Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3-sp3) bonds in asymmetric fashion

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Module - 04
Enolate alkylation of several carbonyl species
Lecture - 20
Chiral Weinreb amide equivalents and related systems

Welcome back everyone. So, in this module 4, lecture 20 we will be mainly discussing this Chiral Weinreb amide based Enolate alkylation and related systems.

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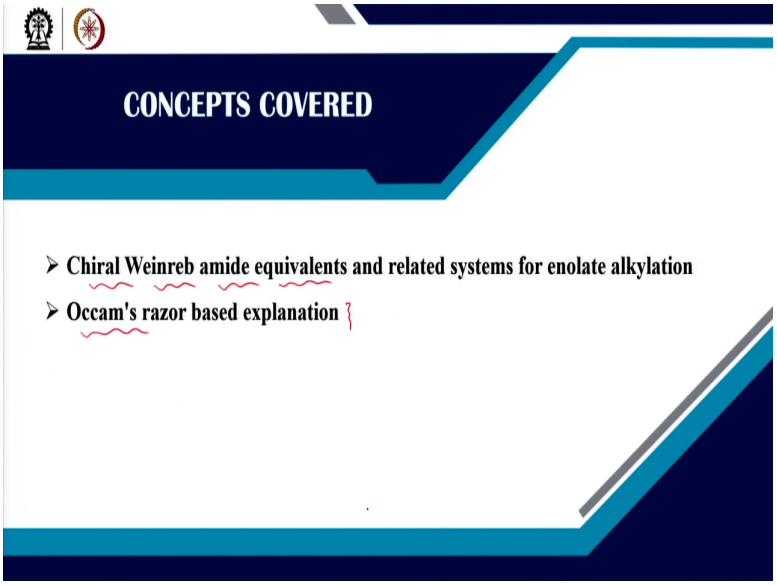

The main content which we will be going to cover in this thing a Chiral Weinreb amide are very useful system and particularly there are few examples where, such amide based equivalents can also be useful for enolate alkylation I will try to give you an explanation, which is a little bit of in a different perspective, which is named as Occam 's razor based explanation.

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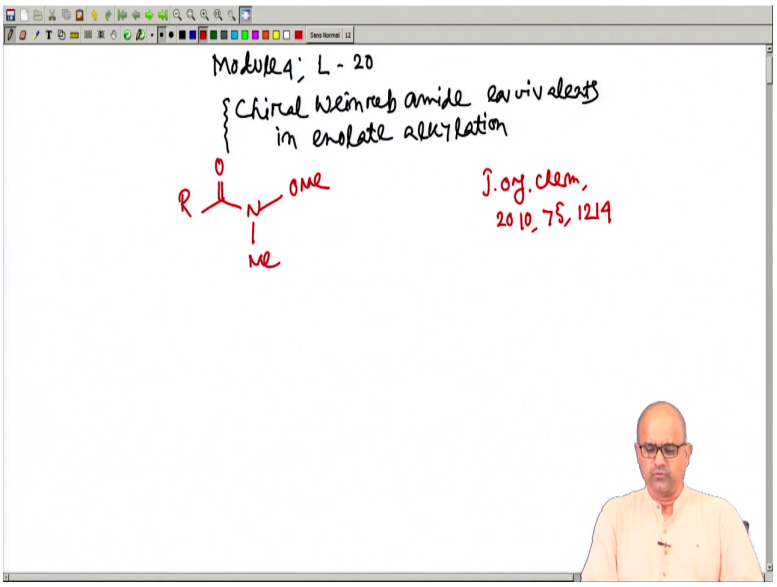

In this module we will be talking about chiral Weinreb amide equivalents in enolate alkylation. Now, Weinreb amide probably all of you are familiar Weinreb amides are a unique amide system where the N group is linked to a O methoxy as well as this methyl.

Now, Professor Davis was the first a pioneer for this chiral Weinreb amide equivalent in its enolate alkylation and whose work was published in Journal of Organic Chemistry in 2010 and we will be mainly discussing its main feature and how such systems are very useful for enolate alkylation.

