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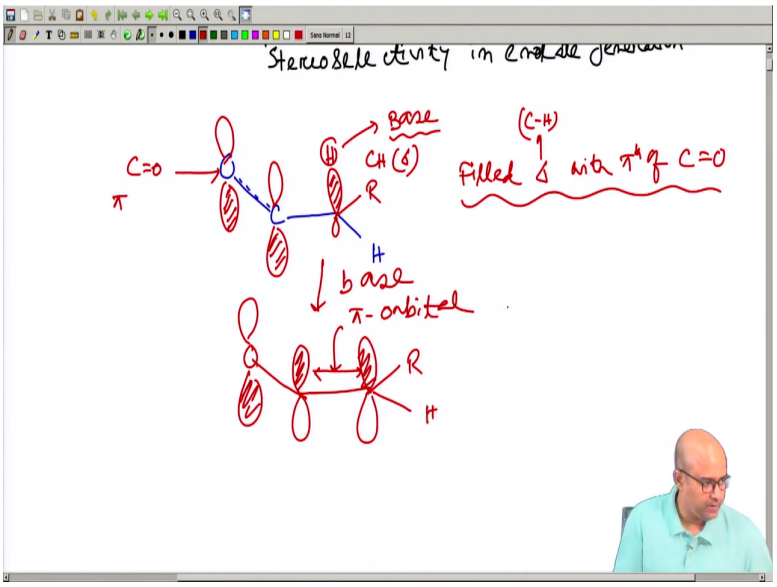

Now, we will be switching over to a very another interesting concept, the stereo selectivity in the enolate generation. Now, this concept was definitely very useful for our purpose, as we will be talking about a how you can react different electrophiles with this enolate to construct new carbon carbon bond format in asymmetric way. Now, let me try to give you a simple drawing. So, where this is oxygen, this is carbon, I mean usual way and then you have this hydrogen where from you will be obstructing the proton and.

So, this is basically a C double bond O to. So, I am just trying to put a dotted line and then I will try to figure it out, its simple explanation in terms of molecular orbital theory. We do not give you in pretty detailed explanation, but just try to draw the HOMO of this initial thing and this is the way we do explain it. So, initially you have another hydrogen and this thing. Now, initially this hydrogen will be abstracted by base, this will be abstracted by base.

Means that the filled sigma orbital is there which, first hydrogen was abstracted by the base. Now, you have to have an effective overlap with this filled sigma, which was created here or the carbon ion with the π star of C double bond O, π star of the C double bond O ok. This is basically the C double bond O π orbital. I mean just we have try to see. Now, this effective overlap with this CH sigma and C double bond O π star this was the main dominating factor in the entire enolate chemistry.

So, that basically creates the new π bond in the enolate. So, now, we can write the π bond, in I mean we keep everything all the parameters similar, you have this, you have this, you have

this, you have this. So, we will be talking about this thing, the remaining you can write other groups like if you have a R group, you have a R group this other hydrogen are still there and this oxygen will be definitely being there ok.

So, now, you can see that. So, this pi orbital we are talking about which is eventually formed in the enolate thing. Now, one prerequisite was definitely there, this prerequisite was a absolutely essential for this enolate generation ok.

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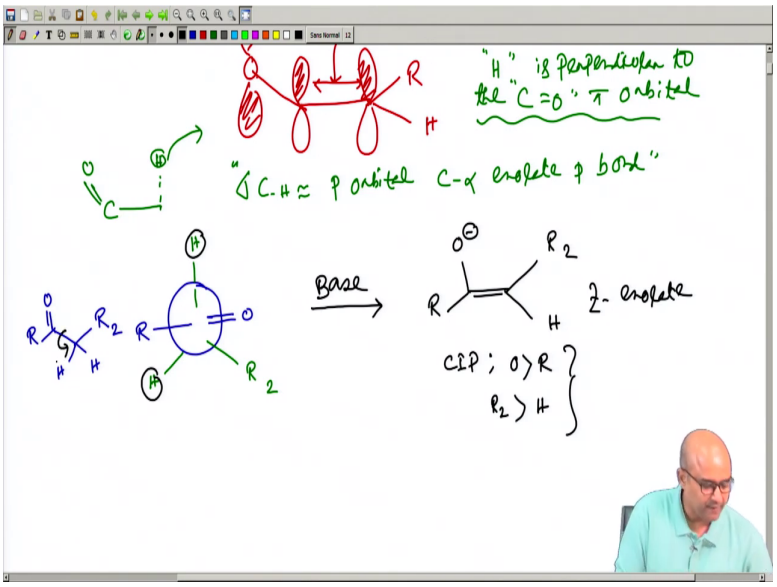

Now, this is usually found that hydrogen which needs to be abstracted is perpendicular to the C double bond O π orbital. And in this way if it fulfills this criteria, the effective overlap eventually will be absolutely good because this sigma C-H orbital ultimately and this things will becomes the p orbital of the C alpha enolate of the π bond. So, this thing was pretty interesting.

So, means that once this C-H, I mean you can just write in another way C double bond O C-H, while saying this in this way. So, if this is kind of a perpendicular. So, the moment it got obstructed and the effective overlap with this C double bond O π star it seems to be pretty much perfectly aligned.

And that basically is one of the main criteria for enolate generation, and based on this criterion the stereoselectivity can now be explained. Now, we will be trying to switch over to a different way of enolate generation. Now, it draws the enolate structure of the starting

material in a Newman presentation way. So, let me first write the compound as it is. So, there are hydrogens here, two hydrogens and there is a non-symmetrical R and R 2.

Now, according to the criteria which we have fixed earlier the carbonyl is associated with this R group fine and then we said that the hydrogen seems to be perpendicular to this ok. So, then you can definitely have this way and this way of the starting material. Now, in this way if you have drawn the initial starting material you find that R and R2 are basically kind of anti to each other.

Now, there are two hydrogens definitely. So, we talked about only one hydrogen, this hydrogen also can be abstracted. Now, if this happens to be obstructed or this happens to be operated by base what you will get? You get R fine, then you get O minus the relative stew chemistry of R and R2. Now, you see the R and R2 are anti to each other ok.

And based on the CIP rule, if according to CIP you will find that oxygen greater than R definitely and here R2 greater than H. So, this enolate is a *Z* enolate fine. So, this could be one of the one of the possibility for an enolate generation, I mean now this is the. Now, there is also another hydrogen which also can be perpendicular if you allow the rotation around the, see the single bond because rotation around is bond is free. So, you can now try to have another drawing of the entire structure.

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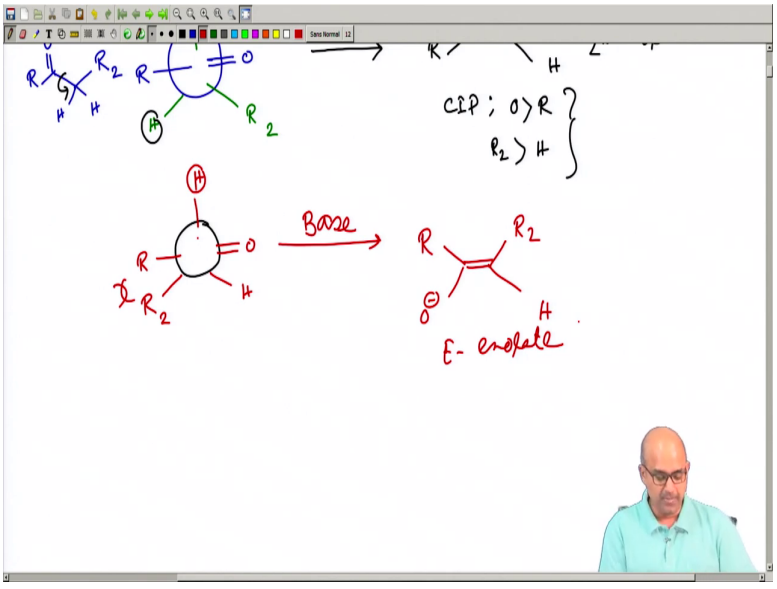

Now, draw another way, another sphere to explain the Newman presentation, ketone your carbonyl is flipping here and then you try to put this hydrogen and this hydrogen; now by this rotation your R and R2 now comes close each enough, ok. Now, this will be definitely giving you a sufficient steric clash, but we are not discussing about the steric clash. So, now, we said that this carbonyl and this hydrogen are perpendicular ok, because this hydrogen has to be perpendicular to have an effective overlap which is the prerequisite initially we framed, now base ok.

So, now you can see that R and R2 will be on the same side. So, R you get this R2 and hydrogen. So, now, you see the oxygen is highest priority and R2 is highest priority. So, this enolate is now *E* enolate. So, this there are two ways you can basically generate the enolate, the stability wise we are not discussing the entire thing. So, the stability parameter will be coming next. Now, actually this is the first explanation for the enolate generation and then we now switch over to a typical model which we call Ireland model.

