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 information of enolates
Lecture - 02
Enolate generation, Structure of enolates and related topic - II

Welcome back students, in continuation with the earlier lecture this is the Professor Samik Nanda. I am talking about this particular course named as Principles and application of enolate alkylation…………...

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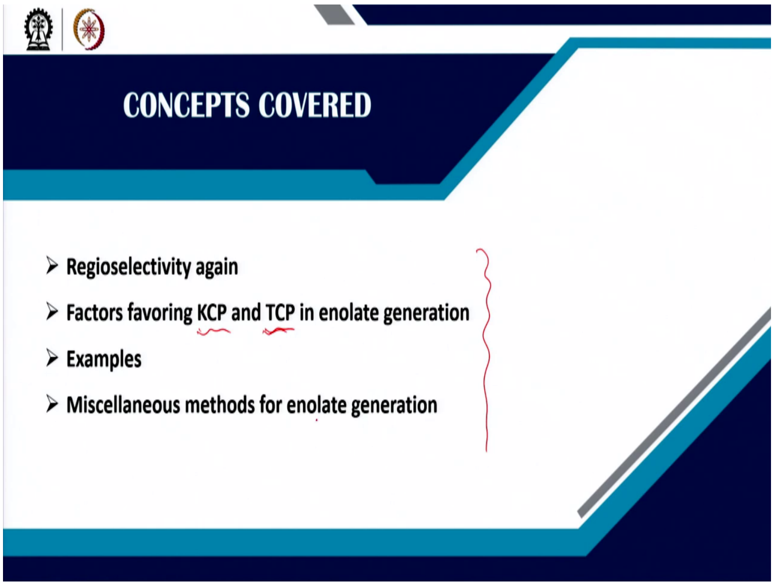

CONCEPTS COVERED

- Regioselectivity again
- Factors favoring KCP and TCP in enolate generation
- Examples
- Miscellaneous methods for enolate generation

And today we will be going to continue the module 1; and the lecture 2 which we mainly cover today or we will be covering today. The regioselectivity issue which we are discussing in the last part of the last lecture. And the main factors which are responsible for governing the regioselectivity concept. We will be also talking about KCP and TCP which are very new terminology might be for you, and subsequently we will talk about few related examples and miscellaneous method for enolate generation.

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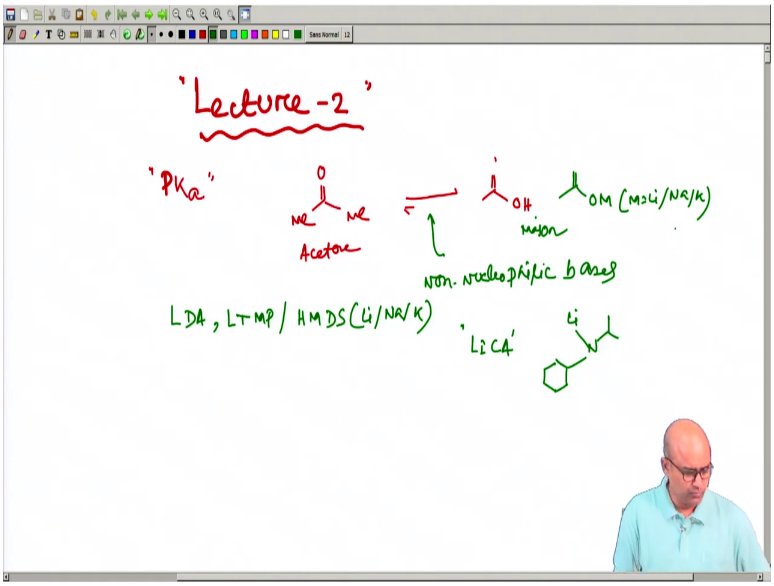

So, welcome back. We are basically discussing different methods of enolate generation. And in the previous class we talked about that Pka as one of the well known parameter for enolate generation. And we said that if you have a carbonyl compound. Let us say very standard acetone as the carbonyl compound, acetone and you wanted to generate enolate from acetone and you want that the most of the acetone has been converted to corresponding enols, something like this.

