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 - 02
Enolate alkylation of several carbonyl species
Lecture - 06
Substrate directed stereocontrol in acyclic and cyclic system

Welcome back students. So, today we will be talking about mainly the next module which is module 2 and we specifically discussed Enolate Alkylation of several carbonyl species. And particularly in this module our first lecture is lecture 6 where we will be mainly talking about Substrate directed stereocontrol in acyclic and cyclic system, will be mainly explaining through normal chalk and talk mode or drawing mode.

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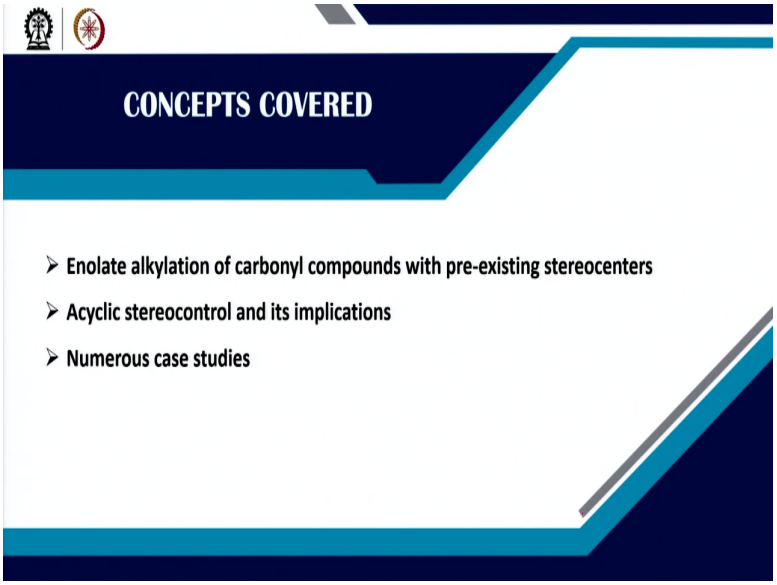

So, what are the concepts we are going to cover today in this lecture? So, we will be mainly talking about enolate alkylation of different carbonyl compounds with pre-existing stereocenter. I am talking about cyclic and stereocontrol cyclic and acyclic stereocontrol and numerous case studies will be mainly talking about.

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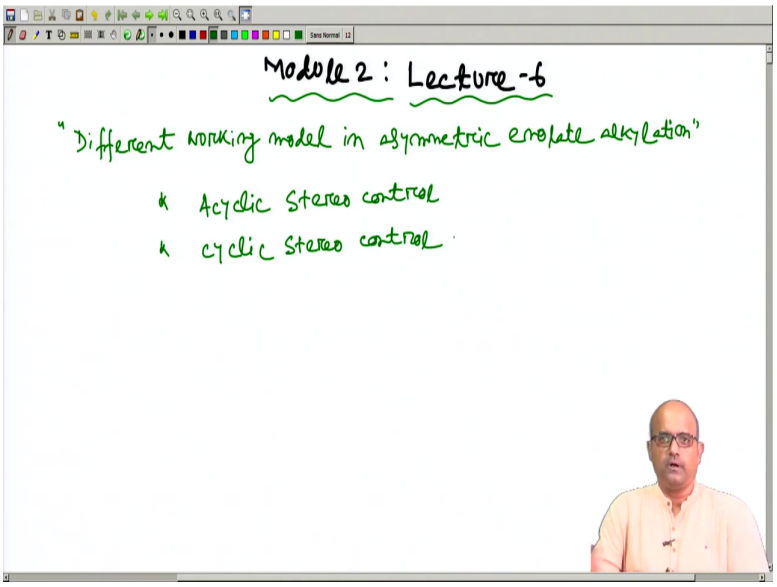

Welcome back students. So, today we will be mainly discussing the next module which is module 2 and I will be talking about lecture 6. And today we will be mainly discussing different working model and we will be mainly using today standard writing technique through a board, different working model in asymmetric stereocontrol or in asymmetric enolate alkylation. Now last class we have discussed that how you can think about controlling the newly generated stereocenter in an enolate alkylation.

There are actually two working models. The first one we called it acyclic stereocontrol and mostly today we will be trying to talk about acyclic stereocontrol and subsequently we have another model which is called cyclic stereocontrol ok. Now, how it works? So, let first start with the acyclic stereocontrol. We will start with the acyclic stereocontrol.

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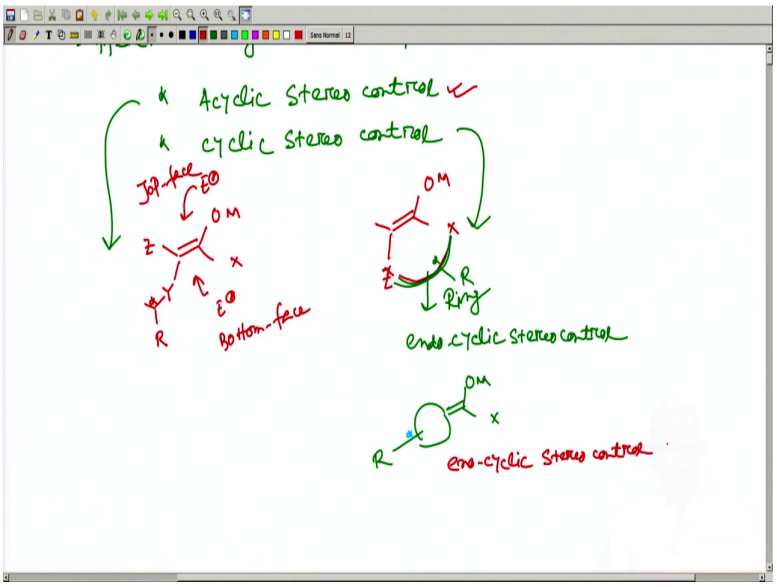

Now, acyclic stereocontrol means that you basically have a typical enolate. Let us say you have an enolate. You have different groups Z and Y and then you will find that particularly you have an extra connectivity here with a carbon-carbon bond and you have a stereocenter here.