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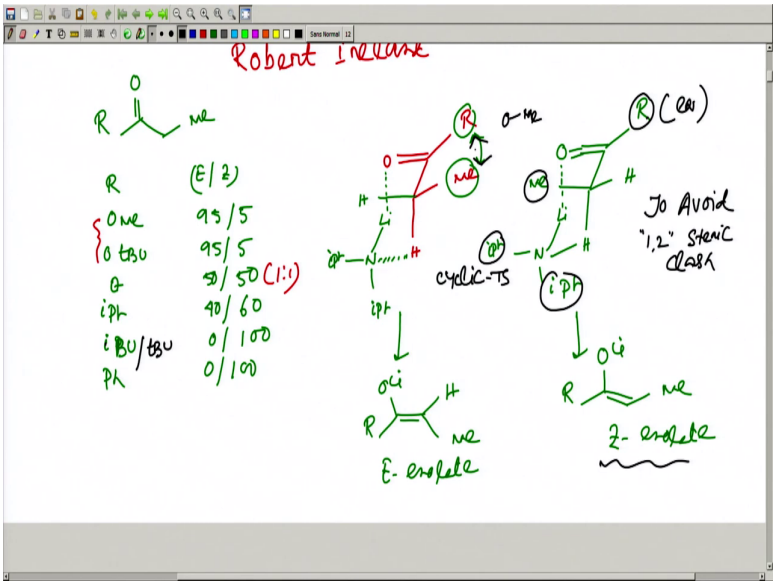

So, Ireland model was first invented by Professor Robert Ireland. We will now discuss Ireland model to explain the relative ratio of the *Z* or *E* enolate it always depends on the substrate structure and the particular substitution pattern. We take this as a standard substrate ok. Now, what I am trying to give you I will give you a ratio of different groups, if R equal to O-methoxy, now this is a *E* by *Z* ratio, if R equal to O-methoxy you get 95 percent of *E*, 5 percent of *Z*.

If is tertiary butyl you get similar ratio 95 by 5. First I will write the ratio then I will explain ethyl 50-50, ethyl 50-50. Little bit bulky group isopropyl its ratio seems to be reversed, it is increasing for percent of *Z*. Tertiary butyl, tertiary butyl you will find that *E* is almost 0 percent most of the compounds are *Z* phenyl similar. So, now, the trend from O-methyl to O tertiarybutyl has been reversed, for ethyl selectivity is 1 : 1.

Now, what happens in reality? Now, let me try to draw the structures in two different perspectives and you need to be big little bit careful for drawing purpose. Now, first I will try to do the ketone in this way, I will put R ok, then here is methyl is there already present again, there is a hydrogen which will be abstracted and I will write the another hydrogen with a green color fine.

Now, for lithium from the base we will try to be coordinate with this carbonyl group and this lithium is now attached with the LDA, because we always used LDA. Now, LDA means there are two iso -propyl group, iPr and one other is another iPr. So, we have drawn a six-member close transition state something like this. Now, in this case if you have seen the R and methyl are on the same side. So, if this transition state operates you basically get R and methyl which is the *E* enolate.

Now, we will be drawing another transition state by keeping everything else similar just by switching the methyl group and other group. So, now, we will try to put a methyl hydrogen this side and the methyl which is there will keep it here ok rest of the part another hydrogen is here. Your; next your lithium is coordinating with the carbonyl your nitrogen and this you finish with two isopropyl on this thing fine.

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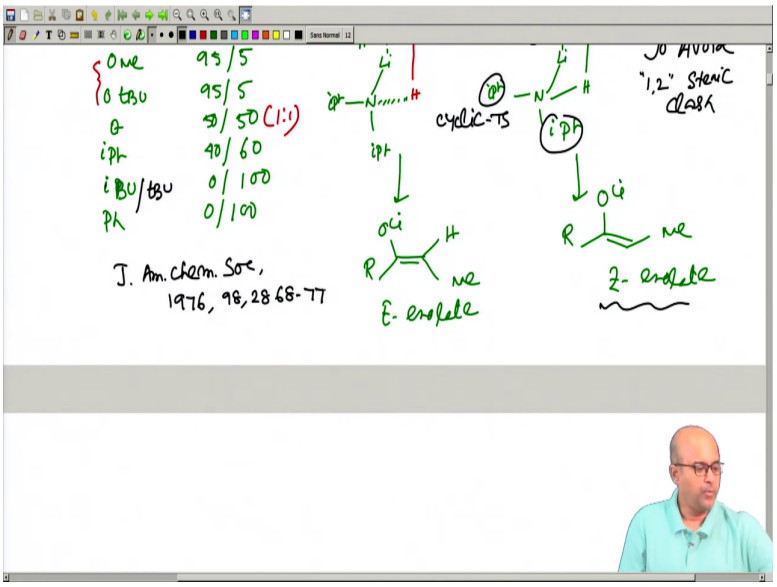

So, now the two drawing was, basically we have drawn. The first one if this models operate or this TS operates, what will be your structure R and methyl on the same side. So, basically you will get R double bond methyl OLi and hydrogen which is basically then we call it *Z*, sorry we call it *E* enolate. *E* enolate means, if you take the CIP rule, the oxygen is highest and methyl is highest here.

Now, from this case you will find that R and your methyl will be opposite you get this product, which is the *Z* enolate. Now, try to explain the behavior. First case R is O methoxy, now O-methoxy means oxygen is there. So, oxygen is there and there are two factors actually, if these groups are sufficiently close enough you get a steric strain which is called as an allylic 1,2 kind of strain 1,2 interaction and they usually follow a 6-member cyclic transition state.

So, this 6-member cyclic TS was quite important, cyclic chair like transition state. Now, this oxygen methyl, oxygen can actually rotate. So, this methyl can be away from this methyl, similar thing happens for tert-butyl also, because oxygen methyl. So, means that is oxygen alkyl group this can rotate and that can be further. So, this strain can be avoided, this steric class and that gives you this for these two substrates it is clear. Now, you keep on increasing steric bulk, where at this other point now the second drawing which is responsible for the *Z* enolate you have a R as ethyl.

So, R is ethyl; ethyl is definitely a bulky group, but not that bulky group you can eventually see the ethyl does not give any selectivity. So, both the TS is operating ok, this is one as well as this one. Isopropyl you keep on increasing the steric bulk. Now, this group is usually occupied an equatorial position of the chair form so, which is most stable one.

Now isopropyl gives you a little excess of *Z* selectivity because if isopropyl and methyl are close enough they have a sufficient steric clash. So, that is why it forces the methyl to go axial and that is why isopropyl prefers this orientation here and forces methyl is this way. That is why *Z* is major in this case. Keep on increasing the static bulk in the R part, isobutyl or ter-tbutyl we can write it can this is isobutyl as well as tert-butyl. You find that in both the cases it is so bulky, it definitely will allow this methyl or isopropyl group here.

So, this methyl is shifted towards the axial position. So, what is happening to avoid to avoid this 1,2 interaction it's kind of an allylic, 1,2 interaction, but anyway I just write a 1 2 steric clash. This group has been switched over, the substrate initially focused the methyl to the axial. Now, this LDA has an isopropyl group, but this is a bit far away. So, this clash can be avoided. So, in this case to avoid this kind of things, isopropyl, tert butyl and phenyl you will be definitely having the *Z* enolate as the major product.

Now, if you are interested to learn something more on the referencing aspect, this you will find in a research journal which is taken from Ireland's original work which is published *in Journal of American Chemical Society* in 1976, this is pretty old paper. And this will give you a fairly good idea that how this stereoselectivity can be modulated. Now, this Ireland model works pretty well for all the cases and most of the cases you based on this Ireland model you can predict whether *Z or E* enolate can selectively be generated.

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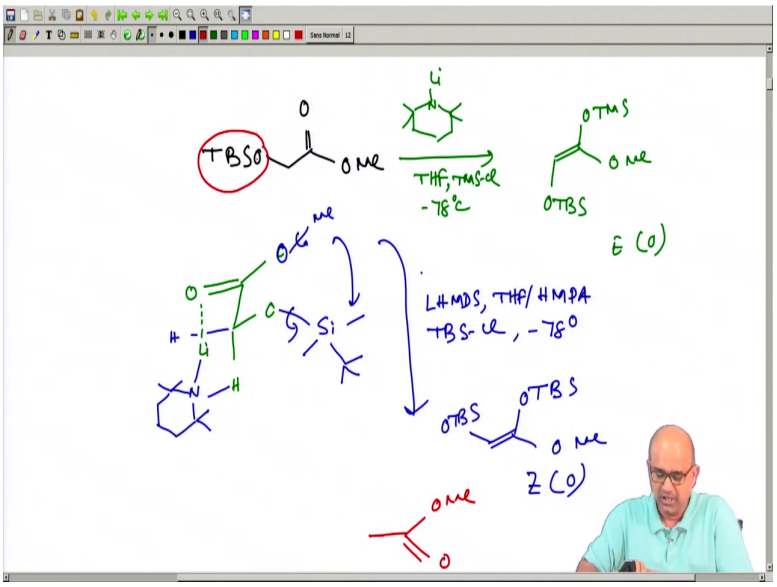

In few cases you can overcome this Ireland model, but there are other criteria will be coming into picture, I will just try to be specific about one such example in one such compound for this thing. If you use a base which is LTMP we already talked about this base in the beginning, this is a sterically bulky base and we use only THF ok. You find that this thing will usually give you and you use a TMSCl as the enol trapping agent minus 78-degree C. So, talking about kinetic enolate deprotonation.

