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 - 07
Aza-Enolate alkylation
Lecture - 32
Ender's RAMP/SAMP, Coltart's cyclic carbamate hydrazone, Ellman's sulfinamide and related systems

Welcome back everyone. We are going to start a new module today which should be module 7 and particularly this module we will be talking about Aza-Enolate alkylation.

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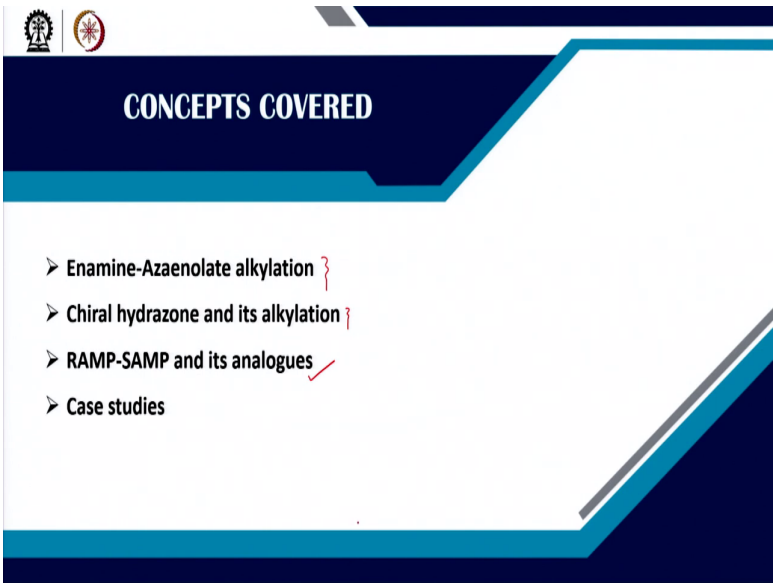

The main content will be different kind of enamine and azaenolate based alkylation and then we will talk about specific system based on in enamine which we talked as chiral hydrazone and its alkylation. And under this category we have well known hydrazone based techniques named as RAMP and SAMP and its analogue we will discuss in the context of enolate alkylation. We will talk about some case studies.

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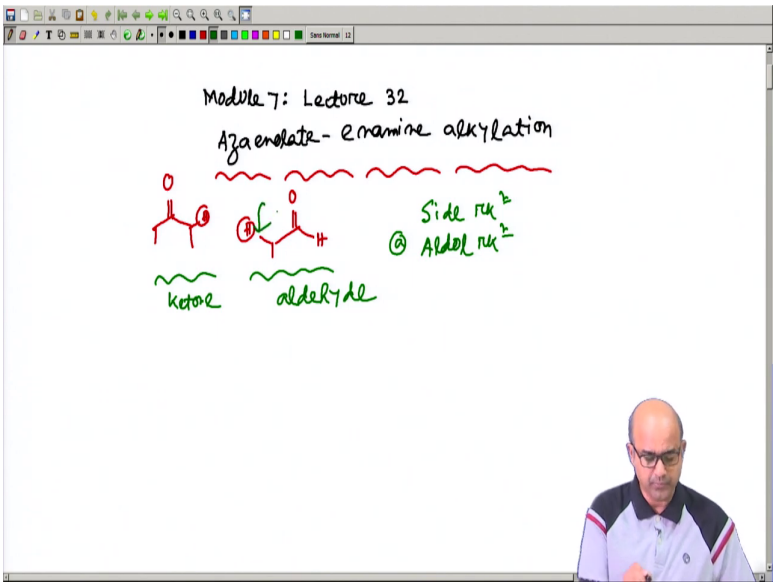

So, in this specific module we will talk about azaenolate and enamine alkylation. Now normally we have seen that if you have a carbonyl compound like ketone or if you have an aldehyde alkylation for those compound in the specific alpha position seems to be often a problematic mainly due to competing side reaction. Now what are the main side reaction for alkylation of ketones or aldehydes?

Usually such enolates are very active and mostly aldol reactions between the carbonyl compound seems to be one of the major side reactions when you are dealing with normal ketone or an aldehyde as in precursor and you are generating enolate. Aldehydes are very highly reactive as all of us know and particularly alpha alkylation of an aldehyde it is really a problematic.

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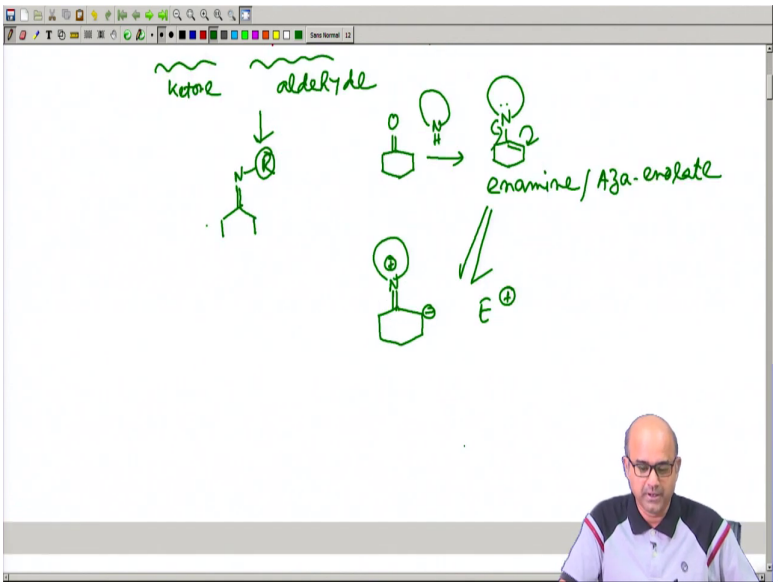

