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 - 29
Williams Oxazinone, Yamada's CHIRAL glycine enolate and related system

Welcome students. In this lecture 29 which falls in the same module, will be mainly talking about several chiral glycine equivalents and mainly talk about Williams oxazinone and Yamada's chiral glycine enolate and related systems.

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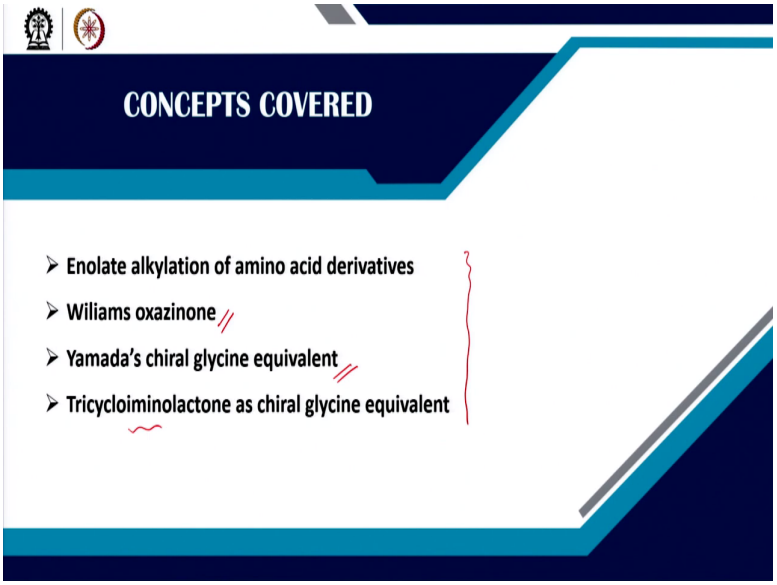

The main contents which we will be covering…… that how chiral glycine enolates can be synthesized and how they can synthetically be manipulated. We will talk about Williams oxazinone as one of the key auxiliary of the chiral glycine enolate equivalent, as well as Yamada's chiral glycine enolate equivalent. And, finally, we just give you a brief hint about tricycloiminolactone either carene derived or camphor derived as a chiral glycine equivalent.

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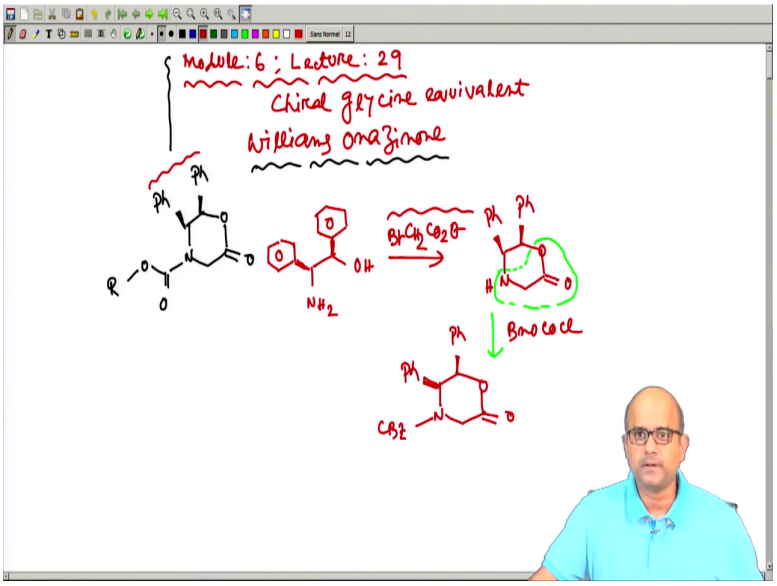

So, in this lecture 29 we will be talking about chiral glycine equivalent and particularly we will be discussing William's oxazinone as one of the well known chiral glycine equivalent. The basic idea was we take suitable auxiliaries in which glycine is one of the integral part, that is what such auxiliaries we call chiral glycine equivalent and you can abstract both the hydrogen present in such auxiliary.

And, then you can sequentially alkylate by replacing both the hydrogens and then you could create this alkylated chiral glycine and its corresponding equivalent. Now, Williams oxazinone the basic structure is a 4-member sorry, 6-member heterocyclic based structure. I will first draw the structure and then we will explain how such compound can be prepared.