Then what you need to use……… you need to use a very strong non nucleophilic bases, non-nucleophilic bases. And in this regard, we have discussed that the Pka of this acetone as well as the Pka of the corresponding conjugate acid of the bases, should be differed almost like 18 to 20 and in that regard we said LDA, bases like LTMP and hexamethyl silazide bases, metal containing things. You can have a lithium, you can have sodium, you can have potassium all are pretty good bases.

There are few other bases like LICA; LICA is lithium isopropyl, then you have a cyclohexyl and you have this thing so it is called LICA Lithium Isopropyl Cyclohexyl Amide, it is similar like LTMP. And in those cases, maximum cases you can actually generate pretty nice enolate thing and where the most of the equilibrium eventually lies on the cases of the enol, you get basically this could be a major product.

Now, if you use bases like LDA, LHM base, LTMP actually the product which you are usually getting the corresponding metallo-enolate. The metal could be lithium if you use

LDA, it could be sodium if you use related bases, it could be potassium ok. So, this is the enolate or the metallo enolate which you can create it. Now, we intended to try to talk about something little bit of different issue before we go for the regioselectivity.

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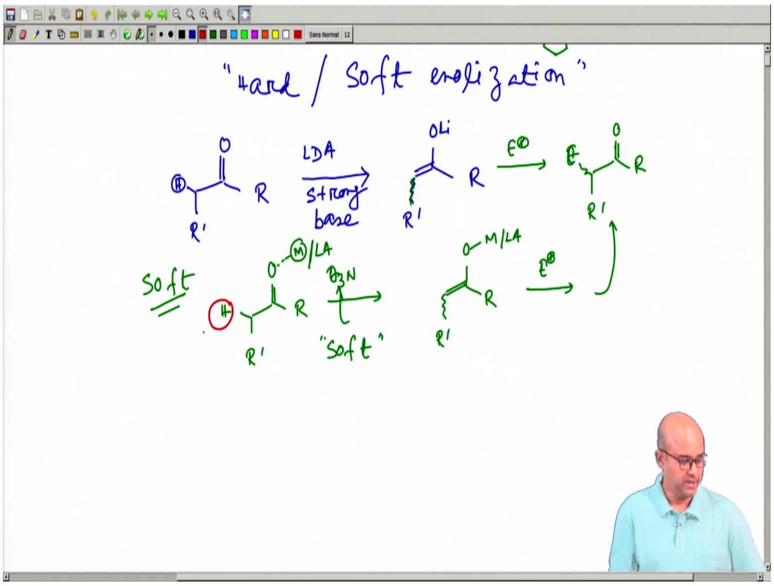

There is a bit unique way of generating enolates and these are methods called hard or soft method for enolate generation. This we just try to give you a little bit of brief overview on hard and soft enolization. Now, normally in the hard method, first we talk about the hard method we will just have a general structure of compound where at this end you definitely have a hydrogen which you need to abstract it.

So, it is a pretty straight forward way of enolate generation and we use strong bases like LDA. And the moment you generate the enolate, the enolate you can trap it as a metal enolate or something like that or let us see you just simply generate the corresponding OM or OLi, R and this R prime.

And there is a fine catch or fine tuning. We did not talk about this particular geometry of the enolate, so we will be coming to this later on. And then immediately you can use the electrophile very rapidly in the reaction mixture and then you get a new carbon bond. Now, why this is called hard enolate? Because we use very strong base and you have a you have a pretty smaller counterpart of the ion which is lithium.

Now, let us talk about the other methods which is we called a soft method of enolization and usually in the soft method we use a different condition and the different condition means, we will be using a base which are not that strong.

So, we use a base let us say base like triethylamine which is not that strong, but before we apply the base initially, we used to activate the carbonyl compound with some coordination. And, this coordination mainly can be done by either a metal or a Lewis acid ok. So, means that the typical coordination of the carbonyl group with the metal helps that soft base or weaker bases to abstract the hydrogen from the corresponding alpha position.

And then eventually you can in the very beginning case you probably can get an enolate something like this where still the coordination or the Lewis acid is moreover like stays over there. And you definitely have a geometrical constraint of the enolate and then you try to use the corresponding electrophile in the earlier way and you can get the same product. So, the basic difference in hard and soft towards the nature of bases you use.

And particularly the M, here it could not be I mean it has it may not be a metal it could be of different thing. Normally, the activation of this carbonyl compound can be done and in the later part, if time permits we will show that this could be a boron based enolate generation could be a titanium based enolate generation where initially the boron act as a Lewis acid.