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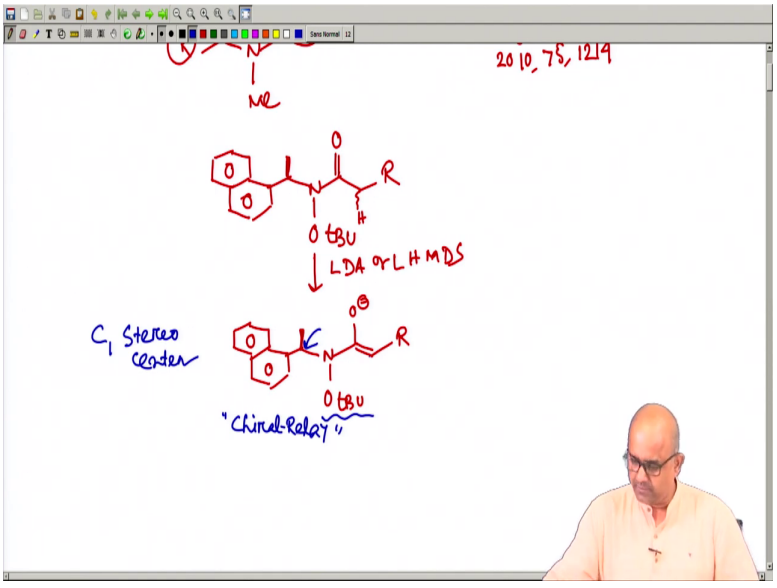

So, let us talk about a simple system in the very beginning; the structural part of such amide was initially we will discuss and particularly this R part here we can have a chiral group as you can see here it is a beta methyl group. Now, this N now having a O tertiary butyl normally Weinreb amide you have a O methyl, but here we will be using a O tertiary butyl and then this was linked with a corresponding carbonyl precursor where you want to generate the enolate.

Now, as evident if you now try to abstract the hydrogen and you generate the enolate by a suitable base let us say LDA or a similar kind of basis like LHMDS you first generate the enolate. So, let me first draw the structure of the enolate, which will be having those functional groups like a naphthyl group was there and then you have this methyl fine, then you have N O tert butyl and you have this O minus and you generate the corresponding enolate.

Now, in this case actually the important point is the stereo centre at C1. So, we can write that C1 stereo centre, which mainly dictates the position of this O tertiary butyl group in the Weinreb amide. Now, this kind of system was later on shown to exhibit a chiral relay system. Now what do we mean by chiral relay, relay means the information of the chirality at this point, which is relayed over here and this particular stereo centre actually governing that how this o tertiary butyl group orients around the enolate plane.

Now, we will try to draw the enolate in a different way in the sense that let me give you a overview.

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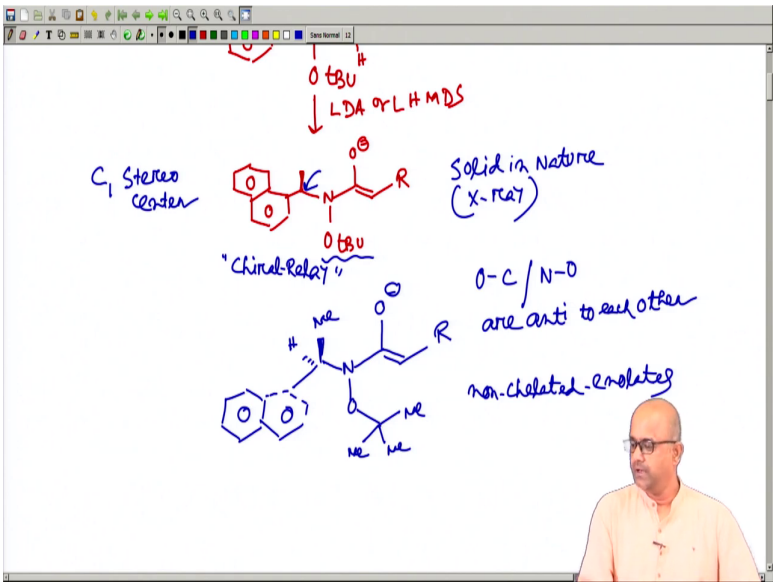

So, first you have this N fine then you have this O you have this tertiary butyl I will write 3 methyl. You need to understand little bit what exactly is happening here you have this N this methyl is above definitely, which is already you are I mean we have taken the thing the hydrogen seems to be below and the naphthyl group actually occupies in the plane in its bit difficult to draw the 3D structure in a 2 dimensional way, but it is basically hanging over in this way.

And now your nitrogen is here and then you have this CO minus of the enolate or C double bond O then this. There are few usual assumptions which actually came from the 3 dimensional structure of these compounds which have been confirmed through the X-ray structure because most of the chiral Weinreb amide are actually solid in nature these compounds are solid in nature.

And as they are solid in nature you can get an X-ray single structure and this X-ray single structure usually you will find that this oxygen C means the enolate. So, oxygen C so, this particular bond O C and the N O. So, O C and the N O are actually anti to each other. So, this is one of the assumption, which actually coming from the crystal structure of those molecule.

