Essentials of Oxidation, Reduction and C-C Bond Formation. Application in Organic Synthesis

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Lecture - 42
C-C Bond Formations: Introduction to Enolate, Enamine and Enol Silyl Ether Based Chemistry

Hello everyone, welcome you to this class of today. I hope you were able to go through what I discussed in the last class. Now what we did in the last class was something to do with the asymmetric reduction.

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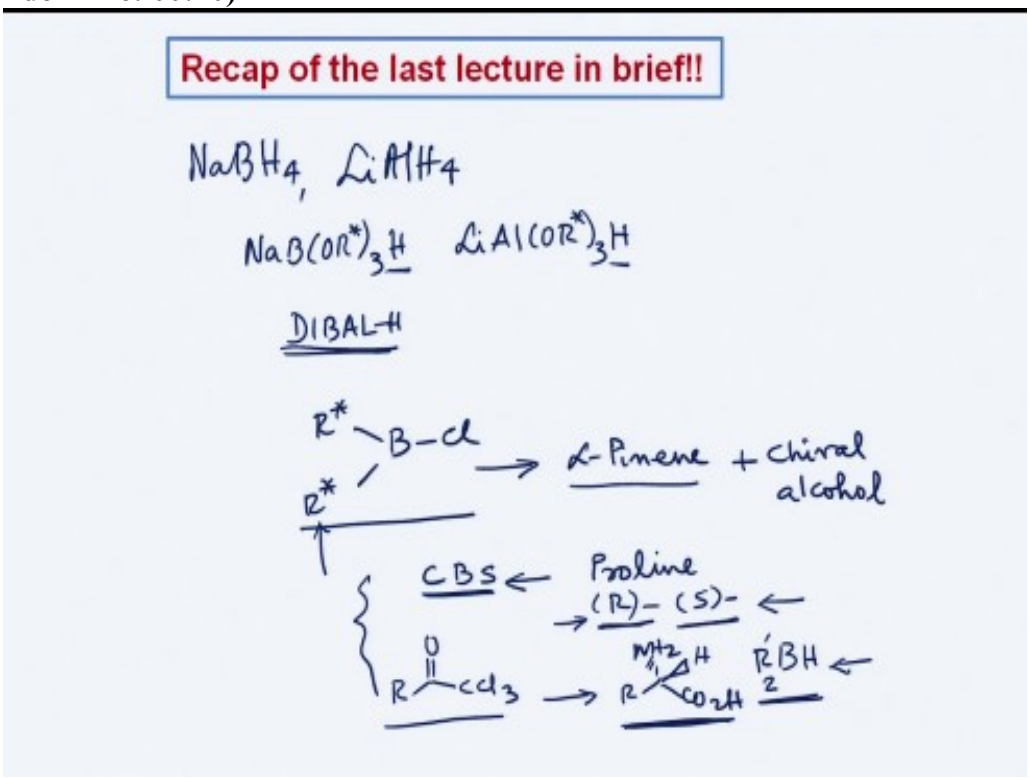

Initially we saw that we can modify the nucleophilic reducing agents such as sodium borohydride or lithium aluminum hydride into the corresponding chirally modified reducing agents, where the hydrogens say up to the three hydrogens we can replace by chiral ligands and such as you can make sodium boro say for example, you have R* 3 H and likewise lithium aluminum we can make it as OR* 3 H.

But of course we can also use even less than three, but as long as there is at least one hydrogen which is present. Likewise this electrophilic DIBAL we can also modify and of course we can make use of the reducing agent for the chiral reductions provided that the DIBAL part is chiral. And like that we saw another reducing agent which was derived from alpha pinene base.

And we saw how that reducing agent which had a boron and a chlorine and then of course we had a part of R*here R* here which led eventually to the reduction of the ketone and of course the alpha pinene which is comes out from the reaction, from the salt, from this particular reducing agent. So this behaves like a reducing agent, but it does not have a hydrogen as a hydride attached to boron directly.

But it is in this particular part, which is what after the hydride is transferred leads to the alpha pinene plus of course we get chiral alcohol. So these are all different types of reducing agents which we discussed. And we also mentioned about this fact that each of these reducing agents is required at least in one mole equivalent. So therefore, it is not something which is useful in a long run or in large scale.

But then we introduced Corey-Bakshi-Shibata ligand or a chiral part which allows modification of the BH_3 and this Corey-Bakshi-Shibata catalyst then allows reduction of the ketones to the corresponding alcohols in a predictable geometry manner. And thus we can before starting we can of course we can choose which kind of Corey-Bakshi-Shibata ligand is to be taken.

As we discussed, it comes from Proline and we can take R-Proline or S-Proline depending on which particular enantiomerically pure alcohol that is required. So obviously, when we start with R-Proline, we get one enantiomer of alcohol of the same molecule, we get S enantiomer if we take the S-Proline or the opposite enantiomer if we take S-Proline.