So, in those cases what was our main solution usually we convert those carbonyl compounds to corresponding imines, usually this was one of the major solution which we have to offer. You usually convert this corresponding carbonyl compound to imine or its enamine. Now early days we have talked about that this kind of stork enamine synthesis probably all of you are familiar when a cyclic ketone was converted to it is corresponding enamine which was named as enamine …… enamine.

Sometimes this kind of compounds you can also refer as azaenolate. Now this aza enolate or enamine can be easily prepared from the corresponding carbonyl compound. If you treat this carbonyl compound with a suitable secondary amine. Now this in enamine can easily be treated as a main precursor for the enamine alkylation or aza enolate alkylation.

The basic idea was similar this nitrogen lone pair is available and you always have a typical system where you can definitely do such this kind of tautomerization. So, these things are usually and then you can react with your electrophiles at this point. Now these electrophiles could be your normal alkyl halide or even other Michael acceptor also you can do a carbon-carbon bond forming reaction. Now stork enamine synthesis was one of the very old work and still it has been regarded as the one of the classic work.

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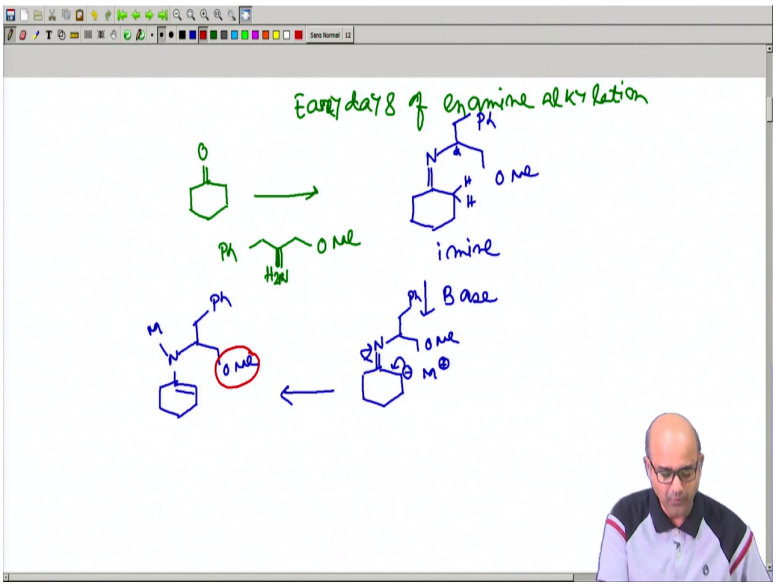

Now, early days of enamine alkylation when people used to react a cyclic carbonyl compound and then you take a cyclic carbonyl compound and then you react with an chiral amine. Now this chiral amine probably you can have derived from corresponding amino acid or other part. Now if you see this kind of chiral amine will be available to you either from commercial sources or from other sources. Now this kind of amine seems to be you can use it for making the enamine.

Now, once you make this imine first you have this CH2 OMe and here you have a group. Now this stereo center was fixed ok. Now once you make this imine, then what you do? You treat with a base. So, this base now abstract your hydrogen and you are going to get an minus with a M plus, if you use a metal containing base. Now such system you can now easily try to do a N center anion and this will be now undergoing a simple imine enamine tautomerization. So, now you see this part this is Ph and this is your CH2OMe. Now this N contains a metal contains a metal which is now here the judicious choice of O methoxy group was done.

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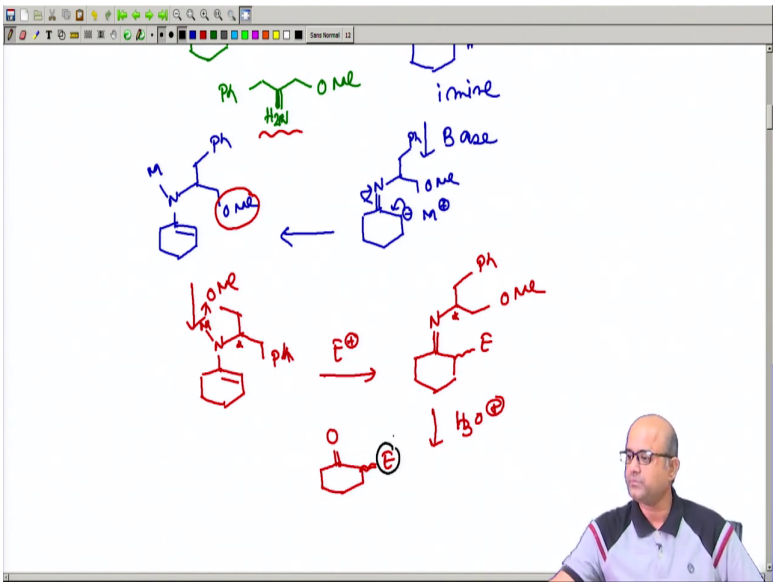

And as a result this O methoxy group you can definitely have a rigid cyclic chelate with this compound. So, what is going to happen? You write in this way. The Ph you can write it and you can have a OMe here which is having a metal and you can definitely have a coordination, now this stereocenter was fixed.