Now, this actually the most important assumption here; now this naphthyl group seems to be little bit far apart from this tert butyl group ok. And that is what so, the and the ground state the methyl is above the plane of the enolate and that basically forces the tert butyl group is pointing towards the enolate.

And normally in most of the cases normally these enolates are non-chelated because you do not have a chelation controlling group this is a non-chelated enolates and as this tertiary butyl group seems to be seems to be actually block the top face of the enolate. So, enolate alkylation was usually preferred to be the opposite of this O tertiary butyl.

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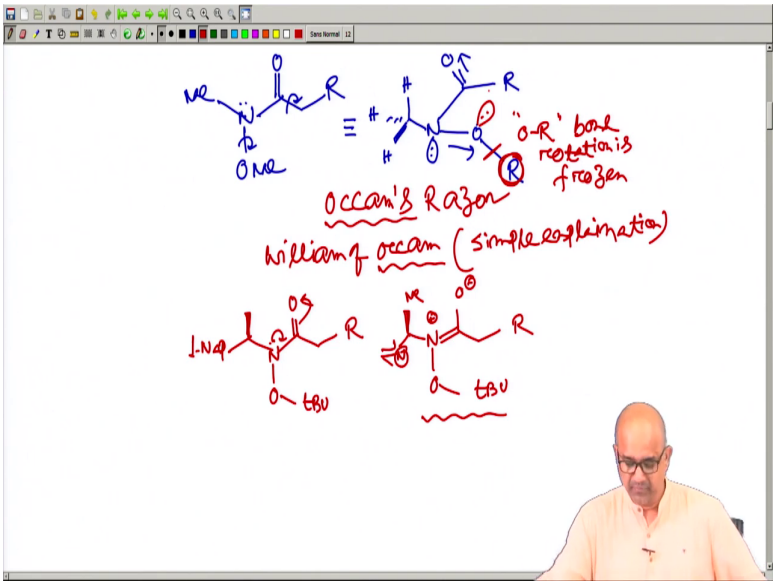

Now, this again we can seem to explain through a few further drawing because this is simplification of drawing. So, let me again try to draw it. So, we are talking about simple Weinreb amide which looks like something CO CH2R ok. Now, let me now try to analyse different conformational features of this thing this C-C bond rotation is free and this N O bond rotation is definitely free.

Now this NCO bond you can have the rotation, but if you allow the amide resonances this bond rotation might not be feasible. So, here we will try to put nitrogen at the very beginning and then the nitrogen lone pair we will try to put in this way ok. And this O we put a R group here it could be methyl it could be tert butyl ok and then you have a sp3 system.

So, here you are having basically three group here you have taken a methyl. So, there will be a simple three group we will just write it ok. Now this O will be so, nitrogen and in this case now your C O is there C O and R now as our initial explanation we said that this dipole seems to be in this way and this N O dipole seems to be this way. So, this would be anti to each other. So, that was a one of the assumption.

So, initially this assumption was usually we called it as an Occam's razor concept. Now this Occam's razor concept was first was a very simple explanation……. Occam actually a philosopher whose full name is William of Occam ok now, this William of Occam actually this Occam is not a chemist who is actually a philosopher.

Now according to this concept I say that if you have a too many competing hypothesis means there might be many other hypotheses you just try to take the simple explanation which seems to explain the whole thing in a best possible way. So, there might be many competing hypothesis you or there might be many competing working model, but you try to assume the simple explanation.

Now, in this case the simple explanation was this that your main assumption was the NCO bond and this N O bond are anti to each other, now here nitrogen is having a lone pair even oxygen is having also a lone pair. So, this will be again anti to each other and then in this way this O-R this tertiary butyl seems to be kind of frozen in this direction. So, this O-R bond rotation is not allowed O-R bond rotation is frozen I mean the way we have to do it. So, these are the simple assumption.

Now, the alkylation seems to eventually take part from the opposite to the lone pair as well as the tertiary butyl group. Now tertiary butyl group is usually in this way it can only come if this dipole is oppositely aligned. So, this was the eventually the explanation and now there could be some other features which we will now try to put it now, in the original system you have a one naphthyl group ok. Then you have a methyl then you have a N you have a O tert butyl you have a CO CH2 R.

Now, if you now assume a simple amide resonance this amide resonance can give you a typical strain system in the sense that you get this O minus C H2 R it will be plus O tert butyl and here you have a methyl here you have a naphthyl group here. Now this kind of system you might be also expecting an allylic strain, but we are not considering allylic strain, and actually usually this kind of strain is definitely will give you the tert butyl group away through this naphthyl ring ok.

