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 - 04
Enolate alkylation of several carbonyl species
Lecture - 19
Myer's ephedrine and related systems

So, welcome everyone. So, today we will be talking about this lecture 19 under module 4 and we are basically discussing Myer's ephedrine and related systems.

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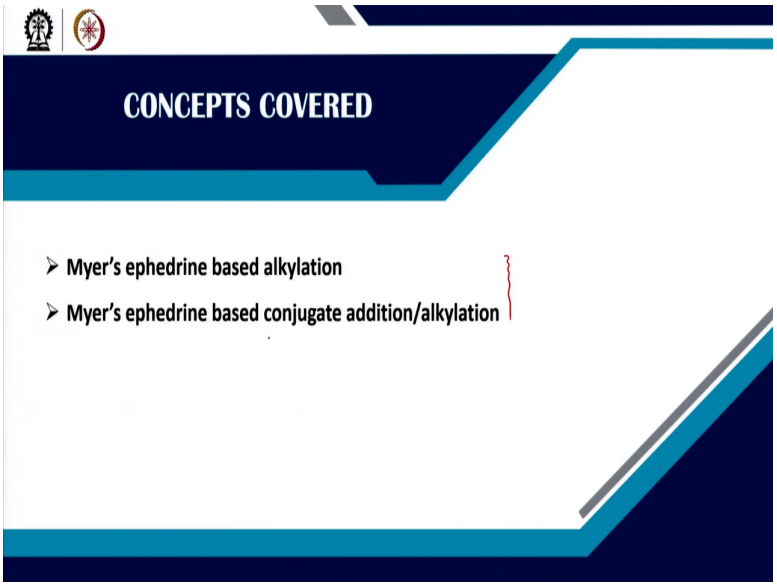

And actually today we will be talking about few more detailed analysis of Myer's ephedrine based alkylation and also Myer's ephedrine based auxiliaries can be used in a sequential manner through conjugate addition which generates the enolate and then we can subsequently alkylate that enolate in asymmetric fashion.

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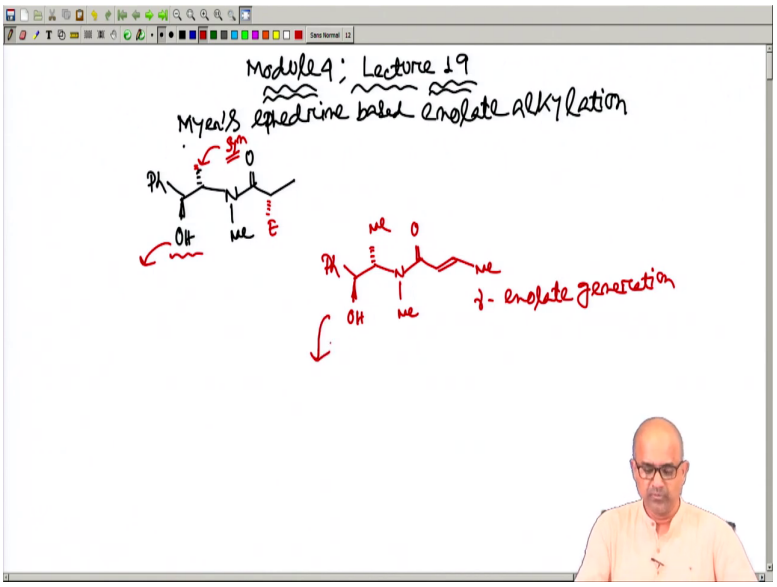

So, in this module let's talk about Myer's ephedrine based enolate alkylation and few of its important feature. In the last class we have basically discussed that how Myer's ephedrine based enolate alkylation can be very useful we said that initially you need to add base and base is usually added in excess because this auxiliary does have a free hydroxy group so, that is involved in the excess base quenching and then you have your secondary amine which is covalently attached to your carbonyl precursor.

Now as a working model or working hypothesis we said that initially this hydroxy seems to be forming the corresponding alkoxide and this alkoxide or O metal is basically this metal part is having a solvent as a coordinating partner ok.

And then this basically from the supramolecular aggregate. So, the beta face of this enolate or the alkoxide seems to be blocked ok and then the alpha face attack is possible the rule of thumb we explained that whatever stereochemistry is present here if it is alpha or if it is beta always syn alkylation takes place. So, means here you have this syn thing.

So, depending on this stereochemistry you can simply predict by a rule of thumb ok. Now let me explain couple of other features for the Myer's ephedrine based auxiliaries. Myer's ephedrine based auxiliary can also be useful for certain other system and this kind of system seems to be not that much popular, but it sometimes can be very useful let us say you have an alpha beta unsaturated system something like this ok.