Now, see whatever stereocenter you can take in the original chiral amine you can now control the addition of the electrophile based on this particular stereo center. Now whatever stereo center is there if it is having alpha the corresponding electrophile will be approaching from the beta phase. So, now this will be the next round of thing depending on this particular group stereochemistry you create a and then your amine this enamine and this imine tautomerism will take place and then you will get back the corresponding imine and you can hydrolyze this in a with simple aqueous workup.

So, this was pretty early days we used to tackle such kind of problems with the amine enamine tautomerization and eventually the chiral controlling element can be coming from a normal primary amine. And so this center you can easily fix based on the stereo center which was present here. Now in the current context people are trying to tackle this problem in a little bit of different way.

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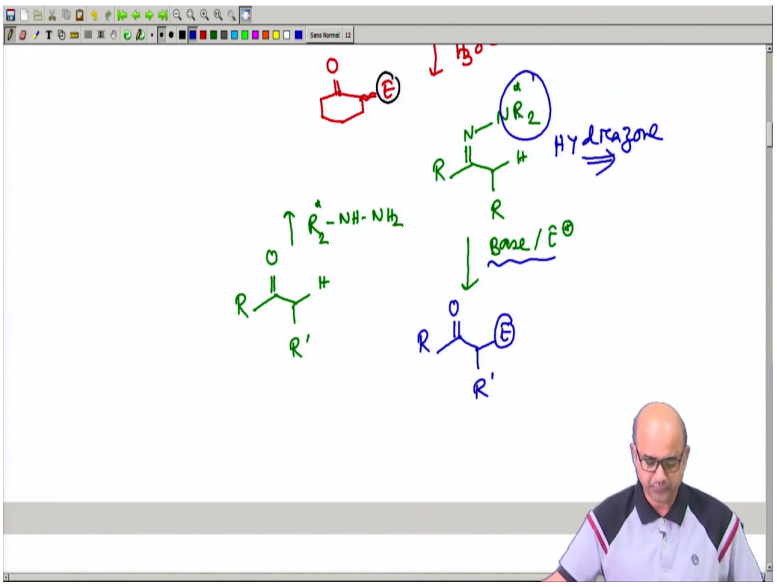

So, let us say if you are having a chiral sorry achiral precursor which might contain a carbonyl group or aldehyde group with an alpha hydrogen or abstractale hydrogen. So, as I said direct alkylation was not possible. So, what you try to do? You first convert it to some derivative and this derivative might be of different thing instead of imine you can also derivative through a hydrazone derivative. You treat with normal this kind of NH NH2.

And then you actually create a chiral or achiral thing. So, you are basically having this NR2 ok. Now this star this particular R group is a chiral group which I am talking about and then you are eventually having an imine kind of system and now you treat with base your electrophile and see by virtue of this particular stereo centre which was present in the chiral hydrazone. So, this will be your hydra zone this will be the now this main precursor of your enolate precursor.

So, treat with base and then you do the cleavage of the hydrazone and you will be actually getting the alkylated aldehyde or alkylated carbonyl compound. So, this was the simple approach we are nowadays following, where you can do an alkylation when in the asymmetric fashion to make a new carbon-carbon bond, if you are reacting with a carbon containing electrophiles.

So, this hydrazone the initial derivative which is basically imine kind of derivative will be coming into picture. Now this hydrazone what are the existing hydrazones available in the literature?

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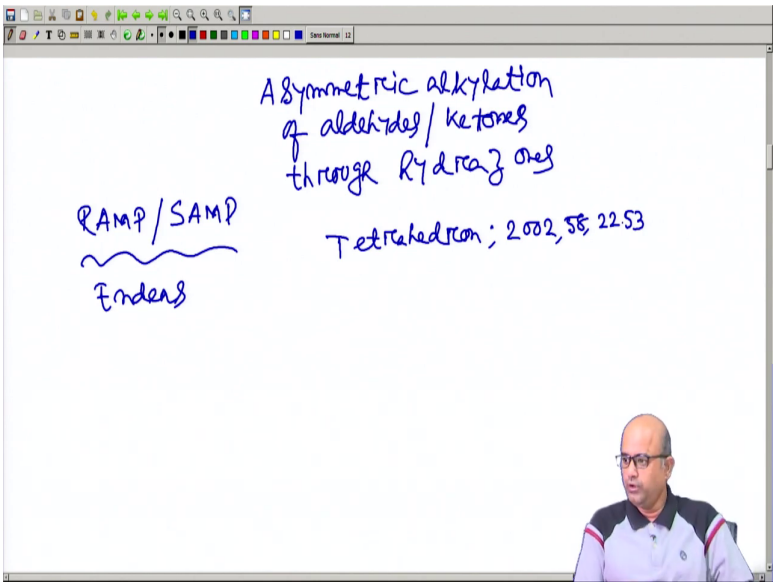

And now we will be trying to talk about a bit of this asymmetric alkylation based on chiral hydrazone and alkylation of aldehydes or ketone ketones through hydrazone. Two well known hydrazones which are very much known in the literature are usually named as these two hydrazones RAMP and SAMP.