So, this was again some kind of estimation or approximation, but mostly the approximation which will try to allow it here the dipole dipole orientation the C double bond 2 and this N O bond are anti to each other ok.

Now, this N double bond and O double bond these are again the lone pair which also due to the electronic repulsion will give you anti orientation. So, now, if this has to be the frozen way that lone pair and R group are now seem to each other and this R group the tertiary butyl group seems to be the now the deciding factor once you generate the enolate from this kind of Weinreb amide.

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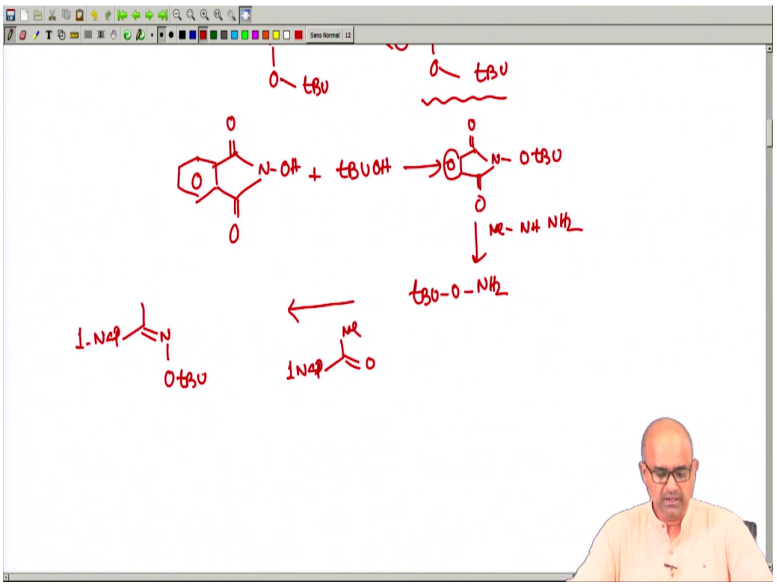

Now, definitely the initial question is how you can make those Weinreb amide? So, this when I mean this kind of chiral Weinreb amide one of the very simple literature procedure was you start with N hydroxy thalimide, which is commercially available.

So, first this compound was reacted with tert butyl tert butanol all and you get the corresponding N O tert butanol ok the aromatic part remains here fine. So, once you get this the synthetic procedure was you actually react with methyl hydrogen and methyl hydrogen actually clips this part and actually which was a very well known reaction you get tert butyl O NH2.

So, tert butyl oxy amine you actually get now, this tert butyl oxy amine was then condensed with a 1 naphthyl methyl C O. So, this C O and this NH2 will now then react. So, basically what we will get you get 1 naphthyl here 1 methyl double bond N a simple amine actually you get, fine.

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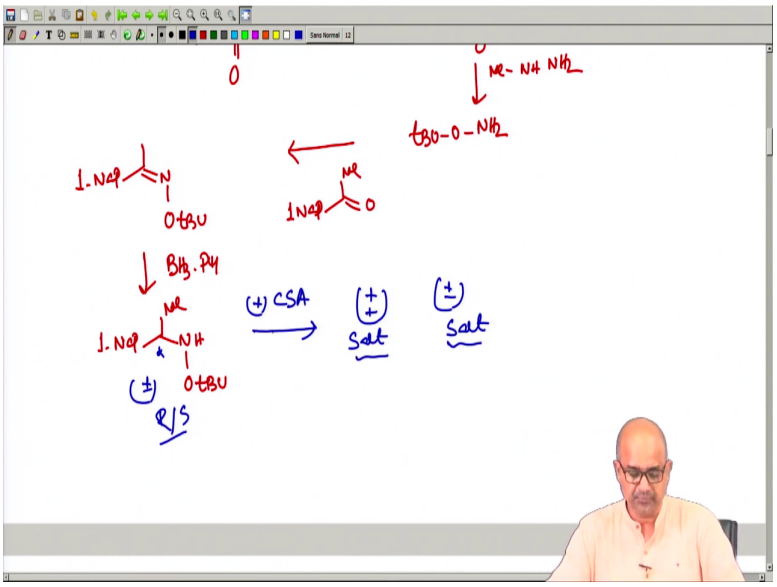

Now, this amine which is simply reduced by a borane pyridine complexes was used even you can reduce this amine with sodium cyanoborohydride. So, you get 1 naphthyl you get methyl and you get corresponding secondary amine, which is kind of a Weinreb amide. Now in this reduction process what you created you created a stereo genic centre.

