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 - 27
Schollkopf's bis-lactim ether and related systems ; Auxiliary induced chiral relay

Welcome back everyone. So, today we are going to start a new module which is module 6 and we will talk about lecture 27 and this module is mainly focused on amino acid derived enolates and it is alkylation.

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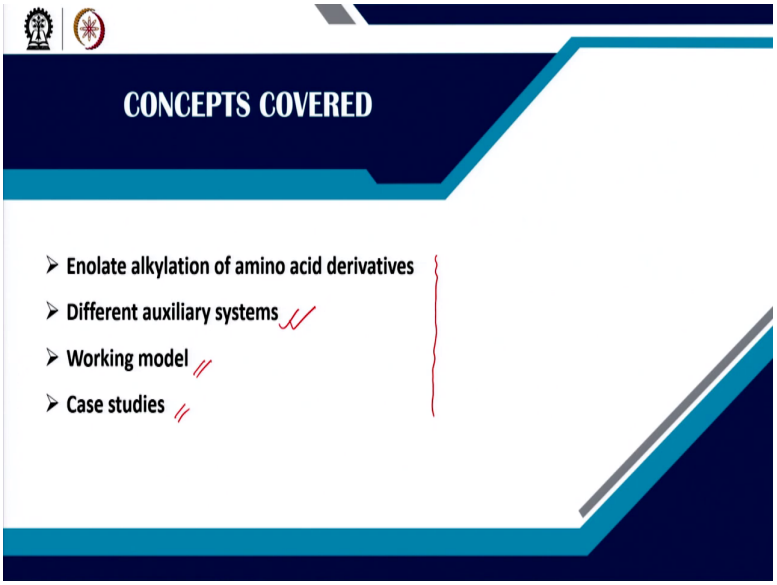

And the main content which we will be talking about this module basically we will be talking about different systems of amino acid derivates enolates and how different auxiliaries as well as relay systems can be used to control the stereochemistry; we will talk about the different working models and case studies.

And mainly we will talk about Schollkopf's bis-lactim ether in this particular slides as well as some chiral relay system and invented by Professor Davies.

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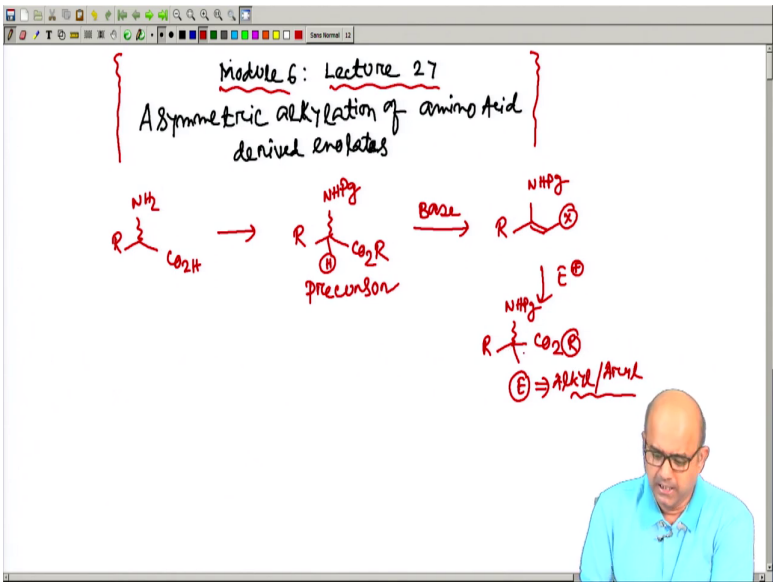

Today we will be studying a new module which is module 6 and we are going to talk about lecture 27 and particularly in this module, we will be talking about asymmetric alkylation of amino acid derived enolate and normally this enolate as you can see such enolate are usually derived from corresponding amino acid derivative, ok.

And there is certain prerequisite your conditions which you need to fulfill usually we never keep the amine group as a free. So, this amine group of the amino acid was usually protected with a suitable protecting group; you can do a double protection or a single protection and this carboxylic acid also is never kept as a free. It usually protected as its ester or even amide.

So, this is the usual precursor which you have to prepare from the corresponding amino acid and then, based on the condition you are going to pick up this acidic hydrogen usually through a base…… which is the standard base we often used and then you will generate the enolate which normally you can write the enolate structure, but eventually if you do not write also is fine.

So, we can have this x you can write just x, ok. Now, the this enolate once you are trying to alkylate particularly with selective electrophile and then you are eventually going to get a corresponding alkylated amino acid where the hydrogen has been replaced by a suitable electrophile, ok. Now, by this method you can eventually prepare substituted amino acid where if E is also an alkyl group, different alkyl group or an allyl group.

So, alkyl, aryl and based on the electrophile you choose you can actually make a quaternary stereo center on this thing. Now, the basic strategy which lies for this amino acid derived enolate alkylation.