They have been developed by a German Scientist Enders……. Dieter Enders, who actually published a nice review in a well known paper named as Tetrahedron. If you are interested, you can go through the review where he documented all the chiral hydrazones and its alkylation and how you can do synthetic manipulation by using this hydrazone. So, in principle what is happening?

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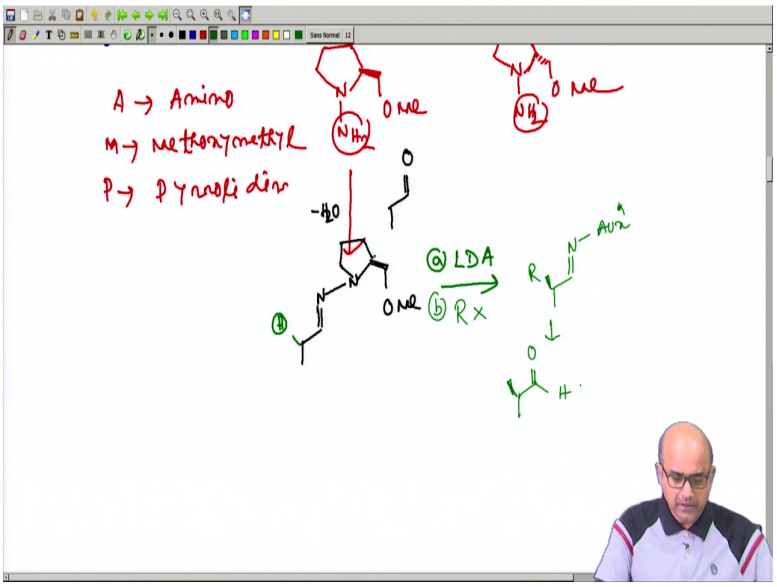

This two hydrazone their structure is actually based on a pyrrolidine structure and in the two position you are having a O methoxy group.

So, based on the CIP rule you actually name them and one will be R and one will be S. So, I have written both the compound as a R just I want to remove it S and then you try to put one will be this. Now the R stands for the rectus or sinister and A stands for amino as this group this compound contain an amino group at the one position ok and this M; M stands for methoxy methyl see you have a CH2OMe group methoxy methyl and P stands for pyrrolidine the five-member heterocycle.

So, these compounds are commercially available and even if you can make in the lab. So, it's name stands for R or S two amino sorry one amino two methoxy methyl pyrrolidine ok. Now what we normally do with this compounds? Let take any of this compound and react with corresponding carbonyl compound let us say you having a simple aldehyde. This kind of aldehyde.

So, first your carbonyl oxygen will condense and you have a dehydration reaction simple hydrazone derivative you will get and this is a five-member thing. So, anyway you will be actually getting this kind of thing. Now see these hydrogens which are alpha to this imine are acidic and now you are going to abstract this thing with a base suitable base and the preferred base as I said non nucleophilic base for LDA would be preferred and then you react with a suitable electrophile.

So, and as the stereo center of this particular carbon is fixed, the O methoxy group actually plays a different role. It also helps in the chelation. The moment it picks up the hydrogen it will be generating a negative charge, it simple amine enaamine tautomerism and this nitrogen now have the Li or the metal. Now this Li will help to undergo a five member rigid chelate formation and then you will be getting corresponding alkylated derivative and here you will be having a new alkylated derivative and the auxiliary you can later on remove.

So, you can later on remove the auxiliaryand what you will be getting? You will be getting this kind of carbonyl compound with an alpha alkylation thing aldehyde alkylation which seems to be extremely difficult under normal circumstances. Now such RAMP or SAMP models you can actually try to use for different compounds.