So, OTMS and you get an O-methyl here and in this case you get OTBS, means O tertiary-butyl di methyl silyl. So, basically what you get,,,, You get an *E* enolate. Now, how you can explain this *E* enolate? This enolate normally you can explain through the typical drawing of the earlier way, you have a C double bond to you have an O-methyl, the Ireland model, you have this you have OTBS fine. So, see OTBS, OMe is same then your lithium part is coming into picture, you have a hydrogen here you have a hydrogen here.

So, these things you can do it and then your nitrogen of the cyclic ring will be coming into structural part which definitely plays a role. See, the 6-member cycle transistor state. Now, as I said this O-methoxy means you can relatively remove this group. So, what we are talking about? An oxygen with a methyl, means this rotation is free; an oxygen with a silicon containing group. So, tertiary-butyldimethyl silyl. Now, as this rotation is free these groups can rotate far apart and thus this steric class can be avoided.

So, this is the most stable one and that gives E1. Now, fine; now in another condition, if you take the same compound you take the same compound, let me write the same take the same compound and you react with a LHMDS, a similar kind of base, THF with HMPA; HMPA is basically a hexamethylphosphoramide which is a lithium solvating reagent and then you use TBS-Cl.

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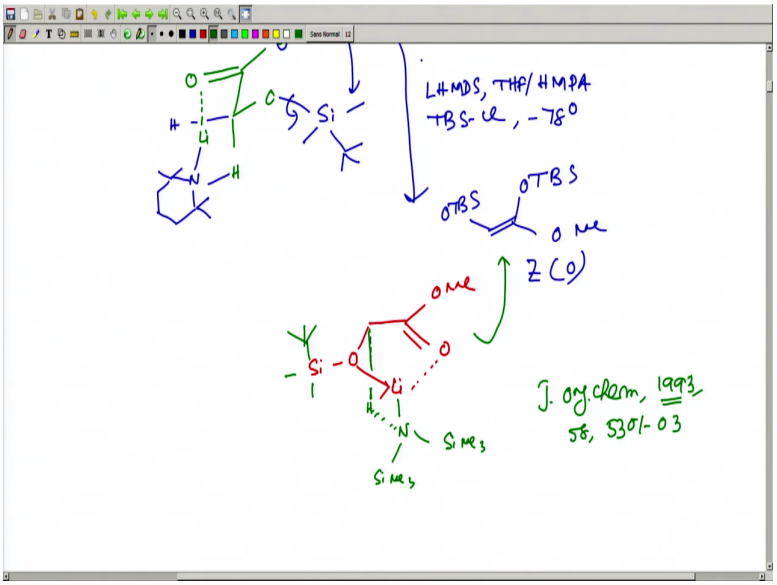

And use low temperature definitely and in this case you find that the enolate structure will be just the opposite regioisomer, use you get OTBS, you get OMe, you get OTBS. So, basically you get now *Z* enolate. Now, how you can explain it? This explanation its basically you here Ireland model is not valid. Now, how you can explain it. Now draw the structures in different way, you have this O-methoxy.

Initial parent compound we are writing in this way O-methoxy and then you write C double bond O. Now, you have to assume that the parent compound is having a TBS group. Now, the TBS group means it's having oxygen. So, further coordination can be possible with the lithium. So, we write oxygen and the silicon part you can basically write it ok.

Now, C double bond O to, now lithium can be probably coordinating in something like this way or something like this. Now, if you try to do in this way, then your hydrogen substrate will be hold like this, the hydrogen which will be abstracted. Now, this lithium is having nitrogen as the base, your $SiMe_3$ which is the component of base $SiMe_3$. See now this is abstracted.

So, this will be the transition state for this way, which allows the lithium of the silicon to coordinate. Now, if this is the main TS, now you can see that OMe and OTBS are opposite to each other and that basically gives you the *Z* enolate. So, this is a few exceptional case of Ireland model and such model really is a very useful model which you can apply in many cases.

And if you are interested you can eventually try to get the reference which has been reported in a Journal of Organic Chemistry paper in 1993 is the page number 58 is the volume. 1980 is the year actually and the page number is 5301. If you require the references, you can just let me know once you are going through the lecture I can supply the references.

So, for the time being we have discussed the enolate stereo selectivity which is essential component for our part and for the subsequent section we pick up from this point, where we left. And then we will enter in the journey of how you can selectively react with this enolates through asymmetric fashion by reacting with different carbon containing electrophile.

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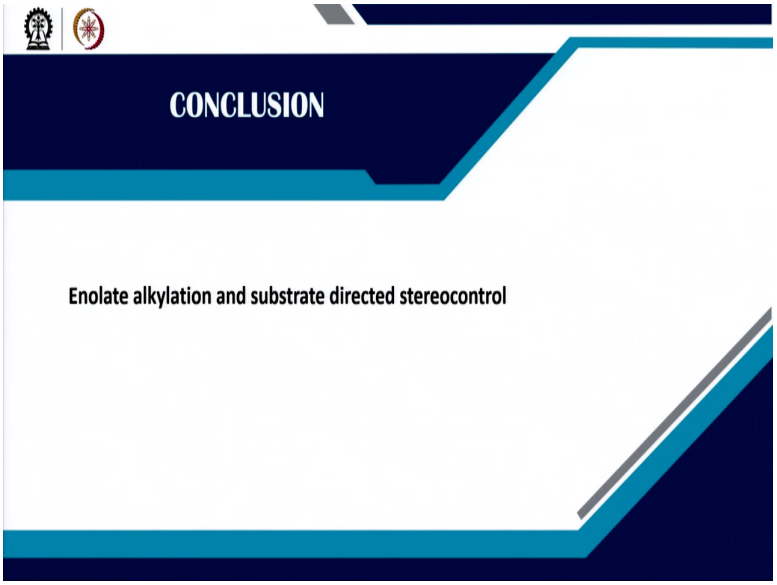

So, as a concluding remark after today's lecture you can eventually say that enolate can be selectively generated and enolate alkylation is very much possible, once you generate the enolate in a stereoselective fashion. So, we will discuss all the topics remaining topics in subsequent section till then have a good time.

And thank you all.

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 - 01
Basic introduction of enolates
Lecture - 05
Different mode of asymmetric induction in enolate alkylation

So, welcome back everyone. And in continuation with our last week's discussion, today we will be talking about lecture 5 in the module 1. And mainly today we will be discussing about few things like we will be again trying to revisit the entire concept, which we discussed in the last class we will then come to our focused point, the Different modes of asymmetric induction in enolate alkylation.

So, let us first start it that what we have discussed in the previous three or four lectures four lectures more precisely ok.

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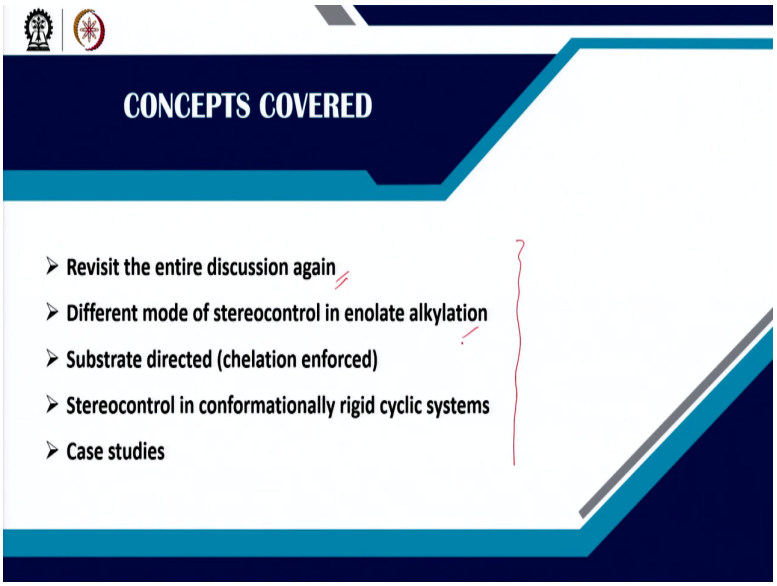

So, we are going to discuss these four or five topics in the today's class mainly the entire discussion will be continuing different mode of stereocontrol and few other topics.

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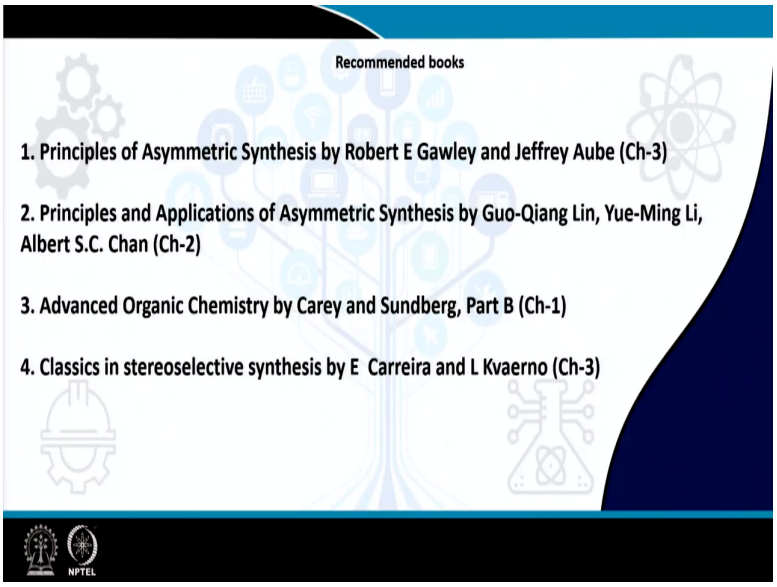

Before we try to discuss the main thing, I will just try to give you a couple of information regarding the standard textbook. Now few text books which seem to be quite useful for a thorough insight about the entire course work. The first test book written by Gawley and Aube was one of the nice books it is named as “Principles of Asymmetric Synthesis”.

