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 - 03
Enolate generation, structure of enolates and related topic – III

So, welcome students again. So, this course entitled as Principles and Application of Enolate Alkylation: A very unique strategy for construction of carbon-carbon bonds in asymmetric fashion. So, today going to talk about lecture 3 which is basically the component of module 1 we are discussing basic structure of enolates and its generation.

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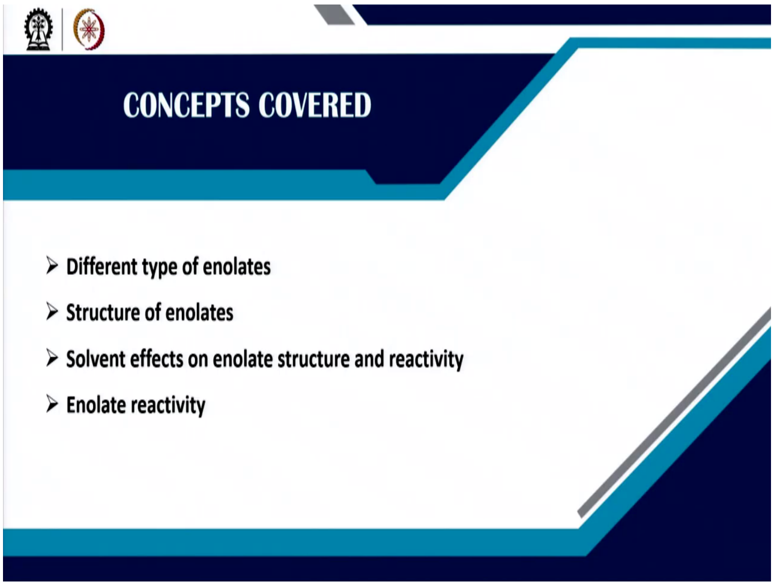

CONCEPTS COVERED

- Different type of enolates
- Structure of enolates
- Solvent effects on enolate structure and reactivity
- Enolate reactivity

And today we will be mainly talking about different methods of enolate generation; it is a very preliminary structure, solvent effects of enolate structure and reactivity how you can control the enolate structure. And then we will be if time permits we will talk about bit of enolate reactivity.

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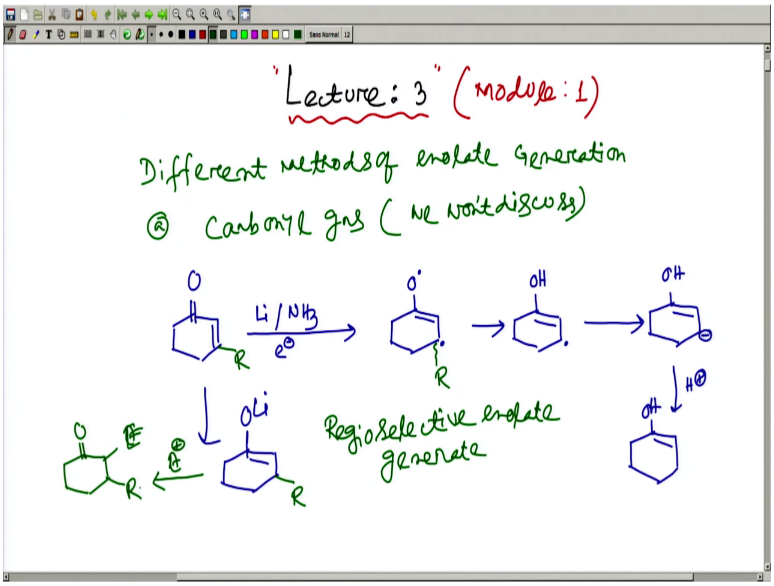

"Lecture: 3" (Module: 1)

Different methods of enolate Generation

ⓐ Carbonyl grs (we won't discuss)

Regioselective enolate generate

So, we are continuing in the lecture 3, in today's class we will mainly try to focus about different methods of enolate generation from a synthetic chemist's perspective. Now these methods of enolate generation essentially mean that it we may not start always from the carbonyl compound. Usually, we have seen that at a very standard way you always start with carbonyl compound ok, but today we are not going to talk about these things. We would not discuss which we have already covered in the previous two classes. So, we will be talking about something else.

Now, one of the very early methods of enolate generation which usually start with a compound having structure something like this an alpha beta unsaturated ketone. Now in this case now if you can try to use a condition which is very similar to like a reductive condition which often we used in the Birch reduction lithium and liquid ammonia based single electron reduction or reductive process. And in this case it has been always found that you can eventually transfer a single electron at the very beginning to this particular thing and then it has been like this ok.