In the Williams oxazinone actually the steric controlling group was these two beta-di-phenyl and this nitrogen was protected as mainly BOC or other esters, ok. Now, you can see that such auxiliary this bis-phenyl or the two phenyl group are usually acting as a steric controlling element.

Now, how such auxiliaries can be prepared? Usually this compound was prepared by taking the corresponding amino alcohol which seems to be commercially available ….. a another phenyl is here and you can put both the phenyl stereochemistry as beta. So, this amino alcohol you actually take and then you react this amino alcohol with bromo-ethyl acetate at the very beginning and it and then you have to fuse with simple glycine at the beginning.

Now, let take this thing and you have a OH and you have a NH2 and you have this part actually sorry bromo ethyl acetate you do not need to take any glycine derivative. This serve as a glycine precursor. So, this Br couples with this NH2 and this CO2 Et couples with this OH and what you will be getting you get this N you have this C double bond O, you have this oxygen, both the phenyls are here and you get this compound.

So, now in this compound you can easily see that this part is your chiral glycine part ok and the pre NH which is later on protected as it is CBZ chloride or other ester. So, you can just write CBZ chloride as the producting group. So, finally, you will be getting this as the main compound this will just write N-CBZ and then you have this phenyl, you have this phenyl.

Now, once you have this compound you can next try to use this compound as your glycine precursor.

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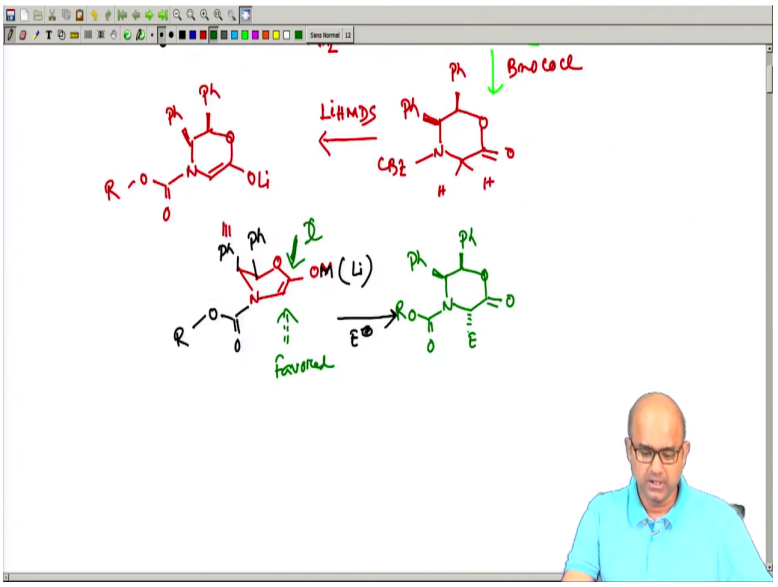

So, first you can easily identify that these two hydrogens we are talking about. So, eventually you can treat this compound with a suitable available base lithium hexa methyl disilazide LiHMDS or LHMDS could be the base of choice. And, once you try to generate the enolate, let me first do the enolate thing in a planar structure with both the phenyl groups are above you have this CBZ group or other group O-R ok.

Now, this compound you can actually write the structure in a 3-dimensional way which seems to be the half chair way you can write as a this and then have this oxygen here and then

this and your enol will be here OM and this is the enolate double bond. And, then you can see that the phenyl one will be this axial pseudo equatorial and this will be axial then you have your C double bond OOR ……CBZ group.

So, it was the usual way sorry this will be a metal means your metal. So, metal could be anything depending on your choice of base. So, as we have taken LHMDS, so, it will be lithium metal. Now, next is your electrophile you can try to attack the electrophile approach the electrophile and definitely as you can see that the enolate the top face seems to be definitely blocked as it is it contains two of the bulky phenyl group.

So, definitely bottom face will be mostly favoured and this will be your incoming electrophile which seems to be approaching from the bottom face now you can write the 2-dimensional way the planar structure. So, electrophile will be below which seems to be controlled by these two bulky phenyl group, ok. As this bulky phenyl group is above so, you always get the electrophile approach through the below face.

Now, you can stop your reaction here or you can subsequently do the double alkylation.