And then we saw how these kind of catalysts or the ligands which can convert ketone like this into an amino acid. And then of course, we can see how these particular molecules can be made unnatural amino acids. So we have a possibility of getting a variety of amino acids, alpha amino acid specifically in chiral in natural or unnatural fashion. So these are the modifications of the catalyst that we discussed.

Of course in this case, we saw that the reducing agent is a borane which can be say you have R' 2, we can have any kind of borane. We have normal borane or BH_3 or we have any catecholborane or any other borane that we can think about using it. So this is what we did in the last class.

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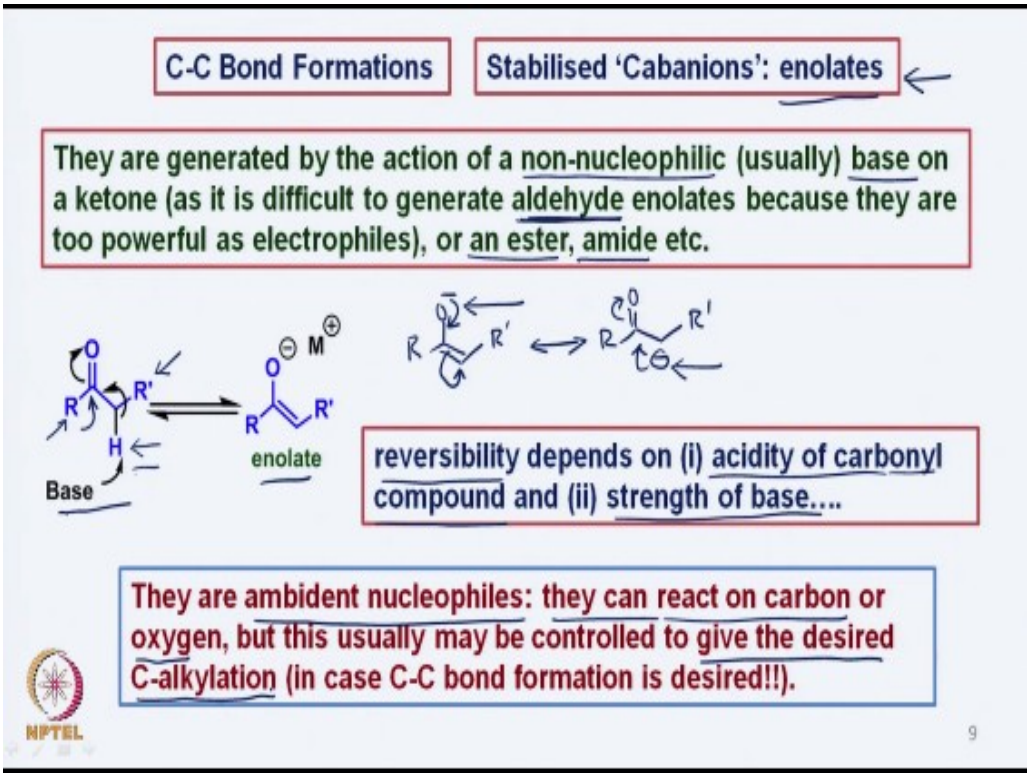

Now we see how the C-C bond formations can be done and C-C bond formation basically initially was done by generating a carbanion which is a stabilized carbanion because it gives enolate. So if we have a ketone, and if we treat with a non-nucleophilic base, so you have a non-nucleophilic base and then react with the ketone, we get an enolate.

We are not taking this aldehyde as a carbonyl part to generate the corresponding enolate because, the enolates generated from aldehydes are very reactive and aldehydes are very electrophilic in the nature and therefore they generally condense with each other. And therefore, it is not very convenient to generate an enolate from an aldehyde.

But then we can take a ketone or we can also take an ester or we can take an amide which are easy to generate the enolate from the corresponding molecules. Now these ketone and the enolate they are reversible. And reversibility depends on acidity of the carbonyl group or the carbonyl compound and strength of the base.

So obviously if this hydrogen here is very acidic due to the electron withdrawing nature of say for example, R' or even R can affect the electrophilicity of this particular carbonyl group and thus the acidity of this hydrogen would vary depending on what substitutions we are putting around. And also we can take a strong base and therefore the strength of the base would also matter.

Because if it is a strong base obviously it will pick up the hydrogen very fast and would not then allow it back for the equilibrium to go. Now this is how a ketone is converted to an enolate and one can see that we can write the enolate as a resonance structure in this fashion that you have the negative charge moving on to the carbon, alpha to the carbonyl group in this fashion.