Now, here definitely the you cannot add an electrophile at the very beginning because you will be probably wondering that where the enolate could be generated the normally this enolate can be generated at this methyl position. So, then it's a gamma enolate generation. So, this gamma enolate generation can be possible.

Though formation of gamma enolate is not very popular, but if there is no other place. So, gamma enolate generation can be possible.

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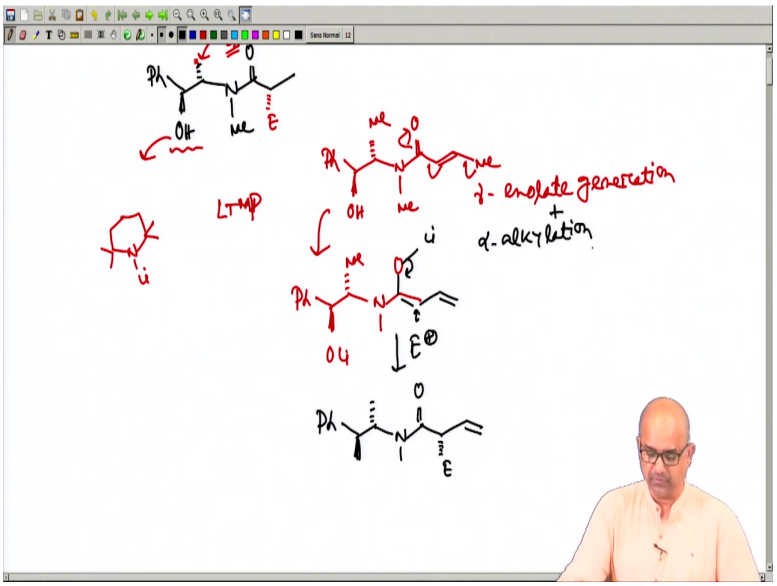

So, in this case you can eventually try to use a base like LTMP we already talked about is lithium tetra methyl piperidide. So, basically this is the structure of LTMP…….. N Li now with this base what is going to happen?

So, initially you can find that it will be this O Li will be always there this methyl and then this N Me CO. So, this hydrogen is going to be abstracted it normally if you try to write this with this and this. So, then you can eventually try to draw the enolate structure in this way ok. So, let me write the O Li double bond and then this one ok now there is a two way the electrophile can attack.

Two-way electrophile can attack electrophile usually can attack to alpha position or could attack at the gamma position and normally this attack at the alpha position seems to be much more preferred because this is very adjacent to the carbonyl. So, the more you go the negative charge the intensity seems to be disappeared.

So, fine. So, with this background information now the electrophile is attacking and you can simply found that this electrophile carbon bond is going to form.

Now, what about the stereochemistry? Definitely the same way as the methyl is here other working model seems to be there. So, it will be 1,4 syn. So, as methyl is alpha. So, N methyl now put the C O and this is the vinyl and this could be the electrophile. So, this is very simple, but you do a gamma enolate generation and then you do a subsequent alpha alkylation. So, this is a combination of a gamma enolate generation, but an alpha alkylation.

So, this reaction was definitely sometimes useful for making compound like this.

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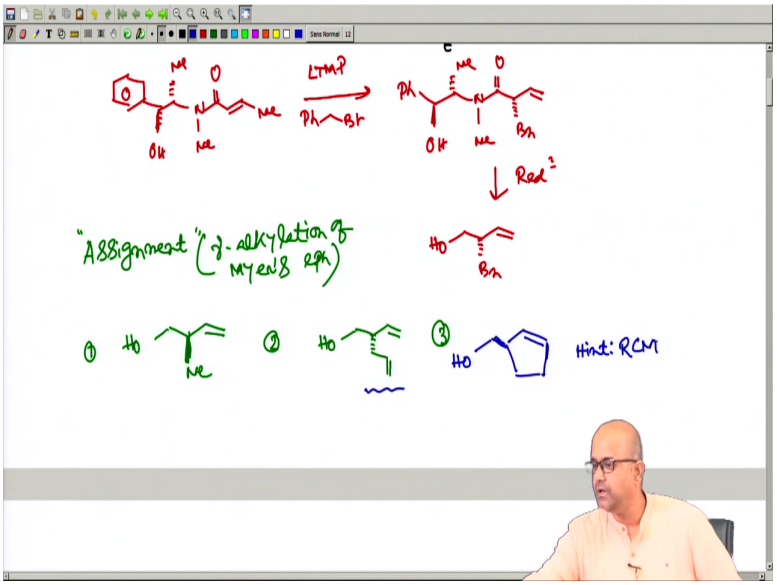

Now, let us try to give you an example for such system in the. So, you can have a Ph the parent compound you have a beta OH you have an alpha methyl you have a N you have a me and then let you it has this structure fine. The reaction condition what I am giving now your base LTMP and I am giving a very highly reactive electrophile benzyl bromide ok.