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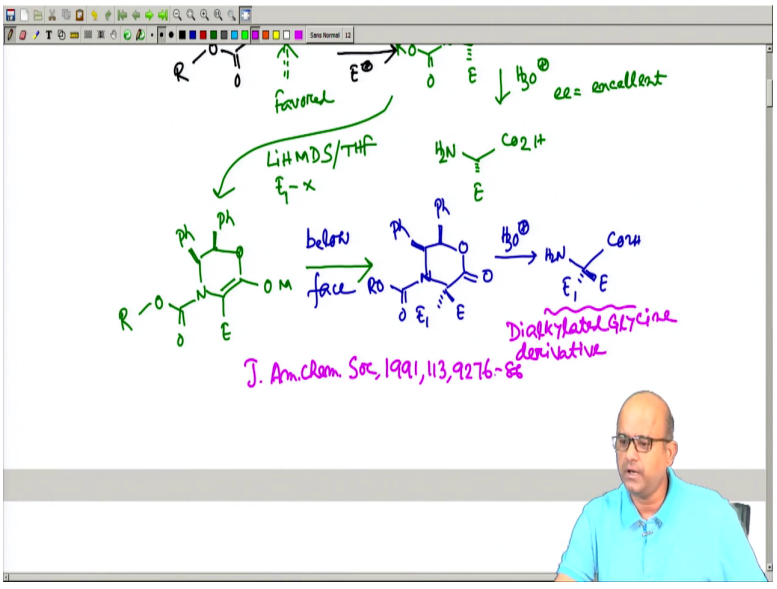

Now, if you stop this reaction here what you do you basically just hydrolyze by H_3O^+ and what you are going to get? You get this E and this is your CO2H and this is your H2 N. So, you can basically think about that you are getting an alkylated glycine derivative. The enantio

selection usually was pretty good the de, which we observe it is most of the cases is pretty good, greater than 99 percent.

Now, the same compound you can actually use in another round of alkylation. So, you can create a di alkylated glycine derivative. The idea was again same you treat with base LiHMDS with a suitable solvent like THF and then you take the second round of electrophile which you can write E1…….. E1X, ok.

Now, this once you have this initial hydrogen abstraction, definitely the enolate would not be now enolate will be eventually you have this O metal and the enolate will now have a planar geometry because the original stereo center is now vanished and you have both the phenyl group here, you have C double bond to O, you have O…… CBZ or other group, ok.

And, now the electrophile on the similar concept it will be attacking from the below face. So, we can write the below face attack. The below face is much more preferred. So, you can write the final structure of the di-alkylated product where the electrophiles. Now, is E1. So, E1 will be now below. The E will be now above, ok. The phenyl both the phenyl will be in the above as it is given in the original structure your N protecting group.

Now, this compound also you can now next hydrolyze and you can get a di-alkylated glycine derivative. So, you can eventually get E1, you have a E depending on your choice of which you choose the electrophile you can get a di alkylated glycine derivative. So, this was the main highlight of the chiral glycine equivalent and you actually get a di-alkylated glycine derivative in a enantiopure fashion.

And, actually you can create unnatural amino acid through this method and this method was very well known. It was reported in a very reputed journal, Journal of American Chemical Society. This work was reported in 1991. This is the corresponding volume and this is the page number.

So, Williams oxazinone based chiral glycine equivalent was pretty well known method and you can easily prepare this oxazinone. As I said you can take the corresponding amino alcohol, react with bromo ethyl ester bromo ethyl acetate actually and then you protect the corresponding free amine-nitrogen with a CBZ or other protecting group, but the best part is this controlling element by this two phenyl group. This was the main controlling element for the asymmetric induction.

Cleavage of this auxiliary as both the cases normally you can do it an acidic hydrolysis. There is other way, you can cleave the auxiliary. But, we are not going to discuss about these things.