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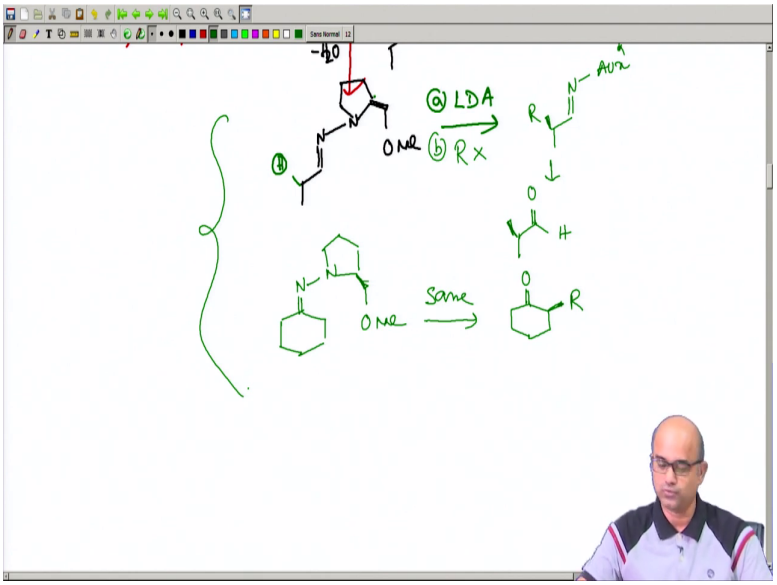

I have just use an aliphatic aldehyde even for cyclic compounds it seems to be quite well known. And I will be explaining that what is the working model, how this reaction takes place and what is the origin of asymmetric induction. For cyclic system also similar kind of things take place as same as earlier and you can actually create the particular carbon-carbon bond in asymmetric fashion. Now all these compounds which we have talked till now a symmetrical compound normally you do not have a regio chemical issues and this is one of the main problem for this Enders RAMP /SAMP method usually it can handle very nicely symmetrical system when you do not have a regio chemical issue.

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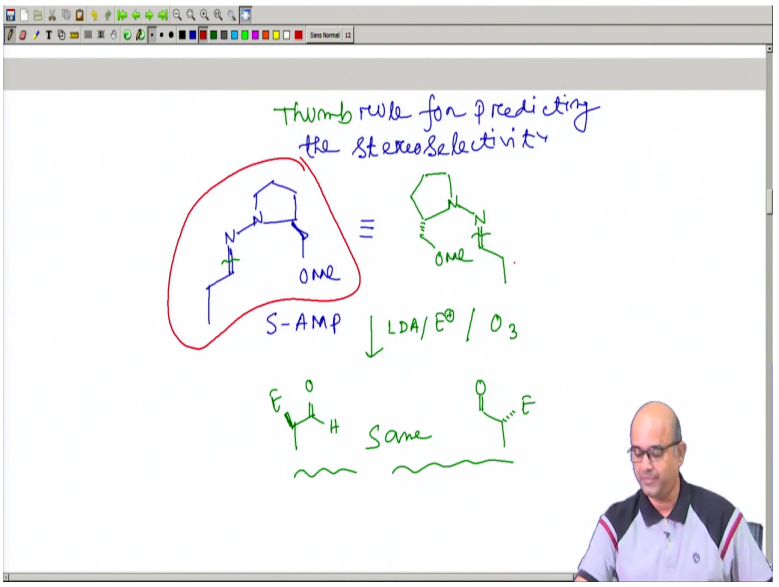

Now let us go to little bit of thumb rule which probably helps you from which hydra zone you can get which alkylated product. Thumb rule for predicting stereo selectivity and then this thumb rule is very important for the exam purpose because normally in the exam purpose if you have to draw the model of the transition state that seems to be little bit time consuming.

So, let us say I will just try to give you a little bit of thumb rule and that normally helps for general purpose, just one minute. So, take a simple aldehyde kind of hydrazone and this is N this OMe. This is coming from a SAMP thing because the stereochemistry of this center is. Now this compound you can also write in a different way just by allowing the rotation of the compound in a different way.

So, you can just write the compound in other way also same compound. This was usually you can write in this way also both the compounds are same ok. Now for if you write either in this fashion or this fashion, if you write in this fashion then your precursor is this precursor is this. So, what you do? You try to do a LDA base. You are reacting with an electrophile E plus followed by you do a hydrolysis or this bond cleavage. Now this bond cleavage you can do it oxidative way ozone analysis was preferred.

Now, fine now just rule of thumb if you write this compound in this way as OMe is beta your electrophile here will be beta. So, you get this absolute configuration of the final component. If you write in this way for this also then you your carbonyl compound will be this yours.

Now see here OMe is below. So, your electrophile is this. Now both these compounds are same.

So, this was kind of a rule of thumb which you can easily do it for such analysis ok. And so just try to remember if you write in this way for one compound and its usually OMe is beta whatever way your aldehyde you have written just written in this way and as this is beta you put your carbonyl electrophile bond in the beta ok. If you write in this way O me is below and then you put electrophile is below. Same model you can also explain in the case of RAMP ok.