So obviously, we can go back here and we can generate the enolate. So it is like a resonance structure and therefore we have a possibility of this being a nucleophile or this being a nucleophile. So it is an ambident nucleophile. These are all ambident nucleophiles. They can react either on carbon or on oxygen. But this can be controlled to give if one wants the C-C bond formation to take place.

So there are factors that we have to look at and there are conditions which you will have to meet with to guide the C-C bond formation via this particular enolate molecule which is having a resonance structure with the anion on the carbon.

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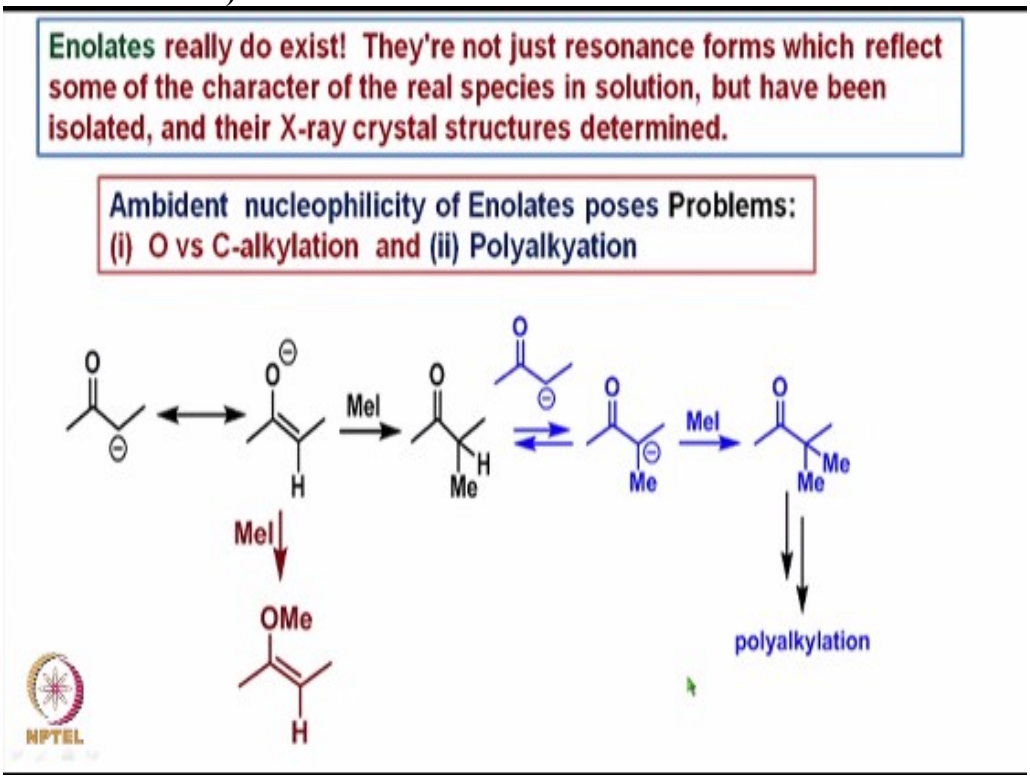

Now enolates really do exist. They are not just resonance forms, which reflect some of the character of the real species in solution, but actually they have been isolated and their X-ray crystal structures determined. So if we have a carbanion of this type, it will exist in its enolate form as a resonance structure and both these anions, one carbanion, one enolate ion would show a nucleophilic character and therefore they are ambident nucleophiles.

One of course leads to C-alkylation and other leads to O-alkylation. So if O-alkylation of this enolate is taking place, then of course we get the corresponding enol ether. And if C-alkylation takes place then we get alpha alkylated ketone like in this case we have alpha methylated ketone. So in addition to this dual character of this particular ambident nucleophile where O and C alkylations can occur and we need to control them if we want one of them to occur.

But in addition to this, we also have a possibility of polyalkylation. That is, this particular ketone can undergo deprotonation here by base present in the reaction medium or by the carbonanion present in the reaction medium to make another carbonanion like this, which can then react with methyl iodide to form a dimethylated compound.

Now this dimethylated compound in principle has three more hydrogens alpha to the carbonyl group, which can be deprotonated and each of them can undergo alkylation eventually to lead to polyalkylation. So these two problems, that is O and C alkylations and also polyalkylation are something that we need to worry about. And therefore, we need to see what are the factors that allow these reactions to be controlled.