And this oxygen of the carbonyl act as a Lewis base, there is a nice coordination and this carbonyl basically getting activated then simple Et_3N like weak bases can actually abstract that alpha hydrogen and you can easily generate the enolate.

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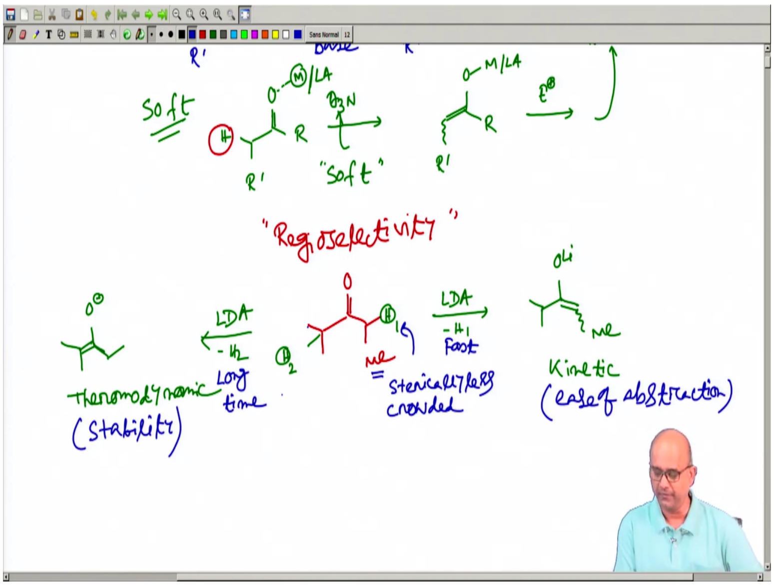

Now, next we will be trying to switch over a different concept which we called the most important part in the enolate generation which we called regioselectivity. This regioselectivity will be coming when you have an unsymmetrical ketone. For simple analysis I will try to take an unsymmetrical ketone of having this structure and I will try to put the hydrogens with a different color.

So, you have one hydrogen here, we have one hydrogen here. So, in this case you will get basically two abstractable hydrogen and then try to see what kind of enols you might be getting. If you use LDA as a base, both the cases you might get the corresponding metallo enolate something like this, if this hydrogen 1 has been abstracted by minus H1, I said this hydrogen get H2.

So, if H1 abstracted what you will get? You can basically get this kind of compound taking the geometrical isomerism as a factor. And if H2 is getting abstracted, you will normally you will get this as a product. Now, these two hydrogens actually behave in a different way.

And for our explanation we now call this enolate as a kinetic method of enolate generation and this we call as a thermodynamic method of enolate generation. Now, why the name comes? Actually this thermodynamic has related to the stability of the enolate. You will see that this particular enolate will be maximum stabilized as this is more substituted olefinic thing, so more hyper-conjugative structure. In this case is the kinetic way of deprotonation means that how easily you can abstract H.

So, kinetic is mainly related to its ease of abstraction, means how easily the hydrogen can be abstracted from the substrate. You will see that this hydrogen has only 1 methyl group in its vicinity and this hydrogen have 2 methyl group in its vicinity. So, that basically implies that this hydrogen is sterically less crowded, sterically less crowded. That means, that when you have a pretty bulky base like LDA, it can be easily abstracted or abstractable and then you do a quick deprotonation.

It is always pretty fast, this kind of kinetic enolization done very fast and for this thermodynamic one basically allow the substrate to react so that it can prefer between kinetics or thermodynamics but definitely as you are allowing for a longer time the stability of this enolate which is the main determining or governing factor ok. So, these two things are very important in our basic understanding of kinetic and thermodynamic control of enolate generation.

