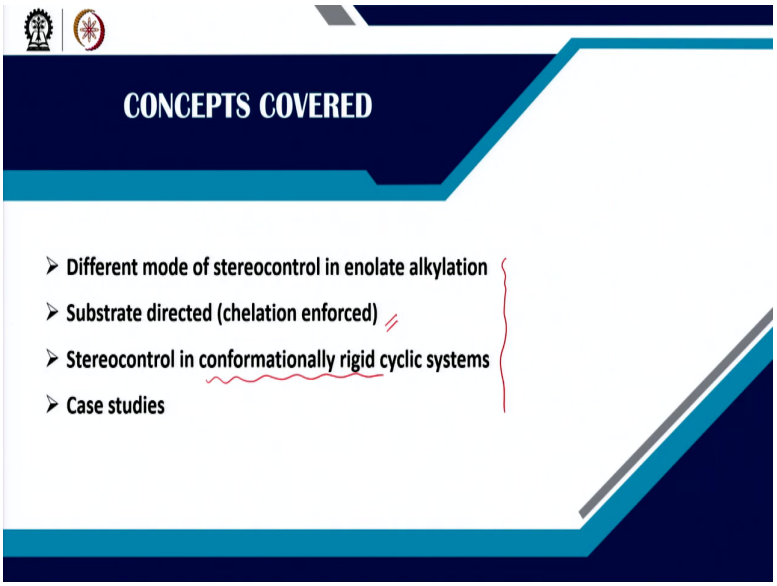
Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3 - sp3) bonds in asymmetric fashion

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

Module - 02
Enolate Alkylation
Lecture - 07
Substrate directed enolate alkylation in bicyclic system

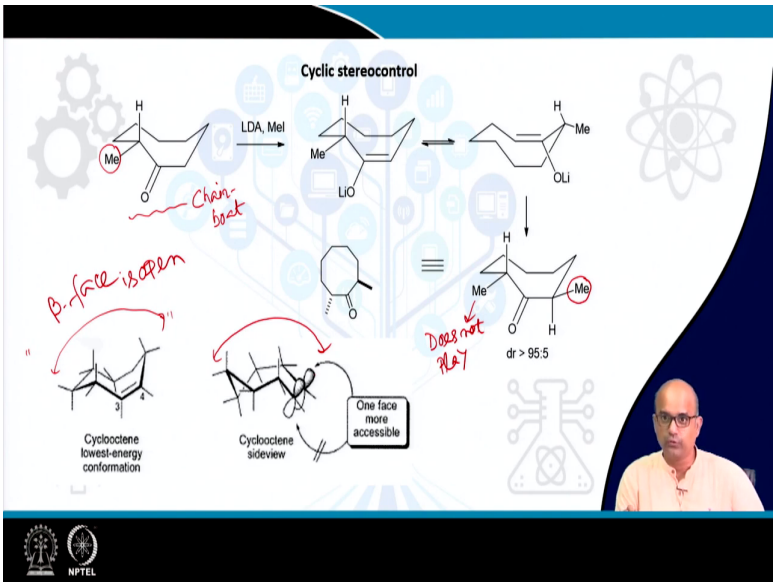
Welcome back students. So, in continuation with our module 2 which is mainly focused on enolate alkylation, today we will be talking about lecture 7 and we are mainly discussing on the substrate directed stereo control in different enolate alkylation. And, today, we will be mainly focusing on enolate alkylation in bicyclic system as well as higher cycloalkanone system.

(Refer Slide Time: 00:50)



So, these are the few topics which you are going to or intended to cover today in today's lecture. Different mode of stereo control in enolate alkylation; substrate directed as you said and mainly this part is going to be focused in little bit detail stereo controlled in conformationally rigid cyclic system. So, that was the one of the most significant part in today's discussion.

(Refer Slide Time: 01:17)



Let us talk about last class we talked about stereo controlling cyclohexanone as well as substituted cyclohexanone, how you can control the enolate alkylation stereochemistry with the help of existing stereo centre. And we said that particularly ring system like cyclohexanone has its own conformational bias and based on that conformational bias you can have a predictive model.

Now, let us talk about little bit of higher order of cycloalkanones like cyclooctanones. We have a 2 methyl cyclooctanone as a parent substrates and this methyl group is alpha to the plane means it occupies the below stereo centre. And, this is you can eventually if you know the conformational behaviour of cyclooctanone, it is basically a mixed kind of confirmation as it is containing a chair up to this part and this part is boat.

So, basically chair as well as boat fused form and this is very well documented in the scientific literature. Now, we will see that once you generate the enolate you get a planar enolate the methyl is equatorial in the chair form. It can eventually undergo conformational flipping to give you another enolate which also having a similar kind. It is basically redrawing the structure.

Now, in this case to understand the enolate alkylation stereochemistry you have to come to here. Now, this part if you see that cyclooctene which is basically the cyclooctene which is a chair as well as boat form and this 3, 4 connectivity is basically the enolate π- bond which is

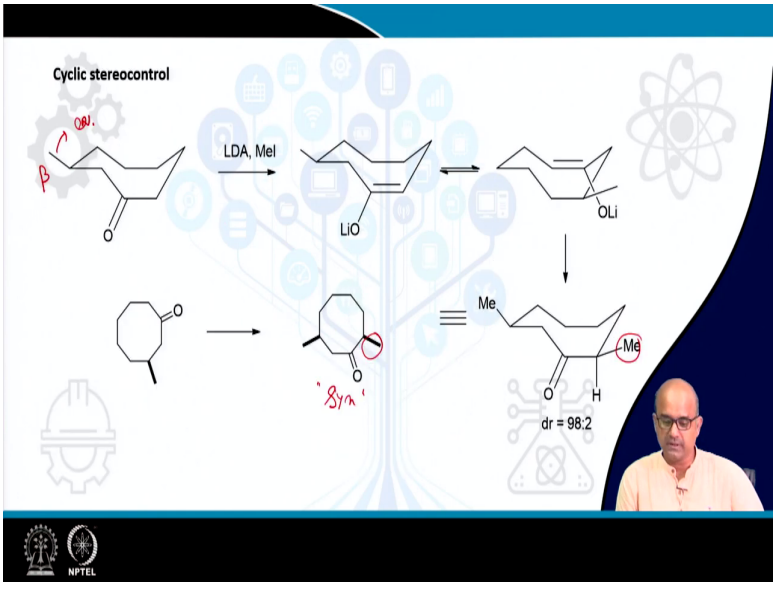
formed. Now, the ring is puckered in such a way the bottom face kind of squeezed and the top face seems to be much more exposed on this length.