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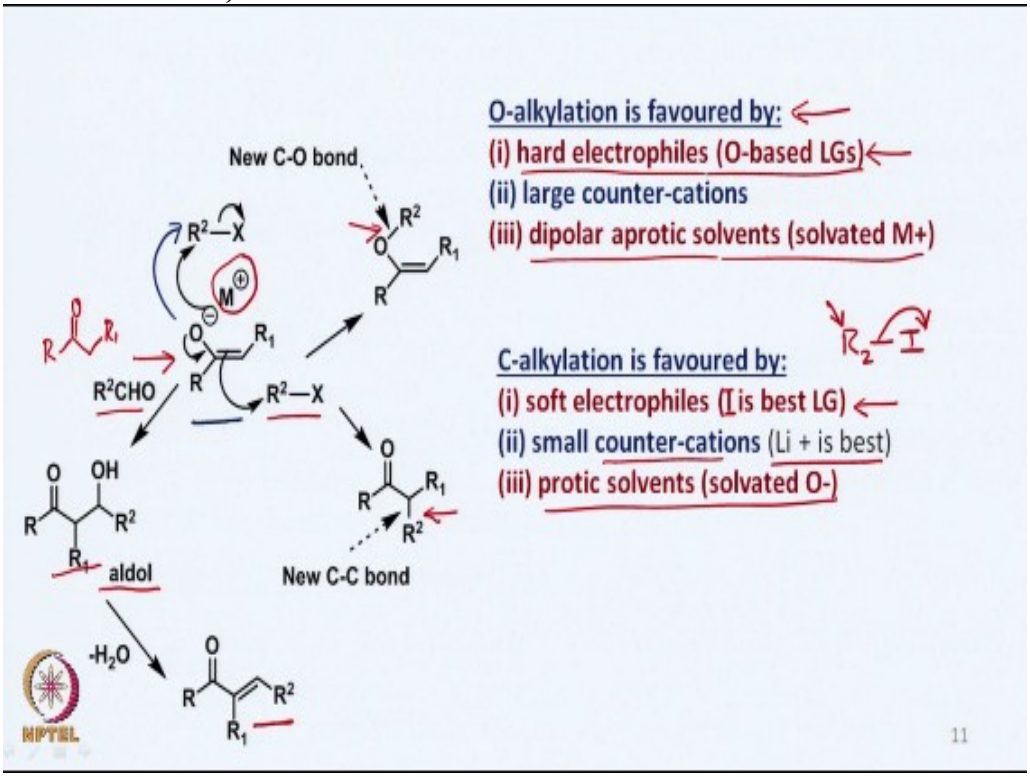

And one thing we can definitely do for O-alkylation or C-alkylation specifically is that, say you start with this particular enolate ion, and if this enolate ion attacks on directly onto the electrophilic agent, then you have a oxygen carbon bond which is formed like this. And of course, if it attacks from the carbon as a nucleophile, then we get the carbon-carbon bond.

Now we can also use an aldehyde to form an aldol of this type which can of course lead to the alpha-beta unsaturated ketone. So these are the things which can be done by the enolate which is formed from the corresponding ketone. So we have a ketone which can then lead to the formation of this enolate and that can allow a O or C alkylation to form and also this kind of alpha-beta unsaturated ketone via the aldol.

Now O-alkylation is generally favored by hard electrophiles where oxygen based leaving groups are there, this is leaving group or you have a large counter-cations. So this particular M+ should be large. So if we have a large counter-cation and then of course the charge is separated and therefore the negative charge can attack directly onto the particular electrophile. And a dipolar aprotic solvents solvate M+.

That means, if we have dipolar aprotic solvents like DMSO or acetonitrile or DMF, they would have a coordination with the M+. And then the M+ is somewhat removed and therefore the O-

negative charge is available for the electrophile to attack. So that is how O-alkylation can be favored. Now if we have a C-alkylation to form, then we have to have soft electrophiles especially when we have a iodide molecules as electrophiles where iodine is, this is I and iodine is a leaving group.

So you have an R say R 2 and I. So this is a leaving group, which is a very soft electrophile. This is a soft electrophile and therefore if we have I as a leaving group then it is easy. At the same time, if we have a small counter-cation, say for example lithium plus. Because it sticks to the oxygen and therefore the negative charge on the oxygen is not easily available for electrophiles to attack.

And therefore the double bond attacks rather than the O- attacking. And of course we have protic solvents, solvated O-. So if we have a protic solvent like methanol or ethanol or something of that sort, then of course the O- of the enolate would have a kind of hydrogen bonding with the proton of the solvent and thus the negative charge is not available for the nucleophilic attack and thus the double bond attacks and then C-alkylation is favored.

So we can do these kinds of modifications and then we can tune the reaction for either O or C alkylation as the case may be. But of course polyalkylations do take place and therefore there should be some more modifications.

