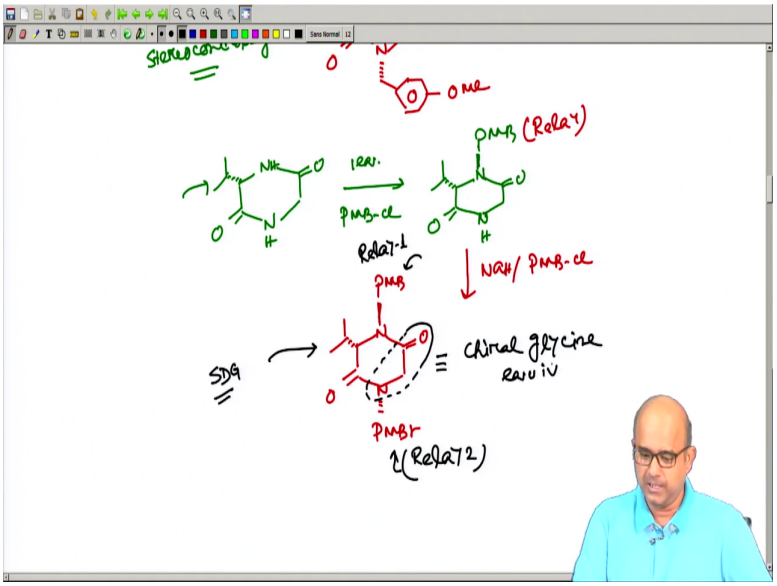

Now, here already the PMB is a bulky group this occupies a beta position. So, the second PMB group definitely has to be in the opposite orientation of the first PMB. So, this is the first PMB, this is the isopropyl which is already present in the molecule this is the CO, this, this, this, now this PMB comes as below.

So, now what I am trying to say? This is the we use a different coloured pen. This is the initial stereo controlling group or stereo directing group SDG stereo directing group, ok. This

group seems to be the relay 1 and this group seems to be the relay 2. So, double relay unit. Now, here once you get this compound this compound basically you can now write as a chiral glycine equivalent.

You can see this part is the chiral glycine part. So, chiral glycine equivalent. So, this is a chiral glycine equivalent. Now, definitely you want to have you want to do some alkylation based on this. So, take this compound take this compound or if you want to write we can just write it this compound again.

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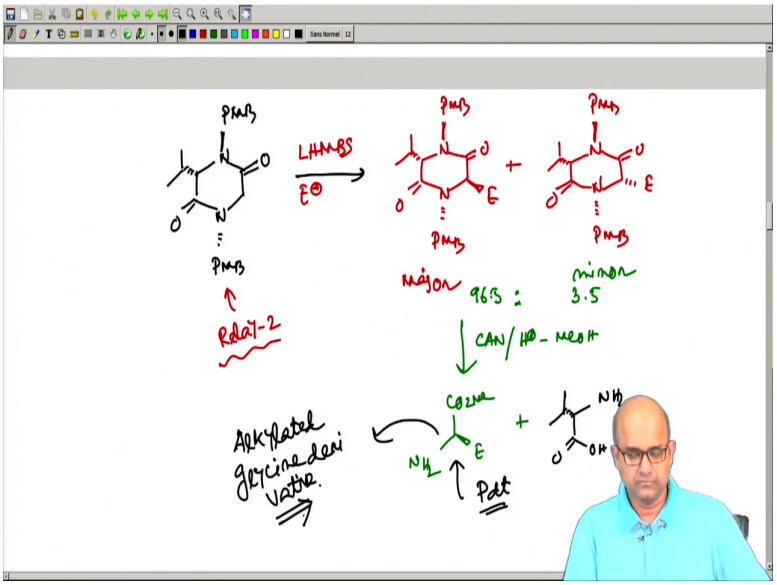

So, this is your structure CO first isopropyl group, the N, this will give the beta PMB the first chiral relay. Then the second chiral relay, which is the above PMB sorry below PMB and then this is your chiral glycine ok, fine. So, you just take this compound and use a base LHMDS was used and then your sample electrophile, ok.

It has been observed that definitely this second relay 2; relay 2 being the close proximity of the enolate. So, this will be now controlling the incoming electrophile. As this PMB is below, the electrophile has to be on the above. So, now we will write that what are the possible product composition? So, this PMB CO, this N, this PMB is below. So, then you basically get the above electrophile and this could be your major product you definitely have a minor product which is the other diastereomer this also you can expected to observe and the means the electrophile is below. So, this PMB, this is the isopropyl group and this is this thing so.

So, what I am trying to say that the relay 2 is becoming the now the stereo controlling group. So, this is the most important part the relay group becoming the final controlling factor. So, this group becomes minor and the diastereo selectivity was it has been found that 96.5 for this compound, 3.5 for this compound, this is very minor compound.

So, once you get this thing then definitely you can just hydrolyze this compound and it was usually the PMB group you can remove by oxidative removal with ceric ammonium nitrate or you can remove with DDQ, and then you can just hydrolyze these things. So, you can let us write ceric ammonium nitrate oxidative removal followed by H plus and methanol treatment.

So, what you will be going to get? You get your E here and this will be your NH2 and your CO2Me. So, one of the thing and then the other part is your auxiliary which you are going to get back from this valine part. So, this will be your CO2H and this will be your NH2. This valine you can use it. So, this is your desired product. This is nothing but an alkylated glycine derivative, right. This is nothing but an alkylated glycine derivative alkylated glycine derivative.

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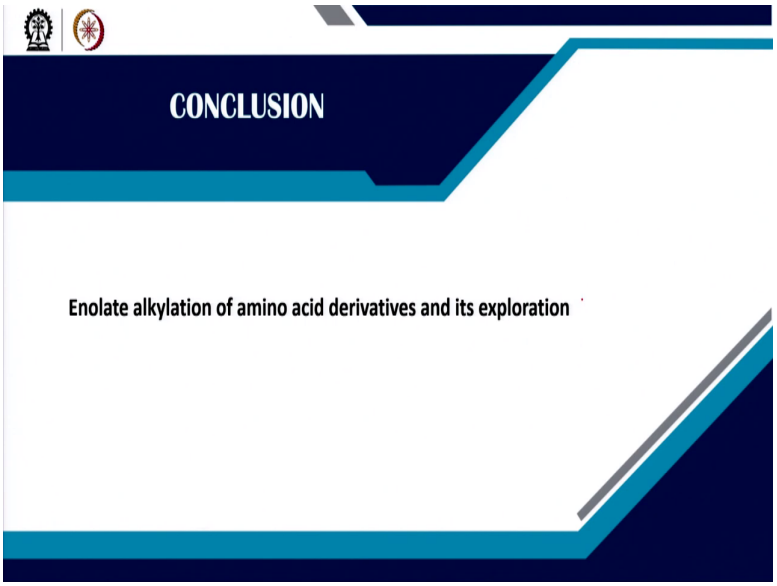

So, we will be trying to discuss some more things or similar kind of things in the subsequent lecture. So, finally, as a concluding remark we can say that enolate alkylation of amino acid derived enolates are pretty useful tool in the asymmetric synthesis and particularly this chiral relay based auxiliary, which have been found enormous application in the field of asymmetric synthesis of amino acid derived enolates and it is alkylation.

Thank you. We will see you in the subsequent lecture.