So, top face or beta face which you call beta face is much more open beta face is open or exposed. So, ring structure that gives you now you can have a definitely side view you just redraw it, this particular HOMO of the enolate you see the HOMO of the enolate it is drawn in this way and now, the ring the top face seems to be much more open or flexible where the bottom face probably squeezed. Bottom face is very much squeezed.

So, eventually the stereo chemistry of this methyl group seems to be not operating at all. It does not take part in anywhere, but the ring dynamics or ring conformational behaviour have a well defined predictive role. So, this face or the beta face is much more accessible where the bottom face only due to the ring structure, the ring is puckered such a way or twisted in such a way the beta face is accessible.

So, now this is the drawing and finally, what we will get the incoming electrophile will definitely attack from the beta face means you get trans. This methyl is already alpha and this methyl has to be beta, but this methyl does not play a role. So, this was the important point, this existing stereo centre probably did not play a role, but the main significant be role was played by the ring structure of the cyclooctene.

(Refer Slide Time: 05:05)

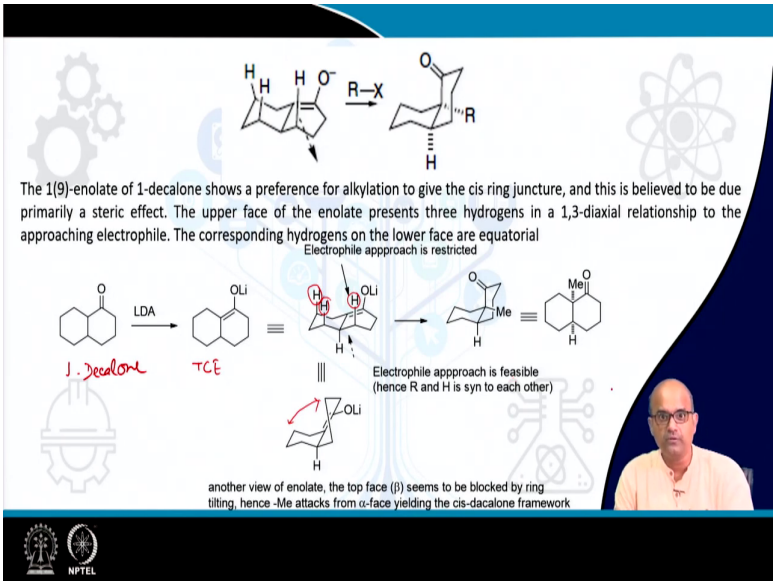


Similarly, a 3 substituted cyclooctanone you have this stereo centre is beta means the methyl group is kind of equatorial, this is a equatorial. Similar way you can actually predict the whole thing again and here as it is beta last slide what we have seen, no matter whether it is alpha or beta the beta face of the cyclooctene ring seems to be much more accessible.

So, here also similar thing happens and the incoming electrophile has to be beta it has to be beta, ok. Now, as the present or the pre existing stereo centre is beta. So, you get one 3 sorry is basically 1, 2, 3, 4, 5, yeah. So, these two methyl is now become seen to each other seen to each other.

So, the ring geometry or ring conformation of the cyclooctene plays a very important role in predicting the enolate geometry as well as the newly formed stereo centre.

(Refer Slide Time: 06:19)



Next we will try to switch over to a very well defined bicyclic system which is named as decalone. Now, decalone are those systems where two cyclohexane rings are fused. Now, first we try to take a decalone which is normally an alpha decalone or 1 decalone. Now, this 1 decalone you take it as a substrate you react with LDA, a thermodynamically controlled enolate generation has been taken place again.

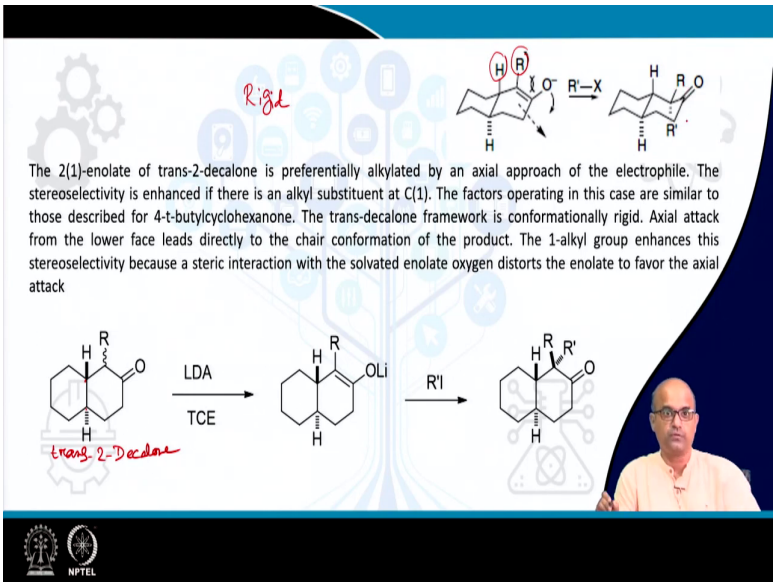
Now, definitely you have to draw a 3-dimensional structure where you can see that the left hand ring is a flat chair and the right hand ring you can basically try to write a half chair way. If you do not like this drawing you can eventually switch over to a more precisely half chair

in this way. Now, you see that in this case if you draw in this way the top face seems to be completely shielded by this three hydrogen these three hydrogen this, as well as this, as well as this.