And then so, the moment you have this what you are going to get you get this OH everything else will be similar the working model just now which you have explained will following the way. So, you basically get the alpha benzyl part here this is your vinyl. Now such system can be very useful if you now try to manipulate through the reductive cleavage it will basically give you the benzyl this and CH2OH.

So, this kind of very good chiral intermediate you can actually create. Now, let me try to give you some assignment. So, this you can eventually try to apply this gamma alkylation. So, assignment based on gamma alkylation on Myer's auxiliary gamma alkylation of Myer's ephedrine based auxiliary.

So, let me just follow the a very simple basic structure I put a methyl here I put a vinyl I put a CH2OH. So, try to be careful about the stereochemistry say beta stereochemistry. So, this is number 1 assignment number 2. So, how you can make this compound this is the assignment ok. So, in compound 2 I will put a structure like this and CH2OH and this was very useful because you can see this is a you can generate a terminal olefin kind of compound and it's an allyl.

So, it clearly indicates that allyl electrophile you can actually add number 3 we will just try to give you a little bit of a different structure. It probably you have to just work it out little bit. So, I am asking you a generating a cyclic compound with this structure the stereochemistry this is the beta 1. So, this seems to be actually if you follow this assignment you can end up with this.

The hint what I am giving for you here the after the alkylation finally, you can do a ring closing metathesis reaction to close the ring to get the double bond ok. Rest of the part is very much similar what we just now discussed ok.

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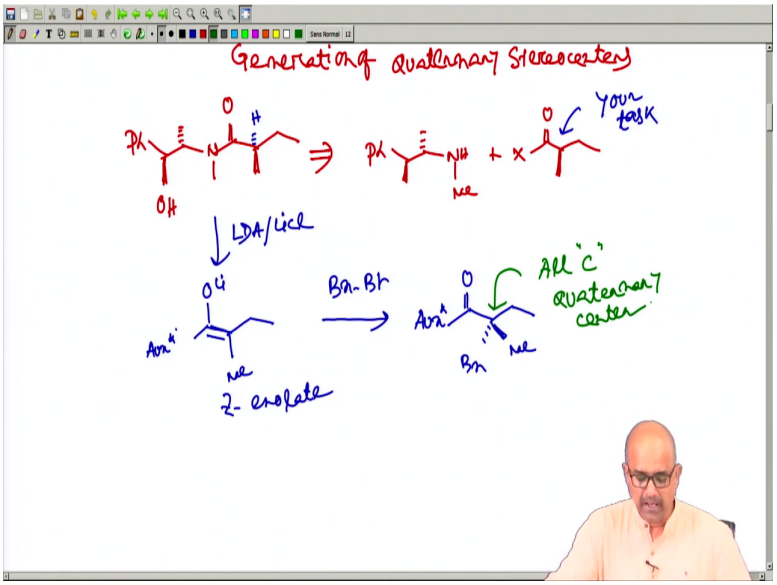

Now, in addition to this part you can also create other thing which will be now discussing and this was pretty interesting generation of quaternary stereo center.

So, quaternary stereo center means, in the carbon you do not have any hydrogen attached to it. So, let me explore that how Myer's ephedrine based auxiliary you can use for creating such all carbon or other quaternary stereo center mainly we are talking about all carbon. So, the parent auxiliary which seems to be quite familiar now you take this N methyl and you try to get something like this.

Now, initially you are starting with a chiral auxiliary ok. Now this chiral auxiliary probably you have to now create how you can create this? Means, first you take this thing your NH Me ok and this pre-existing chiral center you can just do it the reaction. Now, this stereo center how you can create that is your task. So, you can basically create by n number of method which we have already discussed even you can use the Myer's ephedrine based auxiliary also now with.

So, a pre-existing stereo center was already there in the molecule fine. LDA was there standard condition lithium chloride everything is there. So, now, the moment you have this enolate we will write O Li this part we let us say we write auxiliary the chiral auxiliary the stereo center which is there will be destroyed because the hydrogen will be abstracted.

So, from sp3 you get a sp2. So, it's a double bond sorry a double bond and then you get this you get these. So, this seems to be the Z enolate. Z enolate was usually preferred in some cases now here if you now try to add the electrophile let us say you add a benzyl bromide. Now, addition of this benzyl bromide will be now dictated by the existing situation is the auxiliary means that entire of this enolate part.