And then it might abstract another electron from the metal and then get a carbanion and quench the oxygen thing by taking hydrogen from ammonia or if you have use the solvent and then these one is further will be acting something like this and then you get a minus here. Now in the other way you can eventually if you see it this minus now abstracts a proton and you get a typical enol kind of species something like this.

So, this is one of the very important ways for regioselective enolate generation which you can eventually try to do it if you also you can write the way that at the end finally, as you have lithium, most preferably you can get a lithium enolated species. And you can also try to get some alkyl group here if alkyl groups are here that alkyl groups remain in this way.

So, this is more or less very safe way of a regioselective enolate generation method through reductive electron transfer by the Birch condition. This works pretty well and this enolate eventually if this enolate is there you can actually quench this enolate by treating with different electrophilic reagent, E plus and then you will get a new carbon electrophilic bond at the adjacent to the carbonyl this is E Actually E…….. So, you will get this kind of; this kind of product.

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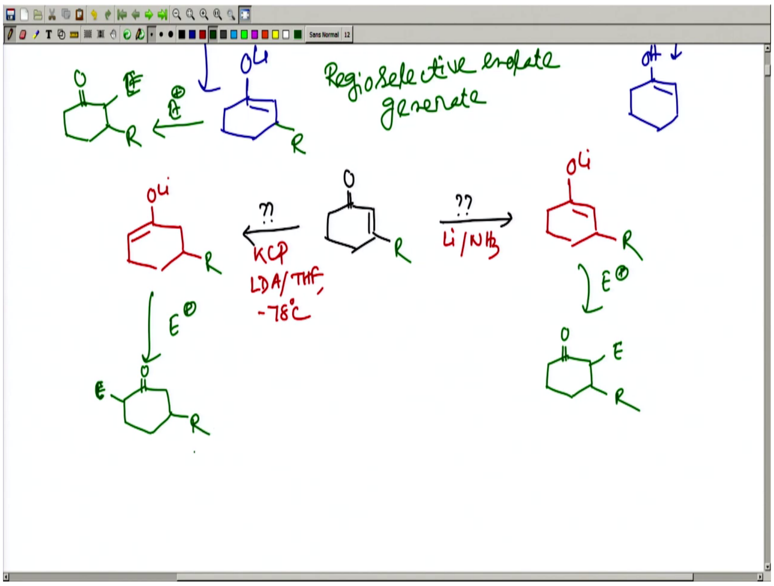

So, this usually gives a very stable way of enolate generation method, but on the contrary now we can give you a different type of discussion. Let us say you have this product. So, there are two possibilities in the normal condition if you try do not use anything if you think that if I want to have this enolate which seems to be like this. Now what condition it will be is a typical kinetically controlled condition which is we all know LDA THF and your minus 78 degree C.

But this case if you wanted to use the enolate which will be like this structure, just now we have discussed the only option is lithium liquid ammonia and you can eventually generate. So, both starting from same precursor you can have access to generating both the enolate.

Now by taking the help of the further electrophilic reaction if you now treat with electrophile you can eventually quench this enolate and you can get a carbon electrophile bond here and from here if you treat with electrophile you can get a different product or regio isomeric product.

So, substituted cyclohexanone of this kind of structure you can eventually create by taking the help of a kinetically controlled enolate generation as well as a reductive method of enolate generation by applying a Birch kind of condition.

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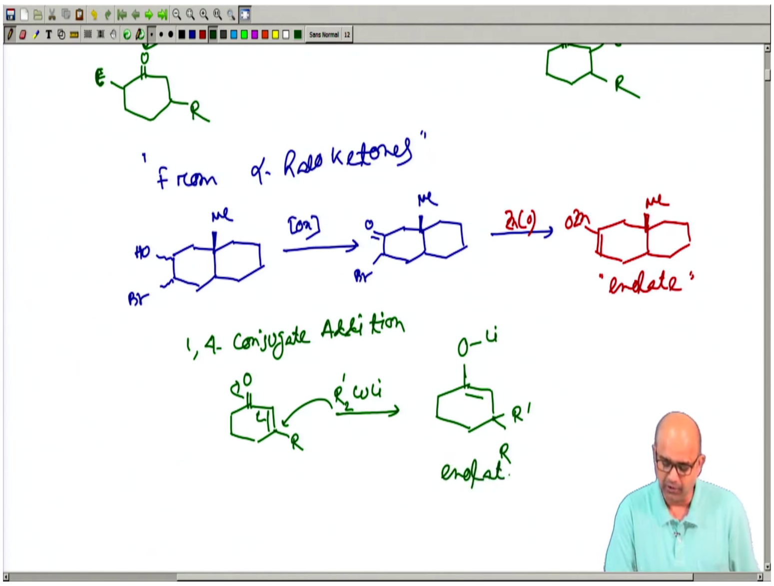

There are few other conditions I will try to use those things the second one which we call it from alpha halo ketones. Now, alpha halo ketones which are also pretty good substrate or precursor from which you can generate the enolate. Let me give you a specific example of such compounds a standard bicyclic compound was chosen. In this bicyclic compound this was such bromohydrin was there. This bromohydrin was initially oxidized with the oxidizing agent and that yields you a corresponding alpha bromo ketone.