Eventually, if you try to draw this way also your ring tilting; ring tilting makes this particular portion is not accessible. So, what if an electrophile has to be approach it definitely will approach from the alpha face or the below face. So, if you like this drawing this line is very straight forward, you can see that the methyl will now approach from this way means this hydrogen and this methyl will be now cis to each other.

And, eventually what you will get? You get a cis decalone structure; cis decalone is this kind of structure. So, that is quite understandable through this kind of drawing and normally for such a decalone system, you can have a very well defined predictive behaviour.

(Refer Slide Time: 08:22)



Things will be a little bit complicated if you are talking about a trans decalone system we take similar kind of. Now, this decalone as the pre existing stereo centre we can see you can eventually try the parent decalone is a trans to decalone.

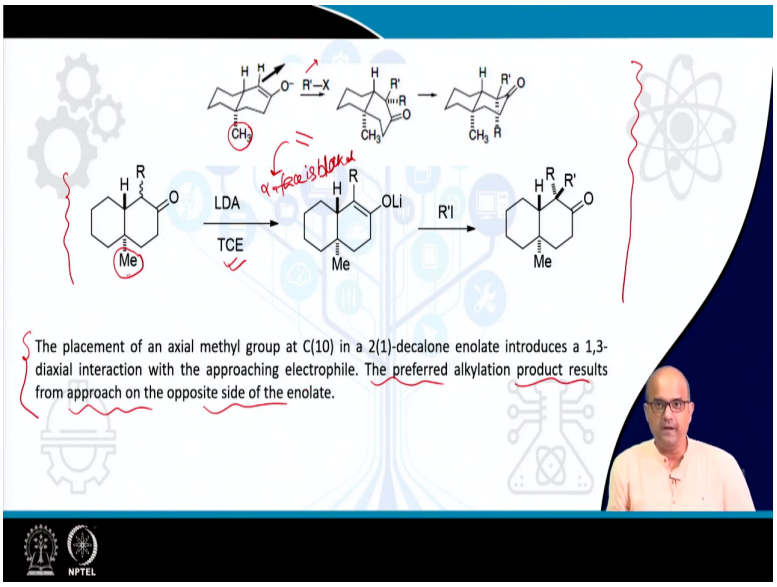
Now, this trans to decalone means the ring junction stereochemistry is trans, ok. Again, there is already containing a stereo centre here, but no matter because we are going to generate the enolate here. So, hydrogen will be abstracted. So, first try to think about the initial drawing.

The moment you generate the enolate, this is rigid. This is rigid. It is more of like a 4-tertiary butyl cyclohexanone. So, rigid so, this cannot flip.

So, this ring is a rigid trans decalone ok. So, means this is fixed. Now, once you generate the flat enolate you see this part. So, you only have alpha face which can be accessible because now see the top face was kind of blocked by this hydrogen as well as this R ok. So, only approach will be definitely having to be from the bottom face. So, we have written the everything here this trans – decalone framework is conformationally very rigid.

Axial attack from the lower face this is definitely has to be axial attack because there is no other way ok and that will give you directly a chair confirmation of the product. And, the particular 1-alkyl group which is already pre-existing enhances this stereo selectivity ok. So, this you can definitely predict.

(Refer Slide Time: 10:09)



There are higher trans 2 – decalone analogs like the examples which we have drawn here. See the first case. First case in the parent compound, in the earlier case we do not have a methyl, now I put an angular methyl group here. Now, methyl group is a little bit sterically bulky compared to the hydrogen group.

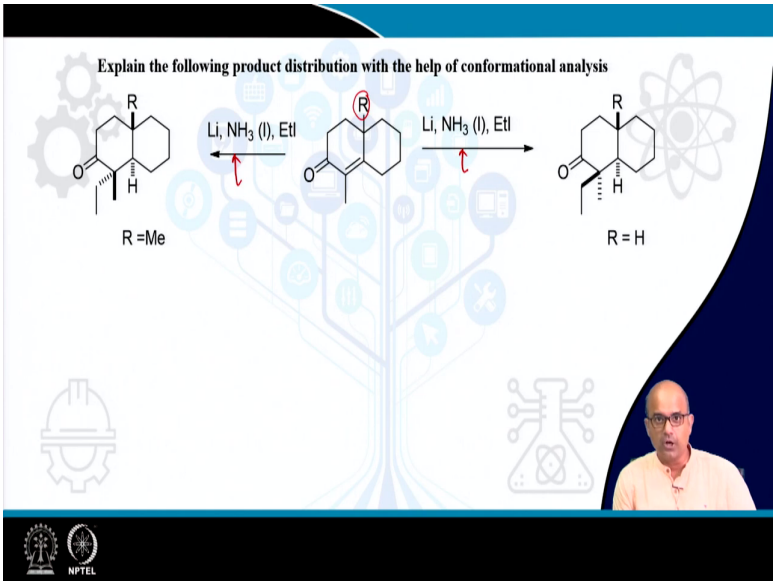
So, now we generate….. take this trans-decalone with an alpha position having a R group. Now, LDA thermodynamically controlled enolate a rigid trans enolate has to be generated fine. Now, where from the incoming electrophile will now approach? You know see that the

bottom face is now blocked. Earlier the bottom face is open, but now the bottom face is blocked by the angular methyl, ok. So, enolate flash is flat. It is a flat sp2 system as you are talking about. The bottom face is definitely blocked.

The bottom face means alpha face. Alpha an alpha face is blocked. So, if alpha face is blocked you definitely do not have any other option. The incoming electrophiles the R prime will coming from the beta face of the equatorial attack.

So, eventually the same thing we have written here. The placement of an axial methyl group at a C10 means this one in a 2 – decalone enolate introduce a 1, 3 – diaxial interaction ok. So, it is up with the approaching electrophiles. The preferred alkylation product now results from an equatorial attack or an opposite side of the enolate.