So, now, this stereogenic centre you have to resolve because this is a racemic compound and actually this was resolved by treating this compound with a camphor sulfonic acid, camphor sulfonic acid a chiral sulfonic acid and if this compound is having R and S camphor sulfonic acid is an only one isomer.

So, you get actually a plus-plus diastereomeric salt and you get a plus-minus diastereomeric salt. So, this salt has been separated as both the compounds you can crystallize it. The moment you actually do the crystallization after that you separate them out and you take any of this compound and now these compounds will be your chiral Weinreb amide.

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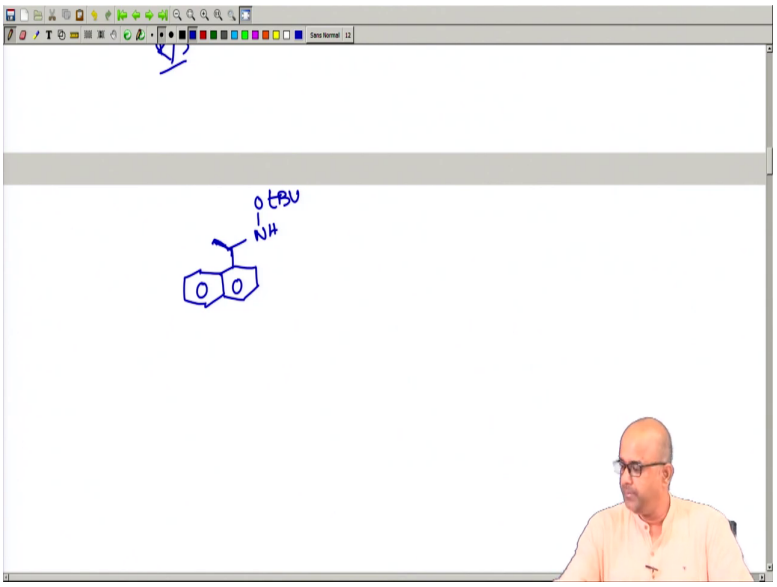

So, structure is now this methyl you can now fix the stereo centre depending on your choice. So, NH O tertiary butyl. So, this will be your starting compound, which you have to prepare initially or we have prepared.

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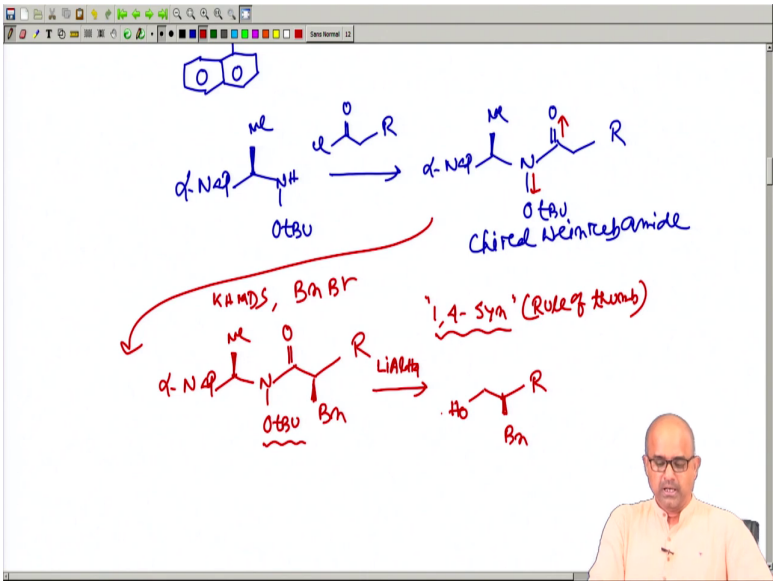

Now, we will write the reaction sequences how it goes. So, alpha naphthyl or 1 naphthyl is here ok and if you follow the references reference which was the shown to you earlier the JOC paper by Professor Davies you can find the literature report how this compound is prepared.

Now, is N O tertiary butyl ok NH now this is your contact point now basically you have to react with a acid chloride. So, simple or acid simple condensation so, that basically give you alpha naphthyl your methyl your N O tertiary butyl C OCH2R now this is your chiral Weinreb amide equivalent.

Now you can see now you can assume the or you can apply the Occam's razor concept the minimalistic approach means this CO bond and this N O bond this dihedral angle should be 180 degree and then this O tertiary butyl should be oriented through this way. So, that the enolate top phase is blocked ok.