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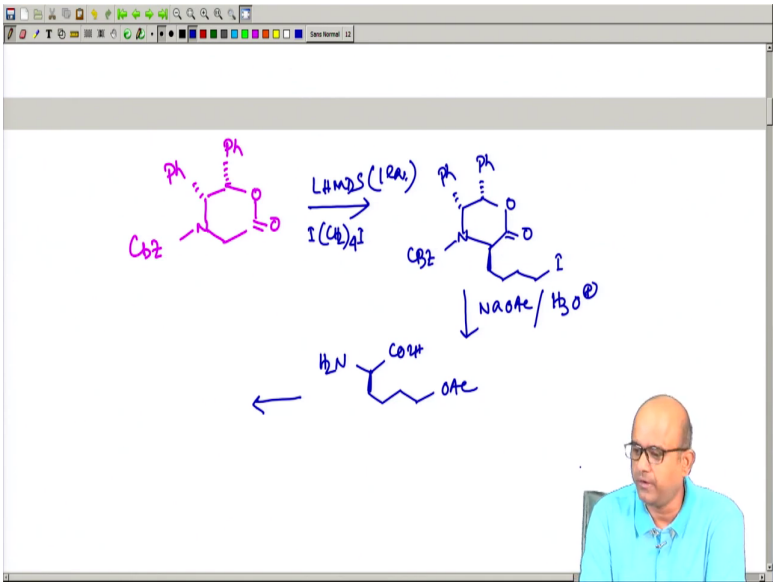

Actually such a Williams oxazinone based method can be used for the synthesis of some unnatural amino acids and we will be talking about some unnatural amino acid synthesis by this method in our next discussion.

We will try to use a Williams oxazinone where both the phenyl is below, just the enantiomer of the initial compound which we have taken. So, this is the chiral glycine equivalent which we are going to take and the reaction which was first done take LHMDS and react with an electrophile which is ICH2 whole 4 I. Fine it is a normal electrophiles and the idea was we will be just doing one equivalent of alkylation.

Now, so, initially we can easily say that it is both the phenyl groups are below. So, definitely the alkylation will be taking part or took place from the above ok. So, you can have C double bond O and you can find that it will be having CH2…… 1 2 3 4 you get this compound, ok.

Now, there is few synthetic exercise I mean other step the pre aldol group was converted to corresponding acetate by treatment with a sodium acetate by normal SN2 reaction and then it was been just doing the hydrolysis to remove the auxiliary. And, then what you are going to

get? You basically get this OAC because this part is the iodo now and then CO2H and the H2N, ok.

This amino acid first usually you will be getting and then there are couple of reactions which people I mean a group of researchers did it for some synthesis of a unnatural amino acid. Now, we will just try to explain that what are the other reactions they made it, but, before that I just try to give you the target molecule which we actually wanted to prepare this by such method.

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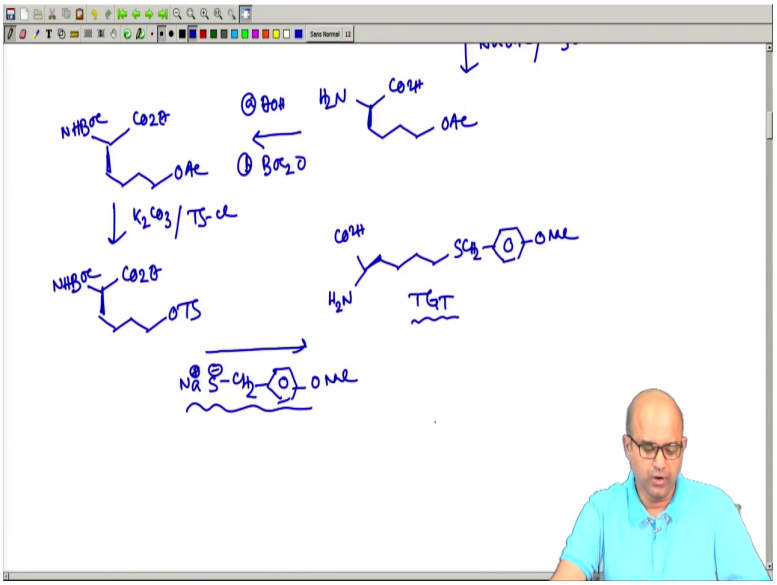

So, they actually wanted to prepare a compound something like this which seems to be an unnatural mono alkylated glycine derivative with this 4 CH2 group is here 1 2 3 4 and then they will be actually trying to put a aromatic ring here. So, this kind of unnatural amino acids they have been they require such unnecessary amino acids for some biological studies.