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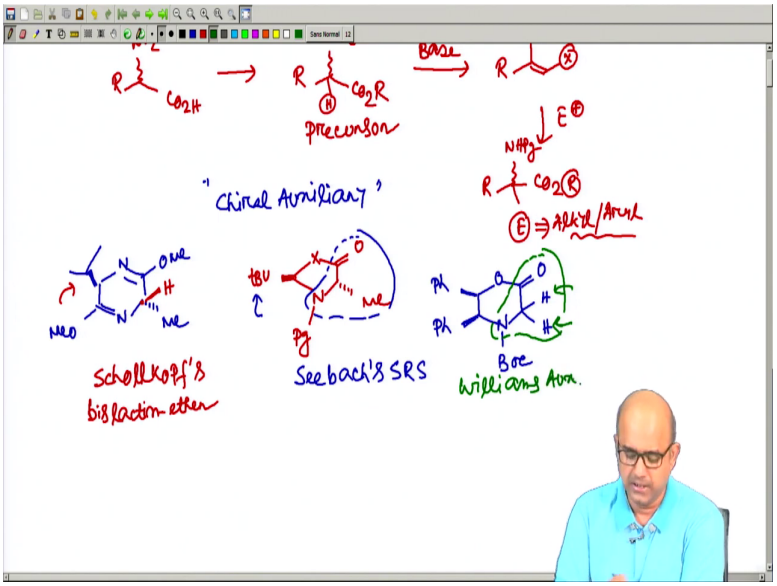

Usually we mainly employ different kind of chiral auxiliaries which all of us have been studied earlier. Now, in this case the auxiliaries will be little bit of different because, that has to be incorporated an amino acid structure in the auxiliary. Very beginning we will try to write some auxiliary structure just for your information and then, later on we will explain all the selective auxiliaries which we were discussing in the class and what will be their mode of asymmetric induction.

The first auxiliary which I am drawing here it's basically based on a heterocyclic compound which is named as pyrazine and this auxiliary is derived by Schollkopf and now, if this auxiliaries usually if you see the structure this particular right hand portion is your amino acid. So, this is the amino acid, where you usually have this it is a alkyl kind of thing and this particular group this isopropyl seems to be you are the steric controlling agent.

Now, normally you cannot see the real structure, we will discuss these things little bit later on this auxiliary was named as Schollkopf's bislactim ether we will explain it later on Schollkopf's bislactim ether. These are basically amide and this amide have been converted to corresponding bislactim ether.

One of the auxiliary we already discussed earlier if you remember the very beginning our self regeneration of stereo center the Seebach auxiliary which is also a kind of an amino acid derived enolate. Now, if you try to think about this kind of auxiliary which we have earlier talked and now this auxiliary this part is your amino acid part right; this is your amino acid part.

So, and this tertiary butyl group which lies on the left hand side it's your steric controlling element. So, Seebach's SRS also you can think about an amino acid derived enolate. Other auxiliaries there is a very well known oxazinone based auxiliary which contains a 6 member framework and this auxiliary was named as Williams oxazinone based auxiliary which contains two bulky phenyl group as a steric controlling element and this auxiliary also if you can write in this fashion which is basically says that there are two hydrogen.

So, this is like a chiral glycine equivalent. So, basically this part is your glycine part, ok. And any of this hydrogen you can abstract sequentially and you can introduce two different alkyl groups. So, this was a Williams auxiliary.

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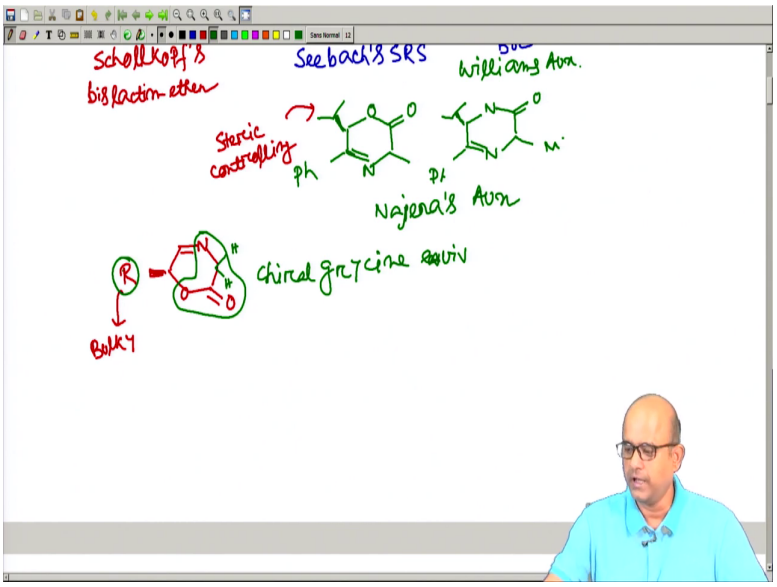

There are other auxiliaries which also will be explaining to you just by drawing their structure and everything else I mean their mode of asymmetric induction we will talk about little bit later on in the subsequent classes. This is a similar kind of auxiliary which was derived by Carmen Najera or yeah just modification of the Williams oxazinone auxiliary here this is having an imine bond.