Now, this alpha bromo ketone you can now use as a precursor and treat this compound with a metallic zinc, simple metallic zinc and you will find that this usually will generate a zinc enolate which you can use it as a normal enolate precursor. So, this is the enolate, but we didn't use a simple carbonyl compound we use an alpha bromo ketone compound.

The number 3, we can use other reaction conditions and one of those important reaction is 1,4 conjugate addition. Now 1,4 conjugate addition which is very famous addition or famous reaction we call it a Michael reaction. Now let us see this also gives you an enolate formation. Now normally this reaction is similar to the Birch type of reaction which just now we did it.

Now, here you treat with a nucleophile, now you probably you use a copper based nucleophile R_2CuLi, the Gilman reagent and then you will find that your nucleophile attacks here you basically get the corresponding enolate. So, you have a carbon-carbon bond formation. Now see this enolate now this enolate subsequently can be trapped with other electrophile to generate a different synthetic intermediates or different species. There are few other ways which also you can use it.

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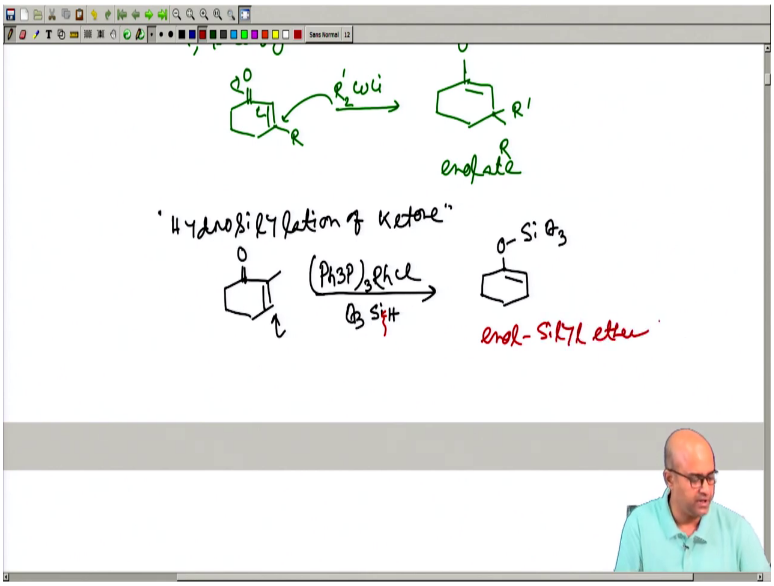

The next one is eventually again a hydrosilylation of ketones this is similar to the Michael type of one which we just now talked. And in this case what was happening the researchers usually use a Michael acceptor and then they treat this compound with a typical catalyst called Wilkinson catalyst and they use a hydride source Et_3SiH.

And this also gives you this silyl enol ether where this hydride was initially transferred with the help of Wilkinson catalyst at this point and then you get O minus the Et_3SiH bond was broken. And this is basically, so Et_3SiH is attacking here you get an enol silyl ether. These are usually very different way of generating the enolates not from the usual way which all of us do it. Now, in the last part we are also talking about few other aspects.

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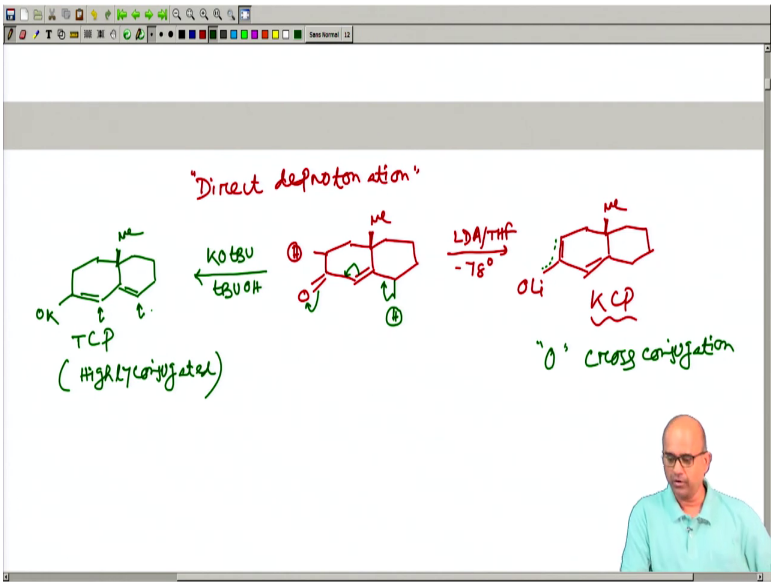

Now, we will be talking about a direct deprotonation which is also a way of generating an enolate. Now direct deprotonation means that let me try to draw a substrate which seems to have this kind of bicyclic structure and this bicyclic structure it is having an alpha beta unsaturated at one end. It contains an angular methyl group. Now this is the only one abstractable hydrogen which is evident from a closed structural look ok.