Now, taking this Weinreb amide you can now try to do the reaction. So, taking this Weinreb amide the base now next is treating with simple base KHMDS could be the base you can use it. So, KHMDS and the electrophile you can choose any electrophile let us say you react with a benzyl bromide the moment you do the benzyl bromide reaction your alpha naphthyl is this and then you have your methyl which is the pre-existing stereo centre your N O tertiary butyl your C double bond O CH2 R.

Now, if the enolate is blocked by the O tertiary butyl group, which seems to be the blocking the alpha face you definitely have the benzyl group in this fashion ok. And here also you can apply the typical rule of thumb the ……..rule of thumb is this 1 2 3 4 is syn remember the similar kind of thing we also got it in the Myers's ephedrine based auxiliary.

So, 1, 4-syn means the methyl and benzyl. So, this rule of thumb you can apply if you do not want to remember exactly what is happening this rule of thumb probably very useful for the exam purpose. Now, you can simply do the cleavage like reductive cleavage or other cleavages, which you can do it here lithium aluminium hydride was chosen and you can actually cleave the amide to corresponding aldehyde or alcohol or other things. So, let me try to write that you get this benzyl you get this R and you get a C H2 OH.

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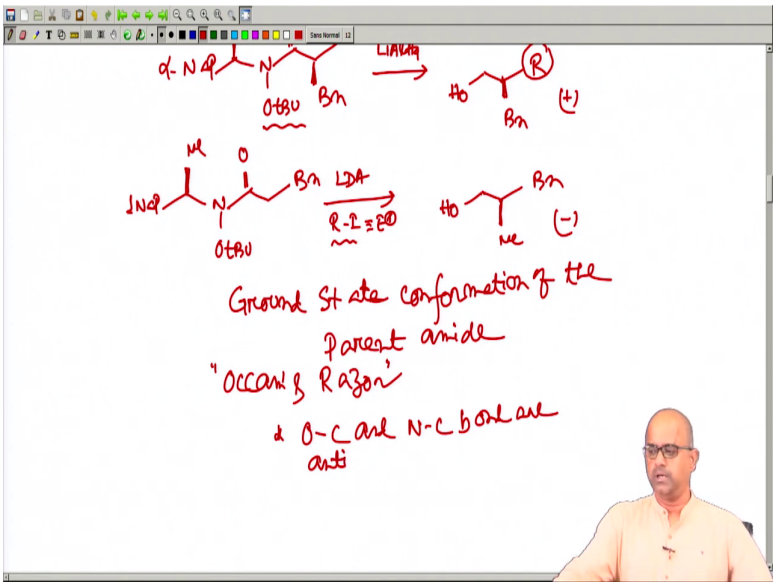

Now, by choosing proper amide you can actually do the similar kind of reaction let us say you want to get the other enantiomer. So, if you want to get the other enantiomer of this compound what Weinreb amide you choose similarly 1 naphthyl is everything is fine your N O tertiary butyl. Now, you can choose a different thing you can initially take the benzyl compound in the auxiliary means you take the corresponding benzyl C H2 COC Li ok.

So, this is your thing and now you do the similar kind of exercises LDA or LHMDS. Now, you add your electrophiles as a RI. So, this R is already there in the initial acid now this R second case these R acting as electrophiles. So, everything remains similar the rule of thumb is 1, 4-syn. So, now, you can find the methyl is here the benzyl is here and you get C H 2 O H. So, this way actually you can get.

So, if this is a plus enantiomer this will be the minus enantiomer you can just do the absolute configuration and you get the two enantiomer product. So, this way is very helpful this chiral Weinreb amide. So, normally we will be not discussing much of this chiral Weinreb amide here the main thing is you actually have to consider or the assumption is sorry the ground state conformation of the parent amide. This was the most important part ground state ground state conformation of the parent amide.

So, that was you have to assume at the very beginning and what was the assumption you can now recall the Occam's razors concept which is the minimalistic approach the only

assumption was basically the O-C and N-C bond or anti peripheral or anti to each other. And if you assume this assumption the rest of the part will fall into normal picture ok.