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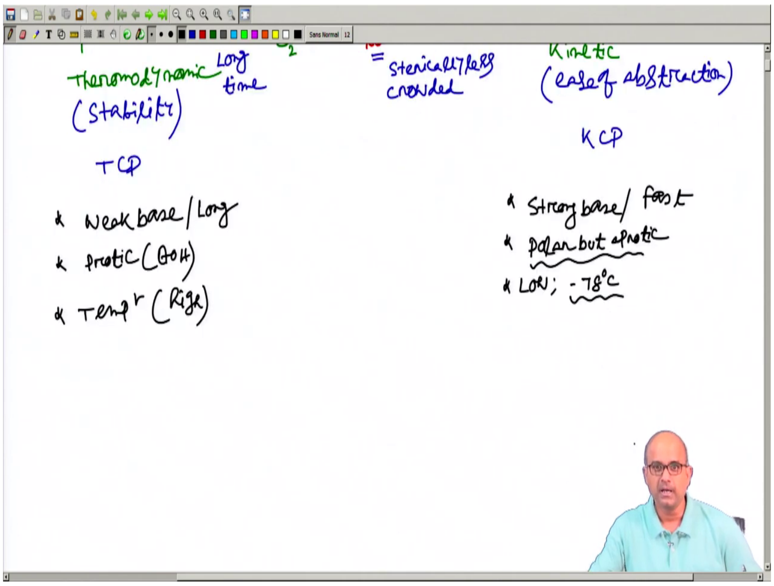

So, we can just go along with two things, is KCP or Kinetically Controlled Product, this is TCP. Now, I will try to write it down the things what basically preferred for this thing. So, in this case TCP and KCP; so, first start with KCP. KCP is means you need a sterically less crowded hydrogen abstraction and using a very strong base. Definitely strong base is always required, you need a strong base the method is very fast, and you need it very fast. In this case the base may not be that that strong.

So, you can eventually try to use weak base also and it is a pretty time consuming. Definitely you can have that, it takes more time because the stability is governed by thermodynamics; that means, governing factor. You can always try to use normally polar but aprotic solvent. Now, why it basically prefers? Aprotic solvent means they can basically donate hydrogen. So, there is a chance that the hydrogen which you have abstracted might undergo exchange.

So, you do not want that. So, you can try to use a polar but aprotic solvent, the most cases which are usually preferred like ether, dimethoxyethane, other solvents which usually preferred. We will be coming to the solvent effect little bit later on. And now in this case you will always find that you can have a protic solvent. Now, protic solvent how it helps like ethanol.

So, protic solvent usually can help in the exchanging process and as is the time consuming they can basically rapidly do the shifting. So, initially you might have the kinetic deprotonation, but after the protic solvent you can exchange and lead you a stable thermodynamic enolate generation after long time. The temperature; temperature could be high usually for thermodynamic enolization you need a high temperature. In this case it is a pretty low temperature, means how fast you can abstract the hydrogen usually a -78 degree centigrade we often use for kinetic deprotonation ok.

So, this 3, 4 parameters which will actually help you to detect that whether you are generated analogies kinetically or thermodynamically controlled. Now, we will be trying to switch over little bit of structural information.

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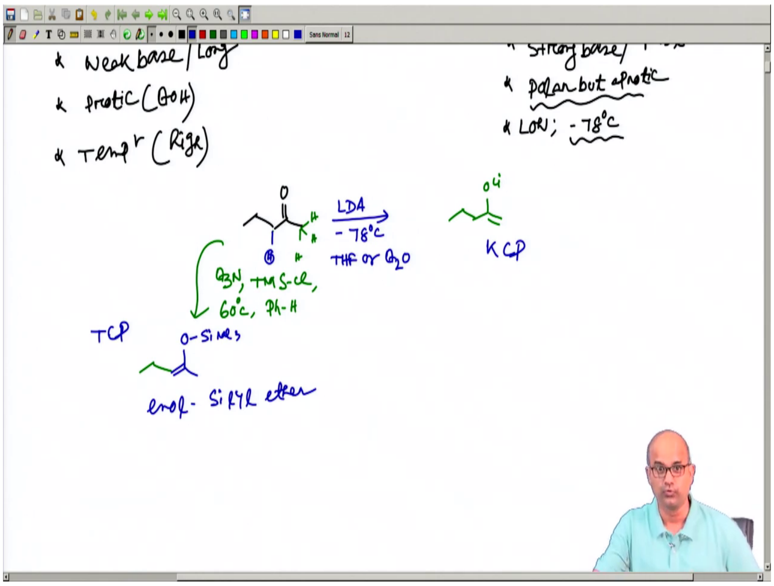

Let me try to give you some structural part. So, we have this carbonyl compound, now you see this carbonyl compound does have a non symmetrical structure. So, you try to use LDA ok, temperature is usually pretty less solvent you can use tetra hydro furan or even other solvent like ether. As I said polar, but aprotic; THF is definitely protic, but it also can be used.