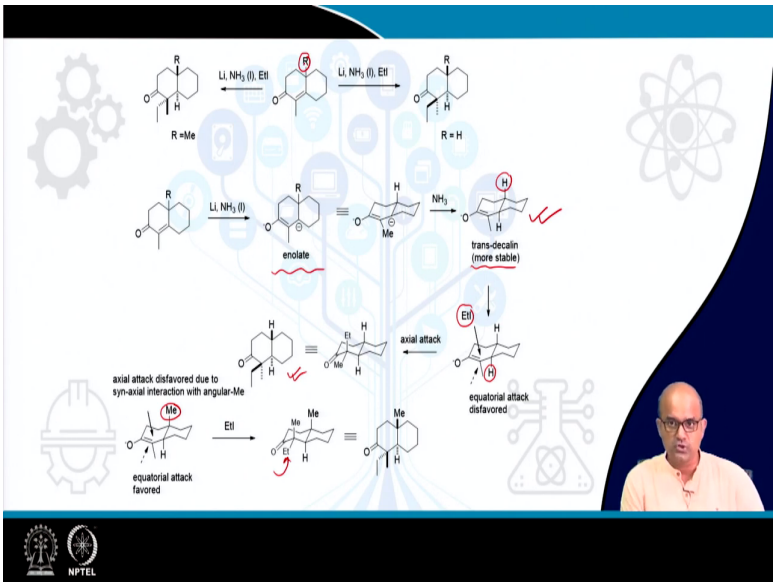
(Refer Slide Time: 12:05)



So, this can be very well explained in terms of a rigid conformational bias of the parent compound. Now, these two examples are the specific example of an enolate generation by Birch condition like lithium ammonia as you said and both the cases will be having a ethyl added as the electrophiles.

Now, the interesting point to note that in one of the cases the angular group is a hydrogen and one case angular group is methyl. So, there must be something is playing on here. So, let us go to exactly what is happening here.

(Refer Slide Time: 12:39)



In the first case when R is methyl let us talk about one by one. So, first the initial compound which you take alpha-beta unsaturated ketone you treat with lithium liquid ammonia…… single electron transfer you basically get the enolate ok. The moment you get the enolate the enolate stereochemistry or the conventional bias you have to draw it.

Now, see definitely if you try to draw in a trans decalin feature that could be much more stable ok. Now, this carbanion accepts the hydrogen from the ammonia as a important source and you get the trans decalin as a more stable enolate now fine. Now, the first case R is hydrogen, fine. So, it is not sterically bulky. So, ethyl added as the electrophile. The ethyl added where from it will come? If it comes from the beta face it gets the axial thing ok. Now, it is having a parent methyl already in the existing form ok.

So, now if it approaches from this one it gets this axial hydrogen in the trans decalin as well as this methyl which is already present. So, there is only one way it can attack, it can attack from the axial or the top attack. So, if it attacks in the top way you basically get this as the major product.

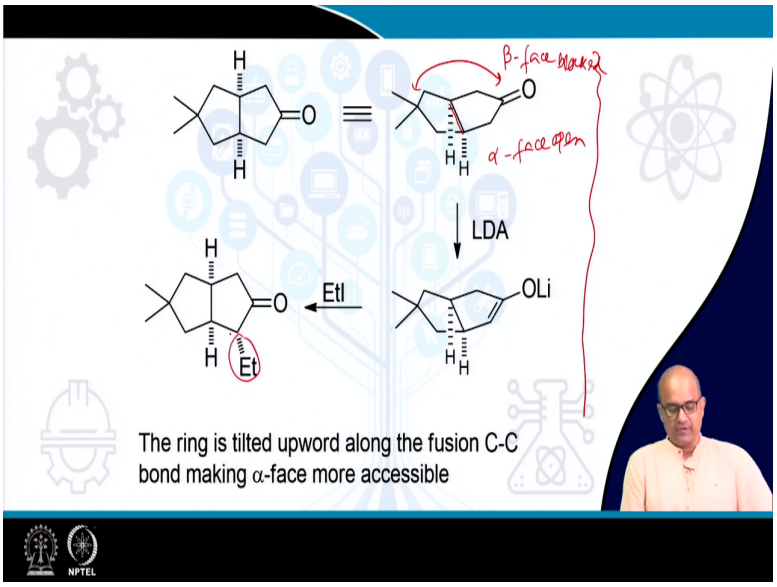
Now, if R is methyl the second case if R is methyl now in the precedence example the or the earlier example you said that if angular position is blocked by the axial methyl you see the top attack is definitely not favoured again. The bottom attack seems to be definitely preferred though it contains a methyl group, but the angle of approach is not directly contacting. So,

you will now get a methyl as a sorry, the ethyl as an electrophile it will be as an equatorial attack.

So, the angular group plays a very important role in predicting the stereochemical behaviour. And obviously, the trans decalin being the major or stable enolate you will definitely try to have this enolate as a main structure and then you can try to predict the existing stereo center how it gives a predictive role.

The mostly the steric factor is the main determining factor in these two examples and you can see that typically this angular group R if it is hydrogen it gives you one diastereomer, if R is methyl it gives you another diastereomer.