And on the similar pattern by replacing the heteroatom with another nitrogen you can basically have another auxiliary which is also derived by Carmen Najera and this auxiliaries are named as Najera's auxiliary. Now, if you see their structure their structures are almost similar. The steric controlling element was of mainly the isopropyl group which contains a bulky isopropyl group and this is basically the steric controlling element in the enolate alkylation.

And these two auxiliaries are there. And in addition "n" number of auxiliaries have been reported in the literature which actually contains a simple chiral glycine enolate equivalent. Now, glycine being the simplest amino acid so, probably this would be a good starting point. So now, if you see this kind of cyclic structure with a bulky group attached here. So, this group is really bulky group, ok. And this kind of auxiliaries are also reported in the literature which are often referred as chiral glycine equivalent.

Now, why glycine equivalent because, this auxiliary if you see this part it is a glycine part right, glycine CH2 NH2 COOH. Now, here you can abstract the hydrogen you can generate the enolate and the alkylation can be controlled by this bulky steric directing group which is normally positioned in this particular thing.

And you have a cyclic assembly so, normally cyclic assembly have a rigid conformational behavior and then, by virtue of this steric element of this particular group you can control the enolate alkylation. In principle this was the most well known strategies for amino acid derive alkylation.

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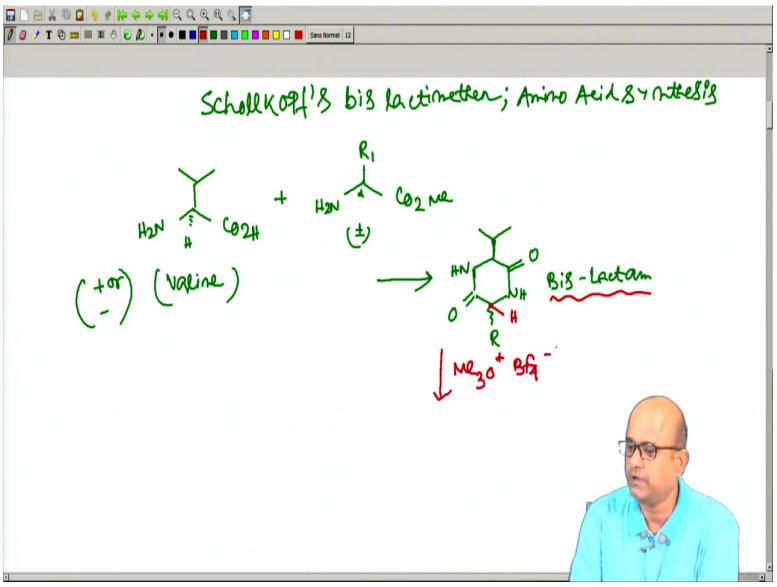

The very beginning we will start with our Schollkopf's bislactim ether which just now we talked about. We will talk about what this Schollkopf's bislactim ether how you can synthesize this bislactim ether and how you can create enolate alkylation of simple amino acid derived enolate when write amino acid synthesis, ok.

Now, first let me talk about it is structural features just one minute. Usually such bislactim ether was prepared by taking a enantiopure amino acid as one of the reacting component. And most of the cases you choose a bulky alpha amino acid like let us say for this case you choose simple valine which is having isopropyl group. Now, this enantiopure amino acid you take it.

So, this is either a plus or minus enantiopure amino acid. So, take this amino acid and then, you choose the amino acid where you want to do the alkylation. So, simple corresponding methyl ester of the amino acid and this is a racemic compound. So, this stereocenter you want to create a new stereocenter. Already a stereocenter is present, but we want to take a racemic thing because you want to abstract the hydrogen.

Now, these two amino acid derivative are first condensed. Now, once they condensed you are basically getting a bislactam. The bislactam structure….. I will first draw let me draw the bislactam structure then, I will explain how this bislactam is going to be formed. Actually one amino acid they are basically an intermolecular condensation kind of reaction and you are going to get this bislactam.

Now, you now analyze this bis-lactam you check this part isopropyl is this isopropyl it is a NHC double bond do. So, this is coming from the valine and this amino acid will basically give you this part. So, this is quite clear and here you are having a hydrogen which you want to abstract.

Because, you want to do alkylation, but there are other hydrogen's which is present in the valine part also. Though there is definitely a sterically bulky group so, what Schollkopf's did Schollkopf's first put or take this compound and treat with an alkylating agent which is very well known alkylating agent it is name is Meerwein salt Me3O +BF 4 minus which is a source of methyl electrophile like methyl iodide.