Now, what are these? So, you basically will get the I am talking about a low temperature means a kinetic enolate generation. So, you have hydrogens which are these, 3 are sterically less crowded. So, eventually you will try to get this as an enolate. See, now on the same compound if you try to use a different condition. The base may not be that much strong. So, you can use a base like triethylamine fine.

Now, triethylamine is fine, but triethylamine does not have a metal counterpart. So, how you can stabilize the enolate? You can do it; you can use a TMS chloride as the enol trapping agent. And then you can use a high temperature 60-degree C solvent you can use, benzene solvent. Now, you see that as this is weak base, high temperature. So, means that we are trying to talk about thermodynamic enolate generation.

So, then in this case this particular hydrogen will be assigning with a blue color can be abstracted and you see this. The moment you have this O minus can be easily reacted with this TMS chloride. And this is the usual way of trapping the enolate and we call this as an enol silyl ether. Enol silyl ethers are pretty good intermediate which probably you might have studied or we will study in the long I mean in the future. So, this will be your kinetically controlled enolate generation, this will be your thermodynamically controlled enolate generation.

So, basically depending on the reaction condition, you can eventually choose which will be the best way to do it.

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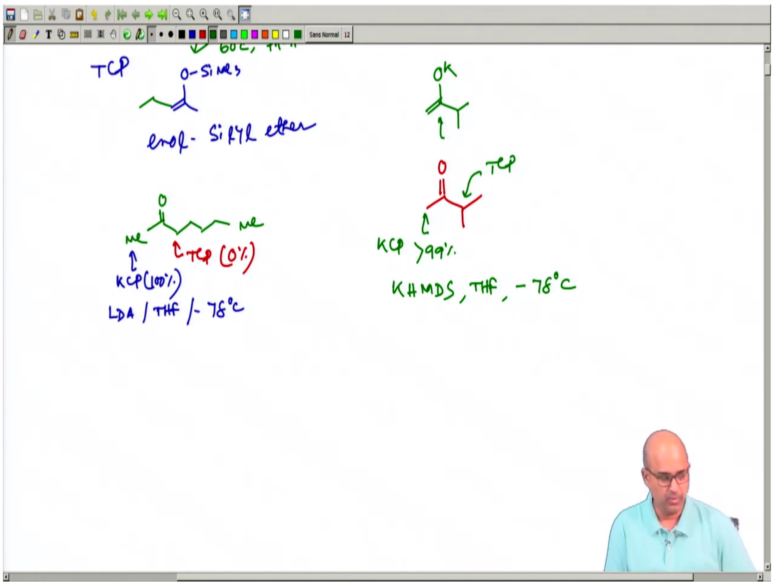

Now let us try to give you a couple of interesting structures and we will try to give you the bit of relative ratio for this thing. So, I am taking a long chain compound, this end is methyl this end is methyl. Now, definitely you can eventually see that this one will always give you the kinetically controlled product.

Now, what is the reaction condition? If you try to use LDA, THF and minus 78 degree C, you will find KCP as a 100 percent product. The TCP which is basically this side, this side is your TCP. So, TCP you get 0 percent, means absolutely no product is formed. Similarly, a similar compound very simple compound a methyl isopropyl ketone, you can easily try to think out this is your KCP condition which is sterically less hindered and this is your TCP based major product.

So, the condition which people have been used KHMDS, potassium-HMDS hexamethyldisilazide and then you can use THF as a solvent minus 78 degree C. And you find that this product was usually you get 99 percent, means you will often get this product which is the OK, which is the kinetically controlled enolate generation. So, this is the usual way you can do it.