(Refer Slide Time: 15:30)



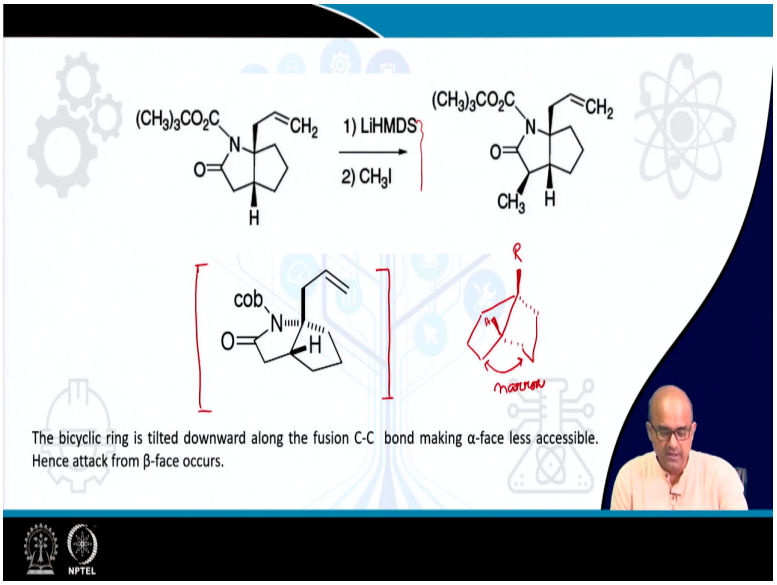
Bicyclic ketone this particular example is very famous. Now, this particular example what it tells you? This particular bicyclic ketone of this system where actually the ring fusion stereochemistry is pretty important. Now, what is happening here? The ring fusion stereochemistry you can see that as the hydrogen are below means hydrogen are below. So, the around the fusion bond the ring is basically tilted. The ring is basically tilted. So, these are below. So, ring is kind of tilted.

Now, the ring is tilted means the top face seems to be squeezed. So, top face means the beta face is kind of blocked whereas, the alpha face seems to be accessible or open. Alpha face is

much more open. Now, such a bicyclic ketone if you now try to generate the enolate you get these things.

Now, this hydrogen as it is pointing towards down that basically forces it basically looks like the palm of your hand where this one cyclopentane is this ring, one cyclopentane is this ring ok and then; that means, that the top face is somehow squeezed and the bottom face is entirely available. And, you can see the ethyl iodide though it is a bulky electrophile, it will basically approach from the bottom face.

(Refer Slide Time: 17:09)



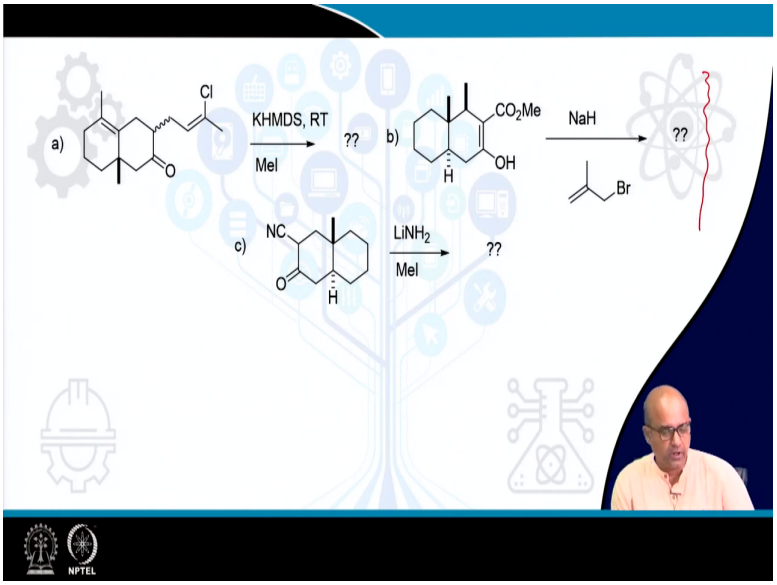
There is a similar kind of example which is also well documented in the literature. The only difference is you have an amide here ok cyclic amide. Now, only difference is we also did it the ring junction stereochemistry is now cis. So, you have a hydrogen, you have a allyl and this compound is treated with LiHMDS and methyl iodide.

Now, see that when in continuation with the earlier ring as the bicyclic ring is tilted downward means as the hydrogen and the allyl are pointing towards above the bicyclic ring is tilted towards down see the drawing which you have drawn it here and that this kind of drawing basically you can also easily practice in your home. So, what you do? You first draw this fusion bond ok and then as relatively stereo chemistry relative stereo chemistry was given, you might be having a hydrogen might be having an alkyl group.

So, now what you trying to do you put these things as this way and cyclopentane is as it is envelope you can try to put this kind of structure, you can try to put this kind of structure ok and you have an another hydrogen as the ring junction here. Now, you can easily see this part was more or less very much squished or narrow as this.

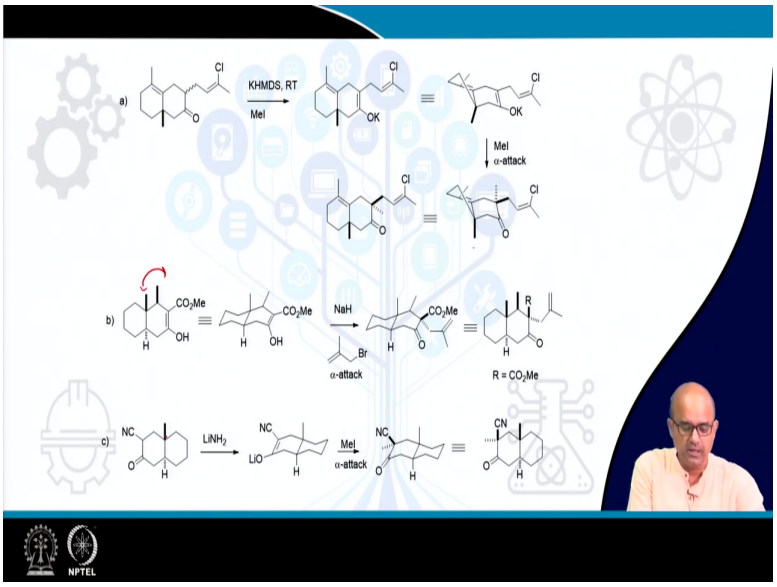
So, one of the enolate face is very much narrow, but on the contrary the top face is more or less openly available. So, always the beta face attack occurs. So, it all depends that how the ring junction stereochemistry is available.

(Refer Slide Time: 19:04)



Now, there are few assignments were actually designed or based on the concept which we talked about.