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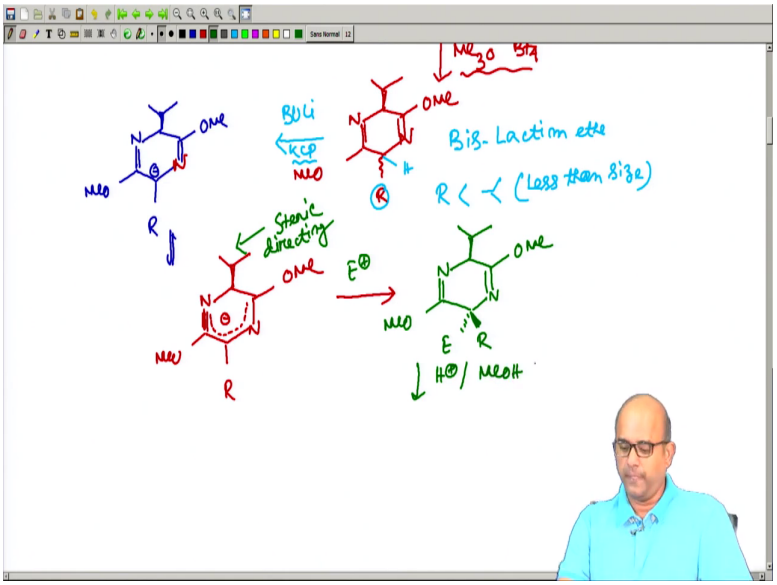

Now, this compound was taken this Merrwein salt and actually this lactam usually this lactam now converted to corresponding bis-lactim ether by simple alkylation because, if you think about the lactam resonances that is the main responsible factor. So, both the cases you will get this kind of bis-lactim ether.

So, lactam is converted to lactim. So, this is called bis-lactim ether ok bis-lactim ether. Now, we will be trying to employ the base for the enolate alkylation and this case I will be using a base let us say you use butyl lithium it is a bulky base ok. And then, you are usually having a hydrogen here, you are having a hydrogen here also. But, definitely you try to maintain in such a way that R is always less than in size than this isopropyl group.

So, this is one of the prerequisite. It means that, the hydrogen present near the R its kinetically more accessible, ok. So, basically you will be trying to do a kinetically controlled deprotonation, ok. And then, once you do it once the hydrogen is abstracted you will get the corresponding enolate or you will basically get the carbanion first. Because, now the initial carbonyl group in the amino acid we have converted to corresponding lactim ether.

So, you get this carbanion, fine. Now this carbanion is a double delocalized because, it is a bis allylic system. So, you can eventually write that this carbanion is extremely stabilized through double delocalization and such system its very much stabilized let me write the we have missed something there will be nitrogen here there will be nitrogen here; just a small printing kind of mistake, ok.

So now, if you can see I put this thing as a we put a OMe here, we put a OMe here a nitrogen a R and this minus is now delocalized through this entire five atoms, ok. So, fine now you are going to react with the electrophile and eventually we will find that this particular group or your isopropyl group seems to be the steric directing group. As this is a beta so, the electrophile seems to be approaching from the alpha, ok.

So, you react with electrophile. The choice of electrophile depends on you that which kind of electrophile you will be using based on your target structure. So, everything remains same and here as initially you are having a R. Now, electrophile seems to be approaching from the below. So, you just write the below bond or the alpha bond and the remaining group will be now beta, ok.

And then, you will be having this compound. This compound upon hydrolysis a simple aqueous hydrolysis or treatment with methanolic H plus you will basically get the corresponding hydrolyzed product means, first you get your desired amino acid where you will have this R is here the ethyl or electro electrophile is there you have this NH2 after the hydrolysis you get the corresponding methyl ester CO2Me.

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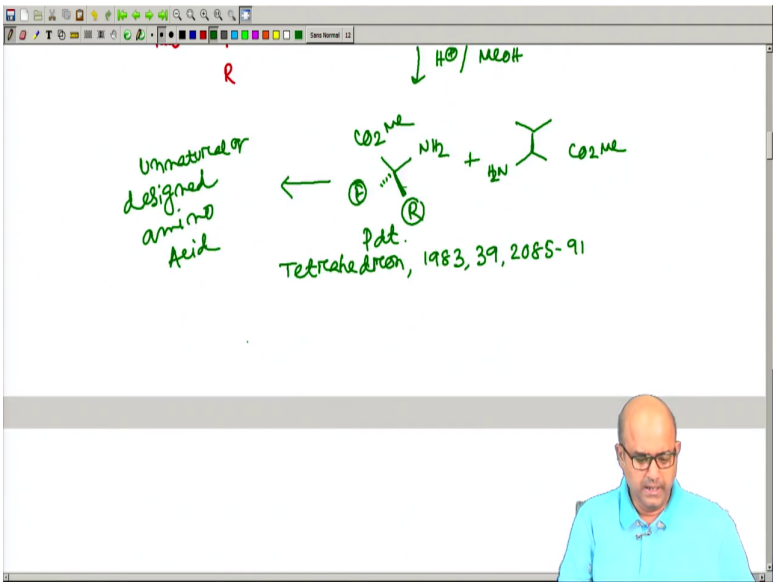

So, this is your desired product in addition the valine which you have taken it is coming back you will be recovering the valine as it is. So, valine is acting as a chiral auxiliary at the very beginning and now this is your desired product. So, you can use this Schollkopf bislactim ether based alkylation and this was little bit of old paper which is first published in a Classical Organic Chemistry Journal *Tetrahedron* in 1983 probably give you a significant application of enolate derived from amino acid derivative.