Now, if you have a stereocenter here means that this stereocenter can direct when an incoming electrophile can approach the trigonal face of the π- enolate. So, this was mainly the main factor. Now, it could be approaching from the top face, which we can call the beta face; top face or you can call it as a bottom face or the below face. So, these things will be mainly dictated by the pre-existing stereo center.

Now, this is a pure case of acyclic stereocontrol. Sometimes things are bit different. Let us say you have a similar kind of enolate OM X, you have; now this with this X and Z, you X and Y or X and Z you have a cyclic formation. Now, this basically it is a cyclic thing, a cycle or an annule or ring structure. Now, in this ring in this ring you might have a pre-existing functional group with a stereocenter.

So, this one is the first one you can fall in the category of acyclic stereocontrol and the second one you can fall in the category of cyclic stereocontrol. So, we will be trying to discuss both the things in detail and in the cyclic stereocontrol there are two different way, in the way we just now drawn. Its endocyclic stereocontrol means, the olefin unsaturation of the enolate, it is within the ring.

And sometimes it may happen that your enolate it is formed outside the ring, so this is a ring and you have a pre-existing stereocenter. See and in this cases we will be calling this kind of stereocontrol as an exocyclic as the enolate is exocyclic. So, this two working model are existing for the cyclic system and acyclic one you have this thing.

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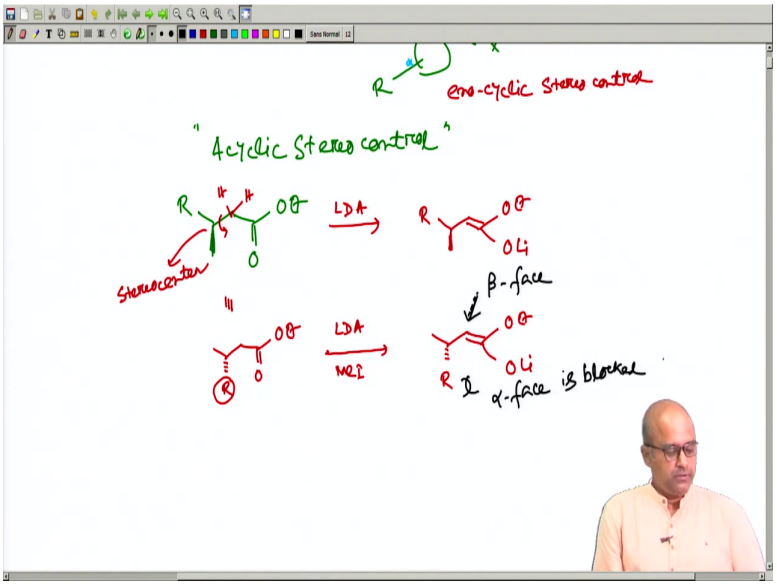

Now, first let us start with the acyclic stereocontrol. The acyclic stereocontrol as we talked about in the acyclic stereocontrol, we will first try to give you a very well known example of a system where you check a compound whose structure is this. Now it means that you do have an acidic hydrogen which you want to abstract by base.

And you do have a pre-existing stereocenter, this is your pre-existing stereocenter. So, this stereocenter should control the newly generated asymmetric center. So, first you treat with base, similar base like LDA which is the most preferred base. The stereocenter does not change at all and you definitely have enolates either Z or E, both the enolates are probably fine.

Now see the moment you try to generate the enolate, you have to think about that this compound you can write in a different way as carbon-carbon single bond rotation is free, because this is very dynamic. So, now, say this compound you can write in this way, both the compounds are same because their absolute configuration is same. R, I did not specify, but the nature of R is very important.

Now, the bulkier the R is now what we are trying to do? You do add a base similar base and you add a electrophile like methyl iodide. Now, it basically means that your stereocontrolling group is blocks the below face of the enolate ok. Now, whatever electrophile is there will try to always attack from the top face or beta face. So, alpha face attack is usually blocked by this bulky group. So, alpha face is blocked.

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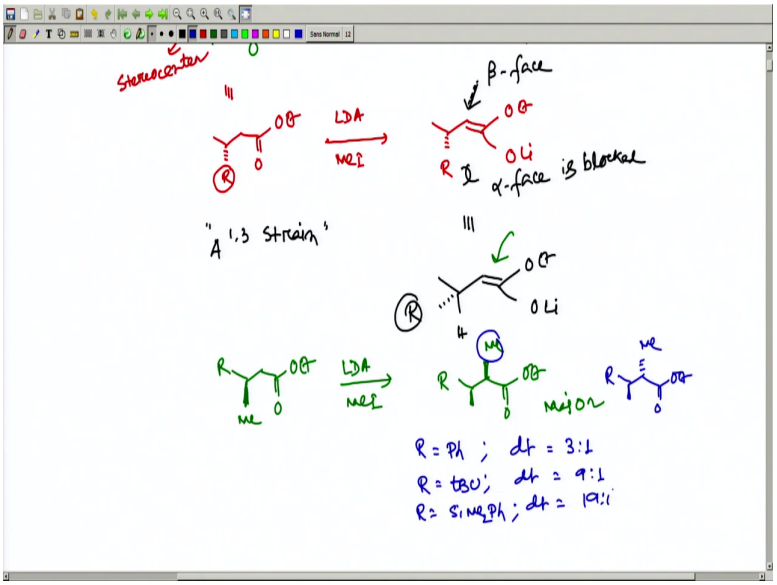

Now, this you can also explain in a different way with a little bit of another factor, which is a very well known factor which is called allylic 1, 3 strain. Now allylic 1, 3 strain, actually dictates the entire thing. If you are not familiar with allylic 1, 3 strain just go through the allylic 1, 3 strain.