But you can apply the rule of thumb the methyl is alpha. So, benzyl seems to be the alpha 1. So, fine auxiliary C double bond O your benzyl seems to be now here. The methyl definitely has to be above if benzyl is below and you are now having this one. Now, this compound is basically what? Starting compound the methyl is above this is methylene above.

So, in principle it's kind of a self regeneration of stereo center, but this is we are not going to talk about the SRS concept here that we have already discussed. So, the point is you can now create an all carbon quaternary center. So, this is called an all carbon because there are all

carbon containing stereogenic center. So, you can call all carbon quaternary center all carbon quat center.

So, this all carbon quaternary stereo center seems to be a challenging task for most of the synthetic organic chemist I mean in this case now you can try to apply other systems which also does work in the similar way and different kind of electrophiles you can eventually try. So, and there are other second or other higher auxiliaries also have been created for this all carbon quaternary center generation.

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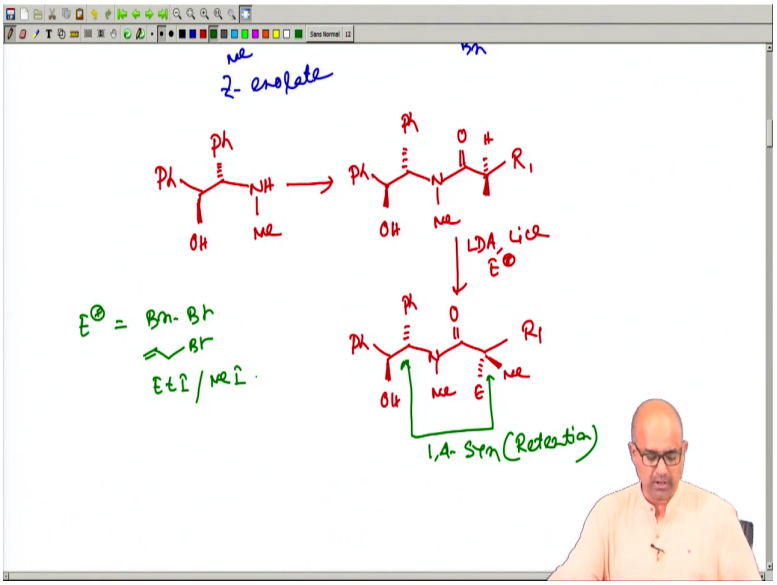

So, one such auxiliary was where instead of the methyl you put another phenyl. So, this is basically an auxiliary which you have to be think about. So, this auxiliary everything remains same now you react this auxiliary as in the case of earlier one, the only difference is you have a phenyl now instead of a methyl group. So, you have this NMe the existing stereo center on the similar way you can eventually write.

We can just write down a R1 here. Now this is the stereo center we are talking about fine. So, now, your LDA lithium chloride and then basically what you need to have? Your electrophile. So, electrophile means, if you trying to use an all carbon quaternary stereo center you will be now what we will be getting Ph OH and as we said the one four syn stereochemistry will be there.

So, as it is a phenyl. So, CO this will be R1 electrophile will be now below and this group is now methyl will be above. So, what we are trying to say now? This that retention of stereo center or this is one four syn. So, we can say 1, 4 syn and if you see the methyl in the parent compound is above. So, also retention of stereochemistry retention. Now this is very interesting way you can do it and what are the electrophiles you can choose?

The electrophile usually a large number of electrophile have been chosen benzyl bromide you can use. So, benzyl you can introduced you can use allyl bromide which seems to be pretty good other primary halite like ethyl iodide methyl iodide you can definitely use. So, a large number of quaternary compound all carbon quaternary stereo center.

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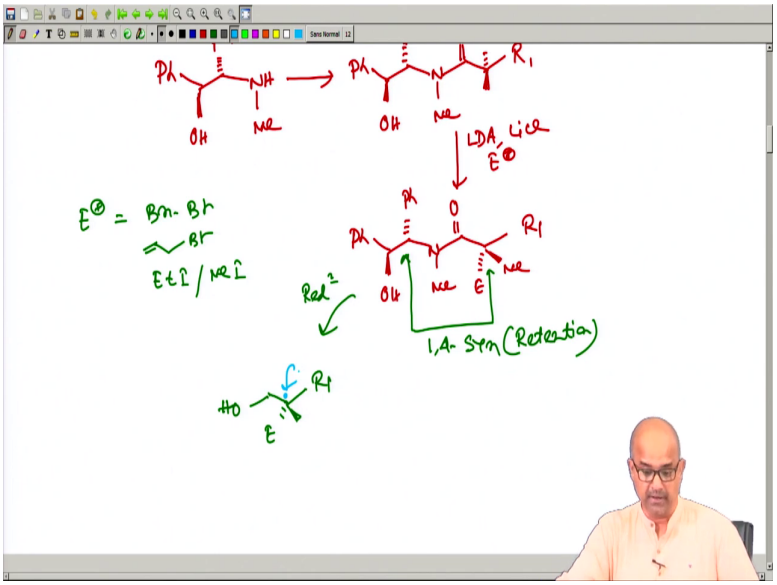