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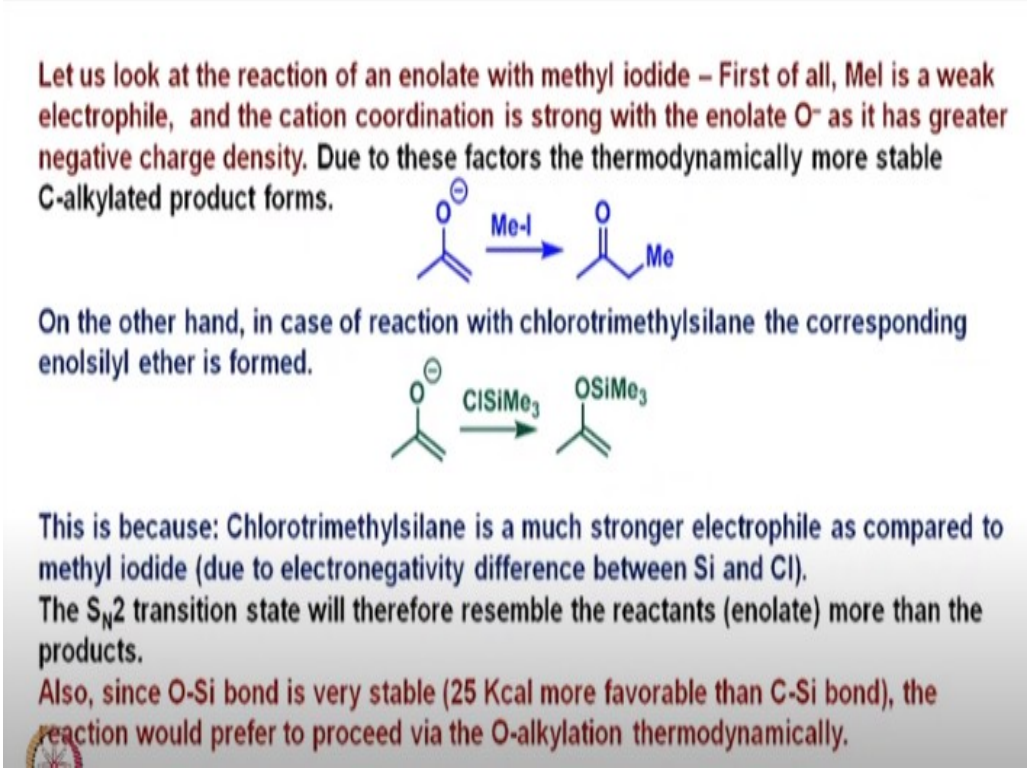

So once again, we just simply recap what we studied just now. Let us take the reaction of an enolate with methyl iodide. First of all methyl iodide is a weak electrophile and the cation coordination is strong with the enolate O- because it has greater negative charge density. Due to these two factors the thermodynamically more stable C-alkylated product forms.

On the other hand in case of reaction with chlorotrimethylsilane the corresponding enol silyl ether is formed as it is shown here. And this is because chlorotrimethylsilane is a much stronger electrophile as compared to methyl iodide due to electronegativity difference between silicon and chlorine. And therefore, as soon as the enolate is formed, the O- reacts quickly with chlorotrimethylsilane to form the enol silyl ether.

In this case the S N 2 transition state will resemble the reactants that is the enolate more than the products. Also since O-Si bond is very stable, 25 kilo calories more favorable than C-Si bond, the reaction prefers to proceed via the O-alkylation thermodynamically. So these are the two other examples where C versus O alkylation can be checked.

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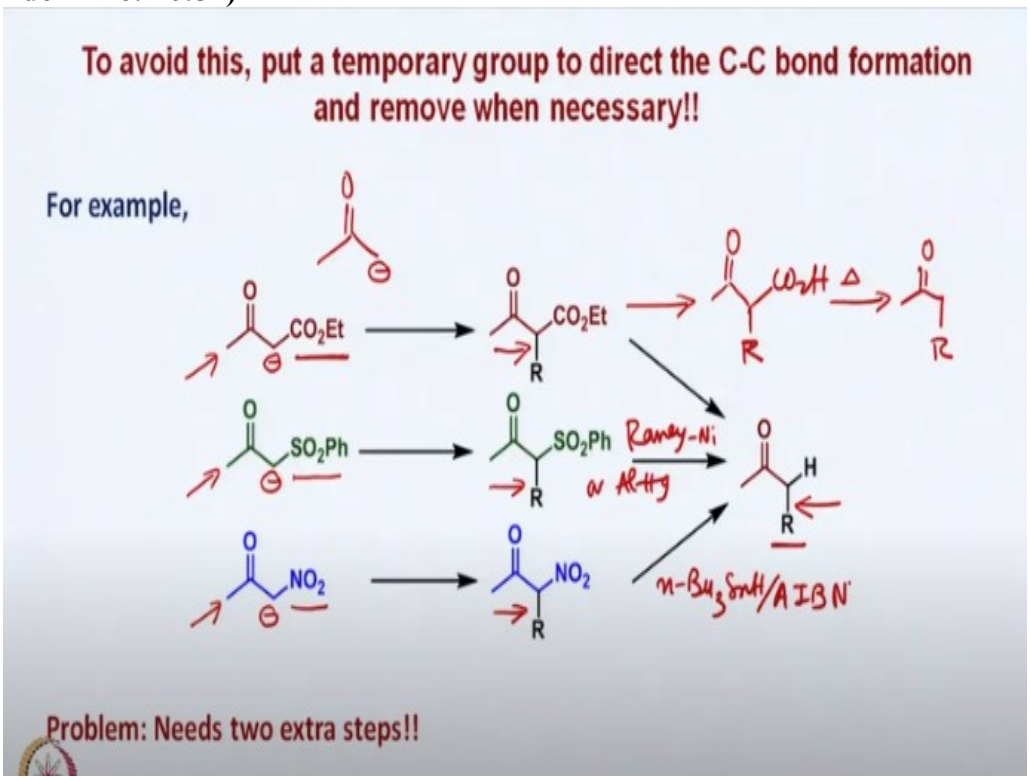