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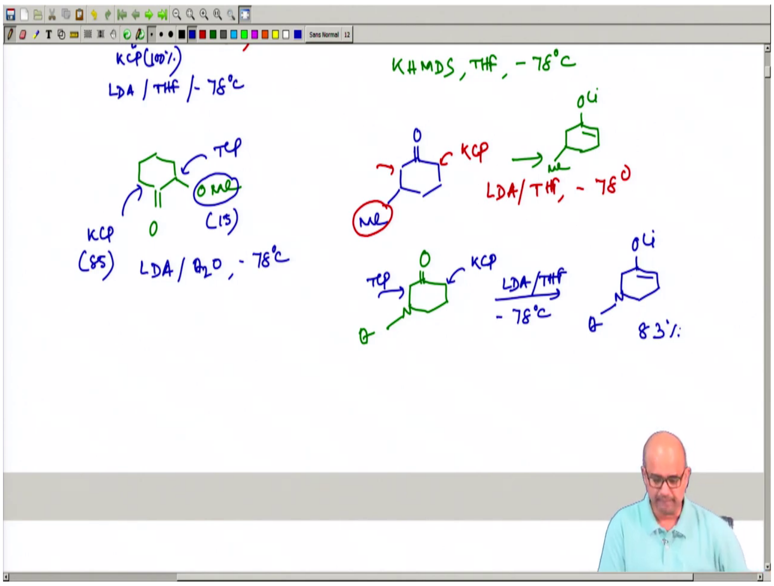

Now, the next examples which we have drawn is acyclic, go for a cyclic compound and you will find that there are few nice example. This two methoxy cyclohexanone OMe group, definitely all of us know that OMe group is having minus I effect but it is also having plus R effect. So, fine so there are two positions, this will be definitely the KCP condition because this is sterically less in their hydrogen and this is the TCP condition.

So, what will be using? If you use a kinetically controlled enolate generation LDA, Et$_2$O, diethyl ether minus 78-degree C. You find that this KCP you will get 85 percent ok and this you will get 15 percent. So, means under this condition KCP is definitely the major product ok. So, these are the few information or kind of background information we will like to share, but there are few other examples which we may be sharing with you right now, as a cyclic structure we have talked about.

Let us say few compounds, let us say this compound. It is a 3 methyl cyclohexanone. Now, 3 methyl cyclohexanone, it is a bit different scenario because methyl group is in the 3 position, again. Now, there are hydrogens here there are hydrogens here. Now, this hydrogen is having adjacent methyl group. So, this will be definitely sterically crowded, but this hydrogen which is sterically less hindered will give you a KCP controlled product fine.

So, eventually what you will try to do? If you use a LDA, THF minus 78-degree C, you will usually observe the kinetically controlled product as the major one means, this hydrogen abstraction OLi methyl. This could be the major product. Similar thing happens when you have a cyclic compound where the structure was having nitrogen at this point. Now, it means that similar kind of things this one would be sterically more hindered, this will be sterically less hindered.

So, this will be again a KCP derived enolate, this will be kind of TCP derived enolate. So, now, let apply the same condition on the substrates LDA, THF minus 78-degree C and you will find that in the, usually what we have predicted like this KCP generated enolate will be the major product and this you obtain as an 83 percent. So, these things will usually give you a very good idea based on the structural information you can actually control the thing.

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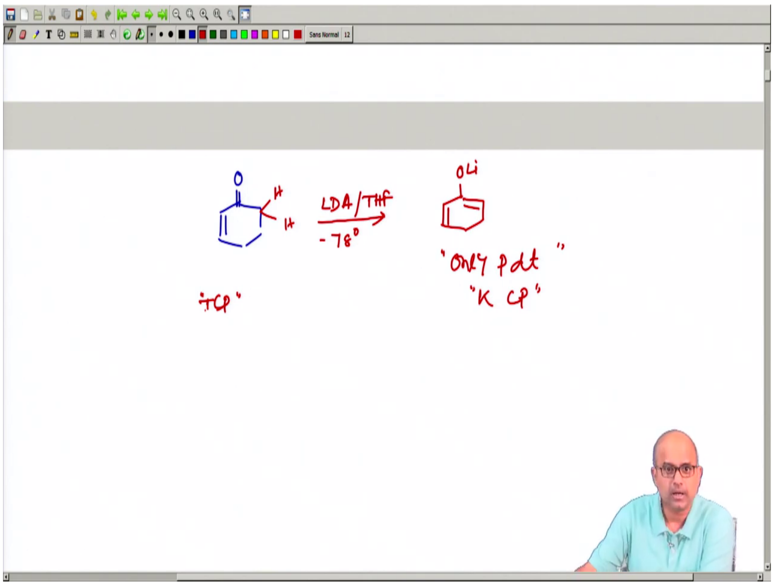

We can also do have a couple of other things which you can modify. So, let us take a structure of a cyclohexanone. Now, this compound it is usually you have an only one hydrogen for abstraction, because remaining its alpha beta conjugated or alpha beta unconjugated things. Now, this compound is a pretty good substrate for enolate generation, you can eventually use LDA, then use a base minus 78-degree C and find that you will generate an enolate.