And particularly this book in chapter 3, which focused mainly on enolate alkylation in asymmetric fashion. The second book by Albert S.C. Chan, also is pretty good book it named “Principles and Applications of Asymmetric Synthesis” and this book particularly chapter 2; we have a huge discussion on this enolate alkylation.

Two standard text book like particularly this book was pretty good Advanced Organic Chemistry by Carey and Sundberg and particularly Part B and Chapter 1, you can have a very general discussion on enolate chemistry and its entire features. Number 4 book, this book by Carreira and L Kvaerno it is mainly focused on an advanced aspects of different conceptual discussion on enolate alkylation So, if the NPTEL authority permits me I will definitely upload all these books in the course work.

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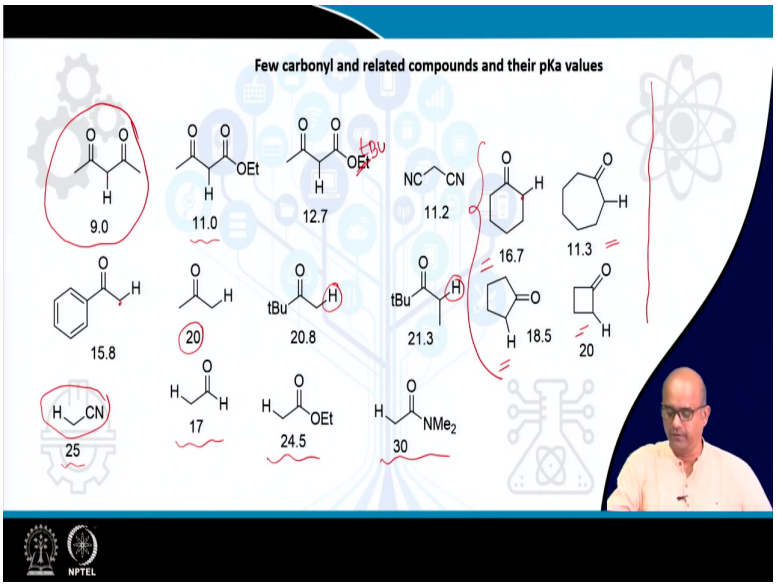

So, coming to the discussion again so, in the last class we have talked about that normally if you have a carbonyl compound with an electron withdrawing group and an abstractable hydrogen you can easily pick up the abstractable hydrogen to generate the carbanion. And we said that pKa, of those carbonyl compounds played a very unique role. We have discussed what are different values of pKa as well as k and it's correlation.

Now see there are series of compounds which have been given in this particular slides and you will find that most of the compounds are carbonyl compound and you can see that they always have an acidic hydrogen like this molecule, which is flanked with two carbonyl group the pKa is closely 9.

So, which seems to be moderately acidic and which can be easily picked up by suitable bases. This compound ethyl acetoacetate all of us are familiar its pKa value is 11, compound like these compounds are basically kind of a repeated I think there will be some other thing it will be a tertiary butyl there might be typing mistake.

Cyclic alkanones also have a considerably acidic character in their hydrogens, alpha hydrogens and you find that we have taken four different cyclic alkanones; starts from cyclobutanone, cyclopentanone, cyclohexanone and cycloheptanone. So, on an average these compounds like cyclobutanone and cyclopentanone have similar kind of pKa value and cyclohexanone and cycloheptanone their pKa value differs a little bit.

Other compounds like benzaldehyde which have acidic hydrogen at this position basically it is acetophenone. Then you have simple acetone which is the standard compound often we used. This kind of tert butyl methyl ketone where this hydrogen is used to be acidic and you see the relative pKa are almost similar there is an extra methyl group here at the for this compound.

And it this hydrogen is to be going to be picked up other compound like this is does not have a carbonyl group, but this is acetonitrile which is attached to an electron withdrawing cyano ……..group ok, and you can see this compound is definitely not that much acidic, but eventually if you try to use a employ a very strong base this also can be hydrogen can be abstracted and you can get kind of a heteroenolate, which contains a nitrogen.

Then you have acetaldehyde which is pretty normal routine aliphatic aldehyde. Other things like ethyl acetate and amide derivative. So, this will eventually give you a quite good idea that how different pKa values and choice of bases for deprotonation. You can deal with that…ok.

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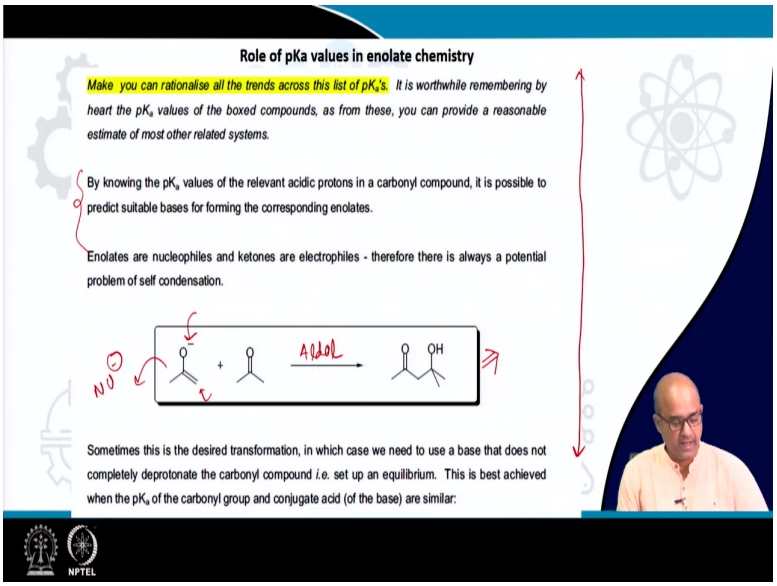

And we already have talked about that what are the essential criteria that what you considered that this mainly the pKa value, knowing the pKa values you are quite sure that what could be the nature of acidity of those compounds ok. And usually as I said the once you generate the enolate which seems to be a nucleophilic in nature.

So, enolates are usually nucleophilic in nature they are ambident nucleophile the nucleophile might be at oxygen center might be at carbon center and if you have a electrophile which is basically a pretty well known aldol reaction self condensation. And this aldol reaction is always a bottleneck or a kind of a problematic in our enolate alkylation. So, we have to make sure that aldol condensation or self-aldol reaction does not takes place ok.

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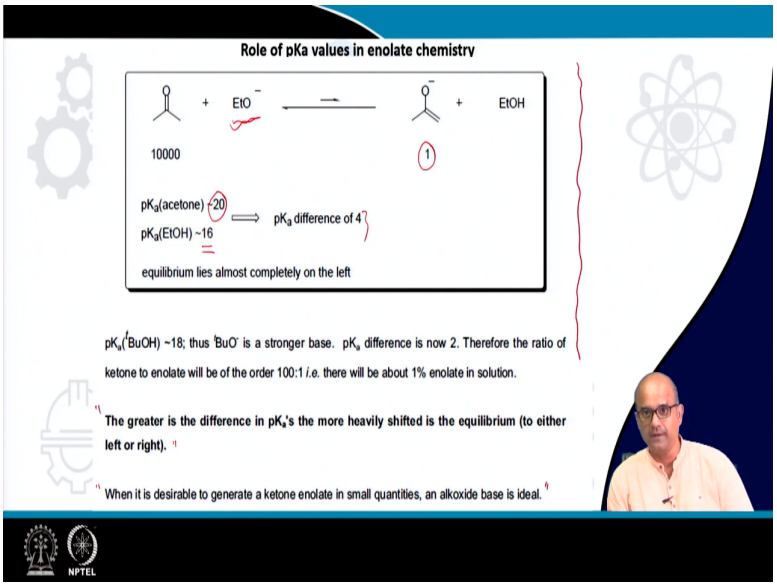

We have also talked about that what should be the differences between the pKa value of the corresponding carbonyl compound as well as pKa value of the conjugate base sorry conjugate acid of the corresponding base. And in those cases we said that the pKa should quite differ. I mean if the numerical value of the pKa seems to be quite large then there will be you have an absolute control for generating the enolate equilibrium mostly shifted towards the enol.

But if you have a bases like sodium ethoxide or sodium tertiary butoxide. You see that pKa of acetone which is the carbonyl compound there is 20 and pKa of ethanol which is the conjugate acid of the ethoxide is 16. So, they are more or less kind of similar and in those cases the equilibrium is not very much changed I mean the equilibrium lies mostly towards ketone very less amount of enolate has been formed.

So, it is really and that is why this kind of bases are not used in enolate alkylation you usually do not prefer such bases in enolate alkylation, but they are preferred for aldol reaction. Now, see we last week we discussed the greater is the difference in pKa. So, the more heavily shifted is the equilibrium towards the mainly the enol or the ketone. And eventually if you are

trying to do an aldol reaction always try to use bases like tertiary butoxide or sodium ethoxide when you basically get a dynamic equilibrium between ketone and in enolate. So, you have an enolate as a nucleophile and ketone as an electrophile. And then they undergo self condensation.