And then you can basically cleave the auxiliaries by different way most preferably if you do a reductive mode of cleavage what will you get? You get this is the electrophile which you can write different electrophile and you get a primary alcohol here. So, see this stereo center are usually fixed ok and this is all carbon quaternary stereo center now such a reaction seems to be pretty interesting.

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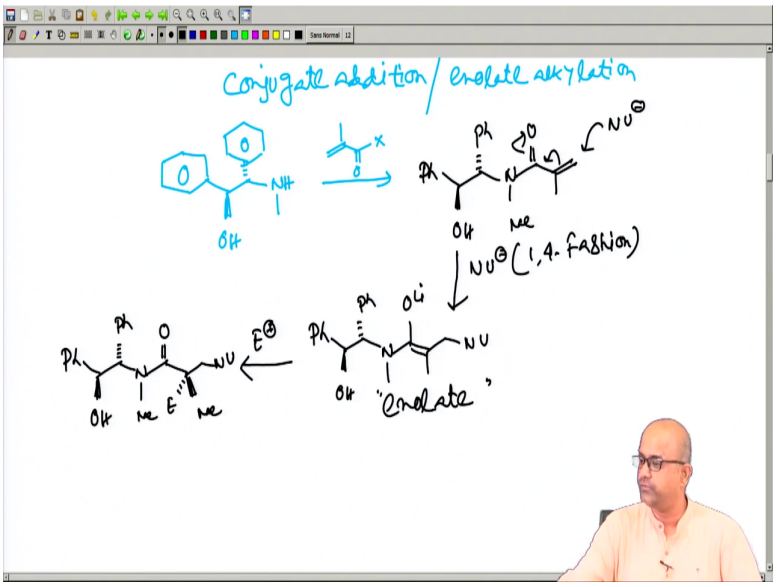

Now, from this we will now next switch over to another concept a conjugate addition followed by subsequent alkylation.

Now, this was again an extension of this Myer's ephedrine based auxiliary based alkylation and here the initial auxiliary seems to be the same auxiliary which earlier also we have used you can choose either a phenyl either a methyl, but a phenyl was usually chosen and then this N methyl this ok. Now as I said conjugate addition means you actually initially you need to react with some alpha beta unsaturated acid derivative.

So, fine now here let me try to write a different colour pen this is the OH, this is the phenyl your nitrogen will now react to give you the corresponding acyl derivative. So, now, you can get this one. Now in this case there will be definitely no enolate abstraction is possible because there is no alpha hydrogen there is no gamma hydrogen also.

So, only thing what could be possible here what people try to explore it first let us say react with a nucleophile the nucleophile will definitely attack in a Michael fashion or 1, 4 fashion. So, if it attacks in a 1, 4 fashion and you are not generating any stereo center here what could be the initial product that is a pretty interesting product. So, what is happening?

The moment the nucleophile is attacking here the normal cases it basically gives you an enolate. The moment you are getting an enolate that is basically opening a further round of alkylation. So, you get first this one. So, this seems to be pretty interesting enolate ok now

this enolate just now we have actually generated in the case of all carbon quaternary stereo center.

Now, with this information in the hand now what we next do will be simply treating some electrophile. So, because this is now the enolate. So, the enolate generation was done through a different way. Now, this enolate everything will be as expected your hydroxy group will now lithiate it and the solvent supra molecular aggregation will be governing the stereo center and you have this similar working model the device or the mnemonic device we set.

So, now you can say this is the electrophile, electrophile will be the 1, 4 syn the methyl will be above and you have the CH2 Nu. So, this also gives you an all carbon quaternary stereo center fine.