(Refer Slide Time: 19:17)

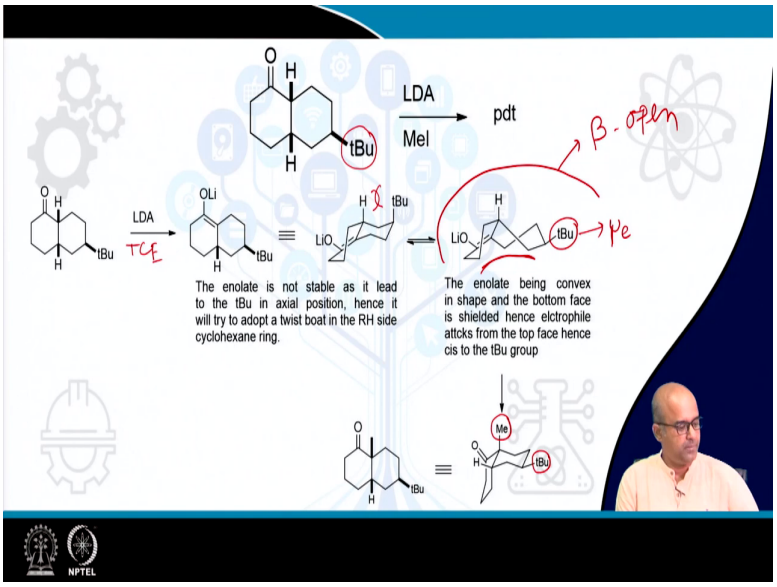


If you try to have a quick look at all the assignment, you can easily do it. Let us talk about the first one the angular group is methyl which is the beta 1. This stereochemistry is going to be destroyed by a for anion generation.

Now, you can see as methyl is above definitely the alpha attack takes place, the proper drawing you can do it through a half chair confirmation and then you can see this methyl and this methyl is opposite to each other. And, you get you can explain the drawing or the final product. This is basically a keto ester a ketone and CO2 Me these compounds already having a two existing methyl at this position angular position you can eventually draw it.

So, no matter you can simply predict that this methyl bromide will be coming from the opposite of this 2 methyl. Similar thing here a cyanide is there. This stereo chemistry does not matter as it (Refer Time: 20:19) be generated angular methyl. So, electrophile will be coming from the opposite to the angular methyl. So, very straight forward very simple, but you need to explain it.

(Refer Slide Time: 20:25)



This particular example is very crucial and very important. You have a bicyclic one decalone system with a tertiary butyl at one of the end. I said LDA methyl iodate you need to predict the product. Now, what happened? Once you generate the enolate in the TCP mode thermodynamically controlled enolate you find this enolate. Now, this enolate you need to draw in the 3-dimensional way.

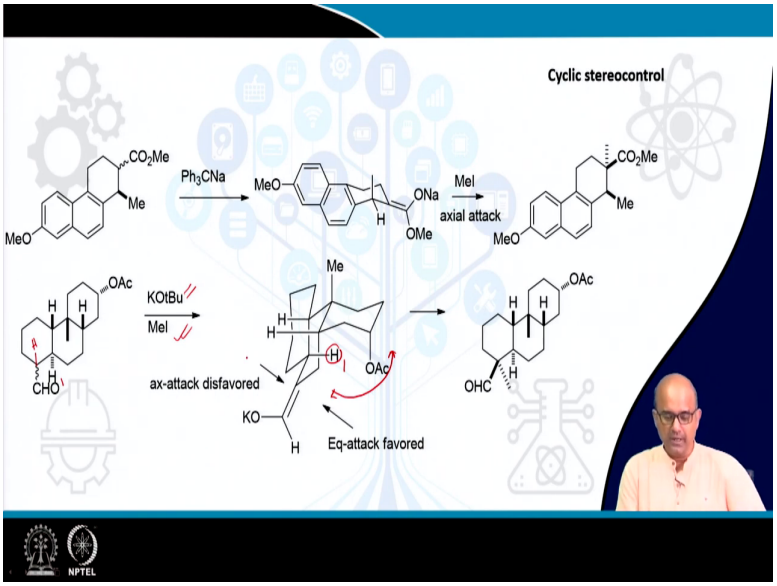
The tertiary butyl group is beta ok. Now, if I draw in this way the tertiary butyl be axial ok, but eventually tertiary butyl group axial means it gives you a huge 1, 3 di axial interaction in the ring. So, tertiary butyl group tried to accommodate in an equatorial position. This can only be possible if the right hand ring flips to a twist boat kind of confirmation, but definitely twist boat is not that much energetically preferable, but still that can put you a tert butyl group in the equatorial way.

So, this is now a pseudo equatorial position it is called pseudo equatorial position ok. Now, see now if you try to draw in this way, the enolate kind of being a being a convex; convex means now see the bottom face seems to be much more squeezed ok, the top face it is much more open. The top face or the beta face is open now. So, if the beta face is open the methyl iodide can attack from the beta.

So, now you see tert butyl and methyl will be cis to each other. So, it is not always necessary that the tert butyl and methyl should be anti to each other because usually we said that tert butyl is above. So, methyl should be anti, but it all depends the ground state confirmation of

the starting material, you need to draw the energy minimize structure and then try to draw the enolate and try to now figure it out how the electrophile incoming electrophile approaches from which face which is easily available.

(Refer Slide Time: 22:42)



There are few systems which we can talk about there are bit of complex system complex means polycyclic system. So, beyond the bicyclic, we can talk about tri cyclic system and these are mainly based on a specific example which are taken from the literature. The first one seems to be quite easy to be done is a methyl is already there is a beta.