This enolate is highly conjugated because it is in the conjugation with the particular compound. So, this is the only product which you might be observed. So, normally this is the way you can expect. So, we will try to have TCP and KCP and as I said for TCP you normally allow longer reaction time.

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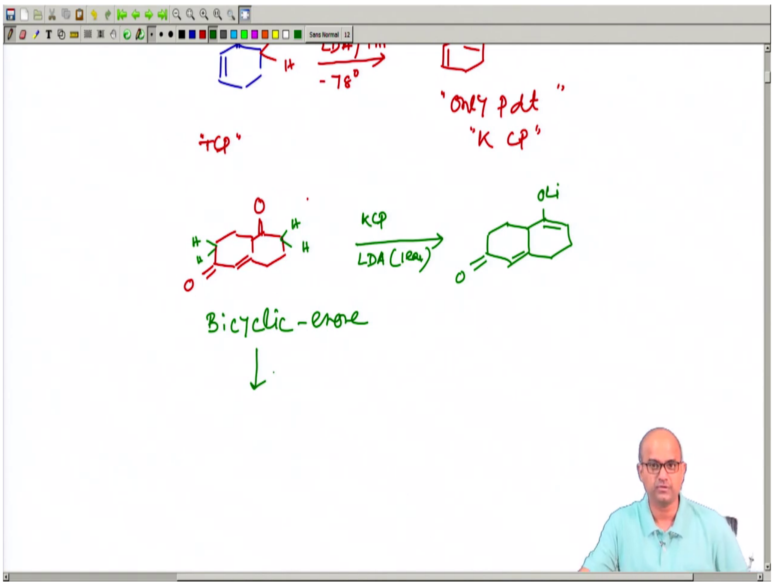

Now, if you have a couple of other issues like main regiochemistry issues which I am talking about let us be it particular about a typical substrate which we will now try to draw it here. This compound it is a bicyclic enone, now this bicyclic enone, you see that this bicyclic enone does have these hydrogens which seems to be kind of easily abstractable, but in addition this left ring also have extra hydrogen.

So, what we try to do? We will be trying to apply a kinetically controlled enolate generation and we use LDA which seems to be exactly one equivalent of LDA. The one equivalent of LDA will assure that the most easily abstractable hydrogen which seems to be this one can only be picked up.

So now, if we try to analyze the final product which you are getting, you see this is OLi and this will be your main product after the kinetically controlled enolate generation.

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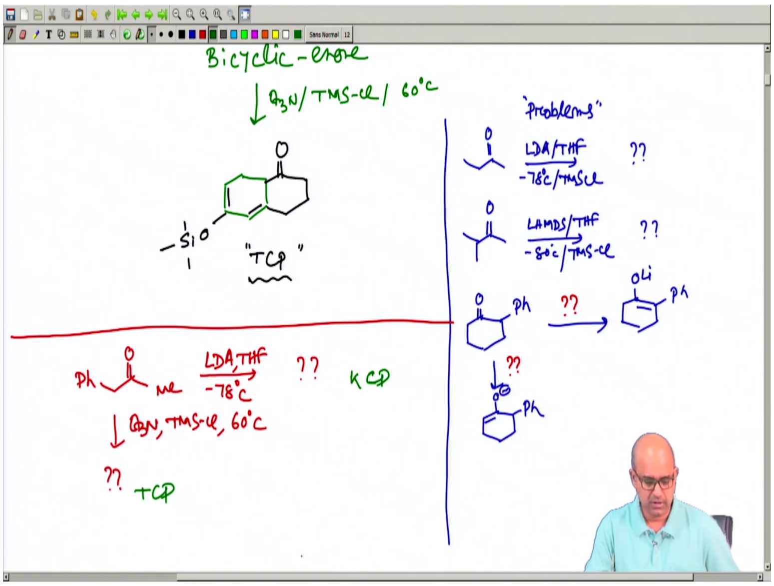

You can definitely treat this compound for a longer time and then you might observe that, once you expose this compound with a non-nucleophilic but not that strong base like let us say triethyl amine and then you trap the enolate with TMS chloride and do this reaction at a little bit of high temperature. Let us say 60-degree Celsius.