Now to avoid this, we can put a temporarily a group to allow C-C bond formation to take place. Suppose if we want C-C bond formation to take place, then we put say for example an ester group. So we want C-C bond formation to take place on to this carbon here. And therefore, we put an extra ester group here. Or we can even put a sulfonyl group here or we can put a nitro group here.

So basically these ester, sulfonyl and the nitro group increase the electrophilicity of the hydrogens which are present and thus formation of an ion is much more easy on to these carbons rather than on to these carbons. So the proton which is on the left hand side of the carbonyl group as you see is less acidic than on the right side which is next to the ester or sulfonyl or the nitro group.

And therefore the deprotonation occurs on to that particular carbon atom and then C-C bond formation readily occurs on these. And also we can choose soft electrophiles because now the anion is stabilized and therefore it is a soft nucleophile and with the help of soft nucleophile we

can use the electrophilic C-C bond formation to take place like this. But then this also of course has some negative points that it you have to introduce these groups and then remove if they are not needed it.

So therefore, it is somewhat inconvenient. As you can see that we can here do the hydrolysis of the ester under basic conditions or under acidic conditions and once we get this carboxylic acid then we heat it and then decarboxylation will give this particular molecule. Likewise we can use here Raney nickel to do this or aluminum amalgam or such kind of things, reducing agents we do it where carbon-sulfur bond is broken.

And similarly here, say you can use tributyltin hydride and AIBN as we discussed earlier, that we can remove the nitro group to the corresponding hydrogen. So these are the various ways by which we can carry out the C-C bond formation in a directive manner and we remove. But then these need two extra steps.

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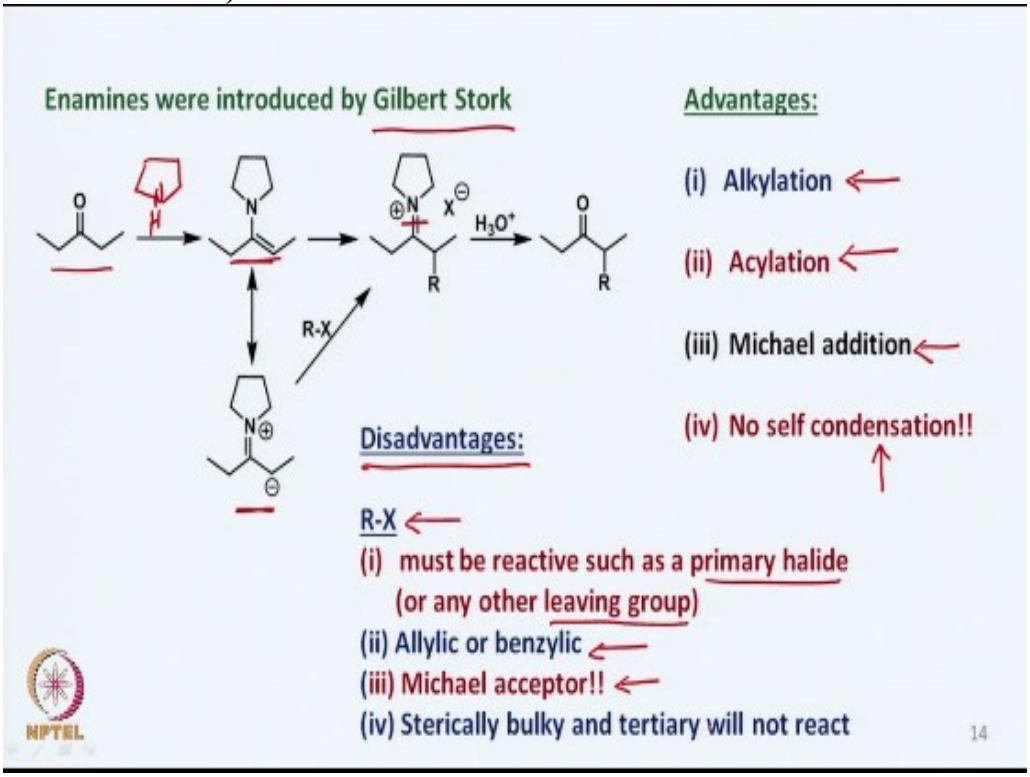