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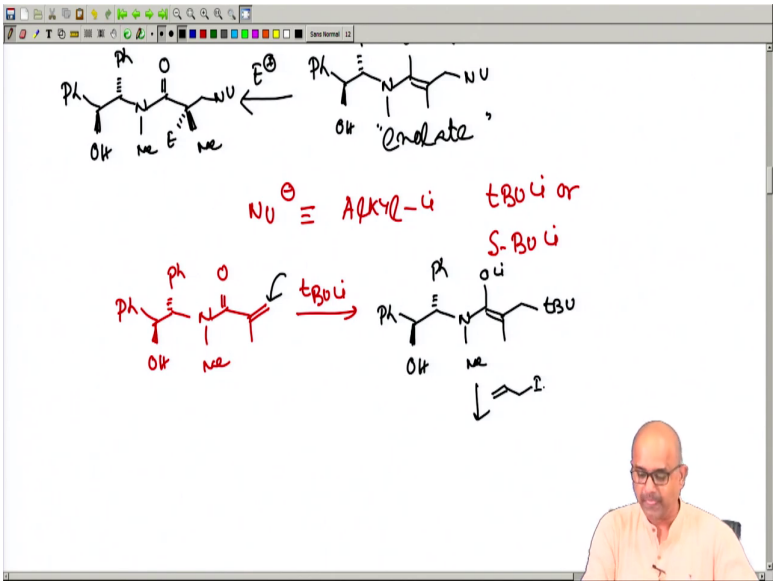

Now, what could be the nucleophile nature? This nucleophile seems to be a very interesting nucleophile most of the cases the nucleophile seems to be an alkyl lithium…….. an alkyl lithium was preferred.

And you will not believe bulky nucleophile like tertiary butyl lithium was even good reactive secondary butyl lithium sec butyl lithium those are also eventually reactive. So, now, let take a simple example of such system or you can find that let us say Ph, you have a OH, you have a phenyl you have a N methyl you have a C double bond O. So, methyl that the initial system ok.

So, now with this compound you first add tart butyl lithium as a nucleophile. So, tart butyl now seems to be attacking at the 1,4 position. So, what we are going to get? You are expected to arrive OH, this Ph this N methyl O lithium this CH2 tertiary butyl. Now, this enolate if you are now reacting with the electrophile let us say react with a very highly reactive allyl iodide or allyl bromide.

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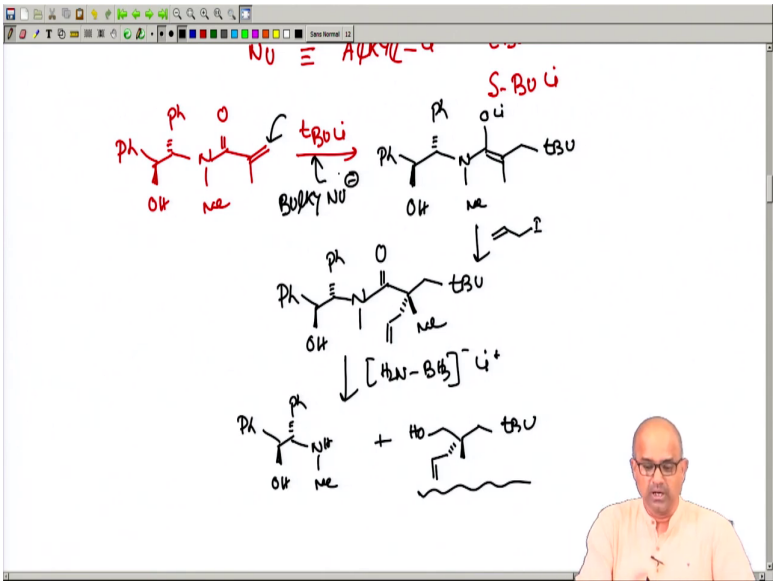

So, what is going to happen? This enolate will then react and you are going to have this PhOH……. a Ph N methyl and C double bond O and then this allyl will be below as the phenyl is below according to a rule of thumb methyl is above and you have a CH tertiary butyl. So, now, see all carbon coordinate stereo center you can create and then if you want to do a reductive cleavage by simple amine borane complexes amine borane complex you can eventually use it.

And you can get compound which sorry ok fine you can you find you can write it down you get the auxiliary back and you get the methyl is here CH2 tertiary butyl a CH2 OH and your allyl and I am telling you such compounds are not easy to make such compounds are usually not easy to make with the and it's a pretty good way of making a enantiomerically pure compound.

So, you can eventually create this and particularly the interesting point is a bulky organolithium…….. a bulky organolithium was used as a nucleophile. So, usually tert

butyl lithium we never used as a nucleophile. So, a bulky nucleophile can be eventually reacted and such reaction seems to be quite interesting.