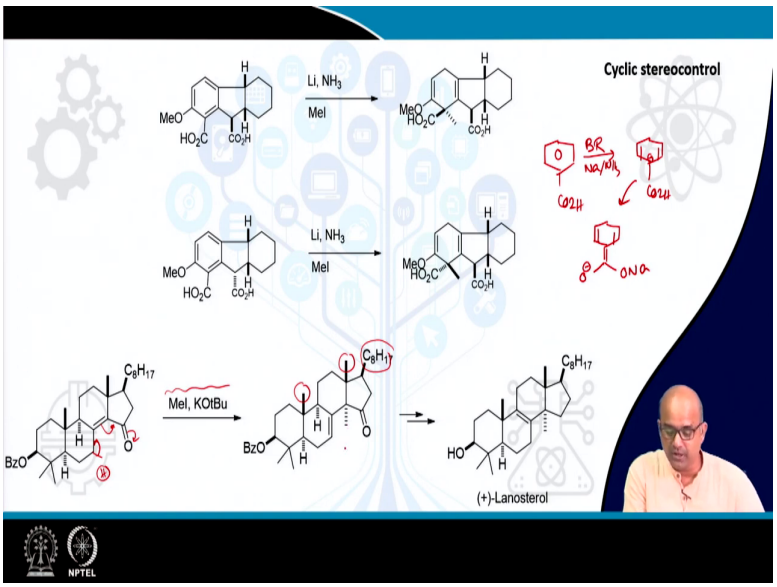
So, you will be having an exocyclic enolate generation ok because enolate will be double bond will be exocyclic or outside of the ring. So, you can definitely try to draw it. Now, as the methyl is above definitely methyl has to be axial way ok. So, you could have a methyl iodide attack from the opposite face because this face seems to be blocked. So, that what does it mean? It means that this methyl and the incoming methyl has to be anti to each other. That is very well understandable.

The second one where a complex per hydrophenanthrene system you treating with potassium tertiary butoxide and methyl iodide. Now, initially you try to draw the ground state confirmation by keeping the relative stereochemistry of this comformation of this all the structures. This is a bit of a difficult if you are not familiar with this drawing. So, this is the hydrogen which will be abstracted which is alpha to the aldehyde. This is hydrogen, fine. So, this you can.

Now, see the initial drawing acyl acidic group is below chair another chair another chair. Now, see this hydrogen, this hydrogen, this methyl and this hydrogen all are kind of. So, this hydrogen is this hydrogen ……. hydrogen 1, hydrogen 1, this is the next hydrogen will be hydrogen 2, then you have this then you have methyl, then you have hydrogen. So, these are all are very perfectly matched.

You draw the exocyclic enolate, fine. Now, you can see that the entire as the ring is tilted this part seems to be more or less squeezed or closed, but this face is entirely available. So, the enolate will be definitely attack through axial attack. Now, you can see the methyl is above. So, this methyl is below that you can explain actually, but anyway until unless you draw the entire structure drawing of the final product sterochemistry will be bit of difficult for you.

(Refer Slide Time: 25:24)



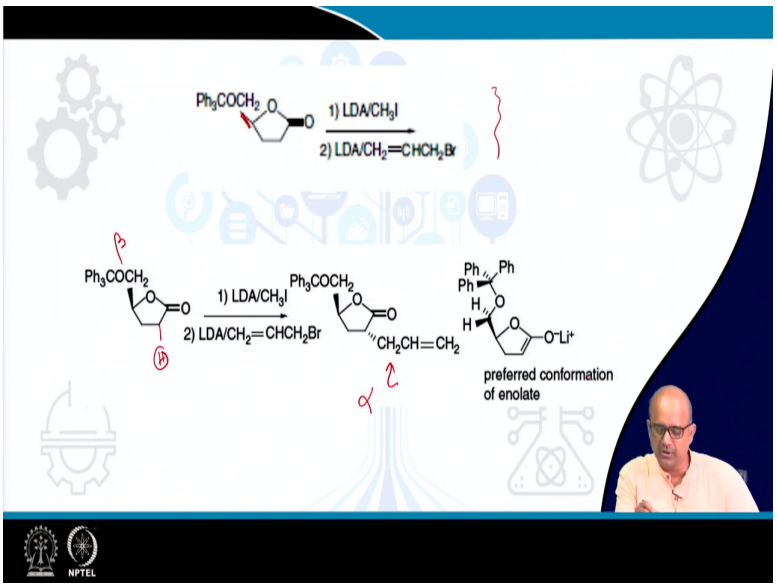
On the similar way you can also explain couple of other things, the first one and the second one is more of like a Birch reduction. If you try to remember if you have a simple benzoic acid benzoic acid which you subject to Birch condition. Birch condition means sodium and liquid ammonia.

Now, this condition usually you know that the deconjugated system will be happening, but definitely you get a carbanion alpha to the carboxylic acid. Now, this is usually will then undergoing an enolate formation O OH or you can have a ONa. Now, this is what? This is an enolatic generation. So, in this way now you can see that the existing compound contains a beta carboxylic acid beta carboxylic acid.

So, the methyl iodide approaches from the opposite to the carboxylic acid very straight forward. Same way this is alpha carboxylic acid so, methyl opposite. This one is a little bit complicated where actually gamma alkylation takes place. Initially the hydrogen there is actually it is a more of like a thermodynamically controlled condition because base is weak. So, this actually abstracts this hydrogen.

So, this is abstracted and you get this is as a enolate. So, this enolate once you get you actually you will now be trying to have this attack on this particular this particular position. Now, see this group is beta, this group is beta, this group is beta. So, methyl is coming to alpha and this is an example or intermediate for the lanosterol synthesis in the cholesterol synthetic pathway.