Now, if this has to be a target molecule you first do the alkylation you actually fix it here, the next part I did not discuss the synthesis we can now discuss the synthesis one after one. So, initially what they do after taking this one? They first esterify this free carboxylic acid with ethanol treatment and the free-amine group……. they actually treat with BOC anhydride. So, they basically get the corresponding BOC derivative. So, you get CO2Et, you get NHBOC ok and this part are all remain similar, 4 CH 2 you get OAc.

Now, next this……. OAc they have to remove it they just do the normal hydrolysis for removing this acetate group. This acetate group was removed by potassium carbonate treatment. They basically get the corresponding alcohol ok and then this corresponding alcohol will be treated with a simple tosyl chloride to get the corresponding OTs derivative.

This part is as usual normal synthetic group manipulation nothing else, but they use it with the Williams oxazinone based thing. So, 4 CH 2 you get the OTs. Now, this OTc was actually replaced by with a another nucleophile and this nucleophile was the CH2 this para methoxy group OMe CH 2 and S minus sodium plus. So, this is the nucleophile they use and then once you do it you get this compound.

Then you remove the CO 2Et and remove the BOC you get this amino acid. Now, this kind of protected amino acid is actually kind of used for some biological studies, but anyway nevertheless we are not interested for this biological studies. We can say that such Williams oxazinone methods can be useful for preparation of mono alkylated glycine derivative. This is basically nothing, but a mono alkylated glycine derivative and then you can use such chemistry for preparing some unnatural amino acid derivative.

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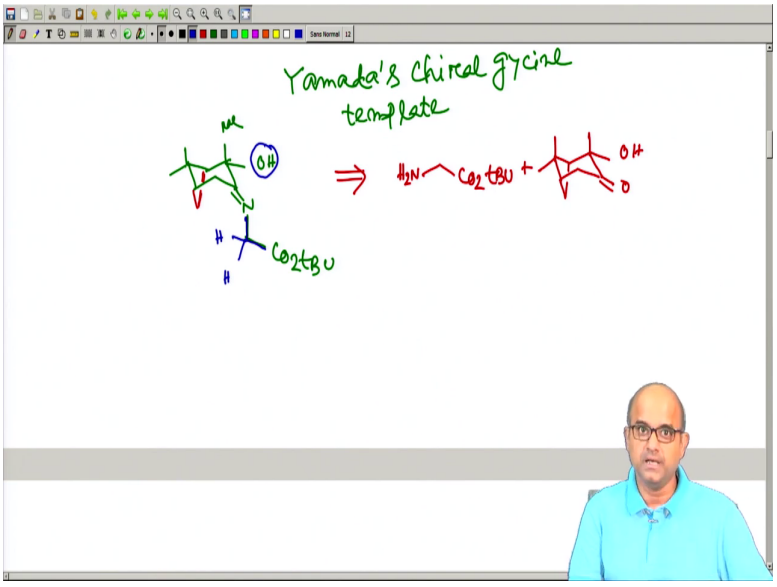

And, next in this glycine derivative we will be this chiral glycine derivative will be using another chiral glycine derivative which is named as Yamada's chiral glycine template. This was first reported by Japanese scientist Yamada and this particular compound, if I will just write let me first write the structure of this compound. This is a bit complex structure.

It is first having a 6-member this thing. It contains an axial methyl and this OH. And, then this part initially was fused with a glycine imine ok CO2 tertiary butyl CO2 tertiary butyl. I will explain how this compound was made and then you have this methyl and then this compound was actually having a 4-member structure at this point with this. This was a very rigid structure, ok.

Now, this compound was usually prepared from corresponding glycine derivative H2N CO2 tertiary butyl and the corresponding ketone which we can write in the cyclohexane chair form. This is actually a naturally occurring ketone which you can get it from the natural sources and this is alpha pinene derived naturally occurring ketone this. So, this ketone was condensed with this glycine derivative to get the corresponding imine, ok.

Now, this imine will now erve as a chiral glycine template. How? See this part is your chiral glycine template. So, this part. So, this CH2 and this CO2 tertiary butyl. So, there are two hydrogens which you can think about abstracting and definitely as this contains a chiral part so, there will be once you generate the enolate this will be basically a aza enolate kind of thing so, first imine and this oxygen might be taking a role once you have this metal enolate. This can help in the chelation.