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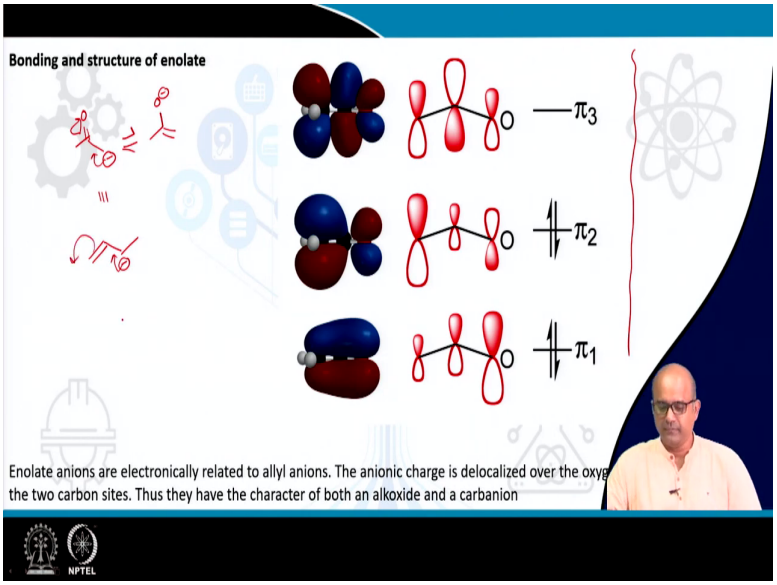

A little bit of bonding and structure of enolate which seems to be quite interesting and actually this enolate once you generate the enols which are usually you can write minus something like this which is actually equivalent to an allyl anion. Allyl anion is something like this and so this simple carbanion now it can undergo a resonating structure to give you this kind of thing.

So, enolate you definitely find that this negative charge is resides either to a carbon or to an oxygen and actually this is a typical HOMO of this initial enolate you see the oxygen here and this is the oxygen. So, this is the homo and this is the next homo where basically the anionic charge is kind of delocalized over the oxygen and the another two carbon sites. So, it was well balanced between the oxygen and the carbon. So, it is more or less similar like the allylic anion which also having a resonating structure something like this.

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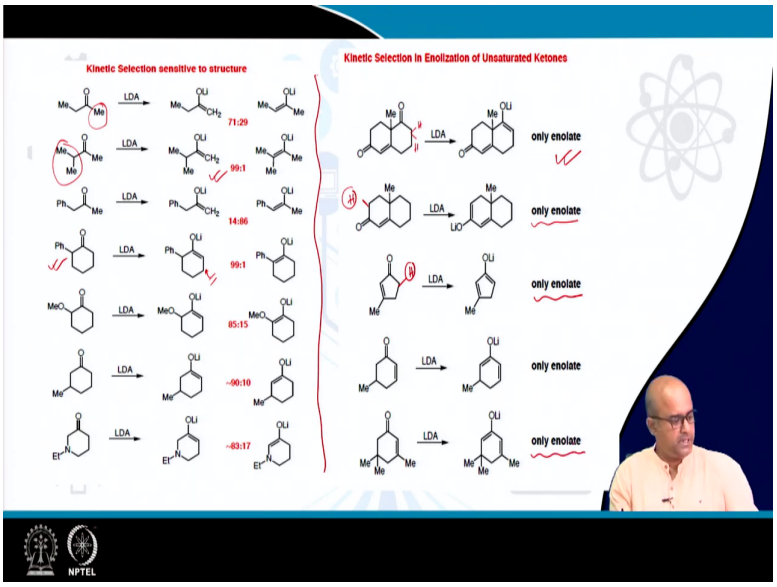

We also discuss that thermodynamic behavior and kinetic behavior of deprotonation and we said that kinetic deprotonation is that way where a less sterically substituted hydrogen is easily picked up by the base. And thermodynamic enolization is that one where you get the thermodynamically more stable enolate ok. Now go to a series of example which you can see it here starting from this compound means there are this hydrogen associated with the methyl group is sterically less hindered or easily accessible.

So, you can see that kinetic deprotonation takes place and you get the kinetically controlled enolate 71 percent and thermodynamic enolate is close to 29 or 30 percent. Similar thing happens in the second example and this case the isopropyl group is so bulky you can have you can see that the kinetic deprotonation takes place in favor of 99 percent. 2- phenyl cyclohexanone so, this basically gives you kinetic deprotonation, and low temperature means kinetically controlled you get 99 percent of this enolate ok.

Similar thing happens here coming to bicyclic system there also you can do a couple of control system; one is this one and one is the alpha beta unsaturated. So, definitely this one will be easily picked up this hydrogen one of the hydrogen will be picked up and you get only this as a major enolate. This is also the alpha beta unsaturated compound and you can easily abstract this hydrogen and you get only this enolate ok.

Cyclopentenone derivative you can easily abstract this hydrogen and you can generate this enolate which is more of like a conjugation. Similar thing in cyclohexanone similar thing

here you can eventually control the generation of enolates by choosing the appropriate reaction condition.

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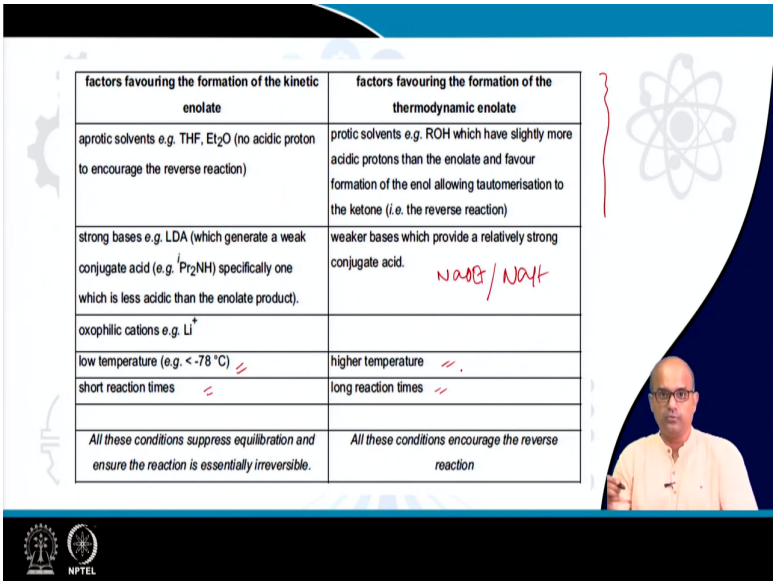

Last class we also discussed it. Now we can discuss in the tabular format. So, basically what happens? Strong bases, strong non nucleophilic bases like LDA or LHMDS basically does this kinetic enolization; weaker bases like sodium ethoxide or other bases like sodium hydride they form first thermodynamic enolate. You need a low temperature as you said you need a higher temperature; shorter reaction time longer reaction time. So, this will basically give you a proper idea.

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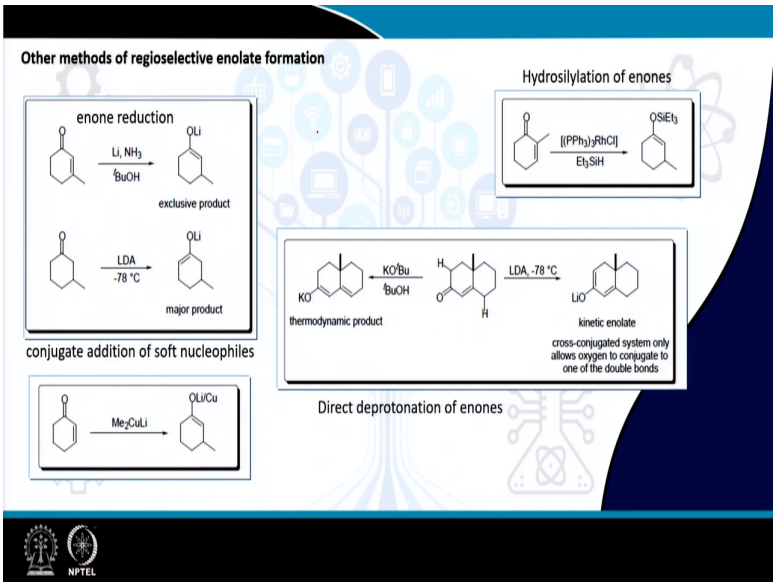

These are few examples where you can find that how different way you can generate the enolate. Last class we discussed it the first one is enone you can specifically reduce through a single electron way which is the Birch pathway and you can generate the enolate. You can generate enolates through alpha beta unsaturated ketone by a Michael addition hydrosilylation of enones also can be done through Wilkinson catalyst and a hydride donor triethylsilyl hydride ok.

And then this is basically a bicyclic enolate you can do a direct deprotonation by two different ways you can do a thermodynamic product thing where this gamma hydrogen can be abstracted. And you can see this is a highly stable product where oxygen also in the conjugation, but this one LDA that picks up this hydrogen where it is a conjugation, but it is not a direct conjugation it is a cross conjugation system. Because, oxygen can take part either in this way conjugation, but not in this way. So, it was not I mean it is not thermodynamically controlled product ok.