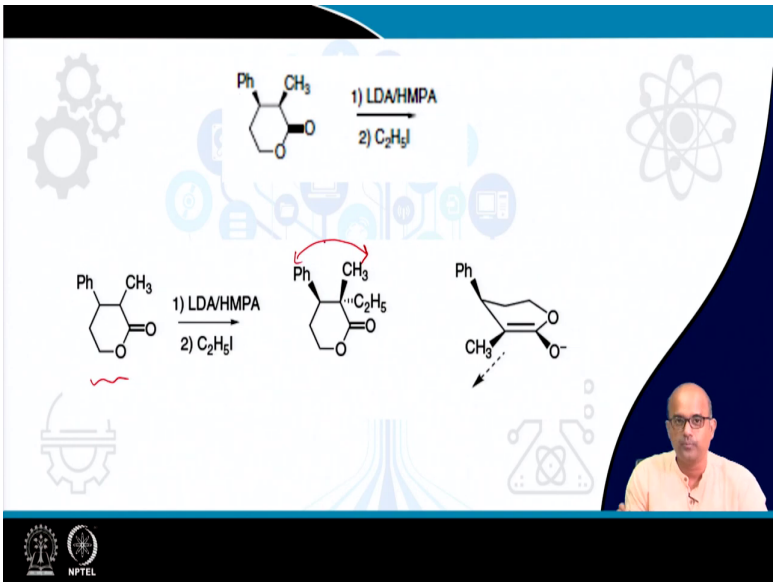
(Refer Slide Time: 27:27)



Now, few more examples which we have discussed in the last class actually this is just like a to give you a refreshing memories. Cyclic stereo control in the 5-member ring if you have a system like this that you have a basically a beta stereo centre here and you see it is a pretty bulky group. It is a trityl group you see trityl group and means that the hydrogen which will be abstracted from here.

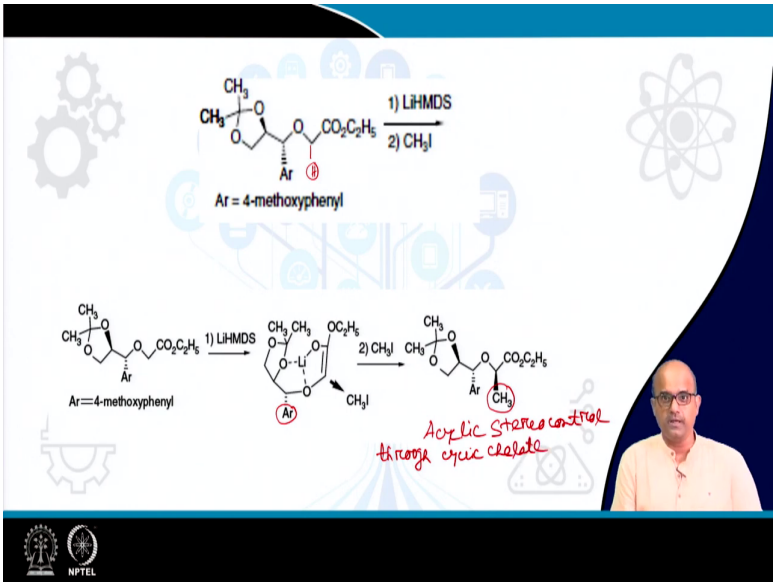
You generate the enolate and then as this is beta this attack will be from alpha face ok. So, this is the paper confirmation of the enolate you can basically try to twist little bit just for drawing.

(Refer Slide Time: 28:19)



This one is pretty simple you have a parent compound where both the phenyl and methyl will be beta means above the plane. So, now, you can eventually try to draw it. The incoming electrophile has to be alpha because it is beta face is exclusively blocked by this two bulky group.

(Refer Slide Time: 28:43)



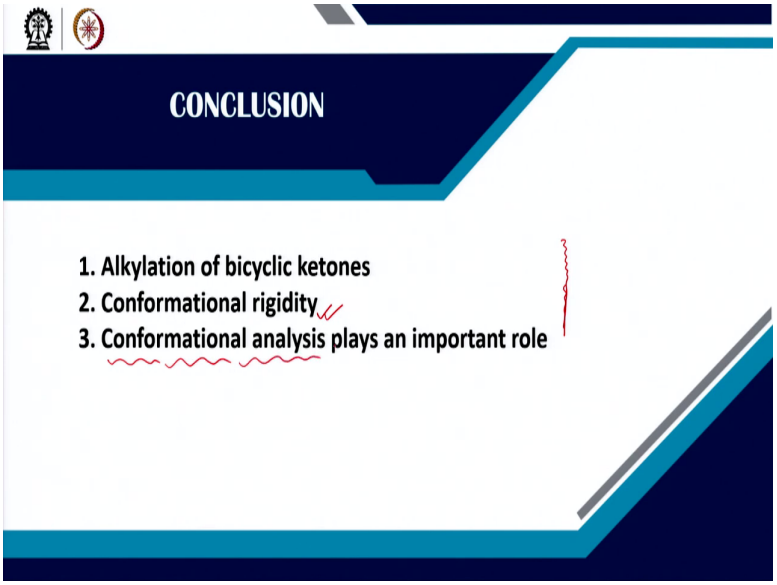
So, these things are pretty much simple and you can eventually try to do it. This example was again an example of an acyclic stereo control, but here what is much more important that one of this oxygen in this acetonide protection can actually take part with this chelate formation

once the enolate is generated by abstraction of this hydrogen ok. So, it forms this kind of things.

Now, the existing stereo center is this is beta. So, beta means the enolate which is there it is also this way. Now, the way it has been drawn actually it was a bit of difficult to conceive, but this aryl group plays important role. This aryl is below, so, this methyl is coming from the opposite way ok. So, this is the main acyclic. So, this structure is kind of a acyclic stereo control, but it acyclic stereo control through a cyclic chelate.

So, it can also have categorized through an acyclic stereo control through cyclic chelate formation. So, at a one side this become acyclic stereo control in the another side it becomes cyclic stereo control.

(Refer Slide Time: 30:07)



So, as a concluding remark we can say that we are basically trying to cover in today's class mainly alkylation of several bicyclic ketones as well as a few polycyclic systems we talked about the conformational rigidity which plays a very important role. The more rigid the conformational is it is having a certain confirmational bias and then you need to know the ground state conformational behaviour of those starting materials or the precursors which plays a very important role.

So, thank you. We will see you again in the subsequent week.