So, let me again try to draw the entire thing the initial parent compound.

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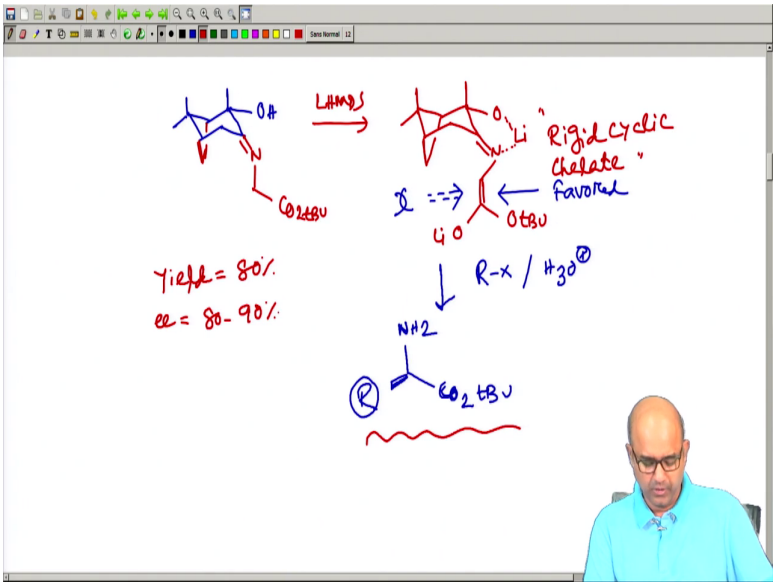

So, drawing will be a bit difficult, but you can just practice this drawing and ……. more you draw more structural information you will actually get it. So, I will use a different colour pain for this bridging, as it is having a cyclobutane bridge actually, fine. And, then here you will be having this your N this CO2 tert butyl.

Now, see initially you get this enol let me first try to react with a base LHMDS ok. So, I will keep the entire structure as same because this part will be remaining similar methyl your OH……. I just put it O then your bridge structure ok the bridge cyclo butane structure and you have this N and then your enol was there you have a O tertiary butyl and you have a O lithium.

Now, if you use excess LHMDS that has to be there actually you find that this gives you a O-Li and this gives you a chelate. So, this kind of rigid cyclic chelate was postulated rigid cyclic chelated enolate. Now, you can see that this enolate which we have just now drawn the back face or this face seems to be kind of blocked by the entire this group, ok or entire of this auxiliary, fine.

Now, this face is the only accessible or favored. So, similar kind of conceptual analysis we earlier have shown you in case of Evan's auxiliary based method; even in the Meyers case also Meyers oxazoline you have a rigid chelate which now controls the approaching electrophile through the pre existing stereo center present in the auxiliary.

So, this will be now you can eventually try to fuse that that what could be your main structural pattern. So, now, you can see the CO2 tertiary CO2 tertiary butyl. You just draw it in this way and we can just try to write and then this R-group will be your we can write this just as it is. If you can write it sorry, NH2 and then you put your this position R. So, any of this I mean this enantiomer of this thing you will be obtaining, but definitely you have to do a hydrolysis. The hydrolysis can be done.

Now, what where from this R is coming? This R is coming from the electrophiles R-X and then you use H_3O^+ …….. So, such reaction was pretty much general and with this Yamada's chiral glycine template you can actually get. The overall yield was pretty good as reported by Professor Yamada. The yield was close to 80 percent and enantio selection was also good, 80 to 90 percent enantiomeric excess for the corresponding amino acid you can usually obtain.

So, this thing was the chiral glycine template and we will just try to talk about few more chiral glycine templates available in the literature.