Allylic 1, 3 strain basically means that once you have allylic system something like this and then you try to draw the same compounds in other way means you try to put this as an allylic π double bond and try to put the hydrogen here in the same plane. So, this everything the CH and this allylic plane writes or resides in a plane and now eventually you can eventually try to put this bulky group R here, by keeping the absolute configuration same.

Now, this is the now your controlling element to combine the electrophile. So, in this case it has been found that now we will try to write the obtained asymmetric induction. So, in if you starting material is this which was given to you, you do have a R here, R I am not specifying, this is methyl.

You react with LDA and methyl iodide, your product which you are going to get it is this compound as a major one. Because just now we explained the electrophile which is the methyl one will always attack from the beta face. Now, let us count the steric parameter of different group. If R equal to simple phenyl, the diastereomeric excess was good, it is simple like 3 is to 1, means this is the major product and the minor product which will be formed it is the other way means this methyl will be below ok, 3 is to 1.

You put a bulky group like tert butyl, the diastereometr ratio seems to be again good 9 is to 1. Further bulky group and in this case if you have a silicon containing group dimethyl phenyl silyl, the diastereomeric ratio seems to be 19 is to 1. So, this is a pure acyclic stereocontrol.

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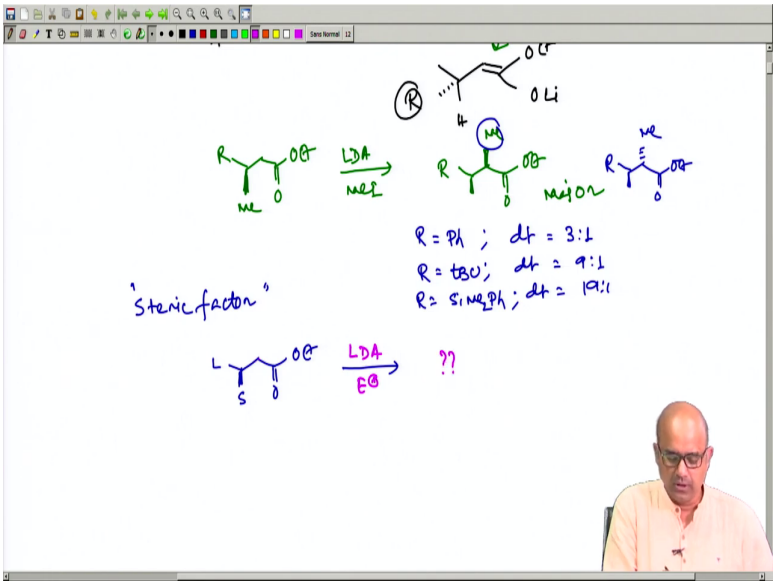

And this stereocontrol can be explained by a steric factor, it is a purely steric factor in the alkylation mode. So, one of the face of the enolate is more accessible, one of the face is less accessible and that is quite evident from different factor. So, in general you can eventually try to write such a compound by putting a different functional group here. You can try to put a small group and you can try to put a large group.

And you can put a working model and you can just explain that how this reactivity differs, E stands for electrophile you can put the working model. So, this working model should work fine for you.

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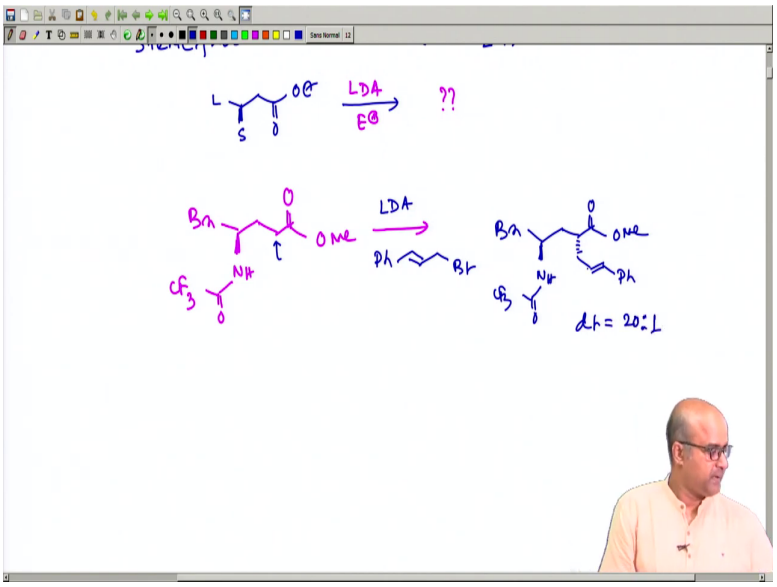

Similar acyclic stereocontrol there are few examples. We will just quickly talk about some of the example. One of the nice example was this system where a NH containing group was act as a main factor, but this in this compound the stereocenter was little bit apart. This is basically a three carbon apart.

So, what you do? You take this compound, treat with a non-nucleophilic base and basically generate an enolate and then you treat with electrophile which is a cinnamyl bromide. You will find that this is the enolate generating carbon. You have a new carbon-carbon bond formation here. Now this NH, which is blocks the beta face by a sterically bulky kind of group and then you will find that the pure steric directed approach.