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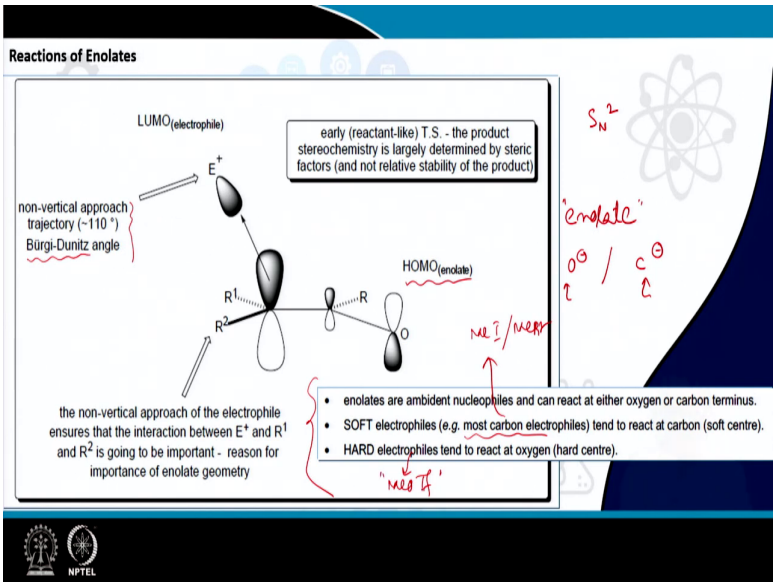

So, these are the different ways which probably we have discussed in the last class. The mode of reactivity of the enolate last class we talked about we said that usually the enolate reaction is kind of a S_N2 type reaction; where the carbon ion which have been generated that basically produce the enolate which is basically the homo of the enolate.

And then the electrophile in the standard S_N2 reaction where the electrophile LUMO is basically kindly approaching and then you will get a new sigma sigma bond and usually the trajectory through which it approaches it roughly follows this Burgi Dunitz trajectory which have been postulated by this two fellow through theoretical calculation as well as crystallography analysis.

And it found that this angle is close to the tetrahedral angle where this angle permits the most effective overlap between the incoming orbital. There is another factor normally the enolates as we said these are ambident nucleophile means that you do have an O minus as well as C minus center. So, O minus and C minus center and normally O minus is a very hard nucleophile site C minus is soft nucleophile site.

So, you can get an O alkylated product you can get a C alkylated product and you can basically explain those things that if you need a soft electrophile like most carbon electrophiles. What are those? Your methyl iodide methyl bromide ok is a soft electrophile and hard electrophiles are like Methyl-triflate. And this gives you an O alkylation. So, these things you can eventually try to get it.

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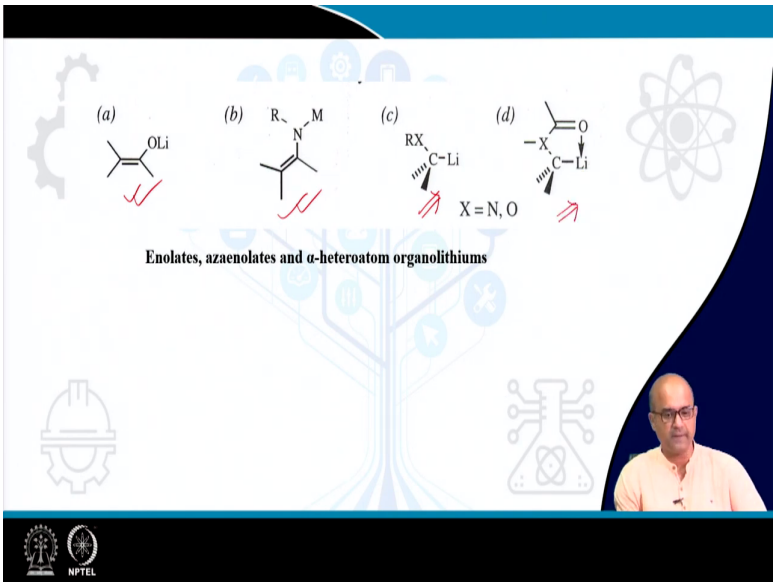

Last class we talked about enolates and different kind of azaenolates. So, this is a free metal lithium species or a carbanion lithium. This is an azaenolate this is normal enolate and if you have a coordinating group that can have an extra conjugation with like amide or other groups this can basically give you an extra stability through chelation ok.

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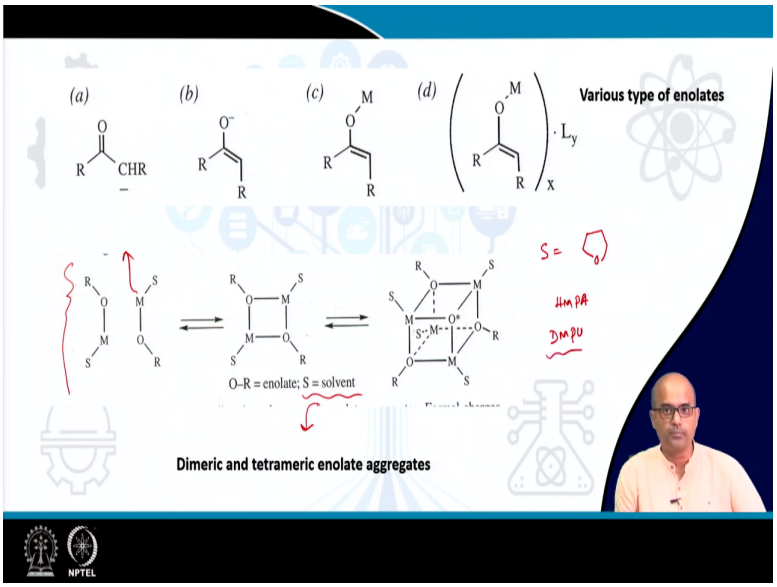

Now, we said that enolates are usually not a monomeric species ok. You can see that we last class we discussed that they could be a dimeric, they could be a different kind of supramolecular aggregates and with the solvent molecule they play a important role. So, this

is the metal center and this is your solvent molecule and this is your typical enolate ROM. And the solvent mainly or mostly is a different coordinating solvent like THF, last class we discussed then you have a HMPA and then we talked about DMPU the dimethyl propyl cyclic urea. So, this kind of solvents is usually you get a supramolecular aggregate.

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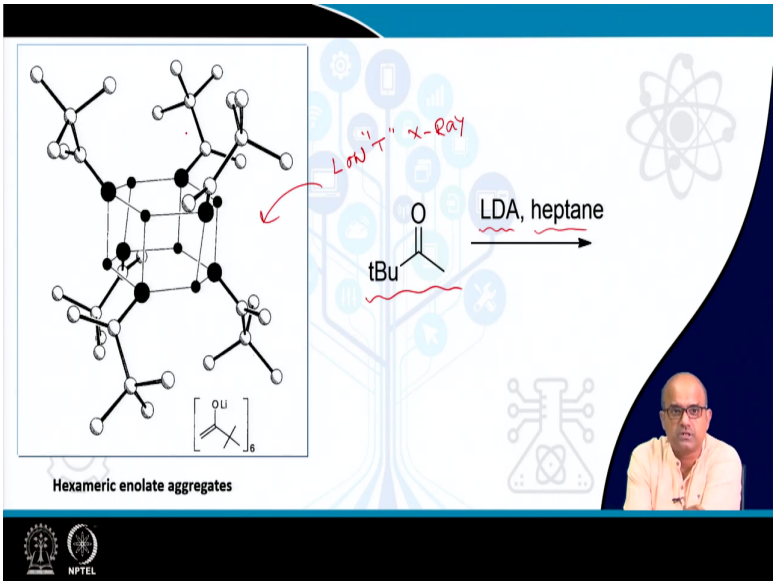

Now, this was taken from literature where you can find that if typically, tert butyl methyl ketone or a pinacolone, which you treat with base LDA in heptane solvent and was, found that this compounds usually forms a hexameric aggregate ok. This is a this is a this is a hexameric aggregate and normally this with this hexameric aggregate which have been proved by low temperature X-ray analysis. And you will find that this compound usually behaves in an aggregate structure supramolecular aggregate structure.

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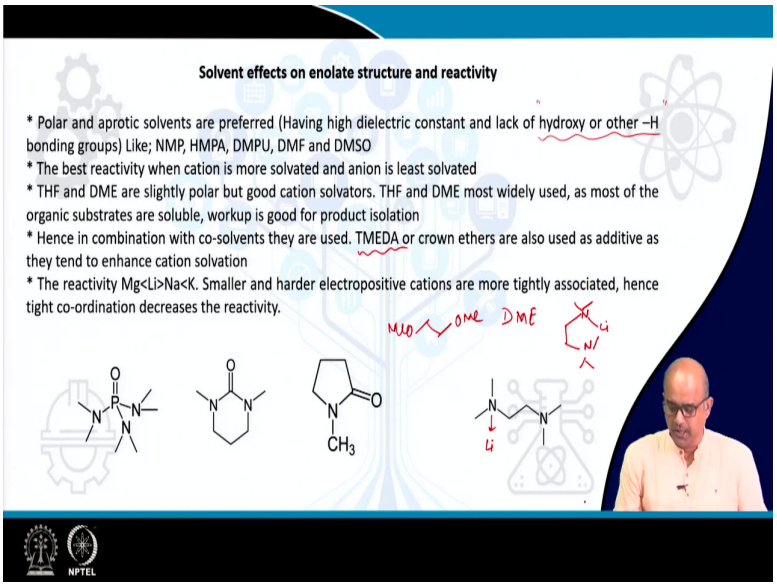

So, that gives you a clear cut idea solvent effect in the last class we already talked about we said that solvents like usually polar solvent, which is having a high dielectric constants and lack of any hydroxy or other group because if you have a hydroxy group you need an excess base.