So, we can simply use LDA, THF, which is the normal kinetically deprotonation fine that all of us know that will lead to a usual way of this, this, this. So, this is a conjugation ok, but you see that the conjugation is not very direct the oxygen is in kind of cross conjugation position. So, this is definitely kinetically controlled enolate and oxygen usually is in cross conjugation because oxygen cannot take part in a direct conjugation because it is not a conjugate network because this and this.

So, if oxygen takes part it will have to have either this way this is the only way and otherwise; now there are hydrogen which is little bit apart which is called gamma hydrogen. Now if you allow the substrate to react for a longer time and you can use a definitely a stronger base, but a pretty bulky base and use a protic solvent which basically allows the proton exchange.

Now if something happens that this hydrogen is abstracted it is there. It is a direct conjugation and you might be expecting that whether it is possible to get the gamma hydrogen abstraction to give you this kind of enolate…… the answer is yes. Now, in this case the system is highly conjugated. The system is highly conjugated and this gives you a pretty well stabilized thermodynamically controlled enolate.

Now such way you can generate the enolate and this enolate definitely has a different reactivity parameter because it can react at this point as well as it can react at this point, as this reactivity discussion we will be doing it little bit later on. We can keep it on that discussion on the subsequent part.

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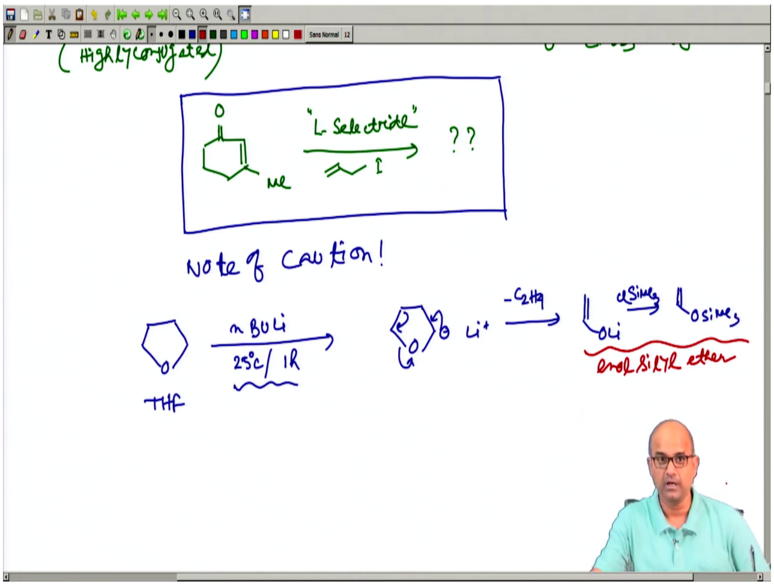

Now, then you can also try to use the Michael way or the 1, 4 conjugation way. I will keep this as an assignment for few of you let me give you a typical example that something like this and I will be using a reagent called L-selectride. L-selectride is a sterically bulky hydride donor. Now normally in this case the L-selectride will be adding on this point in a Michael fashion and then if you use an electrophile allyl iodide. Let me give you the; I mean; you have to predict the product which was formed in this reaction. So, please work on it based on the thing which we have just now discussed.

One note of caution for enolate generation…. What I am saying note of caution because, this note of caution was pretty important. Now, actually in most of the cases we use THF as a solvent. Now, THF structure is this tetrahydrofuran, now THF if you use a base like normally butyl lithium we never used as an enolate chemistry for energy generation because it is a bulky based strong base, but nucleophilic character.

Now, this compound if you use THF in nbutyllithium at room temperature you will find that initially this hydrogen will be abstracted and you get a minus and Li plus. Now this one will be then later on will help to cleave this THF ring and actually ethylene gas will be evolved and if you can trap this reagent you first get a enolate and this can be easily trapped with TMS chloride, Me_3SiCl you can actually get a vinyl TMS ether.

Now, why I said note of caution actually only for that reason THF reaction if you are doing at low temperature that is fine, but if you are using a THF reaction with n-Butyllithium at room temperature or higher temperature for some other reactions you might end up with this kind of enol-Silyl ether. So, you have to be bit careful on conducting reaction with THF and n-Butyllithium at higher temperature, you should not do it that basically is a bit risky for doing it.