And your new carbon-carbon bond formation will be taking place through the opposite way of the existing stereocenter, which was you can eventually try to get this compound. So, I think yeah this is the compound you will get. So, diastereomeric ratio was which was usually obtained is 20 is to 1 for the major compound. Such a good stereocontrol can be explained only through acyclic stereocontrol.

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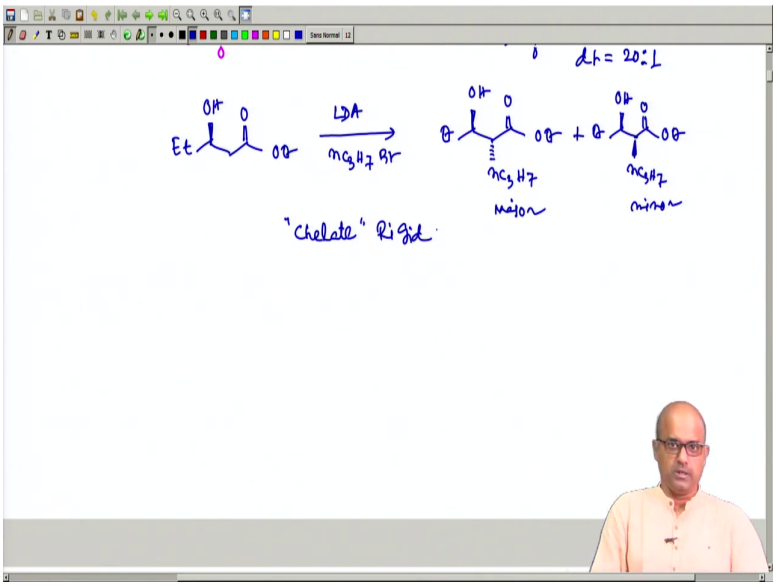

Next let us talk about a little bit of other issues, where one has to consider different aspects. We will take a hydroxy acid or hydroxy ester something like this. Now, this particular compound if I use a base like LDA and an electrophile like say nC3H7Br. The observe diastereoselectivity was found pretty good and you can see that the main or major product which was obtained was having this absolute configuration.

The other product which is the minor one or the other diastereoisomer will be having very less ratio. So, how you can explain these things? Because in this case you would not find the steady factor is definitely a matter, but the hydroxy group is there. So, hydroxy group might be playing some role. Remember in the when you talked about the model we said sometimes if you have a chelating group you may formed a chelate rigid chelate.

Now, this kind of rigid chelate also gives you a clear cut stereocontrol. Now, continuing to that next page we will be discussing the thing.

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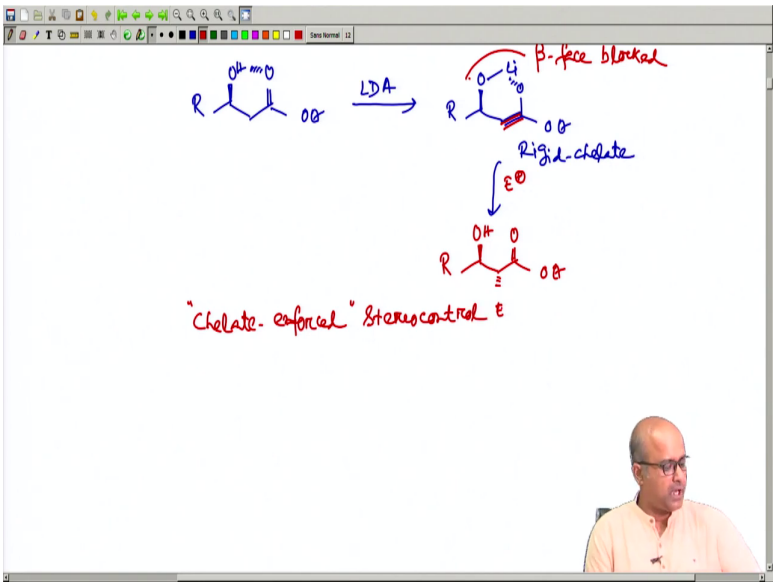

So, let us talk about something like this. You put a general terminology R…….. O and then we will find that the very beginning when you have something like this. And the starting compound you might have an intramolecular hydrogen bonding for the chelate, fine. So, simply treat with a base and that eventually replaces the hydrogen with a lithium and you now see this kind of enolate formation is be there.

So, this rigid chelate was the main factor in predicting the stereoselectivity. Now, in this rigid chelate you see that as that rigid chelate with oxygen basically blocks the beta face of the enolate. So, enolate is this face and your entire chelate. So, the beta face was blocked, beta face is blocked.

As the beta face is blocked you can eventually found that alpha face is the only accessible face. And now you react with the electrophile and you will find that electrophile will simply approaching from the opposite face of the enolate. And you will get this one as a major product. You can eventually try to explain the drawing through a different perspective also, but eventually this will serve your normal purpose.

So, for hydroxy acid or this kind of hydroxy ester you can find that this chelate enforced and this is you can call it chelate enforced stereocontrol and such stereocontrol was pretty good and you can explain or you can have a predictable amount of selectivity for a series of compound.