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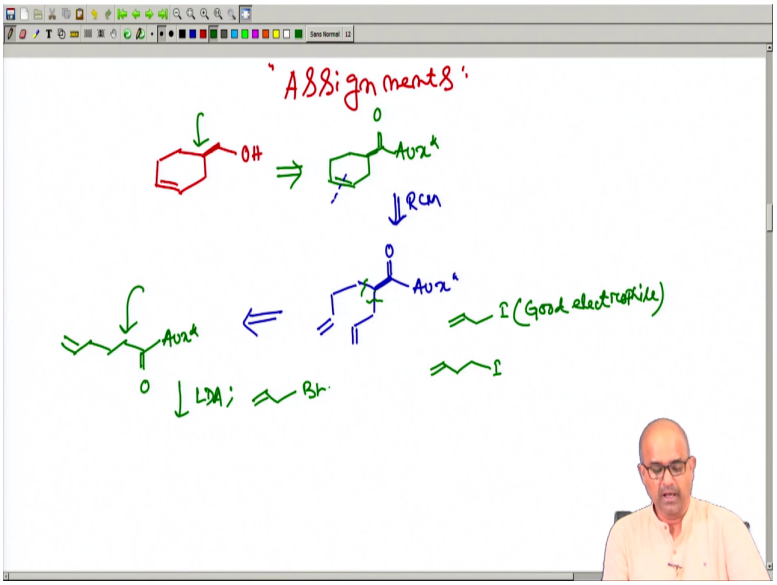

Now, to discuss something else probably we will now again go back to few assignments. So, I always believe that more assignments you do your concept will be much more clear and you can eventually try to approach or try to explore some new assignments, which will be pretty much helpful for your exam purpose.

So, the first assignments you can eventually use any of the auxiliaries till now which we have discussed. Now such a compound probably initially you said ok what you are talking about definitely a cyclic compound was given as a target molecule and this stereo centre has to be fixed by assuming, by exploring any of the auxiliaries let us do a simple retro, which says that if you try to have this kind of auxiliary means the auxiliary was here you can do a reductive cleavage.

Now, this stereo centre you need to be taken care ok, now in this part probably you can think about by making this ring through a ring closing metathesis reaction which seems to be quite good. So, what we now trying to do we will keep the auxiliary like this you can take any auxiliary and we will now try to put this as this kind of bond because we have to make a six-member ring. So, you properly carbon is number of carbon now you can see these bonds can be easily connected through a RCM reaction.

Now, where from you get this auxiliary this was you can eventually choose any of this point you can connect you can disconnect either this part or this part. If you connect this part, you will be having an allyl bromide as an electrophile if you connected this part as a homo allylic iodide. So, you can choose this way either this as the electrophile or this as an electrophile now, definitely allyl iodide is a very good electrophile. So, probably this route can be chosen, because allyl iodides are much more reactive than corresponding homo allyl iodide.

So, now you can simply take let us say you take any of the auxiliaries and we can just straightly straight forward go back or to write. So, you can have this. So, you have a CH 2 CH2 C H2 there will be 3 carbon C 2…. C 2 C H 2 ok and now you here will be your 1 2 3, here will be your typical carbonyl and then you can put the auxiliary at your choice here. Now this auxiliary you can use either your Evans or Opplozer or your Myer's ephedrine

Now, only this part you are now trying to use the base. So, this will be your base LDA and you can use the allyl bromide or allyl iodide as the electrophile.

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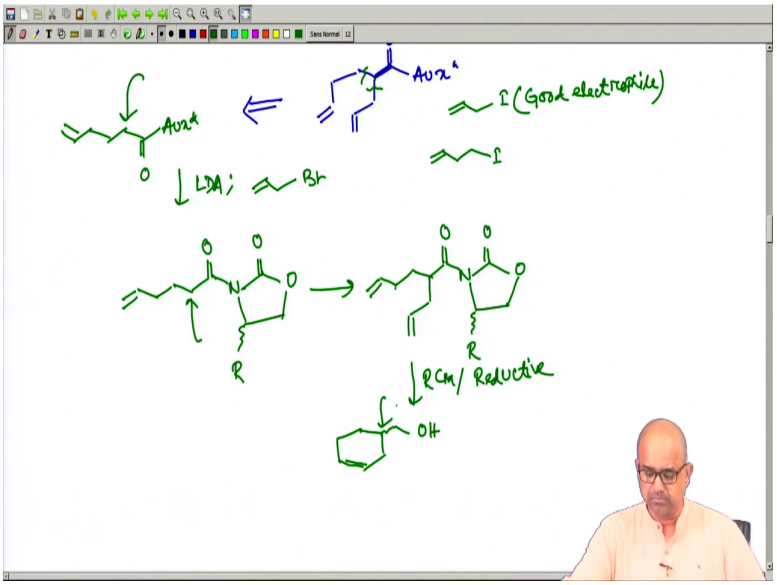

Now, we can eventually try to complete the synthesis now let me try to just draw a simple Evans auxiliary based method for you now, this choice of this group you can actually choose it because what stereo chemistry you require that you can fix it. So, you can try to put it 1 2 3 yes. So, this will be the correct precursor at the very beginning and next your electrophile will be coming here and once you do the alkylation with the allyl iodide your stereochemistry I

did not mention here because you have to draw a little bit in a proper way. So, now, you are having this allyl thing.