And that is you can basically control now that unnatural amino acids based on this R and E you can synthesize. So, this was gives you an access of different unnatural or designed amino acid or designed amino acid. So, this you can control by reacting with this Schollkopf's bis lactim ether you can actually synthesize. Now, next we will try to have a little bit of a different concept before you go to other thing. It is similar once the Schollkopf have this bis lactim ether.

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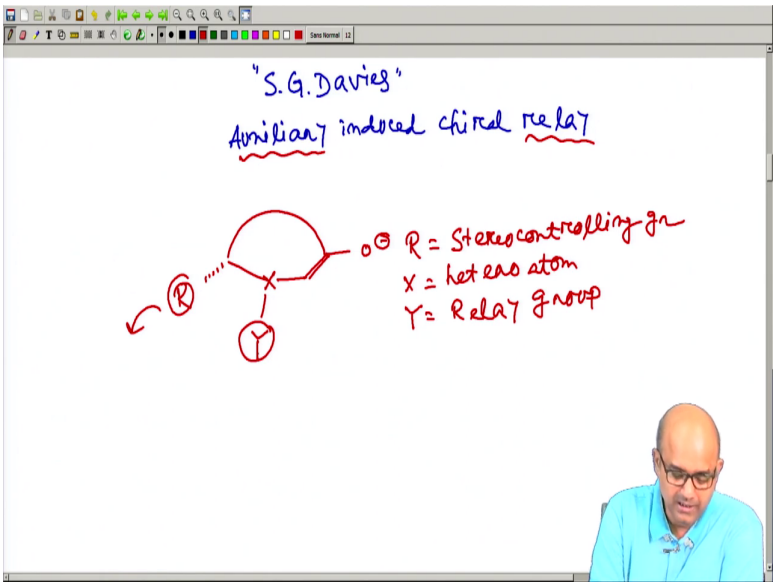

People are trying to use the similar concept and particularly this fellow S G Davies who was kind of thinking in a different way and he actually proposed that probably auxiliary is fine, but we will try to do something else and he was first to pioneer a term called auxiliary induced chiral relay.

Now, this relay term was quite interesting the relay means initially you have an auxiliary and this auxiliary whose main role is to supply the proper stereo chemical bias or the steric orientation. Now, this auxiliary gives you a relay to a next atom. Let me talk with a simple drawing that will be quite clear.

In a usual auxiliary what is happening you have this kind of enolate…. let me draw a simple enolate this is a simple enolate and X is a heteroatom it might be attached with Y also and then, it probably if I can try to do a cyclic structure it can have something like this; and one of the carbon contains a steric directing group, ok.

So, this is your main auxiliary structure. Now, in the earlier case we are saying that this R. So, R main role is stereo controlling group it's a stereo controlling group fine controlling group. And now here you are saying that this X, X is a heteroatom could be nitrogen in the most of the cases as you are talking about amino acid derived enolate and Y, this Y it's a relay group.

Now, this relay group the role we are we will be discussing right now. Now, as R is alpha of the enolate plane. So, this Y can actually have two different orientation. If Y could be also alpha then R alpha and Y alpha means that, enolate alkylation has to be always from the beta. Now, sometimes it happens that depending on the nature of R the Y can adopt a beta conformation.

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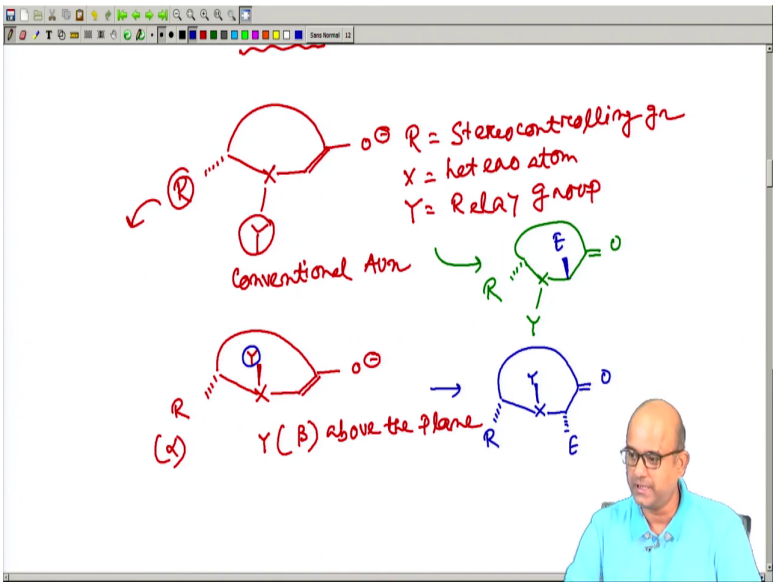

So, this will be quite interesting. Now, this initial drawing it is a very simple conventional auxiliary design conventional auxiliary because, Evans or other auxiliaries we have seen. Now, let us say we have a heteroatom here and then as usual the enolate is there fine we make a cyclic structure and auxiliary is definitely below. Now, I am saying that due to presence of this thing the Y probably adopt a beta structure beta orientation.