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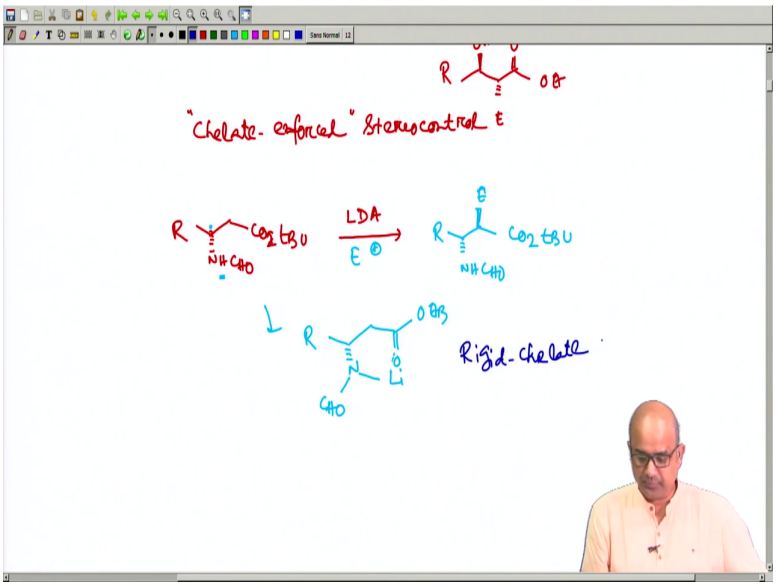

But it is not only limited to the oxygen containing compound, other compound also gives you a similar kind of control if you have a like nitrogen containing compound like NHCHO and you may have this kind of ester CO, sorry it is a CO2 tertiary butyl and then in this case you have a another R group, just a general thing.

And in this case also you will find that this NHCHO might be having a typical role. You treat with a base and as this will be blocking the alpha face because the stereocenter here where this nitrogen is pointing towards below the plane ok. So, then you add your electrophile and you will find that the incoming electrophile will be approaching from the opposite face of the this.

Now, how you can draw the chelate? The chelate you can basically you have to draw it. You can let me try to just do a very simplification of drawing. You write this NH kind of thing. But initially this hydrogen seems to be acidic, so you can eventually try to write this NLi. Because this is adjacent to the carbonyl group and fine then you have this C double bond O with O tertiary butyl. So, you basically have this chelate.

So, it is a 1 2 3 4 5 6, six membered chelate. And you can now eventually fix the rigid chelate. So, with this rigid chelate your electrophile seems to be pretty much approaching the normal thing. So, these two are the example of typical rigid chelate formation in the acyclic mode. Acyclic mode, acyclic stereocontrol mainly governed by this steric parameter in the existing pre-existing stereocenter.

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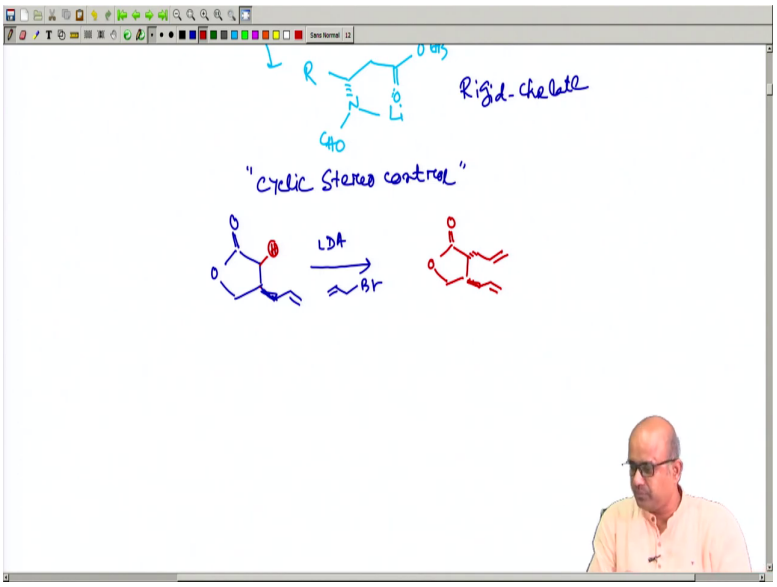

But on the contrary the cyclic stereocontrol seems to be pretty well defined because cyclic system as all of us know have a well defined conformational bias ok. Now, we will be quickly talking about few cyclic system, which we just now; let us talk about a typical cyclic system which is having this kind of structure.

Now this is a five membered lactone or butyrolactone is already having a pre-existing chiral center which is beta allyl group. You treat with a base LDA and then you treat with another electrophile which is another allyl bromide and it is very easy to predict as the parent compound the allyl group is beta. So, this is the beta 1.

So, in this case it will be alpha 1 because here you will be abstracting this hydrogen to generate the enolate and the so, cyclic stereocontrol is much more easy to predict than the acyclic one, because cyclic system has a well defined conformational bias.

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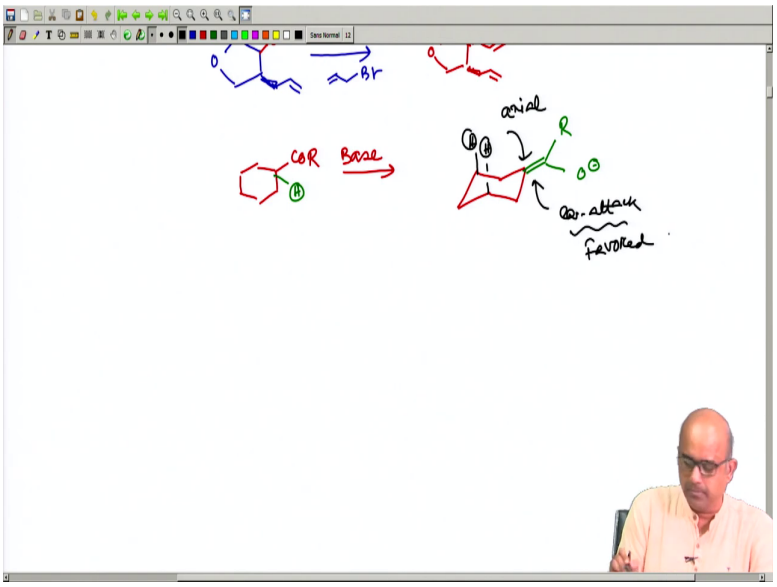

Now, things will be little bit simple if you take a cyclohexanone system, let us take a cyclohexanone system something like this. Now, cyclohexanone system as all of us know cyclohexanone if you try to generate an enolate by abstracting the hydrogen which is here which is this hydrogen ok.