And that can also give a protonation to the corresponding enolate bases like NMP, HMP, DMPU are preferred this is DMPU this is the NMP. The best reactivity of the cation is more solvated means that if your cation is solvated by the solvent. So, anion is naked or free. So, those cases you get an extended reactivity for those enolate.

THF and DME, dimethoxy ethane are slightly polar dimethoxy ethane means basically you have this structure OMe, DME this is also good cation solvator ok and sometimes you can use extra coordinating aging like tetramethylethylenediamine.

Now, this nitrogen can eventually give you extra coordination and usually it happens that you get a cyclic time kind of coordination with these things. So, these compounds often help for cation solvating agent. There is certain reactivity for the metal enolate the metal counterpart, but we are not going to discuss it because this does not be not that much useful for our purpose.

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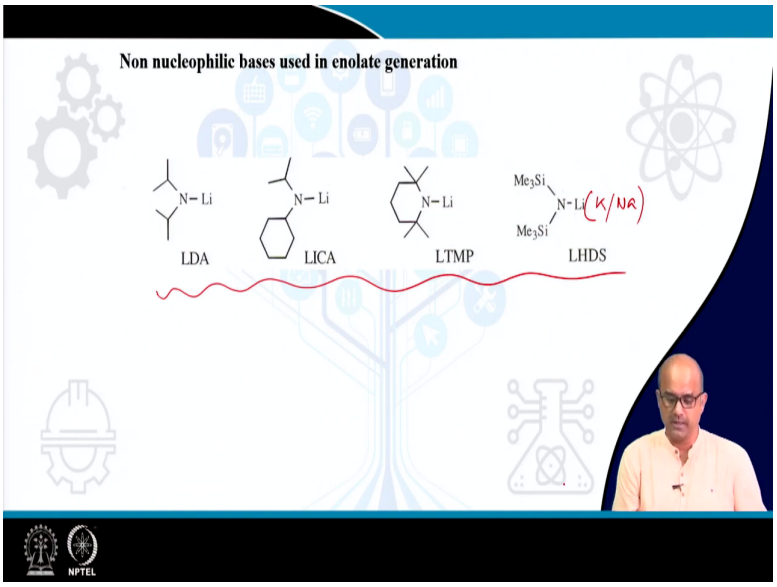

The bases we said a series of non-nucleophilic bases you can use LDA is the most preferably used, LICA means lithium isopropylcyclohexylamide. LTMP is this base LHDS all and you can replace l with other bases like potassium or sodium. So, these bases are usually pretty good and non-nucleophilic sterically bulky bases.

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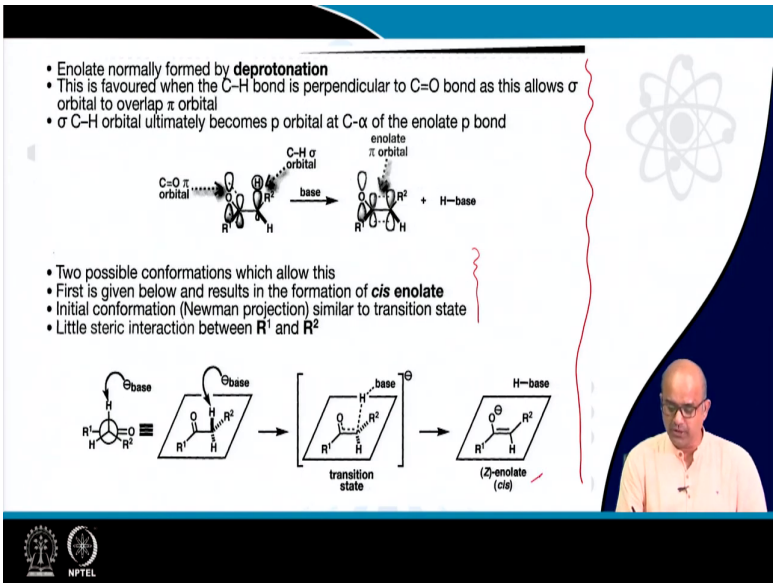

We also said the stereochemistry of the entire hydrogen abstraction we usually said that in the deprotonation step when the CH bond, CH bond of the adjacent alpha hydrogen is perpendicular to the corresponding C double bond O bond. The deprotonation must be

effectively very good and in terms of molecular orbital we have also explained you can eventually try to draw the Newman presentation way and you will find that there would be existing two transition states one will lead to Z enolate.

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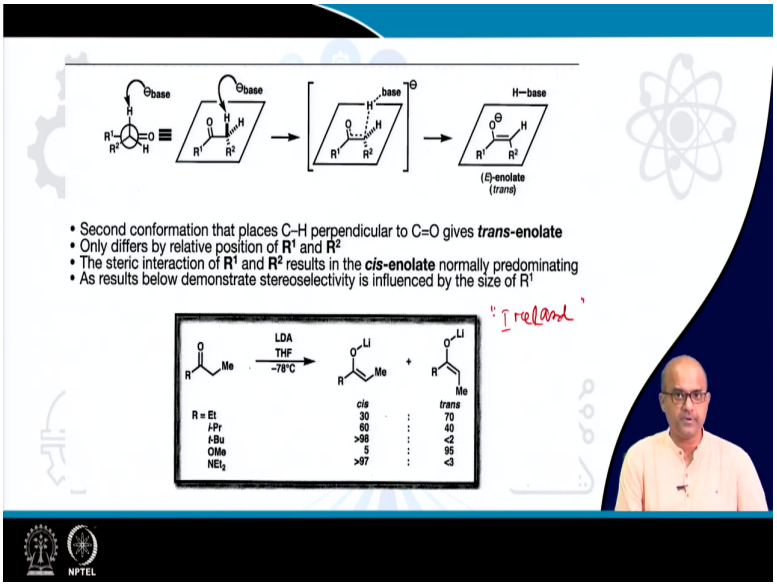

And another will lead to *E* enolate and you have an effective model which can be explained little bit later on or we already talked about this Ireland model. In the Ireland model we have already explained that in the Ireland model you can actually predict like this model.

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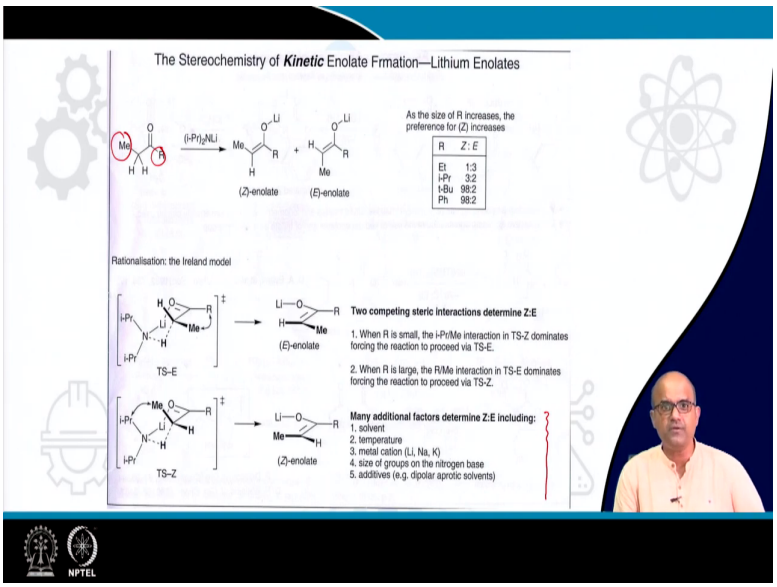

You can actually predict that based on the substitution pattern of this corresponding carbonyl group *Z* or *E* enolate specifically their ratio can be controlled. Usually it goes through a six-member cyclic transition states and you will find that there are two competing interaction. The competing interactions are normally a one two eclipsed kind of interaction in another case this is a one three diaxial interaction.

And these interactions are normally arisen due to a closed chair six-member chair formation things ok. And this *Z* and *E* stereo chemistry you can eventually predict through the Ireland model which is an experimentally validated in some cases and most of the cases it works pretty well.