So, R is alpha and this Y has a beta orientation or above the plane. Now, if Y becomes above the plane; that means that, once electrophile seems to approaching it gets a close encounter with the Y which is above the plane. So, in these cases the nearest group Y controls the electrophilic attack. So, in the first case let me now try to draw the final product based on the structure.

So in the first case, your X is here, Y is here and we are assuming that R is alpha Y is alpha. So, definitely the electrophile seems to be electrophile seems to be coming from let me control the entire drawing this is will be your R and electrophile will be always beta ok, fine.

Now, the second case so, basically what we will get you always get the trans kind of product it.

Now, in this case what you will get, in this case you write X is here you have this; you have this ketone. The Y occupies a beta orientation, then you choose the typical ring you have the auxiliary here and now you see we are saying that is a 1,2 induction. So, the Y is now becoming a stereo controlling group. So, you get this product. So, both the diastereomers you can actually create if you have a proper relay group.

So, this is the role of a relay group. So, in one case the relay group and the auxiliary are in the same orientation. So, that is very conventional because both the groups are below so, electrophile comes from the opposite. In the second case, the auxiliary group and the relay are in the opposite orientation and that creates a bit confusion because, the electrophile when it approaches to the enolate it gets the proximal or the proximity of the relay group.

Now, relay group is above the plane. So, this was first coined out by Professor Davies based on the idea he actually did a series of experiment and then we just are trying to highlight what kind of precursor he took and then, we will explain…… it is explanation.

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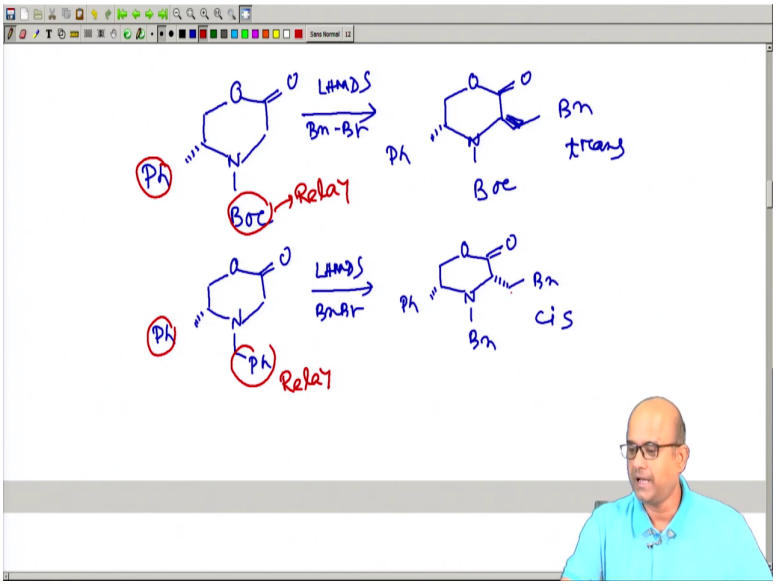

So, in the first case you see the heteroatom we are basically talking about a nitrogen. And then, so if you have this kind of precursor or it is basically a chiral glycine equivalent what you do you treat with LHMDS as a base and then, react with an electrophile which is a

benzyl bromide, ok. Now, it has been found that you actually can get the benzyl group above in Boc. So, basically what you will get? You get a trans product 1, 3 trans.

Nevertheless, if you have a similar kind of substrate the only difference what you now do instead of the Boc you now put a CH2Ph here and then the auxiliary have the similar structure. Now, you just apply the same condition LHMDS and benzyl bromide. Surprisingly you actually get a different level of asymmetric induction and the stereochemistry was to get a cis and that was quite interesting, you get a cis stereochemistry with a benzyl product.

Now, the explanation will draw or we will give you what I am trying to say that you have this auxiliary which is a stereo controlling element and this group first Boc and the second group Ph now acting as a relay. So, these groups are now acting as a relay in the overall process. It means that, one case phenyl and Boc are both in the same plane; in another case phenyl and benzyl has to be in the opposite orientation because as benzyl if has to be above, then the electrophile benzyl can come from the below.

So, let me go through a quick analysis of both the thing, then we will be explaining this thing in detail on the subsequent part.