Now, this hydrogen if you abstract you usually get this kind of exocyclic enolate ok. Now this exocylic enolate there are two ways the electrophile can approach. The first one is this way through the axial approach and this one is the equatorial attack. Now as all of us know during the axial attack, it actually faces several interactions which is non-stabilizing interaction.

Mainly the interaction is caused by this, 1, 3 diaxial group. The angle is definitely the typical Burgi-Dunitz trajectory or the Agami trajectory. in the equatorial attack somehow you do not get that those kind of steric bias. So, equatorial attack is usually favored in a normal system that was the way you can explain it.

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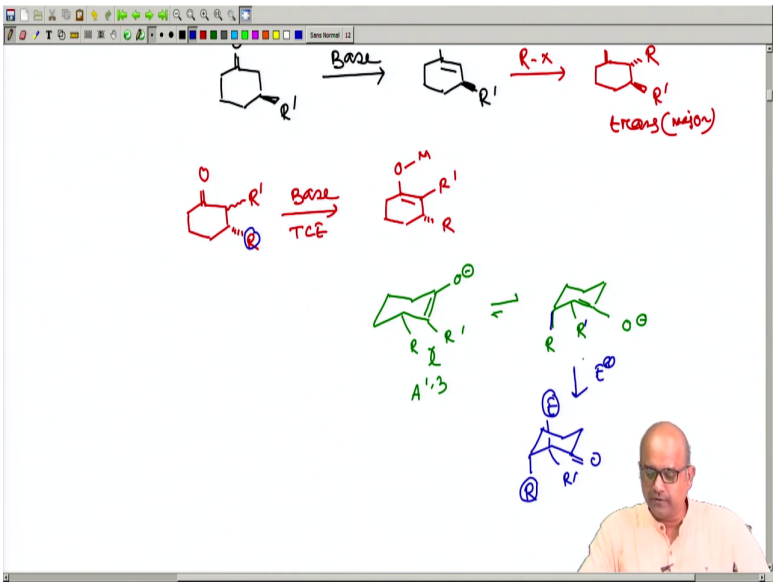

So, by predicting similar kind of working model you can eventually try to explain a couple of things, which we will be next just try to give you a discussion. Let us talk about you have a simple cyclic (Refer Time: 23:48), but the three position you have a methyl group or a R prime group. Now, this is very easy to a predict this kind of system.

Because this kind of system usually you will find that the moment you generate the enolate you have a base. we would not draw in much complex way. We will be simplifying in a two dimensional way and find that this is the main thing. Now, R prime is already blocking the beta face.

So, what you will be having? You will be simply having this R prime and now your electrophile is a R x. So, you will find that this will be typically 1, 2 anti or trans. So, this product is major. And this was basically a three substituted cyclohexanone. You can easily predict a series of compounds and most of the cases these compounds are very well defined. The thing will be somewhat complicated if you let us say have a compound something like this.

You have a pre-existing stereocenter at the three position ok and also you have a stereocenter here. But this stereocenter does not make any sense because at the very beginning you are trying to destroy the stereocenter through hydrogen abstraction through a thermodynamically controlled enolate generation. So, you do a TCE ok this is R existing is a alpha stereocenter. So, you generate O with a metal is and R prime.

Now this compound, you can eventually try to draw the two different way. So, first one you try to draw this way. So, this way means you have this enolate O minus and you try to have this R prime. And as this one is below, so it is kind of equatorial R ok. And now here this drawing means that if these two groups are pretty bulky they will have a severe one two eclipsed interaction or which is close to a allylic ones strain ok. So, this is usually not very much recommended.

So, this molecule usually trying to adopt a conformational switching, where this R group tries to have a pseudo axial position and then your enolate kind of thing will be having this and having this. So, this might be little bit a preferred geometry and you try to have this one and then this moment once you try to give it, the axial attack will actually have preferred.

So, finally, what you will get? You will treat with an electrophile. So, usually you get this. You get a; this is already there. You have R, this is basically the R prime. You have this R prime, you have this R and this electrophile now comes here. So, usually what we are trying to say that this R these R this R and the electrophile seems to be anti to each other seems to be anti to each other. So, this is well this can be well explained through this kind of pathway.