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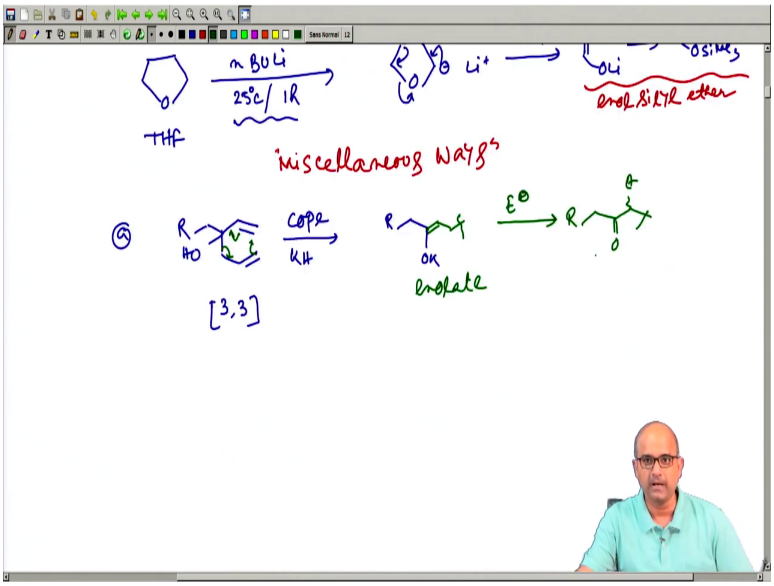

Other way of generating enolates we just spend some time, we call it miscellaneous method miscellaneous ways. Maybe I can give you some homework or assignment which probably you can do it. Let us start with a simple system where you can find that this kind of compound if you try to; now what is the system is basically a conjugated system.

But, not sorry it is not conjugated, but it is a 3,3 system. 3,3 means this kind of compounds can rapidly undergo a sigmatropic rearrangement or Cope rearrangement. The moment it undergoes Cope rearrangement you can eventually find that this Cope rearrangement product is nothing but an enolate. If you use a base like potassium hydride it can give you O minus or K and then it can undergo a 3,3 sigmatropic rearrangement which is very known to us and that will eventually lead you a enolate.

See this is the enolate the remaining structure I do not write. So, this is basically enolate. So, the 3,3 sigma tropic reaction also you can have a enolate. Now this enolate you can simply can keep up or react with the electrophile. So, eventually what we will get? You get a CO and as the regioselective it already means electrophiles has to come from this place.

The rest of the structure I did not write, but you can eventually try to do it. So, there are eventually there are few other ways like this particular example the miscellaneous method you can use the enolate generation. We will talk about another miscellaneous method which is also very important.

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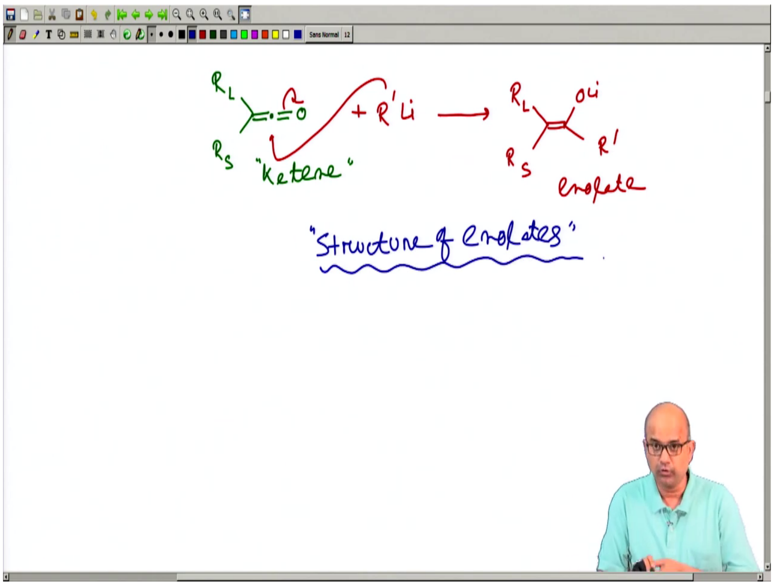

Now, this miscellaneous method deals with a ketene kind of compounds. Now ketenes are compounds which are very specific intermediate which you have might seen or might you have encountered in different chemical reaction mainly the Arndt-Eistert synthesis when which you have studied in the undergraduate days. Now, such a ketene you can usually generate and if you react with a lithium species normally this lithium being a nucleophile, it will seem to attack here ok. And what we will get? You eventually get an enolate this is nothing but an enolate.