So you know Gilbert Stork at Columbia University introduced enamines as we can see that we can take a ketone and react with a base sorry, this secondary amine like say pyrrolidine and then we can get the enamine, which is of course in resonance with this kind of species. So we have an enamine and when R-X is added the negative charge attaches to the R, we can get here and then hydrolysis leads to the generation of the ketone.

So this way we can do alkylation. We can also do a acylation. We can do Michael addition and there is no self-condensation in these cases. So that is something very useful as advantages. But what are the disadvantages of these Stork enamine reaction is that the R-X has to be very reactive, preferably a primary halide or any other leaving group like tosylate or mesylate or triflate or whatever.

And it is better to have an allylic or benzylic groups as R-X or Michael acceptor. Unfortunately, the sterically bulky and tertiary R-X type of electrophilic molecules do not react with this, these enamines. So there are some problems which are associated with it.

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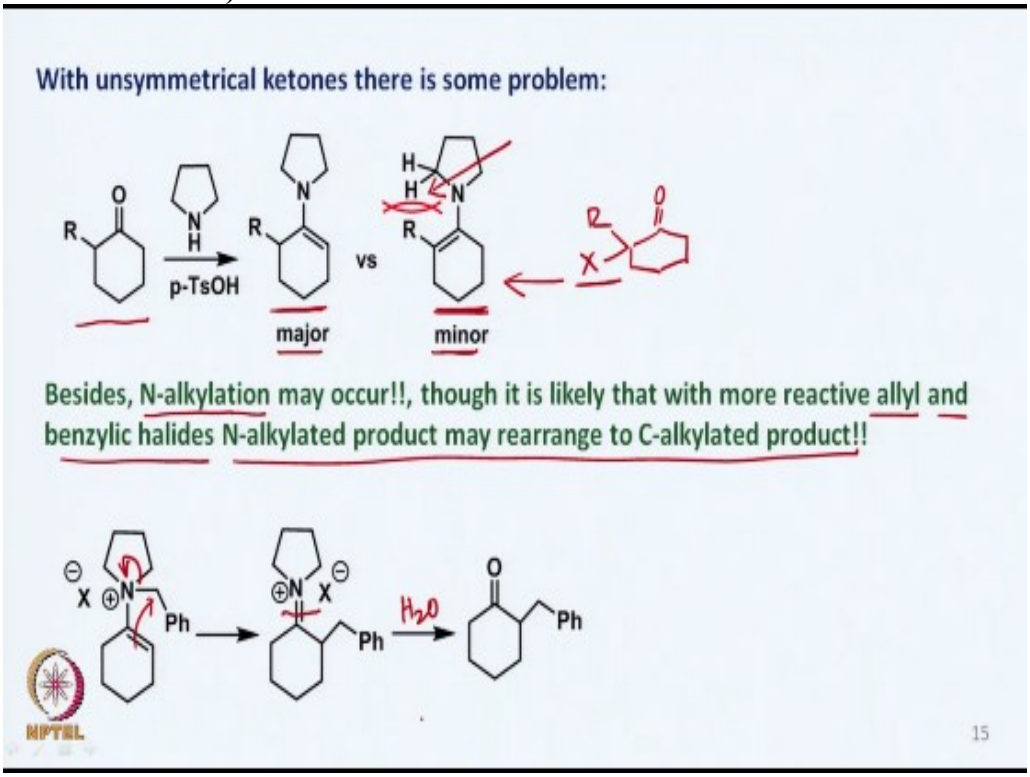

At the same time, with unsymmetrical ketones also there is a little problem. Suppose we start with an unsymmetrical ketone like this and we make the enamine by reacting with the pyrrolidine and para-Toluenesulfonic acid and eventually we get we expect to get either of the two enamines. Because it is an unsymmetrical ketone and therefore when the enamine is formed, it could form on this side or it will form on this side.

So the major one that is formed is this and the minor one is this. Now why it is minor is because the hydrogens which are present here give this kind of steric hindrance to this R group and therefore, there is a steric repulsion and then the compound form is in minor amount. But if we want this enamine for the say electrophilic reaction on to this particular part of the molecules, you want to introduce here say X, whatever X maybe, then it is not very easy using enamine.