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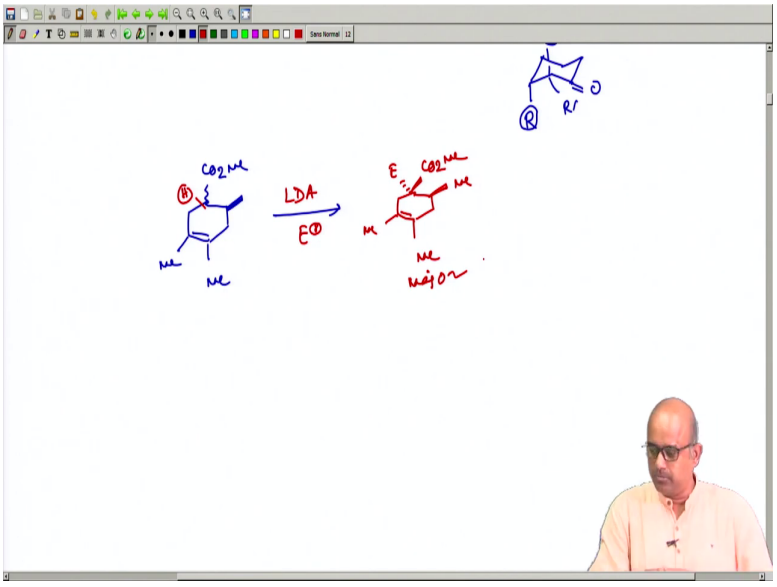

Few other systems like if you have a pre-existing stereocenter in the molecule, but also you have a double bond. But the enolate you which will be generating it is not a endocyclic, you can have exocyclic enolate generation. Now see here, if you abstract this hydrogen, this

enolate will be generating in the exocyclic of the ring. Now you treat with a LDA and let us say you treat a electrophile.

So, what product you will be expecting as a major one? It is very simple. The existing stereocenter is beta ok. So, the electrophile will be alpha just opposite to the existing stereocenter. So, you will eventually end up with this one as a major product. So, this kind of predictive stereochemistry was very much well explained and you can explain it.

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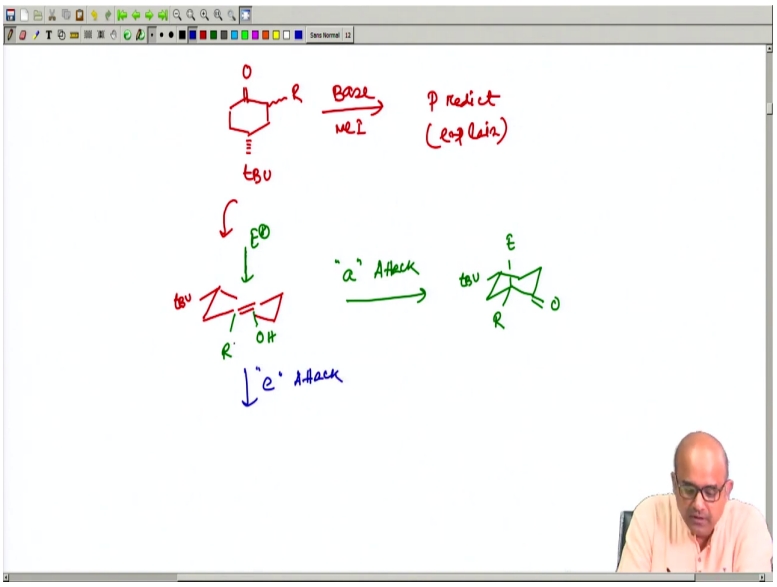

The next slide we will be trying to talk about or you can give you a assignment probably. Let us say you have a compound where you do have a tertiary butyl group in the four position ok. And you have a stereocenter here, but that does not matter because anyway you are going to destroy the stereocenter. You take base as a LDA and you react with methyl iodide. You predict the product. You have to predict it and explain. Mainly you have to explain it.

So, this has to do with the existing stereocenter in the final product. Now for this actually if you are not familiar with this to explain it, you need to do little bit of tweaking. So, first let us try to draw the enolate geometry once you do it. Now, this enolate geometry we will now be drawing in the half chair form because cyclohexane is a half chair.

Now, tertiary butyl; tertiary butyl is a below, so it tertiary butyl is a pseudo equatorial position ok. And your enolate; we will be drawing in a different color is a OLi or you can write OH ok, whatever it is does not matter. This R is now part of this thing, so this is basically one of

the way. Now, flat enolate; now, electrophile can be attack from the top face. If it attacks from the top face, so, which basically means that an axial attack, a axial attack.

Now, this axial attack, which will eventually lead to a parent chair form of the cyclic alkanone. So, four position is the tertiary butyl which is always equatorial and now see axial attack means your electrophile now becomes the axial and this is the R group; so this you get one product. Now, here you might say that I will be having an equatorial attack which might be also operating. Now for this equatorial attack means, it has to be attacked from this way.

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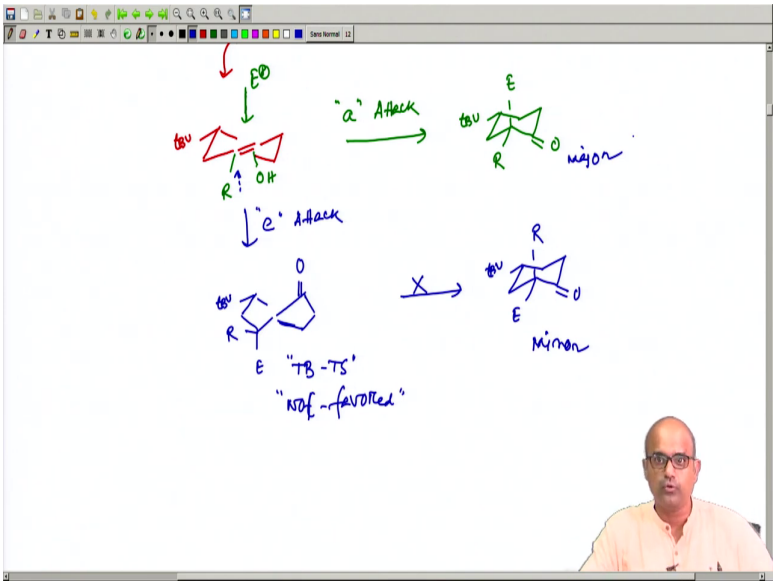

Now, for the equatorial attack we will draw the transition states in a different way and the moment it attacks moment it the it basically will have to be go through a twist boat type transition state. And this twist boat like transition state what usually this is your tert butyl which is the pseudo equatorial in the twist boat because now this you see the electrophile is here and your R is here.