See this is enolate this enolate you can further react with different compound. Now such a ketene normally; so there is numerous way to generate the ketene and you can eventually play with this ketene in different form. So, we probably do not talk much in this sense and then we just try to give you a little bit of other information where the information will be now switch into structure of enolates. So, generation of enolates is fine we have discussed couple of assignments we have given you couple of assignments.

In the subsequent section we will also give you more assignments and we will in the NPTEL course work you will also deal with few assignments in the enolate generation. Now, structure of enolates, in this part we will mainly focused on how this enolate are mainly having the structural aspects in the solution phase.

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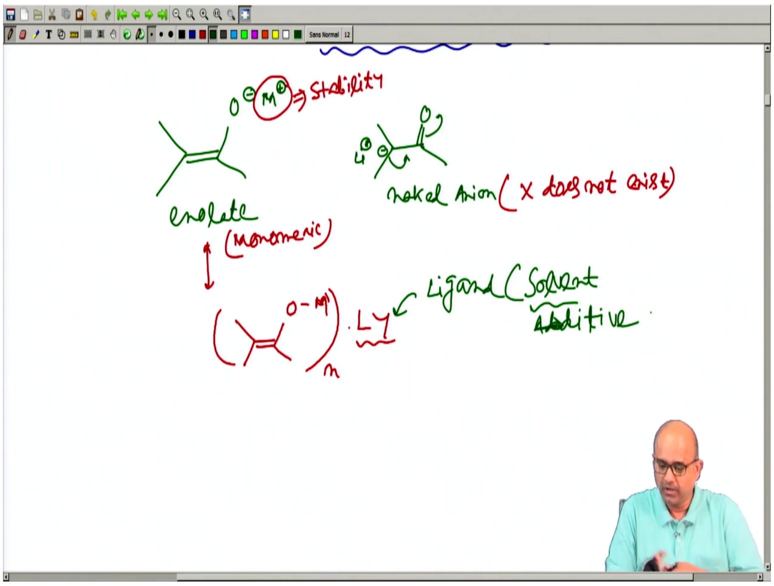

Normally, when you are trying to take an enolates or generate an enolate there are few aspects of the structural part. So, this is a simple enolate which you might have generated ok. Now this enolate will be O minus and corresponding M plus as usual you can see it. But, at the very beginning which you have seen that the corresponding compound might be I mean where you have generated the enolate having a structure something like this the minus or Li plus.

So, this is a naked anion or a normal carbanion ok or in few cases, if you having some other structural aspects, but these two are the main things. So, first you generate the naked anion and then you create this kind of enolate right. So, now metal combination or metal coordination is one of the main factor which is responsible for enolate stability. So, enolate stability is mainly governed by the correlation with the metal and usually in the naked anion it does not exist.

So, always this naked anion it does not exist, it has to be go from for the keto to enolate instantaneously ok. And now this enolate the way I have drawn it seems to be a monomeric species means a monomeric thing, but in reality enolates are not a monomeric species and you will find that these enolates usually do aggregates in different way and their structures are varied.

So, this kind of aggregation usually is mainly possible and this aggregation happens with usually with a ligand. So, this aggregation was one of the main factor, now this LY actually stands for a ligand. Ligand means it could be a solvent or could be an external additive. These things we need to be discuss little bit probably today or if time permits we will be talking about these things little bit later on.

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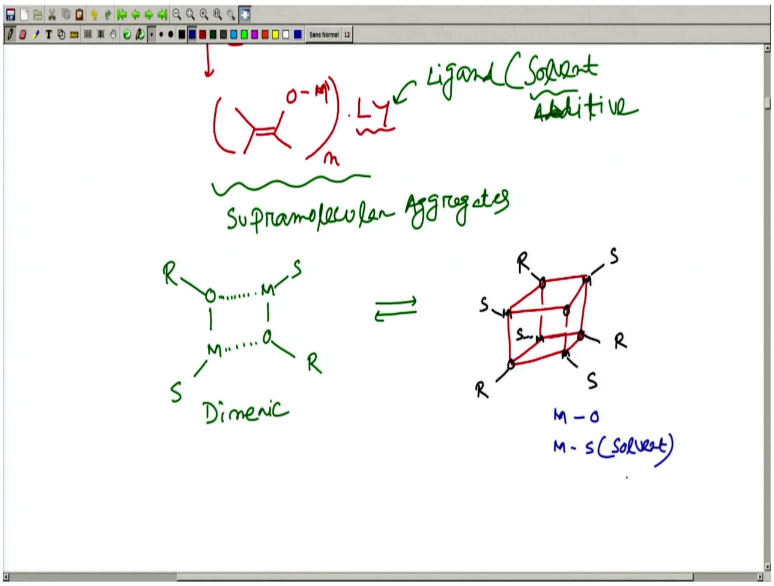

Now, let us coming to again the structural aspects so how this enolates looks like? So, now I can write the entire enolates and these things I can call it supramolecular aggregates. So, these are non-monomeric aggregates …….supramolecular aggregates and such aggregation of enolate structure have been proved by low temperature X-ray technique even in many cases low temperature MIR technique also been used. So, I can write simple R the entire group of thing the oxygen is there and you have a metal ok.