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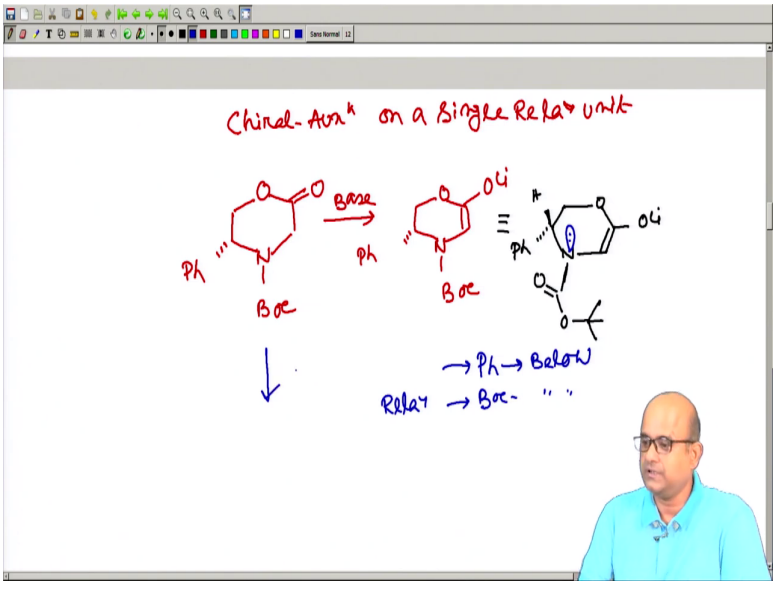

So, in this case we call this as a chiral auxiliary system on a single relay unit; there are different relay where you have a double relay unit. Now, the single relay unit what is happening just now we talked about a single relay unit, ok. Now, the single relay unit you

basically have an amino acid derived precursor N C double bond to Boc ok; this part is your vinyl. So, first you treat with a base LHMDS. So, eventually what you will get? You get the enolate.

The enolate means this N get a Oli. Now, we are going to draw the three dimensional structure for such compound. So, here it was usually potentially viewed that this kind of compound might be adopting a structure something like this. Though we usually do not do a half chair kind of thing just for sake of simplicity. Now, phenyl is below ok phenyl is below this hydrogen is above. Now, here you have this kind of structure N C double bond O this O and this third butyl.

So, what I am assuming that we I am assuming that this lone pair is this way and this group is this way. Now, actually this could be the most preferred orientation because, if you have to put the entire Boc group on the above that will give you a severe non bonding interaction with the ring hydrogen as well as with the oxygen lone pair. So, that is not recommended now, this phenyl and tertiary butyl this is the amide bond this is the amide.

So, tertiary butyl can orient itself away to the phenyl group. Now, what does it mean? It means that, a phenyl group is below and the Boc group is also the below. So, phenyl is the original steric directing group and Boc is the relay group. Now, you see as both are below once you do the alkylation; once you do the alkylation it is very simple you will definitely get the c double bond to the benzil on the above side, ok.

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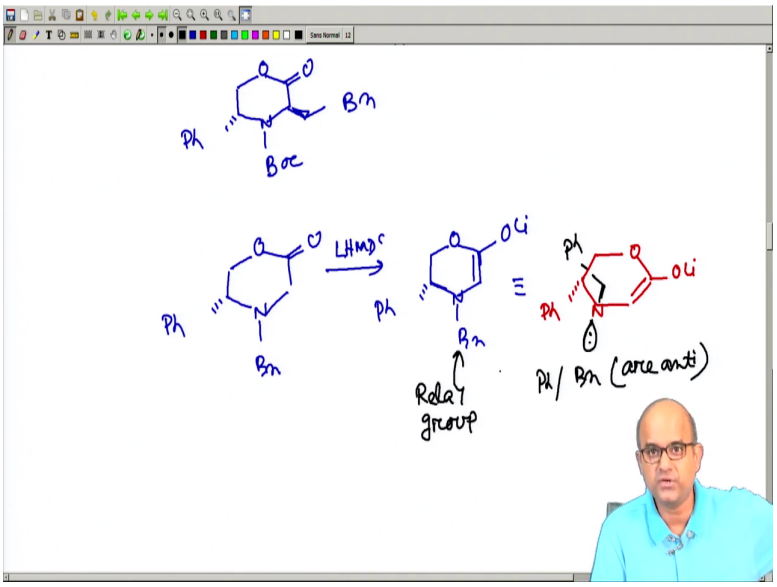

So, this was the first explanation for the initial part. The second part, if you now change the group from Boc to benzyl. Now, in this case you just change the group from Boc to a benzyl you just put a benzyl here everything remains same. Now, this compound if you now analyze or treat with a base LHMDS.

So, initially you are going to get the corresponding enolate which seems to be O Li this N Bn …….P h. Now, we will try to draw it structure and see how this looks like. So, everything will be similar as we have drawn in the earlier structure. Now, in this case this will be not a Boc, this will be a benzyl.