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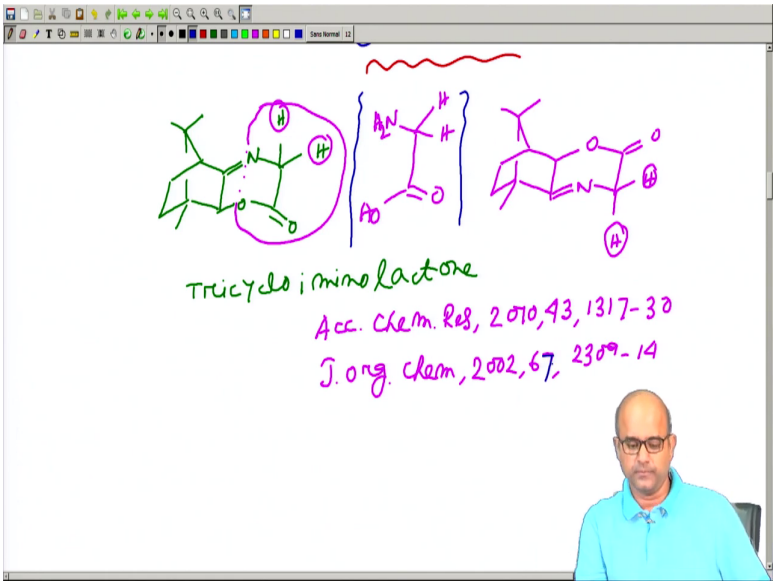

And, probably in the next lecture we will talk in detail, but before we end today's lecture. I will just try to give you a one such chiral glycine template which seems to be very much interesting. It is based on a tri cyclo imino lactone. Now, you see the structure. The structure will be pretty much interesting and this actually based on a chiral glycine equivalent.

Now, this compound was name as tricycloiminolactone. Now, such tricycloiminolactone if you see the structure, this structure was definitely based on a camphor derived auxiliary. And, then this part is your glycine part ok this part is your completely glycine part, ok and such chiral tricycloiminolactone actually you can make both the corresponding tricycloiminolactone and you will find that both the tricycloiminolactone are usually camphor derived and both the cases you actually.

So, there normally can be derived from the same tricycleiminolactone and the idea was this hydrogen can be abstracted by base and you can subsequently alkylate it with the electrophile and you can get chiral glycine derivative. Now, this was reported in account of chemical research. This is this result was bit recent. It was invented by a Chinese group and the first report came in JOC paper, later that they actually reviewed this work in account of chemical research in 2010. And, then this was find the initial paper was published in 2002.

In the next class, we will be talking about how this auxiliary or tricycloiminolactone can be used as a chiral glycine equivalent and if you can see this is basically what this is nothing. But, just you can write this is the CO2H and this is your NH2 part and this is the two hydrogen part. So, this is this compound can be regarded as a simple chiral glycine equivalent and this is the glycine part. So, you can correlate that this compound as a glycine equivalent, ok.

We will discuss the main features of this compounds in the subsequent lecture.

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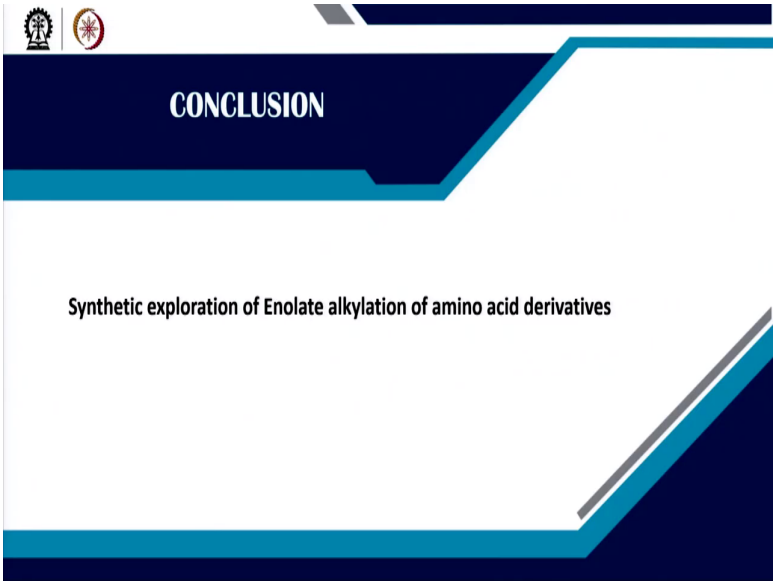

So, as a concluding remark we can say that synthetic exploration of enolate alkylation and this chiral glycine enolate equivalents are pretty useful synthetic tools in the asymmetric synthesis, and probably chiral glycine enolate equivalent are very useful to prepare mono alkylated as well as di-alkylated glycine in enantiopure fashion.

Thank you we will see you in the subsequent lectures.