Because enamines themselves will not form in a major amount. Besides N-alkylation the C-alkylation, N-alkylation also occurs. And it is possible that in cases where allylic and benzylic halides are dealt with, N-alkylated product may rearrange to the C-alkylated product. But if it does not, for example here, it can rearrange in this fashion after the N-alkylation has happened.

Then of course, we get the C-alkylation and then when the hydrolysis is done from here, then of course we can get the corresponding ketone. But then if such a rearrangement does not take place, this kind of N to C-alkylation, then of course we have a problem. So there are problems associated with it. Nevertheless, it has been a very useful method.

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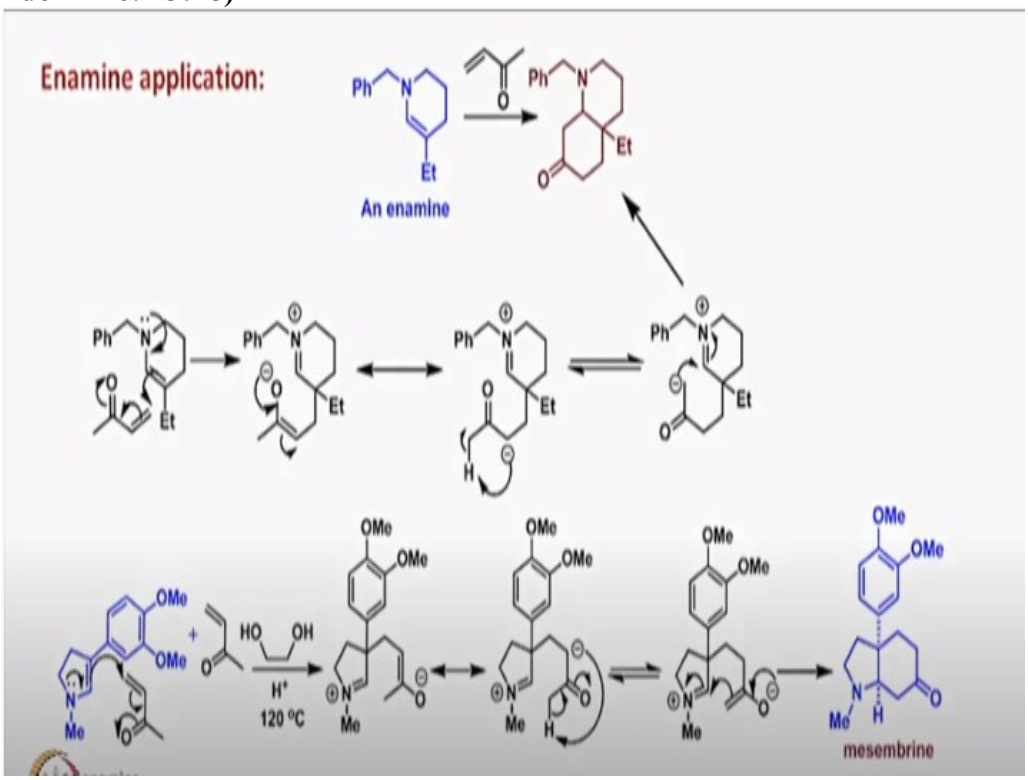

Like for example as you can see, that if we take an enamine of this kind and react with an alpha-beta unsaturated ketone such as methyl vinyl ketone, then we get this particular type of bicyclic molecule in one step. How does this reaction occur? That this enamine reacts with the methyl vinyl ketone in Michael addition fashion to lead to the formation of this particular enolate which is in resonance with the corresponding carbanion like this.

This carbanion then picks up the proton from the other side of the carbonyl group and generates the anion here. And this anion then undergoes cyclization to form the bicyclic product. In a similar fashion, if we take another enamine like this, then it reacts with methyl vinyl ketone in ethylene glycol under acidic conditions at 120 degrees. Again the Michael addition takes place to form this enolate.

This enolate is in resonance with the corresponding carbonanion like this, similar to what we observed here. Now this anion then takes up the proton from here, generates another anion, which of course will be existing in the form of enolate also. And this enolate then undergoes cyclization to form a molecule which is called as mesembrine, which is a natural product. So that is how reactions of enamines take place and they are useful in many synthetic operations.

However, we know that there are some problems associated with the enamine chemistry. And thus there should be some other way of addressing these issues. So from that angle, we will look at the other aspects of C-C bond formation, what are the further developments that have taken place and eventually, the aim is to make sure that we get optically pure C-C bond formation because that is also a very important.

In addition to asymmetric reduction or asymmetric oxidation we also need to have methods which allow asymmetric C-C bond formation to take place. And therefore, we will look at several ways of how the developments have occurred in terms of allowing C-C bond formation to take place in asymmetric fashion. So we will take up the remaining part in the next class and then see how we can proceed further.

Till then you can take care of these kind of things that I have discussed today and then be ready for the next class. Till then bye. Thank you.