Now, in this case you have this enolates or this hydrogen which can be essentially be picked up and that can give you a more stable conjugated enolate. So, these things might be unaltered and you try to have this as well as this. Now, you see this will be having this kind of enolate generation.

So, this definitely is a TCP product thermodynamically controlled product and this TCP product you can also generate. So, based on this TCP and KCP numerous problems can be framed. Let me give you couple of problem so which you can eventually try to get. So, I will try to give you few problems which were actually based on the KCP concept and TCP concept. So, you have to predict that what will be the major product. So, take the very simple one.

You take this ethyl methyl ketone, you treat with LDA THF minus 78-degree C, and TMS chloride. So, means that we are talking about a kinetically way of enolate generation. You have to draw the structure, you have to draw the structures and you have to predict. The next one we switch over to a little bit of complicated system, just we use the earlier one, we use

LHMDS as a base we use THF and minus 80-degree C or minus 78-degree centigrade use TMSCl.

So, we have to predict the product which you can explain, a cyclic compound I will try to assign you here, a 2 phenyl cyclohexanone. Now, 2 phenyl cyclohexanone you I can frame the problem in this way, I wanted to have this enolate as well as I wanted to frame this enolate. Now, we have to predict what could be the reaction condition here, what could be the reaction condition here.

So, you can eventually see their structures and you can just predict that whether these are under thermodynamic enolate generation or a kinetic enolate generation. So, that could basically give you a pretty good idea. The last one in addition to this one I can just try to give you another problem which is also similar kind of things, just little bit structural change is there, so you have a benzyl methyl ketone. So, if you try to use the LDA condition THF minus 78-degree C, you predict the product.

And in this case another condition I will be using triethyl amine and I will be using a TMS chloride at 60 degree centigrade, you have to predict the product. So, basically what I am meaning to say that. In this case I am asking for a TCP to operate and in this case sorry this case we are talking about a KCP means kinetically controlled enolate generation. And in this case we are talking about a TCP thermodynamically controlled energy generation. So, both the way you can basically switch over.

So, probably in the next class we will continue discussing on other topic.

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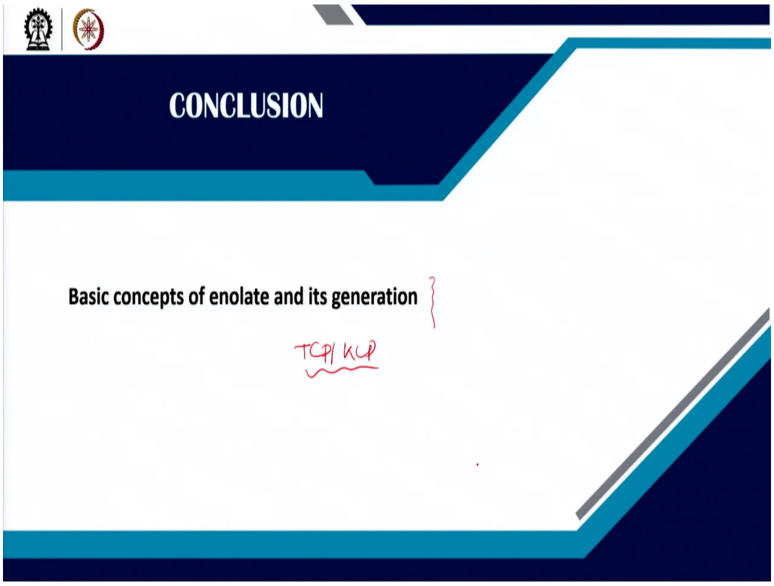

CONCLUSION

Basic concepts of enolate and its generation

TCP/ KCP

So, as a concluding remark, today we have mainly covered different method of enolate generation, the basic concept and we mainly talked about other issues based on TCP as well as KCP which are self-explanatory. If you go back to the today's lecture, we have covered those things and we will continue discussing.

Thank you all, we will see you again in the subsequent lecture. Have a good day.