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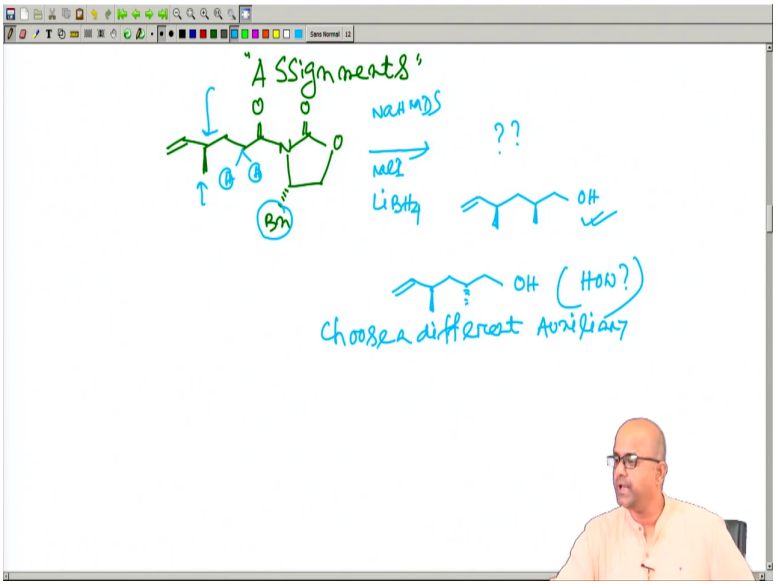

Now, in terms of such thing probably we can now talk about few assignments maybe those assignments are based on a different concept or different auxiliaries we just try to see that whether you are familiar with all those auxiliaries ok. Let us start with the again little bit refreshing the memories start with very simple old auxiliaries which all of us are familiar and if I now try to write the structure you can easily say that this is the Evans auxiliary.

Now, the main idea was whatever auxiliary we are discussing in the class basically you can choose any of the auxiliaries to get your desired transformation or desired target but the concept was you should be quite clear in your concept.

So, one such auxiliary was given to you. Now, this auxiliary already having a pre existing stereo center in the carbonyl compound and this part is the auxiliary part ok. The idea was just now in the Myer's ephedrine auxiliary we have already seen that this one N system we can do it now this is a methyl which is pre existing.

Now, if you abstract the hydrogen from this enolate and you react with an electrophile you can find that the incoming electrophile now gives you a 1, 3 syn or anti. Now this benzyl is below ok. So, definitely let me write the reaction now. So, I am trying to give you a

NaHMDS ok. As a base methyl added as the electrophile and then I am trying to give you reductive cleavage with lithium borohydride.

So, you can eventually find that what could be the product and I can just tell you the product will be very simple product will be basically 1 ,3 syn this product ok. Now if I wanted to get this product just the opposite stereo center the other diastereomer how we can get it? Means then we have to choose a different auxiliary. So, you can just write choose a different auxiliary with different steric parameter.

So, these things you should be quite familiar and just by choosing your proper auxiliary you can actually control the thing.

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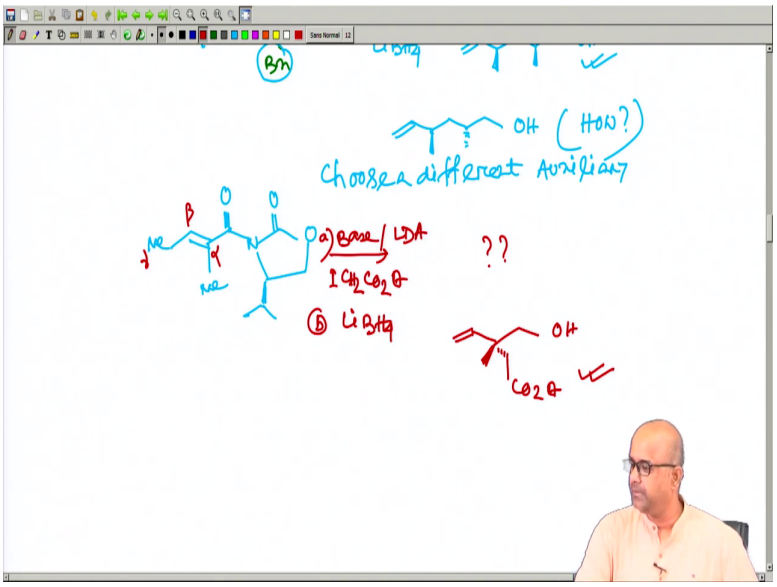

Now, few minutes ago we talked about a gamma alkylation. Now, gamma alkylation is not limited only to the Myer's auxiliary based method you can also it can also be possible for other auxiliary based methods also. So, let me try to give you an example for a gamma alkylation based thing.

Now, we can see that here alpha alkylation is not possible because this is the alpha carbon this is the beta, this is the gamma. So, definitely whatever has to be done it has to be the gamma way. If you now try to treat with a base you can eventually find that. So, I can just write the base and then I will give you an electrophile a I CH2 CO2 Et. So, this could be electrophile ok.