So, nitrogen now we can put it here, ok. Now, phenyl group is below. Now in this case, actually this phenyl and this benzyl forces this thing to an opposite orientation. In earlier case you have a Boc, but here you do not have a Boc, you have an alkyl group and these two alkyl if they will come on the same plane there will be severe steric interaction. So, to avoid that this phenyl and benzyl are anti to each other anti.

So, now you see that the relay group the this is the relay group. So, relay group which actually occupies a beta orientation; that means that the incoming electrophile now we can simply do it here incoming electrophile will be approaching the enolate approaching the enolate from an opposite faceof the relay group.

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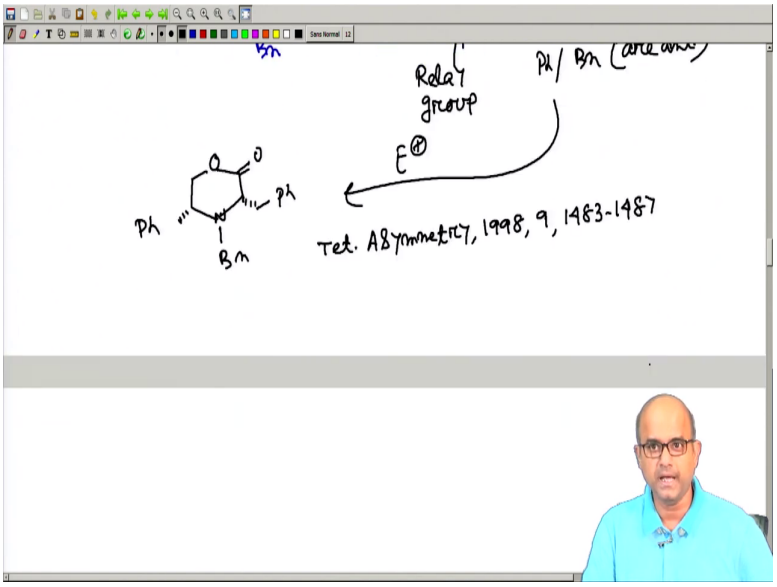

So, that was the beauty of such system; it was eventually similar kind of observation we have seen in the SRS strategy the originally developed by Seebach's just by changing the protecting group you can actually control the enolate alkylation. Now here, Professor Davies preferred this name as a relay. Now, this relay was first probably I mean there are many papers one of the paper I am just going to highlight it was reported in Tetrahedron asymmetry one of the old classical paper in the organic chemistry it came in 1998.

So, little bit ago and then this is the page number. So, this particular idea will give you that auxiliary you can actually have tuned it in a different way; you put a steric directing group and then in addition you put a relay group. Now based on the auxiliary which is present the relay group can orient it is self either alpha or beta and as the enolate and the relay group are in close proximity now, the relay group becomes the stereo controlling factor.

And based on the similar kind of similar kind of relay based auxiliary you can do alkylation on several amino acid derived enolate. In the subsequent classes we will talk about more examples.

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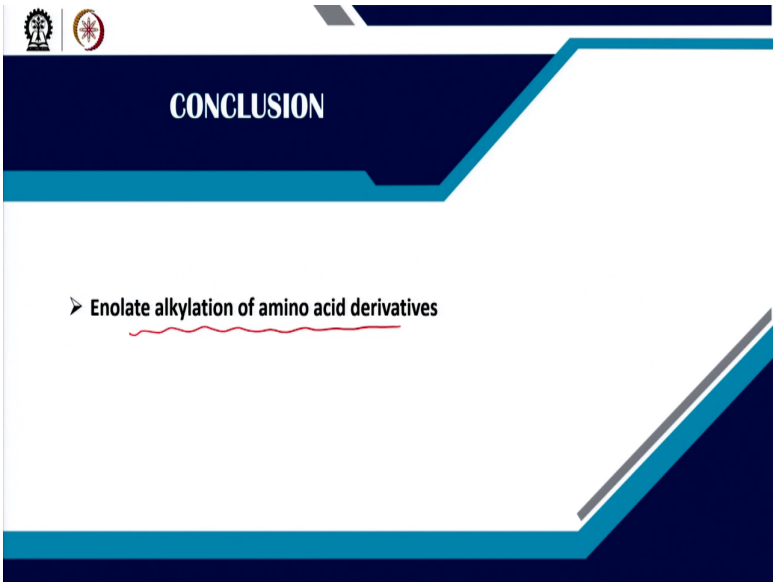

So, as a conclusion you can say that enolate alkylation of different amino acid derived enolates can nicely be or judiciously be tuned by certain amount of chiral auxiliaries and you can actually make those auxiliaries in the lab. And initial part we talked about Schollkopf's bis lactim based ethers and then, finally we talked about Davis chiral relay system. Where a

stereo controlling group controls the orientation of the relay and then that relay group actually controls the incoming electrophile from which phase it will be approaching.

Thank you in the subsequent section we will talk about more enolate derived alkylation.