So, tert butyl and electrophile are cis in nature and your ketone is here. So, now, this twist boat TS was energetically not very favorable, it is not very favorable. So, not favored, because twist boat is very strained in nature. So, now, if this has to be the approach, what we will get as a main product?

Now, the main product you will be getting that tert butyl and your electrophile is in the cis and you get this one as a major product. But usually as this is not favored, so this pathway

would not be operated and if somehow you get this product that should be a minor one ok and this will be the major product. So, a series of cyclic stereocontrol we have actually explained.

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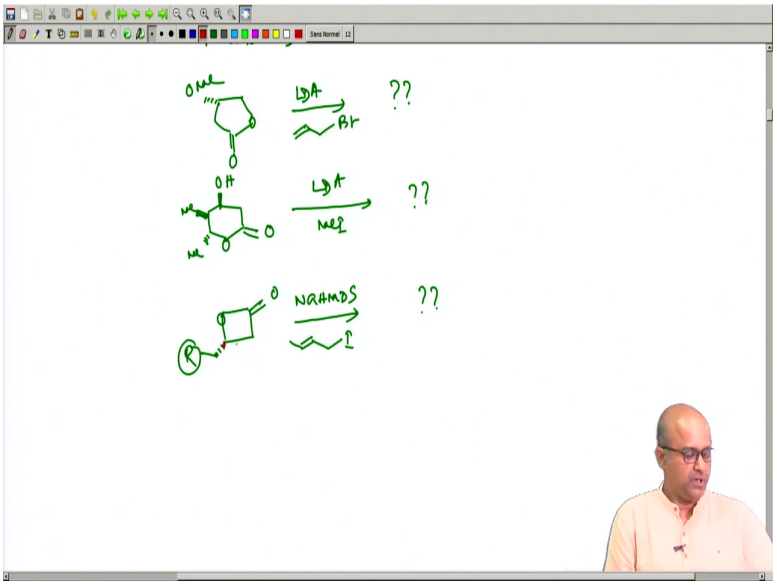

And actually we will find that there are few examples which probably I can try to provide you few assignments or take home problems which you can just solve in your extra time. So, let us try to be a little bit faster. You have a butyrolactone and you just try to take it as a OMe group, treat with a base LDA and treat with allyl bromide, so predict the product. This could be a simple one.

Thus next one is basically a delta lactone where you have couple of stereocenter present, this OH, this methyl, there is another methyl. Now, interesting point is both the methyl are trans to each other. So, LDA and then you treat with methyl iodide. You predict the product with the stereochemistry.

Now, you can eventually try to find out that the two groups are beta, one group is alpha. So, more the effect of the beta group is prominent here. Definitely you have to think in that way. The last example, which we will be talking about a cyclobutanone or cyclic lactone, which is a four membered lactone, a beta lactone and here you do have a pretty bulky group.

I do not specifically mention the group because there is no point of discussing that one. But if you use a base like NaHMDS and then you use a electrophile like crotyl iodide, you can

predict it. Simple one to induction because this is alpha, so, electrophile has to be beta. So, anyway we will be trying to talk about more things in the next week.

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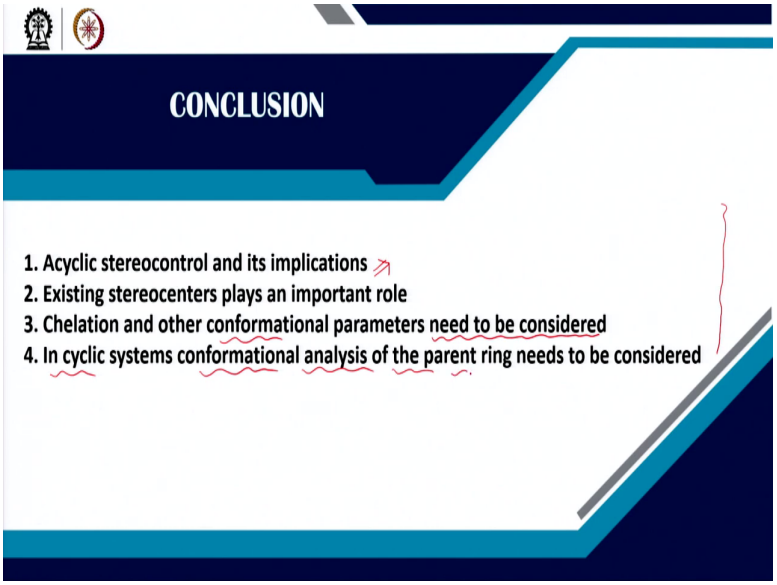

So, as a concluding remark, after this half an hour or so discussion what we can conclude? We can say that we have talked about or discussed about acyclic stereocontrol in some acyclic carbonyl system, where pre-existing stereocenters plays very important role.

Chelation which forms a rigid chelate and other conformational parameters need to be considered when you are going to predict the absolute stereocontrol in the final product. And mainly in cyclic system, the conformational analysis plays a very important role, because cyclic system you always do have a conformational bias because the rings having a typical tendency to adopt a well defined conformational structures, ok.

So, we will be trying to talking about related things in the subsequent lectures. Till then have a good time, good bye.