So, number 1 is base what base you choose? A base LDA then you get this and then I will give you a reductive cleavage condition lithium borohydride. So, you need to predict the product this assignment is basically quite interesting and actually what product you will get? I can definitely write it. So, this part is the abstraction of the hydrogen initially you get the vinyl part, a methyl is already there ok the methyl is already there.

So, you can write the methyl and here is your CH2 OH now this group is above. So, definitely this CH CO2 Et will be this way ok and if this is this way then methyl has to be above. So, this compound you will finally, get, but the mode of asymmetric induction you need to basically explain and you need to do it I think you can easily do it by normal way.

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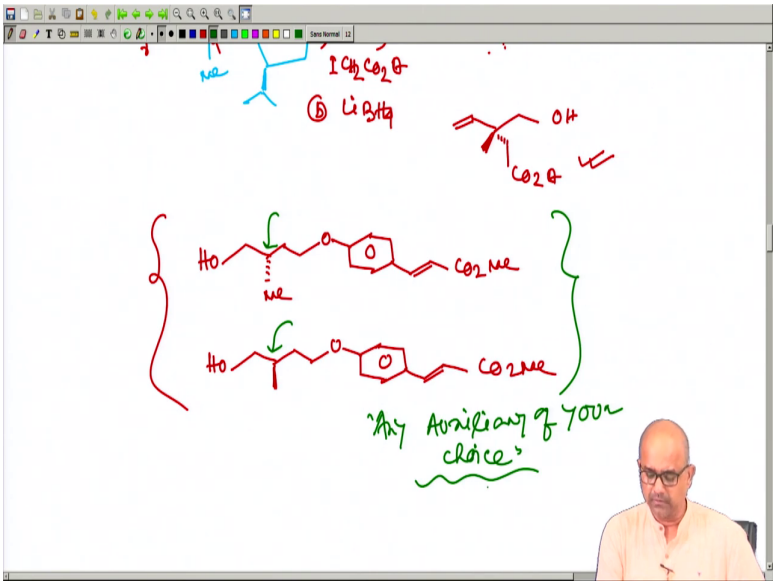

I will just try to stop in one particular point let me try to give you one two I mean two simple assignments, but this assignment I am not going to do it for you please try to do it and you can eventually use any auxiliaries of your choice any auxiliary of your choice do not worry about the other functional group which was present in the molecule those are may not be very much useful these are just given for you to give you the correct or to help you to draw the correct structure.

So, two of the enantiomer of the target molecule you have to actually synthesize. Now, in both the compound you have seen that the only difference is the stereo center here ok. So, you can eventually try to use any auxiliaries of your choice any auxiliary of your choice any

auxiliary of your choice and that you can eventually try to do it. So, please try to solve this assignment we will see you in subsequent classes.

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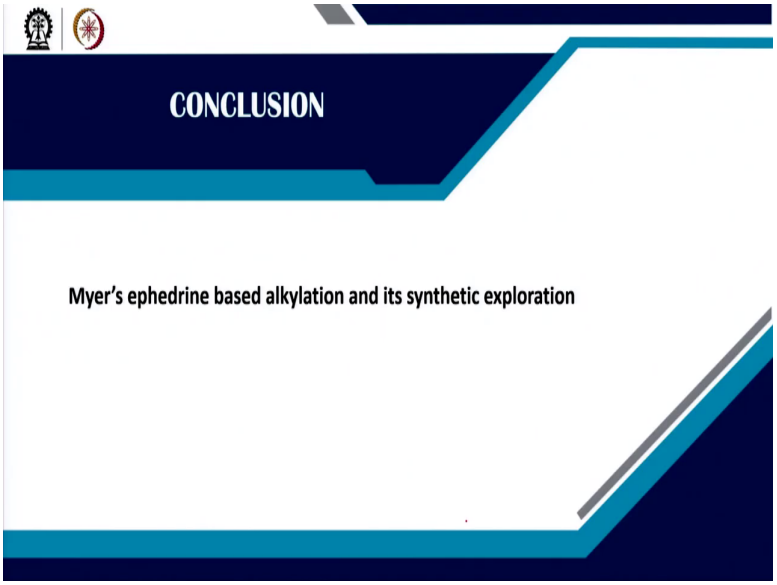

So, as a concluding remark you can say that Myer's ephedrine seems to be quite efficient and very good auxiliaries in terms of newly generated stereo center it gives very high asymmetric induction and such auxiliaries have found wide application in the field of synthetic organic chemistry as is evident that from couple of applications in the industry also so…….

Thank you and see you all in subsequent classes.