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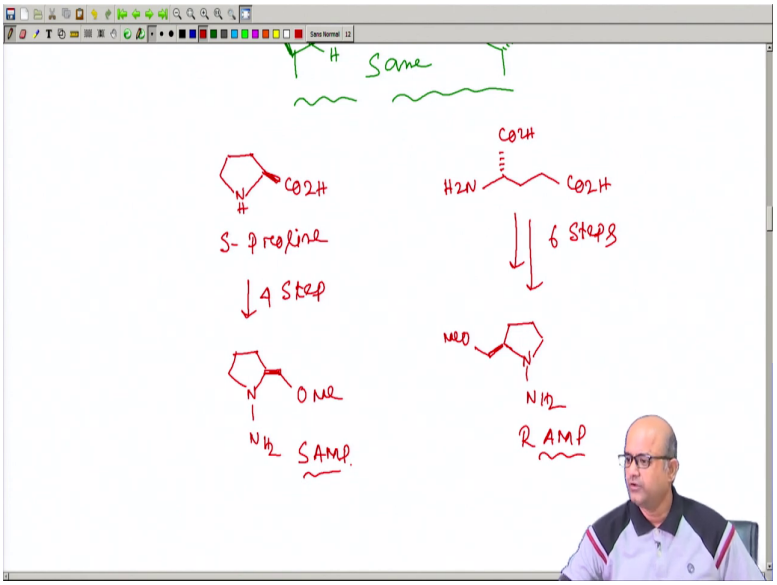

Now, how you can prepare this RAMP and SAMP? This are not very much difficult. Actually you can buy it from the commercial suppliers or otherwise if you want to make it you can make it. We are not going to talk about those synthetic procedures because these are commercially available. Actually you can make this compound from S-proline one of the naturally occurring amino acid. So, from S-proline you can actually make 4 step synthesis to give you a SAMP hydrazone SAMP hydrazone you can get the RAMP one you usually can make it you have to do it in a different amino acid. This is usually not from a proline.

But, you can make it from the corresponding glutamine acid ok. From this way you can actually make it in the 6 steps, you know these steps are reported. So, I am not discussing it, but eventually both the compounds are commercially available. So, if you want to make these compounds in the lab it is also doable. You can just follow the literature procedure. So, this is your SAMP and this is your RAMP.

So, both the RAMP or SAMP are commercially available and definitely those are little bit of expensive, but if you having a bit of resources in your lab you can make it. So, we are just not talking about their synthetic procedure.

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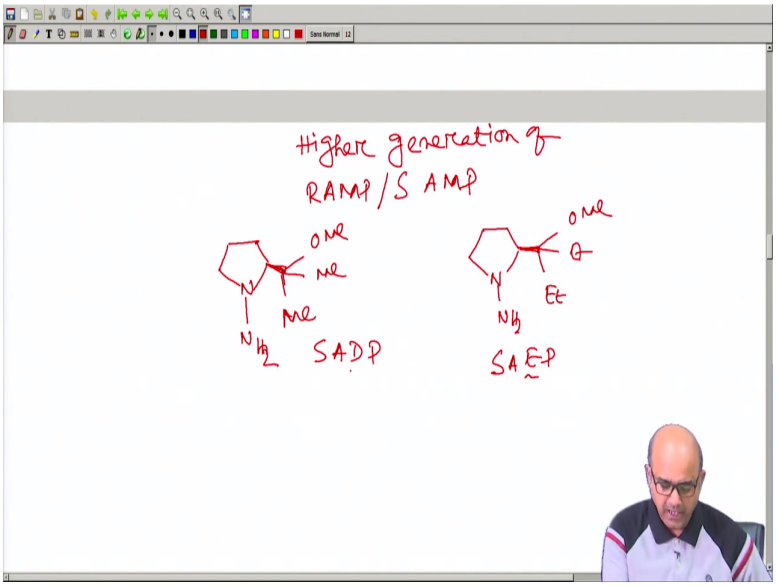

Now, coming to this RAMP /SAMP there are some higher analog for this RAMP/ SAMP. Now before we talk about the origin of asymmetric induction there are some higher generation of RAMP /SAMP analogue and these compounds are basically modified version of RAMP /SAMP analogue.

Though their mode of asymmetric induction everything remains similar. So, only change what people have been tried in the case it is NNH2 ok sorry, This is the NNH2 the hydrogen and the this part they actually do some changing where O methoxy remains same. They put some methyl and they put some extra methyl. So, these groups are basically a helping in the to give you more steric congestion. This was named as SADP ok.

And similarly other compounds are also known in the literature like few other compounds which are known in the literature. OMe group remains same because that is actually helpful for the chelation ethyl and ethyl this compounds are known. This is called SAEP, you can just this E stands for ethoxymethyl and this is stands for dimethoxymethyl and anyway such compounds are known and there are usually good. Now come to the coming to the origin of asymmetric induction for some RAMP /SAMP based alkylation.

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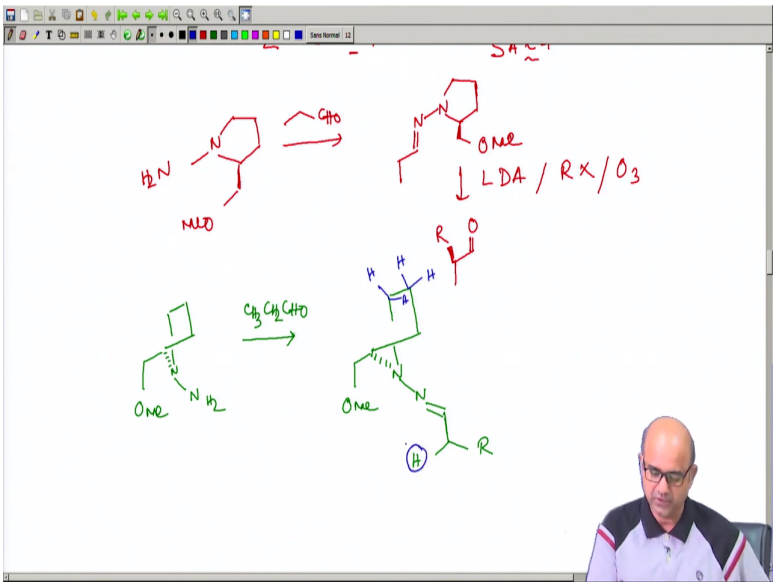