So, this metal will try to coordinate with the solvent as I am saying ok. So, let us say you have a monomeric enolate and then on the another monomeric enolate we can write it in this way. M S this O R see both the enolates I have written a different way. So, now one of the enolate oxygen will try to coordinate with the metal of the other enolate and like this. So, from a simple monomeric now it comes a dimeric aggregate fine. So, dimeric aggregate it has been will be fine.

Now, this dimeric aggregate you can eventually try to get other complex aggregate if you allow more time. So, let us see I will try to write a typical cubical structure which is familiar to all of us a typical I mean just to show that ok. So, now you can fill it up of this different space of these things. So, you see this is an O oxygen R. So, in this case you put corresponding metal with solvent and again you put O and R. So, here also you put metal with solvent.

Now, here in same case you put oxygen and metal. The similar way you just do the coordination and you feel the entire vertexes with a different kind of atom. Different kind of atom means the monomeric form is normally aggregated. So, see now you have a tetrameric aggregated and you see there are 4 different modes of enol and everything you can just try to get a different kind of aggregation. So, always you your point of contact are a metal with oxygen metal with oxygen and then metal with the solvent. Now, this is the solvent molecule. So, solvent plays a very important role.

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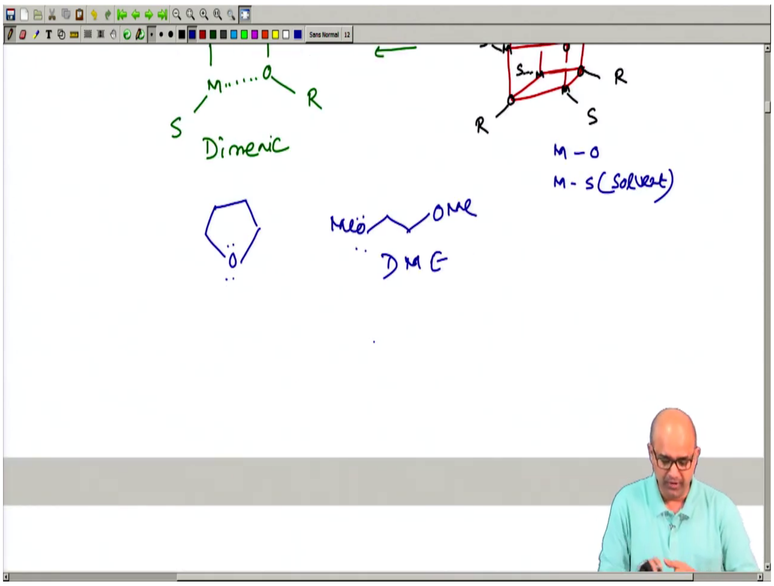

And normally solvent like THF or like solvents which play very important role, THF Tetrahydrofuran, Dimethoxyethane MeO−CH_2-CH_2OMe, DME plays a very important role because these solvents can coordinate with this lone pair with the corresponding metal and it can basically stabilize the corresponding metal part of the enolate. The metal is more solvated and then the enolate it becomes much more nucleophile in nature and the solvent which we often choose I will give a little bit time 1… 2 minute for the solvent.

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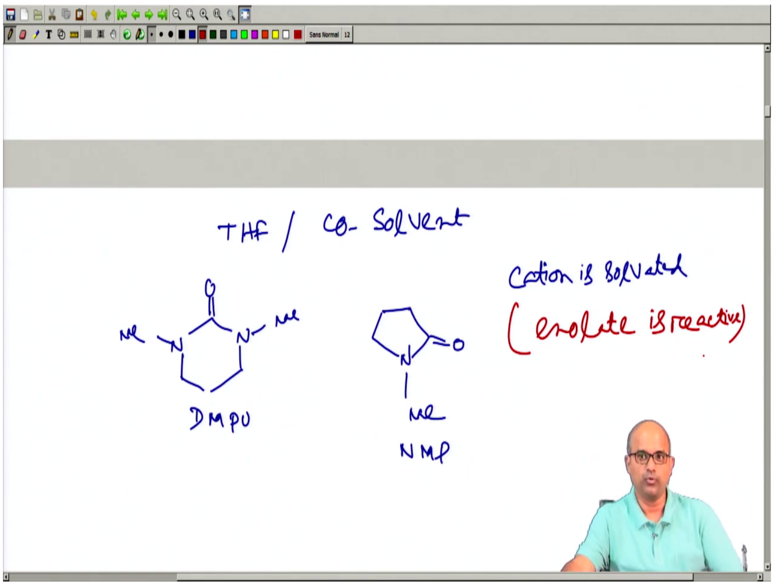

We found that most of the time with THF and DME you use some co solvent. Co solvents are those which can stabilize the enolate or stabilize the counterpart of the corresponding metal with coordination, the solvent like this Dimethylpropyleneurea (DMPU) which can ……..N-Methyl-pyrrolidone. So, see this solvent are having a pretty good cation solvating agent.