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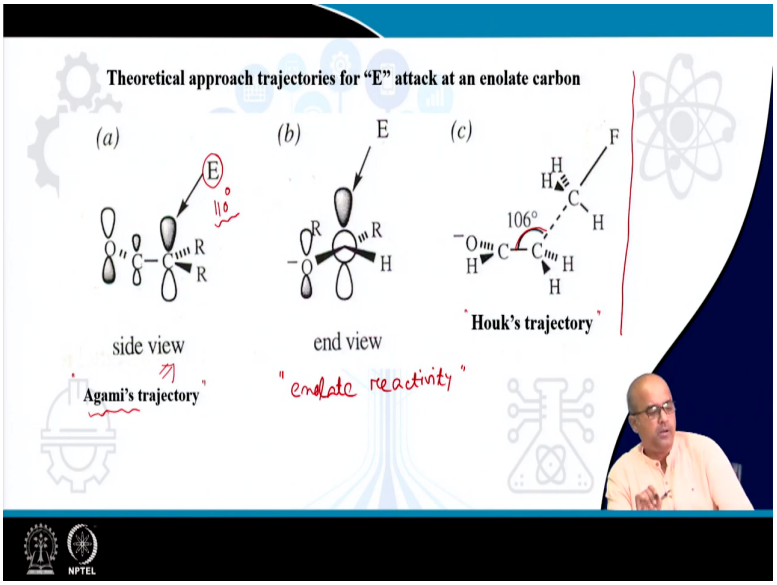

Now, coming to the focal point of our discussion that once this enolate has been generated how this enolates will react with different electrophile and you can make a new carbon carbon bond forming reaction, we call it enolate reactivity. And few minutes ago we said that enolate enolate alkylation is nothing but a similar kind of S_N2 type reaction.

And usually there are two well defined hypothesis have been proposed by two different scientist. The first one is Agami's trajectory which is postulated by French scientist Agami, but anyways this we just try to give you normal idea we are not going to discuss about in detail. In Agami's trajectory is similar like that it basically follows a follows a trajectory when you have this generate this enolate.

So, this enolate HOMO was approached by the LUMO of the electrophile ok now this approach should be very close to the tetrahedral angle of the hybridization which we earlier said that is close to Burgi Dunitz trajectory it is close to 110 degree angle. So, this angle basically was estimated based on a couple of theoretical calculation and this approach through this angle gives the maximum amount of overlap.

So, this was the trajectory where through electrophile approaches. This you can eventually try to draw a Newman presentation formula for the similar transition states. Later on Houk's also K N Houk from university of California los Angeles he actually also predicted a similar kind of theory where he said that usually a similar kind of angle close to 110 which is very again close to the tetrahedral bond angle. This angle Houk proposed, that 106 degrees. So, in both the cases the angle was closely associated with the tetrahedral bond angle.

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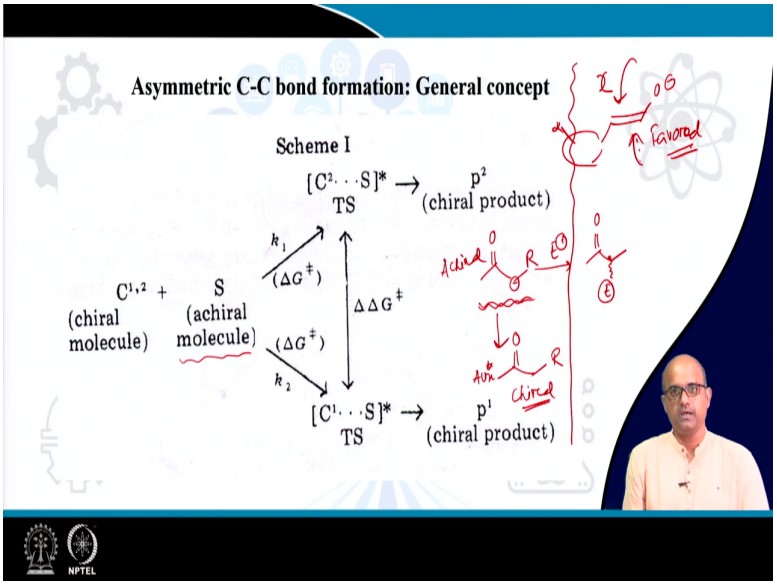

Now, in the main concept in the asymmetric alkylation what we are trying to say you basically have an enolate species or a carbanion species and you are trying to attack or trying to react with an electrophile and what you will get? You will be basically you will get a new carbon electrophile bond. Now the moment you create a carbon electrophile bond you are eventually trying to create a new stereogenic center here ok.

Now this stereogenic center so, initial the enolate was achiral species. Now how you can generate or how you can conceptualize that how you can create new stereo center with

absolute stereo control. The idea was first you take achiral molecule which is our carbonyl compound.

Somehow you create a chiral atmosphere around the achiral molecule either through covalent attachment with some small organic molecule, which you called chiral auxiliary we will explain it later on the moment you first create achiral compound and then somehow you create a chiral atmosphere somewhere here. So, initial achiral molecule is this and then this molecule you are trying to have a covalent attachment through something.

And now the existing chirality or pre existing chirality in the auxiliary will now basically detect that the moment you generate the enolate it gives you a flat sp^2 trigonal face, mean sp^2 is trigonal which is the planar basically. Now, you will be having a two different approach as this is the planar phase planar pi enolate face and you do have a something a chiral attachment here or stereo chemistry. Now, one of this face might be sterically then non accessible and this face or the bottom face might be favorable.

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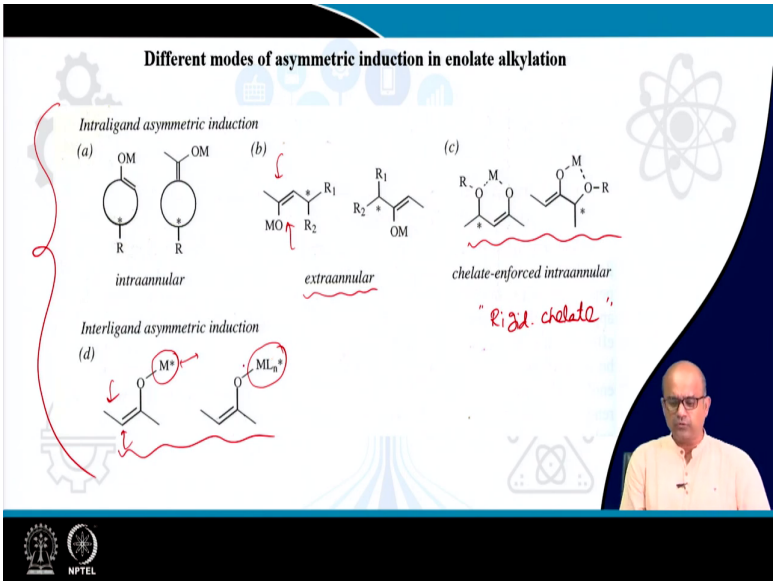

So, in this way you can actually controls the enolate alkylation. There are different factors which will be discussed little bit later on mostly we can categorize this three or four different points and once you generate the enolate, if in the substrates you have a pre existing stereo center that basically controls the incoming electrophilic approach and you can create or you can modulate the new stereo center, which is called intra annular means within the ring is called cyclic stereo control.

Extra annular means you have an acyclic stereo control. The enolate usually contains some pre-existing stereo center in the molecule where absolute configuration is fixed. Now definitely as I said just now the electrophile can approach from this phase or from this phase and this stereo center will now dictate from which phase it attacks. Sometimes it happens that enolate contains a coordinating group where it can make a cyclic chelate which is a rigid cyclic compound means rigid chelate.

Now this kind of rigid chelate was effectively very good in controlling the stereo selectivity of the incoming electrophile. And sometimes the fourth point you have a metal which is coordinating with the enolate. Now, this metal you can create a chiral atmosphere or you can put a ligand which is chiral in nature.

So, basically the essential the enolate you are trying to put a chiral metal species on the enolate or you associated a metal which is a having a chiral ligand in its periphery. So, in those cases also now the electrophile when it attacks it can be controlled by this chirality element in the metal as well as the ligand associated in the metal.

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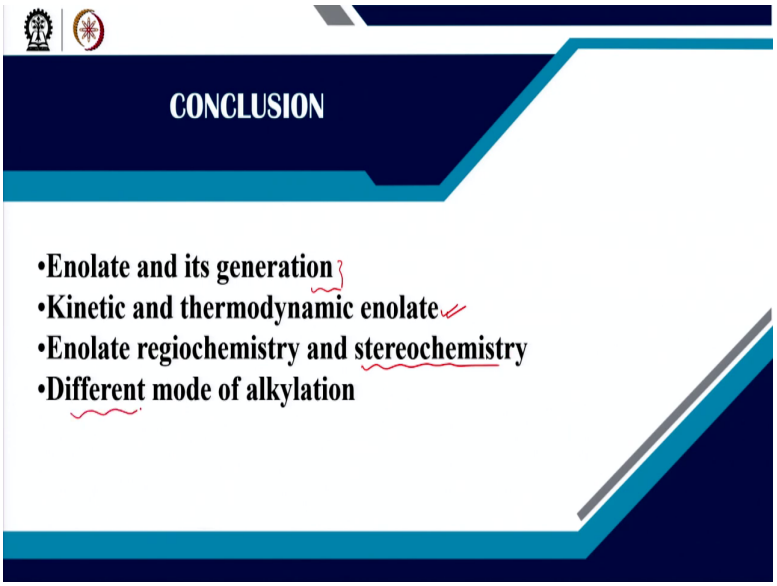

So, roughly this three or four different approaches, we will be we will be discussing in our subsequent classes. So, as a concluding remark today basically we have revisited the entire concept of enolates and its generation. We talked about couple of pKa values for different compounds.

We also again revisited the concept of kinetics and thermodynamic enolate generation and how you can control it and mainly we talked about stereoselectivity of enolate generation mainly the Ireland concept we have revisited. And particularly different mode of alkylation we also talked about and this gives you a better idea that how you can control the entire process of alkylation. Thank you. We will see you in the next class with the remaining topics.

Thank you once again.