This could be our last part for this today's lecture. Take a typical any of this compound. Let us say take the SAMP ok and just take this SAMP react with an aldehyde, where you want to do the alkylation. So, if you just write the compound. So, it will be N……..N, this part OMe fine and as according to the working model which just now we said if you try to do the LDA and rx the electrophile followed by ozone enolatic cleavage. You just said that this will be OMe is beta in this way.

So, R will be beta and you get the corresponding aldehyde, now fine. Now the origin of asymmetric induction you can eventually write it through a way and you need to spend a little bit of time because this drawing was a bit crucial. I will just try to write it in this way. You just twist the compound in a envelope kind of way and put your nitrogen here ok and this CH2OMe here. So, this drawing was initially required for the parent RAMP or SAMP compound.

Now, initially you have your aldehyde or carbonyl compound which you are going to . So, again write the path this is your N, you have to write this as a envelope kind of thing a little bit of bigger way ok. The CH2OMe is here and then you have another N you have double bond, then you put H and R ok. Now this working model will be actually mainly gives you a picture that this envelope structure will have 2 methylene with a 2 hydrogen as this way.

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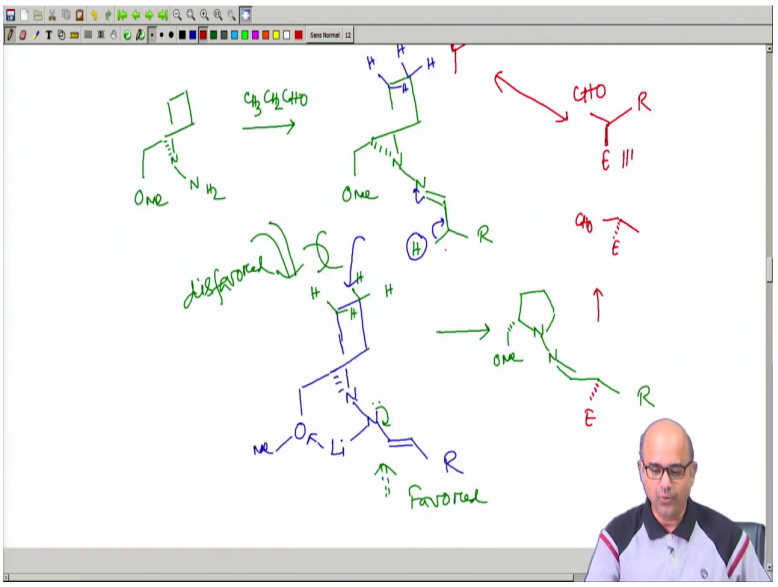

Now, this hydrogen is going to be abstracted fine, this is we all know. Now this hydrogen is going to be abstracted and if this is going to be abstracted what you can again write. This will be the nitrogen, this is your then this bridge structure. You just make the five-member ring and then this will be your if this is abstracted you have this and you get this as a N minus ok. So, this N then followed by you put a N and then you have this kind of azaenolate and the this will be now lithium or metal and you have a now a CH2 OMe

Now, you basically get a rigid chelate here. Now this is the transition state which probably is bit difficult to draw and the origin of asymmetric induction you find that this compound does not have any sterically bulky group. So, through the help of cryo-NMR and Ctyo X-ray such structure actually was proved and then people have I mean Prof. Enders have identified that these two bridge methylene group was the main responsible factor.

So, that alkylation from the top face of the electrophile seems to be hindered by this two bridged methylene group. So, this was disfavoured, but alkylation from the bottom face of the enolate was favored. So, this was kind of a steric crowding or steric destabilization created by the bridged methylene with this two hydrogen.

So, hydrogen is not always small …… try to remember. Now if you try to write such compounds in this way, then you again take the compound. You can now write in a normal drawing that CH2OMe could be in this way. Your nitrogen you put it in this way. Now for the

so initially this will be now this N minus after the chelation it comes here and this will be the enolate alkylation pattern ok.

So, then you will be having this as this and then right R and as we said the electrophile will be now having in this way. So, after hydrolysis definitely if you try to rearrange the way I have drawn this kind of structure was difficult to visualize because it is CHO, but you can easily try to point it out, it will be R it will be your electrophile and it will be your CHO.

So, you can easily identify that how this origin of asymmetric induction will be created. You just open this compound these are basically kind of a similar compound provided that you have a E instead of R. So, anyway this is very simple way not simple way exactly actually in the drawing seems to be bit of crucial for your part. Now once you do this asymmetric alkylation what we will be next doing for this hydra zone.