Now, see. So, 1 2 3 4 5 6 you can do the RCM reaction you can do the RCM reaction and then you can do the reductive cleavage, this is a very simple example of making a molecule like this, where you can think about using a simple auxiliary based approach and then you can close the ring. So, this kind of intermediate is very useful for the different application.

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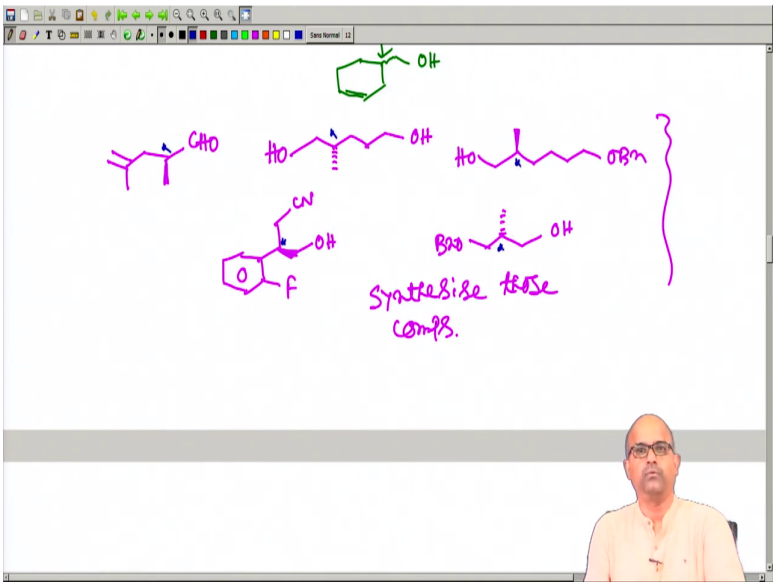

Let me quickly give you some more assignments which you might be find useful for your subsequent problem solving approach. So, this is one of the compound I just write a couple of compound which probably you can you need to explore it when you have a time. So, please try to give some time and most of the cases these compounds contain a single stereo genic centre. So, you can eventually try to choose which auxiliary you will be using and then you need to use what electrophile and I guess this will be quite simple.

Let me write few more thing and I am sure that you will be enjoying doing those assignments because these are simple some of the assignments might be already taught you in the earlier classes, but still if you want to give it as a try you just try it. And now as we have talked about many auxiliaries you can eventually try to use all the auxiliaries possible to solve this particular problem.

So, we can see that we can give the problem as a synthesize those compound synthesize those compounds so; obviously, you have to take care of the proper stereo centre because most of all the compounds have a single stereo centre and. So, enantiomerically pure you have to make those compound.

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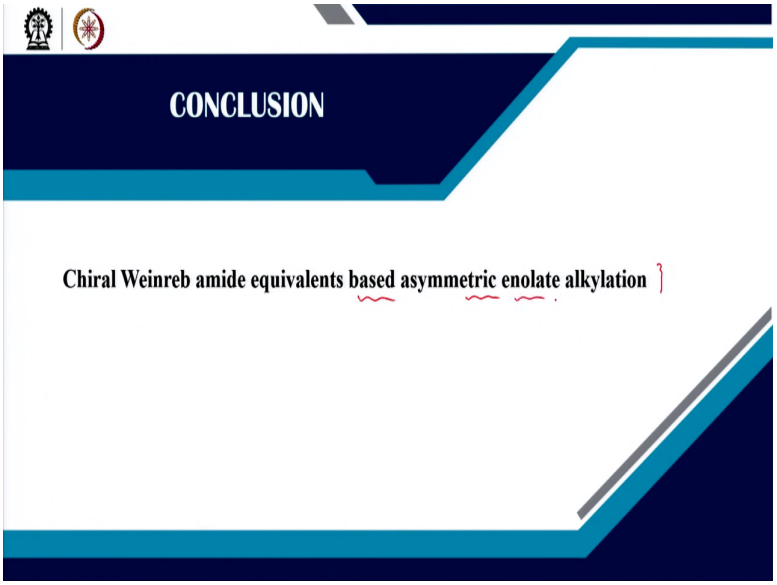

So, as a conclusion after this lecture you can see that chiral Weinreb amide and its corresponding equivalents, which are very useful for asymmetric enolate alkylation and that could give you a very useful chiral intermediates after the enolate alkylation was performed. So, in the subsequent section we will discuss other things.

Thank you and have a good time.