And sometimes; so, the more this cation gets solvated cation is solvated solvated are stabilized and the enolate becomes much more reactive enolate is reactive. So, the more the cation is solvated the enolate becomes much more reactive.

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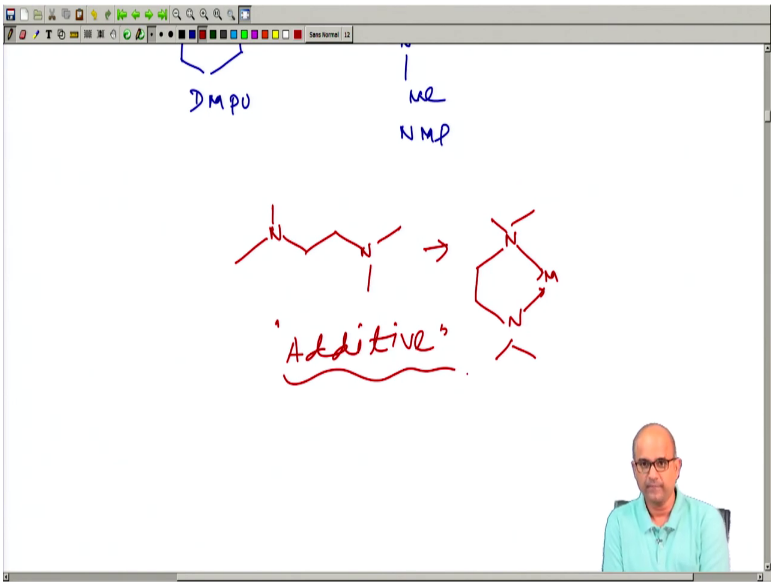

In some cases, we also use some additive which can stabilize this thing the most used additive is EDTA Ethylenediaminetetraacetic acid which is usually coordinated coordinate with the corresponding metal in this type of way metal ok. And so this kind of additives also pretty useful for the enolate generation and founded this kind of polar, but aprotic solvents plays a very important role for enolate generation.

So, in the next class we talk about little bit of different thing we will explain the molecular orbital picture of the enolates and how enolate can be stereo specifically deprotonated to give you z as well as e enolate and that is the basis of our main course of this asymmetric alkylation of enolates ok.

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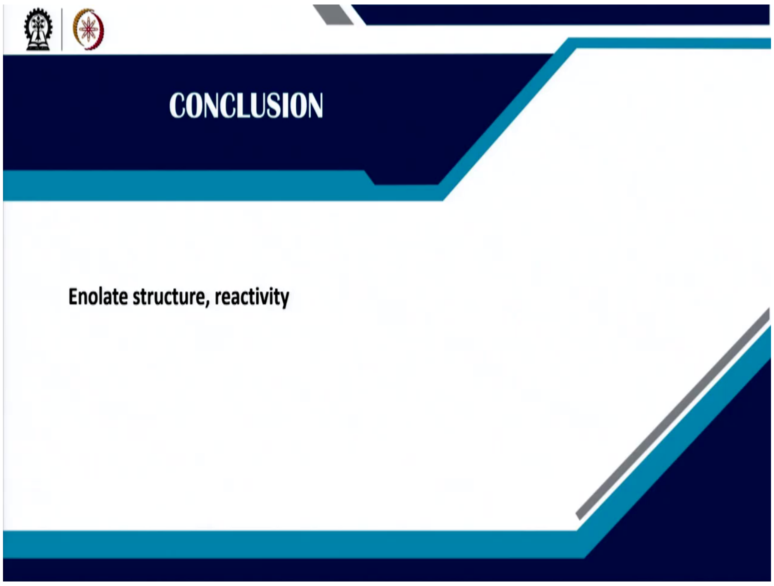

CONCLUSION

Enolate structure, reactivity

So, as a concluding remark we can say that in the today's class we talked about enolate structure, how different way you can generate the enolates and as a reactivity parameter it is dependent on the solvent structure. And we will be talking about more of the things in subsequent classes till then goodbye to all of you have a very pleasant day.

Thank you.