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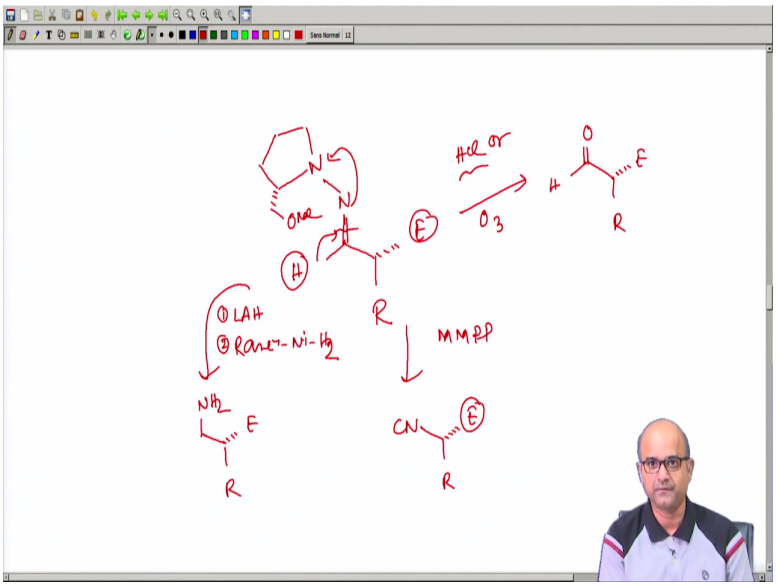

Now, you will see that this hydra zone your alkylation part was done. You have introduced an electrophile in the asymmetric fashion ok. The pyrrolidine ring was still there. So, you have to remove it and the way people have been done it in a numerous way the normal thing is you can actually do a HCL mediated cleavage which is hydrolytic cleavage or you can do an oxidative cleavage.

So, this oxidative cleavage actually cleaves it here and then you correspondingly get a carbonyl compound either an aldehyde or a ketone either you do a hydrolytic cleavage by

HCl or do ozonolytic cleavage ok. You can actually do a reductive cleavage also if you can try to use a lithium aluminium hydride kind of thing. Normally first a lithium aluminum hydride followed by a Raney nickel and hydrogen.

You will get a reductive cleavage and this reductive cleavage. What it will give you? It will give you E and R and this CN bond will be reduced to CH2 NH2. So, this kind of compounds you get and then if you are trying to do with some other treatment you can actually end up with other things like if you are treating with MMPP mono magnesium per phthalate this hydrogen removal can be done and that basically gives you an oxidative cleavage and it gives you a cyanide in this position.

So, normally you get a cyanide with a R and E. These are few synthetic transformations you can handle with the handle with this kind of RAMP/ SAMP based hydrazone. So, in the next class we will be talking about different synthetic uses of this RAMP/ SAMP and how such strategy synthetically manipulated for a large number of chiral intermediate synthesis as well as natural product synthesis. We will see you with lots of other information regarding this RAMP and SAMP based alkylation in the subsequent lecture.

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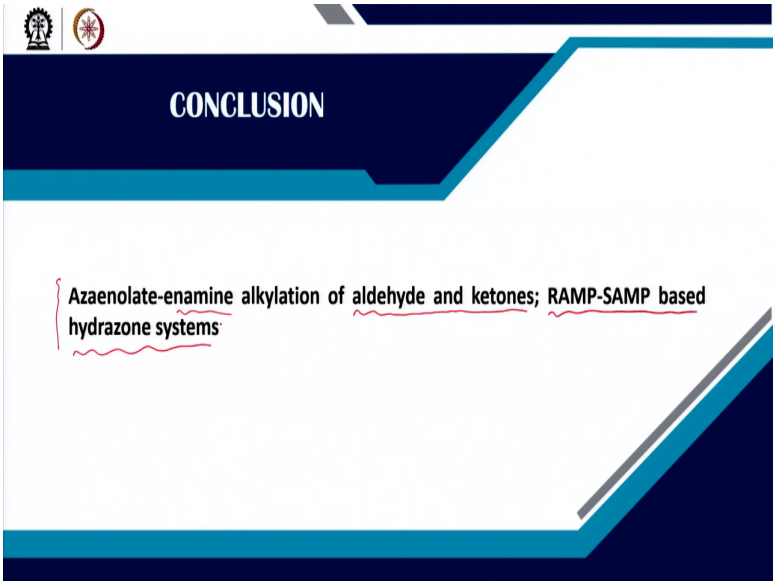

So, as a conclusion we can say that after this lecture we have identified azaenolate based dynamic alkylation is a powerful tool and particularly very useful for specific aldehydes and ketones where direct alkylation is difficult and then you can convert corresponding enamine and then we do the alkylation. And RAMP/SAMP based alkylation which is invented by

Prof. Enders seems to be one of the very good component in this particular system. Thank you, we will discuss subsequent lectures remaining other topic.

Thank you.